H_2O (15 ml) were added. After standing 2 hr, the solvents were evaporated. The obtained white solid was crystallized from acetone yielding **19** (4.3 g, 83%), mp 210–212°. *Anal.* ($C_{13}H_{14}O_4N_2$) C, H, N.

5-Hydroxy-5-benzylbarbituric Acid (20). Compound **20** was prepared from **13** (3.6 g, 0.0165 mol) in the same way as described for compound **19**. Obtained was **20** (2.9 g, 75%), mp 222–225° (lit.[16] mp 213–215°). *Anal.* ($C_{11}H_{10}O_4N_2$) C, H, N.

5-Hydroxy-5-(1-phenylethyl)barbituric Acid (21). Compound **21** was obtained from **12** (2.0 g, 0.0086 mol) in the same way as described for the preparation of compound **19**. Obtained was **21** (1.42 g, 66%), mp 204–205°. *Anal.* ($C_{12}H_{12}O_4N_2$) C, H, N.

5-Hydroxy-5-(2-phenylpropyl)barbituric Acid (22). Compound **22** was obtained from **14** (15 g, 0.061 mol) in the same way as described for the preparation of compound **19**. Obtained was **22** (10.5 g, 65.5%), mp 206–208°. *Anal.* ($C_{13}H_{14}O_4N_2$) C, H, N.

5-Hydroxy-5-(1-phenyl-2-propyl)barbituric Acid (23). To a solution of H_2O_2 (30%, 4 ml) in AcOH (40 ml) was added **15** (2.5 g, 0.01 mol). The mixture was heated at 65° until a clear solution was obtained and then stirred at 25° for 16 hr. MeOH (35 ml) and H_2O (25 ml) were added, and stirring was continued for 1 hr. The solvents were evaporated to give **23** (1.5 g, 58%), a pale yellow oil which solidified on standing. Compound **23** was used without further purification.

5-Hydroxy-5-(*p*-chlorobenzyl)barbituric Acid (24). Compound **24** was prepared from **16** (10.1 g, 0.04 mol) in the same way as described for the preparation of compound **23**. Obtained was **24** (7.6 g, 71%), mp 243–245°, which was used without purification.

5-Hydroxy-5-(*p*-methoxybenzyl)barbituric Acid (25). Compound **25** was prepared from **17** (7.44 g, 0.03 mol) in the same way as described for the preparation of compound **19**. Obtained was **25** (5.9 g, 74%), mp 222–223°. *Anal.* ($C_{12}H_{12}O_5N_2$) C, H, N.

5-Hydroxy-5-(1-*p*-nitrophenylethyl)barbituric Acid (26). Compound **26** was prepared from **18** (8.3 g, 0.03 mol) in the same way as described for the preparation of compound **19**. Crystallization from THF gave **26** (7 g, 79.5%), mp 282–286°. *Anal.* ($C_{12}H_{11}O_6N_3$) C, H, N.

5-Propionoxy-5-(1-phenylpropyl)barbituric Acid (27). To a solution of H_2SO_4 (3.8 ml) in propionic acid (20 ml) was added **19** (2.5 g, 0.01 mol). The mixture was stirred at 65° for 16 hr, cooled, and poured over ice. $NaHCO_3$ was added until pH 7.8 was reached. The product was extracted into EtOAc and the solvent was evaporated. Chromatography on silica gel using C_6H_6–EtOAc (4:1) gave the product which was crystallized from acetone–hexane (1:1, 20 ml) to give **27** (1.4 g, 44%), mp 156–158°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-benzylbarbituric Acid (28). Compound **28** was obtained from **20** (1.0 g, 0.00417 mol) in the same way as described for the preparation of compound **27**. Obtained was **28** (0.7 g, 58%), mp 174.5–176°. *Anal.* ($C_{14}H_{14}O_5N_2$) C, H, N.

5-Propionoxy-5-(1-phenylethyl)barbituric Acid (29). Compound **29** was prepared from **21** (5 g, 0.0216 mol) in the same way as described for the preparation of compound **27**. Obtained was **29** (4.54 g, 69%), mp 186–186.5°. *Anal.* ($C_{15}H_{16}O_5N_2$) C, H, N.

