Synthesis and Pharmacological Properties of "Soft Drug" Derivatives Related to Perhexiline

Gilbert Marciniak,† Dominique Decolin,‡ Gérard Leclerc,*,† Nicole Decker, and Jean Schwartz

Institut de Pharmacologie (UA 589 CNRS), Département de Pharmacochimie, Faculté de Médecine, 11 rue Humann, 67000 Strasbourg, France, and Faculté des Sciences Pharmaceutiques et Biologiques (UA 597 CNRS), 30 rue Lionnois, 54000 Nancy, France. *Received May 3, 1988*

In the hope of reducing the toxicity of perhexiline, a series of 27 cyclohexylaralkylamines II based on the "soft drug" concept and incorporating an amide function were synthesized. In a preliminary screening, compounds were evaluated for their α-adrenolytic activities. Several derivatives, especially *N*-(cyclohexylphenylmethyl)-2-(cyclohexylmethylamino)acetamide (**3**), *N*-(cyclohexylphenylmethyl)-2-(homoveratrylmethylamino)acetamide (**7**), and *N*-[2-(cyclohexylamino)ethyl]-α-cyclohexylbenzeneacetamide (**23**) had the same activity range as perhexiline in vitro in rat aorta strips. The in vitro metabolism of these three molecules was then investigated and compared to that of perhexiline. The effect upon the α-adrenolytic activity of introducing various *N*-aralkylamine groups on II was examined. Structure/activity relationships are discussed.

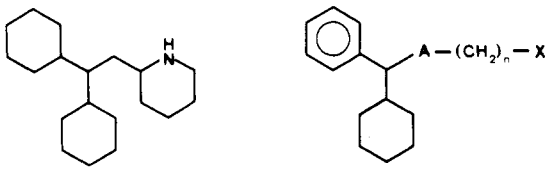
Angina pectoris is one of the most frequent clinical syndromes associated with ischemic heart disease, due to an imbalance between myocardial oxygen consumption and supply. The main therapeutic agents used to treat this disease are nitrates, β-blockers, and calcium channel blockers.[1,2] Perhexiline maleate belongs to the latter class of compounds and is sometimes classified in the aralkylamine subgroup.[3] Its mode of action remains unknown. Perhexiline is effective in treating angina[4] but its use is limited by its side effects such as hepatotoxicity,[5] weight loss,[6] and peripheral neuropathy.[7] These undesirable effects might be related to slow metabolism and accumulation of the molecule in these patients.[8] Leclerc et al.,[9] hoping to reduce these side effects, reported in a previous paper a series of cyclohexylaralkylamine derivatives related to perhexiline. Several of them were more active than perhexiline, but they displayed chronic toxicity similar to that of perhexiline.[10] We thought that the "soft drug" approach developed by Bodor[11,12] could be applied to this problem. "Soft drugs" can be defined as "biologically active chemical compounds (drugs) which might structurally resemble known active compounds (soft analogues) or could be entirely novel types of structures, but which are all characterized by a predictable in vivo destruction (metabolism) to non-toxic moieties, after they achieve their therapeutic effect. The metabolic disposition of the soft drug takes place at a controllable rate in a predictable manner." Starting from this principle, and on the basis of work from our laboratory, we decided to synthesize molecules of general structure II (Chart I), to evaluate some of their pharmacological properties, and to investigate the in vitro metabolism of those which present the best α-adrenolytic activity.

We chose first an amide function (CON< or >NCO) in A as the labile center. This function was expected to give a good compromise between chemical stability and in vivo degradation. We varied the nature of X, which was either a primary, secondary, or tertiary amine, or a heterocycle, such as the imidazolyl or imidazolinyl rings that are present in some α-adrenolytic compounds, e.g., phentolamine or RS 21361.[13]

Chemistry

The compounds prepared in this study are listed in Table I and their syntheses are shown in Schemes I–VI. The reaction of α-cyclohexylbenzenemethanamine (**28**) with the appropriate chloroalkanoyl chloride gave the chloroalkylamides **29a–c** (Scheme I), which were treated with the requisite amine, with or without solvent (methods A, B, and C) to give compounds **1–7**, **13**, **14**, and **17**.

Chart I



I (perhexiline) II

A = labile group that must control the metabolism; X = amino group or heterocycle group (imidazolyl, imidazolinyl); n = 1–3

N-Methylamide derivatives **11** and **12** (Scheme II) were prepared in an identical manner to Scheme I except that the initial amine was *N*-methyl-α-cyclohexylbenzenemethanamine (**31**), which was prepared in three steps from the commercial ketone **30**, in a 67% yield.

The synthesis of **18** (compound II with A = NHCO and n = 1) is shown in Scheme III. It involved the formation of **34** from acid **33**, which was converted to the hydrochloride salt and hydrogenated over PtO_2 (method D).

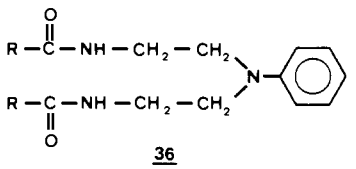
For the synthesis of compounds **22–25** (A = CONH), two pathways were used, as shown in Scheme IV. The first (method E) involved the formation of the acylaziridine **35**, which was then reacted with a secondary amine in acetone. When cyclohexylamine was used to synthesize **23**, compound **36** was the major product isolated (56%), as was

† Faculté de Médecine.
‡ Faculté des Sciences Pharmaceutiques et Biologiques.

(1) Charlier, R. *Antianginal Drugs*; Springer-Verlag: New York, 1971.
(2) Winbury, M. M.; Abiko, Y. *Perspectives in Cardiac Vascular Research*; Raven: New York, 1979; Vol. 3.
(3) Spedding, M. *Trends Pharmacol. Sci.* **1985**, *3*, 109.
(4) Teo, K. K.; Kelly, J. G.; Darby, J. F.; Ennis, J. T.; Horgan, J. H. *Clin. Pharmacol. Ther.* **1983**, *34*, 744.
(5) Howard, D.; Russel, J. *Br. Med. J.* **1976**, *1*, 133.
(6) Pilcher, J. *Postgrad. Med. J.* **1978**, *54*, 663.
(7) Lhermite, F.; Fardeau, M.; Chedru, F.; Mallecourt, J. *Br. Med. J.* **1976**, *1*, 1256.
(8) Shah, R. R.; Oates, N. S.; Idle, J. R.; Smith, R. L.; Lockhart, J. D. *Br. Med. J.* **1982**, *284*, 295.
(9) Leclerc, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1982**, *25*, 709.
(10) Foncin, J. F.; Vu-Ngoc Huyen, D.; Cathala-Jacquier, F., Synthelabo Laboratories, Internal Report.
(11) Bodor, N. *Trends Pharmacol. Sci.* **1982**, *3*, 53.
(12) Bodor, N.; Oshiro, Y.; Loftsson, T.; Katovich, M.; Caldwell, W. *Pharmacol. Res.* **1984**, *3*, 120.
(13) Timmermans, P. B. M. W. M.; Van Zwieten, P. A. *J. Med. Chem.* **1982**, *25*, 1389.

