Improved Synthesis of 3-Methylcholanthrene

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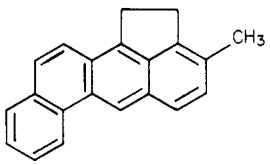
An improved synthesis of 7-methylindan-4-yl 1-naphthyl ketone (**3**), an important precursor of 3-methylcholanthrene (**1**), has been developed. The key intermediates for **3**, 4-cyano-7-methylindan (**2a**) and 4-(ethoxycarbonyl)-7-methylindan (**2b**), were conveniently prepared in high yields by reaction of 1-(1-pyrrolidino)-cyclopentene (**6**) with sorbonitrile (**5a**) or ethyl sorbate (**5b**), followed by aromatization with sulfur. 1-Naphthylmagnesium bromide (**4b**) in the presence of cuprous iodide reacted cleanly with 4-(chloromethanoyl)-7-methylindan (**12**) to give **3**. The Friedel–Crafts acylation of naphthalene with **12** afforded 84% of **3** and 16% of β isomer **13**. Alternatively, **3** was prepared in 75% yield by condensation of Grignard reagent **4b** with **2a** in THF. Thermal annelation of **3** afforded **1** in 41.5% yield.

3-Methylcholanthrene (3-MECA, **1**) has attracted considerable attention because of its widespread use in biochemical experimentation for cancer research. 3-MECA was first discovered by Wieland and Dane[1] in 1933 by degradation of deoxycholic acid (yield 5%). Due to the lack of an efficient degradation process,[1-3] there has been continual interest aimed at the development of an efficient synthesis of 3-MECA. The first synthetic route by Fieser and Seligman[4] in 1935 was an eight-step synthesis. A year later, the same authors described an improved seven-step synthesis for 3-MECA.[5] The key intermediate chosen by Fieser et al. was 4-cyano-7-methylindan (**2a**) which was then converted to 7-methylindan-4-yl 1-naphthyl ketone (**3**), important precursor for 3-MECA. Thermal annelation of **3** gave 3-MECA. Recently, Harvey et al.[6] reported a four-step synthesis starting with *N,N*-diethyl-2-lithionaphthamide and 4-methylindanone. As 3-MECA can be readily prepared by thermal cyclization of **3**, our research efforts have been directed to the synthesis of the precursor **3** and its intermediates. We now report a novel synthesis of **3**. This synthetic approach to **3** is operationally simpler, safer, and more economical than the prior method and is readily adaptable to industrial production.



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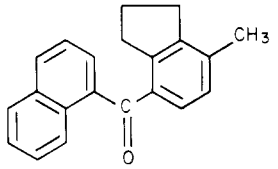
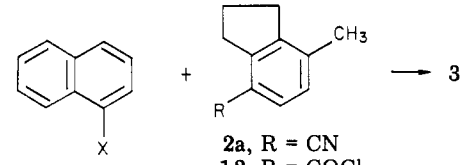


3



4a, X = H
b, X = MgBr
c, X = CuMgBr

2a, R = CN
12, R = COCl

Results and Discussion

An approach involving a reaction between naphthalene (or its organometallic derivative **4**) and 7-methylindan, having at C-4 a carboxylic functional group (or its synthetic equivalent, **2a** or **12**), can be envisioned for the direct synthesis of **3**.

In this approach, the required key intermediates are 4-cyano-7-methylindan (**2a**) and 4-(chloromethanoyl)-7-methylindan (**12**). The success of this approach rests heavily on the development of a suitable method for construction of an indan ring. It is reported that a cycloaddition reaction between an enamine of cyclopentanone and methyl 2,4-pentadienoate gave 4-(methoxycarbonyl)-7,7a-dihydroindan in high yields.[7,8] Thus, by suitable choice of the number and type of atoms bridging a diene and a dienophile, the 1,4-cycloaddition can be the method of choice for obtaining a skeleton of indan having at C-4 a versatile functional group (ester, nitrile, etc.).

