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"SYNTHETIC STUDIES ON GIBBERELLINS"

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SUMMARY

A. Synthesis of Methyl- 2 methoxy- 8 methylene- 10 β methyl 4b(α)H- gibba- A- triene- 1 carboxylate.

A synthetic route to gibberellin A_4 with the potential of being adapted to the synthesis of gibberellic acid has been investigated.

Terracinoic acid, a degradation product of terramycin, has been elaborated to methyl- 2 methoxy- 8 methylene- 10 β methyl- 4b(α)H- gibba- A- triene- 1 carboxylate a tetracyclic compound in which rings B and C have the un-natural trans-fusion (i.e. epimeric at 4b). The stereochemistry of this tetracyclic compound has been deduced from a study of the N. M. R. spectra of related compounds.

A preliminary investigation into the possibility of adapting this route to the synthesis of rings C and D of gibberellic acid has been made.

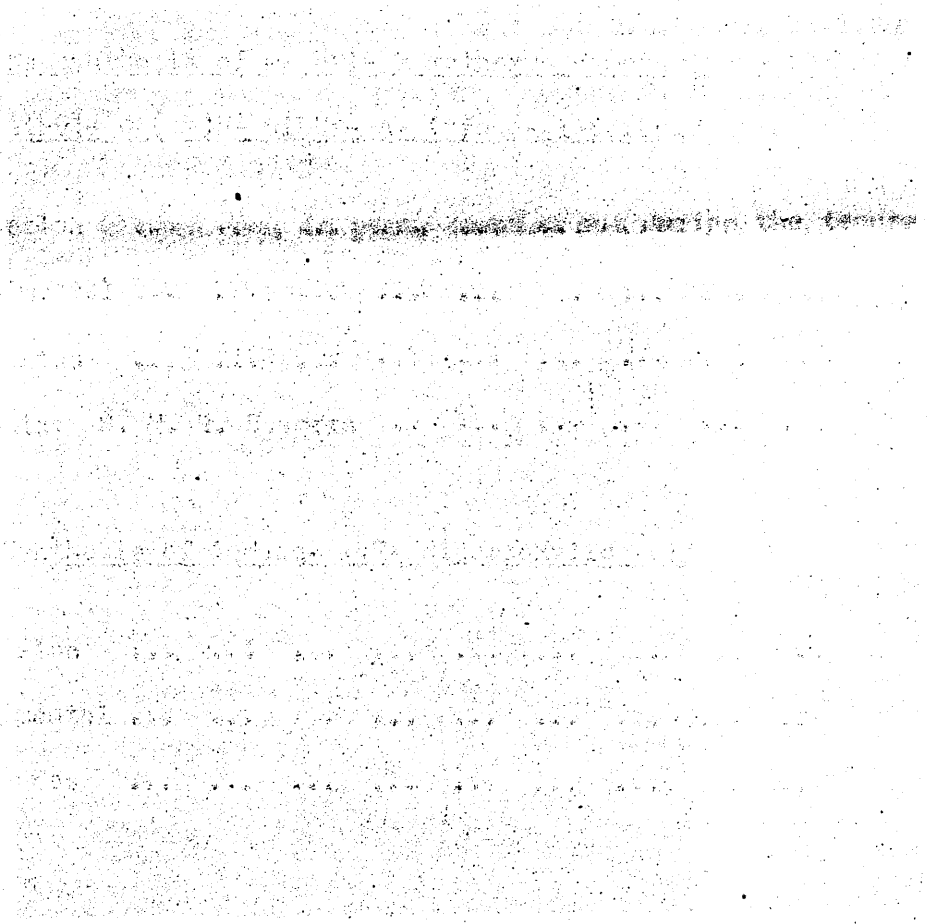
Attempts have been made unsuccessfully to functionalise an unactivated methyl group in terracinoic acid and a variety of derivatives.

B. Synthesis of Indane- 1,7- Dicarboxylic Acid.

A possible synthetic route to the AB ring system of several gibberellins has been investigated.

Benzaldehyde was converted to indane- 1,7- dicarboxylic acid

in a ten step synthesis but the route was abandoned at this point because of poor yields in an internal Friedel-Crafts acylation step.



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INTRODUCTION

The gibberellins, a group of tetracyclic diterpene acids, were discovered by Japanese chemists during the course of an intensive investigation into a soil-borne fungal disease of rice-seedlings ("bakanae" or "foolish-seedlings" disease).

In 1926, Kurosawa[1] showed that similar physiological effects were produced on treatment with cell-free culture fluids of the fungus Gibberella fujikuroi. In 1938, Yabuta and his co-workers[2a,b] succeeded in isolating the active principles of these culture fluids as crystalline substances which they named gibberellin A and gibberellin B.

These substances, however, proved to be mixtures and it was not until the development of suitable chromatographic techniques that Curtis and Cross[3] were able to isolate a pure compound with high physiological activity, gibberellic acid (GA_3) (1).

Further studies also showed the presence of gibberellins A_1, A_2 and A_4 (2) in the fungus.[4] Although the initial discovery of the gibberellins was as extra cellular metabolites of a fungus which is a plant pathogen, further investigation[4] has shown that they are natural constituents of green plants. Studies over the last twenty years have shown that the gibberellins (of which there are some twenty-seven known at present[5a,b,c]) are able to control growth and developmental processes in plants by stimulating cell division and elongation.[6a,b] For example, treatment with gibberellins breaks dormancy in seeds, induces germination and accelerates the growth of seedlings.[6a] They also possess the characteristic and specific properties of reversing the mutant form in

the case of certain genetic dwarfs, for example the dwarf character in peas[7], substituting for a certain photo periodic regime in plants sensitive to day length and for low temperature in some species which require vernalisation.

It is thought that gibberellins promote such developments either by stimulating the synthesis of R.N.A. polymerase or by activating already present, but inactive, enzymes. The R.N.A. polymerase is involved in the synthesis of messenger R.N.A. and the result is the de novo synthesis of proteins such as α-amylase and phosphorylase. This increase in activity at a cellular level could be responsible for the effects observed on gibberellin treatment.

The structures of this group of compounds was the subject of a long and arduous chemical jigsaw puzzle[8a,b] until the final confirmation of the structure and stereochemistry of gibberellic acid (1) was achieved by X-ray structure analysis.[9] The structures of the other gibberellins have been elucidated by interconversion and correlation of various derivatives and degradation products with the acid (1) and the corresponding derivatives and degradation products of the acid (1).

Biogenetic studies, begun in parallel to the structural elucidation, have shown that the gibberellins should be regarded as modified tetracyclic diterpenes of the kaurene type incorporating four molecules of mevalono-lactone (3)[10]. The biosynthesis is thought to proceed through formation of geranyl geranyl pyrophosphate (4)[11,12] and cyclisation to the labdadienol (5)[11]. This dienol (5) has been shown[13] to be incorporated (as its pyrophosphate) during the biosynthesis of GA_3 (1). The incorporation of the

labdadienol (5) takes place through the formation of (-) kaurene[14] (7), possibly through the (-) pimaradiene precursor (6) although, as yet, no tricyclic intermediates have been isolated.[13]

The subsequent modification of (-) kaurene (7) to the gibberellins involves oxidation of ring B followed by ring contraction. It has been demonstrated[15] that this conversion takes place through the successive formation of (-) kaur-16-en-19-oic acid (8; R = H) and (-) 7 β hydroxy-kaur-16-en-19-oic acid (8; R = OH) followed by ring contraction to the gibbane aldehyde (9; R_1 = CHO; R_2 = H). (This is in agreement with an earlier proposal.[16])

Various hydroxylations and oxidations of this aldehydo-acid (9; R_1 = CHO; R_2 = H) yield the bewildering variety of C_{19} and C_{20} gibberellins found in nature.[16,17] For example, simple oxidation yields gibberellin A_{12} (9; R_1 = CO_2H; R_2 = H). The biogenetic pathway from the gibbane aldehyde (9; R_1 = CHO; R_2 = H) to the C_{19} lactonic gibberellins is not known with certainty at present but it has been suggested[16] that hydroxylation precedes the oxidative steps. Several of the more recently isolated gibberellins illustrate the stepwise oxidation of the C_{4a} methyl group which may constitute the pathway adopted by plants and fungus to bring about the synthesis of these complex metabolites [e.g. A_{17} (10), A_{23} (11), A_{24} (12)][5a,b]. Recent papers by Hanson et al[12,17] summarise the evidence for geranyl geranyl precursors and the oxidative modifications of ring A obtained from a wide variety of labelling studies and suggests the lactone formation in the C_{19} gibberellins may result from a Bayer-Williger type oxidation of a C_{4a} carbonyl function followed

by solvolysis of the resultant ester.[12] In his review on diterpene biosynthesis[17], he suggests the order in which lactonisation and hydroxylation at C_7 may take place.

Because of the structural and stereochemical complexity of the gibberellins, the ease with which they rearrange[6] and the potential commercial viability of any synthesis due to their remarkable biological activity, these molecules have long presented an intriguing challenge to the synthetic organic chemist.

Initially, the syntheses were devoted to confirmation of the structures of degradation products of gibberellic acid (1) as part of the effort directed to finding the structure and stereochemistry of the gibberellins. Examples of this type of synthesis are shown in the syntheses by Mulholland et al of the tetracarboxylic acid (13)[18] produced by stepwise degradation[19] of gibberellic acid (1) and 1,7 dimethylfluorene[20] (14) at 350°. Syntheses such as these led to the determination of the structures of gibberone[19] (15) and gibberic acid[19] (16).

Although gibberone (15) and gibberic acid (16) are degradation products of gibberellic acid (1) their syntheses can be considered as the beginning of the attempts to synthesize the gibberellins since they possess the gibbane skeleton (17) and, like most of the synthetic studies, act as model compounds for the achievement of the ultimate goal in this field - the synthesis of the naturally occurring metabolites.

Loewenthal[22] and Raphael[23] achieved the synthesis of gibberone (15) by constructing the bicyclo [3,2,1] CD ring system on a suitably substituted indanone. The most interesting step in these syntheses was the

use by Loewenthal of boron trifluoride -acetic acid to close ring D by a cyclodehydration (18 → 19), a method which he later improved by the use of naphthalene-2-sulphonic acid.[24] Gibberic acid (16) was also synthesised[25] by Loewenthal using a similar approach.

Stork and his co-workers were also active in this field and, in achieving the synthesis of the gibbane alcohol(20)[26] by the elegant cyclisation of the ethynyl ketone(21)[27] using potassium, ammonium sulphate and tetrahydrofuran in liquid ammonia, became one of the first to synthesize a molecule with the naturally occurring CD ring structure.

Another, less successful, attempt was made by Dolby and Iwomoto[28] who attempted the acid catalysed cyclisation of the dienone (22; R = O) and the allylic alcohol (22; R = CH_3, OH) both of which bear a formal relationship to the known[13] labdane precursor (5). However, the desired products (22; R = O ⟶ 23, 24) and (22; R = CH_3, OH ⟶ 25) were not isolated. The dienone (22; R = O) gave more than a dozen products on attempted cyclisation under a variety of conditions while the alcohol (22; R = CH_3, OH) yielded the substituted octalin (26).

In addition to these synthetic efforts directed towards synthesis of the gibberellins, mention should also be made of Ireland's masterly synthesis of hibaene (27)[29] in the course of which he synthesised a compound (28) from the tricyclic keto acetal (29) by a series of high yield transformations. The tetracyclic compound (28) contains the CD ring system of the gibberellins and was smoothly rearranged in a stereo-specific manner by analogy with the well-known gibberellic acid (1) - gibberic acid (16) transformation[19] to yield the expected product of

defined stereochemistry.

A challenge equal to that posed by the construction of the CD ring structure is the synthesis of ring A analogs.

The problem was first tackled by Mori et al[30] who, while attempting to define the structure of ring A of gibberellic acid (1), synthesized a series of thirteen cyclohexane γ and δ lactones. One of these lactones (30) synthesised from 1 methyl- 2 hydroxy- 5 keto cyclohexan- 1-oic acid proved to be the C_2 epimer of ring A of the natural product. A similar approach to this problem by Moffat[31] resulted in the synthesis of the ring A analogue of gibberellin A_4 (2).

The lactone synthesised was shown to be epimeric with the lactone (30) synthesised by Mori[30] and epimerised to (30) in dilute aqueous alkali by what was suggested by Cornforth[32b] to be a retro-aldol mechanism. This behaviour has been observed in the gibberellins[32a] and appears to occur by the same mechanism.[33]

A better model was obtained by Loewenthal[34] and his co-workers in the formation of the lactone (31) from the readily available[34,35] 2 methoxy 5,6,7,8 tetrahydronaphth-1-oic acid (32) by the reaction sequence (32 ⟶ 33 ⟶ 34 ⟶ 31). Dolby[36] has also solved this problem by tackling it in a completely different manner. Reaction of the substituted cyclopentanone (35) with homoallyl magnesium bromide yielded the olefinic lactone (36) after saponification. Oxidation and aldol condensation then afforded a mixture of epimeric alcohols (37) which were separated to yield the desired α hydroxylactonic product.

Various groups[37a,b] have attempted the synthesis of the gross gibberellin structure, mainly from hydrofluorene-type precursors, but although several promising approaches have been published, a great deal of work still remains to be done in most cases.

House, in a series of papers[38] investigating synthetic routes to the gibberellins and related compounds, has used this approach in his synthesis of epiallo-gibberic acid precursor (38).

The indanone ester (40) was prepared either from o tolualdehyde by standard procedures or by a 1,4 Grignard reaction between 1,1,2 tricarbomethoxy ethylene and o tolyl magnesium chloride in the presence of anhydrous cupric acetate followed by Friedel-Crafts cyclisation of the derived o tolyl succinic anhydride and methylation. This ester (40) was carbomethoxylated, using dimethyl carbonate and sodium hydride, then converted to the related enol acetate (41) by reaction with acetic anhydride and perchloric acid as catalyst. Hydrogenation followed by acid catalysed elimination of acetic acid from the acetoxy diester (41) yielded (42) which afforded the desired adduct (38; R = CH_3) following a Diels-Alder reaction with 1,3 butadiene at elevated temperature and pressure.

Further investigation[39] on the general applicability of this reaction scheme showed, however, that a substituent at C_7 of the dienophile (42) was necessary to prevent thermal isomerisation to the less stable[38,39] $\Delta^{1,2}$ compound before Diels-Alder addition took place.

Another example of this type of approach is the intermediate (43) recently synthesized by Nakanishi.[37a] The initial Diels- Alder reaction

of 1(p methoxyphenyl) butadiene with 2 methyl-3,3 dicyano-ethyl acrylate yields a diene ester (44) which on saponification and anhydride formation affords the substituted cyclohexene (45). Treatment of (45) with aluminium chloride yields the hydrofluorene (46) easily converted to (43) by treatment with p nitroperbenzoic acid followed by acetylation.

Kitahara[40] chose a novel approach to this problem in his synthesis of the acetylenic perhydrofluorenone (47). Reaction of the substituted furan (48) with maleic anhydride yielded (49) which on catalytic hydrogenation and esterification afforded (50). Treatment of this triester (50) with sodium hydride gave the perhydrofluorene derivative (51) which on alkylation with prop-2-ynyl bromide and base treatment yielded the ether-cleaved product (52). This product (52) aromatised on reaction with acetic anhydride- dimethyl sulphoxide to give (47).

By far the most active group engaged in the synthesis of these secondary metabolites has been the Tokyo group headed by Matsui, Mori and Sumiki. These workers have synthesized a wide variety of hydrofluorene derivatives including 7-desmethyldihydrogibberone[41] (53) and epigibberic acid[42] (4b epimer of 16) in an almost uninterrupted investigation into the bakanae fungus since Yabuta first isolated a crystalline gibberellin[2a,b] more than thirty years ago.

As well as the hydrofluorene approaches, this group have also investigated a lengthy approach via hydrophenanthrene intermediates. An example is the synthesis of the triacetoxy ester (54) containing the gibbane skeleton,[43]

6-methoxy-α-tetralone was converted by standard procedures[44] into the substituted phenanthrene derivative (55). Ring closure with boron-trifluoride-acetic acid-acetic anhydride gave, after ketalisation and hydrogenation, the tetracyclic ketal (56) in low yield.[44]

Wolff-Kishner reduction, followed by removal of the protecting group and borohydride reduction afforded the expected mixture of epimeric alcohols.[45] This was followed by Birch reduction, hydrolysis, methylation and reduction to yield the epimeric alcohols (57; R = H).[45,46]

Acetylation yielded the acetate (57; R = Ac) which was cleaved by reductive ozonolysis to a keto aldehyde.[46] Chromatography of this aldehyde yielded[46] the gibbane compound (58) by internal aldol condensation. A subsequent paper[47] discussed the oxidative modification of the C_1 α-methyl group in (57; R = Ac) to an acetate grouping via the bromo-ether (59) to give (60). By a series of transformations[43] analogous to those used in the synthesis[46] of (58), this triacetate (60) was converted to a gibbane aldehyde which on oxidation and esterification afforded (54).

The culmination of the Japanese chemists' efforts was the formal total synthesis of gibberellins A_2 (61), A_4 (2), A_9 (62) and A_{10} (63) from o xylene[48].

The synthesis was achieved in five stages by interrelating various degradation products of GA_3 (1) and then using the degradation products obtained from natural sources as relay compounds.

Firstly epigibberic acid (C_{4b} epimer of 16), a product of treatment of gibberellic acid with hot dilute mineral acid[49], was synthesized

from o xylene in a twenty-one stage synthesis.[42] Epigibberic acid was in turn converted to the ester (64) by a standard five step synthesis[48,50] followed by separation of epimeric products. This ester (64) was a new degradation product[50] of gibberellic acid (1) and served as the first relay compound. Transformation of (64) to the dienone (65) was achieved in ten stages utilizing a bromination - dehydrobromination technique. Since a previous publication[51] by Mori et al had been concerned with the synthesis of gibberellin C (66), the product of acid catalysed rearrangement of GA_1, in eight stages from (65) using triphenyl methyl sodium and carbon dioxide as carboxylating agents, reduction of the endocyclic ring A double bond being carried out with Pd - C and hydrogen and lactonisation being effected by sulphuric acid treatment, this completed the synthesis of gibberellin C (66). This in turn completed the formal total synthesis of the gibberellins since other authors[32] had converted gibberellin C (66) into gibberellin A_4 (2) by the reaction sequence (66 $\longrightarrow$ 70) in 5% yield using sodium borohydride and phosphorus pentachloride. Gibberellin A_4 (2) had itself been transformed into A_2 (61)[53], A_9 (62)[54] and A_{10} (63)[55].

In the present investigation, approaches were made to a synthesis of a model compound for rings A and B of gibberellic acid (1) and gibberellin A_4 (2).

Consecutively with this, a model compound of the CD ring system in A_4 (2) was synthesized from terracinoic acid (71), a degradation product of terramycin (72). This model compound possesses an aromatic ring which has the potential of being converted to ring A of the naturally

occurring metabolites.

Also studied were attempts to functionalise the benzylic methyl group in this acid (1) and its derivatives.

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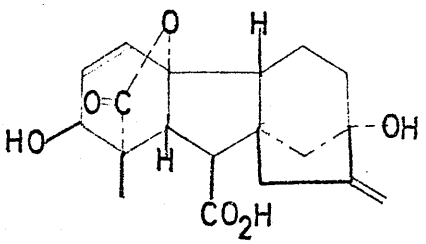
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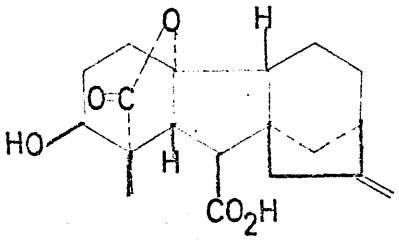
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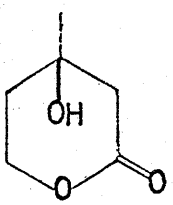
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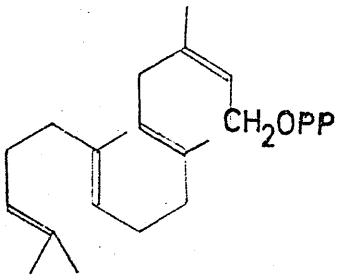
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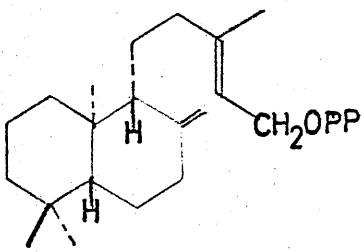
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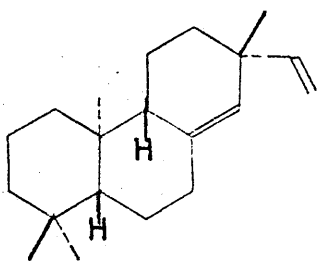
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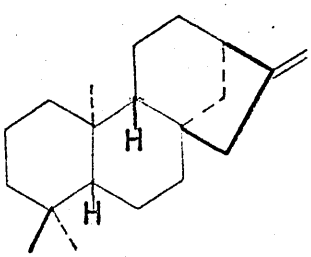
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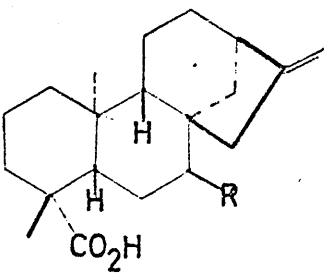
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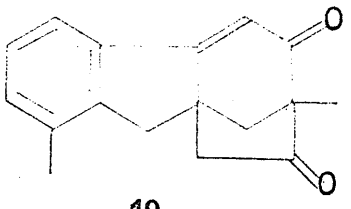

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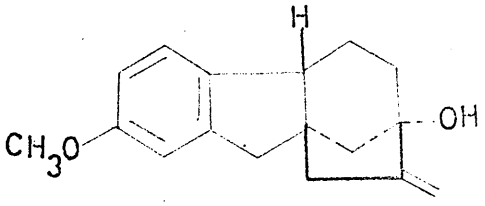

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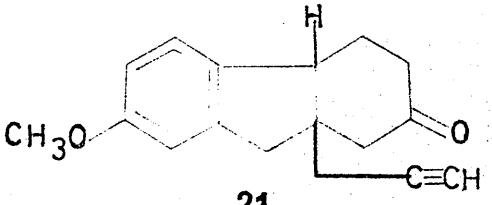

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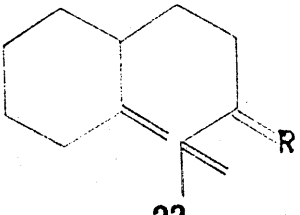

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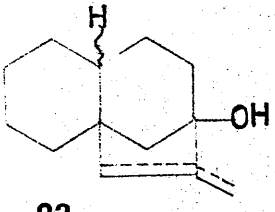

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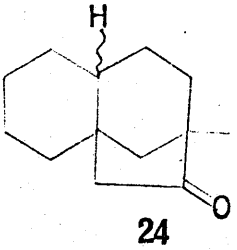

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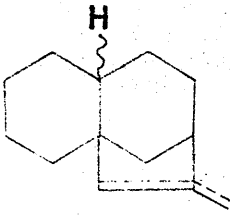

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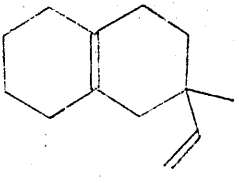

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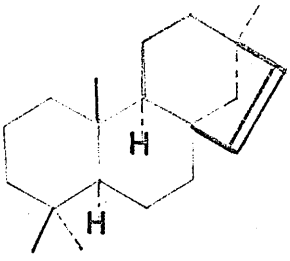

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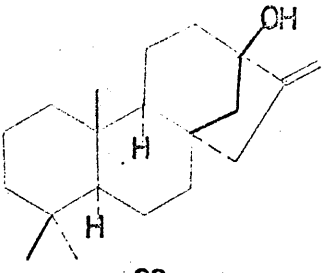

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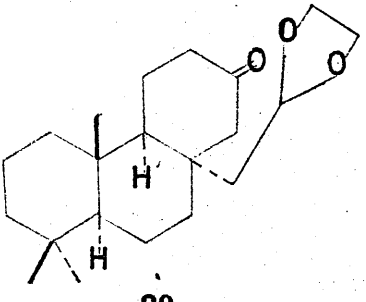

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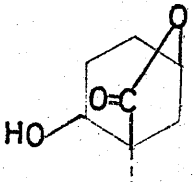

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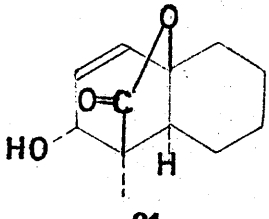

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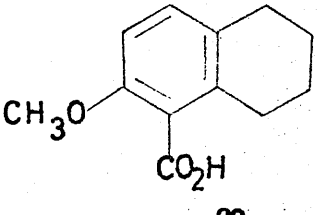

