6(*S*)-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*S*,*R*). The protocol was the same as that for compound **5**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*R* (0.513 g, 2.2 mmol) to yield 150 mg (15%): mp 147–148 °C; R_f = 0.37 (CMA 70:5:3); $[\alpha]^{20}_D$ −6.3° (*c* 3, methanol); ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1, CONH-Ar), 8.98 (br s, 1, NH), 8.75 (br s, 1, NH), 8.55 (m, 1, naphthyl H), 7.86 (m, 1, naphthyl H), 7.6–7.4 (m, 5, naphthyl H, $bz_{2,6}$H), 7.1 (d, 2, $bz_{3,5}$H, *J* = 7.2 Hz), 7.00 (d, 1, naphthyl H, *J* = 9 Hz), 4.42 (m, 1, $CH_2CH(OH)CH_2$, 4.18 (m, 2, $-OCH_2CH(OH)-$), 3.28 (m, 2, $-CH(OH)CH_2(NH)-$), 3.14 (m, 1, $NHCH(CH_3)CH_2$), 2.34 (t, 2, CH_2CH_2CONH, *J* = 9 Hz), 2.24 (s, 3, bz-CH_3), 1.86 (m, 1, $CH(CH_3)CH_2$), 1.7–1.5 (m, 3, $CH(CH_3)CH_2$, CH_2CH_2CONH), 1.5–1.3 (m, 2, $CH(CH_3)CH_2CH_2$), 1.27 (d, 3, $-CH(CH_3)-$, *J* = 9 Hz). Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6(*S*)-[[3-(1-Naphthyloxy)-2(*S*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*S*,*S*). The protocol was the same as that for compound **5**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*S* to yield 170 mg (17%): mp 146–146.5 °C; R_f = 0.37 (CMA 70:5:3); $[\alpha]^{20}_D$ −9.3° (*c* 3, methanol); ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1, CONH-Ar), 9.16 (br s, 1, NH), 8.73 (br s, 1, NH), 8.30 (m, 1, naphthyl H), 7.90 (m, 1, naphthyl H), 7.63–7.4 (m, 5, naphthyl H, $bz_{2,6}$H), 7.08 (d, 2, $bz_{3,5}$H, *J* = 7.2 Hz), 7.00 (d, 1, naphthyl H, *J* = 9 Hz), 4.42 (m, 1, $CH_2CH(OH)CH_2$), 4.19 (m, 2, $-OCH_2CH(OH)-$), 3.30 (m, 2, $-CH(OH)CH_2(NH)-$), 3.15 (m, 1, $NHCH(CH_3)CH_2$), 2.35 (t, 2, CH_2CH_2CONH, *J* = 9 Hz), 2.22 (s, 3, bz-CH_3), 1.88 (m, 1, $CH(CH_3)CH_2$), 1.7–1.5 (m, 3, $CH(CH_3)CH_2$, CH_2CH_2CONH), 1.5–1.3 (m, 2, $CH(CH_3)CH_2CH_2$), 1.30 (d, 3, $-CH(CH_3)-$, *J* = 9 Hz). Anal. ($C_{27}H_{34}N_2O_3$) C, H, N.

6(*R*)-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*R*,*R*). The protocol was similar to that of compound **5**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*R* to yield 140 mg (14%): mp 146–147 °C, $[\alpha]^{20}_D$ +9.3° (*c* 3, methanol); the values for R_f and NMR were identical with that of compound **10**-*S*,*S*. Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6(*R*)-[[3-(1-Naphthyloxy)-2(*S*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*R*,*S*). The protocol was similar to that of compound **5**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*S* to yield 130 mg (13%): mp 147–148 °C, $[\alpha]^{20}_D$ +6.1° (*c* 3, methanol); the values for R_f and NMR were identical with that of compound **5**-*S*,*R*. Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-(*S*)-heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*R*,*S*). Compound **15**-*R* (1.28 g, 3.2 mmol) in DMSO (4 mL) was cooled to 0 °C and water (1 mL) containing NaOH (0.92 g) was added dropwise over a period of 15 min. The solution remained at 0 °C for 45 min and at room temperature for 10 min. Ice water was added to the solution and the product was extracted into ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure to give the crude epoxide as a brownish oil. This oil was used without further purification.

A mixture of compound **20**-*S* (1.1 g, 2.2 mmol) in 0.1 N NaOH (5 mL) was extracted with dichloromethane. The solvent was removed under reduced pressure and the residue was suspended in DMSO (20 mL). This was combined with the epoxide formed above and the solution was stirred at 90 °C for 22 h. The reaction was monitored by TLC (CMA 85:10:5) for the disappearance of starting amine. After 22 h, the product was cooled and water (10 mL) was added to the solution. The solution was extracted into dichloromethane, dried with $MgSO_4$, and filtered. The crude product was concentrated under vacuum. A flash column was run with 3:1 dichloromethane/2-propanol. the appropriate fractions were collected and concentrated under vacuum. The residue was brought up in CH_2Cl_2 and dry HCl gas was bubbled through. The solvent was removed under reduced pressure and the product was recrystallized from ethanol and ether. A portion of the recrystallized product was prepared for biological testing by lyophilizing it from methanol/water to yield 150 mg (13%): mp 147.5–148 °C; R_f = 0.38 (CMA 95:5:3); $[\alpha]^{20}_D$ +8.1° (*c* 3, methanol); ^{1}H NMR (MeOD) δ 8.3 (m, 1, naphthyl H), 7.85–7.7 (m, 3, naphthyl H, $bz_{3,5}$H), 7.6–7.5 (d, 2, $bz_{2,6}$H, *J* = 9 Hz), 7.5–7.3 (m, 4, naphthyl H), 6.9 (d, 1, naphthyl H, *J* = 7.2 Hz), 4.2 (m, 2, $-OCH_2CH(OH)-$), 3.8 (m, 1, $CH_2CH(OH)CH_2$), 3.3–3.0 (m, 3, $-CH(OH)CH_2NHCH(CH_3)-$), 2.42 (t, 2, $-CH_2CH_2CONH-$, *J* = 7.2 Hz) 1.8–1.4 (m, 6, $-CH(CH_3)CH_2CH_2CH_2-$), 1.24 (d, 3, $CH(CH_3)$, *J* = 5.4 Hz). Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

