Nucleosides. XVI. The Synthesis of 2′,3′-Dideoxy-3′,4′-didehydro Nucleosides[1]

JIŘÍ ŽEMLIČKA,* JOSEPH V. FREISLER, ROBERT GASSER, AND JEROME P. HORWITZ

Michigan Cancer Foundation, Detroit, Michigan 48201, and
Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan 48207

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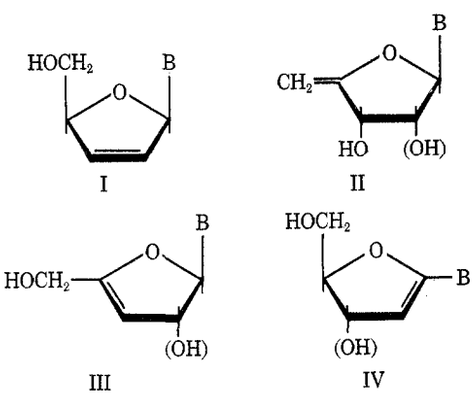
A general approach to 3′,4′-unsaturated nucleosides (**15a–d**) is described which proceeds from a 2′-deoxynucleoside uronic acid ester (**2a–d, 3, 8**) *via* a facile elimination reaction effected on the corresponding 2′-deoxy-3′-*O*-methylsulfonylribonucleoside uronic acid ester (**4a–e**), by the action of either triethylamine or sodium benzoate in DMF. Selective reduction of the carbalkoxy function of the intermediate 3′,4′-unsaturated nucleoside uronic esters (**5a–d, 11**) was accomplished with sodium bis(methoxyethoxy)aluminum hydride. Catalytic (Pd/C) hydrogenation of **5a** in ethanol affords a single isomer, ethyl 3′-deoxythymidine uronate (**17**), which on hydride reduction yields a product identical with 3′-deoxythymidine. Degradation of **4a** to thymine and ethyl furoate was observed on treatment with potassium *tert*-butoxide. The same course of reaction was observed in the reaction of either **2a** or **5a** with dimethylformamide dineopentyl acetal. Attempts to induce the elimination reaction in the case of **4a** with pyridine led instead to the substitution product, ethyl 3′-deoxy-3′-(*N*-pyridinium)thymidine uronate methyl sulfonate (**6**). The elements of pyridinium sulfonate are readily eliminated from **6** on treatment with sodium benzoate in DMF. Unlike pyridine, 2,6-lutidine converts **4a** to **5a**. Reaction of ethyl 2′,3′-di-*O*-methylsulfonyluridine uronate (**4e**) with $(C_2H_5)_3N$ in DMF gave ethyl 5-(uracil-1-yl)furoate (**13**) in high yield. The same product (**13**) was obtained on treatment of ethyl uridine uronate (**2d**) with diphenyl carbonate. The relationship of these elimination reactions to the conversion of uridine uronic acid (**1d**) to 5-(uracil-1-yl)furoic acid (**13**) in refluxing acetic anhydride is discussed. Moreover, the application of the latter conditions to thymidine uronic acid (**1a**) leads to 3′-deoxy-3′,4′-didehydrothymidine uronic acid (**14**), which was characterized as the ethyl ester **5a**. The nmr spectra of **5a–d, 11**, and **15a–d** are discussed.

As a result of studies conducted in this laboratory and others, methods have been developed to introduce both endo- and exocyclic unsaturation into the sugar moiety of a wide spectrum of nucleosides.[2] In point of fact, of the four possible (mono-) olefinic nucleosides (I–IV), only recently has a successful approach to 1-(2-deoxy-D-*threo*-pent-1-enofuranosyl)pyrimidines (IV) been described.[2s] However, only I and II have to date received detailed physicochemical[3] and biochemical[2k,2r,4] study.

In the last several years, synthetic avenues leading to 2′,3′-unsaturated nucleosides (I) have been the subject of several detailed studies.[2f–21] In contrast, the literature concerned with routes to corresponding 3′,4′-unsaturated derivatives (III) is limited to descriptions



B = nucleobase

of base-catalyzed decyclizations of the acetal (ketal) moiety of 2′,3′-*O*-alkylideneribonucleoside 5′-carboxaldehydes[2m,n] and a 2′,3′-*O*-alkylideneribonucleoside uronic acid ester[2o] or of the cyclic ether linkage in 5′-deoxy-5′-fluoro-2,3′-anhydrothymidine.[2q] In addition, analogous pyrimidine and purine (1- and 9-, respectively) 2,3-dideoxy-3,4-didehydro-β-D-erythrofuranosyl (2,3-dihydrofuran) derivatives have been obtained by an interesting decarboxylative elimination reaction on 2′-deoxynucleoside uronic acids.[2p] These reports comprise the principal literature on III.

The present communication describes a general approach to III *via* the facile elimination of methylsulfonic acid from 2′-deoxy-3′-*O*-methylsulfonylribonucleoside uronic acid esters (**4**). At the outset, it was anticipated that activation of $H_{4'}$ by the carbalkoxy group in **4** would facilitate proton abstraction at $C_{4'}$ over the favored $H_{2'}$ protons and thereby alter the di-

(1) (a) Presented in part at the Joint Conference of the Chemical Institute of Canada and American Chemical Society, Toronto, Canada, May 1970, Abstract No. CARBO-5. (b) Preliminary communication: J. Žemlička, R. Gasser, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **92**, 4744 (1970).

(2) (a) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, **88**, 5684 (1966); (b) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *ibid.*, **88**, 1549 (1966); **90**, 4993 (1968); (c) M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, *J. Heterocycl. Chem.*, **4**, 313 (1967); (d) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 4323 (1971); (e) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972); (f) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. DaRooge, and M. Noel, *J. Amer. Chem. Soc.*, **86**, 1896 (1964); (g) J. P. Horwitz, J. Chua, and M. Noel, *Tetrahedron Lett.*, 1343 (1966); (h) J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966); (i) G. Etzold, R. Hintsche, G. Kowollik, and P. Langen, *Tetrahedron Lett.*, 2463 (1971); (j) W. V. Ruyle, T. Y. Shen, and A. A. Patchett, *J. Org. Chem.*, **30**, 4353 (1965); (k) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **12**, 543 (1969); **10**, 1066 (1967); (l) G. Kowollik, K. Gaertner, G. Etzold, and P. Langen, *Carbohyd. Res.*, **12**, 301 (1970); (m) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969; U. S. Patent 3,457,255 (1969); *Chem. Abstr.*, **72**, 3727 (1970); (n) P. Howgate, A. S. Jones, and J. R. Tittensor, *Carbohyd. Res.*, **12**, 403 (1970); (o) K. N. Nagpal and J. P. Horwitz, *J. Org. Chem.*, **36**, 3743 (1971); (p) J. Žemlička, R. Gasser, J. Freisler, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **94**, 3213 (1972); (q) G. Kowollik, K. Gaertner, and P. Langen, *Tetrahedron Lett.*, 1737 (1971); (r) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 115; (s) V. I. Borodulina-Shvets, I. P. Rudakova, and A. M. Yurkevich, *Zh. Obshch. Khim.*, **41**, 2801 (1971).

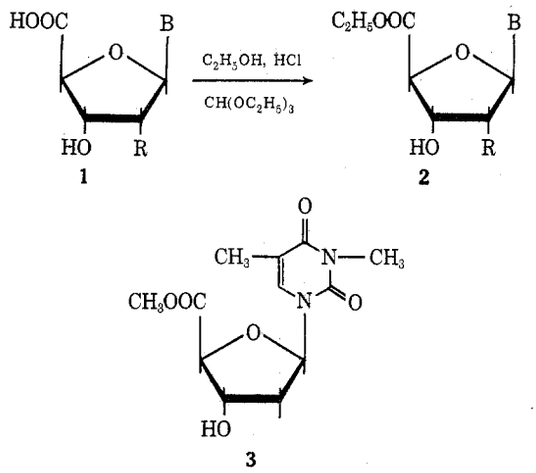
(3) (a) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967); (b) D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.*, **91**, 824 (1969); (c) D. W. Miles, W. H. Innskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *ibid.*, **92**, 3872 (1970); (d) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970); (e) D. W. Miles, M. J. Robins, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **62**, 22 (1969).

(4) (a) A. M. Doering, M. Jansen, and S. S. Cohen, *J. Bacteriol.*, **92**, 565 (1966); (b) M. R. Atkinson, M. P. Deutscher, A. Kornberg, A. F. Russell, and J. G. Moffatt, *Biochemistry*, **8**, 4897 (1969).

rection of β elimination to introduce 3′,4′ rather than 2′,3′ unsaturation.[5]

The requisite 1-(ethyl 2-deoxy-β-D-*erythro*-pentofuranosyluronate)pyrimidines (ethyl 2′-deoxynucleoside uronates[6]) were obtained by a new procedure in which esterification of the acids I[7a-c] was effected in high yield with a mixture of ethanol, triethyl orthoformate, and anhydrous hydrogen chloride (Scheme I).

SCHEME I

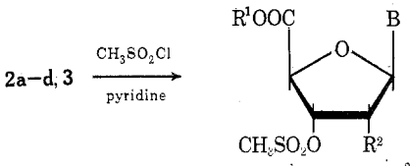


1a, 2a, B = thymine; R = H
1b, 2b, B = uracil; R = H
1c, 2c, B = 5-fluorouracil; R = H
1d, 2d, B = uracil; R = OH

It is worthy of note that the method is apparently of general application and would be valuable where the use of more conventional procedures of esterification would be precluded for a particular consideration. For example, the reaction of thymidine uronic acid (**1a**) with diazomethane leads to N_3 alkylation as well as the desired esterification[2p] to give **3**. On the other hand, diazomethane is the reagent of choice for the preparation of methyl 2′-deoxyadenosine uronate (**9**) (*cf.* Scheme VI) from the acid **8**[2p] because of the acute sensitivity of purine 2′-deoxynucleosides toward acid.

