Facile Synthesis of Fused Purines from 8-Aminotheophylline

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Fused purines **3a-f** were prepared by one-step from 8-aminotheophylline (**1**) and α,ω-dibromoalkanes in *N,N*-dimethylformamide in the presence of sodium hydride. Reaction of **3c-e** with chloroacetyl chloride followed by treatment with dimethylamine gave **6a-c**. A one-step reaction of **1** with ethyl bromopropionate gave 1,3-dimethyl-1,2,3,4,6,7,8,9-octahydropyrimido[2,1-*f*]purine-2,4,8-trione (**7b**). Facile syntheses of **7a,c,d** from **1** were also carried out.

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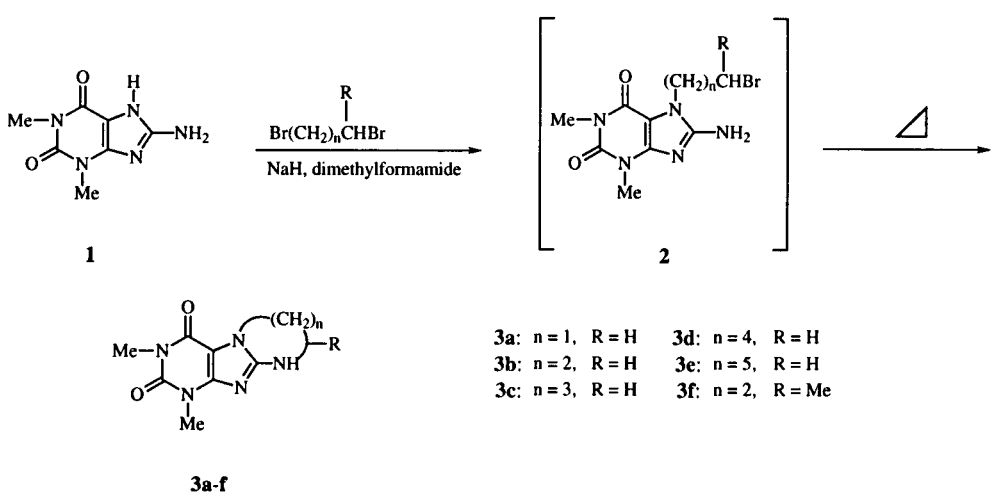
Purine derivatives such as theophylline, caffeine, and theobromine are widely distributed in nature and have some important biological activities. We thought it might be interesting to utilize theophylline for the synthesis of fused purines and examine their pharmacological activities. This paper deals with facile synthesis of fused purines **3a-f** and **7b** from 8-aminotheophylline (**1**) [1]. Eckstein, *et al.* [2] synthesized **3a-c** *via* three steps from 8-halotheophylline by the reaction with *N*-(ω-bromoalkyl)phthalimide. As we reported earlier [3] we found that if alkylations of **1** with alkyl halides in *N,N*-dimethylformamide in the presence of sodium hydride were carried out below 90°, 8-amino-7-alkylpurines were obtained regioselectively. We imagined that the reaction of **1** with α,ω-dibromoalkane might give fused purines in one-pot by conducting the reaction initially below 90° to give 8-amino-7-(ω-haloalkyl)purines **2** as intermediates and later elevating the reaction temperature for cyclization between the 8-amino group and the 7-haloalkyl group. As shown in Scheme 1 reaction of **1** with α,ω-dibromoalkanes was carried out in dimethylformamide in the presence of two molar equivalents of sodium hydride at room temperature. Then the reaction temperature was elevated to 90-120° and the reaction was continued for 2 hours to give fused purines **3a** (87%), **3b** (93%), **3c** (88%) and **3f** (63%). However, yields of eight membered ring fused compound **3d** (28%) and nine membered ring fused compound **3e** (14%) were poor. With regard to compound **3f** another possible structure could be possible. Thus, **3f** was methylated with dimethyl sulfate to give 6,7,8,9-tetrahydro-1,3,8,9-tetramethylpyrimido[1,2-*f*]purine-2,4(1*H*,3*H*)-dione **4**, whose C-methyl group in the ^{1}H-nmr spectrum was shifted to higher field than that of **3f** due to steric constriction. Moreover, the nuclear Overhauser effect (NOE) difference spectrum of **4** confirmed its structure (Scheme 2).

