TABLE II

In Vitro INHIBITION OF MOUSE BRAIN MONOAMINE OXIDASE

	Molar concn				
	10^{-5}	5×10^{-5}	10^{-4}	5×10^{-4}	I_{50}[a]
Test compd					
Iproniazide	37	88	97		1.5
1	32		75	97	2.5
3	49		92	97	1.0
4	61		90	99	0.4
5	56		95	100	0.6
6	39		87	100	1.7
8	14		51	86	7.0
9	22		72	93	3.5
10	46		87	98	1.2
11	17		70	94	4.0
18	65	87	93	100	0.3

[a] Concn $\times 10^{-5}$ *M* for 50% inhibition of MAO activity.

of scintillation fluid and the radioactivity was measured. A blank contg boiled enzyme was carried through the entire procedure. The reported results are the averages of replicates and the average variation in the same experiment was ±5%. The I_{50} was derived from a graph of the log concn/per cent inhibition.

Chemistry. I.—The *N*-nitrosoamines were prepd by the method of Hartman and Roll.[13] HCl was replaced by AcOH, the reaction was carried out under N_2 (HONO is lost by reaction with O_2), and the mixt was heated to 60–70° after the addn of the $NaNO_2$ soln. The compds were distd and anald, but can be used crude in the redns. The nmr spectra show split Me and CH_2 peaks.

Typical LAH Redn of the *N*-Nitrosoamine. 1-(*m*-Chlorobenzyl)-1-methylhydrazine (4).—A suspension of LAH (114 g, 3.0 moles) in anhyd Et_2O (2.5 l.) was heated to a gentle reflux under N_2, and a soln of *m*-chloro-*N*-methyl-*N*-nitrosobenzylamine (268 g, 1.45 moles) in THF (500 ml) was added dropwise over 3–4 hr. H_2 evoln began immediately. The mixt was refluxed overnight, cooled under N_2, and H_2O (120 ml) was added *dropwise with caution* followed by 20% NaOH (90 ml) and H_2O (420 ml). The slurry was filtered, and the filtrate concd and distd to yield **4**, 227 g (92%). See Table I for physical constants. The yields in Table I are based on starting nitroso compd.

II.—The benzyl halides were prepd by the reaction of the benzyl alcohol with excess concd HCl, HBr, or with excess $SOCl_2$ (pyridine catalysis in $CHCl_3$ or 1,2-$C_2H_4Cl_2$ soln should be used particularly for ortho-substituted examples—see **7**, Table I). If the toluene was the commercial starting material, it was treated with NBS (used crude after removal of the succinimide and CCl_4) or with Br_2 and light. The presence of the α,α-dibromotoluene in the NBS product reduces the yield.

Typical Alkylation of Methylhydrazine with an Ortho-Substituted Benzyl Halide. 1-(*o*-Chlorobenzyl)-1-methylhydrazine (3).—To a mixt of methyl hydrazine (161 g, 3.5 moles) and anhyd EtOH was added with stirring *o*,α-dichlorotoluene (161 g, 1.0 mole). The mixt was refluxed 1 hr after the temp began to fall. It was concd *in vacuo*, made alk (50% NaOH), and extd (Et_2O). The exts were washed with H_2O, dried ($MgSO_4$), concd, and distd to yield **3**, 158 g (92%). See Table I for physical characteristics. The yields in Table I are based on the starting alcohol or toluene with the exception of **3**, **20**, and **22** where the benzyl chlorides were commercial.

III.—The aroyl chlorides were prepd by the use of $SOCl_2$ on the commercial arom carboxylic acids and were used crude or were commercially available.

Typical Aroylation of Methylhydrazine and LAH Redn of the Resulting Mixt. 1-(*m*-Methoxybenzyl)-1-methylhydrazine (9).—A mixt of methylhydrazine (170 g, 3.7 moles) and H_2O (680 g) was cooled to 0° and with stirring a soln of crude *m*-methoxybenzoyl chloride (300 g, 1.76 moles) in THF (400 ml) was added. The mixt was stirred overnight and extd (Et_2O). The exts were dried ($MgSO_4$), concd, and used crude. A mixt of LAH (114 g, 3.0 moles) and THF (1.5 l.) was heated to 30–40° under N_2, and a soln of the crude *m*-methoxybenzoic acid 1-methylhydrazide in THF (300 ml) was added dropwise. The H_2 evoln was monitored,[17] and the mixt was refluxed overnight, cooled under N_2, and worked up as in I to yield **9**, 158 g (47%). See Table I for physical data. The yields in Table I are based on the starting aryl carboxylic acid or acid chloride if commercial.

Synthesis and Hypotensive Activity of Benzamidopiperidylethylindoles[1]

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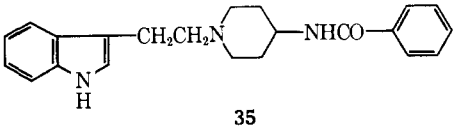
The synthesis and hypotensive activity of a series of indole piperidine amides are described. One member of the series—3-[2(4-benzamidopiperid-1-yl)ethyl]indole (indoramin) (**35**)—has undergone intensive pharmacological investigation. The sustained hypotensive action of **35** is believed to be due to a combination of local anesthetic and α-receptor blocking properties.

