Antitumor Testing. CD_1 mice, weighing 18–20 g, were implanted subcutaneously in the right ventrolateral area with 4×10^7 sarcoma 180J tumor cells. Test substances were dissolved or suspended in sterile deionized water, and treatment, 1.0 mL, was given intraperitoneally shortly after implantation and once daily thereafter for a total of eight treatments. Mice were sacrificed 1 day after the last treatment. An antitumor effect was defined as ≥50% reduction in tumor growth.

Acknowledgment. The authors are indebted to the Physical Chemistry Department, Hoffmann-La Roche Inc., for providing IR, UV, NMR, and MS data and to Dr. J. F. Blount for providing an X-ray analysis of compound **5**.

Antihypertensive Ureidopiperidines

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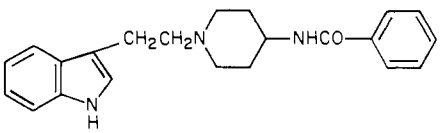
The synthesis of a series of 1-aralkyl-4-ureidopiperidines is reported. These compounds are related to the benzamidopiperidines exemplified by indoramin. Some of the ureidopiperidines are more potent antihypertensive agents than their benzamidopiperidine counterparts. Two examples, 1-(2-thenoyl)-3-[1-[2-(3-indolyl)ethyl]piperid-4-yl]urea and 1-(2-thenoyl)-3-[1-[4-(4-fluorophenyl)-4-oxobutyl]piperid-4-yl]urea (**19** and **58**), emerged as the most potent antihypertensive agents in this series.

Previous publications from these laboratories[1-3] have dealt with the origins and development of indoramin and related benzamidopiperidines. Indoramin is an antihypertensive agent incorporating competitive postsynaptic α-adrenoceptor antagonist and myocardial membrane stabilizing properties. Therapeutic advantages of this mechanism of action have been reviewed.[4,5] As an extension of this work, we now report the synthesis and pharmacological activities of a variety of ureidopiperidines, in which the benzamido group of indoramin (**67**, Table II) and related compounds has been replaced by aryl or aroylureido substituents.



indoramin (67)

It has been found that some of these compounds show equivalent or enhanced antihypertensive activities as compared with their benzamidopiperidine counterparts. Testing for antihypertensive activities has been carried out in DOCA/saline or renal hypertensive rats.[6,7,9] The general structure at the head of Table I indicates the range of modifications covered in this work. Compounds are listed in Table I in order of increasing length of the –A– chain which links the R_1 and piperidine moieties. An important limitation in scope is that compounds where –A– is CH_2 are excluded. This is because a profound shift in biological profile has been discovered among these latter compounds, which are virtually devoid of antihypertensive activity, suggesting potential therapeutic utility as psychotropic agents, and they will therefore be the subject of a separate publication.

Chemistry. Methods used to prepare the compounds described in this publication can be grouped into eight general types. These are illustrated in Scheme I by representative examples for each of the methods (A to H), which are the same examples as are exemplified under Experimental Section. Methods used for individual compounds are indicated by code letters in Table I. Method A involves reaction of an isocyanate (R_3NCO) or isothiocyanate (R_3NCS) with an appropriately substituted 4-aminopiperidine. This is the most generally applicable and widely used method. Method B involves hydrolysis of a 1-(4-piperidyl)-3-acylurea or thiourea to give the 3-unsubstituted urea or thiourea. The former can also be obtained directly from the corresponding aminopiperidine by reaction with potassium cyanate (method A'). Method C involves reacylation of a primary urea, as obtained by method A' or B, with an acid chloride (R_3COCl). Method D involves alkylation of a 1-unsubstituted 4-ureidopiperidine with an aralkyl halide or tosylate, such as 3-(2-bromoethyl)indole. Method E involves reaction of an aroyl cyanamide with an appropriately substituted 4-aminopiperidine. Method F involves reduction of a carbonyl-containing A chain to give a hydroxy-substituted A chain. Method G involves reaction of an epoxide with an appropriately substituted 4-aminopiperidine. Method H involves reduction of a carbonyl group in the A chain to a methylene group. The most widely used methods are A to D. In all but three instances (compounds **1**, **33**, and **44**), compounds were isolated and tested as hydrochloride salts. Diastereoisomeric benzodioxans (**28–38**) were either obtained by fractional crystallization or by starting with a pure diastereoisomeric bromo alcohol or epoxide precursor. Stereochemical assignments were based on analysis of NMR data by methods similar to those of Howe et al.[8]

Results

An evaluation of the antihypertensive activities of compounds in Table I was carried out in conscious renal hypertensive (RHR) or DOCA/saline hypertensive rats.[6,7] Systolic blood pressure was measured by an indirect tail-cuff technique.[9] Results are presented in Table II.

