Synthesis and Cardiovascular Activity of a New Series of Cyclohexylaralkylamine Derivatives Related to Perhexiline

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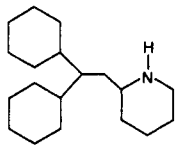
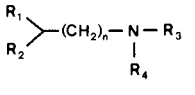
A series of 24 cyclohexylaralkylamine derivatives related to perhexiline has been synthesized and screened for cardiovascular activity. All the compounds contained an exocyclic amine which was substituted either by an alkyl, cycloalkyl, or aralkyl group. In the hope of further reducing toxicity, the synthesis of *p*-tolyl- and *p*-hydroxyphenyl derivatives **23** and **24** was undertaken. The effect of separating the cyclohexylamine moiety with respect to the aromatic nucleus has been systematically examined. The pharmacological investigations were directed to a search for compounds having an activity better than perhexiline according to the following order of criteria: (1) α-adrenolytic activity; (2) increase of coronary blood flow; (3) calcium antagonism. Several compounds were more potent and exhibited lower toxicity than perhexiline. Further detailed pharmacological investigations (tension time index and decreased cardiac work) have led to the selection of *N*,2-dicyclohexyl-2-phenethylamine (**3**) for clinical trials, which are now under way.

Effective antianginal drugs are still needed owing to the ever increasing number of patients suffering from heart diseases. Perhexiline maleate [Pexid, 1,1-dicyclohexyl-2-(2-piperidyl)ethane (I)],[1] recently introduced in the market in Europe, has proven to be very effective in the treatment of angina pectoris,[2-4] although its mechanism of action remains unknown.



I. Perhexiline



II. n = 0-4

However, it is of somewhat limited interest because of the hepatotoxicity,[5] weight loss,[6] and peripheral neuropathy[7] which it induces. Singlas et al.[8] proposed that patients developing peripheral neuropathy metabolize the drug more slowly than those patients who do not show this side effect. In the hope of reducing the serious adverse effects of perhexiline, we thought that it would be of interest to examine the activity of compounds of general formula II in which the secondary amine group is "exocyclic". In the light of the work of Singlas, we have also examined the influence of introducing an aromatic ring (R_1, R_2, R_3, or R_4 = aryl) on the biological activity. In this article, we describe the synthesis of 24 derivatives of general formula II and some of their cardiovascular properties.

Chemistry. Compounds of type A (general formula II, $n = 1$) were prepared according to Scheme I, which involves as a main step the reduction of an amide intermediate with BH_3/Me_2S. The hydrogenation of the aromatic nucleus of **3** at 60 °C under 50 atm during 4 days led to **4** in 45% yield.

Compounds of type B (general formula II, $n = 2$), which possess a 3,3-dicyclohexylpropylamine moiety, were prepared from 3,3-diphenylpropionic acid (Scheme II). Catalytic hydrogenation of the carefully purified starting acid using a rhodium catalyst under 50 atm led to 3,3-dicyclohexylpropionic acid, which was then converted to the amine B. Compound **15** was also synthesized from diphenylpropionic acid by careful reduction using a larger excess of PtO_2. The intermediate acid was then transformed into **15** as above.

Methylation of **10** via the Eschweiler–Clarke reaction gave the *N*-methyl derivative **11**. We also prepared (Scheme III) derivatives **16–19** containing the adamantyl group, which could be considered as an analogue of the dicyclohexyl moiety of perhexiline.

To obtain **20** (formula II, $n = 0$) required a different procedure. Dicyclohexyl ketone was condensed with cyclohexylamine in the presence of $TiCl_4$. The resulting imine was then reduced under atmospheric pressure to give **20** in 38% yield. The *N*,4,4-tricyclohexylbutylamine **21** (formula II, $n = 3$) was prepared from 3,3-dicyclohexylpropionic acid using the Arndt–Eistert reaction (Scheme IV).

The isolated diazo ketone was heated with cyclohexylamine in the presence of $AgNO_3$ to afford the expected amide. This was finally reduced by $LiAlH_4$/THF in **21**. The higher homologue derivative **22** (formula II, $n = 4$) was prepared as illustrated in Scheme V, which involves a malonate alkylation as the main step. The 5,5-diphenylpentanoic acid obtained after saponification of the diester intermediate gave **22** in an overall yield of 28%.

Of interest in this study of structure–activity relationships[9] was the 4-OH derivative **23** and the 4-Me derivative **24**. The synthesis of the 4-OH derivative **23** is shown in Scheme VI. Nitration of the commercially available 2-phenyl-2-cyclohexylacetic acid in concentrated H_2SO_4 between −10 and 0 °C afforded, after recrystallization from C_6H_{14}–CCl_4, the pure *p*-NO_2 derivative in 55% yield. Catalytic reduction of the NO_2 group, followed by diazotization and decomposition of the diazonium salt in boiling dilute sulfuric acid, led to the phenol derivative. This was followed by the esterification of the acid fraction prior to the benzylation of the phenol group. After saponification, the resulting acid was heated as described previously to

