Synthetic Studies towards Complex Diterpenoids. Part 13.[1] Stereospecific Synthesis of Intermediates to the Diterpene Alkaloids and the C_{20}-Gibberellins by a Novel Rearrangement of Angularly Fused Cyclobutanones

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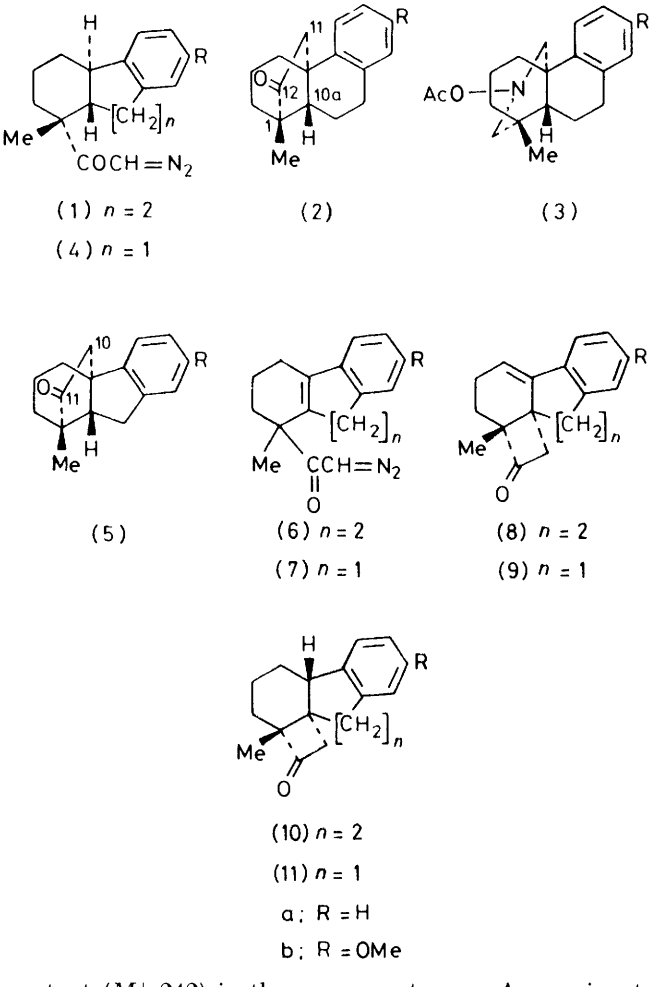
A new stereospecific rearrangement of the saturated cyclobutanones (10a and b) and (11a and b) to the respective bridged cyclopentanones (2a and b) and (5a and b) using triethyloxonium tetrafluoroborate is described. Rearrangement studies of the specific labelled ketone [$^2H_2$]-(10a) indicate that the process is intramolecular. Sulphuric acid-catalysed rearrangement of (10a) produces the unsaturated methyl ketone (13). Transformation of the tetracyclic ketones (5a and b) to some angularly functionalised hydrofluorene synthons (14a and b) to the C_{20}-gibberellins has been achieved.

SEVERAL long term programmes have been initiated in these laboratories [2,3] aimed specifically at the development of stereocontrolled synthetic methods for elaboration of the crucial ring-A substituent patterns of the *Garrya* and *Atisine* groups of complex diterpene alkaloids [4] and angularly functionalised C_{20}-gibberellins.[5] One of these approaches culminated [2] in a method for a stereospecific synthesis of the tetracyclic ketones (2a and b) through a copper-catalysed regioselective intramolecular oxo-carbenoid C–H insertion reaction in the respective diazomethyl ketones (1a and b). These ketones were transformed [2] to the key intermediate tetracyclic acylamines (3a and b), some of which had already been converted into atisine, veatchine, and gibberellin A_{15}. An attempted oxo-carbenoid insertion reaction [2,3] of the hydrofluorene diazomethyl ketone (4a),[6] however, failed to give the desired product (5a) in isolable yield.

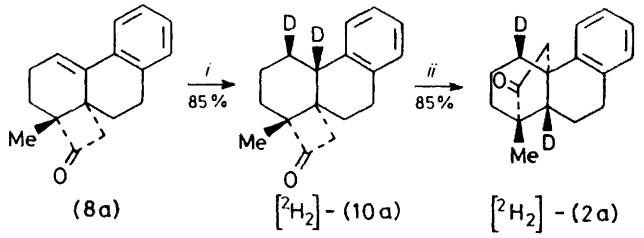
We have previously reported [7] a simple and efficient synthetic route to the angularly fused unsaturated cyclobutanones (8a and b) and (9a and b) by intramolecular *C*-alkylations of the easily accessible $\beta\gamma$-unsaturated α'-diazomethyl ketones (6a and b) and (7a and b) and their stereoselective hydrogenation to the saturated cyclobutanones (10a and b) and (11a and b). We now describe in detail [1b] a new rearrangement of these saturated cyclobutanones to the respective bridged cyclopentanones (2a and b) and (5a and b). We also present our results on the mechanism of this novel rearrangement and on the transformations of the tetracyclic ketones to some key hydrofluorene synthons in the synthesis of C_{20}-gibberellins.

