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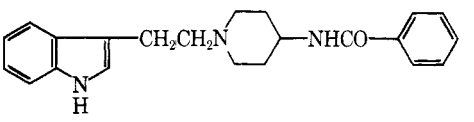
The synthesis of a series of 1-aralkyl derivatives of 4-benzamidopiperidine and related compounds is reported. Some of these compounds show greater activity than indoramin as hypotensive agents, antihistamines, and α-adrenoceptor antagonists.

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

Table I

Compd	R_1	A	R_2	X	Crystn solvent	Mp, °C	% yield	Method	Formula
			A. Pyridinium Salts						
1	C_6H_5	CH_2	$COCH_3$	Cl	DMF	237–238	78	A	$C_{14}H_{15}ClN_2O$
2	C_6H_5	CH_2	COC_6H_4-*p*-OCH_3	Cl	EtOH	>200 dec	54	A	$C_{20}H_{19}ClN_2O_2$
3	C_6H_5	CH_2	COC_6H_4-*p*-NO_2	Cl	EtOH	210–215	24	A	$C_{19}H_{16}ClN_3O_3$
4	C_6H_5	CH_2CH_2	COC_6H_5	Br	EtOH + Et_2O	200–203	49	A	$C_{20}H_{19}BrN_2O$
5	3,4-$(CH_3O)_2C_6H_3$	CH_2CH_2	$COCH_3$	I	EtOH	201–202	49	A	$C_{17}H_{21}IN_2O_3$
6	C_6H_5	$COCH_2$	COC_6H_5	Br	EtOH	170–172	96	A	$C_{20}H_{17}BrN_2O_2 \cdot 0.5C_2H_5OH$
7	C_6H_5	OCH_2CH_2	COC_6H_5	Br	EtOH	176–180	43	A	$C_{20}H_{19}BrN_2O_2$
8	2-$CH_3C_6H_4$	$NHCOCH_2CH_2$	H	Cl	EtOH	219–220	78	A	$C_{15}H_{18}ClN_3O$
			B. 1,2,5,6-Tetrahydropyridines						
9	C_6H_5	CH_2	COC_6H_5		EtOH	214–215	14	B	$C_{19}H_{20}N_2O \cdot (COOH)_2$
10	C_6H_5	CH_2CH_2	COC_6H_5		MeOH–H_2O	115–117	90	B	$C_{20}H_{22}N_2O$

confirmed in man,[4-7] and some of the compounds described herein may have further advantages in the treatment of cardiovascular disease and in conditions where potent and selective α blockers or antihistamines are likely to be useful.

Chemistry. The methods used to prepare the compounds described in this publication were in general similar to those previously reported.[1-3] Quaternary salts (Table IA) were obtained from the appropriately substituted 4-aminopyridines (method A). Two of these salts were reduced with $NaBH_4$ to give tetrahydropyridines (Table IB, method B), but as these showed only slight hypotensive activity, no further examples were prepared. Most of the pyridinium salts were reduced with Raney nickel to the corresponding piperidines (Table II, method C). The primary amine **96** was also obtained in this way, but other 4-aminopiperidines were obtained by hydrolysis of acetamido or benzamidopiperidines (method D). Acylation of these amines provided one route to the corresponding benzamidopiperidines (method E). Most of the compounds in Table II were prepared by alkylation of 4-benzamidopiperidine[3] (4-BAP) with an aralkyl halide, tosylate, epoxide, or alcohol (method F). Five different sets of conditions were used for these alkylations, the first three of which applied to halides or tosylates and were respectively F_1, DMF–Et_3N; F_2, 2-PrOH–K_2CO_3; and F_3, K_2CO_3 (no solvent). The latter conditions, where the two reactants were intimately mixed with powdered K_2CO_3 and heated on a steam bath, generally gave the highest yields. It was not essential to convert alcohols to halides or tosylates, since they could be condensed directly with 4-BAP in the presence of Raney nickel (F_4). Method F_5 involved alkylation of 4-BAP with an epoxide. Some examples were obtained by transformations carried out on substituents attached to ring R_1 (method G). These transformations were G_1, reduction of $-NO_2$; G_2, acylation of NH_2; G_3, demethylation of -OMe; and G_4, alkylation of -OH. Reductions involving the linking chain A (method H) consisted of H_1, reduction of C=O to CHOH; H_2, reduction of C=O to CH_2; and H_3, reductions of olefinic linkages. Compound **13** was prepared by a Mannich reaction (method I). In two examples, introduction of a Me substituent on the amide N was achieved by reduction of an *N*-carbethoxy group (method J). Compound **102** was obtained by reaction of the corresponding side-chain ester with aniline (method K). Finally, compound **87** was prepared by resolution of **86** (method L).