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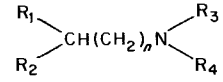
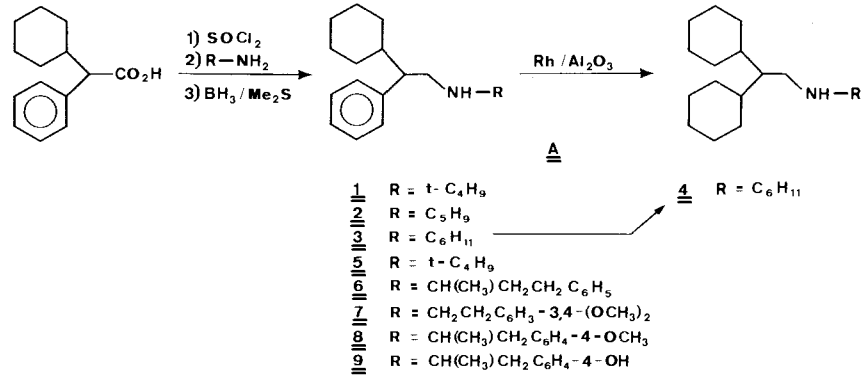
Table I. Physical Properties of Aralkylamine Derivatives



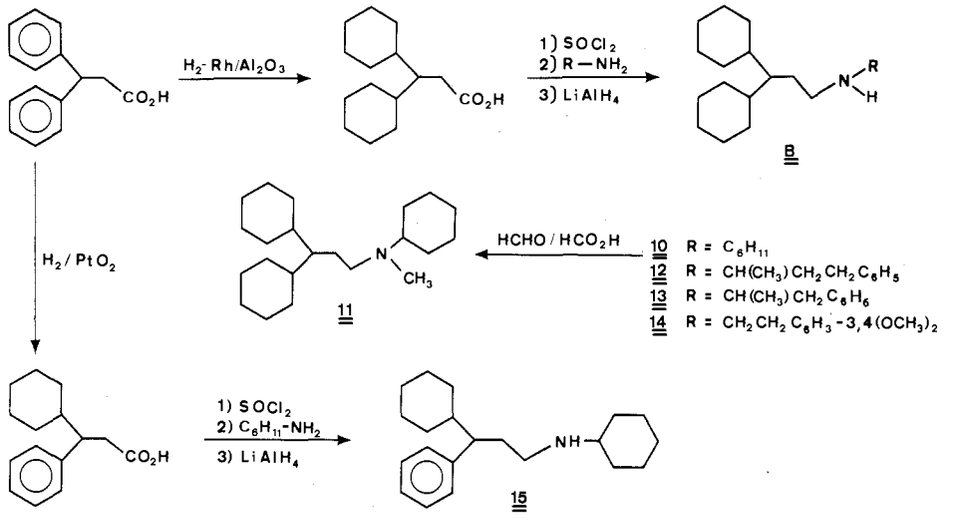
no.	R_1	R_2	R_3	R_4	n	mp, °C	crystn solvent[a]	emp formula	prepn method[b]	yield,[c] %
1	C_6H_{11}	C_6H_5	*t*-Bu	H	1	251–253	A	$C_{18}H_{29}N\cdot HCl$	I	57.4
2	C_6H_{11}	C_6H_5	C_5H_9	H	1	154–156	A	$C_{19}H_{29}N\cdot HNO_3$	I	50
3	C_6H_{11}	C_6H_5	C_6H_{11}	H	1	154–156	A	$C_{20}H_{31}N\cdot HNO_3$	I	73
4	C_6H_{11}	C_6H_{11}	C_6H_{11}	H	1	221–223	B	$C_{20}H_{37}N\cdot C_4H_4O_4$[g]	I	29
5	C_6H_{11}	C_6H_5	$CH(CH_3)CH_2C_6H_5$	H	1	171–173[d]	C	$C_{23}H_{31}N\cdot C_4H_4O_4$[g]	I	49
6	C_6H_{11}	C_6H_5	$CH(CH_3)CH_2CH_2C_6H_5$	H	1	168–170	D	$C_{24}H_{34}N\cdot C_4H_4O_4$[g]	I	54
7	C_6H_{11}	C_6H_5	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	H	1	174–176	B	$C_{24}H_{33}NO_2\cdot C_4H_4O_4$[g]	I	41
8	C_6H_{11}	C_6H_5	$CH(CH_3)CH_2C_6H_4$-4-OCH_3	H	1	150–152	C	$C_{24}H_{33}NO\cdot C_4H_4O_4$[g]	I	6.2
9	C_6H_{11}	C_6H_5	$CH(CH_3)CH_2C_6H_4$-4-OH	H	1	159–161	A	$C_{23}H_{31}NO\cdot HNO_3$	I	2.4
10	C_6H_{11}	C_6H_{11}	C_6H_{11}	H	2	189–191	A	$C_{21}H_{39}N\cdot HCl$	II	48
11	C_6H_{11}	C_6H_{11}	C_6H_{11}	CH_3	2	143–145	C	$C_{22}H_{41}N\cdot C_4H_4O_4$[g]	II	33
12	C_6H_{11}	C_6H_{11}	$CH(CH_3)CH_2CH_2C_6H_5$	H	2	201–203	B	$C_{25}H_{41}N\cdot C_4H_4O_4$[g]	II	59
13	C_6H_{11}	C_6H_{11}	$CH(CH_3)CH_2C_6H_5$	H	2	220–222	E	$C_{24}H_{39}N\cdot C_4H_4O_4$[g]	II	21
14	C_6H_{11}	C_6H_{11}	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	H	2	167–169	D	$C_{25}H_{41}NO_2\cdot C_4H_4O_4$[g]	II	51
15	C_6H_{11}	C_6H_5	C_6H_{11}	H	2	202–204	A	$C_{21}H_{39}N\cdot HCl$	II	15.8
16	H	1-Ad[e]	C_6H_{11}	H	1	164–166	A	$C_{18}H_{31}N\cdot C_4H_4O_4$[g]	III	41
17	H	1-Ad	$CH(CH_3)CH_2CH_2C_6H_5$	H	1	144–146	A	$C_{22}H_{33}N\cdot C_4H_4O_4$[g]	III	28
18	H	1-Ad	$CH(CH_3)CH_2C_6H_5$	H	1	135–137	C	$C_{21}H_{31}N\cdot C_4H_4O_4$[g]	III	47
19	H	1-Ad	$CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$	H	1	259–261	A	$C_{22}H_{33}NO_2\cdot HCl$	III	35
20	C_6H_{11}	C_6H_{11}	C_6H_{11}	H	0	247–249	A	$C_{19}H_{35}N\cdot HCl$	*f*	38
21	C_6H_{11}	C_6H_{11}	C_6H_{11}	H	3	187–189	A	$C_{22}H_{41}N\cdot HCl$	IV	18
22	C_6H_{11}	C_6H_{11}	C_6H_{11}	H	4	208–210	F	$C_{23}H_{43}N\cdot C_4H_4O_4$[g]	V	8
23	C_6H_{11}	C_6H_4-4-OH	C_6H_{11}	H	1	244–246	A	$C_{20}H_{31}NO\cdot HCl$	VI	8.3
24	C_6H_{11}	C_6H_4-4-CH_3	C_6H_{11}	H	1	190–192	B	$C_{21}H_{33}N\cdot C_4H_4O_4$[g]	VII	17

