g) was added slowly to the THF solution. The reaction mixture was refluxed for 2 h. Excess $LiAlH_4$ was destroyed by careful addition of wet THF. The reaction mixture was filtered, and the solvent was removed under vacuum at 50 °C. The diol crystallized upon removal of the solvent. The diol was recrystallized from methanol to yield crystals, mp 191–193 °C (lit.[12] mp 193–195 °C).

Chol-5-ene-3β,24-diol 3,24-Bis(trimethylsilyl ether). The diol **3** (0.100 g) was dissolved in 2 mL of dry pyridine. To this solution was added 0.5 mL of a 9:1 mixture of *N,O*-bis(trimethylsilyl)acetamide and trimethylchlorosilane. The solution was maintained at 25 °C for 24 h. Solvent and excess reagent were removed at 2 mmHg and 50 °C: mass spectrum (70 eV), *m/e* (rel intensity) 504 (4), 414 (18), 285 (7), 255 (3), 129 (100), 95 (65), 75 (53), 73 (96), 69 (76).

Authentic Samples. Chol-5-ene-3β,24-diol. 3β-Hydroxychol-5-en-24-oic acid (**4**; 0.100 g) was dissolved in 20 mL of anhydrous THF. $LiAlH_4$ (0.100 g) was added slowly. The reaction mixture was stirred at reflux for 18 h. Wet THF was added slowly to destroy excess $LiAlH_4$. The reaction mixture was filtered, and THF was removed under vacuum at 50 °C. The product was recrystallized from methanol to yield crystals, mp 190–193 °C (lit.[12] mp 193–195 °C).

Chol-5-ene-3β,24-diol 3,24-Bis(trimethylsilyl ether). The trimethylsilyl ether was prepared as previously described: mass spectrum (70 eV), *m/e* (rel intensity) 504 (5), 414 (18), 285 (35), 255 (14), 129 (63), 95 (43), 75 (70), 73 (100), 69 (58).

Chol-5-ene-3β,24-diol 3,24-Diacetate. The diacetate was prepared as previously described: mp 127–129 °C (lit.[12] mp 127–129 °C).

Conclusion

The preparation of **3** from cholesterol offers a new and relatively efficient method for the utilization of cholesterol as a starting material in steroid synthesis. Although **3** itself is of no pharmaceutical importance, conversion of this compound to 25-hydroxycholesterol is a very straightforward synthetic problem compared with the existing method for synthesizing this compound.[14-16] Further degradation of **3** to the 20-keto steroids is also possible. The method described for the oxidation of cholesterol is being extended to sitosterol and campesterol, the two most abundant sterols.

Acknowledgment. This work was supported by the Pennsylvania Research Corp. and by the National Institutes of Health. We are also grateful to Dr. Robert D. Minard for the mass spectra.

Registry No. **1**, 17398-36-6; **2**, 71129-66-3; **3**, 54668-67-6; **3** bis-(Me_3Si) derivative, 71129-67-4; **4**, 5255-17-4; 6-nitrocholesterol acetate, 1912-54-5; cholesterol, 57-88-5.

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Isolation, Structure Elucidation, and Partial Synthesis of Xestosterol, a Biosynthetically Significant Sterol from the Sponge *Xestospongia muta*

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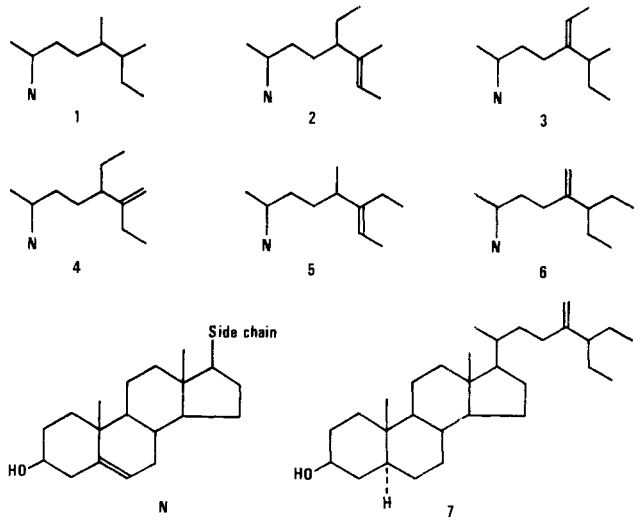
Received May 15, 1979

The major component of the sterol constituents of the Carribean sponge *Xestospongia muta* is a new C_{30} sterol—xestosterol—characterized by the "elongated" side chain depicted by structure **6**, as was confirmed by partial synthesis. The probable biological function of **6** or similar sterols in sponges is emphasized.

