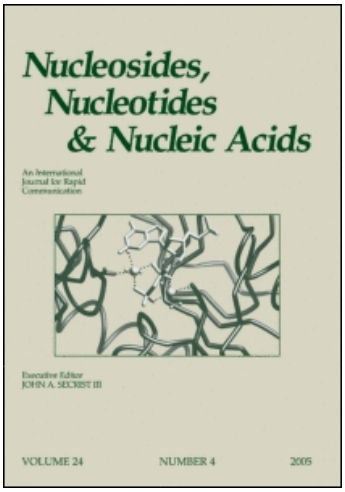

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Synthesis of Acyclic Nucleoside Analogs Related to Barbituric Acid

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SYNTHESIS OF ACYCLIC NUCLEOSIDE ANALOGS RELATED TO BARBITURIC ACID

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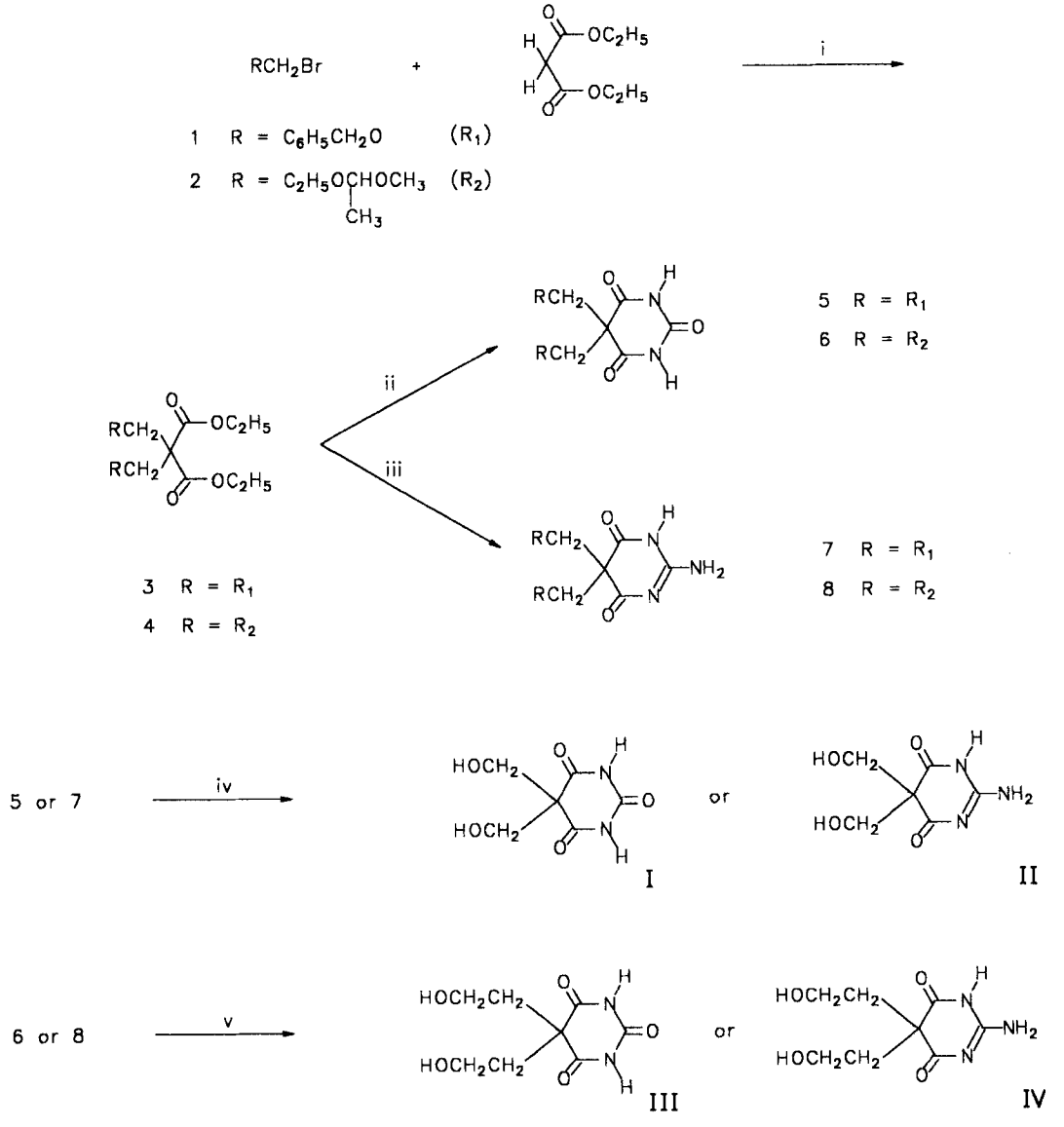
Abstract: The syntheses of the pyrimidine analogs 5,5-dihydroxymethyl-2,4,6-pyrimidine -trione **I**, 2-amino-5,5-dihydroxymethyl-4,6-pyrimidinedione **II**, 5,5-di(2-hydroxyethyl)-2,4,6-pyrimidinetrione **III**, and 2-amino-5,5-di(2-hydroxyethyl)-4,6-pyrimidinedione **IV** are described.

