Pergamon

Tetrahedron 56 (2000) 7685–7690

TETRAHEDRON

Reaction of 7-(2-Mesyloxy-2-phenylethyl)theophylline with Amines: Synthesis of 1,2,3,6-Tetrahydro-6-imino-2-oxo-7*H*-purine Derivatives

Shigetada Kozai, Kyoko Ogimoto and Tokumi Maruyama*

Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

Received 21 June 2000; accepted 2 August 2000

Abstract—Theophylline was converted to 7-(2-phenyl-2-methanesulfonyloxy)ethyl congener and the product was treated with ammonia or primary amines in a mixture solution of water and organic solvents. Two products were proven to be the styrene analogue and 7-(2-amino-2-phenylethyl)theophylline. The structure of the third product was elucidated as the 1,2,3,6-tetrahydro-6-imino-2-oxo-7*H*-purine derivatives by spectroscopic analysis including HMBC correlation and X-ray crystallography.

Introduction

Theophylline, a xanthine derivative, has been used for the treatment of the bronchi. Many derivatives of xanthine have been reported to exert interesting biological activity such as inhibition of phosphodiesterases (PDEs),[1] adenosine receptor antagonists[2] and calcitonin-inducing activities.[3] Recently, the iminooxopurines, amidine analogues of xanthine, have emerged as strong inhibitors of PDEs. Sawanishi et al.[4] reported that 1,6-cycloalkyl-1,2,3,6-tetrahydro-6-imino-2-oxo-9*H*-purine (**A**) is a strong PDE IV inhibitor and shows tracheal-relaxant activity (Fig. 1). Also tetracyclic guanines (**B**) which possess 1,2,3,6-tetrahydro-2-imino-6-oxo-7*H*-purine structure have been shown to be potent and selective inhibitors of the cGMP-hydrolizing enzyme PDE1 and PDE5.[5]

However, synthesis of these compounds was achieved by ring construction, and conversion of commercially available caffeine or theophylline to iminooxopurine, an amidine analogue of xanthine, has not been examined. Since amidines are important as precursors of the drug,[6] several methods to prepare these compounds from amide have been developed. For instance, imidate salt was prepared by treatment of amide with triethyloxonium tetrafluoroborate and converted into amidines.[6a,7] Also 1-methyl-2-pyrrolidone was reacted with chlorosulfonyl isocyanate followed by hydrolysis with aqueous sodium hydroxide to give 2-imino-1-methylazacarbocycles.[8] We report here a new method for the synthesis of the 7-substituted-1,2,3,6-tetrahydro-6-imino-2-oxo-7*H*-purine from theophylline.

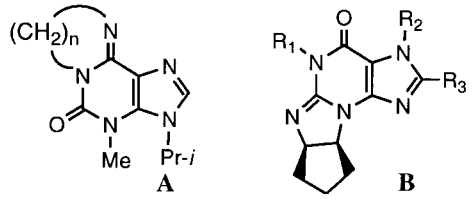

Figure 1. Phosphodiesterase inhibitors.

Results and Discussion

We attempted the conversion of caffeine to amidine congener. For instance, caffeine (**1**) was successively treated with triethyloxonium tetrafluoroborate and ammonia.[6a,7] However, the ring-opening product (**2**) was obtained in a low yield. It is speculated that the initial attack of the reagent at oxygen is difficult since much more electron-rich nitrogen receives a preferential attack of the electrophile (Chart 1). Another trial using chlorosulfonyl isocyanate and alkali as reagents recovered caffeine.[8] The authors postulated that the carbocation at the side-chain is favored to attack the exocyclic oxygen without affecting ring nitrogen of caffeine. Thus, the 2-hydroxy-2-phenylethyl derivative (**4a**) was prepared from theophylline (**3a**) in 2 steps and converted to the mesylate (**4b**) by the conventional manner (Chart 2). Then **4b** was treated with 28% ammnia in the mixture of dioxane and MeOH. After work-up of the reaction mixture, the products were separated by silica gel chromatography. From the first fraction, the styrene analogue (**5**), which shows absorption maximum at 308 nm on UV spectrum, was obtained. The most polar substance from the third fraction was proven as the

Keywords: amidines; X-ray crystallography; xanthates.