Rearrangement † of the strained cyclobutanone (10a) with an excess of triethyloxonium tetrafluoroborate (Meerwein Reagent [9]) in methylene chloride at room temperature afforded the known tetracyclic ketone (2a) [2,10] in 95% yield. The corresponding methoxy-analogue (10b) under the same conditions produced (2b) [2] in excellent yield. To evaluate the possible mechanism of this novel rearrangement of strained cyclobutanones to cyclopentanones we next studied the reaction of [4,4a-$^2H_2$]-(10a) (Scheme 1), prepared by catalytic reduction of the styrenoid ketone (8a) with deuterium. The labelled ketone indicated >99% D_2 content (M^+ 242) in the mass spectrum. A prominent isotopic shift in the mass spectra of the [$^2H_2$]- and [$^2H_0$]-ketones was exhibited in the base peak at *m/e* 200 (M − 42) with respect to *m/e* 198. The ^1H n.m.r.



† For recent examples of rearrangements of cyclobutanes and cyclobutanones see ref. 8.

spectral data also supported the structure of the deuteriated ketone. The reaction of [4,4a-$^2H_2$]-(10a) with triethyloxonium tetrafluoroborate was monitored by observation of the i.r. spectra at *ca.* 12 h intervals. Complete disappearance of the cyclobutanone C=O band was indicated after *ca.* 6 days in comparison to 12—16 h for the [$^2H_0$]-ketone. The rearranged cyclopentanone [$^2H_2$]-(2a), isolated in 85% yield, was shown to be identical (mixed m.p. and t.l.c.) with the [$^2H_0$]-ketone. The i.r. spectra (in $CHCl_3$) of this product and the unlabelled ketone showed identical bands except for a strong C–D stretch at 2 160 cm^{-1} in that of the former. The mass spectrum exhibited the molecular ion as the base peak at *m/e* 242 correspondng to >99% D_2. The ^1H n.m.r. spectrum (in $CDCl_3$ at 60 MHz) of the deuteriated ketone [$^2H_2$]-(2a) was identical with that of the non-deuteriated ketone except that a partly masked broad unresolved triplet at δ 1.96 [assigned to the C-10a proton in (2a)] was absent. Moreover, the splitting pattern of the multiplets between δ 1.16—2.04, accounting for *ca.* 9 protons in the unlabelled ketone (2a),

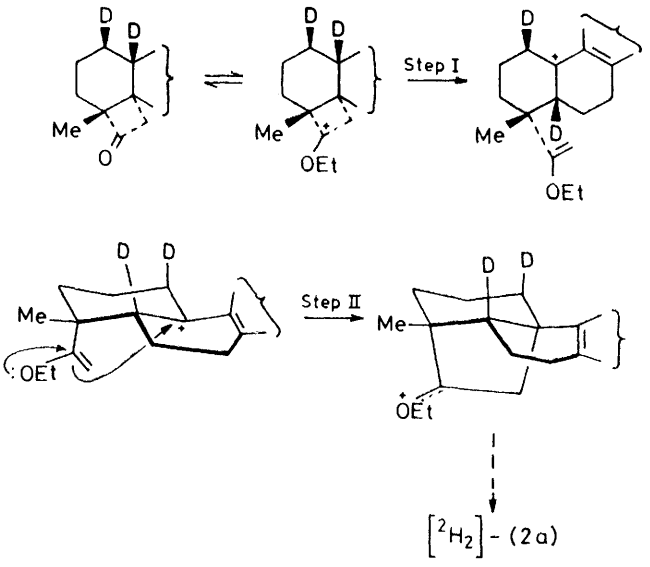


SCHEME 1 *Reagents: i*, D_2, Pd–C(10%) EtOH; *ii* $Et_3O^+BF_4^-$ CH_2Cl_2 (6 days)

exhibited a considerable difference and integrated to *ca.* 7 protons for the deuteriated compound along with a clear separation of the inner lines of the *gem*-$COCH_2$ protons at *ca.* δ 2.38. The intramolecular nature of this rearrangement is clearly established from this experiment. Based on this result, the following mechanism may be advanced for this rearrangement. The pronounced isotope effect observed in the rearrangement of [$^2H_2$]-(10a) clearly indicates step I (Scheme 2) as the possible rate-determining step in this novel rearrangement.

