SYNTHETIC STUDIES IN THE GIBBERELLIC ACID FIELD

T H E S I S

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for the degree of Doctor of Philosophy

by

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SUMMARY

A. The structural, stereochemical and biogenetic studies on gibberellic acid and the gibberellins are reviewed. An account of the synthetic approaches to the degradation products of gibberellic acid is also provided.

B. Various synthetic routes to gibberone, a degradation product of gibberellic acid, have been investigated. The main synthetic approach, which involved the preparation of suitably oriented spiro-compounds from 4-methylindan-1-one, provided us with a tricyclic intermediate which is theoretically capable of elaboration to gibberone. An attempted cyclisation of this intermediate provided us with a product which possessed physical properties similar to 6-oxo-gibberone. The exact nature of this product awaits elucidation. An attempt to prepare the ozonolysis product of gibberone is also described.

C. Synthetic approaches to gibberic acid, an acid-catalysed rearrangement product of gibberellic acid, have been explored. These involved the initial preparation of either a suitably substituted coumarin or indanone. Attempts to convert these compounds to a suitable tricyclic intermediate are described. Promising results have been obtained from investigations concerning a route to gibberic acid which involves the use of spiro-type compounds. The latter route is essentially similar to that used for gibberone.

Acknowledgments

I wish to thank Professor R.A. Raphael and Dr. A.I. Scott for their help and advice during the course of this work. Their interest and guidance have been a constant source of encouragement to me.

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CONTENTS

HISTORICAL

(1) Gibberellic Acid

(a) Structure

In 1926, the Japanese plant pathologist E. Kurosawa made the important discovery[1] that cell-free filtrates made from pure cultures of the fungus Gibberella fujikuroi grown on synthetic media would, if applied to healthy rice seedlings, produce the elongation symptoms characteristic of the Bakanae disease in rice. It therefore seemed almost certain that a metabolic product of the fungus, produced when it grew in either the host plant or in culture media, was responsible for the enhanced growth.

This observation was rapidly followed up in Japan and it was soon shown that many other species of plant responded by extra growth. The conditions of production of the active material were studied, using the response of rice seedlings as a crude form of bioassay. Work on extraction and purification of the active material proceeded at the same time, and it was found that it could be absorbed on charcoal and eluted with certain organic solvents.

Eventually in 1938-39, a crystalline material was obtained[2,3] in yields of about 10 mg/l. of crude culture media, which would stimulate growth if applied to the roots of seedlings. This substance was originally named

gibberellin B, but subsequently called gibberellin A[3]. Further work on the chemistry of gibberellin A and on its physiological properties was published in Japan and will be discussed later.

More recently, interest in the growth-promoting metabolites of Gibberella fujikuroi has spread, and from this increased attention has resulted the discovery of other active compounds which are related chemically and also in physiological activity. These compounds are known as the gibberellins (A_1,A_2,A_4,A_5) and gibberellic acid (gibberellin A_3)[4,5,6]. The last-named component was first obtained in pure form independently and almost simultaneously in Britain[4] and the U.S.

Gibberellic acid can now be produced in much greater yields than either of the gibberellins and more detailed and fruitful work on its chemistry has been carried out.

Gibberellic acid is a colourless, crystalline, optically active monobasic acid which melts with decomposition at 233-235°C. The analysis, equivalent weight and molecular weight (confirmed by the X-ray method) show its formula to be $C_{19}H_{26}O_6$.[4]

Gibberellic acid gives a negative ferric chloride test and does not reduce Fehlings solution or ammoniacal silver nitrate solution. It is unstable to alkali and mineral acid and is rapidly oxidised by alkaline potassium permanganate. A weak positive nitrochromic acid test indicated the presence of a primary or secondary hydroxyl group and this was confirmed by the infrared spectrum (Table 1) and by the preparation of a monoacetyl derivative. Gibberellic acid also yielded a p-bromophenacyl ester and a neutral monomethyl ester. Acetylation of the latter gave methyl acetylgibberellate which was also obtained by esterification of acetylgibberellic acid[7].

