Halo Sugar Nucleosides. II.[1] Iodination of Secondary Hydroxyl Groups of Nucleosides with Methyltriphenoxyphosphonium Iodide[2]

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The reactions of 5′-protected derivatives of thymidine with methyltriphenoxyphosphonium iodide in DMF at room temperature leads to the formation of the corresponding 3′-deoxy-3′-iodonucleosides with retention of configuration. This has been shown to occur *via* the very rapid formation of an intermediate O²,3′-cyclonucleoside which is subsequently opened by iodide ion. The reaction of **1** with the *cis*-vicinal diol grouping in 5′-protected uridine derivatives does not give iodinated products but rather a mixture of 2′(3′)-O-methylphosphonates which has also been prepared from the nucleoside and methylphosphonic acid in the presence of dicyclohexylcarbodiimide. Specific synthesis of uridine 3′-O-methylphosphonate and of the 2′- and 3′-O-methylphosphonate esters of 1-(β-D-arabinofuranosyl)uracil are also reported from methylphosphonic acid and the appropriately blocked nucleosides. The reaction of 2′,5′-di-O-trityluridine and **1** has been examined in both DMF at 25° and in hot benzene. In DMF the major product was the expected 1-(3-deoxy-3-iodo-2,5-di-O-trityl-β-D-xylofuranosyl)uracil, and there was also some selective hydrolysis of the 5′-O-trityl substituent. In benzene there was also inversion of configuration during iodination and an unexpected selective loss of the 2′-O-trityl group during work-up. Attempted reaction of 1-(2,5-di-O-trityl-β-D-xylofuranosyl)uracil with **1** in hot benzene gave a plethora of products from which only a pair of phosphorus diastereoisomers of 1-(β-D-xylofuranosyl)uracil 3′-O-(phenyl methylphosphonate) could be isolated after acidic hydrolysis. In DMF, however, slow iodination occurred giving 3′-deoxy-3′-iodo-2′,5′-di-O-trityluridine. Iodination of 3′-O-acetyluridine in DMF was not accompanied by acetyl migration and gave 3′-O-acetyl-2′,5′-dideoxy-2′,5′-diiodouridine.

In a previous paper[1] we have described the very facile iodination of the primary 5′-hydroxyl group of pyrimidine ribo- or deoxyribonucleosides through reaction with methyltriphenoxyphosphonium iodide (**1**).[3] Such reactions in dimethylformamide (DMF) are very rapid and give the corresponding 5′-deoxy-5′-iodonucleosides in high yield within a few minutes at room temperature. Attempted use of this iodination reaction with purine nucleosides, however, leads predominantly to the formation of the corresponding N³,5′-cyclonucleosides. In this paper we present the results of our studies on the reaction of **1** with secondary hydroxyl groups in various types of nucleosides.

The reaction of 5′-O-p-nitrobenzoylthymidine (**2a**)[4] with **1** in DMF required roughly 10 hr at 23° to reach completion and gave crystalline 3′-deoxy-3′-iodo-5′-O-*p*-nitrobenzoylthymidine (**5a**) in 85% yield. This product, with retention of configuration at $C_{3'}$, is perhaps unexpected since the generally accepted mechanism of the Rydon reaction[1,3] calls for inversion of configuration leading to the *threo* iodide (**6**). The *erythro* configuration was confirmed by synthesis of the same compound (**5a**) *via* *p*-nitrobenzoylation of 3′-deoxy-3′-iodothymidine (**5d**) obtained from 3′-O-mesyl-5′-O-tritylthymidine *via* the O²,3′-cyclonucleoside **4b**.[5,6] In a similar way, iodination of 5′-O-acetylthymidine (**2b**) with **1** in DMF gave 5′-O-acetyl-3′-deoxy-3′-iodothymidine (**5b**), mild alkaline hydrolysis of which gave the known **5d**. Further confirmation of the stereochemistry of the iodination reaction came from the reaction of 5′-O-tritylthymidine (**2c**) with **1** which gave a 67% yield of crystalline 3′-deoxy-3′-iodo-5′-O-tritylthymidine (**5c**) which was identical with an authentic sample *via* a different route.[5,6]

The observed retention of configuration is explained by the reaction sequence **2** → **5** involving displacement of the phenoxyphosphonium ion from **3** as diphenyl methylphosphonate and formation of the O²,3′-cyclothymidine (**4**). Subsequent opening of **4** by iodide then gives the observed *erythro* iodide (**5**). Similar interventions of O²,3′-cyclonucleosides have been invoked to explain retention of configuration during displacement of 3′-O-mesyl functions by halides,[5,6] azide,[7] carboxylate,[8] and imide[9] ions.

Direct confirmation of this idea came from examination of the reactions after short periods of time. Thus, after only 5 min of reaction between **2a** and **1**, tlc showed the complete absence of **2a** and the formation of 5′-O-*p*-nitrobenzoyl-O²,3′-cyclothymidine (the conjugate base of **4a**) which was isolated crystalline in 53% yield. The identical compound was also obtained *via* *p*-nitrobenzoylation of O²,3′-cyclothymidine (**4c**). As the reaction of **2a** and **1** was allowed to proceed the gradual disappearance of **2a** and the formation of **5a** could be readily followed by tlc. In a similar way, the reaction of 5′-O-tritylthymidine (**2c**) with **1** in either DMF or pyridine led to very rapid disappearance of the starting material and isolation of the crystalline O²,3′-cyclonucleoside (conjugate base of **4b**)[10] in 70% yield.

While iodination of 5′-O-tritylthymidine did give the 3′-iodo derivative (**5c**) in 67% yield, some loss of the trityl group occurred and led to the formation and isolation of a small amount of 3′,5′-dideoxy-3′,5′-diiodothymidine (**7a**). The same diiodothymidine (**7a**) was also obtained in 76% yield by direct iodination of thymidine with an excess of **1**, and a similar reaction with deoxyuridine gave 2′,3′,5′-trideoxy-3′,5′-diiodouridine (**7b**) in 84% yield. The configuration of the 3′-iodo function in **7a** and **7b** is based upon analogy with the above results and the nmr spectra of these compounds. Examination of the nmr spectra of many different 3′-substituted thymidine analogs has shown that, in those compounds with the *erythro* configuration, the $C_{2'}$ protons have very similar chemical shifts and

(1) For part I, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).

(2) A preliminary account of part of this work has appeared: J. P. H. Verheyden and J. G. Moffatt, *J. Amer. Chem. Soc.*, **86**, 2093 (1964).

(3) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 224 (1953).

(4) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).

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

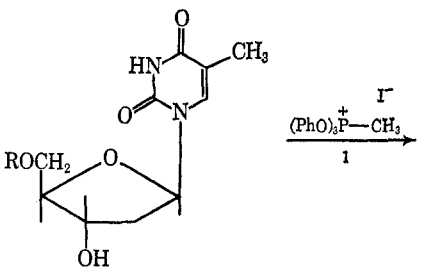
(6) K. E. Pfitzner and J. G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).

(7) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, **29**, 2076 (1964).

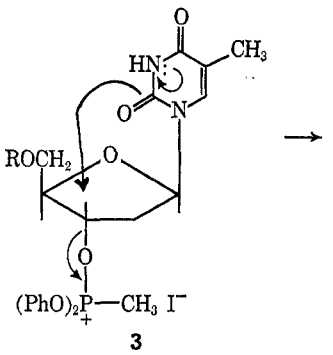
(8) J. J. Fox and N. C. Miller, *ibid.*, **28**, 936 (1963).

(9) N. C. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964).

(10) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).



2a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = trityl



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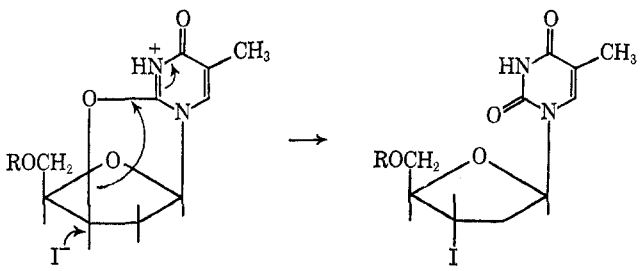
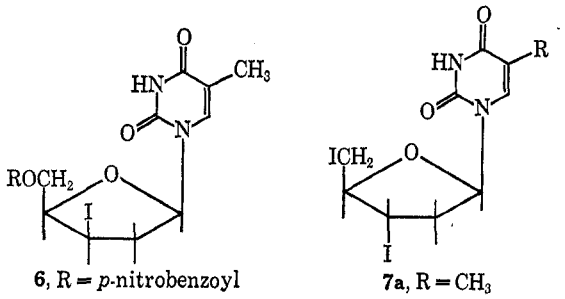


4a, R = nitrobenzoyl
b, R = trityl
c, R = H

5a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = trityl
d, R = H



6, R = *p*-nitrobenzoyl

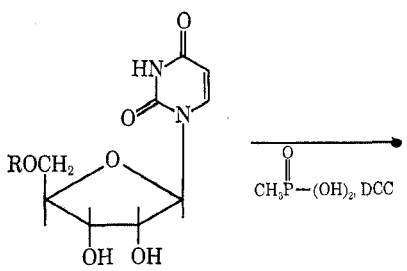
7a, R = CH_3
b, R = H

frequently occur as overlapping signals. In contrast, the $C_{2'}$ protons in compounds having the *threo* configuration have markedly different chemical shifts and are separated from each other by 0.5–1 ppm. A second differentiation can be made from the appearance of the $C_{1'}$ proton although this is likely to be less reliable than the above. In compounds with the *erythro* configuration, the coupling constants between $C_{1'}H$ and the two $C_{2'}$ protons ($J_{1',2'a}$ and $J_{1',2'b}$) are very similar and $C_{1'}H$ appears as a triplet while, in the *threo* compounds, $J_{1',2'a}$ and $J_{1',2'b}$ are different and $C_{1'}H$ appears as a quartet. A complete survey of the nmr data upon which these generalities are based will be described shortly.[11]

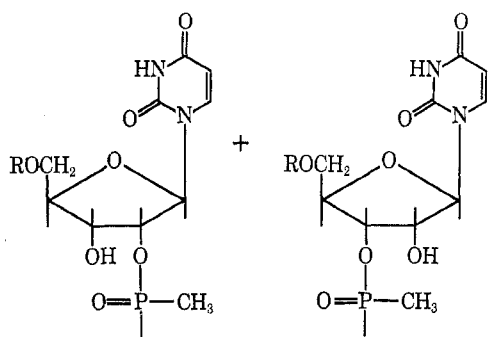
(11) J. P. H. Verheyden and J. G. Moffatt, unpublished results.

