Pergamon

Tetrahedron 55 (1999) 751–758

TETRAHEDRON

Synthesis and Spectroscopic Analysis of Acyclic C-Nucleosides and Homo-C-Analogues from 1-(Chloroalkyl)-1-aza-2-azoniaallene Salts

Najim A. Al-Masoudi,[1*] Yaseen A. Al-Soud,[2] and Armin Geyer[1*]

1. Department of Chemistry, University of Konstanz, D-78457 Konstanz, Germany.
2. Department of Chemistry, Al al-Bayt University, Al-Mafraq, Jordan.

Received 21 September 1998; revised 9 November 1998; accepted 10 November 1998

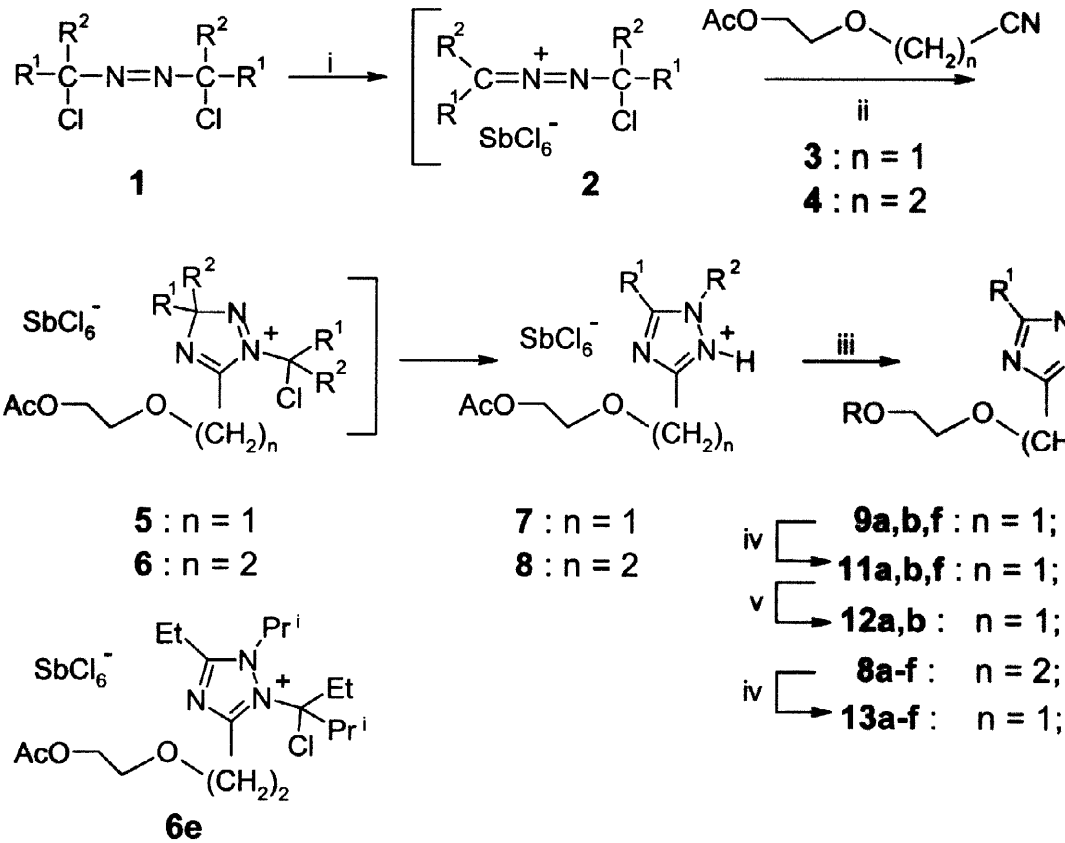
Dedicated to Professor J. C. Jochims on the occasion of his 65 birthday

Abstract Treatment of α,α´-dichloroazo compounds **1** with $SbCl_5$ afforded the 1-(chloroalkyl)-1-aza-2-azoniaallene salts (**2**) which reacted in a 1,3-dipolar cycloaddition with the acetoxy nitriles **3** and **4** to the 1,2,4-triazolium salts **5** and **6**, respectively. **5** and **6** rearranged spontaneously to the protonated 1,2,4 triazoles **7** and **8**, respectively. The salts **7** were *in situ* hydrolyzed to the acyclic 1,2,4-triazole C-nucleosides **9** which gave the free nucleosides **11a,b,** and **f** after deblocking. Treatment of **8** with NaOMe resulted in the de-acetylation along with the hydrolysis of the salts to the free homonucleosides **13a-f**.

The use of acyclonucleoside analogues as antiviral chemotherapeutic agents has stimulated extensive research in the synthesis of this class of compounds [1-3]. The discovery of 9-[(2-hydroxyethoxy)methyl)]guanine [4,5] (Acyclovir, ACV, Zovirax®) as a potent antiherpetic drug [6] was followed by a great number of chemical analogues of ACV. Benzylacyclouridines [7] were described as potent inhibitors of uridinephosphorylase [8], as-triazine acyclonucleosides showed remarkable inhibition of orotidylatephosphoribosyltransferase [9]. Some acyclic 1,2,4-triazole C-nucleosides [10] lacked antiviral properties against HSV-1 and 2 along with other viruses. In recent years, there is also considerable interest in synthesis and the biological activity of homonucleosides [11-13]. We describe the synthesis of acyclic 1,2,4-triazole C-nucleosides and their homo analogues *via* the 1,3-dipolar cycloaddition of 1-(chloroalkyl)-1-aza-2-azoniaallene salt (**2**) [14-18] with the acyclic cyanide moieties **3** [19] and **4**, respectively. A review of acyclonucleosides appeared recently [20].