Nucleoside analogs which have proven to be useful for the inactivation of viral biological functions are generally modeled on the familiar nucleic acid subunits, with modifications introduced so as to permit binding to, but potentially to inhibit virally induced enzymes[1,2]. The synthesis of acyclic nucleoside analogs broadened this approach to therapy by introducing analogs in which the sugar moiety has been drastically altered[2,3]. To develop new biologically active compounds, nucleosides with both modified base and sugar moieties were prepared[4 – 8]. A special category of these analogs are the C-nucleosides[3,9 – 11]. While barbituric acid derivatives are well known as hypnotic agents, they have not to our knowledge been utilized as structural units in potential antiviral drugs. We describe here the synthesis of a new series of compounds (**I**, **II**, **III**, and **IV** (Scheme 1)) in which the pyrimidine ring of barbituric acid has been incorporated, as well



SCHEME 1: i $NaOC_2H_5$; ii $(NH_2)_2CO$, NaOEt; iii $(NH_2)_2CNH$, NaOEt; iv BCl_3; v H^+.

as a novel acyclic structural element. These analogs can be viewed as being related to C-nucleosides in which an acyclic moiety is attached at C-5 of a pyrimidine ring[10,11]. Our synthesis of these compounds is related to an investigation into the behavior of prochiral nucleotide analogs in template-directed oligomerization reactions[12 – 14]. Structures **I-IV** possess a plane of symmetry coincident with the pyrimidine ring. This feature suggests that they might be incorporated into a new set of stereoregular "nucleic acid-like" analogs. Because of their relationship to other classes of analogs, however, their possible biological activity may be of interest.

To introduce functional groups at the C-5 position of barbituric acid (2,4,6-pyrimidinetrione) and 2-amino-4,6-pyrimidinedione we choose the classical malonic ester synthesis. We used the bisfunctional benzylbromomethyl ether[15] (**1**) and 1-bromo-2-(ethoxyethoxy)ethane[16] (**2**) as alkylating agents. Both hydroxyl protecting groups are rather stable in basic conditions and are easily removed by treatment with boron trichloride and Dowex (H^+), respectively. After bis-alkylation of the α,α-positions of diethylmalonate, the corresponding protected pyrimidine analogs were formed by condensing with urea and guanidine, respectively [17] (Scheme 1).