The observed partial loss of a trityl group in the reaction above is probably a consequence of the release of hydrogen iodide during formation of the cyclonucleoside (**4b**). Comparable loss of acid labile protecting groups during iodination of primary hydroxyl groups has not been noted since acidic by-products are not formed. Loss of the trityl group could be prevented by addition of 2 molar equiv of pyridine to the reaction mixture. Under these conditions, the formation of the $O^2,3'$-cyclonucleoside (**4b**) was still very rapid, but its subsequent opening by iodide ion was considerably retarded. Such an observation is entirely consistent with the known requirement for acid catalysis during opening of cyclonucleosides.[8] Acid catalysis by phenol, which is also released during reactions of **1**, does not seem to be sufficient for this purpose since prolonged treatment of **4b** with 2 equiv each of sodium iodide and phenol in DMF led to no apparent reaction. On the other hand, the reaction of free $O^2,3'$-cyclothymidine (**4c**) with **1** in DMF readily gave the crystalline diiodo compound **7a** in 58% yield. Since the latter reaction was run on a microscale it is entirely possible that the presence of traces of water led to hydrolysis of **1** with formation of the required acid. Indeed, the reaction of **4b** with pyridine hydriodide in DMF at 25° for 2 days gave **5c** in high yield.

The iodination of free *cis*-vicinal hydroxyl groups does not appear to be feasible using the reagent **1** although, as will be seen shortly,[11] some related halogenating agents may be satisfactorily employed. The reaction of 5′-O-*p*-nitrobenzoyluridine (**8a**) with **1** in anhydrous DMF gave no indication of the formation of



8a, R = *p*-nitrobenzoyl
b, R = acetyl



9a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = H

10a, R = *p*-nitrobenzoyl
b, R = acetyl
c, R = H

less polar products. In addition to unreacted **8a**, the major product was an extremely polar material that was shown to be a monoanion by paper electrophoresis at pH 3 or 7.6. Following hydrolysis of the *p*-nitrobenzoyl group from this substance a mixture of uridine

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF NUCLEOSIDE METHYLPHOSPHONATES[a]

	C_5H	C_6H	$C_{1'}H$	$C_{2'}H$, $C_{3'}H$, and $C_{4'}H$[b]	$C_{5'}H_2$	PCH_3
9c + 10c	5.98 (d, 8 Hz)	7.92 (d, 8 Hz)	5.94 (d, 5 Hz)[c]	4.1–4.6 (m)	3.88 (m)	1.28 (d, 16 Hz)
	5.91 (d, 8 Hz)	7.89 (d, 8 Hz)				1.33 (d, 16 Hz)
10c	5.90 (d, 8 Hz)	7.88 (d, 8 Hz)	5.93 (d, 5 Hz)	4.1–4.6 (m)	3.88 (m)	1.32 (d, 17 Hz)
19b	5.87 (d, 8 Hz)	7.87 (d, 8 Hz)	6.19 (d, 4 Hz)	4.1–4.6 (m)	3.91 (m)	1.34 (d, 17 Hz)
22	5.87 (d, 8 Hz)	7.81 (d, 8 Hz)	6.29 (d, 5 Hz)	4.1–4.5 (m)	3.85 (m)	1.14 (d, 17 Hz)

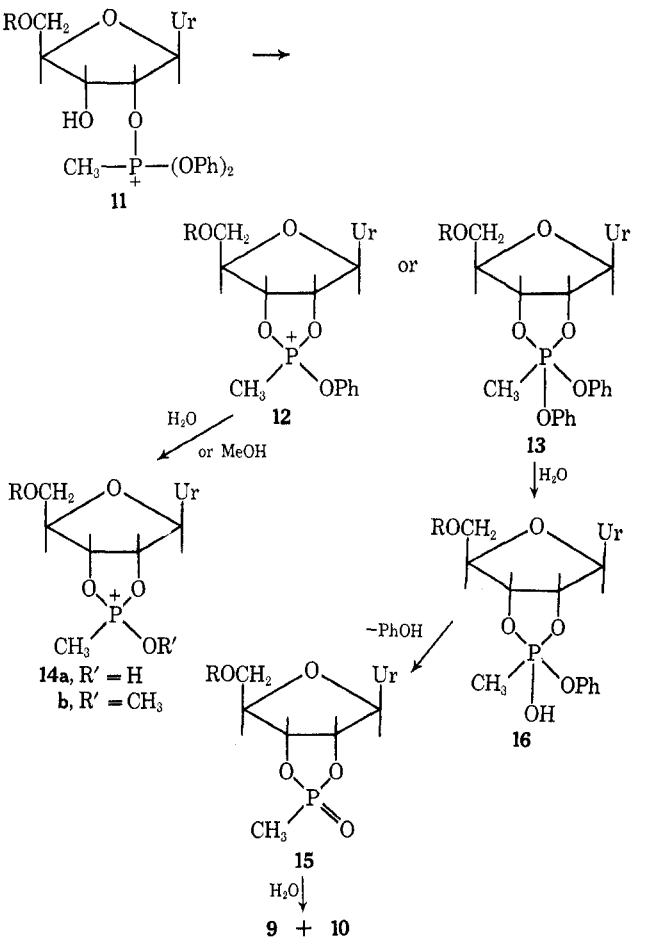
[a] Determined in D_2O at 100 MHz relative to an internal standard of 2,2-dimethyl-2-silapentane 5-sulfonate. [b] The $C_{2'}H$,$C_{3'}H$, and $C_{4'}H$ are usually superimposed upon each other and upon the HDO signal. In the case of **22** the $C_{2'}H$ signal was clearly resolved at 80° and appeared as an octet with $J_{1',2'} = 4$ Hz, $J_{2',3'} = 3$ Hz, and $J_{P,H} = 9$ Hz. [c] The second, lower intensity doublet is superimposed upon the C_5H and $C_{1'}H$ signals and cannot be precisely assigned.

2′(3′)-O-methylphosphonates (**9c**, **10c**)[12] was isolated by ion-exchange chromatography. An identical mixture was obtained by reaction of **8a** with methylphosphonic acid in the presence of dicyclohexylcarbodiimide.[13] Unexpectedly, the *p*-nitrobenzoyl group was hydrolyzed from the resulting compounds (**9a**, **10a**) during ion-exchange chromatography and a mixture of the free 2′(3′)-O-methylphosphonates (**9c**, **10c**) was once again obtained. Loss of the *p*-nitrobenzoyl group was avoided by use of preparative tlc on microcrystalline cellulose and the protected derivatives (**9a**, **10a**) were isolated and shown to be chromatographically and electrophoretically identical with the products from **8a** and **1** prior to hydrolysis.

The two isomers **9c** and **10c** could not be separated by paper or ion-exchange chromatography but could be distinguished by nmr spectroscopy since the C_5H, C_6H, and PCH_3 resonances appeared as pairs of doublets in a ratio of roughly 2:1 (see Table I). Definitive assignments of the observed resonances to each isomer could be made following a specific synthesis of the 3′-O-methylphosphonate ester (**10c**) from 2′,5′-di-O-(4-methoxytetrahydropyran-4-yl)uridine[14] and methylphosphonic acid in the presence of DCC and showed the 3′ ester to be the major isomer. Since the signal due to $C_{1'}H$ of the minor isomer could not be readily assigned, it was impossible to further confirm this conclusion using the empirical rules of Fromageot, *et al.*[15]

Very similar results were obtained from the reaction of 5′-O-acetyluridine (**8b**) with **1** which gave a mixture of 5′-O-acetyluridine 2′(3′)-O-methylphosphonates (**9b**, **10b**) and the corresponding deacetylated products (**9c**, **10c**) that were indistinguishable from the products from the carbodiimide condensation of **8b** and methylphosphonic acid.

The formation of **9c** and **10c** can be explained *via* attack of the *cis*-vicinal hydroxyl on the initial adduct (**11** or its 3′ isomer) giving **12** or **13**. Hydrolysis of **12** or **13** can then give the cyclic phosphonate **15** *via* either **14a** or **16**, and further rapid hydrolysis would then lead to the observed 2′(3′)-O-methylphosphonates. Alternatively, the accumulated **12** could react with methanol during work-up of the reaction giving a methoxyphosphonium compound (**14b**) which could undergo rapid dealkylation by iodide ion once again forming **15**.



The above mechanism appears to require the accumulation of a cyclic intermediate (**12** or **13**) which undergoes decomposition only during work-up of the reaction. Since acylic oxyphosphonium salts such as **3** are known to undergo intramolecular displacement with formation of O^2,3′-cyclothymidine derivatives, it would appear likely that **12** could also undergo attack at $C_{2'}$ by the 2-carbonyl group of the uracil ring with formation of the O^2,2′-cyclouridine 3′-O-(phenyl methylphosphonate) (**18b**).[16] There were, however, no observable neutral products of this sort formed during reaction of

(12) It has previously been noted that the reaction of vicinal diols with **1** leads to acidic products that were assumed to be phosphites [J. B. Lee and M. M. El Sawi, *Chem. Ind. (London)*, 839 (1960)] but were later referred to as phosphonates [J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966)].

(13) A similar preparation of 6-azauridine 2′(3′)-O-methylphosphonate has been described by A. Holy, *Collect. Czech. Chem. Commun*, **32**, 3713 (1967).

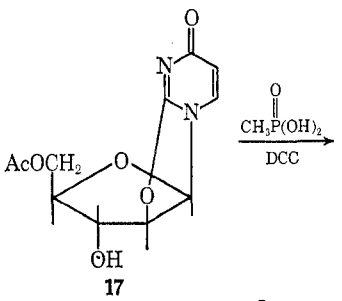
(14) C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Amer. Chem. Soc.*, **89**, 3366 (1967). We are very grateful to Dr. N. P. Damodaran of this laboratory for a sample of this compound.

(15) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, J. E. Sulston, and D. R. Trentham, *Tetrahedron*, **22**, 705 (1966).

