Diterpenoids. Part XVIII.[1] Synthesis and Stereochemistry of 1,2,3,4,-4a,9a-Hexahydro-1β,4aα-dimethylfluorene-1α,9-dicarboxylic Acids

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A reduced fluorene derivative (III) regarded as a basic skeleton of gibberellins was previously synthesized from (−)-abietic acid (I) by a benzilic acid rearrangement of a diketo-ester (II). The four possible stereoisomers, the 1,2,3,4,4a,9a-hexahydro-1β,4aα-dimethylfluorene-1α,9-dicarboxylic acids (VIII), (IX), (XIV), and (XV), and their esters, (X), (XI), (XII), and (XIII), have been prepared from (III) for the synthesis of the gibberellin skeleton. Their stereochemistry is discussed.

CHEMICAL conversion of diterpenoids having a reduced phenanthrene skeleton [*e.g.*, (−)-abietic acid (I)] into compounds having a reduced fluorene skeleton (*e.g.* gibberellin, the plant growth-promoting substance) is an attractive problem. In the sixties, this problem was independently investigated both by I.C.I.[2] and our own group.[3] Benzilic acid rearrangement of the diketo-ester (II), obtained from (−)-abietic acid (I), gave the hydroxy-diacid (III) under alkaline conditions. The rearranged acid (III) clearly had a reduced fluorene skeleton, but its stereochemistry [2] was open to discussion.†

Since structure (IV), lacking the hydroxy-group of the hydroxy-diacid (III), is close to that of C_{20}-gibberellin (*e.g.*, gibberellin A_{12}), compound (IV) could be regarded as a potential intermediate for the synthesis of natural diterpenoids. Four possible stereoisomers are possible owing to the two asymmetric centres at C-9 and C-9a of the diacid (IV); all of these have been synthesized as reported herein.

The hydroxy-diacid (III) obtained by a benzilic acid rearrangement was chosen as the starting material. First, the hydroxy-diacid (III) and the ester [2] (V) were dehydrated by sulphuric acid–acetic acid at 100° to give the Δ^9-acid ‡ (VII) and the Δ^9-ester ‡ (VI) respectively. The ester (VI) was readily hydrolysed to give the acid (VII) (reflux, KOH–ethylene glycol).

Catalytic hydrogenation of the unsaturated diacid (VII) with 10% palladium–charcoal gave a stereoisomeric mixture consisting of the saturated diacids (VIII) and (IX). Fortunately the differential solubility of the two isomers in ether–light petroleum allowed them to be separated in a crystalline form. Methylation (CH_2N_2) of the isomeric diacids (VIII) and (IX) gave respectively, the methyl ester (X) as crystals and the methyl ester (XI) as an oil.

Alkaline treatment of the isomeric diesters (X) and (XI) under mild conditions (MeONa–MeOH, room temp.) produced epimerization at the C-9 position and transformed the compounds into the stable crystalline isomers (XII) and (XIII). Epimerization of the diester (XI) was accomplished by treatment with alumina; (X) was recovered unchanged when similarly treated. Both compounds were unchanged when heated under reflux in methanol.

The stable diester (XIII) was hydrolysed (reflux, KOH–ethylene glycol–H_2O, 1·5 hr.) to a diacid (XV). In contrast, its isomer (XII) was only partially hydrolysed to a half ester (XVI) under the same conditions; more drastic conditions (reflux, KOH–diethylene glycol–H_2O, 1·5 hr.) gave the diacid (XIV). The half-ester (XVI) gave the diacid (XIV) upon drastic hydrolysis. Both the diacids (XIV) and (XV) were converted into the corresponding stable diesters (XII) and (XIII) by methylation (CH_2N_2).

The resulting four esters (X), (XI), (XII), and (XIII) and acids (VIII), (IX), (XIV), and (XV) have distinctive physical characteristics (m.p., i.r., and n.m.r. spectra)

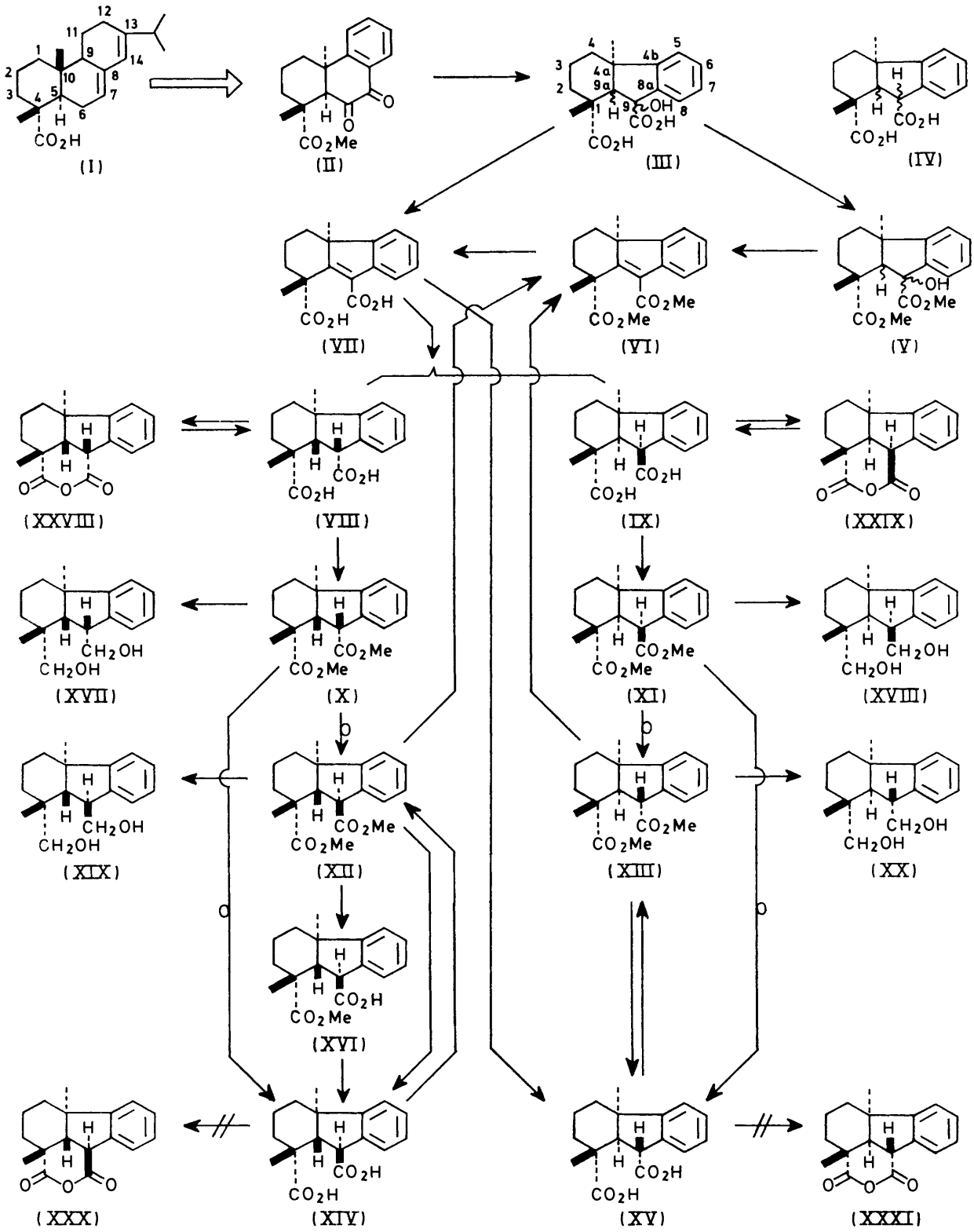
† A report on its stereochemistry will be published in near future.

