Synthesis of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(heteroaryl)-pyridine-3,5-dicarboxylates as Calcium Channel Antagonists

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The Hantzsch condensation of the heteroarylcarboxaldehydes **3a-c** with alkyl acetoacetates **4a-c** and alkyl 3-aminocrotonates **5a-b** afforded the respective dialkyl 1,4-dihydro-2,6-dimethyl-4-(heteroaryl)-pyridine-3,5-dicarboxylates **6a-f** possessing a C-4 4-quinolinyl, 8-quinolinyl or 1-oxido-4-pyridinyl substituent. Calcium channel antagonist structure-activity relationships acquired indicate that i) the position of the quinolyl nitrogen atom was not a determinant of activity, ii) increasing the size of the C-3 and C-5 alkyl ester substituents decreases potency and iii) a C-4 1-oxido-4-pyridinyl substituent abolishes activity. The most active, and equipotent C-4 4-quinolinyl **6a** and 8-quinolinyl **6b** analogs, were approximately 8-fold less potent calcium channel antagonists than the reference drug nifedipine.

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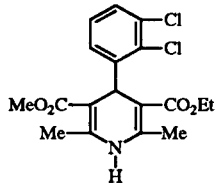
Introduction.

Vasculature-selective Hantzsch 1,4-dihydropyridine calcium channel antagonists, that close the L-type voltage dependent calcium channel, such as felodipine (**1**) exhibit a minimal inotropic effect and are useful for the treatment of hypertension and vasospasm [1]. Structure-activity relationships for dialkyl 1,4-dihydro-2,6-dimethyl-4-aryl-3,5-pyridinedicarboxylates indicate that the nature and position of aryl ring substituents are determinants of calcium channel antagonist activity where the potency order is generally *ortho* ≥ *meta* >> *para* [2,3]. Changes in the substitution pattern at the C-3, C-4 and C-5 positions of the 1,4-dihydropyridine system alter potency, tissue selectivity [4,5], and the conformation (degree of ring pucker) of the 1,4-dihydropyridine ring, which correlated well with activity. The most potent compounds show the smallest degree of ring distortion from planarity. Hantzsch 1,4-dihydropyridines, in the solid state, exist in a boat conformation where the C-4 substituted-phenyl ring is perpendicular (pseudoaxial) to the 1,4-dihydropyridine ring. Strain due to non-bonded interactions between the C-3, C-4 and C-5 1,4-dihydropyridine substituents is relieved most notably by puckering of the 1,4-dihydropyridine ring and distortion of the bond angles about C-4 [3,6,7].

In an earlier study, we showed that a 4-(pyridinyl) substituent **2** is bioisosteric with a 4-(nitrophenyl) substituent on a 1,4-dihydropyridine ring where *ortho-*, *meta-* and *para*-nitrophenyl are bioisosteric with 2-pyridinyl, 3-pyridinyl, and 4-pyridinyl, respectively [8]. These results indicate that the position of the pyridinyl nitrogen free electron-pair, and/or charge distribution [9,10] in the pyridinyl ring, may be capable of electrostatic binding to the α_1-subunit binding site of the L-type calcium channel receptor [11] and ultimately a determinant of calcium channel antagonist activity. As part of our on-going program to study the structure-function relationship of calcium channels, we now report the syntheses and *in vitro* calcium channel antagonist activities for dialkyl 1,4-dihydro-2,6-dimethyl-4-(quinolinyl)pyridine-3,5-dicarboxylates **6a-e**, and the related C-4 1-oxido-4-pyridinyl analog **6f**.



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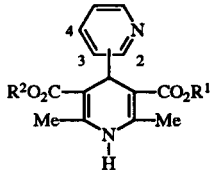

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Chemistry.

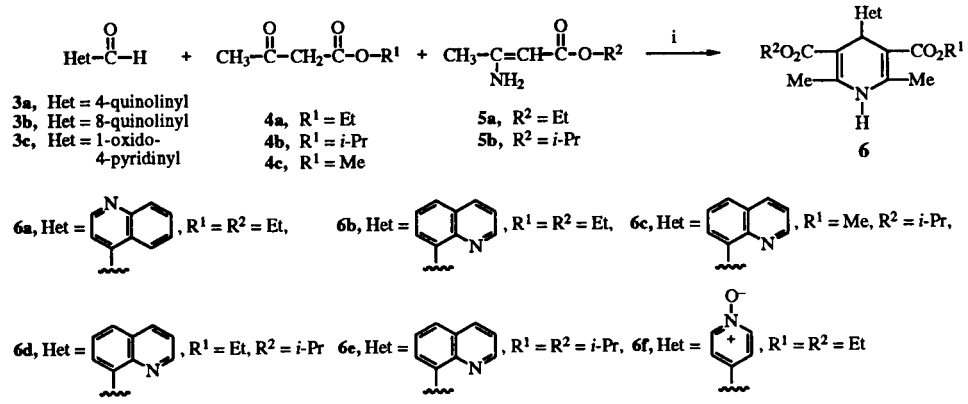
The dialkyl 1,4-dihydro-2,6-dimethyl-4-(heteroaryl)-pyridine-3,5-dicarboxylates **6a-f** were synthesized using a three-component modified Hantzsch reaction [12,13]. Accordingly, condensation of the respective heteroarylcarboxaldehyde **3a, 3b** or **3c** with the alkyl acetoacetate **4a, 4b** or **4c** and an alkyl 3-aminocrotonate **5a** or **5b** in ethanol at reflux afforded the respective 1,4-dihydropyridine product **6a-f** in 28-86% yield as illustrated in Scheme 1. This modified Hantzsch reaction provides superior yields of unsymmetrical 1,4-dihydropyridine compounds such as **6c** and **6d**.