* Corresponding author. Tel: +81-886-22-9611; fax: +81-886-55-3051; e-mail: maruyama@ph.bunri-u.ac.jp

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00683-9

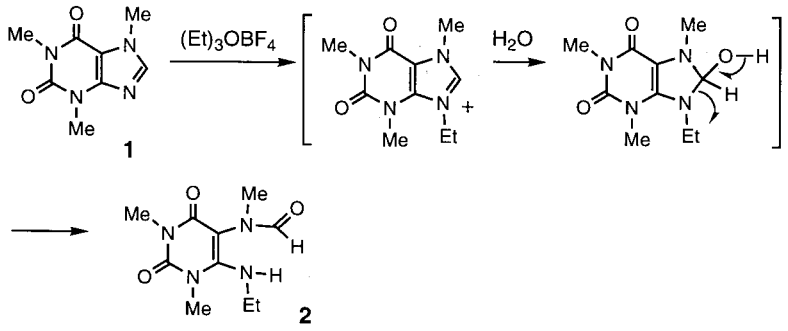

Chart 1.

Table 1. Yields of the products obtained by the reaction of the mesylate (**4b**) with amines

	5 (%)	**6a–c** (%)	**7a–c** (%)
a series; R=H	31	3.3	40
b series; R=CH_3	3.2	43	23
c series; R=C_2H_5	4.3	7.6	45

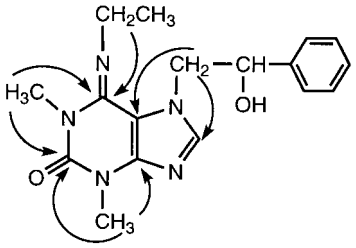

Figure 2. HMBC correlations of **7c** in $CDCl_3$.

2-amino-2-phenylethyl compound (**6a**). The second fraction was evaporated to produce the new compound (**7a**) as white crystals. The UV spectrum of **7a** was different from the caffeine analogue such as **1**, **3b** and **4a**,**b** and showed an absorption maximum at 297.5 nm in an acidic condition. The bathochromic effect in the acidic condition suggests a modification of the chromophore. Reaction of **4b** with primary amines also gave **7b**,**c** (Table 1). The imino-oxopurine structure was confirmed by HMBC spectrum of the N^6-ethyl derivative (**7c**) which shows a C–H correlation between methylene protons of ethyl group and C6 (Fig. 2). The presence of the ethyl group near C6 strongly suggests that a nucleophilic attack of amines at C6 occurred during the reaction. Podona et al. reported that neighboring group participation of the side-chain was observed in the reaction of *N*-(2-bromoethyl)glutarimide with primary amine to afford *N*-(2-hydroxyethyl)imino-glutarimide.[9] Consequently the new products were estimated as imino-oxopurines (**7a**–**c**). The structure of **7a** was finally determined by the X-ray diffraction method (Fig. 3). The mechanism to form **7a**–**c** could be explained as the following: At first the carbocation (**S-1**) was formed from starting

