was pH 7.4, 0.1 M phosphate buffer. Competitive inhibition of human AChE as well as reactivation of AChE after inhibition with GD and EPMP were performed as described previously.[22-24]

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Registry No. 1a, 102941-46-8; 1a·HCl, 102941-27-5; 1b, 102941-47-9; 1b·HCl, 90507-14-5; 1c, 102976-77-2; 1c·HCl, 99481-60-4; 1d, 99481-58-0; 1e, 99481-61-5; 1e·oxalate, 99481-62-6; 1f, 102941-28-6; 1g, 102941-29-7; 1h, 99481-59-1; 1i, 102976-75-0; 1j, 102976-76-1; 1k, 102941-30-0; 1k·oxalate, 102941-31-1; 1l, 102941-48-0; 1l·HCl, 102941-32-2; 1m, 102941-49-1; 1m·HCl, 102941-33-3; 1n, 102941-34-4; 1o, 102941-35-5; 1p, 102941-50-4; 1p·HCl, 102941-36-6; 1q, 102941-37-7; 1r, 102941-38-8; 1s, 102941-39-9; 1t, 102941-40-2; 1u, 102941-51-5; 1u·HCl, 102941-41-3; 1v, 102941-42-4; 1w, 102941-52-6; 1w·HCl, 102941-43-5; 1x, 102941-44-6; 1y, 102941-55-9; 1y·HCl, 102941-45-7; $C_6H_5COCH_3$, 98-86-2; 4-$BrC_6H_4COCH_3$, 99-90-1; 4-$H_3COC_6H_4COCH_3$, 100-06-1; 4-$H_3CC_6H_4COCH_3$, 122-00-9; 4-$NCC_6H_4COCH_3$, 1443-80-7; $C_6H_5COCCl{=}NOH$, 4937-87-5; 4-$BrC_6H_4COCCl{=}NOH$, 7733-43-9; 4-$H_3COC_6H_4COCCl{=}NOH$, 33108-93-9; 4-$H_3CC_6H_4COCCl{=}NOH$, 33108-89-3; 4-$NCC_6H_4COCCl{=}NOH$, 102941-53-7; $(C_2H_5)_2N(CH_2)_2SH$·HCl, 1942-52-5; $(CH_3)_2N(CH_2)_2SH$·HCl, 13242-44-9; $(CH_3)_2N(CH_2)_3SH$·HCl, 55778-17-1; 4-$ClC_6H_4COCH_3$, 99-91-2; 4-$FC_6H_4COCH_3$, 403-42-9; 4-(2-$C_{10}H_7$)$C_6H_4COCH_3$, 93-08-3; $(C_2H_5)_2N(CH_2)_2SH$, 100-38-9; $(CH_3)_2N(CH_2)_2SH$, 108-02-1; $((CH_3)_2CH)_2N(CH_2)_2SH$, 5842-07-9; 4-$ClC_6H_4COCH_2Br$, 536-38-9; 4-$FC_6H_4COCH_2Br$, 403-29-2; 4-(2-$C_{10}H_7$)$C_6H_4COCH_2Br$, 102941-54-8; 4-$(CH_3)_2N(CH_2)_2SCH_2COC_6H_4Cl$, 102941-56-0; 4-$(C_2H_5)_2N(CH_2)_2SCH_2COC_6H_4Cl$, 102941-57-1; $(CH_3)_2N(CH_2)_2SCH_2COC_{10}H_7$, 102941-58-2; 4-$(C_2H_5)_2N(CH_2)_2SCH_2COC_6H_4F$, 102941-59-3; 4-$((CH_3)_2CH)_2N(CH_2)_2SCH_2COC_6H_4Cl$, 102976-78-3; 4-$(CH_3)_2N(CH_2)_2SCH_2COC_6H_4F$, 102941-60-6; acetylcholine esterase, 9000-81-1.

Long-Acting Dihydropyridine Calcium Antagonists. 1. 2-Alkoxymethyl Derivatives Incorporating Basic Substituents

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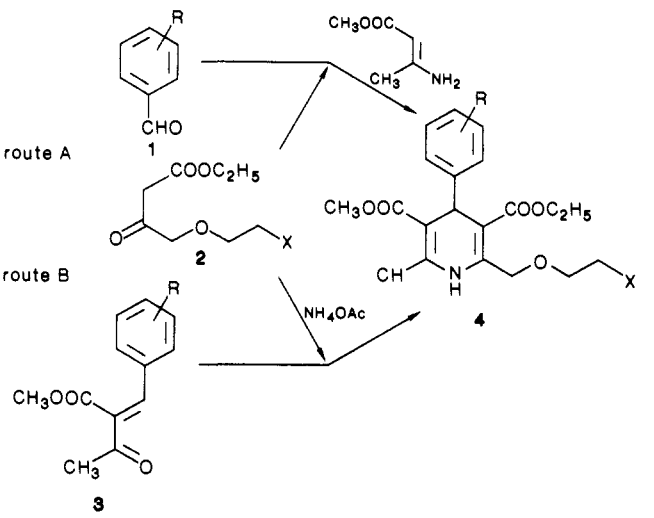
A series of dihydropyridines substituted at the 2-position by basic side chains are described and their potencies as calcium antagonists listed. One compound, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (17, amlodipine) was found to be comparable in potency to nifedipine and to have an elimination half-life of 30 h in dogs. Oral bioavailability approached 100%, and hemodynamic responses were gradual in onset and long-lasting in effect. The two enantiomers have been prepared, and the bulk of the activity was found to reside with the (-) isomer, 18. X-ray crystallographic studies, carried out on a close analogue of 17, suggest the existence of a weak hydrogen bond between the side-chain oxygen and the proton on the ring nitrogen.

Because of their vasodilator properties calcium channel blockers are important drugs in the treatment of angina[1] and hypertension.[2] Thus, in the heart, coronary dilatation increases the supply of oxygen and nutrients and coronary vasospasm may be prevented. Peripheral vasodilatation lowers the oxygen demand of the heart via a reduction in cardiac work and also accounts for the antihypertensive properties of these drugs.

Three structurally distinct compounds, nifedipine, diltiazem, and verapamil, have led the way toward defining the overall biological profile of this new class of drugs. Our research program on calcium blockers focused on the 1,4-dihydropyridines (DHPs) typified by nifedipine, since this chemical class offered both high potency and scope for wide structural variation. The aim of our work was to produce a drug comparable in overall pharmacological profile to nifedipine, but with superior bioavailability and, most importantly, with a duration of action allowing a once-a-day dosage regimen in man.

In commencing our program we noted that nearly all the DHP drugs then under investigation were essentially neutral molecules with low aqueous solubilities. The exception was nicardipine,[3,4] which differed from the other DHPs in possessing a basic side chain attached to the ester moiety at the 3-position of the DHP ring. However, despite improved aqueous solubility and good absorption, the systemic availability of nicardipine after oral administration was low due to a marked first-pass effect in the liver,[5] as appears to be common for the DHP series.

Scheme I



† Department of Chemistry.
‡ Department of Biology.