[a] A = EtOAc/MeOH; B = MeCN/MeOH; C = EtOAc; D = EtOAc/MeCN: E = 2-PrOH/MeOH; F = 2-PrOH. [b] Numbers I–VII refer to the schemes. A typical preparation procedure is given under Experimental Section for each number. [c] Yield expressed from the starting material. [d] Literature[16] mp 167–168 °C. [e] Ad = adamantyl. [f] See Experimental Section. [g] $C_4H_4O_4$ = maleate.

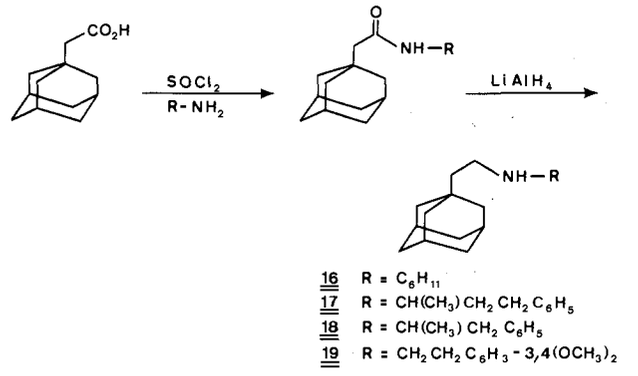
Scheme I



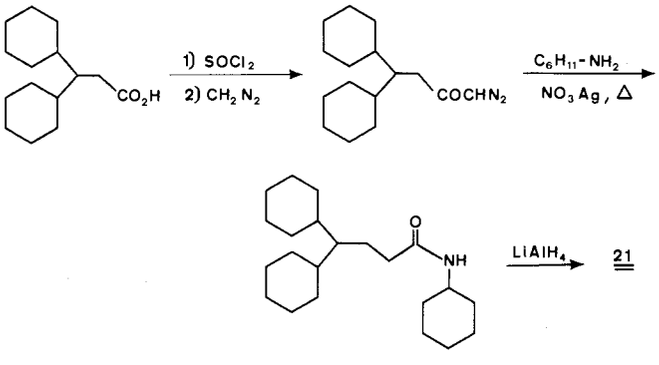
Scheme II



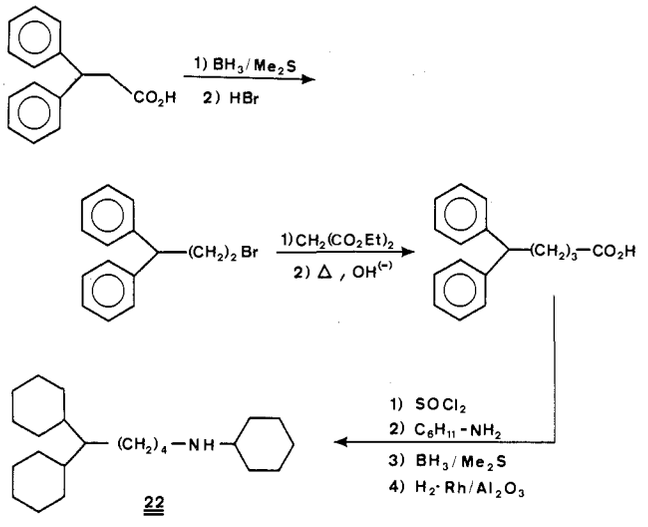
Scheme III



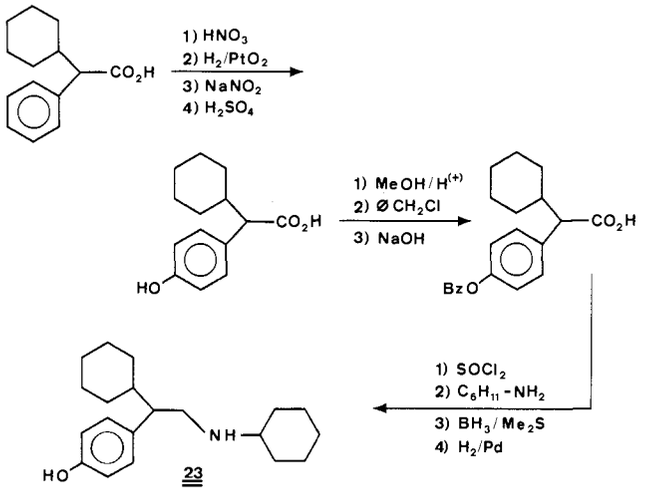
Scheme IV



Scheme V



Scheme VI



give **23** in 23% overall yield.

The synthesis of **24** is depicted in Scheme VII. Tolylacetonitrile was alkylated with cyclohexyl bromide/$NaNH_2$ in benzene, and the resulting nitrile was hydrolyzed with 48% aqueous HBr under drastic conditions (80 h, reflux). The acid thus obtained was then converted to **24** using classical methods.

Biological Results

The pharmacological investigations were directed to a search for compounds having an activity better than that of perhexiline according to the following order of criteria: (1) α-adrenolytic activity; (2) increase of coronary blood flow; (3) calcium antagonism activity. These biological data are shown in Table II.

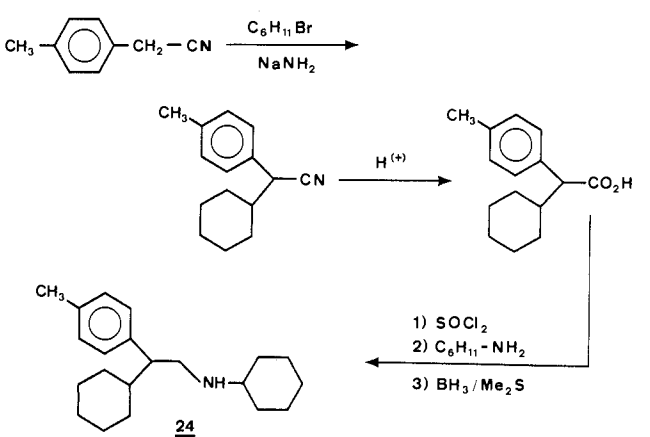
Several of the compounds listed in Table II show higher α-adrenolytic activity than perhexiline. Examination of the alicyclic series shows the following order of potency: **20** < **4** = **10** > **21**. Thus, the best activity was obtained among compounds of the