(16) Other work from this laboratory has shown that the related 2′,3′-acetoxonium ion of uridine undergoes specific attack at $C_{2'}$ by the 2-keto group giving 3′-O-acetyl-O^2,2′-cyclouridine; see S. Greenberg and J. G. Moffatt, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, Abstract C54.

8a with 1, and the absence of the hydrolysis product 1-(β-D-arabinofuranosyl)uracil 3′-O-methylphosphonate (19b) in the isolated products (9c, 10c) was confirmed by nmr spectroscopy. The apparent lack of attack by the uracil ring in 12 is perhaps due to a decreased electrophilicity of the alkoxy groups ($C_{2'}$ or $C_{3'}$) relative to those in alkoxydiphenoxyphosphonium species such as 3. Even less electrophilic character is shown by trialkoxyphosphonium salts as indicated by the high temperatures required for the Arbusov reaction which involves dealkylation by iodide ion.[17]

A synthesis of the authentic arabinoside 19b was achieved through the condensation of 5′-O-acetyl-O^2,2′-cyclouridine (17)[18] with methylphosphonic acid using DCC and gave the 3′-O-methylphosphonate (18a) which was hydrolyzed with acid and then with ammonium hydroxide giving 19b in an overall yield of 97% from 17. The preparation of 17 was conveniently achieved in 89% yield through reaction of 5′-O-acetyl-2′-O-tosyluridine[19] with triethylamine in pyridine under reflux for 2 hr. Under these conditions there was no loss of the acetyl group and no formation of the isocytosine derivatives which accompany the use of methanolic ammonia.[20] Selective hydrolysis of the acetyl group from 17 can be accomplished by treatment with methanolic triethylamine at 37° which leads to direct crystallization of O^2,2′-cyclouridine in 90% yield.



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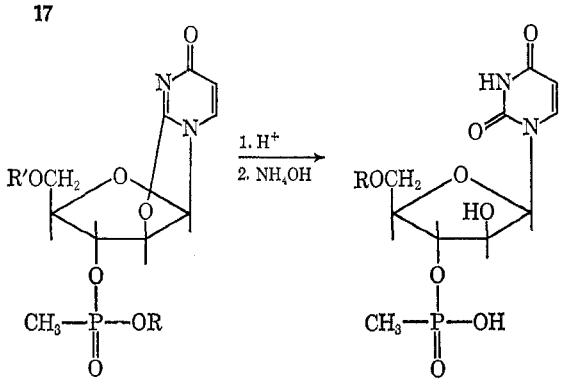
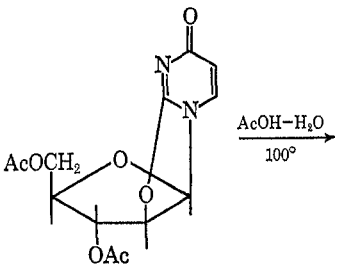


18a, R = H; R′ = acetyl
b, R = C_6H_5; R′ = p-nitrobenzoyl

19a, R = acetyl
b, R = H

The synthesis of 1-(β-D-arabinofuranosyl)uracil 2′-O-methylphosphonate (22) was also accomplished *via* treatment of 3′-5′-di-O-acetyl-O^2,2′-cyclouridine (20)[18] with 50% acetic acid giving crystalline 1-(3,5-di-O-acetyl-β-D-arabinofuranosyl)uracil (21). Under these conditions there was relatively little solvolysis of the cyclonucleoside leading to compounds with the *ribo* configuration as shown by borate electrophoresis following hydrolysis of the acetyl groups from the crude reaction mixture. Subsequent condensation of 21 with methylphosphonic acid in the presence of DCC followed by hydrolysis of the acetyl groups gave 22 in 87% yield.



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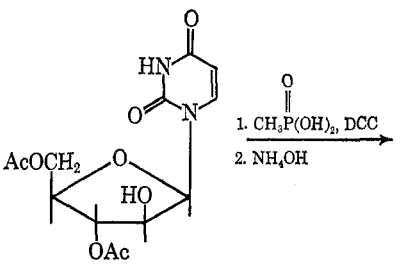

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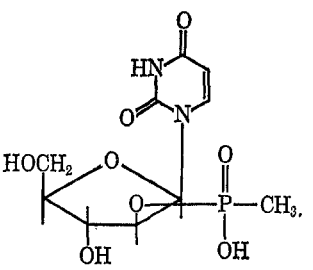

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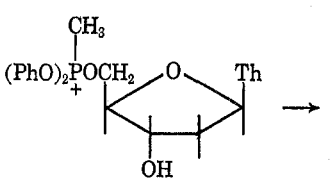
Another somewhat related case of intramolecular participation by a free hydroxyl group was observed during selective iodination of the 5′-hydroxyl group of thymidine with 1.[1] During this reaction a compound which we have characterized by nmr and mass spectrometry as thymidine 3′,5′-cyclic methylphosphonate (25) was isolated in 3% yield. This suggests attack by the 3′-hydroxyl group upon the phosphorus atom of the initial 5′-alkoxyphosphonium intermediate (23) with formation of the cyclic phosphonium salt (24) or the related phosphorane (*cf.* 12 or 13) which decomposes during work-up giving 25. Being a six-membered cyclic phosphonate, 25 does not undergo further hydrolysis to acidic products as did the five-membered analog 15.



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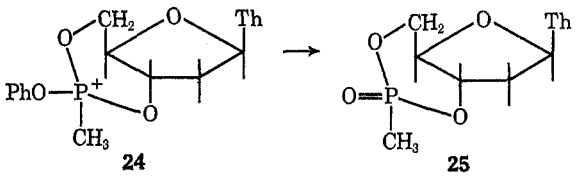
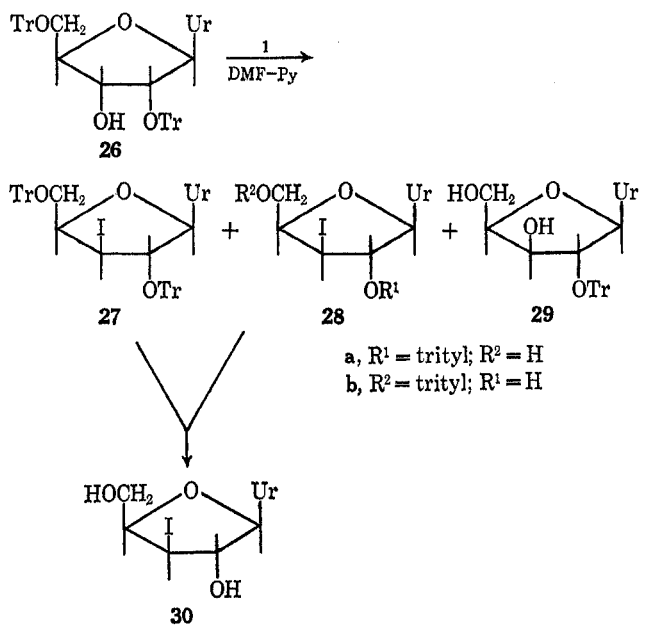


24 25

(17) G. M. Kosolapoff, *Org. React.*, **6**, 273 (1951).
(18) D. M. Brown, D. B. Parihar and A. R. Todd, *J. Chem. Soc.*, 4242 (1958).
(19) D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).
(20) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *ibid.*, 3028 (1958).

Recently, Johnston[21] reported that the reactions of both 2′,5′-di-O-trityluridine (**26**) and 1-(2,5-di-O-trityl-β-D-xylofuranosyl)uracil (**31**) with **1** in benzene at 50° for 18 hr give the 3′-deoxy-3′-iodo derivative (**27**) with the *xylo* configuration. Neither **27** nor its detritylated derivative (**30**) was obtained in pure form and the structures were deduced by hydrogenolysis of **30** to give 3′-deoxyuridine and by its conversion into O²,2′-cyclouridine upon treatment with base. While the known reluctance of uridine derivatives to form O²,3′-cyclo derivatives.[22,23] offers a tentative explanation for the observed inversion of configuration during conversion of **26** to **27**, the reason for the reported retention of configuration during the reaction with **31** remains obscure.

In our hands the reaction of **26** with **1** was carried out both in benzene at 50° according to Jonhston and in DMF at room temperature in the presence of a little pyridine to minimize the hydrolysis of trityl groups. The reaction in DMF for 24 hr contained three major tritylated uridine derivatives which were isolated by preparative tlc giving crystalline 1-(3-deoxy-3-iodo-2,5-di-O-trityl-β-D-xylofuranosyl)uracil (**27**, 32%), 1-(3-deoxy-3-iodo-2-O-trityl-β-D-xylofuranosyl)uracil (**28a**, 12%), and 1-(2-O-trityl-β-D-xylofuranosyl)uracil (**29**, 15%). The isolation of these compounds required quite extensive chromatography and hence the yields, which are of analytically pure material, are probably not optimal. Hydrolysis of either **27** or **28** with acetic acid gave the same noncrystalline 3′-deoxy-3′-iodonucleoside (**30**) which gave O²,2′-cyclouridine almost



quantitatively upon reaction with 0.05 *N* ethanolic potassium hydroxide presumably *via* the 2′,3′-*ribo*-epoxide. These results appear to confirm the overall inversion of configuration reported by Johnston during iodination of **26** in hot benzene. The selective loss of the 5′-O-trityl group during formation of **28a** and **29** is of some interest and was confirmed by nmr spectroscopy in DMSO-d_6 which showed the free hydroxyl group of **28a** as a triplet at 4.94 ppm clearly demonstrating it to be primary in nature. In a similar way, the 3′ and 5′ hydroxyls of **29** appear as an exchangeable doublet and triplet at 5.08 and 4.65 ppm, respectively. The inversion of configuration of the hydroxyl group during formation of **29** strongly suggests that at least some O²,3′-cyclonucleoside was formed during this reaction and subsequently underwent hydrolysis during work-up. In the presence of pyridine it is probably not surprising that this hindered cyclonucleoside did not undergo detectable opening by iodide ion.

