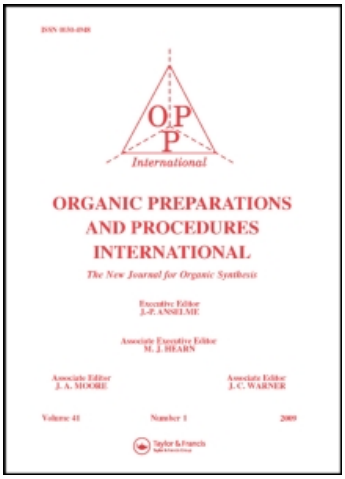

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SYNTHESIS OF 5-ALKYLAMINO- AND 5-DIALKYLAMINO-5-DEOXYTHYMIDINE AND 5'-DEOXY-XYLO-THYMIDINE ANALOGS

Wojciech Urjasz[a]; Lech Celewicz[a]; Krzysztof Golankiewicz[a]
[a] Faculty of Chemistry, Adam Mickiewicz University, Poznan, POLAND

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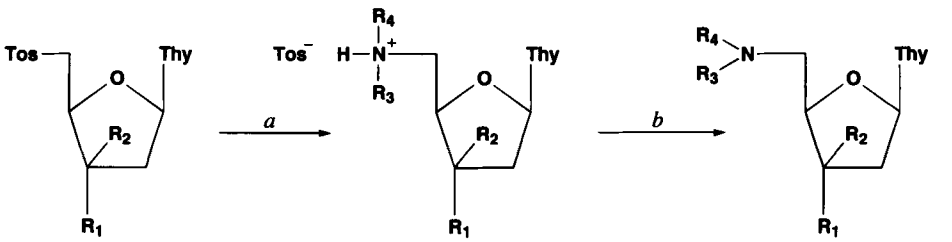
SYNTHESIS OF 5'-ALKYLAMINO- AND 5'-DIALKYLAMINO-5'-DEOXYTHYMIDINE AND 5'-DEOXY-XYLO-THYMIDINE ANALOGS

Submitted by (05/12/94)

Wojciech Urjasz, Lech Celewicz and Krzysztof Golankiewicz*

Faculty of Chemistry, Adam Mickiewicz University
Grunwaldzka 6, 60-780 Poznan, POLAND

The discovery of the significant antiviral activity of the 5'-amino, 3'-amino and 3',5'-diamino analogs of thymidine[1] has stimulated the interest in this type of compounds. The 5'-amino analog of thymidine is a good competitive inhibitor of the phosphorylation of thymidine by thymidine kinase[2,3] and a modest inhibitor of thymidylate kinase.[4] Besides, the 5'-amino analog of thymidine had been shown to be a good inhibitor of the replication of Herpes simplex virus (HSV) in cell culture.[5] In continuation of our research in this field,[6] we are presenting the synthesis of 5'-N-substituted 5'-amino-5'-deoxythymidine and 5'-amino-5'-deoxy-*xylo*-thymidine [1-(2,5-dideoxy-5-amino-β-D-*threo*-pentofuranosyl)thymine] derivatives as the potential antiviral agents. Earlier reports concerning the synthesis of 5'-N-substituted 5'-deoxy nucleosides of adenosine,[7,8] and guanosine[9] and 5'-ethylamino-5'-deoxythymidine[10] have appeared. However, the reported procedure for the synthesis of **3c** gives a mixture of two products **2c** and **3c** and unreacted **1a**. We were able to isolate **3c** in only 35% yield according to this procedure. This paper describes an improved procedure of synthesis of new 5'-N-substituted 5'-amino-5'-deoxythymidyne and 5'-amino-5'-deoxy-*xylo*-thymidine derivatives in good yields.



