AMP formed was determined in the remaining supernatant fraction by the double-column method of Salomon et al.[27] and corrected for recovery of the carrier cyclic AMP. Protein was determined by the method of Lowry.[28] Results are expressed as percent of total radioactive nucleotide present as cyclic AMP (percent conversion).

The binding of [^{3}H]dihydroalprenolol to β-adrenergic receptors and displacement by the fluorinated amines were measured by a modification of the methods of Bylund and Snyder[29] and Alexander,[30] as previously described by Nimitkitpaisan and Skolnick,[24b] except that the final tissue pellet was resuspended in 60 volumes of Tris-HCl buffer (50 mM, pH 8). Under these conditions, the binding of [^{3}H]dihydroalprenolol was linear with respect to protein concentrations; K_d values for dihydroalprenolol were estimated to be about 1 nM by Scatchard analysis, and specific binding represented 55% of total binding. Measurement of [^{3}H]WB-4101 to α-adrenergic receptors and displacement by the fluorinated amines were determined by the method of U'Prichard et al.[6a] Under these conditions, the K_d value for [^{3}H]WB-1401 was 1.4 nM, and specific binding represented 60% of total binding.

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Synthesis and Antihypertensive Activity of 2-Benzamido-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines

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The synthesis and antihypertensive activity of a series of 2-benzamido-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizines are reported. A number of these compounds exhibit extremely potent hypotensive properties (e.g., *N*-methylbenzamides **42**, **48**, and **50** and *N*-ethylbenzamide **53** cause drops of 110, 103, 79, and 83 mmHg, respectively, in systolic blood pressure in the spontaneous hypertensive rat at the screening dose of 50 mg/kg po). Structure–activity relationships for the entire series are discussed.

Some years ago, the synthesis and hypotensive properties of a series of benzamidopiperidylethylindoles were reported.[1] From this group of compounds, the 4-benzamido derivative **1** (indoramin) was shown to possess potent antihypertensive activity[2-4] and was chosen as a candidate for further investigation.

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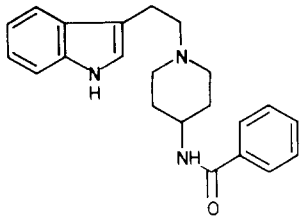
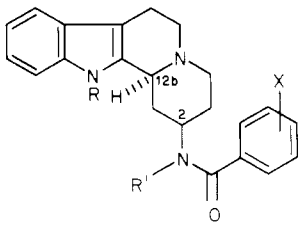


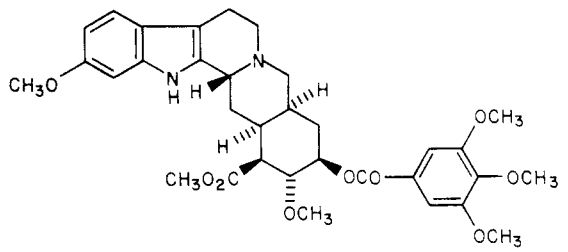
1

In conjunction with a continuing program directed at the development of a potent, side-effect-free hypotensive agent, we decided to synthesize a series of 2-benzamido-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines **2**.[5]



2

These compounds are arrived at by a formal cyclization between the 2 position on the piperidine ring of **1** and the α position of the indole. Compounds of this structural type not only possess the obvious relationship to **1** but also contain the octahydroindolo[2,3-*a*]quinolizine moiety present in the useful naturally occurring antihypertensive, reserpine **3**. We were also intrigued by the possibility of



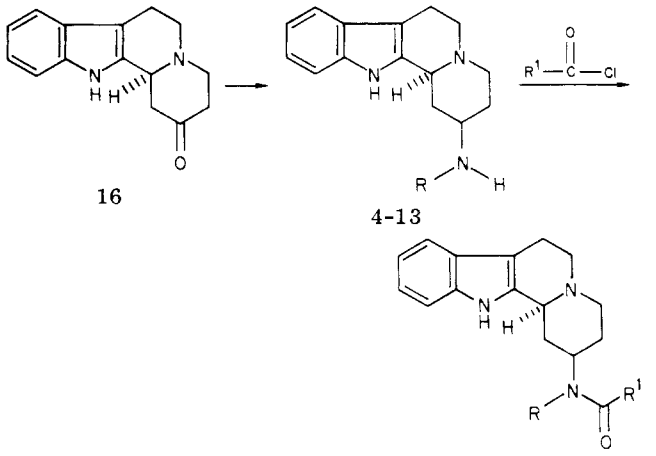
3

preparing both C-2 benzamido diastereomers and delineating how this subtle change in stereochemistry would affect pharmacologic activity. In this paper, the synthesis and hypotensive properties of these 2-benzamido-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines **2** are reported.

Chemistry. Our basic approach to the preparation of the desired benzamides **2** (Scheme I) was to synthesize the appropriate amines **4–13** (Table I) by various methods from the known 2-oxo compound **16**[6] and then acylate these amines with the requisite acid chloride. It was assumed that separation of mixtures of C-2 isomers, where desirable, could be more easily performed chromatographically at the amide stage than at the amine stage.