Marine organisms have been the source of numerous sterols possessing side chains with unusual alkylation patterns.[1] Sterols with "extended" side chains, which have been encountered in sponges, are of particular interest. Aplysterol (**1**) and its 24(28)-dehydro[2] and 25-dehydro[6] analogues stelliferasterol (**2**),[3,4] isostelliferasterol (**3**),[3] and strongylosterol (**4**)[4,5] are all characterized by an extra carbon atom attached to C-26. Such compounds were found in several cases[2,3,6] to be the major sterol components of a sponge, and strongylosterol is even the sole sterol of the sponge *Strongylophora purissima*.[5] This suggests that they play a functional role, most likely in cell membrane stabilization. The reason why these special sterols—which have no terrestrial counterparts—are used instead of cholesterol remains an open question,[7,8] but it is clear that the elucidation of this problem could shed new light on the functional mechanism of membranes in general.

More recently, verongulasterol (**5**), a *minor* sterol from the sponge *Verongia cauliformis*,[6] was found to possess the unique feature of being alkylated at *both* C-26 and C-27



positions. However, it is present in such small amounts that it could not possibly play a functional (i.e., membrane)

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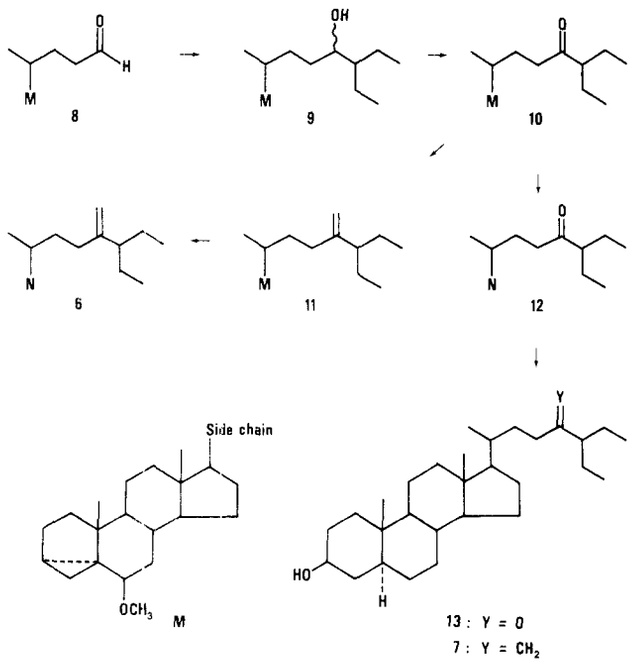
0022-3263/79/1944-3385$01.00/0

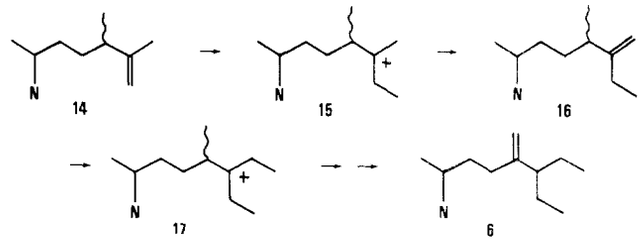
Scheme I



role and probably is just a metabolite. We wish now to report the discovery of a new sterol characterized by this same alkylation pattern as the *major* component of the sterol fraction from the sponge *Xestospongia muta*. Analysis by gas chromatography (GC) showed that one peak represented 71% of the total peak area. Thin-layer chromatography (TLC) with silica gel–silver nitrate plates[9] allowed the isolation of this new sterol which was named xestosterol and whose structure was shown to be **6**. Therefore, it appears that sterols with side chains elongated at C-26 and C-27 might also play a significant role in membrane function, and it is conceivable that this feature may also reflect itself in unusual phospholipid constituents, especially as far as the fatty acid chains are concerned. Among the minor components of the sterol mixture, the closely related steroid xestostanol (**7**) was also isolated.

The mass spectrum of xestosterol (**6**) is very similar to that of fucosterol:[10] the two spectra are practically identical below their m/e 314 base peak, and show virtually no peaks between the latter and the molecular ion. This suggested a 24(28) double bond, and a 24-methylene group was deduced from the fact that the 360-MHz ^{1}H NMR spectrum displays two signals at 4.68 and 4.77 ppm. In the methyl region of the spectrum, all the signals are separated. By comparison with previously reported data,[3] the two singlets at 0.683 and 1.009 ppm and the doublet

Scheme II



at 0.942 ppm were assigned to the C-18, C-19, and C-21 methyl groups, respectively. The remaining triplet at 0.809 ppm, accounting for six protons, could then only be explained by the 26,27-dimethyl structure proposed.