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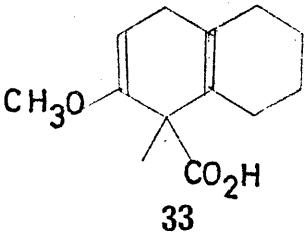

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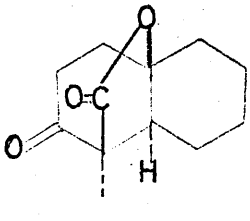

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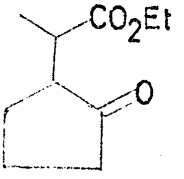

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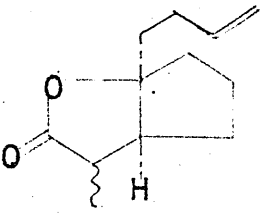

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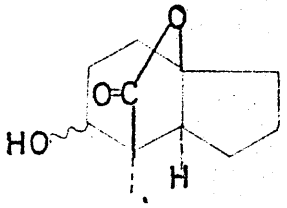

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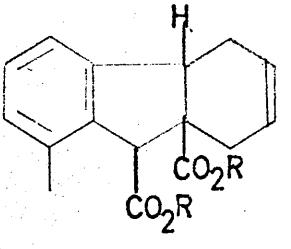

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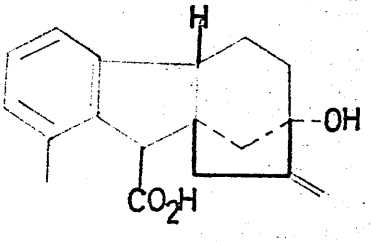

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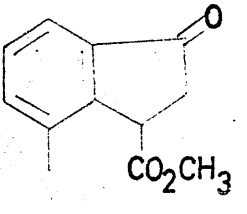

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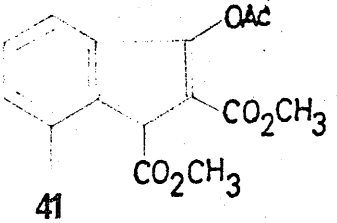

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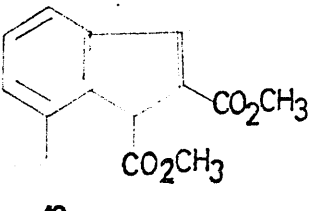

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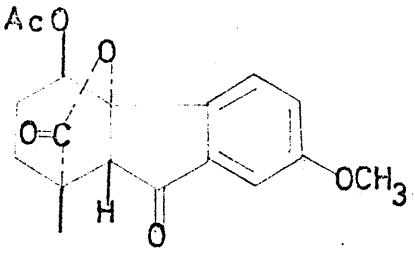

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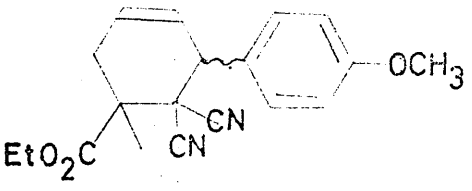

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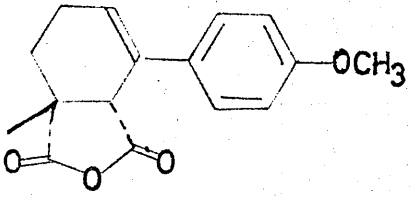

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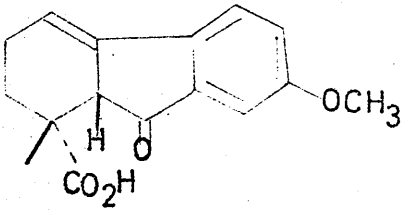

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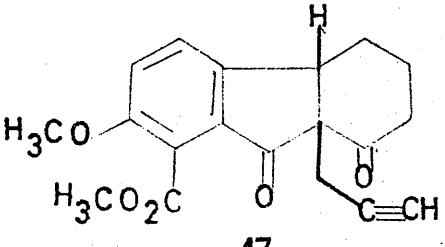

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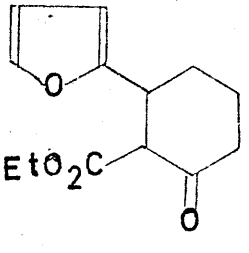

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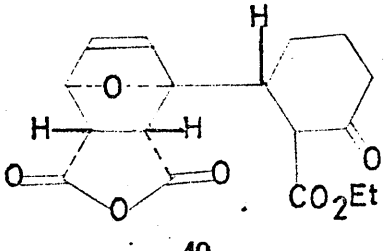

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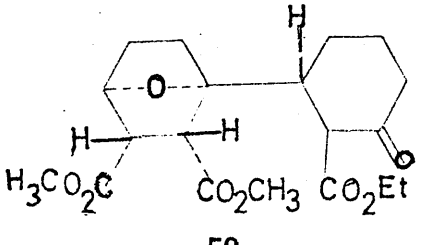

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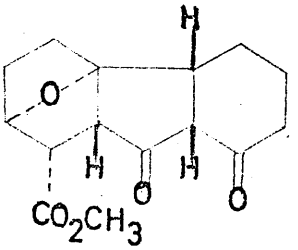

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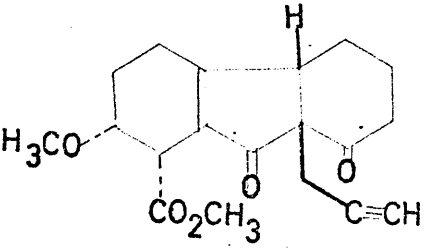

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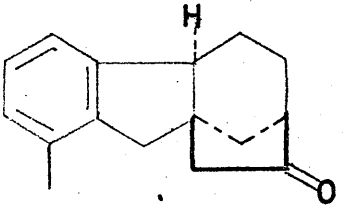

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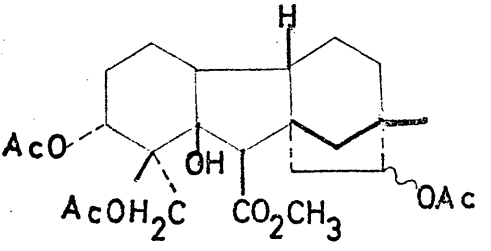

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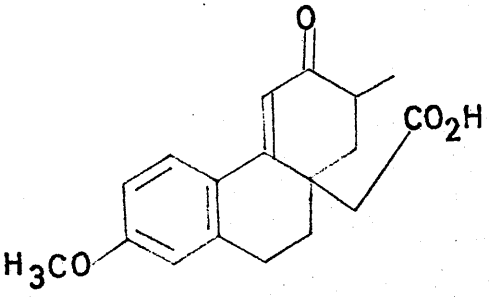

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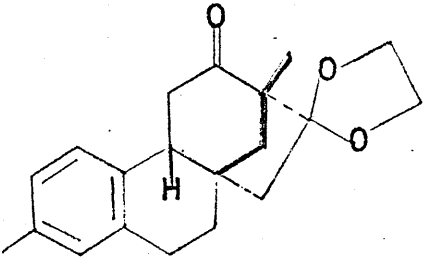

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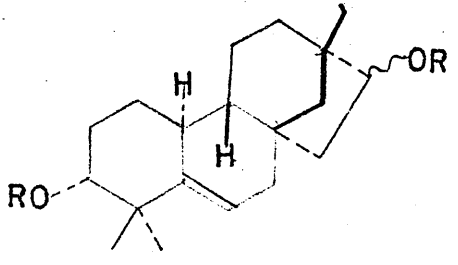

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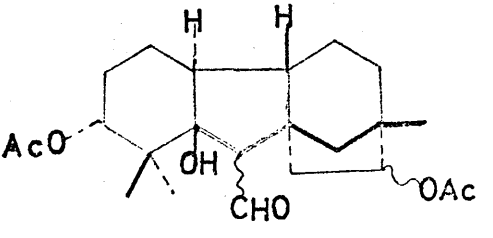

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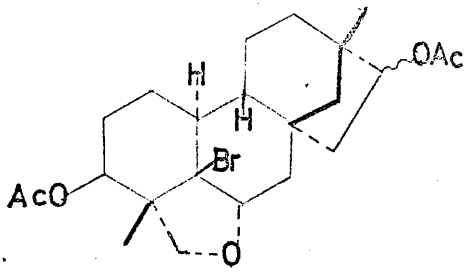

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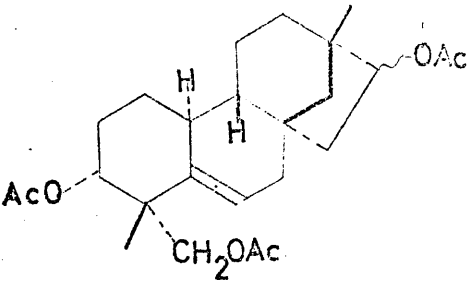

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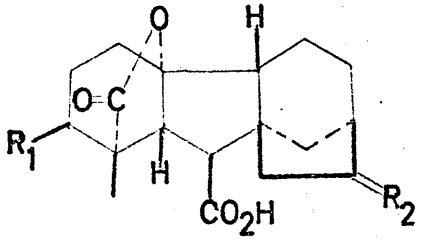
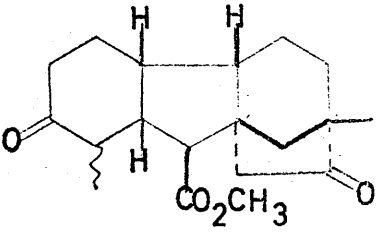


	R_1	R_2
61	OH	CH_3, OH
62	H	$=CH_2$
63	H	CH_3, OH



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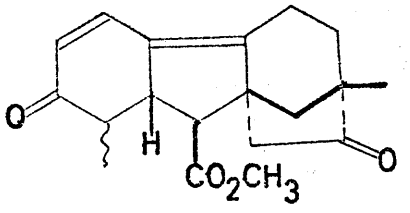

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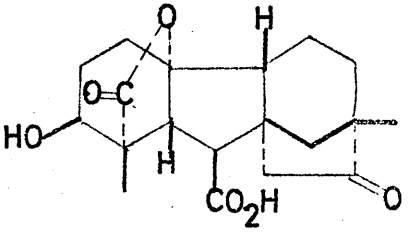

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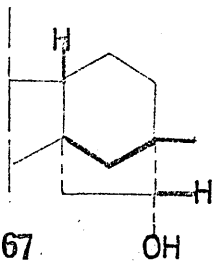

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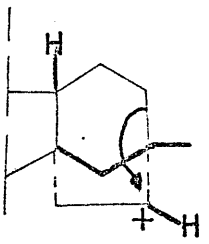

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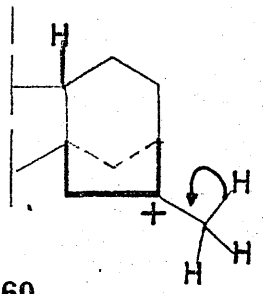

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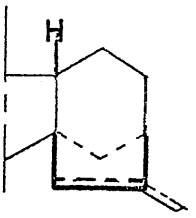

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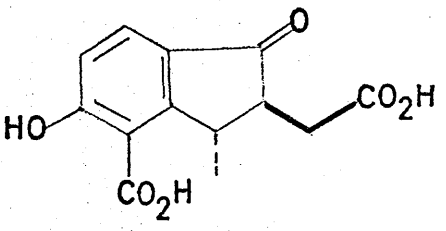

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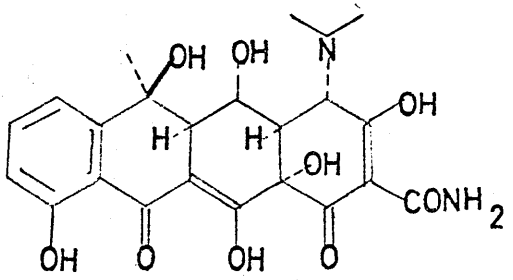

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A. THE SYNTHESIS OF METHYL-2METHOXY-8-METHYLENE-10 β METHYL-4b(α)H-GIBBA-A-TRIENE-1-CARBOXYLATE.

On account of the structural complexity of the gibberellins, it was decided to direct synthetic studies towards gibbane derivatives incorporating as much as possible of the functionality and stereochemistry found in the natural metabolites. It was felt that, in this way, experience which could prove invaluable in attempts at the total synthesis of gibberellic acid (1) and gibberellin A_4 (2) would be gained.

The starting material chosen for these studies was terracinoic acid, (3β-methyl-4-carboxy-5-hydroxy-indan-1-one)-2 α acetic acid, (3; R = H), the readily available alkaline degradation product of terramycin (4)[1]. This acid (3; R = H), was chosen for two reasons. Firstly, the substituents in the five-membered ring of the acid (3; R = H) were such that there existed the potential of constructing the CD ring system of the gibberellins on a pre-formed indanone derivative. It was envisaged that this could be carried out by a route similar to that used in such syntheses as those of gibberone (5)[2] and epigibberic acid (6)[3].

Secondly, the aromatic ring possessed functionality suitably disposed for conversion to ring A of the gibberellins by reductive methylation and lactonisation in a manner originally designed to be applied to indane-1, 7-dicarboxylic acid (see part B) and which was later successfully applied by Loewenthal[4] to 2 methoxy-5,6,7,8-tetrahydronaphth-1-ioc acid.

Alkaline hydrolysis of terramycin (4) followed by methylation with ethereal diazomethane[1] yielded dimethyl terracinoate methyl ether (3; R = CH_3) in 32% yield from terramycin.

This material possessed the same physical characteristics as that

described[1] in the literature. N. M. R. investigation of the racemic ester (3; R = CH_3) confirmed the presumed trans disposition of the substituents at C_2 and C_3 by application of the Karplus equation[5] to the vicinal coupling constants for the protons on these carbon atoms. [Benzylic hydrogen τ 6.55 (octet); J = 7,2 Hz; Benzylic methyl group τ 8.63 (d); J = 7 Hz.] The 2 Hz coupling of H_3 with H_2 indicated an angle of 115° between those protons which are, therefore, trans oriented as must also be the C_3 methyl group and the C_2 acetic acid residue.

Michael annellation of dimethyl terracinoate methyl ether (3; R = CH_3) with methyl vinyl ketone and sodium methoxide[2] afforded the tricyclic acid (7; R = H) in 80% yield. Confirmation of the structure assigned to this acid (7; R = H) was achieved by a combination of various spectroscopic measurements. Infra-red spectroscopy revealed the presence of the carboxyl group ($\nu^{cm^{-1}}_{Nujol}$ 3500 - 2600). It has been suggested in analogous cases[2,6,7] that the acid function arises from an intramolecular lactonisation (8) - elimination reaction during the addition of methyl vinyl ketone.

The extended "cinnamoyl-type" chromophore was evident in both the infra-red ($\nu^{cm^{-1}}_{Nujol}$ 1640) and ultra-violet (λ^{nm}_{max} 326) spectra. As is the case with the majority of compounds considered in this discussion, the N. M. R. spectrum revealed the significant structural details of the molecule in a more definite manner than did the other spectral methods. The C_5 (Gibbane Numbering) vinylic hydrogen was evident as a singlet at τ 3.60 and the carboxyl proton could be seen, centred at τ 4.5, as a

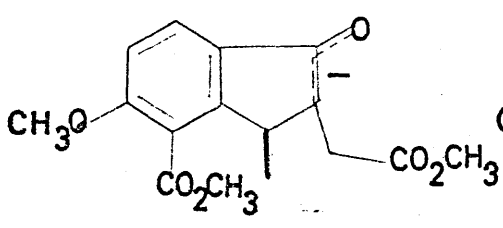
broad absorption (which disappeared on D_2O exchange). The presence of a molecule of methanol of crystallisation observed in the analysis of this acid was also confirmed. This methyl singlet (τ 6.55) disappeared dramatically on D_2O exchange as the methanol was partitioned between the two phases. G.C. - M.S. examination of the methyl ester (7; R = CH_3), confirmed the molecular weight as 358 ($C_{20}H_{22}O_6$ requires 358) and also revealed the presence of a minor component with a parent ion at m/e 326. It was thought that this minor component was the tetracyclic diketone (17) formed by thermal cyclisation on the G. L. C. column; this was later confirmed by comparison with an authentic sample.

(Note: Analysis of the acid (7; R = H) was only accomplished with difficulty, probably because of a facile loss of acetic acid which left a residual fluorene structure more resistant to complete combustion.

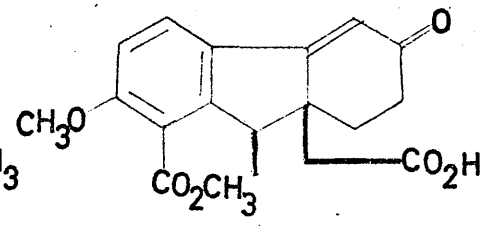
Analysis was finally achieved by prolonged combustion in the presence of cobalt oxide as catalyst).

The stereochemistry shown for the acid (7; R = H) is based on analogy with the mechanism proposed by Mori[8] for the addition of methyl vinyl ketone to 3-carboxy-indan-1-one-2-acetic acid derivatives. In short, this involves Michael addition of methyl vinyl ketone to a planar anion (the stereochemistry of this process being controlled by the C_3 carboxyl group). This gives a tricyclic ketone in which the carboxyl and acetic acid groups are cis related and is followed by base catalysed epimerisation of the C_9 carboxyl group to give the more stable trans relationship.

In our case the planar enolate anion (i) gives as the sole product the cis (methyl to acetic acid) compound (7; R = H) which is incapable of epimerisation



(i)



(7; R = H)

Attempts to define unambiguously the steric relationship of this methyl group to ring D in the related diketone (17) by Nuclear Overhauser Effects[9] were inconclusive.

It is interesting to note that annellation in similar cases has not always led to the expected products. In the synthesis of the 7-deoxy epiallogibberic acid methyl ester norketone (9)[10], the ester (10) gave, as in this case, the product of "normal" Michael addition (11), probably via (12) and/or (13). However, in the reaction of the indanone (14), a vinylogous β keto ester, with methyl vinyl ketone an anomalous product (15 or 16) was formed[11]. Obviously, in this case (14), the developing carbanion was formed at C_3 and it was suggested[11] that this did not happen in (10) because the C_4 methyl group prevented maximum

$p - \pi$ overlap.

The acid (7; R = H) on treatment with naphthalene-2-sulphonic acid in refluxing toluene[6] was cyclised in good yield to the unsaturated diketone (17). Infra-red examination showed absorption at 1740 and 1660 cm^{-1} as well as the olefinic absorption at 1620 cm^{-1}. The ultra-violet spectrum showed a bathochromic shift (λ_{max}^{nm} 250, 308, 340) predicted by analogy.[6,12] This may possibly be explained by Moore and Fisher's suggestion[12]. They suggest that the strain involved in the construction of the bicyclic ring may in some way be localised and increase the ease of excitation of the electrons in the chromophore.

The N. M. R. spectrum showed the bridgehead C_7 proton as a very fine triplet at τ 6.43 ($J < 2$ Hz) in addition to the other significant features seen in the spectrum of the acid (7; R = H). (The N. M. R. spectrum of this and other compounds is more fully discussed in the Appendix to this section.)

The problem that now presented itself was to differentiate in some way between the two ketone functions of (17).

In previous cases published this has been achieved, albeit in low yield (4 - 30%), by selective ketalisation of the cyclopentanone carbonyl group. [e.g. in the synthesis of gibberone (4)[2] and the hydrophenanthrene derivative (18)[13].] However, in this case, attempted ketalisation of (17) under a variety of conditions (e.g. ethylene glycol/naphthalene-2-sulphonic acid/benzene; ethylene glycol/adipic acid/benzene[14]; ethylene glycol/p T. S. A./dichloroethane[10]) did not yield the desired product. The only products isolated were starting material

and much more polar products. These more polar products were tentatively identified as the mono and bis ethylene glycol esters of the acid (7; R = H) produced by Lewis acid catalysed cleavage of the non-enolisable β diketone system in (17) and had been observed previously in similar circumstances.[2,13]

A second approach was based on the known[15] reaction of αβepoxy ketones with hydrazine. For example, the reaction of isophorone oxide (19)[16] affords (20) on treatment with excess hydrazine hydrate at room temperature.[15]

If this reaction had been successful, an unsaturated benzylic alcohol (21) would have been formed which would have been amenable to hydrogenolytic removal of the hydroxyl function with concomitant saturation of the olefinic bond. This hydrogenation may also have allowed for precise control of the stereochemistry of hydrogenation at C_{4b} by a suitable choice of hydrogenation catalyst.

In the event, however, treatment of the diketone (17) under a wide variety of conditions yielded only unreacted starting material or demonstrated once again the ease with which the bicyclic system is cleaved to form the tricyclic acid (7; R = H) or ester (7; R = CH_3).

Another method employed in an attempt to overcome the problem of differentiation was hydrogenolysis. The diketone (17) was reduced by sodium borohydride to a mixture of epimeric diols (22; R = H). However, the attempted hydrogenolytic removal of the allylic alcohol in acid medium failed. The product was shown, after Jones oxidation, to consist solely of the diketone (23), identical in all respects with a genuine sample prepared subsequently.

Other methods of reductively removing the cyclohexenone system likewise failed. Hydrogenation of the derived acetates (22; R = Ac) under basic conditions[17] appeared only to saturate the olefinic bond and no reaction was observed on treatment of the acetates with zinc and acetic acid.

In the synthesis of α and β eudesmol[18], it was shown that on reaction of (24) with one mole of ethane dithiol, the enone carbonyl function was thioketalised in a highly selective manner. With this reaction in mind, the diketone (17) was treated with ethane dithiol (1 mole) in methanol at 0°. The principal product isolated was shown by spectroscopic and chromatographic comparison to be the tricyclic methyl ester (7; R = CH_3) produced by catalytic cleavage of the β diketone.

Treatment of (17) with excess ethane dithiol for a shorter time did not result in any reaction.

The fifth, and ultimately successful, approach chosen involved selective reduction and protection (as the acetate) of the cyclopentanone function. It is known that the mechanism of sodium borohydride reduction proceeds through attack on that carbonyl carbon atom which has the greatest electron deficiency and that the rate of reduction is lowered by resonance which tends to reduce this deficiency.[19] For these reasons, it seemed reasonable to expect that not only should reduction by sodium borohydride proceed in a stepwise manner but also that the cyclopentanone group should be reduced in the first step.

A sample of the diketone (17) was reacted with excess sodium borohydride under standard conditions and aliquots were taken at defined intervals. G.C. - M.S. examination of these aliquots established that, as expected, reduction proceeded in a stepwise fashion and infra-red examination confirmed that it was indeed the cyclopentanone carbonyl group which was reduced first.

The reaction time for optimum yield of cyclopentanol was 2 minutes 20 seconds. (in AnalaR solvents). (See graphs I and II).

The reaction was repeated on a larger scale and quenched at the optimum time shown by G. L. C. examination. The crude alcohol (25; R = H) was converted to the keto acetate (25; R = AC) by acetylation with acetic anhydride in pyridine and purified by crystallisation. In this manner, the unsaturated keto acetate (25; R = Ac) was obtained as a single epimer in 70% overall yield. Although G. L. C. examination of the products of reduction had shown a small peak [ca. 7 - 8% of the peak attributable to (25; R = H)] which might have been an epimer at C_8, no trace of the other epimeric acetate was found in the recrystallised sample.

This method of differentiation between the two carbonyl groups, while initially more tedious, proved to be much more satisfactory than the low yield ketalisation methods employed previously in this field by other workers.

It seems safe to assume that hydride reduction had taken place almost exclusively from the least hindered α-face of the molecule and that,

therefore, the acetate (25; R = Ac) isolated as a single epimer had the 8β configuration. A high dilution infra-red examination of the keto alcohol (25; R = H) confirmed this view; intramolecular hydrogen bonding of the alcohol to the C_6 keto group was evident ($\nu^{cm^{-1}}_{\text{bonded OH}}$ 3,520).

The validity of the structure assigned to the keto acetate (25; R = Ac) was evident from its spectral characteristics. The infra-red spectrum showed the presence of the enone system ($\nu^{cm^{-1}}_{CHCl_3}$ 1665); the absence of cyclopentanone absorption at 1750 cm^{-1} and the appearance of acetate ester absorption ($\nu^{cm^{-1}}_{CHCl_3}$ 1730, 1240). The unaffected cinnamoyl chromophone (λ^{nm}_{max} 328.5; ε, 23,000) was evident in the U.V. spectrum. The N. M. R. spectrum indicated that the only change in molecular structure was about the cyclopentanone system and showed the presence of an acetate methyl group[τ 8.02(s)].

Owing to the difficulty encountered in selective reaction of one of the carbonyl functions in (17), it was decided that while the above work was in progress attempts would be made at the complete removal of both ketone functions in the molecule.

