Synthesis of Benzo[*a*]pyren-1-ol

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Benzo[*a*]pyren-1-ol has been synthesized from phenanthrene-9-carbaldehyde in six steps. An initial Knoevenagel reaction gives *trans*-β-phenanthren-9-ylacrylic acid, which is reduced catalytically to β-(9,10-dihydrophenanthren-9-yl)propionic acid. Cyclization of the propionic acid by use of anhydrous hydrogen fluoride gives 5,6,6a,7-tetrahydrobenz[*de*]anthracen-4-one, which on condensation with methyl succinate followed by decarboxylation yields β-(7*H*-benz[*de*]anthracen-4-yl)propionic acid. It is suggested that the benzanthracenylpropionic acid arises *via* an acid-catalysed disproportionation during the decarboxylation of (5,6,6a,7-tetrahydro-4*H*-benz[*de*]-anthracen-4-ylidene)succinic acid. Benzo[*a*]pyren-1-ol is obtained from cyclization of the benzanthracenyl-propionic acid with anhydrous hydrogen fluoride: dehydrogenation of the expected 3,6-dihydrobenzo[*a*]pyren-1(2*H*)-one to the phenol occurs spontaneously during this step.

RECOGNITION that arene oxides are the primary intermediates in the metabolism of aromatic compounds [1] and the implications that arene oxides are the cytotoxic and carcinogenic agents formed from these hydrocarbons *in vivo* [2] has stimulated interest [2] in the metabolism of carcinogenic polycyclic aromatic hydrocarbons such as benzo[*a*]pyrene.[3-5] A complete set of phenols from a given hydrocarbon would be required for definitive metabolism and carcinogenesis studies, but such a series has not yet been obtained owing to the magnitude of the synthetic problem; for example there are twelve possible isomeric benzo[*a*]pyrenols. Non-availability of adequate reference standards has led to confusion in the literature. Metabolic formation of benzo[*a*]pyren-1-ol (8) is a case in point for in some studies this phenol is considered a major metabolite [4] while in others [5] it has not been detected.

No synthesis of benzo[*a*]pyren-1-ol (8) has been reported although the preparation of 1-methoxybenzo[*a*]-pyrene ‡ has been described.[6] This synthesis involved introduction of a 6-chloro-substituent into the parent hydrocarbon as a blocking group, acetoxylation at C-1, saponification, methylation, and finally hydrogenolysis to remove the blocking group. The procedure is impractical in that difficult separations of isomers are required at several stages and the overall yield is less

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‡ This compound was formerly described as 10-methoxybenzo-[*a*]pyrene.

[1] J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 1972, **28**, 1129.

[2] D. M. Jerina and J. W. Daly, *Science*, 1974, in the press.

[3] H. L. Falk, P. Kotin, S. S. Lee, and A. Nathan, *J. Nat. Cancer Inst.*, 1962, **28**, 699; P. Sims, *Biochem. Pharmacol.*, 1967, **16**, 613.

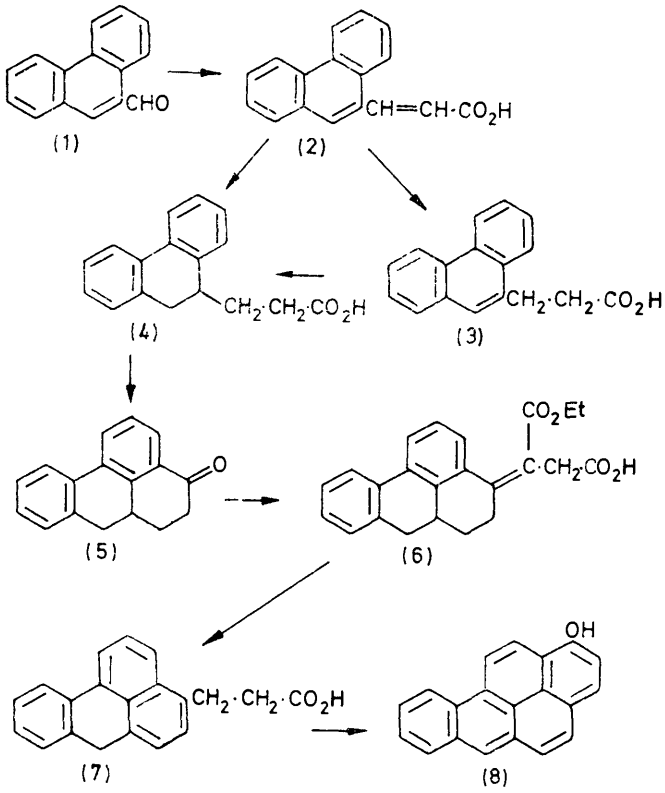
[4] A. H. Conney, E. C. Miller, and J. A. Miller, *J. Biol. Chem.*, 1957, **228**, 753; I. Berenblum and R. Schoental, *Cancer Res.*, 1946, **6**, 699; D. S. Tarbell, E. G. Brooker, P. Seifert, A. Vanterpool, C. J. Claus, and W. Conway, *ibid.*, 1956, **16**, 37.