Biological Results.

The *in vitro* calcium channel antagonist activities of compounds **6a-f**, determined as the molar concentration of test compound causing a 50% decrease in the slow component, or tonic contractile response, (IC_{50} ± SEM(standard error means), n = 3) in guinea pig ileum longitudinal smooth muscle induced by the muscarinic agonist carbachol (1.6×10^{-7} *M*), were determined graphically from the dose-response curves [14]. The results are summarized in Table 1.

A comparison of the activities of the equipotent 4-quinolinyl **6a** and 8-quinolinyl **6b** isomers indicates that

Scheme 1 [a]



[a] Reagents and conditions: i, EtOH, reflux, 18-48 hours.

the position of the quinolinyl nitrogen is not a determinant of calcium channel antagonist activity. In the 8-quinolinyl series of compounds **6b-e**, increasing the size of the alkyl ester substituents decreases potency [**6b** ($R^1 = R^2 = Et$) > **6e** ($R^1 = R^2 = i$-Pr); **6b** ($R^1 = R^2 = Et$) > **6d** ($R^1 = Et$, $R^2 = i$-Pr)]. These results indicate that small R^1 and R^2 alkyl ester substituents such as Et, or preferably Me which would be expected to reduce the non-bonded interactions between the C-3, C-4 and C-5 substituents, should be selected when a large C-4 substituent such as 8-quinolinyl is present on the 1,4-dihydropyridine ring system. This structure-activity relationship differs from previous results for compounds **2** possessing a C-4 2-, 3- or 4-pyridinyl substituent where increasing the size of the alkyl ester substituents generally increased potency [8]. The C-4 8-quinolinyl ring system (**6b**, $IC_{50} = 1.20 \times 10^{-7}$ *M*) is bioisosteric with a C-4 2-pyridinyl substituent present in **2** ($R^1 = R^2 = Et$, $IC_{50} = 1.77 \times 10^{-7}$ *M*) [8].

Table 1

Calcium Channel Antagonist Activities for Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(heteroaryl)pyridine-3,5-dicarboxylates **6a-f**

Compound	R^1	R^2	Heterocyclic Substitutent	Calcium channel antagonist act:ivity IC_{50} (*M*) [a]
6a	Et	Et	4-quinolinyl	$1.21 \pm 0.11 \times 10^{-7}$ (3)
6b	Et	Et	8-quinolinyl	$1.20 \pm 0.12 \times 10^{-7}$ (3)
6c	Me	i-Pr	8-quinolinyl	$5.23 \pm 0.17 \times 10^{-6}$ (3)
6d	Et	i-Pr	8-quinolinyl	$6.75 \pm 0.28 \times 10^{-5}$ (3)
6e	i-Pr	i-Pr	8-quinolinyl	$3.23 \pm 0.48 \times 10^{-5}$ (3)
6f	Et	Et	1-oxido-4-pyridinyl	$> 1.0 \times 10^{-4}$ (3)
Nifedipine [b]				$1.43 \pm 0.19 \times 10^{-8}$ (8)

[a] The molar concentration of antagonist test compound causing a 50% decrease in the slow component, or tonic contractile response, ($IC_{50} \pm$ SEM) in guinea pig ileum longitudinal smooth muscle by the muscarinic agonist carbachol (1.6×10^{-7} *M*) was determined graphically from the dose-response curves. The number of experiments is shown in brackets. [b] Reference calcium channel antagonist drug (Adalat®).

