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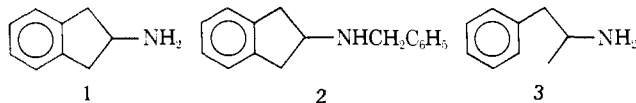
2-Aminoindans of Pharmacological Interest

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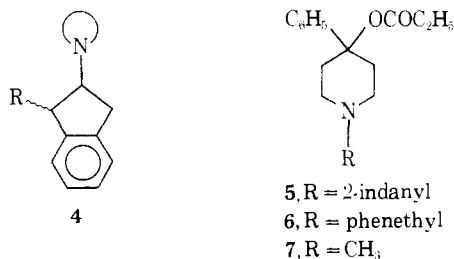
2-Aminoindans in which the amine moiety consists of various cyclic amine derivatives including morpholino, hexamethyleneimino (potential sympathomimetic agents), and 4-acyloxy-4-phenylpiperidino derivatives (potential analgetic agents) were prepared and tested for antiinflammatory, analgetic, pharmacodynamic, and neuropharmacologic activity. No marked antiinflammatory or blood pressure effects were noted. Compound 10j exhibits strong amphetamine type activity; 10h and 18c, respectively, possess analgetic activity approximately equal to and one-half that of meperidine.

2-Aminoindans have been noted to possess interesting biological properties. For example, 2-aminoindan (1) exhibits significant bronchodilating¹ and analgesic properties² and 2-benzylaminoindan (2) possesses significant bronchodilating properties.¹ Both 1 and 2 may be considered cyclic analogs of amphetamine (3).

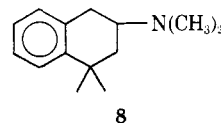


Because of (a) the limited information available on 1-(2'-indanyl) cyclic amine derivatives, (b) the pronounced analgesic activity of 2-aminoindan, and (c) other significant biological activity³ of existing 2-aminoindans, a number of 1-(2'-indanyl) cyclic amines 4 were investigated. Furthermore, 1-(2'-indanyl)-4-phenyl-4-piperidyl propionate (5) represents a conformationally restrained relative of the corresponding analgesic 6. The former also is a hybrid of 2-aminoindan and 1-methyl-4-phenyl-4-piperidyl propionate (7), both analgesics. In compounds such as 6, the *N*-arylalkyl substituent is free to assume

various conformations. In view of the variation of biological activity with changes in conformation of drug molecules, it was of interest to synthesize and to study pharmacologically compounds such as 4 and 5 in which the conformational variations have been restrained. The in-



vestigation of 4 (R = CH₃) was undertaken with the goal of producing derivatives in which rotation about the indan C-2 to nitrogen bond is restrained by steric interaction of the methyl group with the methylene hydrogens adjacent to the nitrogen. Further impetus for the synthesis of de-



† Abstracted in part from a dissertation submitted by E. S. to the Graduate School, University of Mississippi, in partial fulfillment of Ph.D. degree requirements, 1970.

