Halo Sugar Nucleosides. I. Iodination of the Primary Hydroxyl Groups of Nucleosides with Methyltriphenoxyphosphonium Iodide[1]

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Reactions of the 5′-hydroxyl group of suitably substituted pyrimidine nucleosides with methyltriphenoxyphosphonium iodide (1) in DMF are very rapid and give the corresponding 5′-deoxy-5′-iodo nucleosides in high yield. Selective iodination of only the primary hydroxyl function in a series of unprotected pyrimidine nucleosides can also be achieved in a number of cases. Iodination of 2′,3′-O-isopropylideneuridine can also be accomplished in pyridine, but in the presence of N,N-diisopropylethylamine there is also formation of 2′,3′-O-isopropylidene-O²,5′-cyclouridine. The reaction of thymidine with an excess of 1 in pyridine gives 5′-deoxy-5′-iodo-O²,3′-cyclothymidine, which is an intermediate in the formation of 3′,5′-dideoxy-3′,5′-diiodothymidine *via* a similar reaction in DMF. In certain cases, the formation of phenyl methylphosphonate esters of secondary hydroxyl groups is also observed. The reactions of 2′,3′-O-isopropylidene derivatives of purine nucleosides, or of free adenosine, with 1 gives the corresponding N³,5′-cyclonucleosides in high yield and only in the case of 2′,3′-O-isopropylideneinosine was any 5′-deoxy-5′-iodo derivative isolated.

Halodeoxy sugars, and in particular the iodo compounds, have been widely used as intermediates in the synthesis of deoxy sugars, unsaturated sugars, amino sugars, etc.[2] Traditionally the conversion of the primary hydroxyl function of a sugar into the corresponding iodide has been accomplished in a two-step process *via* preliminary conversion into a suitable sulfonate ester[3] followed by heating with sodium iodide in a solvent such as acetone. In most cases, displacement of secondary tosylates in this way proves to be considerably more difficult although certain 4-tosylpyranosides have been found to react quite satisfactorily.[2] Iodo sugars have also been prepared *via* reaction of epoxides with Grignard reagents[4] or with salts[5] and by oxidation of hydrazine derivatives with iodine.[6]

In 1953 Rydon and his colleagues published the first of a significant series of papers on methods for the halogenation of alcohols using quasiphosphonium halides.[7] The major reagents developed were methyltriphenoxyphosphonium iodide (1) and iodotriphenoxyphosphonium iodide (2) which were prepared as crystalline

$(C_6H_5O)_3\overset{+}{P}-CH_3\ \bar{I}$ (1) $\qquad$ $(C_6H_5O)_3\overset{+}{P}-I\ \bar{I}$ (2)

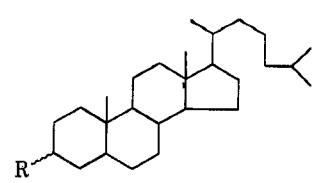
compounds through reaction of triphenyl phosphite with methyl iodide and with iodine respectively.[8] While 1 and 2 are depicted as ionic species, the contributions of pentacovalent forms, especially in nonpolar solvents should not be excluded.[8] Physical studies on the related triphenylphosphine dihalides have indicated that the extent of ionic behavior is a function of solvent polarity.[9]

The reaction of 1 with alcohols is assumed to proceed *via* nucleophilic attack on phosphorus with expulsion of phenol and formation of the alkoxyphosphonium salt 3 which then collapses to the alkyl iodide and diphenyl methylphosphonate.

$$+\ ROH \longrightarrow (C_6H_5O)_2\overset{+}{P}(CH_3)-OR\ I^- \longrightarrow RI + (C_6H_5O)_2P(=O)-CH_3$$

3

Such a concerted mechanism requires that the conversion of an alcohol into the corresponding iodide should be accompanied by an inversion of configuration. Early work[7a,b] showed that reaction of optically active octan-2-ol with either 1 or 2 gave iodides with low optical rotations indicative of net inversion accompanied by extensive racemization. Since these experiments were done at elevated temperatures, racemization is not surprising in view of the well-known ease of nucleophilic attack by iodide ion upon alkyl iodides.[10] It has recently been shown that the iodination of cholestanol **4a** with triphenylphosphine diiodide does indeed proceed with inversion of configuration giving the axial 3α-iodo compound **4b**.[11] Subsequent treatment of **4b** with



4a, R = β-OH
b, R = α-I
c, R = β-I

(1) 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).

(2) For recent reviews on halodeoxy sugars, see (a) J. E. G. Barnett, *Advan. Carbohyd. Chem.*, **22**, 177 (1967); (b) S. Hanessian, *Advan. Chem. Ser.*, **74**, 159 (1968).

(3) For reviews, see (a) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953); (b) D. J. Ball and F. W. Parrish, *ibid.*, **23**, 233 (1968).

(4) (a) F. H. Newth, G. N. Richards, and C. F. Wiggins, *J. Chem. Soc.*, 2356 (1950); (b) G. N. Richards and L. F. Wiggins, *ibid.*, 2442 (1953); (c) N. F. Taylor and G. M. Riggs, *ibid.*, 5600 (1963).

(5) (a) J. P. Horwitz, J. Chua, M. A. da Rooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966); (b) C. L. Stevens, N. A. Nielsen, and B. Blumbergs, *J. Amer. Chem. Soc.*, **86**, 1894 (1964).

(6) D. M. Brown and G. H. Jones, *J. Chem. Soc., C*, 252 (1967).

(7) (a) S. R. Landauer and H. N. Rydon, *ibid.*, 2224 (1953); (b) D. G. Coe, S. R. Landauer, and H. N. Rydon, *ibid.*, 2281 (1954); (c) H. N. Rydon and B. L. Tonge, *ibid.*, 3043 (1956); (d) H. N. Rydon, *Chem. Soc., Spec. Publ.*, **8**, 61 (1957).

(8) See, *e.g.*, C. S. L. Baker, P. D. Landor, S. R. Landor, and A. N. Patel, *J. Chem. Soc.*, 4348 (6519).

(9) (a) K. Issleib and W. Seidel, *Z. Anorg. Allg. Chem.*, 228, 201 (1956); (b) G. A. Wiley and W. R. Stone, *Tetrahedron Lett.*, 2321 (1967); (c) G. S. Harris and M. F. Ali, *ibid.*, 37 (1968).

(10) (a) E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935); (b) C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Amer. Chem. Soc.*, **87**, 4579 (1965).

(11) A. V. Bayless and H. Zimmer, *Tetrahedron Lett.*, 3811 (1968).

sodium iodide in hot acetone led to epimerization of the iodo function giving the thermodynamically more stable equatorial 3β-iodo derivative **4c**. The same situation occurs during iodination of cholestanol with the Rydon reagent (**1**), crystalline 3α-iodocholestane being obtained in 57% yield. No evidence for the presence of the 3β-iodo isomer was found under the mild reaction conditions.

Other evidence for inversion of configuration during halogenation of alcohols with triphenylphosphine dihalides has been presented,[12] and isolation of the intermediate alkoxyphosphonium salts has been achieved.[12,13]

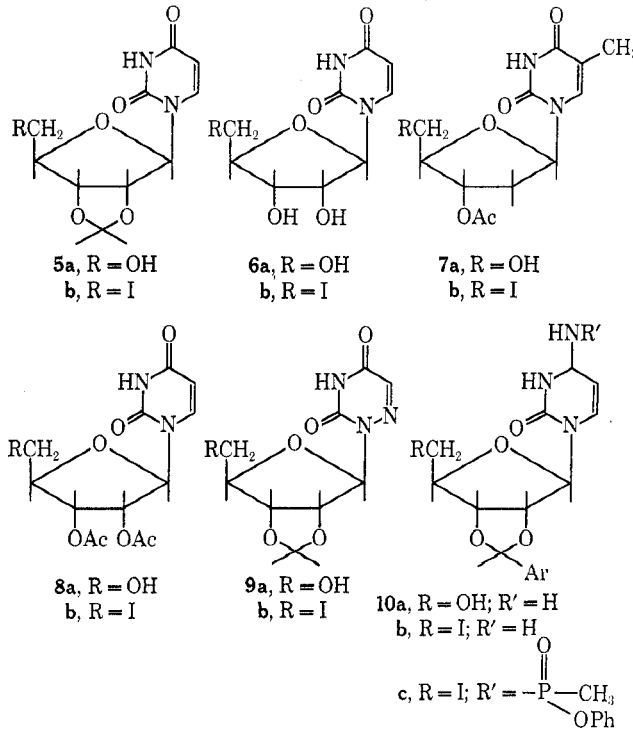
The first applications of the Rydon reagent (**1**) in the carbohydrate field were reported in 1960 by Kochetkov, *et al.*,[14] and by Lee and El Sawi.[15] The work of both groups has pointed out that caution must be used in interpreting the reactions of **1** with substituted sugars in boiling benzene. Thus, the reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose with **1** did not give the expected 3-deoxy-3-iodo derivative as originally reported[15] but rather 6-deoxy-6-iodo-1,2:3,5-di-O-isopropylidene-α-D-glucofuranose with migration of an acetal group.[16] Also it has recently been shown[17] that the major product from reaction of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside with **1** is a 5-deoxy-5-iodoallofuranoside rather than the expected 4-deoxy-4-iodoallopyranoside.[18] In spite of these problems, the Rydon reagent has provided a valuable, but not often used, method for the preparation of iodo sugars.

