tered, and the solvent was removed *in vacuo*. The powder was pulverized and dried *in vacuo* at 40° for 2 hr. The yield was essentially quantitative by TLC.

Six grams of impure erythromycin 2′-glutaryl-*N*-dicyclohexylurea was dissolved in 25 ml of anhydrous acetone, and the solution was filtered and placed on a column packed by acetone slurry with 427 g silica gel[7] (70–325 mesh). The column was eluted with anhydrous acetone at a rate of 12 ml/min, and tubes numbering 30–79 were collected and pooled. The solvent was removed at room temperature, and 2.4 g of pure erythromycin 2′-glutaryl-*N*-dicyclohexylurea was collected.

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Preparation and Pharmacological Screening of Indanethylamines Related to Tryptamine

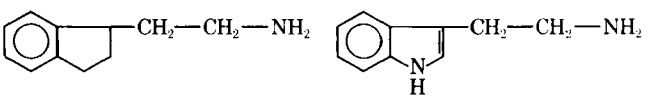
JOHN B. DATA[x], MICHAEL L. TAYLOR, and MARIO FORCIONE

Abstract □ A series of mono- and di-*N*-substituted 2-(1-indanyl)-ethylamines was prepared and screened for monoamine oxidase inhibition and serotonin antagonism. Synthetic methods for their preparation are described, and the procedures used for their screening along with the activity found are discussed.

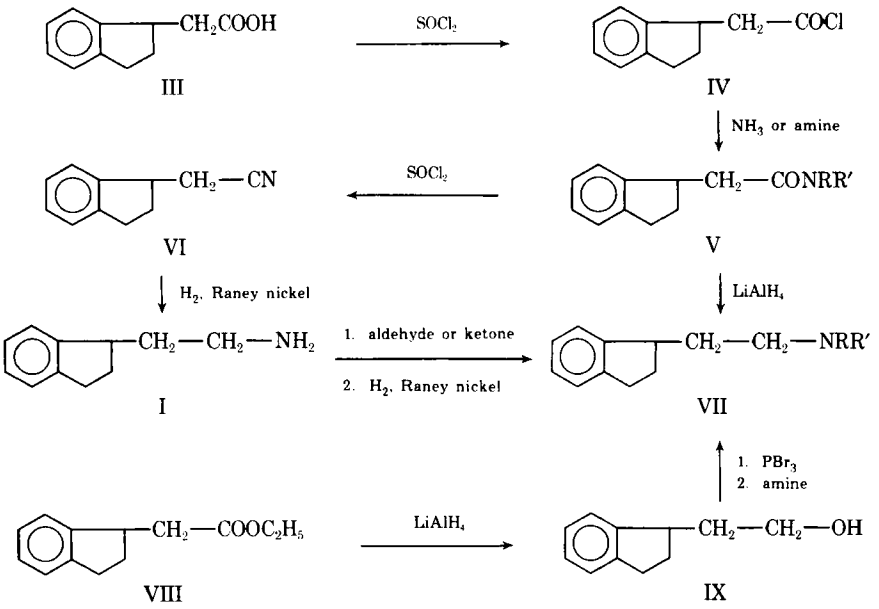
Keyphrases □ Indanethylamines, related to tryptamine—synthesis and pharmacological screening for monoamine oxidase inhibition and serotonin antagonism □ Tryptamine-related compounds—synthesis and screening of indanethylamines as monoamine oxidase inhibitors and serotonin antagonists □ Monoamine oxidase inhibition—synthesis and screening of indanethylamines □ Serotonin antagonism—synthesis and screening of indanethylamines

During an investigation in these laboratories directed toward the synthesis of compounds related to reserpine, the occasion arose to prepare 2-(1-indanyl)-ethylamine (I). The close isosteric relationship of I to tryptamine (II) aroused interest with reference to its pharmacological activity.