A continuing interest in indole derivatives incorporating a tryptamine residue as potential antihypertensive agents stemmed from our work with 1,4-bis(indolylethyl)piperidines.[2] In that series, the indolylethyl moiety attached to the piperidine 4 position was not an essential feature for retention of antihypertensive activity. It could, for instance, be replaced without detriment by a 3-carbethoxy-2,4-dimethylpyrrol-5-ylethyl group.[3]

We decided to retain the indolylethylpiperidine moiety of the earlier series while varying the 4 substituent of the piperidine ring, concentrating in particular on amino derivatives, which had received little attention in the past. It was soon discovered that the 4-benzamido derivative **35** (indoramin) was a potent hypotensive agent. Detailed pharmacological investigation of **35** has since revealed a combination of properties that seems likely to be advantageous in the treatment of cardiovascular disease in man.[4–6]

This compound then became the prototype for an extensive synthetic program designed to investigate structure–activity relationships and to optimize activity.



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(1) Presented in part at the IV International Congress of Medicinal Chemistry, Clermont-Ferrand, France, Sept 1968. J. L. Archibald, *Chim. Ther.*, **3**, 397 (1968).

(2) J. L. Archibald, T. Baum, and S. J. Childress, *J. Med. Chem.*, **13**, 138 (1970).

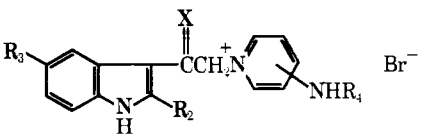
(3) J. L. Archibald, *J. Heterocycl. Chem.*, **3**, 409 (1966).

(4) B. J. Alps, J. L. Archibald, E. S. Johnson, and A. B. Wilson, *Cardiovasc. Res.*, 62 (1970).

(5) B. J. Alps, E. S. Johnson, and A. B. Wilson, *Brit. J. Pharmacol.*, **40**, 151P (1970).

(6) B. J. Alps, M. Hill, E. S. Johnson, and A. B. Wilson, *ibid.*, **40**, 153P (1970).

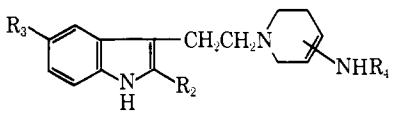
TABLE I



Compd	R_2	R_3	R_4	X	Posn of NHR_4	Crystn solvent	% yield	Mp, °C	Formula
1	H	H	H	H_2	4	H_2O	76	268–270	$C_{15}H_{16}BrN_3$
2	H	H	H	H_2	3	EtOH	34	190–192	$C_{15}H_{16}BrN_3$
3	H	H	H	H_2	2	EtOH	32	228–230	$C_{15}H_{16}BrN_3$
4	H	H	H	O	4	EtOH	79	312–315	$C_{15}H_{14}BrN_3O$[a]
5	H	H	$COCH_3$	H_2	4	EtOH	82	202–203	$C_{17}H_{18}BrN_3O \cdot C_2H_5OH$
6	CH_3	H	$COCH_3$	H_2	4	EtOH	60	205–207	$C_{18}H_{20}BrN_3O$[a]
7	CH_3	OCH_3	$COCH_3$	H_2	4	EtOH	41	258–259	$C_{19}H_{22}BrN_3O$[a]
8	H	H	COC_6H_5	H_2	4	EtOH	66	267–269	$C_{22}H_{20}BrN_3O \cdot H_2O$
9	H	H	COC_6H_5	H_2	3	EtOH	77	266–267	$C_{20}H_{22}BrN_3O$
10	H	H	COC_6H_5	O	4	H_2O	73	248–250	$C_{22}H_{18}BrN_3O_2 \cdot H_2O$[a]
11	H	H	COC_6H_4Cl-*p*	H_2	4	EtOH–H_2O	69	274–276	$C_{22}H_{19}BrClN_3O$
12	H	H	$COC_6H_4NO_2$-*p*	H_2	4	EtOH	21	220–225	$C_{22}H_{19}BrN_4O_3 \cdot H_2O$
13	H	H	$COC_6H_4CH_3$-*o*	H_2	4	MeOH	73	129–131	$C_{23}H_{22}BrN_3O$
14	H	H	$COCH(C_6H_5)_2$	H_2	4	EtOH–Et_2O	20	224–226	$C_{29}H_{26}BrN_3O$
15	H	H	$CO_2CH_2C_6H_5$	H_2	4	EtOH	59	176–178	$C_{23}H_{22}BrN_3O_2$

[a] Anal. were obtd for the elements C, H, Br.

TABLE II



Compd	R_2	R_3	R_4	Posn of NHR_4	Crystn solvent	Mp, °C	% yield	Formula	Hypotensive activity[a]
16	H	H	$COCH_3$	4	MeCN	193–195	56	$C_{17}H_{21}N_3O$	+++[b,c]
17	CH_3	H	$COCH_3$	4	H_2O–EtOH	225–226	71	$C_{18}H_{23}N_3O$	+++[b,d]
18	CH_3	OCH_3	$COCH_3$	4	MeCN	176–178	57	$C_{19}H_{25}N_3O_2$	+[d]
19	H	H	COC_6H_5	4	H_2O–EtOH	209–211	95	$C_{22}H_{23}N_3O$	+ to ++[c]
20	H	H	COC_6H_5	3	MeCN	180–182	86	$C_{22}H_{23}N_3O$	+[c]
21	H	H	COC_6H_4Cl-*p*	4	DMSO	228–230	37	$C_{22}H_{22}ClN_3O$	+++[b,c]
22	H	H	$COC_6H_4CH_3$-*o*	4	MeCN	187–189	65	$C_{23}H_{25}N_3O$	+[c]
23	H	H	$COCH(C_6H_5)_2$	4	EtOH	197–198	83	$C_{29}H_{29}N_3O$	+[c]
24	H	H	$CO_2CH_2C_6H_5$	4	EtOH	162–164	69	$C_{23}H_{25}N_3O_2$	+[c]

[a] Falls in blood pressure were < 20 mm, +; 20–35 mm, ++; 35–50 mm, +++; at a dose of 5 mg/kg, iv. [b] Effect obtained at high doses only (10–20 mg/kg, iv). [c] Acute ip LD_{50} in mice >400 mg/kg. [d] Approx ip LD_{50} in mice 127–400 mg/kg.