As part of a general program on the synthesis of nucleosides containing modified sugars, we have undertaken a broad study of methods suitable for the direct halogenation of hydroxyl functions in the sugar moiety of nucleosides. In this and paper II[19] we describe the reactions of a wide range of nucleosides with the Rydon reagent while in a forthcoming paper we will discuss similar reactions using other mechanistically related reagents.

The preparation of methyltriphenoxyphosphonium iodide (**1**) was carried out essentially as described by Rydon[7a] except that a smaller excess of methyl iodide and a shorter reaction time were employed. An oil bath was also found to be preferable to a heating mantle in order to avoid local overheating and coloration (see Experimental Section).

While most previous iodinations using **1** have been carried out in hot benzene, the low solubility of many nucleoside derivatives, and of pure **1** itself in this solvent, have led us to use dimethylformamide (DMF) in our studies. Dimethyl sulfoxide seems less satisfactory since there is rapid coloration of the reaction mixture presumably due to oxidation of iodide ion to iodine in this solvent.[20] The use of DMF appears to promote the iodination reaction which occurs at room temperature and is frequently extremely fast. In general, the iodination of the primary hydroxyl group of a suitably protected pyrimidine nucleoside is found to be complete within 10 min at 20–25°. For example, 2′,3′-O-isopropylideneuridine (**5a**) was allowed to react with 2 equiv of **1** in DMF for 15 min and, after destruction of excess reagent by addition of methanol,[21] pure 5′-deoxy-5′-iodo-2′,3′-O-isopropylideneuridine (**5b**)[22] was isolated by direct crystallization in 96.5% yield. Subsequent acidic hydrolysis then gave 5′-deoxy-5′-iodouridine (**6b**) identical with a sample prepared according to Brown, *et al.*[23]

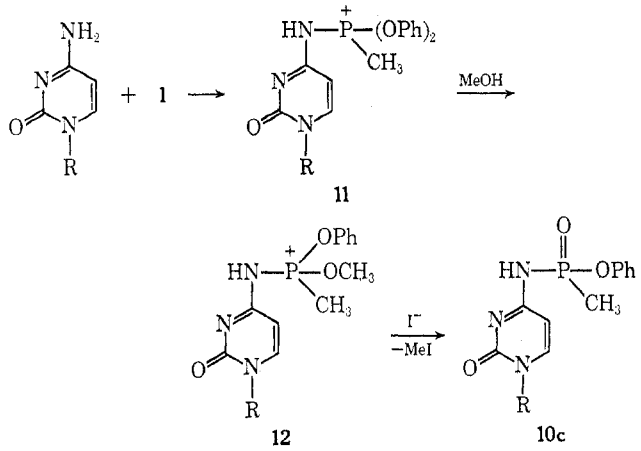
In very similar ways the reactions of 3′-O-acetylthymidine (**7a**) and of 2′,3′-di-O-acetyluridine (**8a**) with **1** in DMF rapidly led to the formation of the corresponding 5′-deoxy-5′-iodo derivatives **7b** and **8b** in isolated yields of 88 and 84%, respectively. The reaction with 2′,3′-O-isopropylidene-6-azauridine (**9a**)[24] was more troublesome, and in spite of an apparently clean reaction as judged by thin layer chromatography, the isolated yield of crystalline 5′-deoxy-5′-iodo-2′,3′-O-isopropylidene-6-azauridine (**9b**) was only 48%. In this case, it was necessary to purify the product by preparative thin layer chromatography in order to obtain crystalline material. The same iodo compound (**9b**) has recently been obtained in somewhat lower yield by displacement of the corresponding 5′-mesylate by iodide ion.[25]



In the cytidine series it becomes clear that the presence of a free amino function on the pyrimidine ring can lead to complications. Thus, reaction of 2′,3′-O-benzylidenecytidine (**10a**) with **1** in DMF led to the

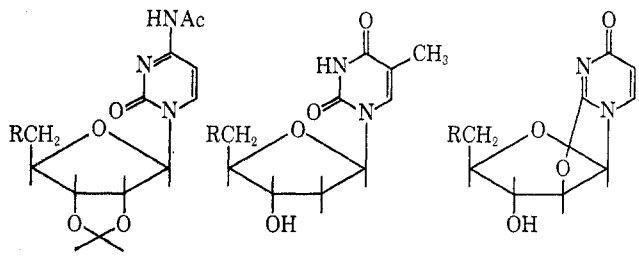
(12) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).
(13) L. Kaplan, *ibid.*, **31**, 3454 (1966).
(14) N. K. Kochetkov, L. I. Kudryashov, and A. I. Usov, *Dokl. Akad. Nauk SSSR*, **133**, 1091 (1960).
(15) J. B. Lee and M. M. El Sawi, *Chem. Ind.* (London), 839 (1960).
(16) N. K. Kochetkov and A. I. Usov, *Tetrahedron*, **19**, 973 (1963).
(17) E. Kefurt, J. Jary, and Z. Samek, *J. Chem. Soc., D*, 213 (1969).
(18) K. S. Adamyanto, N. K. Kochetkov, and A. I. Usov, *Izv. Akad. Nauk SSSR*, 1311 (1967).
(19) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, in press.
(20) R. A. Strecker and K. K. Andersen, *ibid.*, **33**, 2234 (1968).
(21) Addition of methanol prior to other work-up is recommended since otherwise hydrogen iodide is released upon addition of water, and partial loss of acid labile protecting groups can result.
(22) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **106**, 113 (1934).
(23) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).
(24) J. Smrt, J. Beránek, and F. Šorm, *Collect. Czech. Chem. Commun.*, **25**, 130 (1960).
(25) J. Zemlička and F. Šorm, *ibid.*, **32**, 576 (1967).

formation of two strongly ultraviolet-absorbing products which were separated by preparative thin layer chromatography. The more polar of these was shown to contain the desired 2′,3′-O-benzylidene-5′-deoxy-5′-iodocytidine (**10b**) which was obtained in 45% yield as a homogeneous syrup and in 34% yield as the crystalline material. The less polar product was unstable and partially decomposed to **10b** on attempted rechromatography or storage. While this substance has not been isolated in pure form, it was shown to contain phosphorus and its nmr spectrum showed both aromatic protons and a roughly 3-proton doublet (J = 17 Hz) at 1.86 ppm which is consistent with the presence of a methylphosphonate moiety. We tentatively suggest that this material is the phenyl methylphosphonate derivative of the 4-amino function of **10b** (**10c**). As will be seen later, phenyl methylphosphonate esters can arise during iodination of secondary hydroxyl groups under certain conditions. The formation of **10c** could involve reaction of the 4-amino group with **1** giving a phosphonium derivative (**11**) which is relatively stable toward iodide ion. Upon addition of methanol, however, phenol could be displaced with formation of a methoxyphosphonium compound (**12**) which can undergo rapid dealkylation by iodide ion giving the observed product (**10c**). If water, rather than methanol, were to attack **11**, direct expulsion of phenol would also give **10c**.