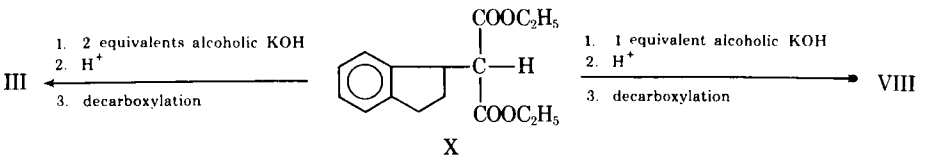
A review of the literature indicated that a biological investigation of I had not been published and only recently was its preparation reported (1). Further search revealed that pharmacological studies with 1-, 2-, and 3-indanylmethyl-, indanylethyl-, and indanylpropylamines have been confined chiefly to phenyl-substituted indanamines (2–8). Very few studies concerning these amines with substituents on the cyclopentano moiety of indan used substituents other than a phenyl group (9, 10). Since most studies



I II



Scheme I—(Structure for R and R' given in Table I)



Scheme II

have been done with amines influenced by the high electron density of the phenyl ring, the question arose as to what pharmacological response would be evident when this factor was absent. This fact, coupled with the isosteric relationship, prompted the preparation of a series of secondary and tertiary 2-(1-indanyl)ethylamines for preliminary pharmacological examination for monoamine oxidase inhibition and serotonin antagonism.

While preparation of these compounds was in progress, a closely related study was announced (11, 12), which made a comparison of the contractile effects on the rat fundus of some 2-indenealkylamines and other heterocyclic isosteres. Shortly after completion of the present study, the hypoglycemic activity of a series of indanamines was reported (13); five amines listed in Table I were a part of that study. Since most of the chemistry (see *Chemistry* section) and the pharmacological studies differ from that of the latter authors, and because of the limited pharmacological data recorded in the literature on compounds of the type reported herein, it is appropriate that this study be reported.

CHEMISTRY

The amines (Table I) were prepared by one of the following three methods (Scheme I). Lahiri and De (13) reported the preparation of five compounds (VIIc, VII*e*, VII*g*, VII*m*, and VII*n*) listed in Table I by lithium aluminum hydride reduction of the corresponding amides to the amines as exemplified by Method C *via* the acid, to the acid chloride, to the amides, and to the amines.

Method A—1-Indanylacetic acid (III) was converted with thionyl chloride to the acid chloride (IV), which was then aminated with aqueous ammonia or with an anhydrous ethereal solution of IV with gaseous ammonia to give the amide V. Dehydration of the amide with thionyl chloride gave 1-indanylacetonitrile (VI), which was reduced with hydrogen in the presence of Raney nickel to 2-(1-indanyl)ethylamine (I). Compound I was allowed to react with either an aldehyde or a ketone to give the Schiff base, which was then reduced *in situ* with hydrogen using Raney nickel as catalyst to the desired amines (VII).

Method B—Ethyl 1-indanylacetate (VIII) was reduced with lithium aluminum hydride to give 2-(1-indanyl)ethanol (IX). The alcohol IX was treated with phosphorus tribromide to give the halide, which was allowed to react with an appropriate amine to give the desired products (VII).

Method C—The substituted amides (V) were obtained from the reaction of IV with an amine. Reduction of the substituted amides with lithium aluminum hydride in tetrahydrofuran gave the desired amines (VII).

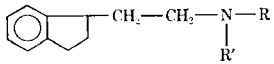
Ethyl 1-indanylacetate (VIII) or the corresponding acid (III) was obtained by selective base hydrolysis of the diethyl 1-indanylmalonate (X) (Scheme II), prepared from sodio diethyl malonate and chlorindan in dry benzene, followed by decarboxylation of the mono- or dicarboxylic acid resulting from acidification of the corresponding potassium salt obtained in the hydrolysis.

EXPERIMENTAL[1]

Diethyl 1-Indanylmalonate—Moffett and Hart (14) reported the preparation of the title compound, but a procedure for its synthesis was not described.

To a stirred suspension of 35.0 g (1.52 g-atom) of finely powdered sodium in 1.5 liters of dry benzene was added dropwise 240.3 g (1.5 moles) of diethyl malonate, and the mixture was then gent-

[1] Melting points were determined by the capillary tube method using a Buchi capillary melting-point apparatus. All melting and boiling points are uncorrected. The phrase "reduced pressure," "*in vacuo*," or the equivalent indicates water aspiration at 12–20 mm. IR data were recorded on a Beckman IR-33 spectrophotometer. NMR spectra were determined with a Jeol MH 60 spectrometer using tetramethylsilane as the internal reference. All benzyl triplets would not be expected to be first-order triplets but give this appearance in the spectra. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.



