# Selective Inhibitors of Cyclic AMP-Specific Phosphodiesterase: Heterocycle-Condensed Purines

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*Received February 10, 1997*[⊗]

To reverse the adverse reactions of alkylxanthines and to develop novel inhibitors of cyclic AMP-specific phosphodiesterase (PDE IV), a series of heterocycle-condensed purines were designed and synthesized. Some of these new compounds had similar or more potent and selective inhibitory activity against PDE IV than known PDE IV inhibitors. The tracheal-relaxant activity of these compounds was closely correlated with their PDE IV-inhibitory activity. Moreover, these purine analogues did not have any positive-chronotropic action or adenosine-antagonistic action on isolated heart preparations, which are the particular adverse reactions of alkylxanthines. Among them, 3,4-dipropyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*i*]-purin-5-one (**1c**), which was the most selective and potent PDE IV inhibitor, did not cause emesis in *Suncus murinus* at a dosage range of 10−100 mg/kg (po), while an imidazole analogue of **1c** (**4c**) and known PDE IV inhibitors such as rolipram and denbufylline caused emesis even at 10 or 30 mg/kg.

## Introduction

The first-generation inhibitors of cyclic nucleotide phosphodiesterase (PDE), such as theophylline and papaverine, have many advantages for clinical use. PDEs have been classified into at least seven families, PDE I to PDE VII,[1] and selective inhibitors of each isoenzyme have been developed as second-generation drugs. Among them, PDE IV inhibitors are now divided into three major families, phenylpyrrolidone derivatives, xanthine derivatives, and pyridopyrimidinedione derivatives, and they have been expected to have potent and selective effects on brain diseases, asthma, and inflammatory diseases.[2−10] On the other hand, their central nervous system side effects, including emesis, limit their therapeutic potential.[4,11−13] The heart and central nervous system actions of xanthine PDE inhibitors may result from inhibition of other types of PDE than PDE IV and from adenosine antagonism.[14−16]

In our studies on the structure−activity relationships of a series of 1,3,7-trialkylxanthines, we indicated that while the 3-substitution increased both tracheal-relaxant action and positive-chronotropic action, substitutions at the 1- and 7-positions were important for bronchoselectivity.[15−17] Especially, elongation of the alkyl group from ethyl to propyl at the 1-position of the xanthine skeleton markedly increased the tracheal relaxant activity, accompanying PDE IV-inhibitory activity and adenosine $A_1$ antagonistic activity. Then, we think that the intramolecular interaction between the alkyl group at the 1-position and the carbonyl group at the 2- or 6-position of the purine skeleton may be important to elicit these activities. In this study, focusing upon the 1,6-intramolecular interaction, we designed and synthesized a series of heterocycle-condensed purines, after fixing the *n*-propyl group at the 3-position and converting the xanthine skeleton to the isoguanine skeleton, and examined their in vitro effects on PDE isoenzymes, tracheal muscle tone, and heart atrium and the emetic effect in *Suncus murinus* (house musk shrew).

## Chemistry

Purine analogues condensed with several heterocyclic rings fused to bond to *i* were synthesized as follows. Since it was assumed that the direct introduction of the propyl group into the condensed purine (**1b**−**5b**) would be difficult to confirm in these positions by spectral analysis, methods were adopted in the preparation of both isomers of *N*-propyl condensed purines **1a**−**5a** and **1c**−**5c** by the route outlined in Schemes 1 and 2.

Treatment of 6-chloro-3,7-dipropylpurin-2-one (**II**), obtained from 3,7-dipropylpurine-2,4-dione (**I**)[17] by chlorination with phosphorus oxychloride, with the aminoalkanols ($n$ = 2, 3) in the presence of triethylamine gave 6-[(hydroxyalkyl)amino]-3,7-dipropylpurin-2-one (**III**, $n$ = 2, 3) in 30−50% yield. Another 6-[(hydroxyalkyl)amino]-3-propylpurin-2-one (**VI**, $n$ = 2, 3, 4) was also prepared by the similar treatment of 3-propyl-6-(1,2,4-triazol-4-yl)purin-2-one (**V**), which was obtained by treatment of 6-amino-3-propylpurin-2-one (**IVb**)[18] with diformylhydrazine, trimethylsilyl chloride, and triethylamine, with the similar aminoalkanols ($n$ = 2, 3, 4) in moderate yield. The condensed purines (**1a, 2a**) were respectively obtained from **III** ($n$ = 2, 3) by treatment with phosphorus oxychloride. The condensed purines (**1b**−**3b**) were also obtained by a similar treatment of **VI** ($n$ = 2, 3, 4) with phosphorus oxychloride, but in a low yield. However, their preparations could be achieved in moderate yield by an alternate method with methanesulfonyl chloride in the presence of tri-

