Synthesis and Hypotensive Properties of Tetrahydroisoquinolines

Ian W. Mathison,* Kathleen C. Fowler, Phillip H. Morgan,† Richard R. Tidwell,† Elizabeth R. Peters,

Department of Medicinal Chemistry

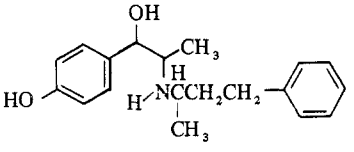
Norbert J. Wojciechowski, James W. Lawson, and Frances K. Hetzer

Materials Science Toxicology Laboratories, Department of Molecular and Quantum Biology, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103. *Received August 17, 1972*

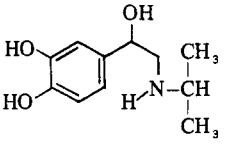
A series of tetrahydroisoquinolines variously substituted at the 2, 5, 6, 7, and 8 positions of the ring system has been synthesized and evaluated as hypotensive agents in the unanesthetized hypertensive rat and for acute toxicity in the mouse and rat. Several compounds demonstrated activity that was comparable to known antihypertensive agents in both the magnitude of the depressor response and the duration of action. The incorporation of aralkyl groupings at the 2 position markedly reduced the toxicity of the compounds, while replacement of the methoxyls of the 5-benzamide moiety with halogens, nitro, or alkyl groupings decreased the hypotensive activity of the molecule. The most active compounds appear to be those possessing the 3,4,5-trimethoxybenzamido grouping at the 5, 6, 7, or 8 position, while maintaining the 2 substituent as methyl.

Our previous studies have been concerned with the cardiovascular activity of variously substituted decahydroisoquinolines and attempts to correlate stereochemistry with pharmacological activity.[1] While some partially reduced tetrahydroisoquinolines were synthesized[2] during the course of this work, little attention was directed to a detailed study of their activities. More recently, we have become interested in agents capable of lowering blood pressure and as a result have reinvestigated the tetrahydroisoquinoline nucleus as a parent molecule for the development of some new agents possessing significant hypotensive properties. Consideration of the structure of the tetrahydroisoquinoline moiety was made in the light of a cyclized version of such hypotensive agents as nylidrin, isoxsuprine, and isoproterenol (see Chart I) and of the hypotensive phenylethylamines such as α-methyldopa.

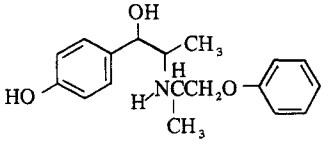
Chart I



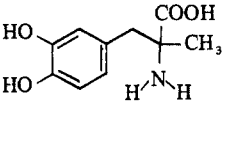
nylidrin



isoproterenol



isoxsuprine

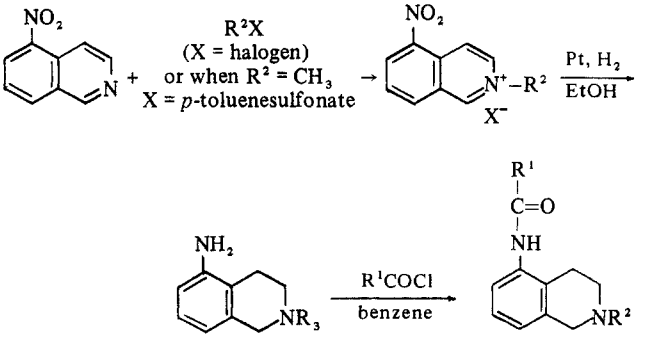


α-methyldopa

During the course of the synthetic program leading to some 5-amino-2-methyldecahydroisoquinolines,[3] it was observed during a general cardiovascular screening procedure in the anesthetized dog that 5-amido-2-methyl-1,2,3,4-tetrahydroisoquinolines possessed significant hypotensive properties. Our previous findings of the absence of any hypotensive activity with the oxygen isostere of this structure, *i.e.*, an ester at position 5 of the tetrahydroisoquinoline,[2] was a very pertinent observation in the decision to pursue this series of new cardiovascular agents. As a result, a series of various 5-amido-2-alkyl- (or aralkyl-) 1,2,3,4-tetrahydroisoquinolines possessing the general formula shown in

†In partial fulfillment of the requirements for the Doctor of Philosophy degree of the University of Tennesse Medical Units.

