Selective Inhibition of the Monosynaptic Spinal Reflex by a Series of Hydroxylated Alkylaminoindans

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5-Hydroxy-2-piperidino-4,5,6,7-tetrahydroindan (**5**) and a number of related tetrahydro and dihydro compounds were prepared by selective mono- and dihydroxylation of the dihydro products from the Birch reduction of various alkylaminoalkylindans, tetralins, benzenes, and isoindolines. Some of these compounds showed a remarkably selective inhibition of the monosynaptic spinal reflex in the segmental cat preparation.

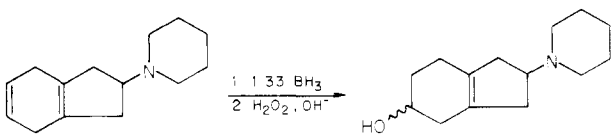
As part of a program directed toward the preparation of a variety of mono- and polyhydroxylated compounds of possible pharmaceutical interest, we had occasion to prepare 5-hydroxy-2-piperidino-4,5,6,7-tetrahydroindan (**5**) as an intermediate for more extensively hydroxylated compounds. Our general pharmacological evaluation of **5** turned up a mild analgetic effect in cats and dogs, and further studies with this compound demonstrated its ability to selectively inhibit the monosynaptic reflex in the cat spinal segmental reflex preparation while leaving the polysynaptic reflex unaltered. Since the test animals showed some stimulation but were otherwise largely unaffected by the drug, we were prompted to prepare and test a number of related compounds, the results of which are the subject of this article.

Chemistry. Compounds 1–32. Preparation of Dienes. The dienes used in the selective hydroxylation reactions to prepare compounds **1–32** were in all cases except **23** prepared by the Birch reduction of an alkylamino aromatic compound. The aromatic starting materials for **1–18** and **31** were prepared by reductive amination of β-indanone (m = 1) or β-tetralone (m = 2), as shown in Scheme I. Both the one step (amine, hydrogen, and catalyst) and two step [enamine or Schiff's base (**37**) formation followed by borohydride reduction] afforded nearly quantitative yields of the alkylaminoindans **38** (m = 1) or aminotetralins **38** (m = 2), which were used without further purification in the Birch reduction to give the dienes **39**.

The diene precursor of **19–22** was prepared from 2-piperidinomethylindene[1] by Birch reduction. The preparation of the requisite 2-alkylisoindoline[2,3] precursors of **24–28**, 2-phenethylpiperidine[4] for the synthesis of **29** and **30**, and 1-dimethylaminopropylindene[5] for **32** was accomplished by standard routes. The diene starting material (**43**) for **23** was prepared from indan-2-acetic acid[6] (**40**) as in Scheme II.

Selective Hydroxylations. The selective monohydroxylation of the disubstituted double bond of the alkylaminodienes (**39**) was achieved with diborane[7] followed by treatment with alkaline hydrogen peroxide (method A). The use of at least 1.33 mol of BH_3 per mole

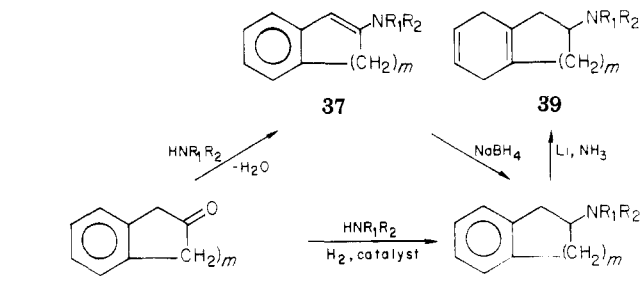
method A



39a **5**

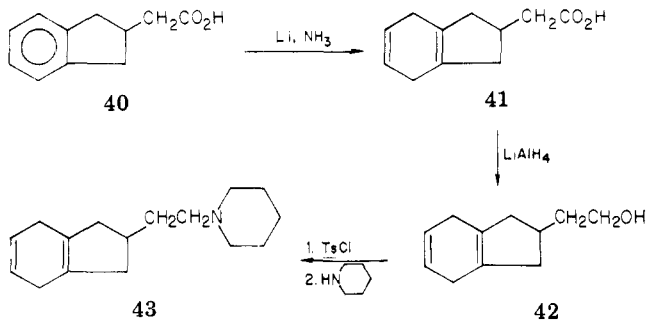
of diene was necessary because of the unreactive complex formed between the amine and the first mole of BH_3. Careful chromatography of the epimeric mixture formed in the preparation of **5** gave the epimers **6** and **7**. Although some differences were noted in the biological activity of **6** and **7** (see Table I), they were not large enough to warrant routine isolation of the isomeric components of the other analogues. The screening was, therefore, done on mixtures of diasteriomers.

Scheme I



	R_1	R_2	m
37-39a	$-(CH_2)_5-$		1
b	$-(CH_2)_4-$		1
c	CH_3	CH_3	1
d	$-C_6H_{11}$	H	1
e	$-n-C_4H_9$	H	1
f	$-(CH_2)_5-$		2

Scheme II

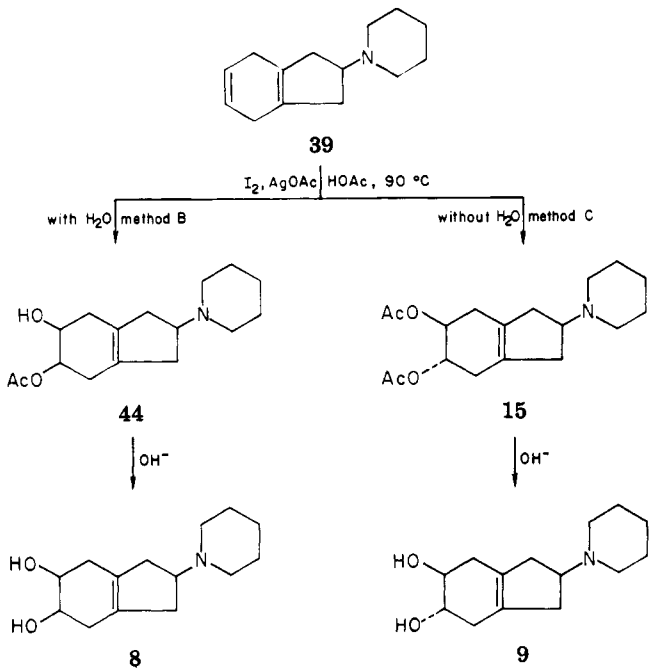


The dihydroxylation of the disubstituted double bond of **39** was achieved via the Prévost reaction,[8] using iodine and silver acetate in hot acetic acid, as shown in Scheme III.

