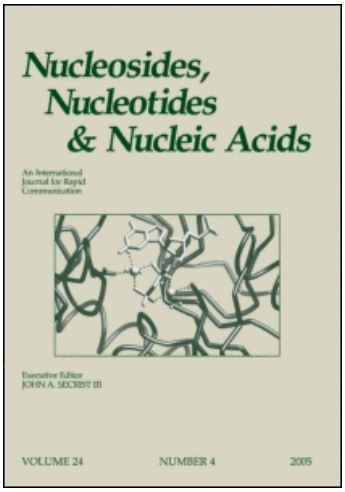

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AS-TRIAZINE DERIVATIVES WITH POTENTIAL THERAPEUTIC ACTION. XXVI.[1] SYNTHESIS OF 5-SUBSTITUTED-6-AZAURACIL ACYCLONUCLEOSIDES

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ABSTRACT: 5-Substituted 6-azauracils were alkylated with (2-acetoxyethoxy)methyl bromide to give protected acyclic nucleosides which were deprotected to afford acyclonucleosides of 5-substituted 6-azauracils. Their structures have been established by the UV and ^{1}H-NMR spectra and by elemental analysis.

Introduction

The successful development of purinic acyclonucleosides, such as acyclovir[2] and gancyclovir,[3-4] as potent antiherpetic agents, has induced the interest in synthesis and evaluation against human herpesviruses also of acyclic nucleosides of pyrimidinic[5-7] and 6-azapyrimidinic[8-10] bases. But these analogs proved to be inactive against herpes simplex viruses type 1 and 2, fact which was attributed to their poor phosphorylation by the virus-induced thymidine kinase.[5-7]

However, the acyclovir-type analogs derived from 5,6-disubstituted uracil proved to be promising as anti-HIV-1 agents, their activity being comparable with that of azidothymidine.[11-12]

In the present study were synthesized as potential antiviral agents acyclovir-type nucleoside analogs, derived from some 5-substituted-thio-6-azauracils which showed biologic (antitumoral and antiviral) activity.[13-16]

Results and Discussion

The starting 5-methylthio-6-azauracil (**1.a**),[17] 5-phenylthio-6-azauracil (**1.b**)[18] and 5-(2-methylthio-ethyl)thio-6-azauracil (**1.c**)[1] were silylated with hexamethyldisilazane (HMDS) and a catalytic amount of trimethylchlorosilane under anhydrous conditions. The

silylated derivatives were then alkylated with (2-acetoxyethoxy)methyl bromide[19] in dry acetonitrile to give the protected acyclonucleosides **3.a-c**, which were purified by silica gel chromatography. These compounds were then deacetylated with sodium methoxide to afford the acyclonucleosides **4.a-c** (Scheme 1).

The site of alkylation was established as N-1 but not N-3 based only on the comparison of UV spectra with their reported methylated[20-21] and ribosylated[22-23] counterparts. The hypsochromic shift of the absorption maximum in the UV spectra of the compounds **3.a-c** and **4.a-c** by passing from acidic and neutral to alkaline media is typical of 1-substituted-6-azauracils.[21-22] If it were 3-substituted 6-azauracils, a very substantial bathochromic shift would be expected in the alkaline spectrum.[21-22]

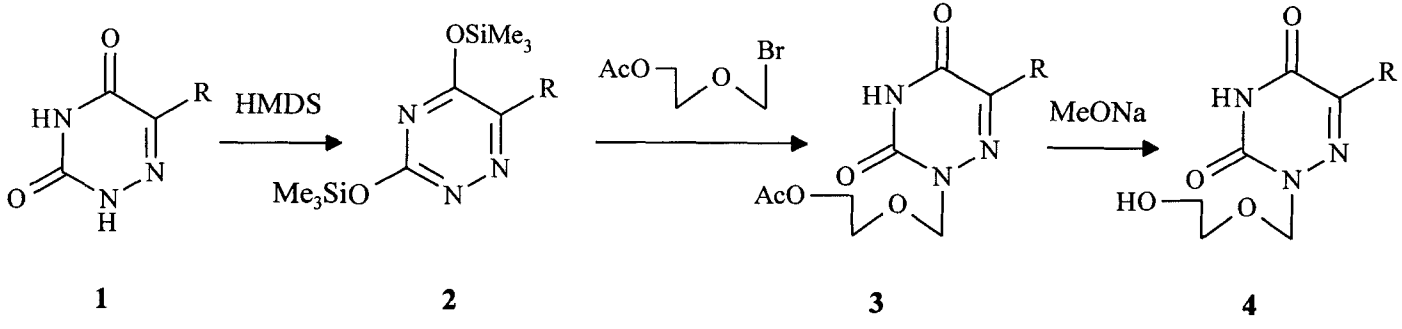
The results of the biological activity evaluation of the compounds **3.a-c** and **4.a-c** will be published elsewhere.

