was added portionwise to a stirred anhydrous EtOH (50 mL). To the solution was added C_2H_5SH (2.9 g, 0.047 mol) and **40** (5.0 g, 0.012 mol). The mixture was heated to reflux for 6 h. The solvent was evaporated to give a residue, which was acidified with 10% HCl and weakly basified with aqueous K_2CO_3. The resulting precipitates were collected, washed with water, and recrystallized from dioxane–water to give 3.5 g (66%) of **39**.

(4-Benzyl-2-morpholinyl)methyl 4-Amino-5-chloro-2-methoxybenzoate (47). To a solution of 4-benzyl-2-(hydroxymethyl)morpholine[19] (2.3 g, 0.011 mol), 4-amino-5-chloro-2-methoxybenzoic acid (1.8 g, 0.0089 mol), and 4-(dimethylamino)pyridine (0.56 g, 0.0046 mol) in DMF (30 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.0 g, 0.010 mol) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for 15 h. After evaporation of the solvent, the residue was diluted with water and extracted with $CHCl_3$. The extract was washed successively with water and brine and dried. The solvent was evaporated to give an oil, which was chromatographed on silica gel with AcOEt–$CHCl_3$ (1:1) to give a solid. The solid was recrystallized from *i*-PrOH to give 2.0 g (57%) of **47**.

5-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxy-*N*-methylbenzamide (48). To a solution of **7b** (6.0 g, 0.024 mol) in THF (60 mL) was added portionwise 60% NaH (1.1 g, 0.028 mol). The mixture was stirred at room temperature for 1 h. Methyl iodide (3.8 g, 0.027 mol) was added to this solution. The resulting mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was diluted with water and extracted with AcOEt. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 6.3 g of 2-[(*N*-acetyl-*N*-methylamino)methyl]-4-benzylmorpholine as an oil, which was dissolved in 10% HCl (120 mL). The solution was refluxed for 16 h. After cooling at 0 °C, the solution was basified with aqueous NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 4.7 g (89%) of 4-benzyl-2-[(methylamino)methyl]morpholine as an oil: ^1H NMR ($CDCl_3$) δ 2.42 (3 H, s, CH_3), 3.49 (2 H, s, CH_2Ph), 7.30 (5 H, s, C_6H_5). A mixture of 4-benzyl-2-[(methylamino)methyl]morpholine (2.2 g, 0.010 mol), 4-amino-5-chloro-2-methoxybenzoic acid (2.0 g, 0.0099 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.9 g, 0.0099 mol), and CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. The mixture was washed successively with water and brine and dried. The solvent was evaporated to give an oil, which was chromatographed on silica gel with $CHCl_3$–CH_3OH (30:1) to give 3.2 g (80%) of **48** as an oil. This oil was converted to the fumarate in a usual manner.

Pharmacology. Five male mice of Std-ddY strain (Japan SLC Inc.) weighing 30–40 g and four male rats of Wistar strain (Japan SLC Inc.) weighing 130–150 g were used. The mice and rats were fasted for 18 h before the experiments.

Gastric Emptying of Semisolid Meal. A test meal (0.05% phenol red in 1.5% aqueous methylcellulose solution) of 0.2 mL per mouse and 1.5 mL per rat was given with a gastric tube. Fifteen minutes later, the animals were sacrificed. The stomach was removed, and the amount of phenol red remaining in the stomach was measured according to the method of Scarpignato.[25] The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of test meal.

Gastric Emptying of Solid Meal. Gastric emptying of solid meal (resin pellets) was measured according to the method of Jacoby.[26] Small resin pellets (Amberlite IRA-93, 1-mm diameter, 40 pellets per rat) were administered through a polyethylene tube (PE-200) into the stomach. One hour later, the animals were sacrificed and the number of pellets remaining in the stomach was counted. The test compounds were orally administered 30 min before administration of the resin pellets.

Effect on Apomorphine-Induced Emesis in Dogs. The antiapomorphine test in dogs was carried out according to the method of Janssen[27] with modification. Male beagle dogs, weighing 10–16 kg, were used. Groups of three to six dogs received a subcutaneous injection of apomorphine hydrochloride (0.3 mg/kg) 2 h after the pretreatment with test compounds. The frequency of emesis was then counted for 1 h.

Acknowledgment. We are grateful to Dr. M. Hashimoto, the director of the laboratories, and Drs. H. Uno and T. Ito for their encouragement throughout this work. Thanks are also due to the staff of our analytical section for elemental analyses and spectral measurements.

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Synthesis, Pharmacological Effects, and Conformation of 4,4-Disubstituted 1,4-Dihydropyridines

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Bayer AG, Pharma-Forschungszentrum, Postfach 10 17 09, D-5600 Wuppertal 1, FRG. *Received June 22, 1989*

4,4-Disubstituted 1,4-dihydropyridines are synthesized by intramolecular addition of sulfinyl carbanions to pyridines. These disubstituted derivatives show a loss of Ca antagonistic potency of up to three powers of 10 both in vitro on aortic rings and in vivo on anaesthetized dogs as compared to examples that are monosubstituted at the 4-position of the DHP ring. As the X-ray structure shows, the 4-aryl substituent is present not in the accustomed axial conformation, but in an equatorial one. This dramatic change in conformation could be the reason for the major loss of activity and would indicate the need for axial conformation of the aryl residue in pharmacologically active 1,4-dihydropyridines. The change in conformation was also confirmed by quantum chemical calculations (AM1).

