Synthetic Studies on Terpenoids. Part XVIII.[1,2] Stereocontrolled Synthesis of (±)-1,2,3,4,4a,9,10,10aα-Octahydro-1α-methylphenanthrene-1β,4aβ-dicarboxylic Acid and the 7-Methoxy-analogue: a Potential Intermediate for Diterpenoid Syntheses

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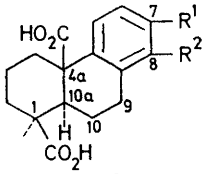
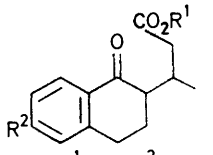
A stereocontrolled synthetic route to (±)-1,2,3,4,4a,9,10,10aα-octahydro-1α-methylphenanthrene-1β,4aβ-dicarboxylic acid (Ia) and the 7-methoxy-analogue (Ib) is described. The present approach differs basically from earlier ones and proceeds through polyhydrobenzindenone intermediates. 2,3,4,5-Tetrahydro-3-methylbenz[*e*]inden-1-one (Va) and the corresponding 7-methoxy-compound (Vb) were transformed through several steps into *cis*-9b-acetonyl-3a,4,5,9b-tetrahydro-3-methylbenz[*e*]inden-1-one (XIIIa) and its methoxy-derivative (XIIIb). These unsaturated diketones underwent intramolecular Michael condensation, affording tetracyclic bridged ketones (XIVa and b), which were converted into the acids (Ia and b). In the methoxy-series, disproportionation of a polyhydrobenzindenone derivative was noted.

THE dibasic acids (Ia—c) and the related tetracyclic ketonic precursors [3] are important synthons for entry into the complex diterpenoid and diterpene alkaloid series. We have reported [4] some approaches to a few related dibasic acids. The synthesis of the acids (Ia and b) has also been reported [3d] from this laboratory. In all earlier approaches, *trans*-octahydrophenanthrene derivatives have been utilized as intermediates. The present synthesis employs polyhydrobenzindenones with defined stereochemistry. This provides access not only to the *trans*-octahydrophenanthrene skeleton, but also to the *cis*-oriented carboxy-groups. There is no stereochemical uncertainty at intermediate stages owing to the presence of a vinylogous hydrogen atom at the ring junction and the formation of the fourth ring under equilibrium conditions. Although a detailed synthetic methodology has been evolved through model studies leading to the preparation of the diacid (Ia), its extension to the methoxy-analogue (Ib) demanded significant modifications at several stages.

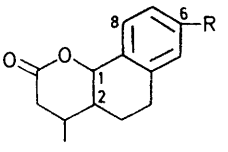
The two polyhydrobenzindenones (Va and b) were prepared from the oxo-acids (IIIa) [5] and (IIIb) which, in turn, were obtained from corresponding 1-tetralones through condensation with ethyl crotonate. The proportions of potassium t-butoxide used for this condensation played a critical role in determining the yield of the methoxy-compound (IIb). The oxo-acids (IIIa and b) were reduced with sodium amalgam to afford the lactones (IVa and b). Treatment of (IVa) with polyphosphoric acid at 80 °C for 1.5 h afforded the ketone (Va). Under identical conditions the methoxy-lactone (IVb) did not provide the unsaturated ketone (Vb); instead, it afforded the didehydro-derivative (VIb). Under milder experimental conditions, the γ-lactone (VII) was a by-product, δ 7.0 (1 H, d, *J* 7 Hz) and 6.72 (2 H, m). The corresponding δ values for the lactone (IVb) are 7.52 and 6.74, showing that in (IVb) one of the aromatic protons, probably H-8, is deshielded by the lactonic oxygen function. This effect is more pronounced in the ketone (Vb) (see below). The formation of (VII) is due to the stabilising effect of the methoxy-group on the benzylic carbocation intermediate. Optimisation of experimental conditions in the above cyclisation reaction ultimately resulted in the isolation of the desired ketone (Vb) in a maximum yield of 12%, along with the aromatic ketone (VIb) (25%), and various proportions of the lactone (VII). Attempts at this stage to identify



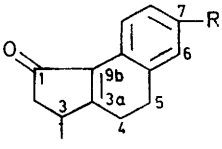
(I) a; $R^1 = R^2 = H$
b; R^1 = OMe, R^2 = H
c; R^1 = H, R^2 = OMe



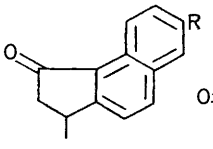
(II) a; R^1 = Et, R^2 = H
b; R^1 = Et, R^2 = OMe
(III) a; $R^1 = R^2 = H$
b; R^1 = H, R^2 = OMe



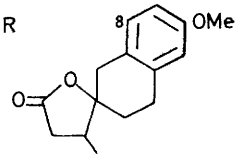
(IV) a; R = H
b; R = OMe



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



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



(VII)

[1] Part XVII, T. K. Sarkar, *J.C.S. Perkin I*, 1973, 2454.

[2] Part of this investigation was presented (P.C.D.) at the 7th International Symposium on the Chemistry of Natural Products, Riga, June 1970; Abstracts, p. 460.