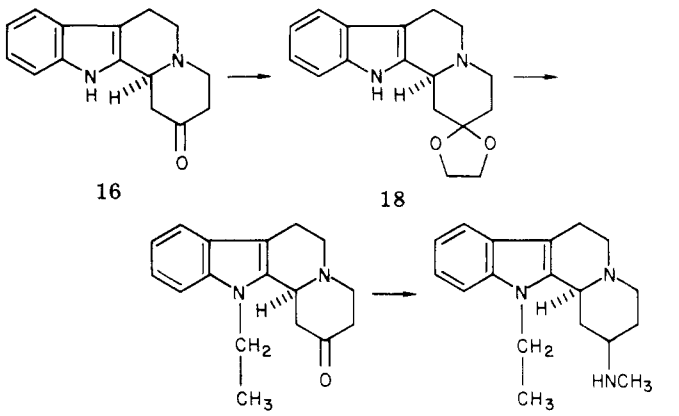
The primary amine **4** was prepared by the reduction of oxime **17** (Table II) with sodium bis(2-methoxyethoxy)-aluminum hydride in refluxing benzene (method A). Alkylamino compounds **5** and **7–9** were synthesized from ketone **16** by condensation with an excess of the appropriate aliphatic amine in the presence of titanium tetrachloride[7] to yield the intermediate imines, which were immediately reduced to the amines with sodium borohydride in ethanol (method B). The arylamines **10** and **11** and aralkylamines **12** and **13** were prepared by refluxing **16** with aniline, benzylamine, or β-phenethylamine in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water to obtain the imines, which were again immediately reduced

Scheme I



16 4-13

Scheme II



16 18 19 6

with sodium borohydride in ethanol (method C).

The ethylindole methylamino derivative **6** was synthesized from **16** in several steps (Scheme II). Ketalization (method D) afforded ketal **18** (Table II), which upon alkylation (ethyl iodide, sodium hydride in dimethylformamide–benzene) and deketalization (method E) provided ethylindole ketone **19** (Table II). Ketone **19** was then converted into **6** using method B as described above.

Two tertiary amino derivatives, **14** and **15** (Table I), were prepared for comparison of their hypotensive properties with those of the primary and secondary amine derivatives. The benzyl methylamino compound **14** was prepared by the reduction of *N*-methylbenzamide **42** with lithium aluminum hydride in refluxing tetrahydrofuran (method F). Cyanamide **15** was synthesized by the action of cyanogen bromide in methanol containing sodium acetate on methylamino derivative **5** (method G).

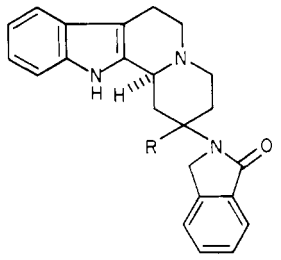
The target amides **20–38** and **40–55** (Table III) were prepared by reacting amines **4–9** with the required acid chloride in chloroform solution in the presence of triethylamine (method H). The γ-lactam analogues **56** and **57** (Table III) were prepared by heating primary amine **4** with ethyl α-bromo-*o*-toluate in dimethylformamide containing anhydrous potassium carbonate (method I). Phenylureas **58** and **59** (Table III) were synthesized by the condensation of primary amine **4** with phenyl isocyanate in chloroform (method J). *p*-Aminobenzamide **39** was prepared by catalytic reduction of the *p*-NO_2 derivative **38** (method K).

The composition of the mixture of isomers obtained during the synthesis of compounds prepared by methods H, I, and J, of course, reflects the composition of the mixture of isomers of primary amine **4** and secondary

Table I. Amines[a]

no.	R_1	R_2	R_3	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent	formula	anal.[d]	change in systolic BP, mmHg, day 3, 2 h postdrug (mg/kg po)
4	H	H	NH_2	17	A	171–173[k]	54.8	benzene	$C_{15}H_{19}N_3$	C,[f] H, N	−9.5 (25)
5	H	H	$NHCH_3$	16	B	204.5–207	54	CH_3CN	$C_{16}H_{21}N_3$	C, H, N	−18 (50)
6	CH_2CH_3	H	$NHCH_3$	19	B	269–271.5[k]	71.5	aq acetone	$C_{18}H_{25}N_3 \cdot 2HCl \cdot 0.5H_2O$	C,[g] H, N	−30 (50)
7	H	H	$NHCH_2CH_3$	16	B	158–162[k]	43.1	CH_3CN	$C_{17}H_{23}N_3$	C,[h] H, N	−4 (50)
8	H	H	$NH(CH_2)_2CH_3$	16	B	130–133	84[e]	CH_3CN	$C_{18}H_{25}N_3$	C, H, N	+27 (50)
9	H	H	NH-c-C_3H_5	16	B	124–127	76[e]	benzene–hexane	$C_{18}H_{23}N_3$	C, H, N[i]	−25 (50)
10	H	H	NHC_6H_5	16	C	160.5–163	37.9	CH_3OH	$C_{21}H_{23}N_3$	C, H, N	−25 (25)
11	H	β-H	α-NHC_6H_5	16	C	170–172.5	10.6	$CHCl_3$–pet. ether	$C_{21}H_{23}N_3$	C, H, N	+5.75 (25)
12	H	H	$NHCH_2C_6H_5$	16	C	151.5–153.5	42.3	CH_3OH	$C_{22}H_{25}N_3$	C, H, N	−53 (50), −8 (25)
13	H	H	$NH(CH_2)_2C_6H_5$	16	C	309–311[k]	52.8	aq EtOH	$C_{23}H_{27}N_3 \cdot 2HCl$	C, H, N, Cl	−16 (50)
14	H	α-H	β-$NCH_3(CH_2C_6H_5)$	42	F	166–168.5	92.7[e]	CH_3CN	$C_{23}H_{27}N_3$	C, H, N	−54 (50)
15	H	α-H	β-$NCH_3(CN)$	5	G	182–185[k]	40.6	benzene	$C_{17}H_{20}N_4$	C, H, N	−51 (50)[j]

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material, unless otherwise noted; yields were not optimized. [d] Analytical results within ±0.4% of theoretical values, unless otherwise noted. [e] Crude yield. [f] C: calcd, 74.65; found, 75.20. [g] C: calcd, 59.17; found, 58.76. [h] C: calcd, 75.79; found, 76.23. [i] N: calcd, 14.93; found, 14.52. [j] Two animals died. [k] Decomposition.