4-Aryl-substituted 1,4-dihydropyridines with structure **1a** (Scheme I) are easily accessible by using the classical method of Hantzsch synthesis.[1] Since the discovery of the coronary vasodilatory and antihypertensive properties of this class of substances,[2–4] a wide range of derivatives has been synthesized,[5–7] all of which, however, bear a hydrogen atom at the 4-position (**1a**), because the classical Hantzsch synthesis and its more recent modifications with aryl ketones instead of aldehydes do not yield the desired 4,4-disubstituted dihydropyridines **1b**.[8,9]

Another method for obtaining dihydropyridines is the addition of carbanions to pyridines. In this case, however,

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(4) Loev, B.; Ehrrich, S. J.; Tedeschi, R. E. *J. Pharm. Pharmacol.* **1972**, *24*, 917.
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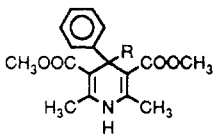
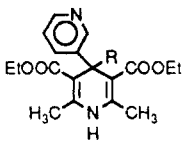
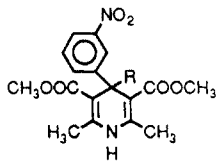
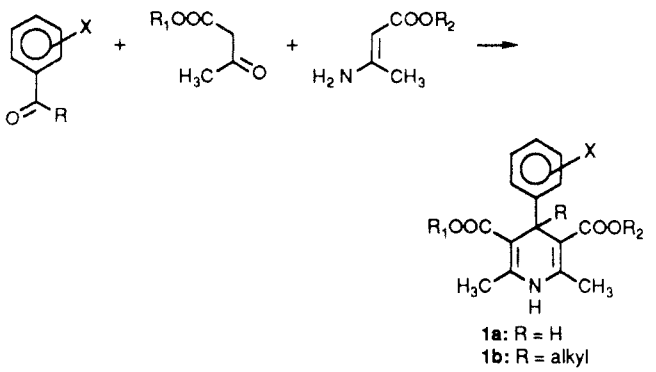
(8) Loev, B.; Snader, K. M.; *J. Org. Chem.* **1965**, *30*, 1914.
(9) Only the 3,5-dinitriles have been prepared with low yields: US Pat. 3.973.025.

0022-2623/90/1833-1413$02.50/0

Table I. Pharmacological Activity of 4,4-Disubstituted 1,4-Dihydropyridines in Comparison with the Monosubstituted Derivatives

	R	compd	inhibn of KCl-induced contraction of rabbit aorta rings (IC_{50}), mg/L	threshold dose (iv) for antihypertensive act. in anaesthetized dogs, mg/kg
	H	8[43,16]	0.04	0.05
	CH_3	**6a**[11]	1.2	3.0
	C_2H_5	**6b**	3.6	
	H	9[44,45]	0.5	0.3
	CH_3	**6c**	9.0	3
	H	10[16,46]	0.002	0.01
	CH_3	**6d**	2.3	0.3

Scheme I



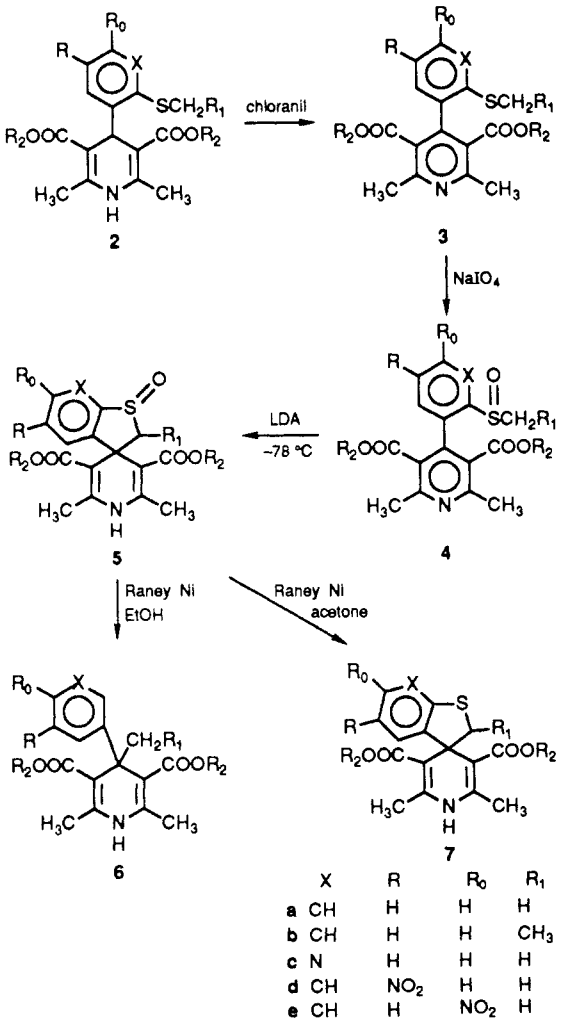
the substitution that already exists in the 4-position is followed by addition to the 2-position.