Jochims and co-workers [14] reported the synthesis of 4,5-dihydro-3H-pyrazonium salts by reacting 1-(chloroalky)-1-aza-2-azoniaallene cations (**2**) with various electron-rich alkenes in the presence of $SbCl_5$. They concluded that the reactive intermediate in such a cycloaddition reaction is the 1-aza-2-azoniaallene hexachloroantimonate. Also some 1,2,4-triazole C-nucleosides [21] were prepared recently *via* the cycloaddition of the intermediates **2** and 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide. In the present study, the cations **2** have been selected for the synthesis of various acyclic C-nucleosides together with their homo analogues. Treatment of **1** with $SbCl_5$ at - 60 °C gave the intermediate **2** which underwent 1,3-dipolar cycloaddition with (2-acetoxyethoxy)methyl cyanide (**3**) [19] and 2-(2-acetoxyethoxy)ethyl cyanide (**4**), respectively. The reactions proceeded one hour at - 60 °C, then one hour at 0 °C, and finally 10 min at r.t. to furnish the [(2-acetoxyethoxy)methyl)]-1,2,4-triazolium hexachloroantimonates (**5**) and the homo analogues **6**, respectively. During or after the formation of the cycloadducts **5** and **6**, the alkyl group at C-5 migrates *via* an [1,2-shift] to N-1, accompanied by the elimination of the ($CClR^1R^2$) group at N-2, leading

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01080-1



i: $SbCl_5$, CH_2Cl_2, - 60 °C
ii: CH_2Cl_2, -60 °C to 23 °C, 130 min
iii: $NaHCO_3$ in H_2O
iv: NaOMe
v: 4-MeC_6H_4COCl, pyridine

7-13	a	b	c	d	e	f
R^1	Me	Me	Et	Me	Et	$(CH_2)_5$
R^2	Me	Et	Et	i-Pr	i-Pr	

finally to the unseparable protonated triazoles **7** and the separable homo analogues **8**, respectively. Unexpectedly, reaction of **2e** with **4** proceeded with the migration of the isopropyl group from C-5 to N-1. The ($CClR^1R^2$) group stayed at N-2, as concluded from the NMR data of salt **6e**. The hexachloroantimonates **8** were separated, recrystallized, and fully analyzed. *In situ* hydrolysis of **7** with aqueous $NaHCO_3$ afforded the acetate derivatives **9a,b,f** as oils in 70, 47 and 49% yield, respectively. Deblocking of **9a,b,f** with 1.2 equivalents of NaOMe proceeded smoothly to the free nucleosides **11a,b,f** as oils in 77, 75 and 87% yield, respectively. Treatment of **8a-f** with 7.5 equivalents of NaOMe resulted in the removal of the acetate groups and the formation of the free homonucleosides **13a-f** as oils in 79, 85, 83, 71 and 85% yield, respectively. Analogous treatment of **6e** with 9.0 equivalents of NaOMe afforded **13e** as oil in 59% yield. An attempt to crystallize **11a,b** was unsuccessful. Therefore, **11a,b** were reacted with 4-methylbenzoyl chloride in dry pyridine at r.t. to furnish **12a,b** as syrups in 75 and 69% yields, respectively. The structures of the nucleosides were proven by homo- and heteronuclear NMR spectroscopic methods and by mass spectra. The ^1H NMR spectra of **9a,b,f** showed similar signal patterns. CH_2-1' appeared as singlets at δ 4.56, 4.57 and 4.56, respectively. The triplets at δ 4.23, 4.25 and 4.25 were attributed to CH_2-4', whereas the triplets at δ 3.79, 3.78 and 3.78 were identified as CH_2-3', respectively. CH_2-1' of the free nucleosides **11a,b,f** appeared as singlets at δ 4.34, 4.50 and 4.37, respectively. CH_2-3' and CH_2-4'

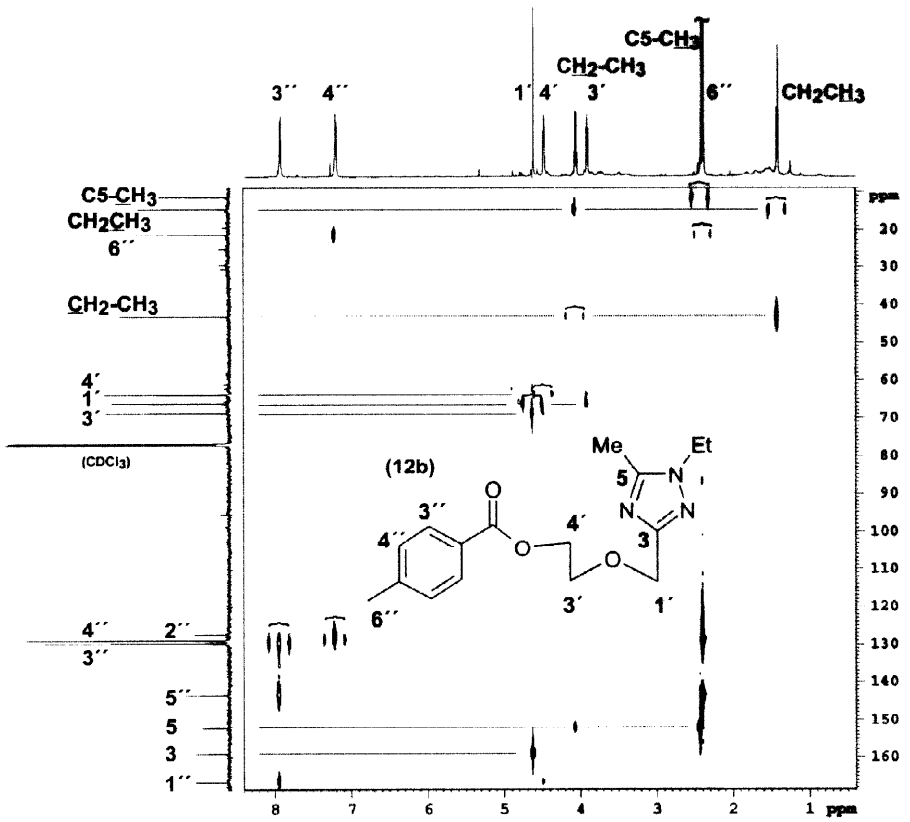


Fig. 1: Gradient selected HMBC spectrum of **12b** in $CDCl_3$ (600 MHz, 300K). One-bond couplings are highlighted by brackets. The C-5′of the triazole couples with the methyl group at $\delta(^1H)$ 2.44. C-4′′ and C-5′′ of the 4-methylbenzoyl group show long-range couplings to the methyl group at $\delta(^1H)$ 2.40.

