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Original paper

Synthesis and calcium channel antagonist activity of dialkyl hexahydro-1,2′,6′-trimethyl[bipyridine]-3′,5′-dicarboxylates

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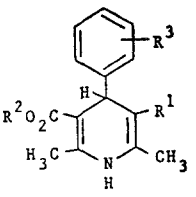
Summary — Reaction of dialkyl 1′,4′-dihydro-2′,6′-dimethyl[bipyridine]-3′,5′-dicarboxylates **2** with methyl iodide yielded the corresponding 4′-(1-methylpyridinium) iodide salts **3** in quantitative yield. The sodium borohydride reduction of **3** in aqueous ethanol gave the corresponding dialkyl hexahydro-1,2′,6′-trimethyl[bipyridine]-3′,5′-dicarboxylate analogs **4**—**5**. The calcium channel antagonist activities for **4**—**5** were determined using the muscarinic receptor-mediated Ca^{2+}-dependent contraction of guinea pig ileal longitudinal smooth muscle. The relative activities for the 3′,5′-diethyl series **5** was 3-tetrahydropyridinyl **5b** > 4-tetrahydropyridinyl **5c** > 2-tetrahydropyridinyl **5a**. Increasing the size of the 3′,5′-alkyl substituents enhanced activity. An approximate 1:1 correlation between the IC_{50} value for the inhibition of [^{3}H]nitrendipine binding and inhibition of the tonic component of the muscarinic-induced contractile response was observed for **4a** and **5b**. NMR studies suggest that the 4′-[2-(1-methyl-1,2,3,6-tetrahydropyridinyl)] ring systems of **4a** and **5a** are anti-periplanar to the 1,4-dihydropyridine ring system.

Résumé — **Synthèse et activité antagoniste des canaux calciques d'hexahydro triméthyl-1,2′,6′[bipyridine]dicarboxylates-3′,5′ de dialkyle.** *La quaternarisation des dihydro-1′,4′ diméthyl-2′,6′[bipyridine]dicarboxylates-3′,5′ de dialkyle* ***2*** *par l'iodure de méthyle a donné les iodures de (méthyl-1 pyridinium)-4′* ***3*** *avec un rendement théorique.* ***3*** *réduit par le borohydrure de sodium dans l'éthanol aqueux, a fourni les dialkyl hexahydrotriméthyl-1,2′,6[bipyridine]dicarboxylates-3′,5′* ***4*** *et* ***5*** *correspondants. L'activité antagoniste des canaux calciques pour* ***4*** *et* ***5*** *a été déterminée par contraction du muscle lisse longitudinal de l'iléon de cobaye dépendant du récepteur muscarinique à médiateur Ca^{2+}. L'activité relative dans la série des dérivés diéthyl-3′,5′* ***5*** *a été: tétrahydropyridinyl-3* ***5b*** *> tétrahydropyridinyl-4* ***5c*** *> tétrahydropyridinyl-2* ***5a****. L'augmentation de la taille des substituants alkyle en 3′ et 5′ a amélioré l'activité. Une corrélation approximative 1:1 entre la valeur de l'*IC_{50} *pour l'inhibition de la liaison de l'*[^{3}*H*]*nitrendipine et l'inhibition du composant tonique de la réponse contractile muscarinique induite a été observée pour* ***4a*** *et* ***5b****. Des études de RMN suggèrent que les systèmes cycliques tétrahydropyridiniques de* ***4a*** *et* ***5a*** *sont anti-périplanaires par rapport au système cyclique dihydro-1,4 pyridinique.*

calcium channel antagonists / 1,4-dihydropyridines / vasodilators / anti-hypertensives

Introduction

Cardiovascular disease is one of the leading causes of death today [1]. The first generation calcium channel antagonist nifedipine **1a**, which exhibits a pronounced vasodilator effect on coronary arteries, is used clinically to treat angina pectoris and hypertension. Changes in the substitution pattern on the 1,4-dihydropyridine ring provided drugs with different tissue selectivity, such as the calcium channel antagonist nimodipine **1b**, which selectively induces cerebral vasodilation [2]. In contrast, the calcium channel agonist Bay K 8644 **1c** exhibits a positive inotropic effect and stimulates smooth muscle contraction [3].