However, by appending the nucleophile to the desired position, we succeeded in forcing addition to the 4-position.[10,11]

Starting with familiar 1,4-dihydropyridines **2**, it was possible to isolate the pyridines **3** after oxidation with chloranil (Scheme II). Further oxidation with periodate yielded the sulfoxides **4**. Deprotonation with lithium diisopropyl amide at −78 °C led to the sulfinyl carbanion, which added spontaneously to the 4-position at −78 °C to form spirodihydropyridine **5**. Removal of the sulfur with Raney nickel in ethanol resulted in the 4,4-disubstituted 1,4-dihydropyridines **6**. The spiro sulfide **7** can also be isolated as an intermediate by performing a milder reaction in acetone.

In the same way as the dihydropyridines used therapeutically, e.g., nifedipine, nisoldipine, or nitrendipine,[12] the corresponding derivatives with nitro substitution in the aryl residue are particularly interesting from the pharmacological point of view.[13] The attempt to obtain the desired derivative **6d** from the nitro derivative **2d** failed. Although **5d** could be obtained, desulfurization

Scheme II



	X	R	R_0	R_1	R_2
a	CH	H	H	H	CH_3
b	CH	H	H	CH_3	CH_3
c	N	H	H	H	C_2H_5
d	CH	NO_2	H	H	CH_3
e	CH	H	NO_2	H	CH_3

without destroying the nitro group proved impossible.

Surprisingly, the desired derivatives were obtained easily by subsequent nitration of **6a** (Scheme III).[14] The results were meta/para mixtures at a ratio of 1:2. No ortho nitro compound was formed. Nitration of the 2-methyl group,

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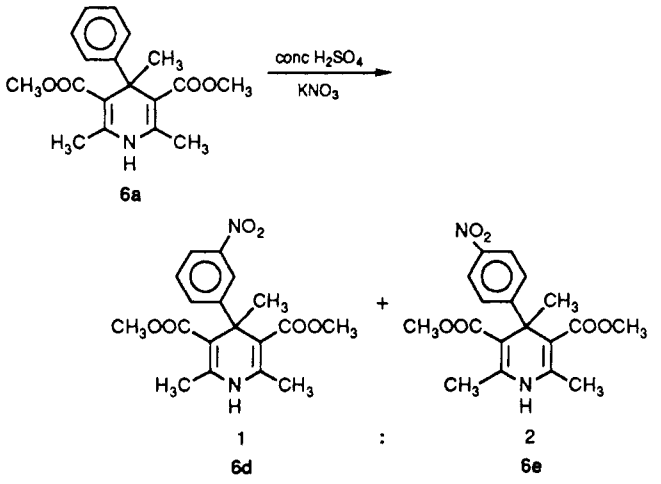
(14) Tirzite, G.; Skrastins, I.; Dubur, G. *Khim. Geterotsikl. Soedin.* **1987**, 68; *Chem. Abstr.* **1987**, *107*, 198035j.

Scheme III



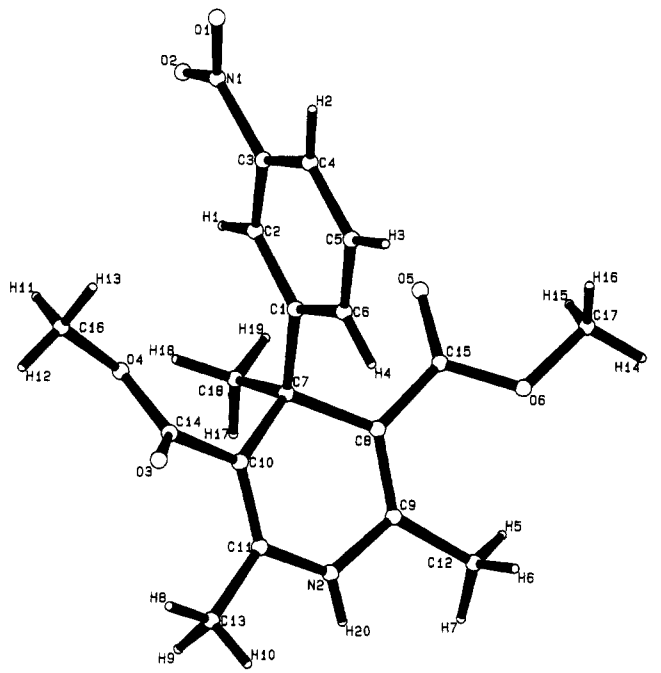


Figure 1. X-ray structure of **6d**.

which had occurred with similar compounds, was not observed.[15]

Results and Discussion

The pharmacological activity of these substances was tested in comparison with the familiar mono-substituted compounds, both in vitro on rings of isolated rabbit aorta and in vivo on anaesthetized dogs (Table I). Table I shows that the 4,4-disubstituted compounds (**6a–d**, R = Me, Et) are less active than the corresponding mono-substituted compounds (**8–10**, R = H). This difference is particularly noticeable in the case of the 3-nitro derivatives **10** and **6d**, where a loss of activity of three powers of 10 is recorded on isolated aorta rings. This dramatic loss of activity following substitution of the hydrogen in the 4-position by methyl was initially very surprising.

