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Registry No. **6**, 71031-58-8; **7**, 71050-16-3; **8**, 70209-37-9; **9**, 71050-13-0; **10**, 71050-14-1; **11**, 71050-15-2; **12**, 71031-59-9; **13**, 71031-60-2.

Syntheses of 8- and 9-Fluorobenzo[*a*]pyrenes and 9-Fluoro- and 10-Fluoro-7,12-dimethylbenz[*a*]anthracenes[1]

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5-Fluoro-3-(2-naphthyl)phthalide (**9**) and 5-fluoro-3-(1-naphthyl)phthalide (**16**) were synthesized by condensation of 2-(4-fluoro-2-lithiophenyl)-4,4-dimethyl-2-oxazoline with 2- and 1-naphthaldehyde, respectively, followed by hydrolysis and cyclization. Reduction of **9** to 4-fluoro-2-(2-naphthylmethyl)benzoic acid (**10**) in 94% yield followed by reaction of **10** with methyllithium afforded the corresponding methyl ketone (not isolated) which on heating with PPA gave 9-fluoro-12-methylbenz[*a*]anthracene (**12**) in 51% yield from **10**. Oxidation of **16** yielded 83% of 4-fluoro-2-(1-naphthoyl)benzoic acid (**17**) which on reaction with methyllithium afforded 78% of 5-fluoro-3-methyl-3-(1-naphthyl)phthalide (**18**). Condensation of **8** with 1-acetonaphthone yielded 41% of **18**. Reduction of **18** afforded an almost quantitative yield of 4-fluoro-2-(1-naphthylethyl)benzoic acid (**19**) which on cyclization by treatment with acetic anhydride, using catalytic zinc chloride, gave an acetate (not isolated) which was reduced by alkaline zinc dust treatment to 10-fluoro-12-methylbenz[*a*]anthracene (**20**) in 84% overall yield from **19**. By bromination with NBS, **12** and **20** were converted in 86–88% yields into 12-(bromomethyl)-9-fluorobenz[*a*]-anthracene (**13**) and 12-(bromomethyl)-10-fluorobenz[a]anthracene (**21**), respectively. Treatment of **13** and **21** with KCN in a phase-transfer medium gave in 75% yields 12-(cyanomethyl)-9-fluorobenz[*a*]anthracene (**14**) and 12-(cyanomethyl)-10-fluorobenz[*a*]anthracene (**22**) which were reduced to the corresponding aldehydes (not isolated) and then cyclized with PPA to 8-fluorobenzo[*a*]pyrene (**4**) (55% overall from **14**) and 9-fluorobenzo[*a*]pyrene (**5**) (42% overall from **22**). Cyclization of **10** with acetic anhydride and $ZnCl_2$ afforded crude 12-acetoxy-9-fluorobenz[*a*]anthracene which was oxidized to 9-fluoro-7,12-benz[*a*]anthraquinone (**24**) in 92% overall yield. Reaction of **24** with methyllithium afforded 7,12-dihydro-7,12-dihydroxy-7,12-dimethyl-9-fluorobenz[*a*]anthracene (**25**) in 77% yield. This was converted into 9-fluoro-7,12-dimethylbenz[*a*]anthracene (**27**) in 81% yield by treatment with HCl followed by reduction with HCl–$SnCl_2$. Treatment of **19** with methyllithium gave 85% of 4-fluoro-2-(1-naphthylethyl)acetophenone (**28**) which on heating with PPA yielded 99% of 10-fluoro-7,12-dimethylbenz[*a*]anthracene (**29**).

The role of 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenes (**1**) as metabolites responsible for the carcinogenic activity of benzo[*a*]pyrene (**2**) has been postulated, and much evidence in support of this concept has been adduced.[3] We wished to synthesize 7-, 8-, 9-, and 10-fluorobenzo[*a*]pyrenes (**3**, **4**, **5**, and **6**) in order to see if any or all would be carcinogenic. The fluorine atoms in **3**–**6**, inclusive, should prohibit any metabolism which would convert **2** to **1**. Hence, if **3**, **4**, **5**, or **6** proves to be carcinogenic, then some metabolism leading to the production of tumors must be involved other than that which produces the diol epoxides **1**.

