Condensed-Purines Syntheses of Tetrahydro-1,4-diazepino[1,2,3-*gh*]purin-2-one and Hexahydro-1,4-diazocino[1,2,3-*gh*]purin-2-one

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1,4-Pyrimido- (2a), 1,4-diazepino- (2b), and 1,4-diazocino[1,2,3-*gh*]purine (2c) were designed as selective cAMP-phosphodiesterase 4 (PDE 4) inhibitors. The desired condensed-purines (2b,c) were synthesized by reaction of 7-aminoalkyl-3-propylpurine-2,4-diones (6b,c) with hexamethyldisilazane by intramolecular cyclization *via* silylation–amination.

Key words 1,4-diazepino[1,2,3-*gh*]purine; 1,4-diazocino[1,2,3-*gh*]purine; condensed-purine; silylation–amination; intramolecular cyclization

Inhibitors of cAMP-phosphodiesterase 4 (PDE 4) exhibit a range of anti-inflammatory/immunosuppressive activities which suggest potential in a wide range of inflammatory and autoimmune diseases.[1)] Most interest to date has centered on clinical evaluation in asthmatic patients.

On the basis of our studies on the structure–activity relationships of alkylxanthine for PDE 4 isoenzyme inhibitors,[2)] we proposed that the interaction between the alkyl group at the 1-position and the oxo group at the 2- or 6-position of the xanthine skeleton was important for these activities, and we discovered the heterocycle[*i*]-condensed purine, 3,4-dipropyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*i*]purin-5-one (**1**) which showed selective PDE 4-inhibitory activity and lacked some of the adverse reactions of xanthine derivatives.[3)] We thought that both the heterocycle-ring fused onto the purine ring and the conversion from a xanthine to a isoguanine skeleton might be important to elicit these activities. On the other hand, in our previous report,[2)] alkyl substitution at the 7-position of the xanthine skeleton increased PDE 1-inhibitory activity and decreased PDE 3-inhibitory activity, without changing the PDE 4-inhibitory activity. In this study, we then designed the novel heterocycle[*g*, *h*]condensed-purines, 1,4-pyrimido- (**2a**) 1,4-diazepino- (**2b**), and 1,4-diazocino[1,2,3-*gh*]condensed-purine (**2c**). In present paper we describe the synthesis of these condensed-purines **2**.

We planned at first the synthesis of [*g*,*h*]condensed-purines **2** by intramolecular cyclization of 7-aminoalkyl-3-propylpurine-2,4-dione (**6**) with phosphorus oxychloride, according to the method of Glushkov.[4)] Treatment of enprofylline (**3**)[5)] with the respective (*N*-benzyloxycarbonyl)-aminoalkyl methanesulfonate (**4**) in the presence of potassium carbonate gave the corresponding [7-(*N*-benzyloxycarbonyl)aminoalkyl]-3-propylpurine-2,4-diones (**5a**, **b**, **c**) in 68—86% yields. Removal of the benzyloxycarbonyl group of **5a**, **b**, **c** by catalytic hydrogenation with 20% palladium hydroxide on carbon gave 7-aminoalkyl-3-propylpurine-2,4-diones (**6a**, **b**, **c**). Although Glushkov obtained [*g*,*h*]condensed-purines (**9a**, **b**) from the reaction of 7-(dialkylaminoalkyl)-3-methylpurine-2,4-diones (**8a**, **b**) with phosphorus oxychloride, we could not obtain the desired condensed-purines **2** from **6** under the same conditions because the intermediate (**7**) degraded during the chlorination–amination