However, the X-ray structure of **6d** in comparison with that of **10**[16] revealed drastic changes in conformation which were caused by the second 4-substitution (Figures 1 and 2). In all X-ray structure analyses of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates known to date, the dihydropyridine skeleton is present in the conformation of a flat boat, the 4-aryl residue holding the pseudoaxial position, i.e., standing virtually perpendicular on the plane of the dihydropyridine, and the hydrogen assuming a pseudoequatorial position[16–33] (**10**, Figure 2). The reason for this is probably steric repulsion of the aryl residue and the two ester groups. The X-ray structure **6d** now shows the first case of an aryl residue in pseudoequatorial position in 1,4-dihydropyridines. As a result of the steric influence of the methyl group, the axial position no longer seems to be the desired conformation.[34]

Table II. Torsion Angle of the Dihydropyridine Ring and Calculated Heat of Formation

compd	torsion angle τ, |deg| (mean values of angles C11–C10–C7–C8 and C10–C7–C8–C9): from X-ray structures	torsion angle τ, |deg| (mean values of angles C11–C10–C7–C8 and C10–C7–C8–C9): from AM1-calcd conformations	AM1-calcd heat of formation, kcal/mol
10	24.3[16]	19.0 (aryl-axial)	−115.8
6d	26.2	13.7 (aryl-axial)	−110.8
		7.6 (aryl-equat)	−112.0
8	28.5[16]	19.4 (aryl-axial)	−118.9
6a		11.2 (aryl-axial)	−113.7
		7.0 (aryl-equat)	−115.0

The different conformations of **10** and **6d** are easily seen in the projection of the two X-ray structures (Figure 2). Surprisingly, the torsion angle τ (Table II) of the dihydropyridine ring in **6d** (26.4°) is even larger than in **10** (24.2°). However, the recently discussed decrease of pharmacological activity by increasing dihydropyridine ring puckering[16,20,23] cannot explain the dramatic loss of activity, because the even more puckered **8** (τ = 28.5°) is up to 50 times more active than **6d** (Table I).

Therefore, we think that the no longer preferred axial position of the aryl residue might be the explanation for the unusual decrease in pharmacological activity of **6d** in comparison to **10**. This finding is another indication that the pharmacologically active conformation of 1,4-dihydropyridines requires an axial position of the 4-aryl residue.[35]

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(17) Mishnev, A.; et al. *Khim. Geterotsikl. Soedin.* **1977**, *9*, 1229.
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(20) Triggle, A. M.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1980**, *23*, 1442.
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(31) McKenna, J. I.; et al. *J. Med. Chem.* **1988**, *31*, 473.
(32) Langs, D. A.; Strong, P. D.; Triggle, D. J. *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.* **1987**, *C34*, 707.
(33) Langs, D. A.; Triggle, D. J. *Mol. Pharmacol.* **1985**, *27*, 544.
(34) The corresponding 3,5-diethyl ester of **6a** exhibits also the phenyl ring in the equatorial position. Leutert, T. Ciba Geigy AG, private communication, Aug 1989.

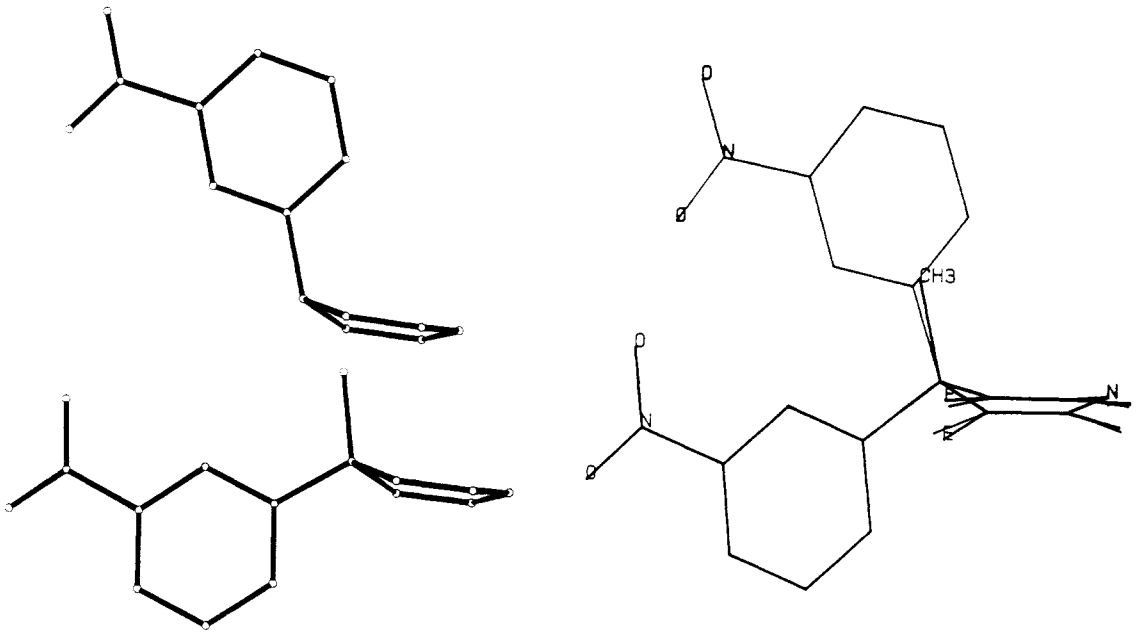

Figure 2. Left: comparison of the X-ray structures of **6d** (bottom) and **10**[16] (top) (for better clarity the residues of the dihydropyridine ring have been removed). Right: Fitted X-ray structures of **6d** and **10**.

Quantum Chemical Calculations. To validate the hypothesis that the change in conformation is due to intramolecular effects and not only to intermolecular effects in the crystal, quantum chemical calculations were carried out. We used the AM1 method[36] with complete geometry optimization. Compounds **10** and **6d** were selected as model compounds. In both cases we used starting geometries with both axial and equatorial positions of the phenyl ring.

