Potentially Carcinogenic Cyclopenta[*a*]phenanthrenes. Part X.[1] Oxygenated Derivatives of the Carcinogen 15,16-Dihydro-11-methylcyclopenta[*a*]phenanthren-17-one of Metabolic Interest

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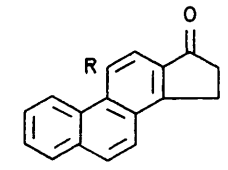
Two metabolites of the title compound, namely the 15-hydroxy- and 11-hydroxymethyl derivatives, and also 15,16-dihydro-2-hydroxycyclopenta[*a*]phenanthren-17-one have been synthesised by adaptations of routes previously described for compounds of this series.

AFTER injection of the carcinogen 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one (Ib) [2] into rats, the major metabolite isolated from the urine was the epoxytrihydroxybenzocyclodecene (II),[1] whereas the non-carcinogenic ketone (Ia) was not metabolised to a similar structure in significant amounts. The epoxy-compound (II) was not found among the *in vitro* metabolites when the carcinogen was incubated with various rat liver preparations in the presence of NADPH and oxygen, but here the major metabolite was the 15-hydroxy-derivative (IIIa), together with smaller amounts of the 16-hydroxy- (IVa) and 11-hydroxymethyl- (Va) ketones.[3] This paper describes the chemical synthesis of (IIIa) and (Va), and of 15,16-dihydro-2-hydroxycyclopenta[*a*]phenanthren-17-one (VIIa) which was required as a model during the elucidation of the structure of the phenolic epoxybenzocyclodecene (VI) formed on treatment of the urinary metabolite with acid.

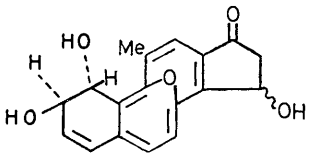
The 15-acetoxy-ketone (IIIb) was readily obtained by either of the methods described for the corresponding derivative of the parent ketone.[4] Treatment of (Ib) with bromine and thallium(III) acetate led directly to the 15-acetate (IIIb), but isolation from the reaction mixture by chromatography was not readily accomplished. Attention was therefore directed towards the second method, acid-catalysed addition to the enone (VIIIb). The carcinogen was readily brominated in good yield with *N*-bromosuccinimide to give the 16-bromo-ketone (IX), the ring D protons of which possessed n.m.r. chemical shifts and coupling constants almost identical with those of 16-bromo-15,16-dihydrocyclopenta[*a*]-phenanthren-17-one, and different from those of the

[1] Part IX, M. M. Coombs and F. E. H. Crawley, *J.C.S. Perkin I*, 1974, 2330.
[2] M. M. Coombs and F. E. H. Crawley, in preparation.
[3] M. M. Coombs, M. Hall, V. A. Siddle, and C. W. Vose, in preparation.
[4] M. M. Coombs, M. Hall, and C. W. Vose, *J.C.S. Perkin I*, 1973, 2236.

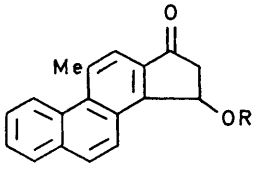
known 15-bromo-derivative of (Ib).[4] Dehydrobromination with triethylamine readily generated the 15-en-17-



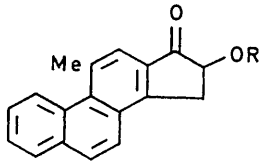
(I) a; R = H
b; R = Me



(II)



(III) a; R = H
b; R = Ac



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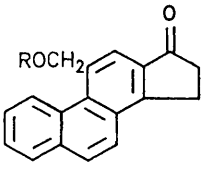
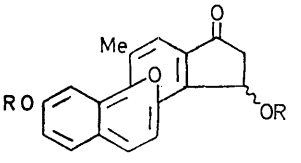
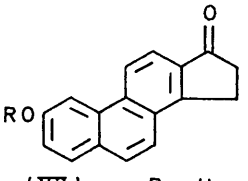
b; R = Ac



