Notes

Cardioactivity and Solid-State Structure of Two 4-Isoxazolyldihydropyridines Related to the 4-Aryldihydropyridine Calcium-Channel Blockers

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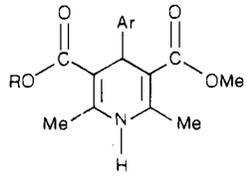
Diethyl 2,6-dimethyl-4-(5-ethyl-3-phenylisoxazol-4-yl)-1,4-dihydroypridine-3,5-dicarboxylate (**5**) and diethyl 2,6-dimethyl-4-(5-isopropyl-3-phenylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**6**) were synthesized, and their molecular structures were determined by X-ray crystallography. In compound **5**, which has an ethyl group at the C5 position of the isoxazole ring, the deviation from planarity in the dihydropyridine (DHP) ring is the smallest of all known DHP derivatives. The dihedral angle between the aromatic ring (the isoxazole) and the DHP ring, which is approximately 90° in similar biologically active dihydropyridines, is somewhat smaller (82.7° and 85.2°, respectively) in these two compounds. In both compounds, one of the ester groups is coplanar with the DHP ring while the other one is out of plane by 14.7° (ethyl) and 18.8° (isopropyl). Both **5** and **6** were found to be vasodilators in the Langendorff assay. The potency of **6** on cardiac flow was similar to that of nifedipine; however, that of **5** was considerably attenuated. Since isoxazolyl analogue **6** lacks the significant negative inotropic activity associated with nifedipine, **6** offers promise as an antihypertensive or antianginal agent.

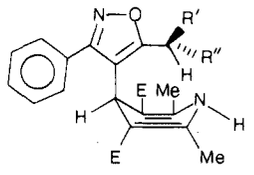
Muscle contraction and neuronal discharge are regulated by the passage of calcium ions into cells through voltage-dependent channels in the cell membrane. Drugs that interfere with the transport of Ca(II) into cells have been found to be useful in the treatment of cardiovascular disorders, such as angina and hypertension.[1] The dihydropyridines (DHPs) are a unique class of potent calcium-channel blocking drugs ("calcium antagonists")[1,2] that suppress the contractility of cardiac and smooth muscle cells by acting at a distinct receptor site on the calcium channel.[1,3] Important representatives of this 4-aryldihydropyridine class are depicted in structures **1–3** (nifedipine, nitrendipine, and nisoldipine, respectively).

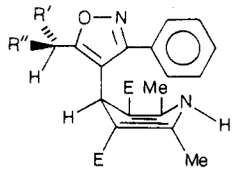


1: R = Me; Ar = 2-nitrophenyl
2: R = Et; Ar = 3-nitrophenyl
3: R = *i*-Bu; Ar = 2-nitrophenyl

The biological activity of the 4-aryldihydropyridines seems to depend on certain key structural and conformational features.[1-3] In the conformational arena, there have been some interesting findings. The aromatic ring at the C4 position must approximately bisect the plane of the DHP ring. Structural studies on nifedipine analogues have shown that the most active compounds possess the smallest deviation from planarity in the DHP ring.[4] MNDO calculations of conformational energies for the ester group at the C3 position suggest that an anti conformation of the ester noncoplanar relative to the DHP ring is associated with Ca(II) antagonism, whereas a nearly coplanar ester arrangement is associated with Ca(II) agonism.[5]

We have been interested in the biological and structural properties of 4-isoxazolyldihydropyridines related to the calcium antagonist nifedipine (**1**) and have already reported on a 5-methylisoxazolyl derivative, **4**, which is equipotent with **1** in the Langendorff assay.[6] In this paper, we discuss the biological activity and solid-state structures of two congeners, **5** and **6**, the latter of which is a robust Ca(II) antagonist.





4: R′ = R″ = H; E = COOEt
5: R′ = H; R″ = Me; E = COOEt

6: R′ = R″ = Me; E = COOEt

Results and Discussion

Synthesis. Compounds **5** and **6** were synthesized according to previously published procedures. 5-Methyl-3-phenylisoxazole-4-carboxylic acid was metalated by the dianion method and quenched with CH_3I to afford the 5-ethyl-3-phenylisoxazole-4-carboxylic acid.[7] The isoxazole acid was reduced to the corresponding alcohol with $LiAlH_4$.[8] The isoxazole alcohol was selectively oxidized to

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(2) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762.
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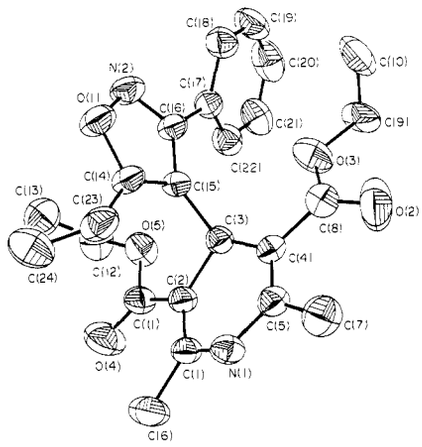

Figure 1. ORTEP drawing of **5** showing thermal ellipsoids.

