

H, Im-CH<sub>2</sub>, 7.05 (s, 1 H, Im-H), 7.3 (s, 1 H, Im-H). Anal. (C<sub>9</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>) C, H, N.

**1-(2-Nitro-1-imidazolyl)-3,3-dimethyl-3-(1-aziridinyl)-2-propanol (23).** 1-Potassio-2-nitroimidazole (3.05 g, 20.2 mmol) in dry CH<sub>3</sub>CN (50 mL) was stirred with 4-bromo-2-methylbut-2-ene (4.75 g, 31.8 mmol) and 18-crown-6 (0.26 g, 0.98 mmol) for 24 h. The suspension was evaporated and redissolved in CHCl<sub>3</sub> (200 mL) and washed with H<sub>2</sub>O (4 × 75 mL) and saturated NaCl (75 mL) and then dried and evaporated to dryness. The residue was purified on silica gel eluting with CHCl<sub>3</sub> to afford 0.8 g (22%) of 1-(3-methylbutenyl)-2-nitroimidazole (21) as a pale yellow oil: NMR (CDCl<sub>3</sub>) δ 1.8 (bs, 6 H, CH=C(CH<sub>3</sub>)<sub>2</sub>), 5.1 (bd, 2 H, Im-CH<sub>2</sub>), 5.4 (m, 1 H, CH=C(CH<sub>3</sub>)<sub>2</sub>), 7.1 (s, 1 H, Im-H), 7.15 (s, 1 H, Im-H).

The above alkene (2.7 g, 14.9 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and heated under reflux with MCPBA (6.29 g, 20.1 mmol) for 1 h, cooled, diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and washed with 10% Na<sub>2</sub>SO<sub>3</sub>(aq) (3 × 150 mL), H<sub>2</sub>O (2 × 150 mL), and saturated NaHCO<sub>3</sub>(aq) (2 × 150 mL). The solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified on silica, eluting with EtOAc, to give 1.8 g (81.7%) of 1-(3,3-dimethyl-2,3-epoxybutyl)-2-nitroimidazole (22) as a pale yellow oil: NMR (CDCl<sub>3</sub>) δ 1.4 (s, 3 H, oxirane 3-CH<sub>3</sub>), 1.45 (s, 3 H, oxirane 3-CH<sub>3</sub>), 3.2 (dd, 1 H, *J* = 3.6 and 8.4 Hz, oxirane 2-CH), 4.3 (dd, 1 H, *J* = 8.4 and 13.5 Hz), and 5.1 (dd, 1 H, *J* = 3.6 and 14.4 Hz), Im-CH<sub>2</sub>, 7.15 (s, 1 H, Im-H), 7.3 (s, 1 H, Im-H).

The oxiranyl synthon 22 (1.09 g, 5.5 mmol) was dissolved in EtOH (1% Et<sub>3</sub>N) (30 mL) and heated under reflux with 1*H*-aziridine (2.0 g, 46.5 mmol) for 10 h. Further aziridine (5 mL, 116 mmol) was then added, and heating was continued for another 4 h. The solution was then evaporated and the residue purified on silica (eluting with CHCl<sub>3</sub>/MeOH/Et<sub>3</sub>N (90:9:1)) to afford, after recrystallization from EtOH (1% Et<sub>3</sub>N), 0.32 g (32.8%) of 23 as a pale yellow solid: mp 127–128 °C; NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 0.78 (s, 3 H, C(CH<sub>3</sub>)<sub>3</sub>), 0.83 (s, 3 H, C(CH<sub>3</sub>)<sub>3</sub>), 1.4 (m, 4 H, 2 × aziridine CH<sub>2</sub>), 4.25 (dd, 1 H, *J* = 10.7 and 13.5 Hz) and 4.92 (dd, 1 H, *J*