general formula II with $n = 1$ or 2. This is also in agreement with the best α-adrenolytic activity exhibited by compounds of the semiaromatic series, such as **3** ($R_2 = C_6H_5$ and $n = 1$), and to a lesser extent by **15** ($R_2 = C_6H_5$ and $n = 2$). It is noteworthy that the nature of the terminal amine did not seem to play a clear

Table II. Biological Properties of Aralkylamine Derivatives

compd	dog coronary flow[a]	α-adrenolytic act.:[b] rat aorta pA_2	Ca antagonism:[b] pig coronary pA_2
1	104.5 ± 46	7.25 ± 0.47	<4.5[d]
2	38.5 ± 12	5.9 ± 1.14	6.2 ± 0.02
3	62 ± 10	7.9 ± 0.15	4.6[d]
4	84 ± 23	7.25 ± 0.22	~4.0[d]
5	157 ± 81	6.9 ± 0.21	6.2 ± 0.35
6	71.5 ± 2	7.6 ± 0.33	6.1 ± 0.08
7	73 ± 10	7.25 ± 0.28	3.6[d]
8	100.5 ± 6	6.0 ± 0.02	5.1[d]
9	105 ± 55	6.35 ± 0.37	4.8[d]
10	130 ± 23	7.25 ± 0.21	4.85[d]
11	67 ± 3	6.15 ± 0.44	4.85[d]
12	c	c	c
13	42 ± 13	<5[d]	5.2 ± 0.63
14	44.5 ± 27	6.3 ± 0.24	4.1[d]
15	156 ± 44	6.8 ± 0.26	5.8 ± 0.11
16	99 ± 13	6.75 ± 0.47	4.7[d]
17	215 ± 128	7.15 ± 0.54	5.1[d]
18	146 ± 21	7.3 ± 0.11	4.85[d]
19	133 ± 55	7.35 ± 0.22	4.8[d]
20	194 ± 106	6.2 ± 0.35	5.45 ± 0.17
21	95.5 ± 28	6.05 ± 0.41	4.6[d]
22	c	c	c
23	133.5 ± 25	7.1 ± 0.30	4.5[d]
24	68 ± 49	6.55 ± 0.67	6.0 ± 0.03
N-methylperhexiline	135 ± 58	6.9 ± 0.42	5.3[d]
perhexiline	37.5 ± 6	6.7 ± 0.03	5.2[d]

[a] Percent of initial increase ± SEM at the dose of 3 mg/kg iv; three dogs used for each experimentation. [b] pA_2 ± SD; the slopes of Schild plots are not significantly different from 1; six isolated organs used for each determination. [c] Insoluble. [d] pD_2' indicating a noncompetitive antagonism.

