never exceeded 5% of total amount of radioligand added in each assay.

For analysis of the binding characteristics of nonlabled test compounds, binding assays were performed with 14 concentrations of the competing molecule, each logarithmic decade subdivided into three increments and each concentration step assayed in duplicate. This protocol allows for a total concentration range of more than four logarithmic decades to be covered in each separate concentration–effect curve (i.e., the highest concentration = 2×10^4 times the lowest concentration studied) and, thus, provides a high-resolution sequence of data points.

Graphic analysis of the data was performed by a computer-aided nonlinear regression, least-squares curve-fitting procedure. Assuming simple Michaelis–Menten kinetics of the interaction between radioligand and competing molecule on any hypothesized number of coexpressed specific receptor types, the computation procedure fits the sigmoidal concentration–effect curve, defined by the law of mass action, to the untransformed data. The analytical procedure allows for evaluation of affinity of the competing molecule for one or more subtypes of receptors which the radioligand nonselectively recognizes as specific binding sites. Calculation of the dissociation constant (K_d) from the observed IC_{50} value (concentration of test compound that causes 50% inhibition of specific binding of the radioligand) was performed by using the formula

$$K_d = IC_{50}(1 + [RL]/K_{RL})$$

where [RL] is the concentration of radioligand and K_{RL} is the affinity of the radioligand for its specific receptors.

The test compounds were dissolved in 95% ethanol at a concentration of 10^{-3} M and diluted 1000-fold in Tris-isosaline containing 0.2% BSA and 2.5% ascorbic acid. The final concentration of ethanol in the incubation cocktail was thus less than 0.02%. This concentration of ethanol has been demonstrated to be without detrimental effect on receptor integrity in the plasma membrane.[15] For a valid calculation of specific binding, the total binding assay (absence of nifedipine) contained the same concentration of ethanol as the nonspecific binding assay.

[^{3}H]Diltiazem Receptor Binding Assay. [^{3}H]Diltiazem binding was performed as described by Ehlert et al.[17a] One hundred microliters of the ice-cold membrane solution (400–600 mg of protein) was added to 0.02–1.0 μM of *d-cis*-[*methyl*-^{3}H]-diltiazem from New England Nuclear (TRK 789, Amersham Corp., 128 Ci/mmol, or NET 847, New England Nuclear, 77 Ci/mmol) and various concentrations of competing molecules in a final volume of 0.25 mL of Tris-isosaline containing 0.2% bovine serum albumin (BSA) and 2.5% ascorbic acid.

The binding reaction was performed at 25 °C as indicated for nitrendipine receptor system. Specific binding of diltiazem was determined as the binding detectable in the absence ("total binding") minus that in the presence of 100 μM unlabled *d-cis*-diltiazem ("nonspecific binding"). Specific binding routinely amounted to 60–75% of the total binding. The amount of radioligand never exceeded 5% of the total amount of radioligand added in each assay.

The evaluation of the affinity of the test compound for the specific diltiazem binding site was performed as indicated for the nitrendipine receptor system. Whenever insoluble in aqueous solutions, the test compounds were dissolved in 95% ethanol at a concentration of 10^{-3} M and diluted 1000-fold in Tris-isosaline containing 0.2% BSA and 2.5% ascorbic acid.

Acknowledgment. We thank Dr. Michael A. Porubcan for NMR assignments, Squibb's analytical department for microanalysis, and Dr. David M. Floyd for helpful discussions.

Registry No. **5**, 137-07-5; **6** (R^1 = 3-NO_2, R^2 = Me), 39562-17-9; **6** (R^1 = 2-NO_2, R^2 = Me), 39562-27-1; **6** (R^1 = 2-CF_3, R^2 = Me), 39561-94-9; **6** (R^1 = 4-NO_2, R^2 = Me), 40641-47-2; **6** (R^1 = H, R^2 = Me), 15768-07-7; **6** (R^1 = 4-OMe, R^2 = Me), 106521-81-7; **6** (R^1 = 3-NO_2, R^2 = Et), 39562-16-8; **6** (R^1 = 3-NO_2, R^2 = Pr-*i*), 39562-25-9; **8**, 106521-82-8; **9**, 106521-83-9; **10**, 106521-84-0; **11**, 106521-85-1; **12**, 106521-86-2; **13**, 106521-87-3; **14**, 106521-88-4; **15**, 106521-89-5; **16**, 106521-90-8; **17**, 106521-91-9; **18**, 106521-92-0; **20**, 106521-93-1; **22**, 106521-94-2; **23**, 95-54-5; **24**, 79923-70-9; 3-nitrobenzaldehyde, 99-61-6; ethyl acetoacetate, 141-97-9.

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

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The sodium borohydride reduction of 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)pyridines **2** and **5** in the presence of methyl, phenyl, or *tert*-butyl chloroformate afforded the respective 4-(dihydropyridinyl)-1,4-dihydropyridines **4** and **6** in good yield. Products **4** comprised a mixture of the 1,2- and 1,6-dihydropyridinyl regioisomers **4a** and **4b** where **4a** was always the predominant regioisomer. Compounds possessing a 4-[dihydro-1-(phenoxycarbonyl)-3-pyridinyl] substituent, such as **26**, were also a mixture of two regioisomers **26a** and **26b**, and each regioisomer existed as a mixture of two rotamers in Me_2SO-d_6 at 25 °C (**26a'**, **26a''**, and **26b'**, **26b''**) due to restricted rotation about the nitrogen-to-carbonyl carbamate bond. The calcium antagonist activities for **4** and **6** were determined by using the muscarinic receptor-mediated Ca^{2+}-dependent contraction of guinea pig ileal longitudinal smooth muscle. The relative order of activities for the 4-(dihydropyridinyl) analogues was 4-(dihydro-3-pyridinyl) > 4-(dihydro-4-pyridinyl). Increasing the size of the C-3(5) alkyl ester substituents increased activity. Compounds having nonidentical ester substituents were more active than those having identical ester substituents. Replacement of the C-3 and/or C-5 ester substituents by a cyano substituent(s) decreased activity significantly. An approximate 1:1 correlation between the IC_{50} value for inhibition of [^{3}H]nitrendipine binding and inhibition of the tonic component of the muscarinic-induced contractile response was observed. The test results suggest that a 4-(dihydropyridinyl) substituent is bioisosteric with a 4-(nitrophenyl) substituent on a 1,4-dihydropyridine ring where *m*- and *p*-nitrophenyl are bioisosteric with the 4-[1,2(1,6)-dihydro-3-pyridinyl] **4** and 4-(1,2-dihydro-4-pyridinyl) **6** isomers, respectively.

The utility of 4-aryl-1,4-dihydropyridines as therapeutic agents in cardiovascular disorders[1,2] has stimulated studies to investigate the geometrical requirements at the dihydropyridine binding site.[3-6] Changes in the substitution pattern at the C-3, C-4, and C-5 positions of the first-

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[‡] Memorial University of Newfoundland.