Biological Results. An evaluation of the hypotensive activities of compounds in Table II was carried out in dialurethane or sodium pentobarbital anesthetized normotensive rats, and diastolic blood pressure was measured directly by carotid artery manometry. Most of the compounds were also examined for antihypertensive activity in conscious renal hypertensive rats. Systolic blood pressure was measured by an indirect tail-cuff technique.[8] Results are listed in Table II. For comparison, indoramin was rated +++ in both of these tests. Antihistamine activity was determined for selected compounds using an isolated guinea-pig ileum preparation. The pA_2 values[9] are given in Table III. α-Adrenoceptor antagonism was determined for selected compounds using an isolated guinea-pig aortic spiral preparation,[10] and the resulting pA_2 values are also listed in Table III. Standard drugs are included for comparison.

It is again evident, as in the case of the heterocyclic derivatives,[1] that there is no consistent correlation between the results obtained with normotensive and hypertensive animals, but this lack of correlation might possibly reflect differences in methodology. The normotensive anesthe-

tized rats were dosed iv and blood pressure was measured directly at 15-min intervals while the hypertensive conscious rats were dosed orally and blood pressure was measured indirectly at 2 hr after dosing.

In general, hypotensive and antihypertensive activity tends to increase with increasing chain length, reaching optimal values when A is a 4-carbon unit. Examples where A is methylene (**11–18**) show only low or moderate hypotensive activities.

Compounds **11**, **17**, and **19** have been previously described,[11] but no pharmacological results were reported. Compounds **19–58** have in common a 2-carbon A chain and can be subdivided into three main categories. Firstly, where A is CH_2CH_2, optimum hypotensive activity occurs when R_1 is phenyl (**19**), 3,4-dichlorophenyl (**31**), 2-naphthyl (**34**), or cyclohexyl (**20**). The last example is of particular interest since it is the only compound where R_1 is alicyclic rather than aromatic, and it is the only example where A = CH_2CH_2 to show good activity in both hypotensive and antihypertensive tests. Other examples with an ethylidene chain to show good antihypertensive activity are **27** (R_1 = 2-aminophenyl) and **28** (R_1 = 3,4-dimethoxyphenyl). No consistent trend is apparent when A = CH_2CH_2 is replaced by A = $COCH_2$ or $CHOHCH_2$. Optimum hypotensive activity for these two chains occurs when R_1 = 3,4-dihydroxyphenyl (**49**) and 1,2,3,4-tetrahydro-6-naphthyl (**54**), respectively. Finally, good antihypertensive activity occurs in one branched chain example (**52**) where A = $CH_2CH(CH_3)$.

Considering next those examples where A is a three-atom chain (**59–65**), good activity in both hypotensive and antihypertensive tests is evident when A = $COCH_2CH_2$ and R_1 = phenyl (**61**). Good hypotensive activity also occurs when A = $CHOHCH_2CH_2$ and R_1 = benzodioxan-6-yl (**63**), whereas good antihypertensive activity results when A = OCH_2CH_2 and R_1 = phenyl (**64**).

The highest activities in the series as a whole are found among the four-atom chain compounds (**66–100**). Good hypotensive activity occurs in two out of three examples where A = $CH_2CH_2CH_2CH_2$ (**67**, R_1 = *p*-fluorophenyl, and **68**, R_1 = tetrahydronaphthyl), in three out of six examples where A = $CHOHCH_2CH_2CH_2$ (**87**, R_1 = phenyl, *d* enantiomer; **89**, R_1 = 2-naphthyl; and **90**, R_1 = tetrahydronaphthyl), in one out of three examples where A = $OCH_2CH_2CH_2$ (**94**, R_1 = 1-naphthyl), and in one out of two examples where A = $:CHCH_2CH_2CH_2$ (**100**, R_1 = di-*p*-fluorophenyl). Within the subdivision A = $COCH_2CH_2CH_2$ (**69–85**), **75–78** and **85** show good hypotensive activity and **69**, **70**, **74**, and **80** show excellent activity. Of these nine, only one (**69**, R_1 = phenyl) also shows good antihypertensive activity. Another compound where A = $COCH_2CH_2CH_2$ to show good antihypertensive activity (**83**, R_2 = cyclohexanecarbonyl) is only moderately hypotensive.

With respect to α-adrenoceptor blocking and antihistamine activities, optimal pA_2 values of 8.4 and 9.6 occur when A = $COCH_2CH_2CH_2$ and R_1 = chlorophenyl or phenyl, respectively. There is no apparent correlation between α-adrenoceptor antagonism and hypotensive or antihypertensive potency.

Optimal hypotensive as well as antihistamine activity in the series as a whole is shown by 1-(3-benzoylpropyl)-4-benzamidopiperidine (**69**). The corresponding 3-(*p*-chlorobenzoylpropyl) derivative **71** is the most potent α-adrenoceptor antagonist in the series.

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.

Methods A–C. The pyridinium salts and 1,2,5,6-tetrahydropyridines in Table I were prepared by standard procedures as described in part 1.[3] Raney nickel catalyzed reduction of the quaternary salts was also carried out as described in part 1.