To this end, reduction of the 4b,5 double bond in both (7) and (17) was studied. These olefinic linkages proved to be peculiarly resistant to reduction under a wide variety of conditions (e.g. H_2/10% Pd - C; H_2/ 5% Rh - Al; Li/NH_3) and afforded only unreduced material or an intractable mixture. Reduction was finally effected by the use of 30% Pd - C catalyst followed by Jones oxidation[20] to reoxidise the products of over reduction. (Later studies on the reduction of the ketoacetate (25; R = Ac)

showed that reduction of the 6-keto group was as facile as reduction of the 4b,5 double bond.)

The spectroscopic properties of the diketone (23) were significantly different from those of the unsaturated material (17). Carbonyl absorption in the infra-red was now only evident at wavelengths greater than 1700 cm^{-1} [$\nu^{cm^{-1}}_{CHCl_3}$ 1721; 1735 (shoulder)]. Similarly, the extended chromophore previously observable in the ultra-violet spectrum had disappeared and absorption now took place at lower wavelengths (λ^{nm}_{max} 239; 290; 335). The N. M. R. spectrum showed the loss of the vinylic hydrogen and an increase in complexity of the methylene absorption. Mass spectroscopy confirmed the molecular weight as 328 ($C_{19}H_{20}O_5$ requires 328).

Removal of the carbonyl functions was initially attempted by formation of the ditosylhydrazone followed by hydride reduction. Caglioti[21] had shown that this is a more efficient method for removal of a carbonyl group than the Bamford-Stevens reaction[22] (treatment of a tosylhydrazone in ethylene glycol with the sodium salt of ethylene glycol).

The yields, with the sole exception of aromatic carbonyl groups, are usually high and the saturated product is normally obtained rather than the olefinic product of the Bamford-Stevens reaction.

However, treatment of the diketone (23) with tosyl hydrazide under more forcing conditions than those employed by Caglioti[21] did not effect formation of the tosyl hydrazone. The recovery of starting material only is, presumably, attributable to steric hindrance at the sites of reaction.

Thioketalisation of the carbonyl functions was also attempted. Examination of the material isolated showed that at least nine products had been formed and the reaction was not pursued.

Treatment of an alcohol with thionyl chloride has been shown[23,24] to bring about either dehydration or replacement of the hydroxyl group by chloride. Such reactions would allow the desired product (26) to be obtained by catalytic or hydride reduction of the product of thionyl chloride treatment of the diol (27).

Accordingly, the ketone (23) was treated with excess sodium borohydride to yield an epimeric mixture of diols (27) (from T. L. C. examination). The structure of these diols (27) was confirmed by the expected changes from (23) on spectroscopic comparison.

The only carbonyl absorption in the infra-red occurred as a sharp peak at 1729 cm^{-1} (aromatic ester) and the hydroxyl absorption was readily apparent (3600 - 3450 cm^{-1}).

The ultra-violet spectrum showed the loss of the long wavelength absorption (λ_{max}^{nm} 235, 288) and the signals from the protons on the carbinol carbon atoms could be detected in the N. M. R. spectrum at τ 5.5 with a slight change occurring at τ 6.0 on D_2O exchange. The mass spectrum showed that an increase in molecular weight by four mass units had taken place. (Parent ion m/e 332; $C_{19}H_{24}O_5$ requires 332). The diol (27) was reacted as described in the literature[24] with thionyl chloride.

The product isolated in high yield proved to be the sulphite ester (28) rather than either of the desired products. The presence of

sulphur in the product was confirmed by a standard sodium fusion test. The infra-red spectrum showed the disappearance of hydroxyl absorption but the absorption expected for the sulphite ester (1200 cm^{-1}) was masked by the solvent. The ultra-violet and the N. M. R. spectra hardly changed and in this case the mass spectrum proved to be more significant. The parent ion was observed at m/e 378 ($C_{19}H_{22}O_6S$ requires 378) and a peak at m/e 314 attributable to loss of sulphur dioxide was also apparent.

The formation of the sulphite ester in >80% yield again indicated the steric control exerted in the hydride reduction of the diketone (23) and allowed the major epimer to be assigned the 6β , 8β configuration.

In view of the high specificity in reduction of the cyclopentanone the minor epimer has presumably the 6α , 8β configuration.

In connection with these attempts to prepare a CD system lacking any functionality, it was found in one instance that treatment of thioketal (30) with Raney nickel produced the gibbatriene ester (26). This reaction was not reproducible.

In view of the successful selective borohydride reduction to the keto alcohol (25; R = H) described earlier, attention was directed to this aspect of the synthesis which appeared to offer most promise as a means of removing the cyclohexenone system and regenerating the cyclopentanone moiety.

Reduction of the keto acetate (25; R = Ac) was readily accomplished in the presence of 30% Pd - C catalyst followed by Jones oxidation to

afford the saturated ketoacetate (29). Again the structure proposed for this acetate (29) was readily confirmed by spectroscopic studies. The infra-red spectrum showed twin carbonyl peaks ($\nu_{Nujol}^{cm^{-1}}$ 1735; 1715) and absence of the double bond absorption previously observed at 1620 cm^{-1}. As in the reduction of diketone (17), the ultra-violet and N. M. R. spectra confirmed the saturation of this bond while the mass spectrum showed that an increase of two mass units in the molecular weight had taken place (Parent ion m/e 372; $C_{21}H_{24}O_6$ requires 372).

The solvent used for this reduction was methyl acetate since trial runs had made it evident that the use of methanol as solvent led to ester exchange on the catalyst surface giving rise, after the oxidation stage, to varying amounts (8 - 10%) of the saturated diketone (23). Use of chloroform as a co-solvent to overcome the limited solubility of (25; R = Ac) in methanol caused this contamination to exceed 80% of the material isolated from the reduction. Reduction in acetic acid yielded the correct product (29) but this too was isolated in an impure form.

That the catalytic hydrogenation had proceeded in a stereospecific manner was apparent from a detailed G. L. C. examination of the product (29) which indicated that only one of the two possible 4b epimers had been produced.

Since the stereochemistry of the keto acetate (29) is of paramount importance so far as the synthesis of natural gibberellins is concerned, an attempt to produce the other 4b epimer was undertaken using a method employed[25] in the steroid field for producing AB cis steriods.

Bouchard and Engels[25] synthesized AB *cis* steroids by reduction of the Δ^4 compounds in the presence of methanol, potassium hydroxide and 4% Pd - $CaCO_3$ catalyst.

Using a close approximation to the conditions specified[25] by these authors, the diketone (17) was hydrogenated for four days. The product obtained, after Jones oxidation, proved identical on a variety of G. L. C. stationary phases to (23) and to a sample of (29) converted to (23) by a combination of methanolysis and oxidation.

Attempts to remove the enone system in (25; R = Ac) directly by hydrogenation of the derived thioketal as a means of obtaining the acetate (31) or its 4b epimer were unsuccessful owing to our inability to prepare the thioketal under a variety of conditions.

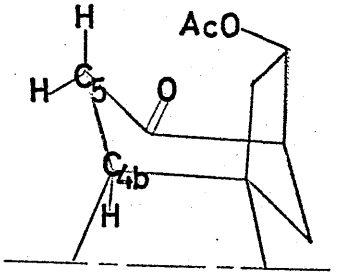
It was thought that the above hydrogenation had produced the epimer with the 4b hydrogen *trans* to the C_{10} methyl group and *trans* to ring D. It seems reasonable to assign the α configuration to this 4b hydrogen in ketoacetate (29) and the related diketone (23) since catalytic hydrogenation would be expected to take place from the least hindered face of the molecule and also since it has been observed that hydrogenation of the $\Delta^{4b,5}$ gibberellins results in that epimer having the 4b hydrogen *trans* oriented with respect to the C_{10} carboxyl group[3,26abc].

This assignment was further strengthened by a study of the N. M. R. spectra of the diketone (23) and the ketoacetate (29) in deuterochloroform and benzene. In the spectrum of (23), upfield solvent shifts were observed for, *inter alia*, the protons attached to C_{4b} (τ 6.7 $\longrightarrow$ 7.44);

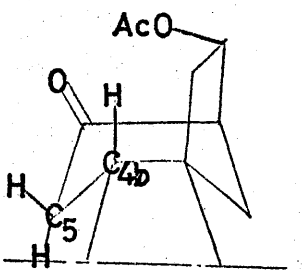
C_5 (~6.9 ⟶ 8.2 τ); C_{10} (~6.7 ⟶ 7.3 τ) and C_{11} (7.65 ⟶ 8.5 τ). In the benzene spectrum of ketoacetate (29) these same shifts were observed to have taken place with the sole exception of one of the C_5 protons. This proton had been deshielded by the acetate function and absorbed at ca. 7.3 τ. This indicated that ring C had adopted a chair conformation and that hydrogenation had taken place from the α face of the molecule.

It would appear, therefore, that construction of the unnatural BC - trans fused ring system had been achieved.

The two possible conformations are (i) and (ii). Only in conformation (i) will the C_5 axial proton be deshielded by the acetate moiety. In conformation (ii) the C_{4b} proton would have been deshielded. This was not observed.



(i)



(ii)

Nuclear Overhauser studies[9] on the acetate (29) and the ketone (23) were not undertaken in view of the inconclusive results obtained above.

Although the N. M. R. evidence would appear to offer proof of the stereochemistry of the tetracyclic ketoacetate (29), an absolutely definitive stereochemistry could only be obtained either by an X-ray

crystallographic study or a circular dichroism comparison of the resolved ketone (32) with 17-norkauran-16-one or 17-norphyllocladan-16-one[27]. An X-ray structure analysis of the chloroketone (33) is in progress.

With the ketoacetate (29) now readily available the next stage in the synthetic scheme - the removal of the C_6 keto function - was studied.

After an initial lack of success at the formation of the thioketal (30), the ketoacetate (29) was transformed in high yield to (30) by treatment with ethane dithiol and boron trifluoride etherate in acetic acid[28] under an inert atmosphere.

Little change was seen in the ultra-violet spectrum (λ_{max}^{nm} 229; 268) of this thioketal (30) and the infra-red spectrum similarly showed little change apart from the fact that the carbonyl absorption now appeared as a symmetrical sharp band both in solution ($\nu_{CHCl_3}^{cm^{-1}}$ 1730) and in a Nujol mull ($\nu^{cm^{-1}}$ 1735).

The N. M. R. spectrum showed the expected multiplet at τ 6.5 - 7.0 (4 protons) for the ethylene group of the thioketal while the mass spectrum showed the parent ion to be m/e 448 ($C_{23}H_{28}O_5S_2$ requires 448).

Desulphurisation of this thioketal (30) with Raney nickel W - 2[29] in refluxing methanol afforded the acetate (31; R = Ac) in good yield. As in the case of the compounds discussed earlier, the structure of this acetate (31; R = Ac) was readily confirmed by spectroscopic investigation. The infra-red ($\nu_{CHCl_3}^{cm^{-1}}$ 1735) and the ultra-violet (λ_{max}^{nm} 231,288) spectrum showed, as would be expected, very little change from the corresponding spectra of (30). The N. M. R. spectrum, on the other hand,

displayed an obviously increased complexity in the region τ 8.0 - 8.4 due to the replacement of the spiro-dithialan ring by two protons and the large complex multiplet (τ 6.5 - 7.0) previously evident was absent. The parent ion in the mass spectrum occurred at m/e 358 ($C_{21}H_{26}O_5$ requires 358) and the spectrum showed, inter alia, the loss of methoxyl, methanol and acetic acid previously noted in the spectra of (25; R = Ac), (29) and (30).

On several occasions, anomalous products were observed to be formed in the above desulphurisation reaction.

Freshly prepared Raney nickel W - 2[29] normally gave the desired acetate (31; R = Ac) in 75 - 80% yield. However, on one occasion, two products were isolated in the ratio 3:1. The minor product was shown to be (31; R = Ac) by comparison with an authentic sample. The major product was assigned structure (26) on the basis of chromotographic and spectroscopic evidence in conjunction with the knowledge that loss of an acetoxyl group during removal of a thioketal had previously been observed.[30] G. L. C. and T. L. C. examination showed that the compound was less polar and more volatile than (31; R = Ac). Mass spectroscopy revealed the molecular weight to be 300 while the N. M. R. spectrum showed the loss of the signal due to the acetate methyl group while confirming the presence of the other methyl groups in the molecule. This reaction could not be repeated.

On another occasion, during a large scale preparation of the acetate (31; R = Ac) G. L. C. examination of the solid isolated by preparative

T. L. C. revealed the presence of seven components (50: 15: 15: 15: 1: 1: 2).

It was originally thought that the formation of these products could have been explained by previously observed phenomena. It is well known[31] that a degree of unsaturation often occurs in Raney nickel desulphurisations and hydrolysis of acetates has also been noted[31] in the presence of basic Raney nickel. A third phenomena observed in these reactions is the epimerisation of alcohols[32] by Raney nickel treatment.

A combination of some or all of these factors could have accounted for the multiplicity of products evident on G. L. C. examination. Accordingly, the mixture was hydrogenated and then treated with methanol/HCl followed by Jones oxidation as described below. G. L. C. examination of the material isolated revealed two components in the ratio 2.1:1.

The major component could be isolated in a pure form by fractional crystallisation from ethyl acetate and was shown to be (32) by direct comparison.

Preparative T. L. C. afforded the minor component homogeneous by G. L. C. The infra-red spectrum of this compound was very similar to that of ketone (32) except for minor differences in the fingerprint region while the ultra-violet spectrum (λ_{max}^{nm} 228, 285) showed only a slight hypsochromic shift when compared to that of (32). A standard sodium fusion test revealed the presence of halogen and this was shown to be chlorine from an examination of the mass spectrum and by elemental analysis. Two parent peaks, two mass units apart, were present in the

ratio 3:1 at m/e 348 and 350. This suggested a formula $C_{19}H_{21}O_4Cl$ ($C_{19}H_{21}O_4Cl^{35}$ requires 348 and $C_{19}H_{21}O_4Cl^{37}$ requires 350)., and a structure in which one chlorine atom has replaced a hydrogen atom in ketone (32).

The structure (33) was suggested by consideration of the most probable position of attack by electrophilic reagents on ring A of (32) and by a comparison of the N. M. R. spectra of (32) and (33). These spectra were superposable except in the aromatic absorption region. The AB quartet due to the C_3 and C_4 protons in (32) was replaced in (33) by a singlet (τ 2.92) corresponding to one aromatic proton. If this chlorine was attached to C_4 then the deshielding effect of a chlorine atom would have altered the values of the chemical shift of the protons on C_{4b} and C_5. This was not observed. However, if the chlorine atom was attached to C_3 then only the C_4 proton would be affected. This was indeed the case. Structure (33) was assigned to this anomalous product.

Confirmation of this structure (33) for the minor component isolated from the mixture was obtained from hydrogenolysis studies.

The product obtained from hydrogenolysis in methanol containing 30% Pd - C or 10% Pd - C + triethylamine[33] followed by Jones oxidation was identical in all respects with ketone (32).

One possible explanation for the formation of ketone (33) is the presence of a trace of chloroform in thioketal (30) during the desulphurisation reaction. Reduction of this chloroform by the hydrogen absorbed on the catalyst would have produced hydrogen chloride which could substitute ring A in the 3-position under the catalytic influence of the

iron[34] present in Raney nickel.

Another equally plausible explanation is the formation of sulphur monochloride by reaction of chloroform, hydrogen chloride or chlorine radicals with the sulphur radicals produced in the reaction. Sulphur monochloride is known[35] to chlorinate aromatic hydrocarbons by itself and also to be a very powerful chlorination catalyst[36].

Either or both of these possibilities may well be the cause of the otherwise seemingly inexplicable formation of the chloroketone (33).

The next part of the synthetic sequence required the reconversion of the protecting acetate function in (31; R = Ac) to a ketone function. This was readily accomplished in the manner described below.

The acetate group in (31; R = Ac) was removed by an ester exchange procedure using methanol/dilute hydrochloric acid at reflux temperature. The desired alcohol (31; R = H) ($\nu_{CCl_4}^{cm^{-1}}$: 3630) was isolated and oxidised by treatment with Jones reagent at 0° to yield the crystalline ketone (32). Chromatographic examination of this ketone (32) revealed the presence of only one epimer confirming the previously observed fact that hydrogenation of the 4b,5 double bond had produced only a single epimer.

The infra-red spectrum showed twin carbonyl absorptions ($\nu_{Nujol}^{cm^{-1}}$ 1740; 1721) and the ultra-violet spectrum exhibited the ketonic $n \rightarrow \pi^*$ transition as a low intensity bond at 294.5 nm. Confirmation of the structure was again obtained from the N. M. R. spectrum (no absorption due to $\underline{CH_3}$-C-O- and AcO - $\underline{CH}$-) and the mass spectrum (parent ion m/e 314; $C_{19}H_{22}O_4$ requires 314).

With the successful transformation of the diketone (17) to the monoketone (32) only one step remained to construct the 4b epimer of the CD ring system of GA_4, viz. the conversion of the C_8 ketone function to an exomethylene group.

Attempted conversion of (32) to the exomethylene compound (34; R = CH_3) initially proved unfruitful.

The Grignard-type reaction, reported by Cainelli et al.,[37] using methylene magnesium iodide afforded only unchanged starting material or, under more forcing conditions, a complex mixture of unidentified products which exhibited no exomethylene absorption on infra-red examination.

Conversion of (32) to the exomethylene compound (34) by use of the Wittig reaction also proved difficult. This reaction was first attempted using the conditions employed by Qasseem, Rogers and Othman[38] but proved unsuccessful as did the use of sodium hydride in dimethyl sulphoxide.[39] The desired product (34; R = H) was finally obtained in high yield by the use of potassium tert-butoxide as the base in accordance with the method employed by Ireland[40] in his synthesis of kaurene and atisirene.

The structure of the exomethylene compound (34) from the Wittig reaction was confirmed by its spectral properties. Although the gross features of the spectra were similar to those observed in the spectra of ketone (32), the exomethylene group was readily apparent on examination. In the infra-red spectrum absorption at 878 cm^{-1} together with lack of cyclopentanone absorption first suggested the success of this reaction.

Examination by N. M. R. confirmed this (broad doublet at τ 5.23; J = 13 Hz). The mass spectrum exhibited a parent ion at m/e 312 ($C_{20}H_{24}O_3$ requires 312).

In order to elaborate the aromatic ring A to the hydroxy γ-lactone feature of most of the gibberellins the ester function had to be hydrolysed to a carboxylic acid in order that Birch reduction and methylation might be effected prior to the acid catalysed lactonisation and vinyl ether hydrolysis. (34; R = CH_3 ⟶ 34; R = H ⟶ 36 ⟶ 37).

It was felt that the C_{10} methyl group, possessing the β stereochemistry of the natural gibberellins, might influence the steric course of methylation at C_1 during this Birch reduction step (34; R = H ⟶ 35) to such an extent that the major product produced would have the wrong stereochemistry relative to the C_{10} substituent.

It was, however, decided to proceed with this investigation since knowledge of the influence of a C_{10} substituent on the stereochemistry of such a methylation would be of value in any synthesis of the gibberellins starting from an indanone possessing a C_3 - methoxycarbonyl substituent. In such a case, the methyl vinyl ketone adduct would have the carbomethoxyl substituent and the acetic acid side chain <u>trans</u>[8]. If one knew approximately the steric control exercised in the methylation step by a C_{10} substituent it would provide a guide as to where in the synthetic scheme epimerisation of the carbomethoxy group should be undertaken to provide the best compromise of stereoselectivity and yield.

Concurrently with the conversion of (32) ⟶ (34; R = CH_3), the keto

acid was readily formed by simple basic hydrolysis of (32). The infra-red spectrum made obvious the presence of the carboxyl moiety ($\nu^{cm^{-1}}_{Disc}$ 3300 - 2800; 1730) and the loss of the methyl ester was evident in the N. M. R. spectrum. This spectrum also showed that the other structural features of the molecule remained intact during the hydrolysis.

Conversion of either (34; R = CH_3) or (35) to the acid (34; R = H) has, in our hands, proved impossible. An attempted Wittig reaction on the keto acid (35), using conditions similar to those employed above, failed. Similarly, attempts to hydrolyse the exomethylene ester (34; R = CH_3) to the acid were completely fruitless. Employing the conditions used in the transformation of (32) $\longrightarrow$ (35) yielded only unchanged ester. Repetition of this reaction using a wide variety of conditions including the use of various co-solvents, lithium iodide[41,42] and concentrated sulphuric acid[43] did not lead to the desired product.

In most cases the material isolated proved to be unreacted starting material while more forcing conditions produced intractable complex mixtures.

In order to circumvent the unforeseen difficulties experienced in hydrolysing the exomethylene ester (34; R = CH_3), it was hoped that the required aromatic acid (34; R = H) might be obtained by hydride reduction of the ester to the alcohol (38) followed by oxidation <u>via</u> the aldehyde to the acid (34; R = H).

Reduction of the ester (34; R = CH_3) to the alcohol (38) was accomplished using lithium aluminium hydride. The infra-red spectrum showed hydroxyl and exomethylene absorption ($\nu^{cm^{-1}}_{CCl_4}$ 3600; 875) but no

carbonyl absorption. In the N. M. R. spectrum both these features were also apparent [$-CH_2OH$ τ 5.18 (s) and $=CH_2$ τ 5.23 (d)] . The mass spectrum showed a parent ion at m/e 284 ($C_{19}H_{24}O_2$ requires 284).

However, oxidation of this material by Jones reagent and zinc permanganate[44] proved unsuccessful.

With the failure of this hydrolysis step, this seemingly promising route drew to a close. The reasons for failure are not obvious and perhaps, with a plentiful supply of ester (34; R = CH_3), the conversion could be achieved by an approach only slightly different from those discussed above but lack of material prevented further attempts at varying the conditions from being made.

Since the construction of rings C and D outlined above provides a model only for gibberellins such as GA_4 (2) but not those such as GA_3 (1) which possess a 7-hydroxyl function, it was decided to undertake a preliminary investigation into the construction of a C_7 substituted compound.

The route envisaged was an acyloin-type closure of a keto ester produced by oxidation and esterification of the hydroxy-acid derived from the lactone (39; R = H).

The keto-ester produced above could also be converted to its C_{9a} epimer by a similar process to that used in the phyllocladene-kaurene correlation[58] and in the determination of the stereochemistry of allogibberic acid.[59] This would provide a route not only to the 4b epimer of

the naturally occurring gibberellic acid CD ring system but also to that occurring naturally. This conversion could be carried out by Claisen condensation of the keto-ester to give a diketone (53). Hydrolysis of this diketone would take place between C_6 and C_7 to yield a keto-acid epimeric at C_{9a} to the starting material.

To investigate the initial feasibility of this route the chloro-ketone (33) was treated with trifluoroperacetic anhydride in methylene chloride and the product, isolated by preparative T. L. C., was subjected to spectroscopic investigation. Although the material isolated had different chromotographic properties from the starting ketone (33), the infra-red spectrum proved to be very similar to the spectrum of (33) and, consequently, was almost useless for identification purposes. However; the N. M. R. spectrum showed not only the same gross structural features observed in (33) but also an additional absorption at τ 5.19 (m) in the position expected for a proton attached to a carbon atom singly bonded to oxygen. The mass spectrum confirmed the structure (39; R = Cl) by showing an increase in molecular weight corresponding to the addition of one atom of oxygen (parent ion m/e 364; $C_{19}H_{21}O_5{}^{35}Cl$ requires 364).

The formation of the lactone (39; R = Cl) shows that the route described above for the construction of the CD ring system of 7-hydroxy gibberellins is, at least initially, feasible.

Attempts to convert the C_{10} methyl group to carboxyl

One serious drawback in the otherwise useful approach to the synthesis of gibberellins from terracinoic acid (3; R = H) was the fact that at some stage in the synthesis the secondary methyl group in the latter compound had to be converted to a carboxyl group. (The C_{10} carboxyl of the gibberellins).

Since it was attached to a benzylic position it was envisaged that elaboration might be achieved by benzylic bromination followed by dehydrobromination, hydroboration and oxidation. An alternative method would be by photochemically induced lactonisation of the aromatic acid group to the methyl carbon followed by hydrolysis and oxidation. Or, more likely, photochemical lactonisation would be to the benzylic carbon and would be followed by elimination, hydroboration and oxidation.

Trial bromination experiments were carried out on dimethyl terracinoate methyl ether (3; R = CH_3) and some of its derivatives.

In no case studied was any success achieved.

The first compound studies was the ester (3; R = CH_3). Treatment of this ester with N-bromosuccinimide and benzoyl peroxide[45,46] did not effect reaction and the only product was unreacted starting material.