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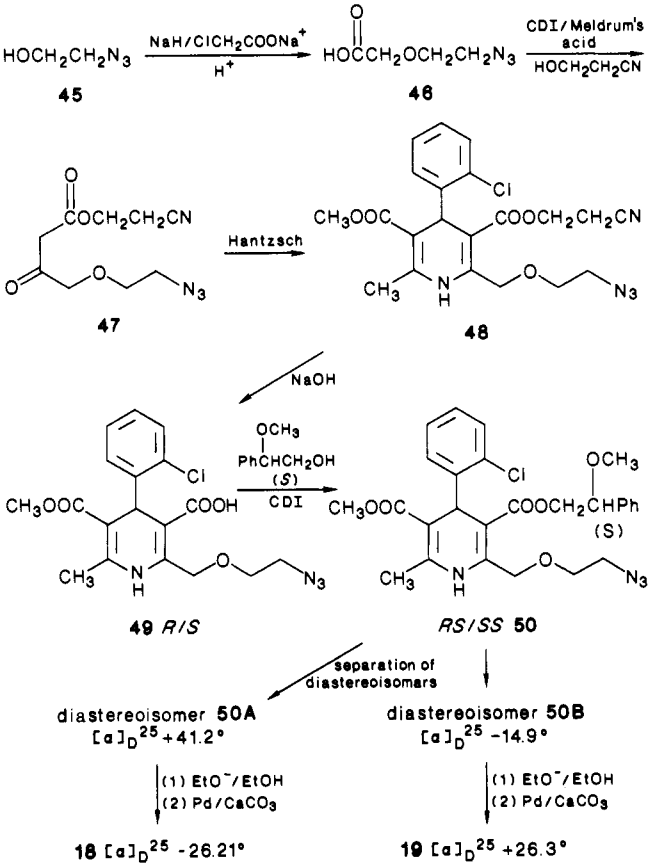
Nevertheless, we chose to focus initially on soluble, basic DHP derivatives, and upon reviewing the prior art it appeared to us that there was scope for synthetic manipulation of the 2-methyl substituent, even though published structure–activity relationships (SAR) on DHPs suggested that lower alkyl substituents were preferred.[6] Accordingly, we decided to introduce a basically substituted alkyl chain linked to the DHP 2-methyl group via an ether oxygen atom. Variation of the basic moiety and the alkyl chain could then be used to optimize the series through changes in pK_a and lipophilicity.

Chemistry. The compounds listed in Table I were synthesized via either of the two routes shown in Scheme I. The keto esters **2** were prepared by reacting the enolate of ethyl 4-chloroacetoacetate with an appropriately substituted sodium alkoxide.[7] Hantzsch condensation of **2** with the required benzaldehyde **1** and methyl 3-aminocrotonate then afforded the DHP (route A). Alternatively, reaction of **2** with ammonium acetate followed by Hantzsch condensation with the Knoevenagal product **3** gave **4** (route B). In the case of compounds **17**, **30**, **31**, **33**, and **35** synthesis was via the azide intermediate **2** (X = N_3) followed by route B to give the corresponding azido DHPs. Reduction of the azides using $Pd/CaCO_3/H_2$ then afforded the primary amino compounds. Compound **17** was also prepared by cleavage of the phthalimido intermediate **41** with methylamine, and this route was employed for **32** and **34**. Compounds **14** and **16** were prepared by reductive debenzylation of **11** and **15**, respectively. Similarly, debenzylation of the appropriate intermediates **4** (X = N-$(CH_3)CH_2Ph$) afforded **27–29**.

The preparation of 2,3-dichloro- and 2-chloro-3-(trifluoromethyl)benzaldehyde **51** was accomplished by reacting *n*-butyllithium with 1,2-dichlorobenzene or 2-chlorobenzotrifluoride at −70 °C and holding the reaction mixture at this temperature during the addition of dimethylformamide.

Synthesis of the enantiomers **18** (−) and **19** (+) of **17** was accomplished as shown in Scheme II starting from 2-azidoethanol **45**. Base cleavage of the dihydropyridine **48** afforded the carboxylic acid **49**, which was then esterified using optically pure *S*-(+)-2-phenylethanol[8] to give **50**. Chromatographic separation of the diastereoisomeric mixture was then carried out to give **50A** and **50B** from which **18** (−) and **19** (+) were prepared, respectively.

Scheme II



Discussion

In vitro calcium antagonist activity was assessed against calcium-induced constriction of potassium-depolarized rat aorta. Negative inotropy was also assessed in vitro, since a high level of cardiac depression was considered clinically undesirable.[9] As may be seen from Table I, compound **5** with a [(dimethylamino)ethoxy]methylene side chain attached to the 2-position of the DHP ring possessed calcium antagonist potency similar to that of nifedipine. Furthermore, **5** showed approximately 4-fold in vitro selectivity for vasculature rather than cardiac tissue. Replacement of the dimethylamino substituent by pyrrolidino **6** or morpholino **7** had little effect on calcium antagonist potency, but replacement by piperazinyl **14** was detrimental, particularly as negative inotropy was largely unaffected. However, alkylation of the 4-piperazinyl nitrogen to give **8** and **9** restored good calcium antagonist activity, but vascular selectivity with respect to negative inotropy remained inadequate. Similarly, increasing the length of the alkyl side chain in **5** and **8** by one methylene unit gave more potent compounds **20** and **21**, but again vascular selectivity was very poor. Simplification of the terminal basic moiety of **5** by removal of one or both methyl groups gave compounds **16** and **17**. In both cases high calcium antagonist potency and a 10-fold separation with respect to negative inotropy were observed.

Removal of the *o*-chloro substituent on the aryl ring of **17** to give **30**, or changing the position of substitution to *m*-**32** or *p*-**35**, reduced potency markedly. This was especially true in the case of **35** and is in accord with previous reports[6] on DHP structure–activity relationships. However, addition of a further electronegative substituent at the meta position of the chloroaryl ring of **17** was acceptable, **33** and **34**, particularly with regard to vascular selectivity. Replacement of the aryl ring of **5** by 2-thienyl **22**, 4-pyridyl **23**, or 1-naphthyl **24** was uniformly adverse.

