Pyrimidines. XII. A Propargyl Claisen Rearrangement in the Pyrimidine Series. Synthesis of Furo- and Pyrano[3,2-*d*]pyrimidines[1]

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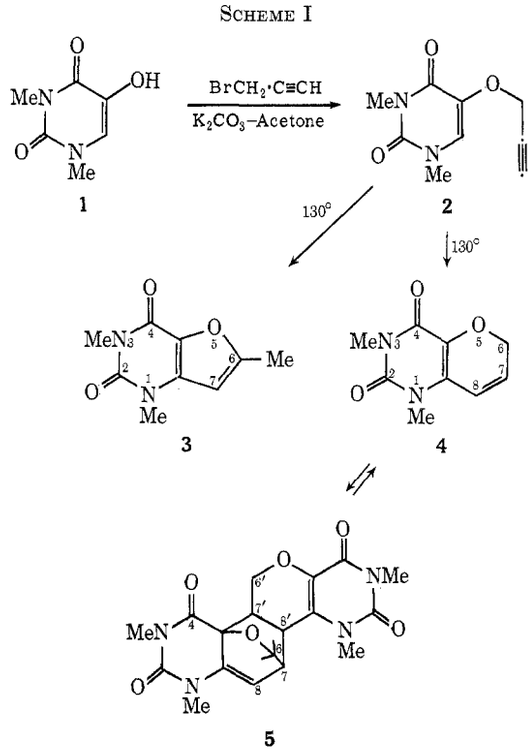
1,3-Dimethyl-5-(2-propynyloxy)uracil (**2**) readily undergoes thermal rearrangement at 130° to give mixtures of 1,3,6-trimethylfuro[3,2-*d*]pyrimidine-2,4-dione (**3**) and 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-dione (**4**). The course of the rearrangement is markedly dependent on solvent and can be directed to give mostly **3** (in DMF), equal amounts of **3** and **4** (in DMSO), or predominantly **4** (in xylene). With prolonged reaction times in xylene, compound **4** dimerizes to give a Diels–Alder adduct (**5**). The observed incorporation of deuterium from labeled **2** into **3** and **4** is consistent with a mechanism involving Claisen-type rearrangement of **2** to give 6-allenyl-1,3-dimethyl-5-hydroxyuracil (**8**), which then rearranges to give either **3** or **4**. An independent synthesis of **8** by photolysis of **4** in chloroform is described, and it is further shown that **8** reverts to **4** at 35° and rearranges to **3** under ionizing conditions. Photolysis of **4** in ethanol affords **3** directly. The 2-propynyl ether of 5-hydroxyuridine rearranges in boiling water to give the corresponding furo[3,2-*d*]pyrimidine nucleoside (**10**). In refluxing toluene, tri-*O*-acetyl-5-(2-propynyloxy)uridine affords the pyrano[3,2-*d*]pyrimidine nucleoside (**11**).

In a recent paper[2] we described a new method for the synthesis of 6-carbon-substituted pyrimidines which involves, as a key step, the Claisen rearrangement of 5-allyloxyuracils to 6-allyl-5-hydroxyuracils. These rearrangements proceed rapidly (10 min) under relatively mild conditions (120°), and this suggested that the corresponding 2-propynyl (propargyl) ethers might also rearrange to products having a newly established carbon–carbon bond at C-6.

Claisen rearrangement of suitable 2-propynyl ethers are known in both the aliphatic and aromatic series.[3] Thus 2-propynyl vinyl ethers rearrange, *via* a cyclic transition state, to allenic carbonyl compounds. Phenyl 2-propynyl ethers afford the corresponding 2*H*-1-benzopyrans (3-chromenes)[4] and these products are apparently formed by rearrangement of an intermediate *o*-allenylphenol.[5] We therefore expected that pyrolysis of 2-propynyl ethers of 5-hydroxyuracils would lead to either 6-allenyl-5-hydroxyuracils or, by further cyclization, to pyrano[3,2-*d*]pyrimidines. At the nucleoside level, these products would serve as intermediates in our program[2] directed toward the synthesis and biological evaluation of 6-substituted pyrimidine nucleosides.

For the present study, the 2-propynyl ether **2** (Scheme I) was prepared by alkylation of 1,3-dimethyl-5-hydroxyuracil (**1**) and subjected to pyrolysis at 130° in a variety of solvents. In dimethylformamide, compound **2** rearranged completely within 60 min, and afforded two products in a ratio of about 10:1. The major component, which crystallized directly from the reaction mixture in 70% yield, was not one of the expected products and was identified as 1,3,6-trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (**3**). The structure of **3** was evident from the nmr spectrum, which shows H-7 as a narrow quartet (δ 6.17) coupled

SCHEME I



(*J* = 0.8 Hz) to the 6-methyl signal at δ 2.45.[6] Compound **3** is identical with a by-product noted during the preparation of **2** from **1** in acetone, and we confirmed that isolated **2** is indeed converted slowly into **3** in acetone at 56°. The minor product formed from **2** in DMF was obtained in larger amounts when the pyrolysis was conducted in DMSO-d_6. The nmr spectrum of the reaction mixture revealed the presence of **3** and showed clearly that the second product was the expected 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione[7] (**4**). In addition to the signals of **3**, this spectrum shows the C-6 protons as a double doublet (δ 4.63 $J_{6,7}$ = 3.8, $J_{6,8}$ = 1.5 Hz) coupled to H-7 and H-8 which each appear as double triplets ($J_{7,8}$

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478).

(2) B. A. Otter, A. Taube, and J. J. Fox, *J. Org. Chem.*, **36**, 1251 (1971).

(3) For reviews covering these rearrangements see (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); (b) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968); (c) H. J. Hansen in "Mechanism of Molecular Migrations," Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971, p 227.

(4) (a) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **11**, 1042 (1963); (b) J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **24**, 2347 (1971); (c) *ibid.*, **23**, 1881 (1970).

(5) J. Zsindely and H. Schmid, *Helv. Chim. Acta*, **51**, 1510 (1968).

(6) (a) Only one example of a furo[3,2-*d*]pyrimidine has been reported previously,[6b] but this was prepared by an ambiguous method and may be a furo[2,3-*d*]pyrimidine. (b) R. G. Jones, *J. Org. Chem.*, **25**, 956 (1960).

