Synthesis and Hypnotic Activities of 4-Thio Analogues of N^3-Substituted Uridines

Shigetada KOZAI,[a] Tokumi MARUYAMA,*[,a] Toshiyuki KIMURA,[b] and Ikuo YAMAMOTO[b]

Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University,[a] Yamashiro-cho, Tokushima 770–8514, Japan and Department of Hygienic Chemistry, Faculty of Pharmaceutical Sciences, Hokuriku University,[b] Kanazawa 920–1181, Japan. Received February 23, 2001; accepted June 4, 2001

Reaction of tri-*O*-acetyluridine (1) with benzyl bromide or 2-chloroacetophenone in the presence of K_2CO_3 gave the N^3-substituted analogues 2a,c. Condensation of 1 with (±)-1-phenylethanol or 3,5-dimethylbenzyl alcohol using the Mitsunobu reaction also gave 2b, d in good yields. These compounds were allowed to react with Lawesson's reagent and were subsequently treated with ammonia to afford the 4-thiouracil derivatives 5a—d. Compounds 5a—c showed moderate hypnotic activity in mice. However, N^3-(3,5-dimethyl)benzyl derivatives 3d, 5d were found to be almost inactive in this assay.

Key words 4-thiouridine; hypnotic activity; central nervous system depressant; Mitsunobu reaction

It has been reported that uridine shows depressant effects toward the central nervous system (CNS). For instance, uridine decreased spontaneous activity in mice and showed protection against seizures caused by penicillin or metrazol.[1,2] In addition, uridine was extracted from the brainstems of 24 h sleep-deprived rats[3] and caused natural sleep following nocturnal infusion into the rat brain.[4,5] However, uridine itself does not possess any hypnotic activity, as determined by loss of the righting reflex in experimental animals. In 1985, it was demonstrated that N^3-benzyluridine exerts hypnotic activity on mice by intracerebroventicular (i.c.v.) administration,[6] and the structure–activity relationship has been further explored.[7—9] It became clear that the introduction of methylbenzyl, as well as a benzyl group, at N^3 of uridine is effective in producing CNS depressant effects.[7b,c] Trials to modify the sugar showed a diminished effect,[7b,e—g] except for N^3-substituted thymidine[7d] and arabinofuranosyluracil.[7h] It has been proven that N^3-phenacyluridine strongly intensifies the sleep induced by pentobarbital (PB) or diazepam.[8a,b] Although N^1-allyl-5,6-substituted 2-thiouracil derivatives have been synthesized and evaluated in terms of sedative-hypnotic activity,[9] no report concerning N^3-substituted 4-thiouridines has appeared. Barbiturates have been in use as a sedative hypnotic since 1903, and 2-thiobarbituric acids (2-thioxohexahydropyrimidine-4,6-dione) continue to be used as short-acting barbiturates. This background prompted us to explore the 4-thio analogues of N^3-substituted uridine. In this paper, we wish to report the synthesis and CNS-depressant effect of N^3-substituted 4-thiouridines (**5a**—**d**).

Synthesis Tri-*O*-acetyl derivatives of N^3-benzyluridine (**2a**) and N^3-phenacyluridine (**2c**) were prepared by the nucleophilic displacement of 2′,3′,5′-tri-*O*-acetyluridine (**1**) with benzyl bromide or 2-chloroacetophenone in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF), according to the published method.[7a,8a] In the case of **2d**, condensation of **1** with 3,5-dimethylbenzyl alcohol using diisopropyl azodicarboxylate and tributylphosphine was employed,[10] since aralkyl halide was not commercially obtainable. Also, (±)-1-phenylethanol was similarly reacted with **1** to give a 1-phenylethyl derivative (**2b**) as a mixture of diastereomers. Compound **2d** was deprotected by treatment with ammonia in MeOH to give **3d**. Next, the synthesis of N^3-substituted 4-thiouridines was explored as follows. Methods concerning the thiation of uracil or uridine have been universally reported. However, the introduction of an alkyl group on N^3 of 4-thiouridine has been difficult because 4-alkylthio derivatives were inevitably formed.[11] Recently, 3-alkyluracils were successfully converted to the 4-thio congener by Lawesson's reagent.[12] We adopted this method for the synthesis of compounds **5a**—**d**. Thus, compound **2a** was refluxed with Lawesson's reagent in benzene to give **4a** in 52% yield, and subsequent treatment of the product with ammonia in MeOH gave N^3-benzyl-4-thiouridine **5a**, which showed an absorption maximum at 330 nm on UV.[13] In a similar manner, compounds **5b**—**d** were prepared from the corresponding N^3-substituted tri-*O*-acetyluridine (**2b**—**d**). To confirm the site of alkylation, the most biologically active compound, **5c**, was subjected to heteronuclear multiple bond connectivity (HMBC) study. As shown in Fig. 1, this compound was demonstrated to be the 3-phenacyl analogue, since correlation between the methylene protons of the phenacyl group and C(4) as well as C(2) was observed.