Table I. 2-Aminoindenes 9 and Indans 10

No.	-N	Method	Yield, %	Mp, °C (recrystn solvent) ^a	Formula ^b
9a	Morpholino	A	100	196–197.5 (C–E)	C ₁₃ H ₁₅ NO ^c
9b	3-Azabicyclo[3.2.2]non-3-yl	A	93	150–152.5 dec (C–E)	C ₁₇ H ₂₁ N
9c	Hexamethylenimine	A	75	103.5–105 (C–E)	C ₁₅ H ₁₉ N ^c
9d	4-Hydroxypiperidino	A	97	137–139 dec (C–E)	C ₁₄ H ₁₇ NO
9e	4-Hydroxy-4-phenylpiperidino	A	95	181–183 dec (C–E)	C ₂₀ H ₂₁ NO
10a	Morpholino	B, C	57, 42	87.5–88 (H)	C ₁₃ H ₁₇ NO
10b	3-Azabicyclo[3.2.2]non-3-yl	B	52	88.5–89.5 (H)	C ₁₇ H ₂₃ N
10c	Hexamethylenimine	B	85	234–236 dec (A)	C ₁₅ H ₂₁ N · HCl
10d	4-Hydroxypiperidino	B	52	164–165 (MC–E)	C ₁₄ H ₁₉ NO
10e	4-Acetoxy-piperidino	E	60	92–93 (H)	C ₁₆ H ₂₁ NO ₂
10f	4-Hydroxy-4-phenylpiperidino	B, D	65, 36	155.5–157 (C–Et)	C ₂₀ H ₂₃ NO ^d
10g	4-Acetoxy-4-phenylpiperidino	E	55	247.5–248 dec (A) ^e	C ₂₂ H ₂₅ NO ₂ · HCl
10h	4-Propionyloxy-4-phenylpiperidino	E	50	236–236.5 dec (A) ^f	C ₂₃ H ₂₇ NO ₂ · HCl
10i	Piperidino	D	55	60–61 (H–Et)	C ₁₄ H ₁₉ N
10j	Pyrrolidino	D	56	46–47.5 (sublimed)	C ₁₃ H ₁₇ N ^g
10k	4-Morpholinocarbonylpiperidino	D	65	164–165 ^h	C ₁₉ H ₂₆ N ₂ O ₂
10l	4-Pyrrolidinocarbonylpiperidino	D	44	156–157 (Cy–B)	C ₁₃ H ₁₅ N ₂ O
10m	3-Pyrrolidinocarbonylpiperidino	D	25	247–249 (E–Et)	C ₁₉ H ₂₆ N ₂ O · HCl
10n	4-Ethylenedioxy-piperidino	D	35	96.8–98 ⁱ	C ₁₅ H ₂₁ NO ₂

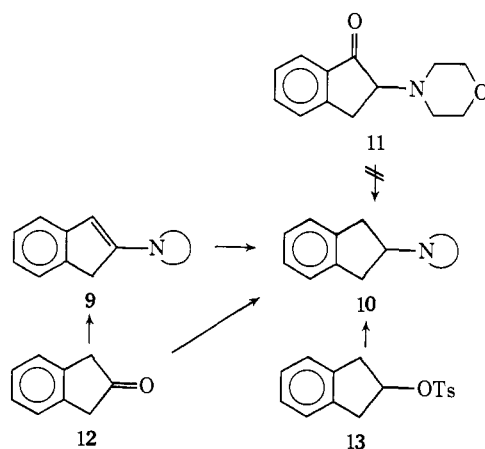
^aA = acetonitrile; B = benzene; C = chloroform; Cy = cyclohexane; E = ethanol; Et = ether; H = *n*-hexane; MC = methylene chloride. ^bInfrared and nmr spectra are consistent with the assigned structures; analyzed for C, H, and N. ^cReference 6. ^dC: calcd, 81.87; found, 81.28. ^eBase, mp 175–177° (C). ^fBase, mp 130–131.5° (Et). ^gC: calcd, 83.37; found, 83.96. H: calcd, 9.15; found, 8.65. ^hEluted through neutral alumina (grade I) using methylene chloride-ethanol (3:2, v/v) as eluent. ⁱEluted through neutral alumina (grade I) using *n*-hexane as eluent.

rivatives of general structure 4 is gained from the report of White⁴ and coworkers that the structurally similar tetralin derivative 8 possesses potent analgesic properties.

The synthesis of the 2-aminoindans 10 and 18 was accomplished as shown in Schemes I and II by the catalytic reduction of the 1-(2'-indenyl) cyclic amines 9 and 17 which were prepared by the condensation of the appropriate cyclic amine with 2-indanones 12 and 16^{5,6} in accordance with the procedure of Blomquist and Moriconi.⁶ Appropriate physical data are presented in Table I.

An alternate synthesis of 1-(2'-indanyl)morpholine (10a) was accomplished by the reaction of morpholine with 2-indanyl tosylate (13)⁷ according to a procedure similar to that used by Sekera and Marvel.⁸ The reduction of a mixture of 2-indanone (12) and various heterocyclic amines also was observed to proceed readily to give 10 in good yield. Attempts to prepare 10a from 2-morpholino-1-indanone (11) by catalytic hydrogenation and other reduction procedures^{9–11} were unsuccessful.