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a: $R^1 = CO_2Me$, $R^2 = Me$, $R^3 = 2 — NO_2$
b: $R^1 = CO_2CH_2CH_2OMe$, $R^2 = CH(Me)_2$, $R^3 = 3 — NO_2$
c: $R^1 = NO_2$, $R^2 = Me$, $R^3 = 2 — CF_3$

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In a previous study [4], we reported the calcium channel antagonist activities for dialkyl 1′,4′-dihydro-2′,6′-dimethyl-[bipyridine]-3′,5′-dicarboxylates. It was therefore of interest to investigate the effect of hydrogenation of the 4′-(pyridinyl) substituent to a 4′-(1-methyltetrahydropyridinyl) ring system and its point of attachment on calcium channel antagonist activity and tissue selectivity. We now report the synthesis and calcium channel antagonist activity of dialkyl hexahydro-1,2′,6′-trimethyl[bipyridine]-3′,5′-dicarboxylates **4** and **5**.

Chemistry

Reaction of dialkyl 1′,4′-dihydro-2′,6′-dimethyl[bipyridine]-3′,5′-dicarboxylates **2** [4] with methyl iodide in acetone at reflux gave the corresponding 4′-(1-methylpyridinium) iodide salts **3** in quantitative yield as illustrated in Scheme 1. Alkylation of the 1′,4′-dihydropyridine nitrogen of **2** did not occur, indicating that the pyridinyl nitrogen is a stronger nucleophile. The 1′,4′-dihydropyridine nitrogen is deactivated towards reactions with electrophiles, since the enamine system is conjugated with the electron-withdrawing ester substituents at C-3′ and C-5′. Sodium borohydride reduction of **3** in aqueous ethanol at 0°C gave the corresponding 4′-(1-methyltetrahydropyridinyl) analogs **4** and **5** in 75—92% yield. The sodium borohydride reduction of **3a** yielded **4a** rather than the 4′-[2-(1-methyl-1,2,5,6-tetrahydropyridinyl)] isomer **4d**. The exclusive formation of **4a** is attributed to regiospecific nucleophilic attack by the borohydride anion at the 6-position of **3a** due to steric hindrance by the 1′,4′-dihydropyridine ring at the 2-position of **3a**. A similar reduction of **3b** gave **4b**, which has the more substituted double bond rather than the 4′-[3-(1-methyl-1,2,3,6-tetrahydropyridinyl)] isomer **4e** [5, 6]. The structures of **4a—c** and **5a—c** were confirmed by ^{1}H NMR double resonance experiments.

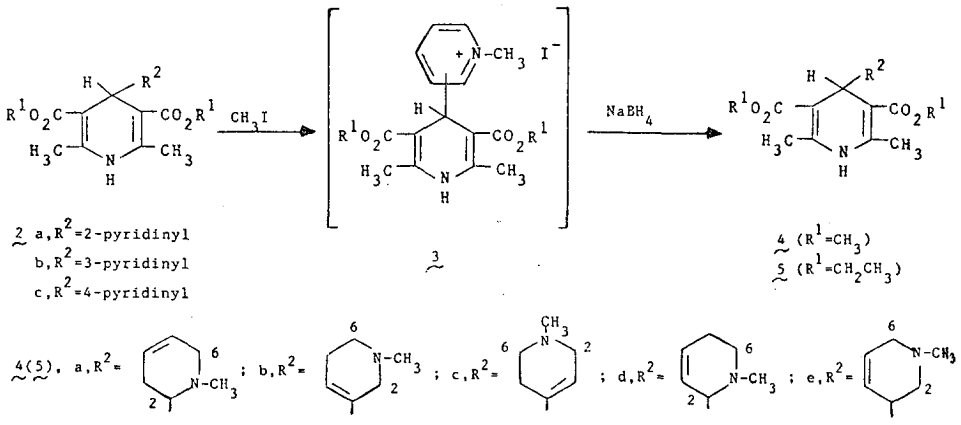
Pharmacology

The calcium channel antagonist activities for **4** and **5**, determined as the concentration needed to produce a 50% inhibition of the muscarinic receptor-mediated Ca^{2+}-dependent contraction of guinea pig ileal longitudinal smooth muscle (using a modified procedure of that reported in [7]), are given in Table I.

