

using DCC/HOBt as coupling reagent gave the crude tetrapeptide, which was purified by silica gel chromatography using 2% MeOH in  $\text{CHCl}_3$  as the eluant. Yield 130.0 mg (80%); mp 118–119 °C; TLC,  $R_f$  0.60 (A). Anal. Calcd for  $\text{C}_{34}\text{H}_{56}\text{N}_4\text{O}_8$ : C, H, N.

**Boc-(S,S)-Sta-Val-Leu-OMe (IV).** Following the procedure described for the preparation of II, the reaction of I (120.4 mg, 0.35 mmol) with Boc-statine<sup>29</sup> (96.25 mg, 0.35 mmol) using DCC/HOBt as the coupling reagent gave the crude tripeptide, which was purified by silica gel chromatography (eluant: 1% MeOH in  $\text{CHCl}_3$ ). Yield 138 mg (79%); mp 165–166 °C; TLC,  $R_f$  0.47 (A). Anal. Calcd for  $\text{C}_{25}\text{H}_{47}\text{N}_3\text{O}_7 \cdot 0.5\text{H}_2\text{O}$ : C, H, N.

**Boc-Phe-Leu-Ala-(S,S)-Sta-Phe-Val-Leu-OMe (7).** Tetrapeptide III (25 mg, 0.0386 mmol) was deprotected by using 4 N HCl-dioxane as described for the synthesis of II. The hydrochloride salt was dried, dissolved in 3 mL of DMF- $\text{CH}_2\text{Cl}_2$  (1:3), and neutralized with 4.25  $\mu\text{L}$  (0.0386 mmol) of NMM. Boc-Phe-Leu-Ala-OH (V)<sup>3</sup> (17.3 mg, 0.0386 mmol), obtained by saponification of the corresponding methyl ester with 0.1 NaOH, and 5.9 mg (0.0386 mmol) of HOBt were added. The mixture was cooled and stirred in an ice bath, 8.0 mg (0.0386 mmol) of DCC was added, and stirring continued for 5 hr at 0 °C and 43 h at room temperature. After filtration and concentration, excess ethyl acetate (30 mL) was added, and the jelly-like material was collected by filtration, washed with water, 1 N  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , saturated  $\text{KHSO}_4$  solution, and  $\text{H}_2\text{O}$ , and dried in vacuo to give 25.0 mg (66%) of the title compound.

Other peptides reported here were synthesized by closely related procedures employing conventional methods and were purified by recrystallization or silica gel chromatography. Physical constants for the final products are listed in Table I.

**N-(tert-Butyloxycarbonyl)-L-valyl-L-valyl-4(S)-amino-6-methylheptanoyl-L-alanine Isoamylamide (14).** This compound was prepared from Boc-Val-OH and Boc-Val-d-Sta-Ala-Iaa<sup>7</sup> in a manner similar to that for the preparation of II. Yield 62%; mp 234–236 °C; TLC,  $R_f$  0.45 (A). Anal. Calcd for  $\text{C}_{31}\text{H}_{59}\text{N}_5\text{O}_6$ : C, H, N.

**N-(tert-Butyloxycarbonyl)-L-valyl-((S)-amino-3(R)-hydroxy-5-phenylpentanoyl-L-alanine Isoamylamide (36).** The title compound was prepared in an analogous manner to the synthesis of Boc-Val-(3S,4S)-AHPPA-Ala-Iaa described by Rich et al.<sup>7</sup> Yield 73%; mp 210–212 °C; TLC,  $R_f$  0.19 (B). Anal. Calcd for  $\text{C}_{29}\text{H}_{48}\text{N}_4\text{O}_6 \cdot 1.5\text{H}_2\text{O}$ : C, H, N.

**Isovaleryl-L-valyl-4(S)-amino-3(R)-hydroxy-5-phenylpentanoyl-L-alanine Isoamylamide (38).** This compound was prepared from the hydrochloride salt of 27 and isovaleryl anhydride. Yield 70%; mp >250 °C; TLC,  $R_f$  0.34 (A). Anal. Calcd for  $\text{C}_{29}\text{H}_{48}\text{N}_4\text{O}_5 \cdot \text{H}_2\text{O}$ : C, H, N.

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## Synthesis and Calcium Channel Antagonist Activity of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates

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The Hantzsch condensation of alkyl acetoacetates 3 with methyl 3-aminocrotonate (4) and pyridinecarboxaldehydes 5 afforded the unsymmetrical alkyl methyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates 6, whereas condensation of 3 with 5 and ammonium hydroxide gave the symmetrical dialkyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates 7. The calcium channel antagonist activities of disubstituted 1,4-dihydro-3,5-pyridinedicarboxylates 6, 7, and 9 were determined with use of the muscarinic-receptor-mediated  $\text{Ca}^{2+}$ -dependent contraction of guinea pig ileal longitudinal smooth muscle. The relative potency order for isomeric pyridinyl analogues 6 and 7 was 2-pyridinyl > 3-pyridinyl > 4-pyridinyl. Increasing the size of the alkyl ester substituents enhanced activity. Compounds having nonidentical ester substituents were more potent than those having identical ester substituents. Replacement of the C-3 and/or C-5 ester substituent(s) by a cyano substituent(s) decreased activity significantly. An approximate 1:1 correlation between the  $\text{IC}_{50}$  value for inhibition of [ $^3\text{H}$ ]nitrendipine binding and inhibition of the tonic component of the muscarinic-induced contractile response was observed. The test results suggest that a 4-(pyridinyl) substituent is bioisosteric with a 4-(nitrophenyl) substituent on a 1,4-dihydropyridine ring system where *o*-, *m*-, and *p*-nitrophenyl are bioisosteric with 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl, respectively.