VII

Table I—Mono- and Di-*N*-substituted 2-(1-Indanyl)ethylamines

Compound	R	R′	Method	Boiling Point (mm)	Yield, %	Hydrochloride Melting Point	Formula	Analysis, %	Calc.	Found
VII*b*	CH_3	H	C	82–83° (0.25)	84	193–194°	$C_{12}H_{18}ClN$	C	68.08	67.94
								H	8.51	8.40
VII*c*	CH_3	CH_3	B	68–70° (0.17)[a]	82	154–155°[a]	$C_{13}H_{20}ClN$	C	69.17	69.19
								H	8.86	8.93
VII*d*	—CH_2—CH_2—CH_2—CH_2—CH_2—		B	117–118° (0.45)	92	219–220°	$C_{16}H_{24}ClN$	C	72.31	72.64
								H	9.03	9.12
VII*e*	CH_3—CH_2—CH_2	H	A	81–82° (0.2)[b]	76	178–179°[b]	$C_{14}H_{22}ClN$	C	70.14	69.86
								H	9.18	8.94
VII*f*	$(CH_3)_2$—CH	H	A	85–90° (0.15)	90	179–180°	$C_{14}H_{22}ClN$	C	70.14	70.13
								H	9.18	9.21
VII*g*	CH_3—$(CH_2)_2$—CH_2	H	A	113–115° (0.25)[c]	98	195–196°	$C_{15}H_{24}ClN$	C	71.00	71.57
								H	9.46	9.72
VII*h*	$(CH_3)_2$—CH—CH_2	H	A	89–90° (0.25)	80	189–190°	$C_{15}H_{24}ClN$	C	71.00	70.91
								H	9.46	9.53
VII*i*	CH_3—CH_2—CH(CH_3)	H	A	100–101° (0.45)	97	158–159°	$C_{15}H_{24}ClN$	C	71.00	70.86
								H	9.46	9.53
VII*j*	$CH_3(CH_2)_5$—CH_2	H	A	90–91° (0.22)	98	196–197°	$C_{18}H_{30}ClN$	C	73.09	73.11
								H	10.15	10.01
VII*k*		H	A	125–126° (0.35)	98	182–183°	$C_{16}H_{24}ClN$	C	72.31	72.53
								H	9.03	9.08
VII*l*	$(CH_3)_3$—C	H	B	101–103° (0.25)	60	199–200°	$C_{15}H_{24}ClN$	C	71.00	71.22
								H	9.46	9.25
VII*m*	CH_3—CH_2	CH_3—CH_2	B	108–110° (0.3)[d]	72	—	$C_{15}H_{23}N$	C	82.94	82.67
								H	10.59	10.49
VII*n*	CH_3—$(CH_2)_2$—CH_2	CH_3—$(CH_2)_2$—CH_2	B	144–146° (0.3)[e]	65	—	$C_{19}H_{31}N$	C	83.51	83.37
								H	11.35	11.32

[a] bp 120–122° (3 mm), mp 153–155° (13). [b] bp 125–127° (1.0 mm), mp 133–134° (13). [c] bp 140–142° (1.1 mm), mp 145–146° (13). [d] bp 108–110° (0.3 mm) (13). [e] bp 144–146° (0.3 mm) (13).

ly refluxed for 15 hr. Freshly prepared 1-chlorindan, 259.3 g (1.7 moles), was added dropwise to the gently refluxing, stirred mixture. After the last addition, the stirring and refluxing were continued for an additional 10 hr. Water, 500 ml, was added to the cold solution to dissolve the solid, the organic layer was separated, and the aqueous solution was extracted once with 200 ml of ether. The combined organic solutions were washed with 100 ml of hydrochloric acid solution (5%) followed by 100 ml of water. The solution was dried with fused sodium sulfate, filtered, and concentrated *in vacuo*, and the residue was distilled. The fraction distilling from about 110 to 165° at 0.1 mm was collected. The distillate was refractionated to give an average yield of 289.0 g (69.8%) of product, bp 132–142° at 0.42 mm, n_{25D} 1.5030 [lit. (14) bp 112° at 0.03 mm, n_{25D} 1.5025]; IR ($CHCl_3$): 5.78 (ester C=O) μm; NMR (CCl_4): δ 7.03 (s, 4, ArH), 4.05 (q, 2, OCH_2), 4.01 (q, 2, OCH_2), 3.25–3.79 (m, 2, two CH), 2.60–3.00 (m, 2, benzylic t at 2.78), 1.78–2.37 (m, 2, CH_2), 1.14 (t, 3, CH_3), and 1.11 (t, 3, CH_3).

