stirred, as in some instances **4c** will begin to precipitate during the extraction.

(40) IR: C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954). NMR: J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959, p 281.

(41) Spectral data were not reported for **8c**.[36] The compound was characterized as an oxime.

(42) The unhydrated base has been prepared by Sugasawa.[14]

(43) The **21** used for this preparation was obtained from a repeat of the initial synthesis and was found by MS to be 84% d_2 and 12% d_1.[22]

(44) One of us acknowledges Dr. J. I. Seeman for discussions on this reaction.

C-5 Substituted Pyrimidine Nucleosides. 1. Synthesis of C-5 Allyl, Propyl, and Propenyl Uracil and Cytosine Nucleosides via Organopalladium Intermediates

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Reaction of 5-chloromercuriuracil nucleosides (**1a,b**) with allyl chloride in the presence of Li_2PdCl_4 gives 5-allyluridine (**2a**) and 5-allyl-2′-deoxyuridine (**2b**), respectively, in good yields with minimal purification. $RhCl_3$ and $Rh(Ph_3P)_3Cl$ do not catalyze this alkylation. Hydrogenation of these 5-allyluracil nucleosides (**2a,b**) to 5-propyluridine (**3a**) and 5-propyl-2′-deoxyuridine (**3b**) occurs readily with no reduction of the pyrimidine ring. Isomerization of **2b** to 5-(1-propenyl)-2′-deoxyuridine (**4**) is achieved in the presence of $Rh(Ph_3P)_3Cl$. A similar reaction sequence with 5-chloromercuricytosine nucleosides (**5a,b**) gives good yields of 5-allyl- and 5-propylcytidines (**6a** and **7a**, respectively) and 5-allyl-, 5-propyl-, and 5-(1-propenyl)-2′-deoxycytidines (**6b**, **7b**, and **8**, respectively), none of which have been reported in the literature previously. Characterization of products includes melting point, ^1H NMR, UV, TLC, elemental analysis, and IR. The probable mechanism and potential biological activities are discussed briefly.

In addition to thymidine, many naturally occurring C-5 substituted pyrimidine nucleosides are found in the RNA and DNA of living organisms,[1-4] although the specific function of the C-5 modification is unknown for most of these. As chemotherapeutic agents many C-5 substituted pyrimidine nucleosides have been shown to exhibit activity against Herpes simplex[5] and vaccinia viruses;[6] one of these, 5-iodo-2′-deoxyuridine, is used clinically[7] against Herpes keratitis infections. Several C-5 substituted pyrimidine nucleosides have been shown to act with varying specificity as inhibitors of certain enzymes, such as the inhibition of nucleoside phosphorylase by 5-trifluoromethyl-2′-deoxyuridine[8] or the mild inhibition of deoxythymidine kinase from human acute myelocytic blast cells by 5-propyl-2′-deoxyuridine.[9] One modified nucleoside, 5-fluoro-2′-deoxyuridine, is an inhibitor of thymidylate synthetase after in vivo 5′-monophosphorylation. Others may act as competitive substrates for enzymes, and many, such as 5-ethyl-2′-deoxyuridine in *E. coli*,[10] may be directly incorporated into DNA.

Many C-5 alkylated uracil nucleosides, such as 5-allyl-2′-deoxyuridine[11] (**2b**) and 5-propyl-2′-deoxyuridine[12] (**3b**), have been synthesized and assayed for biological activity. Studies with 5-allyl-2′-deoxyuridine (**2b**) have shown the following: **2b** inhibits the growth of Herpes simplex virus (HSV) I and II, without being cytotoxic;[5,9] **2b** as its 5′-monophosphate exhibits only weak inhibition of deoxythymidylate synthetase;[13] and it was reported that **2b** also inhibits nucleoside phosphorylase[14] in HeLa cells as efficiently as 5-trifluoromethyl-2′-deoxyuridine.[8] (Recently it has been shown that **2b** is a competitive substrate for horse liver thymidine phosphorylase[15] rather than an inhibitor.) Biological assays of 5-propyl-2′-deoxyuridine (**3b**) have shown that **3b** weakly inhibits both mitochondrial and cytoplasmic deoxythymidine kinases of acute myelocytic blast cells.[9,16] It (**3b**) also inhibits growth of HSV I transformed HeLa cells which are deficient in deoxythymidine kinase, without being cytotoxic.[5] When *E. coli* is grown in the presence of **3b**, the *E. coli* show much more resistance to damage by UV light,[17] presumably due to less UV-induced dimerization after incorporation of **3b** into the DNA.

Like the corresponding halogenated 2′-deoxyuridines, the C-5 halogenated 2′-deoxycytidines show pronounced biological activity.[9,18] With the exception of 5-ethylcytidine and 5-ethyl-2′-deoxycytidine,[21] alkylated cytosine nucleosides with two or more carbons at C-5 have not been available for study, but in analogy to the alkylated uracil nucleosides the C-5 alkylated cytosine nucleosides may exhibit significant biological activity.

In light of their known and potential biological effects, much recent effort[11,12,19-28] has been directed towards the synthesis of C-5 substituted pyrimidine nucleosides. We have been particularly interested in obtaining nucleosides with carbon chains attached at C-5. Synthetic approaches to date have usually involved synthesis of a C-5 substituted pyrimidine and condensation of this with a suitably protected and activated sugar followed by deprotection and separation of the α and β anomers.[11,12,20-24] In order to overcome some of the drawbacks inherent in this procedure, we sought a general synthetic route beginning with the unprotected parent nucleosides. Recent results in this laboratory have established that pyrimidine nucleosides can be substituted at the C-5 position via organopalladium intermediates.[27,28] The 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b,** which are readily available from uridine, 2′-deoxyuridine, cytidine, and 2′-deoxycytidine,[25,26] respectively, can react with olefins in the presence of Pd(II) to give the corresponding C-5 alkylated nucleosides directly. Although this general coupling reaction is similar to the results seen with phenylmercuric chloride and allyl chloride in the presence of Pd(II),[29] some interesting differences are observed. The present paper describes the following: (1) the reaction of allyl chloride with the 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b** and Li_2PdCl_4 to form 5-allyluridine[27] (**2a**), 5-allyl-2′-deoxyuridine (**2b**), 5-allylcytidine (**6a**), and 5-allyl-2′-deoxycytidine (**6b**), respectively; (2) the subsequent reduction of these 5-allylpyrimidine nucleosides to 5-propyluridine (**3a**), 5-propyl-2′-