The uronic acid esters (**2a–d** and **3**), on treatment with methylsulfonyl chloride in pyridine at −20°, gave the corresponding 3′-*O*-methylsulfonates (**4a–d**) in excellent yields (Scheme II). Elimination of the methylsulfonyloxy function from **4a–d** was readily effected with triethylamine in dimethylformamide (DMF) at 100° to give the 3′,4′-unsaturated esters[8] **5a–d** in

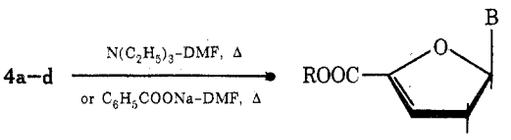
SCHEME II



4a, B = thymine; $R^1 = C_2H_5$; R^2 = H
b, B = uracil; $R^1 = C_2H_5$; R^2 = H
c, B = 5-fluorouracil; $R^1 = C_2H_5$; R^2 = H
d, B = N^3-methylthymine; $R^1 = CH_3$; R^2 = H
e, B = uracil; $R^1 = C_2H_5$; $R^2 = CH_3SO_2O$

good yields and high purity (Scheme III). The same transformation may be accomplished by substitution

SCHEME III



5a, B = thymine; R = C_2H_5
b, B = uracil; R = C_2H_5
c, B = 5-fluorouracil; R = C_2H_5
d, B = N^3-methylthymine; R = CH_3

of sodium benzoate for triethylamine, which gave, for example, **5a** in 88% yield on heating **4a** in DMF at 100°. By contrast, the unsaturated ester **5a** could not be detected after refluxing **4a** in pyridine for 10 hr. Instead, a crystalline product was obtained (46% yield) which, on the basis of spectral data and elemental analysis, was assigned the structure[9] ethyl 3′-deoxy-3′-(*N*-pyridinium)thymidine uronate methyl sulfonate (**6**). The assignment of an erythro configuration to the pyridinium moiety in **6** is not rigorous but is based on the detection of ethyl 2,3′-anhydrothymidine uronate (**7**, 27% yield) along with **6** when the same reaction is carried out at 100° for 16 hr. The salt **6** then presumably arises *via* attack of pyridine at $C_{3'}$ of **7**, leading to the introduction of the nucleophile in the ("down") erythro configuration. Apart from the configurational assignment at $C_{3'}$, it was found that elimination of pyridinium methylsulfonate from **6** readily occurred on heating with sodium benzoate in DMF to give **5a** in 70% yield.

The reaction of **4a** with 2,6-lutidine, unlike pyridine, gave the 3′,4′-unsaturated ester **5a**, though in rather low (20%) yield, instead of a substitution product. Presumably the steric requirements of the methyl groups in 2,6-lutidine simply preclude the possibility of nucleophilic displacement at $C_{3'}$ of the anhydro nucleoside **7**, but these bulk effects apparently do not deter proton abstraction at $C_{4'}$ and consequent elimination (Scheme IV). Degradation of **4a** to thymine (76% yield) occurred at room temperature on treatment with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) for 0.5 hr. A plausible reaction path leading to thy-

(5) A similar approach has recently been used for the preparation of α,β-unsaturated uronates in the carbohydrate series: (a) J. Kiss and K. Noack, *Carbohyd. Res.*, **16**, 245 (1971); (b) J. Kiss and F. Burckhardt, *Helv. Chim. Acta*, **53**, 100 (1970); (c) J. Kiss, *Carbohyd. Res.*, **10**, 328 (1969); (d) J. Kiss, *Tetrahedron Lett.*, 1983 (1970); (e) J. Kiss and F. Burckhardt, Abstracts, Joint Conference of the Chemical Institute of Canada and American Chemical Society, Toronto, Canada, May 1970, CARBO-40.

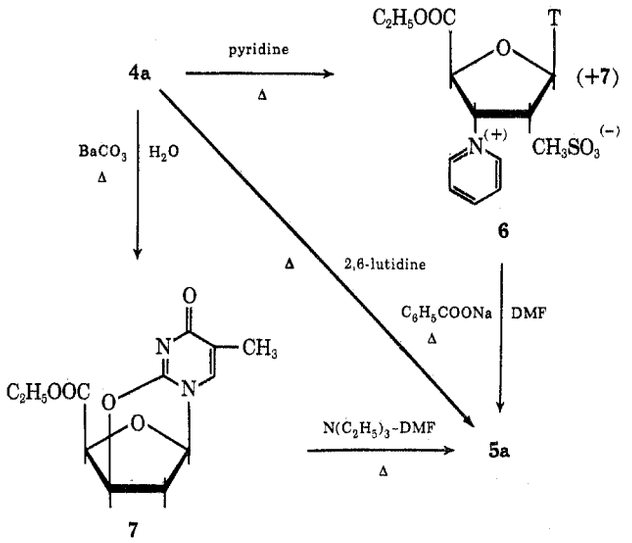
(6) According to a nomenclature devised in ref 7a an alternate name for this group of compounds would be ethyl 2′-deoxynucleoside 5′-carboxylates.

(7) (a) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and A. R. Todd, *J. Chem. Soc.*, 1149 (1963); (b) K. Imai and M. Honjo, *Chem. Pharm. Bull.*, **13**, 7 (1965); (c) K. C. Tsou, N. J. Santora, and E. E. Miller, *J. Med. Chem.*, **12**, 173 (1969).

(8) Application of systematic nomenclature to, *e.g.*, **5b** and **15b** leads to the names (−)-(*R*)-2,3-dihydro-2-(uracil-1-yl)-5-carbethoxyfuran and (−)-(*R*)-2,3-dihydro-2-(uracil-1-yl)-5-hydroxymethylfuran, respectively. In this paper we have adopted a nomenclature based on parent nucleosides. Thus, **5b** would be ethyl 2′,3′-dideoxy-3′,4′-didehydrouridine uronate and **15b** 2′,3′-dideoxy-3′,4′-didehydrouridine. According to the nomenclature suggested earlier[2h] for 2′,3′-unsaturated nucleosides, the name of **15b** could also be 2′,3′-dideoxy-3′-uridinene and that of **5b** ethyl 2′,3′-dideoxy-3′-uridinene uronate.

(9) A compound similar to **6**—*N*-[*trans*-2-hydroxy-*trans*-4-(1-thyminyl)-cyclopentyl]pyridinium hydroxide (inner salt and hydrochloride)—was prepared before: K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, **84**, 3748 (1962).

SCHEME IV



T = thymine

mine would involve consecutive elimination reactions (Scheme V), the first of which would lead to **5a**. Abstraction of a proton from $C_{2'}$ in **5a** is obviously facilitated by transmission of the effect of the carbalkoxy group through the conjugated system and thereby a second elimination can proceed to give thymine and ethyl furoate. No attempt was made to isolate and characterize the latter. The same course of reaction was observed on heating of **5a** with sodium azide in DMF and as well from the action of dimethylformamide dineopentyl acetal on **2a** or **5a** in DMF.

The intervention of 2,3′-anhydro-2′-deoxy nucleosides in the formation of pyrimidine 2′,3′-unsaturated nucleosides from 1-(2-deoxy-3-*O*-methylsulfonyl-β-D-*erythro*-pentosyl)pyrimidines is currently accepted on the basis of earlier studies.[2h] The intermediacy of a corresponding anhydro derivative **7** in the conversion of **4a** to **5a** was presumed but could not be detected. A test of the validity of the hypothesis required the preparation of ethyl 2,3′-anhydrothymidine uronate (**7**) which was obtained (67% yield) by refluxing **4a** in aqueous barium carbonate.[10] The latter, incidentally, is the reagent of choice for the preparation of **7**. After treatment of **7** with Et_3N–DMF for 2 hr at 100°, tlc showed the reaction mixture to consist of a *ca.* 1:1 mixture of unchanged **7** and olefinic ester **5a**. The same transformation in Et_3N–DMSO-d_6 at 100° showed $t_{1/2}$ ~110 min as deduced from the rate of disappearance of the C_6 proton in the nmr spectrum of **4a**. By contrast, the conversion of **4a** to **5a** in the same base–solvent system, but at 50°, showed $t_{1/2}$ ~29 min. The findings therefore preclude the interposition of an anhydro nucleoside in the formation of **5a** from **4a**.

The possibility must be recognized that elimination in **4a–d** with triethylamine occurs *via* a two-step process of the Elcb type, involving proton abstraction at $C_{4'}$ as the initial step followed by release of the methylsulfonyloxy group in the second step. This mechanism, which is characterized by unimolecular elimination of methylsulfonate anion from the conjugate base of **4**, is considered to be dominant in reactions leading to an olefinic double bond that is conjugated with a carbonyl group. The same pathway may well apply to the formation of **5a** from the action of triethylamine on ethyl 2,3′-anhydrothymidine uronate (**7**). Indeed, the rate data probably reflect the poorer leaving group characteristics of the thyminyloxy group *vis a vis* the methylsulfonyloxy function.[11]

The scheme of reactions proceeding to **5a–d** was successfully extended to a synthesis of methyl 2′,3′-dideoxy-3′,4′-didehydroadenosine uronate (**11**). Thus, methyl *N*-dimethylaminomethylene-2′-deoxyadenosine uronate (**10**), obtained by the interaction of **9** and dimethylformamide dimethyl acetal,[12] was first treated with methylsulfonyl chloride in pyridine at −20°. The crude 3′-*O*-methylsulfonate derivative was converted to **11** by sequential refluxing in triethylamine–dioxane and methanol to effect elimination and removal of the dimethylaminomethylene[12] (protecting) group, respectively (Scheme VI).

