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SYNTHETIC STUDIES TOWARDS COMPLEX DITERPENOIDS—VI[1]

NEW SYNTHETIC ROUTES TO TETRACYCLIC BRIDGED-BICYCLO[3.2.1]OCTANE INTERMEDIATES BY INTRAMOLECULAR ALKYLATION REACTIONS THROUGH α-DIAZOMETHYL KETONES OF HYDROAROMATIC γ,δ-UNSATURATED ACIDS

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Abstract—Two new synthetic routes to a number of tetracyclic intermediates, for the total synthesis of some diterpenoids incorporating the bicyclo[3.2.1]octane moiety, are described. The syntheses of the bicyclo[3,2,1]octane derivatives begin with preparation of the hydroaromatic γ,δ-unsaturated acids **6**, **15** and **17**, and proceed via the α-diazomethyl ketones to the corresponding pentacyclic ketones **20**, **24** and **26** by an intramolecular carbenoid insertion reaction, followed by a *regiospecific* acid-catalysed cleavage of the aromatic conjugated cyclopropane bond to the respective unsaturated ketones **27**, **29** and **30**. The second route to these unsaturated ketones involves a single step boron trifluoride etherate catalysed intramolecular alkylation in the corresponding α-diazomethyl ketones. The tetracyclic ketones **31**, **34** and **35** were obtained in quantitative yields by a *regiostereospecific* hydrogenolytic cleavage of the aromatic conjugated cyclopropane bond in the respective pentacyclic precursors with Pd–C in ethanol. Under the same conditions, reduction of the styrenoid bond in the ketones **29** and **30** proceeds stereospecifically leading to **34** and **35** respectively, whereas the unsaturated ketone **27** gave a mixture of epimeric ketones **31** and **32** in a ratio of 69:31.

THE BRIDGED bicyclo[3.2.1]octane forms an integral part in a large class of tetracyclic diterpenoids.[3] This ring system, differing in the stereochemical relationship and substituent patterns, constitutes the C/D rings in the plant hormone-gibberellins, kaurene-phyllocladene and stachene groups of widely distributed diterpenes, and in the tetracarbocyclic diterpene alkaloids. In this paper we describe[4] two new simple routes to the stereospecific syntheses of a few model compounds and potential bridged-ring intermediates having the appropriately functionalized tetracyclic carbon skeletal structures[5] for elaborations of the peripheral substitution patterns, for instance, of gibberellins, phyllocladene and hibaene.

Our synthetic plan for introducing the functionalized bicyclo[3.2.1]octane bridged ring system fused in a hydroaromatic moiety, (*shown by the general scheme*) involves the intramolecular alkylation of γ,δ-unsaturated α-diazomethyl ketones (I) based upon the following two reactions: (i) The facile intramolecular carbenoid insertion by the copper-catalysed thermal decomposition of the diazoketone (I) followed by

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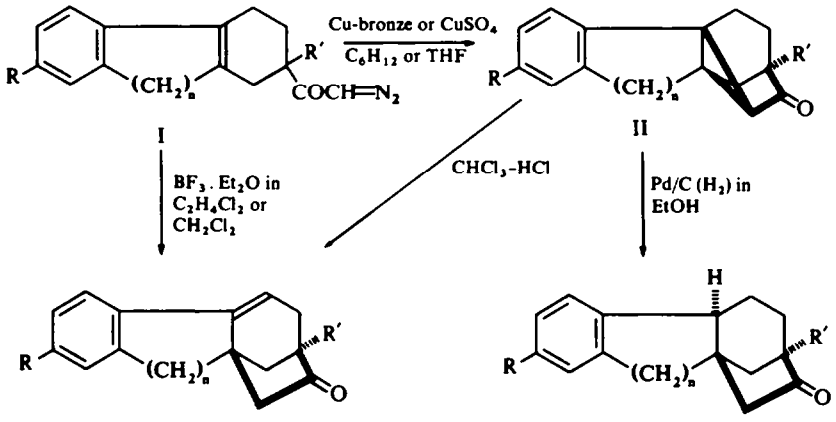
the *regiospecific* acid-induced or reductive cleavage of the aromatic conjugated cyclopropane bond in the resulting product (II). (ii) The BF_3–Et_2O catalysed intramolecular alkylation of I.

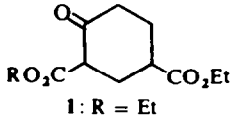
SCHEME I



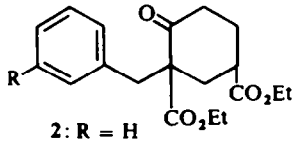
n = 1 and 2; R = H and OMe; R′ = H and Me

Synthesis of the intermediate γ,δ-unsaturated acids

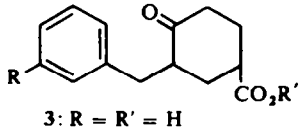
The readily available ketoester **1**,[6] on alkylations,[7] with both benzyl chloride and *m*-methoxybenzyl chloride in the presence of sodium dust in benzene–DMF afforded the corresponding alkylation products **2** and **5** in 87% and 66% yields respectively. On treatment with refluxing aqueous hydrochloric acid–acetic acid mixture, the alkylated β-keto-diester **5** underwent simultaneous hydrolysis, decarboxylation and cyclodehydration, and the γ,δ-unsaturated acid **6**, m.p. 213°, was isolated in 47% yield, after crystallisations of the solid product separating out directly from the dark black hydrolysate. No other characterizable products could be obtained from the reaction. The *des*methoxy analogue **2**, on the otherhand, under the same hydrolytic conditions produced only the decarboxylated keto-acid **3** in 70% yield. However, the numerous attempted cyclization of the ketoester **4** with conc sulphuric acid alone or in benzene and polyphosphoric acid under various conditions[1] failed.



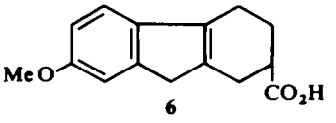
1: R = Et
7: R = CH_2Ph



2: R = H
5: R = OMe



3: R = R′ = H
4: R = H; R′ = Me
8: R = OMe; R′ = Et

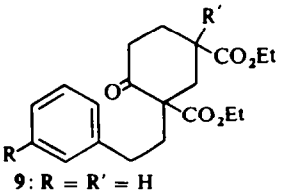


6

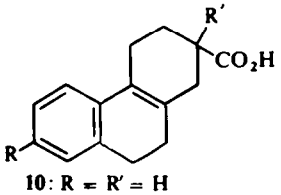
In an attempt to develop a more efficient synthesis of the acid **6** we explored a variation of the above route. The ketodiester **1**, on heating with benzyl alcohol according to Johnson *et al.*[8] afforded the β-ketobenzylethyl ester **7** in excellent yield. Alkylation of **7** with *m*-methoxybenzyl chloride yielded a viscous liquid after removal of the unreacted components. It was directly hydrogenated in ethyl acetate in the presence of 10% Pd–C. The debenzylated product, on distillation, afforded the presumed ketoester **8** in 71% yield, characterized by UV and IR spectra. This, on cyclodehydration with polyphosphoric acid[1] and alkaline hydrolysis gave the acid **6** in only 39% yield.

