Halo Sugar Nucleosides. III.[1] Reactions for the Chlorination and Bromination of Nucleoside Hydroxyl Groups

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The replacement of various hydroxyl functions in the sugar moiety of nucleosides by chlorine or bromine can be achieved through reaction with carbon tetrahalides and triphenylphosphine in DMF or DMAC. The reactions with primary hydroxyl groups are rapid and efficient while reactions of the secondary hydroxyl groups of 2′-deoxy nucleosides are slower. In the latter case, the chlorination reaction occurs principally with inversion of configuration while bromination proceeds mainly with retention of configuration. Pyrimidine nucleosides containing a free, *cis*-2′,3′-diol undergo quite selective chlorination of the 2′-hydroxyl function with retention of configuration. Mechanisms are discussed for these reactions. The nature of some side reactions between carbon tetrahalides, triphenylphosphine, and DMF are discussed. A recently described preparation of 3′-chloro-3′-deoxyuridine has been reexamined and found to give predominantly 5′-*O*-acetyluridine and derivatives of 2′-chloro-2′-deoxyuridine.

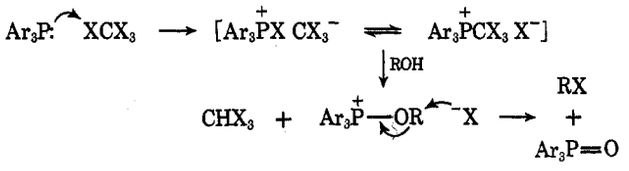
In recent papers from this laboratory, the reactions of methyltriphenoxyphosphonium iodide with suitably protected nucleosides has been shown to lead to the efficient replacement of either primary or secondary hydroxyl groups by iodo functions.[1,2] The resulting iodo sugar nucleosides can then be used in a variety of reactions leading to deoxy, amino, and unsaturated derivatives. In the present paper we outline the use of several reagents suitable for the related conversion of nucleoside hydroxyl groups to chloro or bromo functions. The resulting products are once again of interest as synthetic intermediates and, in some cases, can also be of primary biological interest.[3-6]

Previously the preparation of chloro and bromo sugar nucleosides has been achieved principally *via* nucleophilic displacement of sulfonyl esters,[7] opening of O^2,2′-cyclouridine with hydrogen halides[8] or, more recently, by direct halogenation of primary hydroxyl groups with Vilsmeier–Haack type complexes derived from thionyl halides with dimethylformamide (DMF)[9] or hexamethylphosphoramide.[10]

Recently considerable interest has centered upon the facile chlorination of hydroxyl groups by reaction with carbon tetrachloride and triphenylphosphine.[11] This type of reaction, which can also be conducted using trialkylphosphine,[12] has been applied to the chlorination and bromination of a few carbohydrates.[11,13] In this paper we describe the application of these and some related reagents to the halogenation of nucleoside hydroxyl groups.[14,15]

While precise mechanistic studies are still lacking, it is generally accepted that these reactions proceed *via* an ionic mechanism as shown below in Scheme I.[16]

SCHEME I

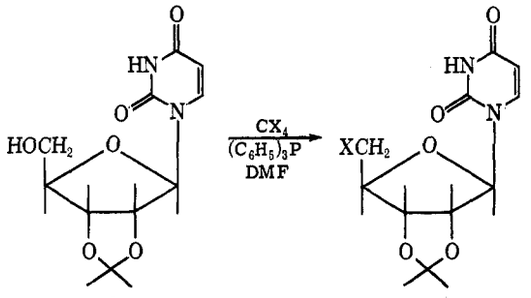


Our first objective was to compare the relative efficiencies of different carbon tetrahalides. Thus, 2′,3′-*O*-isopropylideneuridine (**1**) was treated under essentially identical conditions with 1 molar equiv each of triphenylphosphine and either CCl_4, CBr_4, or CI_4 in DMF at room temperature. By thin layer chromatography it was shown that the 5′-chloro (**2a**), 5′-bromo (**2b**), and 5′-iodo (**2c**) nucleosides were formed in yields of 86, 71, and 37% after 18 hr and the crystalline products were isolated in yields of 70, 55, and 17%, respectively. While no effort has been made to optimize yields and the above reactions were done using only 1 molar equiv of each reactant, it is clear that these methods are quite suitable for the chlorination and bromination of the primary hydroxyl groups of nucleosides. The iodination reaction, however, is poor under these conditions and rather similar results were obtained by others during halogenation of lincomycin derivatives.[13b]

For preparation of the 5′-iodo nucleoside **2c**, the use of methyltriphenoxyphosphonium iodide is much to be preferred.[1,2] Successful iodination of **1** was also achieved using iodotriphenylphosphonium iodide,[17,18] prepared from iodine and triphenylphosphine in DMF, **2c** being obtained in 59% yield.

(1) For part II, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2868 (1970).
(2) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).
(3) W. Jahn, *Arch. Exp. Pathol. Pharmakol.*, **251**, 95 (1965).
(4) E. T. Reese, L. B. Townsend, and F. W. Parrish, *Arch. Biochem. Biophys.*, **125**, 175 (1968).
(5) P. Langen and G. Kowollik, *Eur. J. Biochem.*, **6**, 344 (1968).
(6) R. Duschinsky, H. Walker, and J. Kára, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, MEDI-68.
(7) See, *e.g.*, (a) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955); (b) W. Jahn, *Chem. Ber.*, **98**, 1705 (1965).
(8) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.* **29**, 558, 564 (1964).
(9) R. F. Dods and J. S. Roth, *ibid.*, **34**, 1627 (1969).
(10) K. Kikugawa and M. Ichino, *Tetrahedron Lett.*, 87 (1971).
(11) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).
(12) J. Hooz and S. S. H. Gilani, *ibid.*, **46**, 86 (1968).
(13) (a) C. R. Haylock, L. D. Melton, K. N. Slessor, and A. S. Tracey, *Carbohyd. Res.*, **16**, 375 (1971); (b) R. D. Birkenmeyer and F. Kagen, *J. Med. Chem.*, **13**, 616 (1970); (c) L. D. Moggel and A. M. Yurkevich, *Zh. Obshch. Khim.*, **40**, 708 (1970); (d) B. T. Lawton, W. A. Szarek, and J. K. N. Jones, *Carbohyd. Res.*, **14**, 225 (1970).
(14) This work has been summarized. See J. P. H. Verheyden and J. G. Moffatt, Abstracts, Joint CIC–ACS Conference, Toronto, Ontario, May 1970, Carbo 10.
(15) Very recently the chlorination or bromination of 2′,3′-*O*-isopropylideneinosine has been described: K. Haga, M. Yoshikawa, and T. Kato, *Bull. Chem. Soc. Jap.*, **43**, 3922 (1970).
(16) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).
(17) K. Issleib and W. Seidel, *Z. Anorg. Allg. Chem.*, **288**, 201 (1956).
(18) Related chlorination and bromination of alcohols has been described by G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

As will be seen later, the failure to iodinate **1** with carbon tetraiodide and triphenylphosphine in DMF is probably, at least in part, due to side reactions involving DMF. In support of this it was shown that a similar reaction using pyridine as the solvent gave **2c** in 76% yield. The use of triphenylphosphine and *N*-iodosuccinimide[19] gave poor results.

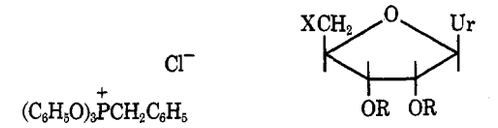


1 **2a**, X = Cl; **b**, X = Br; **c**, X = I

While iodination reactions using carbon tetraiodide are preferably not carried out in DMF, the latter solvent is generally well suited for chlorination and for bromination of primary alcohols (see later). The chlorination of **1** to **2a** is also quite satisfactory in hexamethylphosphoramide (HMPT) but does not proceed in dimethyl sulfoxide. Polar solvents such as DMF, dimethylacetamide (DMAC), and HMPT permit satisfactory reactions at room temperature, while the use of solvents such as carbon tetrachloride, in which nucleosides are frequently poorly soluble, normally requires heating.[18]

Chlorination of **1** could also be readily achieved in 70% yield *via* reaction with benzyltriphenoxyphosphonium chloride (**3**)[20] in DMF, but, since the reagent is a syrup that is difficult to handle and store, the use of carbon tetrachloride and triphenylphosphine is preferred.

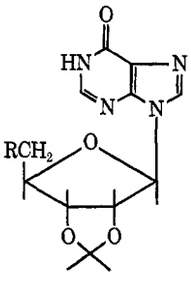
Since the reaction conditions remain relatively neutral, particularly if the reaction is finally quenched with methanol rather than water, common protecting groups on the sugar prove to be stable. Thus, reaction of 2′,3′-di-*O*-acetyluridine (**4a**) readily gave 2′,3′-di-*O*-acetyl-5′-chloro-5′-deoxyuridine (**4b**) in 50% yield even on a small scale.



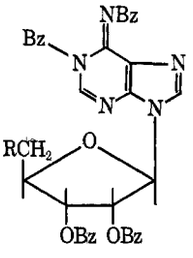
3

4a, R = Ac; X = OH
b, R = Ac; X = Cl
c, R = H; X = OH
d, R = H; X = Br
e, R = H; X = Cl

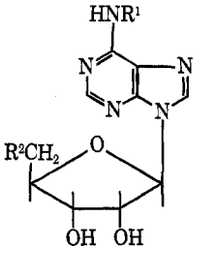
In a recent paper[15] the chlorination of 2′,3′-*O*-isopropylideneinosine (**5a**) to the corresponding 5′-chloro-5′-deoxy compound (**5b**) was achieved in high yield through reaction with triphenylphosphine and carbon tetrachloride in triethyl phosphate at 100°. These authors report, however, that the reaction did not proceed using DMF as solvent. This claim is in contrast to our results where chlorination in DMF at room temperature led to crystalline **5b** in 80% yield. In a similar way, the reaction of **5a** with carbon tetrabromide and triphenylphosphine in dimethylacetamide (DMAC) gave the 5′-bromo compound **5c** in 49% yield. In this latter case, DMAC was used rather than DMF in an effort to reduce the side reactions involving DMF. Chlorination of N^1,N^6,2′-*O*,3′-*O*-tetrabenzoyladenosine (**6a**)[21] also proceeded smoothly, giving the corresponding 5′-chloro-5′-deoxy nucleoside (**6b**) in 86% yield. Treatment of the latter compound with methanolic ammonium hydroxide at 23° for 3 hr removed the 2′-*O*, 3′-*O*, and N^1 benzoyl groups fairly selectively, giving crystalline N^6-benzoyl-5′-chloro-5′-deoxyadenosine (**7a**) in 46% yield. More prolonged hydrolysis removed all four benzoyl groups, giving 5′-chloro-5′-deoxyadenosine (**7b**) which, from its nmr spectrum, was clearly very pure but which consistently showed a broad melting point lower than that previously described for this compound.[10] This melting behavior is entirely to be expected for **7b**, since in the absence of an N^6-benzoyl group, the thermal formation of N^3,5′-cycloadenosine is a facile process.[2,22]



5a, R = OH; **b**, R = Cl; **c**, R = Br



6a, R = OH; **b**, R = Cl



7a, R^1 = Bz; R^2 = Cl
b, R^1 = H; R^2 = Cl

Fairly selective 5′ halogenation of unprotected nucleosides can also be achieved. Thus, free uridine and thymidine were directly converted into their 5′-bromo (**4d**) and 5′-chloro (**18c**)[23] derivatives in yields of 55 and 73% by reaction with 2 equiv of the appropriate carbon tetrahalide and triphenylphosphine. Attempted selective chlorination of cytidine was complicated by signifi-

(19) A related bromination of simple alcohols has been described by S. Tripett, *J. Chem. Soc.*, 2337 (1962), and has been applied to some carbohydrates and nucleosides: M. M. Ponpipom and S. Hanessian, *Carbohyd. Res.*, **18**, 342 (1971).