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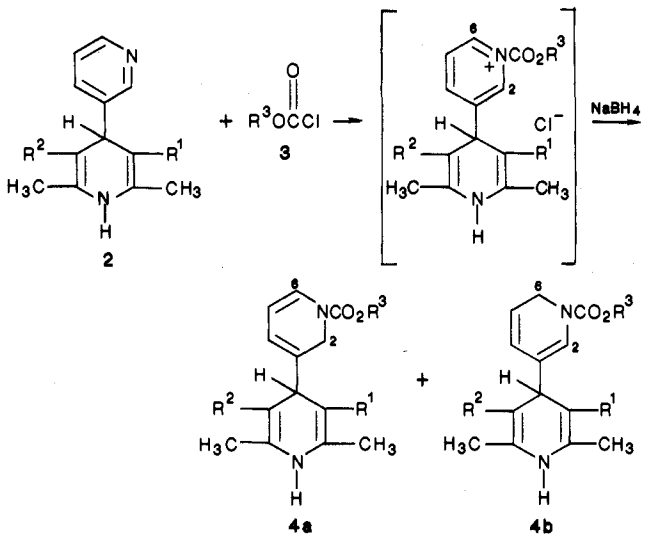
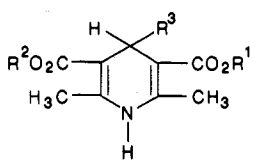
Scheme I



R^1, R^2 = CO_2Me, CO_2Et, CO_2-*i*-Pr, CO_2-*i*-Bu, CN; R^3 = Me, *t*-Bu, Ph

generation calcium antagonist nifedepine (**1a**) alters potency,[3] tissue selectivity,[7-13] and the conformation[14,15] of the 1,4-dihydropyridine ring.

In a previous study, we reported the calcium channel antagonist activities for dialkyl 1,4-dihydro-2,6-dimethyl-4-(pyridinyl)-3,5-pyridinedicarboxylates.[16] It was therefore of interest to investigate the effect that reduction



1a: R^1 = R^2 = Me; R^3 = 2-O_2N-C_6H_4

b: R^1, R^2 = Me, Et, *i*-Pr, *i*-Bu, $CH_2CH_2NMe_2$; R^3 = 2-, 3-, 4-pyridinyl

of the 4-(pyridinyl) substituent of **1b** to a 4-(dihydropyridinyl) ring system and its point of attachment, in conjunction with a variety of C-3 and C-5 ester substituents, had on calcium channel antagonist activity and tissue selectivity. We now report the synthesis and calcium channel antagonist activity for 3,5-disubstituted 4-(dihydropyridinyl)-1,4-dihydro-2,6-dimethylpyridines **4** and **6**.

Chemistry

The 3,5-disubstituted 4-[1,2(1,6)-dihydro-3-pyridinyl]-1,4-dihydropyridines **4** were prepared by using a modification of a procedure reported by Fowler[17] as illustrated in Scheme I. Thus, reaction of the 4-(3-pyridinyl) analogues **2**[16] with methyl, *tert*-butyl, or phenyl chloroformate (**3**) in methanol at −65 °C in the presence of sodium borohydride afforded a mixture of the 4-(1,2-dihydro-3-pyridinyl) **4a** and 4-(1,6-dihydro-3-pyridinyl) **4b** regioisomers in 56–78% yield, as illustrated by Scheme I and summarized in Table I. The 1-(*tert*-butoxycarbonyl) analogues **15** and **21** were prepared by using a modified procedure employing di-*tert*-butyl dicarbonate, rather than *tert*-butyl chloroformate, since reactions using the latter reagent did not proceed. All attempts to separate the regioisomers **4a** and **4b** by column or TLC chromatographic techniques failed.

The ^{1}H NMR spectrum of **7** (Me_2SO-d_6) indicated that the product was a mixture of regioisomers having 4-[1,2-dihydro-1-(methoxycarbonyl)-3-pyridinyl] (**7a**) and 4-[1,6-dihydro-1-(methoxycarbonyl)-3-pyridinyl] (**7b**) substituents present in a ratio of 9:7 as indicated by the integrals for the NH resonances, which appeared as singlets at δ 8.89 and 8.98, and the H-6 and H-2 resonances, which appeared at δ 6.56 and 6.36, respectively.

The ^{1}H NMR spectra for those compounds possessing a 4-[1,2(1,6)-dihydro-1-(phenoxycarbonyl)-3-pyridinyl] substituent, such as **11–14**, **20**, **23**, **26**, and **28**, were more complex than that of **7a**/**7b**. The ^{1}H NMR spectrum of **26** exhibited two doublets at δ 6.94 (**26a′**) and 6.75 (**26a″**) for H-6 (1 H total) and two singlets at δ 4.52 (**26a″**) and 4.3 (**26a′**) for H-2 (1 H each) of **26a**, and it exhibited two singlets at δ 6.92 (**26b″**) and 6.68 (**26b′**) for H-2 (1 H total) and two singlets at δ 4.58 (**26b′**) and 4.36 (**26b″**) for H-6 (1 H each) of **26b**. This spectral data suggested the presence of two rotamers that differ in configuration about the nitrogen-to-carbonyl bond. The difference in configuration is likely due to restricted rotation about the N–CO (carbamate) bond, due to its double-bond character.[18,19] These results indicate that each of the regioisomers **26a** and **26b** existed in two different rotameric configurations **26a′**, **26a″** and **26b′**, **26b″**, respectively.

The presence of rotamers was confirmed since the ^{1}H NMR spectrum of **26a**/**26b** (Me_2SO-d_6) at 115 °C exhibited near or complete coalescence of the resonances for those protons exhibiting dual resonances due to the presence of rotamers. The original spectrum was obtained upon cooling the sample to 25 °C. Increasing the temperature to 115 °C lowered the energy barrier to rotation about the N–CO bond to give a single set of resonances representative of the average chemical shifts for the populations of both rotamers. The presence of rotamers was observed only for those derivatives possessing a (phenyloxy)carbonyl substituent at the 1-position of the 1,2-(1,6)-dihydropyridinyl ring. This observation suggests that the (phenyloxy)carbonyl substituent of the carbamate moiety confers a greater double-bond character to the N–CO bond than a 1-methoxy or *tert*-butoxy group for this