Consideration of the compounds in Table I led to **5**, **16**, **17**, and **34** being selected for further pharmacological evaluation on the basis of their in vitro calcium antagonist potency and vascular selectivity. Accordingly, these compounds were administered intravenously to instrumented, anesthetized dogs, and the effects on coronary blood flow and cardiac output were used to assess both potency and duration of action. Coronary blood flow was measured by the hydrogen clearance method,[9] cardiac output by thermodilution, and the decreases in coronary and systemic vascular resistance derived from the quotient of arterial blood pressure and either coronary flow or cardiac output. The results, given in Table II, show that all four compounds produced similar, dose-related reductions in cor-

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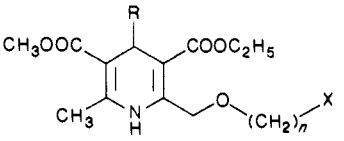
Table I. Data for Compounds Used in Study



no.	n	R	X	route	mp, °C	recrystn solvent[a]	formula[b]	% yield	Ca IC_{50}[c]	neg inotropy,[d] IC_{25}
5	2	2-ClC_6H_4	$N(CH_3)_2$	A	118–120	EtOAc	$C_{22}H_{29}ClN_2O_5 \cdot HCl$[a]	6	8.1	7.5
6	2	2-ClC_6H_4	c-NC_4H_8	A	81	DIPE	$C_{24}H_{31}ClN_2O_5$	5	7.9	7.7
7	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2O$	B	72–74	EtOAc/ petrol	$C_{24}H_{31}ClN_2O_6$	14	7.8	7.5
8	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH_3$	A	165	EtOAc/ CH_3OH	$C_{25}H_{34}ClN_3O_5 \cdot 2C_4H_4O_4$	21	8.0	7.9
9	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH(CH_3)_2$	A	172–173	EtOAc/ CH_3OH	$C_{27}H_{38}ClN_3O_5 \cdot 2C_4H_4O_4$	18	8.2	8.0
10	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NPh4F$	B	107	EtOAc/ CH_3OH	$C_{30}H_{35}ClFN_3O_5$[e]	3	7.9	7.3
11	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH_2Ph$-4Cl	B	216–217	EtOAc/ CH_3OH	$C_{31}H_{37}Cl_2N_3O_5 \cdot 2C_2H_2O_4$	19	8.0	7.4
12	2	2-ClC_6H_4	c-NC_5H_9-4-$N(CH_3)_2$	A	154–155	EtOAc	$C_{27}H_{38}ClN_3O_5 \cdot 2C_4H_4O_4$	13	6.4	7.1
13	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2N(CH_2)_2N(C_2H_5)_2$	A	167–169	CH_3OH/ acetone	$C_{30}H_{45}ClN_4O_5 \cdot 3C_4H_4O_4$	11	6.0	7.1
14	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NH$	B	70	acetone	$C_{24}H_{32}ClN_3O_5 \cdot 2C_2H_2O_4$[e]	15[f]	6.8	7.4
15	2	2-ClC_6H_4	$N(CH_3)CH_2Ph$	A	181	CH_3OH	$C_{28}H_{33}ClN_2O_5 \cdot C_2H_2O_4$	15	7.4	7.3
16	2	2-ClC_6H_4	$NHCH_3$	A	211	CH_3OH	$C_{21}H_{27}ClN_2O_5 \cdot C_2H_2O_4$	67[g]	8.5	7.5
17	2	2-ClC_6H_4	NH_2	B	178–179	EtOAc	$C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$	80[h]	8.1 + 0.3	7.2 + 0.09
18(−)	2	2-ClC_6H_4	NH_2	A	158	IPA/ DIPE	$C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$		8.7	NT
19(+)	2	2-ClC_6H_4	NH_2	A	165–167	IPA/ DIPE	$C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$		5.8	NT
20	3	2-ClC_6H_4	$N(CH_3)_2$	B	77–78	Et_2O/ petrol	$C_{23}H_{31}ClN_2O_5$	13	8.6	8.6
21	3	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH_3$	B	210–212	CH_3OH/ EtOAc	$C_{26}H_{36}ClN_3O_5 \cdot 2C_2H_2O_4$	6	8.4	8.2
22	2	2-thienyl	$N(CH_3)_2$	A	98	DIPE/ petrol	$C_{20}H_{28}N_2O_5S$	12	6.9	6.6
23	2	4-pyridyl	$N(CH_3)_2$	A	100–101	DIPE/ petrol	$C_{21}H_{29}N_3O_5$	16	6.1	6.0
24	2	1-naphthyl	$N(CH_3)_2$	A	108–109	EtOAc	$C_{26}H_{32}N_2O_5$	8	7.1	7.7
25	2	2-$CF_3C_6H_4$	$N(CH_3)_2$	A	177	acetone	$C_{23}H_{29}F_3N_2O_5 \cdot C_2H_2O_4$[e]	7	7.4	7.6
26	2	3-$NO_2C_6H_4$	$N(CH_3)_2$	A	174–175	acetone	$C_{22}H_{29}N_3O_7 \cdot HCl$	11	8.0	7.1
27	2	2-$CH_3C_6H_4$	$NHCH_3$	A	190–192	Et_2O/ petrol	$C_{22}H_{30}N_2O_5 \cdot C_2H_2O_4$[e]	18	7.2	7.2
28	2	2-$OCH_3C_6H_4$	$NHCH_3$	A	103–105	Et_2O/ petrol	$C_{22}H_{30}N_2O_6$[i]	22	7.2	7.1
29	2	2-Cl-6-F-C_6H_4	$NHCH_3$	A	165–166	Et_2O/ petrol	$C_{21}H_{26}ClFN_2O_5 \cdot HCl$[j]	20	7.9	7.6
30	2	Ph	NH_2	B	112–114	EtOAc	$C_{20}H_{26}N_2O_5 \cdot HCl$[k]	77[h]	6.8	6.2
31	2	2-F-C_6H_4	NH_2	B	152	Et_2O/ CH_3OH	$C_{20}H_{25}FN_2O_5 \cdot C_4H_4O_4$	52[h]	7.8	6.6
32	2	3-Cl-C_6H_4	NH_2	A	101–103	EtOAc	$C_{20}H_{25}ClN_2O_5$	11[l]	7.9	6.6
33	2	2,3-$Cl_2C_6H_3$	NH_2	B	171–173	hexane	$C_{20}H_{24}Cl_2N_2O_5 \cdot C_4H_4O_4$[k]	8[h]	7.9	6.6
34	2	2Cl,3-$CF_3C_6H_3$	NH_2	A	122	hexane	$C_{21}H_{24}ClF_3N_2O_5$	67[l]	8.5	7.3
35	2	4-ClC_6H_4	NH_2	B	146–148	EtOH	$C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$[k]	7	6.0	6.0
36	2	2-ClC_6H_4	N_3	B	145–146	CH_3OH	$C_{20}H_{23}ClN_4O_5$	11	NT	NT
37	2	Ph	N_3	B	124	CH_3OH	$C_{20}H_{24}N_4O_5$	12	NT	NT
38	2	2-FC_6H_4	N_3	B	129–130	CH_3OH	$C_{20}H_{23}FN_4O_5$	10	NT	NT
39	2	2,3-$Cl_2C_6H_3$	N_3	B	141	CH_3OH	$C_{20}H_{22}Cl_2N_4O_5$	17	NT	NT
40	2	4-ClC_6H_4	N_3	B	117–118	CH_3OH	$C_{20}H_{23}ClN_4O_5$	40	NT	NT
41	2	2-ClC_6H_4	phthalimido	A	146–147	CH_3OH	$C_{28}H_{27}ClN_2O_7$	25	NT	NT
42	2	3-ClC_6H_4	phthalimido	A	146–148	CH_3OH	$C_{28}H_{27}ClN_2O_7$	18	NT	NT
43	2	2Cl,3-$CF_3C_6H_3$	phthalimido	A	178	CH_3OH	$C_{29}H_{26}ClF_3N_2O_7$	35	NT	NT
44	2	2-ClC_6H_4	$NHSO_2$-c-C_4H_8O	B	155–157	IPA	$C_{24}H_{32}ClN_3O_8S$	75	NT	NT
nifedipine									8.4	7.5