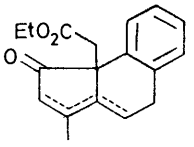
[3] (*a*) R. B. Turner, G. D. Diana, G. E. Fodor, K. Gebert, D. L. Simmons, A. S. Rao, O. Roos, and W. Wirth, *J. Amer. Chem. Soc.*, 1966, **88**, 1786; (*b*) R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Coll. Czech. Chem. Comm.*, 1966, **31**, 602; (*c*) T. Matsumoto, M. Yanagiya, E. Kawakami, T. Okuno, M. Kakizawa, S. Yasuda, Y. Gama, J. Omi, and M. Matsunaga, *Tetrahedron Letters*, 1968, 1127; (*d*) U. R. Ghatak and S. Chakrabarty, *J. Amer. Chem. Soc.*, 1972, **94**, 4756.

[4] P. N. Chakrabortty, A. K. Banerjee, S. K. Ghosh, P. R. Dutta, A. S. Sarma, and P. C. Dutta, *Indian J. Chem.*, 1974, **12**, 948.

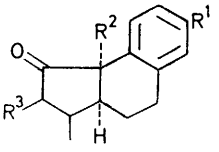
[5] B. Belleau, *J. Amer. Chem. Soc.*, 1951, **73**, 5149.

the demethoxy-didehydro-derivative (VIa)[6] in the mother liquor left after separation of (Va) did not offer any conclusive data (see Experimental section). To explore the possibility of utilizing the aromatic ketone (VIb) in this synthesis, partial reduction[7] of this ketone with sodium in liquid ammonia and ethanol was attempted. The dihydro-derivative (Vb) was obtained in an excellent yield. Evidently compound (Vb) is present in the reaction mixture as its carbanion, prohibiting further reduction.[7c]

The unsaturated ketone (Va) was alkylated with ethyl bromoacetate in the presence of potassium t-pentyl oxide; the product, obtained in moderate yield, was a mixture of double-bond isomers (VIII), as revealed (n.m.r.). Catalytic hydrogenation of (VIII) afforded the saturated compound (Xa). The same product was obtained through catalytic reduction of (Va) [affording the saturated ketone (IXa) as its *cis*-isomer[8]] followed by alkylation with ethyl bromoacetate. *cis*-Stereochemistry at the ring junction is presumably maintained in this alkylation product.[9] The ester (Xa) was brominated and the crude product was subjected to dehydrobromination[10] with hexamethylphosphoramide to furnish the unsaturated oxo-ester (XIa) in an overall yield of 50%. Alkaline hydrolysis then gave the acid (XIb). The vinylic proton signal in the n.m.r. spectrum of (XIb) appeared as a quintet at δ 5.96 (J 1.0 Hz), a pattern probably arising from equivalent allylic coupling



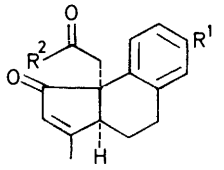
(VIII)



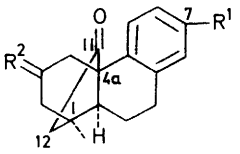
(IX) a; R^1=R^2=R^3=H
b; R^1=OMe, R^2=R^3=H
(X) a; R^1=R^3=H, R^2=CH_2·CO_2Et
b; R^1=OMe, R^2=CH_2·CO_2Me, R^3=H
c; R^1=OMe, R^2=CH_2·CO_2H, R^3=H
d; R^1=OMe, R^2=CH_2·CO_2Me, R^3=Br

with the 3-methyl group and the 3a-proton. Consequently, the 3-methyl signal was a triplet at δ 2.12 (J 1.0 Hz). The corresponding methyl ester was homogeneous on t.l.c.

For the preparation of the methoxy-acid (XIIb), the ketone (Vb) was similarly alkylated with methyl bromoacetate, and separation of the product from the parent ketone was attempted through alkaline hydrolysis of the reaction mixture. A crystalline acid, from which



(XI) a; R^1=H, R^2=OEt
b; R^1=H, R^2=OH
(XII) a; R^1=R^2=OMe
b; R^1=OMe, R^2=OH
(XIII) a; R^1=H, R^2=Me
b; R^1=OMe, R^2=Me



(XIV) a; R^1=H, R^2=O
b; R^1=OMe, R^2=O
(XV) a; R^1=H, R^2=S·$[CH_2]_2$·S
b; R^1=OMe, R^2=S·$[CH_2]_2$·S
(XVI) a; R^1=H, R^2=H_2
b; R^1=OMe, R^2=H_2

80% of the total quantity could be obtained as a sharp-melting compound, and a neutral fraction were obtained after hydrolysis. The n.m.r. spectrum of this acid showed the methyl signal as a doublet at δ 1.1 (3 H, J 6 Hz), as expected for a saturated secondary methyl function, and there was no evidence for a vinylic proton. The methoxy-signal, a sharp singlet at δ 3.72, revealed that a single compound was present. Mass spectral data and elemental analyses suggested that it was a dihydro-derivative of the expected product. The same acid was obtained through alkylation of the saturated ketone (IXb), prepared by catalytic reduction of (Vb), and hydrolysis of the product. These facts suggest the structure (Xc) with the indicated stereochemistry. The neutral fraction was identified as the didehydro-derivative (VIb). The acid (Xc) is evidently a product of disproportionation, often observed in dihydronaphthalene derivatives[11] and dihydrobenzenes,[12] under

[6] A. Rahaman and A. E. Gastaminza, *Rec. Trav. chim.*, 1962, **81**, 645.

[7] (*a*) S. Mejer and S. Respondek, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1966, **14**, 611; (*b*) D. K. Banerjee, E. J. Jacob, and N. Mahishi, *Steroids*, 1970, **16**, 733; (*c*) A. J. Birch and G. S. R. Subba Rao, *Austral. J. Chem.*, 1970, **23**, 547.

