Synthesis of Cyclopentano-1,2,3,4-tetrahydroisoquinolines. Novel Heterocyclic Systems

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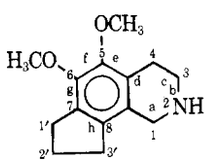
The synthesis of the previously unreported dimethoxy-substituted 5,6-cyclopentano[*f*]- and 7,8-cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinolines is described. Following numerous attempts to synthesize these new ring systems from various indan derivatives using standard isoquinoline ring closures, a procedure involving the acid-catalyzed Pictet-Spengler closure of the Schiff base of 4,5-dimethoxy-6- (and 7-) aminoethylindan was developed. The use of the chemical shift reagent $Eu(DPM)_3$ was of particular importance in the elucidation of the structures of the intermediate 4,5-dimethoxyindan-6- (and 7-) aldehydes (**11** and **10**).

Our continued interest in heterocycles of medicinal interest[1] has more recently prompted an investigation of the synthesis of the previously unreported tricyclic cyclopentano-1,2,3,4-tetrahydroisoquinolines having the cyclopentane ring at the 7,8 (*h*) (**1**) and 5,6 (*f*) (**2**) positions. The initial approach involved attempts to synthesize the cited compounds by the addition of the nitrogen-containing ring to an indan system by way of a Pictet–Spengler type ring closure of compound **3** shown below. Attempts were also made to effect ring closure on the acetamido analog **4** using the Bischler–Napieralski method.



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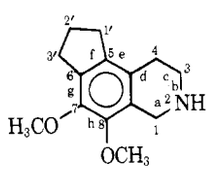

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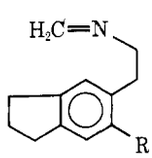

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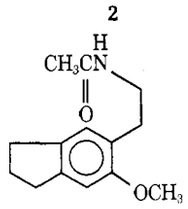


4

R = CH_3, OCH_3

Repeated attempts varying conditions of temperature, time, and solvent as well as closing reagent yielded no identifiable ring-closed product. However, utilization of the Pictet–Spengler reaction on 4,5-dimethoxyindan (**9**) yielded the sought products in respectable yields. The overall reaction sequence starting from 2,3-dimethoxybenzaldehyde is shown in Scheme I. Assignment of the position of the aldehyde grouping in the isomeric aldehydes **10** and **11** was made on the basis of their nmr spectra. The solid aldehyde **10**, which crystallized from the isomeric mixture, showed signals (CCl_4) at δ 2.02 (m, 2, CH_2), 2.84 (t, 2, CH_2), and 3.15 (t, 2, CH_2) corresponding to the methylenes of the cyclopentane ring at positions 2, 3, and 1, respectively. Addition of a chemical shift reagent $Eu(DPM)_3$ very clearly separated these methylene signals to produce peaks at δ 2.66 (m, 2, 2-CH_2), 3.61 (t, 2, 3-CH_2), 4.66 (t, 2, 1-CH_2). The liquid aldehyde (**11**) on the other hand showed only two signals for the methylenes of the cyclopentane ring; one at δ 2.04 (m, 2, 2-CH_2) and a second complex signal at 2.52–3.22 (4, 1- and 3-CH_2). On addition of the shift reagent the complex peak at δ 2.52–3.22 was better defined into a triplet (3.48) accounting for the methylenes at positions 1 and 3.