5-Propionoxy-5-(2-phenylpropyl)barbituric Acid (30). Compound **30** was prepared from **22** (2.5 g, 0.0096 mol) in the same way as described for the preparation of compound **27**. Obtained was **30** (2.0 g, 65.5%), mp 160–162°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-(1-phenyl-2-propyl)barbituric Acid (31). Compound **31** was prepared from **23** (1.5 g, 0.0058 mol) in the same way as described for the preparation of compound **27**. Obtained was **31** (0.8 g, 43%), mp 123–126°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-(*p*-chlorobenzyl)barbituric Acid (32). Compound **32** was prepared from **24** (7.6 g, 0.028 mol) in the same way as described for the preparation of compound **27**. Crystallization from EtOAc gave **32** (6.3 g, 69.5%), mp 222–223°. *Anal.* ($C_{14}H_{13}O_5N_2Cl$) C, H, N, Cl.

5-Propionoxy-5-(*p*-methoxybenzyl)barbituric Acid (33). Compound **33** was prepared from **25** (1 g, 0.038 mol) in the same way as described for the preparation of compound **27**. Crystallization from MeOH–H_2O (2:1) gave **33** (0.8 g, 66%), mp 215–219°. *Anal.* ($C_{15}H_{16}O_6N_2$) C, H, N.

5-Propionoxy-5-(1-*p*-nitrophenylethyl)barbituric Acid (34). A mixture of **26** (1.0 g, 0.0034 mol), H_2SO_4 (5 ml), methanesulfonic acid (10 ml), and propionic acid (25 ml) was stirred at 85° for 48 hr. The solution was cooled and poured into ice water (150 ml). The precipitate was removed by filtration and crystallized from EtOAc–petroleum ether (1:1). Obtained was **34** (0.71 g, 59%), mp 240–241°. *Anal.* ($C_{15}H_{15}O_7N_3$) C, H, N.

(1-Phenylpropyl)-*N*-monocarbamidomalondiamide (35). To a solution of sodium (54.8 g, 2.38 mol) in EtOH (800 ml) was added urea (240 g, 4 mol) and compound **3** (278.34 g, 1 mol). The mixture was heated at reflux 16 hr and then cooled, and a portion of the solvent was evaporated until a total volume of 1 l. was achieved. Ice water (800 ml) was added and the solution acidified with HCl to pH 2. The solid was removed by filtration, washed with water, and crystallized from EtOH. Obtained was **35** (218 g, 83%), mp 188–189°. *Anal.* ($C_{13}H_{17}O_3N_3$) C, H, N.

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Benzamidopiperidines. 2. Heterocyclic Compounds Related to Indoramin

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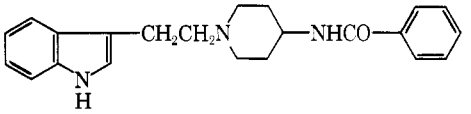
The synthesis and biological properties of some heterocyclic compounds related to indoramin are described. These are derivatives of 4-benzamidopiperidine with a side chain linking the piperidine to a heterocyclic ring. A clear separation between antihypertensive and hypotensive activities is noted among these compounds. None are as potent as indoramin in either hypotensive or antihypertensive tests.

The synthesis and hypotensive activity of benzamidopiperidylethylindoles were first described in 1968.[1] A more detailed study was published in 1971[2] in which structure–activity relationships were extensively investigated in indolylalkyl derivatives of benzamidopiperidines with particular emphasis on modifications of the amide moiety. No compound was found to be clearly superior to the parent 3-[2-(4-benzamidopiperid-1-yl)ethyl]indole (indoram-

in). Further evaluation in animals and man has substantiated the α-adrenoceptor antagonist, antihistamine, and hypotensive properties described for indoramin.[3-8] It was therefore of interest to extend the investigation of benzamidopiperidines by replacement of indole with other heterocyclic rings. No alterations were made to the benzamidopiperidine portion of these compounds in view of the lack of advantage resulting from such changes in the indole series in the majority of instances.