6-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-(*R*)-heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*R*,*R*). The reaction conditions and amounts were identical with that for compound **4**-*R*,*S* except compound **20**-*R* was used, yielding 148 mg (13%): mp 147–148 °C; $[\alpha]^{20}_D$ +8.8° (*c* 3, methanol); R_f = 0.38 (CMA 95:5:3); ^{1}H NMR (MeOD) δ 8.3 (m, 1, naphthyl H), 7.85–7.7 (m, 3, naphthyl H, $bz_{3,5}$H), 7.6–7.5 (d, 2, $bz_{2,6}$H, *J* = 9 Hz), 7.5–7.3 (m, 4, naphthyl H), 6.9 (d, 1, naphthyl H, *J* = 7.2 Hz), 4.35 (m, 1, $CH_2CH(OH)CH_2$), 4.2 (m, 2, $-OCH_2CH(OH)-$), 3.4–3.0 (m, 3, $-CH(OH)CH_2NHCH(CH_3)-$), 2.42 (t, 2, $-CH_2CH_2CONH-$, *J* = 7.2 Hz), 1.85–1.4 (m, 6, $-CH(CH_3)CH_2CH_2CH_2-$), 1.27 (d, 3, $CH(CH_3)$, *J* = 5.4 Hz). Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

Acknowledgment. We are grateful to Drs. K. Melmon and M. Khan and their co-workers for carrying out the pharmacological assays for this study. In addition, we acknowledge the National Institutes of Health (Grant No. HL26340), Sigma Xi Research Honor Society, and the California Foundation for Biochemical Research for their generous financial support.

Antihypertensive Dihydropyridines with 1,4,4-Trisubstitution

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Received September 26, 1988

Dihydropyridines with 1,4,4-trisubstitution were synthesized and tested for antihypertensive activity in a spontaneously hypertensive rat model. This substitution pattern on the dihydropyridine nucleus differs markedly from that found most active in the structure–activity relationship established for nifedipine-like compounds. However, some were found to significantly lower blood pressure at testing doses (30 mg/kg, ip and 100 mg/kg, po) for up to 24 h. Methyl 1,4-dihydro-4,4-dimethyl-1-pyridinepropanoate (**2**-1), for example, lowered blood pressure 71 mmHg at 30 mg/kg, ip and the effect endured for greater than 24 h. Unlike prototypical dihydropyridines such as nifedipine, these compounds did not seem to have any effect on calcium channels.

Dihydropyridines as a chemical class have been widely explored as cardiovascular agents in recent years. Nifedipine (1) has been approved for clinical use as an antianginal agent and represents the type of dihydropyridine structure found useful in both antianginal and antihypertensive therapy. A large body of evidence regarding the structural requirements for these activities has accrued[1]

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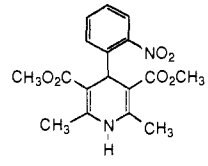


1, Nifedipine

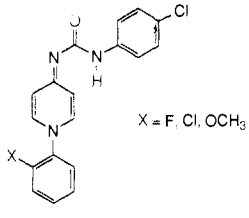
and the structure–activity relationship (SAR) is seemingly well defined. Currently available evidence supports that optimal activity will be achieved if the following conditions are satisfied: no substitution on the dihydropyridine nitrogen, 2,6-dialkyl substitution on the ring, electron-withdrawing substituents on positions 3 and 5, and a single aromatic ring substituent at position 4.

We chose to explore a group of dihydropyridines radically different from 1. Although we maintained the dihydropyridine nucleus, other functionalities departed markedly from accepted SAR for cardiovascular activity. With these changes it was considered possible that the same SAR may not apply and new structures with unique activity might result.

The chemical instability of dihydropyridines is well known.[2] There is a strong tendency to aromatize by oxidation to the pyridine nucleus. Previously synthesized medicinal agents, such as 1, have circumvented this problem by 3,5-disubstitution with electron-withdrawing substituents which rendered the nitrogen essentially nonbasic. Consequently, the driving force to aromatize was minimized. Despite this improvement in stability, the major deactivation of these compounds still results from conversion to the corresponding pyridine.[3]

Our strategy in this regard was to remove the hydrogens which are susceptible to oxidation. Thus we set out to synthesize molecules of the general structures **2** and **3** which have both substitution on nitrogen as well as 4,4-disubstitution. These new structures were evaluated for potential cardiovascular utility by assessing antihypertensive and coronary vasodilating activity.