Table 1 - Infrared Absorption Maxima. (Cross[7])

	Nujol		Dioxan	
	CO	OH	CO	OH
Gibberellic acid	1746	3305,3390	1784,1736	3470
Acetate	1765,1736	3400	1786,1740	-
Ester	1770,1711	3490	1777,1720	-
Ester acetate	1761,1740,1733	3510	-	-

The infrared spectrum of gibberellic acid in Nujol

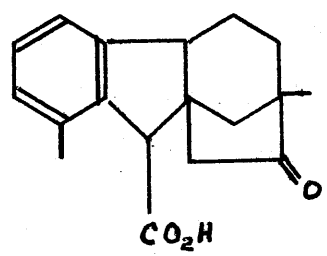
showed no absorption in the region normally associated with carboxylic-OH in solid (dimeric) acids; nevertheless the band at 1736 cm^{-1} (dioxan) was assigned to aliphatic carboxyl for the following reasons:-

(a) Gibberellic acid formed a methyl ester without the uptake of water.

(b) The infrared spectrum excluded other acidic groupings such as a β-diketone (also negative ferric chloride test).

When gibberellic acid was treated with a small excess of 0.1N sodium hydroxide at room temperature a second equivalent of alkali was consumed; this, considered with the fact that the infrared spectra of the acid and its derivatives (Table 1) in dioxan solution showed strong bands at 1780 cm^{-1}, led Cross to suggest that gibberellic acid possessed a saturated γ-lactone ring. The remaining oxygen atom was considered to be present as an unreactive, possibly tertiary alcohol group since the infrared spectrum of methyl acetylgibberellate possessed a band at 3510 cm^{-1}. It has also been reported[8] that gibberellic acid forms a diacetyl derivative.

The ultraviolet spectrum of methyl acetylgibberellate showed no maximum in the range 220-320 mu indicating the absence of an aromatic ring while the presence of two double bonds was shown by microhydrogenation experiments[7].



(I)

The above evidence accounted for all the oxygen atoms and indicated that gibberellic acid was a tetracyclic dihydroxylactonic acid. Further information about the ring system was gained from a study of the two products of acid hydrolysis[7]. Mild acid hydrolysis (normal hydrochloric acid at 0°C.) of gibberellic acid yielded, among other products, allogibberic acid, $C_{18}H_{20}O_3$, together with a molecule of carbon dioxide. If the hydrolysis was conducted at 100°C. the allogibberic acid isomerised to gibberic acid, $C_{18}H_{20}O_3$.

The evidence for the structures assigned to these compounds is given in the sequel.

Gibberic acid

Gibberic acid (1) was originally assigned the formula $C_{19}H_{22}O_3$ by Yabuta et al[9]. Subsequently, analyses and equivalent weight determinations on gibberic acid and its derivatives established the formula $C_{18}H_{20}O_3$ whence it followed that the hydrolysis of gibberellic acid involved the loss of carbon dioxide and water[7].

The formation of an oxime, a methyl ester, and an oxime ester demonstrated that gibberic acid was a keto-acid. The infrared spectrum (Table 2), with a strong band at 1741 cm^{-1}, indicated that the keto group was present in a five-membered ring while the band at 1717 cm^{-1} was assigned to an aliphatic carboxyl group.

Table 2 - Infrared Absorption[7]

	Nujol		Dioxan	
	CO	OH	CO	OH
Gibberic acid[a]	1717,1741	3290	1740	-
Methyl gibberate[b]	1736	-	-	-

a. In CCl_4 solution, OH absorption at 3525 cm^{-1}.

b. In CCl_4 solution, absorption at 1745 cm^{-1} with intensity corresponding to two carboxyl groups.