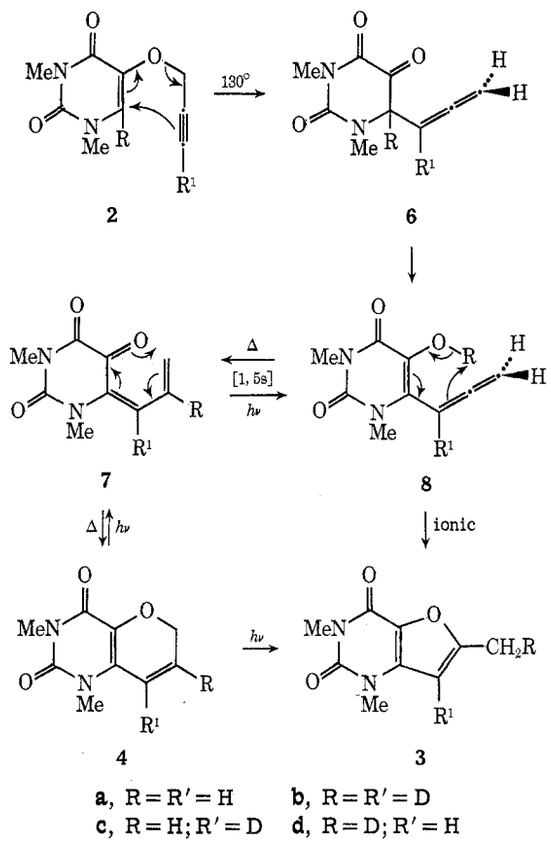
(7) This compound appears to be the first example of the pyrano[3,2-*d*]-pyrimidine ring system.

= 10 Hz), centered at δ 6.25 and 6.65, respectively. These parameters are similar to those reported for 2*H*-1-benzopyran.[8] The relative amounts of the two products (**3** and **4**) formed from **2** in DMSO vary according to the dryness of the solvent. Thus **3** and **4** are formed in nearly equal amounts in DMSO-d_6 containing ~1% of added water, whereas in anhydrous DMSO-d_6 the ratio changes to 3:1 in favor of the pyranopyrimidine **4**. Compound **4** was also obtained as the major product (49% yield) from the pyrolysis of **2** in a nonpolar solvent, namely xylene, and in this case the furopyrimidine **3** was formed in only ~3% yield. The reaction in xylene was not as clear-cut as in DMF and DMSO-d_6 and some decomposition occurred. Moreover, with longer reaction times, the yield of **4** decreased at the expense of a third product (**5**), which appears to be a Diels–Alder adduct formed from two molecules of **4**. Evidence for the basic structure of **5** came from molecular weight determination and from the nmr spectrum, which confirmed that **5** was an asymmetrical dimer. The 220-MHz spectrum showed signals attributable to four methyl groups and eight other protons. The low-field proton (H-8) occurs as a doublet (δ 5.75, $J_{7,8}$ = 7 Hz) coupled to a multiplet (H-7, ~3.28) that is partially obscured by the methyl signals. The 6′ methylene protons were well separated at δ 4.30 and 3.63 (J_{gem} = 12, $J_{6'a,7'} \cong 0$, $J_{6'b,7'}$ = 4 Hz), presumably because of the proximity of the 4-oxo group in both the endo and exo configurations.[9] A two-proton signal at δ 4.14 was assigned to the C-6 methylene protons; the remaining multiplets at δ 3.10 and 2.88 were assigned to H-7′ and H-8′. Step **4** → **5** is reversible, in agreement with the Diels–Alder formulation, and heating **5** in DMSO-d_6 at 130° leads to the partial reappearance of **4** as shown by the nmr spectrum. The furopyrimidine **3**, unlike **4**, is thermally stable and was unchanged during 24 hr in DMSO-d_6 at 130°.

The above results demonstrate that the course of rearrangement of **2** at 130° is markedly dependent on solvent and can be directed to give mixtures in which either **3** or **4** (or **5**) predominate. In contrast, aryl 2-propynyl ethers are reported to give *only* 2*H*-1-benzopyran derivatives when heated in either *N*,*N*-diethylaniline (~215°)[4a,b] or DMF.[4c] However, the mechanism proposed by Zsindely and Schmid[5] to account for the formation of these 2*H*-1-benzopyrans can also be used to account for the formation of both **3** and **4** from **2**. This mechanism (Scheme II) involves a Claisen-type rearrangement (**2** → **6**), followed by enolization to give the 6-allenyl-5-hydroxyuracil **8**. A [1,5] sigmatropic hydrogen shift in **8a** leads to **7a**, which then cyclizes to the pyranopyrimidine **4a**. This sequence predominates in xylene and to a lesser extent in dry DMSO. Alternatively, the allene **8a** can undergo an ionic ring closure to give the furopyrimidine **3a** in a manner similar to the ring closure of *o*-allenylphenol to 2-methylbenzofuran catalyzed by sodium methoxide.[5] This route predominates in DMF, which presumably contains basic impurities, competes favorably in moist DMSO, but becomes negligible in xylene.

As noted above, the rearrangement **2a** → **3a** has no parallel occurrence in the thermal rearrangement of

SCHEME II



2 **6** **7** **8** **4** **3**

a, R = R′ = H **b**, R = R′ = D
c, R = H; R′ = D **d**, R = D; R′ = H

phenyl 2-propynyl ethers.[10] A possible reason for this difference is that the electron-withdrawing effect of the uracil ring in intermediate **8a** would be greater than that of the phenyl ring in the analogous *o*-allenylphenols. The central allene carbon atom in **8a** would therefore be electron deficient relative to the corresponding phenyl compounds, and hence would be more susceptible to nucleophilic attack by the hydroxyl group.

