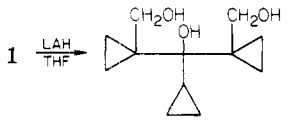
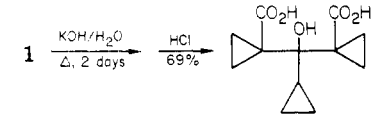


(4)

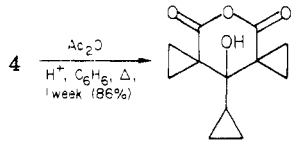
3



(5)

4

not yield the corresponding anhydride by azeotropic removal of water (catalytic *p*-toluenesulfonic acid in refluxing benzene); however, acetic anhydride in refluxing benzene with acid catalysis for 1 week sucessfully gave the desired anhydride **5** (eq 6).



(6)

5

In conclusion, the base-catalyzed condensation of ethyl cyclopropanecarboxylate allows simple entry into tricyclopropyl compounds. The difficulty in generating the anion of cyclopropyl esters, acids, and nitriles can be attributed to lower acidity as well as abnormally high reactivity of the anion[17] because of little resonance stabilization.[18]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. All reactions involving strong bases (LDA, trityllithium, or KH) were run under nitrogen in glassware which was flamed out. Tetrahydrofuran was distilled from potassium. Microanalyses were performed by Atlantic Microlab. Infrared spectra were obtained on Perkin-Elmer Models 237B, 257, and 297 spectrometers. Proton NMR spectra were determined on a Varian T-60 and EM-390 spectrometers. Hydrogen-decoupled ^{13}C NMR spectra were recorded on a JEOL PFT-100 spectrometer. Mass spectra were obtained on a Hewlett-Packard Model 5992-B GC/MS.

Preparation of Diester 1. Diisopropylamine (14.6 mL, 104 mmol) was dissolved in 60 mL of THF and the solution cooled to 0 °C. A solution of *n*-butyllithium/hexane (38.3 mL of 2.5 M solution, 96 mmol) was added, and the reaction mixture was stirred for 30 min and cooled to −78 °C. Ethyl cyclopropanecarboxylate (18.2 g, 160 mmol) in 30 mL of THF was added dropwise over 15 min, and the resulting solution was stirred for 30 min at −78 °C and allowed to warm to room temperature over 1 h. The reaction mixture was poured into 100 mL of saturated aqueous NaCl, and this was extracted with three 50-mL portions of ether which were combined, dried over $MgSO_4$, and concentrated to give 13.8 g (87%) of crude product. Recrystallization from hexane gave 9.5 g (60%) of pure crystals: mp 36–37 °C; ^1H NMR (CCl_4) 0.2–0.6 (m, 5 H), 0.6–1.6 (m, 8 H), 1.25 (t, J = 7 Hz, 6 H), 2.1 (s, 1 H), 4.2 (q, J = 7 Hz, 4 H); ^{13}C NMR ($CDCl_3$)[19] δ −0.67 (t, CH_2), 11.64 (t, CH_2), 14.08 (q, CH_3), 14.26 (d, CH), 32.80 (s, C), 60.60 (t, CH_2), 69.86 (s, C), 174.28 (s, C); IR (KBr) 3420, 3100, 3000, 1710, 1360, 1295, 1130, 1000 cm^{-1}; mass spectrum, *m/e* 280, 265, 251, 223, 197, 177.

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.20.

Reduction of Diester 1 to Triol 3. Lithium aluminum hydride (0.23 g, 6.0 mmol) was added to 50 mL of THF under N_2 at −78 °C, and 1.48 g (5.00 mmol) of diester **1** in 10 mL of THF was added dropwise. The reaction mixture was allowed to warm to room temperature and to stir for 5 days. Excess hydride reagent was quenched with methanol, and 1 mL of saturated aqueous Na_2SO_4 was added. This mixture was stirred for 10 min, anhydrous $MgSO_4$ was added, and the crude triol was isolated after filtration and concentration. Recrystallization from hexane/ether gave 1.00 g (94%) of the triol after drying under vacuum; mp 69–70 °C.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 65.20; H, 9.05. Calcd for $C_{12}H_{20}O_3 \cdot {}^1/_2H_2O$: C, 65.10; H, 9.57.

