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SYNTHETIC STUDIES DIRECTED TO GIBBERELLINS AND RELATED COMPOUNDS[1]

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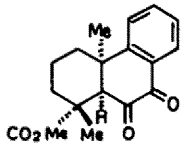
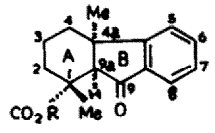
Abstract—A stereoselective total synthesis of (±)1β,4a-α-dimethyl-*cis*-1,2,3,4,4a,9a-hexahydrofluoren-9-one-1α-carboxylic acid (II), has been described. The intermediates involved in this synthesis have been thoroughly investigated and evidence for their stereochemistry presented.

THE chemical conversions[2–5] of the normal hydrophenanthrene diterpenoids or their ring B-seco derivatives to the corresponding B-nor derivatives, featuring the characteristic hydrofluorene ring system of the plant growth active substances, gibberellins,[6] have received increased attention. The first endeavour in this direction was due to Ohta,[2] who transformed the *enantiomer* of methyl 6,7-diketo-5-iso-desoxypodocarpate (I),[2,7] derived from the abietic acid, to the keto acid II through oxidative opening of the B-ring, followed by pyrolytic cyclization of the corresponding tricarboxylic acid. The keto-acid II was reduced to the acid III. Subsequently, a single step transformation of the diketo-ester I to the hydroxy acid IV through benzillic acid rearrangement was realized by two groups.[3a,b,4] On controlled oxidation, the acid IV was converted to the keto-acid II. Grove and Riley[4] represented the keto-acid II by *cis* A/B ring structure, Ohta[2] and Tahara *et al.*[3a,b] did not specify the stereochemistry at the ring junction. However, the keto-acid II and the acid III have been correlated recently[3c] to the authentic samples of known stereochemistry and will be mentioned (*vide infra*).

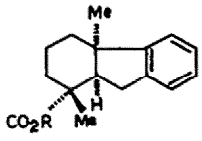


I



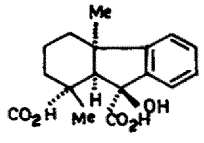
II R = H

V R = Me



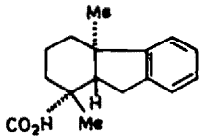
III, R = H

VI, R = Me



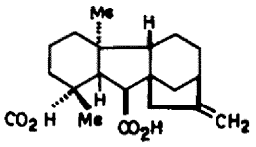
IV

In continuation to our synthetic studies[8] in the field of C-aromatic diterpenoid resin acids, our interest was directed towards the total synthesis of B-nor diterpene model, such as V, which has all the desired stereochemical* and structural features



(i)

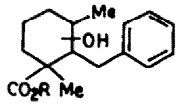
for its conversion to the gibberellin-A_{12},[6d] a C_{20}-gibberellin having the following structure. While the C-9 carbonyl function in V would in principle allow the introduction of the carboxylic acid residue at this position, a OMe group in the aromatic

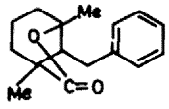


ring at C-7 would serve for its conversion to a α-β-unsaturated ketonic function *via* Birch reduction[9] and subsequent building up the D-ring through well-established methods.[10]

The present report describes a stereoselective route to the total synthesis of (±)-1β,4aα-dimethyl-*cis*-1,2,3,4,4a,9a-hexahydrofluorene-1α-carboxylic acid (III)† and the corresponding (±)-keto-acid II.

Preliminary considerations directed that the simplest entry to the hydrofluorene system of the type III, if possible, would be through acid-catalysed cyclialkylation[11] of a substituted benzylcyclohexanol, the corresponding olefin or the lactone of the following type.

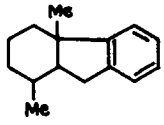




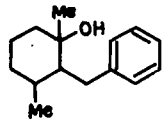
In addition to its directness and simplicity, such a scheme appealed from a stereochemical standpoint (*vide infra*). Although no definite example of the formation of hydrofluorene system through cyclialkylation of a simple or a substituted benzylcyclohexanol or the corresponding olefins was reported in the literature,[12,13] it appeared to deserve thorough investigation.[13] Studies[13] carried out to ascertain this possibility uncovered some new facts of possible mechanistic importance in addition to providing a simple synthetic route to the hydrofluorene derivative VII through cyclialkylation of the corresponding open-chain benzylcyclohexanol VIII with polyphosphoric acid (PPA) under kinetically controlled process.

* Tahara and Hoshino[3c] have very recently reported a conversion of V to a mixture of *cis* ester VI and *trans* ester (i), through the catalytic reduction of the corresponding enol-acetate.

† Although formulas of only one *enantiomer* are drawn, all the synthetic compounds taken to represent a racemate, even when the prefix (±) is omitted.



VII



VIII

The major problem in the projected plan thus clarified, experiments were designed for the synthesis of the intermediates along the line we successfully exploited for podocarpic acid and related syntheses.[14]

The alkylation of ethyl-4-keto-2-methyl-2-cyclohexene carboxylate (IX; Hagemann's ester)[15] with benzyl chloride in the presence of potassium-t-butoxide as the base afforded the desired condensation product X[16] in 86% yield. The same alkylation reaction has been reported by Barnes and Sedlak[16] to afford only 55% yield of the product X, by using sodium ethoxide in ethanol. The major, if not the complete course of alkylation at the C-3 position in the ambident anion IXA,[17] derived from the Hagemann's ester IX is now well-established.[14b,18,19] The alkaline hydrolytic decarboxylation of X with boiling aq-ethanolic potassium hydroxide solution, afforded the ketone XI[16] in 91% yield. Conjugate addition[14] of hydrogencyanide residue to the unsaturated ketone XI with a boiling aqueous-ethanolic potassium cyanide solution followed by alkaline hydrolysis *in situ*, afforded 2-benzyl-3-methyl-3-carboxy-cyclohexanone (XII) in 85% yield as a crystalline solid. The stereochemistry depicted for this acid (XII) followed from its mode of formation and also from the analogy[20] of the stereochemical results obtained in similar transformation.

The acid XII was converted to the corresponding methyl ester with methanol–sulphuric acid. Although the liquid methyl ester (XIII) yielded a single 2,4-*dinitro*-

