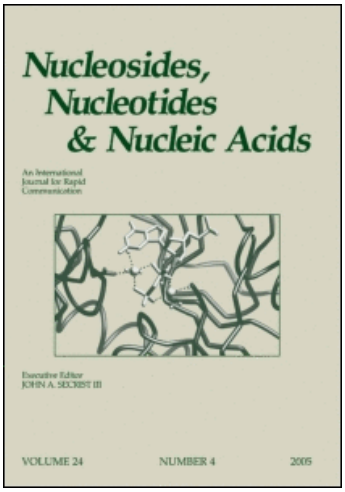

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Nucleosides. II. Synthesis and Properties of 3,4-Diaryl-4,5-dihydro-1-(β-D-ribofuranosyl)-1,2,4-triazole-5-thiones

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Nucleosides 2[1]: Synthesis and Properties of 3,4-Diaryl-4,5-Dihydro-1-(β-D-Ribofuranosyl)-1,2,4-Triazole-5-Thiones

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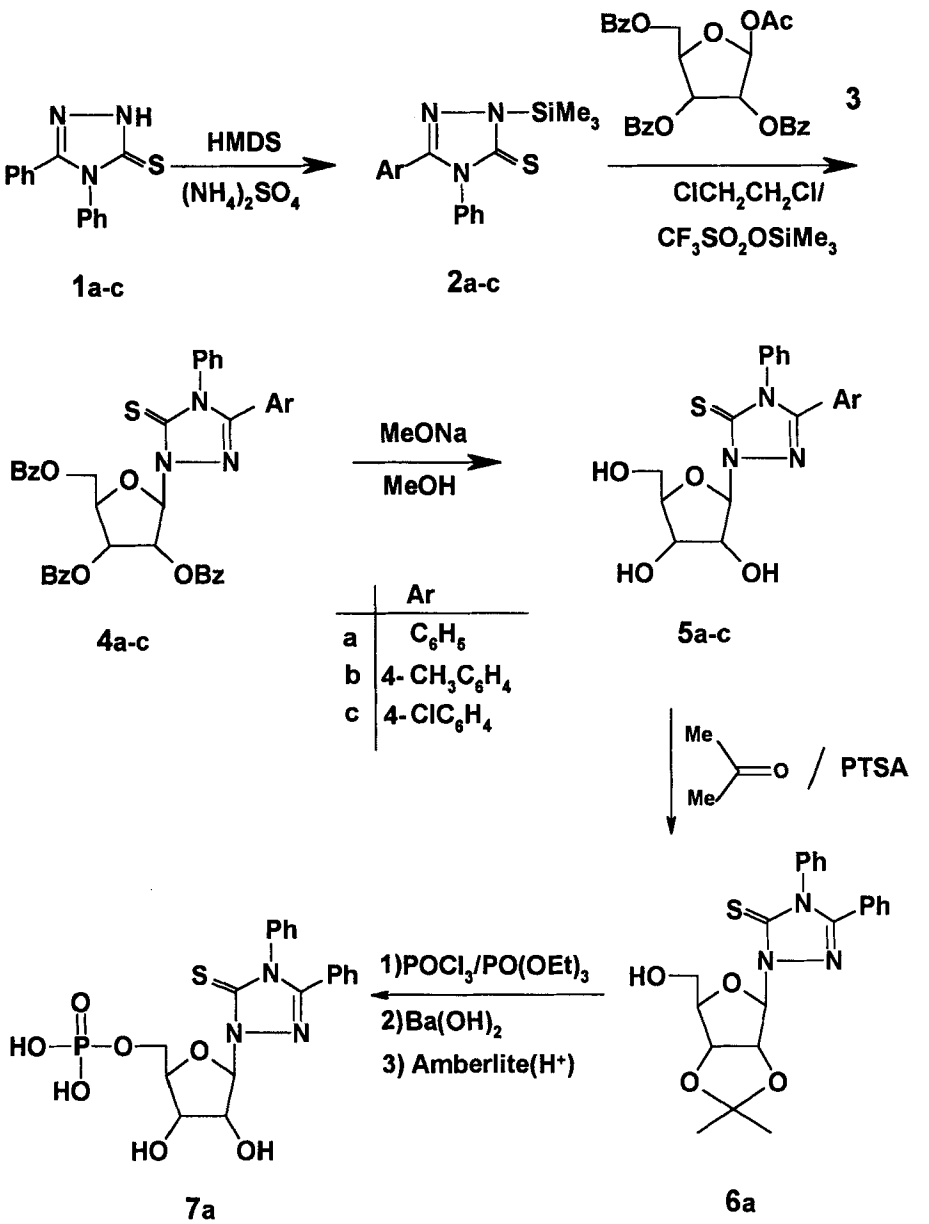
Abstract: 3,4-Diaryl-4,5-dihydro-1,2,4-triazole-5-thiones (**1a-c**) were silylated to give compounds (**2a-c**) which were condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**3**) in the presence of trimethylsilyl trifluoromethane sulfonate to afford the corresponding nucleosides **4a-c**. Treatment of **4a-c** with sodium methoxide in methanol at room temperature afforded the debenzoylated nucleosides **5a-c**. The reaction of **5a** with acetone in the presence of p-toluenesulfonic acid gave the 2`, 3`-isopropylidene derivative (**6a**). Phosphorylation of **6a** with phosphoryl chloride and triethylphosphate followed by treatment with barium hydroxide afforded barium 3,4-diphenyl-4,5-dihydro(β-D-ribofuranosyl)-1,2,4-triazole-5-thione-5`-monophosphate, which gave after lyophilization the free acid (**7a**).