Having attained the synthesis of the hydrofluorene derivative **6** through simple steps amenable to a large scale preparation of this key intermediate γ,δ-unsaturated acid, we next explored this sequence for the syntheses of the corresponding hydrophenanthrene analogues **10**, **15** and **17**.

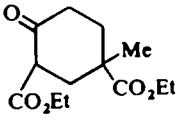
The alkylations[7] of **1** with β-phenethyl bromide and β-*m*-methoxyphenethyl bromide in benzene—DMF in the presence of sodium dust gave the desired products **9** and **11** in 38% and 30% yields respectively. Treatment of **9** with refluxing aqueous hydrochloric acid–acetic acid mixture afforded the crystalline unsaturated acid **10** in 52% yield. Under the same or various other acidic hydrolytic conditions the corresponding methoxy derivative **11** failed to produce any crystalline product. In each case we were unable to characterize any of the products from the viscous semisolid reaction mass. Similarly, attempted hydrolytic cyclodehydration of the substituted β-ketoester **13**, prepared in 30% yield by alkylation of **12**,[9] failed to afford any useful product. The difficulties to generalize the application of the alkylation-cyclodehydration method for the synthesis of these intermediates are mainly due in the cyclodehydration step, which appears to be highly specific depending upon the aromatic substituent as well as the ring size of the resulting product. Low yields in the alkylation step with β-phenethyl halides further aggravate the situation, particularly in the synthesis of the methoxy substituted hydrophenanthrene derivatives. We next turned to the use of Diels–Alder reaction for preparation of the hydrophenanthrene derivatives **15** and **17**, which were briefly reported in a few patents.[10]



9: R = R' = H
11: R = OMe: R' = H
13: R = OMe: R' = Me



10: R = R' = H
15: R = OMe: R' = H
17: R = OMe: R' = Me



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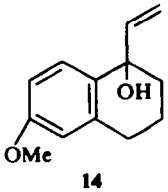

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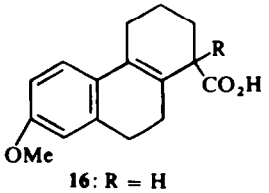


16: R = H
18: R = Me

The crude carbinol **14** prepared by the condensation of vinylmagnesium bromide with 6-methoxy tetralone, on Diels–Alder reaction* with methyl acrylate followed by short acidic treatment afforded a complex mixture of tricyclic esters. The UV maxima at 260 nm (log ε 3·9) and 273 nm (log ε 3·8) indicated the presence of almost equal amounts of the tri- and tetrasubstituted styrenoid bonds in this mixture. Prolonged treatment of this mixture with dry hydrogen chloride in chloroform completed the isomerization of the styrenoid bond as was evidenced from the shift of the UV maximum to 273 nm (log ε 4·2). On alkaline hydrolysis of the ester mixture, a crystalline acid product was obtained in good yield, which on fractional crystallization resulted in a partial separation of the pure isomeric acid (**15**), m.p. 188–189° and **16**, m.p. 149°. While the m.p. of the acid **15** is close to that of the reported[10a] m.p. for this acid, the structure of the lower melting acid has been assigned from analogy (see below).

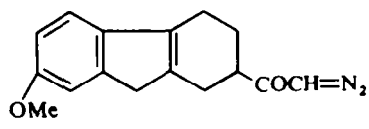
The Diels–Alder condensation of **14** with methylmethacrylate according to the reported procedure[10b] proceeded smoothly to give a mixture of the isomeric hydrophenanthrene esters from which the desired acid **17**, m.p. 156° was isolated by the controlled alkaline hydrolysis. The unsaponified ester on drastic alkaline hydrolysis afforded the known acid **18**, prepared in this laboratory through an unambiguous route.[1]

Intramolecular alkylations of the α-diazomethyl ketones

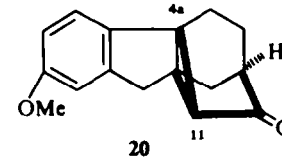
Syntheses of the bridged-ring pentacyclic ketones and unsaturated tetracyclic ketones. The crude acid chloride obtained from the reaction of the sodium salt of the acid **6** with oxalyl chloride was directly reacted with an excess of diazomethane in ether with or without the addition of triethylamine. The crystalline diazoketone **19**, having the characteristic IR bands, was directly subjected to intramolecular cyclization[11] by treatment with anhydrous copper sulphate in boiling THF or with copper bronze in boiling cyclohexane and the pentacyclic bridged compound **20** was isolated in 24–27% overall yield from **6**. The UV, IR and NMR of this material is consistent with the assigned structure. Repeating the same sequence of reaction, the acids **10**, **15** and **17** were converted to the corresponding diazoketones **21**, **23** and **25**, which on intramolecular cyclizations on treatment with copper bronze in boiling cyclohexane produced the pentacyclic ketones **22**, **24** and **26** respectively in 40–55% overall yields. The structure of these compounds were consistent with the spectral data.