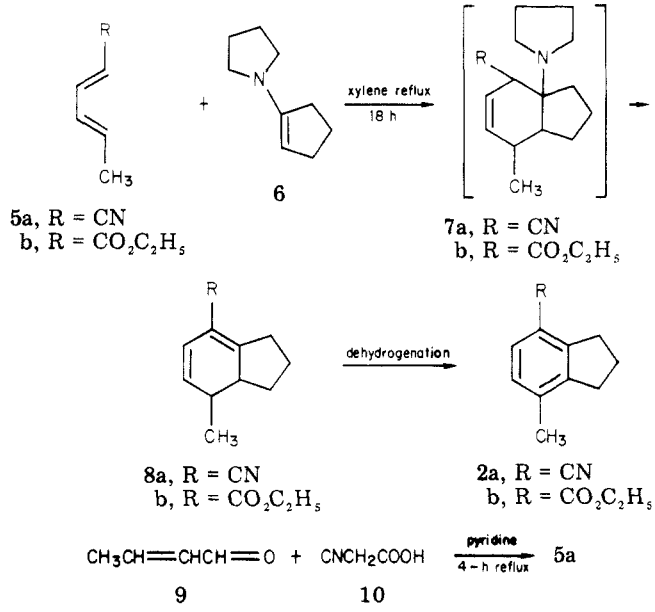
Sorbonitrile (**5a**) was conventiently prepared by condensation of crotonaldehyde (**9**) with cyanoacetic acid (**10**) in pyridine (50% yield; see Scheme I). The syntheses of both 8a and 8b were smoothly accomplished in high yields (76–80%) through the 1,4-cycloaddition in refluxing xylene at atmospheric pressure of the electron-rich pyrrolidine enamine of cyclopentanone (**6**) to the electron-poor butadienyl derivatives (**5a** or **5b**). It is of interest to note that while the cycloaddition was complete in refluxing xylene (140 °C) after 18 h, the same reaction in refluxing dioxane (100 °C) afforded only 50% conversion. Two products were isolated: the expected 1,3-cyclohexadienes (**8**) and the corresponding aromatized compounds (**2**), which were obtained presumably by dehydrogenation of **8** in the course of the reaction. VPC and ^{1}H NMR showed that dehydrogenated compounds **2** were the major components of the mixtures (ca. 80%). Experimental conditions required for oxidation of **8** to **2** with a variety of oxidizing agents have been examined. The oxidation of the dihydroindans **8** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[8] or chloranil to the corresponding indans (**2**) was achieved in refluxing toluene for 18 h. In our hands, the dehydrogenation proceeded even better with sulfur at 185–230 °C for 30 min. The yield was 60% after purification. In contrast to the reported literature, the attempted dehydrogenation of **8** with platinum on carbon or manganese dioxide[7a,9] in refluxing toluene for 48 h failed to afford **2**, while prolonged heating (4 days) gave **2** in very moderate yields. The above two-step synthesis of indans **2a** and **2b**

(1) Wieland, H.; Dane, E. *Z. Physiol. Chem.* **1933**, *219*, 240.
(2) Fieser, L. F.; Newman, M. S. *J. Am. Chem. Soc.*, **1935**, *57*, 961.
(3) Cook, J. W.; Haslewood, G. A. D. *J. Am. Chem. Soc.* **1934**, 428.
(4) Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1935**, *57*, 228.
(5) Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1936**, *58*, 2482.
(6) (a) Jacobs, S. A.; Harvey, R. G., paper presented at the 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 24–30, **1980**; Abstract No. 106. (b) Jacobs, S. A.; Harvey, R. G. *Tetrahedron Lett.* **1981**, 1093. (c) Bachta et al. reported on eight-step synthesis of 3-MECA starting with 7-methyl-1,2-naphthalic anhydride. However, no reaction details were given. Buchta, E.; Gullich, F. *Angew. Chem.* **1958**, *70*, 190.

