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New Route for the Synthesis of 2-Thiouracil Analogues of 3′-Azido-2′,3′-dideoxy Nucleosides

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Summary. Reaction of 3-azido-5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-*D-erythro*-pentofuranoside (**5**) with silylated 2-thiouracil and 5-alkoxy-2-thiouracils in the presence of trimethylsilyl trifluoromethanesulfonate afforded an anomeric mixture of the corresponding 3′-azido-2′,3′-dideoxy-2-thiouridine derivatives with the α-anomer as the main product. Deprotected nucleosides were obtained by treatment with tetrabutylammonium fluoride.

Keywords. 3′-Azido-2′,3′-dideoxy-2-thiouridines; 5-Alkoxy-2-thiouracils; Nucleoside synthesis.

Ein neuer Weg zur Synthese von 2-Thiouracil-Analogen von 3′-Azido-2′,3′-dideoxy-Nucleosiden

Zusammenfassung. Die Reaktion von 3-Azido-5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-*D-erythro*-pentofuranosid (**5**) mit silyliertem 2-Thiouracil und 5-Alkoxy-2-thiouracil in Gegenwart von Trimethylsilyltrifluormethansulfonat ergab eine anomere Mischung der entsprechenden 3′-Azido-2′,3′-dideoxy-2-thiouridin-Derivate, wobei das α-Anomer das Hauptprodukt darstellte. Die ungeschützten Nucleoside wurden mittels Behandlung mit Tetrabutylammoniumfluorid erhalten.

Introduction

3′-Azido-3′-deoxythymidine [1] (*AZT*) was found by Mitsuya and coworkers [2] to be a potent inhibitor of the replication of HIV. Since *AZT* causes severe side effects and generally acts suppressively to bone marrow [3], many other nucleoside analogues with anti-HIV activity have been synthesized and their structural-antiviral relationships have been investigated [4]. Nucleosides with an azido group in *erythro* 3′-position exhibit high antiviral activity. Also the uracil analogue (*AZU*) and the 5-ethyluracil derivatives are highly active [5, 6], the activity, however, decreases with higher alkyl group. Also introduction of a methoxy or ethoxy group at the 5-position of *AZU* showed moderate antiviral activity [6]. There is, therefore, still a demand for compounds that are at least as active, but less toxic than *AZT*.

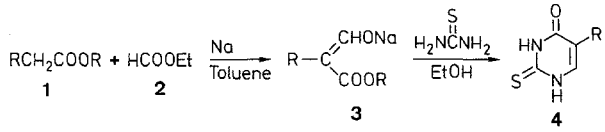
The lipophilicity, cytotoxicity and the anti-HIV activities were studied for some 4-thio analogues of *AZT*, 2′,3′-dideoxy-3-flourothymidine (*FddThd*) and 2′,3′-dideoxyuridine [7-11]. The oxygen-sulfur exchange at the C-4 carbonyl of several modified natural nucleosides including *AZT* enhanced the lipophilicity and, con-

sequently the delivery to the central nervous system of the thio analogues without compromising the anti-HIV activities of the parental structure [8]. The 4-thio analogues of *FddThd* was found to be a promising antiviral agent with low cytotoxicity.

As recorded in the literature [7 – 11] oxygen-sulfur exchange for natural nucleosides was done through a complicated strategy to achieve 2-thiothymidine whereas 4-thiothymidine was obtained by direct thionation. It is of great interest to find a convenient route for the synthesis of 2-thiouracil analogues of *AZT* aiming to get analogues less toxic and at least as active as *AZT* against human immunodeficiency virus. For this purpose we chose to couple 2-thiouracils with an appropriate azido sugar since similar couplings have been reported for the synthesis of nucleosides from 2-thiouridine [12]. 3-Azido-5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-α,β-*D-erythro*-pentofuranoside (**5**) was synthesized according to a simple four steps method [13] in our laboratory with a slight modification by one of us [14]. 2-Deoxy-*D*-ribose was treated with HCl/CH_3OH, followed by 5-O protection using *tert*-butyl(diphenyl)chlorosilane. A subsequent Mitsunobu reaction afforded a 3-iodo derivative which on heating with excess sodium azide in *DMF* gave the azido compound **5**.