indoramin

Chemistry. 4-Benzamidopiperidine[2] (4-BAP) is the common starting material for the syntheses to be described. Methods A and B involve alkylation or acylation of 4-BAP as the final step. Mannich and Michael-type reactions with 4-BAP comprise methods C and D. Sequences in which an acyclic precursor is combined with 4-BAP and then cyclized to form the required heterocyclic ring are collectively designated method E. Finally, modification of side chains by reduction constitutes method F. However, although the reactions are arranged in this way, the diverse nature of the products renders it impractical to give general conditions for each method and, in most cases, it has been necessary to describe reactions individually in the Experimental Section. Where starting materials were novel, brief details have been included in the Experimental Section.

Biological Results. An evaluation of the hypotensive activities of members of the series was carried out in dialurethane or sodium pentobarbital anesthetized normotensive rats using carotid artery manometry to measure diastolic blood pressure. Most of the compounds were also examined for antihypertensive activity in conscious renal hypertensive rats using oral doses of 40–75 mg/kg. Systolic blood pressure was measured by an indirect tail-cuff technique.[9] Results are shown in Table I. For comparison indoramin is rated +++ in both of these tests. Antihistamine activity was determined for compounds **1–3**, **9**, and **15** using an isolated guinea-pig ileum preparation. The pA_2 values[10] were 8.3, 6.7, 8.4, 6.8, and 8.1, respectively. Compound **19** caused noncompetitive antagonism of histamine in this test. Under the same conditions, a pA_2 value of 8.9 was obtained for chloropheniramine.

The most noteworthy result of replacing the indole ring of indoramin by other heterocycles is that there is no longer any direct correlation between hypotensive and antihypertensive activities. The most active compounds in anesthetized normotensive rats were **5** and **15**, whereas in conscious renal hypertensive rats, **1**, **2**, **16**, and **18** were most effective in lowering blood pressure. None of the current examples were as effective as indoramin in either of these tests. Evidently indole remains the optimal heterocyclic substituent so far studied, with pyridine, benzothiophene, or benz[*g*]indole almost as effective in hypertensive, but not normotensive, animals, and pyrrole or quinoline most effective alternatives to indole in normotensive animals. An interesting contrast between antihistamine and hypotensive properties is evident when comparing the 4- and 2-pyridyl compounds **1** and **2**. Whereas **1** is a markedly more potent antihistamine, it is less hypotensive than **2**.

Experimental Section

Melting points are uncorrected. Ir spectra supporting the assigned structures were obtained for all compounds. Nmr spectra of representative examples also confirm the structures. C, H, and N analyses were obtained for all compounds and were within ±0.4% of the theoretical values.

Method A. 1-[2-(5-Phenylthien-2-yl)ethyl]-4-benzamidopiperidine (14). 2-(2-Hydroxyethyl)-5-phenylthiophene was converted into 2-(2-hydroxyethyl)-5-phenylthiophene *p*-toluenesulfonate (mp 93°) by standard procedures. The tosylate (3.59 g, 0.01 mol) was added to 4-BAP (2.04 g, 0.01 mol) and K_2CO_3 (2.07 g, 0.015 mol) in 2-PrOH (50 ml) and refluxed 18 hr. Filtration of the hot mixture and cooling the filtrate to 0° gave the product (1.23 g) which was recrystallized from EtOH.

1-[2-(3-Benzo[*b*]thienyl)ethyl]-4-benzamidopiperidine (16). 3-(2-Hydroxyethyl)benzo[*b*]thiophene *p*-toluenesulfonate (mp 56–58°) was obtained from the corresponding alcohol and converted into the product following the procedure for 14.

1-[2-(2-Quinolyl)ethyl]-4-benzamidopiperidine (15). 2-(2-Hydroxyethyl)quinoline (5.0 g, 0.029 mol) in $SOCl_2$ (15 ml) was heated at 50° for 20 min. Excess $SOCl_2$ was removed and the residue was added to 4-BAP (4.7 g, 0.023 mol) and K_2CO_3 (12.0 g, 0.087 mol) in DMF (25 ml). The mixture was stirred under reflux for 18 hr, cooled, and shaken with H_2O and Et_2O. The Et_2O extracts were dried and evaporated and the residue in MeCN was acidified with dry HCl to give the product as a dihydrochloride.