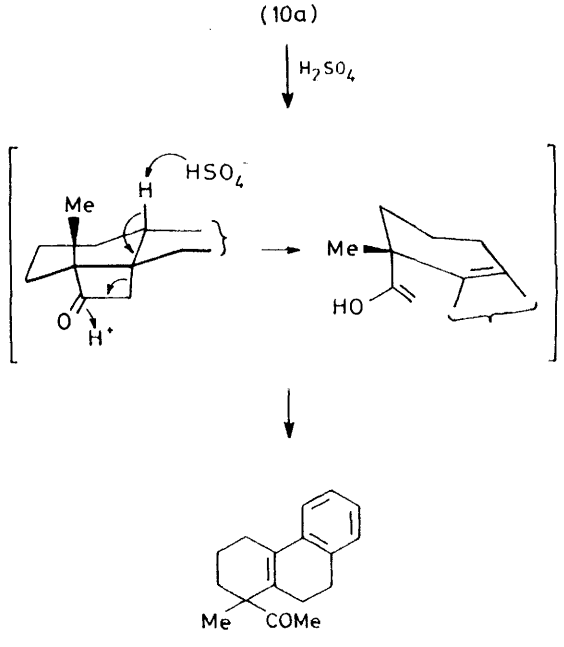
The triethyloxonium tetrafluoroborate-catalysed rearrangement of the hydrofluorone ketone (11a) required a somewhat longer reaction time (*ca.* 24 h) and afforded the bridged-cyclopentanone (5a) in excellent yield. The corresponding methoxy-analogue (11b), under identical conditions gave the analogous rearranged ketone (5b) in 93% yield (Scheme 3). The spectral data of the rearranged ketones are in complete agreement with the assigned structures. Further structural proof for (5a and b) was obtained by their benzylic oxidation [11] with chromium trioxide–acetic acid to the respective crystalline diketones (12a and b). The stereochemistry of (11a and b) has been assigned from their mode of formation by analogy with the respective hydrophenanthrene derivatives of established stereochemistry. The highly efficient stereospecific rearrangement of the angularly fused cyclobutanones to the bridged cyclopentanones in both the hydrophenanthrene and hydrofluorene series clearly indicates the generality of this reaction.

During our preliminary studies on the rearrangement



SCHEME 2

of the aforementioned cyclobutanones with a variety of acidic reagents, we observed [12] an interesting transformation of (10a) to the unsaturated methyl ketone (13) [13] in excellent yield, using sulphuric acid in benzene at low temperature. This rearrangement is readily visualised



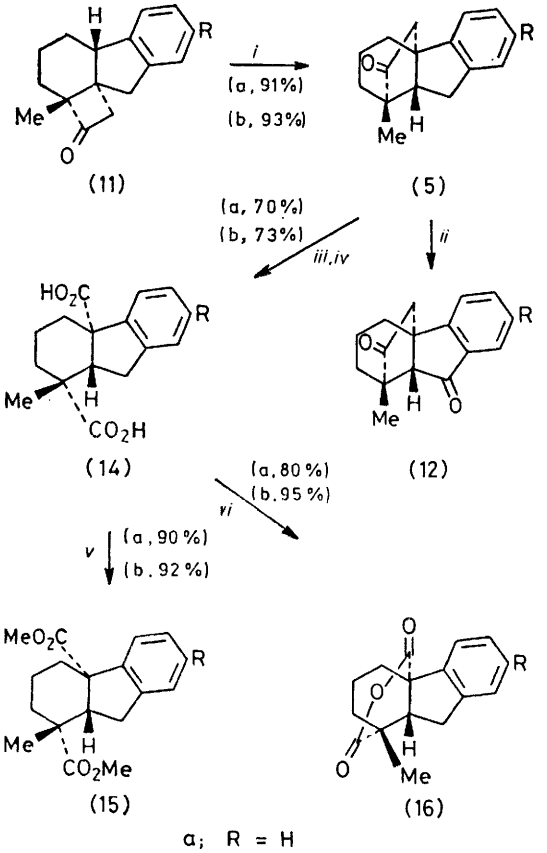
(13)

SCHEME 3

as proceeding through cleavage of the strained protonated cyclobutanone (10a) in a concerted (or stepwise) path as depicted in Scheme 3.

With the development of this simple stereospecific

synthetic method for the tetracyclic ketones (5a and b) we next used the sequence of reactions earlier developed [2,3] in the hydrophenanthrene series, for the introduction of C-4, C-10 (corresponding hydrofluorene numbers C-1 and C-4a) functions of some C_{20}-gibberellins in the *trans*-hydrofluorene skeleton with the appropriate stereochemistry. Thus, the ketone (5a) was condensed with ethyl formate in the presence of a large excess of sodium hydride under forcing conditions. The crude hydroxymethylene derivative was directly oxidised with alkaline hydrogen peroxide to afford the crystalline dicarboxylic acid (14a) in 70% overall yield. In an identical sequence, the methoxy-ketone (5b) gave the dicarboxylic acid (14b) in 73% yield. The diacids (14a and b) were further characterised through their respective dimethyl esters (15a and b) and their anhydrides (16a and b) (Scheme 4).