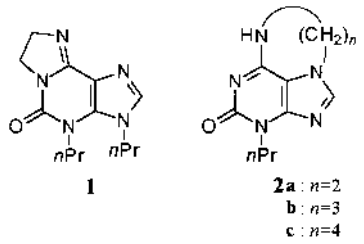

Chart 1

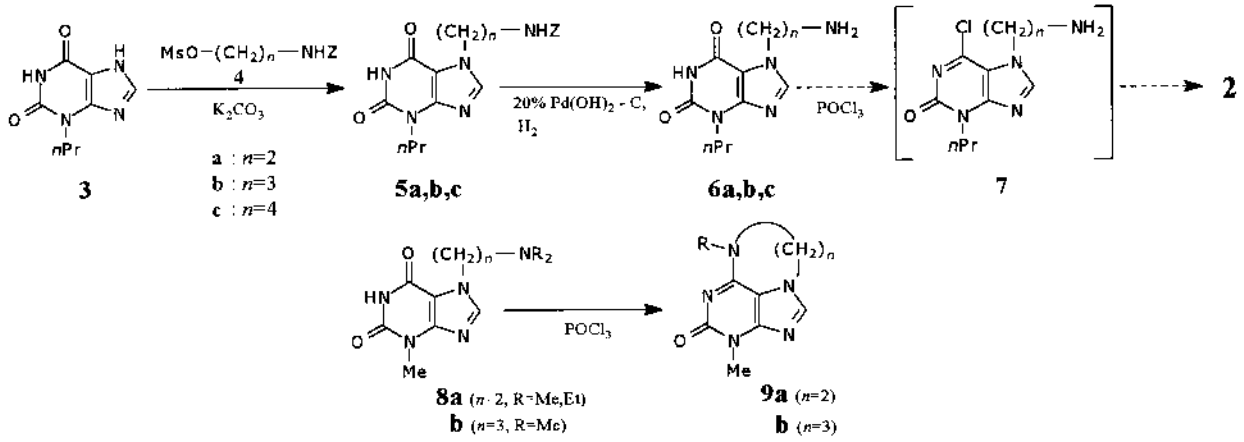

Chart 2

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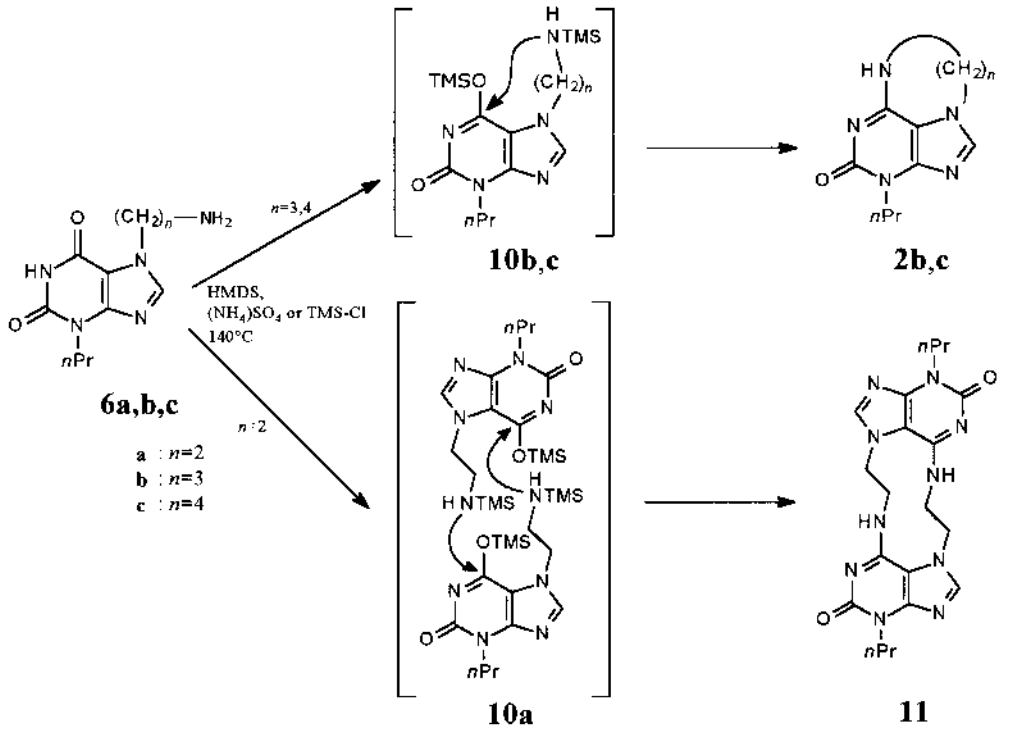

Chart 3

reaction (Chart 2).