1a, R_1 = OH, R_2 = H
1b, R_1 = H, R_2 = OH

2a-f, R_1 = OH, R_2 = H
2g-h, R_1 = H, R_2 = OH

3a-f, R_1 = OH, R_2 = H
3g-h, R_1 = H, R_2 = OH

a) R_3R_4NH, CH_3CN, for **3a-f** 90°, 7 hrs; for **3g-h** 120°, 16 hrs. b) Dowex 50Wx2
Ts = Tosyl, Thy = thymin-1-yl, R_3 and R_4 see Table

A series of compounds **3a-f** was obtained by the reaction of 5'-O-tosylthymidine **1a** and the appropriate amine in acetonitrile. In the first step, 5'-O-tosylthymidine was converted into the toluenesulfonate salt of 5'-amino-5'-deoxythymidine **2a** by aminolysis. Compounds **2a-f** were converted to the free bases **3a-f** by passing through the cation-exchange resin Dowex 50 Wx2. The liberated *p*-toluenesulfonic acid was eluted with water and then compounds **3a-f** were desorbed by 1N ammonium hydroxide. Substituted 5'-amino-5'-deoxy-*xylo*-thymidine derivatives **3g-h** were obtained in a

similar way but under more forcing conditions. Thus in the case of compounds **3g-h**, it was necessary to perform the reaction at higher temperature and for longer reaction times.

TABLE. Yields and Melting Points of Compounds **3a-h**

Compound	R_3	R_4	Yield (%)	mp(°C) [a]
3a	H	CH_3	82	156-157 (EtOH)
3b	CH_3	CH_3	85	147-149 (EtOH)
3c	H	CH_2CH_3	87	164-165 (EtOH) reported[10] 161-163 (EtOH:Et_2O 1:1)
3d	H	$CH_2CH_2CH_3$	80	144-145 (EtOH)
3e	H	$CH_2CH{=}CH_2$	82	145-147 (EtOH:MeOH 10:1)
3f	H	CH_2Ph	85	140-142 (EtOH)
3g	H	CH_2CH_3	70	158-160 (EtOH:AcOEt 3:1)
3h	CH_3	CH_3	78	173-175 (EtOH)

a) Crystallization solvent in parenthesis.

Because in ^1H NMR spectra of compounds **3g** and **3h** in DMSO-d_6, the signals of H-2" and H-5" of **3g** and **3h** in DMSO-d_6 appeared in the same region as that of the solvent, the spectra were also recorded in pyridine-d_5 (pyridine absorbs in the region 7.2-8.7 ppm).

EXPERIMENTAL SECTION

Melting points were determined on a Boetius apparatus and are uncorrected. Satisfactory microanalyses were obtained on Perkin-Elmer 240 elemental analyser. UV spectra were recorded on a Shimadzu UV-160 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on Varian-Gemini 300 MHz spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated plates (0.2 mm) and column chromatography was performed on Merck silica gel 60H (5-40 μm). The compounds **1a** and **1b** were prepared according to the literature methods.[11-13]

Preparation of Compounds 2a-h.- To a solution of **1a** or **1b** (1.2 g, 3.03 mmol) in acetonitrile (24 mL), an appropriate amine (18.04 mmol) was added. The reaction mixture was heated in a sealed glass tube at 90° at 7 hrs (**2a-f**) or at 120° for 16 hrs (**2g-h**). After cooling, the tube was opened and the reaction mixture was evaporated under reduced pressures. The residue was dissolved in 100 mL of water, treated with charcoal and the mixture was refluxed for 10 min. The mixture was then filtered through a Celite pad. After evaporation of the solvent, compounds **2a-h** were obtained as white powders.

Preparation of 5'-N-substituted Amino Nucleosides 3a-h.- A solution of **2** (0.6 g) in water (12 mL) was applied to a column (4 x 6 cm) of Dowex 50 Wx2 (H^+) (50-100 mesh). The column was eluted with methanol (200 mL), then with water (400 mL) in order to remove *p*-toluenesulfonic acid and finally the amino nucleosides **3** were eluted with 1N ammonium hydroxide in nearly quantitative yield. The fractions containing **3** were combined, evaporated under reduced pressure and the solid

residue was crystallized. Before crystallization, compounds **3g** and **3h** were purified by flash column chromatography (95 g of silica gel) using as a eluent $CHCl_3$-CH_3OH-NH_4OH (20:10:1). The products **3a-h** were dried *in vacuo* over phosphorus pentoxide.