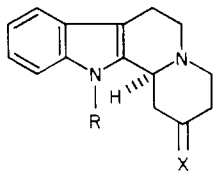
56, R = α-H
57, R = β-H

amines **5–9**. Primary amine **4**, which was prepared by Vitride reduction of oxime **17**, was an approximately 70:30 mixture of 2α-H,12bα-H/2β-H,12bα-H isomers.[8] On the other hand, secondary amines **5–9**, prepared by the sodium borohydride reduction of 2-imino derivatives, contained greater than 90% the 2α-H,12bα-H isomer.[8] The mixture of isomers could be separated at the amide stage by chromatography on silica gel using varying strengths of methanol/chloroform (1–10%).[10] A number of benzamides derived from **4** were separated in this manner to afford pure minor 2β-H,12bα-H isomers, as well as the major 2α-H,12bα-H isomers. However, due to the very small amount of 2β-H,12bα-H isomer present in amines **5–9**, only one pair of isomers (**42** and **43**) derived from these amines was separated.

The structural assignments of the pure isomeric 2-substituted compounds described above were made on the basis of chemical and spectral evidence. It is well established that, in the absence of any overwhelming steric factors, hydride reduction of cyclic ketones and imines with the more common hydride reagents ($NaBH_4$, $LiAlH_4$, etc.) afford a preponderance of the *more stable* reduction product.[11] In the case of reduction of oxime **17** and the imines derived from ketones **16** and **19**, one would consequently anticipate the major product to be the 2α-H,12bα-H isomer (with the amino substituent equatorial). This expected stereochemical course has been corroborated in several cases by careful examination of the IR spectra utilizing some observations made by Gribble and Nelson on the two isomeric 2-*tert*-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines.[9] These authors found that the presence of the large *tert*-butyl group in an axial position was sufficient to cause an energetically unfavorable flip of the quinolizine ring juncture from the original trans arrangement to the normally less stable cis C/D ring fusion. This conformational flip was detected by the absence of Bohlmann bands in the IR spectrum of the 2β-H,12bα-H isomer. Similarly the minor 2β-H,12bα-H benzamides **28**, **31**, **43**, and **57** do not show Bohlmann bands in their IR spectra, while the corresponding 2α-H,12bα-H benzamides **27**, **30**, **42**, and **56** exhibit these bands. Even in the cases where Bohlmann bands are present in the IR spectra of the minor isomers, their intensity is diminished in comparison to that of the major (2α-H,12bα-H) isomers, indicating some contribution by the cis C/D conformation. The above discussed chemical and IR evidence unequivocally establishes the stereochemistry of the isomeric products to be as indicated in Table III.

Pharmacology and Structure–Activity Relationships. The target benzamides of general formula **2**, as well as the intermediate amines, were evaluated for antihypertensive activity using spontaneous hypertensive rats (SHR). The data generated for the target series are included in Table III. On analyzing these data, several structure–activity relationships are readily apparent. In a number of cases, activity is significantly increased in going from the secondary benzamide to the identically

Table II. Intermediates[a]



no.	R	X	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent	formula	anal.[d]
17	H	NOH	16		250–253[f]	54	xylene	$C_{15}H_{17}N_3O$	C, H, N
18	H	$-OCH_2CH_2O-$	16	D	195–198	85.7[e]	benzene–hexane	$C_{17}H_{20}N_2O_2$	C, H, N
19	CH_2CH_3	O	18	E	133–136	77.1[e]	benzene–hexane	$C_{17}H_{20}N_2O$	C, H, N

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material, unless otherwise noted; yields were not optimized. [d] Analytical results within ±0.4% of theoretical values, unless otherwise noted. [e] Crude yield. [f] Decomposition.

substituted tertiary *N*-methylbenzamide. For example, secondary benzamides **21**, **26**, **27**, and **37** are essentially devoid of SHR activity, while the corresponding tertiary *N*-methylbenzamides **42**, **45**, **46**, and **52** respectively exhibited a marked antihypertensive response. However, there is a slight diminution of activity as the size of the benzamide nitrogen substituent is increased from methyl (**42**) to ethyl (**53**) and then a more striking decrease in hypotensive response as the size of this substituent increases to *n*-propyl (**54**) and cyclopropyl (**55**). Substitution of the indole nitrogen of **42** with an ethyl group (**44**) also leads to a moderate reduction in SHR activity. Finally, if the *N*-methyl and the ortho position of the benzoyl benzene ring of markedly active compound **42** are connected in a formal cyclization to obtain γ-lactam **56**, antihypertensive activity is totally abolished.

As stated previously, we had hoped to be able to prepare both C-2 benzamido diastereomers and examine how this minor stereochemical difference would affect antihypertensive activity. Unfortunately, due to unfavorable isomer ratios and tedious chromatographic separations, only several of the minor 2β-H,12bα-H isomers (**23**, **25**, **36**, **43**, and **59**) were isolated in amounts sufficient for SHR screening. Comparison of the SHR data for these compounds with that for the corresponding 2α-H,12bα-H isomers (**22**, **24**, **35**, **42**, and **58**, respectively) fails to reveal a recurrent pattern for the effect of C-2 stereochemistry on hypotensive response. The minor isomers of the *p*-CH_3 and *m*-CH_3 secondary benzamides, **23** and **25**, respectively, appear to be more active than the corresponding 2α-H,12bα-H isomers **22** and **24**. On the other hand, the 2β-H,12bα-H isomers of the *o*-Br secondary benzamide **36** and the unsubstituted *N*-methylbenzamide **43** are substantially less potent than the corresponding major isomers **35** and **42**, respectively. Finally, the stereochemical difference seems to have little effect when the activities of the isomeric phenylureas **58** and **59** are compared.