Vorbrüggen reported that silylation–amination of inosine with hexamethyldisilazane (HMDS) and amine in the presence of a catalyst gave the corresponding adenosines in high yields.[6] However, intramolecular cyclization *via* silylation–amination with HMDS has not been reported previously. Therefore, intramolecular cyclization *via* silylation–amination was examined as a means of synthesizing **2**. Compound **6** was treated with HMDS in the presence of ammonium sulfate or trimethylchlorosilane as catalyst in pyridine at 140 °C. As a result, the desired condensed-purine **2b**, **c** ($n=3,4$) were obtained from **6b**, **c** in 46% and 70% yields, respectively. This reaction involves silylation of the oxo group at the 6-position and amino group, followed by replacement reaction between trimethylsilanol and the amino group in one-pot. However, the same reaction of **6a** ($n=2$) led to **11** *via* dimerization of the intermediate **10a** because the alkyl chain of **10a** might be too short to allow the intramolecular cyclization. The structures of **2b**, **c** and **11** were assigned on the basis of ^{1}H-NMR and mass spectral data. For example, the ^{1}H-NMR spectrum of **2b** showed signals at 0.90, 1.81 and 4.07 ppm assignable to the propyl group, and at 2.30, 3.94 and 4.31 ppm assignable to the methylene group of the 1,4-diazepine ring, and at 7.64 and 10.57 ppm indicating aromatic and NH protons, respectively. The mass spectra (MS) of **2b**, **c** showed peaks at *m/z* 233 (M^+) and 247 (M^+), respectively, however that of **11** showed a peak at *m/z* 438 (M^+) (Chart 3).

In conclusion, the first syntheses of heterocycle[*g*,*h*]condensed-purines **2b** and **2c** have been first achieved by intramolecular cyclization of **6b**, **c** using HMDS in the presence of ammonium sulfate or trimethylchlorosilane as a catalyst. Although the PDE 4-inhibitory activity of **2b** and **2c** were evaluated, along with **1** and XT-44[2] *in vitro*, according to the published methods,[3] **2b** and **2c** showed no inhibitory activity against PDE 1, PDE 3 or PDE 4 (Table 1). However, these results indicate that introduction of a heterocycle-ring to the [*i*]-position of purine is important to elicit PDE 4-inhibitory activity, although [*g*,*h*]-condensation removes the inhibitory activities against PDE 1 and PDE 3 isoenzymes.

Table 1. PDE Inhibitory Activities of **2b** and **2c**

Compd. No	IC_{50} (μM)		
	PDE 1	PDE 3	PDE 4
2b	>100	>100	>100
2c	>100	>100	>100
1	—	>100	3.00
XT-44	—	>100	3.47

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Hitachi 270-30 spectrometer and MS were measured with a JEOL-DX300 instrument. ^{1}H-NMR was recorded on a JEOL-EX90A spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz (Hz). Micro analyses were performed in the Micro analytical Laboratory of this faculty by Mrs. T. Kuroda. Yields and physicochemical data of the [7-(*N*-benzyloxycarbonyl)aminoalkyl]-3-propyl-purine-2,4-dione (**5**), 7-aminoalkyl-3-propylpurine-2,4-dione (**6**) and the condensed-purines (**2b**, **c**) are summarized in Tables 2, 3, 4 and 5, respectively.

***N*-Benzyloxycarbonylaminoalkyl Methanesulfonate (4)** General Procedure: To a solution of *N*-benzyloxycarbonylaminoalkanol[7] (0.01 mol) in CH_2Cl_2 (30 ml) was added triethylamine (0.012 mol) and methanesulfonyl chloride (0.012 mol) with stirring at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, water was added, and the mixture was extracted with AcOEt. The extracts were washed with brine, dried, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography using hexane–AcOEt (3 : 1) as an eluent to give **4**.

