Nucleic Acid Related Compounds. 39. Efficient Conversion of 5-Iodo to 5-Alkynyl and Derived 5-Substituted Uracil Bases and Nucleosides[1]

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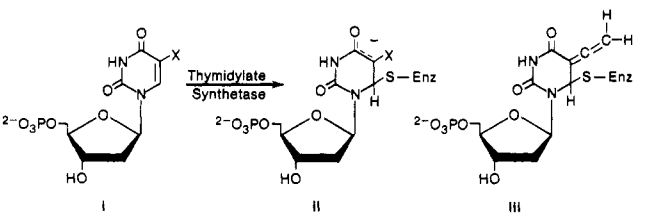
Coupling of terminal alkynes with 5-iodo-1-methyluracil and 5-iodouracil nucleosides (protected as their *p*-toluyl esters) proceeded in high yields in the presence of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide in warm triethylamine. Several of the subsequently deprotected 5-alkynyl-2′-deoxyuridines, including the parent 5-ethynyl-2′-deoxyuridine, had antiviral activity, and their 5′-monophosphates inhibited thymidylate synthetase. Hydrogenation of the 5-alkynyl side chain can be controlled to give (*Z*)-5-alkenyl- or the saturated 5-alkyl-2′-deoxyuridines. This provides a stereocontrolled route to the known 5-ethyl- and 5-*n*-hexyl-2′-deoxyuridines as well as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU). Hydration of the triple bond gave the corresponding uracil-5-alkanone products in favorable cases.

A broad spectrum of biological activity has been described for 5-substituted uracil bases and nucleosides. The well-known cancer chemotherapeutic drug 5-fluorouracil and antiviral agents 5-iodo-2′-deoxyuridine and 5-(trifluoromethyl)-2′-deoxyuridine have been in clinical use for a number of years. More recently a variety of 5-substituted 2′-deoxyuridine derivatives have been synthesized and evaluated as antiherpes agents.[3] One highly potent and selective antiviral drug of this class, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU),[4] is presently undergoing clinical evaluation. The herpes simplex genome codes for a thymidine kinase with a substrate tolerance that readily accepts 5-substituents as large as the 2-bromoethenyl side chain.[5]

Pronounced cytotoxicity and significant antiviral activity have been reported for 5-ethynyl-2′-deoxyuridine.[4,6,7] Inhibition of thymidylate synthetase by 5-ethynyl-2′-deoxyuridylate also has been noted.[6,8,9] Enzymes including 2′-deoxyuridylate hydroxymethylase[10] and aminoacyl transfer ribonucleic acid synthetases[11] as well as the extensively studied thymidylate synthetase[12] are thought to function by initial Michael attack of an enzyme-bound nucleophile (probably the sulfhydryl group of a cysteine) at C6 of the enone system of uracil. Attack of the enolate anion of the initial adduct (ii, X = F) of 5-fluoro-2′-deoxyuridylate (i, X = F) with thymidylate synthetase occurs on $N^{5,10}$-methylenetetrahydrofolate to give a covalent ternary complex (enzyme–drug–cofactor).[12] Michael



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attack of the enzyme at C6 of 5-ethynyl-2′-deoxyuridylate (i, X = C≡CH) has been postulated to result in transient formation of a highly reactive α-keto allene system (iii).[8,9,13]

Syntheses of 5-ethynyl-2′-deoxyuridine had previously involved construction of the heterocycle, coupling with a functionalized 2-deoxy sugar, and separation of the resulting anomeric mixture.[6,14] We now report details of a convenient and high-yield coupling procedure[1b] that provides direct access to 5-alkynyluracil bases and nucleosides from terminal alkynes and readily available[15] 5-iodouracil derivatives. Several of these 5-alkynyluracil nucleosides have antiviral activity,[16] and the derived 5-alkynyl-2′-deoxyuridylates inhibit thymidylate synthetase.[9] Transformations of the alkynyl side chain have been explored briefly to give BVDU and other alkenyl, alkyl, and alkanone substitutents.

Bergstrom[17] first applied the palladium-catalyzed coupling of alkenes with 5-mercuri or 5-iodo derivatives of uracil nucleosides, on the basis of the pioneering studies of Heck.[18] Daves,[19] Jones and Walker,[20] Mertes,[21] and their co-workers have since reported syntheses of C5-linked uracil nucleosides with carbon side chains based on these precedents. Bergstrom had reported[17b] that attempts to couple 5-chloromercuri- or 5-iodouridine with phenylacetylene by using Heck's procedures gave starting uridine or a complex mixture. Sonogashira et al.[22] had described a modified approach by including a copper(I) catalyst for coupling terminal alkynes with aryl and vinyl halides. Edo

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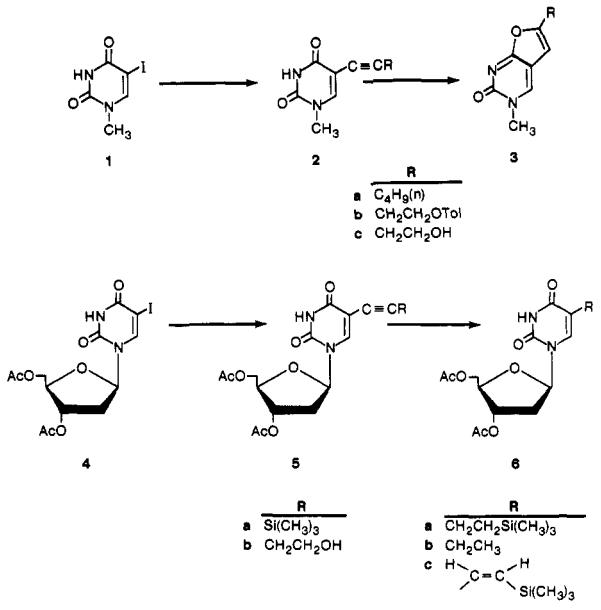
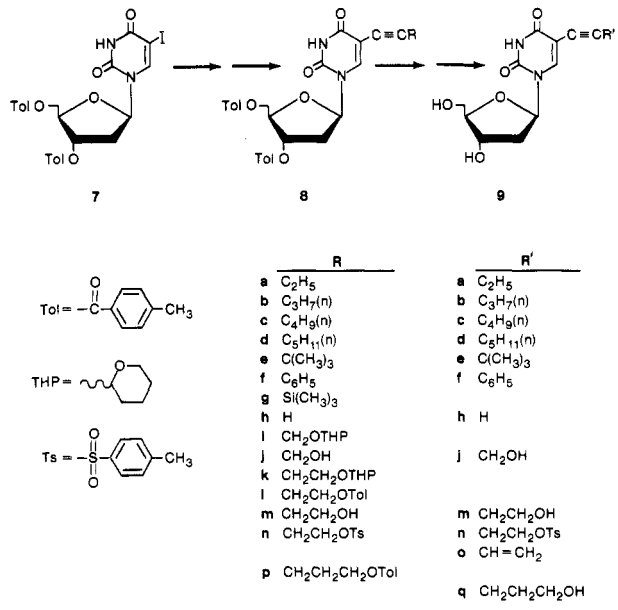
Scheme I



Scheme II



and co-workers[23] had applied this method to substituted nitrogen heterocycles. Our adaptation of this general procedure allowed smooth and efficient coupling of terminal alkynes with 5-iodo-1-methyluracil and protected 5-iodouracil nucleosides under mild conditions.[1b] A more complex coupling sequence that results in variable product yields has since been noted by Pichat.[24]

Treatment of 5-iodo-1-methyluracil (1) with hexyne[1c] in triethylamine at 50 °C for 2 h in the presence of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide under a nitrogen atmosphere gave an 84% yield of 5-hexynyl-1-methyluracil[1c] (**2a**) (see Scheme I) after processing and column chromatography over silica. A 9% yield of the fluorescent 6-*n*-butyl-3-methylfurano[2,3-*d*]-pyrimidin-2-one (**3a**) was recovered from later column fractions. Treatment of **2a** with CuI in triethylamine/methanol at reflux gave **3a** in 92% yield. Similar cyclizations have been noted in Stephens–Castro couplings of *o*-iodoanilines with copper(I) acetylides[25] and by treatment of (*E*)-5-(2-bromovinyl)uracil with strong base.[26]

The extent of cyclization was markedly dependent on the reactants. A 77% yield of 1-methyl-5-[4-(*p*-toluyloxy)butynyl]uracil (**2b**) was obtained by direct crystallization of the product from coupling 1 with 4-(*p*-toluyloxy)butyne. Only a minor amount of the fluorescent byproduct (presumably **3b**) was observed. Coupling of 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**4**) with (trimethylsilyl)acetylene gave 5-[(trimethylsilyl)ethynyl]-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**5a**) in 80% yield. However, coupling of **4** with hexyne, 4-(*p*-toluyloxy)butyne, and 4-(tetrahydropyranyloxy)- or 4-(trityloxy)butyne under the same conditions gave the cyclized furano[2,3-*d*]pyrimidin-2-one compounds as major products. Thin-layer chromatography indicated that cyclization of the 5-alkynyluracil products also occurred during workup. This was moderated by addition of solid disodium EDTA to the warm coupling mixture before processing. This modification was employed in a coupling of **4** with 4-(trityloxy)butyne. Detritylation and chromatographic analysis gave starting **4** (7%), deiodinated **4** (3′,5′-di-*O*-acetyl-2′-deoxyuridine, 11%), product 5-(4-hydroxybutynyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**5b**, 61%), and cyclized furano[2,3-*d*]pyrimidin-2-one (9%).