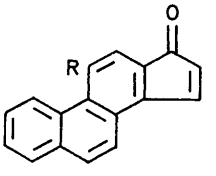
(V) a; R = H
b; R = Ac



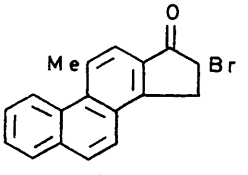
(VI) a; R = H
b; R = Ac



(VII) a; R = H
b; R = Ac



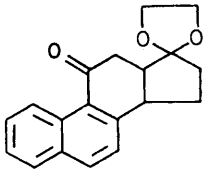
(VIII) a; R = H
b; R = Me



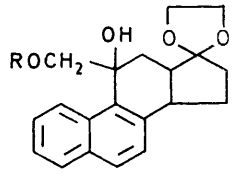
(IX)

one (VIIIb). This compound was not isolated, but was identified by its characteristic four-banded u.v. spectrum which was very similar to that of the unsubstituted enone (VIIIa).[4] It appeared to be appreciably more stable than the latter, giving rise to insoluble, pink decomposition products only slowly. Moreover, acid-catalysed addition of water to the double bond occurred very slowly, being still incomplete after 48 h at ambient temperature. Recourse was therefore made to acid-catalysed addition of acetic acid to this double bond, for it is known that this occurs some 700 times faster than acid-catalysed hydration of the double bond in the analogous system indenone.[5] By using acetic acid containing 5% of sulphuric acid, addition was essentially complete within 1 h and the 15-acetoxy-17-ketone (IIIb) was obtained directly by crystallisation in about 40% yield. It was essential to remove the triethylamine hydrobromide before the addition of the acid; failure resulted in regeneration of the 16-bromoketone (IX). The reason for this surprising result is not clear, for acetate attacks as expected at C-15. There was evidence for a small proportion of the 15-bromide in the material recovered. Attempted alkaline hydrolysis of the acetate (IIIb) led to degradation, but hydrolysis with sulphuric acid in tetrahydrofuran gave the 15-hydroxy-compound (IIIa) in moderate yield.

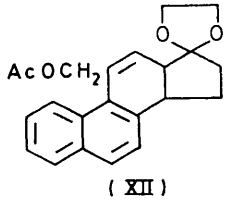
Hydroxymethyl derivatives of methyl substituted polycyclic aromatic hydrocarbons have been prepared directly by oxidation with lead tetra-acetate,[6] but under these conditions the carcinogen (Ib) is converted largely into the 16-acetate (IVb).[7] For synthesis of the 11-hydroxymethyl derivative (Va) we therefore used the convenient intermediate (X).[8] Grignard reagents prepared from benzyl chloromethyl ether and chloromethyl methyl ether failed to react with this ketone, presumably owing to steric hindrance, but addition to the carbonyl group occurred in reasonable yield with the ylide from trimethylsulphonium iodide.[9] The expected epoxide was not isolated, for when the reaction was worked up by acidification to pH 2—3 with dilute acetic acid the product obtained was the 11-hydroxy-11-hydroxymethyl acetal (XIa). Absence of i.r. carbonyl absorption and of a methyl singlet in its n.m.r. spectrum indicated this structure. In addition, the methylene



(X)



(XI) a, R = H
b; R = Ac



(XII)

protons of the hydroxymethyl group appeared as an AB quartet with geminal coupling of 11·5 Hz. The

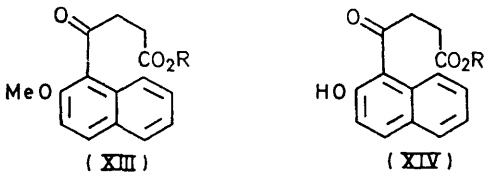
[5] P. H. Lacey and D. C. C. Smith, *J. Chem. Soc.* (*C*), 1971, 41.
[6] G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 1939, 801; E. Boyland and P. Sims, *Biochem. J.*, 1965, **95**, 780.
[7] M. M. Coombs, *J. Chem. Soc.* (*C*), 1969, 2484.
[8] M. M. Coombs, *J. Chem. Soc.* (*C*), 1966, 955.
[9] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.

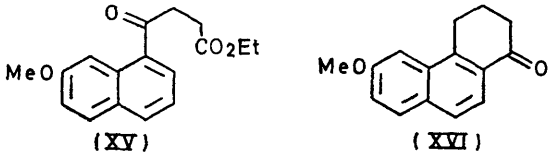
base peak in the mass spectrum, *m/e* 295, corresponds to the loss $\cdot CH_2OH$ from the molecular ion.