Prolonged reduction of (3; R = CH_3) with sodium borohydride afforded three products (ratio 3:4:1) identified by their spectral characteristics and, except for the minor product, by analogy with the known course of reduction of indan-1-one-2-acetic acid.[47]

The least polar product was shown to be the cis-fused lactone (40) formed by intramolecular cyclisation of the alcohol having the substituents at C_1 and C_2 cis. The infra-red spectrum clearly showed the γ-lactone and ester carbonyl absorptions ($\nu^{cm^{-1}}_{CHCl_3}$ 1775; 1728) and exhibited no hydroxylic absorption. This structure was confirmed by a study of the N. M. R. spectrum.

The second product proved to be the alcohol (41) produced by reduction of the ketone in (3; R = CH_3) from the same side as the C_2 side chain. The alcohol (41) was readily identified by hydroxyl absorption in the infra-red spectrum at 3515 cm^{-1} and in the N. M. R. spectrum at τ 6.7 (-O-H; disappeared on D_2O exchange).

The most polar product was identified as a mixture of the epimeric diols (42). The infra-red spectrum showed the hydroxyl absorption as a broad band ca. 3400 cm^{-1} and only one carbonyl absorption band was present (1720 cm^{-1}). The N. M. R. spectrum revealed that reduction of the aliphatic ester had taken place from the absence of the methyl singlet (τ 6.32) which had been observed in the spectrum of the starting material (3; R = CH_3). Further examination revealed that this product, although crystalline, was indeed a mixture of epimers at C_1. The absorption of the benzylic methyl group appeared as two distinct doublets (τ 8.80; 8.84) because of the deshielding effect of the alcohol group in the epimer in which it is cis to the C_3 methyl group. The ratio of epimers (ca. 4:3) proved to be similar to the ratio of alcohol (41) to lactone (40).

Reaction of (40), (41) and (42) with N-bromosuccinimide in the

presence of benzoyl peroxide[45,46] resulted, in each case, in the formation of a complex mixture of products and the reactions were not further pursued.

N-bromosuccinimide treatment[45,46] of the acetate (31; R = Ac) with or without the addition of benzoyl peroxide in methylene chloride at room temperature or in chloroform at reflux temperature produced no reaction.

An attempt at functionalisation of C_{10} in the diketone (17) was also made.

Reaction of this diketone (17) in a variety of solvents (CH_2Cl_2, $CHCl_3$, EtOH) with or without the addition of a radical initiator yielded the same product in all cases.

T. L. C. examination showed this material to be homogeneous and less polar than starting material. The infra-red spectrum displayed three carbonyl absorptions ($\nu_{Nujol}^{cm^{-1}}$ 1755; 1718; 1675) and the ultra-violet spectrum, while confirming the presence of the extended chromophore present in (17), exhibited a small bathochromic shift (λ_{max}^{nm} 349; 313; 253). The mass spectrum confirmed that one atom of bromine had been incorporated with the concomitant loss of one hydrogen atom. (Two parent ions of equal intensity at m/e 404 and 406; $C_{19}H_{17}O_5{}^{79}Br$ requires 404; $C_{19}H_{17}O_5{}^{81}Br$ requires 406).

The position of the bromine atom was revealed by examination of the N. M. R. spectrum. The signal at τ 3.89 observed in the spectrum of the starting diketone (17) for the isolated C_5 vinylic proton disappeared and one half of the aromatic AB quartet attributable to the absorption of the C_4 proton had moved downfield to τ 1.3 due to deshielding

by the C_5 bromine atom.

On the basis of this evidence, structure (43) was assigned to this product.

The course of what at first seems an anomalous reaction can be rationalized by consideration of the high nucleophilic character at C_5 in the resonance form (44).

An analogy for this type of reaction is found in the reaction of a 6 alkyl-uracil (45) with N-bromosuccinimide to give the corresponding 5-bromouracil (46)[48]. Here the high electron density is provided by the enamine nitrogen. In both (45) and (17) the developing carbanoid carbon is further stabilized by the adjacent carbonyl group.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. All boiling points are uncorrected.

Infra-red solution spectra were recorded on a Unicam S. P. 100 double beam spectrophotometer equipped with an S. P. 130 sodium chloride prism-grating double monochromator on a Perkin-Elmer P.E. 225 spectrophometer. Routine infra-red solution spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The infra-red spectra of nujol mulls and of liquid films were recorded on a Unicam S. P. 200 spectrophotometer.

Ultra-violet spectra were recorded on a Unicam S. P. 800 spectrophotometer as methanol solutions.

Nuclear magnetic resonance spectra in part A were recorded on a Varian HA-100 100 mega Herz spectrometer and in part B on a Perkin Elmer R 10 60 mega Herz spectrometer unless otherwise stated.

Mass spectral data were recorded on an A. E. I. M.S. 12 spectrometer.

Gas -liquid chromatography was performed on Pye Argon and Perkin Elmer F.11 chromatographs.

Thin layer chromatoplates were prepared from Merck's "Kieselgel G" and thick layer preparative chromatoplates from "Kieselgel HF 254".

Gas-liquid mass spectral analyses were carried out on an L. K. B. spectrometer.

Microanalyses were carried out by Mr. J. M. L. Cameron, B.Sc., and his staff.

Unless otherwise stated petroleum ether refers to that fraction of boiling range 60 - 80°.

All solutions were dried over anhydrous magnesium sulphate.

Terracinoic Acid (3; R = H)

Terramycin hydrochloride (100 g) was converted to the dihydrate (4) of the free base by adjusting the pH of the aqueous solution to pH6 (using a pH meter) and collecting the precipitate after one hour.[49]

The dihydrate was degraded by the method of Pasternack et al.[1] to yield terracinoic acid (26g; 46%) (3; R = H), m.p. 232 - 234d. (sealed tube), as colourless prisms from ethyl acetate. (Lit.[1] 233 - 234d).

$\nu_{\text{Nujol}}^{\text{cm}^{-1}}$ 3500 - 2500 (broad); 1710 (m); 1680 (s); 1580 (m).

$\lambda_{\text{max}}^{\text{nm}}$ 216 (, 12,450); 241(, 12,620); 282(, 8,950).

Dimethyl Terracinoate Methyl Ether (3; R = CH_3)

Terracinoic acid (3; R = H) (20.0g) in dioxan (400 ml) was treated with a large excess of ethereal diazomethane. After standing overnight, T. L. C. examination showed two products to be present and the mixture was accordingly chromatographed on silica (1 Kg.).

Elution with chloroform (2.2l) followed by 10% EtOAc in $CHCl_3$ (4.6l) yielded, after recrystallisation from ether-petrol, the title compound (16 g) as colourless needles, m.p. 85 - 86° (sealed tube). (Lit.[1] 83 - 84°).

(Found: C, 63.10; H, 5.92. Calculated for $C_{16}H_{18}O_6$: C, 62.76; H, 6.29%).

$\nu_{\text{Nujol}}^{\text{cm}^{-1}}$: 1730 (s); 1705 (s); 1590 (m); 860 (m).

$\nu_{CHCl_3}^{cm^{-1}}$: 1732 (s); 1710 (s); 1575 (m).

λ_{max}^{nm} : 210 (ε , 15,000); 228 (ε , 22,200); 268 (ε , 15,700); 292 (ε , 9,050).

N. M. R. See Appendix.

Further elution yielded material (3.2 g) which appeared from T. L. C. and I.R. examination to be a mixture of dimethyl terracinoate and its methyl ether.

(1,2,3,9a Tetrahydro-7 methoxy-8 methoxycarbonyl- 9β methyl- 3 keto- 9a (β) fluorenyl) acetic acid (7; R = H).

The method used was similar to that adopted by Loewenthal et al. in the synthesis of gibberone (5)[2].

Dimethyl terracinoate methyl ether (3; R = CH_3) (3 g) in sodium-dried benzene (20 ml) was added to a solution of sodium (1.18 g) in dry methanol (50 ml) with stirring at 0° under nitrogen. Redistilled methyl vinyl ketone (2.31 g) in methanol (5 ml) was added dropwise over 20 minutes to the stirred solution after which the mixture was left to reach room temperature overnight.

After acidification with acetic acid, the reaction mixture was evaporated almost to dryness under reduced pressure. Water and chloroform were added and the organic layer was extracted several times with ice-cold aqueous sodium carbonate solution (5%). The combined carbonate extracts were acidified (HCl) under a layer of benzene and then extracted

twice with chloroform.

The combined organic extracts were washed (NaCl), dried and evaporated to yield a light yellow foam (3.17 g). Recrystallisation from methanol gave the acid (7; R = H) as bright yellow prisms (2.71 g) m. p. 111 - 112° (sealed tube). (Found: C, 64.00; H, 6.44. $C_{19}H_{20}O_6 \cdot CH_3OH$ requires: C, 63.82; H, 6.43%).

The inclusion of a solvent molecule in the crystal lattice was confirmed by the other physical data.

$\nu^{cm^{-1}}_{Nujol}$: 3500 - 2600 (broad); 1725 (s); 1640 (s); 1630 (shoulder); 1600 (shoulder); 1576 (m); 880 (w); 830 (s).

λ^{nm}_{max}: 248 (ε , 9,700); 301 (shoulder) (ε , 12,600); 328 (ε , 20,400).

N. M. R. See Appendix.

A sample of this acid was methylated using ethereal diazomethane to afford the methyl ester (7; R = CH_3) as a pale yellow microcrystalline powder, m.p. 163 - 164°, from benzene-petrol.

$\nu^{cm^{-1}}_{CHCl_3}$: 1732 (s); 1654.5 (s); 1618.5 (s); 1600 (m); 1576 (s).

GC - MS examination of this ester (7; R = CH_3) confirmed the molecular weight (358) and also showed the presence of an artefact (M.W. - 326) formed on G. L. C. examination.

The artefact proved to be the tetracyclic diketone (17) on subsequent comparison.

Methyl-2 methoxy- 6,8 diketo- 10 β methyl-gibba-A, 4b-tetraene-1 carboxylate (17)*

The half-ester (7; R = H) (1.027 g) was refluxed in toluene in the presence of naphthalene-2-sulphonic acid (100 mg) for 24 hours with azeotropic separation of water.[6]

The cooled solution was washed with 10% aq. potassium bicarbonate solution, then with water or brine, dried and the toluene removed under reduced pressure to yield (17) (827 mg). This diketone (17) was shown to be homogeneous by T. L. C. and formed light yellow microcrystalline needles, m.p. 249 - 250° (sealed tube), on recrystallisation from CH_2Cl_2/ diisopropyl ether. (Found: C, 69.67; H, 5.71. $C_{19}H_{18}O_5$ requires: C, 69.92; H, 5.56%).

G.C. - M.S..: Parent ion, m/e. 326. ($C_{19}H_{18}O_5$ requires 326).

$\nu_{Nujol}^{cm^{-1}}$: 1740 (s); 1660 (s); 1620 (m); 1600 (s); 840 (m).

$\nu_{CHCl_3}^{cm^{-1}}$: 1750 (s); 1662 (s); 1620 (m); 1596 (s); 1584 (m).

λ_{max}^{nm} : 250 (ε , 8,800); 308 (ε , 12,300); 340 (ε , 21,800).

N. M. R. See Appendix.

Attempted preparation of Methyl- 2 methoxy- 6 keto- 8 ethylenedioxy- 10β methyl-gibba- A,4b- tetraene- 1 carboxylate (47).

(a) To ethylene glycol (1 ml) and naphthalene-2-sulphonic acid (5 mg),

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* Numbering as in the parent hydrocarbon, gibbane.

which had been refluxing for 2 hours in benzene with azeotropic separation of water, was added the unsaturated diketone (17) (25 mg). Reflux was continued for a further 16 hours.

The solution was allowed to cool, the benzene replaced with chloroform, then washed with dilute sodium bicarbonate solution, water and dried.

Evaporation of the solvent followed by T. L. C. examination revealed the presence of two components more polar than starting material. From I.R. examination, and by analogy with results obtained previously,[2,13] these were assigned the structures of the mono and bis ethylene glycol esters of the unsaturated acid (7; R = H).

(b) Diketone (17) (10 mg), adipic acid (2 mg)[14] and ethylene glycol (0.5 ml) were heated under reflux in benzene in a Dean and Stark water separator.

After 16 hours, the solution was cooled, diluted and washed ($NaHCO_3$: NaCl, 1:1). The aqueous washings were extracted with benzene and the combined extracts washed (1 x H_2O), filtered through Celite 535 and evaporated to yield unreacted diketone (17) (8.5 mg).

Attempted preparation of Methyl-2 methoxy- 4b,5 epoxy- 6,8 diketo- 10β methyl-gibba-A- triene- 1 carboxylate (48).

(a) The diketone (17) (25 mg) was stirred in methanol (15 ml) containing 4 $\bar{N}$ sodium hydroxide (0.5 ml) and hydrogen peroxide (100 vol.) (1.0 ml)[16] for 24 hours at 25°C.

After this time, water was added and the mixture extracted with chloroform. The chloroform extracts were washed (H_2O), dried and evaporated to yield a product (11 mg) shown to be the tricyclic dicarboxylic ester (7; R = CH_3) by I.R., U.V. and G. L. C. comparison.

(b) To a solution of the diketone (17) (10 mg) in pyridine (3 ml) was added sodium hypochlorite solution (4 ml)[50].

After 45 minutes stirring, water was added and the solution acidified. The acidic solution was extracted with chloroform and the organic extracts washed (3 x NaCl), dried and evaporated to yield a yellow oil (7.5 mg). I.R. and T. L. C. examination showed this oil to be a mixture of diketone (17) and the ring-opened acid (7; R = H) together with an appreciable amount of decomposition products.

(c) The diketone (17) (10 mg), sodium tungstate (1 mg) and excess hydrogen peroxide (100 vols.) in methanol were heated under reflux overnight.[51] (U.V. examination after 1 hour had shown the enone chromophone still to be present although it had suggested that some opening of the non-enolisable β diketone system had taken place.).

The solvent was removed from the cooled solution under reduced pressure and the residue dissolved in chloroform. The solution was washed with water (x 3) and the washings extracted with chloroform (x 1). The combined chloroform extracts were dried and evaporated to yield an oil (8.8 mg) which soon solidified. This was shown to be the tricyclic

ester (7; R = CH_3) by comparison with an authentic specimen.

(d) The diketone (17) (10 mg) was stirred at room temperature in dry benzene (10 ml) in the presence of tert.-butyl hydroperoxide (6 μl) and a 35% methanolic solution of Triton- B (0.56μ l).[52]

After 20 hours, the reaction mixture was washed with water. The aqueous washings were saturated with salt and extracted with chloroform. The combined organic extracts were dried and evaporated to give a crystalline solid (10.5 mg) which was shown to be a 4:1 mixture of starting diketone (17) and the ring-opened ester (7; R = CH_3) by G. L. C. examination.

(e) The diketone (17) (10 mg) was stirred at room temperature in methylene chloride with m - chloroperbenzoic acid (6 mg) for 24 hours.

U.V. examination showed the extended chromophone still to be present.

Accordingly, the mixture was refluxed for 16 hours and again U.V. examination showed no change. The methylene chloride was replaced with chloroform and the solution was refluxed for 72 hours. After washing with base and brine, the solution was dried and evaporated. I.R., U.V., G. L. C. and T. L. C. examination showed only starting material together with a trace of acidic material to be present.

Attempted preparation of Methyl-2 methoxy- 8 keto (or acetoxy)- 10β methyl- gibba- A- triene- 1 carboxylate (32 or 31; R = Ac)

(a) To the diketone (17) (100 mg) in dioxan: water (10:1), sodium borohydride (30 mg) was added in portions. After addition was complete, the mixture was stirred at room temperature for 4 hours.

The reaction mixture was then neutralized (pH 7) by dropwise addition of dilute sulphuric acid and poured into ammonium sulphate solution. The ammonium sulphate solution was extracted with chloroform, the chloroform extract washed (brine), dried and evaporated to yield an oil (98 mg) shown by T. L. C. to be two components (22; R = H). $\left[\nu_{film}^{cm^{-1}} \quad 3500 \text{ (broad)} \right]$.

This material (96 mg) was hydrogenated for three hours in methanol in the presence of 30% Pd - C catalyst and glacial acetic acid (1 ml). After Jones oxidation of the material isolated, the product was shown by G. L. C. comparison to consist almost entirely (~90%) of the saturated diketone (23).

(b) The diketone (17) (75 mg) was reduced with excess sodium borohydride to an epimeric mixture of diols (22; R = H) as described above. The mixture of diols (75 mg) thus obtained was dissolved in pyridine (10 ml), acetic anhydride (5 ml) added and the mixture stored at 0° for 16 hours.

After the usual work-up, a light yellow oil (70 mg) was isolated.

$\nu_{film}^{cm^{-1}}$: 1730 (s); 1600 (shoulder); 1595 (m); 1250 (s) .

The crude diacetate mixture (22; R = Ac) (35 mg) in methanol was hydrogenated for 15 hours in the presence of 30% Pd - C catalyst (20 mg) and piperidine (0.5 ml).[17]

The usual work-up afforded a colourless oil (29.5 mg) [$\nu_{film}^{cm^{-1}}$: 1725 (s); 1595 (m); 1260 (s)] shown by G. L. C. examination to be a mixture of eleven products (ca. 1:2:1:4:1:3:4:4:1:1:2).

It appeared that the only reaction that had taken place was saturation of the double bond and, perhaps, some hydrogenolysis of the methoxyl group in ring A. However, the reaction was not further investigated due to the complexity of the mixture and since GC - MS examination could not be carried out (probably because of decomposition of the sample in the instrument).

(c) The mixture of epimeric acetates (22; R = Ac) (35 mg) prepared above was heated under reflux in acetic acid (8 ml) in the presence of zinc dust (100mg) for 16 hours.

The cooled solution was filtered, diluted with chloroform, washed (H_2O), dried and evaporated to yield a yellowish oil (26.5 mg).

The I.R. and U.V. of this oil was essentially identical with that of crude diacetate (22; R = Ac) while G. L. C. examination showed four main components. The reaction was not further investigated since it appeared that no reduction had taken place and that only starting material had been isolated.

Attempted preparation of Methyl- 2 methoxy- 6,8 diketo- 10 β methyl- gibba- A,4b- tetraene- 1 carboxylate- 6 ethylene mercaptole (49).

(a) The diketone (17) (10 mg), ethane dithiol (2.5μ l) and boron trifluoride etherate (0.1 ml) in methanol were stored at 0° for 19 hours.[18] After this time, the fluorescence produced by the addition of the Lewis acid had disappeared. After the usual work up, a yellowish oil (11.5 mg) which soon solidified was isolated.

By I.R., U.V. and G. L. C. comparison with a genuine sample, this solid was shown to consist principally of the ring-cleaved methyl ester (7; R = CH_3) (ca. 90%) as well as a small amount of starting ketone (17) (ca. 5%).

(b) The unsaturated diketone (17) (25 mg) and ethane dithiol (7.5 mg) were stirred at room temperature for one hour in glacial acetic acid with p-toluene sulphonic acid (2 mg) as catalyst.[53]

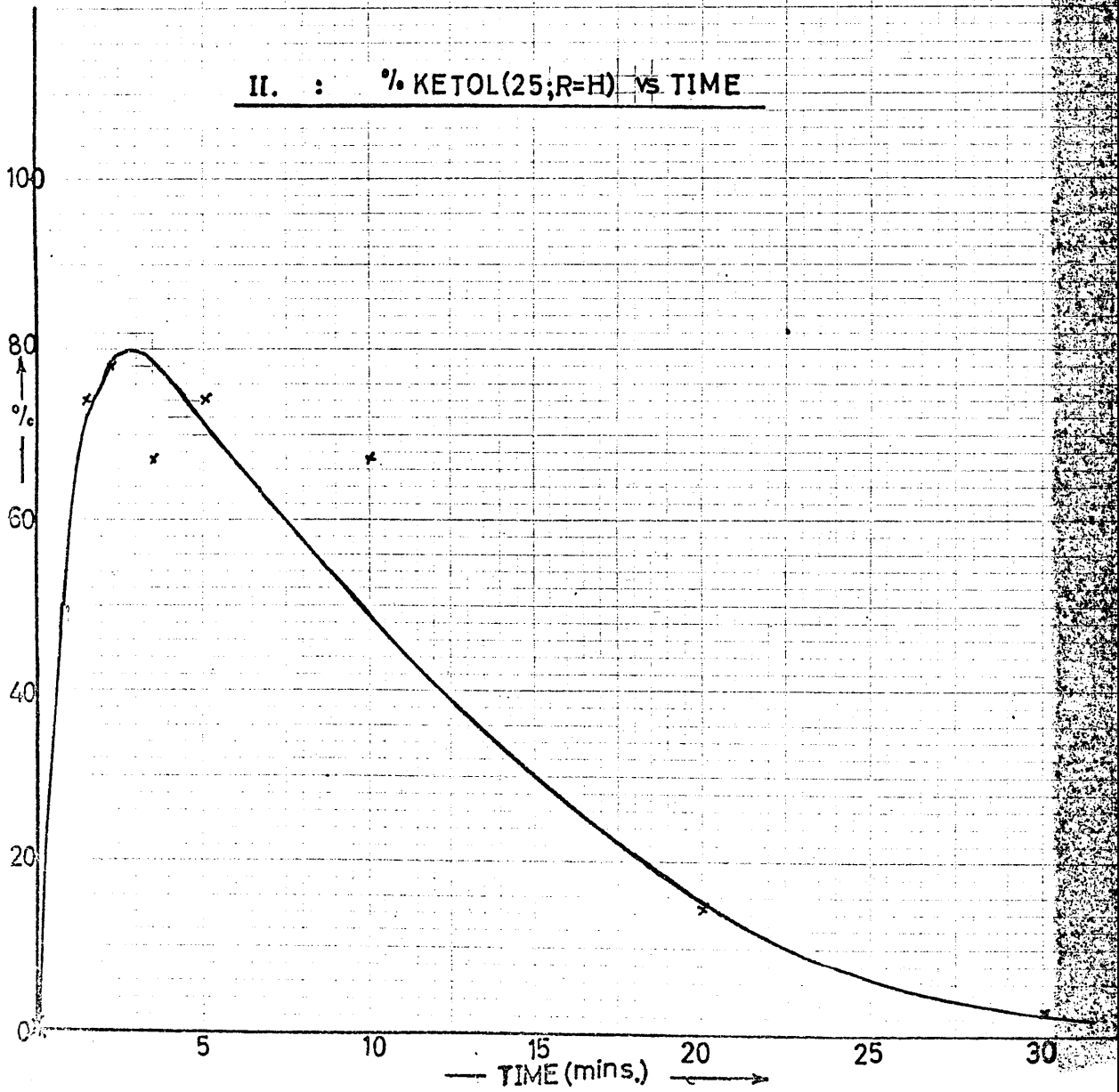
The solution was poured into water and extracted with chloroform. The organic extracts were washed (H_2O; 5% NaOH solution; H_2O) and dried.

Evaporation of the solvent afforded a light yellow oil (18.5 mg) shown by direct comparison to be starting material.