A number of synthetic approaches were developed to meet various objectives, depending, for instance, on which part of the molecule required systematic alteration. Scheme I depicts most of the major synthetic routes employed and is restricted, for clarity, to the synthesis of **35** itself. The original route to **35** involved quaternization of 4-benzamidopyridine with 3-(2-bromoethyl)indole, followed by Raney Ni catalyzed reduction. This proved satisfactory only on a small scale owing to the insolubility of the quaternary salt **8**. In an alternative two-stage process, $NaBH_4$ reduction of **8** gave the tetrahydropyridine **19** in excellent yield, but catalytic reduction of **19** was complicated by elimination of benzamide with resultant erratic yields of **35**. Quaternary salts and tetrahydropyridines prepared in this way are listed in Tables I and II. 3-Benzamido compounds were prepared in the same way as the 4 isomers.

Approaches which progressed through aminopiperidine intermediates **25–29** were investigated next, since these enable easy variation of the amide portion of **35**. The amine **25** was readily obtained on a small scale by reduction of the quaternary salt **1**, but again insolubility prevented satisfactory large scale operation. The acetamido quaternary salt **5**, however, was more soluble and less resistant to reduction. The acetamidopiperidine **30**[7] was hydrolyzed to the amine **25** which was reacylated with BzCl as well as with a large number of other acid chlorides (method F). The amine **25** was alkylated on the indole N with Me or benzyl halide to give either **27** or the corresponding 1-benzylindolamine. Amines substituted in the indole 2 and/or 5 positions or in the chain linking the indole and piperidine rings were also prepared. The amine **28** was obtained by hydrogenolysis of the *N*,*O*-dibenzyl compound **85**.

The most satisfactory approach to the large scale preparation of **35** involved alkylation of 4-benzamidopiperidine (**86**, Scheme I). This was prepared by hy-

(7) B. L. Zenitz. U. S. Patent 3,238,215 (1966).