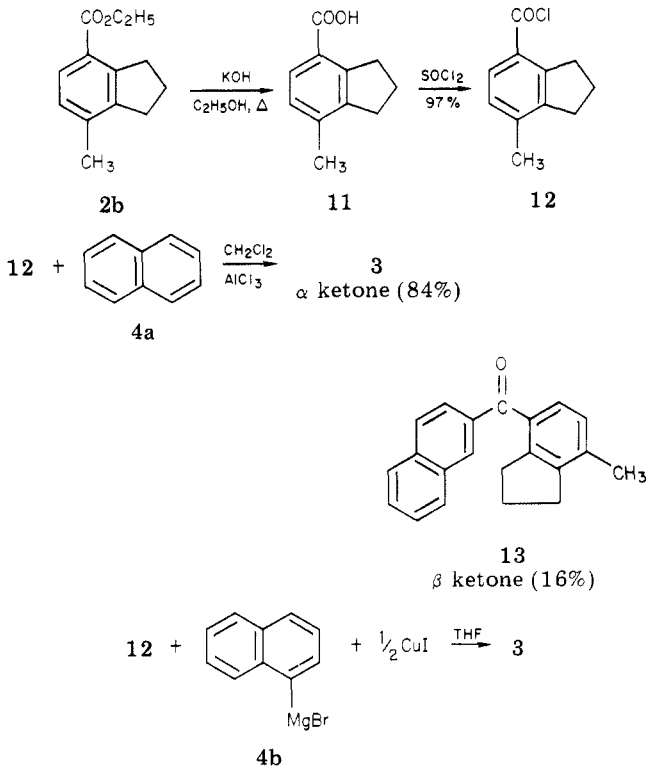
(7) (a) Danishefsky, S.; Cunningham, R. *J. Org. Chem.* **1965**, *30*, 3676. (b) Berchtold, G. A.; Ciabattoni, J.; Tunick, A. A. *Ibid.* **1965**, *30*, 3679.
(8) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.
(9) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

0022-3263/81/1946-3429$01.25/0

Scheme I



Scheme II

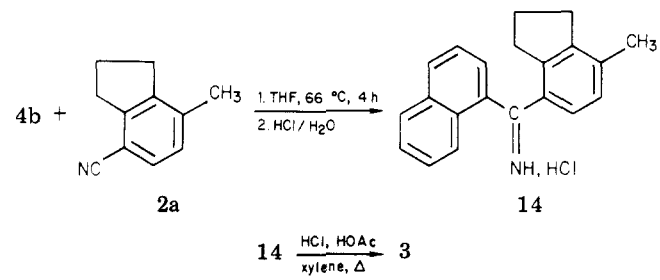


proceeded much more efficiently than those described previously and now provides convenient access on a large scale to ketone **3** and, hence, to 3-MECA (**1**). An additional advantage of the two-step procedure described here is that it obviates the need for the sealed-bomb reaction at high temperature.

The synthesis of 7-methylindan-4-yl 1-naphthyl ketone (**3**) from **2b** was accomplished by conversion of **2b** to the acid chloride **12** followed by either Friedel–Crafts acylation with naphthalene (**4a**) or organometallic reaction with 1-naphthylmagnesium bromide (**4b**) in the presence of cuprous iodide. The syntheses are outlined as shown in Scheme II. It is well documented[10] that Friedel–Crafts

(10) Baddeley, G. *J. Chem. Soc.* **1949**, 99 and references cited therein.

Scheme III



acylation of naphthalene can give regioselectively the α isomer if the reaction is carried out in a chlorinated solvent with a preformed complex (RCO^+, $AlCl_4^-$) as the acylating agent. Attempted acylation of naphthalene with the acid chloride **12** in dichloromethane at 40 °C afforded 84% of the α isomer **3** which was accompanied by 16% of the undesired β isomer (**13**). While Friedel–Crafts acylation is economical, the serious limitation of this reaction for the synthesis of ketone **3** is the presence of the undesired β isomer, which will be reflected in the yields and purity of 3-MECA (**1**). The high purity of **3** is of primary concern in the synthesis of pure 3-MECA. It is now established[11,12] that the reaction of a Grignard reagent in the presence of cuprous iodide with an acid chloride can be an effective synthesis of ketones. The reaction of the organocopper reagent of 1-bromonaphthalene (**4c**) in THF with the acid chloride **12** at 45 °C for 0.5 h afforded the desired isomer **3**. The organometallic reagent reacted so cleanly with **12** that the α ketone **3** could be isolated as a crystalline solid from hexane (70% yield); consequently, no high-vacuum/high-temperature distillation was required as was necessary in previous syntheses. Alternatively, the α isomer **3** was prepared in THF from the Grignard reagent **4b**[13] and 7-cyano-3-methylindan (**2a**), the synthetically equivalent of **2b**. The reaction scheme is outlined as shown in Scheme III.

