g, 0.062 mol) in 200 mL of tetrahydrofuran was added dropwise over 30 min 43.6 mL of 1.6 M *n*-butyllithium (0.070 mol) in hexane under a nitrogen atmosphere. Following completion of the addition, the solution was stirred for 10 min at 0 °C and then cooled to −30 °C. The cold solution next was added via cannulation over a 20-min period to a stirred solution of 1-bromo-4-chlorobutane (36.0 g, 0.21 mol) in 130 mL of ether chilled to −50 °C. Following completion of the addition, the reaction mixture was warmed to −20 °C and quenched with 150 mL of saturated sodium chloride solution chilled to 0 °C.

During the workup the various extracts were kept as cool as possible. The organic layer was separated, washed with water, and the desired product was extracted therefrom with three 400-mL portions of 1 N hydrochloric acid. The aqueous acidic layer was washed with diethyl ether and the ether extracts were discarded. The acidic aqueous solution was then made alkaline by the dropwise addition of 50% aqueous sodium hydroxide. The resulting alkaline solution was extracted several times with diethyl ether, and the ethereal extracts were combined, washed with water, and dried over K_2CO_3. Evaporation of the solvent under reduced pressure at 10 °C afforded the chloro enamine **12b** as an oil which was dissolved in 1100 mL of acetonitrile containing 23 g (0.15 mol) of sodium iodide and 17 g of K_2CO_3 (0.12 mol). The reaction mixture was heated at reflux temperature with stirring under nitrogen for 20 h. The reaction mixture was filtered, and the solvent was removed by evaporation under reduced pressure. The crude product thus formed was dissolved in a mixture of 480 mL of 1 N sodium hydroxide and 1000 mL of diethyl ether, and the mixture was stirred vigorously for 45 min. The ethereal layer then was separated, washed with saturated aqueous sodium chloride, and dried over K_2CO_3. Removal of the solvent by evaporation under reduced pressure afforded the product as an oil, which, upon bulb-to-bulb distillation, provided 12.0 g of **13b** (71%). The perchlorate salt was prepared from the free base and the product obtained crystallized from ethanol/isopropyl ether (1:1): mp 152–153 °C. Anal. ($C_{18}H_{26}NO_5Cl$) C, H, N.

2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (14b). A solution of **13b** (10.5 g, 0.039 mol) in 138 mL of ethanol containing 1.1 g of platinum oxide was stirred at room temperature for 16 h under a hydrogen atmosphere of 60 psi. The hydrogenation mixture was filtered to remove the catalyst and the filtrate evaporated to dryness and bulb-to-bulb distilled at 180 °C (0.1 mm) to yield **14b**, 9.9 g (93%). Anal. ($C_{18}H_{27}NO$) C, H, N. The hydrochloride salt was prepared from the free base and recrystallized from ethyl acetate: mp 142–144 °C. Anal. ($C_{18}H_{28}NOCl$) C, H, N.

4a-(3-Methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (16). A solution of **14b** (5.5 g, 0.02 mol) in 50 mL of 1,2-dichloroethane was added dropwise to vinylchloroformate (9 mL, 0.04 mol) and 8.6 g (0.06 mol) of proton sponge in 150 mL of 1,2-dichloroethane at 0 °C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature then refluxed for 2 h. The mixture was filtered, and the solvent was removed by evaporation under vacuum. The residue was taken up in ether and washed with cold 1 N HCl and water. The ether layer was dried over potassium carbonate, filtered, and evaporated to dryness. The resulting residue (4.9 g), comprising the vinyl carbamate, was refluxed for 1 h in 200 mL of ethanol and 200 mL of ethanol saturated with gaseous hydrochloric acid. The mixture was evaporated to dryness and the residue partitioned between ether and 1 N sodium hydroxide. The ether layer was washed with water, dried over K_2CO_3, and evaporated to dryness. The resulting oil was purified by bulb-to-bulb distillation at 190 °C (0.1 mm) to yield 4.3 g (88%). Anal. ($C_{16}H_{23}NO$) C, H, N. The hydrochloride salt was prepared from the free base and recrystallized from isopropyl ether/ethanol (1:1): mp 181–183 °C. Anal. ($C_{16}H_{24}NOCl$) C, H, N.

Registry No. **2**, 73224-22-3; **10a**, 73224-20-1; **10b**, 102573-71-7; **11**, 102538-16-9; **12b**, 102538-17-0; **13b**, 102538-18-1; **13b**·perchlorate, 102538-19-2; **14b**, 102538-20-5; **14b**·hydrochloride, 102538-21-6; **15**, 102538-22-7; **16**, 102538-23-8; **16**·hydrochloride, 102538-24-9; *m*-bromoanisole, 2398-37-0; 1-ethyl-4-piperidone, 3612-18-8; 1-methyl-4-piperidone, 1445-73-4; 1-bromo-4-chlorobutane, 6940-78-9; vinyl chloroformate, 5130-24-5.