= 1.5 and 13.5 Hz), Im-CH<sub>2</sub>, 5.07 (d, 1 H, *J* = 6.2 Hz, OH), 7.14 (s, 1 H, Im-H), 7.59 (s, 1 H, Im-H); NMR (CDCl<sub>3</sub>) δ 0.92 (s, 3 H, C(CH<sub>3</sub>)<sub>3</sub>), 0.98 (s, 3 H, C(CH<sub>3</sub>)<sub>3</sub>), 1.5 (m, 2 H) and 1.53 (m, 1 H) and 1.61 (m, 1 H), 2 × aziridine CH<sub>2</sub>, 3.66 (dd, 1 H, *J* = 1.7 and 10.1 Hz, CHOH), 4.10 (dd, 1 H, *J* = 10.2 and 13.5 Hz) and 4.9 (dd, 1 H, *J* = 1.7 and 13.5 Hz), Im-CH<sub>2</sub>, 4.2 (br, 1 H, OH), 7.08 (d, 1 H, *J* = 1.1 Hz, Im-H), 7.27 (d, 1 H, *J* = 1.1 Hz, Im-H). Anal. (C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>) C, H, N.

**1,2-cis-2,3-trans-3-Aziridin-1-yl-2-hydroxy-1-(2-nitroimidazol-1-yl)cyclohexane (26).** 1-Cyclohex-2-enyl-2-nitroimidazole was prepared and epoxidized with MCPBA as described previously.<sup>18</sup> The anti-isomer 24 was isolated as unreacted starting material when a mixture of isomers was used for the following reaction. The syn-isomer 25 reacts with aziridine, but could be obtained in pure form when the above epoxidation was carried out with dried peroxy acid as described previously.<sup>18</sup>

The oxiranyl synthon 25 (0.5 g, 2.4 mmol) was refluxed in 40 mL of EtOH (1% Et<sub>3</sub>N) with 1*H*-aziridine (2.0 g, 46.5 mmol) for 1.5 h. The solution was evaporated to dryness and the residue purified on silica, eluting with CHCl<sub>3</sub>/MeOH/Et<sub>3</sub>N (90:9:1), to give 0.15 g (26%) of 26 as a pale yellow solid, recrystallized from acetone: mp 204–206 °C; NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 1.12 (dd, 1 H, *J* = 6.0 and 3.3 Hz, aziridine-H syn to *N*-cyclohexane bond), 1.16 (dd, 1 H, *J* = 6.0 and 3.4 Hz, aziridine-H anti to *N*-cyclohexane bond + 4ax,4eq,5ax,5eq,6eq-H), 2.17 (dq, 1 H, *J* = 11.4 and 3.4 Hz, 6ax-H), 3.34 (m, 1 H, 3-H), 3.91 (m, 1 H, 2-H), 5.11 (d, 1 H, *J* = 5.6 Hz, OH), 5.49 (d ca. t, 1 H, *J* = 11.9 and 3 Hz, 1-H), 7.15 (d, 1 H, *J* = 0.7 Hz, Im-4H), 7.67 (d, 1 H, *J* = 0.7 Hz, Im-5H); EIMS 252.1222 (calcd for C<sub>11</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> 252.1240).

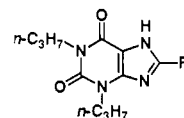
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## Communications to the Editor

### 7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one: A Potent and Water-Soluble Adenosine A<sub>1</sub> Antagonist

Adenosine elicits a wide variety of physiological responses<sup>1</sup> via interactions with two major subtypes of extracellular receptors, designated as A<sub>1</sub> and A<sub>2</sub>. The two receptor subtypes were originally defined in terms of different effects on adenylate cyclase. A<sub>1</sub> receptors exhibit relatively high affinity to adenosine in binding studies (nM) and some are coupled to and inhibit adenylate cyclase. In contrast, A<sub>2</sub> receptors exhibit low affinity to adenosine (μM) and some are coupled to, but stimulate adenylate cyclase.<sup>2,3</sup>

Considerable effort to search for selective antagonists has been invested in order to elucidate the physiological



compound		R
1	(CPX)	cyclopentyl
2	(KF15372)	dicyclopropylmethyl
3	(KW-3902)	3-noradamantyl
10	(KFM19)	3-oxocyclopentyl