Pharmacological Results

The hypnotic activities of the N^3-substituted 4-thiouridine were assayed according to previously established procedures,[7] and the results are presented in Table 1 and Fig. 2. By comparison with the earlier result of N^3-benzyluridine (**3a**, 36±2 min),[7b] 4-thio congener (**5a**) exhibited better hypnotic activity (84±10 min) when administered to mice by i.c.v. injection at 2.0 μmol/mouse. This is the first demonstration that N^3-substituted 4-thiouridine has CNS-depressant activity. In contrast, **5a** reduced a prolongation of PB-induced sleep by 24% compared with **3a**. In the series of N^3-(1-phenylethyl) derivatives, it was reported that a uracil congener (**3b**) caused only 7 min sleep at the same dosage.[7b] However, the 4-thiouridine derivative (**5b**) showed moderate hypnotic activity (58±15 min). The PB-induced sleep-promoting activity of **5b** was similar to that **3b**.[7b] These results indicate that N^3-benzyl (**5a**) or the N^3-(1-phenylethyl) derivative (**5b**) of 4-thiouracil show enhanced hypnotic activity and decreased PB-induced sleep-promoting activity compared to the corresponding uracil congener (**3a**, **b**). Although **5c** showed the most potent hypnotic activity (96±19 min)

* To whom correspondence should be addressed. e-mail: maruyama@ph.bunri-u.ac.jp

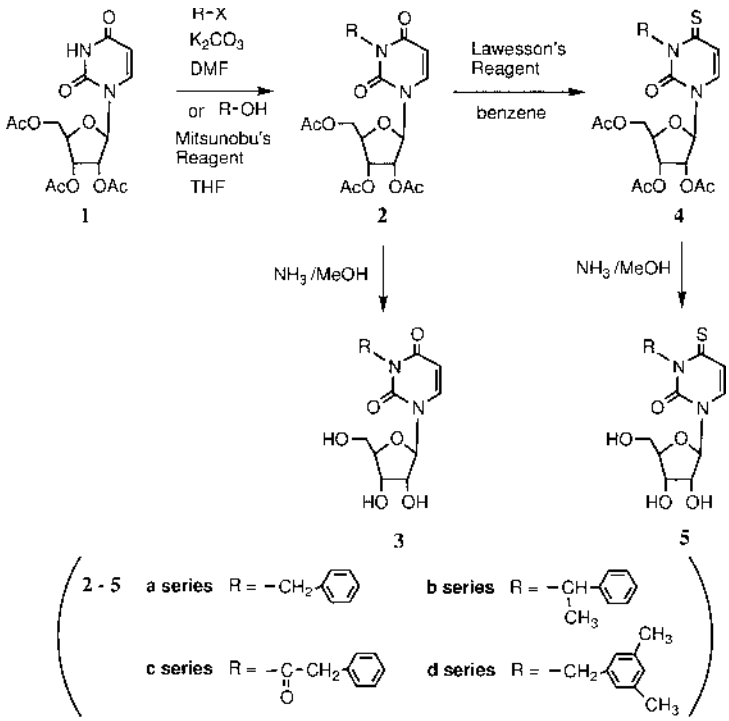

Chart 1

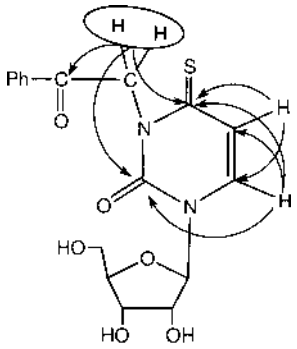

Fig. 1. Selected HMBC Correlations of **5c** in DMSO-d_6

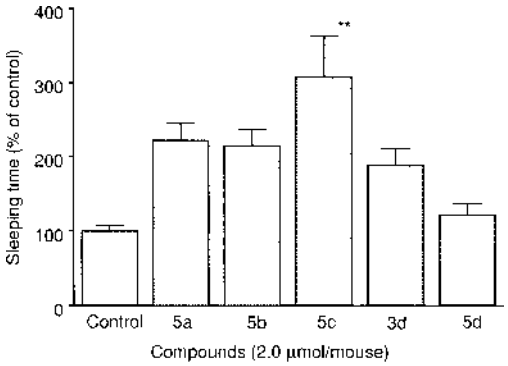

Fig. 2. Effects of N^3-Substituted 4-Thiouridine and Related Compounds on Pentobarbital-Induced Sleep by i.c.v. Injection to Mice

** $p<0.01$ *vs.* control. The reported data for compounds **3a**, **3b** and **3c** is 292, 231 and 230%, respectively.[7b,8a]

Table 1. Hypnotic Activities of N^3-Substituted 4-Thiouridines and Related Compounds by i.c.v. Injection to Mice

Compound[a]	Hypnotic activity[b] (min)	n/n[c]
Control	None	0/8
3a[7b]	36±2	
5a	84±10	6/8
3b[7b]	7	
5b	58±15	5/6
3c	184±13	7/7
5c	96±19	6/7
3d	None	0/8
5d	None	0/8

a) Compounds were administered by i.c.v. injection at the dose of 2.0 μmol/mouse. *b*) Results are expressed as the mean sleeping time (min)±S.E.M. "None" indicates no hypnotic activity. *c*) Ratio of animals which slept to animals tested.