Method D. 1-(3-Benzoylpropyl)-4-aminopiperidine (81). 1-(3-Benzoylpropyl)-4-benzamidopiperidine (**69**, 0.5 g) was suspended in 5 *N* HCl (10 ml) and refluxed for 6 hr. On cooling, crystals of benzoic acid separated out and were removed by filtration. The filtrate was basified (K_2CO_3) and the liberated oil extracted into $CHCl_3$ (2 × 50 ml). The bulked organic extracts were washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil which slowly crystallized (0.30 g, 94%). The crude base was dissolved in a little EtOH and acidified with EtOH–HCl. The resulting 1-(3-benzoylpropyl)-4-aminopiperidine dihydrochloride was filtered off, washed with a little cold EtOH, and dried to give colorless needles (0.38 g).

Method E. 1-(3-Benzoylpropyl)-4-(3,4-methylenedioxybenzamido)piperidine (82). Compound **81** (3.19 g, 0.01 mol) was stirred in a mixture of $CHCl_3$ (50 ml) and H_2O (20 ml) in which was dissolved K_2CO_3 (8.28 g, 0.006 mol). 3,4-Methylenedioxybenzoyl chloride (1.84 g, 0.01 mol) in $CHCl_3$ (10 ml) was added dropwise over 10 min and stirring continued 6 hr. The organic phase was then separated, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give a cream solid. This was dissolved in a minimum of EtOH–HCl and Et_2O added to induce crystallization. Filtration afforded colorless needles of **82** hydrochloride three-quarter hydrate (3.88 g).

Method F_1. 1-[2-(1,2,3,4-Tetrahydro-6-naphthyl)-2-oxoethyl]-4-benzamidopiperidine (53). A solution of 6-chloroacetyl-1,2,3,4-tetrahydronaphthalene (20.87 g, 0.10 mol), 4-benzamidopiperidine (20.40 g, 0.10 mol), and Et_3N (11.1 g, 0.11 mol) in DMF (200 ml) was stirred for 3 days at room temperature. The resulting crystals were collected, washed (H_2O), dried, and dissolved in EtOH. Acidification with EtOH–HCl gave **53** hydrochloride (31.3 g).

Method F_2. 1-[2-(*p*-Methoxyphenyl)ethyl]-4-benzamidopiperidine (21). 2-(*p*-Methoxyphenyl)ethanol *p*-toluenesulfonate ester (1.53 g, 0.005 mol), 4-BAP (1.02 g, 0.005 mol), and anhydrous K_2CO_3 (1.10 g, 0.008 mol) were refluxed in 2-PrOH (50 ml) for 8 hr; then the hot mixture was filtered. The product which crystallized on cooling was recrystallized from EtOAc to give **21** (1.17 g).

Method F_3. 1-(3-Benzoyl)propyl-4-benzamidopiperidine (69). An intimate mixture of 4-BAP (4.08 g, 0.02 mol), K_2CO_3 (2.76 g, 0.02 mol), and 4-chlorobutyrophenone (3.64 g, 0.02 mol) was heated on a steam bath with stirring for 1 hr. The resulting solid was washed (H_2O), dried, and recrystallized from EtOH–HCl and Et_2O to give **69** hydrochloride quarter-hydrate (3.89 g).

Method F_4. 1-(2-Phenyl)ethyl-4-benzamidopiperidine (19). 2-Phenylethanol (0.61 g, 0.005 mol), 4-BAP (1.02 g, 0.005 mol), and W7 Raney nickel (*ca.* 2 g) were stirred under reflux in xylene for 16 hr. Liberated H_2O was separated by a Dean and Stark head. Filtration of the hot mixture allowed the product (0.85 g) to crystallize from the filtrate or cooling.

Method F_5. 1-[1-(4-Acetamidophenoxy)-2-hydroxyprop-3-yl]-4-benzamidopiperidine (92). A solution of 2,3-epoxy-1-(4-acetamidophenoxy)propane (5.18 g, 0.025 mol) and 4-BAP (6.13 g, 0.045 mol) in 2-PrOH (250 ml) was refluxed 24 hr, cooled, and filtered. The resulting solid was recrystallized from 2-PrOH to give **92** quarter-hydrate (7.41 g).

Method G_1. 1-[2-(4-Aminophenyl)ethyl]-4-benzamidopiperidine (24). Compound **23** (3.0 g) was hydrogenated in absolute EtOH (400 ml) at 3.25 kg/cm² and 20° for 3 hr in the presence of PtO_2 (300 mg). The catalyst was filtered off and the filtrate evaporated to give a foam which was crystallized from PhH–*n*-hexane to give **24** (2.3 g).

Method G_2. 1-[2-(4-Acetamidophenyl)ethyl]-4-benzamidopiperidine (25). Compound **24** (2.3 g) was heated under reflux for 2 hr in Ac_2O (22 ml) and pyridine (100 ml). The solution was kept at 5° for 24 hr; then the crystalline product (1.5 g) was collected, washed (Et_2O), and dried.

