N-[2(1H)-Pyridon-1-ylcarbonyl]-L-phenylalanine Methyl Ester (29). A mixture of isocyanate **39** (1.02 g, 5 mmol) and 2-pyridone (0.48 g, 5 mmol) in 5 mL of dioxane was refluxed for 2 h. Removal of the solvent in vacuo left a viscous oil (1.4 g, 93%): IR (neat) 1720 cm^{-1} (C=O); NMR ($CDCl_3/Me_4Si$) δ 8.3 (d, 1 H), 7.2 (s, 7 H), 6.5 (d, 1 H), 6.3 (d, 1 H), 4.8 (t, 1 H), 3.6 (s, 3 H), 3.1 (d, 2 H). Anal. ($C_{16}H_{16}N_2O_4$) C, H, N.

N-(Succinimid-1-ylcarbonyl)-L-phenylalanine Methyl Ester (30). A 1.02-g (5 mmol) sample of isocyanate **39** and 0.58 g (5 mmol) of *N*-hydroxysuccinimide were refluxed in 5 mL of dioxane for 2 h. Evaporation of the solvent left a viscous oil (1.52 g, 95%): IR (neat) 3300 cm^{-1} (NH br), 1770 (C=O), 1725 (C=O); NMR ($CDCl_3/Me_4Si$) δ 7.3 (s, 5 H), 4.5 (d, 1 H), 3.7 (s, 3 H), 3.2 (d, 2 H), 2.8 (s, 4 H). Anal. ($C_{15}H_{16}N_2O_6$) C, H, N.

N-(1H-Imidazol-1-ylcarbonyl)-2-phenethylamine (18). A 2.94-g (20 mmol) sample of 2-phenylethyl isocyanate and imidazole (1.36 g, 20 mmol) in 20 mL of dioxane were refluxed under nitrogen for 2 h. Removal of the solvent in vacuo left a white residue, which was recrystallized from CH_2Cl_2/hexane to give 3.7 g (86%) pure product: mp 101–103 °C; IR (KBr) 3200 cm^{-1} (NH), 1700 (C=O); NMR ($CDCl_3/Me_4Si$) δ 8.1 (t, 1 H), 7.8 (s, 1 H), 7.3 (s, 1 H), 7.1 (s, 5 H), 6.7 (s, 1 H), 3.3 (t, 2 H), 2.7 (t, 2 H). Anal. ($C_{12}H_{13}N_3O$) C, H, N.

Succinimido N-(2-Phenylethyl)carbamate (24). A 2.94-g (0.02 mol) sample of 2-phenylethyl isocyanate, 2.30 g (0.02 mol) of *N*-hydroxysuccinimide, and 20 mL of dioxane were refluxed under nitrogen for 2 h. Removal of the solvent left a solid residue, which was recrystallized from CH_2Cl_2/hexane to yield 4.62 g (88%) pure product: mp 138–139 °C; IR (KBr) 3260 cm^{-1} (NH), 1730 (C=O, br); NMR ($CDCl_3/Me_4Si$) δ 7.3 (s, 5 H), 5.6 (br s, 1 H), 3.4 (q, 2 H), 2.8 (t, 2 H), 2.7 (s, 3 H). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

1-[(2-Phenylethyl)carbamoyl]-2(1H)-pyridone (21). A 2.94-g (20 mmol) sample of 2-phenylethyl isocyanate and 1.90 g (20 mmol) of 2-pyridone in 20 mL of dioxane were refluxed for 2 h. Recrystallization of the solid residue yielded 4.2 g (87%) of product: mp 52–53 °C; IR (KBr) 3100 cm^{-1} (NH br), 1700 and 1650 (C=O); NMR ($CDCl_3/Me_4Si$) δ 8.3 (d, 1 H), 7.2 (s, 6 H), 6.4 (d, 1 H), 6.2 (d, 1 H), 3.5 (t, 2 H), 2.7 (t, 2 H). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

Potassium Oxo[(2-phenylethyl)amino]methanesulfonate Salt (16). 2-Phenylethyl isocyanate (2.94 g, 20 mmol) in 10 mL of dioxane was mixed with potassium metabisulfite (2.22 g, 10 mmol) in 10 mL of water and the mixture stirred overnight. The precipitated solid was collected by suction and washed with acetone. A 5.13-g (96%) sample of pure salt was obtained: IR (KBr) 3300 cm^{-1} (NH), 1660 (C=O); NMR (Me_2SO-d_6) δ 7.3 (s, 5 H), 3.5 (t, 2 H), 2.8 (t, 3 H). Anal. ($C_9H_{10}NSO_4K$) C, H, N, S.