among the 4-thio series, its activity was almost half that of **3c** (184±13 min). It is indicated that the oxygen of the 4 position of the uracil ring is important in the hypnotic activity of **3c**. However, **5c** caused a prolongation of PB-induced sleep and its activity was more than 30% stronger compared with the reported data of **3c**.[8a] Since N^3-benzyluridines bearing a methyl group onto the benzene ring, *i.e.* *o*-, *m*- and *p*-methylbenzyl derivatives, have been proved to be better CNS-depressants than N^3-benzyluridine (**3a**),[7b,c] the activity of N^3-(3,5-dimethylbenzyl)uridine (**3d**) and its 4-thio congener (**5d**) was also examined. However, the hypnotic activity of **3d** and **5d** was poor, and **3d** showed the weakest PB-induced sleep-prolonging activity in this series.

In conclusion, N^3-benzyl- (**5a**) or N^3-(1-phenylethyl)-4-thiouridine (**5b**) enhanced hypnotic activity compared with the original compounds **3a** and **5a**, respectively. However, the strong hypnotic activity of N^3-phenacyluridine (**3c**) was reduced to half by 4-thio modification, as shown in Table 1. This tendency was reversed in the PB-induced sleep-prolonging activity. The PB-induced sleeping time of **5a** was shorter than that of **3a**, and **5c** showed more prolongation than **3c**.

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low-resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on a Varian UNITY 200 (200 MHz) or UNITY 600 (600 MHz) in $CDCl_3$ [or dimethyl sulfoxide (DMSO)-d_6] with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with Silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography, and Silica gel 60 (Merck 7734, 60—200 mesh) was employed for column chromatography.

***N*^{3}-Benzyl-2′,3′,5′-tri-*O*-acetyluridine (2a). General Procedure for 2c** To a solution of 2′,3′,5′-*O*-triacetyluridine (**1**, 3.7 g, 10 mmol) in DMF (50 ml) was added potassium carbonate (1.04 g, 7.5 mmol) and benzyl bromide (1.62 ml, 15 mmol), and they were stirred at 50 °C for 1 h; then acetic acid (0.9 ml) was added and the mixture was concentrated to a small volume. The residue was partitioned between $CHCl_3$ (50 ml) and water (50 ml). The organic layer was dried over $MgSO_4$, and the residual solution was chromatographed over a column of Silica gel G (3.1×40 cm) using 33—66% AcOEt in hexane (1 l) to give a caramel (3.8 g, 83%). ^{1}H-NMR ($CDCl_3$) δ: 7.27—7.46 (6H, m, H6, C_6H_5), 6.04 (1H, d, J=4.4 Hz, H1′), 5.84 (1H, d, J=8.1 Hz, H5), 5.29—5.34 (2H, m, H 2′, H3′), 5.09 (2H, d, J=2.7 Hz, CH_2), 4.34 (3H, br s, H4′, H5′), 2.12 (3H, s, Ac), 2.11 (3H, s, Ac), 2.05 (3H, s, Ac). UV λ_{max} (MeOH) nm: 258.5. MS *m/z*: 460 (M^+).