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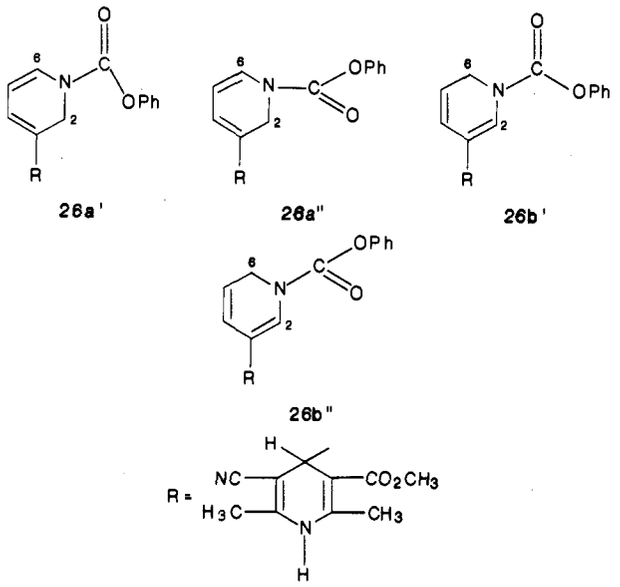


class of nifedipine analogues. This may be due to the electron-withdrawing effect of the phenyl group since rotamers were not observed for compounds having an electron-donating 1-methyl or *tert*-butyl substituent. In all reactions, the 1,2-dihydropyridinyl regioisomer **4a** was the predominant product. Steric effects due to the parent 1,4-dihydropyridine ring substituents are expected to be greatest at the C-2 position of the intermediate pyridinium salt, which would result in preferential formation of the 4-(1,6-dihydropyridinyl) regioisomer **4b**. Since the ratio of **4a** to **4b** was always greater than 1, factors other than steric effects must be operable. The oxygen atoms of the C-3 and/or C-5 ester carbonyl substituents may have an orientation in which the lone-electron pairs, and/or the π electrons of the carbonyl moiety itself, complex with borohydride directing regioselective attack at the C-2 position, which is in closer proximity. This would explain the regioselective formation of the 1,2-dihydropyridinyl isomer **4a**, which was the predominant product in all reactions.

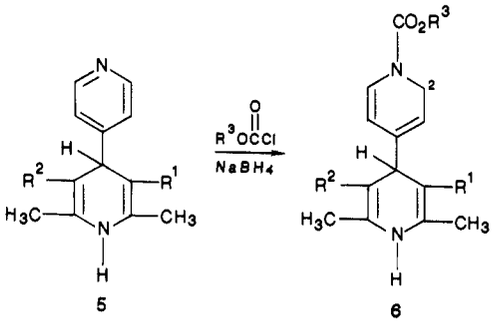
The reaction of 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-(4-pyridinyl)pyridines **5** with methyl, *tert*-butyl, or phenyl chloroformate (**3**) in the presence of sodium borohydride afforded the corresponding 4-(1,2-dihydro-4-pyridinyl) analogues **6** as illustrated in Scheme II and summarized in Table I. The 4-[1,2(1,6)-dihydro-2-pyridinyl] analogues were not prepared since the chloroformates **3** failed to react with the 4-(2-pyridinyl) analogue of **5**.

Pharmacology

The calcium channel antagonist activities for 4 and **6**, determined as the concentration to produce 50% inhibition of the muscarinic receptor-mediated Ca^{2+}-dependent contraction of guinea pig ileal longitudinal smooth muscle,[20] are given in Table I. It was most convenient to determine the ID_{50} by using a muscarinic agonist. A comparative investigation of 15 compounds screened by using either high K^+ depolarization or the muscarinic agonist showed that there was no significant difference between the ID_{50} values obtained by either method. Previous studies have also shown the KCl and muscarinic tonic responses in guinea pig ileal longitudinal smooth muscle to be equivalent.[21,22]

(20) The procedure used is a modification of the experimental protocol reported. Triggle, C.; Swamy V.; Triggle, D. *Can. J. Physiol. Pharmacol.* **1979**, *57*, 804.

Scheme II



Structure–Activity Discussion

Nifedipine and related compounds, in the solid state, exist in a boat conformation where the C-4 substituted-phenyl ring exists in a sterically favored orientation perpendicular to the 1,4-dihydropyridine ring. Strain due to nonbonded interactions involving the C-3, C-4, and C-5 substituents is relieved predominantly by puckering of the 1,4-dihydropyridine ring and distortion of the bond angle about C-4.[3,14,15] Calcium channel antagonist activity is relatively independent of the electronic character of the phenyl substituents but is highly dependent upon their size.[23,24] The negative inotropic activity of nifedipine analogues is determined primarily by the steric and lipophilic and/or steric substituent properties for the C-4 aryl ring and C-3(5) ester substituents.[24]

In view of the fact that activity is relatively independent of the electronic character of the C-4 phenyl substituents but highly dependent on steric size for nifedipine and its analogues, we formulated a hypothesis that similarly positioned C-4 dihydropyridinyl ring systems should exhibit an activity profile where 4-(dihydro-2-pyridinyl) > 4-(dihydro-3-pyridinyl) > 4-(dihydro-4-pyridinyl). 4-[1,2-Dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-2-pyridinyl], 4-[1,2-dihydro-1-[[alkyl(or phenyl)oxy]-carbonyl]-3-pyridinyl], and 4-[1,2-dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-4-pyridinyl] ring systems may be bioisosteric with a C-4 phenyl ring having ortho, meta, and para substituents, respectively. The steric effect that a 1-[[alkyl(or phenyl)oxy]carbonyl]substituent in the 4-(1,2-dihydropyridinyl) ring system can induce is expected to be comparable to that of a substituent such as nitro or trifluoromethyl attached to a phenyl ring. A three-dimensional structure comparing a meta-substituted phenyl analogue (**44**) with a 4-[1,2-dihydro-1-[[alkyl(or phenyl)-oxy]carbonyl]-3-pyridinyl] analogue (**45**) is illustrated below. Similar structural comparisons can be proposed for ortho- and para-substituted-phenyl analogues with the 2-(1,2-dihydropyridinyl) and 4-(1,2-dihydropyridinyl) analogues, respectively. The structure of the 4-[1,6-(1,2)-dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-3-pyridinyl]analogue **45** is expected to have some conformational differences relative to the nifedipine analogue **44**, since the 1,2-dihydropyridinyl ring system is more puckered than the planar phenyl ring system. The diene moiety is quasi-planar, but there is considerable distortion at the 1,6-dihydropyridinyl N-1 and C-2 positions of **45**. Examina-

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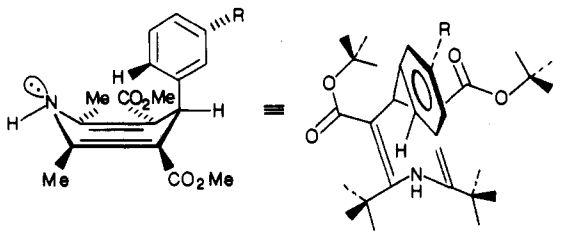
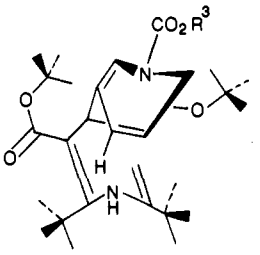


44



45

tion of Dreiding models indicates significant nonbonded interactions for **45** between the ring substituents, especially at C-3, C-4, and C-5, similar to that observed for **44**. The 1,4-dihydropyridinyl C-4 carbon of both **44** and **45** is chiral when the C-3 and C-5 ester substituents are different.