‡ The diacid (VII) and the diester (VI) were synthesized *via* the Δ^9-anhydride obtained from the hydroxy-diacid (III).[2]

[1] Preliminary communication: *Chem. Pharm. Bull.* (*Japan*), 1970, **18**, 859. Part XVII, A. Tahara and Y. Ohtsuka, *ibid.*, 1971, **19**, 1768.

[2] J. F. Grove and B. J. Riley, *J. Chem. Soc.*, 1961, 1105.

[3] A. Tahara, *Chem. Pharm. Bull.* (*Japan*), 1961, **9**, 252; A. Tahara and O. Hoshino, *ibid.*, **9**, 655; *Sci. Papers Inst. Phys. Chem. Res.* (*Japan*), 1962, **56**, 84, 88.


(I)
(II)
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a
b
c

which distinguishes them from each other. Furthermore, the diols (XVII), (XVIII), (XIX), and (XX) formed by $LiAlH_4$-reduction of the isomeric esters (X), (XI), (XII), and (XIII) respectively also have characteristic physical properties.

In order to examine whether or not the reduced fluorene skeleton was retained during the alkaline C-9 epimerization [(X) ⟶ (XII) and (XI) ⟶ (XIII)], the stable esters (XII) and (XIII) were converted into the original unsaturated ester (VI). The experiments were carried out by *N*-bromosuccinimide bromination with addition of benzoyl peroxide [(XII) refluxed in CCl_4 for 40 hr.; (XIII) refluxed in CCl_4 for 6 hr. after being stirred overnight at room temperature] and successive dehydrobromination (KOH–H_2O).

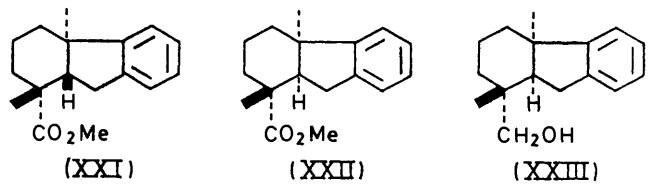
The four diesters as well as the diacids or diols, synthesized *via* catalytic hydrogenation of the diacid (VII) and successive C-9 epimerization, are expressed as a general formula (IV) and, accordingly, correspond to all the possible stereoisomers having asymmetric centres at C-9 and C-9a.

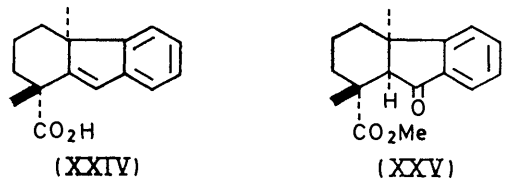
Their structure including stereochemistry will be discussed below:

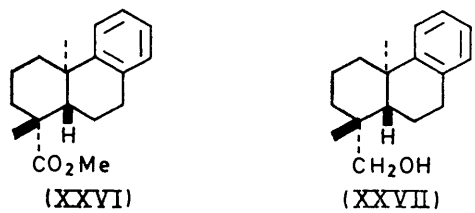
(1) *Determination of the* A/B-*Ring Junction.*—The diesters having a *cis*-A/B ring junction have a non-steroidal conformation; this is proved later. From molecular models of the stable forms (XII) and (XIII) of the four diesters, the C-9 methoxycarbonyl group is located far from the C-4a methyl group so that anisotropic interaction can be considered to be negligible. Accordingly, the chemical shift of the C-4a methyl in the *trans*-isomer (XXI) (τ 9·18) and the *cis*-isomer (XXII) (τ 8·84) which lack methoxycarbonyl groups at C-9 may be compared with that for the diesters (XII) (τ 9·13) and (XIII) (τ 8·82). This observation indicates clearly that one, (XII), of the diesters has a *trans*-A/B ring junction and the other, (XIII), has a *cis*-one.

It was assumed that the *cis*-compound (XXII) should also have a nonsteroidal form as in the diester (XIII). Since a comparison of the chemical shifts for the ester (XXII) (4a-Me, τ 8·84) and the corresponding alcohol (XXIII) (4a-Me, τ 8·61) showed the presence of a strong anisotropic effect between the C-1 methoxycarbonyl group and the C-4a methyl group, this assumption was taken to be correct.

