



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_ D. \_\_\_\_\_

Re: P1.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención en Fase Nacional PCT para "DERIVADO HEMISULFATO ANHIDRO CRISTALINO DE AZIDO CITOSINA".-Clase C07H 19/06.-Expediente número 05-054.870.-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 18 de Abril de 2008.

2. De acuerdo con el Concepto Técnico No. **918** se tiene que:

"Como consecuencia de la búsqueda de anterioridades de materia relacionada con la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- **Nucleoside analogues, Chemistry, biology and medical applications", R. T. WALKER ET. AL. (EDS), J. G. MOFFATT, 1979, Plenumm press, New York, Page(s) 71-164.**

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión 486, anexo me permito presentar a ese Despacho copia de los siguientes documentos solicitados:

- \* **Nucleoside analogues, Chemistry, biology and medical applications", R. T. WALKER ET. AL. (EDS), J. G. MOFFATT, 1979, Plenumm press, New York, Page(s) 71-164.**

**LLOREDA & CIA. S. A.**

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4. En vista de lo anterior, ruego a usted tomar atenta nota y proceder de conformidad.

Señor Superintendente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

# Nucleoside Analogues

Chemistry, Biology, and Medical Applications

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## CHEMICAL TRANSFORMATIONS OF THE SUGAR MOIETY OF NUCLEOSIDES†

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The last two decades have witnessed the proliferation of a rather vast literature concerning the synthesis and biological properties of nucleoside analogues. These interesting compounds can be roughly subdivided into two major groups--those containing modified heterocyclic bases, and those in which the sugar moiety has been altered and is no longer ribose or 2-deoxyribose as found in nucleic acids. Base analogues have in general been prepared either via N-glycosidation of suitably modified heterocycles or by structural transformations of the base moiety in existing nucleosides. Both of these approaches will be considered in detail during this meeting by my colleagues Drs. Vorbrüggen, Robins and Townsend. In a related way, nucleosides containing modified carbohydrate moieties have frequently been prepared via glycosidation of an appropriate purine or pyrimidine base with a suitable derivative of the desired sugar. Alternatively, a great deal of effort has been devoted to the development of specific chemical transformations suitable for introducing the desired modifications into the sugar moiety of intact nucleosides. It is this latter approach that has particularly fascinated the group in our laboratory and that I wish to review for you today. The subject is, however, a rather vast one, encompassing an enormous number of references, and accordingly I must, of necessity, be somewhat selective in what I specifically mention. Accordingly, I have decided to restrict my attentions to analogues of pentofuranosyl nucleosides and to make almost no mention of hexose derivatives.

†Contribution No. 527 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California, U.S.A.

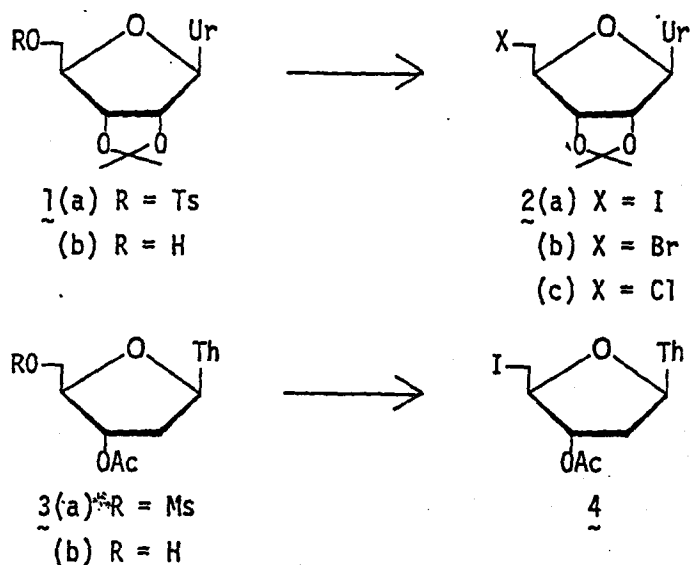
other than a few derived from pentoses. Also, a number of reactions which proceed by rather complex, multistep mechanisms will not be covered in detail and, in many cases, only representative examples of general reaction types will be considered. Much of the earlier literature on this general subject has been reviewed,<sup>1</sup> and major emphasis will be placed on more recent results.

In an effort to produce some order in an otherwise rather chaotic subject, I have decided to organize the material according to the position on the pentofuranose moiety that is undergoing modification and the nature of the functional group being introduced. Since reactions at the primary 5'-hydroxyl function are, in general, facile and mechanistically simple, they will be considered first and then be followed by discussion of modifications at the 2'-, 3'-, 4'- and 1'-positions.

## I. 5'-MODIFIED NUCLEOSIDES

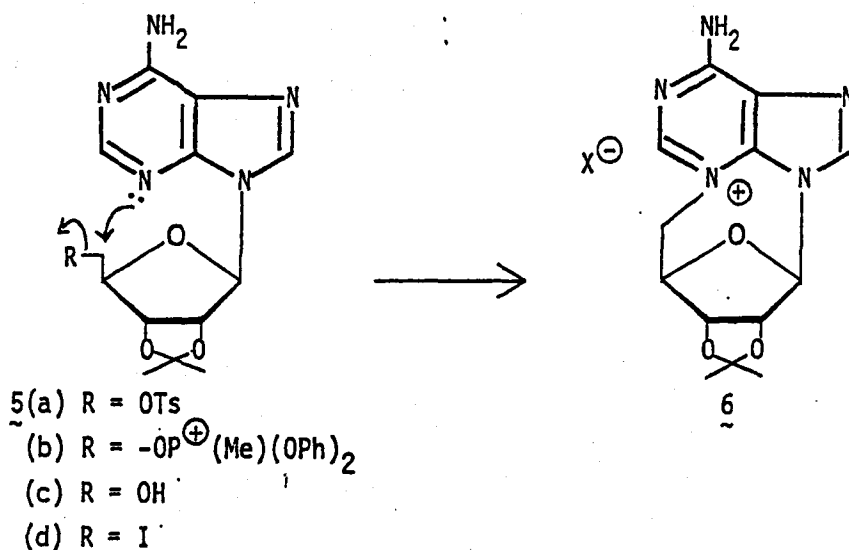
### A. 5'-Halogenated Nucleosides

Halogenated derivatives have played a key role in the development of nucleoside analogues because of the ease with which they can be transformed into deoxy, amino, thio and unsaturated compounds. As applied to pyrimidine nucleosides, the classical synthetic method involves simple nucleophilic displacement of a suitable 5'-O-sulfonate ester by an appropriate halide salt. In this way 2',3'-O-isopropylidene-5'-O-tosyluridine (1a) was readily converted into the corresponding 5'-deoxy-5'-iodouridine derivative (2a) by treatment with sodium iodide in hot acetone.<sup>2</sup> In the deoxynucleoside series, a very similar treatment of 3'-O-acetyl-5'-O-mesylthymidine (3a) with sodium iodide gave the 5'-iodo derivative (4) as part of the pioneering work of Michelson and Todd.<sup>3</sup> Since those times, many examples of this general type of reaction leading to variously substituted pyrimidine 5'-deoxy-5'-halonucleosides have been recorded. Most frequently the synthetically useful 5'-iodo derivatives have been prepared in this way,<sup>4</sup> but a number of 5'-bromo-<sup>5</sup> and 5'-fluoro<sup>6</sup> compounds have also been obtained via reaction of 5'-O-tosyl or 5'-O-mesyl-nucleosides with the appropriate tetrabutylammonium halides in dimethylformamide.

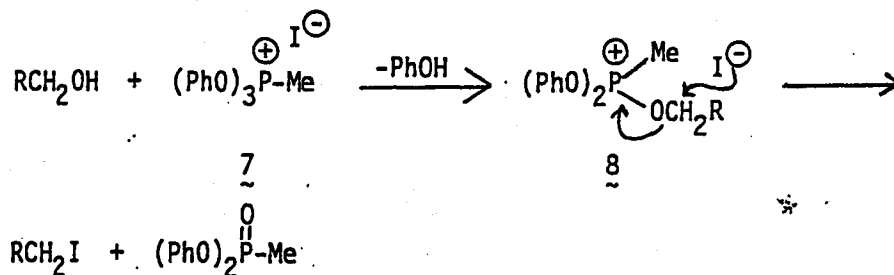


In a few cases, isolable intermediates other than the 5'-O-sulfonates have been used in nucleophilic displacement reactions. Thus, it has been shown by Duchinski, et al.<sup>7a</sup> and by Lichtenthaler and Müller<sup>7b</sup> that 5'-O-nitrate esters of pyrimidine nucleosides can be adequately displaced upon treatment with iodide or azide ion.

Attempted direct application of the sulfonate displacement reaction to purine nucleosides has led to only very limited success due to the propensity for competitive intramolecular displacement by N<sup>3</sup> of the purine ring. Thus, treatment of 2',3'-O-isopropylidene-5'-O-tosyladenosine (5a) in hot acetone, in the presence or absence of sodium iodide, leads to the rapid separation of the N<sup>3</sup>,5'-cycloadenosine derivative 6 in high yield.<sup>8</sup> Similar observations have been made in the guanosine,<sup>9a</sup> inosine<sup>9a</sup> and tubercidin<sup>9b</sup> series. Fortunately, Jahn<sup>10</sup> has observed that acylation of the 6-amino group on the adenine ring substantially reduces the nucleophilicity of N<sup>3</sup> and allows displacement of the -O-tosyl group by external nucleophiles such as halide ions in preference to cyclonucleoside formation. Jahn's original work made use of N-formyl and N-acetyl derivatives for this purpose, but subsequent work using a variety of other halogenation methods (see later) has shown that benzylation is also highly effective.



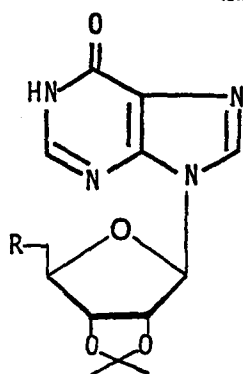
A number of reactive phosphorus containing reagents have also proved to be most useful for the preparation of 5'-halogenated nucleosides. One of these is methyltriphenoxyphosphonium iodide (7), a stable compound readily prepared from triphenyl phosphite and methyl iodide.<sup>11</sup> The Rydon reagent (7) is thought to react with alcohols with formation of the corresponding iodo compound according to the following mechanism:



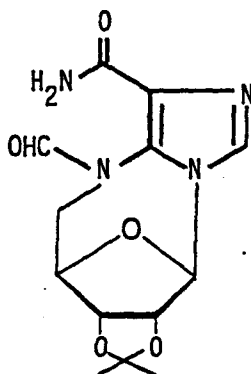
Lee<sup>12a</sup> and Kochetkov<sup>12b</sup> have used the reaction of 7 with a number of simple carbohydrate derivatives in benzene under reflux in order to effect iodination. Its use in the nucleoside series has been carefully explored by Verheyden and Moffatt<sup>11b,13</sup> using dimethylformamide as the solvent since most nucleosides and the reagent 7 have limited solubility in benzene. In dimethylformamide the iodination of primary nucleoside hydroxyl groups is extremely rapid, reactions of 2',3'-O-isopropylideneuridine (1b) and 3'-O-acetylthymidine (3b) with a small excess of 7 giving the crystalline 5'-deoxy-5'-iodo compounds, 2a and 4, in yields of 96 and 88% after only 10 min reaction at room temperature.<sup>11b</sup> For

extension to the cytidine series, it was of importance to initially acylate the 4-amino function since otherwise the formation of an N-(methyl-phenoxyphosphinyl) derivative constituted a serious side reaction.<sup>11b</sup> Using N<sup>4</sup>-acetyl-2',3'-O-isopropylidencytidine, however, the crystalline 5'-deoxy-5'-iodo derivative was obtained in 91% yield.<sup>11c</sup> It was also possible to effect fairly selective iodination at the 5'-position in unprotected nucleosides, treatment of free uridine and thymidine with 1.1 equivalents of **7** giving the crystalline 5'-deoxy-5'-iodonucleosides in yields of 65 and 63%.<sup>11b</sup> A number of other applications of **7** for the iodination of diverse nucleosides have been described (e.g., references 4e, 11c and 14).

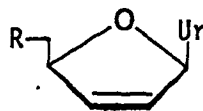
Once again, direct application of the Rydon reagent (**7**) to purine nucleosides in dimethylformamide was complicated by the formation of N<sup>3</sup>,5'-cyclonucleosides due to intramolecular displacement of diphenyl methylphosphonate from the initial intermediate corresponding to **8** (e.g. **5b**). Thus, reaction of 2',3'-O-isopropylideneadenosine (**5c**) with **7** in dimethylformamide led to the immediate precipitation of the N<sup>3</sup>,5'-cycloadenosine iodide **6** (X = I) in almost quantitative yield. Even free adenosine could be converted into N<sup>3</sup>,5'-cycloadenosine iodide in 50% yield.<sup>11b</sup> 2',3'-O-Isopropylideneinosine (**9a**) shows a somewhat reduced tendency towards cyclonucleoside formation, reaction with **7** in dimethylformamide giving a modest yield of the 5'-deoxy-5'-iodo derivative (**9b**) in addition to 76% of the cyclonucleoside hydrolysis product **10**.<sup>15</sup>



- 9(a)** R = OH  
 (b) R = I  
 (c) R = Br  
 (d) R = N<sub>3</sub>



**10**



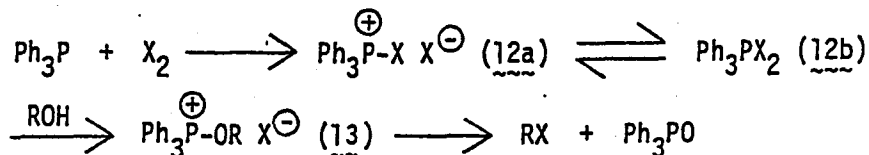
- 11(a)** R = OH  
 (b) R = N<sub>3</sub>  
 (c) R = NH<sub>2</sub>

Subsequently it has been found that by using dichloromethane or tetrahydrofuran, initially at a low temperature, as solvents

for the reaction, a variety of 2',3'-O-isopropylidene purine nucleosides can be converted into their 5'-iodo derivatives in excellent yields.<sup>16a</sup> Thus, for example, the reaction of 9a and 7 led to the isolation of the crystalline 5'-iodo derivative (9b) in 87% yield. This method is clearly useful for the preparation of synthetically useful 5'-deoxy-5'-iodo purine nucleosides, and has already been exploited by Srivastava, *et al.*<sup>16b</sup> for the iodination of certain imidazole nucleosides.

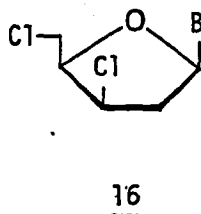
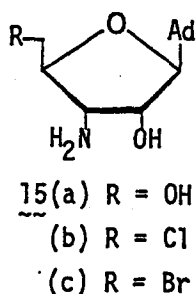
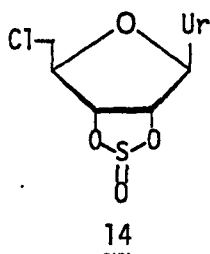
Several mechanistically related reagents based upon triphenylphosphine have also proved useful for the halogenation of nucleoside hydroxyl groups. One such method involves the use of triphenylphosphine and carbon tetrahalides, a procedure largely developed by Lee and Nolan.<sup>17</sup> The reactions of 2',3'-O-isopropylideneuridine (1b) in dimethylformamide with triphenylphosphine and CCl<sub>4</sub>, CBr<sub>4</sub> or CI<sub>4</sub> lead to the corresponding 5'-halo compounds (2c, 2b and 2a) without difficulty.<sup>18</sup> The yield of the chloro compound 2c was high, while those of 2b and 2a were progressively smaller. The reduced yields for the bromination and iodination reactions appear to be related to side reactions occurring with dimethylformamide since these are strikingly improved when pyridine is used as the solvent. The chloronucleoside, 2c, was also prepared in 70% yield using the rather unstable benzyltriphenoxyposphonium chloride, an analogue of the Rydon reagent 7.<sup>18</sup> The triphenylphosphine-carbon tetrachloride mixture has also been used for the 5'-chlorination of 2',3'-O-isopropylideneinosine (80-86%)<sup>18,19</sup> and N<sup>6</sup>,N<sup>6</sup>,O<sup>2'</sup>,O<sup>3'</sup>-tetrabenzoyl adenosine (86%)<sup>18</sup> as well as of the unprotected nucleosides uridine (55%), thymidine (73%), N<sup>4</sup>-acetylcytidine (58%)<sup>18</sup> and N<sup>4</sup>-benzoyl-2'-deoxycytidine (57%).<sup>11c</sup> In particular, it might be noted that 5'-iodination<sup>11c</sup> and chlorination<sup>20</sup> of the unsaturated nucleoside 11a can be achieved in high yields without allylic rearrangement using 7 and triphenylphosphine-carbon tetrachloride respectively.

Iodination and bromination reactions can also be advantageously accomplished using equimolar amounts of triphenylphosphine and either iodine or bromine. These reactions proceed via the formation of triphenylphosphine dihalides which can be either ionic (12a) or covalent (12b) depending upon solvent polarity.<sup>21</sup> Upon reaction with an alcohol, an oxytriphenylphosphonium salt (13), presumably identical to that from the triphenylphosphine-carbon tetrahalide reaction, is formed and collapses to the halide and triphenylphosphine oxide.



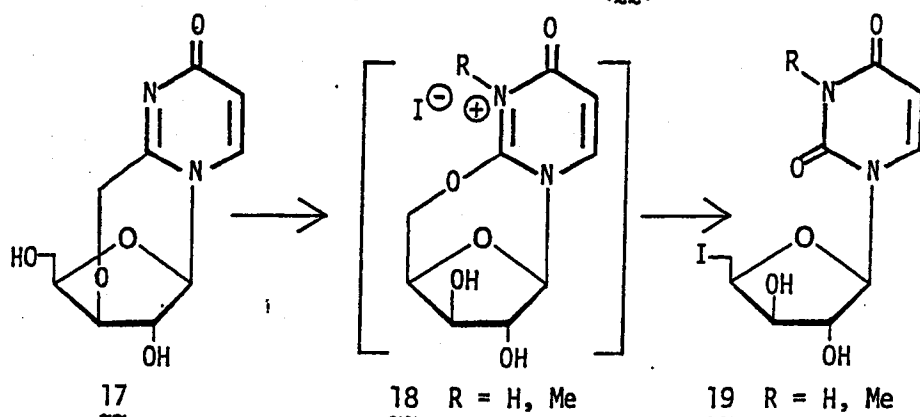
In our experience the use of triphenylphosphine and iodine in dimethylformamide provides a reasonably successful conversion of 1b to 2a (59%)<sup>18</sup> and has also been the reagent of choice for the preparation of certain iodinated sugars.<sup>22</sup> Haga, et al.<sup>19</sup> have, however, reported that comparable reactions of 2',3'-O-isopropylideneinosine (9a) with triphenylphosphine and iodine or bromine do not proceed well in dimethylformamide but are successful in triethyl phosphate at 80°. The reactions of adenosine derivatives with 11 have also been examined by Verenikina, et al.<sup>23</sup> but appear to lead predominantly to glycosidic cleavage.

Considerable success has been met in the simple chlorination and bromination of both purine and pyrimidine nucleosides using thionyl chloride and thionyl bromide. In certain cases thionyl chloride alone has proved useful for the chlorination of 2',3'-O-isopropylidene nucleosides,<sup>24a</sup> while others have used thionyl halides in dimethylformamide or the preformed halomethylenedimethylammonium halides<sup>24b</sup> for the same purposes. The most striking applications, however, are in the selective chlorination or bromination of the 5'-hydroxyl group in unprotected nucleosides upon treatment with the thionyl halide in hexamethylphosphoramide.<sup>25</sup> It has been pointed out that purification of the thionyl halide is essential,<sup>25b</sup> and in some cases an intermediate 2',3'-cyclic sulfite (14) has been isolated.<sup>26</sup> In certain cases the use of trialkyl phosphates as the solvent has been recommended<sup>25b,27</sup> as, for example, in the conversion of 3'-amino-3'-deoxyadenosine (15a) into the 5'-chloride (15b) and 5'-bromide (15c) in yields of 87 and 95%.<sup>27</sup> It is interesting to note that while unprotected ribo- and arabinofuranosyl nucleosides lead to preferential 5'-halogenation, 2'-deoxynucleosides give 2',3',5'-trideoxy-3',5'-dichloro- $\beta$ -D-threo-furanosyl compounds (16), albeit in somewhat reduced yields.<sup>25b,c,d</sup>



Some success has also been achieved in the 5'-chlorination of both 2',3'-O-isopropylideneuridine, or uridine itself, using arsenic trichloride in dimethylformamide, presumably via the generation of chloromethylenedimethylammonium chloride.<sup>28</sup> Finally, it should be noted that in certain cases 5'-iodonucleosides are the somewhat surprising major products arising from rearrangement

reactions involving 2,3'-anhydro- $\beta$ -D-xylofuranosyl nucleosides. Thus, Kikugawa, *et al.*<sup>29</sup> have shown that treatment of 17 with sodium iodide and acetic acid at 100°, or with methyl iodide in dimethylformamide at room temperature, gives the 5'-deoxy-5'-iodo- $\beta$ -D-xylofuranosyl nucleosides (19), presumably via rearrangement to the activated 2,5'-anhydro nucleosides (18).



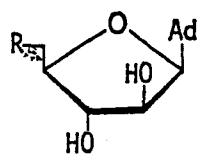
#### B. 5'-Nitrogen Substituents

Since azide ion is a particularly effective nucleophile in aprotic dipolar solvents, the majority of 5'-azido, and 5'-amino nucleosides arising from their reduction, have been prepared via direct  $S_N2$  displacement reactions of 5'-sulfonate esters. In the pyrimidine series, Horwitz, *et al.*<sup>30</sup> have demonstrated the conversion of 1a and 5'-O-tosylthymidine into the corresponding 5'-azido nucleosides upon treatment with lithium azide in hot dimethylformamide. This general reaction has been broadly extended to a variety of 5-substituted 2'-deoxyuridine and 2'-deoxycytidine derivatives by Lin and Prusoff.<sup>31</sup> Similar methods have been successfully used for the preparation of 5'-azido derivatives of 1- $\beta$ -D-arabinofuranosylcytosine<sup>32</sup> and 1- $\beta$ -D-xylofuranosyluracil.<sup>33</sup> It has been shown by Hata, *et al.*<sup>34</sup> that the reactions of various ribonucleosides containing unprotected sugars with triphenylphosphine, carbon tetrabromide and an excess of lithium azide in dimethylformamide lead directly to the 5'-azido compounds in good yields.

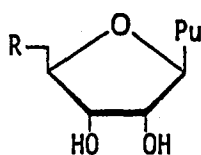
Applications of azide displacement in the purine nucleoside series essentially follow the patterns observed during iodination reactions. Thus, prior N<sup>6</sup>-acylation of the 2',3'-O-isopropylidene derivatives of 5'-O-tosyl- or 5'-O-mesyladenosine,<sup>10,35</sup> guanosine<sup>35</sup> and tubercidin<sup>36</sup> permits the preparation of the 5'-azido compounds with little concomitant formation of N<sup>3</sup>,5'-cyclonucleosides. The high nucleophilicity of azide ion and the reduced tendency of inosine derivatives to form N<sup>3</sup>,5'-cyclonucleosides permits the

direct formation of 5'-azido-5'-deoxy-2',3'-O-isopropylidene-inosine (9d) from the 5'-O-tosylate in 73% yield.<sup>37</sup> By use of the somewhat more reactive 5'-O-p-nitrobenzenesulfonyl derivative of 9a, the azide displacement can be conducted rapidly at room temperature.<sup>37</sup> Similarly, N<sup>6</sup>,O<sup>3'</sup>-diformyl-5'-O-tosyl-2'-deoxy-adenosine has been successfully converted into the corresponding 5'-azide.<sup>35</sup>

It is significant that 2,3'-O-isopropylidene derivatives of both purine and pyrimidine nucleosides show a greater tendency towards N<sup>3</sup>,5'-cyclonucleoside formation than do their unprotected analogues. Accordingly, it has proved possible to directly prepare 5'-azido-ara A (20b) from the corresponding 5'-O-tosylate (20a)<sup>38</sup> and to obtain a variety of 5'-alkylamino-5'-deoxy-guanosine<sup>39</sup> and adenosine<sup>40</sup> derivatives (21b) from the 5'-O-tosyl nucleosides (21a) and the corresponding free amines.



20(a) R = OTs

(b) R = N<sub>3</sub>

21(a) R = OTs

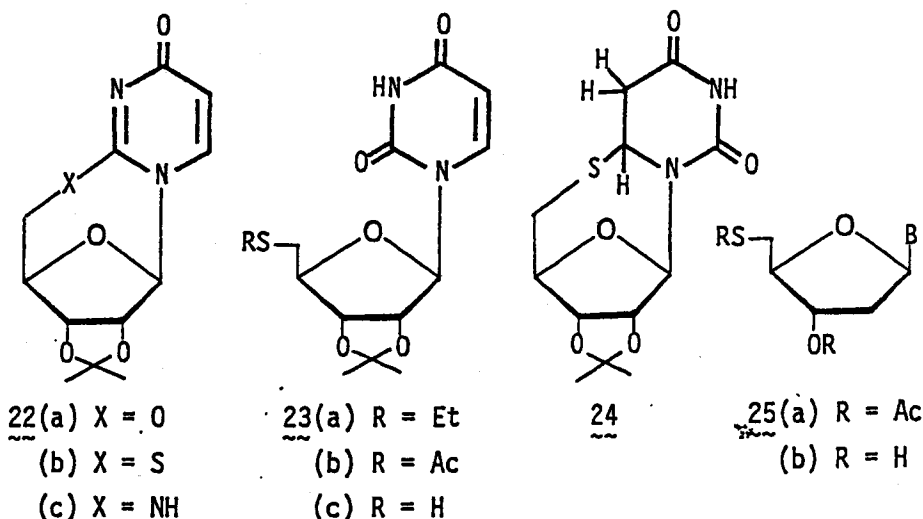
(b) R = NH Alkyl

The preparation of 5'-amino nucleosides, however, has most frequently been accomplished by palladium catalyzed reduction of the corresponding azido compounds. Such reductions are generally facile and have been used, *inter alia*, for the preparation of the 5'-amino derivatives of uridine,<sup>30</sup> thymidine,<sup>30</sup> adenosine,<sup>10,35</sup> deoxyadenosine,<sup>35</sup> 9-β-D-arabinofuranosyladenine,<sup>38</sup> 5-trifluoromethyl-2'-deoxyuridine,<sup>31a</sup> 1-β-D-arabinofuranosylcytosine,<sup>32</sup> 1-β-D-xylofuranosyluracil<sup>33</sup> and tubercidin.<sup>36</sup> In certain cases the presence of other catalytically reducible functions has required the use of different reductive methods. Thus, several 2',3'-unsaturated 5'-amino nucleosides (11c) were prepared by treatment of their azido counterparts (e.g. 11b) with hydrogen sulfide in pyridine<sup>41</sup> and a variety of 5-halo-5'-amino nucleosides in the 2'-deoxyuridine and 2'-deoxycytidine series were obtained via reduction of the azides with triphenylphosphine and ammonia.<sup>31b</sup>

### C. 5'-Sulfur Substituted Nucleosides

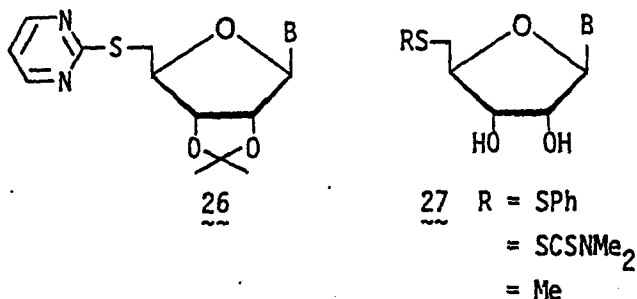
5'-Thionucleosides have been of some interest, both in their own right and as precursors of 5'-deoxynucleosides via desulfurization. These compounds have usually been approached via S<sub>N</sub>2 displacement reactions using a variety of sulfur nucleophiles. An

early example<sup>42</sup> was the preparation of the 5'-ethylthiouridine derivative (23a) via reaction of the 0<sup>2</sup>,5'-cyclonucleoside (22a) with sodium ethylmercaptide, which is to be contrasted with the attack at C<sub>2</sub> of the pyrimidine ring using hydrogen sulfide and triethylamine. The reaction of 2',3'-O-isopropylidene-5'-O-tosyluridine (1a) with potassium thioacetate successfully leads to the 5'-acetylthionucleoside (23b), but attempted generation of the free 5'-thiol with base is complicated by the formation of an equilibrium mixture of the desired 23c and the 5,6-dihydro-cyclonucleoside 24 formed via intramolecular conjugate addition to the enone system.<sup>43</sup> As in previously mentioned cases, the presence of the 2',3'-O-acetonide appears to favor such a cyclization, and upon acidic treatment 23b is converted predominantly into 5'-thiouridine, which shows no further tendency to undergo conjugate addition. For similar reasons the 3'-O-acetyl-5'-O-tosyl derivatives of thymidine and 5-fluoro-2'-deoxyuridine can be converted into the corresponding 5'-thioacetates (25a) and thence subjected to acidic deacetylation giving the 2',5'-dideoxy-5'-thionucleosides (25b) without difficulty.<sup>43</sup>



Several rather novel methods have been developed specifically for the preparation of 5'-deoxy-5'-thionucleosides as precursors of the corresponding 5'-deoxy compounds. Thus, the direct condensation of a variety of 2',3'-O-isopropylidene nucleosides with pyrimidine-2-thiol in the presence of dimethylformamide dioneopentyl acetal has been shown by Holy<sup>44</sup> to lead to the substituted 5'-thionucleosides 26 in good yields. This reaction appears to be quite specific for the 5'-hydroxyl function and can be conducted in 62% yield on free uridine.<sup>44</sup> Also, Nakagawa and Hata<sup>45</sup> have shown that unprotected nucleosides can be reacted with a variety of disulfides in the presence of tributylphosphine to

generate the corresponding 5'-thionucleosides (27) by way of thiophosphonium and oxyphosphonium intermediates.



