and evaporated to yield an oil. Trituration of this oil with 5 mL of cold hexane affords 70 mg (53%) of crude acid 1. Recrystallization from hexane furnishes 30 mg of pure 1 as pale yellow crystals: mp 153–154 °C; $^1$H NMR ($CDCl_3$) δ 6.93 (1 H, t), 6.33 (1 H, s), 6.16 (1 H, d), 5.76 (1 H, s), 3.36 (1 H, br s), 3.16 (1 H, d), 2.33 (3 H, s), 1.76 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.06 (3 H, s); IR ($CH_2Cl_2$) $\nu_{max}$ 1680, 1600 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 302 (ε 50 000); MS, *m/e* (rel intensity) 316 (10.36). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.91. Found: C, 75.58; H, 9.13.

**7,8-Epoxy-7,8-dihydroretinol (3).** To a stirring solution of ester **2** (520 mg, 1.57 mmol) in 6 mL of THF under a nitrogen atmosphere at −78 °C is added 3.5 mL of 1 M diisobutylaluminum hydride in hexane over a period of 20 min. After the addition is complete, the mixture is stirred for 20 min more at −78 °C and is then allowed to warm to −20 °C, at which point 2 mL of water is added. The resulting mixture is warmed to room temperature, and 10 mL of ether is added. The ether phase is separated and washed with water (3 × 10 mL). Removal of solvent under reduced pressure affords alcohol **3** (450 mg, 94%) as a pale yellow oil. Purification may be achieved by chromatography on Woelm activity V alumina, eluting with ether/hexane (30:70). Pure alcohol **3** is a colorless oil (405 mg, 85%): $^1$H NMR ($CDCl_3$) δ 6.10–6.66 (3 H, m), 5.63 (1 H, t), 4.23 (2 H, d), 3.40 (1 H, m), 3.13 (1 H, d), 1.83 (3 H, s), 1.70 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.06 (3 H, s); IR (neat) $\nu_{max}$ 3450, 1690 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 284 (ε 35 000); MS, *m/e* (rel intensity) 302 (1.06). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99. Found: C, 79.66; H, 9.80.

**7,8-Epoxy-7,8-dihydroretinal (4).** To a stirring solution of alcohol **3** (130 mg, 0.43 mmol) and three drops of triethylamine in 5 mL of pentane under a nitrogen atmosphere is added 400 mg of γ-$MnO_2$. The reaction course is monitored by thin-layer chromatography (silica gel, 30:70 ether/hexane). After the starting material disappears (about 20 min), 10 mL of ether is added, and the mixture is filtered. Removal of solvent affords 100 mg (77%) of yellow oil which is shown by $^1$H NMR to be a 80:20 mixture of aldehydes **4** and **6**. Preliminary purification may be effected by chromatography on Woelm activity V alumina, eluting with hexane/ether (85:15). In this manner, 40 mg (31%) of a mixture of **4** and **6** was obtained. The two diastereomers are rather difficult to separate, mainly because they are somewhat unstable. We succeeded in obtaining 15 mg of the pale yellow aldehyde **4**, of 95% purity, for analytical and biological evaluation: $^1$H NMR ($CDCl_3$) δ 10.00 (1 H, d), 5.66–6.83 (4 H, m), 3.30 (1 H, m), 3.03 (1 H, d), 2.3 (3 H, s), 1.76 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.03 (3 H, s); IR ($CCl_4$) $\nu_{max}$ 1660, 1613, 1600 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 337 (ε 27 000); MS, *m/e* (rel intensity) 300 (7.06); high-resolution MS: $C_{20}H_{28}O_2$ requires *m/e* 300.2089. Found: *m/e* 300.2088.

**Acknowledgment.** Support for this work was provided by a contract from the National Cancer Institute (CP-75934).

**Registry No.** 1, 71685-87-5; **2**, 71685-88-6; **3**, 71685-89-7; **4**, 71685-90-0; **5**, 71748-35-1; **6**, 71748-36-2; **7**, 71685-91-1; **8**, 71685-92-2; **9**, 71685-93-3; **10**, 38448-31-6; methyl (*E*)-3-formylbut-2-enoate, 40835-18-5; triethyl phosphite, 122-52-1; β-ionone, 14901-07-6.