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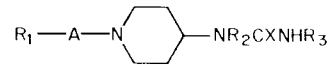
Table I. Antihypertensive Ureidopiperidines



no.	R_1	A	R_2	X	R_3	crystn solvent	mp, °C	% yield	method	formula[c]
1	indol-3-yl	CH_2CH_2	H	O	H	MeOH	212	85, 89	B, A′	$C_{16}H_{22}N_4O$[d]
2	indol-3-yl	CH_2CH_2	H	O	C_6H_5	EtOH	214–219	69	A	$C_{22}H_{26}N_4O\cdot HCl\cdot 0.5H_2O$
3	indol-3-yl	CH_2CH_2	H	O	C_6H_4-4-Cl	MeOH	244	81	A	$C_{22}H_{25}ClN_4O\cdot HCl\cdot 0.5H_2O$
4	indol-3-yl	CH_2CH_2	H	O	C_6H_3-3,4-Cl_2	EtOH	258	74	A	$C_{22}H_{24}Cl_2N_4O\cdot HCl$
5	indol-3-yl	CH_2CH_2	H	O	C_6H_4-4-OCH_3	EtOH	220	87	A	$C_{23}H_{28}N_4O_2\cdot HCl\cdot H_2O$
6	indol-3-yl	CH_2CH_2	H	O	C_6H_4-3-CH_3	EtOH	229	76	A	$C_{23}H_{28}N_4O\cdot HCl$
7	indol-3-yl	CH_2CH_2	H	O	C_6H_4-2,6-$(CH_3)_2$	EtOH	240	52	A	$C_{24}H_{30}N_4O\cdot HCl$[e]
8	indol-3-yl	CH_2CH_2	H	O	C_6H_4-2-CF_3	EtOH	234	82	A	$C_{23}H_{25}F_3N_4O\cdot HCl$
9	indol-3-yl	CH_2CH_2	H	O	C_6H_4-3-CF_3	EtOH	200	37	A	$C_{23}H_{25}F_3N_4O\cdot HCl$
10	indol-3-yl	CH_2CH_2	H	O	$(CH_2)_3CH_3$	IPA-EtOAc	195–197	22	D	$C_{20}H_{30}N_4O\cdot HCl\cdot 0.25H_2O$
11	indol-3-yl	CH_2CH_2	H	O	C_6H_{11}	EtOH	222	58	A	$C_{22}H_{32}N_4O\cdot HCl\cdot H_2O$
12	indol-3-yl	CH_2CH_2	H	S	H	EtOH	228–229	69	B	$C_{16}H_{22}N_4S\cdot HCl$
13	indol-3-yl	CH_2CH_2	H	S	C_6H_5	EtOH	225	84.5	A	$C_{22}H_{26}N_4S\cdot HCl$
14	indol-3-yl	CH_2CH_2	CH_3	S	C_6H_5	EtOH	194	28	A	$C_{23}H_{28}N_4S\cdot HCl$
15	indol-3-yl	CH_2CH_2	H	S	COC_6H_5	MeOH	212–215	60	B	$C_{23}H_{26}N_4OS\cdot HCl\cdot 0.25H_2O$
16	indol-3-yl	CH_2CH_2	H	O	COC_6H_5	MeOH	248	63	A	$C_{23}H_{26}N_4O_2\cdot HCl$
17	indol-3-yl	CH_2CH_2	CH_3	O	C_6H_5	EtOH	218	33	A	$C_{23}H_{28}N_4O\cdot HCl\cdot 0.25H_2O$
18	indol-3-yl	CH_2CH_2	CH_3	O	COC_6H_5	IPA	224–225	45	A	$C_{24}H_{28}N_4O_2\cdot HCl\cdot 0.5H_2O$
19	indol-3-yl	CH_2CH_2	H	O	2-thenoyl	MeOH	247	25	C	$C_{21}H_{24}N_4O_2S\cdot HCl\cdot 0.5H_2O$
20	indol-3-yl	CH_2CH_2	H	NH	COC_6H_5	Et_2O-EtOH	160–170 dec	81	E	$C_{23}H_{26}N_5O\cdot 2HCl\cdot H_2O$
21	1-CH_3-indol-3-yl	CH_2CH_2	H	O	COC_6H_5	MeOH	233–234	51	A	$C_{24}H_{28}N_4O_2\cdot HCl$
22	indol-3-yl	CH_2CH_2	H	O	COC_6H_{11}	MeOH, Et_2O, EtOH	236	48	C	$C_{23}H_{32}N_4O_2\cdot HCl\cdot 0.5H_2O$
23	indol-3-yl	CH_2CH_2	C_2H_5	O	C_6H_5	MeOH	218–220	30	A	$C_{24}H_{30}N_4O\cdot HCl\cdot H_2O$
24	C_6H_5	CH_2CH_2	H	O	COC_6H_5	EtOH-H_2O (4:1)	215–216	46	H	$C_{21}H_{25}N_3O_2\cdot HCl$