In this paper the syntheses of 8-fluorobenzo[*a*]pyrene (**4**), 9-fluorobenzo[*a*]pyrene (**5**), 9-fluoro-7,12-dimethylbenz[*a*]anthracene (**27**), and 10-fluoro-7,12-dimethylbenz[*a*]anthracene (**29**) are described. The synthesis of **4** (Scheme I) and that of **5** (Scheme II) are patterned after the route used to synthesize 4-fluorobenzo[*a*]pyrene[4] from 5-fluoro-12-methylbenz[*a*]anthracene.[5] The final ring closure of 9-fluoro-12-(formylmethyl)benz[*a*]anthracene (**15**) to **4** went in 52% yield and that of 10-fluoro-12-(formylmethyl)benz[*a*]anthracene (**23**) to **5** went in 42% yield. The syntheses of **27** and **29** are outlined in Scheme III. In the conversion of **25** to **26** evidently a mixture of chloromethyl methyl compounds was produced, as the product melted over a wide range. However, reduction of this mixture produced a high yield (81%) of pure **27**.

Experimental Section[6]

4,4-Dimethyl-2-(4-fluorophenyl)oxazoline (7*). 4-Fluorobenzoyl chloride (Aldrich Chemical Co.) in CH_2Cl_2 was added to a solution of 2-amino-2-methyl-1-propanol in CH_2Cl_2 at 0 °C as described for 4-bromobenzoyl chloride[7] yield the amide, mp 85–87 °C, in 93% yield. This was treated with $SOCl_2$ and

(1) This work was supported by Grant 5R01CA-07394 from the National Cancer Institute, DHEW.

(2) Postdoctoral Research Associate.

(3) Jerina, D. M.; Thakker, D. R.; Yogi, H.; Levin, W.; Wood, A. W.; Conney, A. H. *Pure. Appl. Chem.* **1978**, *50*, 1033; Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H. "Polycyclic Hydrocarbons and Cancer"; Academic Press: New York, 1978; Vol. 1, p 189.

(4) Blum, J.; Bergmann, E. D. *J. Org. Chem.* **1967**, *32*, 344.

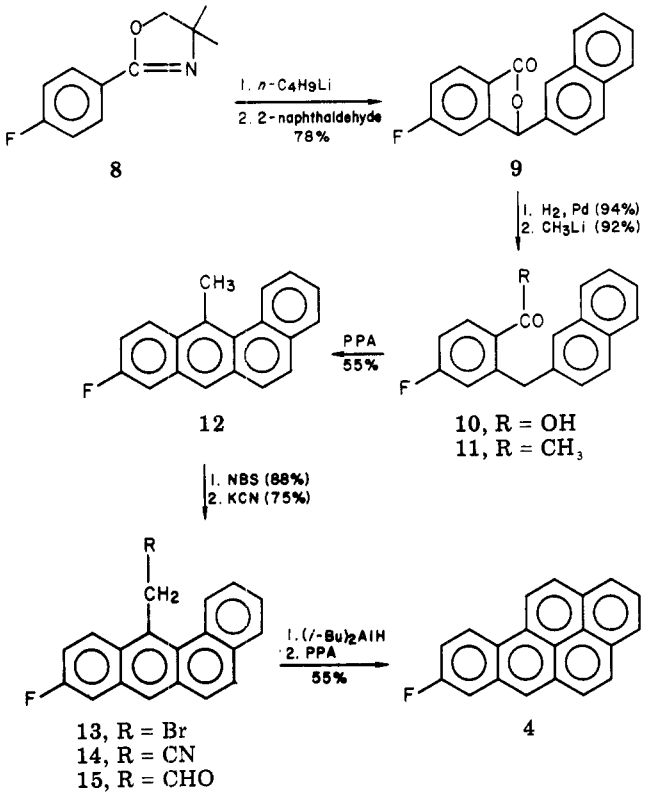
(5) Bergmann, E. D.; Blum, J. *Ibid.* **1962**, *27*, 527.

(6) All new compounds marked with an asterisk gave analyses (Galbraith Microanalytical Laboratories) within ±0.3% of theory, and the NMR spectra (in $CDCl_3$) were consistent with the postulated structures. The terms "conventional workup" or "worked up as usual" mean that an ether–benzene solution of the product was washed with dilute acid and/or alkali and then with saturated brine and filtered through anhydrous $MgSO_4$. The solvent was then removed on a rotary evaporator.