1-(2-Pyrimidyl)-4-benzamidopiperidine (8). 2-Chloropyrimidine (11.5 g, 0.01 mol), 4-BAP (20.4 g, 0.1 mol), and K_2CO_3 (28.0 g, 0.203 mol) were stirred at 130° for 5 hr in DMF (150 ml). The cooled mixture was poured into H_2O and the product (27.0 g, 96%) was collected by filtration.

1-[*N*-(5-Ethoxycarbonyl-4-phenylthiazol-2-yl)carbamoylmethyl]-4-benzamidopiperidine (11). 2-(α-Chloroacetamido)-5-ethoxycarbonyl-4-phenylthiazole (820 mg, 0.0025 mol), 4-BAP (515 mg, 0.0025 mol), and Et_3N (280 mg, 0.0028 mol) in DMF (15 ml) were stirred at room temperature 18 hr. H_2O and ice were added; then the solid was collected and recrystallized from EtOH to give the product (850 mg).

1-[2-(*p*-Chlorophenyl)thiazol-4-yl]methyl-4-benzamidopiperidine (13). 2-(*p*-Chlorophenyl)-4-chloromethylthiazole (1.83 g, 0.0075 mol) and 4-BAP (1.53 g, 0.0075 mol) were allowed to react under the same conditions as used for 11 to give product (2.65 g).

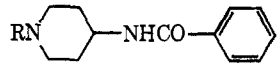
1-[2-[4-(*p*-Chlorophenyl)-2-phenylthiazol-5-yl]ethyl]-4-benzamidopiperidine (12). 5-(2-Chloroethyl)-4-(*p*-chlorophenyl)-2-phenylthiazole was prepared by conventional procedures from 4-(*p*-chlorophenyl)-2-phenylthiazole-5-acetic acid and used to alkylate 4-BAP under similar conditions to those used for 14 to give the product.

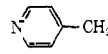
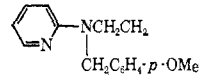
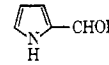
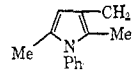
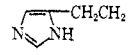
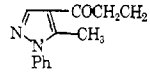
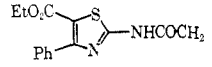
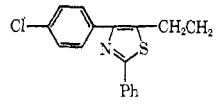
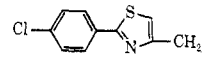
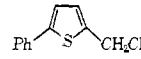
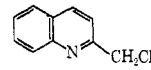
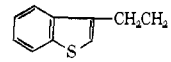
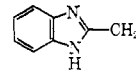
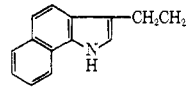
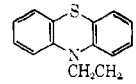
Method B.[11] **1-(Pyrrol-2-yloxalyl)-4-benzamidopiperidine (4).** A solution of redistilled pyrrole (13.4 g, 0.2 mol) in Et_2O (50 ml) was added to a stirred solution of oxalyl chloride (20 ml, 0.235 mol) in Et_2O (250 ml) at −50°. Stirring and cooling were maintained for 1 hr; then the solution was poured into a vigorously stirred mixture of $NaHCO_3$ (50 g, 0.6 mol) in H_2O (300 ml) and 4-BAP (40 g, 0.196 mol) in $CHCl_3$ (200 ml). The mixture was kept at 0° for 40 hr; then the solid was collected and recrystallized from EtOH–H_2O to give the product hydrate (40 g).

Method C. 1-[2-(4-Pyrimidyl)ethyl]-4-benzamidopiperidine (7). 4-BAP hydrochloride (2.4 g, 0.01 mol), H_2O (1.0 ml), 4-methylpyrimidine (0.94 g, 0.01 mol), and 39.4% aqueous formaldehyde (0.80 ml, 0.01 mol) were mixed in the order listed, heated at 100° for 1 hr, and then left 18 hr at room temperature. The mixture was adjusted to pH 8 with 2 *N* NaOH solution and extracted with $CHCl_3$. Evaporation of the dried extracts and treatment of the residue with EtOH–HCl followed by recrystallization from EtOH gave the product hydrochloride (0.20 g).