Ethyl 1-Indanylacetate—Diethyl 1-indanylmalonate, 138.0 g (0.5 mole), was combined with 33.1 g (0.5 mole) of potassium hydroxide (85%) in 1.0 liter of ethanol (95%), and the solution was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and 100 ml of water was added to the residue. The solution was extracted with two 50-ml portions of ether and then acidified with hydrochloric acid (37%). The oily layer was separated off, the aqueous layer was extracted exhaustively with ether, and the combined organic fractions were dried over fused sodium sulfate. The dry, ethereal solution was concentrated under reduced pressure, and the residue was flash distilled. The fraction that distilled up to about 170° (5–10 mm) was collected as decarboxylation occurred. The distillate was fractionated to yield 65.0 g (64.0%) of product, bp 100–105° (0.55 mm). The analytical sample was collected at 100° (0.55 mm); n_{20D} 1.5158; IR (film): 5.77 (ester C=O) μm; NMR (CCl_4): δ 7.02 (s, 4, ArH), 4.03 (q, 2, OCH_2), 3.17–3.66 (m, 1, CH), 1.40–3.00 (m, 5, including benzylic t at 2.78), and 1.17 (t, 3, CH_3).

Anal.—Calc. for $C_{13}H_{16}O$: C, 76.44; H, 7.90. Found: C, 76.24; H, 7.80.

1-Indanylacetic Acid—To a gently refluxing, stirred solution of 46.3 g (0.7 mole) of potassium hydroxide (85%) in 300 ml of ethanol (75%), 82.8 g (0.3 mole) of diethyl 1-indanylmalonate was added at a rate to maintain refluxing and the refluxing and stirring were continued for an additional 3 hr. To the cold solution was added 200 ml of water, and the solution was concentrated *in vacuo* to a volume of about 300 ml. The solution was extracted once with 200 ml of ether and acidified with hydrochloric acid (37%) while being kept cold, and then the organic acid was removed by exhaustive extraction with ether. The dried, ethereal solution was concentrated under reduced pressure, a small amount of powdered glass was added to the residue, and the mixture was heated in a Wood's metal bath at 110–130° (internal) for 2 hr and then at 150–160° for 1 hr. The reaction mixture was fractionally distilled to give the title compound in average yields of 45.0 g (87.0%), bp 128–130° (0.45 mm) or 148–152° (3.0 mm). A small sample of the solid was recrystallized from *n*-heptane to give a white product, mp 60–61° [lit. (19) mp 60–61°]; IR (NaBr): 5.92 (acid C=O) μm; NMR (CCl_4): δ 12.29 (s, 1, COOH, H^+ eliminated by D_2O shake), 7.03 (s, 4, ArH), 3.17–3.68 (m, 1, CH), and 1.47–3.03 (m, 7, including benzylic t at 2.78).

2-(1-Indanyl)ethanol—To a stirred suspension of 13.7 g (0.36 mole) of powdered lithium aluminum hydride in 500 ml of anhydrous ether was added, at a rate to maintain vigorous reflux, 61.2 g (0.3 mole) of ethyl 1-indanylacetate in 200 ml of anhydrous ether. After the last addition the mixture was stirred at gentle refluxing for 6 hr and cooled. Then 14.0 ml of water, 14.0 ml of sodium hydroxide solution (15%), and 42 ml of water were added consecutively with caution and rapid stirring. Stirring was continued for 20 min, the solid was filtered off, and the precipitate was washed with ether. The combined ethereal solution was concentrated to a thick syrup to which was added 200 ml of ethanol (75%) and 10.0 g of potassium hydroxide (85%). After refluxing the solution for 2 hr, most of the alcohol was removed *in vacuo*, 75 ml of water was added, and the mixture was exhaustively extracted with ether. The combined extracts were washed twice with 50 ml of water, dried with fused sodium sulfate, and filtered, and the solution was concentrated under vacuum. The residue was rapidly distilled under 1–4 mm pressure to give 45–50 g of distillate which, when fractionated, gave an average yield of 40.0 g (82.0%) of product distilling at 107–108° (1.1 mm). The analytical sample was collected at 107° (1.1 mm); n_{20D} 1.5500; IR (film): 2.75–3.25 (broad) and 6.77 (primary alcohol OH) μm; NMR (CCl_4): δ 6.93 (s, 4, ArH), 4.20 (s, 1, OH), 3.57 (t, 2, CH_2), 2.88–3.27 (m, 1, CH), 2.68 (t, 2, benzylic), and 1.17–2.50 (m, 4, cyclic CH_2 and CH_2O).

Anal.—Calc. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.79; H, 9.13.