Treatment of a methanolic solution of the crude reaction mixture from iodination of **10a** with a slight excess of hydrochloric acid led to immediate hydrolysis of the 4-amino substituent and crystallization of the hydrochloride of **10b** in 90% yield. Subsequent treatment of the latter with sodium bicarbonate then gave crystalline **10b** as the free base in 89% yield. As might be expected, acylation of the cytosine amino group eliminated this problem, and iodination of N^4-acetyl-2′,3′-O-isopropylidenecytidine (**13a**) gave the corresponding crystalline 5′-deoxy-5′-iodo derivative (**13b**) in 91% yield.[26]

While it can be seen from the accompanying paper[19] that secondary hydroxyl groups of nucleosides also react with **1**, it is possible to effect selective iodination of only the primary hydroxyl function. Thus, brief reaction of thymidine (**14a**) with 1.1 equiv of **1** in DMF gave crystalline 5′-deoxy-5′-iodothymidine (**14b**)[27] in 63% yield, and in a similar way direct reaction of uridine (**6a**) gave the 5′-deoxy-5′-iodo derivative (**6b**) in 65% yield, the latter compound being identical with that obtained by acidic hydrolysis of **5b**. In a somewhat more demanding test it proved possible to effect fairly selective iodination of the 5′-hydroxyl group of O^2,2′-cyclouridine (**15a**)[28] without excessive cleavage of the rather labile anhydro linkage. After 10-min reactions in DMF, thin layer chromatography showed complete disappearance of the starting material and formation of a major, less polar product. Isolation of this material by preparative thin layer chromatography gave an 80% yield of somewhat impure material, and rechromatography was accompanied by considerable decomposition, crystalline 5′-deoxy-5′-iodo-O^2,2′-cyclouridine (**15b**)[29] being obtained in 31% yield.



Since **1** decomposes in the presence of traces of moisture to release hydrogen iodide, care must be taken to avoid loss of acid labile protecting groups. Since the iodination of primary hydroxyl groups is so rapid, loss of isopropylidene groups has not proved to be a problem, but, during the slower reactions of secondary hydroxyls, some loss of trityl groups is evident.[19] It was thus of interest to see whether the iodination reaction could be conducted in the presence of a base to neutralize any acidic by-products. Indeed, it was found that reaction of 2′,3′-O-isopropylideneuridine (**5a**) with **1** gave the 5′-deoxy-5′-iodo derivative (**5b**) essentially quantitatively within 15 min in various mixtures of DMF and pyridine or in pyridine alone. Upon more prolonged reactions there was a gradual accumulation of the 5′-deoxy-5′-pyridinium derivative (**16**) which was characterized by its electrophoretic mobility and ultraviolet spectrum, both of which were identical with an authentic sample.[30] After a 2-hr reaction only about 10% **16** had been formed. Attempts to use a small excess of the relatively nonnucleophilic base N,N-diisopropylethylamine in place of pyridine led to the formation of brown impurities and to the isolation of a 16% yield of 2′,3′-O-isopropylidene-O^2,5′-cyclouridine (**17**)[28] in addition to **5b**. It is not clear whether the formation of **17** is a consequence of base-catalyzed displacement of iodide ion from **5b** or of an increased nucleophilicity of the 2-carbonyl group toward displacement of the phosphonium moiety in the intermediate **18**. Some evidence in favor of the latter route comes from the isolation of the cyclonucleoside **17** in 21% yield following reaction of **5a** with methyltriphenoxyphosphonium perchlorate and N,N-diisopropylethyl-

(26) This reaction is part of a separate study and will be reported in detail later: J. P. H. Verheyden, J. Smejkal, and J. G. Moffatt, unpublished results.

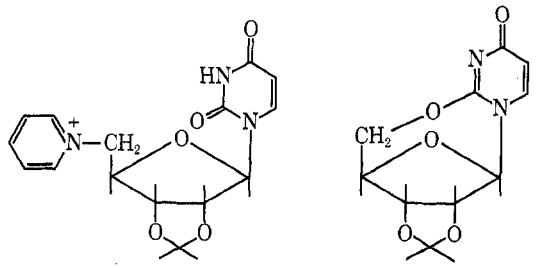
(27) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(28) A. Hampton and A. W. Nicol, *Biochemistry*, **5**, 2076 (1966).

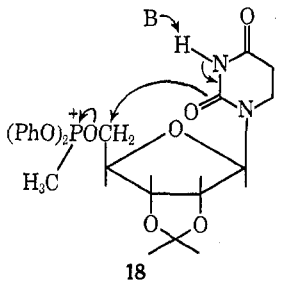
(29) D. M. Brown, W. Cochrane, E. H. Medlin, and S. Varadarajan, *J. Chem. Soc.*, 4873 (1956).

(30) H. Peter and J. G. Moffatt, unpublished experiments.

amine. The perchlorate salt was prepared *in situ* from **1** and silver perchlorate in DMF, and its use led only to **17** and unreacted **5a** with formation of no observable iodo compounds.



16 **17**



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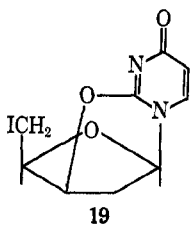
While the addition of bases has relatively minor effect upon the iodination of primary hydroxyl groups, the reaction with secondary hydroxyls in pyrimidine nucleosides is markedly changed. While, as will be seen in the accompanying paper,[19] the reaction of thymidine with excess **1** in DMF gives 3′,5′-dideoxy-3′,5′-diiodothymidine in high yield, the comparable reaction in pyridine gives mainly 5′-deoxy-5′-iodo-O^2,3′-cyclothymidine (**19**) which was isolated in crystalline form in 43% yield. The structure of (**19**) is based upon its typical O^2,3′-cyclothymidine ultraviolet spectrum and upon its elemental analyses and nmr spectrum. It has been shown[19] that iodination of the 3′-hydroxyl group of pyrimidine deoxynucleosides with **1** involves initial formation of the O^2,3′-cyclonucleoside which subsequently undergoes nucleophilic attack by iodide ion giving the 3′-iodo nucleoside with overall retention of configuration. Since nucleophilic opening of cyclonucleosides is known to be an acid-catalyzed process,[31] such reactions in pyridine are blocked at this stage thus explaining the accumulation of **19**.

While selective iodination of O^2,2′-cyclouridine (**15a**) with 1.4 equiv of **1** in DMF gave the 5′-iodo derivative (**15b**) in quite good yield, the use of a larger excess of Rydon reagent in the presence of N,N-diisopropylethylamine or pyridine led to an unexpected result. After a brief reaction time the starting material had completely disappeared with formation of two major products and a considerable number of minor products all showing the typical ultraviolet spectra of O^2,2′-cyclouridine. The two major products, which had very similar chromatographic mobilities, were isolated together in 42% yield and shown to be an almost equal mixture of the phosphorus diastereoisomers of 5′-deoxy-5′-iodo-O^2,2′-cyclouridine 3′-O-(phenyl methylphosphonate) (**22**), both of which were obtained in crystalline form. In the accompanying paper[19] further examples of the formation of phenyl methylphosphonate esters are to be found and in general, it appears that their formation is favored when the displacement of the phosphonium moiety in the intermediate **3** is sterically hindered. In the present case, there is presumably rapid formation of the 3′,5′-di-O-(methyldiphenoxyphosphonium) intermediate (**20**) and subsequent displacement of the 5′ group by iodide ion. Because of the existing O^2,2′-anhydro linkage, there is no opportunity for intramolecular displacement of the 3′ group by the uracil ring; owing to the rigid *syn* configuration in O^2,2′-cyclonucleosides, there is considerable hindrance to the approach of iodide ion from the β face of the ribose ring. This presumably leads to an accumulation of the 3′-oxyphosphonium intermediate (**21**) which undergoes reaction with either water or methanol, as previously outlined in the conversion of **11** to **10c**, giving the diastereoisomers (**22**). The isomers of **22** also appear to be the major by-products during the previously mentioned selective iodination of **15a** in the absence of amine.