Attempts to apply this same approach to the synthesis of a 3′-deoxy-3′,4′-didehydroribonucleoside uronic acid ester have to date been unsuccessful. Thus, the reaction of ethyl 2′,3′-di-*O*-methylsulfonyluridine uronate **4e** with either triethylamine or sodium benzoate in DMF or simply refluxing in pyridine gave instead ethyl 5-(uracil-1-yl)furoate (**12**) in high yields. The same product was obtained, albeit in lower yield (38%), on treatment of **2d** with diphenyl carbonate and sodium bicarbonate in DMF (Scheme VII). The structure of **12** follows from its nmr spectrum, which is characterized by two AB systems, one assignable to the uracil (H_5 and H_6) moiety and the other to the furan ($H_{3'}$ and $H_{4'}$) ring.

The course of the reaction is readily explained in terms of two base-catalyzed elimination reactions, the first of which affords the anticipated product ethyl 2′-*O*-methylsulfonyl-3′-deoxy-3′,4′-didehydrouridine uronate. It is likely that the latter is then converted to the corresponding 2,2′-anhydro nucleoside, which undergoes a second elimination reaction to give **12**. The presumed double-elimination sequence leading to **12** is reminiscent of the conversion of uridine uronic acid (**1d**) to furoic acid derivative **13** in refluxing acetic anhydride.[7a] A corresponding sequence of reactions can be envisioned for the latter transformation, which proceeds presumably from an intermediate 2′,3′-di-*O*-acetyluridine uronic acid. Support for the requisite initial elimination is derived from the conversion of thymidine uronic acid to 3′-deoxy-3′,4′-didehydrothymidine uronic acid (**14**) in refluxing acetic anhydride. The identity of **14** was established by esterification with triethyl orthoformate in ethanolic H_2SO_4, which produced a product identical with **5a** in all respects (Scheme VIII).

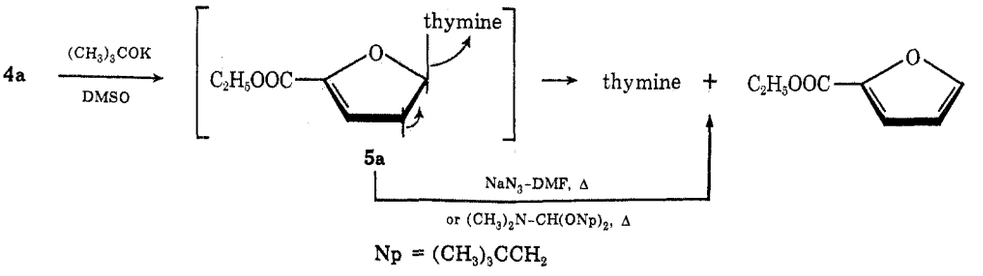
Selective reduction of **5** to the corresponding pyrimidine 2′,3′-dideoxy-3′,4′-didehydroribonucleosides (**15a–c**) was accomplished in yields ranging from 30 to 50% with sodium bis(methoxyethoxy)aluminum hydride in a mixture of benzene and tetrahydrofuran or dioxane (Scheme IX). The same reaction conditions

(10) G. Etzold, R. Hintsche, and P. Langen, German Patent 65,794 (1969); *Chem. Abstr.*, **71**, 91828 (1969).

(11) The fact that no difference between both types of leaving groups was observed in the elimination of 5′-*O*-trityl-3′-*O*-methylsulfonylthymidine and 5′-*O*-trityl-2,3′-anhydrothymidine[2h] may be explained by the "swamping effect" of a strong base (potassium *tert*-butoxide) used.

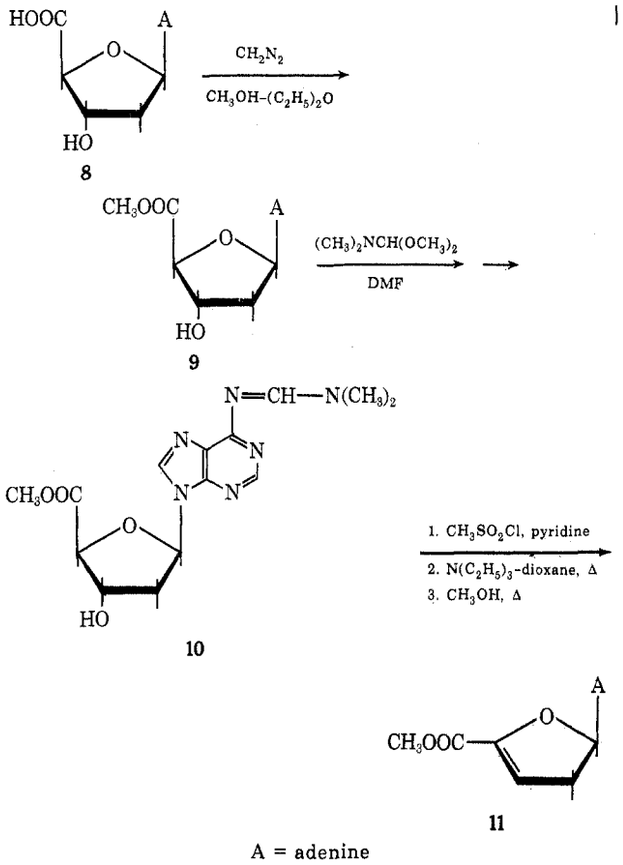
(12) (a) J. Žemlička and A. Holý, *Collect. Czech. Chem. Commun.*, **32**, 3159 (1967); (b) J. Žemlička, *ibid.*, **28**, 1060 (1963).

SCHEME V

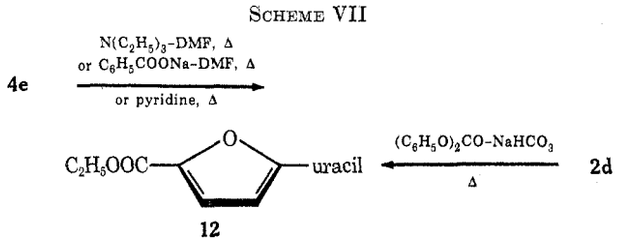


Np = $(CH_3)_3CCH_2$

SCHEME VI



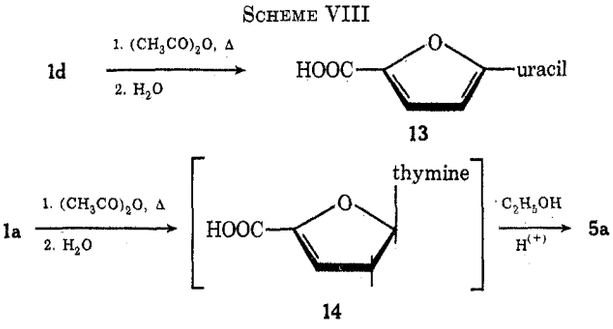
SCHEME VII



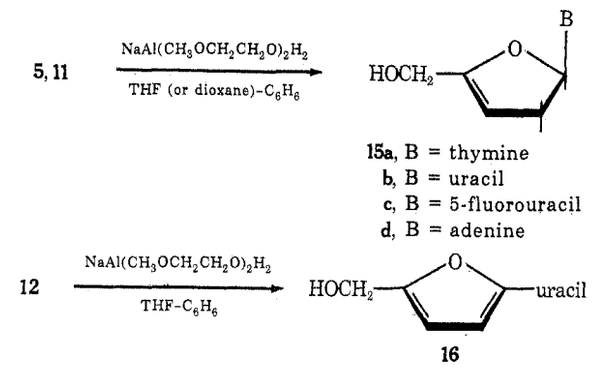
were successfully extended to the reduction of **11** and **12** to 5-(uracil-1-yl)furfuryl alcohol (**16**) and 2′,3′-dideoxy-3′,4′-didehydroadenosine (**15d**), respectively. Excess reagent in all of the reductions was destroyed with ethanol and the removal of sodium ion was accomplished with Dowex 50 (NH_4^+). The form of the resin proved to be critical to the success of the isolation procedure. Thus, the use of Dowex 50 in either the H^+ or $C_5H_5NH^+$ form led to extensive product decomposition.

Recent studies have shown that catalytic (Pd/C) hydrogenation of the olefinic double bond in pyrimidine

SCHEME VIII



SCHEME IX



and purine 3′-deoxy-3′,4′-didehydroribonucleosides leads to an epimeric mixture (β-D- and α-L-) of 3′-deoxy ribonucleosides.[2m,o,13] In contrast, hydrogenation (Pd/C) of **5a** in ethanol surprisingly affords a single product which has tentatively been assigned the structure ethyl 3′-deoxythymidine uronate (**17**). The ORD curve of **17** is similar to that of **2** and **4**. The chemical shift of H_6 corresponds to a nucleoside that shows preference for an anti conformation.[14] The reduction of **17** with sodium bis(methoxyethoxy)-aluminum hydride yields a product identical with 3′-deoxythymidine[15] (**18**) (Scheme X). However, this conversion cannot be offered as rigorous structure proof of **17**, since the possibility of concurrent epimerization at $C_{4'}$ under the conditions of reduction cannot be excluded. There remains, in addition, the question of the high stereoselectivity observed in the catalytic reduction of **17**, which may in some manner be related to the absence of the 2′-OH group coupled, possibly, with the influence of the aglycon.

(13) On the other hand, hydrogenation of a 4′,5′-unsaturated uridine derivative was highly stereoselective if not stereospecific.[2c]

(14) J. Žemlička and J. P. Horwitz, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., April 1971, No. CARB-35. The whole problem will be discussed separately elsewhere.

(15) (a) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955); (b) K. E. Pfitzner and J. G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).