It should be noted that in contrast to the corresponding hydrophenanthrene derivatives, the intramolecular carbenoid insertion in the hydrofluorene derivative **19** produced considerable amount of polymeric materials evidently arising through the intermolecular coupling reaction, thereby, decreasing the yield of **20**. This may be due to the difference in proximity of the reacting centres in the two systems. Examination of Dreiding models clearly shows that in the case of **19**, the reacting double bond is a considerable distance away from the carbenoid centre due to the planarity in the cyclohexene ring imposed in the hydrofluorene system. Fawzi and Gutsche[12] found that the spacial proximity of the olefinic bond to the diazomethyl

* The acid **6** and related γ,δ-unsaturated acids have been prepared by similar sequence in about 30–50% yields from the respective 1-indanones: U. R. Ghatak and P. C. Chakraborti, *manuscript in preparation.*



19



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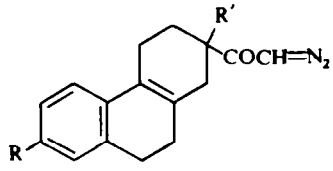
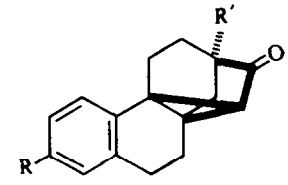
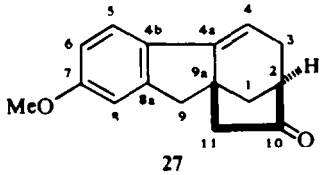


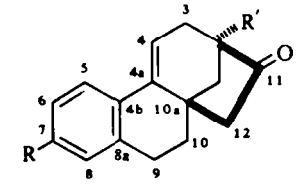
21: R = R' = H
23: R = OMe; R' = H
25: R = OMe; R' = Me



22: R = R' = H
24: R = OMe; R' = H
26: R = OMe; R' = Me



27



28: R = R' = H
29: R = OMe; R' = H
30: R = OMe; R' = Me

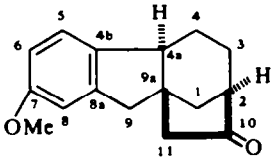
group is an important factor in determining the success of the intramolecular cyclization, while the nature of the substitution at the double bond appears to have little effect.

It has been clearly established from the studies in this laboratory[13] that the cyclopropane bond conjugated with the aromatic ring is *regiospecifically* cleaved under acid conditions. In accordance with this, treatment of the pentacyclic ketone **20** with dry hydrogen chloride in chloroform afforded the unsaturated ketone **27** in 89% yield as the only isolable product. It showed the styrenoid band at 266 nm (log ε 4·30) in the UV and a single cyclopentanone band at 1735 cm^{-1} in the IR along with an olefinic proton at 5·70 δ in the NMR. Similar cleavage reaction of the ketones **22, 24** and **26** produced the unsaturated tetracyclic ketones **28, 29** and **30** in 90–95% yields. All these compounds show the characteristic spectral data in accordance with the assigned structures. We next investigated Lewis acid catalyzed intramolecular alkylations of the diazoketones[14] **19, 23** and **25** through π-bond participation.[15] The reaction of the diazoketones **19, 23** and **25** in dilute 1,2-dichloroethane or dichloromethane solution afforded the desired unsaturated bridged ketones **27, 29** and **30** respectively, in 40–45% yields. In each case considerable amount of polymeric materials were formed.*

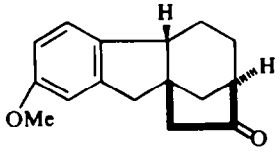
* In their preliminary communication (Ref. 15*a*), Mander *et al.* reported the formation of **27** and **29** in 97% and 90% yields respectively, by reacting the corresponding α-diazoketones with HBF_4 in nitromethane.

Catalytic reduction of the cyclopropenoid bridged-ring pentacyclic ketones and the Tetracyclic unsaturated ketones

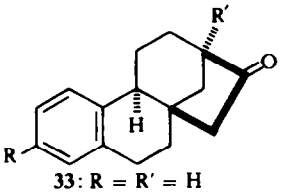
Hydrogenolysis of the aromatic conjugated cyclopropane bond has been studied by many workers.[16] However, to our knowledge no definite conclusion regarding the stereochemical outcome in this process has been recorded. In order to evaluate the synthetic possibilities, we studied the regio- and stereoselectivity of the hydrogenolysis of the pentacyclic ketones. The aromatic conjugated C-4a, C-11 cyclopropane σ-bond in the pentacyclic ketone **20** underwent rapid *regiostereospecific* hydrogenolytic cleavage with "inversion" at the C-4a asymmetric centre with 10% Pd-C in ethanol, resulting in the tetracyclic ketone **31**, m.p. 133°, in almost quantitative yield. The structural and stereochemical homogeneity of this ketone was established from the spectral comparison with the racemic 4aβ-epimer **32**, synthesised by Baker *et al.** The mass spectral fragmentation patterns of the epimeric ketones **31** and **32** (mol. ion *m/e* 242) are identical and do not show any stereochemical discrimination. The IR spectra of the ketones **31** and **32** are, however, quite different in the "finger print region" (1600–650 cm^{-1}). The CO frequency† of **31** is ν_{KBr} 1744: ν_{CCl_4} 1746 cm^{-1} and of the epimeric ketone **32** is ν_{KBr} 1746: ν_{CCl_4} 1747 cm^{-1}. The very close CO frequencies of these bridged-ketones are rather in contrast to what have been observed in a series of 10-oxo gibbane derivatives[17] having ester functionality at C-8 or C-9 (fluorene numbering, see **31**). There is a tendency for C-4aα isomers to exhibit C-10 CO absorption in the IR near 1740 cm^{-1}, whereas C-4aβ epimers absorb near 1730 cm^{-1}. Finally the NMR spectra of the ketones **31** and **32** in C_6D_6 at 100 MHz show significant difference,[17] especially the benzylic C-9 methylene protons forming AB-quartet. In the 4aα-ketone **31** this quartet appears at δ_A 2·53, δ_B 2·23, J_{AB} = 14 Hz, whereas in the 4aβ ketone **32** this appears at δ_A 2·71, δ_B 2·33, J_{AB} = 16 Hz. Also the C-4a bridgehead proton at δ 2·54 in **31** appears as a quartet with $J_{H4a\ -\ H4\,equ.}$ ($\theta \backsim 180°$) = 11 Hz and $J_{H4a\ -\ H4\,axial}$ ($\theta \backsim 40°$) = 4 Hz, in **32**, this proton is less well resolved but again appears at δ 2·53.



31



32



33: R = R′ = H
34: R = OMe; R′ = H
35: R = OMe; R′ = Me

* A. J. Baker, personal communication (*cf* Ref 5*c*). We are indebted to Dr. Baker for these comparison spectral data.

† Recorded under high resolution on a Unicam Sp 100 Spectrophotometer.

The small difference (1·5 Hz) in the OMe singlets in **31** and **32** enables the isomer composition from the reduction of C-4, 4a double bond in **27** to be readily determined (see below).

Catalytic hydrogenation (with 10% Pd/C in EtOH) of the C-4, 4a double bond in the ketone **27** produced a mixture* of 4aα and 4aβ ketones **31** and **32** in a ratio of 61 : 39, as determined from the NMR (Experimental). Although the pure 4aα ketone **31** has been isolated in about 40% yield from this mixture by fractional crystallization, we have so far failed to resolve the mixture further. The attempted GLC, TLC or column chromatographic separations of these mixtures were unsuccessful. The stereochemical outcome in the reduction of **27** is in close agreement with the results reported[18] for the hydrogenation of C-4, 4a double bond in gibberone and further confirms the view[18,19] that in absence of the C-9 substituent there is not much stereoselectivity in the reduction of this type of double bond in gibbene systems.