CHART–I

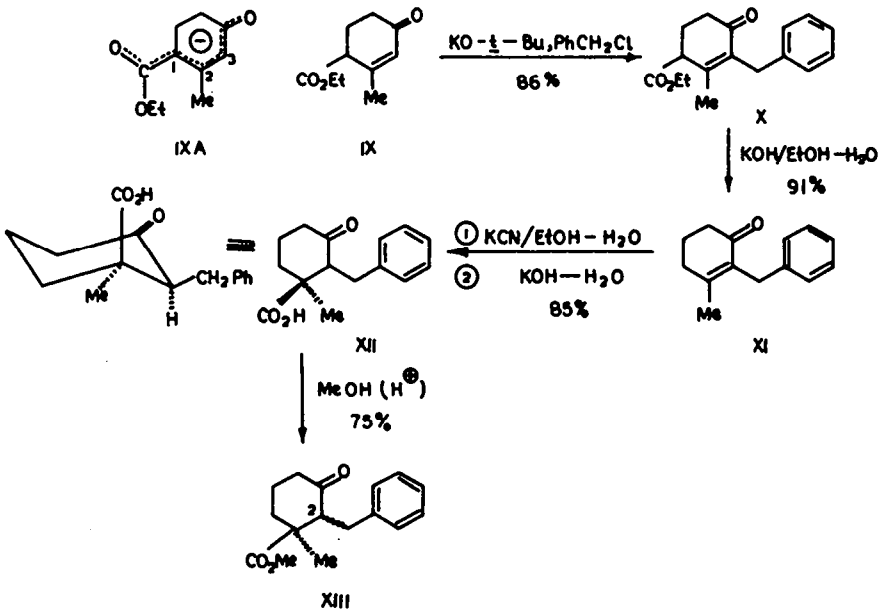
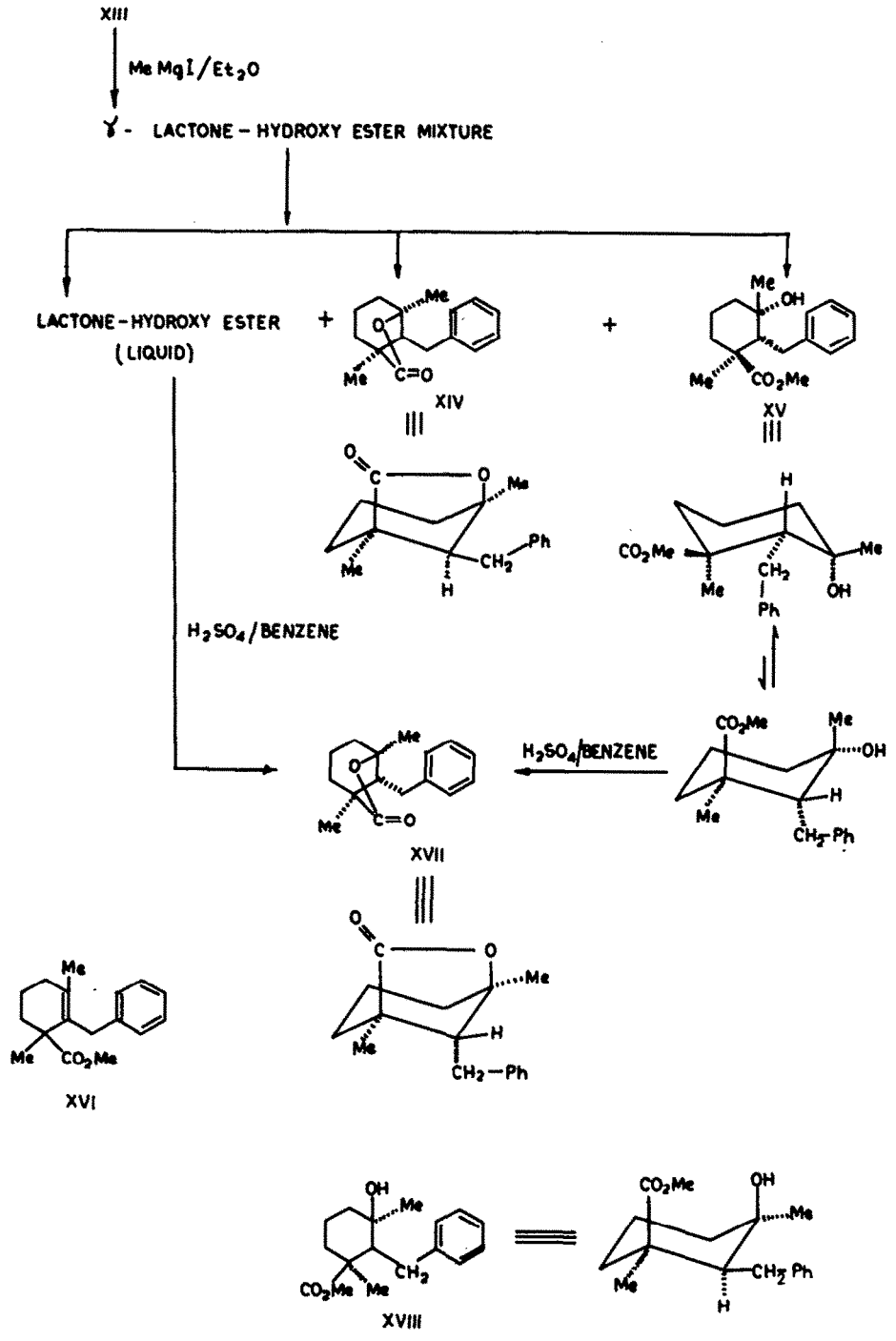


CHART-2

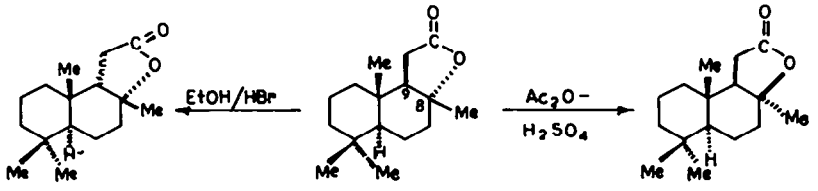

XIII
MeMgI/Et2O
γ- LACTONE – HYDROXY ESTER MIXTURE
LACTONE-HYDROXY ESTER
(LIQUID)
XIV
XV
H2SO4/BENZENE
H2SO4/BENZENE
XVII
XVI
XVIII

phenylhydrazone derivative, it showed two overlapping spots in the TLC, presumably due to the epimeric mixture arising from equilibriation at C-2.

The methyl ester XIII on condensation with MeMgI under controlled conditions yielded a γ-lactone–hydroxy ester mixture, as revealed from the IR. On fractional crystallizations, the γ-lactone XIV, m.p. 106° (IR band at 1765 cm^{-1}) and a hydroxy ester XV, m.p. 73° (IR band at 1722 and 3550 cm^{-1}) were obtained in about 8–10% and 60% yields respectively. The remaining liquid which failed to crystallize showed strong ester and weak γ-lactone bands in the IR. The yields of the lactone XIV and the hydroxy ester XV did not change appreciably when the crude Grignard product was distilled with catalytic amount of iodine.[21] On refluxing the crude Grignard product with a few crystals of iodine in benzene, the yield of the lactone XIV increased to 46% and that of the hydroxy ester XV reduced to about 28%. Refluxing with toluene-*p*-sulphonic acid in benzene afforded the lactone XIV and the hydroxy ester XV in 19% and 50% yields respectively. However, in all experiments, no pure unsaturated ester XVI could be isolated, although presence of unsaturated compound was revealed in the reactions with bromine and permanganate solutions, with the liquid mother liquors obtained from these reactions. When the hydroxy ester XV or the liquid γ-lactone–hydroxy ester mixture, left in the mother liquor after separation of XIV and XV, were treated with sulphuric acid in benzene solution at 0°, the only isolable product was an isomeric γ-lactone (XVII), m.p. 80·5° (IR band at 1765 cm^{-1}) obtained in about 57% yield. The γ-lactone XIV was, however, completely destroyed on such treatment. This experiment indicates that the above lactonization in benzene–sulphuric acid probably proceeds through a kinetically controlled process and of the two isomeric lactones (XVII and XIV) thus produced, only the former survives under the reaction conditions.[22]

The formation of the lactone XIV in the aforementioned Grignard product from XIII, even without acidification or heating, probably arises[23] from the isomeric hydroxy ester, such as XVIII among the reaction products, originating from the addition of MeMgI, through a nonstereospecific[24] path. With refluxing toluene-*p*-sulphonic acid or iodine, other epimeric hydroxy ester, e.g., XV are also probably converted to the stable lactone XIV through *epimerization* of the benzyl group.