[5] A. Borgen, H. Darvey, N. Castagnoli, T. T. Crocker, R. E. Rasmussen, and I. Y. Wang, *J. Medicin. Chem.*, 1973, **16**, 502; N. Kimoshita, B. Shears, and H. V. Gelboin, *Cancer Res.*, 1973, **33**, 1937.

[6] J. W. Cook, R. S. Ludwiczak, and R. Schoental, *J. Chem. Soc.*, 1950, 1112.

than 0·5%. Furthermore, the proof of structure for this material consisted of direct oxidation to give, in unstated yield, a material thought to be the 1,6-dione; this procedure may have been selective for a minor isomeric contaminant and may not be valid in the light of more recent studies.[7] The synthesis of the free phenol from phenanthrene-9-carbaldehyde (1) is described here (Scheme). The key steps were those involved in the elaboration of the tetracyclic ketone (5).

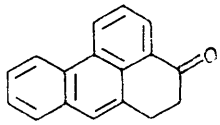
Modification of the procedure of Bachmann and Kloetzel [8] provided *trans*-β-phenanthren-9-ylacrylic acid (2) from (1) in high yield. Quantitative reduction of (2) to the propionic acid (3) was achieved with hydrogen (1 atm) at room temperature over 5% palladium–charcoal in contrast to the earlier study [8] which employed sodium amalgam. Direct cyclization of the acid (3) was not attempted since it has been shown [8,9] that a mixture



(1) (2) (4) (3) (5) (6) (7) (8)

SCHEME

of 5,6-dihydrobenz[*de*]anthracen-4-one (9) and 2,3-dihydrocyclopenta[*l*]phenanthren-1-one (10) results in which the undesired isomer (10) predominates. Furthermore, the ketone (9) was reported to be stable only in solution.[9] Thus, methods were sought to reduce (3) to β-(9,10-dihydrophenanthren-9-yl)propionic acid (4); the latter must cyclize in the desired direction and the resulting ketone (5) was not expected to suffer from the instability associated with structure (9).



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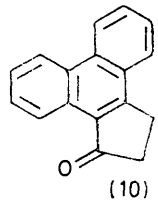

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Both chemical and catalytic procedures for the reduction of (3) were explored. Reduction with sodium and boiling pentan-1-ol or propan-1-ol produced a mixture of reduced phenanthrenylpropionic acids which n.m.r. spectroscopy and mass spectral analysis showed to be principally hexa- and octa-hydro-compounds. Reduction with lithium–ammonia (the procedure of Rabideau and Harvey [10] for the synthesis of 9-alkyl- and 9,10-dialkyl-9,10-dihydrophenanthrenes) gave a complex mixture of reduced phenanthrenylpropionic acids. Although copper–chromium oxides at high temperature and pressure are known to be effective [11] for the reduction of phenanthrene to 9,10-dihydrophenanthrene, Badger *et al.*[12] report that only β-(*sym*-octahydrophenanthren-9-yl)propionic acid can be obtained by reduction of (3) under a variety of different conditions of temperature and pressure. The products obtained from hydrogenation in a Parr apparatus over palladium–charcoal were very dependant on solvent, temperature, and amount of catalyst. At 65°, use of equal amounts of 10% palladium–charcoal and substrate gave as major product β-(*sym*-octahydrophenanthren-9-yl)propionic acid. Lowering the temperature or the amount of catalyst gave a mixture of unreduced starting material and di-, tetra-, and octa-hydrophenanthrenylpropionic acids (mass spectral and n.m.r. analyses). In the best procedure, which minimized the extent of over-reduction, 50% by weight of 5% palladium–charcoal in acetic acid was used under 4 atm of hydrogen at room temperature, to provide a 30—40% yield of β-(9,10-dihydrophenanthren-9-yl)propionic acid (4) directly from (2).*

The dihydrophenanthrenylpropionic acid (4) was cyclized with anhydrous hydrogen fluoride, and the resulting ketone (5), without further purification, was subjected to a Stobbe reaction with diethyl succinate in the presence of potassium t-butoxide. The crude half-ester product [most probably (6)] was refluxed with hydrochloric acid in acetic acid, but instead of the expected β-(5,6,6a,7-tetrahydro-4*H*-benz[*de*]anthracen-4-ylidene)propionic acid (11) the benzanthracenylpropionic acid (7) and a compound thought to be β-(5,6,6a,7-tetrahydro-4*H*-benz[*de*]anthracen-4-yl)propionic acid (12) were obtained. Cyclization of (12) with anhydrous

* Further attempts to improve the yield for this reduction are being made.