The SHR data in Table III clearly indicates that substitution of the benzamide benzene ring has a profound effect on antihypertensive activity. However, as was found to be the case in the indoramin series,[1] there seems to be no simple relationship between benzene ring substitution and degree of activity. In addition, substitution in other parts of the molecule, most notably on the benzamide nitrogen, can alter the effect of aromatic ring substitution. There is, nonetheless, one pattern present which is worth mentioning briefly. In both secondary and tertiary benzamide series, in every case where more than one positional isomer for a given aromatic substituent has been prepared and one of these isomers is the meta-substituted analogue, this compound is the most active of the group. Thus, *m*-CH_3 secondary benzamide **24** is more active than either **22** or **26**, and *m*-OCH_3 secondary benzamide **29** is more active than the para-isomer **27**. Likewise, in the tertiary benzamide series, the *m*-F isomer **48** is significantly more potent than its para-isomer **47**, and the *m*-Cl compound **50** is strikingly more active than its ortho and para isomers **51** and **49**, respectively. In addition, both of the polysubstituted benzamides tested (**30** and **40**) contain at least one meta substituent and have good antihypertensive activity.

Several compounds (e.g., **42**, **46**, and **52**) were evaluated in additional cardiovascular assays in an effort to elucidate the predominant mechanism of action for this series of potent hypotensive agents. When these benzamides were tested in the isolated spleen assay[12] and the standard challenges procedure in dogs,[13] it was readily apparent that the primary mechanism of action of these materials was through α-adrenergic receptor blockade. Although α blockade was for some time not viewed to be the most desirous of methods for the control of hypertension, it is hoped that expanded clinical experience with agents such as indoramin and prazosin will enable us to find agents which maximize the therapeutic properties of α blockers while minimizing side effects.

Experimental Section

The structures of all compounds are supported by IR (Perkin-Elmer 727) and ^1H NMR (JEOL C60HL; tetramethylsilane) spectra. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Labs, Skokie, Ill. Results are within ±0.4% of the theoretical values, unless otherwise noted in the tables. Solvents used were dried as follows: benzene by distillation from phosphorus pentoxide, dimethylformamide by distillation from barium oxide, and tetrahydrofuran by distillation from lithium aluminum hydride. Chromatographies were performed on silica gel 60 (70–230 mesh).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine 2-Oxime (17). A mixture of 3.6 g (15.0 mmol) of ketone **16**, 1.57 g (23.0 mmol) of hydroxylamine hydrochloride, 18 mL of anhydrous pyridine, and 18 mL of absolute ethanol was refluxed for 5 h, at which point the product had precipitated from solution. Removal of the solvent in vacuo, followed by trituration with ether and filtration, gave a crude product in a hydrated form.[14] Suspension of the solid in 20 mL of water, followed by treatment with 90 mL of 10% aqueous sodium hydroxide solution and then neutralization of the orange-red solution to pH 7 with 175 mL of 2 N hydrochloric acid, led to the precipitation of the crude product in an anhydrous form as a solid weighing 2.76 g (72%): mp s 245.5, 246.5–249.5 °C dec. Recrystallization from xylene afforded 2.07 g (54%) of colorless solid **17**, mp s 246, 250–253 °C dec.

2-Amino-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-

quinolizine (4). Method A. To a mixture of 2.8 g (10.9 mmol) of **17** and 70 mL of dry tetrahydrofuran was added 15 mL (51.2 mmol) of Vitride [sodium bis(2-methoxyethoxy)aluminum hydride, 70% in benzene], as fast as the rate of hydrogen evolution would allow. After 1 h at room temperature, the mixture was refluxed overnight under nitrogen and then cooled in an ice bath while 85 mL of 10% aqueous sodium hydroxide solution was added. After vigorously stirring the mixture, the phases were separated and the aqueous phase was extracted with chloroform (3 × 50 mL). The combined extracts were washed with 50 mL of 10% aqueous sodium hydroxide solution, 50 mL of water, and 50 mL of saturated sodium chloride solution, dried (Na_2SO_4), and concentrated to a yellow oil, which solidified upon trituration with ether. The crude product was filtered, washed (hexane), and dried to afford 2.29 g (87%) of pale-yellow solid, mp s 167, 170 °C dec. Recrystallization from benzene yielded 1.44 g (55%) of pale yellow **4**, mp s 169, 171–173 °C dec.

2-(Methylamino)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (5). Method B. Approximately 40 mL (0.7 mol) of methylamine was distilled from sodium into a suspension of 24.03 g (0.1 mol) of **16** in 400 mL of dry benzene and 600 mL of dry ether at −10 °C under nitrogen. A solution of 5.6 mL (0.052 mol) of titanium tetrachloride in 50 mL of dry benzene was then added dropwise to the stirred mixture while holding the temperature at −10 °C. After 30 min, the mixture was warmed to room temperature and stirred until IR no longer showed the ketone carbonyl (2 h). The mixture was filtered and the solids were washed thoroughly with a 2:1 benzene/ether solution. The combined filtrate and washings were concentrated in vacuo to an orange gum, which was dissolved in 400 mL of absolute ethanol and treated with 3.8 g (0.1 mol) of sodium borohydride. After stirring overnight at room temperature under nitrogen, the solution was diluted with 1.0 L of water, stirred for 30 min, and then cooled. The precipitated solid was filtered off and washed with water and petroleum ether to afford, after drying, 16.03 g of pale-yellow solid, mp 199–202 °C. The filtrate was concentrated in vacuo to remove most of the ethanol and then extracted with dichloromethane (2 × 250 mL) and chloroform (200 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to a yellow solid, which on trituration with an ether/petroleum ether mixture afforded 6.80 g of yellow solid, mp 192–196 °C. The total weight of crude product was 22.83 g (89%). Properties of **5**, and of **6–9** prepared in a similar manner, are included in Table I.