The calcium channel test results (see Table I) indicate that replacement of the *o*-nitrophenyl ring of nifedipine (**1a**) by a 4-[1,2(1,6)-dihydro-1-(methoxycarbonyl)-3-pyridinyl] substituent as for **7a/7b** resulted in an 18-fold reduction in activity. On the other hand, **7a/7b** was 6.5 times more active than the analogous 4-(3-pyridinyl) analogue **1**.[16] In the 4-(3-dihydropyridinyl) series, increasing the size of the C-3(5) alkyl ester substituents for compounds **7–18** having symmetrical ester groups increased potency where the isopropyl (**9**, **13**, **17**) and ethyl (**8**, **12**, **16**) analogues exhibited a greater activity than the methyl (**7**, **11**, **15**) analogues. However, a further increase in ester substituent size was not beneficial since the isobutyl analogues (**10**, **14**, **18**) were nearly equiactive with the corresponding methyl ester analogues (**7**, **11**, **15**). On the other hand, compounds **19–23**, having unsymmetrical alkyl ester substituents, exhibited a greater potency than analogues having the same symmetrical ester substituents. Thus, the relative activities for compounds possessing C-3 isobutyl and C-5 methyl ester substituents was **19** > **7** and **10**; **20** > **11** and **14**; and **21** > **15** and **18**. Similar results were obtained for compounds **22–24**, having C-3 isopropyl and C-5 methyl ester substituents where the activity of **22** > **7** and **9**; **23** > **11** and **13**; and **24** > **15** and **17**. The 3-isobutyl 5-methyl analogue **19** was nearly equiactive with nifedipine. Compounds **7–24**, having methoxycarbonyl, phenoxycarbonyl, and *tert*-butoxycarbonyl substituents attached to the 1-position of the 4-(dihydropyridinyl) ring, were investigated to determine the electronic and steric effects of the 1-[alkoxy(or phenyloxy)carbonyl] substituent upon activity. The 1-(methoxycarbonyl) analogues **7**, **8**, **10**, **19**, and **22**, with the exception of **9**, which was less active than the 1-(*tert*-butoxycarbonyl) analogue **17**, were more active than the *tert*-butoxycarbonyl analogues **15**, **16**, **18**, **21**, and **24** and the 1-(phenoxycarbonyl) analogues **11**, **12**, **13**, **14**, **20**, and **23**. Replacement of one (**25**) or both (**27**) *C*-(methoxycarbonyl) substituent(s) by a cyano substituent(s) resulted in a significant reduction in activity relative to **7**. This decrease in potency may be due to the reduced substituent volume of the cyano group, resulting in fewer nonbonded interactions 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 substituent by COMe or CN greatly reduced potency.[3,24]

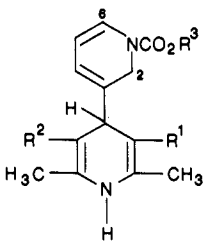
The 4-(dihydro-4-pyridinyl) analogues were generally less potent than the corresponding 4-(dihydro-3-pyridinyl) isomers (**7** > **30**, **8** > **31**, **9** > **32**, **10** > **33**, **19** > **39**, **20** > **40**, **21** > **42**, and **27** > **43**) although exceptions were observed (**36** > **14** and **38** > **18**). The activity exhibited by the 4-[1,2-dihydro-1-(methoxycarbonyl)-4-pyridinyl] analogue **30** was similar to that reported for the 4-(4-nitrophenyl) analogue of nifedipine, which is in agreement with the proposed bioisosteric hypothesis. Increasing the size of the symmetrical alkyl ester substituents enhanced activity, with isopropyl (**32**) > isobutyl (**33**) > ethyl (**31**) > Me (**30**).

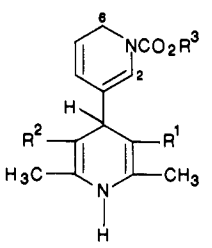
Compounds **4** were a mixture of 4-[1,2-dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-3-pyridinyl] **4a** and 1,6-dihydropyridinyl **4b** regioisomers, which could not be separated (see Table I). It is not known whether the potencies of the two regioisomers differ. The presence of rotamers for compounds **4** having a 1-[(phenyloxy)carbonyl] substituent does not appear to have a significant effect on activity since several respective 1-(methoxycarbonyl) and 1-(phenoxycarbonyl) analogues exhibited similar activities (**19** and **20**; **22** and **23**; **33** and **36**; **39** and **40**). A number of antagonist compounds (**10**, **13**, **14**, **18**, **33**, **36**, and **38**) appear to have a longer duration of action based on the increased length of time required for recovery of the original control agonist response. For example, the time required for a tissue to recover from inhibition by nifedipine or the 3-(methoxycarbonyl) 5-isobutyl analogue **21** was always less than 30 min. However, the degree of recovery after inhibition by the other compounds was marginal even after an hour or more. For instance, the recovery response to compound **18** was only 53% of control after 3.5 h. These longer acting compounds all possess symmetrical isobutyl or isopropyl C-3 (C-5) ester substituents, which may bind more strongly to the calcium channel receptor or receptor protein.

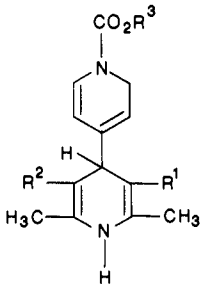
The smooth muscle inhibitory activities (ID_{50}) of the 4-(dihydropyridinyl)-1,4-dihydropyridine analogues **7**, **11**, **13**, and **15** and the nifedipine analogues **1** have been compared with their apparent binding affinity (KD_{50}) for the specific nitrendipine binding sites in guinea pig ileal smooth muscle membrane (see Table II). The approximate 1:1 correlation between the IC_{50} values for inhibition of binding and inhibition of the tonic component of the *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD) induced contractile response indicates that the 4-(dihydropyridinyl)-1,4-dihydropyridines **7**, **13**, and **15** and nifedipine analogues **1** interact with the same dihydropyridine binding site as nifedipine.[21] Some deviation in this correlation was observed for **11**, whose antagonist activity was 14-fold more sensitive than its binding capacity. This observation suggests that **11** may be acting by a different receptor interaction mechanism and should be further investigated.