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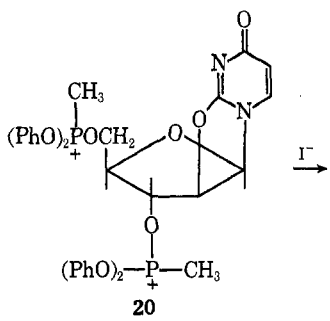

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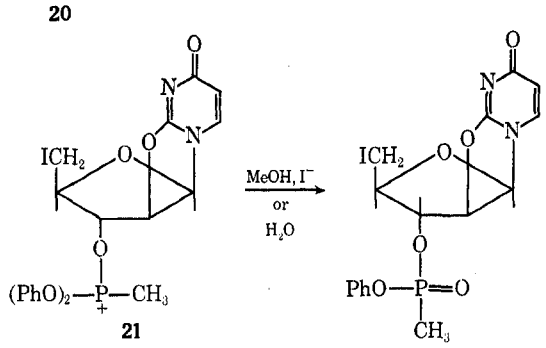


21 **22**

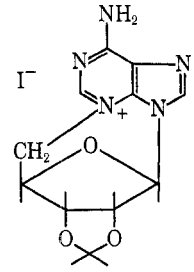
Direct application of the iodination reaction to purine nucleosides leads to cyclonucleosides. Thus, reaction of either 2′,3′-O-isopropylideneadenosine or 2′,3′-O-isopropylideneguanosine with **1** in DMF leads to very rapid and essentially quantitative formation of the N^3,5′-cyclonucleoside salts (**23** and **24**). Both compounds were obtained crystalline and characterized by their ultraviolet spectra and their electrophoretic and chromatographic mobilities, all of which were identical with those of **23**[32] and **24**[33] prepared by heating the

(31) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

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

(33) (a) E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1577 (1961). (b) R. E. Holmes and R. K. Robins, *ibid.*, **28**, 3483 (1963). We thank Dr. R. K. Robins for samples of 2′,3′-O-isopropylidene-N^3,5′-cycloinosine and its tosylate salt.

appropriate 5′-tosylates with sodium iodide. A similar reaction with 2′,3′-O-isopropylideneinosine gave crystalline 2′,3′-O-isopropylidene-N³,5′-cycloinosine (**25**)[33b] in 76% yield along with 15% 5′-deoxy-5′-iodo-2′,3′-O-isopropylideneinosine (**26**). The latter compound was only recently obtained by displacement of the corresponding 5′-tosylate[34] and its formation, albeit in low yield, from our reaction with **1** is a further indication of the somewhat reduced tendency of inosine derivatives, relative to other purine nucleosides, to form N³,5′-cyclonucleosides.[33]



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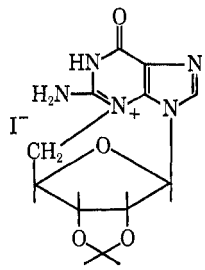

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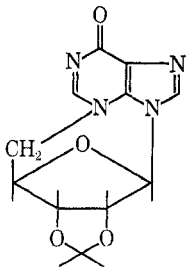

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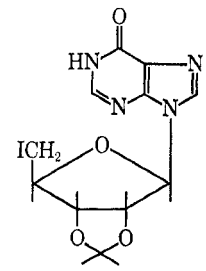

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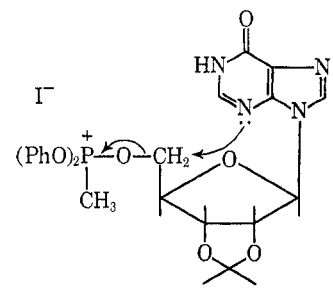
The formation of N³,5′-cyclonucleosides is clearly a consequence of the very facile attack by N³ of the purine ring upon C⁵′ of the phosphonium intermediate (**27**) with expulsion of diphenyl methylphosphonate. The reduced propensity for such an intramolecular displacement in the inosine series permits some competitive attack by iodide ion on **27** leading to the 5′-iodo derivative **26**. The intermediacy of an ionic cyclonucleoside **28**, similar to that isolated by Holmes and Robins,[33b] was detected by paper chromatography but only the nonionic form (**25**) was isolated following a work-up involving addition of pyridine.



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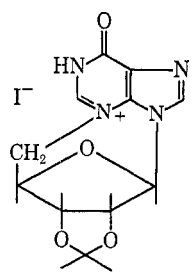
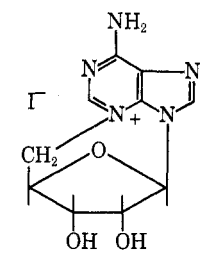


28



29

Treatment of unprotected adenosine with 1 equiv of **1** in DMF for 5 min gave a major, very polar material and two less polar, minor by-products. Following extraction into water crystalline N³,5′-cycloadenosine iodide (**29**) was obtained in 50% yield. Unprotected N³,5′-cycloadenosine salts have recently been obtained upon heating either 5′-O-tosyl- or 5′-O-sulfamoyladenosine in DMF at 100° but have not been characterized.[35] The two minor products appear from their nmr spectra to be phenyl methylphosphonate esters of adenosine but were not obtained in sufficient amounts for detailed study.

From the work described in this paper, it is clear that the Rydon reagent (**1**) provides a very efficient method for the iodination of the primary hydroxyl function of pyrimidine nucleosides. The reaction is very rapid and the overall yields are generally considerably higher than those obtained *via* the two-step tosylation and displacement route. In the accompanying paper[19] iodination of secondary hydroxyl groups is discussed.

Experimental Section

Methods.—Thin layer chromatography (tlc) was done on 0.25-mm layers of Merck silica gel HF and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of the same silica. Nuclear magnetic resonance (nmr) spectra were obtained using a Varian HA-100 spectrometer and chemical shifts are recorded in parts per million downfield from an internal standard of TMS. Mass spectra were obtained using an Atlas CH-4 instrument with a direct inlet system and optical rotatory dispersion (ORD) spectra using a Jasco ORD/UV-5 instrument. All instrumental analyses were performed by the staff of the Analytical Laboratory of Syntex Research, and elemental analyses were obtained from the laboratory of Dr. A. Bernhardt, Mülheim, Germany, or from the Analytical Laboratory of the University of California, Berkeley, Calif. We are particularly grateful to Dr. M. Maddox, Mr. J. Murphy, and Miss J. Tremble and to Dr. L. Tökes for their help with nmr and mass spectra, respectively.

Methyltriphenoxyphosphonium Iodide (1).[7a]—Triphenyl phosphite (52 ml, 0.2 mol) and methyl iodide (16 ml, 0.26 mol) were mixed in a 250-ml flask fitted with a very efficient 3-ft condenser and a thermometer well. The flask was placed in a 90° oil bath and the temperature of the bath was slowly raised to 125° over 8 hr while the pot temperature rose slowly from 70 to 85° and then rapidly to 115°.[36] This temperature was then maintained for 12–14 hr and, upon cooling and seeding, the mixture crystallized to a solid brown mass. Dry ether (100 ml) was added and the product was carefully broken up with a spatula. The resulting crystalline material was then repeatedly washed by decantation with fresh dry ethyl acetate until the washings were only light colored.[37] The amber crystals were then dried and stored *in vacuo* giving 80 g (90%) of **1** suitable for direct use: nmr (rigorously dry $CDCl_3$) 3.11 ppm (d, 3, $J_{P,H}$ = 16.5 Hz, PCH_3), 7.45 (m, 15, aromatic). If the sample was not prepared in a drybox appreciable amounts of diphenyl methylphosphonate were formed as indicated by a doublet ($J_{P,H}$ = 18 Hz) at 1.84 ppm. In all subsequent reactions **1** was always weighed and handled in a drybox under a nitrogen atmosphere.

3α-Iodocholestane (4b).[38]—Cholestanol (0.78 g, 2 mmol) and **1** (1.81 g, 4 mmol) were dissolved in anhydrous DMF (10 ml) and

(34) A. Hampton, M. Bayer, V. S. Gupta, and S. Y. Chu, *J. Med. Chem.*, **11**, 1229 (1968).

(35) D. A. Shuman, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **91**, 3391 (1969).

(36) If the reaction is worked up as soon as the internal temperature reaches 115°, **1** is obtained in a very light-colored form but only in about 50% yield.

(37) Ethyl acetate is much preferable to ether for this purpose and a much lighter colored product is obtained. Compound **1** has recently become available from Eastman Kodak Co. in a dark-colored crystalline form that can be readily purified by treatment with ethyl acetate as above.

