A Thesis

entitled

"Synthetic Studies on Gibberellins"

submitted to the

University of Glasgow

for the degree of Doctor of Philosophy

in the Faculty of Science

by

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Summary

This thesis describes the investigation of two possible synthetic routes to 3-methoxy-6α-carbomethoxy-16-oxogibb-A-triene (I), an intermediate of potential significance in the synthesis of the plant hormone gibberellin A_4.

The first synthetic route required the preparation of a substituted indanone which was eventually achieved *via* a hydrofluorenone intermediate. Elaboration of this indanone to 3-methoxy-6α-carbomethoxy-12,16-dioxogibb-1,3,5(10),9-tetraene was accomplished, but the final step in this approach, hydrogenation of the latter compound to give the required keto-ester (I), could be effected only in low yield. In the course of this investigation a novel one-step conversion of a cyclohexene oxide to a *trans* 7,9-dioxabicyclo(4.3.0)nonane was effected.

The second synthetic approach to the intermediate (I) involved elaboration of a bicyclo(3.2.1)octanone, but lack of time did not permit the more detailed study which this approach required.

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The author is also indebted to the research students and staff of this department from whom he has learned a great deal, both chemical and non-chemical, and with whom he is proud to have been associated.

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Summary

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The first synthetic route required the preparation of a substituted indanone which was eventually achieved *via* a hydrofluorenone intermediate. Elaboration of this indanone to 3-methoxy-6α-carbomethoxy-I2,I6-dioxogibb-I,3,5(I0),9-tetraene was accomplished, but the final step in this approach, hydrogenation of the latter compound to give the required keto-ester (I), could be effected only in low yield. In the course of this investigation a novel one-step conversion of a cyclohexene oxide to a *trans* 7,9-dioxabicyclo(4.3.0)nonane was effected.

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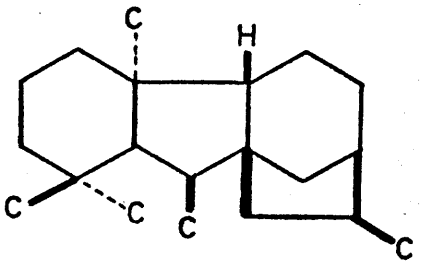

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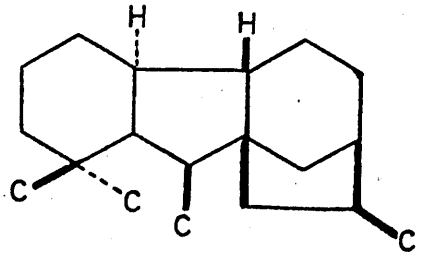

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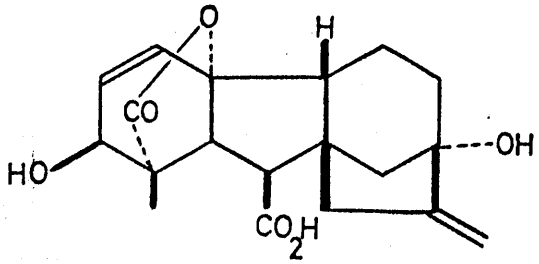

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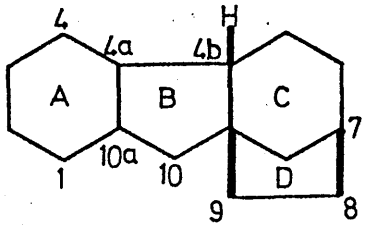
Introduction.

"Chemists in far flung laboratories have undertaken the formidable task of reproducing gibberellic acid and related structures by chemical synthesis. The result of their effort to date has been an almost unprecedented outpouring of ingenious synthetic designs and highly original new synthetic methods."

E.J. Corey 1971.

The gibberellins were discovered as a result of studies by Japanese scientists into a soil borne disease of rice, the Bakanae disease, caused by the fungus gibberella fujikoroi. It was in 1939 that Yabuta and Hayashi[1] first isolated a crystalline plant growth regulating substance from cell-free extracts of the fungus and for which they coined the name gibberellin. Until 1954 almost all publications on the gibberellins were Japanese; access to the numerous early Japanese papers has been greatly simplified by the publication by Stodola[2] of his " Source book on gibberellin, 1828-1957 ".

The gibberellins, which are diterpenoid acids, are endogenous plant hormones associated with the regulation of plant growth[3] and can be divided into two groups, namely C_{20}-(1) and C_{19}-(2) gibberellins. The structure and absolute stereochemistry of gibberellic acid (gibberellin A_3) (3) was finally established in Glasgow by X-ray structure analysis



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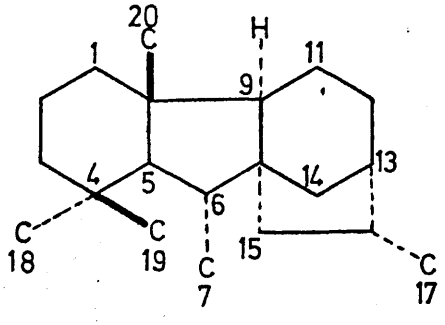


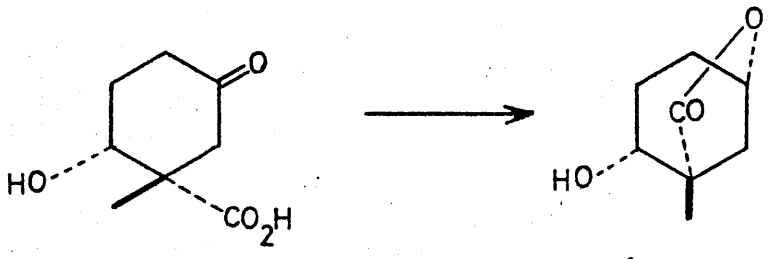
(5)

and circular dichroism measurements.[4] The structures of the other gibberellins (of which about forty are known at present) have been determined by interconversion and correlation with the acid (3), its derivatives and degradation products.

Gibberellins have been named and numbered according to two different conventions. Firstly, nomenclature may be based on the hydrocarbon gibbane[5] numbered as shown in (4). This has been the system used until recently when support has been found for the second system, diterpene nomenclature. This latter convention[6] is based on the hypothetical diterpene gibberellane (5), with the numbering as shown. Although diterpene numbering of gibberellins maintains the consistency with other polycyclic terpenoid systems[7], the use of gibberellane nomenclature is often clumsy and unwieldy especially for synthetic intermediates which lack C_7, C_{17}, C_{18}, C_{19} and C_{20} carbon atoms. In this thesis gibbane nomenclature and gibberellane numbering will be used.

Since the early 1960's a vast amount of research has been directed towards the laboratory synthesis of gibberellins.[8] This has been motivated by the potential commercial viability of any synthesis due to their remarkable biological activity and the synthetic challenge of being able to reproduce in the laboratory such a structurally and stereochemically complex array of functionality (eg. gibberellic acid (3)).

This introduction will discuss the synthesis of gibberellins and related synthons. The biosynthesis has been comprehensively reviewed by McMillan[3] and is not described here.


O
HO
CO2H
O
CO
HO

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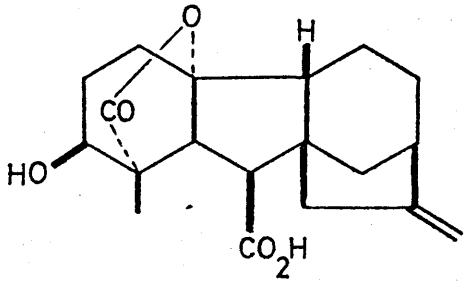
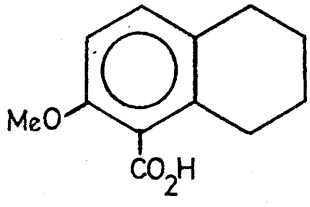
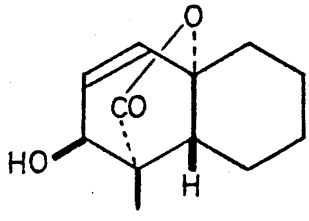

O
H
CO
HO
CO2H

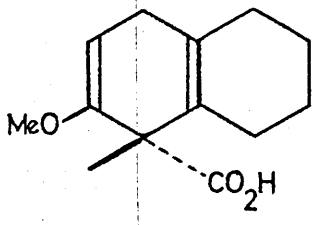
(7)


MeO
CO2H

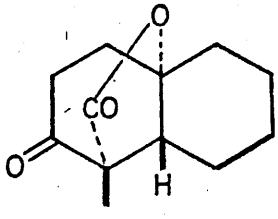
(8)


O
CO
HO
H

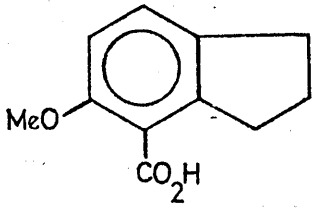
(9)


MeO
CO2H

(10)


O
CO
O
H

(11)


MeO
CO2H

(12)

Synthetic approaches to the gibberellins can conveniently be described under three main headings :

(a) Construction of the ring A system.

(b) Construction of the bicyclo(3.2.I)octane CD ring system.

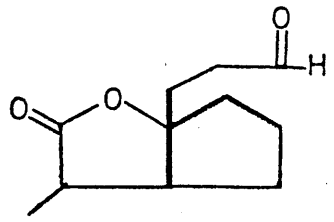
(c) The synthesis of hydrofluorenes.

(a) Construction of the ring A system.

In I96I Mori was engaged in studies concerning the structure of ring A of gibberellic acid[8b](3). His approach, which was rather inelegant if effective, was to synthesise a series of γ and δ lactones. He prepared thirteen in all, one of which, (6), turned out to be the C-3 epimer of ring A of gibberellin A_4 (7). Moffat[9], using a somewhat similar synthetic approach, prepared the ring A analogue of gibberellin A_4 (7) and showed that it was epimerised to (6) by aqueous alkali. Similar behaviour has been observed in the gibberellins[I0] and probably occurs by a retro-aldol mechanism[II].

Loewenthal,[I2] starting from the acid (8), has constructed a more useful model, (9), of ring A of gibberellic acid (3) by the sequence (8 ⟶ I0 ⟶ II ⟶ 9), although a similar sequence starting from the indane (I2) might have been even more useful.

Dolby [I3] has constructed the ring A analogues of both



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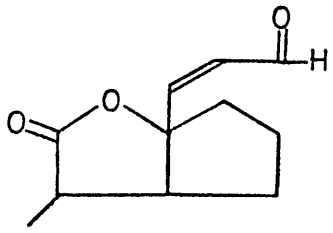

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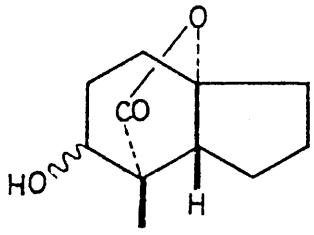

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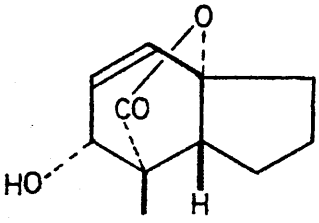

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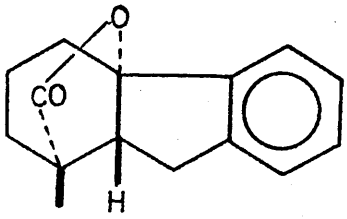

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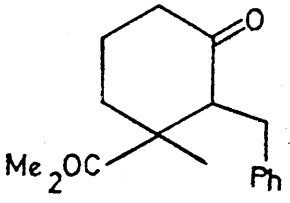

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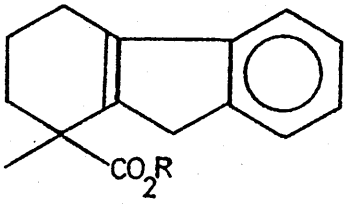
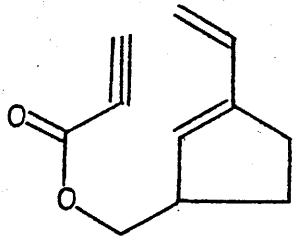


(18) R=Me

(19) R=H



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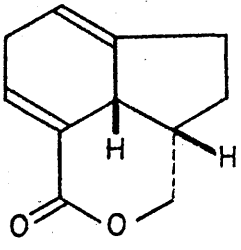

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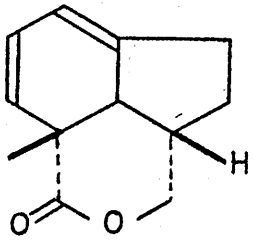

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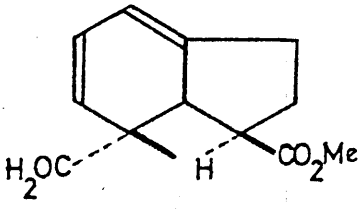

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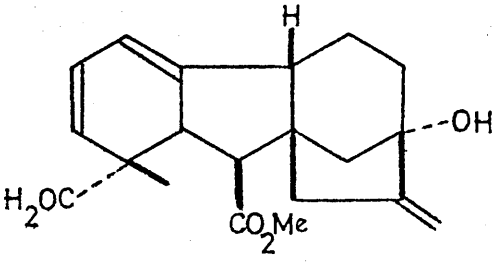

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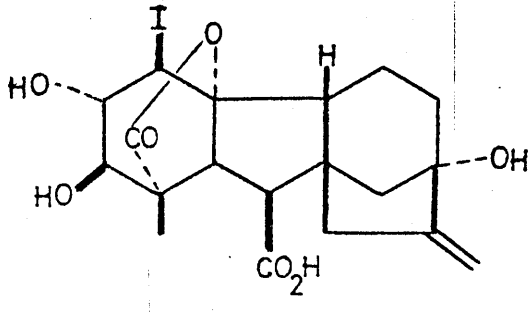


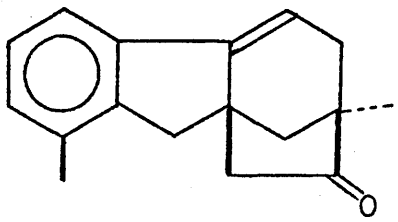
(25)

gibberellic acid (3) and gibberellin A_4 (7) by using an aldol cyclisation procedure suggested by the known C-3 hydroxyl epimerisation[10]. The readily prepared lactones (I3) and (I4) were cyclised using potassium t-butoxide as reagent to give the alcohols (I5a) and (I5b) respectively. The required axial alcohols were produced by oxidation to the corresponding ketones and stereoselective reduction using aluminium iso-propoxide. Although this method is an interesting study in synthetic design, its use in the total synthesis of gibberellins would present problems.

Ghatak[14] has prepared the lactone (I6) by application of the sequence (I7 ⟶ I8 ⟶ I9 ⟶ I6), but again it is possible to see difficulties which would arise if this procedure were applied to a total synthesis.

Probably the most promising approach is that which Corey[15] has recently described. The key step was the intramolecular Diels-Alder cyclisation of the readily prepared diene ester (20) to form the lactone (2I) which was alkylated to (22). Hydrolysis of the lactone function and oxidation gave the ester-acid (23) after selective methylation via an iodolactone intermediate.

The triene acid (24), of which (23) is the ring AB analogue, was previously elaborated to methyl gibberellate (3, methyl ester) by regioselective oxidation with m-chloroperbenzoic acid to give, after saponification and iodine treatment, the lactone (25). Conversion of the latter to



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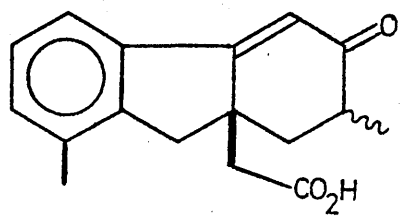

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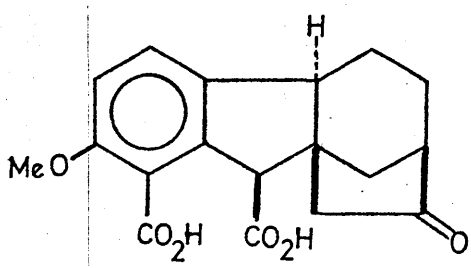

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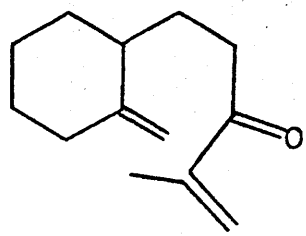

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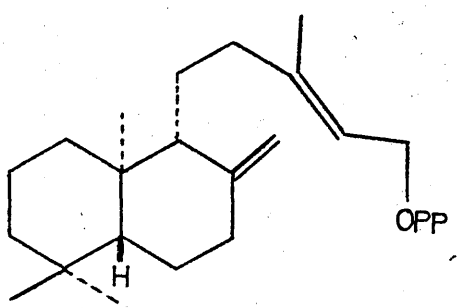

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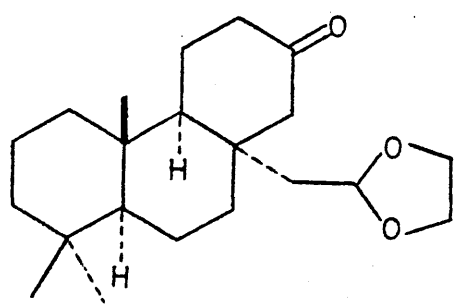

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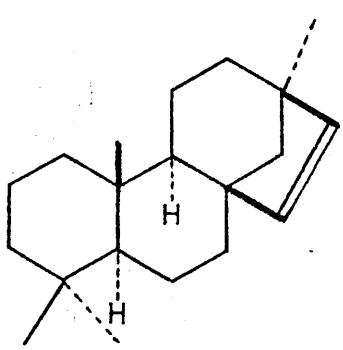

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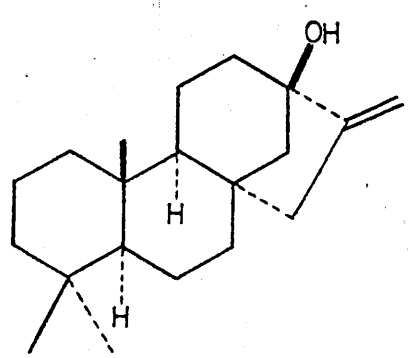


(33)

the desired product was achieved by (a) trifluoroacetylation, (b) elimenation with zinc dust and (c) detrifluoroacetylation with aqueous sodium bicarbonate.

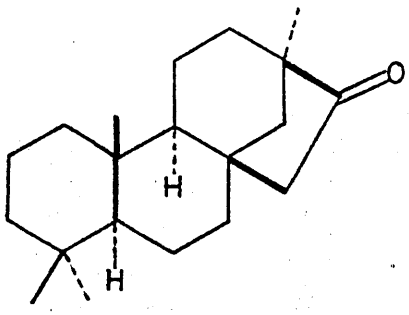
(b) Construction of the bicyclo(3.2.I)octane CD ring system.

(I) Acid catalysed cyclisations.

Loewenthal[I6] and Raphael[I7] independently synthesised gibberone (26), a degradation product of gibberellic acid (3), by the annelation of a suitably substituted indanone to give the tricyclic acid (27). This acid was treated with boron trifluoride-acetic acid to close ring D by cyclodehydration. The last step in this sequence has been improved upon [I8] by using naphthalene-I-sulphonic acid and has found use in subsequent syntheses using the same approach,[I9] notably Loewenthal's synthesis of the diacid (28) of unnatural stereochemistry at the BC ring junction.[I9(c)]

In an attempt to mimic the known biogenisis of the CD ring system, Dolby and Iwomoto[20] treated the diene (29) with acid under a variety of conditions. Although (29) bears a formal relationship to the labdane biogenetic precursor[2I] (30) of gibberellic acid (3), the product was invariably an intractable oil comprising more than a dozen components.

At this point mention might be made of the efficient method by which Ireland[22] transformed the keto-acetal (3I) into hibaene (32). (3I) Was elaborated *via* a series of high yield reactions to the allylic alcohol (33) which



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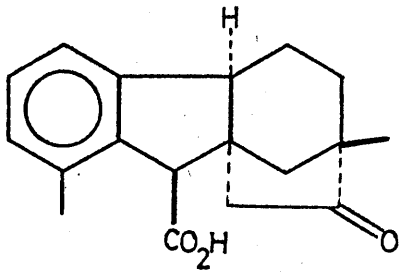

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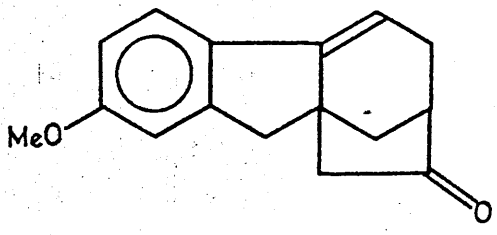

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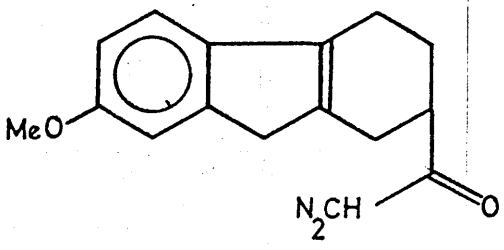

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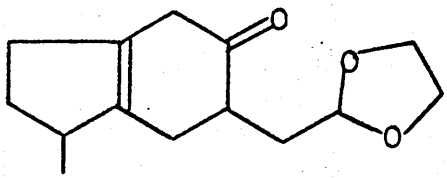

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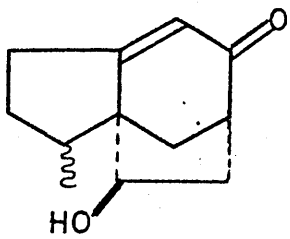

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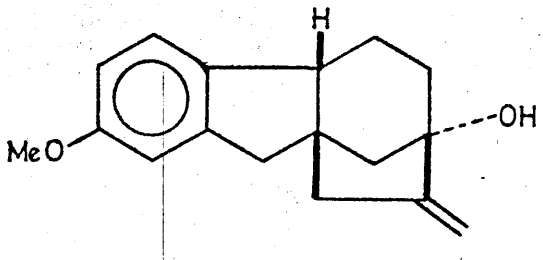

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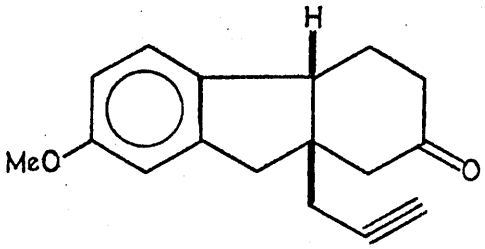


(41)

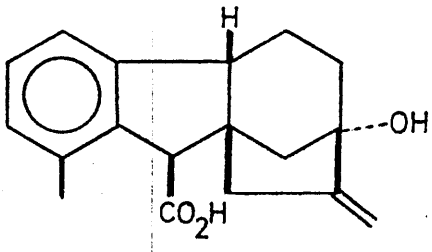
contains the CD ring system of gibberellic acid (3). This alcohol was rearranged in acid solution to the ketone (34) by analogy with the well established [23] gibberellic acid (3)-gibberic acid(35) transformation. The final conversion to hibaene (32) was effected by reduction of the ketone function and dehydration *via* the derived tosylate.

An interesting approach has been the cyclisation of unsaturated diazoketones which Ghatak [24] and Mander[25] have attempted. Both of these workers independently prepared the keto-olefin (36) from the diazoketone (37) by acid treatment. Ghatak[26] has also studied the stereochemistry of hydrogenation of the cyclopropanes and olefins produced from such keto-carbenoid additions. In general the $\Delta^{9,11}$ gibbenes produced from acid catalysed cyclisations are hydrogenated to the unnatural configuration at C-9 unless a suitably oriented C-6 substituent is present,[19d] although exceptions have been noted.[26]

By a novel procedure, Wiesner[27] cyclised the unsaturated keto-acetal (38) by heating in 80% acetic acid to give a mixture of tricyclic epimers (39) in high yield.

(2) Base catalysed cyclisations.

The CD ring analogue (40) of gibberellin A_3 (3) was prepared by Stork[28] by reductive cyclisation of the acetylenic ketone[29] (41) using potassium in liquid ammonia/tetrahydrofuran.



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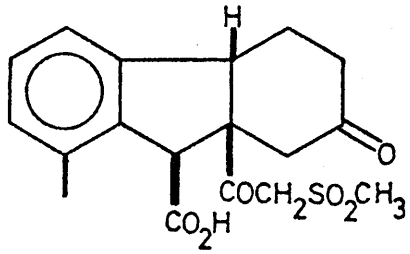

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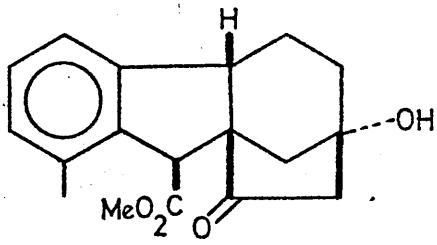

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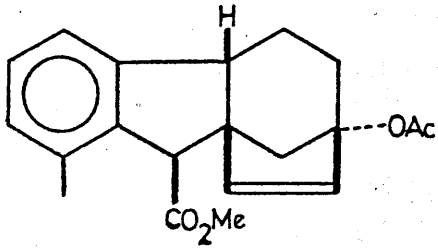

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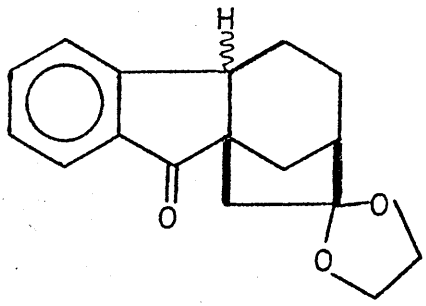

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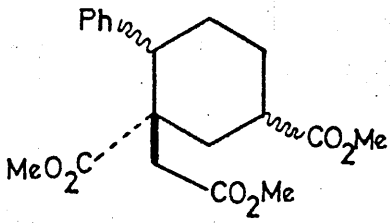

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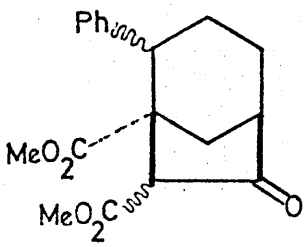

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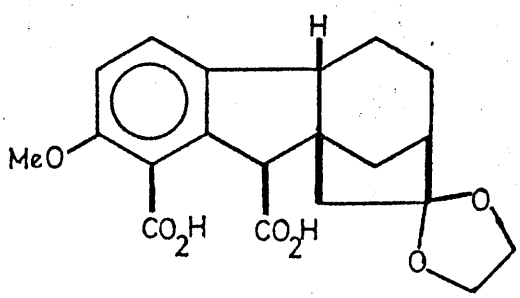

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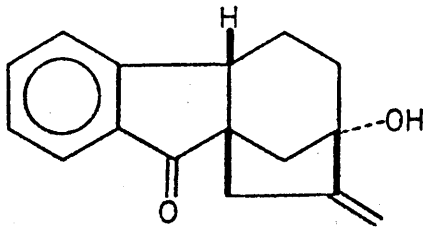

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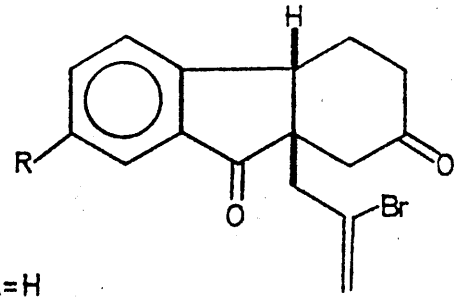
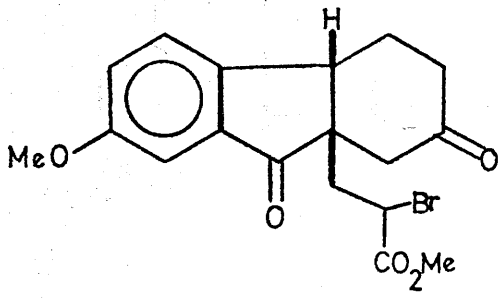


(51) R=H

(52) R=OMe



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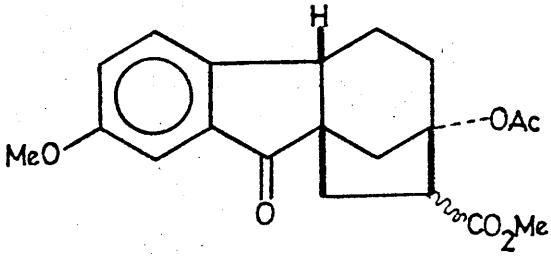

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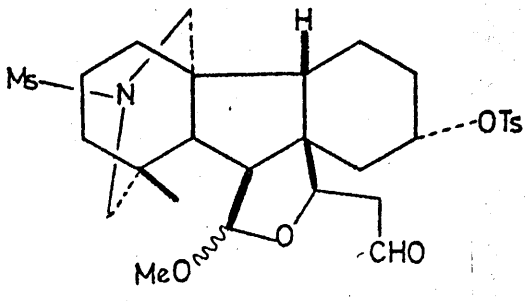

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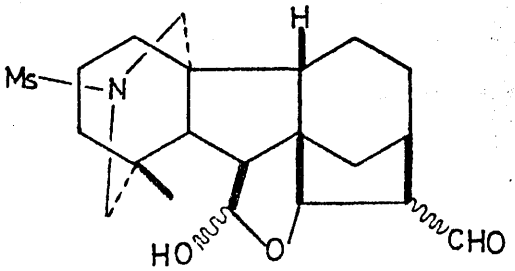


(56)

Another route to the bridgehead hydroxylated biclo(3.2.I)-octane system has been described by House[30] in his synthesis of epiallogibberic acid (42). Base catalysed cyclisation of the diketosulphone (43) followed by a procedure involving reduction with aluminium amalgam in water gave the required product (44) after methylation. In this case the ketone function is in an unsuitable position and was converted to (45) before elaboration to (42).