2-(1-Indanyl)ethyl Bromide—To a stirred solution of 54.1 g (0.2 mole) of phosphorus tribromide in 200 ml of carbon tetrachloride at 0–5° was added dropwise 48.6 g (0.3 mole) of 2-(1-indanyl)ethanol; then the reaction mixture was removed from the ice bath. After standing for 24 hr the solution was poured onto 500 g of cracked ice, the organic layer separated, the aqueous layer was exhaustively extracted with carbon tetrachloride, and the combined extractions were washed with two 50-ml portions of sodium hydroxide (5%) followed by two 50-ml portions of water. The organic layer was dried with fused sodium sulfate, filtered, concentrated, and fractionated to yield 40.5 g (60.0%) of the bromide, bp 100–104° (0.3 mm); n_{20D} 1.5675; NMR (CCl_4): δ 6.93 (s, 4, ArH), 2.50–3.67 (m, 5, including benzylic t at 2.70 and CH_2 at 3.23), and 1.00–2.50 (m, 4, $-CH_2CH_2Br$).

Anal.—Calc. for $C_{11}H_{13}Br$: C, 58.68; H, 5.82. Found: C, 58.92; H, 6.21.

Acetamides—These compounds were synthesized from freshly prepared, crude or distilled, 1-indanylacetyl chloride and aqueous ammonia or an amine.

1-Indanylacetyl Chloride—To 52.8 g (0.3 mole) of 1-indanylacetic acid in 300 ml of benzene was added 54.0 g (0.45 mole) of thionyl chloride, and the solution was very gently refluxed for 5 hr. The benzene and excess thionyl chloride were removed under vacuum from a warm (35–40°) water bath, the residue was dissolved in 100 ml of dry benzene, and the solution was concentrated as before. This crude product may be used to prepare the amide or purified further by fractionation of the residue, bp 142–145° (10 mm) [lit. (15) bp 146° (11 mm)]; IR ($CHCl_3$): 5.50 (acetyl C=O) μm; NMR (CCl_4): δ 6.97 (s, 4, ArH), 3.10–3.66 (m, 1, CH), and 1.00–3.09 (m, 6, including benzylic t at 2.78).

1-Indanylacetamide—The crude 1-indanylacetyl chloride obtained above was added dropwise with stirring into 300 ml of ammonium hydroxide (28% NH_3). The solid was filtered off, transferred to a container, and then washed with 150 ml of potassium hydroxide (4%). The mixture was allowed to stand 2 hr, and the solid was filtered off and air dried. The average yields of crude product melting at 95–96° were 50.9 g (96.9%). A small sample was recrystallized several times from carbon tetrachloride to give a pure white product, mp 98–99° [lit. (15) mp 90°]; IR (KBr): 6.16 (amide C=O) μm; NMR (CF_3COOH): δ 7.13 (s, 4, ArH), 3.30–3.77 (m, 1, CH), and 1.50–3.16 (m, 6, including benzylic t at 2.80).

N-Methyl-1-indanylacetamide—To prepare the amide, anhydrous methylamine was bubbled into 600 ml of vigorously stirred anhydrous ether maintained at 10–15° while 35.4 g (0.18 mole) of freshly distilled 1-indanylacetyl chloride was added dropwise. The solid amide was filtered with suction and washed with water and then ether. The ethereal filtrate was removed by concentration *in vacuo*, and the solid residue was washed with water and combined with the main product to yield 31.3 g (92.0%) of crude product. After one recrystallization from water–methanol, the title compound was obtained, mp 72–73°; IR (NaBr): 5.87 (amide C=O) μm; NMR (CCl_4): δ 7.63 (broad s, 1, NH), 7.00 (s, 4, ArH), 3.24–3.60 (m, 1, CH), and 1.33–2.97 (m, 9, including d, CH_3 at 2.60).

Anal.—Calc. for $C_{12}H_{15}NO$: C, 76.19; H, 7.93. Found: C, 76.29; H, 8.00.

1-Indanylacetonitrile—To a suspension of 35.0 g of crude 1-indanylacetamide (mp 95–96°) in 300 ml of benzene was added 36.0 g (0.3 mole) of thionyl chloride, and the mixture was gently refluxed for 5 hr. Excess thionyl chloride and benzene were removed under vacuum, 150 ml of ether was added, and the ethereal solution was shaken with 75 ml of water followed by 150 ml of sodium hydroxide (3%). The organic layer was dried over fused sodium sulfate, filtered, and concentrated. The residue was fractionated to give 28.2–30.1 g or 90–96% yields (based on 0.2 mole of pure amide) of product, bp 96–98° (0.14 mm); n_{20D} 1.5411; IR (film): 4.43 (CN) μm; NMR (CCl_4): δ 6.98 (s, 4, ArH) and 1.17–3.67 (m, 7 including 1, CH at 3.15).

