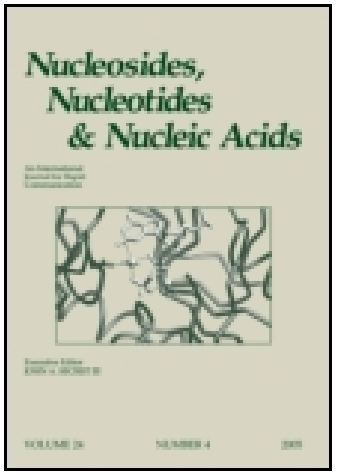

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Synthesis of AZT analogues: 7-(3-azido-2hydroxypropyl)-, 7-(3-amino-2-hydroxypropyl)-, 7-(3-triazolyl-2-hydroxypropyl)theophyllines

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SYNTHESIS OF AZT ANALOGUES: 7-(3-AZIDO-2-HYDROXYPROPYL)-, 7-(3-AMINO-2-HYDROXYPROPYL)-, 7-(3-TRIAZOLYL-2-HYDROXYPROPYL)THEOPHYLLINES

El Sayed H. El Ashry, Adel Abdel-Rahman, Nagwa Rashed, Laila F. Awad, and Hanaa A. Rasheed □ *Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt*

□ *Nucleophilic displacement of the tosyloxy group in 7-(2-hydroxy-3-*p*-toluenesulfonyloxypropyl)theophylline (**1**) with azide anion afforded 7-(3-azido-2-hydroxypropyl)theophylline (**2**). Reduction of the 3-azido group in **2** with $Ph_3P/Py/NH_4OH$ afforded the 3-amino derivative **4**, alternatively obtained by regioselective amination of 7-(2,3-epoxypropyl)theophylline (**3**). Selective acetylation of **4** gave the N-acetyl derivative **5**. 1,3-Dipolar cycloaddition of the azide group in 2 with N^1-propargyl thymine (6) afforded the regioisomeric triazole **7**.*

Keywords AZT; Azido-2-Hydroxypropyltheophylline; Thymine; Triazōle; Cycloaddition

INTRODUCTION

Significant progress has been accomplished in the search for new therapeutic agents for treatment of viral diseases,[1] where nucleoside analogues are of great interest.[2–8] Among these nucleoside analogues, 3′-azido-3′-deoxythymidine (AZT)[9,10] has been used for the treatment of human immunodeficiency virus (HIV) and became a lead nucleoside in antiviral therapy. However, the clinical use of such anti-HIV nucleosides is hampered by drug resistance[9] and toxicity problems.[10] These limitations had led to a search for new agents possessing more selective antiviral activities with low toxicity problems. In this regard, replacing the furanosyl moiety by a more simplified one such as that in acyclonucleosides has presented analogues of potential value as new leads.[2] Theophylline analogues with an acyclic moiety became attractive AZT analogues. The 7-(3-azido-2-hydroxypropyl)theophylline and its 3-amino as well as 3-(1,2,3-triazolyl) analogues have been selected as target compounds in this publication. The latter

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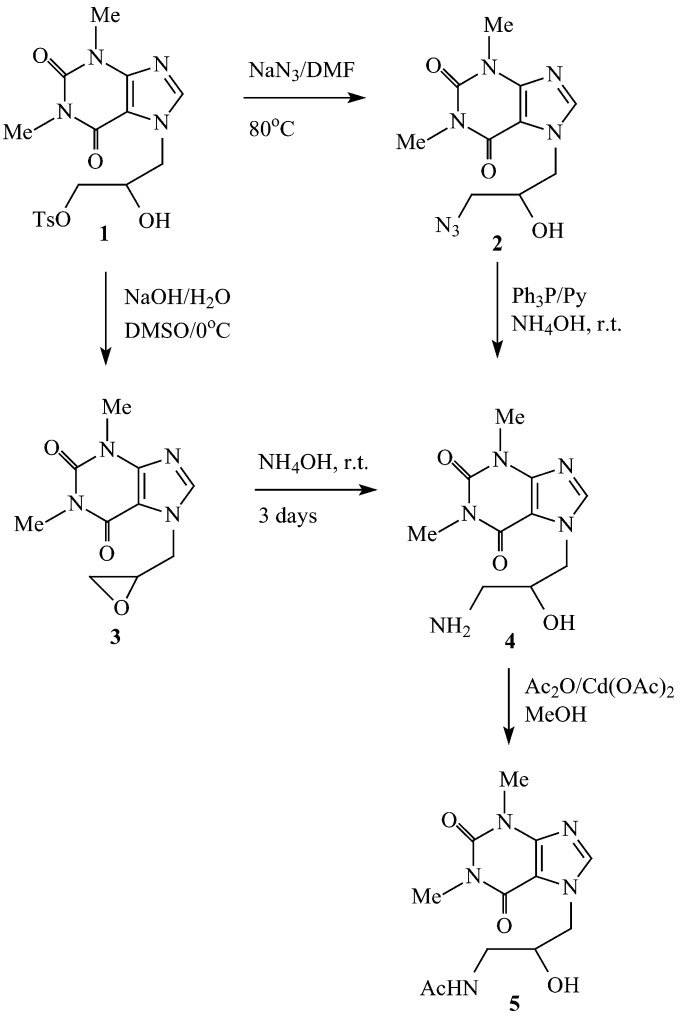
analogue would possess three important heterocyclic rings linked to each other by flexible methylene and propyl groups as linkers, which could result in better flexibility of the thymine, triazole, and theophylline rings when adopted in a biological target.[11]