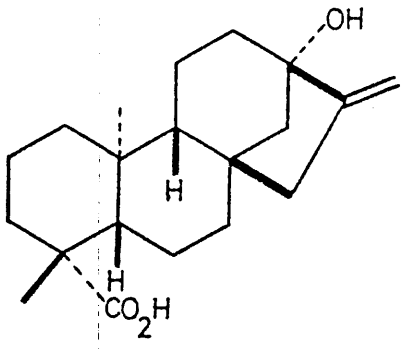
In her synthesis of the gibbane (46) Gerber [3I] used a Dieckmann cyclisation to construct the CD ring system, (47⟶48). This approach has recently been taken up by Baker[32] and used to good effect in his synthesis of the advanced gibberellin synthon (49).

The hydroxy-ketone (50) was prepared by Corey [33] from the bromodiketone (5I) using di-n-butylcopper lithium in ether at -50°. A similar cyclisation of (52) via an intramolecular Grignard reaction carried out by Ziegler[34] was unsuccessful, although he obtained the tetracyclic compound (54) from (53) by an internal Reformatsky reaction after quenching the reaction mixture with acetic anhydride.

In his total synthesis of gibberellin A_{I5}, Nagata[35] effected the ring D closure of the complex synthon (55) to give (56) by using pyrrolidine in methanol/N-methylpyrrolidone followed by acid hydrolysis.

(3) Radical-anion cyclisations.

Cook[36] has used an acyloin condensation to construct



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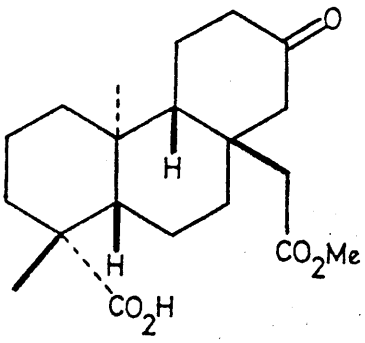

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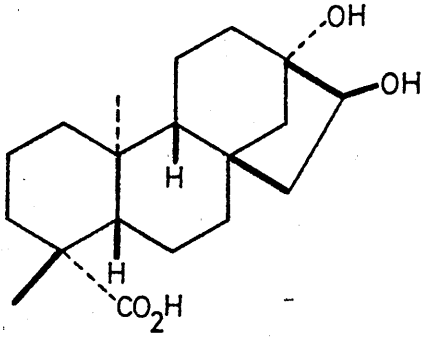

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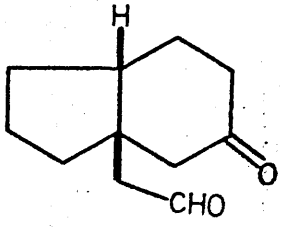

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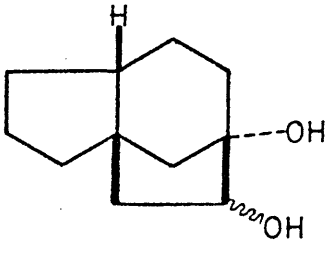

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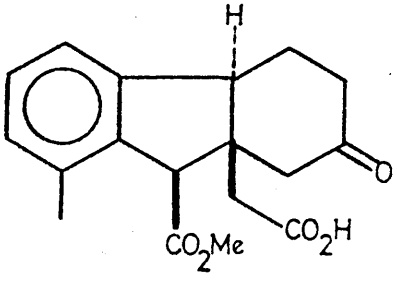

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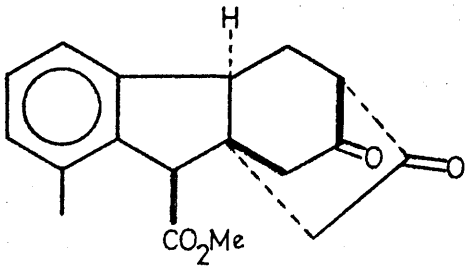

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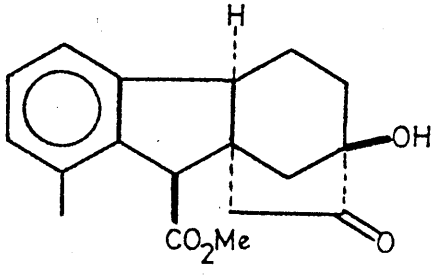

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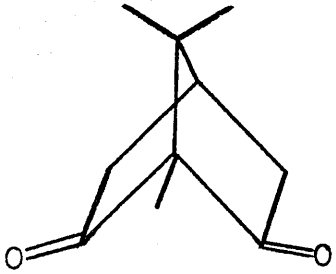

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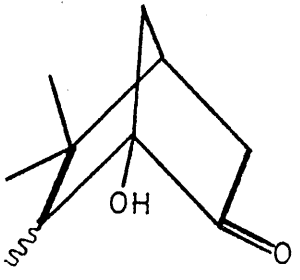


(66)

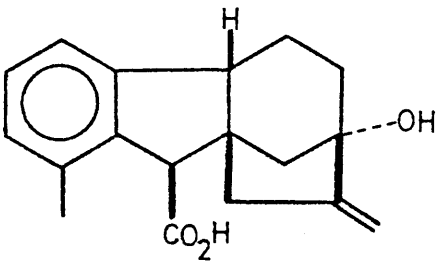
the bicyclo(3.2.I)octane system in his synthesis of steviol (57). The keto-ester (58) was converted to the diol (59) under carefully controlled conditions using sodium in liquid ammonia/tetrahydrofuran.

A method described by Corey[37] involved a pinacol type cyclisation. The keto-aldehyde (60) was treated with magnesium amalgam and dimethyldichlorosilane in tetrahydrofuran to give the diol (6I) after desilylation. The success of the method relies upon the trapping of the intermediate as its silyl ether. This approach could well have general application and Corey's group are already applying it to a projected total synthesis of gibberellic acid[37] (3).

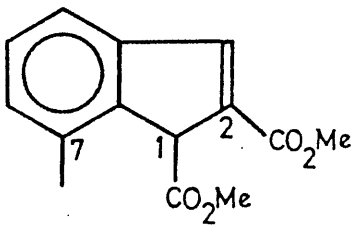
A method of transforming a <u>trans</u> fused BC ring system into a <u>cis</u> fused BCD ring system has been demonstrated by Mori[38]. The keto-acid (62) was readily converted to the bicyclo(2.2.2)octane derivative (63) which was subjected to pinacol reduction conditions yielding the <u>cis</u> fused CD ring gibbane (64). A precedent for this reaction was the observation[39] that the pinacol reduction of the diketone (65) gave ketol (66).

(c) <u>The synthesis of hydrofluorenes.</u>

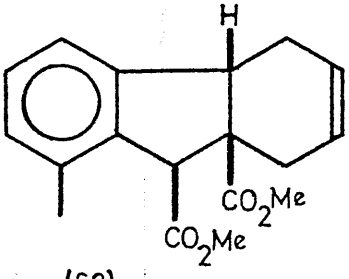
An obvious route to the gibbane skeleton (4) lies in the preparation of hydrofluorenes which are suitably functionalised for conversion to tetracyclic synthons by the methods discussed above. Examples of such hydrofluorenes are (27), (37), (4I), (43), (52), (53) and (62).



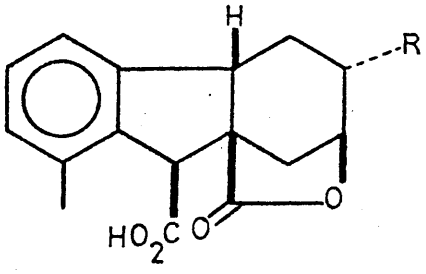
(42)



(67)

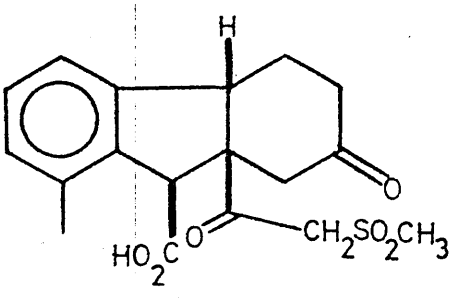


(68)

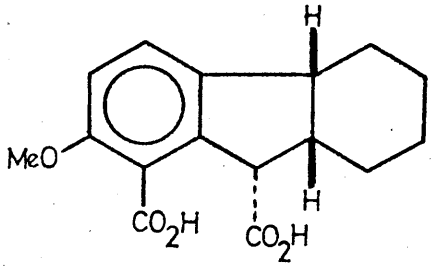


(69) R = I

(70) R = H



(43)



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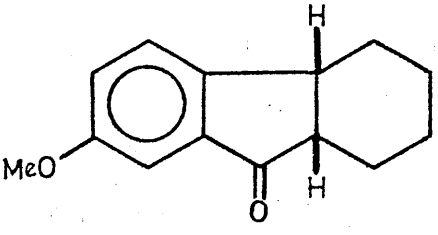
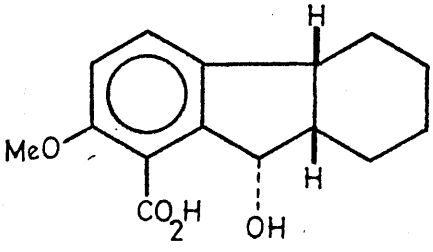


(72)



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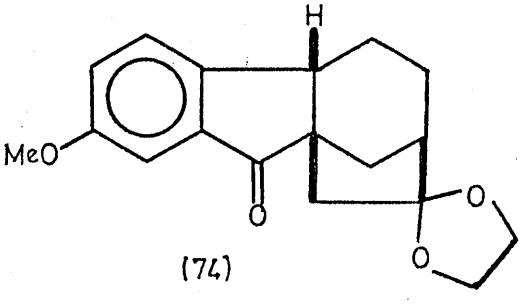

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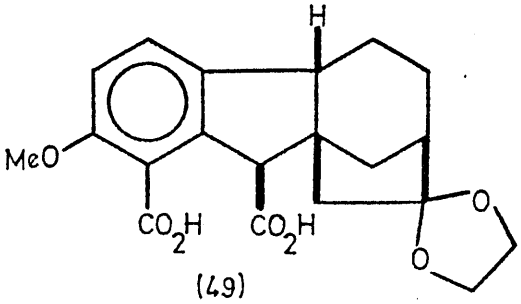


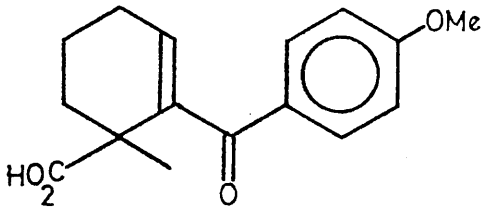
(49)

In a series of papers investigating routes to the gibberellins and related compounds, House[30] has synthesised epiallogibberic acid (42) using this approach. Diels-Alder addition of the diester (67) to butadiene gave the cis fused hydrofluorene (68). Treatment of the derived diacid with iodine in aqueous sodium bicarbonate gave the iodo-lactone (69) which was reduced to the dehalogeno compound (70) with tri-n-butyltin hydride. Treatment with dimethyl-sulphone anion followed by oxidation gave the diketosulphone (43) which was converted to epiallogibberic acid (42) as described earlier.

A limiting factor in this procedure was found to be[40] that a substituent at C-7 of the dieneophile (67) is required to prevent thermal isomerism to the less stable $\Delta^{1,2}$ compound before Diels-Alder addition takes place.

In a study of the 7-methoxyhexahydrofluorene system, House describes an elegant synthesis of the diacid (7I)[41]. The known ketone (72) was converted to the corresponding alcohol which was regioselectively carboxylated using n-butyllithium, sodium t-butoxide and carbon dioxide yielding the acid (73). Dehydration, carboxylation with methyl lithium and carbon dioxide, and hydrogenation gave the diacid (7I). A similar sequence by Baker[32(b)] has been successful when applied to the gibbane (74) to give (49).

In a novel procedure, Jackman[42] photolysed the anisoyl-cyclohexene (75) to an epimeric mixture of acids (76) in



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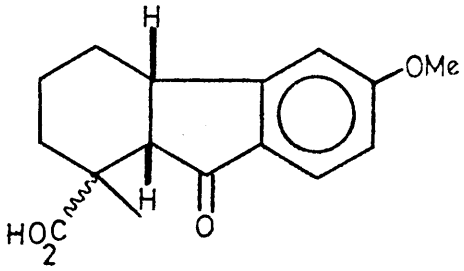

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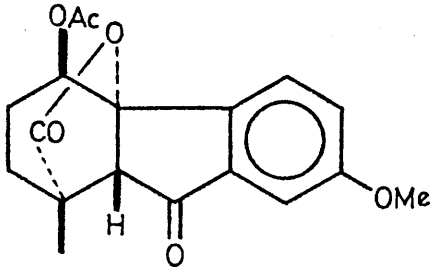

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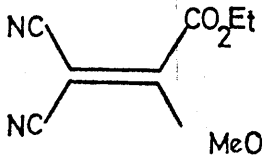

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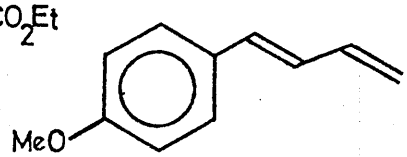

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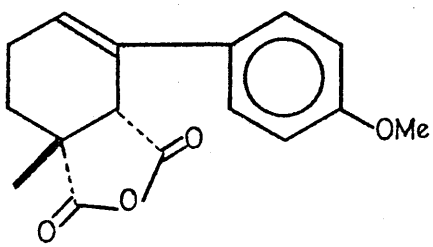

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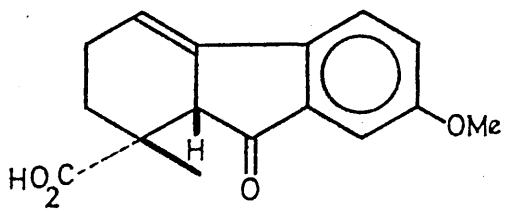

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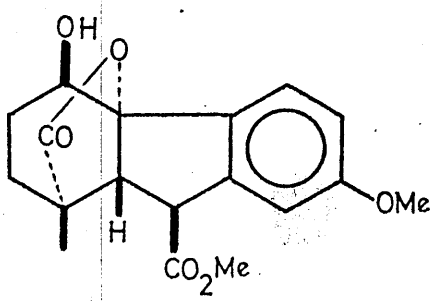

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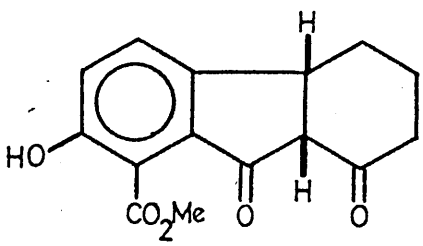

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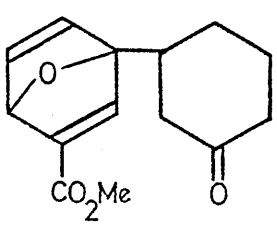

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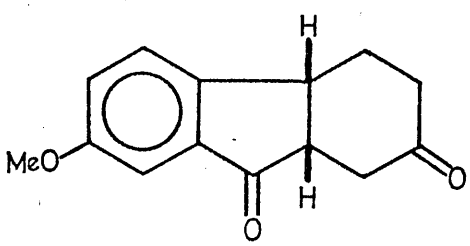

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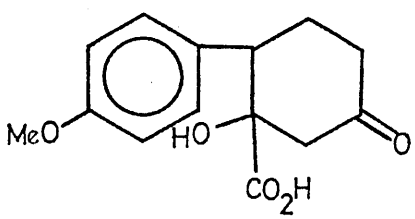


(86)

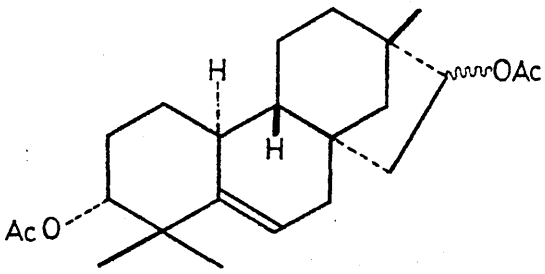
nearly quantitative yield.

Using the hydrofluorene approach, Nakanishi[43] prepared the lactone (77) which he describes as " a promising intermediate in the synthesis of C-I9 gibberellins." Diels-Alder addition of the dienophile (78) to the diene (79) followed by hydrolysis, decarboxylation and dehydration gave the anhydride (80). Treatment of this latter compound with aluminium chloride gave the hydrofluorenone (8I) easily converted to (77) with p-nitrobenzoic acid followed by acetylation. This approach has been recently extended[44] to produce the ring B carboxylic acid (82).

Kitahara[45] chose a novel approach to this problem in his synthesis of the hydrofluorene (83). The keto-diester (84), prepared by a Diels-Alder reaction, was cyclised to (83) in 80% yield using boron trifluoride etherate.

Ziegler[34] has used an efficient method for the preparation of the diketone (85) by condensing p-methoxyphenylpyruvic acid with methyl vinyl ketone to give the acid (86) in high yield. Dehydration, reduction with zinc in acetic acid and finally acid catalysed cyclodehydration gave the desired diketone (85).

By far the most prolific group engaged in the synthesis of gibberellins has been the Japanese group headed by Mori, Matsui and Sumiki. In an almost uninterupted series of publications since Yabuta and Hayashi first isolated a crystalline gibberellin[I], these workers have synthesised a wide variety of hydrofluorene



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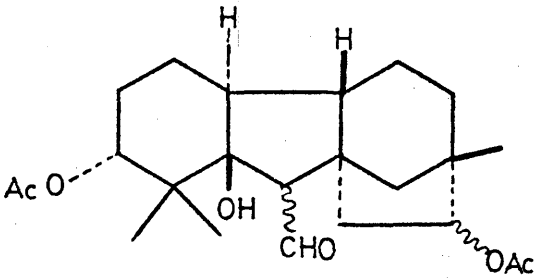

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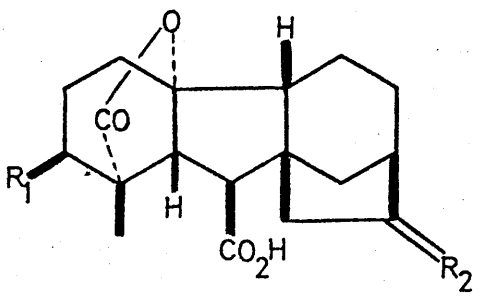
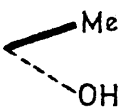
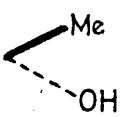
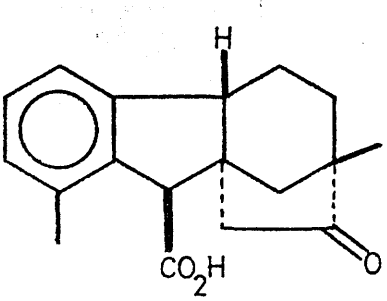


	R_1	R_2
(89)	OH	
(90)	H	CH_2
(91)	H	



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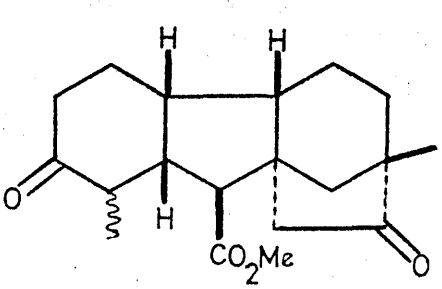


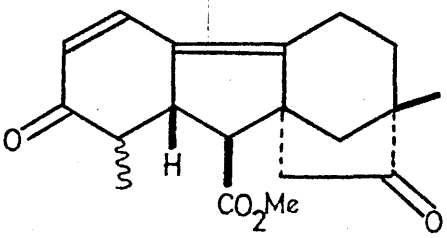
(93)

derivatives.[46]

As well as the hydrofluorene approach, Mori[47] has employed a sequence involving ring contraction of a hydrophenanthrene derivative. The olefin (87) was prepared by a rather lengthy procedure and ozonised using a reductive work up. The resulting keto-aldehyde underwent aldol cyclisation to give the gibbane compound (88).

In 1968 the Japanese group reported[48] the total synthesis of gibberellins A_2 (89), A_4 (7), A_9 (90) and A_{10} (91) from o-xylene. The synthetic route involved five separate stages and was achieved by correlation with a variety of degradation products of gibberellic acid which were used as relay compounds. Although these total syntheses establish the structures of these gibberellins on a chemical basis, the synthetic labyrinth by which they were achieved combined with their incalculably small overall yields renders them of no practical value and of doubtful synthetic importance. Also, X-ray crystal structure analysis is currently such a reliable technique that structure determination of complex molecules by chemical synthesis is no longer a practicable method. It is for these reasons that the total synthesis of gibberellins is not discussed here at length.

The first stage in the total synthesis was the conversion of o-xylene into epigibberic acid (92) in a twenty-one stage sequence.[50] Epigibberic acid, which was available as a degradation product of gibberellic acid, was then elaborated to the diketo-ester (93) in a five step procedure



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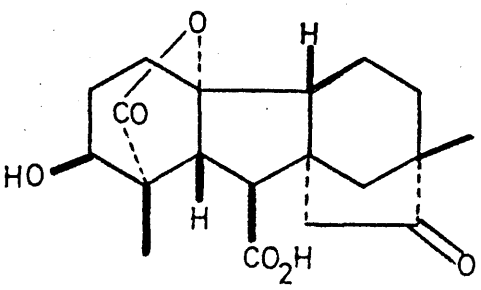

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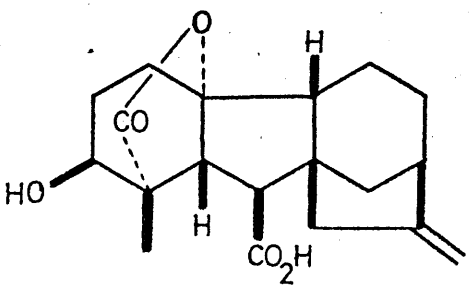

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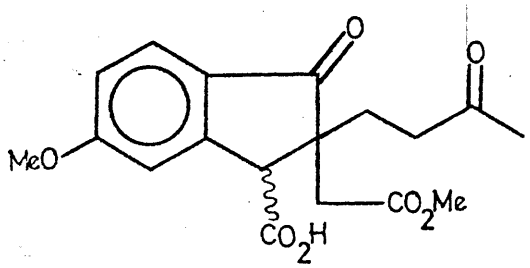

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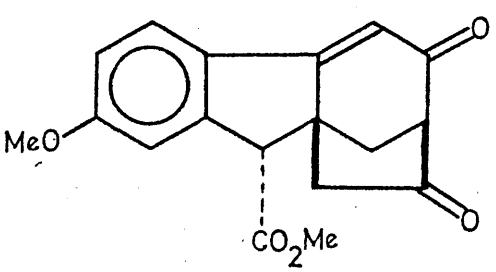

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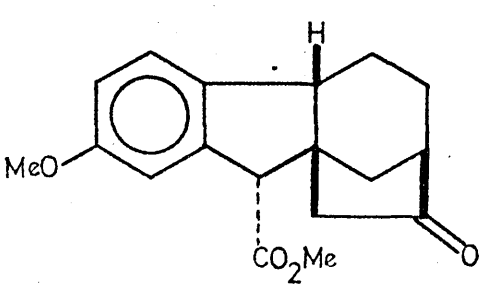

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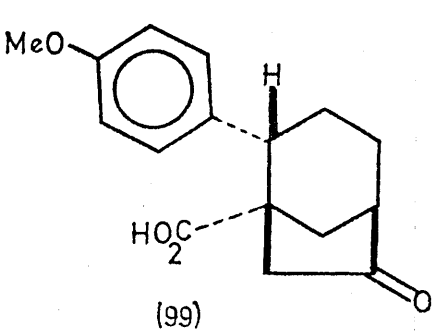

(99)

followed by separation of the epimeric products.[48] This ester was shown to be identical to a new degradation product obtained from gibberellic acid[48] and served as the first relay compound. Transformation of (93) into the dienone (94) was achieved in ten steps using a bromination-dehydrobromination procedure. The partial synthesis of gibberellin C (95) from (94) had been described by Mori[49] and the conversion of gibberellin C to gibberellin A_4 (7) had also been reported by Cross.[5I] This then constituted a formal total synthesis of gibberellin A_4 which had itself been transformed into gibberellins A_2 [52] (89), A_9 [53] (90) and A_{10} [54] (9I).