1,2,3,4,6,7,12,12b-Octahydro-2-(phenylamino)indolo[2,3-*a*]quinolizine (10). Method C. A mixture of 2.4 g (0.01 mol) of **16**, 1.02 g (0.011 mol) of aniline, 0.1 g of *p*-toluenesulfonic acid monohydrate, and 100 mL of benzene was refluxed for 3.5 h with removal of water by means of a Dean–Stark trap containing 4Å molecular sieves. At this point, IR no longer showed ketone carbonyl. The benzene was removed in vacuo and the reddish residue dissolved in 50 mL of absolute ethanol. This solution was treated with 0.38 g (0.01 mol) of sodium borohydride. After stirring overnight at room temperature, the solution was diluted with an equal volume of water and stirred for several minutes. The ethanol was removed in vacuo and the aqueous residue extracted with dichloromethane (3 × 50 mL). The organic extracts were washed with 50 mL of saturated sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo to a red oil which solidified upon trituration with 25 mL of ether, giving 2.44 g (77%) of crude yellow solid. Recrystallization from methanol afforded 1.21 g (38%) of light-orange solid **10**,[15] mp 160.5–163 °C. Properties of **10**, and of **11–13** prepared in a similar manner, are included in Table I.

2-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine Ethylene Ketal (18). Method D. To a solution of 9.61 g (0.04 mol) of **16** in 1.2 L of benzene was added 10 mL of ethylene glycol and 9.13 g (0.048 mol) of *p*-toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 18 h under nitrogen into a Dean–Stark trap containing 4Å molecular sieves, cooled, diluted with 1.2 L of ether, and washed with 600 mL of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 1.0 L of 1:1 ether/benzene, and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to an orange oil. Trituration with ether and cooling afforded 9.75 g (86%) of yellow crystalline solid **18**. Recrystallization of a 2-g portion afforded 1.75 g of yellow crystalline solid: mp s 193, 195–198 °C.

12-Ethyl-2-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (19). Method E. To a solution of 7.11 g (25.0 mmol) of **18** in 125 mL of dry dimethylformamide and 125 mL of dry benzene at 0 °C under nitrogen was added 0.66 g (27.5 mmol) of sodium hydride. After 30 min at 0 °C, 2.15 mL (28.8 mmol) of ethyl bromide was added. After 1.5 h at 0 °C and 2 h at room temperature, another 0.12 g (5.0 mmol) of sodium hydride and 0.37 mL (5.0 mmol) of ethyl bromide were added, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into 1.0 L of ice–water and extracted with 800 mL and then 400 mL of a 1:1 ether/benzene mixture. The combined organic extracts were washed with water (2 × 800 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 7.30 g (94%) of viscous orange oil.

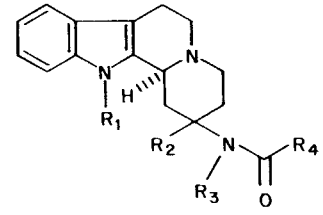
The crude *N*-ethyl ketal from above (7.19 g, 23.0 mmol) was dissolved in 250 mL of 6 N hydrochloric acid and stirred at room temperature under nitrogen for 21 h, cooled to 0 °C, and basified with 50% aqueous sodium hydroxide solution. The mixture was extracted with ether (4 × 250 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to an oily orange solid. Trituration with ether containing a little petroleum ether and cooling afforded 4.76 g (77%) of golden yellow crystalline solid **19**. Recrystallization of 600 mg of this material from benzene/hexane afforded 410 mg of yellow crystalline solid, mp s 130, 133–136 °C.

2-(*N*-Benzyl-*N*-methylamino)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (14). Method F. To a suspension of 0.85 g (22.3 mmol) of lithium aluminum hydride in 35 mL of dry tetrahydrofuran was added, as rapidly as possible, a suspension of 4.0 g (11.1 mmol) of **42** in 100 mL of tetrahydrofuran. After a 3-h reflux under nitrogen, the reaction mixture was quenched with saturated aqueous sodium sulfate solution at 0 °C and filtered, and the salts were washed with 1:1 ether/THF and then with ether. The filtrate was concentrated in vacuo to a colorless foam, which solidified upon trituration with a mixture of 100 mL of petroleum ether and 25 mL of ether. After cooling for 2 h in ice–water, the solid was filtered and washed with petroleum ether to afford 3.55 g (93%) of crude solid: mp s 162, 163.5–165.5 °C. Recrystallization from acetonitrile afforded 2.79 g (73%) of pure **14**, mp 166–168.5 °C.

2-(*N*-Cyano-*N*-methylamino)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (15). Method G. To a mixture of 3.83 g (15.0 mmol) of **5**, 2.25 g (39.0 mmol) of anhydrous sodium acetate, and 45 mL of dry methanol at 0 °C was added dropwise, with stirring under nitrogen, a solution of 1.59 g (15.0 mmol) of cyanogen bromide in 10 mL of methanol. After 30 min, the solvent was removed in vacuo, and the resulting solid was partitioned between 25 mL of 10% aqueous sodium hydroxide solution, 50 mL of water, and 100 mL of chloroform. The phases were separated, the aqueous phase was extracted with 100 mL of chloroform, and the combined organic extracts were washed with 50 mL of water and 50 mL of saturated sodium chloride solution and dried (Na_2SO_4). Concentration in vacuo gave a pale-yellow foam, which solidified upon trituration with ether. Chromatography on 180 g of silica gel and elution with 2% methanol/chloroform afforded 2.34 g (56%) of crude solid. Recrystallization from benzene afforded 1.71 g (41%) of colorless solid **15**, mp s 180, 182–185 °C dec.