0022-2623/88/1831-2289$01.50/0 © 1988 American Chemical Society

also observed by Thyrum and Day.[14]



36

However, **23** could be obtained by using excess cyclohexylamine (method E'). The second pathway (method F) was via the *N*-(2-chloroethyl)amide derivative **37**. Synthesis pathways for compounds II, where A = NHCO and X represents either an imidazoyl or an imidazolinyl group, are described in Scheme V. Cyanoalkylamides **38a,b** were obtained by heating **29a,b** with NaCN in DMSO and transformed to their corresponding imidate hydrochloride (HCl, EtOH).[15] Without purification, these salts were reacted either with ethylenediamine[16] (method G) to give the corresponding 2-imidazolinyl derivatives **8** and **15** or with aminoacetaldehyde diethyl acetal followed by acid-catalyzed hydrolysis and ring closure[17] to give the 2-imidazolyl derivative **16** (method H). However, only traces of **9** were obtained with this procedure, so finally **9** was produced by reacting **28** with *N*-benzyl-2-imidazoleacetic acid ethyl ester, **39** (prepared by ethanolysis of *N*-benzyl-2-(cyanomethyl)imidazole),[18] followed by hydrogenolysis of adduct **40** (method I). The 4-substituted imidazole **10** was prepared by heating **28** with ethyl 4-imidazoleacetate[19] **41** in a sealed tube at 190 °C for 24 h (method J).

Scheme VI shows the synthesis of compounds II, where A = CONH and X = imidazolyl or imidazolinyl. Nitriles **42a,b** were prepared with the Schotten–Bauman procedure[20] and transformed as described in Scheme V to give **19**, **26** and **20**, **27**. Coupling **31** with 4-(aminomethyl)-imidazole,[21] **43**, by a standard procedure,[22] gave the 4-substituted heterocycle **21** at a 34% yield (method K).

Results and Discussion

The cyclohexylaralkylamides described in this study were initially tested for their α-adrenolytic activity. On rat aorta (see the methods section), several of those compounds tested (**3**, **7**, and **23**; see Table I) show α-adrenolytic activities comparable ($pA_2 \sim 6.6$) to that of perhexiline ($pA_2 = 6.7$), confirming the modest influence of the labile group upon this activity. Similarly, converting the CONH into a NHCO group has little effect, as is shown by comparing the couples **13** and **23**, **8** and **19**, **9** and **20**, and **15** and **26**.

In the NHCO series, the N-methylation of the amide link reduced the activity, thus **2** > **11** and **3** ≫ **12**. As far as the length of the side chain was concerned, the activity was $n = 1 > 2 \sim 3$; thus **2** > **13** ~ **17**. The presence of a secondary or tertiary amine increased the activity; thus **3** = **2** ≫ **1**. Introducing various *N*-aralkylamine moieties

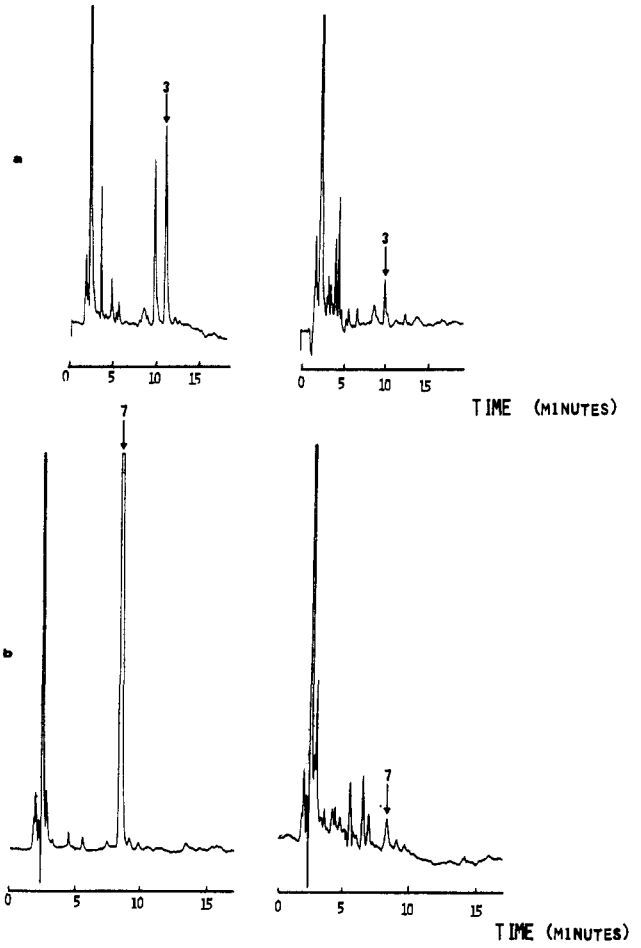


Figure 1. Chromatographic profiles obtained for **3** (a) and **7** (b), before (left) and after (right) incubation (30 min) with rat liver microsomes.

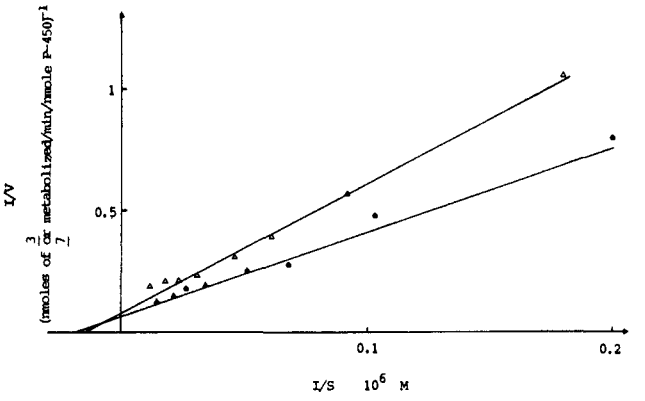


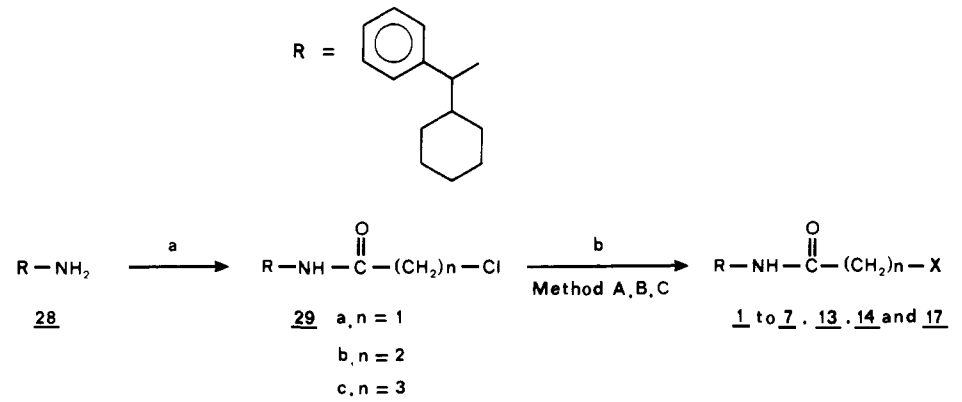
Figure 2. Double-reciprocal plots used to compute K_m and V_{max} for **3** (△) and **7** (▲).

found in several potent α-adrenergic agents[23-25] gave moderately active compounds **5**, **6**, **7**, and **14**. The presence of an imidazolyl or imidazolinyl ring has no clear positive effect. Thus, for $n = 1$, **8** = **9** but for $n = 2$, **15** > **16**.