SCHEME 4 *Reagents: i* $Et_3O^+BF_4^-$, CH_2Cl_2 (24 h); *ii*, CrO_3, AcOH, H_2O; *iii*, NaH, HCO_2Et, C_6H_6; *iv*, aq. NaOH, H_2O_2 (30%); *v*, CH_2N_2, Et_2O; *vi*, MeCOCl

In conclusion, a novel intramolecular rearrangement of some easily accessible angularly fused cyclobutanones has been successfully developed and utilised as the key step in the synthesis of appropriately angularly functionalised hydrophenanthrene and hydrofluorene derivatives of complex diterpenoids. Further applications of this sequence for the synthesis of C_{20}-gibberellins will be reported in due course.

EXPERIMENTAL

Melting points were determined for samples in open capillary tubes in a sulphuric acid bath. I.r. spectra were recorded on Perkin-Elmer model 21 and Beckman Acculab 4 instruments for solutions in chloroform. U.v. spectra were recorded on a Beckman DU spectrophotometer for solutions in 95% ethanol. ^{1}H N.m.r. spectra were recorded at 60 MHz on a Varian Associates model T-60A spectrometer with Me_4Si as an internal standard. Column chromatography was performed on neutral alumina 'Standardised for chromatographic analysis acc. to Brockmann' (M/s. Sarabhai M. Chemicals) (30 g alumina per g of compound). T.l.c. was performed using plates coated (0.2 mm thickness) with Kieselgel G (type 60) (E. Merck). Microanalyses were performed by Mrs. C. Dutta of this laboratory.

The procedure involved in the general work-up involved extraction of organic matter with a water-immiscible solvent (3—4 times), washing of the extract with brine, and drying with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the material. Petroleum and light petroleum refer to fractions boiling in the ranges 60—80° and 40—60 °C, respectively.

Rearrangement of Saturated Cyclobutanones (10a *and* b) *with Meerwein Reagent.* (±)-1β-*Methyl*-1,2,3,4,4a,9,10,10aβ-*octahydro*-1α,4aα-*ethanophenanthren*-12-*one* (2a).—Triethyloxonium tetrafluoroborate [14] was prepared from boron trifluoride–ether (5 ml, 39.6 mmol) in dry ether (30 ml) and epichlorohydrin (2.5 ml). The crystalline reagent, freed from ether by passing dry nitrogen, was dissolved in anhydrous dichloromethane (6 ml) under dry nitrogen, and to this a solution of the saturated cyclobutanone (10a) (200 mg, 0.83 mmol) in dichloromethane (8 ml) was added at room temperature (25—35 °C) in one portion with stirring. The mixture was allowed to stir for 16 h at room temperature when the colourless solution slowly turned to amber. The mixture was decomposed by adding saturated aqueous sodium carbonate until alkaline. The organic layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with water and dried (Na_2SO_4). The light brown semi-solid left after removal of the solvent was dissolved in petroleum and filtered through a short-packed neutral alumina column (10 g) to afford (2a) as a white solid (190 mg, 95%), m.p. 114—116 °C, a portion of which was recrystallised from ether to afford an analytically pure sample, m.p. and mixed m.p. 117—118 °C, identical (i.r. and n.m.r. spectra) with an authentic sample.[2]

(±)-7-*Methoxy*-1β-*methyl*-1,2,3,4,4a-9,10,10aβ-*octahydro*-1α,4aα-*ethanophenanthren*-12-*one* (2b).—A solution of the cyclobutanone (10b) (200 mg, 0.74 mmol) in anhydrous dichloromethane (8 ml) was added to a magnetically stirred solution of triethyloxonium tetrafluoroborate [from boron trifluoride–ether (5 ml), ether (30 ml), and epichlorohydrin (2.5 ml)] in dichloromethane (6 ml) at room temperature. Stirring was continued for 16 h. Decomposition by saturated aqueous sodium carbonate and work-up as described above afforded the rearranged ketone (2b) as a yellow solid (180 mg, 90%), m.p. 122—126 °C, a portion of which was recrystallised from ether to afford an analytically pure sample, m.p. and mixed m.p. 130 °C, identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.[2]

Catalytic Reduction of the Unsaturated Cyclobutanone (8a) *with* D_2. (±)-1β-*Methyl*-[4,4aβ-$^2H_2$]-1,2,3,4,4aβ,9,10,10aβ-*octahydro*-1α,10aα-*ethanophenanthren*-12-*one* [$^2H_2$]-(10a) (*performed by* C. R. ENZELL and I. WAHLBERG).—The ketone (8a) (300 mg) in ethanol (10 ml) was stirred under D_2 in the

presence of palladium–charcoal (10 mg, 10%) for 7 h to give the crude product (300 mg), which was crystallised twice from light petroleum to afford the labelled ketone [$^2H_2$]-(10a), 260 mg (85%), m.p. and mixed m.p. with the [$^2H_0$]-ketone 102 °C; δ ($CDCl_3$) 1.10 (s, 3 H, $\rangle CCH_3$), 1.48—3.18 (complex m, 11 H) {n.m.r. spectrum of [$^2H_0$]ketone δ 1.10 (s, 3 H, $\rangle C{-}CH_3$), 1.20—2.40 (m, 8 H, methylenes), 2.50—3.25 (complex m, 5 H, ArC*H* and ArCH_2), and 7.10 (m, 4 H, ArH)}; *m/e* 242 (M^+, 5%), 214 (5), 200 (100), and 185 (95).