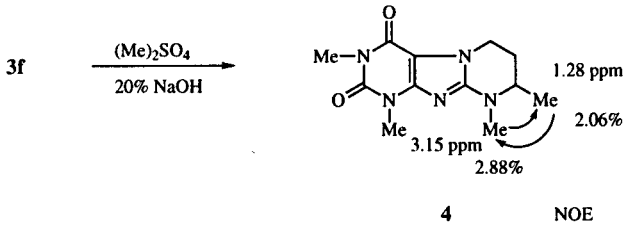
Reaction of **3c-e** with chloroacetyl chloride followed by treatment with 50% dimethylamine gave 10-(*N,N*-dimethylglycyl)-1,3-dimethyl-6,7,8,9-tetrahydro-10*H*-[1,3]diazepino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6a**) (86%), 11-(*N,N*-dimethylglycyl)-1,3-dimethyl-6,7,8,9,10,11-hexahydro-[1,3]diazocino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6b**) (99%) and 12-(*N,N*-dimethylglycyl)-1,3-dimethyl-6,7,8,9,10,11-hexahydro-12*H*-[1,3]diazonino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6c**) (69%) (Scheme 3).

As for the synthesis of lactam ring fused purines, Kamath *et al.* [4] synthesized 1,3-dimethyl-1,2,3,4,6,7,-8,9-octahydropyrimido[2,1-*f*]purine-2,4,8-trione (**7b**) *via*

