Potentially Carcinogenic Cyclopenta[*a*]phenanthrenes. Part VI.[1] 1,2,3,4-Tetrahydro-17-ketones

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Cyclisation of 2-oxo-5-(5,6,7,8-tetrahydro-2-naphthyl)cyclopentaneacetic acid led to both angular and linear ring-fused products from which were derived 1,2,3,4,15,16-hexahydrocyclopenta[*a*]phenanthren-17-ones and 1,2,7,8,9,10-hexahydrocyclopent[*a*]anthracen-3-ones.

ESSENTIAL structural features associated with a high degree of carcinogenicity in compounds of the cyclopenta[*a*]phenanthrene series appear to be the presence of a methyl substituent at C-11 and a C=C or C=O double bond at C-17.[2] Reduction of the 11,12-double bond in the potent carcinogen 11-methyl-15,16-dihydrocyclopenta[*a*]phenanthren-17-one (I) abolishes activity, but the effect of reduction elsewhere in this molecule has not been studied. 1,2,3,4-Tetrahydrodibenz[*a*,*h*]anthracene retains carcinogenic activity comparable with that of the fully aromatic hydrocarbon,[3] and it was therefore of interest to prepare the 1,2,3,4-tetrahydro-derivative of compound (I), namely the ketone (IIb). Additionally, knowledge of the u.v. absorption of this ketone was of importance in connection with the structural elucidation of a major metabolite of the carcinogen (I) in the rat.[4]

The syntheses of the ketones (IIa and b) followed the general scheme employed in Part I.[5] 6-Acetyl-1,2,3,4-tetrahydronaphthalene[6] was converted into its furfurylidene derivative (III), which with hot acid gave the dioxoheptanoic acid (IV). Cyclisation of the latter under alkaline conditions led to the cyclopentenone acid (Va), which was reduced with lithium in liquid ammonia to the cyclopentanone acid (VIa). Over-reduction was difficult to avoid when catalytic hydrogenation over palladium was employed to reduce this tetrasubstituted double bond, and the cyclopentane acid (VIb) was isolated as a by-product.

In the naphthalene series, phosphoric acid-catalysed cyclisation of the analogue of (VIa) occurs exclusively in the angular sense to yield a phenanthrene derivative. In the present case lack of the strongly directing, fused aromatic ring led to a 1 : 4 mixture of the angular

[1] Part V, M. M. Coombs and S. B. Jaitly, *J. Chem. Soc.* (*C*), 1971, 230.

[2] M. M. Coombs and C. J. Croft, *Progr. Exp. Tumor Res.*, 1969, **11**, 69; also unpublished observations.

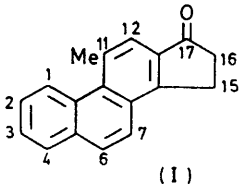
[3] W. Lijinsky, H. Garcia, B. Terracini, and U. Saffiotti, *J. Nat. Cancer Inst.*, 1965, **34**, 1.

[4] F. E. H. Crawley, unpublished work.

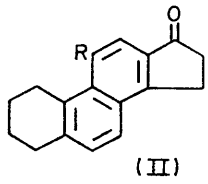
[5] M. M. Coombs, *J. Chem. Soc.* (*C*), 1966, 955.

[6] M. S. Newman and H. V. Zahn, *J. Amer. Chem. Soc.*, 1943, **65**, 1097.

(VIIa) and linear (VIIIa) diketones. Each selectively gave a monoacetal [(VIIb) and (VIIIb)] on acid-catalysed exchange with 2-ethyl-2-methyl-1,3-dioxolan.

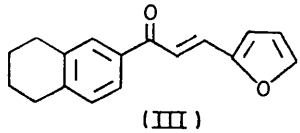


(I)

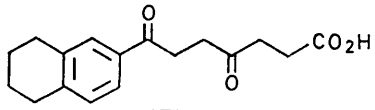


(II)

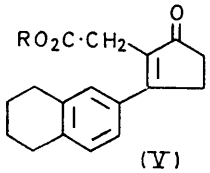
a; R = H
b; R = Me



(III)

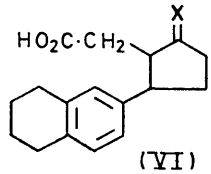


(IV)



(V)

a; R = H
b; R = Me



(VI)