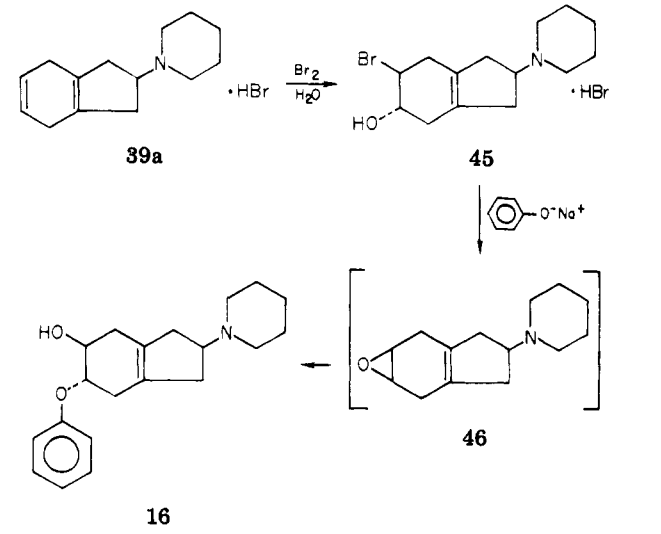
In the presence of water (method B) the *cis*-diol monoacetate **44** was formed, but under anhydrous conditions (method C), the *trans*-diol diacetate was obtained. The initial monoacetate product in method B could be isolated, as in the preparation of **27**, but these relatively unstable products were normally hydrolyzed to the diols for purification.

Although the addition of an electrophilic reagent to a double bond would be expected to favor the more substituted olefinic position, the steric bulk of the Simonini complex[8] in the Prévost reaction and the close proximity of a protonated nitrogen in **39** must preclude reaction at the more substituted double bond. Indeed, in the preparation of **9**, none of the product of addition to the tetrasubstituted double bond, subsequently prepared as **31**, was discovered in the final product mixture after hydrolysis.

Scheme III



Scheme IV

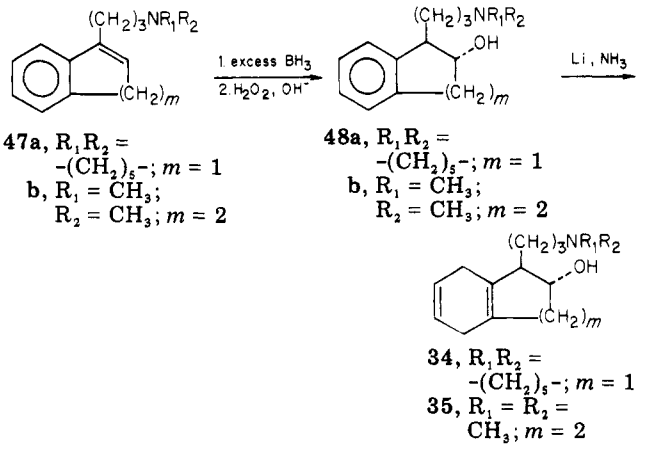


Hydroxylation of the disubstituted double bond of **39** could also be achieved using the action of bromine water on the hydrobromide salt, to give the bromohydrin **45** as shown in Scheme IV. Treatment of **45** with phenoxide afforded the phenoxy ether **16**, presumably via the epoxide **46**. As with the Prévost reaction there was observed exclusive reaction at the less substituted double bond, again apparently due to the difficult approach of the bromonium ion to the crowded tetrasubstituted double bond which is additionally hindered by a nearby, positively charged nitrogen.

Whereas the hydroxylation of the diene system of **39** had proceeded in an anomalous fashion with iodine–silver acetate, and with bromine water, the reaction of the same system with 1 equiv of performic acid resulted in attack on the more highly substituted double bond, as expected, and gave a high crude yield of the diol **31**.

Compounds 33–36. The amino alcohol precursors to **34** and **35** were prepared from the alkylaminoalkylindene[9] **47** (m = 1), or alkylaminoalkyldihydronaphthalene[10] **47** (m = 2) via hydroboration, to give the aromatic compound **48**. Birch reduction gave the final products as shown in Scheme V.

Scheme V

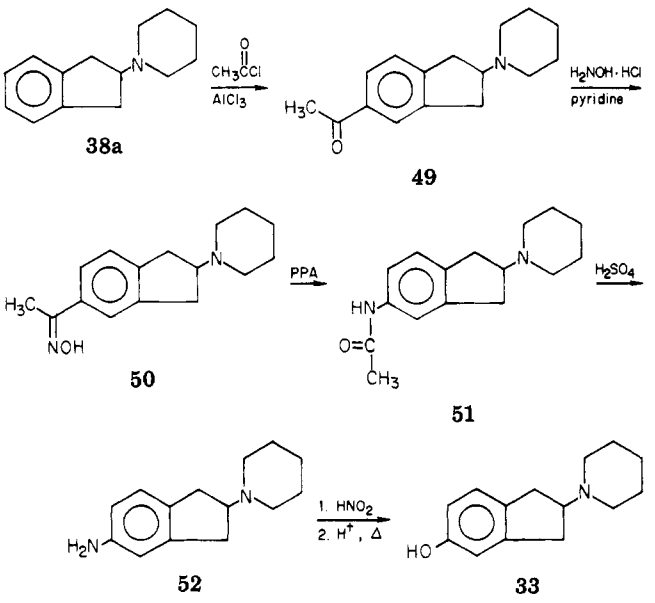


47a, R_1R_2 = $-(CH_2)_5-$; m = 1
b, R_1 = CH_3; R_2 = CH_3; m = 2

48a, R_1R_2 = $-(CH_2)_5-$; m = 1
b, R_1 = CH_3; R_2 = CH_3; m = 2

34, R_1R_2 = $-(CH_2)_5-$; m = 1
35, R_1 = R_2 = CH_3; m = 2

Scheme VI



The reaction sequence in Scheme VI was used to prepare 5-hydroxy-2-piperidinoindan[11] (**33**) from **38a**. The acylation of **38a** occurred exclusively at the 5 position, avoiding the mixtures that might be expected from a more direct nitration–reduction sequence to **52**.

