New 1,4-Dihydropyridine Derivatives Combining Calcium Antagonism and α-Adrenolytic Properties

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A series of twelve 1,4-dihydropyridine derivatives incorporating an α-adrenergic moiety in one of the ester chains was synthesized. The compounds were evaluated for their calcium antagonist activities by the inhibition of [^{3}H]nitrendipine binding and, in vitro, on pig coronary artery. Their α_1- and α_2-adrenolytic effects were assessed from their inhibition of [^{3}H]prazosin and [^{3}H]yohimbine binding and, in vitro, on rat aorta and guinea pig vas deferens. Compounds **6** and **9**–**11** displayed strong calcium antagonist activities, identical with that of nicardipine. The moderate α-adrenolytic properties observed were attributed to the presence of α-adrenergic moieties. The four chiral derivatives **6a** (*R,R*), **6b** (*S,S*), **6c** (*S,R*), and **6d** (*R,S*) with an *N*-methyl-*N*-(benzodioxanylmethyl)amino group on the ester chain were prepared and tested as done previously. Some structure–activity relationships are discussed.

The important role of Ca^{2+} ions in the excitation–contraction coupling of cardiac and smooth muscle is widely recognized.[1,2] One of the main pathways by which extracellular Ca^{2+} enters the cell is the specific membrane channels. Calcium channel blockers have been increasingly used in cardiovascular research and therapy. These compounds include drugs with various chemical structures. The most potent and most specific belong to the 1,4-dihydropyridine class (nifedipine, nicardipine, nitrendipine, nimodipine, PN 200-110). Since they inhibit myocardial transmembrane Ca^{2+} influx, they are useful in treating angina pectoris, cardiac arrhythmia, and hypertrophic cardiomyopathy.[3,4] They also have vasodilator effects by inhibiting Ca^{2+} influx into vascular cells and are therefore used as antihypertensive agents.

Prazosin, which possesses α_1-postsynaptic specificity,[5,6] reduces arterial pressure and total peripheral resistance[7] without increasing heart rate.[8,9] Jee and Opie[10] have shown that nifedipine added to prazosin in the treatment of hypertension elicits an acute hypotensive response in treatment of hypertension. So the combination of calcium and α_1-antagonist properties may be advantageous and provide useful antihypertensive agents which would not lead to consistent reflex activation of the adrenergic system.

To this end, we synthesized twelve 1,4-dihydropyridine derivatives incorporating an α-adrenergic moiety in one of the ester chains[11] and evaluated their calcium antagonist and α-adrenolytic properties. The results of this study are described in the present paper.

Chemistry

The racemic compounds listed in Table I were prepared by the two general synthesis routes shown in Scheme I, which involved variants of the Hantzsch reaction.[12,13]

The reaction (route A) of alkyl aminocrotonate (**1**) with nitrobenzaldeyde (**2**) and acetoacetate (**3**) at reflux in a suitable solvent (e.g., MeOH, EtOH, 2-PrOH) gave the 1,4-diydropyridine derivatives G in ca. ≈35% yield. The second pathway (Route B) involved the reaction of nitrobenzylidene acetoacetate **4**[14] with aminocrotonate **5**. This method, which appeared to give consistently better yields (34–71%) and easier purification, was generally used.

Compounds **5** were prepared by reacting **3** with NH_3 at 0 °C in MeOH. The synthesis of the aminocrotonate derivatives **3** is shown in Scheme II. The reaction of the requisite amine **7** with 2-bromoethanol gave the corresponding amino alcohol compounds **8**, which were treated with diketene at 70–80 °C to give compounds **3** (R_2 = H). In the case of **3**, with $R_2 = CH_3$, in order to avoid any uncertainty as to the position of the methyl group, we chose to react amines **7** with chloroacetone followed by $NaBH_4$ reduction (overall yield 86%) instead of reacting **7** with propylene oxide or with bromo-2-propanol.

The four chiral derivatives, **6a–d**, were prepared according to the reaction sequence outlined in Scheme III. Thus, 2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin enantiomers **10S** and **10R** were obtained by condensation in NaH/DMF of catechol with glycidyl tosylates **9R** or **9S**, prepared according to the sharpless procedure.[15] Treating each of the enantiomers of **10** with $SOCl_2$ in pyridine, followed by condensation of the resulting chlorides **11** with 2-(dimethylamino)ethanol, gave the amino alcohol derivatives **12** (*R* and *S*) at an overall 30% yield from tosylates **9**. Finally, each of the four stereoisomers of **6a–d** were prepared (route C) by reacting aminoalcohols **12R** and **12S** with 1,4-dihydropyridine derivatives **13R** and **13S**[16] at 75 °C in the presence of DCC/DMAP and DMF as a solvent.[17]