A comparable reaction between **26** and **1** in benzene at 50° as described by Johnston[21] appeared to give the same ditrityl iodo compound (**27**) when an aliquot of the crude reaction mixture was examined by tlc. When the reaction was worked up, however, there was selective loss of the 2′-O-trityl group and syrupy 1-(3-deoxy-3-iodo-5-O-trityl-β-D-xylofuranosyl)uracil (**28b**) was isolated in 41% yield together with only 7% **27**. The aqueous phase during work-up of the reaction was only slightly acidic (pH 3–4) and the reason for the consistent and specific loss of the 2′-O-trityl group remains obscure. The isomeric monotrityl derivatives **28a** and **28b** were clearly resolved from each other by tlc and once again the presence of only a free 2′-hydroxyl group in **28b** was confirmed by its nmr spectrum in DMSO. The nmr spectrum of **28b** in $CDCl_3$ was remarkably different and indicated extensive conformational changes (see Experimental Section). Since pure **1** has only poor solubility in benzene, the reaction mixture was never homogeneous even when using twice the amount of solvent specified by Johnston.[21] A comparable reaction in refluxing benzene for 17 hr gave similar results with isolation of 52% **28b** and only a trace of **27**. Acidic hydrolysis of either **27** or **28b** gave **30** which was chromatographically identical with that from the reaction in DMF and subsequent alkaline treatment once again gave O²,2′-cyclouridine.

No reason is apparent for the selective loss of the 5′-O-trityl group during the reaction in DMF and of the 2′-O-trityl group in the benzene reaction. Model experiments on the reaction of **26** with about 1 molar equiv of trifluoroacetic acid in benzene and in DMF clearly showed that hydrolysis to a mixture of uridine and monotrityl uridine rapidly occurred in benzene but not in DMF. No clear-cut preference for removal of a specific trityl group could be discerned.

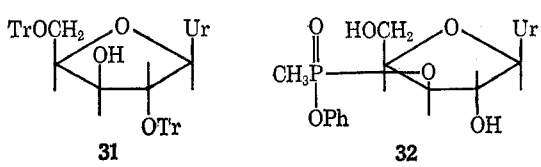
Recent work by Kitugawa, *et al.*,[24] has shown that, while 2′,5′-di-O-trityl-O²,3′-cyclouridine does not react with sodium iodide and benzoic acid, more acidic conditions leading to loss of trityl groups result in the formation of 1-(5-deoxy-5-iodo-β-D-xylofuranosyl)uracil *via* an interesting series of rearrangements. The iodination reactions reported above give products with the 3′-deoxy-3′-iodo *xylo* configuration and thus do not involve the intermediacy of O²,3′-cyclonucleosides. In the case of the 5′-hydroxy-3′-iodo compound **28a** there is no question from the nmr spectrum that the 5′-hydroxyl group is free, and hence unexpected rearrangements such as observed by Kitugawa, *et al.*,[24] did not occur.

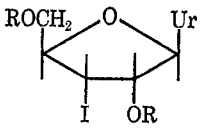
The reaction of 1-(2,5-di-O-trityl-β-D-xylofuranosyl)-uracil (**31**)[22] with **1** was also examined in both benzene

(21) G. A. R. Johnston, *Aust. J. Chem.*, **21**, 513 (1968).
(22) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961).
(23) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961).
(24) (a) K. Kitugawa and T. Ukita, *Chem. Pharm. Bull.*, **17**, 775 (1969); (b) K. Kitugawa, M. Schino, and T. Ukita, *ibid.*, **17**, 785 (1969).

and DMF. In benzene under the conditions described by Johnston[21] at least ten significant ultraviolet absorbing products, many of which contained trityl groups, were present and no effort was made to separate and characterize them. Following acidic hydrolysis of the crude mixture, the number of resolved spots was considerably reduced but only a very faint spot had the same mobility as **30**. Two compounds were isolated, albeit in quite low yield, by preparative tlc and both of these were shown to contain phosphorus. While neither was analytically pure, they could be tentatively identified by nmr spectroscopy as the phosphorus diastereoisomers of 1-(β-D-xylofuranosyl)uracil 3′-O-(phenyl methylphosphonate) (**32**). The *xylo* configuration for compounds **32** is based primarily upon the mechanism that we have proposed for the formation of phenyl methylphosphonate esters from hindered alcohols and **1**.[1] It is difficult to conceive of a mechanism involving inversion of configuration during phosphonate formation, and the small amount of **32** available has prevented any serious effort at providing a chemical confirmation of the proposed structure.

The reaction of **31** with **1** in DMF behaved in quite a different fashion. The reaction appeared to be very slow and even after 7 days at 37° unreacted **31** was the predominant product. The reagent **1** was, however, still present and rapidly iodinated a sample of 2′,3′-O-isopropylideneuridine added to a small aliquot. After 8 days, even after further addition of **1**, unreacted **31** was still the major component and the mixture was worked up. Once again there was extensive loss of a trityl group during the work-up since very little unreacted **31** was then present and the major product isolated by preparative tlc was 1-(2-O-trityl-β-D-xylofuranosyl)uracil (**29**) which was obtained in 47% yield. A ditrityl iodonucleoside was also obtained in 15% yield and found to have a melting point vastly different from that of *xylo* compound **27**. The two compounds were clearly distinguishable by tlc and by their nmr spectra and the product from the DMF reaction is considered to be 3′-deoxy-3′-iodo-2′,5′-di-O-trityluridine (**33a**). Thus, in this case, where the intermediacy of cyclonucleosides was not possible, iodination did take place with inversion of configuration. Hydrolysis of the trityl groups from **33a** led to quite unexpected complications. Under the same conditions used without difficulty for **27** or **28** pure **33a** gave 3′-deoxy-3′-iodouridine (**33b**), uracil, a monotrityl-3′-deoxy-3′-iodo-



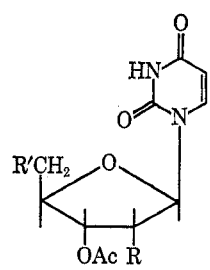


33a, R = trityl
b, R = H

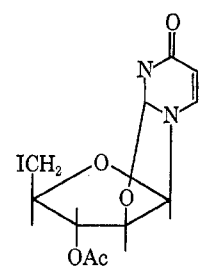
uridine, and uridine in a molar ratio of 6:3:1:1. The free uridine definitely had the *ribo* configuration as shown by borate electrophoresis and the reason for the formation of this compound and of uracil remains unknown. Treatment of **33b** with ethanolic potassium hydroxide under the same conditions used to convert **30** into O²,2′-cyclouridine gave only unreacted **33b** and a trace of uracil. This is consistent with the known difficulty in preparing O²,3′-cyclouridine derivatives[22,23] and further supports the *ribo* configuration for **33**.

Thus, while the reaction of **31** in benzene is so complex that we cannot exclude the formation of 3′-deoxy-3′-iodo *xylo* compounds, we have no evidence for iodinated products with other than the expected *ribo* configuration in DMF.

Johnston has also reported that iodination of 3′,5′-di-O-acetyluridine with **1** in benzene at 50° is accompanied by acetyl migration and leads to a mixture of 2′-deoxy-2′-iodo and 3′-deoxy-3′-iodo derivatives. We have, however, successfully iodinated 3′-O-acetyluridine (**34a**)[25] with **1** in DMF without detectable acetyl migration. Prior to this experiment we showed by nmr spectroscopy that **34a** undergoes no detectable acetyl migration during storage in DMF for 24 hr. The reaction of **34a** with **1** in DMF was followed by tlc which showed that after 15 min the nucleoside had completely disappeared, being converted into a less polar material with a uridine spectrum (presumably **34b**) and a more polar product with a typical O²,2′-cyclouridine spectrum (**35**). During the next few



34a, R; R′ = OH
b, R = OH; R′ = I
c, R; R′ = I
d, R; R′ = H



35

hours the former disappeared and was sequentially replaced by **35** and the final product, 3′-O-acetyl-2′,5′-dideoxy-2′,5′-diiodouridine (**34c**), which was ultimately isolated as a homogeneous syrup in 46% yield. In order to prove convincingly that acetyl migration had not occurred, this material was hydrogenolyzed and the nmr spectrum of the resulting product was taken without any purification. The resulting spectrum was clearly that of pure 3′-O-acetyl-2′,5′-dideoxyuridine (**34d**) without the presence of any detectable isomers. The nmr spectrum of analytically pure **34d** was identical with that of the crude hydrogenolysis product prior to any work-up. This experiment convincingly shows that iodination in DMF can be achieved without complications due to acyl migration.

The results reported in this and the previous paper[1] clearly point out the versatility of **1** as a reagent for use in nucleoside chemistry and we will shortly report on a variety of reactions involving the iodonucleosides prepared in the present work.

(25) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).

Experimental Section

General methods are described in the previous paper.[1]

3′-Deoxy-3′-iodo-5′-O-*p*-nitrobenzoylthymidine (5a).—A solution of 5′-O-*p*-nitrobenzoylthymidine (391 mg, 1 mmol)[4] and **1** (1 g, 2 mmol) in anhydrous DMF (10 ml) was stored at 25° for 24 hr. Methanol (2 ml) was added and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate, extracted with aqueous sodium thiosulfate and water, dried (Na_2SO_4), and evaporated *in vacuo* giving a syrup that was chromatographed on two preparative tlc plates using chloroform–ethyl acetate (3:2). The major ultraviolet-absorbing band was eluted with acetone giving 514 mg of a homogeneous syrup that was crystallized from chloroform–hexane giving 425 mg (85%) of **5a** with mp 154–155°: λ_{max}^{MeOH} 261 mμ (ε 21,700); nmr ($CDCl_3$) 1.81 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.86 (q, 2, $J_{1',2'}$ = 5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 4.5–5.6 (m, 4, $C_{3'}H$, $C_{4'}H$, $C_{5'}H_2$), 5.97 (t, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.13 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H), 8.27 (s, 4, Ar), 9.32 (br s, 1, NH).

Anal. Calcd for $C_{17}H_{16}N_3O_7I$: C, 40.73; H, 3.22; N, 8.38. Found: C, 40.88; H, 3.14; N, 8.21.

The identical compound was obtained from 3′-deoxy-3′-iodothymidine (86 mg, 0.25 mmol)[5,6] and *p*-nitrobenzoyl chloride (51 mg, 0.27 mmol) in pyridine.