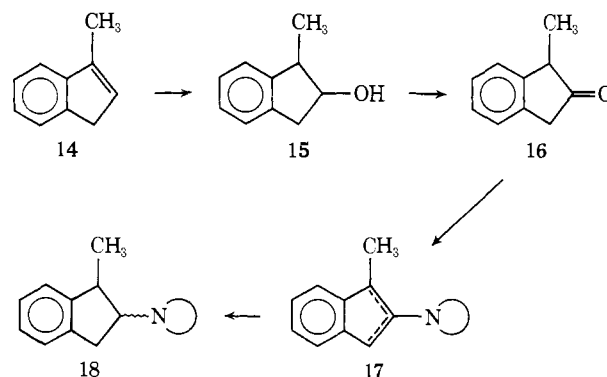
Scheme I



The synthesis of 1-methyl-2-indanol (15) was accom-

plished by methylation of indene to give 14, followed by hydroboration using a procedure utilized by Brown and Rao.¹² The oxidation of the alcohol 15 using Jones reagent according to the procedure described by Djerassi and associates¹³ provided 1-methyl-2-indanone (16) along with *o*-acetylphenylacetic acid. Contrary to the observation reported by Blomquist and Moriconi,⁶ the 1-methyl-2-indanone obtained by this method appears to be relatively stable. No decomposition was noted after 3 months at 0°.

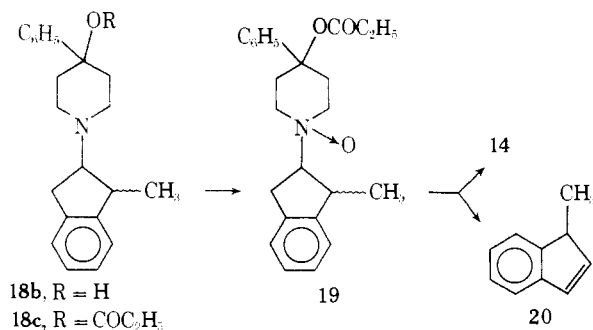
Scheme II



The stereochemistry of 1-(1'-methyl-2'-indanyl)-4-phenyl-4-piperidyl propionate (18c) was investigated *via* the Cope reaction¹⁴ since the nmr spectrum was not sufficiently useful to permit delineation of the structure. Moreover, Huebner and associates¹⁵ have reported that the use of nmr data for stereochemical investigation of 1,2-disubstituted indans may not be unequivocal.

The *N*-oxide 19 was prepared by the method of Cope and Ciganek.¹⁶ Pyrolysis was performed by injection of an ether solution of the *N*-oxide into a gas chromatograph with the injection chamber at 200°. The respective methylindenes were confirmed by injection of authentic samples. The composition of the mixture formed from 19 was found to be approximately 86% 1-methylindene (20) and

14% 3-methylindene (14). From the nature of the Cope reaction and consideration of molecular models of 19, this ratio of methylindenes indicates a predominance of the *cis* isomer of 18c.



Biological Results. All of the compounds in Table I, with the exception of 9a-c and 10j, were tested for anti-inflammatory activity using the Evans blue carrageenan pleural fusion model¹⁷ and found to be inactive at an oral dose of 316 mg/kg. Little or no activity against cathepsin D¹⁸ at 1.00 mM concentration was observed for 10c, 10f, 10k, and 10m.

Compounds 10b, 10c, 10e, 10k, 10m, and 17a, screened for pharmacodynamic effects in acute anesthetized dogs at iv doses of 1-8 mg/kg, caused a slight decrease in arterial pressure of short duration with the exception of 10m which was of long duration. An increase in respiratory rate and minute volume was noted with 10b, 10c, 10e, and 18a. The heart rate and intestinal tone and motility were decreased with 10k and 10m. Some evidence of adrenergic blockage was observed with 10e and 10m.

Compounds 10j, 10k, 10m, and 18a were screened ip (six mice per dose) for neuropharmacologic activity.¹⁹ A strong amphetamine-type activity was noted with 10j at 30 mg/kg (1 death), 10 mg/kg (1 death), and 3 mg/kg (no deaths). A long duration of activity occurred at 10 mg/kg. Mild CNS depression occurred with 10k at 100 mg/kg (no deaths); 30 mg/kg produced no apparent effects. Mild to moderate CNS stimulation was produced by 18a at 100 mg/kg (no deaths); 30 mg/kg resulted in mild sedation. Compound 10m at 100 mg/kg (4 deaths) produced mild clonic convulsions and loss of righting reflex; at 30 mg/kg (no deaths) transient clonic convulsions and disorientation occurred.