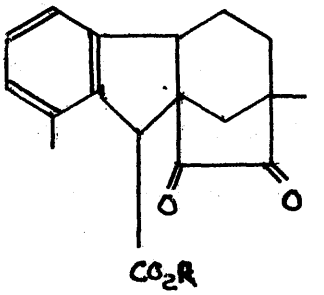
The ultraviolet spectrum of gibberic acid (Table 3) was consistent with the presence of an aromatic ring while its resistance to hydrogenation was taken as evidence for the absence of ethylenic bonds. A consideration of these facts and the formula of gibberic acid led Cross to suggest that the basic structure was that of a tetracyclic keto-acid containing an aromatic ring[7].

Table 3 - Ultraviolet Absorption

	$\lambda_{max.}$	log ε
Gibberic acid	265, 274, 300	2.56, 2.47, 1.49
Gibberic acid[a]	265.5, 273.5, 292	2.63, 2.56, 1.69
Methyl gibberate	265, 273, 294	2.53, 2.45, 1.61

a. In 0.1N NaOH. The other spectra were measured in EtOH.

Yatazawa and Sumiki[10] demonstrated that oxidation of gibberic acid with selenium dioxide gave a yellow acid (gibberdionic acid) for which (in agreement with their formula for gibberic acid) they proposed the formula $C_{19}H_{20}O_4$.



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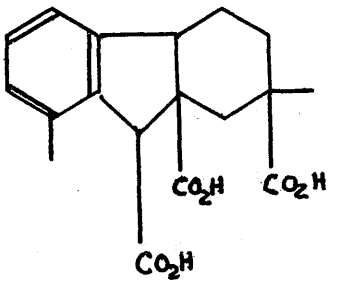
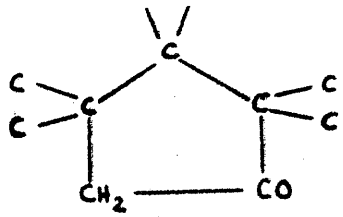


(3)

Further oxidation with hydrogen peroxide resulted in the loss of carbon dioxide and the formation of a dicarboxylic acid for which they proposed the formula $C_{17-18}H_{22-24}O_6$. This result was explained by assuming that gibberdionic acid had the partial structure $C_{16}H_{18}(COOH)\cdot CO\cdot CHO$. These experiments were repeated by Cross with somewhat different results. Selenium dioxide oxidation afforded gibberdionic acid, $C_{18}H_{18}O_4$, (2; R = H). Having assigned a five-membered ring ketone to gibberic acid Cross concluded that gibberdionic acid must be a cyclic α-diketone[7]. Evidence for an α-diketone structure has been obtained in the following way.

Oxidation of gibberdionic acid with alkaline hydrogen peroxide under the conditions described by Yatazawa and Sumiki[10] yielded only a trace of carbon dioxide and an acid, $C_{18}H_{20}O_6\cdot\frac{1}{2}H_2O$, which was shown to be the tricarboxylic acid (3) by analysis of its trimethyl ester for methoxyl. Gibberdionic acid would give a tricarboxylic acid if it contained an α-diketone grouping but not if it had the structure suggested by Yatazawa and Sumiki[10]. Further evidence for an α-diketone structure has been provided[7] by infrared and ultraviolet determinations. The infrared spectrum of methyl gibberdionate showed carbonyl bands (Nujol) at 1736 cm^{-1} (ester), 1750 cm^{-1} and 1764 cm^{-1} (five-membered ring α-diketone; cf. camphorquinone 1748 cm^{-1} and



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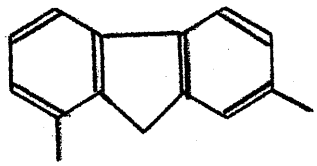

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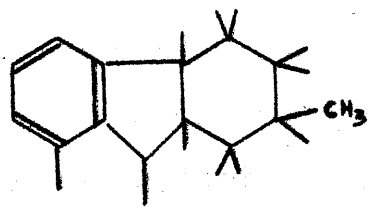

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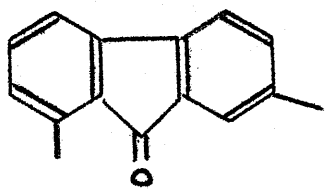