Apart from any commercial considerations the availability of useful amounts of synthetic gibberellins and their derivatives could lead to a greater understanding of structure-activity relationships in these compounds, possibly by selective labeling techniques (e.g. ^{14}C, ^{13}C, ^{3}H); this in turn could facilitate the design of less complex structures with similar biological activity.

This thesis investigates two possible routes to a potentially useful gibberellin synthon. The objectives of the project were as follows:

(a) The efficient synthesis of the indanone (96).

(b) The conversion of (96) into the gibbane (97) and the reduction of (97) to the keto-ester (98).

(c) The elaboration of the known bicyclo(3.2.I)octane derivative (99) to the keto-ester (98).

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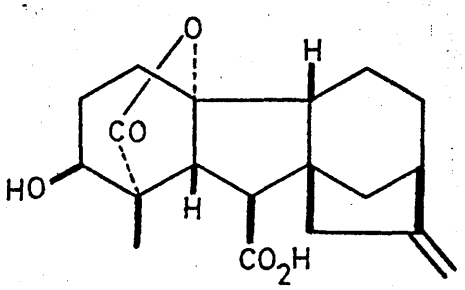
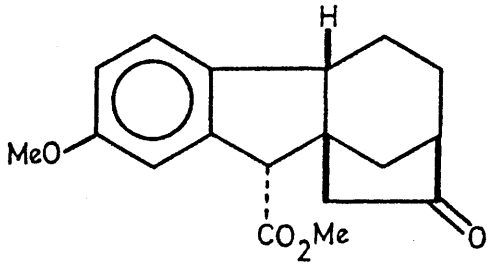


(1)

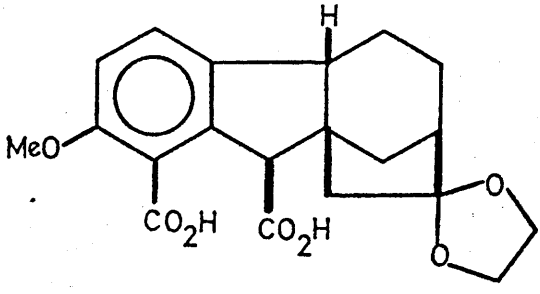
Discussion.

The total synthesis of gibberellin A_4 (I) presents the organic chemist with a formidable challenge. This complex molecule contains four different functional groups and eight centres of chirality in its tetracyclic carbon framework. In addition, the gibberellins are known to be labile to a variety of reaction conditions; this is especially true of the functionality in ring A and is borne out by the extensive literature on the degradative work which was used to determine the structures of the gibberellins.[I] From the foregoing introduction it is apparent that a number of research groups have directed their efforts to gibberellin synthesis, but so far a useful total synthesis has been elusive. The general approach to date has been twofold, a) the preparation of suitably functionalised gibbanes and b) synthesis and elaboration of ring AB and ring CD model compounds to give analogues of the actual structure and stereochemistry found in the gibberellins. Application of these combined sequences should hopefully result in a total synthesis.

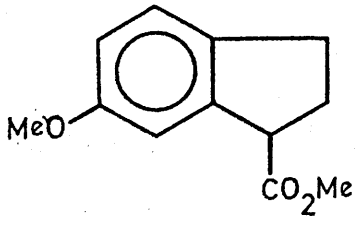
This general approach follows the fundamental rule for the synthesis of a complex molecule: to work back from the final goal breaking down the problem into a number of intermediate objectives and working to complete each objective in turn. The results of previous work in the field, both synthetic and degradative, should be borne in mind since they


H
MeO
CO2Me
O

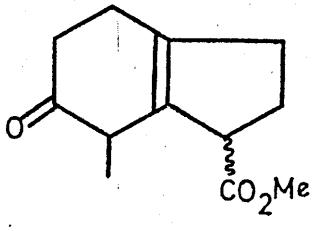
(2)


H
MeO
CO2H
CO2H
O
O

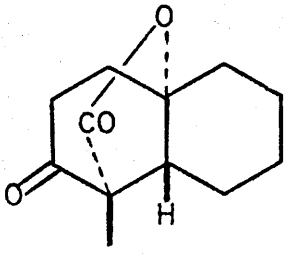
(3)


MeO
CO2Me

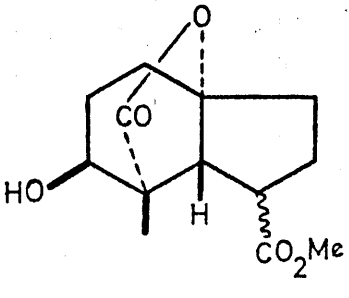
(4)


O
CO2Me

(5)


O
CO
O
H

(6)


O
CO
HO
H
CO2Me

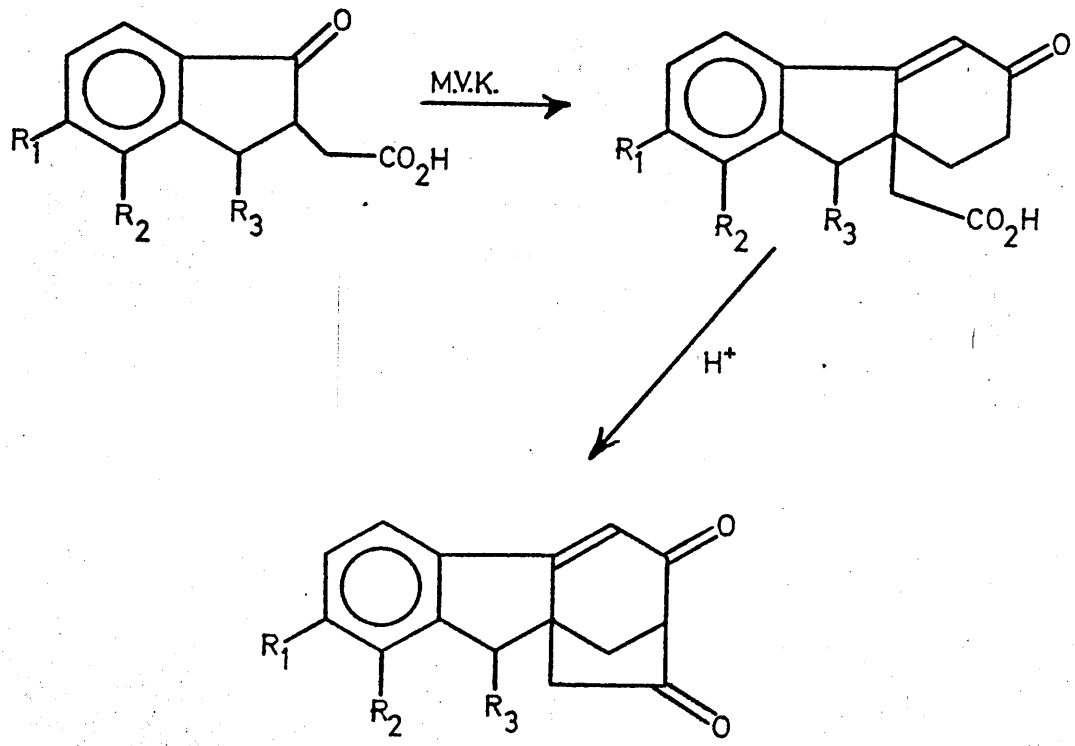
(7)

may have a bearing on the success of the project.

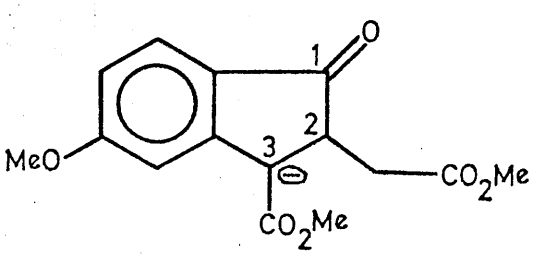
The work to be described in this thesis had as its objective the synthesis of the gibbane keto-ester (2), an intermediate which had hitherto eluded synthesis.[2] It was hoped that if this keto-ester could be readily synthesised, it might afford an alternative and more economic route to the gibbane diacid (3), previously synthesised by the Glasgow group.[3] It was also felt that keto-ester (2) would offer a greater flexibility than the diacid (3) in its further elaboration towards the ultimate goal.

In this project two potential routes were envisaged for the preparation of the keto-ester (2). Upon successful synthesis of (2), elaboration of its ring AB analogue (4) to the ring AB analogue of gibberellin A_4 (I) could be investigated. A possible method would be reductive methylation of (4) followed by acid treatment to (5), by analogy with Loewenthal's preparation of (6)[4]. Regio-selective carboxylation[5] followed by lactonisation and stereo-selective reduction of the ketone function[6] could give the desired product (7). Transformation of the C-I6 keto function in (2) to an exomethylene group has ample precedent in the literature.[7] Carboxylation of (2) to give the diacid (3) after obvious subsequent steps would also be a possibility.

The choice of the gibbane (2) as the key intermediate was made for three reasons. Firstly, it contains the necessary tetracyclic carbon framework and exhibits the desired cis-fused BC ring system. Secondly, it posesses



SCHEME 1



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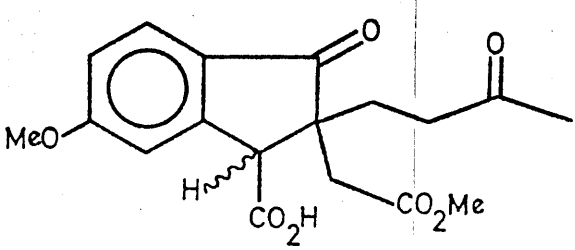


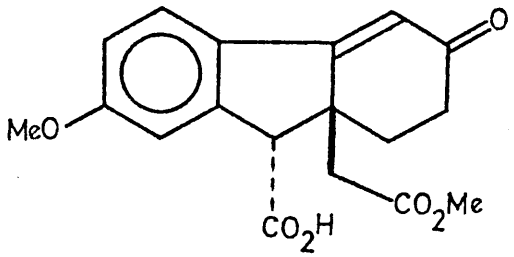
(9)

three functional groups suitably disposed for elaboration to the functionality found in the gibberellins; and thirdly, as has been mentioned, two plausible synthetic routes to the gibbane (2) were apparent.

(I)

An attractive route to gibbane compounds has been the annelation of a suitably substituted indanone using methyl vinyl ketone, followed by acid treatment (scheme I).[8] Although initially attractive, this approach suffers from a number of difficulties. Firstly, the preparation of an appropriately functionalised indanone has proved difficult. Secondly, the annelation procedure fails[9] when R_I=-oMe, R_2=-H and R_3=-CO_2Me (scheme I). In this case initial anion formation at C-3 (8) leads to products by alkylation at this centre instead of at C-2. Another difficulty is that when R_I=-oMe, R_2=-Me and R_3= -CO_2H the later Birch reduction of the benzene ring is apparently unsuccessful.[10] Removal of the enone system from the tetracyclic diketone (scheme I) has presented problems, notably ring D re-opening[8a] However, Loewenthal[8b] has recently described an elegant hydrogenation procedure which selectively removes the enone function leaving the ring D ketone unaffected. Finally, stereocontrol over the BC ring fusion depends on the orientation of the C-6 substituent during hydrogenation of the 9,II double bond.[11]

In the light of this knowledge it was considered that a synthesis of the keto-ester (2) might be achieved as follows : cyclisation of the indanone acid (9) to the



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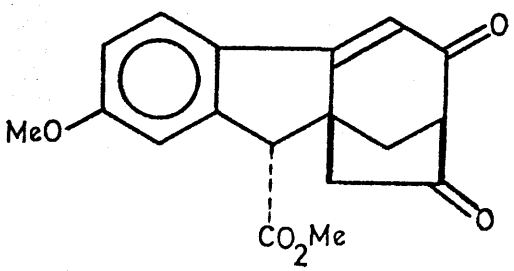

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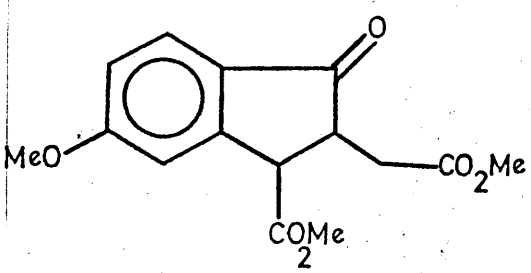

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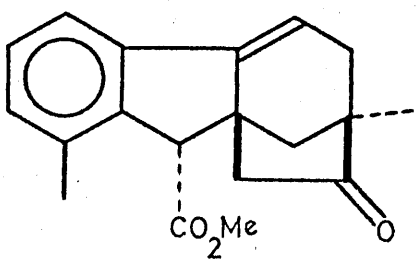


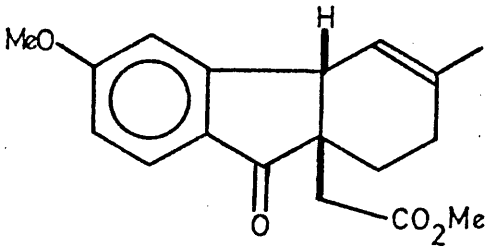
(13)

tricyclic enone (I0) followed by acid treatment should produce the tetracyclic gibbane diketone (II). Application of Loewenthal's hydrogenation procedure[8b] to (II) would hopefully give the desired gibbane (2). Matsui[9] has attempted the preparation of the enone (I0) by annelation of the indanone (I2) with methyl vinyl ketone but, as mentioned above, the product obtained resulted from alkylation at the C-3 position.

The approach to the synthesis of (2) to be described in this thesis attempted to circumvent the undesired C-3 alkylation found by Matsui by constructing the indanone (9) in which the ketobutyl group required for the annelation sequence was attached at C-2 by a non-alkylative procedure.

A possible pitfall in this approach which could occur when cyclising the indanone (9) to the fluorenone (I0) under basic conditions would be the removal of the ketobutyl grouping by a retro-Michael process. This process could even lead, by a subsequent Michael addition of the liberated methyl vinyl ketone, to the undesired C-3 alkylated indanone.

In his synthesis of gibberic acid, Loewenthal[II] showed that the trans orientation of a C-6 carbomethoxy group with respect to the C-I5, C-I6 carbon bridge in Δ 9,II gibbenes (eg. I3) is the more stable. This trans relationship is also the requirement[II] for hydrogenation of the 9, II double bond to give the cis BC ring fusion found in gibberellins. Thus if the methyl ester (II) could be formed under equilibrating conditions, this would lead to the desired stereochemistry and solve the problem of stereocontrol at C-9. In BC cis



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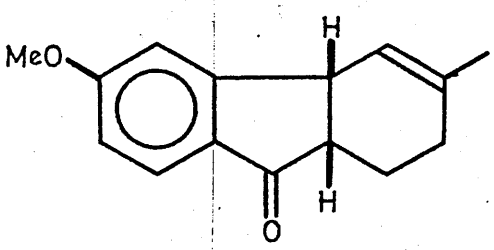

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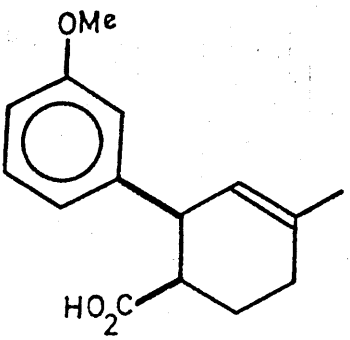

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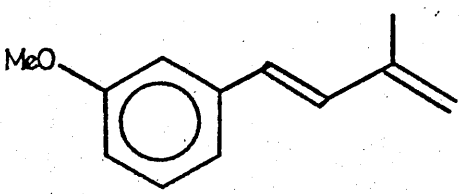

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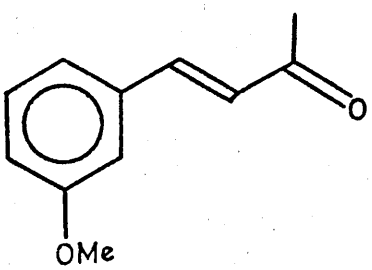
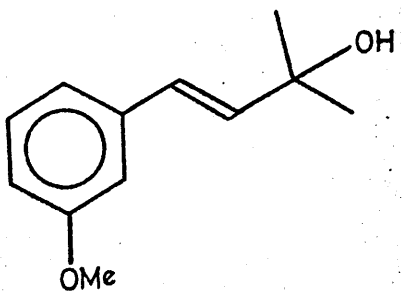


(18)

fused gibbanes the natural cis orientation of the C-6 carboxyl group[I2] with respect to the two carbon bridge is the more stable.

Thus the first requirement of this project was a good synthetic route to the indanone (9) from a precursor which contained a masked ketobutyl group. A possible solution to this problem was seen in the oxidative cleavage of the olefin function of the keto-ester (I4) which should give the indanone (9) directly. The keto-ester (I4) should be available by alkylation of the ketone (I5) with methyl bromoacetate. (I5) might be prepared by cyclisation of the cyclohexene (I6) which should itself be available by Diels-Alder addition of the diene (I7) to acrylic acid.[I3] The stereochemistry of (I4) would probably be as shown, since alkylation of hydrofluorenones is known to result in the more stable cis fused ring system.[I4]

With a general plan in mind work was begun on the synthesis of the first objective, the indanone (9). Condensation of m-methoxybenzaldehyde with acetone in aqueous sodium hydroxide gave an 86% yield of m-methoxybenzalacetone[I5,I6] (I8). Conversion of (I8) to the diene (I7) was carried out on a small scale using a Wittig reaction. Thus the enone (I8) was treated with a five-fold molar excess of methylene triphenylphosphorane to give the diene (I7) in 84% yield. Because of the large excess of reagent required in this reaction, the preparation of (I7) on a larger scale was conveniently carried out in a two step process. The ketone (I8) was

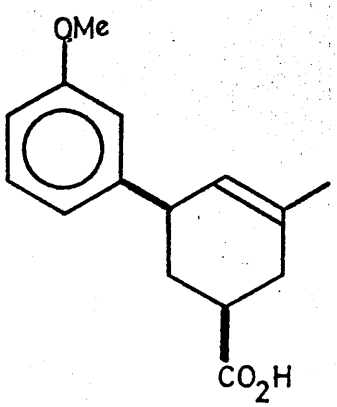


(19)

treated with methylmagnesium iodide in ether to give the alcohol (I9) which was readily dehydrated to give (I7) either by distillation from potassium bisulphate or by refluxing in toluene containing toluene-_p_- sulphonic acid. The overall yields of both methods were over 80%. The Grignard reaction also produced a small amount of 4-_m_-methoxy phenylpentan-2-one corresponding to I,4 conjugate addition of the reagent to the enone (I8) (detected by carbonyl absorption at I720 cm^{-I} in the i.r.). This material was removed after dehydration of the alcohol either at the distillation stage or by passage through a short column of alumina using light petroleum as eluant.

An interesting feature of this Grignard reaction was its sensitivity during work up to the amount of reagent used. If one molar equivalent of reagent was used the isolation of the product was straightforward, but if two or more equivalents were used the addition of saturated ammonium chloride solution during work up resulted in the precipitation of elemental iodine. Removal of the iodine with sodium thiosulphate solution eventually gave an intractable oil. Presumably the excess unreacted reagent was in some way being oxidised by the product. It was found useful to add dry acetone to the reaction mixture before work up to destroy any excess reagent.

The diene (I7), when refluxed with acrylic acid in toluene for I6 hours, gave a 70% yield of the cyclohexene acid (I6) as a single crystalline isomer. The aryl and carboxyl groups in

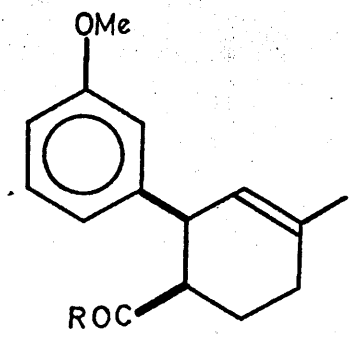


(20)

this compound were considered to be cis related by analogy with similar reactions.[17] The other possible position isomer (20), which could in theory be formed, was not detected. This was expected on the basis of " the principle of maximum overlap of non-bonding orbitals " whereby the aryl group of the diene and the carboxyl group of the dienophile should align themselves as closely as possible so as to achieve the greatest thermodynamic stability in the transition state. This would result in the formation of (I6) at the expense of (20). The structure of (I6) was confirmed by its spectral characteristics and its subsequent reactions. That migration of the double bond had not occurred was shown by a singlet methyl signal in its proton n.m.r. spectrum at I.75$ and also by a multiplet at 3.68$ consistent with the presence of a benzylic-allylic proton.

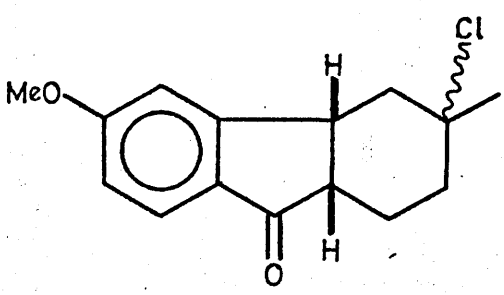
It was found that the acid (I6) could conveniently be prepared in a single process from the alcohol (I9) and acrylic acid by refluxing the reactants in toluene while removing water from the reaction vessel with a Dean-Stark trap. Acrylic acid was sufficiently acidic to catalyse dehydration of the alcohol to form the diene (I7) which underwent the Diels-Alder addition. Purification of the product was effected by base extraction followed by careful acidification to avoid the possibility of lactonisation.

Attempts were now made to cyclise the acid (I6) to the hydrofluorenone (I5). It was expected that this cyclisation would proceed rapidly to give the compound with the methoxyl group in the required C-6 position because of the activating



(16) R = OH

(21) R = Cl



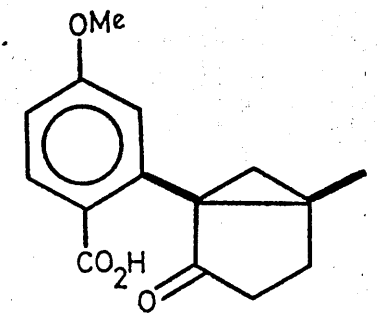
(22)

a = ∝ Cl

b = β Cl

influence of this group and the well known preference for methoxybenzenes to undergo *para* rather than *ortho* electrophilic substitutions. Also, the reaction ought to be easily monitored by u.v. spectroscopy because of the change of the chromophore to a 5-methoxyindan-I-one type. However, treatment of the acid (I6) with polyphosphoric acid while raising the temperature slowly produced only an intractable brown gum. Use of 80% sulphuric acid at room temperature gave no better results and it was decided to attempt the cyclisation *via* the derived acid chloride. The failure of direct acid treatment was attributed to the expected reactivity of the trisubstituted double bond in (I6) which could give rise to products from carbonium ion formation at the tertiary centre. For example, lactonisation across the cyclohexene ring could occur. This reactivity was also observed in later experiments.

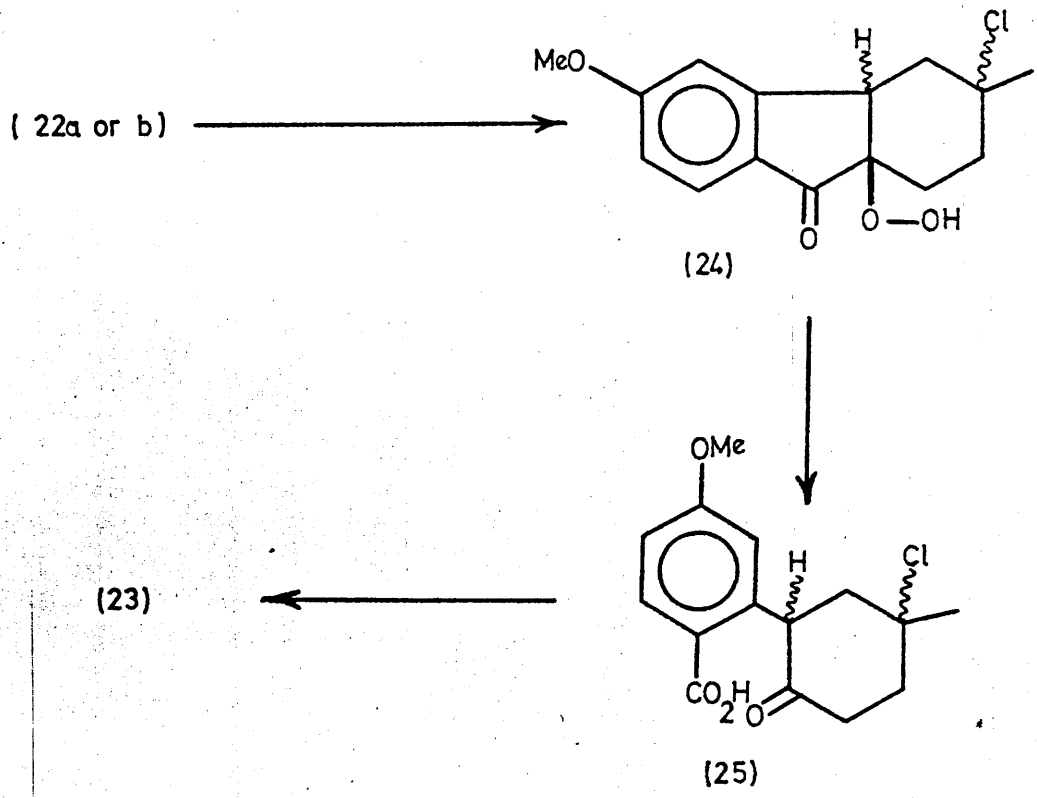
With the failure of the above acid catalysed cyclisation of the acid (I6), attention was turned to the Friedel-Crafts cyclisation of the acid chloride (2I) derived from (I6). Initially the cyclisation of this acid chloride was carried out at room temperature in methylene chloride solution by the slow addition of I.I molar equivalents of aluminium chloride over 0.75 hours. The major product, however, showed no vinylic protons in its n.m.r. spectrum and had a sharp methyl singlet at I.54δ . The u.v. spectrum (λ max. 268, 288 and 294 nm) was consistent with a 5-methoxyindan-I-one system and the compound was assigned the structure (22a or b), confirmed by elemental analysis and by a qualitative test for halogen.



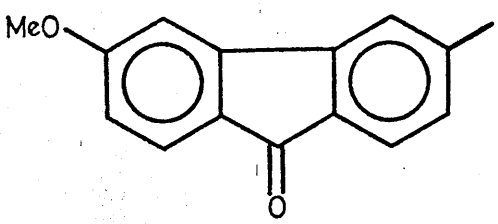
(23)

Evidently the hydrogen chloride released during the cyclisation had added rapidly to the reactive double bond. The cis ring fusion was assumed from the stereochemistry of the cyclohexene precursor and from the known preferred cis ring fusion of hexahydrofluorenones.[14] The stereochemistry of the chloro- and methyl groups relative to the other chiral centres was not determined.