Scheme I



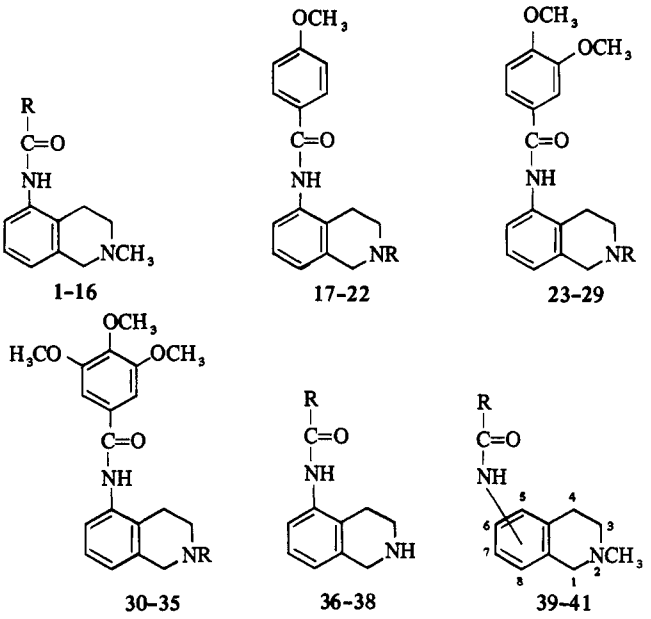
Scheme I has been synthesized and evaluated for hypotensive activity. Preliminary studies conducted in deoxycorticosterone hypertensive rats demonstrated that some of these tetrahydroisoquinolines produced significant reductions in mean systolic blood pressure for periods up to 24 hr following the administration of single doses.[4] The synthesis, biological activity, and structure-activity relationships in these series of compounds will be discussed.

Chemistry. The synthetic pathway, in general, followed the scheme outlined in Scheme I. Synthesis of the alkyl or aralkyl halides introduced at the heterocyclic nitrogen which were not commercially available was carried out according to reported procedures (Chart II). The compounds synthesized, purification solvent, and other physical data are outlined in Table I. Changes were made at both positions R^1 and R^2 accounting for approximately 40 compounds. In most cases the free bases were synthesized; where difficulties in purification were encountered, the corresponding hydrochloride salt was prepared.

Pharmacological Evaluation. Hypertension was induced in 30-day-old (50 g) male CD strain rats obtained from the Charles River Breeding Laboratories by subcutaneously implanting about the dorsal surface of the neck, a wax-formulated sustained release pellet[5] containing 10 mg of deoxycorticosterone acetate (DCA). The animals were maintained on Wayne laboratory chow but immediately after implantation 1% NaCl solution was substituted in place of their drinking water, a procedure which facilitates the development of hypertension.

Hypertension was regarded as established when mean systolic blood pressure was above 150 mm. This level of pres-

Chart II. General Formulas of Tetrahydroisoquinolines Shown in Table I



sure was attained usually 30–40 days after the day of implant.

Systolic blood pressure was indirectly measured in the caudal arteries of prewarmed (40°), unanesthetized, but restrained animals by a pneumatic pulse transducer placed distal to an automated tail pressure cuff (Narco Bio-Systems Inc.) and recorded on a physiograph. Rats were kept at a temperature of 40° during the time that systolic blood pressure determinations were being made in order to minimize variations in pressure due to alterations in arterial tone provoked by changes in ambient temperature.

Prior to the experiments, animals were accustomed to the measurement handling procedure several times during the preceding weeks. Following the control readings on test day, the compound under investigation was administered by intraperitoneal injection either in solution or as a suspension in 1% tragacanth to groups consisting usually of 6 DCA-hypertensive rats. Blood pressure was redetermined at 1-, 2-, 4-, and 24-hr intervals following injection. Mean values for the group at the various measurement periods were calculated from the individual average values. The mean difference from predrug control levels along with its associated standard error was calculated at each time period. The sta-

Table I. Physical Data of Variously Substituted Tetrahydroisoquinolines (for Structures of Compounds, see Chart II)