Pharmacology. The compounds were tested in the unanesthetized, decerebrate, acute spinal cat[12] for effects on the reflexes elicited by electrical stimulation of a segment of the spinal cord (see the Experimental Section for a more complete description of the preparation). The biological response of interest consisted of a decrease in the amplitude of the monosynaptic reflex with little, if any, effect on the polysynaptic reflex.

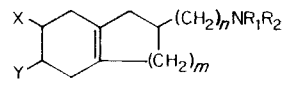
The activities recorded in Tables I–III ranged from no effect to marked inhibition of the monosynaptic response. The duration of the effect ranged from less than 15 min to greater than 2 h.

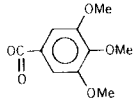
Discussion

The observation of monosynaptic spinal reflex (MSR) inhibition in this series of compounds seems to depend on the presence of a moderate-sized tertiary amine attached to a five-membered ring containing unsaturation and also probably requires the presence of additional hydroxylation somewhere in the molecule.

To illustrate these generalizations, the following comparisons are made. The n-butyl- (**13**) and cyclohexyl- (**4**) amines (secondary) are inactive but the piperidine (**5**) and

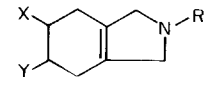
Table I. 2-Alkylaminoalkyltetrahydroindans and -octalins



Compd	X	Y	n	m	R_1	R_2	Method of synthesis[b]	Yield, %[c]	Mp, °C	Recrystn solvent	Formula[d]	Spinal reflex response[a]						Dose, iv, mg/kg (n)[e]
												Monosynaptic			Polysynaptic			
												Direction	Act.	Duration	Direction	Act.	Duration	
1	OAc	*cis*-OAc	0	1	CH_3	CH_3	D[f]	51	140–143	CH_3CN–ether	$C_{15}H_{23}NO_4 \cdot C_7H_8O_3S$	↓	+	+++	↓	+		5
2	OAc	*cis*-OAc	0	1	CH_3	CH_3	D[f]	48	150–152	CH_3CN–ether	$C_{15}H_{23}NO_4 \cdot C_7H_8O_3S$		0			0		5
3	OH	*cis*-OH	0	1	CH_3	CH_3	B	58	130–132	Benzene	$C_{11}H_{19}NO_2$	↑	+			0		5
4	OH	H	0	1	C_6H_{11}	H	A	30	110–111	Ethyl acetate–hexane	$C_{15}H_{25}NO$		0			0		5
5	OH	H	0	1	-$(CH_2)_5$-		A	50	94–96	Ether–petr ether	$C_{14}H_{23}NO$	↓	++++	+++		0		2 (10)
5												↓	++++	++++		0		10
6	OH	H	0	1	-$(CH_2)_5$-		A[g]	20	103–106	Ether	$C_{14}H_{23}NO$	↓	+++	++		0		2 (2)
7	OH	H	0	1	-$(CH_2)_5$-		A[h]	17	113–115	Ether	$C_{14}H_{23}NO$	↓	++++	++++		0		2 (2)
8	OH	*cis*-OH	0	1	-$(CH_2)_5$-		B	72	156–168	Benzene	$C_{14}H_{23}NO_2$	↓	+	+		0		5
9	OH	*trans*-OH	0	1	-$(CH_2)_5$-		C	63	156–158	Benzene	$C_{14}H_{23}NO_2$	↓	+++	++		0		5
10	OAc	*cis*-OAc	0	1	-$(CH_2)_5$-		D	43	73–88	Hexane	$C_{18}H_{27}NO_4$	↓	+++	++++		0		5 (2)
11		H	0	1	-$(CH_2)_5$-		D[i]	50	77–81	Hexane	$C_{24}H_{33}NO_5$		0			0		5
12	OH	H	0	1	-$(CH_2)_4$-		A	49	81–89	Ether–hexane	$C_{13}H_{21}NO$	↓	++	++	↓	+	+	5
13	OH	H	0	1	*n*-C_4H_9	H	A[j]	51	69–75	Hexane	$C_{13}H_{23}NO$		0			0		5
14	OH	H	0	1	*n*-C_4H_9	CH_2Ph	A	43	45–60	*k*	$C_{20}H_{29}NO \cdot HCl$	↓	++	+++		0		5
15	OAc	*trans*-OAc	0	1	-$(CH_2)_5$-		D	54	212–214	CH_3CN–ether	$C_{18}H_{27}NO_4 \cdot C_7H_8O_3S$		0			0		5
16	OH	*trans*-OPh	0	1	-$(CH_2)_5$-			16	174–187	CH_2Cl_2–hexane	$C_{20}H_{27}NO_2$		++	+				5
17	OH	*cis*-OH	0	2	-$(CH_2)_5$-		B	39	143–145	CH_3CN	$C_{15}H_{25}NO_2$		0			0		5
18	OAc	*cis*-OAc	0	2	-$(CH_2)_5$-		D	32	225–229	CH_2Cl_2–ethyl acetate	$C_{19}H_{29}NO_4 \cdot HCl$		0			0		5
19	OH	H	1	1	-$(CH_2)_5$-		A	23	186–187	2-Propanol–ether	$C_{15}H_{25}NO \cdot HCl$	↓	+	++		0		5
20	OH	*trans*-OH	1	1	-$(CH_2)_5$-		C	37	120–121	CH_2Cl_2–hexane	$C_{15}H_{25}NO_2$	↓	++	+++		0		5
21	OAc	*trans*-OAc	1	1	-$(CH_2)_5$-		D	67	170–172	CH_3CN–ether	$C_{19}H_{29}NO_4 \cdot C_7H_8O_3S$	↓	++	+		0		5
22	OH	*cis*-OH	1	1	-$(CH_2)_5$-		B	45	80–84	CH_2Cl_2–hexane	$C_{15}H_{25}NO_2$		0			0		5
23	OH	H	2	1	-$(CH_2)_5$-		A	14	178–183	Ethanol–ether	$C_{16}H_{27}NO \cdot HCl$	↓	++	++		0		5