The central role played by S-adenosylmethionine in biological methylation reactions has stimulated considerable interest in the preparation of 5'-thionucleosides in the purine series. Much of this has been based upon the work of Baddiley and Jamieson,<sup>46</sup> who have shown that 2',3'-O-isopropylidene-5'-O-tosyladenosine will react with sodium mercaptides in liquid ammonia to form the corresponding 5'-alkylthio derivatives. Numerous analogues of S-adenosylhomocysteine have been prepared in related ways,<sup>47</sup> frequently using 5'-chloro-5'-deoxyadenosine as the reactive intermediate, and certain compounds (e.g. 27, B = Ad, R = *i*-butyl) have been found to function as inhibitors of methyl transferases.<sup>48</sup> Similar reactions have also been extensively applied to nucleosides other than adenosine,<sup>37,49</sup> and to deoxynucleosides.<sup>47a,50</sup> In a few cases free 5'-thiopurine nucleosides (e.g. 27, R = H) have been prepared either by direct displacements using sodium hydrogen sulfide<sup>37</sup> or via the intermediacy of hydrolyzable intermediates. Thus, nucleophilic displacements using trilithium thiophosphate<sup>27</sup> or sodium triphenylmethylmercaptide<sup>47a</sup> have given substituted derivatives that can be cleaved to the free 5'-thiols.

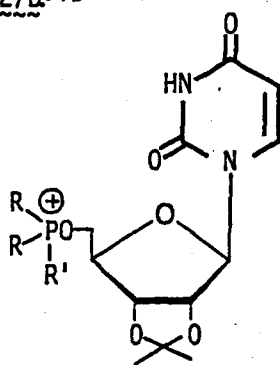
#### D. 5'-Cyclonucleosides

The formation and reactions of cyclonucleosides of various types have played central roles in the development of nucleoside chemistry.<sup>51</sup> In many cases the 5'-cyclonucleosides do not strictly fit into the scope of this review, since the carbohydrate skeleton remains intact and is only connected covalently to the heterocyclic base. Nevertheless, a brief review of the various types of cyclonucleosides is in order.

In the pyrimidine series there are two basic types of 5'-cyclonucleosides, those in which C<sub>5'</sub> is attached to C<sub>2</sub> of the heterocyclic base via various linkages, and those in which the linkage is to C<sub>6</sub>. The first type is historically older and more frequently encountered. Thus, Brown, *et al.*<sup>52</sup> showed in 1957 that

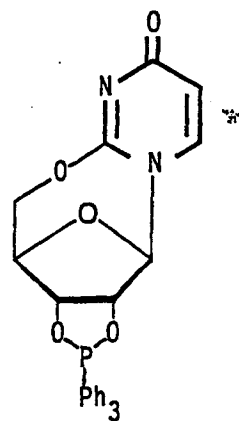
5'-deoxy-5'-iodo-2',3'-O-isopropylideneuridine (2a) readily reacts with silver acetate, presumably via a carbonium ion mechanism, to form 2',3'-O-isopropylidene-0<sup>2</sup>,5'-cyclouridine (22a).<sup>53a</sup> In a similar way, treatment of 5'-deoxy-5'-iodothymidine with silver acetate in acetonitrile,<sup>54a</sup> or of 3'-O-acetyl-5'-O-mesylthymidine with strong organic bases,<sup>54b</sup> led to the formation of the 0<sup>2</sup>,5'-cyclothymidine derivatives. The same type of intramolecular displacement by a C<sub>2</sub>-carbonyl group of sulfonate or halide groups at the 5'-position has been applied to numerous other pyrimidine nucleosides including cytidine,<sup>55a</sup> 6-azauridine,<sup>55b</sup> 2'-deoxycytidine<sup>55c</sup> and a 6-oxopyrimidine derivative.<sup>56</sup> The sulfur and nitrogen bridged cyclonucleosides (22b, c) have also been obtained by intramolecular displacement of 5'-O-tosylate groups in 2-thiouridine and isocytidine derivatives.<sup>57</sup>

In principle, the formation of an 0<sup>2</sup>,5'-cyclonucleoside should be possible whenever a reactive leaving group is generated at C<sub>5'</sub> in the absence of an effective external nucleophile. One such approach has been developed by Wada and Mitsunobu<sup>58a</sup> through reaction of 2',3'-O-isopropylideneuridine (2b) with triphenylphosphine and diethyl azodicarboxylate. Such a mixture leads to the formation of the 5'-oxyphosphonium species (27a), which undergoes intramolecular displacement by 0<sup>2</sup> of the uracil ring giving the 0<sup>2</sup>,5'-cyclonucleoside (22a) in 80% yield. A similar reaction with free uridine led to the crystalline 0<sup>2</sup>,5'-cyclouridine-2',3'-phosphorane (28), which could be readily hydrolyzed to the 2',3'-diol.<sup>58b</sup> Along related lines, the reaction of 2b with methyltriphenoxyphosphonium perchlorate (prepared *in situ* from 7 and silver perchlorate) gave a modest yield of 22a via the presumed intermediate 27b.<sup>11b</sup>



27(a) R, R' = Ph

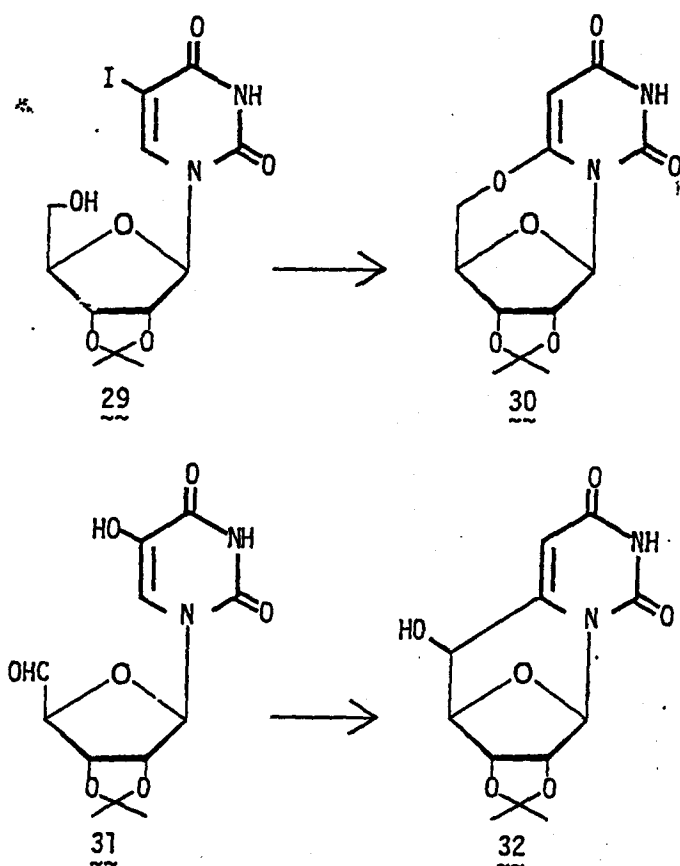
(b) R = OPh, R' = Me



28

The second major class of pyrimidine-5'-cyclonucleosides is that involving the linkage of C<sub>5'</sub> to C<sub>6</sub> of the pyrimidine ring.

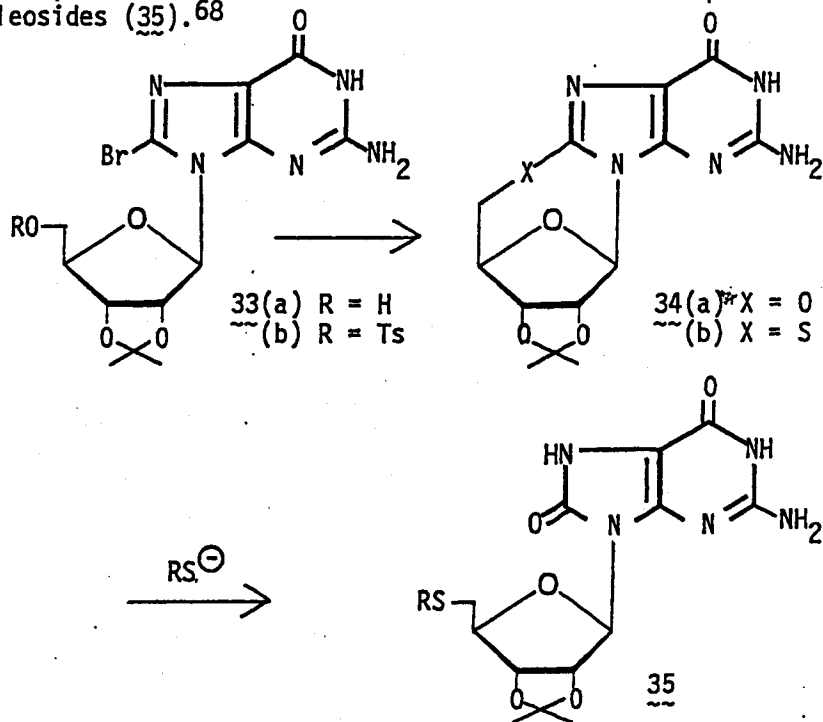
One route to such compounds involves a base catalyzed conjugate addition-elimination sequence in 5-iodopyrimidine ribo- or deoxyribonucleosides,<sup>59</sup> as in the conversion of 5-iodouridine (29) to 5',6-cyclouridine (30). A similar route has also been used in the cytidine series.<sup>59</sup> Several related compounds containing sulfur and nitrogen in the cyclonucleoside bridge (cf. 22b, c) have also been prepared via generation of 5'-thio- and 5'-amino-5-bromouridine derivatives via a similar mechanism.<sup>60</sup> Finally, a few cyclonucleosides (32) in which C<sub>5</sub> is directly bonded to C<sub>6</sub> have been ingeniously prepared via an aldol type of reaction in a 5-hydroxy nucleoside 5'-aldehyde (31) followed by removal of the enolized C<sup>5</sup>-oxygen function.<sup>61</sup> A methylene homologue of 32 has also been prepared via diazomethane induced ring expansion of the 5'-ketone derived from 32.<sup>61b</sup>



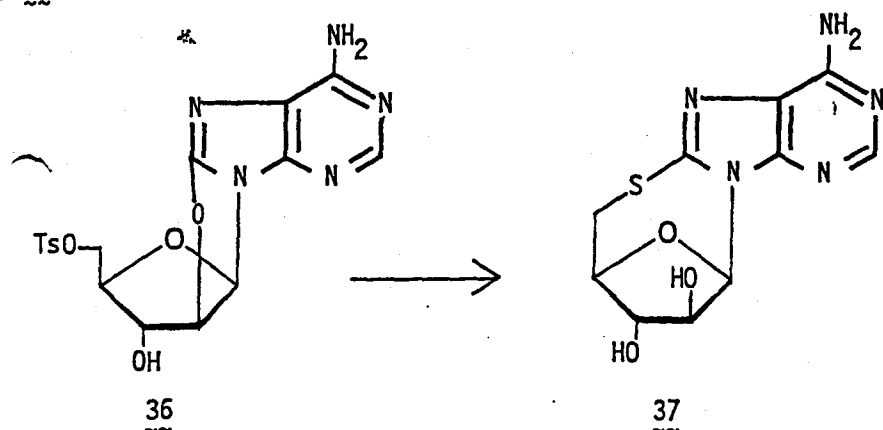
In the purine series, mention has already been made of the ease with which intramolecular displacement of leaving groups at C<sub>5</sub> by attack of N<sup>3</sup> leads to N<sup>3</sup>,5'-cyclonucleosides (e.g. 6).<sup>8,9</sup> This type of reaction, using the readily displaced 5'-O-tosyl

group, has been applied in the adenosine,<sup>8</sup> guanosine,<sup>9a,49a</sup> inosine<sup>9a</sup> (see, however, Reference 15 for the corrected structure 10), and tubercidin<sup>9b</sup> series. Related displacement of the 5'-O-(di-p-nitrophenyl phosphate) group has also been observed in the 2',3'-O-isopropylidene-guanosine series,<sup>62</sup> and activation of the 5'-position can also be achieved using reactions of dimethyl-formamide acetals with xanthosine<sup>63a</sup> and formycin.<sup>63b</sup> In the latter case N<sup>2</sup> of the pyrazole ring is the preferred nucleophile. As mentioned earlier, reaction of 2',3'-O-isopropylidene-purine nucleosides with the Rydon reagent (7) in dimethylformamide provides a convenient source of N<sup>3</sup>,5'-cyclonucleosides.<sup>11b</sup> The latter reaction has also been successfully applied to certain 5-aza-7-deazapurine nucleosides<sup>64</sup> as part of a frequently employed chemical confirmation of the  $\beta$ -configuration of purine nucleosides.<sup>65</sup>

A large body of work, much due to Ikehara, et al.,<sup>66</sup> has been directed toward the synthesis and reactions of various 8,5'-cyclo-nucleosides such as 34. The oxygen bridged compounds (e.g. 34a) are generally prepared by treatment of 8-bromo-2',3'-O-isopropylidene nucleosides (e.g. 33a) with sodium hydride, a reaction that is readily applied in the adenosine<sup>67</sup> and guanosine<sup>68</sup> series. It might be noted that reactions of 34a with various sulfur nucleophiles (e.g. H<sub>2</sub>S-pyridine, potassium thioacetate, potassium thiocyanate) lead to the formation of the 5'-thio-8-oxopurine nucleosides (35).<sup>68</sup>

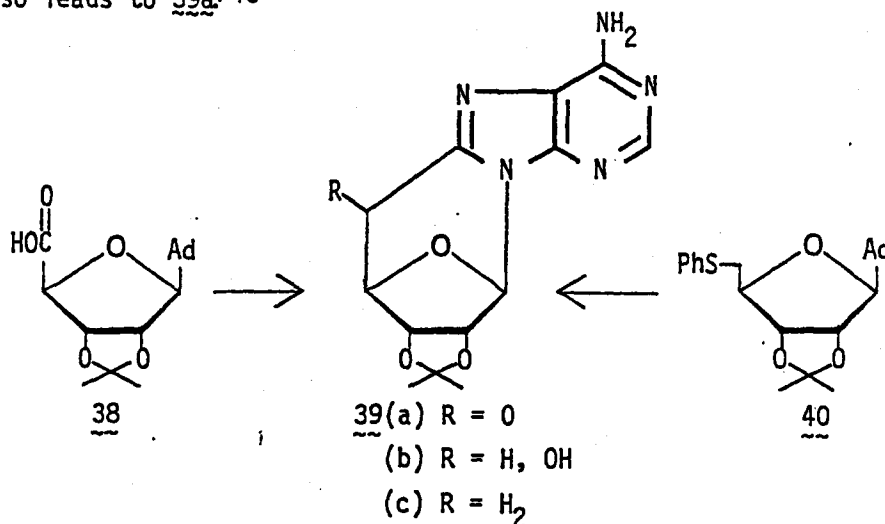


The sulfur bridged cyclonucleosides (e.g. 34b) have been readily prepared via treatment of the 8-bromo-5'-O-tosyl (or mesyl) nucleosides with hydrogen sulfide in pyridine.<sup>69</sup> The latter reaction has been applied to variously substituted adenosine and guanosine derivatives and the sulfur atom has been both reduced with Raney nickel<sup>69a-c</sup> and oxidized using chlorine or hydrogen peroxide<sup>69d</sup> to generate 5'-deoxy- and 5'-deoxy-5'-sulfonic acid nucleosides respectively. In a related way, several 8,5'-iminocycloadenosine derivatives (adenine analogues of 34 with X = NH) have been prepared via reaction of the 8-bromo-5'-O-tosyl nucleoside with hydrazine followed by oxidative cleavage of the N-N bond.<sup>70</sup> The 8,5'-thiocycloadenosine derivative having the arabinofuranosyl configuration (37) has been prepared via intramolecular rearrangement of an 8,2'-cyclonucleoside (36, see later) upon treatment with sodium sulfide.<sup>71</sup> A related treatment of the 8,3'-cyclonucleoside leads to the  $\beta$ -D-xylofuranosyl isomer of 37.<sup>71</sup>



A few examples of direct carbon-carbon bonding of C<sub>5'</sub> to C<sub>8</sub>, a type of linkage which has been shown to arise from anaerobic photolysis of 5'-deoxyadenosylcobalamine,<sup>72</sup> have also been reported. The first of these was the formation, in very low yield, of the 8'-keto-8,5'-cycloadenosine derivative 39a upon treatment of 2',3'-diisopropylideneadenosine 5'-carboxylate (38) with methyl-lithium.<sup>73</sup> The diastereomeric 5'-alcohols (39b) could be derived by borohydride reduction of 39a. In a much more efficient process, Matsuda, et al.<sup>74</sup> have reported that photolysis of 5'-deoxy-2',3'-diisopropylidene-5'-phenylthioadenosine (40) in the presence of triethylphosphite leads to the 8,5'-cyclonucleoside 39c in 66% yield. Selenium dioxide oxidation of 39c generated 39a in high yield<sup>74b</sup> but with somewhat different properties than those by the other route.<sup>73</sup> In this case borohydride reduction stereospecifically gave the 5(S) alcohol 39b that could be inverted via the mesylate. A similar method is also applicable in the adenosine<sup>74a</sup> and guanosine<sup>74b</sup> series. The alternative approach

using photolysis of 2',3'-O-isopropylidene-8-phenylthioadenosine also leads to 39a.<sup>74c</sup>



#### E. 5'-Deoxynucleosides

In general, 5'-deoxynucleosides have been prepared via either catalytic or radical induced reduction of appropriate 5'-deoxy-5'-halonucleosides or by desulfurization of 5'-deoxy-5'-thionucleosides using activated nickel. In view of the large number of compounds of the above two classes that have been prepared, both classes of reaction have been widely exploited under rather standard conditions. A partial list of compounds prepared via palladium catalyzed hydrogenolysis of 5'-halo compounds includes the 5'-deoxy analogues of uridine,<sup>4a</sup> 2'-deoxyuridine,<sup>4d</sup> thymidine,<sup>3,4d</sup> 2'-deoxycytidine,<sup>4e</sup> cytidine,<sup>11c</sup> adenosine,<sup>75</sup> tubercidin,<sup>9b</sup> and 3'-deoxythymidine.<sup>3</sup>

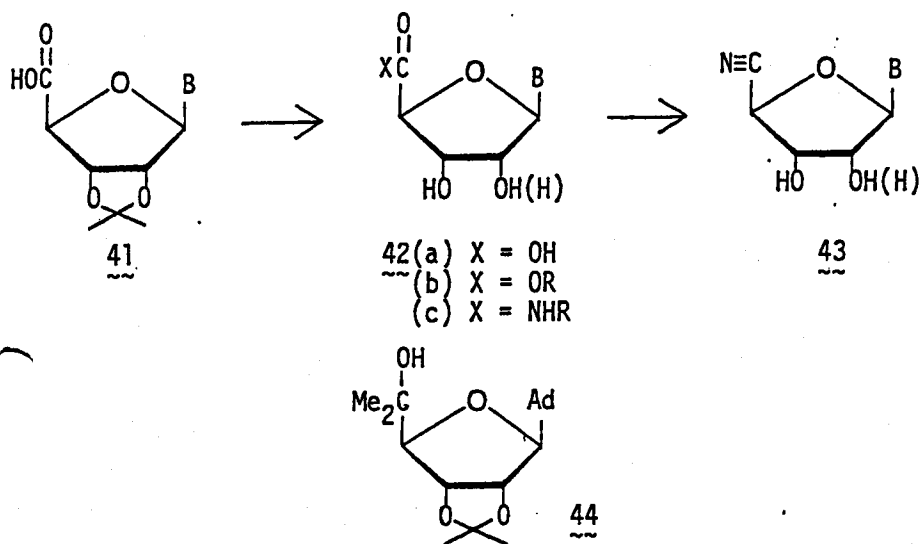
Radical induced dehalogenation in the presence of tributylstannane is particularly well suited for reduction of chlorosugar nucleosides which are generally resistant to catalytic hydrogenation. This technique has been used for the preparation of the 5'-deoxy derivatives of uridine,<sup>5,25c,26</sup> 5-fluorouridine,<sup>26</sup> 5-methyluridine,<sup>25c</sup> 2'-deoxyuridine,<sup>5</sup> 1-β-D-arabinofuranosylthymine,<sup>25c</sup> adenosine,<sup>25c</sup> 9-β-D-arabinofuranosyladenine,<sup>25c</sup> 3'-deoxythymidine,<sup>25c</sup> 2',3'-dideoxyadenosine,<sup>25c</sup> toyocamycin,<sup>25c</sup> and sangivamycin.<sup>25c</sup>

Nickel catalyzed desulfurization of 5'-thionucleosides has been used to prepare the 5'-deoxy analogues of uridine,<sup>44</sup> cytidine,<sup>44</sup> thymidine,<sup>44</sup> 6-azauridine,<sup>44</sup> inosine,<sup>44</sup> guanosine,<sup>49a</sup> and 2'-deoxyadenosine,<sup>50</sup> while the 8,5'-thiocyclonucleosides have been the precursors of 5'-deoxyadenosine<sup>69a,b</sup> and 5'-deoxyguanosine.<sup>69c</sup>

### F. 5'-Carbonyl Derivatives of Nucleosides

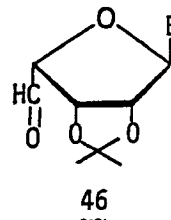
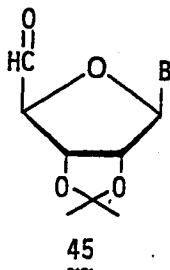
Aldehydes and carboxylic acid derivatives are amongst the most synthetically useful functional groups in organic chemistry. Accordingly, considerable work has been devoted to oxidation reactions of the 5'-hydroxyl group in nucleosides. For the preparation of nucleoside 5'-carboxylates (42a), direct treatment of the free nucleoside with oxygen or hydrogen peroxide in the presence of a platinum catalyst at a slightly alkaline pH has been found to be a generally successful procedure.<sup>76</sup> By its use, successful syntheses of the 5'-carboxylate analogues of uridine,<sup>76e</sup> 5-fluorouridine,<sup>76b</sup> adenosine,<sup>76e</sup> thymidine,<sup>76e</sup> guanosine,<sup>76c</sup> and a variety of 5-substituted pyrimidine nucleosides<sup>76d</sup> have been recorded. Catalytic oxidation of the 5'-hydroxyl terminus of short oligodeoxynucleotides has been considered as a route for stepwise degradation.<sup>76a,e</sup>

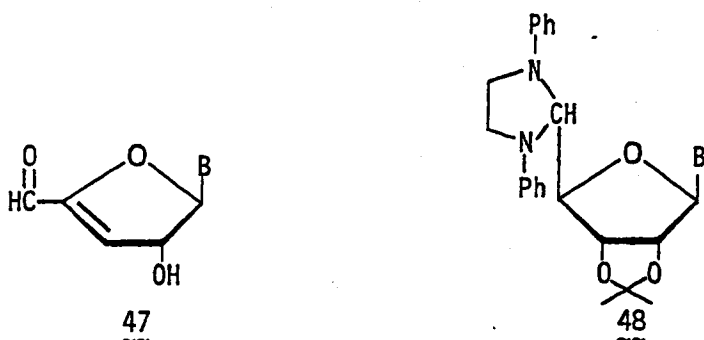
Chemical oxidation of protected nucleosides has also proved to be useful, with treatment of 2',3'-O-isopropylideneadenosine with alkaline potassium permanganate providing the corresponding 5'-carboxylate (41) in yields of up to 80%.<sup>77a</sup> While this method is also successful with 2-amino-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)purine,<sup>77b</sup> and with certain imidazole nucleosides,<sup>77e</sup> it has been reported as unsuitable with the uridine, inosine or guanosine derivatives.<sup>77b</sup> Successful oxidation of 2',3'-O-isopropylideneinosine has, however, been reported using chromic oxide in acetic acid.<sup>78</sup>



The carboxylic acids (41 and 42a) from a number of nucleosides have been converted into a variety of simple esters (42b) via both direct coupling methods<sup>77c,d,e,79</sup> and initial formation of the acid chloride using thionyl chloride.<sup>78,80</sup> This type of compound has been actively investigated since ethyl adenosine 5'-carboxylate (42, B = Ad, X = OH) has been shown to possess interesting cardiovascular properties.<sup>77d,80c</sup> A number of simple 5'-carboxylic acid amides (42c) have also been prepared by aminolysis of the corresponding esters<sup>79b,c,e</sup> and also by direct carbodiimide coupling of the acids with amines and amino acids.<sup>79a,81</sup> In addition, the simple amides derived from adenosine, uridine, thymidine, 5-halouridines and 6-azauridine (42c, R = H) have been dehydrated to the corresponding nitriles (43).<sup>76d,79b,c</sup> Methyl 2',3'-O-isopropylideneadenosine 5'-carboxylate has also been converted in 30% yield into the tertiary alcohol 44 via reaction with methylmagnesium iodide,<sup>77c</sup> and this yield has been increased to 95% by modification of reaction conditions.<sup>82</sup>

While adenosine 5'-aldehyde was recognized in 1962 as a product from the photolysis of Vitamin B<sub>12</sub>,<sup>83</sup> the synthesis of nucleoside 5'-aldehyde derivatives in pure form proved to be a challenging goal. The development by Pfitzner and Moffatt of the dimethylsulfoxide-dicyclohexylcarbodiimide method of oxidation<sup>84</sup> provided the element of selectivity that was necessary since the mechanism of that reaction<sup>85</sup> does not permit the otherwise facile overoxidation of aldehydes to carboxylic acids. In the original work with this oxidative method it was shown that 2',3'-O-isopropylideneadenosine and other suitably blocked compounds such as 3'-O-acetylthymidine could be converted with reasonable efficiency into the corresponding 5'-aldehydes (e.g. 45). Purification of these compounds, however, proved to be exceedingly difficult since during any attempted chromatography on silica gel or related adsorbants the aldehyde underwent partial epimerization to the  $\alpha$ -L-lyxofuranosyl aldehyde (46) or elimination of the acetal or ester function giving unsaturated aldehydes (e.g. 47).<sup>86</sup>

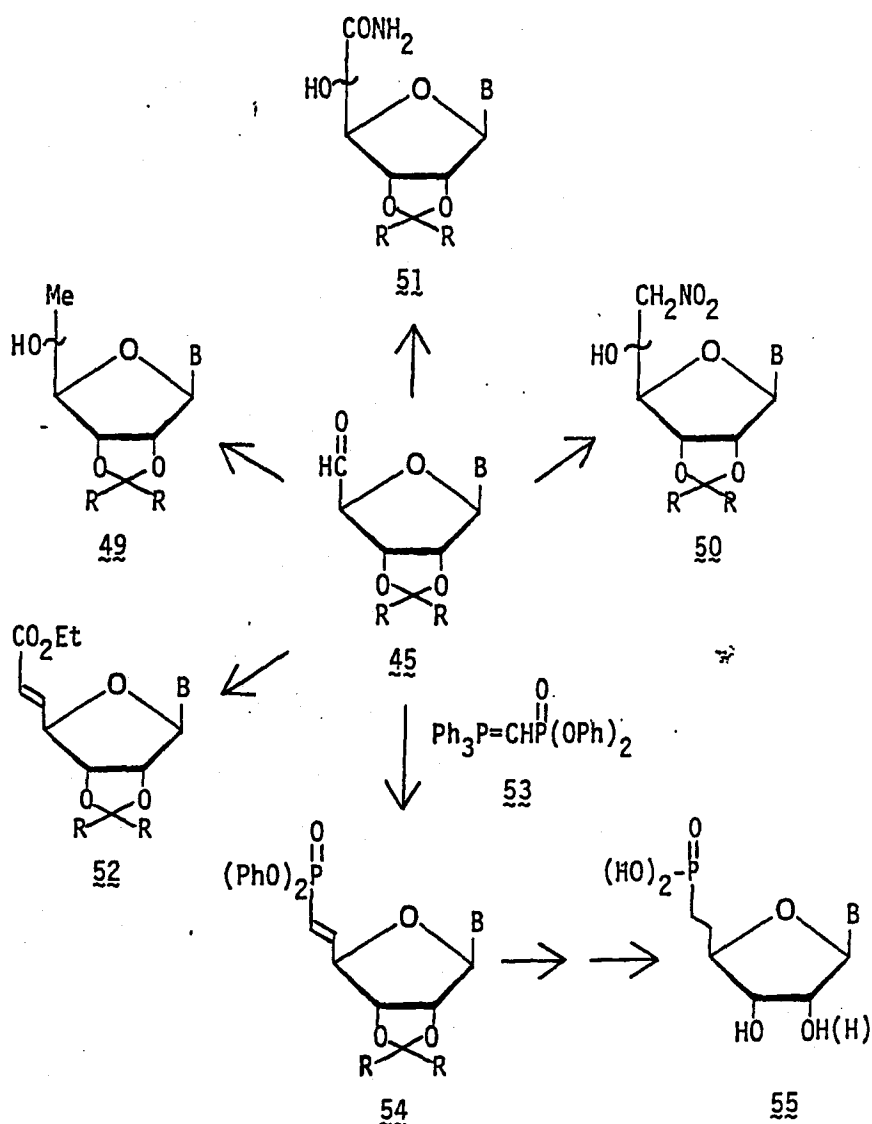




Because of these problems in purification of the aldehydes, a considerable number of studies on the reactions of these versatile intermediates were done using the crude products of oxidation reactions and led to variable results. A satisfactory solution to this problem was found with the discovery that variously protected nucleoside 5'-aldehydes (45) form crystalline 1,3-diphenylimidazolidine derivatives (e.g. 48) upon reaction with N,N'-diphenylethylenediamine.<sup>87a</sup> These derivatives in general have low solubilities in methanol and can be isolated in satisfactory yield from crude oxidation reaction mixtures by direct crystallization. Regeneration of the free 5'-aldehyde function (e.g. 45) can then be accomplished by mild acidic treatments that do not affect other desirable protecting groups. We have found that treatment with a slight excess of p-toluenesulfonic acid monohydrate in a mixture of acetone and methylene chloride at 0°, or with an acidic ion exchange resin in aqueous dioxane, is suitable for the cleavage step. Using the imidazolidine procedure, purified 5'-aldehydes derived from 2',3'-O-acetals of uridine,<sup>87a,d</sup> N<sup>6</sup>-benzoyl-adenosine,<sup>82,87b</sup> N<sup>4</sup>-acetylcytidine,<sup>87c,d</sup> N<sup>4</sup>-benzoylcytidine,<sup>87c</sup> 5-acetoxyuridine,<sup>61</sup> Virazole,<sup>87e</sup> and S-methyl-6-thioinosine,<sup>87f</sup> as well as of 3'-O-acetyl- and 3'-O-benzylthymidine,<sup>87c,f</sup> have been prepared. In addition, crude 5'-aldehydes derived from oxidation of suitably protected derivatives of adenosine,<sup>88a,b</sup> uridine,<sup>88c</sup> 6-chloropurineriboside,<sup>88d</sup> 2,6-dichloropurineriboside,<sup>88d</sup> 5-fluoro-2'-deoxyuridine,<sup>88e</sup> 9-β-D-arabinofuranosyladenine,<sup>88f</sup> thymidine,<sup>88g</sup> inosine,<sup>87f</sup> guanosine,<sup>87f</sup> and 2'-deoxycytidine<sup>87f</sup> have been prepared and directly used in a variety of reactions.

