of BSTFA and redistilled acetonitrile at room temperature in a 3.5-mL glass screw-cap vial equipped with a Teflon-lined rubber septum. Silylated products were analyzed by GC on a 3% OV-17 column that was temperature programmed from 90 to 150 °C at 4 °C/min and then held isothermally at the upper temperature. When the injector port temperature was above 200 °C, GC analysis of silylated **2** produced three peaks with retention times of 4.1, 5.7, and 15.9 min. GC/MS analysis and comparison with authentic standards showed that the three peaks were monosilylated 2-pyrrolidinone, 2-pyrrolidinone (**12**), and *N*-(trimethylsilyl)-squamolone (**11**), respectively. Lowering the GC injector port to 190 °C or below resulted in an almost complete disappearance of the first two peaks. In the case of silylated **1** a single GC peak with a retention time of 14.8 min was observed. Silylated **1** is shown as the *N,N*-bis(trimethylsilyl) derivative **13**, since there does not appear to be significant resonance stabilization in the *O*-silyl form.[15] However, other structures for this derivative cannot be excluded.

Registry No. **1**, 75548-99-1; **2** (squamalone), 40451-67-0; **3**, 56-12-2; **4**, 2609-10-1; **5**, 108-55-4; **6**, 25335-74-4; **7**, 75506-69-3; **8**, 75506-70-6; **9**, 75506-71-7; **10**, 19055-93-7; **11**, 75506-72-8; **12**, 616-45-5; **13**, 75506-73-9; glutaric acid monoamide, 25335-74-4.

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Synthesis of Isoquinolines from Indenes[1]

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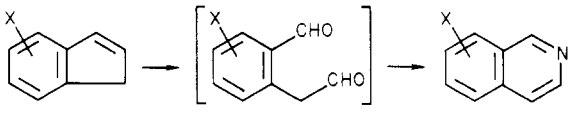
A general procedure for the synthesis of isoquinolines from appropriately substituted indenes is described. Ozonolysis of the indenes followed by reductive workup gives intermediate homophthalaldehydes which are treated with ammonium hydroxide to give the isoquinolines. This "one-pot", three-step reaction sequence was applied to the formation of all of the mono-*C*-methyl-substituted isoquinolines in a regiospecific manner. The procedure is applicable to both electron-withdrawing and electron-donating substituents on the indene system. In this manner the 6- and 7-nitro-, -bromo-, and -iodoisoquinolines were prepared.

In 1964, Fields[2] in a study of amozonolysis of cycloolefins observed that indene is ozonized in the presence of aqueous ammonia and an emulsifier to give an aldehydoamino hydroperoxide which ultimately forms the fully aromatic isoquinoline. We felt that this approach to isoquinolines would offer certain advantages to the more conventional syntheses.[3] By removing the site of heterocyclic ring formation from a position on the homonuclear ring, as it is in Bischler-Napieralski[4] and Pomeranz-Fritsch[5] syntheses, one eliminates the need for activation of that ring toward electrophilic aromatic substitution[6] and ensures regioselectivity in the isoquinoline formation. Also, the product is the fully aromatic isoquinoline and not a dihydro derivative. Since the Fields approach has received little synthetic attention,[7] we undertook a study of the synthesis of isoquinolines from indenes, and the results of that study are presented in this paper.

We chose to pursue a stepwise sequence from the indene to the isoquinoline rather than the heterogeneous procedure of Fields. Thus our general approach could be achieved from an appropriate indene via a homophthalaldehyde intermediate which upon treatment with ammonia should give the fully aromatic isoquinoline (see Scheme I).

Scheme I



Results and Discussion

Isoquinoline from Indene. The initial study to demonstrate the feasibility of our proposed procedure involved the conversion of indene to isoquinoline. It was found that treatment of a methanolic solution of indene with ozone produced a methoxyhydroperoxide[8] which was reduced with dimethyl sulfide[9] to give homophthalaldehyde. Ammonium hydroxide was added to the reaction mixture without workup, and after the mixture was allowed to stand overnight, isoquinoline was produced.