Enzyme Assays and Inhibition Studies. Human leukocyte elastase was assayed by mixing 10 μL of a 3.4×10^{-5} M enzyme solution (in 0.05 M sodium acetate buffer, pH 5.5), 50 μL of dimethyl sulfoxide, and 940 μL of Tris–buffer, pH 7.2, in a thermostated test tube. After equilibration at 25 °C, a 100-μL aliquot was transferred to a thermostated cuvette containing 890 μL of Tris–buffer and 10 μL of a 3.15×10^{-2} M solution of (methoxysuccinyl)-Ala-Ala-Pro-Val-p-nitroanilide. The change in absorbance was monitored at 410 nm for 2 min. In a typical inhibition run, 50 μL of a 3.4×10^{-4} M solution of the appropriate inhibitor in dimethyl sulfoxide was mixed with 10 μL of a 3.4×10^{-5} M enzyme solution and 940 μL Tris–buffer in a constant temperature bath. One hundred microliter aliquots were withdrawn at different time intervals and transferred to a cuvette containing substrate, 10 μL of a 3.15×10^{-2} M solution, and 890 μL of Tris–buffer. After incubation for 30 s, the absorbance was monitored for 2 min at 410 nm. The inhibitor to enzyme ratio varied between 10 and 50, depending on the potency of the inhibitor. The method of Kitz and Wilson[16] was used to analyze the data, and the results were expressed in terms of the bimolecular rate constant, $k_{obsd}/[I]$ M^{-1} s^{-1}.

Acknowledgment. The generous financial support of the National Institutes of Health is deeply appreciated (NHLBI Grant HL30798-02).

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Analogues of Caffeine and Theophylline: Effect of Structural Alterations on Affinity at Adenosine Receptors

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A variety of analogues of caffeine and theophylline in which the 1-, 3-, and 7-methyl substituents have been replaced with *n*-propyl, allyl, propargyl, and isobutyl and, in a few cases, with chloroethyl, hydroxyethyl, or benzyl were assessed for potency and selectivity as antagonists at A_1- and A_2-adenosine receptors in brain tissue. Caffeine and theophylline are nonselective for these receptors. Nearly all of the 22 analogues of caffeine are more potent than caffeine itself at adenosine receptors. Replacement of the 1-methyl moiety with *n*-propyl, allyl, or propargyl substituent has little effect on potency at the A_1 receptor while enhancing potency about 7- to 10-fold at the A_2 receptor. 3,7-Dimethyl-1-propylxanthine is only slightly (1.4-fold) more potent than caffeine at the A_1 receptor while being 10-fold more potent at the A_2 receptor. 1,3-Di-*n*-propyl-7-methylxanthine is also selective for the A_2 receptor, being 8-fold more potent than caffeine at the A_1 receptor and 40-fold more potent at the A_2 receptor. A number of other caffeine analogues including 3,7-dimethyl-1-*n*-propylxanthine, 7-allyl-1,3-dimethylxanthine, and 1,3-dimethyl-7-propargylxanthine are also somewhat selective for the A_2 receptor. The most potent caffeine analogue was 1,3-di-*n*-propyl-7-propargylxanthine, which was about 100-fold more potent than caffeine at both A_1 and A_2 receptors. The 10 theophylline analogues were relatively nonselective except for the 1-ethyl analogue and the 1,3-diallyl analogue, which were selective for the A_2 receptor, and the 1,3-di-*n*-propyl, 1,3-diisobutyl, and 1,3-dibenzyl analogues, which were somewhat selective for the A_1 receptor. 1,3-Di-*n*-propylxanthine was 20-fold more potent than theophylline at the A_1 receptor and 5-fold more potent at the A_2 receptor.