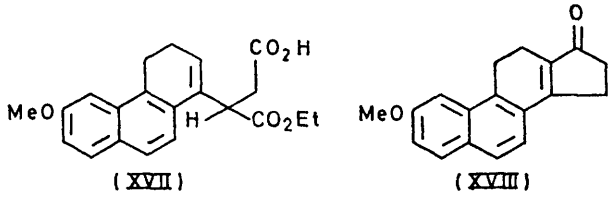
Protection of the primary hydroxy-group by mild acetylation, followed by dehydration with phosphoryl chloride and pyridine gave the Δ^{11}acetal (XII) in which the methylene protons of the acetoxymethyl group were equivalent, appearing as a singlet. Aromatisation of ring C was completed by dehydrogenation with dichlorodicyanobenzoquinone (DDQ); removal of the acetal function with acid led to the fully aromatic acetoxymethyl ketone (Vb) with u.v. absorption very similar to that of the ketone (Ib). Mild alkaline hydrolysis finally yielded the required 11-hydroxymethyl ketone (Va).

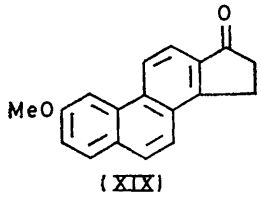
For the synthesis of the 2-phenolic-17-ketone (VIIa) the route previously employed [10] was followed, starting from the tricyclic ketone (XVI). The latter was prepared from anisole by a six-step sequence, after abandoning a potentially shorter route by way of Friedel–Crafts succinylation of 2-methoxynaphthalene. Although this reaction was stated [11] to yield solely 3-(2-methoxy-1-naphthoyl)propionic acid (XIIIa) in unstated yield when carbon disulphide was used, employing these conditions Bachmann and Horton [12] isolated the required 7-methoxy-1-naphthoyl isomer as the ethyl ester (XV) in *ca.* 10% yield, but obtained none of the 2-methoxy-isomer (XIIIa). In our hands, repetition of the succinylation according to these authors led to a small amount of (XV) together with a much larger quantity of the phenolic ester (XIVb). The latter was readily methylated with diazomethane to the 2-methoxy-1-naphthoyl ester (XIIIb), but attempted methylation with dimethyl sulphate and alkali failed, giving only the phenolic acid (XIVa). This partly explains the above discrepancy, for the former authors [11] stated merely that the reaction was 'worked up in the usual way,' whereas the latter specify treatment of the crude Friedel–Crafts product with dimethyl sulphate and alkali before esterification and distillation. Nevertheless, it is not clear why the original authors did not also observe extensive demethylation with aluminium chloride in boiling carbon disulphide.

Stobbe condensation of the tricyclic ketone (XVI) with diethyl succinate yielded the half-ester (XVII) which was cyclised with acetic anhydride and anhydrous zinc chloride. The product (XVIII), readily identified by its u.v. spectrum characteristic of 11,12,15,16-tetrahydro-17-ketones of this series,[10] was dehydrogenated by prolonged heating with chloranil in toluene. The yield of the cyclopenta[*a*]phenanthrenone (XIX) was *ca.* 50%; reaction with DDQ occurred more quickly, but the yield was less. Demethylation with boron tribromide [13] below 0° yielded the 2-hydroxy-17-ketone (VIIa), isolated as its more soluble acetate (VIIb). The free 2-phenol resembled in most respects the known 3-, 6-, and 7-phenols,[7] except that with alkali the u.v. maximum at 274·5 nm gave place to two maxima of similar intensity at 245 and 296 nm, instead of the simple bathochromic shift shown by the maxima of these other phenols. This behaviour was also exhibited by the metabolite derivative (VIa),[1] with a transition from 278 nm (neutral) to maxima of equal intensity at 255 and 299 nm in alkaline solution. The n.m.r. signals due









to the aromatic protons in these two compounds are compared in the Table. Very similar chemical shifts are

N.m.r. chemical shifts (τ) and coupling constants (*J*/Hz) of aromatic protons in (VIb) and (VIIb) measured at 100 MHz in $CDCl_3$

