soluble, but high molecular weight, aryldihydro-*s*-triazines synthesized by Baker and Ashton (12).

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Synthesis, Toxicity, and Cardiovascular Properties of *N*-Aralkyl- and *N*-Acyl-5-aminoethylindans

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Abstract □ Secondary amines and amides of 5-aminoethyl-6-methoxyindan and 5-aminoethyl-6-methylindan were synthesized, and the blood pressure lowering effects and accompanying changes in heart rate were evaluated in the unanesthetized desoxycorticosterone acetate hypertensive rat. The acute toxicities of the compounds were determined in mice. The amines were significantly more potent than the amides as antihypertensive agents and also were more toxic. 5-(3,4-Dimethoxybenzyl)aminoethyl-6-methylindan produced the greatest depression in systolic blood pressure at the dose level studied. Structure–activity relationships relevant to blood pressure lowering, heart rate, and toxicity are discussed.

Keyphrases □ Indans, various substituted—synthesized, cardiovascular properties and toxicity evaluated, rats □ Cardiovascular properties—various substituted indans evaluated □ Toxicity—various substituted indans evaluated □ Structure–activity relationships—various substituted indans evaluated for toxicity and cardiovascular properties

The recent synthesis of cyclopentanoisoquinolines (1, 2) is a continuation of interest in the cardiovascular activity of substituted and reduced isoquinolines (3–6). During the synthesis of the novel cyclopentano[*h*]- and [*f*]-1,2,3,4-tetrahydroisoquinolines (1, 2), some previously unreported substituted aminoethylindans (1) were produced as intermediates to the desired products.

In an attempt to search exhaustively for antihypertensive agents, these intermediates were screened in the desoxycorticosterone acetate hypertensive rat for their blood pressure lowering effects. The hypotensive properties noted with the few intermediates in this screening test prompted preparation of derivatives of the aminoethylindan nucleus in the hope that blood pressure lowering activity might be enhanced and some structure–activity relationships could be developed. This approach was further encouraged by the report of Troxler and Hofmann (7) that certain *N*-substituted aminoethylindans possessed significant hypotensive activity.

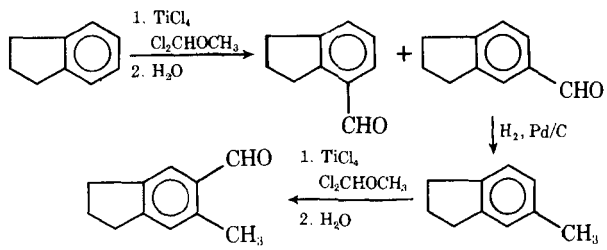
The synthesis of eight compounds is reported here, together with the mouse approximate LD_{50} (ALD_{50}) and the effects of the compounds on systolic blood pressure and heart rate in the hypertensive rat.

EXPERIMENTAL

Chemistry—The synthesis of the precursor molecules (5-aminoethyl-6-methoxyindan and 5-aminoethyl-6-methylindan) for the current series was reported previously in connection with the synthesis of the cyclopentano-1,2,3,4-tetrahydroisoquinolines (1, 2). The amide derivatives were synthesized from the precursor aminoethylindans by the classic acylation with the appropriate acyl chloride in the presence of a base. Compound VIII was prepared from the aminoethylindan by condensation with 3,4-dimethoxybenzaldehyde, followed by catalytic hydrogenation of the resulting Schiff base. The synthetic pathway for the preparation of the compounds is shown in Schemes I–III.

Physical properties and analytical data of the synthesized compounds are shown in Table I. All melting points were determined on a melting-point apparatus[1] and are uncorrected. IR spectra were determined[2] in potassium bromide and were characteristic of the compounds reported. Elemental analyses[3] were within ±0.4% of the theoretical values.

Biological Methods—Acute toxicity determinations were performed in female Swiss-Webster mice, 15–24 g. Compounds were administered



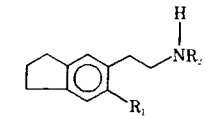
Scheme I

[1] Swissco.

[2] Beckman IR 33.

[3] Galbraith Laboratories, Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz.