Protection of nucleoside hydroxyl groups as *p*-toluyl esters provided organic-soluble and easily crystallized products in ~95% yields. We have recently described procedures for high-yield iodination (and chlorination) of uracil compounds that gave 5-iodo-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**7**; see Scheme II) in 98% crystallized yield.[15] Coupling reactions using **7** proceeded smoothly with minimal formation of deiodinated and furano[2,3-*d*]pyrimidin-2-one byproducts. Treatment of **7** with hexyne under the usual conditions gave 5-hexynyl-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**8c**) in 89% purified yield.[27] Scheme II gives the structures and Table I lists characterization data for the 5-alkynyl-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine products.

Treatment of the 5-(trimethylsilyl)ethynyl compound (**8g**) with potassium fluoride/tetraethylammonium bromide effected removal of the trimethylsilyl group to give the known[14] 5-ethynyl-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**8h**) in 84% yield. Complete deprotection of **8g** occurred in 0.2 N sodium methoxide in dry methanol to give crude 5-ethynyl-2′-deoxyuridine[6,14] (**9h**) quantitatively. This provides a stereocontrolled sequence from 2′-deoxyuridine to **9h** (~75% overall yield) that makes this compound accessible for further biological evaluation. Analogous deprotection of the other *p*-toluyl ester products (**8**) gave the 2′-deoxyuridine derivatives (**9**) noted in Scheme II and characterized by the data listed in Table II.

Protection of ω-hydroxyalkynes as tetrahydropyranyl (THP) acetals or *p*-toluyl esters gave derivatives that underwent smooth coupling with the 5-iodouracil compounds. Acid-catalyzed removal of the THP group from **8i** and **8k** gave the 5-(ω-hydroxyalkynyl)-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridines (**8j** and **8m**, respectively). Treatment of **8m** with *p*-toluenesulfonyl chloride/pyridine gave the ω-to-

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(27) Coupling of unprotected 5-iodouracil nucleosides with hexyne under the typical conditions did not proceed, and more strenuous treatment gave mixtures of products. Usual treatment of 5-bromo-3′,5′-di-*O*-acetyl-2′-deoxyuridine with hexyne resulted in a sluggish reaction. The 5-chlorouracil compounds tried did not undergo coupling with hexyne under the usual conditions.

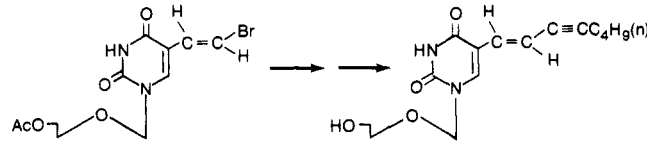
Table I. Characterization Data for 5-Alkynyl-3',5'-di-*O*-*p*-toluyl-2'-deoxyuridine Intermediates

compd	mp, °C	yield, %	calcd C	calcd H	calcd N	found C	found H	found N	characteristic ^{1}H NMR spectral peaks,[a,b] δ
8a	224–225	91	*c*						1.04 (t, 3, CH_2CH_3), 2.30 (q, 2, CH_2CH_3), 2.40 (br s, 6, $ArCH_3$'s), 6.25 (t, 1, H1')
b	*c*	85	*c*						0.94 (t, 3, CH_2CH_3), 1.44 (m, 2, CH_2CH_3), 2.28 (t, 2, C≡CCH_2), 2.40 (br s, 6, $ArCH_3$'s), 6.28 (dd, 1, H1')
c	213–214	90	68.37	5.92	5.14	68.33	5.72	4.83	[d] 0.90 (m, 3, CH_2CH_3), 2.38 (s, 6, $ArCH_3$'s), 6.34 (dd, 1, H1'), 7.25 (d, 4, aromatic), 7.72 (s, 1, H6), 7.91 (d, 4, aromatic)
d	197–201	77	*c*						[d] 0.91 (m, 3, CH_2CH_3), 2.21 (t, 2, C≡CCH_2), 2.44 (s, 6, $ArCH_3$'s), 6.40 (dd, 1, H1'), 7.25 (d, 4, aromatic), 7.78 (s, 1, H6), 7.95 (d, 4, aromatic)
e	228–231	91	*c*						1.12 (s, 9, $C(CH_3)_3$), 2.40 (br s, 6, $ArCH_3$'s), 6.23 (t, 1, H1')
f	*c*	91	*c*						2.26 and 2.40 (s and s, 3 and 3, $ArCH_3$'s), 6.30 (t, 1, H1'), 7.2–7.9 (m, 13, aromatic), 8.09 (s, 1, H6)
g	255–256	85	64.27	5.75	5.00	64.22	5.62	4.94	[e] 0.12 (s, 9, $Si(CH_3)_3$), 2.40 (br s, 6, $ArCH_3$'s), 6.30 (dd, 1, H1')
i	*f*	72	65.77	5.69	4.65	65.75	5.56	4.62	2.40 (s, 6, $ArCH_3$'s), 4.31 (dd, 2, C≡CCH_2), 6.25 (t, 1, H1') 8.02 (s, 1, H6)
j	194–197	90	64.86	5.05	5.40	64.54	4.99	5.24	2.40 (s, 6, $ArCH_3$'s), 4.19 (s, 2, C≡CCH_2), 6.26 (t, 1, H1'), 8.00 (s, 1, H6)
k	164–165	85	66.22	5.88	4.54	65.75	6.00	4.53	[g] 2.39 (br s, 6, $ArCH_3$'s), 6.23 (t, 1, H1')
l	*f*	85	68.30	5.27	4.31	67.99	5.22	4.56	[d] 2.41 (m, 9, $ArCH_3$'s), 2.66 (t, 2, C≡CCH_2), 4.28 (t, 2, CH_2O), 6.40 (dd, 1, H1')
m	236–238	90	65.41	5.30	5.26	65.33	5.36	5.14	2.40 (m, 8, $ArCH_3$'s and C≡CCH_2), 3.49 (m, 2, CH_2OH), 4.80 (t, 1, CH_2OH), 6.28 (dd, 1, H1')
n	*f*	65	62.96	4.99	4.08	62.54	5.32	4.01	2.40 (m, 9, $ArCH_3$'s), 2.66 (t, 2, C≡CCH_2), 4.02 (t, 2, CH_2OTs), 6.28 (t, 1, H1')
p	*f*	87	68.66	5.46	4.21	68.35	5.53	4.09	1.86 (m, 2, $CH_2CH_2CH_2$), 2.37, 2.39, 2.41 (3 s, 3, 3, and 3, $ArCH_3$'s), 2.48 (t, 2, C≡CCH_2), 4.32 (t, 2, CH_2OTol), 6.30 (t, 1, H1')

[a] Spectra were determined at 100 MHz in Me_2SO-d_6 with Me_4Si as internal standard unless otherwise noted. [b] Unresolved multiplets with extensive overlap for most sugar protons (and some side-chain protons), the aromatic protons (sometimes overlapping H6), and the broad singlet for NH at δ 9–12 are not listed. [c] Deprotected without further characterization. [d] $CDCl_3$. [e] $CDCl_3$/Me_2SO-d_6. [f] Softening with no distinct melting range. [g] 200 MHz.

syloxy product (**8n**). Deprotection of **8n** with 0.1 N NaOMe/MeOH gave **9n**. Treatment of **8n** with potassium *tert*-butoxide in acetonitrile followed by methanol gave 5-(but-3-en-1-ynyl)-2′-deoxyuridine (**9o**).

An example of a conjugated ynene system attached in the reverse orientation at C5 was obtained by coupling hexyne with the vinologous bromo acyclonucleoside analogue 1-[(2-acetoxyethoxy)methyl]-(*E*)-5-(2-bromovinyl)-uracil[28] (**10**). The resulting product was deacetylated to



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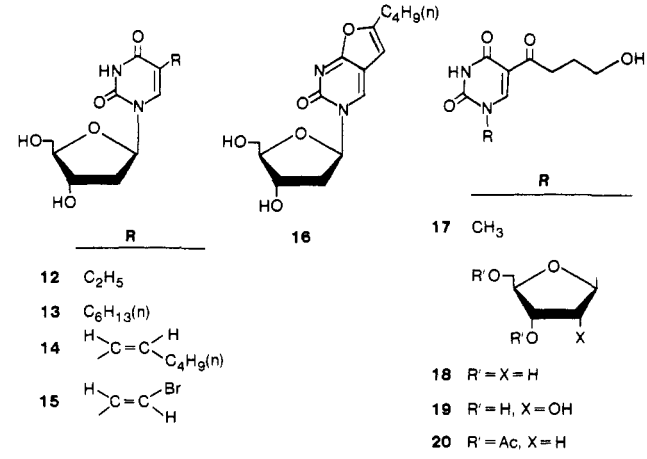
give 1-[(2-hydroxyethoxy)methyl]-(*E*)-5-(oct-1-en-3-ynyl)uracil (**11**). Retention of the *E* stereochemistry was indicated by the large vinylic coupling constant (J = 16 Hz) measured at 400-MHz resolution.