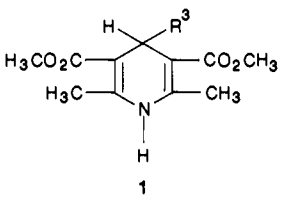
Compounds possessing nonidentical ester substituents at the C-3 and C-5 positions have a chiral center at C-4. Studies are now in progress to determine whether the enantiomers exhibit different potencies. The calcium antagonist test results suggest that a 4-(dihydropyridinyl) substituent is bioisosteric with a 4-(nitrophenyl) substituent on a 1,4-dihydropyridine ring system where *m*- or *p*-nitrophenyl are bioisosteric with 4-[1,2(1,6)-dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-3-pyridinyl] and 4-[1,2-dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-4-pyridinyl], respectively. The observed potency sequence where 3-(**4**) > 4-(**6**) is consistent with this postulate since it is well-documented that the potency sequence for substituted

Table I. Some Physical and Calcium Antagonist Activity Data for 3,5-Disubstituted 4-[Dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]pyridinyl]-1,4-dihydro-2,6-dimethylpyridines


7-29a


7-29b


30-43


1

no.	R^1	R^2	R^3	mp, °C	yield, %	ratio[a] a:b	formula	anal.	channel antag act.:[b] ID_{50},[c] M
7	CO_2Me	CO_2Me	Me	158–160	73	9:7	$C_{18}H_{22}N_2O_6$	C, H, N	$(5.89 \pm 2.2) \times 10^{-7}$ (4)
8	CO_2Et	CO_2Et	Me	115–116	75	2:1	$C_{20}H_{26}N_2O_6$	C, H, N	$(1.8 \pm 0.5 \times 10^{-7}$ (3)
9	CO_2-*i*-Pr	CO_2-*i*-Pr	Me	151–153	69	7:3	$C_{22}H_{30}N_2O_6$	C, H, N	$(1.31 \pm 0.2) \times 10^{-7}$ (4)
10	CO_2-*i*-Bu	CO_2-*i*-Bu	Me	138–139	76	5:3	$C_{24}H_{34}N_2O_6$	C, H, N	$(7.71 \pm 1.7) \times 10^{-7}$ (3)
11	CO_2Me	CO_2Me	Ph	147–149	56	3:1	$C_{23}H_{24}N_2O_6$	C, H, N	$(3.69 \pm 0.5) \times 10^{-6}$ (4)
12	CO_2Et	CO_2Et	Ph	162–164	57	4:3	$C_{25}H_{28}N_2O_6$	C, H, N	$(8.65 \pm 0.3) \times 10^{-7}$ (4)
13	CO_2-*i*-Pr	CO_2-*i*-Pr	Ph	114–116	58	4:3	$C_{27}H_{32}N_2O_6$	C, H, N	$(1.67 \pm 0.2) \times 10^{-6}$ (3)
14	CO_2-*i*-Bu	CO_2-*i*-Bu	Ph	172–174	62	2:1	$C_{29}H_{36}N_2O_6$	C, H, N	$(6.46 \pm 0.9) \times 10^{-6}$ (3)
15	CO_2Me	CO_2Me	*t*-Bu	91–92	32	2:1	$C_{21}H_{28}N_2O_6$	C, H, N	$(5.77 \pm 0.3) \times 10^{-6}$ (4)
16	CO_2Et	CO_2Et	*t*-Bu	152–154	69	2:1	$C_{23}H_{32}N_2O_6$	C, H, N	$(6.72 \pm 0.9) \times 10^{-7}$ (4)
17	CO_2-*i*-Pr	CO_2-*i*-Pr	*t*-Bu	148–150	75	7:3	$C_{25}H_{36}N_2O_6$	C, H, N	$(1.14 \pm 0.3) \times 10^{-7}$ (4)
18	CO_2-*i*-Bu	CO_2-*i*-Bu	*t*-Bu	153–155	78	2:1	$C_{27}H_{40}N_2O_6$	C, H, N	$(3.42 \pm 0.4) \times 10^{-6}$ (3)
19	CO_2-*i*-Bu	CO_2Me	Me	181–183	78	3:1	$C_{21}H_{28}N_2O_6$	C, H, N	$(3.1 \pm 0.7) \times 10^{-8}$ (4)
20	CO_2-*i*-Bu	CO_2Me	Ph	162–163	63	10:3	$C_{26}H_{30}N_2O_6$	C, H, N	$(4.5 \pm 1.5) \times 10^{-8}$ (3)
21	CO_2-*i*-Bu	CO_2Me	*t*-Bu	oil	65	3:1	$C_{24}H_{34}N_2O_6$	C, H, N	$(1.28 \pm 0.1) \times 10^{-7}$ (4)
22	CO_2-*i*-Pr	CO_2Me	Me	100–103	53	7:3	$C_{20}H_{26}N_2O_6$	H, N; C[d]	$(1.58 \pm 4.3) \times 10^{-7}$ (3)
23	CO_2-*i*-Pr	CO_2Me	Ph	102–105	35	3:1	$C_{25}H_{28}N_2O_6$	N; C, H[e]	$(9.0 \pm 1.7) \times 10^{-7}$ (4)
24	CO_2-*i*-Pr	CO_2Me	*t*-Bu	136–138	72	4:1	$C_{23}H_{32}N_2O_6$	C, H, N	$(2.37 \pm 0.3) \times 10^{-7}$ (4)
25	CO_2Me	CN	Me	125–127	73	5:3	$C_{17}H_{19}N_3O_4$	C, H, N	$(5.16 \pm 1.2) \times 10^{-5}$ (3)
26	CO_2Me	CN	Ph	131–132	62	11:9	$C_{22}H_{21}N_3O_4$	C, H, N	NF[f]
27	CN	CN	Me	136–138	75	5:3	$C_{16}H_{16}N_4O_2$	C, H, N	$(3.39 \pm 0.25) \times 10^{-5}$ (4)
28	CN	CN	Ph	151–153	65	7:3	$C_{21}H_{18}N_4O_2$	C, H, N	NT
29	CN	CN	*t*-Bu	145–147	73	2:1	$C_{19}H_{22}N_4O_2$	C, H, N	NT
30	CO_2Me	CO_2Me	Me	182–184	74	NA[g]	$C_{18}H_{22}N_2O_6$	C, H, N	$(7.47 \pm 0.5) \times 10^{-6}$ (3)
31	CO_2Et	CO_2Et	Me	145–148	76	NA	$C_{20}H_{26}N_2O_6$	C, H, N	$(2.43 \pm 0.2) \times 10^{-6}$ (3)
32	CO_2-*i*-Pr	CO_2-*i*-Pr	Me	oil	75	NA	$C_{22}H_{30}N_2O_6$	C, H, N[h]	$(1.01 \pm 0.2) \times 10^{-6}$ (4)
33	CO_2-*i*-Bu	CO_2-*i*-Bu	Me	161–163	79	NA	$C_{24}H_{34}N_2O_6$	C, H, N	$(1.72 \pm 0.2) \times 10^{-6}$ (4)
34	CO_2Me	CO_2Me	Ph	159–161	65	NA	$C_{23}H_{24}N_2O_6$	C, H, N	NT
35	CO_2Et	CO_2Et	Ph	128–129	61	NA	$C_{25}H_{28}N_2O_6$	C, H, N	NT
36	CO_2-*i*-Bu	CO_2-*i*-Bu	Ph	167–169	63	NA	$C_{29}H_{36}N_2O_6$	C, H, N	$(5.1 \pm 1.6) \times 10^{-7}$ (3)
37	CO_2Et	CO_2Et	*t*-Bu	165–167	67	NA	$C_{23}H_{32}N_2O_6$	C, H, N	NT
38	CO_2-*i*-Bu	CO_2-*i*-Bu	*t*-Bu	126–128	73	NA	$C_{27}H_{40}N_2O_6$	C, H, N	$(2.03 \pm 0.5) \times 10^{-6}$ (4)
39	CO_2Me	CO_2-*i*-Bu	Me	171–173	79	NA	$C_{21}H_{28}N_2O_6$	C, H, N	$(1.76 \pm 0.5) \times 10^{-6}$ (4)
40	CO_2Me	CO_2-*i*-Bu	Ph	168–169	67	NA	$C_{26}H_{30}N_2O_6$	C, H, N	$(8.1 \pm 3.5) \times 10^{-5}$ (3)
41	CO_2-*i*-Pr	CO_2Me	*t*-Bu	173–175	70	NA	$C_{23}H_{32}N_2O_6$	C, H, N	NT
42	CO_2-*i*-Bu	CO_2Me	*t*-Bu	148–149	73	NA	$C_{24}H_{34}N_2O_6$	C, H, N	$(1.18 \pm 0.2) \times 10^{-6}$ (4)
43	CN	CN	Me	157–159	65	NA	$C_{16}H_{16}N_4O_2$	C, H, N	$(6.75 \pm 2.5) \times 10^{-5}$ (2)[i]
nifedipine (1)			2-O_2N-C_6H_4						$(1.4 \pm 0.19) \times 10^{-8}$ (18)
1			3-O_2N-C_6H_4						4.0×10^{-9}[j]
1			4-O_2N-C_6H_4						3.2×10^{-6}[j]
1			2-pyridyl						$(2.32 \pm 0.19) \times 10^{-6}$[k]
1			3-pyridyl						$(3.83 \pm 0.83) \times 10^{-6}$[k]
1			4-pyridyl						$(5.0 \pm 1.1) \times 10^{-6}$[k]