5′-O-*p*-Nitrobenzoyl-O²,3′-cyclothymidine (4a).—5′-O-*p*-Nitrobenzoylthymidine (391 mg, 1 mmol) and **1** (1 g, 2 mmol) were allowed to react in DMF (1.5 ml) at 25° for 15 min. Addition of ethanol and cooling to −15° gave 130 mg of **4a** as very pale yellow needles. The evaporated mother liquors were partitioned between water and ethyl acetate and further amounts of **4a** were separated from both phases (total yield 197 mg, 53%). This compound is extremely insoluble and could only be recrystallized from hot DMSO–ethanol giving 170 mg of white needles of mp 252–254°: λ_{max}^{MeOH} 254 mμ (ε 19,900); mass spectrum (70 eV) *m/e* 373 (M^+), 247 (M − thymine), 206 (M − *p*-$NO_2C_6H_4COOH$), 167 (*p*-$NO_2C_6H_4COOH$), 126 (thymine).

Anal. Calcd for $C_{17}H_{15}N_3O_7$: C, 54.69; H, 4.05; N, 11.26. Found: C, 54.63; H, 4.09; N, 11.21.

The identical compound was also obtained by reaction of O²,3′-cyclothymidine (10 mg) with *p*-nitrobenzoyl chloride (18 mg) in a mixture of DMF (0.5 ml) and pyridine (0.01 ml). Pure **4a** (8 mg, 47%) crystallized directly from the reaction medium with mp 252–254°.

The ethyl acetate phase from the above reaction (0.93 g) was purified by preparative tlc using two developments with chloroform–ethyl acetate (3:2) giving 160 mg (32%) of **5a** with mp 154–155°.

5′-O-Acetyl-3′-deoxy-3′-iodothymidine (5b).—5′-O-Acetylthymidine (171 mg, 0.6 mmol) and **1** (271 mg, 0.6 mmol) were allowed to react as above in DMF (5 ml). Chromatography on a column of neutral alumina using methylene chloride–methanol (19:1) followed by crystallization from methylene chloride–ether–hexane gave 120 mg (50%) of **5b** with mp 134–135°: λ_{max}^{MeOH} 266 mμ (ε 10,600); nmr ($CDCl_3$) 1.94 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.15 (s, 3, OAc), 2.7–2.9 (m, 2, $C_{2'}H_2$), 4.15 (m, 1, $C_{3'}H$), 4.40 (m, 1, $C_{4'}H$), 4.47 (d, 2, $J_{4',5'}$ = 2 Hz, $C_{5'}H_2$), 6.11 (q, 1, $J_{1',2'a}$ = 4 Hz, $J_{1',2'b}$ = 6 Hz, $C_{1'}H$), 7.34 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Anal. Calcd for $C_{12}H_{15}N_2O_5I$: C, 36.56; H, 3.84; N, 7.12. Found: C, 36.81; H, 4.06; N, 7.13.

Treatment of **5b** (60 mg) with 0.2 *N* sodium hydroxide in 80% methanol for 30 min followed by neutralization with Dowex 50 (H^+) resin and crystallization from water gave 38 mg (72%) of **5d** with mp 165.5–166° (lit.[6] mp 166°): nmr (pyridine-d_5) 1.87 ppm (d, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.65 (q, 2, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.71 (m, 2, $C_{5'}H_2$), 4.1–4.5 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.23 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 6.14 (t, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.76 (q, $J_{allylic}$ = 1.5 Hz, C_6H); mass spectrum (70 eV) *m/e* 352 (M^+), 334 (M − H_2O), 227 (M − thymine), 226 (thymine).

5′-O-Trityl-O²,3′-cyclothymidine (4b).—5′-O-Tritylthymidine (970 mg, 2 mmol) and **1** (1.0 g, 2 mmol) were reacted with anhydrous pyridine for 1 hr. After addition of methanol (1 ml) the solvent was evaporated *in vacuo* and ethyl acetate was added giving a yellow precipitate that was shown to be a mixture of N-methylpyridinium iodide and pyridine hydriodide. The filtrate was washed with dilute sodium thiosulfate and water, dried, and evaporated. Addition of ether gave 655 mg (70%) of pure **4b** which was recrystallized from methanol and melted at 148–153°, resolidified at 200°, and remelted at 225–227° much as described by Horwitz, *et al.*:[10] λ_{max}^{MeOH} 250 (sh, ε 8600) 227 mμ (sh, ε 15,000); ORD (MeOH) positive Cotton effect with a peak at 276 mμ (Φ +9900°), crossover at 264 mμ and a trough at 245 mμ (Φ −23,800°); nmr ($CDCl_3$) 1.88 ppm (d, 3, C_5Me), 2.32 (hex, 1, J_{gem} = 13 Hz, $J_{1',2'a}$ = 3.5 Hz, $J_{2'a,3'}$ = 3.5 Hz, $C_{2'a}H$), 2.68 (q, 1, J_{gem} = 13 Hz, $J_{2'b,3'}$ = 0.5 Hz, $J_{1',2'b}$ = 0 Hz, $C_{2'b}H$), 3.35 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.26 (hex, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 7 Hz, $C_{4'}H$), 5.09 (br s, 1, $C_{3'}H$), 5.49 (d, 1, $J_{1',2'a}$ = 3.5 Hz, $C_{1'}H$), 6.95 (q, $J_{allylic}$ = 1.5 Hz, C_6H), 7.2–7.5 (m, 15, Ar).

3′-Deoxy-3′-iodo-5′-O-tritylthymidine (5c).—5′-O-Tritylthymidine (1.21 g, 2.5 mmol) and **1** (2.4 g, 5 mmol) were dissolved in DMF (20 ml). After 15 min tlc (chloroform–ethyl acetate, 65:35) showed almost complete conversion to **4b** which was then slowly converted to **5c**. After 24 hr methanol (5 ml) was added and the reaction was worked up as usual. The chloroform soluble material was dissolved in methanol (5 ml) from which 994 mg (67%) of **5c** crystallized with mp 158–159° (lit.[5,6] mp 147–148°, but samples of material with both melting points had identical infrared, nmr, and ultraviolet spectra): λ_{max}^{MeOH} 267 mμ (ε 10,200); nmr ($CDCl_3$) 1.50 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.77 ppm (q, 2, $J_{1',2'}$ = 5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.51 (m, 2, $C_{5'}H_2$), 4.25 (m, 1, $C_{4'}H$), 4.46 (q, 1, $J_{2',3'}$ = 8 Hz, $J_{3',4'}$ = 8 Hz, $C_{3'}H$), 6.12 (t, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.62 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Anal. Calcd for $C_{29}H_{27}N_2O_4I$: C, 58.60; H, 4.68; N, 4.71; I, 21.35. Found: C, 58.56; H, 4.86; N, 4.64; I, 21.14.

Hydrolysis of **5c** with 80% acetic acid at 100° for 15 min gave 3′-deoxy-3′-iodothymidine of mp 166–166.5° (lit.[5,6] 166–167°): nmr (DMSO-d_6) 1.78 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.65 (q, 2, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}H_2$), 3.71 (m, 2, $C_{5'}H_2$), 4.1–4.5 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.23 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 6.14 (t, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.77 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

Preparative tlc (carbon tetrachloride–acetone, 2:1) of the mother liquors from crystallization of **5c** gave 70 mg of the crystalline diiodo compound **7a** (see below).

3′,5′-Dideoxy-3′,5′-diiodothymidine (7a). A.—Thymidine (2.42 g, 10 mmol) and **1** (12 g, 26 mmol) were allowed to react overnight in DMF (100 ml). The usual work-up followed by direct crystallization from chloroform–hexane gave 3.51 g (76%) of **7a** which melted at 74–77°, resolidified as needles, and melted at 121–123°: λ_{max}^{MeOH} 265 mμ (ε 9000); nmr ($CDCl_3$) 1.95 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5CH_3), 2.65–2.90 (m, 2, $C_{2'}H_2$), 3.58 (d, 2, $J_{4',5'}$ = 3 Hz, $C_{5'}H_2$), 4.08 (q, 1, $J_{2',3'}$ = $J_{3',4'}$ = 8 Hz, $C_{3'}H$), 3.92 (hex, 1, $J_{3',4'}$ = 8 Hz, $J_{4',5'}$ = 3 Hz, $C_{4'}H$), 6.18 (q, 1, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 7 Hz, $C_{1'}H$), 7.48 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H), 9.20 (br s, 1, NH); mass spectrum (15 eV) *m/e* 462 (M^+), 335 (M − I), 337 (M − thymine), 206 (M − 2HI), 126 (thymine), and 81 (M − thymine − 2HI).

Anal. Calcd for $C_{10}H_{12}N_2O_3I$: C, 25.99; H, 2.62; N, 6.06; I, 54.93. Found: C, 25.88; H, 2.55; N, 5.96; I, 54.75.

B.—O²,3′-cyclothymidine (6.7 mg, 30 μmol) and **1** (40 mg, 93 μmol) were allowed to react overnight in DMF (0.5 ml) and after addition of methanol the mixture was evaporated to dryness. Preparative tlc using chloroform–acetone (9:1) gave a major band which was eluted and crystallized from chloroform–hexane giving 8 mg (58%) of **7a** identical with that above.

2′,3′,5′-Trideoxy-3′,5′-diiodouridine (7b).—2′-Deoxyuridine (228 mg, 1 mmol) and **1** (1 g, 2 mmol) were allowed to react overnight in DMF (5 ml). After the usual work-up the chloroform-soluble material was chromatographed on a column of silicic acid using a gradient (0–30%) of acetone in chloroform. Crystallization of the major peak from chloroform–hexane gave 375 mg (84%) of **7b** which sintered at 77–80° and melted at 136–139°: λ_{max}^{MeOH} 260 mμ (ε 11,200); nmr ($CDCl_3$) 2.65–2.95 ppm (m, 2, $C_{2'}H_2$), 3.59 (br d, 2, $J_{4',5'}$ = 2.5 Hz, $C_{5'}H_2$), 3.85–4.2 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.80 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.19 (q, $J_{1',2'a}$ = 7 Hz, $J_{1',2'b}$ = 5 Hz, $C_{1'}H$), 7.67 (d, $J_{5,6}$ = 8 Hz, C_6H), 9.55 (br s, 1, NH); mass spectrum (70 eV) *m/e* 337 (M − uracil), 321 (M − I), 210 (M − uracil − I), 112 (uracil), 81 (M − uracil − 2HI).

Anal. Calcd for $C_9H_{10}N_2O_3I_2$: C, 24.13; H, 2.25; N, 6.25. Found: C, 24.37; H, 2.43; N, 6.17.