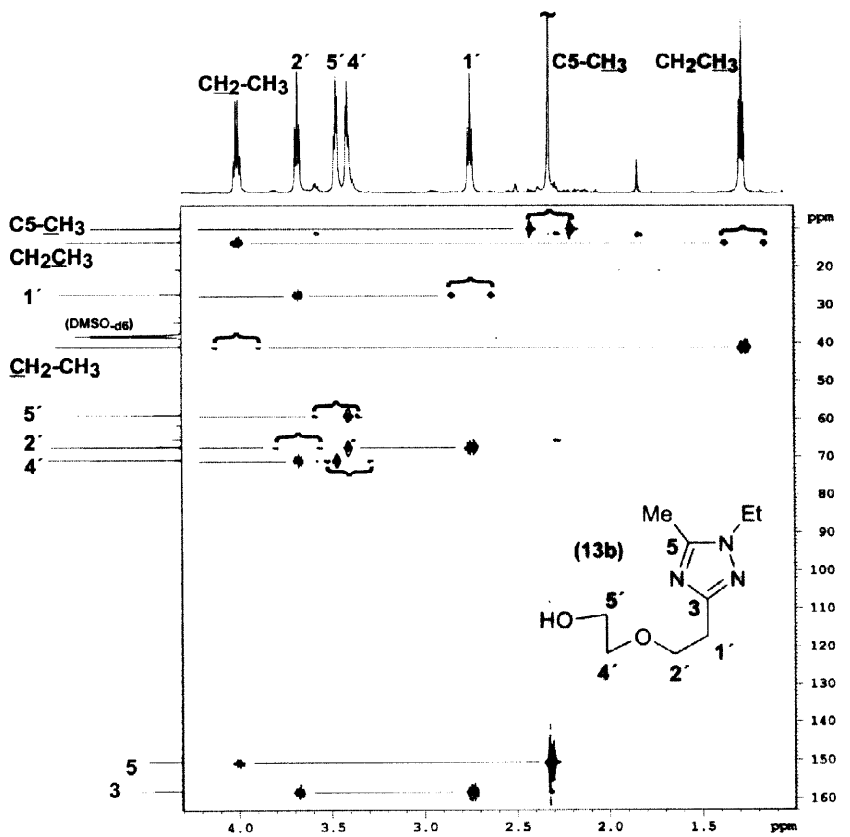


Fig. 2: Gradient selected HMBC spectrum of **13b** in $DMSO_{d6}$ (600 MHz, 300K). One-bond couplings are highlighted by brackets. Both pairs of methylene groups are assigned via their hetreonuclear long-range couplings.

resonated as multiplets in the region δ 3-91 - 3.37. The alkyl groups at N-1 and C-5 were assigned. The structures of **11a,b** were further characterized as 4-methylbenzoates **12a,b**. **12b** was selected for further NMR spectroscopic studies and Fig. 1 shows the gradient selected HMBC spectrum [22]. The carbonyl group (C-1'') at δ 166.5 shows a $^3J_{C,H}$ correlation to CH_2-4' at δ 4.48. CH_2-1' was identified from its heteronuclear correlation to C-3'. C-5' shows a $^2J_{C,H}$ coupling to the methyl protons at δ 2.44.

The ^{1}H NMR spectra of the homo analogues **8a-f** were characterized by the presence of the NH signals in the region δ 12.0 - 12.2 while the protons CH_2-5' appeared at lower field (δ 4.23, 4.20, 4.19, 4.94 and 4.23 respectively). CH_2-2' of **8a-f** resonated as triplets in the region δ 3.78 - 3.72 with J values between 5.6 - 5.8 Hz. The triplets at the region δ 3.63 - 3.69 with J values between 4.3 - 4.6 Hz were assigned to CH_2-4'. CH_2-1' appeared between δ 2.93 - 3.07 as triplets with coupling constants of 5.6 - 6.5 Hz. The ^{13}C NMR spectra of **8a-f** contained the resonance signals C-3 and C-5 of the triazole ring at higher field between δ 156 - 153.5 and δ 154.8 - 150.0, respectively. Fig. 2 shows the gradient selected HMBC spectrum of the deprotected homonucleoside **13b**. C-3 at lowest field is identified from its correlation to the ethyl group and to one methylene group (CH_2-1') of the glycol moiety. CH_2-1' shows $^3J_{H,H}$ couplings to CH_2-2'. C-2' shows a heteronulear long-range correlation to the CH_2-4' methylene group.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded at Bruker AC-250, WM-250, and DRX 600 spectrometers. The signal assignments for protons were verified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^{1}H-^{13}C COSY or HMQC experiments. The cycloadditions were performed with exclusion of moisture. Melting points are not corrected. Column chromatography was performed on silica gel (70 - 230 mesh; Merck).

2-(2-Acetoxyethoxy)ethyl cyanide (**4**). A solution of 2-(2-hydroxyethoxy)ethyl cyanide [22] (4.0 g, 34.78 mmol) in dry pyridine (50 mL) and acetic anhydride (30 mL) was kept at r.t. for 5 h. The solution was evaporated to dryness and the residue was co-evaporated with EtOH (4 x 30 mL). Column chromatography with the solvent mixture $CHCl_3$/MeOH (99 : 1) afforded pure **4** (4.86 g, 89 %) as an oil. ^{1}H NMR ($CDCl_3$): 4.22 (t, 2H, CH_2-6); 3.71 (m, 4H, CH_2-3, CH_2-5); 2.64 (t, 2H, CH_2-2). ^{13}C NMR ($CDCl_3$): 170.4 (CO); 117.5 (CN); 68.6, 65.3 (C-3, C-5); 62.7 (C-6); 20.4 (CH_3); 18.3 (C-6). m/z (FAB) 157 (M^+).

1,5-Dialkyl-3-[(2-acetoxyethoxy)methyl]-1H-1,2,4-triazoles (**9**):

General procedure. A solution of $SbCl_5$ (3.0 g, 10 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred, cold solution (- 60 °C) of **1** (10 mmol) and 2-(acetoxyethoxy)methyl cyanide (**3**) [19] (1.43 g, 10 mmol) in CH_2Cl_2 (20 mL). After stirring for 2 h at - 60 °C, 1 h at 0 °C and 10 min at r.t., pentane (100 mL) was added. The residue was dissolved in CH_3CN (60 mL). After cooling to 0 °C, an aqueous solution of $NaHCO_3$ (8.40 g, 100 mmol in 100 mL H_2O) was added. The mixture was stirred at r. t. for 2 h and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The residual oil was purified by column chromatography using $CHCl_3$ and then $CHCl_3$/MeOH (95 : 5) as eluents.