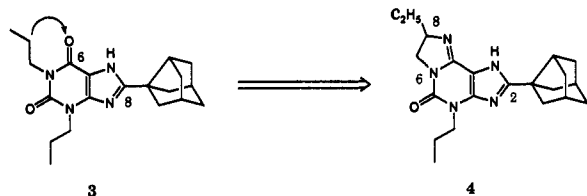
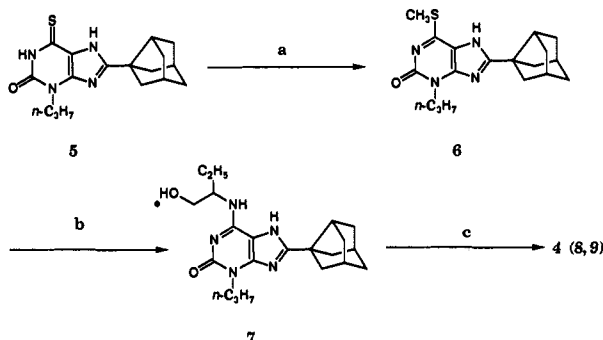
Figure 1. Chemical structure of xanthine derivatives.

role of adenosine and develop therapeutic agents.<sup>4,5</sup> Although many selective adenosine A<sub>1</sub> antagonists such as 1 (DPCPX)<sup>6</sup> and 2 (KF15372)<sup>7</sup> are recently available

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## Scheme I

Scheme II<sup>a</sup>

<sup>a</sup> Reaction conditions: (a)  $\text{CH}_3\text{I}$  (1.5 equiv)/ $\text{NaOH}$  (aq)- $\text{EtOH}$ , room temperature; (b) 2-amino-1-butanol (5 equiv),  $\text{DMSO}$ ,  $150^\circ\text{C}$ ; (c)  $\text{SOCl}_2$ , reflux.

(Figure 1), their pharmacological studies have been hampered by low water solubility. Thus we have screened for a water-soluble and potent adenosine  $A_1$  antagonist.

As an initial structural approach, we considered the xanthines as a reasonable starting point for the development of such a compound. We recently reported that introduction of the conformationally restricted cyclopentyl moiety into the 8-position of 1,3-dipropylxanthines enhanced the  $A_1$  antagonism and the 8-(3-noradamantyl)-substituted xanthine **3** (KW-3902) was identified to be a selective and the most potent  $A_1$  receptor antagonist reported to date.<sup>8</sup> Like many other xanthines, however, **3** shows low water solubility, which precludes the development of a parenteral dosage form. Therefore, basic non-xanthine compounds, with similar structural and functional features, became the initial targets. The design of these compounds involved "constraining" the 1-propyl group present in **3** onto the pyrimidine ring to form a tricyclic ring system as shown in Scheme I. The oxygen at the 6-position was replaced by nitrogen. Formation of an acid salt of such a basic dihydroimidazole should increase the water solubility. Critical to the early success of this approach would be demonstration of adenosine  $A_1$  antagonism and improved water solubility.

As shown in Scheme II, 6-thioxanthine derivative **5** was treated with methyl iodide (1.5 equiv) in aqueous alkaline solution, to afford 6-(methylthio)-8-(3-noradamantyl)-3-propyl-7H-purin-2(3H)-one (**6**; yield 74%).<sup>9</sup> Reaction of

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Table I.  $A_1$  and  $A_2$  Receptor Binding and Water Solubility of Adenosine Antagonists

compd	$K_{i1}$ , <sup>a</sup> nM		$K_i$ ratio $A_2/A_1$	solubility, <sup>b</sup> $\mu\text{g/mL}$	
	$A_1$	$A_2$		water	saline
1	$6.4 \pm 0.35$	$590 \pm 48$	92	3.3	NT
2	$3.0 \pm 0.21$	$430 \pm 5.8$	140	8.5	5.8
3	$1.3 \pm 0.12$	$430 \pm 30$	290	0.5	0.6
10	15	2700	180	220	200
4	$5.7 \pm 0.51$	330	58	3200	990
8(R)	$2.7 \pm 0.09$	290	107	3000	NT
9(S)	120	250	2.1	2900	NT