Table 2. Physical Properties for Compounds **5** and **6**

Compd. No.	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
					C	H	N
5a	86	203—204	MeOH	$C_{18}H_{21}N_5O_4$	58.21 (58.26)	5.70 (5.95)	18.86 (18.59)
5b	68	195—196	MeOH	$C_{19}H_{23}N_5O_4$	59.21 (59.19)	6.01 (5.95)	18.17 (18.01)
5c	70	135—136	MeOH	$C_{20}H_{25}N_5O_4$	60.14 (60.41)	6.31 (6.31)	17.53 (17.30)
6a	83	174—175	MeOH–AcOEt	$C_{10}H_{15}N_5O_2$	50.61 (50.40)	6.40 (6.15)	29.51 (29.29)
6b	95	129—130	MeOH–AcOEt	$C_{11}H_{17}N_5O_2$	52.58 (52.83)	6.82 (6.55)	27.89 (27.68)
6c	99	130—131	MeOH–AcOEt	$C_{12}H_{19}N_5O_2$	54.32 (54.22)	7.22 (7.02)	26.40 (26.23)

Table 3. Spectral Data for Compound **5** and **6**

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR
5a[a)]	3352, 1714, 1684	0.86 (3H, t, J=7.2 Hz), 1.65 (2H, sext., J=7.2 Hz), 3.40—3.52 (2H, m), 3.87 (2H, t, J=7.2 Hz), 4.26 (2H, t, J=5.5 Hz), 4.96 (2H, s), 7.31 (5H, s), 7.88 (1H, s), 11.10 (1H, br s)
5b[b)]	3408, 1694	0.98 (3H, t, J=7.2 Hz), 1.71 (2H, sext., J=7.2 Hz), 2.05 (2H, quint., J=6.2 Hz), 3.19 (2H, t, J=6.2 Hz), 4.02 (2H, t, J=7.2 Hz), 4.31 (2H, t, J=6.2Hz), 5.12 (2H, s), 7.35 (5H, s), 7.64 (1H, s), 7.89 (1H, br s)
5c[b)]	3348, 1714, 1688	0.98 (3H, t, J=7.3 Hz), 1.55—2.01 (6H, m), 3.22 (2H, t, J=6.2 Hz), 4.03 (2H, t, J=7.3 Hz), 4.25 (2H, t, J=6.2 Hz) 5.09 (2H, s), 7.33 (5H, s), 7.57 (1H, s), 8.76 (1H, br s)
6a[a)]	3356, 1694	0.87 (3H, t, J=7.3 Hz), 1.66 (2H, sext., J=7.3 Hz), 2.89 (2H, t, J=6.0 Hz), 3.44 (2H, br s), 3.87 (2H, t, J=7.3 Hz), 4.16 (2H, t, J=6.0 Hz), 7.97 (1H, s)
6b[c)]	3360, 1700	0.95 (3H, t, J=7.4 Hz), 1.76 (2H, sext., J=7.4 Hz), 2.05, (2H, quint., J=7.0 Hz), 3.99 (2H, t, J=7.4 Hz), 4.38 (2H, J=7.0Hz), 7.96 (1H, s)
6c[b)]	3464, 1698, 1620	0.97 (3H, t, J=7.3 Hz), 1.45—2.13 (6H, m), 2.82 (2H, t, J=6.7 Hz), 4.02 (2H, t, J=7.3 Hz), 4.28 (2H, t, J=6.7 Hz), 7.59 (1H, s), 8.53 (1H, br s)

NMR spectra were recorded in *a*) DMSO-d_6; *b*) $CDCl_3$ and *c*) CD_3OD.

Table 4. Physical Properties for [*g*,*h*]Condensed-Purines **2b**, **c** and **11**

Compd. No.	Catalyst	Yield (%)	mp (°C) (recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
2b	$(NH_4)_2SO_4$	70	282—283 (AcOEt–MeOH)	$C_{11}H_{15}N_5O$	56.63 (56.83)	6.48 (6.56)	30.02 (30.12)
2c	TMS-Cl	46	273—274 (AcOEt–MeOH)	$C_{12}H_{17}N_5O$	58.28 (58.19)	6.69 (6.73)	28.32 (28.23)
11	$(NH_4)_2SO_4$	34	>290 (MeOH–H_2O)	$C_{20}H_{26}N_{10}O_2$	54.78 (54.50)	5.98 (6.07)	31.94 (31.88)