In view of the reactivity of aldehyde groups, suitably protected nucleoside 5'-aldehydes have emerged as versatile intermediates for diverse reactions. Much of our own work in this area has been reviewed.<sup>89</sup> For example, the reaction of methylmagnesium halides with the crude aldehydes derived from 2',3'-O-isopropylideneadenosine<sup>88a</sup> and 2',3'-O-anisylideneadenosine<sup>88b</sup> has led to low yields of the 6'-deoxy-β-D-allofuranosyl nucleoside

(e.g. 49) and its  $\alpha$ -L-talofuranosyl epimer. Use of the pure aldehyde derived from N<sup>6</sup>-benzoyl-2',3'-O-isopropylideneadenosine (45, B = NBzAd, R = Me), however, led to much increased yields of the epimeric carbinols (49).<sup>82</sup> Similarly, base catalyzed condensations of crude adenosine 5'-aldehyde<sup>88b</sup> and 3'-O-acetylthymidine 5'-aldehyde<sup>88g</sup> with nitromethane have led to modest yields of the epimeric nitroalcohols corresponding to 50. Once again, use of pure 2',3'-O-cyclohexylideneuridine 5'-aldehyde<sup>90</sup> and N<sup>6</sup>-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde<sup>91</sup> in comparable reactions has led to very high yields of the corresponding nitroalcohols (50).



Condensation of 2',3'-O-cyclohexylideneuridine 5'-aldehyde with sodium cyanide followed by intermediate oxidative hydrolysis with hydrogen peroxide led to the separable  $\beta$ -D-allo- and  $\alpha$ -L-taluronamides (51), these compounds proving to be key intermediates in the synthesis of uracil polyoxin C.<sup>87a</sup> This reaction has also been applied to crude 2',3'-O-isopropylideneadenosine 5'-aldehyde by Hampton, *et al.*<sup>92</sup> giving the corresponding hydroxyamides (51).

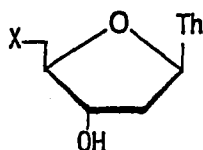
Several examples of the application of Wittig type reactions to nucleoside 5'-aldehydes have also been described. Thus, Montgomery, *et al.*<sup>88d</sup> have condensed several crude aldehydes (45, R = Me, B = Ad, 6-Cl purine, 6-MeS purine) with ethoxycarbonylmethylenetriphenylphosphorane and obtained the desired acrylate 52 in yields of 50-70%. A comparable reaction with the uridine analogue (45, B = Ur, R = Me) was also satisfactory,<sup>87f</sup> although under different conditions it was reported to give only degradation products.<sup>88c</sup>

In our own work we have had a particular interest in the use of diverse nucleoside 5'-aldehydes as precursors of the isosteric phosphonate analogues of nucleotides (55). The general synthetic route devised for these compounds involved condensation of the protected aldehydes (45) with diphenoxymethylmethylenetriphenylphosphorane (53) to give the *trans* vinylphosphonates (54), which were reduced and deprotected in several ways.<sup>93</sup> This sequence has been extensively investigated by Dr. G. H. Jones in this laboratory and used for the preparation of phosphonate analogues of many natural and unnatural ribo- and deoxyribonucleoside 5'-phosphates.<sup>94</sup> The identical method has been extended by others to the synthesis of phosphonate analogues of Virazole 5'-phosphate,<sup>87e</sup> and 5-fluoro-2'-deoxyuridine 5'-phosphate,<sup>88e</sup> but has achieved only partial success in the 6-chloro- and 6-methylthiopurine riboside series.<sup>88d</sup>

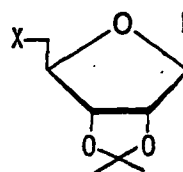
The reduction of appropriate derivatives of adenosine 5'-aldehyde using sodium borotritide has been used by several groups for the preparation of 5'-<sup>3</sup>H-adenosine.<sup>95</sup> Other workers have used stereoselective reduction of 45 (B = N<sup>6</sup>-BzAd, R = Me) and its 5'-deuterio analogue using hydride reducing agents in the presence of chiral ligands to produce selectively 5'-deuterated analogues of adenosine.<sup>87b,96</sup> From the above it is clear that only the sulfoxide-carbodiimide method of oxidation has found wide use in the preparation of nucleoside 5'-aldehyde derivatives. A closely related oxidation of 2',3'-O-isopropylideneadenosine using a ketenimine and dimethylsulfoxide has, however, been used by Harmon, *et al.*<sup>97</sup> with the resulting aldehyde being isolated as its 2,4-dinitrophenylhydrazone. Also, photolysis of 2',3'-acetals of 5'-azido-5'-deoxyuridine and adenosine in benzene has been shown to generate the corresponding 5'-aldehydes, which were reduced to the 5'-deuterionucleosides with sodium borodeuteride.<sup>98</sup>

## G. 5'-Carbon Substituted Nucleosides

Relatively few examples of reactions forming new carbon-carbon linkages at C5' of a preexisting nucleoside are available. Most of these constitute condensation reactions involving nucleoside 5'-aldehydes or carboxylic acids and have been considered in the preceding section. Only occasionally have carbon substituents at C5' been introduced by other means. One of these is via direct nucleophilic displacement of 5'-O-tosylate or 5'-halide substituents by cyanide ion. It was shown by Etzold, et al.<sup>99a</sup> that 5'-deoxy-5'-iodothymidine reacts with sodium cyanide in dimethylsulfoxide to form the 5'-cyano nucleoside (56a) in 44% yield. The latter can be catalytically reduced to the 6'-aminohexofuranosyl compound (56b) and then deaminated to the 6'-hydroxy counterpart (56c) without difficulty. Alternatively, the 5'-O-tosylate (57a) in the uridine and adenosine series can be converted into the 5'-cyano compound (57b) using potassium cyanide and a crown ether in methanol, but the corresponding 5'-iodo compounds do not give the desired nitriles.<sup>99b</sup> Oxidative hydrolysis of 57b gave the 5'-deoxyuronamide (57c) and the uronic acid (57d). Finally, an intriguing 3',5'-cyclopropyl nucleoside (58) has been prepared via electrolysis of 3',5'-dideoxy-3',5'-diiodothymidine.<sup>100</sup>

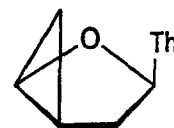


56(a) X = CN

(b) X = CH<sub>2</sub>NH<sub>2</sub>(c) X = CH<sub>2</sub>OH

57(a) X = OTs

(b) X = CN

(c) X = CONH<sub>2</sub>(d) X = CO<sub>2</sub>H

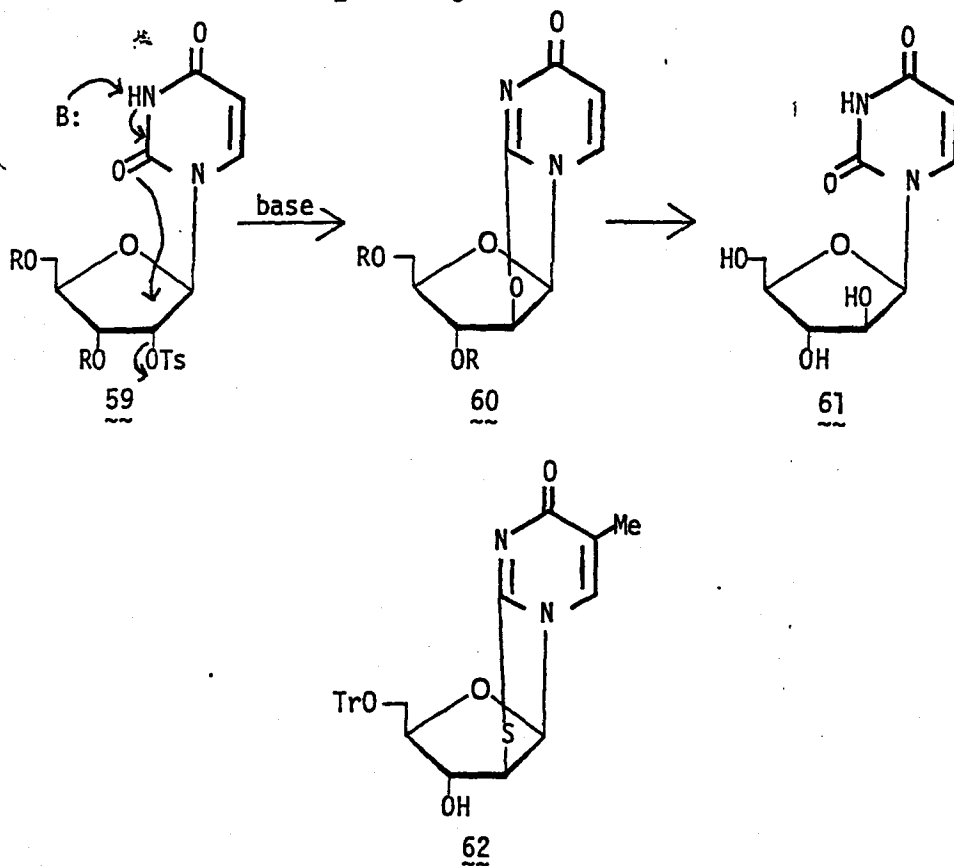
58

## II. 2'-MODIFIED NUCLEOSIDES

## A. 2'-Cyclonucleosides and Their Hydrolysis Products

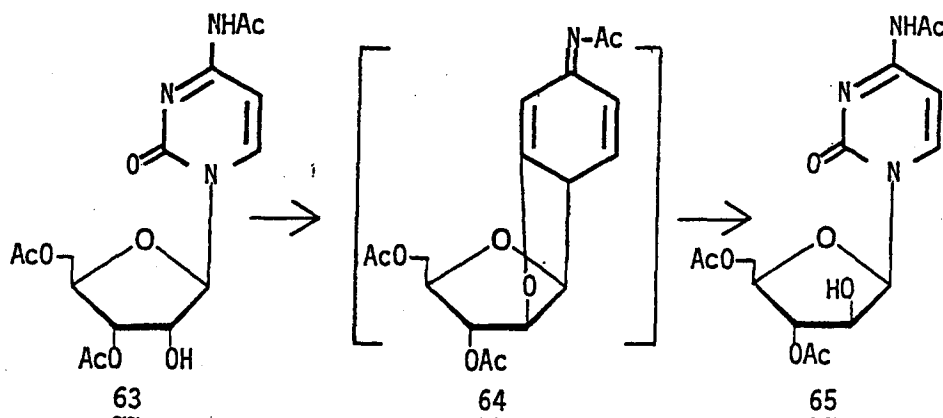
Synthetic manipulations involving the 2'-position in pyrimidine ribonucleosides are intractably intertwined with intramolecular participations by substituents on the heterocyclic base leading to cyclonucleosides. In turn, most convenient methods for inverting the configuration at C<sub>2'</sub> in pyrimidine ribonucleosides in order to generate the corresponding β-D-arabinofuranosyl nucleosides involve hydrolysis of an intermediate O<sup>2</sup>,2'-cyclo-nucleoside, and hence the two types of compounds will be considered

together. Three major classes of 2'-cyclonucleosides are known in which C<sub>2'</sub> is linked to C<sub>2</sub> or C<sub>6</sub> of a pyrimidine ring or to C<sub>8</sub> of a purine ring via various heteroatoms. Historically, the first examples involved treatment of, e.g., 2'-O-tosyl-5'-O-trityluridine (59) with alcoholic ammonia or sodium acetate giving the O<sup>2</sup>,2'-cycloauridine (more correctly, 2,2'-anhydro-1-β-D-arabinofuranosyluracil)<sup>53</sup> derivative 60 that could then be readily hydrolyzed to 1-β-D-arabinofuranosyluracil (61).<sup>101</sup> A similar route was used with the related 5-methyl-2'-O-tosyluridine,<sup>102</sup> and when applied to the corresponding 2-thiothymine derivative led to the sulfur bridged 2,2'-cycloauridine (62) that could be hydrolyzed and de-sulfurized to thymidine.<sup>103</sup> The selective formation of O<sup>2</sup>,2'-cyclonucleosides from 2',3'-di-O-mesyluridine derivatives has been described in both the uridine<sup>54b,104a</sup> and 6-azauridine<sup>104b</sup> series, and 2',3',5'-tri-O-mesyluridine is the starting material for a complex series of rearrangement reactions leading to inversion of configuration of both C<sub>2'</sub> and C<sub>3'</sub>.<sup>104a,c</sup>

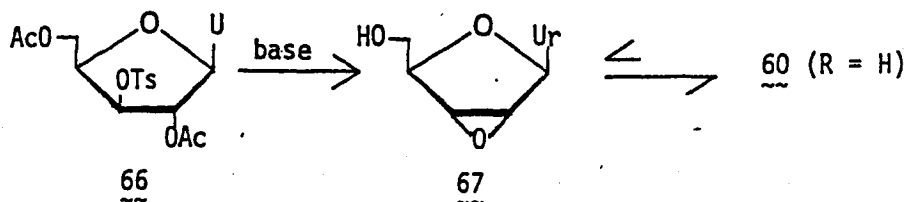


Less information is available regarding the formation of O<sup>2</sup>,2'-cyclocytidine derivatives via 2'-O-sulfonyl derivatives, although

a host of other methods have been developed for this purpose. Thus, it has been reported that tosylation of  $N^4,03',05'$ -triacetylcytidine (63) leads to formation of the  $N^4$ -acetyl- $02',2'$ -cyclo-nucleoside (64) that undergoes spontaneous hydrolysis to the arabinofuranoside (65) due to a labelizing effect of the  $N^4$ -acyl function.<sup>105</sup> Recently a series of  $N^4$ -acylated derivatives of 1- $\beta$ -D-arabinofuranosylcytosine have been reported to possess useful antitumor properties.<sup>106</sup> Treatment of 2',3'-di- $0$ -mesyl-5'- $0$ -tritylcytidine with hot aqueous methanol leads to a 3'- $0$ -mesyl- $02',2'$ -cyclocytidine in good yield.<sup>107</sup>

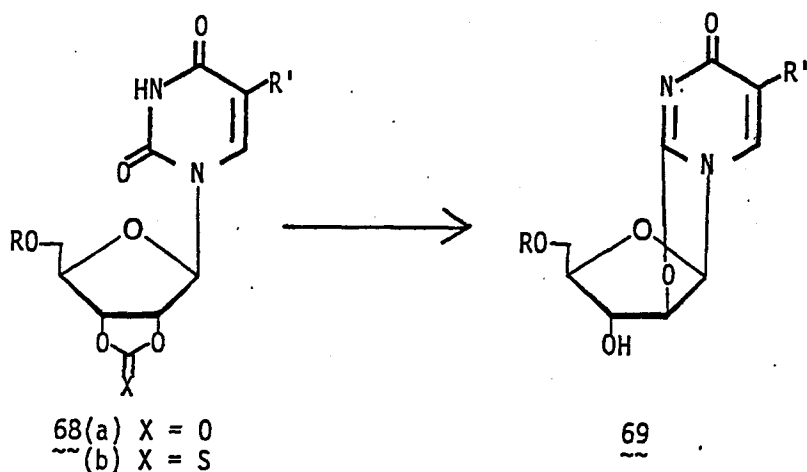


The formation of  $02',2'$ -cyclouridine, as well as its 5-fluoro- and 5-methyl analogues, has also been achieved via generation of the 2',3'-ribo epoxide 67 from the readily available 3'- $0$ -tosyl- $\beta$ -D-xylofuranosyl nucleosides (66) upon treatment with base. The ribo epoxides in the pyrimidine series appear to be in equilibrium with the  $02',2'$ -cyclonucleoside, with the equilibrium being far on the side of the latter.<sup>108</sup> A comparable reaction with the cytosine equivalent of 66 leads directly to the preparation of 1- $\beta$ -D-arabinofuranosylcytosine in 75% yield due to concomitant hydrolysis of the  $02',2'$ -cyclocytidine intermediate.<sup>108b</sup> The generation of a 2',3'-ribo epoxide upon treatment of 1-(3- $0$ -acetyl-2- $0$ -mesyl- $\beta$ -D-arabinofuranosyl)-2-thiouracil with sodium methoxide leads to the sulfur bridged 2,2'-cyclouridine analogous to 62.<sup>57c,d</sup>

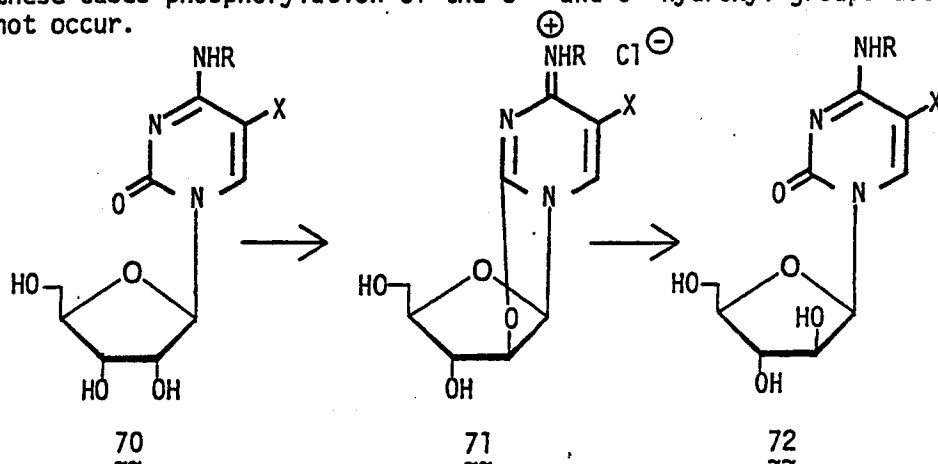


Interest in both the chemical and biological properties of pyrimidine  $02',2'$ -cyclonucleosides has led to the development of

numerous methods for their preparation. In most cases these involve the generation of either an uncharged or positively charged 2'- or 2',3'-derivative that undergoes intramolecular attack by O<sup>2</sup> at C<sub>2</sub>' leading to a thermodynamically more stable O<sup>2</sup>,2'-cyclo-nucleoside frequently bearing the appropriate 3'-substituent. One such useful method involves heating uridine with diphenyl carbonate and sodium bicarbonate in dimethylformamide<sup>109a</sup> or hexamethylphosphoramide.<sup>109b</sup> The 2',3'-O-carbonate (68a) resulting from transesterification is the intermediate in this reaction, and it has been shown that carbonates such as 68a, prepared in independent ways, similarly generate O<sup>2</sup>,2'-cyclocytidine derivatives upon heating with sodium bicarbonate.<sup>110</sup> As might be expected, treatment of 3',5'-di-O-trityluridine with diphenyl carbonate and sodium bicarbonate also leads to 3',5'-di-O-trityl-O<sup>2</sup>,2'-cyclocytidine, and in this case the reaction proceeds via displacement of the acyclic 2'-O-phenyl carbonate rather than a cyclic carbonate.<sup>110</sup> The use of diphenyl carbonate has also been extended to a variety of 5-substituted uridine and 6-azauridine derivatives,<sup>111a,b</sup> as well as to a 4',5'-olefin analogue<sup>111c</sup> and to some structurally related thiazolo[5,4-d]pyrimidine nucleosides,<sup>111d</sup> with considerable success. With 5-fluoroisocytidine the corresponding nitrogen bridged cyclonucleoside was obtained,<sup>111e</sup> but application to cytidine leads to the formation of 1-β-D-arabinofuranosylcytosine since the initially formed O<sup>2</sup>,2'-cyclocytidine (71, R, X = H) is readily hydrolyzed under mildly alkaline conditions.<sup>112</sup> The generation of 2',3'-cyclic carbonates can also be achieved via treatment of 5'-O-trityluridine or its 6-aza analogue with carbonyldiimidazole in dimethylformamide.<sup>113</sup> Subsequent heating of the resulting carbonates with imidazole in dimethylformamide then generates the O<sup>2</sup>,2'-cyclonucleoside in high yield. Comparable reactions using thiocarbonyldiimidazole, however, lead directly to the O<sup>2</sup>,2'-cyclo-nucleoside (69) via the more reactive 2',3'-O-thiocarbonate (68b).<sup>114</sup>



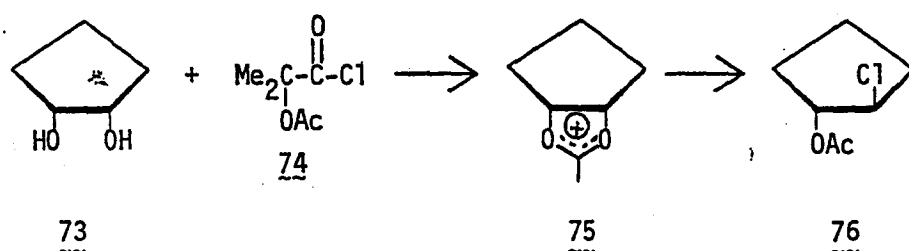
Along very similar lines, a number of other polyfunctional reagents have been found to effectively convert pyrimidine nucleosides into their 0<sup>2</sup>,2'-cyclo derivatives. The prototype of this kind of reaction was the observation that treatment of uridine with phosphorus oxychloride in ethyl acetate in the presence of one equivalent of water under reflux led to high yields of 3',5'-di-O-acetyl-0<sup>2</sup>,2'-cyclouridine (60, R = Ac.)<sup>115</sup> With the realization of the significant antitumor activity of 0<sup>2</sup>,2'-cyclocytidine (71, R, X = H),<sup>116</sup> much effort has been devoted to facile methods for its synthesis. Application of the phosphorus oxychloride method to cytidine and to a variety of its C<sub>5</sub>-halogenated<sup>117a</sup> and N<sup>4</sup>-substituted<sup>117b</sup> derivatives (70) has led to reasonably efficient syntheses of the corresponding 0<sup>2</sup>,2'-cyclocytidine salts (71) that can be readily hydrolyzed to the related 1-β-D-arabinofuranosyl-cytosines (72) with mild aqueous base. It should be noted that in these cases phosphorylation of the 3'- and 5'-hydroxyl groups does not occur.



The comparable reaction of cytidine with the Vilsmeier-Haack reagent prepared from phosphorus oxychloride and dimethylformamide leads quite rapidly to 0<sup>2</sup>,2'-cyclocytidine hydrochloride and then more gradually to its 5'-chloro-5'-deoxy derivative.<sup>118a</sup> This reaction has also been applied to 4'-thiocytidine.<sup>118b</sup> The use of phosphoryl leaving groups is, in fact, of historical importance since the first preparation of 0<sup>2</sup>,2'-cyclocytidine involved the heating of cytidine-2'(3')-phosphate with polyphosphoric acid leading to a phosphorylated derivative of 71 (X, R = H) that could be enzymatically cleaved to the free cyclonucleoside.<sup>118c</sup> Subsequently, activation of cytidine 2',3'-cyclic phosphate with reagents such as trimethylsilyl chloride, tosyl chloride and diphenyl phosphorochloridate has also been used to generate 0<sup>2</sup>,2'-cyclocytidine 3'-phosphate.<sup>118d-f</sup> Along similar lines, cytidine can also be converted in moderate yield into 0<sup>2</sup>,2'-cyclocytidine upon treatment with thionyl chloride in dimethylformamide,<sup>119a</sup> whereas in acetonitrile cytidine 2',3'-cyclic sulfite is the

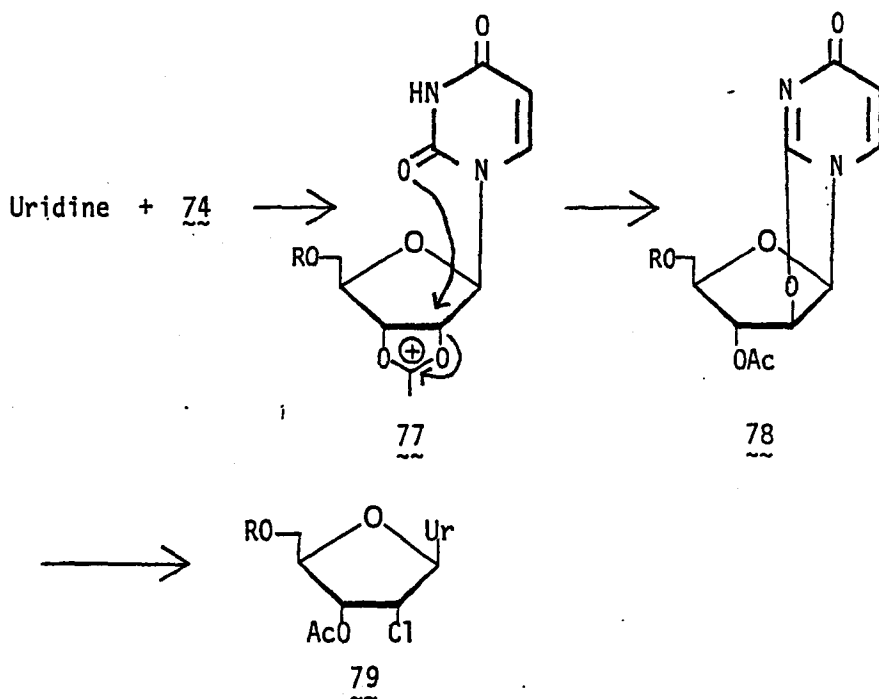
initial product and this can be transformed, in an overall yield of 73%, into  $O^2,2'$ -cyclocytidine by mild acidic treatment.<sup>119b</sup> The use of sulfuryl chloride leads to both  $O^2,2'$ -cyclonucleoside formation and chlorination of C5 of the pyrimidine ring.<sup>120</sup>

A reaction that has been of particular interest to our own group involves treatment of pyrimidine nucleosides with 2-acetoxyisobutyryl chloride (74). Reagents related to 74 were originally shown by A. R. Mattocks<sup>121</sup> to convert vicinal diols into chloroethyl acetates. A careful study of this reaction with model compounds showed that it proceeded via conversion of a cyclic cis diol (73) into an acetoxonium ion (75) that underwent subsequent attack by chloride giving a trans chloro acetate (76).<sup>122</sup>



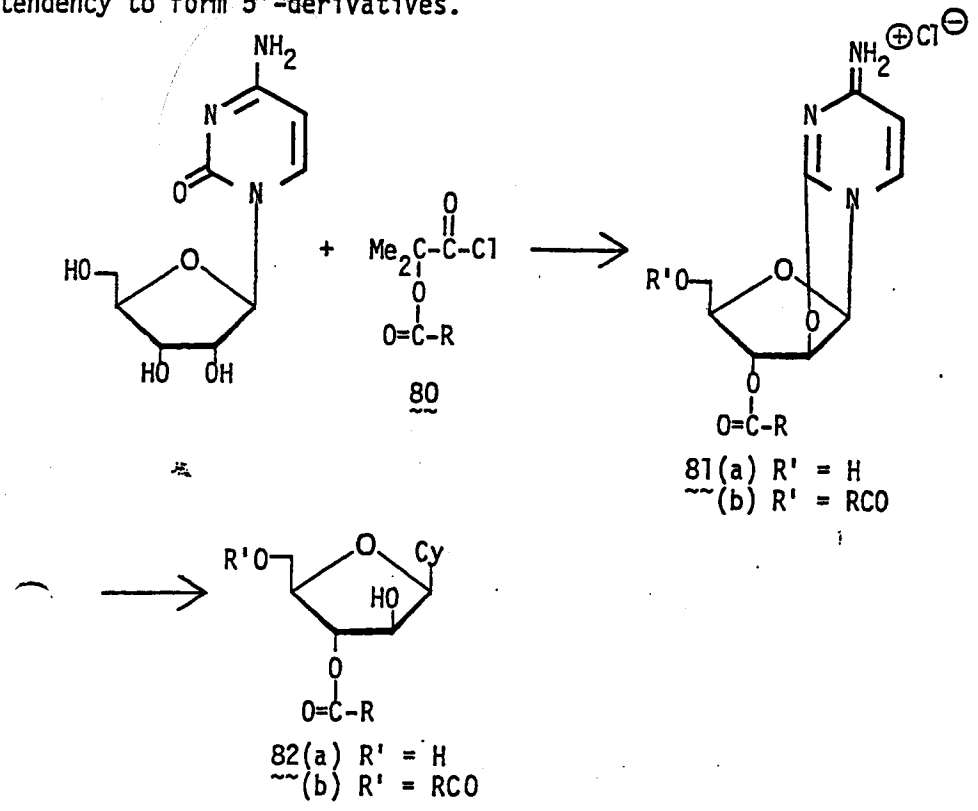
Applied to uridine, it was shown that treatment with an excess of 74, either neat or in a variety of solvents, at  $80^\circ$  led to 3'-O-acetyl-2'-chloro-2'-deoxyuridine (79) in which the 5'-hydroxyl group was either free or substituted as its 2-acetoxyisobutyryl ester or 2,5,5-trimethyl-1,3-dioxolan-4-one-2-yl ether. This aspect of the work will be discussed under 2'-halogenation. The retention of stereochemistry in this reaction, as opposed to the inversion observed in the conversion of 73 to 76, was interpreted as indicating the intermediacy of the  $O^2,2'$ -cyclonucleoside, and, indeed, upon brief treatment of uridine with 74 in nitromethane the crystalline hydrochloride of 3'-O-acetyl- $O^2,2'$ -cyclouridine (78), R = H, was isolated.<sup>122</sup>

Clearly, the initially formed acetoxonium ion (77) underwent preferential opening by attack of  $O^2$  to generate the 3'-O-acetyl- $O^2,2'$ -cyclonucleoside (78). As will be seen subsequently, in the absence of a participating carbonyl group on the pyrimidine ring the acetoxonium ions corresponding to 77 are opened by halide ion in the usual way leading to trans chloro acetates.