TABLE III

Compd	I: R1	I: R2	I: R3	I: R4	A	Posn of NHR4	Crystn solvent	Mp. °C	% yield	Method	Formula	Hypotensive activity[a]
25	H	H	H	H	C_2H_4	4	MeCN	106–110	78	A, B	$C_{15}H_{21}N_3 \cdot H_2O$	+++[b,j]
26	H	CH_3	H	H	C_2H_4	4	EtOH–H_2O	186–188	21	A	$C_{16}H_{23}N_3 \cdot C_2H_2O_4$[c]	++[f,k]
27	CH_3	H	H	H	C_2H_4	4	MeCN	102–104	73	C	$C_{16}H_{23}N_3 \cdot H_2O$	+[j]
28	H	H	OH	H	C_2H_4	4		180	93	D(iii)	$C_{15}H_{21}N_3O \cdot 2HCl \cdot 0.5H_2O$	+++[e,j]
29	H	H	H	H	$COCH_2$	4	$CHCl_3$	203–205	40	A	$C_{15}H_{19}N_3O$	++[j]
30	H	H	H	$COCH_3$	C_2H_4	4	MeCN	167–168	70	G	$C_{17}H_{23}N_3O$	++[j]
31	H	CH_3	H	$COCH_3$	C_2H_4	4	EtOH–H_2O	83–85	51	G	$C_{18}H_{25}N_3O \cdot 3H_2O$	+++[j]
32	H	CH_3	OCH_3	$COCH_3$	C_2H_4	4	EtOAc	193–195	70	E	$C_{19}H_{27}N_3O_2$	+[j]
33	H	H	H	$CO(CH_2)_2CH_3$	C_2H_4	4	EtOAc	148–150	53	F	$C_{19}H_{27}N_3O$	+[j]
34	H	CH_3	H	$CO(CH_2)_2CH_3$	C_2H_4	4	EtOH–H_2O	100–103	29	F	$C_{20}H_{29}N_3O \cdot H_2O$	+++[d,j]
35	H	H	H	COC_6H_5	C_2H_4	4	EtOH–H_2O	208–210	92	E, F, G, H, I	$C_{22}H_{25}N_3O$	+++[h,i]
36	H	H	H	COC_6H_5	C_2H_4	3	EtOH–H_2O	135–140	39	G	$C_{22}H_{25}N_3O$	+[j]
37	H	H	H	$COC_6H_4CH_3$-*o*	C_2H_4	4	MeCN	186–189	62	F	$C_{23}H_{27}N_3O$	+++[i]
38	H	H	H	$COC_6H_4CH_3$-*m*	C_2H_4	4	MeCN	172–174	56	F	$C_{23}H_{27}N_3O$	+[j]
39	H	H	H	$COC_6H_4CH_3$-*p*	C_2H_4	4	EtOH–H_2O	200–202	55	F	$C_{23}H_{27}N_3O$	+++[e,i]
40	H	H	H	$COC_6H_4OCH_3$-*o*	C_2H_4	4	MeCN	152–154	50	F	$C_{23}H_{27}N_3O_2$	++[i]
41	H	H	H	$COC_6H_4OCH_3$-*m*	C_2H_4	4	MeCN	149–150	75	F	$C_{23}H_{27}N_3O_2$	+++[i]
42	H	H	H	$COC_6H_4OCH_3$-*p*	C_2H_4	4	EtOH–H_2O	290–292	54	F	$C_{23}H_{27}N_3O_2 \cdot HCl \cdot H_2O$	+[i]
43	H	H	H	COC_6H_4Cl-*o*	C_2H_4	4	MeCN	163–164	38	F	$C_{22}H_{24}ClN_3O$	+++[i]
44	H	H	H	COC_6H_4Cl-*p*	C_2H_4	4	EtOH	230–232	25	G	$C_{22}H_{24}ClN_3O$	++[i]
45	H	H	H	$COC_6H_4CF_3$-*m*	C_2H_4	4	EtOH–H_2O	186–188	56	F	$C_{23}H_{24}F_3N_3O$	+[i]
46	H	H	H	$COC_6H_3(2,6\text{-}Cl_2)$	C_2H_4	4	EtOH	297–301	59	F	$C_{22}H_{23}Cl_2N_3O \cdot HCl \cdot 0.25H_2O$	+ to ++[i]
47	H	H	H	$COC_6H_3(2,6\text{-}(OCH_3)_2)$	C_2H_4	4	EtOH–Et_2O	243–246	43	F	$C_{24}H_{29}N_3O_3 \cdot HCl \cdot 0.5H_2O$	++[d,j]
48	H	H	H	$COC_6H_3(3,4\text{-}(OCH_3)_2)$	C_2H_4	4	EtOH	271–273	60	F	$C_{24}H_{29}N_3O_3 \cdot HCl \cdot 0.25H_2O$	++[i]
49	H	H	H	$COC_6H_2(3,4,5\text{-}(OCH_3)_3)$	C_2H_4	4	EtOH–H_2O	105–108	79	F	$C_{25}H_{31}N_3O_4 \cdot H_2O$	+[i]
50	H	H	H	Piperonyl	C_2H_4	4	EtOH–H_2O	189–190	58	F	$C_{23}H_{23}N_3O_3$	+++[i]
51	H	H	H	$COC_6H_4C_6H_5$-*p*	C_2H_4	4	EtOH	271–272	56	F	$C_{28}H_{29}N_3O \cdot 0.25H_2O$	+[i]
52	H	H	H	$COC_6H_4CO_2H$-*o*	C_2H_4	4	EtOH–H_2O	165–170	55	M	$C_{23}H_{25}N_3O_3 \cdot H_2O$	+[i]
53	H	H	H	$COCH_2C_6H_5$	C_2H_4	4	MeCN	165–168	58	F	$C_{23}H_{27}N_3O$	++[j]
54	H	H	H	$COCH_2OC_6H_5$	C_2H_4	4	EtOH	238–240	52	F	$C_{23}H_{27}N_3O_2 \cdot HCl$	+[k]
55	H	H	H	$COCH_2CH_2C_6H_5$	C_2H_4	4	EtOH	265–268	35	F	$C_{24}H_{29}N_3O \cdot HCl$	+[j]
56	H	H	H	COC_6H_{11}	C_2H_4	4	EtOH–H_2O	182–184	58	H	$C_{22}H_{31}N_3O$	+[j]
57	H	H	H	Adamantoyl	C_2H_4	4	EtOH	295–299	58	F	$C_{26}H_{35}N_3O \cdot HCl$	++[k]
58	H	H	H	CO(indol-3-yl)	C_2H_4	4	Me_2CO–H_2O	242–244	13	F	$C_{24}H_{26}N_4O$	++[i]
59	H	H	H	CO(2-furyl)	C_2H_4	4	EtOH–H_2O	146–148	81	F	$C_{20}H_{23}N_3O_2$	++[i]
60	H	H	H	$COCH(C_6H_5)_2$	C_2H_4	4	EtOH–H_2O	160–162	56	F	$C_{29}H_{31}N_3O$	+[i]
61	H	CH_3	H	COC_6H_5	C_2H_4	4	EtOH–H_2O	209–211	51	F	$C_{23}H_{27}N_3O$	++[i]
62	H	CH_3	H	COC_6H_4Cl-*p*	C_2H_4	4	EtOH–Et_2O	243–245	34	F	$C_{23}H_{26}ClN_3O \cdot HCl$[g]	+[i]
63	H	CH_3	H	$COC_6H_4OCH_3$-*p*	C_2H_4	4	EtOH	112–114	55	F	$C_{24}H_{29}N_3O_2 \cdot H_2O$	+++[e,i]
64	H	CH_3	OCH_3	COC_6H_5	C_2H_4	4	EtOAc	180–181	59	F	$C_{24}H_{29}N_3O_2$	+[i]
65	CH_3	H	H	COC_6H_5	C_2H_4	4	EtOH–H_2O	178–179	61	F	$C_{23}H_{27}N_3O$	++[i]
66	CH_3	H	H	COC_6H_4Cl-*p*	C_2H_4	4	EtOH	212–214	71	F	$C_{23}H_{26}ClN_3O$	+++[e,i]
67	CH_3	H	H	$COC_6H_4CH_3$-*p*	C_2H_4	4	EtOH	198–199	71	F	$C_{24}H_{29}N_3O$	+[i]