The hydrogenolysis of the pentacyclic ketones **24** and **26** produced the B/C-*trans* ketones **34** and **35** in almost quantitative yields. In contrast to the hydrofluorene derivative **27**, the unsaturated ketones **28**, **29** and **30**, on hydrogenation, again produced only the *trans* ketones **33**, **34** and **35** in quantitative yields. While the stereochemistry of the ketone **35** was assigned after direct comparison with an authentic sample,[20] the stereochemical assignment to the other two ketones **33** and **34** has been made in analogy with this as well as from a knowledge of the stereochemical outcome reported in the reduction of similar systems.[21]

The utility of the tetracyclic ketones **34** and **35** towards the synthesis of, for example, gibberellins is already established.[22]

The scope of these intramolecular alkylation reactions for the synthesis of complex diterpenoids and their key degradation products will be reported in our forthcoming publications elsewhere.

EXPERIMENTAL†

Diethyl cyclohexan-1-one-2,4-dicarboxylate (**1**)

Ethyl acrylate (190 g) was added dropwise to an ice-cold soln of diethyl malonate (100 g) in EtOH containing NaOEt [Na (1 g) in abs EtOH (100 ml)]. The mixture was left overnight and later refluxed for 1 hr. On acidification and usual working up, ethyl γ,γ-dicarbethoxy-pimelate (209 g, 95%), b.p. 180–85°/0·5 mm was obtained. This was hydrolysed by refluxing with conc HCl (685 ml) for 20 hr and the soln was evaporated to dryness. A small sample of the acid after washing with cold ether melted at 113–114° (lit.[23] m.p. 114–115°). The light brown crude acid was esterified by refluxing for 25 hr with a soln of benzene

* In our preliminary communication (Ref. 4) this product referred to as a pure isomer, m.p. 115°, is in fact an eutectic mixture of **31** and **32**.

† The compounds described are all racemic forms and the term α,β have only relative significance referring to the orientation of substituent groups according to steroid nomenclature. The fluorene and phenanthrene numbering systems are used throughout this paper, even in the discussion of gibbane skeletons. M.ps (taken in open capillary in H_2SO_4-bath) and b.ps are uncorrected. The purity of all compounds were determined by TLC on *ca* 0·2 mm silica gel—G using benzene–methanol and benzene–light petroleum as the solvent systems. The spots were located by exposing the dried plates to iodine vapour. Light petroleum (b.p. 60–80°) was used for column chromatography. Elemental analyses were performed by Mrs. C. Dutta in the Microanalytical laboratory of this Institute. UV were determined in 95% EtOH soln on a Beckman DU-Spectrophotometer by Mr. A. Ghosal. We express our thanks to these services. Unless otherwise mentioned IR were determined in $CHCl_3$ soln on a PE model-21 double beam recording spectrophotometer and the NMR data were obtained on a Varian A-60 D instrument and refer to TMS as internal reference.

(400 ml), 95% EtOH (270 ml) and conc H_2SO_4 (30 ml) with continuous azeotropic removal of water by means of a Dean Stark trap. After usual working up *ethyl pentan*-1,3,5-*tricarboxylate* (144 g, 90%), b.p. 182–185°/6 mm (lit.[6] b.p. 150–154°/1 mm) was obtained. It was finally subjected to Dieckmann condensation in presence of Na in benzene according to Sen Gupta[6] to afford **1**, b.p. 140°/4 mm (lit.[24] b.p. 180°/20 mm) in 80% yield.

2-Benzyl-cyclohexan-1-one-4-carboxylic acid (**3**)

To an ice-cold stirred suspension of Na dust (1·7 g) in anhyd thiophene-free benzene (75 ml) under N_2 was added dropwise a soln of **1** (16·2 g) in dry benzene (30 ml). The mixture was left overnight at room temp. Dry DMF (10 ml) was added dropwise to dissolve the Na salt followed by benzyl chloride (10 g). After 3 to 4 hr of stirring at room temp NaCl began to separate and the stirring was continued for another 4 hr. The mixture was then heated under reflux for 28 hr. The cooled mixture was diluted with a large volume of water, the benzene layer separated and the aqueous layer was extracted with ether. The combined organic layer was washed repeatedly with water and dried (Na_2SO_4). Removal of solvent and distillation of the residue afforded a thick *liquid* (19·3 g, 87%), b.p. 176–178°/0·3 mm; λ_{max} 260 nm (log ε 3·03); ν_{max} 1725 cm^{-1} (s).

The keto-diester **2** (6·3 g) was heated under reflux for 24 hr with glacial AcOH (96 ml), conc HCl (44 ml) and water (31 ml). The mixture was concentrated under reduced pressure (40–45 mm) in an oil bath at 120°. The resulting thick brown gum was diluted with water, and extracted with ether, after saturation with NaCl. The ethereal extract was washed with brine, and repeatedly with saturated Na_2CO_3aq. The regenerated acid obtained on acidification of the combined alkaline washings was taken up in ether. The ethereal extract was washed with brine and dried (Na_2SO_4). Removal of solvent yielded a yellowish white solid (3·7 g), which was crystallized from ether–light petroleum as flakes (3·4 g, 70%), m.p. 114–115°; λ_{max} 260 nm (log ε 2·81), 270 nm (log ε 2·68) and 287 nm (log ε 2·35); ν_{max} 1710 cm^{-1}. (Found: C, 72·0; H, 6·8. $C_{14}H_{16}O_3$ requires: C, 72·4; H, 6·9%).

Methyl 2-benzyl-cyclohexan-1-one-4-carboxylate (**4**)

The acid **3** (3·4 g) was dissolved in dry ether (50 ml) and treated with an ethereal soln of diazomethane. The resulting product was worked up to afford a *liquid* (3·2 g, 90%), b.p. 160–165°/0·2 mm, λ_{max} 260 nm (log ε 2·47), 265 nm (log ε 2·41) and 287 nm (log ε 2·12); ν_{max} 1710 cm^{-1}. (Found: C, 72·9; H, 7·3. $C_{15}H_{18}O_3$ requires: C, 73·1; H, 7·4%).