Introduction:

A large number of unnatural nucleoside derivatives have been shown to inhibit infection caused by viruses[2]. Since their discovery, a large number of substituted 4,5-dihydro-1,2,4-triazole-5-thiones have been synthesized in the last two decades as many of them have been demonstrated to exhibit broad spectrum of biological activities such as analgesic, antibacterial, anti-fungal and anti -inflammatory properties[3-7]. S-Glycoside derivatives of some of 3,4-dihydro-1,2,4-triazole-3-thiones were reported to show LD_{50} 200-1780 mg/kg body weight in white mice and significant antiinflammatory, analgesic and antihypoxic activities[3,8] . 1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) is known as antiviral[9].



Scheme 1

Results and Discussion:

As a part of our on-going program for developing new nucleoside derivatives as antisense oligonucleotides, we report here synthesis of 1,2,4-triazole nucleosides and their phosphorylation.The starting 3,4-diaryl-1,2,4-triazole-5-thiones (**1a-c**), were prepared by the reported methods[3,10-12]. Their silylation with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the corresponding trimethylsilylated derivatives (**2a-c**). Treatment of the latter with 1-O-acetyl-2,3,5-O-benzoyl-β-D-ribofuranose (**3**) in 1,2-dichloroethane using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a catalyst following the method of Vorbruggen[9] gave the corresponding β-anomeric protected N-nucleoside derivatives (**4a-c**) in good yields. The compounds **4a-c** were debenzoylated with sodium methoxide in methanol at room temperature to afford the free nucleosides (**5a-c**) (Scheme 1). Compound **5a** was protected at 2`- and 3`-OH groups by reaction with acetone in the presence of p-toluene sulfonic acid at room temperature to give the 2`,3`-isopropylidene nucleoside **6a**, which was converted to the C-5`-monophosphate derivative (**7a**), by treatment of **6a** with phosphoryl chloride and triethyl phosphate followed by a saturated solution of barium hydroxide[13] and then the barium salt was converted to the free acid by using cation exchange resin (Amberlite, IR 120, H^+) and lyophilization by water (Scheme 1).

