

Synthesis and Hypotensive Properties of Tetrahydroisoquinolines

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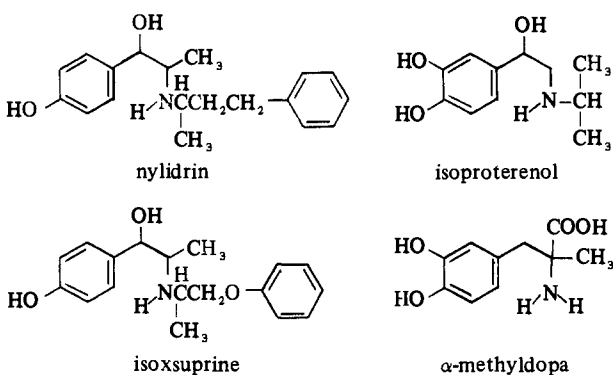
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A series of tetrahydroisoquinolines variously substituted at the 2, 5, 6, 7, and 8 positions of the ring system has been synthesized and evaluated as hypotensive agents in the unanesthetized hypertensive rat and for acute toxicity in the mouse and 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.

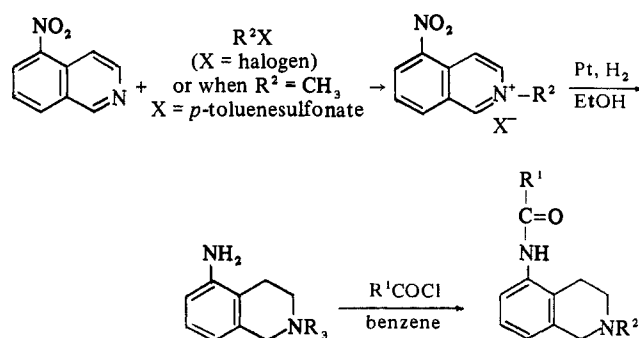
Our previous studies have been concerned with the cardiovascular activity of variously substituted decahydroisoquinolines and attempts to correlate stereochemistry with pharmacological activity.¹ While some partially reduced tetrahydroisoquinolines were synthesized² during the course of this work, little 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 -methyl dopa.

Chart I



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

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.

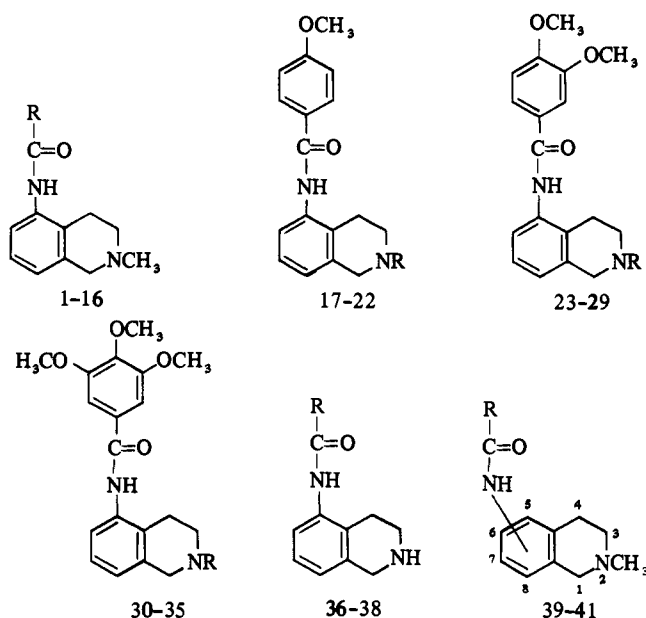
Chemistry. The synthetic pathway, in general, followed the scheme outlined in Scheme I. Synthesis of the alkyl or aralkyl halides introduced at the heterocyclic nitrogen which were not commercially available was carried out according to reported procedures (Chart II). The compounds synthesized, purification solvent, and other physical data are outlined in Table I. Changes were made at both positions R¹ and R² 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 pellet⁵ 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-