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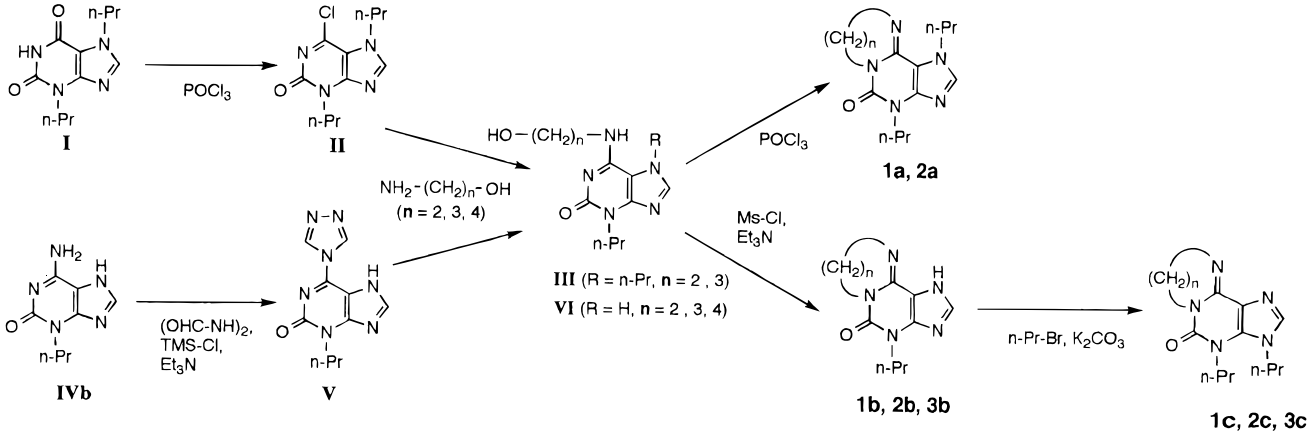
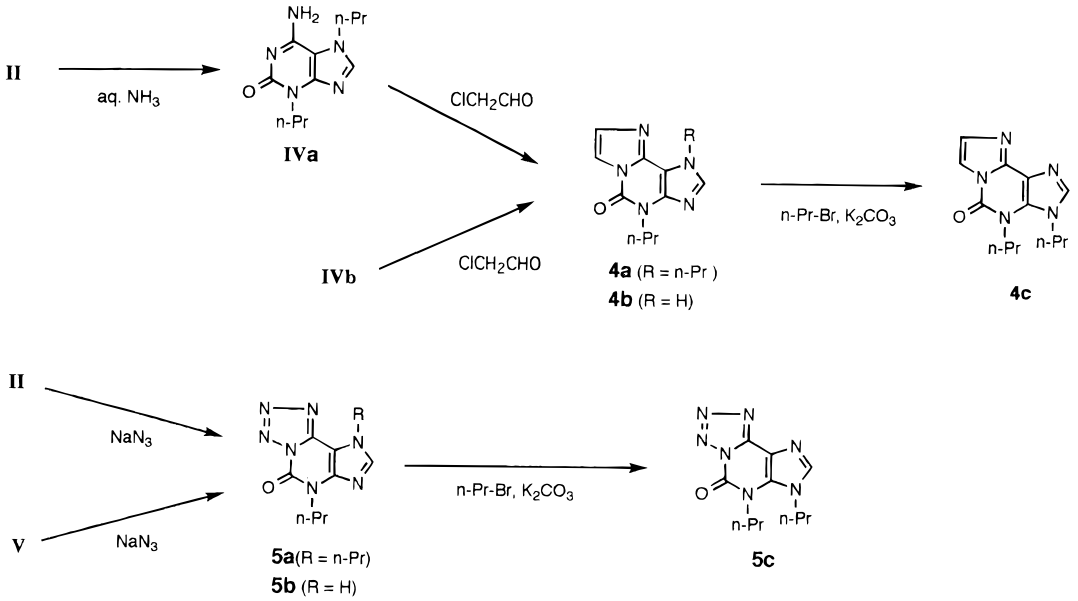
[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1997.