Analogues of 1,3-Dipropyl-8-phenylxanthine: Enhancement of Selectivity at A_1-Adenosine Receptors by Aryl Substituents

J. W. Daly,* W. L. Padgett, and M. T. Shamim

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, Laboratory of Bioorganic Chemistry, Bethesda, Maryland 20205. *Received September 13, 1985*

The effect of a variety of aryl substituents on the potency and selectivity of 19 analogues of 1,3-dipropyl-8-phenylxanthine as antagonists at A_1- and A_2-adenosine receptors in brain tissue was determined. The 4-sulfamoylphenyl and 4-carbamoylphenyl analogues are potent and somewhat selective for the A_1 receptor. None of the dihydroxyphenyl analogues are remarkably potent, but all are selective for the A_1 receptor. 1,3-Dipropyl-8-(2-hydroxy-4-methoxyphenyl)xanthine is the most selective A_1 antagonist of the analogues with a A_1/A_2 potency ratio of about 90.

8-Phenyltheophylline is the parent member of a variety of potent adenosine receptor antagonists. Originally discovered as a result of screening xanthines and other heterocycles as adenosine antagonists in fibroblasts,[1] 8-phenyltheophylline has been employed as a potent antagonist of adenosine-elicited responses in many biochemical[1-10] and physiological[11-22] studies. Three considerations have prompted the preparation and investigation of further 8-phenylxanthines as adenosine antagonists. These are (i)

(1) Bruns, R. F. *Biochem. Pharmacol.* **1981**, *30*, 325.
(2) Smellie, F. W.; Davis, C. W.; Daly, J. W.; Wells, J. N. *Life Sci.* **1979**, *24*, 2475.
(3) Bruns, R. F.; Daly, J. W.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5547.
(4) Wu, P. H.; Phillis, J. W.; Nye, M. J. *Life Sci.* **1982**, *31*, 3857.
(5) Fredholm, B. B.; Persson, C. G. A. *Eur. J. Pharmacol.* **1982**, *8*, 673.
(6) Bruns, R. F.; Daly, J. W.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2077.
(7) Daly, J. W.; Padgett, W.; Shamim, M. T.; Butts-Lamb, P.; Waters, J. *J. Med. Chem.* **1985**, *28*, 487.
(8) Fredholm, B. B.; Jonzon, B.; Lindren, E.; Lindstrom, K. *J. Neurochem.* **1982**, *39*, 165.
(9) Ukena, D.; Furler, R.; Lohse, M. J.; Engle, G.; Schwabe, U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *326*, 233.
(10) Munshi, R.; Hansske, F.; Baer, H. P. *Eur. J. Pharmacol.* **1985**, *111*, 107.
(11) Griffith, S. G.; Meghji, P.; Moody, C. J.; Burnstock, G. *Eur. J. Pharmacol.* **1981**, *75*, 61.
(12) Hillyard, P. A.; Nials, A. T.; Skidmore, I. F.; Vardey, C. J. *Br. J. Pharmacol.* **1984**, *83*, 337.
(13) Burnstock, G.; Hills, J. M.; Hoyle, C. H. V. *Br. J. Pharmacol.* **1984**, *81*, 533.
(14) Corradetti, R.; Moroni, F.; Passani, M. B.; Pepeu, G. *Eur. J. Pharmacol.* **1984**, *103*, 177.

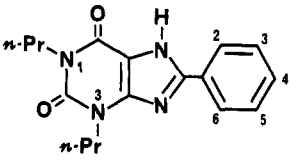
Table I. Effect of Aryl Substituents on the Activity of 1,3-Dipropyl-8-phenylxanthines at A_1- and A_2-Adenosine Receptors of the Central Nervous System

no.	aryl substituent(s)	K_i,[a] nM		A_2/A_1
		A_1 receptor	A_2 receptor	
1	none[b]	13 ± 3	300 ± 80	23
2	4-hydroxy[b]	2.9 ± 0.8	50 ± 10	17
3	4-methoxy	14 ± 8	95 ± 7	7
4	4-acetoxy	8.0 ± 1.0	12 ± 2	1.5
5	4-amino	27 ± 2	28 ± 3	1.0
6	4-acetamido	25 ± 1	55 ± 8	2.3
7	4-dimethylamino	45 ± 7	100 ± 23	2.2
8	4-sulfo[b]	210 ± 50	710 ± 230	3.4
9	4-sulfamoyl	8.5 ± 1.1	115 ± 11	15
10	4-carboxy[b]	170 ± 30	110 ± 20	0.6
11	4-carbamoyl	7 ± 1	72 ± 11	10
12	2-amino-4-chloro[b]	2.5 ± 1.0	1000 ± 30	400
13	2,4-diamino[b]	4.6 ± 0.8	13 ± 6	2.8
14	2,3-dihydroxy	33 ± 3	210 ± 40	6.4
15	2,4-dihydroxy	15 ± 4	400 ± 80	27
16	2,5-dihydroxy	360 ± 90	3500 ± 350	9.7
17	2-hydroxy-4-methoxy	11 ± 4	980 ± 10	89
18	2-methoxy-4-chloro	420 ± 150	>3,000	>7
19	2,6-difluoro	51 ± 20	290 ± 43	5.9
20	3-chloro-4-hydroxy	36 ± 9	140 ± 20	3.9

[a] IC_{50} values were obtained as described (see Experimental Section) and K_i values calculated in a standard manner.[7] Values are means ± SEM for two to four separate determinations, each determination being done in triplicate. [b] Values from ref 7.

potency (see ref 6), (ii) selectivity for the two subclasses of adenosine receptors, the so-called A_1 and A_2 receptors (see ref 7), and (iii) solubility (see ref 7, 23). The last factor is important to pharmacokinetics and drug availability for in vivo usage.