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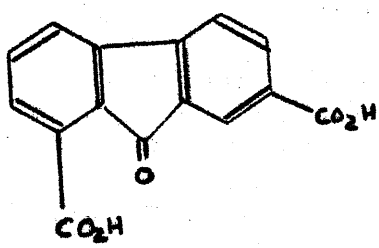

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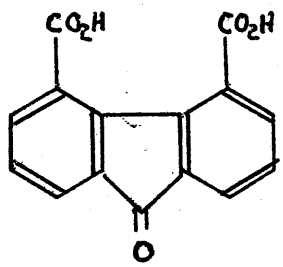
1760 cm^{-1}). The absence of hydroxyl and double bond in the infrared spectrum suggested a non-enolisable α-diketone and this deduction was supported by the ultraviolet spectrum which was almost identical with that of gibberic acid (Table 3) in both ethanolic and 0.1N sodium hydroxide solution. (α-diketones, in which adjacent carbon atoms carry hydrogen atoms, readily enolise and, in consequence, have an ultraviolet spectrum characteristically different from that of the parent monoketone). Thus gibberic acid contained a $-CH_2-CO-$ grouping so situated in a five-membered ring as to preclude the enolisation of gibberdionic acid. It was postulated, therefore, that gibberic acid had the partial structure (4).[7,11]

Selenium dehydrogenation of gibberic acid to 1:7-dimethylfluorene (gibberene) (5)[7,12,14] and oxidation to benzene-1:2:3-tricarboxylic acid[11,13] in significant yield established the presence of the hexahydrofluorene nucleus (6). Gibberene was also obtained by mild dehydrogenation of the tricarboxylic acid (3) derived from gibberdionic acid.[7] Confirmation for the structure of gibberene has been provided by degradation and synthesis.[12] Oxidation of gibberene with potassium permanganate in acetone gave gibberenone (7) $C_{15}H_{12}O$, which, on more prolonged permanganate oxidation in pyridine, furnished fluorenone-1:7-dicarboxylic acid (8). An unambiguous



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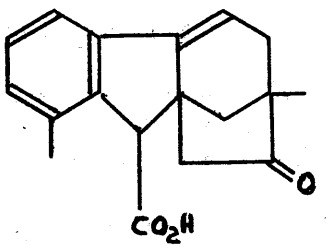
synthesis of gibberene, gibberenone, and fluorenone-1:7-dicarboxylic acid, based on the work of Lonthrop and Goodwin[15], by Mulholland and Ward[12] as a final proof of structure. Yabuta et al. who have also worked on the structure of gibberene postulated that the diacid obtained from gibberene might be fluorenone-4:5-dicarboxylic acid (9).[14] This suggestion was later invalidated by Mulholland and Ward who synthesised this compound by an unambiguous route and showed that its melting point depressed the diacid obtained by degradation.[16]

Since gibberene could be obtained from both gibberic acid (1) and the tricarboxylic acid (3) obtained from gibberdionic acid (2), Cross et al. concluded that during the selenium dehydrogenation of gibberic acid no skeletal rearrangement had occurred.[11,17] Thus the dehydrogenation of gibberic acid involved the elimination of the methylene carbonyl bridge ($-CH_2-CO-$) and the methylene group of this bridge was attached to a quaternary carbon atom. Since the enolisation of the 1:2-diketone system of gibberdionic acid was precluded (p.11), it was suggested that the carbonyl group of the bridge was also attached to a quaternary carbon atom. The position of the methylene carbonyl group was finally determined by the following series of reactions. Oxidation of gibberic acid with alkaline potassium permanganate at $0^{o}C.$ yielded



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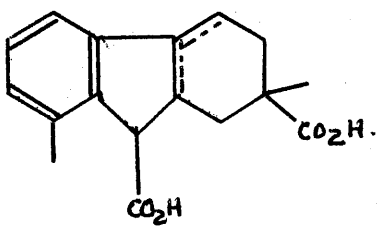