(20) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953). This reagent is more conveniently prepared than the corresponding methyl derivative due to the volatility of methyl chloride.

(21) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Amer. Chem. Soc.*, **84**, 430 (1962).

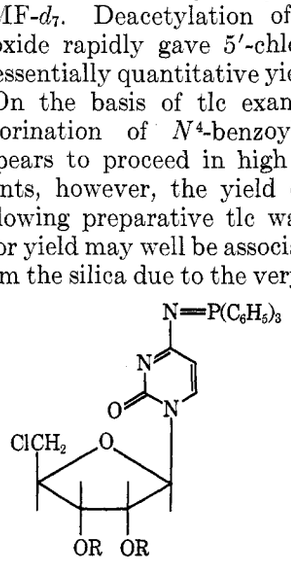
(22) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(23) D. M. Brown, W. Cochran, E. H. Medlin, and S. Varadarajan, *ibid.*, 4873 (1956).

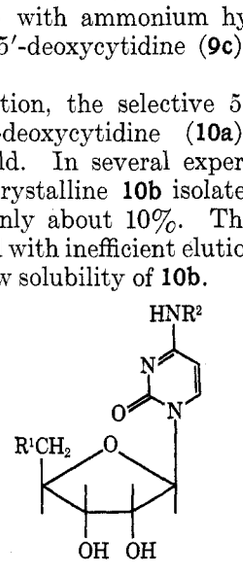
cant side reactions involving the 4-amino group on the cytosine ring. Many products were formed, including one crystalline material considered to be the iminophosphorane **8a**. The location of the chlorine function at $C_{5'}$ in **8a** was indicated by periodate oxidation and was confirmed by nmr spectroscopy, which showed the expected 1.3 ppm downfield shifts of the $C_{2'}$ and $C_{3'}$ protons upon acetylation to **8b**. A related formation of heterocyclic iminophosphoranes through reactions of aminotriazines with triphenylphosphine and chlorine has been described.[24]

This side reaction can be avoided by prior protection of the cytosine amino group, and selective chlorination of N^4-acetylcytidine (**9a**) gave crystalline N^4-acetyl-5′-chloro-5′-deoxycytidine (**9b**) in 58% yield. The presence of a free 2′,3′-diol was confirmed by a positive periodate test and by a 1.3 ppm downfield shift of the nmr resonance due to the $C_{2'}$ and $C_{3'}$ protons upon addition of trichloroacetyl isocyanate[25] to a solution of **9b** in DMF-d_7. Deacetylation of **9b** with ammonium hydroxide rapidly gave 5′-chloro-5′-deoxycytidine (**9c**)[10] in essentially quantitative yield.

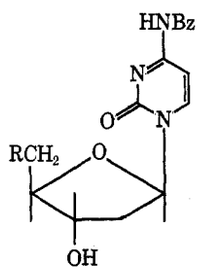
On the basis of tlc examination, the selective 5′-chlorination of N^4-benzoyl-2′-deoxycytidine (**10a**)[26] appears to proceed in high yield. In several experiments, however, the yield of crystalline **10b** isolated following preparative tlc was only about 10%. This poor yield may well be associated with inefficient elution from the silica due to the very low solubility of **10b**.



8a, R = H
b, R = Ac



9a, R^1 = OH; R^2 = Ac
b, R^1 = Cl; R^2 = Ac
c, R^1 = Cl; R^2 = H



10a, R = OH
b, R = Cl

The halogenation of secondary hydroxyl groups using reagents such as methyltriphenoxyphosphonium iodide[2] or combinations of triphenylphosphine and carbon tetrahalides[12,27] is known to normally proceed with inversion of configuration. Our earlier work, however, has shown that iodination of the 3′-hydroxy function in thymidine derivatives occurs with retention of configuration, this being explained by intervention of an O^2,3′-anhydro nucleoside as an intermediate.[1] It has now been shown that reaction of 5′-*O*-*p*-nitrobenzoylthymidine (**11a**) with triphenylphosphine and iodine also leads to 3′-deoxy-3′-iodo-5′-*O*-*p*-nitrobenzoylthymidine (**14a**) with complete retention of stereochemistry. The reaction is, however, sluggish and the crystalline product was isolated in only 47% yield. There was no indication of the formation of isomeric products.

The chlorination of 5′-*O*-tritylthymidine (**11b**) using triphenylphosphine and carbon tetrachloride in DMF at room temperature was quite different in that two crystalline, isomeric 3′-chloro-3′-deoxy nucleosides were formed. These were separated by preparative tlc and the less polar isomer (15% yield) was shown to have the erythro configuration **14b** by its identity with the product formed in 70% yield from authentic O^2,3′-anhydro-1-(2′-deoxy-5′-*O*-trityl-β-D-*threo*-pentofuranosyl)-thymine (the conjugate base of **13**, R = Tr)[1] and pyridine hydrochloride in DMF. The more polar, major product, isolated in 35% yield, retained its 5′-*O*-trityl function, and nmr decoupling studies clearly showed the retention of both $C_{2'}$ protons as well as of the $C_{3'}$, $C_{4'}$, and $C_{5'}$ protons. Accordingly, it must be assigned the structure 1-(3-chloro-2,3-dideoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**15a**). Both **14b** and **15a** were readily detritylated to the corresponding 3′-chloro nucleosides **14c** and **15b**.

It seems clear that the 3′-oxyphosphonium intermediate **12** can react in two different ways depending upon the nature of the halide ions present. In the case of iodide ion, both the size of the anion and its relatively low nucleophilicity in aprotic solvents such as DMF[28] conspire to prevent halide attack at $C_{3'}$ from the relatively hindered β face. Accordingly, the alternative SN2 displacement by the C_2 carbonyl group of the thymine ring takes precedence, leading to the O^2,3′-anhydro nucleoside **13**. As described previously,[1] **13** is then opened by halide ion, leading to the observed 3′-deoxy-3′-iodo-5′-*O*-tritylthymidine (**14d**) with overall retention of configuration. On the other hand, in the presence of chloride ion, which is both smaller and more nucleophilic than iodide in DMF,[27] direct SN2 displacement of the oxyphosphonium function by halide ion can compete favorably with the intramolecular process. Accordingly, the chlorination reaction leads principally to the inverted *threo*-3′-chloro derivative **15a** and to smaller amounts of **14b**.

The threo configuration of **15a** was confirmed by an independent synthesis of this compound from **14d** and lithium chloride in hot DMF. Here, once again, chloride ion can apparently compete favorably with the thymine carbonyl group in SN2 displacement of the 3′-iodo function. Treatment of **14d** with excess lithium chloride in DMF at 23° for 4 days led to no **15a**, thus ruling out **14d** as an intermediate in the formation of the threo isomer.

The reaction of free thymidine led, as expected, to initial chlorination at the primary 5′ position followed by slower reactions. Using 3 equiv of triphenylphos-

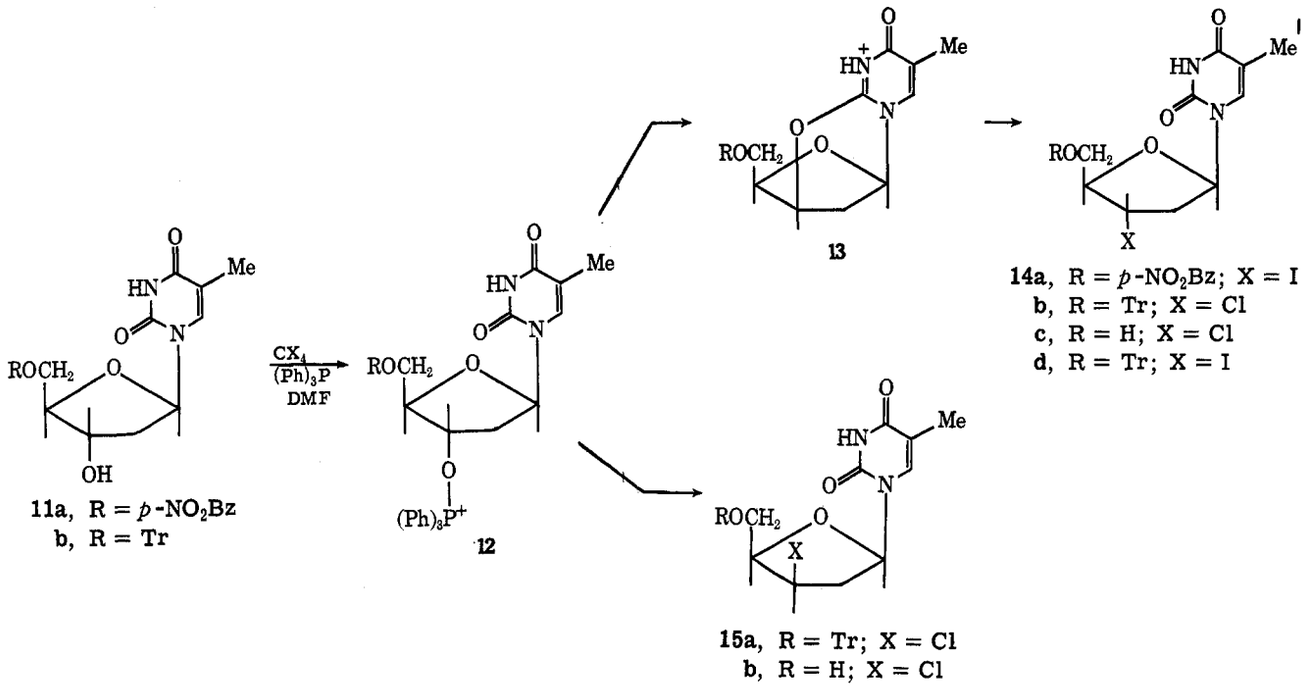
(24) (a) G. Gotsmann and M. Schwarzmann, *Justus Liebigs Ann. Chem.*, **729**, 106 (1969); (b) H. W. Roesby and H. H. Giere, *Chem. Ber.*, **102**, 2330 (1969).