Methyl- 2 methoxy- 6 keto- 8 acetoxy- 10 β methyl- gibba - A,4b- tetraene- 1- carboxylate (25; R = Ac)

To a stirred solution of the diketone (17) (10 mg) in AnalaR dioxan water (1:1; 20 ml) at 0°, was added sodium borohydride (20 mg) in one

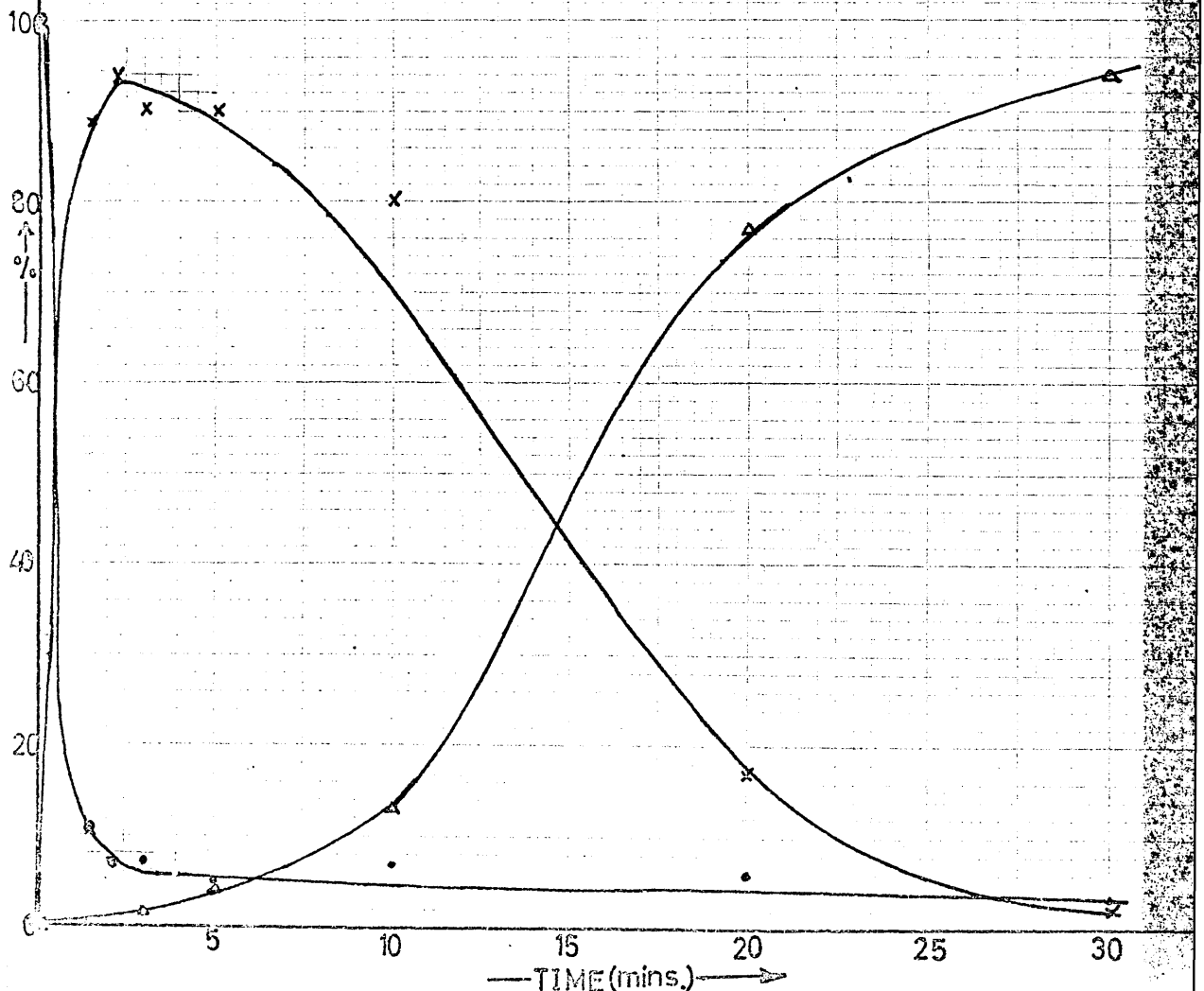
II. : % KETOL(25;R=H) vs TIME



I. : RELATIVE PERCENTAGES OF KETOL(25; R=H):

DIKETONE(17) AND DIOL(22 R=H)

vs TIME



(25; R = Ac) (736 mg) as light yellow prisms, m. p. 222.5 - 224° (sealed tube), homogeneous by G. L. C. (Found: C, 67.94; H, 5.05. $C_{21}H_{22}O_6$ requires: C, 68.09; H, 5.99%).

$\nu_{CHCl_3}^{cm^{-1}}$: 1730 (s); 1655 (s); 1620 (m); 1240 (m).

λ_{max}^{nm} : 248 (ε , 11,250); 300 (ε , 15,800); 328.5 (ε , 23,000).

N. M. R. See Appendix.

M. S. Parent ion m/e 370 ($C_{21}H_{22}O_6$ requires 370).

Other significant peaks: 339, 338, 310, 239 (Base Peak).

Model Reduction of the 4b,5 double bond in (1,2,3,9a Tetrahydro- 7 methoxy- 8 methoxycarbonyl- 9 β Methyl- 3 keto- 9a β fluorenyl)- acetic acid (7; R = H) and its methyl ester (7; R = CH_3)

(a) The ester (7; R = CH_3) (149.5 mg) was hydrogenated in methanol containing 4 $\bar{N}$ sodium hydroxide solution (0.5 ml) in the presence of 10% Pd - C catalyst (100 mg). After 1 hour, the catalyst was removed by filtration, the methanol was evaporated under reduced pressure and the residue dissolved in ether and water.

The aqueous layer was extracted with ether and the combined ethereal extracts washed (H_2O), dried and evaporated to yield a solid (55 mg) which, by I.R. and U.V. was identical with the starting ester (7; R = CH_3).

The aqueous layer was acidified and ether extracted. After the usual work-up, a yellowish oily solid (83.3 mg) which yielded prisms

(m.p. 109 - 110°; sealed tube) on recrystallisation from methanol was isolated.

By I.R., U.V. and T. L. C. comparison, the compound was shown to be the half-acid (7; R = H).

(b) The half-acid (7; R = H) (100 mg) in methanol, was hydrogenated for 16 hours in the presence of 10% Pd - C (50 mg).

T. L. C. examination of the product showed the presence of five components and a sample was subjected to Jones oxidation to oxidise any products of over-reduction. T. L. C. examination of this material showed eight components.

Owing to the complexity of the mixture this reaction was not pursued.

(c) The diester (7; R = CH_3) (53 mg), in methanol, was hydrogenated in the presence of 5% Rhodium on alumina catalyst (25 mg) for 1 hour.

After the usual work up, the product (50 mg) isolated was identical in all respects with starting material.

(d) The above reaction was repeated using a 1:1 ratio of catalyst to ester (7; R = CH_3) (50 mg); the time of hydrogenation was extended to 16 hours.

Again, unchanged starting material (44 mg) was isolated.

(e) Lithium (50 mg) was added with stirring to dry ammonia (50 ml)

(distilled from sodium) cooled in an acetone - Drycold bath at -60°. The ester (7; R = CH_3) (44 mg) in T.H.F.: ether (1:1) was added to the resulting blue solution.[54] After 1½ hours, ammonium chloride (2 g) was added and the ammonia allowed to evaporate.

Chloroform and water were added. The organic layer was washed (H_2O, brine), dried and evaporated to yield an oil (28 mg) which proved to be a very complex mixture of products on T. L. C. examination.

Acidification of the basic layer followed by chloroform extraction and the usual washing procedures yielded another oil (8 mg) which also proved to be a mixture by T. L. C. examination in an acid solvent system.

The reaction was abandoned.

(f) The acid (7; R = H) (100 mg) was hydrogenated for 1 hour in methanol in the presence of 30% Pd - C catalyst (20 mg).

After Jones oxidation of the derived colourless oil (88 mg) (to reoxidise any products of over-reduction), T. L. C. examination showed one main product which appeared to have lost the enone absorption previously apparent on U.V. and I.R. examination.

The material was methylated (ethereal diazomethane) and purified by preparative T. L. C.

Two components were isolated. The lower band was shown to be G. L. C. pure and G.C. - M.S. examination showed the highest peak to have m/e 345 (parent not observable) ($C_{20}H_{24}O_6$ requires m/e 360). The upper band consisted of three components by G. L. C. examination: the

major component also had m/e 345 (no parent observable).

From the spectral data, it was concluded that hydrogenation appeared to have been accomplished. However, since the system was simply a model for the reduction of diketone (17) the identity of the products was not further pursued.

Methyl- 2 methoxy- 6,8 diketo- 10 βmethyl- 4b(α) H- gibba- A⇔ triene- 1 carboxylate (23)

(a) The unsaturated diketone (17) (25 mg) in glacial acetic acid (5 ml) was heated under reflux with stirring. To this solution was added zinc dust (500 mg) during 1 hour after which reflux was continued for a further 45 minutes.[55]

The cooled solution was filtered and the zinc dust washed with a little acetic acid. The combined acetic acid fractions were evaporated by azeotroping with benzene under reduced pressure to afford a yellowish oil which yielded a yellow solid on trituration with ether.

From T. L. C. and I.R. comparison, the main component was unreacted starting material.

(b) The above reaction was repeated extending the time of reflux to 16 hours. The yellow solid (24.5 mg) which was isolated proved to be mainly unreacted starting material.

(c) The diketone (17) (50 mg), dissolved in AnalaR methanol, was added

to 30% Pd - C (20 mg). The mixture was hydrogenated overnight and, as T. L. C. showed the presence of two components, the mixture was treated with Jones reagent to reoxidise any products of over reduction. The product (47 mg) from this treatment was homogeneous on T. L. C. examination.

G.C. - M.S. examination, however, showed five components to be present (in the approximate ratio 2:2:5:5:85). The molecular weight of the major component was shown to be 328 ($C_{19}H_{20}O_5$ requires 328).

Recrystallisation from ethyl acetate yielded (23) (42 mg), m. p. 236-236.5d. (sealed tube), as colourless microprisms. (Found: C, 69.59; H, 5.97. $C_{19}H_{20}O_5$ requires: C, 69.50; H, 6.14%).

$\nu_{CHCl_3}^{cm^{-1}}$: 1752.5 (s); 1733.5 (shoulder); 1721 (s).

λ_{max}^{nm} : 239 (ε , 3,500); 290 (ε , 3620); 335 (ε , 1890).

N. M. R. See Appendix

M. S. Parent ion m/e 328 ($C_{19}H_{20}O_5$ requires 328).
Other significant peaks: 297, 296, 286, 231 (Base Peak).

Attempted formation of the ditosylhydrazone of Methyl- 2 methoxy- 6,8 diketo- 10 βmethyl- 4b(α)H- gibba- A- triene- 1 carboxylate (23).

The saturated diketone (23) (10 mg) was refluxed for 20 hours in AnalaR methanol with p-toluene sulphonyl hydrazide (20 mg). Evaporation of the solvent and T. L. C. comparison showed that only unreacted starting material had been isolated.

Attempted formation of Methyl- 2 methoxy- 6,8 diketo- 10 β methyl- 4b(α)H gibba- A- triene- 1 carboxylate- 6,8 diethylene mercaptole (50).

The diketone (23) (10 mg), in methanol at 0°, was treated with ethane dithiol (2.5 μ l) and boron trifluoride etherate (0.1 ml)[18]. After 19 hours, the usual work-up afforded an oil (8.9 mg). However, this reaction was abandoned since G. L. C. examination showed the presence of at least nine products.

Methyl- 2 methoxy- 6,8 dihydroxy- 10 β methyl- 4b(α)H gibba- A- triene- 1 carboxylate (27).

To the diketone (23) (25 mg) in dioxan: water (10:1) was added excess sodium borohydride in portions with stirring. After 6 hours the mixture was acidified (pH6) by dropwise addition of dilute sulphuric acid. The acidified solution was poured into ammonium sulphate solution and the sulphate solution extracted with chloroform. The combined organic extracts were washed (brine), dried and evaporated to yield a mixture of diols (27) (25 mg) shown to be principally one component by T. L. C. examination.

Recrystallisation of this mixture from ethyl acetate-petrol yielded a colourless crystalline solid (20 mg), m. p. 168 - 168.5° (sealed tube). (Found: C, 68.90; H, 7.41. $C_{19}H_{24}O_5$ requires: C, 68.65; H, 7.28%).

$\nu^{cm^{-1}}_{CHCl_3}$: 3520; 3440; 1729 (s).

λ_{max}^{nm} : 235 (ε , 5,100); 288 (ε , 3,630).

N. M. R. : Complex spectrum which showed the expected features.

Benzylic methyl group (τ 8.9; J = 7 Hz); 2 methoxyl groups (τ 6.1; 6.2) and an aromatic AB quartet (2H: τ 2.95; 3.30; J = 8 Hz). The spectrum underwent a slight change on D_2O exchange.

M. S. Parent ion m/e 332 ($C_{19}H_{24}O_5$ requires 332).

Methyl- 2 methoxy- 6,8 dihydroxy- 10 βmethyl- 4b(α)H gibba-A- triene- 1 carboxylate- 6,8 sulphite ester (28).

To the diol (27) (12.5 mg) in chloroform at room temperature was added thionyl chloride (0.1 ml)[24] purified by distillation from linseed oil.[56]

After 30 minutes stirring, water was added and the layers separated. The aqueous layer was extracted with chloroform and the combined chloroform extracts washed (H_2O), dried and evaporated to yield a colourless crystalline solid (13.9 mg).

This compound was T. L. C. pure and was shown to contain sulphur by a sodium-fusion test. Recrystallisation from benzene-petrol yielded the sulphite ester (28) (9.0 mg) as colourless needles, m. p. 196 - 8°d. (sealed tube). (Found: C, 60.55; H, 5.82. $C_{19}H_{22}O_6S$ requires: C, 60.31; H, 5.86%).

$\nu_{CHCl_3}^{cm^{-1}}$: 1729 (s).

λ_{max}^{nm} : 230 (ε , 7,600); 288 (ε , 3,450).

N. M. R. Complex spectrum similar to that of diol (27) above but did not change on D_2O exchange.

M. S. Parent ion m/e 378 (Base Peak). ($C_{19}H_{22}O_6S$ requires 378). Other significant peaks at m/e 314; 253; 83.

Methyl- 2 methoxy- 6 keto- 8 acetoxy- 10 β methyl- 4b(α)H gibba- A- triene- 1 carboxylate (29).

The keto acetate (25; R = Ac) (50 mg) was hydrogenated overnight in methyl acetate in the presence of 30% Pd - C catalyst (50 mg).

The product isolated after filtration of the catalyst and removal of the solvent under reduced pressure was treated with Jones reagent. The usual work up yielded an off-white solid (50 mg) (pure by G. L. C. and T. L. C.). Recrystallisation from ethyl acetate-petrol afforded (29) as colourless needles, m. p. 229 - 230° (sealed tube). (Found: C, 67.85; H, 6.60. $C_{21}H_{24}O_6$ requires: C, 67.73; H, 6.50%.)

$\nu_{CHCl_3}^{cm^{-1}}$: 1735 (shoulder); 1720 (s); 1590 (m).

$\nu_{Nujol}^{cm^{-1}}$: 1735 (s); 1715 (s); 1600 (m).

λ_{max}^{nm} : 229 (ε , 6,150); 288 (ε , 2,260).

N. M. R. Similar to that of ketoacetate (25; R = Ac) but showed the disappearance of the olefinic absorption observed in that spectrum at

τ 3.77. See also Appendix.

M. S. Parent ion m/e 372 (Base Peak). ($C_{21}H_{24}O_6$ requires 372). Other significant peaks m/e 341; 340; 312.

Notes:

a) Methyl acetate was used in the hydrogenation of (25; R = Ac) since earlier experiments had shown that ester exchange on the catalyst took place in methanol solution to give approximately 10% of diketone (23) after Jones oxidation.

The correct product (29) was obtained when acetic acid was used as solvent but the product thus obtained was not as pure as that produced by reduction in methyl acetate solution.

b) G. L. C. examination showed that the 6-keto group was just as readily reduced as the 4b, 5 double bond.

Methyl- 2 methoxy- 6,8 diketo- 10 β methyl- 4b(α)H gibba- A- triene- (23) by the method of Bouchard and Engels.[25]

(a) Hydrogenation of the diketone (17) (10 mg) in the minimum amount of methanol in the presence of 1% Pd - $CaCO_3$ catalyst (8 mg) and potassium hydroxide (1.44 mg)[25] for four days yielded the saturated diol (27) and a small amount of unreacted starting material.

Jones oxidation of this diol (27) yielded the saturated diketone (23) identical in all respects to that derived from (29) by a combination of methanolysis and oxidation and to a sample of (23) produced by hydrogenation of (17) in the presence of 30% Pd - C.

G. L. C. data on diketone (23) derived by all of the above methods.

Column	T°C	Standard	R_x
(i) 1%QF-1	225	a	0.83
(ii) 1%SE-30	225	b	0.575
(iii) 1%OV-22	240	a	0.56
(iv) 1%OV-17	225	a	0.67

a. Standard was cholest-4-en-3-one. b. Standard was C_{28} alkane.

(b) Hydrogenation of diketone (17) (10 mg) in the minimum amount of methyl acetate as solvent for 4 days in the presence of 1% Pd - $CaCO_3$ catalyst (8 mg) and potassium hydroxide (1.44 mg)[25] yielded mainly unreacted starting material (from G. L. C. comparison). A minor component was tentatively identified as (25; R = H) by G. L. C. comparison with the authentic specimen prepared above.

Attempted formation of Methyl- 2 methoxy- 6 keto- 8 acetoxy- 10β methyl- gibba- A,4b- tetraene- 1 carboxylate - 6 ethylene mercaptole (51).

(a) To the unsaturated ketoacetate (25; R = Ac) (10 mg) in AnalaR dioxan was added ethane dithiol (0.5 ml) and freshly distilled boron trifluoride etherate (10 µl).

A bright green fluorescence was observed and the solution was kept

at 0^{o} for 16 hours.

At the end of this time, water and chloroform were added. The organic layer was washed ($1\bar{N}$ NaOH; brine), dried and evaporated to give a solid (7 mg).

G. L. C. comparison showed that the solid residue was in fact unreacted ketoacetate (25; R = Ac).

(b) The keto-acetate (25; R = Ac) (10 mg) in AnalaR acetic acid (5 ml) was treated with ethane dithiol (0.5 ml) and p-toluene sulphonic acid (1 mg).[53]

After standing overnight, the usual work up procedures afforded a solid (7.5 mg) shown by chromatographic comparison to be unreacted starting material.

(c) The ketoacetate (25; R = Ac)(10 mg) was added to ethane dithiol (5 ml) and to this mixture was added freshly distilled boron trifluoride etherate (0.5 ml).[28]

The mixture was stirred at room temperature for 3 hours by which time the solution had turned dark brown. After pouring into $1\bar{N}$ NaOH, the solution was extracted with chloroform. The combined chloroform extracts were washed ($1\bar{N}$ NaOH solution), dried and evaporated to yield a solid (5 mg) shown by the evidence of I.R., U.V. and T. L. C. comparison to be unreacted starting material.

(d) The ketoacetate (25; R = Ac) (5 mg) in ethane dithiol (0.25 ml)

was stirred overnight at room temperature.[28]

The usual work-up afforded only an evil smelling liquid thought to be polymeric sulphides.

(e) To the ketoacetate (25; R = Ac) (5 mg) in acetic acid (15 ml) was added ethane dithiol (0.25 ml) and freshly distilled boron trifluoride etherate (0.25 ml).[28] The solution was heated under reflux for one hour and then allowed to cool for 2 hours. At the end of this time the originally bright green fluorescent solution had turned dark red.

Again the only product isolated was a liquid thought to be polymeric sulphides.

Methyl- 2 methoxy- 6 keto- 8 acetoxy- 10 βmethyl- 4b(α)H gibba- A-triene- 1 carboxylate- 6 ethylene mercaptole (30).

(a) Ketoacetate (29) (10 mg) in dioxan was treated with ethane dithiol (0.5 ml) and freshly distilled boron trifluoride etherate (10μl).

The mixture was kept at 0° for 16 hours and then allowed to stand for 1 hour at room temperature.

To this solution, water and chloroform were added. The organic layer was washed with 1$\bar{N}$ NaOH to remove the ethane dithiol, then with brine, dried and evaporated to yield a solid (8 mg) shown to be unreacted ketoacetate (29) by G. L. C. comparison.

(b) The ketoacetate (29) (125 mg) in glacial acetic acid was treated

with ethane dithiol (2.5 ml) and freshly distilled boron trifluoride etherate (2.5 ml)[28] under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 hours.

After work-up, the desired thioketal (30) (65 mg) and unreacted ketoacetate (29) (50 mg) were isolated by preparative T. L. C. The thioketal was obtained as colourless prisms, m. p. 204.5 - 205.5, on recrystallisation from carbon tetrachloride-petrol. (Found: C, 61,85; H, 6.27. $C_{23}H_{28}O_5S_2$ requires: C, 61,60; H, 6.29%).

$\nu_{CHCl_3}^{cm^{-1}}$: 1730 (s).

$\nu_{Nujol}^{cm^{-1}}$: 1735 (s)

λ_{max}^{nm} : 229 (ε , 8,100); 286(ε , 2,850).

N. M. R. Similar to that of ketoacetate (29) but showed also the presence of a large complex multiplet at τ 6.5 - 7. (4 protons.)

M. S. Parent ion m/e 448 ($C_{23}H_{28}O_5S_2$ requires 448).

Other significant peaks: m/e 417; 287; 355 (Base Peak), 295 (Base Peak) 279; 237.

Later, it was demonstrated that, by altering the ratio of ethane dithiol:boron trifluoride etherate from 1:1 to 2:1 and by extending the time of reaction to 40 hours, the yield was raised to 90% and no unreacted starting material was isolated.

Methyl- 2 methoxy- 8 acetoxy- 10 βmethyl- 4b(α)H-gibba- A- triene- 1 carboxylate (31; R = Ac).

The thioketal (30) (149 mg) and a large excess of Raney nickel W - 2[29] were heated under reflux for 16 hours in methanol: dioxan (40 ml; 2.5:1) with stirring. The cooled solution was filtered and the residual Raney nickel washed with chloroform. The combined organic filtrates were washed (brine) dried and evaporated.

Preparative T. L. C. yielded the title compound (97 mg) as colourless prisms, m. p. 148 - 149°, on recrystallisation from carbon tetrachloride-petrol. (Found: C, 70.40; H, 7.34. $C_{21}H_{26}O_5$ requires: C, 70.37; H, 7.31%).

$\nu^{cm^{-1}}_{CCl_4}$: 1735 (s); 1590 (m); 1240 (m).

$\nu^{cm^{-1}}_{Nujol}$: 1730 (s); 1595 (m); 1245 (m).

λ^{nm}_{max} : 231 (ε , 6,500); 288 (ε , 2,950).

N. M. R.: The spectrum showed the usual features of an aromatic AB quartet τ 2.95; 3.27 (J = 8Hz) ; 2 methoxyl groups τ 6.13 (s); 6.22 (s) ; an acetate methyl group τ 8.20 (s) and a benzylic methyl group τ 8.89 (d); J = 7 Hz . The large complex multiplet (τ 6.5 - 7.0) attributable to the thioketal protons was missing. Also, as expected, the complexity of the methylene region had increased.

M. S. Parent ion m/e 358 (Base Peak) ($C_{21}H_{26}O_5$ requires 358). Other significant peaks: m/e 326; 298; 248; 239; 212; 149; 110.

Methyl- 2 methoxy- 10 βmethyl-4b(α)H gibba- A- triene- 1 carboxylate (26).

The thioketal (30) (10 mg) was heated under reflux for 16 hours in methanol-dioxan (2:5:1) with stirring in the presence of a large excess of freshly prepared Raney nickel W - 2.[29]

After the usual work up, two products in the ratio 3:1 were isolated by preparative T. L. C.

The minor component (1.45 mg) was shown to be the acetate (31; R = H) by direct comparison. The major product (4.5 mg) was assigned structure (26) on the basis of spectral and chromatographic evidence.

$\nu_{CCl_4}^{cm^{-1}}$: 1740 (s); 1255 (s).

N. M. R. (60 MHz) : Aromatic AB quartet τ 2.40; 3.10 (J = 8 Hz) ; 2 methoxyl groups τ 6.11 (s); 6.13 (s) ; benzylic methyl group τ 8.8 (d); J = 7 Hz .

M. S. Parent ion m/e 300 (Base Peak). ($C_{19}H_{24}O_3$ requires 300).

Methyl- 2 methoxy- 3 Chloro- 8 keto- 10 β methyl- 4b(α)H gibba- A-triene- 1 carboxylate (33)

The thioketal (30) (1.45g) was refluxed overnight with stirring in methanol:dioxan (150ml ; 2.5:1) in the presence of a large excess of Raney nickel W - 2[29]. After the usual work up, an off-white solid (1 g) was isolated. This solid was homogeneous on T. L. C. but G. L. C. examination revealed the presence of seven components (50:15:15:15:1:1:2).

Reduction and methanolysis followed by Jones oxidation as detailed

below afforded an off-white solid (510 mg) after preparative T. L. C. This was shown by G. L. C. to consist of two components (2.1:1). Fractional crystallisation followed by preparative T. L. C. of the mother liquors (10 x 10% EtOAc) yielded pure samples of the two components.

These were shown to be the ketone (32) (302 mg) (see below) and the chlorine containing compound (33) (136.5 mg). Recrystallisation from ethyl acetate-petrol afforded colourless prisms, m. p. 149 - 151°. (Found: C, 64.50; H, 5.91. $C_{19}H_{21}O_4Cl$ requires: C, 65.25; H, 6.05%).

$\nu_{CCl_4}^{cm^{-1}}$: 1740 (s); 1735 (shoulder).

$\nu_{Nujol}^{cm^{-1}}$: 1740 (s); 1720 (s).

λ_{max}^{nm} : 228 (ε , 10,800); 285 (ε , 4,050)

N. M. R. : Exactly the same as that of ketone (32) except that aromatic AB quartet has been replaced by 1 proton singlet (τ 2.92).

M. S. Two isotopic parent ions m/e. 348 and 350 (ratio 3:1) ($C_{19}H_{21}O_4{}^{35}Cl$ requires 348 and $C_{19}H_{21}O_4{}^{37}Cl$ requires 350 in ratio 3:1).