Scheme 1

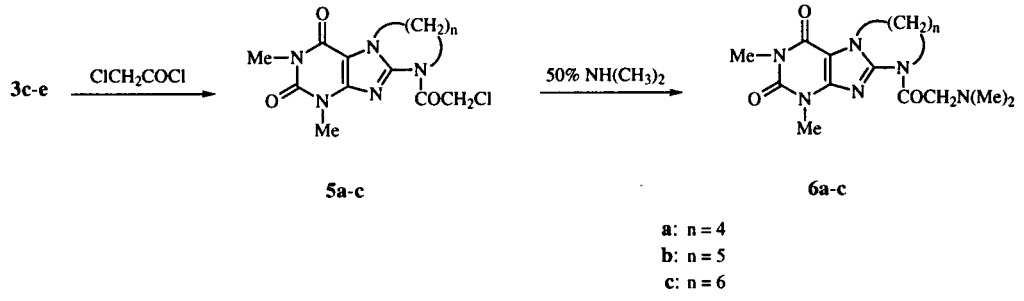


Scheme 2

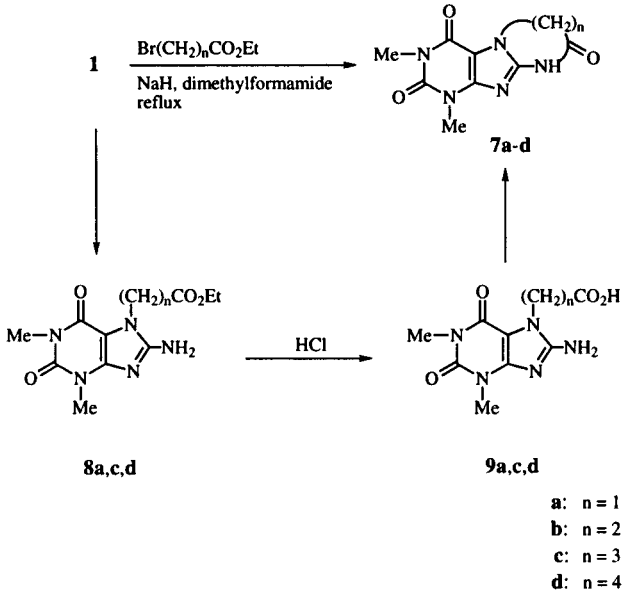


reaction of **1** with ethyl bromoacetate (n = 1), ethyl 4-bromo-*n*-butyrate (n = 3) or 5-bromovaleric acid ethyl ester (n = 4) did not afford the expected tricycles **7a,c,d**, but provided intermediates **8a,c,d**. Thus, compounds **8a,c,d** were hydrolyzed to give the corresponding carboxylic acids **9a,c,d**, which were cyclized by using diphenylphosphoryl azide [5]. The total yields of **7a,c,d** from **1** were **7a** (77%), **7c** (46%) and **7d** (19%) (Scheme 4).

Scheme 3



Scheme 4



five steps from 8-bromotheophylline. We examined the facile synthesis of lactam ring fused purines from **1**. An attempted one-pot reaction of **1** with ethyl bromopropionate successfully gave **7b** in 88% yield. However, the

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IR-180 spectra photometer. Mass spectra were measured with a JEOL JMS-DX 300 mass spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL GSX-400 spectrometer using tetramethylsilane as internal standard. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet.

General Procedure for the Reaction of 8-Aminotheophylline (**1**) with α,ω-Dibromoalkanes. Synthesis of **3a-f**.

8-Aminotheophylline (**1**) (195 mg, 1.0 mmole) was added to *N,N*-dimethylformamide (20 ml) and the mixture was heated to reflux until **1** was dissolved. Sodium hydride (2.0 mmoles) was added, followed by the addition of α,ω-dibromoalkane (1.0 mmole). After being stirred under reflux for 4 hours, the reaction mixture was concentrated *in vacuo* and poured into water. The mixture was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. The solvent was distilled and the residue was purified by column chromatography on silica gel eluting with a mixture of chloroform-methanol (20:1).

1,3-Dimethyl-6,7-dihydro-8*H*-imidazo[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**3a**).

This compound was obtained in 87% yield as colorless prisms, mp 271-272° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.39 (3H, s, N-CH_3), 3.51 (3H, s, N-CH_3), 4.06-4.12 (2H, m, CH_2CH_2), 4.30-4.75 (2H, m, CH_2CH_2), 4.52 (1H, br s,

NH); ir (potassium bromide); ν max 3205 cm^{-1} (NH), 1710 cm^{-1} (C=O); ms: m/z 221 (M^+).

Anal. Calcd. for $C_9H_{11}N_5O_2$: C, 48.87; H, 5.01; N, 31.66. Found: C, 48.61; H, 5.04; N, 31.59.

1,3-Dimethyl-6,7,8,9-tetrahydropyrimido[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**3b**).

This compound was obtained in 93% yield as colorless prisms, mp >300° (from 2-methoxyethanol); ^1H nmr (deuteriochloroform): δ 2.15 (2H, m, $CH_2CH_2CH_2$), 3.37 (3H, s, N-CH_3), 3.48 (3H, s, N-CH_3), 4.41-4.50 (2H, m, $CH_2CH_2CH_2$), 4.27 (2H, m, $CH_2CH_2CH_2$), 5.09 (1H, br s, NH); ir (potassium bromide): ν max 3210 cm^{-1} (NH), 1725 cm^{-1} (C=O); ms: m/z 235 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 50.62; H, 5.63; N, 29.56.

1,3-Dimethyl-6,7,8,9-tetrahydro-10*H*-[1,3]diazepino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**3c**).

This compound was obtained in 88% yield as colorless prisms, mp 240-241° (from ethanol); ^1H nmr (deuteriochloroform): δ 1.90 (4H, m, $CH_2(CH_2)_2CH_2$), 3.19 (2H, m, $CH_2(CH_2)_2CH_2$), 3.38 (3H, s, N-CH_3), 3.49 (3H, s, N-CH_3), 4.15-4.57 (2H, m, $CH_2(CH_2)_2CH_2$), 5.01 (1H, br s, NH); ir (potassium bromide): ν max 3240 cm^{-1} (NH), 1700 cm^{-1} (C=O); ms: m/z 249 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.87; H, 6.00; N, 28.01.