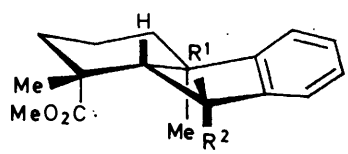
Further proof of the stereochemistry of the A/B-ring fusion was given by thermodynamically controlled reduction of the unsaturated diacid (VII) with lithium–ethylamine. The methyl ester of the sole reduction product was identified as the diester (XIII). In general, *cis*-A/B ring fusion in analogous reduced fluorene systems is considered to be likely because (i) the product of the reduction of the unsaturated acid (XXIV) with lithium–ethylamine is the isomer (XXII) having *cis*-A/B ring fusion [4] and (ii) an oxo-ester (XXV) having a *cis*-A/B ring fusion is the stable form; [4] thus the stable compound (XV) is believed to have a *cis*-A/B ring junction. Accordingly, the unstable isomers (X) and (XI) before C-9 epimerization should have the structure corresponding to A/B-ring fusion of the stable esters (XII) and (XIII) respectively.







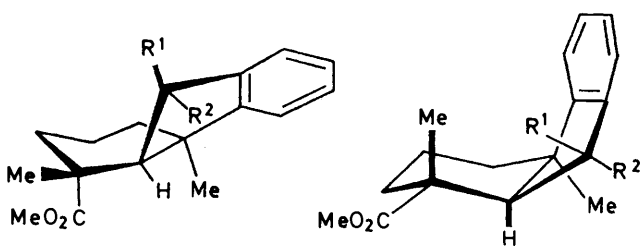
(2) *Configuration of the Methoxycarbonyl Group at C-9.*—Molecular models of the isomers (X) and (XII) having a *trans*-A/B ring junction show that the *quasi-axial* (*qu.-ax.*) (α-configuration) methoxycarbonyl group



A/B-*trans*

(X) $R^1 = H, R^2 = CO_2Me$

(XII) $R^1 = CO_2Me, R^2 = H$



Nonsteroidal form Steroidal form

A/B-*cis*

(XI) $R^1 = CO_2Me, R^2 = H$

(XIII) $R^1 = H, R^2 = CO_2Me$

at C-9 is undoubtedly more sterically hindered than the *quasi-equatorial* (*qu.-eq.*) (β-configuration) one. In the case of other isomers, (XI) and (XIII), having a *cis*-

[4] A. Tahara, O. Hoshino, and T. Ohsawa, *Chem. Pharm. Bull.* (*Japan*), 1969, **17**, 68.

A/B ring junction, the nonsteroidal conformation has a more hindered *qu.-ax.* (β-configuration) methoxycarbonyl group at C-9 than *qu.-eq.* (α-configuration) one; the steroidal conformation, however, gives rise to approximately equal hindrance for the *qu.-ax.* methoxycarbonyl substituent at C-9 as that for the *qu.-eq.* group. Since the nonsteroidal conformation may be assigned to (XI) and (XIII) as will be described later, there is a definite difference in stability between *qu.-ax.* and *qu.-eq.* substituents in both isomers having *trans-* [(X) and (XII)] and *cis*-A/B ring fusion [(XI) and (XIII)].

From a consideration of the stability of the methoxycarbonyl group at C-9, alkaline epimerization at that position [(X) ⟶ (XII) and (XI) ⟶ (XIII)] should result in the conversion of *qu.-ax.* [α-configuration in the *trans*-isomer (X) and β in *cis*-isomer (XI)] to *qu.-eq.* [β-configuration in *trans*-isomer (XII) and α in *cis*-isomer (XIII)].

In view of the results so far achieved, the configurational relation between the hydrogens at C-9a and C-9 in the unstable isomers (X) and (XI) would be β-*cis* and α-*cis*, respectively. Taking it into account that the unstable diacids (VIII) and (IX) are hydrogenated products of the Δ^9-ester (VII), the assigned configurations are consistent with *cis*-addition of hydrogen during catalytic hydrogenation.

The above assignments are further supported by anhydride formation. As shown from molecular models, it is evident that the unstable diacids [9aβ-H and 9α-CO_2H in (VIII); 9aα-H and 9β-CO_2H in (IX)] can form anhydrides whilst the stable diacids [9aβ-H and 9β-CO_2H in (XIV); 9aα-H and 9α-CO_2H in (XV)] cannot. Thus, when the unstable diacids (VIII) and (IX) were refluxed in acetic anhydride, they formed the anhydrides (XXVIII) and (XXIX), respectively, in a satisfactory yield. An attempt under the same condition failed for the stable diacids [(XIV) ⟶// (XXX) and (XV) ⟶// (XXXI)]. The anhydrides (XXVIII) and (XXIX) of the unstable diacids were hydrolysed (KOH aq.) under a mild condition and successively methylated (CH_2N_2) to give the original diesters (X) and (XI).

(3) *Conformation of an Isomer having* cis-A/B *Ring Fusion.*—The preferred conformation of the *cis*-isomers (XI) and (XIII) will be first discussed in terms of the relationship between the vicinal coupling constant (J) and the corresponding dihedral angle (ϕ) between the protons at C-9 and C-9a. Using the equation of Williamson and Johnson,[5] the coupling constants were calculated from the dihedral angle of conformational models of the unstable *cis*-isomer (XI) (ϕ in nonsteroidal form = 30°, calc. J = 7·5 Hz; ϕ in steroidal form = 25°, calc. J = 8·2 Hz) and the stable isomer (XIII) (ϕ in nonsteroidal form = 150°, calc. J = 12 Hz; ϕ in steroidal form = 95°, calc. J = 0·12 Hz).

As shown by the calculated J values, although there is no great difference in coupling constants between the conformations of the unstable isomer (XI), the J value of the nonsteroidal form is very different from that of the other steroidal conformation of the stable one (XIII). Accordingly, the observed J value of the stable diester (XIII) [11 Hz; *cf.* 9 Hz in the unstable diester (XI)] can be compared with the corresponding calculated value (12 Hz for nonsteroidal and 0·12 Hz for steroidal form). Thus the *cis*-diester (XIII) has a nonsteroidal conformation.