N^3-Phenacyl-2′,3′,5′-tri-*O*-acetyluridine (**2c**): Compound **2c** was obtained as a caramel (2.34 g, 96%) from **1** (1.85 g, 5 mmol). ^{1}H-NMR ($CDCl_3$) δ: 7.98—8.01 (2H, m, two of C_6H_5), 7.46—7.62 (4H, m, H6, three of C_6H_5), 6.03 (1H, d, J=4.6 Hz, H1′), 5.90 (1H, d, J=8.1 Hz, H5), 5.33—5.42 (4H, m, H 2′, H3′, CH_2), 4.36—4.36 (3H, m, H4′, H5′), 2.15 (3H, s, Ac), 2.11 (3H, s, Ac), 2.10 (3H, s, Ac). UV λ_{max} (MeOH) nm: 246. High-resolution mass spectrometry (HR-MS) *m/z*: 488.1423 (M^+, $C_{23}H_{24}N_2O_{10}$ requires 488.1431).

***N*^{3}-(1-Phenylethyl)-2′,3′,5′-tri-*O*-acetyluridine (2b). General Procedure for 2d** To a mixture of **1** (3.7 g, 10 mmol) and (±)-1-phenylethanol (2.4 ml, 20 mmol) in dry tetrahydrofuran (THF) (100 ml) was added triphenylphosphine (5.25 g, 20 mmol) and diisopropyl azodicarboxylate (4 ml, 20 mmol). The solution was stirred at 50 °C for 6 h, then concentrated over a small volume. The residual solution was chromatographed over a column of Silica gel G (4.2×30 cm) using 20—75% AcOEt in hexane (2 l) to give a caramel (2.86 g, 60%). ^{1}H-NMR ($CDCl_3$) δ: 7.21—7.41 (6H, m, H6, Ph), 6.24—6.28 (1H, m, CH), 6.07 (1H, dd, J=3.7, 5.4 Hz, H1′), 5.82 (1H, d, J=8.1 Hz, H5), 5.21—5.28 (2H, m, H 2′, H3′), 4.31—4.33 (3H, m, H4′, H5′), 2.13 (3H, d, J=2.2 Hz, Ac), 2.10 (3H, s, Ac), 2.09 (3H, s, Ac), 1.82—1.88 (3H, m, CH_3). UV λ_{max} (MeOH) nm: 260. HR-MS *m/z*: 474.1628 (M^+, $C_{23}H_{26}N_2O_9$ requires 474.1638).

N^3-(3,5-Dimethylbenzyl)-2′,3′,5′-tri-*O*-acetyluridine (**2d**): Compound **2d** was obtained as a caramel (10.5 g, 72%) from **1** (11.1 g, 30 mmol). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (1H, d, J=8.1 Hz, H6), 7.04 (2H, br s, two of C_6H_3), 6.89 (1H, br s, one of C_6H_3), 6.07 (1H, dd, J=2.2, 2.6 Hz, H1′), 5.84 (1H, d, J=8.1 Hz, H5), 5.31—5.36 (2H, m, H 2′, H3′), 5.02 (2H, dd, J=13.6, 21.2 Hz, CH_2), 4.35 (3H, br s, H4′, H5′), 2.28 (6H, s, CH_3 (2) 2.13 (3H, s, Ac), 2.11 (3H, s, Ac), 2.06 (3H, s, Ac). UV λ_{max} (MeOH) nm: 259. HR-MS *m/z*: 488.1783 (M^+, $C_{24}H_{28}N_2O_9$ requires 488.1795).