Table I—Physical Data of *N*-Substituted Aminoethylindans



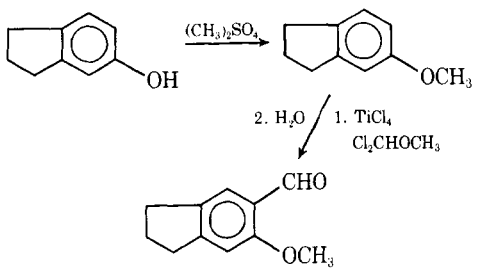
Compound	R_1	R_2	Formula	Melting Point	Yield, %	Basic Catalyst	Recrystallization Solvent	Analysis, %	Calc.	Found
I	CH_3O	C_6H_5CO	$C_{19}H_{21}NO_2$	104-106°	23	Sodium carbonate	Ether	C	77.26	77.42
								H	7.17	7.26
								N	4.74	4.70
II	CH_3O	$3,4,5\text{-}(CH_3O)_3C_6H_2CO$	$C_{22}H_{27}NO_5$	144-145°	27	Sodium carbonate	Ethyl acetate	C	68.55	68.71
								H	7.06	6.93
								N	3.63	3.61
III	CH_3O	$C_6H_5CH_2CO$	$C_{20}H_{23}NO_2$	135°	54	Potassium bicarbonate	Ether	C	77.63	77.48
								H	7.51	7.55
								N	4.52	4.49
IV	CH_3O	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CO$	$C_{22}H_{27}NO_4$	115°	42	Potassium bicarbonate	Ethanol	C	71.51	71.52
								H	7.38	7.45
								N	3.79	3.78
V	CH_3	H·HCl	$C_{12}H_{18}ClN$	229-231°	89	—	Cold dilute hydrochloric acid	C	68.07	68.15
								H	8.56	8.48
								Cl	16.74	16.61
								N	6.62	6.02
VI	CH_3	$C_6H_5CH_2CO$	$C_{20}H_{23}NO$	125.5-127°	42	Triethylamine	Benzene	C	81.87	81.68
								H	7.90	8.07
								N	4.77	5.08
VII	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CO$	$C_{22}H_{27}NO_3$	144-145°	48	Triethylamine	Benzene	C	74.75	74.53
								H	7.69	7.46
								N	3.69	3.90
VIII	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3CH_2\cdot HCl$	$C_{21}H_{28}ClNO_2$	223-224°	60	—	Acetonitrile-ethanol	C	69.69	69.63
								H	7.79	7.96
								Cl	9.97	9.75
								N	3.87	3.87

Table II—Acute Toxicity in Mice and Cardiovascular Activity in Desoxycorticosterone Hypertensive Rats of *N*-Substituted Aminoethylindans

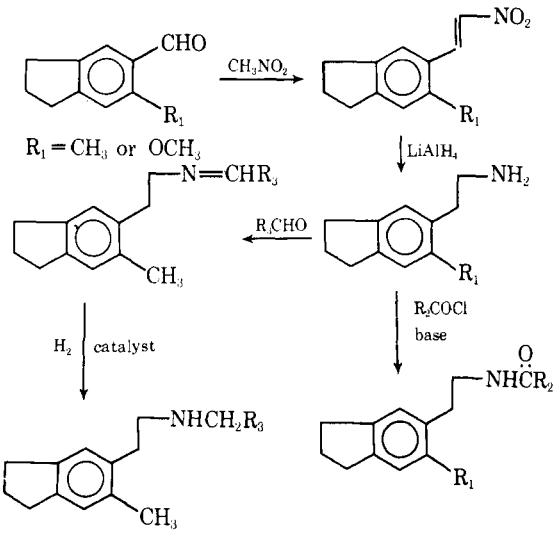
Compound	*n* (Mice)	Mouse ALD_{50}, mg/kg ip	Cardiovascular Activity: Dose, mg/kg ip	*n* (Rats)	Controls[a]	Mean Change in Pressure and Heart Rate from Control ± *SE*[b]: 1 hr	2 hr	4 hr	24 hr
I	10	>1000[c]	100[c]	6	200 ± 8 (393 ± 23)	−18 ± 8[d] (−20 ± 23)	−24 ± 7[d] (+9 ± 30)	−12 ± 6 (−14 ± 18)	−13 ± 4[d] (−67 ± 22[d])
II	10	>1000[c]	100[c]	6	210 ± 14 (353 ± 12)	−27 ± 8[d] (+23 ± 28)	−35 ± 13[d] (+10 ± 28)	−12 ± 8 (+47 ± 29)	−16 ± 4 (−4 ± 10)
III	12	1000–1500[c]	100[c]	6	206 ± 11 (382 ± 19)	−32 ± 7[d] (+13 ± 12)	−24 ± 5[d] (+54 ± 25)	−21 ± 4[d] (+19 ± 21)	−13 ± 4[d] (+61 ± 12[d])
IV	15	500–1000[c]	100[c]	6	202 ± 8 (389 ± 29)	−10 ± 4[d] (+23 ± 29)	−10 ± 2[d] (+57 ± 31)	−19 ± 3[d] (+14 ± 12)	−19 ± 4[d] (−27 ± 24)
V	43	79–89[e]	10[e]	6	181 ± 6 (299 ± 13)	−24 ± 8[d] (+32 ± 17)	−24 ± 4[d] (+34 ± 14)	−15 ± 5[d] (+25 ± 11)	−6 ± 4 (−4 ± 11)
			25[e]	6	185 ± 6 (349 ± 22)	—[f]	—[f]	−18 ± 4[d] (+20 ± 21)	−11 ± 2[d] (−26 ± 14)
VI	6	>1000[c]	100[c]	5	179 ± 10 (325 ± 7)	−7 ± 7 (+17 ± 17)	−2 ± 6 (+24 ± 11)	−1 ± 7 (+23 ± 13)	−3 ± 10 (+2 ± 17)
VII	6	>1000[c]	100[c]	6	195 ± 8 (354 ± 19)	−2 ± 6 (+43 ± 10[d])	−4 ± 9 (+47 ± 12[d])	+2 ± 5 (+37 ± 15[d])	−3 ± 7 (+22 ± 12)
VIII	20	140–178[c]	100[c]	6	186 ± 6 (366 ± 16)	−58 ± 4[d] (−55 ± 17[d])	−60 ± 7[d] (0 ± 14)	−47 ± 2[d] (+4 ± 8)	−17 ± 2[d] (−14 ± 10)
0.9% NaCl	—	—	1 ml/kg	12	183 ± 8 (351 ± 14)	+5 ± 4 (+18 ± 12)	+4 ± 3 (+25 ± 14)	−2 ± 3 (+6 ± 6)	0 ± 3 (0 ± 14)
Methyldopa	—	—	50[c]	6	205 ± 9 (378 ± 22)	−31 ± 4[d] (+106 ± 26[d])	−50 ± 4[d] (+104 ± 28[d])	−48 ± 6[d] (+31 ± 39)	−16 ± 5[d] (−19 ± 12)
Guanethidine	—	—	10[e]	5	197 ± 11 (427 ± 27)	−25 ± 8[d] (−67 ± 28[d])	−46 ± 9[d] (−101 ± 24[d])	−44 ± 6[d] (−95 ± 22[d])	−27 ± 6[d] (−81 ± 26[d])