Replacement of the C-4 4-quinolinyl substituent present in **6a** ($IC_{50} = 1.21 \times 10^{-7}$ *M*) by a 1-oxido-4-pyridinyl substituent as in **6f** ($IC_{50} = > 1.0 \times 10^{-4}$ *M*) abolished calcium channel antagonist activity. The most active 4-quinolinyl **6a** and 8-quinolinyl **6b** compounds were approximately 8-fold less potent calcium channel antagonists than the reference drug nifedipine.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capilliary apparatus and are uncorrected. Nuclear magnetic resonance resonance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer. The assignment of exchangeable protons (N*H*) was confirmed by the addition of deuterium oxide. Infrared spectra were acquired using a Nicolet 5DX-FT spectrometer. Silica gel column chromatography was carried out using Merck 7734 (60-200 mesh) silica gel. 4-Quinolinecarboxaldehyde (**3a**), 1-oxido-4-pyridinecarboxaldehyde (**3c**), ethyl acetoacetate (**4a**), methyl acetoacetate (**4c**), ethyl 3-aminocrotonate (**5a**) and isopropyl 3-aminocrotonate (**5b**) were purchased from the Aldrich Chemical Co. Isopropyl acetoacetate (**4b**) was purchased from the Lancaster Chemical Co. 8-Quinolinecarboxaldehyde (**3b**) was synthesized by the selenium dioxide oxidation of 8-methylquinoline (purchased from the Aldrich Chemical Co.) using a literature procedure [15].

General Procedure for the Synthesis of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(heteroaryl)pyridine-3,5-dicarboxylates **6a-f**.

A mixture of the heteroarylcarboxaldehyde **3a, 3b** or **3c** (1 mmole), the alkyl acetoacetate **4a, 4b** or **4c** (1 mmole) and the alkyl 3-aminocrotonate **5a** or **5b** (1 mmole) in ethanol (50 ml) was heated at reflux until the reaction had gone to completion, 18-48 hours. Removal of the solvent *in vacuo*, purification of the residue obtained by silica gel column chromatography using ethyl acetate-hexane (2:1, v/v for **6a-d** and **6a-f**; 1:4, v/v for **6e**) as eluent, and then recrystallization of the product from ethyl acetate-hexane (1:1, v/v) yielded the respective product **6a-f**. The percentage yield, mp, ir and ^{1}H nmr spectral data for **6a-f** are reported below.

Diethyl 1,4-Dibydro-2,6-dimethyl-4-(4-quinolinyl)pyridine-3,5-dicarboxylate (**6a**).

This compound was obtained in a yield of 78%, mp 203-204°; ir (potassium bromide): ν 3182 (NH), 1691 (CO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 2.38 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me's*), 3.90 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$), 5.84 (s, 1H, 1,4-dihydropyridine H-4), 6.47 (s, 1H, N*H*), 7.47 (d, $J_{2,3}$ = 4.8 Hz, 1H, quinolyl H-3), 7.59 (ddd, $J_{5,6} = J_{6,7}$ = 8.0, $J_{6,8}$ = 1.0 Hz, 1H, quinolyl H-6), 7.70 (ddd, $J_{6,7} = J_{7,8}$ = 8.0, $J_{5,7}$ = 1.0 Hz, 1H, quinolyl H-7), 8.09 (dd, $J_{5,6}$ = 8.0, $J_{5,7}$ = 1.0 Hz, 1H, quinolyl H-5), 8.64 (d, $J_{7,8}$ = 8.0 Hz, 1H, quinolyl H-8), 8.80 (d, $J_{2,3}$ = 4.8 Hz, 1H, quinolyl H-2).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.24; H, 6.35; N, 7.41.

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(8-quinolinyl)pyridine-3,5-dicarboxylate (**6b**).

This compound was obtained in a yield of 31%, mp 160-161°; ir (potassium bromide): ν 3188 (NH), 1698 (CO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.80 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 2.26 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me's*), 3.88 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$), 5.72 (s, 1H, 1,4-dihydropyridine H-4), 6.25 (s, 1H, N*H*), 7.29 (dd, $J_{2,3}$ = 5.0, $J_{3,4}$ = 8.0 Hz, 1H, quinolyl H-3), 7.40 (t, $J_{5,6} = J_{6,7}$ = 7.5 Hz, 1H, quinolyl H-6), 7.56-7.67 (m, 2H, quinolyl H-5 and H-7), 8.13 (dd, $J_{3,4}$ = 8.0, $J_{2,4}$ = 1.5 Hz, 1H, quinolyl H-4), 8.93 (dd, $J_{2,3}$ = 5.0, $J_{2,4}$ = 1.5 Hz, 1H, quinolyl H-2).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.13; H, 6.60; N, 7.18.

3-Isopropyl 5-Methyl 1,4-Dihydro-2,6-dimethyl-4-(8-quinolinyl)pyridine-3,5-dicarboxylate (**6c**).