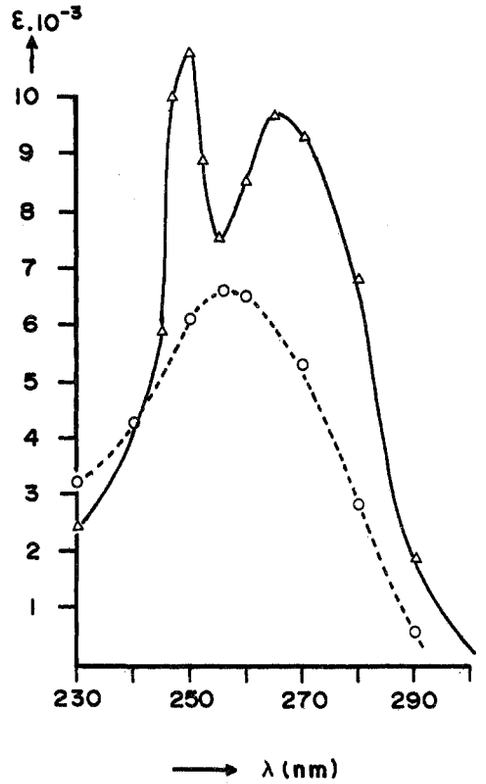


Figure 1.—Comparison of the uv spectra of thymidine, ethyl 1,2-*O*-isopropylidene-3′-deoxy-α-D-glyceropent-3-enofuranuronate[5a] and ethyl 3′-deoxy-3′,4′-didehydrothymidine uronate (**5a**): ——, superposed spectra of thymidine and 1,2-*O*-isopropylidene-3′-deoxy-α-D-glyceropent-3-enofuranuronate (the latter was taken from the literature[5a]); – – – –, spectrum of **5a**.

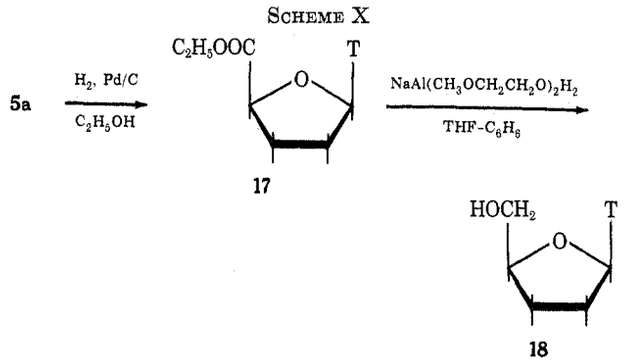
Spectral studies of **5a–d**, **11**, and **15a–d** revealed several interesting properties of this new class of nucleosides in addition to providing the requisite evidence for the location of the olefinic double bond. In accord with the assignments, infrared spectra showed the carbonyl bond of the conjugated ester at lower wavenumbers[16] than that observed for the precursory saturated derivatives. Unexpectedly, the carbonyl (ester) bonds of ethyl 2′,3′-dideoxy-3′,4′-didehydroadenosine uronate (**11**) and isopropyl 3′-deoxy-3′,4′-didehydroadenosine uronate[20] both appear at *ca.* 10 cm^{-1} higher[17] than the band assigned to the carbonyl ester of **5a**.

The introduction of 3′,4′ unsaturation into **5a–d** is accompanied by a hypsochromic shift of 5–12 nm in the ultraviolet absorption λ_{max} which reverts to the value(s) characteristic of the pyrimidine nucleosides, including the 2′,3′-unsaturated derivatives, on selective reduction of the carbethoxy group to **15c**. It was recognized that the shift in λ_{max} observed with **5a–d** might be an artifact of superposition of the chromophoric systems comprising the aglycon and unsaturated sugars. However, this possibility would appear remote in view of the fact that a composite spectrum

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 181.

(17) This phenomenon may be tentatively explained by a Michael addition type of interaction (*vide supra*) between N_3 of adenine residue in a syn-like conformation and $C_{3'}$, which would result in a decreased double-bond character of the olefinic linkage between $C_{3'}$ and $C_{4'}$ and hence an increase in wavenumber of the carbonyl group. A similar interaction between N_3 and carbonyl ester group of a purine ribonucleoside uronate has been invoked to account for the increased wave numbers of the carbonyl groups relative to 2′,3′-*O*-isopropylidene derivatives: H. J. Fritz, R. Machat, and R. R. Schmidt, *Chem. Ber.*, **105**, 642 (1972).

SCHEME X



T = thymine

(Figure 1) derived from ethyl 1,2-*O*-isopropylidene-3-deoxy-α-D-*glycero*-pent-3-enofuranuronate[5a] and thymidine shows two (independent) maxima at 265 and 250 nm. Accordingly, the observed shift in **5a–d** is real and represents an interaction of the two chromophoric systems.

Models indicate the possibility of an effective overlap of π orbitals comprising the 2-carbonyl of the aglycon and the extended conjugation of the sugar where **5a** is in a syn conformation. As a consequence of orbital overlap, an anhydro-nucleoside-like structure, tantamount to the transition state of an intramolecular Michael addition, would be approximated in an excited state and thereby account for the observed hypsochromic shifts in **5a–d**.

No comparable shift was noted with **11**, which is somewhat surprising since, in a syn conformation or an approximation thereof, an interaction between N_3 of adenine and $C_{3'}$ of the unsaturated sugar would be similarly anticipated.[17] However, the uv spectrum of **11** is different from the superimposed spectra of 2′-deoxyadenosine and ethyl 1,2-*O*-isopropylidene-3-deoxy-α-D-*glycero*-pent-3-enofuranuronate.[5a]

The nmr spectra of **5a–d**, **11**, and **15a–d** show, in accord with the infrared data, a single olefinic proton ($H_{3'}$) in the sugar moiety which appears as a triplet and, as expected, is shifted markedly upfield following reduction of the carbethoxy group to a primary alcohol. The anomeric proton in **5a–d** and **15a–c** appears as a multiplet of four having the same spacings observed for $H_{1'}$ in the 2′,3′-dideoxy-3′,4′-didehydroerythrofuranosyl nucleosides[2p] (Table IX).

In contrast to **5a–d** the anomeric proton in the adenine derivative **11**, for reasons which are not evident, appears as a triplet, though the multiplet of four reappears on reduction to **15d**. These differences point to some change in the conformation of the sugar moiety of **11** relative to **5a–d** and **15d**, but the present evidence precludes any firm conclusion. Double-resonance studies with **5b** show that both $H_{1'}$ and $H_{3'}$ are coupled with $H_{2'}$ (and/or $H_{2''}$).

Experimental Section

General Procedures.—See reference 2p. Thin layer chromatography (tlc) was performed as described previously[2p] in solvents S_1 (chloroform–methanol, 9:1) and S_2 (chloroform–methanol, 4:1) or on 2 mm thick 20 × 20 cm fixed layers of Stahl's silica gel F-254 (Merck, Darmstadt, Germany). Tetrahydrofuran (THF) and dioxane were distilled from $LiAlH_4$ and stored over sodium wire. Starting uronic acids **1a–d** and **8** were of the same quality as described previously.[2p] Yields of products,

TABLE I

ETHYL NUCLEOSIDE URONATES

Compd	Yield,[a] %	Mp,[b] °C	Calcd/Found C, %	H, %	N, %	λ_{max}, nm[c] ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)	Optical rotations,[d] deg $[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
2a	86	244–245	50.70	5.67	9.86	264	237	11.2	28.6	62.8	20
		(239–241)	50.78	5.64	9.65	(7.9)	(3.5)				
2b	71	242–244	48.89	5.22	10.37	261	230	25.2	64.6	134.8	24
		(238–240)	48.97	5.16	10.38	(7.9)	(1.6)				
2c	91							47.6			22
		(259–260)[e]									
2d	86	252–254	46.15	4.93	9.79	262	230	7.6	27.2	79.8	21
		(249–250)[f]	46.23	4.94	9.76	(10.3)	(1.8)				

[a] Crude product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] *c* 0.5 (DMF). [e] Literature (different procedure[7c]) gives mp 258–262° (yield 32.6%). [f] Literature (different procedure[7a]) gives mp 237–239°.

TABLE II

NMR CONSTANTS (DMSO-d_6) AND CARBONYL ESTER FREQUENCIES OF ETHYL NUCLEOSIDE URONATES

Compd	Chemical shifts, δ (number of protons, multiplicity) H_6	$H_{1'}$	H_5	$H_{4'} + H_{3'}$	CH_2 of C_2H_5O	$H_{2'}$	CH_3 of C_2H_5O	ν_{CO}, cm^{-1}
2a	7.92	6.36[a]		~4.4[b]	4.21	2.12[c]	1.27[d]	1725
	(1, d)	(1, q)		(2, m)	(2, q)	(2, m)	(3, t)	1742
2b	8.11	6.35[e]	5.73[f]	4.43[b]	4.20	2.15[c]	1.26	1724
	(1, d)	(1, t)	(1, d)	(2, s)	(2, q)	(2, m)	(3, t)	1738
								1750
2c	8.47	6.33[g]		4.43[b]	4.22	2.15[c]	1.25	
	(1, d)	(1, t)		(2, m)	(2, q)	(2, m)	(3, t)	
2d	8.00	5.97[h]	5.73[f]		~4.18[c]		1.24	1752
	(1, d)	(1, d)	(1, d)		(6, m)		(3, t)	

[a] Middle peak poorly resolved. [b] Partially overlapped with CH_2 of C_2H_5O. [c] Poorly resolved. [d] 5-CH_3: δ 1.83 (3, d). [e] Asymmetrical triplet (*cf.* ref 2p, figure 2). [f] Overlapped with OH signal(s). [g] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [h] $J_{1',2'}$ = 6 Hz.