Thus, diethylmalonate treated with 2 eq. sodium ethanolate and subsequently with 3 eq. of the bromide (**1**) in acetonitrile at room temp., produced α,α-dibenzyloxymethyl diethylmalonate (**3**) in 36% yield. The synthesis of α,α-di(2-[ethoxyethoxy]ethyl)diethylmalonate (**4**) was carried out in 35% yield by treating diethylmalonate with 2 eq. sodium ethanolate and subsequently with 2 eq. of the bromide (**2**) in ethanol under reflux. 5,5-Dibenzyloxymethyl-2,4,6-pyrimidinetrione (**5**) was prepared in 70 % yield by condensing (**3**) with urea in the presence of sodium ethanolate. 2-Amino-5,5-dibenzyloxymethyl-4,6-pyrimidinedione (**7**) was synthesized in 64% yield by condensing (**3**) with guanidine in the presence of sodium ethanolate. The condensation of (**4**) with urea or guanidine in sodium ethanolate is slightly less effective. 5,5-Di(2-[ethoxyethoxy]ethyl)-2,4,6-pyrimidinetrione (**6**) was prepared in 55% yield and 2-amino-5,5-di(2-[ethoxyethoxy]ethyl)-4,6-pyrimidinedione (**8**) was prepared in 57% yield. The dihydroxymethyl-containing analogs I and II were obtained by debenzylation of (**5**) and (**7**), in 70-75% yield. The dihydroxyethyl-containing analogs III and IV were obtained in 90-92% yield by acid hydrolyses of (**6**) and (**8**). The biological activity of compounds **I**, **II**, **III** and **IV** is being evaluated.

Experimental

Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer, ultraviolet spectra with a Beckman DU-40 spectrophotometer, and proton nuclear magnetic resonance spectra with a Varian EM 390 spectrophotometer. Chemical shifts are reported as δ values with tetramethylsilane as an internal standard. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Column chromatography was performed on Merck silicagel 60 (70-230 mesh). Dowex 50W-X8 (H^+) was purchased from Bio-Rad Laboratories.

Benzyl bromomethyl ether **1**

HBr was bubbled at 0°C through a stirred mixture of 32.4 g benzyl alcohol (300 mmol), 15 g paraformaldehyde and 300 ml CH_2Cl_2 for 4 h. The resulting solution was dried over $CaCl_2$, filtered and evaporated. Purification was by distillation *in vacuo*.

Yield; 58.2 g (290 mmol, 96%). Bp; 79-85°C at 0.4 mm Hg. IR (neat); 2900, 1120, 740, 690. ^{1}H-NMR (CCl_3D); 6.4 (s, 5H, Ph), 5.7 (s, 2H, CH_2Br), 4.7 (s, 2H, $PhCH_2$).

1-Bromo-2-(ethoxyethoxy)ethane **2**

To a mixture containing 81.5 g (0.65 mol) 2-bromoethanol, 1.2 g pyridinium p-toluenesulfonate, and 200 ml CH_2Cl_2, was added 80 ml (1.47 mol) ethyl vinyl ether at 0°C. After 1 h at 0°C, the mixture was extracted with water. The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulting oil was purified by destillation *in vacuo*.

Yield; 93 g (0.46 mol, 72%). Bp; 70-73°C at 20 mm Hg. IR (neat); 2880, 2960, 1100, 1375. ^{1}H-NMR (CCl_3D); 4.8 (q, 1H, CH), 3.4 (m, 6H, CH_2Br), 1.2 (t+d, 6H, CH_3).

α,α-Dibenzyloxymethyl diethylmalonate **3**

Sodium ethanolate was prepared from 2.3 g sodium (100 mmol) in 100 ml ethanol. To this mixture 8.0 g diethylmalonate (50 mmol) was added. After refluxing for 15 minutes the solvent was evaporated under reduced pressure. Acetonitrile (100 ml) was added to the residue. Benzyl bromomethyl ether **1** (30 g,150 mmol) was added dropwise at 10°C. The resulting suspension was stirred for 2 h at room temperature. After filtration 200 ml dichloromethane was added and the solution was washed with water. The organic phase was dried over $MgSO_4$, filtered and evaporated. The product was purified by chromatography over silicagel in toluene.