Having demonstrated that this "one-pot", three-step reaction sequence would indeed give isoquinoline from indene, we directed our efforts toward optimizing the yields. First, it was found that the dimethyl sulfide reduction of the methoxy hydroperoxide was best carried out in the presence of solid sodium bicarbonate which presumably removes any acids formed in the ozonolysis and prevents acetal formation between the homophthalaldehyde and the methanol solvent. Next, optimal reaction times were determined for both the reduction and amination steps. Choosing an arbitrary amination time of 24

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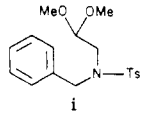

i

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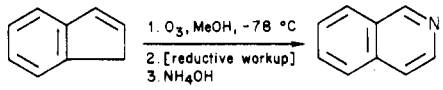
0022-3263/80/1945-5312$01.00/0

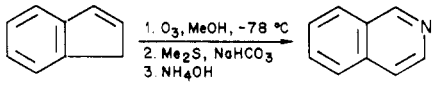
Table I. Preparation of Isoquinolines from Indenes



indene		isoquinoline			% yield[b]	
structure	ref	structure	mp [bp (mmHg)],[a] °C	ref	method A[c]	method B[d]
indene	*e*	isoquinoline	[68 (0.5)]	20	79	76
3-CH_3	21	1-CH_3	[71-72 (1)]	22	57	96
2-CH_3	23	3-CH_3	65-66	24	60	70
1-CH_3	21	4-CH_3	[83-84 (0.1)]	25	92	75
7-CH_3	26	5-CH_3	39-41	27	66	69
6-CH_3	26	6-CH_3	88.5-89.5	28	61	53
5-CH_3	26	7-CH_3	74-75	28, 29	83	49
4-CH_3	26	8-CH_3	87-88	30	82	
4,7-$(CH_3)_2$	31	5,8-$(CH_3)_2$	233-236 dec[f]	32	77	
5-NO_2	13	7-NO_2	169-172	33	61	
5-Br	*a*	7-Br	67-69	34	58	
5-I	*a*	7-I	124-128 dec	*a*	58	
6-NO_2	*a*	6-NO_2	122.5-123	35	67	
6-Br	16	6-Br	42-43	36	70	
6-I	*a*	6-I	86-88 dec	*a*	66	
5,6-$(CH_3O)_2$	19	6,7-$(CH_3O)_2$	92-93	37	61	

[a] This work. [b] Isolated yields. [c] Method A, Me_2S and $NaHCO_3$ as reductive workup conditions. [d] Method B, Raney Ni/H_2 as reductive workup condition. [e] Commercially available from Aldrich Chemical Co. [f] This is the melting point of the picrate salt.

h, indene was ozonized and reduced with dimethyl sulfide (3 equiv) in the presence of solid sodium bicarbonate (eq 1). It was found that after 4 h the reaction appeared to



(1)

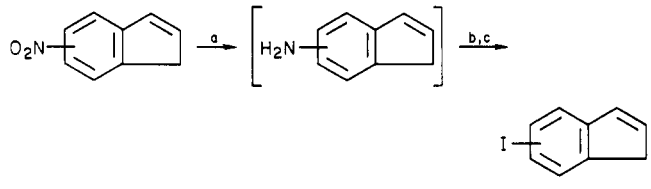
be complete. In a similar manner and with an arbitrary reduction time of 11 h, the resulting crude solution of homophthalaldehyde was treated with aqueous ammonium hydroxide (30 equiv). After 5 h, amination was found to be essentially complete. When these conditions were applied to the conversion of indene to isoquinoline, consistent isolated yields of 73–82% were obtained. Other variants in the reaction conditions such as temperature and use of ammonium chloride instead of ammonium hydroxide were investigated but did not improve the yields.

Methylated Isoquinolines. In order to show both the generality and regiospecificity of the procedure we set out to synthesize all of the carbon-substituted methylisoquinolines, a feat which had not yet been accomplished by the utilization of only one reaction system.

The appropriately substituted indenes are all known (see Table I for references) and were generally prepared by reduction ($NaBH_4$) of the corresponding indanone and dehydration ($MgSO_4$) of the resulting indanol. It should be pointed out that the regiospecificity in indanones with substitution in the homonuclear ring is achieved by cyclization of an appropriate β-tolylpropionic acid,[10] giving the 4- and 6-isomers, or by cyclization of an appropriate α-bromopropiophenone,[11] giving the 5- and 7-isomers.

With the requisite methyl-substituted indenes in hand, they were subjected to the general procedure for preparation of isoquinoline described earlier. The results of this study are shown in Table I. As can be seen, two methods of reductive workup were investigated. First, the normal method of employing dimethyl sulfide in the presence of solid sodium bicarbonate gave consistent yields of 60–90%.