2-(*N*-Methylbenzamido)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (42 and 43). Method H. To a stirred solution of 4.54 g (18.0 mmol) of **5** in 100 mL of chloroform containing 2.5 mL (18.0 mmol) of triethylamine was added dropwise under nitrogen at 0 °C a solution of 2.1 mL (18.0 mmol) of benzoyl chloride in 50 mL of chloroform. After 30 min at 0 °C and 3 h at room temperature, 50 mL of 10% aqueous sodium hydroxide solution was added with vigorous stirring. After several minutes, the precipitated solid, 0.72 g of pure 2α-H,12bα-H isomer **42**, was filtered off and the phases of the filtrate were separated. The aqueous phase was extracted with chloroform (3 × 50 mL), and the combined extracts were washed with 100 mL of water, dried (Na_2SO_4), and concentrated in vacuo to a solid mixture of isomers. Recrystallization from acetonitrile afforded an additional 3.22 g of crude solid **42** (3.94 g total, 60% yield). Recrystallization from acetonitrile and then from chloroform afforded 2.76 g (42%) of colorless solid 2α-H,12bα-H isomer **42**, mp s 223, 227–228 °C.

Table III. Amides[a]



compd	R_1	R_2	R_3	R_4	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent	formula	anal.[d]	change in systolic BP, mmHg,[i] day 3, 2 h postdrug (mg/kg po)
20	H	H	H	CH_3	4	H	267-270[j]	29.9	CH_3CN	$C_{17}H_{21}N_3O$	C, H, N	−20 ± 9.7 (50)
21	H	α-H	H	C_6H_5	4	H	235-239[j]	23.2	CH_3CN	$C_{22}H_{23}N_3O$	C, H, N	+1 ± 9.3 (50)
22	H	α-H	H	C_6H_4-*p*-CH_3	4	H	270-272[j]	26.2	C_2H_5OH	$C_{23}H_{25}N_3O$	C, H, N	−18 ± 17.5 (50)
23	H	β-H	H	C_6H_4-*p*-CH_3	4	H	229-232	9.8	CH_3CN	$C_{23}H_{25}N_3O$	C, H, N	−32 ± 12.4 (25)
24	H	α-H	H	C_6H_4-*m*-CH_3	4	H	205.5-208.5	38.8	benzene	$C_{23}H_{25}N_3O$	C, H, N	−49 ± 10.0 (50)
25	H	β-H	H	C_6H_4-*m*-CH_3	4	H	199-203[j]	8.5	benzene	$C_{23}H_{25}N_3O$	C,[f] H, N	−53 ± 17.3 (25)
26	H	α-H	H	C_6H_4-*o*-CH_3	4	H	225-227[j]	26.5	CH_3CN	$C_{23}H_{25}N_3O$	C, H, N	+13 ± 19.5 (50)
27	H	α-H	H	C_6H_4-*p*-OCH_3	4	H	275.5-277.5	38.5	C_2H_5OH	$C_{23}H_{25}N_3O_2$	C, H, N	+10 ± 5.4 (25)
28	H	β-H	H	C_6H_4-*p*-OCH_3	4	H	204-207.5[j]	2.1	benzene	$C_{23}H_{25}N_3O_2$	C, H, N	nt
29	H	α-H	H	C_6H_4-*m*-OCH_3	4	H	208-210	33.4	benzene	$C_{23}H_{25}N_3O_2$	C, H, N	−18 ± 9.2 (50)
30	H	α-H	H	C_6H_2-3,4,5-$(OCH_3)_3$	4	H	258-260[j]	26.3	CH_3CN	$C_{25}H_{29}N_3O_4$	C, H, N	−25 ± 8.3 (25)
31	H	β-H	H	C_6H_2-3,4,5-$(OCH_3)_3$	4	H	223-226[j]	2.0	benzene	$C_{25}H_{29}N_3O_4$	C, H, N	nt
32	H	α-H	H	C_6H_4-*p*-F	4	H	250-253.5[j]	45.3	CH_3CN	$C_{22}H_{22}FN_3O$	C, H, N, F	−24 ± 4.4 (25)
33	H	α-H	H	C_6H_4-*p*-Cl	4	H	259-261	39.3	CH_3CN	$C_{22}H_{22}ClN_3O$	C, H, N, Cl	−3 ± 7.6 (50)
34	H	α-H	H	C_6H_4-*o*-Cl	4	H	232.5-235[j]	32.8	CH_3CN	$C_{22}H_{22}ClN_3O$	C, H, N, Cl	−26 ± 15.0 (50)
35	H	α-H	H	C_6H_4-*o*-Br	4	H	241-244[j]	30.5	CH_3CN	$C_{22}H_{22}BrN_3O$	C, H, N, Br	−24 ± 3.5 (50)
36	H	β-H	H	C_6H_4-*o*-Br	4	H	244.5-247[j]	11.9	CH_3CN	$C_{22}H_{22}BrN_3O$	C, H, N, Br	+18 ± 26.2 (50)
37	H	α-H	H	C_6H_4-*m*-CF_3	4	H	231-234	27.9	CH_3CN	$C_{23}H_{22}F_3N_3O$	C, H, N, F	−3 ± 11.3 (50)
38	H	α-H	H	C_6H_4-*p*-NO_2·HCl	4	H	251.5-252.5[j]	19.8	aq C_2H_5OH	$C_{22}H_{22}N_4O_3$·HCl	C, H, N, Cl	+15 ± 37.8 (50)
39	H	α-H	H	C_6H_4-*p*-NH_2	38	K	274.5-277.5[j]	52.7	CH_3CN	$C_{22}H_{24}N_4O$	C, H, N	−31 ± 8.6 (50)
40	H	α-H	H	C_6H_3-3,4-(-OCH_2O-)	4	H	238.5-242[j]	24.3	benzene	$C_{23}H_{23}N_3O_3$	C, H, N	−52 ± 3.9 (50)
41	H	H	H	2-furyl	4	H	185-188[j]	34.2	CH_3CN	$C_{20}H_{21}N_3O_2$	C, H, N	0 (50)
42	H	α-H	CH_3	C_6H_5	5	H	227-228	42.7	$CHCl_3$	$C_{23}H_{25}N_3O$	C, H, N	−103 ± 11.5 (50), −41 ± 5.3 (10), −19 ± 6.5 (5)
43	H	β-H	CH_3	C_6H_5	5	H	254-256	3.4	CH_3CN	$C_{23}H_{25}N_3O$	C, H, N	−17 ± 10.8 (15)
44	C_2H_5	H	CH_3	C_6H_5	6	H	185-188	65.4	CH_3CN	$C_{25}H_{29}N_3O$	C, H, N	−67 ± 12.0 (50) −63 ± 3.9 (25)
45	H	H	CH_3	C_6H_4-*o*-CH_3·0.5H_2O	5	H	264-267[j]	40.0	$CHCl_3$/ether	$C_{24}H_{27}N_3O$·0.5H_2O	C,[g] H, N	−44 ± 5.0 (50)
46	H	α-H	CH_3	C_6H_4-*p*-OCH_3	5	H	172-175	57.5	CH_3CN	$C_{24}H_{27}N_3O_2$	C, H, N	−50 ± 7.9 (50), −72 ± 22.0 (25) −86 ± 11.4 (10), −53 ± 15.1 (5)
47	H	H	CH_3	C_6H_4-*p*-F	5	H	229-231[j]	43.0	CH_3CN	$C_{23}H_{24}FN_3O$	C, H, N	−20 ± 7.6 (50)