Method G_3. 1-[2-(3,4-Dihydroxyphenyl)ethyl]-4-benzamidopiperidine (29). Compound **28** (12.2 g, 0.032 mol) in dry CH_2Cl_2 (400 ml) was added dropwise with stirring to BBr_3 (40 g, 0.16 mol) in dry CH_2Cl_2 (120 ml) at −50°. When the addition was complete, the solution was kept at room temperature for 48 hr; then H_2O (100 ml) was added with stirring. The resulting precipitate was collected and crystallized from EtOH. Recrystallization

Table II. 1,4-Disubstituted Piperidines R_1AN⟨⟩$—NR_2R_3$

Compd	R_1	A	R_2	R_3	Crystn solvent	Mp, °C	% yield	Method	Formula	Hypotensive act.[a]	Antihypertensive act.[b]
11	C_6H_5	CH_2	COC_6H_5	H	EtOH–Et_2O	237 dec	86	E	$C_{19}H_{22}N_2O \cdot HCl$	++	
12	3,4-OCH_2O-C_6H_3	CH_2	COC_6H_5	H	2-PrOH	179.5–180.5	78	F_2	$C_{20}H_{22}N_2O_3 \cdot 0.5H_2O$	+	++
13	2-OH-5-AcNH-C_6H_3	CH_2	COC_6H_5	H	EtOH	242	36	I	$C_{21}H_{25}N_3O_3$	±	
14	C_6H_5	CH_2	COC_6H_{11}	H	EtOAc	158 dec	72	E	$C_{19}H_{28}N_2O$	+	
15	C_6H_5	CH_2	*f*	H	2-PrOH	165 dec	94	E	$C_{20}H_{22}N_2O_3$	+	
16	C_6H_5	CH_2	COC_6H_4-*m*-OCH_3	H	2-PrOH	154 dec	82	E	$C_{20}H_{24}N_2O_2$	±	
17	C_6H_5	CH_2	COC_6H_4-*p*-CH_3	H	2-PrOH	161 dec	67	E	$C_{20}H_{24}N_2O$	±	
18	C_6H_5	CH_2	$COCH_3$	H	H_2O	139–140	83	C	$C_{14}H_{20}N_2O$	+	
19	C_6H_5	CH_2CH_2	COC_6H_5	H	EtOH + H_2O	166–168	81	C, F_4	$C_{20}H_{24}N_2O$	+++	
20	C_6H_{11}	CH_2CH_2	COC_6H_5	H	EtOH	174–175	45	F_1	$C_{20}H_{30}N_2O$	+++	+++[g]
21	4-CH_3O-C_6H_4	CH_2CH_2	COC_6H_5	H	EtOAc	178	69	F_2	$C_{21}H_{26}N_2O_2$	++	±
22	4-Cl-C_6H_4	CH_2CH_2	COC_6H_5	H	2-PrOH	190–195	65	F_2	$C_{20}H_{23}ClN_2$	++	++
23	4-NO_2-C_6H_4	CH_2CH_2	COC_6H_5	H	PhH + P (40)	209–216	99	F_2	$C_{20}H_{23}N_3O_3$	+	±
24	4-NH_2-C_6H_4	CH_2CH_2	COC_6H_5	H	PhH + *n*-hexane	193–195	85	G_1	$C_{20}H_{25}N_3O$	±	±
25	4-AcNH-C_6H_4	CH_2CH_2	COC_6H_5	H	EtOH + H_2O	270–275	56	G_2	$C_{22}H_{27}N_3O_2$	++	++
26	2-NO_2-C_6H_4	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	236–241	11	F_2	$C_{20}H_{23}N_3O_3 \cdot HCl$	++	++[g]
27	2-NH_2-C_6H_4	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	264	57	G_1	$C_{20}H_{25}N_3O \cdot 2HCl$	++	+++
28	3,4-$(CH_3O)_2$-C_6H_3	CH_2CH_2	COC_6H_5	H	EtOH	194–195	82	E	$C_{22}H_{28}N_2O_2$	±	+++
29	3,4-$(HO)_2$-C_6H_3	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	265–267	24	G_3	$C_{20}H_{24}N_2O_3 \cdot HBr \cdot 0.5H_2O$	±	±[g]
30	3,4,5-$(CH_3O)_3$-C_6H_2	CH_2CH_2	COC_6H_5	H	EtOH	193–194	33	F	$C_{20}H_{30}N_2O_4 \cdot H_2O$	++	+[g]