[8] (*a*) R. E. Juday, B. Bukawa, K. Kaiser, and G. Webb, *J. Medicin. Chem.*, 1970, **13**, 314, and references cited therein; (*b*) R. Muneyuki and H. Tanida, *J. Amer. Chem. Soc.*, 1968, **90**, 656; (*c*) P. T. Lansbury, F. R. Hilfiker, and W. L. Armstrong, *ibid.*, p. 534.

[9] (*a*) F. E. Ziegler and M. E. Condon, *J. Org. Chem.*, 1971, **36**, 3707; (*b*) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Amer. Chem. Soc.*, 1962, **84**, 2614.

[10] (*a*) R. Hanna, *Tetrahedron Letters*, 1968, 2105; (*b*) C. Berger and M. Franck-Neumann, *ibid.*, p. 3451.

[11] (*a*) H. Tournier, R. Longaray, and J. Dreux, *Tetrahedron Letters*, 1970, 21, and other papers in this series; (*b*) W. von E. Doering and J. W. Rosenthal, *J. Amer. Chem. Soc.*, 1967, **89**, 4534; (*c*) A. Gaiffe and R. Pallaud, *Compt. rend.*, 1964, **259**, 4722.

[12] D. P. Wyman and I. H. Song, *J. Org. Chem.*, 1967, **32**, 4139.

acidic, basic, or other conditions (*viz.* catalytic or thermal). The same process may also operate during the formation of the aromatic compound (VIb) from (IVb), although no direct evidence is available [*e.g.* isolation of the tetrahydro-derivative (IXb) from the polyphosphoric acid cyclisation (see Experimental section)]. In another set of experiments, the condensation product from (Vb) was purified by evaporative distillation and its n.m.r. spectrum was recorded. There was evidence of a vinylic proton (*ca.* 5%) and the saturated methyl signal corresponded closely to three protons. These details show that disproportionation takes place mostly at the alkylation stage. It probably proceeds through hydride transfer from the carbanion generated during this reaction.[12] We were interested as to whether any such dismutation occurred during alkylation of the demethoxy-ketone (Va). From a detailed analysis of the n.m.r. spectrum of (VIII), it appeared that disproportionation, if any, was of minor significance, as expected from the results of cyclisation of (IVa), leading to (Va).

The acid (Xc) was next converted into the methyl ester (Xb), which on bromination afforded the crystalline bromo-derivative (Xd). N.m.r. spectroscopy showed this to be a single stereoisomer: the ester methyl and methoxy-signals were sharp singlets at δ 3.47 and 3.72, respectively, and the signals due to the 3-methyl group and the 2-proton were both distinct doublets at δ 1.26 (*J* 6 Hz) and 4.24 (*J* 12 Hz), respectively. Dehydrobromination of (Xd) with hexamethylphosphoramide afforded the unsaturated ester (XIIa), which on hydrolysis furnished the crystalline acid (XIIb) in 80% yield. The methoxy-signal of (XIIb) was again a sharp singlet at δ 3.72 and the vinyl proton and vinyl methyl signals closely resembled those of the demethoxy-acid (XIb).

The two unsaturated acids (XIb) and (XIIb) could be smoothly converted into the unsaturated diketones (XIIIa and b) in good yields through condensation [13] of the corresponding carboxylic *O*-ethylcarbonic anhydrides with diethyl ethoxymagnesiomalonate and hydrolysis [14] of the product. In the presence of a catalytic amount of potassium t-butoxide in t-butyl alcohol, these ketones underwent an intramolecular Michael reaction,[15] affording the tetracyclic diketones (XIVa and b) in excellent yields. The products lacked the characteristic n.m.r. signals of the vinylic systems of their precursors and showed new quaternary methyl singlets at δ *ca.* 1.3. The diketone (XIVa) could be converted into the monothioacetal (XVa) in *ca.* 50% yield. Different experimental conditions were required to obtain the monothioacetal (XVb) in good yield. Desulphurisation of these thioacetals with Raney nickel afforded the monoketones (XVIa and b) in moderate yields. Formylation of these monoketones and oxidation of the formyl derivatives with hydrogen peroxide in alkaline solution furnished the acids (Ia and b) in good yields. Their structures were confirmed by mixed m.p. determinations with the respective authentic stereoisomers and the corresponding dimethyl esters.[3d]

[13] D. S. Tarbell and J. A. Price, *J. Org. Chem.*, 1957, **22**, 245.
[14] T. M. Dawson, P. S. Littlewood, B. Lythgoe, T. Medcalfe, M. W. Moon, and P. M. Tomkins, *J. Chem. Soc.* (*C*), 1971, 1292.

EXPERIMENTAL

M.p.s were taken for samples in open capillaries in a sulphuric acid bath. U.v. spectra were recorded for solutions in 95% ethanol with a Beckmann DU spectrophotometer (manually operated), and i.r. spectra with a Perkin-Elmer 21 instrument for solutions in chloroform. N.m.r. spectra were determined with Varian A-60D and T-60 instruments (tetramethylsilane as internal reference). Mass spectra were recorded with a CEC 21-110B double-focusing spectrometer. G.l.c. was carried out on a Varian Aerograph 1868-4 instrument. T.l.c. plates were coated (0.2 mm thick) with silica gel G (200 mesh) and spots were located by exposing the dried plates to iodine vapour. Petroleum refers to the fraction of b.p. 60—80°. The compounds described are all racemic forms.