Adenosine has a variety of roles in modulating the function of the cardiovascular, endocrine, and nervous system.[1] Definition of the nature of the receptors involved in such roles has been hindered by the lack of selective antagonists for the two proposed classes of adenosine receptors, the so-called A_1 (Ri) and A_2 (Rs) receptors. Caffeine (1) and theophylline (24) represent prototypes of a wide range of xanthine antagonists for adenosine receptors. But caffeine, theophylline, and most of the other

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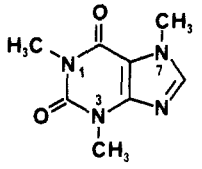

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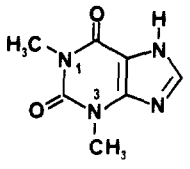

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xanthines show limited selectivity for A_1 and A_2 receptors.[2,3] An increase in size of the 1- and 3-alkyl substituents on theophylline can confer some selectivity for the A_1 adenosine receptor subclass.[3] The effects of systematically replacing the 1-, 3-, and 7-methyl substituents of caffeine and theophylline with *n*-propyl, allyl, and propargyl moieties on activity at central A_1 and A_2 receptors have now been evaluated. The results provide the basis for further development of selective adenosine antagonists.

Results and Discussion

Caffeine and theophylline exhibit a variety of pharmacological actions including antiasthmatic, diuretic, respiratory stimulant, central stimulant, cardiac stimulant, and analgesic adjuvant activities (see ref 3). Such activities may prove to reflect blockade of A_1- and/or A_2-adenosine receptors. Further xanthines, thus, have the potential for both development as clinical agents and as research tools.

The size of the alkyl substituents at the 1- and 3-position of theophylline markedly affects activity at adenosine receptors. The optimal size appears to be *n*-propyl for both A_1 and A_2-adenosine receptors.[3] Further increases in the size of the alkyl substituents causes a marked decrease in activity, particularly at the A_2 receptor.[3] Virtually nothing is known of the effect of varying the 1-, 3-, and 7-substituents on the activity of caffeine. The present study was designed to probe the effect of replacing methyl groups of caffeine and theophylline with *n*-propyl and with unsaturated entities of similar size, namely, allyl and propargyl. The latter, more polar substituents were expected to enhance water solubility of analogues compared to corresponding *n*-propyl compounds.

Caffeine. Replacement of the 1-methyl moiety of caffeine (1) with *n*-propyl, allyl, or propargyl (compounds **2–4**) increases activity at the A_1 receptor only slightly if at all while causing a marked increase at the A_2 receptor (Table I). The resultant analogues are, thus, quite selective (7–10-fold) for the A_2 receptor. Indeed, these three caffeine analogues are the most selective A_2 receptor antagonists yet reported.

Replacement of the 3-methyl substituent of caffeine with *n*-propyl or isobutyl (compounds **5**, **6**) causes a significant increase in activity at both A_1 and A_2 receptors. These two analogues exhibit some selectivity for A_2 receptors. Efforts to prepare 3-allyl-1,7-dimethylxanthine and 1,3-dimethyl-3-propargylxanthine by reaction of 1,7-dimethylxanthine with allyl bromide or propargyl bromide were unsuccessful.

Replacement of the 7-methyl substituent of caffeine with *n*-propyl, allyl, or propargyl (compounds **7–9**) increases activity compared to caffeine and yields analogues with slight selectivity for the A_2 receptor. A 7-(β-chloroethyl) substituent (compound **10**) increases activity, while a 7-(β-hydroxyethyl) substituent (compound **11**) decreases activity. The 7-(β-acetoxyethyl) analogue (compound **12**) has activity similar to that of caffeine. A 7-benzyl substituent (compound **13**) increases activity.

A limited series of caffeine analogues with variations in two of the substituents were prepared. The 1,3-dipropyl and 1,3-diallyl analogues (compounds **14**, **15**) are more potent than caffeine at both A_1 and A_2 receptors and both are selective for the A_2 receptor: 1,3-Dipropyl-7-methylxanthine (compound **15**) has an A_1/A_2 potency ratio of 6 (Table I). The various 1-methyl-3-isobutyl-7-substituted-xanthine analogues (compounds **16–19**) of caffeine are nonselective, albeit more potent than caffeine.

A limited number of caffeine analogues with variations in all three substituents were prepared. 1,3,7-Tripropylxanthine (compound **20**) and the 7-allyl, 7-propargyl, and 7-benzyl derivatives (compounds **21–23**) of 1,3-dipropylxanthine are very potent at both A_1 and A_2 receptors. However, there is little selectivity except for 7-allyl-1,3-dipropylxanthine (compound **21**), which shows some selectivity for the A_2 receptor.