Scheme II[a]



[a] (a) Sulfurated $NaBH_4$, THF. (b) $NaNO_2$, 20% H_2SO_4. (c) KI.

A second method using catalytic hydrogenation over a Raney nickel (W-2) catalyst gave comparable yields except in the cases of 1-methylisoquinoline and 7-methylisoquinoline. In the former case a much higher yield was obtained with the catalytic hydrogenation method, while in the latter case the dimethyl sulfide procedure was better. In practice the dimethyl sulfide procedure is more convenient and is considered to be the method of choice.

Homonuclear, Electron-Withdrawing-Substituted Isoquinolines. In order to demonstrate that our procedure was not impaired by the presence of electron-withdrawing substituents in the homonuclear ring, we carried out the preparation of nitro-, bromo-, and iodoisoquinolines. The molecules with substitution in the 6- and 7-positions of the isoquinoline ring system were chosen because these positions are the most inaccessible by direct reaction on isoquinoline. Again, before our procedure could be tested the appropriate indenes were required.

The 5-substituted indenes were prepared from the known 6-nitroindan-1-one[12] and 5-nitroindene.[13] The 5-iodoindene was prepared from the 5-nitroindene by reduction to the amine with sulfurated sodium borohydride[14] followed by diazotization and conversion of the diazonium salt to the iodo compound (see Scheme II). No attempts were made to maximize the yields in these reactions.

Attempts to produce the 5-bromoindene by a Sandmeyer reaction on the unstable 5-aminoindene obtained above

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were unsuccessful. Therefore the bromine group was introduced prior to reduction of the indanone by published procedures. Conversion of the nitro group to an amino group was achieved by catalytic hydrogenation. Now the Sandmeyer reaction was successful, and the 6-bromoindan-1-one[15] was converted to the desired 5-bromoindene by reduction to the indanol followed by dehydration.

In the 6-substituted indene series, the 6-bromoindene was known[16] and the nitro and iodo derivatives were prepared from 5-aminoindan-1-one.[17] First, 5-nitroindan-1-one was obtained by pertrifluoroacetic acid oxidation[18] of the aminoindanone. Next, the 6-nitroindene was obtained by sodium borohydride reduction of the nitroindanone followed by dehydration of the crude nitroindanol. Finally, the 6-iodoindene was prepared in a manner similar to that for its 5-substituted counterpart (see Scheme II).

These electron-withdrawing-substituted indenes were subjected to the general procedure for preparation of isoquinoline described earlier by employing the dimethyl sulfide reductive workup of the methoxy hydroperoxide. The results of this study are also shown in Table I. The presence of the electron-withdrawing substituent seems to have little effect on isoquinoline formation, with consistent yields of 60–70% being obtained. It should be noted that this represents, to our knowledge, the first time that 6- and 7-iodoisoquinolines have been prepared.

Homonuclear, Electron-Releasing-Substituted Isoquinolines. Finally, to demonstrate that electron-releasing groups substituted on the indene molecule would be compatible with our general procedure, we converted 5,6-dimethoxindene[19] into 6,7-dimethoxyisoquinoline in 61% yield (see Table I).

Summary

A general procedure for the synthesis of isoquinolines from appropriately substituted indenes by a "one-pot", three-step reaction sequence has been described. This procedure allows the formation of all the *C*-methyl-substituted isoquinolines in a regiospecific manner. The procedure is also applicable to both electron-withdrawing and electron-donating substituents on the indene system, giving rise to homonuclear-substituted isoquinolines. In this manner the 6- and 7-iodoisoquinolines have been prepared for the first time.

Experimental Section

Boiling points were recorded at gauge pressure and are reported uncorrected. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are reported uncorrected. All crystalline products were white unless otherwise stated. Infrared spectra were obtained on a Beckman IR-8 spectrometer with only selected absorptions being reported. Nuclear magnetic resonance (^1H) spectra were obtained on a Varian EM-360 instrument. Chemical shifts are reported in δ values downfield relative to internal tetramethylsilane. High-resolution mass spectra were determined by Mr. Kei Miyano on a Du Pont 21-492B mass spectrometer.