While the reaction of **2a** with **4b** to yield the ketimine **14** in ether and benzene at reflux required 18 h for completion in the previous synthesis, the same reaction in THF was complete after 4 h at reflux. Hydrolysis of **14** with a mixture of hydrochloric and acetic acids afforded **3** in 75% yield after recrystallization from hexane.

The thermal cyclization at 400 °C of the ketone **3** leading to 3-MECA by the Elbs reaction was successfully achieved in 41.5% following the procedure described by Fieser and Seligman.[5]

Experimental Section

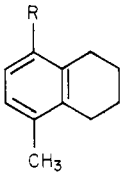
General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B infrared grating spectrometer. Proton NMR spectra were obtained with a Varian A-60 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer with Me_4Si as an internal standard. Chemical shifts are expressed in δ units. High-resolution mass spectra were measured with an AEI-MS902 mass spectrometer. UV spectra were recorded on a Cary Model 118 spectrometer. TLC analysis was conducted on E Merck 60 CF-254, UV-active, silica gel precoated plates. VPC analyses were performed on a Varian 2100 gas chromatograph by using the following columns: (A) 6 ft × 2 mm glass column packed with

(11) (a) Luong-Thi, N. T.; Riviere, H. *J. Organomet. Chem.* **1974**, *77*, C52. (b) Dubois, J. E.; Boussu, M. *Tetrahedron Lett.* **1970**, 2523.

(12) (a) Posner, G. H. *Org. React.* **1975**, *22*, 253. (b) Normant, J. F. *J. Organomet. Chem. Libr.* **1976**, *1*, 219.

(13) (a) Normant, H. *Bull. Soc. Chim. Fr.* **1957**, 728. (b) Normant, H. *Adv. Org. Chem.* **1960**, *2*, 1.

Table I. ^{1}H NMR Data[a] of 4-Substituted 7-Methylindan



R (compd)	chemical shift								
	CO_2CH_2	$CO_2CH_2CH_3$	CH_3	C_2 H	C_1 H	C_3 H	C_6 ArH	C_5 ArH	COOH
$CO_2C_2H_5$ (**2b**)[b]	4.30 (q, J = 7.5)	1.37 (t, J = 7.5)	2.28 (s)	1.85-2.55 (m)	2.83 (t, J = 7.5)	3.28 (t, J = 7.5)	6.93 (d, J = 8)	7.69 (d, J = 8)	
COOH (**11**)[c]			2.24 (s)	1.80-2.40 (m)	2.82 (t, J = 7.5)	3.25 (t, J = 7.5)	7.09 (d, J = 8)	7.73 (d, J = 8)	12.0-12.8 (br s)
COCl (**12**)[d]			2.30 (s)	1.90-2.50 (m)	2.86 (t, J = 7.5)	3.20 (t, J = 7.5)	7.10 (d, J = 8)	7.94 (d, J = 8)	
CN (**2a**)[d]			2.30 (s)	1.90-2.40 (m)	2.90 (t, J = 7.5)	3.07 (t, J = 7.5)	7.06 (d, J = 8)	7.25 (d, J = 8)	

[a] Chemical shifts expressed in δ units; J values are given in hertz; d = doublet, t = triplet, q = quartet, m = multiplet. [b] In CCl_4. [c] In Me_2SO. [d] In $CDCl_3$.