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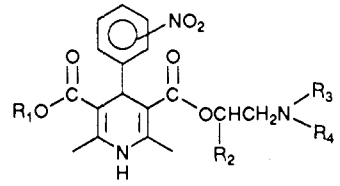
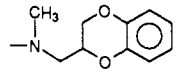
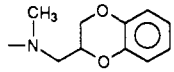
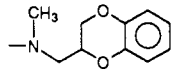
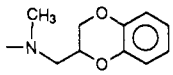
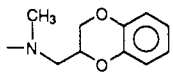
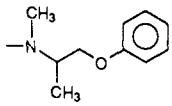
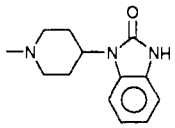
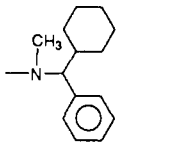
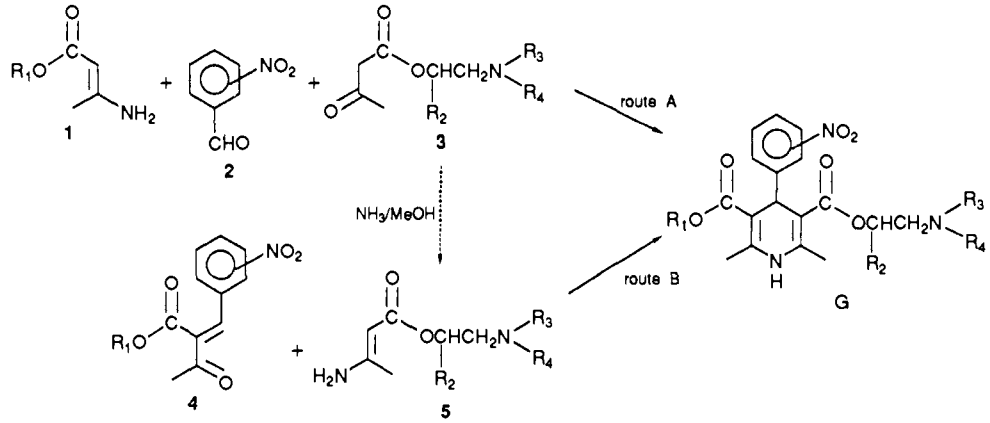
Table I. Physicochemical Data of the 1,4-Dihydropyridine Derivatives



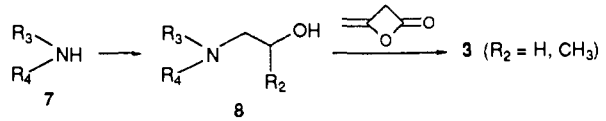
no.	NO_2	R_1	R_2	$-N(R_3)(R_4)$	route	yield, %[a]	formula[b]	mp, °C[c]
6 (±)	3-NO_2	Me	H		B	59	$C_{28}H_{31}N_3O_8 \cdot HCl \cdot {}^1/_2H_2O$	120
6a (*R*,*R*)					C	52		120
6b (*S*,*S*)					C	55		120
6c (*S*,*R*)					C	60		120
6d (*R*,*S*)					C	64		120
9	2-NO_2	Me	H		B	34	$C_{28}H_{31}N_3O_8 \cdot {}^3/_4H_2O$	oil
10	3-NO_2	Me	Me		B	62	$C_{29}H_{33}N_3O_8 \cdot HCl \cdot {}^1/_2H_2O$	120
11	3-NO_2	i-Pr	H		A	39	$C_{30}H_{35}N_3O_8 \cdot HCl \cdot {}^1/_4H_2O$	130
12	3-NO_2	i-Pr	Me		A	31	$C_{31}H_{37}N_3O_8 \cdot HCl$	124
13	3-NO_2	Me	H		B	71	$C_{28}H_{33}N_3O_7 \cdot HCl \cdot {}^1/_4H_2O$	94
14	3-NO_2	Me	H		B	56	$C_{30}H_{33}N_5O_7 \cdot C_2H_2O_4 \cdot {}^1/_2H_2O$[d]	156
15	3-NO_2	Me	H		B	57	$C_{32}H_{39}N_3O_6 \cdot HCl \cdot {}^1/_2H_2O$	138

[a] Yields of the last step. [b] All compounds were analyzed for C, H, and N, and analyses were within ±0.4% of theoretical values. [c] Approximate melting point of compounds not recrystallized. [d] $C_2H_2O_4$, hydrogen oxalate, recrystallized from EtOAc/MeOH.

Scheme I



Scheme II



All dihydropyridines were purified by column chromatography on silica gel, followed by salt formation with HCl gas and washing with Et_2O. Attempts to crystallize these

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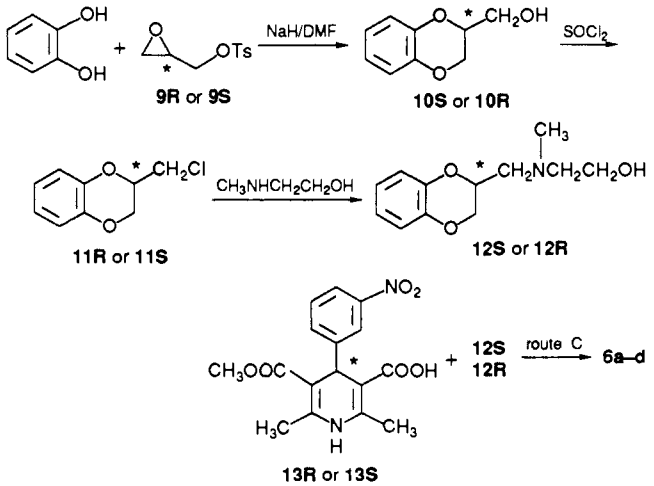
Table II. Biological Data of the 1,4-Dihydropyridine Derivatives