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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 ₆ H ₅	152.5–153	C ₁₇ H ₁₉ N ₂ O	C, H, N	Bz	35
2	-C ₆ H ₁₁	158–159.5	C ₁₇ H ₂₃ N ₂ O	C, H, N	EtAc	62
3	-C ₆ H ₄ -2-F	229–230	C ₁₇ H ₁₈ N ₂ OClF	C, H, N, Cl, F	EtOH	13
4	-C ₆ H ₄ -2-Cl	189.5–191.5	C ₁₇ H ₁₇ N ₂ OCl	C, H, N, Cl	EtOH	74
5	-C ₆ H ₄ -2-Br	206.5–208.5	C ₁₇ H ₁₇ N ₂ OBr	C, H, N, Br	EtOH	61
6	-C ₆ H ₄ -2-I	215–216.5	C ₁₇ H ₁₇ N ₂ OI	C, H, N, I	MeOH	91
7	-C ₆ H ₄ -2-NO ₂	196.5–198	C ₁₇ H ₁₇ N ₂ O ₃	C, H, N	EtOH	53
8	-C ₆ H ₄ -4-OCH ₃	169.5–171.5	C ₁₈ H ₂₀ N ₂ O ₂	C, H, N	EtOH	59
9	-C ₆ H ₃ -2,6-(OCH ₃) ₂	191–192	C ₁₉ H ₂₂ N ₂ O ₃	C, H, N	Bz	39
10	-C ₆ H ₃ -3,4-(OCH ₃) ₂	160–161.5	C ₁₉ H ₂₂ N ₂ O ₃	C, H, N	EtOH	46
11	-C ₆ H ₃ -2,6-(CH ₃) ₂	199.5–201	C ₁₉ H ₂₂ N ₂ O	C, H, N	EtOH	17
12	-C ₆ H ₃ -2,6-(C ₂ H ₅) ₂	185.5–187.5	C ₂₁ H ₂₆ N ₂ O	C, H, N	EtOH	30
13	-C ₆ H ₂ -3,4,5-(OCH ₃) ₃	143–143.5	C ₂₀ H ₂₄ N ₂ O ₄	C, H, N	Bz	72
14	-C ₆ H ₂ -2,4,5-(OCH ₃) ₃	159.5–160.5	C ₂₀ H ₂₄ N ₂ O ₄	C, H, N	EtOH	65
15	-CH ₃	137.5–138.1	C ₁₇ H ₁₆ N ₂ O	C, H, N	Bz	56
16	-C ₆ H ₃ -3,4-(OCH ₂ O)	205.5–206.5	C ₁₈ H ₁₈ N ₂ O ₃	C, H, N	EtOH	65
17	-C ₃ H ₇	162.5–163.5	C ₂₀ H ₂₄ N ₂ O ₂	C, H, N	EtOH	70
18	-CH ₂ C ₆ H ₅	176–177	C ₂₄ H ₂₄ N ₂ O ₂	C, H, N	EtOH	76
19	-CH ₂ C ₂ H ₄ -4-OCH ₃	157.5–159.5	C ₂₇ H ₂₆ N ₂ O ₃	C, H, N	EtOH	57
20	-(CH ₂) ₂ C ₆ H ₅	174–175.5	C ₂₅ H ₂₆ N ₂ O ₂	C, H, N	EtOH	62
21	-(CH ₂) ₃ C ₆ H ₅	142–143	C ₂₆ H ₂₈ N ₂ O ₂	C, H, N	EtOH	60
22	-(CH ₂) ₃ C ₆ H ₄ -2-OCH ₃	120–121	C ₂₇ H ₃₀ N ₂ O ₃	C, H, N	EtOH	55