25	indol-3-yl	$COCH_2$	H	O	COC_6H_5	MeOH	269–270	98	D	$C_{23}H_{24}N_4O_3\cdot HCl\cdot H_2O$
26	1,4-benzodioxan-2-yl	$COCH_2$	H	O	COC_6H_5	MeOH	160–161	76	D	$C_{23}H_{25}N_3O_5\cdot HCl$
27	C_6H_5	$COCH_2$	H	O	COC_6H_5	IPA	210–212	92	D	$C_{21}H_{23}N_3O_3\cdot HCl\cdot 0.25H_2O$
28	1,4-benzodioxan-2-yl	$CHOHCH_2$[a]	H	O	COC_6H_5	MeOH	212–214	12	F, G	$C_{23}H_{27}N_3O_5\cdot HCl\cdot 0.25H_2O$[f]
29	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	COC_6H_5	MeOH	213–216	8	D, F, G	$C_{23}H_{27}N_3O_5\cdot HCl$
30	1,4-benzodioxan-2-yl	$CHOHCH_2$[a]	H	O	C_6H_5	EtOH	214–216	4	A	$C_{22}H_{27}N_3O_4\cdot HCl$
31	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	C_6H_5	EtOH	214–215	28	A	$C_{22}H_{27}N_3O_4\cdot HCl$
32	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	C_6H_{11}	EtOAc	214–216	47	A	$C_{22}H_{33}N_3O_4\cdot HCl$
33	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	COC_6H_4-4-OCH_3	C_6H_5	198–199	15	A	$C_{24}H_{29}N_3O_6\cdot 0.5H_2O$
34	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	C_6H_4-4-OCH_3	EtOH-EtOAc	204–206	30	A	$C_{23}H_{29}N_3O_5\cdot HCl$
35	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	COC_6H_4-4-F	EtOH	227–228	42	D	$C_{23}H_{26}FN_3O_5\cdot HCl$
36	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	S	COC_6H_4-Cl	EtOH	187–189	20	A	$C_{23}H_{26}N_3ClO_4S\cdot HCl\cdot 0.5H_2O$
37	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	O	C_6H_4-4-Cl	EtOH	205–207	16	A	$C_{22}H_{26}ClN_3O_4\cdot HCl\cdot 0.25H_2O$
38	1,4-benzodioxan-2-yl	$CHOHCH_2$[b]	H	S	C_6H_5	IPA-Et_2O	204–206	53	A	$C_{22}H_{27}N_3O_3S\cdot HCl$
39	C_6H_5	$CHOHCH_2$	H	O	COC_6H_5	MeOH	244–246	48	G	$C_{21}H_{25}N_3O_3\cdot HCl\cdot 0.5H_2O$
40	indol-3-yl	$(CH_2)_3$	H	O	COC_6H_5	EtOH-Et_2O	268–269	38	D	$C_{24}H_{28}N_4O_2\cdot HCl$
41	indol-3-yl	$CO(CH_2)_3$	H	O	C_6H_5	MeOH-Et_2O	243–244	39	A	$C_{24}H_{28}N_4O_2\cdot HCl$
42	indol-3-yl	$CO(CH_2)_3$	H	O	COC_6H_5	EtOH-EtOAc	238–240	48	A	$C_{25}H_{28}N_4O_3\cdot HCl\cdot 0.5H_2O$
43	indol-3-yl	$CO(CH_2)_3$	H	O	2-thenoyl	EtOH	246–247	32	C	$C_{23}H_{26}N_4O_3S\cdot HCl\cdot H_2O$
44	C_6H_5	$CO(CH_2)_3$	H	O	H	BuOAc	159	67	B	$C_{16}H_{23}N_3O_2$
45	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_5	EtOH	190	78	A	$C_{22}H_{27}N_3O_2\cdot HCl$
46	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_4-4-OCH_3	EtOH	199	59	A	$C_{23}H_{29}N_3O_3\cdot HCl$