Comparative Rearrangement Studies of [$^2H_2$]-(10a) *and* (10a) *to the Respective Bridged Cyclopentanones* [$^2H_2$]-(2a) *and* (2a).—Triethyloxonium tetrafluoroborate [prepared from boron trifluoride–ether (10 ml), ether (60 ml), and epichlorohydrin (5 ml)] was dissolved in anhydrous dichloromethane (12 ml). One third of this solution (*ca.* 5 ml) was rapidly transferred by a pipette to a dry flask already under a nitrogen atmosphere. The solution of deuteriated cyclobutanone [$^2H_2$]-(10a) (120 mg, 0.49 mmol) in dichloromethane (7 ml) was added to the flask and the mixture was stirred magnetically. To the remaining reagent solution was added a solution of the cylobutanone (10a) (250 mg, 1.04 mmol) in dichloromethane (12 ml). Stirring at room temperature was continued for both reactions for 12 h. Aliquot portions were withdrawn from each of the sets, decomposed with aqueous sodium carbonate, and worked up in the usual way. The i.r. spectrum of the deuteriated compound indicated that only a small part (*ca.* 10%) of [$^2H_2$]-(10a) had rearranged to the respective cyclopentanone while (10a) had undergone practically complete rearrangement within the same time. The latter compound was decomposed and worked up in the usual way to afford (2a). Stirring of the reaction mixture containing [$^2H_2$]-(10a) was continued (*ca.* 6 days) until the i.r. band at 1 765—1 770 cm^{-1} completely disappeared. The reaction mixture, after the usual work-up, afforded [$^2H_2$]-(2a) as a light yellow solid (102 mg, 85%), m.p. 114—116 °C. A small portion of it was recrystallised from light petroleum to afford a pure sample, m.p. and mixed m.p. with the [$^2H_0$]-ketone 118 °C; $\nu_{max.}$ 1 735, 2 160, and 2 930 cm^{-1}; δ ($CDCl_3$) 1.03 (s, 3 H, CH_3), 1.26—2.08 (m, 7 H), 2.38br (d, 2 H, $COCH_2$), and 2.71—2.95 (m, 2 H, ArCH_2) [n.m.r. of (2a): δ 1.03 (s, 1 H, $\rangle CCH_3$), 1.16—1.81 (m, 8 H, methylenes), 1.98 br (t, *J* 3 Hz, 1 H, methine), 2.35 br (s, 2 H, $COCH_2$), and 2.71—2.91 (m, 2 H, ArCH_2)]; *m/e* 242 (M^+, 100%) 199 ($M^+ - CH_3CO$,22), 197 ($M^+ - C_3H_5D_2$,34), and 185 ($M^+ - C_3H_5O$, 34).

Rearrangement of (10a) *with Concentrated Sulphuric Acid.* 1-*Acetyl*-1-*methyl*-1,2,3,4,9,10-*hexahydrophenanthrene* (13).—Ice-cold concentrated H_2SO_4 (1.2 ml) was added dropwise to a stirred and cooled (*ca.* −10 °C) solution of (10a) (100 mg, 0.417 mmol) in dry benzene (1.2 ml). Stirring at this temperature was continued for 1 h. The yellow reaction mixture was poured onto crushed ice and worked up with ether to afford a gummy solid (92 mg), $\nu_{max.}$ 1 700 and 1 600 cm^{-1}, which was dissolved in petroleum and filtered through a short column of neutral alumina to afford the ketone (13) (60 mg, 60%) as a white solid, m.p. and mixed m.p. 84—86 °C, identical (i.r. and n.m.r.) with an authentic sample.[13]

(±)-1β-*Methyl*-1,2,3,4,4a,9aβ-*hexahydro*-1α,4aα-*ethanofluoren*-11-*one* (5a).—A solution of the cyclobutanone (11a) (1.4 g, 6 mmol) in anhydrous dichloromethane (40 ml) was treated with a magnetically stirred solution of triethyloxonium tetrafluoroborate [prepared from boron trifluoride–ether (10 ml), ether (60 ml), and epichlorohydrin (4.7 ml)] in dichloromethane (30 ml) for 24 h under the conditions described for (2a). Decomposition of the dark brown reaction mixture with saturated aqueous sodium carbonate followed by usual work-up furnished a dark brown liquid which on distillation at 135—140 °C at 0.4 mmHg (bath temperature) afforded the ketone (5a) (1.28 g, 91%) (Found: C, 85.0; H, 8.0. $C_{16}H_{18}O$ requires C, 84.91; H, 8.02%); $\nu_{max.}$ 1 730 cm^{-1}; δ (CCl_4) 0.70 (s, 3 H, $\rangle CCH_3$), 1.2—3.5 (complex m, 11 H, methylenes and methine), and 7.06 (s, 4, ArH); *m/e* 226 (M^+, 100%), 198 (32), 183 (71), 169 (45), and 155 (38).