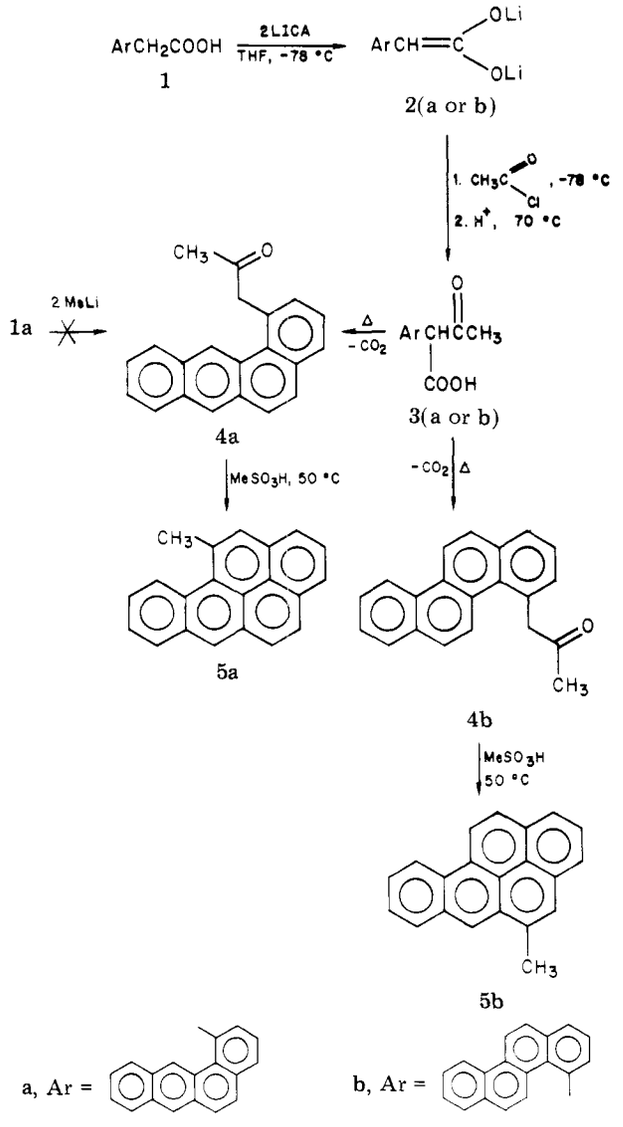
## New Synthesis of 5-Methylbenzo[*a*]pyrene and 11-Methylbenzo[*a*]pyrene [1,2]

Richard S. Bodine and Guido H. Daub*

*Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131*

*Received May 10, 1979*

In the course of developing useful syntheses of the potent carcinogen benzo[*a*]pyrene labeled with $^{13}$C (90%) at each of the peripheral carbon atoms, we had available the arylacetic acids **1a** and **1b**[3] which are likely intermediates for the preparation of 11-methylbenzo[*a*]pyrene (**5a**) and 5-methylbenzo[*a*]pyrene (**5b**) via the ketones **4a** and **4b**, respectively. Attempts to prepare the ketone **4a** by the




addition of 2 equiv of methyllithium to a THF solution of the acid[4] **1a** failed, the only product isolated being the unreacted acid **1a**. Apparently the second equivalent of methyllithium converted the lithium salt of the acid to the dilithium enolate **2a** rather than to the methyl ketone **4a**.

Since the dilithium enolates of carboxylic acids containing at least one α-hydrogen are readily prepared[5] and lithium enolates of esters have been shown to react with acid chlorides to form substituted β-keto esters,[6] we investigated the reaction of the dilithioenolate **2a** with acetyl chloride.[7] Indeed, the reaction of 1-benz[*a*]anthraceneacetic acid (**1a**) with 2 equiv of lithium *N*-isopropylcyclohexylamide (LICA) in THF at −78 °C followed by treatment with acetyl chloride afforded 2-(benz[*a*]anthracen-1-yl)-3-oxobutanoic acid (**3a**) which was decarboxylated at 120–130 °C to give 1-(benz[*a*]anthracen-1-yl)-2-

(1) From the Dissertation presented by R. S. Bodine in partial fullfillment for the Ph.D., Dec 1979.