In the case of the familiar 1,4-dihydropyridine **10** only *one* minimum was found: the conformation bearing the phenyl ring in the axial position. The calculations indicate that the equatorial conformation of **10** does not exist as a local minimum on the energy hypersurface. In the case of the 4,4-disubstituted compound **6d** the results are quite different. Depending on the starting geometries, two different minima were found: the conformation with the equatorial position of the phenyl group is 1.2 kcal/mol more stable than the axial one. Calculations on **8** and **6a** established very similar results (see Table II). These calculations are in accordance with the experimental X-ray structures. They explain the change in conformation by intramolecular interactions only. It should be said, however, that there are some differences between the calculated torsion angles and the experimental findings by X-ray structure analysis. It is known that 1,4-dihydropyridines with identical substituents in the 4-position exhibit torsion angles of $\approx 0°$, synonymous with planarity of the dihydropyridine ring.[37,38]

Unsymmetrical substitution in the 4-position causes a torsion of the dihydropyridine ring to a flat boat with torsion angles τ of 20–30° (e.g., compounds **10** and **8**, Table II). Therefore, it had been expected that the introduction of a second substituent into the 4-position of **10** would cause a decrease of the torsion angle, in agreement with the obtained AM1 calculations (Table II, example **6d**). Thus, the large torsion angle τ of **6d** (26.2°) was unexpected. This may be due to intermolecular interactions or limitations of the AM1 calculations.

Experimental Section

(1) Pharmacology. (A) Isolated Rabbit Aorta. Rings of rabbit aorta were suspended in Tyrode solution (37 °C). KCl-induced contractions were recorded by using strain gauges. Table I shows the drug concentrations that reduce a control contraction, induced by 40 mM KCl, by 50% (for details, see ref 39).

(B) Anaesthetized Dogs. The antihypertensive effects of the compounds were measured in pentobarbital-anaesthetized dogs. In Table I, the lowest concentrations that reduced the systolic blood pressure by more than 10% are given. The compounds were dissolved in Adalat placebo solution [60 g of glycerine, 100 g of water and 969 g of poly(ethylene glycol) 400] and administered via the femoral vein (for further details see ref 39).

(2) Single-Crystal X-ray Structure Determination of 6d. Lattice constants and intensity data were measured at 297 K on an Enraf-Nonius CAD4 automated diffractometer using graphite-monochromatized Cu Kα radiation. Unit cell dimensions were obtained by least-squares methods from the adjusted angular settings of 25 high-angle reflections. The crystal data are as follows: monoclinic space group $P2_1/c$, a = 9.3185 (7) Å, b = 16.124 (1) Å. c = 14.779 (2) Å, β = 124.94 (1)°, V = 1820.2 Å^3, and Z = 4, ρ_{calc} = 1.314 g/cm^3. Data collection was performed to $\theta <$ 52° in the $\omega - 2\theta$ scanning mode. A total of 2137 reflections was collected. By direct methods (MULTAN) the 26 non-hydrogen atoms were located. The H positions were calculated geometrically. Full matrix least-squares refinement was carried out with anisotropic temperature factors for non-H atoms, isotropic factors for H atoms, by using all reflections with $I > 3.0\sigma(I)$ and sin $\theta/\lambda < 0.5$ Å^{-1}. The final R (unweighted, 1641 reflections, 315 variables) was 0.042.

(3) Chemistry. All melting points are uncorrected and were determined by using a Tottoli (Büchi) apparatus. All structures were confirmed by NMR spectroscopy and microanalysis. NMR spectra were recorded in the solvents specified, using AM 200 and AM 250 (Bruker) apparatus. The mass spectra were recorded with the CH5 of Finnigan MAT (Bremen).

(35) Similar conclusions could also be drawn from rigid tetrahydropyridines: Baldwin, J. J.; et al. *J. Med. Chem.* **1987**, *30*, 690.

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(37) In the case of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate see: Lenstra, A.; Petit, G.; Damisse, R.; Alderweireldt, F. *Bull. Soc. Chim. Belg.* **1979**, *88*, 133.

(38) In the case of 3,5-dicyano-1-ethyl-2,4,4,6-tetramethyl-1,4-dihydropyridine see: Huml, K.; Jecny, J. *Acta Crystallogr.* **1979**, *B35*, 444.

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(A) Dimethyl 2,6-Dimethyl-4-[2-(methylthio)phenyl]-pyridine-3,5-dicarboxylate (3a). A mixture of dimethyl 2,6-dimethyl-4-[2-(methylthio)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**2a**)[40] (347 g, 1.00 mol) and chloranil (296 g, 1.25 mol) was stirred in 4 L of toluene at 120 °C for 8 h. After cooling, the solution was filtered by suction, and the filtrate was washed four times with 2 N NaOH and twice with water, dried, and concentrated in the rotary evaporator. The residue was recrystallized from ether/petroleum ether to give **3a** (307 g, 89%): mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 2.6 (s, 6 H), 3.5 (s, 6 H), 6.9–7.4 (m, 4 H) ppm. Anal. ($C_{18}H_{19}NO_4S$) C, H, N.