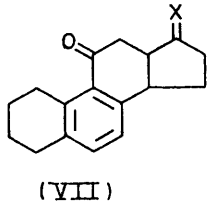
a; X = O
b; X = H

The structures of these compounds followed from their i.r. spectra, which in both cases indicated a conjugated carbonyl group, and from the characteristic n.m.r. signals of their aromatic protons. Those of (VIIb) consisted of an AB quartet centred at τ 2·88, whereas those of (VIIIb) formed two rather broad 'singlets' at τ 2·22 and 2·98. Ring closure of the cyclopentane acid (VIb) with phosphoric acid gave mainly the linear monoketone (VIIIc), with evidence of a second ketone, probably the angular isomer (VIIc).

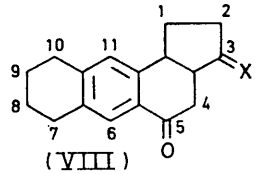
Cyclisation of (Va) by heating with acetic anhydride led to a mixture of two isomeric acetoxy-ketones, (IX) and (Xa), readily distinguished by their n.m.r. spectra, the aromatic region of the latter consisting of three well resolved one proton singlets. In confirmation, dehydrogenation of (IX) with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (DDQ) yielded the known 11-acetoxy-15,16-dihydrocyclopenta[*a*]phenanthren-17-one,[7] and similar dehydrogenation of the tetrahydroanthracen-3-one (Xa) gave 5-acetoxy-1,2-dihydrocyclopent[*a*]-anthracen-3-one (XIa). The u.v. absorption of this compound was similar to that of its 5-deacetyl derivative (XIb) described later.

The acetal (VIIb) was converted into the ketone (IIb) by reaction with methylmagnesium iodide followed by treatment with acid in the presence of nitrobenzene.[5] The unsubstituted tetrahydro-ketone (IIa) was prepared from (VIIb) by reduction with sodium borohydride and subsequent treatment with acid and nitrobenzene. In contrast to the high yields of phenanthrenes previously obtained with this dehydration–dehydrogenation reaction,[5] the yields of naphthalenes obtained in the present work were poor. Since it was essential to conserve for biological evaluation the small quantity of (IIb) obtained, this ketone was characterised by mass spectrometry. The base peak was the molecular ion, *m/e* 250. The next most abundant ion was at *m/e* 222 (13·5%), corresponding to $M - CO$, and for which a metastable peak at *m/e* 197·3 was observed.

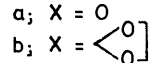
In a similar manner the linear acetal (VIIb) furnished 1,2,7,8,9,10-hexahydrocyclopent[*a*]anthracen-3-one (Xb). Dehydrogenation with DDQ gave the corresponding

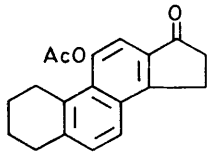


(VII)

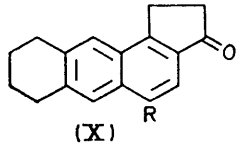


(VIII)

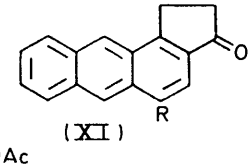
a; X = O
b; X = 
c; X = H_2



(IX)



(X)



(XI)

a; R = OAc
b; R = H

1,2-dihydro-compound (XIb), with u.v. absorption characteristics almost identical with those of 2-acetylanthracene.[8]

EXPERIMENTAL

Reagents and apparatus were generally as described in previous Parts of this series.

6-*Furfurylideneacetyl*-1,2,3,4-*tetrahydronaphthalene* (III).—To a solution of 6-acetyl-1,2,3,4-tetrahydronaphthalene [6] (202 g; b.p. 146° at 10 mmHg) in 2-furaldehyde (99 g) and ethanol (720 ml) was added aqueous sodium hydroxide (8% w/v; 2 ml) dropwise during 20 min. After 18 h at room temperature the pale yellow crystals were collected and recrystallised from ethanol to yield the *furfurylidene compound* (III), m.p. 68—69° (Found: C, 80·8; H, 6·35. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%), $\lambda_{max.}$(EtOH) 238·5

[7] R. Robinson, *J. Chem. Soc.*, 1938, 1395.

[8] R. A. Friedel and M. Orchin, 'Ultraviolet Spectra of Aromatic Compounds,' Chapman and Hall, London, 1951, spectrum No. 393.