Structure—Activity Discussion

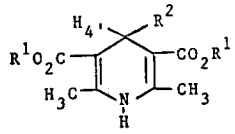
The nature and position of substituents present at the C-3′, C-4′ and C-5′ positions of nifedipine and related analogs are important determinants of activity, tissue selectivity [2, 8—13] and conformation (degree of ring pucker) of the 1′,4′-dihydropyridine ring which correlate well with activity [14—16]. Structure—activity correlations indicate that activity is highly dependent upon the size of the C-4′ phenyl substituents but relatively independent of their electronic character, *viz* electron-donating or electron-attracting properties [17, 18]. In an earlier study, we demonstrated that a 4′-(pyridinyl) substituent was isosteric with a 4′-(nitrophenyl) substituent on a 1′,4′-dihydropyridine ring system where *ortho*-, *meta*- and *para*-nitrophenyl were bioisosteric with 2-pyridinyl, 3-pyridinyl and 4-pyridinyl, respectively [4]. Since activity is relatively independent of the electronic character of the C-4′ phenyl [17, 18] and pyridinyl [4] substituents but highly dependent upon their steric size for nifedipine and related analogs, it was anticipated that similarly positioned C-4′ 1-methyltetrahydropyridinyl ring systems would exhibit an activity profile in which **4a (5a)** > **4b (5b)** > **4c (5c)**.

The calcium channel test results (see Table I), for the 3′,5′-dimethyl series **4**, indicate the relative activity order was 3-tetrahydropyridinyl **4b** > 2-tetrahydropyridinyl **4a** > 4-tetrahydropyridinyl **4c**, whereas in the related 3′,5′-diethyl series **5**, it was 3-tetrahydropyridinyl **5b** > 4-tetrahydropyridinyl **5c** > 2-tetrahydropyridinyl **5a**. The decreased activity of **4c** relative to **4a** in comparison to the increased activity of **5c** relative to **5a** may be due to the greater steric effect exhibited by the 3′,5′-diethyl substituents of **5** relative to the 3′,5′-dimethyl substituents of **4**. The steric effects of the 3′,5′-diethyl substituents influence activity, since the 3′,5′-diethyl compounds **5a—c** were more potent than the corresponding 3′,5′-dimethyl analogs **4a—c**. The relative activities observed for **4** and **5** differ from those reported



Scheme 1.

Table I. Some physical and calcium channel antagonist activity (CCAA) data for dialkyl hexahydro-1,2′,6′-trimethyl[bipyridine]-3′,5′-dicarboxylates **4** and **5**.

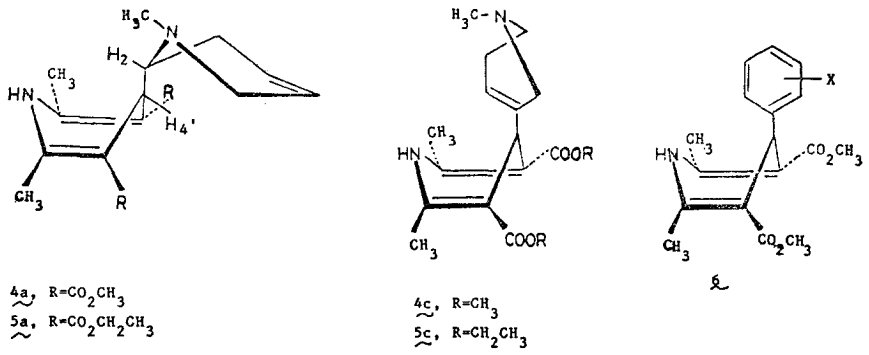


Compd	R^1	R^2	mp (°C)	Yield (%)	Formula	Anal.	CCAA[a]: IC_{50}(M)[b]
4a	Me	2-thp[c]	159—161	78	$C_{17}H_{24}N_2O_4$	C, H, N	$6.4 \pm 0.24 \times 10^{-5}$
4b	Me	3-thp[d]	161—162	90	$C_{17}H_{24}N_2O_4$	C, H, N	$3.43 \pm 0.5 \times 10^{-6}$
4c	Me	4-thp[e]	133—134	92	$C_{17}H_{24}N_2O_4$	C, H, N	$1.81 \pm 0.5 \times 10^{-4}$
5a	Et	2-thp	131—133	76	$C_{19}H_{28}N_2O_4$	C, H, N	$1.3 \pm 0.05 \times 10^{-5}$
5b	Et	3-thp	125—126	87	$C_{19}H_{28}N_2O_4$	C, H, N	$1.1 \pm 0.7 \times 10^{-6}$
5c	Et	4-thp	114—116	95	$C_{19}H_{28}N_2O_4$	C, H, N	$4.96 \pm 1.33 \times 10^{-6}$
Nifedipine							$1.4 \pm 0.19 \times 10^{-8}$[f]