The overall mechanism requires that the acetylenic hydrogen (R′) of **2** becomes located at C-8 of **4** and C-7 at **3**. Similarly, H-6 (R) of **2** becomes H-7 in **4** and incorporates into the methyl group of **3**. The observed incorporation of deuterium into both **3** and **4** is consistent with these requirements. Labeled starting material was prepared by adding sodium deuterioxide and D_2O to a solution of **2a** in DMSO-d_6. This resulted in rapid exchange of both H-6[11] and the acetylenic hydrogen, and afforded **2b** in crystalline form. Pyrolysis of **2b** in DMSO-d_6 at 130° gave the furopyrimidine **3b**, which was characterized by absence of the H-7 signal in the nmr spectrum and the appearance of the deuterated methyl group as a two-proton triplet with $J_{H,D}$ = 2.3 Hz. This product also contained a small amount of monodeuterated material (**3c**), and this could arise

(8) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

(9) As shown by examination of Dreiding models. Diels–Alder condensation can lead to eight isomers and a definitive structure is not offered at this time.

(10) (a) However, Kwart and George[10b] have shown that phenyl 2-propynyl sulfide does rearrange to 2-methylbenzothiopene. This compound is formed in part *via* a mechanism analogous to that above, but the main route involves a thermal thiopropynylic rearrangement (Ph S·CH_2·C:CH → Ph S·CH:C:CH_2) to give phenyl allenyl sulfide, which itself undergoes thio-Claisen rearrangement. Ring closure of the resulting *o*-propynylthiophenol then gives the benzothiophene. These authors further state that thermal propynylic rearrangements do not occur with oxy substrates, and it is therefore unlikely that the furopyrimidine **3** is formed *via* a similar route. (b) H. Kwart and T. J. George, *Chem. Commun.*, 433 (1970).

(11) Base-catalyzed deuterium exchange of H-6 appears to be a general reaction of 1,3,5-trisubstituted 5-hydroxyuracils and is currently under further investigation in this laboratory.

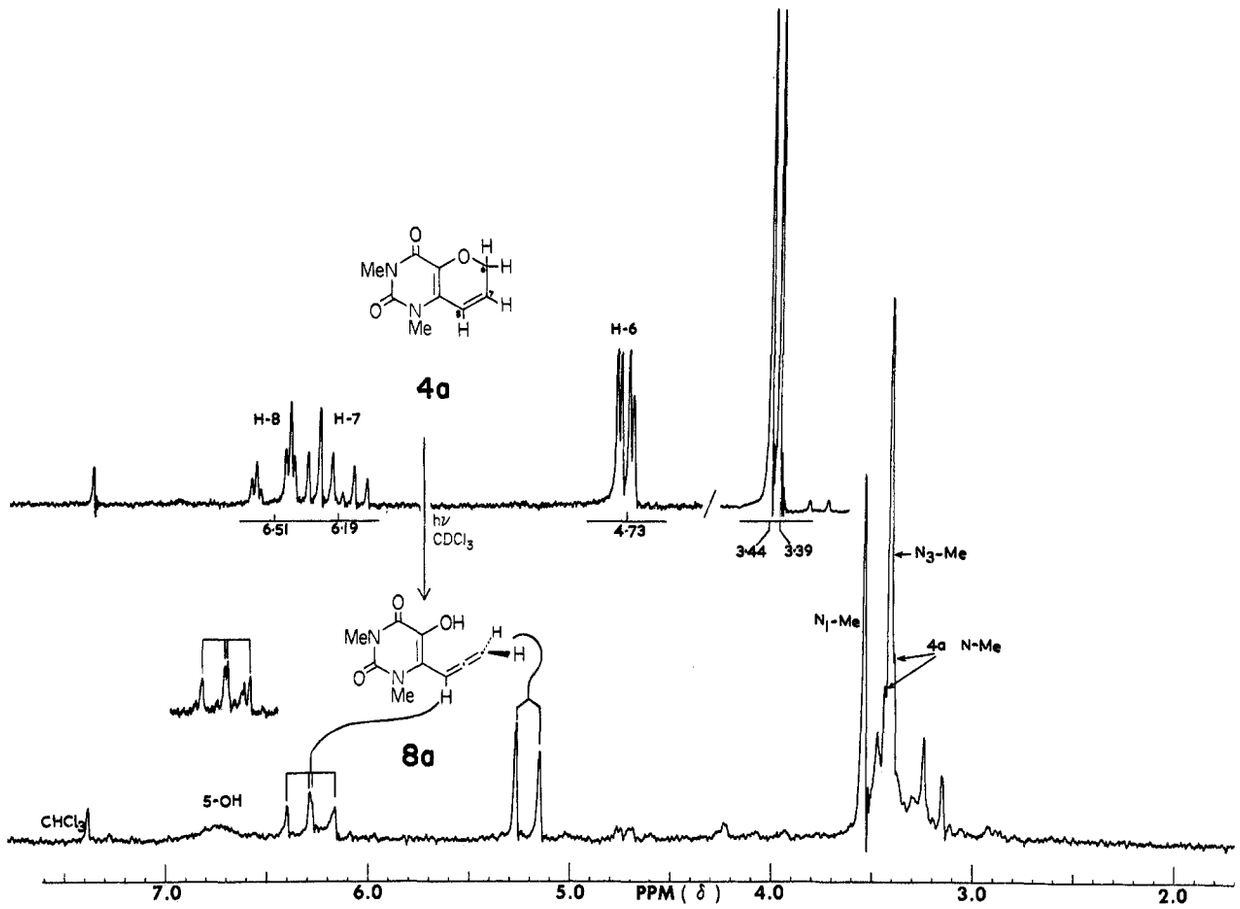


Figure 1.—60-MHz spectrum of compound **4a** in $CDCl_3$ (above) and spectrum obtained with the same solution after 3-hr uv irradiation (below). The 5-OH signal was shifted from ~δ 6.3 by addition of 1 drop of DMSO-d_6. The allenic protons give an AB_2 spectrum in which the ratio $J/\delta_B - \delta_A$ is such (0.11) that the A band appears as a four-line multiplet rather than as a triplet expected for a first-order system [P. L. Corio, *Chem. Rev.*, 60, 363 (1960)]. The inset spectrum, showing the A band multiplicity more clearly, was obtained from a different run.

either from partially deuterated starting material (**2c**) or by reexchange of the **8b** 5-OD group by water invariably present in DMSO-d_6. Pyrolysis of **2b** in xylene afforded the 7,8-dideuterio compound **4b**, as required by the mechanism, but this product was accompanied by substantial amounts of the monodeuterated **4c**. Again, this could be formed from **2c** or from **8c** generated by reexchange of **8b**, although the source of hydrogen in this case is not clear.