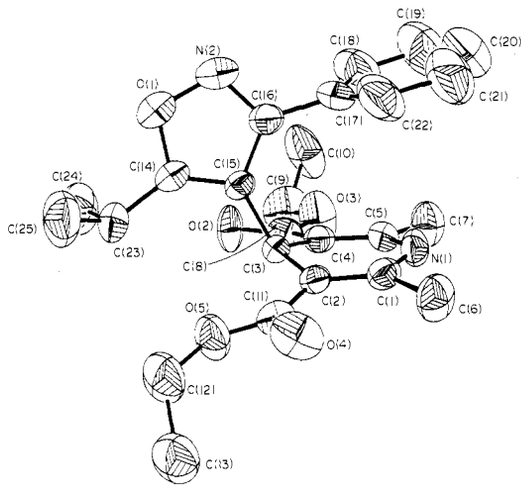

Figure 2. ORTEP drawing of **6** showing thermal ellipsoids.

the aldehyde with TEMPO,[9] and the aldehyde was subjected to a modified Hantzsch procedure with ethyl acetoacetate and ammonia and a high-pressure technique.[10]

The 5-isopropyl-3-phenylisoxazole-4-carboxylic acid was prepared from the 5-ethyl-3-phenylisoxazole-4-carboxylic acid by subsequent metalation and quenching with CH_3I, and the product was carried through the same sequence as that described for the 5-ethyl derivative.

Solid-State Structures of 5 and 6. Single-crystal X-ray diffraction studies were performed on **5** and **6**. Crystallographic data for **5** and **6** are collected in Table I; bond distances and bond angles, selected torsional angles, atomic coordinates, and anisotropic thermal parameters for **5** and **6** are contained in Tables II–VIII in the supplementary material.[11] ORTEP drawings of **5** and **6**, showing their molecular conformations and atom-labeling schemes, are depicted in Figures 1 and 2.

As in other dihydropyridines, the DHP ring adopts a boat conformation.[12] The four double bonded carbons (C1–C2, C4–C5) constitute the plane of the ring with N1 and C3 being 0.0745 and 0.1507 Å above the plane (5-ethyl); for the 5-isopropyl, these distances are 0.1044 and 0.2466 Å, respectively. In the 5-ethyl-DHP, the deviation from planarity defined by the six torsion angles of the ring atoms is the smallest of all DHP derivatives (45.4°). In comparison, the most active nifedipine derivative is 52.1° while the active 5-methylisoxazolyl-DHP (**4**) is 65.7°.[6] On the other hand, the 5-isopropyl derivative shows a fairly high deviation from planarity with 72.6°.

Table I. Crystallographic Data for **5** and **6**

	5-ethyl-DHP (**5**)	5-isopropyl-DHP (**6**)
formula	$C_{24}H_{28}N_2O_5$	$C_{25}H_{30}N_2O_5$
molecular weight	424.51	438.53
crystal class	monoclinic	monoclinic
a, Å	14.829 (2)	34.35 (3)
b, Å	8.697 (2)	9.618 (2)
c, Å	17.751 (4)	14.837 (3)
β, deg	104.74 (2)	97.58 (4)
V, Å^3	2214 (1)	4831 (2)
Z	4	8
D, g cm^{-1}	1.19	1.13
space group	$P2_1/c$	$C2/c$
μ, cm^{-1}	0.84	0.79
crystal size, mm^3	0.50 × 0.33 × 0.33	0.41 × 0.50 × 0.08
$F(000)$	904	1872
T, K	294	294
2θ range, deg	2.37–45	3.41–50
no. of measured reflections	3282	4771
no. of unique reflections with $F > 3\sigma(F)$	2133	2921
R	0.0717	0.0781
R_w ($w = 1/[\sigma^2(F) + g(F)^2]$)	0.0773	0.0815
g	0.0011	0.0012
no. of parameters refined	307	310

Due to steric hindrance, the isoxazole ring in both compounds is not exactly perpendicular to the DHP ring (85.2° for the ethyl-DHP and 85.3° for the isopropyl-DHP). This is also shown by the torsion angles C2–C3–C15–C14 and C4–C3–C15–C14, which should both be close to 60° if the aromatic ring bisects the DHP ring. These angles are 52.5° and −73.1° for **5** and −107.5° and −126.6° for the **6**, which translates to −72.5° and 53.8° if one takes into account that **6** has the isoxazole ring tilted in the opposite direction from **5**.