The above assumption was supported by the differences in chemical-shift due to C-4a methyl group. Although the anisotropic effect of the methoxycarbonyl group at C-9 on the C-4a methyl must be taken into account for the steroidal form of the stable diester (XIII; *qu.-eq.*-CO_2Me), the effect exists in neither conformation of the unstable isomer (XI; *qu.-ax.*-CO_2Me). Accordingly, the conformation at the *cis*-A/B ring junction can be discussed in terms of the anisotropic effect of the methoxycarbonyl group at C-1 on the C-4a methyl of the unstable diester (XI) there being no effect of the C-6 methoxycarbonyl on the C-4a methyl. The methoxycarbonyl at C-1 of the diester (XI) is located close to the C-4a methyl group in the nonsteroidal conformation, but is far from the C-4a methyl in the steroidal form. The spatial relation of the two groups in the nonsteroidal conformation resembles that in the podocarpic-type compound (XXVI).

As reported previously,[6] the methoxycarbonyl group at C-4 influences the C-10 methyl group of the ester (XXVI) (10-Me, τ 8·97); thus, chemical shifts due to the C-10 methyl are towards a lower magnetic field when the ester (XXVI) is converted into the alcohol (XXVII) (10-Me, τ 8·82). If the unstable reduced fluorene ester (XI) has a nonsteroidal form, the chemical shift of the 4a-methyl group should be similar to that in the reduced phenanthrene ester (XXVI). In fact, the 4a-Me chemical shift for (XI) (τ 8·81) is reduced in the alcohol (XVIII) (τ 8·67) thus supporting a nonsteroidal conformation for the *cis*-isomer (XI) and, thus, (XIII).

EXPERIMENTAL

All m.p.s except mixed m.p.s were measured with a Kofler block and are uncorrected. N.m.r. spectra were measured at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal reference; high-resolution mass spectra were taken with a JMS-01SG spectrometer.

Dehydration of Dimethyl 1,2,3,4,4a,9a-*Hexahydro*-9-*hydroxy*-1β,4aα-*dimethylfluorene*-1α,9-*dicarboxylate* (V).—A solution of the hydroxy-diester (V) (200 mg.) in AcOH (10 ml.)–conc. H_2SO_4 (5 drops) was heated at 98—102° for 2 hr. After water (*ca.* 1 ml.) had been added to the reaction mixture, half the solvent was evaporated off under reduced pressure. The mixture was diluted with water and extracted with ether. The ether extract was washed with aqueous Na_2CO_3, and then saturated aqueous NaCl; it was then dried (Na_2SO_4) and evaporated to give pale yellow needles (182 mg.). The crystals were recrystallized

[5] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623.

[6] A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (*Japan*), 1964, **12**, 1458; A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, 1965, **21**, 2133.

from MeOH–H_2O to give needles (165 mg.), m.p. 117—119°; the compound was identical (m.p., mixed m.p., and i.r.) with the unsaturated diester (VI) synthesized *via* Grove's route.[2]

Alkaline Hydrolysis of Dimethyl 2,3,4,4a-*Tetrahydro*-1β,4aα-*dimethyl*-1H-*fluorene*-1α,9-*dicarboxylate* (VI).—A solution of the unsaturated diester (VI) (200 mg.) and KOH (800 mg.) in ethylene glycol (20 ml.)–H_2O (0·8 ml.) was heated under reflux for 90 min. and then diluted with H_2O. The mixture was acidified and extracted with ether. The extract was washed with H_2O and then with 10% aqueous KOH; the alkaline extract was acidified and extracted with ether. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to give crude crystals (207 mg.). The crystals were recrystallized from MeOH–H_2O to afford needles (176 mg.), m.p. 200·5—201·5°; the compound was identical (m.p., mixed m.p., and i.r.) with the unsaturated diacid (VII) synthesized *via* Grove's route.[2]

Dehydration of 1,2,3,4,4a,9a-*Hexahydro*-9-*hydroxy*-1β,4aα-*dimethylfluorene*-1α,9-*dicarboxylic Acid* (III).—A solution of the hydroxy-diacid (III) (200 mg.) in AcOH (10 ml.)–conc. H_2SO_4 (5 drops) was treated as in the case of the dehydration of the diester (V). The crystals (163 mg.) obtained were recrystallized from MeOH–H_2O to give needles (154 mg.), 198—199°; the compound was identical (m.p. and g.l.c. of diester) with the unsaturated diacid (VII) synthesized *via* Grove's route.[2]

Catalytic Hydrogenation of 2,3,4,4a-*Tetrahydro*-1β,4aα-*dimethyl*-1H-*fluorene*-1α,9-*dicarboxylic Acid* (VII). 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (VIII) *and* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (IX).—A solution of the dicarboxylic acid (VII) (1·500 g.) in MeOH (250 ml.) was stirred in the presence of 10% Pd–C (1·00 g.) under a hydrogen atmosphere at room temperature. After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated to give the residue. Ether containing a little light petroleum was added to this to give crystals (330 mg.), m.p. 222—224°; these were filtered off and the filtrate was evaporated to give the oil. Some of the crystalline material (70 mg.) was purified by chromatography on silicic acid–Celite (1 : 1) (5 g.) to obtain an analytical sample. The crystals (57 mg.) which were eluted with light petroleum–ether (4 : 1) were recrystallized from MeOH–H_2O to give needles (42 mg.) (VIII), m.p. 233—235° (Found: C, 70·85; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%); $\nu_{max.}$ (KBr) 1714, 1695, 1247, 777, and 775 cm.$^{-1}$; τ (sparing solubility in $CDCl_3$) 8·76 (s, 3H, 4a-Me) and 8·525 (s, 3H, 1-Me).