Scheme VII



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role in this respect. In the adamantyl series, cyclohexylamine (**16**), homoamphetamine (**17**), amphetamine (**18**), and homoveratrylamine (**19**) moieties engendered the same α-adrenolytic activities. This is no longer true for the semiaromatic series, where the observed sequence is C_5H_9 (**2**) < *t*-Bu (**1**) < C_6H_{11} (**3**), or for the alicyclic series, where the observed sequence is C_6H_{11} (**10**) ≫ amphetamine (**13**) < homoveratrylamine (**14**). The presence of a free NH group is also not essential. Thus, if *N*-methyl derivative **11** is 8 times less active than NH derivative **10**, *N*-methylperhexiline is ~2 times more active than perhexiline. All these facts indicate that this portion of the molecule is an area in which structural changes can be tolerated. When compared to perhexiline, 19 out of the 24 molecules studied were found to have greater potency in the coronary blood flow test. Of these compounds, some were alicyclic (**4**, **10**, **11**, **16**, and **20–22**) and some contained an aromatic nucleus (**2**, **3**, **5–9**, **12–15** and **23**), indicating that aromatic character is not important for hemodynamic activity. Alicyclic compound **20** is equipotent with perhexiline as far as calcium antagonism is concerned, but it is much less active than compounds **2**, **5**, **6**, and **24**, which possessed an aromatic group and which were up to 10 times more active than perhexiline.

Further detailed pharmacological investigations (tension-time index and decreased cardiac work) have led to the selection of compound **3** for clinical trials, which are now under way.

Experimental Section

Pharmacology. In Vivo. Mongrel dogs of either sex weighing from 15 to 25 kg were fasted overnight with free access to water. Anesthesia was induced by pentobarbital (25 mg/kg iv; maintained by periodic adminstration of 1 mg/kg iv) associated with levopromazine (0.5 mg/kg im). Polyethylene catheters were placed in the femoral artery and vein. After tracheal intubation, the thorax was opened at the level of the fourth rib, and the animal was ventilated (20 cycles/min, 150–300 mL/cycle).

The anterior intraventricular artery (IVA) was freed from the surrounding tissue. After 1 h of rest, an electromagnetic detector (Nycotron 1603) was placed on the IVA to allow continuous measurement of the coronary flow. Drugs were injected in the femoral vein at doses of 0.3–1 and 3 mg/kg. The increase in coronary blood flow was expressed in percentage with reference to the period preceding the injection of 3 mg/kg (Table II).

In Vitro. α-Adrenergic activity was determined on aorta,[10] and calcium antagonism was determined on pig coronary.[11] Final results were expressed as pA_2 or pD_2' values. pA_2 was determined according to the technique of Arunlakshana and Schild,[12] which has been developed by Miesch et al.[13] pD_2' values, calculated according to Ariens and Van Rossum,[14] were used to measure noncompetitive antagonism. The antagonist was added to the bath 30 min before the assay.

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(11) T. Godfraind and A. Kaba, *Br. J. Pharmacol.*, 36, 549 (1969).
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α-Adrenergic Activity. α-Adrenolytic activity was measured on the descending thoracic branch of the rat aorta, contracted by norepinephrine. Helically cut strips of rat aorta, 1.5- to 2-cm long and 3- to 4-mm wide, were prepared as described by Liebau, Distler, and Wolff.[10] Preparations were suspended in 20-mL baths containing Krebs–Henseleit solution, kept at 37 °C, and bubbled with a mixture of 95% oxygen and 5% carbon dioxide. They were set up at a resting tension of 2 g and allowed to stabilize for approximately 2 h before the experiment.

Calcium Antagonism. Antagonism of calcium-induced contraction was measured on the depolarized coronary of pig as described by Godfraind and Kaba.[11] Helically cut strips of pig coronary, 2- to 2.5-cm long and 3- to 4-mm wide, set up at a resting tension of 0.5 g, were suspended in a modified Krebs–Henseleit solution (1.25 mmol/L of $CaCl_2$). The pig coronary was then suspended in a new Krebs solution free of calcium and containing EDTA (2.10^{-4} mol/L). Finally, the antagonism of calcium-induced contraction (3.10^{-5} to 10^{-2} mol/L) was measured on the coronary, depolarized by a solution of KCl (100 mmol/L).

Chemistry. Melting points were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ solution with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer spectrometer using Me_4Si in a capillary as an external reference. The spectral data were consistent with the assigned structures. All compounds were analyzed for C, H, and N and gave results within ±0.4% of the theoretical values.