In both compounds, the ester group that is on the same side as the 3-phenyl group shows disorder. Therefore, there are two preferred torsional angles for the carbonyl oxygen with respect to the DHP double bond. In the 5-ethyl derivative, these angles are 14.7° and −7.8°, but in the 5-isopropyl-DHP, they are 163.4° and −172.7°. Thus, the carbonyl group in **5** is syn while the carbonyl group in **6** is anti with respect to the DHP double bond.

The other ester group, which is on the same side as the 5-alkyl group, shows a syn conformation in both compounds. However, the carbonyl group in the 5-ethyl compound is approximately synperiplanar with respect to the double bond (−0.4°) while the carbonyl group of the 5-isopropyl derivative has a torsional angle of 18.8°.

For the 5-ethyl derivative, the orientation of the phenyl ring with respect to the isoxazole ring is comparable to that in other 3-phenyl- or 5-phenylisoxazoles[13] a 37.8° dihedral angle between the planes of the isoxazole and phenyl rings is observed. The same angle was 33.0° in the 5-methyl compound, 4.[6] The 5-isopropyl-DHP, however, shows a drastic increase in the dihedral angle. The isoxazole and phenyl rings are almost perpendicular to each other (83.5°).

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(11) See paragraph at the end of this article regarding supplementary material.
(12) Fossheim, R. *J. Med. Chem.* **1986**, *29*, 305.
(13) Cannas, M.; Cristini, A.; Marongiu, G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 237.

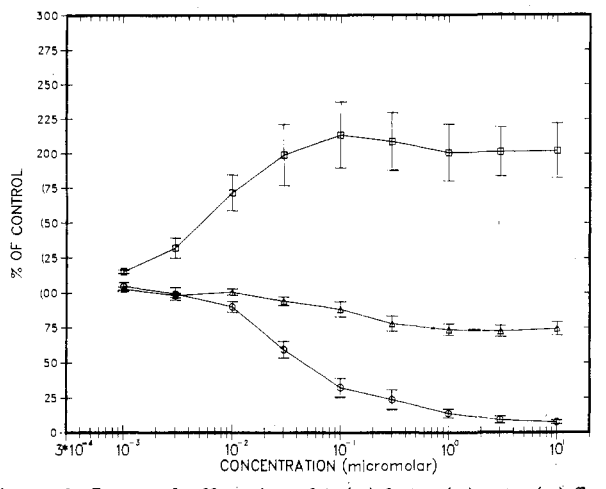

Figure 3. Langendorff testing of 1; (○) force, (△) rate, (□) flow; $N = 6$. Control values: force = 3.4 ± 0.6 g; rate = 196.7 ± 9.6 bpm; flow = 4.1 ± 0.4 mL/min.

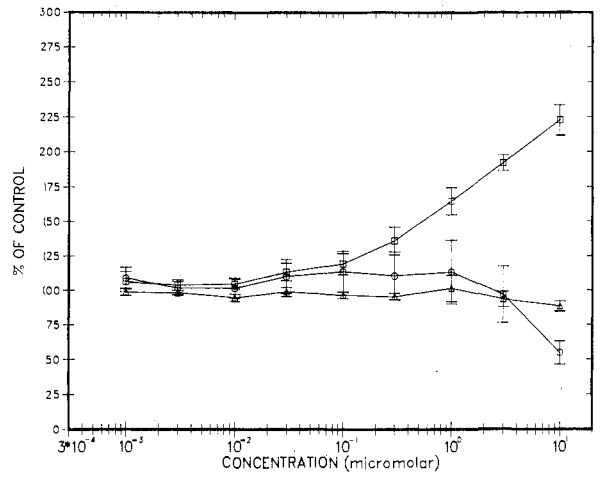

Figure 4. Langendorff testing of 5; (○) force, (△) rate, (□) flow; $N = 6$. Control values: force = 4.2 ± 0.9 g; rate = 161.7 ± 12.2 bpm; flow = 4.8 ± 0.2 mL/min.