S0022-2623(97)00089-7 CCC: $14.00 

**Scheme 1**




**Scheme 2**




ethylamine. The condensed purines (**4a** and **4b**) were prepared by treatment of 40% $ClCH_2CHO$ with **IVa**, which was obtained by ammonialysis of **II**, and **IVb**. The condensed purines (**5a** and **5b**) were synthesized by treatment of sodium azide in ethanol from **II** and **V**, respectively. Alkylation of **1b**−**5b** with *n*-propyl bromide in the presence of potassium carbonate afforded regioisomeric *N*-propyl condensed purines (**1c**−**5c**). Yields and physicochemical data of the heterocycle-condensed purines (**1**−**5**) are summarized in Table 1.

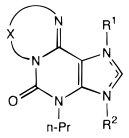
## Pharmacological Results and Discussion

The inhibitory activities of the heterocycle-condensed purines on PDE I, III, and IV are summarized together with those of reference compounds, the nonselective PDE inhibitor theophylline, selective PDE IV inhibitors 1-*n*-butyl-3-*n*-propylxanthine (XT-44)[9] and Ro 20−1724,[19] and the PDE III inhibitor amrinone,[20] in Table 2.

Compounds **1**−**3** did not influence PDE I and III enzyme activities at 100 $\mu$M, and among them, compounds substituted with an *n*-propyl group at the 7- or 9-position of the purine skeleton selectively inhibited PDE IV activity. The PDE IV inhibitory potency was higher in the 9-alkyl substituents than in the 7-substituents and became weak with increases in the member of the condensed heterocycles. Then, the dihydroimidazole ring of compounds **1** which were highly potent, was converted to the imidazole (**4**) or triazole ring (**5**). Compounds **4** inhibited PDE IV activity more strongly than compounds **1**, but also showed PDE I inhibitory activity, and so had lowered selectivity for PDE IV. The PDE IV inhibitory activities of compounds **5** were weak, compared with those of compounds **1**. These results indicate that the intramolecular interaction between the alkyl chain at the 1-position and the oxo group at the 6-position of the xanthine skeleton is important for selective PDE IV inhibitory activity. Consequently, compounds **1a**, **1c**, **2c**, and **3c** selectively inhibited PDE IV with equal or more potency than the reference compounds XT-44 and Ro 20−1724.

Next, the pharmacological activities of the condensed purines were investigated. As shown in Table 3, these compounds except for compounds **5** had stronger tracheal-relaxant activity than theophylline, and there was a close relationship between the tracheal-relaxant activity (−log $EC_{50}$) and the PDE IV-inhibitory activity (−log $IC_{50}$) of all compounds synthesized in this study (Figure 1). On the other hand, compounds **1**, **2**, **3**, and **5** did not show positive chronotropism in the right atrium (Table 3). Persson et al.[14] had described for the effects

**Table 1.** Physicochemical Data for Heterocycle-Condensed Purines (**1**−**5**)



| compd | X | $R^1$ | $R^2$ | yield[a] (%) | mp (°C) | recryst solv | formula[b] |
|---|---|---|---|---|---|---|---|
| **1a** | $-(CH_2)_2-$ | *n*-Pr | | 51 | 73−4 | $Et_2O$ | $C_{13}H_{19}N_5O$ |
| **1b** | $-(CH_2)_2-$ | H | | 63 | >290 | MeOH−AcOEt | $C_{10}H_{13}N_5O$ |
| **1c** | $-(CH_2)_2-$ | | *n*-Pr | 64 | 101−2 | pet. ether | $C_{13}H_{19}N_5O$ |
| **2a** | $-(CH_2)_3-$ | *n*-Pr | | 74 | 104−5 | $CH_2Cl_2-i$-$Pr_2O$ | $C_{14}H_{21}N_5O$ |
| **2b** | $-(CH_2)_3-$ | H | | 63 | >290 | MeOH−AcOEt | $C_{11}H_{15}N_5O$ |
| **2c** | $-(CH_2)_3-$ | | *n*-Pr | 38 | 87−8 | pet. ether | $C_{14}H_{21}N_5O$ |
| **3b** | $-(CH_2)_4-$ | H | | 31 | 239−40 | AcOEt | $C_{12}H_{17}N_5O$ |
| **3c** | $-(CH_2)_4-$ | | *n*-Pr | 46 | oil | | $C_{15}H_{23}N_5O$[c] |
| **4a** | −CH=CH− | *n*-Pr | | 68 | oil | | $C_{13}H_{17}N_5O$[c] |
| **4b** | −CH=CH− | H | | 82 | 298−9 | MeOH | $C_{10}H_{11}N_5O$ |
| **4c** | −CH=CH− | | *n*-Pr | 42 | oil | | $C_{13}H_{17}N_5O$[c] |
| **5a** | −N=N− | *n*-Pr | | 88 | 160−1 | EtOH | $C_{11}H_{15}N_7O$ |
| **5b** | −N=N− | H | | 82 | 227−8 | MeOH | $C_8H_9N_7O$ |
| **5c** | −N=N− | | *n*-Pr | 40 | 157−8 | $CH_2Cl_2-i$-$Pr_2O$ | $C_{11}H_{15}N_7O$ |