The sample was dried at 60 °C under vacuum overnight: mp 82–83 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.1–0.6 (m, 8 H), 0.7–1.4 (m, 5 H), 2.4 (br s, 3 H), 3.4 (d, J = 12 Hz, 2 H), 4.0 (d, J = 12 Hz, 2 H); IR (KBr) 3300, 3000, 1420, 1020, 990, 930 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.91; H, 9.52.

Preparation of Diacid 4. The diester **1** (1.48 g, 5.00 mmol) and potassium hydroxide (2.0 g, 36 mmol) in 45 mL of water were refluxed for 24 h and then cooled. Dilute HCl was added until the pH was 3, and the mixture was filtered. The crude solid was recrystallized from acetone/hexane to give 0.85 g (71%) of crystalline product: mp 160–163 °C; ^1H NMR (acetone-d_6, 90 MHz) −0.5–0.0 (m, 3 H), 0.1–1.0 (m, 10 H), 6.0 (br s, 3 H); IR (KBr) 3500, 2400–3300, 1680, 1420, 1310, 1195, 1030 cm^{-1}.

This diacid (72 mg, 0.30 mmol) was stirred with 38 mg (1.0 mmol) of LAH in 25 mL of THF for 2 days at room temperature. Workup as usual for the LAH reductions gave 50 mg (0.23 mmol, 77%) of material identical by ^1H NMR and TLC with the triol **3**.

Preparation of Anhydride 5. The diacid **4** (0.400 g, 1.67 mmol) was combined with acetic anhydride (0.51 g, 5.0 mmol) and *p*-toluenesulfonic acid (20 mg) in 50 mL of benzene, and the resulting solution was refluxed for 24 h and then cooled. Ammonia was bubbled through the reaction mixture until no more precipitate was formed. This was filtered, and the filtrate was concentrated to give 0.32 g (86%) of crystalline product: mp 84–88 °C; ^1H NMR (acetone-d_6) 0.4–0.7 (m, 5 H), 1.2–1.7 (m, 8 H), 3.7 (s, 1 H); IR (KBr) 3420, 3000, 1780, 1735, 1380, 1340, 1260, 1085, 1065, 1010 cm^{-1}.

Acknowledgment. We thank Dr. Stanford Smith and W. J. Layton for their assistance with the ^{13}C NMR spectra.

Registry No. **1**, 74808-31-4; **3**, 74808-32-5; **4**, 74808-33-6; **5**, 74824-37-6; ethyl cyclopropanecarboxylate, 4606-07-9; acetic anhydride, 108-24-7.

(17) Ester enolates are known to undergo self-condensation at room temperature: Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.

(18) The *tert*-butyl ester of cyclopropanecarboxylic acid was allowed to react with LDA (1.1 equiv) at −78 °C, quenched with allyl bromide (2.5 equiv), and allowed to warm to room temperature. No alkylation was observed, and the starting material was recovered.

(19) Multiplicities were determined from an off-resonance-decoupled (ORD) spectrum.

Synthesis of 8-Fluoro- and 10-Fluoro-3-methylcholanthrenes. Observations on the Elbs Reaction[1]

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Received May 6, 1980

The carcinogenic hydrocarbon 3-methylcholanthrene, **1**, has best been synthesized by means of the Elbs reaction,[3] a ring closure reaction which involves pyrolysis of 7-methyl-4-(1-naphthoyl)hydrindene, **2**, at temperatures near 400 °C. Recently we have become interested in

(1) This work was supported by Grant No. CA07394 from the NCI, department of HEW.

(2) Postdoctoral research associate.

(3) See Fieser, L. F. *Org. React.* **1942**, *1*, 129.