31	3,4-$(Cl)_2$-C_6H_3	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	286	39	F_3	$C_{20}H_{22}Cl_2N_2O \cdot HCl$	+++	+
32	2,6-$(Cl)_2$-C_6H_3	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	286	41	F_3	$C_{20}H_{22}Cl_2N_2O \cdot HCl$	±	±
33	1-Naphthyl	CH_2CH_2	COC_6H_5	H	PhH	160–162	66	F_1	$C_{24}H_{26}N_2O$	±	
34	2-Naphthyl	CH_2CH_2	COC_6H_5	H	2-PrOH	190–193	87	F_1	$C_{24}H_{26}N_2O$	+++	+
35	1-Indenyl	CH_2CH_2	COC_6H_5	H	EtOH + H_2O	148–149	17	F_2	$C_{23}H_{26}N_2O$	++	
36	3,4-$(CH_3)_2$-C_6H_3	CH_2CH_2	COC_6H_5	H	EtOH + Et_2O	276	41	F_3	$C_{22}H_{28}N_2O \cdot HCl \cdot H_2O$	++	+
37	3,4-$(CH_3O)_2$-C_6H_3	CH_2CH_2	$COCH_3$	H	EtOH + H_2O	152–154	65	C	$C_{17}H_{24}N_2O_3$	±	
38	3,4-$(CH_3O)_2$-C_6H_3	CH_2CH_2	H	H	EtOH	260–263	60	D	$C_{15}H_{24}N_2O_2 \cdot 2HCl$	±	
39	3,4-$(HO)_2$-C_6H_3	CH_2CH_2	H	H	EtOH	287–290 dec	51	G_3	$C_{13}H_{20}N_2O_2 \cdot 2HCl$	±	±
40	3,4-$(CH_3O)_2$-C_6H_3	CH_2CH_2	COC_6H_4-*o*-Cl	H	EtOH + Et_2O	250–252	49	E	$C_{22}H_{26}ClN_2O_3 \cdot HCl$	+	
41	3,4-$(CH_3O)_2$-C_6H_3	CH_2CH_2	*f*	H	EtOH + Et_2O	285–288	47	E	$C_{23}H_{28}N_2O_5 \cdot HCl \cdot 2H_2O$	±	±
42	2-Naphthyl	CH_2CH_2	H	H	EtOH	>300 dec	68	D	$C_{17}H_{22}N_2 \cdot 2HCl$	±	±
43	2-Naphthyl	CH_2CH_2	COC_6H_{11}	H	EtOH + Et_2O	232–233	70	E	$C_{24}H_{32}N_2O \cdot HCl$	++	±
44	2-Naphthyl	CH_2CH_2	$CO_2C_2H_5$	H	EtOH + Et_2O	240	40	E	$C_{20}H_{26}N_2O_2 \cdot HCl$		
45	2-Naphthyl	CH_2CH_2	H	CH_3	EtOH + Et_2O	281	52	J	$C_{18}H_{24}N_2 \cdot 2HCl \cdot H_2O$		
46	2-Naphthyl	CH_2CH_2	COC_6H_5	CH_3	EtOH + Et_2O	283	84	E	$C_{25}H_{28}N_2O \cdot HCl$	++	++
47	C_6H_5	$COCH_2$	COC_6H_5	H	2-PrOH + H_2O	168	49	F_2	$C_{20}H_{22}N_2O_2$	++	±
48	C_6H_5	$CHOHCH_2$	COC_6H_5	H	MeOH + H_2O	178–180	51	H_1	$C_{20}H_{24}N_2O_2$	++	++[g]
49	3,4-$(HO)_2$-C_6H_3	$COCH_2$	COC_6H_5	H	2-PrOH	220 dec	52	F_2	$C_{20}H_{22}N_2O_4 \cdot 0.25H_2O$	+++	+
50	3,4-$(Cl)_2$-C_6H_3	$COCH_2$	COC_6H_5	H	EtOH–Et_2O	226	34	F_1	$C_{20}H_{20}Cl_2N_2O_2 \cdot HCl$	±	
51	3,4-$(Cl)_2$-C_6H_3	$CHOHCH_2$	COC_6H_5	H	EtOH–Et_2O	270	75	H_1	$C_{20}H_{22}Cl_2N_2O_2 \cdot HCl$	±	±
52	C_6H_5	$CH_2CH(CH_3)$	COC_6H_5	H	EtOH	238 dec	30	F_2	$C_{21}H_{26}N_2O \cdot HCl \cdot 0.5H_2O$	++	+++
53	1,2,3,4-H-6-naphthyl	$COCH_2$	COC_6H_5	H	EtOH	270 dec	76	F_1	$C_{24}H_{28}N_2O_2 \cdot HCl$	++	±
54	1,2,3,4-H-6-naphthyl	$CHOHCH_2$	COC_6H_5	H	EtOH + Et_2O	253 dec	71	H_1	$C_{24}H_{30}N_2O_2 \cdot HCl$	+++	±
55	4-HO-C_6H_4	$COCH(CH_3)$	COC_6H_5	H	EtOH + EtOAc	224 dec	60	F_3	$C_{21}H_{24}N_2O \cdot HCl \cdot 0.5H_2O$	±	±