An attempt was now made to dehydrochlorinate the chloro-compound (22a or b) in the hope that the desired product (15) might result. A sample of (22a or b) was treated with 1,5-diazabicyclo(4.3.0)non-5-ene in refluxing toluene but the product was an oil which showed no vinylic protons in its n.m.r. spectrum. A solution of (22a or b) in 20% methanolic potassium hydroxide was refluxed overnight and gave, in moderate yield, a crystalline acidic substance which contained no vinylic protons and which was shown to be a benzoic acid of the constitution $C_{15}H_{16}O_4$. Its formulation as an aryl acid was established from its i.r. spectrum (ν max. 1708 and 2500-3500 cm^{-1}) and its observed shift to shorter wavelength u.v. absorption (λ max. 250 $\longrightarrow$ 244 nm) when treated with sodium hydroxide solution. The formula was inferred from elemental analysis and high resolution mass spectrometry. The compound also contained a ketone function as evidenced by an absorption at 1685 cm^{-1} and the fact that it stained orange on t.l.c. when treated with d.n.p. reagent. From these data and a detailed study of its proton n.m.r. spectrum (see experimental section) this artifact was tentatively assigned the bicyclo(3.1.0.) structure (23). This can be



SCHEME 2



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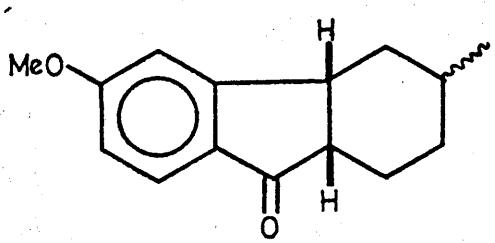


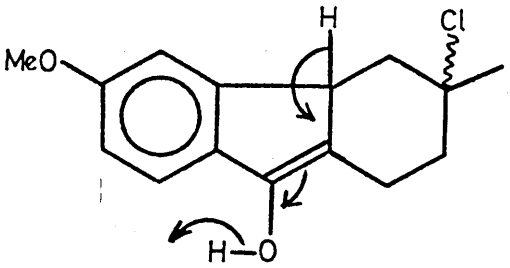
(27)

rationalised mechanistically as shown in scheme 2; peroxides present in the methanolic potassium hydroxide used as reagent could have reacted with (22a or b) to form the hydroperoxide (24), which, under base catalysis, might rearrange to the keto-acid (25). Elimenation of hydrogen chloride across the ring would give (23). This elimenation would be assisted by the benzylic proton being doubly activated.

Peroxide oxidations of this type α to ketones *via* the enol form are well known,[18] as is the rearrangement of the resulting α-ketohydroperoxides to keto-acids.[18] However, when the reaction was repeated, apparently under identical conditions, no acidic material was detected and several further attempts met with no success. The products of these later experiments consisted of the fluorenone[31] (26) and the hexahydrofluorenone (27). The reason for the inability to repeat the preparation of (23) can only be explained by peroxide impurities being present in one batch of methanolic potassium hydroxide used as reagent but not in others.

In one experiment the chloro compound (22a or b) was refluxed in 20% methanolic potassium hydroxide with a constant stream of air passing through the solution. This resulted in the isolation of only the fluorenone (26) in 65% yield.

The occurrance of the hexahydrofluorenone (27) from base treatment of (22a or b) was interesting, since it implied a disproportionation reaction as well as elimenation



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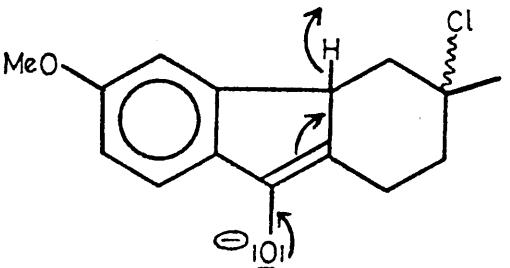

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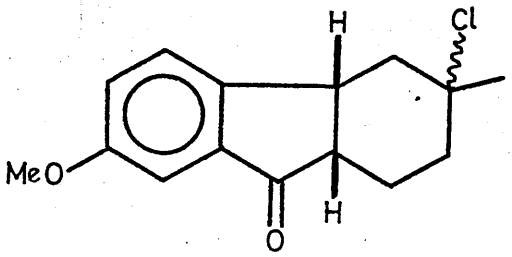

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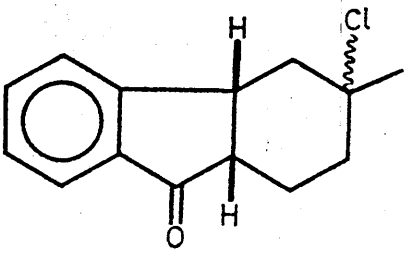

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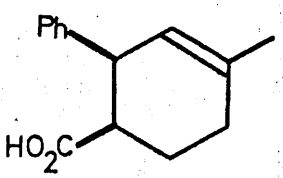

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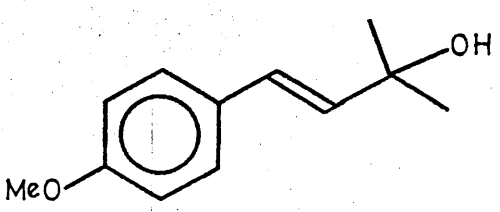

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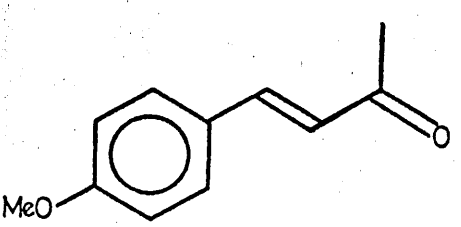
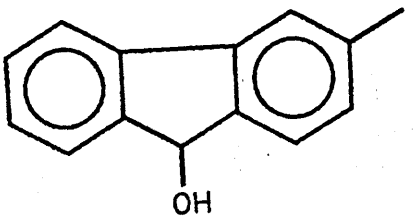


(34)

of hydrogen chloride. Such a disproportionation, favoured by the aromatic stability of the fluorenone, requires an intermolecular hydride transfer. This might occur *via* the enol form of the ketone as shown in (28) or the enolate as in (29). No similar behaviour of analogous compounds was found in the literature.

Because of the unusual behaviour of the chloro compound (22a or b) it was decided to investigate more fully base treatment of chloro-hexahydrofluorenones to discover if any acid material analogous to (23) could be formed and if the disproportionation described above was a general reaction. Chloro-hexahydrofluorenones (30) and (3I) were chosen for study because of their resemblance to (22a or b) and to discover whether or not the methoxyl group influenced the reactivity.

These compounds were prepared by a route similar to that used for the preparation of the chloro compound (22a or b). In the synthesis of (3I), the acid chloride derived from the known[I3] acid (32) was dissolved in methylene chloride and treated with aluminium chloride in a stoppered vessel. This gave the chloro compound (3I), the structure of which was confirmed by its spectral data and elemental analysis. Compound (30) was prepared by refluxing the alcohol (33) with acrylic acid in toluene followed by Friedel-Crafts cyclisation *via* the derived acid chloride with concomitant addition of hydrogen chloride to the double bond. The alcohol (33) was available from the reaction of methyl



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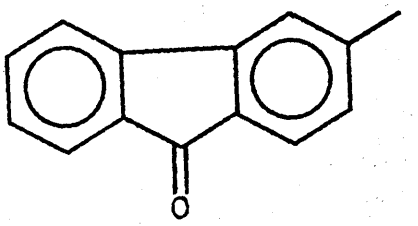

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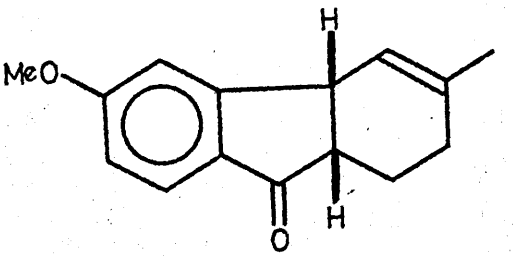


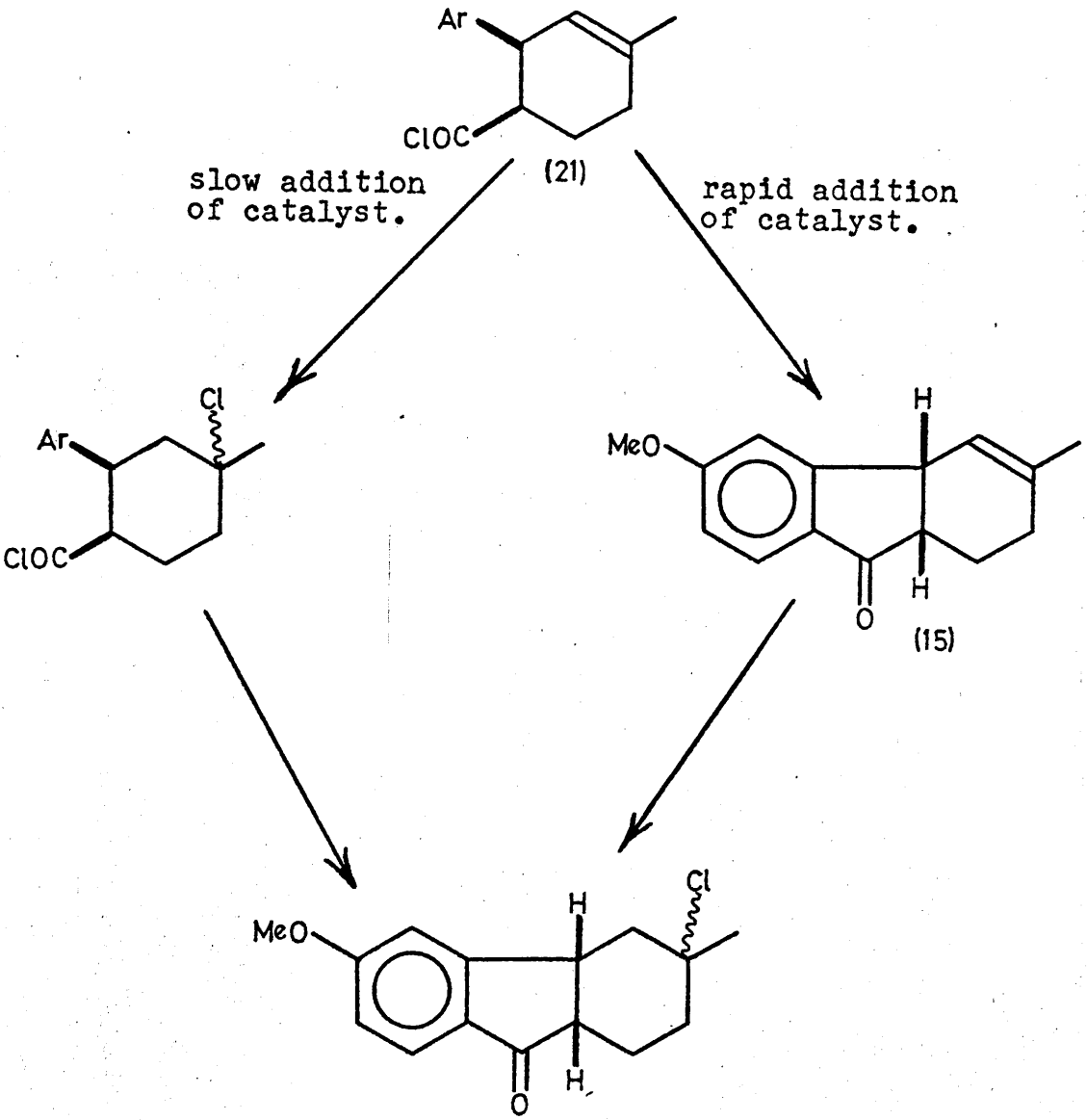
(15)

magnesium iodide with the enone (34). The structure of (30) was again evident from its spectral data and elemental analysis.

Both chloro compounds (30) and (31) were treated with 20% methanolic potassium hydroxide under reflux but neither gave any acid product. Thus base treatment of (30) gave at least five unidentified products (by t.l.c.). The only readily identifiable product of the five or more compounds resulting from similar treatment of (31) was the known[19] fluorenol (35). The appearance of this compound does at least show that hydride transfer had occurred.

In one chromatographic separation of the products of base treatment of (31) the mixture was lined onto a chromatoplate and the solvent removed in a current of hot air. Subsequent development and extraction gave the fluorenone [20] (36) in about double the yield of the fluorenol (35) previously isolated. Aerial oxidation had obviously occurred and no fluorenol was detected. The increased yield of fluorenone (36) in this experiment over fluorenol (35) in the previous case shows that some other easily oxidisable precursor to the fluorenone (36) was present in the product mixture.

Since the chloro compound (22a or b) could not be dehydrochlorinated to the tetrahydrofluorenone (15) required for the synthesis of (2), the Friedel-Crafts cyclisation of (21) was subjected to closer study in an effort to find conditions whereby the tetrahydrofluorenone (15) could be



(22)

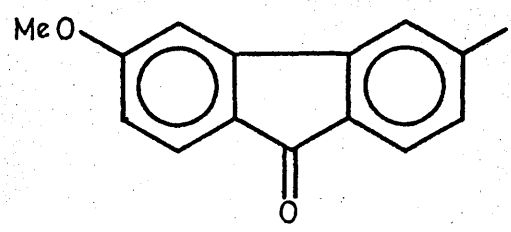
a = ∝ Cl

b = β Cl

SCHEME 3

obtained directly.

In the original experiment the Lewis acid had been added over a period of about 0.75 hours to a methylene chloride solution of the acid chloride (2I). In searching for the correct Friedel-Crafts conditions the most obvious procedure to try was the rapid addition of catalyst to the substrate. The result of this attempt was the isolation of a 70% yield of a chloro compound which was not identical to the chloro compound produced in the original Friedel-Crafts cyclisation of (2I). The product of the present reaction was thought to be epimeric at C-3 with the chloro compound previously prepared. The spectra of these two compounds were similar but not identical and they had different melting points. The occurrance of these two epimers can be explained by consideration of the different reaction conditions under which they were formed. Slow addition of catalyst would initially cyclise a small amount of the acid chloride releasing hydrogen chloride which could add to uncyclised material. If cyclisation of the chlorocyclohexane thus produced was faster than cyclisation of the cyclohexene then addition of hydrogen chloride would be to a cyclohexene; viz. addition before cyclisation. In support of this hypothesis it should be mentioned that inspection of molecular models indicated greater ring strain in the tetrahydrofluorenone (I5) than in the corresponding hydrogen chloride addition compound (22a or b). Thus the transition state leading to cyclisation might be more favourable for the chloro-cyclohexane than for the cyclohexene (scheme 3).



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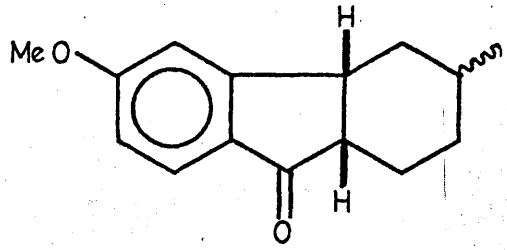
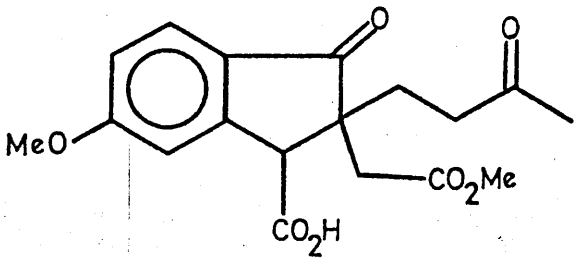


(27)

In the second case, rapid addition of catalyst might effect cyclisation before addition of hydrogen chloride, so that the latter reaction would involve a tetrahydrofluorenone and not a cyclohexene as before. It is reasonable to suppose that addition to a double bond in two different structural systems could well result in a different stereochemical outcome. That cyclisation before addition occurred in the latter case was shown by treating the acid chloride (2I) with powdered aluminium chloride in one portion and quenching the reaction after exactly 0.25 hours by pouring the mixture onto ice. This resulted in the isolation of the required tetrahydrofluorenone (I5) in good yield. The structure of this compound was evident from its spectral data and elemental analysis. Notably its n.m.r. spectrum showed a one vinylic proton multiplet at 5.6$ establishing the presence of the double bond.

For the sake of completeness, the chloro compound (22b or a), obtained by rapid addition of aluminium chloride to the acid chloride (2I),and the hydrofluorenone (I5) were also treated with methanolic potassium hydroxide. The chloro compound gave an almost identical product distribution to that of similar treatment of its C-3 epimer; viz. a mixture of the fluorenone (26) and the hexahydrofluorenone (27). The product obtained from base treatment of (I5) consisted of the same components in almost quantitative stoichiometric amounts. In neither case was any acidic material isolated.

Although there was stereochemical ambiguity concerning



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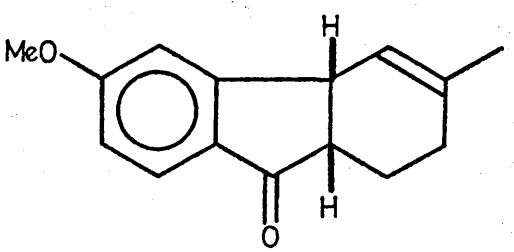

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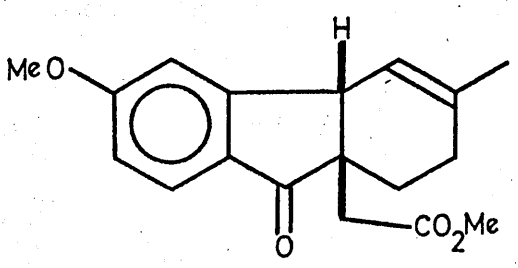
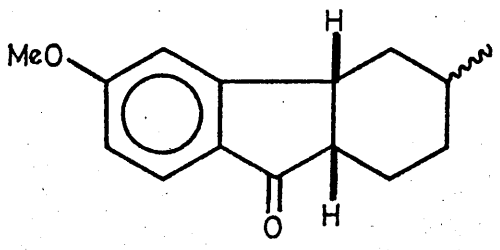


(14)

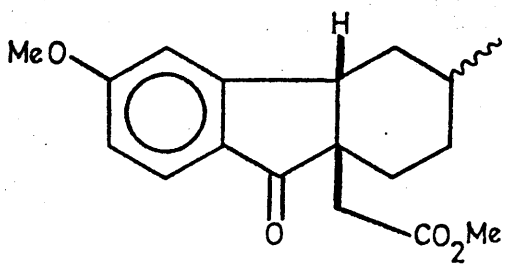
the structures of the chloro compounds (22a and b), further study in this area was outwith the scope of the objective of the thesis; *viz.* the synthesis of the gibbane intermediate (2).

With the hydrofluorenone (I5) now readily available, the next step in the synthesis of the indanone (9) was the alkylation of (I5) with methyl bromoacetate to produce the keto-ester (I4). The ketone (I5) was treated with potassium *t*-butoxide in ether followed by addition of methyl bromoacetate. The oily product consisted of at least five unidentified compounds (t.l.c.) which were separated by chromatography and analysed by u.v. spectroscopy. No material with the characteristic 5-methoxyindan-I-one chromophore was detected. Also, when the ketone (I5) was treated with potassium *t*-butoxide without addition of alkylating agent no starting ketone or other material with the required chromophore was recovered. The use of sodium hydride and sodium methoxide as bases in further attempts gave only the unreacted ketone (I5). Sodium hydride in refluxing glyme gave rise to a number of highly polar substances none of which exhibited the desired chromophore.

The failure of (I5) to undergo alkylation had not been anticipated but perhaps can be rationalised by recognising the highly active nature of the 4a benzylic-allylic proton which is also vinylogously related to the ketone function in (I5). Abstraction of this proton presumably leads to breakdown of the hydrofluorenone structure. As a simple test of this explanation a sample of the ketone (I5) was



(27)



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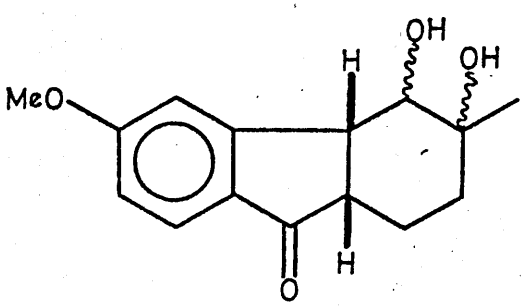


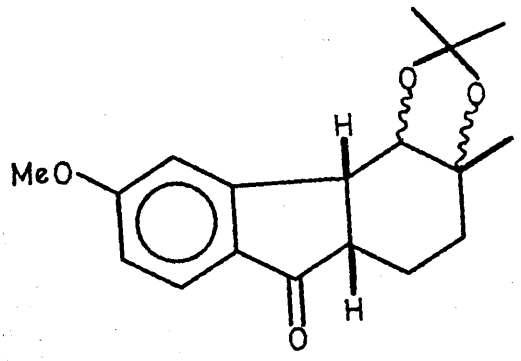
(38)

hydrogenated over 10% palladium on charcoal to give the corresponding dihydro compound (27) which was readily alkylated using potassium t-butoxide and methyl bromoacetate to give the ester (37) in high yield. The cis fused ring junction was assumed from similar alkylations in the hydrofluorenone system.[14]

It was interesting to note that the ketone (27), produced by hydrogenation of (15), was identical to the ketone resulting from potassium hydroxide treatment of the chloro compounds (22a and b) and of the olefin (15). Since base treatment of (27) would result in the more stable cis ring fusion,[14] and since hydrogenation of (15) would be unlikely to effect any epimerisation, this further established the cis fused ring junction in (15). It is also noteworthy that both methods of producing (27) result in the same, but undetermined, stereochemistry at C-3.

The products of the above described potassium t-butoxide treatment of the ketone (15) were compared (t.l.c.) with the products of potassium hydroxide treatment of (15) described earlier, but no correlation was observed.

Since the ketone (27) readily underwent alkylation, it was envisaged that the non-alkylation of (15) might be overcome by replacing the olefinic double bond in (15) with some synthetic equivalent prior to alkylation. Since this double bond was to be oxidised later in the sequence, the diol (38) seemed a suitable substrate for alkylation. In order to avoid O-alkylation of the alcohol groups, (38)



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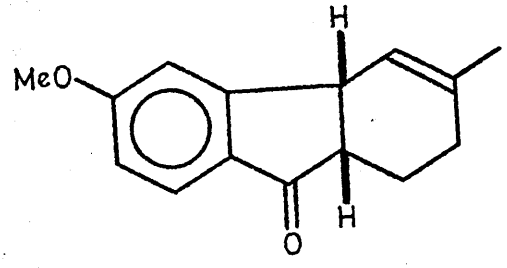

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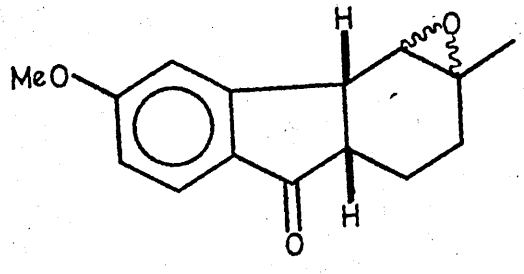
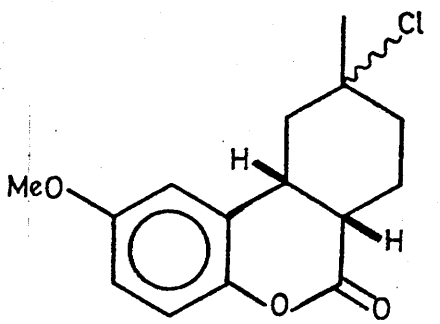


(40)

could conveniently be protected as the corresponding acetonide (39). A possible method was available for the conversion of the olefin (I5) to the acetonide (39) via the epoxide (40). This consisted of preparing the epoxide (40) from the olefin (I5) by standard methods and treating it with boron trifluoride etherate in dry acetone to give the acetonide (39) directly.[2I] The mechanism of this reaction involves attack by the carbonyl oxygen of the solvent and has been shown to proceed in a trans fashion.[2I] Ring opening of the necessarily cis epoxide (40) would thus give a trans fused acetonide. The stereochemistry with respect to the other chiral centres would depend upon the orientation of the epoxide precursor and might possibly result in a mixture of isomers. The transformation of a cyclohexene oxide to a trans acetonide had not yet been attempted and the first such acetonide had only recently been prepared[22] and under rather forcing conditions. Standard methods for the preparation of trans acetonides from trans I,2 cyclohexane diols have failed.[23] It was with some interest then, that this procedure was attempted.

The olefin (I5), in methylene chloride, was treated with m-chloroperbenzoic acid at 0^{o} to give a 74% yield of the epoxide (40) as a single isomer. The cis ring fusion was assumed to be still intact but the orientation of the epoxy group was undetermined. The n.m.r. spectrum of this compound showed no vinylic protons and exhibited a broadened singlet at 3.I0S consistent with an oxirane proton.



(41)

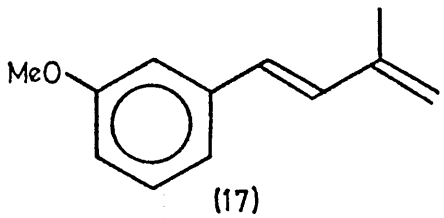
In one preparation of the epoxide (40) crude olefin was used as starting material which apparently contained a small amount of the chloro compound (22b or a) as impurity. The first crystalline material isolated from this reaction was a small amount of the chloro-lactone (41), obviously formed by Baeyer-Villiger oxidation of the ketone function of the chloro compound (22b or a). The structure of this artifact was evident from its spectral data and from elemental analysis.

The epoxide (40) was now treated with boron trifluoride etherate in dry acetone to give, after careful work up, the acetonide (39) in excellent yield. The structure, if not the stereochemistry,of this compound was apparent from its spectral data. I.r absorption at 1365 and 1375 cm^{-1} confirmed the presence of a gem dimethyl group. Its n.m.r. spectrum clearly showed the two acetonide methyl groups as non-equivalent singlets, and a doublet at 4.50δ indicated the dioxalane proton.

This acetonide (39) was readily hydrolysed to the diol (38) in high yield by treatment with dilute mineral acid at room temperature. Attempts to regenerate the acetonide (39) from the diol (38) by standard methods were unsuccessful. Thus refluxing the diol in acetone using a variety of acid and Lewis acid catalysts gave only the starting diol, (38) unchanged. This is in accord with the known resistance to acetonide formation of trans I,2 cyclohexane diols[23] and confirms the trans relationship of the hydroxyl groups in (38).