The size of the alkyl substituents at the 1- and 3-position markedly affects potency with 1,3-dipropyl-8-phenyltheophylline (1) being many fold more potent than 8-phenyltheophylline at adenosine receptors of the central nervous system.[6] Substituents on the 8-phenyl ring can further increase potency[1,3-7] and in some cases can enhance selectivity for the A_1 receptor.[6,7] Although incorporation of an 8-phenyl group markedly increases the activity of theophylline and other 1,3-dialkylxanthines as adenosine antagonists, this moiety also confers extremely limited water solubility. The low solubility appears likely to limit the potential usefulness of 8-phenylxanthines as in vivo research tools and in possible application as therapeutic agents. Other xanthines (caffeine, theophylline) have antiasthmatic, diuretic, respiratory stimulant, cardiac stimulant, central stimulant, and analgesic adjuvant activities (see ref 7, 24 and references therein). The most selective and potent A_1-adenosine receptor antagonist yet reported is 8-(2-amino-4-chlorophenyl)-1,3-dipropylxanthine,[6,7] which has a water solubility of <2 μM. This may limit its application due to irreversible effects and binding to proteins (see ref 14). Polar substituents such as a *p*-sulfo or *p*-carboxy group on the 8-phenyl ring can increase water solubility markedly but also reduce the selectivity for the A_1 receptor.[6] The present study has explored the effect of other polar aryl substituents and combination of aryl substituents on the potency and selectivity of 1,3-dipropyl-8-phenylxanthine (1) as an adenosine receptor antagonist.



1

Results and Discussion

1,3-Dipropyl-8-(4-hydroxyphenyl)xanthine (compound 2) has been previously reported to be a potent adenosine antagonist with modest selectivity (17-fold) toward the A_1 receptor.[7] The potencies of 2 at adenosine receptors are greater than those of the parent 1,3-dipropyl-8-phenylxanthine (compound 1), while the selectivity is similar. The 4-methoxy analogue (compound 3) is only somewhat less potent and selective than the phenolic parent (compound 2). This suggested the use of a 4-carboxymethyl ether of compound 2 as the basis for a "functionalized congener" approach to adenosine antagonists: Certain amide derivatives developed in this approach proved both potent and selective for the A_1 receptor.[23] The 4-acetoxy analogue (compound 4) had somewhat reduced potency compared to the phenolic parent and *no* selectivity.

The 4-amino analogue (compound 5) and the 4-acetamido analogue (compound 6) are not particularly potent or selective. The dimethylamino analogue (compound 7) is even less potent. Efforts to obtain pure samples of the methiodide of compound 7 have not been successful. The 4-amino series of analogues, thus, does not appear particularly promising for further development.

The highly water soluble 8-(*p*-sulfophenyl)theophylline and 1,3-dipropyl-8-(4-sulfophenyl)xanthine (compound 8) have proven useful research tools that block both A_1- and A_2-adenosine receptors (see ref 7, 24 and references therein). Such ionized sulfo analogues do not penetrate into cells,[25] thus eliminating any side effects on intracel-

(15) Challis, R. A. J.; Budohoski, L.; McManus, B.; Newholme, E. A. *Biochem. J.* **1984**, *221*, 915.
(16) Collis, M. G.; Palmer, D. B.; Saville, V. L. J. *Pharm. Pharmcol.* **1985**, *37*, 278.
(17) Burnstock, G.; Hoyle, C. H. V. *Br. J. Pharmacol.* **1985**, *85*, 291.
(18) Sugio, K.; Daly, J. W. *Life Sci.* **1984**, *35*, 1575.
(19) Edvinsson, L.; Fredholm, B. B. *Br. J. Pharmacol.* **1983**, *80*, 631.
(20) Clanachan, A. S. *Can. J. Physiol. Pharmacol.* **1981**, *59*, 603.
(21) Budohoski, L.; Challis, R. A. J.; Cooney, G. L.; McManus, B.; Newsholme, E. R. *Biochem. J.* **1984**, *224*, 327.
(22) Kennedy, C.; Burnstock, G. Eur. *J. Pharmacol.* **1985**, *111*, 49.
(23) Jacobson, K. A.; Kirk, K. L.; Padgett, W. L.; Daly, J. W. *J. Med. Chem.* **1985**, *28*, 1334.
(24) Daly, J. W. *J. Med. Chem.* **1982**, *25*, 1197.

lular enzymes including phosphodiesterases. The 4-sulfamoyl analogue (compound **9**) is much more potent than the *p*-sulfo parent (compound **8**) and exhibits selectivity for the A_1 receptor. This suggests the preparation of various N-substituted 4-sulfamoyl analogues for investigation as potent and possibly selective adenosine antagonists. Recently, analogues of this structural type have been reported to be potent antagonists of brain A_1 receptors.[26] Disubstitution at the sulfonamido nitrogen is poorly tolerated and 8-[4-(N,N-dipropylsulfamoyl)-phenyl]theophylline is inactive with a K_i value of $\gg$55 000 nM at both the A_1 and the A_2 receptor (data not shown).