That the dihydropyridine nucleus could display antihypertensive activity without the strict limitations imposed by previously documented SAR was demonstrated within a limited series of related pyridinylidene arylureas (4). Although antihypertensive activity was shown, this latter group of compounds reportedly acted by a different mechanism than 1.[4]

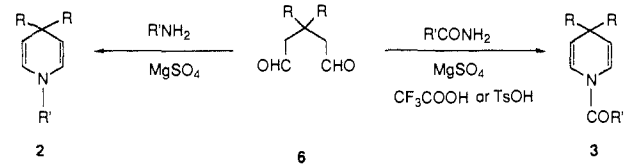


4

Chemistry

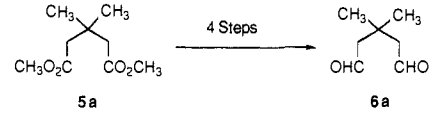
Syntheses of **2** and **3** are shown in Scheme I and are based on reports from Fraenkel and co-workers in which they synthesized simple dihydropyridine amides such as 3 for NMR studies.[5]

Scheme I[a]



[a] See Table I for list of specific **2** and **3** synthesized.

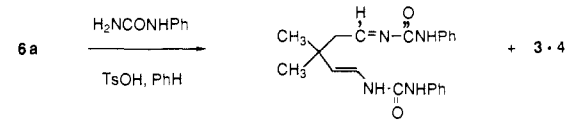
Scheme II



Glutaraldehyde derivative **6a** was prepared as described previously[6] in an efficient four-step sequence from the diester **5a** (Scheme II), available from commercial diacid. This involved an acyloin condensation, subsequent reduction to the diol, and oxidative ring opening in 67% overall yield. On the other hand, **6b** and **6c** were available directly from the corresponding diesters **5b** and **5c** by careful reduction using diisobutylaluminum hydride at -78 °C. We obtained **5b** (Scheme III) by modification of the sequence reported by Ivanov[7] in which 2 mol of lithio acetonitrile anion, generated by treatment of acetonitrile with lithium diisopropylamide rather than lithium amide as reported, were sequentially added to benzophenone followed by hydrolysis and esterification. Friedel–Craft condensation of 2 mol of anisole with acetonedicarboxylic acid[8] followed by esterification as indicated in Scheme IV was the source of **5c**.

Dialdehydes **6a** and **6c** were subjected to a double condensation with primary amides under acidic conditions (see Scheme I) to yield **3**. In all cases the condensations were aided by azeotropic removal of water and/or the presence of a dehydrating agent such as powdered anhydrous magnesium sulfate. These were the conditions described by Fraenkel[6] and we found them to be applicable to the synthesis of a number of different dihydropyridine amides. We also found, as reported by others,[9] that this reaction could be extended to the synthesis of dihydropyridines **2** by substituting primary amines and performing the condensation under neutral conditions, i.e. without added acid catalyst (see the Experimental Section).

In the case of amide condensations in which there was also a basic center in the starting material, such as **3-3** and **3-7**, it was necessary to use greater than 1 equiv of acid. If ureas were used in condensation with glutaraldehyde adducts to form **3-4**, **3-2**, and **3-11**, the reactions were run at a considerably higher dilution in THF and the starting material was added slowly to minimize the formation of side products such as 7 which arose from addition of 2 mol of urea to a single mole of glutaraldehyde.



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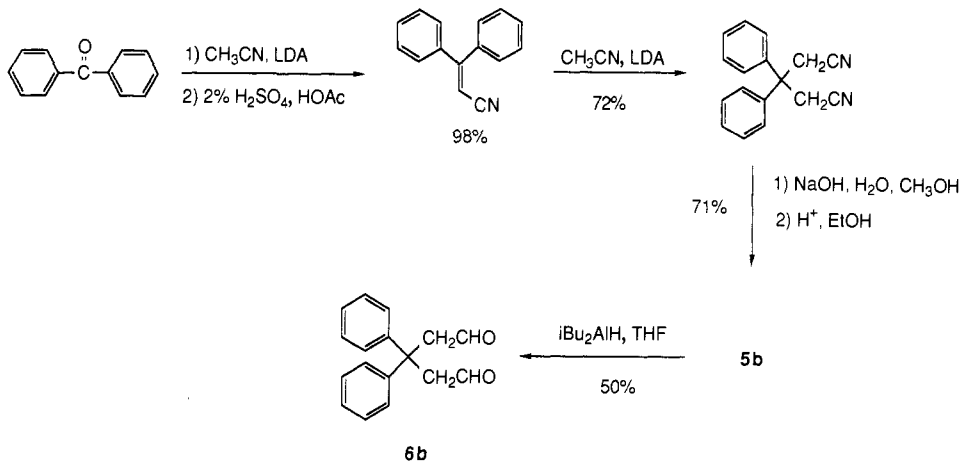
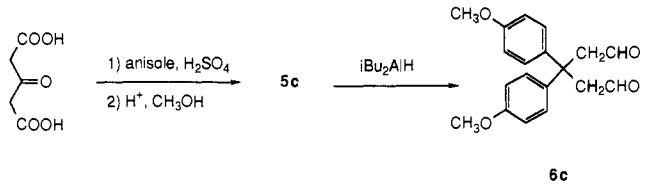
(1) Pous, J.; Blancafort, P.; Castaner, J.; Serradell, M.; Mealy, N. *Drugs Future* **1981**, *6*, 427.
(2) Meyer, A.; Stout, D. *Chem. Rev.* **1982**, *82*, 223.
(3) Meyer, H. *Calcium Antagonists and Cardiovascular Disease*; Opie, L. H., Ed.; Raven Press: New York, 1984; Chapter 15.
(4) Ludden, C.; Scriabine, A.; Ulm, E.; Morgan, G.; Fisher, M.; Ruyle, W. *Experentia* **1979**, *35*, 799.
(5) Foos, J.; Killian, W.; Rizvi, S.; Unger, M.; Fraenkel, G.; *Tetrahedron Lett.* **1978**, 1407.
(6) Foos, J.; Steel, F.; Rizvi, S.; Fraenkel, G.; *J. Org. Chem.* **1979**, *44*, 2522.
(7) Ivanov, H.; Anghelova, I. *C. R. Acad. Bull. Sci.* **1965**, *18*, 529.
(8) Korgaonkar, U.; Samant, S.; Deodhar, K.; Kulkarni, R. *Indian J. Chem.* **1981**, *20B*, 572.
(9) Kosower, E.; Sorensen, T. *J. Org. Chem.* **1962**, *27*, 3764.