[a] Mean systolic blood pressure (mm Hg) ± *SE*. Numbers in parentheses represent mean heart rate (beats per minute) ± *SE*. [b] Mean difference in systolic blood pressure from control (mm Hg) ± *SE*. Numbers in parentheses represent mean difference in heart rate from control (beats per minute) ± *SE*. [c] Administered as a suspension in 1% tragacanth. [d] Significant change from control, $p < 0.05$, by Newman–Keuls *a posteriori* test. [e] Administered as a solution in distilled water. [f] No readings possible at this time period, no perceptible pulse; respiration and movement artifacts.

in aqueous solutions or as suspensions in 1% tragacanth by the intraperitoneal route to groups of three or more mice. The LD_{50} values were estimated from the results obtained by administering two or more dose levels of each compound, usually spaced 0.3 logarithmic interval or less, to these groups of mice. Animals were observed for up to 72 hr following injection, but the toxicity values reported in Table II represent the outcome 24 hr after administration.



Scheme II



Scheme III

The indirect measurements of blood pressure and heart rate were determined in male Charles River rats made hypertensive (systolic blood pressure >150 mm Hg) by subcutaneously implanting a wax-formulated pellet containing 10 mg of desoxycorticosterone acetate as previously described (8, 9). Systolic blood pressure was measured in the caudal arteries of prewarmed (40°), unanesthetized, restrained animals by a pneumatic pulse transducer placed distal to an automated tail pressure cuff and was recorded on a physiograph[4]. Heart rate was determined from the amplified pulse waves recorded during the blood pressure measurements. Prior to the actual experiments, animals were accustomed to the measurement handling procedure several times during the preceding weeks.

Control systolic blood pressure and heart rates were determined in a group of usually six hypertensive rats on each day. A compound for evaluation was administered by intraperitoneal injection either in solution or as a suspension at 24-hr intervals following injection. Mean values of the group for these parameters at a particular measurement period were calculated, and then the mean difference from control, along with its associated standard error, was calculated for each period. The statistical significance of the changes produced by a compound was tested by an analysis of variance and the Newman–Keuls *a posteriori* test (10) when *F* was significant. A probability level of 0.05 or less was accepted as a significant change (Table II).

All compounds synthesized in this series, except V, were tested at a dosage level of 100 mg/kg. Compound V was relatively more toxic in the mouse, and it was evaluated at two lower dosage levels, 10 and 25 mg/kg. Methyldopa and guanethidine sulfate, two known antihypertensive agents, were included as reference standards. Another group of hypertensive rats was injected with 0.9% NaCl in a dose of 1 ml/kg. The latter group was included as a placebo group for the entire study.