(25) V. W. Goodlet, *Anal. Chem.*, **37**, 431 (1965).

(26) B. A. Otter and J. J. Fox in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. A. Tipson, Ed., Interscience, New York, N. Y., 1968, p 285.

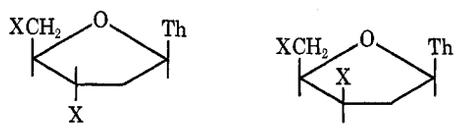
(27) (a) D. Brett, I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Ind. (London)*, 1017 (1969); (b) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970).

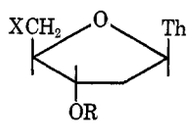
(28) W. M. Weaver and J. D. Hutchinson, *J. Amer. Chem. Soc.*, **86**, 261 (1964).



phine and an excess of carbon tetrachloride in DMF, two major nucleoside products were, once again, found and isolated in crystalline form by preparative tlc. The minor product, isolated in only 5% yield, had a melting point identical with that described for 3′,5′-dichloro-3′,5′-dideoxythymidine (**16a**) prepared previously by a different route and convincingly characterized by reconversion to the 5′-chloro-5′-deoxy-*O*²,3′-anhydro nucleoside with base.[29] The major product, in 63% yield, was also a 3′,5′-dichloro nucleoside by nmr studies and is, accordingly, 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**17a**). Clearly, the smaller size of the 5′-chloro group as compared with the 5′-*O*-trityl derivative makes direct SN2 displacement of the 3′-oxyphosphonium group by chloride ion an even more preferred process relative to anhydro nucleoside formation.

The dibromination of thymidine using triphenylphosphine and carbon tetrabromide was a much less efficient process, since even after 7 days reaction, 5′-bromo-5′-deoxythymidine (**18a**)[30] was isolated in 60% yield. Only small amounts of dibromo compounds were formed, the known erythro isomer **16b**[30] being obtained in 12% yield and the threo isomer **17b** in 4% yield. In spite of the low yields during bromination of the secondary 3′-hydroxy group, it is clear that the process with retention of configuration (*via* the anhydro nucleoside) is preferred over that leading to inversion. The increasing proportion of products with the threo configuration as one considers the iodination, bromination, and chlorination of thymidine derivatives can thus be directly related to the decreasing sizes and increasing nucleophilicities in DMF of the corresponding halide ions.





Further support for the stereochemical assignments of the various 3′-halo nucleosides above comes from an examination of the 100-MHz nmr spectra of these compounds. It has previously been noted[1] that the nmr spectra of many differently substituted 1-(2-deoxy-β-D-pentofuranosyl)thymines possessing the erythro configuration show very similar chemical shifts for the $C_{2'a}$ and $C_{2'b}$ protons which appear as partially or completely overlapping signals. On the other hand, compounds with the threo configuration show chemical shift differences of 0.5–1 ppm for these protons which then appear as well-separated ABXY patterns. While a discussion of the nmr spectra of many such compounds will appear shortly,[31] it is sufficient for the moment to say that the various pairs of 3′-halogenated compounds (*e.g.*, **14** and **15**, **16** and **17**) can be readily distinguished and characterized by this means.

While chlorination of both primary and secondary hydroxyl groups by this route is an efficient process, the low yields observed during bromination at the 3′ position of thymidine can be explained, at least in part, by the isolation of a by-product from this reaction. This crystalline substance behaved as an ultraviolet-absorbing cation upon electrophoretic examination and on the basis of its very simple nmr spectrum is considered

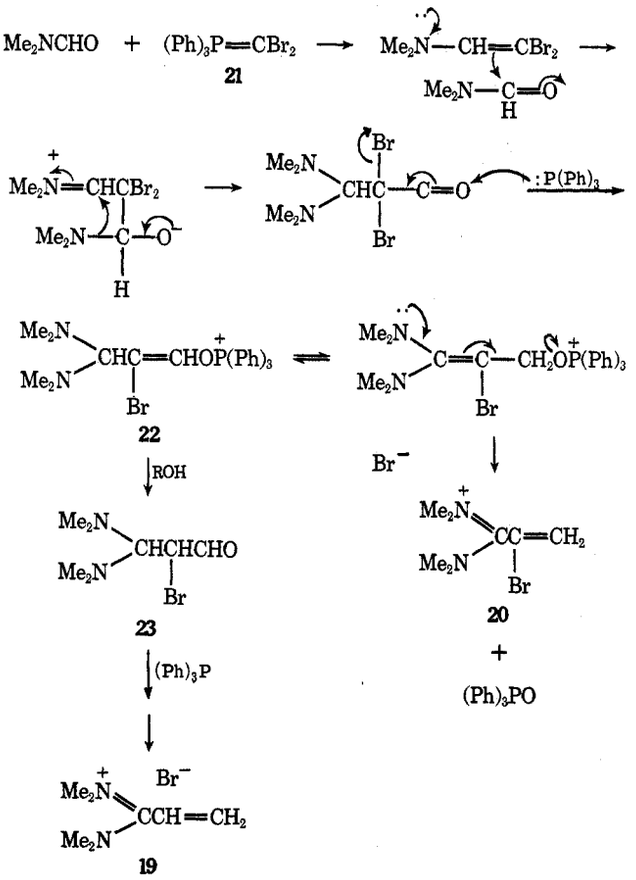
(29) Y. Mizuno, T. Ueda, K. Ikeda, and K. Miura, *Chem. Pharm. Bull.*, **16**, 262 (1968).

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

(31) J. P. H. Verheyden, M. L. Maddox, and J. G. Moffatt, in preparation.

to be N,N,N',N'-tetramethylacrylamidinium bromide (**19**). This compound crystallizes as a tenacious 2:1 complex with carbon tetrabromide, the presence of the latter confirmed by analysis, quantitative glc, and mass spectrometry.

In the absence of thymidine, a solution of triphenylphosphine and carbon tetrabromide in DMF deposits a crystalline compound similar to **19** but lacking one vinyl proton. This compound is assigned the structure **20** and once again crystallizes with 0.5 equiv of carbon tetrabromide. From this same reaction, **19** was also isolated in addition to large amounts of triphenylphosphine oxide and dimethylamine hydrobromide. Several relatively complex mechanisms can be suggested for the formation of **19** and **20** involving initial reaction of DMF with the dibromomethylenephosphorane (**21**) known to be formed from triphenylphosphine and carbon tetrabromide.[32] The use of triphenylphosphine and carbon tetrabromide in a ratio of 2:1, conditions known to favor the formation of **21** in other solvents,[32] leads to increased amounts of **19**. A suggested mechanism follows.



In the presence of an alcohol the oxyphosphonium salt **22** can undergo solvolysis with attack on phosphorus[33] giving the bromo aldehyde **23** and $(Ph_3)POR^+$. Subsequent attack by triphenylphosphine upon the oxygen of **23** can then give the debrominated product **19** by a process similar to that used to form **19**.[34]

(32) (a) F. Ramirez, N. B. Desai, and N. McKelvie, *J. Amer. Chem. Soc.*, **84**, 1745 (1962); (b) R. Rabinowitz and R. Marcus, *ibid.*, **84**, 1312 (1962).

(33) A. J. Speziale and R. D. Partos, *ibid.*, **87**, 5068 (1965).

(34) For a review of the reactions of α-halocarbonyl compounds with phosphorus derivatives, see (a) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 117; (b) B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1965, p 133.

The low yields achieved during iodination of even primary hydroxyl groups (*e.g.*, **1**) using carbon tetraiodide and triphenylphosphine in DMF is probably a reflection of an even greater tendency toward side reactions such as those above. In support of this idea, we have found that a comparable reaction of **1** using pyridine rather than DMF gave **2c** in 76% yield. As was the case using methyltriphenoxyphosphonium iodide,[1] however, it is likely that the use of a basic solvent such as pyridine will not facilitate the halogenation of nucleoside secondary hydroxyl groups, since nucleophilic opening of anhydro nucleosides such as **13** is known to be acid catalyzed.

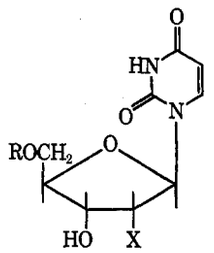
Our earlier work showed that iodination of vicinal diols using methyltriphenoxyphosphonium iodide failed due to nucleophilic displacement of phenolate ion from the oxyphosphonium intermediate by the adjacent hydroxyl group.[1] Since such a displacement is not possible using oxytriphenylphosphonium intermediates, the present methods should be suitable for use with cis vicinal diols. Accordingly, the reaction of 5′-*O*-acetyluridine (**24a**) with triphenylphosphine and carbon tetrachloride in DMF was found to give crystalline 5′-*O*-acetyl-2′-chloro-2′-deoxyuridine (**24b**) in 38% yield. The structure of **24b** was deduced by deacetylation to the known 2′-chloro-2′-deoxyuridine (**24c**)[35] and was confirmed by nmr spectroscopy. Thus, the presence of a free 3′-hydroxyl group was demonstrated by the sharpening of the signal due to $C_{3'}H$ (confirmed by decoupling studies) upon addition of D_2O. In a similar way, the direct chlorination of free uridine gave 17% of 5′-chloro-5′-deoxyuridine (**4e**)[9] and 68% of crystalline 2′,5′-dichloro-2′,5′-dideoxyuridine (**25**). Once again, the free hydroxyl group of **25** was located at $C_{3'}$ by decoupling experiments, irradiation of $C_{3'}H$ causing the D_2O-exchangeable doublet at 6.10 ppm ($C_{3'}OH$) to collapse to a singlet, and by acetylation which led to a 1 ppm downfield shift of $C_{3'}H$ but to only minor shifts of the other sugar protons. The ribo configuration of **25** was confirmed by further chlorination of authentic **24c**, which gave crystalline **25** identical with that above.