	(VIb)	(VIIb)
H-1	1·33 ($J_{1.3}$ 2)	1·62 ($J_{1.3}$ 2)
H-3	2·58 ($J_{1.3}$ 2, $J_{3.4}$ 8)	2·59 ($J_{1.3}$ 2, $J_{3.4}$ 8)
H-4	2·04 ($J_{3.4}$ 8)	2·08 ($J_{3.4}$ 8)
H-6	~2·20 ($J_{6.7}$ 8)	2·17 (2H, s)
H-7	~2·02 ($J_{6.7}$ 8)	
H-11		1·48 ($J_{11.12}$ 8)
H-12	2·16 (1H, s)	2·11 ($J_{11.12}$ 8)

observed for H-3, -4, and -12, while the presence of the 11-methyl group in (VIb) causes H-1 to resonate at *ca.* 0·3 p.p.m. to lower field than that in (VIIb), as has been previously observed with similar compounds. However, H-6 and -7 in (VIIb) are accidentally equivalent, appearing as a strong singlet at τ 2·17 while in (VIb) they form an AB quartet. One proton, probably

[10] M. M. Coombs, S. B. Jaitly, and F. E. H. Crawley, *J. Chem. Soc.*, (*C*), 1970, 1266.
[11] W. F. Short, H. Stromberg, and A. E. Wilds, *J. Chem. Soc.*, 1936, 319.
[12] W. E. Bachmann and W. J. Horton, *J. Amer. Chem. Soc.*, 1949, **69**, 58.
[13] J. F. W. McOmie and M. L. Watts, *Chem. and Ind.*, 1963, 1658.

H-6, resonates at τ *ca.* 2·20 whereas the other (H-7) appears at *ca.* 2·02 indicating attachment of the electronegative ring oxygen at the adjacent carbon atom (C-8). A similar deshielding of H-7 in the metabolite (II) was observed [1] when compared with its triacetate lacking this ring oxygen atom.

EXPERIMENTAL

Materials and methods were generally as described in previous parts of this series. I.r. spectral data for compounds marked with an asterisk are listed in Supplementary Publication No. SUP 21216 (2 pp.).*

16-*Bromo*-15,16-*dihydro*-11-*methylcyclopenta*[a]*phenanthren*-17-*one* (IX).—The carcinogen (Ib) (2·46 g, 10 mmol) in carbon tetrachloride (100 ml) was boiled under reflux with *N*-bromosuccinimide (2·14 g) for 3 h adjacent to a 150 W lamp. After cooling, the precipitated succinimide was filtered off, and the orange solution was washed with water, dried, and evaporated to give a solid (2·21 g). Recrystallisation from benzene yielded the 16-*bromo*-11-*methyl-ketone* (IX) (1·55 g), m.p. 168° (unchanged by further recrystallisation) (Found: M^+, 324·0141. $C_{18}H_{13}BrO$ requires M, 324·0149); $\nu_{max.}$ (Nujol) 1720 (C=O), 870, 827, 800, 770, 758, and 675 cm^{-1}, $\lambda_{max.}$ (EtOH) 274·5, 359, and 377 nm, τ ($CDCl_3$) 4·06 (q, J 2 and 6 Hz, H-16), 6·7 (q, J 2 and 20 Hz, H-15), and 6·51 (q, J 6 and 20 Hz, H-15).

15-*Acetoxy*-15,16-*dihydro*-11-*methylcyclopenta*[a]*phenanthren*-17-*one* (IIIb).—*From the enone* (VIIIb). The bromo-ketone (IX) (1·06 g) was dissolved in pure tetrahydrofuran (THF) (100 ml) and treated with triethylamine (2·0 ml). Aliquot portions were removed at intervals and diluted with ethanol for u.v. spectrophotometry; after *ca.* 30 min, conversion into the enone (VIIIb), $\lambda_{max.}$ 256, 288, 298, and 312 nm, appeared to be complete. Dichloromethane (100 ml) was added and the solution was washed with water to remove triethylamine hydrobromide. After addition of a mixture of glacial acetic acid (180 ml) and conc. sulphuric acid (20 ml) aliquot portions were removed, diluted with acetic acid, and their u.v. spectra observed. After 1 h, when conversion into the product, $\lambda_{max.}$ 266 nm, was complete, more dichloromethane was added and the reaction mixture was washed several times with water, with sodium hydrogen carbonate solution, again with water, and dried. Evaporation and crystallisation of the residue from ethanol gave red needles (0·4 g), m.p. 196—204°. Several recrystallisations from this solvent with the addition of charcoal yielded the 15-*acetoxy*-11-*methyl*-17-*ketone* (IIIb)* as pale pink needles, m.p. 209—210° (Found: C, 78·85; H, 5·15. $C_{20}H_{16}O_3$ requires C, 78·95; H, 5·3%), $\lambda_{max.}$ (EtOH) 266 (log ε 4·81), 301 (4·30), 356 (3·11), and 374 nm (3·19).