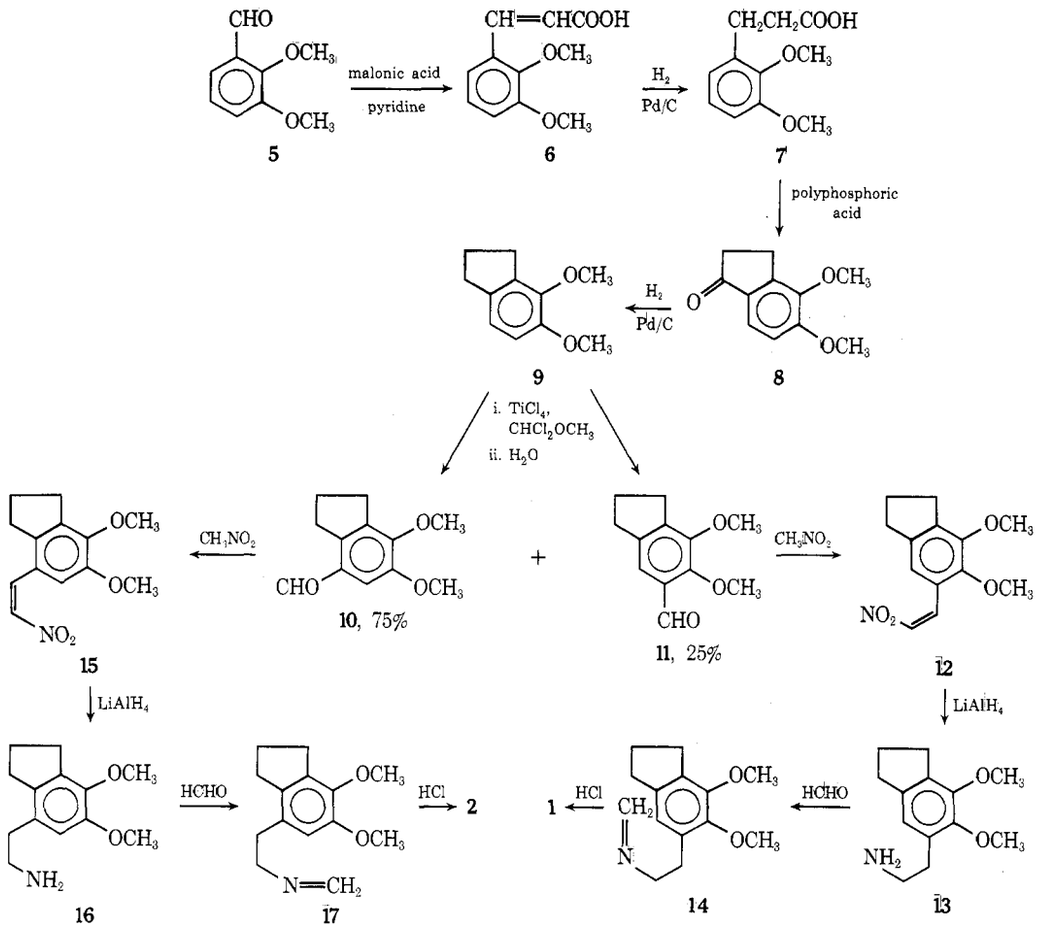
Attempts were also made to correlate the signals for the methoxyl groupings using 2,3-dimethoxybenzaldehyde (2,3-DMB) and 3,4-dimethoxybenzaldehyde (3,4-DMB) as reference compounds. As anticipated, the methoxyls of 2,3-DMB were separated (CCl_4) (6 Hz) to a greater extent than the methoxyls of 3,4-DMB (singlet at 2.20). Addition of $Eu(DPM)_3$ resulted in a shift which magnified the separation to the extent of 28 Hz for the methoxyls of 2,3-DBM and 4 Hz for the 3,4-DMB methoxyl protons. It was expected that a similar situation might be apparent with compounds **10** and **11**. The methoxyl signals indeed were separated to a greater extent (4 Hz) in **11** (*cf.* 2,3-DMB) than in **10** (2 Hz) (*cf.* 3,4-DMB). Addition of the shift reagent however did not produce results comparable to the dimethoxybenzaldehydes (33 Hz for **10**; 14 Hz for **11**) presumably due to the additional substitution on the aromatic ring resulting in steric hindrance to the binding of the shift reagent.