[7] C. R. Raha, L. K. Keefer, and J. Loo, *J. Chem. and Eng. Data*, 1973, **18**, 332.

[8] W. E. Bachmann and M. C. Kloetzel, *J. Amer. Chem. Soc.*, 1937, **59**, 2207.

[9] H. Dannenberg and H.-J. Kessler, *Annalen*, 1959, **620**, 32.

[10] P. W. Rabideau and R. G. Harvey, *J. Org. Chem.*, 1970, **35**, 25.

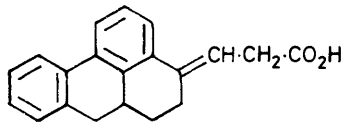
[11] D. D. Phillips, *Org. Synth.*, Coll. Vol. IV, 1963, p. 313.

[12] G. M. Badger, W. Carruthers, J. W. Cook, and R. Schoental, *J. Chem. Soc.*, 1949, 169.

hydrogen fluoride gave a compound with a mass spectrum consistent with the benzopyrenone structure (13). The u.v. spectrum of (7) was similar to that of 7*H*-benz[*de*]anthracene and showed maxima close to those reported for 4-methyl-7*H*-benz[*de*]anthracene, but differed markedly from those of 1*H*- and 3*H*-benz[*de*]anthracenes.[9] The most logical explanation for this result is that an acid-catalysed disproportionation occurs during the decarboxylation. Cook *et al.*[6] report that the products from the analogous decarboxylation of the half-ester (14) are the β-(7*H*-benz[*de*]anthracen-3-yl)propionic acid (15) and the reduced benzanthracenylpropionic acid (16). During the pilot synthetic studies it became clear that solutions of the ketone (5) and the benzanthracenylpropionic acid (7) were readily autoxidized; consequently all the synthetic steps beyond the formation of (5) were then carried out under nitrogen and where possible in the dark.

The cyclization of (7) with anhydrous hydrogen fluoride was expected to give predominantly the six-membered cyclic ketone (17) with a small amount of the isomeric five-membered cyclic ketone (18), by analogy with the pericyclization of β-(1-naphthyl)propionyl chloride.[13] However, very little reaction occurred under the conditions that readily cyclized the acid (4). That this was due to the slowness of the cyclization at room temperature was confirmed both by leaving the reactants in hydrogen fluoride for a week and by carrying out the cyclization at an elevated temperature in a steel bomb. T.l.c. showed that under both conditions (7) was consumed. Surprisingly, the major product was neither (17) nor (18); instead dehydrogenation occurred to provide the desired benzo[*a*]pyren-1-ol (8) directly. Apparently the initial product (17) is aromatized during the course of the reaction; all attempts to prevent this oxidative aromatization were unsuccessful.

The *O*-methyl derivative of (8) was prepared by use of dimethyl sulphate. Its u.v. spectrum is similar to that reported for 1-methoxybenzo[*a*]pyrene.[14,15] The present synthesis of (8) improves upon the earlier synthesis of the methyl ether[6] and lends additional credence to the reports[4] which suggest that this compound is a metabolite from the hydrocarbon.



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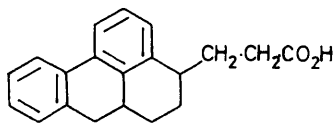

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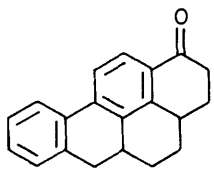

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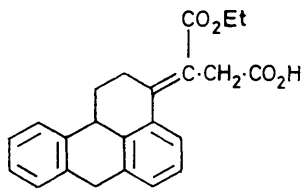

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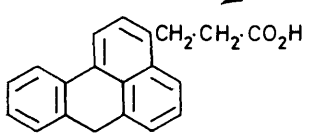

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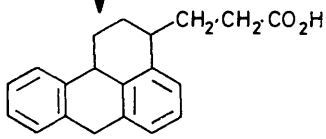