In the CONH series, compounds displayed the same activity, whatever n was. Surprisingly, here the activity was highest for the secondary amine derivative **23**. The morpholino derivative **25** was ca. 30 times less active than

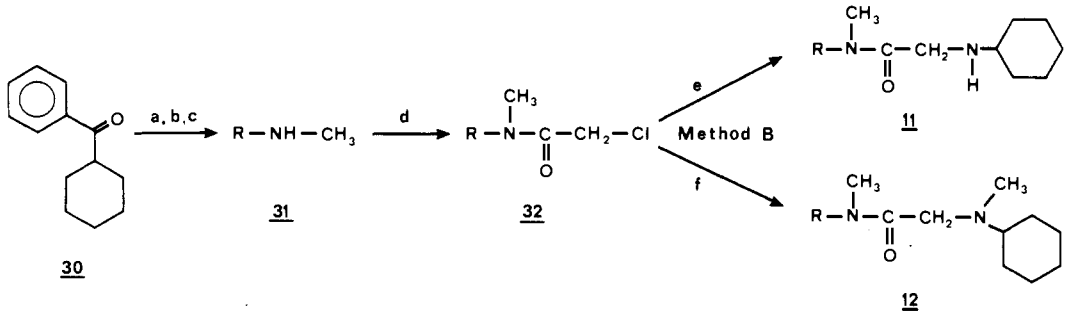
(14) Thyrum, P.; Day, A. R. *J. Med. Chem.* **1965**, *8*, 107.
(15) Houben, J.; Pfankuch, E. *Chem. Ber.* **1926**, *59B*, 2397.
(16) Klarer, W.; Urech, E. *Helv. Chim. Acta* **1944**, *27*, 1762.
(17) Caroon, J. M.; Clark, R. D.; Kluge, A. F.; Olah, R.; Repke, D. B.; Unger, S. H.; Michel, A. D.; Whiting, R. L. *J. Med. Chem.* **1982**, *25*, 666.
(18) Kornfeld, E. C.; Wolf, L.; Lin, T. M.; Slater, I. H. *J. Med. Chem.* **1968**, *11*, 1028.
(19) Pyman, F. L. *J. Chem. Soc.* **1911**, *99*, 668.
(20) Goldberg, A. A.; Kelly, W. I. *J. Chem. Soc.* **1947**, 1369.
(21) Bastiaansen, L. A. M.; Godefroi, E. F. *J. Org. Chem.* **1978**, *43*, 1603.
(22) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(23) Leclerc, G.; Decker, N.; Schwartz, J. *Arzneim.-Forsch.* **1985**, *35*, 1357.
(24) Decker, N.; Quennedey, M. C.; Rouot, B.; Schwartz, J.; Velly, J. *J. Pharm. Pharmacol.* **1982**, *34*, 107.
(25) Ariens, E. J. *N. Y. Acad. Sci.* **1967**, *139*, 606.

Scheme I[a]



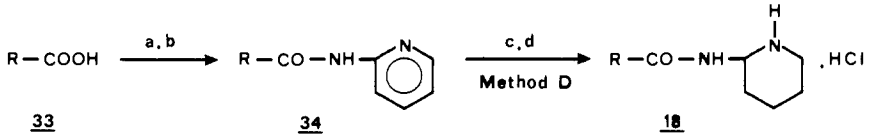
[a] (a) $Cl(CH_2)_nCOCl$, Et_3N; (b) XH (Et_3N); for the definition of X, see Table I.

Scheme II[a]



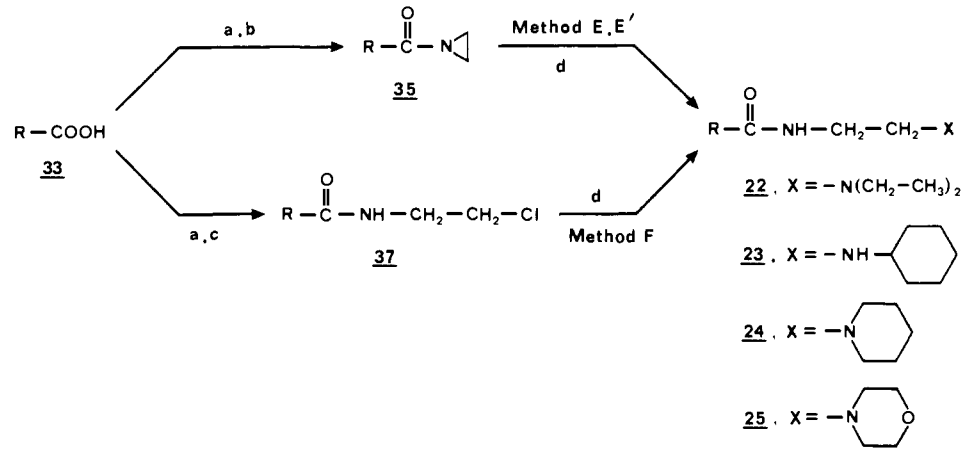
[a] For definition of R, see Scheme I. (a) $NaBH_4$; (b) PBr_3; (c) methylamine; (d) $ClCH_2COCl$; (e) cyclohexylamine; (f) *N*-methylcyclohexylamine.

Scheme III[a]



[a] For definition of R, see Scheme I. (a) $SOCl_2$; (b) 2-aminopyridine; (c) 1 equiv of HCl; (d) H_2/PtO_2.

Scheme IV[a]



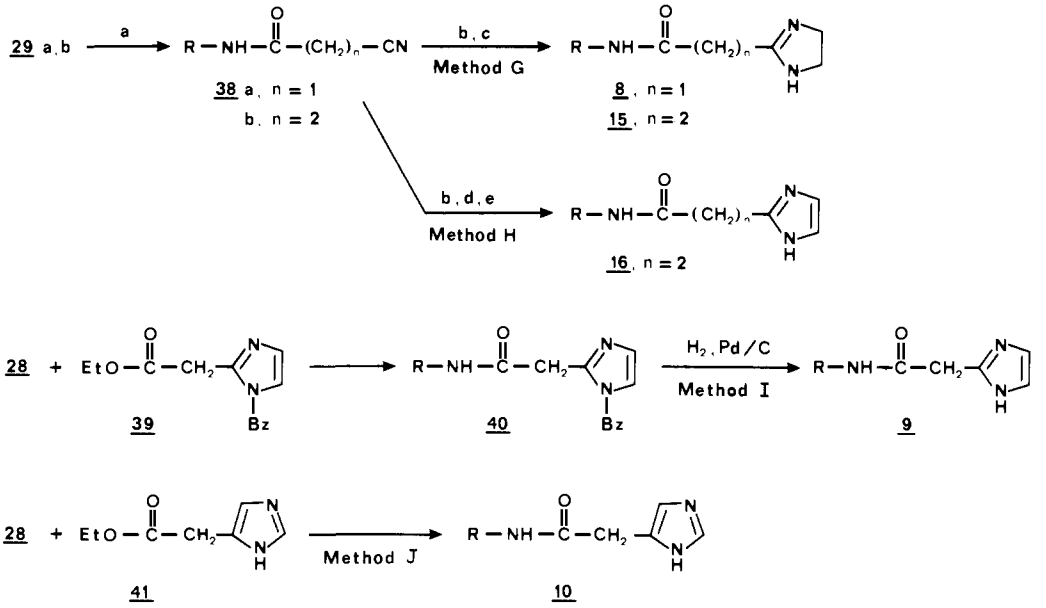
[a] For definition of R, see Scheme I. (a) $SOCl_2$; (b) aziridine, KOH; (c) 2-chloroethylamine hydrochloride, Et_3N; (d)

the piperidine analogue **24**. As before, the 4-substituted imidazole derivative, **21**, had a very low activity. In conclusion, several of the compounds in this study had interesting α-adrenolytic activities, of the same order as perhexiline. As previously indicated, the undesirable effects of perhexiline might be related to slow metabolism and accumulation. As compounds **3**, **7**, and **23** show α-adrenolytic activities comparable to that of perhexiline, the question still remained to know whether these compounds are metabolized more actively than perhexiline.