By comparison with **6**, xestostanol (**7**) has a mass spectrum where all the peaks are shifted by two more mass units, but the spectra are otherwise very similar above m/e 270. This suggested a sterol with the same side chain but without a double bond in the nucleus. The ^{1}H NMR spectrum indeed shows the same signals for the 24-methylene group, the methyls of the side chain, and the 3α proton, but the peak of the proton on C-6 is not present, and the C-19 methyl appears at 0.804 ppm, thus suggesting a 3β-hydroxy-5α-androstane nucleus.

To confirm these structural proposals, we synthesized **6** and **7** by the unambiguous route outlined in Scheme I. The starting material 6β-methoxy-3α,5-cyclocholan-24-al (**8**) was obtained from methyl 3β-hydroxy-5-cholenate by known procedures.[11] Treatment with 3-pentyllithium[12] gave the alcohol **9** which was oxidized to 26,27-dimethyl-6β-methoxy-3α,5-cyclocholestan-24-one (**10**). Wittig condensation and removal of the protecting group yielded xestosterol (**6**). To obtain xestostanol (**7**), the ketone **10** was deprotected and catalytically hydrogenated to give 3β-hydroxy-26,27-dimethyl-5α-cholestan-24-one (**13**), from which **7** was obtained by Wittig reaction.

Samples of natural and synthetic xestosterol (**6**) proved to be indistinguishable. The melting points and specific rotations are in good agreement, the coinjection in GC gives only one peak, and the 360-MHz ^{1}H NMR, MS, and infrared spectra are identical. In the case of xestostanol (**7**), the MS and NMR spectra are identical, and coinjection in GC gives one single peak.

In terms of biosynthesis, it is not clear whether xestosterol is synthesized de novo by the sponge, results from side-chain elongation of a dietary sterol precursor, or is all together a dietary constituent. The few radioactive labeling experiments that have been performed[13] in *Verongia* species do not offer definitive conclusions about the biosynthesis of sterols with side chains extended by alkylation at C-26 and C-27. For xestosterol (**6**), we can assume, as in the case of verongulasterol (**5**),[7] that codisterol (**14**)[14] or the recently isolated[15] 24-epicodisterol serves as the starting point (Scheme II). Standard biomethylation via *S*-adenosylmethionine (SAM) would lead to the carbonium ion **15** and, after proton loss from C-27, to $\Delta^{25(27)}$-dehydroaplysterol (**16**). Repetition of the alkylation at the Δ^{25} double bond would then give the xestosterol side chain **6**, after deprotonation of the ionic

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intermediate **17** and isomerization of the resulting double bond. Alternatively, the Δ^{24} double bond could be generated by a biological hydrogenation–dehydrogenation sequence.

We hope to undertake labeling experiments that shed more concrete information on this intriguing biosynthetic question, and we have work underway to examine the role of xestosterol in cell membrane function.

Experimental Section

General Methods. For isolation and monitoring of purification the La Jolla coauthors used a Waters high-pressure LC setup (M6000 pump, UK6 injector, R401 differential refractometer, two μC_{18} columns (4 mm i.d. × 30 cm) in series, eluent methanol–water 92:8), a Varian HR220/Nicolet TT100 FT NMR instrument, and a Hewlett-Packard 5710A gas chromatograph equipped with a 3% SP2250 column and a flame-ionization detector (carrier gas helium, oven temperature 260 °C). In Stanford, GC was performed under the same conditions with a Hewlett-Packard 402 A chromatograph equipped with a 3% OV-17 column. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian XL-100 (100-MHz) or Bruker HXS-360 (360-MHz) spectrometers. The chemical shifts are given in ppm with Me_4Si as internal standard, and the coupling constants are in hertz. The mass spectra were recorded at 70 eV on AEI MS-9 (low-resolution) or Varian MAT 711 (high-resolution) mass spectrometers using a direct inlet system. Specific rotations were recorded on a Perkin-Elmer 141 polarimeter and IR spectra on a Perkin-Elmer 421 spectrometer using KBr pellets. The melting points (uncorrected) were determined on a Thomas-Hoover "Unimelt" capillary melting point apparatus.