No.	Substituent R	Mp, °C	Formula	Analyses	Purification solvent	% yield
1	$-C_6H_5$	152.5–153	$C_{17}H_{18}N_2O$	C, H, N	Bz	35
2	$-C_6H_{11}$	158–159.5	$C_{17}H_{23}N_2O$	C, H, N	EtAc	62
3	$-C_6H_4$-2-F	229–230	$C_{17}H_{18}N_2OClF$	C, H, N, Cl, F	EtOH	13
4	$-C_6H_4$-2-Cl	189.5–191.5	$C_{17}H_{17}N_2OCl$	C, H, N, Cl	EtOH	74
5	$-C_6H_4$-2-Br	206.5–208.5	$C_{17}H_{17}N_2OBr$	C, H, N, Br	EtOH	61
6	$-C_6H_4$-2-I	215–216.5	$C_{17}H_{17}N_2OI$	C, H, N, I	MeOH	91
7	$-C_6H_4$-2-NO_2	196.5–198	$C_{17}H_{17}N_3O_3$	C, H, N	EtOH	53
8	$-C_6H_4$-4-OCH_3	169.5–171.5	$C_{18}H_{20}N_2O_2$	C, H, N	EtOH	59
9	$-C_6H_3$-2,6-$(OCH_3)_2$	191–192	$C_{19}H_{22}N_2O_3$	C, H, N	Bz	39
10	$-C_6H_3$-3,4-$(OCH_3)_2$	160–161.5	$C_{19}H_{22}N_2O_3$	C, H, N	EtOH	46
11	$-C_6H_3$-2,6-$(CH_3)_2$	199.5–201	$C_{19}H_{22}N_2O$	C, H, N	EtOH	17
12	$-C_6H_3$-2,6-$(C_2H_5)_2$	185.5–187.5	$C_{21}H_{26}N_2O$	C, H, N	EtOH	30
13	$-C_6H_2$-3,4,5-$(OCH_3)_3$	143–143.5	$C_{20}H_{24}N_2O_4$	C, H, N	Bz	72
14	$-C_6H_2$-2,4,5-$(OCH_3)_3$	159.5–160.5	$C_{20}H_{24}N_2O_4$	C, H, N	EtOH	65
15	$-CH_3$	137.5–138.1	$C_{12}H_{16}N_2O$	C, H, N	Bz	56
16	$-C_6H_3$-3,4-(OCH_2O)	205.5–206.5	$C_{18}H_{18}N_2O_3$	C, H, N	EtOH	65
17	$-C_3H_7$	162.5–163.5	$C_{20}H_{24}N_2O_2$	C, H, N	EtOH	70
18	$-CH_2C_6H_5$	176–177	$C_{24}H_{24}N_2O_2$	C, H, N	EtOH	76
19	$-CH_2C_6H_4$-4-OCH_3	157.5–159.5	$C_{25}H_{26}N_2O_3$	C, H, N	EtOH	57
20	$-(CH_2)_2C_6H_5$	174–175.5	$C_{25}H_{26}N_2O_2$	C, H, N	EtOH	62
21	$-(CH_2)_3C_6H_5$	142–143	$C_{26}H_{28}N_2O_2$	C, H, N	EtOH	60
22	$-(CH_2)_3C_6H_4$-2-OCH_3	120–121	$C_{27}H_{30}N_2O_3$	C, H, N	EtOH	55
23	$-C_3H_7$	146.5–147.5	$C_{21}H_{26}N_2O_3$	C, H, N	EtOH	70
24	$-CH_2C_6H_5$	138.5–139.5	$C_{25}H_{26}N_2O_3$	C, H, N	EtOH	38
25	$-CH_2C_6H_4$-4-Br	176.5–177.5	$C_{25}H_{25}N_2O_3Br$	C, H, N, Br	EtAc	71
26	$-CH_2$-C_6H_4-4-OCH_3	142–143.5	$C_{26}H_{28}N_2O_4$	C, H, N	EtOH	12
27	$-(CH_2)_2C_6H_5$	156.5–157.5	$C_{25}H_{28}N_2O_3$	C, H, N	EtOH	51
28	$-(CH_2)_3C_6H_5$	129.5–131.5	$C_{27}H_{30}N_2O_3$	C, H, N	EtOH	63
29	$-(CH_2)_3C_6H_4$-2-OCH_3	118–119	$C_{28}H_{32}N_2O_4$	C, H, N	EtOH	34
30	$-C_3H_7$	158.5–159.5	$C_{22}H_{28}N_2O_4$	C, H, N	EtOH	15
31	$-CH_2C_6H_5$	156.5–157.5	$C_{26}H_{28}N_2O_4$	C, H, N	Ligroin (90–120°)-EtOH	7
32	$-CH_2C_6H_4$-4-OCH_3	236–238	$C_{27}H_{31}N_2O_5Cl$	C, H, N, Cl	EtOH	38
33	$-(CH_2)_2$-C_6H_5	155–156	$C_{27}H_{30}N_2O_4$	C, H, N	EtOH	18
34	$-(CH_2)_3$-C_6H_5	144–145	$C_{28}H_{32}N_2O_4$	C, H, N	EtOH	48
35	$-(CH_2)_3$-C_6H_4-2-OCH_3	157.5–159	$C_{29}H_{34}N_2O_5$	C, H, N	EtOH	51
36	$-C_6H_4$-4-OCH_3	289–290	$C_{17}H_{19}N_2O_2Cl$	C, H, N, Cl	H_2O	43
37	$-C_6H_3$-3,4-$(OCH_3)_2$	286–287	$C_{18}H_{21}N_2O_3Cl$	C, H, N, Cl	MeOH	74
38	$-C_6H_2$-3,4,5-$(OCH_3)_3$	270–271.5	$C_{19}H_{23}N_2O_4Cl$	C, H, N, Cl	MeOH	86
39	$-C_6H_2$-3,4,5-$(OCH_3)_3$ (6 position isomer)	233.5–235	$C_{20}H_{25}N_2O_4Cl$	C, H, N, Cl	H_2O	80
40	$-C_6H_2$-3,4,5-$(OCH_3)_3$ (7 position isomer)	157.5–158	$C_{20}H_{24}N_2O_4$	C, H, N	EtOH	84
41	$-C_6H_2$-3,4,5-$(OCH_3)_3$ (8 position isomer)	177–178.3	$C_{20}H_{24}N_2O_4$	C, H, N	EtOH	70