[a]Inhibition of contractile response to CD (*cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide).
[b]The concentration of antagonist causing a 50% decrease in the slow component or tonic response ($IC_{50} \pm$ SEM, $n = 3$) in the guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist CD was determined graphically from the dose—response curves.
[c]2-thp: 2-(1-methyl-1,2,3,6-tetrahydropyridinyl).
[d]3-thp: 3-(1-methyl-1,2,5,6-tetrahydropyridinyl).
[e]4-thp: 4-(1-methyl-1,2,5,6-tetrahydropyridinyl).
[f]$n = 18$.

for the pyridinyl analogs **2** [4] where **2a** ($2.32 \pm 0.19 \times 10^{-6}$) > **2b** ($3.83 \pm 0.83 \times 10^{-6}$) > **2c** ($5.0 \pm 1.1 \times 10^{-6}$) and nifedipine analogs where, in most cases, *ortho*-nitrophenyl > *meta*-nitrophenyl > *para*-nitrophenyl [14, 18].

X-ray crystallographic studies of 1′,4′-dihydropyridines **6**, structurally related to nifedipine, indicate that **6** exists in a boat-type conformation with the greatest degree of distortion at the nitrogen (N-1′) and tetrahedral carbon (C-4′) where both atoms are displaced in the same direction. The degree of ring puckering is dependent upon the repulsive interactions between the ring substituents. The C-4′ phenyl substituent exists in a 'priapic' orientation in which it is perpendicular to the 1′,4′-dihydropyridine ring [14]. The ^{1}H NMR spectrum of **4a** showed the C-4H′ as a doublet at δ 4.3 having a $J_{2,4'}$ coupling constant of 7.72 Hz. Vicinal coupling constants are dependent upon the dihedral angle between the H—C—C—H bonds involved [19] and these two parameters may be correlated using the Karplus equation [20—22]. The Karplus equation is useful for obtaining approximate dihedral angles, although it must be used with caution. Application of this equation suggested a dihedral angle C-2H—C-4H′ of either 158.1° or 10.3°. A plausible three dimensional conformation for **4a** which places the 1′,4′-dihydropyridine ring anti-periplanar to the 2-tetrahydropyridinyl moiety would be most favored ($\varphi = 158.1°$). A C-2H—C-4H′ dihedral angle of 10.3° would be less favorable, since it would force the two heterocyclic rings into a *quasi syn*periplanar conformation where non-bonded interactions would be expected to increase. Therefore, it would seem unlikely that the molecule would adopt a conformation in which the dihedral angle is 10.3°. An alternate conformation to that proposed for **4a**, in which the 1′,4′-dihydropyridine ring is pseudoequatorial to the tetrahydropyridine ring, would position the tetrahydropyridine ring perpendicular to the 1′,4′-dihydropyridine ring. This conformation for **4a**, which is similar to that of **4b**, **c**, is less feasible, since there would be considerable non-bonded interactions between the C-3′, C-4′ and C-5′ substituents for an HC-2—C-4′H bond angle of either 10.3 or 158.1°. Furthermore, the conformation proposed for



Scheme 2.

4a is consistent with the observations that a 2-substituent in a tetrahydropyridine or piperidine ring adopts the axial orientation as indicated in the structure for **4a** [23—25]. Similarly, **5a** exhibited a $J_{2,4'}$ coupling constant of 8.88 Hz which would correspond to a C-2H—C-4H′ bond angle of 173.5°. The increased bond angle for **5a** relative to **4a** may be due to the greater steric effects of the 3′,5′-diethoxycarbonyl substituents.