48	H	H	CH_3	C_6H_4-*m*-F	5	H	234–238[i]	65.4	$CHCl_3$	$C_{23}H_{24}FN_3O$	C, H, N	−110 ± 21.8 (50), −76 ± 6.0 (25)
49	H	H	CH_3	C_6H_4-*p*-Cl	5	H	221–223[i]	78[e]	CH_3CN	$C_{23}H_{24}ClN_3O$	C, H, N	−6 ± 19.0 (50)
50	H	H	CH_3	C_6H_4-*m*-Cl	5	H	238–241[j]	63.3	$CHCl_3$	$C_{23}H_{24}ClN_3O$	C, H, N	−79 ± 13.6 (50), −54 ± 7.6 (25)
51	H	H	CH_3	C_6H_4-*o*-Cl	5	H	261–264[j]	66.0	$CHCl_3$	$C_{23}H_{24}ClN_3O$	C, H, N	−13 ± 8.7 (25)
52	H	H	CH_3	C_6H_4-*m*-CF_3	5	H	174–176[j]	33.5	CH_3CN	$C_{24}H_{24}F_3N_3O$	C, H, N, F	−48 ± 9.0 (50), −56 ± 10.0 (25)
53	H	H	C_2H_5	C_6H_5	7	H	222–226[j]	73.0	$CHCl_3$	$C_{24}H_{27}N_3O$	C, H, N	−83 ± 19.5 (50), −92 ± 11.8 (25)
54	H	H	*n*-C_3H_7	C_6H_5	8	H	220.5–223	84[e]	CH_3CN	$C_{25}H_{29}N_3O$	C, H, N	−16 ± 5.5 (50)
55	H	H	c-C_3H_5	C_6H_5	9	H	133–138	47.0	*i*-C_3H_7OH	$C_{25}H_{27}N_3O$	C, H, N	−26 ± 10.0 (50)
56	H	α-H		$-CH_2C_6H_4$-*o*-	4	I	257.5–260.5[j]	30.8	toluene	$C_{23}H_{23}N_3O$	C, H, N	+2 ± 5.5 (50)
57	H	β-H		$-CH_2C_6H_4$-*o*-	4	I	216–219[j]	7.6	CH_2Cl_2/ether	$C_{23}H_{23}N_3O$	C, H, N	nt
58	H	α-H	H	NHC_6H_5	4	J	199–202[j]	17.6	CH_3CN	$C_{22}H_{24}N_4O$	C, H, N	−22 ± 6.1 (50)
59	H	β-H	H	NHC_6H_5	4	J	221–224[j]	5.9	$CHCl_3$	$C_{22}H_{24}N_4O$	C, H, N	−6 ± 12.0 (25)
indoramin hydrochloride (1)												−79 (50)

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material, unless otherwise noted; yields were not optimized. [d] Analytical results within ±0.4% of theoretical values, unless otherwise noted. [e] Crude yield. [f] C: calcd, 76.85; found, 77.36. [g] C: found, 74.84. [h] H: calcd, 6.41; found, 6.00. [i] All values are plus or minus SEM. [j] Decomposition.

Three additional crops were obtained from the mother liquor: the second crop (0.77 g) was an isomeric mixture, while the third and fourth crops contained only the more polar isomer (0.21 g). The second crop and the mother liquors were combined and chromatographed on 40 g of silica gel. Elution with 5% methanol/chloroform solution afforded 0.18 g of oil, which upon trituration with ether afforded another 0.12 g of crude, more polar isomer. Recrystallization of the crude material (0.33 g total, 5.1% yield) from acetonitrile afforded 0.22 g of pure 2β-H,12bα-H isomer **43**, mp s 252, 254–256 °C. Properties of **42** and **43**, and of **20–38** and **40–55** prepared in a similar manner, may be found in Table III.