Table 5. Spectral Data for [g,*h*]Condensed-Purines **2b**, **c** and **11**

Compd. No.	MS (*m/z*)	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
2b	233 (M^+)	3452, 1638	0.98 (3H, t, J=7.5 Hz), 1.81 (2H, sext., J=7.5 Hz), 2.30 (2H, quint., J=5.3 Hz), 3.94 (2H, t, J=5.3 Hz), 4.07 (2H, t, J=7.5 Hz), 4.31 (2H, t, J=5.3 Hz), 7.64 (1H, s), 10.57 (1H, br s)
2c[a)]	247 (M^+)	3456, 1698, 1620	0.97 (3H, t, J=7.4 Hz), 1.60—2.15 (6H, m), 3.74 (2H, t, J=5.6 Hz), 4.07 (2H, t, J=7.4 Hz), 4.28 (2H, t, J=5.6 Hz), 7.59 (1H, s), 9.82 (1H, br s)
11	438 (M^+)	3436, 1676, 1614	0.79 (6H, t, J=7.5 Hz), 1.54 (4H, sext., J=7.3 Hz), 3.76 (4H, t, J=7.5 Hz), 4.48—4.67 (4H, m), 8.31 (2H, s)

a) NMR spectrum was recorded in $CDCl_3$.

4a: Yield: 90%; HR-MS *m/z*: 273.0761 (Calcd for $C_{11}H_{15}NO_5S$: 273.0761). ^{1}H-NMR ($CDCl_3$) δ; 2.99 (3H, s), 3.57 (2H, t, J=5.2 Hz), 4.30 (2H, t, J=5.2 Hz), 4.72 (2H, s), 5.24 (1H, br s), 7.35 (5H, s). IR (KBr) cm^{-1}: 3408, 1718.

4b: Yield: 92%; HR-MS *m/z*: 287.0821 (Calcd for $C_{12}H_{17}NO_5S$: 287.0827). ^{1}H-NMR ($CDCl_3$) δ; 1.95 (2H, quint., J=6.0 Hz), 2.99 (3H, s), 3.13—3.36 (2H, m), 4.28 (2H, t, J=6.0 Hz), 5.10 (2H, s), 5.24 (1H, br s), 7.35 (5H, s). IR (KBr) cm^{-1}: 3424, 1712.

4c: Yield: 90%; HR-MS *m/z*: 301.0985 (Calcd for $C_{13}H_{19}NO_5S$: 301.0984). ^{1}H-NMR ($CDCl_3$) δ; 1.64—1.86 (4H, m), 3.00 (3H, s), 3.24 (2H, t, J=6.1 Hz), 4.24 (2H, t, J=6.1 Hz), 4.68 (1H, br s), 5.10 (1H, s), 7.35 (5H, s). IR (KBr) cm^{-1}: 3416, 1714.

[7-(*N*-Benzyloxycarbonyl)aminoalkyl]-3-propylpurine-2,4-dione (5) General Procedure: To a mixture of enprofylline **3** (15.5 mmol) and anhydrous K_2CO_3 (18.6 mmol) in dimethylformamide (DMF) (60 ml) was added (*N*-benzyloxycarbonyl)aminoalkyl methanesulfonate **4** (18.6 mmol) at 0 °C, the mixture was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (15 : 1) as an eluent to give **5**.

7-Aminoalkyl-3-propylpurine-2,4-dione (6) General Procedure: To a solution of **5** (8 mmol) in MeOH (200 ml) was added 20% palladium hydroxide on carbon (30 mg), and the mixture was shaken under hydrogen (3 atom) for 2 h. The catalyst was removed and the filtrate concentrated *in vacuo*, and the residue crystallized to yield **6**.

Formation of Condensed-Purine (2b, c) General Procedure: To a solution of **6** (2 mmol) and HMDS (1.29 g, 8 mmol) in pyridine (15 ml) was added $(NH_4)_2SO_4$ (50 mg) or trimethylchlorosilane (2 mmol) and the mixture was stirred at 140 °C for 24 h. After cooling and addition of MeOH (20 ml), the reaction mixture was stirred at room temperature for 15 min and concentrated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (4 : 1) as an eluent to give **2b**, **c**.

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