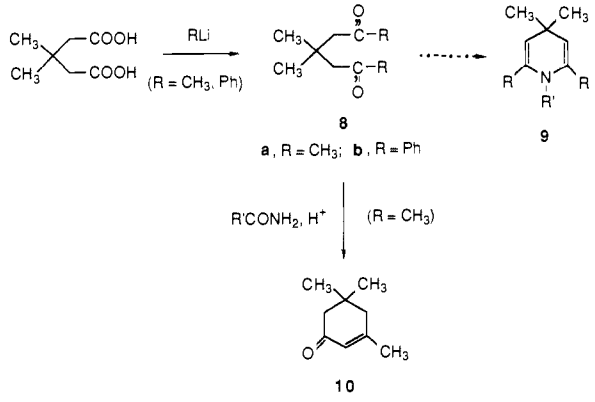
Scheme III



Scheme IV



Scheme V



To further approximate structures such as nifedipine (**1**), we attempted to synthesize 2,6-disubstituted analogues such as **9** (see Scheme V). The required starting material, dimethyl ketone **8a**, had been previously reported[10] but we found was more conveniently available by treatment of 3,3-dimethylglutaric acid with methyllithium.[11] However, the same reaction of 3,3-diphenylglutaric acid with methyllithium unexplicably failed to give the 4,4-diphenyl analogue of **8a**. Attempts to condense **8a** with either amides or amines under the reaction conditions used to form **2** or **3** were unsuccessful in formation of **9**. When **8a** was heated in reluxing benzene in the presence of acid, the sole product was aldol product **10**, regardless of whether an equivalent of an amide was present or not. If **8a** was heated with an equivalent of a primary amine, a product of unknown structure was formed that was identical by ^{1}H NMR and gas chromatographic retention time with the product formed when **10** was treated with the amine in refluxing benzene. In an effort to obviate aldol condensation products, the diphenyl ketone **8b** was synthesized by the addition of phenyllithium to the diacid.[12] This molecule, unlike **8a**, did not have the enolizable protons available to make it susceptible to aldol reaction. However, all attempts to react **8b** with amines were unsuccessful and gave no reaction.

Amides used in the syntheses of **3** which were not commercially available were synthesized by treating the carboxylic acid with oxalyl chloride in DMF followed by addition of ammonia. Pyrrole-2-carboxamide was synthesized by a literature procedure.[13]

Results and Discussion

As described in the Experimental Section, antihypertensive activity of these limited analogue series was tested in spontaneously hypertensive rats (SHR) at doses of 30 mg/kg, ip and 100 mg/kg, po. Changes in mean arterial pressure (MAP) were monitored for 24 h after dosing to illustrate the time course of drug effect.

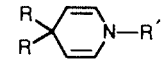
Several compounds showed marked antihypertensive activity after a 30 mg/kg, ip dose; several also showed moderate activity after 100 mg/kg oral dosing. Table I lists maximum changes in MAP sorted by descending antihypertensive activity at the 30 mg/kg, ip dose. Intensity of ip activity was not predictive of oral activity. Possibly, variations in the nitrogen substituents within the dihydropyridine (**2**) and dihydropyridine amide (**3**) series lead to route-dependent differences in distribution and metabolism. Since absorption and metabolism obscure intrinsic activity less after ip than after oral dosing, SAR discussions will focus on ip activity.

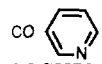
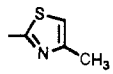
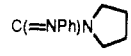
Despite the limited series from which to evaluate SAR, 4,4-dimethyl substitution shows clear advantage over aromatic ring substituent counterparts. Thus, with ip administration the following comparisons in ability to decrease hypertensive MAP were evident: **3-1 > 3-3, 2-3 > 2-7, 3-5 > 3-10, 3-2 > 3-11, 2-4 = 2-5**. In each of these cases the dimethyl substitution proved superior or in one case equal to the diphenyl or di-*p*-methoxyphenyl substitution when the rest of the molecule was identical. This is in contrast to documented SAR seen with dihydropyridine compounds such as **1** (see ref 1) in which the most active compounds contained a substituted phenyl substituent at the 4-position of a dihydropyridine.

Comparing dihydropyridines (**2**) to dihydropyridine amides (**3**) did not reveal any consistent effect of ring nitrogen character. In general, no advantage based on

(10) Bianchetti, G.; Pocar, D.; Stadi, R.; Croce, P.; Vigevani, A. *Gazz. Chim. Ital.* **1967**, *97*, 872.
(11) Jorgenson, M.; *Org. React.* **1970**, *16*, 1. Tegner, C. *Acta Chem. Scand.* **1952**, *6*, 782.
(12) Zimmerman, H.; Pincock, J. *J. Am. Chem. Soc.* **1973**, *95*, 3246.
(13) Barnett, G.; Anderson, H.; Loader, C. *Can. J. Chem.* **1980**, *58*, 409.