The 4-carboxy analogue (compound **10**) is relatively water soluble but was reported to be not particularly potent as an adenosine antagonist and exhibited no significant selectivity.[7] However, as in the case of the 4-sulfamoyl analogue, removal of the negative charge of the carboxylate in the 4-carbamoyl analogue (compound **11**) results in a marked increase in potency at the A_1 receptor to afford a somewhat selective A_1-receptor antagonist. This suggests the preparation of various N-substituted 4-carbamoyl analogues for investigation as potent and possibly selective adenosine antagonists.

A potent and selective A_1-adenosine receptor antagonists is 8-(2-amino-4-chlorophenyl)-1,3-dipropylxanthine (compound **12**).[6,7] However, its limited water solubility and difficulties in preparation prompted an examination of other disubstituted aryl analogues. Recently, **12** has been reported to be a noncompetitive antagonist of A_1-adenosine receptor mediated responses.[13] The 2,4-diamino analogue (compound **13**) is not selective for the A_1 receptor. This is perhaps not unexpected since the 4-amino (compound **5**), 4-acetamido (compound **6**), and 4-dimethylamino (compound **7**) analogues are not selective or only slightly selective.

Three of the possible dihydroxy aryl analogues were prepared. The 2,3-dihydroxy analogue (compound **14**) is not particularly potent or selective, while the 2,4-dihydroxy analogue (compound **15**) has a 27-fold selectivity for the A_1 receptor. The 2,5-dihydroxy analogue (compound **16**) is relatively weak at both receptors. A 2-hydroxy-4-methoxy analogue (compound **17**) is relatively potent and selective (90-fold) for the A_1 receptor. This suggests the possible application of the "functionalized congener" approach[23] to development of a series of congeners from a 2-hydroxy-4-carboxymethoxy analogue, as has been previously reported for the 4-carboxymethoxy series.[23] Such an approach is in progress.

The remaining disubstituted analogues (compounds **17–19**) are not particularly potent or selective. The results with the analogue containing a 2-methoxy (compound **17**) substituent suggest that a small polar substituent (OH, NH_2) at this position is required in combination with a para substituent for potency and selectivity as antagonists toward the A_1 receptor. The 2,6-difluoro analogue (compound **18**) shows reduced activity at the A_1 receptor compared to the parent 1,3-dipropyl-8-phenylxanthine, while activity at the A_2 receptor is unchanged. The 3-chloro substituent of compound **19** markedly reduces activity particularly at the A_1 receptor compared to 1,3-dipropyl-8-(4-hydroxyphenyl)xanthine (compound **2**). Presumably, a 3-iodo will have a similar or greater effect precluding use of an ^{125}I derivative of compound **2** for radioligand binding. The present results serve to delineate structural features and strategies that may lead to development of potent and selective adenosine antagonists.

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. The synthesis of 1,3-dipropyl-8-phenylxanthine (**1**), 1,3-dipropyl-8-(4-hydroxyphenyl)xanthine (**2**), 1,3-dipropyl-8-(4-sulfophenyl)xanthine (**8**), and 8-(4-carboxyphenyl)-1,3-dipropylxanthine (**10**), and 1,3-dipropyl-8-(2,4-diaminophenyl)xanthine (**13**) have been described.[6,7] 8-(2-Amino-4-chlorophenyl)-1,3-dipropylxanthine (**12**) was from Research Biochemical Inc. (Wayland, MA).

1,3-Dipropyl-8-(4-methoxyphenyl)xanthine (3). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 100 mL of MeOH–HOAc (5:1) was added dropwise 0.86 mL (0.007 mol) of *p*-anisaldehyde in 20 mL of MeOH. The reaction mixture was stirred for 45 min and allowed to stand overnight. Solvent was removed in vacuo to give a white precipitate, which was removed by filtration and washed with acetone. Recrystallization with DMF/acetone afforded 0.9 g (53%) of 1,3-dipropyl-8-(4-methoxyphenyl)xanthine. Oxidative cyclization had occurred spontaneously; mp 288 °C. Anal. ($C_{18}H_{22}N_4O_3$) C, H, N.

1,3-Dipropyl-8-(*p*-acetoxyphenyl)xanthine (4). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–AcOH (5:1) was added dropwise 0.90 g (0.0055 mol) of 4-acetoxybenzaldehyde in 25 mL of MeOH. The reaction mixture was stirred at room temperature for 30 min and allowed to stand overnight. Solvent was removed in vacuo and MeOH added to precipitate the product, which was removed by filtration, washed with acetone, and dried. Recrystallization with DMF/acetone afforded 0.72 g (39%) of 1,3-dipropyl-8-(*p*-acetoxyphenyl)xanthine. Oxidative cyclization had occurred spontaneously; mp >300 °C. Anal. ($C_{19}H_{22}N_4O_4$) C, H, N.