In a previous work,[26] we have shown that perhexiline was not metabolized by rat liver microsomes. This result was in accordance with the accumulation of the molecule ob-

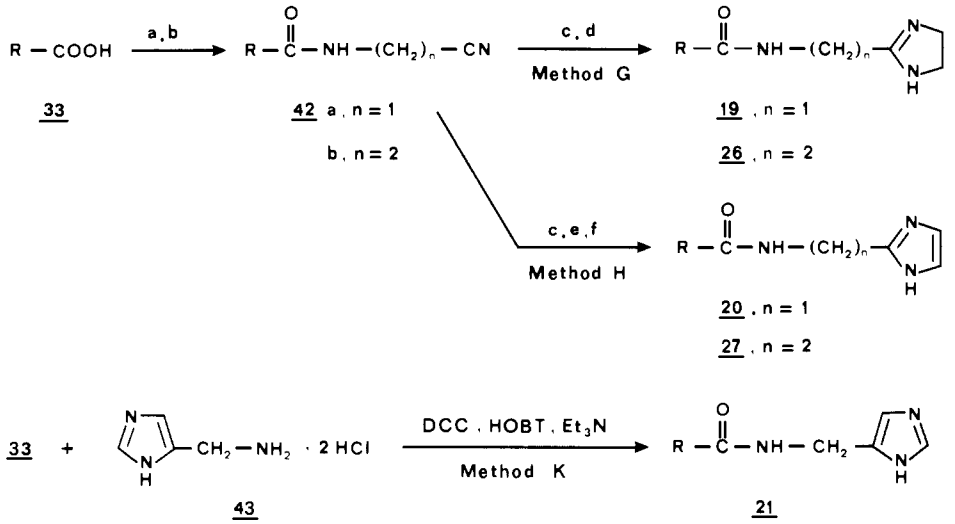
(26) Decolin, D.; Batt, A. M.; Ziegler, J. M.; Siest, G. *Biochem. Pharmacol.* **1986**, *55*, 2301.

Scheme V[a]



[a] For definition of R, see Scheme I. (a) NaCN; (b) EtOH, HCl; (c) $H_2NCH_2CH_2NH_2$; (d) $H_2NCH_2CH(OEt)_2$; (e) 2 N HCl.

Scheme VI[a]



[a] For definition of R, see Scheme I. (a) $SOCl_2$; (b) $H_2N(CH_2)_nCN$; (c) EtOH, HCl; (d) $H_2NCH_2CH_2NH_2$; (e) $H_2NCH_2CH(OEt)_2$; (f) 2 N HCl.

served in vivo. By contrast, among the three molecules tested, compounds **3** and **7**, but not **23**, are well metabolized by rat liver microsomes (Figure 1). This was confirmed by the kinetic parameters obtained for **3** (K_m = 6.7 × 10^{-5} M and V_{max} = 12.5 nmol of substrate metabolized min^{-1} (nmol of cytochrome P-450)$^{-1}$) and **7** (K_m = 5.2 × 10^{-5} M and V_{max} = 14.1 nmol of substrate metabolized min^{-1} (nmol of cytochrome P-450)$^{-1}$) (Figure 2). For these two molecules, the V_{max} values were in the same order as the value obtained for the most actively metabolized molecule in the previous series[9,27] (K_m = 21 × 10^{-5} M and V_{max} = 17 nmol of metabolized substrate min^{-1} (nmol of cytochrome P-450)$^{-1}$).

These results, combined with those obtained concerning the α-adrenolytic activity, allow us to propose the compounds **3** and **7** as possible good substitutes for perhexiline. The involvement of cytochrome P-450 to the metabolism of the molecules has been confirmed by the complete inhibition of their metabolism with 10^{-5} M of octylamine, which is a specific inhibitor of cytochrome P-450. In vitro and in vivo pharmacological investigations have been published.[27,28] Interestingly, these compounds were found to be very effective inhibitors (10^{-8} M range) of [^{3}H]batrachotoxinin binding[29] and might interact with sodium channels.

Experimental Section

Chemistry. Melting points were determined 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 R24 B spectrometer with Me_4Si as an internal standard. All spectra of compounds described here agreed with their assigned structures.

(27) Decker, N.; Grima, M.; Velly, J.; Marciniak, G.; Leclerc, G. *Arzneim.-Forsch.*, in press.

(28) Decker, N.; Grima, M.; Velly, J.; Marciniak, G.; Leclerc, G.; Schwartz, J. *Arzneim.-Forsch.*, in press.

(29) Velly, J.; Grima, M.; Marciniak, G.; Spach, M. O.; Schwartz, J. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1987**, *335*, 176.

Method A. *N*-(Cyclohexylphenylmethyl)-2-aminoacetamide (1). Compound **29a** (194 mg, 0.7 mmol) in 33% NH_4OH (10 mL) and EtOH (10 mL) was heated in a sealed tube at 60 °C for 24 h. After cooling, the solution was extracted twice with EtOAc (25 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness to give 160 mg (89%) of pure 1 as a white solid: NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 2.1 (s, 2 H, D_2O exchangeable), 3.3 (s, 2 H), 4.75 (t, J = 8 Hz, 1 H), 7.2 (s, 5 H), 7.7 (d, J = 9 Hz, 1 H); IR ($CHCl_3$) cm^{-1} 3400, 1675.

Method B. *N*-(Cyclohexylphenylmethyl)-2-cyclohexylaminoacetamide (2). Compound **29a** (2.5 g, 9.4 mmol) was heated at reflux for 3 h in cyclohexylamine (10 mL). The mixture was filtered and the precipitate washed with EtOAc. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel eluted with $CHCl_3$/MeOH 95:5 to give 2.61 g (84%) of pure **2**: NMR ($CDCl_3$) δ 0.7–2.2 (m, ~22 H), 1.5 (s, 1 H, D_2O exchangeable), 3.25 (s, 2 H), 4.8 (t, J = 8 Hz, 1 H), 7.2 (s, 5 H), 7.9 (d, J = 9 Hz, 1 H); IR ($CHCl_3$) cm^{-1} 3340, 1665.

Method C. *N*-(Cyclohexylphenylmethyl)-2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]acetamide (5). A mixture of **29a** (1.32 g, 4.96 mmol), Et_3N (0.55 g, 5.46 mmol), and (2,3-dihydro-1,4-benzodioxin-2-yl)methanamine[30] (0.82 g, 4.96 mmol) was heated under reflux for 24 h in benzene (20 mL). After cooling, the residue was filtered and the filtrate was evaporated to dryness to give a brown oil, which was purified by column chromatography on silica gel eluted with EtOAc to give 1.47 g (75%) of pure **5** as a pale yellow oil: NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 2.0 (s, 1 H, D_2O exchangeable), 2.85 (d, J = 7 Hz, 2 H), 3.3 (s, 2 H), 3.8–4.4 (m, 3 H), 4.75 (t, J = 8 Hz, 1 H), 6.85 (s, 4 H), 7.25 (s, 5 H), 7.6 (d, J = 9 Hz, 1 H); IR ($CHCl_3$) cm^{-1} 3360, 1660.

Method D. *N*-(2-Piperidinyl)-α-cyclohexylbenzeneacetamide (18). The hydrochloride salt of **34** (1 g, 3 mmol) in MeOH (30 mL) was hydrogenated with PtO_2 (0.15 g) on a Parr apparatus until the theoretical amount of H_2 had been taken up. The catalyst was removed by filtration and the filtrate was evaporated. A minimum amount of $CHCl_3$ was added to precipitate 0.45 g (44%) of **18**·HCl as a white solid: mp (hydrochloride) 213–215 °C (*i*-PrOH/*i*-Pr_2O).

Method E. *N*-[2-(Diethylamino)ethyl]-α-cyclohexylbenzeneacetamide (22). Acylaziridine **35** (1 g, 4.1 mmol) in acetone (10 mL) was reacted under reflux for 15 h with 0.3 g (4.1 mmol) of diethylamine. The solvent was evaporated and the residue was chromatographed on silica gel, eluted with hexane/EtOAc/Et_3N 60:35:5 to give 1.16 g (90%) of pure **22**: mp (base) 90 °C (petroleum ether) (lit.[31] mp (base) 84–86 °C).