Examination of the aldehyde protons of **10** and **11** in conjunction with the aldehyde protons of 2,3-DMB and 3,4-DMB provided further evidence for the assignments of **10** and **11**. In both 3,4-DMB and **11** the aldehyde signal was located downfield from the aldehyde of 2,3-DMB and **10** (δ 10.5 and 10.24 *vs.* 9.76 and 9.90, respectively), further supporting the analogous location of the aldehyde in **10** with 2,3-DMB and **11** with 3,4-DMB. The aromatic signals in **10** and **11** were not of great significance in the structural assignment.

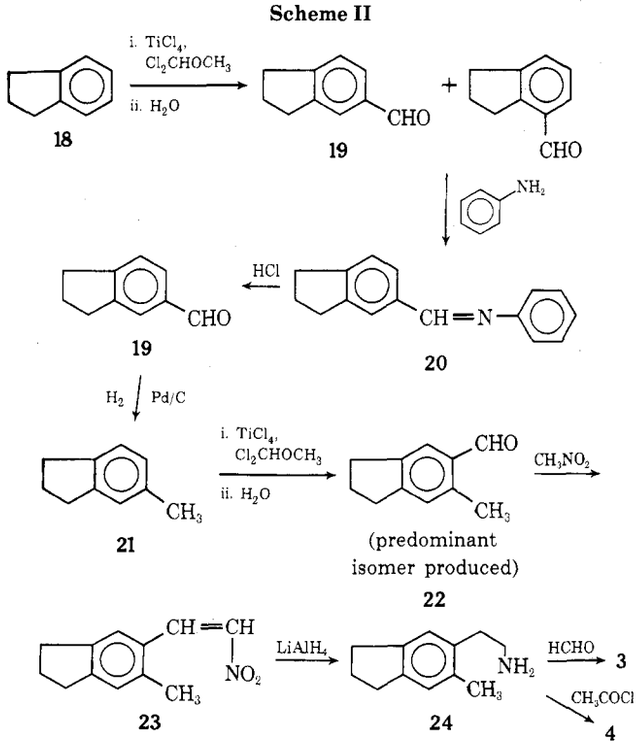
The aldehydes were converted to the nitrovinyl derivatives[2] which on $LiAlH_4$ reduction in high dilution[3] gave the corresponding dimethoxyaminoethylindans (**13** and **16**). Formation of the intermediate Schiff base (**14** and **17**) using formaldehyde followed by the Pictet–Spengler acid-catalyzed ring closure yielded the hydrochloride salt of the desired 7,8-cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (**1**) and 5,6-cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (**2**). The absence of aromatic protons in the nmr spectrum in addition to microanalytical and ir spectral data confirmed the successful ring closures.

The preparation of compounds **3** and **4** (where R = CH_3) was achieved from indan as shown in Scheme II. The identity of the isolated anilide[4] **20** was determined by hydrolysis to the known aldehyde[4] **19**. Nmr data confirmed the location of the aldehyde grouping: δ 7.35 [d, 1, CH= (7)], 7.69 [d, 1, CH= (6)], 7.74 [s, 1, CH= (4) overlapped with CH= (6)]. Reduction of **19** to the methyl derivative **21** followed by a second formylation yielded **22**. Confirmation of the structure of **22** was made from a comparison of the nmr spectrum of **22** with that of **21**. Compound **21** showed the 4, 6, and 7 protons as a multiplet at about δ 7.08. Aldehyde **22**, however, showed as expected one proton at δ 7.08 (4 proton) and one at 7.58 (7 proton). Coupled with a downfield shift of the methyl signal (δ 2.68) these data clearly indicated the location of the CHO grouping at the 6 position. Treatment of **22** with nitromethane followed by reduction

Scheme I



Scheme II



with $LiAlH_4$ yielded the desired aminoethylindan (**24**) which readily gave the imine **3** and acetamide **4**. The preparation of **3** and **4** where R = OCH_3 was accomplished by a modified procedure involving the use of *N*-methylformanilide[5] to introduce the aldehyde grouping.

Experimental Section

All melting points were determined on a Swissco melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-33 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Varian Autoprep model 700 chromatograph. Nmr spectra were recorded on Varian A-60 and Perkin-Elmer R24 spectrometers. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Chemalytics, Tempe, Ariz.

