4-Methoxy-2-nitrophenylalanine.—A solution of 5.0 g of ethyl 2-acetamido-2-(4-methoxy-2-nitrobenzyl)malonate in 50 ml of concentrated HCl was heated under reflux for 3 hr. The reaction mixture was placed in the refrigerator for 1 hr to effect crystallization. The resulting crystals were removed by filtration to give 2.70 g (74%) of product, mp 212–214°. The hydrochloride salt (1 g) was dissolved in a minimum amount of water, and dilute NH_4OH was added dropwise to pH 7.0 to precipitate 0.7 g (81%) of the base, mp 212–214° dec. Paper chromatograms of the product in 1-butanol–acetic acid–water (4:1:1) and 65% pyridine showed one spot, R_f 0.48 and 0.74, respectively.

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.03; N, 11.66. Found: C, 50.13; H, 4.94; N, 11.40.

2-Amino-4-methoxyphenylalanine.—A solution of 0.7 g of 4-methoxy-2-nitrophenylalanine in 100 ml of 75% methanol was hydrogenated under 3.52 kg/cm² of hydrogen pressure using palladium black as a catalyst for 3 hr. After removing the catalyst by filtration, the filtrate was concentrated. The resulting solution was cooled in the refrigerator to yield 0.55 g (89%) of desired product. Following recrystallization from water, the product melted at 184.5–186.5°. Paper chromatograms of the product in 1-butanol–acetic acid–water (4:1:1) and 65% pyridine showed one spot, R_f 0.52 and 0.82, respectively.

Anal. Calcd for $C_{10}H_{14}N_2O_3 \cdot H_2O$: C, 52.62; H, 7.04; N, 12.23. Found: C, 52.53; H, 7.03; N, 12.18.

Microbiological Assays.—For *E. coli* 9723, a previously described inorganic salts medium[11] was employed, and the organism was incubated at 37° for about 16 hr. For *L. dextranicum* 8086, the same assay procedure was employed as previously reported.[4] In all assays the amount of growth was determined photometrically at 625 mμ with a Bausch and Lomb Spectronic 20 spectrophotometer, in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at 0 absorbance. For *E. coli* the data in Table II are recorded as absorbance readings which are related to the milligrams of dry cells calculated from a standard curve of mg of dry cells/ml vs. absorbance readings.

(11) E. H. Anderson, *Proc. Natl. Acad. Sci. U. S.*, **30**, 120 (1944).

N-Methyl-N-2-propynyl-1-indanamine. A Potent Monoamine Oxidase Inhibitor

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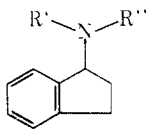
The synthesis of a series of tertiary indanamines and related compounds containing an N-2-propynyl substituent is described. Among this series are two (**1** and **10**, Table I) which are among the most potent monoamine oxidase inhibitors yet reported. Some activity–structure correlations have been made.

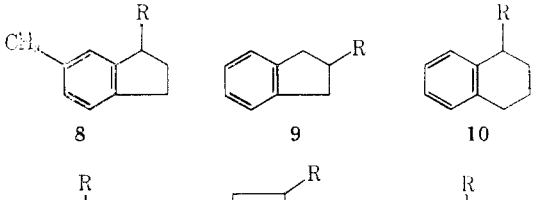
Our continuing interest in incorporating the indane grouping in molecules of potential pharmacological value, an activity which has already led to antihistamines,[1] analgesics, and monoamine oxidase inhibitors,[2] prompted us to synthesize a propynylamine containing this moiety. This followed the report of the monoamine oxidase inhibitory activity of N-methyl-N-2-propynylbenzylamine (pargyline).[3] The first compound prepared, N-methyl-N-2-propynyl-1-indanamine (**1**),[4] showed approximately 20 times the activity of pargyline and is indeed in certain tests the most potent, irreversible monoamine oxidase inhibitor known. We also wish to report on a few congeners of **1** prepared to explore activity–structure relationships (Table I).

The synthesis of these tertiary amines was straightforward. The requisite primary amines were formylated or acylated, reduced to the secondary amine with lithium aluminum hydride, and finally alkylated with propargyl bromide in the presence of sodium carbonate. For the preparation of large quantities of **1** a more economical procedure was developed by Dr. W. Rosen in which the intermediate N-methylindanamine was prepared from 1-chloroindane and methylamine.