Otherwise, the latter oil was again crystallized from ether containing light petroleum to give prisms (742 mg.), m.p. 177—181·5°. A portion of the crystalline material (200 mg.) was chromatographed on silicic acid–Celite (1 : 1) (10 g.) to obtain an analytical sample. The oil (198 mg.) separated from the light petroleum–ether (4 : 1) elution was crystallized from light petroleum–ether to give prisms (149 mg.) (IX), m.p. 181·5—184° (Found: C, 70·95; H, 7·1. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%), $\nu_{max.}$ (KBr) 1713, 1695, 1230, 763, and 755 cm.$^{-1}$; τ 8·895 and 8·77 (s, 3H each; 1- and 4a-Me).

Methylation of 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (VIII) *and* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (IX). *Dimethyl* 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (X) *and Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XI).—Methylation of dicarboxylic acids (VIII) (100 mg.) and (IX) [containing 4·5% of (VIII) having *trans*-A/B ring fusion] (150 mg.) with an excess of CH_2N_2–ether solution gave crystals and oil, respectively. The crystals were recrystallized from MeOH–H_2O to give prisms (X) (100 mg.), m.p. 132—134° (Found: C, 71·95; H, 7·85. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ (KBr) 1730, 1720, 1235, 1200, 1167, 1150, and 773 cm.$^{-1}$; τ 8·89 (s, 3H, 4a-Me), 8·57 (s, 3H, 1-Me), 6·39 (s, 3H, CO_2Me), 6·275 (s, 3H, CO_2Me), 7·725 (d, 1H, *J* 8·5 Hz, 9aβ-H), and 5·85 (d, 1H, *J* 8·5 Hz, 9β-H).

The oil was chromatographed on silica gel (8 g.) with light petroleum–ether (19 : 1) as eluant to give two fractions of oil (106 mg. and 32 mg.). Gas-liquid chromatography (1·5% OV-17 on Shimalite W, 4 mm. × 1·8 m., 220°) of both fractions showed that the latter oil was a mixture consisting of (X) (R_t = 4·0 min.) and (XI) (R_t = 3·5 min.); the former fraction was pure (XI) (Found: C, 71·8; H, 7·65. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ (film) 1735 (shoulder), 1728, 1235, 1194, 1144, and 762 cm.$^{-1}$; τ 8·81 (s, 6H, 1- and 4a-Me), 6·34 (s, 6H, 1- and 9-CO_2Me), 6·77 (d, 1H, *J* 9·0 Hz, 9aα-H), and 5·77 (d, 1H, *J* 9·0 Hz, 9α-H).

Epimerization of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (X). *Dimethyl* 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XII).—A solution of the diester (X) (110 mg.) in MeONa–MeOH [Na metal (240 mg.) in MeOH (40 ml.)] was set aside at room temperature for 4 days. After the solvent had been removed under reduced pressure, the resulting residue was diluted with H_2O and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give crystals (109 mg.); these were recrystallized from MeOH–H_2O to give plates (98 mg.) (XII), m.p. 124—126° (Found: C, 72·35; H, 7·8. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ (KBr) 1728, 1142, 773, and 745 cm.$^{-1}$; τ 9·125 (s, 3H, 4a-Me), 8·805 (s, 3H, 1-Me), 6·305 (s, 3H, CO_2Me), 6·205 (s, 3H, CO_2Me), 7·62 (d, 1H, *J* 1·15 Hz, 9aβ-H), and 5·48 (d, 1H, *J* 11·5 Hz, 9α-H).

The diester (X) was treated with neutral alumina (5 days at room temp.) or MeOH (refluxed for 60 min.) under the same conditions as for the diester (XI). The resulting crystals were identical (n.m.r.) with the starting material (X).

Epimerization of Dimethyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XI). *Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII).—(1) *Epimerization by* MeONa–MeOH. A solution of the oily diester (XI) (24 mg.) in MeONa–MeOH [Na metal (10 mg.) in MeOH (5 ml.)] was set aside for 20 hr. at room temperature. The solvent was removed under reduced pressure and the resulting residue was diluted with H_2O and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give crystals (24 mg.), which were recrystallized from MeOH–H_2O to give needles (XIII) (15 mg.), m.p. 111—113° (Found: C, 72·1; H, 7·8. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ (KBr) 1740, 1720, 1215, 1167, and 765 cm.$^{-1}$; τ 8·82 (s, 3H, 4a-Me), 8·72 (s, 3H, 1-Me), 6·27 (s, 3H, CO_2Me), 6·17 (s, 3H, CO_2Me), 6·55 (d, 1H, *J* 11·0 Hz, 9aα-H), and 5·99 (d, 1H, *J* 11·0 Hz, 9β-H).

(2) *Epimerization by* Al_2O_3*–treatment.* Neutral alumina (3 g.) was added to a solution of the oily diester (XI) (23 mg.) in ether (2 ml.) and the solvent was evaporated. The mixture was set aside for 4 days at room temperature and then extracted with ether. Evaporation of the ether gave crystals (17 mg.), which was identical (m.p., mixed m.p., i.r., n.m.r.) with the epimerized diester (XIII).

However, the diester (XI) was not epimerized by refluxing in MeOH for 60 min.

Drastic Alkaline Hydrolysis of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XII). 1,2,3,4,4a,9aβ-*Hexahydro*-1β,9aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (XIV).—A solution of the diester (XII) (50 mg.) and KOH (200 mg.) in diethylene glycol (5 ml.)–H_2O (0·2 ml.) was refluxed for 90 min. and then diluted with H_2O. The resulting mixture was acidified and extracted with ether. The extract was washed with H_2O, then 10% aqueous KOH and the alkaline extract was acidified, extracted again with ether. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to give crude crystals (50 mg.), which were recrystallized from light petroleum–ether to give needles (XIV) (27·5 mg.), m.p. 262·5—264° * (Found: C, 70·8; H, 7·25. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%), $\nu_{max.}$ (KBr) 1710, 1300, 1220, 771, and 745 cm.$^{-1}$; τ 9·02 (s, 3H, 4a-Me), 8·67 (s, 3H, 1-Me), 7·58 (d, 1H, *J* 11·0 Hz, 9aβ-H), and 5·38 (d, 1H, *J* 11·0 Hz, 9α-H).