(log ε 3·60) and 342 nm (4·23), $\nu_{max.}$(Nujol) 1670 (CO), 1015, 980, 886, 820, 808, 730, and 700 cm^{-1}.

4,7-*Dioxo*-7-(5,6,7,8-*tetrahydro*-2-*naphthyl*)*heptanoic Acid* (IV).—The furfurylidene compound (III) (210 g) was heated under reflux with conc. hydrochloric acid (195 ml) and ethanol (750 ml) for 9 h. The ethanol was removed under diminished pressure, and the dark gum which remained was boiled with a mixture of conc. hydrochloric acid (432 ml), glacial acetic acid (1073 ml) and water (1073 ml) for 2 h. The hot solution was decanted from the tar through a pad of glass wool and the crystals which separated on cooling were collected. The mother liquor was returned to the flask and boiled with the tar for 2 h. After seven repetitions of this cycle the crystalline material amounted to 165 g; recrystallisation from ethyl acetate gave the *diketo-acid* (IV) as needles, m.p. 115—116° (Found: C, 70·75; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%), $\lambda_{max.}$(EtOH) 215·5 (log ε 4·14) and 258 nm (4·06), $\nu_{max.}$ (Nujol) 1680—1740 (CO), 918, and 802 cm^{-1}.

5-*Oxo*-2-(5,6,7,8-*tetrahydro*-2-*naphthyl*)*cyclopent*-1-*ene-acetic Acid* (Va).—A solution of the diketo-acid (IV) (10 g) in water (960 ml) containing potassium hydroxide (20 g) was maintained at 95° for 1 h. Charcoal was added and the hot solution was filtered, cooled, and acidified with conc. hydrochloric acid (128 ml). The precipitated *acid* (V) was collected, washed with water, and dried (9·7 g); it was sufficiently pure for the next stage. A sample crystallised from n-butanol had m.p. 133—134° (Found: C, 75·35; H, 6·65. $C_{17}H_{18}O$ requires C, 75·55; H, 6·7%), $\nu_{max.}$(Nujol) 1730, 1675 (CO), 957, 822, and 810 cm^{-1}. The *methyl ester* (Vb) formed pale yellow needles (from ethanol), m.p. 93—94° (Found: C, 76·3; H, 6·75. $C_{18}H_{20}O_3$ requires C, 76·05; H, 7·1%), $\lambda_{max.}$(EtOH) 225·5 (log ε 3·39) and 284 nm (3·60).

Reduction of the Unsaturated Acid (Va).—(a) *With lithium in liquid ammonia.* The acid (Va) (1·0 g) in dry tetrahydrofuran (10 ml) was added to a solution of lithium (400 mg) in liquid ammonia (375 ml) during 5 min, with cooling in acetone–solid carbon dioxide. Ammonium chloride (40 g) was then added during 20 min, followed by tetrahydrofuran (50 ml), and the mixture was stirred at room temperature for 14 h. Water was added and the aqueous layer was acidified and extracted with ether. Removal of the solvent left 2-oxo-5-(5,6,7,8-tetrahydro-2-naphthyl)cyclopentaneacetic acid (VIa) (1·0 g) as brown gum which ran as a single spot, R_F 0·20, on t.l.c. (5% ethyl acetate–dichloromethane); $\lambda_{max.}$(EtOH) 273 and 279 nm, $\nu_{max.}$ 1750 (five-membered ring ketone), 1710 (CO_2H), 910, 827, and 810 cm^{-1}.

(b) *By hydrogenation over palladium.* The acid (Va) (24·2 g, 0·1 mol), dissolved in ethanol (150 ml), was shaken with 5% palladium–charcoal in hydrogen. After 10 days 1·5 times the calculated amount of gas had been consumed, and the majority of the starting material had been reduced. Filtration and evaporation left a pale brown gum (20·4 g), which crystallised from ethanol to yield 2-(5,6,7,8-*tetrahydro*-2-*naphthyl*)*cyclopentaneacetic acid* (VIb) (8·5 g), m.p. 116—117° (Found: C, 78·7; H, 8·4. $C_{17}H_{22}O_2$ requires C, 79·05; H, 8·6%), $\lambda_{max.}$(EtOH) 208 (log ε 3·98), 217 (3·83), 270 (2·90), and 279 nm (2·97), $\nu_{max.}$(Nujol) 1710 (CO_2H), 916, 830, and 812 cm^{-1}. On t.l.c. (5% ethyl acetate–dichloromethane) the brown gum revealed three spots, R_F 0·12 (Va), 0·20 (VIa), and 0·53 (VIb). A similar result was obtained when palladium–calcium carbonate was employed.