The ketone (5a) in ethanol on warming (*ca.* 5 min) with a saturated aqueous solution of an equimolecular mixture of semicarbazide hydrochloride and sodium acetate (4 mol. excess) and cooling to room temperature afforded the semicarbazone. Recrystallisation from methanol afforded an analytical sample, m.p. 235—238 °C (decomp.) (Found: C, 71.9; H, 7.4. $C_{17}H_{21}N_3O$ requires C, 72.05; H, 7.47%).

(±)-7-*Methoxy*-1β-*methyl*-1,2,3,4,4a,9aβ-*hexahydro*-1α,4aα-*ethanofluoren*-11-*one* (5b).—A solution of the ketone (11b) (1.2 g, 4.6 mmol) in anhydrous dichloromethane (40 ml) was treated similarly with a magnetically stirred solution of triethyloxonium tetrafluoroborate [from boron trifluoride–ether (10 ml), ether (60 ml), and epichlorohydrin (4.7 ml)] in dichloromethane (30 ml) for 24 h. Decomposition of the dark brown mixture by saturated aqueous sodium carbonate followed by usual work-up afforded a dark brown liquid which on distillation at 120—125 °C and 0.1 mmHg (bath temperature) afforded the ketone (5b) as a colourless mobile liquid (1.12 g, 93%) (Found: C, 79.7; H, 8.1. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.86%); $\nu_{max.}$ 1 730 cm^{-1}; δ (CCl_4) 0.75 (s, 1 H, $\rangle CCH_3$), 1.25—3.3 (complex m, 11 H, methylenes and methine), 3.71 (s, 3 H, OCH_3), and 6.57—7.03 (m, 3 H, Ar*H*); *m/e* 256 (M^+, 100%), 241 (10), 228 (68), 213 (34), 199 (19), and 185 (37).

The semicarbazone of (5b), recrystallised from methanol, had m.p. 216—217 °C (decomp.) (Found: C, 69.2; H, 7.55. $C_{18}H_{23}N_3O_2$ requires C, 68.98; H, 7.40%).

Oxidation of the Bridged Ketones (5a) *and* (5b). (±)-1β-*Methyl*-1,2,3,4,4a,9aβ-*hexahydro*-1α,4aα-*ethanofluoren*-9,11-*dione* (12a).—To a magnetically stirred solution of the ketone (5a) (700 mg, 3.09 mmol) in glacial acetic acid (9.6 ml) was added a solution of chromium trioxide (1.4 g, 14 mmol) in glacial acetic acid (6.4 ml) and water (4 ml) when the mixture became hot. It was stirred for 48 h at room temperature and warmed to 60 °C for 2 h. After diluting the mixture with water (*ca.* 70 ml), the organic material was extracted into ether. The extract was washed with 2% aqueous sodium hydroxide and water and dried (Na_2SO_4). Removal of the ether afforded a pale yellow liquid (550 mg); $\nu_{max.}$ 1 730, 1 710, and 1 600 cm^{-1}. T.l.c. in benzene–ethyl acetate (4 : 1 v/v) showed the presence of two components (R_F *ca.* 0.5 and 0.6). The product was subjected to column chromatography on neutral alumina which led to the isolation of two fractions. Fraction 1, a pale yellow liquid (310 mg) eluted with light petroleum, was identical with the starting ketone (5a) (t.l.c. and i.r.). Fraction 2, a white crystalline solid, (160 mg, 38% based on recovered ketone), m.p. 85—86 °C, was eluted with benzene–light petroleum (1 : 3 v/v). Recrystallisation from ether–light petroleum afforded the pure *diketone* (12a), m.p. 94 °C [t.l.c. in benzene–ethyl acetate (4 : 1 v/v) showed a single spot, R_F (*ca.* 0.5)] (Found: C, 79.85; H, 6.55. $C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71%); $\nu_{max.}$ 1 730, 1 710, and 1 600 cm^{-1}; $\lambda_{max.}$ 248 and 295 nm (log ε 3.9 and 3.3); δ ($CDCl_3$) 0.71 (s, $\rangle CCH_3$), 1.70—2.33 (m, 6 H, methylenes), 2.79 (H_A) and 2.87 (H_B) (AB q, *J* 5 Hz, $-COCH_2-$ overlapped with the singlet at 2.81

for $COCH\langle$); *m/e* 240 (M^+, 100%), 225 (41), 212 (27), 197 (42), and 183 (23).