4,5-Dimethoxy-1-indanone (8). 2,3-Dimethoxybenzaldehyde (**5**) was treated with malonic acid in pyridine according to the procedure of Koo, *et al.*,[6] to yield 2,3-dimethoxycinnamic acid (**6**). Low pressure (45 psi) hydrogenation of **6** (25.0 g) over Pd/C (1.75 g) in glacial acetic acid afforded quantitative yields of β-(2,3-dimethoxyphenyl)propionic acid (**7**). Treatment of **7** with polyphosphoric acid at 60° according to the procedure of Koo[7] yielded 4,5-dimethoxy-1-indanone (**8**), mp 71–72° (lit.[7] 74–75°).

4,5-Dimethoxyindan (9). A mixture of 52.6 g (0.275 mol) of **8**, 3.00 g of 5% Pd/C, 100 ml of glacial acetic acid, and 20 drops of concentrated HCl was hydrogenated at 45 psi and room temperature until hydrogen uptake ceased. Following filtration of the used catalyst, two methods may be used to work up the reaction.

A. The acid was neutralized with dilute NaOH and the product extracted from the aqueous phase with ether. The ether was removed by distillation and crude **9** was distilled under reduced pressure, bp 133–135° (15 mm) [lit.[8] bp 124–125° (14 mm)] yielding 42.0 g (86.4%) of clear liquid. Infrared analysis showed the absence of carbonyl absorption.

B. Most of the acetic acid was removed on the rotary evaporator and the remaining liquid was distilled as before giving **9** with no significant difference in yield from that obtained in A.

4,5-Dimethoxy-7-indanaldehyde (10). To a solution of 10.0 g (0.056 mol) of **9**, 24.0 g (0.126 mol) of titanium tetrachloride, and

104 ml of CH_2Cl_2 in a 250-ml 3-necked flask fitted with a thermometer and condenser and magnetically stirred, 11.0 g (0.096 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise at 0°. Hydrogen chloride gas was liberated during the course of the reaction. After vigorous evolution of HCl had subsided, the reaction solution was allowed to slowly warm to room temperature and was stirred for 1–2 hr. The solution was refluxed for 6 hr and cooled and the reaction mixture poured over 200 ml of ice and water (ether and salt were added at this point to increase the volume of the organic phase, to invert the two layers and to break emulsions). The organic phase was washed with 2 × 100 ml of 8% $NaHCO_3$ solution and 1 × 100 ml of water and dried over Na_2SO_4. After removal of the solvent by distillation, the mixture of aldehyde isomers was distilled under high vacuum [bp 115–126° (0.28 mm)] giving 10.2 g of the aldehydes (88%). The 7-position aldehyde (**10**) which crystallized from the liquid was filtered This process was repeated several times by seeding the filtrate followed by cooling. Gas chromatography showed the white crystalline solid to be one component of the two component mixture. In this way 4.24 g of white solid was obtained, mp 41–44°, yield 38.5%. A small sample was recrystallized from petroleum ether to obtain material for elemental analyses. The nmr spectrum (CCl_4) showed signals at δ 2.02 (m, 2, J = 8.0 Hz, 2-CH_2), 2.84 (t, 2, J = 8.0 Hz, 3-CH_2), 3.15 (t, 2, J = 8.0 Hz, 1-CH_2), 3.79 (s, 3, 4-OCH_3), 3.82 (s, 3, 5-OCH_3), 7.05 (s, 1, 8-H), 9.90 (s, 1, CHO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.98; H, 6.84. Found: C, 70.03; H, 6.66.