Ozonolyses were performed in a flask fitted with a Claisen adapter and a glass-fritted gas inlet. Ozone was generated with a Welsbach T-23 ozonator (V = 100 V, O_2 flow = 0.02 L/min), and a 10% potassium iodide solution was used as an indicator to determine the point at which ozone was in excess. The petroleum ether used was reagent grade with a boiling range of 30–60 °C. Drying of organic extracts during the workup was done over anhydrous sodium sulfate. Reactions were done in oven-dried (150 °C) glassware under a dry nitrogen atmosphere and were stirred magnetically unless otherwise stated.

The purity of isolated products was determined by GLC analysis (35-m, SE-30 glass capillary column) for liquids (all compounds exhibited a single peak) and TLC analysis for solids (all compounds exhibited a single spot in at least two solvent systems).

General Procedure for Conversion of Indenes to Isoquinolines. Method A (Table I). Dimethyl Sulfide Reductive Procedure. A solution of the indene (10–20 mmol) in methanol (50 mL; in cases where the indene was not soluble 5 mL of CH_2Cl_2 was used as a cosolvent) was cooled to −78 °C (dry ice–acetone bath) and ozonized (see the introduction to the Experimental Section). The reaction mixture was purged with nitrogen and removed from the cooling bath. Sodium bicarbonate (2 g) and dimethyl sulfide (0.2 mL/mmol of indene) were added; the flask was stoppered, shaken, and allowed to stand at room temperature for 6–10 h. Ammonium hydroxide (20 mL) was added; the flask was again stoppered, swirled, and allowed to stand for 6–12 h. The resulting mixture was poured into water (100 mL) and extracted with methylene chloride. The organic extracts were combined, washed with water and brine, dried, and concentrated. Either distillation or chromatography on basic alumina yielded the pure isoquinoline.

Method B (Table I). Raney Nickel Reduction Procedure. A solution of the indene (10–20 mmmol) in methanol (60 mL) was cooled to −78 °C (dry ice–acetone bath) and ozonized (see the introduction to the Experimental Section). The reaction mixture was purged with nitrogen and placed in a carbon tetrachloride–dry ice bath. Raney nickel catalyst (0.1 g/mmol of indene) was added, and the mixture was stirred under a hydrogen atmosphere. After the uptake of 1 equiv of hydrogen, ammonium hydroxide (20 mL) was added, and the flask was stoppered, swirled, and allowed to stand for 16–22 h at room temperature. The reaction mixture was worked up and purified in the same manner described for method A.

5-Iodoindene. To a solution of sulfurated sodium borohydride[14] [prepared by adding dry tetrahydrofuran (50 mL) to a solid mixture of 0.741 g (19.6 mmol) of sodium borohydride and 1.87 g (58.5 mmol) of precipitated sulfur] was added 1.00 g (6.21 mmol) of 5-nitroindene[13] in dry tetrahydrofuran (5 mL). After the mixture was stirred for 16 h at room temperature, water was carefully added, and the mixture was extracted with ether. The ether extracts were combined and exhaustively washed with water and brine. The unstable 5-aminoindene was not isolated but extracted from the ether layer with three portions (10 mL) of 20% sulfuric acid. The acid extracts were cooled in an ice bath to 0 °C, and 0.442 g (6.48 mmol) of sodium nitrite in water (2 mL) was added over a period of 2 min. The resulting solution was stirred for 10 min at 0 °C, and then a solution of 1.03 g (6.20 mmol) of potassium iodide in water (4 mL) was added. The flask was wrapped in aluminum foil and stirred for 30 min. The resulting black tar was transferred to a separatory funnel and extracted with methylene chloride. The organic extracts were combined,

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washed with water and brine, dried, and concentrated. Elution from Florisil (50:50 CH_2Cl_2–C_5H_{12}) gave 0.299 g (1.24 mmol, 20% yield) of oily 5-iodoindene: NMR ($CDCl_3$) δ 3.33 (m, 2 H), 6.48 (m, 1 H), 6.82 (m, 1 H), 7.0–7.8 (m, 3 H); IR (neat) 3070 (m), 945 (m), 864 (s), 820 (s), 692 cm^{-1} (s); high-resolution mass spectrum calcd for C_9H_7I m/e 241.9590, found m/e 241.9615.