Isolation and Separation of the Sterol Mixture from *Xestospongia muta*. *Xestospongia muta* was collected on Lighthouse Reef, Belize, and preserved by freezing. Steeping of the chopped sponge in methanol at room temperature and partitioning of the evaporated residue between ether and water gave an extract, from which the sterols (0.2% of the weight of the frozen sponge) were isolated by column chromatography on silica gel. GC analysis showed one main peak (71% of the total peak area) with a relative retention time of 2.2 (cholesterol 1.0). The sterol acetates were separated into five fractions by argentic TLC.[15] Xestosterol (**6**) was found to be the sole constituent of the fraction of R_f 0.22–0.33 (yield of isolated product 46% of the free sterols). From the fraction of R_f 0.33–0.40, xestostanol (**7**) was isolated by reverse-phase high-pressure LC (yield 4% of the free sterols).

26,27-Dimethyl-6β-methoxy-3α,5-cyclocholestan-24ξ-ol (9). A 50% dispersion of lithium[12] powder in oil (0.175 g, 12.6 mmol of Li) was washed several times with dry pentane in an atmosphere of nitrogen and covered with 10 mL of dry petroleum ether. To the stirred suspension was added a solution of 0.64 g (6.0 mmol) of 3-chloropentane[16] in 10 mL of dry petroleum ether, and the mixture was refluxed for 3 h. After cooling at 0 °C, a solution of 1.00 g (2.68 mmol) of the aldehyde **8** in 20 mL of dry ether was added. The solution was stirred for 5 min and then hydrolyzed with 5% aqueous HCl. The organic phase was diluted with 50 mL of ether, washed with water until neutral, and dried and the solvent was evaporated. The residue was purified by column chromatography on silica gel. Elution with dichloromethane removed some nonpolar impurities, and **9** was eluted with 4:1 petroleum ether–ethyl acetate: yield 0.640 g (54%) of an oily solid; ^{1}H NMR (100 MHz) 0.72 (3, s, C-18 Me), 0.97 (6, t, J = 7 Hz, C-28 and C-29 Me), 0.98 (3, d, J = 6 Hz, C-21 Me), 1.02 (3, s, C-19 Me), 2.77 (1, m, C-6 H), 3.31 (3, s, OMe), 3.54 ppm (1, m, C-24 H); mass spectrum, m/e (rel intensity) 444 (M^+, $C_{30}H_{52}O_2$, 17), 429 (27), 412 (24), 389 (38), 341 (8), 255 (15), 213 (15), 55 (100).

26,27-Dimethyl-6β-methoxy-3α,5-cyclocholestan-24-one (10) and 3β-Hydroxy-26,27-dimethylcholest-5-en-24-one (12). Chromium trioxide (0.8 g, 8 mmol) was added to a solution of 1.3 mL of pyridine in 10 mL of dichloromethane. After the solution was stirred for 15 min, the alcohol **9** (0.465 g, 1.05 mmol) in 10 mL of dichloromethane was poured into the mixture, and stirring was continued for 10 min. Ether (80 mL) was added, and the mixture was filtered through Florisil and washed with more ether. The solution was extracted twice with 20 mL of cold, 10% aqueous HCl and then with water until neutral. After drying, evaporation of the solvent yielded 0.435 g (94%) of oily **10**. Treatment with *p*-toluenesulfonic acid in boiling aqueous dioxane[17] for 15 min gave, after column chromatography on silica gel (3:1 hexane–ethyl acetate), **12** as a crystalline white solid (74%): mp 117–119 °C; ^{1}H NMR (100 MHz) 0.68 (3, s, C-18 Me), 0.84 (6, t, J = 7 Hz, C-28 and C-29 Me), 0.92 (3, d, J = 6 Hz, C-21 Me), 1.01 (3, s, C-19 Me), 3.5 (1, m, C-3 H), 5.36 ppm (1, m, C-6 H); mass spectrum, m/e (rel intensity) 428 (M^+, $C_{29}H_{48}O_2$, 29), 413 (9), 410 (27), 395 (12), 314 (32), 255 (19), 213 (33), 71 (100).