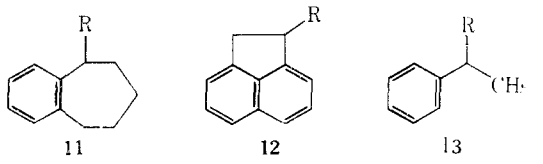
Changing the N-methyl substituent of **1** to hydrogen (**2**), ethyl (**3**), or 2-propynyl (**4**) lessened activity. Exchanging the N-2-propynyl substituent of **1** for



1, R′ = CH_3; R″ = $CH_2C{\equiv}CH$
2, R′ = H; R″ = $CH_2C{\equiv}CH$
3, R′ = C_2H_5; R″ = $CH_2C{\equiv}CH$
4, R′ = $CH_2C{\equiv}CH$; R″ = $CH_2C{\equiv}CH$
5, R′ = CH_3; R″ = $CH_2C{=}CH_2$
6, R′ = H; R″ = $C(CH_3)_2C{\equiv}CH$
7, R′ = CH_3; R″ = $C(CH_3)_2C{\equiv}CH$



8 9 10



11 12 13

R = $N(CH_3)(CH_2C{\equiv}CH)$

allyl (**5**) destroyed activity. Where the substituent was 1,1-dimethylpropynyl (**6** and **7**), activity was also lessened. Nuclear methyl substitution in **1** (**8**) or substitution of a 2- for a 1-indanyl residue (**9**) resulted in compounds about one-fourth as active as the parent. Ring enlargement of the five-membered, alicyclic ring of indane (**10**) gave the most active compound in the series which showed a 50% increase in activity over that of **1**. Enlarging the alicyclic ring to seven members (**11**), however, again lessened activity.

(1) C. F. Huebner, E. M. Donoghue, P. Wenk, E. Sory, and J. A. Nelson, *J. Am. Chem. Soc.*, **82**, 2077 (1960).

(2) C. F. Huebner, E. M. Donoghue, P. L. Strachan, P. Beak, and E. Wenkert, *J. Org. Chem.*, **27**, 4465 (1962).

(3) L. R. Swett, W. B. Martin, J. D. Taylor, G. M. Everett, A. A. Wykes, and Y. C. Glotish, *Ann. N. Y. Acad. Sci.*, **107**, 891 (1963).

(4) The authors would be pleased to fill any requests for this potent monoamine oxidase inhibitor from interested biochemical and pharmacological investigators for animal use.

Table I

No.	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Descending order of MAO inhib
		Substituted 1-Indanamine Hydrochlorides							
1	195–197	$C_{13}H_{15}N \cdot HCl$	70.41	7.21	6.32	70.24	7.48	6.72	2
2	178–179	$C_{12}H_{13}N \cdot HCl$	69.38	6.75	6.75	69.44	7.00	6.82	6
3	128–130	$C_{14}H_{17}N \cdot HCl \cdot 0.25H_2O$	70.00	7.70	5.83	70.36	7.64	5.74	6
4	160–163	$C_{15}H_{15}N \cdot HCl$	73.26	6.53	5.72	73.54	6.73	5.51	6
5	139–141	$C_{13}H_{17}N \cdot HCl$	69.78	8.05	6.26	70.05	8.25	6.23	6
6	239–240	$C_{14}H_{17}N \cdot HCl$	71.33	7.64	5.95	71.15	7.80	5.85	5
7	135–137	$C_{15}H_{19}N \cdot HCl \cdot 0.5H_2O$	69.60	8.13	5.42	69.25	8.13	5.11	6
		Related Compounds							
8	212–214	$C_{14}H_{17}N \cdot HCl$	71.33	7.64	5.95	71.16	7.81	5.77	4
9	201–203	$C_{13}H_{15}N \cdot HCl$	70.41	7.21	6.32	70.16	7.11	6.55	4
10	168–170	$C_{14}H_{17}N \cdot HCl \cdot 0.25H_2O$	70.00	7.70	5.83	70.43	7.65	5.71	1
11	168–170	$C_{15}H_{19}N \cdot HCl \cdot 0.25H_2O$	70.71	8.08	5.52	71.13	8.01	5.52	6
12	215–216	$C_{16}H_{15}N \cdot HCl$	74.53	6.21	5.44	74.39	6.13	5.52	3
13	168–170	$C_{12}H_{15}N \cdot HCl$	68.75	7.63	6.67	68.57	7.84	6.42	4

Fusion of an extra aromatic ring to **1** at the 3,3a positions gave the acenaphthene derivative (**12**) with an insignificant decrease in activity. Finally in **13**,[5] where the indane ring is opened, the activity is one-fourth that of **1**.