The 1,4-dihydropyridine calcium channel antagonists nifedipine (1a) and its *o*- $\text{CF}_3$  analogue (1b) exhibit negative inotropic and marked muscle relaxant properties.<sup>1,2</sup> Nifedipine is used clinically as an antianginal agent in the treatment of ischemic heart disease.

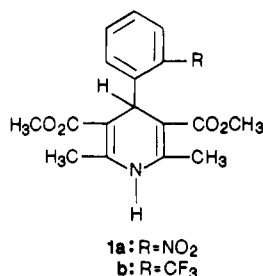
Structure-activity correlations for dialkyl 1,4-dihydro-2,6-dimethyl-4-aryl-3,5-pyridinedicarboxylates indicate that the nature and position of substitution in the aryl ring

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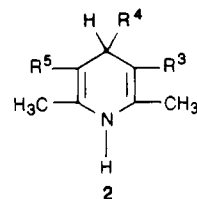
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are important determinants of activity. A para phenyl substituent invariably decreases activity, whereas ortho or meta substitutions generally increase activity.<sup>1,3</sup> Ester substituents in the C-3 and C-5 positions of the 1,4-dihydropyridine ring provide optimum activity<sup>3</sup> and may influence the pharmacodynamic and pharmacokinetic properties substantially.<sup>4,5</sup> Compounds having different ester substituents at the C-3 and C-5 positions possess a chiral center at C-4, and stereoselectivity of antagonism is observed.<sup>3,6-9</sup>

Although a large number of 1,4-dihydropyridines possessing a 4-(substituted phenyl) substituent have been investigated, very few compounds having a 4-(pyridinyl) substituent have been studied. The pyridinyl analogues **2a-c**,<sup>1</sup> **2d-g**,<sup>10</sup> **2h**,<sup>11</sup> and **2i**,<sup>12</sup> have been reported. It was therefore of interest to carry out a detailed study to determine the effect that the point of attachment of the 4-(pyridinyl) substituent in conjunction with a variety of C-3 and C-5 ester substituents had on pharmacological activity. We now describe the synthesis and calcium channel antagonist activity of dialkyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates **6**, **7**, and **9**.

**Chemistry.** The alkyl methyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates **6a-l** were prepared by a modified Hantzsch reaction,<sup>13</sup> with use of a procedure reported by Iwanani et al.<sup>14</sup> Thus, condensation of the alkyl acetoacetate **3** with methyl 3-aminocrotonate **4** and the pyridinecarboxaldehyde **5** afforded **6a-l** in 63–77% yield as illustrated in Scheme I. The symmetrical product **6** (R = CH<sub>3</sub>), resulting from condensation of **4** with **5**, was usually present as a minor contaminant. Aromatization of the 1,4-dihydropyridine product also occurred, but the aromatic pyridine never constituted more than 10% of the reaction products.



R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
a CO <sub>2</sub> Et	2-pyridyl	CO <sub>2</sub> Et
b CO <sub>2</sub> Et	3-pyridyl	CO <sub>2</sub> Et
c CO <sub>2</sub> Et	4-pyridyl	CO <sub>2</sub> Et
d CO <sub>2</sub> CH <sub>2</sub> - <i>i</i> -Bu	3-pyridyl	CO <sub>2</sub> CH <sub>2</sub> - <i>i</i> -Bu
e CO <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub>	3-pyridyl	CO <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub>
f CO <sub>2</sub> CH <sub>2</sub> - <i>i</i> -Bu	2-pyridyl	CO <sub>2</sub> CH <sub>2</sub> - <i>i</i> -Bu
g CO <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub>	2-pyridyl	CO <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub>
h COMe	3-pyridyl	COMe
i NO <sub>2</sub>	3-pyridyl	CO <sub>2</sub> Et
j NO <sub>2</sub>	4-pyridyl	CO <sub>2</sub> Me

Symmetrical dialkyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates **7a-l** were prepared by reaction of the alkyl acetoacetates **3** with pyridinecarboxaldehydes **5** and ammonium hydroxide to give **7** in 62–94% yield (see Scheme II).

Reaction of 3-aminocrotonitrile **8** with methyl 3-aminocrotonate (**4**) and the pyridinecarboxaldehyde **5** afforded the unsymmetrical 3-(methoxycarbonyl)-5-cyano products **9a, b**<sup>1</sup> whereas reaction of **8** (2 equiv) with **5** gave the symmetrical 3,5-dicyano analogues **9c, d** as illustrated by Scheme III.

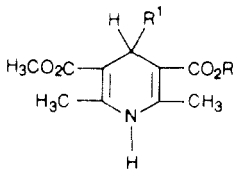
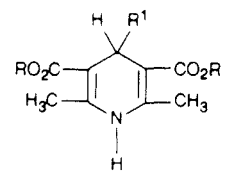
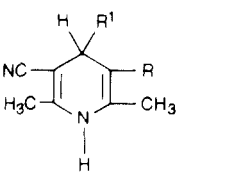
**Pharmacology.** The calcium channel antagonist activities for **6**, **7**, and **9**, determined as the concentration to produce 50% inhibition of the muscarinic-receptor-mediated Ca<sup>2+</sup>-dependent contraction of guinea pig ileal longitudinal smooth muscle,<sup>15</sup> are given in Table I.