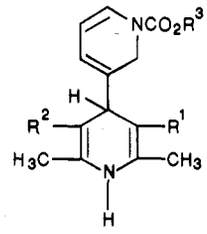
[a] The ratio was determined from the integrals for the NH singlet and the H-6(**a**) and H-2(**b**) resonances for each regioisomer, which were well-resolved. [b] Inhibitory activity on contractile response to *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD). [c] The concentration of antagonist causing a 50% decrease in the slow component or tonic response ($ID_{50} \pm$ SEM) in the guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist CD was determined graphically from the dose–response curve. The number of experiments is shown in parentheses. [d] Anal. Calcd: C, 61.54. Found: C, 59.13. Exact mass calcd: 390.1791. Found: 390.1790. [e] Anal. Calcd: C, 66.37; H, 6.19 Found: C, 65.62; H, 5.14. Exact mass calcd: 452.1947. Found: 452.1925. [f] NT, not tested. [g] NA, not applicable. [h] Exact mass calcd. for $C_{22}H_{30}N_2O_6$: 418.2103. Found: 418.2057. During TLC purification, **32** undergoes partial conversion to diisopropyl 1,4-dihydro-2,6-dimethyl-4-(4-pyridinyl)-3,5-pyridinedicarboxylate, mp 198–199 °C (lit.[16] mp 199–200 °C). [i] $ID_{50} \pm$ range value. [j] Lit.[21] values. [k] Lit.[16] values.

phenyl derivatives is generally ortho > meta > para.[3,24]

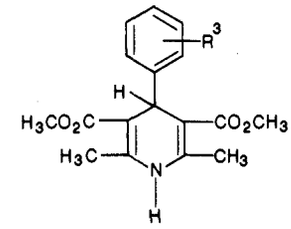
Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard with a Bruker AM-300 or Varian EM-360A spectrometer. Infrared spectra ($CHCl_3$ unless otherwise noted) were taken on a Nicolet 5DX spectrometer. Mass spectra were measured with a Hewlett-Packard 5995A spectrometer. NMR, IR, and mass spectral data 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 ±0.4% of theoretical

Table II. Pharmacological and Binding Activities for 1,4-Dihydropyridine Analogues of Nifedipine



7-15



1

no.	R^1	R^2	R^3	pharmacol:[a] ID_{50}, -log	binding:[b] KD_{50}, -log
7	CO_2Me	CO_2Me	Me	6.23 ± 0.37	5.61 ± 0.02
11	CO_2Me	CO_2Me	Ph	5.43 ± 0.14	4.25 ± 0.01
13	CO_2-*i*-Pr	CO_2-*i*-Pr	Ph	5.78 ± 0.12	5.60 ± 0.08
15	CO_2Me	CO_2Me	*t*-Bu	5.24 ± 0.05	4.74 ± 0.08
nifedipine (1)			2-NO_2	8.29 ± 0.4[c]	9.08 ± 0.14[c]
1			3-NO_2	8.40 ± 0.4[c]	9.97 ± 0.18[c]
1			4-NO_2	5.49 ± 0.41[c]	6.52 ± 0.24[c]

[a] The negative log of the concentration of antagonist causing a 50% inhibition of the tonic CD response in the guinea pig ileal longitudinal smooth muscle preparation. [b] The negative log of the concentration of antagonist causing 50% displacement of specific binding of [^{3}H]nitrendipine to guinea pig ileal smooth muscle membrane. [c] Lit.[21] values (mean ± SEM, $n \geq 4$).

values when indicated by the symbols of the elements. Flash chromatography was performed by utilizing Merck 60 silica gel with hexane/ethyl acetate (1:1 v/v) as eluant on a 3 × 25 cm column. The 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-[3-(4)-pyridinyl]pyridines **2** and **5** were prepared as described previously.[16]

General Procedure for the Preparation of 3,5-Disubstituted 4-[1,2(1,6)-Dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-3-pyridinyl]-1,4-dihydro-2,6-dimethylpyridines 4a/4b (7–14, 16–20, 22–29). Sodium borohydride (1.9 g, 50 mmol) was added to a solution of the 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-(3-pyridinyl)pyridine **2** (10 mmol) in methanol (20–40 mL) precooled to −65 °C. After 10 min, a solution of methyl (phenyl or *tert*-butyl) chloroformate (**3**; 15 mmol) in dry ether (5–10 mL) was added dropwise with stirring. The reaction was allowed to proceed for 4–6 h at −65 °C with stirring. The reaction mixture was poured onto crushed ice (50 mL) and allowed to come to room temperature, and the crude product was isolated by filtration or extraction with dichloromethane (4 × 50 mL). The organic extracts were dried ($MgSO_4$), the solvent was removed in vacuo, and the solid product **4a/4b** was purified by flash chromatography (3 × 25 cm) using hexane/ethyl acetate (1:1 v/v) as eluant. The regioisomers **4a/4b** could not be separated by column chromatography or TLC. The ratio of the two regioisomers **4a/4b** was determined from the ^{1}H NMR integrals for the NH singlet for each regioisomer and the H-6(**a**) and H-2(**b**) resonances, which were well-resolved.