***N*-*tert*-Butyl-2-cyclohexyl-2-phenylethylamine (1).** A suspension of α-cyclohexylphenylacetic acid (21.8 g, 0.1 mol) in $SOCl_2$ (14.9 g, 0.125 mol) was heated at 70 °C for 3 h. Excess $SOCl_2$ was removed in vacuo. To the residue, dissolved in benzene (50 mL), were added *tert*-butylamine (7.3 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) dissolved in benzene (30 mL). The resulting mixture was stirred for 1 h and stripped free of solvent to afford crude amide, which was filtered, washed with water (3 times 50 mL), and dried to yield 23.2 g of amide (85%). To this amide dissolved in a minimum of anhydrous THF and kept under argon was added BH_3–Me_2S complex (25.5 mL, 255 mmol) dissolved in anhydrous THF (50 mL). After 48 h, the excess complex was destroyed by adding MeOH, and the solvents were evaporated to give crude 1 (18.5 g, 84%). It was purified as a HCl salt, which was recrystallized from EtOAc–MeOH (17 g, 57.4%), mp 252 °C.

Compounds **2**, **3**, and **5–9** (Table I) were similarly prepared.

***N*,2,2-Tricyclohexylethylamine (4).** A solution of **3** (6.4 g, 22 mmol) in MeOH (100 mL) and H_2O (0.4 mL) containing a 5% Rh/Al_2O_3 catalyst (0.44 g) was hydrogenated under 50 kg/cm^2 at 60 °C for 4 days. After the solution was cooled, the catalyst was filtered, and the solvents were evaporated in vacuo. The resulting amide was purified on a SiO_2 column using hexane–Et_2NH (98:2) as eluent. The stable maleate was then prepared. See Table I.

***N*,3,3-Tricyclohexylpropylamine (10).** A solution of pure 3,3-diphenylpropionic acid (9.5 g, 42 mmol, recrystallized from a MeOH solution containing a large amount of charcoal) in MeOH (100 mL) containing a 5% Rh/Al_2O_3 catalyst (1 g) was hydrogenated under 50 kg/cm^2 at 60 °C for 2 days. After the solution was cooled, the catalyst was filtered, and the solvents were evaporated under vacuum to afford 9.3 g of acid, which was recrystallized from MeOH. This acid (8.4 g, 88%) was heated with $SOCl_2$ as described for the preparation of I and then with cyclohexylamine (1 equiv) and triethylamine (1 equiv) dissolved in benzene (50 mL). The resulting amide (10.4 g, 32.5 mmol) was filtered, thoroughly washed with water, dried, and reduced with $LiAlH_4$ (4.8 g, 130 mmol) in THF (100 mL). After 48 h of reflux, the solution was cooled on ice, and water was carefully added. The milky solution was filtered through Celite and extracted with Et_2O. The Et_2O extracts were dried ($MgSO_4$) and bubbled with gaseous HCl. The hydrochloride obtained was recrystallized from EtOAc–MeOH (6.9 g, 48%), mp 189–191 °C.

Compounds **12–14** (Table I) were similarly prepared.

***N*,3,3-Tricyclohexyl-*N*-methylpropylamine (11).** A stirred solution of **10** (3.05 g, 10 mmol) in 40% aqueous formaldehyde (2.2 mL, 30 mmol) and formic acid (2.07 g, 45 mmol) was heated to 100 °C for 12 h. After the solution was cooled, 10% aqueous NaOH (50 mL) was added. The solution was saturated with K_2CO_3 and extracted 3 times with Et_2O. The pooled ethereal extracts were dried and evaporated to afford a crude derivative (2.7 g), purified as a maleate. An analytical sample was obtained by recrystallization from EtOAc, mp 143–145 °C.

N-Methylperhexiline was similarly prepared.

***N*,3-Dicyclohexyl-3-phenylpropylamine (15).** A solution of diphenylpropionic acid (17 g, 75 mmol) in AcOH (170 mL) containing PtO_2 (1 g) was hydrogenated under atmospheric pressure. The reduction was monitored by TLC and was stopped after ~3 equiv of H_2 was absorbed. The catalyst was filtered, and the solvent was evaporated to give mixture of 3,3-diphenylpropionic acid, 3-cyclohexyl-3-phenylpropionic acid (major), and 3,3-dicyclohexylpropionic acid. The mixture was heated with $SOCl_2$ and allowed to react with cyclohexylamine to afford a crude mixture of amides (18 g), which were purified by SiO_2 column chromatography (360 g) using hexane–EtOAc–$N(Et)_3$ (85:10:5) as eluent. The crude amide (6.9 g, 30%) was then reduced by $LiAlH_4$ in THF as described for the preparation of **10**. The hydrochloride of **15** (3.5 g, 55%) was recrystallized from EtOAc–MeOH, mp 201–204 °C.

***N*-Cyclohexyl-2-(1-adamantyl)ethylamine (16).** To a solution of 1-adamantanecarbonyl chloride (12.5 g, 58 mmol) in dry benzene (100 mL) was added dropwise and simultaneously cyclohexylamine (1 equiv) and triethylamine (1 equiv) in benzene (30 mL). After 2 h, the excess solvents were evaporated under vacuum, and the residue was filtered, washed with H_2O, and dried to afford the crude amide (12.7 g, 80%). This amide was dissolved in THF (150 mL) and reduced with $LiAlH_4$ as described for the preparation of **10**. The crude amine (8.5 g) was purified as a maleate, mp 164–166 °C.