The method of Nilson²⁰ as modified by Funderburk, *et al.*,²¹ was used to determine ip analgetic activity of 10h (ED₅₀ 8.3 mg/kg), 10g (inactive at 10 mg/kg and only slightly active at 20 mg/kg), and 18c (ED₅₀ 15.0 mg/kg). The LD₅₀ of 10h and 18c was observed to be 325 and 350 mg/kg, respectively. Marked CNS depressant activity was noted with 18c at analgetic doses.

Additional studies are necessary in order to delineate the relationship of stereochemistry in the amphetamine series to biological activity; however, the marked amphetamine type activity of 10j suggests that conformational rigidity in the amphetamine series may have a positive effect on activity. The conformational rigidity of 10h, on the other hand, has an adverse effect on analgetic activity since 10h is about equal to, whereas 6 is approximately 25 times as active as, meperidine.²² Placing further restrictions on the flexibility of the molecule as in 18c causes a further reduction in analgetic activity. On the basis of the limited data available it appears that conformational flexibility of the *N*-aralkyl group is important in analgetics related to 6. Studies are continuing in order to more clearly define these conformational requirements.

Experimental Section†

1-(2'-Indenyl) Cyclic Amines 9 (Table I). Method A. A slightly modified procedure of Blomquist and Moriconi⁹ was followed. 2-Indanone and the appropriate secondary amine were respectively dissolved in dry C₆H₆ (20 ml/0.01 mol of 2-indanone) and refluxed until H₂O ceased to collect in a H₂O separator. The solution was concentrated to about one-third volume and cooled. The product was removed by filtration and recrystallized or recovered as an oil by evaporation of the solvent.

1-(2'-Indanyl) Cyclic Amines 10 (Table I). Method B. The enamine was dissolved in warm glacial HOAc or absolute EtOH and hydrogenated over Pd/C or PtO₂ (preferred) on a Parr hydrogenator at approximately 50 psi and at 40-60° for 24 hr. The catalyst was removed by filtration and the solvent evaporated under water aspirator pressure. The residual HOAc was neutralized with 10% Na₂CO₃ and the product extracted into CHCl₃. The CHCl₃ solution was washed with H₂O and dried over Na₂SO₄. Evaporation of the solvent and recrystallization of the residue gave the desired product. When EtOH was used as solvent, the product was recovered as in method D.

Method C. A mixture of 3 ml (0.034 mol) of morpholine, 30 ml of toluene, 0.5 g of K₂CO₃, and 5 g (0.017 mol) of 2-indanyl tosylate (prepared by the method of Bodot, Jullien, and LeBlanc⁷ from 2-indanol) was refluxed for about 24 hr. The reaction was followed by tlc [Brinkmann's MN silica gel S-HR sheets were used; chromatograms were developed with CHCl₃-EtOH (10:1) and visualized in an iodine chamber] until no tosylate could be detected. The mixture thereafter was treated with 40 ml of CHCl₃, filtered, washed with H₂O, and dried over Na₂SO₄. Evaporation of the solvent gave a product with a melting point and infrared spectrum identical with that obtained *via* method B.

Method D. A modified procedure similar to that described by Hancock and Cope²³ was used. A solution of 2-indanone (0.038 mol) and 0.05 mol of the appropriate secondary amine in absolute EtOH was hydrogenated in the presence of PtO₂ on a Parr hydrogenator at approximately 50 psi at room temperature for 24 hr. The catalyst was removed by filtration and the solvent evaporated. The residue was dissolved in hexane and eluted two times with hexane through a neutral alumina (grade I) column. When glacial HOAc was used as the solvent, the product was obtained as described in method B.