1-[3-(1-Phenyl-5-methylpyrazol-4-yl)-3-oxopropyl]-4-benzamidopiperidine (10). 4-Acetyl-5-methyl-1-phenylpyrazole (4.0 g, 0.02 mol), 4-BAP (4.08 g, 0.02 mol), concentrated HCl (3.0 ml), and paraformaldehyde (1.8 g, 0.03 mol) were dissolved in EtOH (50 ml) and heated under reflux for 24 hr. The solution was concentrated and H_2O was added to induce crystallization of the product hydrochloride hydrate (4.27 g).

1-(2,5-Dimethyl-1-phenylpyrrol-3-ylmethyl)-4-benzamidopiperidine (6). A solution of 4-BAP (23.9 g, 0.12 mol) in dioxane (200 ml), AcOH (200 ml), and 40% aqueous formaldehyde (100 ml) was cooled to 5° and a solution of 2,5-dimethyl-1-phenylpyrrole (20.0 g, 0.12 mol) in dioxane (200 ml) was added slowly with stirring. The mixture was stirred for 1 hr at room temperature and then 1 hr at 70°. It was then extracted with Et_2O and the aqueous layer was basified with 10 *N* NaOH solution and extracted with $CHCl_3$. Evaporation of the washed and dried $CHCl_3$ extracts gave a brown tar which partly solidified on standing 3 days. Trituration with Et_2O and crystallization from MeOH–H_2O gave the product hydrate (7.37 g).

Table I. 4-Benzamidopiperidines 

No.	R	Crystn solvent	Mp, °C	Method	% yield	Formula[e]	Hypotensive act.[a,f]	Antihypertensive act.[b,g]
1		EtOH–H_2O	193–195	D	80	$C_{19}H_{23}N_3O$	±	+++
2		EtOH	202–203	D	68	$C_{19}H_{23}N_2O \cdot 2HCl \cdot 0.25H_2O$	+ (+)	+++
3		PhH–P (60)[d]	132–134	E	48	$C_{27}H_{32}N_4O_2 \cdot 0.5H_2O$	+	
4		EtOH–H_2O	124–125	B	58	$C_{18}H_{19}N_3O_3 \cdot H_2O$	±	
5		EtOH	138–139	F	75	$C_{18}H_{23}N_3O_2$	++ (+)	±
6		MeOH–H_2O	191	C	15	$C_{25}H_{29}N_3O \cdot H_2O$	±	++
7		EtOH	221–222	C	6	$C_{18}H_{22}N_4O \cdot HCl$	±	+
8		DMF–H_2O	204–205	A	96	$C_{16}H_{18}N_4O$	±	±[c]
9		EtOH	228–230	E	61	$C_{17}H_{22}N_4O \cdot 2HCl \cdot H_2O$	++	+
10		EtOH–H_2O	181–183	C	53	$C_{25}H_{28}N_4O_2 \cdot HCl \cdot H_2O$	+	+
11		EtOH	189–190	A	69	$C_{26}H_{28}N_4O_4S$	±	±
12		EtOH–H_2O	199–200	A	20	$C_{29}H_{28}ClN_3OS$	++	±[c]
13		DMF–H_2O	219–220	A	86	$C_{22}H_{22}ClN_3OS$	++	±
14		EtOH	161–162	A	32	$C_{24}H_{26}N_2OS$	+	±[c]
15		MeCN	198 dec	A	19	$C_{23}H_{25}N_3O \cdot 2HCl$	++ (+)	
16		EtOH	242–245	A	39	$C_{22}H_{24}N_2OS \cdot HCl \cdot 0.5H_2O$	±	+++
17		EtOH	241–243	E	16	$C_{21}H_{24}N_4O \cdot 0.25H_2O$	±	
18		EtOH	285 dec	E	29	$C_{26}H_{27}N_3O \cdot HCl \cdot 0.5H_2O$	++	+++
19		EtOH–Et_2O	221	E	28	$C_{26}H_{27}N_3OS \cdot HCl \cdot 0.25H_2O$	++	±