This compound was obtained in a yield of 36%, mp 192-193°; ir (potassium bromide): ν 3183 (NH), 1704 (CO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.56 and 1.08 (two d, J = 6.2 Hz, 3H each, $CHMe_2$), 2.26 and 2.28 (two s, 3H each, 1,4-dihydropyridine C-2 and C-6 *Me's*), 3.38 (s, 3H, CO_2CH_3), 4.63 (septet, J = 6.2 Hz, 1H, $CHMe_2$), 5.59 (s, 1H, 1,4-dihydropyridine H-4), 6.23 (s, 1H, N*H*), 7.30 (dd, $J_{2,3}$ = 5.0, $J_{3,4}$ = 8.0 Hz, 1H, quinolyl H-3), 7.41 (t, $J_{5,6} = J_{6,7}$ = 8.0 Hz, 1H, quinolyl H-6), 7.56-7.66 (m, 2H, quinolyl H-5 and H-7), 8.04 (dd, $J_{3,4}$ = 8.0, $J_{2,4}$ = 1.5 Hz, 1H, quinolyl H-4), 8.95 (dd, $J_{2,3}$ = 5.0, $J_{2,4}$ = 1.5 Hz, 1H, quinolyl H-2).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.12; H, 6.37; N, 7.25.

3-Isopropyl 5-Ethyl 1,4-Dihydro-2,6-dimethyl-4-(8-quinolinyl)-pyridine-3,5-dicarboxylate (**6d**).

This compound was obtained in a yield of 28%, mp 96-97°; ir (potassium bromide): ν 3217 (NH), 1696 (CO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.50-0.53 (m, 6H total, $CO_2CH_2CH_3$ and CO_2CHCH_3), 0.73 (d, J = 6.1 Hz, 3H, CO_2CHCH_3), 2.78 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me's*), 3.73 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.66 (septet, J = 6.1 Hz, 1H, $CHMe_2$), 5.59 (s, 1H, 1,4-dihydropyridine H-4), 6.23 (s, 1H, N*H*), 7.43 (dd, $J_{2,3}$ = 4.3, $J_{3,4}$ = 8.3 Hz, 1H, quinolyl H-3), 7.55-7.63 (m, 2H, quinolyl H-5 and H-7), 7.85-7.95 (m, 1H, quinolyl H-6), 8.20 (dd, $J_{3,4}$ = 8.3, $J_{2,4}$ = 1.7 Hz, 1H, quinolyl H-4), 8.91 (dd, $J_{2,3}$ = 4.3, $J_{2,4}$ = 1.7 Hz, 1H, quinolyl H-2).

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.10; H, 6.31; N, 7.00.

Diisopropyl 1,4-Dihydro-2,6-dimethyl-4-(8-quinolinyl)pyridine-3,5-dicarboxylate (**6e**).

This compound was obtained in a yield of 40%, mp 162-163°; ir (potassium bromide): ν 3201 (NH), 1698 (CO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.50 and 0.71 (two d, 6H each, $CHMe_2$), 2.71 (s, 6H, 1,4-dihydropyridine C-2 and C- 6 *Me's*), 4.64 (septet, J = 6.1 Hz, 1H, $CHMe_2$), 5.59 (s, 1H, 1,4-dihydropyridine H-4), 6.23 (s, 1H, N*H*), 7.41 (d, $J_{2,3}$ = 4.2 Hz, 1H, quinolyl H-3), 7.56 (d, $J_{5,6} = J_{6,7}$ = 8.1 Hz, 2H, quinolyl H-5 and H-7), 7.88 (t, $J_{5,6} = J_{6,7}$ = 8.1 Hz, 1H, quinolyl H-6), 8.18 (dd, $J_{3,4}$ = 8.3, $J_{2,4}$ = 1.8 Hz, 1H, quinolyl H-4), 8.90 (dd, $J_{2,3}$ = 4.2, $J_{2,4}$ = 1.8 Hz, 1H, quinolyl H-2).

Anal. Calcd. for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.70; H, 6.58; N, 6.77.

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(1-oxido-4-pyridinyl)-pyridine-3,5-dicarboxylate (**6f**).

This compound was obtained in a yield of 86%, mp 218-220°; ir (potassium bromide): ν 3172 (NH), 1688 (CO_2), 1231 (NO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 2.38 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me's*), 4.12 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$), 5.02 (s, 1H, 1,4-dihydropyridine H-4), 7.21 (s, 1H, N*H*), 7.31 (d, $J_{2,3} = J_{5,6}$ = 7.0 Hz, 2H, 1-oxido-4-pyridinyl H-3 and H-5), 8.10 (dd, $J_{2,3} = J_{5,6}$ = 7.0, $J_{2,6}$ = 1.5 Hz, 2H, 1-oxido-4-pyridinyl H-2 and H-6).

Anal. Calcd. for $C_{18}H_{22}N_2O_5 \cdot 1/4\ H_2O$: C, 61.62; H, 6.61; N, 7.98. Found: C, 61.77; H, 6.35; N, 7.94.

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