Org. Chem., 28, 178 (1963).
(37) R. Schwyzer, R. Schiller, S. Seelig, and G. Sayers, *FEBS Lett.*, 19, 229 (1971).
(38) S. Seelig and G. Sayers, *Arch. Biochem. Biophys.*, 154, 230 (1973).
(39) M. W. Draper, R. B. Merrifield, and M. A. Rizack, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 32, 490 (1973).
(40) R. B. Merrifield, *Advan. Enzymol.*, 32, 221 (1969).
(41) J. Blake and C. H. Li, *J. Amer. Chem. Soc.*, 90, 5882 (1968).
(42) G. R. Marshall in "Pharmacology of Hormonal Polypeptides and Proteins," N. Back, L. Martini, and R. Paoletti, Ed., Plenum Press, New York, N. Y., 1968, p 48.
(43) L. D. Markley and L. C. Dorman, *Tetrahedron Lett.*, 1787 (1970).
(44) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jap.*, 40, 2164 (1967).
(45) J. Lenard and A. B. Robinson, *J. Amer. Chem. Soc.*, 89, 181 (1967).
(46) M. Rodbell, *J. Biol. Chem.*, 239, 375 (1964).
(47) R. J. Ho, *Anal. Biochem.*, 36, 105 (1970).
(48) M. S. Raben, R. Landolt, F. A. Smith, K. Hofmann, and H. Yajima, *Nature (London)*, 189, 681 (1961).
(49) E. J. Ariens and A. M. Simonis, *J. Pharm. Pharmacol.*, 16, 137 (1964).
(50) C. H. Li and W. Oelofsen in "The Adrenal Cortex," A. B. Eisenstein, Ed., Little, Brown and Co., Boston, Mass., 1967, p 196.
(51) H. Yajima, Y. Okada, Y. Kinomura, and H. Minami, *J. Amer. Chem. Soc.*, 90, 527 (1968).
(52) J. Ramachandran and V. Lee, *Biochem. Biophys. Res. Commun.*, 41, 358 (1970).
(53) C. H. Li, J. Ramachandran, and D. Chung, *J. Amer. Chem. Soc.*, 86, 2711 (1964).
(54) K. Hofmann and H. Yajima, *ibid.*, 83, 2289 (1961).
(55) M. Nakamura, *J. Biochem. (Tokyo)*, 71, 1029 (1972).
(56) P. A. Desaulles and W. Rittel, *Proc. Roy. Soc. Med.*, 60, 906 (1967).
(57) B. Riniker and W. Rittel, *Helv. Chim. Acta*, 53, 513 (1970).
(58) R. Maier, P. L. Barthe, L. Schenkel-Hulliger, and P. A. Desaulles, *Acta Endocrinol. (Copenhagen)*, 68, 458 (1971).
(59) G. I. Tesser and J. T. Buis, *Recl. Trav. Chim. Pays-Bas*, 90, 444 (1971).
(60) K. Inouye, A. Tanaka, and H. Otsuka, *Bull. Chem. Soc. Jap.*, 43, 1163 (1970).
(61) K. Inouye, K. Watanabe, K. Namba, and H. Otsuka, *ibid.*, 43, 3873 (1970).
(62) M. Ide, A. Tanaka, M. Nakamura, and T. Okabayashi, *Arch. Biochem. Biophys.*, 149, 189 (1972).
(63) M. Nakamura, A. Tanaka, M. Hirate, and S. Inoue, *Endocrinol. Jap.*, 19, 383 (1972).
(64) M. Nakamura and A. Tanaka, *ibid.*, 19, 395 (1972).
(65) M. Nakamura, M. Ide, T. Okabayashi, and A. Tanaka, *ibid.*, 19, 443 (1972).
(66) M. Fujino, C. Hatanaka, and O. Nishimura, *Chem. Pharm. Bull.*, 18, 771, 1288 (1970).
(67) R. Geiger, *Justus Liebigs Ann. Chem.*, 750, 165 (1971).
(68) B. F. Gisin, *Helv. Chim. Acta*, 56, 1476 (1973).
(69) H. Matsubara and R. M. Sasaki, *Biochem. Biophys. Res. Commun.*, 35, 175 (1969).
(70) V. P. Dole, *J. Clin. Invest.*, 35, 150 (1956).