[a] DIPE, diisopropylether; petrol, 60–80 °C petroleum ether. [b] All compounds were analyzed for C, H, and N to within ±0.4% of the theoretical value. [c] Negative logarithm of the molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized rat aorta by 50%. Nifedipine was used as the standard compound, standard deviation ±0.01. [d] Negative logarithm of the molar concentration required to depress contraction in the isolated Langendorff-perfused guinea pig heart by 25%. Nifedipine was used as the standard compound, standard deviation ±0.26. [e] Monohydrate. [f] Yield based upon debenzylation of compound 11. [g] Yield based upon debenzylation of compound 15. [h] Yield based upon reduction of the azido intermediate. [i] C: calcd, 63.15; found, 63.65. [j] C: calcd, 52.8; found, 53.25. [k] Hemihydrate. [l] Yield based upon cleavage of the phthalimido intermediate.

onary vascular resistance. Adverse effects on cardiac electrical or mechanical function were minimal.[10] Hemodynamic responses were gradual in onset but once established were maintained throughout the period of the

Table II. Percent Decrease in Coronary Vascular Resistance in Dogs

compd	intravenous dose, μg/kg		
	150	450	1500
5, $n = 3$	64.8	68.9	74.7
16, $n = 3$	46.2	73.8	78.6
17, $n = 3$	35.4	69.5	76.9
34, $n = 2$	52.6	75.7	81.7

experiments (up to 7 h). Compound 17 (amlodipine) was further evaluated in conscious, renal-hypertensive dogs where single oral doses of 0.5, 1.0, and 2.0 mg/kg produced slowly developing falls in blood pressure (maximum 15 ± 3, 21 ± 5, and 38 ± 4 mmHg, respectively) accompanied by dose-related tachycardias.[11] At the highest dose, maximum effect was achieved after approximately 7 h, whereas the response to nifedipine had already returned to control by this time.

Pharmacokinetic studies on amlodipine[12] were carried out in dogs, and it was found that oral bioavailability approached 100%, thus satisfying one of the major objectives of the program. In addition, the elimination half-life was approximately 30 h due to moderate plasma clearance (11 mL/min per kg) and a high volume of distribution (25 L/kg). To our knowledge, a plasma half-life of such magnitude is unprecedented in a DHP derivative. For example, felodipine[13] and nicardipine,[5] which are structurally related to amlodipine and are also undergoing clinical evaluation, are more typical of the series (Table III). Data from these pharmacokinetic studies also demonstrated that during chronic once-daily administration plasma levels of amlodipine achieved a steady state after the fourth consecutive dose, at which time concentrations were twice those seen after a single dose. Thus, optimal hemodynamic response to amlodipine can be achieved after low-dose subacute administration so that precipitous falls in blood pressure are avoided and side effects minimized and the once-daily dosage regime should improve patient compliance. Amlodipine is currently undergoing phase III clinical trials for hypertension and angina.

In vitro evaluation of the enantiomers of amlodipine shows the (−) isomer 18 to be twice as active as the enantiomeric mixture in the rat aorta. The (+) isomer 19 was in turn some 1000 times less active (Table I). The absolute configuration of 18 was found to be *R*.[14]

In X-ray crystallographic analysis has been carried out on compound 44, a suitably crystalline but nonbasic derivative of amlodipine. As may be seen from Figure 1, the oxygen atom in the side chain and the hydrogen atom on the DHP nitrogen are essentially coplanar. The interatomic distance is 2.03 Å, and this indicates the existence of an intramolecular hydrogen bond. The relationship of physiocochemical parameters to the unique pharmacological profile of amlodipine is currently under investigation.

Experimental Section

Pharmacology. (a) **Calcium Antagonism.** The ability of the compounds to block voltage-sensitive calcium channels and thus inhibit transmembrane calcium flux is determined by their effectiveness in reducing the response of isolated vascular tissue to an increase in calcium ion concentration in vitro under depolarized conditions. The test is performed by mounting spirally cut strips of rat aorta with one end fixed and the other attached to a force transducer. The tissue is immersed in a bath of modified Krebs–Henseleit solution containing 45 mM K^+ and zero calcium. Calcium chloride is added to the bath to give a final calcium ion concentration of 2 mM. The change in tension caused by the resulting contraction of the tissue is noted. The bath is drained and fresh saline solution added, and, after 45 min, the procedure is repeated with the particular compound under test present in the saline solution. The concentration of compound required to reduce the response by 50% is recorded.

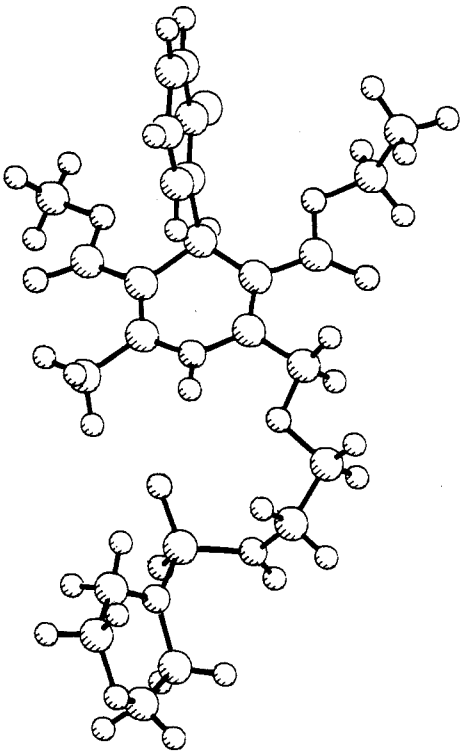


Figure 1. X-ray crystallographic structure of 2-{2-[(1-morpholinosulfonyl)aminoethoxy]methyl}-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (44).

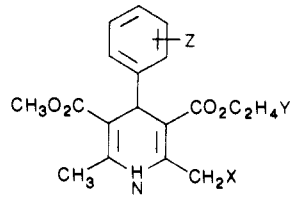
(b) Negative Inotropy. Isolated hearts, from male guinea pigs, were perfused by the Langendorff technique, with Krebs–Henseleit solution at 37 °C. A force transducer was attached to the apex of the heart in order to measure the force and rate of contraction. Increasing concentrations of test compound were added to the perfusate at 10-min intervals, and the effect of these additions on the force and rate of contraction was assessed.

Chemistry. All melting points are uncorrected. The structures of all compounds were confirmed by IR and ^1H NMR spectra. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer, and the ^1H NMR spectra were obtained with a Varian XL-100-15 using $CDCl_3$ as solvent unless otherwise indicated. HPLC work was carried out by using a Waters Prep. 500 machine.