Uridine 2′(3′)-O-Methylphosphonate (9c, 10c). A.—5′-O-Nitrobenzoyluridine (196 mg, 0.5 mmol)[16] and **1** (0.5 g, 1 mmol) were allowed to react overnight in DMF (2 ml) and after addition of methanol (1 ml), the mixture was evaporated to dryness. The residue was partitioned between water and ether, the aqueous phase (7800 OD units at 260 mμ) being a roughly equal mixture

of unreacted **8a** and a monoanion by paper electrophoresis at pH 7.6. Concentrated ammonium hydroxide (2.5 ml) was added and, after 30 min at 25°, paper electrophoresis showed hydrolysis of the *p*-nitrobenzoyl group to be complete. After partial evaporation of the solvent the solution was applied to a 3 × 30 cm column of DEAE Sephadex (HCO_3^-), washed with water, and eluted with a linear gradient of triethylammonium bicarbonate (4 l., 0.005–0.2 *M*) giving two ultraviolet-absorbing peaks. The second of these, (2140 OD units at 273 mμ, 0.21 mmol), was shown to be *p*-nitrobenzoic acid, while the first (1740 OD units at 260 mμ, 35%) was a chromatographically homogeneous mixture of **9c** and **10c**. The first peak was evaporated to dryness and residual bicarbonate was carefully removed by repeated evaporation with methanol. An aqueous solution of the final residue was passed through a 1 × 10 cm column of Dowex 50 (H^+) resin and the acidic effluent was partially evaporated *in vacuo* prior to neutralization to pH 6 with sodium hydroxide. After evaporation to dryness, the residue was dissolved in methanol (1 ml) and precipitated by addition of acetone (12 ml) giving the sodium salts of **9c** and **10c** (65 mg, 33%) as the trihydrate. After drying *in vacuo* at 60°, the hygroscopic monohydrate was obtained with λ_{max}^{MeOH} 260 mμ (ε 9950); see Table I for nmr.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot H_2O$: C, 33.15; H, 4.45; N, 7.74. Found: C, 33.40; H, 4.50; N, 7.20.

B.—5′-O-*p*-Nitrobenzoyluridine (98 mg, 0.25 mmol), methylphosphonic acid (60 mg, 0.5 mmol),[26] and dicyclohexylcarbodiimide (206 mg, 1 mmol) were dissolved in anhydrous pyridine (4 ml). After 2 hr water (0.5 ml) was added and after a further 30 min the mixture was diluted with water, filtered, evaporated to dryness, and partitioned between water and ether. The aqueous phase was adjusted to pH 8.5 and chromatographed on a 2 × 34 cm column of DEAE Sephadex as above. Two peaks were obtained, the second (2270 OD units at 270 mμ, 91%) being *p*-nitrobenzoic acid[27] and the first (2235 OD units at 260 mμ, 89.5%) being a chromatographically homogeneous mixture of **9c** and **10c**. The latter material was isolated as above giving 80 mg of the sodium salt with identical nmr ultraviolet and chromatographic behavior with that from the material from method A.

5′-O-*p*-Nitrobenzoyluridine 2′(3′)-O-Methylphosphonate (9a, 10a).—A reaction was carried out exactly as above in B except that purification was effected by preparative tlc on microcrystalline cellulose (Avicel) using 1-butanol–acetic acid–water (5:2:3) rather than by ion-exchange chromatography. Elution of the single intense uv-absorbing band with methanol followed by isolation as the sodium salt as above gave 108 mg of the sodium salts of **9a** and **10a** as an off-white solid that was chromatographically homogeneous and identical with the initial product in A or B above: $\lambda_{max}^{H_2O}$ 261 mμ. The elemental analysis indicated the presence of some nonnitrogenous contaminants presumably originating from the cellulose plates.

Uridine 3′-O-Methylphosphonate (10c).—A solution of DCC (300 mg, 1.6 mmol), 2′,5′-di-O-(4-methoxytetrahydropyran-4-yl)uridine (0.37 mmol),[14] and methylphosphonic acid (0.8 mmol) in anhydrous pyridine (5 ml) was kept for 4 hr, and water (2 ml) was then added. The mixture was evaporated to dryness, partitioned between water and ether, and filtered, and the aqueous phase was evaporated to dryness. The residue was treated with 80% acetic acid for 2 hr 25°, evaporated to dryness, adjusted to pH 8, and chromatographed as before on a 2 × 30 cm column of DEAE Sephadex. A single ultraviolet-absorbing peak (3620 OD units at 260 mμ, 97%) was obtained, and **10c** was isolated as above as its sodium salt (125 mg): $\lambda_{max}^{H_2O}$ 260 mμ (ε 10,100); ORD (H_2O) positive Cotton effect with a peak at 282 mμ (Φ +1000°), crossover at 270 mμ and a trough at 251 mμ (Φ −2500°); the nmr spectrum (see Table I) indicated the presence of less than 5% 2′ isomer.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot 2H_2O$: C, 31.59; H, 4.77; N, 7.37. Found: C, 31.19; H, 4.97; N, 6.66.

5′-O-Acetyl-O²,2′-cyclouridine (17).—A solution of 5′-O-acetyl-2′-O-tosyluridine (664 mg, 2.5 mmol)[19] in pyridine (30 ml) and triethylamine (30 ml) was heated under reflux for 2 hr under nitrogen. After evaporation of the solvent, the residue was dissolved in methylene chloride (10 ml) from which 295 mg of pure **17** with mp 166–167° (lit.[18] mp 168–169°) rapidly crystallized. The mother liquors were passed through a 1 × 15 cm column of Dowex-1 (acetate) resin and the effluent was evaporated and crystallized from methanol–ethyl acetate giving a further 65 mg (total yield 89%) of pure **17**. An analytical sample had mp 169–170°: λ_{max}^{MeOH} 225 (ε 8400) and 249 mμ (7700); nmr (DMSO-d_6) 1.92 ppm (s, 3, OAc), 3.97 (d, 2, $J_{4',5'}$ = 5.5 Hz, $C_5{}'H_2$), 4.28 (q, 1, $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 5 Hz, $C_4{}'H$), 4.40 (m, 1, $C_3{}'H$), 5.24 (d, 2, $J_{1',2'}$ = 5.5 Hz, $C_2{}'H_2$), 5.85 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.05 (br s, 1, $C_3{}'OH$), 6.34 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_1{}'H$), 7.88 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H).

O²,2′-Cyclouridine.—A solution of **17** (1.08 g) in methanol (40 ml) and distilled triethylamine (40 ml) was stored at 25° for 4 days during which time O²,2′-cyclouridine (825 mg, 90%) separated as white crystals with mp 235–237° (lit.[20] mp 234–236°) and was identical with an authentic sample.

1-(β-D-Arabinofuranosyl)uracil 3′-O-Methylphosphonate (19b).—A solution of DCC (82 mg, 0.4 mmol), methylphosphonic acid (20 mg, 0.2 mmol), and **17** (26 mg, 0.1 mmol) in anhydrous pyridine (2 ml) was kept for 3 hr at 23°. Water (0.5 ml) was added; the mixture was diluted with water, filtered, evaporated to dryness, and partitioned between water and ether. Upon electrophoresis at pH 7.6, the aqueous phase contained a single ultraviolet-absorbing product with the ultraviolet spectrum of **17**.

This solution was passed through a 1 × 10 cm column of Dowex 50 (H^+) resin and the acidic effluent was concentrated *in vacuo* to roughly 10 ml and heated at 100° for 15 min. At this time, the solution had λ_{max} 262 mμ and concentrated ammonium hydroxide (2 ml) was added. After 1 hr at 25° the solution was evaporated and chromatographed on a 2 × 30 cm column of DEAE Sephadex (HCO_3^-) as before.[28] The single ultraviolet-absorbing peak (972 OD units at 262 mμ, 97% overall from **17**) was isolated as above giving 34 mg of the sodium salt of **19b** as the dihydrate: $\lambda_{max}^{H_2O}$ 262 mμ (ε 10,000); nmr in Table I.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot 2H_2O$: C, 31.59; 4.76; N, 7.37. Found: C, 31.1; H, 4.5; N, 6.6.

1-(3,5-Di-O-acetyl-β-D-arabinofuranosyl)uracil (21).—3′,5′-Di-O-acetyl-O²,2′-cyclouridine (150 mg)[18] was heated at 100° for 1 hr in 50% acetic acid (2 ml) and then evaporated to dryness leaving a froth that was separated by preparative tlc using chloroform–methanol (9:1) into four bands. The fastest band[29] contained 96 mg of a chromatographically pure syrup that was crystallized from benzene–hexane giving 84 mg (53%) of **21** with mp 78–79°: λ_{max}^{MeOH} 258 mμ (ε 10,000); ORD positive Cotton effect with a peak at 278 mμ (Φ +15,700°), crossover at 266 mμ and a trough at 250 mμ (Φ −23,300°); nmr ($CDCl_3$) 2.12 (s, 6, OAc), 4.1–4.3 (m, 1, $C_4{}'H$), 4.32 (q, 1, J_{gem} = 9 Hz, $J_{4',5'a}$ = 4 Hz, $C_5{}'_aH$), 4.51 (q, 1, J_{gem} = 9 Hz, $J_{4',5'b}$ = 4 Hz, $C_5{}'_bH$), 4.66 (q, 1, $J_{1',2'}$ = 3 Hz, $J_{2',3'}$ = 1 Hz, $C_2{}'H$), 5.08 (br s, 1, $C_3{}'H$), 5.55 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.13 (d, 1, $J_{1',2'}$ = 3 Hz, $C_1{}'H$), 7.71 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{16}N_2O_8$: C, 47.55; H, 4.91; N, 8.54. Found: C, 47.28; H, 5.19; N, 8.36.

1-(β-D-Arabinofuranosyl)uracil 2′-O-Methylphosphonate (22).—Dicyclohexylcarbodiimide (83 mg, 0.4 mmol) was added to an anhydrous pyridine solution **21** (33 mg, 0.1 mmol) and methylphosphonic acid (20 mg, 0.2 mmol). After 24 hr the mixture was worked up in the usual way and then treated for 1 hr with dilute ammonium hydroxide prior to chromatography on a column of DEAE Sephadex (HCO_3^-) as above. The single ultraviolet-absorbing peak (870 OD units at 262 mμ, 87%) was isolated as before giving 37 mg of the somewhat hygroscopic sodium salt of **22** which appeared to contain 1 mol equiv of sodium bicarbonate: $\lambda_{max}^{H_2O}$ 262 mμ (ε 9900); ORD positive Cotton effect with a peak at 277 mμ (Φ +18,500), crossover at 261 mμ and a trough at 244 mμ (Φ −19,900); see Table I for nmr data.