RESULTS AND DISCUSSION

Two approaches were used for the synthesis of the target compounds. The first approach was done by a nucleophilic displacement of a leaving group at the C-3′ of 7-[(2-hydroxy-3-*p*-toluenesulfonyloxy)propyl]theophylline (**1**),[12] available by selective tosylation of the primary hydroxylgroup of 7-(2,3-dihydroxypropyl)theophylline, with sodium azide in DMF at 80°C for 6 h to give (3-azido-2-hydroxypropyl)theophylline (**2**) in 87% yield. The structure of the 3-azido derivative **2** was verified by the presence of azide absorption band at 2099 cm^{-1} in its IR spectrum. Both of H-3′ and H-3″ are shieled in the ^1H NMR spectrum, as a result of the azido group, and resonated as doublet of doublets at δ 3.39 and 3.53, compared to those in **1** that appear at δ 4.03.[12] Conversion of the azido group in **2** to the amino group was carried out by treatment with triphenylphosphine and concentrated ammonium hydroxide solution in pyridine at room temperature to give the respective 3′-amino derivative **4**.

The second approach toward the amination at the C-3′ was carried out via opening of an oxirane ring such as that in **3**. The latter was prepared by treatment of **1** with sodium hydroxide solution in DMSO at 0°C to furnish the corresponding 7-(2,3-epoxypropyl) theophylline **3** in 75% yield. Its structure was established on the basis of ^1H NMR spectral data that showed the absence of the signal corresponding to the 2′-hydroxyl group as well as an upfield shift of the signals of H-3′ and H-3″ to resonate at δ 2.53 and 2.84, whereas H-2′, H-1′, and H-1″ were assigned to downfield signals. Regioselective base-catalyzed oxirane ring cleavage of **3** with concentrated ammonium hydroxide solution at room temperature for three days gave **4** in 95% yield. The mass spectrum of **4** showed a molecular ion peak at m/z 253 in agreement with its molecular formula $C_{10}H_{15}N_5O_3$. Selective acetylation of the amino group was done by reaction of **4** with acetic anhydride in absolute methanol and cadmium acetate as a catalyst to give **5**. The ^1H NMR spectrum of the *N*-acetyl derivative **5** in $CDCl_3$ showed signals corresponding to the NH proton at δ 7.93 as a singlet (D_2O exchangeable) in addition to the OH proton at δ 5.24 (D_2O exchangeable). Acetylation of the amino group resulted in a downfield shift of the of H-3′ and H-3″ signals in **5** from δ 2.70 and 2.93 respectively, in its precursor **4** (Scheme 1).

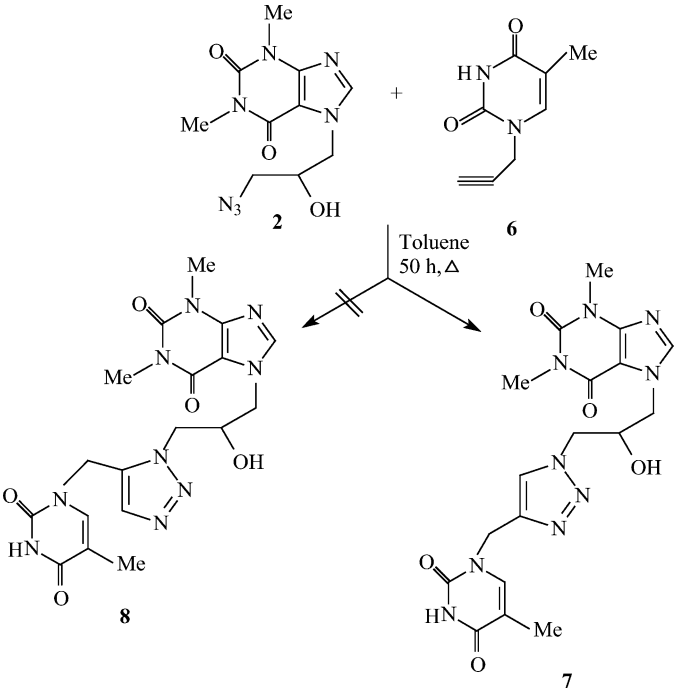
Ribavirin, a powerful antiviral nucleoside having a broad spectrum of activity against RNA and DNA viruses.[13] is representative of 1,2,4-triazole-nucleosides, which exhibit pronounced biological activities. Also, 1,2,3-triazole analogues[14] showed potent anti-HIV-1 activities. Both findings