1,3-Dipropyl-8-(*p*-aminophenyl)xanthine (5). To a stirred solution of 2.74 g (0.02 mol) of *p*-aminobenzoic acid in 150 mL of EtOAc was added dropwise 8.47 mL (0.06 mol) of trifluoroacetic anhydride in 20 mL of EtOAc, and the mixture was then stirred for 4 h. The white precipitate was filtered and dried to give 4.5 g (97%) of *p*-[(trifluoroacetyl)amino]benzoic acid. To a mixture of 1.4 g (0.0064 mol) of *p*-[(trifluoroacetyl)amino]benzoic acid in 8 mL of DMF and 1.0 mL (0.0064 mol) of diisopropylcarbodiimide was added dropwise 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 80 mL of MeOH. The reaction mixture was then stirred for 45 min and allowed to stand overnight. Removal of solvent in vacuo gave a yellowish precipitate, which was removed by filtration and dried. This crude benzamido product was refluxed for 15 min in 40 mL of DMF and 50 mL of 10% NaOH. The precipitate obtained on cooling was removed by filtration and dried. Recrystallization with DMF/MeOH gave 1.04 g (64%) of 1,3-dipropyl-8-(*p*-aminophenyl)xanthine; mp >300 °C. Anal. ($C_{17}H_{21}N_5O_2$) C, H, N.

1,3-Dipropyl-8-(4-acetamidophenyl)xanthine (6). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–AcOH (5:1) was slowly added to 0.90 g (0.0055 mol) of 4-acetamidobenzaldehyde in 25 mL of MeOH. The reaction mixture was stirred at room temperature for 30 min and allowed to stand overnight. The solvent was removed in vacuo, and the resulting solid was removed by filtration and dried to give 0.3 g (53%) of crude 1,3-dipropyl-5-[(4-acetamidobenzylidene)-amino]uracil. The crude product was refluxed with 10 mL of $SOCl_2$ for 15 min to affect oxidative cyclization, and the excess $SOCl_2$ was removed in vacuo. The residue was neutralized with 50% NH_4OH. Solids were removed by filtration and dried. Recrystallization with DMF–MeOH yielded 0.22 g (74%) of 1,3-dipropyl-8-(4-acetamidophenyl)xanthine: mp >300 °C. Anal. ($C_{19}H_{23}N_5O_3 \cdot {}^1/_2H_2O$) C, H, N.

1,3-Dipropyl-8-[4-(dimethylamino)phenyl]xanthine (7). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–AcOH (5:1) was added dropwise 0.82 g (0.0055 mol) of *p*-(dimethylamino)benzaldehyde in 25 mL of MeOH. The reaction mixture was stirred for 30 min and allowed to stand overnight. After removal of solvent in vacuo, the residue was washed with acetone. Recrystallization with DMF–acetone af-

(25) Heller, L. J.; Olsson, R. A. *Am. J. Physiol.* **1985**, *248*, H907.
(26) Hamilton, H. W.; Ortwine, D. F.; Worth, D. F.; Badger, E. W.; Bristol, J. A.; Bruns, R. F.; Haleen, S. J.; Steffen, R. P. *J. Med. Chem.* **1985**, *28*, 1071.

forded 1.24 g (70%) of 1,3-dipropyl-8-[4(dimethylamino)-phenyl]xanthine. Oxidative cyclization had occurred spontaneously; mp >300 °C. Anal. ($C_{19}H_{25}N_5O_2$) C, H, N.

1,3-Dipropyl-8-(*p*-sulfamoylphenyl)xanthine (9). To a solution of 3.01 g (0.015 mol) of *p*-sulfamoylbenzoic acid in 50 mL of DMF and 20 mL of MeOH was added 2.35 mL (0.015 mol) of diisopropylcarbodiimide followed by 2.26 g (0.01 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH. The reaction mixture was refluxed for 30 min, and the solvent was removed in vacuo. Et_2O was added and the precipitate was removed by filtration and dried to give 1.67 g (40%) of crude 1,3-dipropyl-6-amino-5-(*p*-sulfamoylbenzamido)uracil. The crude product 1.6 g (0.0038 mol) was dissolved in 100 mL of 10% NaOH and refluxed for 15 min. The reaction mixture was allowed to cool and neutralized with concentrated HCl to yield a white precipitate, which was removed by filtration, dried, and recrystallized with DMF/MeOH to afford 1.10 g (74%) of 1,3-dipropyl-8-(*p*-sulfamoylphenyl)xanthine: mp >300 °C. Anal. ($C_{17}H_{21}N_5O_4S$) C, H, N.

1,3-Dipropyl-8-(*p*-carbamoylphenyl)xanthine (11). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–HOAc (5:1) was added dropwise 0.83 g (0.0055 mol) of *p*-carboxybenzaldehyde in 40 mL of MeOH, followed by stirring for another 15 min. The precipitate was removed by filtration, washed with MeOH, and dried to give 1.44 g (80%) of crude 1,3-dipropyl-6-amino-5-[(*p*-carboxybenzylidene)amino]-uracil. A mixture of 1.07 g (0.003 mol) of crude aminouracil and 5 mL of $SOCl_2$ was refluxed for 15 min to affect oxidative cyclization. The excess $SOCl_2$ was removed in vacuo and the residue neutralized with 50% NH_4OH. The white precipitate was filtered and dried to yield 0.84 g (79%) of 1,3-dipropyl-8-(*p*-carbamoylphenyl)xanthine. An analytical sample was obtained by recrystallization from DMF/MeOH: mp >300 °C. Anal. ($C_{18}H_{21}NO_3 \cdot {}^1/_2H_2O$) C, H, N.

