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Bis-Adeninyl and Bis-Uracilyl Hexadiyne Derivatives of Nucleobases

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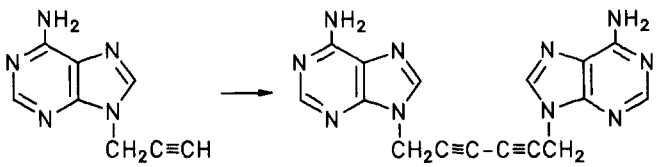
Abstract. Propargyl derivatives of adenine, uracil and N(3)-substituted uracil have been prepared. Rigid 2,4-hexadiyne chains in dimeric compounds were obtained by Eglintons's oxidative dimerization with copper (II) acetate.

The very recent interest for acyclic and macrocyclic compounds constructed from diacetylenic fragments emerges from very interesting properties of diacetylenes.[1-4] For example, incorporated into macrocyclic structure, the diacetylenes can serve as multidentate ligands for transition metal clusters[3] or underwent lithium-induced cyclisation reactions yielding polycyclic aromatic systems.[5] Also, the diacetylenes are known to polymerize in the solid state by exposure to UV light, γ-radiation or thermal annealing.[6] Such polymerizations are of interest for preparation of novel allotropes of carbon[7] or materials with conducting or nonlinear optical properties.[8]

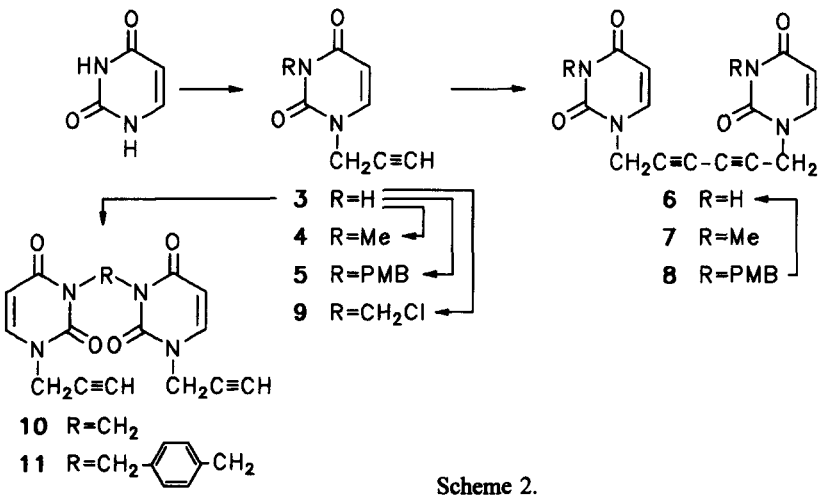
In the present work we describe the syntheses of bis-adenyl and bis-uracilyl diacetylene derivatives **2** and **6**, respectively. Such bis-nucleobase diacetylene derivatives have been prepared with the idea to give, upon polymerization, elongated rod-like polymeric molecules with appended nucleobase binding and recognition sites. On the other hand, derivatives **2** and **6** possesing complementary nucleobases may be expected to recognize themselves in solution, and possibly self-organize into supramolecular assemblies based on intermolecular pyridine-purine hydrogen bonding.[9]



1 **2**

Scheme 1.

To prepare the compounds containing two identical nucleobases connected by a tether with diacetylenic fragment, we have chosen as the first step, the preparation of adenine-N(9) and uracil-N(1) propargyl derivatives **1** and **3**, respectively, and their conversion by oxydative coupling in the second step into respective diacetylenic derivatives **2** and **6**. Although the N(9)-alkylation of adenine by propargyl bromide (compound **1**, Scheme 1) was reported recently,[10] the 1-propargyluracil (**3**) has not been prepared yet. We have prepared **3** (m.p. 168-70 °C) (Scheme 2) in 63% yield by reaction of uracil (previously protected at C(2)-O and C(4)-O using bis(trimethylsilyl)acetamide) with propargyl bromide in acetonitrile.



Scheme 2.

The formation of 2,4-hexadiyne unit between two purine bases by oxidative dimerization of alkylated purine was reported for caffeine, but without any experimental data.[11] To prepare **2** and **6**, we have tried at first the classical Eglinton's method of oxidative coupling of acetylenic compounds using $Cu(OAc)_2 \cdot H_2O$ in pyridine.[12,13] This method in pyrimidine series gave good results only with N(3)-protected uracil compounds **4** (m.p. 187-9 °C) and **5** (m.p. 115-7 °C), giving the coupled products **7** (m.p. 183-5 °C) and **8** (m.p. 184-6

Table 1. ^{1}H-Nmr Data (δ in ppm, J in Hz, internal standard TMS, solvent DMSO-d_6)

	H-C(6), d (J in Hz)	H-(5), d (J in Hz)	$CH_2N(3)$ s	H-C(1'), d (J in Hz)	H-C(3'), t (J in Hz)	other
1				5.03 (2.5)	3.47 (2.5)	8.20 (s, H-C(8)), 8.17 (s, H-C(2)), 7.30 (s, NH_2)
2				5.20 s	-	8.18 (s, H-C(8)), 8.18 (s, H-C(2)), 7.31 (s, NH_2)
3	7.70 (7.9)	5.63 (7.8)		4.51 (2.4)	3.43 (2.5)	11.39 (bs, H-N(3))
4	7.76 (7.9)	5.78 (7.9)		4.58 (2.5)	3.45 (2.5)	3.17 (s, N(3)-CH_3)
5	7.78 (7.9)	5.81 (8.0)	4.91	4.58 (2.2)	3.45 (2.4)	7.25 (d, arom.), 6.87 (d, arom.), 3.72 (s, OCH_3)
6	7.70 (7.9)	5.64 (7.9)		4.68 s	-	11.44 (bs, H-N(3))
7	7.75 (7.9)	5.78 (7.9)		4.74 s	-	3.17 (s, N(3)-CH_3)
8	7.74 (7.9)	5.79 (7.9)	4.89	4.72 s	-	7.14 (d, arom.), 6.84 (d,arom.), 3.70 (s, OCH_3)
9	7.86 (8.0)	5.87 (8.0)	5.67	4.62 (2.5)	3.50 (2.4)	
10	7.71 (8.0)	5.73 (8.0)	5.90	4.54 (1.9)	3.45 (2.5)	
11	7.78 (7.9)	5.81 (8.1)	4.97	4.59 (2.3)	3.40 (2.0)	7.23 (m, arom.)