Anal. Calcd for $C_{10}H_{14}N_2O_8PNa \cdot NaHCO_3$: C, 28.07; H, 3.53; N, 6.54. Found: C, 27.41; H, 3.32; N, 6.57.

Reaction of 2′,5′-Di-O-trityluridine (26) with 1. A. In DMF.—A solution of **26** (728 mg, 1 mmol) and **1** (678 mg, 1.5 mmol) in DMF (15 ml) containing pyridine (0.4 ml) was kept at 25° for 24 hr. Methanol (2 ml) was added and after 30 min the solvent was evaporated to dryness and the residue was separated by preparative tlc on two plates using two developments with carbon tetrachloride–ethyl acetate (9:1) giving a strong ultra-

(26) A generous gift from the Hooker Chemical Co.

(27) A sample immediately prior to ion-exchange chromatography still maintained its 5′-O-nitrobenzoyl group.

(28) Paper chromatography using 1-butanol–acetic acid–water (5:2:3) showed that roughly half of the acetyl group was lost during acidic hydrolysis of **18a**. R_f values were 0.47 (**17**), 0.09 (**18a**), 0.18 (**19a**), and 0.08 (**19b**).

(29) By hydrolysis with ammonium hydroxide followed by borate electrophoresis[30] the other bands were tentatively identified as a diacetyluridine (26 mg), a monoacetylarabinosyluracil (14 mg), and unchanged **20** (9 mg).

(30) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960).

violet-absorbing band on the origin and a second major band which was partially contaminated with diphenyl methylphosphonate. Rechromatography of the latter band using carbon tetrachloride–ethyl acetate (3:1) gave 310 mg of a homogeneous solid that was crystallized from methanol giving 256 mg (32%) of **27** with mp 146.5–147.5°: λ_{max}^{MeOH} 260 mμ (ε 11,000); nmr ($CDCl_3$) 2.93 ppm (q, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.26 (d, 1, $J_{2',3'}$ = 0 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 3.48 (m, 1, $C_{4'}H$), 3.49 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 6 Hz, $C_{5'b}H$), 4.55 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 5.66 (q, 1, $J_{5,6}$ = 8 Hz, J_{5,N_3H} = 1.5 Hz, C_5H), 6.41 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 7.1–7.6 (m, 30, Ar), 7.65 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 8.98 (br s, 1, N_3H).

Anal. Calcd for $C_{47}H_{39}N_2O_5I$: C, 67.31; H, 4.68; N, 3.34. Found: C, 67.27; H, 4.62; N, 3.16.

Rechromatography of the band on the origin of the original plates using two developments with chloroform–methanol (93:7) gave two major products. The faster of these was eluted giving 70 mg (12%) of **28a** as a homogeneous syrup with λ_{max}^{MeOH} 260 mμ (ε 9600); nmr ($CDCl_3$) 3.46 (br s, 1, $C_{3'}H$), 3.5–3.85 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.51 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{2'}H$), 5.69 (d, 1, $J_{5,6}$ = 8.5 Hz, C_5H), 6.43 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.68 (d, 1, $J_{5,6}$ = 8.5 Hz, C_6H), 8.80 (br s, 1, NH); nmr (DMSO-d_6) shows in addition 4.94 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$).

Anal. Calcd for $C_{28}H_{25}N_2O_5I$: C, 56.38; H, 4.23; N, 4.70. Found: C, 55.68; H, 4.23; N, 4.37.

The slower band (75 mg, 15%) was crystallized from methanol giving 50 mg of **29** with mp 147–149°: λ_{max}^{MeOH} 260 mμ (ε 9900); nmr ($CDCl_3$) 3.66 (br s, 1, $C_{4'}H$), 3.9–4.15 (m, 3, $C_{3'}H$ and $C_{5'}H_2$), 4.25 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 5.50 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.97 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 7.2–7.5 (m, 15, Ar), 7.47 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); nmr (DMSO-d_6) shows in addition 4.65 (t, 1, $J_{H,OH}$ = 6 Hz, $C_{5'}OH$), 5.08 (d, 1, $J_{H,OH}$ = 4 Hz, $C_{2'}OH$). Hydrolysis with 80% acetic acid at 100° for 1 hr gave only 1-β-D-xylofuranosyluracil as judged by borate electrophoresis[20] and tlc using ethyl acetate–methanol (9:2).

Anal. Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.38; N, 5.76. Found: C, 68.91; H, 5.44; N, 5.63.

B. In Benzene.[21]—**1** (1.36 g, 3 mmol) was added to a solution of **26** (728 mg, 1 mmol) in anhydrous benzene (75 ml) giving a suspension that was stirred and heated at 50° for 18 hr. Tlc using carbon tetrachloride–ethyl acetate (85:15) showed the absence of **26** and **28a** and a heavy spot of **27**. After addition of methanol (2 ml) the mixture was evaporated, dissolved in ethyl acetate, extracted with thiosulfate and then water, dried ($MgSO_4$), and evaporated leaving 1.6 g of a syrup that now contained very little **27**, the major product moving near **28a**. Preparative tlc using carbon tetrachloride–ethyl acetate (7:3) gave a major band containing 240 mg (41%) of **28b** as a syrup that resisted crystallization: λ_{max}^{MeOH} 261 mμ (ε 9800); nmr ($CDCl_3$), 3.26 ppm (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 3.58 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 5 Hz, $C_{5'b}H$), 4.2 (m, 1, $C_{4'}H$), 4.29 (br s, 1, $C_{3'}H$), 4.83 (s, 1, $C_{2'}H$), 5.68 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.70 (s, 1, $C_{1'}H$), 7.2–7.6 (m, 15, Ar), 7.66 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); nmr (DMSO-d_6) 3.1–3.5 (m, 2, $C_{5'}H_2$ superimposed upon DMSO), 4.10 (m, 1, $C_{4'}H$), 4.36 (q, 1, $J_{2',3'}$ = 3 Hz, $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.52 (quint, 1, $J_{1',2'}$ = $J_{2',3'}$ = 3 Hz, $J_{H,OH}$ = 6 Hz becoming t, $J_{1',2'}$ = $J_{2',3'}$ = 3 Hz with D_2O, $C_{2'}H$), 5.48 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.62 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 6.34 (d, 1, $J_{H,OH}$ = 6 Hz, $C_{2'}OH$).

Anal. Calcd for $C_{28}H_{25}N_2O_5I$: C, 56.38; H, 4.23; N, 4.70. Found: C, 55.73; H, 4.39; N, 4.26.

A faster moving band contained 60 mg (7%) of **27** identical with that above. A comparable reaction in refluxing benzene for 17 hr raised the yield of **28b** to 52%.

1-(3-Deoxy-3-iodo-β-D-xylofuranosyl)uracil (30).—A solution of **28b** (90 mg) in 80% acetic acid was heated at 100° for 1 hr, evaporated to dryness, and freed from tritanol by preparative tlc using chloroform–methanol (9:1). The single nucleoside band was eluted giving a yellow syrup that was treated with charcoal giving 38 mg (72%) of **30** as a foam: λ_{max}^{MeOH} 261 mμ (ε 9900); ORD (MeOH) positive Cotton effect with a peak at 282 mμ (Φ +14,200°), crossover at 261 mμ and a broad trough at 245 mμ (Φ −13,700°); nmr (pyridine-d_5) 4.0–4.5 ppm (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.86 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 5–5.5 Hz, $C_{3'}H$), 5.29 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ 5 Hz, $C_{2'}H$), 5.81 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.48 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 8.36 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_9H_{11}N_2O_5I$: C, 30.52; H, 3.13; N, 7.91. Found: C, 30.81; H, 3.11; N, 7.91.

Acid and Alkali Treatment of 27, 28a, and 28b.[21]—Solutions of **27**, **28a**, and **28b** (4 mg) in 80% acetic acid were separately treated at 60° for 1 hr, and the resulting 3′-iodonucleosides were isolated by tlc using chloroform–methanol (9:1). The eluted materials were dissolved in 0.05 *N* ethanolic potassium hydroxide (0.05 ml), heated in sealed capillaries at 80° for 30 min, and then purified by tlc using acetone–methanol (3:1). In each case, there was almost complete conversion to O²,2′-cyclouridine (λ_{max} 225 and 250 mμ) which was eluted and crystallized from methanol with mp 235–237°.

Reaction of 1-(2,5-Di-O-trityl-β-D-xylofuranosyl)uracil (31) with 1. A. In DMF.—A solution of **31** (450 mg, 0.62 mmol)[22] and **1** (420 mg, 0.9 mmol) in DMF (10 ml) containing pyridine (0.3 ml) was kept at 37° for 7 days at which point unreacted **31** was by far the major product. A further 420 mg of **1** was added, and, after 24 hr at 37°, the mixture was worked up in the usual way, tlc now showing almost complete loss of one trityl group. Preparative tlc using two developments with carbon tetrachloride–ethyl acetate (87:13) gave a sharp band just ahead of diphenyl methylphosphonate and an intense band on the origin. The homogeneous fast band (76 mg, 15%) was crystallized from methanol giving 57 mg of **33a** with mp 254–256°: λ_{max}^{MeOH} 261 mμ (ε 9400); nmr ($CDCl_3$) 3.12 ppm (m, 2, $C_{5'}H_2$), 3.45 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 1.5 Hz, $C_{3'}H$), 3.88 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.68 (br s, 1, $C_{4'}H$), 5.07 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.54 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.0–7.6 (m, 30, Ar), 7.64 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 8.84 (br s, 1, NH).

Anal. Calcd for $C_{47}H_{39}N_2O_5I$: C, 67.31; H, 4.69; N, 3.34. Found: C, 67.39; H, 5.07; N, 3.32.

Preparative tlc of the band on the origin using chloroform–acetone (7:3) gave 140 mg (47%) of **29** which was crystallized from methanol with 147.5–149.5° and found to be identical with the sample obtained earlier.