3a: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9400. ^1H NMR (DMSO-d_6): δ 1.79 (s, 3H, 5-CH_3), 2.10 (m, 2H, H-2', H-2"), 2.32 (s, 3H, 5'N-CH_3), 2.67 (m, 2H, H-5', H-5"), 3.77 (m, 1H, H-4'), 4.17 (m, 1H, H-3'), 6.13 (t, 1H, J = 6.9 Hz, H-1'), 7.64 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ 12.25 (5-CH_3), 36.36 (C-2'), 38.79 (C-3'), 53.33 (5'N-CH_3), 71.30 (C-5'), 83.57 (C-1'), 85.27 (C-4'), 109.38 (C-5), 136.18 (C-6), 150.25 (C-2), 163.50 (C-4).

Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.64; H, 6.63; N, 16.34

3b: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9300. ^1H NMR (DMSO-d_6): δ 1.79 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.14 (m, 2H, H-2', H-2"), 2.20 (s, 6H, 5'N-$(CH_3)_2$), 3.35 (m, 2H, H-5', H-5"), 3.82 (m, 1H, H-4'), 4.10 (m, 1H, H-3'), 6.12 (t, 1H, J = 6.9 Hz, H-1'), 7.60 (d, 1H, J = 1.1 Hz, H-6), 11.29 (br s, 1H, 3N-H). ^{13}C NMR (DMSO-d_6): δ 12.40 (5-CH_3), 38.38 (C-2'), 45.71 (C-3'), 61.10 (5'N-$(CH_3)_2$), 71.91 (C-5'), 83.86 (C-1'), 84.19 (C-4'), 109.27 (C-5), 135.96 (C-6), 150.20 (C-2), 163.49 (C-4).

Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.39; H, 7.28; N, 15.51

3c: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9600. ^1H NMR (DMSO-d_6): δ 1.02 (t, 3H, J = 7.1 Hz, 5'N-C-CH_3), 1.80 (d, 3H, J = 1.0 Hz, 5-CH_3), 2.11 (m, 2H, H-2', H-2"), 2.56 (q, 2H, J = 7.1 Hz, 5'N-CH_2), 2.69 (m, 2H, H-5', H-5"), 3.77 (m, 1H, H-4'), 4.19 (m, 1H, H-3'), 6.14 (t, 1H, J = 6.9Hz, H-1'), 7.68 (d, 1H, J = 1.0 Hz, H-6). ^{13}C NMR (DMSO-d_6): δ 12.20 (5-CH_3), 15.20 (5'N-CH_2-CH_3), 38.91 (C-2'), 43.86 (C-3'), 51.10 (5'N-CH_2), 71.21 (C-5'), 83.56 (C-1'), 85.73 (C-4'), 109.28 (C-5), 136.10 (C-6), 150.30 (C-2), 163.58 (C-4).

Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.45; H, 6.68; N, 15.69

3d: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9600. ^1H NMR (DMSO-d_6): δ 0.87 (t, 3H, J = 7.3 Hz, 5'N-C-C-CH_3), 1.43 (sextet, 2H, J = 7.3 Hz, 5'N-C-CH_2), 1.79 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.11 (m, 2H, H-2', H-2"), 2.54 (t, 2H, J = 6.8 Hz, 5'N-CH_2), 2.71 (m, 2H, H-5', H-5"), 3.78 (m, 1H, H-4'), 4.19 (m, 1H, H-3'), 6.14 (t, 1H, J = 6.9 Hz, H-1'), 7.64 (d, 1H, J = 1.1 Hz, H-6). ^{13}C NMR (DMSO-d_6): δ 11.72 (5'N-CH_2-CH_2-CH_3), 12.14 (5-CH_3), 22.50 (5'N-CH_2-CH_2), 38.79 (C-2'), 51.07 (C-3'), 51.50 (5'N-CH_2), 71.20 (C-5'), 83.59 (C-1'), 85.48 (C-4'), 109.31 (C-5), 136.09 (C-6), 150.22 (C-2), 163.47 (C-4).