47	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_4-3-CH_3	EtOH	182	34	A	$C_{23}H_{29}N_3O_2 \cdot HCl$[g]
48	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_3-2,6-$(CH_3)_2$	EtOH	214	40	A	$C_{24}H_{31}N_3O_2 \cdot HCl$
49	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_4-2-CF_3	EtOH	194	29	A	$C_{23}H_{26}F_3N_3O_2 \cdot HCl$
50	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_4-4-Cl	EtOH	245	65	A	$C_{22}H_{26}ClN_3O_2 \cdot HCl$
51	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_3-3,4-Cl_2	EtOH	218	46	A	$C_{22}H_{25}Cl_2N_3O_2 \cdot HCl$
52	C_6H_5	$CO(CH_2)_3$	H	O	C_6H_4-3-CF_3	EtOH	192–195	43	A	$C_{23}H_{26}F_3N_3O_2 \cdot HCl \cdot H_2O$
53	C_6H_5	$CO(CH_2)_3$	H	S	C_6H_5	EtOH-Et_2O	221	56	A	$C_{22}H_{27}N_3OS \cdot HCl$
54	C_6H_5	$CO(CH_2)_3$	H	S	COC_6H_5	EtOH-Et_2O	187	26	A	$C_{23}H_{27}N_3O_2S \cdot HCl \cdot 0.25H_2O$
55	C_6H_5	$CO(CH_2)_3$	H	O	COC_6H_5	EtOH	202	52	A, C	$C_{23}H_{27}N_3O_3 \cdot HCl \cdot 2H_2O$
56	C_6H_5	$CO(CH_2)_3$	H	NH	COC_6H_5	MeOH	238–244	34	E	$C_{23}H_{28}N_4O_2 \cdot 2HCl \cdot 2H_2O$[h]
57	C_6H_5	$CO(CH_2)_3$	H	O	2-thenoyl	EtOH-Et_2O	118–119	13	A	$C_{21}H_{25}N_3O_3S \cdot HCl$
58	4-F-C_6H_4	$CO(CH_2)_3$	H	O	2-thenoyl	EtOH-Et_2O	218–219	20	A	$C_{21}H_{24}FN_3O_3S \cdot HCl \cdot 0.25H_2O$
59	4-F-C_6H_4	$CO(CH_2)_3$	H	O	COC_6H_5	EtOH	207–208	9	D	$C_{23}H_{26}FN_3O_3 \cdot HCl \cdot H_2O$
60	2-CH_3O-C_6H_4	$OCH_2CHOHCH_2$	H	O	COC_6H_5	MeOH	186–188	22	G	$C_{23}H_{29}N_3O_5 \cdot HCl \cdot H_2O$
61	4-CH_3CONH-C_6H_4	$OCH_2CHOHCH_2$	H	O	COC_6H_5	EtOH	232–233	70	G	$C_{24}H_{30}N_4O_5 \cdot HCl \cdot 0.25H_2O$
62	1-naphthyl	$OCH_2CHOHCH_2$	H	O	COC_6H_5	EtOH	114–116	30	D	$C_{26}H_{29}N_3O_4 \cdot HCl \cdot 0.25H_2O$
63	2-CH_3O-C_6H_4	$OCH_2CHOHCH_2$	H	O	C_6H_5	EtOH	191–193	27	G	$C_{22}H_{29}N_3O_4 \cdot HCl \cdot 0.25H_2O$
64	1-naphthyl	$OCH_2CHOHCH_2$	H	O	C_6H_5	EtOH	236–238	27	D	$C_{25}H_{29}N_3O_3 \cdot HCl$
65	2-CH_3O-C_6H_4	$OCH_2CHOHCH_2$	H	O	COC_6H_4-4-OCH_3	IPA	203–205	29	G	$C_{24}H_{31}N_3O_6 \cdot HCl$
66	2-CH_3O-C_6H_4	$OCH_2CHOHCH_2$	H	O	COC_6H_4-4-F	EtOH-EtOAc	194–195	18	G	$C_{23}H_{28}FN_3O_5 \cdot HCl \cdot 0.5H_2O$

[a] Threo isomer. [b] Erythro isomer. [c] All compounds were analyzed for C, H, and N, and results were within ±0.4% of theoretical values for the formulas given, except where indicated by superscript in this column. [d] C: calcd, 67.10; found, 67.56. [e] N: calcd, 13.12; found, 12.63. [f] N: calcd, 9.01; found, 8.50. [g] C: calcd, 63.60; found, 64.07. [h] C: calcd, 55.09; found, 55.60.