Ethyl 4-[2-(Dimethylamino)ethoxy]acetoacetate (2, X = NMe_2). (Dimethylamino)ethanol (12.5 g, 0.14 mol) was dissolved in dry THF (50 mL) and added dropwise to a stirred suspension of NaH (6.5 g, 0.14 mol, 50% dispersion in oil) in dry THF (50 mL). After addition was complete, the mixture was stirred for 1 h and then cooled in an ice bath. Ethyl 4-chloroacetoacetate (18 g, 0.14 mol) in dry THF (50 mL) was added dropwise over a period of 1 h and the reaction mixture stirred at room temperature overnight and then poured into a mixture of ice water (100 mL) and concentrated HCl (20 mL). Salt was added to saturate the aqueous layer (pH 8), and the mixture was extracted with EtOAc (4 × 200 mL). Extracts were dried ($MgSO_4$), filtered, and evaporated to an oil. This was dissolved in acetonitrile (100 mL) and then washed with 60–80 °C light petrol (50 mL) to remove mineral oil. Evaporation of the acetonitrile gave 2 (X =

(10) Burges, R. A.; Carter, A. J.; Gardiner, D. G.; Higgins, A. J. *Br. J. Pharmacol.* **1985**, *85*, 281P.
(11) Dodd, M. G.; Machin, i.; Baird, J. R. C. *Br. J. Pharmacol.* **1985**, *85*, 335P.
(12) Beresford, A. P.; Humphrey, M. J.; Stopher, D. A. *Br. J. Pharmacol.* **1985**, *85*, 333P.
(13) Humphrey, M. J.; Stopher, D. A., unpublished work.
(14) The absolute configuration was obtained from an analogue of 44 having *S*-(+)-2-methoxy-2-phenylethyl as the C-3-ester.

Table III. Pharmacokinetic Data for Amlodipine,[a] Felodipine,[b] and Nicardipine[c] in Dogs after Intravenous Administration



compd	Z	Y	X	plasma clearance, mL/min per kg	vol of distribution, L/kg	plasma half-life, h
amlodipine	2-Cl	H	$OCH_2CH_2NH_2$	11	25	30
felodipine	2,3-Cl_2	H	H	38	3.6	1.0
nicardipine	3-NO_2	$CH_3(NCH_2C_6H_5)$	H	37	3.5	1.0

[a] Reference 12. [b] Reference 13. [c] Reference 5.

NMe_2) as an oil: yield 16.2 g (47%) characterized by its NMR spectrum δ 1.26 (3 H, t), 2.26 (6 H, s), 2.52 (2 H, t), 3.59 (2 H, t), 3.6 (2 H, br), 4.11 (2 H, s), 4.16 ppm (2 H, q).

The keto esters **2** used in the preparation of compounds **6–13** and **15** were prepared similarly to the above starting from the appropriate aminoethanol, or aminopropanol in the case of compounds **20** and **21**. 2-Azidoethanol and 2-phthaliimidoethanol were used as starting materials for the preparation of **36–40** and **41–43**. All these ketoesters were characterized by their NMR spectra and were stored at 0 °C in order to minimize polymerization.

The dihydropyridines (**4**) were prepared from the keto esters (**2**) by the method of Hantzsch. In a typical procedure, the aldehyde (**1**) and the ketoester (**4**) were heated under reflux in a suitable organic solvent (e.g., ethanol) for about 15 min, and then the aminocrotonate was added (route A). After a small amount of acetic acid was added to neutralize the solution, heating was continued under reflux for 16–20 h and the dihydropyridine **4** isolated and purified by conventional techniques.

Alternatively, the keto ester (**2**) was heated in ethanol with ammonium acetate (route B) and the resultant crotonate then reacted with the Knoevenagel product **3** by heating at reflux temperature for 2–5 h.

2-[[2-(Dimethylamino)ethoxy]methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (5, Route A). Ethyl 4-[(dimethylamino)ethoxy]acetoacetate (**2**, X = NMe_2; 18 g, 0.15 mol) and 2-chlorobenzaldehyde (11.5 g, 0.09 mol) were dissolved in EtOH (40 mL) and heated at reflux for 15 min. Methyl 3-aminocrotonate (10 g, 0.087 mol) and acetic acid (5 mL) were then added, and heating was continued overnight (16 h). The cooled reaction mixture was then evaporated to dryness and the residue partitioned between toluene (200 mL) and saturated aqueous Na_2CO_3 (40 mL) to remove acetic acid. The toluene solution was then extracted with 2 N HCl and MeOH (10:1, 200 mL and 20 mL) annd the aqueous extract basified with ammonia and extracted with $CHCl_3$ (2 × 30 mL). The chloroform extracts were dried (Na_2CO_3), filtered, and evaporated to dryness. The residue was then chromatographed on silica gel using methylene chloride as the eluent, and the appropriate fractions were combined and evaporated to give a solid, which was dissolved in EtOAc and added to ethereal HCl. The resultant precipitate was filtered off and recrystallized from EtOAc to give **5** as the hydrochloride salt: yield 2.5 g (6%); mp 118–120 °C. Anal. ($C_{22}H_{29}ClN_2O_5$·HCl) C, H, N.

2-[[3-(Dimethylamino)propoxy]methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (20, Route B). Ethyl 4-[3-(dimethylamino)propoxy]acetoacetate (**2**, X = CH_2NMe_2; 23 g, 0.1 mol) was converted to the corresponding 3-aminocrotonate ester by heating in ethanol (50 mL) with ammonium acetate (8 g) for 20 min under reflux. Methyl 2-(2-chlorobenzylidine)acetoacetate (**3**, R = 2-chloro; 26 g, 0.11 mol) was added and the mixture heated under reflux for 2.5 h. The reaction mixture was then evaporated to dryness and partitioned between toluene (200 mL) and saturated aqueous sodium carbonate (100 mL) to remove acetic acid. The toluene layer was then extracted with 2 N HCl (3 × 100 mL), and the combined aqueous acid extracts were neutralized to pH 6.0 with solid sodium carbonate, saturated with sodium chloride, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried (Na_2CO_3), filtered, and evaporated to dryness. The residue was dissolved in a little toluene and chromatographed on a silica gel column using methylene chloride as the eluent. Appropriate functions were combined and evaporated to dryness, and the residue was crystallized from ether/60–80 °C light petroleum (1:1) to give the title compound: yield 6.3 g (13%); mp 77–78 °C. Anal. ($C_{23}H_{31}ClN_2O_5$) C, H, N.

2-Chloro-3-(trifluoromethyl)benzaldehyde. 2-Chloro-1-(trifluoromethyl)benzene (54.15 g, 0.3 mol) was dissolved in dry THF (500 mL) and cooled to −68 °C, with stirring, under a nitrogen atmosphere. To this was added dropwise *n*-butyl lithium (180 mL of a 1.6 M solution in hexane) keeping the temperature below −60 °C. After stirring at this temperature for 2 h DMF (22 mL, 0.3 mol) in dry THF (100 mL) was added dropwise, still keeping the reaction mixture temperature below −60 °C. The reaction was then slowly allowed to warm to room temperature, and after stirring for 17 h distilled H_2O (200 mL) was added. The organic phase was separated off, and the aqueous liquors were extracted with ether (2 × 150 mL). The combined ether extracts, plus the organic phase, were washed with saturated brine, dried ($MgSO_4$), filtered, and evaporated to give an orange oil.