compd	inhibn of [^{3}H]yohimbine binding, IC_{50}, M	inhibn of [^{3}H]prazosin binding, IC_{50}, M	α_2-lytic activity, guinea pig vas deferens, IC_{50}, M	α_1-lytic activity, rat aorta, IC_{50}, M	inhibn of [^{3}H]nitrendipine binding, IC_{50}, M	Ca^{2+} antagonism, pig coronary, IC_{50}, M
6	4.8×10^{-7}	5.0×10^{-7}	$>1.0 \times 10^{-6}$ (4)	4.0×10^{-5} (5)	1.0×10^{-10}	4.5×10^{-9} (14)
6a (*R*,*R*)	4.0×10^{-6}	2.4×10^{-6}	$\gg 1.0 \times 10^{-6}$ (2)	1.0×10^{-5} (14)	1.8×10^{-11}	1.5×10^{-9} (7)
6b (*S*,*S*)	1.4×10^{-7}	2.3×10^{-6}	$>1.0 \times 10^{-4}$ (3)	$>3.0 \times 10^{-5}$ (9)	2.8×10^{-9}	1.0×10^{-8} (6)
6c (*S*,*R*)	1.9×10^{-5}	2.0×10^{-6}	1.0×10^{-5} (5)	$\gg 1.0 \times 10^{-5}$ (8)	1.0×10^{-9}	2.5×10^{-9} (6)
6d (*R*,*S*)	2.1×10^{-7}	1.9×10^{-6}	$\gg 1.0 \times 10^{-6}$ (2)	3.0×10^{-5} (9)	c	c
9	2.7×10^{-7}	3.0×10^{-7}	$>1.0 \times 10^{-6}$ (5)	$>1.0 \times 10^{-5}$ (7)	7.0×10^{-11}	4.0×10^{-9} (11)
10	4.7×10^{-7}	1.0×10^{-6}	$\gg 1.0 \times 10^{-5}$ (4)	$\gg 1.0 \times 10^{-4}$ (6)	5.0×10^{-11}	3.8×10^{-9} (9)
11	8.3×10^{-7}	3.5×10^{-6}	$>1.0 \times 10^{-6}$ (3)	$\gg 3.0 \times 10^{-5}$ (5)	6.0×10^{-11}	4.0×10^{-9} (10)
12	2.0×10^{-6}	3.9×10^{-6}	$\gg 1.0 \times 10^{-6}$ (4)	$\gg 3 \times 10^{-5}$ (7)	3.4×10^{-9}	1.5×10^{-7} (7)
13	4.8×10^{-7}	3.8×10^{-7}	6.7[a] (2)	7.0×10^{-5} (6)	7.3×10^{-11}	1.3×10^{-8} (7)
14	1.6×10^{-6}	4.1×10^{-8}	$\gg 1.0 \times 10^{-6}$ (3)	1.0×10^{-5} (11)	6.0×10^{-10}	1.0×10^{-6} (8)
15	1.6×10^{-5}	7.5×10^{-5}	$>1.0 \times 10^{-4}$ (3)	$>1.0 \times 10^{-4}$ (4)	3.8×10^{-9}	$>1.0 \times 10^{-5}$ (7)
yohimbine	9.1×10^{-9}	1.0×10^{-6}	7.59 ± 0.11[b] (6)	6.46 ± 0.23[b] (8)		
prazosin	1.4×10^{-7}	6.0×10^{-10}		10.99 ± 0.28[b] (8)	3.0×10^{-6}	
phentolamine	1.0×10^{-8}	1.0×10^{-8}		8.01 ± 0.27[b] (11)		
nicardipine	1.4×10^{-6}	3.6×10^{-6}	$>1.0 \times 10^{-5}$ (1)	$>1.0 \times 10^{-5}$ (3)	2.6×10^{-11}	3.0×10^{-10} (9)

[a] Graphical estimation of pA_2. [b] $pA_2 \pm$ standard error. Number of experimental values in parentheses. [c] Not dose dependent.

Scheme III



salts were unsuccessful, except for **14**, which was transformed as an oxalate salt and crystallized from EtOAc/MeOH. Thus, the dihydropyridines **6**, **6a–d**, **9–13**, and **15** were tested as amorphous solids.

Biological Results and Discussion

Calcium antagonist activities were evaluated by the inhibition of [^{3}H]nitrendipine binding on rat cerebral cortex and, in vitro, on the $CaCl_2$-induced contraction of depolarized pig coronary artery.

α_1- and α_2-adrenolytic effects were assessed from the inhibition of [^{3}H]prazosin and [^{3}H]yohimbine binding on rat cerebral cortex preparation and, in vitro, on rat aorta and guinea pig vas deferens, against norepinephrine and clonidine.

For the binding studies, the activities of compounds were expressed as the molar concentration of drug that inhibited 50% (IC_{50}) of the maximum specific binding of the ligand. For the in vitro studies, the activities were expressed as the molar concentration of drug that inhibited 50% (IC_{50}) of the maximum effect of the agonist.

Nicardipine (a 1,4-dihydropyridine calcium antagonist), prazosin (an α_1-blocker agent), yohimbine (an α_2-blocker agent), and phentolamine (a nonselective α-blocker agent) were included in the study as references. The IC_{50} or pA_2 values of the compounds are listed in Table II.

The eight racemic 1,4-dihydropyridine derivatives **6** and **9–15** inhibited the [^{3}H]prazosin binding, with IC_{50} values ranging from 4.1×10^{-8} to 7.5×10^{-5} M. None of them were as potent as prazosin ($IC_{50} = 6.0 \times 10^{-10}$ M). The most potent derivatives, **9**, **10**, and **14**, were 12–88 times more potent than nicardipine. Compound **14** with a 4-(benzimidazolinyl)piperidinyl group was the most active ($IC_{50} = 4.1 \times 10^{-8}$ M) and was only 4 times less potent than phentolamine ($IC_{50} = 1.0 \times 10^{-8}$ M), another well-known α-blocker drug.

In vitro tests on rat aorta showed that the compounds were much less active than prazosin. IC_{50} values for the most potent derivatives (**6a**, **13**, and **14**) varied from 1.0×10^{-5} to 7.0×10^{-5} M whereas that of nicardipine was $>10^{-5}$ M.