<sup>a</sup>  $A_1$  binding was carried out with  $N^6$ -[ $^3\text{H}$ ]cyclohexyladenosine in guinea pig forebrain membranes as described,<sup>8</sup> and  $A_2$  binding was carried out with  $N$ -[ $^3\text{H}$ ]ethyladenosin-5'-uronamide in the presence of 50 nM cyclopentyladenosine in rat striatal membranes.<sup>8</sup> Concentration-inhibition curves were carried out in duplicate with five or more concentrations of each test agent, and  $\text{IC}_{50}$  values were calculated from computerization of logit log curve.  $\text{IC}_{50}$  values were converted to  $K_i$  values as described.<sup>16</sup> When the assays were carried out three or more times, standard errors (SEM) are given in the table. <sup>b</sup> Compounds (10 mg) were agitated in water (2.5 mL) at  $20^\circ\text{C}$  for 1 h. After filtration, content of compounds in water (solubility) was assessed by HPLC analysis [YMC AM-312 (ODS) column (Yamamura Kagaku); eluent,  $\text{CH}_3\text{CN}$ -0.05 M phosphate buffer solution (pH 3.0); detector (UV), 295 nm; column temperature  $40^\circ\text{C}$ ].

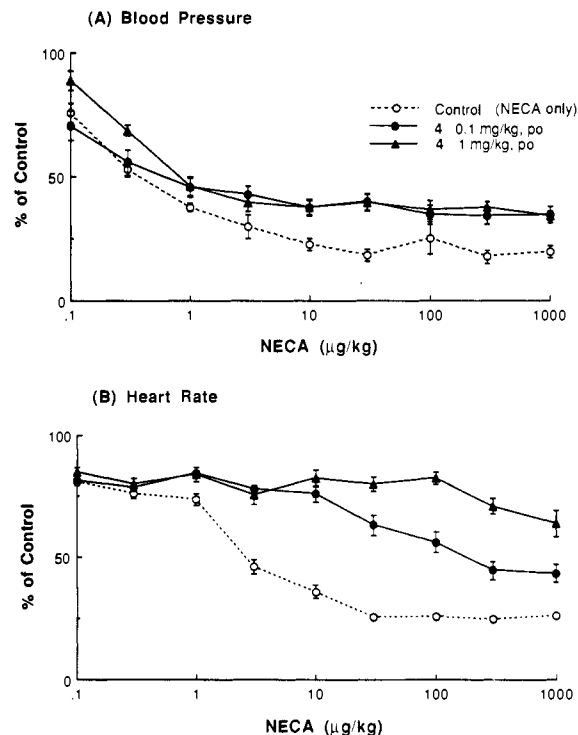
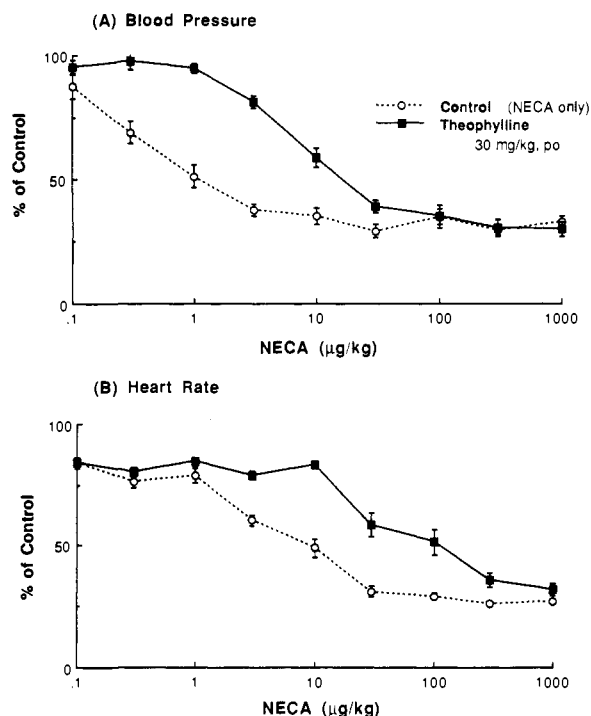


Figure 2. Effect of compound **4** on NECA-induced (A) hypotensive and (B) bradycardic responses in anesthetized rats. The dotted line shows the effects of NECA. Compound **4** was dissolved with saline and administered orally at the doses of 0.1 and 1 mg/kg, respectively. One hour later, increasing doses of NECA were given intravenously and the changes in diastolic blood pressure and heart rate were recorded. Data are expressed as the mean  $\pm$  SEM ( $n = 6-10$ ).