[a] Decreases in diastolic blood pressure of 30 mm or more, sustained for at least 15 min, are graded according to cumulative iv dose: 1.6–3.2 mg/kg, +++; 6.4–12.8 mg/kg, ++; 25.6 mg/kg, +; falls of <30 mm, ±. [b] Falls in systolic pressure 2 hr after an oral dose of 75 mg/kg: <15 mm, ±; 15–30 mm, +; 30–50 mm, ++; >50 mm, +++. [c] Oral dose of 40 mg/kg. [d] P (60) refers to petroleum ether, bp 60–80°. [e] C, H, and N analyses were obtained on all compounds and were within ±0.4% of theory. [f] Hypotensive and antihistamine activities were determined by Dr. B. J. Alps and his colleagues. [g] Antihypertensive activities were determined by Dr. T. Baum and his colleagues.

Method D. 1-[2-(4-Pyridyl)ethyl]-4-benzamidopiperidine (1). A mixture of 4-vinylpyridine (578 mg, 0.01 mol), 4-BAP (1.02 g, 0.005 mol), AcOH (330 mg), and MeOH (4 ml) was refluxed for 8 hr, cooled, and evaporated. The residue in H_2O was basified with K_2CO_3 and the solid collected. Recrystallization from EtOH–H_2O gave the product (1.24 g).

1-[2-(2-Pyridyl)ethyl]-4-benzamidopiperidine (2). The product was prepared in the same way as 1 and isolated as the dihydrochloride quarter-hydrate.

Method E. 1-[2-(4-Imidazolyl)ethyl]-4-benzamidopiperidine (9). 4-BAP (2.4 g, 0.012 mol) in EtOH (15 ml) was added to hydroxymethyl vinyl ketone (2.0 g, 0.23 mol). An exothermic reac-

tion occurred and 2-(4-benzamidopiperidino)ethyl hydroxymethyl ketone crystallized out and was recrystallized from EtOH (3.2 g, mp 154.5°). The foregoing intermediate (3.0 g, 0.01 mol) in EtOH (10 ml) was added to a mixture of cupric acetate (5 g), 0.880 ammonia (40 ml), and 40% aqueous formaldehyde (3 ml) and heated at 100° for 1 hr. The Cu salt was collected, suspended in hot H_2O, and brought to pH 3. H_2S was passed in until there was no further precipitation; then the mixture was filtered and the filtrate was evaporated. Trituration of the residue with EtOH gave the product dihydrochloride hydrate (2.37 g).

1-[2-(2-Benzimidazolyl)ethyl]-4-benzamidopiperidine (17). A mixture of 4-BAP (2.0 g, 0.0098 mol), ethyl 3-bromopropionate (1.30 g, 0.01 mol), and K_2CO_3 (2.0 g, 0.015 mol) in 2-PrOH (25 ml) was refluxed for 18 hr and filtered while hot and the filtrate allowed to cool whereupon 1-(2-ethoxycarbonylethyl)-4-benzamidopiperidine (1.93 g, mp 112–113°) crystallized. The foregoing intermediate (3.16 g, 0.01 mol) was added to o-phenylenediamine (1.08 g, 0.01 mol) in 4 *N* HCl (10 ml) and the solution was refluxed for 2 hr, cooled, and filtered. The solid was recrystallized from EtOH to give the product as a quarter-hydrate (0.58 g).

1-[2-(3-Benz[*g*]indolyl)ethyl]-4-benzamidopiperidine (18). 1-(4,4-Diethoxybutyl)-4-benzamidopiperidine[2] (3.48 g, 0.01 mol) was added portionwise to a solution of 1-naphthylhydrazine hydrochloride (1.95 g, 0.01 mol) in 25% aqueous acetic acid (15 ml) with stirring at 80°. Stirring and heating were continued for 2.5 hr; then the mixture was left for 3 days. Recrystallization of the precipitate from EtOH gave the product as a hydrochloride hemihydrate (1.28 g).