[a] Yield was of final procedure and purified product. [b] All compounds analyzed for C, H, N; analytical results were within ±0.4% of the theoretical values. [c] High-resolution MS spectral data.

**Table 2.** PDE Inhibition of Heterocycle-Condensed Purines[a]

| | $IC_{50} \pm$ SEM ($\mu$M) | | |
|---|---|---|---|
| compd | PDE I | PDE III | PDE IV |
| **1a** | >100[b] | >100 | 5.1 ± 0.2 |
| **1b** | >100 | >100 | >100 |
| **1c** | >100 | >100 | 1.6 ± 0.3 |
| **2a** | >100 | >100 | 49 ± 3 |
| **2b** | >100 | >100 | >100 |
| **2c** | >100 | >100 | 4.7 ± 0.7 |
| **3b** | >100 | >100 | >100 |
| **3c** | >100 | >100 | 13 ± 3 |
| **4a** | 14 ± 3 | >100 | 1.9 ± 0.5 |
| **4b** | >100 | >100 | 3.1 ± 0.1 |
| **4c** | 40 ± 5 | >100 | 1.4 ± 0.2 |
| **5a** | >100 | >100 | 18 ± 4 |
| **5b** | >100 | >100 | >100 |
| **5c** | >100 | >100 | 39 ± 7 |
| theophylline | 356 ± 46 | 240 ± 21 | 81 ± 6 |
| XT-44 | 149 ± 12 | >300 | 2.2 ± 0.1 |
| Ro 20−1724 | >300 | >300 | 4.8 ± 1.4 |
| amrinone | >300 | 16 ± 3 | 101 ± 1 |

[a] Each experiment was done using over five concentrations containing the $IC_{50}$ of each compound. [b] >100 or >300 $\mu$M, which is the limiting concentration soluble in the assay buffer.

**Table 3.** In Vitro Pharmacological Activities of Heterocycle-Condensed Purines

| compd | Tracheal relaxation $EC_{50} \pm$ SEM ($\mu$M) | Positive chronotropic action $EC_{20} \pm$ SEM ($\mu$M) | Adenosine antagonism $pA_2$ |
|---|---|---|---|
| **1a** | 2.5 ± 0.6 | >100[a] | |
| **1b** | 31 ± 6 | >100 | |
| **1c** | 1.0 ± 0.2 | >100 | |
| **2a** | 8.2 ± 0.6 | >100 | |
| **2b** | 22 ± 1 | >100 | |
| **2c** | 2.1 ± 1.0 | >100 | |
| **3b** | 53 ± 5 | >100 | |
| **3c** | 2.5 ± 0.2 | >100 | |
| **4a** | 0.7 ± 0.3 | 84 ± 10 | |
| **4b** | 1.6 ± 0.2 | 90 ± 8 | |
| **4c** | 0.5 ± 0.0 | 19 ± 4 | |
| **5a** | 51 ± 8 | >100 | |
| **5b** | >100 | >100 | |
| **5c** | 68 ± 5 | >100 | |
| theophylline | 28 ± 2 | 88 ± 6 | 4.53 |
| XT-44 | 0.45 ± 0.15 | 61 ± 6 | 6.23 |
| Ro 20−1724 | 0.12 ± 0.01 | >100 | |
| amrinone | 7.4 ± 1.0 | 62 ± 19 | |