26,27-Dimethylergosta-5,24(28)-dien-3β-ol (*Xestosterol*) (6). In an atmosphere of nitrogen, 0.50 g of a 57% NaH dispersion in oil (12 mmol NaH) was washed several times with pentane. Dry dimethyl sulfoxide (Me_2SO) (7.5 mL) was added, and the mixture was heated with stirring at 75–80 °C until no more hydrogen evolved (1 h). The solution was cooled on an ice bath, and 5.00 g (12.4 mmol) of methyltriphenylphosphonium iodide in 50 mL of Me_2SO was added. After 15 min, the ketone **10** (0.435 g, 0.983 mmol) in 10 mL of ether was added, and stirring was continued for 6 h at room temperature. The reaction mixture was poured into 250 mL of methanol–water (1:1) and extracted with 250 mL of pentane. The organic solution was washed several times with methanol–water and dried. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel. Elution with dichloromethane yielded 0.214 g (49%) of oily **11**. Treatment by acetic acid and zinc acetate followed by alkaline hydrolysis[18] gave, after recrystallization from acetone–water, 0.129 g (62%) of **6**: mp 123–124 °C; $[\alpha]^{20}_D$ −33° ($CHCl_3$); ^{1}H NMR (360 MHz) 0.683 (3, s, C-18 Me), 0.809 (6, t, J = 7.3 Hz, C-29 and C-30 Me), 0.942 (3, d, J = 6.5 Hz, C-21 Me), 1.009 (3, s, C-19 Me), 3.53 (1, m, C-3 H), 4.68 and 4.77 (2, 2 s, C-28 H_2), 5.36 ppm (1, m, C-6 H); mass spectrum, m/e (rel intensity) 426.3875 (M^+, $C_{30}H_{50}O$, 16; calcd 426.3862), 411 (5), 408 (5), 393 (3), 314 (100), 299 (20), 283 (9), 281 (13), 271 (26), 255 (3), 253 (3), 229 (12); IR 3450, 2960, 1660, 1480, 1390, 1060, 895 cm^{-1}. Natural xestosterol showed mp 123.5–125 °C and $[\alpha]^{20}_D$ −32°.

3β-Hydroxy-26,27-dimethyl-5α-cholestan-24-one (13). To a solution of 0.429 g (1.00 mmol) of the ketone **12** in 40 mL of ethyl acetate was added 50 mg of 10% palladium on activated carbon. The mixture was stirred in an atmosphere of pure hydrogen for a total of 24 h. During that time, the catalyst was twice filtered off and replaced. Filtration and evaporation of the solvent gave 0.383 g (89%) of crude **13** which was used in the next step without further purification: ^{1}H NMR (100 MHz) 0.65 (3, s, C-18 Me), 0.80 (3, s, C-19 Me), 0.84 (6, t, J = 7 Hz, C-28 and C-29 Me), 0.92 (3, d, J = 6 H C-21 Me), 3.6 ppm (1, m, C-3 H); mass spectrum, m/e (rel intensity) 430 (M^+, $C_{29}H_{50}O_2$, 10), 415 (2), 412 (5), 397 (4), 359 (3), 341 (4), 316 (18), 299 (14), 253 (15), 233 (14), 215 (20), 71 (100).

26,27-Dimethyl-5α-ergost-24(28)-en-3β-ol (7). The Wittig reaction described for the preparation of **6** was exactly repeated with 0.380 g (0.882 mmol) of **13**. Purification of the product by column chromatography on silica gel (dichloromethane followed by 3:1 hexane–ethyl acetate) and recrystallization from acetone–water gave 0.244 g (65%) of **7**: mp 124–125 °C; $[\alpha]^{20}_D$ +23° ($CHCl_3$); ^{1}H NMR (100 MHz) 0.653 (3, s, C-18 Me), 0.801 (6, t, J = 7 Hz, C-29 and C-30 Me), 0.804 (3, s, C-19 Me), 0.922 (3, d, J = 6 Hz, C-21 Me), 3.6 (1, m, C-3 H), 4.68 and 4.75 (2, 2 s, C-28 H_2); mass spectrum, m/e (rel intensity) 428.4034 (M^+, $C_{30}H_{52}O$, 12; calcd 428.4018), 413 (5), 316 (100), 301 (18), 285 (4), 273 (26), 255 (3), 233 (11).

Acknowledgment. We thank Dr. Lois Durham for the NMR spectra and Annemarie Wegmann and R. G. Ross for the mass spectra. We acknowledge financial support from the National Institutes of Health (Grants GM-06840 and AM-04257) and use of a 360-MHz NMR spectrometer made possible by grants from the National Science

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Foundation (GP 23633) and the National Institutes of Health (RR-0711). C.T. thanks the "Fonds National Suisse de la Recherche Scientifique" for a grant. D.B.S. is indebted to Professor D. J. Faulkner, Scripps Institution of Oceanography, for a postdoctoral fellowship under NIH Grant No. AI-11969. Our use of the NMR/MS facility at UCSD was supported by NIH Grant No. RR-708. *X. muta* (class Demospongiae, order Haplosclerida) was collected by Professor D. J. Faulkner and colleagues during a collecting trip aboard R/V αHelix; the sponge was identified by Dr. K. Ruetzler, Smithsonian Institution, Washington, DC.

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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Received March 26, 1979

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.

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(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.

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