***N*,1,1-Tricyclohexylmethylamine (20).** To a solution of dicyclohexyl ketone (4.3 g, 22 mmol) and cyclohexylamine (6.55 g, 66 mmol) in anhydrous Et_2O (12 mL) was added dropwise under argon a solution of $TiCl_4$ (1.22 mL, 11 mmol) in hexane (15 mL). After stirring for 0.5 h, the mixture was heated at reflux for 1–5 h and left aside overnight. Following filtration of the TiO_2 formed, the solution was evaporated to an oily residue, which was taken up in MeOH (80 mL). This solution was hydrogenated over a 10% Pd/C (0.43 g) at atmospheric pressure. After 2 days, the reduction mixture was filtered, evaporated under reduced pressure, and treated with ethereal HCl. The resulting salt was recrystallized from a mixture of EtOAc–MeOH (9:1) to afford 2.6 g (38%) of **20** as white crystals, mp 247–249 °C.

***N*,4,4-Tricyclohexylbutylamine (21).** To a cold solution of 3,3-dicyclohexylpropionyl chloride (2.57 g, 10 mmol) in Et_2O (25 mL) was added a solution of CH_2N_2 (~1 g) in Et_2O (50 mL). After 12 h, the ether was evaporated and the yellow crystalline residue (2.6 g, 100%) was recrystallized from petroleum ether (1.5 g, 58%). To a hot solution of this diazo ketone in dioxane (9.2 mL) was added, simultaneously, a solution of cyclohexylamine (2.84 g, 28.6 mmol) in dioxane (6 mL) and a solution of a 10% aqueous $AgNO_3$ (0.6 mL). The mixture was refluxed for 1 h, filtered on Celite, and evaporated under reduced pressure to give a crude amide (1.1 g, 5.7%), which was reduced to the corresponding amine (66.7%) using $LiAlH_4$/THF as described in the preparation of **10**. Recrystallization of the HCl salt from EtOAc–MeOH gave an analytical sample (0.55 g, 69%), mp 187–189 °C.

***N*,5,5-Tricyclohexylpentylamine (22).** 3,3-Diphenylpropionic acid (45 g, 0.2 mol) was reduced with BH_3/Me_2S (26.6 mL, 0.26 mol) in THF (150 mL) as for **1** to afford a quantitative yield of 3,3-diphenylpropanol (43 g). This alcohol was heated at reflux in 48% aqueous HBr (340 mL) for 24 h. The solvents were evaporated under reduced pressure, and the crude bromo derivative was purified by SiO_2 column chromatography using hexane as eluent to afford pure bromo compound (45.8 g, 83%). This oily intermediate was added dropwise to a solution of sodium diethyl malonate which had been prepared from diethyl malonate (27.7 g, 0.173 mol) and Na (14 g, 0.173 g/atom) in *n*-BuOH (90 mL). This solution was heated under reflux for 3 h, cooled, and then treated with a 50% aqueous KOH solution (25.8 g, 0.46 mol) and heated under reflux for 2 days.

The solvents were thoroughly evaporated, the mixture was acidified with 6 N HCl, and the aqueous solution was extracted 3 times with EtOAc. The pooled organic phases were dried ($MgSO_4$), filtered, and evaporated to afford a diacid, which was slowly heated to 200 °C. When the CO_2 evolution had ceased, the oily residue was triturated with petroleum ether to give 5,5-

diphenylpentanoic acid (25.4 g, 50%). This acid was then heated with $SOCl_2$, followed by cyclohexylamine, and the corresponding amide was reduced as described for the preparation of 1. The crude amine was purified as its nitrate salt and recrystallized from EtOAc (12 g, 33%), mp 156 °C. The aromatic rings were finally reduced as described in the preparation of 4. The maleate of 22 was recrystallized from 2-PrOH: yield 51%; mp 208–210 °C.