1-(2-Hydroxyethyl)-4-benzamidopiperidine (20). 4-BAP (20.4 g, 0.1 mol), 2-bromoethanol (15.0 g, 0.12 mol), and K_2CO_3 (27.6 g, 0.2 mol) were intimately mixed and suspended in methyl ethyl ketone (20 ml). The mixture was stirred at 100° for 2 hr and filtered hot and the residue washed well with hot MEK. Evaporation of the filtrate and recrystallization of the residue from EtOAc gave the product (15.5 g), mp 133° (hydrochloride mp 189°).

1-(2-Chloroethyl)-4-benzamidopiperidine Hydrochloride (21). $SOCl_2$ (2.3 g, 0.019 mol) and **20** (3.7 g, 0.015 mol) in benzene (20 ml) were stirred and refluxed 3 hr, then cooled, and filtered. Recrystallization from EtOH–Et_2O gave the product hydrochloride (2.9 g), mp 239°.

1-[2-[*N*-(*p*-Methoxybenzyl)-*N*-(2-pyridyl)amino]ethyl]-4-benzamidopiperidine (3). 2-(*p*-Methoxybenzyl)aminopyridine (3.11 g, 0.0145 mol) was added to $LiNH_2$ [from Li (120 mg, 0.017 mol) and liquid NH_3] in benzene (170 ml). After refluxing 2 hr, **21** (5.29 g, 0.0155 mol) was added portionwise. The mixture was refluxed 6.5 hr, cooled, and filtered. Petroleum ether (bp 60–80°) was added to the filtrate to induce crystallization. Recrystallization from PhH–P (60) gave the product hemihydrate (3.20 g).

1-[2-(Phenothiazin-10-yl)ethyl]-4-benzamidopiperidine (19). A suspension of **21** (5.03 g, 0.015 mol) in xylene (30 ml) was added during 50 min to phenothiazine (3.75 g, 0.019 mol) and sodamide (0.87 g, 0.022 mol) in boiling xylene (90 ml). The mixture was refluxed 3 hr, cooled, and washed with H_2O. Evaporation of the dried xylene layer gave crude product (5.32 g) which was converted to the product hydrochloride quarter hydrate (2.51 g).

Method F. **1-[2-Hydroxy-2-(2-pyrrolyl)ethyl]-4-benzamidopiperidine (5).** Compound **4** (3.4 g, 0.0105 mol) in THF (80 ml) was added to a stirred suspension of $LiAlH_4$ (1.9 g, 0.05 mol) in THF (100 ml). The suspension was refluxed 3 hr, followed by dropwise addition of H_2O (5.5 ml), and the inorganic material was filtered off. Evaporation of the filtrate and recrystallization of the residue from EtOH gave the product (2.5 g).

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Benzamidopiperidines. 3. Carbocyclic Derivatives Related to Indoramin

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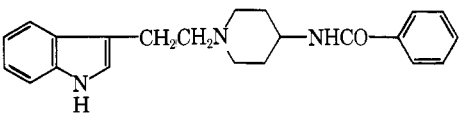
The synthesis of a series of 1-aralkyl derivatives of 4-benzamidopiperidine and related compounds is reported. Some of these compounds show greater activity than indoramin as hypotensive agents, antihistamines, and α-adrenoceptor antagonists.

In part 2[1] the investigation of compounds related to indoramin[2,3] was extended to cover a variety of derivatives in which the indole ring had been replaced by other heterocyclic systems. The present study deals with those compounds where the indole ring of indoramin has been replaced by a variety of aryl groups, and the length and nature of the chain linking these groups to the piperidine ring have been extensively modified. These compounds are listed (in Table II) in order of increasing chain length.

Hypotensive and antihypertensive activities have been determined for most members of the series (Table II), and selected compounds have also been investigated for α-adrenoceptor antagonism and antihistamine activity (Table III). More detailed pharmacological evaluations of



indoramin

some of these compounds have been carried out and will be reported elsewhere.

Structural modifications within the series have resulted in useful variations of the pharmacological profiles such that some of these compounds are more potent and selective than indoramin with respect to individual biological properties. The antihypertensive, antihistamine, and α-adrenoceptor blocking activities of indoramin have been