Except for compound **15**, the racemic derivatives inhibited the [^{3}H]yohimbine binding over a similar dose range than the [^{3}H]prazosin binding. Compound **14** had an affinity 40 times greater for [^{3}H]prazosin binding sites than for [^{3}H]yohimbine binding sites whereas the other derivatives were slightly more potent on α_2- than on α_1-receptors. In the guinea pig vas deferens, IC_{50} values were generally greater than 1.0×10^{-6} M except for compound **13**, which displayed a presynaptic α_2-adrenolytic activity (pA_2 6.7).

All the compounds inhibited [^{3}H]nitrendipine binding. Three of them, **12**, **14**, and **5**, were clearly less potent than nicardipine. On the contrary, the five other compounds were in the same range of activity as nicardipine.

Compounds **9–13** were ca. 10 times less potent than nicardipine on depolarized pig coronary artery. In this test, compound **15** was almost inactive.

The results obtained with the four chiral derivatives **6a** (*R*,*R*), **6b** (*S*,*S*), **6c** (*S*,*R*), and **6d** (*R*,*S*) shed further light on their steric requirements. As far as calcium antagonism is concerned, it appears that the most potent substance in binding experiments, **6a** (*R*,*R*) ($IC_{50} = 1.8 \times 10^{-11}$ M), but not on pig coronary artery ($IC_{50} = 1.5 \times 10^{-9}$ M), has an *R* configuration at the 4-position of the dihydropyridine ring. The *S* analogue, **6c** (*S*,*R*), is ca. 55 times less active in binding experiments and equipotent on pig coronary artery with **6a** (*R*,*R*). The α_1-adrenolytic activity appears in the micromolar range and is not affected by the stereochemistry of the benzodioxan ring. A potent α_2-adrenergic activity (ca. 0.1 μM) resides mostly in an *S* configuration at the benzodioxan ring whereas an *R* configuration favors a lower α_2 activity. Indeed, **6d** (*R*,*S*) is ca. 20 times more potent in binding experiments than its *R* analogue, **6a** (*R*,*R*).

The results of this study show that several 1,4-di-

hydropyridine derivatives do have some α-adrenolytic activity and strong calcium antagonist activity.

In binding experiments, the α-adrenolytic activities, although moderate, were slightly higher than that of nicardipine and could be attributed to the presence on the side chain of α-adrenergic moieties (for example, **9**, **13**, **14**). This moderate activity, also obtained in dual α–β-adrenergic compounds,[18] could be due to the fact that the α-adrenergic moieties chosen are only partially complementary with the α-adrenoceptor, whereas in the case of prazosin and yohimbine, there is a high degree of structural complementarity between the molecule and the receptor.[19] No molecule but **13** showed α_2-adrenolytic presynaptic activity at 10^{-6} M. Conversely to yohimbine, the molecules reduced the contractions of electrically stimulated vas deferens at 10^{-5} M. Therefore, they do not increase the neuronally released noradrenaline and do not exhibit an α_2-adrenolytic presynaptic activity at this concentration. As expected, in [^{3}H]prazosin and [^{3}H]yohimbine binding experiments, replacing the methyl ester with an isopropyl group or substituting the side chain had no marked effect on the α_1 and α_2 activities of the compounds. Displacing the aromatic nitro group from the 2- to the 3-position had no effect either on the binding experiments or on the in vitro α-adrenolytic and calcium antagonist assays.

In [^{3}H]nitrendipine binding experiments, methylating the alkyl chain of **9** and **10** or replacing the methyl ester with an isopropyl group had no noticeable effect on this activity. However, when both substituents were present (compound **12**), the potency was 130 times lower.

In short, we synthesized a series of compounds combining potent calcium antagonist and modest α-adrenolytic activities. The α_1 and α_2 activities were higher in binding experiments than in in vitro studies. Indeed, α-adrenolytic activity is difficult to quantify in isolated organ preparations because it is masked by the calcium antagonist activity. However, it emerged that not all the compounds are clearly selective for the α_1- or α_2-receptors; only **14** was selective for α_1-receptors in binding experiments.

The use of chiral compounds showed that the higher calcium antagonist activity resides in an *R* configuration of the dihydropyridine nucleus whereas the higher α_2-adrenolytic residues in an *S* configuration of the benzodioxan ring. Very recently, analogous compounds exhibiting the same pharmacological profile have been described.[20,21] The interest of BM 20064, another compound belonging to this class of combined α-adrenoceptors and calcium channel antagonists, has just been confirmed.[22]

Experimental Section

Chemistry. Melting points were taken on a calibrated Kofler hot-stage apparatus and are uncorrected. IR spectra were measured in $CHCl_3$ with a Beckman IR 33 spectrophotometer. NMR spectra (60 MHz) were recorded on a Hitachi–Perkin-Elmer R 24 B spectrometer with Me_4Si as internal standard. All spectra of compounds described here tallied with their assigned structures. Optical rotations were taken on a Perkin-Elmer 241 polarimeter, using 0.6-cm^3 capacity cells (10-cm path length).

General Procedure for the Synthesis of Acetoacetate Derivatives 3. Diketene (50 mmol) was added dropwise to stirred, preheated (70–80 °C) amino alcohols **8** (50 mmol), or their toluene solutions. When this was completed, the mixture was stirred for 3 h at 70–80 °C. The acetoacetates **3** thus formed were used in the next reaction without further purification or after brief purification by column chromatography on silica gel. Yields were generally quantitative.