***N*,2-Dicyclohexyl-2-(*p*-hydroxyphenyl)ethylamine (23).** To an ice-cold solution (0 °C) of concentrated H_2SO_4 (146 mL) containing α-cyclohexylphenylacetic acid (87.3 g, 0.4 mol) was added dropwise (1 drop every 15 s) concentrated HNO_3 (13 mL). The temperature was kept between 0 and 10 °C, and after 1 h, the mixture was poured into crushed ice. The yellow crystals were filtered, washed several times with H_2O, dried, and recrystallized from cyclohexane–CCl_4 (95:5) to afford 58.1 g (55%) of pure *p*-NO_2 derivative, which was catalytically reduced using PtO_2 (1 g) under 1 kg/cm^2 pressure of H_2. The amine obtained (50 g, 97.5%) was dissolved in H_2O (200 mL) and H_2SO_4 (47.2 mL). The aqueous solution was ice-cooled and diazotized by the dropwise addition of $NaNO_2$ (15.9 g, 0.23 mol) in H_2O (40 mL). The temperature was maintained at 0–5 °C for 1 h, and the solution was then slowly added to a boiling solution with H_2O (200 mL) and H_2SO_4 (22 mL). After 0.25 h, the mixture was cooled, and the brown gum was dissolved in a 10% aqueous Na_2CO_3 solution. The solution was decolorized with charcoal and cooled, and the pH was adjusted to 1 with dilute HCl. The gummy residue was taken up in Et_2O, dried, filtered, and evaporated to afford 27.5 g of crystals after trituation with CCl_4 (100 mL). Recrystallization from CCl_4–$(i\text{-}Pr)_2O$ gave a sample (18.7 g, 38%) that was homogeneous on TLC. A solution of this phenol in MeOH (50 mL) and H_2SO_4 (1 mL) was heated under reflux for 12 h. The mixture was cooled, made alkaline ($NaHCO_3$), and extracted with EtOAc. After evaporation, the methyl ester was purified by SiO_2 column chromatography using graded mixtures of hexane–EtOAc. The viscous ester thus obtained was then benzylated by refluxing for 12 h in EtOH (75 mL) containing 11 g (80 mmol) of K_2CO_3, benzyl chloride (9 mL, 78 mmol), and NaI (1 g). H_2O (800 mL) was added, and the product was extracted with EtOAc (3 × 250 mL) after acidification. The pooled organic phases were dried and evaporated, and the residue was submitted to SiO_2 column chromatography (450 g). Cyclohexane–EtOAc (95:5) eluted the pure ester (19.9 g, 78.4%) as a colorless oil, which slowly crystallized. The ester was saponified (450 mL of a 1:1 mixture of 10% aqueous NaOH and EtOH) for 2 h. The EtOH was removed under reduced pressure, and the aqueous phase was acidified and extracted with EtOAc (3 × 100 mL). This acid (16.3 g, 85.4%) was heated at 70 °C for 3 h in a solution of $SOCl_2$ (3.6 mL) in benzene (40 mL) as described for 1. The resulting acid chloride was reacted then with cyclohexylamine, and the amide was reduced with BH_3/Me_2S. The resulting amine was treated with ethereal HCl, and the HCl salt was debenzylated over Pd/C under 1 kg/cm^2 pressure of H_2. After 4 days, the solution was filtered (Celite) and evaporated to afford crude 23 (11.05 g). An analytical sample (9.6 g, 8.3%) was obtained as heavy crystals from EtOAc–MeOH, mp 244–246 °C.

***N*,2-Dicyclohexyl-2-*p*-tolylethylamine (24).** To sodamide (8.3 g, 220 mmol) in dry benzene (30 mL) was added to *p*-tolylacetonitrile (26.2 g, 200 mmol) during a period of 10 min. The red mixture was stirred and refluxed for 3 h. The heat was then removed, and bromocyclohexane (32.6 g, 200 mmol) in benzene (20 mL) was added at such a rate as to maintain a vigorous reflux. Stirring and refluxing were continued for 12 h. The reaction mixture was cooled, and H_2O (100 mL) was added. The water layer was discarded, the benzene phase was filtered on Celite, and the filtrate was evaporated under vacuum. The oily residue was chromatographed on basic alumina using hexane as eluent to afford pure nitrile (20.7 g, 48%), which slowly crystallized.

The general procedure of Weston[15] was followed in the HBr hydrolysis of the α-cyclohexyl-*p*-tolylacetonitrile to α-cyclohexyl-*p*-tolylacetic acid. The latter was obtained in an 82% yield: mp 142–143 °C; IR ($CHCl_3$) ν 1710 (CO) cm^{-1}. The acid was then transformed into its acid chloride and reacted with cyclohexylamine as described for the synthesis of 1. The resulting amide was finally reduced to 3 using BH_3/Me_2S. The maleate of 3 was recrystallized from CH_3CN and a few drops of MeOH, mp 190–192 °C.

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Inhibitors of Blood Platelet Aggregation. Activity of Some 1*H*-Benz[*de*]isoquinolinecarboximidamides on the in Vivo Blood Platelet Aggregation Induced by Collagen

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A series of 33 1*H*-benz[*de*]isoquinolinecarboximidamides has been prepared and tested in the rat after intraperitoneal (ip) and/or oral (po) administration for their ability to inhibit the in vivo blood platelet aggregation induced by collagen. In this aggregation test, a considerable number of active compounds were found. Fourteen compounds were active when administered ip [0.2 (mmol/kg)/day], five of which also exhibited significant po activity. One compound was toxic after ip administration but was found to be active after po administration without apparent toxicity. It is thought that the solubility of the drug in water is an important factor for the resorption after oral administration and, hence, for its oral activity.

Blood platelets play an important role in hemostasis as well as in thrombosis. Moreover, blood platelets are assumed to play a key role in arterial diseases of various kinds. Drugs that are able to modulate blood platelet functions may find therapeutic use against arterial thrombosis and its consequences, such as myocardial infarction and stroke. A significant number of compounds are claimed as blood platelet aggregation inhibitors; however, in most cases their activity was only assessed in in vitro tests. In vitro tests are very useful to profile compounds which have been proven to be active blood platelet aggregation inhibitors. Some of these tests, e.g., the TXB_2 assay,[1] the malondialdehyde assay,[2] the serotonin uptake inhibition test,[3] the collagen-induced release inhibition test,[4] etc., are widely used and also in our laboratory ap-

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