Our method of determining monoamine oxidase activity was that described by two of us.[6] The test drug is administered to a group of mice, and this is followed in 3–4 hr with a reserpine derivative [methyl 17-O-(tetrahydro-2-pyranyl)reserpate] which by itself causes sedation. The increase in spontaneous activity due to the monoamine oxidase inhibitory effect of the test drug is measured in the jiggle cage. The antagonism of this sedative effect of methyl 17-O-(tetrahydro-2-pyranyl)reserpate is presumably related to the prevention of the destruction of the catecholamines liberated centrally by this compound. More detailed biochemical investigations of the monoamine oxidase inhibitory activity of **1** in several organs and against several amine substrates using both *in vitro* and *in vivo* techniques (Drs. L. Mâitre and M. Staehelin, Research Laboratories, CIBA Ltd., Basle) also showed the very high degree of activity of **1** (about 20 times that of pargyline).

Experimental Section[7]

N-Methyl-1-indanamine.—To a solution of acetic formic anhydride (0.2 mole) (prepared by stirring 20.4 ml of acetic anhydride and 8.6 ml of formic acid on a water bath at 50–60° for 2 hr then cooling to room temperature) was added dropwise with stirring, 0.15 mole of 1-indanamine at such a rate that the temperature never rose above 40°. After stirring for 30 min, 60 ml of ether was added, and the solution was stirred at room temperature overnight. The reaction mixture was diluted with ether, washed twice with water, twice with saturated $NaHCO_3$ solution, with 5% HCl, and finally with water. The organic layer was dried over $MgSO_4$ and the ether was evaporated; the residue solidified (mp 92–95°). A tetrahydrofuran solution of the formamide (0.08 mole) was added with stirring to a suspension of 6.15 g (0.16 mole) of $LiAlH_4$ in 50 ml of tetrahydrofuran at a rate sufficient to maintain gentle reflux. The reaction mixture was refluxed for 5 hr then allowed to stand at room temperature overnight before decomposing by the cautious addition of 6 ml of water, 12 ml of 12% NaOH, and finally 24 ml of water. The inorganic material was filtered, and the filtrate was dried over $MgSO_4$ and evaporated. The residue was distilled *in vacuo*, and a small portion was converted to the hydrochloride for analysis; mp 144–146°.

Anal. Calcd for $C_{10}H_{13}N \cdot HCl \cdot H_2O$: C, 63.85; H, 7.70; N, 7.40. Found: C, 64.00; H, 7.63; N, 7.55.

The following compounds were prepared in this manner.

N-Methyl-2-indanamine hydrochloride, mp 230–233°. *Anal.* Calcd for $C_{10}H_{13}N \cdot HCl$: C, 65.40; H, 7.64; N, 7.64. Found: C, 66.01; H, 7.93; N, 7.93.

N,6-Dimethyl-1-indanamine hydrochloride, mp 146–148°. *Anal.* Calcd for $C_{11}H_{15}N \cdot HCl$: C, 66.88; H, 8.12; N, 7.10. Found: C, 67.27; H, 8.04; N, 7.27.

1,2,3,4-Tetrahydro-N-methyl-1-naphthylamine maleate, mp 105°. *Anal.* Calcd for $C_{11}H_{15}N \cdot C_4H_4O_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.76; H, 6.70; N, 4.93.

6,7,8,9-Tetrahydro-N-methyl-5H-benzocyclohepten-5-amine hydrochloride, mp 180–182°. *Anal.* Calcd for $C_{12}H_{17}N \cdot HCl$: C, 68.08; H, 8.50; N, 6.61. Found: C, 67.84; H, 8.42; N, 6.60.

N-Methyl-α-phenylethylamine hydrochloride, mp 165–167°. *Anal.* Calcd for $C_9H_{13}N \cdot HCl$: C, 62.96; H, 8.16; N, 8.16. Found: C, 63.25; H, 8.27; N, 8.30.

N-Methylacenaphthen-1-amine hydrochloride, mp 200–201°. *Anal.* Calcd for $C_{13}H_{13}N \cdot HCl \cdot 0.25H_2O$: C, 69.65; H, 6.48; N, 6.26. Found: C, 69.88; H, 6.27; N, 6.53.

N-Acetyl-1-indanamine.—To a rapidly stirred mixture of 12 g (0.09 mole) of 1-indanamine and 30 g of ice was added 18.5 g (0.18 mole) of acetic anhydride followed by sufficient 40% KOH solution to make the reaction basic (~100 ml). After cooling, the acetyl compound was filtered and dried; mp 110–112°, yield 12 g.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.12; H, 7.49; N, 7.75

N-Ethyl-1-indanamine Hydrochloride.—The above acetyl compound was reduced with $LiAlH_4$ as described for the formyl compounds, mp 214–216°.