1-(2'-Indanyl)-4-acyloxypiperidines 10e,g,h (Table I). Method E. A mixture of the appropriate alcohol, C₆H₆ (0.003 mol of alcohol/10 ml of C₆H₆), 0.02 mol of C₅H₅N, and excess anhydride (molar ratio of alcohol to anhydride, 1:10) was refluxed for 1-5 days. The reaction was followed by tlc as described in method C until the alcohol was no longer detected. The mixture was then concentrated under reduced pressure. The residue was treated with cold 10% K₂CO₃, washed with H₂O, and extracted with CHCl₃. The extract was treated with a mixture of activated charcoal and grade I neutral alumina (1:1, wt/wt), warmed, and filtered. Evaporation of the CHCl₃ and recrystallization of the residue gave the desired esters.

The hydrochlorides were prepared by passing HCl through a solution of the ester in C₆H₆.

3-Methylindene (14). A procedure resembling that described by Thiele and Buhner²⁴ was used. A stirred solution of 100 g (0.86 mol) of indene, 800 ml of dry Et₂O, and 130 g (0.92 mol) of CH₃I was treated in portions, *via* Gooch addition technique, with 150 g (1.34 mol) of *tert*-BuOK. The reaction mixture was stirred overnight, washed with H₂O, and dried over MgSO₄. Evaporation of the Et₂O produced an oil which was distilled through a spinning band column to give 66 g (64%) of product, bp 80-84° (18 mm) [lit.²⁵ bp 76-78° (11 mm)]. Glc indicated 96% purity; retention volume was identical with 3-methylindene synthesized by a method similar to that described by Elsner and Parker²⁶ for the synthesis of alkylindenes; ir (CS₂) was identical with that reported for 3-methylindene by the American Petroleum Insti-

† All melting points were taken on a Thomas-Hoover Uni-melt capillary melting point apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer 137 or 257 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60A or a Jeolco C-60-HI, spectrometer. The nmr sample solutions consisted of 50-100 mg of a sample per 0.5 ml of solvent with tetramethylsilane as the internal reference. Unless otherwise stated all glc analyses were performed on a Perkin-Elmer 900 gas chromatograph fitted with flame ionization detectors and columns (213 × 0.513 cm) packed with Chromosorb W containing a concentration of 10% SE-30 (OH).

tute;²⁷ nmr (CCl₄) was identical with that of Bosch and Brown²⁸ for 3-methylindene.

1-Methyl-2-indanol (15). The procedure of Brown and Rao¹² for direct conversion of olefins to alcohols was used. To a mixture of 10 g (0.077 mol) of 3-methylindene, 14 g of diglyme, and 1 g (0.03 mol) of NaBH₄ was added a solution of 4.8 g (0.034 mol) of BF₃-Et₂O in 7 ml of diglyme while cooling the reaction vessel with H₂O. After standing for 1 hr at room temperature, the mixture was treated dropwise with 10 ml of H₂O, followed by 20 ml of 3 N NaOH, and thereafter with 20 ml of 30% H₂O₂ at such a rate as to maintain a moderate reflux. The mixture was treated with 80 ml of ice H₂O and extracted with Et₂O. The extract was washed with H₂O, dried over MgSO₄, filtered, and evaporated. The residue was distilled to give 9.2 g (80%) of product, bp 70-72° (0.25 mm), 120-124° (15 mm). Glc analysis (using Carbowax on Chromosorb W) indicated one significant component.

A 3,5-dinitrobenzoate was prepared in the usual manner and recrystallized from a mixture of EtOH and acetone: mp 151-152°. Anal. (C₁₇H₁₄N₂O₆) C, H, N.

1-Methyl-2-indanone (16). A procedure similar to that described by Diersassi and associates¹³ using Jones reagent was utilized. A cold (Dry Ice-acetone bath) solution of 10 g (0.068 mol) of 15 in 800 ml of acetone was stirred rapidly and treated in one portion with 32 ml of standard Jones reagent. The mixture was allowed to warm to 0°, treated with 500 ml of ice H₂O, and extracted with Et₂O. The ether extract was washed with H₂O, dried over MgSO₄, filtered, and evaporated to produce an oil containing a white solid. The oil was extracted with cyclohexane leaving a solid (1.7 g) which was collected by filtration. The cyclohexane extract was evaporated and the residue distilled to yield 5.3 g (53%) of product, bp 108-111° (15 mm). Crystallization of the oil from cyclohexane gave a solid, mp 59.5-61.5° (lit.²⁹ mp 62-63°). A semicarbazone was prepared in the usual manner and recrystallized from Et₂O-EtOH, mp 175-177° (lit.^{6,28} mp 195°). Anal. (C₁₁H₁₃N₃O) C, H, N.