The crude oil was then added to aqueous sodium bisulfite solution (65 g in 600 mL of H_2O) and heated at 60 °C for 0.5 h. The solution was extracted with methylene chloride (3 × 100 mL), and the aqueous phase was acidified with concentrated H_2SO_4 to pH 1.0 and heated at 100 °C for an additional 0.5 h.

The resultant aqueous solution was extracted with methylene chloride (3 × 200 mL) and the combined organic extracts dried ($MgSO_4$), filtered, and evaporated to give the title compound as a colorless solid, which was recrystallized from hexane: yield 42 g (68%); mp 43–44 °C. Anal. ($C_8H_4ClF_3O$) C, H.

2-[[2-(Methylamino)ethoxy]methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (16). A solution of 2-[[2-(*N*-benzyl,*N*-methylamino)ethoxy]methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine oxalate (**15**; 4.3 g, 7 mmol) in methanol (220 mL) was added to a prehydrogenated suspension of 10% (by weight) palladium on charcoal (0.4 g) in methanol (50 mL). Stirring under hydrogen at 50 psi at room temperature for 18 h resulted in complete removal of the benzyl group. After removal of the catalyst by filtration, the solution was evaporated to dryness to give a solid, which was recrystallized from methanol to give the oxalate salt of the title compound **16**: yield 2.4 g (67%); mp 211 °C. Anal. ($C_{21}H_{27}ClN_2O_5$·$C_2H_2O_4$) C, H, N.

Compounds **27–29** were prepared in similar manner from the appropriate dihydropyridines **4** (X = $N(CH_3)CH_2Ph$). These intermediates were not isolated and were used directly in the debenzylation procedure.

Compound **14** was prepared from **11** by the same reductive debenzylation.

2-[(2-Azidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (36). A solution of 2-azidoethanol (160 g, 1.84 mol) in TMF (300 mL) was added over 40 min to a suspension of sodium hydride (114 g, 80% dispersion in oil) in THF (500 mL). The mixture

was stirred at room temperature for 1 h and then cooled in ice water. Ethyl 4-chloroacetoacetate (276 g, 1.68 mol) in THF (250 mL) was then added dropwise over a period of 2 h. The mixture was stirred at room temperature for an additional 16 h and diluted with EtOH (150 mL), and the pH was adjusted to 6–7 with HCl. Sufficient water was added to dissolve the solids, and the layers were then separated. The organic layer was evaporated to dryness, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was further extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$), filtered, evaporated to give ethyl 4-(2-azidoethoxy)acetoacetate, which was shown by GLC to be 73% pure. A mixture of this crude product and ammonium acetate (92.3 g) in EtOH (600 mL) was heated under reflux for 1 h, allowed to cool to room temperature, and then treated with 2-(2-chlorobenzylidene)acetoacetate (286.6 g, 1.2 mol). The mixture was heated under reflux for 5 h and then evaporated to dryness. The residue was stirred with MeOH (1.5 L) for 16 h, and the resulting solid was collected and crystallized from MeOH to give the title compound: 78 g (11%); mp 145–146 °C. Anal. ($C_{20}H_{23}ClN_4O_5$) C, H, N.

In a similar manner, the azides **37–40** were prepared from 2-azidoethanol and the appropriate benzaldehydes.

2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (17). A suspension of 2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (**36**; 103 g, 0.24 mol) in EtOH (2.5 L) was stirred for 1 h at room temperature under an atmosphere of hydrogen in the presence of 5% palladium on calcium carbonate (40 g). The reaction mixture was filtered and evaporated, and the residue was treated with a solution of maleic acid (22 g) in EtOH (100 mL). The mixture was then stirred at room temperature for 2 h and the resultant solid collected, washed with EtOH, and recrystallized from EtOAc to give **17**: yield 100 g (80%); mp 178–179 °C. Anal. ($C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$) C, H, N.

Compounds 30, 31, 33, and **35** were also prepared by the above method starting from the appropriate azido intermediates.

2-[(2-Phthalimidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (41). Ethyl 4-[2-(phthalimido)ethoxy]acetoacetate (200 g, 0.62 mol) was dissolved in 2-propanol (1000 mL), and to this was added 2-chlorobenzaldehyde (88.1 g, 0.62 mol) and methyl 3-aminocrotonate (72.2 g, 0.62 mol). The mixture was heated under reflux for 21 h, cooled, and evaporated to dryness. The residual oil was dissolved in acetic acid (1000 mL) and stirred overnight. The resultant precipitate was collected, washed with a little acetic acid, and then slurried in methanol (300 mL). Filtration gave a white solid, which was recrystallized from methanol to give **41**: yield 83.25 g (25%); mp 146–147 °C. Anal. ($C_{28}H_{27}ClN_2O_7$) C, H, N.

2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (20). 2-[(2-Phthalimidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (**41**; 80 g, 0.15 mol) was stirred in 33% ethanolic methylamine solution (1067 mL) at room temperature for 3 h. The solvent was then evaporated and the residue slurried in EtOH (300 mL) and then filtered. To the filtrate was added maleic acid (17.4 g), and the mixture was stirred for 3 h and the resultant precipitate filtered, washed with EtOH, and recrystallized from EtOAc to give **20**: yield 38.4 g (60%, mp 178–179 °C. Anal. ($C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$) C, H. Compounds **32** and **34** were also prepared by the above method starting from the appropriate phthalimido intermediates.

(2-Azidoethoxy)acetic Acid (46). A suspension of sodium 2-azidoethoxide (76 g, 0.7 mol) in dry THF (400 mL) was added portionwise to a stirred suspension of sodium chloroacetate (48.5 g, 0.42 mol) and tetrabutylammonium iodide (10 g) in dry THF (400 mL) and heated under reflux for 24 h. After cooling, water (50 mL) was added to the reaction, the THF evaporated, and the residue taken up in water (300 mL) and washed with methylene chloride (3 × 200 mL). The aqueous layer was acidified (pH 1) with hydrochloric acid, saturated with sodium chloride, and extracted with methylene chloride (4 × 200 mL). Organic extracts were combined, dried ($MgSO_4$), and evaporated to give the title compound as a pale-brown liquid (15.5 g). Continuous extraction of the latter aqueous solution with methylene chloride gave a further 14.7 g of product. The total yield of clean product (adjudged by NMR) was 29.2 g (47%), and this was used without further purification.