Each experiment was done using over five concentrations containing the $EC_{50}$ or $EC_{20}$ of each compound. [a] >100 $\mu$M, which is the limiting concentration soluble in the assay buffer.

of *N*-alkyl substitutions of xanthine skeleton: 1-alkylation is important for adenosine antagonism and for many extrapulmonary effects, 3-alkylation augments bronchodilator potency, 7-alkylation decreases bronchodilator potency, and 9-alkylation causes general loss of potency. We, however, have reported that prolongation of alkyl chain length at both 1- and 7-positions of the xanthine skeleton is significant to increase in selective tracheal relaxation and PDE IV inhibition, but also increases the affinity for the adenosine receptors.[15−17] In this study, the condensed purines retained the potent PDE IV-inhibitory activity and tracheal-relaxant activity and abolished the adverse effects of xanthine derivatives, such as heart stimulation and adenosine antagonism. Their tracheal-relaxant activity was further increased by introduction of an *n*-propyl group at the 7- or 9-position, which was reported to decrease the xanthine actions.[14] Therefore, the condensed purines developed in this study might possess new properties chemically and pharmacologically different from those of the xanthine derivatives. Consequently, we could obtain selective PDE IV inhibitors devoid of the defects of xanthines. Compounds **4**, which had potent tracheal-relaxant activity, however, showed a weak heart stimulation, although they had not the PDE III-inhibitory activity and adenosine-antagonistic action in the heart. This may be due to their activity on PDE I (Table 2).

Finally, we explored the emetic effects of compounds **1c** and **4c**, which showed potent PDE IV-inhibitory activity, comparing with known and differently structured PDE IV inhibitors, a xanthine derivative, denbufylline,[21] and a phenylpyrroridine derivative, rolipram,[22] in the suncus, which is an animal model for emesis.[23] As shown in Table 4, although compound **1c** did not show emetic effect at the range 10−100 mg/kg, po, not only rolipram and denbufylline but also compound **4c** clearly caused emesis at 10 or 30 mg/kg. Regarding the mechanism for emetic side effect of PDE IV inhibitors, now the most accepted theory is that the binding affinity for the rolipram-binding site, distinct from the PDE IV catalytic domain, has been correlated

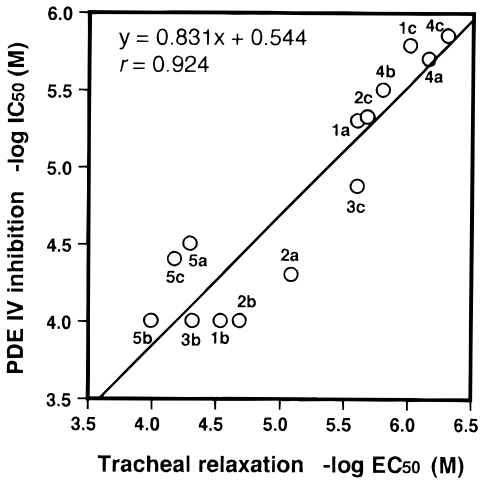



**Figure 1.** Correlation beween the tracheal relaxant activity ($-\log EC_{50}$) and the PDE IV inhibitory activity ($-\log IC_{50}$) in heterocycle-condensed purines. Each point with a compound number is from results presented in Tables 2 and 3.

**Table 4.** Emetic Effects of PDE IV Inhibitors in the Suncus[a]

| compd | dose (mg/kg, po) | no. of animals with emesis/ no. of test animals |
|---|---|---|
| 0.5% CMC | | 0/3 |
| 1c | 100 | 0/3 |
| | 30 | 0/3 |
| | 10 | 0/3 |
| 4c | 10 | 3/3 |
| rolipram | 10 | 3/3 |
| denbufylline | 30 | 3/3 |

[a] Compounds were suspended or dissolved in 0.5% CMC and orally administered to male suncus, and emetic behaviors of the animal were observed for 60 min.

with the emetic potency.[24] Compound **1c** may lack affinity for the rolipram-binding site, but its dihydroimidazole analogue **4c** has an emetic liability similar to that of rolipram and other PDE IV inhibitors.