TABLE III

ALKYL 3′-*O*-METHYLSULFONYLNUCLEOSIDE URONATES

Compd	Yield,[a] %	Mp,[b] °C	Calcd/Found C, %	H, %	N, %	S, %	λ_{max}, nm[c] ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)	Optical rotations,[d] deg $[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
4a	87	130–133	43.09	5.01	7.73	8.85	264	235	14.1[g]	31.7	55.6	23
		(100–101)	43.28	4.99	7.73	8.65	(11.4)	(3.0)				
4b	91						259	228				
		(103–104)					(10.5)	(2.4)				
4c	82	149–150	39.34	4.13	7.65		266	232	48			23
			39.36	4.13	7.50		(8.0)	(2.4)				
4d	86	106–108	43.09	5.01	7.73	8.85	264	235	30.2	71.6	142.8	23
		(90–95)	43.24	5.10	7.53	9.10	(7.5)	(2.5)				
4e[f]	80	188–189	35.29	4.10	6.33	14.50	259	230	46.4	109.6	210	22
		(182–184)	35.46	4.09	6.35	14.25	(11.7)	(3.2)				

[a] Crude product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] *c* 0.5 (DMF, for **4d** $CHCl_3$). [e] Transition point. [f] 2′,3′-Bis-*O*-methylsulfonyl derivative. [g] *c* 1.

melting points, and physical constants are summarized in Tables I–IX.

Ethyl Nucleoside Uronates (2a–d).—To a stirred suspension of the uronic acid (**1a–d**, 20 mmol) in 100 ml of ethanol was added 10 ml of triethyl orthoformate and the mixture, cooled externally by an ice bath, was saturated with hydrogen chloride. A crystalline product separated and, after *ca.* 18 hr at room temperature, dry ether (100 ml) was added and the product was collected, washed with ether, and air dried. Yields, analyses, and spectral data are summarized in Tables I and II.

Alkyl 3′-*O*-Methylsulfonylnucleoside Uronates (4a–d).—To a solution of **2a–d** or **3** (1.6 mmol) in 10 ml of pyridine chilled to −20° was added 0.14 ml (1.9 mmol) of methylsulfonyl chloride and the reaction mixture was then maintained at 0° for *ca.* 22 hr. Additional methylsulfonyl chloride (1.9 mmol) was introduced and after another 20-hr interval the reaction was judged to be complete on the basis of tlc (S_2). Pyridine hydrochloride was removed by filtration and the filter cake was washed with 5 ml of pyridine. The filtrate, diluted with 5 ml of ethanol, was evaporated to dryness and the residue was partitioned between chloroform (20 ml) and a saturated solution of sodium bicarbonate (10 ml). The chloroform layer was washed with water and the dried ($MgSO_4$) extract was evaporated to a syrup which solidified either upon evaporation from ethanol or by trituration with ethanol alone or ethanol–ether and cooling to −20°. The solid was suspended in petroleum ether and collected. For **4c** the work-up of the reaction mixture was modified as follows. After evaporation of the pyridine–ethanol mixture, the residue was applied to two plates of loose-layered silica gel GF 254, and chromatographed in solvent S_2. The major uv-absorbing band was eluted with methanol and the eluate was treated first with Norit, then filtered through a Celite bed. Evaporation of the solvent produced an amorphous material which crystallized from methanol (see Tables III and IV).

Ethyl 2′,3′-Di-*O*-methylsulfonyluridine Uronate (4e).—A solution of 0.57 g (2.0 mmol) of ethyl uridine uronate (**2d**) in 10 ml of pyridine cooled to 0° was treated with 0.31 ml (4 mmol) of methylsulfonyl chloride and the reaction mixture was maintained at this temperature overnight. A second portion of methylsulfonyl chloride (0.14 ml, 1.9 mmol) was added and the reaction was allowed to continue (0°) for an additional 24 hr. The work-up of the reaction mixture followed that described above for **4a–d** with the exception that the major portion of **4e**, because of its limited solubility, crystallized from chloroform

TABLE IV

NMR CONSTANTS ($CDCl_3$) AND CARBONYL ESTER FREQUENCIES OF ALKYL 3′-*O*-METHYLSULFONYLNUCLEOSIDE URONATES

	Chemical shifts, δ (number of protons, multiplicity)										
Compd	H_6	$H_{1'}$	H_5	$H_{4'} + H_{3'}$		CH_2 of C_2H_5O	CH_3SO_2	$H_{2'}$	5-CH_3	CH_3 of C_2H_5O	ν_{CO}, cm^{-1}
4a	7.83	6.42		5.48[a]	4.78	4.31	3.17	~2.52[a]	1.95	1.35	1755
	(1, d)	(1, q)		(1, d)	(1, s)	(2, q)	(3, s)	(2, m)	(3, d)	(3, t)	
4b	8.02	6.37	5.75	5.46	4.77	4.27	3.14	~2.55[a]		1.30	1722
	(1, d)	(1, q)	(1, d)	(1, d)	(1, s)	(2, q)	(3, s)	(2, m)		(3, t)	1735
											1742
4c[b]	8.22	6.27[c]		5.58	4.85	4.23	3.32	*d*		1.27	1743
	(1, d)	(1, t)		(1, m)	(1, s)	(2, q)	(3, s)			(3, t)	
4d	7.75	6.42		5.47	4.78	3.81[e]	3.10	~2.54[a]	1.95		1753
	(1, d)	(1, q)		(1, m)	(1, s)	(3, s)	(3, s)	(2, m)	(3, d)		
4e[b,f]	7.75	6.00[g]	5.71	5.49[h]	4.48	4.19	3.34[i]	*Cf.* $H_{4'} + H_{3'}$		1.15	1753
	(1, d)	(1, d)	(1, d)	(2, d)	(1, d)	(2, q)	(3, s)			(3, t)	

[a] Poorly resolved. [b] DMSO-d_6. [c] Secondary splitting owing to a long-range coupling with fluorine (*cf.* ref 2p). [d] Hidden under DMSO-d_5 peak. [e] CH_3O: CH_3N (3, s) at δ 3.28. [f] 2′,3′-Bis-*O*-methylsulfonyl derivative. [g] $J_{1',2'} = 3$ Hz. [h] $H_{3'} + H_{2'}$. [i] Another CH_3SO_2 (3, s) at δ 3.27.

TABLE V

ALKYL 2′,3′-DIDEOXY-3′,4′-DIDEHYDRORIBONUCLEOSIDE URONATES

						λ_{max}, nm[c]	λ_{min}, nm				
	Yield,[a]	Mp,[b]	Calcd/Found			(ε ×	(ε ×	Optical rotations,[d] deg			Temp,
Compd	%	°C	C, %	H, %	N, %	10^{-3})	10^{-3})	$[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	°C
5a	75	229–231	54.13	5.30	10.52	256	230	−115.8	−258	−466.8	24
		(217–219)	54.18	5.38	10.48	(6.5)	(3.2)				
5b	71	158–160	52.38	4.80	11.11	254	226				
		(148–152)	52.68	4.78	11.10	(13.1)	(5.2)	−101.2	−227.4	−414	24
5c	54	200–201	48.89	4.10	10.37	254	228	−152.8[e]			24
			48.68	3.92	10.22						
5d	76	138–139	54.13	5.30	10.52	254	230	−105	−237.8	−433.8	22
		(135–137)	53.88	5.28	10.31	(6.8)	(3.9)				

[a] Crude tlc homogeneous product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] $CHCl_3$ (*c* 0.5). [e] DMF (*c* 0.5).

TABLE VI

NMR CONSTANTS ($CDCl_3$) AND CARBONYL ESTER FREQUENCIES OF ALKYL 2′,3′-DIDEOXY-3′,4′-DIDEHYDRORIBONUCLEOSIDE URONATES

	Chemical shifts, δ (number of protons, multiplicity)							
Compd	H_6	$H_{1'}$	$H_{3'}$	CH_2 of C_2H_5O	$H_{2'}$	5-CH_3	CH_3 of C_2H_5O	ν_{CO}, cm^{-1}
5a	6.94[a]	6.82[b]	6.03	4.28	3.20[c]	2.34	1.32	1724
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)	(3, s)	(3, t)	
5b	7.25	6.82	6.07	4.29	3.08[c]	5.76[d]	1.32	1727
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)	(1, d)	(3, t)	
5c[e]	7.92	6.74[f]	6.15[c]	4.27	3.24[c]		1.28	1724
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)		(3, t)	
5d	6.98[a]	6.85[b]	6.03	3.30[g]	3.07[c]	1.91		1715
	(1, d)	(1, q)	(1, t)	(3, s)	(2, m)	(3, d)		1735

[a] Partially overlapped with $H_{1'}$. Both signals are perfectly separated in DMSO-d_6. [b] Partially overlapped with H_6. [c] Poorly resolved. [d] H_5. [e] DMSO-d_6. [f] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [g] CH_3O: CH_3N at δ 3.80 (3, s).

TABLE VII

2′,3′-DIDEOXY-3′,4′-DIDEHYDRO RIBONUCLEOSIDES

						λ_{max}, nm[a]	λ_{min}, nm				
	Yield,	Mp,	Calcd/Found			(ε ×	(ε ×	Optical rotation,[b] deg			Temp,
Compd	%	°C	C, %	H, %	N, %	10^{-3})	10^{-3})	$[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	°C
15a	53	105–110[c]	52.51[d]	5.51	12.25	267	235	−134.6	−297.4	−522.2	23
			52.32	5.29	11.99	(8.7)	(2.4)				
15b	50	125–128[e]	50.35[d]	4.93	13.05	261	231	−150.4	−326.8	−583	25
			50.18	4.82	12.77	(7.6)	(1.8)				
15c	31[f]	139–140[g]	46.44[d]	4.11	12.04	268	238				
			46.60	4.05	11.84	(7.4)	(3.1)				
15d	46	182–183	50.72[h]	4.84	29.57	260	230	−221	−489.4	−861	25
			50.38	4.81	29.83	(9.9)	(1.7)				

[a] 95% ethanol. [b] *c* 0.5 (dioxane). [c] Transition point, melting at 160–165°, decomposition above 230°. [d] Calculated for compound containing $^1/_4H_2O$. [e] Resolidifies and then decomposes above 250°. [f] Product from tlc was crystallized from methanol, mp 135–136°. [g] Product from tlc was filtered off after addition of ether and dried for analysis at 100° over P_2O_5. [h] Calculated for compound containing $^1/_6H_2O$.