General Procedure for the Synthesis of Aminocrotonate Derivatives 5. NH_3 was bubbled for 3 h into a solution, cooled to 0 °C, of substituted acetoacetate **3** (60 mmol) in MeOH (10 mL). The reaction flask was tightly stoppered and stirred at 0 °C for 24 h. Solvent and excess NH_3 were evaporated to dryness to give crude aminocrotonate derivatives **5** which were used as such for the next step.

General Procedure for the Synthesis of Dihydropyridines 6–12. Route A: 1-Methyl-2-[*N*-methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]ethyl Isopropyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (12). A mixture of 3-nitrobenzaldehyde (0.66 g, 4.3 mmol), isopropyl 3-aminocrotonate[23] (0.57 g, 4 mmol), and 1-methyl-2-[*N*-methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)-methyl]amino]ethyl acetoacetate (1.1 g, 3.6 mmol) in 2-PrOH (20 mL) was heated overnight under reflux and argon. The solvent was then evaporated and the residue purified by column chromatography (hexane/EtOAc/MeOH 55:40:5) to give 0.65 g (31%) of **12**, as a yellow oil: NMR ($CHCl_3$) δ 1.1 (3 H, d, J = 7 Hz, CH–CH_3), 1.25 [6 H, d, J = 7 Hz, CH–$(CH_3)_2$], 2.25 (3 H, s, N–CH_3), 2.35 (6 H, s =C–CH_3), 2.5 (4 H, m, CH_2–N–CH_2), 3.8–4.35 (3 H, m, O–CH_2–CH–O), 4.95 [2 H, m, $(CH_3)_2$–CH and COO–CH], 5.05 (1 H, s, C–H 1,4-dihydropyridine), 5.9 (1 H, s, N–H), 6.8 (4 H, s, Ar–H benzodioxan), 7.2–8.1 (4 H, m, Ar–H nitrophenyl); IR ($CHCl_3$) 3420 (N–H), 1660 cm^{-1} (COO).

Route B: 2-[*N*-Methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]ethyl Methyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6). A mixture of methyl 2-(3-nitrobenzylidene)acetoacetate[24] (2.5 g, 10 mmol) and 2-[*N*-methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-amino]ethyl aminocrotonate (3 g, 10 mmol) in EtOH (30 mL) was heated under reflux and argon for 2 h. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc 40:60) to give 3.2 g (59%) of pure **6**: NMR ($CDCl_3$) δ 2.0 (3 H, s, N–CH_3), 2.3 (6 H, s, =C–CH_3), 2.7 (4 H, t, J = 6 Hz, CH_2–N–CH_2), 3.6 (3 H, s, O–CH_3), 3.8–4.4 (5 H, m, COO–CH_2 and O–CH–CH_2–O), 5.1 (1 H, s, C–H 1.4 dihyd ropyridine), 6.35 (1 H, s, N–H), 6.8 (4 H, s, Ar–H benzodioxan), 7.2–8.2 (4 H, m, Ar–H nitrophenyl); IR ($CHCl_3$) 3440 (N–H), 1700 cm^{-1} (COO).

General Procedure for the Synthesis of the Amino Alcohol Derivatives 8 (R_2 = H). A solution of amine **7** (50 mmol), Et_3N (60 mmol), and 2-bromoethanol (60 mmol) in toluene (100 mL) was heated under reflux for 4–15 h (the reaction was monitored by TLC). After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The crude amino alcohols **8** obtained were purified by distillation or by silica gel column chromatography. This procedure gave the following results.

***N*-Methyl-*N*-(2-hydroxyethyl)(2,3-dihydro-1,4-benzodioxin-2-yl)methanamine**: yield 76%, bp 111 °C/0.1 mmHg, lit.[25] 124 °C/0.15 mmHg.

***N*-Methyl-*N*-(2-hydroxyethyl)-1-phenoxy-2-propanamine**: yield 83%, bp 126 °C/0.08 mmHg, lit.[26] 106 °C/0.02 mmHg.

***N*-(2-Hydroxyethyl)-4-(2-oxo-1-benzimidazolinyl)-piperidine**: yield 66%, mp 201 °C (CH_3CN/MeOH).

***N*-Methyl-*N*-(2-hydroxyethyl)-α-cyclohexylbenzenemethanamine**: yield 80%, bp 115 °C/0.1 mmHg.

General Procedure for the Synthesis of the Amino Alcohol Derivatives 8 (R_2 = CH_3). *N*-Methyl-*N*-(2-hydroxypropyl)(2,3-dihydro-1,4-benzodioxin-2-yl)methanamine. Chloroacetone (7.57 g, 82 mmol) was added dropwise to a stirred

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solution of *N*-methyl(2,3-dihydro-1,4-benzodioxin-2-yl)methanamine (12.24 g, 68 mmol) and Et_3N (8.3 g, 82 mmol) in toluene (60 mL). When this was completed, the mixture was heated overnight under reflux. The resulting suspension was then filtered, and the filtrate was evaporated to dryness to give 16 g (99%) of crude amino ketone; IR ($CHCl_3$) 1720 cm^{-1} (>C=O). This amino ketone (16 g, 68 mmol), dissolved in MeOH (70 mL), was treated with $NaBH_4$ (2.57 g, 68 mmol), and the mixture was stirred for 15 h at room temperature. Water (100 mL) was added and MeOH was evaporated. The mixture was extracted with Et_2O (2 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated to give 14 g (86%) of pure amino alcohol: bp 123 °C/0.12 mmHg, lit.[27] 139 °C/0.3 mmHg; IR ($CHCl_3$) 3460 cm^{-1} (>CH–OH).