Results and Discussion

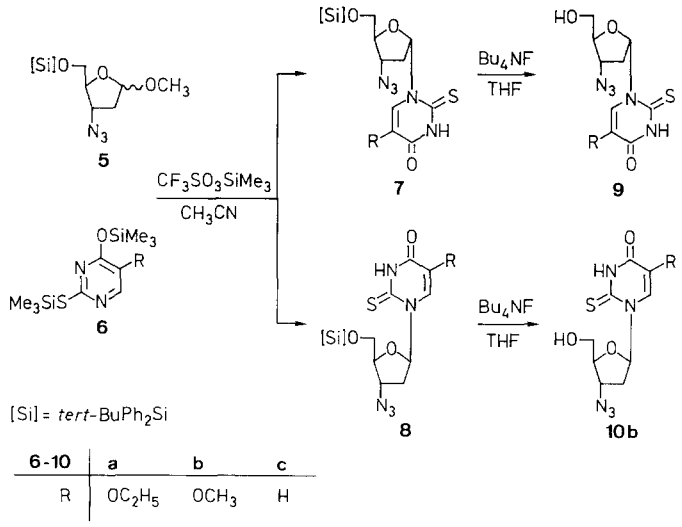
In the present study we used the Chesterfield method reported in Ref. [15], by which 5-alkoxy-2-thiouracils (**4a, b**) were prepared by formylation of the proper alkyl alkoxyacetate, then treating the crude product with thioarea. The 5-ethoxy-



	a	b
R	OC_2H_5	OCH_3

2-thiouracil (**4a**) was prepared in (49%) yield. The 2-thiouracils **4** were silylated in dry acetonitrile with 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*). The silylated bases **6** were coupled [16] under nitrogen with 3-azido-5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-*D-erythro*-pentofuranoside (**5**) using trimethylsilyl triflate (*TMS*-triflate) as a catalyst.

Coupling of **6a** and **5** gave an α/β mixture of **7a** and **8a** [5 : 3]: It was only possible to isolate the α protected form **7a** in a state of purity. Deprotection with tetrabutylammonium fluoride (*TBAF*) gave **9a**. Coupling of **6b** and **5** gave an α/β mixture of **7b** and **8b** [2 : 1]. Chromatographic purification using silica column did not afford separation of the two anomers. Deprotection with *TBAF* followed by column separation made it possible to separate the α form **9b** and the β form **10b**, but both contaminated with traces of *TBAF*. HPLC separation was used to get rid of the *TBAF*. Coupling of silylated 2-thiouracil **6c** gave **7c** and **8c** in the ratio of 2 : 1. Chromatographic treatment of the mixture on a silica column gave the pure α form **7c** and an α/β mixture of **7c** and **8c**. Treatment of **7c** with *TBAF*



gave complete deprotection and afforded **9c**. The observed shifts of C-2 (174.56 ppm) and C-1′ (91.50 ppm) in the ^{13}C-NMR spectrum of the uracil derivative **9c** clearly show glycosidation on a nitrogen atom and not on the sulfur of 2-thiouracil when compared with ^{13}C-NMR spectra of N, O, and S-methylated thiouracil derivatives [17]. For **9c** we also observed a characteristic downfield shift of the anomeric carbon in relation to C-1′ in *AZT* [18] whereas an upfield shift should have been expected for N-3 glycosidation of 2-thiouracil as deduced from the chemical shifts of the methyl group in methylated uracil and 2-thiouracil derivatives. N-1 glycosidation in **9c** was further confirmed by an undecoupled ^{13}C-NMR spectrum which showed a long range coupling from 1′-H to C-6, the latter giving the coupling constants 3, 11, and 186 Hz. The anomeric configuration in the nucleosides was based on ^{1}H-NMR spectra: The 4′-H proton of the α-anomers appears downfield from that observed for the β-anomers, and although less characteristic, the 5′-H protons of the α-anomer appear upfield from those observed for the β-anomer [19, 20]. The assignments were confirmed by comparison of ^{1}H-NMR and ^{13}C-NMR spectra with those of *AZT* and its corresponding α-anomer [18].