2-Aminoindans of Pharmacological Interest

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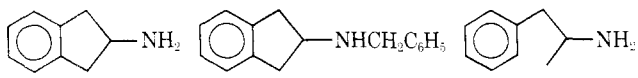
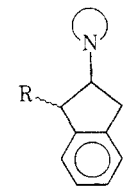
2-Aminoindans in which the amine moiety consists of various cyclic amine derivatives including morpholino, hexamethyleneimino (potential sympathomimetic agents), and 4-acyloxy-4-phenylpiperidino derivatives (potential analgetic agents) were prepared and tested for antiinflammatory, analgetic, pharmacodynamic, 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 bronchodilating[1] and analgesic properties[2] and 2-benzylaminoindan (**2**) possesses significant bronchodilating properties.[1] Both **1** and **2** may be considered cyclic analogs of amphetamine (**3**).

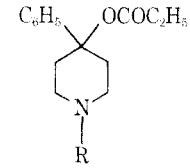


1 **2** **3**

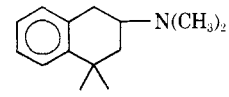
Because of (a) the limited information available on 1-(2′-indanyl) cyclic amine derivatives, (b) the pronounced analgesic activity of 2-aminoindan, and (c) other significant biological activity[3] of existing 2-aminoindans, a number of 1-(2′-indanyl) cyclic amines **4** were investigated. Furthermore, 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 investigation of **4** (R = CH_3) 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-



4



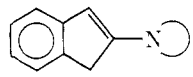
5, R = 2-indanyl
6, R = phenethyl
7, R = CH_3



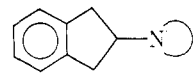
8

† 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**



9



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	Hexamethyleneimino	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	Hexamethyleneimino	B	85	234–236 dec (A)	$C_{15}H_{21}N \cdot HCl$
10d	4-Hydroxypiperidino	B	52	164–165 (MC–E)	$C_{14}H_{19}NO$
10e	4-Acetoxypiperidino	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]	$C_{22}H_{25}NO_2 \cdot HCl$
10h	4-Propionoxy-4-phenylpiperidino	E	50	236–236.5 dec (A)[f]	$C_{23}H_{27}NO_2 \cdot HCl$
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]	$C_{19}H_{26}N_2O_2$
10l	4-Pyrrolidinocarbonylpiperidino	D	44	156–157 (Cy–B)	$C_{19}H_{26}N_2O$
10m	3-Pyrrolidinocarbonylpiperidino	D	25	247–249 (E–Et)	$C_{19}H_{26}N_2O \cdot HCl$
10n	4-Ethylenedioxypiperidino	D	35	96.8–98[i]	$C_{16}H_{21}NO_2$

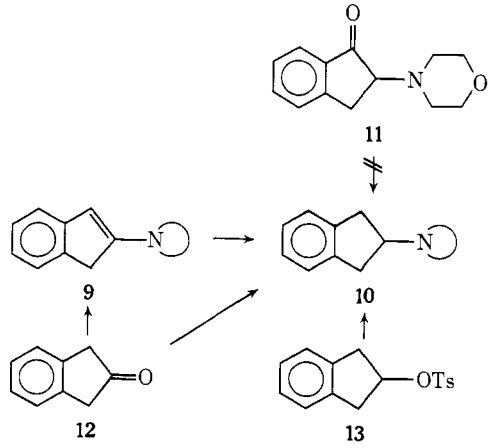
[a] A = acetonitrile; B = benzene; C = chloroform; Cy = cyclohexane; E = ethanol; Et = ether; H = *n*-hexane; MC = methylene chloride. [b] Infrared and nmr spectra are consistent with the assigned structures; analyzed for C, H, and N. [c] Reference 6. [d] C: calcd, 81.87; found, 81.28. [e] Base, mp 175–177° (C). [f] Base, mp 130–131.5° (Et). [g] C: calcd, 83.37; found, 83.96. H: calcd, 9.15; found, 8.65. [h] Eluted through neutral alumina (grade I) using methylene chloride–ethanol (3:2, v/v) as eluent. [i] Eluted through neutral alumina (grade I) using *n*-hexane as eluent.

rivatives of general structure 4 is gained from the report of White[4] 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.