(2*R*)- and (2*S*)-2-(Hydroxymethyl)-2,3-dihydro-1,4-benzodioxin (10S and 10R).[28] A solution of catechol (7.2 g, 65.7 mmol) in DMF (50 mL) was added dropwise to a suspension of NaH (3.0 g, 60% oil dispersion, equivalent to 74.9 mmol) in DMF (25 mL) under argon. After the suspension was stirred for 30 min at room temperature, a solution of (*R*)-(−)-glycidyl tosylate[15] (10 g, 43.8 mmol) in DMF (50 mL) was added dropwise. After being stirred for 10 h at room temperature, the reaction mixture was poured into ice water and extracted with Et_2O (3 × 50 mL). The ethereal layer was washed with 1 N NaOH and brine. Evaporation of the dried ($MgSO_4$) organic layer gave 3.97 g of crude **10S**, which was purified by silica gel column chromatography (CH_2Cl_2) followed by crystallization from light petroleum–Et_2O (8:2) to give 1.5 g (21%) of **10S** as a white solid, $[\alpha]_D$ −30.3 (*c* 1.09, EtOH). By an analogous procedure, (*S*)-(+)-glycidyl tosylate gave **10R** at an 18% yield, $[\alpha]_D$ +30.5 (*c* 1.05, EtOH), lit.[29] $[\alpha]_D$ +34. (*c* 0.1, EtOH).

(2*R*)- and (2*S*)-2-(Chloromethyl)-2,3-dihydro-1,4-benzodioxin (11R and 11S). To an ice-cold solution of **10S** (3.7 g, 22.3 mmol) in dry pyridine (20 mL) was added dropwise Cl_2SO (1.8 mL, 24.5 mmol). After being stirred for 3 h at 100 °C, the reaction mixture was poured onto 1 N HCl and extracted with Et_2O (3 × 25 mL). The solvent was dried ($MgSO_4$) and evaporated to give an oil which was purified by distillation to give 2.8 g (68%) of **11R**: bp 77 °C/0.2 mmHg, lit.[30] 80 °C/0.7 mmHg; $[\alpha]_D$ −20.3 (*c* 1.18, EtOH). Compound **11S** was obtained similarly from **10R** at a 70% yield, $[\alpha]_D$ +18.3 (*c* 1.20, EtOH).

(2*R*)- and (2*S*)-2-[*N*-Methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]ethanol (12R and 12S). A solution of **11S** (530 mg, 2.87 mmol) and 2-(dimethylamino)ethanol (2.25 g, 30 mmol) in EtOH (15 mL) was heated overnight in a sealed tube at 120 °C. Solvent and excess reagent were evaporated to give a residue, which was taken up in Et_2O and washed with 1 N HCl (3 × 20 mL). Evaporation of the dried ($MgSO_4$) organic extracts gave crude **12** (70%), which was used as such for the next step, $[\alpha]_D$ +32.0 (*c* 1.06, EtOH). Amino alcohol **12S** was obtained similarly from **11R** at a 75% yield, $[\alpha]_D$ +32.1 (*c* 1.06, EtOH).

Route C: General Procedure for the Synthesis of Chiral 6a Derivatives. A mixture of chiral dihydropyridine **13R** or **13S**, (500 mg, 1.5 mmol), chiral amino alcohol **12R** or **12S** (372 mg, 1.67 mmol), dicyclohexylcarbodiimide (345 mg, 1.67 mmol) and 4-(dimethylamino)pyridine (25 mg, 0.20 mmol) in DMF (10 mL) was heated under argon at 75 °C. After 48 h, the reaction mixture was poured into ice water, solids were removed by filtration, and the remaining solution was extracted with Et_2O (3 × 15 mL). Evaporation of the dried ($MgSO_4$) organic phase gave a residue which, after purification as for racemic **6** (route B), gave the corresponding chiral derivative (Table I): **6d** (*RS*)·HCl, $[\alpha]_D$ +70.1 (*c* 1.07, EtOH); **6c** (*SR*)·HCl, $[\alpha]_D$ −67.5 (*c* 1.09, EtOH); **6b** (*S-S*)·HCl, $[\alpha]_D$ −96.9 (*c* 0.98, EtOH); **6a** (*RR*)·HCl, $[\alpha]_D$ +100.8 (*c* 1.06, EtOH).

Pharmacology. Binding Experiments. Plasma membrane preparations from rat cerebral cortex and rat heart were obtained as described by Schwartz and Velly[31] for [^{3}H]nitrendipine binding and by Rouot et al.[32] for [^{3}H]prazosin binding. Protein concentration was determined with the method of Lowry et al.[33] For the binding assays, 1 mL of plasma membrane preparation (1 mg of protein) was incubated with 0.1 nM [^{3}H]nitrendipine (NEN, 80 Ci/mmol) or [^{3}H]prazosin (NEN, 18 Ci/mmol) and increasing concentrations of 1,4-dihydropyridine derivatives in 50 mM Tris-HCl buffer, pH 7.4 (total volume 2 mL). Incubation was carried out at 25 °C for 90 min for [^{3}H]nitrendipine binding and for 20 min for [^{3}H]prazosin binding. Bound and free ligands were separated by rapid filtration through Whatman GF/B filters. The filters were rapidly washed with 20 mL of 50 mM Tris-HCl buffer, pH 7.4, and transferred to counting vials containing 10 mL of scintillation mixture (Packard 299 TM). Radioactivity was measured in a Packard counter. Nonspecific binding was determined in the presence of 10^{-5} M nitrenedipine or 10^{-4} M norepinephrine for [^{3}H]nitrendipine or [^{3}H]prazosin binding, respectively. IC_{50} was the drug concentration that inhibited the maximum specific binding of the ligand by 50%. For each drug, three determinations were performed, each point being done in triplicate. Data shown in Table II are means of the three IC_{50}.