[a] Direction ↓ indicates inhibition of response relative to control; activity ++++ = >80% inhibition, +++ = 50–80%, ++ = 20–50%, + = 0–20%; duration ++++ = >2 h, +++ = 1–2 h, ++ = 0.25–1 h, + = <15 min. [b] See Experimental Section for general description of the various methods. Where none is designated, individual compound is described. [c] Calculated from immediate precursor (see Method of Synthesis). [d] Analysis performed for all elements, except oxygen, on all compounds. Analytical results were within ±0.4% of the theoretical values. [e] Number of tests with each drug (n) = 1 for all except where indicated. [f] Isomers separated as two different crops on crystallization from acetonitrile–ether. [g] From pooling of early fractions from preparation of 5. [h] From pooling of later fractions from preparation of 5. [i] 3,4,5-Trimethoxybenzoyl chloride used in acylation instead of acetic anhydride. [j] From catalytic debenzylation (Pd/C in ethanol) of 14. [k] Precipitated from ether by anhydrous HCl and isolated as an amorphous powder.

Table II. *N*-Alkyltetrahydroisoindolines

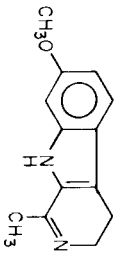


Compd	X	Y	R	Method of synthesis[b]	Yield, %[c]	Mp, °C	Recrystn solvent	Formula[d]	Spinal reflex response[a] Monosynaptic Direction	Act.	Duration	Polysynaptic Direction	Act.	Duration	Dose, iv, mg/kg (n)[e]
24	OH	*cis*-OH	CH_3	B	41	133–134	Ethyl acetate	$C_9H_{15}NO_2$	↓	+			0		5 (2)
25	OAc	*trans*-OAc	CH_3	D	51	91–92	Hexane	$C_{13}H_{19}NO_4$		0			0		5
26	OH	*trans*-OH	CH_3	C	65	140–141	Ethyl acetate	$C_9H_{15}NO_2$	↓	+	+		0		5 (2)
27	OAc	*cis*-OH	CH_3	B[f]	24	129–130	Ethanol–ether	$C_{11}H_{17}NO_3 \cdot C_6H_{13}NO_3S$		NT					
28	OH	H	C_6H_{11}	A	33	92–94	Ether–hexane	$C_{14}H_{23}NO$	↓	+	+		0		5

[a–e] See corresponding footnotes *a–e* in Table I. [f] Base hydrolysis omitted. Free base liberated with bicarbonate and converted to salt in conventional manner.

pyrrolidine (**12**) compounds (tertiary, but of roughly equivalent size to **4** and **13**) have activity. The dimethylamine compound **1** has weak activity compared to the piperidine analogue **10**, indicating a minimum requirement in the size of the amine. When the five-membered ring of **10** is expanded to a six-membered ring, as with **18**, all activity is lost, as in the case when the ring is conceptually "cleaved" in the open-chain compound **30**. Moving the amine one or two carbons away from the five-membered ring, as with compounds **19** and **23**, decreases activity, and moving the amine nitrogen into the ring, as in **28**, almost eliminates activity. The relative positions of amine, hydroxyl, and double bond can be altered, as illustrated with compound **34**. When the side chain is attached to a six-membered ring, however, activity is abolished, as in **35**. Finally it is interesting to note that the unsaturation of the five-membered ring may be provided by an aromatic ring, as in **33**.

A search of the literature has revealed that specific drug-related inhibition of the MSR has not been studied extensively. Two compounds, harmaline[13] (**53**) and coniine[14] (**54**), have been reported to have the same effect observed with our series of compounds. The activity of both drugs is specific, but coniine has a relatively weak effect.



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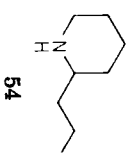

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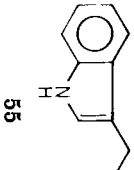
The variety of structural types of active compounds raises the question of their mode of action. A recent report[15] supports the presence of both noradrenergic and tryptaminergic systems in the cat spinal cord. Tryptamine (**55**) and methoxamine (**56**) both potentiate the monosynaptic and polysynaptic reflexes. The potentiation by



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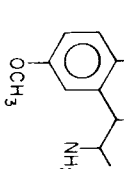

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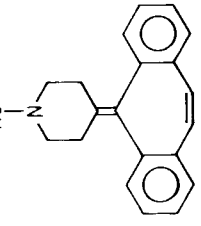
tryptamine can be blocked completely by cyproheptadine (**57**) but is unaffected by phenoxybenzamine (**58**) and, conversely, the effects of methoxamine are blocked by



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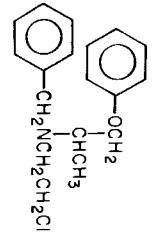

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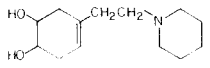
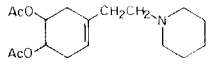
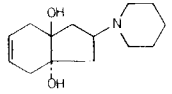
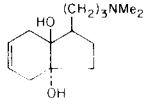
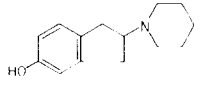
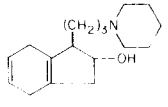
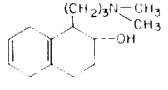
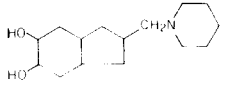
phenoxybenzamine and are largely unaffected by cyproheptadine. Although the critical experiments have not been run, we suggest that harmaline may be a specific blocker of the tryptaminergic system in cat spinal cord, based on its structural relationship to tryptamine and 5-hydroxytryptamine, another potentiator[16] of the reflex responses. Similarly, the series of compounds discussed in this paper would seem to have structural features in common with both types of potentiators and may in fact affect both systems.