Using this procedure, we obtained **7a/7b** (ratio 9:7): yield 73%; IR 3340 (NH) and 1680–1710 (CO_2, NCO_2) cm^{-1}; NMR (Me_2SO-d_6) **7a**, δ 2.3 (s, 6 H, $=CCH_3$), 3.63 (s, 6 H, CO_2CH_3), 3.7 (s, 3 H, NCO_2CH_3), 4.2 (s, 2 H, C_2-H), 4.36 (s, 1 H, 1,4-dihydropyridinyl C_4-H), 5.22 (d, $J_{4,5}$ = 5.5 Hz of d, $J_{5,6}$ = 6.1 Hz, 1 H, C_5-H), 5.52 (d, $J_{4,5}$ = 5.5 Hz, 1 H, C_4-H), 6.56 (d, $J_{5,6}$ = 6.1 Hz, 1 H, C_6-H), 8.89 (s, 1 H, NH, exchanges with deuterium oxide); NMR (Me_2SO-d_6) **7b**, δ 2.3 (s, 6 H, $=CCH_3$), 3.63 (s, 6 H, CO_2CH_3), 3.7 (s, 3 H, NCO_2CH_3), 4.16 (s, 2 H, C_6-H), 4.36 (s, 1 H, 1,4-dihydropyridinyl C_4-H), 5.56 (d, $J_{4,5}$ = 10.3 Hz, 1 H, C_5-H), 5.8 (d, $J_{4,5}$ = 10.3 Hz, C_4-H), 6.36 (s, 1 H, C_2-H), 8.98 (s, 1 H, NH, exchanges with deuterium oxide). These assignments were confirmed by double resonance experiments.

In a similar procedure, we obtained **26a/26b** (ratio 11:9): yield 62%; IR 3352 (NH), 2232 (CN), and 1704 (NCO_2); NMR (Me_2SO-d_6) **26a**, δ 2.0 (s, 6 H, $=CCH_3$), 3.38 (s, 3 H, CO_2CH_3), 4.0 or 4.1 (two closely spaced singlets or a singlet, respectively, 1 H, 1,4-dihydropyridinyl C_4-H), 4.3 and 4.52 (br s, 1 H each, C_2-H), 5.42 (m, 1 H, C_5-H), 5.86 (m, 1 H, C_4-H), 6.75 and 6.94 (2 d, $J_{5,6}$ = 7 Hz, 1 H total, C_6-H), 7.23–7.6 (m, 5 H, $CO_2C_6H_5$), 9.61 (s, 1 H, NH, exchanges with deuterium oxide); NMR (Me_2SO-d_6) **26b**, δ 2.0 (s, 6 H, $=CCH_3$), 3.38 (s, 3 H, CO_2CH_3), 4.0 or 4.1 (two closely spaced singlets or a singlet, respectively, 1 H, 1,4-dihydropyridinyl C_4-H), 4.36 and 4.58 (br s, 1 H each, C_6-H), 5.9–6.02 (m, 2 H, C_4-H, C_5-H), 6.68 and 6.92 (br s, 1 H total, C_2-H), 7.23–7.6 (m, 5 H, $CO_2C_6H_5$), 9.5 (s, 1 H, NH, exchanges with deuterium oxide). These assignments for **26a/26b** were confirmed by double resonance studies. When the ^{1}H NMR spectrum (δ) of **26a/26b** was determined at 115 °C (Me_2SO-d_6), the two doublets at δ 6.94 and 6.75 (H-6 of **26a**) underwent nearly complete coalescence to one doublet at δ 6.85; the two singlets at δ 6.92 and 6.68 (H-2 of **26b**) coalesced to a singlet at δ 6.75; the two broad singlets at δ 4.58 and 4.36 (H-6 of **26b**) became a broad singlet at δ 4.45; and the two singlets at δ 4.52 and 4.3 (H-2 of **26a**) coalesced to a sharp singlet at δ 4.4. Compounds **15** and **21** were prepared by an alternate procedure. Di-*tert*-butyl dicarbonate (1.08 g, 4.97 mmol) was added to a solution of the 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-(3-pyridinyl)pyridine **2** (3.31 mmol) in methanol (50 mL) precooled to 0 °C with stirring. After 10 min, sodium borohydride (0.63 g, 16.5 mmol) was added, and the reaction was allowed to proceed at 0 °C for 8 h with stirring. The products **15** and **21** were isolated as described previously.

General Procedure for the Preparation of 3,5-Disubstituted 4-[1,2-Dihydro-1-[[alkyl(or phenyl)oxy]carbonyl]-4-pyridinyl]-1,4-dihydro-2,6-dimethylpyridines 6 (30–43). Sodium borohydride (1.9 g, 50 mmol) was added to a solution of the 3,5-disubstituted 1,4-dihydro-2,6-dimethyl-4-(4-pyridinyl)pyridine **5** (10 mmol) in methanol (20–40 mL) precooled to −65 °C. After 10 min, a solution of methyl (phenyl or *tert*-butyl) chloroformate (**3**; 15 mmol) in dry ether (5–10 mL) was added dropwise with stirring, and the reaction was completed as described previously for the preparation of **4** to yield **6** as summarized in Table I.

Using this procedure, we obtained **30**: yield 74%; IR 3310 (NH) and 1710 (CO_2, NCO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 2.24 (s, 6 H, $=CCH_3$), 3.6 (s, 6 H, CO_2CH_3), 3.66 (s, 3 H, NCO_2CH_3), 4.18 (br s, 2 H, C_2-H), 4.38 (s, 1 H, 1,4-dihydropyridinyl C_4-H), 5.05 (m, 1 H, C_3-H), 5.12 (m, 1 H, C_5-H), 6.62 (d, $J_{5,6}$ = 7 Hz, 1 H, C_6-H), 8.92 (s, 1 H, NH, exchanges with deuterium oxide).

In a similar procedure, we obtained **36**: yield 63%; IR 3368 (NH) and 1688–1720 (CO_2, NCO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 0.93 (d, J = 7 Hz, 12 H, $CO_2CH_2CH(CH_3)_2$), 1.92 (m, 2 H, $CO_2CH_2CH(CH_3)_2$), 2.3 (s, 6 H, $=CCH_3$), 3.88 (m, 4 H, $CO_2CH_2CH(CH_3)_2$), 4.28 and 4.48 (2 br s, 1 H each, C_2-H), 4.56 (s, 1 H, 1,4-dihydropyridinyl C_4-H), 5.22 (br s, 1 H, C_3-H), 5.32 (d, $J_{5,6}$ = 8.6 Hz, C_5-H), 6.69 and 6.88 (2 d, $J_{5,6}$ = 8.6 Hz, 1 H, C_6-H), 8.92 (s, 1 H, NH, exchanges with deuterium oxide).