The presently described synthesis of 5-alkynyluracil products presented a potentially facile route to known biologically active 5-alkyl- and -alkenyl-2′-deoxyuridines. Hydrogenation of 5-ethynyl-2′-deoxyuridine (**9h**) over palladium on carbon gave the known antiviral agent 5-ethyl-2′-deoxyuridine[29] (**12**) in 93% yield. Similarly efficient reduction of the 5-hexynyl compound (**9c**) gave 5-*n*-hexyl-2′-deoxyuridine[30a] (**13**). Cytostatic activity in mammalian cells had been reported for **13**.[30b] However, a minimal activity response was seen with our pure **13** in the standard murine leukemia L1210 cell system.[16] Hydrogenation of 5-[(trimethylsilyl)ethynyl]-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**5a**) gave 5-[(trimethylsilyl)ethyl]-(**6a**) plus 5-ethyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6b**) in 67% and 23% yields, respectively.

Careful partial hydrogenation of the 5-hexynyl compound **9c** over Lindlar catalyst with quinoline in acetone gave 83% of (*Z*)-5-hexenyl-2′-deoxyuridine (**14**) plus 10%



R

12 C_2H_5

13 $C_6H_{13}(n)$

14 (*Z*)-$CH=CHC_4H_9(n)$

15 $CH=CHBr$

16

17 CH_3

18 R′ = X = H

19 R′ = H, X = OH

20 R′ = Ac, X = H

of the saturated 5-*n*-hexyl compound **13**. Separation of these products from a trace of starting **9c** was effected by preparative reverse-phase HPLC. The smaller vinylic coupling constant (J = 11.5 Hz) at 400-MHz resolution was consistent with the cis geometry[31] for **14**. A 12% NOE

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Table II. Characterization Data for 5-Alkynyl-2′-deoxyuridines

compd	mp, °C	UV pH 6 max, nm (ε)	UV pH 6 min, nm (ε)	UV pH 13 max, nm (ε)	UV pH 13 min, nm (ε)	calcd C	calcd H	calcd N	found C	found H	found N
9a[e]	178–179	293 (10 600), 232 (10 800)	258 (3000)	287 (8500), 230 (13 000)	262 (4500)	53.97	5.92	9.68	54.00	5.80	9.85
b[e]	139–144	292 (10 800), 230 (12 300)	257 (3200)	287 (8700), 230 (14 700)	260 (4600)	55.44	6.31	9.24	55.73	6.20	9.35
c	136–138	293 (11 700), 233 (11 600)	256 (3300)	287 (9300), 232 (12 800)	260 (4500)	58.43	6.54	9.09	58.21	6.52	8.88
d	130–132	293 (11 000), 234 (11 000)	259 (3000)	290 (9100), 233 (13 300)	264 (4600)	59.61	6.88	8.69	59.88	6.91	8.57
e[g]	104–109	292 (11 300), 232 (12 200)	258 (3600)	287 (9200), 229 (14 500)	260 (4700)	55.21	6.80	8.58	55.26	6.22	8.57
f	174–176	307 (16 300), 279 (12 200), 264 (13 300)	286 (12 200), 271 (12 100), 240 (9400)	305 (16 500), 282 (13 800), 266 (12 500)	287 (13 600), 271 (12 300), 246 (9400)	62.19	4.91	8.53	62.29	4.87	8.70
j	182–184	288 (11 000), 234 (12 700)	259 (4600)	287 (9600), 234 (12 700)	262 (4700)	51.06	5.00	9.92	50.89	4.97	9.87
m	163–165	293 (12 000), 233 (12 000)	257 (3500)	288 (9600), 228 (14 200)[h]	261 (4700)	52.70	5.44	9.46	52.39	5.68	9.29
n[g]	102–104	292 (13 500), 228 (24 800)	257 (4400)	287 (10 100), 228 (26 100)	262 (5700)	51.28	5.16	5.98	51.22	4.92	6.12
o[e]	>200 dec	301 (14 400) (8 other max)		298 (14 100) (3 other max)		54.35	5.26	9.75	54.47	4.98	9.54
q	163–164	292 (11 300), 232 (11 300)	257 (3400)	287 (9000) 232 (13 300)[h]	261 (4700)	54.19	5.85	9.03	54.05	6.01	9.07

compd	^{1}H NMR spectral peaks, δ, for nonexchangeable protons[a] H2′,2″[b]	H5′,5″[b]	H4′[b]	H3′[b]	H1′[c]	H6[d]	other peaks
9a[e]	2.12	3.60	3.80	4.24	6.12	8.12	1.12 (t, 3, CH_2CH_3), 2.38 (q, 2, CH_2CH_3)
b[e]	2.12	3.60	3.80	4.24	6.13	8.13	0.98 (t, 3, CH_2CH_3), 1.52 (m, 2, CH_2CH_3), 2.34 (t, 2, $C{\equiv}CCH_2$)
c	2.10	3.57	3.78	4.22	6.10	8.08	[f]0.88 (m, 3, CH_2CH_3), 1.44 (m, 4, $CH_2CH_2CH_3$), 2.32 (m, 2, $C{\equiv}CCH_2$)
d	2.11	3.58	3.79	4.22	6.10	8.08	[f]0.89 (m, 3, CH_2CH_3), 1.38 (m, 6, $CH_2CH_2CH_2CH_3$), 2.36 (m, 2, $C{\equiv}CCH_2$)
e[g]	2.10	3.59	3.78	4.24	6.09	8.06	[f]1.22 (s, 9, $C(CH_3)_3$)
f	2.17	3.62	3.82	4.26	6.14	8.40	7.4 (m, 5, phenyl)
j	2.12	3.59	3.80	4.24	6.13	8.20	4.24 (d, 2, $C{\equiv}CCH_2OH$)
m	2.10	3.55	3.80	4.24	6.14	8.14	2.50 (m, 2, $C{\equiv}CCH_2$), 3.55 (m, 2, CH_2OH)
n[g]	2.10	3.60	3.80	4.20	6.10	8.09	[f]2.40 (s, 3, $ArCH_3$), 2.74 (t, 2, $C{\equiv}CCH_2$), 4.20 (m, 2, CH_2OTs), 7.44 and 7.80 (A_2X_2, 4, aromatic)
o[e]	2.12	3.59	3.80	4.24	6.10[b]	8.27	5.67 (m, 2, $CH{=}CH_2$), 6.10 (m, $CH{=}CH_2$)
q	2.10	3.50	3.80	4.20	6.11	8.10	[f]1.60 (m, 2, $CH_2CH_2CH_2$), 2.50 (m, 2, $C{\equiv}CCH_2$), 3.50 (m, 2, CH_2OH)

[a] Spectra were determined in Me_2SO-d_6 with Me_4Si as an internal standard at 200 MHz unless otherwise noted. [b] Multiplet. [c] Apparent triplet. [d] Singlet. [e] Isolated as the hemihydrate. [f] 100 MHz. [g] Isolated as the monohydrate. [h] Shoulder.

enhancement of the vinyl 2-proton signal upon irradiation of the 1-proton corroborated this assignment. No *E* isomer was observed by analytical HPLC or in the 400-MHz ^1H NMR spectrum. Similar partial reduction of the 5-[(trimethylsilyl)ethynyl] compound **5a** in ethyl accetate gave (*Z*)-5-[2-(trimethylsilyl)ethenyl]-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6c**) as the highly predominant product. The large vinylic coupling constant (J = 15 Hz) for **6c** parallels data reported for the *E* and *Z* β-(trimethylsilyl)styrenes.[32] A 22% NOE enhancement of the vinyl 2-proton signal upon irradiation of the 1-proton at 400 MHz again corroborated the *Z* assignment for **6c**.

Treatment of (*Z*)-β-(trimethylsilyl)styrene with bromine/carbon disulfide at −100 °C and processing with acetonitrile was reported to give mainly (*Z*)-β-bromostyrene.[33] Crude **6c** was subjected to these conditions followed by deprotection with methanolic ammonia. However, the known antiviral agent (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**15**, BVDU)[4,20] was obtained in 40% yield after purification by HPLC. This reaction was not examined further since the *Z* isomer of **15** had been obtained by this stage of our investigation.[34]

We briefly examined the conversion of certain 5-alkynyl to 5-alkanone compounds. Antiviral and thymidylate synthetase inhibitory activities have been reported for 5-formyl-2′-deoxyuridine and its 5′-phosphate, respectively.[35] Facile hydration of 5-ethynyl- (**9h**) to 5-acetyl-2′-deoxyuridine occurred under mild-acid conditions.[36] However, hydrophobic 5-alkynyl-2′-deoxyuridine compounds from the present study were resistant to hydration in acidic dioxane/water solutions. Prolonged treatment of 5-hexynyl-2′-deoxyuridine (**9c**) with mercury(II) sulfate in aqueous dioxane gave the cyclized 6-*n*-butyl-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)furano[2,3-*d*]pyrimidin-2-one (**16**) in 36% yield. Starting **9c** and minor products were also present, but no significant quantity of the expected ketone was formed. Compound **16** was prepared in 82% yield by treatment of **9c** with copper(I) iodide in hot triethylamine/methanol.