1,3-Dipropyl-8-(2,3-dihydroxyphenyl)xanthine (14). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–HOAc (5:1) was added dropwise 0.76 g (0.0055 mol) of 2,3-dihydroxybenzaldehyde in 20 mL of MeOH. The reaction mixture was stirred for 30 min and allowed to stand overnight. The yellow precipitate obtained on evaporation of solvent in vacuo was washed with MeOH, filtered, and dried to give 1.2 g (69.4%) of crude 1,3-dipropyl-6-amino-5[(2,3-dihydroxybenzylidene)amino]uracil. A solution of 1.15 g (0.033 mol) of crude amino uracil in 10 mL of $SOCl_2$ was refluxed for 15 min to affect cyclization. The excess $SOCl_2$ was removed in vacuo, and the residue was neutralized with 50% NH_4OH. The precipitate was removed by filtration and recrystallized from DMF/MeOH to yield 0.91 g (80%) of 1,3-dipropyl-8-(2,3-dihydroxyphenyl)xanthine: mp 296 °C dec. Anal. ($C_{17}H_{20}N_4O_4$) C, H, N.

1,3-Dipropyl-8-(2,4-dihydroxyphenyl)xanthine (15). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–HOAc (5:1) was added dropwise 0.76 g (0.0055 mol) of 2,4-dihydroxybenzaldehyde in 40 mL of MeOH. The reaction mixture was stirred for 30 min and allowed to stand overnight. The solvent was removed in vacuo, and the residue was removed by filtration and washed repeatedly with MeOH. Recrystallization from DMF/MeOH gave 1.25 g (72%) of 1,3-dipropyl-8-(2,4-dihydroxyphenyl)xanthine. Oxidative cyclization had occurred spontaneously. mp >300 °C. Anal. ($C_{17}H_{20}N_4O_4$) C, H, N.

1,3-Dipropyl-8-(2,5-dihydroxyphenyl)xanthine (16). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–HOAc (5:1) was added 0.76 g (0.0055 mol) of 2,5-dihydroxybenzaldehyde in 30 mL of MeOH. The reaction mixture was stirred for 30 min and allowed to stand overnight. The volume of solvent was reduced in vacuo and Et_2O added. The precipitate was washed with MeOH and dried to yield 1.71 g (100%) of crude 1,3-dipropyl-6-amino-5-[(2,5-dihydroxybenzylidene)amino]uracil. A mixture of 1.17 g (0.0049 mol) of the crude aminouracil and 8.5 mL of $SOCl_2$ was refluxed for 15 min to affect cyclization. After evaporation of solvent in vacuo, the residue was triturated with 50% NH_4OH, filtered, and recrystallized with DMF/MeOH to yield 1.68 g (41%) of 1,3-dipropyl-8-(2,5-dihydroxyphenyl)xanthine: mp >300 °C. Anal. ($C_{17}H_{20}N_4O_4$) C, H, N.

1,3-Dipropyl-8-(2-hydroxy-4-methoxyphenyl)xanthine (17). To a solution of 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 50 mL of MeOH–HOAc (5:1) was added dropwise 0.84 g (0.0055 mol) of 2-hydroxy-4-methoxybenzaldehyde in 40 mL of MeOH. The reaction mixture was stirred for 30 min and allowed to stand overnight. The solvent was removed in vacuo and acetone added to yield a precipitate, which was washed with acetone and crystallized from MeOH–acetone to give 0.85 g (48%) of 1,3-dipropyl-8-(2-hydroxy-4-methoxyphenyl)xanthine. Oxidative cyclization had occurred spontaneously; mp >300 °C. Anal. ($C_{18}H_{22}N_4O_4$) C, H, N.

1,3-Dipropyl-8-(2-methoxy-4-chlorophenyl)xanthine (18). To a solution of 1.03 g (0.0055 mol) of 2-methoxy-4-chlorobenzoic acid in 40 mL of MeOH was added dropwise 0.69 g (0.0055 mol) of diisopropylcarbodiimide in 10 mL of MeOH followed by 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 40 mL of MeOH. The reaction mixture was stirred for 1 h and solvent removed in vacuo to give a white solid, which was removed by filtration, washed with H_2O, and dried to give 1.74 g (88%) of crude 1,3-dipropyl-6-amino-5-(2-methoxy-4-chlorobenzamido)uracil. A mixture of 1.73 g (0.0044 mol) of the crude benzamidouracil in 25 mL of acetone and 100 mL of 10% NaOH was refluxed for 2 h. The solvent was removed in vacuo and the residue was dissolved in 50 mL of H_2O. The aqueous solution was acidified with concentrated HCl to give a white precipitate, which was removed by filtration, dried, and recrystallized from DMF/H_2O to afford 1.44 g (87%) of 1,3-dipropyl-8-(2-methoxy-4-chlorophenyl)xanthine: mp >300 °C. Anal. ($C_{18}H_{21}N_4O_3Cl \cdot H_2O$) C, H, N.