68	CH_3	H	H	$COC_6H_4OCH_3$-*p*	C_2H_4	4	EtOH	198–199	74	F	$C_{24}H_{29}N_3O_2$	+[i]
69	$CH_2C_6H_5$	H	H	COC_6H_5	C_2H_4	4	EtOH	152–153	35	F	$C_{29}H_{31}N_3O$	+[j]
70	$CH_2C_6H_5$	H	H	COC_6H_4Cl-*p*	C_2H_4	4	EtOH	193–194	57	F	$C_{29}H_{30}ClN_3O$	+++[e,i]
71	$CH_2C_6H_5$	H	H	$COC_6H_4OCH_3$-*p*	C_2H_4	4	EtOH	191–192	62	F	$C_{30}H_{33}N_3O_2$	+[i]
72	H	H	OH	COC_6H_5	C_2H_4	4	EtOH–H_2O	246–248	68	F	$C_{22}H_{25}N_3O_2 \cdot 0.25H_2O$	++[i]
73	H	H	OCH_3	COC_6H_5	C_2H_4	4	MeCN	174	52	I	$C_{23}H_{27}N_3O_2$	++[f,i]
74	H	H	H	COC_6H_5	$COCH_2$	4	EtOH	205–207	94	F, H	$C_{22}H_{23}N_3O_2$	+++[e,i]
75	H	H	H	COC_6H_4Cl-*p*	$COCH_2$	4	EtOH	231–233	83	F	$C_{22}H_{22}ClN_3O_2$	+[i]
76	H	H	H	$COC_6H_4OCH_3$-*p*	$COCH_2$	4	EtOH–H_2O	227–229	74	F	$C_{23}H_{25}N_3O_3$	+[i]
77	CH_3	H	H	COC_6H_5	$COCH_2$	4	EtOH–Et_2O	273–277	35	H	$C_{23}H_{25}N_3O_2 \cdot HCl$	*f*
78	H	H	H	COC_6H_5	$CHOHCH_2$	4	EtOH	206–207	57	L	$C_{22}H_{25}N_3O_2$	++[f,i]
79	H	H	H	COC_6H_5	COCO	4	EtOAc	266–268	48	D(i)	$C_{22}H_{21}N_3O_3$	+[i]
80	H	H	OCH_2-C_6H_5	COC_6H_5	COCO	4	DMF–H_2O	264	97	D(i)	$C_{29}H_{27}N_3O_4$	
81	H	H	H	COC_6H_5	$COCH_2CH_3$	4	MeCN	226–229	42	K	$C_{23}H_{25}N_3O_2$	++[f,i]
82	H	H	H	COC_6H_5	$(CH_2)_3$	4	EtOH–H_2O	179–180	69	J	$C_{23}H_{27}N_3O$	+[j]
83	H	H	H	COC_6H_5	CH_2	4	EtOH	219–222	45	K	$C_{21}H_{23}N_3O \cdot HCl$	++[f,j]
84	H	H	H	$CH_2C_6H_5$	C_2H_4	4	C_6H_6	132–134	20	D(ii)	$C_{22}H_{27}N_3$	+[j]
85	H	H	OCH_2-C_6H_5	$CH_2C_6H_5$	C_2H_4	4	EtOH	210	85	D(ii)	$C_{29}H_{33}N_3O \cdot 2HCl \cdot 0.5H_2O$	

[a] Falls in blood pressure were <20 mm, +; 20–35 mm, ++; 35–50 mm, +++; at a dose of 5 mg/kg iv. [b] Toxic. [c] C: calcd, 62.2; found, 61.7. [d] Transient. [e] Effect obtd at high dosse only (10–20 mg/kg, iv). [f] Fatal. [g] Anal. for C, H, Cl. [h] Acute LD_{50} in rats: 1800 mg/kg, orally; 500 mg/kg ip. [i] Acute LD_{50} in mice >400 mg/kg ip. [j] Approx LD_{50} in mice 127–400 mg/kg ip. [k] Approx LD_{50} in mice 40–127 mg/kg ip.

drogenolysis of 1-benzyl-4-benzamidopiperidine[8] or from 4-benzamidopyridine, either by quaternization with $PhCH_2Cl$, followed by sequential $NaBH_4$ and catalytic reduction or, alternatively, by reduction of 4-benzamidopyridine in Ac_2O to give 1-acetyl-4-benzamidopiperidine which was selectively hydrolyzed to **86**. Alkylation of **86** with a variety of indolylalkyl halides or tosylates provided products in which the length and nature of the linking chain and substitution in the indole ring were altered. Acylation of **86** with the appropriate indole-3-glyoxylyl chloride provided the glyoxylamides **79** and **80**, the three carbonyl groups of the latter being reduced by LAH to give **85** as an intermediate to **28** and **72**.

Mannich reactions with **86** and indole and with **86** and 3-acetylindole gave products **83** and **81**, while a Mannich reaction with **86** and propiolaldehyde diethyl acetal provided **87** which was readily reduced to **88** (Scheme I). Fischer cyclization occurred when **88** was allowed to react with *p*-methoxyphenylhydrazine to give a good yield of **73**. When phenylhydrazine was used, only a low yield of **35** was obtained.

Biological Activity.—An evaluation of the hypotensive actions of members of the series was made in dialurethane-anesthetized (0.7 ml/kg, ip) normotensive rats. Results are shown in Tables II and III. Some

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compounds were also examined for antihypertensive activity in conscious renal hypertensive rats using oral doses of 20–40 mg/kg. Systolic blood pressure was measured by an indirect tail-cuff technique. Results were in general agreement with those obtained in anesthetized normotensive rats when blood pressure was measured directly. Compound **35** was selected for further evaluation of effect on general hemodynamics in sodium pentobarbital anesthetized cats (30 mg/kg iv). Low dosages (0.1–3.2 mg/kg iv) induced significant sustained decreases in aortic systolic and diastolic pressures (>40 mm) compared with measurements in control animals. The compound was devoid of an adrenergic β-receptor blocking action on the heart, but was found to possess local anesthetic membrane stabilizing properties, and to exert an adrenergic α-receptor blocking action. In common with many compounds in the series it was found to cause potent competitive antagonism of histamine.