1,5-Dimethyl-3-[(2-acetoxyethoxymethyl)-1H-1,2,4-triazole (**9a**): From **1a** (1.83 g). Yield: 1.50 g, 70%, oil. ^{1}H NMR ($CDCl_3$): 4.56 (s, 2H, CH_2-1'); 4.23 (m, 2H, CH_2-4'); 3.79 (m, 2H, CH_2-3'); 3.80, 2.44 (2s, 6H, N-CH_3 C_5-CH_3); 2.07 (s, 3H, $COCH_3$). m/z ($C_9H_{15}N_3O_3$) (EI) 213 (M^+).

1-Ethyl-5-methyl-3-[(2-acetoxyethoxy)methyl]-1H-1,2,4-triazole (**9b**): From **1b** (2.11). Yield: 1.07 g, 47%, oil. ^{1}H NMR ($CDCl_3$): 4.57 (s, 2H, CH_2-1'); 4.25 (t, 2H, J 4.7 Hz, CH_2-4'); 4.08 (q, 2H, J 7.3 Hz, N-CH_2CH_3); 3.78 (t, 2H, J 4.8 Hz, CH_2-3'); 2.44 (s, 3H, C_5-CH_3); 2.04 (s, 3H, $COCH_3$); 1.44 (t, 3H, N-CH_2CH_3). m/z ($C_{10}H_{17}N_3O_3$) (FAB>0) 228 (MH^+).

6,7,8,9-Tetrahydro-2-[(2-acetoxyethoxy)methyl]-1H-1,2,4-triazolo[1,5-a]azepine (**9f**): From **1f** (2.35 g). Yield: 1.24 g, 49%, oil. ^{1}H NMR ($CDCl_3$): 4.56 (s, 2H, CH_2-1'); 4.25 (m, 4H, CH_2-4', CH_2-10); 3.78 (m, 2H, CH_2-3'); 2.95 (m, 2H, CH_2-6); 1.85 (m, 2H, CH_2-8); 1.76 (m, 2H, CH_2-9); 1.53 (m, 2H, CH_2-7). m/z ($C_{12}H_{19}N_3O_3$) (FAB>0) 254 (MH^+).

1,5-Dialkyl-3-[(2-hydroxyethoxy)methyl]-1H-1,2,4-triazoles (**11**):

General Procedure. A solution of **9** (1.0 mmol) in NaOMe (10 mL) [from Na (135 mg, 5.88 mmol)] was stirred at r. t. for 3 h. The reaction mixture was neutralized with Amberlite IR 120 (H^+) and filtered. The resine was washed with MeOH (20 mL) and the combined filtrates were evaporated to dryness. The residual oil was purified by column chromatography using $CHCl_3$/MeOH (95 : 5) as eluent.

1,5-Dimethyl-3-[(2-hydroxyethoxy)methyl]-1H-1,2,4-triazole (**11a**): Yield: 131 mg, 77%, oil. ^{1}H NMR (DMSO-d_6): 4.34 (s, 2H, CH_2-1'); 3.72 (s, 3H, N-CH_3); 3.47 - 3.39 (m, 5H, CH_2-3', CH_2-4', OH); 2.22 (s, 3H, C_5-CH_3). (DMSO-d_6): 159.2 (C-3); 153.4 (C-5); 65.5 (C-3'); 62.9 (C-1'); 56.4 (C-4'); 35.1 (N-CH_3); 11.1 (C_5-CH_3). m/z ($C_7H_{13}N_3O_2$) (FAB>0) 172 (MH^+).

1-Ethyl-5-methyl-3-[(2-hydroxyethoxy)methyl]-1H-1,2,4-triazole (**11b**): Yield: 138 mg, 75%, oil. ^{1}H NMR (DMSO-d_6): 5.76 (s, 1H, OH); 4.50 (s, 2H, CH_2-1'); 4.14 (q, 2H, J 7.1 Hz, N-$\underline{CH_2}CH_3$); 3.51 - 3.42 (m , 4H, CH_2-3', CH_2-4'); 2.51 (s, 3H, C_5-CH_3); 1.34 (t, 3H, J 7.1 Hz, N-$CH_2\underline{CH_3}$). ^{13}C NMR (DMSO-d_6): 155.8 (C-3); 151.6 (C-5); 64.1 (C-3'); 62.1 (C-1'); 54.9 (C-4'); 43.3 (N-$\underline{CH_2}CH_3$); 14.3 (N-$CH_2\underline{CH_3}$); 10.6 (C_5-CH_3). m/z ($C_8H_{15}N_3O_3$) (FAB>0): 186 (MH^+); 208 (MNa^+).

6,7,8,9-Tetrahydro-2-[(2-acetoxyethoxy)methyl]-1H-1,2,4-triazolo-[1,5-a]azepine (**11f**): Yield: 184 mg, 87%, oil. ^{1}H NMR (DMSO-d_6): 4.37 (s, 2H, CH_2-1'); 4.18 (t, 2H, J 5.0 Hz, CH_2-10); 4.47 (m, 1H, OH); 3.91 (m, 2H, CH_2-4'); 3.37 (m, 2H, CH_2-3'); 2.86 (t, 2H, J 2.5 Hz 2.5 Hz, CH_2-6); 1.79 (t, 2H, J 4.8 Hz, CH_2-8); 1.68 (t, 2H, J 4.4 Hz, CH_2-9); 1.58 (t, 2H, J 5.5 Hz, CH_2-7).^{13}C NMR (DMSO-d_6): 153.9 (C-3); 156.7 (C-5); 72.4 (C-3'); 63.1 (C-1'); 60.6 (C-4'); 51.4 (C-10); 29.7 (C-8); 27.2 (C-9); 26.4 (C-6); 24.7 (C-7). m/z ($C_{10}H_{17}N_3O_2$) (FAB>0) 212 (MH^+).