°C) in 53% and 61% yield, respectively (Scheme 2), while in the case of free uracil **3** the method failed and we could not isolate bis-uracil compound **6**. This compound was then prepared indirectly by the cleavage of *p*-methoxybenzyl group (PMB) in **8** with $AlCl_3$/anisole,[14] in almost quantitative yield. The recently introduced modification of Eglinton's reaction, using acetonitrile as solvent instead of pyridine,[15,16] offered better results, enabling us to prepare **6** (not melting up to 330 °C) directly from **3** (73%), and other coupled compounds in shorter reaction times (2-3 h instead of 24 h) and in higher yields (**8** in 86%). The bis-adenine compound **2** (m.p. 196-8 °C) was prepared in the solvent mixture acetonitrile-pyridine 10:1 or 5:1 in 78% yield.

Continuing our work on methylene-bridged nucleoside analogs,[17,18] we have connected two molecules of 1-propargyluracil (**3**) by a methylene bridge between corresponding N(3)-atoms, using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as proton abstracting agent, in dichloromethane. Besides the bridged compound **10** (m.p. 163-5 °C) (69%), also the N(3)-chloromethyl compound **9** (m.p. 148-50 °C) was isolated as a minor product (5%). *p*-Xylylene-bridged compound **11** (m.p. 234-6 °C) was prepared in an analogous way starting from **3** and α,α'-dibromo-*p*-xylene using DBU, in acetonitrile as reaction solvent (63%). In the attempts of oxidative coupling of bridged compounds **10** and **11**, using copper (II) acetate in high-dilution conditions to give macrocycle compounds, we obtained almost insoluble high melting (> 330 °C) products, that we were unable to characterize. Their IR and NMR spectra (in DMSO-d_6 at 80 °C), however, suggest that the propargyl chains were transformed into hexadiyne ones. Also, the coupled compounds **2** and **6** are high melting and poorly soluble compounds so that attempted association or polymerization experiments in solution were impossible.[19] Attempts to polymerize compounds **2** and **6** in solid state (thermal annealing)[6] did not succeed.

Table 2. ^{13}C-Nmr Data (δ in ppm, internal standard TMS, solvent DMSO-d_6)

	C(4)	C(2)	C(6)	C(5)	C(2')	C(3')	$CH_2N(3)$	C(1')	other
1					78.38	75.90	-	32.31	156.07,152.76, 149.15, 140.17 118.62
2					744.58	67.61	-	32.91	156.10, 152.90 149.14, 140,19 118.56
3	164.09	150.09	144.98	102.20	78.95	76.35	-	37.13	
4	162.49	150.44	142.90	100.85	78.50	76.13		37.75	27.43
5	162.28	150.64	143.27	101.04	78.37	76.22	43.03	37.93	158.60,129.54, 129.09, 113.77 55.13
6	162.87	149.95	143.68	101.64	74.27	67.61	-	37.02	
7	162.47	150.79	142.95	101.02	74.72	67.72	-	38.71	27.43
8	162.24	150.68	143.35	101.19	74.66	67.83	43.12	37.98	158.64,129.57, 129.06, 113.83 55.30
9	160.84	149.62	144.53	100.79	78.97	76.24	49.55	38.15	
10	161.85	150.13	143.49	101.12	78.42	76.33	46.53	37.61	
11	162.09	150.54	143.05	100.87	78.07	76.06	43.18	37.81	135.94, 127.63

The synthetic work directed to preparation of derivatives of compounds **2** and **6** carrying substituents at nucleobases in order to improve their solubility, is in progress.

Spectra. UV spectra of all compounds show a maximum at 260-264 nm coming from nucleobase chromophore. In IR spectra propargyl compounds are characterized by a strong sharp band at 3230-3270 cm^{-1} and a weak one at 2110 cm^{-1}, which both disappear in coupled compounds.

In ^{1}H-NMR spectra, signals of C(1')-H atoms in propargyl compounds **3-5, 9-11** appear as doublets at approx. 4.5 ppm; in coupled compounds they are, in the form of singlets, shifted slightly downfields for about 0.15 ppm (Table 1), while signals of C(3')-H atoms are placed at about 3.45 ppm as triplets and disappear in coupled compounds. In ^{13}C-NMR spectra signals of C(1') atoms in coupled compounds are as well shifted slightly downfields (for 0.6-1.0 ppm) relative to corresponding propargyl compounds, while signals of other propargyl C-atoms are shifted strongly upfields (C(2') for 3.5-4.3 ppm, C(3') for 6.1-6.9 ppm, in adenine derivative even 8.1 ppm) (Table 2).

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19. Spectroscopic data of **2** and **6** shown in Tables 1. and 2. have been obtained from DMSO-d_6 at 80 °C. Analytical samples of **3-5** and **7-11** were prepared by recrystallization from methanol or acetonitrile, compounds **2** and **6** were analyzed as crude products. All of them had correct elemental analysis data.

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