Table III. Amines Structurally Related to 5

Compd	Structure	Method of synthesis[b]	Yield, %[c]	Mp, °C	Recrystn solvent	Formula[d]	Spinal reflex response[a]						Dose, iv, mg/kg (n)[e]
							Monosynaptic			Polysynaptic			
							Direction	Act.	Duration	Direction	Act.	Duration	
29		B	26	155-156	2-Propanol-acetone-ether	$C_{13}H_{23}NO_2 \cdot HCl$		0			0		5
30		D	56	152-153	CH_2CN-ether	$C_{24}H_{27}NO_4 \cdot C_7H_8O_3S$		0			0		5
31		E	84	114-121	Benzene	$C_{14}H_{23}NO_2$	↑	+	+	↓	+	+	5
32		E	14	99-101	Ether	$C_{14}H_{25}NO_2$	↓	+			0		5
33				243-246	Ethyl acetate	$C_{14}H_{19}NO$	↓	++++	+		0		5
34			43	174-178	2-Propanol-ether	$C_{17}H_{27}NO \cdot HBr$	↓	++	+++		0		5
35			52	139-141	2-Propanol-ether	$C_{15}H_{25}NO \cdot HCl$		0			0		5
36			24	90-117	Hexane	$C_{15}H_{27}NO_2$		0			0		5

[a-e] See corresponding footnotes a-e in Table I.

Regardless of the mechanism of inhibition, **5** and related compounds effectively inhibit the electrically evoked monosynaptic reflex and also block the physiological monosynaptic reflex (knee jerk). Since the active drugs do not result in motor deficit in cats (2–4 mg/kg iv or 10 mg/kg po), it would be of interest to see the clinical effect of this inhibition and whether they could represent a new class of specific muscle relaxants.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds had consistent NMR and IR spectra. Elemental analyses were performed by the Analytical Department of The Squibb Institute for Medical Research. Each synthetic method is illustrated by a specific example and is accompanied by a list of compounds prepared by this procedure. "Alumina" for chromatography refers to "Woelm neutral or basic for column chromatography" adjusted with water to the designated activity. GC was run in a nitrogen stream on a Varian Aerograph 1200. TLC was done in the appropriate solvent using 0.20-mm aluminum oxide neutral type E precoated aluminum sheets with F-254 indicator and visualization under UV light as well as iodine vapors.

Preparation of Dienes for Compounds 1–32. The following two-step procedure was employed for the preparation of the diene precursors of compounds **1–3** and **5–18** (Table I) and compound **31** (Table III), using the appropriate primary or secondary amine instead of dimethylamine.

2-Dimethylaminoindan (38c). To a chilled solution of 100 g (2.2 mol) of dimethylamine in 900 mL of benzene was added 161 g (1.2 mol) of 2-indanone and 0.1 g of toluenesulfonic acid. The mixture was allowed to come to room temperature over 1 h and then refluxed under a water separator until water was no longer evolved. The mixture was stripped to an oil, taken up in 2 L of methanol, and treated with 35 g (0.92 mol) of $NaBH_4$ in portions over 1 h, $T \leq 40$ °C. The mixture was stirred an additional 2 h and then water was added to liberate the solid amine. This was filtered, taken up in ether, dried (K_2CO_3), and evaporated to 152 g (78%) of solid **38c**, which was used without further purification in the next step.

2-Dimethylamino-4,7-dihydroindan (39c). A sample of **38c** (80 g, 0.5 mol) was added to 2 L of liquid NH_3, and the mixture was treated with 50 g (7.2 mol) of lithium in portions. After stirring 1 h, the mixture was treated with 400 mL of absolute ethanol over 1.5 h to discharge the blue color, and the NH_3 was then evaporated with the aid of a water bath. Ether and water were added, and the aqueous mixture was reextracted with ether. Drying of K_2CO_3 and evaporation left 76 g (94%) of **39c** which was used in the hydroxylation reactions without further purification.

An alternate one-step procedure was used for the preparation of the diene precursor for **4**.

2-Cyclohexylamino-4,7-dihydroindan (39d). A mixture of 19.8 g (0.15 mol) of 2-indanone and 18.0 g (0.18 mol) of cyclohexylamine in 250 mL of absolute ethanol and 2.0 g of 5% Pd/C was hydrogenated at 50 °C and 40 psi for 6 h, cooled, and filtered. The rapidly darkening solution was evaporated to an oil, taken up in ether, and treated with an excess of HCl in 2-propanol. The solid was filtered and recrystallized from ethanol to give 30 g (80%) of 2-cyclohexylaminoindan hydrochloride (**42d**) in two crops. Treatment with caustic gave the free base, 24 g (0.11 mol), which was added as a solution in 50 mL of ether to 2 L of liquid NH_3 with stirring. Ethanol (77 mL, 1.6 mol) was added, followed by lithium (23 g, 3.3 g-atoms) over 0.5 h. The reaction mixture was stirred for 1 h and then treated with ethanol until white. The NH_3 was evaporated and the residue cooled in an ice bath. Water was added, the product was extracted with ether, and the organics were dried (K_2CO_3) and evaporated to yield 20.4 g (84%) of **39d** (20% aromatic by NMR). A portion was converted to its hydrochloride salt and recrystallized from 2-propanol to give a white solid, mp 252–254 °C. Anal. ($C_{15}H_{23}N$·HCl) C, H, N, Cl.

The precursor dienes used for compounds **19–22**, **24–30**, and **32** were prepared by the lithium–ammonia reduction of the corresponding aromatic compounds which were in turn prepared by known routes, i.e., for **19–22**,[1] **24–27**,[2] **28**,[3] **29** and **30**,[4] and **32**.[5]

The preparation of **43**, the diene precursor for **23**, was accomplished as follows.

2-(2-Piperidinoethyl)-4,7-dihydroindan (43). Indan-2-acetic acid[6] (**44**) (31.5 g, 0.18 mol) was dissolved in 100 mL of ether and added to 1.5 L of liquid NH_3. To this was added 28 g (4 g-atoms) of lithium ribbon over 1.5 h, and the mixture was stirred for 1 h and then treated with ethanol until white. After evaporation of NH_3, water was added, the mixture extracted with ether, and the aqueous mixture acidified with 20% HCl. The oily acid was extracted into ether, dried ($MgSO_4$), and evaporated to 32 g of crude, semisolid 4,7-dihydro-2-acetic acid (**41**).