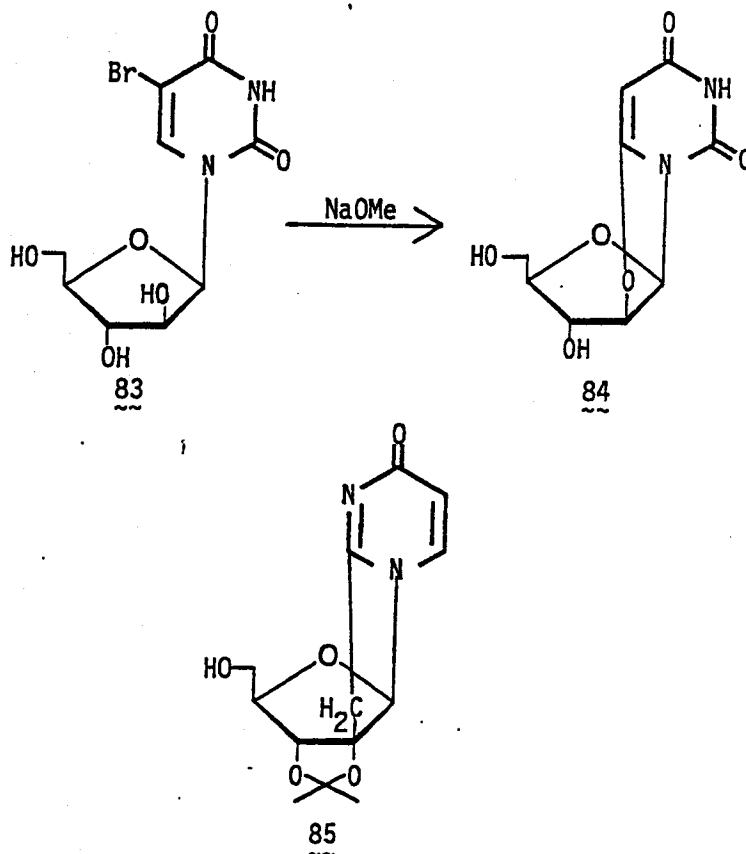
The reaction of 74 with cytidine proceeds in essentially the same way except that the resulting 3'-O-acetyl-0<sup>2</sup>,2'-cyclocytidine hydrochloride (81a, R = Me) shows very little tendency to be opened by chloride ion and is isolated in high yield.<sup>123a</sup> In reactions conducted at 80° in solvents such as acetonitrile, pure 81a (R = Me) crystallizes directly from the mixture. Similar reactions at room temperature, however, lead predominantly to the 5'-O-trimethyldioxolane ether of 81, which can be selectively hydrolyzed under very mild acidic conditions. This reaction has been extended to a wide range of cytidine analogues including the 5-halo, 5-methyl, 5-dimethylamino, N<sup>4</sup>-dimethyl, and 6-aza derivatives and in each case gives the corresponding 3'-O-acetyl-0<sup>2</sup>,2'-cyclocytidine hydrochlorides.<sup>123a</sup> With 2-thiocytidine<sup>123a</sup> and 2-thio-6-azacytidine,<sup>123f</sup> the sulfur bridged cyclonucleosides were obtained. By reacting cytidine with analogues of 74 in which the acetyl group is replaced by saturated or unsaturated acyl groups containing up to 22 carbon atoms (80), the corresponding 3'-O-acyl-0<sup>2</sup>,2'-cyclocytidine hydrochlorides (81a) are obtained.<sup>123b</sup> Subsequent treatment of these compounds, and their 3',5'-di-O-acyl counterparts (81b),<sup>123c</sup> with pyridine-methanol leads to selective cleavage of the anhydro linkage leading to the 3'-O-acylated or 3',5'-di-O-acylated derivatives of 1-β-D-arabinofuranosylcytosine (82a,b).<sup>123d</sup> The compounds 81 and 82 show interesting antitumor and antiviral activities that are strongly dependent upon the nature of the acyl substituents.<sup>123b-e</sup> The reaction of cytidine,

and of 5-fluorouridine, with 0-acetylsalicyloyl chloride<sup>123b,124</sup> is mechanistically closely related to that with 74 and gives the 3'-0-acetyl-0<sup>2</sup>,2'-cyclocytidine hydrochlorides without any apparent tendency to form 5'-derivatives.



A number of other routes to 3'-0-acyl-0<sup>2</sup>,2'-cyclo nucleosides, presumably via the generation of 2',3'-0-acyloxonium ions, have also been briefly explored. These include the treatment of 2',3'-0-methoxyethylideneuridine with trimethylsilyl chloride,<sup>125a</sup> treatment of cytidine with carboxylic acid anhydrides in the presence of boron trifluoride,<sup>125b</sup> the reaction of 5'-0-acetyluridine, cytidine and 5-bromocytidine with silicon tetraacetate or silicon tetrachloride in acetic acid,<sup>125c</sup> and heating of a 3-0-benzoyl-2-mesyl- $\beta$ -D-arabinofuranosyluracil with sodium benzoate.<sup>125d</sup>

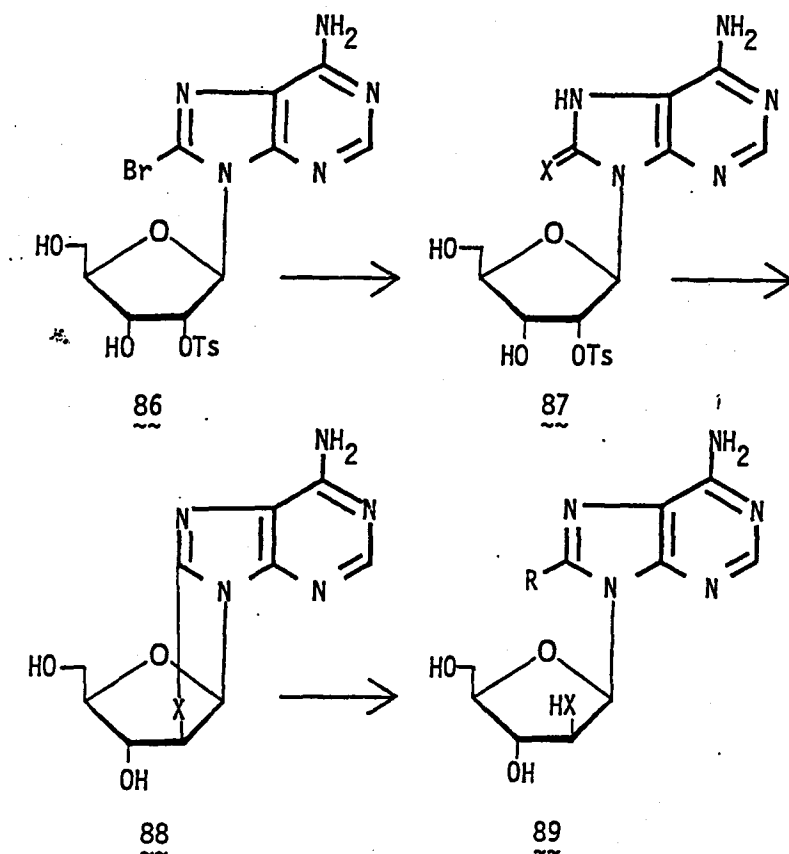
A few examples of 2',6-cyclo nucleosides (84) have also been reported via conjugate addition of the C2'-hydroxyl group to C6 in 4-pyrimidine-1- $\beta$ -D-arabinofuranosides (83) followed by elimination of hydrogen halide. Such reactions have been applied to both the uracil<sup>126</sup> and cytosine<sup>127</sup> series and 84 has subsequently been converted to 4-thiouracil and cytosine derivatives in conventional ways. Finally, a carbon bridged 2,2'-cyclo uridine derivative (85) has been prepared via photolysis of a 2-(dimethyloxosulfonium-

methylene)pyrimidine nucleoside.<sup>128</sup>

In the purine series, much effort has been devoted by Ikehara, et al.<sup>66</sup> to the preparation and reactions of 8,2'-cyclonucleosides (e.g. 88, X = O). In essence, these syntheses usually involve the generation and intramolecular collapse of an 8-hydroxy-2'-O-tosyl purine nucleoside (87) via solvolysis of the corresponding 8-bromo derivative (86). In earlier work the 2'-O-sulfonyl group was introduced by random or partially selective sulfonylation,<sup>129</sup> but more recently advantage has been taken of the selective 2'-O-tosylation of adenosine via the 2',3'-O-dibutylsilylene derivatives<sup>130</sup> that can also be applied to 8-bromoadenosine and 8-bromoguanosine.<sup>131</sup>

This work has been further extended to the preparation of a variety of 8,2'-cyclonucleosides containing sulfur<sup>132</sup> (e.g. 88, X = S) and hydrazine<sup>133</sup> bridges via displacement of the 8-bromo function in 86 by the appropriate nucleophiles. In addition, the generation of 8-mercaptapurine nucleoside 2',3'-O-carbonates, via the use of diphenyl carbonate, leads to the selective formation of

the 8,2'-thiocyclonucleosides in generally good yields.<sup>134</sup> Along similar lines, the reaction of 8-bromoadenosine-2',3'-sulfite with thiourea leads preferentially to 88 (X = S) in 70% yield.<sup>135</sup> The 2',3'-ribo epoxide moiety, obtained via the readily available 2'-O-acetyl-3'-O-tosyl- $\beta$ -D-xylofuranosyl nucleosides, can also be opened by an 8-mercapto group leading to the 8,2'-thiocyclonucleoside.<sup>136</sup>

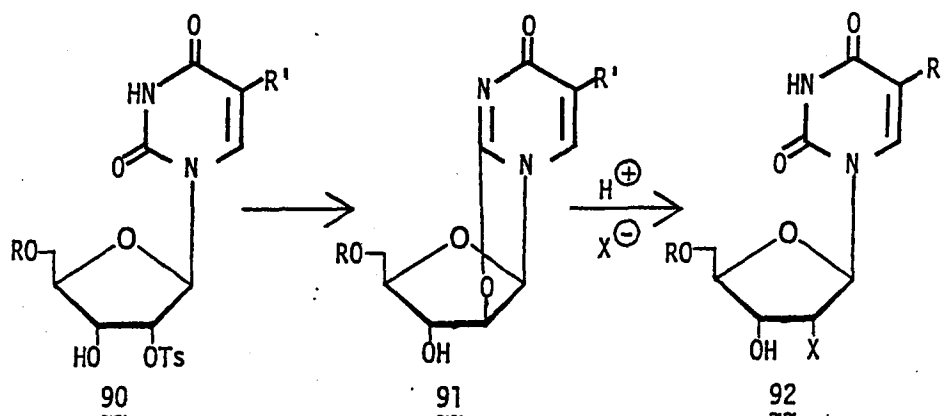


Considerable effort has also been directed towards the nucleophilic opening of 8,2'-cyclonucleoside linkages with formation of variously 8-substituted 9- $\beta$ -D-arabinofuranosylpurines (89, R = OH, SH, NHR; X = O, S).<sup>129,132,135,136</sup> The direct desulfurization of 8,2'-thiocyclonucleosides (88, X = S) provides a method for the conversion of purine ribonucleosides into their 2'-deoxy counterparts.<sup>132a,b,134c,136</sup>

#### B. 2'-Halogenated Nucleosides

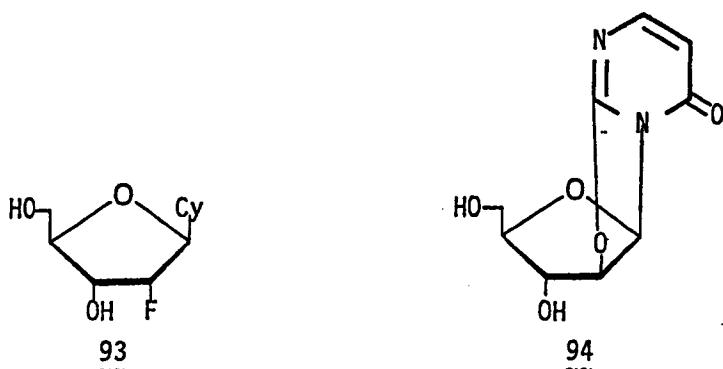
The development of syntheses of 2'-deoxy-2'-halogeno-

nucleosides has, to a large extent, been closely linked to the chemistry of 2'-cyclonucleosides since the latter compounds frequently function as intermediates. The early work of Brown, *et al.*<sup>101b,138</sup> originally showed that reaction of 5'-O-acetyl-2'-O-tosyluridine and its 5-methyl analogue (90) with sodium iodide in acetonylacetone gave the crystalline 2'-deoxy-2'-iodouridine derivative (92) with retention of configuration. It was correctly inferred that the 0<sup>2</sup>,2'-cyclonucleoside (91) was an intermediate in this reaction. Subsequently this type of reaction has been extended to treatment of the 5'-O-trityl analogue of 90 with a wide range of halide salts leading, in each case, to analogues of 92.<sup>139</sup> In certain cases the intermediate 0<sup>2</sup>,2'-cyclonucleoside could be isolated from these reactions. It is interesting that direct treatment of unprotected uridine with triphenylphosphine and carbon tetrachloride leads to a 68% yield of crystalline 2',5'-dichloro-2',5'-dideoxyuridine of unequivocal configuration.<sup>18</sup> Once again, the *ribo* configuration of the product supports the intermediacy of an 0<sup>2</sup>,2'-cyclouridine derivative.



The ease of formation of 0<sup>2</sup>,2'-cyclouridine derivatives by diverse methods already described has made these compounds prime starting materials for the synthesis of 2'-halogenated pyrimidine nucleosides such as 92. This approach was initially developed by Fox, *et al.*<sup>140</sup> who showed that treatment of 0<sup>2</sup>,2'-cyclouridine (91, R, R' = H), or its 5-methyl analogue (R' = Me), with the appropriate hydrogen halides in dioxane led to the formation of the 2'-chloro, 2'-bromo, 2'-fluoro and 2'-iodo derivatives (92) in good yields. Protonation of the cyclonucleoside at N<sup>3</sup> is an important prelude to nucleophilic attack by halide ion, and comparable reactions of pure 91 with sodium iodide are not successful. The crystalline hydrochloride salt of 0<sup>2</sup>,2'-cyclouridine can, however, be converted into the 2'-chloro derivative simply upon heating in dioxane.<sup>140b</sup> The electronic equivalent of protonation can also be achieved by methylation, reaction of 0<sup>2</sup>,2'-cyclouridine with methyl iodide in

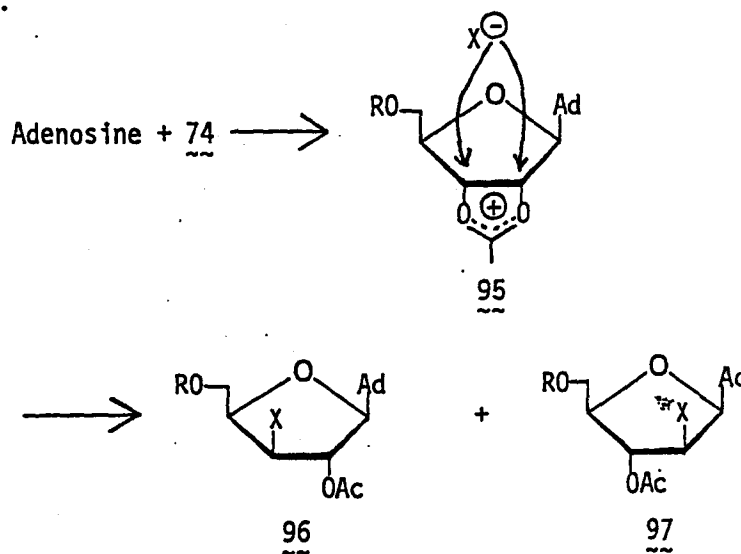
dimethylformamide at room temperature leading to 2'-deoxy-2'-iodo-N<sup>3</sup>-methyluridine in 77% yield.<sup>29b</sup> Further applications of the opening of 0<sup>2</sup>,2'-cyclouridine derivatives and analogues using hydrogen chloride in dimethylformamide have also been reported.<sup>111a,113a,141</sup> Also, the opening of 2'-<sup>3</sup>H-0<sup>2</sup>,2'-cyclouridine with hydrogen bromide has provided a convenient stereospecific synthesis of 2'-bromo-2'-deoxy-2'-<sup>3</sup>H-uridine for mechanistic studies,<sup>142</sup> whereas reaction of the cyclonucleoside with bromine in chloroform leads to bromination at both C<sub>5</sub> and C<sub>2'</sub> (92, X, R' = Br, R = H).<sup>143</sup> Successful conversion of 0<sup>2</sup>,2'-cyclocytidine salts to 2'-deoxy-2'-fluorocytidine (93) can be achieved in 40% yield via treatment with potassium fluoride and a crown ether in carefully dried dimethylformamide,<sup>144a</sup> and is also possible upon heating the cyclonucleoside hydrofluoride in dimethylformamide.<sup>144b</sup> Some caution must be exercised in the opening of cyclonucleosides with hydrogen fluoride since it has been shown that, unlike the results in dioxane,<sup>113b,140</sup> treatment of 0<sup>2</sup>,2'-cyclouridine with liquid hydrogen fluoride leads to a novel rearrangement giving 94.<sup>145</sup>



As mentioned earlier, the reactions of nucleosides with 2-acetoxyisobutryl halides provide a useful route to halosugar derivatives of defined stereochemistry. Treatment of uridine with 24 in various solvents leads to 3'-O-acetyl-2'-chloro-2'-deoxyuridine derivatives (79) via the 2',3'-O-acetoxonium ion (77) and the 0<sup>2</sup>,2'-cyclonucleoside (78).<sup>122</sup> Acetonitrile is an advantageous solvent, but in acetic acid the reaction gives a very high yield of 3',5'-di-O-acetyl-2'-chloro-2'-deoxyuridine.<sup>122</sup> In dimethylformamide the formation of by-products is apparent, a major one being identified as 3'-O-acetyl-2',5'-dichloro-2',5'-dideoxyuridine.<sup>20</sup> Comparable reactions of pseudouridine,<sup>146a,b</sup> 5'-deoxy-5'-fluorouridine,<sup>146c</sup> 5'-deoxy-5'-bromouridine<sup>146c</sup> and 6-azauridine<sup>146d</sup> have all led to comparable 3'-O-acetyl-2'-chloro-2'-deoxyribonucleosides. In the case of pseudouridine some controversy exists since in one case<sup>146a</sup> there appears to be considerable

anomerization of the nucleoside while in the other,<sup>146b</sup> halogenation appears to occur both at C<sub>2</sub>' and C<sub>3</sub>', according to subsequent reduction studies. Halogenation at C<sub>2</sub>' and C<sub>3</sub>' has also been observed during reaction of 5'-O-benzoyluridine with 2-O-acetyl-salicyloyl chloride, a reagent that is mechanistically closely related to 74.<sup>146e</sup> There is very little tendency towards formation of 2'-halogenated derivatives in reactions of cytidine with 74, the 0<sup>2</sup>,2'-cyclonucleoside (81) being the predominant product.

Application of the 2-acetoxyisobutyryl halide reaction to purine nucleosides takes a rather different course. Thus, reaction of adenosine with 74, or the corresponding acyl bromide, leads initially to the acetoxonium ion (95), which undergoes opening by halide ion to give the isomeric trans haloacetates (96 and 97) bearing a diastereomeric trimethyldioxolanone-2-yl ether at the 5'-positions in a ratio of roughly 9:1.<sup>147a</sup> In general, the reactions with the acyl bromide are more convenient since they proceed at room temperature and the bromo function is more easily reduced catalytically. Deacetylation of 96 and 97 to give the free halo-nucleosides can be achieved under acidic or mildly basic conditions.

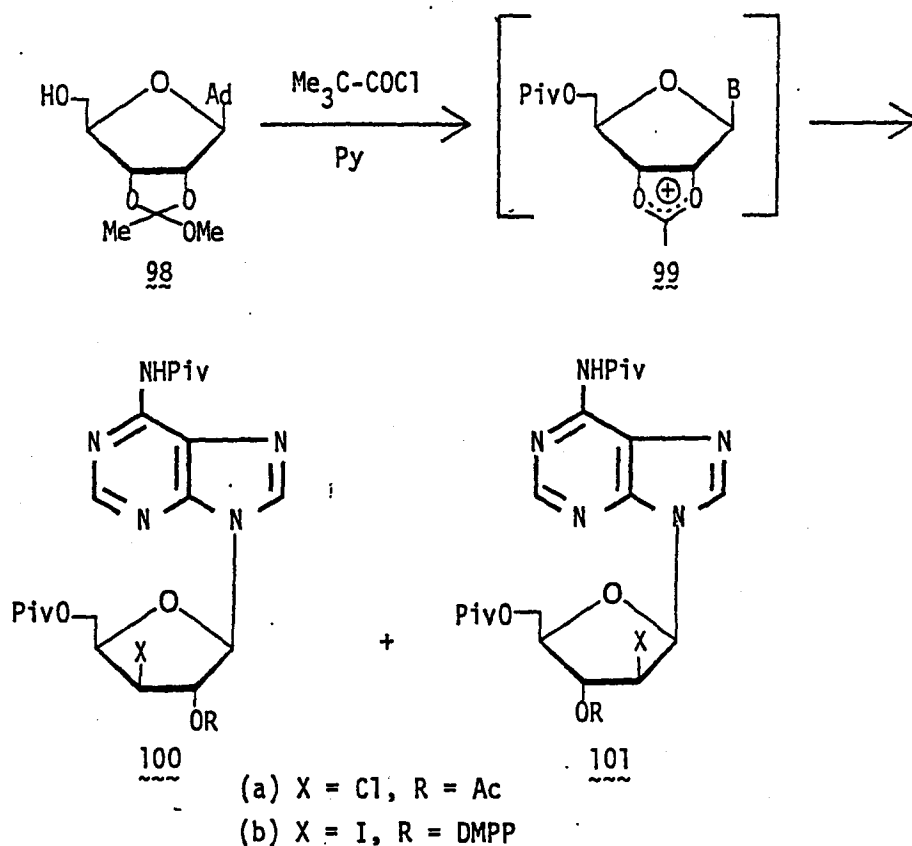


Comparable reactions have also been studied using other purine nucleosides such as formycin,<sup>147b</sup> inosine<sup>147c,d</sup> and guanosine derivatives.<sup>147c</sup> In each case a pattern similar to that with adenosine was observed, with predominant formation of the 3'-halo xylo compound (cf. 96) and only low yields of the 2'-halo arabino isomers (cf. 97). The comparable reaction between tubercidin and 2-acetoxyisobutyryl bromide was unique in that there was no indication of the formation of any of the 2'-halogenated isomer, the 3'-bromo xylo derivative (cf. 96) being formed almost quantitatively.

Comparable results have also been reported by Robins, et al. for the reactions of 74 with tubercidin and formycin.<sup>148</sup> The only other major point of difference between these reactions is a remarkable specificity with respect to the nature of the 5'-substituent in the products. Thus, reactions of adenosine, tubercidin, cytidine and inosine in acetonitrile lead exclusively to products in which the C<sub>5</sub>-oxygen is in the form of a trimethyldioxolanon-2-yl ether, while in comparable reactions the products from formycin are only 5'-O-(2-acetoxyisobutyrate) esters. The nature of the 5'-substituent in the uridine series was strongly solvent dependent,<sup>122</sup> and no clear explanation of these effects is apparent.

Results very similar to those obtained using 2-acetoxyisobutyryl halides can be achieved through the reactions of 2',3'-O-methoxyethylidene derivatives of purine nucleosides with pivaloyl chloride in hot pyridine. These results have recently been reviewed by Robins<sup>149</sup> and hence will not be considered in detail. In essence, the reaction of the adenosine orthoester (98) leads, once again, to a mixture of the 3'-chloro-3'-deoxy-β-D-xylofuranosyl nucleoside (100a) and its 2'-chloro-2'-deoxy-β-D-arabinofuranosyl isomer (101a) in which the former predominates.<sup>150</sup> This reaction is somewhat complicated by the simultaneous formation of minor amounts of analogues of 100a and 101a in which the acetates are replaced by 4,4-dimethyl-3-pivaloxypent-2-enoyl (DMPP) esters. As in the case of reactions of 2-acetoxyisobutyryl halides, these products are the result of trans opening of an intermediate 2',3'-O-acetoxonium ion (99) arising by acid catalyzed collapse of the orthoester.

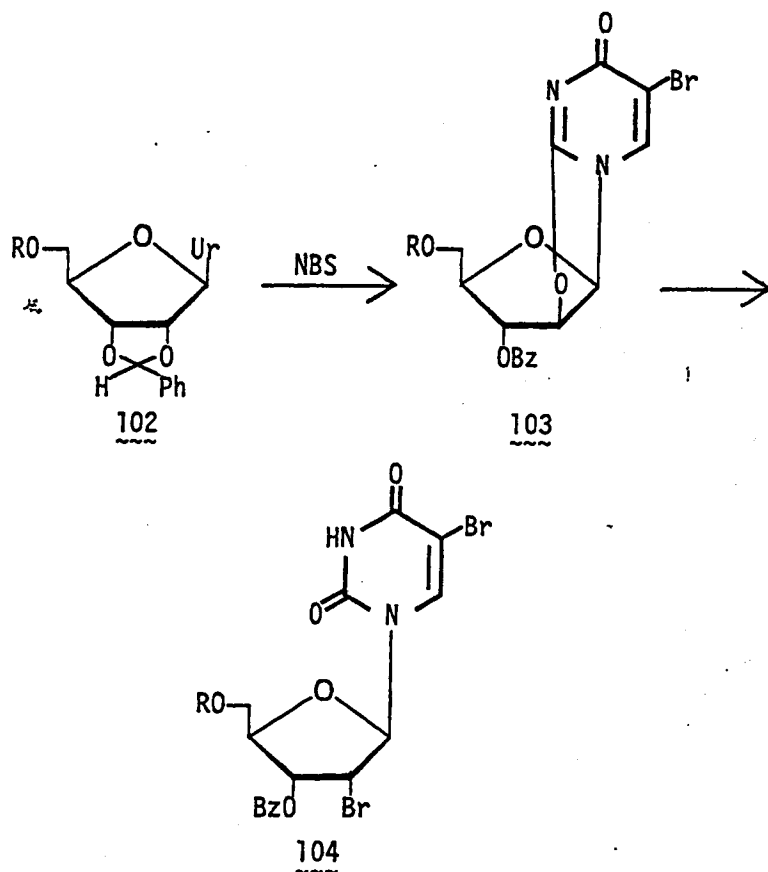
By conducting such reactions in the presence of an excess of sodium iodide, the iodinated nucleosides (100b and 101b) were produced, together with several minor elimination products.<sup>150a,b</sup> These iodinated nucleosides, like their other halogenated analogues,<sup>147</sup> constitute versatile intermediates for the preparation of other modified nucleosides to be discussed later. The reaction of 2',3'-O-methoxyethylidene derivatives of tubercidin<sup>150c</sup> and guanosine<sup>150d,f</sup> with pivaloyl chloride alone, or in the presence of excess sodium iodide, once again gave the 3'-halo xylo derivatives with no apparent formation of the 2'-halo arabino isomers.<sup>150c</sup> A similar result was obtained from reaction of tubercidin with 74 in the presence of an excess of sodium iodide.<sup>150e</sup> The reactions of 2',3'-orthoesters of adenosine<sup>151a</sup> and inosine<sup>151b</sup> with pivaloyl chloride in the presence of excess sodium iodide have also been examined by Mengel, et al.<sup>166</sup> leading to 100b and 101b or their inosine analogues.



The generation of 2',3'-acyloxonium ions by other routes has also found some application in the preparation of 2'-halo-ribo-nucleosides. Thus, while the reaction of 2',3'-O-methoxyethylideneuridine with trimethylsilyl chloride in acetonitrile was early described as leading to 3'-O-acetyl-0<sup>2</sup>,2'-cyclo-uridine,<sup>125a</sup> the comparable reaction in nitromethane under reflux for 1.5 hr gives 3'-O-acetyl-2'-chloro-2'-deoxyuridine (**78**, R = H) in 48% yield.<sup>125a</sup> It has also been shown that treatment of 2',3'-O-benzylideneuridine (**102**, R = H) with N-bromosuccinimide leads to the 2',5-dibromo derivative (**104**, R = H), and a 3'-O-benzoyl-5-bromo-0<sup>2</sup>,2'-cyclo-uridine (**103**, R = Ac) has been detected as an intermediate in a closely related case.<sup>152</sup>

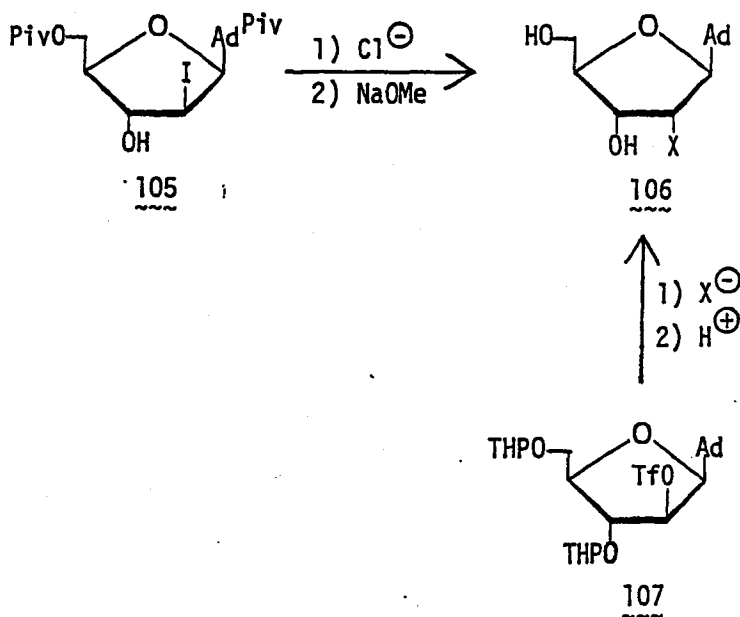
In a remarkably facile process it has been demonstrated that treatment of uridine,<sup>153a</sup> 6-azauridine<sup>113b</sup> and 5-fluorouridine<sup>153b</sup> with acetyl bromide or propionyl bromide in acetonitrile under reflux leads to 3',5'-di-O-acyl-2'-bromo-2'-deoxyuridines together with some 2',3',5'-tri-O-acyl derivatives. The bromination reactions once again presumably arise via 2',3'-O-acyloxonium- and

0<sup>2</sup>,2'-cyclonucleoside intermediates. The comparable reaction with cytidine gives mainly 3',5'-di-O-acetyl-0<sup>2</sup>,2'-cyclocytidine and only a little 2'-bromo derivative.<sup>153a</sup> Also, treatment of uridine,<sup>125c</sup> 5-bromouridine<sup>125c</sup> and pseudouridine<sup>154</sup> with silicon tetrachloride in acetic acid leads to modest yields of the 2'-chloro-2'-deoxynucleosides, presumably via the 0<sup>2</sup>,2'-cyclo derivatives.



It should be noted that 2'-halogenated purine nucleosides with the arabino configuration (97, 101) are readily available, albeit in low yield, by use of the 2-acetoxyisobutyryl halide<sup>47</sup> or pivaloyl chloride<sup>50</sup> methods. No direct method is available for the conversion of a purine ribonucleoside into a 2'-halogenated derivative with retention of configuration. Several lengthier routes have, however, been developed to prepare this type of product. Firstly, it has proved possible to directly invert the configuration of a 9-(2-deoxy-2-iodo-β-D-arabino-furanosyl)adenine derivative (105, obtained from 101b by selective cleavage of the 3'-O-DMPP group with permanganate) by treatment

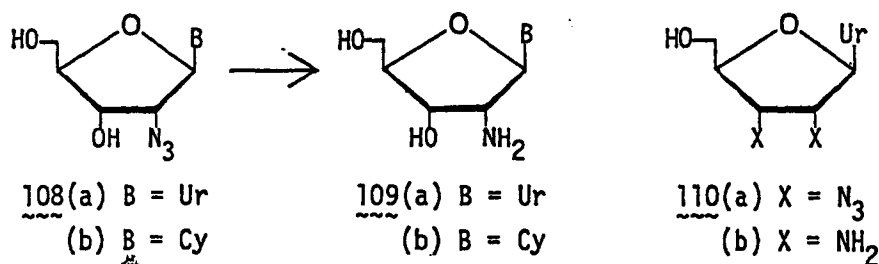
with lithium chloride in dimethylformamide at 100°. <sup>151a</sup> An alternative process involves the direct displacement of the 2'-O-tri-fluoromethylsulfonyl group from the 3',5'-bis-O-tetrahydropyranyl derivative (107) by soluble halide salts or other nucleophiles in dimethylformamide or hexamethylphosphoramide. <sup>155</sup> In this way the 2'-chloro, 2'-bromo, 2'-iodo and 2'-fluoro analogues of adenosine (106) have been prepared.