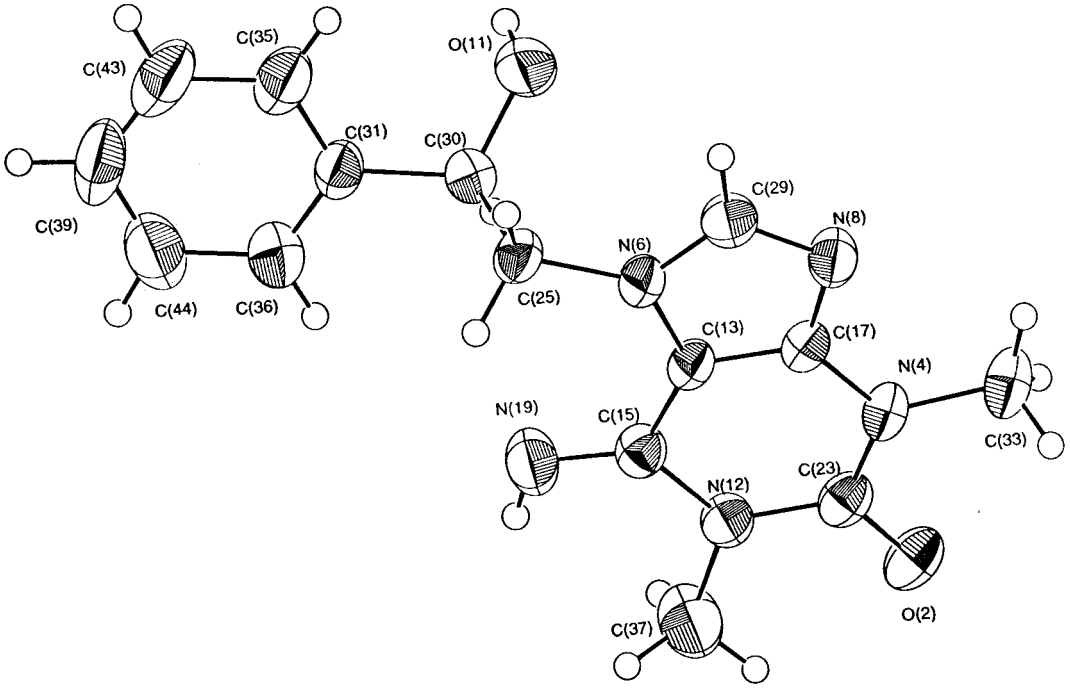

Figure 3. ORTEP drawing of compound **7a**.

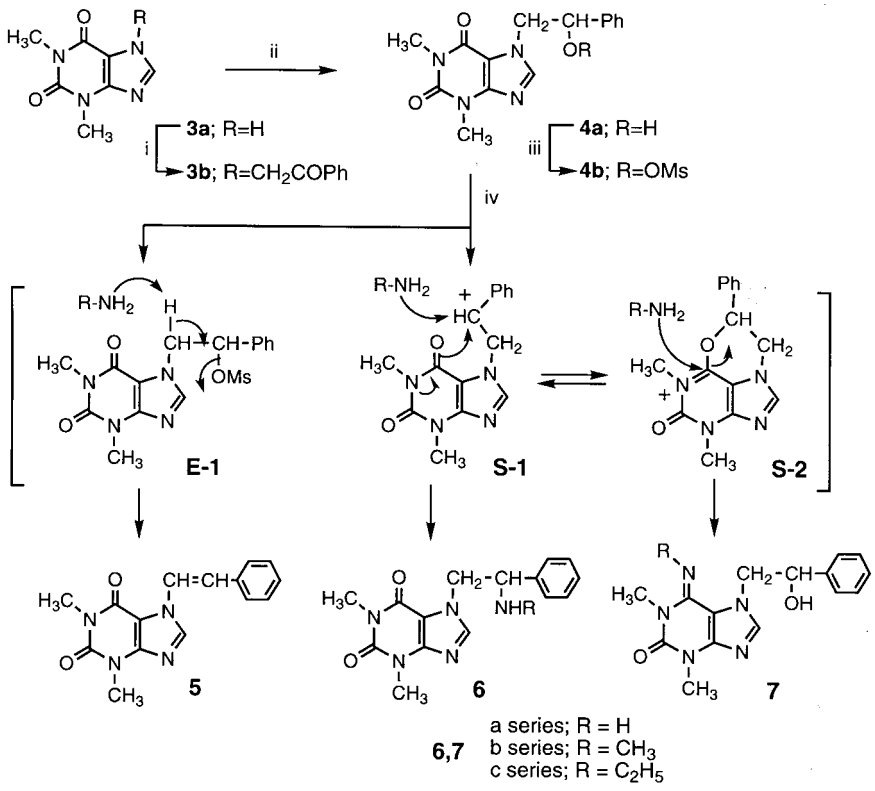

Chart 2. (i) $PhCOCH_2Cl$, K_2CO_3, acetone-DMF, (ii) $NaBH_4$, MeOH–*i*PrOH, (iii) MsCl, pyridine (iv) R–NH_2 in 1,4-dioxane.

material, then intramolecular electrophilic attack of the cation to the O6 formed the ammonium of the ring structure (**S-2**). Nucleophilic substitution of ammines at C6 and the subsequent elimination of proton formed **7a**–**c** (Chart 2). The ratio of the amidine derivatives (**7**) to the substitution product (**6**) is changeable by the amines. The reason is under investigation.