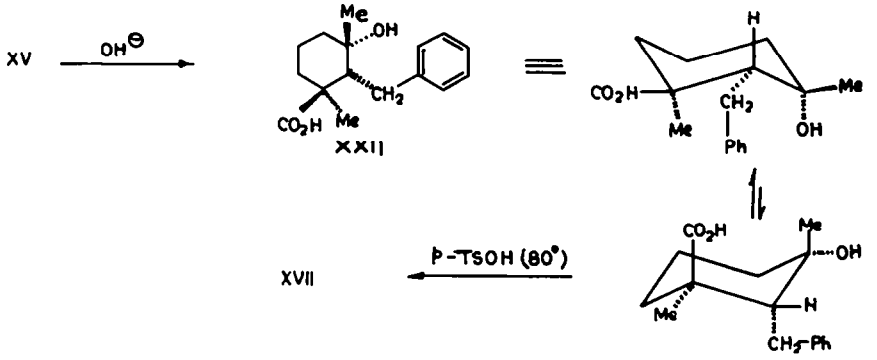
The stereochemistry of a lactone may depend on the reaction conditions and the nature of the reagents. It has been shown by Corey and Sauers[25a] and by Lucius[25b] that nor-ambreinolide (XIX) is converted to the isomeric lactone XX, involving epimerization at C-8, with H_2SO_4/AcO, whereas EtOH/HBr effects epimerization at C-9, leading to the lactone XXI.



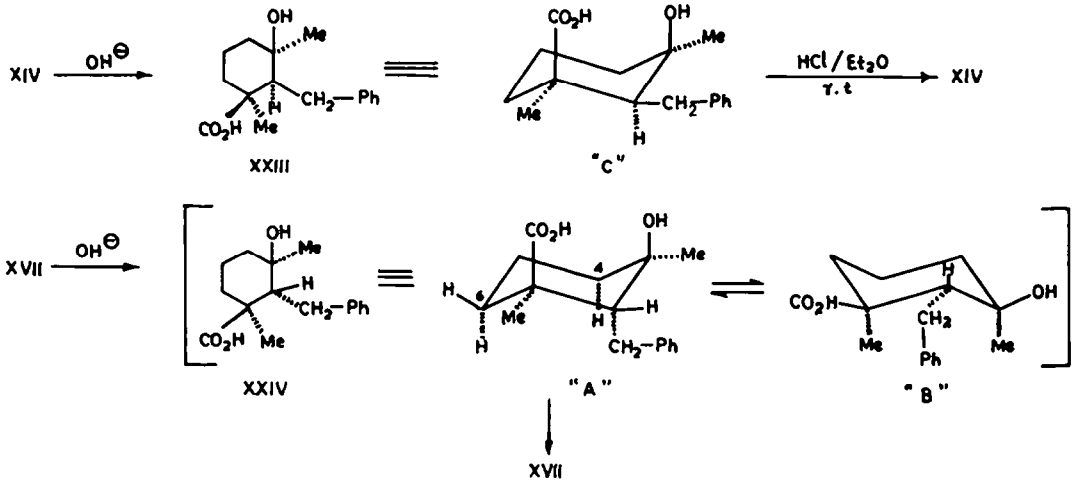
XXI XIX XX

Evidence for the stereochemical assignments of the hydroxy ester XV and the lactones XIV and XVII were obtained from the results presented below:

On alkaline hydrolysis, hydroxy ester XV yielded the corresponding hydroxy acid XXII, m.p. 148°, besides a small quantity of the lactone XVII. This hydroxy acid was recovered unchanged on treatment with a few drops of HCl in $EtOH/H_2O$ at room temperature; however, converted to the lactone XVII on treatment with toluene-*p*-sulphonic acid in boiling benzene. Failure of the hydroxy acid XXII to lactonization under mild acid treatment strongly suggests the assigned *trans* relationship of the hydroxyl and the carboxyl groups in this acid and the corresponding ester XV. The formation of only the lactone XVII from the hydroxy acid XXII correlates their stereochemistry as shown below:

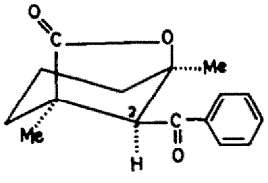


Further, a close similarity was observed in the nature and the stereochemistry of the cyclization products from XV and XVII with $AlCl_3$–HCl, which could be clearly explained from their depicted stereochemical assignments.[13] The alkaline hydrolysis of the lactone XIV yielded a hydroxy acid XXIII, m.p. 99–100° (single carbonyl band in IR at 1690 cm^{-1}); low carbon percentage in the analytical results showed possible inclusion of water. This hydroxy acid transformed to the parent lactone XIV with an ethereal HCl solution at room temperature. The hydroxy acid XXIV, from the hydrolysis of the lactone XVII, however, readily relactonized to the starting lactone during its isolation. The observed stabilities of the hydroxy acids XXIII and XXIV throw considerable light to their stereochemistry and can be easily explained from the conformational analysis on the basis of their assigned stereochemistry (*shown below*).

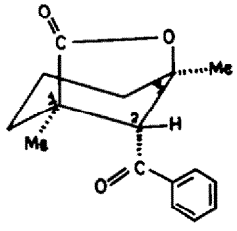


The hydroxy acid XXIV would be energetically unfavoured, because of the additional non-bonded 1,3-diaxial interactions, arising from the axial benzyl group with the axial hydrogens at C-4 and C-6 in the conformer (A), or a strong 1,3-diaxial Me–Me interaction in the conformer (B), compared to that of the isomeric hydroxy acid XXIII, probably existing mostly in the conformation (C). This explains easy lactonization of the hydroxy acid XXIV, which partly relieve the non-bonded interactions, involving the axial hydroxyl and the carboxyl groups in this highly crowded molecule.

The final evidence for the stereochemical assignments of the lactones XIV and XVII are revealed in the NMR spectra in $CDCl_3$ of the keto-lactones XXV, m.p. 132–133° (IR bonds at 1768 and 1680 cm^{-1} and XXVI, m.p. 142–143° (IR bonds at 1770 and 1670 cm^{-1}) obtained through CrO_3–HAc oxidation of the lactones XIV and XVII respectively. The axially oriented proton at C-2 in the keto-lactone XXV appears as a singlet at τ 6·20, whereas the corresponding equatorially disposed proton in XXVI shows this singlet at τ 6·04; in agreement with the observed differences of such proton signals in cyclohexane ring.[26]



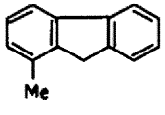
XXV



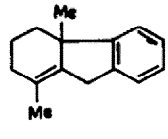
XXVI

It may be mentioned that attempted equilibriation studies of the epimeric keto-lactones (XXV and XXVI) with MeOH—NaOMe did not produce useful results. In both cases, base treatment resulted in a closely similar mixture of complex products, which could not be purified or characterized.