The chemical structures of nucleoside derivatives (**4a-c**) were established and confirmed on the basis of elemental analyses and spectral data (IR, UV, ^{1}H-NMR). The ^{1}H-NMR spectra of **4a-c** showed in each case a doublet at δ 6.69-6.72 assigned to the anomeric proton of the ribose moiety with spin-spin coupling constant ($J_{1',2'}$) equal to 2.0 Hz which confirms the β-anomeric configuration. This is in accord with the results for other 2,3,5-tri-O-benzoyl-1-β-D-ribofuranosyl-1,2,4-triazole derivatives[9]. The UV spectra of **4a-c** indicated that the reaction proceeded selectivity to give N-ribofuranosyl derivatives. This is because the UV spectrum of **4a,** ($\lambda_{max.}$, EtOH, 270 nm)[14] is identical to that of 4,5-dihydro-1-(N-β-glucopyranosyl)-3-methyl-4-phenyl-1,2,4-triazole-5-thione ($\lambda_{max.}$, EtOH, 269 nm)[14]. Furthermore, the IR spectrum of **4a** showed a characteristic band at 1170 cm^{-1} due to the C=S. Moreover, hydrolysis of **4a** with 5% hydrochloric acid afforded the 3,4-diphenyl-4,5-dihydro-1,2,4-triazole-5-thione (**1a**) as the sole product, whereas 3,4-diphenyl-4,5-dihydro-1,2,4-triazole-5-one derivative (**8**) was not detected. This finding is consistent with the assigned N-nucleoside structure.

Experimental :

UV Spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5, IR spectra were recorded for KBr discs on a Perkin-Elmer FTIR

(1650) spectrophotometer, ^{1}H-NMR spectra were recorded on a Bruker AC 250 MHz and on a Varian Gemini 200 MHz NMR spectrometer using TMS as an internal standard; Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schull and column chromatography on Merck silica gel 60 (particle size 0.063-0.20 mm). Melting points were measured on Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

3,4-Diaryl-4,5-dihydro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-5-thiones 4a-c.- A mixture of 3,4-diaryl-1,2,4-triazole-5-thione[3,10-12] **1** (10 mmol) and dry hexamethyldisilazane (50 ml) was heated under reflux for 8 h with a catalytic amount of ammonium sulfate (50 mg). After the clear solution was cooled, it was evaporated to dryness under anhydrous condition to give the silylated derivative **2**, which was dissolved in 50 ml of dry 1,2-dichloroethane. To this was added a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **3** (4.80 g, 9.8 mmol) in dry 1,2-dichloroethane (25 ml) was then added. The mixture was cooled in ice bath and a solution of trimethylsilyl trifluoromethanesulfonate (2 ml, 10 mmol) in dry 1,2-dichloroethane (10 ml) was added dropwise. It was stirred at room temperature for 24 h, and then diluted with chloroform (200 ml), washed with a saturated solution of aqueous sodium bicarbonate (150 ml), water (3x150 ml) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel with 1% methanol in chloroform as eluent to afford white solid which was crystallized from dioxane- ethanol (2:1) to yield colorless crystals of the corresponding nucleoside derivative **4.**

Compound **4a** : Yield (80%); mp 216-217°C; $\lambda_{max.}$(EtOH) (nm) 270; ν(cm^{-1}) (KBr) 1765 (CO), 1170 (CS); δ($CDCl_3$) 4.60-4.75 (m, 1H, 4`-H); 4.8-4.9(m,2H,5`,5``-H); 6.2-6.3(m,1H,3`-H), 6.35-6.45(m,1H,2`-H), 7.1(d,1H, $J_{1`,2`}$=2.0Hz, 1`-H,); 7.25-8.20(m,25H,Ar-H). Anal. Found: C,68.8; H,4.4; N,6.4; S,4.9. $C_{40}H_{31}N_3O_7S$ requires; C,68.87; H,4.45; N,6.02; S,4.59.

Compound **4b:** Yield (85%); mp 203-205°C; $\lambda_{max.}$(EtOH) (nm) 270; ν(cm^{-1}) (KBr) 1760(CO), 1175(CS); δ($CDCl_3$) 2.3(s,3H,CH_3); 4.6-4.7(m,1H,4`-H); 4.75-4.90(m,2H,5`,5``-H), 6.1-6.2(m,.1H,3`-H); 6.3-6.4(m,1H,2`-H); 7.1(d,1H, $J_{1`,2`}$=2.5Hz, 1`-H,); 7.25-8.10(m,24H,Ar-H). Anal. Found: C,69.10; H,4.5; N,6.0; S,4.4. $C_{41}H_{33}N_3O_7S$ requires; C,69.20; H,4.64; N,5.91; S,4.50.