Although nitrogen of caffeine is facilitated to the electrophilic attack, the carbocation at the side-chain of N7 is able to attack regio-specifically at exocyclic oxygen (O6) of theophylline derivative. Nucleophilic substitution of the intermediate with ammonia or primary amines afforded 1,2,3,6-tetrahydro-6-imino-2-oxo-7*H*-purines **7a**–**c**. This is the first report that describes the conversion of the 1-alkyl-6-oxopurine to the amidine analogue.

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. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ 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. X-ray reflection data were collected with a Mac Science MXC18 diffractometer using MoKα radiation (λ=0.71073 Å).

Reaction of caffeine (1) with alkylating agent and ammonia. To a suspension of caffeine (**1**, 970 mg, 5 mmol) in dry CH_2Cl_2 (10 mL) was added 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2 (5 mL, 5 mmol) and stirred at room temperature overnight. The solution was concentrated to dryness, to which anhydrous ether (10 mL) was added. The insolubles were collected by filtration to give a solid. The product was dissolved in saturated ammonia solution in MeOH (10 mL) and stirred at room temperature for 3 days. Then, the solution was filtered to remove insoluble materials. The filtrate was evaporated and chromatographed over a column of silica gel (2×32 cm) using 0–12% EtOH in $CHCl_3$ (2 L) to give 6-ethylamino-5-[(*N*-formyl-*N*-methyl)amino]-1,3-dimethyluracil (**2**) as white crystals (83 mg, 7%): mp 137.5–138.5°C; UV λ_{max} (MeOH) nm: 272 (log ϵ=4.22); UV λ_{max} (0.05 M HCl) nm: 272 (log ϵ=4.24); MS *m/z*: 240 (M^+); the structure of the product was determined by X-ray diffraction method as shown in Fig. 4.

7-Phenacyltheophylline (3b). To a solution of theophylline (**3a**, 5.4 g, 30 mmol) in a mixture of DMF (120 mL) and acetone (120 mL) was added potassium carbonate (4.98 g, 36 mmol) and 2-chloroacetophenone (6.96 g, 45 mmol) and the mixture was stirred at room temperature for 2 h. The solution was neutralized by addition of acetic acid (4.2 mL) and evaporated to a small volume, then the residue was partitioned between $CHCl_3$ (500 mL) and water (500 mL). The organic layer was evaporated to give a