SCHEME 1

attracted attention toward the synthesis of their analogues. 1,3-Dipolar cycloaddition reaction of azides to acetylenes is an efficient method to obtain 1,2,3-triazole rings in acyclo- and carboacyclonucleosides.[14–17] It is known[14] that the reaction is controlled by electronic and steric factors. In general, such addition tends to give mainly the isomer with electron-withdrawing groups at the 4-position and electron-donating group at the 5-position. On the other hand, the sterically less hindered isomer tends to be the major isomer. Although both 4- and 5-substituted 1,2,3-triazole derivatives have been obtained from such reactions, the former regioisomer was the major one.[15–17] Reaction of azide **2** and 1-(propargyl)thymine (**6**) in refluxing toluene for 50 h gave only the sterically less hindered regioisomer **7**, in 43% yield, rather than **8** (Scheme 2). The structure of **7** was established

from its ^{1}H NMR spectrum, which showed a singlet signal for H-5 at δ 8.06 in agreement with the formation of the 4-methylene 1,2,3-triazole derivative **7**.[14,18,19]



SCHEME 2

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP1025 spectrometer. EI mass spectra were recorded on a Varian MAT 311A spectrometer. ^{1}H NMR spectra were recorded with a Bruker AC 300 MHz spectrometer. The chemical shifts are expressed on the δ scale using Me_4Si as a standard and *J*-values are given in Hz. TLC was performed on Merck Silica Gel 60 F254 with detection by UV light. Microanalyses were performed in the unit of Microanalysis at the Faculty of Science, Cairo University.

7-(3-Azido-2-hydroxypropyl)theophylline (2). A mixture of **1**[12] (2.00 g, 4.9 mmol) and sodium azide (0.39 g, 6.0 mmol) in dry DMF (10 mL) was heated for 3 h at 80°C. The solvent was then removed under reduced pressure and the resulting residue was purified by column chromatography using hexane:ethyl acetate (4:1) to afford **2** (1.18 g, 87% yield) as white crystals; mp 100–102°C; IR(KBr): 1647, 1662 (CON), 2099 (N_3), and 3441 cm^{-1} (OH).

^{1}H NMR, ($CDCl_3$) δ_H: 3.27, 3.49 (2s, 3 H each, 2 NMe), 3.39 (dd, 1 H, $J_{2',3'}$ 4.8 Hz, $J_{3',3''}$ 12.6 Hz, H-3′), 3.53 (dd, 1 H, $J_{2',3''}$ 3.3 Hz, H-3″), 4.25 (m, 2 H, H-1′,2′), 4.51 (d, 1 H, $J_{1',1''}$ 10.2 Hz, H-1″), 4.76 (bs, 1 H, D_2O exchangeable, OH), 7.72 (s, 1 H, H-8). Anal. Calcd. for $C_{10}H_{13}N_7O_3$ (279.11): C, 43.01; H, 4.69; N, 35.11. Found: C, 43.90; H, 5.10; N, 35.16.

7-(2,3-Epoxypropyl)theophylline (3). A stirred solution of sodium hydroxide (0.16 g, 4 mmol) in water (3 mL) and DMSO (2 mL) at 0°C, compound **1** (0.5 g, 1.22 mmol) was added over 5 min. After an additional 15 min of stirring, the solution was poured into ice water and the mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and then evaporated in vacuo. The residue was purified by column chromatography using petroleum ether:ethyl acetate (5:1) to give **3** (0.21 g, 75% yield) as white crystals; mp 130–134°C; IR (KBr): 1262 (epoxide), 1656 and 1696 cm^{-1} (CON). ^{1}H NMR ($CDCl_3$) δ_H: 2.53 (t, 1 H, $J_{2',3'}$ 2.4 Hz, H-3′), 2.84 (t, 1 H, $J_{2',3''}$ 4.2 Hz, H-3″), 3.34, 3.53 (2s, 3 H each, 2 NMe), 4.11–4.16 (m, 2 H, H-1′, H-2′), 4.32 (dd, 1 H, $J_{1'',2'}$ 2.7 Hz, $J_{1',1''}$ 13.2 Hz, H-1″), 7.55 (s, 1 H, H-8). Anal. Calcd. for $C_{10}H_{12}N_4O_3$ (236.09): C, 50.84; H, 5.12; N, 23.72. Found: C, 50.36; H, 4.77; N, 23.36.

7-(3-Amino-2-hydroxypropyl)theophylline (4).