Diethyl 2-(m-*methoxybenzyl*)-*cyclohexan*-1-*one*-2,4-*dicarboxylate* (**5**)

Ethyl cyclohexan-1-one-2,4-dicarboxylate (**1**: 16·4 g) was condensed with *m*-methoxybenzyl chloride (11 g) in presence of Na-dust (1·7 g) under the conditions described for **2**. The resulting product was worked up to afford a liquid (16·2 g, 66%), b.p. 190–200°/0·2 mm; λ_{max} 275 nm (log ε 3·41); ν_{max} 1725 cm^{-1}. (Found: C, 65·8; H, 7·5. $C_{20}H_{26}O_6$ requires: C, 66·3; H, 7·2%).

7-*Methoxy*-1,2,3,4-*tetrahydrofluoren*-2-*carboxylic acid* (**6**)

The ketodiester **5** (8·5 g) was heated under reflux for 2 hr under N_2 with glacial AcOH (85 ml), conc HCl (40 ml) and water (6 ml). On cooling a solid separated which was filtered off. The filtrate was refluxed for further 7 hr and kept in an ice-box when more solid separated. The combined solid was taken up in large volume of EtOAc and the soln was washed with water and dried (Na_2SO_4). Removal of solvent left a brown solid which was repeatedly crystallized from EtOAc as greenish white needles (2·7 g, 47%), m.p. 213°; λ_{max} 266 nm (log ε 4·31); ν_{max} 1700 cm^{-1}. (Found: C, 73·6; H, 6·6. $C_{15}H_{16}O_3$ requires: C, 73·8; H, 6·6%).

Benzyl 4-*carbethoxy-cyclohexan*-1-*one*-2-*carboxylate* (**7**)

A soln of **1** (10 g) in distilled benzyl alcohol was transferred into a 50 ml claisen flask and the mixture was heated in an oil bath at 170–175° for 3 hr when EtOH distilled out. A low vacuum was applied to remove excess of benzyl alcohol and the residue was directly distilled to afford a thick colourless *liquid*, (12 g, 95%), b.p. 170–175°/0·2 mm, ν_{max} 1720(s), 1659(s), 1490(w), 1450(m), 1420, 1390(m) cm^{-1}. (Found: C, 67·1; H, 6·7. $C_{17}H_{20}O_5$ requires: C, 67·1; H, 6·6%).

Ethyl 2-(m-*methoxybenzyl*)-*cyclohexan*-1-*one*-4-*carboxylate* (**8**)

The ketodiester **7** (13 g) was alkylated with *m*-methoxybenzyl chloride (10 g) in presence of Na (1 g)

under the conditions as described for **5**. Removal of solvent after usual working up gave a liquid which was heated at 150° in an oil bath under reduced pressure to remove excess of halide present. The pale-yellow residue became very viscous. It was diluted with EtOAc (50 ml) and subjected to hydrogenation in presence of Pd–C (10%, 200 mg) at room temp and pressure. Since hydrogen was not consumed in appreciable amounts the catalyst was filtered off, fresh catalyst (1 g) added and hydrogenated, when uptake of H_2 was rapid and completed within 1 hr. The catalyst was filtered off and the filtrate was heated under reflux for 1½ hr. Removal of solvent left a pale yellow liquid which on distillation afforded a colourless liquid (9 g, 71%) with b.p. 170–175°/0·1 mm; λ_{max} 274 nm (log ε 3·29), 280 nm (log ε 3·26); ν_{max} 1720–35(s), 1600(s), 1590, 1500(w), 1455(s), 1380(m) cm^{-1}. Analytically pure sample could not be obtained.

Cyclization of ketoester **8** *and hydrolysis to* **6**

To a well-stirred homogeneous soln of P_2O_5 (54 g) in orthophosphoric acid (85%, 36 ml) was added the ketoester **8** (6 g) in dry ether (15 ml). The mixture was stirred at room temp for 1 hr and at 60–65° for ½ hr when it gradually assumed a deep red colour. The mixture was decomposed with crushed ice and extracted repeatedly with ether. The ethereal extract was thoroughly washed with satd Na_2CO_3 aq followed by brine and dried (Na_2SO_4). Removal of solvent left a yellow liquid (3·3 g), λ_{max} 276 nm (log ε 4·16) which was directly used for hydrolysis. The dark brown gummy acidic material (700 mg) obtained from alkaline washings could not be characterized.

The neutral residue (3·3 g) was heated under reflux under N_2 for 2 hr with KOH (3 g) water (3 ml) and ethylene glycol (27 ml). The mixture was diluted and extracted with ether. The aqueous layer was acidified with ice cold 6N HCl and was extracted with $CHCl_3$. The organic layer was washed with brine and dried. Removal of solvent left a yellow solid which on crystallization from THF–light petroleum gave yellowish white needles, (2 g, 39%), m.p. and m.m.p. 209–210° with the sample described above; λ_{max} 266 nm (log ε 4·31).

Diethyl 2-(β-*phenethyl*)*cyclohexan*-1-*one*-2,4-*dicarboxylate* (**9**)

The ketodiester **1** (23 g) was alkylated with β-phenethyl bromide (21 g) in presence of Na-dust (2·5 g) in dry DMF (15 ml) and dry benzene (150 ml) following the same conditions as described for **2** to afford the desired condensation product (11·8 g, 38%), b.p. 135–136°/0·15 mm; λ_{max} 255 nm (log ε 3·27); ν_{max} 1725 cm^{-1}. (Found: C, 68·9; H, 7·5. $C_{20}H_{26}O_5$ requires: C, 69·3; H, 7·6%).

1,2,3,4,9,10-*Hexahydrophenanthrene*-2-*carboxylic acid* (**10**)

The alkylated ketodiester **9** (11·8 g) was refluxed under N_2 for 24 hr with glacial AcOH (180 ml), conc HCl (85 ml) and water (60 ml). The mixture was concentrated under reduced pressure. The resulting product was diluted with water and repeatedly extracted with ether. The ethereal extracts were washed with sat NaCl aq and sat $NaHCO_3$ aq. The alkaline washings on acidification with excess of cold 6N HCl and extraction with ether, drying (Na_2SO_4) and removal of solvent yielded a light yellowish solid acid, which on crystallization from EtOAc–light petroleum afforded the acid **10** (4 g, 52%) in colourless flakes, m.p. 203–204°; λ_{max} 267 nm (log ε 4·06); ν_{max}^{nujol} 1695 cm^{-1}. (Found: C, 78·6; H, 7·0. $C_{15}H_{16}O_2$ requires: C, 78·9; H, 7·1%).