In Vitro Tests. α_1-Adrenolytic Activity on Rat Aorta. Helically cut strips of rat aorta, 1.5–2 cm long and 3–4 mm wide, were prepared as described by Liebau et al.[34] Preparations were suspended in 20-mL baths containing tyrode solution kept at 37 °C, bubbled with a mixture of 95% O_2 and 5% CO_2 and made up as follows, in mM: NaCl 141.2; KCl, 5.6; $MgSO_4 \cdot 7H_2O$, 1.42; $CaCl_2 \cdot 2H_2O$, 2.28; NaH_2PO_4, 1.42; $NaHCO_3$, 29; glucose, 11.98; and Na_2 EDTA, 0.006. They were set up at a resting tension of 2 g and allowed to stabilize for approximately 1 h before the experiment. β-Receptors were blocked with propranolol at 10^{-6} M for 30 min. Contractions were measured isometrically with a Statham G 10 B. Since we found that the first dose–response curve for most tissues differed from subsequent responses, all tissues were exposed to the agonist concentration that produced 70–80% of maximum response and then washed every 15 min for 60 min. Then two cumulative dose–response curves with noradrenaline (10^{-10}–10^{-7} M) were established before and after adding the antagonist. Preincubation with the antagonist lasted 30 min. Each preparation was tested with only one concentration. Ascorbic acid (1.13 × 10^{-5} M) was present during the elaboration of each noradrenaline dose–response curve. Antagonistic effects are expressed in terms of pA_2 for competitive antagonists, according to Arunlakshana et al.[35] When the antagonism was not competitive, it has been expressed as IC_{50} (the molar concentration of antagonist inhibiting the maximum effect of the agonist by 50%), according to Ariens and Van Rossum.[36]

α_2-Adrenolytic Activity on Guinea Pig Vas Deferens. Vasa deferentia were prepared as described by Drew[37] and Spedding.[38] They were set up in 20-mL baths containing a modified tyrode solution maintained at 36 °C, with the following composition (mM): NaCl, 137; KCl, 2.7; $MgCl_2$, 1.1; $CaCl_2$, 1.8; $NaHCO_3$, 11.9; NaH_2PO_4, 0.4; and glucose, 5.5. In addition, the tyrode solution, which was gassed with 95% O_2 and 5% CO_2, contained atropine (1.7 × 10^{-6} M) to exclude the effects of cholinergic nerve stimulation. Resting tension was set at 1 g, and after a 30-min equilibration period, responses were measured isometrically with an Ugo Basile strain gauge. Vasa deferentia were set up between two platinum ring electrodes (ring diameter 5 mm, distance between rings 30 mm) and stimulated with a square wave pulse stimulator (Stimulator T, Hugo Sachs Elektronik) at a frequency of 6 Hz and a voltage 50% above the threshold (duration 1 ms at 15-s intervals). Then two cumulative dose–response curves

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with clonidine (2.0×10^{-10}–2.0×10^{-8} M) were established before and after the antagonist.

Calcium Antagonism on Depolarized Pig Coronary Artery. Antagonism of calcium-induced contraction was measured on depolarized pig coronary artery, as described by Godfraind and Kaba.[39] Helically cut strips of pig coronary artery, 2–2.5 cm long and 3–4 mm wide, set up at a resting tension of 0.5 g, were suspended in a modified Krebs–Henseleit solution, composed as follows, in mM: NaCl, 112; KCl, 5; $NaHCO_3$, 25; KH_2PO_4, 1; $MgSO_4$, 1.2; $CaCl_2$, 1.25; and glucose, 11.5. After an hour's stabilization, the pig coronary was suspended in a new calcium-free Krebs solution containing Na_2EDTA at 2×10^{-4} M. Finally, the antagonism of calcium-induced contraction (3×10^{-5}–10^{-2} M) was measured on the coronary artery, depolarized with a solution containing no $CaCl_2$ but with KCl (100 mM) and NaCl (17 mM). Preincubation with the antagonist lasted 30 min.