Further evidence for the mechanism shown in Scheme II was obtained from a study of the photochemistry of the pyranopyrimidine **4**. This study was undertaken because of the serendipitous finding that storage of dilute alcohol solutions of **4** under fluorescent lighting for several days resulted in a gradual shift of the uv absorption maximum from 350 (**4**) to ~280 mμ, a value close to that of the furopyrimidine **3**.[12] Controlled irradiation of **4** (2×10^{-4} *M*) in ethanol, using a high-pressure mercury lamp, afforded a set of uv-spectral curves passing through isosbestic points and a final curve (20 min) identical with the spectrum of **3**. On a preparative scale, crystalline **3** was isolated in 90% yield. No intermediates were observed spectrally in the photolysis of **4** in ethanol, but irradiation in methanol resulted in the rapid appearance of a broad peak at 315 mμ which subsequently disappeared in a dark reaction to form **3**. This difference may be caused by the presence of water in the ethanol solutions of **4**. The absorption at 315 mμ also appeared when **4** was irradiated in chloroform, and by conducting the photolysis in deuteriochloroform it was possible to monitor the formation of the intermediate by nmr spectroscopy. After 2 hr, the nmr spectrum (Figure 1) shows a major product which gives rise to a hydroxyl signal, and a doublet at δ 5.21 coupled to a four-line multiplet at δ 6.28. The multiplicity and large coupling constant[3a] (7.0 Hz) is fully consistent with the allene structure **8a** for the photointermediate. This assignment is supported by the ir spectrum of the reaction mixture, which shows a hydroxyl peak at 3450 cm^{-1} and peaks at 1930 and 1960 cm^{-1} characteristic[3a] of allenes. The first step in the ring contraction **4a** → **3a** presumably involves the formation of intermediate **7a**; a similar ring opening has been proposed previously[13] to account for the formation of colored photoproducts from 2*H*-1-benzopyrans. A photochemical [1,5] hydrogen shift then converts **7a** into allene **8a**,[14] the postulated inter-

(12) A similar, but smaller difference is seen in the uv spectra of 2*H*-1-benzopyrans (λ_{max} ~310 mμ, ref 4) and benzofuran [λ_{max} 244, 281 mμ: G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 3438 (1956)].

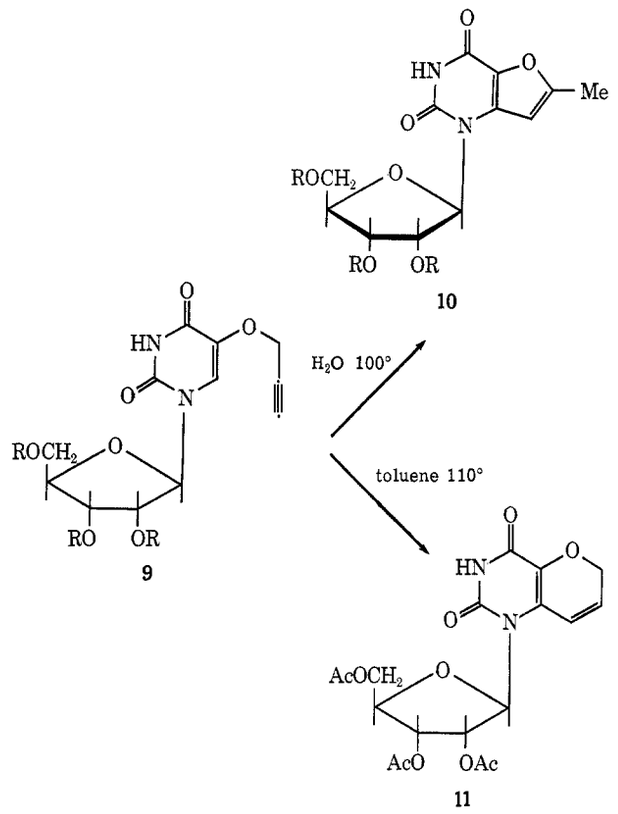
(13) J. Kolc and R. S. Becker, *J. Phys. Chem.*, **71**, 4045 (1967).

(14) Similar photochemical formation of allenes involving 1,5 hydrogen shifts has been observed previously with acyclic conjugated trienes [for example, H. Prinzbach and E. Druckrey, *Tetrahedron Lett.*, 2959 (1965), and references cited therein] and conjugated dienoic acids [K. J. Crowley, *J. Amer. Chem. Soc.*, **85**, 1210 (1963), discussed in R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 32].

mediate in the thermal rearrangement of **2**. Allene **8a** was detected on thin layer chromatograms as a ferric chloride positive spot but an attempt to isolate it by preparative chromatography was unsuccessful. It was not possible, therefore, to subject compound **8a** to the pyrolytic conditions described earlier. However, **8a** does revert slowly to pyranopyrimidine **4a** when kept overnight at the nmr probe temperature (~35°), and can be converted into **3** by dilution of the deuteriochloroform solution with ethanol or methanol. Addition of sodium deuterioxide to the solution of **8a** resulted in instantaneous deuteration of the 5-OH group and very rapid ring closure of the resulting **8d** to **3d**.[15] Compound **3d** was identified from the nmr spectrum, which shows the deuteriomethyl signal as a six-line multiplet ($J_{H,D}$ = 2.3, $J_{allylic}$ = 0.8 Hz), and by comparison of the uv spectrum and chromatographic mobility with **3a** prepared by pyrolysis of **2a**.

Extension of these pyrolysis procedures to the uridine series has led to the synthesis of both furo- and pyrano-[3,2-*d*]pyrimidine nucleosides. The 2-propynl ether **9** (R = H, Scheme III) was prepared by selective alkylation of 5-hydroxyuridine. That **9** contains an O-5 rather than an N-3 alkyl substituent was confirmed by a negative ferric chloride test, and by the uv spectrum which failed to show the bathochromic shift (~280 → 305 mμ) in alkali with results from ionization of the 5-hydroxy group in 1,3-disubstituted 5-hydroxyuracils.[16] Compound **9** (R = H) rearranged smoothly in boiling water to give the corresponding furopyrimidine **10**, which was identified by comparison of the uv and nmr spectral parameters with **3**. The pyranopyrimidine **11** was not observed in this solvent, as would be expected from the mechanism. Refluxing the tri-*O*-acetate (**9**, R = $COCH_3$) in toluene, however, afforded an amorphous product whose nmr and uv characteristics (compared with **4**) were fully consistent with the pyranopyrimidine structure **11**. Studies on the chemistry of nucleosides **10** and **11** are currently in progress.