Diethyl 2(β-m-*methoxyphenethyl*)*cyclohexan*-1-*one*-2,4-*dicarboxylate* (**11**)

The alkylation of **1** (28 g) with β-*m*-methoxyphenethyl bromide (30 g) in presence of Na-dust (2·9 g) in DMF (22 ml) and benzene (175 ml) following the conditions as described above gave the desired product **11**, (19 g, 38%), b.p. 190–195°/0·2 mm; λ_{max} 258 nm (log ε 3·71); ν_{max} 1600(m) and 1720(s) cm^{-1}. (Found: C, 67·0; H, 7·4. $C_{21}H_{28}O_6$ requires: C, 67·0; H, 7·5%).

Diethyl 2-(β-m-*methoxyphenethyl*)-4-*methylcyclohexan*-1-*one*-2,4-*dicarboxylate* (**13**)

Compound **12** (30 g) was alkylated with β-*m*-methoxyphenethyl bromide (20·5 g) in DMF–benzene in presence of Na-dust (2 g) as described above to afford the desired alkylated product (11 g, 30%), b.p. 195–198°/0·3 mm; λ_{max} 258 nm (log ε 3·81); ν_{max} 1600(m) and 1720(s) cm^{-1}. (Found: C, 67·6; H, 7·7. $C_{22}H_{30}O_6$ requires: C, 67·7; H, 7·8%).

Repetition of the above alkylation reaction using K-dust in benzene or t-BuOK in DMSO afforded only 20–25% yields of the alkylated product.

7-Methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (**15**) *and 7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1-carboxylic acid* (**16**)

The procedure of Goldberg, *et al.*[10b] reported for **17** was adopted with modification.

A mixture of the crude 6-methoxy-1-vinyltetral-1-ol (16·7 g) prepared[25] from the condensation of 6-methoxytetral-1-one (17 g) with vinyl magnesium bromide in THF, dry thiophene-free benzene (90 ml), I_2 (200 mg), quinoline (0·2 ml) and freshly distilled methyl acrylate (25 g, 0·2 mole) were heated to reflux with a Dean Stark water separator for 9 hr. The red soln was then cooled in ice and a stream of dry HCl was passed through it for 1 min and the deep violet soln left at room temp for 2 hr. This mixture was then washed with sat NaCl aq, 5% $NaHCO_3$ aq, 10% $Na_2S_2O_3$ aq and sat NaCl aq. After removal of benzene under reduced pressure, distillation of the residual red oil afforded a pale yellow liquid (17·7 g), b.p. 175–180°/0·6 mm: λ_{max} 260 nm (log ε 3·9) and 273 nm (log ε 3·8). The above mixture of isomeric ketoester (12 g) was dissolved in dry chloroform (120 ml) and a stream of dry HCl was passed through this soln at 0° until it was saturated with the gas. Thereafter, the deep blue soln was kept at room temp for ½ hr and chloroform evaporated to leave a pale yellow oil (12 g): λ_{max} 273 nm (log ε 4·2). This was dissolved in MeOH (120 ml) and refluxed under N_2 for 2 hr with a soln of KOH (12 g) in water (12 ml). After cooling the red soln was diluted with water (500 ml) and extracted with ether. The alkaline portion was acidified in the cold with ice-cold 6N HCl and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). Removal of the solvent afforded a yellow crystalline material (10·1 g), m.p. 135–145°: λ_{max} 273 nm (log ε 4·2). It was found to be a mixture of two isomeric acids **15** and **16** and which were separated by repeated fractional crystallizations from EtOAc–light petroleum. The less soluble isomer **15** melted at 188–189° (lit.[10a] m.p. 184–188°): λ_{max} 273 nm (log ε 4·2). (Found: C, 74·1; H, 7·1. Calcd. for $C_{16}H_{18}O_3$: C, 74·3; H, 7·0%). The other isomer **16** had the m.p. 149°: λ_{max} 273 nm (log ε 4·2). (Found: C, 74·3; H, 7·2%).

The isomeric acids **15** and **16** were isolated in a ratio of about 60:40. However, a considerable amount of the mixed acid could not be separated.

7-Methoxy-2-methyl-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (**17**) *and 7-methoxy-1-methyl-1,2,3,4,9,10-hexahydrophenanthrene-1-carboxylic acid* (**18**)

The acid **17**, m.p. 156° (lit.[10b] m.p. 153·5–154·5°): λ_{max} 275 nm (log ε 4·1). (Found: C, 74·8; H, 7·2. Calcd. for $C_{17}H_{20}O_3$: C, 74·9; H, 7·4%) was prepared according to the reported procedure.[10b] The isomeric acid **18** m.p. and m.m.p. 139°, with an authentic sample[1] was isolated after drastic alkaline hydrolysis[1] of the unhydrolysed ester[10b] from the Diels–Alder reaction product and hydrolysis with methanolic-KOH soln.

Preparation of diazoketones and carbenoid insertion reactions

α-Diazomethyl ketone **19**. The acid **6** (2 g) was taken in abs EtOH (200 ml) and the warm suspension was neutralized with a 10% soln of NaOEt in EtOH using phenolphthalein as indicator. The solvent was removed under reduced pressure. To the sodium salt, dry benzene (25 ml × 4) was added and distilled off (4 times) to remove traces of moisture and EtOH. The salt was finally dried at 80–85°/10 mm (oil bath) for 4 hr. It was taken in dry benzene and the suspension was cooled in ice bath. To it was added pyridine (0·5 ml) and oxalyl chloride (4 ml) and thoroughly shaken for 5 min. It was kept at room temp for 30 min more and finally heated at 60° for 1 hr. The precipitated NaCl was filtered off. On removal of the solvent under reduced pressure the acid chloride was obtained as dark solid. The ice cold soln of the crude acid chloride in dry ether was added dropwise to a cold ethereal soln of diazomethane (prepared from 4 g of N-methylnitrosourea) with or without the addition of triethylamine (1 ml) and left overnight. The separated salt was filtered off (when TEA was used) and solvent removed from the filtrate to afford the diazoketone as a yellow solid, m.p. 103° (lit.[15a] m.p. 98–99°): ν_{max} 2115(s), 1630(m) cm^{-1}.