The sustained hypotensive action of **35** could be accounted for by combined cardioinhibitory actions (*i.e.*, decreased myocardial contractile force, bradycardia, and decreased cardiac output), by virtue of its membrane stabilizing properties on the heart, and decreased peripheral resistance due to partial adrenergic α-receptor blockade of vasoconstrictor tone.

Structure–Activity Relationship.—Structural features necessary for a high level of hypotensive activity may be summarized as follows. The 4-benzamido group is necessary, except in very few examples where there is a 2 substituent on the indole ring and/or a double bond in the piperidine ring, *e.g.*, **16**, **17**, and **31**. No

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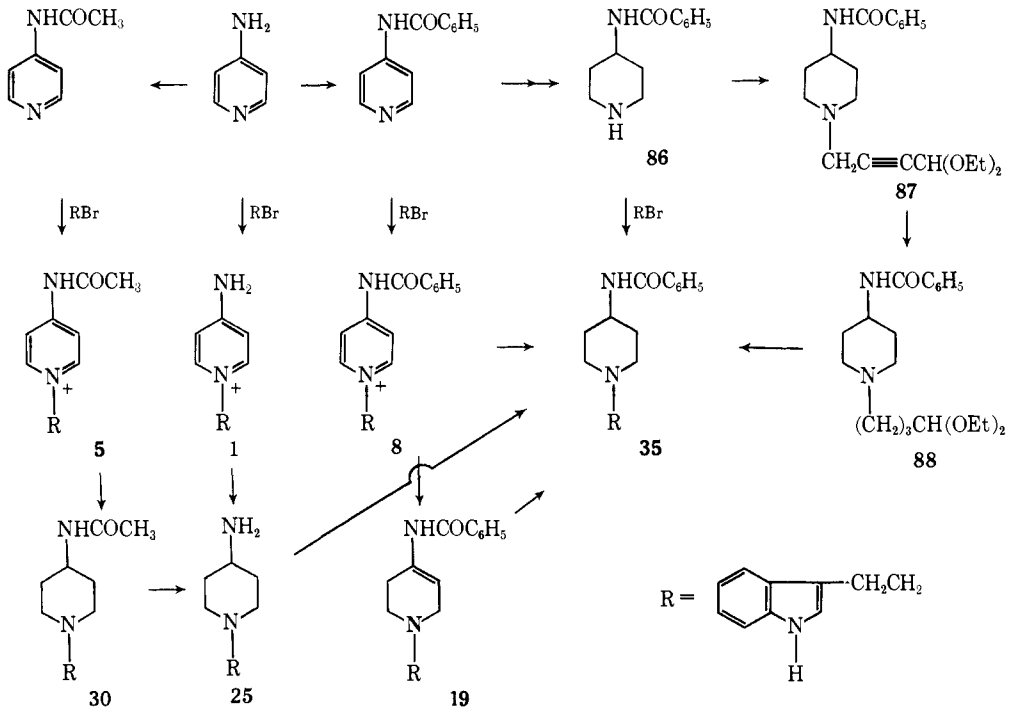
SCHEME I



simple relationship exists between substitution in the benzene ring and degree of activity; furthermore the effect of such substitution may be markedly altered by substitution elsewhere in the molecule. Thus para substitution of CH_3 does not greatly reduce activity (**39**), but *p*-OCH_3 only retains high activity when there is also an indole-2-CH_3 (**63**). *m*-OCH_3 does not reduce activity (**41**) nor does *o*-CH_3 (**37**) or *o*-Cl (**43**). Multisubstitution reduces activity except for **50**.

Substituents on the indole N generally decrease activity, but as previously exemplified may counteract an undesirable substituent in the benzene ring, *e.g.*, **44** and **66**. Indole 2 substituents have a variable effect, whereas 5 substituents are generally less desirable. Alteration of the ethylene linkage between the indole and piperidine rings reduces activity, except for **74**.

The quaternary compounds listed in Table I did not produce a potentially useful lowering of blood pressure except at high doses. Biological results are therefore not included in Table I.

Experimental Section[9]

Benzamidopyridines were either known or were prepd by standard procedures.

4-Benzamidopiperidine (86).—1-Benzyl-4-benzamidopiperidine[8] in EtOH was hydrogenated in the presence of 10% Pd/C at 50° and 3.25 kg/cm². The product (mp 136–137°) was recrystd from EtOAc. The same product was obtd by catalytic reduction of 4-benzamidopyridine in Ac_2O, followed by hydrolysis of the resulting 1-acetyl-4-benzamidopiperidine, and by quaternization of 4-benzamidopyridine with $PhCH_2Cl$, followed by $NaBH_4$ reduction of the quaternary salt, and catalytic reduction of the resulting 1-benzyl-1,2,5,6-tetrahydropyridine.

Quaternary Salts (Table I). 4-Benzamido-1-[2-(3-indolyl)-ethylpyridinium Bromide (8).—A soln of 4-benzamidopyridine (1.98 g) and 3-(2-bromoethyl)indole (2.24 g) in EtOH (15 ml) was refluxed for 2 hr, and the cryst product (3.13 g, mp 264–266°) was collected by filtration from the hot reaction mixt. Recrystn gave the hydrate.