**Structure-Activity Discussion.** Changes in the substitution pattern at the C-3, C-4, and C-5 positions of the first-generation calcium antagonist nifedipine alter potency, tissue selectivity,<sup>16-22</sup> and the conformation (degree of ring pucker) of the 1,4-dihydropyridine ring, which correlated well with the activity. The most active compounds exhibited the smallest degree of ring distortion from planarity. Nifedipine and related analogues, in the solid state, exist in a boat conformation where the C-4 substituted phenyl ring is perpendicular to the 1,4-dihydropyridine ring. Although the substituted-phenyl substituent at C-4 exists in the sterically preferred "priapic" orientation, there is significant strain in these molecules due to nonbonded interactions involving ortho substituents on the phenyl ring. This strain is relieved most notably by puckering of the dihydropyridine ring and distortion of the bond angles about C-4.<sup>3,23,24</sup> Structure-

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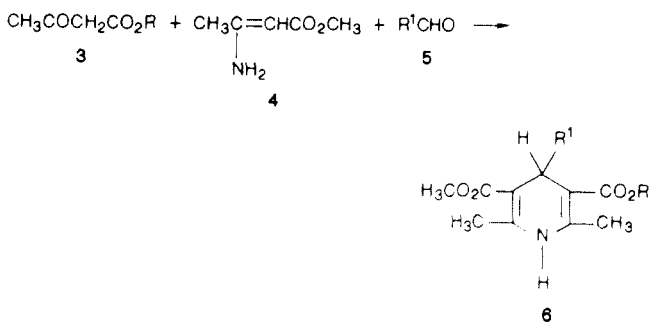
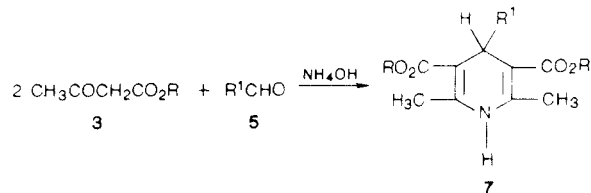
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**Table I.** Some Physical and Calcium Channel Antagonist Data for 3,5-Disubstituted 1,4-Dihydro-2,6-dimethyl-4-(pyridinyl)pyridines 6, 7, and 9

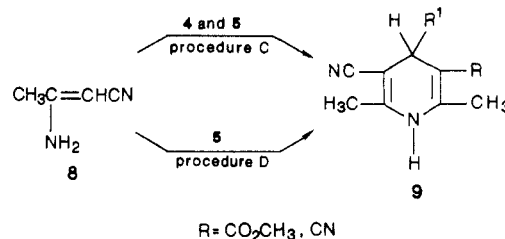




no.	R	R <sup>1</sup>	procedure	mp, °C	yield, %	formula	anal.	calcium channel antagonist act.: <sup>a</sup> ID <sub>50</sub> , M <sup>b</sup>
6a	Me	2-pyridyl	A	239–241	77	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(2.32 ± 0.19) × 10 <sup>-6</sup> (3)
6b	<i>i</i> -Pr	2-pyridyl	A	186–188	68	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(9.56 ± 1.4) × 10 <sup>-8</sup> (3)
6c	<i>i</i> -Bu	2-pyridyl	A	162–164	72	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(4.1 ± 0.17) × 10 <sup>-8</sup> (3)
6d	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	2-pyridyl	A	183–184	76	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>4</sub>	C, H, N	(4.36 ± 0.5) × 10 <sup>-5</sup> (4)
6e	Me	3-pyridyl	A	249–250	76	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(3.83 ± 0.83) × 10 <sup>-6</sup> (3)
6f	<i>i</i> -Pr	3-pyridyl	A	176–178	63	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(9.7 ± 4.6) × 10 <sup>-8</sup> (3)
6g	<i>i</i> -Bu	3-pyridyl	A	180–182	68	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(5.6 ± 0.6) × 10 <sup>-8</sup> (3)
6h	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	3-pyridyl	A	192–194	70	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>4</sub>	C, H, N	(3.3 ± 0.5) × 10 <sup>-5</sup> (4)
6i	Me	4-pyridyl	A	190–192	67	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(5.0 ± 1.1) × 10 <sup>-6</sup> (2) <sup>c</sup>
6j	<i>i</i> -Pr	4-pyridyl	A	199–200	73	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(5.6 ± 1.6) × 10 <sup>-7</sup> (3)
6k	<i>i</i> -Bu	4-pyridyl	A	126–127	76	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(2.2 ± 0.7) × 10 <sup>-7</sup> (3)
6l	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	4-pyridyl	A	144–145	67	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>4</sub>	C, H, N	(5.13 ± 0.4) × 10 <sup>-5</sup> (4)
7a	Et	2-pyridyl	B	194–195	89	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(1.77 ± 0.03) × 10 <sup>-7</sup> (3)
7b	<i>i</i> -Pr	2-pyridyl	B	192–193	86	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(1.25 ± 0.2) × 10 <sup>-7</sup> (3)
7c	<i>i</i> -Bu	2-pyridyl	B	152–153	88	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(9.36 ± 1.4) × 10 <sup>-8</sup> (4)
7d	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	2-pyridyl	B	205–207	94	C <sub>22</sub> H <sub>32</sub> N <sub>4</sub> O <sub>4</sub>	C, H, N	NT <sup>d</sup>
7e	Et	3-pyridyl	B	189–191	84	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(3.4 ± 1.2) × 10 <sup>-7</sup> (3)
7f	<i>i</i> -Pr	3-pyridyl	B	213–215	87	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(2.57 ± 0.6) × 10 <sup>-7</sup> (3)
7g	<i>i</i> -Bu	3-pyridyl	B	169–171	90	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(1.4 ± 0.6) × 10 <sup>-7</sup> (3)
7h	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	3-pyridyl	B	152–153	78	C <sub>22</sub> H <sub>32</sub> N <sub>4</sub> O <sub>4</sub>	C, H, N	(1.79 ± 0.2) × 10 <sup>-4</sup> (4)
7i	Et	4-pyridyl	B	183–186	77	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	NT
7j	<i>i</i> -Pr	4-pyridyl	B	224–226	76	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(2.31 ± 0.67) × 10 <sup>-7</sup> (4)
7k	<i>i</i> -Bu	4-pyridyl	B	167–169	78	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	(5.8 ± 291) × 10 <sup>-7</sup> (3)
7l	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub>	4-pyridyl	B	161–163	62	C <sub>22</sub> H <sub>32</sub> N <sub>4</sub> O <sub>4</sub>	C, H, N	NT
9a	CO <sub>2</sub> Me	3-pyridyl	C	242–244	73	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	NT
9b	CO <sub>2</sub> Me	4-pyridyl	C	195–197	63	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	(8.77 ± 0.4) × 10 <sup>-5</sup> (3)
9c	CN	3-pyridyl	D	229–230	63	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub>	C, H, N	(3.57 ± 0.72) × 10 <sup>-4</sup> (3)
9d	CN	4-pyridyl	D	234–236	66	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub>	C, H, N	(1.3 ± 0.2) × 10 <sup>-4</sup> (2) <sup>c</sup>
nifedipine								(1.4 ± 0.19) × 10 <sup>-8</sup> (18)