(2) Supported in part by Grant No. CA 16871 from the National Cancer Institute, DHEW.

(3) R. S. Bodine, M. Hylarides, G. H. Daub, and D. L. VanderJagt, *J. Org. Chem.*, **43**, 4025 (1978).

(4) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(5) D. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); **92**, 1396 (1970).

(6) M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).

(7) One example of the reaction of an acid chloride with a dilithium enolate of a carboxylic acid has been reported by A. P. Krapcho, E. G. K. Jahngen, Jr., and D. S. Kashdan, *Tetrahedron Lett.*, 2721 (1974), using ethyl chloroformate.

0022-3263/79/1944-4461$01.00/0 

propanone (**4a**) in 65% overall yield from the acid **1a**. Cyclization of the ketone **4a** with methanesulfonic acid readily afforded 11-methylbenzo[*a*]pyrene (**5a**) in 74% yield (47% overall from **1a**).

Fieser and Heymann[8] had previously prepared **5a** in 15% overall yield from the 1,2,3,4-tetrahydro derivative of **1a**, and its synthesis in eight steps from anthrone in 6% overall yield has been reported by Patton and Daub.[9]

A similar series of steps was performed on 4-chryseneacetic acid (**1b**), affording in sequence the keto acid **3b** which was decarboxylated to give the ketone **4b** (46% overall yield from **1b**) and finally 5-methylbenzo[*a*]pyrene (**5b**) via cyclization with methanesulfonic acid (65% yield or 30% overall from **1b**). Fieser and Hershberg[10] had previously reported the synthesis of **5b** in two steps from 2,3-dihydrobenzo[*a*]pyren-6(1*H*)-one (9% crude yield).

## Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1$H NMR spectra were obtained on a Varian EM-360 spectrometer using $Me_4Si$ as an internal standard, and IR spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. Product purity and reaction progress were monitored with analytical thin-layer chromatography using 2.5 × 10 cm Analtech plates coated with silica gel GF. Elemental analyses were performed by Ruby Ju of the Department of Chemistry.

**1-(Benz[*a*]anthracen-1-yl)-2-propanone (4a).** To a mixture of 1.70 g (12.0 mmol) of *N*-isopropylcyclohexylamine and 10 mL of anhydrous THF, cooled to −78 °C and under a $N_2$ atmosphere, was added 7.5 mL of 1.6 M butyllithium (12.0 mmol) in hexane. This mixture was recooled to −78 °C, and 1.15 g (4.0 mmol) of 1-benz[*a*]anthraceneacetic acid[3] (**1a**), mp 203–204 °C, in 35 mL of anhydrous THF was added dropwise at a rate which maintained the temperature of the reaction mixture below −75 °C.[11] After addition was complete, the cooling bath was removed, and the dark green solution was allowed to warm to room temperature. After stirring 1 h at room temperature, the solution was recooled to −78 °C, 0.30 mL (4.2 mmol) of acetyl chloride was added all at once, and stirring at −78 °C was continued for 1 h. The brown complex was hydrolyzed by the dropwise addition of 2 mL of concentrated HCl in 8 mL of THF at a rate which maintained the temperature below −70 °C. The mixture was allowed to warm to room temperature, and water and ether were added. The layers were separated, and the ether layer was extracted with two portions of 5% HCl and one each of water and saturated salt, dried over $MgSO_4$, and filtered, and the ether removed under reduced pressure, providing **2-(benz[*a*]anthracen-1-yl)-3-oxobutanoic acid (3a)** as a yellow oil: IR (neat) 3200–2750 (br, COOH), 2935 (s), 1725 (C=O), 1645 (C=O), 1236, 1067, 1050, 885, 760, 745 cm$^{-1}$.