The quite selective reactions of the $C_{2'}$-hydroxyl groups in **24a** and in free uridine were also apparent in the cytidine series, since reaction of N^4-benzoylcytidine (**26a**)[36] gave 30% of N^4-benzoyl-5′-chloro-5′-deoxycytidine (**26b**) and N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (**26c**) in 41% yield. The former compound was, as expected, periodate positive, while the free 3′-hydroxyl of **26c** was confirmed by acetylation giving **26d** which showed a 0.85 ppm downfield shift of $C_{3'}H$ relative to **26c**.

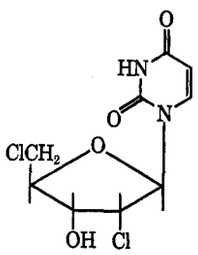
While we have provided convincing evidence that the 2′-chloro function of **24b** and of **25** has, indeed, the ribo configuration arising *via* an $O^2,2'$-anhydro nucleoside intermediate, the configuration at $C_{2'}$ in **26b** is based essentially upon analogy with the results in the uridine series. The selective reactivity of the 2′-hydroxyl group in 2′,3′-diols such as uridine, **24a**, and **26a** finds analogy in the well-known selective 2′-tosylation of 5′-

(35) (a) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); (b) R. J. Cushley, J. F. Codington, and J. J. Fox, *Can. J. Chem.*, **46**, 1131 (1968).

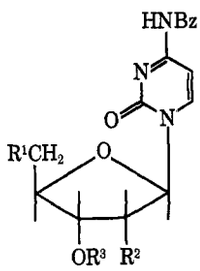
(36) K. A. Watanabe and J. J. Fox, *Angew. Chem., Int. Ed. Engl.*, **5**, 579 (1966).



24a, R = Ac; X = OH
b, R = Ac; X = Cl
c, R = H; X = Cl



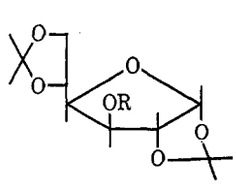
25



26a, $R^1 = R^2 = OH$; $R^3 = H$
b, $R^1 = Cl$; $R^2 = OH$; $R^3 = H$
c, $R^1 = R^2 = Cl$; $R^3 = H$
d, $R^1 = R^2 = Cl$; $R^3 = Ac$

substituted uridine derivatives,[37] and the preferential formation of 2′-*O*-methyl nucleosides using diazomethane.[38] While we cannot totally rule out the formation of 3′-halogenated nucleosides, their formation, if at all, must be in very low yield.

In the past, all efforts to directly halogenate the 3′-hydroxyl function of 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (**27a**) have been accompanied by acetal migration and have led to 6-deoxy-6-halo-1,2,3,5-di-*O*-isopropylidene-α-D-glucofuranoses.[13,39] We have found that reaction of **27a** with carbon tetrachloride and triphenylphosphine in DMF at room temperature leads to a major product that does not contain chlorine and is identical with the 3′-*O*-formyl derivative **27b** prepared using formic–acetic anhydride. Here, once again, the use of DMF as solvent can lead to by-products, but comparable reactions using other solvents have not been studied. It should be recalled that chlorination with inversion of configuration of the corresponding 1,2,5,6-di-*O*-isopropylidene-α-D-allofuranose isomer proceeds slowly, but without difficulty, in refluxing carbon tetrachloride.[13] The formation of **27b** has also been



27a, R = H
b, R = CHO

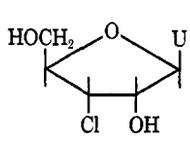
suggested during reactions with chloromethylene dimethyliminium chloride,[39] but the product was not characterized.

(37) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

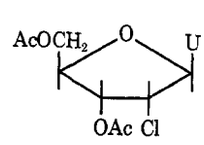
(38) (a) D. M. G. Martin, C. B. Reese, and G. F. Stephensen, *Biochemistry*, **7**, 1406 (1968); (b) J. B. Gin and C. A. Dekker, *ibid.*, **7**, 1413 (1968).

(39) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 2163 (1969), and references cited therein.

Finally, Dods and Roth[9,40] have reported the unusual observation that, while reaction of uridine with arsenic trichloride in DMF at 160° gave 5′-chloro-5′-deoxyuridine (**4e**) in 51% yield, the corresponding reaction in DMAC at 127° gave 3′-chloro-3′-deoxyuridine (**28**) in an isolated yield of 20%. A previous preparation of **28** was described by Kowollik and Langen[41] *via* the reaction of an O^2,3′-anhydro nucleoside with hydrogen chloride, but, more recently, Kikugawa and Ukita[42] have shown that the product of this reaction is indeed 1-(5-chloro-5-deoxy-β-D-xylofuranosyl)uracil arising by an intriguing rearrangement. We were, accordingly, interested in the mechanism by which **28** was formed, and, in particular, in the unusual role apparently played by DMAC. An examination of the data provided for **28**,[9,40] however, led to some doubts as to the correctness of the proposed structure. In particular, the ultraviolet absorption spectrum had an extinction coefficient of 7400 (*cf.* the value of 10,000 for normal uridine derivatives) and its chromatographic mobility was far from what would be expected. Thus, the R_f value of **28** (0.76) during paper chromatography in 1-butanol–water (86:14) was reported to be almost twice that of 5′-chloro-5′-deoxyuridine (R_f 0.42) in the same system. In our experience, the chromatographic mobilities of 5′-chloro- (**4e**) and 2′-chloro- (**24c**) uridines are very similar both by tlc and paper chromatography in many solvents, including that used by Dods and Roth[9,40] (R_f 0.44 and 0.48, respectively), and we would anticipate that **28** would also be comparable. An R_f value of 0.52 reported for 1-(5-chloro-5-deoxy-β-D-xylofuranosyl)uracil[41] is also very similar. We, accordingly, have carefully repeated this experiment four times using purified reagents and adhering closely to the described procedure. Paper and thin layer chromatography of the crude reaction mixtures do indeed generally resemble what has been described, but we have found the use of different solvent systems to greatly facilitate the preparative separation without altering the relative order of the bands.[43] The fastest band, corresponding to **28**, was, as described, rather unstable and during rechromatography underwent considerable degradation, but its major component was positively identified as 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**29**) by



28



29

the identity of its melting point, infrared, and nmr spectra with those of an authentic sample.[35b,44] The degradation products of **29** resulted from deacetylation and included **24a** and **24c**, both identified by comparison with authentic samples. The other original bands were identified as **24c** and its monoacetyl derivatives, 5′-*O*-acetyluridine (43%) and some 5′-chloro-5′-deoxyuridine as well as 25% unreacted uridine. The various

(40) R. F. Dods, Ph.D. Thesis, University of Connecticut, 1968.

(41) G. Kowollik and P. Langen, *Chem. Ber.*, **101**, 235 (1968).

(42) K. Kikugawa and T. Ukita, *Chem. Pharm. Bull.*, **17**, 1775 (1969).

(43) As described, a reaction mixture from 2 g of uridine was separated on only five 8 × 8 in. plates with a 1 mm layer of silica, an extremely heavy loading for such a complex mixture.

(44) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).

acetylated compounds undoubtedly arise *via* Vilsmeier–Haack type adducts of DMAC with arsenic trichloride.

1-(β-D-Xylofuranosyl)uracil (once again with an unexpected R_f value twice that of uridine while we find these compounds to have R_f 0.23 and 0.18 in the same system) was reported to be present in the reaction mixture and also to be the product of both acidic and alkaline treatment of **28**. We have been unable, by borate electrophoresis in the presence of an authentic sample, to detect the presence of this compound in the crude reaction mixtures either before or after acidic hydrolysis under the conditions described.[9,40]

Unfortunately, a sample of **28** was no longer available from Drs. Dods or Roth for comparison, but in our hands we have been unable to detect the formation of this compound by the route described. It is entirely possible that the above workers were the victims of a fortuitous circumstance since **29** contaminated by only 7–8% of ammonium chloride, a certain by-product of this reaction, would give an elemental analysis close to that observed. The structure **29** (R_f 0.76 in our hands) would adequately explain both the anomalous chromatographic mobility and the low extinction coefficient.[45] It cannot, however, explain the deviation in melting point between that reported for **28** and **29**, and a resolution of this question must await a reliable independent synthesis of **28**.[46]

Taken in conjunction with the use of reagents such as methyltriphenoxyphosphonium iodide,[1,2] the triphenylphosphine–carbon tetrahalide reagents make the synthesis of a wide range of halo sugar nucleosides possible. Work on some quite unrelated halogenating agents will be reported shortly.[47]

Experimental Section

General Methods.—The general methods used are similar to those described previously.[1] Melting points are recorded using a hot-stage microscope and are corrected. Assignments of sugar protons in nmr spectra are generally confirmed by decoupling experiments. Further confirmation of the structural assignments of most compounds was obtained from ORD and mass spectral data, the details of which are not reported. Nuclear magnetic resonance spectra are recorded in Tables I and II.

5′-Chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine (2a). A. Using Triphenylphosphine–CCl_4.—Carbon tetrachloride (176 mg, 1.16 mmol) was added to a solution of **1** (284 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) in anhydrous DMF (10 ml). After 18 hr at 23° the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc using CCl_4–acetone (3:2). Elution of the major band followed by crystallization from chloroform–hexane gave 212 mg (70%) of **2a**, mp 180–181° (reported[9] mp 175–177°), λ_{max}^{MeOH} 259 mμ (ε 10,600).

Anal. Calcd for $C_{12}H_{15}N_2O_5Cl$ (302.7): C, 47.61; H, 4.99; N, 9.26; Cl, 11.72. Found: C, 47.67; H, 4.95; N, 9.11; Cl, 11.58.

B. Using Benzyltriphenoxyphosphonium Chloride (3).—A solution of **1** (426 mg, 1.5 mmol) and **3** (1.5 g, 3 mmol)[20] in anhydrous DMF (5 ml) was kept at room temperature for 2.5 hr. After addition of methanol (1 ml) the solvent was evaporated and the residue was purified by preparative tlc using CCl_4–ethyl acetate (9:1). Elution of the major band and crystallization from chloroform–hexane gave 316 mg (70%) of **2a** identical with that from A.

5′-Bromo-5′-deoxy-2′,3′-*O*-Isopropylideneuridine (2b).—A solution of **1** (284 mg,[5] 1 mmol), triphenylphosphine (262 mg, 1 mmol), and CBr_4 (545 mg, 1.05 mmol) in anhydrous DMF (10 ml) was kept at 23° for 18 hr. It was then evaporated to dryness and purified as for **2a** above, giving, after crystallization from chloroform–hexane, 191 mg (55%) of **2b**, mp 184–186° (reported[23] mp 184–186°), λ_{max}^{MeOH} 259 mμ (ε 10,200).