<sup>a</sup> Inhibitory activity on contractile response to *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD). <sup>b</sup> The concentration of antagonist causing a 50% decrease in the slow component or tonic response (ID<sub>50</sub> ± SEM) in the guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist CD was determined graphically from the dose-response curves. The number of experiments is shown in parentheses. <sup>c</sup> ID<sub>50</sub> ± range value. <sup>d</sup> NT, not tested.

**Scheme I****Scheme II**

activity studies indicate that activity is relatively independent of the electronic character (electron-donating or

**Scheme III**

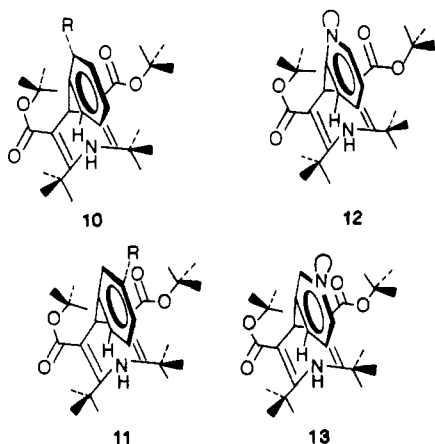
-attracting) of the phenyl substituents but is highly dependent on their size.<sup>1,2</sup> Rodenkirchen et al. concluded, for a group of nifedipine analogues, that the negative inotropic effect depended primarily on steric and on lipophilic and/or steric substituent properties for the C-4 aryl and C-3(5) ester substituents, respectively.<sup>2</sup>

Since activity is relatively independent of the electronic character of the C-4 phenyl substituents but highly dependent on steric size for nifedipine analogues, we formulated a hypothesis that similarly positioned C-4 pyridinyl ring systems should exhibit an activity profile where C-4-substituted 2-pyridinyl are more active than 3-pyridinyl, which are in turn more active than 4-pyridinyl, analogues. The pyridinyl nitrogen has an orbital with a

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lone electron pair. If this orbital is viewed as a substituent, the 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl ring systems may be bioisosteric with a phenyl ring having ortho, meta, and para substituents, respectively. The steric effect that an orbital with an electron pair can induce is obviously much smaller than that of a substituent attached to a phenyl ring, which could result in a decreased activity. Some three-dimensional structures comparing ortho- (10) and meta-substituted-phenyl (11) analogues with 2-pyridinyl (12) and 3-pyridinyl (13) analogues, respectively, are illustrated below.



The calcium channel test results (see Table I) indicate that replacement of the *o*-nitrophenyl substituent of nifedipine (1a) by a 2-pyridinyl (6a), 3-pyridinyl (6e), or 4-pyridinyl (6i) substituent resulted in about a 100-fold decrease in activity. A comparison of the activities of the isomeric pyridinyl analogues 6a, 6e, and 6i shows that the 2-pyridinyl isomer (6a) was more potent than the 3-pyridinyl isomer (6e), which in turn was more potent than the 4-pyridinyl isomer (6i). Similar potency sequences were observed for compounds having C-3 *i*-Pr and C-5 methyl substituents (6b > 6f > 6j) and C-3 *i*-Bu and C-5 methyl substituents (6c > 6g > 6k) as well as C-3 and C-5 *i*-Bu substituents (7c > 7g > 7k). In the 2-pyridinyl series (6a-c, 7b, c), replacement of the C-3 methyl substituent of 6a by an *i*-Pr moiety (6b) increased activity and replacement by an *i*-Bu group (6c) enhanced activity even further. Similar increases in potency were observed for the 3-pyridinyl (6g > 6f > 6e) and 4-pyridinyl (6g > 6j > 6i) series. Compounds having nonidentical ester substituents were more potent than compounds having identical ester substituents for compounds 6 and 7. For example, the potency of 6b was greater than that of 6a and 7b, and the activity of 6c was greater than that of 6a and 7c. Similar results were also observed in the 3-pyridinyl series where 6b was more potent than 6e, and 6g was more active than 6e and 7g, and in the 4-pyridinyl series where 6j was more potent than 6i, and 6k was more potent than 6i and 7k. Compounds 6 and 7 having nonidentical ester substituents have a chiral center at C-4, and the racemate was not resolved.