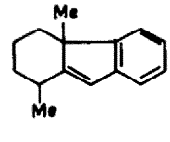
Cyclization studies referred earlier in this paper, established[13] that the substituted benzylcyclohexanol of the type VIII cyclizes to the corresponding hydrofluorene VII, with PPA at a reaction temperature of about 80–85°. When the hydroxy ester XV was cyclized with PPA under this condition, a neutral liquid, having a strong ester and a weak γ-lactone bands in the IR was obtained along with the acid III, m.p. 170–171° in about 2% yield. On alkaline hydrolysis the neutral fraction afforded the same acid III in 57% yield, which showed UV maxima at 260 mμ (log ε 2·94), 266 mμ (log ε 3·14) and 273 mμ (log ε 3·14), characteristic of the hydrofluorene system.[13] The dehydrogenation of the acid III with Pd/C (10%) yielded 1-methylfluorene (XXVII). The neutral product left after the hydrolysis shows a γ-lactone band in the IR, and in the UV, it shows a band at 258 mμ (log ε 3·68), presumably due to the hydrocarbons XXVIII and XXIX in the mixture, arising through the elimination of carbomethoxyl group. On dehydrogenation it afforded 1-methylfluorene (XXVII). The acid III was esterified with diazomethane to afford the corresponding methyl ester VI, m.p. 48°.



XXVII

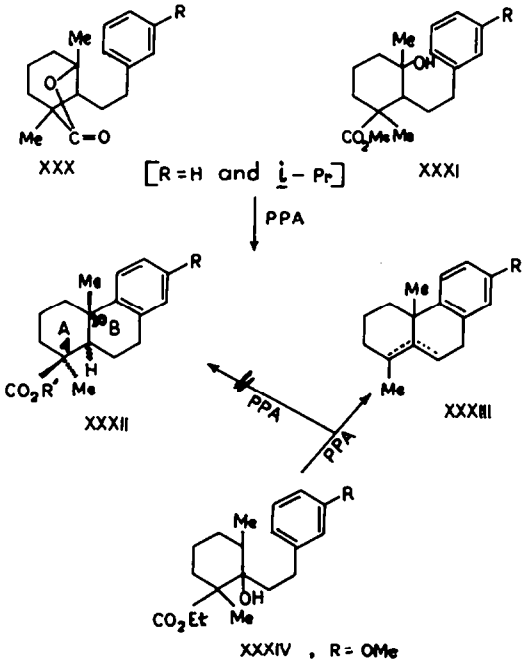


XXVIII



XXIX

On attempted cyclization with PPA at 67–68° and 85–86°, the lactone XIV was recovered completely or partially unchanged mixed with a neutral liquid. However, with PPA treatment at 120° for 1 hr, this lactone was completely transformed to a liquid hydrocarbon mixture (probably XXVIII and XXIX), which again yielded 1-methylfluorene (XXVII) on dehydrogenation. Cyclization of the isomeric lactone XVII also gave practically the same results. It may be mentioned that in parallel cases studied[14] in this laboratory, PPA cyclization of the lactone–ester mixture XXX and XXXI yielded the corresponding cyclized acids (XXXII, R′ = H) and the esters (XXXII, R′ = Me) along with a considerable amount of the hydrocarbon mixture XXXIII. Barltrop and Day[27] observed complete elimination of the carboethoxyl group in the product from the cyclization of the hydroxy ester XXXIV or the corresponding dehydrated ester.

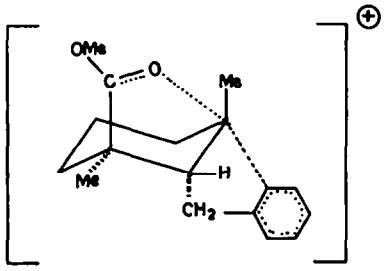


These results along with the present series of experiments again confirm the belief that the PPA cyclization process is a complex one[28] and a slight variation in the experimental condition or the structure[29] of the reactants can unpredictably change the nature of the final products.

The stereochemical assignment to the acid III was based on the following considerations. The acid-catalysed cyclialkylation process in producing the compounds of the type XXXII have been found to follow a remarkable degree of stereoselectivity in generating always the *trans* C-4, C-10 methyl groups [14,27,29,30*] (with both *cis* and/or *trans* A/B ring junction). Similar stereochemical control in the cyclization of XV would be expected to give rise to the desired *trans* orientation of the C-1, 4a-methyl groups as depicted in the structure III. A transition state in the PPA cyclization

* A detailed stereochemical analysis on the mechanistic course in this type of cyclizations will be reported shortly, U. R. Ghatak and N. R. Chatterjee, *unpublished results*.

of XV may be represented by XXXV with the axial sp^2-hybridized carbomethoxyl group in preference to that of the sp^3-methyl group,[14] having a higher "A" value[31] from a consideration of steric factors only. Further, such disposition of the ester function favours its C=O group to participate in the transition state (as depicted in XXXV) thereby lowering the activation energy of the transition complex. We are

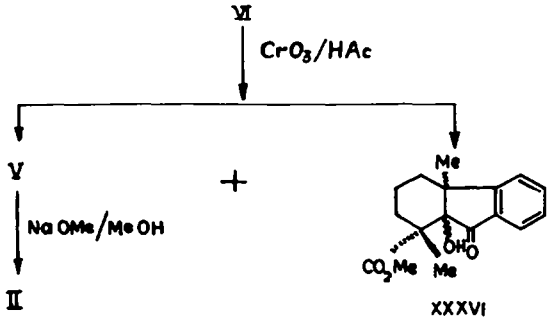


XXXV

tempted to conclude the cyclialkylation of XV with PPA proceeds through an irreversible* process and without epimerization at C-2. Such conclusion further supports the suggested transition state XXXV and leads to the complete stereochemical assignment of the cyclized product III. This assignment has been conclusively established (*vide infra*).

On oxidation with chromic acid in aqueous acetic acid the methyl ester VI afforded the liquid keto-ester V; [IR bands at 1709 and 1725 cm^{-1}, UV λ_{max} 247 mμ (log ε 4·15) and 292 mμ (log ε 3·41)] in 30% yield, besides the recovered starting ester (VI, ca. 15%) and a solid, m.p. 216°, in about 10% yield. The solid compound (m.p. 216°) shows strong IR bands at 1708 and 1728 cm^{-1}, characteristic of the 5-membered aromatic conjugated ketone group[13] and a saturated ester function in addition to a weak hydroxyl band at 3610 cm^{-1}. In the UV, the compound shows absorption maxima at 248 mμ (log ε 4·07) and 293 mμ (log ε 3·40) which further confirmed the presence of an aromatic conjugated ketone function in it. From its elemental analyses, spectral data and its behaviour in the chromatographic column, the structure XXXVI can be assigned to this, originating through over-oxidation[7] of the keto-ester V.

CHART-3



XXXVI

* e.g. The cyclization of XV under reversible condition ($AlCl_3$-HCl) which led to an entirely different result has been published in a short communication, Ref. 13.