Method E′. *N*-[2-(Cyclohexylamino)ethyl]-α-cyclohexylbenzeneacetamide (23). Acylaziridine **35** (0.26 g, 1.06 mmol) in cyclohexylamine (1 mL) was heated at 100 °C for 24 h. The excess amine was removed in reduced pressure and the resulting residue was chromatographed on silica gel, eluted with EtOAc/Et_3N 95:5 to give 0.35 g (96%) of pure **23**, as a beige solid: NMR ($CDCl_3$) δ 0.7–2.2 (m, 22 H), 1.4 (s, 1 H, D_2O exchangeable), 2.7 (t, J = 5.5 Hz, 2 H), 2.95 (d, J = 10 Hz, 1 H), 3.2 (t, J = 5.5 Hz, 2 H), 6.15 (br s, 1 H), 7.25 (s, 5 H); IR ($CHCl_3$) cm^{-1} 3450, 1665. When cyclohexylamine was reacted with an equivalent amount of **35** in toluene (100 °C, 24 h), the *N*,*N*-bis[2-(2-cyclohexyl-2-phenylacetamido)ethyl]cyclohexylamine (**36**) was the major product obtained (56% yield): mp 169–171 °C (hexane/toluene); NMR ($CDCl_3$) δ 0.7–2.2 (m, ~33 H), 2.5 (t, J = 5 Hz, 4 H), 2.95–3.2 (m, 6 H), 6.3 (br s, 2 H), 7.2 (s, 10 H); IR ($CHCl_3$) cm^{-1} 3430, 3290, 1640.

Method F. Compound **23** could be also prepared in 47% yield by heating **37** (3.5 mmol) with cyclohexylamine (5 mL) at 90 °C for 3 h.

Method G. *N*-(Cyclohexylphenylmethyl)-2-(4,5-dihydro-1*H*-imidazol-2-yl)acetamide (8). A mixture of **38a** (1 g, 3.9 mmol) and absolute ethanol (0.72 g, 15.6 mmol) in anhydrous ether (10 mL) was saturated with HCl gas at 0 °C. The reaction flask was tightly stoppered and stored in a refrigerator for 48 h. The solvent was evaporated to dryness at 20 °C to give the corresponding crude imidate hydrochloride, which was dissolved, without purification, in absolute ethanol (10 mL) and treated at 0 °C with ethylenediamine (0.234 g, 3.9 mmol). The solution was stirred for 1 h at that temperature and for 2 h at room temperature and then filtered. The filtrate was evaporated and the residue was dissolved in 1 N HCl. The acidic phase was extracted with EtOAc and the organic phase was discarded. Solid K_2CO_3 was added until pH ~9 and the aqueous phase was thoroughly extracted with $CHCl_3$. After drying ($MgSO_4$) and evaporation of the solvent, 1 g (85%) of **8** was obtained as a beige solid: NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 3.1 (br s, 2 H), 3.5 (s, 4 H), 4.65 (t, J = 8 Hz, 1 H), 5.1 (br s, 1 H, D_2O exchangeable), 7.1 (s, 5 H), 8.75 (d, J = 9 Hz, 1 H); IR ($CHCl_3$) cm^{-1} 3440, 3310, 1655.

Method H. *N*-[(1*H*-Imidazol-2-yl)methyl]-α-cyclohexylbenzeneacetamide (20). Nitrile **42a** (2 g, 7.8 mmol) was transformed to its imidate hydrochloride as described in method G. A mixture of the crude imidate, 1.35 g (10.1 mmol) of aminoacetaldehyde diethyl acetal, and EtOH (15 mL) was heated at reflux for 18 h. Evaporation of the solvent gave an oil, which was mixed with 2 N HCl (30 mL) and heated at 60 °C for 24 h. The mixture was extracted with EtOAc. The aqueous layer was basified with solid K_2CO_3 and thoroughly extracted with $CHCl_3$. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 1.67 g (72%) as a beige solid: NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 3.2 (d, J = 10 Hz, 1 H), 4.25 (s, 2 H), 6.8 (s, 2 H), 7.2 (s, 5 H), 9.2 (br s, 1 H), 10.0 (s, 1 H, D_2O exchangeable); IR ($CHCl_3$) cm^{-1} 3460, 3300, 1660.

Method I. *N*-(Cyclohexylphenylmethyl)-2-(1*H*-imidazol-2-yl)acetamide (9). The benzyl derivative **40** (2.36 g, 6.1 mmol) was hydrogenated under 440 psi in EtOH (50 mL) with palladium–charcoal (10%) catalyst (0.3 g) at 50 °C for 24 h. After removal of the catalyst, the solvent was evaporated and the residue was purified on silica gel, eluted with EtOAc/Et_3N 95:5, giving 1.13 g (63%) of **9** as a white solid: NMR ($CDCl_3$/DMSO) δ 0.7–2.2 (m, 11 H), 3.65 (s, 2 H), 4.7 (t, J = 8 Hz, 1 H), 6.9 (s, 2 H), 7.2 (s, 5 H), 8.6 (d, J = 9 Hz, 1 H) (imidazole NH not visible); IR ($CHCl_3$) cm^{-1} 3420, 3270, 1660.

Method J. *N*-(Cyclohexylphenylmethyl)-2-(1*H*-imidazol-4-yl)acetamide (10). Amine **28** (0.74 g, 3.9 mmol) and 4-imidazoleacetic acid ethyl ester (41)[20] (0.6 g, 3.9 mmol) were heated at 190 °C for 24 h in a sealed tube. After cooling, the resulting brown solid was purified on silica gel, eluting with EtOAc/Et_3N 95:5 to give 0.88 g (76%) of pure **10**: NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 3.55 (s, 2 H), 4.75 (t, J = 8 Hz, 1 H), 6.8 (s, 1 H), 7.2 (s, 5 H), 7.55 (s, 1 H), 7.95 (d, J = 9 Hz, 1 H), 10.15 (s, 1 H); IR ($CHCl_3$) cm^{-1} 3490, 3300, 1670.

Method K. *N*-[(1*H*-Imidazol-4-yl)methyl]-α-cyclohexylbenzeneacetamide (21). A mixture of **33** (1.93 g, 8.82 mmol), 4-(aminomethyl)imidazole dihydrochloride[21] (1.5 g, 8.82 mmol), 1-hydroxybenzotriazole hydrate (2.39 g, 17.64 mmol), and THF (30 mL) was neutralized with Et_3N (1.79 g, 17.64 mmol), treated at 0 °C with 2 g (9.7 mmol) of dicyclohexylcarbodiimide, and stirred at room temperature for 48 h. The mixture was filtered, and the filtrate was evaporated to dryness. The crude product was chromatographed over silica gel with EtOAc/MeOH/Et_3N 85:10:5 as eluent to give 0.9 g (33%) of **21**: NMR ($CDCl_3$/DMSO) δ 0.7–2.2 (m, 11 H), 3.2 (d, J = 10 Hz, 1 H), 4.25 (br s, 2 H), 6.7 (s, 1 H), 7.3–7.6 (m, 5 H), 8.0–8.3 (br s, 3 H, two D_2O exchangeable); IR ($CHCl_3$) cm^{-1} 3440, 3360, 1660.

α-Cyclohexylbenzenemethanamine (28) was synthesized in an overall 74% yield from cyclohexyl phenyl ketone with a procedure similar to that described earlier:[32] bp 100 °C (0.5 mmHg) (lit.[25] bp 140 °C (10 mmHg)).