1,5-Dimethyl-3-{[2-(4-methylbenzoyloxy)ethoxy]methyl}-1H-1,2,4-triazole (**12a**): 4-Methylbenzoyl chloride (0.18 g, 1.17 mmol) was added to a solution of **11a** (0.10 g, 0.58 mmol) in dry pyridine (5 mL) at 0 °C, then left at r. t. for 5 h. Few drops of water was added with stirring for 1 h, then partitioned between $CHCl_3$ (20 mL) and 10% H_2SO_4 (3 x 15 mL). The organic phase was shaken with dil. solution of $NaHCO_3$ (20 mL) and finally with water (10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness to give an oil, which was purified on a column of silica (10 g), using $CHCl_3$-MeOH (98:2) as eluent to give **12a** as pure oil (0.21 g, 75 %). ^{1}H NMR ($CDCl_3$): 7.94 (d, 2H, J 8.2 Hz, CH-3''); 7.71 (d, 2H, J 8.2 Hz, CH-4''); 4.62 (s, 2H, CH_2-1'); 4.48 (t, 3H, J 4.7 Hz, CH_2-4'); 3.90 (t, 2H, J 4.7 Hz, CH_2-3'); 3.77 (s, 3H, N-CH_3); 2.43 (s, 2H, C_5-CH_3); 2.40 (s, 3H, CH_3-6''). ^{13}C NMR ($CDCl_3$): 166.6 (C-1''); 159.1 (C-3); 152.9 (C-5); 143.7 (C-5''); 129.7 (C-3''); 128.9 (C-4''); 126.9 (C-2''); 68.8 (C-3'); 66.2 (C-1'); 62.3 (C-4'); 35.0 (N-CH_3); 21.6 (C-6''); 11.7 (C_5-CH_3). m/z ($C_{15}H_{19}N_3O_3$) (FAB>0): 290 (MH^+); 312 (MNa^+).

1-Ethyl-5-methyl-3-{[2-(4-methylbenzoyloxy)ethoxy]methyl}-1H-1,2,4-triazole (**12b**): 4-Methylbenzoyl chloride (0.16 g, 0.90 mmol) was added to a solution of **11b** (0.10 g, 0.54 mmol) in dry pyridine (5.0 mL) as described for the synthesis of **12a**. The oily product was purified by column chromatography with $CHCl_3$/MeOH (49:1) to give **12b** (0.11 g, 69%) as an oil. ^{1}H NMR (600 MHz, $CDCl_3$): 7.94 (d, 2H, J 8.2 Hz, CH-3''); 7.21 (d, 2H, j 8.2 Hz, CH-4''); 4.62 (s, 1H, CH_2-1'); 4.49 (t, 2H, J 4.9 Hz, CH_2-4'); 4.02 (q, 2H, J 7.2, 14.5, Hz, N-$\underline{CH_2}CH_3$); 3.89 (t, 2H, J 4.9 Hz, CH_2-3'); 2.41 (s, 3H, C_5-CH_3); 2.31 (s, 3H, CH_3-6''); 1.42 (t, 3H, J 7.2 Hz; N-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$): 166.5 (C-1''); 159.1 (C-3); 151.9 (C-5); 143.5 (C-5''); 129.8 (C-3''); 129.1 (C-3''); 127.3 (C-2''); 68.8 (C-3'); 66.3 (C-1'); 63.9 (C-4'); 43.2 (N-$\underline{CH_2}CH_3$); 21.6 (C-6''); 14.9 (N-$CH_2\underline{CH_3}$), 11.6 (C_5-CH_3). m/z ($C_{16}H_{21}N_3O_3$) (FAB>0) 304 (MH^+).

1,5-Dialkyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexachloroantimonates (**8**): *General procedure*. A solution of $SbCl_5$ (1.5 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a cold (- 60 °C), stirred solution of **1** (5.0 mmol) and (2-acetoxyethoxy)ethyl cyanide (**4**) (0.78 g, 5.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at - 60 °C for 1 h, at 0 °C for 1 h, and at r. t. for 10 min. Pentane (50 mL) was added slowly and the crude precipitate was filtered and dried. Recrystallization from CH_2Cl_2/ether gave hexachloroantimonate salt.

1,5-Dimethyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexachloroantimonate (**8a**): From **1a** (0.92 g). Yield: 1.63 g, 58%; m.p. 129 - 131 °C dec. ^{1}H NMR (CD_3CN): 12.02 (s, 1H, NH); 4.23 (t, 2H, J 4.5 Hz; CH_2-5'); 3.88 (s, 3H, CH_3); 3.76 (t, 2H, J 4.5 Hz, CH_2-5'); 3.69 (t, 2H, J 4.5 Hz, CH_2-4'); 3.06 (t, 2H, J 5.6 Hz, CH_2-1'); 2.66 (s, 3H, CH_3); 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (CD_3CN): 172.3 (C=O); 153.5 (C-3); 152.1 (C-5); 70.1 (C-4'); 67.6 (C-2'); 64.3 (C-5'); 37.7 (N-CH_3); 26.8 (C-1'); 21.3 ($COCH_3$); 10.7 (C_5-CH_3). (Found: C, 21.12; H, 3.09; N, 7.52. Calcd for $C_{10}H_{18}Cl_6N_3O_3Sb$ (MW 562.7): C, 21.34; H, 3.22; N, 7.47%). m/z (FAB) 228 (M^+)

1-Ethyl-5-methyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexachloroantimonate (**8b**): From **1b** (1.06 g). Yield: 1.84 g, 64%; m.p. 81 - 83 °C dec. ^{1}H NMR (CD_3CN): 12.01 (bs, 1H, NH); 4.21 (m, 4H, CH_2CH_3, CH_2-5'); 3.77 (t, 2H, J 5.6 Hz, CH_2-2'); 3.69 (t, 2H, J 4.0 Hz, CH_2-4'); 3.07 (t, 2H, J 5.6 Hz, CH_2-1'); 2.68 (s, 3H, C_5-CH_3); 2.04 (s, 3H, $COCH_3$); 1.46 (t, 3H, J 7.1 Hz, CH_2CH_3). ^{13}C NMR (CD_3CN): 172.5 (C=O); 153.7 (C-3); 151.3 (C-5); 70.0 (C-4'); 67.6 (C-2'); 64.3 (C-5'); 46.2 (CH_2CH_3); 26.9 (C-1'); 21.3 ($COCH_3$); 14.0 (CH_2CH_3); 10.6 (C_5-CH_3). (Found: C, 23.03; H, 3.42; N, 7.38. Calcd for $C_{11}H_{20}Cl_6N_3O_3Sb$ (MW 576.7): C, 22.91; H, 3.50; N, 7.29%). m/z (FAB) 242 (M^+).