Treatment of 5-(4-hydroxybutynyl)-1-methyluracil (**2c**) with mercury(II) sulfate in aqueous solution at 50 °C for 2 h resulted in isolation of 5-(4-hydroxybutanoyl)-1-methyluracil (**17**) in 78% yield. A minor amount (~5%) of the cyclized furano[2,3-*d*]pyrimidin-2-one (**3c**) was also formed. Similar conversions of the 5-(4-hydroxybutynyl)-2′-deoxyuridine (**9m**) and uridine compounds to the corresponding ketones, 5-(4-hydroxybutanoyl)-2′-deoxyuridine (**18**) and uridine (**19**), were effected in 64% and 67% yields. However, treatment of 5-(4-hydroxybutynyl)-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**8m**) with mercury(II) sulfate in aqueous dioxane resulted in reisolation of starting **8m**. Treatment of **8m** with mercury(II) acetate in hot trifluoroacetic acid resulted in loss of ultraviolet light absorption. The more water-soluble 5-(4-hydroxybutynyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**5b**) was hydrated to the 5-(4-hydroxybutanoyl) product **20** in 59% yield.

Conclusions

This study has provided a convenient and high-yield procedure for coupling terminal alkynes with 5-iodo-1-methyluracil and readily available[15] *p*-toluyl-protected 5-iodouracil nucleosides. A four-stage sequence from 2′-deoxyuridine to 5-ethynyl-2′-deoxyuridine was effected in ~75% overall yield. Hydrogenation of the alkynyl products can be controlled to give (*Z*)-5-alkenyl- or saturated 5-alkyluracil compounds. Previously reported 5-ethyl-, 5-*n*-hexyl-, and (*E*)-5-(2-bromovinyl)-2′-deoxyuridines (that have been prepared by base/sugar coupling as anomeric mixtures) were obtained with absolute anomeric purity on starting from naturally occurring 2′-deoxyuridine. Certain 5-(ω-hydroxyalkanoyl)uracil products were obtained by hydration of their ω-hydroxyalkynyl precursors. Antiviral[16] and thymidylate synthetase inhibitory activity[9] were found with certain of the 5-alkynyl-2′-deoxyuridine compounds.

Experimental Section

Melting points were determined on a Reichert microstage block and are uncorrected. Ultraviolet (UV) spectra were recorded on a Cary 15 spectrophotometer. The high-field NMR laboratory of this department obtained ^1H spectra on Varian 100 and Bruker WH-200 and WH-400 spectrometers with Me_4Si as an internal standard. Me_2SO-d_6 was used as the solvent, and spectra were determined at 100 MHz unless otherwise noted. Elemental analyses were determined by the microanalytical laboratory of this department or Schwarzkopf Microanalytical laboratory.

Thin-layer chromatography (TLC) was performed on Merck No. 5735 silica gel sheets by using the upper phase of *n*-PrOH/H_2O/EtOAc (1:2:4) as the developing solvent, unless otherwise noted, with sample detection under 2537-Å light. Preparative TLC was performed on Whatman PLK5F silica gel plates with a sample preloading zone. Column chromatography was effected by using J. T. Baker 5-3405 or Mallinckrodt CC-7 silica gel. Analytical HPLC was performed on a Whatman Partisil ODS-2 C-18 and preparative HPLC on a Waters Bondapak C-18 reverse-phase column by using acetonitrile/water at the indicated composition. Evaporations were effected at room temperature by using a Buchler rotary evaporator equipped with a Dewar dry-ice condenser under water-tap aspirator or mechanical oil pump vacuum.

Reagent grade pyridine and triethylamine were refluxed over and then distilled from calcium hydride. Reagent grade acetonitrile was refluxed over and distilled from phosphorus pentoxide. Anhydrous methanol was prepared by using magnesium turnings. Other reagent grade solvents were redistilled before use. "Hexane" refers to the fraction of petroleum ether (Skellysolve B) boiling from 63 to 65 °C upon redistillation. Copper(I) iodide was purchased from Fisher Scientific Co. Bis(triphenylphosphine)-palladium(II) chloride was prepared in 94% yield according to the procedure of Burmeister and Basolo.[37]

Alkynes were purchased from Farchan Division, Chemsampco Inc., and Petrarch Systems Inc. and were redistilled before use if necessary. Preparation of 3-(2-tetrahydropyranyloxy)propyne[38] and 4-(2-tetrahydropyranyloxy)butyne[39] followed the literature methods. One preparation of 4-(trityloxy)butyne was made by using trityl chloride and 3-butynol in pyridine followed by the usual processing and crsyallization of the product from ethanol. This material was used without further purification in one condensation reaction with 3′,5′-di-*O*-acetyl-5-iodo-2′-deoxyuridine (vide infra).

All coupling reactions were performed under an atmosphere of oxygen-free nitrogen, and the solvent (or solution) was vigorously deoxygenated with N_2 prior to addition of catalysts.

4-(*p*-Toluyloxy)butyne. A stirred solution of 14 g (0.2 mol) of 3-butynol in 100 mL of pyridine was cooled to 0 °C and treated with 34 g (0.22 mol) of *p*-toluyl chloride. The solution was warmed to 50 °C, stirred for 1 h, and evaporated. The residue was dissolved in 100 mL of $CHCl_3$, washed thoroughly with 1 M H_2SO_4/H_2O and then H_2O (2 × 50 mL), dried (Na_2SO_4), and

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evaporated to give a faintly yellow oil. This was distilled at 95–100 °C (0.5 mmHg) and then cooled to give 32.5 g (86%) of the title compound as colorless crystals. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.63; H, 6.37.

5-(*p*-Toluyloxy)pentyne was prepared from 4-pentynol in a manner identical with that described above for its lower homologue. The title compound was obtained as a colorless oil, bp 110 °C (0.5 mmHg). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 7.00.

5-Hexynyl-1-methyluracil (2a). A suspension of 1.26 g (5 mmol) of 5-iodo-1-methyluracil[15] (1) in 60 mL of Et_3N was vigorously deoxygenated with oxygen-free nitrogen. Hexyne (820 mg, 10 mmol), $(Ph_3P)_2PdCl_2$ (25 mg), and CuI (25 mg) were added, and the suspension was stirred at 50 °C for 2 h under N_2. The mixture was evaporated thoroughly to dryness, and the residue was dissolved in 100 mL of $CHCl_3$. This solution was washed with 5% disodium EDTA/H_2O (2 × 50 mL), and 50 mL of H_2O, dried (Na_2SO_4), and evaporated to a small volume. This solution was applied to a column (100 g) of Mallinckrodt silica, and the column was developed with $CHCl_3$/MeOH (9:1). Evaporation of appropriate earlier fractions gave 864 mg (84%) of crystalline **2a**. This was recrystallized from hexane/acetone to give **2a**: mp 134–135 °C; NMR δ 0.90 (m, 3, CH_2CH_3) 1.50 (m, 4, $CH_2CH_2CH_3$), 2.40 (m, 2, $C{\equiv}CCH_2$), 3.22 (s, 3, NCH_3), 7.93 (s, 1, H6), 11.44 (br s, 1, NH). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.79; H, 6.85; N, 13.51.

Later fractions were pooled and evaporated to give 88 mg (9%) of 6-*n*-butyl-3-methylfurano[2,3*d*]pyrimidin-2-one (**3a**). This was recrystallized from 95% EtOH (with diffusion of Et_2O)[40] to give **3a**: mp 190–192 °C (with sublimation at 179 °C); NMR δ 0.91 (m, 3, CH_2CH_3), 1.50 (m, 4, $CH_2CH_2CH_3$), 2.64 (t, 2, $ArCH_2$), 3.48 (s, 3, NCH_3), 6.40 (t, $^4J \approx 1$ Hz, 1, H5), 8.43 (s, 1, H4). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.10; H, 6.76; N, 13.76.

6-*n*-Butyl-3-methylfurano[2,3-*d*]pyrimidin-2-one (3a). Treatment of 309 mg (1.5 mmol) of **2a** in 10 mL of Et_3N/MeOH (3:7) with 10 mg of CuI at reflux for 4 h under N_2 was followed by evaporation of the solution. The dry residue was dissolved in 20 mL of $CHCl_3$, washed with 5% disodium EDTA/H_2O (2 × 20 mL), and 20 mL of H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized as described to give 285 mg (92%) of **3a** that was identical with the **3a** byproduct from the preceding experiment.

1-Methyl-5-[4-(*p*-toluyloxy)butynyl]uracil (2b). A 1.26-g (5 mmol) sample of **1** was suspended in 60 mL of deoxygenated Et_3N, and 1.88 g (10 mmol) of 4-(*p*-toluyloxy)butyne, 25 mg of $(Ph_3P)_2PdCl_2$, and 25 mg of CuI were added. The suspension was stirred at 50 °C for 1.5 h under N_2 followed by processing as described above for the conversion of **1** to **2a** prior to chromatography. Evaporation of the organic phase to dryness gave a white solid that was triturated with Et_2O (2 × 50 mL) to give 1.32 g (85%) of TLC homogeneous **2b**. This product was recrystallized from EtOH to give **2b**: mp 147–150 °C; NMR δ 2.38 (s, 3, $ArCH_3$), 2.84 (t, 2, $C{\equiv}CCH_2$), 3.20 (s, 3, NCH_3), 4.31 (t, 2, CH_2OTol), 7.34 (d, 2, aromatic), 7.90 (m, 3, H6 and aromatic), 11.48 (br s, 1, NH). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.24; N, 9.00.