1,3-Dimethyl-6,7,8,9,10,11-hexahydro[1,3]diazocino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**3d**).

This compound was obtained in 28% yield as colorless prisms, mp 214-216° (from ethanol); ^1H nmr (deuteriochloroform): δ 2.08 (6H, m, $CH_2(CH_2)_3CH_2$), 3.39 (3H, s, N-CH_3), 3.44 (3H, s, N-CH_3), 3.46-3.62 (2H, m, $CH_2(CH_2)_3CH_2$), 4.62 (2H, m, $CH_2(CH_2)_3CH_2$), 4.90 (1H, s, NH); ir (potassium bromide): ν max 3260 cm^{-1} (NH), 1690 cm^{-1} (C=O); ms: m/z 263 (M^+).

Anal. Calcd. for $C_{12}H_{17}N_5O_2$: C, 54.75; H, 6.49; N, 26.62. Found: C, 54.57; H, 6.90; N, 26.43.

1,3-Dimethyl-6,7,8,9,10,11-hexahydro-12*H*-[1,3]diazonino[1,2-*f*]-purine-2,4(1*H*,3*H*)-dione (**3e**).

This compound was obtained in 14% yield as colorless prisms, mp 227-228° (from ethanol); ^1H nmr (deuteriochloroform): δ 1.62 (8H, m, $CH_2(CH_2)_4CH_2$), 3.39 (3H, s, N-CH_3), 3.46 (3H, s, N-CH_3), 3.47-3.62 (2H, m, $CH_2(CH_2)_4CH_2$), 4.62 (2H, m, $CH_2(CH_2)_4CH_2$), 4.78 (1H, br s, NH); ir (potassium bromide): ν max 3300 cm^{-1} (NH), 1685 cm^{-1} (C=O); ms: m/z 277 (M^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_2$: C, 56.30; H, 6.91; 25.27. Found: C, 56.58; H, 7.05; N, 25.61.

6,7,8,9-Tetrahydro-1,3,8-trimethylpyrimido[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**3f**).

This compound was obtained in 63% yield as colorless prisms, mp >300° (from methanol); ^1H nmr (deuteriochloroform): δ 1.33 (3H, d, J = 6.2 Hz, $CHCH_3$), 1.81-2.20 (2H, m, CH_2CH_2CH), 3.37 (3H, s, NCH_3), 3.48 (3H, s, NCH_3), 3.63-3.74 (1H, m, CH_2CH_2CH), 4.03 (2H, m, CH_2CH_2CH), 6.88 (1H, br s, NH); ir (potassium bromide): ν max 3400 cm^{-1} (NH), 1690 cm^{-1} (C=O); ms: m/z 249 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.01; H, 6.02; N, 28.11. Found: C, 53.15; H, 5.92; N, 27.97.

6,7,8,9-Tetrahydro-1,3,8,9-tetramethylpyrimido[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**4**).

A solution of **3f** (249 mg, 1 mmole) in dimethyl sulfate (1 ml) was heated to 140°. After being stirred for one hour, the solution was cooled to 0°. Sodium hydroxide aqueous solution (20%, 10 ml) was added to the above solution and the mixture was stirred for one hour. The usual workup was carried out to give colorless prisms (33 mg, 13%), mp 274-276° (from methanol); ^1H nmr (deuteriochloroform): δ 1.28 (3H, d, J = 6.6 Hz, $CHCH_3$), 1.93-2.23 (2H, m, CH_2CH_2CH), 3.15 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 3.52 (3H, s, NCH_3), 3.53 (1H, m, CH_2CH_2CH), 4.08-4.38 (2H, m, CH_2CH_2CH); ir (potassium bromide): ν max 3400 cm^{-1} (NH); ms: m/z 263 (M^+).