(±)-7-*Methoxy*-1β-*methyl*-1,2,3,4,4a,9aβ-*hexahydro*-1α,4aα-*ethanofluorene*-9,11-*dione* (12b).—To a magnetically stirred solution of the ketone (5b) (300 mg, 1.17 mmol) in glacial acetic acid (3.6 ml) was added a solution of chromium trioxide (360 mg, 3.6 mmol) in glacial acetic acid (2.4 ml) and water (1.5 ml). The mixture became hot. It was stirred for 48 h at room temperature and then warmed to 60 °C for 30 min. Work-up as described above for the preparation of (12a) followed by removal of the ether afforded a pale yellow liquid (255 mg), $\nu_{max.}$ 1 740, 1 715, and 1 615 cm^{-1}. T.l.c. in benzene–ethyl acetate (4 : 1 v/v) showed two spots (R_F *ca.* 0.5 and *ca.* 0.6). Careful chromatography of the product on neutral alumina gave two fractions. Fraction 1, a pale yellow liquid eluted with benzene–light petroleum (1 : 3 v/v) was identical with the starting ketone (5b) (t.l.c. and i.r.). Fraction 2, a white crystalline solid (64 mg, 36% based on recovered ketone) was eluted with benzene–light petroleum (1 : 1 v/v). Recrystallisation from ether–light petroleum afforded the pure *diketone* (12b), m.p. 83—84 °C; t.l.c. in benzene–ethyl acetate (4 : 1 v/v) showed a single spot (R_F *ca.* 0.5) (Found: C, 75.45; H, 6.95. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71%); $\nu_{max.}$ 1 740, 1 715, and 1 615 cm^{-1}; $\lambda_{max.}$ 222, 252, and 325 nm (log ε 4.2, 3.7, and 3.2); δ ($CDCl_3$) 0.75 (s, 3 H, $\rangle CCH_3$), 1.51—2.35 (m, 6 H, methylenes), 2.77 (H_A) and 2.89 (H_B) [AB q, *J* 5 Hz, $COCH_2$, overlapped with a singlet at δ 2.81 ($COCH\langle$)], and 3.88 (s, 3 H, OCH_3); *m/e* 270 (M^+, 100), 242 (29), and 227 (88).

Hydroxymethylation followed by Oxidation of the Bridged Ketones (5a) *and* (5b). (±)-1β-*Methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylic Acid* (14a).—A magnetically stirred suspension of sodium hydride (3.6 g, 0.15 mmol) in dry benzene (5 ml) was cooled in an ice-bath under nitrogen. A small portion (*ca.* 0.2 ml) of a solution of the ketone (5a) (1.07 g, 4.7 mmol) in dry benzene (8 ml) was added followed by addition of a drop of dry methanol. The remainder of the solution was then added dropwise at an even rate. After complete addition, the reaction mixture was stirred for an additional 30 min in the cold. Ethyl formate (4 ml, 48.8 mmol) was then added dropwise to the stirred mixture and stirring was continued for a further 2 h and then left overnight. The excess of sodium hydride was decomposed by dropwise addition of methanol to the cooled reaction mixture followed by water (200 ml). The neutral material was extracted with ether to afford a small amount of a brown gum which was not characterised.

The basic aqueous part and the washings were chilled together and acidified with 6N-HCl. The organic material was extracted with ether to afford the hydroxymethylene ketone (1.0 g, 83%) as a brown gum, $\nu_{max.}$ 1 710, 1 660, and 1 600 cm^{-1}, which responded to the ferric chloride colour reaction. This product, without further purification, was dissolved in aqueous sodium hydroxide (70 ml; 10%) and maintained at 10—15 °C (bath temperature). To it was added dropwise with stirring aqueous hydrogen peroxide (35 ml; 30%) over 20—25 min. A vigorous reaction started immediately after addition of a few drops of the hydrogen peroxide solution. Stirring was continued for an additional 2 h. A second aliquot of aqueous sodium hydroxide (35 ml; 10%) was added in one portion followed by dropwise addition of hydrogen peroxide solution (25 ml; 30%). The mixture was stirred for 3 h and then allowed to sit overnight after which time the initial pink colour of the solution had disappeared completely. The mixture was diluted with water and the neutral material was extracted with ether. The negligible residue left after evaporation of the ether was rejected.

The combined basic aqueous part and the washings were chilled together and acidified with ice-cold 6N-HCl. The separated white solid acid was filtered off and repeatedly washed with cold water. The filtrate was extracted with ethyl acetate to afford an additional amount of the acid. The combined product was crystallised from ethanol–acetone to afford the *acid* (14a) (900 mg, 70%), m.p. 206—207 °C (decomp.) (from tetrahydrofuran–light petroleum) (Found: C, 69.85; H, 6.6. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%); $\nu_{max.}$ (Nujol) 1 700 cm^{-1}.