Anal. Calcd. for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.16; H, 7.23; N, 14.90

3e: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9400. ^1H-NMR (DMSO-d_6): δ 1.78 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.10 (m, 2H, H-2', H-2"), 2.69 (d, 2H, 5'N-CH_2), 3.18 (m, 2H, H-5', H-5"), 3.78 (m, 1H, H-4'), 4.19 (m, 1H, H-3'), 5.03-5.20 (m, 2H, =CH_2), 5.78-5.91 (m, 1H, -CH=), 6.14 (t, 1H, J = 6.9 Hz, H-1'), 7.65 (d, 1H, J = 1.1 Hz, H-6). ^{13}C NMR (DMSO-d_6): δ 12.17 (5-CH_3), 38.87 (C-2'), 50.49 (C-3'), 51.84 (5'N-CH_2), 71.23 (C-5'), 83.56 (C-1'), 85.62 (C-4'), 109.32 (C-5), 115.11 (=CH_2), 136.07 (-CH=), 137.29 (C-6), 150.22 (C-2), 163.47 (C-4).

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.18; H, 6.70; N, 15.20

3f: UV (CH_3OH): λ_{max} 265 nm, ε_{max} 9500. ^1H NMR (DMSO-d_6): δ 1.73 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.10 (m, 2H, H-2', H-2"), 2.68 (t, 2H, J = 5.8 Hz, 5'N-CH_2), 3.74 (m, 2H, H-5', H-5"), 3.81 (m, 1H, H-

4'), 4.21 (m, 1H, H-3'), 6.14 (t, 1H, J = 6.7 Hz, H-1'), 7.19-7.33 (m, 5H, Ph), 7.60 (d, 1H, J = 1.2 Hz, H-6), 11.24 (br s, 1H, 3N-H). ^{13}C NMR (DMSO-d_6): δ 12.15 (5-CH_3), 38.87 (C-2'), 50.54 (C-3'), 53.10 (5'N-CH_2), 71.21 (C-5'), 83.53 (C-1'), 85.66 (C-4'), 109.35 (C-5), 126.34 (arom), 127.61 (arom), 127.91 (arom), 135.97 (C-6), 140.57 (arom), 150.27 (C-2), 163.54 (C-4).

Anal. Calcd. for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.74; H, 6.25; N, 12.61

3g: UV (CH_3OH): λ_{max} 266 nm, ε_{max} 9300. ^{1}H NMR (DMSO-d_6): δ 1.01 (t, 3H, J = 7.1 Hz, 5'N-C-CH_3), 1.76 (d, 3H, J = 1.0 Hz, 5-CH_3), 1.84 (dd, 1H, J = 2.5 Hz, J = 14.2 Hz, H-2'), 2.55 (q, 2H, J = 7.1 Hz, 5'N-CH_2), 2.80 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-5"), 2.89 (dd, 1H, J = 5.3 Hz, J = 12.5 Hz, H-5'), 3.81 (m, 1H, H-4'), 4.23 (dd, 1H, J = 3.4 Hz, J = 4.7 Hz, H-3'), 6.06 (dd, 1H, J = 2.6 Hz, J = 8.5 Hz, H-1'), 7.84 (d, 1H, J = 1.0 Hz, H-6). ^{1}H NMR (pyridine-d_5): δ 1.05 (t, 3H, J = 7.1 Hz, 5'N-C-CH_3), 1.94 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.25 (dd, 1H, J = 2.3 Hz, J = 14.7 Hz, H-2'), 2.64 (m, 3H, H-2", 5'N-CH_2), 3.22 (dd, 1H, J = 5.2 Hz,J = 12.5 Hz, H-5"), 3.31 (dd, 1H, J = 4.9 Hz, J = 12.5 Hz, H-5'), 4.01 (m, 1H, H-4'), 4.58 (dd, 1H, J = 3.3 Hz, J = 4.7 Hz, H-3'), 6.71 (dd, 1H, J = 2.9 Hz, J = 8.7 Hz, H-1'), 8.32 (d, 1H, J = 1.2 Hz, H-6). ^{13}C NMR (DMSO-d_6): δ 12.44 (5-CH_3), 15.06 (5'N-CH_2-CH_3), 40.62 (C-2'), 43.72 (C-3'), 47.95 (5'N-CH_2), 69.22 (C-5'), 82.60 (C-1'), 83.05 (C-4'), 108.55 (C-5), 137.02 (C-6), 150.31 (C-2), 163.50 (C-4).