tistical significance of the changes produced by the compounds was tested by an analysis of variance and the Newman-Keuls *a posteriori* test when F was significant. A probability level of 0.05 or less was accepted as a significant change in blood pressure.

Most of the compounds were screened at a dose of 50 mg/kg in this preliminary pharmacological study, although some were administered at higher dose levels.

Acute toxicity determinations were conducted in female Swiss-Webster mice weighing 17-25 g. Compounds were administered either in solution or as suspensions in 1% tragacanth by the intraperitoneal route to groups of animals consisting of three or more mice per group. LD_{50} values were estimated from the results obtained by administering two or more graded (usually logarithmically spaced) doses of each compound. Mice were observed for up to 72 hr following injection of the compounds, but the toxicity values reported were on the basis of a 24-hr observation period.

Acute toxicity determinations were also conducted in adult Charles River rats weighing 250-500 g in a manner similar to that described above for the acute toxicity mouse studies. In the interest of conserving compound for the rat hypotensive screening program, and without inferring that the toxicity values in the two species are necessarily similar, only a few compounds in the series were studied in the rat.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are corrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer Model 137B Infracord spectrophotometer and all compounds possessed the requisite spectra for the proposed structures. Where analyses are indicated, analytical results were within ±0.3% of the theoretical values. As a general synthetic method, the undernoted sequence was used.

General Method. 5-, 6-, 7-, or 8-nitroisoquinoline (1.0 mol) was refluxed with the appropriate alkyl or aralkyl halide (1.1 mol) in absolute ethanol for a period of 120 hr. The yellow precipitate of the quaternary salt which appeared on cooling was filtered and combined with the residue obtained from evaporation of the filtrate. The total solids were recrystallized. The quaternary salt obtained from above was then dissolved in MeOH and hydrogenated over PtO_2 (approximately 5% by weight of salt used) at 40-50 psi. The hydrogenation was normally complete within 18 hr at which time the catalyst was filtered and the solvent removed by rotary evaporation. The residual solid in most cases was not purified and was used as the crude material in the acylation step. The crude 5-, 6-, 7-, or 8-amino-2-alkyl- (or aralkyl-) 1,2,3,4-tetrahydroisoquinoline hydrohalide salt (1.0 mol) was suspended in anhydrous benzene or pyridine and treated with the appropriate acid chloride (1.1 mol) under reflux for as long as 144 hr. The solvent was removed by evaporation and the sticky residue was thoroughly treated with 10% Na_2CO_3 solution. The residue (which was very often tacky) was washed several times with dry Et_2O and the resulting powdery product recrystallized from a suitable solvent as indicated in Table I.

Results and Discussion

The pharmacological data obtained are shown in Tables II and III. Examination of the data shown in Tables II and III indicates that compounds have been synthesized having a wide range of toxicity and similarly a broad spectrum of hypotensive activity. In the interest of conserving compound, compounds whose lethal dose was above 1000 mg/kg in the mouse were generally not put through the antihypertensive screening program. As can be seen from Table II, 14 compounds possessed these high LD_{50} values. It is interesting to note that generally the compounds in this category possessed aralkyl groupings on the heterocyclic nitrogen; additionally, the nature of the functional grouping at position 5 did not seem to be too critical. For example, compounds **18-22** possess the 4-methoxybenzamide at the 5 position while compounds **24-29** and **31-35** possess the 3,4-dimethoxybenzamido and 3,4,5-trimethoxybenzamido groupings, respectively (compound **32** appears to be an exception).