Experimental Part

2-Thio-5-ethoxyuracil [**4a**; $C_8H_8N_2O_2S$]

A mixture of ethyl ethoxyacetate (**1**, 13.2 g, 100 mmol) and ethyl formate (**2**, 7.4 g, 100 mmol) was added dropwise to a stirred suspension of sodium (2.3 g, 100 mmol) in dry toluene (30 ml), the temperature being kept below 30°C. Next day the toluene layer was decanted off and the remaining toluene was evaporated under reduced pressure. Then to the crude, viscous methyl sodio-β-hydroxy-α-methoxyacrylate (**3**) were added dry absolute ethanol (15 ml) and thiourea (7.6 g, 100 mmol). The mixture was stirred for 1 h at room temperature, then boiled under reflux for 5 h. After cooling, the solid was collected and dissolved in water (60 ml) and the solution was neutralized with 6 *M* hydrochloric acid. The precipitated solid product was collected and dried at 100°C, recrystallized from water, giving 5-ethoxy-2-thiouracil (**4a**) as pale yellow crystals, m.p. 230°C; yield 8.46 g (49%). ^{1}H-NMR ($CDCl_3$) δ 1.26 (3H, t, J=7 Hz, CH_3), 3.85 (2H, q, OCH_2), 7.03 (1H, s, 6-H). ^{13}C-NMR ($CDCl_3$) δ 14.24 (CH_3), 64.90 (OCH_2), 121.82 (C-6), 138.78 (C-5), 157.22 (C-4), 171.25 (C-2). MS: m/z (%) = 172 (M^+, 100), 144 (64), 57 (89), 28 (42).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α,β-D-erythro-pentofuranosyl)-2-thiouracils **7** *and* **8**. *General Procedure*

The proper 2-thiouracil (6 mmol) was silylated by heating with excess hexamethyldisilazane (*HMDS*, 12 – 18 ml) and $(NH_4)_2SO_4$ (30 mg) for 3 – 5 h to achieve a clear solution. The *HMDS* was evaporated under reduced pressure leaving the silylated base **6**. A solution of trimethylsilyl trifluoromethanesulfonate (2.2 ml, 12 mmol) in dry CH_3CN (10 ml) was added dropwise under nitrogen at −10°C to a stirred solution of the silylated base **6** (6 mmol in 40 ml dry CH_3CN) mixed with a solution of methyl 3-azido-5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-α,β-*D-erythro*-pentofuranoside (**5**, 2.05 g, 5 mmol) in dry CH_3CN (30 ml). The temperature was raised slowly to 20°C (30 min). The reaction was followed by TLC until completion (2 h). The reaction mixture was diluted with CH_2Cl_2 (250 ml) and treated with ice-cold saturated aqueous solution of $NaHCO_3$ (250 ml). The CH_2Cl_2 solution was separated, washed with water (3 × 100 ml), dried over Na_2SO_4 and evaporated in vacuo to give a mixture of **7** and **8**.

Chromatographic Separation of **7** *and* **8** *and Their Deprotection to Give* **9** *and* **10**

7a, **8a**, **9a**: Coupling of **5** with 5-ethoxy-2-thiouracil **6a** gave an α/β mixture (5/3) of **7a** and **8a**. On a silica gel column ($CHCl_3$:CH_3OH = 98 : 2) it was only possible to separate **7a** as a pure compound. Deprotection of **7a** was done by dissolving the nucleoside **7a** (0.89 mmol) in *THF* (10 ml) and adding 1 *M* Bu_4NF (*TBAF*) in *THF* (8.8 ml) dropwise at 0°C. After 30 min the solvent was evaporated, CH_2Cl_2 and ice-cold aqueous saturated $NaHCO_3$ were added, then the CH_2Cl_2 phase was evaporated and the product **9a** was purified on a silica gel column ($CHCl_3$:CH_3OH = 98 : 2). Impurities of *TBAF* were removed by HPLC with 20% ethanol in water on a reversed phase column (RP-18, 15 µm, 300 A).