56	4-HO-C_6H_4	$CHOHCH(CH_3)$	COC_6H_5	H	EtOH	>130 dec	27	H_1	$C_{21}H_{26}N_2O_3 \cdot HCl \cdot 0.75H_2O$	+	±
57	*c*	$COCH_2$	COC_6H_5	H	EtOH + H_2O	153 dec	24	F_2	$C_{30}H_{40}N_2O_2$	++	
58	*c*	$CHOHCH_2$	COC_6H_5	H	EtOH + H_2O	253 dec	78	H_1	$C_{30}H_{42}N_2O_2 \cdot HCl \cdot H_2O$	+ (+)	++
59	C_6H_5	$CH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	237	33	F_3	$C_{21}H_{26}N_2O \cdot HCl \cdot 0.25H_2O$	++	
60	2-Indenyl	$CH_2CH_2CH_2$	COC_6H_5	H	2-PrOH	157–159	74	F_3	$C_{24}H_{28}N_2O$	++	+++
61	C_6H_5	$COCH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	194	80	F_3	$C_{21}H_{24}N_2O_2 \cdot HCl$	+++	+++
62	3,4-$O(CH_2)_2O$-C_6H_3	$COCH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	198	65	F_3	$C_{23}H_{26}N_2O_4 \cdot HCl \cdot 0.25H_2O$	+	
63	3,4-$O(CH_2)_2O$-C_6H_3	$CHOHCH_2CH_2$	COC_6H_5	H	MeOH + EtOAc + Et_2O	193–197	45	H_1	$C_{23}H_{28}N_2O_4 \cdot HCl$	+++	+
64	C_6H_5	OCH_2CH_2	COC_6H_5	H	EtOH + Et_2O	207	73	F_3	$C_{20}H_{24}N_2O_2 \cdot HCl$	++	+++
65	2-CH_3O-C_6H_4	OCH_2CH_2	COC_6H_5	H	EtOH + Et_2O	193	77	F_3	$C_{21}H_{26}N_2O_3 \cdot HCl$	++	±
66	C_6H_5	$CH_2CH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	241	75	F_3	$C_{22}H_{28}N_2O \cdot HCl \cdot 0.25H_2O$	++	+
67	4-F-C_6H_4	$CH_2CH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	228	16	H_2	$C_{22}H_{27}FN_2O \cdot HCl \cdot 0.5H_2O$	+++	+[i]
68	1,2,3,4-H-6-naphthyl	$CH_2CH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	250	15	H_2	$C_{26}H_{34}N_2O \cdot HCl \cdot 0.25H_2O$	+++	+
69	C_6H_5	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	241	84	F_3	$C_{22}H_{26}N_2O_2 \cdot HCl \cdot 0.25H_2O$	++++	+++
70	4-F-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	258	26	F_1, F_3	$C_{22}H_{25}FN_2O_2 \cdot HCl$	++++	++[h]
71	4-Cl-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	242–243	46	F_3	$C_{22}H_{25}ClN_2O_2 \cdot HCl$	++	+
72	4-Br-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	268	72	F_3	$C_{22}H_{25}BrN_2O_2 \cdot HCl$	+	±
73	4-CH_3O-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH	225	47	F_3	$C_{23}H_{23}N_2O_3 \cdot HCl \cdot H_2O$	++	++
74	4-$(CH_3)_3C$-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	268	53	F_3	$C_{26}H_{34}N_2O_2 \cdot HCl$	++++	±
75	2,4-$(CH_3)_2$-C_6H_3	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	215	43	F_3	$C_{24}H_{30}N_2O_2 \cdot HCl$	+++	±
76	2,5-$(CH_3)_2$-C_6H_3	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	190	42	F_3	$C_{24}H_{30}N_2O_2 \cdot HCl$	+++	±
77	2-Naphthyl	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH	251	39	F_3	$C_{26}H_{28}N_2O_2 \cdot HCl \cdot 0.75H_2O$	+++	+
78	1,2,3,4-H-6-naphthyl	$COCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	221	38	F_3	$C_{26}H_{32}N_2O_2 \cdot HCl \cdot H_2O$	+++	±
79	4-HO-C_6H_4	$COCH_2CH_2CH_2$	COC_6H_5	H	2-PrOH + EtOH	276	43	F_1	$C_{22}H_{26}N_2O_3 \cdot HCl$	+	+
80	*d*	$COCH_2CH_2CH_2$	COC_6H_5	H	MeOH + EtOAc	207	11	G_4	$C_{28}H_{39}N_3O_4 \cdot 2HCl \cdot H_2O$	++++	+
81	C_6H_5	$COCH_2CH_2CH_2$	H	H	EtOH	276	91	D	$C_{15}H_{22}N_2O \cdot 2HCl$	±	±
82	C_6H_5	$COCH_2CH_2CH_2$	*f*	H	EtOH + Et_2O	236	88	E	$C_{23}H_{26}N_2O_4 \cdot HCl \cdot 0.75H_2O$	++	±
83	C_6H_5	$COCH_2CH_2CH_2$	COC_6H_{11}	H	MeOH + Et_2O	231	57	E	$C_{22}H_{32}N_2O_2 \cdot HCl \cdot 0.5H_2O$	++	+++
84	C_6H_5	$COCH_2CH_2CH_2$	COC_6H_4-*p*-Cl	H	EtOH	261	81	E	$C_{22}H_{25}ClN_2O_2 \cdot HCl$	++	+
85	C_6H_5	$COCH_2CH_2CH_2$	$CO_2C_2H_5$	H	EtOH + Et_2O	221	39	E	$C_{18}H_{26}N_2O_3 \cdot HCl \cdot 0.25H_2O$	+++	
86	C_6H_5	$CHOHCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	221	56	H_1	$C_{22}H_{28}N_2O_2 \cdot HCl$	++	++
87	C_6H_5[e]	$CHOHCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	238		L	$C_{22}H_{28}N_2O_2 \cdot HCl$	+++	
88	4-F-C_6H_4	$CHOHCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	241 dec	49	H_1	$C_{22}H_{27}FN_2O_2 \cdot HCl$	++	++
89	2-Naphthyl	$CHOHCH_2CH_2CH_2$	COC_6H_5	H	MeOH + EtOAc	241	54	H_1	$C_{26}H_{30}N_2O_2 \cdot HCl \cdot 0.5H_2O$	+++	+
90	1,2,3,4-H-6-naphthyl	$CHOHCH_2CH_2CH_2$	COC_6H_5	H	MeOH + EtOAc	239	84	H_1	$C_{26}H_{34}N_2O_2 \cdot HCl \cdot 0.25H_2O$	+++	±
91	C_6H_5	$CHOHCH_2CH_2CH_2$	H	CH_3	EtOH	196	50	J	$C_{16}H_{26}N_2O \cdot 2HCl$		
92	4-AcNH-C_6H_4	$OCH_2CHOHCH_2$	COC_6H_5	H	2-PrOH	226–228	54	F_5	$C_{23}H_{29}N_3O_4 \cdot 0.25H_2O$	±	
93	1-Naphthyl	$OCH_2CHOHCH_2$	COC_6H_5	H	EtOH + H_2O	139–141	84	F_3	$C_{25}H_{25}N_2O_3$	++	±
94	1-Naphthyl	$OCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	228 dec	53	F_1	$C_{25}H_{28}N_2O_3 \cdot HCl$	+++	+
95	2-CH_3-C_6H_4	$NHCOCH_2CH_2$	COC_6H_5	H	2-PrOH	195–197	65	F_2	$C_{22}H_{27}N_3O_2$	±	
96	2-CH_3-C_6H_4	$NHCOCH_2CH_2$	H	H	2-PrOH	208–210	67	C	$C_{15}H_{23}N_3O \cdot 2HCl \cdot H_2O$	±	
97	$(C_6H_5)_2$	$:C:CHCH_2CH_2$	COC_6H_5	H	EtOH	220–230 dec	38	F_3	$C_{28}H_{30}N_2O \cdot HCl \cdot 0.25H_2O$	++	+
98	$(4\text{-F-}C_5H_4)_2$	$:C:CHCH_2CH_2$	COC_6H_5	H	EtOH	273	28	F_3	$C_{28}H_{28}F_2N_2O \cdot HCl \cdot 0.5H_2O$	+	
99	$(C_6H_5)_2$	$:CHCH_2CH_2CH_2$	COC_6H_5	H	EtOH	269	62	H_3	$C_{28}H_{32}N_2O \cdot HCl$	++	+
100	$(4\text{-F-}C_6H_4)_2$	$:CHCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	257	31	H_3	$C_{28}H_{30}F_2N_2O \cdot HCl$	+++	+
101	C_6H_5	$COCH_2CH_2CH_2CH_2$	COC_6H_5	H	EtOH + EtOAc	230	47	F_3	$C_{23}H_{28}N_2O_2 \cdot HCl$	++	++
102	C_6H_5	$NHCOCH_2CH_2CH_2$	COC_6H_5	H	EtOH + Et_2O	203	67	K	$C_{22}H_{27}N_3O_2 \cdot HCl \cdot 0.5H_2O$	++	