B. In Benzene.—A mixture of **31** (450 mg, 0.62 mmol) and **1** (920 mg, 2 mmol) in anhydrous benzene (4 ml) was stirred at 50° for 18 hr as described by Johnston.[21] After the usual work-up, the ethyl acetate phase was shown by tlc to contain at least ten ultraviolet-absorbing products among which **33a**, **28**, and unreacted **31** could not be detected. Rather than attempt isolation of individual components the entire mixture was treated with 80% acetic acid at 100° for 1 hr, evaporated to dryness, and purified by preparative tlc using methylene chloride–ethanol (19:1). Two bands located in the region of a monoiodo nucleoside (**30**) were eluted and rechromatographed giving the phosphorus diastereoisomers of **32** which did not give acceptable analyses. The faster isomer (38 mg, 15%) was a syrup with λ_{max}^{MeOH} 262 mμ; nmr (acetone-d_6) 1.78 (d, 3, $J_{P,CH}$ = 17 Hz, PCH_3), 3.59 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.22 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{2'}H$), 4.65 (m, 1, $C_{4'}H$), 4.97 (oct, 1, $J_{H,P}$ = 9 Hz, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 0.5 Hz, $C_{3'}H$), 5.57 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.79 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{1'}H$), 7.1–7.4 (m, 5, Ar), 7.60 (d, 1, $J_{5,6}$ = 8 Hz, C_6H). The slower isomer (16 mg, 6%) had λ_{max}^{MeOH} 262 mμ; nmr (acetone-d_6) 1.70 (d, 3, $J_{P,CH}$ = 18 Hz, PCH_3), 3.42 (d, 2, $J_{4',5'}$ = 7 Hz, $C_{5'}H_2$), 4.63 (d, 1, $J_{1',2'}$ = 1 Hz, $C_{2'}H$), 4.92 (oct, $J_{P,H}$ = 9 Hz, $J_{2',3'}$ = 1 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 5.65 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.85 (d, 1, $J_{1',2'}$ = 1 Hz, $C_{1'}H$), 7.1–7.5 (m, 5, Ar), 7.68 (s, 1, $J_{5,6}$ = 8 Hz, C_6H).

Attempted hydrolysis of the phenyl methylphosphonate moiety from **32** by treatment with 1 *N* sodium hydroxide at 120° failed, uracil being the only neutral product formed.

Acidic and Alkaline Treatment of 33.—A solution of **33** (4 mg) in 80% acetic acid was heated at 100° for 15 min, evaporated to dryness, and separated by tlc using methylene chloride–methanol (9:1) giving four ultraviolet-absorbing bands in addition to tritanol. These were eluted and identified spectrally and chromatographically as uridine, uracil, 3′-deoxy-3′-iodouridine, and a monotrityl-3′-deoxy-3′-iodouridine (increasing mobilities) in molar ratios of 1:3:6:1. Alkaline treatment of the 3′-deoxy-3′-iodouridine fraction under the same conditions used for **30** gave only unreacted **30** and a trace of uracil with no formation of O²,2′-cyclouridine.

3′-O-Acetyl-2′,5′-dideoxy-2′,5′-diiodouridine (34c).—3′-O-Acetyluridine (286 mg, 1 mmol)[25] and **1** (1.8 g, 4 mmol) were allowed to react at 25° in DMF (20 ml) for 20 hr; the reaction was followed by tlc using chloroform–methanol (9:1) (see text). After addition of methanol the mixture was worked up as usual and the ethyl acetate phase purified by preparative tlc using chloroform–acetone (9:1). Elution of the major band gave 230 mg (46%) of **34c** as a clear syrup: λ_{max}^{MeOH} 256 mμ (ε 10,500); ORD (MeOH) positive Cotton effect with a peak at 275 mμ (Φ +4700°), crossover at 267 mμ and a trough at 250 mμ (Φ −9200°); nmr ($CDCl_3$) 2.20 ppm (s, 3, OAc), 3.56 (d, 2,

$J_{4',5'}$ = 4 Hz, $C_5'H_2$), 4.05 (hex, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 4 Hz, $C_4'H$), 4.54 (q, 1, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 6 Hz, $C_2'H$), 4.96 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 2.5 Hz, $C_3'H$), 5.88 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.37 (d, 1, $J_{1',2'}$ = 8.5 Hz, $C_1'H$), 7.61 (d, 1, $J_{5,6}$ = 8 Hz, C_6H), 9.81 (br s, 1, NH); mass spectrum (70 eV) *m/e* 506 (M^+), 379 (M − I), 319 (M − I − AcOH), 192 (M − I_2 − AcOH).

Anal. Calcd for $C_{11}H_{12}N_2O_5I_2$: C, 26.11; H, 2.39; N, 5.54. Found: C, 26.04; H, 2.43; N, 5.08.

3'-O-Acetyl-2',5'-dideoxyuridine (34d).—A solution of **34c** (85 mg) in 85% methanol (8 ml) containing sodium acetate (84 mg) was hydrogenated for 2 hr at 25° in the presence of 10% palladium on charcoal (32 mg). The mixture was then filtered through Celite, evaporated, and partitioned between ethyl acetate and very dilute aqueous sodium thiosulfate. Evaporation of the organic phase left 21 mg (50%) of **34d** as crystals, mp 182–183°. An analytical sample from chloroform–hexane had mp 185.5–186°: λ_{max}^{MeOH} 260 mμ (ε 10,200); ORD (MeOH) positive Cotton effect with a peak at 283 mμ (Φ +4400°), crossover at 273 mμ and a trough at 254 mμ (Φ −10,000°); nmr of the crude or recrystallized sample ($CDCl_3$) was very sharp with 1.42 ppm (d, 3, $J_{4',5'}$ = 6.5 Hz, $C_5'H_3$), 2.12 (s, 3, OAc), 2.16 (oct, 1, J_{gem} = 15 Hz, $J_{1',2'a}$ = 8 Hz, $J_{2'a,3'}$ = 6.5 Hz, $C_2'_aH$), 2.54 (oct, 1, J_{gem} = 15 Hz, $J_{1',2'b}$ = 6 Hz, $J_{2'b,3'}$ = 3 Hz, $C_2'_bH$), 4.23 (oct, 1, $J_{4',5'}$ = 6.5 Hz, $J_{3',4'}$ = 3 Hz, $C_4'H$), 4.88 (quint, 1, $J_{2'b,3'}$ = $J_{3',4}$ = 3 Hz, $J_{2'a,3'}$ = 6.5 Hz, $C_3'H$), 5.81 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.21 (q, 1, $J_{1',2'a}$ = 8 Hz, $J_{1',2'b}$ = 6 Hz, $C_1'H$), 7.46 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.14; H, 5.96; N, 10.76.

Registry No.—**4a,** 25442-40-4; **4b,** 25442-42-6; **5a,** 14260-81-2; **5b,** 14259-59-7; **5c,** 25442-44-8; **7a,** 14260-87-8; **7b,** 14260-83-4; **9c,** 25383-77-1; **10c,** 25442-45-7; **17,** 25383-78-2; **19b,** 25442-46-0; **21,** 25383-79-3; **22,** 25383-80-6; **27,** 25383-81-7; **28a,** 25442-47-1; **28b,** 25383-82-8; **29,** 25442-48-2; **30,** 24514-27-0; **32,** 25442-49-3; **33a,** 25383-84-0; **34c,** 25383-85-1; **34d,** 25442-50-6; 3'-deoxy-3'-iodothymidine, 14260-82-3; methyltriphenoxyphosphonium iodide, 17579-99-6.

Synthesis of *p*-Aminobenzoyl Peptides[1a,b]

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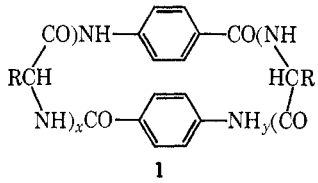
Cyclic peptides incorporating *p*-aminobenzoic acid are proposed as enzyme models. The *p*-aminobenzoyl residues may provide a relatively apolar cavity and substrate binding site, and the peptide bridges joining the *p*-aminobenzoyl residues allow the placement of functional side chains which can serve as a catalytic site. The synthesis of glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproic acid dihydrobromide (**4**) was carried out using the solid-phase method of peptide synthesis. Peptide **4** was cyclized using excess N,N'-dicyclohexylcarbodiimide in aqueous methanol to give *cyclo*-(glycyl-*p*-aminobenzoylglycyl-*im*-benzyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (**3**). Peptide **3** was hydrogenated to give *cyclo*-(glycyl-*p*-aminobenzoylglycyl-L-histidylglycyl-*p*-aminobenzoyl-ε-aminocaproyl) (**2**), a simple example of the proposed class of peptides. The peptide was not sufficiently soluble in water to test its validity as an enzyme model. The saponification of *p*-aminobenzoyl peptide esters proceeds without major side reactions, contrary to reports in the literature. *p*-Aminobenzoyl peptides are cleaved by sodium in liquid ammonia.

The use of cyclic molecules as enzyme models has been explored in recent years. Synthetic cyclic peptides[2–5] and cycloamyloses[6–9] have been investigated. We propose molecules of the type **1** as enzyme models. The incorporation of *p*-aminobenzoyl residues into a cyclic peptide provides a relatively apolar cavity that, in aqueous solution, might act as a substrate binding site. The peptide bridges between the *p*-aminobenzoyl residues allow the placement of functional side chains which can serve as a catalytic site. The preparation of *p*-aminobenzoyl peptides using conventional methods of peptide synthesis has received limited attention,[10–13] and the solid-phase method has not been used at all. In this communication we report the synthesis of the cyclic heptapeptide **2**, and also our investigation of two side reactions accompanying the synthesis of *p*-aminobenzoyl peptides.



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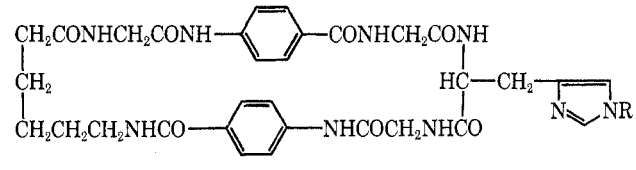

2, R = H
3, R = $C_6H_5CH_2$–

The synthesis of **2** is outlined in Figure 1. The linear heptapeptide **4** was prepared by the solid-phase method of Merrifield,[14] starting with N-*t*-butyloxy-

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