(38) We are grateful to Mr. E. K. Hamamura for this experiment.

stored for 2 hr at 25°. After addition of methanol (1 ml), the mixture was diluted with chloroform and extracted with dilute aqueous sodium thiosulfate followed by water. After drying (Na_2SO_4) the solvent was evaporated and the residue was chromatographed on a column of silicic acid using hexane. The major peak was evaporated giving 640 mg of **4b** which was crystallized from acetone giving 562 mg (57%) of pure product with mp 112–113°; $[\alpha]^{23}D$ +36.9° (lit.[11] mp 111.5–112.5°; $[\alpha]^{20}D$ +32.2°; and for β isomer mp 105.5–107°); nmr ($CDCl_3$) 0.65 ppm (s, 3, $C_{18}H_3$), 0.79 (s, 3, $C_{19}H_3$), 0.86 (d, 6, J = 6 Hz, $C_{26}H_3$ and $C_{27}H_3$), 0.90 (d, 3, J = 6 Hz, $C_{21}H_3$), 4.95 (m, 1, C_3H).

Iodination of 2′,3′-O-Isopropylideneuridine (5a). (A) In DMF Alone.—2′,3′-O-Isopropylideneuridine (10 g, 35.2 mmol) and **1** (32 g, 70 mmol) were dissolved in anhydrous DMF (140 ml) and after 15 min at 25° methanol (5 ml) was added. After 10 min the solvent was evaporated *in vacuo* and the residue was dissolved in chloroform. After extraction with aqueous sodium thiosulfate and then water, the chloroform layer was dried (Na_2SO_4) and evaporated giving a colorless syrup containing **5b**, phenol, and diphenyl methylphosphonate. Crystallization from chloroform by slow addition of hexane gave 13.4 g (96.5%) of pure **5b**: mp 165–166° (lit.[22] mp 164°); λ_{max}^{MeOH} 259 mμ (ε 10,500); nmr ($CDCl_3$) 1.34 ppm (s, 3, CMe_2), 1.55 (s, 3, CMe_2), 3.34 (q, 1, J_{gem} = 10 Hz, $J_{4',5'a}$ = 5 Hz, $C_{5'a}H$), 3.52 (q, 1, J_{gem} = 10 Hz, $J_{4',5'b}$ = 6.5 Hz, $C_{5'b}H$), 4.25 (hex, 1, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 6 Hz, $C_4'H$), 4.79 (q, 1, $J_{2',3'}$ = 6.5 Hz, $J_{3',4'}$ = 3.5 Hz, $C_3'H$), 5.03 (q, 1, $J_{1',2'}$ = 2 Hz, $J_{2',3'}$ = 6.5 Hz, $C_2'H$), 5.63 (d, 1, $J_{1',2'}$ = 2 Hz, $C_1'H$), 5.75 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 7.35 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Treatment of **5b** (788 mg, 2 mmol) with 80% acetic acid (18 ml) at 100° for 90 min gave 620 mg (87.5%) of 5′-deoxy-5′-iodouridine (**6b**) of mp 184–185° after crystallization from ethanol (see below).

(B) In the Presence of N,N-Diisopropylethylamine.—A solution of **5a** (142 mg, 0.5 mmol), **1** (250 mg, 0.5 mmol), and N,N-diisopropylethylamine (260 mg, 2 mmol) in DMF (3 ml) was kept overnight at 25° and then evaporated to dryness *in vacuo* after addition of methanol (1 ml). Upon addition of ethyl acetate a brown precipitate (60 mg) separated and was discarded. After extraction with water, the organic phase was dried (Na_2SO_4) and purified by preparative tlc using acetone–methanol (9:1) which gave **5b**, unreacted **5a**, and a slow moving band. Elution of the latter and crystallization from ethanol gave 21 mg (16%) of 2′,3′-O-isopropylidene-O²,5′-cyclouridine (**17**) which decomposed from 228 to 280° (lit.[23] decomposition above 190°): λ_{max}^{MeOH} 236 mμ (ε 13,900); ORD (MeOH) negative Cotton effect with minimum at 245 mμ (Φ −16, 100°) and zero rotation at 233 mμ; nmr (d_6-DMF) 1.33 ppm (s, 3, CMe_2), 1.43 (s, 3, CMe_2), 4.27 (d, 1, J_{gem} = 12 Hz, $C_{5'a}$), 4.67 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.77 (br s, 1, $C_4'H$), 5.0 (s, 2, $C_2'H$ and $C_3'H$), 5.85 (s, 1, $C_1'H$), 5.98 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 8.12 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

(C) In the Presence of Silver Perchlorate.—Silver perchlorate (230 mg, 1.1 mmol) and **1** (500 mg, 1.1 mmol) were dissolved in DMF (3 ml) giving a yellow precipitate of silver iodide. N,N-Diisopropylethylamine (3 ml) and **5a** (284 mg, 1 mmol) were added, and after 10 min methanol (1 ml) was added to the dark mixture. After filtration through Celite, the solvent was evaporated and the residue was separated by preparative tlc using acetone–methanol (9:1). In addition to a band of unreacted **5a** a major band of **17** was observed and eluted. Crystallization from ethanol gave 55 mg (21%) of **17** identical with that above.

3′-O-Acetyl-5′-deoxy-5′-iodothymidine (7b).—A solution of 3′-O-acetylthymidine (4.26 g, 15 mmol) and **1** (10.0 g, 22 mmol) in DMF (50 ml) was kept at 25° for 1 hr and then evaporated to dryness after addition of methanol (5 ml). The residue was dissolved in chloroform, washed with thiosulfate and water, dried, evaporated, and crystallized from chloroform–hexane giving 5.20 g (88%) of **7b** with mp 132–132.5° (lit.[39] mp 131°); nmr ($CDCl_3$) 1.95 ppm (d, 3, $J_{allylic}$ = 1 Hz, C_5Me), 2.10 (s, 3, OAc), 2.1–2.4 (m, 2, $C_2'H_2$), 3.4–3.7 (AB of ABC, 2, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 3 Hz, $C_5'H_2$), 3.9 (m, 1, $C_4'H$), 5.1 (m, 1, $C_3'H$), 6.32 (q, 1, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 7.5 Hz, $C_1'H$), 7.57 (q, $J_{allylic}$ = 1 Hz, C_6H).

2′,3′-Di-O-acetyl-5′-deoxy-5′-iodouridine (8b).—A solution of 2′,3′-di-O-acetyluridine (6.4 g, 19.5 mmol) and **1** (13 g, 30 mmol) in DMF (100 ml) was kept at room temperature for 2 hr. After addition of methanol (10 ml) the solvent was evaporated and a chloroform solution of the residue was washed with aqueous thiosulfate and water. After drying (Na_2SO_4) the solvent was evaporated and the residue crystallized from chloroform (20 ml) by slow addition of hexane giving 7.2 g (84%) of **8b** with mp 162–164°. An analytical sample had mp 163–164°; λ_{max}^{MeOH} 259 mμ (ε 10,400); ORD (MeOH) positive Cotton effect with a peak at 272 mμ (Φ +2800°), zero rotation at 252 mμ, and a minimum at 232 mμ (Φ −2400°); nmr ($CDCl_3$) 2.11 ppm (s, 3, OAc), 2.15 (s, 3, OAc), 3.54 (d, 2, $J_{4',5'}$ = 4 Hz, $C_5'H_2$), 4.11 (q, 1, $J_{3',4'}$ = $J_{4',5'}$ = 4 Hz, $C_4'H$), 5.22 (q, 1, $J_{3',4'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, $C_3'H$), 5.40 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $C_2'H$), 5.85 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.08 (d, 1, $J_{1',2'}$ = 6 Hz, $C_1'H$), 7.58 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{15}N_2O_7I$: C, 35.64; H, 3.45; N, 6.39. Found: C, 35.89; H, 3.49; N, 6.29.

5′-Deoxy-5′-iodo-2′,3′-O-isopropylidene-6-azauridine (9b).—A solution of **9a** (285 mg, 1 mmol) and **1** (1 g, 2 mmol) in DMF (5 ml) was stored for 30 min at 25° and worked up as above using ethyl acetate in place of chloroform. The dried organic phase was purified by preparative tlc using two successive developments with chloroform–ethyl acetate (3:2). Elution of the major band with acetone gave 190 mg (48%) of crystalline **9b** which was recrystallized from chloroform–hexane with mp 178–181° (lit.[25] mp 176–181); λ_{max}^{MeOH} 261 mμ (ε 6700); nmr ($CDCl_3$) 1.36 and 1.56 ppm (s, 3, CMe_2), 3.24 (d, 2, $J_{4',5'}$ = 7.5 Hz, $C_5'H_2$), 4.43 (hex, 1, $J_{4',5'}$ = 7.5 Hz, $J_{3',4'}$ = 3 Hz, $C_4'H$), 4.81 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz, $C_3'H$), 5.07 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{1',2'}$ = 1 Hz, $C_2'H$), 6.38 (d, 1, $J_{1',2'}$ = 1 Hz, $C_1'H$), 7.51 (s, 1, C_5H).