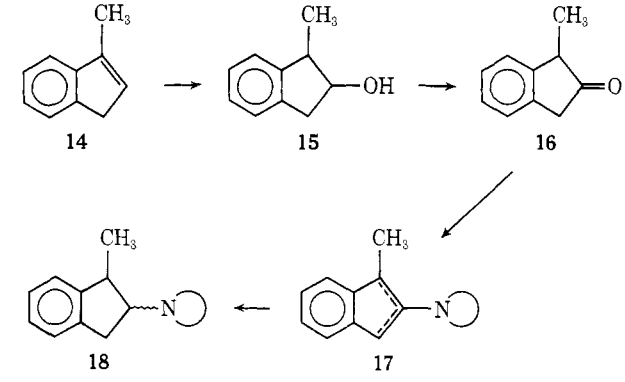
An alternate synthesis of 1-(2′-indanyl)morpholine (**10a**) was accomplished by the reaction of morpholine with 2-indanyl tosylate (13)[7] according to a procedure similar to that used by Sekera and Marvel.[8] The reduction of a mixture of 2-indanone (12) and various heterocyclic amines also was observed 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 accomplished 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 associates[13] 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°.

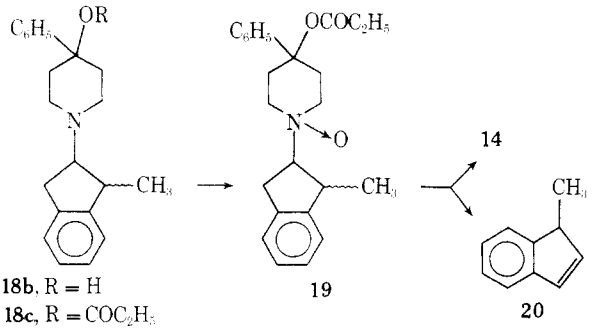
Scheme II



The stereochemistry of 1-(1′-methyl-2′-indanyl)-4-phenyl-4-piperidyl propionate (**18c**) was investigated *via* the Cope reaction[14] since the nmr spectrum was not sufficiently useful to permit delineation of the structure. Moreover, Huebner and associates[15] 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**.



18b, R = H
18c, R = COC_2H_5

19 20

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 model[17] and found to be inactive at an oral dose of 316 mg/kg. Little or no activity against cathepsin D[18] at 1.00 m*M* 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 blockade 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 Nilson[20] as modified by Funderburk, *et al.*,[21] was used to determine ip analgetic activity of **10h** (ED_{50} 8.3 mg/kg), **10g** (inactive at 10 mg/kg and only slightly active at 20 mg/kg), and **18c** (ED_{50} 15.0 mg/kg). The LD_{50} 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 Moriconi[6] was followed. 2-Indanone and the appropriate secondary amine were respectively dissolved in dry C_6H_6 (20 ml/0.01 mol of 2-indanone) and refluxed until H_2O ceased to collect in a H_2O 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 PtO_2 (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% Na_2CO_3 and the product extracted into $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and dried over Na_2SO_4. 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 K_2CO_3, and 5 g (0.017 mol) of 2-indanyl tosylate (prepared by the method of Bodot, Jullien, and LeBlanc[7] 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 $CHCl_3$–EtOH (10:1) and visualized in an iodine chamber] until no tosylate could be detected. The mixture thereafter was treated with 40 ml of $CHCl_3$, filtered, washed with H_2O, and dried over Na_2SO_4. 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 Cope[23] 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 PtO_2 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, C_6H_6 (0.003 mol of alcohol/10 ml of C_6H_6), 0.02 mol of C_5H_5N, 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% K_2CO_3, washed with H_2O, and extracted with $CHCl_3$. 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 $CHCl_3$ and recrystallization of the residue gave the desired esters.

The hydrochlorides were prepared by passing HCl through a solution of the ester in C_6H_6.

3-Methylindene (14). A procedure resembling that described by Thiele and Buhner[24] was used. A stirred solution of 100 g (0.86 mol) of indene, 800 ml of dry Et_2O, and 130 g (0.92 mol) of CH_3I 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 H_2O, and dried over $MgSO_4$. Evaporation of the Et_2O 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 Parker[26] for the synthesis of alkylindenes; ir (CS_2) 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-HL 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 (CCl_4) was identical with that of Bosch and Brown[28] for 3-methylindene.

1-Methyl-2-indanol (15). The procedure of Brown and Rao[12] 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 $NaBH_4$ was added a solution of 4.8 g (0.034 mol) of BF_3-Et_2O in 7 ml of diglyme while cooling the reaction vessel with H_2O. After standing for 1 hr at room temperature, the mixture was treated dropwise with 10 ml of H_2O, followed by 20 ml of 3 *N* NaOH, and thereafter with 20 ml of 30% H_2O_2 at such a rate as to maintain a moderate reflux. The mixture was treated with 80 ml of ice H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, 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.* ($C_{17}H_{14}N_2O_6$) C, H, N.