7b, **8b**, **9b**, **10b**: 5-Methoxy-2-thiouracil gave an α/β mixture (30%, 2 : 1) of **7b** and **8b** which was inseparable on a silica gel column. The mixture was deprotected by Bu_4NF as described for **7a**/**8a**, followed by separation on a silica column with $CHCl_3$ to give separate fractions of **9b** and **10b** contaminated with Bu_4NF. HPLC with 20% ethanol on a reversed phase column (RP-18, 15 µm, 300 A) was used to get rid of the *TBAF* contamination.

7c, **8c**, **9c**: 2-Thiouracil (**6c**) gave an α/β mixture of **7c** and **8c** in the ratio 2/1 from which **7c** was separated by chromatography on silica gel with $CHCl_3$:CH_3OH = 98 : 2. Deprotection of **7c** as described above for **7a**/**8a** gave the deprotected α-nucleoside **9c**.

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-ethoxy-2-thiouracil (**7a**)

Yield 0.5 g (18%). ^{1}H-NMR ($CDCl_3$) δ 1.09 (9 H, s, *tert*-butyl), 1.43 (3 H, 5, J = 7 Hz, CH_3), 2.30 (1 H, m, 2′ α-H), 2.99 (1 H, dt, J = 15 and 7 Hz, 2′ β-H), 3.73 (2 H, d, J = 4 Hz, 5′-H), 3.97 (2 H, m, OCH_2), 4.30 (1 H, d, J = 7 Hz, 3′-H), 4.42 (1 H, m, 4′-H), 6.76 (1 H, m, 1′-H), 7.21 (1 H, s, 6-H), 7.44 – 7.66 (10 H, m, arom H), 9.96 (1 H, s, NH). ^{13}C-NMR ($CDCl_3$) δ 14.29 (CH_3), 19.03 (Me_3C), 26.74 (Me_3C), 38.73 (C-2′), 61.66 (C-3′), 64.31 (C-5′), 65.98 (OCH_2), 87.71 (C-4), 91.94 (C-1′), 120.88 (C-6), 127.87, 130.02, 135.41 (aryl), 139.21 (C-5), 156.24 (C-4), 170.12 (C-2). IR (film) 2115 cm^{-1} (N_3).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-methoxy-2-thiouracil (**7b**)

^{1}H-NMR ($CDCl_3$) δ 1.09 (9 H, s, *tert*-butyl), 2.31 (1 H, m, 2′ α-H), 3.0 (1 H, m, 2′ β-H), 3.73 (2 H, d, J = 3.94 Hz, 5′-H), 3.79 (3 H, s, OCH_3), 4.34 (1 H, d, J = 7 Hz, 3′-H), 4.44 (1 H, m, 4′-H), 6.76 (1 H, dd, J = 7.2 Hz, 1′-H), 7.20 (1 H, s, H-6), 7.44 – 7.65 (10 H, m, arom H), 9.80 (1 H, s, NH). ^{13}C-NMR ($CDCl_3$) δ 19.07 (Me_3C), 26.79 (Me_3C), 39.73 (C-2′), 57.10 (OCH_3), 61.71 (C-3′), 64.38 (C-5′), 87.72

(C-4'), 91.97 (C-1'), 119.52 (C-6), 127.90, 130.05, 135.45 (aryl), 140.34 (C-5), 155.90 (C-4), 170.28 (C-2). IR (film) 2110 cm^{-1} (N_3).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2-thiouracil (**7c**)