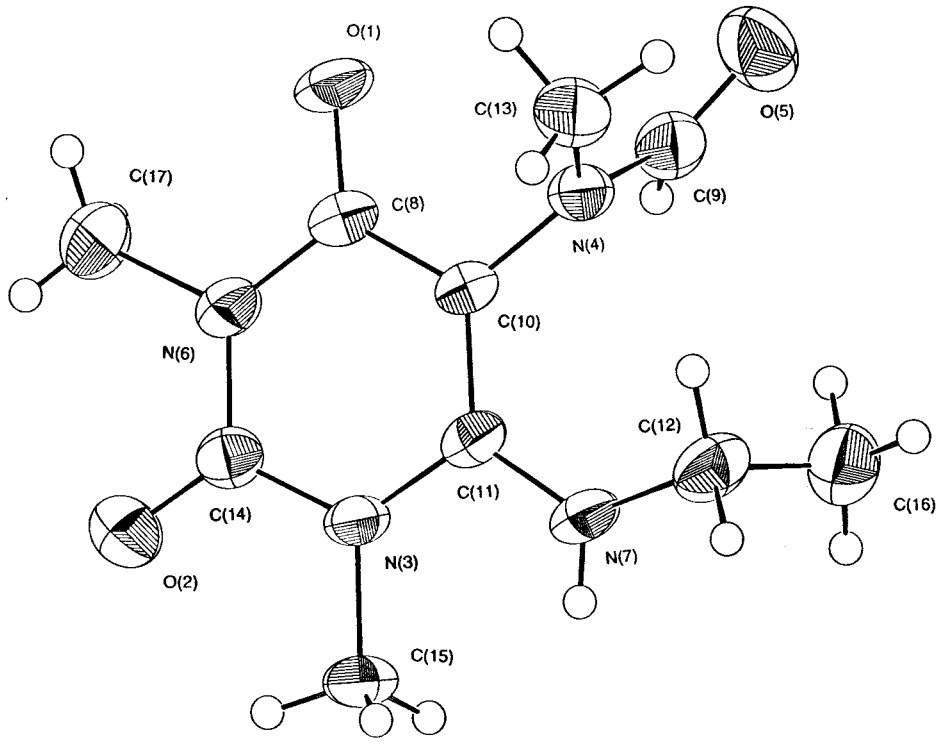

Figure 4. ORTEP drawing of compound **2**.

residue, which was recrystallized from MeOH to afford **3b** as white crystals (8.3 g, 93%): mp 188.5–189°C; ^{1}H NMR ($CDCl_3$) δ: 7.50–8.06 (6H, m, Ph, H-8), 5.82 (2H, m, CH_2), 3.63 (3H, s, CH_3), 3.35 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 273 (log ϵ=4.04); MS *m/z*: 298 (M^+); Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.21; H, 4.71; N, 18.77.

7-[(2-Hydroxy-2-phenyl)ethyl]theophylline (4a). To a solution of **3b** (4.4 g, 14.8 mmol) in a mixture of MeOH (60 mL) and *i*-PrOH (60 mL) was added $NaBH_4$ (1.25 g, 33 mmol) and the mixture was refluxed for 1 h. Then, the solution was concentrated to a small volume and the residue was partitioned between $CHCl_3$ (200 mL) and water (200 mL). The organic layer was dried over $MgSO_4$, evaporated and the solid was crystallized from EtOH to give **4a** as white crystals (4.2 g, 94%): mp 155–156°C; ^{1}H NMR ($CDCl_3$) δ: 7.31–7.41 (6H, m, Ph, H-8), 5.10–5.17 (1H, m, *CH*–Ph), 4.69 (1H, dd, *J*=3.1, 13.9 Hz, one of CH_2), 4.17–4.28 (1H, m, one of CH_2), 3.62 (1H, d, *J*=3.5 Hz, OH), 3.56 (3H, s, CH_3), 3.40 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 273 (log ϵ=3.93); MS *m/z*: 300 (M^+); Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.65. Found: C, 59.60; H, 5.53; N, 18.41.

7-[(2-Methanesulfonyloxy-2-phenyl)ethyl]theophylline (4b). To a solution of **4a** (3.7 g, 12.3 mmol) in pyridine (37 mL) was added methanesulfonyl chloride (4.36 mL, 55 mmol) and the mixture was stirred at room temperature for 1 h. Then, water (6.2 mL) was added to the solution. The mixture was concentrated to a small volume and the residue was partitioned between $CHCl_3$ (250 mL) and water (250 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was crystallized from toluene to afford **4b** as white crystals (3.28 g, 70%); 146–147°C. ^{1}H NMR ($CDCl_3$) δ: 7.61 (1H, s, H-8), 7.43–7.53 (5H, m, Ph), 5.99 (1H, dd, *J*=2.9, 9.2 Hz, *CH*–Ph), 4.77 (1H, dd, *J*=3.1, 14.5 Hz, one of CH_2), 4.39–4.51 (1H, m, one of CH_2), 3.61 (3H, s, CH_3), 3.44 (3H, s, CH_3), 2.72 (3H, s, CH_3). UV λ_{max} (MeOH) nm: 273 (log ϵ=3.93); MS *m/z*: 378 (M^+). Anal. Calcd for $C_{16}H_{18}N_4O_5S$: C, 50.78; H, 4.79; N, 14.80. Found: C, 51.22; H, 5.01; N, 14.82.