Greater detail is given for the DOCA/saline rat results, since a majority of the compounds were evaluated in this model. RHR results are given where DOCA/saline results were unavailable, and both results are given in some instances for comparative purposes. The mean starting systolic pressure for each group of four rats in the DOCA/saline model is given as an indication of the extent to which hypertension was established (a range of starting systolic pressures for the RHR model is given in footnote *b*). The percentage falls in systolic blood pressure in the DOCA/saline model are recorded at 2, 6, and 24 h after dosing to give some indication of duration of action. Activities at three doses (50, 25, and 10 mg/kg po) are given for several of the more active examples. In some instances these do not indicate a simple dose–response relationship. More extensive evaluation will be needed in order to clarify this aspect. Percentage falls in systolic pressure in the RHR model were recorded at 1.5 and 4 h after dosing, and the results in Table II signify that the indicated pressure drops were observed at either or both of these time points.

Marked antihypertensive activities were observed with eight examples (compounds **16–19**, **22**, **45**, **58**, and **59**), of which five were (indolylethyl)piperidines and three were (benzoylpropyl)piperidines. Thus, it appears that either indolylethyl or benzoylpropyl substituents on the piperidine ring nitrogen can provide the most active antihypertensive agents in this series. This parallels experience with the benzamidopiperidines, where optimal length for the chain linking the aryl moiety with the piperidine 1 position was 2 carbons for indole and 4 for phenyl or substituted phenyl.[1,3] Halogen substitution in the benzene ring of the benzoylpropyl compounds appeared to be beneficial, but no advantageous indole substitutents were discovered.

Benzodioxan analogues (**26** and **28–38**) were not notable for their antihypertensive activity, but one example (**29**) did dramatically decrease heart rate (51.5 and 48.5% of starting levels at 2 and 6 h after dosing). This effect was confined to the erythro isomer, as was the modest antihypertensive activity of **31**.

Modification to the urea portion of the molecule can be most easily considered in terms of the general structure at the head of Table I. Replacement of R_2 = H by R_2 = alkyl had a variable effect. In one sequence where examples with R = H, CH_3, and C_2H_5 were examined (**2**, **17**, and **23**), R = CH_3 (**17**) was optimal. In other examples, R = CH_3 was not better than R = H. Replacement of urea (X = O) by thiourea (X = S) generally decreased activity. Antihypertensive activity was in most cases greatest when R_3 was aroyl or heteroaroyl.

Among the eight highly active examples mentioned earlier, compounds **19** and **58** were the most promising in that they retained marked activity at the lowest doses tested (10 mg/kg po). Comparing these with their closest analogues, it appears that 2-thenoyl is a slightly more beneficial substituent on the terminal nitrogen of the urea than is benzoyl and that when the indolylethyl moiety is replaced by benzoylpropyl it should have a *p*-fluoro substituent for optimal activity. Thus, an overall optimal structure emerges as

where R = indol-3-yl (**19**) or 4-F-$C_6H_4COCH_2$ (**58**).

Experimental Section

Melting points are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer and ^1H NMR

Table II. Antihypertensive Activity[a]