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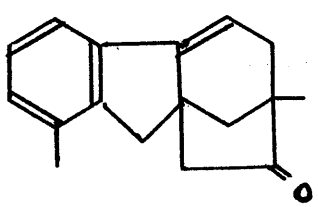
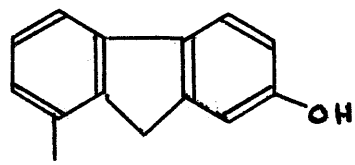


(12)

dehydrogibberic acid (10) whose ultraviolet spectrum (Table 4) indicated that a double bond had been introduced in conjugation with the aromatic ring. Dehydrogibberic acid did not undergo either acid or alkaline hydrolysis and regenerated gibberic acid on catalytic reduction. It was rapidly degraded by further treatment with alkaline permanganate at 25°C. and yielded a dibasic acid, $C_{17}H_{18}O_4$, identical with that described by the Japanese workers[18]. Like dehydrogibberic acid, the dibasic acid had a double bond in conjugation with the aromatic ring as shown by the ultraviolet spectrum (Table 4) and took up 1 mol. of hydrogen catalytically. The infrared spectrum showed that the five-membered ring ketone of gibberic acid had been lost. Cross et al., therefore, assigned the structure (11) to the dibasic acid and postulated that, during the oxidation, the methylene carbonyl bridge had been cleaved and that the tertiary carboxylic group formed had been lost as carbon dioxide.[11]

Decarboxylation of dehydrogibberic acid (10) with palladium-charcoal or charcoal alone at 230°C. furnished the neutral ketone, gibberone (12). Yabuta et al. have also reported the isolation of gibberone in 17% yield by direct dehydrogenation of gibberic acid with selenium at 300-330°C. but they wrongly assigned the molecular formula, $C_{18}H_{18}O$, to it.[14] This work was later confirmed by



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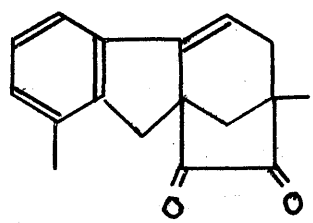


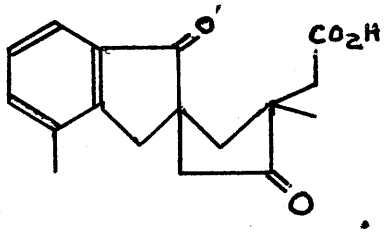
(14)

Cross et al. who also isolated 1:7-dimethylfluorene and three phenolic compounds from the reaction product.[11] One of the phenolic compounds has been shown to be 7-hydroxy-1-methylfluorene (13); the structures of the other two remain to be elucidated although spectroscopic evidence has suggested hydroxyfluorene-type structures.

Table 4 - Ultraviolet Absorption Maxima (mu) in Ethanol.

	λ_{max}	log ε
(1)	265,274,300	2.56,2.47,1.49
(10)	260,269,290,300	4.14,4.09,3.50,3.44
(11)	265	4.01
(12)	259,269,290,301	4.13,4.07,3.62,3.62
(14)	250,257,267,290,301	4.14,4.21,4.10,3.65,3.65
(5)	269,275,293,297,304	4.44,4.37,3.95,3.90,3.95
(21; R = Me)	266,271,280,294,305	4.28,4.39,4.25,3.73,3.39

The infrared spectrum of gibberone showed the five-membered ring ketone absorption at 1745 cm^{-1} (CCl_4) and the ultraviolet spectrum (Table 4) indicated that the double bond, revealed by catalytic hydrogenation, was conjugated with the aromatic ring. Gibberone was stable to hydrolysis by acid or alkali. It yielded 1:7-dimethylfluorene with selenium at 360°C. and was oxidised by selenium dioxide in ethanol at 140°C. to a five-membered ring 1:2-diketone gibberdione (14) which, like gibberdionic acid, had almost identical ultraviolet spectra in ethanol and sodium hydroxide solution. The spectra closely resembled that of



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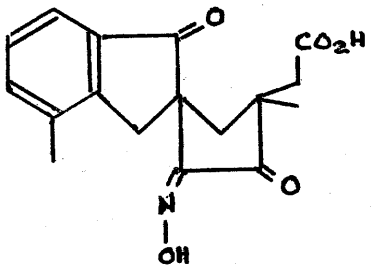
gibberone (Table 4).