Reaction of 4b with ammonia. To a solution of **4b** (500 mg, 1.32 mmol) in 1,4-dioxane (30 mL) was added 25% ammonia (1 mL, 15 mmol) and heated in a steel tube at 100°C overnight. After cooling, the solution was concentrated to a small volume, and chromatographed over a column of silica gel (2.6×18 cm) using 0–25% MeOH in AcOEt. From the first fraction 7-(2-phenylvinyl)theophylline (**5**) was obtained as a white solid (116 mg, 31%): mp 185.5–187.5°C; ^{1}H NMR ($CDCl_3$) δ: 8.04 (1H, s, H-8), 8.01 (1H, d, *J*=14.7 Hz, CH), 7.32–7.50 (5H, m, Ph), 6.98 (1H, d, *J*=15.0 Hz, CH), 3.63 (3H, s, CH_3), 3.59 (3H, s, CH_3); UV λ_{max} (MeOH) nm (log ϵ): 269 (4.21), 308 (4.24); MS *m/z*: 282 (M^+); Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.59; H, 4.47 N, 19.70. The third fraction was evaporated and the residue was crystallized from MeOH to give 7-(2-hydroxy-2-phenylethyl)-1,3-dimethyl-1,2,3,6-tetrahydro-6-imino-2-oxo-7*H*-purine (**7a**) as white crystals (157 mg, 40%): mp 148–148.5°C; ^{1}H NMR ($CDCl_3$) δ: 7.29–7.39 (5H, m, Ph), 7.01 (1H, s, H-8), 5.14(1H, dd, *J*=2.9, 5.8 Hz, *CH*–Ph), 4.86 (1H, dd, *J*=2.9, 14.3 Hz, one of CH_2), 4.39 (1H, dd, *J*=6.2, 14.3 Hz, one of CH_2), 3.53 (3H, s, CH_3), 3.42 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 277 (log ϵ=3.99), λ_{max} (0.05 M HCl) nm: 297.5 (log ϵ=4.04); MS *m/z*: 299 (M^+); Anal. Calcd for $C_{15}H_{17}N_5O_2 \cdot 0.1H_2O$: C, 59.82; H, 5.76; N, 23.26. Found:

C, 59.86; H, 5.70 N, 23.30. Evaporation of the fourth fraction gave 7-(2-amino-2-phenylethyl)theophylline (**6a**) as a white solid (13 mg, 3.3%): mp 152.5–154°C. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.37 (5H, m, Ph), 7.29 (1H, s, H-8), 4.35–4.54 (2H, m, *CH*–Ph and one of CH_2), 4.27–4.35 (1H, m, one of CH_2), 3.59 (3H, s, CH_3), 3.45 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 274.0 (log ϵ=3.92), UV λ_{max} (0.05 M HCl) nm: 274 (log ϵ=3.96); MS *m/z*: 299 (M^+); Anal. Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.15; H, 5.71 N, 23.31. Also **4a** was obtained from the second fraction in 3.2% yield.

Reaction of 4b with methylamine. To a solution of **4b** (500 mg, 1.32 mmol) in 1,4-dioxane (30 mL) was added 40% methylamine (1 mL, 12.9 mmol) and heated in a steel tube at 80°C overnight. A similar work-up of the solution as described in the section of **7a** and separation by a column of silica gel (2.6×24 cm) using 0–12.5% MeOH in AcOEt gave three products. From the third fraction, 7-[(2-hydroxy-2-phenyl)ethyl]-1,3-dimethyl-1,2,3,6-tetrahydro-6-methylimino-2-oxo-7*H*-purine (**7b**) was obtained as white crystals (96 mg, 23%): mp 153–154.5°C; ^{1}H NMR ($CDCl_3$) δ: 7.28–7.37 (5H, m, Ph), 6.90 (1H, s, H-8), 5.08 (1H, dd, *J*=3.0, 6.3 Hz, *CH*–Ph), 4.70 (1H, dd, *J*=3.0, 14.6 Hz, one of CH_2), 4.30 (1H, dd, *J*=6.3, 14.3 Hz, one of CH_2), 3.57 (3H, s, CH_3), 3.48 (3H, s, CH_3), 3.47 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 282.5 (log ϵ=4.00), UV λ_{max} (0.05 M HCl) nm: 310 (log ϵ=4.09); MS *m/z*: 313 (M^+); Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.45; H, 6.17; N, 22.38. The fourth fraction was evaporated to give 7-[(2-methylamino-2-phenyl)ethyl]theophylline (**6b**) as white crystals (180 mg, 43%): mp 160–161°C; ^{1}H NMR ($CDCl_3$) δ: 7.28–7.36 (5H, m, Ph), 7.10 (1H, s, H-8), 4.44 (2H, dd, *J*=0.8, 6.9 Hz, CH_2), 4.03 (1H, t, *J*=6.3 Hz, *CH*–Ph), 3.57 (3H, s, CH_3), 3.44 (3H, s, CH_3), 2.32 (3H, s, NCH_3); UV λ_{max} (MeOH) nm: 274 (log ϵ=3.93), UV λ_{max} (0.05 M HCl) nm: 274 (log ϵ=3.96); MS *m/z*: 313 (M^+); Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.20; H, 6.10; N, 22.34. Compound **5** was obtained from the first fraction as white crystals in 3.2% yield. Also starting material was recovered from the second fraction in 19% yield.