Table I. Antihypertensive Testing in Spontaneously Hypertensive Rat (SHR)



no.	R	R′	max change in BP,[a] mmHg 30 mg/kg, ip	max change in BP,[a] mmHg 100 mg/kg, po
2-1	CH_3	$CH_2CH_2CO_2CH_3$	−71 ± 11	−19 ± 5
2-2	CH_3	$(CH_2)_4CO_2CH_3$	−58 ± 11	−11 ± 8
3-1	CH_3	$COCH_2NMe_2$	−52 ± 8	−39 ± 11
2-3	CH_3	$(CH_2)_3CO_2CH_3$	−42 ± 8	−45 ± 7
3-2	CH_3	$CONHCH_3$	−34 ± 4	−41 ± 12
2-4	CH_3	$CH_2CH_2NMe_2$	−32 ± 5	−10 ± 7
2-5	Ph	$CH_2CH_2NMe_2$	−30 ± 6	−14 ± 6
3-3	Ph	$COCH_2NMe_2$	−29 ± 4	−12 ± 5
3-4	CH_3	CONHPh	−24 ± 4	−15 ± 4
3-5	CH_3	COPh	−21 ± 10	−27 ± 7
3-6	CH_3	$COCH_2(3,4\text{-}(OMe)_2Ph)$	−21 ± 8	23 ± 9
3-7	CH_3		−19 ± 10	−26 ± 6
3-8	CH_3	$COCHPh_2$	−9 ± 8	−6 ± 5
2-6	Ph	$CH_2CH_2(3,4\text{-}(OMe)_2Ph)$	−7 ± 4	−7 ± 7
3-9	CH_3		6 ± 6	−7 ± 4
2-7	4-OMePh	$(CH_2)_3CO_2CH_3$	11 ± 6	−21 ± 7
3-10	Ph	COPh	11 ± 5	12 ± 6
2-8	CH_3		14 ± 5	−21 ± 4
3-11	Ph	$CONHCH_3$	17 ± 8	−11 ± 4
2-9	CH_3		27 ± 7	19 ± 11
1	(nifedipine)		−71 ± 8	−68 ± 7

[a] Mean ± SEM. $n = 3$.

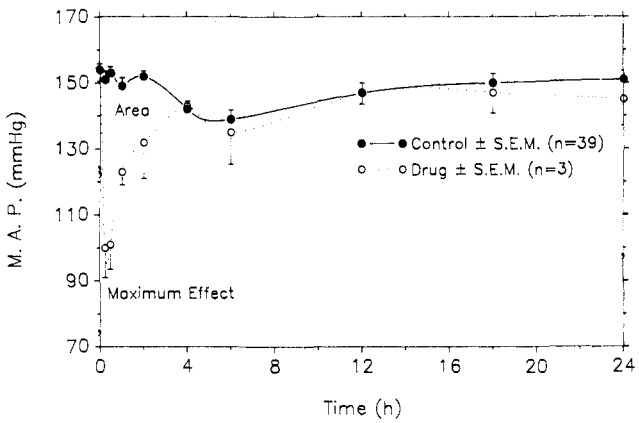


Figure 1. Mean arterial pressure after a single intraperitoneal 30 mg/kg dose of compound **3-1** in spontaneously hypertensive rats.

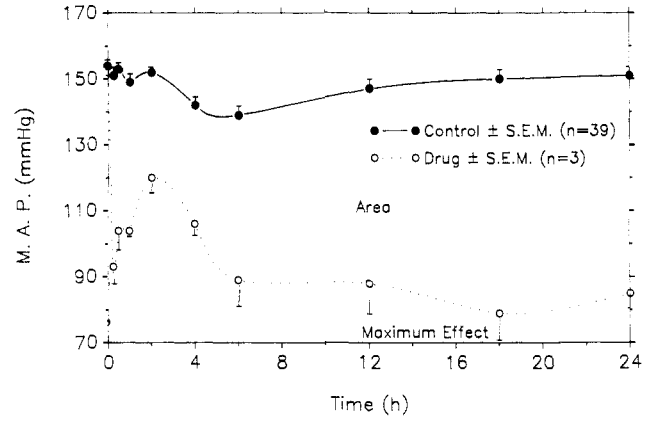


Figure 2. Mean arterial pressure after a single intraperitoneal 30 mg/kg dose of compound **2-1** in spontaneously hypertensive rats.

relative nitrogen basicity was apparent. A direct comparison can be made in two cases where the only difference in structure is the substitution of a carbonyl for methylene. We found that **3-1** decreased MAP to a greater extent than **2-4** (52 vs 32 mmHg), but that **2-5** and **3-3** were approximately equiactive.

A second noteworthy point of SAR was the apparent advantage of an alkyl chain ester substituent on the nitrogen. Three of the four most active compounds, **2-1**, **2-2**, and **2-3**, have this characteristic. Whether this substituent structurally corresponds to the ester functionality often seen in the 3- and 5-positions of compounds such as **1** is not clear.