Methyl- 2 methoxy- 8 keto- 10 βmethyl- 4b(α)H gibba-A- triene- 1 carboxylate (32).

(a) The chloroketone (10 mg) in methanol was hydrogenated for 16 hours in the presence of 30% Pd - C (10 mg). After the usual work up followed by Jones oxidation to reoxidise any products of over-reduction, the product was shown to be identical with a sample of the ketone (32) prepared below by chromatographic comparison.

(b) The above hydrogenation was repeated using 10% Pd - C (10 mg) catalyst and a molar equivalent of triethylamine[33] in methanol as solvent.

G. L. C. examination of the material isolated from this reaction showed that, although hydrogenolysis was incomplete, the product was a mixture of ketone (32) and its chlorine containing analogue (33).

(c) The acetate (31; R = Ac) (55 mg) was refluxed for 16 hours in methanol: dioxan (35 ml; 6:1) containing dilute hydrochloric acid (2 ml).

At the end of this time the cooled solution was poured into chloroform, washed (brine) dried and evaporated to yield a colourless oil (47 mg) shown to be homogeneous by T. L. C. examination.

$\nu_{CCl_4}^{cm^{-1}}$: 3630; 3580; 1740.

This product was treated with Jones reagent at 0°. Preparative T. L. C. of the material isolated from this oxidation yielded ketone (32) as an off-white powder (27.6 mg).

An analytical sample recrystallised from benzene-petrol afforded colourless prisms, m. p. 173.5 - 175° (Found: C, 72.75; H, 7.12. $C_{19}H_{22}O_4$ requires: C, 72.79; H, 7.05%)

$\nu_{CCl_4}^{cm^{-1}}$: 1746; 1735 (shoulder).

$\nu_{Nujol}^{cm^{-1}}$: 1740; 1721

λ_{max}^{nm} : 232 (ε , 7,550); 294.5 (ε , 3,450).

N. M. R. The spectrum, while being very similar to that of acetate (31; R = Ac), showed the loss of an acetate methyl group and the proton α to the acetoxyl residue.

M. S. Parent ion m/e 314 (Base Peak). ($C_{19}H_{22}O_4$ requires 314).
Other significant peaks: m/e 282; 239; 212; 199; 141; 115; 106; 99.

Methyl- 2 methoxy- 8 methylene- 10 β methyl- 4b(α)H gibba- A- triene- 1 carboxylate (34; R = CH_3).

(a) The keto ester (32) (10 mg) together with methylene iodide (10 mg) in dry ether was added dropwise to magnesium amalgam[37] [prepared by stirring magnesium (20 mg) with mercury (5 g) for 4 hours].

The mixture was stirred under nitrogen for 2 hours then refluxed for 30 minutes. The cooled ethereal solution was decanted from the magnesium and washed (10% H_2SO_4). The sulphuric acid washings were extracted with ether and the combined organic extracts were washed (brine), dried and evaporated. T. L. C. and I.R. examination of the residue showed principally starting material and a little unidentified material which did not exhibit exomethylene absorption.

(b) The above reaction was repeated using ketone (32) (10 mg) methylene iodide (10 mg), magnesium (1.5 mg) and mercury (14 g). After stirring for 1 hour, the mixture was heated under reflux for 2 hours.

Again, the only identifiable product isolated after work-up proved to be the ketone (32).

(c) The ketone (10 mg) and methylene iodide (10 mg) were added as detailed above to magnesium amalgam prepared from magnesium (1.2 g) and mercury (40 g) . After stirring for 4 hours and refluxing for 2 hours under nitrogen, the usual-work up afforded 7 products on T. L. C. examination. No exomethylene absorption was detected on I.R. examination.

(d) To triphenyl methyl phosphonium bromide (6.27 mg), suspended in ether under nitrogen, was added an excess of n - butyl lithium[38]. The mixture was stirred overnight and then filtered through a glass plug into a solution of the ketone (32) (5 mg) in dry ether under nitrogen.

The resulting solution was stirred for 16 hours under nitrogen at room temperature. The ether was replaced by dry T. H. F. and this solution was refluxed for 2 hours, still under nitrogen.

Removal of the solvent and examination by T. L. C. showed only starting material to be present.

(e) Methylene triphenyl phosphorane, prepared as before except that excess triphenyl methyl phosphonium bromide was used rather than excess n - butyl lithium, was added through a glass-wool plug to an ethereal solution of the ketone (32) (1.4 mg) under nitrogen.

The yellow reaction mixture was stirred for 72 hours in a nitrogen atmosphere at room temperature and then the ether was replaced by dry T. H. F. The resulting yellow solution was refluxed for 16 hours under nitrogen.

The solvent was removed under reduced pressure and the ether soluble fraction of the residue examined by I.R. No trace of exomethylene absorption was observed.

After partitioning the ether insoluble fraction between water and chloroform, the chloroform extract was examined by I.R. Again, the spectrum showed no trace of exomethylene absorption.

The aqueous layer was acidified and extracted with chloroform. After drying and evaporating the organic solvent, the residue was examined. Once again, the I.R. spectrum showed no exomethylene absorption.

No starting material was recovered.

(f) To a suspension of triphenyl methyl phosphonium bromide (400 mg; 4:1 molar excess) stirring under nitrogen in dry ether (10 ml) was added a 0.8 $\bar{M}$ tertiary butanolic solution of potassium tertiary butoxide (1.6 ml). The mixture was stirred at room temperature for 30 minutes.

The ketone (32) (87.4 mg) in the minimum volume of dry benzene was added to the resulting yellow suspension. The solution was stirred for 16 hours in a nitrogen atmosphere.[40]

At the end of this time, water was added and the layers separated. The aqueous layer was washed with ether:pentane (1:1) and the combined organic extracts washed (water), dried and evaporated. Preparative T. L. C. afforded the title compound (77.2 mg).

Recrystallisation from pentane at -10° yielded clusters of colourless needles, m. p. 128 - 9°. (Found: C, 77.11, 76.80; H, 7.94, 7.78.

$C_{20}H_{24}O_3$ requires: C, 76.89; H, 7.74%).

$\nu^{cm^{-1}}_{CCl_4}$: 1720; 1595; 1280; 880.

$\nu^{cm^{-1}}_{Nujol}$: 1732; 1250; 878

λ^{nm}_{max} : 232 (ε , 6,000); 289 (ε , 2,500).

N M. R. See Appendix.

M. S. Parent ion m/e 312 (Base Peak). ($C_{20}H_{24}O_3$ requires 312)

Other significant peaks: m/e 281; 280; 212; 165; 141; 128; 115.

1 Carboxy- 2 methoxy- 8 keto- 10 β methyl- 4b(α)H-gibba- A- triene (35).

The keto ester (32) (32 mg) was refluxed in 1$\bar{N}$ NaOH (10 ml) containing dioxan (3 ml) for 16 hours. After washing the cooled solution with ethyl acetate, the aqueous solution was acidified (HCl) and extracted thoroughly with ethyl acetate. The organic extracts, after the usual washing and drying procedures, were evaporated to yield the keto-acid (35) (23 mg) as an off-white powder on recrystallisation from ethyl acetate-petrol.

An analytical sample, recrystallised from ethyl acetate, had m. p. 271 - 2° (colourless microprisms) (Found: C, 72.00; H, 6.60. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%).

$\nu^{cm^{-1}}_{Disc}$: 3300 - 2800; 1730; 1710.

λ^{nm}_{max} : 230 (ε , 7,100); 285 (ε , 2,500).

N. M. R. See Appendix.

Attempted preparation of 1 Carboxy- 2 methoxy- 8 methylene- 10 β methyl- 4b(α)H gibba- A- triene. (34; R=H).

(a) The keto acid (35) (3.4 mg) was reacted with triphenyl methylene phosphorane as described above for the preparation of the exomethylene compound (34; R = CH_3). During the course of the reaction, the stirred mixture turned colourless.

After the usual work up, only starting material (2.9 mg) was isolated.

(b) The ester (34; R = CH_3) (5 mg) was refluxed overnight in $2\bar{N}$ NaOH: dioxan (15 ml; 2:1). Normal acid-base separation procedures yielded a neutral compound (3.6 mg) identified by I.R. and T. L. C. comparison as starting material.

Other hydrolytic techniques attempted unsuccessfully were:

(c) $1\bar{N}$ NaOH/dioxan

(d) $2\bar{N}$ NaOH/methanol

(e) conc. H_2SO_4/ water[43]

(f) LiI/collidine[41]

(g) LiI/dimethyl formamide[42]

(h) 6N HCl/ t -BuOH

(i) The ester (34; R = CH_3) (6 mg) in dry ether (7 ml) was treated with $LiAlH_4$ (10 mg). After 4 hours stirring, saturated sodium sulphate solution was added to destroy the excess hydride. The solution was

dried and evaporated to yield the alcohol (33) (5.5 mg) as a colourless oil.

$\nu_{CCl_4}^{cm^{-1}}$: 3600; 1255; 1030; 875.

N. M. R. : The spectrum was very similar to that of the starting material but showed the appearance of a two proton singlet (τ 5.18) and the loss of the ester methoxyl group.

M. S. Parent ion m/e 284 ($C_{19}H_{24}O_2$ requires 284).

This alcohol (33) was treated with Jones reagent at 0°. After the usual work up, the only product isolated proved to be a neutral compound assigned the aldehyde structure (52) (2.8 mg after preparative T. L. C.).

$\nu_{CCl_4}^{cm^{-1}}$: 1700; 880.

Oxidation of this aldehyde (52) using silver oxide, sodium cyanide and methanol[57] proved unsuccessful. Only starting aldehyde was isolated after 4 days stirring at room temperature.

A further attempt at oxidation of this aldehyde was made using zinc permanganate in acetone at 0° as described by Cornforth.[44]

T. L. C. examination of the acidic fraction isolated after work up revealed the presence of five components.

No starting material was isolated and the reaction was not further pursued.

(1 Carbomethoxy- 2 methoxy- 3 chloro- 7 β hydroxy- 9 β methyl- fluorenyl) 4 β acetic acid lactone (39).

To a solution of hydrogen peroxide (90%: 20 µl) in ice cold methylene chloride (dried by distillation from P_2O_5) was added trifluoroacetic anhydride (230 µl) with swirling.

This solution was added slowly to an ice-cold solution of ketone. (33) (14 mg) in dry methylene chloride. The resulting solution was heated under reflux for 16 hours. The cooled solution was washed (brine; saturated $NaHCO_3$ solution; brine), dried and evaporated. The lactone (39) (8.4 mg), homogeneous by G. L. C., was isolated by preparative T. L. C. Recrystallisation from ether-petrol afforded a colourless microcrystalline solid, m. p. 156 - 159°.

$\nu_{CCl_4}^{cm^{-1}}$: 1740; 1735 (shoulder).

N. M. R. : The spectrum was very similar to that of the chloroketone (33) but showed an additional 1 proton multiplet at τ 5.19.

M. S. Two parent ions were observed at m/e 364 and 366 in the ratio 3:1. ($C_{19}H_{21}O_5{}^{35}Cl$ requires 364 and $C_{19}H_{21}O_5{}^{37}Cl$ requires 366 in the ratio 3:1).

Chromatographic properties of hydrofluorene derivatives

(OVER....)

I. T. L. C. Rf Values

COMPOUND	SOLVENT	Rf
3(R=CH_3)	50%	0.5
7(R=H)	A[b]	0.5
17	75%	0.6
23	75%	0.8
25(R=Ac)	75%	0.55
26	30%	0.75
27	75%	0.2
28	50%	0.9
29	50%	0.5
30	50%	0.75
31(R=Ac)	30%	0.45
32	25%	0.37
33	25%	0.40
34	10%	0.5
35	A	0.5
39	40%	0.4

(a) Percentage refers to ethyl acetate in 40 - 60 petrol.

(b) A refers to a benzene:dioxan:acetic acid solvent system in the ratio 90:25:4.

II. G. L. C. Rx Values.

COMPOUND	Rx [a]	Rx [b]
3(R=CH_3)	0.155[c]	0.135[c]
7(R=CH_3)	0.92	1.09
17	1.12	2.4
23	0.56	0.92
25(R=Ac)	1.31	1.66
26	0.24	-
27	-	0.7
29	0.83	0.82
31(R=Ac)	0.57	0.32
32	0.41	0.32
33	0.54	0.48
34	0.193[c]	0.066[c]

(a) Rx values refer to 1% SE - 30 column using n - C_{28} alkane as standard. All temperatures 225° except where stated.

(b) Rx values refer to 1% QF -1 column using cholest-4-en-3-one as standard. All temperatures 225° except where stated.

(c) Temperature of column = 200°.

Attempted bromination of Dimethyl Terracinoate methyl ether (3; R = CH_3).

Dimethyl terracinoate methyl ether (3; R = CH_3) (25 mg) was stirred at room temperature for 48 hours in dry carbon tetrachloride containing freshly recrystallised N-bromo-succinimide (15 mg) and benzoyl peroxide[45,46] (1.5 mg). At the end of this time, the solution was filtered and evaporated. T. L. C. examination showed that only starting material was present.

Sodium borohydride reduction of dimethyl terracinoate methyl ether (3; R = CH_3)

The keto diester (3; R = CH_3) (50 mg) in AnalaR methanol was stirred overnight at room temperature in the presence of excess sodium borohydride.

At the end of this time, the pH was adjusted to 7 by the dropwise addition of dilute sulphuric acid. The solution was then poured into saturated ammonium sulphate solution and this aqueous solution was extracted with ether. The organic extracts were washed (brine), dried and evaporated to yield a colourless oil (467 mg).

Three products were isolated by preparative T. L. C. (Rf 0.75; 0.55; 0.4 after 2 runs in 50% EtOAc - 40-60 petrol).

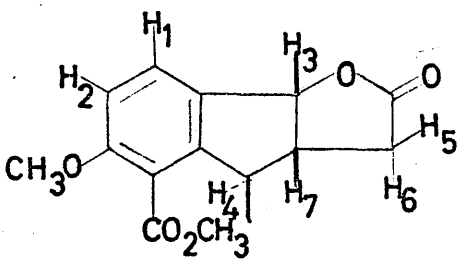
The least polar component was identified as the expected (1α hydroxy-3 β methyl- 4 carbomethoxy- 5 methoxy indanyl) 2 α acetic acid lactone (40) (146.7 mg) obtained as colourless needles, m. p. 96.5 - 97.5°, on recrystallisation from ethyl acetate-petrol. (Found: C, 65.22; H, 5.94.

$C_{15}H_{16}O_5$ requires: C, 65.21; H, 5.84%).

$\nu_{CHCl_3}^{cm^{-1}}$: 1775; 1728; 1595.

λ_{max}^{nm} : 233 (ε , 5,500); 288 (ε , 2940).

N. M. R. (60 MHz):



	τ		JHz
H_1	2,45)		
		) AB quartet	8
H_2	3.05)		
H_3	4.05 (d)		6
H_4	6.55 (m)		-
$H_{5,6,7}$	6.95 - 7.8 (3H, complex)		
- OMe groups	6.08 (s)		-
	6.1 (s)		-
$-CH_3$ group	8.75		7

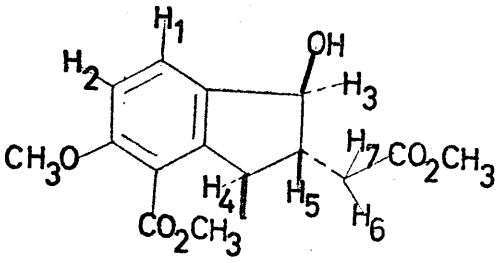
The major component (Rf. 0.55) (196.7 mg) was identified as Methyl (1β hydroxy- 3 β methyl- 4 carbomethoxy- 5 methoxy indanyl) 2α acetate (41), m. p. 76° (colourless prisms from ethyl acetate-petrol). (Found: C, 62.35; H, 6.63. $C_{16}H_{20}O_6$ requires: C, 62.32; H, 6.54%).

$\nu_{CHCl_3}^{cm^{-1}}$: 3590; 3510; 1725.

λ_{max}^{nm} ; 230 (ε , 6,150); 287.5 (ε , 3,340).

N. M. R. (60 MHz):

	τ		JHz
H_1	2.6)		
		) AB quartet	8
H_2	3.15)		



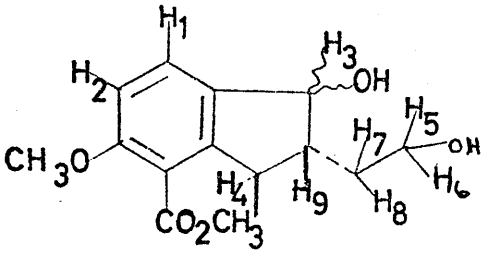
	τ	JHz
H_3	5.15 (d)	7
-OH	6.7 (s) (disappears on D_2O exchange).	
$H_{4,5,6,7}$	6.95 - 8 (complex)	
Aromatic -OMe groups	6.12 (s) 6.2 (s)	
Aliphatic -CMe group	6.3 (s)	
$-CH_3$ group	8.8(d)	7

The minor product (Rf 0.4) isolated proved to be a mixture of the epimeric diols, 1 Hydroxy-2α-(2-hydroxy ethyl)- 3β-methyl- 4 carbomethoxy- 5 methoxy indane (42), obtained as colourless prisms (60 mg), m. p. 105 - 8°, from ethyl acetate-petrol (Found: C, 64.29; H, 7.23. $C_{15}H_{20}O_5$ requires: C, 64.27; H, 7.19%).

$\nu^{cm^{-1}}_{Nujol}$: 3400 (broad); 1720.

λ^{nm}_{max} : 236 (ε , 6,700); 287(ε , 2,950).

N, M. R. (60 MHz) :



	τ	JHz
H_1	2.6)	
	) AB quartet	8
H_2	3.15)	
H_3	4.9 (m)	
	5.1 (m) 2 epimers	-
2 - OH	7.3 (broad) (disappear on D_2O exchange)	-

	τ	JHz
H_4) H_5) H_6)	Hidden under aromatic methoxyl absorption	-
H_7) H_8) H_9)	7.9 - 8.4 (complex)	-
- OMe groups	6.1 (s)	
	6.2 (s)	-
- CH_3 group	8.80 (d)	7
	8.84 (d)	7
	(2 epimers)	

Reaction of Lactone (40) with N - Bromosuccinimide.

The lactone (40) (25 mg) was stirred for 16 hours in dry carbon tetrachloride with freshly crystallised N-bromosuccinimide (16.1 mg) and benzoyl peroxide (1.5 mg). The solution was then refluxed for thirty minutes[45,46] during which time the cloudiness which had been apparent vanished.

After the usual work up, T. L. C. examination of the residue showed the presence of seven components. The reaction was not investigated further.

Reaction of Diol (42) with N-bromosuccinimide.

The mixture of epimeric diols (42) (10 mg) was reacted with

N-bromosuccinimide (6 mg) and benzoyl peroxide (1 mg) in an exactly analogous fashion to that described above for lactone (40).

Examination of the residue isolated showed the presence of five components. The reaction was not investigated further.

Reaction of Alcohol (41) with N-bromosuccinimide.

The alcohol (41) (25 mg), N-bromosuccinimide (14.5 mg) and benzoyl peroxide (1.5 mg) were stirred at room temperature in carbon tetrachloride.

After 2 hours the solution turned light brown. This colour disappeared after a further hour.

T. L. C. examination of the residue isolated by filtration and evaporation showed the presence of four products. No attempt was made to identify the products and the reaction was abandoned.

Methyl-2methoxy- 5 bromo- 6,8 diketo- 10 β methyl-gibba-A,4b- tetraene- 1 carboxylate (43).

The unsaturated diketone (17) (10 mg) was stirred for 24 hours at room temperature in chloroform containing freshly recrystallised N-bromosuccinimide (6.0 mg).

Evaporation of the solvent and preparative T. L. C. of the residue yielded a yellow microcrystalline solid (8.0 mg), m.p. 208 - 210° (benzene-petrol).

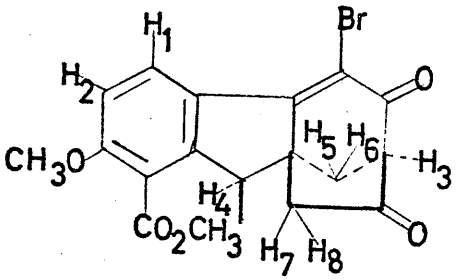
This compound was shown to contain halogen by a Bielstein test

and a sodium fusion test. It was identified as the brominated diketone (43) by spectral evidence.

$\nu_{Nujol}^{cm^{-1}}$: 1755; 1718; 1675; 1603; 1575.

λ_{max}^{nm} : 253; 313 (shoulder); 349.

N. M. R.



	τ	JHz
H_1	1.3)	
	) AB quartet	8
H_2	2.94)	
H_3	6.2 (q)	3,3
H_4	6.42 (q)	7
H_5	6.56 (q)	16,3
H_6	6.88 (q)	16,3
$H_{7,8}$	6.3 (2 overlapping doublets)	17
2-OMe groups	6.4 (s) (2 superimposed singlets)	
$-CH_3$ group	8.7 (d)	7

M. S. Two parent ions of equal intensity at m/e 404, 406 ($C_{19}H_{17}O_5{}^{79}Br$ requires 404; $C_{19}H_{17}O_5{}^{81}Br$ requires 406.

As expected [48], the reaction gave the same product under slightly different conditions.

The conditions employed were:

(i) N. B. S., benzoyl peroxide, $CHCl_3$

(ii) N. B. S., EtOH

(iii) N. B. S., CH_2Cl_2

(iv) N. B. S., benzoyl peroxide, CH_2Cl_2.

Treatment with excess N-bromosuccinimide did not effect further reaction.

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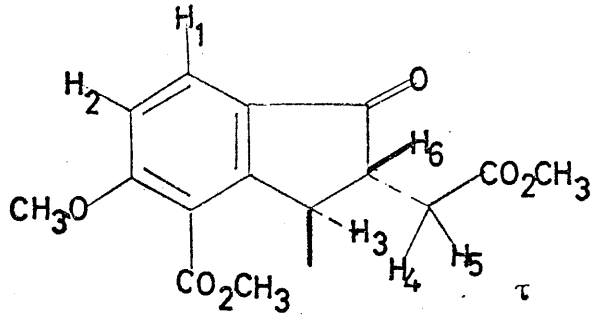
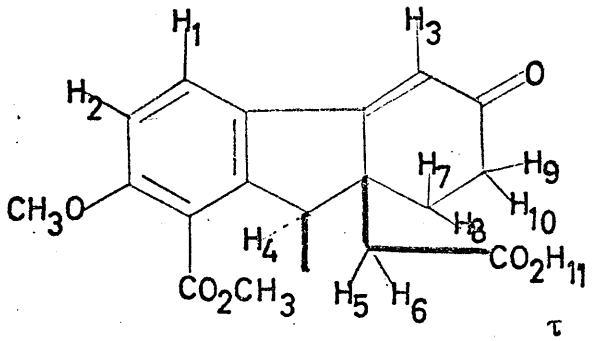
APPENDIX

1. Dimethyl terracinonate methyl ether (3: R = CH_3)



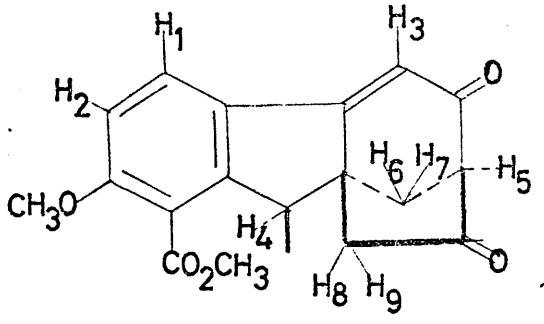
	τ	J Hz
H_1	2.23)	
	) AB quartet	8
H_2	3.04)	
H_3	6.65 (octet)	2,7
H_4)		
)		
H_5)	7.0 - 7.45	
)		
H_6)	(complex multiplet; 3H)	-
Aromatic - OCH_3 groups	6.09 (s) (6H)	
Aliphatic - OCH_3 group	6.32 (s) (3H)	
CH_3 - group	8.63 (d)	7

2. (1, 2, 3, 9a Tetrahydro - 7 methoxy - 8 methoxycarbonyl - 9 β Methyl 3 keto - 9a (β) fluorenyl) acetic acid (7; R = H).