Anal. Calcd for $C_{12}H_{15}N_2O_5Br$ (347.18): C, 41.51; H, 4.35; N, 8.07. Found: C, 41.57; H, 4.78; N, 7.69.

5′-Bromo-5′-deoxyuridine (4d).—A solution of uridine (244 mg, 1 mmol), triphenylphosphine (524 mg, 2 mmol), and CBr_4 (664 mg, 2 mmol) in DMF (5 ml) was kept for 24 hr at 23°, diluted with methanol, and evaporated to dryness. Preparative tlc using chloroform–methanol (85:15) gave a number of bands. Elution of the band faster than unreacted uridine gave 170 mg (55%) of **4d** which crystallized very slowly from methanol, giving 85 mg (27%), mp 180–183° (reported[23] mp 182–184°), λ_{max}^{MeOH} 260 mμ (ε 9900).

5′-Chloro-5′-deoxythymidine (18c).—A solution of thymidine (484 mg, 2 mmol), triphenylphosphine (700 mg, 2.7 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 23° for 24 hr and then quenched with methanol. The solution was then evaporated and the residue was crystallized from methanol, giving pure **18c**. Preparative tlc of the mother liquors using chloroform–acetone (7:3) followed by recrystallization of the combined products from methanol gave 380 mg (73%) of **18c**, mp 193–195°, λ_{max}^{MeOH} 266 mμ (ε 9400).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.35; H, 5.17; N, 10.78.

5′-Deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (2c). A. With Triphenylphosphine–Carbon Tetraiodide.—A solution of **1** (284 mg, 1 mmol), carbon tetraiodide (520 mg, 1 mmol), and triphenylphosphine (262 mg, 1 mmol) in pyridine (5 ml) was kept at room temperature for 16 hr and then evaporated to dryness. The residue was dissolved in chloroform, washed with aqueous sodium thiosulfate and water, dried, and purified by preparative tlc using CCl_4–ethyl acetate (65:35). Crystallization of the major product from chloroform–hexane gave 300 mg (76%) of **2c**, mp 166–167°, identical with an authentic sample.[2]

A similar reaction using anhydrous DMF (10 ml) as solvent gave crystalline **2c** in only 17% yield.

B. Using Triphenylphosphine and Iodine.—A solution of **1** (248 mg, 1 mmol), triphenylphosphine (262 mg, 1 mmol), and iodine (254 mg, 1 mmol) in anhydrous DMF (5 ml) was kept at room temperature for 24 hr, then evaporated to dryness. The residue was purified by preparative tlc using CCl_4–acetone (3:2) and the major product was crystallized from chloroform–hexane, giving 233 mg (59%) of **2c** identical with that from A.

2′,3′-di-*O*-Acetyl-5′-chloro-5′-deoxyuridine (4b).—A solution of **4a** (109 mg, 0.33 mmol), triphenylphosphine (88 mg, 0.33 mmol), and CCl_4 (0.1 ml, 1 mmol) in DMF (2 ml) was kept at 20° for 18 hr and evaporated to dryness. Preparative tlc using ethyl acetate followed by crystallization from chloroform–hexane gave 58 mg (50%) of **4b**, mp 152–154°, λ_{max}^{MeOH} 258 mμ (ε 9900).

Anal. Calcd for $C_{13}H_{15}N_2O_7Cl$ (346.5): C, 45.02; H, 4.33. Found: C, 44.86; H, 4.55.

Attempted Chlorination of Cytidine.—A solution of cytidine (243 mg, 1 mmol), triphenylphosphine (786 mg, 3 mmol), and CCl_4 (0.5 ml) in DMF (10 ml) was kept for 4 hr at 23°. After addition of methanol (3 ml) and evaporation to dryness, the residue was separated by preparative tlc using chloroform–methanol (93:7), giving triphenylphosphine oxide and three slower bands. The two slower bands were complex mixtures and elution of the faster band gave 140 mg (27%) of **8a**, mp 220.5–221.5° from methanol, λ_{max}^{MeOH} 289 mμ (ε 22,100).

Anal. Calcd for $C_{27}H_{25}N_3O_4PCl$ (521.93): C, 62.13; H, 4.82; N, 8.05. Found: C, 62.28; H, 4.72; N, 8.00.

Acetylation of this material with pyridine and acetic anhydride gave the chromatographically homogeneous 2′,3′-di-*O*-acetyl derivative (**8b**) which was not obtained crystalline. See Tables I and II for nmr.

N^4-Acetyl-5′-chloro-5′-deoxycytidine (9b).—A solution of **9a** (570 mg, 2 mmol), triphenylphosphine (570 mg, 2.2 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 20° for 24 hr. Since unreacted **9a** remained, a further 285 mg of triphenylphosphine was added. After 24 hr methanol (1 ml) was added and the solvent was evaporated *in vacuo*, leaving a syrup that was dissolved in chloroform (10 ml). Addition of benzene (10 ml) gave a precipitate (625 mg) that was crystallized from methanol, giving 355 mg (58%) of **9b**, mp 217–218°, λ_{max}^{MeOH} 299 mμ (ε 7200), 248 (15,600), 214 (16,900).

(45) Recalculation of the reported ultraviolet data using the increased molecular weight of **29** raises the ε value from 7400 to 9800, a figure typical of uracil nucleosides.

(46) We have made our observations available to Drs. Dods and Roth, who agree with our conclusions: Dr. J. S. Roth, personal communication.

(47) Unpublished work by S. Greenberg, A. F. Russell, and J. G. Moffatt.

TABLE I

NMR CHEMICAL SHIFTS AT 100 MHZ

Compd	Solvent[a]	$C_{1'}H$	$C_{2'a}H$	$C_{2'b}H$	$C_{3'}H$	$C_{4'}H$	$C_{5'a}H$	$C_{5'b}H$	C_5H	C_6H	C_5Me	Other
2a	C	5.73 (d)	5.04 (dd)		4.92 (dd)	4.40 (dt)	3.73 (dd)	3.88 (dd)	5.82 (d)	7.36 (d)		1.42, 1.43 (CMe_2), 9.55 (br s, NH)
2b	C	5.65 (d)	5.00 (dd)		4.85 (dd)	4.36 (dt)	3.51 (dd)	3.66 (dd)	5.74 (d)	7.32 (d)		1.36, 1.57 (s, CMe_2), 7.69 (br s, NH)
4b	C	6.15 (d)	5.38 (m)		5.38 (m)	4.42 (m)	3.88 (2, br d)		5.85 (d)	7.56 (d)		2.09, 2.13 (s, Ac), 11.62 (br s, NH)
4d	P	6.58 (d)	4.76 (m)		5.57 (m)	4.57 (m)	3.96 (2, m)		5.81 (d)	7.85 (d)		
4e	P	6.64 (d)	4.80 (m)		4.65 (m)	4.65 (m)	4.12 (m)	4.12 (m)	5.84 (d)	7.90 (d)		
5b	P	6.49 (d)	5.54 (dd)		5.25 (dd)	4.60 (dt)	3.83 (dd)	3.98 (dd)	5.84 (d)			1.38, 1.59 (s, CMe_2), 8.32, 8.43 (C_2H), C_8H)
5c	P	6.51 (d)	5.57 (dd)		5.28 (dd)	4.65 (dt)	3.69 (dd)	3.86 (dd)				1.39, 1.59 (s, CMe_2), 8.35, 8.49 (C_2H, C_8H)
6b	C	6.57 (d)	6.25 (dd)		6.06 (dd)	4.79 (dt)	4.05 (2, br d)					7.45, 7.92 (m, Ar), 8.45, 8.73 (C_2H and C_8H)
7a	P	6.71 (d)	5.35 (dd)		4.94 (dd)	4.79 (dt)	4.08 (dd)	4.24 (dd)				7.45, 8.30 (m, Ar), 8.90 (s, 2, C_2H, C_8H)
7b	P	6.61 (d)	5.35 (dd)		4.91 (dd)	4.72 (dt)	4.06 (dd)	4.22 (dd)				8.18 (s, NH_2), 8.52, 8.57 (s, C_2H, C_8H)
8a	P	6.59 (d)	4.55 (m)		4.55 (m)	4.55 (m)	4.09 (m)	4.09 (m)	6.43 (d)	8.1 (d)		7.45, 8.1 (m, Ar)
8b	P	6.48 (d)	5.85 (m)		5.85 (m)	4.41 (m)	3.95 (d)	3.95 (d)	6.37 (d)	7.75–8.1		1.85, 1.96 (s, OAc), 7.4, 7.9 (m, Ar)
9b	P	6.60 (d)	4.82 (dd)		4.70 (m)	4.70 (m)	4.22 (2, m)		8.45 (d)	8.70 (d)		2.27 (s, NAc)
9c	P	6.64 (d)	4.6 (m)		4.6 (m)	4.6 (m)	4.13 (2, m)		6.00 (d)	7.93 (d)		8.4 (br s, NH_2)
10b	P	6.76 (dd)	2.45 (ddd)	2.89 (ddd)	4.76 (ddd)	4.54 (m)	4.02 (d)	4.02 (d)	7.71 (d)	8.33 (d)		7.48, 8.22 (m, Ar)
14b	C	6.34 (dd)	2.63 (dd)	2.63 (dd)	4.56 (dd)	4.19 (ddd)	3.40 (dd)	3.54 (dd)		7.53	1.50[d]	7.30 (m, Ar), 9.10 (br s, NH)
14c	P	6.80 (dd)	2.65 (ddd)	2.88 (ddd)	4.92 (ddd)	4.37 (dd)	4.01 (dd)	4.17 (dd)		8.00	1.82	
15a	C	6.15 (dd)	2.33 (ddd)	2.95 (ddd)	4.45 (m)	4.21 (m)	3.37 (dd)	3.61 (dd)			1.83	7.1–7.6 (m, Ar and C_6H)
15b	P	6.55 (dd)	2.56 (ddd)	3.10 (ddd)	4.91 (ddd)	3.4 (m)	3.40 (m)	3.40 (m)		7.87	1.94	
16a	C	6.30 (t)	2.63 (dd)	2.63 (dd)	4.4 (m)	4.4 (m)	3.90 (d)	3.90 (d)		7.40	1.93	
16b	C	6.25 (t)	2.73 (dd)	2.73 (dd)	4.38 (m)	4.38 (m)	3.75 (br d)	3.75 (br d)		7.40	1.92	9.60 (br s, NH)
17a	C	6.24 (dd)	2.43 (ddd)	3.08 (ddd)	4.65 (ddd)	4.27 (dt)	3.85 (d)	3.85 (d)		7.50	1.97	9.35 (br s, NH)
17b	C	6.21 (dd)	2.56 (ddd)	3.25 (ddd)	4.65 (ddd)	4.13 (ddd)	3.55 (dd)	3.70 (dd)		7.59	1.94	9.55 (br s, NH)
18a	P	6.83 (dd)	2.46–2.63 (m)	2.46–2.63 (m)	4.77 (dt)	4.44 (dt)	3.86 (d)	3.86 (d)		7.62	1.93	
18c	P	6.90 (t)	2.55 (m)	2.55 (m)	4.84 (m)	4.49 (dt)	4.03 (2, d)			7.67 (d)	1.92 (d)	
24b	A	6.10 (d)	4.65 (dd)		4.43 (br t)	4.20 (m)	4.20 (m)	4.20 (m)	5.74 (d)	7.72 (d)		1.08 (s, Ac), 5.00 (br s, 3′-OH), 10.15 (br s, NH)
25	D	6.03 (d)	4.72 (dd)		4.15 (m)	4.15 (m)	3.90 (m)	3.90 (m)	5.72 (br d)[b]	7.66 (d)		6.10 (d, $J_{3',OH}$ = 6 Hz, $C_{3'}OH$)[c]
26b	D	5.89 (d)	3.9–4.3 (m)		3.9–4.3 (m)	3.9–4.3 (m)	3.9–4.3 (m)	3.9–4.3 (m)	7.39 (d)	8.19 (d)		7.60, 8.05 (m, Ar), 5.34, 5.60 (d, $J_{H,OH}$ = 5 Hz, $C_{2'}OH$, $C_{3'}OH$)
26c	P	6.72 (d)	5.27 (dd)		4.91 (dd)	4.76 (ddd)	4.17 (dd)	4.33 (dd)	7.74 (d)	8.44 (d)		7.55, 8.25 (m, Ar)
26d	P	6.60 (d)	5.48 (dd)		5.76 (dd)	4.46 (dt)	4.14 (m)	4.14 (m)	7.68 (d)	8.25 (dd)		2.05 (s, OAc)