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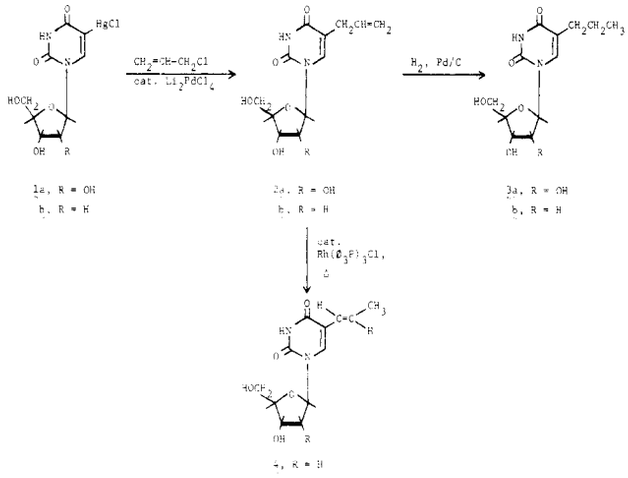
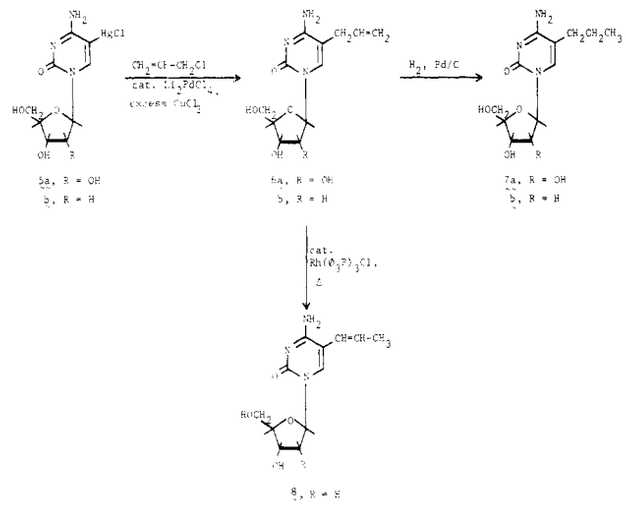
Scheme I



Scheme II



deoxyuridine (**3b**), 5-propylcytidine (**7a**), and 5-propyl-2′-deoxycytidine (**7b**), respectively; and (3) the conversion of the 5-allylpyrimidine nucleosides **2b** and **6b** to 5-(1-propenyl)-2′-deoxyuridine (**4**) and 5-(1-propenyl)-2′-deoxycytidine (**8**), respectively. This constitutes the first synthesis of 5-(1-propenyl)-2′-deoxyuridine (**4**) and 5-allyl-, 5-propyl-, and 5-(1-propenyl)cytosine nucleosides (**6–8**) reported in the literature to date.

Results and Discussion

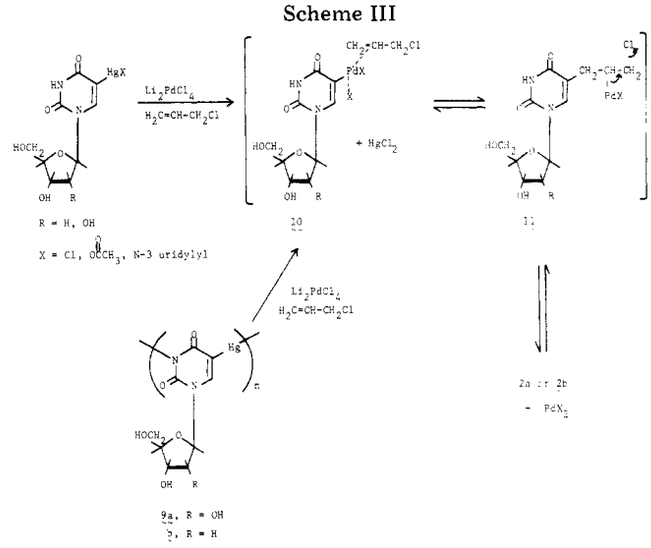
Reactions of C-5 Mercurated Nucleosides with Allyl Chloride. Our initial focal point was the investigation of the reactions of the mercuri nucleosides **1a,b** and **5a,b** with allyl chloride in the presence of palladium(II). When 5-chloromercuri-2′-deoxyuridine (**1b**) was suspended in methanol and allyl chloride and Li_2PdCl_4 were added, the insoluble mercuri nucleoside (**1b**) rapidly disappeared.[30] In this and related reactions the product was purified by precipitation of the metals as sulfides followed by column chromatography of the crude product on silica gel. The purified product was identified as 5-allyl-2′-deoxyuridine (**2b**) on the basis of ^1H NMR, melting point, IR, UV, elemental analysis, and comparison of these with the literature.[11] This and subsequent repetitions have given yields of 72–92% after column chromatography of the crude product.[31] The reaction of 5-chloromercuriuridine (**1a**) with allyl chloride in the presence of Li_2PdCl_4 goes with equal facility,[27] giving 5-allyluridine (**2a**) in 78–84% yields.[31] (See Scheme I.)

Due to the potential toxicity of the mercuri nucleosides and to further simplify the preparation of the 5-allyl nucleosides from the parent uracil nucleosides, we attempted to develop a "one-pot" procedure whereby uridine, for example, could be mercurated and then treated with allyl chloride and Li_2PdCl_4 to give **2a** directly. In pursuit of this goal, uridine and mercuric acetate were warmed in water for several hours, giving a thick white suspension of C-5 mercurated uridine.[26] Direct addition of allyl chloride and Li_2PdCl_4 in methanol at room temperature gave **2a** in 44% overall yield after purification by column chromatography, with 30% recovery of uridine. This method resulted in a lower overall yield of **2a** from uridine (44% vs. over 60% for the first method[32]), but it had the advantage of minimizing handling of the mercuriuridine necessary in the first method. This second, or "one-pot", method has also been applied in the synthesis of **2b** with an overall yield of 34% from 2′-deoxyuridine, again with recovery of substantial amounts of the parent nucleoside, 2′-deoxyuridine (ca. 20%). A repetition of this "one-pot" method with uridine in methanol rather than water as solvent resulted in less than 20% yield of **2a** with 75% of the material recovered as uridine. This is in agreement with earlier results which had suggested that the mercuration step proceeds much less efficiently in methanol than in water.[33]

The general pathway involved may be similar to that suggested for the reaction of phenylmercuric chloride with allyl chloride in the presence of Pd(II).[29] As indicated in Scheme III, the metal–metal exchange of Pd(II) for Hg(II) is apparently crucial for coupling of the allyl chloride to the mercuri nucleoside,[35] although the actual Pd(II) species reacting to form **10** may include a uridylyl species as a ligand(s). Binding studies have shown that Pd(II) can bind well to N-3 of thymidine or uridine in ratios of 1:2 at a pH well below that necessary for deprotonation,[34] and consequently any uridylyl species present may be serving as a ligand(s) for the Pd(II).[35] When **1a** was stirred with allyl chloride in methanol and no Pd(II) species were present, the insoluble[30] **1a** had not disappeared after 48 h at room temperature and an additional 72 h at reflux. Isolation of the white solid by filtration gave better than 94% recovery of a solid identified as **1a** by IR and NMR spectroscopy. With the exclusion of allyl chloride but in the presence of 1.1 equiv of Li_2PdCl_4, the insoluble[30] **1a** disappeared, but more slowly than in the presence of allyl chloride. Apparently the inclusion of an olefin in the reaction mixture is not necessary for the metal exchange, although its presence may increase the rate.