3% OV-17 on Chrom W-AW-DMCS, 80/100 mesh; (B) 6 ft × 2 mm glass column packed with 10% OV-17 on Chrome W-AW-DMCS. VPC coupled with mass spectrometric analysis was performed on a Hewlett-Packard 5930A GC/MS/Data System instrument. Elemental analysis was performed by the Research Laboratories of Eastman Kodak Co.

Reagents and Solvents. Ethyl sorbate was purified by vacuum distillation bp 80–81 °C (15 mm) [lit. 85 °C (20 mm)].[14] 1-(1-Pyrrolidino)cyclopentene was prepared by the method of Stork et al.:[15] 79%; bp 89 °C (15 mm) (lit. bp 88–92 °C). Tetrahydrofuran (Kodak reagent grade) was dried over molecular sieves prior to use. The purified grade cuprous iodide (Fisher Chemical Co.) was used without purification. All reactions involving the enamine of cyclopentanone and organometallic reagents were performed under nitrogen.

Condensation of 1-(1-Pyrrolidino)cyclopentene (6) with Ethyl Sorbate (5b). A solution of ethyl sorbate (**5b**); 490.63 g, 3.5 mol) and enamine **6** (480.27 g, 3.5 mol) in 1600 mL of xylene was heated under reflux overnight. The cooled reaction mixture was washed successively with 10% hydrochloric acid and water and dried over anhydrous magnesium sulfate. The crude product was obtained by concentration of the xylene: yield 584 g (80%); IR (liquid film) 1709 (ν C=O ester), 1645, 1600, 1282, 1130, 769 cm^{-1}. In addition to the signals of the aromatized compound **2b**, which are given in Table I, some characteristic NMR signals belonging to the dihydro compound (**8b**) are as follows: δ 0.95 (3 H, d, J = 6.5 Hz, CH_3), 1.28 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$). The ^{1}H NMR indicated that a 1:4 mixture of the dihydro compound **8b** and the aromatized compound **2b** was present.

4-(Ethoxycarbonyl)-7-Methylindan (2b). A mixture of **8b** and **2b** (185.7 g, 0.9 mol) and 28.8 g (0.9 mol) of sulfur were heated at 230 °C for 30 min. After the mixture cooled, the residue was distilled under vacuum to give 111 g, (60.4%) of **2b**: bp 110–112 °C (0.45 mm); IR (liquid film) 1709 (ν C=O ester), 1600 (aromatic), 1282, 1266, 1130, 769 cm^{-1}; ^{1}H NMR data are given in Table I; ^{13}C NMR ($CDCl_3$) δ 14.46 (CH_3 of the ester), 19.45 (CH_3 substituted at C-7), 24.39 (C-2), 31.23 (C-1), 34.36 (C-3), 60.22 (CH_2 of the ester group); 127.19 (C-6), 128.54 (C-5), 134.98 (C-7), 138.55 (C-4), 144.83 (C-7a), 146.34 (C-4a), 167.99 (CO_2 ester); high-resolution mass spectrum, m/e (relative intensity, assignment) 204.1135 (65, M^+); TLC (benzene/dioxane/acetic acid, 60/42/2) R_f 0.69.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.50; H, 7.90.

4-(7-Methylindan)carboxylic Acid (11). To a solution of 102.2 g (0.5 mol) of **2b** in 1.2 L of ethanol was added a solution of 140 g (2.5 mol) of potassium hydroxide in 50 mL of water. The resulting green reaction mixture was refluxed under nitrogen overnight. The ethanol was removed in vacuo, and the resulting gray residue was dissolved in 1.2 L of water. The aqueous solution was washed with 300 mL of dichloromethane, cooled to 10 °C, and acidified with 215 mL (2.5 mol) of concentrated hydrochloric acid. After acidification, the resulting pink solid was stirred for an additional 30 min at 10 °C and collected. It was washed with water and dried in a vacuum oven at 70 °C for 3 days. The yield of **11** was 84 g (95%): mp 227–229 °C (lit.[16] mp 228–229 °C); IR (KBr) 1664 (ν C=O acid), 3226–2500 (ν_{OH}, acid) 947 cm^{-1}; ^{1}H NMR data are given in Table I.