Anal. Calcd. for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.95; H, 6.88; N, 26.94.

10-Chloroacetyl-1,3-dimethyl-6,7,8,9-tetrahydro-10*H*-[1,3]-diazepino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**5a**).

A mixture of **3c** (249 mg) and chloroacetyl chloride (2.5 ml) was refluxed for one hour to obtain a clear solution. The excess chlroacetyl chloride was distilled. The residue was washed with water and neutralized with 5% sodium bicarbonate solution and was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. Evaporation of chloroform gave crystalline powder in 94% yield, mp 198-199°; ^1H nmr (deuteriochloroform): δ 1.94 (4H, m, $CH_2(CH_2)_2CH_2$), 3.42 (3H, s, NCH_3), 3.55 (3H, s, NCH_3), 3.80 (2H, m, $CH_2(CH_2)_2CH_2$), 4.33 (2H, s, $COCH_2Cl$), 4.58 (2H, m, $CH_2(CH_2)_2CH_2$); ir (potassium bromide): ν max 1700 cm^{-1} (C=O); ms: m/z 325 (M^+).

11-Chloroacetyl-1,3-dimethyl-6,7,8,9,10,11-hexahydro-[1,3]diazocino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**5b**).

The reaction of **3d** (263 mg) with chloroacetyl chloride (2.5 ml) was carried out by the same procedure as that described for **5a**. The title compound was obtained in 80% yield, mp 209-211°; ^1H nmr (deuteriochloroform): δ 1.60-1.94 (6H, m, $CH_2(CH_2)_3CH_2$), 3.43 (3H, s, N-CH_3), 3.56 (3H, s, N-CH_3), 3.88 (2H, m, $CH_2(CH_2)_3CH_2$), 3.97 (2H, s, $COCH_2Cl$), 4.40 (2H, t, J = 5.6 Hz, $CH_2(CH_2)_3CH_2$); ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ms: m/z 339 (M^+).

12-Chloroacetyl-1,3-dimethyl-6,7,8,9,10,11-hexahydro-12*H*-[1,3]diazonino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**5c**).

The reaction of **3c** (277 mg) with chloroacetyl chloride (3.0 ml) was caried out by the same procedure as that described for **5a**. The title compound was obtained in 70% yield, mp 198-199°; ^1H nmr (deuteriochloroform): δ 1.52-1.60 (4H, m, $CH_2CH_2(CH_2)_2CH_2CH_2$), 1.87-1.96 (4H, m, $CH_2CH_2(CH_2)_2CH_2CH_2$), 3.43 (3H, s, N-CH_3), 3.56 (3H, s, N-CH_3), 3.80 (2H, m, $CH_2(CH_2)_4CH_2$), 3.85 (2H, s, $COCH_2Cl$), 4.44 (2H, t, J = 5.9 Hz, $CH_2(CH_2)_4CH_2$); ir (potassium bromide): ν max 1700 cm^{-1} (C=O); ms: m/z 353 (M^+).

10-(*N*,*N*-Dimethylglycyl)-1,3-dimethyl-6,7,8,9-tetrahydro-10*H*-[1,3]diazepino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6a**).

A mixture of **5a** (325 mg), 50% dimethylamine aqueous solution (3 ml), and benzene (10 ml) was refluxed for one hour until clear solution was obtained. The solvent was distilled and water was added to the residue, which was extracted with chloroform.

The extract was dried and the solvent was distilled. The residue was recrystallized from ethanol, yield 86%, mp 196-197°; ^{1}H nmr (deuteriochloroform): δ 1.83-1.84 (4H, m, $CH_2(CH_2)_2CH_2$), 2.07 (6H, s, $COCH_2N(CH_3)_2$), 3.29 (2H, s, $COCH_2N$), 3.42 (3H, s, NCH_3), 3.56 (3H, s, NCH_3), 3.77 (2H, m, $CH_2(CH_2)_2CH_2$), 4.47 (2H, m, $CH_2(CH_2)_2CH_2$); ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ms: m/z 334 (M$^+$).