4,5-Dimethoxy-7-nitrovinylindan (15). To a 100-ml 3-necked round-bottom flask fitted with a condenser and thermometer and magnetically stirred was added 12.97 g (0.063 mol) of **10**, 3.00 g (0.039 mol) of ammonium acetate, 13.0 ml (0.292 mol) of CH_3NO_2, and 40 ml of glacial acetic acid. This was heated for 1–2 hr at 112°. As the reaction solution began to cool the entire solution solidified. After this was cooled in an ice bath and the solvent was removed by filtration, the solid was washed with a small volume of acetic acid giving fine yellow needles (9.55 g) after thorough drying. The filtrate was poured into 300 ml of ice and water which precipitated a slightly gummy, yellow-brown solid. This gave an additional 1.43 g of crystalline solid after drying and crystallizing from methanol giving a total yield of 10.98 g (70%). An analytical sample melted at 128–130°: nmr ($CDCl_3$) δ 2.16 (m, 2, 2-CH_2), 3.02 (t, 4, 1- and 3-CH_2), 3.87 (s, 3, 4-OCH_3), 3.93 (s, 3, 5-OCH_3), 6.91 (s, 1, 6-H), 7.49 (d, 1, J = 14 Hz, =$CHNO_2$), 8.10 (d, 1, J = 14 Hz, **CH**=$CHNO_2$).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.79; H, 6.12; N, 5.53.

4,5-Dimethoxy-7-aminoethylindan (16). To a slurry of 15.0 g (0.395 mol) of $LiAlH_4$ and 500 ml of anhydrous ether in a 5-l. 3-necked flask fitted with a condenser, mechanical stirrer, and dropping funnel was added 20.0 g (0.084 mol) of **15** dissolved in 2 l. of ether. The addition was made over a period of ~4 hr while refluxing the ether slurry. When addition was complete, refluxing was continued for an additional 1–2 hr. After the addition of 20 g of Celite and then 70 ml of water slowly, dropwise, with cooling in an ice bath, the supernatant ether was decanted and the salts were washed with fresh ether several times, followed by decantation and finally filtration. The solvent was removed by distillation and more thoroughly on the rotary evaporator. Cooling in an ice bath gave 15.91 g (90%) of a slightly yellow solid: mp 45–48°; ir (liquid film) 1605 (aromatic C=C and NH_2), 3190, 3300, 3370 cm^{-1} (NH_2). High vacuum distillation gave an analytical sample.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.22; H, 8.49; N, 6.18.

7,8-Dimethoxycyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2). To 11.1 ml of formalin in a round-bottom flask heated at 60–70° and magnetically stirred was added 10.95 g (0.049 mol) of **16** (dissolved in 22 ml of methanol) rapidly dropwise. After 50 min of heating, the solvent was thoroughly removed on the rotary evaporator. The ir spectrum showed absence of primary amine stretching vibrations at 3190, 3300, and 3370 with a weakening in intensity of the peak at 1605 cm^{-1}. This material was dissolved in 55 ml of 23% HCl and heated on the water bath with stirring at 50–60° for 30 min. The water–acid solvent was removed on the evaporator and the residue was dried overnight in a vacuum oven giving a hard solid which yielded 11.14 g (84.1%) of **2** when crystallized from acetonitrile–absolute alcohol: mp 232–235° dec; nmr ($CDCl_3$) δ 2.10 (m, 2, 2′-CH_2), 2.82 (m, 4, 1′- and 3′-CH_2), 3.42 (broad m, 2, 1-CH_2), 3.79 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 4.30 (broad s, 2, > $^+NH_2$), and absence of an aromatic proton signal.

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.58; H, 7.36; N, 5.33; Cl, 13.29.

4,5-Dimethoxy-6-indanaldehyde (11). The 6-indanaldehyde was obtained by high vacuum (20–50μ) fractional distillation of the mixture of aldehydes remaining after repeated crystallization and filtering of the 7-aldehyde, **10**. The 6-aldehyde distilled as a pure substance in the first fractions followed by a mixture of the aldehydes and finally the pure 7-aldehyde. The 6-aldehyde was a liquid at room temperature but crystallized when refrigerated. An approximate mp (11°) was obtained from the temperature of a mixture of the solid in equilibrium with the liquid; nmr (CCl_4) showed δ 2.04 (m, 2, 2-CH_2), 2.52–3.22 (m, 4, 1- and 3-CH_2), 3.87 (s, 3, 5-OCH_3), 3.94 (s, 3, 4-OCH_3), 7.32 (s, 1, 7-H), 10.24 (s, 1, CHO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.13; H, 6.87.