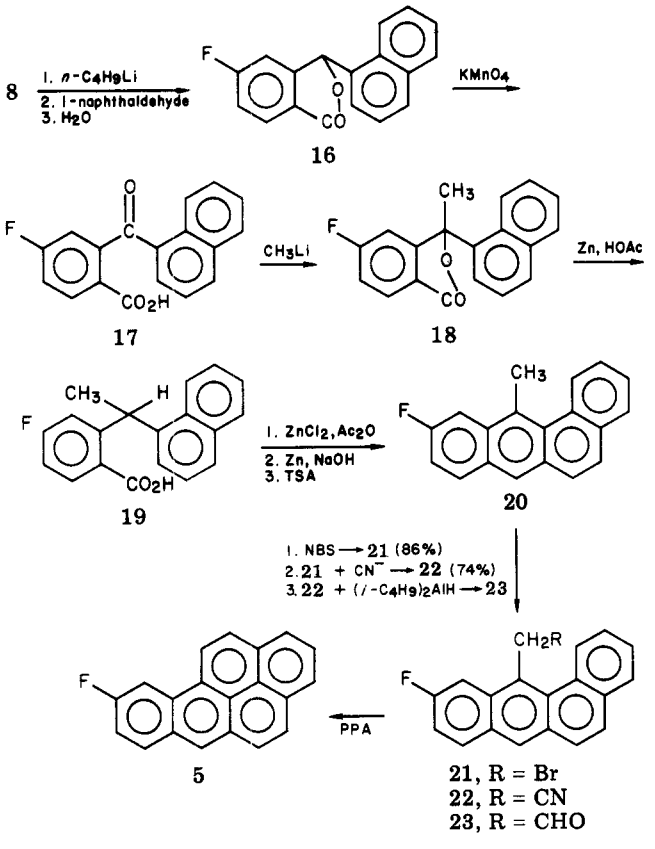
(7) Meyers, A. I.; Temple, D. C.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.

0022-3263/79/1944-3388$01.00/0

Scheme I



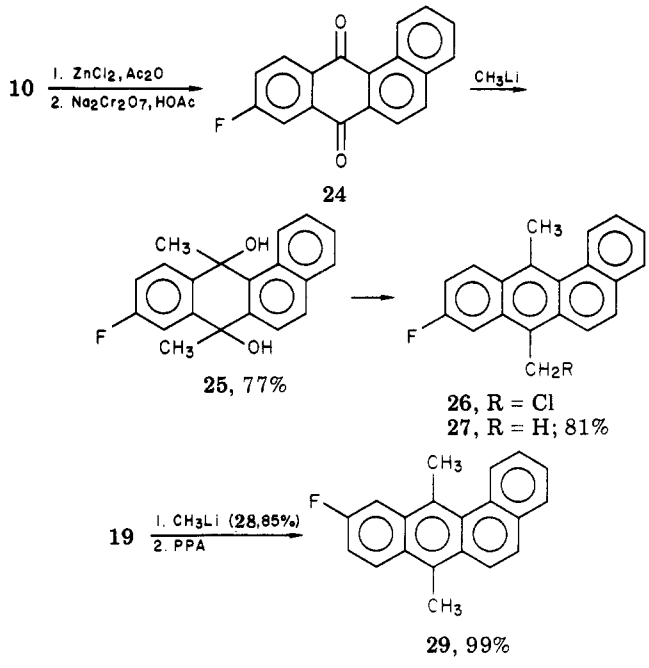
Scheme II



the product distilled after treatment as described[7] to yield 7*, bp 83–84 °C (0.5 mm), in 68% yield from the acid chloride.

5-Fluoro-3-(2-naphthyl)phthalide (9*). To a stirred solution under N_2 of 18.0 g (93 mmol) of 8 in 120 mL of dry ether cooled by a dry ice–chlorobenzene bath was added 60 mL of 1.6 M butyllithium (Aldrich, 96 mmol) in hexane during 20 min. After 1 h a solution of 16.0 g (111 mmol) of 2-naphthaldehyde in 120 mL of ether was added rapidly. The colorless reaction mixture

Scheme III



was allowed to warm to room temperature and left overnight. The oil obtained by a conventional workup was refluxed with a solution of 150 mL of concentrated HCl in 300 mL of water for 4.5 h. The solid which was collected and washed with water after cooling was held at reflux with a solution of 10 g of NaOH and 100 mL of water for 1 h. The acidic product was collected on acidification with HCl and washed with dilute $NaHCO_3$ and water to yield 20.2 g (78%) of **9**, mp 162–164 °C. This material was suitable for use in the next step. The analytical sample, mp 168.0–168.5 °C, was obtained by three recrystallizations from benzene–alcohol.