Gibberone, on oxidation with chromic oxide, yielded a monobasic keto-acid, $C_{17}H_{18}O_4$, which was probably identical with the uncharacterised acid obtained in the same way by Yabuta et al.[14] Cross et al.[11] assigned the structure (15) to this acid for the following reasons. The ultraviolet spectrum with peaks at 250 mu ($\log\varepsilon$ 4.18) and 295 mu ($\log\varepsilon$ 3.55) was characteristic of an indanone-type structure, further confirmation for which was gained from the infrared spectrum which showed peaks at 1744 (five-membered ring ketone), 1738 (monomeric carboxyl carbonyl) and 1717 cm^{-1} (indanone carbonyl). The formation of this acid (15) from gibberone without loss of carbon and with the addition of three oxygen atoms was consistent with the oxidation of a trisubstituted double bond to a keto-acid. The absence of β-diketone or β-keto acid functions in (15) was confirmed by its stability to dilute acid or alkali while its stability to neutral permanganate at room temperature, or chromic oxide in acetic acid at 75°C., confirmed the presence of a 2:2-disubstituted indanone structure. (2:2-dimethylindan-1-one was stable under these conditions while 2-methyl- and 2:3-dimethylindan-1-one were oxidised). From the above evidence Cross et al.[11] concluded that the keto-acid (15) was a 2:2-disubstituted indan-1-one and since it had retained the partial structure (4),



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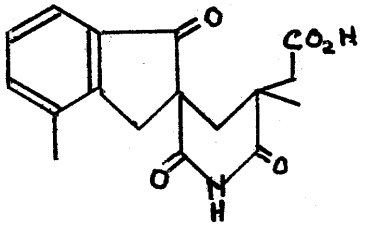

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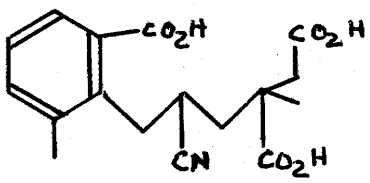

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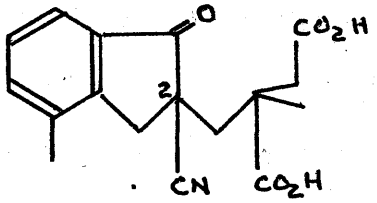
originally present in gibberic acid, the five-membered ring was assigned to position 2, as in (15).

Permanganate oxidation of (15) in the presence of magnesium nitrate[19,20] yielded, among other products, benzene-1:2:3-tricarboxylic acid, 3-methylphthalic acid and β-methyltricarballylic acid. This was consistent with structure (15), further proof of which was provided by cleavage of both non-benzenoid rings and by an unambiguous synthesis of the product.[21] Thus the keto acid (15) was converted to the α-hydroxyimino-compound (16) by treatment with butyl nitrite and sodium methoxide.[22] Beckmann rearrangement of (16) with polyphosphoric acid gave the isomeric imide carboxylic acid (17): with toluene-p-sulphonyl chloride and sodium hydroxide, however, a tricarboxylic acid (18) was obtained which contained the expected cyano-group (band at 2250 cm^{-1}). That both ketone functions in the acid (15) had been eliminated was confirmed by the infrared spectrum (absence of absorption due to saturated five-membered ring ketone) and by the ultraviolet spectrum (λ_{max} 233, 284, 293 mu : $\log\varepsilon$ 3.89, 3.21 and 3.08 respectively) which showed the absence of the indanone chromophore and was typical of a trisubstituted benzoic acid. The cyano-tricarboxylic acid, which formed an intramolecular five-membered ring anhydride when heated with acetic anhydride, was thus assigned the structure (18) and was