To this point discussion of activity has focused on the maximal antihypertensive effect without regard to its time course. In fact, some compounds with significant maximal antihypertensive activity in Table I were only transiently effective. For example, 3-1 decreased MAP 52 mmHg (Table I). However, blood pressure had returned to control levels within 3 h after dosing, as illustrated in Figure 1. By contrast, compounds such as **2-1** had antihypertensive

Table II. Total Antihypertensive Activity: Area between Drug and Control MAP Curves after a 30 mg/kg, ip Dose[a]

no.	total antihypertensive act. (mmHg × h)
2-1[b]	1365
2-2	943
2-3	696
3-3	362
3-7	291
2-4	281
3-5	210
3-1[c]	132

[a] See the Experimental Section for an explanation of this calculation. [b] See Figure 2. [c] See Figure 1.

Table III. Product Purification Methods

no.	purification[a]	yield, %	mp/bp	formula
2-1	D	58	60–2 °C/0.05 mmHg	$C_{11}H_{17}NO_2$
2-2	C, D	34	82–90 °C/0.1 mmHg	$C_{13}H_{21}NO_2$
2-3	D	26	95 °C/0.2 mmHg	$C_{12}H_{19}NO_2$
2-4	D	45	60 °C/0.2 mmHg	$C_{11}H_{20}N_2$
2-5	C	49	60–3 °C	$C_{21}H_{24}N_2$
2-6	C, MeOH	36	76.5–78.5 °C	$C_{27}H_{27}NO_2$
2-7	C, MeOH	18	36–8 °C	$C_{24}H_{27}NO_4$
2-8	C	37	oil	$C_{11}H_{14}N_2S$
2-9	salt[b]	7	163–5 °C	$C_{18}H_{23}N_3 \cdot 1.5C_4H_4O_4$
2-10	C, MeOH	47	60–2 °C	$C_{27}H_{27}NO_2$
3-1	salt[c]	34	179–181 °C	$C_{11}H_{18}N_2O \cdot C_4H_4O_4$
3-2	C	38	129–131 °C	$C_9H_{14}N_2O$
3-3	salt[d]	17	242–244.5 °C	$C_{21}H_{22}N_2O \cdot HCl$
3-4	C	58	128–130 °C	$C_{14}H_{16}N_2O$
3-5	C	50	57–9 °C	$C_{14}H_{15}NO$
3-6	C	65	86–89.5 °C	$C_{17}H_{21}N_3O$
3-7	C, salt[e]	23	120–2 °C	$C_{13}H_{14}N_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$
3-8	*i*-PrOH	26	168–171 °C	$C_{21}H_{21}NO$
3-9	C	25	oil	$C_{12}H_{14}N_2O$
3-10	C, MeOH	35	91–3 °C	$C_{24}H_{19}NO$
3-11	C, CH_3CN	38	180–2 °C	$C_{19}H_{18}N_2O$

[a] Description of the purification method for the final product: C, column chromatography; D, distillation; salt indicates formation of an acid addition to form crystalline solid; solvents when listed indicate recrystallization. If more than one method is listed, a series of purification methods was carried out in the order given. [b] 1.5 fumarate recrystallized from *i*-PrOH/Et_2O. [c] Maleate recrystallized from CH_3CN. [d] HCl recrystallized from MeOH/Et_2O. [e] Oxalate hydrate recrystallized from EtOH/Et_2O/hexane.

activity of greater than 24-h duration (Figure 2). To further clarify these differences Table II ranks compounds according to total antihypertensive activity, i.e. the area between drug and control MAP curves. This derived area takes both intensity and duration of antihypertensive effect into account (see the Experimental Section). The total antihypertensive activity shown by compounds **2-1**, **2-2**, and **2-3** was equivalent to maintaining these SHR at normotension for 24, 21, and 16 h, respectively (Table II).

In order to compare the character of the compounds described in this study vs previously described dihydropyridines such as nifedipine, they were tested for effects on cardiac contractile force, rate, and coronary blood flow in isolated, perfused guinea pig hearts (Langendorff's preparation[14]). Compounds from the current series showed no significant effects at concentrations up to 10 mM, whereas **1**, through calcium entry blockade, increased coronary flow (a measure of vasodilitation) to 150% of control and decreased contractile force to 85% of control at a concentration of 0.013 mM. Our experience has been that all compounds shown by direct tests to inhibit calcium influx and tension development in isolated vascular smooth muscle preparations also show active coronary vasodilation in the Langendorff heart. Although effects of **2** and **3** on calcium influx were not directly tested, their inability to produce coronary vasodilitation suggests that they are not calcium entry blockers. The mechanism by which these compounds exert their antihypertensive effects is currently unresolved but apparently is different than nifedipine's.

The current series of compounds was synthesized with the assumption that the unstable dihydropyridine nucleus is determinant for cardiovascular activity of compounds such as nifedipine, **1**. The molecules described have retained this nucleus. However, it has been stabilized by a different substitution pattern than found in **1**. Preliminary testing has shown potential antihypertensive activity within the series, although the mechanism of this activity appears different than nifedipine's. Further studies are needed to explore in detail the usefulness of these compounds.

(14) Gleason, M.; Gill, A.; Brannan, M.; Flaim, S. *Pharmacology* **1986**, *33*, 76.

Experimental Section

All compounds in Table I were characterized by ^1H NMR on either a Bruker AM 360WB, Varian EM 390, or Varian EM 360 spectrometer. Elemental analyses (C, H, N) were determined by Atlantic Micro-Analysis of Atlanta, GA, for all compounds in Table I and were all within 0.4% of the calculated values. Melting points (see Table III) were obtained on a Thomas-Hoover capillary immersion apparatus and are uncorrected.