Ethyl β-(1,2,3,4-*Tetrahydro*-1-*oxo*-2-*naphthyl*)*butyrate* (IIa) *and the Corresponding Oxo-acid* (IIIa).—The oxo-ester (IIa) was prepared in 55% yield through condensation of 1-tetralone with ethyl crotonate, by following the procedure of Belleau [5] for an allied condensation; b.p. 150—155° at 0.4 mmHg (Found: C, 73.5; H, 7.5. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%), $\lambda_{max.}$ 249 and 292 nm (log ε 4.1 and 3.3), $\nu_{max.}$ 1 730 and 1 680 cm^{-1}. Hydrolysis of this ester with aqueous 10% potassium hydroxide (1.5 mol. equiv.) under reflux for 6 h afforded the oxo-acid (IIIa) (90%), m.p. 101—102° (lit.,[5] 101—102°).

Ethyl β-(1,2,3,4-*Tetrahydro*-6-*methoxy*-1-*oxo*-2-*naphthyl*)-*butyrate* (IIb) *and the Corresponding Oxo-acid* (IIIb).—Under the above conditions, the *oxo-ester* (IIb) was obtained in 30% yield. The yield improved to 70% by use of 0.1 g atom of base (potassium t-butoxide); b.p. 170—175° at 0.3 mmHg (Found: C, 70.1; H, 7.5. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.6%), $\nu_{max.}$ 1 730, 1 670, and 1 600 cm^{-1}. Hydrolysis of this ester with aqueous 10% potassium hydroxide (1.5 mol. equiv.) by heating under reflux for 6 h afforded the oxo-acid (IIIb) (87%), m.p. 128—132° (from ethyl acetate) (Found: C, 68.7; H, 6.8. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.8%), $\nu_{max.}$ 1 700, 1 670, and 1 600 cm^{-1}.

β-(1,2,3,4-*Tetrahydro*-1-*hydroxy*-2-*naphthyl*)*butyric Acid Lactone* (IVa).—To a stirred solution of the oxo-acid (IIIa) (20 g) in aqueous 10% sodium carbonate (200 ml), sodium amalgam (4%; 500 g) was added in small portions at room temperature over 5 h with occasional addition of sulphuric acid (4N) to maintain a low alkali concentration. The mixture was left overnight, acidified with sulphuric acid (10N) in the cold, warmed to *ca.* 50 °C (4 h), then left at room temperature for 10 h and extracted with ether. The extract was washed with saturated sodium hydrogen carbonate solution, dried, and evaporated. The residue on distillation afforded the *lactone* (IVa) (10 g), b.p. 150—152° at 0.6 mmHg, m.p. 116—118° (from ethyl acetate–petroleum), evidently a mixture of diastereoisomers (Found: C, 77.3; H, 7.5. $C_{14}H_{16}O_2$ requires C, 77.7; H, 7.5%), $\nu_{max.}$ 1 735 cm^{-1}.

β-(1,2,3,4-*Tetrahydro*-1-*hydroxy*-6-*methoxy*-2-*naphthyl*)-*butyric Acid Lactone* (IVb).—The oxo-acid (IIIb) (10 g) was reduced by the foregoing procedure to afford the

[15] Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, 1971, **27**, 5157.

lactone (IVb) (5.5 g), m.p. 108—110° (from ethyl acetate–petroleum) (Found: C, 72.9; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.4%), $\nu_{max.}$ 1 735 and 1 600 cm^{-1}, δ 7.52 (1 H, d, *J* 7 Hz, aromatic), 6.74 (2 H, m, aromatic), 5.1 (1 H, m, H-1), 3.78 (3 H, s, O·CH_3), and 1.1 (3 H, d, *J* 6 Hz, C·CH_3).

2,3,4,5-*Tetrahydro*-3-*methylbenz*[e]*inden*-1-*one* (Va).—To stirred polyphosphoric acid [from phosphorus pentaoxide (280 g) and orthophosphoric acid (85% w/w; 150 ml)] at 80 °C was added the lactone (IVa) (40 g) in one portion. After stirring for 1.5 h at 80 °C, the mixture was decomposed (ice) and extracted with ether. The extracts, after washing with aqueous 10% potassium hydroxide, were concentrated, and the residue was distilled to afford the ketone (Va) (16 g), b.p. 140—142° at 0.3 mmHg, m.p. 100—101° (from petroleum) (Found: C, 84.8; H, 7.0. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%), $\lambda_{max.}$ 230 and 292 nm (log ε 4.1 and 3.7), $\nu_{max.}$ 1 665 cm^{-1}; red 2,4-*dinitrophenylhydrazone*, m.p. 242° (from ethyl acetate) (Found: C, 63.1; H, 4.8. $C_{20}H_{18}N_4O_4$ requires C, 63.5; H, 4.8%).

2,3-*Dihydro*-7-*methoxy*-3-*methylbenz*[e]*inden*-1-*one* (VIb).—Under the above conditions the lactone (IVb) afforded, after chromatographic purification, the *ketone* (VIb) (25%), m.p. 105—106° (from petroleum) (Found: C, 79.4; H, 6.2. $C_{15}H_{14}O_2$ requires C, 79.6; H, 6.2%), $\lambda_{max.}$ 243 and 300 nm (log ε 4.6 and 3.9), $\nu_{max.}$ 1 660 and 1 600 cm^{-1}. Most of the residue was polymeric material.