The calcium channel test results suggest that a 4-(pyridinyl) substituent is bioisosteric with a 4-(nitrophenyl) substituent on a 1,4-dihydropyridine ring system where *o*-, *m*-, and *p*-nitrophenyl are bioisosteric with 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl, respectively. The observed potency sequence where 2-pyridinyl > 3-pyridinyl > 4-pyridinyl is consistent with this postulate since it is well-documented that the potency sequence for substituted phenyl derivatives is generally ortho > meta > para.<sup>23</sup> If one assumes that activity is relatively independent of the electronic effects of substituents in the phenyl ring of

nifedipine analogues but highly dependent upon their size,<sup>1,2</sup> then the position of the nitrogen atom of the pyridinyl ring should not be a significant determinant of activity. However, the position of the nitrogen would be relevant if the steric effect of the free electron pair on nitrogen is a determinant of activity. Furthermore, if the position of the nitrogen and the free electron pair did not influence activity, then the potencies of the 2-, 3-, and 4-pyridinyl analogues would be expected to be similar. The observation that the potency of 2-pyridinyl is greater than that of 3-pyridinyl, which in turn is greater than that of 4-pyridinyl, is consistent with this concept of bioisosterism.

The nature of the C-3 and C-5 ester substituents has a significant effect on activity. An increase in steric and/or lipophilic properties of the ester substituent caused a significant increase in potency in the 2-, 3-, and 4-pyridinyl analogues 6 and 7. For example, 6c, having C-3 *i*-Bu and C-5 Me substituents, was nearly equiactive with nifedipine. The importance of steric effects exhibited by the ester substituents is further illustrated by the observation that activity decreases as nonbonded interactions between the C-3 and/or C-5 ester substituents and the pyridinyl substituent decrease, thereby correlating with the observed potency order 2- > 3- > 4-pyridinyl. This would explain the increased potency observed on increasing the size of the ester substituents (e.g., 6c > 6b > 6a) and the decreased potency as the distance between the ester substituents and the pyridinyl nitrogen is increased (e.g., 6b > 6f > 6j).

There is restricted rotation about the bond joining C-4 and the aromatic ring in nifedipine analogues.<sup>23,24</sup> Compounds 6 and 7 having either one or two isopropyl ester substituents at C-3 and/or C-5 exhibited two doublets in the proton NMR spectrum. The difference in chemical shifts (magnetic nonequivalence,  $\Delta\delta = 0.05$ –2.0) indicates that the geminal methyl substituents of the isopropyl substituent exist in different magnetic environments. The geminal methyl groups of isobutyl substituents were also magnetically nonequivalent irrespective of whether C-4 was chiral or nonchiral. This chemical nonequivalence may be due to the diastereotopic character of the geminal methyl groups, which imparts chiral character to the 1,4-dihydropyridine ring even when C-4 is not chiral.<sup>23</sup> Compounds 6i and 6l, which have a 4-pyridinyl substituent attached to C-4 of the 1,4-dihydropyridine ring, displayed two resolved doublets for H-2 and H-6 as well as H-3 and H-5. The nonequivalence of these two sets of protons is most likely due to restricted rotation about the C-4–C-4 bond and/or nonbonded interactions between the ester substituents and the 4-pyridinyl ring system.

Replacement of one (9b) or both (9c, d) ester substituents by a cyano substituent(s) resulted in a significant reduction in activity relative to 6e and 6i. This decrease in activity is most likely due to the reduced substituent volume of the cyano substituent resulting in less nonbonded interaction between the C-3, C-4, and C-5 substituents. This observation is consistent with the reported structure–activity correlation that replacement of an ester group by COMe or CN greatly reduces activity.<sup>1,3</sup>

The X-ray crystal structure of various nifedipine analogues has shown that the N-1 hydrogen participates in an intermolecular hydrogen bond with a neighboring carbonyl oxygen. On the other hand, in some 3-pyridinyl analogues, the pyridine nitrogen is involved in a strong intermolecular hydrogen bond with the N-1 hydrogen.<sup>24</sup> The effect that these short intermolecular contacts have on topological differences and binding with the 1,4-dihydropyridine Ca<sup>2+</sup> channel binding site is not known.

The 4-(pyridinyl)-1,4-dihydropyridine analogues **6c**, **7c**, **7g**, and **7k** were competitive inhibitors of specific [ $^3\text{H}$ ]-nitrendipine binding<sup>25</sup> with  $\text{IC}_{50}$  values of  $2.5 \times 10^{-8}$ ,  $8 \times 10^{-8}$ ,  $8.5 \times 10^{-8}$  and  $1 \times 10^{-7}$  M, respectively. The approximate 1:1 correlation between the  $\text{IC}_{50}$  values for inhibition of [ $^3\text{H}$ ]-nitrendipine binding and inhibition of the tonic component of the CD-induced contractile response (Table I) indicates that the 4-(pyridinyl)-1,4-dihydropyridines **6** and **7** interact with the same dihydropyridine binding site as nitrendipine and nifedipine.<sup>25</sup>

### Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in  $\text{CDCl}_3$  or  $\text{Me}_2\text{SO}-d_6$  with  $\text{Me}_4\text{Si}$  as internal standard with a Bruker AM-300 or Varian EM-360A spectrometer. Infrared spectra ( $\text{CHCl}_3$  unless otherwise noted) were taken on a Nicolet 5DX spectrometer. Mass spectra were measured with a Hewlett-Packard 5995A spectrometer. NMR, IR, and mass spectra were in agreement with the assigned structures. All of the products described gave rise to a single spot on TLC with three different solvent systems of low, medium, and high polarity. Microanalyses were within  $\pm 0.4\%$  of theoretical values for all elements listed. Flash column chromatography was carried out with Merck 60 silica gel. Column chromatography was performed with J. T. Baker 60–200-mesh silica gel. Methyl 3-aminocrotonate was prepared by using the literature procedure.<sup>14</sup>

**Isopropyl Acetoacetate and Isobutyl Acetoacetate (3, R = *i*-Pr and *i*-Bu).** Sodium metal (6.9 g, 0.3 mol) was added to a mixture of methyl acetoacetate (116 g, 1 mol) and isopropyl (or isobutyl) alcohol (2 mol). Dry toluene (150 mL) was added, and the reaction mixture was heated under reflux for 15 h. The methanol formed during the reaction was removed by distillation as a toluene-methanol azeotrope. Excess toluene and alcohol were removed in vacuo and the isopropyl (isobutyl) acetoacetate **3** was isolated upon distillation in vacuo.

**2-(*N,N*-Dimethylamino)ethyl Acetoacetate (3, R =  $(\text{CH}_2)_2\text{NMe}_2$ ).** Sodium metal (13.8 g, 0.2 mol) was added to *N,N*-dimethylethanolamine (89 g, 1 mol), and the mixture was heated to 70–80 °C. When all the sodium metal had dissolved, diketene (86 g, 1 mol, 50% acetone solution) was added dropwise. The temperature of the reaction was maintained between 70 and 80 °C for 24 h. The crude acetoacetate was used for the Hantzsch condensation reaction since distillation resulted in partial decomposition: yield 82.7 g, 47.8%; bp 140 °C (3 mm) (lit.<sup>14</sup> bp 103 °C (2 mm)).

**Procedure A. General Method for the Preparation of Alkyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates 6a–l.** The alkyl acetoacetate **3** (0.1 mol) was added to a solution of the pyridinecarboxaldehyde **5** (10.7 g, 0.1 mol) in ethanol (50 mL), and then methyl 3-aminocrotonate (8.9 g, 0.1 mol) was added with stirring. The reaction mixture was heated at reflux for 12–16 h and then poured onto crushed ice (100 mL). The crude product **6** was separated from the mixture by filtration or by extraction with dichloromethane. The combined organic extracts were dried ( $\text{MgSO}_4$ ), and the solvent was removed in vacuo. The solid dihydropyridine obtained was, in most cases, purified by elution from a silica gel column (5 cm  $\times$  65 cm) using ethyl acetate-acetone (9:1, v/v) as eluant.

However, **6b**, **6f**, and **6j** were purified by flash chromatography with hexane-ethyl acetate-ether (1:1:1, v/v/v) as eluant. This solvent system provided a good separation of the desired products **6b**, **6f**, and **6j** from the respective dimethyl dicarboxylates **6a**, **6e**, and **6i** formed as byproducts, which eluted from the column after the desired products. The 3-isobutyl-5-methyl compounds **6c**, **6g**, and **6k** were purified by silica gel column chromatography (5 cm  $\times$  65 cm) with ethyl acetate-hexane (1:1, v/v) as eluant.

Using this procedure, we obtained **6b**: yield 68%; IR 3160 (NH) and 1688 ( $\text{CO}_2$ )  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.05 and 1.2 (2 d,  $J$  = 7 Hz, 3 H each,  $\text{CO}_2\text{CH}(\text{CH}_3)_2$ ), 2.2 (s, 6 H,  $=\text{CCH}_3$ ), 3.6 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.9 (m, 1 H,  $\text{CO}_2\text{CH}(\text{CH}_3)_2$ ), 5.2 (s, 1 H, 1,4-dihydro-

pyridinyl C<sub>4</sub>-H), 7.0–7.8 (m, 3 H, C<sub>3</sub>-H, C<sub>4</sub>-H, C<sub>5</sub>-H), 8.5 (d,  $J$  = 5 Hz, 1 H, C<sub>6</sub>-H), 9.47 (s, 1 H, NH, exchanges with deuterium oxide).

**Procedure B. General Method for the Preparation of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates 7a–l.** The alkyl acetoacetate **3** (0.2 mol) was added to a solution of the pyridinecarboxaldehyde **5** (10.7 g, 0.1 mol) in ethanol (50 mL), and then ammonium hydroxide (14 g, 0.4 mol, 30% w/v) was added with stirring. The yellow mixture was heated under reflux for 12–16 h, cooled to 25 °C and poured onto crushed ice (100 mL). The crude product **7** was separated from the reaction mixture by filtration or extraction with dichloromethane. The combined organic extracts were dried ( $\text{MgSO}_4$ ) and the solvent was removed in vacuo. The solid dihydropyridine **7** obtained was, in most cases, purified by elution from a silica gel column (5 cm  $\times$  65 cm) with ethyl acetate-acetone (9:1, v/v) as eluant. However, diisopropyl (diisobutyl) 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates **7b**, **7c**, **7f**, **7g**, **7j**, and **7k** were purified by elution from a silica gel column (5 cm  $\times$  65 cm) with ethyl acetate-hexane (7:3, v/v) as eluant.