(c) *Hydrogenation of the methyl ester* (Vb). This ester (29·4 g) was reduced over palladium–charcoal as in (b) until t.l.c. showed absence of the starting material. The product was saponified to yield a brown gum (27·5 g), t.l.c. (dichloromethane) of which showed the presence of the cyclopentanone acid (VIa), R_F 0·65, accompanied by the cyclopentane acid (VIb), R_F 0·85.

11-*Acetoxy*-1,2,3,4,15,16-*hexahydrocyclopenta*[a]*phenanthren*-17-*one* (IX) *and* 5-*acetoxy*-1,2,7,8,9,10-*hexahydrocyclopent*[a]*anthracen*-3-*one* (Xa).—The cyclopentenone acid (Va) (5 g) was heated under reflux with acetic anhydride (40 ml) for 1 h. The needles (1·5 g) which separated on cooling were collected and crystallised repeatedly from benzene and from n-butanol to give the *acetoxyanthracenone* (Xa), m.p. 228—229° (Found: C, 77·45; H, 6·0. $C_{19}H_{18}O_3$ requires C, 77·55; H, 6·15%), $\lambda_{max.}$(EtOH) 263 (log ε 4·57), 287 (3·91), 297·5 (3·96), 308 (3·86), 338 (3·67), and 352 nm, (3·69), $\nu_{max.}$(Nujol) 1765 and 1190 (acetate), 1695 (conj. CO), 1050, and 908 cm^{-1}, τ 2·31, 2·40, and 2·62 (each 1H, s, aromatic).

The acetic anhydride mother liquor was poured into water (500 ml) and extracted with dichloromethane; the extract was washed with water, dried, and evaporated. The crystalline residue (3·4 g) was recrystallised from benzene and sublimed to yield the *acetoxyphenanthrenone* (IX), m.p. 207—208° (Found: C, 77·1; H, 5·95. $C_{19}H_{18}O_3$ requires C, 77·55; H, 6·15%), $\lambda_{max.}$(EtOH) 222 (log ε 4·27), 257·5 (4·84), 286 (4·00), 296 (4·04), 307 (3·91), 340 (3·72), and 352 nm (3·81), $\nu_{max.}$(Nujol) 1760, 1206 (acetate), 1700 (conj. CO), 1040, 907, and 810 cm^{-1}.

The acetoxy-ketone (IX) (73 mg), DDQ (141 mg), and dry benzene (4 ml) were boiled together for 21 h. The solution, containing precipitated hydroquinone, was diluted with ether (10 ml) and filtered. Removal of solvent from the washed filtrate and sublimation of the residue gave 11-acetoxy-15,16-dihydrocyclopenta[*a*]phenanthren-17-one, m.p. and mixed m.p. 215—216°.

The acetoxy-ketone (Xa) (290 mg) and DDQ (567 mg) were boiled together in dry benzene (8 ml) for 24 h. The product, isolated as already described, was chromatographed on silica gel, with ethyl acetate–dichloromethane (1 : 20) as eluant. Fractions homogeneous by t.l.c. were pooled and sublimed to yield 5-acetoxy-1,2-dihydrocyclopent[*a*]anthracen-3-one (XIa), m.p. 231—233°, $\lambda_{max.}$(EtOH) 264·5 (log ε 4·48), 277 (4·45), 329 (3·53), 347 (3·58), 364 (3·61), 378 (3·55), and 398 nm (3·47).