After the successful preparation of the acetonide (39), attempts were now made to alkylate it α to the ketone with methyl bromoacetate. These attempts, however, met with no more success than did the attempts to alkylate the olefin (I5). Treatment of (39) with potassium t-butoxide in ether followed by addition of methyl bromoacetate gave a series of highly polar compounds none of which exhibited the required 5-methoxyindan-I-one chromophore. Indeed, treatment of the acetonide with the above base but without addition of alkylating agent gave a mixture of highly polar compounds among which no starting ketone or other material with the required chromophore was detected (t.l.c.). Similar attempts using other bases and solvents gave no better results. The failure of this reaction must presumably again be attributed to activation of the benzylic proton and its abstraction by base and subsequent breakdown of the hydrofluorenone system. The possibility that ring strain in the required enolates of (I5) and (39) inhibited their formation was not considered to be a major factor after inspection of molecular models of these structures.

Other more exotic methods of alkylation, which might be effected under neutral conditions, were considered. For example carbene addition to the enol acetate of (39) [24] and subsequent manipulations, if the enol acetate could be prepared. However, at this point a parallel investigation into a slightly different synthetic route to the keto-ester (I4) had proved moderately successful, and the first approach described above was abandoned.



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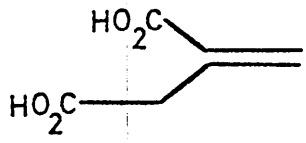

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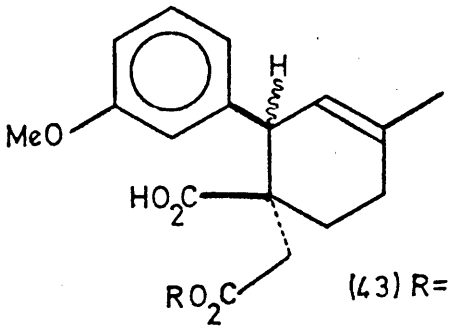
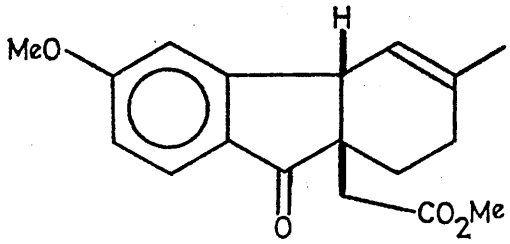


(43) R=H

(45) R=Me

a=∝ H, b= β H



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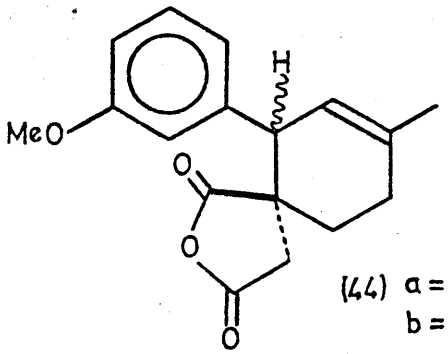
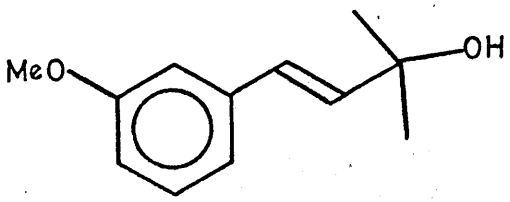


(44) a = ∝ H
b = β H



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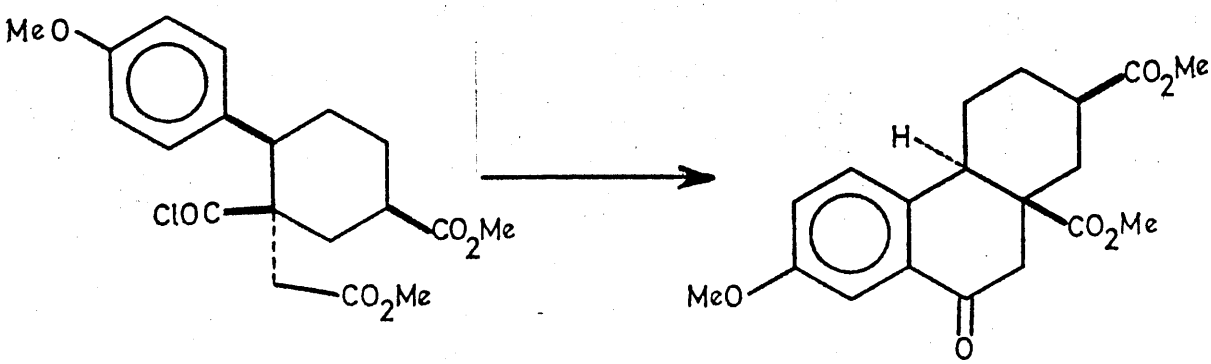
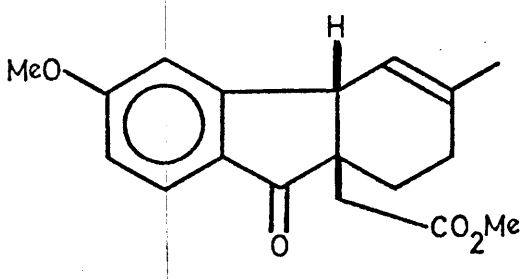


This second approach consisted of reacting the diene (I7) with itaconic acid (42) instead of with acrylic acid as before. This should give the diacid (43) as a mixture of epimers from which the anhydrides (44a and b) would be available. Methanolysis of these anhydrides might be expected to give the half esters (45a and b) by regioselective ring opening of the anhydrides at the less hindered centre. These half esters require only to undergo Friedel-Crafts cyclisation to give the required keto-ester (I4), together with its 4a epimer. However, an analogous sequence had failed at the Friedel-Crafts stage by formation of the corresponding hydrophenanthrene instead of the required hydrofluorene (scheme 4).[25] The acid chloride had evidently undergone transesterification before or during cyclisation. It was in the light of this knowledge that the above approach had not been attempted earlier, but now it was decided to put it to the test.

Diels-Alder addition of itaconic acid (42) to the diene (I7) was effected in refluxing toluene and gave a 3:2 epimeric mixture (g.l.c.) of the anhydrides (44a and b) in 91% yield by dehydration of the initially formed diacids (43a and b). An identical result was obtained when the alcohol (I9) was used in place of the diene (I7). The anhydrides (44a and b) resisted methanolysis in refluxing methanol, but were readily opened to the half esters (45a and b) by treatment with sodium methoxide in dry methanol at 0°. In routine preparations of (45a and b) it was found convenient to purify the crude half esters at this stage by



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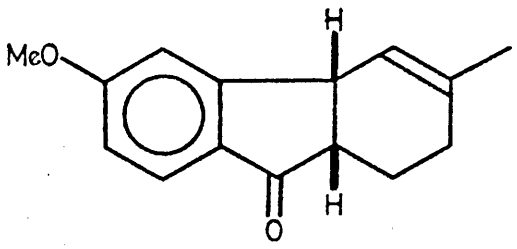
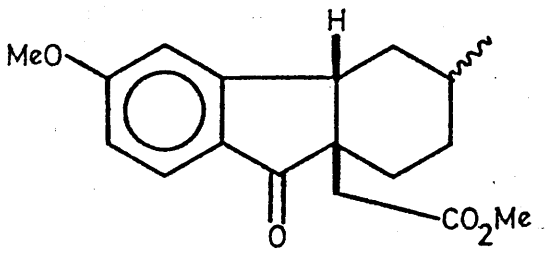


(15)



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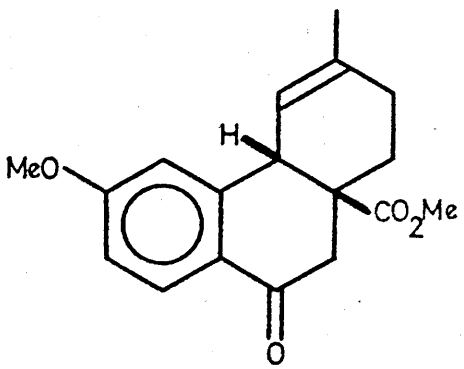

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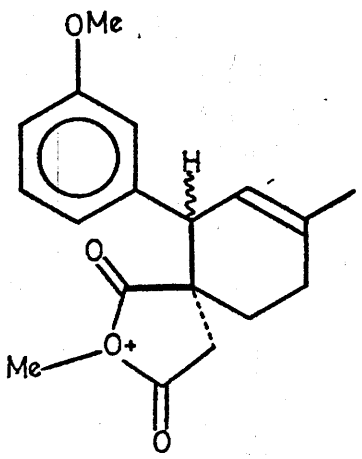


(47)

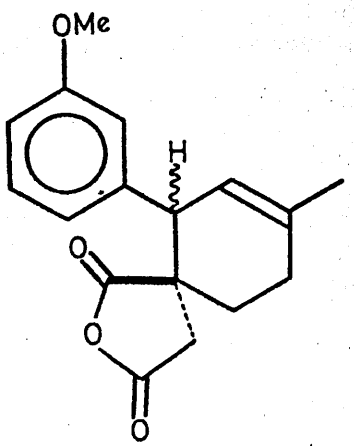
base extraction followed by careful acidification to avoid lactonisation. The acids (45a and b) were converted to the corresponding acid chlorides by treatment with oxalyl chloride in benzene at room temperature. The yield of this reaction was effectively quantitative as determined by i.r. spectroscopy (no hydroxyl absorption and carbonyl bands at 1790 and 1725 cm^{-1} only). Friedel-Crafts cyclisation of these acid chlorides was effected in methylene chloride solution using 1.1 molar equivalents of aluminium chloride as catalyst. The experience gained in the Friedel-Crafts cyclisation of the acid (16) proved useful and the first crystalline material isolated after work up proved to be a 16.5% yield of the required keto-ester (14). The structure of this compound was established from its spectral characteristics and from spectral comparisons with the analogous ketones (15) and (37). The position of the double bond was confirmed by a double irradiation experiment on its proton n.m.r. spectrum. In this experiment the vinylic proton signal at 5.80δ sharpened considerably on double irradiation at 3.75δ the benzylic resonance.

From the mother liquors of the above Friedel-Crafts reaction a second crop of crystals was obtained (39%) which proved to be the not unexpected hydrophenanthrene (46). As has been suggested,[25] the active intermediate in the cyclisation was probably the anhydride-like cationic species (47), generated by neighbouring group attack on the complexed acid chloride. Cyclisation could thus take place at either of the two possible carbonyl centres. Inspection of molecular

models suggested much greater strain in the trans fused hydrofluorenone than in the corresponding cis fused compound. In the case of the hydrophenanthrenes no real preference for cis or trans ring fusion was predicted. It was thus thought that the particular epimer of the acid chloride from acids (45a and b) which could lead to the cis fused hydrofluorenone (I4) did in fact do so, and that cyclisation of the other epimer led to the cis fused hydrophenanthrene (46). Some trans fused hydrophenanthrene might also be formed at the expense of the cis hydrofluorene resulting in the observed low yield of (I4), but this was not verified. It was thus only by remarkable luck that any of the required isomer was isolated at all.

The isomeric ketones (I4) and (46) were readily distinguishable by comparison of their u.v. spectra with the u.v. spectrum of the 6-methoxyhydrofluorenone (I5). An interesting difference in their n.m.r. spectra was the appearance of the two protons of the pendant acetic ester group in (I4) as a distorted AB quartet with a large geminal coupling constant; the corresponding protons in (46) situated α to the ketone function, appeared only as a slightly broadened singlet.

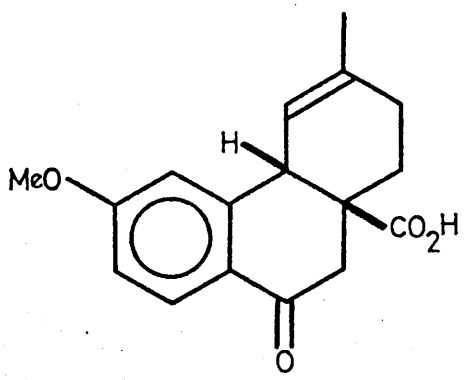
Having obtained only a low yield of the ketone (I4) in the Friedel-Crafts step, attempts were now made to improve the yield of (I4) from the half esters (45a and b). It was reasoned that if the active electrophilic intermediate in the cyclisation was in fact the oxonium species (47), then



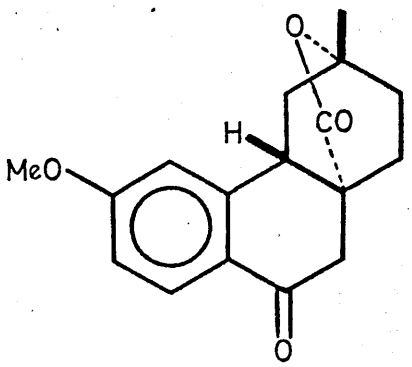
(44) a = ∝ H
b = β H

its formation from the acid chloride might be inhibited by having the ester group in (45a and b) derived from a bulkier, more hindered alcohol. Thus the anhydrides (44a and b) were treated with sodium iso-propoxide to give the corresponding iso-propyl half esters which were cyclised by the same method as for the methyl half esters. The resulting oily product was analysed by t.l.c. and was shown to consist of two major compounds. Preparative separation (t.l.c.) of these substances followed by u.v. spectral examination indicated that the ratio of hydrophenanthrene to hydrofluorene was about 2:I This was no improvement over the previous method which gave a similar ratio of the two compounds as determined by g.l.c. analysis.

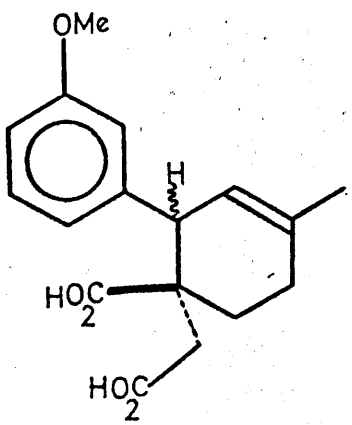
The possibility of cyclising the anhydrides (44a and b) directly was now investigated. This had not been tried before because it was hoped that transesterification of the acid chloride might not occur. However, since this hope was not fulfilled, the direct cyclisation of the anhydrides was predicted to give at least as good a result as the first method while elimenating two steps. One disadvantage, however, was that purification of the anhydrides by base extraction prior to cyclisation was not possible. This purification of the non-crystalline epimeric mixture of anhydrides had been possible in the previous cyclisation at the half ester stage. An advantage of this procedure was that there was no possibility of hydrogen chloride addition to the double bond. The anhydrides (44a and b) in methylene chloride were treated with aluminium chloride and gave after



(48)



(49)

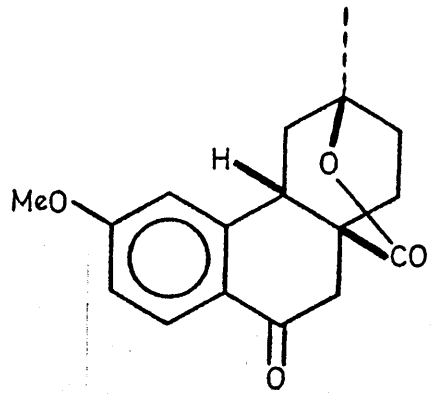


(50) a = α H
b = β H

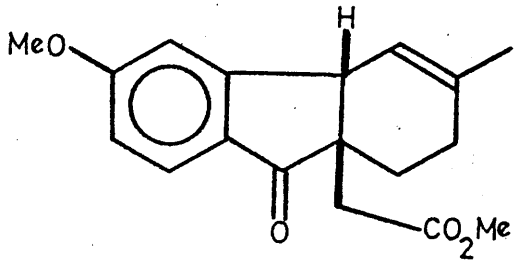
work up, a yellowish oil. A sample of this oil was treated with diazomethane and analysed by g.l.c. which showed that the ratio of hydrophenanthrene to hydrofluorene was again about 2:I. Repeated crystallisation of the original acidic products eventually gave about a I0% yield of the hydrophenanthrene acid (48) , identical to a sample prepared by alkaline hydrolysis of the ester (46).

In one Friedel-Crafts cyclisation experiment the methanol used for the preparation of the half esters (45a and b) was not rigorously dried and, after the usual procedures, the first crystalline material isolated from the final work up proved to be a 9% yield of the lactone (49). The formation of this compound can be rationalised by recognising that sodium hydroxide in the methoxide used for opening the anhydrides (44a and b) could give rise to the diacids (50a and b). Mineral acid treatment of these acids after base extraction could selectively lactonise that epimer in which the tertiary carboxyl group is axial. This epimer would be the one in which both acetic acid and aryl groups adopted the preferred equatorial orientation. Subsequent cyclisation would then give (49). This type of lactonisation could also occur in the case of the half ester (45a) and may account for one of the unidentified products from the internal Friedel-Crafts reaction of (45a and b).

For comparison purposes it was decided to lactonise the acid (48) which had been assigned the <u>cis</u> fused ring junction. Thus the acid (48) was treated with methanesulphonic acid at



(51)



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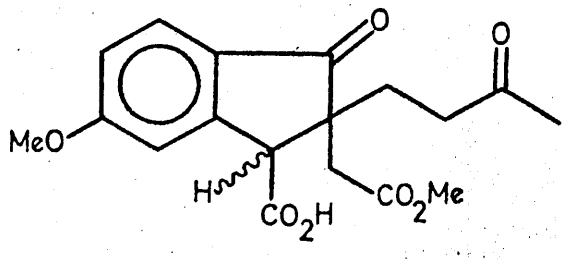
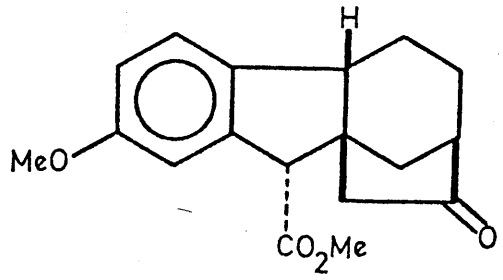


(9)

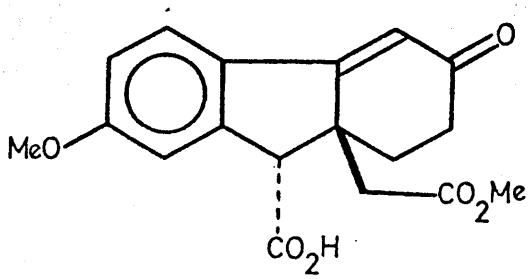
room temperature to give the lactone (51) in high yield. Lactones (49) and (51) were spectroscopically similar but varied widely in physical properties.

Although the ketone (14) could be prepared only in low yield, the large scale on which this preparation could be carried out made useful amounts available and the synthetic sequence was advanced to its next stage - the oxidation of the double bond of (14) to give the required indanone (9). The first method employed oxidation with a mixture of sodium periodate and potassium permanganate in aqueous acetone,[26] but resulted only in the recovery of the starting ketone. During this procedure the reduced manganate ion should have been re-oxidised to permanganate by the periodate; however, a brown precipitate of manganese dioxide was observed and no further oxidation took place. There seemed no obvious explanation for this.

A second attempt was successful when the ketone (14) was ozonised at -78° in ethyl acetate to give, after oxidative work up, a 65% yield of acidic material. This oily product resisted all attempts at crystallisation and was shown by n.m.r. to be a mixture of epimers. Partial inversion at the C-3 position had evidently occurred. Complete characterisation of this material was not attempted and it was used in the next step without further purification. Spectral examination did, however, reveal that the 5-methoxyindan-1-one system was still intact (u.v.), and a signal at 4.50δ in its n.m.r. spectrum suggested that the C-3 proton was both benzylic and α to a carboxyl group.



(2)



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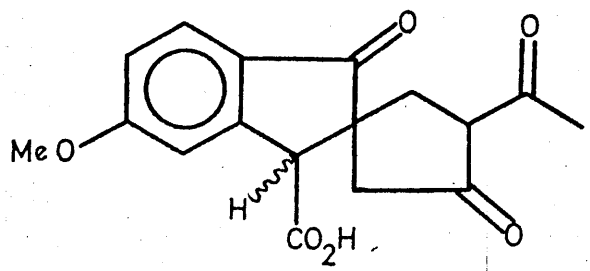
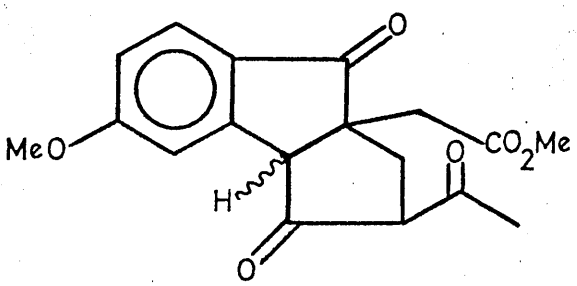


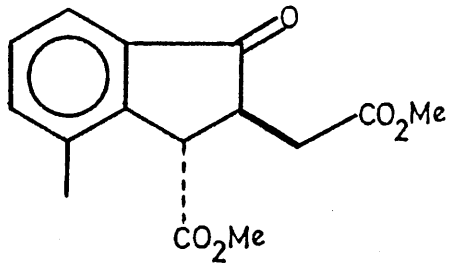
(52)



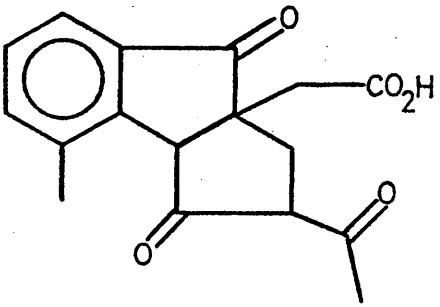
(53)

With the apparently successful preparation of the indanone (9) completed, the next stage in the synthesis of the tetracyclic keto-ester (2), conversion of (9) to (2), was embarked upon. Reaction conditions for the aldol cyclisation of (9) to the tricyclic enone (I0) were inferred from the conditions used for the annelation of indanones using methyl vinyl ketone and from a similar cyclisation described by Raphael.[27] However, treatment of the indanone (9) with strong bases under a variety of conditions gave no product exhibiting the characteristic chromophore of the conjugated "cinnamoyl" system of (I0). At this point it was thought that the possible retro-Michael reaction, which could compete with cyclisation, was occurring so fast that no cyclisation at all was taking place. Accordingly, attempts to cyclise the indanone (9) were made using acid catalysts as well as trying to effect cyclisation via an enamine intermediate.[28] As far as could be determined, however, only starting material was recovered in each case.

One puzzling feature of the products of strong base treatment of the indanone (9) was that when an aliquot was removed directly from the reaction vessel during an experiment it showed an absorption maximum at about 300nm. Addition of a few drops of mineral acid to the contents of the u.v. cell resulted in an immediate return to shorter wavelength absorption. The PH dependence of the u.v. absorption maximum suggested that a β-diketone was being formed,[30] the most likely structures of which were (52) and (53). This hypothesis was substantiated when an analogous reaction was



(54)



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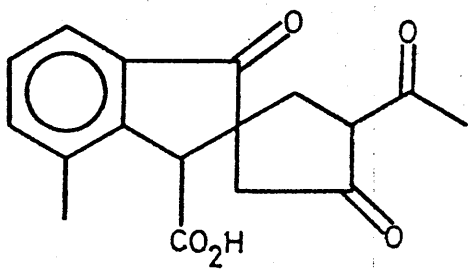

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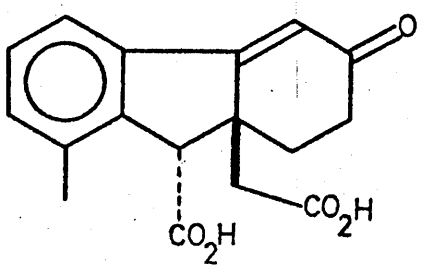

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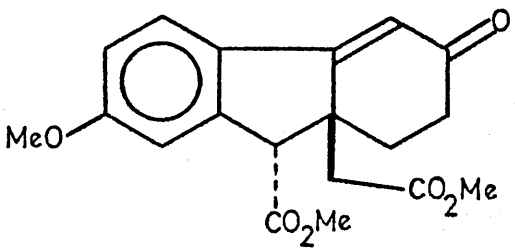
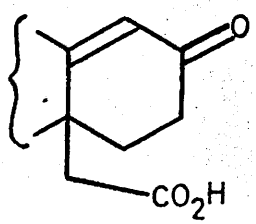


(58)

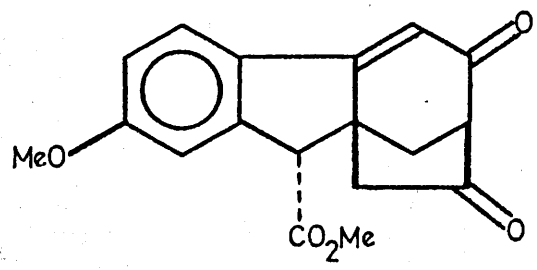
found in the literature. During the annelation of the indanone (54) with methyl vinyl ketone, Matsui[29] found that the first intermediate was a β-diketone, (55), (56), or both. Subsequent conversion of this intermediate diketone to the required enone (57) was effected simply by treatment with aqueous sodium hydroxide. Accordingly, the indanone (9) was treated with sodium methoxide in methanol followed by aqueous sodium hydroxide. This procedure gave a yellow oil which on methylation with diazomethane and chromatographic purification on alumina gave the tricyclic diester (58) as yellow crystals in 31% yield. An identical result was obtained when the indanone (9) was treated directly with aqueous sodium hydroxide followed by the above manipulations. The moderate yield of (58) was attributed to the competitive retro-Michael reaction mentioned earlier.

The structure of the tricyclic enone (58) was evident from its spectral characteristics. Its n.m.r. spectrum showed the enone vinylic proton as a sharp singlet at 6.20δ and the benzylic proton appeared similarly at 4.54δ. The u.v. spectrum showed the long wavelength absorption typical of the extended "cinnamoyl" system. I.r. spectroscopy showed the unsaturated ketone absorption at 1660 cm^{-1}. The stereochemistry was considered to be as shown since the conditions under which cyclisation of (9) took place were strongly basic and equilibration to the more stable <u>trans</u> isomer would be expected by analogy with Loewenthal's[II] observations.

With the successful conversion of the indanone (9) to



(59)



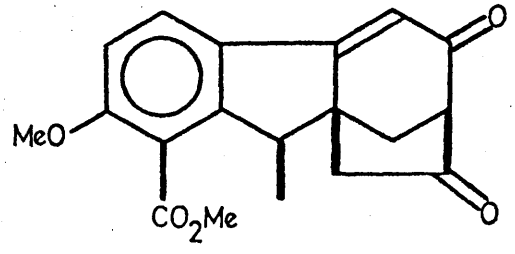
(11)

to the tricyclic enone (58) accomplished, there remained but one further stage before the gibbane skeleton was constructed, namely the closure of ring D. This had previously been effected by acid catalysed cyclodehydration of enone acids of general structure (59). Since it had been elected to handle the tricyclic enone as its dimethyl ester (58), and since saponification could cause undesired retro reactions, the final ring closure was carried out using the diester, a reaction for which there was no precedent, but no obvious reason for failure.