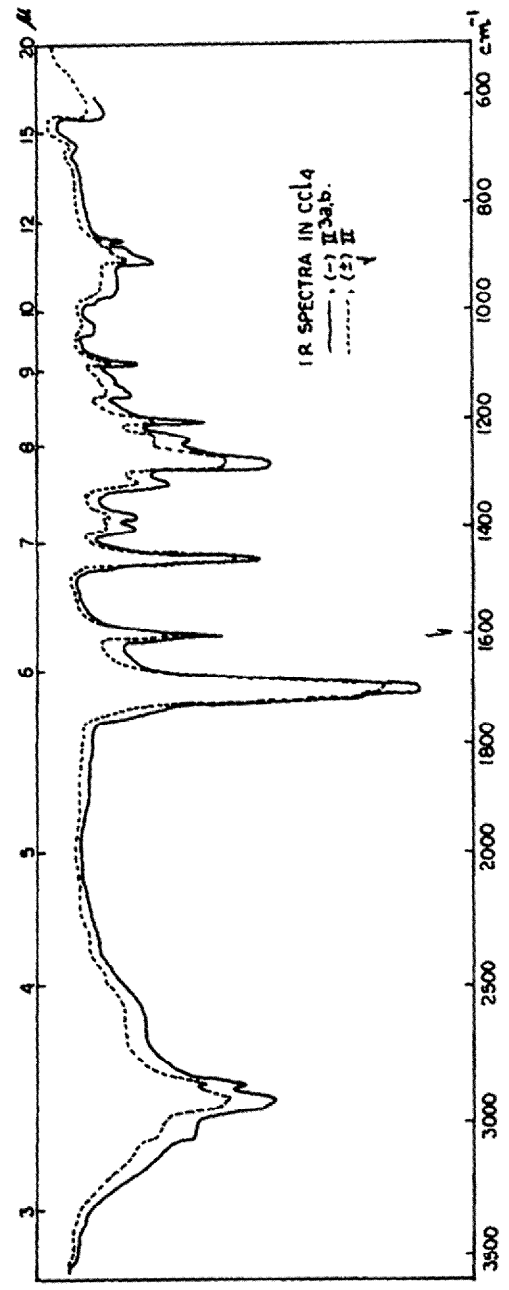

IR SPECTRA IN CCl4
——, (−) II 3a,b.
------, (±) II
μ
cm⁻¹
3
4
5
6
7
8
9
10
12
15
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600

FIG 1.

Treatment of the keto-ester V with excess of sodium methoxide in refluxing methanol afforded the (±)-keto-acid II, m.p. 123–124°, in 80% yield. Its IR spectrum (CCl_4) kindly measured for comparison by Dr. Tahara, is identical (Fig. 1) in all respects with that of the sample of (−)-keto-acid II, prepared by Tahara *et al.*[3a,b] from the naturally occurring source. The corresponding methyl esters also show identical retention times in GLC (through the courtesy of Dr. Tahara), which established the assigned stereochemistry of the synthetic keto-acid II at C-1 and 4a centers. Since this acid was derived from the keto-ester V through equilibriating conditions it should be represented by the stable *cis* A/B ring junction.[32,33]

The catalytic reduction (Pd–C, 10%) of the keto-acid II in ethanol in the presence of perchloric acid yielded the acid III, which correlates the stereochemistry of these two acids at the ring junction at C-9a.

After the publication of our preliminary communication assigning the *cis* ring junction to the acids II and III, Tahara and Hoshino[3c] have prepared the optically active *trans* ester (i) through conversions from the natural diterpenoids and transformed their optically active keto-acid II to the ester VI which was found[3c] to be identical with the ester prepared from Ohta's optically active sample and our synthetic (±) ester VI, and different from the *trans* ester (i) through IR and GLC comparisons.

This conclusively established our assigned stereochemistry to these compounds.

EXPERIMENTAL*

2-Benzyl-3-methyl-4-carbethoxy-Δ²-cyclohexenone (X).

Potassium (20·2 g) was dissolved in excess of dry t-butanol and the latter distilled off until a solid appeared in the flask. After cooling at room temp, IX (95 g) was added in one lot with shaking. The scarlet red colour formed initially turned into a straw-yellow solid mass in a few min and was allowed to stand for ½ hr. Benzyl chloride (100 g) was added slowly with shaking and the mixture was heated under reflux for 16 hr. The cold product was acidified with 6N HCl and extracted with ether. The product on distillation afforded a colourless liquid (122 g, 86%) b.p. 160–165° (0·4 mm), [lit.[16] b.p. 160–164° (0·35 mm)] λ_{max} 240 mμ (log ε 4·0), ν_{max} 1730 cm^{-1} (s), 1665 cm^{-1} (s) and 1642 cm^{-1} (m). In the TLC it showed single spots in various solvents systems. It afforded a semicarbazone which was crystallized from aqueous EtOH, m.p. 130–132° [lit.[16] m.p. 131–133°].

2-Benzyl-3-methyl-Δ²-cyclohexenone (XI)

A soln of KOH (100 g) in water (100 ml) and EtOH (700 ml) was added to X (120 g) and was heated under reflux for 12 hr (N_2). The cold mixture was slowly acidified with conc HCl (125 ml), the ppt was filtered off, then most of EtOH was removed by distillation, and the residue was diluted with water. The mixture was extracted with ether, and the combined organic layers were washed with 2% Na_2CO_3 aq, followed by water and dried over Na_2SO_4. The product on distillation afforded a clear mobile liquid (80 g, 91%), b.p. 128–130° (0·4 mm). [Lit.[16] b.p. 123–126° (0·3 mm)], λ_{max} 242 mμ (log ε 4·0), ν_{max} 1672 cm^{-1} (s) and 1643 cm^{-1} (m). It showed single spots in the TLC in MeOH–benzene (1:19) and pet. ether:AcOEt (9:1) systems.

* The compounds described here are all racemic forms and the term α,β- have only relative significance referring to the orientation of substituent groups according to steroid nomenclature. M.ps (taken in open capillary in H_2SO_4—bath) and b.ps are uncorrected. TLC plates (20 × 30 cm) were coated with silica-gel-G (RSco, 200 mesh), having a thickness of about 0·2 mm, and the spots were located by exposing the dried plates in I_2 vapour. Pet. ether refers the fraction b.p. 40–60. UV were determined in 95% EtOH, on a Beckman DU-Spectrophotometer by Mr. A. Ghosal, and the IR were determined in $CHCl_3$ soln, on a PE model-21, double beam recording spectrophotometer. NMR spectra (compounds XXV and XXVI) were kindly recorded by Dr. P. M. Nair, N. C. L. Poona, and compound VI by Professor R. B. Bates, Tuscon, Arizona; in $CDCl_3$ soln at 60 Mc. Microanalyses were performed by Mrs. Chhabi Dutta of this laboratory. We express our thanks for these services.

2-Benzyl-3-methylcyclohexanone-3-carboxylic acid (XII)

To a soln of XI (100 g) in 95% EtOH (940 ml) a soln of KCN (104 g) in water (600 ml) was added. The reaction mixture assumed a green colour and was allowed to stand at room temp for some time when it turned into yellowish-brown. It was finally heated under reflux on a steam-bath for 14 hr. On cooling, a soln of KOH (140 g) in water (1600 ml) was added to the reaction mixture and heated under reflux for another 90 hr. The cold soln was poured in iced-water, acidified carefully with conc HCl, saturated with NaCl and the organic material extracted with ether. From the ethereal extracts, the acidic material was isolated by washing with 5% Na_2CO_3 aq and extraction with ether after acidification with 6N HCl, which afforded a solid cake (105 g; 85%), on removal of the solvent and trituration with pet. ether. A portion of this was crystallized from AcOEt–pet. ether in colourless rosettes, m.p. 153·5–154°. (Found: C, 73·16; H, 7·28. $C_{15}H_{18}O_3$ requires: C, 73·14; H, 7·37%.)