Activation of the C-5 position of uridine to increase the effective electron density is necessary to achieve olefin coupling, either by conversion to **1a** or a C-5 halogenated uridine. Reaction of **1a** or 5-iodouridine with methyl acrylate in the presence of Pd(II) has been shown[27,28] to give good yields (57

Scheme III



and 53%, respectively) of methyl 3-(5-uridylyl)propenoate. However, when uridine was stirred in methanol with an excess of methyl acrylate and 1.1 equiv of palladium acetate, the major product isolated after 40 h at room temperature was uridine in better than 75% recovery. No trace of the methyl 3-(5-uridylyl)propenoate was observed.

As indicated in Scheme III, the overall allylic coupling reaction is theoretically catalytic with respect to Pd(II). Experimentally, levels below 0.2 equiv of Li_2PdCl_4 per equiv of mercuri nucleoside result in decreased yields, even after extended periods of time. This has been noted in other similar reactions.[29] There appears to be at least two factors which might account for this partially catalytic behavior. (1) Pd(II) and allyl chloride can form inactive π-allyl complexes;[36,37] indeed, the formation of these complexes may be catalyzed by amines.[37] Although these π-allyl Pd(II) complexes are apparently not formed in anhydrous methanol,[36] enough may be formed due to trace water or the presence of mercury species, for example, to account for the less than catalytic behavior of the Pd(II) seen experimentally. (2) The other factor may be partial inactivation of Pd(II) due to binding at N-3 of the nucleosides,[34] although the pH of the reaction mixture is such that this effect should be weak. However, even if bound to N-3 of the nucleoside, the Pd(II) may still be able to catalyze the coupling reaction, as discussed earlier. Levels of Pd(II) as low as 0.02 equiv of Li_2PdCl_4 per equiv of mercuri nucleoside have been used with success if an excess of cupric chloride was included in the reaction mixture. Although Cu(II) apparently does not promote the allylation directly, it may minimize these and other factors limiting the catalytic behavior of Pd(II) by (1) serving as a one-electron acceptor for the reoxidation of any Pd(0) formed during the reaction or (2) by displacing any Pd(II) bound at N-3 of the nucleosides by competition and/or concentration effects since Cu(II),[38] as well as other metals,[39] has been shown to bind weakly at N-3 of uridine and thymidine. For example, when **1a** was reacted with allyl chloride in the presence of 0.02 equiv of Li_2PdCl_4 and 2.2 equiv of $CuCl_2$, purification gave a product identical with **2a** by ^1H NMR spectroscopy, TLC, and melting point in 64% yield. The reaction may also proceed satisfactorily with less than 1 equiv of cupric chloride. Although the inclusion of Cu(II) experimentally enhances the catalytic potential of Pd(II) in this reaction, the exact nature of the interaction has not been studied.[40]

Although most reactions of the mercuri nucleosides with olefins[27,28] have given products analogous to those obtained with phenylmercuric chloride and olefins,[29,41,42,45] one interesting exception is the reaction of 5-mercuriuridine[26] (**9a**) with allyl alcohol in the presence of Li_2PdCl_4. 3-(5-Uridylyl)-propionaldehyde was expected to be the major product by HPdX elimination from the intermediate analogous to **11**.[33,43] Little 5-allyluridine was expected. When 5-mercuriuridine[35] was reacted with 10 equiv of allyl alcohol in the presence of excess Li_2PdCl_4 in methanol, the only product recovered in greater than 60% yield after column chromatography on Sephadex G-25 was identical with 5-allyluridine (**2a**) by ^1H NMR spectroscopy and TLC in systems A, B, and C (see Experimental Section). None of the expected 3-(5-uridylyl)-propionaldehyde was detected. The 5-allyluridine (**2a**) may be formed by either elimination of HOPdX from the intermediate analogous to **11** to form **2a** directly or by formation of allyl chloride from the alcohol in situ and subsequent addition to form **2a**.[43]

Of even more interest synthetically is the reaction between 5-chloromercuricytidine[26] (**5a**) or 5-chloromercuri-2′-deoxycytidine[26] (**5b**) and allyl chloride. When **5b** was stirred in methanol with allyl chloride for 2.5 h in the presence of 0.24 equiv of Li_2PdCl_4 and 1.2 equiv of $CuCl_2$, the only product observed after purification was a white solid identified as 5-allyl-2′-deoxycytidine (**6b**) on the basis of melting point, ^1H NMR, IR, UV, and elemental analysis in 77% yield. This and subsequent repetitions have shown yields of **6b** to be 65–80%. Similarly, the reaction between **5a** and allyl chloride gave 5-allylcytidine (**6a**) in 70% yield. (See Scheme II.)

The synthesis of **6b** can also be accomplished directly from 2′-deoxycytidine (or its HCl salt) in a procedure similar to the "one-pot" method for synthesis of **2a** or **2b**, without isolating intermediates. The HCl salt of 2′-deoxycytidine was warmed with mercuric acetate in water and cooled, the solvent was removed to near dryness, and allyl chloride, Li_2PdCl_4, and $CuCl_2$ were added. Purification of the product gave a solid identified as **6b** on the basis of ^1H NMR spectroscopy and TLC in 53% yield after column chromatography. As noted earlier for uridine analogues, this "one-pot" method has the advantage of minimizing the handling of the presumably toxic mercuri nucleoside, but it results in lower overall yields from 2′-deoxycytidine (53% vs. 67% for the first method[44]).

Thus, the reactions of **5a** or **5b** with allyl chloride to form **6a** or **6b**, respectively, appear to proceed with a facility equal to that of the uridine series. These results are in contrast to those seen in the arylmercuric salt series.[45] When strong coordinating substituents such as amino groups are present when attempting to couple olefins to arylmercuric salts in the presence of Pd(II), the reaction does not proceed due to formation of an unreactive complex.[37,45] However, the exocyclic amino group of **5a** or **5b** does not appear to inhibit the allylation reaction, at least in the presence of excess cupric chloride. This may be due to direct competition of the copper species with Pd(II) for binding sites since Cu(II) has been shown to bind to N-3 and the C-2 exocyclic oxygen of cytidine simultaneously.[38] This competition would presumably free the Pd(II) from its unreactive complex and allow allylation to proceed. This supposition is borne out by the reaction of 5-acetoxymercuricytidine[46] with 10 equiv of allyl chloride and 1.1 equiv of Li_2PdCl_4 in methanol. With no copper species present, this reaction gave the desired **6a** in only 33% yield. When 1.1 equiv of cupric chloride is included and only 0.05 equiv of Li_2PdCl_4 is present, **6a** can be isolated in 60% yield. Apparently the inclusion of an excess of cupric chloride circumvents the inactivation of the Pd(II), allowing the palladium to regain its ability to catalyze the coupling reaction, even though ca. 0.2 equiv of Li_2PdCl_4 must still be used to maximize yields even in the presence of excess cupric chloride.