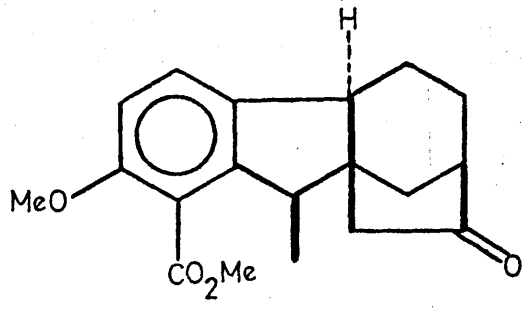
Treatment of the diester (58) with naphthalene-2-sulphonic acid in refluxing benzene gave the required tetracyclic diketo-ester (II) in high yield as a single isomer. The mother liquors of this reaction consisted almost entirely (t.l.c.) of the unreacted diester (58) which could be recycled in a subsequent reaction.

The structure of (II) was apparent from its spectral data, notably the characteristic shift to longer wavelength u.v. absorption (328 $\longrightarrow$ 340nm) on going from the tricyclic (58) to the tetracyclic structure (II)[8a]. The stereochemistry of (II) was assumed to be as shown, again by analogy with Loewenthal's findings.[II]

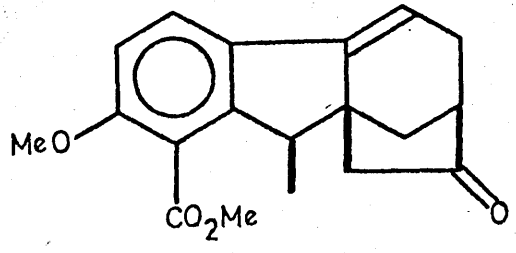
Another possible method of effecting the cyclisation (58 $\longrightarrow$ II) has been described by Loewenthal[8b] and consists of treating a tricyclic enone of type (59) with trifluoroacetic acid/trifluoroacetic anhydride at room temperature. However, when applied to the diester (58) a much reduced



(60)



(61)

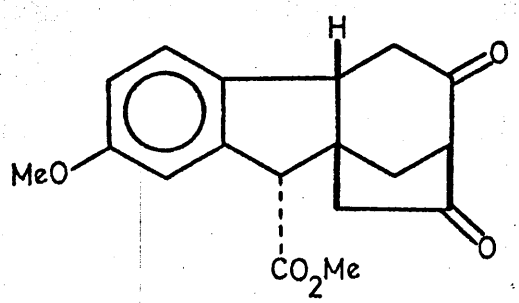


(62)

yield of (II) was obtained.

The last remaining step in the synthesis of the key intermediate (2) was the removal of the enone system in ring C of (II). Because of the low yields encountered in two of the steps leading to (II), viz. preparation of the keto-ester (I4) and cyclisation of the indanone (9), a high yield conversion of (II) to (2) was necessary to make synthetically useful amounts of (2) available for further elaboration. The hydrogenation procedure described by Loewenthal[8b] seemed ideal for this purpose. Before committing any valuable starting material it was decided to carry out some model experiments in order to optimise the reaction conditions. It was known that the product distribution of such a hydrogenation reaction was sensitive to a variety of factors[32] and it was thought that a useful test compound would be one which would give a known compound as the required product. A small amount of the gibbane (60) was available[8a] and the expected product (6I) of hydrogenation/hydrogenolysis of this compound was known[8a].

Thus a super-active catalyst was prepared by prehydrogenating a mixture of palladium chloride and purified charcoal in pure acetic acid until uptake was complete. To the catalyst mixture was added a warm solution of the gibbane (60) in acetic acid and the whole was hydrogenated at 50° for 0.75 hours. The product of this reaction was, quite unexpectedly, the keto-olefin (62), the structure of which was inferred from spectral data. Notably, the enone carbonyl



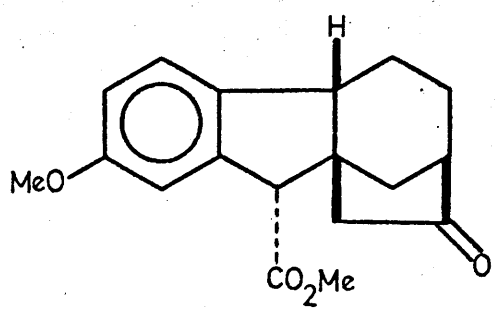
(63)

absorption of the starting compound was absent in its i.r. spectrum and a chromophore consistent with a styrene type of structure was observed in the u.v.. A signal at 5.64δ in its n.m.r. spectrum confirmed the presence of the double bond.

Further confirmation for the structure assigned to (62) was obtained by hydrogenation of (62) using I0% palladium on charcoal as catalyst which gave a high yield of the known gibbane (6I), established by comparison with the spectra and melting point of an authentic sample of (6I).[3I]

Removal of the C-I2 ketone function from (60) presumably proceded by an initial rapid hydrogenation to an allylic alcohol which underwent hydrogenolysis. The reason why the olefinic double bond should remain unaffected and yet later hydrogenate rapidly under apparently less forcing conditions, is not clear.

With reaction conditions for the proposed reduction of the enone (II) to the keto-ester (2) available, attempts were now made to effect this transformation. Thus (II) was hydrogenated as described above, but the main product in this case was the diketone (63), resulting from simple hydrogenation of the olefinic double bond. A g.c.m.s. analysis of the mother liquors of the above reaction showed no material with the required molecular weight of 300. Some variations on the hydrogenation procedure were tried. Addition of a few drops of perchloric acid resulted only

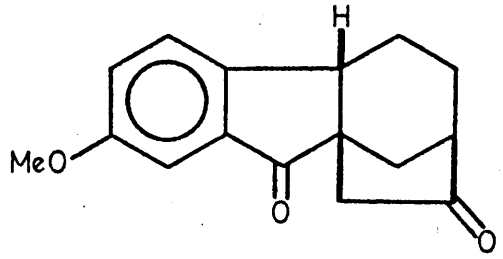


(2)

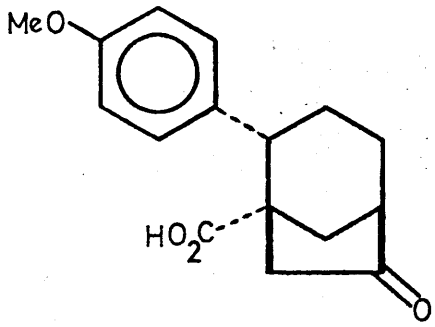
in the destruction of the catalyst. A longer period of hydrogenation had no effect at all. Since it was suspected that an allylic alcohol might be an intermediate in the hydrogenation reaction, a sample of the enone (II) was treated with sodium borohydride to give a mixture of alcohols which was subjected to the hydrogenation process without characterisation. The product of this reduction was oxidised with Jones reagent and analysed by g.c.m.s., but again no material with the required molecular weight was detected.

Finally, the hydrogenation of (II) was carried out at the higher temperature of 100^{o} and, after chromatographic separation of the products, a low yield (Ca. 4%) of an oily substance was obtained, which was shown by high resolution mass spectrometry to have the required constitution $C_{18}H_{20}O_4$. I.r. examination of this material showed carbonyl absorption maxima consistent with ester and cyclopentanone groupings. The mass spectrum of this compound showed an M^{+} minus-42 fragment indicating the loss of ketene, a process which is thought to occur at the CD- two carbon bridge and which has been observed in similar gibbane systems.[33] From these data and from the precursor and reaction conditions from which this substance was obtained, it is difficult to assign a structure other than (2) to this compound. However, since lack of material prevented full characterisation and lack of time prevented the preparation of larger amounts of the substance, its true identity was not unambiguously defined.

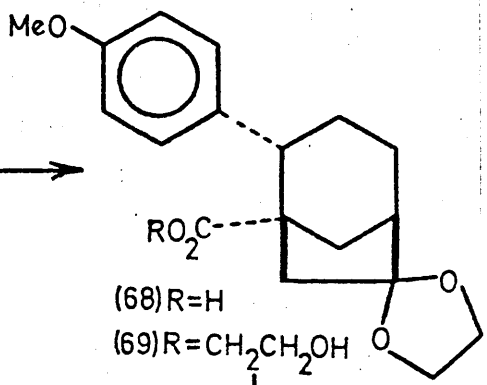
Why the enone (II) should not undergo efficient



(64)

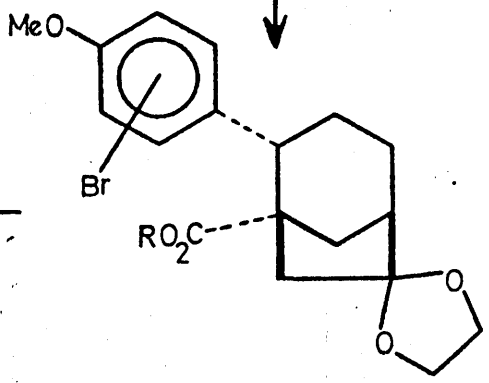


(65)



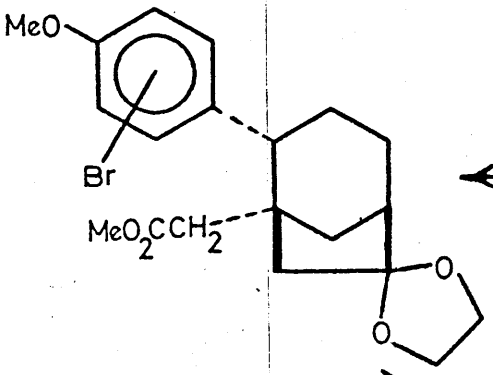
(68) R=H

(69) R=CH_2CH_2OH



(71) R=H

(70) R=CH_2CH_2OH



(66)

(2)

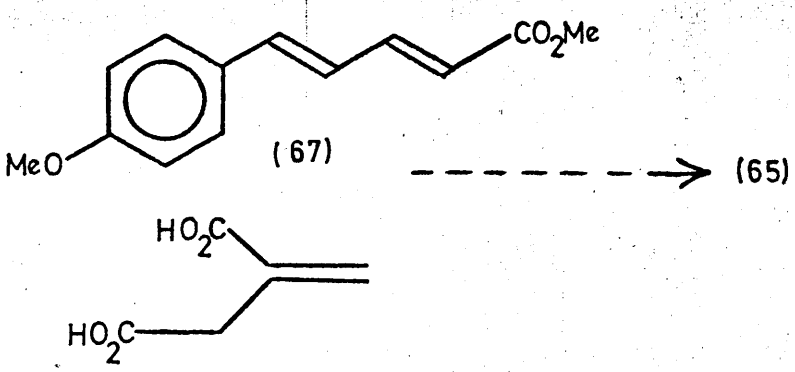
SCHEME 5

reduction to (2) under conditions which reduced similar systems was not clear. It is noteworthy, however, that the reduction of (60) to (6I) and the reduction described by by Loewenthal[8b] both had carbomethoxy groups in the substrate at the C-4 position, and both gave rise to the unnatural trans stereochemistry at the BC ring junction. Reduction of (II), which had no C-4 substituent, would be expected to result in the cis BC ring fusion, dictated by the stereochemistry of the C-6 substituent.[II]

Other methods for the removal of the enone system from (II) were contemplated, but the procedures available in the literature all involved circuitous, low yield routes;[II,29,8a] and attention was now turned to the second, alternative approach to the synthesis of the keto-ester (2).

(2)

In their synthesis of the diketone (64), Baker and Goudie[34] prepared the bicyclo(3.2.I.) octanone (65) in which the aryl and carboxyl groups are cis related. Any method of cyclising the carboxyl group, or an appropriate derivative, to the anisyl group would thus result in a gibbane of the required cis BC ring fusion (eg. 64). It was envisaged that the keto-ester (2) might be available from the keto-acid (65) by the following sequence: protection of the ketone function of (65) as its ethylene ketal followed by monobromination of the benzene ring; homologation of the acid function and esterification would then give (66) which should be convertible to (2) by base treatment via a


CO2Me
MeO
(67)
(65)
HO2C
HO2C

benzyne intermediate[35] (scheme 5). The position of bromination of the anisyl group would be unimportant since either possible isomer would give rise the same benzyne. Homologation of the acid function *via* the derived diazoketone in an Arndt-Eistert procedure should be possible.

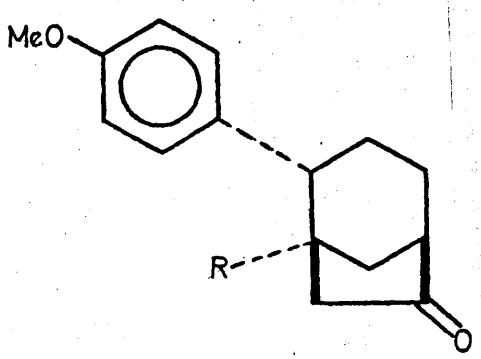
Thus the keto-acid was prepared in a multistep sequence[36] starting from the Diels-Alder addition product of itaconic acid to the diene (67). Because of the necessary separation of isomers at one stage in the sequence, the final yield of (65) was rather low. It was hoped that if initial experiments proved successful, then the entire mixture of (65) and its accompanying C-2 epimer might be subjected to the sequence (65 ⟶ 2) in the hope of separating the isomers at the final cyclisation step by selective reaction of the *cis* isomer to the preferred *cis* BC gibbane (2). This type of separation had been effected on the same mixture of isomers in the preparation[34] of (64).

In an attempt to ketalise the C-6 ketone function of (65), this keto-acid was treated with ethylene glycol and toluene-*p*-sulphonic acid in refluxing benzene. The product of this reaction was a mixture of the required crystalline ketal acid (68) and the corresponding oily hydroxyethyl ester (69), obviously formed by esterification of the acid with ethylene glycol. These two compounds were readily separable by virtue of the base solubility of the acid, but attempts to obtain the acid without esterification occurring were unsuccessful. It was also noteworthy that on prolonged

reaction the ratio of ketal acid to ketal ester remained almost constant. It thus appeared that ketalisation and esterification occurred at comparable rates and that esterification could be followed by ketalisation but not vice versa. No significant amount of unketalised ester was detected. The ketal ester (69) was readily converted to the ketal acid in good yield by alkaline hydrolysis.

Attempts to mono-brominate the ketal acid (68) were now undertaken. When (68) was treated with bromine in carbon tetrachloride solution in the presence of ferric bromide the product was a brown tar which showed at least seven highly polar products on t.l.c.. Bromine treatment of (68) without catalyst gave an oil which appeared to contain mono and di-bromo compounds by mass spectrometry and which was unresolvable on t.l.c.. The n.m.r. spectrum of this oil was uninformative. However, when the ketal ester (69) was treated with bromine in carbon tetrachloride solution without added ferric bromide, the rapid precipitation of an oil was observed and after work up and chromatographic separation on silica a good yield of the oily monobrominated ester ketal (70) was obtained. The position of bromination in the aromatic ring was not clear, but as was mentioned earlier, this was not important in the overall reaction scheme. The success of the bromination evidently lay in the insolubility of the reaction product in carbon tetrachloride.

It was now intended to hydrolyse the bromo ester (70)



(72) $R=CH_2CO_2H$

(73) $R=COCHN_2$

to the corresponding acid (71) prior to homologation of the acid function, but several attempts using aqueous sodium hydroxide at various concentrations gave only a mixture of products which again were unresolvable by t.l.c. and which defied all attempts at crystallisation. I.r. and n.m.r. spectra of these mixtures were inconclusive. It thus appeared that the required ketal acid (71) was not going to be readily available.

In parallel with the above experiments attempts were made to discover if the hindered acid group of the parent keto-acid (65) could be homologated to the acetic acid (72). Thus (65) was treated with oxalyl chloride in benzene to give the corresponding acid chloride which was added to an excess of diazomethane in ether at 0°. This resulted in the formation of the diazoketone (73) as evidenced by an absorption in its i.r. spectrum at 2010 cm^{-1}. Wolff rearrangement of diazoketones has been effected in two ways; firstly, rearrangement of the diazoketone may be catalysed by silver oxide or other metal catalyst,[37] and secondly by heating in the absence of catalyst in a high boiling solvent.[38] Attempted rearrangement of (73) by the first method by adding a slurry of silver oxide to the diazoketone in aqueous dioxane gave a mixture of three or more acidic products none of which were identified. However, when the diazoketone (73) was heated at 180° in collidine containing benzyl alcohol[38] followed by saponification of the resulting benzyl ester, the major product, according to its spectral data, was the required acetic acid (72).

Thus, although homologation of the acid group of (65) could be achieved, the preparation of the bromo compound (7I) was not immediately possible and for this reason and lack of time this approach to the synthesis of the keto-ester (2) was suspended. In addition to the above difficulty, it was found that when the mixture of (65) and its accompanying C-2 epimer plus other unavoidable impurities were subjected to the sequence (65 ⟶ 70), a black, intractable tar was obtained.

It would appear that if this route was to have any chance of success a means of introducing the bromine group into the aromatic ring at an early stage would have to be considered. Also, to obviate the necessity of separating isomers at some stage, a stereospecific synthesis of the bicyclo(3.2.I)octanone (65) would be advantageous.

Experimental

All melting points were determined on a Kofler microscope hot-stage and are uncorrected unless otherwise stated.

Routine infrared (i.r.) spectra (liquid films, potassium bromide discs) were recorded on Pye Unicam S.P. 200 or Perkin-Elmer 257 spectrophotometers; solution i.r. spectra were recorded by Mrs. F. Lawrie on either a Perkin-Elmer 257 spectrophotometer or a Unicam S.P. 100 double beam spectrophotometer, equipped with an S.P. 130 sodium chloride prism grating double monochromator operated under vacuum. High resolution i.r. spectra (at high dilution, i.e. at approximately 0.003M concentration in carbon tetrachloride) were recorded on this latter spectrophotometer.

Ultra-violet (u.v.) spectra were measured on a Pye Unicam S.P. 8000 spectrophotometer as solutions in 95% ethanol.

Nuclear magnetic resonance (n.m.r.) spectra were obtained on Varian T-60 and H.A. 100 spectrometers, using approximately 0.3M solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as an internal standard. Coupling constants (J) were measured in Hertz (Hz).

Analytical gas-liquid chromatography (g.l.c.) was carried out on a Pye Argon chromatograph equipped with a β-ionisation detector. All compounds were analysed on a 5% QF-1 column at a temperature of either 200 or 225 degrees centigrade.

Mass spectra were recorded on a G.E.C.-A.E.I. M.S.I2 spectrometer. High resolution mass measurements were made on an A.E.I. M.S. 902S machine. The figures quoted for the molecular ion (M) refer to the m/e value.

Microanalyses were carried out by Miss F. Cowan, Mrs. W.W. Harkness and their staff.

Thin layer chromatoplates were spread with Merck Kieselgel G and developed in ethyl acetate/light petroleum. Preparative chromatoplates were spread with Merck Kieselgel HF254.

Light petroleum refers to that fraction which boils within the range 60-80°.

Solutions were dried over either anhydrous magnesium sulphate or anhydrous sodium sulphate.

Combined gas chromatography-mass spectrometry (g.c.m.s.) analyses were carried out on an L.K.B.9,000 instrument.

I-(m-methoxyphenyl)-trans-but-I-en-3-one (I8).

This compound was prepared in 86% yield by an identical method to that used for the preparation of the corresponding p-methoxy isomer.[I5,I6] Acetone was condensed with m-methoxybenzaldehyde in aqueous sodium hydroxide to give the enone (I8) as a pale yellow oil, b.p. I40° at I torr (lit. b.p. I73° at 8 torr[I6]); δ 2.35 (3H, s, CO-CH_3), 3.80 (3H, s, OMe), 6.63 (IH, d, J=I6Hz, vinyl H), 7.40 (IH, d, J=I6Hz, vinyl H) and 7.00 (4H, m, aryl H).

I-(m-methoxyphenyl)-3-methyl-trans-buta-I,3-diene (I7).

Method I.

To a stirred suspension of triphenylmethylphosphonium bromide (39g) in dry ether (200 ml) was added potassium t-butoxide (I3g) and stirring continued for 2h. The enone (I8) (5g) in dry ether (25ml) was added at room temperature over 0.5h and the reaction mixture was stirred for a further I6h. The reaction mixture was poured onto ice and the organic layer separated, washed twice with brine, dried and the solvent removed. The residual brown oil was extracted with five portions of light petroleum and the combined extracts filtered and solvent removed to give the diene (I7) as a colourless mobile oil (4.2g, 84%), b.p. I20° at 0.02 torr; ν max. (thin film) I580, I600, 960, and 780 cm^{-1}; λ max. 280 nm (ε 28,000); δ 2.00 (3H, s, vinyl Me), 3.80 (3H, s, OMe), 5.I0 (2H, s, C=CH_2), 6.35-7.40 (6H, m, vinyl

and aryl H) (Found: M=174.10436. $C_{12}H_{14}O$ requires M=174.10446).

Method 2.

To a stirred suspension of magnesium turnings (5g) in ether (50ml) was added, under dry nitrogen, methyl iodide (32g) in ether (50ml). After 0.75h all the magnesium had dissolved and the enone (18) (18g) in ether (50ml) was added at 0° over 1h and stirring continued for a further 2h. Dry acetone was added until no more heat was evolved and the reaction mixture treated with saturated aqueous ammonium chloride (40ml). The organic layer was separated, washed twice with brine, dried and the solvent removed to give 1-(m-methoxyphenyl)-3-methyl-trans-but-1-en-3-ol (19.5g) as a colourless oil, ν max. (liquid film) 3460, 1580, 1600, 980, and 780 cm^{-1}; δ 1.40 (6H, s, gem di-Me), 2.35 (1H, s, OH), 3.75 (3H, s, OMe), 6.10-7.4 (6H, m, vinyl and aryl H).

Dehydration of the crude alcohol was effected in two ways:

a) Distillation of the alcohol (19) from potassium bisulphate (500mg) at 0.02 torr gave the pure diene (17) (14.8g, 82% based on starting enone) identical with the material prepared as described in method 1.

b) Refluxing the alcohol (19) in toluene (250ml) containing toluene-p-sulphonic acid (100mg) followed by removal of solvent and passage through a short column of neutral alumina with light petroleum gave, after removal of solvent, the diene (17) (15.2g, 84% based on starting enone) identical with the material prepared

by method I.

cis 2-(m-methoxyphenyl)-4-methylcyclohex-3-ene-I-carboxylic acid (I6).

Method I.

A mixture of the diene (I7) (2.7g), acrylic acid (2.5g) and hydroquinone (I5mg) in toluene (25ml) was refluxed under nitrogen for I6h. The reaction mixture was cooled, extracted twice with sodium carbonate solution and the combined extracts acidified to PH-5 with dilute hydrochloric acid. Ether extraction, followed by washing with brine, drying and solvent removal gave the crude acid. Excess acrylic acid was removed by dissolving the crude product in xylene and evaporating to dryness. Re-solution in ethyl acetate (3ml) and trituration with light petroleum gave crystals of the pure acid (2.8g, 70%), m.p. I27-I28°; ν max. (KBr) I690 and 3,000 cm^{-1}; λ max. 273 nm (ε 25I0) and 280 nm (2470); δ I.75 (3H, s, vinyl Me), 2.00 (4H, m, aliphatic H), 2.80 (IH, m, CO-CH), 3.68 (IH, m, benzylic H), 3.70 (3H, s, OMe), 5.54 (IH, br.d, vinyl H), 6.60 (4H, m, aryl H) and II.0(IH, s, OH) (Found: C, 73.09; H, 7.I2%. $C_{I5}H_{I8}O_3$ requires: C, 73.I4; H, 7.37%).

Method 2.

A mixture of the alcohol (I9) (20g), acrylic acid (I8g) and hydroquinone (30mg) in toluene (250ml) was refluxed for I6h with constant separation of water using a Dean-Stark trap. The reaction was worked up as described in method I above

giving the cyclohexene acid (I6) (23.4g, 70%) identical to the material prepared by method I.

3-Methyl-6-methoxy-I,2,4aβ,9aβ-tetrahydro-9-fluorenone (I5).

(I) The acid (I6) (I00mg) in polyphosphoric acid (2ml) was stirred while the temperature of the mixture was raised by about I° per minute. The reaction was monitored by u.v. spectroscopy and when the temperature reached 85-90° a change in the chromophore was observed. The mixture was poured onto ice, extracted with ether, washed with sodium bicarbonate solution, then with brine, dried and the solvent removed to give a brown gum which could not be resolved on t.l.c. and which appeared to be polymeric in nature.

(2) The acid (I6) (I00mg) in 80% sulphuric acid (2ml) was stirred at room temperature and the reaction monitored by u.v. spectroscopy and t.l.c. After 2h the mixture was poured onto ice, extracted with ether, washed with sodium bicarbonate solution, then brine, dried and the solvent removed to give a brown oil which consisted of at least five highly polar compounds.

(3) To a solution of the acid (I6) (IIg) in dry benzene (I50ml) was added oxalyl chloride (7ml) and the mixture stirred for 2h. Solvent and excess reagent were removed under reduced pressure and the resulting acid chloride (2I)

(νmax. 1790 cm^{-1}) was dissolved in methylene chloride (500ml). To this vigorously stirred solution was added aluminium chloride (7.0g) in one portion. After exactly 15min. the reaction mixture was poured onto ice, extracted with chloroform, washed once with brine, twice with sodium carbonate solution and once again with brine. Drying and removal of solvent gave the crude product which was crystallised from ethyl acetate/light petroleum to give the pure ketone (6.5g, 64%) as colourless prisms, m.p. 106-108°; ν max. (KBr) 1690 cm^{-1}; λ max. 269nm (ε 11,800), 288nm (9,000), 293nm (8,500); δ 1.60 (3H, s, vinyl Me), 1.85 (4H, m, aliphatic H), 2.80 (1H, m, CO-CH), 3.75 (1H, m, benzylic H), 3.80 (3H, s, OMe), 5.60 (1H, br.d, vinyl H), 6.90 (2H, m, aryl H), 7.65 (1H, d, J=8Hz, aryl H) (Found: C, 78.82; H, 6.98%. $C_{15}H_{16}O_2$ requires: C, 78.92; H, 7.06%)

3β-chloro-3α-methyl-6-methoxy-1,2,3,4,4aβ,9aβ-hexahydro-9-fluorenone (22a or b).

To a stirred solution of the acid chloride (21) (from 5g acid), prepared as described in the preparation of (15) above, in methylene chloride (250ml) was added aluminium chloride (3.4g) over 0.75h and stirring continued for 2h in a stoppered flask. The reaction was worked up as for the preparation of (15) above and the product crystallised from ethyl acetate giving the pure ketone (3.9g, 68%), m.p. 126-127°; ν max.

(KBr) 1695 cm^{-1}; λ max. 268nm (ε 11,900), 288nm (8,600) and 294nm (8,300); δ 1.54 (3H, s, Cl-CMe), 1.70-2.58 (6H, m, aliphatic H), 2.80 (1H, m, CO-CH), 3.70 (1H, m, benzylic H), 3.88 (3H, s, OMe), 6.92 (2H, m, aryl H) and 7.74 (1H, d, J=9Hz, aryl H) (Found: C, 67.91; H, 6.40%. $C_{15}H_{17}O_2Cl$ requires: C, 68.00; H, 6.46%).