[a] Solvents are acetone-d_6 (A), $CDCl_3$ (C), DMSO-d_6 (D), and pyridine-d_5 (P). [b] Becoming dd ($J_{6,NH}$ = 2 Hz) at 60° and a sharp doublet with D_2O. [c] Location of 3′-OH confirmed by acetylation which led to a 1.0 ppm downfield shift of $C_{3'}H$. [d] All thymidine derivatives show a roughly 1 Hz allylic coupling of C_5Me.

TABLE II
COUPLING CONSTANTS (cps) FOR COMPOUNDS IN TABLE I

Compd	$J_{1',2'a}$	$J_{1',2'b}$	$J_{2'a,3'b}$	$J_{2',3'}$	$J_{2'b,3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$
2a	2.0			6.5		3.5	5.5	5.5	11.5	8
2b	2.0			6.5		3	5.5	5.5	10	8
4b	6					*a*	4			8
4d	4.5			4.5		*a*	*a*			8
4e	4			*a*		*a*	*a*	*a*	*a*	8
5b	2.5			6		3	6	7	11	
5c	2			6		3	6	7	10	
6b	5.5			5.5		4	4			
7a	5			5		5	5	5	12	
7b	4.5			4.5		4.5	5	4.5	11	
8a	2.5			*a*		*a*	*a*	*a*	*a*	8
8b	4			*a*		*a*	5	5	*a*	7
9b	3.5			5.0	*a*	*a*	*a*	*a*	*a*	8
9c	3.0			*a*		*a*	*a*	*a*	*a*	7.5
10b	6.0	6.0	13	6.0	4.0	4.0	4			8
14b	6	6		6	6	5	2.5	2.5	11	
14c	6	6	14	7	6	5	3	2.5	12	
15a	3	7	16	1	1.5	*a*	4.5	6.5	10	
15b	4	7.5	15	2	6	3.5	*a*	*a*	*a*	
16a	6.5	6.5		6.5	6.5	*a*	*a*	*a*	*a*	
16b	6	6		6	6	*a*	2	2		
17a	4	8	15	1	6.5	3.5	6	6		
17b	3.5	8	16	1	6	3	7.5	6	10	
18a	6.5	6.5	*a*	3	3	3.5	5	5		
18c	7.5			*a*		5	4	4		
24b	5	5		5	5	5	*a*	*a*	*a*	8
25	7			4.5		*a*	*a*	*a*	*a*	8
26b	4			*a*		*a*	*a*	*a*	*a*	8
26c	3.5			5		6	3	3	12	8
26d	5			6		6	5.5	5.5		8

[a] Not resolved.

Anal. Calcd for $C_{11}H_{14}N_3O_5Cl$ (303.7): C, 43.50; H, 4.64; N, 13.83; Cl, 11.67. Found: C, 43.18; H, 4.39; N, 13.82; Cl, 11.65.

5'-Chloro-5'-deoxycytidine (9c).—Concentrated ammonium hydroxide (17.5 ml) was added to a solution of **9b** (1.06 g, 3.5 mmol) in methanol (17.5 ml) and briefly warmed to obtain a clear solution. After 10 min at 23° the mixture was evaporated to dryness and crystallized from methanol, giving 890 mg (97%) of **9c**, mp 163.5–164.5° (reported[10] mp 160–168° dec), $\lambda_{max}^{pH\ 1}$ 213 mμ (ε 9600), 279 (12,400).

Anal. Calcd for $C_9H_{12}N_3O_4Cl$ (261.67): C, 41.31; H, 4.62; N, 16.06; Cl, 13.55. Found: C, 41.10; H, 4.68; N, 15.93; Cl, 13.43.

N^4-Benzoyl-5'-chloro-2',5'-dideoxycytidine (10b).—A solution of **10a** (658 mg, 2 mmol),[26] triphenylphosphine (1.5 g, 6 mmol), and CCl_4 (1.5 g, 10 mmol) in DMF (30 ml) was kept at 23° for 16 hr and then evaporated to dryness after addition of methanol (5 ml). The dried residue, which contained one major product by tlc, was purified by preparative tlc on three plates using chloroform–methanol (19:1). Elution of the major band (R_f 0.4) gave only 68 mg (10%) of **10b**, which was recrystallized from methanol, mp >300°, λ_{max}^{MeOH} 260 mμ (ε 23,000), 304 (10,000).

Anal. Calcd for $C_{16}H_{16}N_3O_4Cl$ (349.75): C, 54.94; H, 4.61; N, 12.01. Found: C, 54.56; H, 4.52; N, 12.00.

5'-Chloro-5'-deoxy-2',3'-*O*-isopropylideneinsoine (5b).—A solution of **5a** (308 mg, 1 mmol), triphenylphosphine (524 mg, 2 mmol), and CCl_4 (0.5 ml) in DMF (10 ml) was kept at 23° for 12 hr and then evaporated to dryness after addition of methanol. The residue was chromatographed on a column containing 100 g of Merck silicic acid deactivated with 6% water using a gradient of 0–10% methanol in chloroform. Evaporation of the pooled major peak and crystallization from methanol gave 260 mg (80%) of **5b**, mp 201–201.5° (reported[15] mp 195°), λ_{max}^{MeOH,H^+} 250 mμ (ε 10,800).

Anal. Calcd for $C_{13}H_{15}N_4O_4Cl$ (326.7): C, 47.78; H, 4.63; N, 17.15. Found: C, 47.54; H, 4.73; N, 17.05.

5'-Bromo-5'-deoxy-2',3'-*O*-isopropylideneinosine (5c).—A reaction between **5a** (616 mg, 2 mmol), triphenylphosphine (1.05 g, 4 mmol), and CBr_4 (664 mg, 2 mmol) in dimethylacetamide (10 ml) was worked up after 16 hr exactly as above for **5b**. The product in the major peak following triphenylphosphine oxide was crystallized from methanol, giving 365 mg (49%) of **5c**, mp 201–203° dec (reported[15] mp 194°), λ_{max}^{MeOH,H^+} 250 mμ (ε 9200).

Anal. Calcd for $C_{13}H_{15}N_4O_4Br$ (317.2): C, 42.06; H, 4.07; N, 15.09. Found: C, 41.87; H, 4.16; N, 15.03.

N^1,N^6-2'-*O*,3'-*O*-Tetrabenzoyl-5'-chloro-5'-deoxyadenosine (6b).—A solution of **6a** (1.32 g, 2 mmol),[21] triphenylphosphine (1.51 g, 6 mmol), and CCl_4 (0.84 ml, 8 mmol) in DMF (16 ml) was kept at room temperature for 24 hr. After addition of methanol the solvent was evaporated and the residue was purified by preparative tlc using benzene–ethyl acetate (2:1). Elution of the major band gave 1.20 g (86%) of **6b**, mp 155.5–156.5° after recrystallization from methanol, λ_{max}^{MeOH} 231 mμ (ε 39,900), 274 (20,700).

Anal. Calcd for $C_{38}H_{28}N_5O_7Cl$ (702.10): C, 65.00; H, 4.02; N, 9.98. Found: C, 64.99; H, 3.88; N, 9.84.

N^6-Benzoyl-5'-chloro-5'-deoxyadenosine (7a) and 5'-Chloro-5'-deoxyadenosine (7b).—Concentrated ammonium hydroxide (8 ml) was added to a solution of **6b** (520 mg) in methanol (50 ml). After 3 hr at 23° the mixture was evaporated to dryness and the residue was crystallized from methanol, giving 130 mg (46%) of **7a**, mp 166.5–167.5°, λ_{max}^{MeOH} 230 mμ (ε 13,200), 279 (19,000).

Anal. Calcd for $C_{17}H_{16}N_5O_4Cl$ (389.80): C, 52.38; H, 4.14; N, 17.97. Found: C, 52.18; H, 4.23; N, 17.88.

A separate sample of **6b** (720 mg) was treated as above for 2 days and then evaporated to dryness. Two recrystallizations from methanol gave 198 mg (68%) of **7b**, mp 140–165° (reported[10] mp 190° dec), λ_{max}^{MeOH} 258 mμ (ε 13,700).

Anal. Calcd for $C_{10}H_{12}N_5O_3Cl$ (285.69): C, 42.03; H, 4.23; N, 24.51. Found: C, 41.61; H, 4.70; N, 24.78.

Chlorination of 5'-*O*-tritylthymidine (11b).—A solution of **11b** (1.94 g, 4 mmol), triphenylphosphine (1.57 g, 4 mmol), and CCl_4 (0.84 ml, 8 mmol) in DMF (10 ml) was kept at 23° for 24 hr, diluted with methanol, and evaporated to dryness. Preparative tlc using methylene chloride–ethyl acetate (3:2) separated triphenylphosphine oxide from two major faster products. Elution of the faster band gave 300 mg (15%) of 3'-chloro-3'-deoxy-5'-*O*-tritylthymidine (**14b**), mp 144–146° from methanol–acetone, λ_{max}^{MeOH} 266 mμ (ε 9500).