***N*^{3}-Benzyl-2′,3′,5′-tri-*O*-acetyl-4-thiouridine (4a). General Procedures for 4b—d** A mixture of **2a** (460 mg, 1 mmol) and Lawesson's Reagent (0.80 g, 2 mmol) in dry benzene (20 ml) was refluxed overnight, then filtrated to remove the precipitation. The filtrate was concentrated over a small volume and chromatographed over a column of Silica gel G (2.3×37 cm) using 16—33% AcOEt in hexane (1 l) to give a caramel (247 mg, 52%). ^{1}H-NMR ($CDCl_3$) δ: 7.24—7.47 (5H, m, C_6H_5), 7.17 (1H, d, J=7.7 Hz, H6), 6.66 (1H, d, J=7.7 Hz, H5), 6.00 (1H, d, J=4.4 Hz, H1′), 5.65 (2H, d, J=13.9 Hz, CH_2), 5.31—5.38 (2H, m, H2′, H3′), 4.36—4.38 (3H, m, H4′, H5′), 2.12 (3H, s, Ac), 2.11 (3H, s, Ac), 2.05 (3H, s, Ac). UV λ_{max} (MeOH) nm: 333. MS *m/z*: 476 (M^+).

N^3-(1-Phenylethyl)-2′,3′,5′-tri-*O*-acetyl-4-thiouridine (**4b**): Compound **4b** was obtained as a caramel (1.03 g, 90%) from **2b** (1.10 g, 2.3 mmol). ^{1}H-NMR ($CDCl_3$) δ: 7.16—7.42 (6H, m, CH, Ph), 7.12 (1H, d, J=7.7 Hz, H6), 6.73 (1H, d, J=7.7 Hz, H5), 5.92—5.99 (1H, m, H1′), 5.14—5.28 (2H, m, H 2′, H3′), 4.28—4.40 (3H, m, H4′, H5′), 2.13 (3H, d, J=2.2 Hz, Ac), 2.08 (3H, s, Ac), 2.07 (3H, s, Ac), 1.86 (3H, d, J=7.0 Hz, CH_3). UV λ_{max} (MeOH) nm: 329.5. HR-MS *m/z*: 490.1404 (M^+, $C_{23}H_{26}N_2O_8S$ requires 490.1410).

N^3-Phenacyl-2′,3′,5′-tri-*O*-acetyl-4-thiouridine (**4c**): Compound **4c** was obtained as a caramel (1.22 g, 60%) from **2c** (1.95 g, 4 mmol). ^{1}H-NMR ($CDCl_3$) δ: 7.46—8.04 (5H, m, C_6H_5), 7.28 (1H, d, J=7.7 Hz, H6), 6.68 (1H, d, J=7.7 Hz, H5), 5.84—6.07 (3H, m, H1′, CH_2), 5.30—5.45 (2H, m, H2′, H3′), 4.38—4.40 (3H, m, H4′, H5′), 2.15 (3H, s, Ac), 2.12 (3H, s, Ac), 2.10 (3H, s, Ac). UV λ_{max} (MeOH) nm: 325. HR-MS *m/z*: 504.1205 (M^+, $C_{23}H_{24}N_2O_9S$ requires 504.1203).

N^3-(3,5-Dimethylbenzyl)-2′,3′,5′-tri-*O*-acetyl-4-thiouridine (**4d**): Compound **4d** was obtained as a caramel (2.17 g, 84%) from **2d** (2.50 g, 5.1 mmol). ^{1}H-NMR ($CDCl_3$) δ: 7.17 (1H, d, J=7.7 Hz, H6), 7.01 (2H, br s, two of C_6H_3), 6.88 (1H, br s, one of C_6H_3), 6.66 (1H, d, J=7.7 Hz, H5), 6.02 (1H, d, J=4.4 Hz, H1′), 5.63 (2H, dd, J=13.9, 31.1 Hz, CH_2), 5.31—5.38 (2H, m, H 2′, H3′), 4.36 (3H, m, H4′, H5′), 2.28 (6H, s, CH_3×2), 2.13 (3H, s, Ac), 2.11 (3H, s, Ac), 2.05 (3H, s, Ac). UV λ_{max} (MeOH) nm: 329.5. HR-MS *m/z*: 504.1584 (M^+, $C_{24}H_{28}N_2O_8S$ requires 504.1567).

***N*^{3}-Benzyl-4-thiouridine (5a). General Procedures for 3b, 5b—d** A solution of **4a** (220 mg, 0.46 mmol) in MeOH (5 ml) saturated with ammonia at 0 °C was stirred at room temperature overnight. The solution was concentrated to a small volume, and crystallization from EtOH gave yellowish crystals. (157 mg, 97%). mp 160—162.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, d, J=7.7 Hz, H6), 7.29 (5H, m, Ph), 6.61 (1H, d, J=7.7 Hz, H5), 5.20—5.74 (4H, m, H1′, 2′OH, CH_2), 5.09—5.20 (2H, m, 3′OH, 5′OH), 3.90—4.10 (3H, m, H2′, H3′, H4′), 3.55—3.73 (2H, m, H5′). UV λ_{max} (MeOH) nm: 330. MS *m/z*: 350 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; N, 7.99. Found: C, 55.02; H, 5.30; N, 8.29.