Anal. Calcd. $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.48; H, 6.75; N, 15.70

3h: UV (CH_3OH): λ_{max} 267 nm, ε_{max} 9600. ^{1}H NMR (DMSO-d_6): δ 1.77 (d, 3H, J = 1.2 Hz, 5-CH_3), 1.82 (m, 1H, H-2'), 2.18 (s, 6H, 5'N-$(CH_3)_2$), 2.67 (dd, 1H, J = 4.4 Hz, J = 13.2 Hz, H-5'), 3.87 (m, 1H, H-4'), 4.18 (dd, 1H, J = 3.11 Hz, J = 4.9 Hz, H-3'), 6.05 (dd, 1H, J = 2.5 Hz, J = 8.6 Hz, H-1'), 7.79 (d, 1H, J = 1.2 Hz, H-6), 11.26 (br s, 1H, 3N-H). ^{1}H NMR (pyridine-d_5): δ 1.95(d, 3H, J = 1.2 Hz, 5-CH_3), 2.22 (dd, 1H, J = 2.7 Hz, J = 14.9 Hz, H-2'), 2.28 (s, 6H, 5'N-$(CH_3)_2$), 2.66 (m, 1H, H-2"), 2.89 (dd, 1H, J = 6.0 Hz, J = 13.1 Hz, H-5"), 3.09 (dd, 1H, J = 5.4 Hz, J = 13.1 Hz, H-5'), 4.04 (m, 1H, H-4'), 4.53 (dd, 1H, J = 3.1 Hz, J = 5.1 Hz, H-3'), 6.69 (dd, 1H, J = 2.6 Hz, J = 8.7 Hz, H-1'), 8.28 (d, 1H, J = 1.2 Hz, H-6), 13.15 (br s, 1H, 3N-H). ^{13}C NMR (DMSO-d_6): δ 12.51 (5-CH_3), 40.54 (C-2'), 45.78 (C-3'), 57.96 (5'N-$(CH_3)_2$), 69.39 (C-5'), 81.63 (C-1'), 83.15 (C-4'), 108.58 (C-5), 136.99 (C-6), 150.33 (C-2), 163.53 (C-4).

Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.45; H, 7.20; N, 15.54

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SYNTHESIS OF 3-VINYLINDOLES FROM 3-ALKYLIDENEINDOL-2(3H)-ONES

Submitted by (05/24/94)

E. M. Beccalli* and A. Marchesini

Istituto di Chimica Organica, Facoltá di Farmacia
Universita' degli Studi di Milano
via Venezian 21, 20133 Milano, ITALY

We recently described a new and facile entry to heterosubstituted-3vinylindoles from 3-[(1-hydroxy-2-substituted)ethylidene]indol-2(3H)-ones[1] and now report another entry to heterosubstituted-3-vinylindoles starting from 3alkylideneindol-2(3H)-ones (**1**).

3-Alkylideneindol-2(3H)-ones are easily obtained by reaction of indol-2(3H)-one (oxindole) with carbonyl compounds.[2] When compounds **1** are treated with excess of ethyl chloroformate and triethylamine in dichloromethane, the corresponding ethyl 3-ethenyl-2-(ethoxycarbonyloxy)indole-1-carboxylates (**2**) are formed; derivatives **3** were also obtained as by-products. Compounds **3** afford compounds **2** by reaction with triethylamine and ethyl chloroformate. The stereochemistry of **2** has been assigned in analogy to that of ethyl-3-[(1-ethoxycarbonyloxy-2-substituted)ethenyl]-2-(ethoxycarbonyloxy) indole-1-carboxylates[1] and the ethyl-3-[2-aryl-1-ethoxycarbonyloxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylates.[3]