Anal.—Calc. for $C_{11}H_{11}N$: C, 84.07; H, 7.00. Found: C, 84.64; H, 7.32.

2-(1-Indanyl)ethylamine (VII*a*)—A mixture of 78.5 g (0.5 mole) of 1-indanylacetonitrile, 300 ml of liquid ammonia, 200 ml of absolute alcohol, a teaspoonful of Raney nickel, and hydrogen at an initial pressure of 1500 psi was heated to 85–90° in a Parr high pressure hydrogenator for 20 hr. After filtering off the catalyst, the solution was concentrated *in vacuo* and the residue was fractionated to give an average yield of 72.5 g (90.0%) of the title compound, bp 85–87° (0.5 mm).

This product was also prepared from 1-indanylacetamide in 87.0% yield by Method C described later. An analytical sample of the amine so prepared, taken at 79° (0.24 mm), gave n_{20D} 1.5472; IR (film): 3.10 (amino NH_2) μm; NMR (CCl_4): δ 7.01 (s, 4, ArH), 0.93 (s, 2, NH_2, $2H^+$ eliminated by D_2O shake), and 1.13–3.35 (complex m, 9).

Anal.—Calc. for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.58; H, 9.69.

The hydrochloride salt, prepared as described later, was recrystallized from ethyl acetate–absolute alcohol to give a pure white product, mp 215–216°.

Anal.—Calc. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.18. Found: C, 66.87; H, 8.45.

Secondary and Tertiary Amines—These amines, listed in Table I, were prepared by one of three methods. Method A involved the formation of a Schiff base from an aldehyde or ketone with 2-(1-indanyl)ethylamine and the reduction of this base *in situ* with Raney nickel and hydrogen under pressure. Method B entailed the reaction of 2-(1-indanyl)ethyl bromide with a primary or secondary amine. Method C utilized the lithium aluminum hydride reduction of 1-indanylacetamide or an *N*-substituted derivative in dry tetrahydrofuran.

In those cases where the amines formed solid hydrochloride salts readily, these were prepared in the usual way from gaseous hydrogen chloride and the amine in anhydrous ether. All salts were recrystallized from an ethyl acetate–absolute alcohol mixture as a solvent.

Method A—A mixture of 16.1 g (0.1 mole) of 2-(1-indanyl)ethylamine, 0.15 mole of ketone or aldehyde, 150 ml of absolute alcohol, and a teaspoonful of Raney nickel was heated to 80–90° for 1 hr in a Parr high pressure hydrogenator. Hydrogen was added to 1500 psi, and the reaction mixture was rocked for 20 hr at 90–100°. After filtering off the catalyst, the filtrate was concentrated under vacuum and the residue was fractionated.

Method B—To 19.1 g (0.085 mole) of 2-(1-indanyl)ethyl bromide in 150 ml of absolute alcohol (solution cooled to 0.5° for low boiling amines) was added 0.3 mole of the required amine, and the solution was heated to 70–90° for 5 hr in a stirring autoclave. The cold reaction mixture was acidified with excess hydrochloric acid solution (10%), the alcohol was removed *in vacuo*, the mixture was extracted several times with ether, and the amine was liberated from its salt with excess solid sodium hydroxide. The base was obtained by exhaustive extraction with ether; the ethereal solutions were dried with fused sodium sulfate, filtered, and concentrated; and the residue was fractionated.

Method C—To a stirred suspension of 18.6 g (0.5 mole) of lithium aluminum hydride in 200 ml of gently refluxing, dry tetrahydrofuran was added 0.14 mole of amide in about 250 ml of dry tetrahydrofuran during 2 hr. After the last addition, refluxing and stirring were continued for 4 hr. To the cold mixture was added consecutively 18.6 ml of water, 18.6 ml of sodium hydroxide (15%), and 57 ml of water. The solid was filtered and washed with ether, the combined dry organic fraction was concentrated under vacuum, and the residue was fractionated.