This study indicated that newly synthesized heterocycle-condensed purines showed selective PDE IV-inhibitory activity and lacked some adverse reactions of xanthine derivatives and known PDE IV inhibitors. In conclusion, we developed 3,4-dipropyl-4,5,7,8-tetrahydro-3*H*-imodazo[1,2-*i*]purin-5-one (**1c**), a potent tracheal relaxant without heart stimulation or emetic action, and it is a new generation of PDE IV inhibitors.

## Experimental Section

**Chemistry.** Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were taken with an Hitachi 270-30 spectrometer, and mass spectra (MS) were measured with a JEOL-DX300 instrument. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on JEOL-PMX 60-SI and JEOL-EX 90A spectrometers. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants ($J$) are given in hertz (Hz).

**6-Chloro-3,7-dipropylpurin-2-one (II).** A solution of **I** (13.6 g, 58 mmol) in $POCl_3$ (60 mL) was heated with reflux for 2 h. The reaction mixture was distilled away in vacuo and the residue was added to ice−water. The mixture was neutralized with solid $K_2CO_3$ and then extracted with $CH_2Cl_2$. The extract was dried over $MgSO_4$ and evaporated in vacuo. The resulting residue was recrystallized from a mixture of $CH_2Cl_2$ and isopropyl ether to give **II** (13.5 g, 92%) as colorless prisms, mp 109−110 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.0 (3H, t, $J$ = 8), 1.05 (3H, t, $J$ = 8), 2.0 (4H, sext, $J$ = 8), 4.50 (4H, t, $J$ = 8), 8.0 (1H, s). IR (KBr) $\nu_{max}$: 1664, 1598 cm$^{-1}$. Anal. ($C_{11}H_{15}N_4OCl$) C, H, N.

**6-[(Hydroxyethyl)amino]-3,7-dipropylpurin-2-one (III, *n* = 2).** A mixture of **II** (2.68 g, 10.5 mmol), aminoethanol (0.78 g, 13 mmol), and triethylamine (2.40 g, 24 mmol) in $CH_2Cl_2$ (15 mL) was refluxed for 4 h, and then added to water. The mixture was extracted with $CH_2Cl_2$ and the extract was washed with brine, dried, and evaporated in vacuo. The residue was chromatographed on alumina using $CH_2Cl_2$−AcOEt (3:1) as an eluent to give 6-[(hydroxyethyl)amino]-3,7-dipropylpurin-2-one (**III**, $n$ = 2)(0.95 g, 32%) as a viscous oil. $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (6H, t, $J$ = 8), 1.90 (4H, sext, $J$ = 8), 3.80 (4H, br s), 4.20 (1H, t, $J$ = 8), 4.30 (1H, t, $J$ = 8), 5.30 (1H, br s), 7.10 (1H, br s), 7.50 (1H, s). IR (KBr) $\nu_{max}$: 3224, 1624 cm$^{-1}$; HRMS ($C_{13}H_{21}N_5O_2$): calcd 279.1695, found 279.1696.

Compounds **III** ($n$ = 3) was prepared by a procedure similar to that described above from **II** and aminopropanol.

**1,4-Dipropyl-4,5,7,8-tetrahydro-1*H*-imidazo[1,2-*i*]purin-5-one (1a).** A mixture of **III** ($n$ = 2) (0.31 g, 1 mmol) and $POCl_3$ (2 mL) was refluxed for 1 h. The reaction mixture was distilled away in vacuo and the residue was poured onto ice−water. The mixture was neutralized by solid $NaHCO_3$, extracted with $CH_2Cl_2$, dried, and evaporated in vacuo. The residue was chromatographed on alumina using $CH_2Cl_2$−AcOEt (6:1) as an eluent to give **1a**.

Compounds **2a** was prepared by a procedure similar to that described above from **III** ($n$ = 3).

**3-Propyl-6-(1,2,4-triazol-4-yl)purin-2-one (V).** To a mixture of 6-amino-3-propyl-7(9*H*)-purin-2-one (**IVb**) (1.02 g, 5.3 mmol) and diformylhydrazine (1.40 g, 16 mmol) in pyridine (20 mL) were added trimethylchlorosilane (8.6 g, 80 mmol) and triethylamine (3.7 g, 37 mmol), and the mixture was stirred for 20 h at 100 °C. The reaction mixture was evaporated in vacuo, the residue was washed successively with $H_2O$ (20 mL) and $CHCl_3$ (20 mL), and the insoluble precipitate was recrystallized from a mixture of $H_2O$ and MeOH to give **V** (0.82 g, 63%) as colorless prisms, mp 263−264 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.93 (3H, t, $J$ = 7), 1.72 (2H, sext, $J$ = 7), 4.05 (2H, t, $J$ = 7). 8.30 (1H, s), 9.44 (2H, s). IR (KBr) $\nu_{max}$: 3500, 1666 cm$^{-1}$. Anal. ($C_{10}H_{11}N_7O$) C, H, N.