Recrystallization of the cyclohexane-insoluble residue from EtOAc-EtOH gave white prisms, mp 164.5-165.5° [lit.³⁰ mp (for *o*-acetylphenylacetic acid) 165-166°].

1-(1'-Methyl-2'-indanyl)morpholine (18a). A solution of 22 ml of C₆H₆, 22 ml of C₇H₈, 2.5 g (0.017 mol) of 16, and 1.7 g (0.020 mol) of morpholine was refluxed until H₂O generation ceased (3-4 hr). Thereafter, the solvents were distilled to leave a viscous residue.

The enamine was dissolved in 50 ml of absolute EtOH, treated with 0.3 g of PtO₂, and hydrogenated on a Parr low-pressure hydrogenator at 50 psi and at 40°. Filtration of the mixture and evaporation of the EtOH gave an oil which was distilled to yield 2.6 g (72%) of 20a, bp 85° (0.025 mm); glc analysis indicated the presence of a single component. Anal. (C₁₄H₁₉NO) C, H, N.

1-(1'-Methyl-2'-indanyl)-4-hydroxy-4-phenylpiperidine Hydrochloride (18b). A solution of 44 ml of C₆H₆, 44 ml of C₇H₈, 5.0 g (0.034 mol) of 16, and 6.5 g (0.037 mol) of 4-hydroxy-4-phenylpiperidine was refluxed overnight and then evaporated to dryness to give a viscous oil. A small portion for nmr determination was eluted through neutral alumina (grade I) using CH₂Cl₂ as eluent.

The crude enamine was dissolved in 100 ml of glacial HOAc and hydrogenated at 60° for approximately 60 hr in the usual manner using 0.3 g of PtO₂ catalyst. Filtration of the mixture and evaporation of the solvent produced an oil which was treated with 100 ml of 5% Na₂CO₃. The aqueous phase was decanted and the gummy residue was treated with 75 ml of 6 N HCl. The aqueous phase was again decanted and the residue was washed with ether, treated with dilute NaOH, and extracted into Et₂O. The extract was dried over MgSO₄ and evaporated to give 5.2 g (56%) of an amber glass. Elution through 63 g of neutral alumina grade I using CHCl₃-Et₂O (5:16) as eluent furnished 3 g of the base. A hydrochloride was prepared in the usual manner and recrystallized from AcOEt-MeOH: mp 230-230.5°. Anal. (C₂₁H₂₆NOCl) C, H, N.

1-(1'-Methyl-2'-indanyl)-4-phenyl-4-piperidyl Propionate Hydrochloride (18c). In accordance with method E, 1.1 g (0.004 mol) of 18b (free base), 6 ml of C₇H₈, 1.2 g of C₅H₅N, and 5 g (0.04 mol) of propionic anhydride produced 1.26 g of an oil which was eluted with benzene through 18.8 g (7 × 2 cm) of neutral grade I alumina to give 0.68 g (46%) of a yellow oil.

A hydrochloride was prepared in the usual manner and recrystallized from Et₂O-MeOH: mp 211-212.5°. Anal. (C₂₄H₃₀NO₂Cl) C, H, N.

1-(1'-Methyl-2'-indanyl)-4-phenyl-4-piperidyl Propionate N-Oxide (19) and Pyrolysis. A solution of 0.1 g of 18c in 1 ml of absolute EtOH was treated with 0.5 ml of H₂O₂ similarly to the procedure described by Cope and Ciganek¹⁶ and allowed to stand for 48 hr. The solid was removed by filtration and dried *in vacuo* for 48 hr at room temperature over P₂O₅. The material appeared gummy and no further attempt at purification was made. The solid was dissolved in ether and injected into a gas chromatograph under the following conditions: (a) injector 200°, (b) column 150°, and (c) manifold 200°. The methylindenes generated were analyzed as 86% 1-methylindene and 14% 3-methylindene. Authentic samples of the two isomeric indenenes were found not to isomerize under these conditions.

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