1-Methyl-2-indanone (16). A procedure similar to that described by Djersassi and associates[13] 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 H_2O, and extracted with Et_2O. The ether extract was washed with H_2O, dried over $MgSO_4$, 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 Et_2O-EtOH, mp 175–177° (lit.[6,28] mp 195°). *Anal.* ($C_{11}H_{13}N_3O$) 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 C_6H_6, 22 ml of C_7H_8, 2.5 g (0.017 mol) of **16**, and 1.7 g (0.020 mol) of morpholine was refluxed until H_2O 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 PtO_2, 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.* ($C_{14}H_{19}NO$) C, H, N.

1-(1′-Methyl-2′-indanyl)-4-hydroxy-4-phenylpiperidine Hydrochloride (18b). A solution of 44 ml of C_6H_6, 44 ml of C_7H_8, 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 CH_2Cl_2 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 PtO_2 catalyst. Filtration of the mixture and evaporation of the solvent produced an oil which was treated with 100 ml of 5% Na_2CO_3. 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 Et_2O. The extract was dried over $MgSO_4$ and evaporated to give 5.2 g (56%) of an amber glass. Elution through 63 g of neutral alumina grade I using $CHCl_3$-Et_2O (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.* ($C_{21}H_{26}NOCl$) 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 C_7H_8, 1.2 g of C_5H_5N, 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 Et_2O–MeOH: mp 211–212.5°. *Anal.* ($C_{24}H_{30}NO_2Cl$) 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 H_2O_2 similarly to the procedure described by Cope and Ciganek[16] and allowed to stand for 48 hr. The solid was removed by filtration and dried *in vacuo* for 48 hr at room temperature over P_2O_5. 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 indenes were found not to isomerize under these conditions.

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References

(1) N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).
(2) L. B. Witkin, C. F. Huebner, F. Goldi, E. O'Keefe, P. Spitaletta, and A. J. Plummer, *J. Pharmacol.*, **133**, 400 (1961).
(3) C. R. Ganellin, *Advan. Drug Res.*, **4**, 163 (1967).
(4) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunwald, and A. I. White, *J. Pharm. Sci.*, **58**, 340 (1969).
(5) W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).
(6) A. I. Blomquist and E. J. Moriconi, *ibid.*, **26**, 3761 (1961).
(7) H. Bodot, J. Jullien, and E. Leblanc, *Bull. Soc. Chim. Fr.*, 41 (1962).
(8) V. C. Sekera and C. S. Marvel, *J. Amer. Chem. Soc.*, **55**, 346 (1933).
(9) L. F. Fieser and R. G. Kennelly, *ibid.*, **57**, 1611 (1935).
(10) Huang-Minlon, *ibid.*, **68**, 2487 (1946).
(11) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *ibid.*, **84**, 1734 (1962).
(12) H. C. Brown and S. Rao, *ibid.*, **81**, 6433 (1959).
(13) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(14) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 361 (1960).
(15) C. F. Huebner, E. M. Donaghur, C. J. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.*, **35**, 1149 (1970).
(16) A. C. Cope and E. Ciganek, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 612.
(17) L. F. Sancillo, and A. Fishman, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 563 (1971).
(18) A. J. Anderson, *Biochem. Pharmacol.*, **17**, 2253 (1968).
(19) S. Irvin, *Psychopharmacologia*, **13**, 222 (1968).
(20) P. L. Nilson, *Acta. Pharmacol. Toxicol.*, **18**, 10 (1961).
(21) W. H. Funderburk, M. H. Foxwell, D. N. Johnson, and J. W. Ward, *Arch. Int. Pharmacodyn. Ther.*, **178**, 446 (1969).
(22) P. A. J. Jansen and N. B. Eddy, *J. Med. Chem.*, **2**, 31 (1960).
(23) E. M. Hancock and A. C. Cope, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 501.
(24) J. Thiele and B. Buhner, *Justus Liebigs Ann. Chem.*, **347**, 266 (1906).
(25) W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Amer. Chem. Soc.*, **78**, 1440 (1956).
(26) B. B. Elsner and K. J. Parker, *J. Chem. Soc.*, 592 (1957).
(27) R. D. Rossini, Ed., "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," American Petroleum Institute Research Project 44, Carnegie Press, Pittsburgh, Pa., 1953.
(28) A. Bosch and R. K. Brown, *Can. J. Chem.*, **42**, 1718 (1964).
(29) O. Wallach and E. Beschke, *Justus Liebigs Ann. Chem.*, **336**, 6 (1904).
(30) H. Weissmann and B. Weissmann, *J. Org. Chem.*, **18**, 30 (1953).