In a preliminary experiment the bromo-ketone (IX) (50 mg) in THF (1·0 ml) was treated with triethylamine (0·1 ml) for 30 min, when the above spectral change had occurred. Addition of 5% sulphuric acid in acetic acid caused an almost immediate change to $\lambda_{max.}$ (HOAc) 277 nm. After 30 min water was added and the product was extracted with dichloromethane as before to yield a pale brown crystalline solid (30 mg), m.p. 146—155°, $\nu_{max.}$ (Nujol) as for (IX), with weak bands at 820, 760, 722, and 700 cm^{-1} possibly caused by the presence of a small quantity of the 15-bromo-17-ketone.[4]

This acetate (IIIb) (130 mg) was boiled for 20 h with 2N-H_2SO_4 (7·5 ml) in THF (15 ml). The dark brown solution was diluted with water and extracted with ethyl acetate. The crude product, which showed several spots on t.l.c., was purified by this method, recovering the material of R_F 0·50 by elution of the silica gel with ethanol. Evaporation of the solvent under reduced pressure gave the 15-hydroxy-11-methyl-17-ketone (IIIa) as a pale cream solid (20 mg), $\lambda_{max.}$ (EtOH) 265 (log ε 4·84), 300 (4·53), 356 (3·29), and 374 nm (3·21). This compound appeared to be rather unstable; rechromatography after keeping it at ambient temperature again showed several spots, and for this reason no attempt was made at further purification.

From (Ib) *with thallium*(III) *acetate and bromine*. The carcinogen (Ib) (150 mg) and thallium(III) acetate (234 mg) were stirred together in carbon tetrachloride (35 ml). Bromine (100 mg) in this solvent (2 ml) was added in one lot, and the mixture was stirred at room temperature for 23 h, when t.l.c. showed that most of the ketone (Ib) had been consumed with the formation of a more polar material identified as the 15-acetate (IIIb) by its R_F value and the greenish blue colour developed at 100° after spraying with ethanolic H_2SO_4. After filtration from the dark precipitate, removal of the solvent gave a bright yellow gum (194 mg) which was chromatographed on a column of silica gel (Hopkins and Williams M.F.C.) (20 g), eluting with dichloromethane containing increasing proportions of ethyl acetate. Fractions containing the acetate (IIIb), but still contaminated with starting material (Ib) (50 mg) were purified further by preparative t.l.c. (silica gel, 1 mm layers; CH_2Cl_2) giving finally an orange solid (11 mg) with i.r. and u.v. spectra identical with those of the pure 15-acetate (IIIb) described above. The chromatographic column remained strongly fluorescent when no more material could be eluted.

17,17-*Ethylenedioxy*-11-*hydroxy*-11-*hydroxymethyl*-11,12,13,14,15,16-*hexahydrocyclopenta*[a]*phenanthrene* (XIa). —Sodium hydride (50% dispersion in oil; 0·35 g) was washed by decantation with light petroleum (b.p. 40—60°). Dry dimethyl sulphoxide (30 ml) was added under nitrogen and the mixture was stirred at 70° until hydrogen evolution ceased. After cooling, dry tetrahydrofuran (30 ml) was added and the mixture was further cooled to −3° before trimethylsulphonium iodide (3·63 g) dissolved in dimethyl sulphoxide was added slowly with stirring, keeping the temperature below 0°. When the addition was complete the oxo-acetal (X) (3·5 g) in a mixture of dimethyl sulphoxide (15 ml) and THF (15 ml) was run in slowly below 0°, and the solution was stirred at this temperature for 2 h. When the reaction mixture had attained room temperature it was poured into water (260 ml) and acidified to pH 2—3 with glacial acetic acid to facilitate extraction with dichloromethane. The extract was washed with water, saturated sodium hydrogen carbonate solution, water, and dried. The gum (3·4 g) left on removal of the solvent under reduced pressure crystallised from benzene–n-hexane as fawn needles (1·3 g); the mother liquor contained mostly starting material. Recrystallisation gave the 11-*hydroxy*-11-*hydroxymethyl acetal* (XIa)* as needles (1·12 g), m.p. 168—170·5° (Found: C, 73·3; H, 6·7%; M^+, 326·1511. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%; M, 326·1518), *m/e* 326 (M^+, 35%), 380 ($M^+ - H_2O$, 20), 295 ($M^+ - CH_2OH$, 100), and 99 (acetal ion, 89); $\lambda_{max.}$ (EtOH) 230·5 (log ε 4·92), 272·5 (3·74), 282 (3·76), and 291 nm (3·62); τ ($CDCl_3$) 6·13 (d, J 11·5 Hz, H_ACH_BOH), 5·67 (d, J 11·5 Hz, $H_AC\mathit{H}_BOH$), and 6·04 (s, OCH_2CH_2O).