Theophylline. Replacement of the 1-methyl substituent of theophylline (**24**) with ethyl (compound **25**) has no effect on activity at the A_1 receptor while causing a marked increase in activity at the A_2 receptor: The 1-ethyl-3-methylxanthine has a 3-fold selectivity for the A_2 receptor (Table II). Replacement of the 1-methyl substituent of theophylline with a β-hydroxyethyl moiety (compound **26**) results in a marked decrease in activity.

Replacement of the 3-methyl substituent of theophylline with isopropyl or isobutyl (compounds **27**, **28**) increases potency slightly at adenosine receptors, while a β-hydroxyethyl moiety (compound **29**) decreases activity.

Replacing both substituents of theophylline with ethyl or propyl (compounds **30**, **31**) increases potency remarkably at adenosine receptors (Table II) as previously reported.[5] Remarkably, in view of the results in caffeine analogues, 1,3-diallylxanthine (compound **32**) is much *less* active than the dipropyl analogue (compound **31**). The 1,3-diisobutyl- and 1,3-dibenzylxanthines (compounds **33**, **34**) show selectivity for the A_1 receptor (Table II) as previously reported for 1-isopentyl-3-isobutylxanthine.[3]

Certain of the present caffeine and theophylline analogues may prove useful for investigation of significance of A_1 and A_2 receptors in various physiological processes. The selectivity (>4-fold) of certain caffeine analogues (compounds **2–4**, **8**, **9**) for A_2 receptors and the selectivity (>3-fold) of certain theophylline analogues (compounds **31**, **33**, **34**) for A_1 receptors is noteworthy, and it may prove possible to further enhance such selectivity through incorporation of appropriate 8-substituted phenyl moieties.[3]

Experimental Section

Melting points were taken on a Kofler block hot stage and are corrected. Mass spectra were determined with a Finnegan 1015 quadrapole (chemical ionization with CH_4 or NH_3) and with VG 70/70 (electron impact, 70 eV) mass spectrometers and were consistent with the structures. Caffeine (**1**), theophylline (**24**), and 3-isobutyl-1-methylxanthine (**28**) were from Sigma Chemical Co. (St. Louis, MO); 7-(β-chloroethyl)theophylline (**10**) and 7-(β-hydroxyethyl)theophylline (**11**) were from Aldrich Chemical Co. (Milwaukee, WI); 7-benzyl-1,3-dimethylxanthine (**19**), 1-ethyl-3-methylxanthine (**25**), 1-(β-hydroxyethyl)-3-methylxanthine (**26**), 3-isopropyl-1-methylxanthine (**27**), 3-(β-hydroxyethyl)-1-methylxanthine (**29**), 1,3-diethylxanthine (**30**), 1,3-dipropylxanthine (**31**), 1,3-diisobutylxanthine (**33**), and 1,3-dibenzylxanthine (**34**) were from G. D. Searle (Chicago, IL). Analytical data and melting points for other xanthines are reported in Table III.

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Table I. Caffeine: Effect of Alterations of the 1-, 3-, and 7-Substitutions on Affinity for Adenosine Receptors