Using this procedure, we obtained **7b**: yield 86%; IR ( $\text{CHCl}_3$ ) 3192 (NH) and 1688 ( $\text{CO}_2$ )  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  1.03 and 1.2 (2 d,  $J$  = 6 Hz, 6 H each,  $\text{CO}_2\text{CH}(\text{CH}_3)_2$ ), 2.2 (s, 6 H,  $=\text{CCH}_3$ ), 4.8 (m, 2 H,  $\text{CH}(\text{CH}_3)_2$ ), 4.96 (s, 1 H, 1,4-dihydropyridinyl C<sub>4</sub>-H), 6.93–7.8 (m, 3 H, C<sub>3</sub>-H, C<sub>4</sub>-H, C<sub>5</sub>-H), 8.4 (m, 1 H, C<sub>6</sub>-H), 8.66 (s, 1 H, NH, exchanges with deuterium oxide).

**Procedure C. General Method for the Preparation of Methyl 3-Cyano-1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-5-pyridinedicarboxylates 9a, b.** 3-Aminocrotononitrile (8.2 g, 0.1 mol) was added to a solution of 3(4)-pyridinecarboxaldehyde **5** (10.7 g, 0.1 mol) and methyl 3-aminocrotonate (8.9 g, 0.1 mol) in ethanol (50 mL) with stirring, and the mixture was heated at reflux for 24 h. The reaction mixture was poured onto crushed ice (100 mL), and the solid product that separated was filtered. Purification of **9a, b** was effected by elution from a silica gel column (5 cm  $\times$  65 cm) with acetone-hexane (2:3, v/v) as eluant.

Using this procedure, we obtained **9a**: yield 73%; IR ( $\text{CHCl}_3$ ) 3192 (NH) and 1656 ( $\text{CO}_2$ )  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  2.2 (s, 6 H,  $=\text{CCH}_3$ ), 3.5 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.7 (s, 1 H, 1,4-dihydropyridinyl C<sub>4</sub>-H), 7.45–8.0 (m, 2 H, C<sub>4</sub>-H, C<sub>5</sub>-H), 8.5–8.86 (m, 2 H, C<sub>2</sub>-H, C<sub>6</sub>-H), 9.8 (s, 1 H, NH, exchanges with deuterium oxide).

**Procedure D. General Method for the Preparation of 3,5-Dicyano-1,4-dihydro-2,6-dimethyl-4-(pyridinyl)pyridines 9c, d.** A solution of 3(4)-pyridinecarboxaldehyde (10.7 g, 0.1 mol) and 3-aminocrotononitrile (17.8 g, 0.2 mol) in ethanol (50 mL) was heated under reflux for 24 h. The products **9c, d** were isolated and purified as described previously for **9a, b**.

Using this procedure, we obtained **9c**: yield 63%; IR ( $\text{CHCl}_3$ ) 3192 (NH) and 2220 (CN)  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  2.1 (s, 6 H,  $=\text{CCH}_3$ ), 4.5 (s, 1 H, 1,4-dihydropyridinyl C<sub>4</sub>-H), 7.36–7.93 (m, 2 H, C<sub>4</sub>-H, C<sub>5</sub>-H), 8.5–8.7 (m, 2 H, C<sub>2</sub>-H, C<sub>6</sub>-H), 9.5 (s, 1 H, NH, exchanges with deuterium oxide).

**Calcium Channel Antagonist Assay.**<sup>15</sup> Male albino guinea pigs (body weight 300–450 g) were sacrificed by decapitation. The intestine was removed above the ileo-cecal junction. Longitudinal smooth muscle segments of 2-cm lengths were mounted under a resting tension of 300–400 mg. The segments were maintained at 37 °C in a 10-mL jacketed organ bath containing oxygenated (100%  $\text{O}_2$ ) physiological saline solution of the following composition (mM): NaCl, 137;  $\text{CaCl}_2$ , 2.6; KCl, 5.9;  $\text{MgCl}_2$ , 1.2; glucose, 11.9 buffered by Hepes-NaOH to pH 7.4. The muscles were equilibrated for 1 h with a solution change every 15 min. Two successive control contractions were elicited at 15-min intervals with  $5 \times 10^{-7}$  M *cis*-2-methyl-4[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD). The isometric contractions were recorded with a force displacement transducer (FT 03C) on a GRASS physiograph. The mean of the two contractile responses was taken as the 100% value for the tonic (slow) component of the response. The muscle was washed with Hepes saline solution and was allowed to reequilibrate. The calcium antagonist was added 10 min before the dose-response for CD was determined. The drug-induced inhibition of contraction was expressed as percent of control. The  $\text{ID}_{50}$  values were graphically determined from the concentration-response curves. The pharmacological test results are summarized in Table I.

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**Competitive [<sup>3</sup>H]Nitrendipine Binding Assay.**<sup>25</sup> The inhibition of [<sup>3</sup>H]nitrendipine binding to a microsomal fraction from guinea pig ileal longitudinal smooth muscle was carried out with use of the procedure reported by Bolger et al.<sup>25</sup>

**Acknowledgment.** We are grateful to the Medical Research Council of Canada (Grant (Grant MT-8992) for financial support of this work and to the Alberta Heritage Foundation for Medical Research for studentships (to L.D. and M.C.L.-K.-K.). We also thank Amy Wong and Elizabeth Erdman for assistance in some of the pharmacological testing.