Anal. Calcd for $C_{29}H_{27}N_2O_4Cl$ (503.0): C, 69.25; H, 5.41; Cl, 7.05. Found: C, 69.14; H, 5.55; Cl, 7.15.

Elution of the slower band and rechromatography using carbon tetrachloride–acetone (2:1) gave 700 mg (35%) of homogeneous 1-(3-chloro-2,3-dideoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**15a**), mp 203–205° from chloroform–hexane, λ_{max}^{MeOH} 265 mμ (ε 9600).

Anal. Calcd for $C_{29}H_{27}N_2O_4Cl$ (503.0): C, 69.25; H, 5.41; N, 5.57. Found: C, 69.14; H, 5.48; N, 5.44.

3′-Chloro-3′-deoxy-5′-*O*-tritylthymidine (14b).—A solution of O^2,3′-anhydro-1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)-thymine (476 mg, 1 mmol)[1] and anhydrous pyridine hydrochloride (460 mg, 4 mmol) in DMF (10 ml) was kept at 23° for 4 days. After evaporation of the solvent, the residue was dissolved in chloroform, washed with water, dried, and evaporated to dryness. Crystallization from methanol gave 341 mg (70%) of **14b** identical in all ways with that above.

1-(3-Chloro-3-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (15a).—A solution of **14d** (594 mg, 1 mmol) and lithium chloride (425 mg, 10 mmol) in DMF (10 ml) was heated at 100° for 30 min. The cooled solution was evaporated and the residue was dissolved in chloroform, filtered, and purified by preparative tlc using chloroform–ethyl acetate (65:35). The major slower moving band was eluted and crystallized from chloroform–hexane, giving **15a** (250 mg, 50%) that was identical with **15a** above by melting point and nmr spectroscopy.

3′-Chloro-3′-deoxythymidine (14c).—A suspension of **14b** (300 mg) in 80% acetic acid (10 ml) was heated at 100° for 30 min, giving a clear solution that was evaporated to dryness. Preparative tlc using ethyl acetate gave a major band containing 170 mg (75%) of **14c**, mp 181–182° from acetone–hexane,[48] λ_{max}^{MeOH} 266 mμ (ε 10,200).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.04; H, 5.11; N, 10.75.

1-(3-Chloro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (15b).—Treatment of **15a** (700 mg) with 80% acetic acid exactly as for **14b** above gave 300 mg (83%) of **15b** as a homogeneous syrup, $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 9100).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.49; H, 5.25; N, 11.07.

3′-Deoxy-3′-iodo-5′-*O*-*p*-nitrobenzoylthymidine (14a).—A solution of **11a** (300 mg, 0.76 mmol), triphenylphosphine (300 mg, 1.1 mmol), and iodine (254 mg, 1 mmol) in DMF (10 ml) was kept at 23° for 14 days and then evaporated to dryness. The residue was dissolved in chloroform, washed with aqueous sodium thiosulfate, and chromatographed on a column of silicic acid using a gradient (0–50%) of ethyl acetate in chloroform. Evaporation of the major peak and crystallization from chloroform–hexane gave 180 mg (47%) of **14a**, mp 154–156°, identical with an authentic sample.

Chlorination of Thymidine.—A solution of thymidine (1.94 g, 8 mmol), triphenylphosphine (6.3 g, 24 mmol), and CCl_4 (4 ml, 40 mmol) in DMF (30 ml) was kept at 23° for 10 days and then evaporated to dryness after addition of methanol. The residue (12 g) was dissolved in ethyl acetate and, after removal of 4 g of tripheny phosphine oxide, chromatographed on a column of silic acid (500 g). Elution with chloroform and then chloroform–ethyl acetate gave a total of 3.6 g of material contaminated with triphenylphosphine oxide. Preparative tlc using carbon tetrachloride:acetone (2:1) gave two main nucleoside-containing bands. Elution of the faster band and crystallization from ethanol gave 100 mg (5%) of 3′,5′-dichloro-3′,5′-dideoxythymidine (**16a**), mp 150–152° (reported[29] mp 150–151°), λ_{max}^{MeOH} 265 mμ (ε 9400), 205 (9000).

Anal. Calcd for $C_{10}H_{12}N_2O_3Cl_2$ (279.13): C, 43.03; H, 4.33; N, 10.04. Found: C, 43.16; H, 4.32; N, 10.19.

Elution of the major, slower band gave 1.4 g (63%) of 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**17a**), mp 144–145° from chloroform–hexane, λ_{max}^{MeOH} 267 mμ (ε 9700), 210 (9300).

Anal. Calcd for $C_{10}H_{12}N_2O_3Cl_2$ (279.12): C, 43.03; H, 4.33; N, 10.03; Cl, 25.40. Found: C, 43.20; H, 4.44; N, 10.10; Cl, 25.28.

Bromination of Thymidine.—A solution of thymidine (1.94 g, 8 mmol), triphenylphosphine (6.30 g, 24 mmol), and CBr_4 (8.00 g, 24 mmol) in DMF (20 ml) was kept at room temperature for 7 days, diluted with methanol, and evaporated to dryness. Addition of ethyl acetate to the residue led to immediate separation of 1.96 g of crystalline **19** (see below). The filtrate was evaporated and applied to a column containing 1 kg of silicic acid. Elution with chloroform and then chloroform–ethyl acetate (9:1 and then 3:1) removed triphenylphosphine oxide with the later fractions also containing a thymidine derivative. These fractions were evaporated, dissolved in ethyl acetate, filtered to remove further phosphine oxide, and purified by preparative tlc using carbon tetrachloride–acetone (2:1) Elution of the major band gave 350 mg (12%) of 3′,5′-dibromo-3′,5′-dideoxythymidine (**16b**), mp 158–159° from chloroform–hexane (reported[30] mp 159°), λ_{max}^{MeOH} 266 mμ (ε 9800).

Further elution of the column with chloroform–ethyl acetate (3:1) gave 102 mg (4%) of pure 1-(3,5-dibromo-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**17b**), mp 146–147° from chloroform–hexane, λ_{max}^{MeOH} 265 mμ (ε 9800), 206 (10,400).

Anal. Calcd for $C_{10}H_{12}N_2O_3Br_2$ (368.05): C, 32.63; H, 3.29; N, 7.61. Found: C, 33.08; H, 3.29; N, 7.42.

Continued elution of the column with acetone gave 1.42 g (60%) of crystalline 5′-bromo-5′-deoxythymidine (**18a**), mp 157–158° dec from methanol–ethyl acetate (reported[30] mp 154 and 129°), λ_{max}^{MeOH} 266 mμ (ε 9800), 207 (10,200).

Anal. Calcd for $C_{10}H_{13}N_2O_4Br$ (305.14): C, 39.36; H, 4.29; N, 9.18; Br, 26.19. Found: C, 39.47; H, 4.42; N, 9.38; Br, 26.16.

Acetylation of **18a** using acetic anhydride in pyridine–DMF gave the 3′-*O*-acetyl derivative (**18b**), mp 158.5–159.5° from chloroform–hexane. The nmr spectrum showed a downfield shift of 0.63 ppm for $C_{3'}H$ relative to **18a** while the other sugar protons remained essentially unchanged.

Anal. Calcd for $C_{12}H_{15}N_2O_5Br$: C, 41.51; H, 4.36; N, 8.07 Found: C, 41.21; H, 4.56; N, 7.95.

***N,N,N′,N′*-Tetramethylacrylamidinium Bromide (19).**—The crystalline material (1.96 g, 22%) which separated from the bromination of thymidine above was recrystallized from acetone–methanol, mp 163–164°, and shown to be a 2:1 complex of **19** and carbon tetrabromide. It moved as a monocharged cation on electrophoresis at pH 7.5. The presence of free CBr_4 was confirmed by quantitative glc using a column of 3% OVI on Gas-Chrom Q[49] at 90° and by the mass spectrum of **19**, which was identical with that of CBr_4: λ_{max}^{MeOH} 310 mμ (ε 33,900), 218 (4800); nmr (DMSO-d_6) 3.08 and 3.26 (s, 6, NMe_2), 5.43 (t, 1, J = 11 Hz, C**H**=CH_2), 7.79 ppm (d, 2, J = 11 Hz, CH=C**H**$_2$).

Anal. Calcd for $C_7H_{15}N_2Br \cdot {}^1/_2CBr_4$: C, 24.15; H, 4.05; N, 7.51; Br, 64.28. Found: C, 24.09; H, 4.04; N, 8.23; Br, 63.99.

***N,N,N′,N′*-Tetramethyl-2-bromoacrylamidinium Bromide (20). A. Using a 1:1 Ratio.**—Addition of CBr_4 (8 g, 24 mmol) to a solution of triphenylphosphine (6.4 g, 24 mmol) in DMF (40 ml) led to an exothermic reaction and separation of a crystalline material. After 24 hr this material (600 mg) was collected and recrystallized from methanol, giving 330 mg of **20** as a 2:1 complex with carbon tetrabromide: mp 204–205°; λ_{max}^{MeOH} 325 mμ (ε 35,100), 218 (6000); nmr (DMSO-d_6) 3.34 and 3.50 (s, 6, NMe_2), 8.31 ppm (s, 2, CBr=C**H**$_2$).

Anal. Calcd for $C_7H_{14}N_2Br_2 \cdot {}^1/_2CBr_4$: C, 19.93; H, 3.12; N, 6.20. Found: C, 19.99; H, 3.16; N, 6.20.

Evaporation of the filtrates from above and crystallization from methanol–ethyl acetate gave 1.0 g of yellow crystals that contained several minor impurities upon electrophoretic examination at pH 7.5. Several recrystallizations from methanol gave pure **19** identical with that above. Crystallization from methanol–benzene of the evaporated mother liquors after removal of **19** gave 1.07 g of dimethylamine hydrobromide,[50] mp 130–135°, identical in every way with an authentic sample. Finally, the mother liquors were partitioned between water and benzene and the organic phase was crystallized to give 6.0 g of triphenylphosphine oxide, mp 155–156°.

B. Using a 2:1 Ratio.—Carbon tetrabromide (4 g, 12 mmol) was added to a solution of triphenylphosphine (6.4 g, 24 mmol) in 30 ml of DMF giving an exothermic reaction which turned brown. After storage for 4 hr at 5° and then at −18° for 48 hr the mixture was filtered under nitrogen and the solid was washed with ethyl acetate, giving 2.5 g of yellow crystals. This was

(48) Very recently a preparation of **14c** was described by G. Etzold, R. Hintsche, G. Kowollik, and P. Langen, *Tetrahedron*, **27**, 2463 (1971). The reported melting point of 171–172° is considerably lower than that we report above.