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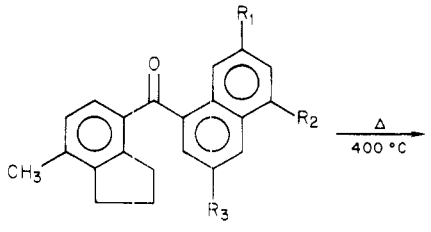
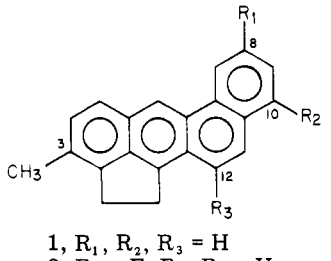
preparing fluorinated and hydroxylated methylcholanthrenes for use by researchers interested in learning if the bay region theory of carcinogenesis[4] is applicable to 1. In this paper we report the synthesis of 8-fluoro-3-methylcholanthrene, 3, and 10-fluoro-3-methylcholanthrene, 4, by the Elbs reaction but the failure of attempts to prepare 10-methoxy-3-methylcholanthrene and 12-fluoro-3-methylcholanthrene. The successful syntheses of 3 and 4 show that fluorinated methylcholanthrenes containing fluorine in the angular benzene ring can be readily prepared. However, the failures to produce 11-fluoro-3-methylcholanthrene[5] and 12-fluoro-3-methylcholanthrene (this paper) show that alternate synthetic schemes to the Elbs route must be developed. The failure to prepare the 10-methoxy compound parallels the failure to produce the 11-methoxy compound previously reported,[6] whereas both 8-methoxy-[6] and 9-methoxy-3-methylcholanthrenes[7] have been prepared.

The substituted 7-methyl-4-(substituted naphthoyl)-hydrindenes, 5–8, were prepared by reaction of the appropriate naphthyl Grignard reagents with 4-cyano-7-methylhydrindene[8] followed by hydrolysis of the imines.



2, R_1, R_2, R_3 = H
5, R_1 = F; R_2, R_3 = H
6, R_2 = F; R_1, R_3 = H
7, R_3 = F; R_1, R_3 = H
8, R_2 = OCH_3; R_1, R_3 = H



1, R_1, R_2, R_3 = H
3, R_1 = F; R_2, R_3 = H
4, R_2 = F; R_1, R_3 = H

Experimental Section[9]

4-(7-Fluoro-1-naphthoyl)-7-methylhydrindene*, 5. The Grignard reagent prepared from 12.5 g of 1-bromo-7-fluoronaphthalene,[10] 9.4 g of ethylene dibromide, and 2.7 g of sublimed magnesium in 200 mL of ether (dried by distillation from Grignard reagent) was treated with a solution of 7.85 g of 4-cyano-7-methylhydrindene[8] in 150 mL of benzene. After being held at reflux for 24 h, the mixture was treated with ammonium chloride solution and concentrated HCl. The pale yellow solid was collected after the usual workup and heated with 200 mL of water for 2.5 h. After the usual workup the product was crystallized from hexene to yield 12.5 g (82%) of 5, mp 104–105 °C.

4-(5-Fluoro-1-naphthoyl)-7-methylhydrindene*, 6. Reaction of 4-cyano-7-methylhydrindene with the Grignard reagent from 1-bromo-5-fluoronaphthalene[11] as above yielded 6, mp 110–111 °C, in 67% yield.

4-(3-Fluoro-1-naphthoyl)-7-methylhydrindene*, 7. In a similar way 1-bromo-3-fluoronaphthalene[12] afforded 7, mp 86–87 °C, in 69% yield. In the preparation of the bromofluoronaphthalene, the reduction of 1-bromo-3-nitronaphthalene to the amino compound, mp 70–71 °C, was effected in 95% yield by heating with iron powder and 65% alcohol with a small amount of concentrated HCl essentially as described for a different nitro compound.[13]

4-(5-Methoxy-1-naphthoyl)-7-methylhydrindene*, 8. 1-Amino-5-bromonaphthalene was prepared as described[11] and converted into 1-bromo-5-methoxynaphthalene[14] which, via the Grignard reagent, was used to prepare 8, mp 108–109 °C, in 60% yield.