**6** with excess 2-amino-1-butanol (5 equiv) in  $\text{DMSO}$  at  $150^\circ\text{C}$  gave 6-[(1-ethyl-2-hydroxyethyl)amino]-8-(3-noradamantyl)-3-propyl-7H-purin-2(3H)-one (**7**; yield 62%). The amino alcohol was converted to 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-*i*]purin-5-

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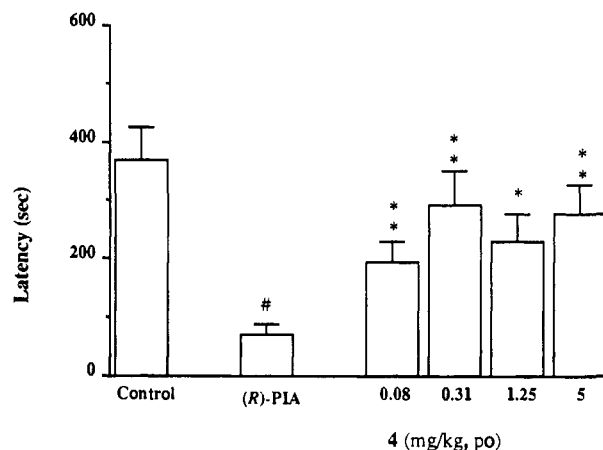


**Figure 3.** Effect of theophylline on NECA-induced (A) hypotensive and (B) bradycardic response in anesthetized rats. Theophylline was suspended with 0.3% Tween 80 and administered orally at the dose of 30 mg/kg. Data are expressed as the mean  $\pm$  SEM ( $n = 6-10$ ).

(4*H*)-one (**4**) on reaction with thionyl chloride under reflux in quantitative yield.<sup>10</sup> Compound **4** was isolated as a HCl salt. Its *R* and *S* enantiomers (**8** and **9**) were similarly prepared from the corresponding optically active 2-amino-1-butanol. These were isolated as *L*-tartrate and *D*-tartrate salts, respectively. Optical purity of **8** and **9** were shown to be >99% and 99%, respectively, by HPLC using a CHIRALCEL OD column.

The data of  $A_1$  and  $A_2$  adenosine receptor binding and water solubility of **1**, **2**, **3**, **4**, **8**, and **9** are displayed in Table I. A nonxanthine type heterocycle **4** exhibited high affinity for adenosine  $A_1$  receptors ( $K_i = 5.7$  nM). As expected, this compound **4** showed much better water solubility (3.2 mg/mL) than those (3.3, 8.5, and 220 µg/mL) of **1**, **2**, and recently reported water-soluble  $A_1$  antagonist **10** (KFM 19).<sup>11</sup> We then examined the biological activity of **4** in vivo. As shown in Figure 2, NECA caused a dose-dependent decrease in heart rate and in blood pressure in anesthetized rats.<sup>12</sup> Compound **4** was orally administered at doses of 0.1 and 1 mg/kg and produced a much larger shift to the right in the NECA dose-response curve for heart rate than for blood pressure. By contrast, theophylline (30 mg/kg, po), a nonselective antagonist, produced equivalent shifts to the right in the dose-response curves (Figure 3). Adenosine is supposed to reduce heart rate via an effect on the  $A_1$  receptor and blood pressure via the  $A_2$  receptor. Thus **4** was identified to be

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**Figure 4.** Effects of **4** on (*R*)-PIA-induced passive avoidance failure in mice. Behavioral testing was performed with a step-through type passive avoidance method as described before.<sup>13,17</sup> As experimental apparatus, two compartments (bright and dark) were used. The dark compartment had a grid floor of stainless rods used to give a foot shock delivered by shock generator (2 mA for 2 s). In the test trial, given 24 h after the acquisition trial, mouse (ddY, male, 22-27 g) was again placed in the bright compartment and the response latency to enter the dark compartment was measured. The latency of animals which did not move into the dark compartment during the observation period was calculated to be 600 s. Intraperitoneal administration of (*R*)-PIA at a dose of 0.3 mg/kg 30 min prior to the acquisition trial, significantly shortened the latency of the step-through response in rats. Compound **4** was orally administered 1 h before training (acquisition trial). Vertical bars represent the mean  $\pm$  SEM. (#)  $p < 0.001$ : significant difference from the normal-control ( $n = 15$ ). (\*)  $p < 0.01$ , (\*\*)  $p < 0.001$ : significant difference from the (*R*)-PIA-treated control (Mann-Whitney U test).

a selective and potent adenosine  $A_1$  antagonist in vivo (in heart). We recently reported that intraperitoneal administration of  $A_1$  receptor agonist such as *N*-[(*R*)-1-methyl-2-phenylethyl]adenosine ((*R*)-PIA) prior to training impaired memory of passive avoidance behavior.<sup>13</sup> Compound **4** was also evaluated using this (*R*)-PIA-induced amnesia model. As shown in Figure 4, oral administration of **4** 1 h before training ameliorated the shortened latency in (*R*)-PIA-treated rats at doses of 0.08-5 mg/kg. Thus **4** showed potent adenosine  $A_1$  antagonism also in CNS.