23	-C ₃ H ₇	146.5–147.5	C ₂₁ H ₂₆ N ₂ O ₃	C, H, N	EtOH	70
24	-CH ₂ C ₆ H ₅	138.5–139.5	C ₂₅ H ₂₆ N ₂ O ₃	C, H, N	EtOH	38
25	-CH ₂ C ₂ H ₄ -4-Br	176.5–177.5	C ₂₅ H ₂₆ N ₂ O ₃ Br	C, H, N, Br	EtAc	71
26	-CH ₂ C ₆ H ₄ -4-OCH ₃	142–143.5	C ₂₅ H ₂₈ N ₂ O ₄	C, H, N	EtOH	12
27	-(CH ₂) ₂ C ₆ H ₅	156.5–157.5	C ₂₅ H ₂₈ N ₂ O ₃	C, H, N	EtOH	51
28	-(CH ₂) ₃ C ₆ H ₅	129.5–131.5	C ₂₇ H ₃₀ N ₂ O ₃	C, H, N	EtOH	63
29	-(CH ₂) ₃ C ₆ H ₄ -2-OCH ₃	118–119	C ₂₈ H ₃₂ N ₂ O ₄	C, H, N	EtOH	34
30	-C ₃ H ₇	158.5–159.5	C ₂₇ H ₂₈ N ₂ O ₄	C, H, N	EtOH	15
31	-CH ₂ C ₆ H ₅	156.5–157.5	C ₂₆ H ₂₈ N ₂ O ₄	C, H, N	Ligroin (90–120°)- EtOH	7
32	-CH ₂ C ₂ H ₄ -4-OCH ₃	236–238	C ₂₇ H ₃₁ N ₂ O ₄ Cl	C, H, N, Cl	EtOH	38
33	-(CH ₂) ₂ C ₆ H ₅	155–156	C ₂₇ H ₃₀ N ₂ O ₄	C, H, N	EtOH	18
34	-(CH ₂) ₃ C ₆ H ₅	144–145	C ₂₈ H ₃₂ N ₂ O ₄	C, H, N	EtOH	48
35	-(CH ₂) ₃ C ₂ H ₄ -2-OCH ₃	157.5–159	C ₂₇ H ₃₀ N ₂ O ₅	C, H, N	EtOH	51
36	-C ₆ H ₄ -4-OCH ₃	289–290	C ₁₇ H ₁₉ N ₂ O ₂ Cl	C, H, N, Cl	H ₂ O	43
37	-C ₆ H ₃ -3,4-(OCH ₃) ₂	286–287	C ₁₇ H ₂₁ N ₂ O ₃ Cl	C, H, N, Cl	MeOH	74
38	-C ₆ H ₂ -3,4,5-(OCH ₃) ₃	270–271.5	C ₁₉ H ₂₃ N ₂ O ₄ Cl	C, H, N, Cl	MeOH	86
39	-C ₆ H ₂ -3,4,5-(OCH ₃) ₃ (6 position isomer)	233.5–235	C ₂₀ H ₂₅ N ₂ O ₄ Cl	C, H, N, Cl	H ₂ O	80
40	-C ₆ H ₂ -3,4,5-(OCH ₃) ₃ (7 position isomer)	157.5–158	C ₂₀ H ₂₄ N ₂ O ₄	C, H, N	EtOH	84
41	-C ₆ H ₂ -3,4,5-(OCH ₃) ₃ (8 position isomer)	177–178.3	C ₂₀ H ₂₄ N ₂ O 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. LD₅₀ 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 underlined sequence was used.