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index issue.

This diol (1·12 g) was acetylated with acetic anhydride and pyridine overnight at room temperature. Chromatography of the product (1·1 g) on alumina (Merck grade II—III) with toluene–ethanol (200 : 1 v/v) gave the 11-*acetoxymethyl*-11-*hydroxy acetal* (XIb)* as a pale yellow glass (0·75 g) (Found: C, 71·8; H, 6·1%; M^+, 368·1617. $C_{22}H_{24}O_5$ requires C, 71·7; H, 6·5%; *M*, 368·1623), *m/e* 368 (M^+, 25%), 350 ($M^+ - H_2O$, 45), 295 ($M - CH_2OAc$, 15), and 99 (acetal ion, 100); $\lambda_{max.}$ 230 (log ε 4·96), 272 (3·74), 282 (3·76), and 291 nm (3·62); τ 7·95 (s, OAc), 6·05 (s, OCH_2CH_2O), 5·98 (d, *J* 11·5 Hz, H_ACH_BOAc), 4·92 (d, *J* 11·5 Hz, H_ACH_BOAc).

15,16-*Dihydro*-11-*hydroxymethylcyclopenta*[a]*phenanthren*-17-*one* (Va).—Redistilled phosphoryl chloride (394 mg, 0·24 ml) was added to a vigorously stirred solution of the acetoxymethyl acetal (XIb) in pyridine (15 ml), cooled in ice. The solution was stirred at 0° for 30 min and then at 79° for 6 h in the absence of moisture. After addition of ice and extraction with ether, a pale orange-yellow gum (211 mg) was obtained which ran as one spot on t.l.c., R_F 0·73 (ethyl acetate–dichloromethane, 1 : 9 v/v) and appeared to be the required 11-acetoxymethyl-Δ^{11}-acetal (XII),* $\lambda_{max.}$ (EtOH) 237·5 (log ε 4·81), 303 (3·88), 315 (3·87), and 336 nm (3·59), similar to the spectrum of the corresponding 11-methyl-Δ^{11}-acetal; τ 7·90 (s, OAc), 7·32 (m, H-13 and -14), 6·00 (s, OCH_2CH_2O), and 4·75 (s, CH_2OAc). Chromatography of a sample of this Δ^{11}-acetal on alumina (Grade III) resulted in decomposition to a number of products, and the acetal was therefore used without further purification.

This material (60 mg), dissolved in benzene (10 ml), was treated with dichlorodicyanoquinone (DDQ) (40 mg) at room temperature for 48 h. The precipitated hydroquinone was collected, and the filtrate was washed with 2N-sodium hydroxide to yield an orange glass (49 mg) which was dissolved in THF, acidified with 5N-hydrochloric acid, and stirred overnight at room temperature. The solution was poured into saturated aqueous sodium hydrogen carbonate and extracted with ether; the product was reacetylated as already described. Chromatography of the product on a column of silica gel (MFC) with toluene–ethanol (50 : 1 v/v) and crystallisation of fractions showing bright blue fluorescence in u.v. light from ethanol gave 11-*acetoxy*-15,16-*dihydrocyclopenta*[a]*phenanthren*-17-*one* (Vb)* as needles (30 mg), m.p. 175—176° (Found: M^+, 304·1093. $C_{20}H_{16}O_3$ requires *M*, 304·1099), *m/e* 304 (M^+, 100%), 245 ($M^+ - CH_3CO_2$, 20), and 231 ($M - CH_2OAc$, 30), $\lambda_{max.}$ (EtOH) 265 (log ε 4·88), 285 (4·50), 300·5 (4·36), 356 (3·32), and 373 nm (3·44); τ [$(CD_3)_2SO$] 7·92 (s, OAc), 7·18 (m, 16-H_2), 6·88 (m, 15-H_2), 4·68 (s, CH_2OAc), and 2·70—1·75 (7H, aromatic).