Anal. Calcd for $C_{11}H_{14}N_3O_5I$: C, 33.43; H, 3.57. Found: C, 33.60; H, 3.55.

2′,3′-O-Benzylidene-5′-deoxy-5′-iodocytidine (10b). (A).—A solution of **10a** (662 mg, 2 mmol)[40] and **1** (2 g, 4 mmol) in DMF (10 ml) was reacted overnight and worked up as usual using ethyl acetate. The resulting syrup (2.86 g) was purified by preparative tlc on 4 plates using acetone–chloroform (1:1). In addition to fast bands of phenol and diphenyl methylphosphonate two intense ultraviolet-absorbing bands were obtained. Elution of the slower band with acetone gave 400 mg (45%) of **10b** as a chromatographically homogeneous syrup from which 300 mg (34%) of crystalline material with mp 175–180° was obtained from ethanol. An analytical sample from acetone had mp 176.5–177.5°; λ_{max}^{MeOH} 278 mμ (ε 12,800); nmr ($CDCl_3$) showing a mixture of benzylidene diastereoisomers with 3.3–3.8 ppm (m, 2, $C_5'H_2$), 4.45 (m, 1, $C_4'H$), 5.0–5.4 (m, 2, $C_2'H$ and $C_3'H$), 5.63 (s, 1, $C_1'H$), 5.80 (br d, 1, $J_{5,6}$ = 7 Hz, C_5H), 5.94 and 6.06 (2s, 1, $ArCHO_2$), 7.45 (m, 6, Ar and C_6H).

Anal. Calcd for $C_{16}H_{16}N_3O_4I$: C, 43.55; H, 3.66; N, 9.53. Found: C, 43.28; H, 3.70; N, 9.79.

Elution of the faster band gave a phosphorus-containing syrup that could not be crystallized and that partially decomposed to **10b** upon storage: λ_{max}^{MeOH} 280 mμ, $\lambda_{max}^{OH^-}$ 270 mμ; nmr (d_5-pyridine) was poor but showed a sharp doublet at 1.86 ppm ($J_{P,H}$ = 17 Hz) and an overabundance of aromatic protons. Brief treatment with methanolic hydrochloric acid gave **10b** (see below).

(B).—A reaction was carried out exactly as in A. After evaporation of the ethyl acetate solution the resulting syrup was dissolved in methanol (4 ml) and upon addition of concentrated hydrochloric acid (0.2 ml) white crystals separated. After 15 min the crystals were removed by filtration, washed with ethanol, and dried *in vacuo* over sodium hydroxide giving 855 mg (90%) of the hydrochloride of **10b**, λ_{max}^{MeOH} 278 mμ. This material (755 mg) was partitioned between ethyl acetate and 0.2 *M* sodium bicarbonate and the organic phase was dried (Na_2SO_4) and evaporated. The resulting syrup was crystallized from acetone giving 770 mg (89%) of **10b** identical with that above.

Iodination of Thymidine with 1. (A) In DMF.—Thymidine (1.94 g, 8 mmol) and **1** (4.35 g, 9.6 mmol) reacted in DMF (20 ml) at room temperature for 10 min. After addition of methanol (10 ml) the mixture was worked up in the usual way giving a syrup that was crystallized from methanol giving 1.61 g (57%) of pure 5′-deoxy-5′-iodothymidine (**14b**) with mp 173–174° (lit.[27] mp 172–173°). Chromatography of the evaporated mother liquors on four preparative plates using carbon tetrachloride–acetone (1:1) gave a further 170 mg (total yield 63%) of **14b**: λ_{max}^{MeOH} 263 mμ (ε 9600); nmr (d_5-pyridine) 1.94 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.54 (q, 1, $J_{1',2'a}$ = 7 Hz, $J_{2'a,3'}$ = 2.5

(39) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 951 (1953).

(40) J. Baddiley, J. G. Buchanan, and A. R. Sanderson, *ibid.*, 3107, (1958).

Hz, $C_{2'a}H$), 2.60 (d, 1, $J_{1',2'b}$ = 7 Hz, $=J_{2'b,3'}$ 0 Hz, $C_{2'b}H$), 3.68 (br d, 2, $J_{4',5'}$ = 6 Hz, $C_{5'}H_2$), 4.24 (hex, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 6 Hz, $C_{4'}H$), 4.7 (m, 1, $C_{3'}H$), 6.86 (t, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 7.67 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

During tlc purification of **14b** a minor, slower moving band was also eluted giving 60 mg of a chromatographically homogeneous product tentatively identified as thymidine 3',5'-cyclic methylphosphonate. The product could not be crystallized and was contaminated with silica so as to give an unsatisfactory elemental analyses: λ_{max}^{MeOH} 262 mμ; nmr ($CDCl_3$) 1.77 ppm (d, 3, $J_{P,H}$ = 18 Hz, PCH_3), 1.91 (d, 3, $J_{allylic}$ = 1 Hz, C_5Me), 2.78 (q, 2, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}H_2$), 3.61 (d, 2, $J_{4',5'}$ = 6 Hz, $C_{5'}H_2$), 4.27 (m, 1, $C_{4'}H$), 5.45 (m, 1, $C_{3'}H$), 6.72 (t, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 7.46 (br s, 1, C_6H); mass spectrum *m/e* 303 (M^+, weak), 287 (M − CH_3, weak), 173, 94, 81.

(B) In Pyridine.—Thymidine (484 mg, 2 mmol) and **1** (2.6 g, 5.5 mmol) were dissolved in pyridine (15 ml) and kept at 25° for 1 hr. After addition of methanol (5 ml) the solvent was evaporated, and the residue was coevaporated several times with methanol. Chromatography of the residue on three preparative tlc plates using ethyl acetate–methanol (1:1) gave a major band (R_f ~0.5) which was eluted and crystallized from acetone giving 340 mg of crude product that still contained an impurity. Rechromatography using two developments with chloroform–methanol (9:1) gave a sharp band that was eluted and crystallized from methanol–ethyl acetate giving 294 mg (43%) of 5'-deoxy-5'-iodo-O^2,3'-cyclothymidine (**19**) with mp 192–192.5°; λ_{max}^{MeOH} 247 mμ (ε 9100); ORD (MeOH) negative Cotton effect with trough at 248 mμ (Φ −24,100°), zero rotation at 226 mμ and a peak at 217 mμ (Φ +5800°); nmr (d_6-DMSO) 1.75 ppm (d, 3, $J_{allylic}$ = 1 Hz), 2.45–2.65 (m, 2, $C_{2'}H_2$), 3.12 (q, J_{gem} = 10 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.27 (q, J_{gem} = 10 Hz, $J_{4',5'b}$ = 7 Hz, $C_{5'b}H$), 4.51 (hex, 1, $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 7–8 Hz, $C_{4'}H$), 5.29 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_{3'}H$), 5.92 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 7.56 (q, $J_{allylic}$ = 1 Hz, C_6H).

Anal. Calcd for $C_{10}H_{11}N_2O_5I$: C, 35.94; H, 3.32. Found: C, 36.07; H, 3.43.