Toxicity of a few of the compounds, namely **1**, **8**, **10**, **13**, **23**, and **30**, was studied in the rat to make sure that the compounds were reasonably safe in doses which were intended to be administered to hypertensive rats. It is of interest to note that the toxicity values determined in these normotensive rats were not essentially different from those obtained in the mouse. While there is some risk in attempting to generalize for the entire series on the basis of these six observations, one may assume that great differences in toxicity between the two species probably do not exist. While the mouse acute toxicity data were not intended to be applied to the rat, on the basis of the studies conducted in both species it appears that rat toxicity values approximate those found in the mouse rather well.

Of most interest, however, was the data obtained from

Table II. Approximate Acute Toxicity (24 hr) of Variously Substituted Tetrahydroisoquinolines in the Mouse and Rat[a]

Compd no.	N[b]	ALD_{50}, mg/kg ip	Compd no.	N[b]	ALD_{50}, mg/kg ip	Compd no.	N[b]	ALD_{50}, mg/kg ip
1	12	125-250[e]	**15**	20	31-62[e]	**29**	8	>1000[c]
	(9)	(125-250[c])						
2	15	188-250[e]	**16**	20	125-250[e]	**30**	9	125-250[e]
							(4)	(125-250[c])
3	17	250-500[d]	**17**	9	125-250[e]	**31**	9	>1000[c]
4	14	125-188[e]	**18**	15	>2000[c]	**32**	22	<31[e]
5	16	125-250[e]	**19**	15	>1000[c]	**33**	10	>1000[c]
6	27	<31[e]	**20**	9	>1000[c]	**34**	12	>1000[c]
7	13	125-250[e]	**21**	10	>1000[c]	**35**	11	>1000[c]
8	15	62-125[e]	**22**	11	>1000[c]	**36**	14	500-1000[c]
	(9)	(32-62[e])						
9	9	250-500[e]	**23**	80	500-631[c]	**37**	13	500-1000[d]
				(27)	(500-1000[c])			
10	19	125-250[e]	**24**	9	>1000[c]	**38**	8	250-500[d]
	(7)	(100-200)[e])						
11	15	125-250[e]	**25**	11	>1000[c]	**39**	20	188-250[d]
12	15	125-250[e]	**26**	12	~2000[c]	**40**	10	250-500[e]
13	9	125-250[e]	**27**	9	500-1000[c]	**41**	9	250-500[e]
	(9)	(100-200[c])						
14	16	68-125[e]	**28**	12	>1000[c]			

[a]Numbers in parentheses refer to toxicity values obtained in the rat. [b]Number of animals dosed. [c]Suspension in 1% tragacanth. [d]Solution in distilled water. [e]Solubilized with the aid of dilute acid.

Table III. Per Cent Change in Systolic Blood Pressure of Unanesthetized Male DCA-Hypertensive Rats Produced by Variously Substituted Tetrahydroisoquinolines and Some Standard Antihypertensive Agents