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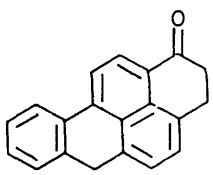

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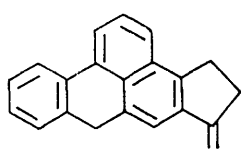

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EXPERIMENTAL

U.v. spectra were recorded with a Cary 15 spectrophotometer. Fluorescence spectra were obtained with a Perkin-Elmer MPF-3L spectrophotometer. Routine ^{1}H n.m.r. spectra were measured on a Varian A60A or HA-100 spectrometer; all the reported spectra were obtained with a Varian 220 MHz spectrometer, except those of compound (2) and 1-methoxybenzo[*a*]pyrene, which were recorded on the 100 MHz instrument. Tetramethylsilane was used as internal standard. Mass spectrometry was carried out with a Hitachi RMU-7 spectrometer (70 eV ionizing voltage). T.l.c. was carried out on silica gel GF_{254} (Merck) and solid–liquid column chromatography on silica gel 60 (EM Reagents).

trans-β-*Phenanthren-9-ylacrylic Acid* (2).—A solution of phenanthrene-9-carbaldehyde (60 g, 0·29 mol; Aldrich)

[13] J. W. Cook and C. L. Hewitt, *J. Chem. Soc.*, 1934, 365.
[14] E. R. Holiday and E. M. Jope, *Cancer Res.*, 1946, **6**, 704.
[15] 'Elsevier's Encyclopaedia of Organic Chemistry,' ed. F. Radt, Elsevier, Amsterdam, 1951, series III, vol. 14, Suppl. p. 706S.

and malonic acid (90 g) in piperidine (1 ml) and pyridine (150 ml) was stirred and heated at 100—105° for 24 h, during which time malonic acid (80 g) and piperidine (11 ml) were added in three portions. At this point t.l.c. with chloroform indicated that all the starting aldehyde had been consumed, and the solution was refluxed for 15 min to ensure complete decarboxylation. The solvent was removed under vacuum and the residue recrystallized to give the acid (2) (54 g, 75%), m.p. 230—233° (from acetic acid) (lit.,[8] 231—233·5°); δ [$(CD_3)_2SO$] 8·87 (2H, m), 8·43 (1H, d), 8·29 (1H, s), 8·17 (2H, m), 7·75 (3H, m), and 6·71 (1H, d).

β-*Phenanthren*-9-*ylpropionic Acid* (3).—The acid (2) (2·48 g) in tetrahydrofuran (250 ml) was reduced with hydrogen at room temperature and atmospheric pressure over 5% palladium–charcoal (0·1 g). Filtration, evaporation, and recrystallization gave the propionic acid (3) (2·2 g, 88%), m.p. 172—173° (from aqueous methanol) (lit.,[8] 173—174°); δ [$(CD_3)_2SO$] 8·82 (2H, m), 8·14 (1H, m), 7·90 (1H, m), 7·68 (5H, m), 3·36 (2H, t), and 2·72 (2H, t).

β-(9,10-*Dihydrophenanthren*-9-*yl*)*propionic Acid* (4).—Sodium (1·6 g) was added over 2 h to a refluxing solution of the propionic acid (3) (0·5 g) in pentan-1-ol (30 ml). The mixture was diluted with water (100 ml) and evaporated to dryness. This was repeated twice to remove the pentanol and the residue was acidified and extracted into ether. The extract was dried ($MgSO_4$) and evaporated and the residue recrystallized with aqueous methanol to give a sticky solid. The proportion of aromatic to aliphatic protons shown by the n.m.r. spectrum of the product indicated that the reduction had proceeded beyond the dihydrophenanthrene. Mass spectral analysis confirmed that the product was a *ca.* 3 : 1 mixture of hexa- and octa-hydrophenanthrenylpropionic acids, respectively. A repeat of the reduction with propan-1-ol in place of pentanol also resulted in extensive reduction of the aromatic system.

In the third reductive procedure a solution of the propionic acid (3) (0·62 g) in tetrahydrofuran (38 ml; freshly distilled from calcium hydride) was added to refluxing ammonia (75—100 ml) containing iron(III) chloride (20 mg) under helium. To this was added lithium metal (55 mg) which had been cut into small pieces and washed in hexane. The mixture was refluxed in helium for 3 h, then quenched with ethanol followed by water, and the resulting mixture was taken to dryness under vacuum. The residue was dissolved in water, extracted with ether, and worked up as in the other reductions. N.m.r. and mass spectral analyses showed the product to be a mixture of reduced phenanthrenylpropionic acids.