2-Benzyl-3-methyl-3-carbmethoxycyclohexanone (XIII)

A cold soln of MeOH (600 ml) and conc H_2SO_4 (60 ml) was added to XII (102 g) and heated under reflux for 60 hr. About two-thirds of the MeOH was removed under reduced press. The remaining liquid was diluted with iced-water and extracted with ether after saturation with NaCl. The ethereal extract was washed with 5% $NaHCO_3$ aq followed by saturated NaCl aq and dried over Na_2SO_4. The product on distillation afforded a thick liquid (81 g; 75%), b.p. 142–145° (0·4 mm). TLC in benzene–MeOH (9:1) showed two overlapping spots. (Found: C, 73·5; H, 7·4. $C_{16}H_{20}O_3$ requires: C, 73·8; H, 7·6%.) It afforded a yellow *2,4-dinitrophenylhydrazone* which was crystallized from AcOEt–MeOH, m.p. 230°. (Found: C, 59·7; H, 4·8. $C_{22}H_{24}N_4O_6$ requires: C, 60·1; H, 5·2%.)

Reaction of XIII *with methylmagnesium iodide*

Lactone of 2β-benzyl-1α,3α-dimethyl-3β-hydroxycyclohexane-1β-carboxylic acid (XIV) *and methyl-2α-benzyl-1α,3β-dimethyl-3α-hydroxycyclohexane-1β-carboxylate* (XV). To a well-stirred ice-cold soln of XIII (60 g) in dry ether (800 ml), an ethereal soln of MeMgI prepared from Mg (9·2 g), MeI (20 ml) and dry ether (120 ml); was added dropwise over a period of 2 hr. Stirring in the cold was continued for additional 2 hr and finally allowed to reach the room temp. After decomposition of the Grignard-complex with ice-cold saturated NH_4Cl aq, the ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal extract was washed with water, 2% $Na_2S_2O_3$ aq, finally with water and dried over Na_2SO_4. Removal of the solvent afforded a thick yellow liquid (55 g); ν_{max} 3550 cm^{-1} (m), 1768 cm^{-1} (s) and 1725 cm^{-1} (s). Portions of this liquid were subjected to following treatments:

(a) The cold Grignard-product (25 g) was triturated with pet. ether and left overnight in an ice-box when a white amorphous solid separated out. The solid, m.p. 60–65° was filtered off and washed with pet. ether. On crystallization from pet. ether it afforded XIV (2 g; 8%), m.p. 106°; ν_{max} 1765 cm^{-1} (s). (Found: C, 78·66; H, 8·25. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25%.)

The filtrate mixed with the pet. ether washings were concentrated to a small volume and left for a few days in an ice-box when crystalline cubes, m.p. 66–68° separated out. On repeated crystallization from pet. ether, XV was obtained as thick colourless needles, m.p. 73° (17 g, 59·5%) which on admixture with the lactone XIV, melted at 45–50°; ν_{max} 3550 cm^{-1} (m) and 1722 cm^{-1} (s). (Found: C, 73·68; H, 8·50. $C_{17}H_{24}O_3$ requires: C, 73·88; H, 8·75%)

The *remaining thick syrup liquid* (6 g) failed to crystallize. It showed in the IR, a strong ester band at 1722 cm^{-1} and a weak γ-lactone band at 1765 cm^{-1}.

(b) The Grignard product (20 g) in dry benzene (250 ml) was heated under reflux for 4 hr with a few crystals of I_2 in a flask fitted with a constant water separator. The cold reaction product was washed with 2% $Na_2S_2O_3$ aq and water. The brown product on distillation afforded a light yellow liquid (17 g), b.p. 163–165° (0·4 mm) which was subjected to fractional crystallization from pet. ether as above when XIV, (8·5 g; 46·2%), m.p. 106° and XV (6·5 g; 28%), m.p. 73° were separated. The *remaining liquid* (2 g) failed to crystallize and showed a strong ester band at 1722 cm^{-1} in the IR.

(c) The crude Grignard product (15 g) on distillation with 2 crystals of I_2 afforded a brown liquid which was taken up in ether and washed with 2% $Na_2S_2O_3$ aq and water. On redistillation, it afforded a yellow liquid (13 g), b.p. 160–165° (0·6 mm) from which XIV, (2 g; 14·6%) m.p. 106° and XV, (9 g; 54%) m.p. 73° were separated by fractional crystallization.

(d) The crude Grignard product (5 g) was heated under reflux for 6 hr in dry benzene (75 ml) with toluene-*p*-sulphonic acid (100 mg) in a flask fitted with a constant water separator. The cold product was washed with 5% Na_2CO_3 aq and water. The distilled product was subjected to fractional crystallization

from pet. ether as described above, when XIV, (0·6 g; 19%) m.p. 106° and XV, (2 g; 50%) m.p. 73°, were separated.

The syrupy liquid after separation of the lactone and the hydroxy ester was not characterized further.

Lactone of 2α-benzyl-1α,3α-dimethyl-3β-hydroxycyclohexane-1β-carboxylic acid (XVII). To a vigorously stirred soln of XV (7 g) in dry benzene (210 ml) at 0°, ice-cold conc H_2SO_4 (210 ml) was added dropwise over a period of 1½ hr and the stirring at the same temp was continued for additional 1 hr. The yellow reaction mixture was poured in crushed ice and extracted with ether after saturation with $(NH_4)_2SO_4$. The ethereal extract was washed with 5% Na_2CO_3 aq, water and dried over Na_2SO_4. Removal of the solvent afforded light yellow solid (3·5 g; 56·5%), which was crystallized from pet. ether in shining colourless rosettes, m.p. 80·5°; ν_{max} 1765 cm^{-1} (s). On admixture with the lactone XIV (m.p. 106°), it melted at 56–62°. (Found: C, 78·52; H, 8·34. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25%.)

The aforementioned uncharacterized *syrupy liquid* (3 g), left after separation of XIV and XV, on treatment with conc H_2SO_4 under the identical experimental conditions yielded XVII (1 g), m.p. 80·5°.

Hydrolysis of the hydroxy–ester XV

2α-Benzyl-1α,3β-dimethyl-3α-hydroxycyclohexane-1β-carboxylic acid (XXII). A mixture of XV (2 g), KOH (3 g), water (2 ml) and ethylene glycol (18 ml) was heated under reflux for 4 hr (N_2). The cold reaction product was diluted with ice-water and extracted twice with ether to remove any neutral material, from which practically nothing could be isolated. The ice-cold aqueous fraction was acidified to pH 2 carefully with dil HCl and extracted with ether. From the ethereal extract, the neutral and acidic materials were separated by washing with 5% Na_2CO_3 aq. The neutral fraction after removal of the solvent yielded XVII (100 mg) m.p. 80·5°. The basic extract after careful acidification yielded a solid acid (1·7 g), m.p. 138–142° which on crystallization from aqueous MeOH in the cold, yielded shining colourless cubes of XXII, m.p. 148°; ν_{max} 1698 cm^{-1} (s). The analytical sample was dried at 26° (0·02 mm) for 60 hr. (Found: C, 72·85; H, 8·46. $C_{16}H_{22}O_3$ requires: C, 73·25; H, 8·45%.)

Studies on the lactonization of the hydroxy–acid XXII

(a) A soln of XXII (200 mg) in aqueous EtOH (2 ml, 50%) was treated with a few drops of conc HCl and was left at room temp for 48 hr. After working up, no neutral material could be isolated. The acid XXII (190 mg) m.p. 148° was recovered unchanged.