Compound **4c**: Yield(78%), mp 220-221°C; $\lambda_{max.}$ (EtOH) (nm) 275; ν(cm^{-1}) (KBr) 1765(CO), 1175(CS); δ($CDCl_3$) 4.6-4.7(m,1H,4`-H); 4.8-

4.9(m,2H,5`,5``-H); 6.15-6.25(m,1H,3`-H); 6.30-6.45(m,1H,2`-H); 7.15(d,1H, J= 2Hz $J_{1',2'}$=2.0Hz, 1`-H,), 7.25-8.20(m,24H,Ar-H). Anal. Found: C,65.5; H,4.0; N,5.7; S,4.2; Cl,4.8. $C_{40}H_{30}N_3ClO_7S$ requires; C,65.62; H,4.10; N,5.74; S,4.37; Cl,4.85.

3,4-Diaryl-4,5-dihydro-1-(β-D-ribofuranosyl)-1,2,4-triazole-5-thiones
5a-c.- A mixture of the protected nucleoside **4** (1 mmol), absolute methanol (20 ml) and sodium methoxide (60 mg, 1.1 mmol) was stirred at room temperature for 24 h. Evaporation of the solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralised with acetic acid . The precipitate was filtered off and afforded upon crystallization from water, the nucleosides **5** as colorless crystals.

Compound **5a:** Yield (72%); mp 202-203°C; ν (cm^{-1}) (KBr) 3365(OH), 1160(CS); δ(DMSO-d_6) 3.4-3.6(m,2H,5`,5``-H); 3.9-4.0(m,1H,4`-H); 4.2-4.3(m,1H,3`-H); 4.4-4.5(m,1H,2`-H); 4.7-4.9(t,1H,5`-OH); 5.2-5.3(d,1H,3`-OH); 5.5-5.6(d,1H,2`-OH); 6.15-6.20(d,1H, $J_{1',2'}$=2.0Hz, 1`-H,); 7.25-7.60(m,10H,Ar-H). Anal. Found: C,58.9; H,4.8; N,10.8; S,8.1. $C_{19}H_{19}N_3O_4S$ requires; C,59.22; H,4.94; N,10.91; S,8.31.

Compound **5b:** Yield(78%); mp 214-215°C; ν (cm^{-1}) (KBr) 3355(OH), 1165(CS); δ(DMSO-d_6) 3.5-3.6(m,2H,5`,5``-H) 3.8-3.9(m,1H,4`-H); 4.2-4.25(m,1H,3`-H); 4.4-4.5(m,1H,2`-H); 4.7-4.9(t,1H,5`-OH); 5.1-5.2(d,1H,3`-OH); 5.4-5.5(d,1H,2`-OH); 6.3(d,1H, $J_{1',2'}$=2.0Hz, 1`-H,); 7.25-7.70(m,9H,Ar-H). Anal. Found: C,60.0; H,5.2; N,10.5; S,7.9. $C_{20}H_{21}N_3O_4S$ requires; C,60.15; H,5.26; N,10.53; S,8.02.

Compound **5c**: Yield(80%); mp 235-236°C, ν (cm^{-1}) (KBr) 3348(OH), 1160(CS); δ(DMSO-d_6) 3.5-3.6(m,2H,5`,5``-H); 3.9-4.0(m,1H,4`-H); 4.2-4.3(m,1H,3`-H); 4.4-4.5(m,1H,2`-H); 4.7-4.8(t,1H,5`-OH); 5.1-5.2(d,1H,3`-OH); 5.4-5.5(d,1H,2`-OH); 6.3(d,1H, $J_{1',2'}$=2.0Hz, 1`-H,); 7.3-7.7(m,9H,Ar-H). Anal. Found: C,54.1; H,4.3; N,10.0; S,7.5; Cl,8.2. $C_{19}H_{18}N_3ClO_4S$ requires; C,54.35; H,4.29; N,10.01; S,7.63; Cl,8.46.