**6-[(Hydroxyethyl)amino]-3-propyl-7(9*H*)-purin-2-one (VI, *n* = 2).** To **V** (3.0 g, 12 mmol) in $CH_3CN$ (15 mL) was added aminoethanol (15 mL), and the mixture was refluxed overnight. The reaction mixture was evaporated in vacuo, then the residue was chramatographed on silica gel using $CHCl_3$−MeOH (3:1) as an eluent to give **VI** ($n$ = 2) (1.60 g, 55%) as colorless prisms, mp 279−281 °C (recryst from MeOH). $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.85 (3H, t, $J$ = 7), 1.59 (2H, sext, $J$ = 7), 3.18−3.96 (6H, m), 5.05 (1H, br s), 7.55 (1H, br s), 7.89 (1H, s), 12.20 (1H, br s). IR (KBr) $\nu_{max}$: 3340, 1644 cm$^{-1}$. Anal. ($C_{10}H_{15}N_5O_2$) C, H, N.

Compounds **VI** ($n$ = 3,4) were prepared by a procedure similar to that described above from **V** and aminoalkanol.

**4-Propyl-4,5,7,8-tetrahydro-1(3*H*)-imodazo[1,2-*i*]purin-5-one (1b).** To a mixture of **VI** ($n$ = 2)(1.55 g, 6.5 mmol) in $CH_2Cl_2$ (50 mL) was added methanesulfonyl chloride (0.90 g, 8.0 mmol) in triethyamine (0.79 g, 8.0 mmol) with stirring at 0 °C for 1 h. The reaction mixture was stirred for 8 h at room temperature and then concentrated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$−MeOH (6:1) as an eluent to give **1b**.

Compounds **2b** and **3b** were prepared by a procedure similar to that described above from **VI** ($n$ = 3) and **VI** ($n$ = 4), respectively.

**6-Amino-3,7-dipropylpurin-2-one (IVa).** A mixture of **II** (1.0 g, 3.9 mmol), EtOH (10 mL), and concentrated $NH_4OH$ (20 mL) was heated at 60 °C for 12 h. The reaction mixture was evaporated in vacuo, and the residue was chromatographed on alumina using AcOEt−EtOH (4:1) as an eluent to give **IVa** (0.60 g, 66%) as colorless prism, mp 114−115 °C (recryst from $CH_2Cl_2$−IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (3H, t, $J$ = 8), 0.95 (3H, t, $J$ = 8), 1.93 (2H, sext, $J$ = 8), 1.98 (2H, sext, $J$ = 8), 4.20 (2H, t, $J$ = 8), 4.30 (2H, t, $J$ = 8), 7.50 (1H, s). IR (KBr) $\nu_{max}$: 3400, 1626 cm$^{-1}$. Anal. ($C_{11}H_{17}N_5O$) C, H, N.

**1,4-Dipropyl-4,5-dihydro-1*H*-imidazo[1,2-*i*]purin-5-one (4a).** A mixture of **IVa** (118 mg, 0.5 mmol), 40% $ClCH_2$-

CHO (300 mg, 1.5 mmol), and EtOH (6 mL) was heated at 120 °C in a sealed tube for 4 h. The reaction mixture was evaporated in vacuo, and the residue was chromatographed on alumina using $CH_2Cl_2$ as an eluent to give **4a**.

Compound **4b** was prepared by a procedure similar to that described above from **IVb**.

**6,9-Dipropyl-5,6-dihydro-9*H*-tetrazolo[5,1-*i*]purin-5-one (5a).** A mixture of **II** (607 mg, 2.4 mmol), $NaN_3$ (416 mg, 6.4 mmol), and EtOH (30 mL) was heated at 100 °C in sealed tube for 1.5 h. The resultant precipitate was removed by filtration, and the reaction mixture was evaporated in vacuo. The residue was recrystallized from EtOH to give **5a**.