TABLE VIII

NMR CONSTANTS (CD_3COCD_3) OF 2′,3′-DIDEOXY-3′,4′-DIDEHYDRO RIBONUCLEOSIDES

Compd	H_6	$H_{1'}$	$H_{3'}$	$H_{5'}$	$H_{2'}$	5-CH_3
15a	7.31	6.65	5.02	4.12	3.07[a]	1.81
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	(3, d)
15b	7.53	6.67	5.07	4.20	2.94[a]	5.70[b]
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	(1, d)
15c	7.60	6.63[c]	5.11[a]	4.14	3.12[a]	
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	
15d[d]	8.25[e]	6.82	5.23[a]	4.07	~3.17[a]	
	(2, s)	(1, q)	(1, t)	(2, s)	(2, m)	

[a] Poorly resolved. [b] H_5. [c] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [d] DMSO-d_6. [e] H_8 + H_2 (two poorly resolved singlets).

TABLE IX

NMR SPLITTING PATTERNS OF THE $H_{1'}$ PROTON OF SOME 2′,3′-DIDEOXY-3′,4′-DIDEHYDRO RIBONUCLEOSIDES

Compd	Multiplicity	Signal width, Hz	$J_{1',2'}$ and $J_{1',2''}$, Hz	Solvent
5a	q	15.5	9.5, 6.0	DMSO-d_6
5a	q	13.0	10.0, 6.0	$CDCl_3$
5a	q	15.5	10.0, 6.0	Pyridine-d_5–D_2O
5b	q	14.5	9.5, 5.0	$CDCl_3$
5c	q[a]	15.5	9.0, 6.0	DMSO-d_6
15a	q	14.0[b]	10.0,[b] 4.5[b]	Acetone-d_6
15b	q	13.0	9.0, 4.0	Acetone-d_6
15c	q[a]	13.0	9.0, 4.0	D_2O
15d	q	12.5	8.0, 4.5	DMSO-d_6–D_2O
11	t	14.5	7.5, 7.5	DMSO-d_6

[a] Secondary splitting caused by a long-range coupling with fluorine (*cf.* ref 2p). [b] The same spacings were also observed in CD_3CN.

during the work-up. Yield, analysis, and spectral data appear in Tables III and IV.

Alkyl 2′,3′-Dideoxy-3′,4′-didehydronucleoside Uronates (5a–d).—A solution of **4a–d** (0.25 mmol) in DMF (2 ml) was heated with triethylamine (0.1 ml, 0.75 mmol) at 100° (bath temperature) for 2 hr and the reaction mixture was evaporated to dryness at 0.1 mm. The residue was either washed with ethanol (2 ml) to give a product (**5a**) homogeneous on tlc or dissolved in chloroform (in the case of **5b** and **5e**) and the solution was worked up as described for the corresponding methylsulfonyl derivatives. Compound **5c** was obtained by direct chromatography of the residue after evaporation of the DMF as described for **4c** (treatment with Norit and Celite was omitted). Analytical samples were recrystallized from ethanol (**5c** from methanol). (See Tables V and VI for corresponding physical constants.)

In a large-scale preparation of **5a** (5.25 g, 14.5 mmol of **4a**) a small amount of an unidentified by-product was isolated. According to tlc (S_1) the latter is neither identical with the ester **2a** nor the anhydro derivative **7**. Pure **5a** was obtained following silica gel (70–325 mesh, 150 g) column (51 × 2.5 cm) chromatography of the crude material. After elution with chloroform (1 l.), **5a** (2.1 g, 54%) was eluted with 2% methanol in chloroform (2 l.). Elution with 5% methanol in chloroform (3 l.) gave the by-product (0.38 g). Crystallization from ethanol gave a solid (0.3 g): mp 170–175°; homogeneous on tlc (S_1); $[\alpha]^{24}D$ −94.8°, $[\alpha]^{24}_{436}$ −221°, $[\alpha]^{24}_{365}$ −416.4° (*c* 0.5, DMF); uv max (95% ethanol) 261, 230 nm.

2′,3′-Dideoxy-3′,4′-didehydro Nucleosides (15a–d).—The unsaturated ester (**5a–c**, **11**) (1 mmol) was dissolved in THF (**11** in dioxane) (40 ml) and to the solution was added dropwise with stirring and with an external ice-bath cooling a 70% stock solution of sodium bis(methoxyethoxy)aluminum hydride in benzene diluted to give 1 mmol of reagent in 1 ml. The progress of reduction was checked by tlc (S_1). Additional 1-mmol portions of the reagent were added at 1- and 2-hr intervals while the reaction mixture was stirred at room temperature. After 3 hr the reduction appeared to be *ca.* 90% complete. Ethanol (20 ml) was added followed by dry Dowex 50 WX (NH_4^+) 100–200 mesh (7 g, 36 mequiv). The mixture was stirred at room temperature for 30–60 min, and the resin was filtered off and washed with ethanol or with THF and methanol. The filtrate was evaporated to dryness and the residual syrup was chromatographed on two plates of silica gel in solvent S_1. The major uv-absorbing bands were eluted with solvent S_2 and evaporated to give a syrup (**15a**) which crystallized when stored at −20°. Crystallization of **15b** was effected by adding ethyl acetate–ether and cooling to −20°. The band of **15c** derived from preparative tlc afforded crystalline material directly. In the case of **15d** the crude product contained adenine (*ca.* 10%) in addition to 5–10% of starting ester (**11**). The solution in DMF was applied to preparative layers and chromatographed in solvent S_1. The band of **15d** was eluted with $CHCl_3$–methanol (1:1) to give, after evaporation, a crystalline product. Yields and constants appear in Tables VII and VIII.

Methyl 2′-Deoxyadenosine Uronate (9).—A stirred suspension of 2′-deoxyadenosine uronic acid (**8**) (1.105 g, 4.17 mmol) in methanol (70 ml) was treated portionwise with a solution of diazomethane in ether until the yellow color persisted and tlc (S_2) showed a single spot (**9**). The solution was evaporated and the residue was chromatographed on five plates of loose layers of silica gel in the solvent S_2. The major band (**9**) was eluted with a mixture of chloroform–methanol (1:1), the eluate was evaporated, and the residue was crystallized from methanol to give **9** (0.6 g, 51.5%): mp 151–152°; $[\alpha]^{25}D$ −19°, $[\alpha]^{25}_{436}$ −48.6°, $[\alpha]^{25}_{365}$ −106.6° (*c* 0.5, DMF); uv max (95% ethanol) 259 nm (ε 9200), min 227 (1400); nmr (DMSO-d_6) δ 8.36 (s, 1, H_8), 8.16 (s, 1, H_2), 7.17 (broad s, 2, NH_2), 6.52 (t, 1, $H_{1'}$), 3.67 (s, 3, CH_3O); ir (KBr) ν_{CO} 1770 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5O_4 \cdot {}^3/_4H_2O$: C, 45.18; H, 5.00; N, 23.95. Found: C, 45.07; H, 5.12; N, 23.63.

Reaction of 4a with Potassium *tert*-Butoxide.—A solution of **4a** (90 mg, 0.25 mmol) and potassium *tert*-butoxide (84 mg, 0.75 mmol) in DMSO (2 ml) was stirred for 30 min at room temperature. An excess of Dry Ice was then added and the mixture was poured immediately into water (25 ml) containing carbon dioxide. The neutral (phenolphthalein) solution was extracted with chloroform (3 × 30 ml) and the dried ($MgSO_4$) extract was evaporated. The residual liquid (presumably ethyl furan-2-carboxylate) was homogeneous on tlc (S_2) and was volatile at 65° (bath temperature) and 0.1 mm. The aqueous layer was evaporated to a volume of *ca.* 10 ml, and the residue was stirred for 30 min with a mixture of excess Dowex 50 WX-4 (pyridinium form, 100–200 mesh) and Dowex 1 X2 (OH form, 200–400 mesh). The resin was filtered off and washed with 50% pyridine (50 ml). The filtrate was evaporated and the residue was coevaporated with a mixture of ethanol and ether to give thymine (24 mg, 76%) identical [tlc (S_2), melting point, and ir spectrum] with an authentic sample.

Reaction of 5a with Sodium Azide.—A mixture of **5a** (0.13 g, 0.5 mmol) and sodium azide (65 mg, 1 mmol) in DMF (5 ml) was heated for 5.5 hr at 120° (bath temperature). After cooling the reaction mixture was filtered, the insoluble portion was washed with DMF, and the filtrate was evaporated at 0.1 mm and 45° (bath temperature). The residue was washed with ethanol (3 ml) to give thymine (50 mg, 79%) identical [tlc (S_2) and melting point] with an authentic sample.

Methyl 2′,3′-Dideoxy-3′,4′-didehydroadenosine Uronate (11).—A solution of the ester **9** (0.1 g, 0.36 mmol) and dimethylformamide dimethyl acetal (0.2 ml, *ca.* 2 mmol) in 10 ml of DMF was held overnight at room temperature. Evaporation of the reaction mixture at 0.1 mm gave a solid (**10**), mp 220–222°, uv max (95% ethanol) 310 nm, min 215.