Experimental

The melting points were determined on a Boëtius heating plate microscope and were not corrected. The preparative column chromatography was performed on silica gel 60 (70-230 mesh ASTM) (Merck), using chloroform as eluent, a flow rate of 100 mL per hour being maintained, and the fractions were collected at 6-minutes intervals. The ultraviolet absorbing substances were determined in eluates by running registration of UV absorption (UVICORD LKB 254 nm). The ultraviolet spectra were recorded on a Cecil CE 6602 spectrophotometer. The ^{1}H-NMR spectra were recorded at 300 MHz on a Varian Gemini-300 spectrometer. Chemical shifts (δ) were expressed in parts per million with tetramethylsilane as an internal standard. The acetonitrile was dried by distillation from phosphorus pentoxide, followed by redistillation from calcium hydride.

1-[(2-Acetoxyethoxy)methyl]-5-methylthio-6-azauracil **3.a**

5-Methylthio-6-azauracil **1.a** (1.59 g, 10 mmol) was suspended in hexamethyldisilazane (20 mL) and then a catalytic amount (1 mL) of trimethylchlorosilane was added. The mixture was heated 2 hours under reflux (150-160°C) with the exclusion of moisture until a clear solution was obtained. Excess hexamethyldisilazane was removed by vacuum distillation (16 mm Hg) and the oily residue was dissolved in dry acetonitrile (50 mL). The solution was cooled to 0°C and a solution of (2-acetoxyethoxy)methyl bromide (1.97 g, 10 mmol) in dry acetonitrile (50 mL) was added dropwise under stirring. The reaction mixture was then stirred at room temperature for 16 hours with the exclusion of moisture. Finally the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The crude oily product was purified by column chromatography. The proper fractions were combined and the eluent was evaporated under reduced pressure. The



1 **2** **3** **4**

a. R = -S-CH_3
b. R = -S-C_6H_5
c. R = -S-CH_2 CH_2 -S-CH_3

Scheme 1

residue was recrystallized from ethanol to give pure 1-[(2-acetoxyethoxy)methyl]-5-methylthio-6-azauracil **3.a** (1.98 g, 72% yield). mp 94-96°C; ^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3, CH_3COO), 2.42 (s, 3, CH_3S), 3.82-3.91 (m, 2, 3'-CH_2), 4.20-4.29 (m, 2, 4'-CH_2), 5.39 (s, 2, 1'-CH_2); UV λ_{max} (log ε): 310 (3.82) (EtOH), 311 (3.80) (0.1 N HCl), 300 (3.70) (0.1 N NaOH). Anal. Calcd. for $C_9H_{13}N_3O_5S$: C, 39.27; H, 4.75; N, 15.26. Found: C, 39.41; H, 4.91; N, 15.48.

1-[(2-Acetoxyethoxy)methyl]-5-phenylthio-6-azauracil **3.b**

5-Phenylthio-6-azauracil **1.b** (2.21 g, 10 mmol) was treated as described above for the preparation of **3.a** to yield the desired product **3.b** (2.39 g, 71%). mp 72-74°C (ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.05 (s, 3, CH_3COO), 3.55-3.62 (m, 2, 3'-CH_2), 4.105-4.15 (m, 2, 4'-CH_2), 5.14 (s, 2, 1'-CH_2), 7.40-7.58 (m, 5, C_6H_5); UV λ_{max} (log ε): 312 (3.67) (EtOH), 312 (3.67) (0.1 N HCl), 303 (3.58) (0.1 N NaOH). Anal. Calcd. for $C_{14}H_{15}N_3O_5S$: C, 49.84; H, 4.48; N, 12.46. Found: C, 49.41; H, 4.61; N, 12.53.