4-(Chloromethanoyl)-7-methylindan (12). A mixture was 28 g (0.16 mol) of **11** and 70.9 mL (0.96 mol) of thionyl chloride was refluxed under nitrogen for 1 h. Excess thionyl chloride was removed at reduced pressure (15 mm). The resulting residue was heated at 40 °C under vacuum (1 mm) for 1 h to remove the last traces of thionyl chloride 30 g (97%), and a viscous oil was obtained, which rapidly crystallized upon standing: IR (KBr) 1754 ν C=O, acid chloride), 1592, 1575 cm^{-1}; ^{1}H NMR data are given in Table I.

7-Methylindan-4-yl 1-Naphthyl Ketone (3). To the 1-naphthylmagnesium bromide[13] prepared from 4.28 g (0.176 mol) of magnesium turnings and 36.44 g (0.176 mol) of 1-bromonaphthalene in 200 mL of THF at 45 °C was added under nitrogen 16.8 g (0.088 mol) of cuprous iodide. After the mixture was stirred for 15 min at 45 °C, a solution of 30 g (0.154 mol) of acid chloride **12** in 200 mL of dry THF was added slowly. After completion of the addition, the mixture was stirred at 45 °C for an additional 0.5 h. The reaction mixture was cooled, poured onto a well-stirred saturated solution of ammonium chloride at 5 °C, and extracted with xylene. The combined organic phase was washed with a dilute potassium carbonate solution and evaporated in vacuo. The residual oil was steam distilled to remove naphthalene and aromatic hydrocarbons. The cooled mixture was extracted with xylene. The organic layer was treated with Norit, dried over anhydrous magnesium sulfate, and evaporated in vacuo to afford 39.2 g (89%) of crude ketone **3** as a brown oil. Hexane was added, and the mixture was slowly cooled to −40 °C. The solid which formed was slowly warmed to room temperature, collected, and dried to give 30.8 g (70.1%) of **3** as a pale yellow solid: mp 83–85 °C; TLC (toluene/acetic acid, 98/2) R_f 0.39; IR (KBr) 1644 (ν C=O), 1593, 1574, 1280, 1250, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90–2.50 (2 H, m, C_2H), 2.30 (3 H, s, CH_3), 2.90 (2 H, t, J = 7.5 Hz, C_1 H), 3.25 (2 H, t, J = 7.5 Hz, C_3H), 6.94 (1 H, d, J = 8 Hz, the aromatic proton of C-6), 7.10–8.40 (8 H, m, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.60 (CH_3), 24.77 (C-2), 31.12 (C-1), 33.91 (C-3), 124.49, 125.88, 126.34, 127.01, 127.44, 127.59, 128.37 (the 9 aromatic carbons having a C–H bond), 133.08, 133.90 (C-9′, C-10′), 136.80 (C-7), 138.09 (C-4), 139.04 (C-1′), 144.78, 146.02

(14) Weast, R. C. "*Handbook of Chemistry and Physics*", 59th ed.; The Chemical Rubber Publishing Co.: West Palm Beach, FL, 1979.
(15) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(16) Murry, R. D. H.; Parker, W.; Raphael, R. A.; Jhaveri, D. B. *Tetrahedron* **1962**, *18*, 55.

(C-4a, C-7a, 199.05 (C=O); UV (CH_3OH) λ_{max} 269 nm (ϵ 14 100); VPC (column A, 230 °C) retention time 4.2 min.

7-Methylindan-4-yl 2-Naphthyl Ketone (13). The β-ketone **13** was prepared following the same procedure for **3** with 2-bromonaphthalene as starting material: IR (film) 1640 ($\nu_{C=O}$), 1590, 1280, 1240, 812, 770, 732 cm^{-1}; NMR ($CDCl_3$)δ 1.80–2.50 (2 H, m, C_2 H), 2.30 (3 H, s, CH_3), 2.88 (2 H, t, J = 7.5 Hz, C_1 H), 3.15 (2 H, t, J = 7.5 Hz, partially overlapped with the triplet centered at 2.88 ppm, C_3-H), 7.05 (1 H, d, J = 8 Hz, the aromatic proton of C-6), 7.30–8.40 (8 H, m, aromatic protons); VPC analysis (column A, 230 °C) retention time 4.7 min; UV (CH_3OH) λ_{max} 216 (ϵ 55 400).