The strong steric interaction between the isopropyl group on the isoxazole and one of the ester groups of the dihydropyridine forces the DHP ring to move toward the 3-phenyl substituent. Thus, the phenyl ring is forced into a perpendicular position. This becomes the most stable conformation since the phenyl ring now lies parallel above the DHP ring. This is the first case where a 3- or 5-phenylisoxazole has the phenyl and isoxazole rings oriented to each other in an almost perpendicular fashion.

Biological Testing. The 4-isoxazolyl-DHP derivatives, along with nifedipine, were evaluated in the isolated Langendorff heart assay (described earlier).[14] Data, as percent of control, for **1**, **5**, and **6** are presented in Figures 3–5. Compound **6** was found to be a vasodilator with a potency similar to that of nifedipine (**1**). However, since isoxazolyl analogue **6** lacks the significant negative inotropic activity associated with nifedipine, it offers promise as an antihypertensive or antianginal agent. By comparison, compound **5** was only a weak vasodilator.

Given the biological activity for these agents, we conclude that the extent of deviation from planarity in the solid state is not a critical parameter in the structure–activity relationship for vasodilation in the isoxazolyl-congener series.

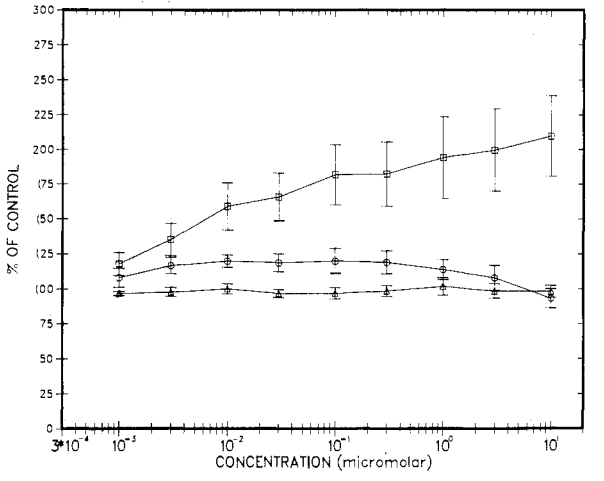

Figure 5. Langendorff testing of **6**; (○) force, (△) rate, (□) flow; $N = 6$. Control values: force = 3.2 ± 0.6 g; rate = 210.0 ± 6.3 bpm; flow = 3.3 ± 0.3 mL/min.

Experimental Section

Mass spectra were measured on a VG 7070 GC/MS instrument with a Model 11/250 data system. The following abbreviations are used: electron impact, EI; chemical ionization, CI; fast atom bombardment, FAB. ^{1}H NMR were obtained on Varian Em-360 or JEOL FX-90Q spectrometers and are reported in ppm downfield from tetramethylsilane as internal standard. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. ^{2}H and ^{13}C NMR were obtained on the JEOL spectrometer. IR spectra were obtained on a Digilab FTS-80 or a Qualimatic spectrometer as neat liquids or melts on NaCl plates unless noted otherwise. Combustion analyses were performed either by Mic Anal Organic Analysis or a LECCO CHN-600 carbon, hydrogen, and nitrogen analyzer. Preparative thin-layer chromatography (PTLC) was performed on a Harrison Associates chromatotron, with silica gel unless specified otherwise. For reactions under inert atmosphere, the inert gas (Ar or N_2) was passed over activated catalyst R3-11 followed by indicator Drierite. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All chromatography solvents (hexane, CH_2Cl_2, $CHCl_3$, EtOAc, and MeOH) were distilled. Organolithium reagents were titrated by the procedure of Ronald.[15]

5-Ethyl-3-phenylisoxazole-4-carboxylic Acid. To 5-methyl-3-phenylisoxazole-4-carboxylic acid (5 g, 0.0246 mol) was added freshly distilled THF (250 mL), and the solution was cooled to −78 °C. A solution of *n*-butyllithium in hexanes (31.2 mL, 1.57 M, 0.0492 mol) was added dropwise, and the resulting slurry was stirred for 2 h. Iodomethane (3.1 mL, 0.048 mol) was then added, by dropwise addition down the side of the flask. The reaction mixture was allowed to warm to room temperature overnight, after which time the THF was removed in vacuo and water was added (250 mL). The solution was washed with methylene chloride (3 × 50 mL), which was discarded, and the pH of the aqueous solution was adjusted to 2 with cold 10% aqueous hydrochloric acid (ca. 50 mL). The solid was extracted into methylene chloride (3 × 50 mL) and dried over anhydrous sodium sulfate. Filtration and concentration provided an off-white solid, which was recrystallized from toluene–hexane to give 5-ethyl-3-phenylisoxazole-4-carboxylic acid (4.32 g, 81%): ^{1}H NMR δ 7.73–7.6 (m, 5 H), 3.2 (q, 2 H), 1.3 (t, 3 H).