Reaction of 4b with ethylamine. To a solution of **4b** (500 mg, 1.32 mmol) in 1,4-dioxane (30 mL) and water (1 mL) was added 2.0 M ethylamine solution in MeOH (4 mL, 8 mmol) and the solution was heated in a steel tube at 100°C overnight. A similar work-up of the solution as described in the section of **7a** and separation by a column of silica gel (2.6×24 cm) using 0–12.5% MeOH in AcOEt gave four products. From the first fraction **5** was obtained as a caramel in 4.3% yield. Second fraction was evapoarted to give 7-(2-methoxy-2-phenylethyl)theophylline as a white solid (26 mg, 6.4%): mp 145–146.5°C; ^{1}H NMR ($CDCl_3$) δ: 7.58 (1H, s, H-8), 7.32–7.42 (5H, m, Ph), 4.54–4.67 (2H, m, CH–Ph and one of CH_2), 4.13–4.27 (1H, m, one of CH_2), 3.62 (3H, s, CH_3), 3.44 (3H, s, CH_3), 3.21 (3H, s, OCH_3); UV λ_{max} (MeOH) nm: 273 (log ϵ=3.95), UV λ_{max} (0.05 M HCl) nm: 273 (log ϵ=3.97); MS *m/z*: 314 (M^+); Anal. Calcd for $C_{16}H_{18}N_4O_3{\cdot}H_2O$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.91; H, 5.49; N, 16.66. Evaporation of the third fraction gave 7-(2-hydroxy-2-phenylethyl)-1,3-dimethyl-6-ethylimino-1,2,3,6-tetrahydro-2-oxo-7*H*-purine (**7c**) as white crystals (195 mg, 45%): mp 157–158°C; ^{1}H NMR ($CDCl_3$) δ: 7.23–7.37 (5H, m, Ph), 6.95 (1H, s, H-8), 5.09 (1H, dd, *J*=3.0, 6.6 Hz, *CH*–Ph), 4.71 (1H, dd, *J*=3.0, 14.3 Hz, one of CH_2), 4.35 (1H, dd, *J*=6.6, 14.3 Hz, one of CH_2), 3.77 (2H, dq, *J*=1.9, 7.1 Hz, CH_2CH_3), 3.55 (3H, s, CH_3), 3.52 (3H, s, CH_3), 1.39 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.9 (C2), 144.4 (C4), 142.8 (C6), 141.7 (Ph), 139.9 (C8), 128.5 (Ph), 127.9 (Ph), 125.7 (Ph), 109.6 (C5), 74.0 (CH_2–*C*H(OH)–), 53.4 (*C*H_2–CH(OH)–), 43.9 (N^6–*C*H_2CH_3), 36.1 (N^1–CH_3), 29.6 (N^3–CH_3), 17.9 (N^6–CH_2*C*H_3); UV λ_{max} (MeOH) nm: 283.5 (log ϵ=4.02), λ_{max} (HCl) nm: 312 (log ϵ=4.12); MS *m/z*: 327 (M^+); Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.57; H, 6.39; N, 21.51. The fourth fraction was evaporated to give 7-(2-ethylamino-2-phenylethyl)theophylline (**6c**) as a caramel (33 mg, 7.6%): ^{1}H NMR ($CDCl_3$) δ: 7.22–7.37 (5H, m, Ph), 7.12 (1H, s, H-8), 4.42 (2H, dd, *J*=0.7, 6.6 Hz, CH_2), 4.03 (1H, t, *J*=6.6 Hz, *CH*–Ph), 3.58 (3H, s, CH_3), 3.44 (3H, s, CH_3), 2.59 (2H, q, *J*=7.3 Hz, CH_2CH_3), 1.05 (3H, t, *J*=7.3 Hz, CH_2CH_3); UV λ_{max} (MeOH) nm: 274, UV λ_{max} (0.05 M HCl) nm: 275; MS *m/z*: 327 (M^+).