1,3-Dipropyl-8-(2,6-difluorophenyl)xanthine (19). To a solution of 0.87 g (0.0055 mol) of 2,6-difluorobenzoic acid in 10 mL of MeOH was added dropwise 0.86 mL (0.0055 mol) of diisopropylcarbodiimide in 10 mL of MeOH followed by 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 40 mL of MeOH. The reaction mixture was stirred for 1 h and solvent removed in vacuo. Et_2O was added and the precipitate was removed by filtration and dried to yield 1.8 g (98.4%) of crude 1,3-dipropyl-6-amino-5-(2,6-difluorobenzamido)uracil. A mixture of 1.5 g (0.0041 mol) of crude benzamidouracil in 40 mL of MeOH and 100 mL of 10% NaOH was refluxed for 45 min. The basic aqueous solution was allowed to cool and acidified with HCl to give a white precipitate, which was filtered and dried. The product was recrystallized from EtOH/CCl_4 to afford 1.3 g (91%) of 1,3-dipropyl-8-(2,6-difluorophenyl)xanthine: mp 184 °C. Anal. ($C_{17}H_{18}N_4O_2F_2$) C, H, N.

1,3-Dipropyl-8-(3-chloro-4-hydroxyphenyl)xanthine (20). To a solution of 1.18 g (0.0055 mol) of 3-chloro-4-acetoxybenzoic acid in 30 mL of MeOH and 20 mL of DMF was added dropwise 0.86 ml (0.0055 mol) of diisopropylcarbodiimide in 10 mL of MeOH followed by 1.13 g (0.005 mol) of 1,3-dipropyl-5,6-diaminouracil in 40 mL of MeOH. The reaction mixture was refluxed for 30 min and solvent removed in vacuo to yield crude 1,3-dipropyl-6-amino-5-(3-chloro-4-hydroxybenzamido)uracil. The crude benzamidouracil was refluxed in 80 mL of 10% NaOH for 30 min. The solution was cooled and acidified and concentrated HCl, and the white precipitate was removed by filtration, dried, and recrystallized with DMF/Et_2O to yield 0.92 g (51%) of 1,3-dipropyl-8-(3-chloro-4-hydroxyphenyl)xanthine: mp >300 °C. Anal. ($C_{17}H_{19}N_4O_3Cl$) 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.[7] 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 in [^{3}H]adenine-labeled guinea pig cerebral cortical slices was assayed as decribed in the presence of 10 μg/mL adenosine deaminase and 30 μM 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone (rolipram, ZK 62711).[7] 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.[7]

Acknowledgment. One of the authors (M.T.S.) was supported by a grant from the International Life Sciences Institute (Washington, DC). The technical assistance of

F. A. Brown Jr. is gratefully acknowledged.

Registry No. 3, 101126-73-2; 4, 102587-79-1; 5, 102587-80-4; 6, 102587-81-5; 7, 102587-82-6; 9, 102587-83-7; 11, 102587-84-8; 14, 102587-86-0; 15, 102587-87-1; 16, 102587-88-2; 17, 102613-60-5; 18, 102587-89-3; 19, 102587-90-6; 20, 102587-91-7; 1,3-dipropyl-5,6-diaminouracil, 81250-34-2; *p*-anisaldehyde, 123-11-5; 4-acetoxybenzaldehyde, 878-00-2; *p*-amino benzoic acid, 150-13-0; *p*-[(trifluoroacetyl)amino]benzoic acid, 404-26-2; 1,3-dipropyl-6-amino-5-(*p*-trifluoroacetylaminobenzamido) uracil, 102587-85-9; 4-acetamidobenzaldehyde, 122-85-0; 1,3-dipropyl-6-amino-5-[(4-acetamidobenzylidene)amino]uracil, 102587-92-8; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-sulfamoylbenzoic acid, 138-41-0; 1,3-dipropyl-6-amino-5-(*p*-sulfamoylbenzamido)uracil, 102613-61-6; *p*-carboxybenzaldehyde, 619-66-9; 1,3-dipropyl-6-amino-5-[(*p*-carboxybenzylidene)amino]uracil, 94781-77-8; 2,3-dihydroxybenzaldehyde, 24677-78-9; 1,3-dipropyl-6-amino-5-[(2,3-dihydroxybenzylidene)amino]uracil, 102587-93-9; 2,4-dihydroxybenzaldehyde, 95-01-2; 2,5-dihydroxybenzaldehyde, 1194-98-5; 1,3-dipropyl-6-amino-5-[(2,5-dihydroxybenzylidene)-amino]uracil, 102587-94-0; 2-hydroxy-4-methoxybenzaldehyde, 673-22-3; 1,3-dipropyl-6-amino-5-(2-methoxy-4-chlorobenzamido)uracil, 102587-95-1; 2,6-difluorobenzoic acid, 385-00-2; 1,3-dipropyl-6-amino-5-(2,6-difluorobenzamide)uracil, 102587-96-2; 3-chloro-4-acetoxybenzoic acid, 70679-89-9; 1,3-dipropyl-6-amino-5-(3-chloro-4-hydroxybenzamido)uracil, 102587-97-3; 2-methoxy-4-chlorobenzoic acid, 57479-70-6.