Anal. Calcd for $C_{11}H_{15}N \cdot HCl$: C, 66.88; H, 8.12; N, 7.10. Found: C, 66.48; H, 8.12; N, 6.84.

N-Methyl-N-propynyl-1-indanamine Hydrochloride (1).—To a stirred mixture of 0.027 mole of N-methyl-1-indanamine and 0.027 mole of Na_2CO_3 in 50 ml of acetone was added dropwise 0.027 mole of propargyl bromide. The reaction mixture was refluxed 4 hr and cooled, and the NaBr was filtered. The acetone was evaporated *in vacuo*, and the residue was converted to the hydrochloride. Compounds **3** and **8–13** were prepared in the same manner.

N,N-Dipropynyl-1-indanamine hydrochloride (**4**) was prepared by the above procedure using 1-indanamine.

N-Allyl-N-methyl-1-indanamine hydrochloride (**5**) was prepared by essentially the same procedure used for the propynyl compounds with the following modifications: the oily residue remaining after evaporation of the acetone was ether insoluble and water soluble; the oil was dissolved in water and made basic with NH_4OH, and the organic material was extracted into ether

(5) This substance was also reported by Swett, *et al.*,[3] to be active.

(6) A. J. Plummer and P. A. Furness, *Ann. N. Y. Acad. Sci.*, **107**, 865 (1963).

(7) All melting points were taken on a Thomas–Hoover melting point apparatus. All hydrochloride salts, unless otherwise indicated, were recrystallized from ethanol.

and dried over $MgSO_4$. When the dry ether solution was treated with 7 *N* ethanolic HCl, a gummy solid precipitated. This hydrochloride was recrystallized from aqueous ethanol–ether.

N-(1,1-Dimethylpropynyl)-1-indanamine Hydrochloride (6). To a stirred mixture of 10.0 g (0.075 mole) of 1-indanamine, 9.5 g (0.09 mole) of Na_2CO_3 and 1.0 g of copper–bronze in 125 ml of acetone was added dropwise, 9.25 g (0.09 mole) of dimethylethynylcarbinyl chloride.[8] The reaction mixture was stirred at room temperature overnight before filtering the inorganic solids. The acetone was evaporated *in vacuo* and a small portion of the residue was converted to the hydrochloride with 7 *N* ethanolic HCl for analysis.

N-(1,1-Dimethylpropynyl)-N-methyl-1-indanamine Hydrochloride (7).—The above compound (**6**) was methylated with formic acid and paraformaldehyde[9] and converted to the hydrochloride.

N-Propynyl-1-indanamine Hydrochloride (2).—A mixture of 2.4 g (0.04 mole) of propargylamine and 3.3 g (0.02 mole) of 1-chloroindane in 25 ml of isopropyl alcohol was refluxed 6 hr. After cooling, the solid propargylamine hydrochloride was filtered and the filtrate was evaporated to dryness. The residue was converted to the hydrochloride.

Primary amines not commercially available were prepared by the formation of the oxime from the corresponding ketone, followed by catalytic reduction (5% Pd–C) of the oxime in AcOH–H_2SO_4 (19:1 by volume). A small portion of the base was converted to the hydrochloride for analysis.

The following compounds were prepared in this manner.

1,2,3,4-Tetrahydro-1-naphthylamine hydrochloride, mp 182–183°. *Anal.* Calcd for $C_{10}H_{13}N \cdot HCl$: C, 65.37; H, 7.64; N, 7.64. Found: C, 65.11; H, 7.74; N, 7.34.

6,7,8,9-Tetrahydro-5H-benzocyclohepten-5-amine hydrochloride, mp 277–278°. *Anal.* Calcd for $C_{11}H_{15}N \cdot HCl$: C, 66.80; H, 8.29; N, 7.08. Found: C, 67.05; H, 8.16; N, 6.97.

Acenaphthen-1-amine hydrochloride, mp 300°. *Anal.* Calcd for $C_{12}H_{11}N \cdot HCl$: C, 70.05; H, 5.84; N, 6.81. Found: C, 69.77; H, 5.94; N, 6.85.