Yield 0.4 g (16%). ^{1}H-NMR ($CDCl_3$) δ 1.09 (9 H, s, *tert*-butyl), 2.34 (1 H, m, 2'α-H), 2.93 (1 H, dt, J=14 and 7 Hz, 2'β-H), 3.72 (2 H, d, J=4 Hz, 5'-H), 4.30 (1 H, d, J=7 Hz, 3'-H), 4.41 (1 H, m, 4'-H), 6.03 (1 H, d, J=8 Hz, m, 5-H), 6.67 (1 H, dd, J=7 and 2 Hz, 1'-H), 7.44 (6 H, m, arom H), 7.58 (1 H, d, J=8 Hz, 6-H), 7.65 (4 H, m, arom H), 10.24 (1 H, s, NH). ^{13}C-NMR ($CDCl_3$) δ 19.06 (Me_3C), 26.75 (Me_3C), 38.97 (C-2'), 61.60 (C-3), 64.28 (C-5'), 87.87 (C-4'), 91.79 (C-1'), 106.04 (C-5), 127.89, 130.05, 132.21, 132.43, 135.42 (aryl), 139.79 (C-6) 159.83 (C-4), 174.56 (C-2). IR (film) 2109 cm^{-1} (N_3).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-ethoxy-2-thiouracil (**8a**)

^{1}H-NMR ($CDCl_3$, selective data) δ 1.10 (9 H, s, *tert*-butyl), 2.20 (1 H, m, 2'α-H), 2.75 (1 H, m, 2'β-H), 3.80 (2 H, d, J=2.4 Hz, 5'-H), 4.24 (1 H, m, 3'-H), 6.72 (1 H, m, 1'-H). ^{13}C-NMR ($CDCl_3$) δ 13.99 (CH_3), 19.24 (Me_3C), 26.94 (Me_3C), 37.63 (C-2'), 59.69 (C-3'), 63.07 (C-5'), 66.58 (OCH_2), 84.83 (C-4'), 89.51 (C-1'), 121.82 (C-6), 128.02, 130.24, 135.18 (aryl), 139.61 (C-5), 156.19 (C-4), 171.01 (C-2). IR (film) 2110 cm^{-1} (N_3).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-methoxy-2-thiouracil (**8b**)

^{1}H-NMR ($CDCl_3$) δ 1.10 (9 H, s, *tert*-butyl), 2.25 (1 H, m, 2'α-H), 2.80 (1 H, m, 2'β-H), 3.75 (3 H, s, OCH_3), 3.85–3.93 (2 H, m, 5'-H), 3.98–4.11 (2 H, m, 3'-H and 4'-H), 6.76 (1 H, m, 1'-H), 7.40 (7 H, m, arom H, 6-H), 7.65 (4 H, m, arom H), 9.90 (1 H, s, NH). ^{13}C-NMR ($CDCl_3$) δ 19.25 (Me_3C), 26.94 (Me_3C), 37.62 (C-2'), 57.58 (OCH_3), 59.65 (C-3'), 63.05 (C-5'), 84.84 (C-4'), 89.53 (C-1'), 120.65 (C-6), 128.03, 130.13, 135.38 (aryl), 140.51 (C-5), 155.90 (C-4), 171.08 (C-2). IR (film) 2115 cm^{-1} (N_3).

1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2-thiouracil (**8c**)

^{1}H-NMR ($CDCl_3$) δ 1.09 (9 H, s, *tert*-butyl), 2.45 (1 H, m, 2'α-H), 2.65 (1 H, m, 2'β-H), 3.85 (1 H, dd, J=12.2 Hz, 5'-H), 3.92 (1 H, m, 4'-H), 4.12 (1 H, dd, 5'-H), 4.30 (1 H, m, 3'-H), 5.65 (1 H, d, J=8 Hz, 5-H), 6.73 (1 H, dd, J=6.5, 4 Hz, 1-H), 7.44–7.65 (10 H, m, arom H), 8.09 (1 H, d, J=8 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ 19.12 (Me_3C), 26.90 (Me_3C), 38.53 (C-2'), 57.97 (C-3'), 62.10 (C-5'), 84.99 (C-4'), 89.06 (C-1'), 106.55 (C-5), 127.99, 130.28, 135.19 (aryl), 139.95 (C-6), 160.03 (C-4), 174.80 (C-2). IR (film) 2109 cm^{-1} (N_3).