2-(2-Naphthylmethyl)-4-fluorobenzoic Acid (10*). A mixture of 5.0 g of **9**, 0.8 g of $PdCl_2$, 5 g of charcoal (Darco W-60), 125 mL each of benzene and 95% alcohol, and 8 drops of concentrated HCl was shaken at 40 psi (initial pressure) of H_2 for 7 h. Conventional workup afforded 4.7 g (94%) of colorless **10**, mp 145–147 °C, suitable for the next step.[8] The analytical sample, mp 153.0–153.5 °C, was obtained by sublimation at 125 °C and 0.5 mm.

9-Fluoro-12-methylbenz[a]anthracene (12*). A solution of 11.2 g (40 mmol) of **10** in 400 mL of ether was treated with 65 mL (104 mmol) of 1.6 M methyllithium (Ventron). After 75 min at room temperature the mixture was treated with saturated NH_4Cl solution and worked up as usual. Chromatography over 200 g of silica gel using 25% benzene in hexane afforded 300 mg (3%) of colorless **12**, mp 154–155 °C, in the first fraction and 9.6 g (87%) of 2-(2-naphthylmethyl)-4-fluoroacetophenone (**11**) as a pale yellow oil (IR, CO at 1690 cm^{-1}), which was directly converted into **12** as follows. A solution of 8.4 g of **11** in 50 mL of dry sulfolane was added to 150 g of 115% PPA at about 100 °C. After 45 min this mixture was poured on ice. A benzene–alcohol solution of the product yielded 4.3 g (55%) of slightly yellow **12**, mp 154–155 °C. The yellow color can be removed with little loss by chromatography over silica gel. In a reaction of 10 mmol of **10** with 34 mmol of CH_3Li at reflux for 2 h the yield of **11** was 50% and that of **12** was 7%. When crude **11** without chromatography was cyclized with PPA, the overall yield of **12** from **10** was 51%.

12-(Bromomethyl)-9-fluorobenz[a]anthracene (13*). A mixture of 700 mg of **12**, 500 mg of NBS, 10 mg of benzoyl peroxide, and 15 mL of CCl_4 was held at reflux for 2 h. Crystallization of the material in the filtrate yielded 800 mg (88%) of yellow **13**, mp 167–169 °C, suitable for further reaction. The analytical sample, mp 172.5–173.5 °C, was obtained by three recrystallizations from benzene–hexane. In other similar ex-

(8) Compare: Newman, M. S.; Wiseman, E. H. *J. Org. Chem.* **1961**, *26*, 3208.

periments the yield of 13 varied from 80 to 85%. Less pure 13 was also present in the mother liquors and could be converted into additional 14.

12-(Cyanomethyl)-9-fluorobenz[*a*]anthracene (14*). In the best experiment a stirred mixture of 5.5 g of **13**, 9.0 g of KCN, 8 drops of Aliquat-336,[9] 200 mL of benzene, and 100 mL of water was held at reflux for 3 h. After addition of 450 mL of benzene, the benzene layer was treated as usual to yield 3.4 g (74%) of **14**, mp 200–203 °C. The analytical sample, mp 202–203 °C, was prepared by recrystallization from benzene. Attempts to react **13** with KCN in 18-crown-6 ether and benzene (reflux 8 h) afforded **14** in only 50% yield. Reaction of **13** with KCN in CH_3CN, 24 h at reflux, gave only a 39% yield of **14**.

8-Fluorobenzo[*a*]pyrene (4*). A solution of diisobutylaluminum hydride (7 mL, Ventron, 20%) in hexane was syringed under N_2 into a dry stirred solution of 1.43 g of **14** in 100 mL of benzene. After 2 h at room temperature the mixture was poured on dilute 5 N H_2SO_4. The washed and dried benzene layer was concentrated to a viscous red oil which had a strong carbonyl bond at 1720 cm^{-1} and no nitrile band. This crude oil was heated at 95–100 °C with 20 g of 115% PPA for 15 min. After a conventional workup the organic product was chromatograhed over 75 g of Woelm basic alumina, activity 1, with benzene–hexane. The desired product was in the highly fluorescent fractions which yielded 0.65 g (48%) of **4**, mp 168–169 °C. The sublimed analytical sample was almost colorless and melted at 167.5–168.0 °C. An additional 4% of **4** could be obtained from the mother liquors.