The choice of solvent and initial Pd(II) complex may also be important in obtaining **6a** or **6b** in reasonable yields. When 5-chloromercuri-2′-deoxycytidine (**5b**) was stirred in 40 mL of methanol at room temperature with 10 equiv of allyl chloride and 1.2 equiv of cupric chloride, the use of 15 mL of 0.1 N Na_2PdCl_4 (0.3 equiv) in water gave only a 26% yield of **6b**. Other results have shown that, although sodium salts are more easily removed from the product by column chromatography on silica gel than lithium salts, yields may be lower and reaction rates slower when using Na_2PdCl_4 as a catalyst rather than Li_2PdCl_4. The inclusion of water alone apparently causes a decrease in yields as well, perhaps due to the formation of inactive π-allyl complexes formed in aqueous solutions.[36]

Reduction of 5-Allylpyrimidine Nucleosides to the 5-Propyl Derivatives. The hydrogenation of 5-allyl nucleosides (**2a,b** and **6a,b**) under a hydrogen atmosphere using an active metal catalyst easily affords the 5-propyl nucleosides (**3a,b** and **7a,b**, respectively) in good purity and high yields (Table I). Crude unchromatogrammed 5-allyl nucleosides are resistant to reduction, apparently due to poisoning of the catalyst by residual sulfides; however, products which have undergone chromatography on silica gel or recrystallization reduce quickly with mild conditions.[47] (See Schemes I and II.)

Table I. Physical Properties and Yields of C-5 Substituted Pyrimidine Nucleosides

Compd	Registry no.	Mp, °C	UV[a] H+ λ_{max} (ϵ)	UV[a] H+ λ_{min} (ϵ)	UV[a] Stock solution λ_{max} (ϵ)	UV[a] Stock solution λ_{min} (ϵ)	UV[a] OH− λ_{max} (ϵ)	UV[a] OH− λ_{min} (ϵ)	TLC R_f in TLC system:[b] A	B	C	D	Yield, %
2a	59240-49-2	175.5	267 (9700)	234 (2600)	267 (9700)	234 (2500)	266 (7500)	247 (4900)	0.43	0.57	0.39	0.64	78
2b	73-39-2	126	267 (9490)	235 (2440)	267 (9540)	235 (2470)	266 (7400)	247 (5000)	0.54	0.69	0.46	0.68	72
3a	38971-54-9	197	267 (8960)	235 (1790)	267 (9090)	235 (1850)	266 (6840)	247 (4090)	0.43	0.60	0.38	0.66	78[c]
3b	27826-74-0	164	267 (8970)	235 (2310)	267 (8960)	235 (2270)	266 (7160)	246 (4670)	0.54	0.68	0.45	0.63	84[c]
4	66270-29-9	178	237 (12490), 293 (7920)	267 (4440)	237 (12540), 293 (7950)	267 (4450)	237 sh (14100), 288 (6590)	273 (5620)	0.55	0.72	0.47	0.69	87[c]
6a	66270-30-2	176	288 (11860)	248 (1270)	278 (8110)	254 (5090)	278 (8190)	255 (6270)	0.16	0.50	0.06	0.40	70
6b	66270-31-3	180	288 (12010)	247 (1140)	278 (8180)	254 (4860)	278 (8350)	254 (4960)	0.28	0.59		0.51	77
7a	66270-32-4	178[d]	288	245	278	256	278	256	0.18	0.52		0.41	92[c]
7b	66270-33-5	183	288 (12160)	245 (1070)	278 (8360)	254 (4710)	278 (8540)	254 (4700)	0.26	0.61		0.51	94[c]
8		157[d]	233 (11820), 298 (6610)	268 (2910)	233 sh (13230), 288 (5100)	271 (4120)	233 sh (13230), 288 (5470)	272 (4530)	0.29	0.64		0.54	40[c]

[a] UV spectra were obtained in aqueous solution at neutral pH, in dilute HCl (pH 1.2), and in dilute NaOH (pH 12.6); wavelengths are reported in nanometers. [b] Thin-layer chromatography (TLC) was accomplished on E. Merck precoated silica gel G60 F-254 (0.25 mm) plastic support TLC sheets (3 × 10 cm); elution was in 5 × 5 × 12 cm chambers lined with filter paper. Solvent systems: A, $CH_3OH/CHCl_3$ (1:3 v/v); B, *n*-BuOH/CH_3OH/concentrated NH_4OH/H_2O (60:20:1:20 v/v); C, CH_3OH/EtOAc (3:17 v/v); D, CH_3OH/EtOAc (3:2 v/v). [c] Yield from respective 5-allyl nucleoside. [d] Showed anomalous melting behavior (see Experimental Section for details).

Isomerization of 5-Allylpyrimidine Nucleosides to the 5-(1-Propenyl) Derivatives. Palladium(II) is known to catalyze the isomerization of allylbenzenes to propenylbenzenes.[29] In general, Pd(II), particularly $PdCl_4^{2-}$, is a very effective catalyst for the isomerization of terminal to internal olefins,[48] especially when conjugation energy is gained. However, in the synthesis of **2b** or **6b** from **1b** or **5b**, respectively, no traces of 5-(1-propenyl)-2′-deoxyuridine (**4**) or 5-(1-propenyl)-2′-deoxycytidine (**8**) are observed even after 72 h at reflux in the presence of Li_2PdCl_4. Since some success had been reported in the isomerization of allylbenzenes,[49] $Pd(CH_3CN)_2Cl_2$ was tried as a catalyst for the isomerization of 5-allyluridine (**2a**) to 5-(1-propenyl)uridine. When **2a** was refluxed in acetonitrile with 0.1 equiv of $Pd(CH_3CN)_2Cl_2$ and the reaction monitered by UV spectroscopy, the λ_{max} of **2a** at 266 nm had not shifted after 24 h, and ^1H NMR spectroscopy after purification showed the sole product to be recovered **2a**.