(3,4-Dimethoxyphenyl)acetamide. Typical Procedure. To a solution of 35.31 g (0.18 mol) of (3,4-dimethoxyphenyl)acetic acid in 345 mL of dry toluene and 34.5 mL of dry DMF at 0 °C under argon was added 16.8 mL (0.19 mol) of freshly distilled oxalyl chloride over 40 min. The reaction was stirred an additional 35 min at 0 °C and then at room temperature for 17 h. The reaction mixture was again cooled to 0 °C and gaseous ammonia slowly bubbled through it for 1 h. The reaction mixture was warmed to room temperature and stirred for 4 h after which the solid was filtered off and partitioned between chloroform and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo, giving 20.84 g of the title compound as an off-white solid, mp 142–144 °C.

1,4-Dihydro-1-[(3,4-dimethoxyphenyl)acetyl]-4,4-dimethylpyridine (3-6). Typical Procedure. In 180 mL of benzene 4.88 g (0.025 mol) of (3,4-dimethoxyphenyl)acetamide was combined with 3.2 g (0.025 mol) of 3,3-dimethylglutaraldehyde (**6a**) and 0.13 g (0.7 mmol) of *p*-toluenesulfonic acid monohydrate (In some cases trifluoroacetic acid was used.) under nitrogen. The reaction mixture was warmed to reflux and water was azeotroped off via a Dean–Stark trap. After 3 h the benzene was evaporated in vacuo, giving 7.74 g of crude product. The crude product was purified by silica gel column chromatography on 375 g of CC-7 silica gel by eluting with a 15% ethyl acetate/hexane solution. The eluate was evaporated to yield a white solid residue which was the title compound. ^1H NMR (90 MHz, $CDCl_3$): δ 1.1 (s, 6 H, CH_3), 3.75 (s, 2 H, CH_2), 3.85 (s, 6 H, OCH_3), 4.7–5.0 (m, 2 H, NCH=C*H*), 6.55 (m, 1 H, NC*H*=CH), 6.75 (m, 3 H, aromatic), 7.1 (m, 1 H, NC*H*=CH).

1,4-Dihydro-4,4-dimethyl-*N*-phenyl-1-pyridinecarboxamide (3-4). A mixture of 4.57 g (0.036 mol) of **6a**, 0.20 g (1.0 mmol) of *p*-toluenesulfonic acid monohydrate, and 8.64 g (0.072 mol) of anhydrous $MgSO_4$ in 300 mL of dry THF was heated to reflux under nitrogen. Phenylurea (4.89 g, 0.036 mol) in 125 mL of dry THF was added over a period of 1 h. Refluxing was continued for an additional 40 min before the reaction mixture was filtered and the filtrate evaporated in vacuo to yield 8.23 g of a brown oil. The crude product was chromatographed on silica gel by eluting with 7.5% ethyl acetate/hexane to yield 4.74 g of the title compound as a white solid.

When the reagents were combined in the normal manner (see procedure for **3-6** above) the desired product was formed along with a side product, proposed to be **7**, in an approximate ratio of 2:1 after column chromatography. ^{1}H NMR of **7**: (60 MHz, DMSO-d_6): δ 1.05 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.95 (bs, 2 H, CH_2), 4.85 (d, 1 H, CCH=C, J = 8 Hz), 5.95 (m, 1 H, C=CHN), 6.6–7.7 (m, 12 H, aromatics, CH=N, NH), 8.9 (s, 1 H, NH), 9.6 (s, 1 H, NH).

3,3-Diphenylglutaraldehyde (6b). To a rapidly stirring solution of 14.24 g (0.04 mol) of diethyl 3,3-diphenylglutarate in 320 mL of dry toluene at −78 °C under argon was added 61.12 mL (0.11 mol) of 1.86 M DIBAL in toluene solution (Aldrich) over a period of 4 min. After 40 min, 40 mL of methanol was added over 4 min to the −78 °C, stirring reaction mixture. After an additional 5 min, 80 mL of water was added over a 5-min period while the temperature of the reaction was kept at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred an additional hour. The reaction mixture was filtered, and the precipitated salts were washed with 300 mL of warmed toluene (100 °C) and then 300 mL of boiling methylene chloride. The organic phase of the filtrate was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a clear oil (11.58 g) that was 77% pure by GLC (SE-30). The oil was used in the next step without further purification.

Methyl 1,4-Dihydro-4,4-dimethyl-1-pyridinebutanoate (2-3). Typical Procedure. Anhydrous HCl was slowly bubbled into a heterogeneous mixture of 20.64 g (0.2 mol) of 4-aminobutyric acid in 200 mL of methanol at room temperature. After addition of the HCl for about 5 min, the reaction mixture warmed to a gentle reflux at which time it was submerged into a 0 °C ice bath. HCl addition was continued for an additional 5 min after the reaction mixture was cooled. The reaction mixture was then placed under nitrogen and refluxed for 17 h. The solvent was evaporated in vacuo to give 30.70 g of a white solid, mp 114–115 °C, which was used without further purification.