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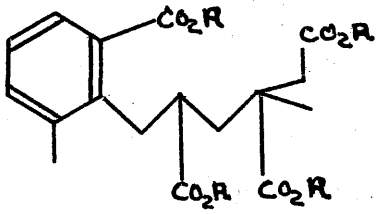

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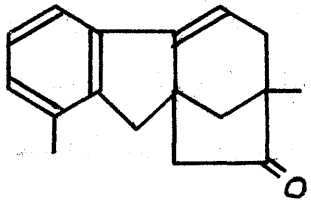

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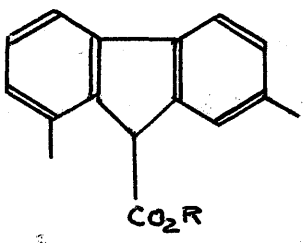
obviously formed by alkaline hydrolysis of the intermediate β-keto-nitrile (19). Finally the cyano-acid (18) was hydrolysed by 50% sulphuric acid to an amorphous tetracarboxylic acid (20; R = H) which furnished two isomeric tetramethyl esters (20; R = Me) on treatment with diazomethane. It was concluded that these esters, which had different optical rotations, were diastereoisomers and that they had been formed by racemisation at the (C_2) centre during hydrolysis of the intermediate β-keto nitrile (19).[11] The structure of the two esters was established by a synthesis of their racemates, the infrared spectra of the esters obtained by degradation and synthesis being identical in carbon tetrachloride solution.[21]

The synthesis of the tetramethyl esters (20; R = Me) finally established the structure of the keto-acid (15) and consequently the structure of gibberone (12). Thus it was concluded that the methylene carbonyl bridge in gibberic acid was attached as in (1) (the possibility that the methylene and carbonyl groups were interchanged was excluded for a further reason, namely, the stability of (15) in aqueous alkali). The remaining problem in the structural elucidation of gibberic acid involved the location of the carboxyl group and this was solved in the following way.

Dehydrogenation of methyl gibberdionate (2; R = Me) with 30% palladium-charcoal at 230°C. yielded methyl



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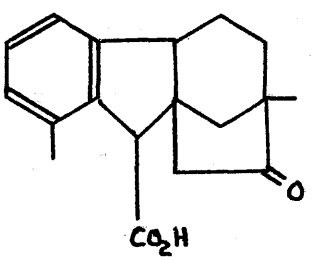
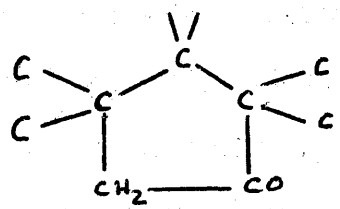


(1)

1:7-dimethylfluorene-9-carboxylate (21; R = Me).[11] The infrared (C = O at 1736 cm^{-1} in CCl_4) and ultraviolet spectra (Table 4, p. 17) of this compound indicated that the ester group was unconjugated while the 9-position for the ester group was favoured by the fact that alkaline hydrolysis gave a small amount of 1:7-dimethylfluorene (5) in addition to the corresponding acid. Structure (21) for the ester was confirmed by synthesis. Thus treatment of the 9-lithium derivative of 1:7-dimethylfluorene with solid carbon dioxide[23] afforded 1:7-dimethylfluorene-9-carboxylic acid (21; R = H), methylation of which with diazomethane gave the methyl ester identical with the ester obtained by dehydrogenation of methyl gibberdionate.

The isolation of this ester by degradation established the position of the carboxyl group in gibberic acid in accordance with the proposed structure (1).