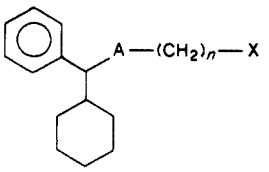
General Procedure for the Preparation of *N*-(Cyclohexylphenylmethyl)chloroalkanamides 29a–c. To a vigorously stirred solution of **28** (10 mmol) and Et_3N (11 mmol) in Et_2O (50 mL) cooled at 0 °C was added dropwise chloroalkanoyl chloride (10 mmol) dissolved in Et_2O (10 mL). The mixture was left for 1 h at 0 °C and for 2 h at room temperature. The suspension was filtered and washed with water. The resulting solid was oven dried at 60 °C and recrystallized from an appropriate solvent to give *N*-(cyclohexylphenylmethyl)-2-chloroacetamide (**29a**) [yield 94%, mp 139–141 °C (*i*-PrOH) (lit.[33] mp 155–156 °C)], *N*-(cy-

(30) Augstein, J.; Green, S. M.; Monro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965**, *8*, 446.

(31) *Chem. Abstr.* **1955**, *43*, 3453*f*, Swiss Pat. 227, 885.

(32) Mousseron, M.; Froger, P. *Bull. Chim. Soc. Fr.* **1947**, 843.

Table I



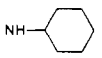
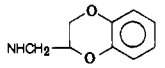
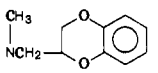
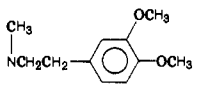
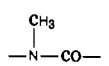
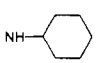
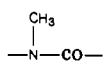
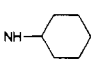
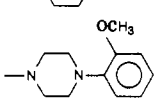
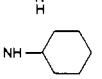
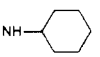
compd	A	n	X	method	% yield[a]	mp, °C	recrystn solvent	formula[b]	α-adrenolytic act. in rat aorta: pA_2[c]
1	NHCO	1	NH_2	A	89	219–221	CH_3CN/MeOH	$C_{15}H_{22}N_2O \cdot C_4H_4O_4$[d]	4.5[e] (3)
2	NHCO	1		B	84	197–199	CH_3CN	$C_{21}H_{32}N_2O \cdot HNO_3$	6.5[e] (10)
3	NHCO	1		B	65	151–153	EtOAc	$C_{22}H_{34}N_2O \cdot C_4H_4O_4$	6.7 ± 0.2 (7)
4	NHCO	1	$N(CH_2CH_3)_2$	B	76	110–112[f]	EtOAc/Et_2O	$C_{19}H_{30}N_2O \cdot HNO_3$	6.0 ± 0.3 (8)
5	NHCO	1		C	75	133–135	EtOAc	$C_{24}H_{30}N_2O_3 \cdot C_4H_4O_4$	6.0 ± 0.2 (6)
6	NHCO	1		C	65	146–148	CH_3CN	$C_{25}H_{32}N_2O_3 \cdot C_2H_2O_4$[g]	6.15 ± 0.2 (8)
7	NHCO	1		C	82	155–157	CH_3CN	$C_{26}H_{36}N_2O_3 \cdot C_2H_2O_4$	6.5 ± 0.6 (5)
8	NHCO	1		G	85	238–240	CH_3CN/MeOH	$C_{18}H_{25}N_3O \cdot C_2H_2O_4$	5.8 ± 0.2 (7)
9	NHCO	1		I	63	240–242	MeOH	$C_{18}H_{23}N_3O \cdot C_2H_2O_4$	5.9 ± 0.1 (6)
10	NHCO	1		J	76	186–188	CH_3CN	$C_{19}H_{23}N_3O \cdot C_4H_4O_4$	5.3 ± 0.1 (11)
11		1		B	49	202–204	EtOAc/MeOH	$C_{22}H_{34}N_2O \cdot C_4H_4O_4$	5.3[e] (5)
12		1		B	62	148–150	EtOAc/Et_2O	$C_{23}H_{36}N_2O \cdot C_4H_4O_4$	4.5[e]
13	NHCO	2		B	59	197–199	CH_3CN	$C_{22}H_{34}N_2O \cdot HNO_3$	6.1 ± 0.1 (7)
14	NHCO	2		C	67	160–162	EtOAc/MeOH	$C_{27}H_{37}N_3O_2 \cdot C_4H_4O_4$	6.0[h] (8)
15	NHCO	2		G	75	167–169	CH_3CN/MeOH	$C_{19}H_{27}N_3O \cdot C_2H_2O_4$	5.4 ± 0.1 (4)
16	NHCO	2		H	15	138–143	CH_3CN	$C_{19}H_{25}N_3O \cdot C_2H_2O_4$	4.2[h] (10)
17	NHCO	3		B	82	>250	CH_3CN	$C_{23}H_{36}N_2O \cdot HNO_3$	5.8[e] (2)
18	CONH	0		D	44	213–215	*i*-PrOH/*i*-Pr_2O	$C_{19}H_{28}N_2O \cdot HCl$	5.5[e] (2)
19	CONH	1		G	85	200–202	EtOH/*i*-Pr_2O	$C_{18}H_{25}N_3O \cdot HCl$	6.1 ± 0.1 (6)
20	CONH	1		H	72	191–193	CH_3CN/MeOH	$C_{18}H_{23}N_3O \cdot C_2H_2O_4$	5.2[e] (4)
21	CONH	1		K	34	159–161	CH_3CN	$C_{18}H_{23}N_3O \cdot C_4H_4O_4$	4.1[h] (5)
22	CONH	2	$N(CH_2CH_3)_2$	E, F	90[i]	189–191[i]	EtOH/Et_2O	$C_{20}H_{32}N_2O \cdot HCl$	5.4 ± 0.3 (6)
23	CONH	2		E′, F	96[k]	179–181	CH_3CN	$C_{22}H_{34}N_2O \cdot HNO_3$	6.6 ± 0.2 (6)
24	CONH	2		E, F	70[i]	212–214	CH_3CN	$C_{21}H_{32}N_2O \cdot C_2H_2O_4$	6.0 ± 0.1 (5)

Table I (Continued)

compd	A	n	X	method	% yield[a]	mp, °C	recrystn solvent	formula[b]	α-adrenolytic act. in rat aorta: pA_2[c]
25	CONH	2		E, F	72[i]	192–194[j]	EtOH/Et_2O	$C_{20}H_{30}N_2O_2 \cdot C_2H_2O_4$	4.5[e] (2)
26	CONH	2		G	69	139–141	CH_3CN/MeOH	$C_{19}H_{27}N_3O \cdot C_2H_2O_4 \cdot {}^1/_2H_2O$	5.7 ± 0.2 (7)
27	CONH	2		H	32	138–140	CH_3CN/MeOH	$C_{19}H_{25}N_3O \cdot C_2H_2O_4$	5.4 ± 0.2 (6)
perhexiline									6.7[h] (2)

[a] Yield of the last step. [b] All compounds were analyzed for C, H, and N and analyses were within ±0.4% of theoretical values. [c] pA_2 ± SD, with the number of experiments in parentheses; the Schild plot slopes were not significantly different from 1. [d] $C_4H_4O_4$: hydrogen maleate. [e] Graphical estimation of pA_2. [f] Literature[30] mp base 94–95 °C. [g] $C_2H_2O_4$: hydrogen oxalate. [h] pAH, indicating noncompetitive antagonism. [i] Yield with method E. [j] Literature[31] mp 169–171 °C. [k] Yield with method E'. [l] Mp base 153–155 °C (EtOH/Et_2O) (lit.[37] mp 152–153 °C).

clohexylphenylmethyl)-3-chloropropanamide (**29b**) [yield 88%, mp 159–161 °C (CH_3CN)], and *N*-(cyclohexylphenylmethyl)-4-chlorobutanamide (**29c**) [yield 53%, mp 99–101 °C (cyclohexane)].