Reduction of the propionic acid (3) (1·0 g) with hydrogen (4 atm) over 10% palladium–charcoal (1·0 g) for 5 h in acetic acid (250 ml) at 65° gave a quantitative yield of β-(*sym*-octahydrophenanthren-9-yl)propionic acid, m.p. 176—178° (from aqueous metanol) (lit.,[12] 179°); *m/e* 258 (M^+).

When the catalytic reduction was repeated with 5% palladium–charcoal (0·1 g) at 65° for 48 h a mixture of phenanthrenyl- and reduced phenanthrenyl-propionic acids was obtained. Careful recrystallization of this mixture from aqueous acetic acid gave a residual mother liquor containing predominantly β-(9,10-*dihydrophenanthren*-9-*yl*)-*propionic acid* (4) with some unchanged starting material in *ca.* 25% yield. The purification of this material is described below.

In the method adopted for the synthesis of the dihydrophenanthrenylpropionic acid (4) a solution of the acrylic acid (2) (2·0 g) in acetic acid (250 ml) was reduced with hydrogen over 5% palladium–charcoal (1·0 g) at room temperature and 4 atm pressure for 24 h. The solution was filtered and worked up as before; evaporation of the mother liquor gave crude β-(9,10-dihydrophenanthren-9-yl)-propionic acid (4) (0·69 g, 34%). Large-scale preparations [the acrylic acid (2) (20 g), catalyst (10 g) and acetic acid (250 ml)] gave 28—41% yields of the crude propionic acid (4). To a solution of this crude material in the minimum of hot benzene was added a concentrated solution of 1,3,5-trinitrobenzene [half the amount by weight of crude (4)], also in hot benzene. Crystals of the trinitrobenzene derivative of the major impurity, β-phenanthren-9-ylpropionic acid (3), were formed on cooling, leaving the desired compound in solution. The purity of the solution was checked by t.l.c. [chloroform–tetrahydrofuran (50 : 50)]. The filtered benzene solution was subjected to column chromatography. The trinitrobenzene was eluted with benzene and the dihydrophenanthrenylpropionic acid with chloroform–tetrahydrofuran (60 : 40). The recrystallized product had m.p. 113—114° (from carbon tetrachloride–petroleum), δ [$(CD_3)_2SO$] 7·76 (2H, m), 7·31 (6H, m), 2·92 (3H, m), 2·17 (2H, m), and 1·52 (2H, m); *m/e* 252 (M^+) (Found: C, 80·9; H, 6·4. $C_{17}H_{16}O_2$ requires C, 80·8; H, 6·5%).

5,6,6a,7-*Tetrahydrobenz*[de]*anthracen*-4-*one* (5).—A solution of the dihydrophenanthrenylpropionic acid (4) (7·3 g) in anhydrous hydrogen fluoride (75 ml) was left for 16 h in a Teflon beaker with a polyethylene cover. The hydrogen fluoride was then removed in a stream of nitrogen and the residue was basified with saturated aqueous sodium carbonate and extracted into benzene. The extract was dried ($MgSO_4$) and evaporated to give the crude *ketone* (5) (7·0 g, 102%) as a yellow solid, *m/e* 234 (M^+), used in the next stage without further purification.

β-(7H-*Benz*[de]*anthracen*-4-*yl*)*propionic Acid* (7).—A solution of diethyl succinate (30 g) and potassium t-butoxide [from potassium (8·8 g)] in freshly distilled t-butyl alcohol (200 ml) was added over 1 h to the ketone (5) in an atmosphere of nitrogen. The mixture was refluxed during this period and for a further 1 h, then acidified with 2M-hydrochloric acid (200 ml) and concentrated under vacuum. The residue was dissolved in ether and the acidic material was extracted into 2M-ammonia. Acidification of the ammonia solution with hydrochloric acid, extraction with ether, drying ($MgSO_4$), and evaporation gave a dark brown oil. A suspension of this in acetic acid (160 ml), concentrated hydrochloric acid (80 ml), and water (60 ml) was refluxed under nitrogen for 16 h, diluted with water (800 ml), and extracted with ether. The ethereal solution was re-extracted with aqueous potassium hydrogen carbonate. Extraction of the acidified aqueous layer with ether gave an ethereal solution which t.l.c. [chloroform–tetrahydrofuran (50 : 50)] showed to contain two major components with similar R_F values. One of these was precipitated when the solution was concentrated and was shown to be β-(7H-*benz*[de]*anthracen*-4-*yl*)*propionic acid* (7) (2·05 g, 24%). This material was purified by vacuum sublimation (190—192° at 0·025 mmHg); it decomposed before it melted; δ [$(CD_3)_2CO$] 8·13 (2H, m), 8·00 (1H, d), 7·57 (1H, t), 7·35 (5H, m), 4·53 (2H, s), 3·37 (2H, t), and 2·73 (2H, t); *m/e* 288 (M^+) (Found: C, 83·3; H, 5·6. $C_{20}H_{11}O_2$ requires C, 83·25; H, 5·6%).