Compd no.	Dose, mg/kg ip	No. of rats	Control[a]	% change in pressure from control ± S.E. 1 hr	2 hr	4 hr	24 hr
1	50	6	206 ± 12	−5.2 ± 2.3[c]	−7.6 ± 2.4[c]	−8.9 ± 2.6[c]	−5.9 ± 1.1[c]
2	50	6	178 ± 7	−2.3 ± 1.6	−2.3 ± 1.6	−5.4 ± 1.0[c]	−11.5 ± 2.2[c]
3	50	6	199 ± 9	−6.5 ± 2.6	−5.3 ± 2.2	−5.2 ± 2.1	−9.1 ± 1.9[c]
4	50	6	190 ± 4	−1.7 ± 1.6	−4.2 ± 2.4	−0.8 ± 1.7	+0.9 ± 2.5
5	50	6	224 ± 8	−4.0 ± 2.3	−4.2 ± 3.5	−8.6 ± 1.7[c]	−9.2 ± 1.4[c]
6	50	6	175 ± 3	−6.8 ± 2.1[c]	−9.9 ± 2.1[c]	−5.7 ± 1.9[c]	−0.7 ± 2.9
7	50	6	198 ± 7	−6.1 ± 1.7	−4.1 ± 3.0	−3.3 ± 4.0	−1.0 ± 3.0
8	50	12	197 ± 4	−6.6 ± 1.5[c]	−9.4 ± 2.5[c]	−7.1 ± 1.8[c]	−4.9 ± 1.8[c]
9	50	6	225 ± 4	−1.0 ± 3.4	−3.0 ± 2.3	−7.9 ± 4.1	−6.2 ± 4.3
10	50	6	195 ± 4	−16.3 ± 2.4[c]	−15.8 ± 2.6[c]	−16.7 ± 2.1[c]	−10.2 ± 2.2[c]
11	50	6	181 ± 8	−6.1 ± 1.7[c]	−2.4 ± 0.6	−5.2 ± 1.8[c]	+2.0 ± 2.1
12	50	6	192 ± 3	−5.7 ± 3.0	−7.5 ± 4.6	−6.1 ± 2.8	+2.1 ± 2.3
13	50	11	198 ± 10	−11.1 ± 2.0[c]	−19.0 ± 3.0[c]	−10.6 ± 3.5[c]	−4.6 ± 1.6[c]
14	50	6	223 ± 10	−6.5 ± 1.7[c]	−8.2 ± 1.9[c]	−6.2 ± 1.7[c]	−2.4 ± 2.4
15	50	6	206 ± 9	+2.8 ± 2.5	+2.2 ± 3.1	−0.6 ± 1.5	+1.4 ± 1.9
16	50	6	194 ± 8	−3.8 ± 1.8	−6.1 ± 4.3	−4.6 ± 2.7	−4.8 ± 2.6
17	50	12	210 ± 10	−11.3 ± 1.9[c]	−17.8 ± 1.4[c]	−10.2 ± 2.8[c]	−6.2 ± 2.0[c]
18	50	6	182 ± 8	−8.8 ± 1.3[c]	−8.7 ± 2.8[c]	−3.7 ± 1.4	−7.4 ± 2.6[c]
18	200	6	186 ± 10	−20.8 ± 4.4[c]	−21.0 ± 3.0[c]	−13.7 ± 4.9[c]	−11.1 ± 4.0[c]
19	100	6	189 ± 8	−8.6 ± 1.5[c]	−10.4 ± 2.0[c]	−4.2 ± 4.5	−1.9 ± 1.8
23	50	12	226 ± 7	−15.1 ± 3.2[c]	−19.6 ± 4.6[c]	−17.9 ± 3.7[c]	−9.3 ± 1.5[c]
23	50	11[b]	141 ± 2	+1.6 ± 2.0	+1.9 ± 2.4	−1.7 ± 1.5	−2.4 ± 1.3
24	200	6	206 ± 5	−15.6 ± 1.9[c]	−17.4 ± 2.1[c]	−14.7 ± 2.9[c]	−11.6 ± 1.9[c]
25	100	6	213 ± 6	−9.9 ± 3.2[c]	−13.9 ± 2.0[c]	−8.5 ± 3.4[c]	−2.3 ± 1.4
26	100	6	226 ± 4	−10.1 ± 1.7[c]	−12.8 ± 2.1[c]	−11.3 ± 1.9[c]	−0.8 ± 1.9
27	200	6	177 ± 8	−19.4 ± 2.2[c]	−17.3 ± 1.9[c]	−11.2 ± 2.9[c]	−12.3 ± 1.8[c]
30	50	6	204 ± 12	−14.0 ± 2.1[c]	−11.8 ± 2.3[c]	−7.1 ± 2.9[c]	−4.5 ± 0.6[c]
31	200	6	217 ± 13	−20.6 ± 2.5[c]	−16.4 ± 1.4[c]	−7.0 ± 1.6[c]	−4.9 ± 2.1
32	100	6	218 ± 6	−19.0 ± 2.2[c]	−18.7 ± 1.8[c]	−11.3 ± 0.9[c]	−1.6 ± 2.6
36	50	6	221 ± 10	−8.8 ± 4.8	−6.5 ± 3.7	−8.3 ± 2.4	−6.4 ± 1.3
37	50	6	221 ± 11	−13.8 ± 2.9[c]	−11.1 ± 3.4[c]	−8.4 ± 1.8[c]	−1.7 ± 2.3
38	50	6	210 ± 17	−12.4 ± 3.9[c]	−12.6 ± 3.6[c]	−4.7 ± 1.4	−8.3 ± 1.2[c]
39	50	6	188 ± 7	−21.6 ± 1.7[c]	−19.4 ± 4.0[c]	−11.9 ± 3.4[c]	−3.8 ± 1.3[c]
40	50	6	213 ± 11	−25.5 ± 2.5[c]	−19.9 ± 2.5[c]	−14.8 ± 2.3[c]	−5.8 ± 1.7[c]
41	50	6	212 ± 10	−25.5 ± 4.9[c]	−20.4 ± 3.4[c]	−12.7 ± 1.0[c]	−9.4 ± 2.9[c]
α-MeDopa	50	6	205 ± 9	−15.2 ± 1.7[c]	−24.4 ± 1.9[c]	−23.1 ± 2.3[c]	−8.1 ± 2.6[c]
Guanethidine	10	6	197 ± 11	−8.8 ± 3.9	−23.2 ± 4.0[c]	−22.2 ± 2.6[c]	−13.4 ± 3.0[c]
0.9% NaCl	0.1 ml/0.1 kg	12	183 ± 8	+2.7 ± 2.0	+2.3 ± 1.5	−1.4 ± 1.7	−0.3 ± 1.7