***N*-Methyl-α-cyclohexylbenzenemethanamine (31).** To a solution of ketone **30** (15.1 g, 80 mmol) in MeOH (80 mL) was added portionwise $NaBH_4$ (3 g). The mixture was stirred for 3 h at room temperature. Water (50 mL) was added and the methanol was evaporated. The aqueous phase was extracted three times with Et_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated to give an oil. The crude alcohol in CCl_4 (50 mL) was treated slowly with PBr_3 (8.15 mL). After 2 h at reflux, water was added. The aqueous phase was discarded and the organic phase was washed with 0.1 N NaOH and H_2O, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 19.9 g of the crude bromo derivative, which was reacted without purification with methylamine (10 mL) in a steel bomb at 120 °C for 8 h. After cooling, excess methylamine was removed, Et_2O was added, and HCl gas was bubbled through to give 6.1 g of **31** as the HCl salt. The yield from ketone **30** was 67%; mp (hydrochloride) 259–261 °C (CH_3CN) (lit.[34] bp 158 °C (23 mmHg)).

***N*-Methyl-*N*-(cyclohexylphenylmethyl)-2-chloroacetamide (32)** was obtained from **31** as described for **29a**: yield 90%; mp 80–82 °C (hexane); NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 2.75 (s, 3 H), 4.0 (s, 2 H), 5.5 (d, J = 10 Hz, 1 H), 7.25 (s, 5 H); IR ($CHCl_3$) cm^{-1} 1635.

***N*-(2-Pyridyl)-α-cyclohexylbenzeneacetamide (34).** Thionyl chloride (4 mL) was added to a stirred suspension of α-cyclohexylbenzeneacetic acid (**33**) (5 g, 23 mmol) in benzene (100 mL). The mixture was heated for 3 h at 70 °C. The solvent was evaporated to dryness to give the corresponding crude acid chloride, **33**, which was added dropwise to a cooled solution of 2-aminopyridine (2 g, 23 mmol) dissolved in pyridine (10 mL). The mixture was heated for 2 h at 70 °C, cooled, and evaporated to dryness. The residue was taken up in EtOAc and washed three times with H_2O. After drying and evaporation of the solvent, the residue was purified on silica gel, eluting with hexane/EtOAc 80:20 to give 5.61 g (83%) of pure **34** as a white solid: mp 151–152 °C (MeOH/H_2O), mp (hydrochloride) 136–146 °C.

***N*-(2-Cyclohexyl-2-phenylacetyl)aziridine (35).** Compound **35** was prepared from commercial acid **33** as previously reported.[35] The crude product was chromatographed on silica gel with hexane/EtOAc 90:10 as eluent to give **35** in a 72% yield, as a while solid: mp 71–73 °C (EtOH/H_2O); NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 2.1 (s, 4 H), 3.4 (d, J = 10 Hz, 1 H), 7.25 (s, 5 H); IR ($CHCl_3$) cm^{-1} 1685.

***N*-(2-Chloroethyl)-α-cyclohexylbenzeneacetamide (37).** To a cooled mixture of 2-chloroethylamine hydrochloride (2.92 g, 25.2 mmol), NaOH (1 g, 25.2 mmol) in water (20 mL), and CH_2Cl_2 (30 mL) were added simultaneously NaOH (0.92 g, 23 mmol) in water (10 mL) and acid chloride **33** (23 mmol). Once addition was completed, the mixture was stirred for 2 h at room temperature and poured into CH_2Cl_2 (50 mL). The organic phase was washed twice with 1 N NaOH, water, and brine and then dried ($MgSO_4$) and evaporated to give 6 g (93%) of pure product as a white solid. A sample was recrystallized from cyclohexane: mp 129–131 °C; NMR ($CDCl_3$) δ 0.7–2.2 (m, 11 H), 3.0 (d, J = 10 Hz, 1 H), 3.5 (s, 4 H), 6.3 (br s, 1 H), 7.25 (s, 5 H); IR ($CHCl_3$) cm^{-1} 3460, 1680.

General Procedure for the Preparation of the *N*-(Cyclohexylphenylmethyl)cyanoalkanamide Derivatives 38a and 38b. A mixture of **29a** or **29b** (10 mmol) and NaCN (50 mmol) was heated in DMSO (10 mL) at 60 °C for 48 h. The reaction mixture was poured into water and filtered to give *N*-(cyclohexylphenylmethyl)-2-cyanoacetamide (**38a**) [yield 70%, mp 114–116 °C (benzene)] and *N*-(cyclohexylphenylmethyl)-3-cyanopropanamide (**38b**) [yield 87% mp 167–169 °C (benzene)].

***N*-Benzyl-2-imidazoleacetic Acid Ethyl Ester (39).** A solution of *N*-benzyl-2-(cyanomethyl)imidazole[19] (2 g, 10.1 mmol) in 95% EtOH (30 mL) previously saturated with HCl was heated at reflux for 2 h. After cooling, the solvent was evaporated to dryness. The residue was recrystallized from CH_3CN to give 2.54 g (89%) of pure **39** hydrochloride as pale yellow crystals: mp 176–178 °C (lit.[36] mp 176–177 °C).

***N*-(Cyclohexylphenylmethyl)-2-(*N*-benzylimidazol-2-yl)acetamide (40).** Amine **28** (1.55 g, 8.2 mmol) and *N*-benzyl-2-imidazoleacetic acid ethyl ester (**39**) (2 g, 8.2 mmol) were heated at 190 °C for 24 h in a sealed tube. After cooling, the resulting brown solid was purified on silica gel, eluting with EtOAc/Et_3N 95:5 to give 2.83 g (89%) of pure **40**: mp (hydrogen oxalate) 204–206 °C (EtOH).

General Procedure for the Preparation of the *N*-(Cyanoalkyl)-α-cyclohexylbenzeneacetamide Derivatives 42a and 42b. The acid chloride of **33** (23 mmol) and NaOH (23 mmol) in water (10 mL) were added simultaneously to a well-stirred solution of aminoacetonitrile sulfate or aminopropionitrile fumarate and NaOH (25 mmol) in H_2O (30 mL). After 2 h at room temperature, the mixture was filtered, washed with water, and dried to give *N*-(cyanomethyl)-α-cyclohexylbenzeneacetamide (**42a**) [yield 44%, mp 162–164 °C (EtOH/H_2O)] and *N*-(2-cyanoethyl)-α-cyclohexylbenzeneacetamide (**42b**) [yield 73%, mp 181–183 °C (EtOH/H_2O)].

Biological and Pharmacological Methods. 1. In Vitro Metabolism Study. This study was carried out with compounds **3**, **7**, and **23**. The molecules were incubated with rat liver microsomes, extracted, and analyzed by HPLC to examine their metabolism. After the incubation time and the quantity of cytochrome P-450 were determined, the kinetic parameters (apparent K_m and V_{max}) were determined.

The microsomal liver fractions from phenobarbital-pretreated male sprague–Dawley rats (180–200 g) [phenobarbital was administered intraperitoneally (80 mg/kg) for 5 days] were prepared by differential centrifugation according to the method of Beaufay et al.[38] The buffer consisted of phosphate (100 mM), DTT (1

(33) Lindberg, U. H.; Nylen, B.; Akerman, B. *Acta Pharm. Suecica* **1968**, *5*, 429.
(34) Cervinka, O.; Fusek, J. *Collect. Czech. Chem. Commun.* **1973**, *38*, 441.
(35) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202.
(36) Macco, A. A.; Godefroi, E. F.; Drouen, J. J. M. *J. Org. Chem.* **1975**, *40*, 252.
(37) Cheney, L. C.; Bywater, W. G. *J. Am. Chem. Soc.* **1942**, *64*, 970.

mM), EDTA (1 mM), glycerol (20%) (v/v).