### C. 2'-Nitrogen Substituted Nucleosides

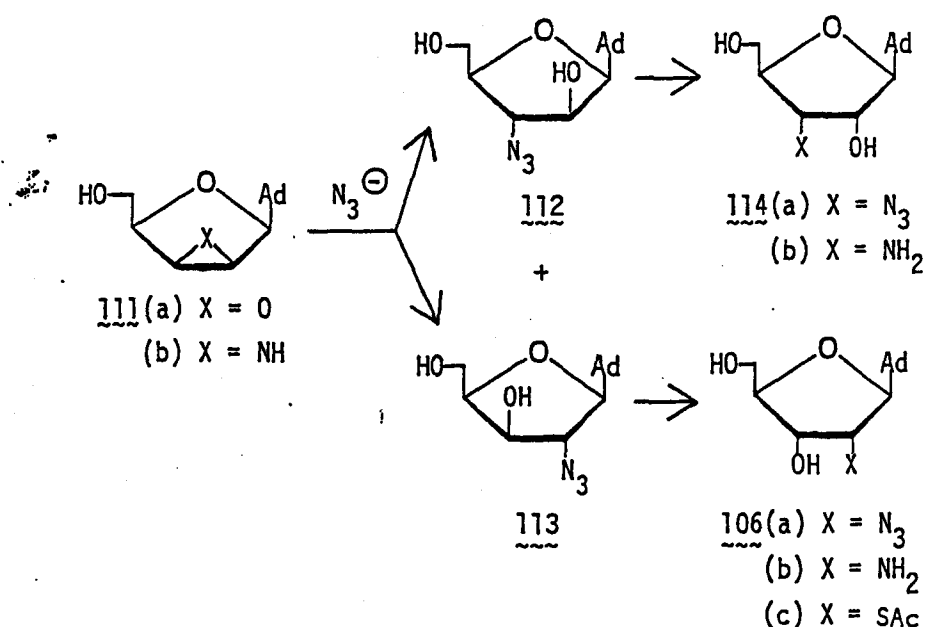
While 2'-amino-2'-deoxyadenosine had been prepared via a condensation of an appropriately blocked 2-aminoribose derivative with adenine, <sup>156</sup> the first transformation of an existing nucleoside into a 2'-amino derivative was done in our own laboratory. <sup>109b</sup> This involved the nucleophilic opening of 0<sup>2</sup>,2'-cyclouridine with azide ion in hexamethylphosphoramide at 150° in the presence of benzoic acid. Subsequent catalytic reduction of the azide moiety in the resulting 108a gave 2'-amino-2'-deoxyuridine (109a), which could be transformed into the cytidine analogue (109b) by conventional means. Our synthetic route has been slightly modified by Hobbs and Eckstein, <sup>158</sup> who have combined the preparation of the cyclonucleoside and its opening into a "one pot" procedure which makes use of the phenol arising as a by-product of the first step as the acid catalyst for the second, and by Sasaki, et al. <sup>193a</sup> using 5'-O-trityl-0<sup>2</sup>,2'-cyclouridine. The conversion of 108a into 2'-azido-2'-deoxycytidine (108b) has also been reported by Hobbs, et al. <sup>157b</sup> via sequential treatment of the 3',5'-diacetate with

thionyl chloride-dimethylformamide and ammonia. Various phosphate esters of the azido and amino nucleosides in both the uridine and cytidine series have also been prepared.<sup>157</sup> An alternative synthesis of 108a has also been reported via in situ generation of 3',5'-di-O-benzoyl-2',2'-cyclouridine upon treatment of 1-(3,5-di-O-benzoyl-2-O-mesyl-β-D-arabinofuranosyl)uracil with azide salts.<sup>159</sup> This work has been extended to the synthesis of 2',3'-diazido- and 2',3'-diamino-2',3'-dideoxyuridines (110a,b) by way of 2',3'-azidonium intermediates.<sup>159</sup>

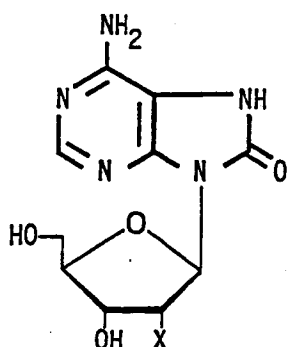


In the purine series, a number of routes have been developed recently for the preparation of 2'-amino nucleosides. One of the first of these involved the nucleophilic opening of the readily available β-D-lyxo epoxide (111a) with lithium azide in dimethylformamide giving 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine (112) and its 2-azido-β-D-xylofuranosyl counterpart (113) in yields of 80% and 8% respectively.<sup>151a</sup> The configuration of the 3'-hydroxyl group in 113 was then inverted via treatment of its mesylate with sodium benzoate followed by deprotection to give 2'-azido-2'-deoxyadenosine (106a), which was catalytically reduced to the amine (106b). In a similar way 112 was converted into the 3'-azido and 3'-amino analogues (114a,b).

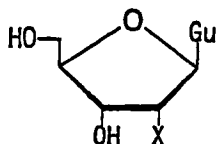
In another approach, 8,2'-cycloadenosine (88, X = O) was opened by azide ion giving the 2'-azido-8-oxo nucleoside (115a), which was transformed into 2'-azido-2'-deoxyadenosine, 2'-azido-2'-deoxyinosine and 2'-azido-2'-deoxy-N<sup>6</sup>-dimethyladenosine by conventional heterocyclic manipulations.<sup>160</sup> Catalytic reduction then generated the 2'-amino nucleosides. The preparation of 2'-azido-2'-deoxyadenosine (106, X = N<sub>3</sub>) has also been achieved via reaction of the protected 2'-trifluoromethylsulfonyl nucleoside (107) with azide ion in hexamethylphosphoramide.<sup>155a</sup> Ikehara, et al.<sup>161a</sup> have independently developed a similar route using the 2'-O-mesyl analogue of 107. In a very similar way 2'-azido-2'-deoxy- and 2'-amino-2'-deoxyguanosine (116a,b) have also been prepared.<sup>161b</sup>



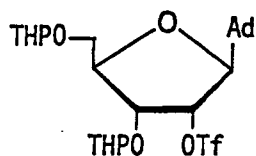
Two routes have also been explored for the preparation of 9-(2-amino-2-deoxy- $\beta$ -D-arabinofuranosyl)adenine (118b). One of these is closely related to those above and involves direct displacement of the 2'-triflate (117) with azide ion in hexamethylphosphoramide to give the 2'-azido compound (118a), which is catalytically reduced to 118b.<sup>162a</sup> The second route proceeds via treatment of a fully silylated derivative of the  $\beta$ -D-lyxo aziridine (111b) with S-ethyl trifluorothioacetate, which leads to the 2'-trifluoroacetamide (118c) that can be hydrolyzed to 118a with alkali.<sup>162b</sup> Finally, it might be mentioned that 2'-azido- and 2'-aminodeoxy derivatives of adenosine and guanosine have been prepared via degradation of 2'-azido-2'-deoxyuridine to 2-azido-1,3,5-tri-O-acetyl-2-deoxyribose that can be coupled with suitable derivatives of adenine and guanine.<sup>158</sup> This method, however, lacks steric control and leads to mixtures of the  $\alpha$ - and  $\beta$ -nucleosides.



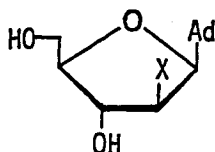
115(a) X = N<sub>3</sub>  
 (b) X = SEt



116(a) X = N<sub>3</sub>  
 (b) X = NH<sub>2</sub>



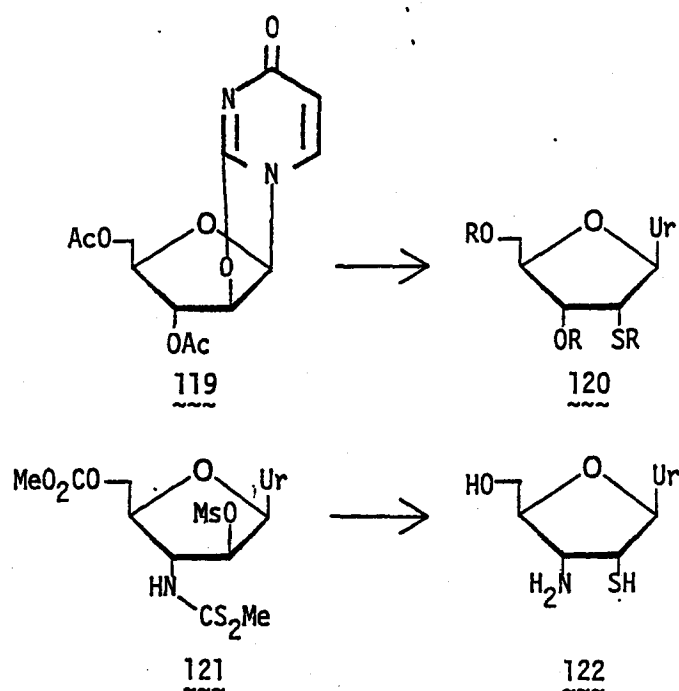
117



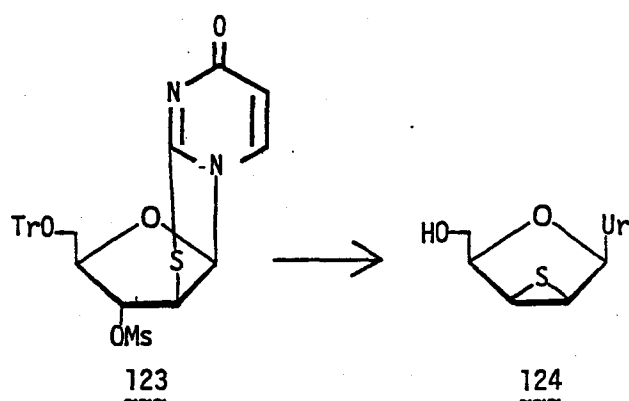
118(a) X = N<sub>3</sub>  
 (b) X = NH<sub>2</sub>  
 (c) X = NHTFA  
 (d) X = SH

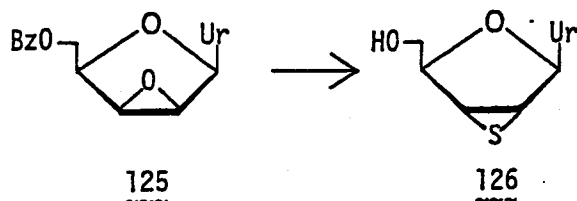
#### D. 2'-Thionucleosides

Initial attempts to open 0<sup>2</sup>,2'-cyclouridine or its 3',5'-diacyl derivatives with potassium thiobenzoate were unsuccessful since uracil was the major product.<sup>163a</sup> Subsequently it was shown that the reaction of 119 with thioacetic acid in dimethylformamide or dioxane led to the 2'-deoxy-2'-acetylthionucleoside 120a in up to 65% yields, and mild hydrolysis then gave 2'-deoxy-2'-thio-uridine (120b).<sup>163b</sup> Attempted preparation of the arabino analogue of 120b via hydrolysis of 2,2'-thiocyclouridine was not successful due to spontaneous conjugate addition of the thiol to C<sub>6</sub> of the uracil ring.<sup>163b</sup> The 2'-thio-3'-amino nucleoside 122 was prepared via intramolecular displacement of the 2'-mesylate in 121 by the 3'-dithiocarbamate moiety followed by a multistep cleavage of the remaining functionalities.<sup>164</sup>



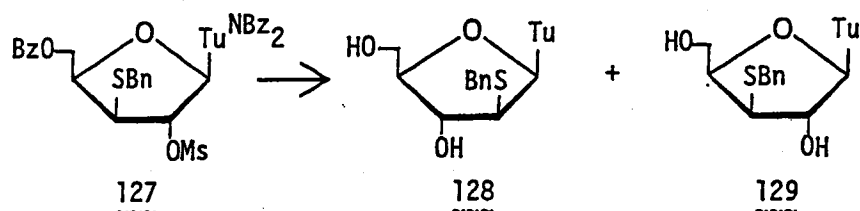
Uridine thioepoxides with both the ribo and lyxo configurations have been prepared by Ueda, et al.<sup>165</sup> The lyxo compound (124) was obtained in a single step by treatment of the thiocyclonucleoside, 123, with methanolic hydrogen chloride. Synthesis of the ribo isomer (126) was more complex and involved opening of the lyxo epoxide (125) with thiocyanate followed by mesylation, reaction with potassium thioacetate and debenzoylation. In view of the spontaneous conversion of the ribo epoxide (67) to 0<sup>2</sup>,2'-cyclouridine,<sup>108</sup> the stability of 126 is remarkable.





In the purine series, most of the routes that have been used for preparation of 2'-thio analogues are extensions of methods already described for other substituents. Thus, Ranganathan has prepared 9-(2-thio- $\beta$ -D-arabinofuranosyl)adenine (118d) via reaction of the 2'-triflate (117) with potassium thioacetate in hexamethylphosphoramide followed by mild acidic and alkaline hydrolyses.<sup>162a</sup> A comparable reaction with 107 led to 2'-acetylthioadenosine (106c),<sup>155a</sup> but attempted hydrolysis of the thioester has not been described.

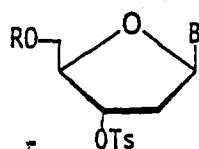
Some success in the direct displacement of the halide in 9-(2-deoxy-2-iodo-5'-O-pivaloyl- $\beta$ -D-arabinofuranosyl)adenine by sodium thiobenzoate has been reported.<sup>166</sup> Attempted deblocking of the rather surprising product, 2',3'-dibenzoyl-5'-O-pivaloyl-2'-thioadenosine, however, led only to glycosidic cleavage. Also, 2'-deoxy-2'-ethylthio-8-oxoadenosine (115b) was prepared by opening of 8,2'-cycloadenosine with sodium ethylmercaptide in dimethylformamide.<sup>137a</sup> A comparable reaction in methanol led to nucleophilic attack at both C2' and C8. Finally, reaction of the tubercidin ribo epoxide by sodium benzylmercaptide followed by mesylation gave the 3'-benzylthio-2'-O-mesyl- $\beta$ -D-xylofuranosyl nucleoside 127. Treatment of the latter with sodium benzoate led, via a lyxo episulfonium ion, to a mixture of the 2-benzylthioarabinofuranosyl and 3-benzylthioxylfuranosyl nucleosides (128 and 129) following debenzoylation.<sup>167</sup>



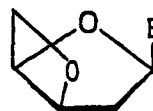
#### E. 2',3'-Unsaturated Nucleosides

2',3'-Unsaturated nucleosides have been prepared via a rather broad range of elimination reactions. The simplest case is exemplified by the work of McCarthy, et al.,<sup>168a</sup> who treated 2'-deoxy-3'-O-tosyladenosine (130a) with sodium methoxide in dimethylformamide and obtained 9-(2,3-dideoxy- $\beta$ -D-glycero-pent-2-enofuranosyl)adenine (132) in 60% yield. The latter compound can be

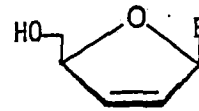
readily reduced to give 2',3'-dideoxyadenosine.



130(a) B = Ad, R = H  
 (b) B = Ur, R = Tr

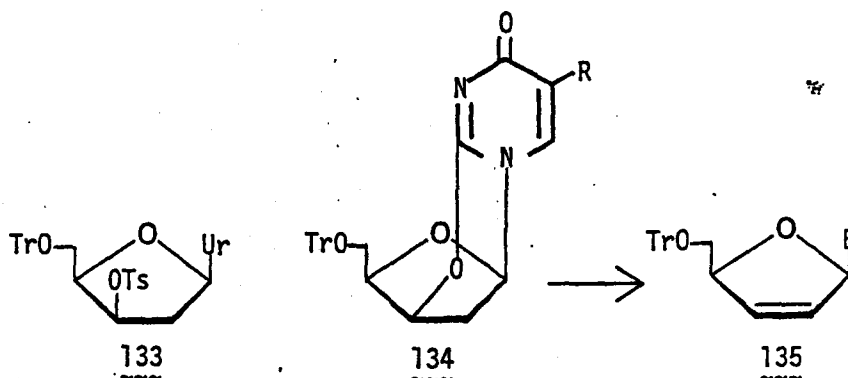


131



132

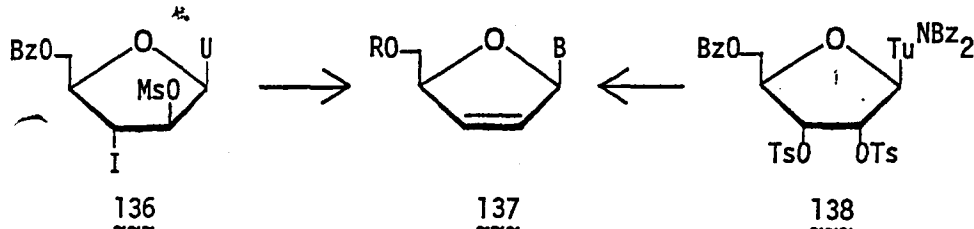
Almost simultaneous work by Horwitz, et al.<sup>168b</sup> showed that using sodium ethoxide in ethanol, 130a was partially converted into the 3',5'-oxide (131) as well as 132. Hence a number of further extrapolations have been done using the 3'-O-mesyl-5'-O-trityl derivatives of 2'-deoxyuridine,<sup>168f</sup> 5-fluoro-2'-deoxyuridine<sup>168c</sup> and 5-trifluoromethyl-2'-deoxyuridine<sup>168d</sup> in order to avoid the formation of 131. Using potassium *t*-butoxide in dimethylsulfoxide at room temperature, the corresponding 2',3'-olefins were obtained in 70-80% yields and could be detritylated with mild acid and considerable care. This reaction has also been applied to the 3'-O-tosyl derivatives 133 with the *D*-threo configuration and once again proceeds readily to give the uridine and thymidine olefins (132) following detritylation.<sup>168e</sup> On the other hand, treatment of 2'-deoxy-3'-O-mesyl-5'-O-trityluridine (130b) with one equivalent of sodium hydroxide in ethanol leads to the formation of the 0<sup>2</sup>,3'-cyclonucleoside 134 rather than to a 2',3'-olefin. Subsequent treatment of 134 with potassium *t*-butoxide in dimethylsulfoxide leads to elimination of the anhydro bridge oxygen with formation of the 2',3'-olefin 135.<sup>168e,f</sup>



Along similar lines, the treatment of 3',5'-dimesyl derivatives of thymidine<sup>168g</sup> and of N<sup>4</sup>-benzoyl-2'-deoxycytidine<sup>168h</sup> with sodium hydroxide leads to the 3',5'-oxides (131), presumably via

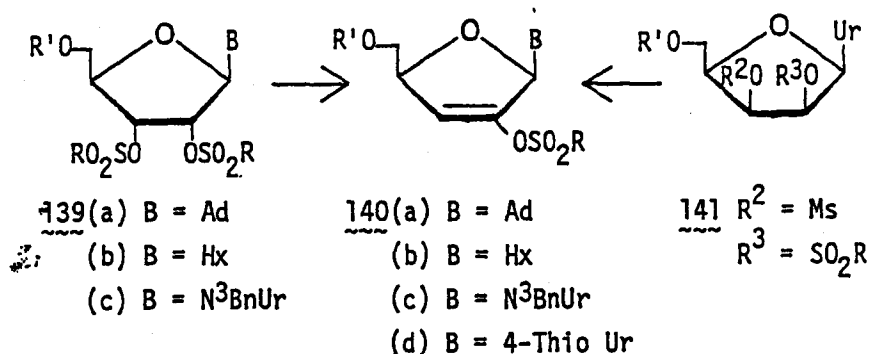
the formation and hydrolysis of the 5'-O-mesyl-0<sup>2</sup>,3'-cyclonucleosides. Treatment of 131 with potassium t-butoxide also generates the 2',3'-olefins (132) derived from uridine and cytidine.

Iodide induced elimination reactions of various iodosugar nucleosides bearing suitable vicinal *trans* leaving groups have also proved to be useful. Thus, Horwitz, et al.<sup>168e</sup> have shown that treatment of the 3'-iodo-2'-O-mesylate, 136 (produced via iodide opening of the related *lyxo* epoxide and mesylation), with sodium iodide in acetone leads to the olefin 137. Similarly, the 3'-iodonucleoside, 101b, produced as the major product from the reaction of pivaloyl chloride and sodium iodide on 2',3'-O-methoxyethylideneadenosine, can be selectively deprotected at C<sub>2'</sub> by treatment with permanganate, mesylated and treated with sodium iodide to produce 2',3'-unsaturated adenosine (132, B = Ad) following hydrolysis of the pivaloyl group.<sup>150b</sup> This same reaction has been applied to the tubercidin series as well.<sup>150c</sup>



The above can also be applied to *cis* vicinal ditosylates, presumably by way of a *trans* iodo derivative, since treatment of the tubercidin ditosylate (138) with zinc and sodium iodide gives a modest yield of 2',3'-unsaturated tubercidin derivatives (137).<sup>169</sup>

Some very interesting results have been obtained by Sasaki, et al.<sup>170</sup> upon treatment of *cis* vicinal ditosylates with base. Thus, reaction of the 2',3'-ditosylates of adenosine (139a) and inosine (139b) with sodium methoxide at 100° led to the enol-tosylates (140a,b) in yields of 55 and 37%, indicating preferential base abstraction of the C<sub>2'</sub>-proton.<sup>170a</sup> A related reaction can also be demonstrated in the uridine series, providing the uracil base is first benzylated at N<sup>3</sup> in order to prevent formation of the 0<sup>2</sup>,2'-cyclonucleoside. Thus, treatment of N<sup>3</sup>-benzyl-3'-di-O-mesyluridine (139c) with sodium benzoate in hot dimethylformamide gives the enolmesylate (140c).<sup>170b</sup> Along similar lines, treatment of 2',3'-di-O-sulfonates in the β-D-lyxofuranosyluracil series (141) with sodium benzoate or sodium carbonate leads to related enolsulfonates or, under more forcing conditions, to 2'-ketones (see later).<sup>170c,d</sup> This reaction has also been done in the 4-thiouracil series and the resulting 140d converted into the S-methyl derivative.<sup>170d</sup>

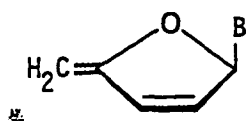


In our own work we have quite carefully examined the chromous ion induced elimination of vicinal halo acetates such as those (e.g. 96, 97) arising from reaction of  $\alpha$ -acetoxyisobutyryl halides with nucleosides.<sup>20</sup> Treatment of either pure 96, or a crude mixture of 96 and 97 ( $\text{X} = \text{Br}$  or  $\text{Cl}$ ), with chromous acetate and ethylenediamine in ethanol at  $-78^\circ$  rapidly led to the formation of the 2'-olefin (132,  $\text{B} = \text{Ad}$ ) and its isolation in crystalline form in 60-65% yield. A by-product in this reaction is 3'-deoxyadenosine, arising from simple chromous ion reduction of the halide. Only minor differences were observed in reactions using the chloro-, bromo- or iodoadenosine derivatives, and the method has been extended to the trans halo acetates derived from tubercidin, formycin, guanosine and inosine, each giving the 2'-olefin in acceptable yields. Application of the chromous acetate reaction to the cis halo acetates (e.g. 79) derived from  $\alpha$ -acetoxyisobutyryl halides and uridine led to only modest yields (30-35%) of the desired 2'-olefins, together with rather marked glycosidic cleavage. Presumably this cleavage is the result of the initially formed  $\text{C}_2$ -radical, which is unique as a major constituent to the uridine series, having an opportunity to collapse via alternative pathways leading either to the desired 2',3'-olefin or to glycosidic cleavage.

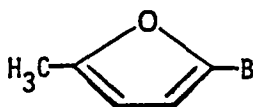
A few more specialized reactions have also been used to generate 2',3'-olefins. Thus, 2',3'-O-thionocarbonate derivatives in both the uridine<sup>171</sup> and tubercidin<sup>169</sup> series have been converted into the corresponding 2',3'-olefins upon reaction with trimethyl phosphite. In both cases, methylation of the heterocyclic base occurs. The uridine thionocarbonate can also be converted to the same olefin in low yield with Raney nickel.<sup>171</sup> Also, extrusion of sulfur from both the ribo and lyxo thioepoxides (126, 124) has been effected with triphenylphosphine giving the olefin 132 ( $\text{B} = \text{Ur}$ ).

Treatment of the D-threo-2',3',5'-trideoxy-3',5'-dichloro-

nucleosides in the pyrimidine series (16, B = Ur, Th) with dilute sodium hydroxide has been shown to give the 2',4'-dienes (142).<sup>172</sup> On the other hand, the related adenosine derivative (16, R = Ad) leads to the furan (143a) while the cytidine and inosine counterparts give mixtures of both types of dienes. This has been explained by a stabilization of the initial 2',4'-dienes (142) through a reduction in acidity of C<sub>1'</sub>-H in those cases where ionization of the heterocyclic base occurs.<sup>172</sup> Finally, an interesting synthesis of 2',3'-olefins in the adenosine, tubercidin and formycin series has been recorded through electrolysis of the mixed trans iodo acetates (e.g. 96, 97) generated through reactions already described.<sup>173</sup>



142 (B = Ur, Th)



143(a) B = Ad  
143(b) B = Th

#### F. 2'-Deoxy- and 2',3'-Dideoxynucleosides

A wide range of 2'-deoxynucleosides has been prepared via either reduction of 2'-halogenated compounds or desulfurization of various 2'-thio derivatives, the preparations of which have already been outlined. In general, rather standard conditions have been used and little further comment is necessary. Thus, palladium catalyzed hydrogenolysis of 2'-bromo and 2'-iodo derivatives has been used to prepare 2'-deoxynucleosides in the uridine,<sup>101b,138b,152a,153a</sup> 5-methyluridine,<sup>138b</sup> 5-fluorouridine,<sup>153b</sup> adenosine<sup>150a</sup> and formycin<sup>147b,150a</sup> series. Catalytic reduction of the sometimes more easily available 2'-chloronucleosides is not usually successful using palladium catalyzed reduction. Fortunately, however, reduction of any of the 2'-halo compounds can be achieved upon treatment of suitable acylated derivatives with tributylstannane in the presence of a radical initiator. By this technique, 2'-deoxy derivatives in the uridine,<sup>113b</sup> 6-azauridine,<sup>111a,113b</sup> 5-methyluridine,<sup>111a</sup> 5-fluorouridine,<sup>111a</sup> pseudouridine,<sup>146b,154</sup> 5'-fluorouridine,<sup>146c</sup> 6-azatidine,<sup>113b</sup> 2'-3H-uridine,<sup>142</sup> L-uridine,<sup>141</sup> 3-β-D-ribofuranosyluracil,<sup>145</sup> 5'-deoxyuridine,<sup>113a</sup> inosine,<sup>151b</sup> adenosine,<sup>150a</sup> guanosine,<sup>150d,f</sup> and β-D-xylofuranosyladenine<sup>151c</sup> series have been successfully prepared.

Another method of classical importance for the preparation of deoxynucleosides involves desulfurization of various 2'-thionucleoside derivatives with Raney nickel. By this route, 2'-deoxy derivatives of 5-methyluridine,<sup>103</sup> adenosine,<sup>132a,166</sup>

guanosine,<sup>134c</sup> tubercidin,<sup>167</sup> 2-chloroadenosine<sup>136</sup> and 9- $\beta$ -D-xylofuranosyladenine<sup>132b</sup> have been obtained, as well as a number of products arising from minor constituents of reactions giving primarily 3'-deoxy compounds to be considered later. Finally, a number of 2',3'-dideoxynucleosides have been obtained via palladium catalyzed reduction of 2',3'-unsaturated nucleosides. These include the 2',3'-dideoxy derivatives of uridine,<sup>168g,168e</sup> 5-methyluridine,<sup>168g</sup> cytidine,<sup>168h</sup> 5-fluorouridine,<sup>168c</sup> adenosine,<sup>150b,168b</sup> 5'-deoxyadenosine<sup>168a</sup> and tubercidin.<sup>150c,e</sup> In addition, it should be pointed out that in our hands palladium catalyzed reduction of the *trans* bromo acetates (e.g. 96, X = Br) leads to the formation of both the expected 3'-deoxynucleosides and the corresponding 2',3'-dideoxy compound.<sup>147a</sup> On the other hand, comparable reduction of the related deacetylated compound leads only to simple reduction of the halide. By this method the 2',3'-dideoxy derivatives of adenosine,<sup>147a</sup> tubercidin,<sup>147b</sup> formycin,<sup>147b</sup> guanosine<sup>147c</sup> and cytidine<sup>153a</sup> have been prepared. It has been suggested that this is the result of a palladium catalyzed *trans* elimination reaction of the bromo acetates to give the 2',3'-unsaturated nucleoside that undergoes further reduction.<sup>147a</sup> A related formation of 2',3'-dideoxyuridine from reduction of 2'-bromo-3'-O-mesyluridine has been reported.<sup>174</sup>

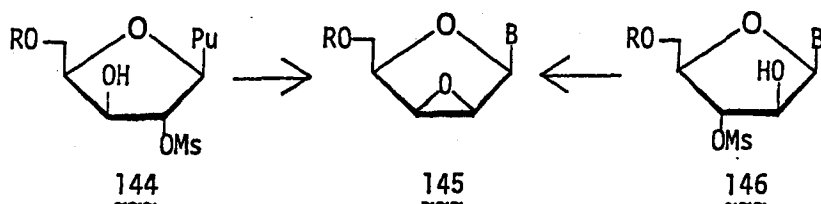
Finally, it has recently been reported that reaction of the 2',3'-O-thionocarbonate of adenosine with tributylstannane leads to the formation of a mixture of 2'- and 3'-deoxyadenosines in yields of 60% and 30%.<sup>175</sup> It is to be expected that comparable reactions of other nucleoside thionoesters will find a valuable place in the preparation of the corresponding deoxy compounds.