1,5-Diethyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexachloroantimonate (**8c**): From **1c** (1.21 g). Yield: 2.07 g, 70%; m.p. 105 - 107 °C dec. ^{1}H NMR (CD_3CN): 12.00 (s, 1H, NH); 4.21 (q, 2H, J 7.1 Hz, CH_2CH_3); 4.19 (t, 2H, J 4.6 Hz, CH_2-5'); 3.78 (t, 2H, J 5.8 Hz, CH_2-2'); 3.68 (t, 2H, J 4.6 Hz, CH_2-4'); 3.07 (q, 2H, J 5.8 Hz, CH_2-1'); 3.04 (q, 2H, J 7.5 Hz, CH_2CH_3); 2.03 (s, 3H, $COCH_3$); 1.46 (t, 3H, J 7.1 Hz, CH_2CH_3); 1.37 (t, 3H, J 7.5 Hz, CH_2CH_3).^{13}C NMR (CD_3CN): 172.3 (C=O); 155.4 (C-3); 153.8 (C-5); 70.0 (C-5'); 67.6 (C-4'); 64.3 (C-2'); 46.3 (CH_2CH_3); 27.0 (C-1'); 21.3 ($COCH_3$); 18.6 (CH_2CH_3); 14.3 (CH_2CH_3); 11.2 (CH_2CH_3). (Found: C, 24.26; H, 3.66; N, 7.20. Calcd for $C_{12}H_{22}Cl_6N_3O_3Sb$ (MW 590.8): C, 24.40; H, 3.75; N, 7.11%). m/z (FAB) 256 (M^+).

1-Isopropyl-5-methyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexaachloroantimonate (**8d**): From **1d** (1.20 g). Yield: 1.92 g, 65%; m.p. 99 - 101 °C dec. ^{1}H NMR (CD_3CN): 12.02 (bs, 1H, NH); 4.71 [m, 1H, $CH(CH_3)_2$]; 4.23 (m, 2H, CH_2-5'); 3.77 (t, 2H, J 5.8 Hz, CH_2-2'); 3.69 (dd, 2H, J 4.3 Hz, CH_2-4'); 3.06 (t, 2H, J 5.7 Hz, CH_2-1'); 2.69 (s, 3H, C_5-CH_3); 2.04 (s, 3H, $COCH_3$); 1.49, 1.47 [2s, 6H, $CH(CH_3)_2$]. ^{13}C NMR (CD_3CN): 172.3 (C=O); 153.5 (C-3); 150.0 (C-5); 69.9 (C-4'); 67.4 (C-2'); 64.1 (C-5'); 53. [$CH(CH_3)_2$]; 26.8 (C-1'); 21.1 [$COCH_3$, $CH(CH_3)_2$]; 10.4 (C_5-CH_3). (Found: C, 23.98; H, 3.64; N, 7.42. Calcd for $C_{12}H_{22}Cl_6N_3O_3Sb$ (590.8): C, 24.40; H, 3.75; N, 7.11%). m/z (FAB) 256 (M^+).

2-(1-Chloro-1-ethyl-2-methylpropyl)-5-ethyl-1-isopropyl-3-[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolium hexachloroantimonate (**6e**): From **1e** (1.34 g). Yield: 2.46 g, 68%; m.p. 125 - 126 °C dec. ^{1}H NMR (CD_3CN): 4.94 [m, 1H, N^1-$CH(CH_3)_2$]; 4.11 (q, 2H, J 3.2 Hz, CH_2CH_3); 3.87 (t, 2H, J 5.5 Hz, CH_2-5'); 3.72 (t, 2H, J 5.6 Hz, CH_2-2'); 3.63 (t, 2H, J 4.6 Hz, CH_2-4'); 3.00 (q, 2H, J 7.3 Hz, CH_2CH_3); 2.93 (t, 2H, J 6.5 Hz, CH_2-1'); 2.63 [m, 1H, N^2-$CH(CH_3)_2$]; 1.97 (s, 3H, $COCH_3$); 1.58 [d, 3H, J 1.5 Hz, N^1-$CH(CH_3)_2$]; 1.56 [d, 6H, N^1-$CH(CH_3)_2$]; 1.37 (t, 3H, J 7.3 Hz, CH_2CH_3); 1.04 [d, 6H, J 6.6 Hz, N^2-$CH(CH_3)_2$]; 0.98 [d, 6H, J 6.6 Hz, N^2-$CH(CH_3)_2$]; 0.93 (t, 3H, J 3.5 Hz, CH_2CH_3). ^{13}C NMR (CD_3CN): 171.5 (C=O); 156.2 (C-3); 154.8 (C-5); 99.4 ([N^2-$CClEt(CHMe_2)$], (C-4'); 68.2 (C-2'); 63.9 (C-5'); 53.1 [N^1-$CH(CH_3)_2$]; 40.4 [N^2-$CClEt(CHMe_2)$]; 33.9 (C-1'); 27.4, 21.5 [N^2-$CClEt(CHMe_2)$]; 21.1, 20.9 [$COCH_3$, N^1-$CH(CH_3)_2$]; 18.3, 17.4 ($2CH_2CH_3$); 10.7, 8.8 ($2CH_2CH_3$). (Found: C, 31.39; H, 4.69; N, 5.96. Calcd for $C_{19}H_{35}Cl_7N_3O_3Sb$ (723.4): C, 31.55; H, 4.88; N, 5.81%). m/z (FAB) 389/391 (M^+).

6,7,8,9-Tetrahydro-2[(2-acetoxyethoxy)ethyl]-1H-1,2,4-triazolo[1,5-a]azepine (**8f**): From **1f** (1.20 g). Yield: 2.17 g, 72%; m.p. 165 - 167 °C dec. ^{1}H NMR (CD_3CN): 4.39 (t, 2H, J 5.0 Hz, CH_2-10); 4.23 (t, 2H, J 4.5 Hz, CH_2-5'); 3.76 (t, 2H, J 5.8 Hz, CH_2-2'); 3.69 (t, 2H, J 4.5 Hz, CH_2-4'); 3.15 (t, 2H, J 5.5 Hz, CH_2-6); 3.05 (t, 2H, J 5.8 Hz, CH_2-1'); 2.02 (s, 3H, $COCH_3$); 1.99 (m, 2H, CH_2-8); 1.93 (m, 2H, CH_2-9); 1.86 (m, 2H, CH_2-7). ^{13}C NMR (CD_3CN): 172.5 (C=O); 156.1 (C-3); 152.6 (C-5); 70.1 (C-5'); 67.6 (C-4'); 64.3 (C-2'); 54.1 (C-10); 33.4 (C-8); 29.5 (C-1'); 26.7 (C-9); 26.4 (C-6); 25.3 (C-7); 23.8 ($CO\underline{C}H_3$). (Found: C, 25.78; H, 3.59; N, 7.04. Calcd for $C_{13}H_{22}Cl_6N_3O_3Sb$ (602.8): C, 25.90; H, 3.68; N, 6.97%). m/z (FAB) 268 (M^+).