1,2,3,4,6,7,12,12b-Octahydro-2-phthalimidinoindolo[2,3-*a*]quinolizine (56 and 57). Method I. A mixture of 3.62 g (15.0 mmol) of amine **4**, 4.37 g (18.0 mmol) of ethyl α-bromo-*o*-toluate, 4.15 g (30.0 mmol) of anhydrous potassium carbonate, and 175 mL of dry dimethylformamide was stirred overnight at 85 °C under nitrogen. The brown reaction mixture was cooled, diluted with chloroform (300 mL), washed with water (3 × 250 mL) and saturated sodium chloride solution (100 mL), and dried (Na_2SO_4). Concentration in vacuo afforded an oil containing DMF. This oil was dissolved in a mixture of benzene (300 mL), ether (300 mL), and dichloromethane (75 mL). This solution was washed with water (250 mL), resulting in an emulsion. The bottom emulsified layer was drawn off, and the top organic layer was washed with water (2 × 250 mL). The water washes and emulsified phase were combined and chloroform was added until the emulsion broke up. The chloroform layer and organic extracts were combined, dried (Na_2SO_4), and concentrated to afford a foam weighing 6.02 g, which solidified upon trituration with ether. The crude solid, which TLC showed to be a mixture of the 2α- and 2β-H isomers, weighed 3.32 g, mp 222–233 °C dec. An additional 0.37 g of crude material from another experiment was combined with this material and chromatographed on 185 g of silica gel. Elution with 2% methanol/chloroform afforded 1.96 g of the major 2α-H,12bα-H isomer **56**, mp s 247, 250.5–256 °C dec (3.2% crude yield). Recrystallization from toluene afforded 1.65 g of **56** as a light-brown solid, mp s 254, 257.5–260.5 °C dec. Further elution of the column, with 2% and then 3% methanol/chloroform, afforded the minor (2β-H,12bα-H) isomer **57**, as a foam. Trituration of this material with a dichloromethane/ether mixture caused solidification to occur. The crude minor isomer, 0.66 g (10.8% crude yield), was recrystallized from dichloromethane/ether to afford 0.41 g of pure **57**, mp s 213, 216–219 °C dec.

***N*-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizinyl)-*N*'-phenylurea (58 and 59). Method J.** A solution of 4.16 g (17.0 mmol) of amine **4** in 100 mL of chloroform was treated dropwise under nitrogen at room temperature with a solution of 2.03 g (17.0 mmol) of phenyl isocyanate in 25 mL of chloroform. After 90 min, the solvent was removed in vacuo, and the gummy residue was triturated with ether (125 mL) and then refrigerated overnight Filtration afforded 4.28 g of crude product as a mixture of isomers. This material was chromatographed on 200 g of silica gel; the less polar isomer was eluted with 3% methanol/chloroform solution and the more polar isomer with 5% methanol/chloroform solution. Crude less polar isomer (1.79 g; 29.2%) was thus obtained. Recrystallization from acetonitrile, followed by azeotropic treatment of the recrystallized material with benzene, removal of the solvent, and trituration with ether, afforded 1.08 g of pure 2α-H,12bα-H isomer **58** mp s 197, 199–202 °C dec. The more polar isomer was obtained as a gum, which solidified upon trituration with ether to afford 0.88 g of crude solid. Trituration with chloroform removed virtually all impurities, to afford 0.61 g (10%) of material. Recrystallization from chloroform afforded 0.36 g of pure 2β-H,12bα-H isomer **59**, mp 221–224 °C.

2-(*p*-Aminobenzamido)-1,2α,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine (39). Method K. A solution of 1.31 g (3.1 mmol) of **38** in 45 mL of 80% aqueous dimethylformamide was hydrogenated overnight over 135 mg of 10% palladium on carbon at 45 psi of hydrogen. The catalyst was filtered off and washed with water and methanol, and the filtrate was made basic with 25 mL of 10% aqueous sodium hydroxide solution. This mixture was extracted with chloroform (1 × 50 mL, 2 × 25 mL). The extracts were washed with saturated sodium chloride solution, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a gum, which solidified upon trituration with ether. The crude solid

weighed 0.93 g: chromatography on 65 g of silica gel along with 0.5 g of previously prepared material afforded a gum upon elution with 2% and then 5% methanol/chloroform. The gum solidified upon trituration with chloroform to afford, in two crops, 0.88 g of solid, mp s 249, 250–253 °C dec (45.1% yield). Recrystallization from acetonitrile afforded 0.59 g of pure **39**, mp s 271, 274.5–277.5 °C dec.

SHR Test for Antihypertensive Activity. Compounds were screened for antihypertensive activity using genetically spontaneous hypertensive rats (SHR) by a standard indirect tail–cuff method.[16] Two rats were placed into a wire basket in an incubator set to 40 °C. Each cage of rats was left to condition in the incubator for 20 min; then the rats were removed and placed in individual trigonal or trapezoidal cages made of Lucite. A tubular inflatable cuff was placed around the base of the tail. A microphone (Narco Bio-Systems or Biodynamics) was placed under the ventral surface of the tail and the tail was strapped down. When the microphone was properly located, the pulse could be detected and was amplified by a universal type amplifier. Each microphone was connected to an individual channel on a recorder, and the pulse was recorded. The cuff was inflated to approximately 300 mmHg. The pulse was thereby obliterated. The pressure in the cuff was slowly released and, as the pressure fell below the systolic pressure, the pulse could again be detected by the microphone. The blood pressure of each rat was determined three to five times from which a mean value was derived. Before any animal was included in the screening program, a 2-week training period was employed to acclimate the animal to the test environment. Also, this procedure permitted the establishment of base-line blood pressure for each animal. Any animal whose blood pressure was less than 175 mmHg was withdrawn from the test group.

In a standard 3-day test, systolic blood pressure readings were made at 0 time (control) on days 1 and 3 and at 2 h after administration of the compound on day 3. Dosing was orally at the dose listed in Table I at 0 h on days 1, 2, and 3 on groups of six animals per test. Activity was determined by comparison of the treatment blood-pressure values with the 0 time (control) blood pressure readings. Comparisons were made using the paired Student's t test method for evaluation of statistical significance.[17] Any drug which caused a drop in blood pressure which exceeded 15 mmHg was considered active.

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(13) Intravenous challenges with epinephrine, norepinephrine, isoproterenol, carbachol, and tyramine were routinely used.
(14) Subsequent reduction of the crude unhydrated oxime to the primary amine **4** using Vitride was found to proceed more readily and in approximately 20% better yield than reduction of the hydrated oxime.
(15) To remove all the methanol from the recrystallized material, it was necessary to melt the solid at 110 °C in vacuo, crush the resolidified material in a mortar and pestle, and dry it further at 80 °C in vacuo.
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