N^3-(1-Phenylethyl)uridine (**3b**): Compound **3b** was obtained as white crystals (506 mg, 97%) from **2b** (712 mg, 1.5 mmol). mp 152.5—154.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, dd, J=6.8, 8.0 Hz, H6), 7.21—7.38 (5H, m, Ph), 6.26 (1H, ddd, J=7.1, 14.3, 17.0 Hz, CH), 5.74 (1H, dd, J=2.7, 8.0 Hz, H5), 5.61 (1H, dd, J=3.8, 18.7 Hz, H1′), 4.16—4.25 (2H, m, H2′, H3′), 4.09—4.13 (1H, m, H4′), 3.91 (1H, ddd, J=2.7, 8.8, 11.7 Hz, H5′a), 3.76 (1H, ddd, J=2.7, 9.1, 11.8 Hz, H5′b), 1.83 (3H, dd, J=4.9, 7.1 Hz, CH_3). UV λ_{max} (MeOH) nm: 264. MS *m/z*: 348 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.94; H, 5.91; N, 8.22.

N^3-(1-Phenylethyl)-4-thiouridine (**5b**): Compound **5b** was obtained as yellowish crystals (317 mg, 87%) from **4b** (490 mg, 1 mmol). mp 169—170.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.89 (1H, d, J=7.5 Hz, H6), 7.19—7.32 (6H, m, Ph, CH), 6.68 (1H, d, J=7.7 Hz, H5), 5.58 (1H, d, J=3.7 Hz, H1′), 5.01—5.49 (3H, m, 2′OH, 3′OH, 5′OH), 3.83—3.97 (3H, m, H2′, H3′, H4′), 3.52—3.73 (2H, m, H5′), 1.79 (3H, d, J=6.8 Hz, CH_3). UV λ_{max} (MeOH) nm: 334. MS *m/z*: 364 (M^+). A*nal*. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69. Found: C, 55.83; H, 5.60; N, 7.81.

N^3-Phenacyl-4-thiouridine (**5c**): Compound **5c** was obtained as yellowish crystals (514 mg, 68%) from **4c** (1.00 g, 2 mmol). mp 157.5—159 °C. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 8.01—8.09 (2H, m, two of C_6H_5), 8.01 (1H, d, J=7.7 Hz, H6), 7.72—7.74 (1H, m, one of C_6H_5), 7.58—7.61 (2H, m, two of C_6H_5), 6.65 (1H, d, J=7.7 Hz, H5), 5.94 (2H, dd, J=17.3, 44.8 Hz, CH_2), 5.76 (1H, d, J=4.4 Hz, H1′), 5.54 (1H, d, J=5.5 Hz, 2′OH), 5.21 (1H, dd, J=4.9, 5.2 Hz, 5′OH), 5.16 (1H, d, J=5.8 Hz, 3′OH), 4.09 (1H, dd, J=4.9, 10.2 Hz, H2′), 4.01 (1H, q, J=5.2 Hz, H3′), 3.91—3.93 (1H, m, H4′), 3.71 (1H, ddd, J=3.3, 5.2, 12.4 Hz, H5′a), 3.61 (1H, ddd, J=3.3, 4.9, 12.4 Hz, H5′b). ^{13}C-NMR (150 MHz, DMSO-d_6) δ: 191.2 (C=O), 189.6 (C4), 148.6 (C2), 133.8 (C6), 134.4, 134.1, 129.0 and 127.9 (C_6H_5), 112.9 (C5), 89.9 (C2′), 84.9 (C4′), 74.1 (C1′), 69.3 (C3′), 60.3 (C5′), 53.4 (CH_2). UV λ_{max} (MeOH) nm: 330.3. MS *m/z*: 378 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40. Found: C, 54.14; H, 4.85; N, 7.55.