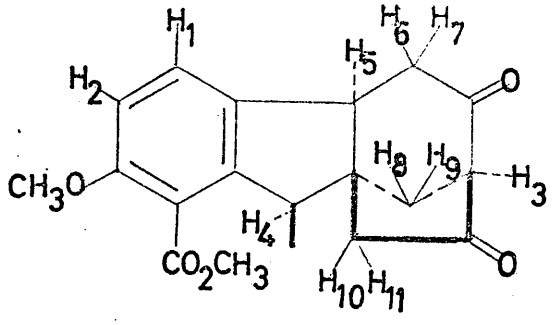
	τ	JH_z
H_1	2.44)	
	) AB quartet	8
H_2	3.13)	
H_3	3.60 (s)	-
H_4	6.85 (q)	7
H_5)		
)	7.6 (2H; s)	-
H_6)		
$H_{7,8,9,10}$	Complex multiplet 7.1 - 8.0 (4H)	
H_{11}	4.48 (broad singlet) Disappears on D_2O exchange.	-
$-OCH_3$ groups	6.11 (s)	
	6.16 (s)	
CH_3OH	6.55 (3H; s) (disappears on D_2O exchange).	
CH_3 - group	8.68 (d)	7

3. Methyl - 2 methoxy - 6,8 diketo - 10 β methyl - gibba - A,4b - tetraene - 1 carboxylate (17).



		τ	JHz
H_1		2.46)	
		) AB quartet	8
H_2		3.04)	
H_3		3.93 (s)	-
H_4		6.47 (q)	7
	(collapses on irradiation at benzylic methyl group)		
H_5		6.43 (t)	<2
	(collapses on irradiation at $H_{6,7}$).		
H_6)			
)	accidentally equivalent	7.49 (t)	<2
H_7)			
	(collapses on irradiation at H_5).		
H_8		7.59)	
		) AB quartet	16
H_9		7.89)	
$-OCH_3$ groups		6.06 (s)	-
		6.09 (s)	-
CH_3 - group		8.76 (d)	7
	(collapses on irradiation at H_4).		

4. Methyl - 2 methoxy - 6,8 diketo - 10 β methyl - 4b(α)H - gibba - A - triene - 1 - carboxylate (23)



(a)	τ	JHz
H_1	2.94)	
	) AB quartet	8
H_2	3.20)	
H_3	ca. 6.14 (obscured by methoxyl signals)	
$H_{4,5,6,7}$	6.6 - 7.2 (complex absorption)	
$H_{8,9,10,11}$	7.4 - 8.1 (complex absorption)	
$-OCH_3$ groups	6.09 (s)	
	6.18 (s)	
CH_3 - group	8.75 (d)	7

(b) Solvent: deuterobenzene.

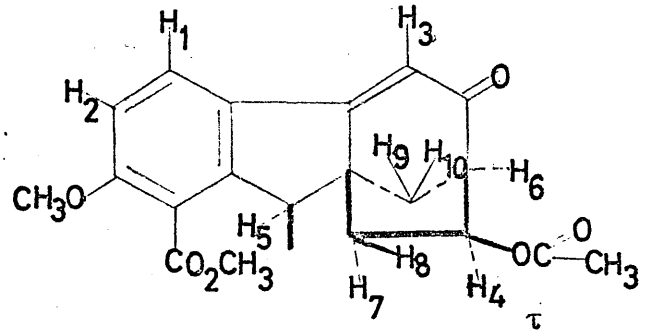
H_1	3.49)	
	) AB quartet	8
H_2	3.67)	
H_3	6.83 (broad s.)	3

Affected by irradiation on -

$H_{8,9}$ - removes small coupling

	τ	JHz
H_4	7.37 (q)	7
Affected by irradiation on benzylic Methyl group - collapses to singlet.		
H_5	7.44 (m) (X part of ABX)	
Affected by irradiation on $H_{6,7}$ - collapses to singlet.		
$H_{6,7}$	ca. 8.24 (m) (AB part of ABX)	
Affected by irradiation on H_5 - removes coupling leaving a quartet.		
$H_{8,9}$	8.54 (d)	3
Affected by irradiation on H_3 - collapses to singlet		
$H_{10,11}$	8.34 (s) (accidentally equivalent)	
$-OCH_3$ groups	6.39 (s)	-
	6.71 (s)	-
CH_3 - group	9.10	7
Affected by irradiation on H_4 - collapses to singlet.		

5. Methyl - 2 methoxy - 6 keto - 8 acetoxy - 10 β methyl gibba - A,4b - tetraene - 1 carboxylate (25; R = Ac)



	τ		JHz
H_1	2.32)		
	)	AB quartet	8.5
H_2	3.00)		
H_3	3.77 (d)		1

(Long range coupling. Collapses on irradiation at H_6)

H_4 ca. 3.40 (octet)

Affected by irradiation on:

H_6 - goes to double doublet	4,10
H_7 - very slight change	4,6
H_8 - goes to double doublet	6,10

H_5 6.55 (q) 7

H_6 ca. 6.60 (multiplet)

Affected by irradiation on

H_4 - removes coupling	ca. 6 Hz
H_9 - very little change	
H_{10} - removes large coupling	

H_7 ca. 7.55 (d.d.)

Affected by irradiation on

H_4 - removes coupling of	10 Hz
H_8 - removes geminal coupling of	15 Hz

	τ	JHz
H_8	ca. 8.55 (complex)	

Affected by irradiation on

H_4 - collapses to broad doublet 15 Hz (J_{7-8})

H_7 - collapses to broad doublet (partially hidden by methyl doublet).

H_{10} - sharpens to quartet. i.e. Removes long range coupling of 2 Hz

H_9	ca. 7.5 (m)	

Affected by irradiation on

H_6 - removes small coupling

H_{10} - removes geminal coupling

H_{10}	ca. 8.0 (m)	

(Partially hidden by acetate methyl group)

Affected by irradiation on

H_6 - removes small coupling

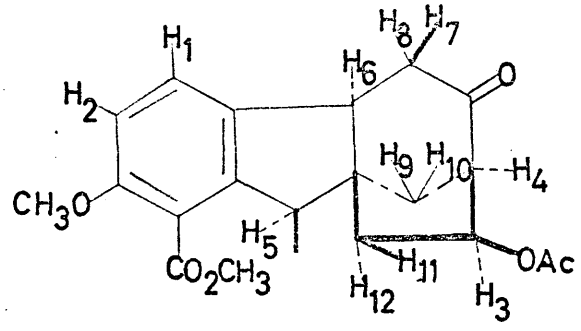
H_8 - removes long range coupling

No irradiation at H_9.

$-OCH_3$ groups	6.06 (s)	
	6.08 (s)	
CH_3CO_2- group	8.02 (s)	-
$-CH_3$ - group	8.76 (d)	7

collapses on irradiation at H_5.

6. Methyl - 2 methoxy - 6 keto - 8 acetoxy - 10 β methyl - 4b(α)H-gibba A - triene - 1 - carboxylate (29).



(a)	τ	JHz
H_1	2.89)	
	) AB quartet	8
H_2	3.18)	
H_3	4.70 (m)	
H_4	ca. 6.1 (m) (obscured by methoxyl signals)	
$H_{5,6,7,8}$	6.7 - 7.4 (complex absorption)	
$H_{9,10,11}$	7.7 - 8.1 (complex absorption)	
H_{12}	ca. 8.8 (m) (obscured by methyl group signals).	
$-OCH_3$ groups	6.06 (s)	
	6.16 (s)	
CH_3 - group	8.75 (d)	7

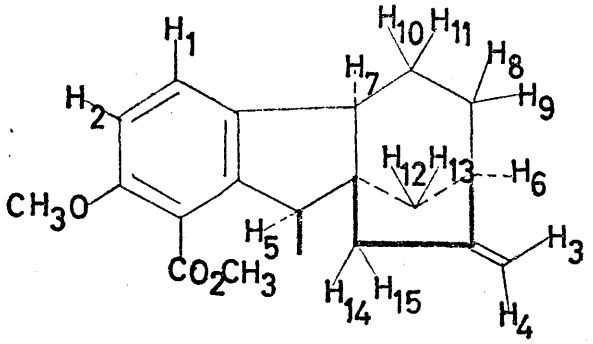
(b) Solvent: Deuterobenzene.

H_1	3.32)	
	) AB quartet	8
H_2	3.64)	
H_3	5.00 (m) (X part of AMX)	

	τ	JHz
	Affected by irradiation on	
	H_4 - removes large coupling	
	H_{11} - removes small coupling	
	H_{12} - removes large coupling	
H_4	7.01 (m)	
	Affected by irradiation on	
	H_3 - removes coupling ca. 9 Hz	
	$H_{9,10}$ - collapses to doublet	
H_5	7.28 (q)	7
	Affected by irradiation on	
	Benzylic methyl group - collapses to singlet.	
H_6	ca. 7.3 (m) (A part of ABX)	
	Affected by irradiation on	
	H_8 - removes small coupling	
H_7	ca. 7.3 (m) (B part of ABX)	
	Affected by irradiation on	
	H_8 - removes large coupling	
H_8	8.20 (m) (X part of ABX)	
$H_{9,10}$	8.70 (d)	3
	Affected by irradiation on	
	H_4 - collapses to broad singlet	
H_{11}	8.1 (m) (A part of AMX)	
	Affected by irradiation on	
	H_3 - removes small coupling leaving doublet with J = 16 Hz	
	H_{12} - removes coupling.	

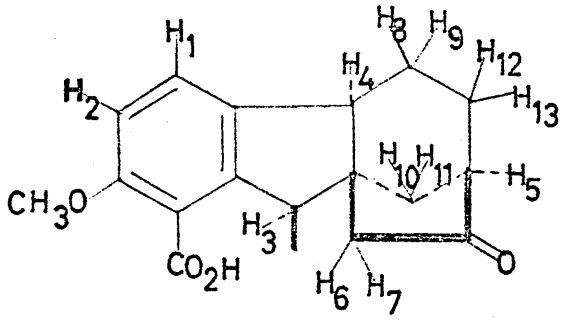
	τ	JHz
H_{12}	8.89 (m) (M part of AMX)	
Affected by irradiation on		
H_3 - removes large coupling		
H_{11} - removes geminal coupling		
$-OCH_3$ groups	6.39 (s)	
	6.72 (s)	
CH_3 CO_2 - group	8.49 (s)	
CH_3 group	8.99 (d)	7

7. Methyl - 2 methoxy - 8 methylene - 10 β methyl - 4b(α)H -gibba - A - triene - 1 carboxylate (34; R = CH_3).



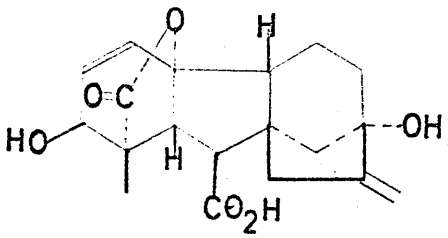
	τ	JHz
H_1	3.05)	
	) AB quartet	8
H_2	3.29)	
H_3)		
)	5.33 (broad d.)	13
H_4)		
H_5	6.95 (q)	6
$H_{6,7}$	ca. 7.3 (complex multiplets)	-
H_{8-15}	7.8 - 8.8 (complex absorption)	
$-OCH_3$ groups	6.17 (s)	-
	6.26 (s)	-
CH_3 - group	8.90 (d)	6

8. 1 Carboxy - 2 methoxy - 3 keto - 10 β methyl - 4b(α)H - gibba - A triene (35).



Solvent: Deuteropyridine.

	τ	JHz
H_1	2.97)	
	) AB quartet	8
H_2	3.20)	
H_3	6.85 (q)	7
H_4	7.3 (m) (X part of ABX)	
H_5	ca. 7.5 (m)	
H_{6-13}	Complex multiplet ca.	7.8 - 8.6
$-OCH_3$ group	6.33 (s)	-
CH_3 - group	8.55 (d)	7



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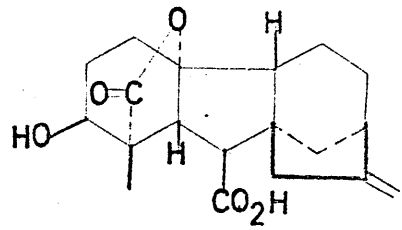

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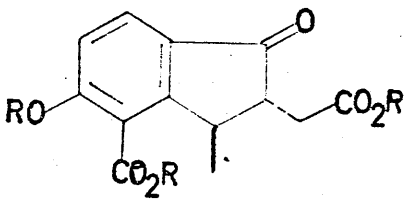

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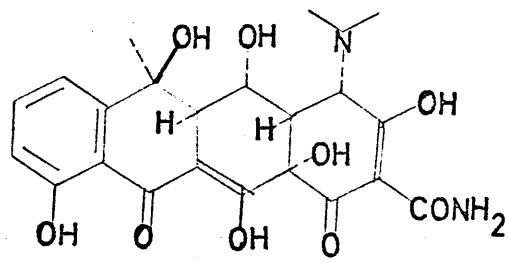

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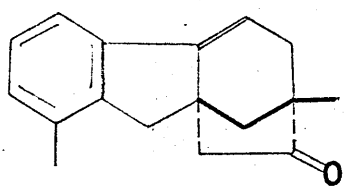

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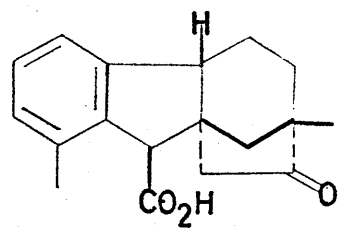

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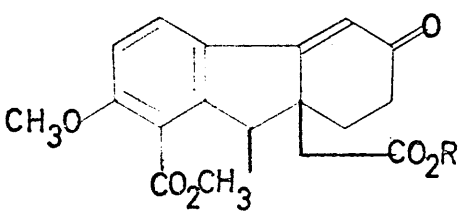

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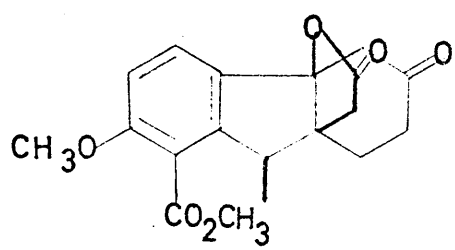

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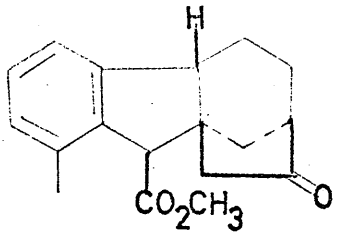

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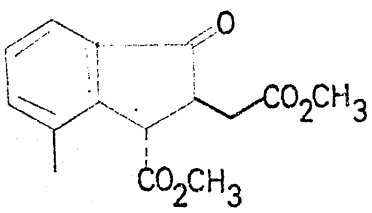

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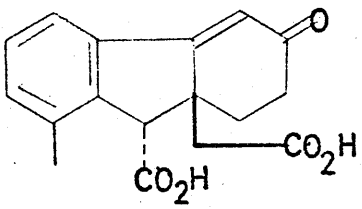

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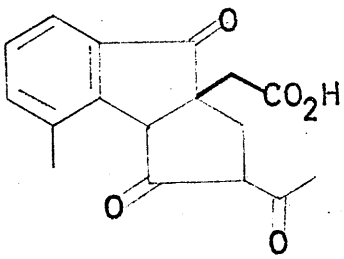

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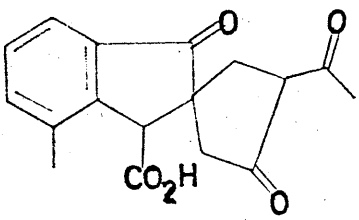

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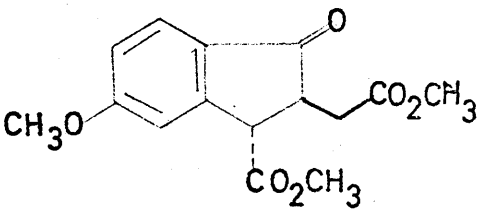

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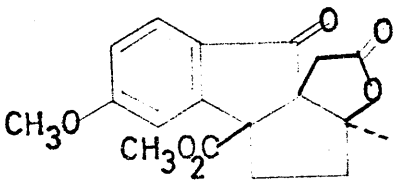

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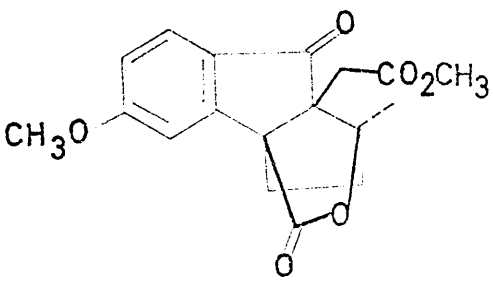

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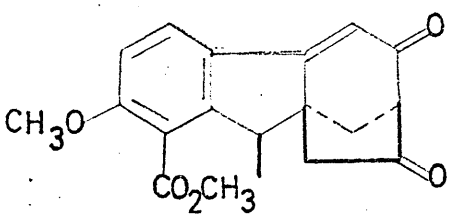

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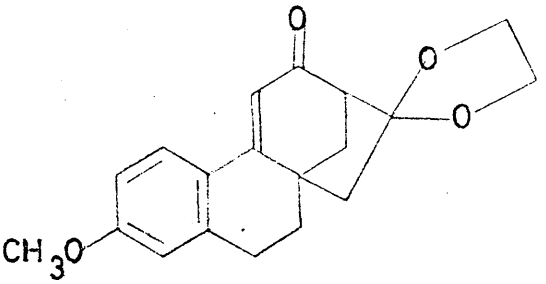

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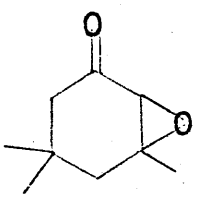

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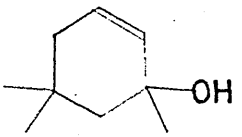

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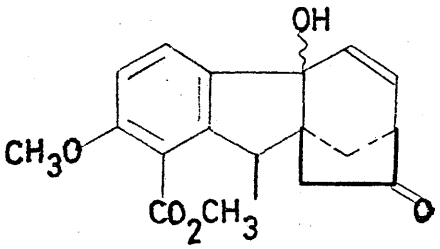

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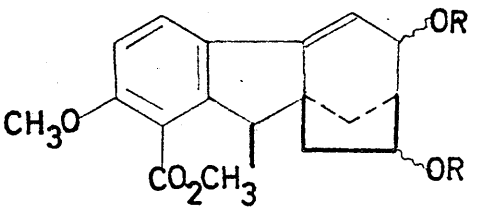

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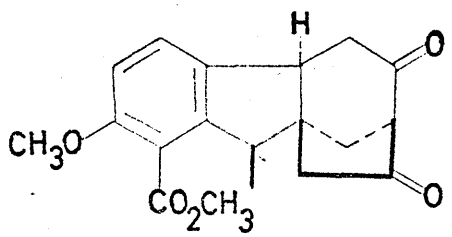

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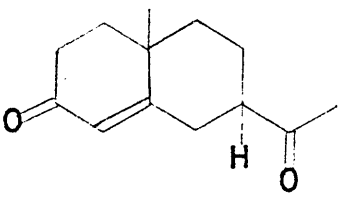

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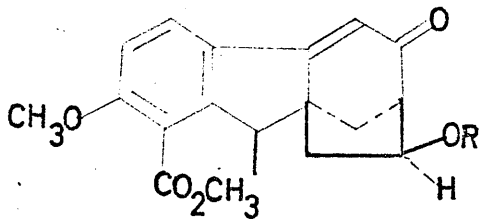

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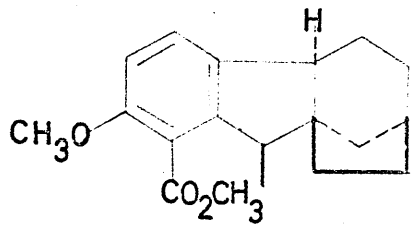

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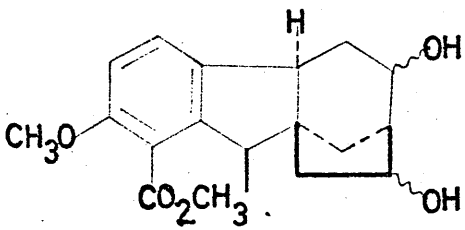

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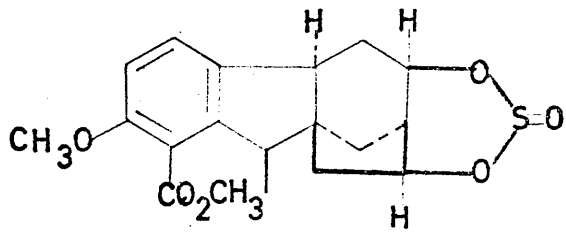

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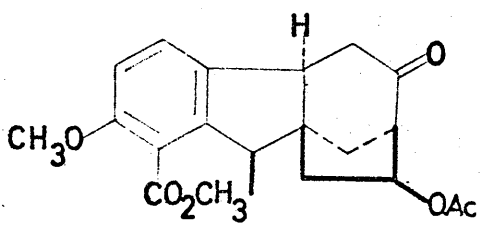

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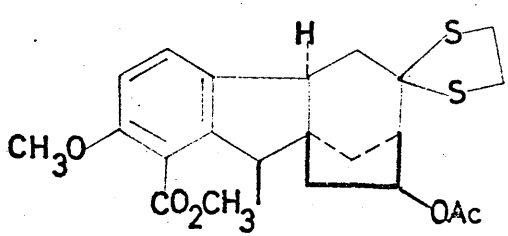

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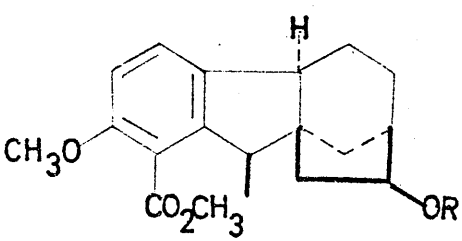

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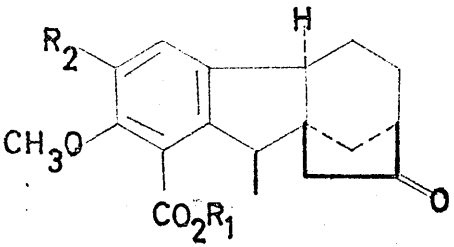
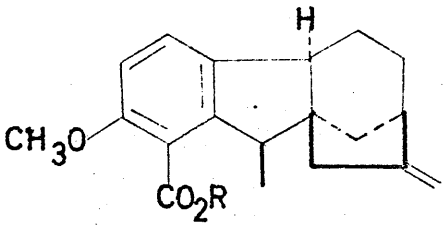


	R_1	R_2
32	CH_3	H
33	CH_3	Cl
35	H	H



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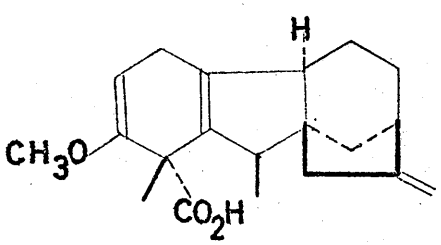

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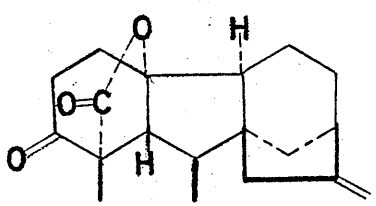

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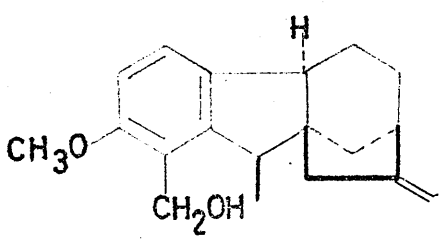

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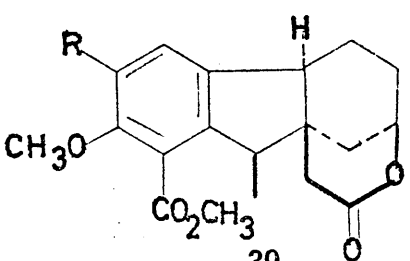

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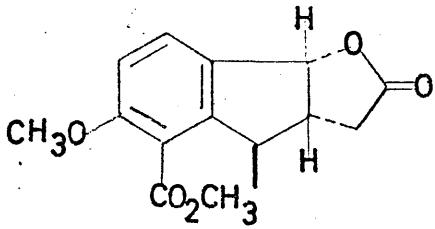

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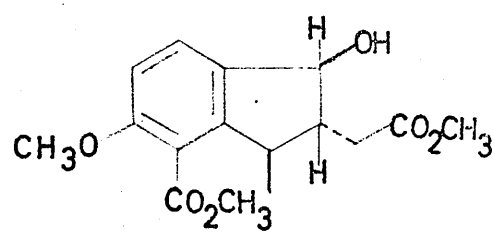

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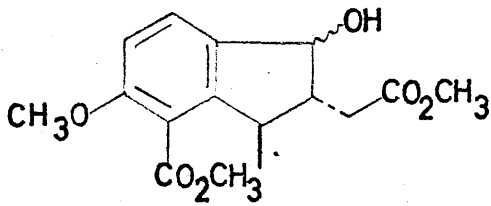