A solution of **10** (1 g, 2.99 mmol) in pyridine (100 ml) was stirred with methylsulfonyl chloride (0.77 ml, 10 mmol) for 3 hr at −20° and then kept for 16 hr at the same temperature. Methanol (25 ml) was added and the solution was evaporated at 30° (0.1 mm). The residue was dissolved in DMF (50 ml), and triethylamine (2.3 ml, 18 mmol) was added. The mixture was held for 1 hr at 0°; the triethylamine hydrochloride was filtered off and washed with a small amount of DMF. The filtrate was evaporated to near dryness, the residue was dissolved in chloroform (50 ml), and the solution was extracted with water (60 ml). The aqueous layer was extracted with chloroform (20 ml), and the combined dried ($MgSO_4$) organic layers were evaporated to a solid residue (0.9 g), which according to uv (95% ethanol), showed *ca.* 50% removal of the *N*-dimethylaminomethylene

group. This material was dissolved in dioxane (50 ml), triethylamine (0.2 ml, 1.5 mmol) was added, and the solution was heated for 2 hr at 100° (bath temperature). The reaction mixture was evaporated and the residue was refluxed for 10 hr in methanol (100 ml). Uv showed that the 6-amino group had been almost completely (94%) deblocked. Evaporation of the solvent and crystallization of the crude product from ethanol gave a solid (0.32 g, 41%), mp 228–230° dec, homogeneous on tlc (S_1). For analysis a portion of the product was chromatographed on loose layer silica gel in S_1 and then recrystallized from ethanol: mp 233° dec; $[\alpha]^{25}D$ −212.6°, $[\alpha]^{25}_{436}$ −472.8°, $[\alpha]^{25}_{365}$ −851.8° (*c* 0.5, dioxane); uv max (95% ethanol) 257 nm (ε 14,900), min 225 (4700); nmr (DMSO-d_6) δ 8.32 (s, 1, H_8), 8.21 (s, 1, H_2), 7.33 (broader s, 2, NH_2), 6.94 (t, 1, $H_{1'}$, $J_{1',2'} = J_{1',2''} = 7.5$ Hz, signal width 14.5 Hz), 6.31 (t, 1, H_3'), 3.74 (s, 3, CH_3O), 3.47 (m, 2, $H_{2'}$).

Anal. Calcd for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.45; H, 4.30; N, 26.72.

Reaction of Ethyl Nucleoside Uronates (2a and 5a) with Dimethylformamide Dineopentyl Acetal.—Compound **5a** (27 mg, 0.1 mmol) was heated for 7 hr at 80–90° (bath temperature) in DMF (1 ml). Tlc (S_1) showed a quantitative decomposition of **5a** to thymine and ethyl furoate. A similar result was obtained with **2a** heated with 2 equiv of dimethylformamide dineopentyl acetal for 13 hr at 90–100° (bath temperature) in DMF.

Ethyl 3′-Deoxy-3′,4′-didehydrothymidine Uronate (5a). A. From Ethyl 2,3′-Anhydrothymidine Uronate (7).—A solution of **7** (2.7 mg, 10 μmol) in 0.1 ml of DMF containing 1 drop of triethylamine was heated for 2 hr at 100° (bath temperature). The mixture was then evaporated at 0.1 mm and room temperature and the residue was examined by tlc (S_1) which showed the presence of olefin **5a** and anhydro nucleoside **7** in an approximate ratio of 1:1.

B. From 4a.—The methylsulfonyl derivative (**4a**, 0.185 g, 0.51 mmol) was added to a solution of sodium benzoate (0.203 g, 1.41 mmol) in DMF, (15 ml) preheated to 100° (bath temperature), and the heating was continued for 1 hr. After cooling the solid was filtered off and washed with DMF (10 ml) and the filtrate was evaporated at 50° (bath temperature) and 0.2 mm. The resultant solid was dissolved in methanol, and the solution was applied to one layer of silica gel and developed in solvent S_1. The uv-absorbing band (R_f *ca.* 0.4) was eluted with the solvent, and the eluate was evaporated to give 0.119 g (88%) of **5a**, mp 225–226°, identical (melting point, uv spectrum) with a sample prepared by a different route (*cf.* Table V).

C. By the Action of 2,6-Lutidine on 4a.—Compound **4a** (0.1 g, 0.28 mmol) was heated in 2,6-lutidine (10 ml) at 100° (bath temperature) for 7 hr and then refluxed for 3.5 hr. After cooling the solution was decanted from a syrupy deposit and the clear solution was evaporated at 0.1 mm and 50° (bath temperature). The residue was washed with ethanol (2 ml) to give 20 mg (27%) of olefin **5a**, mp 215–219°, identical (mixture melting point, ir spectrum) with a sample obtained by an alternate method (*cf.* Table V).

D. From the Pyridinium Derivative (6).—A solution of **6** (0.11 g, 0.25 mmol) and sodium benzoate (72 mg, 0.5 mmol) in DMF (5 ml) was heated for 30 min at 90° (bath temperature). After cooling, the insoluble portion was filtered off and washed with DMF, and the filtrate was evaporated at 0.1 mm and 45° (bath temperature). The solid residue was treated with a saturated solution of sodium bicarbonate (10 ml) and the mixture was extracted with chloroform (2 × 20 ml). The organic layer was dried ($MgSO_4$) and evaporated to give **5a** (47 mg, 71%), mp 231–233°, identical [melting point, tlc (S_1), ir spectrum] with a sample prepared by another route (*cf.* Table V).

E. From 1a and Acetic Anhydride Followed by Esterification.—Compound **1a** (0.258 g, 1 mmol) in acetic anhydride (10 ml) was stirred under reflux for 30 min. After cooling, excess ice was added and the stirring was continued until the mixture was homogeneous. The solution was then evaporated and the residue was coevaporated several times with water to give a solid which was collected after addition of ether (0.165 g), melting point ill defined (decomposition above 170°). This material was dissolved in DMF (5 ml), the solution was filtered through a Celite bed, and ether (200 ml) was added to the filtrate. After filtration and cooling to −20°, a precipitate (56 mg) was obtained (mp 150–160°) containing, according to the nmr, *ca.* 42% of **1a** (or its 3′ acetate) and 58% of **14**: nmr (DMSO-d_6) δ 7.94 (H_6 of **1a**), 7.32 (H_6 of **14**), 6.70 ($H_{1'}$), 6.03 ($H_{3'}$ of **14**), 2.82 [$(CH_3)_2N$ of DMF], 1.8 (CH_3 of thymine).

In another experiment, **1a** (0.5 g, 1.95 mmol) was refluxed in acetic anhydride (20 ml) for 2 hr and the reaction mixture was worked up as described above. The residue was dried by azeotropic distillation with a mixture of ethanol (30 ml) and benzene (30 ml). After removal of *ca.* one-half of the solvent mixture, ethyl orthoformate (0.63 ml, 3.75 mmol) was added at room temperature followed by ethanol (20 ml) and 1 drop of concentrated H_2SO_4. The reaction mixture was maintained for 3 days at ambient temperature. Excess sodium bicarbonate was then added and the solids were collected. The filter cake was washed with chloroform, then ethanol, and the washings were evaporated. The residue was chromatographed on one loose layer of silica gel S_1, the zone of ester (**5a**) was eluted with S_2, and the eluate was evaporated. The residue was washed with ethanol–ether to give 80 mg (15%) of **5a**, mp 227–230°, identical on the basis of ir with an authentic sample.

Kinetics of Elimination on 4a or 7.—A solution of 0.0553 mmol of **4** or **7** in DMSO-d_6 (0.25 ml) was preheated to 50° in the nmr probe. Triethylamine (0.02 ml, 0.2 mmol) was added and the decrease of the H_6 signal of the starting material was followed as a function of time for a period of 1 hr. Half-time for the conversion of **4a** to **5a** was 29 min. With anhydro derivative **7** no reaction was observed after 2 hr. Elevation of the temperature to 100° initiated elimination but the kinetic data were not readily reproducible (*ca.* $t_{1/2}$ 110 min.).

Ethyl 2,3′-Anhydrothymidine Uronate (7).—A solution of compound **4a** (0.1 g, 0.277 mmol) was heated in pyridine (5 ml) for 16 hr at 100° (bath temperature). The reaction mixture was evaporated, and the residue was washed with ethanol to give a solid which was collected. The filtrate was applied to one plate of silica gel (loose layer) which was developed in the solvent S_2. Three major uv-absorbing bands were detected (in the order of increasing mobility): compound **6** (at the origin), product **7**, and **4a** near the front. Compound **7** was eluted with a mixture of chloroform–methanol (3:1), the eluate was evaporated, and **7** (20 mg, 27%), which was homogeneous on tlc (S_2), mp 191–193°, crystallized from ethanol and was dried at 100° (10^{-3} mm): mp 227–229° (sinters at *ca.* 210°); $[\alpha]^{23}D$ −64.2° (*c* 0.5, H_2O); uv max (95% ethanol) 244 nm (ε 6200), min 219 (3700); nmr (DMSO-d_6) δ 7.65 (d, 1, H_6), 6.02 (poorly resolved d, 1, $H_{1'}$), 5.48 (poorly resolved d, 1, $H_{4'}$), 4.98 (d, 1, $H_{3'}$), 4.13 (q, 2, CH_2 of C_2H_5O), *ca.* 3.3 ($H_{2'}$ overlapped with DMSO-d_5), 1.78 (d, 3, CH_3 of thymine), 1.14 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1755 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.16; H, 5.32; N, 10.48.

A mixture of compound **4a** (63 mg, 0.176 mmol) and barium carbonate (17 mg, 0.088 mmol) was heated at 90° in water (5 ml) with stirring for 30 min, whereupon the solution became clear. After 15 min tlc (S_2) showed the absence of **4a** and the presence of **7**. After cooling, the solution was evaporated at 1.5 mm and room temperature. The solid residue was dissolved in methanol and applied to one layer of silica gel which was developed in the solvent S_2. The major uv-absorbing band was eluted with methanol, the eluate was evaporated, and the solid was crystallized from ethanol to give **7** (33 mg, 69%), mp 218–220°, identical in all respects with the sample of **7** prepared by the alternate route described above.