4,5-Dimethoxy-6-nitrovinylindan (12). In a 2-l. 3-necked flask fitted with a condenser and thermometer and magnetically stirred, 126.7 g (0.613 mol) of **11**, 29.3 g (0.380 mol) of ammonium acetate, 127 ml (2.82 mol) of nitromethane, and 390 ml of acetic acid were heated at 112° for 45 min. After cooling in the refrigerator and scratching with a glass rod the solution crystallized. After filtering and washing with a few ml of cold acetic acid the product was dried under vacuum overnight and recrystallized from methanol yielding 104.4 g (68%) of yellow needles: mp 103.5–104.5°; nmr ($CDCl_3$) δ 2.12 (m, 2, 2-CH_2), 2.92 (m, 4, 2- and 3-CH_2), 3.95 (s, 3, 4-OCH_3), 3.99 (s, 3, 5-OCH_3), 7.16 (s, 1, 7-H), 7.76 (d, 1, J = 14 Hz, **CH**=$CHNO_2$), 8.24 (d, 1, J = 14 Hz, CH=**CH**NO_2).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.45; H, 6.17; N, 5.84.

4,5-Dimethoxy-6-aminoethylindan (13). To 9.2 g (0.242 mol) of $LiAlH_4$ in 400 ml of anhydrous ether was added 12.17 g (0.048 mol) of **12** in 1 l. of anhydrous ether dropwise over a period of 4 hr while refluxing; this was followed by refluxing for a further 2 hr. After the addition of 15 g of Celite and decomposition of excess $LiAlH_4$ with 40 ml of H_2O (while cooling in an ice bath), the ether was decanted and the salts were washed twice with ether, followed by decantation and finally filtration. The ether was removed by distillation and the product distilled yielding 7.42 g (68%): bp 101–103° (75 μ); ir (liquid film) 1576 (NH_2 and aromatic C=C), 3180, 3240, and 3365 cm^{-1} (NH_2).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.68; H, 8.71; N, 6.35.

5,6-Dimethoxycyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1). To 7.42 ml of formalin in a 100-ml boiling flask, 7.42 g (0.033 mol) of **13** in 15 ml of methanol was added dropwise with magnetic stirring and warming. After heating at 70–75° for 45 min, the mixture was rinsed into a separatory funnel with 3 × 50 ml of benzene. The benzene layer was washed with 3 × 100 ml of water and then the benzene was thoroughly removed on the evaporator. The ir spectrum showed absence of NH stretching and weakening of intensity of the band at 1576 cm^{-1}. This material weighed 8.72 g and was dissolved in 39 ml of 23% HCl followed by heating at 50–60° for 30 min. The aqueous acid was removed on the rotary evaporator yielding an oily, viscous substance which was dried in a vacuum oven in the presence of P_2O_5. A tacky hygroscopic solid was obtained which was crystallized from ether–ethanol giving fine needles, mp 215.5–216.5°. Further experimentation showed acetonitrile–ethanol to be a better recrystallization solvent. The nmr spectrum ($CDCl_3$ + D_2O) gave signals at δ 2.09 (m, 2, 2′-CH_2), 2.49–3.59 (m, 8, 3, 4, 1′ and 3′-CH_2), 3.79 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 4.16 (s, 2, 1-CH_2), and absence of an aromatic proton signal.

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.47; H, 7.33; N, 5.15; Cl, 13.36.