This compound (25 mg) in ethanol (8 ml) was hydrolysed with 5% sodium hydroxide solution (0·3 ml) at room temperature for 2 h. Addition of water and extraction with chloroform gave the 11-*hydroxymethyl*-17-*ketone* (Va)* crystallised from chloroform–n-hexane as fine, pale yellow needles (13 mg), m.p. 190—192° (Found: M^+, 262·0987. $C_{18}H_{14}O_2$ requires *M*, 262·0993), *m/e* 262 (M^+, 100%), 234 ($M^+ - CO$, 20), 235 ($M^+ - CHO$, 45), and 233 ($M^+ - CH_2OH$, 18), $\lambda_{max.}$ (EtOH) 264·5 (log ε 4·85), 285 (4·51), 300 (4·32), 356 (3·29), and 372·5 nm (3·41).

Preparation of 6-*Methoxy*-3,4-*dihydrophenanthren*-1(2H)-*one* (XVI).—3-*p*-Anisoylpropionic acid [14] (from anisole; 45%) was reduced with amalgamated zinc and hydrochloric acid to 4-*p*-methoxyphenylbutyric acid [15] (70%). Cyclisation with tin(IV) chloride gave 7-methoxytetralone [12] (65%). A Reformatsky reaction with methyl 3-bromocrotonate [16] followed by isomerisation of the product gave 4-(7-methoxy-1-naphthyl)butyric acid (50%) which was cyclised to the methoxy-ketone (XVI), m.p. 104—105° (lit.,[12] 102—103·5°) (62%).

Succinylation of 2-*Methoxynaphthalene*.—2-Methoxynaphthalene (79 g) was treated as described,[12] giving a distillate (36·5 g), b.p. 178—190° at 0·4 mmHg. Dissolution in hot methanol and cooling gave the ethyl ester (XV) as a finely divided, crystalline solid (3·2 g), m.p. 72—74·5° (lit.,[12] 79·5—81°). Evaporation of the methanol and crystallisation of the residue from benzene yielded bright yellow prisms (20·5 g) of *ethyl* 3-(2-*hydroxy*-1-*naphthoyl*)*propionate* (XIVb), m.p. 95—96° (Found: C, 70·6; H, 6·05. $C_{16}H_{16}O_4$ requires C, 70·55; H, 5·9%), $\nu_{max.}$ (Nujol) 3295 (OH), 1729 (ester C=O), and 1670 cm^{-1} (aryl C=O). Methylation of (XIVb) (1·0 g) with an excess of diazomethane in ether gave an oil which rapidly crystallised to yield the methoxy-ester (XIIIb) (0·95 g), m.p. 43—45° (lit.,[11] 41—42°), $\nu_{max.}$ (Nujol) 1727 and 1700 cm^{-1}. Saponification of (XIVb) (0·5 g) with warm 2N-NaOH gave the *acid* (XIVa) (0·34 g), m.p. 105—106° (Found: C, 68·55; H, 5·15. $C_{14}H_{12}O_4$ requires C, 68·85; H, 4·95%), $\nu_{max.}$ (Nujol) 1700 and 1620—1610s,br cm^{-1}. The same product was also obtained when dimethyl sulphate was added to the alkaline solution of (XIVb).

2-*Methoxy*-11,12,15,16-*tetrahydrocyclopenta*[a]*phenanthren*-17-*one* (XVIII).—*Stobbe reaction*. The methoxy-ketone (XVI) (7·60 g) and diethyl succinate (9 ml) were heated under reflux with potassium t-butoxide [from t-butyl alcohol (25 ml) and potassium (1·45 g)] for 90 min in an atmosphere of dry nitrogen. After being kept at room temperature overnight, the reaction mixture was acidified to pH 5—6 with 2N-hydrochloric acid and extracted with dichloromethane. The latter solution was thoroughly extracted with dilute aqueous ammonium hydroxide; acidification of the alkaline solution with 2N-hydrochloric acid liberated the half-ester (XVII) which formed a brown gum (9·56 g), not obtained crystalline, but which ran as a single spot on t.l.c.