5-Fluoro-3-(1-naphthyl)phthalide (16*). Treatment of 18.0 g of **8** with butyllithium and then 1-naphthaldehyde (Aldrich) just as described above for the synthesis of **9** afforded 21.3 g (82%) of **16**, mp 136–139 °C, suitable for use in the next step. The analytical sample, mp 146.0–147.5 °C, undoubtedly a polymorphic form, was obtained by recrystallization from benzene–hexane.

4-Fluoro-2-(1-naphthoyl)benzoic Acid (17*). To the stirred, heated mixture formed from 11.2 g of **16**, 160 mL of 25% KOH, and 80 mL of pyridine was added 9.6 g of powdered $KMnO_4$ during 1 h. After 5 h the hot mixture was filtered with a filter aid, and the residue was washed with water. The filtrate and washings were worked up as usual to yield 9.85 g (83%) of **17**, mp 203–206 °C, suitable for further work, and 5% of **16** from the neutral fraction. The analytical sample of **17** melted at 209–210 °C on crystallization from ethyl acetate–benzene.

5-Fluoro-3-methyl-3-(1-naphthyl)phthalide (18*). To a stirred solution under N_2 of 9.0 g of **17** in 200 mL of THF was added by syringe 50 mL of 1.6 M methyllithium at room temperature. After a 30-min heating to reflux, the mixture was stirred at 20–25 °C overnight. After the usual workup, 7.0 g (78%) of **18**, mp 158–160 °C, was obtained. This proved identical with a sample produced in 41% yield by the reaction of **8** with 1-acetonaphthone (Aldrich). The analytical sample melted at 160–161 °C.

4-Fluoro-2-(1-naphthylethyl)benzoic Acid (19). A stirred mixture of 12.0 g of **18**, 60 g of zinc dust,[10] activated by washing with dilute HCl, water, and methanol, and 250 mL of acetic acid was held at reflux for 20 h and poured on ice. After the usual workup 12.0 g (almost quantitative) of **19**, mp 168–170 °C, was obtained. The analytical sample, mp 170–171 °C, was obtained by crystallization from benzene–hexane.

10-Fluoro-12-methylbenz[*a*]anthracene (20*). A mixture of 4.6 g of **19**, 20 mL of acetic anhydride, 24 mL of acetic acid, and 0.2 g of $ZnCl_2$ was held at reflux for 1.5 h and poured on ice. The crude solid thus obtained was washed with water, air-dried, and suspended in a mixture of 25 g of zinc dust, activated by washing with a solution of 0.1 g of $CuSO_4 \cdot 5H_2O$ in 100 mL of water, 160 mL of 10% NaOH, and 30 mL of toluene. This stirred mixture was held at reflux for 24 h. After the mixture was cooled, organic product was taken into 500 mL of benzene. After the solution was washed with water and saturated salt solution, the benzene layer was refluxed over 0.5 g of *p*-toluenesulfonic acid for 1 h. After the usual workup there was obtained (after chromatography over 150 g of silica gel eluting with 10% benzene in hexane) 3.4 g (84%) of **20**, mp 125–127.5 °C. The sublimed analytical sample melted at 126–127 °C. The above alkaline reduction of the acetate of a benz[*a*]anthracenol is far superior to the reductions of benz[*a*]anthracenones.

12-(Bromomethyl)-10-fluorobenz[*a*]anthracene (21*). A stirred mixture of 2.6 g of **20**, 2.0 g of NBS, 100 mg of benzoyl peroxide, and 50 mL of CCl_4 was held at reflux for 2 h and filtered. Crystallization of the material in the filtrate from benzene–hexane yielded 2.9 g (86%) of **21**, mp 166–168 °C. The analytical sample (benzene–hexane) melted in the same range.

12-(Cyanomethyl)-10-fluorobenz[*a*]anthracene (22*). A stirred mixture of 2.4 g of **21**, 5.0 g of KCN, 150 mL of benzene, 80 mL of water, and 8 drops of Aliquat-336[9] was held at reflux for 2 h. After the usual workup there was obtained 1.5 g (74%) of **22**, mp 182–184 °C, suitable for further use. The analytical sample, crystallized from benzene–hexane, melted at 184–185 °C and had an IR nitrile band at 2250 cm^{-1}.