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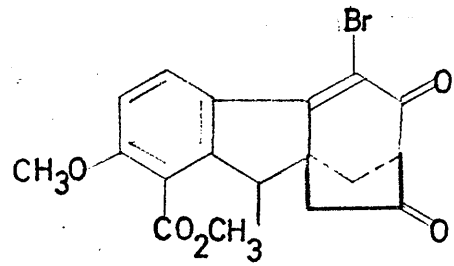

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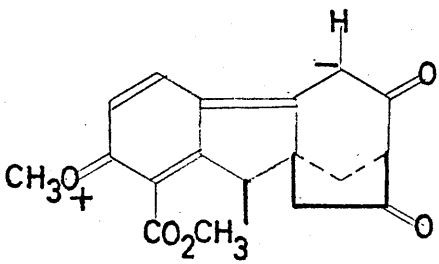

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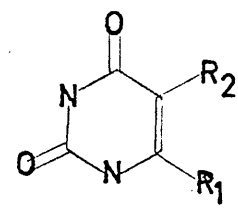
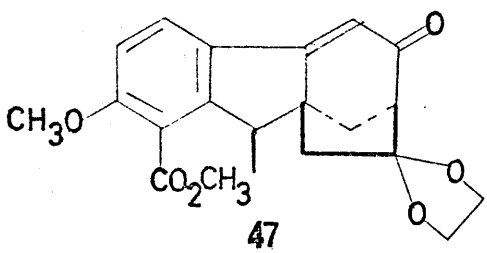


	R_1	R_2
45	Alkyl	H
46	Alkyl	Br



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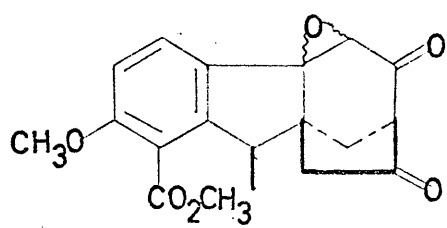

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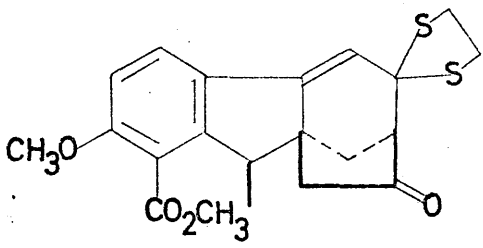
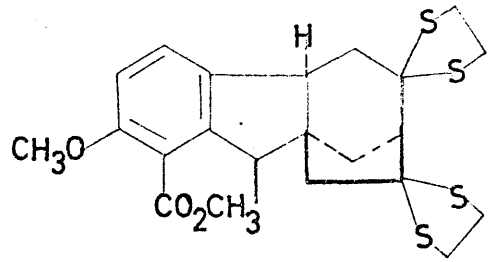
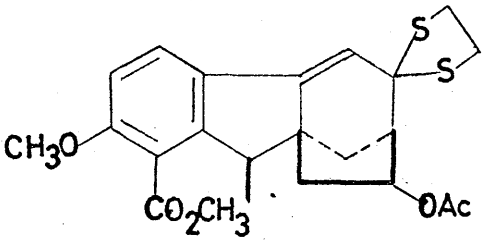

S
S
CH3O
CO2CH3
O

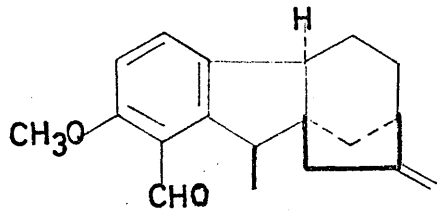
49


H
S
S
CH3O
CO2CH3
S
S

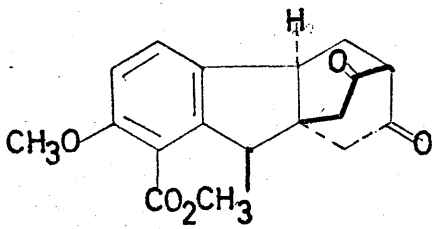
50


S
S
CH3O
CO2CH3
OAc

51


H
CH3O
CHO

52


H
O
CH3O
O
CO2CH3

53

B. SYNTHESIS OF INDANE-1,7-DICARBOXYLIC ACID.

As part of a programme aimed at the synthesis of compounds containing significant structural features of the gibberellins, it was decided to attempt the synthesis of the perhydroindanolactone (1) which contains the AB rings of GA_4 (2).

The route is summarised in Flow Sheet 1. This approach was chosen for two reasons. Firstly, if the synthesis had been successfully completed it would have provided a model closer to the AB ring geometry of the gibberellins than any yet synthesized. Secondly, the route offered the possibility of being readily adaptable to the total synthesis of gibberellic acid (3) and gibberellin A_4 (2).

This could have been carried out by protection of the ketone function in (8) followed by transformation to (16) or to a masked form(17). This ketodiacid (16) possesses the potential of being converted to the gibberellins by a combination of the route envisaged for the synthesis of (1) and the approach discussed above.

Unfortunately, the approach had to be abandoned at an advanced stage for the reasons outlined below.

Benzaldehyde (4) was smoothly converted[1] to diethyl benzalmalonate (5) by condensation with diethyl malonate. Reaction of this adduct (5) with potassium cyanide in aqueous ethanolic solution followed by acid hydrolysis[2] resulted in formation of phenyl succinic acid (6; R = H) without isolation of the intermediate β cyano, β phenyl ethyl propionate.

The anhydride (7), formed by acetyl chloride dehydration, was transformed[3] in high yield to indan-1-one-3 carboxylic acid (8: R = H).

Initial attempts at Clemmensen reduction of the indanone acid (8; R = H) by the Martin[4] two-phase modification were unsuccessful. The desired acid (9; R = H) was, however, obtained by the use of a method similar to that of Donbrow[5] or by hydrogenolysis in glacial acetic acid in the presence of 10% Pd - C catalyst.

Conversion to the acid chloride (10) was easily achieved by heating the acid (9; R = H) under reflux in thionyl chloride. Reaction of this 1-hydrindenyl chloride (10) with lead thiocyanate in dry benzene[6] led to the formation of 1-hydrindenyl isothiocyanate (11) in high yield.

The cyclisation of (11) to 1 thio - 3 keto- 1,2,3,4,5 pentahydro-cyclopent [d e] isoquinoline (12) using the conditions of Smith and Kan [6] afforded initially only intractable tars. (This reaction had been observed[6] to take place in simple benzenoid systems in yields varying between 65 and 25%).

Repetition of the reaction, in the presence of hydroquinone during the isolation procedure, yielded the desired isoquinolone (12) in poor yield (2.3% crude).

The failure of this reaction might in part be attributed to the steric requirements which the Friedel-Crafts cyclisation imposed upon the essentially linear isothiocyanate(11).

It has been observed[7a,b,c] that in analogous systems such as (18) cyclisations of this type do not lead to the expected ring closure product. This had led to the claim that such a ring system may be incapable of existence due to steric strain. This has been shown to be erroneous[8] and an alternative explanation suggested by Rapaport and

Pasky[8] might be valid in this case and in the case of the isothiocyanate (11) also.

If the attacking isothiocyanate moiety must enter the benzene ring at an angle simultaneous with or immediately following aromatic carbon-hydrogen bond rupture then the linear isothiocyanate may be unable to accommodate this requirement and still approach close enough to form a bond.

This approach would be made even more difficult because of steric congestion if, as is very probable, the mechanistic requirements involve complex formation with the Lewis acid catalyst during the transition state. Under such circumstances, intermolecular acylation leading to polymeric species would be favoured.

Indane - 1,7 - dicarboxylic acid (13; R = H) which was obtained from alkaline hydrolysis of the isoquinolone (12) was characterised as the corresponding dimethyl ester (13; R = CH_3). Spectral investigation of this ester (13; R = CH_3) revealed the expected absorptions in the infra-red ($\nu_{c=o}^{c\ m^{-1}}$ 1740, 1725) and ultra-violet ($\lambda_{max}^{n\ m}$ 235,287).

The N. M. R. spectrum added further evidence for the structure (13: R = CH_3) assigned. As well as the two ester methyl singlets and five aliphatic protons the substitution pattern of the aromatic ring was shown to be 1,2,3 trisubstituted with the three aromatic protons forming an A B X system (J_{AB} = 8; J_{AX} = 2; J_{BX} = 8 Hz). Mass spectrometry and analysis confirmed the assigned structure.

At this stage, this approach was abandoned due to the disappointing

yields obtained in a late stage (11 → 12) of the synthesis. Conversion of (13 → 14 → 15 → 1) *via* Birch reduction, lactonisation and hydroboration was not studied.

It should be noted, however, that the perhydronaphthoic acid lactone (19) synthesized by Loewenthal and his co-workers[4] was obtained by a similar sequence to that originally envisaged for the transformation of (13 → 1) (See introduction).

EXPERIMENTAL

Diethyl Benzalmalonate (5)

Diethyl malonate and commercial benzaldehyde were condensed as described in the literature[1] to yield diethyl benzalmalonate (86%) as a colourless oil; b.p. 138 - 142°/ 0.3 mm. (lit. b.p. 140 - 142°/ 4 mm,[1,10] 90%)

This oil was homogeneous by T. L. C. $\nu^{cm^{-1}}_{film}$ 1715 (v.s.); 1620 (s); 700 (m).

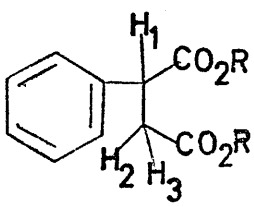
Phenyl Succinic Acid (6; R = H)

Phenyl succinic acid was prepared from diethyl benzalmalonate as described in the literature.[2] The crude material was sufficiently pure for further reaction.

A sample recrystallized from water yielded colourless needles; m. p. 163 - 166° (lit.[11] 168°) [T. L. C. pure as the dimethyl ester (6; R = CH_3)].

$\nu^{cm^{-1}}_{Nujol}$ 1700 (s); 1600 (m); 740 (s); 710 (s).

N. M. R. (6; R = CH_3)



τ	
2.7 (s)	5 aromatic protons
5.9 (q)	H_1 (X part of ABX)
7.0 (m)	H_2, H_3 (AB part of ABX).

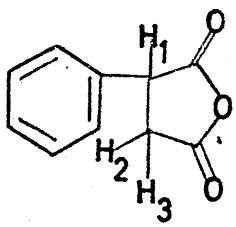
Phenyl Succinic Anhydride (7)

Phenyl succinic acid (6; R = H) (50g.) was refluxed with freshly distilled acetyl chloride (100 ml.). After thirty minutes the solid dissolved; reflux was continued for a further two hours.

Excess acetyl chloride and acetic acid were removed by distillation and the residual oil distilled in vacuo to yield a pale yellow viscous oil (40.4 g; 90%), b. p. 137 - 140°/0.08 mm., which solidified on cooling. Recrystallisation from ether gave the anhydride (7) as colourless prisms, m. p. 51.5 - 52.5° (lit.[11] 54°).

$\nu^{cm^{-1}}_{Nujol}$ 1860 (m); 1790 (s); 740 (w); 710 (m).

N. M. R.



τ	
2.65 (s)	5 aromatic protons
5.85 (q)	H_1 (X part of ABX)
6.8 (m)	H_2H_3 (AB part of ABX).

Indan-1-one-3-carboxylic acid (8; R = H)

The title compound was prepared by Friedel-Craft cyclisation of the anhydride (7) as described in the literature.[3]

Recrystallisation from water afforded the indanone as colourless plates (87%), m. p. 50 - 51° (lit[3] 83 - 84° as $.1H_2O$). Removal of the water of crystallisation in vacuo yielded a microcrystalline powder,

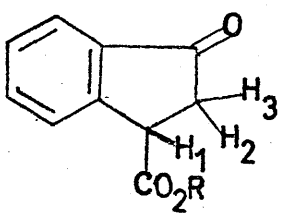
m. p. 117 - 118° (lit[3] 120°).

T. L. C. examination of the acid showed it to be one compound and, as the methyl ester (8; R = CH_3), to be identical with a genuine sample.

$\nu_{Nujol}^{cm^{-1}}$ 1725 (s); 1700 (s); 1600 (m); 765 (s)

λ_{max}^{nm} 213 (ε , 8,700); 245(ε , 10,170); 290 (ε , 2,090).

N. M. R. (8; R = CH_3)



τ	
2.4 (m)	4 aromatic protons
5.7 (q)	H_1 (X part of ABX)
6.95 (m)	H_2H_3 (AB part of ABX)

Indane-1-Carboxylic Acid (9; R = H)

(a) Indan-1-one-3-carboxylic acid (8; R = H) (5g) was heated under reflux for 20 hours with freshly amalgamated zinc (15g.) in a 1:1 mixture of HCl (conc.) and water (40 ml.).

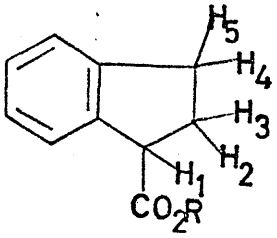
The cooled mixture, on constant ethyl acetate extraction, yielded the required acid (3.4 g; 72%), m. p. 55.5 - 56° (acidified water), as colourless needles. (lit.[5] 56°).

The product was T. L. C. pure both as the acid (9; R = H) and as the methyl ester (9; R = CH_3).

$\nu_{Nujol}^{cm^{-1}}$ 1710 (s); 760 (m)

λ_{max}^{nm} 215 (ε , 4,350); 266 (ε , 710); 273 (ε , 710).

N. M. R. (9; R = CH_3)



τ	
2.75 (b.s.)	4 aromatic protons
5.92 (q)	H_1
7.0 (m)	H_4, H_5
7.55 (m)	H_2, H_3

(b) The indanone carboxylic acid (8; R = H) (1.0g) was hydrogenated at room temperature and 1 atmosphere pressure over 10% Pd - C (200 mg.) in the minimum volume of AnalaR acetic acid. After 16 hours the solution was filtered to remove the catalyst and evaporated under reduced pressure.

Recrystallisation from water yielded indane-1-carboxylic acid (9; R = H) (820 mg.) as colourless needles identical in all respects with the product of Clemmensen reduction.

1-Hydrindenyl Chloride (10)

Indane-1-carboxylic acid (9; R = H) (2.9 g.) was heated under reflux with purified[12] thionyl chloride for four hours. (i.e. until evolution of HCl had ceased). After removal of excess thionyl chloride, distillation under reduced pressure afforded the acid chloride (10) (2.16g; 86%), b. p. 146 - 148°/ 20 mm, as an almost colourless liquid.

$\nu_{film}^{cm^{-1}}$ 1800 (s); 760 (m).

(note: in further runs the crude acid chloride was sufficiently pure for conversion to 1-hydrindenyl isothiocyanate (11) directly).

1-Hydrindenyl Isothiocyanate (11)

The acid chloride (10) (2.1g) was refluxed with lead thiocyanate (4.1g) in dry benzene (20 ml.) for 5 hours.[6] The solution was filtered while still warm and the benzene was removed under reduced pressure. The residue was distilled in vacuo to yield the title compound (11) (1.9g; 80%), b. p. 105 - 110°/0.3 mm, as a very pale yellow oil.

$\nu_{film}^{cm^{-1}}$ 2000 (v.s.); 1735 (s); 760 (m).

λ_{max}^{nm} 214 (ε , 10,450); 265(ε , 5,990).

1 Thio-3 keto-1,2,3,4,5 pentahydro-cyclopent [de] isoquinoline (12)

1-Hydrindenyl isothiocyanate (11) (3.0g) was dissolved in sym tetrachloroethane (30 ml.) and added in one portion to powdered aluminium chloride (6.1g)[6].

The mixture was stirred for 2 hours with evolution of hydrogen chloride.

After destruction of the complex with HCl (1 $\bar{N}$), the solvent was removed by steam distillation in the presence of hydroquinone. The

product (12) (70 mg; 2.3% crude) was isolated by filtration of the cooled distilland.

$\nu_{Nujol}^{cm^{-1}}$ 1645 (s); 1595 (m).

λ_{max}^{nm} 226; 247; 295; 307; 428.

An analytical sample, prepared by sublimation of the crude material, afforded orange-red prisms, m. p. 165 - 170° d.

(Found: C, 64.95; H, 4.34; N, 7.05.

$C_{11}H_9ONS$ requires: C, 65.02; H, 4.46; N, 6.90%).

Dimethyl Indane-1,7-Dicarboxylate (13; R = CH_3)

The crude cyclisation product (12) (150 mg) was heated under reflux in 25% aq. potassium hydroxide solution for 48 hours.[6]

The resulting solution was cooled, acidified and extracted with ether. The ethereal solution was treated with diazomethane, dried ($MgSO_4$) and evaporated under reduced pressure.

The residual solid yielded the desired product (45 mg, 25%) as colourless prisms (m. p. 80 - 82°) on sublimation.

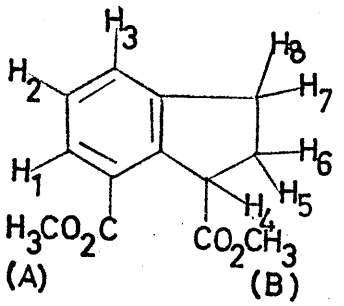
(Found: C, 66.79; H, 6.18.

$C_{13}H_{14}O_4$ requires: C, 66.65; H, 6.02%)

$\nu_{CCl_4}^{cm^{-1}}$ 1740 (s); 1725 (s).

λ_{max}^{nm} 235, (ε , 4,750); 287 (ε , 1,095).

N. M. R.



τ	J (Hz)	
2.23 (q)	8,2	H_1 (X part of ABX)
2.68	8,2	H_3 (A part of ABX)
2.8	8,8	H_2 (B part of ABX)
5.58 (q)		H_4 (X part of ABX)
7.05 (q)		H_7H_8 (CD part of ABCD)
7.70 (m)		H_5H_6 (AB part of ABX AB part of ABCD)
6.26 (s)		Methyl group A
6.43 (s)		Methyl group B

M. S.

Parent ion m/e 234

($C_{13}H_{14}O_4$ requires 234).

Chromatographic properties of Indane Derivatives.

T. L. C. Rf values.

COMPOUND	SOLVENT	Rf
5	15%[a]	0.6
6 (R = CH_3)	15%	0.5
8 (R = H)	A[b]	0.6
8 (R = CH_3)	20%	0.4
9 (R = H)	A	0.75
9 (R = CH_3)	20%	0.8
13 (R = CH_3)	20%	0.55

a Percentage refers to ethyl acetate in 40 - 60 petroleum ether.

b A is a benzene: dioxan: acetic acid solvent system in the ratio 90:25:4.

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10. Note given in reference 1 that b. p. varies with degree of superheating and rapidity of distillation.

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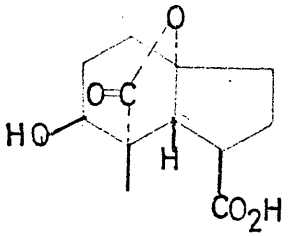

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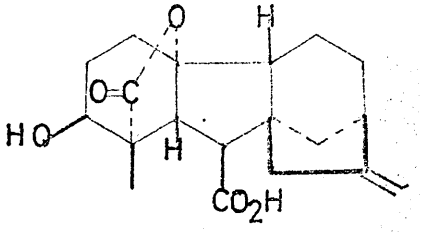

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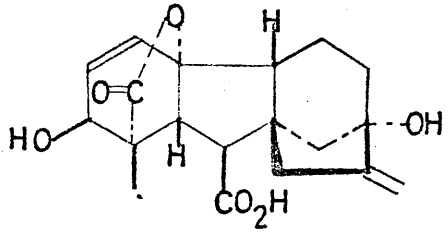

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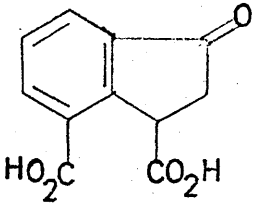

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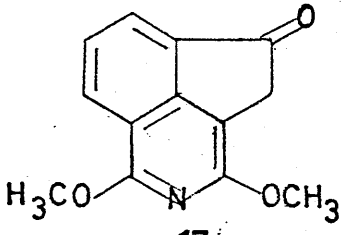

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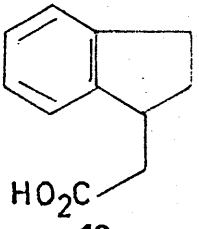

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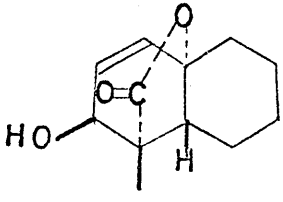
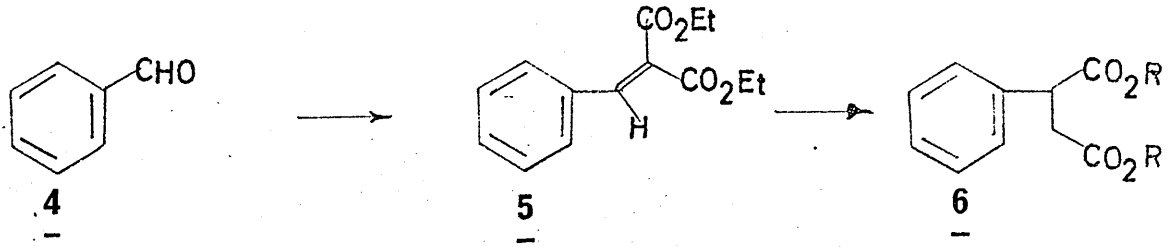


19

FLOW SHEET 1



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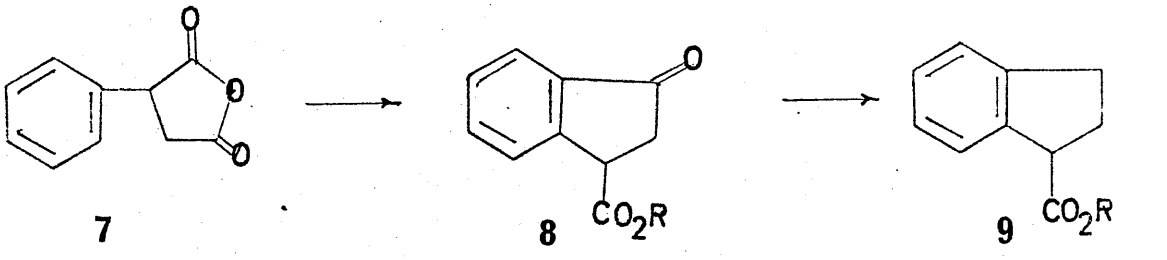

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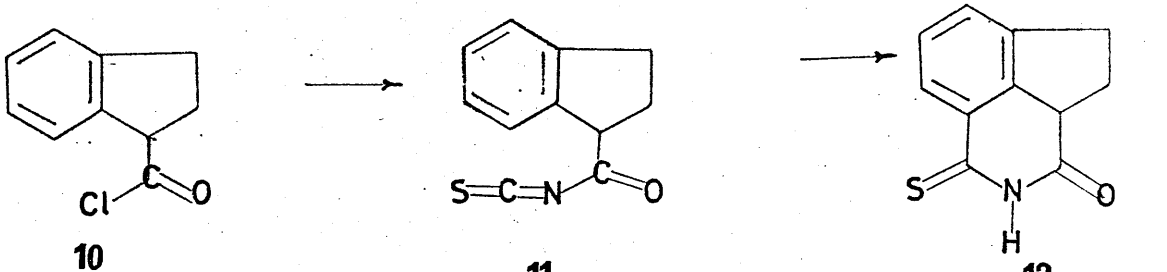

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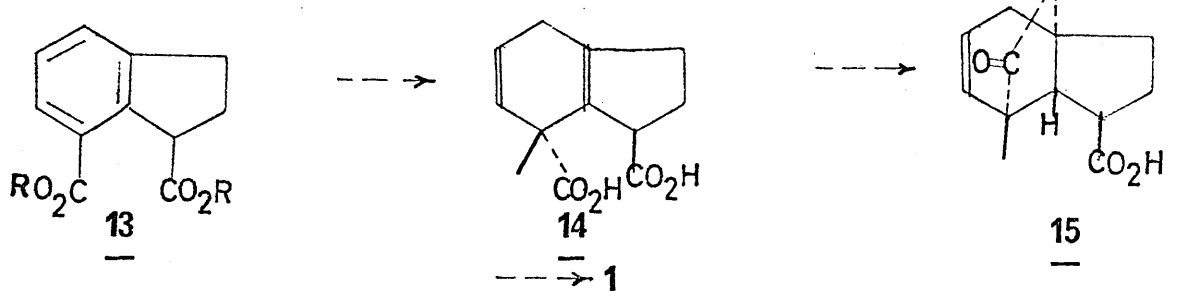

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→ 1