General Method. 5-, 6-, 7-, or 8-nitroisquinoline (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 PtO₂ (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-tetrahydroisquinoline 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% Na₂CO₃ solution. The residue (which was very often tacky) was washed several times with dry Et₂O 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 anti-hypertensive screening program. As can be seen from Table II, 14 compounds possessed these high LD₅₀ 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 Various Substituted Tetrahydroisquinolines 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 (9)	125–250 ^e (125–250 ^c)	15	20	31–62 ^e	29	8	>1000 ^c
2	15	188–250 ^e	16	20	125–250 ^e	30	9 (4)	125–250 ^e (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 (9)	62–125 ^e (32–62 ^e)	22	11	>1000 ^c	36	14	500–1000 ^c
9	9	250–500 ^e	23	80 (27)	500–631 ^c (500–1000 ^c)	37	13	500–1000 ^d
10	19 (7)	125–250 ^e (100–200 ^e)	24	9	>1000 ^c	38	8	250–500 ^d
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 (9)	125–250 ^e (100–200 ^c)	27	9	500–1000 ^c	41	9	250–500 ^e
14	16	68–125 ^e	28	12	>1000 ^c			

^aNumbers in parentheses refer to toxicity values obtained in the rat. ^bNumber of animals dosed. ^cSuspension in 1% tragacanth. ^dSolution in distilled water. ^eSolubilized 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 \pm S.E.			
				1 hr	2 hr	4 hr	24 hr
1	50	6	206 \pm 12	-5.2 \pm 2.3 ^c	-7.6 \pm 2.4 ^c	-8.9 \pm 2.6 ^c	-5.9 \pm 1.1 ^c
2	50	6	178 \pm 7	-2.3 \pm 1.6	-2.3 \pm 1.6	-5.4 \pm 1.0 ^c	-11.5 \pm 2.2 ^c
3	50	6	199 \pm 9	-6.5 \pm 2.6	-5.3 \pm 2.2	-5.2 \pm 2.1	-9.1 \pm 1.9 ^c
4	50	6	190 \pm 4	-1.7 \pm 1.6	-4.2 \pm 2.4	-0.8 \pm 1.7	+0.9 \pm 2.5
5	50	6	224 \pm 8	-4.0 \pm 2.3	-4.2 \pm 3.5	-8.6 \pm 1.7 ^c	-9.2 \pm 1.4 ^c
6	50	6	175 \pm 3	-6.8 \pm 2.1 ^c	-9.9 \pm 2.1 ^c	-5.7 \pm 1.9 ^c	-0.7 \pm 2.9
7	50	6	198 \pm 7	-6.1 \pm 1.7	-4.1 \pm 3.0	-3.3 \pm 4.0	-1.0 \pm 3.0
8	50	12	197 \pm 4	-6.6 \pm 1.5 ^c	-9.4 \pm 2.5 ^c	-7.1 \pm 1.8 ^c	-4.9 \pm 1.8 ^c
9	50	6	225 \pm 4	-1.0 \pm 3.4	-3.0 \pm 2.3	-7.9 \pm 4.1	-6.2 \pm 4.3
10	50	6	195 \pm 4	-16.3 \pm 2.4 ^c	-15.8 \pm 2.6 ^c	-16.7 \pm 2.1 ^c	-10.2 \pm 2.2 ^c
11	50	6	181 \pm 8	-6.1 \pm 1.7 ^c	-2.4 \pm 0.6	-5.2 \pm 1.8 ^c	+2.0 \pm 2.1
12	50	6	192 \pm 3	-5.7 \pm 3.0	-7.5 \pm 4.6	-6.1 \pm 2.8	+2.1 \pm 2.3
13	50	11	198 \pm 10	-11.1 \pm 2.0 ^c	-19.0 \pm 3.0 ^c	-10.6 \pm 3.5 ^c	-4.6 \pm 1.6 ^c
14	50	6	223 \pm 10	-6.5 \pm 1.7 ^c	-8.2 \pm 1.9 ^c	-6.2 \pm 1.7 ^c	-2.4 \pm 2.4
15	50	6	206 \pm 9	+2.8 \pm 2.5	+2.2 \pm 3.1	-0.6 \pm 1.5	+1.4 \pm 1.9