1-[(2-Acetoxyethoxy)methyl]-5-(2-methylthio-ethyl)thio-6-azauracil **3.c**

5-(2-Methylthio-ethyl)thio-6-azauracil **1.c** (2.19 g, 10 mmol) was treated as described above for the preparation of **3.a** to yield the desired product **3.c** (2.38 g, 71%). mp 91-93°C (ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3, CH_3COO), 3.20-3.30 and 3.72-3.80 (m, 2, S-CH_2CH_2-S), 3.81-3.90 (m, 2, 3'-CH_2), 4.19-4.29 (m, 2, 4'-CH_2), 5.36 (s, 2, 1'-CH_2); UV λ_{max} (log ε): 311 (3.79) (EtOH), 311 (3.75) (0.1 N HCl), 300 (3.69) (0.1 N NaOH). Anal. Calcd. for $C_{11}H_{17}N_3O_5S_2$: C, 39.40; H, 5.11; N, 12.53. Found: C, 39.45; H, 5.21; N, 12.61.

1-[(2-Hydroxyethoxy)methyl]-5-methylthio-6-azauracil **4.a**

To 60 mL of dry methanol was added 0.23 g (10 mmol) of sodium metal. After the completion of the hydrogen evolution, 1-[(2-acetoxyethoxy)methyl]-5-methylthio-6-azauracil **3.a** (1.65 g, 6 mmol) was added and the stirring was continued for 2 hours at room temperature. Thin-layer chromatography indicated that the deprotection was complete. DOWEX 50x8 (H^+) resin was added under stirring until the pH was 5. The mixture was filtered, the resin washed with methanol and the combined filtrate evaporated. The residual powder was recrystallized from ethanol to give pure **4.a** (1.28 g, 92% yield). mp 143-145°C; ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3, CH_3S), 3.79 (bs, 4, 3'-CH_2 and 4'-CH_2), 5.40 (s, 2, 1'-CH_2); UV λ_{max} (log ε): 311 (3.80) (EtOH), 311 (3.81) (0.1 N HCl), 300 (3.69) (0.1 N NaOH). Anal. Calcd. for $C_7H_{11}N_3O_4S$: C, 36.04; H, 4.75; N, 18.01; S, 13.74. Found: C, 36.11; H, 4.81; N, 18.53; S, 13.85.

1-[(2-Hydroxyethoxy)methyl]-5-phenylthio-6-azauracil **4.b**

1-[(2-Acetoxyethoxy)methyl]-5-phenylthio-6-azauracil **3.b** (1.44 g, 6 mmol) was treated as described above for the preparation of **4.a**. After recrystallization from dichloromethane, pure **4.b** (1.69 g, 96%) was obtained. mp 143-146°C; ^{1}H-NMR ($CDCl_3$): δ 3.47-3.54 (m, 2, 3'-CH_2), 3.60-3.68 (m, 2, 4'-CH_2), 5.15 (s, 2, 1'-CH_2), 7.40-7.57 (m, 5, C_6H_5); UV λ_{max} (log ε): 311 (3.73) (EtOH), 312 (3.72) (0.1 N HCl), 304 (3.62) (0.1 N NaOH). Anal. Calcd. for $C_{12}H_{13}N_3O_4S$: C, 48.80; H, 4.43; N, 14.22. Found: C, 48.71; H, 4.51; N, 14.53.

1-[(2-Hydroxyethoxy)methyl]-5-(2-methylthio-ethyl)thio-6-azauracil **4.c**

1-[(2-Acetoxyethoxy)methyl]-5-(2-methylthio-ethyl)thio-6-azauracil **3.c** (1.65 g, 6 mmol) was treated as described above for the preparation of **4.a**. After recrystallization from ethanol, pure **4.c** (1.62 g, 93%) was obtained. mp 123-125°C; ^{1}H-NMR ($CDCl_3$): δ 2.75-2.86 and 3.18-3.29 (m, 2, S-CH_2CH_2-S), 3.78 (bs, 4, 3'-CH_2 and 4'-CH_2), 5.38 (s, 2, 1'-CH_2); UV λ_{max} (log ε): 311 (3.80) (EtOH), 312 (3.79) (0.1 N HCl), 301 (3.68) (0.1 N NaOH). Anal. Calcd. for $C_9H_{15}N_3O_4S_2$: C, 38.84; H, 5.15; N, 14.32; S, 21.86. Found: C, 39.01; H, 5.21; N, 14.53; S, 21.93.

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