Crystal data

*Crystal data of **2**:* Recrystallized from ethanol; Monoclinic, space group $P2_1/c$, a=7.888(0) Å, b=9.757 (0) Å, c=15.305 (0) Å, β=97.473 (0)°, V=1167.900(0) Å^3, Z=4. Program using to solve structure: maXus *SIR*92. Program using to refine structure: maXus. The structure refined by full matrix least-squares; Refinement on F, R=0.052, wR=0.090, S=1.966.

*Crystal data of **7a**:* Recrystallized from ethanol; Monoclinic, space group $P2_1/c$, a=11.078 (4) Å, b=14.248 (4) Å, c=18.696 (6) Å, β=90.20 (3)°, V=2950.930(2) Å^3, Z=8. Program using to solve structure: maXus *SIR*92. Program using to refine structure: maXus. The structure refined by full matrix least-squares; Refinement on F, R=0.047, wR=0.056, S=1.944.

References

1. Beavo, J. A. *Physiol. Reviews* **1995**, *75*, 725–748.
2. (a) Sauer, R.; Maurinsh, J.; Reith, U.; Fulle, F.; Klotz, K.-N.; Muller, C. E. *J. Med. Chem.* **2000**, *43*, 440–448. (b) Kim, Y.-C.; Ji, X.; Linden, J.; Jacobson, K. A. *J. Med. Chem.* **2000**, *43*, 1165–1172 and the references cited therein.
3. Gilbert, A. M.; Caltabiano, S.; Roberts, D.; Sum, S. F. W.; Francisco, G. D.; Lim, K.; Asselin, M.; Ellingboe, J. W.; Kharode, Y.; Cannistraci, A.; Francis, R.; Trailsmith, M.; Gralnick, D. *J. Med. Chem.* **2000**, *43*, 1223–1233 and the references cited therein.
4. Sawanishi, H.; Suzuki, H.; Yamamoto, S.; Waki, Y.; Kasugai, S.; Ohya, K.; Suzuki, N.; Miyamoto, K.; Takagi, K. *J. Med. Chem.* **1997**, *40*, 3248–3253.
5. Ahn, H.-S.; Bercovici, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gundes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Manna, M.; McKittrick, B.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.;

Silverman, L.; Smith, E.; Stamfoord, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkowski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196–2210.
6. (a) Rasmussen, C. R.; Gardocki, J. F.; Plampin, J. N.; Twardzik, B. L.; Reynolds, B. E.; Molinari, A. J.; Schwartz, N.; Benetts, W. W.; Price, B. E.; Marakowski, J. *J. Med. Chem.* **1978**, *21*, 1044–1054. (b) Grisar, J. M.; Claxton, G. P.; Wiech, N. L.; Lucas, R. W.; MacKenzie, R. D.; Goldstein, S. *J. Med. Chem.* **1973**, *16*, 885–893. (c) Barsky, L. I.; Bencze, W. L. *J. Med. Chem.* **1971**, *14*, 40–44.
7. Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, *33*, 1679–1681.
8. Rama Rao, K.; Nageswar, Y. V. D.; Srinivasa, T. N.; Sattur, P. B. *Synth. Comm.* **1988**, *18*, 877–880.
9. Podona, T.; Lazar, S.; Coudert, G.; Guillaumet, G. *Tetrahedron* **1993**, *49*, 4619–4626.