	RHR		DOCA/saline rats						RHR		DOCA/saline rats				
	dose, mg/kg		dose, mg/kg		% falls[d]				dose, mg/kg		dose, mg/kg		% falls[d]		
no.	po	act.[b]	po	SP[c]	2 h	6 h	24 h	no.	po	act.[b]	po	SP[c]	2 h	6 h	24 h
1	40	28						34			50	190	17	*	*
2	40	29						35			50	183	17	*	*
3	40	21						36			50	175	*	*	*
4	40	15						37			50	178	*	*	*
5	40	27						38			50	182	26	*	*
6	40	14						39			50	182	21	*	*
7	75	±						40			50	191	*	*	*
8	40	±						41			50	187	*	*	*
9			50	208	*	*	*	42			50	187	16	*	*
10			50	172	*	29	*	43			50	181	*	*	*
11			50	176	15	*	*	44							
12			50	189	20	*	*	45	40	39	50	205	31	24	*
13	40	21						46	40	±					
14			50	172	*	*	*	47	40	21					
15			50	200	*	*	*	48	40	±					
16	40	48	50	179	49	49	38	49			50	208	20	20	*
			25	171	51	48	21	50			50	200	30	25	*
			10	178	36	*	*	51			50	169	35	35	18
17			50	174	54	52	26	52			50	177	*	*	*
			25	180	44	38	20	53	50	20					
			10	168	24	29	*	54			50	186	36	32	*
18			50	186	40	*	*	55			50	169	21	*	*
19			50	193	47	38	38				25	178	28	26	*
			25	171	43	46	*				10	173	22	*	*
			10	169	50	46	*	56			50	188	*	*	*
20			50	165	*	*	*	57			50	190	30	*	*
21			50	172	26	28	*	58			50	179	49	45	21
22			50	173	48	52	*				25	174	35	28	*
			25	181	54	54	*				10	171	48	36	16
			10	170	30	27	*	59			50	184	43	31	*
23			50	170	*	*	*	60			50	189	17	*	*
24			50	180	*	*	*	61			50	179	*	*	*
25			50	178	*	*	*	62			50	185	*	*	*
26			50	181	*	*	*	63			50	212	27	*	−27
27			50	166	−23	*	*	64			50	170	*	*	*
28			50	174	*	*	*	65			50	162	*	*	*
29			50	178	*[e]	*[e]	*	66			50	196	*	*	*
30			50	182	*	*	*	67	40	38	50	198	41	45	38
31			50	171	35	*	*				25	178	25	29	*
32			50	172	26	*	*				10	197	33	31	*
33			50	165	*	*	*								

[a] There were four rats per group in each experiment. Since the majority of compounds were tested in DOCA/saline rats, these results are presented in greater detail. Where DOCA/saline rat results are unavailable, conscious renal hypertensive rat (RHR) results are presented instead. For comparative purposes, both results are given in some instances. [b] Activity (RHR) is expressed as percentage falls in systolic blood pressure (from starting levels in the range 160–200 mmHg) at 1.5 and/or 4 h after the indicated oral dose in mg/kg; decreases of <10% being represented by the symbol ±. [c] Starting systolic blood pressure in mmHg. [d] Percentage falls in systolic blood pressure at the indicated times after the indicated doses: All results were analyzed for statistically significant differences from control values using Student's t test; nonsignificant values ($p > 0.05$) are indicated by asterisk. [e] Marked bradycardia, with falls in heart rate of >40%.

spectra were obtained on a Varian EM360 instrument. Key IR absorbances are indicated for the exemplified compounds. Samples were prepared as Nujol mulls. NMR spectra were generally determined with Me_2SO-d_6 solutions because the compounds were not sufficiently soluble in $CDCl_3$. Spectra supported the assigned structures but were complex and not generally well resolved. Details are therefore not included. C, H, and N analyses were within ±0.4% of theoretical values, except where indicated in Table I.