On prolonged reaction a spot of increasing intensity appeared near the origin during tlc with ethyl acetate–methanol (1:1). Elution of this material with methanol gave a syrup with λ_{max}^{MeOH} 260 mμ and shoulders at 255 and 265 mμ. Paper electrophoresis at pH 7.5 showed the product to be a cation with a mobility identical with that of an authentic salt of **16**.[30]

5'-Deoxy-5'-iodouridine (6b).—Uridine (244 mg, 1 mmol) and **1** (640 mg, 1.5 mmol) were allowed to react for 1 hr at 25° in DMF (5 ml). After the usual work-up using chloroform, the product was found in the aqueous phase and was recovered by continuous extraction into ethyl acetate. Evaporation of the solvent left 230 mg (65%) of crystalline **6b** that was recrystallized from methanol giving 140 mg of analytically pure product with mp 184–185° (lit.[28] mp 182–183°); λ_{max}^{MeOH} 260 mμ (ε 10,400); nmr (d_5-pyridine) 3.67 ppm (q, 1, J_{gem} = 10 Hz, $J_{4',5'a}$ = 5 Hz, $C_{4'}H$), 3.81 (q, 1, J_{gem} = 10 Hz, $J_{4',5'b}$ = 5 Hz, $C_{5'b}H$), 4.35 (q, 1, $J_{3',4'}$, $J_{4',5'a}$, $J_{4',5'b}$ = 5 Hz, $C_{4'}H$), 4.51 (t, 1, $J_{2',3'}$, $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.81 (t, 1, $J_{1',2'}$, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 5.85 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.64 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.95 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Iodination of O^2,2'-Cyclouridine (15b). (A) In DMF.—O^2,2'-Cyclouridine (451 mg, 2 mmol) and **1** (1.8 g, 4 mmol) were allowed to react in DMF (10 ml) for 10 min at 25°. After addition of methanol the reaction was evaporated to dryness and directly chromatographed on two preparative plates using acetone. The major band was eluted giving 450 mg of a syrup containing one major spot and two close moving impurities (**22**). Rechromatography using two successive developments with acetone led to considerable decomposition and crystallization of the major band from ethanol gave 175 mg (31%) of 5'-deoxy-5'-iodo-O^2,2'-cyclouridine (**15b**) with mp 194–195° (lit.[29] mp 194–195°); λ_{max}^{MeOH} 245 mμ (ε 8050), 223 (9,250); ORD (MeOH) positive Cotton effect with a peak at 260 mμ (Φ +12,000°), zero rotation at 247 mμ and a trough at 226 mμ (Φ −31,000°); nmr (d_6-DMSO) 2.97 ppm (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 7.5 Hz, $C_{5'a}H$), 3.20 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 6.5 Hz, $C_{5'b}H$), 4.15 (rough hex, 1, $J_{4',5'}$ = ~7 Hz, $J_{3',4'}$ = 2 Hz, $C_{4'}H$), 4.35 (m, 1, $C_{3'}H$), 5.26 (q, 1, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 1 Hz, $C_{2'}H$), 5.88 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.14 (d, 1, $J_{H,OH}$ = 4.5 Hz, $C_{3'}OH$), 6.37 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.81 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); mass spectrum *m/e* 336 (M^+), 254 (I_2^+), 192, 127 (I^+), 112 (uracil).

(B) In the Presence of N,N-Diisopropylethylamine.—O^2,2'-Cyclouridine (1.13 g, 5 mmol), **1** (6.4 g, 14 mmol), and N,N-diisopropylethylamine (2.6 g) were allowed to react for 15 min at 25° in DMF (50 ml). After addition of methanol (1 ml) and evaporation to dryness, ethyl acetate was added giving 1.0 g of a precipitate which contained at least seven very polar spots all with λ_{max} 247 and 225 typical of O^2,2'-cyclouridine. The ethyl acetate supernatant was extracted with saturated aqueous sodium chloride, decolorized with charcoal, and evaporated to dryness. Addition of ether (150 ml) gave 1.01 g (42%) of white crystals which contained equal amounts of the diastereoisomers of **22**. Preparative tlc using acetone cleanly separated these compounds. The slower isomer was crystallized from methanol: mp 222–224°: λ_{max}^{MeOH} 225 mμ (ε 9800), 247 (8800); ORD (MeOH) positive Cotton effect with peak at 260 mμ (Φ +10,600°), zero rotation at 247 mμ and a trough at 227 mμ (Φ −26,000°); nmr (d_6-DMSO) 1.82 ppm (d, $J_{P,H}$ = 18 Hz, PCH_3), 2.92 (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.2 (m, 1, $C_{5'b}H$), 4.32 (m, 1, $C_{4'}H$), 5.19 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{P,H}$ = 8 Hz, $C_{3'}H$), 5.62 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{2'}H$), 5.90 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.45 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.1–7.6 (m, 5, Ar), 7.95 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{16}H_{16}N_2O_6IP$: C, 39.20; H, 3.29; N, 5.72. Found: C, 39.19; H, 3.27; N, 5.87.

The faster moving isomer was crystallized from ethanol: mp 196–197°: λ_{max}^{MeOH} 225 mμ (ε 9800), 247 (8600); ORD (MeOH) positive Cotton effect with a peak at 265 mμ (Φ +4100°), zero rotation at 252 mμ and a trough at 227 mμ (Φ −26,000°); nmr (d_6-DMSO) almost identical with that of the slower isomer.

Anal. Calcd for $C_{16}H_{16}N_2O_6IP$: C, 39.20; H, 3.29; N, 5.72. Found: C, 38.95; H, 3.31; N, 6.08.

2',3'-O-Isopropylidene-N^3,5'-cycloadenosine Iodide (23).—2',3'-O-Isopropylideneadenosine (307 mg, 1 mmol) and **1** (1.4 g, 3 mmol) were allowed to react overnight in DMF (15 ml). After addition of methanol the solvent was evaporated and upon addition of ethyl acetate 400 mg (96%) of pure **23** separated as a white precipitate. Crystallization from ethanol gave colorless crystals with mp 280–282° dec (lit.[32] mp 277° dec); $\lambda_{max}^{H_2O}$ 273 mμ (ε 15,400), 220 mμ (ε 20,700); ORD (H_2O) negative Cotton effect with a trough at 272 mμ (Φ −4600°), zero rotation at 257 mμ, a shoulder at 232 mμ (Φ +10,000°), and a peak at 212 mμ (Φ +35,000°);[41] nmr (d_5-pyridine) 1.35 and 1.55 (s, 3, CMe_2), 3.39 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.83 (q, 1, J_{gem} = 14 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.67 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 4.84 (m, 1, $C_{4'}H$), 5.01 (d, 1, $J_{2'3'}$ = 6 Hz, $C_{2'}H$), 6.04 (s, 1, $C_{1'}H$), 7.86 (s, 1, C_8H), 9.56 (s, 1, C_2H). The spectrum in d_6-DMSO gave less resolution of the sugar protons and led to a large solvent shift of the C_2H and C_8H protons which appeared at 8.60 and 8.76 ppm.

N^3,5'-Cycloadenosine (29).—Adenosine (267 mg, 1 mmol) and **1** (500 mg, 1.1 mmol) were allowed to react for 5 min in DMF (5 ml) and after addition of methanol (1 ml) the mixture was evaporated to dryness. Addition of ethyl acetate gave a white crystalline residue that was dissolved in water and repeatedly extracted with ethyl acetate to remove two relatively nonpolar byproducts. Evaporation of the aqueous phase and crystallization of the residue from methanol gave 189 mg (50%) of **29** which melted with decomposition at 215–230°: $\lambda_{max}^{H_2O}$ 220 mμ (ε 21,700), 273 (13,500); ORD (H_2O) negative Cotton effect with a trough at 272 mμ (Φ −7970°), zero rotation at 237 mμ and a peak at 235 mμ (Φ +615°); nmr (d_6-DMSO) 3.99 ppm (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.30 (m, 1, $C_{3'}H$), 4.69 (br s, 2, $C_{5'}H_2$), 4.90 (br s, 1, $C_{4'}H$), 6.41 (s, 1, $C_{1'}H$), 8.49 (s, 1, C_2H or C_8H), 8.72 (s, 1, C_2H or C_8H).

Anal. Calcd for $C_{10}H_{12}N_5O_3I$: C, 31.84; H, 3.21; N, 18.57. Found: C, 32.02; H, 3.38; N, 18.45.

2',3'-O-Isopropylidene-N^3,5'-cycloguanosine Iodide (24).—2',3'-O-Isopropylideneguanosine (323 mg, 1 mmol) and **1** (640 mg, 1.4 mmol) were allowed to react overnight in DMF (10 ml). After addition of methanol, evaporation to dryness, and addition of ethyl acetate, 375 mg (87%) of crystalline **24** was obtained. Recrystallization from aqueous acetone gave needles with mp above 300°; $\lambda_{max}^{H_2O}$ 219 mμ (ε 37,800), 265 (11,000); $\lambda_{max}^{pH\,2}$ 228 mμ (ε 18,500), 260 (sh, 11,000); $\lambda_{max}^{pH\,12}$ 220 mμ (ε 36,400), 260 (9800) all in agreement with earlier reports;[33] nmr (d_6-DMSO) 1.24 and 1.46 ppm (s, 3, CMe_2), 3.99 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 4.55 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 4.77 (q, 1, J_{gem} = 14

(41) These data are in agreement with those of others: (a) A. Hampton and A. W. Nichol, *J. Org. Chem.*, **32**, 1688 (1967); (b) D. W. Miles, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967).

Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.93 (m, 1, $C_{4'}H$), 5.00 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 6.53 (s, 1, $C_{1'}H$), 8.10 (s, 1, C_8H).

Iodination of 2',3'-O-Isopropylideneinosine.—2',3'-O-Isopropylideneinosine (616 mg, 2 mmol) and **1** (1.7 g) were allowed to react overnight in DMF (10 ml) containing pyridine (0.8 ml). After addition of methanol and evaporation of the solvent, the residue was partitioned between water and chloroform. Pyridine (0.5 ml) was added to the aqueous phase and the solvent was evaporated leaving a crystalline residue that was recrystallized from ethanol giving 470 mg (76%) of 2',3'-O-isopropylidene-N^3,5'-cycloinosine (**25**) with mp 265–268° (lit.[33b] mp 266–269°); $\lambda_{max}^{H_2O}$ 252 mμ (ε 6500); $\lambda_{max}^{pH\ 2}$ 253 mμ (ε 7300); $\lambda_{max}^{pH\ 12}$ 253 mμ (ε 6700) and changing to λ_{max} 269 mμ (ε 11,300) within 2 hr; nmr (d_5-pyridine) 1.23 and 1.46 ppm (s, 3, CMe_2), 3.04 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 1.5 Hz, $C_{5'a}H$), 4.83 (m, 1, $C_{4'}H$), 4.93 (s, 1, $J_{2',3'}$ = $J_{3',4'}$ = 0 Hz, $C_{3'}H$ or $C_{2'}H$), 4.95 (s, 1, $C_{3'}H$ or $C_{2'}H$), 5.10 (q, 1, J_{gem} = 14 Hz, $J_{4',5'}$ = 2.5 Hz, $C_{5'a}H$), 6.39 (s, 1, $C_{1'}H$), 8.02 (s, 1, C_2H or C_8H), 8.91 (s, 1, C_2H or C_8H).

Anal. Calcd for $C_{13}H_{14}N_4O_4 \cdot H_2O$: C, 50.64; H, 5.23; N, 18.18. Found: C, 50.61; H, 5.40; N, 18.34.

Evaporation of the chloroform phase left a syrup (1.04 g) that was crystallized from ethanol giving 65 mg of 5'-deoxy-5'-iodo-2',3'-O-isopropylideneinosine (**26**) as needles of mp 195–197° dec (lit.[34] mp 203–204° dec). Chromatography of the mother liquors on a column of silicic acid using a gradient (0–30%) of methanol in chloroform gave a further 70 mg (total yield 15%) of **26**: λ_{max}^{MeOH,H^+} 249 mμ (ε 11,600); $\lambda_{max}^{MeOH/OH^-}$ 254 mμ (ε 12,200); nmr (d_6-DMSO) 1.52 and 1.32 ppm (s, 3, CMe_2), 3.41 (m, 2, $C_{5'}H_2$), 4.35 (h, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 6.5 Hz, $C_{4'}H$), 4.99 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 5.45 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 6.24 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 8.16 (s, 1, C_2H or C_8H), 8.36 (s, 1, C_2H or C_8H); ORD (H_2O) negative Cotton effect with a trough at 285 mμ (Φ −3300°) and a peak at 255 mμ (Φ −580°).

Anal. Calcd for $C_{13}H_{15}N_4O_4I$: C, 37.33; H, 3.62; N, 13.40. Found: C, 37.55; H, 3.82; N, 13.71.

Registry No.—**1**, 17579-99-6; **5a**, 362-43-6; **8b**, 14842-09-2; **10b**, 24498-13-3; **15b**, 24453-27-8; **19**, 24453-28-9; **22**, 24453-29-0; **29**, 24453-30-3; **14a**, 50-89-5.

Nucleosides. LXV. Synthesis and Reactions of Some Pyrimidine 2',6-Anhydronucleosides[1]

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The synthesis of a series of 4-substituted 2-oxo-6-hydroxypyrimidine 2',6-anhydronucleosides (4-oxo, 4-thio, 4-methylthio, 4-hydroxylamino, and 4-amino) is described, and their chemical properties are compared with certain 5',6-anhydronucleosides. These 2',6-anhydro compounds undergo facile ring opening in aqueous base to give the corresponding 6-oxo-1-β-D-arabinofuranosylpyrimidines, but unlike the 5',6-anhydronucleosides they are exceedingly stable in dilute aqueous acid. Treatment of either 4-amino- or 4-methylthio-1-β-D-arabinofuranosylpyrimidine-2,6-dione with aqueous acid gives 2',6-anhydro-1-(β-D-arabinofuranosyl)barbituric acid as the major product. In anhydrous base the 4-amino- and 4-methylthio-2',6-anhydro compounds undergo rearrangement to their 2',2-anhydro isomers. A plausible mechanism for this rearrangement is given.

Although pyrimidine nucleosides containing a 5',6-anhydro linkage (for example **1**) are now well known,[2-4] only one example (**2**) of the corresponding 2',6-anhydro system has been reported.[5,6] This study deals with the synthesis of a series of 2',6-anhydronucleosides and demonstrates that their chemical properties differ in several important respects from those of the 5',6-anhydro compounds.

The 2',6-anhydronucleoside **2**, which is readily prepared by treatment of arabinosyl-5-bromouracil with sodium methoxide in methanol,[5,7] was converted into a series of 4-substituted derivatives as outlined in Scheme I. These transformations involve the 4-thione **7**, a key intermediate that was prepared in 78% yield by thiation of the dibenzoate **4** with P_2S_5 in refluxing 1,4-dioxane.[8] Attempts to prepare the 4-amino nucleoside **9** by treatment of the 4-thione **7** with alcoholic ammonia under a variety of conditions resulted in either no reaction or in considerable degradation with very low yields (<10%) of the desired product **9**. Similarly, treatment of the 4-methylthio nucleoside **8** with either liquid or alcoholic ammonia failed to give acceptable yields of **9**. As will be shown later, the low yields of **9** obtained in these amination reactions are due in part to unexpected rearrangements of the 4-methylthio nucleoside **8** and of **9** itself.

A satisfactory synthesis of the 4-amino nucleoside **9** was achieved *via* the 4-hydroxylamino nucleoside **12**. The 4-methylthio derivative **8** (obtained *via* **10**) reacted with an excess of hydroxylamine in methanol to give **12** directly. Under the same conditions, however, the 4-thione **10** afforded an intermediate bishydroxylamino compound[9] **11** which underwent acid-catalyzed elimination of hydroxylamine to give **12** in 66% yield. Reduction of **12** using palladium–charcoal catalyst gave the 4-amino nucleoside **9**. Attempts to deaminate **9** with nitrous acid, as part of the structural proof, failed

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(2) B. A. Otter. E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).

(3) D. Lipkin, C. Cori, and M. Sano, *Tetrahedron Lett.*, 5993 (1968).

(4) P. K. Chang, *J. Org. Chem.*, **30**, 3913 (1965).

(5) B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, **33**, 3593 (1968).

(6) M. Honjo, Y. Furukawa, N. Nishikawa, K. Kamiya, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **15**, 1076 (1967).

(7) Compound **2** has also been prepared[6] by reductive dehalogenation of the corresponding 5-iodo nucleoside. The latter compound was isolated (yield unstated) from a mixture of products obtained by iodination of 1-β-D-arabinofuranosylcytosine.

(8) This reagent combination (P_2S_5–dioxane) affords higher yields of 4-thiones in a shorter reaction time than the conventional P_2S_5–pyridine system (R. S. Klein, *et al.*, manuscript in preparation) for the thiation of nucleosides. With the conventional system **7** was obtained in only ~50% yield after a 24-hr reaction period. The authors are indebted to Dr. M. P. Kotick of this institute for suggesting the applicability of the P_2S_5–dioxane reagent to nucleosides.

(9) An intermediate bishydroxylamino compound has also been observed in the hydroxylamination of 4-thiouridine; see I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *J. Med. Chem.*, **11**, 144 (1968), and references therein.