5-Bromoindene. To 0.258 g (1.22 mmol) of 6-bromoindan-1-one[15] in methanol (25 mL) cooled to 0 °C was added 0.046 g (1.21 mmol) of sodium borohydride. After the ebullition of hydrogen ceased, the mixture was warmed to room temperature and stirred 1 h. The mixture was poured into water and extracted with methylene chloride. The organic extracts were combined, washed with water and brine, dried, and concentrated to give a quantitative yield of crude 6-bromoindan-1-ol which was used without purification.

A mixture of the crude indanol, 20% sulfuric acid (10 mL), and ethylene glycol (10 mL) was heated to 75 °C. After 20 h, the mixture was cooled and extracted with methylene chloride. The organic extracts were combined, washed with saturated sodium bicarbonate solution, water and brine, dried, and concentrated. Elution from Florisil (50:50 CH_2Cl_2–C_5H_{12}) gave 0.183 g (0.94 mmol, 77% yield) of oily 5-bromoindene: NMR ($CDCl_3$) δ 3.30 (t, J = 1 Hz, 2 H), 6.52 (dt, J = 6, 1 Hz, 1 H), 6.78 (dt, J = 6, 1 Hz, 1 H), 7.30 (broadened s, 2 H), 7.50 (broadened s, 1 H); IR (neat) 3070 (s), 1600 (m), 950 (s), 880 (s), 805 (s), 690 (s), 655 cm^{-1} (m); high-resolution mass spectrum calcd for $C_9H_7{}^{81}Br$ m/e 195.9711, found m/e 195.9712.

5-Nitroindan-1-one. To methylene chloride (85 mL) was added without stirring 90% hydrogen peroxide (4.54 mL). The hydrogen peroxide was not miscible with the solvent and separated as the lower layer. The flask was cooled to 0 °C and stirred. To this cooled solution was added trifluoroacetic anhydride (28.6 mL, 0.20 mol) over a 20-min period. After the addition was complete, the ice bath was removed, and the solution was stirred at room temperature for 30 min. A solution of 5.89 g (40.1 mmol) of 5-aminoindan-1-one[17] in methylene chloride (50 mL) was added dropwise over a 30-min period, and the resulting mixture was stirred for 13 h. The reaction mixture was poured into water, extracted with saturated sodium bicarbonate solution and brine, dried, and concentrated to give 3.95 g (22.3 mmol) of 5-nitroindan-1-one (56% yield). Recrystallization from ether–pentane produced yellow crystalline material, mp 131–132.5 °C (lit.[38] mp 133–134 °C).

6-Nitroindene. To 1.0 g (5.65 mmol) of 5-nitroindan-1-one in methanol (50 mL) cooled to 0 °C was added 0.429 g (11.3 mmol) of sodium borohydride. After ebullition of hydrogen ceased, the ice bath was removed, and the solution was stirred 3 h at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. The organic extracts were combined, washed with water and brine, dried, and concentrated to give 0.832 g (4.65 mmol) of yellow crystalline 5-nitroindan-1-ol which was used without purification.

A mixture of the crude indanol, benzene (50 mL), and p-toluenesulfonic acid (0.40 g) was refluxed by using a Dean–Stark trap. After 3 h, the purple reaction mixture was cooled, transferred to a separatory funnel, washed with saturated sodium bicarbonate solution, water and brine, dried, and concentrated to give a dark brown solid. Elution from Florisil (60:40 CH_2Cl_2–C_5H_{12}) gave 0.745 g (4.63 mmol) of crystalline 6-nitroindene (82% yield). Recrystallization from methanol gave light yellow needles: mp 78–79 °C; NMR ($CDCl_3$) δ 3.50 (s, 2 H), 6.93 (s, 2 H), 7.43 (d, J = 8 Hz, 1 H), 8.22 (br d, J = 8 Hz, 1 H), 8.27 (s, 1 H); IR (KBr) 3085 (m), 1605 (m), 1498 (s), 1330 (s), 885 (m), 835 (m), 813 (m), 760 (m), 698 cm^{-1} (m); high-resolution mass spectrum calcd for $C_9H_7NO_2$ m/e 161.0477, found m/e 161.0491.