(B) Dimethyl 2,6-Dimethyl-4-[2-(methylsulfinyl)-phenyl]pyridine-2,5-dicarboxylate (4a). **3a** (104 g, 0.40 mol) was dissolved in 500 mL of acetone and mixed with a sodium periodate solution (77.0 g, 0.36 mol, dissolved in 500 mL of water). The mixture was stirred at room temperature overnight, filtered by suction, and washed with acetone and the filtrate concentrated in the rotary evaporator. The residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and recrystallized from ether to give **4a** (72 g, 64%): mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3 H), 2.61 (s, 6 H), 3.6 (s, 6 H), 7.0–8.2 (m, 4 H) ppm. Anal. ($C_{18}H_{19}NO_5S$) C, H, N.

(C) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(2′,3′-dihydro-1′-benzothiophene 1′-oxide) (5a). Diisopropylamine (25.2 mL, 0.25 mol, distilled from KOH) was dissolved in 200 mL of anhydrous tetrahydrofuran (THF) under N_2 and mixed with *n*-butyllithium (153 mL, 0.25 mol, 15% in hexane) at 0 °C. This solution was cannulated into a solution of **4a** (45.2 g, 0.125 mol) in 400 mL of THF which had been cooled to −78 °C. The solution was subsequently quenched with methanol and ammonium chloride and 1 L of water added. Suction filtration, washing with water, and drying at 100 °C yielded **5a** (36.1 g, 80%): mp 286–289 °C dec; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.15 (s, 3 H), 2.2 (s, 3 H), 3.2 (s, 3 H, 3.3 (s, 3 H), 3.4 (d, J = 13 Hz, 1 H), 4.2 (d, J = 13 Hz, 1 H), 7.2–7.8 (m, 4 H) ppm. Anal. ($C_{18}H_{19}NO_5S$) C, H, N.

(D) Dimethyl 4-Phenyl-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6a). **5a** (10.8 g, 30.0 mmol) was dissolved in 600 mL of 75% aqueous ethanol, mixed with 100 g of Raney nickel, and refluxed for 5 h. After cooling, the solution was filtered by suction, the filtrate concentrated, and the residue recrystallized from ethyl acetate to yield **6a** (7.0 g, 74%): mp 148–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.1 (s, 6 H), 3.2 (s, 6 H), 5.6 (s, br, NH), 6.9–7.5 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$) δ 19.4, 25.8, 43.5, 50.3, 110.2, 125.0, 127.1, 127.9, 139.8, 150.9, 163.7 ppm. Anal. ($C_{18}H_{21}NO_4$) C, H, N.

(E) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(2′,3′-dihydro-1′-benzothiophene) (7a). **5a** (10.8 g, 30 mmol) was refluxed in 300 mL of acetone with 100 g of Raney nickel for 45 min, separated from the nickel by suction after cooling, concentrated by evaporation, and crystallized from ether. The yield was 6.9 g (67%) of **7a**: mp 167–168 °C (ether); ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 6 H), 3.4 (s, 6 H), 3.7 (s, 2 H), 6.3 (s, br, NH), 6.0–7.1 (m, 4 H) ppm. Anal. ($C_{18}H_{19}NO_4S$) C, H, N.

(F) Dimethyl 2,6-Dimethyl-4-[2-(ethylthio)phenyl]-pyridine-3,5-dicarboxylate (3b). Dimethyl 2,6-dimethyl-4-[2-(ethylthio)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**2b**) (90 g, 0.25 mol) was reacted in accordance with method A to yield **3b** (70 g, 78%): mp 77–79 °C (ligroin); ^{1}H NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 3 H), 2.5 (s, 6 H), 2.7 (q, J = 7 Hz, 2 H), 3.35 (s, 6 H), 6.7–7.2 (m, 4 H) ppm. Anal. ($C_{19}H_{21}NO_4S$) C, H, N.

(G) Dimethyl 2,6-Dimethyl-4-[2-(ethylsulfinyl)phenyl]-pyridine-3,5-dicarboxylate (4b). **3b** (70 g, 0.2 mol) was reacted in accordance with method B to yield **4b** (47 g, 64%): mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 3 H), 2.65 (s, 3 H), 2.7 (s, 3 H), 2.7 (q, J = 7 Hz, 2 H), 3.6 (s, 6 H), 7.0–8.2 (m, 4 H) ppm. Anal. ($C_{15}H_{21}NO_5S$) C, H, N.

(H) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(2′-methyl-2′,3′-dihydro-1′-benzothiophene 1′-oxide) (5b). **4b** (47.1 g, 0.125 mol) was reacted in accordance with method C. Protonation with water/ammonium chloride was followed by concentration, extraction with CH_2Cl_2, drying over Na_2SO_4, concentration, dissolution in acetone, and crystallization by the addition of ether, yielding **5b** (19.1 g, 40.7%) in the form of a mixture of diastereomers: mp 200–206 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 and 1.6 (2 d, J = 7 Hz, together 3 H), 2.2 (2 s, together 6 H), 3.1–3.3 (3 s, together 6 H), 3.5–4.1 (m, 1 H), 7.1–7.8 (m, 4 H) ppm. Anal. ($C_{19}H_{21}NO_5S$) C, H, N, S.