[a] Mean systolic blood pressure (mm) ± S.E. [b] Normotensive rats. [c] <0.05 level of significance by Newman-Keuls *a posteriori* test.

the hypotensive screening. A number of compounds were not studied in the hypertensive rat in view of the poor activities noted in other structures within the series which possessed similar types of substituents. A number of compounds emerged which very clearly possessed significant hypotensive activity. From Table III it is apparent that compounds **10, 13, 17, 23, 30, 31, 37–41** produced significant responses at the 50 mg/kg dose, while **18, 24, 27,** and **32** produced significant depressions at higher dose levels. It is also apparent that the duration of action (an important parameter in the development of an antihypertensive agent) and time of maximal effect varied somewhat among these compounds. However, a peak at 1 or 2 hr following administration of the drug appeared most common. With the exception of compounds **2, 10, 13, 17, 18, 23, 24, 27, 30, 38–41**, blood pressure appeared to have essentially returned to the control level 24 hr following administration of drug. The cited compounds, however, appeared to cause or induce a significant depression of blood pressure and are currently being given further consideration in additional pharmacological studies.

The activity of α-methyldopa and guanethidine, two known antihypertensive agents, was included in our studies with DCA-hypertensive rats. It will be noted in Table III that both of these compounds produce significant depressions in mean systolic blood pressure. The magnitude of the changes produced by these two compounds, in the doses employed, was essentially similar and amounted to about a 22–24% reduction in pressure from control levels. The peak response time was reached about 2–4 hr following administration of the compounds and the compounds were active throughout 24 hr. This level of activity and duration was also observed with compounds **13, 18, 23, 24, 27, 39–41**. Hypertensive rats receiving a placebo injection of 0.9% NaCl and treated in a manner similar to that followed when investigating the tetrahydroisoquinoline compounds showed no significant change in systolic pressure at any time throughout this experiment. A group of normotensive rats was also included in this study. This group of rats was administered compound **23** in a dose of 50 mg/kg, a dose identical with that which had previously been given to a group of DCA-hypertensive rats. It will be seen in Table III that this dose did not produce any significant changes in mean systolic pressure at any of the monitored time periods. The lack of a response in normotensive animals is not necessarily a unique observation with compound **23**. Other investigators have shown that hypertensive rats respond to such agents as chlorothiazide, α-methyldopa, pargyline, ecolid, and others with significant decreases in pressure, while normotensive animals administered equivalent doses of these agents show little or no effect.[6] It would appear that the results observed with compound **23** support the need for utilizing some

form of experimental animal hypertension in an effective antihypertensive screening program. These studies would also support the fact that this tetrahydroisoquinoline is an antihypertensive compound rather than a hypotensive agent.

In the interest of developing some structure-activity relationships, the structural modifications will be considered under the six general types synthesized as shown in Chart II.

A. Compounds 1-16. This group constituted the largest series and all compounds possessed the $-CH_3$ substituent at the 2 position with variations at position 5 of the tetrahydroisoquinoline nucleus. An early study had shown that the acetamido grouping at the 5 position (**15**) produced no effect on blood pressure; as a result the synthesis of aromatic analogs was carried out varying the substituents on the benzamido moiety. The effects of halogens, methoxyl, methyl, and nitro groupings were ascertained. It ought to be noted that the unsubstituted benzamide possessed some small degree of hypotensive activity; however, substitution of the benzamide moiety with 3,4-dimethoxy (**10**) or 3,4,5-trimethoxy (**13**) yielded compounds with significantly increased activity. All other substitutions did not appear to enhance the activity of the molecule. The positional isomers of the methoxy compounds **10** and **13** (*i.e.*, **9** and **14**) were devoid of activity. Our intention was to produce steric hindrance at the amide function as a means of prolonging activity; however, in this instance this was unsuccessful and led us to consider that hydrolysis of the amide function plays no major role in the duration of activity in this series of compounds. Compound **16** may be considered to possess the methoxyl groups of compound **10** incorporated in a ring structure. This modification of the free methoxyls of **10** yielded a compound which was inactive. Replacement of the benzamide moiety with a cyclohexamide grouping (**2**) produced a compound which had peak activity at the 24-hr time period. In view of the increase in lipid solubility of such a compound compared with the benzamide, one is lead to speculate on the importance of partition function on activity. However, it is also apparent that this compound produced significant depression of blood pressure only after 4 hr, suggesting that increased lipid solubility, while prolonging the activity, also has an effect of prolonging the onset of activity which is perhaps not quite so desirable.