The chloro compound (22b or a) epimeric with the above chloro compound (22a or b) at C-3 was prepared by adding aluminium chloride (3.4g) to a methylene chloride (250ml) solution of the acid chloride (21) (from 5g acid) in one portion. The reaction was stirred for 2h in a stoppered flask and was worked up as for the above preparation of the ketone (15). Crystallisation from ethanol/acetone gave the pure chloro ketone as colourless prisms (3.8g, 71%), m.p. 136-137°; ν max. (KBr) 1698 cm^{-1}; λ max. 268nm (ε 10,900), 286nm (8,300), 292nm (7,900); δ 1.78 (3H, s, Cl-CMe), 1.60-2.45 (6H, m, aliphatic H), 2.70 (1H, m, CO-CH), 3.40 (1H, m, benzylic H), 3.84 (3H, s, OMe), 6.85 (2H, m, aryl H) and 7.73 (1H, d, J=9Hz, aryl H) (Found: C, 68.12; H, 6.61%. $C_{15}H_{17}O_2Cl$ requires: C, 68.00; H, 6.46%)

The presence of halogen in the above chloro compounds was demonstrated by the green coloration produced when a sample of each substance was placed on a clean copper wire and burnt in a clean bunsen flame.

Base treatment of the chloro-ketones (22a or b) and (22b or a).

(I)
The ketone (22a or b) (I20mg) in toluene (I5ml) containing I,5 diazabicyclo(4.3.0)non-5-ene (60mg) was refluxed for I6h. The solution was treated with dilute hydrochloric acid and extracted with ethyl acetate washed,dried and solvent removed. This gave an oily residue which contained a small amount of the starting ketone (t.l.c.) but examination by n.m.r. spectroscopy showed no evidence of vinylic protons in the mixture.

(2)
The ketone (22a or b) (Ig) was dissolved in 20% methanolic potassium hydroxide solution (60ml) and the mixture rufluxed for I6h without exclusion of air. The reaction mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed, dried and the solvent reduced to a small volume. Addition of a few drops of light petroleum gave, after three days at 0-5°, crystals of a compound (0.28g, 29%) which was thought to be Iβ-(2'-carboxy-5'-methoxyphenyl)-5β-methyl-bicyclo (3.I.0)hexan-2-one (23), m.p. 200-202°; ν max. (KBr) I708, I685 and 2,500-3,500 cm^{-1}; λ max. 250nm (ε 8,370) and 2I0nm (I4,750); λ max. (basified with sodium hydroxide) 244nm; δ I.06 (3H, s), I.42 (2H, s), 2.00-2.50 (4H, m), 3.84 (3H, s), 6.82 (2H, m), 8.I4 (IH, d, J=9Hz) and I0.53 (IH, br.s). (Found: M= 260.I04678; C, 69.42; H, 6.42%. $C_{I5}H_{I6}O_4$ requires: M= 260.I0485I; C, 69.2I; H, 6.20%).

Treatment of a sample of the above compound (23) with excess

etheral diazomethane followed by removal of solvent gave the corresponding methyl ester as an oil which showed ν max. (CCl_4) I725 and I735 cm^{-1}; δ I.06 (3H, s), I.46 (2H, s), 2.00-2.55 (4H, m), 3.82 (3H, s), 3.87 (3H, s), 6.82 (2H, m) and 8.06 (IH, d, J=9Hz).

(3) The above base treatment of the chloro compound (22a or b) was repeated in an apparently identical manner but several attempts gave none of the above product (23). The material produced consisted of a mixture of 3-methyl-6-methoxy-9-fluorenone (26) (240mg, 28%) and the hexahydrofluorenone (27) (520mg, 60%) after chromatography on silica. The hexahydrofluorenone was identical in all respects to the material prepared by hydrogenation of the ketone (I5). The fluorenone (26) was crystallised from di-isopropyl ether/light petroleum and had m.p. II4.5-II5.5° (corrected) (lit.[3I] m.p. I27°); ν max. (KBr) I698 cm^{-1}; λ max. (cyclohexane) 222nm (ε I2,500), 260 (5I,000), 275nm (39,000), 297nm (I0,300), 322nm (3,I00) and 338nm (2,400); δ 2.40 (3H, s, aryl Me), 3.90 (3H, s, OMe) and 6.60-7.60 (6H, m, aryl H) (Found: C, 80.60; H, 5.58%. $C_{I5}H_{I2}O_2$ requires: C, 80.33; H, 5.39%)

(4) The chloro-ketone (22a or b) (430mg) in 20% methanolic potassium hydroxide solution (30ml) was refluxed for I6h with a constant flow of air through the solution. The reaction was worked up as described in (2) above to give, after chromatography on silica, the fluorenone (230mg, 65%) identical to the fluorenone (26) prepared above.

(5) The chloro-ketone (22b or a) isomeric at C-3 with the chloro-ketone (22a or b) was treated in an identical manner to that described in (2) above. No acid product was detected by sodium carbonate extraction of the product mixture and the products were the same as for the procedure described in (3) above in essentially the same yields.

Base treatment of the keto-olefin (I5).

The keto-olefin (I5) (250mg) was treated with potassium hydroxide in the usual way and gave the fluorenone (26) (80mg) and the hexahydrofluorenone (27) (I50mg) as the only products.

Base treatment of the chloro-ketone (30).

The chloro-ketone (30) (I70mg) was treated with 20% methanolic potassium hydroxide solution (I5ml) in the usual way to give an oily residue which consisted of at least five compounds (t.l.c.) none of which could be extracted with aqueous sodium carbonate or readily identified.

Base treatment of the chloro-ketone (3I).

The chloro-ketone (3I) (I80mg) was treated with methanolic potassium hydroxide solution (I5ml) in the usual way to give a mixture of at least five compounds (t.l.c.) none of which could be extracted with aqueous sodium carbonate. Preparative chromatographic separation of these substances

on silica and subsequent spectral examination resulted in the identification of the known[19] 3-methylfluoren-9-ol (35) (15mg), m.p. 146-147°; ν max. (CCl_4) 3605 cm^{-1}; δ 2.06 (1H, br.s, OH), 2.40 (3H, s, aryl Me), 5.42 (1H, s, benzylic H) and 7.00-7.70 (7H, m, aryl H). The other components of the mixture could not be induced to crystallise and were not identified.

In one chromatographic separation of the products of the above reaction the solvent was blown off the lined but undeveloped chromatoplate using hot air. This was accompanied by the appearance of a yellow coloration in the adsorbed material. Subsequent development and extraction gave the fluorenone (36) (32mg), m.p. 69° (lit.[20] m.p. 68°); ν max. (KBr) 1707 cm^{-1}; δ 2.20 (3H, s, aryl Me) and 6.95-7.80 (7H, m, aryl H). In this separation no fluorenol (35) was detected.

2β-Phenyl-4-methylcyclohex-3-ene-1β-carboxylic acid (32).

This compound was prepared in 78% yield by the method of Alder[13] to give the acid (32) m.p. 164-165° (lit.[13] m.p. 159°); ν max. (KBr) 2,400-3,500 and 1710 cm^{-1}; δ 1.75 (3H, s, vinyl Me), 1.50-2.30 (4H, m, aliphatic H), 2.80, (1H, m, CH-CO), 3.80 (1H, m, benzylic H), 5.50 (1H, br.d, vinyl H), 7.20 (5H, s, aryl H) and 11.40 (1H, s, OH).

3ξ-methyl-3ξ-chloro-I,2,3,4,4aβ,9aβ-hexahydro-9-fluorenone (3I).

To a solution of the acid (32) (Ig) in dry benzene (30ml) was added oxalyl chloride (Iml) and the mixture stirred for 2h. Solvent and excess reagent were removed under reduced pressure and the resulting acid chloride (ν max I8I0 cm^{-1}) was dissolved in methylene chloride (I00ml). Aluminium chloride (650mg) was added over 0.75h and stirring continued for a further I6h in a closed vessel. The reaction mixture was poured onto ice, extracted with chloroform, washed once with brine, twice with aqueous sodium carbonate and once more with brine. The solution was dried and the solvent removed to give the crude ketone. Crystallisation from ethyl acetate/light petroleum gave the pure chloro-ketone (3I) as colourless prisms (820mg, 76%) m.p. I30-I3I°; ν max. (KBr) I7I3 cm^{-1}; λ max. 245nm (ε I7,900) and 285nm (4,900); δ I.55 (3H, s, CCl-Me), I.60-3.00 (7H, m, aliphatic H and CO-CH), 3.75 (IH, m, benzylic H) and 7.50 (4H, m, aryl H) (Found: C, 7I.80; H, 6.62%. $C_{I4}H_{I5}OCl$ requires: C, 7I.64; H, 6.44%)

2β-(p-methoxyphenyl)-4-methylcyclohex-3-ene-Iβ-carboxylic acid.

I-(p-methoxyphenyl)but-I-en-3-one (34) (5g) in dry ether was added dropwise over Ih to a stirred solution of methyl magnesium iodide (from I.3g magnesium) in dry ether (50ml), and the mixture stirred for a further Ih. Dry acetone was

added slowly until no more heat was evolved and the mixture treated with saturated ammonium chloride solution (10ml). The organic layer was separated, washed with brine, dried and the solvent removed to give an oily alcohol (ν max. 3480cm^{-1}). The crude alcohol (33) was dissolved in toluene (50ml) containing acrylic acid (3.5g) and hydroquinone (15mg) and the entire mixture was refluxed for 16h with constant separation of water using a Dean-Stark trap. The cooled reaction mixture was extracted with sodium carbonate solution and the extract acidified to PH5 with dilute hydrochloric acid. The organic material was dissolved in ether, washed with brine, dried and the solvent removed to give the crude acid. Crystallisation from ethyl acetate/ light petroleum gave the pure cyclohexene acid as colourless prisms (4.5g, 64% based on starting enone) m.p. 136-137°; ν max. (KBr) 2,500-3,600 and 1715 cm^{-1}; λ max. 275nm (ε 1750), 286nm (1460); δ 1.80 (3H, s, vinyl Me), 1.65-2.40 (4H, m, aliphatic H), 2.85 (1H, m, CO-CH), 3.80 (3H, s, OMe), 3.90 (1H, m, benzylic H), 5.50 (1H, br.d, vinyl H), 7.80 and 7.15 (4H, dd, J=9Hz, aryl H) and 10.55 (1H, br.s, OH) (Found: C, 73.26; H, 7.60%. $C_{15}H_{18}O_3$ requires: C, 73.14; H, 7.37%).

3ξ-Chloro-3ξ-methyl-7-methoxy-1,2,3,4,4aβ,9aβ-hexahydro-9-fluorenone (30).

To a stirred solution of the acid from the previous preparation (1g) in dry benzene (40ml) was added oxalyl chloride (0.8g)

and stirring continued for a further 2h. Solvent and excess reagent were removed under reduced pressure to give the acid chloride as a clear oil (ν max. I805 cm^{-1}). This acid chloride was dissolved in methylene chloride (80ml) and treated with aluminium chloride (0.55g) in portions over 0.75h with stirring. The stirred mixture was left for I6h then poured onto ice, extracted with chloroform, washed once with brine, twice with sodium carbonate solution and once again with brine. Drying and removal of solvent gave the crude ketone. Crystallisation from ether/light petroleum gave the pure chloro-ketone (30) as colourless needles (0.73g,68%) m.p. I24-I25°; ν max. (KBr) I7I2 cm^{-1}; λ max. 249nm (ε I0,800) and 3I9nm (4,200); δ I.50 (3H, s, CCl-Me), I.60-2.60 (6H, m, aliphatic H), 2.80 (IH, m, CO-CH), 3.60 (IH, m, benzylic H), 3.80 (3H, s, OMe) and 7.25 (3H, m, aryl H) (Found: C, 68.30; H, 6.57%. $C_{I5}H_{I7}O_2Cl$ requires: C, 68.05; H, 6.47%).

Attempted alkylation of the keto-olefin (I5).

(I)

To a stirred solution of the ketone (I5) (I00mg) in anhydrous ether (I0ml) was added potassium t-butoxide (50mg) and stirring continued at room temperature for Ih. Methyl bromoacetate (60mg) in anhydrous ether (5ml) was added over 0.25h and the reaction mixture stirred for a further Ih. The mixture was poured onto ice, the organic layer separated, washed with brine, dried and the solvent removed. The

resulting yellowish oil (93mg) consisted of at least five compounds by t.l.c. analysis. Preparative chromatographic separation of these compounds on silica followed by u.v. spectral examination showed that none of these products exhibited the typical 5-methoxyindan-I-one chromophore.

(2)

The ketone (I5) (I00mg) was treated as in (I) above except that no methyl bromoacetate was added. No starting ketone was found among the four or more compounds which resulted. Separation of these substances by preparative t.l.c. and u.v. spectral examination again showed no material with the required chromophore.

(3)

To a stirred solution of the ketone (I5) (I00mg) in dry ether (I0ml) was added a 60% suspension (25mg) of sodium hydride in benzene. The mixture was stirred for 2h and methyl bromoacetate (50mg) in dry ether (5ml) was added over 0.25h and stirring continued for Ih. Dry ethanol was carefully added until effervescence ceased and the mixture was poured onto ice. After the usual manipulations the starting ketone was recovered in the absence of any other product.

(4)

Method (3) above was repeated except that dry sodium methoxide (40mg) was used instead of sodium hydride. The starting ketone was recovered almost quantitatively.

(5)

To the ketone (I5) (I00mg) in dry dimethoxyethane (I0ml) was added methyl bromoacetate (50mg) and a 60% suspension (25mg) of sodium hydride in benzene. The mixture was refluxed for 8h and was monitored by t.l.c. After the usual work up procedure a mixture of at least four highly polar compounds was obtained. Separation followed by u.v. spectral examination showed that none of these compounds exhibited the typical 5-methoxyindan-I-one chromophore.

3ξ-methyl-6-methoxy-I,2,3,4,4aβ,9aβ-hexahydro-9-fluorenone (27).

A mixture of the keto-olefin (I5) (5g) and I0% palladium on charcoal (I00mg) in ethyl acetate (50ml) was hydrogenated at room temperature and atmospheric pressure until I.I molar equivalents of hydrogen were absorbed. The catalyst was filtered off and removal of solvent gave the reduction product (5g, I00%). Crystallisation from di-isopropyl ether/light petroleum gave the required ketone (27) as fine needles m.p. 80-8I°; ν max. (KBr) I700 cm^{-1}; λ max. 269nm (ε I4,000), 288nm (I0,300) and 295 (9,900); δ 0.90 (3H, d, J=6Hz, aliphatic Me), I.60 (7H, m, aliphatic H), 2.75 (IH, m, CO-CH), 3.35 (IH, m, benzylic H), 3.90 (3H, m, OMe), 6.90 (2H, m, aryl H) and 7.70 (IH, J=9Hz, d, aryl H) (Found: C, 78.20; H, 7.7I%. $C_{I5}H_{I8}O_2$ requires: C, 78.23; H, 7.88%).

Methyl (3ξ-methyl-6-methoxy-9-oxo-I,2,3,4,4aβ,9a-hexahydro-9aβ-fluorenyl)acetate (37).

A solution of the ketone (27) (80mg) in dry ether (I0ml) was treated with potassium t-butoxide (85mg) and the mixture stirred for 2h under nitrogen. Methyl bromoacetate (60mg) in dry ether (5ml) was added dropwise over 0.5h and stirring continued for a further Ih. The reaction mixture was poured onto ice, extracted with ether, washed with brine, dried and the solvent removed to give the crude keto-ester as an oil. After much trial and error the pure keto-ester was eventually obtained in a crystalline form (82mg,78%) as fine colourless needles from ether/light petroleum and gave m.p. 76-77.5°; ν max. (KBr) I703 and I740 cm^{-1}; λ max. 269nm (ε I5,800), 287nm (I2,800) and 295nm (I2,000); δ 0.90 (3H, d, J=6Hz, aliphatic Me), I.I0-2.20 (7H, m, aliphatic H), 2.60 and 2.75 (2H, dd, J=I6Hz, ester methylene), 3.30 (IH, m, benzylic H), 3.50 (3H, s, ester OMe), 3.90 (3H, s, aryl OMe), 6.90 (2H, m, aryl H) and 7.70 (IH, d, J=9Hz, aryl H) (Found: C, 7I.72; H, 7.49%. $C_{I8}H_{22}O_4$ requires: C, 7I.50; H, 7.33%)

3ξ-Methyl-6-methoxy-I,2,3,4,4aβ,9aβ-hexahydro-3ξ,4ξ-epoxy--9-fluorenone (40).

To a stirred suspension of disodium hydrogen phosphate (5g) and m-chloroperbenzoic acid (3g) in dry methylene chloride

(50ml) was added the olefin (I5) (Ig) in dry methylene chloride (25ml) at 0° over 0.25h and stirring continued for a further 2h at 0°. The reaction mixture was washed with brine, with sodium carbonate solution and again with brine. Drying and removal of solvent gave the crude epoxide which was crystallised from ethyl acetate/light petroleum to give the pure epoxide as colourless prisms (790mg,74%), m.p. I53-I54°; ν max. (KBr) I695 and 3030 cm^{-1}; λ max. 269nm (ε I3,700), 290nm (I0,700) and 298nm (I0,I00); δ I.20 (3H, s, epoxide Me), I.30-2.20 (4H, m, aliphatic H), 2.65 (IH, m, CO-CH), 3.I0 (IH, br.s, epoxide H), 3.80 (IH, br.s, benzylic H), 3.90 (3H, s, OMe), 7.00 (2H, m, aryl H) and 7.70 (IH, d, J=8Hz, aryl H) (Found: C, 73.77; H, 6.83%. $C_{I5}H_{I6}O_3$ requires: C, 73.75; H, 6.60%)

3β-chloro-3β-methyl-6-methoxy-9-oxa-I0-oxo-I,2,3,4,4aβ,9,I0,I0aβ-octahydrophenanthrene (4I).

In one preparation of the epoxide (40) crude starting olefin (I5) was used instead of recrystallised material. After the procedure described above the first crystalline material which was isolated was the title compound (32mg from Ig crude olefin) m.p. I59-I60°; ν max. (KBr) I757 cm^{-1}; λ max. 238nm (ε 8,200) and 282nm (4,800); δ I.63 (3H, s, CCl-Me), I.70-2.60 (6H, m, aliphatic H), 2.94 (IH, m, CO-CH), 3.30-3.56 (IH, m, benzylic H), 3.76 (3H, s, OMe), 6.74 (2H, m, aryl H) and 6.90 and 6.98 (IH, d, J=8Hz, aryl H) (Found: C, 63.92; H, 6.I8%. $C_{I5}H_{I7}O_3Cl$ requires: C, 64.I7; H, 6.I0%).

3ξ-methyl-3ξ,4ξ-dihydroxy-6-methoxy-I,2,3,4,4aβ,9aβ-hexahydro--9-fluorenone, 3,4-acetonide (39).

(I)

To a solution of the epoxide (40) (0.5g) in dry acetone (20ml) at room temperature was added freshly distilled boron trifluoride etherate (0.Iml) and the mixture stirred for 0.5h. Anhydrous potassium carbonate (0.25g) was added and the suspension stirred vigorously for 0.5h. The mixture was then filtered through celite and the solvent removed followed by re-solution in ethyl acetate. This solution was filtered and reduced to a small volume to give, after trituration with light petroleum, prisms of the acetonide (39) (580mg,86%) m.p. I66-I67°; ν max. (KBr) I690, I365 and I375 cm^{-1}; λ max. 269nm (ε I7,400), 286nm (I3,200) and 295nm (II,300); δ I.05 (3H, s, cyclohexane Me), I.50 (3H, s, acetonide Me), I.55 (3H, s, acetonide Me), I.80-2.40 (4H, m, aliphatic H), 2.90 (IH, m, CO-CH), 3.85 (IH, m, benzylic H), 3.90 (3H, s, OMe), 4.50 (IH, d, J=Hz, dioxalane H), 7.00 (2H, m, aryl H) and 7.70 (IH, d, J=8H aryl H) (Found: C, 7I.70; H, 7.48%. $C_{I8}H_{22}O_4$ requires: C, 7I.50; H, 7.33%).

(2)

Attempted preparation from the diol (38).

The diol (38) (50mg) in dry acetone (I5ml) containing toluene-p-sulphonic acid (5mg) was refluxed for 36h. The mixture was filtered through basic alumina and the solvent

removed to give the starting diol (38) (48mg) as the only product. This procedure was repeated using anhydrous copper sulphate and boron trifluoride etherate (3 drops) instead of the sulphonic acid. In each case the starting diol was recovered in the absence of any other product.

3ξ-Methyl-3ξ,4ξ-dihydroxy-6-methoxy-I,2,3,4,4aβ,9aβ-hexahydro-9-fluorenone (38).

To a stirred solution of the acetonide (39) (60mg) in ether (8ml) was added dilute hydrochloric acid (5 drops) and stirring continued for 0.5h. The mixture was washed with sodium carbonate solution, then with brine, dried and the solvent removed to give the crude diol. Crystallisation from ethyl acetate/light petroleum afforded needles of the pure diol (49mg,93%) m.p. I57-I58°; ν max. (KBr) 3360, 3455 and I685 cm^{-1}; λ max. 269nm (ε II,200), 284nm (8,900) 292nm (7,800); δ I.25 (3H, s, O-C-Me), I.I5-2.50 (4H, m, aliphatic H), 2.65-3.35 (5H, m, CO-CH, CH-O, benzylic H and 2 -OH), 3.83 (3H, s, OMe), 6.83 (IH, dd, J_1=9Hz, J_2=2Hz, aryl H), 7.II (IH, d, J=2Hz, aryl H) and 7.60 (IH, d, J=9Hz, aryl H). (Found: C, 68.97; H, 6.62%. $C_{I5}H_{I8}O_4$ requires: C, 68.69; H, 6.92%).

Attempted alkylation of the acetonide (39).

(I)

To a stirred solution of the acetonide (39) (I00mg) in dry

ether (10ml) under nitrogen was added potassium t-butoxide (50mg) and stirring continued for 1h. Methyl bromoacetate (50mg) in dry ether (5ml) was added over 0.25h and stirring continued for a further 1h. The mixture was poured onto ice, extracted with ether, washed, dried and the solvent removed to give a brownish oil (96mg) which consisted of at least four highly polar compounds (t.l.c.). Chromatographic separation on silica followed by u.v. spectral examination detected no material which exhibited the characteristic 5-methoxyindan-1-one chromophore. Also, treatment of the acetonide with potassium t-butoxide as above but without addition of methyl bromoacetate gave a mixture of five or more highly polar compounds among which no starting ketone or other material with the required chromophore was detected by the analysis described above.

(2)

To a solution of the acetonide (39) (100mg) in dry dimethoxyethane (20ml) was added a 60% suspension (25mg) of sodium hydride in benzene together with methyl bromoacetate (50mg) and the mixture was refluxed for 8h. The reaction was monitored by t.l.c. and after this time was treated with dry ethanol until effervescence ceased. The mixture was poured onto ice, extracted with ether, washed with brine, dried and the solvent removed to give a dark brown oil (92mg) which consisted of at least five compounds by t.l.c. After the usual analysis none of these substances was found to exhibit the required chromophore. An identical result was obtained when the above procedure was repeated

but without the addition of methyl bromoacetate.

(3)

To a solution of the acetonide (39) (I00mg) in dry ether (20ml) was added sodium methoxide (30mg) and the solution refluxed under nitrogen for Ih. Methyl bromoacetate (50mg) in dry ether (5ml) was added at room temperature and the solution refluxed for a further 2h. After the usual work up the starting ketone (82mg) was recovered. The only other material present (t.l.c.) was a small amount of a highly polar substance which did not exhibit the expected u.v. absorption.

I-carboxy-2-(m-methoxyphenyl)-4-methylcyclohex-3-enyl acetic acid anhydrides (44a and b).

(I)

The diene (I7) (2g) was heated with itaconic acid (42) (I.5g) at I35° without solvent for two hours. The product consisted of a polymeric tar which could not be analysed by t.l.c.

(2)

A mixture of the diene (I7) (20g), itaconic acid (20g) and hydroquinone (2oomg) in toluene (500ml) was refluxed for 72h with constant separation of water using a Dean-Stark trap. The cooled solution was filtered to remove excess itaconic acid and the solvent was removed under reduced pressure to give the crude anhydrides (3Ig 9I%) which were

conveniently purified at the next step in the sequence by base extraction. A sample of the crude anhydrides was purified by preparative t.l.c. and showed νmax.(liquid film) I780 and I850 cm^{-1}; λ max. 273nm and 280nm ; δ I.60-2.40 (7H, m, aliphatic H), 2.80-3.00 (2H, m, anhydride CH_2), 3.80-4.00 (4H, m, OMe and benzylic H), 5.40 (IH, m, vinyl H) and 6.60-7.30 (4H, m, aryl H) (Found: M=286.I205I. $C_{I7}H_{I8}O_4$ requires: M=286.I2050). G.l.c. analysis of the above anhydride mixture showed the epimers in a ratio of 3:2. When the above reaction was repeated using the alcohol (I9) in place of the diene (I7) an identical result was obtained.

Methyl (3-methyl-6-methoxy-9-oxo-I,2,4aβ,9a—tetrahydro--9aβ-fluorenyl)acetate (I4).

To a solution of sodium methoxide (from I.7g sodium) in dry methanol (250ml) was added at 0° the mixture of anhydrides (44a and b) (20g) in dry methanol (I00ml) and the mixture stirred for Ih. The solvent was removed under reduced pressure and the resulting sodium salt dissolved in dilute aqueous sodium carbonate and washed with ether. The aqueous layer was acidified to PH5 with dilute hydrochloric acid and the organic material taken into ether, washed with brine, dried and the solvent removed to give the half esters (45a and b) (20.9g,94%) as a mixture of epimers (by n.m.r.) which showed νmax. (liquid film) 2,500-3,500 and I690-I750 cm^{-1}. This material was dissolved in dry benzene (250ml),

treated with oxalyl chloride (I5g) and the mixture stirred for 2h. Excess reagent and solvent were removed under reduced pressure and the resulting acid chloride ester (22g, I00%) (ν max. I780 and I730 cm^{-1}) dissolved in dry methylene chloride (800ml). Aluminium chloride (9.5g) was added all at once and the reaction was stirred vigorously for exactly 0.25h. The mixture was then poured onto ice, extracted with chloroform, washed once with brine, twice with sodium carbonate solution and once again with brine. After drying and removal of solvent the crude product was redissolved in ethyl acetate and trituration with light petroleum gave the pure keto-ester (I4) as colourless needles (3.45g,I6.5%) m.p. I32-I33°; ν max. (KBr) I695 and I732 cm^{-1}; λ max. 270nm (II,600), 288nm (8,600) and 295nm (8,200); δ I.50-2.I0 (4H, m, aliphatic H), I.70 (3H, s, vinyl Me), 2.65 and 2.85 (2H, dd, J=I6Hz, ester methylene H), 3.52 (3H, s, ester OMe), 3.75 (IH, m, benzylic H), 3.86 (3H, s, aryl OMe), 5.80 (IH, m, vinyl H), 6.90 (2H, m, aryl H) and 7.72 (IH, d, J=8Hz, aryl H) (Found: C,7I.92; H, 6.76%. $C_{I8}H_{20}O_4$ requires: C, 7I.98; H, 6.7I%).