Cyclization of the diazoketone **19** *to the pentacyclic ketone* **20**

(a) The crude diazoketone **19** was dissolved in dry THF (100 ml) and added dropwise to a stirred suspension of anhyd $CuSO_4$ (1 g) in refluxing THF (50 ml) during 1½ hr. The mixture was refluxed for 8 hr more, cooled and filtered. Removal of solvent from the filtrate afforded a dark brown solid which was taken up in minimum quantity of benzene and chromatographed through neutral alumina. Fractions eluted with light petroleum afforded a yellowish white solid (530 mg, 27%), which was crystallized from EtOAc–light petroleum as cubes, m.p. 121°: λ_{max} 248 nm (log ε 4·01): δ_{CDCl_3}, 3·2 (br.S, $ArC\underline{H_2}$-), 3·8 (s, OCH_3): ν_{max} 1710 cm^{-1}. (Found: C, 79·9; H, 6·8. $C_{16}H_{16}O_2$ requires: C, 80·0; H, 6·7%).

(b) When the crude diazoketone **19** (prepared from 1·5 g of the acid **6**) in cyclohexane (200 ml) was heated under reflux in presence of Cu-bronze (0·5 g) the ketone **20** was obtained in 24% overall yield.

Cyclization of the diazoketone **21** *to the pentacyclic ketone* **22**

A soln of the crude **21** (1·0 g; ν_{max} 2115 and 1630 cm^{-1}), prepared from **10** (1·0 g) following the procedure described above, in dry purified cyclohexane (150 ml) was heated under reflux with a suspension of copper-bronze (0·5 g) for 18 hr. On cooling, the mixture was filtered from the insoluble materials and the latter was washed with chloroform. The combined filtrate was concentrated under reduced pressure to afford a thick yellow gum (606 mg) which solidified on standing, m.p. 88–90°. Two crystallizations from light petroleum gave pure **22** (500 mg, 51%), m.p. 99–100°: λ_{max} 238 nm (log ε 4·1), ν_{max} 1715 cm^{-1}. (Found: C, 85·4; H, 7·4. $C_{16}H_{16}O$ requires: C, 85·6; H, 7·1%).

Cyclization of the diazoketone **23** *to pentacyclic ketone* **24**

The crude **23** (m.p. 128–131° (d); ν_{max} 2110, 1640 and 1610 cm^{-1}), prepared from **15** (2 g), on cyclization following the procedure as for **22** afforded an orange solid, which was chromatographed on neutral alumina (40 g). The desired pentacyclic ketone was eluted with pet. ether; yield 850 mg (41%), m.p. 115–117°: ν_{max} 1710(s) and 1610(m) cm^{-1}. The analytical sample was crystallized from ether in shining plates, m.p. 117° (lit.[15a] m.p. 108–110°). (Found: C, 79·9; H, 6·8. $C_{17}H_{18}O_2$ requires: C, 80·3; H, 7·1%).

Cyclization of the diazoketone **25** *to pentacyclic ketone* **26**

The crude **25**, prepared from **17** (1·2 g) on cyclization under the above conditions afforded a brown solid. It was chromatographed on neutral alumina (30 g) and elution with light petroleum furnished the desired **26** (700 mg, 55%), m.p. 137–139°: λ_{max} 248 nm (log ε 4·12); ν_{max} 1710(s) and 1610(m) cm^{-1}. An analytical sample, m.p. 140°, was obtained after crystallization from EtOAc–light petroleum. (Found: C, 80·3; H, 7·5. $C_{18}H_{20}O_2$ requires: C, 80·5; H, 7·5%).

Acid-catalysed cleavages of the bridged pentacyclic ketones

Cleavage of the ketone **20**: 7-*methoxy*-1,2,3,9a-*tetrahydro*-2,9a-*ethanofluoren*-10-*one* (**27**). To a solution of **20** (270 mg) in dry $CHCl_3$ (50 ml) was passed dry HCl gas for 1½ hr when the colour gradually turned red. Removal of solvent left a solid which was crystallized from EtOAc–light petroleum ether as light needles, m.p. 129–130°; (240 mg, 89%): λ_{max} 266 nm (log ε 4·30): ν_{max} 1735(s) cm^{-1}: δ_{CDCl_3} 3·05 (br.d., —Ar—CH_2—), 3·80 (s, OMe), 5·70 (br.t, =C<u>H</u>—). (Found: C, 80·2; H, 6·8. $C_{16}H_{16}O_2$ requires: C, 79·97; H, 6·7%).

Cleavage of the ketone **22**

1,2,3,9,10,10a-*Hexahydro*-2,10a-*ethanophenanthrene*-11-*one* (**28**). Cleavage of **22** (200 mg) in dry $CHCl_3$ (40 ml) with dry HCl gas at room temp for 1 hr yielded a liquid product which on evaporative distillation at 135° (bath temp)/0·1 mm afforded the unsaturated **28** (185 mg, 93%) as a thick yellow glassy solid: λ_{max} 265 nm (log ε 4·17); ν_{max} 1730 cm^{-1} (cyclopentanone); δ_{CDCl_3} 6·23 (br. t =C<u>H</u>—). The product could not be induced to crystallize. (Found: C, 85·7; H, 7·3. $C_{16}H_{16}O$ requires: C, 85·6; H, 7·2%).

It afforded a yellow 2,4-*dinitrophenylhydrazone* derivative, which was crystallized from EtOAc–light petroleum, m.p. 190–192°. (Found: C, 65·3; H, 5·2. $C_{22}H_{20}O_4N_4$ requires: C, 65·3; H, 5·0%).

Cleavage of the ketone **24**

7-*Methoxy*-1,2,3,9,10,10a-*hexahydro*-2,10a-*ethanophenanthren*-11-*one* (**29**). The cleavage of **24** (200 mg) with dry HCl in $CHCl_3$ under the above conditions afforded the unsaturated **29** (190 mg, 95%). It was crystallized from EtOAc, m.p. 115° (lit.[15a] m.p. 115–116°): λ_{max} 270 nm (log ε 4·2); ν_{max} 1730 cm^{-1}. (Found: C, 80·4; H, 7·2. $C_{17}H_{18}O_2$ requires: C, 80·3; H, 7·1%).

Cleavage of ketone **26**

7-*Methoxy*-2-*methyl*-1,2,3,9,10,10a-*hexahydro*-2,10a-*ethanophenanthren*-11-*one* (**30**). The ketone **26** (200 mg) on cleavage with dry HCl in $CHCl_3$ afforded the unsaturated **30** (196 mg, 95%) which on crystallization from EtOAc–light petroleum melted at 142°: λ_{max} 270 nm (log ε 4·2); ν_{max} 1730 cm^{-1}. (Found: C, 80·3; H, 7·4. $C_{18}H_{20}O_2$ requires: C, 80·5; H, 7·5%).