5-Ethyl-3-phenylisoxazole-4-carbinol. To a solution of 5-ethyl-3-phenylisoxazole-4-carboxylic acid (2.59 g, 0.0119 mol) in THF (150 mL) at 0 °C was added lithium aluminum hydride (.45 g, 0.0118 mol, in pellet form). The solution was allowed to come to room temperature with stirring overnight, after which time the slurry was transferred to an Erlenmeyer flask (1 L), and sodium sulfate decahydrate was added until the foaming subsided. Celite (4.5 g) was then added, and the slurry was filtered and

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washed with methylene chloride (150 mL). The combined THF and methylene chloride washes were concentrated and flash distilled on a Kugelrohr apparatus [120 °C/(0.25 mmHg)] to give the product as an oil (1.7 g, 70% yield): ^{1}H NMR δ 7.7–7.8 (m, 2 H), 7.3–7.4 (m, 3 H), 4.49 (s, 2 H), 2.79 (q, 2 H, J = 7.5 Hz), 1.29 (t, 3 H, J = 7.5 Hz); ^{13}C NMR δ 173.1, 162.4, 129.5, 128.6, 128.1, 112.0, 53.1, 19.1, 12.1; IR 3509, 3077, 1626, 1449, 1418, 1212, 1018, 922, 775, 742 cm^{-1}; mass spectrum, m/z (relative intensity) 203 (51), 175 (9), 174 (81.5), 144 (100), 130 (19.8). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.09; H, 6.87; N, 6.86.

5-Ethyl-3-phenylisoxazole-4-carboxaldehyde. To a solution of 5-ethyl-3-phenylisoxazole-4-carbinol (1.69 g, 8.33 mmol) in 40 mL of DMF was added tetramethylpiperdinyloxy free radical (TEMPO, 0.1 g, 0.6 mmol) and cuprous chloride (0.15 g, 1.5 mmol). Oxygen was bubbled through the solution slowly with stirring for 28 h. The solution was then poured into aqueous 10% HCl and extracted with ether (3 × 75 mL). The combined ether fractions were washed with water (5 × 100 mL) and dried over anhydrous sodium sulfate. Filtration and concentration gave the product as an oil (1.17 g, 70%): ^{1}H NMR δ 9.9 (s, 1 H), 7.4–7.7 (m, 5 H), 3.17 (q, 2 H), 1.39 (t, 3 H).

Diethyl 2,6-Dimethyl-4-(5-ethyl-3-phenylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (5). An aerosol dispersion tube was charged with 5-ethyl-3-phenylisoxazole-4-carboxaldehyde (1 g, 4.98 mmol), ethanol (50 mL), ethyl acetoacetate (1.5 mL, 11.7 mmol), and aqueous ammonia (0.3 mL, 28.7% solution). The mixture was warmed to 100 °C for 24 h (during which time the pressure gauge registered 8 psi). The solution was cooled and concentrated, and the product (5) was precipitated with ether–petroleum ether (1.2 g, 57%): mp 126–129 °C (cor); ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 4 H), (s, 4 H), 7.26 (s, 1 H), 5.05 (s, 1 H), 4.85 (s, 1 H), 4.05 (m, 4 H, J = 7.08 Hz), 2.91 (q, 2 H, J = 7.6 Hz), 1.95 (s, 6 H), 1.36 (t, 3 H, J = 7.32 Hz), 1.18 (t, 6 H, J = 7.08 Hz); ^{13}C NMR δ 169.8, 167.4, 163.5, 143.9, 131.0, 129.4, 128.3, 127.5, 118.5, 101.0, 59.6, 29.1, 25.9, 19.1, 14.4, 11.5; IR ν_{max} 3333, 1759, 1695, 1538, 1418, 1258, 1156, 1124, 1075, 1053, 939, 840, 780–755 cm^{-1}; MS, m/z (relative intensity) 424 (12.8), 423 (21.5), 395 (10.3), 379 (9.5), 377 (33.6), 351 (41), 349 (83.3), 321 (92.8), 252 (41.9), 248 (79), 216 (22.8), 206 (57), 57 (100). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65. Found: C, 67.79; H, 6.56.