4-Acetamido-1-[2-(5-methoxy-2-methylindol-3-yl)ethyl]pyridinium Bromide (7).—5-Methoxy-2-methylindole-3-acetic acid (50 g) in THF (400 ml) was added dropwise to a stirred suspension of LAH (50 g) in THF (800 ml). The mixt was refluxed 1 hr, then H_2O (150 ml) was added dropwise, and the inorg material was filtered off and washed well by suspending in Et_2O. Evapn of the combined Et_2O phases provided 3-(2-hydroxyethyl)-5-methoxy-2-methylindole as a cryst solid (45.3 g, 96.7%), mp 98–101°. This alcohol (45.3 g) was added as quickly as possible to boiling 48% HBr (450 ml). One minute later the soln was poured onto ice (1 kg) and extd with Et_2O. The exts were washed twice with satd $NaHCO_3$ soln, dried (K_2CO_3), and evapd to provide 3-(2-bromoethyl)-5-methoxy-2-methylindole as an oil (56.3 g). This oil was dissolved in MeCN (225 ml) and a soln of 4-acetamidopyridine (28.4 g) in MeCN (120 ml) was added. After 3 hr at room temp the cryst product (58.7 g, 81.7%) was collected.

Tetrahydropyridines (Table II). 3-[2-(4-Benzamido-1,2,5,6-tetrahydropyrid-1-yl)ethyl]indole (19).—To a stirred suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (8) (2.0 g) in MeOH (100 ml) was added $NaBH_4$ (6.0 g) portionwise over 30 min. Stirring was contd 1 hr after the addn, and the ppt was collected, washed (MeOH), and dried to give the crude product (1.55 g), mp 205–207°. Recrystn from MeOH raised the mp to 209–211°.

Piperidines (Table III). 3-[2-(4-Aminopiperid-1-yl)ethyl]indole (25). **Method A.**—4-Amino-1-[2-(3-indolyl)ethyl]pyridinium bromide (1) (3.18 g) in 90% EtOH (300 ml) contg Et_3N (1.0 g) and W-7 Raney Ni (*ca.* 3 g) was hydrogenated at 80° and 56.25 kg/cm² 18 hr. The catalyst was filtered off and the filtrate was evapd. The residue was shaken with 2 *N* NaOH until it crystd to give the hydrate (1.94 g).

Method B.—3-[2-(4-Acetamidopiperid-1-yl)ethyl]indole (**30**) (43.0 g) was dissolved in 2 *N* HCl (430 ml) and refluxed for 2.5 hr. The reaction mixt was cooled, filtered, and basified with 10 *N* NaOH to give the hydrate (36.4 g).

3-[2-(4-Aminopiperid-1-yl)ethyl]-1-methylindole (27). **Method C.**—3-[2-(4-Aminopiperid-1-yl)ethyl]indole (**25**) (13.05 g) was added portionwise to $NaNH_2$ in liq NH_3 (from 2.5 g of Na and *ca.* 500 ml of NH_3). After stirring 1 hr, CH_3I (7.8 g) in dry Et_2O (100 ml) was added dropwise. Stirring was contd at room temp until NH_3 had evapd; then H_2O (100 ml) was added dropwise to the residue. The resulting solid was collected and recrystd from MeCN contg 1% of H_2O to give the hydrate (10.16 g).

(9) Melting points are uncor. Ir spectra supporting the assigned structures were obtd for all compounds. C, H, and N analysis were obtd for all compounds except where noted in the tables and were within ±0.4% of the theor values except where noted in Table III. Nmr spectra of 15 representative compounds fully supported the assigned structures.

4-Benzamido-1-(5-benzyloxyindole-3-glyoxyloyl)piperidine (80). Method D(i).—5-Benzyloxyindole-3-glyoxylyl chloride[10] (23.2 g) was added portionwise to a stirred soln of 4-benzamidopiperidine (30.2 g) in dry 1,2-dimethoxyethane. After 1 hr the solid was collected and suspended in H_2O (1 l.) for 1 hr. The product (34.49 g) was filtered off, washed (H_2O), and dried. An anal. sample was recrystd from DMF–$2H_2O$.

5-Benzyloxy-3-[2-(4-benzylaminopiperid-1-yl)ethyl]indole (85). Method D(ii).—Compd **80** (33.88 g) was added portionwise to a stirred, refluxing suspension of LAH (20 g) in dry THF. Stirring and refluxing were contd for 4 hr, then H_2O (20 ml) and 2 *N* NaOH (40 ml) were added dropwise. Filtration and evapn of the filtrate plus washings gave an oil which was dissolved in hot EtOH and acidified with dry HCl. The product crystd on cooling as the dihydrochloride, hemihydrate (31.03 g).

3-[2-(4-Aminopiperid-1-yl)ethyl]-5-hydroxyindole (28). Method D(iii).—Compd **85** (10.0 g) in H_2O (100 ml) and MeOH (100 ml) was hydrogenated in the presence of 5% Pd/C (1.0 g) at 50° and 3.52 kg/cm² for 5 hr. Evapn of the filtered soln gave the product as a pink foam (6.29 g) which analyzed correctly for the dihydrochloride, hemihydrate.

3-[2-(4-Acetamidopiperid-1-yl)ethyl]-5-methoxy-2-methylindole (32). Method E.—3-[2-(4-Acetamido-1,2,5,6-tetrahydropyrid-1-yl)ethyl]-5-methoxy-2-methylindole (**18**) (4.66 g) in 50% aq AcOH (50 ml) was hydrogenated for 18 hr at 3.52 kg/cm² and 50° in the presence of PtO_2 (500 mg). After filtering off the catalyst and evapg the filtrate, the residue was dissolved in H_2O and basified with K_2CO_3. Extn with $CHCl_3$ and evapn of the dried exts gave a foam which was chromatogd on basic alumina. The purified product was crystd from EtOAc as colorless prisms (3.27 g).