7-Methylindan-4-yl 1-Naphthyl Ketone (3) by Friedel–Crafts Acylation. To a solution of 97.4 g (0.5 mol) of acid chloride (**12**) in 200 mL of dichloromethane was added 66.7 g (0.5 mol) of aluminum chloride. After the mixture was stirred for 20 min at 35 °C, a solution of 64.1 g (0.5 mol) of naphthalene in 200 mL of dichloromethane was added at such a rate that a gentle reflux was maintained. After the addition, the reaction mixture was refluxed for 1 h and then cooled to room temperature. Most of the dichloromethane was removed. A cold solution of 10% HCl (300 mL) was added to the well-stirred viscous residue cooled in an ice bath. After being stirred for 25 min, the mixture was extracted with xylene. The combined organic phase was washed with 300 mL of a 0.5 N solution of potassium carbonate and evaporated in vacuo. The residual oil was steam distilled. The cool mixture was extracted with xylene. The organic layer was treated with Norit and dried over anhydrous magnesium sulfate. The yield of the crude product (oil), after removal of the xylene in vacuo, was 109 g (76%). The VPC analysis (column A, 230 °C) indicated a mixture of two isomers: α isomer **3** (84%, retention time 4.2 min) and β-isomer **13** (16%, retention time 4.7 min).

2,4-Hexadienenitrile (Sorbonitrile, 5a). A mixture of 255.2 g (3 mol) of cyanoacetic acid and 210 g (3 mol) of crotonaldehyde in 360 mL of pyridine was refluxed (96 °C) for 4 h. To the cooled red homogeneous reaction mixture (10 °C) was added slowly 350 mL of a 6.6 N solution of sulfuric acid. After being stirred and cooled, the reaction miiture was extracted with dichloromethane. The combined organic layer was washed with water and rotoevaporated in vacuo at 20 °C. The residual oil was distilled in the presence of a small amount of hydroquinone to afford 140 g (50%) of **5a**: bp 70–70.5 °C (15 mm); IR (neat) 2200 ($\nu_{C\equiv N}$), 1635, 1600 (conjugated diene), 1445, 990, 725 cm^{-1}; NMR (CCl_4) δ 1.90 (3 H, dd, $^3J_{C=CHCH_3}$ = 6 Hz, $^4J_{HC=CCH_3}$ = 3 Hz, CH_3), 5.05–7.50 (4 H, m, the four vinylic protons); ^{3}VPC (column B, programmed from 100 to 200 °C) indicated that the product is a mixture of three geometric isomers; mass spectrum, m/e (relative intensity, assignment), 93.0576 (33, M^+); TLC (toluene/acetic acid, 98/2 R_f 0.27; UV (CH_3OH) λ_{max} 253 nm (ϵ 12 100).

Condensation of 1-(1-Pyrrolidino)cyclopentene (6) with Sorbonitrile (5a). A mixture consisting of 252.4 g (3 mol) of cyclopentanone, 213.4 g (3 mol) of pyrrolidine, and 900 mL of xylene was stirred at gentle reflux; water was collected with a Dean–Stark condenser. When there was no more water separated from the condensed liquid, the reaction was cooled to ca. 40 °C, and 279.4 g (3 mol) of **5a** was added rapidly to the enamine solution. The reaction mixture was refluxed overnight. The mixture was cooled, and 830 mL of a 15% solution of HCl was added. After being stirred for 15 min, the mixture was extracted with xylene. The combined extracts were washed with water, dried over anhydrous potassium carbonate, and evaporated in vacuo to afford 359.3 g (76.2%) of a mixture of oil and white solid (needles), IR (neat) 2200 cm^{-1} ($\nu_{C\equiv N}$). The NMR spectrum (CCl_4) was almost the same as that of pure **2a** described below, except for δ 0.85–1.10 (3 H, m, CH_3) which belonged to the dihydro compound **8a**. VPC analysis (column B, from 130 to 300 °C) showed that the product was a mixture of two products: **2a** (83.2%) and **8a** (16.8%).