5-(4-Hydroxybutynyl)-1-methyluracil (2c). A 3.12-g (10 mmol) sample of **2b** was added to 300 mL of NH_3/MeOH (saturated at ~5 °C), and the suspension was stirred at 25 °C for 7 days. The resulting solution was evaporated, and the residue triturated with Et_2O (3 × 50 mL) to give 1.93 g (99%) of **2c** as a colorless powder. This product was recrystallized from 95% EtOH to give 1.7 g (88%) of **2c**: mp 204–208 °C; NMR (400 MHz) δ 2.50 (t, $C{\equiv}CCH_2$), 3.20 (s, 3, NCH_3), 3.52 (t, 2, CH_2OH), 4.85 (br s, 1, OH), 7.95 (s, 1, H6), 11.50 (br s, 1, NH). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.44; H, 5.34; N, 14.46.

3′,5′-Di-*O*-acetyl-5-iodo-2′-deoxyuridine (4). A solution of 7.8 g (25 mmol) of 3′,5′-di-*O*-acetyl-2′-deoxyuridine[41] and 5.69 g (35 mmol) of ICl in 250 mL of CH_2Cl_2 was heated at reflux for 3 h and then cooled. Water (200 mL) was added, and the stirred mixture was treated with the *minimum* quantity of 2% $NaHSO_3/H_2O$ necessary to decolorize the excess ICl. The organic phase was separated and washed with H_2O (2 × 200 mL), dried (Na_2SO_4), and evaporated. The resulting faintly yellow oil was dissolved in 100 mL of warm 98% EtOH, and this was cooled at −18 °C. The colorless crystals were filtered and washed with cold EtOH to give 9.65 g (88%) of **4** after drying: mp 157–159 °C (lit.[42] mp 158–160 °C); NMR δ 2.06 and 2.08 (2 s, 3 and 3, OAc's), 6.12 (t, 1, H1′), 8.03 (s, 1, H6), 11.72 (br s, 1, NH), plus sugar proton multiplets. Anal. Calcd for $C_{13}H_{15}IN_2O_7$: C, 35.63; H, 3.45; N, 6.39. Found: C, 35.80; H, 3.27; N, 6.32.

3′,5′-Di-*O*-acetyl-5-[2-(trimethylsilyl)ethynyl]-2′-deoxyuridine (5a). To 300 mL of deoxygenated Et_3N was added 3.51 g (8 mmol) of **4** followed by 1.57 g (16 mmol) of (trimethylsilyl)acetylene, 120 mg of $(Ph_3P)_2PdCl_2$, and 120 mg of CuI. The suspension was stirred at 50 °C for 3 h under N_2, evaporated thoroughly to a solid brown foam, and processed as in the conversion of **1** to **2a**. Chromatography was effected by using a column of silica (150 g) packed in benzene with benzene/EtOAc (8:2) as the eluant. Appropriately pooled fractions were evaporated to give 2.62 g (80%) of **5a** as a colorless solid foam. This was crystallized from EtOH to give 2.22 g (68%) of **5a** as colorless plates: mp 178–179 °C; NMR δ 0.10 (s, 9, $Si(CH_3)_3$), 2.06 and 2.09 (2 s, 3 and 3, OAc's), 6.10 (t, 1, H1′), 7.94 (s, 1, H6), 11.68 (br s, 1, NH), plus sugar proton multiplets. Anal. Calcd for $C_{18}H_{24}N_2O_7Si$: C, 52.93; H, 5.92; N, 6.86. Found: C, 52.83; H, 6.02; N, 6.74.

3′,5′-Di-*O*-acetyl-5-(4-hydroxybutynyl)-2′-deoxyuridine (5b). A 2.63-g (6 mmol) sample of **4**, 3.75 g (12 mmol) of 4-[(triphenylmethyl)oxy]butyne, 90 mg of $(Ph_3P)_2PdCl_2$, and 50 mg of CuI in 250 mL of deoxygenated Et_3N were stirred at 50 °C for 2.5 h under N_2. Solid disodium EDTA (1 g) was added followed by processing as in the conversion of **1** to **2a**. The yellow solid foam was treated directly with 85% HOAc/H_2O at 50 °C for 1.5 h. Evaporation of this solution followed by addition and evaporation of toluene gave a solid foam that was chromatographed on a column of Mallinckrodt silica (150 g) with EtOAc as the eluant. Early fractions contained starting **4** (172 mg, 7%) followed by the deiodinated product, 3′,5′-di-*O*-acetyl-2′-deoxyuridine (198 mg, 11%). The title compound **5b** (1.39 g, 61%) came next followed by 3-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-hydroxyethyl)furano[2,3-*d*]pyrimidin-2-one (204 mg, 9%). The latter two compounds did not crystallize under several conditions. A small sample of **5b** was deprotected by using NH_3/MeOH to give 5-(4-hydroxybutynyl)-2′-deoxyuridine (**9m**) (see Table II for characterization data). Similar deprotection of the final product eluted gave 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-hydroxyethyl)furano[2,3-*d*]pyrimidin-2-one (140 mg, 88%). This compound was recrystallized from EtOH with diffusion of Et_2O to give a product: mp 162–164 °C; UV (pH 6 or 13) λ_{max} 328, 245, 225 nm (ε 6700, 11 500, 14 600), λ_{min} 267, 239 nm (ε 500, 11 100); NMR δ 2.20 (m, 2, H2′,2″), 2.78 (t, 2, $ArCH_2$), 3.70 (m, 4, H5′,5″ and CH_2OH), 3.90 (m, 1, H4′), 4.24 (m, 1, H3′), 6.16 (t, 1, H1′), 6.43 (s, 1, H5), 8.64 (s, 1, H4). Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.36; H, 5.65; N, 9.19.

5-Hexynyl-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (8c). To 160 mL of deoxygenated Et_3N was added 2.36 g (4 mmol) of 5-iodo-3′,5′-di-*o*-*p*-toluyl-2′-deoxyuridine[15] (**7**) followed by 656 mg (8 mmol) of hexyne, 60 mg of $(Ph_3P)_2PdCl_2$, and 60 mg of CuI. The resulting suspension was stirred at 50 °C for 4 h under N_2 and then thoroughly evaporated to dryness. The resulting yellow oil was dissolved in 200 mL of $CHCl_3$, washed with 5% disodium EDTA/H_2O (2 × 100 mL), and 100 mL of H_2O, dried (Na_2SO_4), evaporated, and redissolved in the minimum volume of hot $CHCl_3$. MeOH (5 volumes) was added, and the resulting precipitate was filtered to give 1.95 g (90%) of colorless and TLC-homogeneous **8c**. This product was recrystallized from $CHCl_3$/MeOH to give **8c**: mp 213–214 °C; UV (EtOH) λ_{max} 289, 238 nm (ε 9500, 34 100), λ_{min} 265 nm (ε 5900); NMR and Anal. (see Table I).

Compounds 8a–g,i,k,l,p were prepared from **7** and the respective terminal alkynes by the procedure for the conversion of

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7 to 8c. Reactions with the more volatile alkynes (e.g., butyne) were effected by using a glass liner in a steel pressure bomb immersed in an oil bath at 55 °C. In cases where a colored reaction mixture resulted, the crude product was purified by passage through a short column of silica with MeOH/$CHCl_3$ (1:9) as the eluant before crystallization from MeOH/$CHCl_3$. See Scheme II and Table I for structures and data.

5-Ethynyl-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (8h). To 50 mL of anhydrous acetonitrile were added 560 mg (1 mmol) of **8g**, 116 mg (2 mmol) of KF, and 420 mg (2 mmol) of Et_4NBr, and the stirred suspension was heated at reflux for 3 h. The resulting clear solution was evaporated, and the residue was dissolved in 80 mL of $CHCl_3$. This solution was washed with H_2O (3 × 80 mL), dried (Na_2SO_4), and evaporated. The resulting white solid was recrystallized from MeOH to give 410 mg (84%) of **8h** that was identical with an authentic sample.[14]

5-(3-Hydroxypropynyl)-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (8j). A solution of 2.71 g (4.5 mmol) of **8i** in 30 mL of CH_2Cl_2/MeOH/CF_3CO_2H (15:10:5) was stirred at 25 °C for 30 min and then was evaporated. Several portions of MeOH were added and evaporated, and the residue was crystallized from MeOH/$CHCl_3$ to give 2.11 g (90%) of **8j** with the properties listed in Table I.

5-(4-Hydroxybutynyl)-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (8m). Treatment of 617 mg (1 mmol) of **8k** for 1.5 h under the conditions described above for **8i** → **8j** gave a residue that was crystallized from 95% EtOH to give 479 mg (90%) of **8m** with the properties listed in Table I.

5-[4-(*p*-Toluenesulfonyloxy)butynyl]-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (8n). A solution of 293 mg (0.55 mmol) of **8m** and 286 mg (1.5 mmol) of tosyl chloride in 20 mL of pyridine was stirred at 25 °C for 18 h and then evaporated. The resulting yellow oil was triturated with hexane (2 × 40 mL), and then 15 mL of MeOH was added. The suspension was cooled at −18 °C for several hours and filtered, and the collected solid was recrystallized from MeOH/$CHCl_3$ to give 246 mg (65%) of **8n** with the properties listed in Table I.