**Registry No.** 3 (R = Pr-*i*), 542-08-5; 3 (R = Bu-*i*), 7779-75-1; 3 (R = (CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>), 6131-49-3; 3 (R = Me), 105-45-3; 3 (R = Et), 141-97-9; 4, 14205-39-1; 5 (R<sup>1</sup> = 2-pyridyl), 1121-60-4; 5 (R<sup>1</sup> = 3-pyridyl), 500-22-1; 5 (R<sup>1</sup> = 4-pyridyl), 872-85-5; 6a, 23125-32-8; 6b, 39562-90-8; 6c, 104196-44-3; 6d, 104196-45-4; 6e, 73349-75-4; 6f, 39562-56-6; 6g, 104196-46-5; 6h, 104196-47-6; 6i, 23125-31-7; 6j, 104196-48-7; 6k, 104196-49-8; 6l, 104196-50-1; 7a, 23125-28-2; 7b, 104196-51-2; 7c, 104196-52-3; 7d, 104196-53-4; 7e, 23125-30-6; 7f, 104196-54-5; 7g, 104196-55-6; 7h, 104196-56-7; 7i, 21197-70-6; 7j, 104196-57-8; 7k, 104196-58-9; 7l, 104196-59-0; 8, 1118-61-2; 9a, 67593-36-6; 9b, 104196-60-3; 9c, 64089-24-3; 9d, 64089-25-4; Ca, 7440-70-2; Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>OH, 108-01-0; NH<sub>4</sub>OH, 1336-21-6; diketene, 674-82-8.

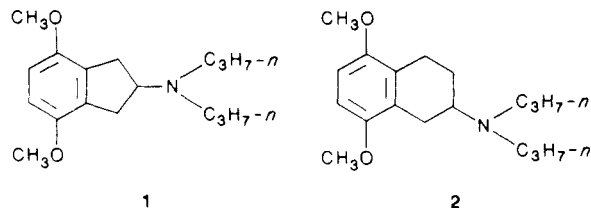
## *p*-Dimethoxy-Substituted *trans*-Octahydrobenzo[*f*]- and -[*g*]quinolines: Synthesis and Assessment of Dopaminergic Agonist Effects

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Division of Medicinal and Natural Products Chemistry, College of Pharmacy, and Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242. Received April 10, 1986

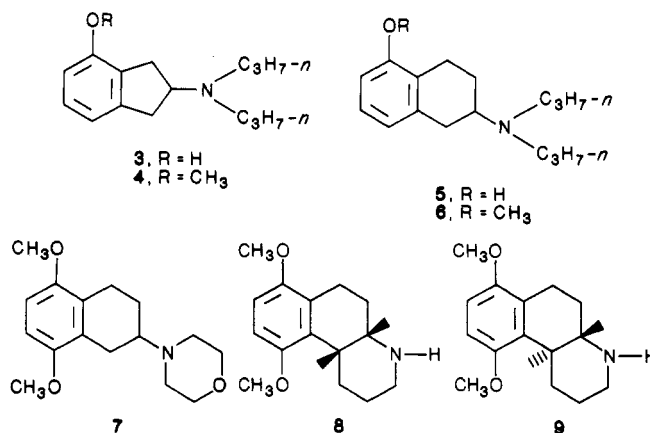
The *N*-*n*-propyl homologues of the title compounds were prepared for further assessment of the ability of the "p-dimethoxy" moiety to confer dopaminergic agonism upon a variety of ring systems. Both the angularly and the linearly annulated *trans*-benzoquinoline ring derivatives displayed prominent DA<sub>2</sub> dopaminergic effects on the peripheral sympathetic nerve terminal and displayed postjunctional dopamine receptor agonist properties in the striatum. It is speculated that the angular octahydrobenzo[*f*]quinoline derivative (but not the linear octahydrobenzo[*g*]quinoline derivative) may owe its dopamine-like effects to metabolic activation phenomena. In contrast, the *cis*-fused isomer of the angularly annulated benzoquinoline was inactive, as was the simple benzene derivative *N,N*-di-*n*-propyl-β-(2,6-dimethoxyphenyl)ethylamine.

2-(Di-*n*-propylamino)-4,7-dimethoxyindan (1) is equipotent to apomorphine in the cat cardioaccelerator nerve assay for DA<sub>2</sub>-receptor agonist effect involving the sympathetic nerve terminal.<sup>1</sup> It is effective following oral administration, and it is a weaker emetic agent than apomorphine.<sup>2</sup> Arneric and Long<sup>3</sup> have suggested that the compound produces its weak and transient hypotensive and bradycardia effects in rats by activation of central dopamine receptors. Compound 1 is significantly more selective than apomorphine in activating prejunctional dopamine receptors (as opposed to postsynaptic receptors) in the rat nigrostriatal pathway.<sup>2</sup> The tetralin congener 2 also demonstrates dopaminergic agonist effects but, in



most assays, the indan derivative 1 is more potent with high efficacy than the tetralin congener 2.<sup>2</sup> Compound 1 suppresses appetite in male rats<sup>4</sup> and it possesses direct α<sub>1</sub>-adrenoceptor agonist and serotonergic agonist activities.<sup>5</sup> It elicits potent effects on sexual behavior in male rats, characterized by increased mounting and ejaculation.<sup>6-8</sup>

The 5-hydroxyindan derivative 3 is a potent DA<sub>2</sub>-receptor agonist,<sup>9</sup> whereas its methyl ether 4 is inert.<sup>9</sup> Similarly, 5-hydroxytetralin 5 is a potent DA<sub>2</sub> agonist,<sup>10</sup> and its methyl ether 6 is inactive.<sup>11</sup> The 5,8-dimethoxy-2-aminotetralin derivative 7 was reported<sup>12</sup> to have no do-



pamine-like effects, and this inactivity was ascribed<sup>12</sup> to the incorporation of the amino group into a ring. De-

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