Compound **5b** was prepared by a procedure similar to that described above from **V.**

**3,4-Dipropyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*i*]purin-5-one (1c).** To a mixture of **1b** (0.29 g, 1.3 mmol) and anhydrous $K_2CO_3$ (0.31 g, 2.2 mmol) in DMF (5 mL) was added *n*-propyl bromide (0.24 g, 2.0 mmol) at room temperature, the mixture was stirred at 60 °C overnight and then added to water. The mixture was extracted with AcOEt and the extract was washed with brine, dried, and concentrated in vacuo. The residue was chromatographed on silica gel using AcOEt−MeOH (10:1) to give **1c**.

Compounds **2c**, **3c**, **4c**, and **5c** were prepared by a procedure similar to that described from **2b**, **3b**, **4b**, and **5b**, respectively.

**In Vitro Pharmacological Methods.** Theophylline was dissolved in Krebs−Henseleit solution or respective assay buffer, and other compounds were dissolved in DMSO. Samples of the stock solution were then diluted in the assay buffer. The final concentration of DMSO used in each assay was below 0.5%, a concentration at which the pharmacological responses were not influenced.

Animals used were male Hartley guinea pigs weighing 300−500 g.

**PDE Inhibition Assay.** $Ca^{2+}$/calmodulin-stimulated cyclic AMP PDE (type I), cyclic AMP-specific PDE (type IV) from the cerebral cortex, and cyclic GMP-inhibited cyclic AMP PDE (type III) from the heart were isolated by the method reported by Reeves et al.[19] The enzyme preparation and various concentrations of a compound were incubated at 30 °C for 10 min, and the cyclic AMP−PDE activity was assayed by the method of Thompson and Appleman.[25] The concentration producing 50% inhibition of cyclic AMP hydrolysis ($IC_{50}$) for each PDE isoenzyme was calculated by the nonlinear least-squares method.

**Tracheal Muscle Relaxation.** Relaxation of the spontaneous tone in isolated tracheal muscle ring chains was measured through an isometric transducer. The tracheal ring-chain preparations were placed in a 10-mL thermostatically controlled organ bath (37 °C) containing Krebs−Henseleit solution (pH 7.4), gassed with 95% $O_2$−5% $CO_2$, and a tension of 0.5 g was applied to the preparation. Isoprenaline (1.0 $\mu$M) was added to produce complete relaxation, and after isoprenaline was washed out, spontaneous tone was allowed to develop. After the tension had become constant, the preparation was treated with cumulative concentrations of a compound. Relaxation by 1.0 $\mu$M isoprenaline was defined as 100%, and the concentration producing 50% relaxation ($EC_{50}$) was calculated.

**Beating Rate of the Right Atrium.** The isolated right atrium was placed in an organ bath (25 °C) filled with Krebs−Henseleit solution aerated with 95% $O_2$−5% $CO_2$. The preparation was allowed to equilibrate under a tension of 0.5 g and then treated with cumulative concentrations of a compound. The beating rate was recorded through a cardiotachometer triggered by isometric contraction of the atria. Data were expressed as 20% increasing concentration ($EC_{20}$) of the unstimulated beating rate.

**Adenosine Antagonism in the Left Atrium.** To examine the effects of compounds on the negative inotropic response to adenosine, the concentration−response curve for the effect of adenosine was measured in a cumulative manner, in the presence of 10 $\mu$M dipyridamol, in preparations treated with each compound for 20 min. The p$A_2$ value was calculated from the concentration−response curves of adenosine in the absence and presence of a test compound.

**In Vivo Emesis Assay.** Compounds were suspended in 0.5% carboxymethylcellulose and orally administered to male *Suncus murinus* (house musk shrew) (52−65 g). After the administration, the emetic behavior was observed for 60 min.

**Acknowledgment.** This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan and the Special Research Fund of Hokuriku University.

**Supporting Information Available:** $^1$H-NMR data for **1a**−**c** to **5a**−**c** (1 page). Ordering information is given on any current masthead page.

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**IVb**: mp >300 °C (recryst from MeOH−$H_2O$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.86 (3H, t, $J$ = 7), 1.65 (2H, sext, $J$ = 7), 3.90 (2H, t, $J$ = 7), 7.50 (1H, br s), 7.85 (1H, s). IR (KBr) $\nu_{max}$: 3328, 3128, 1662, 1606 cm$^{-1}$. Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.65; H, 5.73; N, 36.27.

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JM970089S