Some success has been reported using Wilkinson's catalyst [$Rh(Ph_3P)_3Cl$] as a reagent for the isomerization of allyl ethers to propenyl ethers.[50] When 5-allyl-2′-deoxyuridine (**2b**) was refluxed in 95% ethanol in the presence of 0.06 equiv of $Rh(Ph_3P)_3Cl$ and the reaction monitored by UV spectroscopy, the λ_{max} slowly shifted from the 267-nm peak of **2b** to 293 nm after 8 h. Evaporation, extraction of the residue with 10% aqueous ethanol, and column chromatography on Sephadex G-10 gave one major product, which was later identified as solely *trans*-5-(1-propenyl)-2′-deoxyuridine (**4**) on the basis of ^1H NMR, UV, IR, melting point, and elemental analysis in 87% yield. The results from ^1H NMR, UV, and TLC in systems A and B were identical with material identified as **4** which was prepared by the reaction of propene with **1b** in the presence of Li_2PdCl_4.[28]

The isomerization of 5-allyl-2′-deoxycytidine (**6b**) to 5-(1-propenyl)-2′-deoxycytidine (**8**) occurs as well, but with somewhat less facility. When **6b** was refluxed in ethanol with 0.2 equiv of $Rh(Ph_3P)_3Cl$ for 30 h, extraction and column chromatography on silica gel yielded an off-white solid. Recrystallization gave a white solid identified as **8** on the basis of ^1H NMR, UV, melting point, and elemental analysis. However, the yield before recrystallization was only 40%, perhaps due to inhibition of the reaction by the binding of rhodium at other sites, presumably at N-3 and the C-2 exocyclic oxygen similarly to other metals.[38,39] Close scrutiny of the ^1H NMR spectrum of **8** appears to indicate that the product may be a 1:3 mixture of cis and trans isomers. The ^1H NMR spectrum of the model compound propenylbenzene shows the $-CH_3$ of the propenyl moiety to be a doublet at δ 1.80 with J = 5.5 Hz for trans isomer,[51] while the *cis*-propenylbenzene gives a doublet at δ 1.72.[52] The ^1H NMR spectrum of **8** shows two doublets, one at δ 1.85 (J = 5 Hz) integrating for 2.25 protons and one at δ 1.74 integrating for 0.75 protons, which have been assigned to the propenyl $-CH_3$ protons of the trans and cis isomers, respectively. The C-6 proton of **8** apparently also exhibits a shift as a result of magnetic differentiation, being split into two unequal singlets at δ 7.95 (0.75 protons) and 7.72 (0.25 protons). The complexity of signals between δ 5.9 and 6.3 precludes any first-order analysis of the chemical shift for the vinylic protons[51,52] in assigning cis or trans stereochemistry.

Some effort has been directed toward developing a more direct synthesis of **4** or **8** from **1b** or **5b**, respectively. Presumably, coupling of allyl chloride with **1b** to give **2b** in the presence of a reagent able to catalyze the isomerization would result in the isolation of **4** directly. Palladium(II) is apparently not an efficient catalyst for the isomerization. Although rhodium(I) as Wilkinson's catalyst can catalyze the isomerization, neither rhodium(I) nor -(III) can accomplish the coupling reaction of allyl chloride to the mercuri nucleoside; both appear to catalyze the demercuration of **1a** or **1b** to uridine or

2′-deoxyuridine, respectively. These results agree with earlier observations; when **1b** is reacted with $Rh(CH_3)I_2(Ph_3P)_2$ in an attempt to methylate[53] **1b** and obtain thymidine, the only isolable nucleoside product is 2′-deoxyuridine. These and other approaches[54] to obtain the 5-(1-propenyl)pyrimidine nucleosides directly from the 5-mercuri nucleosides have not been pursued further at this time.

Conclusion

From the unprotected pyrimidine nucleosides, the mercuration and subsequent alkylation by coupling of the mercuri nucleoside to allyl chloride offer a facile method for the synthesis of the C-5 substituted uracil and cytosine nucleosides, most of which have not been reported elsewhere. The synthetic routes described in this paper have several advantages over any methods appearing in the literature to date: (1) coupling of allyl chloride to the nucleoside gives regiospecific addition at the olefin terminus to form only the C-5 allyl nucleoside (no isopropenyl isomers are observed); (2) the coupling reaction is nearly catalytic in Pd(II) rather than requiring equimolar amounts as with the coupling of olefins,[28,41,42,45] thus minimizing cost; (3) the isolation and purification of the alkylated nucleosides (particularly **4** and **8**) are much easier than when separating products obtained from reaction of the mercuri nucleosides with propylene and Pd(II),[28] and yields by this method are higher; (4) the allylic coupling reaction has potential use in the synthesis of longer and more complex substituents at C-5 of the pyrimidine nucleosides, particularly since the coupling reaction can tolerate many other functional groups;[28,41,42,45] and (5) the allylic coupling reaction gives 5-alkylated pyrimidine nucleosides in good yields after two or three steps, as opposed to many steps involved with consequent low yields for most of the approaches reported to date.[11,12,20-24] In addition, one of the major advantages of the alkylation method discussed in this paper over most prior syntheses is its ability to utilize the intact unprotected pyrimidine nucleosides as starting materials. This not only eliminates the protection–deprotection steps necessary otherwise, but also allows the use of the usually desired β anomer directly, circumventing the mixture of anomers obtained in many reactions. Consequently, this approach should be very useful synthetically in the introduction and elaboration of substituents at C-5 of uracil and cytosine nucleosides.

The reactions of 5-mercuripyrimidine nucleosides with more complex allylic halides in the presence of metals have been investigated and will be reported elsewhere.

Experimental Section

General. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-360 spectrometer in D_2O, and values reported are in ppm downfield from sodium 2,2,3,3-tetradeuterio-3-trimethylsilylpropionate as an internal standard. Quantitative UV spectra were recorded on a Cary 17 spectrophotometer in H_2O, and the pH indicated was obtained by diluting 20.00 mL of stock solution to 23.00 mL with 1.0 N HCl or 1.0 N NaOH (final pH approximately 1.2 or 12.6, respectively). IR spectra were recorded on a Beckman IR-8 in solid KBr using polystyrene for calibration. Elemental analyses were determined by Chemalytics, Inc., Tempe, Ariz. Thin-layer chromatography (TLC) was carried out using 3 × 10 cm E. Merck 60F-254 chromatogram sheets (0.25 mm silica gel) in 5 × 5 × 12 cm chambers lined with filter paper and four different TLC systems (relative proportions are v/v): system A, $CH_3OH/CHCl_3$ (1:3); system B, *n*-$BuOH/CH_3OH$/concentrated NH_4OH/H_2O (60:20:1:20); system C, CH_3OH/EtOAc (3:17); and system D, CH_3OH/EtOAc (3:2). Column chromatography was generally accomplished using Woelm activity I silica gel from ICN Pharmaceuticals (70–230 mesh) packed in 2-cm (i.d.) columns, and the column eluate was monitored using a LBK 8300 Unicord II UV detector. Hydrogenations were carried out at room temperature under a hydrogen atmosphere using 10% Pd/C from MCB as a catalyst. Evaporations were accomplished using Rinco rotating evaporators under an aspirator or a mechanical oil pump vacuum at 40 °C or lower. Final drying of products was done at 65 °C for 24 h over P_2O_5 at less than 0.1 mmHg. Low-resolution mass spectra consistent with the indicated structures have been obtained for compounds **2–4**.[55]

The mercuri nucleosides (**1a,b** and **5a,b**) were prepared by methods described elsewhere[26] from nucleosides purchased from Sigma and mercuric acetate purchased from Mallinckrodt. The allyl chloride was obtained from Aldrich (98% pure), the palladium(II) chloride from Matthey Bishop, and the tris(triphenylphosphine)chlororhodium from Eastman. Starting materials were used without further purification.