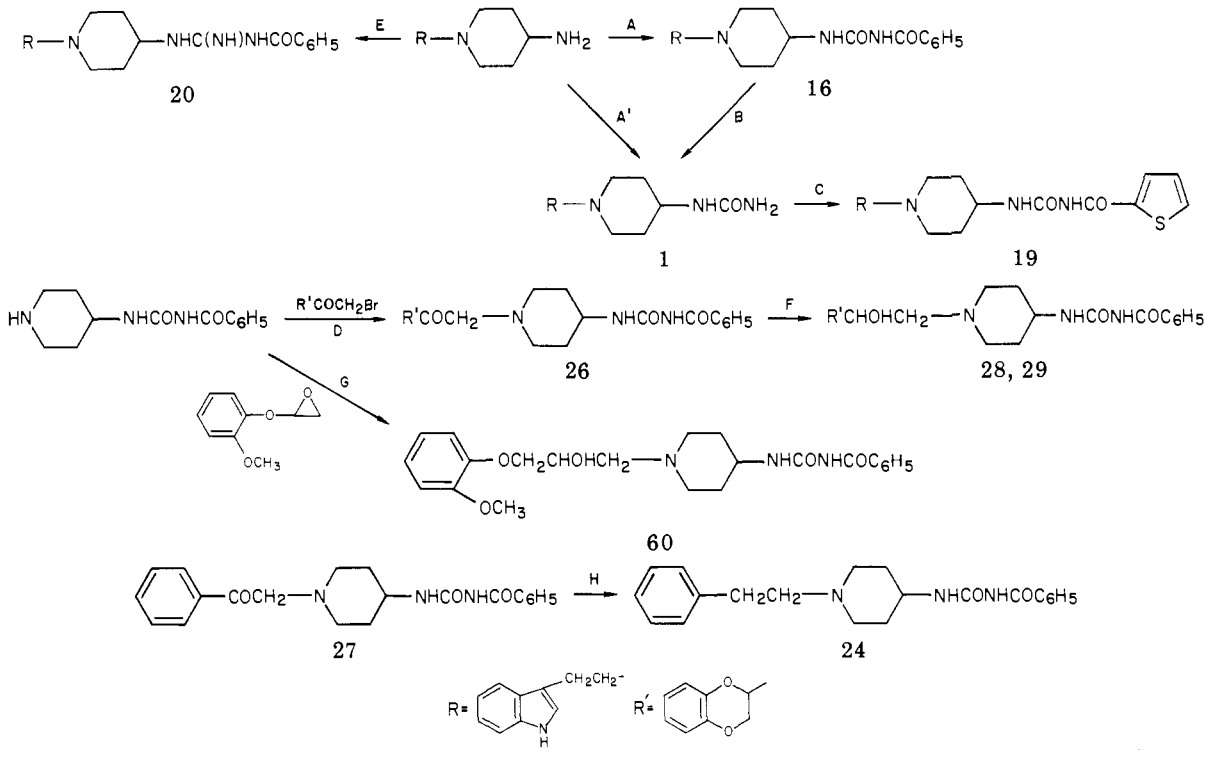
Method A. 1-Benzoyl-3-[1-[2-(3-indolyl)ethyl]piperid-4-yl]urea (16). To a solution of 3-[2-(4-aminopiperidyl)ethyl]indole[1] (2.09 g, 8 mmol) in dry benzene (150 mL) was gradually added benzoyl isocyanate (1.29 g, 8.8 mmol) in benzene (100 mL). The mixture was stirred at room temperature overnight and then evaporated. Treatment of the residue in ethanol with ethanol–HCl gave the hydrochloride (2.21 g): IR 3350–3100, 2700–2200, 1690–1660 (C=O), 1540 (amide II), 740, 715, 700 cm^{-1}.

Method B. 1-[1-[2-(3-Indolyl)ethyl]piperid-4-yl]urea (1). 1-Benzoyl-3-[1-[2-(3-indolyl)ethyl]piperid-4-yl]urea hydrochloride (16; 1.18 g, 2.76 mmol) was heated under reflux in 2 N NaOH solution (20 mL) for 1 h. The reaction mixture was cooled and the title compound (0.678 g) was filtered and recrystallized from MeOH: IR 3400–3100, 1650 (C=O), 1590–1560 (amide II), 740 cm^{-1}. (1 has also been prepared by method A′; details at end of Experimental Section.)

Method C. 1-(2-Thenoyl)-3-[1-[2-(3-indolyl)ethyl]-piperid-4-yl]urea (19). To a suspension of compound 1 (0.35 g, 1.22 mmol) in dry benzene (2 mL) containing anhydrous pyridine (0.12 g) was added dropwise 2-thenoyl chloride (0.18 g, 1.23 mmol). The mixture was refluxed for 2 h, cooled, and filtered. The precipitate was washed (H_2O), dried, and converted to the product hydrochloride (0.13 g) in MeOH–HCl: IR 3400–3000, 2700–2300, 1680–1660 (C=O), 1540 (amide II), 1270, 840, 730 cm^{-1}.

Method D. 1-Benzoyl-3-[1-[2-(1,4-benzodioxan-2-yl)-2-oxoethyl]piperid-4-yl]urea (26). 4-(Benzoylureido)piperidine (2.46 g, 10 mmol) and 2-(bromoacetyl)-1,4-benzodioxan[8] (2.57 g, 10 mmol) in dry dimethylformamide (40 mL) were stirred at room temperature while triethylamine (1.1 g) was added, and the suspension was stirred for 1 h. A large excess of H_2O was added, and the remaining solid (4.2 g) was collected, dried, suspended in MeOH (40 mL), and made just acid with MeOH–HCl to give the product hydrochloride (3.51 g): IR 3300–3000, 2800–2400,

Scheme I



1725 (C=O), 1680 (C=O), 1540 (amide II), 1260, 745, 700 cm^{-1}.