(b) The acid XXII (500 mg) in benzene (25 ml) was refluxed for 5 hr with toluene-*p*-sulphonic acid (50 mg). The cold soln was washed with water, 5% Na_2CO_3 aq followed by water and dried over Na_2SO_4. Removal of the solvent yielded colourless solid (440 mg) which was crystallized from pet. ether, m.p. 80·5°, alone or mixed with the lactone XVII, ν_{max} 1765 cm^{-1} (s).

Hydrolysis of the lactone XIV

2β-Benzyl-1α,3α-dimethyl-3β-hydroxycyclohexane-1β-carboxylic acid (XXIII). The lactone XIV (300 mg) was refluxed for ½ hr with a soln of KOH (300 mg) in aqueous EtOH (3 ml, 50%). The cold reaction mixture was diluted with water and extracted with ether to remove any neutral material. The ice-cold aqueous layer was acidified with H_3PO_4 (45% w/w) and extracted with ether. The solvent was evaporated *in vacuo* in the cold and the resiudal XXIII (250 mg), was crystallized from ether–pet. ether in an ice-box, as shining stars, m.p. 99–100°; ν_{max} 1690 cm^{-1} (s). On admixture with the lactone XIV (m.p. 106°), this solid melted at 80–85°. The analytical sample was dried at 28° (0·02 mm) for 60 hr. (Found: C, 70·70; H, 8·35. $C_{16}H_{22}O_3 \cdot \frac{1}{2}H_2O$ requires: C, 70·82; H, 8·54%.)

Lactonization of the hydroxy acid XXIII. The acid XXIII (50 mg) in ether (10 ml) was mixed with 2 to 3 drops of conc HCl and left at room temp for 48 hr. The ether layer was washed with water, 5% Na_2CO_3 aq followed by water and dried over Na_2SO_4. Evaporation of the solvent afforded the solid (43 mg) which was crystallized from pet. ether in fine colourless needles, m.p. 106°, alone or mixed with the lactone XIV; ν_{max} 1765 cm^{-1} (s).

Attempted hydrloysis of the lactone XVII. Hydrolysis and working up of XVII (200 mg) was performed as described earlier. During the evaporation of the solvent at room temp *in vacuo*, the acid relactonized to the starting material, m.p. 80·5°, alone or mixed with XVII.

Oxidation of the lactone XIV

Lactone of 2β-benzoyl-1α,3α-dimethyl-3β-hydroxycyclohexane-1β-carboxylic acid (XXV). The lactone XIV (350 mg) in glacial AcOH (6 ml) was mixed with a soln of CrO_3 (500 mg) in water (1·5 ml) and

glacial AcOH (6 ml). After keeping at room temp for 18 hr the mixture was heated in a boiling water-bath for 1 hr. The cold reaction mixture was diluted with water, saturated with NaCl and extracted with ether. The ethereal extract was washed with water, 3% NaOH aq until alkaline, followed by water and dried over Na_2SO_4. The solid obtained after removal of the solvent was crystallized from ether–pet. ether in long colourless needles of XXV (140 mg; 35%), m.p. 132–133°: λ_{max} 250 mμ (log ε 4·1); ν_{max} 1768 cm^{-1} (s), 1680 cm^{-1} (s) and 1595 cm^{-1} (w). (Found: C, 74·22; H, 7·13. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%.)

Oxidation of the lactone XVII

Lactone of 2α-benzoyl-1α,3α-dimethyl-3β-hydroxycyclohexane-1β-carboxylic acid (XXVI). The lactone XVII (350 mg) in glacial AcOH (6 ml) was oxidized with a soln of CrO_3 (500 mg) in water (1·5 ml) and glacial AcOH (6 ml) under the same experimental conditions described above. After working up, the neutral fraction was crystallized from ether–pet. ether in colourless stars of XXVI (150 mg; 38%), m.p. 142–143°; λ_{max} 250 mμ (log ε 4·00); ν_{max} 1770 cm^{-1} (s), 1670 cm^{-1} (s) and 1595 cm^{-1} (w). (Found: C, 74·42; H, 7·20. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%.)

Equilibriation experiments with keto-lactones XXV *and* XXVI *with methanolic* NaOMe

The keto-lactone XXV, m.p. 132–133° (50 mg), was added to a soln of Na (25 mg) in MeOH (10 ml) and was refluxed for 4½ hr. After removal of the MeOH under reduced press, the product was diluted with water and extracted with ether. The ethereal extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the product was crystallized from ether–pet. ether, m.p. 120–122°. In TLC with benzene MeOH (19:1), it showed four spots, two of these (*minor spots*) corresponding to the keto-lactones XXV and XXVI. It could not be purified by chromatography over silica gel.

The keto-lactone XXVI, m.p. 142–143°, was also treated with methanolic NaOMe under the same experimental conditions. After working up, the product was crystallized from ether–pet. ether, m.p. 120–122°, alone or mixed with the above compound. This also showed exactly similar behaviour in TLC, like the compound described above.

PPA cyclization of hydroxy-ester XV

1β-4aα-Dimethyl-cis-1,2,3,4,4a,9a-hexahydrofluoren-1α-carboxylic acid (III). To a well-stirred homogeneous soln of polyphosphoric acid, prepared by heating P_2O_5 (16 g) and H_3PO_4 (12 ml, 85% w/w) for about 10 min in a water-bath, the hydroxy-ester XV (5 g) was added. The stirring at 80–81° was continued for 1 hr. The deep-bluish green reaction product was cooled and decomposed with crushed ice. The organic material was extracted with ether, washed with 5% Na_2CO_3 aq followed by water and dried over Na_2SO_4. The basic extract was acidified with HCl and extracted with ether. A solid acid III (100 mg; 2%) was isolated which was crystallized from AcOEt–pet. ether, m.p. 170–171°. The *neutral fraction* afforded a clear mobile liquid (4·2 g) b.p. 125–130° (0·3 mm), ν_{max} 1765 cm^{-1} (w) and 1729 cm^{-1} (s). This liquid (4 g) was gently refluxed for 3½ hr under N_2 with a soln of KOH (6 g) in water (3 ml) and ethylene glycol (37 ml). The cold reaction product was diluted with water, acidified with dil HCl, and extracted with ether. The ethereal extract was washed with 5% Na_2CO_3 aq and water. On cooling the alkaline washings, the sodio-salt of the acid separated out as silky white flakes, which was acidified and extracted with ether to afford colourless III (2·5 g; 57%) which was crystallized from AcOEt in colourless stout needles, m.p. 170–171° alone or mixed with the aforementioned sample; λ_{max} 260 mμ (log ε 2·94), 266 mμ (log ε 3·14) and 273 mμ (log ε 3·14); ν_{max} 1700 cm^{-1} (s). (Found: C, 78·46; H, 8·24. $C_{16}H_{20}O_2$ requires: C, 78·62; H, 8·19%.) In TLC with benzene–MeOH (9:1) it showed a sharp single spot.

The acid III, m.p. 170–171° (100 mg), was dehydrogenated with Pd/C (10%, 50 mg) at 320–330° for 30 hr. On chromatography over neutral alumina (20 g), the pet. ether elute afforded 1-methylfluorene (40 mg), m.p. 84–85° alone or mixed with an authentic sample; λ_{max} 265 mμ (log ε 4·37), 289 mμ (log ε 3·77) and 300 mμ (log ε 3·85).