Anal. Calcd. for $C_{15}H_{22}N_6O_3$: C, 53.89; H, 6.63; N, 25.15. Found: C, 53.86; H, 6.85; N, 25.15.

11-(*N,N*-Dimethylglycyl)-1,3-dimethyl-6,7,8,9,10,11-hexahydro[1,3]diazocino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6b**).

The reaction of **5b** (339 mg) with a 50% aqueous solution of dimethylamine (3 ml) in benzene (10 ml) was carried out by the same procedure as that described for the synthesis of **6a**. The title compound **6b** was obtained in 79% yield, mp 144-145°; ^{1}H nmr (deuteriochloroform): δ 1.52-1.57 (4H, m, CH_2CH_2-$CH_2CH_2CH_2$), 1.88 (2H, m, $CH_2CH_2CH_2CH_2CH_2$), 2.20 (6H, s, $N(CH_3)_2$), 3.43 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 3.74 (2H, $CH_2CH_2CH_2CH_2CH_2$), 4.40 (2H, m, $CH_2CH_2CH_2CH_2CH_2$); ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ms: m/z 348 (M$^+$).

Anal. Calcd. for $C_{16}H_{24}N_6O_3$: C, 55.17; H, 6.94; N, 24.14. Found: C, 54.93; H, 6.91, N, 24.10.

12-(*N,N*-Dimethylglycyl)-1,3-dimethyl-6,7,8,9,10,11-hexahydro-12*H*-[1,3]diazonino[1,2-*f*]purine-2,4(1*H*,3*H*)-dione (**6c**).

The reaction of **5c** (353 mg) with a 50% aqueous solution of dimethylamine (3 ml) in benzene (10 ml) was carried out by the same procedure as that described for the synthesis of **6a**. The title compound **6c** was obtained in 69% yield, mp 142-143°; ^{1}H nmr (deuteriochloroform): δ 1.56-1.75 (8H, m, $CH_2(CH_2)_4$-CH_2), 2.17 (6H, s, $N(CH_3)_2$), 3.43 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 3.60 (2H, m, $CH_2(CH_2)_4CH_2$), 4.34 (2H, m, CH_2-$(CH_2)_4CH_2$); ir (potassium bromide): ν max 1700 cm^{-1} (C=O); ms: m/z 362 (M$^+$).

Anal. Calcd. for $C_{17}H_{26}N_6O_3$: C, 56.33; H, 7.23; N, 23.19. Found: C, 56.35; H, 7.17; N, 23.12.

1,3-Dimethyl-1,2,3,4,6,7-hexahydro-8*H*-pyrimido[2,1-*f*]purine-2,4,7-trione (**7a**).

To a solution of **9a** (26.7 mg, 0.1 mmole) in dried *N,N*-dimethylformamide (4 ml) was added triethylamine (0.25 mmole). The above mixture was cooled to 0° and diphenylphosphorylazide (0.11 mmole) was added. The mixture was stirred at room temperature for 12 hours. The mixture was concentrated *in vacuo* and water was added. The mixture was extracted with chloroform and the solvent was distilled. The residue was purified by silica gel column chromatography. The title compound **7a** was obtained in 91% yield, mp >300° (from 2-methoxyethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.40 (3H, s, NCH_3), 3.56 (3H, s, NCH_3), 4.65 (2H, s, CH_2CO), 11.88 (1H, br s, NH); ir (potassium bromide): ν max 3400 cm^{-1} (NH), 1710 cm^{-1} (C=O); ms: m/z 235 (M$^+$).

Anal. Calcd. for $C_9H_9N_5O_3$: C, 45.96; H, 3.83; N, 29.79. Found: C, 45.75; H, 3.97; N, 29.81.

1,3-Dimethyl-1,2,3,4,6,7,8,9-octahydropyrimido[2,1-*f*]-purine-2,4,8-trione (**7b**).