no.	substituent position 1	3	7	K_i,[a] μM A_1	A_2	A_1/A_2
1	CH_3	CH_3	CH_3	55 ± 11	50 ± 5	1.1
2	*n*-propyl	CH_3	CH_3	38 ± 9	5 ± 1	9.5
3	allyl	CH_3	CH_3	47 ± 11	6.5 ± 0.7	7.2
4	propargyl	CH_3	CH_3	45 ± 4	6 ± 1	7.5
5	CH_3	*n*-propyl	CH_3	24 ± 6	9 ±y 3	2.7
6	CH_3	isobutyl	CH_3	19 ± 8	7 ± 1	2.7
7	CH_3	CH_3	*n*-propyl	21 ± 6	11 ± 3	1.9
8	CH_3	CH_3	allyl	33 ± 2	10 ± 2	3.3
9	CH_3	CH_3	propargyl	12 ± 3	4.1 ± 0.2	2.9
10	CH_3	CH_3	β-chloroethyl	8 ± 2	4.5 ± 1.2	1.8
11	CH_3	CH_3	β-hydroxyethyl	105 ± 15	135 ± 8	0.8
12	CH_3	CH_3	β-acetoxyethyl	40 ± 7	68 ± 3	0.6
13	CH_3	CH_3	benzyl	6 ± 1	14 ± 4	0.4
14	*n*-propyl	*n*-propyl	CH_3	7 ± 3	1.2 ± 0.2	5.8
15	allyl	allyl	CH_3	18 ± 8	4 ± 1	4.5
16	CH_3	isobutyl	*n*-propyl	13 ± 2	11 ± 5	1.2
17	CH_3	isobutyl	allyl	13 ± 2	8.5 ± 1.4	1.5
18	CH_3	isobutyl	propargyl	3.1 ± 0.1	2.8 ± 0.2	1.1
19	CH_3	isobutyl	benzyl	9 ± 2	11 ± 5	0.8
20	*n*-propyl	*n*-propyl	*n*-propyl	2.6 ± 0.4	1.4 ± 0.3	1.9
21	*n*-propyl	*n*-propyl	allyl	1.9 ± 0.1	0.7 ± 0.0	2.7
22	*n*-propyl	*n*-propyl	propargyl	0.6 ± 0.2	0.4 ± 0.2	1.5
23	*n*-propyl	*n*-propyl	benzyl	1.0 ± 0.2	1.5 ± 0.3	0.7

[a] IC_{50} values were obtained as described (see Experimental Section) and K_i values calculated in standard means.[3] Values are means ± SEM for two to five separate determinations, each determination being done in triplicate.

Table II. Theophylline: Effect of Alterations of the 1- and 3-Substituents on Affinity for Adenosine Receptors

no.	substituent 1	3	K_i,[a] μM A_1	A_2	A_1/A_2
24	CH_3	CH_3	14 ± 3	14 ± 2	1.0
25	ethyl	CH_3	15 ± 4	5 ± 1	3.0
26	β-hydroxyethyl	CH_3	85 ± 7	50 ± 14	1.7
27	CH_3	isopropyl	12 ± 4	6 ± 1	2.0
28	CH_3	isobutyl	7 ± 2	8 ± 4	0.9
29	CH_3	β-hydroxyethyl	60 ± 10	80 ± 10	0.8
30	ethyl	ethyl	3.3 ± 0.2	3.0 ± 1.2	1.1
31	*n*-propyl	*n*-propyl	0.7 ± 0.3	2.7 ± 0.8	0.3
32	allyl	allyl	10 ± 2.1	5 ± 2	2.0
33	isobutyl	isobutyl	0.5 ± 0.2	1.7 ± 0.7	0.3
34	benzyl	benzyl	2.0 ± 0.8	14 ± 5	0.14

[a] IC_{50} values were obtained as described (see Experimental Section) and K_i values calculated in standard means.[3] Values are means ± SEM for two to five separate determinations, each determination being done in triplicate.

Alkylation of Xanthines. (1) General Procedure. This procedure is a modification of the method used by Garst et al.[6] To a stirred suspension of 4.5 mmol of 1,3-dialkylxanthine and 0.7 g of anhydrous K_2CO_3 in 8 mL of DMF was added dropwise 5 mmol of alkyl halide. The reaction mixture was heated at 35 °C for the time indicated in Table III and the volatile material removed under vacuo. Product was isolated by one of the following methods. (A) H_2O was added to precipitate the product followed by chilling in ice, filtration, and drying. The crude product was purified by recrystallization from the solvent specified in Table IV. (B) H_2O was added and the H_2O–DMF mixture was evaporated in vacuo. The residue was extracted with several portions of EtOAc. The combined extracts were dried over $MgSO_4$ and filtered and solvent evaporated in vacuo. Recrystallization with the appropriate solvent gave a pure compound.