[a]Cumulative iv doses producing a fall in diastolic blood pressure of 30 mm or more, sustained for at least 15 min: 0.8 mg/kg, ++++; 1.6 or 3.2 mg/kg, +++; 6.4 or 12.8 mg/kg, ++; 25.6 mg/kg, +. Falls of <30 mm, ±. [b]Falls in systolic blood pressure 2 hr after an oral dose of 40 mg/kg: >50 mm, +++; 50–30 mm, ++; 30–15 mm, +; <15 mm, ±. [c]R_1 = 5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl. [d]R_1 = 4-(2-hydroxy-*N*-isopropylaminopropoxy)phenyl. [e]*d* enantiomer. [f]R_2 = 3,4-methylenedioxybenzoyl. [g]Oral dose of 75 mg/kg. [h]Oral dose of 10 mg/kg. [i]Oral dose of 2.5 mg/kg.

Table III

Compd	α blockade pA_2	Antihistamine pA_2	Compd	α blockade pA_2	Antihistamine pA_2
19		7.1	**74**	6.6	
31	7.35	8.4	**75**	7.2	8.0
34	7.4	7.6	**76**	7.5	7.7
47	5.8		**78**	6.9	
48	6.6		**79**	7.0	8.9
59	7.1	8.6	**80**	8.1	
60	7.4		**82**	6.4	
61	6.6		**83**	6.9	
63	6.6		**88**	6.6	6.5
64	5.9		**90**	6.05	7.0
66	6.95	7.4	**92**		7.0
67	6.4	7.5	**100**	5.9	
68	6.6		Phentolamine	7.6	5.5
69	7.7	9.6	Thymoxamine	6.9	6.7
70	7.5	8.6	Chloropheniramine	<6.9	8.9
71	8.4	7.7	Indoramin	7.4	8.2
72	6.9				

from EtOH–Et_2O gave **29** hydrobromide hemihydrate (6.0 g).