5-Indanaldehyde (19). A solution of indan (**18**, 50 g, 0.423 mol) and 300 ml of CH_2Cl_2 were cooled to 0° in an ice–salt bath before 106.5 g (0.562 mol) of titanium tetrachloride was poured in. After additional cooling, 64.35 g (0.560 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise allowing the evolution of HCl gas to subside before removing the ice bath and stirring for 30 min. The mixture was poured over 600–700 ml of ice and water, well shaken, and then washed with water, 200 ml of 10% Na_2CO_3 solution, and finally with water. Often ether was added to invert the phases before washing. The solvent was evaporated and the residual dark oil was distilled under high vacuum giving a major fraction, 38.42 g (84%), bp 132–133° (15–16 mm). Gas chromatography showed the presence of two components with similar retention times in a ratio of ~20:80. The compounds were assumed to be the 4- and 5-aldehydes, the 5-aldehyde being present in greatest quantity and having the longest retention time. They were separated by formation of the anilide, and identified by recrystallization from acetonitrile followed by hydrolysis of the crystalline product. This

yielded a liquid which gave a single peak on the gas chromatograph which corresponded to the compound with greatest retention time. The anilide gave a melting point, 85–86°, which agreed with the value for 5-indanaldehyde anilide.[4] The literature does not mention the formation of an isomeric mixture during an alternate complex synthesis of **19**. The nmr spectrum ($CDCl_3$) gave signals at δ 2.16 (m, 2, 2-CH_2), 2.99 (t, 4, 1- and 3-CH_2), 7.35 (d, 1, J = 9 Hz, 7-H), 7.69 [d, 1, J = 9 Hz, CH= (6)], 7.74 [s, 1, CH= (4) overlapped with CH= (6)].

5-Methylindan (21). Low pressure (45 psi) hydrogenation of 16.78 g (0.115 mol) of **18** over 2.5 g of 5% Pd/C in 30 ml of glacial acetic acid and 25 drops of concentrated HCl yielded the desired compound. After Celite was added to the reaction mixture and filtration, the filtrate was made basic with 40 g (1 mol) NaOH in 300 ml of water at 0°. This was extracted with 3 × 90 ml of ether; the ether solution was washed with water, dried over Na_2SO_4, and concentrated. The concentrated liquid was distilled at atmospheric pressure, bp 197–198° [lit.[9] bp 74° (11 mm)], yielding 12.70 g (84%) of clear liquid. The nmr spectrum ($CDCl_3$) gave signals at δ 2.04 (m, 2, 2-CH_2), 2.33 (s, 3, CH_3), 2.89 (t, 4, 1- and 3-CH_2), 7.03 (m, 3, =CH).

5-Methyl-6-indanaldehyde (22). To 12.70 g (0.096 mol) of **21** in 55 ml of CH_2Cl_2 at 0° was added 24.70 (0.132 mol) of titanium tetrachloride. After cooling, 13.30 g (0.134 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise. After the evolution of HCl gas had subsided, the reaction mixture was poured over 225 ml of ice and water in a separatory funnel. Additional CH_2Cl_2 was added and the organic phase was washed with 100 ml of water followed by 2 × 100 ml of 10% $NaHCO_3$ solution. The precipitate which formed in the organic phase was dissolved by addition of ether. After washing again with 200 ml of water and drying over Na_2SO_4 the solvent was evaporated and the remaining dark liquid was distilled giving a clear liquid: bp 152–154° (18 mm); 10.51 g (68%); nmr (CCl_4) δ 2.06 (m, 2,2-CH_2), 2.57 (s, 3, CH_3), 2.90 (t, 4, 1- and 3-CH_2), 7.02 (s, 1, 4 =CH), 7.52 (s, 1, 7 =CH).

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.54. Found: C, 82.19; H, 7.55.

5-Methyl-6-nitrovinylindan (23). To 8.00 g (0.050 mol) of **22** in a round-bottom flask fitted with a condenser, magnetically stirred and heated in an oil bath, was added 13.00 g (0.213 mol) of CH_3NO_2, 1.25 g (0.016 mol) of ammonium acetate, and 27 ml of glacial acetic acid. After the solution was heated at an oil bath temperature of 95° for 18 hr, the flask was cooled to room temperature, scratched with a glass rod, and refrigerated. A crystalline product (6.06 g, 55%) was obtained by filtering, reducing the volume of the filtrate, and collecting additional material. Recrystallization from methanol gave an analytical sample: mp 84.5–86.5°; nmr ($CDCl_3$) δ 2.05 (m, 2, 2-CH_2), 2.42 (s, 3, 5-CH_3), 2.90 (t, 4, J = 7 Hz, 1- and 3-CH_2), 7.13 (s, 1, 4-H), 7.36 (s, 1, 7-H), 7.45 (d, 1, J = 13 Hz, =$CHNO_2$), 8.28 (d, 1, J = 13 Hz, C**H**=$CHNO_2$) (the doublet at 7.45 overlapped the singlet at 7.36).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.24; N, 6.69.