Monoamine Oxidase Inhibitory Assay.—Comparative experiments were performed in which graded doses of the test substance (*N*-methyl-*N*-2-propynyl-1-indanamine hydrochloride (**1**) in this instance) and the standard, pargyline in 1% aqueous solution, were administered subcutaneously to two groups of three mice. After a period of 4 hr, 2.5 mg of methyl 17-*O*-(tetrahydro-2-pyranyl)reserpate as a 5% solution in polyethylene glycol diethylacetamide (4:1) was injected subcutaneously, and the animals were placed three to a cage in an activity recorder. The activity of the mice was recorded for a period of 90 min. A dosage ranging from 2.5 to 20 mg/kg sc of **1** was employed. An abrupt increase in the activity of the mice was observed when the dosage of **1** had reached 10 mg/kg. The observed increase in activity was greater than that produced by 100 mg/kg sc of pargyline and slightly less than that produced by 120 mg/kg. In a similar manner, products **2**–**13** were assayed and the results were expressed in decreasing order of activity of **1** in Table I. A second type of comparative study (as illustrated using **1**) was also made. Two groups of three mice (one of which served as a control) were injected subcutaneously with 2.5 mg/kg of methyl 17-*O*-(tetrahydro-2-pyranyl)reserpate. After 30 min when sedation and ptosis were quite obvious in all of the animals, one of the groups received 40 mg/kg sc of **1**. Within 30–40 min the animals so treated had become alert and active, and all evidence of ptosis had disappeared. The untreated controls were still deeply sedated, did not move about, and still showed marked ptosis. At a dose of 200 mg/kg pargyline produced no obvious decrease in the sedation or degree of ptosis when administered to animals previously treated with methyl 17-*O*-(tetrahydropyranyl)reserpate. At a dose of 400 mg/kg there was some reduction in sedation and the degree of ptosis, but the animals were still sluggish in their action and had not recovered to the degree approaching that noted after 20 mg/kg of **1**.

(8) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Am. Chem. Soc.*, **72**, 3542 (1950).

(9) C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **26**, 3776 (1961).

Thyromimetics. VI. The Synthesis and Biological Screening of 3,5-Diiodothyroacetic and -propionic Acid Analogs

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Several 3,5-diiodothyroacetic and -propionic acids as well as certain of their ether and ester derivatives were prepared and examined for hypocholesteremic activity. The interesting 2′,3′-dimethyl compounds were studied further in other thyromimetic assays. The compounds, in general, had weak cholesterol-lowering activity although a desired separation of activities was evident in compounds IIIb, IVa, and IVb.

Jorgensen and co-workers[1,2] have shown within a series of dialkyl-3,5-diiodothyronines and 3,5-diiodo-4′-deoxythronines that the 2′,3′-dimethyl analogs were among the most active compounds. Subsequently, these workers[3] showed that the phenyl ether of 3,5-diiodotyrosine had cholesterol-lowering activity. Herman, Lee, and Parker,[4] in studying the hypocholesteremic activity of thyroxine-like compounds, have reported that 3,5-diiodo-3′,5′-dimethyl compounds have activity comparable to that of the corresponding 3,3′,5,5′-tetraiodo analogs. Other studies[5–7] have shown that alteration of the alanine side chain of 3,5-diiodothyronines has a significant effect on the nature and magnitude of the elicited biological responses. Thus, the synthesis of several dialkyl-3,5-diiodothyroacetic and -propionic acids, certain of their ether and ester derivatives, as well as the phenyl ethers of 4-hydroxy-3,5-diiodophenylacetic and -propionic acids was undertaken. Specifically, it was hoped that these compounds would lower plasma cholesterol levels without at the same time increasing calorigenic or cardiac responses. A second more

(1) E. C. Jorgensen and P. N. Kaul, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 653 (1959).

(2) E. C. Jorgensen, N. Zenker, and C. Greenberg, *J. Biol. Chem.*, **235**, 1732 (1960).

(3) E. C. Jorgensen, P. A. Lehman, C. Greenberg, and N. Zenker, *Science*, **237**, 3832 (1962).

(4) R. G. Herman, C. C. Lee, and R. Parker, *Arch. Intern. Pharmacodyn.*, **133**, 284 (1961).

(5) N. R. Stasilli, R. L. Kroc, and R. I. Meltzer, *Endocrinology*, **64**, 62 (1959).

(6) B. Blank, C. M. Greenberg, and C. F. Kerwin, *J. Med. Chem.*, **7**, 53 (1964).

(7) B. Blank, E. G. Rice, F. R. Pfeiffer, and C. M. Greenberg, *ibid.*, **9**, in (1966), paper V in this series.