Drastic Alkaline Hydrolysis (*with Epimerization at C*-9) *of Dimethyl* 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (X).—The diester (X) (50 mg.) was hydrolysed under the same conditions as those described for the diester (XII). The resulting crystals (54 mg.) were recrystallized from light petroleum–ether to give prisms (36 mg.), which were identical (m.p., mixed m.p., i.r.) with those of epimerized diacid (XIV).

Alkaline Hydrolysis of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XII). 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α-*methoxycarbonyl*-9β-*carboxylic Acid* (XVI).—A solution of the diester (XII) (50 mg.) and KOH (200 mg.) in ethylene glycol (5 ml.)–H_2O (0·2 ml.) was refluxed for 60 min. The mixture was treated as described for the drastic alkaline hydrolysis of the diester (XII). The oil (55 mg.) obtained was chromatographed on silicic acid–Celite (1 : 1) with light petroleum–ether (9 : 1) as eluant to give crystals. These were recrystallized from light petroleum–ether to give prisms of (XVI) (23 mg.), m.p. 167—168·5° (Found: C, 71·65; H, 7·35. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·35%), $\nu_{max.}$ (CCl_4) 1740, 1715, and 1130 cm.$^{-1}$; τ 9·125 (s, 3H, 4a-Me), 8·73 (s, 3H, 1-Me), 6·295 (s, 3H, 1-CO_2Me), 7·58 (d, 1H, *J* 12 Hz, 9aβ-H), and 5·45 (d, 1H, *J* 12 Hz, 9α-H).

Alkaline Hydrolysis of 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α-*methoxycarbonyl*-9β-*carboxylic Acid* (XVI).—A solution of the half-ester (XVI) (16 mg.) and KOH (90 mg.) in diethylene glycol (2 ml.)–H_2O (0·1 ml.) was refluxed for 60 min. The mixture was treated as in the case of alkaline hydrolysis of the diester (XII). The resulting crystals (22 mg.) were chromatographed on silicic acid–Celite (1 : 1) (5 g.) with light petroleum–ether (4 : 1) as eluant to give crystals (14 mg.). Recrystallization of the crystals from light petroleum–ether gave needles (7 mg.), m.p. 257—260°, which were identical (m.p., mixed m.p., i.r., n.m.r.) with the diacid (XIV).

Alkaline Hydrolysis of Dimethyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII). 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (XV).—A solution of the diester (XIII) (70 mg.) and KOH (300 mg.) in ethylene glycol (7 ml.)–H_2O (0·3 ml.) was refluxed for 90 min. The mixture was treated as described for the alkaline hydrolysis of the diester (XII). The resulting powder (74 mg.) was chromatographed on silicic acid–Celite (1 : 1) (7 g.) with light petroleum–ether (4 : 1) as eluant to give crystals (60 mg.). Recrystallization of the crystals from light petroleum–ether gave needles (XV) (48 mg.), m.p. 161—163° (Found: C, 70·4; H, 7·15. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%), $\nu_{max.}$ (KBr) 1695, 1301, 1225, and 754 cm.$^{-1}$; τ 8·65 (s, 6H, 1- and 4a-Me), 6·57 (d, 1H, *J* 10·5 Hz, 9aα-H), and 6·04 (d, 1H, *J* 10·5 Hz, 9β-H).

Alkaline Hydrolysis (*with Epimerization at C*-9) *of Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XI).—A solution of the oily diester (XI) (510 mg.) and KOH (2 g.) in ethylene glycol (25 ml.)–H_2O (1 ml.) was refluxed for 90 min. The mixture was treated as described for the alkaline hydrolysis of the diester (XII). The resulting pale yellow powder (480 mg.) was chromatographed on silicic acid–Celite (1 : 1) (50 g.) with light petroleum–ether (4 : 1) as eluant to give crystals. A portion (30 mg.) was recrystallized from light petroleum–ether to give needles (19 mg.), m.p. 158—160° which were identical (m.p., mixed m.p., i.r., and n.m.r.) of those of the epimerized diacid (XV).

Methylation of 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (XIV) *and* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (XV).—Crystalline material obtained by treatment of the diacid (XIV) (138 mg.) and (XV) (150 mg.) with an excess of CH_2N_2–ether solution was recrystallized from MeOH–H_2O to give prisms (106 mg.), m.p. 123—125° and needles (130 mg.), m.p. 111—113°, respectively. From physical constants (m.p., mixed m.p., i.r., and n.m.r.) these products were identified as the diester (XII) and the diester (XIII) respectively.

Lithium Aluminium Hydride Reduction of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (X). 1,2,3,4,4a,9aβ-*Hexahydro*-1α,9α-*dihydroxymethyl*-1β,4aα-*dimethylfluorene* (XVII).—$LiAlH_4$ (36 mg.) was added to a solution of the diester (X) (31 mg.) in dry ether (16 ml.) and the mixture was refluxed for 6 hr. The mixture was diluted with H_2O, the ether layer was separated, and the water layer was extracted with ether. The combined ether extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give crystals (33 mg.); these were chromatographed on neutral alumina (5 g.) with light petroleum–ether (1 : 2) as eluant to give crystals (25 mg.). These were recrystallized from light petroleum–ether to give needles (XVII) (17 mg.), m.p. 153·5—155° (Found: C, 78·35; H, 9·1. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%), $\nu_{max.}$ (KBr) 3170, 1060, 1052, 1030, and 751 cm.$^{-1}$; τ 8·80, and 8·72 (s, 3H, 1- and 4a-Me); R_t = 11·6 min. (1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°).