A 15-g sample (0.084 mol) of **41** was refluxed with 4.2 g (0.11 mol) of $LiAlH_4$ in 300 mL of diethyl ether overnight under nitrogen. Excess reagent was destroyed with sodium carbonate solution, and the filtrates were evaporated to 12.4 g (90%) of crude oily 2-(4,7-dihydroindan-2-yl)ethanol (**42**).

A 12-g sample of **42** (0.075 mol) in 200 mL of dry pyridine at 0 °C was treated with 28.5 g (0.1 mol) of toluenesulfonyl chloride, stirred until dissolved, and then stored at 5 °C for 18 h. The resulting solution was poured onto 1 L of water and cracked ice and stirred for 0.75 h, and the resulting oil was extracted into ether, washed with 18% HCl and then with water, dried over K_2CO_3, and evaporated to an oil. The oily tosylate was taken up in 300 mL of toluene, treated with 15 mL of piperidine, and refluxed for 6 h. Ether and water were added, the aqueous mixture was separated, and the organics were dried over K_2CO_3 and evaporated to 14.5 g (84%) of **43**, pure enough, as judged by NMR, for use in the hydroxylation step. A sample was converted to its hydrobromide salt and recrystallized from 2-propanol to give a white solid, mp 198–201 °C. Anal. ($C_{16}H_{25}N$·HBr) C, H, N.

Syntheses of Compounds 1–15 and 17–32. Methods A–E. 4,5,6,7-Tetrahydro-2-piperidino-5-indanol (5). Method A. 1-(4,7-Dihydro-2-indanyl)piperidine (**39a**) (19.3 g, 0.093 mol) was dissolved in 200 mL of dry THF. A solution of 1 M BH_3 in THF (93 mL) was added dropwise in 40 min. The mixture was left stirring overnight; then the solvent was removed in vacuo. The viscous residue was dissolved in 200 mL of 95% ethanol and 9.0 g (0.2 mol) of NaOH was added, followed by dropwise addition of 30% H_2O_2 (24 mL, 0.2 mol). After refluxing 2.5 h the mixture was taken to near dryness in vacuo and the residue was extracted four times with ether. The ether extracts were dried over $MgSO_4$ and the ether was removed in vacuo leaving 24.5 g of oil. The oil was chromatographed on activity grade II neutral alumina. After starting material was eluted with ether, product was eluted first with ether and then with mixtures of ether plus chloroform up through pure chloroform. All fractions with the same retention time on GC using a $^1/_8$ in. × 5 ft OV 17 column at 190 °C totaled 10 g of product (~50%). A pool of fractions in the middle of the elution (contents 2.6 g) was recrystallized from ether–petroleum ether to give 1.6 g, mp 94–96 °C. The comparison of the IR of this middle fraction with the spectra of the early and late product fractions indicated that the material was a mixture of epimers.

Using method A, the following monohydroxylated compounds were prepared: **4**, **12**, **14**, **19**, **23**, and **28**.

5,6-*cis*-2-(Dimethylamino)-4,5,6,7-tetrahydro-5,6-indandiol (3). Method B. A mixture of 32.6 g (0.2 mol) of **39c** and 80 g (0.48 mol) of silver acetate in 400 mL of acetic acid and 20 mL of water was treated with 50 g (0.4 g-atom) of iodine in four portions over 15 min. The mixture was stirred vigorously and heated for 2 h at 100 °C, cooled, and filtered; the salts were washed with acetic acid. Evaporation gave an oil which was taken up in 1 L of MeOH, basified with 20% NaOH, and allowed to stand at room temperature overnight. Water (300 mL) was added and the mixture evaporated to residual aqueous solution. Extraction first with ether and then with chloroform gave, on drying (Na_2SO_4) and evaporation, a total of 32 g of solid diol. One crystallization from 650 mL of benzene gave 23 g (58%) of **3**, mp 130–132 °C. Two crystallizations of a 4-g sample from 100 and 200 mL of benzene with Darco treatment gave 3.2 g, mp 130–132 °C.

Using method B, the following *cis*-diols were prepared: **8**, **17**, **22**, **24**, and **29**.

5,6-*trans*-4,5,6,7-Tetrahydro-2-piperidino-5,6-indandiol (9). Method C. A solution of 50.5 g (0.25 mol) of **39a** in 1 L of dry acetic acid (fresh bottle) was treated with 83.5 g (0.50 mol) of dry silver acetate under N_2. The stirred suspension was then treated portionwise with 63.5 g (0.25 mol) of I_2 over 0.5 h. The stirred

mixture was then heated to 90–95 °C for 3 h, cooled, filtered, and taken to dryness. The residue was dissolved in 250 mL of MeOH and treated with 50 mL of 50% NaOH with stirring. After stirring overnight, the solution was diluted with water and the product extracted into $CHCl_3$. After drying and solvent removal, the crude product was taken up in hot *i*-PrOH and the solution rendered turbid with ether. A 25-g first crop was obtained. Further crops of 12 g were obtained on rework: total crude yield, 37 g (63%); mp 149–167 °C. The IR indicated the absence of the cis isomer. Recrystallization of 6.0 g of first crop material twice from benzene provided 2.8 g of pure material, mp 156–157.5 °C.

Method C was used to prepare compounds **9**, **20**, and **26**.

5,6-*trans*-4,5,6,7-Tetrahydro-2-piperidino-5,6-indandiol Diacetate Ester *p*-Toluenesulfonate Salt (1:1) (15). Method D. A solution of 10 g (0.045 mol) of **9** in 200 mL of pyridine was treated at room temperature with 100 mL of acetic anhydride. The solution was allowed to stand for 24 h and then evaporated in vacuo at 30 °C to a thick oil. Ether and saturated sodium bicarbonate were added until effervescence ceased. The organic layer was dried ($MgSO_4$) and evaporated to an oil. The oil was taken up in 100 mL of ether, diluted with hexane (400 mL), and cooled overnight at −15 °C. The solution was decanted from a small amount of dark oil and evaporated to 9 g (64%) of a tan crystalline mass. A 1.3-g sample of free base (4 mmol) in 20 mL of acetonitrile was treated with 0.79 g (4 mmol) of toluenesulfonic acid monohydrate in 20 mL of the same solvent. The mixture was warmed briefly on a steam cone and then treated with 150 mL of dry ether. The crystalline salt (1.7 g, 85%) was collected and recrystallized from acetonitrile–ether to give 1.3 g of the analytical sample, mp 212–214 °C.