IR and NMR Spectra—The structures of all amines were supported by IR and NMR spectra. The IR spectra (film) for all secondary amines gave a weak peak between 6.19 and 6.24 μm for the N—H bending vibration and a moderate peak between 3.00 and 3.03 μm for the C—N vibration. All tertiary amines gave a moderate peak between 8.36 and 8.46 μm and also at 9.73 μm for the C—N vibration.

The NMR spectra (CCl_4) for all amines gave absorption peaks within the values expressed (in δ) as follow: *(a)* protons (s, ArH), 7.00–7.09; *(b)* two protons (t, benzylic), 2.78–2.80; *(c)* one proton (m, CH), 2.93–3.50; *(d)* one proton for secondary amines (s, N—H), 0.46–0.55, except for VII*k* which occurred at 0.33; all such protons could be eliminated by D_2O shake; *(e)* all $-CH_3$ groups one or more carbons removed from the amino nitrogen gave singlets or doublets as required, 0.90–1.0; for VII*b* and VII*c*, 2.25 and 2.13, respectively; and *(f)* the $-CH_2-$ groups appeared as complex multiples at 1.00–3.50 (including benzylic and CH indicated above) which varied in position with the nature of the *N*-substitutions and which integrated for the total number of protons required.

Table II—Monoamine Oxidase Inhibition Studies and Mouse Head Twitch Response

Compound	Name	Monoamine Oxidase Inhibition	Total Number of Head Twitches
VII*a*	2-(1-Indanyl)ethylamine	325	7
VII*b*	*N*-Methyl-2-(indanyl)-ethylamine	350	5
VII*c*	*N,N*-Dimethyl-2-(indanyl)ethylamine	145	21
VII*d*	*N*-[2-(1-Indanyl)ethyl]-piperidine	61	5
VII*e*	*N*-Propyl-2-(1-indanyl)-ethylamine	181	16
VII*f*	*N*-Isopropyl-2-(1-indanyl)-ethylamine	48	5
VII*g*	*N*-Butyl-2-(1-indanyl)-ethylamine	164	29
VII*h*	*N*-Isobutyl-2-(1-indanyl)-ethylamine	0	2
VII*i*	*N*-*sec*-Butyl-2-(1-indanyl)-ethylamine	73	5
VII*j*	*N*-Heptyl-2-(1-indanyl)-ethylamine	40	32
VII*k*	*N*-Cyclopentyl-2-(1-indanyl)ethylamine	0	2
XII	1-Methyl-D-lysergic acid butanolamide dimaleate	—	0
XIII	Iproniazid phosphate	100	87
	Control	0	11

PHARMACOLOGY

All compounds except VII*l*, VII*m*, and VII*n* were examined following the *in vitro* procedure of Wurtman and Axelrod (16) for monoamine oxidase inhibition and the *in vivo* mouse head twitch method of Corne *et al.* (17) for both monoamine oxidase inhibition and serotonin antagonism.

Monoamine Oxidase Inhibition (*In Vitro*)[2]—This method consists of incubating a mixture of radioactive tryptamine, rat liver homogenate, and a monoamine oxidase inhibitor for a suitable length of time, extracting the labeled indoleacetic acid formed, and then determining the level of radioactivity in the liquid *via* liquid scintillation spectrometry.

A male Holtzman rat was sacrificed by cervical dislocation, and the liver was rapidly excised and placed in crushed ice moistened with isotonic potassium chloride. A coaxial homogenizer was used to homogenize 200 mg of liver in 10 ml of cold isotonic potassium chloride. A 1.0-ml aliquot of the homogenate was withdrawn and homogenized with 9.0 ml of cold isotonic potassium chloride so that the final concentration of 2 mg/ml was obtained. To a 15-ml centrifuge tube containing 0.5 ml of 0.1 *M* phosphate buffer (pH 7.9), 0.05 ml of radiolabeled tryptamine (0.01 μCi/10^{-8} mole), 1.0 ml of inhibitor solution, and 4.2 ml of distilled water was added 0.25 ml of the rat liver homogenate. A blank was prepared containing all reagents but with 1.0 ml of water substituted for the inhibitor solution and 0.25 ml of distilled water substituted for the homogenate. A standard was prepared containing the homogenate and all reagents but with 1.0 ml of distilled water substituted for the inhibitor. The tubes were incubated in air for 20 min and then 2.0 ml of 2 *N* hydrochloric acid was added fol-