β-(5,6,6a,7-*Tetrahydro*-4H-*benz*[de]*anthracen*-4-*yl*)*propionic Acid* (12) *and* 3,3a,4,5,5a,6-*Hexahydrobenzo*[a]*pyren*-1(2H)-*one* (13).—The second component from the foregoing

Stobbe reaction was chromatographed, and after some impurities had been eluted with benzene was itself eluted with chloroform. A portion of the product (0·75 g), thought to be β-(5,6,6a,7-tetrahydro-4*H*-benz[*de*]anthracen-4-yl)propionic acid, was dissolved in anhydrous hydrogen fluoride (20 ml). After 16 h the hydrogen fluoride was removed in a stream of nitrogen and the residue was neutralized with saturated iced sodium carbonate and extracted into chloroform. The extract was dried ($MgSO_4$) and evaporated. The residue (0·60 g, 85%) showed *m/e* 274 (M^+), consistent with the expected benzopyrenone (13). This material was not characterized further.

Since solutions of the above materials, especially (7), were found to be very sensitive to oxidation, during the reactions and work-up the solutions were kept under nitrogen and the flasks were wrapped in aluminium foil.

Benzo[a]*pyren*-1-*ol* (8).—A solution of the benzanthracenylpropionic acid (7) (1·0 g) in anhydrous hydrogen fluoride (75 ml) enclosed in a steel bomb under nitrogen was heated in a steam-bath. After 15 h the hydrogen fluoride was removed in a stream of nitrogen and the residue was dissolved in tetrahydrofuran and treated with solid sodium carbonate. The solution was filtered and evaporated to dryness and the residue was sublimed at 230° and 0·025 mmHg to give the bright yellow *benzo*[a]*pyren*-1-*ol* (8) (0·33 g, 35%). This product contained a small amount of an orange impurity which was removed by a second sublimation. The benzopyrenol decomposed before it melted; δ ($[CD_2]_4O$) 11·15 (1H, s) 9·07 (1H, m), 9·04 (1H, d), 8·66 (1H, d), 8·39 (1H, s), 8·21 (1H, m), 7·90 (1H, d), 7·77 (2H, s), 7·73 (1H, m), 7·69 (1H, m), and 7·37 (1H, d); *m/e* 268 (M^+) (Found: C, 89·5; H, 4·5. $C_{20}H_{12}O$ requires C, 89·5; H, 4·5%), $\lambda_{max.}$ (MeOH) 258 (log ε 4·59), 266 (4·60), 287 (4·47), 298 (4·54), 361sh (3·96), 381 (4·23), 388 (4·27), 399 (4·28), and 415 (3·70). Excitation of a methanolic solution of the phenol at 280, 300, and 340 nm resulted in fluorescence at 430 with a shoulder at 445 nm.

1-*Methoxybenzo*[a]*pyrene*.—A crude sample of the benzopyrenol (8) from cyclization of the benzanthracenylpropionic acid (7) (50 mg) was dissolved in a solution of potassium hydroxide (3 g) in water (5 ml) and methanol (2 ml) and heated on a steam-bath for 0·5 h with dimethyl sulphate (0·5 ml). The methoxybenzopyrene was extracted into benzene and purified by column chromatography (carbon tetrachloride as eluant). The yellow solid product had δ ($CDCl_3$) 8·99 (1H, m), 8·90 (1H, d), 8·65 (1H, d), 8·36 (1H, s), 8·19 (1H, m), 7·95 (1H, d), 7·74 (4H, m), 7·38 (1H, d), and 4·13 (3H, s), *m/e* 282 (M^+), $\lambda_{max.}$ (n-hexane) 259, 268, 287, 298, 340, 358, 368sh, 373sh, 377, 386, 389, 392, 397, and 412 (since the purity of the ether was not certain, log ε values are not recorded).

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