1,5-Dialkyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole analogues (**13**): *General procedure*. A solution of **8** (1.78 mmol) in NaOMe (10 mL) [from Na (7.5 and 9.0 mol. equiv.) was stirred at r. t. for 4 - 5 h. The salt was removed by filtration and the filtrate was neutralized with Amberlite IR 120 (H^+). The resin was washed with MeOH (15 mL) and the solvent was removed from the combined extracts. The residual oil was purified on a short column using $CHCl_3$/MeOH (9:1) as eluent.

1,5-Dimethyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole (**13a**): From **8a** (1.0 g) and Na (0.31 g, 13.37 mmol). Yield: 0.26 g, 79%, oil. ^{1}H NMR (DMSO-d_6): 4.73 (bs, 1H, OH); 4.64 (t, 2H, J 4.5 Hz, CH_2-5'); 3.66 (s, 3H, N-CH_3); 3.63 (t, 2H, J 7.2 Hz, CH_2-2'); 3.39 (t, 2H, J 4.5 Hz, CH_2-4'); 2.72 (t, 2H, J 7.2 Hz, CH_2-1'); 2.29 (s, 3H, C_5-CH_3). ^{13}C NMR (DMSO-d_6): 158.1 (C-3); 152.2 (C-5); 71.9 (C-4'); 68.7 (C-2'); 60.2 (C-5'); 34.6 (N-CH_3); 11.2 (C_5-CH_3). m/z (FAB> 0) 186 (MH^+), 208 (MNa^+).

1-Ethyl-5-methyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole (**13b**): From **8b** (1.03 g) and Na (0.31 g, 13.37 mmol). Yield: 0.30 g, 85%, oil. ^{1}H NMR (600 MHz, DMSO-d_6): 4.46 (s, 2H, CH_2-1'); 4.00 (q, 2H, J 7.0 Hz, N-$\underline{CH_2}CH_3$); 3.67 (t, 2H, J 7.0 Hz, CH_2-2'); 3.46 (t, 2H, J 5.0 Hz, CH_2-5'); 3.39 (t, 2H, J 5.0 Hz, CH_2-4'); 2.73 (t, 2H, J 7.0 Hz, N-$CH_2\underline{CH_3}$). ^{13}C NMR (DMSO-d_6): 159.0 (C-3); 151.3 (C-5); 71.9 (C-4'); 68.9 (C-2'); 60.2 (C-5'); 42.3 (N-$\underline{CH_2}CH_3$); 28.5 (C-1'); 14.8 (N-$CH_2\underline{CH_3}$); 11.1 (C_5-CH_3). m/z (FAB>0) 200 (MH^+); 222 (MNa^+).

1,5-Diethyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole (**13c**): From **8c** (1.05 g) and Na (0.29 g, 12.69 mmol). Yield: 0.30 g, 83%, oil. ^{1}H NMR (600 MHz, DMSO-d_6): 4.20 (q, 2H, J 7.0 Hz, N-$\underline{CH_2}CH_3$); 3.77 (t, 2H, J 6.1 Hz, CH_2-2'); 3.45 (t, 2H, J 5.0 Hz, CH_2-5'); 3.42 (t, 2H, J 5.0 Hz, CH_2-4'); 3.00 (t, 2H, J 6.1 Hz, CH_2-1'); 2.98 (q, 2H, J 7.5 Hz, C_5-$\underline{CH_2}CH_3$); 1.34 (t, 3H, J 7.0 Hz, C_5-$CH_2\underline{CH_3}$); 1.28 (t, 3H, N-$CH_2\underline{CH_3}$). ^{13}C NMR (DMSO-d_6): 154.5 (C-3); 153.8 (C-5); 71.9 (C-4'); 66.8 (C-2'); 59.9 (C-5'); 43.8 (N-$\underline{CH_2}CH_3$); 26.3 (C-1'); 14.0 (N-$CH_2\underline{CH_3}$); 12.2 (N-$CH_2\underline{CH_3}$); 10.8 (C_5-$CH_2\underline{CH_3}$). m/z (EI) 195 (M^+ - H_2O).

1-Isopropyl-5-methyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole (**13d**): From **8d** (1.05 g) and Na (0.31 g, 12.44 mmol); Yield: 0.28 g, 71%, oil. ^{1}H NMR (CD_3CN): 4.97 (bs, 1H, OH); 4.45 [m, 1H, $\underline{CH}(CH_3)_2$]; 3.69 (t, 2H, J 7.2 Hz, CH_2-2'); 3.46 (t, 2H, J 4.0 Hz, CH_2-5'); 3.41 (t, 2H, J 4.2 Hz, CH_2-4'); 2.33 (s, 3H, C_5-CH_3); 2.76 (t, 2H, J 7.2 Hz, CH_2-1'); 1.34, 1.32 [d, 6H, $CH(\underline{CH_3})_2$]. ^{13}C NMR (DMSO-d_6): 158.9 (C-3); 150.7 (C-5); 71.9 (C-4'); 68.7 (C-2'); 60.1 (C-5'); 48.7 [$\underline{CH}(CH_3)_2$]; 28.7 (C-1); 22.9 [$CH(\underline{CH_3})_2$]; 11.2 (C_5-CH_3). m/z (FAB>0) 214 (MH^+).