Calcium Channel Antagonist Assay.[20] 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 length 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% O_2) physiological saline solution of the following composition (mM): NaCl, 137; $CaCl_2$, 2.6; KCl, 5.9; $MgCl_2$, 1.2; glucose, 11.9 buffered by Hepes/NaOH, 9 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 5×10^{-7} M *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD). The isometric contractions were recorded with a force displacement transducer (FT 03.D) 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 ID_{50} values were graphically determined from the concentration–response curves. The pharmacological test results are summarized in Table I.

Competitive [^{3}H]Nitrendipine Binding Assay.[21] The inhibition of [^{3}H]nitrendipine binding to a microsomal fraction from guinea pig ileal longitudinal smooth muscle was carried out by using the procedure reported by Bolger et al.[21]

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Registry No. **2** ($R_1 = R_2 = CO_2Me$), 73349-75-4; **2** ($R_1 = R_2 = CO_2Et$), 23125-30-6; **2** ($R_1 = R_2 = CO_2$-*i*-Pr), 104196-54-5; **2** ($R_1 = R_2 = CO_2$-*i*-Bu), 104196-55-6; **2** ($R_1 = CO_2$-*i*-Bu, $R_2 = CO_2Me$), 104196-46-5; **2** ($R_1 = CO_2$-*i*-Pr, $R_2 = CO_2Me$), 39562-56-6; **2** ($R_1 = CO_2Me$, $R_2 = CN$), 67593-36-6; **2** ($R_1 = CN$, $R_2 = CN$), 64089-24-3; **5** ($R_1 = R_2 = CO_2Me$), 23125-31-7; **5** ($R_1 = R_2 = CO_2Et$), 21197-70-6; **5** ($R_1 = R_2 = CO2$-*i*-Pr), 104196-57-8; **5** ($R_1 = R_2 = CO_2$-*i*-Bu), 104196-58-9; **5** ($R_1 = CO_2Me$, $R_2 = CO_2$-*i*-Bu), 104196-49-8; **5** ($R_1 = CO_2$-*i*-Pr, $R_2 = CO_2Me$), 104196-48-7; **5** ($R_1 = R_2 = CN$), 64089-25-4; **7a**, 106457-24-3; **7b**, 106457-25-4; **8a**, 106457-26-5; **8b**, 106457-27-6; **9a**, 106457-28-7; **9b**, 106457-29-8; **10a**, 106457-30-1; **10b**, 106457-31-2; **11a**, 106457-32-3; **11b**, 106457-33-4; **12a**, 106457-34-5; **12b**, 106457-35-6; **13a**, 106457-36-7; **13b**, 106457-37-8; **14a**, 106457-38-9; **14b**, 106457-39-0; **15a**, 106457-40-3; **15b**, 106457-41-4; **16a**, 106457-42-5; **16b**, 106457-43-6; **17a**, 106457-44-7; **17b**, 106457-45-8; **18a**, 106457-46-9; **18b**, 106457-47-0; **19a**, 106457-48-1; **19b**, 106457-49-2; **20a**, 106457-50-5; **20b**, 106457-51-6; **21a**, 106457-52-7; **21b**, 106457-53-8; **22a**, 106457-54-9; **22b**, 106457-55-0; **23a**, 106457-56-1; **23b**, 106457-57-2; **24a**, 106469-33-4; **24b**, 106457-58-3; **25a**, 106457-59-4; **25b**, 106457-60-7; **26a**, 106457-61-8; **26b**, 106457-62-9; **27a**, 106457-63-0; **27b**, 106457-64-1; **28a**, 106457-65-2; **28b**, 106457-66-3; **29a**, 106457-67-4; **29b**, 106457-68-5; **30**, 106457-69-6; **31**, 106457-70-9; **32**, 106457-71-0; **33**, 106457-72-1; **34**, 106457-73-2; **35**, 106457-74-3; **36**, 106457-75-4; **37**, 106457-76-5; **38**, 106469-34-5; **39**, 106457-77-6; **40**, 106457-78-7; **41**, 106457-79-8; **42**, 106469-35-6; **43**, 106457-80-1; $ClCO_2Me$, 79-22-1; $ClCo_2Bu$-*t*, 24608-52-4; $ClCO_2Ph$, 1885-14-9.

Steroidal Silicon Side-Chain Analogues as Potential Antifertility Agents

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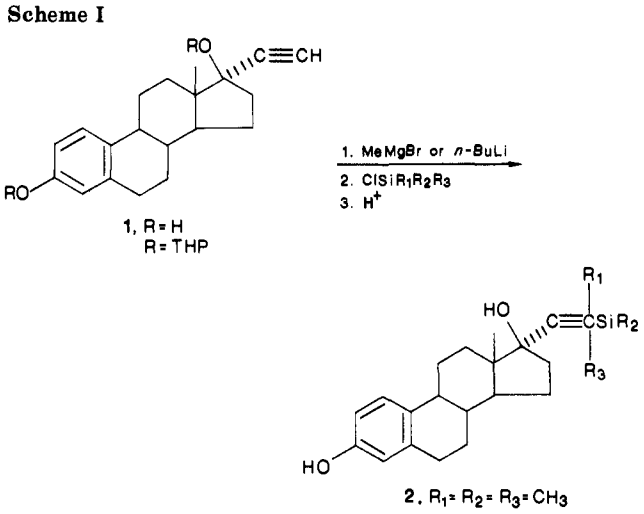
A number of silicon-substituted analogues of ethynylestradiol that exhibit modified and enhanced biological activities have been synthesized. Particularly noteworthy are a group of [(trialkylsilyl)ethynyl]estradiol analogues that exhibit high antifertility potency and markedly reduced estrogenic activity. The best compounds synthesized are 17α-[(triethylsilyl)ethynyl]estradiol (**5**) and 17α-[(*tert*-butyldimethylsilyl)ethynyl]estradiol (**33**), which show a separation of antifertility from estrogenic activity in the rat. The results of structure–activity studies indicate a good correlation between the observed biological activities and the calculated van der Waals volumes of the three variable silicon substituents.

Oral contraceptives, because of their long-term benefit-to-risk ratio, have been considered a major scientific advance in family planning since their introduction in 1960. However, the adverse side effects associated with the estrogenic components (ethynylestradiol or mestranol) of the "pill" have led to persistent anxieties among regulatory agencies, doctors, and users.[1] Estrogens have been implicated in breast cancer, endometrial carcinoma, and thromboembolic diseases.[2] Because of these concerns, the development of new estrogens as potential antifertility agents should focus on obtaining antifertility activity accompanied by a greatly diminished estrogenic activity.

Previous studies[3] have indicated that silicon-containing compounds used as medicinal agents can retain and/or improve their biological profile in comparison with that of their corresponding carbon isostere. For example, toxicity of the silacarbamate analogues of meprobamate was less than that of their carbon analogues at equipotent biological activities.[4] Furthermore, the trimethylsilyl ether of testosterone, Silandrone, has been described as a clin-

Scheme I



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