16	50	6	194 \pm 8	-3.8 \pm 1.8	-6.1 \pm 4.3	-4.6 \pm 2.7	-4.8 \pm 2.6
17	50	12	210 \pm 10	-11.3 \pm 1.9 ^c	-17.8 \pm 1.4 ^c	-10.2 \pm 2.8 ^c	-6.2 \pm 2.0 ^c
18	50	6	182 \pm 8	-8.8 \pm 1.3 ^c	-8.7 \pm 2.8 ^c	-3.7 \pm 1.4	-7.4 \pm 2.6 ^c
18	200	6	186 \pm 10	-20.8 \pm 4.4 ^c	-21.0 \pm 3.0 ^c	-13.7 \pm 4.9 ^c	-11.1 \pm 4.0 ^c
19	100	6	189 \pm 8	-8.6 \pm 1.5 ^c	-10.4 \pm 2.0 ^c	-4.2 \pm 4.5	-1.9 \pm 1.8
23	50	12	226 \pm 7	-15.1 \pm 3.2 ^c	-19.6 \pm 4.6 ^c	-17.9 \pm 3.7 ^c	-9.3 \pm 1.5 ^c
23	50	11 ^b	141 \pm 2	+1.6 \pm 2.0	+1.9 \pm 2.4	-1.7 \pm 1.5	-2.4 \pm 1.3
24	200	6	206 \pm 5	-15.6 \pm 1.9 ^c	-17.4 \pm 2.1 ^c	-14.7 \pm 2.9 ^c	-11.6 \pm 1.9 ^c
25	100	6	213 \pm 6	-9.9 \pm 3.2 ^c	-13.9 \pm 2.0 ^c	-8.5 \pm 3.4 ^c	-2.3 \pm 1.4
26	100	6	226 \pm 4	-10.1 \pm 1.7 ^c	-12.8 \pm 2.1 ^c	-11.3 \pm 1.9 ^c	-0.8 \pm 1.9
27	200	6	177 \pm 8	-19.4 \pm 2.2 ^c	-17.3 \pm 1.9 ^c	-11.2 \pm 2.9 ^c	-12.3 \pm 1.8 ^c
30	50	6	204 \pm 12	-14.0 \pm 2.1 ^c	-11.8 \pm 2.3 ^c	-7.1 \pm 2.9 ^c	-4.5 \pm 0.6 ^c
31	200	6	217 \pm 13	-20.6 \pm 2.5 ^c	-16.4 \pm 1.4 ^c	-7.0 \pm 1.6 ^c	-4.9 \pm 2.1
32	100	6	218 \pm 6	-19.0 \pm 2.2 ^c	-18.7 \pm 1.8 ^c	-11.3 \pm 0.9 ^c	-1.6 \pm 2.6
36	50	6	221 \pm 10	-8.8 \pm 4.8	-6.5 \pm 3.7	-8.3 \pm 2.4	-6.4 \pm 1.3
37	50	6	221 \pm 11	-13.8 \pm 2.9 ^c	-11.1 \pm 3.4 ^c	-8.4 \pm 1.8 ^c	-1.7 \pm 2.3
38	50	6	210 \pm 17	-12.4 \pm 3.9 ^c	-12.6 \pm 3.6 ^c	-4.7 \pm 1.4	-8.3 \pm 1.2 ^c
39	50	6	188 \pm 7	-21.6 \pm 1.7 ^c	-19.4 \pm 4.0 ^c	-11.9 \pm 3.4 ^c	-3.8 \pm 1.3 ^c
40	50	6	213 \pm 11	-25.5 \pm 2.5 ^c	-19.9 \pm 2.5 ^c	-14.8 \pm 2.3 ^c	-5.8 \pm 1.7 ^c
41	50	6	212 \pm 10	-25.5 \pm 4.9 ^c	-20.4 \pm 3.4 ^c	-12.7 \pm 1.0 ^c	-9.4 \pm 2.9 ^c
α -MeDopa	50	6	205 \pm 9	-15.2 \pm 1.7 ^c	-24.4 \pm 1.9 ^c	-23.1 \pm 2.3 ^c	-8.1 \pm 2.6 ^c
Guanethidine	10	6	197 \pm 11	-8.8 \pm 3.9	-23.2 \pm 4.0 ^c	-22.2 \pm 2.6 ^c	-13.4 \pm 3.0 ^c
0.9% NaCl	0.1 ml/ 0.1 kg	12	183 \pm 8	+2.7 \pm 2.0	+2.3 \pm 1.5	-1.4 \pm 1.7	-0.3 \pm 1.7

^aMean systolic blood pressure (mm) \pm S.E. ^bNormotensive 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 -methyl dopa 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 -methyl dopa, pargyline, ecdolid, 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 $-\text{CH}_3$ 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 led 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 non-toxic agents, *i.e.*, those having LD_{50} values >1000 mg/kg. In this series it is apparent that a substituent at 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 com-

pound 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.

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