Data included in the table (UV spectroscopy and TLC) are not included in the Experimental Section.

General Allylation Procedure. The mercuri nucleoside to be allylated was weighed into a recovery flask, a designated volume of CH_3OH was added, and the solution was stirred at room temperature with a magnetic stirrer, with the insoluble mercuri nucleoside forming a thick white suspension. (If $CuCl_2$ was to be included, the designated amount was added at this point.) An exess of allyl chloride (usually 10–12 equiv) was pipetted in, followed by the addition of the indicated volume of 0.10 N Li_2PdCl_4 in CH_3OH (usually 0.2–0.3 equiv). The suspension was stirred for the designated time at room temperature, with all solid usually disappearing within the first 0.5 h. Hydrogen sulfide gas was bubbled through for less than 1 min, and the reaction mixture was vacuum filtered through Celite to remove the precipitated metal sulfides. The yellow filtrate was rotary evaporated to dryness, leaving an off-white solid.

Column chromatography was accomplished using a 2-cm (i.d.) column packed with the indicated amount of silica gel in $CHCl_3$. The product was added and eluted with a column volume of 5 vol % of CH_3OH in $CHCl_3$ (followed by a column volume of 10 vol % of CH_3OH in $CHCl_3$ for cytosine nucleosides). The column was then eluted with increasing vol % mixtures of CH_3OH in $CHCl_3$ in 1% increments. Each increment was about one-half the column volume, and the range of increments is indicated in the specific procedure. The eluate was collected in 7-mL fractions and monitored by absorbance at 254 nm. Fractions containing the major peak were combined, and the solvent was removed by rotary evaporation to leave the product as a white solid. The solid was then dried for 18–24 h at 65 °C at less than 0.1 mmHg pressure and weighed. Recrystallization was accomplished from the indicated solvent, and the product was washed with ether and dried. If the product did not recrystallize, the silica gel column treatment was repeated to remove residual impurities, and the product was dried and recrystallized as indicated.

5-Allyluridine (2a). Method A. A 3.29-g (6.87 mmol) sample of 5-chloromercuriuridine (**1a**) was stirred in 50 mL of CH_3OH and treated with 5.0 mL (61 mmol) of allyl chloride and 15 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.5 mmol) as described in the general allylation procedure. The reaction mixture was stirred overnight, treated with H_2S, and chromatographed on a column of 150 g of silica gel using increments of 8–18 vol % of CH_3OH in $CHCl_3$. The dried product was a white solid (1.52 g, 78%). Recrystallization from acetone or acetonitrile gave **2a** as white crystals: mp 175.5–176 °C (lit.[22] mp 175–176 °C); IR (KBr) 3405, 1703, 1655, 1460, 1270, 1100, 1040, 915 cm^{-1}; ^1H NMR (D_2O) δ 7.74 (s, 1), 5.94 (d, 1, J = 4 Hz), 5.90 (m, 1), 5.21 (dm, 1, J = 11 Hz), 5.19 (dm, 1, J = 17 Hz), 4.25 (m, 3), 3.88 (narrow m, 2), 3.07 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.59; H, 5.51; N, 9.82.

Method B. A 1.21-g (4.96 mmol) sample of uridine was dissolved in 5 mL of H_2O. A solution of 1.74 g (5.46 mmol) of mercuric acetate in 20 mL of H_2O was added, and the clear solution was stirred at 50 °C for 4 h. Sodium acetate (0.98 g, 7.2 mmol) was added. After 16 h, the solution cooled to room temperature, and 4.0 mL (50 mmol) of allyl chloride and 5.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.5 mmol) were added followed by the addition of 0.4 g (0.3 mmol) of $CuCl_2$. After 6 h, the grey suspension was treated with H_2S, filtered, and chromatographed on a column of 70 g of silica gel similar to method A. The dried product was a white solid (620 mg, 44% from uridine). Recrystallization from CH_3CN gave white crystals identical with product **2a** of method A by ^1H NMR spectroscopy, TLC, and melting point (370 mg of uridine (30%) was recovered from the column).

Method C. A 980-mg (2.0 mmol) portion of **1a** and 590 mg (4.4 mmol) of $CuCl_2$ were stirred in 15 mL of CH_3OH at room temperature. Then 0.5 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.05 mmol) and 1.7 mL (21 mmol) of allyl chloride were added. After 8 h, the solution was treated with H_2S and filtered, the solvent was removed from the filtrate, and the crude product was chromatographed on a column of 60

g of silica gel eluting with EtOAc/EtOH (4:1 v/v). The major product was an off-white solid (370 mg, 64%) identical with **2a** by ^{1}H NMR spectroscopy, TLC, and melting point.

5-Allyl-2′-deoxyuridine (2b). A 5.99-g (12.9 mmol) portion of 5-chloromercuri-2′-deoxyuridine (**1b**) was stirred in 125 mL of CH_3OH, 10.0 mL (123 mmol) of allyl chloride and 30 mL of 0.1 N Li_2PdCl_4 in CH_3OH (3.0 mmol) were added, and the solution was stirred for 3 h. Treatment with H_2S and chromatography on a column of 225 g of silica gel as outlined in the general allylation procedure using 8–18 vol % of CH_3OH in $CHCl_3$ gave a white solid (2.49 g, 72%) after drying. Recrystallization from CH_3CN yielded **2b** (1.9 g) as white crystals: mp 125.5–127.0 °C (lit.[11] mp 126–128 °C); IR (KBr) 3460, 1670, 1460, 1280, 1092, 760 cm^{-1}; ^{1}H NMR (D_2O) δ 7.70 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 5.9 (complex m, 1), 5.15 (dm, 1, J = 11 Hz), 5.08 (dm, 1, J = 17 Hz), 4.48 (m, 1), 4.03 (m, 1), 3.84 (narrow m, 2), 3.07 (d, 2, J = 6 Hz), 2.41 (dd, 2, J_1 = 5.5 Hz, J_2 = 7 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.87; H, 5.93; N, 10.51.

5-Propyluridine (3a). A solution of 302 mg (1.06 mmol) of 5-allyluridine (**2a**) in 10 mL of CH_3OH was pipetted into a 500-mL hydrogenation flask over 50 mg of 10% Pd/C and washed in with 15 mL of CH_3OH, and the system was sealed, evacuated with an aspirator, repressurized with 20 psig H_2, and stirred at room temperature for 1.5 h. The system was reevacuated, and the solution was gravity filtered to remove Pd/C. The solvent was removed from the clear filtrate by rotary evaporation and dried to leave a white solid (236 mg, 78%). Recrystallization from CH_3CN gave **3a** as white crystals: mp 197–198 °C; IR (KBr) 3540, 3440, 1660, 1470, 1274, 1100, 1055 cm^{-1}; ^{1}H NMR (D_2O) δ 7.79 (s, 1), 5.96 (narrow m, 1), 4.3 (complex m, 3), 3.91 (narrow m, 2), 2.30 (t, 2, J = 7 Hz), 1.5 (m, 2), 0.90 (t, 3, J = 6 Hz).

Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.27; H, 6.19; N, 9.80.

5-Propyl-2′-deoxyuridine (3b). A solution of 890 mg (3.3 mmol) of 5-allyl-2′-deoxyuridine (**2b**) in 30 mL of CH_3OH was put into a hydrogenation flask over 100 mg of 10% Pd/C. The system was sealed, evacuated, repressurized with 30 psig H_2, and stirred at room temperature for 6 h. The system was evacuated, the solution gravity filtered, and the solvent removed from the clear filtrate by rotary evaporation. The dried product was a white solid (760 mg, 84%). Recrystallization from CH_3CN or H_2O yielded **3b** as white crystals: mp 164.0–164.5 °C (lit.[12] 162 °C); ^{1}H NMR (D_2O) δ 7.70 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 4.52 (m, 1), 4.08 (m, 1), 3.84 (narrow m, 2), 2.33 (m, 4), 1.5 (m, 2), 0.90 (t, 3, J = 6 Hz).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.03; H, 6.47; N, 10.06.

5-(1-Propenyl)-2′-deoxyuridine (4). A solution of 1.30 g (4.86 mmol) of 5-allyl-2′-deoxyuridine (**2b**) in 50 mL of 95% EtOH was stirred, $Rh(Ph_3P)_3Cl$ (278 mg, 0.3 mmol) was poured in slowly, a reflux condenser was added to the flask, and the mixture was heated to reflux in an oil bath. The reaction was monitored by UV adsorption, and after 8 h at reflux the λ_{max} had shifted from 266 to 293 nm. After 12 h at reflux, the mixture was cooled, concentrated to ca. 5 mL, and extracted four times with 20-mL portions of 10% EtOH. The 80 mL of 10% EtOH extract was concentrated to ca. 10 mL, giving a tan suspension. This suspension was chromatographed on a column (2 × 40 cm) of Sephadex G-10 eluting with 10% EtOH, and the eluate was monitored by UV spectroscopy at 254 nm, resulting in one major peak. Fractions contained in the peak were analyzed by TLC in system A, and fractions showing only one spot at R_f 0.54 were combined. The solvent was removed by rotary evaporation, leaving the dried product as a white solid (1.14 g, 87%). Recrystallization from CH_3CN yielded **4** as white crystals: mp 178.0–178.5 °C dec; IR (KBr) 3490, 3390, 3220, 1697, 1674, 1480, 1380, 1280, 1090, 1030, 978 cm^{-1}; ^{1}H NMR (D_2O) δ 8.24 (s, 1), 6.56 (t, 1, J = 6.5 Hz), 6.4 (broad m, 1), 6.3 (d, 1, J = 17 Hz, indicating trans stereochemistry), 4.69 (m, 1), 4.20 (m, 1), 3.98 (narrow m, 2), 2.43 (dd, 2, J_1 = 5.5 Hz, J_2 = 7 Hz), 1.85 (d, 3, J = 5.5 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.88; H, 5.95; N, 10.67.

5-Allylcytidine (6a). A 1.22-g (2.55 mmol) sample of 5-chloromercuricytidine (**5a**) was stirred in 40 mL of CH_3OH. As described in the general allylation procedure, 410 mg (3.1 mmol) of $CuCl_2$, 2.2 mL (27 mmol) of allyl chloride, and 6.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.6 mmol) were added consecutively, and the mixture was stirred for 7 h at room temperature. Treatment with H_2S and filtration were followed by neutralization with saturated $NaHCO_3$ solution. Chromatography on a column of 70 g of silica gel using increments of 18–28 vol % of CH_3OH in $CHCl_3$ followed by rotary evaporation gave the product as a white crystalline solid (510 mg, 70%). Recrystallization from CH_3CN yielded **6a** as white crystals: mp 176.0–176.5 °C dec; IR (KBr) 3400, 3220, 1655, 1600, 1480, 1295, 1105, 1055, 790 cm^{-1}; ^{1}H NMR (D_2O) δ 7.77 (s, 1), 6.0 (broad m, 1), 5.92 (narrow m, 1), 5.20 (dm, 1, J = 10 Hz), 5.12 (dm, 1, J = 18 Hz), 4.2 (complex m, 3), 3.88 (narrow m, 2), 3.11 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.97; H, 5.71; N, 14.65.

5-Allyl-2′-deoxycytidine (6b). Method A. A 2.84-g (6.14 mmol) portion of 5-chloromercuri-2′-deoxycytidine (**5b**) was stirred in 65 mL of CH_3OH. Cupric chloride (1.0 g, 7.4 mmol), 5.0 mL (61 mmol) of allyl chloride, and 15.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.5 mmol) were added consecutively as per the general allylation procedure. The mixture was stirred at room temperature for 2.5 h and then treated with H_2S, filtered, and chromatographed on a column of 82 g of silica gel using 18–28 vol % of CH_3OH in $CHCl_3$. The dried product was a white solid (1.26 g, 77%). Recrystallization from CH_3CN yielded **6b** as white crystals: mp 180.0–180.5 °C dec; IR (KBr) 3490, 3330, 1650, 1597, 1460, 1430, 1290, 1198, 1098, 1070, 1055, 1012, 920 cm^{-1}; ^{1}H NMR (D_2O) δ 7.77 (s, 1), 6.32 (t, 1, J = 6.5 Hz), 5.9 (broad m, 1), 5.23 (dm, 1, J = 10 Hz), 5.17 (dm, 1, J = 18 Hz), 4.49 (m, 1), 4.06 (m, 1), 3.85 (narrow m, 2), 3.14 (d, 2, J = 6 Hz), 2.35 (m, 2).

Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.87; H, 6.65; N, 15.42.

Method B. A 1.34-g (5.09 mmol) sample of 2′-deoxycytidine·HCl was dissolved in 10 mL of H_2O. Mercuric acetate (1.78 g, 5.4 mmol) was poured in slowly and washed in with 5 mL of H_2O, and the clear solution was heated to 75 °C in an oil bath. After 4.5 h, ca. three-fourths of the solvent was removed by rotary evaporation, and 25 mL of CH_3OH was added. Allyl chloride (4.5 mL, 55 mmol), 820 mg (6.1 mmol) of $CuCl_2$, and 12.8 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.28 mmol) were added consecutively while stirring at room temperature. After 4.0 h, the red solution was treated with H_2S, filtered, and chromatographed on a column of 80 g of silica gel eluting with increments of 18–28 vol % of CH_3OH in $CHCl_3$. The dried product is an off-white solid (720 mg, 53%). Repetition of the silica gel column treatment gave 360 mg (27% from 2′-deoxycytidine·HCl) of white solid identical with the product of method A (**6b**) by ^{1}H NMR spectroscopy, melting point and TLC in systems A and B.