3-[2-(4-Benzamidopiperid-1-yl)ethyl]indole (35). Method F.—3-[2-(4-Aminopiperid-1-yl)ethyl]indole (**25**) (2.61 g) in dry CH_2Cl_2 (100 ml) was stirred with K_2CO_3 (2.76 g) in H_2O (50 ml) at 5° while BzCl (1.69 g) in CH_2Cl_2 (20 ml) was added during 10 min. The mixt was kept at 5° for 18 hr, then the product was filtered off, washed, and dried, giving 2.95 g, 85%. An anal. sample was recrystd from EtOH–H_2O.

Method G.—4-Benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (**8**) (3.0 g) in 91% EtOH (300 ml) contg Et_3N (0.8 g) was hydrogenated in the presence of freshly prepared W-7 Raney Ni catalyst (*ca.* 3 g) at 28.12 kg/cm² and 50° for 4 hr. After filtering off the catalyst, the filtrate was evapd and the residue was shaken with $CHCl_3$ and 2 *N* NaOH. The resulting insol material (1.61 g, mp 203–206°) was collected and dried. Recrystn from EtOH gave the product (1.34 g), as colorless needles.

Method H.—A mixt of 3-(2-bromoethyl)indole (200 mg), 4-benzamidopiperidine (200 mg), and Et_3N (108 mg) in dry DMF (5 ml) was stirred at room temp overnight. H_2O (10 ml) was slowly added whereupon the product (225 mg, 72.5%) crystd. The yield was increased (287 mg, 92.5%) when an extra equiv of 4-benzamidopiperidine was used in place of the Et_3N. The base (215 mg) in MeOH (12 ml) was made just acid with dry HCl and the boiling MeOH was gradually replaced with EtOAc until the dist temp reached 68°, at which point crystn occurred to give the hydrochloride (227 mg), mp 230–232°. Recrystn from MeOH–*i*-PrOH gave a different cryst modification, mp 258–260°.

5-Methoxy-3-[2-(4-benzamidopiperid-1-yl)ethyl]indole (73). Method I(i).—4-Benzamidopiperidine (62 g) was added to a stirred suspension of cupric acetate (1.1 g) and paraformaldehyde (9.5 g) in dry dioxane (300 ml). Propiolaldehyde diethyl acetal (38.6 g) was then added and stirring was contd at 80° under N_2 for 24 hr. The hot reaction mixt was filtered and the filtrate was evapd. Recrystn of the solid residue from a mixt of EtOAc and petr ether (bp 60–80°) gave 4-benzamido-1-(4,4-diethoxybut-2-ynyl)piperidine (**87**) (84.6 g, 82%), mp 130°.

Method I(ii).—The product of part i (70 g) in EtOH (1 l.) was hydrogenated in the presence of 10% Pd/C (7 g) at 3.52 kg/cm² for 0.5 hr. Evapn of the filtrate after removal of the catalyst and recrystn of the residue from petr ether gave 4-benzamido-1-(4,4-diethoxybutyl)piperidine (**88**) (61.29 g, 86.5%), mp 95°.

Method I(iii).—The product of part ii (3.48 g) was added portionwise to a soln of *p*-methoxyphenylhydrazine·HCl (1.75 g) in 25% aq AcOH (15 ml) with stirring at 80° which was contd for 2.5 hr. The cooled mixt was dild with ice water, basified with K_2CO_3, and extd with $CHCl_3$. Evapn of the combined and dried exts gave a brown oil. Crystn from MeCN gave 5-methoxy-3-[2-(4-benzamidopiperid-1-yl)ethyl]indole (**73**) (1.95 g).

3-[3-(4-Benzamidopiperid-1-yl)propyl]indole (82). Method J.—A mixt of 4-benzamidopiperidine (1.02 g), 3-(3-hydroxypropyl)indole tosylate (1.73 g), and K_2CO_3 (1.38 g) in *i*-PrOH (25 ml) was stirred and refluxed for 24 hr. The filtrate from the hot reaction mixt crystd on cooling to give the crude product (1.83 g, 100%), mp 174–178°. Recrystn from EtOH–H_2O gave the anal. pure product.

3-[3-(4-Benzamidopiperid-1-yl)-1-oxopropyl]indole (81). Method K.—A mixt of 3-acetylindole (1.57 g), 4-benzamidopiperidine (2.0 g), 40% aq CH_2O (1.0 g), and AcOH (0.8 g) in EtOH (25 ml) was stirred for 4 hr. The product was filtered off and recrystd from MeCN to give colorless needles (1.53 g).

3-[2-(4-Benzamidopiperid-1-yl)-1-hydroxyethyl]indole (78). Method L.—3-[2-(4-Benzamidopiperid-1-yl)-1-oxoethyl]indole (**74**) (0.9 g) in MeOH (50 ml) was treated dropwise with $NaBH_4$ (1.0 g) in H_2O (9 ml) and 2 *N* NaOH (1 ml). The mixt was stirred under reflux for 2 hr, cooled, and evapd. The residue was slurried with H_2O and the resulting crystals were collected and recrystd from EtOH to give the product (511 mg) as colorless needles.

3-[2-(4-[2-Carboxybenzamido]piperid-1-yl)ethyl]indole (52). Method M.—3-[2-(4-Aminopiperid-1-yl)ethyl]indole (**25**) (1.0 g) in $CHCl_3$ (50 ml) was stirred at 40° and phthalic anhydride (570 mg) was added portionwise. The resulting solid was collected after 2 hr, and recrystd from EtOH–H_2O to give the hydrate (855 mg).

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