Method E. 1-Benzoyl-3-[1-[2-(3-indolyl)ethyl]piperid-4-yl]guanidine (20). Benzoylcyanamide (0.6 g, 4.1 mmol) and 3-[2-(4-aminopiperidyl)ethyl]indole (0.65 g, 2.5 mmol) were refluxed in toluene (50 mL) for 16 h. The solvent was evaporated in vacuo and the residue was dissolved in the minimum volume of hot EtOH and was made just acid with EtOH–HCl. Et_2O was added to induce crystallization, and the solid was collected, washed with EtOAc, and dried to give the product hydrochloride hydrate (1.3 g): IR 3500–3000, 2800–2400, 1690 (C=O), 1620 (C=N), 1260, 740, 695 cm^{-1}.

Method F. 1-Benzoyl-3-[1-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]piperid-4-yl]urea Threo Isomer 28 and Erythro Isomer 29. Compound **26** (7.21 g, 17 mmol) was suspended in MeOH (80 mL) and stirred at room temperature. $NaBH_4$ (1.0 g, 26 mmol) in 2 N NaOH solution (10 mL) was added dropwise and stirring was continued for a further 1 h. H_2O (250 mL) was added, and the resulting solid (5.4 g) was collected and dried. Nine recrystallizations from *n*-butyl acetate gave **28** as the free base (1.19 g). This was converted to **28**·HCl·0.25H_2O (0.96 g) in MeOH–HCl: IR 3400–3000, 2800–2400, 1690–1670 (C=O), 1540 (amide II), 1260, 1080, 750, 700 cm^{-1}. The mother liquors from the first five recrystallizations were combined, evaporated, and recrystallized from *n*-butyl acetate four times to give **29** as the free base (0.9 g). This was converted to **29**·HCl (0.63 g) in MeOH–HCl: IR 3370, 3300, 3100–3000, 2800, 2400, 1700, 1675 (C=O), 1530 (amide II), 1265, 1075, 745, 720 cm^{-1}. The assignment of the stereochemistry of these diastereoisomers (**28** and **29**) was based on separate syntheses from authentic *threo*- and *erythro*-2-(2-bromo-2-hydroxyethyl)-1,4-benzodioxan (method D). The stereochemistry of these bromo intermediates was readily confirmed by NMR analysis similar to that used by Howe et al.[8]

Method G. 1-Benzoyl-3-[1-[3-[3-(2-methoxy)phenoxy]-2-hydroxypropyl]piperid-4-yl]urea (60). 4-(Benzoylureido)-piperidine (1.3 g, 55 mmol) and 2-(2,3-epoxypropoxy)anisole (0.9 g, 50 mmol) were refluxed in 2-propanol (50 mL) for 24 h. The crystalline product obtained on cooling the solution was collected, dissolved in chloroform, and chromatographed on alumina, eluting with chloroform. Evaporation of the fractions containing pure product and treatment with MeOH–HCl gave the product hydrochloride hydrate (0.53 g): IR 3400–3000, 2800–2400, 1690–1680 (C=O), 1550 (amide II), 1270, 1250, 1120, 745, 705 cm^{-1}.

Method H. 1-Benzoyl-3-[1-(2-phenethyl)piperid-4-yl]urea (24). Compound **27** (4.85 g, 12.4 mmol) in MeOH (50 mL) was stirred for 30 min with a solution of $NaBH_4$ (1.0 g, 26 mmol) in 2 N NaOH (10 mL). Water was added, and the precipitated solid was collected, dried, and converted into the product hydrochloride in EtOH–HCl and recrystallized from EtOH–H_2O to give **24**·HCl (2.2 g): IR 3300–3000, 2800–2400, 1680 (C=O), 1540 (amide II), 1270, 710, 700 cm^{-1}.

Method A'. 1-[1-[2-(3-Indolyl)ethyl]piperid-4-yl]urea (1). Potassium cyanate (40.56 g, 0.5 mol) was added to a stirred solution of 3-[2-(4-aminopiperidyl)ethyl]indole (109.8 g, 0.45 mol) and concentrated hydrochloric acid (41 mL, 0.45 mol) in water (2 L). The solution was heated on a steam bath for 0.5 h and then cooled in ice. Collection of the precipitate gave the title product (115.4 g), identical with the product from the example given under method B.

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