SCHEME III



Experimental Section

General Procedures.—Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet, infrared, and nuclear magnetic resonance spectra were determined on Unicam SP800, Perkin-Elmer Infracord, and Varian A-60 spectrometers, respectively. Nmr data for compound **5** were obtained with a Varian HR-200 instrument at Rockefeller University; in all cases first-order values are given for chemical shifts (δ, measured from internal tetramethylsilane) and coupling constants (hertz, obtained from spectra recorded at expanded sweep widths). Ultraviolet irradiations were carried out with a Hanovia 450-W high-pressure mercury lamp equipped with a Pyrex filter. Thin layer chromatography was performed on Merck silica gel GF_{254}; preparative separations were carried out on 20 × 20 cm plates coated with 30 g of silica gel PF_{254}. All evaporations were carried out under reduced pressure. Microanalyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

1,3-Dimethyl-5-(2-propynyloxy)uracil (2).—Propargyl bromide (23.8 g, 0.2 mol) and potassium carbonate (13.8 g, 0.1 mol) were added to a solution of 1,3-dimethyl-5-hydroxyuracil[17] (**1**) (15.6 g, 0.1 mol) in acetone (300 ml). The mixture was stirred and refluxed for 14 hr, at which time tlc (EtOAc–benzene, 4:1, $FeCl_3$ spray) indicated absence of starting material. The solids were removed and the filtrate was concentrated to give several crops (14 g, 72%) of crystalline material, mp 137–139°. Recrystallization from acetone afforded pure **2**: mp 140–142°; uv λ_{max}^{EtOH} 278, λ_{min} 245 mμ; ir (KBr disc) 3250 (≡CH stretch) and 2130 cm^{-1} (C≡C stretch); nmr (DMSO-d_6) δ 7.64 (s, 1, H-6), 4.65 (d, 2, CH_2, J = 2.4 Hz), 3.57 (t, 1, CH), 3.30 (s, 3, NCH_3), and 3.18 ppm (s, 3, NCH_3); nmr ($CDCl_3$) δ 7.15 (s, 1, H-6), 4.70 (d, 2, CH_2, J = 2.4 Hz), 3.39 and 3.34 (s, 6, $N_{1,3}CH_3$), and 2.56 ppm (t, 1, CH). The propynyl signals are closely similar to those reported[18] for phenyl-2-propynyl ether (CCl_4, CH_2, d at δ 4.63 and CH, t at δ 2.35 ppm, J = 2.4 Hz).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.62; H, 5.09; N, 14.46.

A final crop (1.6 g) of crystals, mp 108–110°, obtained from the concentrated reaction mixture was shown (nmr) to be a mixture of **2** and **3**.

Rearrangement of 2 in DMF. Preparation of 1,3,6-Trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (3).—A solution of **2** (3 g) in 25 ml of analytical grade DMF was kept at 130° for 1 hr. The crystals that separated on cooling were collected and washed with petroleum ether (bp 30–60°). Recrystallization from hot ethanol afforded pure **3** (2 g, 66%): mp 210–211°; uv λ_{max}^{EtOH} 281, 241 sh, λ_{min} 258, 234 mμ; nmr ($CDCl_3$) δ 6.17 (q, 1, H-7, J_{7,CH_3} = 0.8 Hz), 3.41 and 3.45 (two singlets, 6 protons,

(15) A similar attempt to follow the incorporation of deuterium from **8d** into the pyranopyrimidine led to some interesting results. Compound **8d** was prepared *in situ* by adding a drop of D_2O to the $CDCl_3$ solution containing **8a**, and kept at room temperature for 36 hr. The nmr spectrum then showed the presence of residual **8d**, the furopyrimidine **3d**, and some nondeuterated pyranopyrimidine (**4a**), which must have been formed from **8a** *via* reexchange of the **8d** 5-OD group by HOD present in the reaction mixture. None of the expected deuterated pyranopyrimidine **4d** was observed. In contrast, a control experiment where **8a** was treated with water instead of D_2O showed that all the allene had disappeared in 36 hr and that pyranopyrimidine **4a** was the sole rearrangement product. These results indicate that the rate of the conversion **8d** → **4d** is so slow relative to the nondeuterated case that furopyrimidine formation becomes competitive under these conditions. A similar conclusion follows from pyrolysis of the dideuterated 2-propynyl ether **2b** in DMSO-d_6, which leads *only* to the dideuterated furopyrimidine **3b**; the same experiment with **2a** leads to both **3a** and **4a**. The magnitude of these effects seems to be too great to attribute solely to the deuterium isotope effects expected in the various steps leading to **4**, and merits further study.

(16) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(17) Prepared according to the procedure described for the corresponding 3-benzyl-1-methyl compound.[16]

(18) M. P. Simonnin, *C. R. Acad. Sci.*, **257**, 1075 (1963).

N-methyls), and 2.45 ppm (d, 3, 6-CH_3); nmr (DMSO-d_6) δ 6.65 (narrow m, 1, H-7, J_{7,CH_3} not fully resolved), 3.35 and 3.21 (two singlets, 6 protons, *N*-methyls), and 2.41 ppm (broadened s, 3, 6-CH_3).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.54; H, 5.10; N, 14.31.

On a smaller scale, the rearrangement of **2** (40 mg) in 0.4 ml of DMF was monitored using nmr spectroscopy. The H-6 (δ 7.67) and CH_2 (4.71) signals of **2** (the remaining signals being obscured by DMF peaks and side bands) disappeared within 1 hr, and were replaced by peaks (H-7, δ 6.67; 6-CH_3, δ 2.47) corresponding to **3**. A small double doublet at δ 4.68 was subsequently identified as the 6-methylene signal of compound **4**. By integration, the **3**:**4** ratio was 10:1.