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-ethoxy-2-thiouracil (**9a**)

^{1}H-NMR ($CDCl_3$) δ 0.99 (3 H, t, J=7.3 Hz, CH_3), 2.30 (1 H, d, J=15 Hz, 2'α), 2.99 (1 H, m, 2'β), 3.76 (2 H, m, 5'-H), 3.99 (2 H, m, OCH_2), 4.38–4.46 (2 H, m, 3'-H and 4'-H), 6.72 (1 H, dd, J=7, 2 Hz, 1'-H), 7.21 (1 H, s, 6-H). ^{13}C-NMR ($CDCl_3$) δ 14.28 (CH_3), 38.65 (C-2'), 61.19 (C-3'), 62.61 (C-5'), 66.05 (OCH_2), 87.88 (C-4'), 91.80 (C-1'), 121.02 (C-6),139.52 (C-5), 156.41 (C-4), 170.17 (C-2). IR (film) 2110 cm^{-1} (N_3).

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-5-methoxy-2-thiouracil (**9b**)

^{1}H-NMR ($CDCl_3$) 2.32 (1 H, m, 2′ α-H), 3.01 (1 H, m, 2′ β-H), 3.78 (2 H, m, 5′-H), 3.81 (3 H, s, OCH_3) 4.34 (1 H, m, 3′-H), 4.45 (1 H, m, 4′-H), 6.75 (1 H, dd, $J=7$, 2 Hz, 1′-H), 7.21 (1 H, s, H-6). ^{13}C-NMR ($CDCl_3$) δ 38.53 (C-2′), 56.87 (OCH_3), 61.25 (C-3′), 62.31 (C-5′), 88.01 (C-4′), 91.80 (C-1′), 119.27 (C-6), 140.16 (C-5), 156.17 (C-4), 169.98 (C-2). IR (film) 2115 cm^{-1} (N_3).

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2-thiouracil (**9c**)

^{1}H-NMR ($CDCl_3$) δ 2.35 (1 H, dt, $J=15$, 3 Hz, 2′ α-H), 2.96 (1 H, dt, $J=15$, 7 Hz, 2′ β-H), 3.73 (1 H, dd, $J=12$, 4 Hz, 5′-H), 3.82 (1 H, dd, $J=12$, 4 Hz, 5′-H), 4.31 (1 H, m, 3′-H), 4.42 (1 H, m, 4′-H), 6.04 (1 H, d, $J=8$ Hz, 5-H), 6.68 (1 H, dd, $J=7$, 3 Hz, 1′-H), 7.60 (1 H, d, $J=8$ Hz, 6-H), 10.24 (1 H, s, NH). ^{13}C-NMR ($CDCl_3$) δ 38.97 (t, C-2′), 60.89 (d, C-3′), 62.72 (t, C-5′), 87.68 (d, C-4′), 91.50 (d, C-1′), 106.19 (dd, C-5), 139.75 (ddd, C-6), 159.90 (dd, C-4),174.56 (dd, C-2). IR (film) 2120 cm^{-1} (N_3).

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-5-methoxy-2-thiouracil (**10b**)

^{1}H-NMR ($CDCl_3$): 2.48 – 2.65 (2 H, m, 2′ α-H, 2′ β-H), 3.92 (1 H, d, $J=12.0$ Hz, 5′-H), 4.01 (1 H, m, 4′-H), 4.14 (1 H, dd, $J=12.0$ Hz, 5′-H), 4.34 (1 H, q, $J=7$ Hz, 3′-H), 6.78 (1 H, dd, $J=7$, 4 Hz, 1′-H), 7.91 (1 H, s, 6-H). ^{13}C-NMR ($CDCl_3$) δ 38.31 (C-2′), 56.84 (OCH_3), 58.19 (C-3′), 60.43 (C-5′), 85.14 (C-4′), 89.86 (C-1′), 119.16 (C-6), 140.76 (C-5), 157.36 (C-4), 170.92 (C-2). IR (film) 2109 cm^{-1} (N_3).

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