These observations indicate that the major portion of the resistance segments were retained after the dissection process.

Responsiveness to intraarterially injected catecholamines was in the same general range as reported for similar preparations (2, 6). The potency ratio between epinephrine and levarterenol of 2.75 (1.95–4.75) agrees closely with that reported by Rogers *et al.* (2) of 2.61 (1.56–3.66).

This isolated artery preparation can provide a useful method of testing vasoconstrictor responses to catecholamines. The arteries may be perfused while hanging in air or submerged in bath fluid in recirculating or nonrecirculating systems. They also may be stored at least overnight in refrigerated Krebs solution without loss of responsiveness to levarterenol, epinephrine, or potassium ion (7). Therefore, it seems to provide one simple alternative to vascular strips or conduit vessels in studies of vascular smooth muscle.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 11, 1974, from the *Department of Pharmacology, University of Texas Medical School at Houston, Texas Medical Center, Houston, TX 77025*

Accepted for publication August 9, 1974.

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N-Substituted Indanamines as Potential Hypoglycemic Agents

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Abstract □ A number of indanamines substituted at the terminal amino nitrogen with various aliphatic, alicyclic, heterocyclic, and aromatic ring systems were synthesized and screened for hypoglycemic activity. None was found to possess significant activity compared to tolbutamide.

Keyphrases □ Indanamines, *N*-substituted—synthesized and screened as hypoglycemic agents □ Hypoglycemic agents, potential—synthesis and screening of *N*-substituted indanamines

Hypoglycemic activity was reported among different types of indanamines (1–4). It was also observed that *n*-butylpyrrolidine alone possesses appreciable hypoglycemic activity but was extremely toxic (1). Furthermore, it is well known that among the sulfonylureas, various alicyclic, heterocyclic, and aromatic ring substitutions at the terminal urea nitrogen atom had a beneficial effect (5–8).

Therefore, attempts were made to incorporate various such ring systems at the terminal amino nitrogen atom of the indanamine ring moiety and to observe the effect on hypoglycemic activity. All of these compounds were prepared by following a reported procedure (1–4). Unlike the previous work, both the amides and the corresponding amine hydrochloride salts were used for the pharmacological evaluation of hypoglycemic activity.

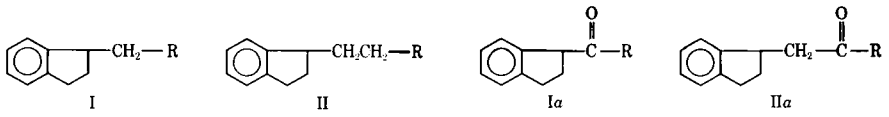
EXPERIMENTAL[1]

Indan-*N*-substituted Carboxamides (Ia and IIa)—These compounds were prepared from indan-1-carboxylic acid (9, 10) (1 mole) and indan-1-acetic acid (11) (1 mole) *via* the acid chloride intermediate (3) by reaction with the corresponding primary or secondary bases (1.5 moles) in the presence of 10% NaOH solution. The amides were either extracted with a suitable solvent or obtained as a crystalline solid, which was subsequently purified by crystallization from suitable solvents. The physical properties, analyses, and hypoglycemic activity of all amides synthesized are given in Table I.

***N*-Substituted Indanamines (I and II)**—The amides (1 mole) so prepared were reduced by lithium aluminum hydride reduction (1.5 moles) in absolute ether. The excess lithium aluminum hydride was decomposed with calculated amounts of 3% NaOH solution and filtered. The filtrate was extracted with cold 2 *N* HCl until it was free from amine. The aqueous layer was basified and extracted with ether, washed, dried, and distilled under reduced pressure.

The amines were characterized as their hydrochloride salts, and these hydrochloride salts were used for hypoglycemic screening. The analyses, physical properties, and hypoglycemic activity of the amines are given in Table I.

[1] All melting points were determined in a Gallenkamp apparatus and are corrected. Boiling points are uncorrected.