5-Propylcytidine (7a). A solution of 104 mg (0.367 mmol) of 5-allylcytidine (**6a**) in 10 mL of CH_3OH was put into a 250-mL hydrogenation flask, and 25 mg of 10% Pd/C was added. The system was evacuated and repressurized with 20 psig H_2. It was stirred at room temperature for 3.0 h and filtered, and the solvent was removed by rotary evaporation. The dried product was a white solid (96 mg, 92%). Recrystallization from CH_3CN yielded **7a** as a white solid: upon heating, it gives off gas at 125–130 °C and chars at 178–182 °C; ^{1}H NMR (D_2O) δ 7.72 (s, 1), 5.95 (narrow m, 1), 4.3 (m, 3), 3.92 (narrow m, 2), 2.27 (t, 2, J = 7 Hz), 1.5 (m, 2), 0.92 (t, 3, J = 6.5 Hz).

Anal. Calcd for $C_{12}H_{19}N_3O_5 \cdot 0.25H_2O$: C, 49.69; H, 6.78; N, 14.48. Found: C, 49.61; H, 6.44; N, 14.07.

5-Propyl-2′-deoxycytidine (7b). A solution of 720 mg (2.7 mmol) of 5-allyl-2′-deoxycytidine (**6b**) in 10 mL of CH_3OH was pipetted into a hydrogenation flask over 50 mg of 10% Pd/C, and the flask was sealed. It was evacuated, repressurized with 20 psig H_2, stirred at room temperature for 2.0 h, and filtered, and the solvent was removed by rotary evaporation. The dried product was a white solid (680 mg, 94%). Recrystallization from EtOH gave **7b** as white crystals: mp 182.5–184.0 °C dec; ^{1}H NMR (D_2O) δ 7.75 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 4.45 (m, 1), 4.09 (m, 1), 3.85 (narrow m, 2), 2.36 (m, 4), 1.53 (m, 2, J = 7 Hz), 0.91 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.45; H, 6.81; N, 15.90.

5-(1-Propenyl)-2′-deoxycytidine (8). A 637-mg (2.38 mmol) portion of 5-allyl-2′-deoxycytidine (**6b**) was dissolved in 20 mL of EtOH and stirred. Solid $Rh(Ph_3P)_3Cl$ (420 mg, 0.45 mmol) was slowly poured in and washed in well with 5 mL of EtOH, and the reaction mixture was brought to reflux. After 4 h at reflux, the λ_{max} had shifted from 278 to 291 nm. After 30 h at reflux, the reaction mixture was concentrated by rotary evaporation to 2–3 mL and extracted four times with 20-mL portions of hot H_2O, and the H_2O extract was centrifuged. The H_2O portions were combined, concentrated to leave an oil, and chromatographed on a column of 85 g of silica gel as described in the general procedure using increments of 18–26 vol % of CH_3OH in $CHCl_3$. The dried product was an off-white solid (252 mg, 40%). Recrystallization from 3% H_2O in acetonitrile gave 8 as white crystals which soften upon heating and slowly decompose above 157 °C: ^{1}H NMR (D_2O) δ 7.95 (s, 0.75, C-6 proton of trans isomer), 7.72 (s, 0.25, C-6 proton of cis isomer), 6.31 (t, 1, J = 6.5 Hz), 6.1 (narrow m, 2),[51] 4.48 (m, 1), 4.08 (m, 1), 3.87 (narrow m, 2), 2.35 (m, 2), 1.85 (d, 2.25, $-CH_3$ of *trans*-propenyl isomer, J = 5 Hz),[51] 1.74 (d, 0.75, $-CH_3$ of *cis*-propenyl isomer, J = 5 Hz).[52]

Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.84; H, 6.18; N, 16.02.

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Registry No.—**1a,** 58931-15-0; **1b,** 65505-76-2; 8 (*trans*-propenyl isomer), 66270-34-6; 8 (*cis*-propenyl isomer), 66270-35-7; allyl chloride, 107-05-1; uridine, 58-96-8; 2′-deoxycytidine·HCl, 3992-42-5.

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(30) In the absence of Li_2PdCl_4 and allyl chloride, the solubility of **1b** in methanol is less than 1 mg/100 mL.
(31) The crude product after column chromatography shows a single spot on TLC and the absence of any structurally related nucleosides of similar chromatographic behavior by ^1H NMR spectroscopy. The material is suitable for further chemical transformations, but it usually must be rechromatographed or recrystallized to obtain analytically pure product due to the presence of residual inorganic salts.
(32) More than a 60% overall yield of **2a** from uridine for the first method is the result of 76% yield on mercuration (see ref 26) followed by 80% yield on coupling with allyl chloride.
(33) When the mercuration of uridine with mercuric acetate was carried out in methanol, the isolated **1a** appeared to have significant (10–30%) uridine as an impurity by ^1H NMR analysis.
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(43) Reactions of phenylmercuric chloride with allyl alcohol in the presence of Pd(II) have been shown to yield 3-phenylpropionaldehyde as the major product (20–50% yield) with less than one-third this amount of allylbenzene observed, even in the presence of a hindered amine. R. F. Heck suggests that the allylbenzene may come from elimination of HOPdX from the intermediate analogous to **11** or from prior substitution of Cl for OH to form allyl chloride in situ; see ref 41.
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(45) R. F. Heck, *J. Am. Chem. Soc.*, **90,** 5518 (1968).
(46) 5-Acetoxymercuricytidine was prepared similarly to 5-acetoxymercuri-2′-deoxycytidine as described in ref 26.
(47) In one instance, reduction of **6b** with an excess of 10% Pd/C gave a white solid which, unlike **7b,** was not soluble in water. A ^1H NMR spectrum taken in Me_2SO-d_6 showed only peaks corresponding to 5-propylcytosine with no resonances evident for any deoxyribosyl protons.
(48) P. M. Maitlis, "The Organic Chemistry of Palladium", Vol. 2, Academic Press, New York, N.Y., 1971, pp 136–142.
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(51) The ^1H NMR spectrum of *trans*-propenylbenzene is available from Sadtler (#20736M) and shows the $-CH_3$ to be a doublet at δ 1.80 with J = 5.5 Hz, with both vinylic protons in the range δ 6.0–6.3.
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(53) A private communication from R. C. LaRock has indicated that $Rh(CH_3)I_2(Ph_3P)_2$ is a useful methylating agent for the alkylation of chloromercuribenzenes to toluene derivatives.
(54) An interesting synthesis of *trans*-propenylbenzene by methylation of styrene with CH_3Li in the presence of Pd(II) has been reported [but potential application to the synthesis of 5-(1-propenyl)pyrimidine nucleosides would require appropriately protected 5-vinyl nucleosides, which are not readily available]; see S.-I. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, **42,** 2870 (1977).
(55) Mass spectra of these and other alkylated pyrimidine nucleosides have been obtained and will be discussed in detail elsewhere.