β-(1,2,3,4-*Tetrahydro*-2-*hydroxy*-6-*methoxy*-2-*naphthyl*)-*butyric Acid Lactone* (VII).—Treatment of a solution of the lactone (IVb) (2 g) in benzene (12 ml) with polyphosphoric acid [from phosphorus pentaoxide (28 g) and orthophosphoric acid (14 ml)] at room temperature with stirring for 1.5 h afforded the isomeric γ-*lactone* (VII) (1.4 g), m.p. 140—141° (from ethyl acetate) (Found: C, 73.2; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.4%), $\lambda_{max.}$ 278 nm (log ε 3.36), $\nu_{max.}$ 1 750 and 1 600 cm^{-1}, δ 7.0 (1 H, d, *J* 7 Hz, aromatic), 6.72 (2 H, m, aromatic), 3.77 (3 H, s, O·CH_3), and 1.1 (3 H, dd, *J* 4.5 and 2 Hz, C·CH_3).

2,3,4,5-*Tetrahydro*-7-*methoxy*-3-*methylbenz*[e]*inden*-1-*one* (Vb).—(a) *From the lactone* (IVb) *with polyphosphoric acid.* An intimate mixture of the lactone (IVb) and polyphosphoric acid, in the proportions of the foregoing experiment, was stirred at 60 °C for 40 min, decomposed (ice), and worked up as in the case of (Va). The residue was chromatographed over neutral alumina. Petroleum eluted the *ketone* (Vb) (12%), m.p. 98—99° (from petroleum) (Found: C, 79.0; H, 7.1. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.1%), $\lambda_{max.}$ 245 and 290 nm (log ε 4.38 and 3.99), $\nu_{max.}$ 1 660 and 1 600 cm^{-1}, δ 8.16 (1 H, d, *J* 9 Hz, aromatic), 6.75 (2 H, m, aromatic), 3.8 (3 H, s, O·CH_3), and 1.25 (3 H, d, *J* 6 Hz, CMe), followed by the aromatic ketone (VIb) (25%). Elution with petroleum–benzene (5 : 1) furnished the γ-lactone (VII) (8—12%).

(b) *From reduction of the ketone* (VIb). To a stirred mixture of anhydrous ammonia (80 ml), the ketone (VIb) (2.1 g), and ethanol (6 ml) was added sodium (2 g) in small pieces. When the blue colour was discharged, ammonium chloride (5 g) was added and the ammonia evaporated off. The residue was dissolved in water and acidified with dilute hydrochloric acid. The precipitated solid was extracted with ether. The ethereal solution was washed with dilute hydrochloric acid (2N) and water, dried, and evaporated. The solid residue was crystallised to afford the unsaturated ketone (Vb) (1.65 g), identical with the foregoing sample.

2,3,3aα,4,5,9bα-*Hexahydro*-3-*methylbenz*[e]*inden*-1-*one* (IXa).—The ketone (Va) (2.8 g) in ethanol (60 ml) was hydrogenated over 10% palladium–charcoal (500 mg). Uptake was complete in 2 h. The usual work-up and distillation of the residue furnished the *ketone* (IXa) (2.5 g) as a liquid, b.p. 130° at 0.3 mmHg (Found: C, 84.1; H, 7.8. $C_{14}H_{16}O$ requires C, 84.0; H, 8.0%), $\nu_{max.}$ 1 740 cm^{-1}. G.l.c. analysis showed that the major constituent was present to the extent of *ca.* 86%. The yellow 2,4-*dinitrophenylhydrazone* had m.p. 210° (from ethyl acetate–methanol) (Found: C, 63.0; H, 5.1. $C_{20}H_{20}N_4O_4$ requires C, 63.1; H, 5.3%).

Alkylation of the Ketone (Va) *with Ethyl Bromoacetate.*—To dry potassium t-pentyl oxide [from potassium (550 mg)] under dry benzene (10 ml) a solution of the ketone (Va) (3 g) in dry benzene (15 ml) was added under nitrogen at room temperature. The mixture was warmed at 60 °C for 1 h, then treated dropwise with ethyl bromoacetate (3.5 g) at 0 °C and left overnight at room temperature. It was then heated under gentle reflux for 6 h and worked up in the usual way. The residue was distilled to furnish, after separation of the parent ketone (1.4 g), the oxo-ester mixture (VIII) (1.3 g) as a thick liquid (three spots on t.l.c.), b.p. 165—170° at 0.2 mmHg (Found: C, 75.9; H, 6.9. Calc. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1%), $\lambda_{max.}$ 230 and 290 nm (log ε 3.9 and 3.4), $\nu_{max.}$ 1 740—1 725br cm^{-1}, δ 6.0 (m, vinylic H), and 1.2 and 2.1 (saturated and vinylic Me).

Ethyl 2,3,3aα,4,5,9b-*Hexahydro*-3-*methyl*-1-*oxobenz*[e]-*inden*-9bα-*ylacetate* (Xa).—(*a*) The foregoing oxo-ester mixture (VIII) (3 g) was hydrogenated in ethanol (30 ml) over 10% palladium–charcoal (800 mg) at room temperature and atmospheric pressure. Uptake was complete in 10 h, affording the *oxo-ester* (Xa) (2.8 g) as a liquid, b.p. 165—170° at 0.2 mmHg (Found: C, 75.2; H, 7.5. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.7%), $\nu_{max.}$ 1 745 and 1 725 cm^{-1}, showing no vinylic proton or vinylic methyl signals in the n.m.r. spectrum.

(*b*) The saturated ketone (IXa) was alkylated with ethyl bromoacetate, as for the alkylation of (Va). The product (35%) was identical with the foregoing sample of (Xa) (i.r., n.m.r., and t.l.c.).