(I) Dimethyl 2,6-Dimethyl-4-ethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (6b). **5b** (7.5 g, 20.0 mol) was dissolved in 150 mL of 75% ethanol and refluxed for 5 h with 50 g of Raney nickel and for 6 h after addition of a further 30 g of Raney nickel. After cooling, the solution was filtered by suction, concentrated, and chromatographed with ether on silica gel. The UV-fluorescent fraction (R_f = 0.52) yielded **6b** (0.75 g, 11%): mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7 Hz, 3 H), 2.1 (s, 6 H), 2.4 (q, J = 7 Hz, 2 H), 5.2 (s, N H), 6.9–7.6 (m, 5 H) ppm; MS 329 (M^+, <1), 301 (30), 300 (100). Anal. ($C_{19}H_{23}NO_4$) C, H, N.

(K) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(2′-methyl-2′,3′-dihydro-1′-benzothiophene) (7b). **6b** (7.5 g, 20 mmol) was reacted in accordance with method E to yield **7b** (0.75 g, 10.5%): mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.5 (d, J = 7 Hz, 3 H), 2.1 (s, 3 H), 2.4 (s, 3 H), 3.4 (2 s, 6 H), 4.5 (q, J = 7 Hz, 1 H), 5.9 (s, NH), 7.0–7.2 (m, 4 H) ppm; MS 359 (M^+, 4), 301 (30), 300 (100), 284 (30), 268 (20). Anal. ($C_{19}H_{21}NO_4S$) C, H, N, S.

(L) Diethyl 2,6-Dimethyl-4-[2-(methylthio)-3-pyridyl]-pyridine-3,5-dicarboxylate (3c). Diethyl 2,6-dimethyl-4-[2-(methylthio)-3-pyridyl]-1,4-dihydropyridine-3,5-dicarboxylate (**2c**)[41] (7.5 g, 20 mmol) was oxidized (method A) to yield **3c** (7.0 g, 94%): mp 52–54 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 7 Hz, 6 H), 2.5 (s, 3 H), 2.65 (s, 6 H), 4.1 (q, J = 7 Hz, 4 H), 7.0 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1 H), 7.3 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1 H), 8.5 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1 H) ppm. Anal. ($C_{19}H_{22}N_2O_4S$) C, H, N.

(M) Diethyl 2,6-Dimethyl-4-[2-(methylsulfinyl)-3-pyridyl]pyridine-3,5-dicarboxylate (4c). **3c** (7.5 g, 20 mmol) was refluxed with *m*-chloroperbenzoic acid (3.8 g, 22 mmol) in 150 mL of CH_2Cl_2 for 1.5 h. After cooling, the solution was washed with soda solution and water, dried over Na_2SO_4, and concentrated. After the solution was triturated with petroleum ether/ether, **4c** (7.5 g, 96%) crystallized: mp 88–91 °C; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7 Hz, 3 H), 1.01 (t, J = 7 Hz, 3 H), 2.65 (s, 3 H), 2.7 (s, 3 H), 2.8 (s, 3 H), 4.05 (q, J = 7 Hz, 2 H), 4.1 (q, J = 7 Hz, 2 H), 7.3–7.6 (m, 2 H), 8.7–9.0 (m, 1 H) ppm. Anal. ($C_{19}H_{22}N_2O_5S$) C, H, N.

(N) [2,6-Dimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(2′,3′-dihydrothieno[2,3-*b*]pyridine 1′-oxide) (5c). **4c** (8.2 g, 21 mmol) was reacted according to method C. The yield was 2.2 g (27%) of **5c**: mp 253–256 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.0 (t, J = 7 Hz, 3 H), 2.2 (s, 3 H), 2.3 (s, 3 H), 3.4 (d, J = 14 Hz, 1 H), 3.6–4.0 (m, 4 H), 4.2 (d, J = 14 Hz, 1 H), 7.4 (dd, J = 8 and 5 Hz, 1 H), 7.7 (dd, J = 8 and 2 Hz, 1 H), 8.4 (s, N H), 8.55 (dd, J = 5 and 2 Hz) ppm. Anal. ($C_{19}H_{22}N_2O_5S$) C, H, N.

(O) Diethyl 4-(3-Pyridyl)-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6c). **5c** (3.9 g, 10 mmol) was reacted with Raney nickel for 45 min as per method D to yield **6d** (2.4 g, 68%): mp 164–167 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 7 Hz, 6 H), 1.9 (s, 3 H), 2.1 (s, 6 H), 3.7 (2 q, J = 7 Hz, 4 H), 6.5 (s, NH), 7.0–7.2 (m, 1 H), 7.6–7.8 (m, 1 H), 8.2–8.4 (dd, J = 5 and 2 Hz, 1 H), 8.7 (d, J = 2 Hz, 1 H) ppm. Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

(P) Dimethyl 2,6-Dimethyl-4-[2-(methylthio)-5-nitrophenyl]pyridine-3,5-dicarboxylate (3d). Dimethyl 2,6-dimethyl-4-[2-(methylthio)-5-nitrophenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**2d**)[42] (117 g, 0.30 mol) was reacted as per

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method A to yield **3d** (95.4 g, 81.9%): mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 2.65 (s, 6 H), 3.6 (s, 6 H), 7.35 (d, J = 3 Hz, 1 H), 8.0 (d, J = 3 Hz, 1 H), 8.2 (dd, J = 7 and 3 Hz, 1 H) ppm. Anal. ($C_{18}H_{18}N_2O_6S$) C, H, N.