Rearrangement of 2 in Xylene. Preparation of 1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (4) and Adduct 5. Run A.—A solution of **2** (1.0 g) in xylene (20 ml) was kept at 130° for 2 hr, at which time tlc (EtOAc–benzene, 4:1) indicated complete loss of starting material. The yellow solution was concentrated to dryness and the residue was dissolved in chloroform. Fractionation of this mixture on four thick layer chromatography plates (EtOAc–benzene, 4:1) and elution of the uv-absorbing zones afforded three fractions (a–c). The nmr spectrum ($CDCl_3$) of the fastest moving component (fraction a, 66 mg) showed it to be a complex mixture containing about 50% of compound **3**. The yield of **3** was therefore ~3%. Concentration of fraction b afforded compound **4** as yellow crystals (485 mg, 48.5%): mp 202–204°; uv λ_{max}^{EtOH} 350, λ_{min} 282 mμ; nmr ($CDCl_3$) δ 6.51 (double triplets, 1, H-8, $J_{8,7}$ = 10 Hz), 6.19 (double triplets, 1, H-7), 4.73 (d d, 2, H-6a,b, $J_{6,8}$ = 1.2, $J_{6,7}$ = 3.8 Hz), and 3.44 and 3.39 ppm (two singlets, 6 protons, *N*-methyls).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.62; H, 5.09; N, 14.46.

Concentration of the remaining fraction (c, R_f ~0) and recrystallization of the dark residue from CH_2Cl_2–EtOH afforded adduct **5** as colorless crystals (268 mg, 27%) which melted indistinctly at 240–246° dec (yellows from 200°): mol wt, found 377 (osmotic pressure), calcd 388; uv λ_{max}^{EtOH} 278, sh 305, λ_{min} 250 mμ; nmr (220 MHz, $CDCl_3$) δ 5.75 (d, 1, H-8, $J_{7,8}$ = 7 Hz), 4.30 (d, 1, H-6′a, J_{gem} = 12, $J_{6'a,7'} \cong$ 0 Hz), 4.14 (m, 2, H-6a, H-6b), 3.63 (q, 1, H-6′b, $J_{6'b,7'}$ = 4 Hz), 3.23 (s, 3, *N*-methyl), 3.10 [4, *N*-methyl superimposed on H-7′ (or H-8′)], and 2.88 ppm [m, 1, H-8′ (or H-7′)]. The remaining protons appeared as a seven-proton group in which two *N*-methyl singlets (δ 3.30 and 3.29) overlapped the H-7 multiplet. Compound **5** was unstable at 130° in DMSO-d_6, as shown by the partial reappearance of signals corresponding to **4** in the nmr spectrum.

Anal. Calcd for $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.68; H, 5.14; N, 14.41.

Run B.—A sample of **2** (1.75 g) was heated in 35 ml of xylene at 130° for 4 hr (instead of 2 hr as above). Concentration of the reaction mixture and fractionation of the residue on a column containing 200 g of Merck silica gel G afforded 407 mg (23%) of compound **4** (eluted with EtOAc–benzene, 4:1) and 713 mg (41%) of compound **5** (eluted with EtOAc–MeOH, 4:1).

Rearrangement of 2 in Acetone.—A solution of **2** (225 mg) in acetone (10 ml) was refluxed for 90 hr and then concentrated to dryness. The nmr spectrum ($CDCl_3$) of the residue showed peaks corresponding to starting material (**2**) and the furopyrimidine **3** in the ratio (by integration) of 6:1.

Rearrangement of 2 in DMSO-d_6.—A sample of **2** (40 mg) in an nmr tube was dissolved (under nitrogen) in 0.4 ml of anhydrous DMSO-d_6. The tightly stoppered tube was heated at 130° in a silicon–oil bath for 45 min, at which time the nmr spectrum showed absence of starting material and presence of **3** and **4**. Integration of the spectrum indicated a **3**:**4** ratio of 1:3. A repeat of this experiment using DMSO-d_6 containing 1% of added water gave a **3**:**4** ratio of 1:1.

1,3-Dimethyl-5-(2-propynyloxy)uracil-6,3′-d_2 (2b).—Two drops of 1 *N* sodium deuterioxide solution was added to a solution of **2a** (125 mg) in 1 ml of DMSO-d_6. After ~1 min the solution was neutralized with 1 *N* DCl, diluted with 2 ml of D_2O, and then cooled. The resulting crystals were washed thoroughly with D_2O and then dried (100°, P_2O_5). The yield of **2b** was 90 mg: mp 139–142°; nmr (DMSO-d_6) δ 4.65 (s, 2, CH_2), 3.30 (s, 3, NCH_3), and 3.18 ppm (s, 3, NCH_3). The original H-6 resonance was just visible at high spectrum amplitudes, indicating that **2c** was present in trace amounts.

1,3,6-Trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione-6α,-7-d_2 (3b).—The nmr solution from above (35 mg of **2b** in 0.4 ml of DMSO-d_6) was heated at 130° for 45 min. The nmr spectrum of the cooled solution indicated that the pyranopyrimidine **4** was absent (*cf.* pyrolysis of **2a** in DMSO-d_6 above) and that the product was the furopyrimidine **3b**. Since the deuteriomethyl signal was partially obscured by the residual CD_2H–solvent peaks, the product was precipitated with water, dried, and dissolved in $CDCl_3$. The nmr spectrum of this solution showed δ 3.45 (s, 3, NCH_3), 3.41 (s, 3, NCH_3), and 2.43 ppm (t, 2, CH_2D, $J_{H,D}$ = 2.3 Hz). A small peak at δ 2.45, partially overlapped by the $-CH_2D$ triplet, indicated the presence of **3c**. The small chemical shift difference (0.8 Hz, measured at 100 Hz sweep width) between the **3b** CH_2D and **3c** CH_3 signals is consistent with previous studies.[19]

1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione-7,8-d_2 (4b) and 1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*-3*H*]-dione-8-*d* (4c).—Pyrolysis (130°) of 170 mg of **2b** in 3.5 ml of xylene for 3 hr, and isolation of the pyranopyrimidine component as in the preparation of **4a** (run A) above, afforded a mixture of **4b** and **4c** with the following nmr spectrum ($CDCl_3$): δ 6.20 (broad t, 0.4, H-7 of **4c**), 4.73 (2, 6-methylene singlet of **4b** overlapping 6-methylene doublet of **4c**), and 3.44 and 3.39 ppm (two singlets, six protons, **4b** and **4c** *N*-methyls). The line widths of the H-7 signal (2.5 Hz) of **4c** indicate a substantial H-7–D-8 coupling constant (expected $J \cong$ 1.5 Hz). Similarly, broadening of the 6-methylene singlet of **4b** (width at half-height = 1.5 Hz, height = 6 cm; *cf.* width of *N*-methyl singlets = 1.0 Hz, height = 25 cm) indicates vicinal and possibly long-range coupling of H-6 with D-7 and D-8.