Ethyl 3aα,4,5,9b-*Tetrahydro*-3-*methyl*-1-*oxobenz*[e]*inden*-9bα-*ylacetate* (XIa).—To a stirred solution of the oxo-ester (Xa) (2.6 g) in dry ether (25 ml), containing a drop of hydrobromic acid (48%), was added dropwise a solution of bromine (1.35 g) in dry carbon tetrachloride (10 ml) at 0 °C over 30 min. The mixture was stirred at 0 °C for another 30 min, diluted with ice–water (20 ml), and left at 10 °C for 12 h. The usual work-up afforded the α-bromoketone (3.1 g) as a gum. This was dissolved in hexamethylphosphoramide (30 ml), and heated at 120—125 °C for 5 h under nitrogen. The mixture was cooled to room temperature, diluted with water, and worked up. The residue on distillation afforded the *oxo-ester* (XIa) (1.3 g), b.p. 168—172° at 0.2 mmHg (Found: C, 75.8; H, 7.0. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%), $\lambda_{max.}$ 228 nm (log ε 4.2), $\nu_{max.}$ 1 725—1 715br cm^{-1}.

3aα,4,5,9b-*Tetrahydro*-3-*methyl*-1-*oxobenz*[e]*inden*-9bα-*ylacetic Acid* (XIb).—The unsaturated oxo-ester (XIa) (1.3 g) was heated under reflux with ethanolic potassium hydroxide (5%; 15 ml) for 8 h and worked up to afford the *oxo-acid* (XIb) (1.05 g), m.p. 178—179° (from ethyl acetate) (Found: C, 74.8; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%), $\lambda_{max.}$ 229 nm (log ε 4.3), $\nu_{max.}$ 1 720 and 1 705 cm^{-1}, δ 7.8—7.0 (4 H, complex m, aromatic), 5.96 (1 H, apparent quintet, *J* 1.0 Hz, H-2), 3.24—2.83 (3 H, complex m)

[probably a multiplet from H-3a (δ 3.20) and two doublets from the side chain methylene protons arising from geminal coupling (δ 3.16 and 2.83, J_{gem} 17 Hz)], and 2.12 (3 H, t, J 1.0 Hz, 3-Me).

The corresponding *methyl ester* (diazomethane esterification), b.p. 160—162° at 0.2 mmHg, gave a single spot on t.l.c. (benzene–ethyl acetate, 5 : 1) (Found: C, 75.3; H, 6.9. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%).

2,3,3aα,4,5,9bα-*Hexahydro-7-methoxy-3-methylbenz*[e]*inden*-1-*one* (IXb).—The unsaturated ketone (Vb) (1.5 g) was hydrogenated in ethanol (20 ml) over 10% palladium–charcoal (300 mg) at room temperature and atmospheric pressure (uptake 1.5 mol. equiv.) to give a mixture of the saturated ketone (IXb) and the corresponding hydroxy-compound. The crude mixture was oxidised with Jones reagent at 0 °C in acetone solution to afford the saturated *ketone* (IXb) (1.2 g), m.p. 98—99° (from petroleum) (Found: C, 77.9; H, 7.9. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.9%), $\nu_{max.}$ 1 745 and 1 600 cm^{-1}. T.l.c. (benzene) revealed a single spot.

2,3,3aα,4,5,9b-*Hexahydro-7-methoxy-3-methyl*-1-*oxobenz*[e]*inden*-9bα-*ylacetic Acid* (Xc).—(*a*) The methoxy-ketone (Vb) (3 g) was alkylated with methyl bromoacetate, as for the alkylation of (Va). The residue obtained after work-up was subjected to evaporative distillation and the fraction boiling in the range 150—185° at 0.2 mmHg was collected (3.1 g). This was hydrolysed with aqueous 10% potassium hydroxide (15 ml) under reflux for 5 h and the acidic (0.95 g) and neutral (1.8 g) fractions were separated. Both fractions solidified. A single crystallisation of the acidic part afforded the pure *oxo-acid* (Xc) (0.75 g), m.p. 150—151° (from ethyl acetate) (Found: C, 71.0; H, 7.1. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%), *m/e* 288 (M^+), $\nu_{max.}$ 1 740, 1 705, and 1 600 cm^{-1}, δ 7.5 (1 H, d, J 6 Hz, aromatic), 6.67 (2 H, m, aromatic), 3.72 (3 H, s, O·CH$_3$), and 1.1 (3 H, d, J 6 Hz, 3-Me). The neutral fraction was crystallised once to afford the aromatic ketone (VIb) (1.5 g), identical with the sample described earlier. In a repeat of the above experiment, the reaction residue was subjected to evaporative distillation and the product of alkylation boiling in the range 175—185° at 0.2 mmHg was collected. The n.m.r. spectrum revealed a minute vinylic proton signal at δ 6.01.

(*b*) The saturated ketone (IXb) (2 g) was alkylated with methyl bromoacetate as in the case of (Vb). The *oxo-ester* (Xb) (900 mg) was separated from the parent ketone (IXb) (identified by mixed m.p.) through evaporative distillation (175—185° at 0.2 mmHg) (Found: C, 71.7; H, 7.5. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%), $\nu_{max.}$ 1 740—1 725br cm^{-1}, δ 7.52 (1 H, d, J 7 Hz, aromatic), 6.65 (2 H, m, aromatic), 3.72 (3 H, s, O·CH$_3$), 3.42 (3 H, s, CO$_2$CH$_3$), and 1.12 (3 H, d, J 6 Hz, 3-Me). This ester was hydrolysed with aqueous 10% potassium hydroxide (10 ml) under reflux for 5 h to afford the acid (Xc), identical with the sample described in (*a*).