5-Methyl-6-aminoethylindan (24). To 10.3 g (0.271 mol) of $LiAlH_4$ and 295 ml of anhydrous ether in a 2-l. 3-necked flask fitted with a 500-ml dropping funnel, condenser with drying tube, and a mechanical stirrer, 13.54 g (0.066 mol) of **23** in 590 ml of anhydrous ether was added dropwise over a period of 4.5 hr at reflux temperature. Refluxing was continued for 2 hr and the mixture was allowed to stand overnight. After 6.0 g of Celite was added, excess hydride was decomposed by the slow dropwise addition of 37 ml of water with stirring and cooling. The white salts were washed several times with ether followed by decantation each time and finally filtration. Removal of the ether by distillation gave a liquid which distilled at 160–162° (15.5 mm) yielding 10.32 g (89.1%) of **22**. Elemental analyses were obtained for the hydrochloride salt of **24**, mp 229–231°.

Anal. Calcd for $C_{12}H_{18}NCl$: C, 68.07; H, 8.56; N, 6.61; Cl, 16.74. Found: C, 68.15; H, 8.48; N= 6/62: Cl, 16.61.

5-Methoxy-6-aminoethylindan. 5-Indanol was methylated with dimethyl sulfate according to the procedure of Hunsberger, *et al.*,[5] and subsequently formylated to yield 5-methoxy-indan-6-aldehyde by way of the Vilsmeir–Haack reaction. The preparation of 5-methoxy-6-aminoethylindan was achieved by reaction with nitromethane to form the nitrovinyl derivative by way of the general procedures outlined by Gairaud.[2] Reduction of this compound with $LiAlH_4$ as described in the preparation of **16** gave the desired product, bp 119–120° (0.3 mm) [lit.[10] bp 115–120° (0.03 mm)]. Our experience with the nitrovinyl derivative yielded a compound with a significantly higher melting point (92–94°) than the reported value for this compound (83–85°[10]).

1-Acetamido-2-(5-methoxy-6-indanyl)ethane (4). To 6.99 g (0.037 mol) of 5-methoxy-6-aminoethylindan in 51 ml of dry dimethylformamide, 4.7 g (0.046 mol) of acetic anhydride in 18.8 ml of benzene was added dropwise at 0° under nitrogen. The solution was slowly warmed to room temperature and stirred overnight and the solvent was removed on the rotary evaporator yielding a slightly yellow oil which solidified on cooling. Crystallization of the crude material (8.67 g) from ethyl acetate gave 5.60 g (71%) of pure material, mp 106–107°.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.32; H, 8.13; N, 6.00.

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Registry No.—1 hydrochloride, 51932-54-8; **2** hydrochloride, 51932-55-9; **4**, 51932-56-0; **8**, 6342-80-9; **9**, 51932-57-1; **10**, 51932-58-2; **11**, 51932-59-3; **12**, 51932-60-6; **13**, 51932-61-7; **14**, 51932-62-8; **15**, 51932-63-9; **16**, 51932-64-0; **17**, 51932-65-1; **18**, 496-11-7; **19**, 30084-91-4; **21**, 874-35-1; **22**, 51932-66-2; **23**, 51932-67-3; **24**, 51932-68-4; **24** hydrochloride, 51932-69-5; 4-indanaldehyde, 51932-70-8; 5-indancarboxanilide, 51932-71-9; 5-methoxy-6-aminoethylindan, 13203-59-3.

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