Yield; 6.73 g (16.8 mmol, 33%) (monosubstituted product yield 37%). IR (neat); 2900 (br), 1700, 1200, 1100, 750, 700. ^{1}H-NMR($CDCl_3$); 7.2 (s, 10H, Ph), 4.5 (s, 4H, $PhCH_2$), 4.1 (q, 4H, $COOCH_2$), 4.0 (s, 4H, CH_2O), 1.1 (t, 6H, CH_3).

α,α-Di(2-[ethoxyethoxy]ethyl)diethylmalonate **4**

Diethylmalonate (16 g, 0.1 mol) was added at 55°C to 150 ml ethanol containing 0.2 mol sodium ethanolate (freshly prepared from 4.6 g Na (0.2 mol)). After reacting for 15 min., 40 g 1-bromo-2-(ethoxyethoxy)ethane **2** (0.2 mol) was added dropwise. The resulting mixture was refluxed for 20 h. The mixture was filtered and evaporated under reduced pressure. The remaining oil was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$, filtered and evaporated. Purification was by destillation *in vacuo*.

Yield; 13.68 g (34.8 mmol, 35%) (monosubstituted product yield 32%). Bp; 127-132°C at 0.4 mm Hg. IR (neat); 2950, 1730, 1480-1020, 980, 850. ^{1}H-NMR (CCl_3D); 4.7 (q, 2H, CH), 4.2 (q, 4H, $COOCH_2$), 3.6 (m, 8H, $COCH_2$), 2.3 (t, 4H, CH_2) 1.3 (m, 18H, CH_3).

General procedure for the syntheses of 5,5-dibenzyloxymethyl-2,4,6-pyrimidinetrione **5** and 5,5-di(2-[ethoxyethoxy]ethyl)-2,4,6-pyrimidinetrione **6**

To 25 ml 1.6 M sodium ethanolate was added 10 mmol α,α-dibenzyloxymethyl diethylmalonate **3** or α,α-di(2-[ethoxyethoxy]ethyl)diethylmalonate **4** and 0.73 g urea (11 mmol). The solvent was evaporated in 4 h at 110°C. To the residue 100 ml water was added and adjusted to pH 6 with 6M HCl. The precipitate was collected by filtration and washed with water.

5,5-Dibenzyloxymethyl-2,4,6-pyrimidinetrione **5**: Yield; 70%. Mp; 207-210°C. (KBr); 3580, 3100, 1700, 1400, 1300, 730, 700. ^{1}H-NMR (CD_3OD); 7.1 (s, 10H, Ph), 4.6 (s, 4H, Ph-CH_2), 3.3 (s, 4H, OCH_2).

5,5-Di(2-[ethoxyethoxy]ethyl)-2,4,6-pyrimidinetrione **6**: Yield; 55%. Mp; 125-127°C. IR (KBr); 3150, 2900, 1700. ^{1}H-NMR (CD_3OD); d 4.6 (q, 2H, CH), 3.5 (m, 8H, CH_2O), 2.2 (t, 4H, CH_2), 1.2 (2× t, 12H, CH_3).

General procedure for the syntheses of 2-amino-5,5-dibenzyloxymethyl-4,6-pyrimidinedione **7** and 2-amino-5,5-di(2-[ethoxyethoxy]ethyl)-4,6-pyrimidinedione **8**

To 10 ml 1.5 M sodium ethanolate was added 2.5 mmol α,α-dibenzyloxymethyl diethylmalonate **3** or α,α-di(2-[ethoxyethoxy]ethyl)diethylmalonate **4** and 0.29 g guanidine.HCl. The solvent was evaporated in 4 h at 110°C. After adding water and adjusting the pH to 6.0 with 6 M HCl, the precipitate was collected by filtration and washed with water.