A similar procedure was used to prepare the following compounds: **1**, **2**, **10**, **18**, **21**, **25**, **27**, and **30**.

3a,7a-*trans*-3a,4,7,7a-Tetrahydro-2-piperidino-3a,7a-indandiol (31). Method E. A solution of 30.5 g of **39a** (0.15 mol) in 250 mL of 98% formic acid was prepared in the cold and treated dropwise with 18.0 g of 30% H_2O_2 during 10 min at 6 °C. After stirring in an ice bath for several hours, the mixture was left overnight at room temperature. The mixture was evaporated in vacuo and the residue taken up in 250 mL of ethanol and treated with 50 mL of 50% NaOH. After standing for 0.5 h the mixture was diluted with water and extracted three times with ether. The extracts were dried (K_2CO_3), freed of solvent, and triturated with hexane. Filtration of the crystalline product afforded 30 g (84%), mp 106–121 °C. Recrystallization of 5.0 g of the diol from benzene afforded 2.0 g of analytical material, mp 114–121 °C.

This method was also used to prepare **32**.

5,6-*trans*-4,5,6,7-Tetrahydro-6-phenoxy-2-piperidino-5-indanol (16). A solution of 24.9 g (0.123 mol) of **39a** in 500 mL of absolute ethanol was acidified with 48% HBr with cooling. Volatile materials were completely removed in vacuo and the solid was suspended in 1 L of water. To this stirred suspension over 1.5 h was added a solution of 19.6 g (0.123 mol) of Br_2 and 50 g of KBr in 400 mL of water at room temperature. The solution was then covered with ether and excess K_2CO_3 added carefully. Extraction with a total of 1 L of ether, drying, and evaporation gave a wet oil which was dried azeotropically with benzene addition and evaporation. Hexane (300 mL) was added to the dry oil and the solution cooled at 5 °C overnight to give 8.8 g (25%) of **45**, mp 165–170 °C dec.

To a solution of 9.4 g (0.1 mol) of phenol in 60 mL of MeOH was added in portions 5.4 g (0.1 mol) of sodium methoxide. While still warm the mixture was treated with 3.5 g (0.012 mol) of **45** in 15 mL of MeOH. After stirring 2.5 days at 25 °C the mixture was refluxed 8 h, cooled, and diluted with $CHCl_3$ and water. The organics were washed with 10% NaOH, dried (Na_2SO_4), and evaporated to 1.8 g of a solid. Hexane (50 mL) was added and the solid filtered in 1 h to give 1.0 g; TLC in $CHCl_3$ showed only one major component. Recrystallization from dichloromethane–hexane gave **16**: 0.9 g (16%); mp 174–187 °C.

Preparation of 2-Piperidino-5-indanol (33). A mixture of 33 g (0.139 mol) of **38a** hydrochloride and 50 mL of acetyl chloride under a drying tube was treated in portions, with ice cooling, with 70 g (0.52 mol) of aluminum chloride. The temperature was gradually raised to 60 °C and held there for 2 h; then another 50 mL of acetyl chloride added with heating for 0.5 h. The hot mixture was poured cautiously onto 3 L of cracked ice, cooled, and made strongly basic with NaOH. Extraction with ether, drying over K_2CO_3, and evaporation gave 35 g of crude 5-acetyl-2-piperidinoindan (**49**).

The ketone **49** (25 g, 0.1 mol) was taken up in 150 mL of dry pyridine and treated with 7.7 g (0.11 mol) of hydroxylamine hydrochloride. The mixture was refluxed 3 h under N_2, cooled, and evaporated to dryness in vacuo. The residue was swirled and shaken with dilute NaOH and a large volume of $CHCl_3$; the organics were separated, dried (K_2CO_3), and evaporated to give 30 g of crude solid oxime **50**. A 16-g (0.062 mol) sample of **50** was taken up in 300 g of PPA and heated on a steam cone for 3 h. The hot mixture was poured into 2 L of cool water and, with cooling, basified with NaOH pellets. The liberated product was extracted with $CHCl_3$, dried (K_2CO_3), and evaporated to a thick oil. Crystallization from water–ethanol afforded 8.0 g (50%) of **51**. A 3-g sample was recrystallized from ethanol–water with Norit treatment to afford the 2.3-g analytical sample, mp 105–109 °C. Anal. ($C_{16}H_{22}N_2O$) C, H, N.

1-(5-Amino-2-indanyl)piperidine (52). A 6-g (0.0232 mol) sample of **51** was taken up in 200 mL of 5% sulfuric acid and refluxed for 3 h. The mixture was cooled and basified with 10% NaOH, and the liberated amine was filtered and dried in air (5 g, 100%). A 3.5-g sample was taken up in methylene chloride, treated with decolorizing carbon, and filtered. To this was added filtered hexane, and the solution was concentrated to 75 mL of mainly hexane. Cooling afforded 2.5 g of yellow **52**, mp 137–139 °C. Anal. ($C_{14}H_{20}N_2$) C, H, N.

2-Piperidino-5-indanol (33). A 2.8-g (0.013 mol) sample of **52** was taken up in 100 mL of 5% sulfuric acid and clarified by filtering through a Hy-Flo pad. The clear yellow solution was cooled in ice and treated over 5 min with a solution of 0.9 g (0.013 mol) of sodium nitrite in 20 mL of water. The cold mixture was stirred at 0–5 °C for 0.5 h and then added over 40 min to 400 mL of vigorously boiling 5% sulfuric acid. After refluxing another 0.5 h the mixture was cooled to room temperature and treated with solid K_2CO_3 until CO_2 evolution ceased. Methylene chloride was added and the brown solid which collected at the interface was retrieved by filtration and washed with water. (This material was soluble in dilute sodium hydroxide.) The solid was suspended in hot absolute ethanol and evaporated to dryness. Crystallization from ethyl acetate gave 1.8 g (64%) of brown crystals, mp 246–247 °C. Norit treatment in ethyl acetate and crystallization afforded the 1.3-g analytical sample of **33**, a bright yellow solid, mp 243–246 °C.