8-Aminotheophylline (1.95 g, 0.1 mole) was added to dried *N,N*-dimethylformamide (600 ml) and heated to reflux until 8-aminotheophylline was dissolved. Sodium hydride (60% mineral oil dispersion, 4.40 g, 0.11 mole) was added and stirred for a period of time. Ethyl 3-bromopropionate (1.81 g, 0.1 mole) was added and stirring and refluxing were continued for 4 hours. The reaction mixture was concentrated *in vacuo* and extracted with chloroform. The extract was washed with water and dried over anhydrous magnesium sulfate. Chloroform was distilled off and the residue was recrystallized from 2-methoxyethanol to give colorless needles, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.84 (2H, J = 7.2 Hz, CH_2CH_2CO), 3.20 (3H, s, N-CH_3), 3.38 (3H, s, N-CH_3), 4.31 (2H, t, J = 7.2 Hz, CH_2CH_2CO), 8.48 (1H, br s, NH); ir (potassium bromide): ν max 3420 cm^{-1} (NH), 1690 cm^{-1} (C=O); ms: m/z 249 (M$^+$).

Anal. Calcd. for $C_{10}H_{11}N_5O_3$: C, 48.20; H, 4.42; N, 28.11. Found: C, 48.04; H, 4.63; N, 27.82.

1,3-Dimethyl-1,2,3,4,6,7,8,9-octahydro-10*H*-[1,3]diazepino[2,1-*f*]-purine-2,4,9-trione (**7c**).

A mixture of compound **9b** (28.1 mg, 0.1 mmole) in dry *N,N*-dimethylformamide (4 ml), triethylamine (0.25 mmole) and diphenylphosphoryl azide (0.11 mmole) was carried out by the same procedure as described in the synthesis of **7a**. The title compound **7c** was obtained in 82% yield, mp >300° (from 2-methoxyethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.37 (2H, m, $CH_2CH_2CH_2$-CO), 2.79 (2H, t, J = 6.9 Hz, $CH_2CH_2CH_2CO$), 3.40 (3H, s, N-CH_3), 3.53 (3H, s, N-CH_3), 4.57 (2H, t, J = 6.6 Hz, $CH_2CH_2CH_2CO$), 8.32 (1H, br s, NH); ir (potassium bromide): ν max 3430 cm^{-1} (NH), 1650 cm^{-1} (C=O); ms: m/z 263 (M$^+$).

Anal. Calcd. for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.94; N, 26.61. Found: C, 49.95; H, 5.13; N, 26.39.

1,3-Dimethyl-6,7,8,9-tetrahydro[1,3]diazocino[2,1-*f*]purine-2,4,10(1*H*,3*H*,11*H*)-trione (**7d**).

The mixture of the compound **9c** (29.5 mg, 0.1 mmole) in dried *N,N*-dimethylformamide (4 ml), triethylamine (0.25 mmole) and diphenylphosphoryl azide (0.11 mmole) was carried out by the same procedure as described for the synthesis of **7a**. The title compound **7d** was obtained in 55% yield, mp 229-231°; ms: m/z 277 (M$^+$).

Ethyl 2-(8-Aminotheophylline-7-yl)acetate (**8a**).

The reaction of **1** (195 mg, 1.0 mmole) with ethyl bromoacetate (167 mg, 1.0 mmole) was carried out by the same procedure as described for the synthesis of **7b**. The title compound **8a** was obtained in 89% yield, mp 269-270° (from ethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.34 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.38 (3H, s, NCH_3), 3.56 (3H, s, NCH_3), 4.29 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.16 (2H, s, CH_2CO), 9.08 (2H, br s, NH_2); ir (potassium bromide): ν max 3400 cm-^{1} (NH), 1700 cm^{-1} (C=O); ms: m/z 281 (M$^+$).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.34; N, 24.91. Found: C, 46.76; H, 5.41; N, 24.76.

Ethyl 4-(8-Aminotheophylline-7-yl)butyrate (**8c**).