(2) Alternate Procedure. A mixture of 20 mmol of 3,7-dialkylxanthine, 20 mL of 10% NaOH, 50 mL of H_2O, and 100 mL of EtOH was refluxed for 15 min. The solution was cooled to room temperature, and 40 mmol of alkyl halide was added dropwise. The reaction mixture was refluxed for the time indicated in Table III and solvent removed in vacuo. The product was isolated by one of the following methods. (C) The residue was dissolved in H_2O followed by acidification with concentrated HCl to give a precipitate, which was removed by filtration and dried. Recrystallization with the solvent indicated in Table III gave a pure compound. (D) H_2O was added to give a precipitate, which was removed by filtration and dried. Evaporation of the filtrate gave

Table III. Synthetic Data[a] and Physical Constants

no.	formula	anal.	mp, °C
2	$C_{10}H_{14}N_4O_2$	C, H, N	138
3	$C_{10}H_{12}N_4O_2$	C, H, N	143
4	$C_{10}H_{10}N_4O_2$	C, H, N	207
5	$C_{10}H_{14}N_4O_2$	C, H, N	100
6	$C_{11}H_{16}N_4O_2$	C, H, N	99
7	$C_{10}H_{14}N_4O_2$	C, H, N	100
8	$C_{10}H_{12}N_4O_2$	C, H, N	103
9	$C_{10}H_{10}N_4O_2$	C, H, N	222
12	$C_{11}H_{14}N_4O_4$	C, H, N	105
13	$C_{14}H_{14}N_4O_2$	C, H, N	157
14	$C_{12}N_{16}N_4O_2$	C, H, N	116
15	$C_{12}H_{14}N_4O_2$	C, H, N	105
16	$C_{13}H_{20}N_4O_2$	C, H, N	102
17	$C_{13}H_{18}N_4O_2$	C, H, N	72
18	$C_{13}H_{16}N_4O_2$	C, H, N	118
20	$C_{14}H_{22}N_4O_2$	H, N, C[b]	59
21	$C_{14}H_{20}N_4O_2$	C, H, N	61
22	$C_{14}H_{18}N_4O_2 \cdot {}^1/_2H_2O$	C, H, N	81
23	$C_{18}H_{22}N_4O_2$	C, H, N	98
32	$C_{11}H_{12}N_4O_2$	C, H, N	158

[a] See Table IV for alkylation conditions and Table V for hydrogenation conditions. [b] C: calcd, 60.43; found, 59.92.

(6) Garst, J. E.; Kramer, G. L.; Wu, Y. J.; Wells, J. N. *J. Med. Chem.* **1976**, *19*, 499.

Table IV. Alkylation of Xanthines

no.	xanthine (mmol)	alkyl halide (mmol)	time, h	isolation method	recryst solvent	yield, %
8	theophylline (10)	allyl bromide (10/15)	4	B	Me_2CO/H_2O	76
9	theophylline (4.5)	propargyl bromide (45)	24	A	$CHCl_3$/MeOH	90
13	theophylline (22.5)	benzyl bromide (30)	12	A	DMF/H_2O	80
6	3-isobutyl-1-methyl- (2.3)	methyl iodide (4.2)	3	B	DMF/H_2O	78
17	3-isobutyl-1-methyl- (4.5)	allyl bromide (5)	4	A	$EtOH/H_2O$	72
18	isobutyl-1-methyl- (4.5)	propargyl bromide (45)	24	B	$MeOH/H_2O$	70
14	1,3-dipropyl- (3.1)	methyl iodide (6.2)	3	B	DMF/Me_3CO	67
21	1,3-dipropyl- (4.2)	allyl bromide (5.2)	4	A	$EtOH/H_2O$	55
22	1,3-dipropyl- (4.5)	propargyl bromide (45)	24	B	$EtOH/H_2O$	71
23	1,3-dipropyl- (2.4)	benzyl bromide (3)	12	A	DMF/H_2O	84
15	1,3-diallyl- (2.4)	methyl iodide (3)	3	B	DMF/H_2O	68
5	3-propyl- (2)	methyl iodide (5)	4	B	DMF/H_2O	79
3	3,7-dimethyl (20)	allyl bromide (40)	22	C	DMF/H_2O	74
4	3,7-dimethyl (20)	propargyl bromide (40)	72	D	DMF/MeOH	71

Table V. Hydrogenation of Xanthines

no.	xanthine (mmol)	solvent system (mL)	recryst solvent	yield, %
2	3,7-dimethyl-1-allyl- (6.6)	DMF–EtOH (50–100)	DMF/H_2O	85
7	7-allyl-1,3-dimethyl- (1.2)	DMF (50)	$CHCl_3/Me_2CO$	85
16	3-isobutyl-1-methyl-7-propargyl- (1.5)	EtOH (100)	$EtOH/H_2O$	83
20	1,3-dipropyl-7-propargyl- (2)	EtOH (100)	$EtOH/H_2O$	58

another crop of crystals, which were removed by filtration with MeOH. The product was purified by recrystallization with the solvent indicated in Table IV.