The preferred conformation for **4b, c** may be significantly different from that of **4a**. The 1′,4′-dihydropyridinyl ring of **4b, c** is attached to an sp^2 hybridized carbon of the tetrahydropyridinyl ring rather than an sp^3 hybridized carbon as in **4a**. It is conceivable that the tetrahydropyridinyl ring of **4b, c** may be approximately perpendicular to the 1′,4′-dihydropyridine ring similar to that reported for nifedipine analogs [14], in which the tertiary nitrogen would be expected to be positioned away from the 1′,4′-dihydropyridine ring system. To decrease the non-bonded interactions between the C-3′, C-4′ and C-5′ substituents, the 1′,4′-dihydropyridine ring could adopt a more planar conformation. If this is the case, **4c** as well as **4b** would have a spatial conformation similar to nifedipine analogs [14]. If these conformational hypotheses are valid, it would be reasonable to expect that **4a** and **5a**, in which the 2-tetrahydropyridinyl ring system may be approximately coplanar with the 1′,4′-dihydropyridine ring system, would be less active than the respective 3-tetrahydropyridinyl isomers **4b** and **5b**, which in turn would be less active than the respective 4-tetrahydropyridinyl isomers **4c** and **5c** in which the 3- and 4-tetrahydropyridinyl ring systems are expected to be perpendicular to the 1′,4′-dihydropyridine ring system. The observed relative activity sequences **5b** > **5c** > **5a** and **4b** > **4c** are consistent with this conformational hypothesis.

The decreased activities of **4b, c** and **5b, c**, relative to nifedipine, could be due to a number of differences. The 3- and 4-(1-methyl-1,2,5,6-tetrahydropyridinyl) rings exhibit a greater degree of ring pucker than the planar *ortho*-nitrophenyl substituent of nifedipine and the π-electron density of the tetrahydropyridinyl ring would be minimal, since it has only one olefinic bond. The decreased activity for **4** and **5** suggests that the conformation and/or degree of unsaturation of the 4′-substituent in the 1′,4′-dihydropyridine ring is relevant to calcium channel antagonist activity and hence to interaction with the 1′,4′-dihydropyridine binding site. A proposed model of the dihydropyridine receptor on the calcium channel suggests that the aryl ring of nifedipine analogs binds to a flat rigid part of the receptor [26]. Increasing the size of the 3′,5′-alkoxycarbonyl substituents increased activity, since **5** were more potent than the corresponding analogs **4**. Similar results were observed for the 4′-(pyridinyl) analogs **2**, where activities in the 10^{-8} M range were observed for compounds having bulky 3′,5′-dialkoxycarbonyl substituents [4].

The dialkyl hexahydro-1,2′,6′-trimethyl[bipyridine]-3′,5′-dicarboxylate analogs **4a, b** and **5b, c** were competitive inhibitors of specific [^{3}H]nitrendipine binding [27] with IC_{50} values of 4.4×10^{-5}, 5.1×10^{-5}, 3.1×10^{-6} and 8.2×10^{-5} M, respectively. The approximate 1:1 correlation between the IC_{50} values for the inhibition of [^{3}H]nitrendipine binding and inhibition of the tonic component of the CD-induced contractile response (Table I) indicates that the tetrahydropyridinyl analogs **4a** and **5b** interact with the same dihydropyridine binding site as nitredipine and nifedipine [27]. A larger discrepancy was observed for **4b** and **5c**, whose antagonist activities were 14- and 16-fold, respectively, more sensitive than their binding capacities. This observation suggests that **4b** and **5c** may be acting on calcium channels by a different type of receptor interaction.

Experimental protocols

Chemistry

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in $CDCl_3$ with Me_4Si as the internal standard with a Bruker AM-300 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 spectra were in agreement with the assigned structures. All of the products described gave rise to a single spot on TLC, using three different solvent systems of low, medium and high polarity. Microanalyses were within ± 0.4% of theoretical values when indicated by the symbols of the elements. The dialkyl 1′,4′-dihydro-2′,6′-dimethyl-[bipyridine]-3′,5′-dicarboxylates **2** were prepared using the previously reported procedure [4].