#### G. 2',3'- and 2',5'-Anhydro Nucleosides

As has already been pointed out, 2',3'-ribo epoxides derived from pyrimidine nucleosides (e.g. 67) cannot generally be isolated because of their rearrangement to 2',2'-cyclo nucleosides. The apparent stability of the thioepoxide 126 is clearly an exception to this generality.<sup>165</sup> Purine ribo epoxides are, on the other hand, readily available compounds that can be prepared via treatment of the *trans* halo acetates (e.g. 96, 97 or 100, 101) with base. Mixtures of such halo acetates containing predominant amounts of the 3'-deoxy-3'-halo- $\beta$ -D-xylofuranosyl isomers (e.g. 96, 100) can be prepared via either reactions of 2-acetoxyisobutyryl halides with purine nucleosides<sup>147</sup> or of pivaloyl chloride with nucleoside 2',3'-orthoacetates.<sup>150,151</sup> Direct treatment of such mixtures, or of individually purified isomers, with bases such as sodium methoxide has led to the ribo epoxides derived from adenosine,<sup>147a,150a,176</sup> tubercidin<sup>147b,150c,d</sup> formycin,<sup>147b,148</sup> inosine,<sup>147c,d,151b</sup> and guanosine<sup>147c,150d,f</sup> in quite acceptable overall yields.

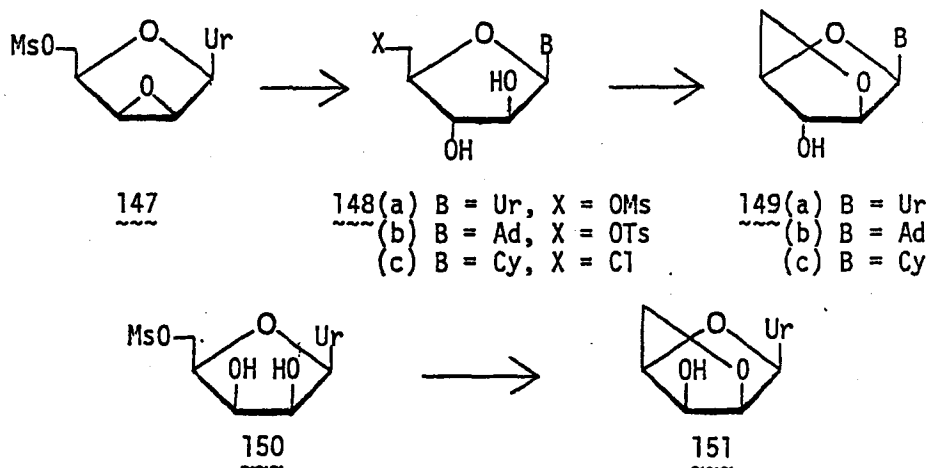
Intramolecular displacement of an 8,2'-cyclonucleoside bridge has also been used to generate a ribo epoxide. Thus, treatment of 8,2'-cycloadenosine (88, X = O) with sodium hydroxide in dimethylsulfoxide gives 2',3'-anhydro-8-oxoadenosine in 88% yield.<sup>177</sup>

2',3'-Anhydro-β-D-lyxofuranosyl nucleosides (lyxo epoxides, 145) are also well known compounds that can, for example, be prepared via base treatment of the readily available 9-(2-O-mesyl-β-D-xylofuranosyl)adenine (144).<sup>178a</sup> The lyxo epoxides in the 6-amino-2-chloropurine,<sup>178b</sup> guanine,<sup>178c</sup> 6-thioguanine<sup>178c</sup> and 4'-thioadenosine<sup>178d</sup> series have been prepared by similar routes. In addition, certain pyrimidine lyxo epoxides are available through base treatment of ribonucleoside 2',3'-di-O-sulfonates. Such reactions proceed by way of 3'-O-sulfonyl-0<sup>2</sup>,2'-cyclonucleosides and 3'-O-sulfonyl-β-D-arabinofuranosyl (146) intermediates and have been used to prepare lyxo epoxides in the N<sup>3</sup>-benzyluracil,<sup>170b</sup> 6-azauracil,<sup>179a</sup> isocytosine<sup>179b</sup> and 6-azaisocytosine<sup>179c</sup> series. In the latter case, the intermediate 3'-O-mesyl-0<sup>2</sup>,2'-cyclo-6-azauridine can be isolated and treated with ammonia. It has also been reported that treatment of either 9-β-D-arabinofuranosyladenine or 9-β-D-xylofuranosyladenine with triphenylphosphine and diethyl azodicarboxylate leads, by way of triphenyloxyphosphonium intermediates, to adenosine lyxo epoxides in very high yields.<sup>180</sup> Syntheses of both the ribo and lyxo thioepoxides (126, 124) in the uracil series have already been mentioned.<sup>165</sup>



A number of 2',5'-anhydro nucleosides have also been prepared by intramolecular displacement reactions. Thus, Doerr, et al.<sup>181a</sup> have reported that opening of the 5'-O-mesyl-lyxo uracil epoxide (147) with acid generates the 5'-O-mesyl-β-D-arabinofuranoside (148a), which is converted into the 2',5'-anhydro nucleoside (149a) with base. Similarly, treatment of 9-(5-O-tosyl-β-D-arabinofuranosyl)adenine (148b) with liquid ammonia leads directly to the 2',5'-oxide (149b).<sup>181b,c</sup> By nucleophilic opening of 147 and a related adenine analogue with sodium benzoxide<sup>181a</sup> and azide ion,<sup>181d</sup> respectively, the corresponding 3'-substituted 2',5'-anhydrides have been directly obtained. In the cytidine series, a reactive 5'-chloro-5'-deoxy-β-D-arabinofuranosyl derivative (148c) is generated by alkaline hydrolysis of 5'-chloro-5'-deoxy-0<sup>2</sup>,2'-cyclocytidine and leads to the corresponding 2',5'-oxide (149c).<sup>181a</sup> It is interesting to note that treatment of 1-(5-O-

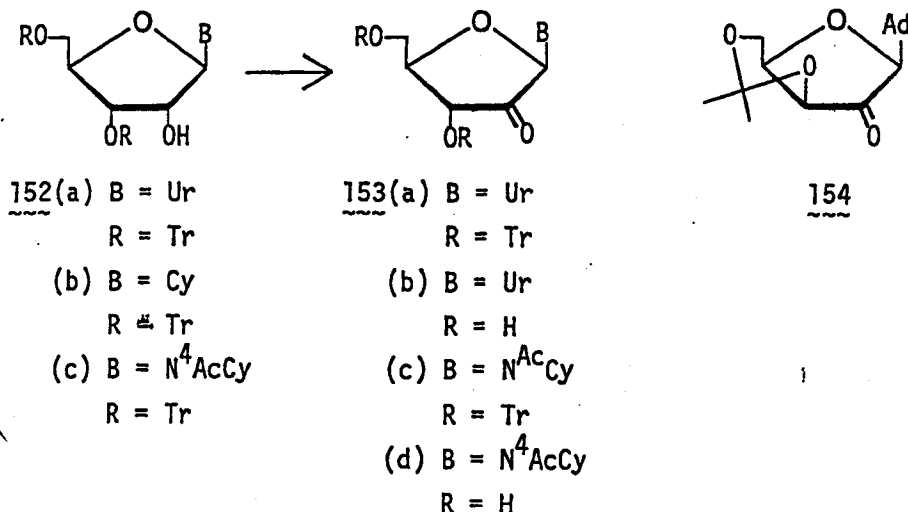
mesyl- $\beta$ -D-lyxofuranosyl)uracil (150) with base leads exclusively to the 2',5'-anhydro derivative 151 with no sign of the 3',5'-anhydro isomer.<sup>181e</sup>



#### H. 2'-Keto Nucleosides

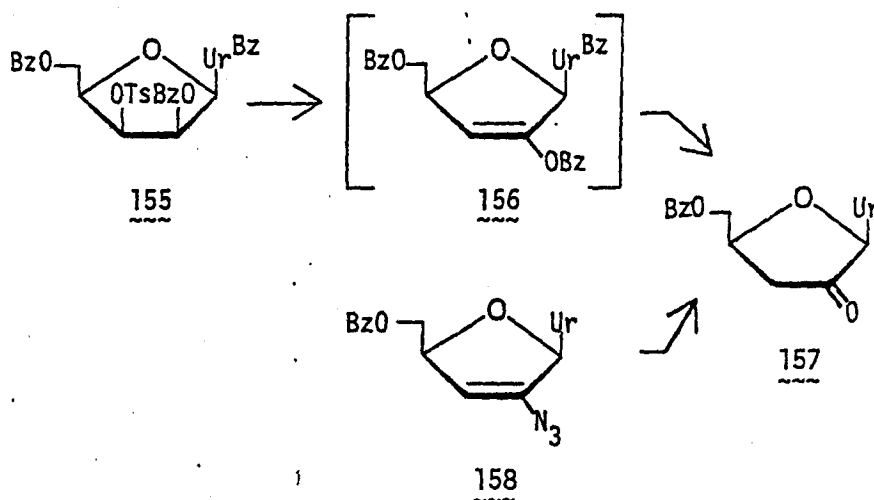
Relatively little work has been done on the direct oxidation of nucleoside 2'-hydroxyl groups to the corresponding carbonyl derivatives. The oxidative cleavage of the vicinal diol grouping to dialdehydes using periodate, and the structure of the resulting products,<sup>182</sup> will not be considered at this time. The dimethylsulfoxide-dicyclohexylcarbodiimide method of oxidation<sup>84</sup> provided the first method combining the power and sensitivity necessary for this purpose. Thus, Cook and Moffatt<sup>183a</sup> initially showed that oxidation of 3',5'-di-O-trityluridine (152a) using DMSO and DCC in the presence of pyridinium trifluoroacetate as the proton source led to the isolation of the 2'-keto nucleoside (153a) in 63% yield. Oxidation could also be achieved in comparable yields using dimethylsulfoxide activated with phosphorus pentoxide or acetic anhydride. Detritylation of 153a to give free 2'-ketouridine (153b) could be effected with anhydrous hydrogen chloride in chloroform. Both 153a and, to a much greater extent, 153b, were very labile under alkaline conditions and readily underwent glycosidic cleavage. Borohydride reduction of either compound led predominantly to products with the  $\beta$ -D-arabinofuranosyl configuration. Similar oxidation of 3',5'-di-O-tritylcytidine (152b) and its N<sup>4</sup>-acetyl derivative (152c) could also be achieved using sulfoxide based oxidants, and the N-acetyl derivative (153c) could be detritylated as above.<sup>183b</sup> Once again, borohydride reduction of either 153c or its diol counterpart (153d) leads predominantly to the related  $\beta$ -D-arabinofuranosyl derivatives, and this route has been used for preparation of 2'-3H- $\beta$ -D-arabinofuranosylcytosine.<sup>183b</sup>

Virtually the only other 2'-keto nucleosides obtained by direct oxidation procedures are 154, which was prepared by ruthenium tetroxide oxidation of 9-(3,5-O-isopropylidene- $\beta$ -D-xylofuranosyl)adenine,<sup>184</sup> and 157, which was obtained in 35% yield by DMSO-acetic anhydride oxidation of the corresponding 3'-deoxy- $\beta$ -D-threo-pentofuranosyl nucleoside.<sup>185</sup>



An interesting alternative route to 2'-keto-3'-deoxyuridine derivatives has been exploited by Sasaki, et al.<sup>170</sup> through elimination reactions of various cis vicinal disulfonates. As previously mentioned, treatment of compounds such as 139 or 141 with sodium carbonate or sodium benzoate leads to the enolsulfonates (140).<sup>170</sup> Under more forcing conditions these compounds undergo cleavage of the sulfonates with formation of the 2'-keto-3'-deoxynucleosides (e.g. 157). A similar reaction on the 2'-O-benzoyl-3'-O-tosyl nucleoside (155) leads, by way of the labile enolbenzoate 156, to the ketone (157).<sup>185</sup> The cytosine analogue of 157 was also prepared by aminolysis of the 4-thiouracil derivative 140d.<sup>170d</sup>

In a rather similar process, the vinyl azide (158) was prepared via treatment of 2'-azido-5'-O-benzoyl-2'-deoxy-3'-O-mesylyridine with potassium *t*-butoxide and then converted to 157 by palladium catalyzed reduction.<sup>159</sup> In view of the great alkaline lability of compounds such as 153, it is remarkable to note that debenzoylation of 157 can be achieved in 36% yield by treatment with triethylamine in hot methanol.<sup>185</sup>



### III. 3'-MODIFIED NUCLEOSIDES

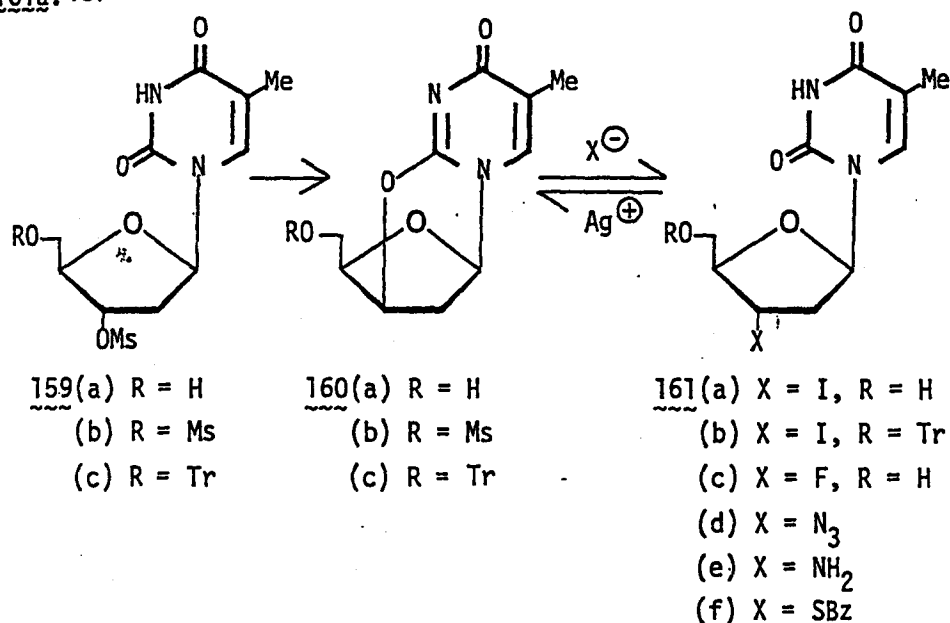
#### A. 3'-Cyclonucleosides and Their Hydrolysis Products

The propensity with which pyrimidine ribonucleosides bearing a suitable leaving group at C<sub>2</sub>' are converted into 0<sup>2</sup>,2'-cyclonucleosides has already been discussed. A large body of work, largely from the laboratories of Todd and Fox, has explored the chemistry of pyrimidine 0<sup>2</sup>,2'- and 0<sup>2</sup>,3'-cyclonucleosides and demonstrated the wealth of reactions in which these substances serve as intermediates. The reader is referred to an excellent review<sup>51</sup> covering much of this work, and only the rather direct synthetic applications will be considered here.

The first evidence for the formation of 0<sup>2</sup>,3'-cyclonucleosides came from the work of Michelson and Todd,<sup>54a</sup> who showed that treatment of 3'-O-mesylthymidine (**159a**) with sodium iodide led to the 3'-iodo derivative (**161a**) with net retention of configuration. They correctly inferred the intermediacy of 0<sup>2</sup>,3'-cyclothymidine (**160a**), and this substance could be regenerated upon treatment of **161a** with silver acetate.

The ease of formation of the 0<sup>2</sup>,3'-cyclo bridge is greater than that leading to 0<sup>2</sup>,5'-cyclothymidine since treatment of 3',5'-di-O-mesylthymidine (**159b**) with ethanolic ammonia leads to 5'-O-mesyl-0<sup>2</sup>,3'-cyclothymidine (**160b**).<sup>3</sup> Using potassium fluoride as the base, however, a 2:1 mixture of **160b** and the isomeric 3'-O-mesyl-0<sup>2</sup>,5'-cyclothymidine is obtained.<sup>6a</sup> Much careful work by Fox and Miller<sup>186</sup> has clarified the formation of 0<sup>2</sup>,3'-cyclothymidine derivatives (**160a,c**) upon treatment of the corresponding

3'-O-mesyl derivatives with one equivalent of sodium hydroxide or even upon refluxing in water. Similar results have been obtained with the 5-fluorouracil analogues of 159, and more vigorous alkaline hydrolysis of the cyclonucleosides leads to the 1-(2-deoxy- $\beta$ -D-threo-pentofuranosyl)pyrimidines with overall inversion of configuration at C<sub>3'</sub> relative to the starting mesylate (159).<sup>186</sup> The use of organic bases such as 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU) allows the conversion of 159c into 160c in almost quantitative yield at room temperature,<sup>54b</sup> and comparable results have also been obtained starting from the 3'-iodothymidine derivative 161a.<sup>187</sup>



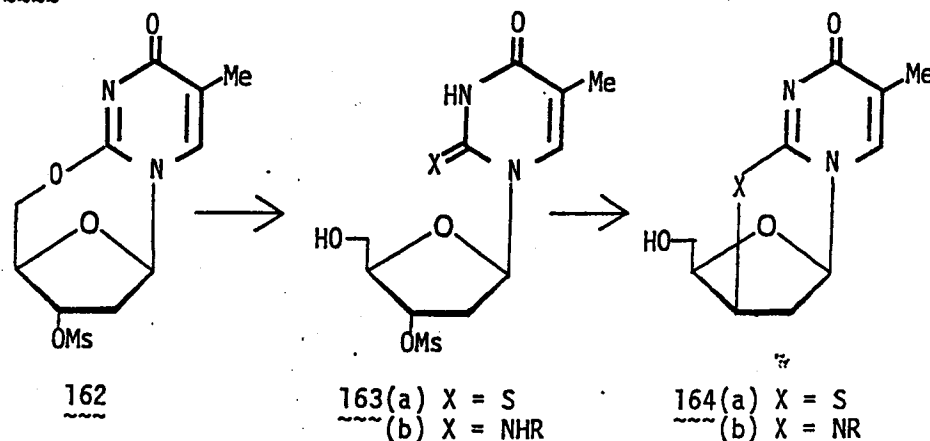
As would be expected, the generation of any efficient leaving group at C<sub>3'</sub> of pyrimidine 2'-deoxynucleosides permits the preparation of the corresponding 0<sup>2</sup>,3'-cyclonucleosides. Oxyphosphonium groups of the general type 8 fit this description, and brief treatment of 5'-O-tritylthymidine with methyltriphenoxyphosphonium iodide in pyridine leads to the isolation of crystalline 160c in 70% yield.<sup>13</sup> A comparable reaction with thymidine itself is accompanied by iodination of the primary hydroxyl group giving 5'-deoxy-5'-iodo-0<sup>2</sup>,3'-cyclothymidine.<sup>11b</sup> Generation of a 3'-oxyphosphonium species analogous to 27a can also be achieved through reaction of 5'-O-tritylthymidine with triphenylphosphine and diethyl azodicarboxylate. When conducted in the presence of methyl iodide, this reaction gives a 50% yield of the cyclonucleoside, 160c, together with a lesser amount of a 3'-iodinated product.<sup>188</sup> An interesting example of the selective formation of 0<sup>2</sup>,3'-cyclonucleosides from unprotected pyrimidine deoxy-

nucleosides involves the reaction of thymidine, 2'-deoxyuridine and 5-fluoro-2'-deoxyuridine with diethyl-(2-chloro-1,1,2-trifluoroethyl)amine in dimethylformamide.<sup>189</sup> These reactions proceed by way of generation of a reactive oxyimmonium species

(161,  $X = Et_2N=\overset{\oplus}{C}\begin{smallmatrix} OR \\ \text{CHFCI} \end{smallmatrix}$ ) that is readily displaced by attack of O<sup>2</sup>

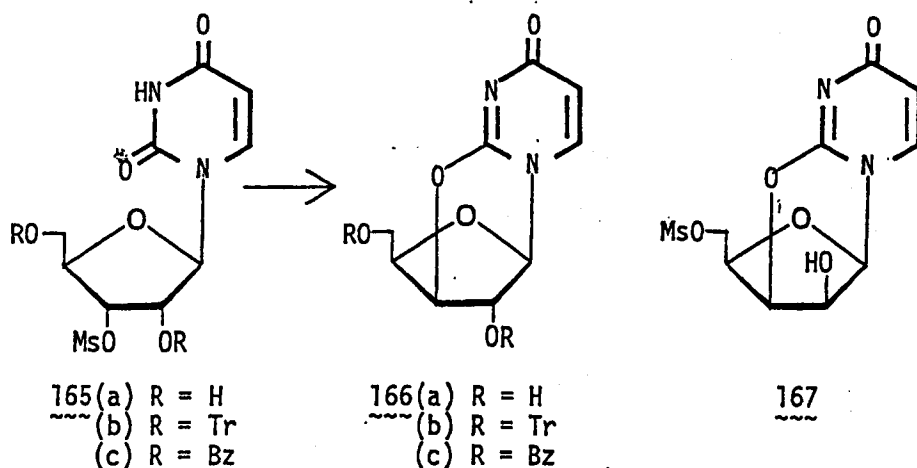
of the pyrimidine ring. In the absence of a strong nucleophile the comparable function at C<sub>5</sub>, is presumably hydrolyzed during work-up. Nitrate esters can also be intramolecularly displaced, and treatment of the 3',5'-dinitrate of 2'-deoxy-5-fluorouridine with very dilute alkali leads to the O<sup>2</sup>,3'-cyclonucleoside 5'-O-nitrate.<sup>7a</sup>

Several sulfur and nitrogen bridged 2,3'-cyclonucleosides have also been described via intramolecular mesylate displacement. Thus, opening of the 3'-O-mesyl-O<sup>2</sup>,5'-cyclonucleoside (162) with hydrogen sulfide generates the 2-thiothymidine derivative (163a) that is converted into the thiocyclonucleoside (164a) with triethylamine.<sup>190a</sup> In a related way, the opening of 162 with ammonia or amine derivatives generates isocytosine derivatives (163b), which spontaneously cyclize to the imino cyclonucleosides (164b).<sup>190b,c</sup>

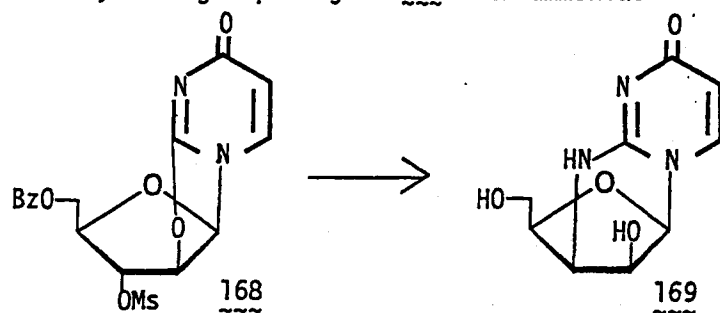


In the pyrimidine ribonucleoside series, the formation of O<sup>2</sup>,3'-cyclonucleosides by intramolecular displacement of 3'-O-sulfonyl derivatives is less facile than comparable reactions with the 2'- and 5'-sulfonates. Thus, 3'-O-mesyluridine (165a) and 3'-O-tosyluridine show little tendency towards formation of O<sup>2</sup>,3'-cyclouridine (166a) under a variety of mildly basic conditions,<sup>191</sup> although such a cyclization does occur with sodium *t*-butoxide in dimethylformamide.<sup>191a</sup> Under more forcing conditions, isomerization of 166a to O<sup>2</sup>,2'-cyclouridine takes place, presumably via the 2',3'-epoxide.<sup>191c</sup> It is interesting to note, however, that

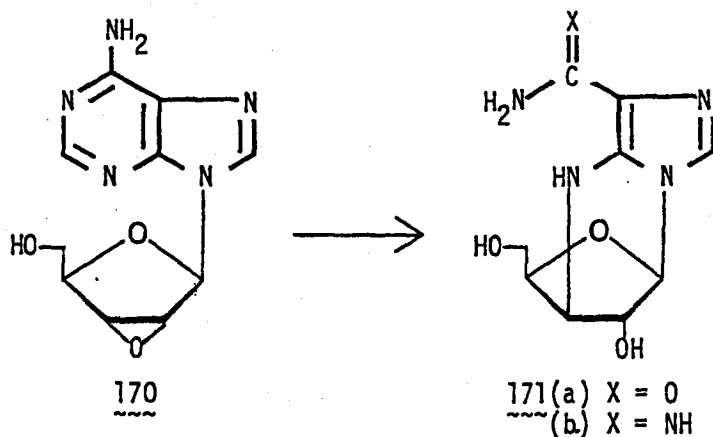
1-(3,5-di-O-mesyl- $\beta$ -D-arabinofuranosyl)uracil is converted into the 0<sup>2</sup>,3'-cyclonucleoside (167) and then hydrolyzed to 1-(5-O-mesyl- $\beta$ -D-lyxofuranosyl)uracil simply upon boiling in water.<sup>104a</sup> Also, 3'-O-mesyl-2',5'-di-O-trityluridine (165b) is readily converted into the cyclonucleoside 166b upon treatment with sodium benzoate in hot dimethylformamide.<sup>191b</sup> A comparable reaction with the 2',5'-dibenzoate (165c) leads to 166c, which undergoes thermal isomerization to 3',5'-di-O-benzoyl-0<sup>2</sup>,2'-cycloouridine via the 2',3'-benzoxonium ion.<sup>191b</sup> The conversion of 3'-O-mesylcytidine, and its 2',5'-di-O-trityl derivative, to the corresponding 0<sup>2</sup>,3'-cyclocytidines with sodium t-butoxide in dimethylformamide has been reported by Mizuno and Sasaki,<sup>192a</sup> and the rather surprising stability of these compounds under alkaline conditions (cf. 0<sup>2</sup>,2'-cyclocytidines--see earlier) has been noted.<sup>192b</sup>



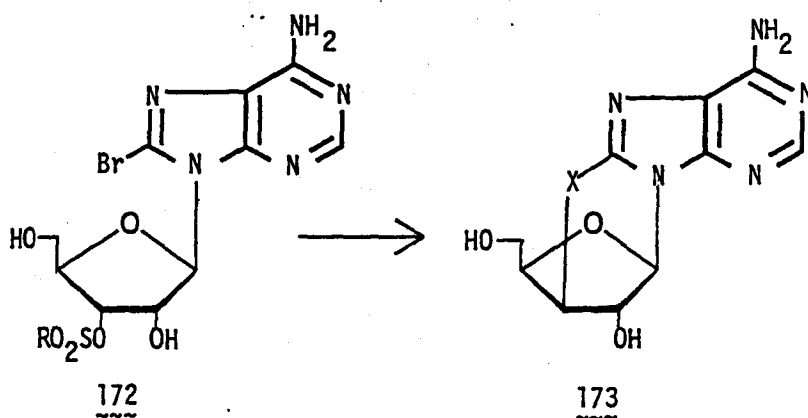
The sulfur bridged analogue of 166b has been prepared by treatment of the 2-thio analogue of 165b with triethylamine,<sup>57d</sup> while reaction of 168 with ammonium azide gives rise to the nitrogen bridged cyclonucleoside 169.<sup>193</sup> This transformation was originally considered to proceed via a 2-azidopyrimidine intermediate<sup>193a</sup> but was subsequently shown through isotope studies to occur, in fact, through opening of 168 with ammonia.<sup>193b</sup>



In the purine series, evidence for the intermediacy of  $N^3,3'$ -cyclonucleosides in certain reactions has been reported,<sup>194</sup> but this species is unstable and undergoes cleavage of the pyrimidine ring. Thus, alkaline hydrolysis of 2',3'-anhydroadenosine (170) leads to the crystalline derivative 171a,<sup>194b,c</sup> whereas upon simply boiling in water the amidine 171b is the product.<sup>194b</sup>



On the other hand, 8,3'-cyclonucleosides of various types are readily available and synthetically useful compounds prepared via treatment of 3'-O-sulfonates of 8-bromopurine nucleosides with oxygen or sulfur nucleophiles.<sup>195</sup> Thus, 8-bromo-3'-O-(2,4,6-triisopropylbenzenesulfonyl)adenosine (172) was converted into its 8-oxo-derivative with sodium acetate followed by mild base, and cyclized to the 8,3'-cyclonucleoside (173) upon heating in dimethylformamide and sodium acetate.<sup>129c</sup> Comparable reactions also occur in the 2'-deoxyadenosine series<sup>129c,195a</sup> and can be extended to the preparation of 8,3'-thiocyclo derivatives in the adenosine,<sup>195b</sup> deoxyadenosine<sup>129c</sup> and guanosine<sup>195c</sup> series by use of thiourea or sodium hydrogen sulfide as the nucleophile.



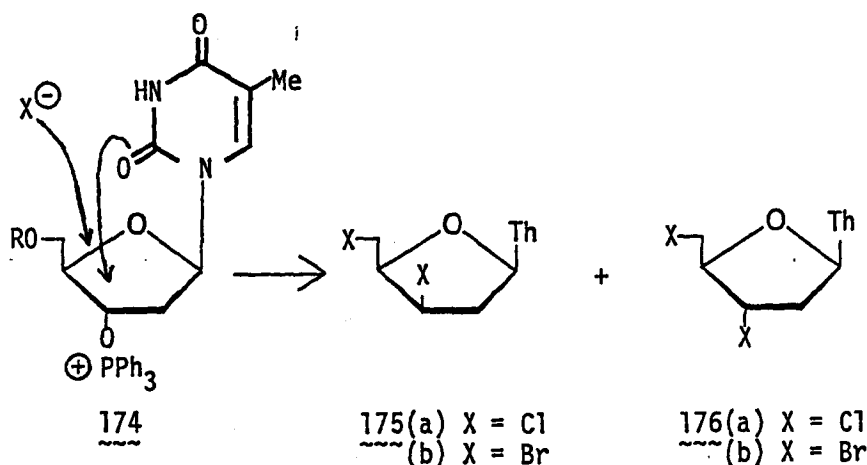
## B. 3'-Halogenated Nucleosides

As was the case for 2'- and 5'-halogenated nucleosides, the earliest preparations of 3'-halogenated compounds involved sulfonate displacement reactions. Thus, the conversion of 3'-O-mesylthymidine (159a) to 3'-deoxy-3'-iodothymidine (161a) with overall retention of configuration due to the intermediary formation of the 0<sup>2</sup>,3'-cyclonucleoside (160a) has already been mentioned and has been extended to the 2'-deoxyuridine series.<sup>196</sup> As would be expected, direct displacement of the 3'-epimer of 159c with iodide ion leads to the same 3'-iodonucleoside 161b as is obtained from 159c via the cyclonucleoside.<sup>197</sup> Applications in the ribonucleoside series are less well defined, with treatment of 3'-O-p-nitrobenzenesulfonyladenine<sup>198a</sup> and 5'-O-acetyl-3'-O-tosyl-6-azauridine<sup>198b</sup> with sodium iodide in hot acetonylacetone giving 3'-deoxy-3'-iodonucleosides that are assumed to have the D-xylo configuration.