Lithium Aluminium Hydride Reduction of Dimethyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XI). 1,2,3,4,4a,9aα-*Hexahydro*-1α,9β-*dihydroxymethyl*-1β-4aα-*dimethylfluorene* (XVIII).—The reaction mixture of the diester (XI) (50 mg.) and $LiAlH_4$ (60

* In our previous communication,[1] the m.p. of this compound was reported as 223—225°, which would presumably be one of the dimorphs.

mg.) in dry ether (30 ml.) was treated as described for the reduction of the diester (X). The resulting oil (45 mg.) was chromatographed on neutral alumina (7 g.) with light petroleum–ether (1 : 2) as eluant to give (XVIII) (40 mg.) as an oil [Found (high resolution mass-spectrometry): *m/e*, 260·1769. $C_{17}H_{24}O_2$ requires *M*, 260·1776], $\nu_{max.}$ (film) 3420, 1030, 765, and 753 cm.$^{-1}$; τ 9·18 (s, 3H, 1-Me) and 8·69 (s, 3H, 4a-Me); R_t = 10·5 min. (1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°).

*Bis-*p*-nitrobenzoate*. The diol (XVIII) (32 mg.) in pyridine (2 ml.) was treated with *p*-nitrobenzoyl chloride (57 mg., 2·5 mol. equiv.). The oil (55 mg.) obtained was twice recrystallized from AcOEt–n-hexane to give the bis-*p*-nitrobenzoate as a powder (26 mg.), m.p. 166·5—169° (Found: C, 66·45; H, 5·7; N, 4·9. $C_{31}H_{30}N_2O_8$ requires C, 66·65; H, 5·4; N, 5·0%), $\nu_{max.}$ (KBr) 1723, 1609, 1530, and 1350 cm.$^{-1}$.

Lithium Aluminium Hydride Reduction of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XII). 1,2,3,4,4a,9aβ-*Hexahydro*-1α,9β-*dihydroxymethyl*-1β,4aα-*dimethylfluorene* (XIX).—The reaction mixture of the diester (XII) (40 mg.) and $LiAlH_4$ (50 mg.) in dry ether (20 ml.) was treated as for the reduction of the diester (X). The oil obtained (37 mg.) was chromatographed on neutral alumina (5 g.) with light petroleum–ether (1 : 2) as eluant to give an oil (XIX) (33 mg.) [Found (by high resolution mass-spectrometry): $M^+ - 18$, *m/e* 242·1665. $C_{17}H_{22}O$ requires 242·1671], $\nu_{max.}$ (film) 3340, 1062, 1030, 790, 765, and 742 cm.$^{-1}$; τ 8·87 and 8·76 (s, 3H, 1- and 4a-Me); R_t = 10·55 min. (1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°).

Bis-3,5-dinitrobenzoate. The diol (XIX) (32 mg.) in pyridine (2 ml.) was treated with 3,5-dinitrobenzoyl chloride (67 mg., 2·37 mol. equiv.). The resulting pale yellow oil was twice recrystallized from AcOEt–n-hexane to give the bis-3,5-dinitrobenzoate as a powder (31 mg.), m.p. 100·5—102° (Found: C, 57·7; H, 4·35; N, 8·55. $C_{31}H_{28}N_4O_{12}$ requires C, 57·45; H, 4·35; N, 8·65%), $\nu_{max.}$ (KBr) 3095, 1737, 1730, 1630, 1548, and 1347 cm.$^{-1}$.

Lithium Aluminium Hydride Reduction of Dimethyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII). 1,2,3,4,4a,9aα-*Hexahydro*-1α,9α-*dihydroxymethyl*-1β,4aα-*dimethylfluorene* (XX).—The reaction mixture of the diester (XIII) (40 mg.) and $LiAlH_4$ (40 mg.) in dry ether (20 ml.) was treated as for the reduction of the diester (X). The resulting oil (41 mg.) was chromatographed on alumina (5 g.) with light petroleum–ether (1 : 2) as eluant to give an oil (27 mg.). The oil was crystallized from MeOH–H_2O to give a powder (XX) (13 mg.), m.p. 119—121° (Found: C, 78·2; H, 9·3. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%), $\nu_{max.}$ (KBr) 3275, 1058, 1040, and 755 cm.$^{-1}$; τ 9·22 (s, 3H, 1-Me) and 8·67 (s, 3H; 4a-Me); R_t = 7·9 min. (1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°).

Bromination and Successive Dehydrobromination of Dimethyl 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XII).—A mixture of the diester (XII) (15 mg.), *N*-bromosuccinimide (40 mg.), and benzoyl peroxide (5 mg.) in CCl_4 (5 ml.) was refluxed for 40 hr. under N_2. The solvent was removed under reduced pressure and 2% aqueous KOH (5 ml.) and MeOH (6 ml.) were added to the resulting residue. The mixture was stirred overnight at room temperature and then diluted with H_2O and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give pale yellow oil (19 mg.); g.l.c. showed this to be a mixture of the unsaturated diester (VI) and the starting diester (XII) [(VI): R_t = 5·55 min. and (XII): 4·40 min. in ratio of 1·5 : 1·0 (ratio of peak area: height × width at half height); 1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°]; the n.m.r. spectrum supported this [pattern due to main compound (VI) τ 8·82, 8·44, 6·33, and 6·06 and due to minor one (XII) τ 9·12, 8·81, 6·27, and 6·17]. The reaction under the same condition as in case of the isomeric diester (XIII) having *cis*-A/B ring fusion gave only the starting material.

Bromination and Successive Dehydrobromination of Dimethyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII).—A mixture of the diester (XIII) (50 mg.), *N*-bromosuccinimide (35 mg.), and benzoyl peroxide (2·0 mg.) in CCl_4 (4 ml.) was stirred overnight at room temperature and then refluxed for 6 hr. under N_2. The resulting mixture was dehydrobrominated as for the diester (XII) mentioned above. The pale yellow crystals obtained (49 mg.) were recrystallized from MeOH–H_2O to give colourless prisms, m.p. 108—114°; these were identical [m.p., mixed m.p., g.l.c. (R_t = 12·1 min.: 1·5% OV-17 on Gaschrom P, 4 mm. × 1·8 m., 200°) and i.r. (CCl_4)] with those of the unsaturated diester (VI).