B. Compounds 17-22. This series was designed to evaluate the effects of various alkyl and aralkyl substituents at the 2 position while maintaining the 5 substituent as the 4-methoxybenzamide grouping. Therefore, effects of varying substituents ought to be compared with compound **8** in series A. It is apparent from Table III that an increase in chain length from methyl to the *n*-propyl substituent (**17**) produced a significant increase in activity but that aralkyl substituents produce little or no enhancement of hypotensive properties at the 50 mg/kg dose. It is of interest to note that **18** (benzyl substituent at the 2 position) at higher dose levels (200 mg/kg) produced significant lowering of blood pressure. This experiment was carried out to assess the possibilities of increasing dosage of the relatively nontoxic agents, *i.e.*, those having LD_{50} values >1000 mg/kg. In this series it is apparent that a substituent at the the 2 position appears essential since the unsubstituted compound (**36**) is a very poor hypotensive agent.

C. Compounds 23-29. These compounds incorporated changes at the 2 position while the 5 substituent was maintained as the 3,4-dimethoxybenzamido grouping. As in the previous series reference should also be made to the appropriate methyl derivative **10**. With the exception of compound **23** the compounds were administered at higher doses. In spite of this they appeared to produce no significant increase in activity over derivative **10**. It is noteworthy that compounds **23**, **24**, and **27** produced significant depression of blood pressure at the 24-hr time period. The latter two compounds possessed lipophilic aralkyl substituents at the 2 position.

D. Compounds 30-35. The series possessed the 3,4,5-trimethoxybenzamido moiety at the 5 position with selected modifications at the 2 position of the heterocyclic ring. It is evident that incorporation of a longer alkyl chain (**30**) did not enhance activity over the CH_3 analog (**13**) and that various aralkyl groupings (**31,32**) were likewise ineffective in producing compounds of greater activity than the methyl derivative **13**, even though high doses were administered. While respectable depressions of blood pressure of 19 and 21% were obtained with **32** and **31**, these activities did not extend beyond the 4-hr period. In view of the above activities, it was decided not to test compounds **33-35**.

E. Compounds 36-38. These compounds were designed to assess the influence of the 2 substituent in the hetero ring. It is apparent from the data in Table III that indeed a 2 substituent is advantageous. While significant depressions of blood pressure were noted with the N-unsubstituted compounds, **37** and **38** (the monomethoxy derivative **36** was devoid of activity), their magnitude was not outstanding compared with some of the other derivatives.

F. Compounds 39-41. These compounds were designed to evaluate the importance of the position in the benzenoid ring of the tetrahydroisoquinoline of the amide substituent. All four positions were evaluated with the substituents maintained as CH_3 at the 2 position and the 3,4,5-trimethoxybenzamido grouping as the mobile grouping. It is apparent that all these compounds, **13** (5 position), **39** (6 position), **40** (7 position), and **41** (8 position), produced significant decreases in blood pressure for periods of 24 hr. It was of interest that this group of compounds possessed the greatest consistent activity within the structural modifications made.

Conclusion

The present studies on variously substituted tetrahydroisoquinolines have demonstrated that this moiety, when substituted at the 2 position with lower alkyl and the 5, 6, 7, or 8 positions with variously methoxylated benzamides, produces compounds with hypotensive activity. Studies with compound **23** in both normotensive and hypertensive rats suggest that this tetrahydroisoquinoline possesses antihypertensive activity comparable to some standard antihypertensive agents. Modifications at the 2 position to incorporate various aralkyl substituents markedly reduced the toxicity of the compounds.

Acknowledgments. The authors express their appreciation to Marion Laboratories, Inc., Kansas City, Mo., for their generous support of this continuing research project.

References

(1) I. W. Mathison, R. C. Gueldner, J. W. Lawson, S. J. Fowler, and E. R. Peters, *J. Med. Chem.*, **11**, 997 (1968).
(2) I. W. Mathison and J. W. Lawson, *Bull. Chim. Therapeutique*, 438 (1968).
(3) I. W. Mathison and R. C. Gueldner, *J. Org. Chem.*, **33**, 2510 (1968).
(4) N. J. Wojciechowski, J. W. Lawson, and I. W. Mathison, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 675 (1971).
(5) F. M. Sturtevant, *Ann. Intern. Med.*, **49**, 1281 (1958).
(6) R. Tabei, S. Spector, W. J. Louis, and A. Sjoerdsma, *Clin. Pharmacol. Ther.*, **11**, 269 (1969).