The *neutral fraction from hydrolysed product* afforded 1 g of a light brown liquid (probably the hydrocarbons XXVIII and XXIX), λ_{max} 258 mμ (log ε 3·68); ν_{max} 1765 cm^{-1} (m). It rapidly decolourized Br_2 in CCl_4 soln. This liquid (100 mg) was dehydrogenated with Pd/C (10%, 50 mg) for 20 hr at 320–330° from which *1-methylfluorene* (XXVII, ca. 20 mg), m.p. 84–85°, alone or mixed with an authentic sample, was obtained after chromatography over alumina.

Methyl-1β,4aα-dimethyl-cis-1,2,3,4,4a,9a-hexahydrofluorene-1α-carboxylate (VI)

The acid III, (0·6 g) was esterified with an ethereal soln of CH_2N_2 in the usual way. The light-yellow

liquid VI (0·6 g) solidified after keeping in an ice-box for 2 days. On crystallization from pet. ether in a cold chamber, it afforded shining thick plates, m.p. 48°, λ_{max} 259 mμ (log ε 2·71), 262 mμ (log ε 2·70), 265 mμ (log ε 2·73) and 272 mμ (log ε 2·75); ν_{max} 1730 cm^{-1} (s). NMR in ($CDCl_3$ soln) at 60 Mc; τ 8·82 (6H, C-1 Me and C-4a Me), 7·17 (2H, C-9—CH_2—), 6·29 (3H, —COOMe). In TLC with benzene–MeOH (19:1), it showed one sharp spot. (Found: C, 78·92; H, 8·47. $C_{17}H_{22}O_2$ requires: C, 79·03; H, 8·58%.)

Studies on PPA cyclization of the lactone XIV

(a) To a well-stirred homogenous soln of PPA, prepared by heating P_2O_5 (4 g) and H_3PO_4 (3 ml) in an oil-bath at 120°, XIV, m.p. 106° (0·9 g) was added when the colour of the reaction mixture changed from light-yellow to deep greenish-blue. Stirring at the same temp was continued for 1 hr. The cold reaction mixture was decomposed with crushed ice, extracted with ether, washed with water, 5% Na_2CO_3 aq followed by water and dried over Na_2SO_4. The product on distillation afforded a clear mobile liquid (0·5 g), b.p. 116–120° (0·5 mm), λ_{max} 257 mμ (log ε 3·7). It rapidly decolourized Br_2 in CCl_4 soln. In the IR it did not show any band in the carbonyl region.

On dehydrogenation of this liquid (100 mg) with Pd/C (10%; 50 mg) at 320–330° for 20 hr, it afforded XXVII, m.p. 84–85°, alone or mixed with an authentic sample.

(b) The lactone was recovered unchanged on treatment with PPA for ½ hr at 67–68°.

(c) Attempted cyclization of the lactone (0·9 g) with PPA for 1 hr at 85–86° yielded the recovered lactone (0·6 g) and a liquid hydrocarbon (0·2 g), λ_{max} 257 mμ (log ε 3·75). It rapidly decolourized Br_2 in CCl_4 soln.

Studies on PPA cyclization of the lactone XVII.

The lactone XVII (0·9 g), m.p. 80·5°, was treated with PPA, prepared from P_2O_5 (4 g) and H_3PO_4 (3 ml) for 1 hr at 120°. After working up in the usual way, a hydrocarbon (0·7 g) was isolated in the neutral fraction. It rapidly decolourized Br_2 in CCl_4 soln. The crude hydrocarbon (200 mg) was dehydrogenated with Pd/C (10%; 100 mg) at 320–330° for 24 hr when XXVII (ca. 40 mg) was obtained, m.p. 84–85°, alone or mixed with an authentic sample. The lactone XVII, was recovered unchanged on treatment with PPA for 1 hr at 82–84°.

(±)-*Methyl*-1β-4aα-*dimethyl*-cis-1,2,3,4,4a,9a-*hexahydrofluoren*-9-*one*-1α-*carboxylate* (V) *and hydroxy keto-ester* (XXXVI)

A soln of VI (1 g) in glacial AcOH (10 ml) was mixed with a soln of CrO_3 (1·4 g) in water (6·5 ml) and glacial ACOH (25 ml) when the reaction mixture became warm. After keeping at room temp for 20 hr, the reaction mixture was heated on a boiling water-bath for 2 hr. The cold reaction mixture was decomposed and neutral material was isolated in the usual way which afforded light yellow liquid (0·7 g) and was purified by chromatography over acid-washed alumina (30 g). The pet. ether elute (450 ml) yielded the unchanged VI (0·15 g; 15%), m.p. 48°, alone or mixed with the authentic sample.

The pet.-ether–benzene (3:1) elute (500 ml) afforded V as a thick colourless liquid (0·31 g; 30%) which was evaporatively distilled at a bath temp of b.p. 130° (0·4 mm); λ_{max} 247 mμ (log ε 4·15) and 292 mμ (log ε 3·41); ν_{max} 1725 cm^{-1} (s) and 1709 cm^{-1} (s). In TLC with benzene–MeOH (9:1), it showed single spot. (Found: C, 74·63; H, 7·52. $C_{17}H_{20}O_3$ requires: C, 74·97; H, 7·40%.)

The ether elute yielded a white solid (0·1 g; 10%), m.p. 216° which was crystallized from AcOEt–pet. ether in shining small stars, m.p. 216°, λ_{max} 248 mμ (log ε 4·07) and 293 mμ (log ε 3·4); ν_{max} 3610 cm^{-1} (w), 1728 cm^{-1} (s) and 1708 cm^{-1} (s). In TLC with benzene–MeOH (9:1), it showed a sharp single spot. (Found: C, 70·75; H, 6·62. $C_{17}H_{20}O_4$ requires: C, 70·81; H, 6·99%.)

(±)-1β,4aα-*Dimethyl*-cis-1,2,3,4,4a,9a-*hexahydrofluoren*-9-*one*-1α-*carboxylic acid* (II)

To a soln of V (272 mg) in MeOH (10 ml) was added a cold soln of NaOMe, prepared from Na (92 mg) and MeOH (15 ml) and the resulting soln was refluxed in a water-bath for 4 hr. The MeOH was removed under reduced press and the residue was diluted with water. The neutral material was removed by extraction with ether, the alkaline layer together with the aqueous washings were acidified with HCl and the acidic material was extracted with ether. Evaporation of the solvent yielded II as colourless solid (200 mg), m.p. 122–123°, which was crystallized from ether–pet. ether in small stars, m.p. 123–124°, λ_{max} 245 mμ (log ε 4·11) and 290 mμ (log ε 3·38); ν_{max} 1725 cm^{-1} (s) and 1705 cm^{-1} (s). In TLC with benzene: MeOH (9:1), it showed a sharp single spot. (Found: C, 74·40; H, 7·18. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%.)

Conversion of keto-acid II *to* III

The keto-acid II (300 mg) in EtOH (15 ml) was hydrogenated in presence of Pd/C (10%, 100 mg) with a drop of perchloric acid (70%). It absorbed two molar equivs of H_2. On working up, the solid acid III (280 mg), m.p. 165–168°, was obtained which on crystallization from AcOEt–pet. ether afforded colourless needles m.p. 168–169° alone or mixed with III, m.p. 170–171°. The identity of these two acids were also established through TLC, IR and UV.

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