The reaction of **1** (195 mg, 1.0 mmole) with ethyl 4-bromobutyrate (195 mg, 1.0 mmole) was carried out by the same procedure as for the synthesis of **7b**. The title compound **8c** was obtained in *58%* yield, mp 183-184° (from ethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.42 (3H, t, J = 7.2 Hz, CH_2CH_3), 2.24 (2H, m, $CH_2CH_2CH_2$), 2.52 (2H, m, $CH_2CH_2CH_2$), 3.50

(3H, s, NCH_3), 3.63 (3H, s, NCH_3), 4.27 (2H, m, $CH_2CH_2CH_2$), 4.31 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.41 (2H, br s, NH_2); ir (potassium bromide): ν max 3400 cm^{-1} (NH), 1690 cm^{-1} (C=O); ms m/z 309 (M^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_4$: C, 50.49; H, 6.15; N, 22.65. Found: C, 50.31; H, 6.02; N, 22.37.

Ethyl 5-(8-Aminotheophyllin-7-yl)valerate (**8d**).

The reaction of **1** (195 mg, 1.0 mmole) with ethyl 5-bromovalerate (209 mg, 1.0 mmole) was carried out by the same procedure as described for the synthesis of **7b**. The title compound **8d** was obtained in 54% yield, mp 139-141° (from ethanol); ^1H nmr (deuteriochloroform): δ 1.26 (3H, t, J = 7.1 Hz, $-OCH_2CH_3$), 1.70 (2H, m, $NCH_2CH_2CH_2CH_2CO$-), 1.85 (2H, m, $-NCH_2CH_2CH_2CH_2CO$-), 2.40 (2H, t, J = 7.1 Hz, $-NCH_2CH_2CH_2CH_2CO$-), 3.38 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 4.08-4.16 (4H, m, $-OCH_2CH_3$ and $-NCH_2CH_2CH_2CH_2CO$-), 4.90 (2H, s, NH_2).

2-(8-Aminotheophyllin-7-yl)acetic Acid (**9a**).

A mixture of **8a** (28 mg, 0.1 mmole) and concentrated hydrochloric acid (3 ml) was refluxed for one hour. The mixture was concentrated *in vacuo* and dissolved in 10% sodium hydroxide solution. The solution was neutralized with 5% dilute hydrochloric acid to give colorless prisms in 95% yield, which was used for the following step without futher purification, mp 284-286°; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.23 (3H, s, NCH_3), 3.41 (3H, s, NCH_3), 4.85 (2H, s, CH_2CO), 6.80 (2H, br s, NH_2), 8.06 (1H, s, COOH); ir (potassium bromide): ν 3380 cm^{-1} (NH), 1680 cm^{-1} (C=O); ms: m/z 253 (M^+).

4-(8-Aminotheophyllin-7-yl)-*n*-butyric Acid (**9c**).

A mixture of **8c** (31 mg, 0.1 mmole) in 3 ml of concentrated hydrochloric acid was carried out by the same procedure as described for the synthesis of **9a**. The title compound **9c** was obtained in 97% yield, mp 274-275°; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.86 (2H, m, $CH_2CH_2CH_2CO$), 2.18 (2H, t, J = 5.4 Hz, $CH_2CH_2CH_2CO$), 3.17 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 4.20 (2H, t, J = 4.7 Hz, $CH_2CH_2CH_2CO$), 6.93 (2H, br s, NH_2), 8.31 (1H, s, COOH); ir (potassium bromide): ν 3390 cm^{-1} (NH), 1700 cm^{-1} (C=O); ms: m/z 281 (M^+).

5-(8-Aminotheophylline-7-yl)valeric Acid (**9d**).

A mixture of **8d** (32 mg, 0.1 mmole) in 3 ml of concentrated hydrochloric acid was carried out by the same procedure as described for the synthesis of **9a**. The title compound **9d** was obtained in 64% yield, mp 223-235°; ms: m/z 295 (M^+).

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