Method a: A mixture of azide **2** (0.56 g, 2.0 mmol) and triphenylphosphine (0.85 g, 3.3 mmol) in pyridine (5 mL) was kept at room temperature for 1 h, then concentrated ammonium hydroxide solution (10 mL) was added and the reaction mixture was allowed to stand for an additional 3 h. The solvent was removed in vacuo and the residue was dissolved in water. The solution was extracted with ether (3 × 20 mL) and then benzene (3 × 20 mL). The aqueous layer was evaporated and the residue was crystallized from ethanol to afford **4** as white crystals (0.25 g, 50% yield), mp 258–260°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 2.63–2.70 (m, 1 H, H-3′), 2.93 (dd, 1 H, $J_{2',3''}$ 2.7 Hz, $J_{3',3''}$ 12.9 Hz H-3″), 3.29, 3.42 (2s, 6 H, 2 NMe), 4.13 (br m, 1 H, H-2′), 4.29 (dd, 1 H, $J_{1',2'}$ 7.2 Hz, $J_{1',1''}$ 13.5 Hz, H-1′), 4.42 (dd, 1 H, $J_{1'',2'}$ 4.5 Hz, H-1″), 8.04 (s, 1 H, H-8). The Ms: m/z 253(M^+). Anal. Calcd. for $C_{10}H_{15}N_5O_3$ (253.12): C, 47.42; H, 5.97; N, 27.65. Found: C, 47.91; H, 6.22; N, 27.88.

Method b: Compound **3** (0.1 g, 0.42 mmol) was stirred with concentrated ammonium hydroxide (28%, 5 mL) at room temperature in a closed flask for 3 days. The reaction mixture was evaporated in vacuo to afford the amino compound 4 (0.095 g, 95% yield); it was identical with that from method a.

7-(3-Acetamido-2-hydroxypropyl)theophylline (5). Compound **4** (0.50 g, 2.0 mmol), cadmium acetate (0.40 g, 1.5 mmol) and acetic anhydride (3.0 mL) were shaken with absolute methanol (10 mL) for 3 h at room

temperature then heated under reflux for 10 min. The reaction mixture was evaporated in vacuo and the residue was dissolved in water (10 mL), then extracted with methylene chloride (4 × 20 mL). The organic layers were collected and evaporated. The residue was crystallized from ethanol to give **5** (0.32 g, 55% yield) as white crystals; mp 180–182°C. IR(KBr): 1604 (C=N) and 1666 (OCN), 1708(NAc), 3121 (NH). ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 1.83 (s, 3 H, Ac), 3.07–3.09 (m, 1 H, H-3′), 3.22, 3.42 (2s, 3 H each, 2 NMe), 3.49–3.83 (m, 2 H, H-1′, H-2′), 4.08 (dd, 1 H, $J_{1',2'}$ 8.4 Hz, $J_{1',1''}$ 13.3 Hz, H-3″), 4.35 (dd, 1 H, $J_{1'',2'}$ 3.1 Hz, $J_{1',1''}$ 13.7 Hz, H-1″), 5.24 (d, 1 H, $J_{2',OH}$ 5.1 Hz, D_2O exchangeable, OH), 7.93 (s, 1 H, D_2O exchangeable, NH), 7.96 (s, 1 H, H-8). Anal. Calcd. for $C_{12}H_{17}N_5O_4$ (295.13): C, 48.81; H, 5.80; N, 23.72. Found: C, 49.31; H, 6.12; N, 24.31.

7-{3-[4-(Thymin-1-yl-methyl)-1,2,3-triazol-1-yl]-2-hydroxypropyl}theophylline (7). A mixture of compounds **2** (0.08 g, 0.5 mmol) and **6** (0.14 g, 0.5 mmol) in dry toluene (5 mL) was heated under reflux for 50 h. The product was filtered off then washed with ethanol. It was crystallized from ethanol to afford **7** (0.096 g, 43% yield) as buff crystals, mp 275–277°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 1.81 (s, 3 H, CH_3), 3.28, 3.49 (2s, 3 H each, 2 NMe), 4.24–4.36 (m, 3 H, H-2′,3′,3″), 4.48, 4.58 (2d, 2 H, $J_{1',1''}$ 11.7 Hz, H-1′,1″), 4.95 (s, 2 H, NCH_2), 5.60 (d, 1 H, $J_{2',OH}$ 4.5 Hz, OH), 7.65 (s, 1 H, thymine-H-6), 8.04 (s, 1 H, theophylline H-8), 8.06 (s, 1 H, triazole-H-5), 11.25 (bs, 1 H, NH). Anal. Calcd. for $C_{18}H_{21}N_9O_5$ (443.17): C, 48.26; H, 4.77; N, 28.22. Found: C, 48.26; H, 4.34; N, 28.22.

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