1-(5-Carbethoxyfur-2-yl)uracil (12).—A sample of **4e** (0.12 g, 0.25 mmol) was heated with triethylamine (0.1 ml, 0.75 mmol) in DMF (2 ml) for 30 min at 100° (bath temperature). The reaction mixture was then evaporated to dryness at 40° (0.1 mm) and the solid residue was washed with ethanol (2 ml) to give **12** (60 mg, 96%): mp 199° (crystallization from ethanol raised the melting point to 201–202°); uv max (95% ethanol) 264, 298 nm (ε 10,500, 11,000), min 232, 278 (4000, 9100); nmr (DMSO-d_6, poorly resolved) δ 7.8 (d, 1, H_6), 5.8 (d, 1, H_5), 7.36 (d, 1, $H_{3'}$), 5.38 (d, 1, $H_{4'}$, poorly resolved), 4.29 (q, 2, CH_2), 1.3 (t, 3, CH_3).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.89; H, 4.08; N, 11.07.

Compound **4a** (0.12 g, 0.25 mmol) was heated in pyridine (5 ml) at 100° (bath temperature) for 13 hr. The reaction mixture was evaporated as described above to give a solid (**12**, 47 mg, 70%) which after washing with a small amount of ethanol, showed mp 198–200°, and was identical according to tlc (S_1), ir, and uv spectra with a sample of **12** prepared by the above route.

Compound **2d** (0.57 g, 2 mmol), diphenyl carbonate (0.64 g, 3 mmol), and sodium hydrogen carbonate (10 mg, 0.12 mmol) were heated with stirring in DMF (2 ml) at 150° for 30 min. After cooling, the brown solution was poured into ether (40 ml), and

the tan solid was filtered off, thoroughly washed with ether, and air dried to give 0.19 g (38%) of **12**, mp 201–202°, identical according to ir and uv with a sample prepared by another method.

A mixture of **4e** (0.12 g, 0.27 mmol) and sodium benzoate (0.145 g, 1.08 mmol) was heated in DMF (5 ml) at 80–90° (bath temperature) for 30 min with stirring. After cooling, the insoluble portion was collected and washed with DMF, and the filtrate was evaporated at 45° (0.1 mm). The residue was partitioned between a saturated solution of sodium hydrogen carbonate (10 ml) and chloroform (2 × 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a white solid (**12**, 60 mg, 89%), mp 194–195°, homogeneous on tlc (S_1). Recrystallization from ethanol raised the melting point to 201–203°; uv and ir spectra were identical with an authentic sample of **12**.

1-(5-Carboxyfur-2-yl)uracil (13).[7a]—A sample of **1d** (0.258 g, 1 mmol) was refluxed with stirring in acetic anhydride (10 ml) for 45 min. The clear solution was allowed to cool and excess ice was added with stirring until the reaction mixture was homogeneous. After the mixture was held overnight at 0°, the solid that was deposited was filtered and washed with a small amount of water to give 0.125 g (57%) of **13**, mp 305° dec; 0.1 g was sublimed at 250–260° (0.1 mm) without decomposition[7a] to give 85 mg of **13**, mp 304–305°; ir (KBr) of the sublimate and starting material were identical; nmr (DMSO-d_6) showed δ 7.83 (d, 1, H_6), 5.87 (d, 1, H_5, $J_{5,6}$ = 8 Hz), 7.34 (d, 1, $H_{3'}$), 6.73 (d, 1, $H_{4'}$, $J_{3',4'}$ = 3 Hz).

Ethyl 3′-Deoxy-3′-(*N*-pyridinium)thymidine Uronate Methyl Sulfonate (6).—A solution of **4a** (0.5 g, 1.38 mmol) in pyridine (25 ml) was refluxed for 10 hr. The crystalline precipitate was then collected and washed with pyridine to give 0.28 g (46%) of **6**: mp 279–280° dec (crystallization from methanol raised the melting point to 283–286° dec); $[\alpha]^{23}D$ −49.6°, $[\alpha]^{23}_{436}$ −104.8°, $[\alpha]^{23}_{365}$ −175.8° (*c* 0.5, H_2O); uv max[18] (water) 260 nm (ϵ 16,100), 235 (4100); nmr[19] (DMSO-d_6, poorly resolved) δ 11.41 (s, 1, δ-pyridine H), 9.45 (d, 2, β-pyridine H), 8.34 (d, 2, α-pyridine H), 7.73 (d, 1, H_6), 6.51 (m, 1, $H_{1'}$), 4.15 (q, 2, CH_2 of C_2H_5O), 3.34 (s, 3, CH_3SO_3), 1.83 (d, 3, CH_3 of thymine), 1.15 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1773 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}N_3O_8S$: C, 48.97; H, 5.25; N, 9.52; S, 7.26. Found: C, 48.70; H, 5.13; N, 9.81; S, 7.08.

Ethyl 3′-Deoxythymidine Uronate (17).—A solution of **5a** (0.2 g, 0.88 mmol) in dioxane–ethanol (2:3, 50 ml) was hydrogenated in a Brown apparatus[20] over 10% palladium on charcoal (0.2 g) for 3 hr at room temperature. The catalyst was filtered off and washed with ethanol, and the filtrate was evaporated. The residue on treatment with ether and petroleum ether gave 0.2 g of **17** (quantitative yield), mp 151–154°, homogeneous on tlc (S_1). A sample for analysis was crystallized from ethanol: mp 166–169°; $[\alpha]^{23}D$ +29.8°, $[\alpha]^{23}_{436}$ +79°, $[\alpha]^{23}_{365}$ +175.2° (*c* 0.5, $CHCl_3$); uv max (95% ethanol) 268 nm (ϵ 8900), 237 (1900); nmr ($CDCl_3$) δ 8.09 (d, 1, H_6), 6.18 (t, poorly resolved, 1, $H_{1'}$), 4.56 (m, 1, $H_{4'}$, poorly resolved), 4.24 (q, 2, CH_2 of C_2H_5O), 2.23 (m, 4, $H_{3'}$ + $H_{2'}$, poorly resolved), 1.94 (d, 3, CH_3 of thymine), 1.29 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1745 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.68; H, 6.07; N, 10.36.

1-(5-Hydroxymethylfur-2-yl)uracil (16).—The reduction of **12** (0.125 g, 0.5 mmol) followed the procedure described for 3′,4′-unsaturated nucleosides **15a–d**. Over a period of 8 hr, a total of 4 mmol of sodium bis(methoxyethoxy)aluminum hydride was added. Dry Dowex 50 WX (NH_4^+) 100–200 mesh (10 g) was introduced and the mixture was stirred at room temperature for 1 hr. The insoluble portion was filtered off and washed with tetrahydrofuran. The filtrate was evaporated and the residue was crystallized from tetrahydrofuran–methanol to give 38 mg of product (36% yield): mp 166–167°; uv max (95% ethanol) 251 nm (ϵ 8600), shoulder 298 (4400), min 240 (7900); nmr (CD_3CN) δ 7.48 (d, 1, H_6), 6.37 (s, 2, $H_{3'}$ + $H_{4'}$), 5.70 (d, 1, H_5), 4.47 (s, 2, CH_2); nmr (D_2O, external TMS) δ 8.13 (d, 1, H_6), 6.95 (s, 2, $H_{3'}$ + $H_{4'}$), 6.38 (d, 1, H_5), CH_2 overlapped with HDO signal.

Anal. Calcd for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.45. Found: C, 51.96; H, 3.95; N, 13.41.

3′-Deoxythymidine (18).—The reduction of **17** (0.402 g, 1.5 mmol) in THF (60 ml) was carried out in essentially the same manner as that described for the unsaturated nucleosides **15a–d**. The total amount of sodium bis(methoxyethoxy)aluminum hydride added in three portions during 3 hr at room temperature amounted to 4 mmol. The reaction mixture was worked up in the same way as that described for the preparation of **16** with the sole exception that in addition to THF, the resin was also washed with ethanol. Crystalline material was obtained after evaporation of the filtrate, which was collected after addition of ether to give 0.24 g (72%) of **18**, mp 132–133°, homogeneous on tlc (S_1). Recrystallization of the solid from ethyl acetate raised the melting point to 142–143° (lit. mp 145°,[15a] 147–149°,[15b] and 149–150°[2h]). The product **18** was identical with an authentic specimen according to uv, ir, and nmr spectra, tlc, and mixture melting point.

Registry No.—**2a**, 37781-47-8; **2b**, 29617-88-7; **2c**, 20105-71-9; **2d**, 37781-50-3; **4a**, 37781-51-4; **4b**, 37781-52-5; **4c**, 29673-92-5; **4d**, 29673-93-6; **4e**, 37781-54-7; **5a**, 29617-89-8; **5b**, 37781-56-9; **5c**, 37781-57-0; **5d**, 29617-92-3; **6**, 37782-84-6; **7**, 29617-91-2; **8**, 4603-70-7; **9**, 37782-86-8; **10**, 37782-87-9; **11**, 37782-88-0; **12**, 37782-90-4; **13**, 37782-91-5; **15a**, 37782-89-1; **15b**, 29617-90-1; **15c**, 37782-93-7; **15d**, 37818-74-9; **16**, 37782-95-9; **17**, 37782-94-8; dimethylformamide dimethyl acetal 4637-24-5.

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(18) Uv data[9] for a similar compound—*N*-[*trans*-4-(thyminyl)cyclopentyl]-pyridinium hydroxide (inner salt)—have been reported: λ_{max} 262 (shoulder), 267, and 280 (shoulder) (ϵ_{max} 13,300, 13,800, and 9180). The corresponding hydrochloride showed λ_{max} 262 (sh), 267, and 280 (sh), (ϵ_{max} 12,530, 13,040, and 8500).

(19) The positions of pyridine protons were assigned in analogy with the literature: L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 64.

(20) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 2829 (1962).