1,2,3,4,13,14,15,16-*Octahydrocyclopenta*[a]*phenanthrene*-11(12H),17-*dione* (VIIa) *and* 1,3a,4,7,8,9,10,11b-*Octahydrocyclopent*[a]*anthracene*-3(2H),5-*dione* (VIIIa).—Phosphoric acid (20 g) and phosphorus pentoxide (20 g) were heated together at 120° for 2·5 h to give a clear solution. The keto-acid (VIa) (5·4 g) was added during 15 s; the mixture was stirred at 120—125° for a further 2·5 min, poured onto ice, and extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution, and dried. The products from three cyclisations (14·7 g) were together chromatographed on a column of silica gel (2·5 kg) with ethyl acetate–dichloromethane (1 : 19); 50 ml fractions were collected. Fractions 114—122 were evaporated and the product (2·2 g) was crystallised from ethanol to afford the *phenanthrenedione* (VIIa), m.p. 111—113° (Found: C, 80·25; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·15%), $\lambda_{max.}$(EtOH) 200 (log ε 4·25), 257 (3·91), and 308 nm (3·33), $\nu_{max.}$(Nujol) 1740 (five-membered ring ketone), 1680 (conj. CO), 990, 930, and 838 cm^{-1}. Fractions 123—

163 were combined and the product (6·4 g) was recrystallised twice from ethanol to yield the *anthracenedione* (VIIIa), m.p. 102—103° (Found: C, 80·45; H, 6·95%), $\lambda_{max.}$(EtOH) 221 (log ε 4·36), 264 (4·12), and 302 nm (3·35), $\nu_{max.}$(Nujol) 1733 (five-membered ring ketone), 1675 (conj. ketone), 1605 (strong, aromatic C=C), 935, and 841 cm^{-1}, τ 2·30 and 2·89 (aromatic singlets).

17,17-*Ethylenedioxy*-1,2,3,4,12,13,14,15,16,17-*decahydrocyclopenta*[a]*phenanthren*-11-*one* (VIIb) *and* 3,3-*Ethylenedioxy*-1,2,3,3a,4,7,8,9,10,11b-*decahydrocyclopent*[a]*anthracen*-5-*one* (VIIIb).—A crude mixture of the diketones (VIIa) and (VIIIa) (7·0 g) was heated with 2-ethyl-2-methyl-1,3-dioxolan (42 ml) and toluene-*p*-sulphonic acid (20 mg) while the more volatile products (10 ml) were slowly removed by distillation. After 5 h the solution was diluted with ether, washed with sodium hydrogen carbonate solution and with water, and dried. The gum (7·0 g) left on evaporation was chromatographed on a column of alumina (Woëlm, grade II) with hexane–ether (1 : 1); 150 ml fractions were collected. Fractions 24—50 yielded material (1·7 g) which was crystallised repeatedly from methanol to yield the *phenanthrene acetal* (VIIb), m.p. 82—83° (Found: C, 76·65; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·45%), $\lambda_{max.}$(EtOH) 218 (log ε 4·29), 256 (3·88), and 309 nm (3·33), $\nu_{max.}$(Nujol) 1680 (conj. ketone), 950, 910, 840, and 812 cm^{-1}. Fractions 51—89 gave material (2·4 g) which crystallised from methanol to give the *anthracene acetal* (VIIIb), m.p. 111—114° (Found: C, 76·5; H, 7·1%), $\lambda_{max.}$(EtOH) 217 (log ε 4·59), 262 (4·30), and 304 nm (3·58), $\nu_{max.}$(Nujol) 1680 (conj. CO), 1610s (aromatic C=C), 1050, 1020, 950, and 915 cm^{-1}.

1,2,3,4,15,16-*Hexahydrocyclopenta*[a]*phenanthren*-17-*one* (IIa).—The oxo-acetal (VIIb) (800 mg), tetrahydrofuran (5·3 ml), water (13 ml), and sodium borohydride (0·26 g) were stirred under reflux for 8 h, after which the pH was brought to 6·5 by careful addition of dilute acetic acid. The mixture was diluted with water and extracted with dichloromethane; removal of the solvent gave a gum (0·60 g) which showed no i.r. carbonyl absorption. This material was dissolved in glacial acetic acid (15 ml) and nitrobenzene (4 ml); addition of conc. hydrochloric acid (4 ml) produced a green colouration. After 30 min under reflux the solution was diluted with water and the nitrobenzene was removed in steam. The partly crystalline residue was extracted with dichloromethane to give a gum (0·40 g) which was chromatographed on a column of silica gel (100 g) in ethyl acetate–toluene (1 : 20). Fractions homogeneous by t.l.c. were combined (80 mg), recrystallised from ethanol, and finally sublimation gave the *hexahydrophenanthren*-17-*one* (IIa), m.p. 145—146° (Found: C, 86·05; H, 6·5. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%), $\lambda_{max.}$(EtOH) 256·5 (log ε 3·96), 282 (3·25), 292·5 (3·27), 333·5 (2·86), and 348 nm (2·91), $\nu_{max.}$(Nujol) 1700 (conj. CO), 1048, 847, 830, and 800 cm^{-1}.