Hydrogenation of Xanthines. The following is a typical procedure (see Table IV for conditions). A mixture of xanthine, solvent, and 10% Pd on C was hydrogenated at 40 psi for 20 min. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. H_2O was added and the precipitate was removed by filtration and dried. An analytical sample was obtained by recrystallization with the solvent indicated in Table V.

7-(β-Acetoxyethyl)theophylline (12). A mixture of 1.2 g (0.0054 mol) of 7-(β-hydroxyethyl)theophylline, 0.0075 g sodium acetate, and 3.3 mL of acetic anhydride was refluxed for 4 h. The reaction mixture was allowed to cool and H_2O was added to hydrolyze the acetic anhydride. The aqueous solution was extracted with several 25-mL portions of EtOAc. The combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to give a white solid, which was washed several times with H_2O, removed by filtration, and dried to afford 1.1 g (77%) of 7-(β-acetoxyethyl)theophylline; mp 105 °C. Anal. ($C_{11}H_{14}N_4O_4$) C, H, N.

1,3-Diallylxanthine (32). The procedure is a modification of that described by Kramer et al.[7] for the preparation of 1,3-dipropylxanthines and other 1,3-dialkylxanthines. To a stirred solution of 4.5 g (0.01 mol) of 1,3-diallyl-6-aminouracil in 80 mL of AcOH–MeOH (2:3) was added dropwise 3.1 g of $NaNO_2$ in 15 mL of H_2O. HCl was added to keep the solution slightly acidic. The mixture was stirred for an additional 15 min and cooled in ice. The purple precipitate was filtered, washed several times with cold water, and dried to yield 3.8 g (81%) of 1,3-diallyl-6-amino-5-nitrosouracil.

A small portion of 3.8 g (0.0161 mol) of 1,3-diallyl-6-amino-5-nitrosouracil was suspended in 10 mL of H_2O made basic with 50% NH_4OH. An aqueous solution of $Na_2S_2O_4$ was added dropwise until the purple color faded. Another small portion of uracil was added to the solution, which was made alkaline and treated with aqueous $Na_2S_2O_4$ until the color faded. This process was repeated until all the nitroso compound was reduced. The clear aqueous solution was acidified with HCl and extracted with several portions of EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to afford 2.5 g (70%) of 1,3-diallyl-5,6-diaminouracil.

A solution of 2.5 g (0.0113 mol) of 1,3-diallyl-5,6-diaminouracil in 50 mL HCOOH was refluxed for 1 h. Excess HCOOH was evaporated in vacuo to give a white solid, which was recrystallized from Me_2CO to yield 2.16 g (76%) of 1,3-diallyl-6-amino-5-formamidouracil.

A mixture of 2.16 g (0.0086 mol) of 1,3-diallyl-6-amino-5-formamidouracil and 150 mL of 10% NaOH was refluxed for 30 min. The clear aqueous solution was filtered, cooled, and acidified with concentrated HCl. The colorless solution was extracted with several portions of EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to give a white solid. Recrystallization form DMF/MeOH afforded 1.3 g (65%) of 1,3-diallylxanthine: mp 158 °C. Anal. ($C_{11}H_{12}N_4O_2$) C, H, N.

Biochemical Assay. Inhibition of binding of 1 nM N^6-[^{3}H]cyclohexyladenosine to A_1-adenosine receptors in rat cerebral cortical membranes was assayed as described.[2] Inhibition of binding by a range of concentrations of xanthine was assessed in triplicate in at least two separate experiments. Inhibition of 2-chloroadenosine-elicited accumulation of [^{3}H]cyclic AMP accumulation in [^{3}H]adenine-labeled guinea pig cerebral cortical slices was assayed as described in the presence of 10 μg/mL adenosine deaminase and 30 μM 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone (rolipram, ZK 62711).[2,3] Inhibition of the response to 15 μM 2-chloroadenosine by a range of concentrations of each xanthine was assessed in triplicate in at least two experiments. K_i values were calculated as described.[2]

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