6-Iodoindene. In a manner similar to that described for the preparation of 5-iodoindene, 0.90 g (5.59 mmol) of 6-nitroindene was reduced with sulfurated sodium borohydride to give an unstable 6-aminoindene which was directly diazotized and reacted with potassium iodide. After workup and chromatography on Florisil (50:50 CH_2Cl_2–C_5H_{12}), 0.098 g (0.40 mmol, 7% yield) of oily 6-iodoindene was obtained: NMR ($CDCl_3$) δ 3.33 (br s, 2 H), 6.50 (m, 1 H), 6.83 (m, 1 H), 7.0–8.2 (m, 3 H); IR (neat) 3070 (m), 975 (m), 945 (m), 905 (s), 872 (s), 818 (s), 775 (m), 740 (s), 695 cm^{-1} (m); high-resolution mass spectrum calcd for C_9H_7I m/e 241.9590, found m/e 241.9624.

7-Iodoisoquinoline. By use of the general procedure for convesion of indenes to isoquinolines, method A, with methylene chloride (5 mL) as a cosolvent, 0.299 g (0.24 mmol) of 5-iodoindene was converted to 0.183 g (0.715 mmol) of crystalline 7-iodoisoquinoline: 58% yield obtained by chromatography (75:25 CH_2Cl_2–C_5H_{12}). Recrystallization from a methylene chloride–petroleum ether mixture produced material: mp 124–128° dec (softening at 118 °C); NMR ($CDCl_3$) δ 6.7–8.0 (m, 4 H), 8.15 (d, J = 7 Hz, 1 H), 8.45 (d, J = 6 Hz, 1 H), 9.10 (s, 1 H); IR (KBr) 942 (s), 830 (s), 800 (s), 638 cm^{-1} (m); high-resolution mass spectrum calcd for C_9H_6NI m/e 254.9543, found m/e 254.9576.

6-Iodoisoquinoline. By use of the general procedure for conversion of indenes to isoquinolines, method A, with methylene chloride (5 mL) as a cosolvent, 0.099 g (0.41 mmol) of 6-iodoindene was converted to 0.068 g (0.27 mmol) of crystalline 6-iodoisoquinoline: 66% yield obtained by chromatography (75% CH_2Cl_2:25% C_5H_{12}); mp 86–88 °C dec; NMR ($CDCl_3$) δ 6.8–8.1 (m, 4 H), 8.25 (dd, J = 6, 1 Hz, 1 H), 8.48 (d, J = 6 Hz, 1 H), 9.17 (s, 1 H); IR (KBr) 940 (m), 810 (s), 738 cm^{-1} (m); high-resolution mass spectrum calcd for C_9H_6NI m/e 254.9543, found m/e 254.9565.

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Registry No. Indene, 95-13-6; 3-methylindene, 767-60-2; 2-methylindene, 2177-47-1; 1-methylindene, 767-59-9; 7-methylindene, 7372-92-1; 6-methylindene, 20232-11-5; 5-methylindene, 7480-80-0; 4-methylindene, 7344-34-5; 4,7-dimethylindene, 6974-97-6; 5-nitroindene, 41734-55-8; 5-bromoindene, 75476-78-7; 5-iodoindene, 75476-79-8; 6-nitroindene, 75476-80-1; 6-bromoindene, 33065-61-1; 6-iodoindene, 75476-81-2; 5,6-dimethoxyindene, 40243-67-2; 1-methylisoquinoline, 1721-93-3; 3-methylisoquinoline, 1125-80-8; 4-methylisoquinoline, 1196-39-0; 5-methylisoquinoline, 62882-01-3; 6-methylisoquinoline, 42398-73-2; 7-methylisoquinoline, 54004-38-5; 8-methylisoquinoline, 62882-00-2; 5,8-dimethylisoquinoline, 75476-82-3; 7-nitroisoquinoline, 13058-73-6; 7-bromoisoquinoline, 58794-09-5; 7-iodoisoquinoline, 75476-83-4; 6-nitroisoquinoline, 70538-57-7; 6-bromoisoquinoline, 34784-05-9; 6-iodoisoquinoline, 75476-84-5; 6,7-dimethoxyisoquinoline, 15248-39-2; isoquinoline, 119-65-3; 5-aminoindene, 75476-85-6; 6-bromoindan-1-one, 14548-39-1; 6-bromoindan-1-ol, 75476-86-7; 5-aminoindan-1-one, 3470-54-0; 5-nitroindan-1-one, 22246-24-8; 5-nitroindan-1-ol, 70840-00-5; 6-aminoindene, 75476-87-8; 5,8-dimethylisoquinoline picrate, 75476-88-9.

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