Under nitrogen, 5.89 g (0.046 mol) of 3,3-dimethylglutaraldehyde, 7.03 g (0.0457 mol) of methyl 4-aminobutanoate hydrochloride, and 9 g of 5-Å molecular sieves were combined in 425 mL of chloroform at room temperature. Triethylamine (7.0 mL, 0.05 mol) was added to the reaction mixture before it was warmed to reflux. After 21 h the reaction mixture was cooled to room temperature and filtered, and the filtrate was evaporated in vacuo to yield 8.56 g of crude product which was distilled (bp 95 °C/0.2 mmHg) to yield 2.5 g of **2-3**. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.05 (s, 6 H, CH_3), 1.90 (m, 2 H, CH_2), 2.35 (t, 2 H, CH_2), 3.05 (t, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.25 (d, J = 8 Hz, 2 H, NCH=C*H*), 5.70 (d, J = 8 Hz, 2 H, NC*H*=CH).

4,4-Dimethyl-2,6-heptanedione (8a). Over 3 h, 163 mL (0.22 mol) of 1.35 M methyllithium in ethyl ether was added dropwise to a stirred, 0 °C solution of 8.00 g (0.05 mol) of 3,3-dimethylglutaric acid in 120 mL of dry ethyl ether/100 mL of THF. The reaction mixture was then warmed to room temperature and stirred 18 h before it was poured into 500 mL of H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 5.23 g of a clear oil which was 72% desired product by GLC (SE-30). ^{1}H and ^{13}C NMR and IR of the crude product proved consistent with the desired structure. This crude material was used without further purification.

3,5,5-Trimethylcyclohex-2-enone (10). When a sample of **8a** was refluxed in benzene with tosic acid either in the presence or absence of an amide, the conditions to form **3**, the sole product was **10**. Its ^{1}H NMR was consistent with that reported in the literature.[15]

Antihypertensive Activity in Conscious, Unrestrained Spontaneously Hypertensive Rats (SHR). Adult male 350–450-g SHR (Charles River, Wilmington, MA) were implanted with a swivelling spring-shielded right carotid arterial cannula under ether anesthesia. Animals were individually housed with ad libitum access to tap water and permitted overnight recovery prior to testing. Compounds uniformly suspended in 1% methylcellulose vehicle were administered intraperitoneally at 30 mg/kg (n = 3) or orally by gavage at 100 mg/kg (n = 3). Concurrent control animals (n = 3) received 1 mL of vehicle by the corresponding route. Blood pressure was monitored continuously for 24 h after dosing with a Buxco automated recording system. Data for selected timepoints (0, 0.25, 0.5, 1, 2, 4, 6, 12, 18, and 24 h) were used to illustrate the time course of mean arterial pressure (MAP) changes. Drug and control time courses were compared to derive maximum change from concurrent control and area between drug and control time course curves (a measure of total antihypertensive activity). Areas under the drug effect time course curves were estimated by the trapezoidal rule. These areas represent the area between the drug and control time course curves.

Acknowledgment. We would like to extend our appreciation to Dr. Steve Flaim for the data from the Langendorff heart experiments.

Registry No. **2-1**, 115933-01-2; **2-2**, 115932-99-5; **2-3**, 115932-98-4; **2-4**, 115932-96-2; **2-5**, 115932-97-3; **2-6**, 123412-11-3; **2-7**, 115933-00-1; **2-8**, 115933-10-3; **2-9**, 123412-13-5; **2-9**·$^3/_2$ fumarate, 123412-14-6; **3-1**, 115933-02-3; **3-1**·maleate, 123412-09-9; **3-2**, 115932-94-0; **3-3**, 115933-03-4; **3-3**·HCl, 115933-08-9; **3-4**, 115933-09-0; **3-5**, 67402-85-1; **3-6**, 115933-04-5; **3-7**, 115933-05-6; **3-7**·oxalate, 123412-10-2; **3-8**, 115932-92-8; **3-9**, 123412-12-4; **3-10**, 115932-93-9; **3-11**, 115932-95-1; **6a**, 67402-86-2; **6b**, 64516-58-1; **6c**, 115933-12-5; **7**, 123412-15-7; **8a**, 16764-90-2; **10**, 78-59-1; $H_2NCH_2CH_2CO_2Me$, 4138-35-6; $H_2N(CH_2)_4CO_2Me$, 63984-02-1; $H_2NCOCH_2NMe_2$, 6318-44-1; $H_2N(CH_2)_3CO_2Me$, 3251-07-8; $H_2NCONHMe$, 598-50-5; $H_2NCH_2CH_2NMe_2$, 108-00-9; $H_2NCONHPh$, 64-10-8; H_2NCOPh, 55-21-0; $H_2NCOCH_2((3,4\text{-}OMe)_2Ph)$, 5663-56-9; $H_2NCOCHPh_2$, 519-87-9; $H_2NCO(CH_2)_2((3,4\text{-}OMe)_2Ph)$, 120-20-7; $HO_2CCH_2((3,4\text{-}OMe)_2Ph)$, 93-40-3; $Ph_2C(CH_2CO_2Et)_2$, 3531-26-8; $Me_2C(CH_2CO_2H)_2$, 4839-46-7; $NH_2(CH_2)_3CO_2H$, 56-12-2; 2-oxo-2-(3-pyridinyl)ethanamide, 98-92-0; 2-oxo-2-(1*H*-pyrrol-2-yl)ethanamide, 4551-72-8; 1-(*N*-phenylamidine)pyrrolidine, 65071-09-2; 4-methyl-2-thiazolamine, 1603-91-4.

(15) Tomoeda, M.; Inuzuka, M.; Furuta, T.; Shinozuka, M.; Takahashi, T. *Tetrahedron* **1968**, 959.