I II Ia IIa

Table I—Physical Data and Hypoglycemic Activity for the *N*-Substituted Indanamines

Compound		R	Boiling Point/mm	Formula	Analysis, % Calc.	Analysis, % Found	n_D^{30}	Melting Point	Average Percent Fall of Blood Sugar: In Normal Intact Rabbits	Average Percent Fall of Blood Sugar: In Alloxan Diabetic Rabbits
1.	Ia	Morpholino	165–170°/0.6–0.65	$C_{14}H_{17}NO_2$	C 72.7 H 7.4 N 6.1	7.25 7.3 5.8	—	92–94°[a]	11.15 ± 2.31	—
2.	Ia	Piperidino	165–168°/2–3	$C_{15}H_{19}NO$	C 78.6 H 8.3 N 6.1	78.4 8.0 6.3	1.5639	—	7.47 ± 1.12	—
3.	Ia	Pyrrolidino	170–176°/0.8–1.0	$C_{14}H_{17}NO$	C 78.1 H 7.9 N 6.5	77.8 7.7 6.4	1.5640	—	17.41 ± 2.40	22.4 ± 4.55
4.	Ia	Cyclohexyl	Solid	$C_{16}H_{21}NO$	C 79.0 H 8.6 N 5.8	79.3 8.3 5.6	—	158.5–161°[a]	14.40 ± 2.32	—
5.	Ia	Benzyl	Solid	$C_{17}H_{17}NO$	C 81.3 H 6.8 N 5.6	81.0 6.7 5.4	—	118.5–120.5°[a]	6.34 ± 1.12	—
6.	Ia	*n*-Hexyl	178–182°/0.65–0.7	$C_{16}H_{23}NO$	C 78.4 H 9.4 N 5.7	78.2 9.1 5.5	—	36–38°[a]	8.80 ± 2.55	—
7.	IIa	Morpholino	160–165°/0.6–0.7	$C_{15}H_{19}NO_2$	C 73.4 H 7.7 N 5.7	73.1 7.5 5.9	—	67–69°[a]	14.26 ± 2.78	—
8.	IIa	Piperidino	175–180°/0.6–0.7	$C_{16}H_{21}NO$	C 79.0 H 8.6 N 5.7	79.2 8.3 5.6	1.5525	—	5.74 ± 1.37	—
9.	IIa	Pyrrolidino	165–168°/0.3–0.35	$C_{15}H_{19}NO$	C 78.6 H 8.3 N 6.1	78.8 8.2 6.3	1.5532	—	4.62 ± 1.24	—
10.	IIa	Cyclohexyl	Solid	$C_{17}H_{23}NO$	C 79.4 H 8.9 N 5.4	79.1 8.6 5.2	—	126–128°[a]	7.95 ± 1.58	—
11.	IIa	Benzyl	Solid	$C_{18}H_{19}NO$	C 81.5 H 7.2 N 5.3	81.1 7.4 5.2	—	85–88°[a]	5.99 ± 1.04	—
12.	IIa	*n*-Hexyl	145–150°/0.45–0.5	$C_{17}H_{25}NO$	C 78.7 H 9.7 N 5.4	78.5 9.6 5.7	1.5341		6.95 ± 1.07	—
13.	I	Morpholino	114–116°/1–2	$C_{14}H_{19}NO$	C 77.4 H 8.8 N 6.5	77.1 8.5 6.2	1.5389	224.5–226.5°[bc]	14.51 ± 3.5	—
14.	I	Piperidino	115–120°/2–3	$C_{15}H_{21}N$	C 83.7 H 9.8 N 6.5	83.5 9.5 6.4	1.5343	220.5–222.5°[bc]	10.76 ± 1.02	–
15.	I	Pyrrolidino	110–115°/0.6–0.7	$C_{14}H_{19}N$	C 83.6 H 9.5 N 7.0	83.3 9.4 6.8	1.5383	217.5–218.5°[bc]	16.62 ± 3.01	21.15 ± 4.21
16.	I	Cyclohexyl	135–137°/0.3–0.35	$C_{16}H_{23}N$	C 83.9 H 10.0 N 6.1	84.2 10.2 5.8	1.5358	214–215°[bc]	5.39 ± 1.73	–

(*continued*)