It is clear from Table I that the *R* and *S* enantiomers **8** and **9** have significantly different affinities for  $A_1$  receptors with the *R* enantiomer (**8**) being more potent. In adenosine agonists, (*R*)-PIA possesses higher affinity for the  $A_1$  receptors than *N*<sup>6</sup>-[(*S*)-1-methyl-2-phenylethyl]adenosine ((*S*)-PIA).<sup>14</sup> In xanthines, 1,3-dipropyl-8-[(*R*)-1-methyl-2-phenylethyl]xanthine is more potent than its *S* isomer at  $A_1$  receptors.<sup>15</sup> This marked stereochemical

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requirement for receptor affinity suggests the hypothesis that the C<sup>8</sup> substituent of a xanthine antagonist is binding in the same region as is the N<sup>6</sup> substituent of an adenosine agonist. In our dihydroimidazopyridine, the *R* enantiomer (C-8) preferred A<sub>1</sub> receptor binding. If a C-8 substituent in the dihydroimidazopyridine of 4, 8, and 9 recognizes the same space as does the N<sup>6</sup> substituent of an adenosine agonist or the C-8 substituent of an xanthine antagonist, a new receptor binding mode for this ligand has to be suggested. On the other hand, Quinn's hypothesis<sup>18</sup> suggests that the dihydroimidazole moieties of enantiomers (8 and 9) might recognize a ribose binding domain and produce different activities in adenosine binding. More detailed analysis of the binding mode for this new class of A<sub>1</sub> antagonists will be the subject of a future report.

Water-soluble A<sub>1</sub> antagonists will be widely applicable in biochemical and pharmacological studies.

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**Supplementary Material Available:** Detailed experimental procedures for the preparation of 4-9, the binding assay, and the pharmacological assays (7 pages). Ordering information is given on any current masthead page.

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### *N*-(1-Oxododecyl)-4 $\alpha$ ,10-dimethyl-8-aza-*trans*-decal-3 $\beta$ -ol: A Potent Competitive Inhibitor of 2,3-Oxidosqualene Cyclase

Inhibition of the enzyme HMG-CoA reductase is an effective approach for the inhibition of de novo cholesterol biosynthesis and the treatment of hypercholesterolemia.<sup>1</sup> HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis; however, its inhibition can lead to an increase in enzyme synthesis.<sup>1b</sup> The enzymes squalene synthase,<sup>2,3</sup> squalene epoxidase,<sup>4</sup> and 2,3-oxidosqualene cyclase (OSC)<sup>5</sup> are attractive targets for drug development since they are positioned in the biosynthetic pathway at a point where sterol synthesis is committed. Therefore, selective inhibition should not interfere with essential non-sterol pathways or result in the accumulation

of steroidal precursors.<sup>2,6</sup> Recently, it has been demonstrated that inhibitors of OSC can regulate HMG-CoA reductase via a putative feedback mechanism involving the formation of C25-oxysterols.<sup>7</sup> Our approach to the design of inhibitors of OSC was initially based on the use of amines as mimics (e.g. 2b-d) of high-energy intermediate carbocations involved in the cyclization of 2,3-oxidosqualene (Scheme I) as previously described.<sup>8-11</sup> However, we have determined that the amine functionality is not necessary for potent OSC inhibition. Furthermore, in HepG2 cells, the 8-azadecalins are more potent inhibitors of other enzymes in the cholesterol biosynthesis pathway than OSC. In this communication, we report the synthesis and activity of an amide derivative of 2c, *N*-(1-oxododecyl)-4 $\alpha$ ,10-dimethyl-8-aza-*trans*-decal-3 $\beta$ -ol (1a), which

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