2′,3′,5′-Tri-*O*-*p*-toluyl-5-[4-(*p*-toluyloxy)butynyl]uridine. Treatment of 4.35 g (6 mmol) of 5-iodo-2′,3′,5′-tri-*O*-*p*-toluyluridine[15] with 1.5 g (8 mmol) of 4-(*p*-toluyloxy)butyne under the general coupling conditions described for the conversion of **7** to **8c** gave 4.33 g (92%) of the crystalline title compound: mp 215–218 °C; NMR ($CDCl_3$) δ 2.40 (br s, 9, $ArCH_3$'s), 2.68 (t, 2, $C{\equiv}CCH_2$), 4.25 (t, 2, CH_2OTol), 6.30 (d, 1, H1′), 7.10–8.05 (m, 13, H6 and aromatic), 8.63 (br s, 1, NH), plus sugar proton multiplets. Anal. Calcd for $C_{45}H_{40}N_2O_{11}$: C, 68.87; H, 5.14; N, 3.57. Found: C, 69.05; H, 5.25; N, 3.79.

5-(4-Hydroxybutynyl)uridine. To 40 mL of 0.1 N sodium methoxide in anhydrous methanol was added 3.92 g (5 mmol) of 2′,3′,5′-tri-*O*-*p*-toluyl-5-[4-(*p*-toluyloxy)butynyl]uridine, and the mixture was stirred at 25 °C for 6 h. TLC indicated that deprotection was complete. The solution was carefully neutralized by addition of Dowex 50-X8 (H^+) resin until moistened pH paper indicated pH ~6. The mixture was filtered, and the resin was washed with MeOH. The combined filtrate was evaporated, and the colorless residue was triturated with Et_2O (3 × 50 mL). The resulting TLC-homogeneous white powder (1.53 g, 98%) was crystallized from 95% EtOH with diffusion of Et_2O[40] to give 1.26 g (81%) of the title compound: mp 213–215 °C; UV (pH 6) λ_{max} 292, 232 nm (ε 12 500, 12 300), λ_{min} 257 nm (ε 3300); UV (pH 13) λ_{max} 287, 230 nm (ε 9900, 14 500), λ_{min} 261 nm (ε 4700); NMR δ 2.50 (m, 2, $C{\equiv}CCH_2$ and solvent), 3.40–4.10 (m, 7, CH_2OH and sugar protons), 4.80–5.40 (m, 4, OH's), 5.76 (d, 1, H1′), 8.18 (s, 1, H6), 11.60 (br s, 1, NH). Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.83; H, 5.18; N, 8.76.

Compounds 9a–f,j,m,q were prepared by deprotection of their corresponding *p*-toluyl ester precursors **8a–f,j(l or m),p** by using 0.1 or 0.2 N NaOMe/MeOH as described in the above procedure for 5-(4-hydroxybutynyl)uridine. An Et_2O/hexane mixture was used in place of Et_2O for trituration of the more lipophilic compounds. Yields of the TLC-homogeneous triturated products usually ranged from 90% to 98%. These solids were recrystallized from MeOH or EtOH with diffusion of Et_2O[40] to give samples with the properties listed in Table II.

5-Ethynyl-2′-deoxyuridine (9h) was prepared directly from the protected 5-[(trimethylsilyl)ethynyl] precursor (**8g**) by using 0.2 N NaOMe/MeOH according to the above general procedure. TLC homogeneous **9h** was obtained quantitatively and could be recrystallized as described to give a product identical with a known sample.[14]

5-[4-(*p*-Toluenesulfonyloxy)butynyl]-2′-deoxyuridine (9n). A 465-mg (0.68 mmol) sample of **8n** was deprotected by using 10 mL of 0.1 N NaOMe/MeOH at 25 °C for 5 h. Processing by the above general procedure gave a colorless solid that was triturated with hexane (3 × 40 mL) and then extracted into Et_2O. This Et_2O solution was allowed to evaporate to a small volume, and 190 mg (60%) of **9n** crystallized as its monohydrate with the properties listed in Table II.

5-(But-3-en-1-ynyl)-2′-deoxyuridine (9o). To 10 mL of anhydrous acetonitrile were added 206 mg (0.3 mmol) of **8n** and 146 mg (1.3 mmol) of potassium *tert*-butoxide. The suspension was stirred vigorously and subjected to ultrasound (sonication in a commercial cleaning bath) for 20 min. TLC (MeOH/$CHCl_3$, 1:9) indicated the complete disappearance of starting **8n**. Anhydrous MeOH (10 mL) was added, and the mixture was stirred at 25 °C for 18 h. Careful neutralization with Dowex 50-X8 (H^+) resin was followed by filtration, washing of the resin with MeOH, and evaporation of the combined filtrate to a small volume. This was chromatographed on a 20 × 20 cm Merck preparative TLC silica plate with MeOH/$CHCl_3$ (1:9). The major UV quenching band was eluted and crystallized with difficulty from EtOH/Et_2O (1:1) with diffusion of Et_2O[40] to give 34 mg (39%) of **9o** as its hemihydrate with the properties listed in Table II.

1-[(2-Hydroxyethoxy)methyl]-(*E*)-5-(oct-1-en-3-ynyl)uracil (11). To 40 mL of deoxygenated Et_3N were added 333 mg (1 mmol) of 1-[(2-acetoxyethoxy)methyl]-(*E*)-5-(2-bromovinyl)uracil[28] (**10**), 250 mg (3 mmol) of hexyne, 15 mg of $(Ph_3P)_2PdCl_2$, and 15 mg of CuI. The mixture was stirred at 50 °C for 1.5 h under N_2 and then processed as described for the conversion of **7** to **8c** with passage through a column (50 g) of silica. The resulting yellow oil (317 mg, 95%) had NMR spectral data in harmony with the expected coupling product. It did not crystallize under several conditions. A 287-mg (0.86 mmol) sample was deprotected with 0.05 N NaOMe/MeOH by using the general procedure to give 191 mg (76%) of **11** as a yellow solid. Recrystallization of this product from EtOH/H_2O gave pale yellow plates of **11**: mp 118–121 °C; UV (EtOH) λ_{max} 267, 240, 229 nm (ε 11 100, 13 400, 14 900), λ_{min} 250, 238 nm (ε 9700, 13 000); NMR (400 MHz) δ 0.92 (t, 3, CH_2CH_3), 1.45 (m, 4, $CH_2CH_2CH_3$), 2.39 (m, 2, $C{\equiv}CCH_2$), 3.54 (m, 4, OCH_2CH_2OH), 4.70 (t, 1, OH), 5.14 (s, 2, NCH_2O), 6.54 (d, J = 16 Hz, 1, vinylic H1), 6.60 (dt, J_{vin} = 16 Hz, $^5J_{2-5}$ = 2 Hz, 1, vinylic H2), 8.00 (s, 1, H6), 11.50 (br s, 1, NH). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.47; H, 7.16; N 9.33.

5-Ethyl-2′-deoxyuridine (12). To a solution of 201 mg (0.8 mmol) of **9h** in 10 mL of EtOH was added 100 mg of 5% Pd/C catalyst, and the suspension was hydrogenated at 1 atm for 1 h. TLC indicated that reaction was complete. Catalyst was removed by filtration and washed with 20 mL of EtOH. The combined filtrate was evaporated to give 198 mg (97%) of **12** as a colorless crystalline solid. This was recrystallized from EtOH with diffusion of Et_2O[40] to give **12**: mp 151–152 °C (lit.[29a,30a] mp 152–153 °C); UV (pH 6) λ_{max} 268 nm (ε 10 400), λ_{min} 236 nm (ε 3300); NMR δ 1.04 (t, 3, CH_2CH_3), 2.06–2.38 (m, 4, H2′, 2″ and CH_2CH_3), 3.61 (m, 2, H5′, 5″), 3.78 (m, 1, H4′), 4.26 (m, 1, H3′), 6.20 (t, 1, H1′), 7.69 (s, 1, H6). Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.25; H, 6.31; N, 10.84.

5-*n*-Hexyl-2′-deoxyuridine (13). Hydrogenation of 154 mg (0.5 mmol) of **9c** (by the above procedure used for **9h** → **12**) followed by recrystallization of the product from acetone/hexane gave 144 mg (92%) of **13**: mp 104–106 °C (lit.[30a] mp 101 °C); UV (pH 6) λ_{max} 269 nm (ε 9300), λ_{min} 236 nm (ε 2400); NMR (400 MHz) δ 0.86–2.20 (5 m, 13, hexyl chain), 3.57 (m, 2, H5′, 5″), 3.77 (m, 1, H4′), 4.23 (m, 1, H3′), 6.19 (t, 1, H1′), 7.70 (s, 1, H6). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.38; H, 7.70; N, 8.81.

3′,5′-Di-*O*-acetyl-5-[2-(trimethylsilyl)ethyl]-2′-deoxyuridine (6a). Hydrogenation of 204 mg (0.5 mmol) of **5a** (by the procedure used for **9h** → **12**) gave two products that were separated by preparative HPLC with 42% CH_3CN/H_2O at a flow rate of 3 mL/min. The first product eluted (38 mg, 22%) was identified by its NMR spectrum as 3′,5′-di-*O*-acetyl-5-ethyl-2′-

deoxyuridine (**6b**). Deprotection of this product gave **12** which was identified by comparison with the sample of **12** prepared above.

Elution of the preparative HPLC column with 42–50% CH_3CN/H_2O gave 137 mg (67%) of the major product (**6a**) that was recrystallized from EtOH to give **6a**: mp 132–134 °C; NMR δ 0.00 (s, 9, $Si(CH_3)_3$), 0.60 (m, 2, CH_2Si), 2.08 (br s, 6, OAc's), 2.30 (m, 4, H2′,2″ and CH_2CH_2Si), 6.18 (t, 1, H1′), 7.38 (s, 1, H6), 11.32 (br s, 1, NH), plus sugar proton multiplets. Anal. Calcd for $C_{18}H_{28}N_2O_7Si$: C, 52.41; H, 6.84; N, 6.79. Found: C, 52.31; H, 6.74; N, 6.69.