Table I—*(Continued)*

17.	I	Benzyl	130–135°/0.8–0.9	$C_{17}H_{19}N$	C	86.1	86.4	1.5667	179–181°[b,c]	7.18 ± 2.30	—
					H	8.0	7.9				
					N	5.9	5.5				
18.	I	*n*-Hexyl	122–132°/0.5–0.6	$C_{16}H_{25}N$	C	83.1	82.8	1.5089	224–227°[b,c]	17.70 ± 4.18	20.32 ± 4.50
					H	10.8	10.5				
					N	6.1	6.3				
19.	II	Morpholino	126–130°/0.6–0.7	$C_{15}H_{21}NO$	C	77.9	77.5	1.5301	199–203°[b,c]	18.36 ± 3.85	22.35 ± 4.22
					H	9.1	9.2				
					N	6.1	5.7				
20.	II	Piperidino	130–135°/0.5–0.6	$C_{16}H_{23}N$	C	83.9	83.8	1.5310	214–216°[b,c]	12.20 ± 1.71	—
					H	10.0	9.9				
					N	6.1	6.4				
21.	II	Pyrrolidino	110–115°/0.9–1.0	$C_{15}H_{21}N$	C	83.7	83.9	1.5335	180–182°[b,c]	11.17 ± 2.64	—
					H	9.8	9.6				
					N	6.5	6.1				
22.	II	Cyclohexyl	115–120°/0.2–0.25	$C_{17}H_{25}N$	C	84.0	83.6	1.5317	178–180°[b,d]	6.11 ± 1.53	—
					H	10.3	10.4				
					N	5.8	5.5				
23.	II	Benzyl	130–135°/0.3–0.35	$C_{13}H_{21}N$	C	86.1	86.2	1.5638	235–237°[b,c]	13.46 ± 1.96	—
					H	8.4	8.1				
					N	5.6	5.1				
24.	II	*n*-Hexyl	118–120°/0.8–0.85	$C_{17}H_{27}N$	C	83.3	83.1	1.5117	202–204°[b,c]	10.98 ± 1.65	—
					H	11.0	11.3				
					N	5.7	5.6				

[a] Alcohol + water. [b] Melting point of amine hydrochloride. [c] Ethyl acetate + absolute alcohol. [d] Ethyl acetate.

Pharmacology—Eight normal healthy male rabbits, 1.5–2.0 kg, were used for hypoglycemic screening. The animals were fasted for 18 hr; after the fasting venus blood was taken, the compounds were given at a dose of 100 mg/kg either in aqueous solution or as a 0.5% carboxymethylcellulose suspension through a stomach tube.

Blood glucose concentration was followed after dosing at 3-hr intervals up to 24 hr. The blood glucose estimation was carried out by the method of Hagedorn and Jensen (12). The peak fall of blood glucose concentration was observed between the 9th and 12th hr.

DISCUSSION AND CONCLUSION

The authors previously reported hypoglycemic activity among indanamines (1–4) and since then have searched for a more potent compound in this series by incorporating various substituents at the terminal amino nitrogen of the indanamine ring moiety. Among the compounds shown in Table I, Compounds 3, 15, 18, and 19 possessed appreciable activity in normal intact rabbits. These compounds were further screened on alloxan-induced (13) diabetic rabbits (Table I).

From the results of screening, it is evident that any substitution at the amino nitrogen is not beneficial for activity. Heterocyclic ring substitution is slightly better than alicyclic and aromatic ring substitution, but the activity is not of the order of tolbutamide to warrant further investigation in the hypoglycemic field. Effect of pyrrolidine ring substitution is not as spectacular as in the case of *n*-butylpyrrolidine itself. The activity pattern and duration of activity of all these compounds are very similar. They all showed peak hypoglycemic activity between 9 and 12 hr, indicating that they probably first undergo some biotransformation to an active metabolite whose elimination pattern is also very similar.

Some compounds were screened for *in vitro* epinephrine biosynthesis inhibitory activity and antianginal and antiviral activity, but none was found to possess significant activity in any of these areas except Compound 18. Compound 18 was reported to possess some bradycardic activity and marked attenuation of peak after isoproterenol administration and hence was designated as a β-blocker.

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ACKNOWLEDGMENTS AND ADDRESSES

Received October 19, 1973, from the *Department of Pharmacy, Jadavpur University, Calcutta-32, India.*

Accepted for publication August 2, 1974.

The authors gratefully acknowledge the financial support extended by the Indian Council of Medical Research and the help of Dr. George Redl of Smith Kline and French Laboratories who provided various reagents and carried out pharmacological screening of some compounds.

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