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Registry No. 4 (3-nitro, R′ = Me), 39562-17-9; 4 (2-nitro, R′ = Me), 39562-27-1; **6**, 112358-09-5; **6**·HCl, 119746-71-3; (*R*,*R*)-**6a**, 119746-72-4; (*R*,*R*)-**6a**·HCl, 119746-73-5; (*S*,*S*)-**6b**, 119746-74-6; (*S*,*S*)-**6b**·HCl, 119746-75-7; (*S*,*R*)-**6c**, 119746-76-8; (*S*,*R*)-**6c**·HCl, 119746-77-9; (*R*,*S*)-**6d**, 119746-78-0; (*R*,*S*)-**6d**·HCl, 119746-79-1; 7 (R_3 = Me, R_4 = 2,3-dihydro-1,4-benzodioxin-2-ylmethyl), 119746-80-4; 7 (R_3 = Me, R_4 = 1-phenoxypropan-2-yl), 119746-81-5; 7 (R_3 = Me, R_4 = CH_2-c-C_6H_{11}), 25756-29-0; 8 (R_2 = H, R_3 = Me, R_4 = 2,3-dihydro-1,4-benzodioxin-2-ylmethyl), 119746-82-6; 8 (R_2 = H, R_3 = Me, R_4 = 1-phenoxypropan-2-yl, 119746-83-7; 8 (R_2 = H, R_3 = Me, R_4 = CH_2-c-C_6H_{11}), 119746-84-8; 8 (R_2R_3 = Me, R_4 = 2,3-dihydro-1,4-benzodioxin-2-ylmethyl), 119746-85-9; **9**, 119746-86-0; **9R**, 113826-06-5; **9S**, 70987-78-9; **10**, 119746-87-1; **10**·HCl, 119746-88-2; **10S**, 98572-00-0; **10R**, 62501-72-8; **11**, 119746-89-3; **11**·HCl, 119746-90-6; **11R**, 119746-91-7; **11S**, 119746-92-8; **12**, 119746-93-9; **12**·HCl, 119746-94-0; **12S**, 119816-26-1; **12R**, 119816-27-2; **13**, 119746-95-1; **13**·HCl, 119746-96-2; **13R**, 76093-33-9; **13S**, 76093-34-0; **14**, 119746-97-3; **14**·oxalate, 119746-98-4; **15**, 119746-99-5; **15**·HCl, 119747-00-1; diketene, 674-82-8; 3-nitrobenzaldehyde, 99-61-6; isopropyl 3-aminocrotonate, 14205-46-0; 1-methyl-2-[*N*-methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]ethyl acetoacetate, 119747-01-2; 2-[*N*-methyl-*N*-[(2,3-dihydro-1,4-benzodioxin-2-yl)-methyl]amino]ethyl aminocrotonate, 119747-02-3; 2-bromoethanol, 540-51-2; *N*-(2-hydroxyethyl)-4-(2-oxo-1-benzimidazolinyl)-piperidine, 119747-03-4; 4-(2-oxo-1-benzimidazolinyl)piperidine, 20662-53-7; chloroacetone, 78-95-5; *N*-methyl-*N*-(2-oxopropyl)-(2,3-dihydro-1,4-benzodioxin-2-yl)methanamine, 119747-04-5; catechol, 120-80-9; 2-(dimethylamino)ethanol, 108-01-0; 2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]methylamino]-1-methylethyl ester 3-amino-2-butenoic acid, 119747-05-6; 2-[[2,3-dihydro-1,4-benzodioxin-2-yl)methyl]methylamino]ethyl ester 3-oxobutanoic acid, 119747-06-7; 2-[methyl(1-methyl-2-phenoxyethyl)amino]ethyl ester 3-amino-2-butenoic acid, 119747-07-8; 2-[4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]ethyl ester 3-amino-2-butenoic acid, 119747-08-9; 2-[(cyclohexylphenylmethyl)methylamino]ethyl ester 3-amino-2-butenoic acid, 119747-09-0; 2-[methyl(1-methyl-2-phenoxyethyl)amino]ethyl ester 3-oxobutanoic acid, 119747-10-3; 2-[4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]ethyl ester 3-oxobutanoic acid, 119747-11-4; 2-[(cyclohexylphenylmethyl)methylamino]ethyl ester 3-oxobutanoic acid, 119747-12-5.

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Book Reviews

Amino Acids and Peptides. Volume 19. Specialist Periodical Reports. J. H. Jones, Senior Reporter. Royal Society of Chemistry, Burlington House, London. 1987. xi + 333 pp. 14 × 22.5 cm. ISBN 0-85186-174-1. $136.00.

The 19th volume of this series continues with the format set by previous volumes. It is a detailed survey of a number of topics related to amino acid (β-lactam) and peptide chemistry. In particular, the review references publications from 1986 on the occurrence of known amino acids; discovery of new natural amino acids; chemical synthesis, resolution, physical and stereochemical studies of amino acids; complete and partial peptide syntheses; synthesis methodology; peptide analogues for physical and medicinal chemical studies; β-lactam chemistry; and metal complexes of amino acids and peptides. The coverage of protein chemistry ended with Volume 16.

Given the nearly hemorrhagic growth of these areas one can sympathesize with the problems of attempting "exhaustive coverage" of a field. This review is not exhaustive, e.g., Chapter 2, Peptide Synthesis "covers the majority of all published literature in this area and only those papers of particular interest are discussed in the general text." Nevertheless, the review is highly representative of the topics covered, and therefore a good starting point for leading references.

The condensed style and paucity of structures and figures make for rough reading, even for the devotee. The level of condensation increases with each volume. In future volumes readability may be enhanced with a simple outline format. Unfortunately, an outline would lack the reporters' editorial comments which can be quite useful and thought provoking.

Readers desiring to scan the 19 volumes to see what has been published through the years on a specific topic, e.g., the synthesis and employment of α-methyl amino acids, will be confronted with the necessity of reading an entire section. Fortunately, each section is only a few pages long. Still, a keyword index would significantly enhance the utility of this series.

Despite these drawbacks the volumes are essential for the practicing peptide chemist. For the novitiate these volumes will become increasingly important. A library cannot be considered a resource for peptide chemistry without these volumes.

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The Alkaloids. Chemistry and Pharmacology. Volume 30. Edited by Arnold Brossi. Academic Press, Inc. San Diego, CA. 1987. ix + 387 pp. 15 × 23 cm. ISBN 0-12-469530-2. $95.00.

It is really not possible to conduct research in the field of alkaloid chemistry without consulting the appropriate volumes of *The Alkaloids*, edited by A. Brossi. The exceptional high value of this series is again well represented in its Volume 30. This treatise provides three comprehensive reviews on three different alkaloid classes covering the developments on their isolation, structure elucidation, biosynthesis, synthesis, reaction, spectroscopy, and pharmacology.

Chapter 1, The Bisbenzylisoquinoline Alkaloids by K. T. Buck, pp 1–202, reviews the titled alkaloids in a very broad sense including the biogenetically related bis alkaloids (e.g., benzyliso-