2-Cyanoethyl 4-(2-Azidoethoxy)-3-oxobutanoate (47). Carbonyldiimidazole (13.75 g, 0.084 mol) and (2-azidoethoxy)acetic acid (11.0 g, 0.08 mol) in dry methylene chloride (150 mL) under N_2 atmosphere were stirred at room temperature for 1 h before adding a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (11.0 g, 0.084 mol) and pyridine (6.1 g) in methylene chloride (50 mL). The mixture was then stirred at room temperature overnight and washed with 2 M hydrochloric acid (2 × 50 mL), and the organic layer was dried ($mgSO_4$) and evaporated to afford a red oil. This oil was dissolved in 3-hydroxyproprionitrile (25 mL) and heated at 70 °C for 3 h. The reaction mixture was cooled and diluted with methylene chloride (75 mL), washed with water (3 × 50 mL), dried over ($MgSO_4$), and evaporated to give a red oil, which was purified by column chromatograph on silica (10% methylene chloride in toluene) to give **47**, 7.5 g (48%), as a pale yellow oil, which was used without further purification.

2-[(2-Azidoethoxy)methyl]-4-(2-chlorophenyl)-3-(2-cyanoethoxycarbonyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (48). A solution of 2-cyanoethyl 4-(2-azidoethoxy)-3-oxobutanoate (7.5 g, 0.04 mol), 2-chlorobenzaldehyde (4.2 g, 0.03 mol), and methyl 3-aminocrotonate (3.45 g 0.03 mol) in ethanol (100 mL) was heated under reflux for 2 h before cooling, and the precipitate was collected by filtration, washed, and dried to give **48**: yield 5.7 g (41%); mp 133–134 °C. Anal. ($C_{21}H_{22}ClN_5O_5$) C, H, N.

2-[(2-Azidoethoxy)methyl]-4-(2-chlorophenyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine-3-carboxylic Acid (49). A suspension of 2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-3-(2-cyanoethoxycarbonyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (5.48 g, 12 mmol) in diglyme (50 mL) and 1 M sodium hydroxide (38 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with water, acidified (pH 1) with dilute hydrochloric acid, and extracted with methylene chloride. The organic extracts were washed, dried ($MgSO_4$), and evaporated to give a yellow solid, which was recrystallized from ethanol to give **49**: yield 3.6 g (74%); mp 156–157 °C dec. Anal. ($C_{18}H_{19}ClN_4O_5$) C, H, N.

2-[(2-Azidoethoxy)methyl]-4-(2-chlorophenyl)-5-methoxycarbonyl-3-[2(*S*)-methoxy-2-phenethoxycarbonyl]-6-methyl-1,4-dihydropyridine (50). A solution of 2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine-3-carboxylic acid (2.13 g, 5 mmol) and carbonyldiimidazole (0.85 g, 5 mmol) in methylene chloride was stirred at room temperature for 15 min and then heated briefly under reflux. The mixture was then evaporated to dryness and the residue taken up in dry THF (50 mL). To this was then added a solution of sodium *S*-(+)-2-methoxy-2-phenylethoxide (prepared by adding an equivalent of sodium hydride to *S*-(+)-2-methoxy-2-phenylethanol[7] (0.8 g, 5 mmol) in dry THF (25 mL)), and the resultant mixture was stirred at room temperature for 1 h. After evaporation to dryness under reduced pressure the residue was taken up in ethyl acetate, washed (2 M hydrochloric acid then brine), dried ($MgSO_4$), filtered, and evaporated. The product was further purified by column chromatography on silica gel (10% methanol in methylene chloride solution) to give 50% as a diastereomeric mixture: yield 2.27 g (80%). Anal. ($C_{27}H_{29}ClN_4O_6$) C, H, N.

Separation of these two diastereomers was achieved by column chromatography on silica gel (methylene chloride as eluent) to give a more polar isomer **50A** (0.4 g) as colorless crystals from DIPE (mp 104–106 °C, $[\alpha]^{25}_D = +41.2°$) and a less polar isomer **50B** (400 mg) similarly crystallized from DIPE (mp 139–140 °C, $[\alpha]^{25}_D$ −14.9°). Isomers **50A** and **50B** were easily distinguished by ^1H NMR ($CDCl_3$), since the resonances of the methoxy group of the chiral C-3 esters occurred at 3.3 and 3.1 ppm, respectively.

(−)-2-[(Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine Maleate (18). A solution of 2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-5-methoxycarbonyl-3-[(2*S*)-methoxy-2-phenethoxycarbonyl]-6-methyl-1,4-dihydropyridine ($[\alpha]^{25}_D$ + 41.2°, 0.370 g, 0.68 mmol) was heated under reflux for 1 h in a solution of ethanol (5 mL) and diglyme (5 mL) containing sodium ethoxide (31 mg).

The cooled reaction mixture was then diluted with water and extracted with methylene chloride. The organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography on silica gel (2% methanol in methylene chloride solution) to give **2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine** (243 mg). This product contained 8% of the corresponding 3,5-bis(ethoxycarbonyl) compound, which was removed by HPLC (using Prep-Pak C-18 column reverse phase with 40:60 water/CH_3CN). The now pure product (136 mg) was hydrogenated in ethanol solution at 15 psi over a 5% $Pd/CaCO_3$ catalyst. Filtration of the hydrogenation solution and evaporation gave a residue, which was purified by column chromatography on silica gel (20% methanol in methylene chloride) to give the title compound 18 (47 mg) as a maleate salt from IPA/DIPE: mp 158 °C; $[\alpha]^{25}_D$ - 26.21° (*c* 1.16, methanol). Anal. ($C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$) C, H, N.

(+)-2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine Maleate (19). By use of a procedure identical to that described for the preparation of **18**, 2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-5-methoxycarbonyl-3-[2(*S*)-methoxy-2-phenethoxycarbonyl]-6-methyl-1,4-dihydropyridine ($[\alpha]^{25}_D$ −14.9°) was converted to the title compound: mp 165–167 °C; $[\alpha]^{25}_D$ +26.3° (*c* 1.06, methanol). Anal. ($C_{20}H_{25}ClN_2O_4$) C, H, N.

2-{[2-[(Morpholinosulfonyl)amino]ethoxy]methyl}-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (44). Morpholinosulfonyl chloride (0.44 g, 2.5 mmol) was added to a solution of 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (1 g, 2.45 mmol) and triethylamine (0.25 g) in methylene chloride (30 mL), and the mixture was stirred at room temperature overnight. The mixture was then poured into ice–water and the layers separated. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and evaporated. The residual oil was chromatographed on silica gel using methylene chloride as eluent, and the appropriate fractions were combined and evaporated to give an oil that crystallized on trituration with 2-propanol. Recrystallization from 2-propanol afforded **44**: yield 1.06 g (75%); mp 155–157 °C. Anal. ($C_{24}H_{32}ClN_3O_8S$) C, H, N.