(Q) Dimethyl 2,6-Dimethyl-4-[2-(methylsulfinyl)-5-nitrophenyl]pyridine-3,5-dicarboxylate (4d). 3d (59 g, 0.15 mol) was dissolved in 500 mL of CH_2Cl_2, mixed portionwise with 3-chloroperbenzoic acid (26 g, 0.15 mmol) at room temperature, and stirred overnight. After workup (method A) **4d** was obtained (56 g, 91%): mp 120–121 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 2.7 (s, 6 H), 3.6 (s, 3 H), 3.7 (s, 3 H), 8.0–8.1 (m, 1 H), 8.3–8.5 (m, 2 H) ppm. Anal. ($C_{18}H_{18}N_2O_7S$) C, H, N, O.

(R) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(5′-nitro-2′,3′-dihydro-1′-benzothiophene 1′-oxide) (5d). 4d (54.7 g, 0.135 mol) was reacted as per method C. Crystallization with ethyl acetate yielded **5d** (17.7 g, 32.3%): mp 257–259 °C; ^{1}H NMR ($CDCl_3$)/CD_3OD) δ 2.2 (s, 3 H), 2.3 (s, 3 H), 3.3 (s, 3 H), 3.4 (s, 3 H), 3.5 (d, J = 13 Hz, 1 H), 4.3 (d, J = 13 Hz, 1 H), 7.7–8.4 (m, 3 H) ppm; MS 406 (M^+, 15), 358 (15), 329 (100), 313 (40), 299 (95), 283 (25). Anal. ($C_{18}H_{18}N_2O_7S$) C, H, N.

(S) Dimethyl 4-(3-Nitrophenyl)-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6d) and Dimethyl 4-(4-Nitrophenyl)-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6e). 6a (6.3 g, 20 mmol) was dissolved in 50 mL of concentrated sulfuric acid at room temperature and mixed portionwise with KNO_3 (2.4 g, 24 mmol) at 0 °C. After 15 min at room temperature, the solution was poured onto ice and filtered by suction and the mixture of **6d** and **6e** separated by Craig distribution (2300 stages, DMF/water). The yield was 0.4 g (5.6%) of **6d**, mp 135–137 °C, and 1.8 g (25%) of **6e**, mp 184–186 °C.

6d: ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.1 (s, 6 H), 3.3 (s, 6 H), 5.5 (s, NH), 7.1–8.4 (m, 4 H) ppm; ^{13}H NMR ($CDCl_3$) δ 19.9, 26.0, 43.9, 50.5, 109.2, 120.3, 122.8, 127.8, 134.1, 141.2, 167.9 ppm. Anal. ($C_{18}H_{20}N_2O_6$) C, H, N.

6e: ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.1 (s, 6 H), 3.2 (s, 6 H), 5.7 (s, NH), 7.6 (d, J = 9 Hz, 2 H), 8.1 (d, J = 9 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 19.7, 25.8, 44.2, 50.4, 108.9, 122.3, 128.8, 141.5, 145.4, 159.6, 168.0 ppm; MS 360 (M^+, 2), 345 (100), 299 (22), 238 (28). Anal. ($C_{18}H_{20}N_2O_6$) C, H, N.

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Supplementary Material Available: Table of bond distances, table of bond angles, table of torsional angles, table of positional parameters, and table of general displacement parameter expressions (4 pages). Ordering information is given on any current masthead page.

Synthesis and Antihyperglycemic Activity of Novel 5-(Naphthalenylsulfonyl)-2,4-thiazolidinediones

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A series of 5-(naphthalenylsulfonyl)-2,4-thiazolidinediones were synthesized and evaluated for antihyperglycemic activity in an insulin-resistant, genetically diabetic db/db mouse model of non-insulin-dependent diabetes mellitus (NIDDM). The sulfones could be synthesized by a novel, selective C-5 sulfonylation of dilithio-2,4-thiazolidinedione with appropriate sulfonyl chlorides. Within this series, naphthalene was found to be superior to other groups for eliciting antihyperglycemic activity, including the *p*-alkoxyphenyl group found in ciglitazone, a prototypical agent for this activity. Attachment of the 5-sulfonyl-2,4-thiazolidinedione moiety to the 2-naphthalene position led to optimum activity. Other linkers between the naphthalene and 2,4-thiazolidinedione rings, such as thio, methylene, oxy, and sulfinyl led to decreased antihyperglycemic activity. The best analogue, 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31,637) was equipotent to ciglitazone in two animal models of NIDDM.

The limitations of oral agents currently employed for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) has led to an ongoing need for new therapies for this disease.[1] The sulfonylureas, which are in current use, suffer from potentially fatal hypoglycemic episodes and from primary or secondary treatment failures.[2] The other major class of oral agents, the biguanides, were banned by the Food and Drug Administration in 1977 due to toxicity problems associated with lactic acidosis.[3]

Advances in the understanding of glucose metabolism and insulin action have led to recent efforts to develop new oral agents for the treatment of NIDDM. Therapeutic agents currently in development act via a variety of different mechanisms to lower glucose levels including inhibition of fatty acid oxidation, α-glycosidase inhibition, antagonism of α_2-adrenoceptors, and inhibition of gluconeogenesis.[4]

One of the most promising approaches for control of NIDDM is through potentiation of peripheral insulin action.[5,6] Ciglitazone (1), a *p*-alkoxybenzyl-substituted thiazolidinedione, represents a prototypical agent for this type of activity.[5] It has antihyperglycemic activity in insulin-resistant animal models without incidence of hypo-

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