8-Fluoro-3-methylcholanthrene*, 3. After 6.0 g of 5 was heated at 405–410 °C for 30 min by means of a sodium nitrate–potassium nitrite salt bath,[12] the product was chromatographed on neutral alumina, using benzene–petroleum ether (1:3), to yield 1.2 g (21%) of pale yellow prisms of 3, mp 182–183 °C.

10-Fluoro-3-methylcholanthrene*, 4. In a similar way 2.0 g of 6 afforded 0.9 g (47%) of 4 as pale yellow prisms, mp 208–209 °C.

Registry No. 3, 74924-89-3; 4, 74924-90-6; 5, 74924-91-7; 6, 74924-92-8; 7, 668-84-8; 8, 74924-93-9; 1-bromo-7-fluoronaphthalene, 13790-91-5; 4-cyano-7-methylhydrindene, 15085-20-8; 1-bromo-5-fluoronaphthalene, 315-56-0; 1-bromo-3-fluoronaphthalene, 343-53-3; 1-bromo-3-nitronaphthalene, 7499-65-2; 3-amino-1-bromonaphthalene, 74924-94-0; 1-amino-5-bromonaphthalene, 4766-33-0; 1-bromo-5-methoxynaphthalene, 74924-95-1.

(4) See ref 1 and 2 in Yagi, H.; Thakker, D. R.; Lehr, R. E.; Jerina, D. M. *J. Org. Chem.* **1979**, *44*, 3439.
(5) Unpublished work by Dr. Kannan in this laboratory.
(6) Fieser, L. F.; Desreux, V. *J. Am. Chem. Soc.* **1938**, *60*, 2255.
(7) Cook, J. W.; de Worms, C. G. M. *J. Chem. Soc.* **1937**, 1825.
(8) Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1936**, *58*, 2482.
(9) All melting points are uncorrected. All compounds marked with an asterisk gave analyses within ±0.3% of the theoretical and NMR spectra consistent with the proposed structures. The phase "worked up in the usual way" means that an ether–benzene solution of the products was washed with dilute Na_2CO_3 solution, dilute HCl, and saturated salt solution and dried by passing through dry $MgSO_4$.
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(11) Newman, M. S.; MacDowell, D.; Swaminathan, S. *J. Org. Chem.* **1959**, *24*, 509.
(12) Newman, M. S.; Galt, R. H. B. *J. Org. Chem.* **1960**, *25*, 214.
(13) Mah, S. A.; Schaffner, P. V. L. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, 160.
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Pyrolysis of Alkyl 2- or 6-Alkoxynicotinates. An Unexpected Decarbalkoxylation Reaction[1]

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During our studies related to the thermal conversion of pyridinol to pyridinone macrocycles (1 → 2) via an O → N rearrangement,[3,4] we conducted preliminary studies on a series of alkyl 2- or 6-alkoxynicotinates in order to define the reaction parameters. When ethyl 2-ethoxynicotinate (3a, R = R′ = Et) was pyrolyzed at 240 °C for 30 h, 4a (30%) was isolated, along with unchanged starting material, whereas at 280 °C for 30 h the exclusive (>95%)

(1) Chemistry of Heterocyclic Compounds. Part 58. For the previous related paper in this series, see: Newkome, G. R.; Kawato, T.; Benton, W. H. *J. Org. Chem.* **1980**, *45*, 626.
(2) On leave from Kyushu University, Fukuoka, Japan, 1977–1979.
(3) (a) Wiberg, K. B.; Shryne, T. M.; Kintner, R. R. *J. Am. Chem. Soc.* **1957**, *79*, 3160. (b) Cohen, L. A.; Witkop, B. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1964; Vol. 2, p 981. (c) Brown, D. J.; Foster, R. V. *J. Chem. Soc.* **1965**, 4911. (d) Rautenstrauch, V. *Helv. Chim. Acta* **1973**, *56*, 2492. (e) Roberts, R. M.; Hussein, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 1950. (f) Ranganathan, S.; Ranganathan, D.; Sidhu, R. S.; Arora, A. K. *Tetrahedron Lett.* **1973**, 3577. (g) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
(4) Tieckelmann, H. *Heterocycl. Compd.* **1974**, *14*, 833–839.

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