Methyl **3aα,4,5,9b-*Tetrahydro-7-methoxy-3-methyl*-1-*oxobenz*[e]*inden*-9bα-*ylacetate*** (XIIa).—The oxo-ester (Xb) (3 g), obtained through esterification of (Xc) with diazomethane, was brominated, as for bromination of (Xa). The *2-bromo-derivative* (Xd) (2.6 g) was obtained as a crystalline solid, m.p. 160° (from ethyl acetate–petroleum) (Found: C, 56.6; H, 5.6. $C_{18}H_{21}BrO_4$ requires C, 56.7; H, 5.5%), δ 7.8 (1 H, d, J 8 Hz, aromatic), 6.67 (2 H, m, aromatic), 4.24 (1 H, d, J 12 Hz, H-2), 3.72 (3 H, s, O·CH$_3$), 3.47 (3 H, s, CO$_2$CH$_3$), and 1.26 (3 H, d, J 7 Hz, 3-Me). This was dehydrobrominated with hexamethylphosphoramide by the procedure described earlier, and the product was purified through evaporative distillation (180—185° at 0.2 mmHg) to afford the unsaturated *oxo-ester* (XIIa) (1.7 g) (Found: C, 71.8; H, 6.6. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%), $\lambda_{max.}$ 229 nm (log ε 4.1), $\nu_{max.}$ 1 720—1 710br cm^{-1}.

3aα,4,5,9b-*Tetrahydro-7-methoxy-3-methyl*-1-*oxobenz*[e]*inden*-9bα-*ylacetic Acid* (XIIb).—The foregoing oxo-ester (XIIa) (2 g) was hydrolysed with aqueous 10% potassium hydroxide (10 ml) under reflux for 6 h to afford the *acid* (XIIb) (1.5 g), m.p. 190° (from ethyl acetate) (Found: C, 71.2; H, 6.4. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%), $\nu_{max.}$ 1 715—1 705br cm^{-1}, δ 7.52 (1 H, d, J 7 Hz, aromatic), 6.67 (2 H, m, aromatic), 5.96 (1 H, apparent quintet, J 1.0 Hz, H-2), 3.72 (3 H, s, O·CH$_3$), and 2.15 (3 H, t, J 1.0 Hz, 3-Me).

9bα-*Acetonyl*-3aα,4,5,9b-*tetrahydro*-3-*methylbenz*[e]*inden*-1-*one* (XIIIa) *and the* **7-*Methoxy-compound*** (XIIIb).—The acid (XIb) (2.56 g), as its mixed anhydride with ethyl hydrogen carbonate was treated with diethyl ethoxy-magnesiomalonate, by the method of Tarbell and Price.[13] The crude neutral product (3.1 g) was hydrolysed by refluxing with a mixture of acetic acid (140 ml), water (28 ml), and toluene-*p*-sulphonic acid (14 g) for 2 h under nitrogen. The cooled mixture was treated with solid sodium carbonate to neutralise the acids, then diluted with water and extracted with ether. Evaporation of the extracts afforded crystalline material and a gummy residue. The solid was separated and the residue was chromatographed over neutral alumina to afford a further crop of crystalline material on elution with benzene–petroleum (1 : 1). A single recrystallisation of the total solid afforded the pure *diketone* (XIIIa) (1.3 g), m.p. 145—146° (from ethyl acetate–petroleum) (Found: C, 80.3; H, 7.3. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%), $\lambda_{max.}$ 231 nm (log ε 4.21), $\nu_{max.}$ 1 720 and 1 700 cm^{-1}, δ 7.8—7.0 (4 H, complex m, aromatic), 5.99 (1 H, quintet, J 1.0 Hz, H-2), 3.3—2.95 (3 H, complex m), 2.12 (3 H, t, J 1.1 Hz, 3-Me), and 2.0 (3 H, s, CO·CH$_3$).

Similar treatment of the acid (XIIb) afforded the *diketone* (XIIIb) (*ca.* 55%), m.p. 111—112° (from ethyl acetate–petroleum) (Found: C, 75.6; H, 7.0. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%), *m/e* 284 (M^+), $\lambda_{max.}$ 229 nm (log ε 4.28), $\nu_{max.}$ 1 715, 1 700, and 1 600 cm^{-1}, δ 7.50 (1 H, d, J 7 Hz, aromatic), 6.6 (2 H, m, aromatic), 5.95 (1 H, quintet, J 1.0 Hz, H-2), 3.72 (3 H, s, O·CH$_3$), 2.12 (3 H, t, J 1.0 Hz, 3-Me), and 2.0 (3 H, s, CO·CH$_3$).

1,9,10,10aα-*Tetrahydro*-1α-*methyl*-2H-1,4aβ-*ethanophenanthrene*-3(4H),11-*dione* (XIVa) *and the* **7-*Methoxy-compound*** (XIVb).—The unsaturated diketone (XIIIa) (300 mg) was stirred under nitrogen with a solution of potassium (20 mg) in t-butyl alcohol (5 ml) at room temperature for 40 h. The mixture was diluted with water and worked up to afford the *tetracyclic diketone* (XIVa) (240 mg), m.p. 171—172° (from ether) (Found: C, 80.0; H, 7.1. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%), $\lambda_{max.}$ 310 nm (log ε 2.57), $\nu_{max.}$ 1 745 and 1 710 cm^{-1}, δ 7.45—7.15 (4 H, m, aromatic), 3.1—2.1 (11 H, complex m, methylene and methine protons), and 1.3 (3 H, s, 1-Me) (no vinylic proton).