Many of the direct halogenation methods described earlier have also found more frequent applications in the preparation of 3'-halogenated nucleosides. For example, the reaction of 5'-O-tritylthymidine, or other 5'-substituted derivatives, with methyltriphenoxyphosphonium iodide (7) in dimethylformamide at room temperature has been shown to give the 3'-deoxy-3'-iodo derivative (161b) in good yields.<sup>13</sup> Once again, the observed retention of configuration in the product confirms the intervention of the 0<sup>2</sup>,3'-cyclonucleoside in these reactions. The use of an excess of 7 with unprotected thymidine or 2'-deoxyuridine similarly leads to high yields of the 3',5'-dideoxy-3',5'-diiodonucleosides.<sup>13</sup> This reaction cannot, however, be extended to use in iodination of cis vicinal diols (e.g. 5'-O-p-nitrobenzoyluridine) since intramolecular reaction of an adjacent free hydroxyl group with the initially formed oxyphosphonium derivative leads, instead, to the formation of methyl phosphonate esters.<sup>13</sup> Treatment of 2',5'-di-O-trityluridine with 7 leads predominantly to 3'-deoxy-3'-iodonucleosides with the β-D-xylo configuration, indicating a direct inversion of configuration rather than initial formation of the 0<sup>2</sup>,3'-cyclonucleoside.<sup>13,199</sup> It has also been reported that reaction of 3',5'-di-O-acetyluridine with 7 in benzene is accompanied by partial acetyl migration, giving a mixture of 2'- and 3'-iodinated products.<sup>199</sup> In our hands, however, the reaction of 3'-O-acetyluridine with 7 in dimethylformamide gives 3'-O-acetyl-2',5'-dideoxy-2',5'-diiodouridine with no indication of acetyl migration.<sup>13</sup>

Unlike the precise steric control that accompanies the reactions of isolated nucleoside secondary hydroxyl groups with the Rydon reagent 7, the related reactions using triphenylphosphine and carbon tetrahalides exhibit some interesting variations.<sup>18</sup> Treatment of thymidine with triphenylphosphine and carbon tetrachloride in dimethylformamide gives the threo 3',5'-dichloro-

nucleoside 175a in 63% yield and only 5% of the erythro derivative 176a. Clearly, the small size and high nucleophilicity of chloride ion allows direct  $S_N2$  attack on the intermediate 174 to compete favorably with cyclonucleoside formation. The comparable reaction with carbon tetrabromide is satisfactory for reaction with the 5'-alcohol but gives only very limited reaction with the secondary alcohol due to competitive reactions with the solvent, dimethylformamide. The erythro (176b) and threo (175b) dibromides were, however, isolated in yields of 12% and 4%, showing that in this case the intermediary formation of the  $O^2,3'$ -cyclonucleoside is once again favored and leads to overall retention of configuration. Essentially no halogenation was obtained using carbon tetraiodide.



Nucleophilic opening of  $O^2,3'$ -cyclonucleosides has been of some value, particularly in the preparation of 3'-fluoro derivatives. Thus, treatment of  $O^2,3'$ -cyclothymidine (160a) or of its 5'-O-mesylate with hydrogen fluoride in dioxane in the presence of aluminum fluoride at  $150^\circ$  gives 3'-deoxy-3'-fluorothymidine (161c) in 35-60% yields.<sup>200a,b</sup> A related reaction using hydrogen chloride gave the 3'-chloro analogue in good yield.<sup>200a</sup> Treatment of 160a with methyl iodide also gives 3'-deoxy-3'-iodo- $N^3$ -methylthymidine without difficulty, and this reaction can be extended to 2',5'-di-O-trityl- $O^2,3'$ -cyclouridine giving the corresponding 3'-deoxy-3'-iodo- $N^3$ -methyluridine derivative.<sup>29b</sup> On the other hand, the reactions of unprotected  $O^2,3'$ -cyclouridine (17) with methyl iodide give exclusively the 5'-iodonucleosides (19, R = Me) presumably via rearrangement of the activated  $O^2,3'$ -cyclonucleoside to its  $O^2,5'$ -cyclo isomer (18, R = Me).<sup>29b</sup> Similar rearrangements leading to, e.g., 19 (R = H) occur upon reactions of 17 with sodium iodide and acetic acid or with hydrogen bromide or hydrogen chloride.<sup>29a</sup> The reaction with hydrogen fluoride, however, appears to give 3'-deoxy-3'-fluoro- and 2'-deoxy-2'-fluorouridines, the latter via

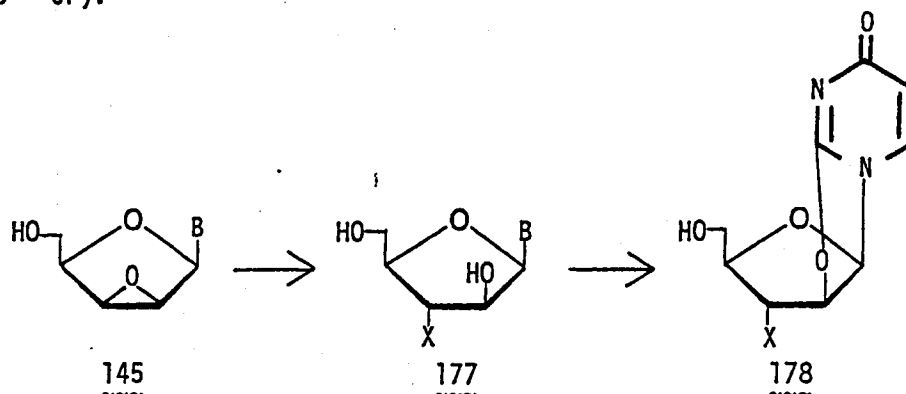
rearrangement to  $O^2,2'$ -cyclouridine, without any appearance of a 5'-fluoro isomer.<sup>200c</sup>

As previously mentioned, the reactions of purine nucleosides with  $\alpha$ -acetoxyisobutyryl halides (e.g. 74) lead principally to the 9-(2-O-acetyl-3'-deoxy-3'-halo- $\beta$ -D-xylofuranosyl)purines (e.g. 96) via attack of halide ion at the less hindered 3'-position of the intermediate 2',3'-acetoxonium ion.<sup>147</sup> In this way products related to 96 have been prepared with considerable ease in the adenosine,<sup>147a,20</sup> tubercidin,<sup>147b,148</sup> formycin,<sup>147b,148</sup> inosine<sup>147c,d</sup> and guanosine<sup>147c</sup> series. The closely related, but somewhat differently protected, compounds 101 also arise as the major products during reactions of 2',3'-O-methoxyethylidene purine nucleosides with pivaloyl chloride in pyridine either in the presence or absence of sodium iodide.<sup>150</sup> This reaction has proved useful for preparation of compounds related to 101 in the adenosine,<sup>150a,b,151a</sup> tubercidin,<sup>150c,e</sup> inosine<sup>151b</sup> and guanosine<sup>150d</sup> series. The two types of reactions above have been very useful in providing intermediates for a variety of other functional transformations discussed elsewhere in this review.

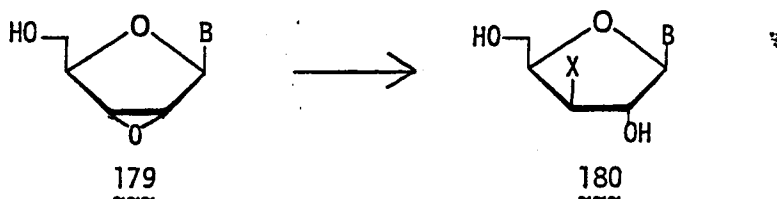
Along similar lines, treatment of 3',5'-di-O-acetyladenosine with lithium bromide or phosphorus tribromide and boron trifluoride leads to moderate yields of 9-(2,5-di-O-acetyl-3-bromo-3-deoxy- $\beta$ -D-xylofuranosyl)adenine (96, R = Ac) via an intermediate 2',3'-O-acetoxonium ion.<sup>201</sup> A similar result was also obtained using the related reaction of adenosine with silicon tetraacetate, phosphorus tribromide and boron trifluoride.<sup>201</sup> The acetoxonium ion 95 can also be generated and opened by treatment of 2',3'-methoxyethylideneadenosine (98) with boron trifluoride in the presence of an excess of bromide or iodide ions.<sup>20</sup> Under these conditions the trans halo acetates with both the xylo (96) and arabino configurations are obtained, but the yields are somewhat lower than those obtained by the methods outlined above. Because of the predominant intervention of  $O^2,2'$ -cyclonucleosides during generation of 2',3'-O-acetoxonium ions in pyrimidine nucleosides, the preparation of 3'-halogenated compounds via such intermediates has been of limited success. Treatment of  $N^4$ -acetylcytidine with acetyl bromide has, however, given 30-40% yields of 1-(2,5-di-O-acetyl-3-bromo-3-deoxy- $\beta$ -D-xylofuranosyl) $N^4$ -acetylcytosine, whereas the corresponding reaction with cytidine itself leads predominantly to 3',5'-di-O-acetyl- $O^2,2'$ -cyclocytidine salts (81).<sup>153a</sup>

Another major route to 3'-halogenated nucleosides with a 2',3'-trans configuration has been through nucleophilic opening of 2',3'-epoxides. Since the epoxides with the  $\beta$ -D-lyxo configuration (145) have been known for many years and are readily available from either 2'-O-mesyl- $\beta$ -D-xylofuranosides (144)<sup>178</sup> or 2',3'-di-O-tosylribofuranosides,<sup>179</sup> much work has centered on these compounds. Treatment of the lyxo epoxides (145) with hydrogen halides

or with halide salts in the presence of acetic acid usually leads almost exclusively to products with the 3'-deoxy-3'-halo- $\beta$ -D-arabinofuranosyl structure (177). In this way uracil derivatives (145, B = Ur) have been converted into 3'-chloro, iodo and fluoro derivatives, 140c, 168e, 202a and the reaction has been extended to the 6-azauracil, 179b cytosine<sup>202b</sup> and adenine<sup>202c</sup> series. A slightly modified pathway is followed for the isocytosine lyxo epoxide since the initially formed 3'-deoxy-3'-halo- $\beta$ -D-arabinofuranosyl nucleoside loses ammonia with formation of the 0<sup>2</sup>,2'-cyclouridine derivative (178) and its hydrolysis product (177, B = Ur).<sup>202e</sup>



Nucleophilic opening of the ribo epoxides (179) is restricted to the purine series because of the previously discussed preferential conversion of the pyrimidine derivatives into 0<sup>2</sup>,2'-cyclo-nucleosides. Preferential attack at C<sub>3</sub>' once again takes place, and in this way the adenosine epoxide (179, B = Ad) has been converted into the various 3'-deoxy-3'-halo- $\beta$ -D-xylofuranosyl derivatives (180, B = Ad).<sup>151c, 194b</sup>



A final, rather intriguing introduction of 3'-halogen involves the reactions of 3'-O-tosyl-0<sup>2</sup>,2'-cyclouridine (178, X = OTs) with halide ions.<sup>202d, 203</sup> Such reactions lead to the 3'-halides with retention of configuration (178, X = halide), and mechanisms involving both "2',3'-cyclic oxonium"<sup>202d, 203a</sup> and "2',3'-onium"<sup>203b</sup> intermediates have been proposed. This reaction has also been applied using sulfide and azide as nucleophiles.<sup>202d</sup>

The preparation of azido nucleosides has also been explored via reaction of, e.g., 5'-O-tritylthymidine with triphenylphosphine and diethyl azodicarboxylate in the presence of hydrazoic acid, which gives the inverted azide 185 by direct displacement.<sup>188</sup> The comparable reactions with 5'-O-trityl-2'-deoxyadenosine and 2',5'-di-O-trityluridine similarly give the corresponding inverted azides.<sup>188</sup>

A widely used route to 3'-amino nucleosides involves the opening of epoxides with nitrogen nucleophiles. The reaction of adenine lyxo epoxide (111a) with sodium azide leads, for example, to the 3'-azido- $\beta$ -D-arabinofuranosyl nucleoside (112) in high yield, together with only traces of the 2'-azido-xylo isomer (113).<sup>151a,208</sup> Similar reactions have been applied to other derivatives of 111a,<sup>181d</sup> as well as to the uracil<sup>209a,b</sup> and cytosine<sup>202b</sup> analogues (145) giving the azides 177 ( $X = N_3$ ). In addition, the uracil<sup>210</sup> and 6-azauracil<sup>179a</sup> lyxo epoxides (145) have been opened with ammonia to generate the 3'-amino- $\beta$ -D-arabinofuranosyl nucleosides (177,  $X = NH_2$ ) directly, and similar results have been reported using treatment of the uracil and N<sup>4</sup>-benzoyl-cytosine lyxo epoxides with boron trifluoride in acetonitrile giving the 3'-acetamido compounds, 177 ( $X = NHAc$ ).<sup>209a</sup>

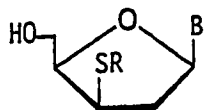
Opening of the ribo epoxides (179) with azide ion has also been examined in the adenine<sup>151a,194b</sup> and hypoxanthine series and in each case gives predominantly the 3'-azidoxylofuranosyl nucleosides (180,  $X = N_3$ ). In certain cases the ribo epoxide (179, B = Ad), or its 2',3'-acetoxonium equivalent, has been generated in situ upon treatment of 9-(2-O-mesyl- $\beta$ -D-arabinofuranosyl)adenine or its 3'-O-acetate with sodium azide. Once again, predominant formation of the 3'-azide (180,  $X = N_3$ ) results.<sup>161a</sup> Virtually all of the azido nucleosides mentioned above have been subjected to catalytic reduction giving the corresponding 3'-amino-3'-deoxy analogues.

#### D. 3'-Sulfur Substituted Nucleosides

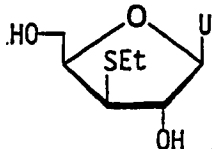
Relatively few free 3'-sulfhydryl nucleosides have been prepared because of the ease with which these compounds are converted into the corresponding disulfides. Thus, for example, 5'-O-trityl-2',3'-cyclothymidine (160c) has been opened with potassium thiobenzoate in the presence of benzoic acid to form, after acid hydrolysis, 3'-benzoylthio-3'-deoxythymidine (161f).<sup>205</sup> Attempted debenzoylation of 161f gave only the disulfide of 3'-thiothymidine. 3'-Thioadenosine has, however, been isolated by careful debenzoylation of the corresponding thiobenzoate<sup>166,211</sup> prepared from reaction of 9-(3-deoxy-3-iodo- $\beta$ -D-xylofuranosyl)adenine with sodium thiobenzoate.<sup>166</sup> Also, the 3'-thiol (186a) has been obtained by careful alkaline hydrolysis of the 2,3'-thiocyclonucleoside 164a.<sup>190a</sup>

Direct nucleophilic displacement of sulfonate esters by sulfides has been successfully used, e.g., to convert 2'-deoxy-3'-O-tosyladenosine into the 3'-ethylthio derivative (186b).<sup>50,212a</sup> In a related way, the reaction of 3'-O-mesyl-2',5'-di-O-trityl-uridine (165b) with sodium ethylmercaptide under forcing conditions gives a modest yield of 187 following detritylation.<sup>212b</sup>

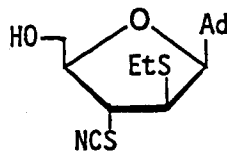
The same compound was obtained in 90% yield from 3',5'-di-O-acetyl-0<sup>2</sup>,2'-cyclouridine, presumably via attack of the mercaptide anion at C<sub>3'</sub> of an intermediate 2',3'-O-acetoxonium ion.<sup>174</sup> This constitutes one of the rare cases where an external nucleophile has reacted with a pyrimidine 2',3'-acetoxonium ion in preference to intramolecular formation of an 0<sup>2</sup>,2'-cyclonucleoside.