Apparent K_m and V_m for Hydroxylation. The incubations (2 mL) contained substrates at concentrations varying from 5×10^{-6} to 8×10^{-5} M, microsomal suspension equivalent to 1.65 nmol of cytochrome P-450 in buffer for **3** and 1 nmol of cytochrome P-450 in buffer for **7**, and a NADPH generating system (NAD, 0.5 mM; NADP, 0.42 mM; glucose 6-phosphate, 3.2 mM; Glucose-6-phosphate dehydrogenase, 175 units/L; $MgCl_2$, 5.5 mM; and Tris·HCl buffer, 5.5 mM, pH 7.4). The incubations were run in duplicate and were started by the introduction of microsomes, incubated by shaking at 37 °C for 7 min for both **3** and **7**, and stopped by the addition of 500 μL of 0.6 N HCl.

The molecules were extracted in two steps. In the first step, 5 mL of cyclohexane was added to the incubation mixture. The tubes were shaken for 10 min and centrifuged at 3000 rpm for 5 min. The organic layer was discarded. The aqueous layer was then alkalinized by adding 1 mL of NaOH (pH >11) and extracted twice with 5 mL of diethyl ether. After 10 min of shaking and 5 min of centrifuging, the diethyl ether was collected and evaporated to dryness in a Rotavapor (Büchi) at 40 °C. The dried residue was extracted twice with 0.6 mL of methanol and transferred into vials (1.5 mL). Methanol was evaporated under nitrogen in a sand bath (40 °C). Then 100 μL of mobile phase was added and 20 μL was injected into the HPLC system.

Chromatographic Conditions. The HPLC system consisted of a LKB 2150 solvent delivery pump (LKB, Bromma, Sweden), an injection valve with a 20-μL sample loop (Model 7125 Rheodyne, Cotati, CA) and a UV–visible detector operating at 254 nm (0.08 AUFS) (Merck, LMC System SM 25).

The mobile phase was 10^{-2} M KH_2PO_4 (pH 3)–acetonitrile (20:80 v/v for **3** and 25:75 v/v for **7**). It was filtered through an HVLP 0.6-μm microfilter (Millipore, Bedford, MA) and pumped at 1.0 mL/min through a reversed-phase column (room temperature) prepacked with Superspher 100 RP-18 e (Lichrocart 250-4, 5 μm; Merck, Darmstadt, FRG).

2. α-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.[39] 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 (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, Na_2EDTA 0.006. The strips 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 norepinephrine (10^{-10}–10^{-7} M) were established before and after addition of the antagonist. Preincubation time with the antagonist was 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.

The α-adrenergic blocking activity was expressed in terms of pA_2 for competitive antagonists according to Arunlakshana and Schild.[40] When the antagonism was not competitive, it was expressed as pAH (–log of the molar concentration of antagonist that inhibits 50% of the maximal effect of the agonist) according to Ariens and Van Rossum.[41]

Acknowledgment. We thank the "Conseil Régional de la Région Alsace" for financial support to purchase the HPLC equipment.

Registry No. 1, 116210-74-3; 1·$C_4H_4O_4$, 116210-74-3; **2**, 114043-40-2; 2·HNO_3, 116211-03-1; **3**, 116210-75-4; 3·$C_4H_4O_4$, 116211-04-2; 4, 19893-59-5; 4·HNO_3, 116211-05-3; **5**, 116210-76-5; 5·$C_4H_4O_4$, 116211-06-4; **6**, 114043-44-6; 6·$C_2H_2O_4$, 116211-07-5; **7**, 114043-43-5; 7·$C_2H_2O_4$, 116211-08-6; **8**, 116210-77-6; 8·$C_2H_2O_4$, 116211-09-7; **9**, 116210-78-7; 9·$C_2H_2O_4$, 116211-10-0; **10**, 116210-79-8; 10·$C_4H_4O_4$, 116211-11-1; **11p**, 116210-80-1; 11·$C_4H_4O_4$, 116211-12-2; **12**, 116210-81-2; 12·$C_4H_4O_4$, 116211-13-3; **13**, 114043-41-3; 13·HNO_3, 116211-14-4; 14, 110101-64-9; 14·$C_4H_4O_4$, 116211-15-5; **15**, 116210-82-3; 15·$C_2H_2O_4$, 116211-16-6; **16**, 116210-83-4; 16·$C_2H_2O_4$, 116211-17-7; **17**, 114043-42-4; 17·HNO_3, 116211-18-8; **18**, 116210-84-5; 18·HCl, 116211-19-9; **19**, 116210-85-6; 19·HCl, 116211-20-2; **20**, 116210-86-7; 20·$C_2H_2O_4$, 116211-21-3; **21**, 116210-87-8; 21·$C_4H_4O_4$, 116211-22-4; **22**, 110248-72-1; 22·HCl, 116211-23-5; **23**, 116210-88-9; 23·HNO_3, 116211-24-6; **24**, 116210-89-0; 24·$C_2H_2O_4$, 116211-25-7; **25**, 116210-90-3; 25·$C_2H_2O_4$, 116211-26-8; **26**, 114043-45-7; 26·$C_2H_2O_4$, 116211-27-9; **27**, 116210-91-4; 27·$C_2H_2O_4$, 116211-28-0; **28**, 23459-35-0; **29a**, 23459-41-8; **29b**, 116211-01-9; **29c**, 112063-68-0; **30**, 712-50-5; 31·HCl, 6276-67-1; **32**, 116210-92-5; **33**, 3894-09-5; **33** (acid chloride), 49802-71-3; **34**, 116211-31-5; 34·HCl, 116210-93-6; **35**, 116210-94-7; **36**, 116210-95-8; **37**, 116210-96-9; **38a**, 116210-97-0; **38b**, 116211-29-1; **39**, 116211-32-6; 39·HCl, 52855-69-3; **40**, 116210-98-1; 40·$C_2H_2O_4$, 116211-33-7; 41, 28782-45-8; **42a**, 116210-99-2; **42b**, 116211-00-8; **43**, 72631-80-2; $(CH_3CH_2)_2NA$, 109-89-7; 3,4-$(OCH_3)_2C_6H_3(CH_2NHCH_3$, 3490-06-0; $H_2N(CH_2)_2$-NH_2, 107-15-3; $H_2NCH_2CH(OEt)_2$, 645-36-3; $ClCH_2COCl$, 79-04-9; $Cl(CH_2)_2COCl$, 625-36-5; $Cl(CH_2)_3COCl$, 4635-59-0; ROH, 945-49-3; RBr, 116211-30-4; $Cl(CH_2)_2NH_2$·HCl, 870-24-6; $H_2NCH_2CN \cdot Y_2$-H_2SO_4, 5466-22-8; $H_2N(CH_2)_2CN$·fumarate, 1119-28-4; cyclohexylamine, 108-91-8; *N*-methylcyclohexylamine, 100-60-7; 2,3-dihydro-1,4-benzodioxin-2-methanamine, 4442-59-5; 2,3-dihydro-*N*-methyl-1,4-benzodioxin-2-methanamine, 2242-31-1; 1-(2-methoxyphenyl)piperazine, 35386-24-4; piperidine, 110-89-4; 2-aminopyridine, 504-29-0; *N*-benzyl-2-(cyanomethyl)imidazole, 21125-22-4; morpholine, 110-91-8.

(38) Beaufay, H.; Amar-Lostesee, A.; Feytmans, E.; Thines-Sempoux, D.; Wibo, M.; Robi, M.; Berthet, J. *J. Cell. Biol.* **1974**, *61*, 201.
(39) Liebau, H.; Distler, A.; Wolff, H. P. *Klin. Wochenschr.* **1966**, *44*, 322.
(40) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *8*, 27.
(41) Ariens, E. J.; Van Rossum, J. M. *Arch. Int. Pharmacodyn. Ther.* **1957**, *110*, 275.