N^3-(3,5-Dimethylbenzyl)-4-thiouridine (**5d**): Compound **5d** was obtained as yellowish crystals (580 mg, 61%) from **4d** (1.26 g, 2.5 mmol). mp 155.5—157 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.92 (1H, d, J=7.3 Hz, H6), 6.88 (3H, br s, C_6H_3), 6.61 (1H, d, J=7.3 Hz, H5), 5.73 (1H, d, J=3.3 Hz, H1′), 5.43—5.63 (3H, m, 2′OH, CH_2), 5.09—5.20 (2H, m, 3′OH, 5′OH), 3.91—4.07 (3H, m, H2′, H3′, H4′), 3.52—3.77 (2H, m, H5′), 2.22 (6H, s, CH_3×2). UV λ_{max} (MeOH) nm: 332. MS *m/z*: 378 (M^+). *Anal*. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.22; H, 5.75; N, 7.65.

References and Notes

1) Krooth R. S., Hsiao W. L., Lam G. F. M., *J. Pharmacol. Exp. Ther*., **207**, 504—514 (1978).
2) Roberts C. A., *Brain Res*., **55**, 291—307 (1973).
3) Komoda Y., Ishikawa M., Nagasaki H., Iriki M., Honda K., Inoue S., Higashi A., Uchizono K., *Biomed. Res*., **4**, 223—228 (1983).
4) Honda K., Komoda Y., Nishida S., Nagasaki H., Higashi A., Uchizono K., Inoue S., *Neurosci. Res*., **1**, 243—252 (1984).
5) Inoue S., Honda K., Komoda Y., Uchizono K., Ueno R., Hayashi O., *Proc. Natl. Acad. Sci. U.S.A*., **81**, 6240—6244 (1984).
6) Yamamoto I., Kimura T., Tateoka Y., Watanabe K., Ho I. K., *Chem.*

Pharm. Bull., **33**, 4088—4090 (1985).
7) *a*) Yamamoto I., Kimura T., Tateoka Y., Watanabe K., Ho I. K., *Res. Commun. Chem. Pathol. Pharmacol*., **52**, 321—332 (1986); *b*) *Idem.*, *J. Med. Chem*., **30**, 2227—2231 (1987); *c*) Koshigami M., Watanabe K., Kimura T., Yamamoto I., *Chem. Pharm. Bull*., **39**, 2597—2599 (1991); *d*) Kimura T., Watanabe K., Takeoka Y., Kondo S., Ho I. K., Yamamoto I., *ibid*., **41**, 1180—1182 (1993); *e*) Sato Y., Utsumi K., Maruyama T., Kimura T., Yamamoto I., Richman D. D., *ibid*., **42**, 595—598 (1994); *f*) Kimura T., Kuze J., Teraoka Y., Kondo S., Ho I. K., Yamamoto I., *Biol. Pharm. Bull*., **19**, 142—145 (1996); *g*) Yao C. S., Kimura T., Watanabe K., Kondo S., Ho I. K., Yamamoto I., *Chem. Pharm. Bull*., **47**, 1802—1804 (1999); *h*) Kimura T., Yao C. S., Watanabe K., Kondo S., Ho I. K., Yamamoto I., *ibid.*, **49**, 111—113 (2001).
8) *a*) Yamamoto I., Kuze J., Kimura T., Watanabe K., Kondo S., Ho I. K., *Biol. Pharm. Bull.*, **17**, 514—516 (1994); *b*) Kimura T., Kuze J., Watanabe K., Kondo S., Ho I. K., Yamamoto I., *Eur. J. Pharmacol*., **311**, 265—269 (1996).
9) Draminski M., Turski K., Tateoka Y., Kimura T., Watanabe K., Kondo S., Ho I. K., Yamamoto I., *Chem. Pharm. Bull*., **46**, 1370—1373 (1998).
10) *a*) Mitsunobu O., *Synthesis*, **1981**, 1—28; *b*) Kozai S., Fukagawa T., Maruyama T., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3145—3136.
11) Wyrzykiewicz E., Nowakowska Z., Bartkowiak G., Kedzia B., *Pol. J. Chem.*, **71**, 201—206 (1997) and the references cited therein.
12) *a*) Clivio P., Fourrey J.-L., Gasche J., Favre A., *J. Chem. Soc.*, *Perkin Trans. 1*, **1992**, 2383—2388; *b*) Clivio P., Fourrey J.-L., *J. Org. Chem*., **59**, 7273—7283 (1994).
13) Fox J. J., Praag D. V., Wempen I., Doerr I. L., Cheong L., Knoll J. E., Eidinoff M. L., Bendich A., Brown G. B., *J. Am. Chem. Soc*., **81**, 178—187 (1959).