3,4-Diphenyl-4,5-dihydro-1-[(2`-3`-isopropylidene)-β-D-ribofuranosyl]-1,2,4-triazole-5-thione 6a.- A mixture of 3,4-Diphenyl-4,5-dihydro-1-β-D-ribofuranosyl-1,2-4-triazole-5-thione **5a** (0.8 g, 2.08 mmol) and p-toluenesulfonic acid (3.6 g) was dissolved in freshly distilled acetone and stirred for 3 h at room temperature. The excess of p-toluenesulfonic acid was neutralized by adding a solution of sodium bicarbonate (0.5 M, 50 ml). After removing the solvent, the slightly yellow residue was extracted with benzene (3

times x 20 ml) and evaporated to dryness. The light yellow powder left was purified by column chromatography (silica gel) using chloroform as eluent to afford the crystalline isopropylidene derivative **6a.** Yield (62%); mp 195-196°C; ν (cm^{-1}) (KBr) 3320(OH), 1145(CS); δ($CDCl_3$) 1.60, 1.32(2 s,6H,$2CH_3$); 3.6-3.8(m,2H,5`,5``-H); 4.2-4.3(m,1H,4`-H); 4.4-4.5(m,2H,2`-H&3`-H); 4.7-4.8(t,1H,5`-OH); 6.1(d,1H, $J_{1`,2`}$=3.0Hz, 1`-H,); 7.2-7.8(m,10H,Ar-H). Anal. Found: C,61.5; H,5.8; N, 9.7; S,7.3. $C_{22}H_{23}N_3O_4S$ requires; C,62.12; H,5.41; N,9.88; S,7.53.

3,4-Diphenyl-4,5-dihydro-1-(β-D-ribofuranosyl)-1,2,4-triazole-5-thione-C-5`- monophosphate 7a.- To a cooled mixture of phosphoryl chloride (0.4 ml, 4.16 mmol) and triethyl phosphate (4 ml) was added **6a** (0.5 g, 1.18 mmol). The mixture was stirred at -20°C for 1 h, then for 1 h at 0°C. The excess phosphoryl chloride was then distilled under reduced pressure and ether was added to the residue. The resulting ether solution was extracted with cold water (3x10 ml). The aqueous layer was collected and barium hydroxide was added till pH 2. The mixture was then heated for 1 h at 70°C and cooled at room temperature. After the pH value of the solution was raised to 8 using barium hydroxide, the solution was then centrifuged. The precipitated barium sulfate was filtered and the filtrate was evaporated. Upon adding absolute ethanol to the residue and cooling the mixture in ice- box for overnight, the barium salt precipitated out, which was collected and washed several times with absolute ethanol to give barium 3,4-diphenyl-4,5-dihydro-1-(β-D-ribofuranosyl)-1,2,4-triazole-5-thione-C-5`- monophosphate. Yield, 300 mg.

Conversion of the barium salt into the free acid 7a: The barium salt (300 mg) was dissolved in distilled water (5 ml) and then applied to a cation exchange resin (Amberlite IR 120, H^+ form, 70 ml). The sample was eluted with distilled water and after lyophilization, the compound **7a** was obtained. Yield (20%); mp 200-202°C; δ(D_2O) 4.0-4.2(m,2H,5`,5``-H); 4.4-4.5(m,1H,4`-H); 4.7-4.75(m,1H,3`-H); 4.9-5.1(m,1H,2`-H); 6.1(d,1H, $J_{1`,2`}$=3.0Hz, 1`-H,); 7.3-7.8(m,10H,Ar-H); ^{31}P-NMR (D_2O)(H_3PO_4 as internal reference) 44.25. Anal. Found: C,45.2; H,4.8; N,8.3; S,6.5. $C_{19}H_{20}N_3O_7SP.2H_2O$ requires; C,45.51; H,4.79; N,8.38; S,6.39.

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