3-methyl-6-methoxy-9-oxo-I0aβ-carbomethoxy-I,2,4aβ,9,I0,I0a-

-hexahydrophenanthrene (46).

The mother liquors remaining after crystallisation of the keto-ester (I4) in the reaction described above were evaporated to dryness and re-dissolved in di-isopropyl ether. The solution was triturated with light petroleum and left

to stand for 6 days at -10°. This resulted in the separation of colourless needles of the hydrophenanthrene (46) (8.5g, 39%) m.p. 104-105°; ν max. (KBr) 1684 and 1735 cm^{-1}; λ max. 276nm (ε 15,000); δ 1.70 (3H, br.s, vinyl Me), 1.75-2.30 (4H, m, aliphatic H), 2.80 (2H, s, CO-CH_2), 3.50 (3H, s, ester OMe), 3.80 (3H, s, aryl OMe), 4.00 (1H, m, benzylic H), 5.35 (1H, m, vinyl H), 6.80 (2H, m, aryl H) and 7.85 (1H, d, J=9Hz, aryl H) (Found: C, 71.77; H, 6.75%. $C_{18}H_{20}O_4$ requires: C, 71.98; H, 6.71%).

G.l.c. analysis of the original reaction product indicated the presence of 24% hydrofluorenone and 52% hydrophenanthrene plus three other unidentified compounds.

Further Friedel-Crafts cyclisations starting from the anhydrides (44a and b).

(I)

The anhydrides (44a and b) (1g) in dry isopropanol (25ml) were treated with sodium isopropoxide (from 180 mg sodium) in isopropanol (15ml) and the mixture stirred for 1h. The solvent was removed and the resulting sodium salt dissolved in dilute sodium carbonate solution and washed with ether. The aqueous solution was acidified to PH5 with dilute hydrochloric acid, extracted with ether, washed with brine, dried and the solvent removed to give the crude acid esters. This material was dissolved in dry benzene and treated with oxalyl chloride (0.8ml) with stirring. The solvent and excess reagent were removed under reduced pressure and the

resulting acid chloride esters(ν max. 1730 and 1800 cm^{-1}) dissolved in methylene chloride (50ml) and treated with aluminium chloride (0.5g) in one portion. The mixture was stirred vigorously for exactly 0.25h then poured onto ice, extracted with chloroform, washed with brine, with sodium carbonate solution and again with brine. After drying and removal of solvent the product consisted of a yellow oil (0.93g) which resisted all attempts at crystallisation. Preparative t.l.c. followed by u.v. spectral analysis indicated that the ratio of hydrophenanthrene to hydrofluorene was about 2:1.

(2)

To a stirred solution of the anhydrides (44a and b) (1g) in dry methylene chloride (50ml) was added aluminium chloride (0.5g) over 0.25h and stirring continued for a further 0.75h. The reaction mixture was poured onto ice, washed with brine and the acidic material taken into sodium carbonate solution. This extract was acidified to PH5 with dilute hydrochloric acid and the organic material extracted with ether, washed with brine, dried and the solvent removed to give a yellowish oil (0.94g). A sample of this oil was treated with excess ethereal diazomethane and analysed by g.l.c. which showed that the ratio of hydrophenanthrene to hydrofluorene was about 2:1. Attempts to crystallise the original acidic products eventually resulted in the isolation of the hydrophenanthrene acid (48) (95mg) identical to the acid prepared by alkaline hydrolysis of the keto-ester (46).

3-Methyl-6-methoxy-9-oxo-10aβ-carboxy-1,2,4aβ,9,10,10a-hexahydrophenanthrene (48).

The hydrophenanthrene ester (46) (1g) was dissolved in a 1:1 mixture (60ml) of methanol and 10% aqueous sodium hydroxide and the solution refluxed for 16h. The reaction mixture was diluted with aqueous sodium carbonate, washed with ether and acidified to PH5 with dilute hydrochloric acid. The organic material was extracted with ether, washed with brine, dried and the solvent removed to give the crude keto-acid. Crystallisation from ethyl acetate/light petroleum gave prisms of the pure acid (48) (0.88g, 92%) m.p. 177-179°; ν max. (KBr) 1675, 1722 and 2,500—3,400 cm^{-1}; λ max. 274nm (ε 14,900); δ 1.62 (3H, s, vinyl Me), 1.80-2.40 (4H, m, aliphatic H), 2.70 (2H, s, $CO-CH_2$), 3.80 (3H, s, OMe), 3.90 (1H, m, benzylic H), 5.30 (1H, br.s, vinyl H), 6.80 (2H, m, aryl H), 7.90 (1H, d, J=9Hz, aryl H) and 10.8 (1H, br.s, OH) (Found: C, 71.59; H, 6.67%. $C_{17}H_{18}O_4$ requires: C, 71.31; H, 6.34%).

3α-hydroxy-3β-methyl-6-methoxy-9-oxo-10aα-carboxy-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene 10aα⟶3α lactone (49).

In one preparation of the keto-ester (14) in which the methanol used for the opening of the anhydride was not efficiently dried, the first crystals which separated from the crude product mixture were those of the title compound.

Recrystallisation from aqueous acetone gave the pure lactone (49) (I.8g,9% from 20g anhydride) m.p. 239-240°; ν max. (KBr) I675 and I730 cm^{-1} ; λ max. 274nm (ε I5,000); δ (trifluoroacetic acid) I.60 (3H, s, O-C-Me), I.90-2.50 (5H, m, aliphatic H), 2.80 (IH, m, aliphatic H), 2.75 and 3.30 (2H, dd, J=I7Hz, CO-CH_2), 3.70 (IH, m, benzylic H), 4.00 (3H, s, OMe), 7.95 (2H, m, aryl H) and 8.20 (IH, d, J=9Hz, aryl H) (Found: C, 7I.60; H, 6.47%. $C_{I7}H_{I8}O_4$ requires: C, 7I.3I; H, 6.34%).

3β-hydroxy-3α-methyl-6-methoxy-9-oxo-I0aβ-carboxy-I,2,3,4,4aβ,9,I0, I0a-octahydrophenanthrene I0aβ $\rightarrow$ 3β lactone (5I).

A solution of the acid ketone (48) (I00mg) in methanesulphonic acid (2ml) was stirred at room temperature for 2.5h. The mixture was poured onto ice, extracted with ethyl acetate, washed with sodium carbonate solution, then with brine, dried and the solvent removed to give the crude lactone (5I). Crystallisation from ethanol gave the pure lactone as colourless plates (87mg,87%) m.p. I87-I88°; ν max. (KBr) I750 and I678 cm^{-1}; λ max. 277nm (ε I4,300); δ I.59 (3H, s, O-C-Me), I.62-2.20 (5H, m, aliphatic H), 2.65 (IH, m, aliphatic H), 2.72 and 3.00 (2H, dd, J=I7Hz, CO-CH_2), 3.40 (IH, m, benzylic H), 3.90 (3H, s, OMe), 6.85 (2H, m, aryl H) and 8.05 (IH, d, J=9Hz, aryl H). (Found: C, 7I.06; H, 6.44%. $C_{I7}H_{I8}O_4$ requires: C, 7I.3I; H, 6.34%).

Methyl (I-oxo-2-[2'-ketobutyl]-3-carboxy-5-methoxy-2-indanyl) acetate (9).

(I)

The keto-ester (I4) (I20mg) in acetone (20ml) was treated with a solution (20ml) which was 0.0I9M in sodium periodate and 0.0034M in potassium permanganate and stirred at room temperature for Ih. The pink colouration due to permanganate ion disappeared and a brown suspension, presumably manganese dioxide, was formed. The acetone was removed under reduced pressure and the organic material extracted with ether. Extraction with sodium carbonate solution followed by acidification, re-extraction with ether, washing with brine drying and removal of solvent gave an impure (t.l.c.) brown smear (2mg). The neutral material was worked up in the usual way to give the starting keto-ester (II2mg).

(2)

The keto-ester (I4) (Ig) in ethyl acetate (50ml) was ozonised at -78° for 2h. The deep blue solution was allowed to warm to room temperature and was purged with nitrogen to remove the last traces of ozone. Removal of solvent under reduced pressure at 25° gave the required ozonide which was oxidatively cleaved by stirring for I6h in a I:2 mixture (50ml) of 30% hydrogen peroxide and glacial acetic acid. The solution was then heated on a steam bath for Ih to decompose the peracid then diluted with ethyl acetate and extracted with sodium carbonate solution. This extract was acidified with dilute hydrochloric acid, extracted with ether,

washed, dried and the solvent removed to give the crude indanone acid (9) (760mg) as a brown oil which could not be persuaded to crystallise. This material showed ν max. 1660-1750 cm^{-1}; λ max. 275, 286 and 292nm; n.m.r. indicated a mixture of epimers and showed a signal at 4.50δ .

Methyl (3-oxo-7-methoxy-9αcarbomethoxy-1,2,3,9a-tetrahydro--9aβ-fluorenyl)acetate (58).

(1)

The indanone (9) (250mg) was dissolved in 90% methanol (20ml) containing pyrrolidine (0.5ml) and glacial acetic acid (0.5ml) and the mixture refluxed for 16h. The reaction was monitored by u.v. spectroscopy and t.l.c. Essentially no change was detected by either method and the characteristic u.v. absorption of the required product was certainly absent. The solvent was removed under reduced pressure and the organic material extracted with ether, washed with brine, dried and the solvent removed to give an oil (241mg) indistinguishable from the starting indanone.

(2)

The indanone (9) (120mg) was dissolved in benzene (15ml) containing toluene-p-sulphonic acid (5mg) and the mixture refluxed for 16h. The reaction was monitored by u.v. spectroscopy and t.l.c. but again no change was detected. The mixture was washed with water, then with brine, dried and the solvent removed to give an oil (118mg) which was

indistinguishable from the starting indanone.

(3)

The indanone (9) (I00mg) was dissolved in 5% methanolic potassium hydroxide (I0ml) and the solution stirred at 50° for 2h. The reaction was monitored by t.l.c. and u.v. spectroscopy. A pronounced shift to longer wavelength absorption was observed (275 → 300nm) when an aliquot of the reaction mixture was transferred directly to the u.v. cell. When a few drops of acid were added, however, the absorption maximum returned to shorter wavelength (277nm). This is consistent with the formation of a β-diketone enolate anion. The reaction mixture was diluted with water, acidified with dilute hydrochloric acid, saturated with sodium chloride and the organic material extracted with ether, washed with brine, dried and the solvent removed to give an oil of which t.l.c. analysis was inconclusive and which did not exhibit the required chromophore.

(4)

The indanone (9) (I00mg) was dissolved in dry methanol (I5ml) containing sodium methoxide (from I5mg sodium) and the mixture refluxed for I6h. The reaction was monitored by t.l.c. and u.v. spectroscopy and showed exactly the same spectral changes as in (3) above. The reaction was worked up as described in (3) above to give an oil (95mg) similar to that obtained in (3) above.

(5)

The indanone (9) (Ig) was dissolved in I0% sodium hydroxide

solution (50ml) and refluxed for I6h. The solution was acidified with dilute hydrochloric acid, extracted with ethyl acetate, washed with brine, dried and the solvent removed to give an oil (990mg) which was treated with excess ethereal diazomethane. Chromatography on alumina, using ethyl acetate (I0%) in light petroleum as eluant, gave the tricyclic enone (58) (3I0mg,3I%). Crystallisation from ether/light petroleum gave yellow prisms of the enone m.p. I25-I26°; ν max. (CCl_4) I660 and I740 cm^{-1}; λ max. 244nm (ε I5,900), 30Inm (I3,000) and 328nm (2I,600); δ 2.05-2.85 (6H, m, aliphatic H and ester methylene H), 3.63 (6H, s, 2 ester OMe), 3.82 (3H, s, aryl OMe), 4.54 (IH, s, benzylic H), 6.20 (IH, s, vinyl H), 6.90 (2H, m, aryl H) and 7.53 (IH, d, J=9Hz, aryl H) (Found: M=344.I25405. $C_{I9}H_{20}O_6$ requires: M=344.I254978).

An identical result was obtained when the oily product of (4) above was used as starting material in this procedure.

3-methoxy-6α-carbomethoxy-I2,I6-dioxogibb-I(I0),2,4,9-tetraene (II).

Method (I).

To a solution of the tricyclic enone (58) (250mg) in dry benzene (I5ml) was added naphthalene-2-sulphonic acid (30mg) and the mixture refluxed for I6h. The reaction mixture was cooled, washed with sodium carbonate solution, then with brine, dried and the solvent removed to give the crude diketone. Crystallisation from ether/light petroleum

afforded the pure diketo-ester (II) as yellow prisms (I77mg, 78%) m.p. I77-I78°; ν max. (CCl_4) I678, I745 and I757 cm^{-1}; λ max. 244nm (ε 6,300), 303nm (8,I00) and 340nm (I7,500); δ 2.50 (4H, m, aliphatic H and $COCH_2$), 3.50 (IH, m, COCHCO), 3.70 (3H, s, ester OMe), 3.83 (3H, s, aryl OMe), 4.I5 (IH, s, benzylic H), 6.I5 (IH, s, vinyl H), 7.00 (2H, m, aryl H) and 7.60 (IH, d, J=8Hz, aryl H) (Found: C, 69.36; H, 5.36%. $C_{I8}H_{I6}O_5$ requires: C, 69.22; H, 5.I6%)

The mother liquors of the above crystallised product were shown (t.l.c.) to consist almost entirely of the unreacted keto-diester and could be re-cycled in a later preparation of (II).

Method (2).

The tricyclic enone (58) (I00mg) was dissolved in a I:I mixture (8ml) of trifluoroacetic acid and trifluoroacetic anhydride and the solution stirred at room temperature for I6h. The mixture was poured onto ice, extracted with ether, washed with brine, dried and the solvent removed to give a yellow oil. Crystallisation from ether/light petroleum gave yellow prisms of the tetracyclic enone (II) (27mg,30%) identical to the material prepared by method (I) above. The mother liquors of the crystallised product consisted almost entirely of unreacted tricyclic diester (58).

Methyl 3-methoxy-6β-methyl-I6-oxo-9αH-gibb-I(I0),2,4-

-triene-4-carboxylate (6I).

A mixture of palladous chloride (I5mg), purified charcoal

(30mg) and pure glacial acetic acid (2ml) was hydrogenated at room temperature and atmospheric pressure until uptake was complete (2-3h). The temperature of the mixture was raised to 50° and the enone (60) (40mg) in pure acetic acid (2ml) was added all at once. The entire mixture was hydrogenated vigorously for 0.75h, then cooled, the catalyst removed by filtration and the solvent removed under reduced pressure to give the crude keto-olefin (62) (38mg) as an oil, ν max. 1730 and 1752 cm^{-1}; λ max. 266,275 and 310nm; δ 1.18 (3H, d, J=7Hz, benzylic Me), 1.50-2.80 (7H, m, aliphatic H), 3.35 (1H, d, J=7Hz, benzylic H), 3.80 (3H, s, ester OMe), 3.86 (3H, s, aryl OMe), 5.64 (1H, m, vinyl H) and 6.76 and 7.34 (2H, dd, J=8Hz, aryl H). This material was dissolved in ethyl acetate (5ml) and hydrogenated over 10% palladium on charcoal at room temperature and atmospheric pressure until uptake was complete (1h). The catalyst was filtered off and the solvent removed under reduced pressure to give, after crystallisation from benzene/light petroleum, the title compound as prisms (27mg, 67%) m.p. 173-174° (lit.[8a] m.p. 173.5-175°) identical by u.v. and i.r. spectroscopy with an authentic sample of (61).

3-Methoxy-6α-carbomethoxy-12,16-dioxo-9βH-gibb-A-triene (63).

The catalyst mixture described above was prepared from palladous chloride (18mg) and charcoal (36mg) and the enone (11) (50mg) in pure glacial acetic acid (2.5ml) added all at once at 50°. The mixture was stirred vigorously under hydrogen for 0.75h then cooled, the catalyst removed by

filtration and the solvent removed under reduced pressure to give a colourless oil. Crystallisation from ethyl acetate /light petroleum gave the pure diketone (32mg,64%) m.p. I97-I98° ; ν max. (KBr) I697, I737 and I758 cm^{-1}; λ max. 280nm (ε 2590) and 286nm (2300); δ I.80-3.40 (8H, m, aliphatic H), 3.90 (3H, s, ester OMe), 3.94 (3H, s, aryl OMe), 4.35 (IH, s, $CHCO_2$), 6.95 (2H, m, aryl H) and 7.35 (IH, d, J=9Hz, aryl H) (Found: M=3I4.II5I4. $C_{I8}H_{I8}O_5$ requires: M=3I4.II54I).

A g.c.m.s. analysis of the mother liquors of the above reaction showed no material with M=300.

3-Methoxy-6α-carbomethoxy-I6-oxo-9βH-gibb-A-triene (2)

(I) The above hydrogenation of the enone (II) was repeated except that hydrogenation was continued for 2h instead of 0.75h as above. The result was identical to that obtained previously.

(2) The hydrogenation procedure was repeated except that 65% perchloric acid (2 drops) was added to the acetic acid solution of the enone before addition to the catalyst mixture. This produced a deep blue coloration and no hydrogen was absorbed.

(3) The tetracyclic enone (II) (IOmg) was dissolved in 95% ethanol (4ml) and water (Iml) added slowly. Excess sodium borohydride in 95% ethanol was added at 0° and stirring

continued for 0.25h. IN sodium hydroxide (2ml) was added and the product was extracted with ethyl acetate, washed with brine, dried and the solvent removed to give a mixture (t.l.c.) of alcohols (νmax. I730 and 3500 cm^{-1}). This material (9mg) was hydrogenated as described above and the product dissolved in acetone (5ml) and treated with Jones reagent (8N,4 drops). Separation of the organic material followed by the usual manipulations gave a mixture of four or more (t.l.c.) compounds none of which (g.c.m.s.) had the required molecular weight of 300.

(4)
The original hydrogenation procedure was repeated on the enone (II) (30mg) except that the temperature of the catalyst mixture was raised to I00° prior to the addition of the substrate. The product was mainly the diketone (63) but chromatographic separation on silica gave an oily substance (ca. 2mg) which showed ν max. (CCl_4) I720 and I740 cm^{-1}; λ max. 280 and 286nm (Found: M=300.I3565 . $C_{I8}H_{20}O_4$ requires M=300.I36I5). The mass spectrum of this compound showed a fragment at m/e 258.

I-carboxy-*anti*-2-(*p*-methoxyphenyl)-6-ethylenedioxo-bicyclo(3.2.I)octane (68).

The keto-acid (65) (500mg) was refluxed for 30h in a mixture of benzene (25ml), ethylene glycol (5ml) and toluene-*p*-sulphonic acid (20mg) with constant separation of water using a Dean-Stark trap. The cooled reaction mixture was

washed with water then extracted with sodium carbonate solution. This extract was acidified to PH8 and saturated with sodium chloride while taking the organic material into a layer of ethyl acetate. Separation of the organic layer followed by drying and removal of the solvent gave the crude ketal acid (I70mg, 29%). Crystallisation from ethyl acetate gave the pure ketal acid as colourless prisms m.p. 244-247°; ν max. (KBr) I7I0 and 2,800-3,600 cm^{-1}; λ max. 227,276 and 283nm; δ I.70-2.50 (9H, m, aliphatic H), 3.30 (IH, m, benzylic H), 3.75 (3H, s, OMe), 3.90 (4H, m, ketal H), 6.80 (2H, d, J=9Hz, aryl H), 7.63 (2H, d, J=9Hz, aryl H) and I0.58 (IH, br.s, OH) (Found: M=3I8.I4764 . $C_{I8}H_{22}O_5$ requires: M=3I8.I467I).

2'-Hydroxyethyl (anti-2-[p-methoxyphenyl]-6—ethylenedioxo-bicyclo[3.2.I]octyl)-I-carboxylate (69).

The neutral organic layer in the above preparation of the ketal acid (68) was washed with brine, dried and the solvent removed to give the crude oily ester (390mg, 6I%). Purification of a sample of this material by preparative t.l.c. gave the pure ketal ester which showed ν max. (liquid film) I735 and 3,500 cm^{-1}; λ max. 227, 276 and 283 nm; δ I.68-2.66 (9H, m, aliphatic H), 3.08 (IH s, OH), 3.I8-3.73 (5H, m, ester methylene H and benzylic H), 3.84 (3H, s, OMe), 4.00 (4H, m, ketal H), 6.90 (2H, dd, J_I=9Hz, J_2=2Hz, aryl H) and 7.30 (2H, dd, J_I=9Hz, J_2=2Hz, aryl H) (found: M=362.I737. $C_{20}H_{26}O_6$ requires: M=362.I729).

When the above ketalisation reaction was curtailed after less than about 30h, a mixture of ketal acid, ketal ester and starting ketone was present in the product (t.l.c.). Prolonged reaction (up to 72h) did not appreciably alter the ratio of ketal ester to ketal acid.

Preparation of the ketal acid (68) from the ester (69).

The ester ketal (69) (300mg) in methanol (20ml) containing I0% sodium hydroxide solution (5ml) was refluxed for I6h. The cooled solution was diluted with water and acidified to PH8 with dilute hydrochloric acid. After saturation with sodium chloride the solution was extracted with ethyl acetate and the extract dried and the solvent removed to give the crude acid. Crystallisation from ethyl acetate gave the pure ketal acid (220mg,84%) identical to the acid (68) prepared previously.

I-Carboxy-anti-2-(bromo-4'-methoxyphenyl)-6-ethylenedioxo-bicyclo(3.2.I)octane (7I).

(I) Attempted preparation from the ketal acid (68).

a) The acid ketal (68) (50mg) in carbon tetrachloride (25ml) was mixed with ferric bromide (5mg) and treated with bromine (2 drops). The reaction was stirred for I0min. and I0% sodium thiosulphate solution (I0ml) was added and the mixture stirred for a further I0min. The organic layer was separated, washed with brine, dried and the solvent removed to give a

brown tar (55mg) which showed at least seven highly polar compounds on t.l.c.

b)
The above procedure was repeated but without the addition of ferric bromide. The resulting oil could not be resolved on t.l.c. and mass spectral analysis showed fragments with a I:2:I isotopic abundance pattern as well as fragments with a I:I pattern indicating mono- and di-bromo compounds. The isotopic abundances of Br^{79} and Br^{8I} are 50.52% and 49.48% respectively. The n.m.r. spectrum of this oil was uninformative.

(2) Attempted preparation from the bromo-ester (70).

The ketal ester (70) (50mg) in methanol (20ml) containing 20% sodium hydroxide solution (5ml) was refluxed for I0h. The cooled solution was diluted with water, acidified to PH8 with dilute hydrochloric acid and saturated with sodium chloride while taking the organic material into a layer of ethyl acetate. The organic layer was separated, dried and the solvent removed to give an oil (42mg) which was not resolved on t.l.c. and which could not be persuaded to crystallise. I.r. and n.m.r. spectra of this oil were inconclusive. This procedure was repeated using lower concentrations (I0%, 5% and 2%) of aqueous sodium hydroxide and in each case t.l.c. showed that the ketal ester was consumed after about 2h producing an unresolvable product.

2'-Hydroxyethyl (anti-2-[bromo-4''-methoxyphenyl]-6-ethylenedioxobicyclo[3.2.I]octyl)-I-carboxylate (70).

To the ketal ester (69) (I00mg) in carbon tetrachloride (30ml) was added bromine (2 drops) and the reaction stirred for 0.25h. The precipitation of an oil was observed and I0% sodium thiosulphate solution (8ml) was added and the mixture shaken until the excess bromine disappeared. The organic layer was separated, washed with brine, dried and the solvent removed to give an oil which was purified by chromatography on silica to give the oily bromo compound (68mg,64%) νmax (liquid film) I730 and 3,500 cm^{-1}; λmax. 286 and 290 nm; δ I.70-2.40 (9H, m, aliphatic H), 2.52 (IH, s, OH), 3.30 (IH, m, benzylic H), 3.62 (4H, m, ester methylene H), 3.80 (3H, s, OMe), 4.I0 (4H, m, ketal methylene H), 7.05 (IH, d, J=8Hz, aryl H) and 7.40 (2H, m, aryl H) (Found: M=442.08II6. $C_{20}H_{25}O_6Br^{8I}$ requires: M=442.08I52).

anti-2-(p-methoxyphenyl)-6-oxobicyclo(3.2.I)octyl-I-acetic acid (72).

The keto-acid (65) (50mg) in benzene (20ml) was treated with excess oxalyl chloride and the mixture stirred for 2h. Solvent and excess reagent were removed under reduced pressure to give the corresponding acid chloride which was added over 0.5h at 0^{o} as a solution in benzene (5ml) to an excess of diazomethane in ether. This solution was left

to stand overnight at 0-5° and the excess diazomethane was destroyed by adding a few drops of acetic acid. The solution was filtered and the solvent removed to give the diazoketone (73) (νmax. 2010 cm^{-1}) which was used in the next step without purification.

(I)

The above diazoketone (from 50mg acid) was dissolved in aqueous dioxane (10ml) and stirred at room temperature while silver oxide (60mg) was added in portions as an aqueous slurry over 0.5h. Stirring was continued for 2h, the mixture filtered and the organic solvent removed under reduced pressure. The organic material was taken up into ethyl acetate, extracted with sodium carbonate solution, acidified with dilute hydrochloric acid and re-extracted with ethyl acetate. The solution was washed,dried and the solvent removed to give an oily mixture (29mg) of three or more compounds (t.l.c.).

(2)

The above diazoketone (from 50mg acid) was dissolved in 2,4,6-collidine (7ml) containing benzyl alcohol (0.5ml) and the mixture was heated at 180° for 5min. To the cooled reaction mixture was added ethyl acetate (20ml) and the mixture washed with dilute hydrochloric acid, then with brine and the solvent removed. The residue was dissolved in methanol (15ml) containing dilute aqueous sodium hydroxide (2ml) and refluxed for 2h. The cooled reaction mixture was diluted with water, washed with ether and acidified with

dilute hydrochloric acid. The organic material was taken into ethyl acetate, washed with brine, dried and the solvent removed to give an oil (32mg) which was purified by chromatography on silica. This resulted in the isolation of the oily acetic acid (72), ν max. (liquid film) 1710-1740 and 2,400-3,600 cm^{-1}; λ max. 276 and 283 nm; δ 1.45 (1H, br.s, OH), 1.70-2.80 (11H, m, aliphatic and α carbonyl H), 3.25 (1H, m, benzylic H), 3.85 (3H, s, OMe), 6.90 (2H, d, J=9Hz, aryl H) and 7.30 (2H, d, J=9Hz, aryl H) (Found: M=288. $C_{17}H_{20}O_4$ requires: M=288).

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