(*Z*)-5-Hexenyl-2′-deoxyuridine (14). To a solution of 308 mg (1 mmol) of **9c** in 100 mL of acetone was added 1 mL of freshly distilled quinoline and 0.5 g of Lindlar catalyst. The mixture was hydrogenated at 1 atm for 80 min at 25 °C. Analytical HPLC (27% CH_3CN/H_2O, flow rate 1 mL/min) showed the virtual absence of starting **9c**. The suspension was filtered and the filter cake washed with 100 mL of acetone. The combined filtrate was evaporated, and the residual yellow oil was chromatographed on a short (10 g) column of silica with $CHCl_3$ as the eluant to remove traces of quinoline. Nucleoside products were eluted with $MeOH/CHCl_3$ (1:9), and appropriate fractions were pooled and evaporated. The colorless solid residue was dissolved in 2 mL of EtOH, and 1-mL portions were subjected to preparative HPLC (22% CH_3CN/H_2O followed by 22–30% CH_3CN/H_2O at a flow rate of 3 mL/min). Appropriate 22% acetonitrile fractions were pooled and evaporated to give 258 mg (83%) of **14** as a crystalline white solid. This was recrystallized from $CHCl_3$ to give **14**: mp 137–139 °C; UV (pH 6) λ_{max} 282, 229 nm (ϵ 7700, 15100), λ_{min} 258 nm (ϵ 4800); UV (pH 13) λ_{max} 278, 228 nm (ϵ 6300, 16900) λ_{min} 265 nm (ϵ 5600); NMR (400 MHz) δ 0.90 (m, 3, CH_2CH_3), 1.30 (m, 4, $CH_2CH_2CH_3$), 2.10 (m, 4, H2′,2″ and $CH{=}CHCH_2$), 3.54 (m, 2, H5′,5″) 3.83 (m, 1, H4′), 4.26 (m, 1, H3′), 5.60 (d t, 1, $CH{=}CHC_4H_9$), 6.03 (d, J_{vin} = 11.5 Hz, 1, $CH{=}CHC_4H_9$), 6.23 (t, 1, H1′), 7.80 (s, 1, H6). Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.78; H, 7.25; N, 8.77.

Appropriately pooled 22–30% acetonitrile fractions were evaporated to give 31 mg (10%) of **13**, identical with the sample of **13** prepared above.

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (15). To a solution of 816 mg (2 mmol) of **5a** in 50 mL of EtOAc were added 0.5 mL of freshly distilled quinoline and 1 g of Lindlar catalyst. The mixture was hydrogenated at 1 atm for 5 h at 25 °C. The catalyst was filtered and washed with 50 mL of EtOAc. The combined filtrate was washed with cold 1 N HCl/H_2O (2 × 30 mL) and H_2O (2 × 30 mL) and evaporated to give 780 mg (95%) of a colorless solid foam. The ^1H NMR spectrum of this crude product revealed the presence of traces of starting **5a** and the fully saturated **6a** along with 3′,5′-di-*O*-acetyl-(*Z*)-5-[2-(trimethylsilyl)ethenyl]-2′-deoxyuridine (**6c**) as the highly predominant component: NMR (400 MHz) δ 0.06 (s, 9, $Si(CH_3)_3$), 2.00 and 2.06 (2 s, 3 and 3, OAc's), 5.77 (d, J_{vin} = 15 Hz, 1, vinylic H2), 6.13 (t, 1, H1′), 6.82 (d, J_{vin} = 15 Hz, 1, vinylic H1), 7.40 (s, 1, H6), plus sugar proton multiplets.

A stirred solution of 369 mg (0.9 mmol) of crude **6c** in 20 mL of CS_2 was cooled to −100 °C and treated dropwise over 20 min with a cold (−80 °C) solution of 144 mg (0.9 mmol) of Br_2 in 5 mL of CS_2. The mixture was stirred for an additional 15 min at −100 °C and then allowed to warm to room temperature. Acetonitrile (10 mL) was added, and the resulting mixture was evaporated to dryness and treated directly with 15 mL of $NH_3/MeOH$ (saturated at ~5 °C) for 18 h at 25 °C. This solution was evaporated, and the resulting oil was purified by preparative TLC with $MeOH/CHCl_3$ (1:9). The major band was eluted, and the colorless residue was further purified by preparative HPLC (14% CH_3CN/H_2O, flow rate 2 mL/min) to give 120 mg (40%) of **15** that was recrystallized and found to be identical with a purified authentic sample of **15**.[20]

5-(4-Hydroxybutanoyl)-1-methyluracil (17). A stirred solution of 1.55 g (8 mmol) of **2c** in 160 mL of hot H_2O was cooled to 50 °C, and 160 mg of $HgSO_4$ was added. The mixture was stirred at 50 °C for 2 h, cooled to 25 °C, and saturated with H_2S. This suspension was filtered by using a Celite pad, and the filter cake was washed with 50 mL of MeOH. The combined filtrate was evaporated, 50 mL of Me_2CO/H_2O (1:1) was added and evaporated, and 50 mL of Me_2CO was added and evaporated. The residual faintly yellow solid was crystallized from Me_2CO to give 878 mg (52%) of **17**. An additional 450 mg (26%) of **17** was recovered by evaporation of the mother liquor and preparative TLC of the residue with $MeOH/CHCl_3$ (1:19) with multiple developments. The faster migrating band was eluted, and the product crystallized from Me_2CO to give a total yield of 1.328 g (78%) of **17**: mp 170–172 °C; NMR (200 MHz) δ 1.65 (m, 2, CH_2CH_2OH), 2.91 (t, 2, $COCH_2$), 3.26 (m, 5, NCH_3 and CH_2OH), 4.44 (m, 1, OH), 8.43 (s, 1, H6), 11.50 (br s, 1, NH). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.67; N, 13.23.

The slower migrating and highly fluorescent band was eluted from the TLC plate to give 76 mg (5%) of a colorless solid that had spectral properties consistent with 6-(2-hydroxyethyl)-3-methylfurano[2,3-*d*]pyrimidin-2-one (**3c**): mp 240–245 °C dec; UV (pH 6 or pH 13) λ_{max} 324, 242, 225 nm (ϵ 5100, 11800, 13400), λ_{min} 265, 236 nm (ϵ 900, 11500); NMR δ 2.77 (t, 2, CH_2CH_2OH), 3.50 (s, 3, NCH_3), 3.70 (m, 2, CH_2OH), 4.78 (t, 1, OH), 6.42 (s, 1, H5), 8.44 (s, 1, H4).

5-(4-Hydroxybutanoyl)-2′-deoxyuridine (18). To a solution of 148 mg (0.5 mmol) of **9m** in 5 mL of H_2O was added 10 mg of $HgSO_4$, and stirring was continued at 25 °C for 2 h. The solution was then saturated with H_2S, and the resulting suspension was applied directly to a preparative TLC plate and multiply developed by using the upper phase of *n*-$PrOH/H_2O$/EtOAc (1:2:4). The major UV quenching band was eluted, and evaporation of solvent gave 101 mg (64%) of **18**. This was crystallized with difficulty from CH_3CN/H_2O to give 48 mg (30%) of **18**·0.5H_2O: mp 89–91 °C; UV (pH 6) λ_{max} 284, 229 nm (ϵ 12600, 9800) λ_{min} 249 nm (ϵ 2400); UV (pH 13) λ_{max} 284, 230 (sh) nm (ϵ 9400, 11000) λ_{min} 258 nm (ϵ 2400); NMR (200 MHz) δ 1.68 (m, 2, CH_2CH_2OH), 2.20 (m, 2, H2′,2″), 2.95 (t, 2, $COCH_2$), 3.41 (m, 2, CH_2OH), 3.59 (m, 2, H5′,5″), 3.86 (m, 1, H4′), 4.24 (m, 1, H3′), 6.13 (t, 1, H1′), 8.66 (s, 1, H6). Anal. Calc for $C_{13}H_{18}N_2O_7$·0.5H_2O: C, 48.30; H, 5.92; N, 8.66. Found: C, 48.40; H, 5.80; N, 8.38.

5-(4-Hydroxybutanoyl)uridine (19). A 312-mg (1 mmol) sample of 5-(4-hydroxybutynyl)uridine was dissolved in 10 mL of H_2O, treated with 20 mg of $HgSO_4$, and processed as described for the above conversion of **9m** to **18**. The 220 mg (67%) of crude **19** obtained from the TLC plate was recrystallized from $MeOH/H_2O$ to give **19**: mp 170–173 °C; UV (pH 6) λ_{max} 284, 230 nm (ϵ 13500, 11300) λ_{min} 251 nm (ϵ 3100); UV (pH 13) λ_{max} 286, 235 (sh) nm (ϵ 10200, 12300) λ_{min} 260 nm (ϵ 4300); NMR (200 MHz) δ 1.65 (m, 2, CH_2CH_2OH), 2.90 (t, 2, $COCH_2$), 3.39 (m, 2, CH_2OH), 3.60 (m, 2, H5′,5″), 3.90 (m, 2, H3′, H4′), 4.10 (m, 1, H2′), 5.81 (d, 1, H1′), 8.74 (s, 1, H6). Anal. Calcd for $C_{13}H_{18}N_2O_8$: C, 47.27; H, 5.49; N, 8.48. Found: C, 47.08; H, 5.52; N, 8.18.