General method for the preparation of dialkyl hexahydro-1,2′,6′-trimethyl-[bipyridine]-3′,5′-dicarboxylates 4a—c and 5a—c

A solution of the dialkyl 1′,4′-dihydro-2′,6′-dimethyl[bipyridine]-3′,5′-dicarboxylate **2** (10 mmol) in acetone (50 ml) was added to iodomethane (4.25 g, 30 mmol) and the mixture was heated under reflux for 7—9 h. The reaction mixture was cooled to 25°C and the solvent was removed *in vacuo* to yield **3**. A solution of the *N*-methylpyridinium salt **3**, in 20 ml of ethanol—water (1:1, v/v) cooled to 0°C, was added to a solution of sodium borohydride (1.9 g, 50 mmol) in absolute ethanol (15 ml) precooled to 0°C. The reaction was allowed to proceed for 5—7 h at 0°C, water (50 ml) was added and the resulting solid was filtered. Recrystallization from aqueous ethanol (1:1, v/v, 10 ml) gave the respective products **4** and **5** (see Table I).

Using this procedure, we obtained dimethyl 1,1′,2,3,4′,6-hexahydro-1,2′,6′-trimethyl[2,4′-bipyridine]-3′,5′-dicarboxylate **4a**: yield 78%; IR: 3280 (NH), 1670 (CO_2), 1630 (C=C) and 1280 (C—N) cm^{-1}, NMR ($CDCl_3$) δ: 1.7—1.9 and 1.9—2.06 (two m, 1H each, C_3—H); 2.33 (s, 6H, =C—CH_3); 2.37 (s, 3H, NCH_3); 2.3—2.56 (m, 1H, C_2—H); 3.12 (m, 2H, C_6—H); 3.75 and 3.77 (two s, 3H each, CO_2CH_3); 4.3 (d, $J_{2,4'}$ = 7.72 Hz, 1H, $C_{4'}$—H); 5.5—5.64 (m, 1H, C_5—H); 5.64—5.8 (m, $J_{4,5}$ = 10 Hz, 1H, C_4—H); 6.38 (s, 1H, NH, exchanges with deuterium oxide). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

Dimethyl 1,1′,2,4′,5,6-hexahydro-1,2′,6′-trimethyl[3,4′-bipyridine]-3′,5′-dicarboxylate **4b** was prepared using a similar procedure: yield 90%; IR: 3340 (NH), CO_2 (1705), 1630 (C=C) and 1280 (C—N) cm^{-1}; NMR ($CDCl_3$) δ 2.1—2.2 (m, 2H, C_5—H); 2.24 (s, 6H, =CCH_3); 2.34 (s, 3H, NCH_3); 2.4 (t, J = 7.19 Hz, 2H, C_6—H); 2.86 (m, 2H, C_2—H); 3.6 (s, 6H, CO_2CH_3); 4.46 (s, 1H, $C_{4'}$—H); 5.48 (m, 1H, C_4—H); 6.06 (s, 1H, NH, exchanges with deuterium oxide). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

In this way, we also obtained dimethyl 1,1′,2,4′,5,6-hexahydro-1,2′,6′-trimethyl[4,4′-bipyridine]-3,′5′,-dicarboxylate **4c**: yield 92%; IR: 3390 (NH), 1670 (CO_2), 1600 (C=C) and 1285 (C—N) cm^{-1}; NMR ($CDCl_3$) δ: 2.12 (m, 2H, C_5—H); 2.2 (s, 3H, NCH_3); 2.3 and 2.32 (two s, 3H each, =CCH_3); 2.42 (t, J = 5.5 Hz, 2H, C_6—H); 2.84 (d, J = 2.5 Hz, C_2—H); 3.7 (s, 6H, CO_2CH_3); 4.49 (s, 1H, $C_{4'}$—H); 5.38 (m, 1H, C_3—H); 6.62 (s, 1H, NH, exchanges with deuterium oxide). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

Pharmacology

Calcium channel antagonist assay (modified from [7])

Male albino guinea pigs (body weight 300—450 g) were sacrified by

decapitation. The intestine was removed above the ileo—caecal junction. Longitudinal smooth muscle segments, 2 cm long, 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 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 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 re-equilibrate. The calcium antagonist was added ten minutes before the dose—response for CD was determined. The drug-induced inhibition of contraction was expressed as percent of control. The IC_{50} values were graphically determined from the concentration—response curves. The pharmacological test results are summarized in Table I.

Competitive [^{3}H]nitredipine binding assay [27]
The inhibition of [^{3}H]nitrendipine binding to a microsomal fraction from guinea pig ileal longitudinal smooth muscle was carried out using the procedure reported by Bolger *et al.* [27].

Acknowledgement

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