The oil was heated to 120–130 °C for 1 h, at which time evolution of $CO_2$ was no longer noted. The brown oil was dissolved in benzene and chromatographed on neutral alumina. The ketone was eluted with 1:1 benzene/ethyl acetate, and removal of solvents under reduced pressure gave a yellow oil which solidified upon standing, affording 0.74 g (65% yield) of **4a** as yellow granular crystals, mp 121–123 °C. An analytical sample was crystallized twice from 95% ethanol as beige needles, mp 125–125.5 °C. In one run, decarboxylation was accompanied by cyclization directly to 11-methylbenzo[*a*]pyrene; however, in all other runs, only the ketone **4a** was formed: TLC $R_f$ 0.24 (benzene); IR (KBr) 1695 (C=O), 1150, 884, 812, 757, 748 cm$^{-1}$; $^1$H NMR ($DCCl_3$) δ 2.2 (3 H, s), 4.5 (2 H, s), 7.3–8.9 (11 H, m). Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.82; H, 5.74.

**11-Methylbenzo[*a*]pyrene (5a).** A solution of 0.74 g (2.6 mmol) of 1-(benz[*a*]anthracen-1-yl)-2-propanone (**4a**), mp 121–123 °C, in 30 mL of methanesulfonic acid under a $N_2$ atmosphere was stirred 30 min at 50 °C. The deep red complex was hydrolyzed by pouring it into ice water, and the pale green precipitate was collected and dried under reduced pressure. The crude product was chromatographed on neutral alumina, eluting with benzene. Removal of the benzene under reduced pressure afforded 0.51 g (74% yield) of **5a** as yellow shiny platelets, mp 161–162.5 °C (lit. mp 168–168.8 °C,[8] 166.5–167.5 °C[9]). Recrystallization from benzene/methanol improved the melting point to 166–166.5 °C which on admixture with an authentic sample was not depressed: TLC $R_f$ 0.66 (benzene).

**1-(Chrysen-4-yl)-2-propanone (4b).** In like manner to that described above for the synthesis of **4a**, the dilithium enolate of 1.15 g (4.0 mmol) of 4-chryseneacetic acid,[3] mp 205–206.5 °C, was allowed to react with 0.30 mL (4.2 mmol) of acetyl chloride. **2-(Chrysen-4-yl)-3-oxobutanoic acid (3b)** was obtained as a pale yellow oil: IR (neat) 3200–2700 (br, COOH), 3025 (s), 1705 (C=O), 1620 (C=O), 1303, 1260, 1220, 840, 761, 682 cm$^{-1}$.

This was directly decarboxylated to the ketone **4b** (0.52 g, 46% yield), mp 106–107 °C. Recrystallization twice from 95% EtOH afforded an analytical sample as beige crystals: mp 107.5–108.5 °C; TLC $R_f$ 0.57 (2:1 benzene/ethyl acetate); IR (KBr) 1700 (C=O), 1158, 863, 825, 760 cm$^{-1}$; $^1$H NMR ($DCCl_3$) δ 2.1 (3 H, s), 4.5 (2 H, s), 7.2–8.9 (11 H, m). Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.61; H, 5.57.

**5-Methylbenzo[*a*]pyrene (5b).** Cyclization of 0.52 g (1.8 mmol) of 1-(chrysen-4-yl)-2-propanone (**4b**), mp 106–107 °C, with 30 mL of methanesulfonic acid was accomplished as described above for **5a**. Removal of the benzene from the eluates afforded 0.32 g (65% yield) of 5-methylbenzo[*a*]pyrene as yellow shiny platelets, mp 164–167 °C. Recrystallization from benzene/methanol gave **5b**: mp 169–170 °C (lit.[10] mp 171–171.5 °C); TLC $R_f$ 0.66 (benzene).

**Registry No.** **1a**, 57652-76-3; **1b**, 57652-73-0; **2b**, 71718-26-8; **3a**, 71718-27-9; **3b**, 71718-28-0; **4a**, 71718-29-1; **4b**, 71718-30-4; **5a**, 16757-80-5; **5b**, 31647-36-6; acetyl chloride, 107-20-0.

(8) L. F. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **63**, 2333 (1941).
(9) J. W. Patton and G. H. Daub, *J. Am. Chem. Soc.*, **79**, 709 (1957).
(10) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 2542 (1938).
(11) One extra equivalent of base was added to ensure the life of **2a** in the presence of the initial acylation product.