Synthesis and β-Adrenergic Receptor Blocking Potency of 1-(Substituted amino)-3-(4-indolyloxy)propan-2-ols

Shanaz M. Tejani-Butt* and David J. Brunswick

Department of Psychiatry, University of Pennsylvania School of Medicine and Neuropsychopharmacology Unit, Veterans Administration Medical Center, Philadelphia, Pennsylvania 19104. *Received February 5, 1985*

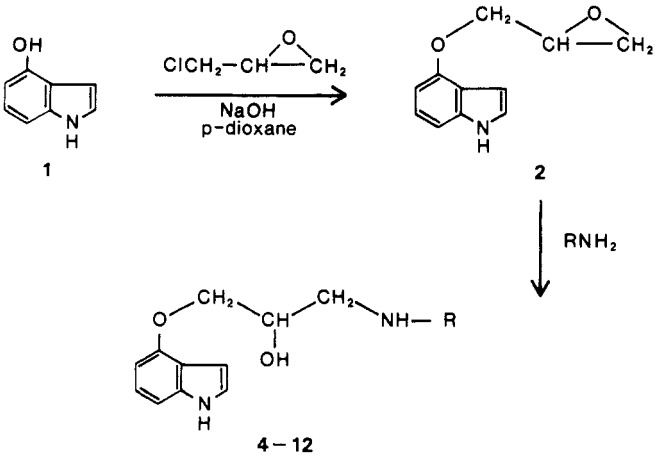
Although (−)-[^{125}I]iodopindolol (IPIN) can be used to label β-adrenergic receptors in the central nervous system in vivo, use of this ligand for receptor imaging studies in humans may be limited due to its relatively poor penetration into the brain. As a first step toward the development of radioligands for imaging studies, we report the synthesis and measurement of in vitro binding affinity to β-receptors of a series of 1-(substituted amino)-3-(4-indolyloxy)-propan-2-ol derivatives. The synthesized compounds vary widely in their lipophilicity as measured by their distribution coefficients between phosphate buffer and octanol at pH 7.4. The affinity of these compounds for β-receptors, as measured by their inhibition of binding of IPIN to rat cortical and cerebellar membranes in vitro, ranges from 2- to 100-fold less potent than pindolol; the most potent compounds have K_i values of 2–5 nM. The radiolabeled analogues of some of these compounds may prove useful for receptor imaging studies.

Considerable effort is being made in the development of techniques for the imaging of human brain receptors in vivo using single photon emission computed tomography (SPECT) and positron emission tomography (PET). A key step in the development of such techniques is the synthesis of suitable radioligands; measurements in humans are now being reported using for example (*R*)-3-quinuclidinyl-4-[^{123}I]iodobenzilate for muscarinic cholinergic receptors using SPECT[1] and 3-*N*-[^{11}C]methylspiperone for brain dopamine receptors using PET.[2]

We are engaged in a program to develop radioligands suitable for the measurement of β-adrenergic receptors in human brain using PET and SPECT. Central β-receptors have been implicated in the etiology and/or treatment of a number of psychiatric and neurologic disorders as well as in the mechanism of action of a number of drugs used in psychiatry.[3,4]

Recently, binding in vivo in the central nervous system (CNS) of rats of the β-adrenergic receptor radioligand (−)-[^{125}I]iodopindolol (IPIN), whose use was first described in vitro by Barovsky and Brooker,[5] was reported.[6,7]

Scheme I



However, IPIN itself does not appear to be a good ligand for use with imaging techniques in humans since its penetrability into the brain is limited.[7] Consequently, it seemed that derivatives of pindolol, particularly those that might have greater penetrability into the CNS, might be useful ligands for β-receptors in brain for use with PET or SPECT.

In this report, the synthesis of a series of derivatives of pindolol in which the group attached to the N-terminal end of the molecule is varied is described as well as their binding affinity to β-receptors in the CNS in vitro. It is hoped that by varying the nature of the N-terminal end of these molecules a compound would be found that has both high affinity for β-receptors and good penetration into the brain. Since lipophilicity is likely to be important in this regard, the distribution coefficient for each compound was also measured between phosphate buffer and octanol at pH 7.4.

(1) Eckelman, W. C.; Reba, R. C.; Rzeszotarski, W. J.; Gibson, R. E.; Hill, T.; Holman, L. B.; Budinger, T.; Conklin, J. J.; Eng. R.; Grissom, M. P. *Science Washington, D.C.* **1984**, *223*, 291.
(2) Wagner, H. N.; Burns, H. D.; Dannals, R. F.; Wong, D. F.; Langstrom, B.; Duelfer, T.; Frost, J. J.; Ravert, H. T.; Links, J. M.; Rosenbloom, S. B.; Lukas, S. E.; Kramer, A. V.; Kuhar, M. J. *Science Washington, D.C.* **1983**, *221*, 1264.
(3) Charney, D. S.; Menkes, D. B.; Heninger, G. R. *Arch. Gen. Psychiatry* **1981**, *38*, 1160.
(4) Middlemiss, D. N.; Buxton, D. A.; Greenwood, D. T. *Pharmacol. Ther.* **1981**, *12*, 419.
(5) Barovsky, K.; Brooker, G. *J. Cyclic Nucleotide Res.* **1980**, *6*, 297.
(6) Brunswick, D. J.; Tondo, L. *Fed. Proc.* **1984**, *43*, 839.
(7) Tondo, L.; Conway, P.; Brunswick, D. J. *J. Pharm. Exp. Ther.* **1985**, *235*, 1.

0022-2623/86/1829-1524$01.50/0