4-Cyano-7-methylindan (2a). A mixture of **8a** and **2a** (107.8 g, ca 0.68 mol) and 17.4 g (0.54 mol) of sulfur were heated to 210–220 °C for 40 min. After cooled, the residue was distilled, and the fraction boiling between 40 and 165 °C (15 mm) was collected. The distillate, which solidified upon cooling, was slurried in 150 mL of heptane and collected. The yield of **2a** as a white solid was 62.8 g (59%): mp 72–74 °C (lit.[5] mp 72.9–73.2 °C); IR (KBr) 2200 ($\nu_{C\equiv N}$), 1600 (aromatic), 1480, 1460 1430, 828 cm^{-1}; the proton NMR data are given in Table I; TLC (toluene/acetic acid, 98/2) R_f 0.39; VPC (column B from 130 to 300 °C) retention time 4.3 min (the product appeared pure by VPC analysis); UV (CH_3OH) λ_{max} 289 nm (ϵ 2140); high-resolution mass spectrum, m/e (relative intensity, assignment), 157.0902 (43, M^+).

7-Methylindan-4-yl 1-Naphthyl Ketimine (14). Reaction of 1-Naphthylmagnesium Bromide with 2a. To the 1-naphthylmagnesium bromide prepared from 7.29 g (0.3 mol) of magnesium turnings and 62.2 g (0.3 mol) of 1-bromonaphthalene in 240 mL of dry THF at about 66 °C was added slowly a solution of 31.4 g (0.2 mol) of **2a**. The resulting brown solution was refluxed for 4 h. About 160 mL of THF was removed by distillation. The reaction mixture was cooled, poured onto a mixture of ice and 228 mL of concentrated hydrochloric acid, allowed to warm up progressively to room temperature, and stirred overnight. The yellow solid was collected and washed with hexane. Ketimine **14** (64.4 g, 100%) was obtained and used without further drying. A sample was dried in a warm oven: mp 217 °C dec; IR (KBr) 3500 (NH stretch), 1630 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.60–3.00 (6 H, m, the protons of the cyclopentane ring), 2.30 (3 H, s, CH_3), 7.10–8.20 (9 H, m, aromatic protons).

7-Methylindan-4-yl 1-Naphthyl Ketone (3). Hydrolysis of 14. A mixture containing 64 g (0.2 mol) of **14**, 262 mL of water, 180 mL of acetic acid, 135 mL of concentrated hydrochloric acid, and 156 mL of xylene was refluxed for 4 h. After the mixture cooled, the xylene solution was separated. The aqueous phase was extracted with xylene. The combined organic extracts were washed with water, dried over anhydrous potassium carbonate, and evaporated in vacuo to afford an oil which slowly crystallized upon standing overnight. Recrystallization from hexane gave 43 g (75%) of **3** as a white solid which appeared pure by TLC analysis (toluene/acetic acid, 98/2); R_f 0.39), mp 83–85 °C. The spectroscopic data were identical with those of an authentic sample.

3-Methylcholanthrene (1). By use of the procedure described by Fieser and Seligman,[5] 3-MECA was prepared: 41.5% yield; mp 179–181 °C (lit.[5] mp 178–179 °C).

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Registry No. 1, 56-49-5; **2a**, 15085-20-8; **2b**, 71042-72-3; **3**, 63665-87-2; **5a**, 1516-01-4; **5b**, 2396-84-1; **6**, 7148-07-4; **8a**, 78064-86-5; **8b**, 71042-73-4; **9**, 4170-30-3; **10**, 372-09-8; **11**, 71042-74-5; **12**, 71042-75-6; **13**, 78064-87-6; **14**, 63549-35-9; 1-bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; naphthalene, 91-20-3; cyclopentanone, 120-92-3; pyrrolidine, 123-75-1.