3′,5′-Di-*O*-acetyl-5-(4-hydroxybutanoyl)-2′-deoxyuridine (20). A stirred suspension of 571 mg (1.5 mmol) of **5b** in 10 mL of H_2O was warmed to effect solution and then cooled to 25 °C. Stirring was continued for 2 h after addition of 30 mg of $HgSO_4$. The solution was saturated with H_2S, and the resulting suspension was evaporated to dryness. EtOAc (~5 mL) was added, and the slurry was applied to a column (50 g) of silica. The column was developed with EtOAc. Appropriate fractions were pooled and evaporated to give 351 mg (59%) of **20** as a white solid foam. This was crystallized from EtOH with diffusion of Et_2O[40] to give colorless needles of **20**: mp 146–148 °C; NMR δ 1.68 (m, 2, CH_2CH_2OH), 2.06 and 2.09 (2 s, 3 and 3, OAc's), 2.94 (t, 2, $COCH_2$), 3.38 (m, 2, CH_2OH), 6.12 (t, 1, H1′), 8.36 (s, 1, H6), 11.68 (br s, 1, NH), plus sugar proton multiplets. Anal. Calcd for $C_{17}H_{22}N_2O_9$: C, 51.26; H, 5.57; N, 7.03. Found: C, 50.95; H, 5.51; N, 6.84.

6-*n*-Butyl-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-furano[2,3-*d*]pyrimidin-2-one (16). Method A. To a solution of 154 mg (0.5 mmol) of **9c** in 10 mL of $Et_3N/MeOH$ (3:7) was added 10 mg of CuI, and the solution was heated at reflux for 3 h. Volatile materials were evaporated, and the residue was taken up in 20 mL of $CHCl_3$ and washed with 2% disodium EDTA/H_2O (2 × 10 mL) and 10 mL of H_2O. The combined aqueous layers were extractd with $CHCl_3$ (2 × 250 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give a white solid. This product was crystallized from EtOH with diffusion of Et_2O[40] to give 126 mg (82%) of **16** as colorless needles: mp 150–152 °C; UV (pH 6) λ_{max} 327, 245, 224 nm (ϵ 6600, 11700, 15400), λ_{min} 268, 239 nm (ϵ 1300, 11400); NMR (200 MHz) δ 0.92 (t, 3, CH_2CH_3),

1.30–1.70 (m, 4, $CH_2CH_2CH_3$), 2.20 (m, 2, H2′,2″), 2.66 (t, 2, $ArCH_2$), 3.91 (m, 2, H5′,5″), 4.24 (m, 1, H3′), 6.18 (t, 1, H1′), 6.44 (s, 1, H5), 8.68 (s, 1, H4). Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.37; H, 6.43; N, 8.91.

Method B. To a solution of 308 mg (1 mmol) of **9c** in 4 mL of dioxane/H_2O (1:1) was added 10 mg of $HgSO_4$, and the mixture was stirred at 25 °C for 48 h. The major, highly fluorescent product (110 mg, 36%) was isolated by preparative TLC and shown to be **16** (mp 150–152 °C), identical with the product of method A.

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Registry No. 1, 45774-47-8; **2a**, 77875-79-7; **2b**, 77875-82-2; **2c**, 85267-59-0; **3a**, 77875-80-0; **3c**, 85267-72-7; **4**, 1956-30-5; **5a**, 85267-60-3; **5b**, 85267-61-4; **6a**, 85282-15-1; **6b**, 59864-07-2; **6c**, 85267-70-5; **7**, 31356-86-2; **8a**, 77875-86-6; **8b**, 77875-87-7; **8c**, 85267-63-6; **8d**, 77875-89-9; **8e**, 77875-90-2; **8f**, 77875-92-4; **8g**, 77875-91-3; **8h**, 69075-43-0; **8i**, 77875-93-5; **8j**, 85267-64-7; **8k**, 77875-94-6; **8l**, 77882-22-5; **8m**, 85267-65-8; **8n**, 85267-66-9; **8p**, 77875-95-7; **9a**, 77875-96-8; **9b**, 77887-18-4; **9c**, 77875-97-9; **9d**, 77875-98-0; **9e**, 77887-19-5; **9f**, 77887-20-8; **9h**, 61135-33-9; **9j**, 77875-99-1; **9m**, 77876-00-7; **9n**, 84559-05-7; **9o**, 84582-78-5; **9q**, 77876-01-8; **10**, 85267-69-2; **11**, 85267-68-1; **12**, 15176-29-1; **13**, 57741-93-2; **14**, 84621-32-9; **15**, 69304-47-8; **16**, 85267-76-1; **17**, 85267-71-6; **18**, 85267-73-8; **19**, 85267-74-9; **20**, 85267-75-0; $(Ph_3P)_2PdCl_2$, 13965-03-2; CuI, 7681-65-4; 4-(*p*-toluyloxy)butyne, 77875-81-1; 3-butynol, 2028-63-9; 5-(*p*-toluyloxy)pentyne, 77875-85-5; 4-pentynol, 2117-11-5; hexyne, 693-02-7; 3′,5′-di-*O*-acetyl-2′-deoxyuridine, 13030-62-1; (trimethylsilyl)acetylene, 1066-54-2; 4-[(triphenylmethyl)oxy]butyne, 75014-48-1; 3-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-hydroxyethyl)furano[2,3-*d*]pyrimidin-2-one, 85267-77-2; 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-hydroxyethyl)furano[2,3-*d*]pyrimidin-2-one, 85267-62-5; 1-butyne, 107-00-6; 1-pentyne, 627-19-0; 1-heptyne, 628-71-7; 3,3-dimethyl-1-butyne, 917-92-0; benzeneethyne, 536-74-3; trimethylsilylethyne, 1066-54-2; 3-(tetrahydropyranyloxy)-1-propyne, 6089-04-9; 4-(tetrahydropyranyloxy)-1-butyne, 40365-61-5; 2′,3′,5′-tri-*O*-*p*-toluyl-5-[4-(*p*-toluyloxy)butynyl]uridine, 77875-84-4; 5-iodo-2′,3′,5′-tri-*O*-*p*-toluyluridine, 77875-83-3; 5-(4-hydroxybutynyl)uridine, 85267-67-0.

Synthesis and Photophysical Properties of Some *endo*-6-Substituted Norcamphors and Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones

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The reactivity of the π* region of photoexcited carbonyl groups was studied by monitoring the fluorescence of a series of substituted norcamphors and pentacycloundecanones. These substrates contained various probes so positioned as to be able to interact directly with the π*-orbital system of the carbonyl group but not the n-orbital system. No significant perturbation of carbonyl fluorescence was caused by weak electron donors (Cl, OR, SR, and OTs), proton sources (OH, CO_2H), electron sinks (C≡N), and abstractable hydrogen atoms (CH_3, CH_2X). By contrast, the dimethylamino group was able to completely quench fluorescence, presumably via an electron-transfer mechanism. These results support the concept of reduced electrophilicity of the π* region of an excited carbonyl group.

With few exceptions the photochemistry of saturated carbonyl compounds has been rationalized in terms of the properties of the electron-deficient (in plane) molecular orbital system that results from promotion of a n electron to the π* orbital. The diminished electron density in the (delocalized) n-orbital system gives rise to its well-known electrophilic properties, e.g., hydrogen abstractions, additions to electron-rich olefins, and type I and II cleavages. On the other hand, relatively little chemistry has been associated with the electron-rich region above and below the plane of the carbonyl group.[2-4] In fact, much of the experimental work does not differentiate between reactions occurring in the two orthogonal planes since no fixed geometrical relationships were imposed on the reacting centers. We have initiated a program whose objectives are to design experiments that will delineate the stereoelectronic requirements of common photochemical reactions. Our approach to these objectives is to examine the properties of rigidly oriented systems that contain various internal probes positioned to interact *only* with the electronic system above (or below) the plane of the carbonyl group.

In this report we detail some studies that utilize the fluorescent properties of alkanones to monitor the reactivity of various probes with π* systems of excited carbonyl groups. The two molecular systems evaluated were a series of 6-*endo*-norcamphors (**1a–f** and **2**) and some pentacycloundecanones (**3a–h**).

Syntheses: Norcamphors. The key starting material for the syntheses of **1a–f** was the keto acid **2** first reported by Beckmann and Geiger.[5] This compound was converted in one step to the methyl ester dimethyl ketal **4** by heating

(1) On leave from Helwan University, Giza, Egypt.
(2) For references and a summary, see: Turro, N. J.; Dalton, J. C.; Farrington, G.; Niemcyzk, M.; Pond, D. M. *J. Am. Chem. Soc.* **1970**, *92*, 6978.
(3) Zimmerman, H. E. *Adv. Photochem.* **1963**, *1*, 183.
(4) A recent theoretical treatment of the problem of hydrogen-atom abstraction by π* orbitals has been presented: Chandra, A. K. *J. Photochem.* **1979**, *11*, 347. It was concluded that the activation energy for this kind of abstraction was higher than that for in-plane abstraction by a half-filled n orbital.
(5) Beckmann, S.; Geiger, H. *Chem. Ber.* **1961**, *94*, 48.

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