5-Ethyl-1-isopropyl-3-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazole (**13e**): From **6e** (1.29 g) and Na (0.29 g, 12.44 mmol). Yield: 0.24 g, 59%, oil. ^{1}H NMR (DMSO-d_6): 4.50 [m, 1H, N-$\underline{CH}(CH_3)_2$]; 3.68 (t, 2H, J 6.9 Hz, CH_2-2'); 3.48 - 3.39 (m, 4H, CH_2-4', CH_2-5'); 2.81 (t, 2H, J 6.9 Hz, CH_2-1'); 2.59 (q, 2H, J 7.6 Hz, C_5-$\underline{CH_2}CH_3$); 1.53, 1.30 [2s, 6H, N-$CH(\underline{CH_3})_2$]; 1.17 (t, 3H, C_5-$CH_2\underline{CH_3}$). ^{13}C NMR (DMSO-d_6): 159.0 (C-3); 155.3 (C-5); 71.9 (C-2'); 68.3 (C-5'); 62.8 (C-4'); 48.6 [N-$\underline{CH}(CH_3)_2$]; 22.3, 20.1 [N-$CH(\underline{CH_3})_2$]; 18.3 (C_5-$\underline{CH_2}CH_3$); 12.3 (C_5-$CH_2\underline{CH_3}$). m/z (FAB>0) 228 (MH^+).

6,7,8,9-Tetrahydro-2-[(2-hydroxyethoxy)ethyl]-1H-1,2,4-triazolo-[1,5-a]-azepine (**13f**): From **8f** (1.07 g) and Na (0.29 g, 12.44 mmol). Yield: 0.32 g, 85%, oil. ^{1}H NMR (600 MHz, DMSO-d_6): 4.37 (m, 2H, CH_2-10); 3.78 (t, 2H, J 6.3 Hz, CH_2-2'); 3.44 (m, 2H, CH_2-5'); 3.40 (m, 2H, CH_2-4'); 3.17 (m, 2H, CH_2-

6); 2.98 (t, 2H, J 6.3 Hz, CH_2-1'); 1.84 (m, 2H, CH_2-8); 1.77 (m, 2H, CH_2-9); 1.71 (m, 2H, CH_2-7). ^{13}C NMR (DMSO-d_6): 155.1 (C-3); 151.8 (C-5); 72.0 (C-4'); 66.7 (C-2'); 66.7 (C-2'); 60.0 (C-5'); 52.5 (C-10); 28.5 (C-8); 26.1 (C-1'); 25.6 (C-9); 23.9 (C-6); 23.0 (C-7). m/z (FAB) 225 (M^+).

Acknowlegement We thank Mrs. M.J. Quelle and Mr. K. Hägele for the mass spectroscopic analyses and Mrs. W.B. Böer for the elemental analyses.

Refereneces

1. Chau, C.K.; Cutler, S.J. *J. Heterocyclic Chem.* **1986**, *23*, 289; Remy, R.J.; Secrist III, J.A. *Nucleos. & Nucleot.* **1985**, *4*, 41.
2. Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507.
3. Tanaka, H.; Miyasaka, T.; Sekiya, K.; Walker, R.T.; De Clercq, E. *Nucleos. & Nucleot.* **1992**, *11*, 447.
4. Elion, G.B.; Furman, J.A.; Fyfe, J.A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H.J *Proc. Natl Acad. Sci. U.S.A.* **1977**, *74*, 5716; Schaefer, H.J.; Beauchamp, L., de Miranda, P. Elion, G.B.; Bauer, D.J.; Collins, P. *Nature* (London) **1978**, *272*, 583.
5. Matsumoto, H.; Kaweko, C.; Yamada, K.; Takeuchi, T.; Mori, T.; Mizuno, Y. *Nucliec Acid Symp. Ser.No.* 17, **1986**.
6. Fiddian, A.P.; Brigden, D.; Yeo, J.M.; Hickmott, E.A. *Antiviral Res.* **1984**, *4*, 99; Dollins, R. *Science* **1985**, *227*, 1296; Collins, P.; Oliver, N.M. *Antiviral Res.* **1985**, *5*, 145; Lory, L.; Spear, P.G. *New Eng. J. Med.* **1986**, *314*, 749.
7. Najuib, F.N.M.; el Kouni, M.H.; Chu, S.H.; Cha, S. *Biochem. Pharmacol.* **1987**, *36*, 2195.
8. Chu, M.Y.W.; Najuib, F.N.M.; Iitzsch, M.H.; el Kouni, M.H.; Chu, S.H.; Cha, S.; Galabersi, P. *Cancer Res.* **1984**, *44*, 1852.
9. Purkayastha, S.; Lazrak, B.H.; Panzica, R.P. *Nucleos. & Nucleot.* **1989**, *8*, 389.
10. Schneller, S.W.; May, J.L.; De Clercq, E. *Croat. Chem. Acta* **1986**, *596*, 307.
11. Sallam, M.A.E.; Towsend, L.B.; Butler, W. *J. Chem. Soc. (S)* **1995**, 54; *J. Chem. Soc.* **1995** (467).
12. Lopezherrara, F.J.; Pina Goazates, M.S.; Parbon Anguas, R. *J. Chem. Soc. Perkin Trans. 1* **1989**, 2401.
13. Doboszewski, B. *Nucleos. & Nucleot.* **1997**, *16*, 1049.
14. Al-Soud, Y.; Wirschun, W.; Hassan, N.A.M Maier, G-M.; Jochims, J.C. *Synthesis* **1998**, 721.
15. Benzing, E. *Liebigs Ann. Chem.* **1960**, *631*, 1.
16. Benzing, E. *Liebigs Ann. Chem.* **1960**, *631*, 10.
17. Al-Soud, Y.A.; Al-Masoudi, W.A.; Abu El-Halawa, R.; Al-Masoudi, N.A. (*submitted*).
18. Al-Masoudi, N.A. et al. (*manuscript in preparation*).
19. Robins, M.J.; Hatfield, P.W. *Can. J. Chem.* **1982**, *60*, 547.
20. El Ashry, E.S.; El Kilany, Y. *Adv. in Hetrocyclic Chem.* **1998**, *69*, 129.
21. Al-Masoudi, N.A.; Hassan, N.A.; Al-Soud, Y.A.; Schmidt, P.; Gaafar, A.E-D.M.; Marino, S.; Schoch, A.; Amer, A.; Jochims, J.C. *J. Chem. Soc. Perkin. Trans. 1* **1998**, 947.
22. CAS **64**: 1603, *60*; Leech, R. E.; Goldsmith, W. E.; U. S. 3, 100, 793 (Cl. 260 - 495.6).