2-Amino-5,5-dibenzyloxymethyl-4,6-pyrimidinedione **7**: Yield; 64%. Mp; 210°C (decomposition). IR (KBr); 3150 (br), 2700 (br), 1700, 1600, 1500, 1400, 730, 700. ^{1}H-NMR (d_6-DMSO); 7.0 (s, 10H, Ph), 3.2 (s, 4H, Ph-CH_2), 3.1 (s, 4H, OCH_2).

2-Amino-5,5-di(2-[ethoxyethoxy]ethyl)-4,6-pyrimidinedione **8**: Yield; 57%. Mp; 210°C (decomposition). IR (KBr); 3300, 3000, 2750, 1600 (br). ^{1}H-NMR (d_6-DMSO); 6.9 (br.s., 3H, NH), 4.5 (q, 2H, CH), 3.4 (m, 8H, CH_2O), 2.3 (t, 4H, CH_2), 1.1 (2× t, 12H, CH_3).

General procedure for deprotection of **5** and **7**

5,5-dibenzyloxymethyl-2,4,6-pyrimidinetrione **5** or 2-amino-5,5-dibenzyloxymethyl-4,6-pyrimidinedione **7** (1.5 mmol) was dissolved in 25 ml dichloromethane. Boron trichloride (6 ml, 1M in dichloromethane) was added to this solution at -78°C. After 2 h the reaction was quenched by adding 20 ml methanol. The solution was neutralized with triethylamine and evaporated at reduced pressure. The products were purified by crystallization from water.

5,5-Dihydroxymethyl-2,4,6-pyrimidinetrione **I**: Yield; 70%. Mp; 210°C (decomposition). IR (KBr); 3000, 1700, 1550, 1480, 1370. UV (H_2O); λ_{max} 256 (pH 10), λ_{max} 254 (pH 2). Anal. calcd. for $C_6H_8N_2O_5$: C, 38.30; H, 4.29; N, 14.89. Found: C, 38.08; H, 4.49; N, 15.71.

2-Amino-5,5-dihydroxymethyl-4,6-pyrimidinedione **II**: Yield; 75%. Mp; 210°C (decomposition). IR (KBr); 3300, 3100, 2800 (br), 1600, 1420, 1350. UV (H_2O); λ_{max} 260 (pH 10), λ_{max} 255 (pH 2). Anal. calcd. for $C_6H_9N_3O_4$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.87; H, 4.64; N, 23.08.

General procedure of deprotection of **6** and **8**

5,5-Di(2-[ethoxyethoxy]ethyl)-2,4,6-pyrimidinetrione **6** or 2-amino-5,5-di(2-[ethoxyethoxy]ethyl)-4,6-pyrimidinedione **8** (1 mmol) was suspended in 1 ml water. Dowex 50

(H^+) was added with stirring to the suspension until a clear solution was formed in 15 min. Prior to filtration the solution was heated to prevent precipitation of **III** or **IV**. After evaporation under reduced pressure, the products were recrystallized in water.

5,5-Di(2-hydroxyethyl)-2,4,6-pyrimidinetrione **III**: Yield; 90%. Mp; 162-167°C. IR (KBr); 3380, 3100, 2900, 1700. ^{1}H-NMR (D_2O + NaOD); 2.9 (t, 4H, CH_2OH), 2.0 (t, 4H, CH_2). UV (H_2O); λ_{max} 238.5nm (pH 10). Anal. calcd. for $C_8H_{12}N_2O_5$: C, 44.45; H, 5.59; N, 12.96. Found: C, 44.58; H, 5.46; N, 12.63.

2-Amino-5,5-di(2-hydroxyethyl)-4,6-pyrimidinedione **IV**: Yield; 92%. Mp; 210°C (decomposition). IR (KBr); 3300, 3000, 2800, 1590. ^{1}H-NMR (D_2O + NaOD); 2.8 (t, 4H, CH_2OH), 1.8 (t, 4H, CH_2). UV (H_2O); λ_{max} 266.5 (pH 10), λ_{max} 257.5 (pH 2). Anal. calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.52. Found: C, 44.95; H, 6.36; N, 19.59.

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