RESULTS AND DISCUSSION

The pharmacological data in Table II show that, with two exceptions (VI and VII), the compounds synthesized significantly lowered systolic blood pressure in the unanesthetized desoxycorticosterone hypertensive rat. The duration of action and time of suggested maximum effect varied somewhat. The greatest hypotensive response generally occurred within 1–2 hr following administration. In some instances (*e.g.*, I and II), this suggested peak response time also was the only time during which the blood pressure was significantly lower than the control value, but other

[4] Narco Bio-Systems Inc., Houston, Tex.

compounds (*e.g.*, III–V and VIII) produced significant lowering of blood pressure which persisted throughout the 24-hr measurement period.

Hypertensive rats receiving a placebo injection of 0.9% NaCl showed no significant changes in systolic blood pressure or heart rate at any time. Methyldopa and guanethidine sulfate, as expected, produced significant depressions in mean systolic blood pressure from control levels.

Group 1—Examination of the amides I–IV, VI, and VII from a structure–activity viewpoint revealed some interesting features. Amides possessing a methoxy group in the 6-position on the indan nucleus (I–IV) clearly exhibited significant antihypertensive activity for varying periods following drug administration. The amides substituted at the 6-position with a methyl group (VI and VII), however, were devoid of hypotensive properties at the dose level studied (100 mg/kg).

This trend is best seen by comparing IV and VII, in which the only difference in structure is the 6-substituent. The methoxy compound (IV) possessed significant blood pressure lowering activity throughout 24 hr, whereas its methyl analog (VII) was inactive as an antihypertensive agent. Significant acceleration in heart rate was noted with VII, and this acceleration may have obviated any significant blood pressure depression. In general, however, significant acceleration of heart rate was not observed and did not appear to be a factor among the other members of this group.

In this group of compounds, III and IV demonstrated the longest duration of action, producing significant depressions in blood pressure over 24 hr. However, differences in the magnitude of the antihypertensive response between III and IV were observed during the 1st and 2nd hr, with III being the most potent during this time. Additionally, the peak hypotensive response of III appeared to be reached at the 1- and 2-hr readings while that of IV was reached during the 4–24-hr observation period.

The decrease in lipid solubility of IV, as a result of the addition of the methoxy groups to the phenylacetamide moiety of III, may explain the differences in the time of onset of the blood pressure lowering effects between these two compounds. The correlation of optimal blood pressure lowering activity with greater lipophilicity was noted previously in studies on antihypertensive decahydroisoquinolines (9). The reflex increase in heart rate that one might anticipate as a result of the hypotensive response was not observed with these compounds; indeed, at the 24-hr time period, significant depression in heart rate was noted with III.

The insertion of a methylene group between the phenyl moiety and the amide group (I and III and II and IV) did not appear to influence the antihypertensive activity.

With the exception of IV, where the LD_{50} was estimated to lie in the 500–1000-mg/kg range, the toxicity results showed that the approximate LD_{50} values were not markedly different from one another and that the compounds were relatively nontoxic.

Group 2—This group comprises amines V and VIII. Antihypertensive activity was noted with both compounds; indeed, VIII produced the greatest depression in blood pressure of the entire series. These two amines were significantly more toxic than their amide counterparts, which neccessitated, in the case of V, the use of much smaller doses for antihypertensive evaluation. Compound VIII, however, was studied at the same dosage level as the Group 1 amides.

The primary amine, V, produced significant depressions in systolic pressure through 4 hr at the low dose of 10 mg/kg. No measurements were possible at the 1- and 2-hr time periods with a high dosage of V (25 mg/kg) due to the inability to detect a tail pulse as well as a greater incidence of movement artifacts in the physiograph recordings with this group of rats. Significant depression of blood pressure, however, was observed at the 4- and 24-hr periods, but data obtained at these points in time showed that there was no difference in the magnitude of the blood pressure response between the two dose levels of V. The blood pressure data show that V appears to be five to seven times more potent than amides I–IV as an antihypertensive agent.

Compound VIII produced substantial depression of blood pressure over 24 hr, which was accompanied at the 1-hr reading by a significant heart rate decrease. The heart rate depression is apparently independent of the blood pressure lowering ability of VIII. This effect is suggested by the fact that, at the 2- and 4-hr measurements, heart rate was not depressed whereas the mean changes in systolic blood pressure were still significantly less than control values and approximately of the same magnitude as the changes observed at the 1-hr period. Like V, the antihypertensive activity of VIII was significantly greater than amides I–IV.

It is evident from the toxicity data that the presence of the aralkyl group in VIII (a secondary amine) decreases the toxicity relative to V (a primary amine). Compound VIII possessed an approximate LD_{50} in the 140–178-mg/kg range, while V was markedly more toxic with a value in the 79–89-mg/kg range.

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