[2] All reagents used were analytical grade. Tryptamine-2-^{14}C was obtained from New England Nuclear Corp. Iproniazid phosphate was provided through the courtesy of Hoffmann-La Roche. The liquid scintillator solution was composed of 0.05% 1,4-bis-2-(5-phenyloxazolyl)benzene and 0.4% 2,5-diphenyloxazole in toluene. All test compounds were examined in the form of the hydrochloride salts. Counting vials were low potassium glass crystallite (A-3305), T. C. Wheaton Co. Samples were counted in a Packard Tri-Carb liquid scintillation spectrometer, model 3003.

lowed by 6.0 ml of toluene. The tubes were shaken by hand to facilitate extraction and then centrifuged for 10 min. A 4.0-ml aliquot of the organic layer was withdrawn and transferred to a counting vial containing 15 ml of liquid scintillation solution. The samples were counted for either 10 min or 10,000 counts, whichever was obtained first. The results obtained at 1×10^{-5} *M* concentration of inhibitor are listed in Table II.

Mouse Head Twitch (*In Vivo*)—5-Hydroxytryptophan[3] (X) produces a characteristic head twitch when injected into mice. The head twitch resembles a strong pinna reflex involving the whole head of the mouse but, unlike the pinna reflex, occurs without tactile stimulation (17). The twitch is due to a central action of 5-hydroxytryptamine (XI) formed by decarboxylation of X. The head twitch response in mice provides a simple and valuable preliminary response to assess the potency of potentiators and antagonists of the central action of XI.

Male albino mice weighing 20–25 g were used. Doses, given on the basis of milligrams of free base per kilogram of body weight, were as follow: 5 mg of 1-methyl-D-lysergic acid butanolamide dimaleate[4] (XII), 50 mg of iproniazid phosphate (XIII), 200 mg of X, and 15 mg of all test compounds.

Five mice were weighed and each was placed in an individual metal box with a wire mesh top. The five mice were given subcutaneous injections of the test compound, spacing the injections 3 min apart. Thirty minutes after giving the test compound, each animal was given X intraperitoneally; 24 min later each mouse was observed over 2 min and the number of head twitches exhibited was counted and recorded. Table II lists the total number of twitches observed for a group of five mice treated with the test compound. Three groups of five mice each received only X, and the total number of head twitches for all of these was averaged.

RESULTS

Several test compounds gave evidence of monoamine oxidase inhibition *in vitro* at concentrations of 1×10^{-5} *M*. Compounds VII*a* and VII*b* exhibited the greatest activity, being about 3.5 times as active as XIII, the reference compound. Only VII*h* and VII*k* gave evidence of being inactive. The remaining test compounds exhibited varying degrees of activity between these two extremes.

Several test compounds gave evidence of monoamine oxidase inhibition *in vivo* at 15 mg/kg. Increases in the number of twitches of 21, 29, and 32 for VII*c*, VII*d*, and VII*j*, respectively, as compared to the control value of 11 reflect monoamine oxidase inhibition by the procedure employed. Thus, these compounds are two or three times as active as the reference compound, XII. A decrease in the number of twitches in relation to the control (X only with no pretreatment gave 11 twitches/2 min/five mice) is indicative of serotonin antagonism; only VII*h* and VII*k* exhibited marked decreases in the number of twitches per mouse observed in the 2-min period as evidenced by two twitches for each compound; these were the most active compounds. Compounds VII*b*, VII*f*, and VII*g* gave only about half as many twitches as the control or five twitches for each of these compounds. These are only about half as active as the latter compounds.

The compounds listed in Table II plus Compound VII*l* were examined by Sobiski (18) for general activity on the central nervous system of mice. A brief summary of this study is given here. Preliminary evaluation suggested that several compounds possessed central myorelaxant and ataractic properties of the type exhibited by the minor tranquilizers. Compounds VII*d*, VII*h*, VII*k*, and VII*l* were active in preventing hindleg extension following intravenously administered pentylenetetrazol; evaluation of these compounds against diphenylhydantoin in the maximal electroshock test showed that VII*h*, VII*k*, and VII*l* were about equiactive with diphenylhydantoin. Compounds VII*a*, VII*d*, and VII*k* exhibited the ability to check hydrochloric acid-induced writhing when compared to morphine sulfate and aspirin, suggesting that they possess analgesic activity. It was not possible to reverse ptosis with any of these indan derivatives, indicating that the marked monoamine oxidase inhibition seen with these compounds *in vitro* was not reflected in this *in vivo* test. Details of the pharmacological evaluation of these compounds are described in Ref. 18.

[3] Sigma Chemical Co.
[4] Sandoz Pharmaceuticals.

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