Photolysis of 4 in Ethanol.—A 2×10^{-4} *M* solution of **4** in ethanol (unprotected from moisture) was irradiated for five 4-min periods. Uv spectral examination at the end of each irradiation period revealed gradual loss of the original absorption (350 mμ) and appearance of a new peak at 281 mμ. Serial curves passed through isosbestic points at 248 and 303 mμ, and the final curve (20 min) was identical with the spectrum of **3**.

For preparative purposes, a solution of **4** (40 mg) in ethanol (200 ml) was irradiated for 1 hr. Concentration of the solution afforded crystalline material (36 mg, 90%), identical (nmr, mixture melting point) with **3** prepared by rearrangement of **2**.

Photolysis of 4 in Methanol.—The uv spectrum obtained after irradiation of **4** in methanol (2×10^{-4} *M*) for 6 min showed a broad peak with λ_{max} 315, λ_{min} 265 mμ. On standing, this peak gradually descreased (half-life ~1 hr) with the concomitant appearance (isosbestics at 291.5 and 237 mμ) of absorption at 281 mμ corresponding to **3**.

Photolysis of 4 in Deuteriochloroform. Preparation of 6-Allenyl-1,3-dimethyl-5-hydroxyuracil (8a).—A sample of **4** (30 mg) was dissolved in $CDCl_3$ (0.5 ml) in an nmr tube, and the solution was irradiated with the tube ~1 cm from the lamp. Nmr monitoring showed that a 2.5–3-hr period was required for almost complete disappearance of **4**. A typical spectrum recorded after 3 hr of irradiation is reproduced in Figure 1; parameters for **8a** measured from the original spectrum are δ ~6.7 (broad peak, 5-OH, shifted from ~6.3 by addition of 1 drop of DMSO-d_6), 6.28 (four-line m, $-CH=$), 5.21 (d, $=CH_2$, J = 7 Hz), 3.53 (s, N_1CH_3), 3.40 ppm (s, N_3CH_3). A sample of the 3-hr reaction mixture diluted with $CDCl_3$ showed peaks at 3450 (OH) and 1930 and 1960 cm^{-1} (allene) in the ir spectrum. Storage of the reaction mixture at ~35° (nmr probe) resulted in complete disappearance of the **8a** signals, and reappearance of signals corresponding to **4**, within a 14-hr period.

Conversion of 8a into 3. A. In Alcohols.—The initial uv spectrum obtained after dilution of the $CDCl_3$ solution containing **8a** with ethanol showed a broad peak with λ_{max} 314, λ_{min} 265 mμ, which rapidly decreased (half-life ~10 min) with simultaneous formation of absorption at 281 mμ corresponding to **3**. Dilution of the $CDCl_3$ solution of **8a** with methanol caused a much slower disappearance of the 314-mμ peak (half-life ~1 hr), with the overall transformation to **3** (isobestics at 237, 291.5 mμ) closely resembling the curves obtained above in the photolysis of **4** in methanol.

B. In Alkali.—Addition of ~0.01 ml of 1 *N* NaOD in D_2O to the $CDCl_3$ solution containing **8a** resulted in almost instantaneous appearance of peaks corresponding to **3d**. Pure material was isolated by thick layer chromatography: nmr ($CDCl_3$) δ 6.17 (narrow m, H-7), 3.41, 3.45 (two singlets, 6 protons,

(19) See J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Spectroscopy," Vol. 2, Pergamon Press, Elmsford, N. Y., 1966, p 1092.

N-methyls), and 2.44 ppm (six-line m, 2, CH_2D, $J_{allylic}$ = 0.8, $J_{H,D}$ = 2.3 Hz); uv λ_{max}^{EtOH} 281, 241 mμ (sh).

5-(2-Propynyloxy)uridine (9, R = H).—Propargyl bromide (19.04 g 0.16 mol) was added to a solution of 5-hydroxyuridine[20] (20.8 g 0.08 mol) in 50% aqueous methanol (500 ml) containing sodium hydroxide (3.2 g 0.08 mol). The mixture was stirred at room temperature for 10 hr, by which time most of the starting material had reacted (tlc, CH_2Cl_2–MeOH, 5:1; $FeCl_3$ spray). Removal of solvent and crystallization of the syrupy residue from methanol afforded 14.7 g (61%) of product, mp 152–153°. A single recrystallization gave pure material: mp 155–156°; uv (pH 1) λ_{max} 276, λ_{min} 242 mμ; (pH 12) λ_{max} 275, λ_{min} 252 mμ; nmr (DMSO-d_6–D_2O) δ 7.80 (s, 1, H-6), 5.81 (m, 1, H-1′), 4.67 (d, 2, $-OCH_2-$, J = 2.3 Hz), ~4.27–3.55 (m, HOD + H-2′, 3′, 4′, 5′a, 5′b), and 3.49 ppm (t, 1, CCH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.16; H, 4.80; N, 9.46.

Tri-*O*-acetyl-5-(2-propynyloxy)uridine (9, R = $COCH_3$).—Acetylation of **9** (R = H) (1.5 g) in acetic anhydride (5 ml)–pyridine (20 ml) for 1 hr at room temperature, and isolation of the product by the standard chloroform extraction and washing procedure, afforded the tri-*O*-acetate as a chromatographically pure amorphous foam (2.1 g, 89%): nmr ($CDCl_3$) δ 7.43 (s, 1, H-6), 6.20 (m, 1, H-1′), 5.37 (m, 2, H-2′ and H-3′), 4.72 d (1, $-OCH_2-$, J = 2.2 Hz), 4.37 (broad s, 3, H-4′ and H-5′a,b), 2.66 (t, 1, CH), and 2.20, 2.12, and 2.10 (three singlets, 9 protons, acetyls). This compound contained considerable amounts of entrapped chloroform which was not removed on storage at 40° under vacuum for 24 hr. At higher temperatures, darkening and partial rearrangement to **11** took place. The nmr spectrum showed more $CHCl_3$ than did a $CDCl_3$ blank run at the same amplitude; the presence of $CHCl_3$ was confirmed by elemental analysis.