1,2,7,8,9,10-*Hexahydrocyclopent*[a]*anthracen*-3-*one* (Xb).—The linear oxo-acetal (VIIIb) (600 mg) was reduced and treated with nitrobenzene and acid as already described for the angular isomer. The *hexahydroanthracen*-3-*one* (Xb) (115 mg), m.p. 158—159°, crystallised from ethanol (Found: C, 86·0; H, 6·50%), $\lambda_{max.}$(EtOH) 245·5 (log ε 4·67), 261 (4·74), 284 (3·92), 295 (4·01), 305 (3·90), 337 (3·48), and 351 nm (3·45), $\nu_{max.}$(Nujol) 1695 (conj. CO), 917, 870, 820, 757 cm^{-1}. Treatment of this ketone with DDQ as already described gave yellow crystals of 1,2-dihydrocyclopent[*a*]-anthracen-3-one (XIb), $\lambda_{max.}$(EtOH) 271 (log ε 4·30), 323 (3·44), 342 (3·26), 360 (3·21), 378 (3·06), and 396 nm (3·14). 2-Acetylanthracene [8] has $\lambda_{max.}$(EtOH) 270, 326, 341, 360, 380, and 398 nm.

1,2,3,4,15,16-*Hexahydro*-11-*methylcyclopenta*[a]*phenanthren*-17-*one* (IIb).—The oxo-acetal (VIIb) (300 mg), dissolved in dry benzene (5 ml), was added to a solution of methylmagnesium iodide [from magnesium turnings (120 mg), methyl iodide (0·30 ml), and dry ether (5 ml)] under dry nitrogen. The mixture was boiled under reflux for 6 h, cooled, poured into a saturated solution of ammonium chloride containing a few drops of conc. hydrochloric acid, and extracted with benzene. The organic layer was washed with sodium hydrogen carbonate solution, and dried. Evaporation left a gum (320 mg) which showed only weak i.r. carbonyl absorption.

This material was treated with acid in the presence of nitrobenzene as described above to give a gum (300 mg). The products from two reactions were combined (620 mg) and chromatographed twice on columns of silica gel in dichloromethane containing 1% v/v ethyl acetate. Fractions containing the desired 11-*methylphenanthren*-17-*one* (IIb), readily detected by its strong purple fluorescence in u.v. light, were homogeneous by t.l.c., but still deeply coloured. Evaporation gave a brown crystalline solid (110 mg) which on sublimation gave colourless material, m.p. 150—152°, $\lambda_{max.}$(EtOH) 223 (log ε 4·23), 261 (4·77), 287 (3·97), 297·5 (4·02), 308 (3·87), 344 (3·69), and 354 nm (3·74), $\nu_{max.}$(Nujol) 1690 (conj. CO), 867, and 808 cm^{-1}, *m/e* 250·13574 (M^+) ($C_{18}H_{18}O$ requires 250·13576), 235, 222, 207, 194, and 179.

Cyclisation of the Cyclopentane Acid (VIb).—This acid (900 mg) was added to a solution of phosphorus pentoxide (3 g) in phosphoric acid (3 ml) which had been equilibrated at 120° for 2·5 h. After 6 min the solution was poured into ice and the green gum was extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution and dried; removal of the solvent left a gum which crystallised. Repeated recrystallisation from ethanol yielded 1,2,3,3a,4,7,8,9,10,11b-*decahydrocyclopent*[a]*anthracen*-5-*one* (VIIIc), m.p. 76—77° (Found: C, 85·2; H, 8·35. $C_{17}H_{20}O$ requires C, 84·95; H, 8·4%), $\lambda_{max.}$(EtOH) 219 (log ε 4·24), 262 (3·98), and 306 nm (3·72), $\nu_{max.}$(Nujol) 1670 (conj. CO), 1605s (aromatic C=C), 912, 872, 862, and 818 cm^{-1}, τ 2·32 and 3·02 (one-proton singlets). T.l.c. (dichloromethane) of the mother liquors revealed a second spot just ahead of (VIIIb). Elution with ethanol gave a solution with $\lambda_{max.}$ 258 and 300 nm, showing that this was probably the angular isomer (VIIc).

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