Similar treatment of (XIIIb) afforded the *tetracyclic ketone* (XIVb) (80%), m.p. 192—193° (from ethyl acetate–petroleum) (Found: C, 75.8; H, 7.1. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%), $\nu_{max.}$ 1 745, 1 710, and 1 600 cm^{-1}, δ 7.32—6.6 (3 H, complex m, aromatic), 3.72 (3 H, s, O·CH$_3$), and 1.25 (3 H, s, 1-Me).

The 3-*Monothioacetals* (XVa *and* b) *of the Diketones* (XIVa *and* b).—To a homogeneous mixture of the diketone (XIVa) (100 mg) and ethanedithiol (160 mg), boron trifluoride–ether complex (5 drops) was added in the cold. The mixture was left at room temperature for 2 h, then diluted with water and worked up. The residue was chromatographed over neutral alumina. Fractions eluted by benzene–petroleum (3 : 1) afforded the *thioacetal* (XVa) (65 mg), m.p. 164—165° (from ether–petroleum) (Found: C, 68.8; H, 6.9. $C_{19}H_{22}S_2O$ requires C, 69.1; H, 6.7%), $\nu_{max.}$ 1 750 cm^{-1}.

The diketone (XIVb) similarly afforded the *monothioacetal* (XVb) (20%), m.p. 173—174° (from ether–petroleum) (Found: C, 66.2; H, 6.8. $C_{20}H_{24}S_2O_2$ requires C, 66.6; H, 6.7%), $\nu_{max.}$ 1 750 and 1 600 cm^{-1}. The yield of (XVb) was improved to 80% by use of a different method. A homogeneous mixture of the diketone (XIVb) (100 mg), ethanedithiol (60 mg), glacial acetic acid (2 ml), and toluene-*p*-sulphonic acid (30 mg) was left at room temperature for 45 min, diluted with water, and worked up. The thioacetal (XVb) (100 mg) was obtained as a crystalline solid.

1,3,4,9,10,10aα-*Hexahydro*-1α-*methyl*-2H-1,4aβ-*ethanophenanthren*-11-*one* (XVIa) *and the* 7-*Methoxy-compound* (XVIb).—The thioacetal (XVa) (200 mg) in a suspension of W-2 Raney nickel [from the alloy (10 g)] in ethanol (40 ml) was heated under reflux for 10 h under nitrogen. The filtered solution was concentrated under reduced pressure and worked up to afford a gum, which on chromatography over neutral alumina afforded [elution with benzene–petroleum (1 : 2)] the *monoketone* (XVIa) (85 mg), m.p. 109—110° (from petroleum) (Found: C, 85.0; H, 8.6. $C_{17}H_{20}O$ requires C, 85.0; H, 8.4%), $\nu_{max.}$ 1 745 cm^{-1}.

The *ketone* (XVIb), similarly prepared from (XVb) in 50% yield, was isolated through chromatography over neutral alumina [elution with benzene–petroleum (1 : 3)]; m.p. 152—153° [from petroleum (b.p. 40—60°)] (Found: C, 80.0; H, 8.3. $C_{18}H_{22}O_2$ requires C, 80.0; H, 8.2%), $\nu_{max.}$ 1 750 and 1 600 cm^{-1}, δ 7.4 (1 H, d, *J* 6 Hz, aromatic), 6.64 (2 H, m, aromatic), 3.72 (3 H, s, O·CH_3), and 1.17 (3 H, s, 1-Me).

1,2,3,4,4a,9,10,10aα-*Octahydro*-1α-*methylphenanthrene*-1β,4aβ-*dicarboxylic Acid* (Ia).—To a suspension of sodium hydride (pre-washed with petroleum; 150 mg) in benzene (10 ml) was added the ketone (XVIa) (160 mg), followed by freshly distilled ethyl formate (6 ml). The mixture was stirred at room temperature under nitrogen for 8 h, and the excess of hydride was then destroyed with a little methanol. Dilution with ether and extraction with water and cold aqueous 2% sodium hydroxide afforded the base-soluble hydroxymethylene derivative (170 mg). This was dissolved in aqueous 10% sodium hydroxide (20 ml) and treated with hydrogen peroxide (30%; 7 ml) at room temperature with stirring. After 2 h, more hydrogen peroxide (7 ml) was added and stirring was continued for 12 h. The mixture was then extracted with ether and the alkaline solution was acidified with dilute hydrochloric acid to afford the diacid (Ia) (140 mg), m.p. 231—232° (decomp.) (from ethyl acetate) (Found: C, 70.8; H, 7.2. Calc. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0%). The dimethyl ester (from diazomethane treatment) had m.p. 134—135° (from petroleum). The m.p.s of the acid (Ia) and its dimethyl ester were not depressed on admixture with authentic [3d] samples (identical by t.l.c. and i.r. comparison).

1,2,3,4,4a,9,10,10aα-*Octahydro*-7-*methoxy*-1α-*methylphenanthrene*-1β,4aβ-*dicarboxylic Acid* (Ib).—The ketone (XVIb) was similarly converted into the methoxy-diacid (Ib) (80%), m.p. 232° (decomp.) (from tetrahydrofuran) (Found: C, 68.2; H, 7.2. Calc. for $C_{18}H_{22}O_5$: C, 67.9; H, 7.0%). The dimethyl ester (from diazomethane treatment) melted at 114° (from petroleum). The m.p.s of the acid (Ib) and its dimethyl ester were not depressed on admixture with the authentic [3d] samples (identical in i.r. and t.l.c. properties).

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