Cyclisation. This half-ester (9·56 g) was dissolved in acetic anhydride (100 ml) and treated with a solution (50 ml) of freshly fused zinc chloride (3·0 g) in glacial acetic acid (150 ml) under reflux in dry nitrogen for 5 h. Water (106 ml) was cautiously added to the cooled solution, followed by conc. HCl (63 ml), and the mixture was boiled under reflux for a further hour. The residue left after removal of the solvents under reduced pressure was dissolved in aqueous 5% KOH (700 ml) and stirred vigorously with dimethyl sulphate (45 ml) for 20 h. The precipitate was collected, washed with water, and dried (5·00 g). Purification by chromatography on a column of alumina (100 g) with hexane–dichloromethane (1 : 1 v/v) gave crystalline material (0·69 g), m.p. 152—153°, and less pure solid (0·54 g). Recrystallisation of the purer sample from methanol yielded the *tricyclic ketone* (XVIII),* m.p. 154—154·5° (Found: C, 81·6; H, 6·25. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%), $\lambda_{max.}$ (EtOH) 273·5 (log ε 4·39), 284 (4·44), and 328 nm (4·30).

15,16-*Dihydro*-2-*methoxycyclopenta*[a]*phenanthren*-17-*one*

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(XIX).—The tetrahydro-ketone (XVIII) (0·88 g) and chloranil (1·20 g, 1·5 mol) were boiled together in dry toluene (100 ml) for 1 week when t.l.c. showed that little of the starting material remained. The dark crystalline precipitate of the hydroquinone was collected, washed with toluene, and the combined toluene solutions were evaporated to a small volume, and placed on a column of silica gel (Hopkins and Williams, MFC). Elution with toluene containing increasing proportions of dichloromethane gave fractions (total 0·63 g) homogeneous by t.l.c. Crystallisation from ethanol yielded the *2-methoxy-17-ketone* (XIX) (0·40 g), m.p. 164—165°, raised to 180—180·5° by two more recrystallisations from this solvent (Found: C, 82·6; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%), $\lambda_{max.}$ (EtOH) 271 (log ε 4·81), 360 (3·45), and 377 nm (3·51); $\nu_{max.}$ (Nujol) 1705—1680 (aryl C=O), 1043, 955, 825, 790, 760, and 720 cm^{-1}.

15,16-Dihydro-2-hydroxycyclopenta[a]*phenanthren-17-one* (VIIa).—The methoxy-ketone (XIX) (0·54 g) in dichloromethane (50 ml) was cooled to −80° and boron tribromide (5 ml) was added. After 1 h the solution was gradually warmed to 0° during 15 min, then poured into ice. The cream coloured precipitate was collected, washed with water, dried, and stirred with dichloromethane. After filtration, acetylation of the solid (0·38 g) gave a product which was crystallised from benzene to yield pale fawn needles of *2-acetoxy-15,16-dihydrocyclopenta*[a]*phenanthren-17-one* (VIIb), m.p. 248—249° (Found: C, 78·55; H, 4·85. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·85%), $\lambda_{max.}$ (EtOH) 265·5 (log ε 4·85), 282·5 (4·46), 296 (4·36), 352 (3·37), and 369 nm (3·39); $\nu_{max.}$ (Nujol) 1755 (acetate C=O), 1695 (aryl C=O), 1015, and 930 cm^{-1}; τ ($CDCl_3$) 6·56 (t, 15-H_2), 7·17 (t, 16-H_2), and 7·61 (CH_3CO_2).

This acetate (100 mg) was hydrolysed by boiling with ethanol (20 ml) containing aqueous 5% NaOH (2 ml) for 1 h. Dilution with N-HCl (40 ml) gave a cream coloured precipitate which was washed with dichloromethane and recrystallised from butan-1-ol. The 2-hydroxy-17-ketone (VIIa)* formed pale yellow needles (29 mg), m.p. 340° (decomp.; sealed, evacuated capillary), $\lambda_{max.}$ (EtOH) 274·5 (log ε 4·74), 366 (3·40), and 383 (3·45) (neutral); 245 (4·59) and 296 (4·62) (alkaline); 257 (4·69) and 310 (3·95) (neutral, after reduction with $NaBH_4$); and 249 (4·73) and 334 nm (4·18) (alkaline, after reduction with $NaBH_4$).

We thank Mr. D. Thomas for the microanalyses and Mr. P. Cook for the mass spectral measurements. C. W. V. thanks the Imperial Cancer Research Fund for a bursary.

[4/1586 *Received*, 30*th July*, 1974]