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Registry No. **1** (R = 2-Cl), 89-98-5; **1** (R = 2-thienyl), 98-03-3; **1** (R = 4-pyridyl), 872-85-5; **1** (R = 1-naphthyl), 66-77-3; **1** (R = 2-CF_3), 872-85-5; **1** (R = 3-NO_2), 99-61-6; **1** (R = 2-CH_3), 529-20-4; **1** (R = 2-OCH_3), 135-02-4; **1** (R = 2-Cl, 6-F), 387-45-1; **1** (R = 3-Cl), 587-04-2; **1** (R = 2-Cl, 3-CF_3), 93118-03-7; **2** (X = $N(CH_3)_2$), 103069-55-2; **2** (X = c-NC_4H_8), 103069-56-3; **2** (X = c-$N(CH_2CH_2)_2O$), 103069-57-4; **2** (X = c-$N(CH_2CH_2)_2NCH_3$), 103069-58-5; **2** (X = c-$N(CH_2CH_2)_2NCH(CH_3)_2$), 103069-59-6; **2** (X = c-$N(CH_2CH_2)_2NPh_4F$), 103069-60-9; **2** (X = c-$N(CH_2CH_2)_2NCH_2Ph4Cl$), 103069-61-0; **2** (X = c-$NC_5H_94N(CH_3)_2$), 103069-62-1; **2** (X = c-$N(CH_2CH_2)_2N(CH_2)_2N(C_2H_5)_2$), 103069-63-2; **2** (X = $N(CH_3)CH_2Ph$, 88150-69-0; **2** (X = N_3), 88150-45-2; **2** (X = phthalimido), 88150-75-8; **3** (R = 2-Cl), 67593-46-8; **3** (R = H), 15768-07-7; **3** (R = 2-F), 39561-90-5; **3** (R = 2,3-Cl_2), 74073-22-6; **3** (R = 4-Cl), 103069-52-9; (±)-**4** (X = $N(CH_3)CH_2Ph$, R = 2-CH_3), 103069-53-0; (±)-**4** (X = $N(CH_3)CH_2Ph$, R = 2-OCH_3), 103069-54-1; (±)-**4** (X = $N(CH_3)CH_2Ph$, R = 2-Cl, 6-F), 103094-35-5; (±)-**5**, 103069-66-5; (±)-**5**·HCl, 103069-00-7; (±)-**6**, 103069-01-8; (±)-**7**, 103069-02-9; (±)-**8**, 103069-03-0; (±)-**8**·$2C_4H_4O_4$, 103069-04-1; (±)-**9**, 103069-67-6; (±)-**9**·$2C_4H_4O_4$, 103094-28-6; (±)-**10**, 103069-05-2; (±)-**11**, 103069-06-3; (±)-**11**·$2C_2H_2O_4$, 103069-07-4; (±)-**12**, 103069-08-5; (±)-**12**·$2C_4H_4O_4$, 103069-09-6; (±)-**13**, 103069-10-9; (±)-**13**·$3C_4H_4O_4$, 103069-11-0; (±)-**14**, 103069-12-1; (±)-**14**·$2C_2H_2O_4$, 103069-13-2; (±)-**15**, 103069-14-3; (±)-**15**·$C_2H_2O_4$, 103069-15-4; (±)-**16**, 103069-16-5; (±)-**16**·$C_2H_2O_4$, 103069-17-6; (±)-**17**, 103069-18-7; (±)-**17**·$C_4H_4O_4$, 103069-19-8; (−)-(*R*)-**18**, 103129-81-3; (−)-(*R*)-**18**·$C_4H_4O_4$, 103188-90-5; (+)-(*S*)-**19**, 103129-82-4; (+)-(*S*)-**19**·$C_4H_4O_4$, 103188-91-6; (±)-**20**, 103069-20-1; (±)-**21**, 103069-21-2; (±)-**21**·$2C_2H_2O_4$, 103069-22-3; (±)-**22**, 103069-23-4; (±)-**23**, 103069-24-5; (±)-**24**, 103069-25-6; (±)-**25**, 103069-26-7; (±)-**25**·$C_2H_2O_4$, 103069-27-8; (±)-**26**, 103069-68-7; (±)-**26**·HCl, 103069-28-9; (±)-**27**, 103069-29-0; (±)-**27**·$C_2H_4O_4$, 103069-30-3; (±)-**28**, 103069-31-4; (±)-**29**, 103069-69-8; (±)-**29**·HCl, 103069-32-5; (±)-**30**, 103069-70-1; (±)-**30**·HCl, 103069-33-6; (±)-**31**, 103069-71-2; (±)-**31**·$C_4H_4O_4$, 103069-35-8; (±)-**32**, 103069-36-9; (±)-**33**, 103069-37-0; (±)-**33**·$C_4H_4O_4$, 103069-38-1; (±)-**34**, 103069-39-2; (±)-**35**, 103069-40-5; (±)-**35**·$C_4H_4O_4$, 103069-41-6; (±)-**36**, 103069-42-7; (±)-**37**, 103069-43-8; (±)-**38**, 103094-29-7; (±)-**39**, 103069-44-9; (±)-**40**, 103069-45-0; (±)-**41**, 103094-30-0; (±)-**42**, 103094-31-1; (±)-**43**, 103094-32-2; (±)-**44**, 103069-46-1; (±)-**45**, 1517-05-1; (±)-**45**·Na, 103069-64-3; (±)-**46**, 79598-48-4; (±)-**47**, 103069-47-2; (±)-**48**, 103069-48-3; (±)-**49**, 103069-49-4; (+)-**50A**, 103094-33-3; (−)-**50B**, 103094-34-4; $(CH_3)_2N(CH_2)_2OH$, 108-01-0; c-$HO(CH_2)_2NC_4H_8$, 2955-88-6; c-$HO(CH_2)_2N(CH_2CH_2)_2O$, 622-40-2; c-$HO(CH_2)_2N(CH_2CH_2)_2NCH_3$, 5464-12-0; c-$HO(CH_2)_2N(CH_2CH_2)_2NCH(CH_3)_2$, 103069-50-7; c-$HO(CH_2)_2N(CH_2)_2NPh4F$, 90096-38-1; c-$HO(CH_2)_2N(CH_2CH_2)NCH_2Ph4Cl$, 55179-20-9; c-$HO(CH_2)_2NC_5H_94N(CH_3)_2$, 103069-51-8; c-$HO(CH_2)_2N(CH_2CH_2)_2N(CH_2)_2NEt_2$, 41465-67-2; $HO(CH_2)_2N(CH_3)CH_2Ph$, 103-76-4; $EtO_2CCH_2COCH_2Cl$, 638-07-3; $H_3CC(NH_2)=CHCO_2CH_3$, 14205-39-1; 2-$F_3CC_6H_4Cl$, 88-16-4; $ClCH_2COONa$, 3926-62-3; $HOCH_2CH_2CN$, 109-78-4; (+)-(*S*)-$PhCH(OCH_3)CH_2OH$, 66051-01-2; c-$O(CH_2CH_2)NSO_2Cl$, 1828-66-6; c-$N_3(CH_2)_2OCH_2COCH_2COCH_2(CO_2)_2C(CH_3)_2$, 103069-65-4; 2-phthalimidoethanol, 3891-07-4; (±)-2-[(2-azidoethoxy)methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl-5-(methoxycarbonyl)-1,4-dihydropyridine, 103094-36-6; calcium, 7440-70-2.

Supplementary Material Available: Table listing X-ray diffraction study data of 2-{[2-[(morpholinosulfonyl)amino]ethoxy]methyl}-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (2 pages). Ordering information is given on any current masthead page.