4,7-Dihydro-1-(3-piperidinopropyl)-2-indanol Hydrobromide (34). 1-[3-(3-Indenyl)propyl]piperidine[7] (**47a**) (48.2 g, 0.2 mol) was dissolved in 400 mL of THF and stirred under N_2 at 0 °C while 400 mL of 1 M BH_3 in THF was added dropwise over a period of 1 h. The mixture was left stirring overnight at room temperature. Most of the solvent was then removed in vacuo. The viscous residue was dissolved in 500 mL of 95% ethanol and treated with 20 g of NaOH, and then 65 mL of 30% H_2O_2 was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 2 h and then heated under reflux for 2.5 h. The mixture was then taken to near dryness in vacuo and the residue was extracted three times with benzene. The benzene extracts were dried and evaporated to leave 57 g of oily product, one spot on TLC (alumina, chloroform), presumed to be 1-(3-piperidinopropyl)-2-indanol (**48a**).

The crude **48a** (~0.2 mol) was dissolved in 300 mL of ether and added to 2 L of liquid NH_3. Lithium ribbon (50 g) was added in small portions over a period of 30 min. After stirring 1.5 h absolute ethanol was added dropwise until the color was discharged (1 L added over a period of 4 h). The NH_3 was allowed to evaporate and the residue was then diluted to 4 L with water. Two ether extracts yielded 62 g of crude diene which became partially crystalline on standing. A 3.5-g sample was converted to the hydrobromide. Two recrystallizations from 2-propanol–ether yielded 1.95 g (43%, based on **47a**) of **34**, mp 174–178 °C.

Compound **35** was prepared by using 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene in the above sequence.

5,6-*cis*-Hexahydro-2-(piperidinomethyl)-5,6-indandiol (36). A solution of 2.5 g (0.01 mol) of **22** in 50 mL of glacial acetic acid with 0.4 g of platinum oxide was hydrogenated at 40 psi for 2 h, when uptake stopped. The catalyst was filtered and washed with glacial acetic acid, the filtrate evaporated, and the residue dissolved

in water, basified with 10% NaOH, and extracted with $CHCl_3$. The organics were dried ($MgSO_4$) and evaporated. Crystallization from a small amount of hexane yielded 0.6 g (24%) of **36**, mp 90–117 °C.

Pharmacological Evaluation. The test animal is the unanesthetized decerebrated cat[16] (midpontine) in which the L-5 to S-2 spinal segments have been exposed, and the spinal cord was cut at L-1. The dorsal and ventral roots of a L-6, L-7, or S-1 segment are attached to two pairs of silver J-type electrodes, and the drugs are administered intravenously over 1–2 min into the right cephalic vein as solutions in physiological saline. The compounds are tested for effects on the ventral reflex response resulting from electrical stimulation of the dorsal root with a monophasic pulse (0.5-ms duration) delivered at a rate of 30/min. The monosynaptic and polysynaptic responses are amplified and displayed on a cathode ray oscilloscope and photographed with a Polaroid camera for subsequent analysis. Administration of the saline vehicle did not affect either response.

The analgetic effect was observed in the incisor tooth pulp preparation[17] using dogs and cats. In both species activity was observed at 5 mg/kg iv.

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Synthesis of 3-(4-Acylaminopiperazin-1-ylalkyl)indoles as Potential Antihypertensive Agents

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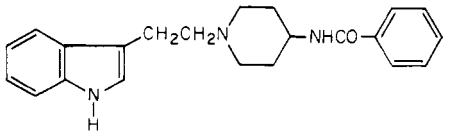
A series of 3-(4-acylaminopiperazin-1-ylalkyl)indoles was synthesized and tested for antihypertensive activity. Compounds with no substituents in the indole portion of the molecule were generally most effective in lowering blood pressure in the spontaneous hypertensive rat model. Of these, several analogues were very potent and lowered blood pressure more than 55 mmHg at oral doses of 100 mg/kg.

Appropriately substituted piperazines often exhibit potent antihypertensive activity.[1] However, derivatives of *N*-aminopiperazine have been much less investigated for their pharmacological effects. In view of the clinically useful antihypertensive properties of indoramin (I),[2] we thought it would be of interest to replace the central portion of this molecule by *N*-aminopiperazine (formula II) and assess the effect of this moiety on blood pressure lowering ability. The hydrazine linkage present in this novel series also exists in other hypotensive agents, most notably hydralazine.



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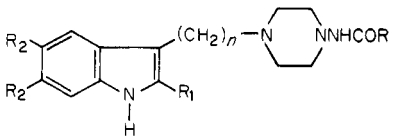

II

Chemistry. The key intermediates, the 3-(4-aminopiperazin-1-ylethyl)indoles (V), were prepared by the method of Speeter and Anthony[3] as shown in Scheme I. This synthetic approach involved acylation of an appropriately substituted indole with oxalyl chloride, reaction of the resulting 3-indoleglyoxylyl chloride (III) with *N*-nitrosopiperazine to give the glyoxamide (IV), and lithium aluminum hydride ($LiAlH_4$) reduction to the corresponding intermediates of type V. Acylation of the *N*-amino group then afforded the target compounds.

Some aspects of this chemistry deserve further comment. The reaction of indole and 2-methylindole proceeded smoothly with oxalyl chloride in ether to precipitate the brightly yellow 3-indoleglyoxylyl chlorides in better than 90% yield. These could be filtered and stored in the cold virtually unchanged for long periods of time. However, in our hands, the glyoxylyl chloride from 5,6-dimethoxy-2-methylindole (III, $R_1 = CH_3$; $R_2 = OCH_3$) was unstable, the reaction mixture rapidly turning purple and yielding no isolable solid. To circumvent this problem, the reaction was carried out at 0 °C in a two-phase chloroform–water system containing potassium carbonate as base. After a brief reaction time, *N*-nitrosopiperazine was added to trap the unstable glyoxyl intermediate. Addition