9-Fluorobenzo[*a*]pyrene (5*). A solution of 0.6 g of **22** was treated with $(i\text{-}C_4H_9)_2AlH$ as in the synthesis of **4** to yield a crude oil which had no IR band at 2250 cm^{-1} and was treated with 10 g of PPA at 95–100 °C for 20 min. Isolation as usual afforded 239 mg (42%) of fine needles of **5**, mp 157.5–158.5 °C. A sublimed sample was analyzed.

9-Fluoro-7,12-benz[*a*]anthraquinone (24*). A mixture of 11.5 g of **10**, 0.6 g of $ZnCl_2$, 48 mL of acetic anhydride, and 50 mL of acetic acid was refluxed for 1.5 h, cooled, and poured on ice. The colorless solid was collected, washed in water, air-dried, and dissolved in 120 mL of acetic acid containing 18 g of $Na_2Cr_2O_7$. After refluxing for 1 h, the cooled mixture was poured into water and the yellow solid was collected, well washed with water, and dried to yield 10.4 g (92%) of **24**, mp 198–200 °C. The analytical sample, mp 200–201 °C, was obtained by recrystallization from benzene–ethanol.

7,12-Dihydro-7,12-dihydroxy-7,12-dimethyl-9-fluorobenz[*a*]anthracene (25*). To a stirred solution of 2.8 g of **24** in 100 mL of ether and 200 mL of benzene at room temperature was added 20 mL of 1.6 M methyllithium. After being held at reflux for 2 h, the mixture was treated with NH_4Cl and worked up as usual to yield 2.4 g (77%) of **25**, mp 185–187 °C.

9-Fluoro-7,12-dimethylbenz[*a*]anthracene (27*). Into a solution at 0 °C of 5.0 g of **25** in 50 mL of ethyl acetate was passed dry HCl to saturation. After the solution was allowed to stand overnight, the solvent was removed, and the residue, crude **26**, was dissolved in 250 mL of dioxane containing 250 mL of concentrated HCl and 50 g of $SnCl_2$. After being heated to reflux for 6 min and allowed to cool for 40 min, the mixture was poured in 1 L of water and the organic matter extracted with 1 L of benzene and worked up as usual. After chromatography over an 8-in. column of basic alumina there was obtained 3.55 g (81%) of **27**, mp 150–151 °C. The analytical sample, mp 150–151.5 °C, was obtained by sublimation. In another experiment we were unable to get more than a small yield of a compound which may have been **26** or its isomer, having the chloromethyl group at 12.

10-Fluoro-7,12-dimethylbenz[*a*]anthracene (29*). To a stirred solution of 5.9 g of **19** in 200 mL of ether was added 35 mL of 1.6 M methyllithium (Ventron) during 15 min. After 3 h at room temperature the mixture was worked up as usual to give 4.95 g (85%) of 4-fluoro-2-(1-naphthylethyl)acetophenone (**28**), mp 88–90.5 °C. The sublimed analytical sample melted at 89.0–90.5 °C. A stirred mixture of 6.0 g of **28** and 120 g of 115% PPA was heated at 95–100 °C for 30 min. The crude product was chromatographed over 180 g of Woelm alumina, activity 1, with 1 L of benzene to yield 5.6 g (99%) of **29**, mp 109.0–110.5 °C. The sublimed analytical sample melted at 107–108 °C.

Registry No. **4**, 71171-92-1; **5**, 71171-93-2; **8**, 71171-94-3; **9**, 71171-95-4; **10**, 71171-96-5; **11**, 71195-55-6; **12**, 71171-97-6; **13**, 71171-98-7; **14**, 71171-99-8; **15**, 71172-00-4; **16**, 71172-01-5; **17**, 71172-02-6; **18**, 71172-03-7; **19**, 71172-04-8; **20**, 71172-05-9; **21**, 71172-06-0; **22**, 71172-07-1; **23**, 71172-08-2; **24**, 71172-09-3; **25**, 71172-10-6; **27**, 71172-11-7; **28**, 71172-12-8; **29**, 71172-13-9; 4-fluorobenzoyl chloride, 403-43-0; 2-amino-2-methyl-1-propanol, 124-68-5; 2-naphthaldehyde, 66-99-9; 1-naphthaldehyde, 66-77-3.

(9) Aliquot 336: methyltricaprylammonium chloride, obtained from the McKerson Corp., Minneapolis, MN.

(10) Analytical Reagent grade, Mallinckrodt, was used. Two other samples of zinc dust gave inferior results.