Method G_4. 1-[3-[4-[2-Hydroxy-3-(*N*-isopropylamino)propoxy]benzoyl]propyl]-4-benzamidopiperidine (80). Compound **79** (12.06 g, 0.03 mol), 1-chloro-3-isopropylaminopropan-2-ol (4.55 g, 0.03 mol), 10 *N* NaOH (9 ml, 0.09 mol), and EtOH (150 ml) were refluxed for 2 days. The mixture was filtered hot and the filtrate was evaporated to dryness. The resulting foam was heated with 2 *N* NaOH solution (150 ml) on a steam bath for 10 min; then the mixture was allowed to stand overnight and the resulting solid was collected, washed (H_2O), and dried. The base was dissolved in MeOH and made just acid with HCl, and EtOAc was added to induce crystallization of **80** dihydrochloride monohydrate (1.85 g).

Method H_1. 1-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]-4-benzamidopiperidine (51). $NaBH_4$ (15.0 g, 0.395 mol) in 0.2 *N* NaOH solution (200 ml) was added during 30 min to a stirred solution of compound **50** (6.45 g, 0.015 mol) in MeOH (260 ml). Stirring was continued for 3 days; then the mixture was refluxed for 2 hr. Filtration of the hot mixture gave 4.83 g of **51** base which was crystallized from EtOH–HCl and Et_2O to give **51** hydrochloride (4.86 g).

Method H_2. 1-[4-(4-Fluorophenyl)butyl]-4-benzamidopiperidine (67). Hydrazine hydrate (80%, 60 ml, 1.0 mol) was added to compound **70** (11.08 g, 0.03 mol, free base) in ethylene glycol (125 ml) and the solution was heated under reflux for 1 hr. KOH (6.0 g, 0.11 mol) was added and excess H_2O and NH_2NH_2 were distilled off until the internal temperature reached 185°. Refluxing was continued at this temperature for 30 min; then the hot solution was poured into cold H_2O (500 ml). The resulting precipitate was collected and twice recrystallized from EtOH–HCl and Et_2O to give **67** hydrochloride hemihydrate (1.85 g).

Method H_3. 1-(4,4-Diphenylbutyl)-4-benzamidopiperidine (99). Compound **97** (4.1 g) in MeOH (250 ml) containing 10% Pd/C (500 mg) was hydrogenated at 3.25 kg/cm² and 50° for 24 hr. The catalyst was filtered off and the residue after evaporation of the filtrate was crystallized from EtOH–HCl to give **99** hydrochloride (2.8 g).

Method I. 1-(5-Acetamido-2-hydroxybenzyl)-4-benzamidopiperidine (13). 4-Acetamidophenol (1.51 g, 0.01 mol) and 39.4% aqueous formaldehyde (1.25 ml, 0.017 mol) were dissolved in 50% aqueous EtOH, and 4-BAP (2.04 g, 0.01 mol) was added. The resulting solution was heated under reflux for 30 min and then left overnight at room temperature. The solid was collected and purified by suspending in boiling EtOH and filtering to give **13** (1.32 g).

Method J. 4-Methylamino-1-(2-naphth-2-ylethyl)piperidine (45). Compound **44** (6.5 g, 0.02 mol, free base) was dissolved in 1,2-dimethoxyethane (DME, 200 ml) and added during 60 min to a stirred suspension of $LiAlH_4$ (4 g, 0.1 mol) in DME (100 ml). After refluxing for 4 hr, the reaction mixture was cooled and water (12 ml) was added cautiously. The inorganic precipitate was filtered off and washed well (DME), and the filtrate and washings were evaporated to give the base which was converted to **45** dihydrochloride hydrate (3.7 g).

Method K. *N*-Phenyl-4-(4-benzamidopiperid-1-yl)butyramide (102). 4-Benzamido-1-(3-methoxycarbonyl)propylpiperidine (5.0 g, prepared from 4-BAP by method F_3) was refluxed in freshly redistilled aniline (25 ml) under N_2 for 18 hr. Filtration of the cooled mixture afforded the free base which was recrystallized from EtOH–HCl and Et_2O to give **102** hydrochloride hemihydrate (4.5 g).

Method L. (+)-1-(4-Phenyl-4-hydroxybutyl)-4-benzamidopiperidine (87). Compound **86** was resolved using (−)-di-*O,O*-*p*-toluoyltartaric acid, and the *d* enantiomer ($[\alpha]^{20}D$ +15.3°) was converted to the hydrochloride.

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