BF_3–Et_2O *Catalysed intramolecular alkylation of the diazoketones*

Conversion of **19** *to* **27**. To a soln of the crude **19**, prepared from the **6**, (1·0 g), in anhyd dichloroethane

(100 ml) or methylene chloride (100 ml), cooled in ice-salt bath ($-10° \sim -5°$), freshly distilled BF_3-Et_2O (0·8 ml) was added. The mixture was swirled briefly and left as such for 1 hr. The brownish-red soln was washed with water, 2% Na_2CO_3 aq and finally with water. The dried (Na_2SO_4) extract was evaporated and the light brown solid (900 mg) was chromatographed on neutral alumina (20 g). Fractions eluted with light petroleum and light petroleum-benzene (9:1 to 7:3) afforded 450 mg (45%) of the colourless solid, m.p. 124°. On recrystallization from EtOAc-light petroleum it afforded the pure **27**, m.p. and m.m.p. 128-129°.

Conversion of **23** *to* **29**. The crude **23**, prepared from the **15** (700 mg), was dissolved in dichloroethane (60 ml) and BF_3-Et_2O (0·5 ml) was added to the soln, precooled in an ice-bath. The mixture was left as such for 1½ hr and after working up in the usual way afforded a dark brown solid mass, which on chromatography over neutral alumina (10 g) afforded 300 mg (43%) of **29**, m.p. and m.m.p. 114-115°.

Conversion of **25** *to* **30**. Repeating the above sequence of reactions the diazoketone prepared from **17** (700 mg), afforded the unsaturated **30** (290 mg, 41%), m.p. and m.m.p. 139-140°.

Catalytic hydrogenolyses of the bridged-ketones and reduction of the unsaturated ketones: 7-*Methoxy*-1,2,3,4,4aα,9a-*hexahydro*-2β,9aβ-*ethanofluoren*-10-*one* (**31**)

(a) *Catalytic hydrogenolysis of* **20**. The ketone **20** (100 mg) in EtOH (20 ml) was hydrogenated in presence of Pd-C (10%, 30 mg). The uptake of H_2 was very fast. Filtration and removal of the solvent from the filtrate gave a solid which was crystallized from light petroleum as cubes, m.p. 133° (92 mg, 92%): λ_{max} 230 nm (log ε 3·75) and 280 nm (log ε 3·45). (Found: C, 79·0; H, 7·7. $C_{16}H_{18}O_2$ requires: C, 79·3; H, 7·5%).

(b) *Catalytic hydrogenation of* **27**. The unsaturated compound (26 mg) was hydrogenated in EtOH (12 ml) in presence of Pd/C (10%, 11 mg) at room temp and pressure. Uptake of H_2 was very fast. The catalyst was filtered and solvent removed under reduced pressure to afford a white solid (24·6 mg), m.p. 115-117°. NMR of this product in $CDCl_3$ at 100 MHz shows two OMe signals ($\sim\delta$ 3·7) separated by 1·5 Hz. From the peak heights as well as direct NMR comparison (through the courtesy of Dr. Baker) with a mixture of the *trans* ketone **31** and *cis* ketone **32**, the ratio of **31** and **32** in the reduction product was determined to be 61:39. GLC, TLC or column chromatography under various conditions failed to resolve the mixture.

1,2,3,4,4aα,9,10,10a-*Octahydro*-2β,10aβ-*ethanophenanthren*-1-*one* (**33**)

Hydrogenation of the unsaturated ketone **28**. The unsaturated ketone **28** (280 mg) in EtOH (30 ml) was hydrogenated in presence of 10% Pd/C (100 mg) to afford the saturated ketone **33** (275 mg, 99%), as a colourless viscous liquid, on evaporative distillation at 140° (bath temp)/0·2 mm: λ_{max} 266 nm (log ε 2·74), 274 nm (log ε 2·73); ν_{max} 1735 cm^{-1}. (Found: C, 84·8; H, 8·1. $C_{16}H_{18}O$ requires: C, 84·9; H, 8·0%).

The 2,4-*dinitrophenylhydrazone* of the ketone **33** was crystallized from EtOAc-light petroleum, m.p. 164-166°. (Found: C, 65·0; H, 5·6; N, 14·1. $C_{22}H_{22}O_4N_4$ requires: C, 65·0; H, 5·4; N, 13·8%).

7-*Methoxy*-1,2,3,4,4aα,9,10,10a-*octahydro*-2β,10aβ-*ethanophenanthren*-11-*one* (**34**)

(a) *Hydrogenolysis of cyclopropylketone* **24**. The bridged ketone **24** (200 mg) in EtOH (20 ml) was hydrogenated in the presence of 10% Pd/C (50 mg) to afford the saturated ketone **34** (180 mg, 90%), m.p. 130-131°, on crystallization from EtOAc: λ_{max} 278 nm (log ε 3·8): ν_{max} 1740 cm^{-1}: δ_{CDCl_3} 3·76 (s), OCH_3). (Found: C, 79·6; H, 7·9. $C_{17}H_{20}O_2$ requires: C, 79·7; H, 7·9%).

(b) *Hydrogenation of the unsaturated ketone* **29**. Catalytic hydrogenation of the unsaturated ketone **29** (100 mg) in EtOH (15 ml) in presence of 10% Pd/C (50 mg) yielded the saturated ketone **34** (80 mg, 80%), m.p. and m.m.p. 130–131°, after crystallization from EtOAc.

7-*Methoxy*-2-*methyl*-1,2,3,4aα,9,10,10a-*octahydro*-2β,10aβ-*ethanophenanthren*-11-*one* (**35**)

(a) *Hydrogenolysis of the cyclopropyl ketone* **26**. Hydrogenolysis of **26** (200 mg) under the above condition afforded (180 mg, 90%) of the saturated ketone **35**, m.p. 139° (lit.[20] m.p. 135·5-136·5°) after crystallization from EtOAc-light petroleum: λ_{max} 278 nm (log ε 3·9): ν_{max} 1740 cm^{-1}: δ_{CDCl_3} 1·06 (s, $-CH_3$), 3·76 (s, OMe). (Found: C, 79·6; H, 8·2. Calcd. for $C_{18}H_{22}O_2$: C, 79·9; H, 8·2%).

The mixed m.p. of this sample remained undepressed with a sample of **35** prepared through a different route by Ogawa and Matsui.[20] Both the samples have identical IR spectra in Nujol.

(b) *Hydrogenation of the unsaturated ketone* **30**. The unsaturated ketone **30** (200 mg) in EtOH (35 ml) on hydrogenation in the presence of 10% Pd/C (75 mg) yielded the saturated ketone **35** (180 mg, 90%), m.p. and m.mp. 139°.

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