Anhydride Formation by 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (VIII). 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Anhydride* (XXVIII).—A solution of the dicarboxylic acid (VIII) (50 mg.) in Ac_2O (3 ml.) was refluxed for 100 min. The crude crystals obtained by evaporation of the solvent under reduced pressure, were twice recrystallized from ether to give (XXVIII) (35 mg.) as prisms, m.p. 161—164° (Found: C, 75·4; H, 6·65. $C_{17}H_{18}O_3$ requires C, 75·55; H, 6·7%), $\nu_{max.}$ (KBr) 1800, 1766, and 995 cm.$^{-1}$; τ 9·00 (s, 3H, 4a-Me), 8·54 (s, 3H, 1-Me), 7·79 (d, 1H, *J* 6·75 Hz, 9aβ-H), and 5·91 (d, 1H, *J* 6·75 Hz, 9β-H).

Alkaline Hydrolysis and Successive Methylation 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*di-of carboxylic Anhydride* (XXVIII) *to Dimethyl* 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (X).—A suspension of the anhydride (XXVIII) (25 mg.) in N-aqueous KOH (6 ml.) was stirred for 17 hr. at room temperature. The mixture was then acidified with aqueous HCl with ice-cooling and then extracted with ether; the extract was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave powder (VIII) (22 mg.), which was methylated with CH_2N_2–ether to give a crystalline product. The n.m.r. spectrum of the product was identical with that of the diester (X). The crude crystals were chromatographed on silica gel (5 g.) with light petroleum–ether (19 : 1) as eluant to give crystals (15 mg.) which were recrystallized from MeOH–H_2O to give prisms (7 mg.), m.p. 132—134°; these were identical (m.p., mixed m.p., i.r.) with those of the diester (X).

Anhydride Formation by 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (IX). 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Anhydride* (XXIX).—A solution of the dicarboxylic acid (IX) (100 mg.) in Ac_2O (5 ml.) was refluxed for 100 min. Removal of the solvent under reduced pressure gave crystals (94 mg.), which were recrystallized from light petroleum–ether to give prisms (XXIX) (44 mg.), m.p. 120·5—122° (Found: C, 75·15; H, 6·65. $C_{17}H_{18}O_3$ requires C, 75·55; H, 6·7%), $\nu_{max.}$ (KBr) 1804, 1752, and

1015 cm.$^{-1}$; τ 9·36 (s, 3H, 1-Me), 8·80 (s, 3H, 4a-Me), 7·655 (d, 1H, *J* 7·0 Hz, 9aα-H), and 5·50 (d, 1H, *J* 7·0 Hz, 9α-H).

Alkaline Hydrolysis and Successive Methylation of 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Anhydride* (XXIX) *to Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylate* (XI) *and Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII).—A suspension of the anhydride (XXIX) (25 mg.) in N-aqueous KOH (6 ml.) was stirred for 17 hr. at room temperature and then treated as for the anhydride (XXVIII). The resulting powder (22 mg.) was methylated with CH_2N_2–ether. The n.m.r. spectrum of the methyl ester showed that it consisted of both isomeric esters (XI) and (XIII) in the ratio 5 : 6 (ratio of peak integral due to C–Me and C–CO_2Me).

Attempted Anhydride Formation with 1,2,3,4,4a,9aβ-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9β-*dicarboxylic Acid* (XIV) *and* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylic Acid* (XV).—The dicarboxylic acids (XIV) and (XV) were treated with Ac_2O under the same condition as for the anhydride formation with the dicarboxylic acid (VIII). Removal of the solvent under reduced pressure gave oils, whose i.r. and n.m.r. spectra were identical with those of the starting materials (XIV) and (XV), respectively.

Thermodynamically Controlled Reduction (*Lithium–Ethylamine*) *and Successive Methylation* (*Diazomethane*) *of* 2,3,4,4a-*Tetrahydro*-1β,4aα-*dimethyl*-1H-*fluorene*-1α,9-*dicarboxylic Acid* (VII) *to give Dimethyl* 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α,9α-*dicarboxylate* (XIII).—Lithium (10 mg.) was added to a solution of the dicarboxylic acid (VII) (40 mg.) in $EtNH_2$ (4 ml.) and the mixture was stirred for 1·5 hr. at room temperature. NH_4Cl (100 mg.) was added and the mixture was stirred for a further 1 hr.; the solvent was then removed. The resulting residue was diluted with H_2O, acidified with aqueous HCl and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and the solvent was removed to give a powder (34 mg.); this was methylated with CH_2N_2–ether. The methylated compound was chromatographed on neutral alumina (5 g.) with light petroleum–ether (9 : 1) as eluant to give crystals (14 mg.). These were recrystallized from MeOH–H_2O to give prisms (7 mg.), m.p. 89—100°, whose i.r. (KBr) and n.m.r. spectra were identical with those of the diester (XIII).

Lithium Aluminium Hydride Reduction of Methyl 1,2,3,4,4a,9aα-*Hexahydro*-1β,4aα-*dimethylfluorene*-1α-*carboxylate* (XXII). 1,2,3,4,4a,9aα-*Hexahydro*-1α-*hydroxymethyl*-1β,4aα-*dimethylfluorene* (XXIII).—A mixture of the ester (XXII) (50 mg.) and $LiAlH_4$ (100 mg.) in dry ether (20 ml.) was treated as for the reduction of the diester (X). The resulting oil (47 mg.) was chromatographed on alumina (5 g.) with light petroleum–ether (20 : 1) as eluant to give an oil (45 mg.). A portion (23 mg.) of this was distilled at 90°/0·002 mmHg, to give an analytical sample of (XXIII) (19 mg.) (Found: C, 83·1; H, 9·55. $C_{16}H_{22}O$ requires C, 83·45; H, 9·65%), $\nu_{max.}$ (film) 3355 and 1030 cm.$^{-1}$; τ 9·08 (s, 3H, 1-Me), 8·61 (s, 3H, 4a-Me), and 6·39 (s, 2H, 1-CH_2OH); R_t = 4·5 min. (1·5% OV-17 on Gaschrom P, 4 mm. × 2 m., 180°).

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