Anal. Calcd for $C_{18}H_{20}N_2O_{10}\cdot 0.13\ CHCl_3$: C, 49.50; H, 4.61; N, 6.37; Cl, 3.29. Found: C, 49.52; H, 4.55; N, 6.13; Cl, 3.29.

1-(β-D-Ribofuranosyl)-6-methylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (10, R = H). Method A.—A solution of **9** (R = H) (1 g) in DMSO (20 ml) was heated at 135° for 1.5 hr. Concentration of the solution to a semisolid (bath 55–60°) and recrystallization from hot water furnished 835 mg (83.5%) of **10** (R = H): mp 246–248°; uv (pH 1) λ_{max} 248, 280, λ_{min} 233, 257; (pH 12) λ_{max} 242 sh, 282; λ_{min} 259 mμ; nmr (DMSO-d_6) δ 10.45 (s 1, NH), 6.95 (broadened s, 1, H-7 allylic coupling not resolved), 5.93 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), ~5.33–4.90 (m, 3, hydroxyls), ~4.50–4.00 (m, 2, H-2′, H-3′), ~4.00–3.50 (m, 3, H-4′, H-5′a,b), and 2.45 ppm (broadened s, 3, 6-CH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.10; H, 4.79; N, 9.19.

Method B.—A solution of **9a** (3 g) in water (75 ml) was refluxed for 3.5 hr (tlc, CH_2Cl_2–MeOH, 5:1). The concentrated solution deposited 2.66 g (88%) of **10** (R = H), mp 246–247°.[21]

1-(Tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (11).—A solution of **9** (R = $COCH_3$) (400 mg) in toluene (20 ml) was refluxed for 3.5 hr, at which time all the starting material had rearranged as shown by the nmr spectrum of an evaporated sample of the reaction mixture. Removal of solvent afforded **11** as an amorphous, yellow solid. Thick layer chromatography (EtOAc–benzene, 4:1; zone eluted with $CHCl_3$) afforded the analytical sample as a rigid foam: uv (pH ~1) λ_{max}^{EtOH} 341, λ_{min} 276; (pH ~ 12) λ_{max}^{EtOH} 343, λ_{min} 294 mμ; nmr ($CDCl_3$) δ 6.55 (m, 1, H-8, $J_{7,8}$ = 10 Hz, $J_{6,8}$ not fully resolved), 6.10 (double triplet, 1, H-7, $J_{6,7}$ = 4 Hz), 5.87–5.25 (m, 3, H-1′, 2′, 3′), 4.68 (dd, 2, H-6a,b, $J_{6,8}$ ~1 Hz), ~4.50–4.08 (m, 3, H-4′,5′a,b), and 2.09 ppm (s, 9, acetyls). Chloroform entrapped in this compound was not removed during 24 hr at 40° under vacuum. Partial decomposition took place at higher temperatures as reflected by darkening and appearance of a peak at ~450 mμ in the uv spectrum at pH 12. Nmr and elemental analysis indicated chloroform.

Anal. Calcd for $C_{18}H_{20}N_2O_{10}\cdot 0.17CHCl_3$: C, 49.08; H, 4.57; N, 6.30; Cl, 4.06. Found: C, 48.81; H, 4.86; N, 5.90; Cl, 3.93.

Registry No.—**2**, 35042-03-6; **3**, 35042-04-7; **4**, 35042-05-8; **5**, 35042-06-9; **9** (R = H), 35042-07-0; **9** (R = $COCH_3$), 35042-08-1; **10** (R = H), 35042-09-2; **11**, 35042-10-5.

(20) D. W. Visser in "Synthetic Methods in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 428.

(21) Boiling water is also the solvent of choice for the Claisen rearrangement of 5-allyloxyuridine to 6-allyl-5-hydroxyuridine (>90% yield). The rearrangement in boiling DMF (79% yield) has been reported[2] previously.

Aminoacyl Derivatives of Nucleosides, Nucleotides, and Polynucleotides. XIV. A General Synthesis of Adenosine 2′(3′)-*O*-Peptidyl Derivatives[1]

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Reaction of the adenosine 2′(3′)-*O*-L-phenylalanyl, -L-leucyl, and -L-alanyl derivatives (**1a–c**) with 5-chloro-8-hydroxyquinoline esters of protected amino acids or dipeptide (**2b–e**) affords the protected adenosine 2′(3′)-*O*-peptidyl derivatives (**3b, 3c, 3g, 3e** and **3f**) in good yields. Removal of protecting groups gives 2′(3′)-*O*-L-phenylalanylphenylalanyl, -L-lysylphenylalanyl, -L-phenylalanylleucyl, -L-leucylalanyl, and -L-serylphenylalanylphenylalanyl adenosines (**3i–m**) in excellent yields. Similarly, 5-chloro-8-hydroxyquinoline acetate (**2a**) acylates 2′(3′)-*O*-L-phenylalanyl adenosine (**1a**) and 2′(3′)-*O*-L-leucyladenosine (**1b**) to give 2′(3′)-*O*-(*N*-acetyl-L-phenylalanyl)-adenosine (**3a**) and 2′(3′)-*O*-(*N*-acetyl-L-leucyl)adenosine (**3d**) in high yields. The usefulness of the described acylation reaction for the synthesis of peptidyl or *N*-acylaminoacyl oligoribonucleotides is discussed.

The 2′(3′)-*O*-aminoacyl derivatives of nucleosides and oligonucleotides may be used as suitable substrates in investigation of the mechanism of the transpeptidation process in ribosomal systems.[3,4] The adenosine 2′,3′-*O*-bisaminoacyl derivatives and 2′(3′)-*O*-peptidyl derivatives represent potential substrates for detailed investigations of the formation of the peptide bond on ribosomes.[5]

In the present paper, we report a general synthesis of adenosine 2′(3′)-*O*-peptidyl derivatives starting from 2′(3′)-*O*-aminoacyladenosines[6] as key intermediates. An earlier paper of this series[7] described the preparation of adenosine 2′(3′)-*O*-peptidyl derivatives con-

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