Diethyl 2,6-dimethyl-4-(5-isopropyl-3-phenylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (6): mp 166–168 °C (cor); ^{1}H NMR ($CDCl_3$) δ 7.388 (m, 5 H), 5.122 (s, 1 H), 5.0 (s, 1 H), 4.04 (m, 6 H), 3.40 (septet, 1 H, J = 7.08 Hz), 1.95 (s, 6 H), 1.35 (d, 6 H, J = 7.08 Hz), 1.16 (t, 6H, J = 7.08 Hz); ^{13}C NMR δ 169.0, 167.5, 143.3, 131.2, 129.5, 128.3, 127.5, 117.6, 110.3, 59.6, 29.1, 25.9, 21.1, 19.2, 14.4; IR ν_{max} 3330, 3064, 2973, 1682, 1492, 1208 cm^{-1}; MS, m/z (relative intensity) 438 (20.5), 437 (34.0), 409 (16.8), 393 (15.0), 366 (20.4), 365 (82.2), 319 (15.4), 292 (57.1), 262 (100), 252 (97.1). Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.48; H, 6.89. Found: C, 68.27; H, 6.63.

Isolated Langendorff Test. Cardioactivity was determined by using the isolated Langendorff heart.[14] The guinea pig heart was perfused at 37 °C with no-recirculating Krebs–Henseleit buffer containing 1.26 mM Ca(II) and 5 mM glucose. It was constantly equilibrated with 95% O_2 and 5% CO_2 to maintain a physiological pH of 7.4. Coronary flow, heart rate, and contractile force were measured simultaneously, while the perfusion pressure was held constant. The test compounds were dissolved in PEG 200 and then added to the perfusion buffer. The response to each test compound, **5**, **6**, and nifedipine (1) was assessed at 1.0, 3.0, and 10.0 μM in each of two hearts. Each heart served as its own control, and any change in the three parameters was reported as percent variation from control. Since these compounds were markedly active compounds, they were subjected to a complete dose–response study involving at least six hearts. Percent of control plots for **5**, **6**, and nifedipine (1) are given in Figures 3–5.

X-ray Data. Crystals of **5** and **6** were obtained by recrystallization from a 1:1 mixture of ethyl acetate and ethyl alcohol. Cell constants were determined by a least-squares fitting of setting angles of the diffractometer (Nicolet R3/m for the 5-ethyl and Syntex $P2_1$ upgraded to Nicolet P3F specifications for the 5-isopropylisoxazolyl-DHP) from 25 reflections between 29° and 31°.

Data were collected by the ω scan technique[16] with graphite monochromatized Mo Kα radiation (λ = 0.710 69 Å). The measured intensities were corrected for Lorentz and polarization effects but not for absorption. The structure was solved with the SHELXTL program.[17] All non-hydrogen atoms were refined anisotropically and restricted to N–H and C–H distances of 0.96 Å. The thermal parameters of all hydrogen atoms were set at 0.1. In both compounds, one of the two ester groups shows disorder: in the 5-ethyl-DHP the carbonyl oxygen and the two carbon atoms of the ester ethyl group all show two equivalent positions, in the 5-isopropyl-DHP the carbonyl oxygen and the CH_3 carbon of the ester ethyl group show two positions. All crystallographic data of the two compounds are listed in Table I. Largest peaks on the final Fourier difference map were 0.353 and −0.436 e/Å^3 for **5** and 0.235 and −0.259 e/Å^3 for **6**. The final R value for the 5-ethyl-DHP was 0.0717 and for the 5-isopropyl-DHP 0.078.

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Registry No. **5**, 111556-67-3; **6**, 111525-14-5; TEMPO, 2564-83-2; 5-methyl-3-phenylisoxazole-4-carboxylic acid, 1136-45-4; 5-ethyl-3-phenylisoxazole-4-carboxylic acid, 91569-55-0; 5-isopropyl-3-phenylisoxazole-4-carboxylic acid, 92029-28-2; 5-ethyl-3-phenylisoxazole-4-carbinol, 99299-07-7; 5-isopropyl-3-phenylisoxazole-4-carbinol, 99299-09-9; 5-ethyl-3-phenylisoxazole-4-carboxaldehyde, 99298-93-8; 5-isopropyl-3-phenylisoxazole-4-carboxaldehyde, 111525-13-4; ethyl acetoacetate, 141-97-9.

Supplementary Material Available: Tables of X-ray parameters for **5** and **6** (7 pages). Ordering information is given on any current masthead page.

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