186(a) B = Th, R = H  
~~~~~(b) B = Ad, R = Et



187



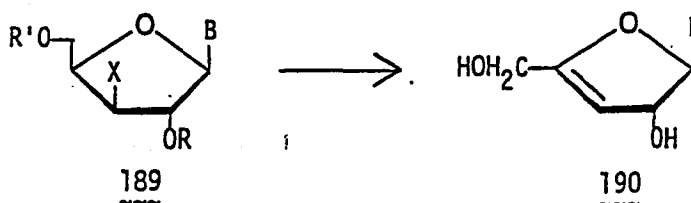
188

As usual, the opening of epoxides has proved to be useful for generation of 3'-thionucleosides. Thus, the adenosine lyxo epoxide (145, B = Ad) could be opened by several sodium mercaptides to give principally the 3'-alkylthio-β-D-arabinofuranosyl compounds (177, X = SR) together with minor amounts of the isomeric 2'-alkylthio-β-D-xylofuranosyl isomers.<sup>213a</sup> Treatment of the S-benzyl derivative (177, X = SBn, B = Ad) with sodium in liquid ammonia liberated the crystalline 3'-thiol (177, X = SH, B = Ad).<sup>213a</sup> Application of this reaction to the 5'-deoxy analogue of 145 (B = Ad) gives similar results, except that in this case the opening is less regiospecific and the 3'-thio- and 2'-thionucleosides are formed in more equal amounts.<sup>213b</sup> Thiocyanate ion has also been used to open lyxo epoxides in the uracil<sup>165</sup> and cytosine<sup>202b</sup> series, the major products in both cases being the 3'-thiocyano derivatives (177, X = SCN). In a related fashion, reaction of 181 with potassium thiocyanate initially generates a lyxo 2',3'-episulfonium ion that is then opened giving the 2',3'-dithio compound 188.<sup>214</sup>

Opening of 2',3'-anhydroadenosine (179, B = Ad) with alkyl mercaptides,<sup>213b,c</sup> or sodium thiobenzoate,<sup>166</sup> is highly regioselective, with only the corresponding 3'-thio products (180, X = S-alkyl, SBz) being isolated. The thiobenzoate could be hydrolyzed giving free 9-(3-thio-β-D-xylofuranosyl)adenine (180, X = SH, B = Ad).<sup>166</sup> Opening of the ribo epoxide derived from tubercidin follows a similar path,<sup>167</sup> and, as previously mentioned, the major product has been isomerized to the 2'-thio-β-D-arabinofuranosyl derivative (128) via an episulfonium intermediate. The high nucleophilicity of mercaptide ions is once again demonstrated by the reaction of 0<sup>2</sup>,2'-cyclouridine with sodium ethylmercaptide, which generates the 3'-ethylthio-β-D-xylofuranosyl derivative (180, X = SEt, B = Ur), presumably via the intermediate ribo epoxide (179, B = Ur).<sup>42</sup>

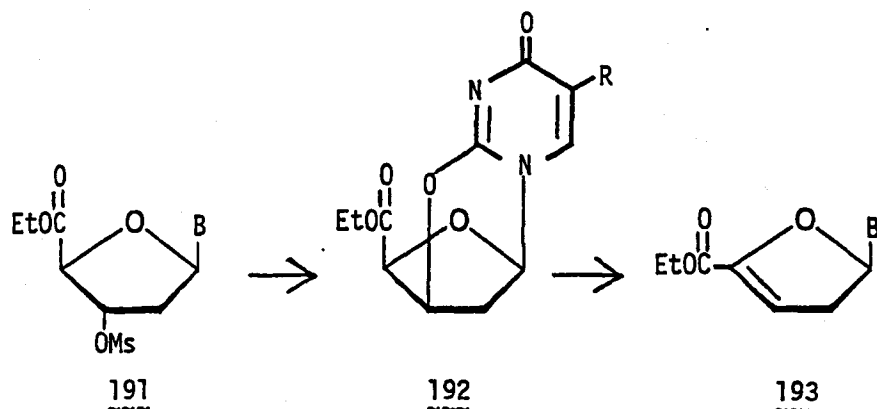
## E. 3',4'-Unsaturated Nucleosides

A number of 3',4'-unsaturated nucleosides have been prepared by way of various elimination processes. One procedure of general utility involves the treatment of variously protected 9-(3-deoxy-3-halo- $\beta$ -D-xylofuranosyl)purines (189, X = halo), prepared either through the use of the previously discussed 2-acetoxyisobutyryl halide<sup>147,148</sup> or the pivaloyl chloride<sup>150,151</sup> reactions, with suitable bases. Thus, for example, the reactions of the 3'-bromo-nucleosides 189 (B = Ad, R = Ac, R' = Me<sub>3</sub>-dioxolanone)<sup>20</sup> or 189 (B = Hx, R, R' = THP)<sup>147d</sup> with 1,5-diazabicyclo[4.3.0]non-5-ene give the 3',4'-olefins 190 (B = Ad, Hx) in yields of up to 70%.

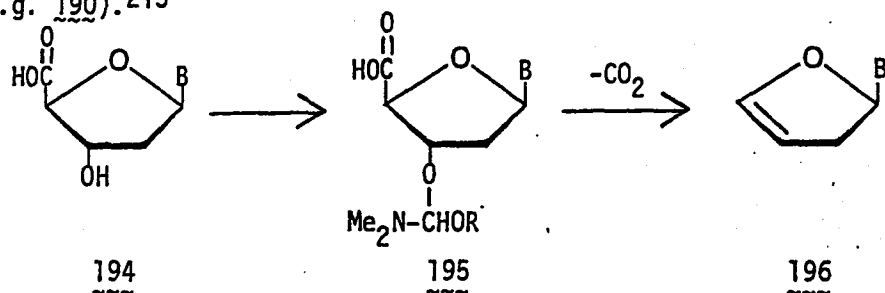


The 3'-iodo compounds (189, X = I, R, R' = acyl) can also be induced to eliminate, giving the corresponding 2',5'-di-O-acylated derivatives of 190 in both the adenosine<sup>150b</sup> and tubercidin<sup>150c</sup> series, upon treatment with silver acetate in pyridine. Formation of the adenosine and tubercidin olefins (190) has also been observed as a minor side reaction during conversion of 189 into the 2',3'-olefins (132) using chromous acetate.<sup>20</sup> The formation of nucleoside-1',3'-dienes (143) from base treatment of 2'-deoxy-nucleosides bearing leaving groups at both C<sub>3</sub>' and C<sub>5</sub>' has already been mentioned.<sup>172,168e</sup>

The methods above generally rely upon the selective abstraction of the C<sub>4</sub>'-proton during the olefin forming reaction. In an effort to increase the acidity of that proton, Horwitz, *et al.*<sup>215</sup> have examined the reactions with bases of nucleoside 5'-uronidic acid esters bearing leaving groups at C<sub>3</sub>'. In this way the 3'-O-mesyl derivatives (191, B = Th, Ur, 5-FUR, Ad) have been treated with triethylamine or sodium benzoate giving the 3',4'-olefins (193) in good yields. These reactions are considered to proceed via the initial formation of the O<sup>2</sup>,3'-cyclonucleosides (192) in the pyrimidine series, and treatment of one such intermediate (192, B = Th) with triethylamine also gives 193.



This type of reaction can be extended to the ribonucleoside series through base catalyzed elimination of a 2',3'-O-isopropylidene group from the corresponding 5'-uronic acid esters<sup>215c</sup> or 5'-aldehydes.<sup>86</sup> Elimination has also been observed upon treatment of methyl-1-(2-O-acetyl-3-O-tosyl-β-D-xylofuranuronosyl)uracil with sodium azide or sodium bicarbonate.<sup>216</sup> Attempted extension to see 5'-uronic acids, however, leads to concerted decarboxylation and elimination giving 3',4'-unsaturated tetrosyl nucleosides (196).<sup>215d</sup> Thus, reaction of thymidine 5'-carboxylic acid (194, 3 = Th) with dimethylformamide dineopentyl acetal leads to 196, presumably by way of the unisolated intermediate 195. This reaction has also been applied in the 2'-deoxyuridine and 5-fluoro-2'-deoxyuridine series.<sup>215d</sup> Selective reduction of the ester functions in 193 can be achieved using sodium bis(methoxyethoxy)-aluminum hydride giving the simple 3',4'-unsaturated nucleosides (e.g. 190).<sup>215</sup>



#### F. 3'-Deoxynucleosides

3'-Deoxynucleosides have, in general, been prepared by the same methods used for other deoxy compounds, namely catalytic or radical induced reduction of 3'-halonucleosides or desulfurization of 3'-thio derivatives. Palladium catalyzed hydrogenolysis

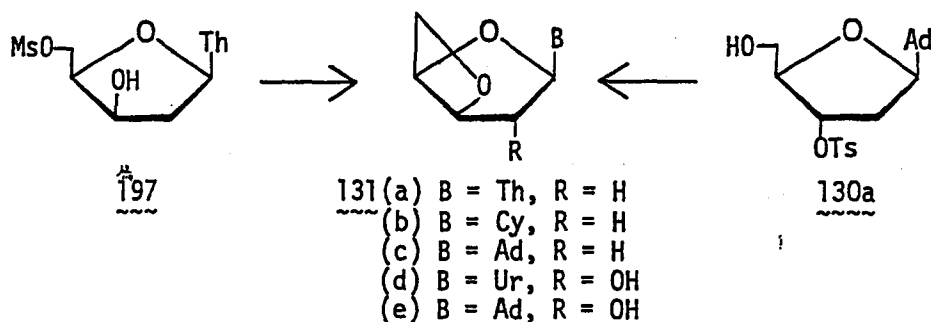
of 3'-iodo- and 3'-bromonucleosides has been used for the preparation of the 3'-deoxy modifications of uridine,<sup>199</sup> cytidine,<sup>153a</sup> thymidine,<sup>196</sup> 2'-deoxyuridine,<sup>196</sup> 6-azauridine,<sup>198b</sup> 1- $\beta$ -D-arabinofuranosyluracil,<sup>168e</sup> adenosine,<sup>147a,150a,198a</sup> tubercidin,<sup>147b,148</sup> formycin,<sup>147b,148</sup> guanosine<sup>147c</sup> and inosine.<sup>147c</sup> Reductions using tributylstannane and a radical inducer such as azobisisobutyronitrile have been used for the synthesis of 3'-deoxy analogues of 6-azauridine,<sup>179a</sup> pseudouridine,<sup>146b</sup> adenosine,<sup>150a</sup> 9- $\beta$ -D-arabinofuranosyladenine,<sup>151c</sup> tubercidin,<sup>150c,e</sup> guanosine<sup>150d,f</sup> and inosine.<sup>151b</sup> A considerable number of 3'-deoxynucleosides have been obtained by desulfurization of various 3'-thionucleosides using Raney nickel or its equivalent. In this way, preparations of the 3'-deoxy analogues of uridine,<sup>212b</sup> thymidine,<sup>190a</sup> adenosine,<sup>204,211</sup> 2'-deoxyadenosine,<sup>50,212a,214</sup> 5'-deoxyadenosine,<sup>213b</sup> 9- $\beta$ -D-arabinofuranosyladenine,<sup>213a</sup> 9-(5-deoxy- $\beta$ -D-arabinofuranosyl)adenine,<sup>213b</sup> 9-(2-amino-2-deoxy- $\beta$ -D-arabinofuranosyl)adenine<sup>204</sup> and guanosine<sup>195c</sup> have been described. In addition, a preparation of 9-(3-deoxy- $\beta$ -D-arabinofuranosyl)adenine has been achieved via treatment of 9-(3-thio- $\beta$ -D-arabinofuranosyl)adenine with trimethyl phosphite and azobisisobutyronitrile.<sup>213a</sup> Finally, a number of 3',4'-unsaturated nucleosides have been catalytically reduced, usually giving mixtures of the 3'-deoxynucleosides in the  $\beta$ -D-erythro- and  $\alpha$ -L-threo-pentofuranosyl series. Such results have been obtained with the olefins (<sup>190</sup>) in which B is adenine<sup>150b</sup> and 7-deazaadenine,<sup>150c</sup> as well as with the unsaturated uronic acid ester <sup>193</sup> (B = Th),<sup>215b</sup> its adenine counterpart<sup>215c</sup> and the decarboxylated derivatives <sup>196</sup>.<sup>215d</sup>

#### G. 3',5'-Anhydro Nucleosides

Several closely related methods have been described for the synthesis of 3',5'-anhydro-2'-deoxy- $\beta$ -D-threo-pentofuranosyl nucleosides (<sup>131</sup>, R = H) which can simply, if somewhat incorrectly, be referred to as 3',5'-anhydro-2'-deoxynucleosides. The simplest of these involves the treatment of 3',5'-di-O-mesylthymidine (<sup>159b</sup>) with two equivalents of sodium hydroxide, a reaction which clearly involves the initial formation of the 5'-O-mesyl-O<sup>2</sup>,3'-cyclic nucleoside (<sup>160b</sup>), which undergoes hydrolysis to <sup>197</sup> and intramolecular displacement of the 5'-mesylate giving <sup>131a</sup>.<sup>168e,217</sup> The same compound is obtained by treating the isolated intermediate (<sup>160b</sup>) with one equivalent of sodium hydroxide.<sup>6,217</sup> Essentially the identical procedure has been applied for the synthesis of the cytosine analogue (<sup>131b</sup>).<sup>168h</sup>

The alternate approach of treating 2'-deoxy-3'-O-tosyladenosine (<sup>130a</sup>) with sodium ethoxide is clearly less efficient since <sup>131c</sup> is obtained in only 14% yield, the major product being the 2',3'-olefin <sup>132</sup> (B = Ad). In the 2'-hydroxylated series, treatment of either the 5'-O-mesyl<sup>181a</sup> or the 5'-deoxy-5'-iodo<sup>29a</sup>

derivatives of 1- $\beta$ -D-xylofuranosyluracil with sodium hydroxide leads to the 3',5'-anhydro derivative 131d, and the latter compound can be epimerized at C<sub>2'</sub> via mesylation, formation of the 0<sup>2</sup>,2'-cyclonucleoside and hydrolysis.<sup>181e</sup> The adenosine analogue 131e can also be conveniently prepared in 68% yield by treating 2',3'-anhydroadenosine (179, B = Ad) with potassium *t*-butoxide in dimethylsulfoxide.<sup>194c</sup> Several attempts to prepare nucleoside 3',5'-sulfides have not been successful due to their facile opening in the presence of hydrogen sulfide or sodium sulfide to form 3',5'-dithiols or the corresponding disulfide.<sup>190a,195b</sup>

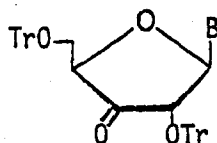


#### H. 3'-Keto Nucleosides

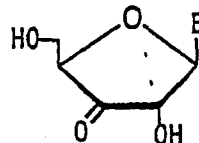
The marked instability of 3'-keto nucleosides has seriously limited the oxidative methods that can be used for their preparation. Oxidation of 2',5'-di-O-trityluridine was, however, successful using the dicyclohexylcarbodiimide-dimethylsulfoxide method and crystalline 198a was obtained in 46% yield.<sup>183a</sup> Comparable results were also obtained using dimethylsulfoxide activated by acetic anhydride or phosphorus pentoxide. Detritylation of 198a could be effected with hydrogen chloride in chloroform giving the free ketone 199a. As was the case with the 2'-ketones (153), these substances undergo rapid glycosidic cleavage in mild base, and borohydride reduction of either 198a or 199a leads to products with the  $\beta$ -D-xylo and  $\beta$ -D-ribo configurations in ratios of roughly 2:1. Very similar results were obtained in the oxidation of 2',5'-di-O-tritylcytidine or its N<sup>4</sup>-acetyl derivative, the corresponding crystalline ketones (198b,c) being obtained in yields of 70-90%.<sup>183b</sup> Detritylation of 198c was successful as above, and borohydride reduction of 198b,c or 199b led to the corresponding  $\beta$ -D-xylo- and  $\beta$ -D-ribonucleosides in ratios of 3:2.

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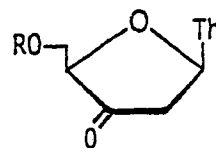
J. G. MOFFATT



- 198(a) B = Ur  
 (b) B = Cy  
 (c) B = N<sup>4</sup>AcCy

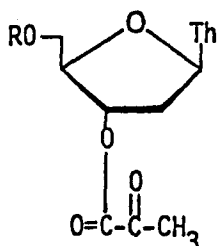


- 199(a) B = Ur  
 (b) B = N<sup>4</sup>AcCy

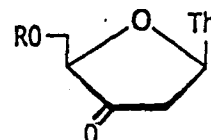
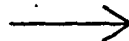


- 200(a) R = Tr  
 (b) R = Bz

Recently a remarkably mild method of oxidation has been developed by Binkley, et al.<sup>218</sup> that has permitted successful oxidations that were not previously possible. This method involves the photolysis of 3'-O-pyruvoyl-5'-O-tritylthymidine (201a) and leads to the isolation of the crystalline 3'-ketone (202a) in 61% yield. The same product is also obtained by oxidation of the 3'-epimer of 201a, and the 5'-O-benzoyl derivative (201b) is also a suitable substrate. As would be expected, 202 is very sensitive to base and exposure to pyridine or silica gel leads to rapid glycosidic cleavage.



- 201(a) R = Tr  
 (b) R = Bz



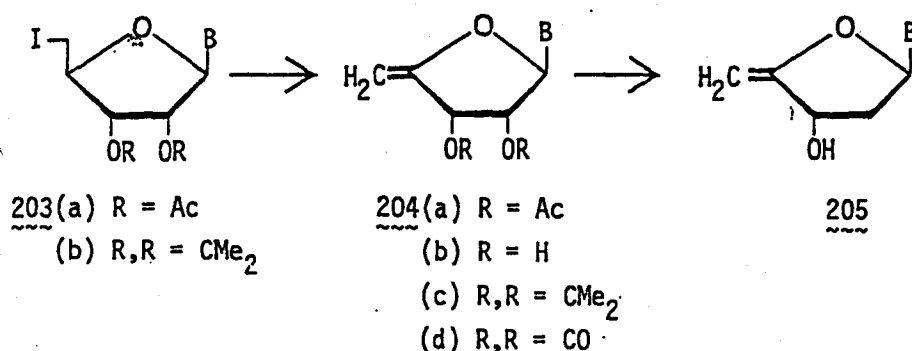
- 202(a) R = Tr  
 (b) R = Bz

#### IV. 4'-MODIFIED NUCLEOSIDES

##### A. 4',5'-Unsaturated Nucleosides

Interest in 4',5'-unsaturated nucleosides has stemmed from the existence of this structural moiety in the antibiotic angustmycin A (207)<sup>219</sup> and the identification of 9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)adenine (204, B = Ad, trivially referred to as adenosin-4'-ene) as a by-product of both alkaline<sup>220a</sup> and enzymatic<sup>220b</sup> reactions of Coenzyme B<sub>12</sub>. They also constitute valuable intermediates for the synthesis of other 4'-modified nucleosides (see later). Syntheses of these compounds are generally based upon the elimination of suitable 5'-substituents,

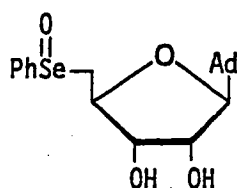
usually iodide or sulfonate. In practice, they are usually conducted either by treatment of a 5'-deoxy-5'-iodonucleosides with silver fluoride in pyridine at room temperature, or by reaction of a 5'-deoxy-5'-iodo- or 5'-O-tosyl nucleoside with a base such as potassium t-butoxide or 1,5-diazabicyclo[4.3.0]non-4-ene (DBN). In our original work,<sup>11c,221</sup> it was shown that 5'-deoxy-5'-iodo-2',3'-O-isopropylideneuridine (203b, B = Ur) did not react cleanly with silver fluoride in pyridine but that the comparable reaction with the 2',3'-di-O-acetyl derivative (203a, B = Ur) gave the desired olefin (204a, B = Ur) in 85% yield. Similar reactions with the N<sup>4</sup>-acetylcytidine,<sup>11c</sup> N<sup>6</sup>,N<sup>6</sup>,O<sup>2'</sup>,O<sup>3'</sup>-tetrabenzoyladenosine,<sup>22</sup> inosine<sup>16a</sup> and N<sup>2</sup>-acetylguanosine<sup>16a</sup> analogues of 203a led in each case to good yields of the 4',5'-olefins that could be deacylated with ammonium hydroxide to liberate the free nucleosides (204b). By the same route, 3'-O-acetyl-5'-deoxy-5'-iodo-thymidine,<sup>11c</sup> 221a 3'-O-acetyl-5'-bromo-3',5'-dideoxyadenosine<sup>221b</sup> and 3',5'-dideoxy-3'-fluorothymidine<sup>200b</sup> have been converted into analogues of 205.



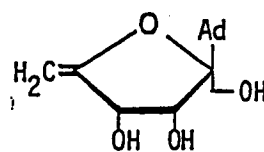
The other major route to 4',5'-olefins is typified by treatment of 2',3'-O-isopropylidene-5'-O-tosyl nucleosides with bases such as potassium t-butoxide or DBN in order to generate the protected olefins 204. Reactions of this sort have been done with various 5'-O-tosyl-2',3'-acetals in the uridine,<sup>222a,b</sup> isocytidine<sup>57b</sup> and adenosine<sup>222c,d,e</sup> series. A number of different isomers of 204 and 205 in the adenosine and deoxyadenosine series have been prepared by Lerner, et al.<sup>221b,222f,g</sup> In view of the acid lability of the vinyl ether function, it is not possible to generate free 4',5'-unsaturated nucleosides using the isopropylidene group for protection. Hence several more labile orthoester protecting groups have been used during syntheses of adenosine-4'-ene and angustmycin A.<sup>222e</sup> It has also proved possible to dehydrohalogenate a number of 2',3'-unprotected nucleosides giving analogues of 204b directly in the adenosine,<sup>16a</sup> guanosine<sup>16a</sup> and 3'-amino-3'-deoxyadenosine<sup>223</sup> series. Very recently a novel and efficient synthesis of adenosine-4'-ene (204b, B = Ad) has been described via thermal collapse of the 5'-deoxy-5'-selenoxide

derivative 206.<sup>224</sup> In a few cases it has proved possible to utilize base catalyzed elimination of a cyclonucleoside bridge to generate a 4',5'-olefin. This has been achieved using both 0<sup>2</sup>,5'-cyclouridine<sup>222a</sup> and 8',5'-cycloadenosine<sup>67</sup> derivatives.

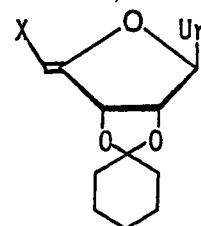
Particular attention has been paid to the synthesis of the nucleoside antibiotic angustmycin A (207), which has been achieved via base catalyzed elimination reactions on suitably protected 6'-O-tosyl-<sup>222e</sup> and 6'-deoxy-6'-iodo-<sup>22</sup> derivatives of psicofuranine. A number of base analogues of angustmycin A have been prepared by similar routes.<sup>22</sup>



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207



208(a) X = OAc

(b) X = NR<sub>2</sub>

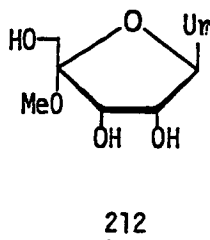
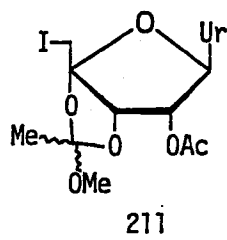
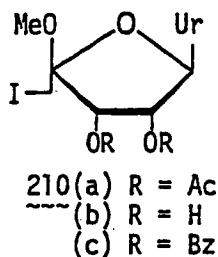
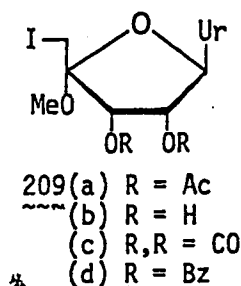
Several C<sub>5</sub>-functionalized derivatives of 4',5'-unsaturated nucleosides (208) have also been prepared. Thus, Secrist, et al.<sup>225a</sup> have succeeded in the conversion of 2',3'-O-cyclohexyldeneuridine 5'-aldehyde [45, B = Ur, R,R = (CH<sub>2</sub>)<sub>5</sub>] into its enol-acetate (208a) and pyrrolidine enamine (208b) derivatives. Comparable enolacetates of suitable derivatives in the adenosine, cytidine and thymidine series were also obtained.<sup>225a</sup>

It should be noted that catalytic reduction of a number of 2',3'-acetal derivatives of 204 have been examined and led, in each case, to almost exclusive delivery of hydrogen from the less hindered β-face leading to 5'-deoxy-α-L-lyxofuranosyl nucleosides.<sup>57b,222a-c,e</sup>

## B. 4'-Methoxy Nucleosides

Interest in the synthesis of 4'-methoxy nucleosides has centered in our own laboratory and has been achieved through the addition of iodine and methanol to suitably protected 4',5'-unsaturated nucleosides.<sup>226</sup> A general review of our work on 4'-substituted nucleosides has been published.<sup>226b</sup> We initially showed that reaction of the 2',3'-di-O-acetyl olefin (204a, B = Ur) with iodine and methanol in the presence of silver acetate led to

a mixture of the desired 5'-deoxy-5'-iodo-4'-methoxyuridine derivative 209a and its C<sub>4'</sub>-epimer (210a) in yields of 16 and 34%, together with two diastereoisomers of the 3',4'-orthoester 211.<sup>226a</sup> The configurational assignments for 209a and 210a could be arrived at by <sup>13</sup>C-NMR spectroscopy, and alkaline hydrolysis gave the free diols (209b) and (210b).



The formation of 211 indicates an undesired participation of the 3'-O-acetyl group in the reactions of the intermediate 4',5'-iodonium ion and suggested the need for a non-participating protecting group. This need was met by the 2',3'-cyclic carbonate (204d, B = Ur), which reacted with iodine and methanol in the presence of lead carbonate to give only the ribo isomer (209c) in 85% yield. A similar result was obtained with the diol (204, R = H, B = Ur), which gave the ribo diol (209b) in 77% yield. The 2',3'-O-isopropylidene compound (204, R,R = CMe<sub>2</sub>, B = Ur) was less satisfactory and gave an inseparable 3:2 mixture of 209 and 210 (R,R = CMe<sub>2</sub>). Conversion of the 5'-iodo group in 209d and 210c to the desired hydroxyl function could be achieved by displacement with lithium benzoate under forcing conditions followed by alkaline hydrolysis giving the desired 4'-methoxyuridine (212) and its α-L-lyxofuranosyl epimer. It is interesting to note that under anhydrous acidic conditions both 209 and 212 are rather readily epimerized to their α-L-lyxofuranosyl isomers.

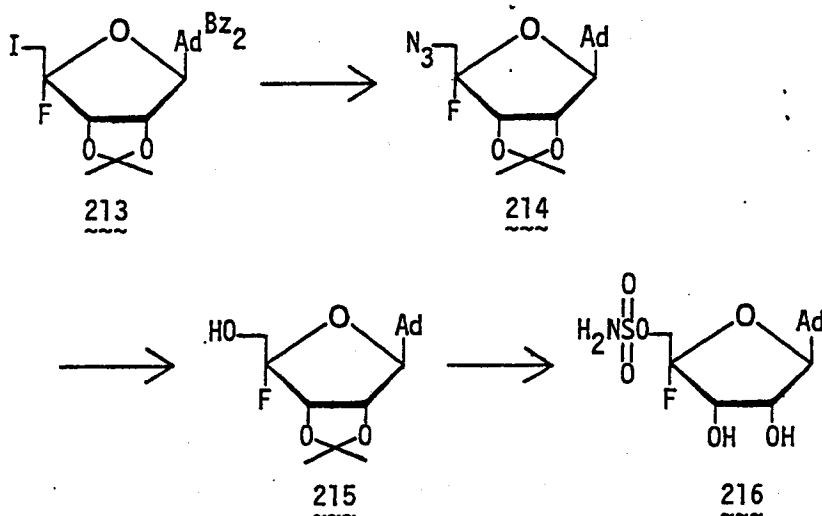
During the course of our work, Sasaki, et al.<sup>227a</sup> reported that the reaction of 204c with N-bromosuccinimide in methanol leads to a crystalline O<sup>2</sup>,4'-cyclonucleoside that could be opened with methanol to give what was considered to be the 5'-bromo equivalent

of 209c. On the basis of NMR evidence we have concluded that the product, isolated in 20% yield, had, in fact, the  $\alpha$ -L-lyxofuranosyl configuration resulting from an epimerization similar to those above. Sasaki<sup>227b</sup> has also reacted the N<sup>6</sup>-benzoyladenine analogue of 204c under similar conditions and isolated a crystalline 5'-bromo-5'-deoxy-4'-methoxy nucleoside of unknown configuration in 60% yield. A related preparation using bromine in methanol generated this same compound and its C<sub>4</sub>'-epimer. A study of the NMR spectra of these compounds leads us to the conclusion that the compound obtained by Sasaki has the  $\alpha$ -L-lyxofuranosyl configuration.<sup>222d</sup>

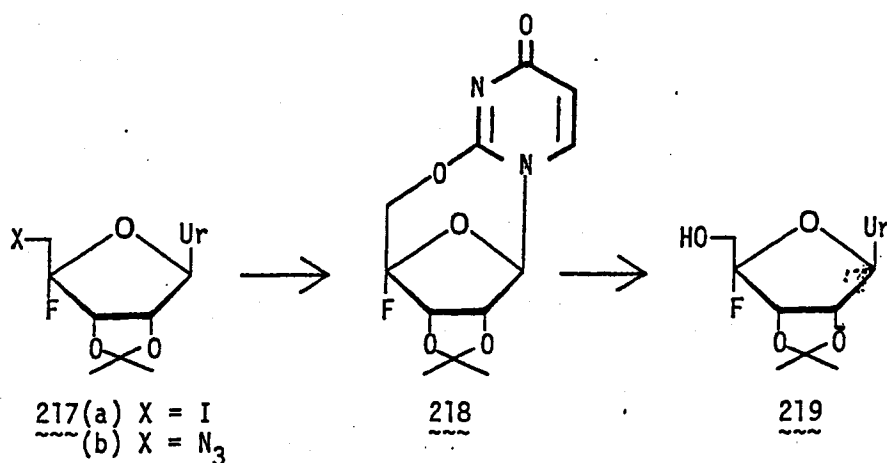
Using methods very similar to those developed in the uridine series, the N<sup>4</sup>-benzoylcytosine analogue of 204b and the N<sup>6</sup>-di-benzoyladenine analogue of 204d were converted exclusively to the N-benzoylated cytidine and adenine analogues of 209b and 209c respectively.<sup>226b</sup> These compounds were, in turn, subjected to benzoate displacement and alkaline hydrolysis to generate free 4'-methoxycytidine and 4'-methoxyuridine. The cytidine derivative could also be obtained via the S-methyl-4-thiouracil analogue of 204d.<sup>226b</sup>

#### C. 4'-Fluoronucleosides

Our interest in 4'-fluoronucleosides stems largely from the identification of the antibiotic nucleocidin as 4'-fluoro-5'-O-sulfamoyladosine (216) and has led to a total synthesis of this compound.<sup>222d</sup> This synthesis involved, as its key step, the addition of iodine fluoride, generated *in situ* from silver fluoride and iodine, to the 4',5'-olefin 204c (B = N<sup>6</sup>Bz<sub>2</sub>Ad). This reaction leads to separable mixtures of the desired N<sup>6</sup>-dibenzoyl-5'-deoxy-4'-fluoro-5'-iodo-2',3'-O-isopropylideneadenosine (213) and its C<sub>4</sub>'-epimer in good yields, but in variable ratios, according to the precise conditions used. In spite of many attempts, all efforts to displace the 5'-iodo group in 213 with a variety of oxygen nucleophiles failed. The only successful displacement that could be achieved was that using lithium azide in dimethylformamide at 95° and, following mild debenzoylation, gave the 5'-azido-4'-fluoronucleoside (214) in high yield. The desired azido to hydroxyl transformation could then be achieved via photolysis in benzene followed by mild acidic hydrolysis of the resulting imine to an aldehyde that was reduced with sodium borohydride. In this way the desired 4'-fluoro-2',3'-O-isopropylideneadenosine (215) could be obtained and converted into nucleocidin (216) by reaction of its derived tributyltin ether with sulfamoyl chloride followed by acidic hydrolysis. A similar sequence has been used for the preparation of the  $\alpha$ -L-lyxofuranosyl epimer of 216.

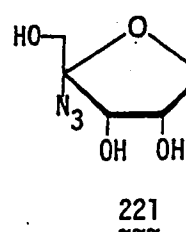
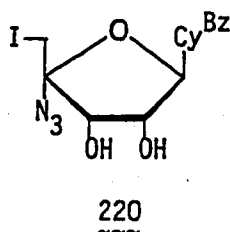


A similar reaction of the 4',5'-unsaturated uridine derivative (204c, B = Ur) with silver fluoride and iodine led exclusively to the desired product 217a with the  $\beta$ -D-ribo configuration, presumably by way of an intermediate 5'-deoxy-5'-iodo-0<sup>2</sup>,4'-cyclo-nucleoside.<sup>228</sup> Once again, azide displacement successfully generated the 5'-azido-4-fluoronucleoside (217b). Since photolysis of the azide was expected to lead to problems due to the uracil ring, 217b was treated with nitrosyl tetrafluoroborate to give the 4'-fluoro-0<sup>2</sup>,5'-cyclonucleoside (218). Mild acidic hydrolysis then gave 4'-fluoro-2',3'-O-isopropylideneuridine (219) that could be converted into its 5'-sulfamate and 5'-phosphate esters and deprotected.



## D. 4'-Azido Nucleosides

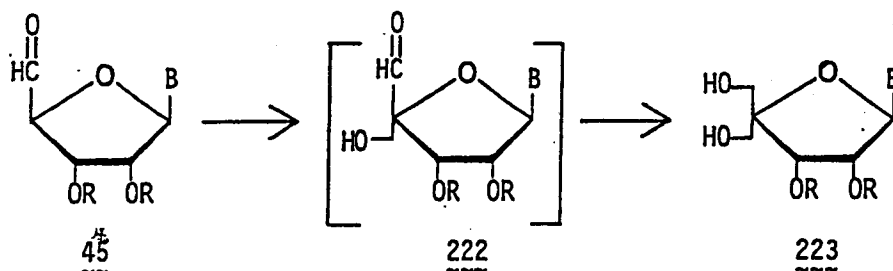
To our knowledge, 4'-azidocytidine (221) is the only 4'-nitrogen substituted nucleoside to be prepared.<sup>229</sup> Its synthesis quite closely follows the general pathway used for the preparation of other 4'-substituted nucleosides. Thus, the reaction of the N<sup>4</sup>-benzoylcytidine-4',5'-olefin (204b, B = N<sup>4</sup>BzCy) with iodine azide leads to the formation of the 4'-azido-5'-iodonucleoside 220, which can be isolated crystalline in 60% yield. Only a very small amount of the C<sub>4</sub>'-epimer of 220 is formed and the configurations are assigned on the basis of NMR evidence. Following benzoylation of all available sites, the 5'-iodide can be displaced with lithium benzoate in dimethylformamide at 105°. Debenzoylation with methanolic ammonia then liberates 4'-azidocytidine (221), which is homogeneous by NMR and chromatographic examination but for which an acceptable elemental analysis has not as yet been obtained.



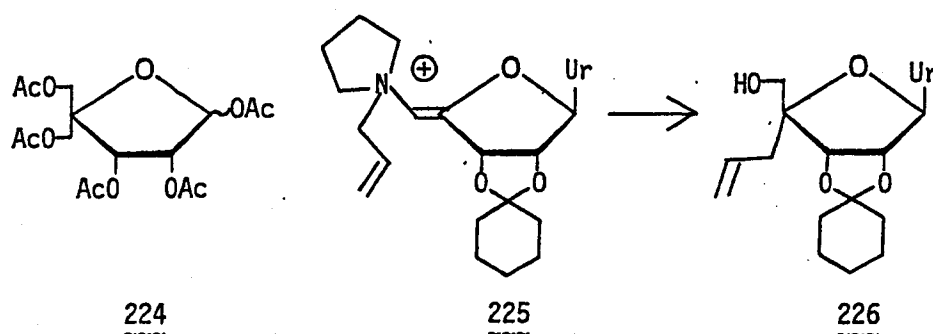
## E. 4'-Hydroxymethyl and Related Carbon Substituted Nucleosides

By far the most widely examined group of nucleosides bearing carbon substituents at C<sub>4</sub>' are the 4'-hydroxymethyl derivatives.<sup>87c,230</sup> Conceptually, these compounds are most easily derived by a mixed aldol condensation between suitable derivatives of nucleoside 5'-aldehydes and formaldehyde followed by reduction of the resulting  $\beta$ -hydroxyaldehyde (222). Initial reactions using 2',3'-O-cyclohexylideneuridine 5'-aldehyde [45, B = Ur, R,R = (CH<sub>2</sub>)<sub>5</sub>] and formaldehyde in the presence of potassium carbonate, however, led predominantly to  $\beta$ -elimination of the acetal with formation of the 3',4'-unsaturated aldehyde that could be reduced to 190 (B = Ur) with sodium borohydride. A similar result was observed starting with N<sup>6</sup>-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde. On the other hand, comparable reactions using 45 [B = Ur, R,R = (CH<sub>2</sub>)<sub>5</sub>] in the presence of sodium hydroxide as the base at room temperature for 16 hr led to the isolation of 2',3'-O-cyclohexylidene-4'-hydroxymethyluridine [223, B = Ur, R,R = (CH<sub>2</sub>)<sub>5</sub>] in 38% yield. Acidic hydrolysis then gave unprotected 4'-hydroxymethyluridine (223, B = Ur, R = H) without difficulty. Similar reactions were carried out on appropriately blocked aldehydes in the adenosine, cytidine and thymidine series giving the corresponding 4'-hydroxymethyl nucleosides after appropriate

deblocking.<sup>87c</sup> In the thymidine series, 3'-O-benzylthymidine 5'-aldehyde was the starting material of choice, and final cleavage of the benzyl ether was achieved by catalytic hydrogenolysis. In all these reactions the initial mixed aldol condensations were apparently very fast, and Cannizzaro reduction of the initial  $\beta$ -hydroxyaldehyde (222) by excess formaldehyde was the rate limiting step. By working the reactions up after only 5-15 min, and reducing the crude product with sodium borohydride, the same protected 4'-hydroxymethyl nucleosides (223) could be obtained in yields of 40-60%.



An attempt was also made to do this reaction with unprotected uridine 5'-aldehyde (45, B = Ur, R = H). Under these conditions, using either the normal Cannizzaro reduction or sodium borohydride, a mixture of 223 (B = Ur, R = H) and its 3'-epimer resulted. A suggested mechanism for this observation involves a reverse aldol cleavage of the initial adduct 222 (R = H) with cleavage of the C<sub>3</sub>-C<sub>4</sub> bond. Reclosure of this product by an aldol mechanism then generates both C<sub>3</sub>-epimers. Similar results were observed in the adenosine series. In an alternative approach, a fairly wide range of 4'-hydroxymethyl nucleosides was also prepared via condensation of the key sugar intermediate (224) with the appropriate heterocyclic bases. 230a



Condensation reactions of the appropriate sugar have also been used to prepare the 3'-epimer of 223 (B = Ad).<sup>231</sup> A

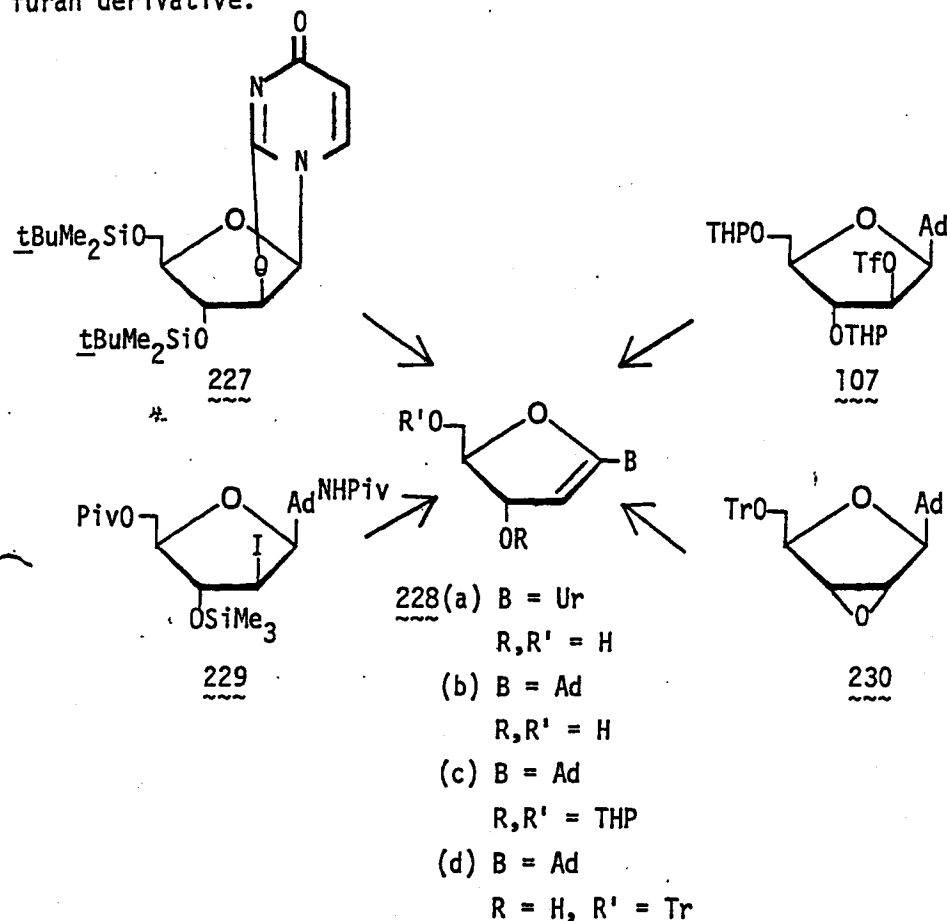
synthesis of 224 has also been described via an interesting photochemical route, and condensation of this substance with an adenine derivative gave an anomeric mixture corresponding to 223 (B = Ad).<sup>232</sup> The physical properties of the  $\beta$ -anomer, however, did not agree with those of a sample prepared by two independent routes as described above. Attempted alkylation of the enamine 210b led only to formation of quaternary ammonium compounds.<sup>225b</sup> By use of allyl bromide, however, the resulting product (225) underwent a Claisen type of rearrangement leading, after hydrolysis and reduction, to the C<sub>4</sub>'-allyl nucleoside 226. The allyl group could then be converted into the corresponding C<sub>4</sub>'-propyl and C<sub>4</sub>'-2-hydroxyethyl nucleosides by conventional means.<sup>225b</sup>

## V. 1'-MODIFIED NUCLEOSIDES

Numerous C<sub>1</sub>'-hydroxymethyl nucleosides (e.g. 207) have been prepared via condensation of ketofuranosyl sugars with heterocycles,<sup>233</sup> but this does not fall within the scope of this review. Similarly, the formation of  $\alpha$ -nucleosides is a frequently encountered situation during the condensations of sugars with purine and pyrimidine bases but is not a readily controlled manipulation from an existing nucleoside. Virtually the only 1'-modification that has been successfully accomplished is the generation of 1',2'-unsaturated nucleosides. It was reported in 1971 that reaction of 2'-bromo-2'-deoxyuridine with reduced hydroxycobalamin led to 1-(2-deoxy-D-erythro-pent-1-enofuranosyl)uracil (228a),<sup>234</sup> but no convincing characterization of the product was provided. Subsequently, Robins and Trip<sup>235a</sup> have described the preparation of crystalline 228a via treatment of 3',5'-bis-O-(t-butyl dimethylsilyl)-O<sup>2</sup>,2'-cylouridine (227) with potassium t-butoxide followed by cleavage of the silyl groups with tetraethylammonium fluoride. Preparation of the adenosine analogue (228b) has also been achieved by treatment of the protected 2'-deoxy-2'-iodo-nucleoside 229 with DBN followed by deblocking with sodium methoxide.<sup>235b</sup> Several protected derivatives of 228 (B = Ad) have also been described. Thus, the reaction of the protected 2'-O-triflate (107) with tetrabutylammonium fluoride led both to the expected 3',5'-bis-tetrahydropyranyl ether of the 2'-fluoro-nucleoside (106, X = F) and to the unsaturated nucleoside 228c.<sup>155a</sup> In all of the above cases palladium catalyzed hydrogenation of the olefins led to mixtures of the  $\alpha$ - and  $\beta$ -anomers of the 2'-deoxynucleosides.

Finally, in unpublished work from this laboratory<sup>194c</sup> it has been shown that treatment of 2',3'-anhydro-5'-O-trityl adenosine (230) with sodium hydride in dimethylsulfoxide leads to the crystalline olefin 228d in 54% yield. Due to the extreme acid lability of such compounds, deprotection could not be achieved, and

extension of this method to the silyl ether analogues of 229 is obvious. Interestingly, attempted palladium catalyzed reduction of 228d led instead to dehydrogenation giving the optically inactive furan derivative.<sup>194c</sup>



**Acknowledgments.** The work described in this review that originated in our own laboratories is the result of the enthusiastic efforts of many co-workers acknowledged in the references. In particular, the efforts of my long-term colleagues Drs. J. P. H. Verheyden and G. H. Jones, who have contributed so richly to our programs over the years, are most gratefully singled out. Many thanks are also due to Ms. Mary Bergstrom for her great skill in the final preparation of the manuscript, and to my family for their understanding during its creation.

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