(±)-*Dimethyl* 1β-*Methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylate* (15a).—The dicarboxylic acid (14a) (250 mg) was esterified with an excess of diazomethane in ice-cold ether. The pale yellow liquid ester was purified by filtration (in petroleum) through a short-packed column of neutral alumina to afford the diester (15a) (250 mg; 93%) as a liquid. An analytical sample was prepared by evaporative distillation, b.p. 123—127 °C at 0.05 mmHg (bath temperature); R_F *ca.* 0.69 [benzene–ethyl acetate (4 : 1 v/v)] (Found: C, 71.65; H, 7.65. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%); $\nu_{max.}$ 1 725 cm^{-1}; δ (CCl_4) 0.90 (s, 3 H, $\rangle CCH_3$), 1.95br (s, 6 H), 2.95 and 3.28 (partially resolved quartet of ABX system, J_{AB} 13, J_{AX} 3, J_{BX} 3 Hz, $ArCH_2$ and signal for 1 H masked under these peaks), 3.55 (s, 3 H, CO_2CH_3), 3.60 (s, 3 H, $^-CO_2CH_3$), and 7.08 (s, 4 H, ArH).

(±)-7-*Methoxy*-1β-*methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylic Acid* (14b).—Following the procedure described for (5a) the ketone (5b) (1.1 g, 4.2 mmol) was converted into its hydroxymethylene derivative by reaction in benzene (12 ml) with sodium hydride (4 g, 0.16 mol) in benzene (10 ml) followed by addition of ethyl formate (8 ml, 97.6 mmol). The hydroxymethylene ketone (1.15 g, 94%, $\nu_{max.}$ 1 710, 1 660, and 1 600 cm^{-1} was obtained as a pink gummy mass which gave a positive ferric chloride colour reaction. This crude product (1.15 g), dissolved in aqueous sodium hydroxide (92 ml; 10%), was oxidised by addition of aqueous hydrogen peroxide (46 ml; 30%) followed by addition of a second portion of aqueous sodium hydroxide (46 ml; 10%) and hydrogen peroxide (30 ml; 30%) after 2 h. The mixture was stirred at room temperature for an additional 3 h and then left overnight. It was diluted with water and worked up with ether. The small amount of residue left after evaporation of the ether was rejected.

The combined basic aqueous part and the washings were chilled and acidified with 6N-HCl. The precipitated solid was filtered off and washed with cold water. The filtrate was extracted with ethyl acetate to afford further acid. The combined solid was crystallised from ethanol–acetone to afford the *acid* (14b) (950 mg, 73%), m.p. 212—213 °C (decomp.) (from tetrahydrofuran–light petroleum) (Found: C, 66.9; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%); $\nu_{max.}$ (Nujol) 1 705 and 1 605 cm^{-1}.

(±)-*Dimethyl* 7-*Methoxy*-1β-*methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylate* (15b).—The dicarboxylic acid (14b) (400 mg) was esterified with an excess of ice-cold ethereal diazomethane. The pale yellow liquid, on filtration through a short-packed neutral alumina column in petroleum, afforded the *diester* (15b) (400 mg, 92%), m.p. 83 °C (from petroleum) (Found: C, 68.45; H, 7.3. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.28%); $\nu_{max.}$ 1 720 and 1 605 cm^{-1}; R_F *ca.* 0.6 [benzene–ethyl acetate (4 : 1 v/v)]; δ (CCl_4) 0.90

(s, 3 H, $\geq CCH_3$), 1.88br (s, 6 H), 2.84 and 3.35 (partially resolved q, J_{AB} 13, J_{AX} 2, J_{BX} 2 Hz, $ArCH_2$, and a signal for 1 H masked under this pattern), 3.50 (s, 3 H, CO_2CH_3), 3.56 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, OCH_3), 6.46—6.61 (mixed dd, 2 H, $J_{6,5}$ 9, $J_{6,8}$ 2 Hz, 6-H), and 6.90 (d, 1 H, $J_{5,6}$ 9 Hz, 5-H); *m/e* 332 (M^+, 79%), 300 (100), 272 (48), 244 (30), 213 (58), and 185 (26).

(±)-1β-*Methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylic Anhydride* (16a).—The dicarboxylic acid (14a) (150 mg) was refluxed with acetyl chloride (4.8 ml) for 2 h when the solid gradually went into solution. The excess of acetyl chloride was distilled out *in vacuo* to afford the crystalline *anhydride* (16a) (115 mg, 80%), m.p. 105 °C (from tetrahydrofuran–light petroleum) (Found: C, 74.7; H, 6.3. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%); $\nu_{max.}$ 1 800 and 1 750 cm^{-1}.

(±)-7-*Methoxy*-1β-*methyl*-1,2,3,4,4a,9aβ-*hexahydrofluorene*-1α,4aα-*dicarboxylic Anhydride* (16b).—The dicarboxylic acid (14b) (200 mg) was refluxed with acetyl chloride (6 ml) for 2 h. The excess of acetyl chloride was distilled out *in vacuo* to afford the crystalline *anhydride* (16b) (170 mg, 95%), m.p. 123 °C (from tetrahydrofuran–light petroleum) (Found: C, 71.4; H, 6.2. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%); $\nu_{max.}$ 1 800, 1 750, and 1 605 cm^{-1}.

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