(49) Applied Science Laboratories, Inc., State College, Pa.

(50) Dimethylamine hydrobromide has recently been isolated during unsuccessful attempts to brominate adenosine derivatives with triphenylphosphine and bromine in DMF: S. G. Verenikina, E. G. Chauser, and A. M. Yurkevich, *Zh. Obshch. Khim.*, **4**, 1630 (1971).

dissolved in methanol to destroy any triphenylphosphine dibromide, evaporated, extracted into ethyl acetate, and crystallized from methanol–ethyl acetate, giving 1.0 g of **19** identical with that above.

5′-*O*-Acetyl-2′-chloro-2′-deoxyuridine (24b).—Triphenylphosphine (1.048 g, 4 mmol) was added in four portions after 2, 4, 6, and 24 hr to a solution of **24a** (572 mg, 2 mmol)[37] and CCl_4 (1 ml) in DMF (10 ml). After 72 hr the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc using two developments with chloroform–methanol (93:7). The major nucleoside band was eluted and rechromatographed using CCl_4–acetone (1:1), giving 230 mg (38%) of **24b**, mp 137–138° from acetone, λ_{max}^{MeOH} 258 mμ (ε 9600).

Anal. Calcd for $C_{11}H_{13}N_2O_6Cl$ (304.7): C, 43.36; H, 4.30; N, 9.20. Found: C, 43.26; H, 4.26; N, 9.77.

Brief treatment of this compound with methanolic sodium methoxide gave 2′-chloro-2′-deoxyuridine (**24c**), mp 205–206° from methanol (reported[35a] mp 207–212° dec) and in all ways identical with an authentic sample prepared by an independent route.[35a]

Chlorination of Uridine.—A solution of uridine (488 mg, 2 mmol), triphenylphosphine (1.6 g, 6 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 23° for 5 days, evaporated to dryness, and separated by preparative tlc using chloroform–methanol (9:1). Two bands moving slower than triphenylphosphine oxide were obtained. Elution of the faster band gave 380 mg (68%) of 2′,5′-dichloro-2′,5′-dideoxyuridine (**25**),[51] mp 159–161° from chloroform–hexane, λ_{max}^{MeOH} 258 mμ (ε 9800).

Anal. Calcd for $C_9H_{10}N_2O_4Cl_2$ (281.10): C, 38.45; H, 3.58; Cl, 25.22. Found: C, 38.42; H, 3.77; Cl, 25.33.

Elution of the slower band gave 90 mg (17%) of 5′-chloro-5′-deoxyuridine (**4e**), mp 173–175° from acetone (reported[9] mp 170–172°), λ_{max}^{MeOH} 260 mμ (ε 10,300).

Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.66): C, 41.15; H, 4.22; N, 10.67. Found: C, 40.96; H, 4.29; N, 10.66.

The identical compounds were also obtained by hydrolysis of **2a** with 90% formic acid at 20° for 18 hr.

Chlorination of N^4-Benzoylcytidine (26a).—A solution of **26a** (694 mg, 2 mmol),[36] triphenylphosphine (1.57 g, 6 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (15 ml) was kept at 23° for 24 hr. Further portions (262 mg each) of triphenylphosphine were added after 1, 2, and 3 days and after a total of 4 days the mixture was evaporated to dryness. The residue was stirred with benzene–ether (1:1) which dissolved most of the triphenylphosphine oxide, leaving 1.3 g of insoluble material which was separated into two bands by preparative tlc using chloroform–methanol (9:1). Elution of the faster band gave 314 mg (41%) of N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (**26c**), mp 165.5–167.5° from methanol, λ_{max}^{MeOH} 261 mμ (ε 25,200), 303 (10,200).

Anal. Calcd for $C_{16}H_{15}N_3O_4Cl_2$ (384.25): C, 50.01; H, 3.95; N, 10.93. Found: C, 49.51; H, 3.94; N, 10.88.

Elution of the slower band gave 220 mg (30%) of N^4-benzoyl-5′-deoxycytidine (**26b**), mp 216–218° from methanol, λ_{max}^{MeOH} 260 mμ (ε 24,300), 304 (ε 10,500)

Anal. Calcd for $C_{16}H_{16}N_3O_5Cl$ (365.77): C, 52.53; H, 4.41; N, 11.48. Found: C, 52.44; H, 4.35; N, 11.61.

3′-*O*-Acetyl-N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (26d).—A solution of **26c** (38 mg, 0.1 mmol), acetic anhydride (0.3 ml), and pyridine (0.03 ml) in DMF (0.3 ml) was kept at 23° for 2 hr, evaporated to dryness, and coevaporated three times with toluene. Two crystallizations from acetone–hexane gave 28 mg (65%) of **26d**, mp 192–193°, $\lambda_{max.}^{MeOH}$ 261 mμ (ε 26,100), 301 (9600).

Anal. Calcd for $C_{18}H_{17}N_3O_5Cl_2$ (426.29): C, 50.71; H, 4.01; N, 9.85. Found: C, 50.85; H, 4.18; N, 9.54.

3-*O*-Formyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (27b).—Triphenylphosphine (655 mg, 2.5 mmol) was added portionwise over 48 hr to a solution of **27a** (269 mg, 1 mmol) and CCl_4 (1 ml) in DMF (5 ml) at which point tlc using CCl_4–acetone (9:1) showed the reaction to be complete. Evaporation of the solvent and preparative tlc was accompanied by considerable degradation. A relatively pure fraction (110 mg, 38%) of **27b** was, however, isolated and shown to be identical with an authentic sample prepared as below by tlc, nmr, and ir spectra.

An authentic sample of **27b** was prepared by treating **27a** (260 mg, 1 mmol) with formic acid (0.2 ml) and acetic anhydride (0.4 ml in pyridine (10 ml) for 4 days at −18°. After careful evaporation of the solvent, the residue was distilled in a short-path apparatus, bp 100° (10^{-3} mm): ν_{max} (neat) 1740 cm^{-1}; nmr ($CDCl_3$) 1.29 (s, 6, CMe_2), 1.39 and 1.50 (s, 3, CMe_2), 4.07 (m, 2, C_6H_2), 4.20 (m, 2, C_4H and C_5H), 4.53 (d, 1, $J_{1,2}$ = 4 Hz, C_2H), 5.35 (br s, 1, C_3H), 5.87 (d, 1, $J_{1,2}$ = 4 Hz, C_1H), 8.10 ppm (s, 1, OCHO).

Anal. Calcd for $C_{13}H_{20}O_7$ (288.29): C, 54.16; H, 6.99. Found: C, 53.84; H, 7.20.

Reaction of Uridine with Arsenic Trichloride in Dimethylacetamide.—Freshly distilled arsenic trichloride (1.86 g, 10.3 mmol, stored over AW-500 molecular sieve to remove traces of HCl) was added in a dry box to a solution of uridine (2.0 g, 8.2 mmol) in freshly dried (molecular sieve) and distilled dimethylacetamide (25 ml). The resulting solution was heated at 127° for 12 hr and then evaporated to dryness *in vacuo*. The residue was dissolved in water (pH <1), rapidly neutralized to pH 7 with ammonium hydroxide, and evaporated to dryness. The residue was extracted with methanol (10 ml), leaving a non-uv-absorbing residue. The extracts were evaporated to dryness and separated into three major bands (R_f's 0.57, 0.40, and 0.21) by preparative tlc using chloroform–methanol (9:1).[52] Elution of the fastest band gave 500–650 mg (four experiments) of material that was rechromatographed using either methylene chloride–acetone (55:45) or chloroform–methanol (4:1). Considerable degradation occurred during the two purifications, the major unchanged material (220 mg) being identified as 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**29**), which was identical with an authentic sample[44] by melting point (128–130°, reported mp 127–130°), nmr, and ir spectra. One of the degradation products was chromatographically identical with 5′-*O*-acetyl-2′-chloro-2′-deoxyuridine (**24b**), and in one experiment 2′-chloro-2′-deoxyuridine, mp 204–206°, was isolated in crystalline form and its structure confirmed by its nmr and ir spectra. The original middle band contained 150–250 mg of a mixture of 2′-chloro-2′-deoxyuridine (**24c**) and its 3′-*O*- and 5′-*O*-monoacetyl derivatives. Elution of the slowest band gave 1.4–1.5 g of a syrup that was rechromatographed on two plates using chloroform–methanol (4:1). The faster band contained 1 g (43%) of 5′-*O*-acetyluridine, which was crystallized from methanol giving 800 mg of **24a**, mp 163–163.5°, identical in every way with an authentic sample.[37] The mother liquor contained some 5′-chloro-5′-deoxyuridine (**4e**). The slower band gave 500 mg (25%) of unreacted uridine.

Registry No.—**2a**, 19556-51-5; **2b**, 19556-52-6; **2c**, 14671-65-9; **4b**, 34627-49-1; **4d**, 19556-55-9; **4e**, 19556-54-8; **5b**, 21017-03-8; **5c**, 31698-26-7; **6b**, 34627-54-8; **7a**, 34627-55-9; **7b**, 892-48-8; **8a**, 34627-57-1; **8b**, 34627-58-2; **9b**, 34627-59-3; **9c**, 31652-78-5; **10b**, 34627-61-7; **14a**, 14260-81-2; **14b**, 34627-62-8; **14c**, 25526-94-7; **15a**, 34627-64-0; **15b**, 34627-65-1; **16a**, 14260-86-7; **16b**, 34627-67-3; **17a**, 34627-68-4; **17b**, 34627-69-5; **18a**, 25905-51-5; **18b**, 34647-05-7; **18c**, 25905-50-4; **19**, 34627-43-4; **20**, 34627-44-6; **24b**, 34627-72-0; **25**, 34627-73-1; **26b**, 34627-74-2; **26c**, 34627-75-3; **26d**, 34627-76-4; **27b**, 34627-77-5; triphenylphosphine oxide, 791-28-6.

(51) The configuration at $C_{2'}$ of **25** was confirmed by preparation of the identical compound *via* reaction of **24c** (131 mg, 0.5 mmol) with triphenylphosphine (140 mg, 0.25 mmol) and CCl_4 (0.11 ml, 1.1 mmol) in DMF (1.5 ml) for 16 hr. Preparative tlc and crystallization from chloroform gave 115 mg (82%) of **25** identical with that above.

(52) The relative positions of the bands was similar to that obtained using 1-butanol–water (86:14)[9] but the resolution was better.