It may be noted that structure (1) was at variance with the views of the Japanese workers[10] who had advanced the partial structure $C_{16}H_{18}(CO_2H)\cdot COCH_3$. In support of this structure, Seta and Sumiki claimed that the crude product obtained by Beckmann rearrangement of gibberic acid oxime gave a good yield of methylamine on vigorous acid hydrolysis.[24] This experiment was repeated by Cross et al. with somewhat different results. In their hands a careful examination of the hydrolysis products of the crude mixture



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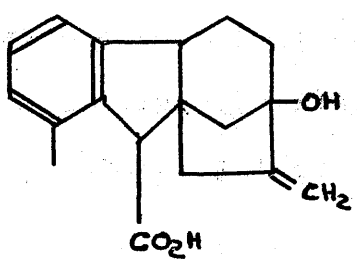

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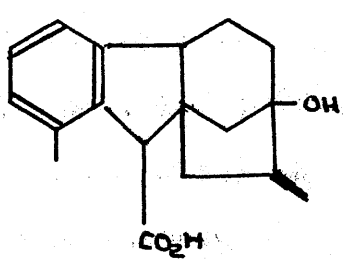


(23)

from the Beckmann rearrangement failed to reveal the presence of methylamine; about 0.5 mol. of ammonia was produced, (estimated as chloroplatinate) a fact which was not inconsistent with partial structure (4). The remainder of the nitrogen originally present in the oxime was shown to be present, as organic nitrogen, in the other hydrolysis products.[11]

Allogibberic acid

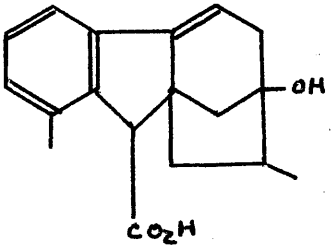
Allogibberic acid, $C_{18}H_{20}O_3$, obtained from gibberellic acid, $C_{19}H_{20}O_6$, by mild hydrolysis with normal hydrochloric acid at 20°C., has been formulated as (22).[17,25] Under more vigorous conditions (normal hydrochloric acid - 100°C./1 hr.) allogibberic acid isomerises to gibberic acid (1).

The ultraviolet spectrum of allogibberic acid (Table 5) suggested that the acid was benzenoid and showed that the aromatic ring and the double bond (shown by hydrogenation experiments[7,25]) were not conjugated. Dihydroallogibberic acid (23) was recovered unchanged (86%) after treatment with normal hydrochloric acid at 100°C. for 1 hour. Ozonolysis of allogibberic acid or its methyl ester yielded 0.4 - 0.5 mol. of formaldehyde whereas dihydroallogibberic was mainly recovered unchanged. The other products formed during ozonolysis were ketones with one carbon atom less than the starting materials. Thus it

was concluded that allogibberic acid contained a terminal methylene group and in support of this the infrared spectrum of methyl allogibberate in ethylidene chloride showed a strong band near 890 cm^{-1} (= CH_2).

Kuhn-Roth estimations on both allogibberic acid and its dihydro derivative gave 1.1 C-methyl groups; the failure to show the expected difference (cf. ref. 26) has been ascribed to the isomerisation of allogibberic to gibberic acid under the strongly acidic conditions used.

The presence of a hydroxyl group in allogibberic acid was indicated by the infrared spectrum of the acid and its methyl ester (1734 cm^{-1} and 3310 cm^{-1}). It was assigned a tertiary nature[17,25] because of the difficulty of acetylation and the failure to oxidise dihydroallogibberic acid to a ketone using chromic oxide in pyridine[27] or permanganate in acetone. In addition, dihydroallogibberic acid failed to furnish a toluene-p-sulphonate or an acetate under normal conditions. When the dihydro-acid (23) was oxidised with potassium permanganate the hydroxyl group was not attacked but a dehydro-derivative $C_{18}H_{20}O_3$ (24) was formed in which a double bond had been introduced in conjugation with the aromatic ring (Table 5). This reaction is analogous to the oxidation of gibberic acid to dehydrogibberic acid[11] (p. 15). The dehydro-derivative (24) was converted into dihydroallogibberic acid (23) by



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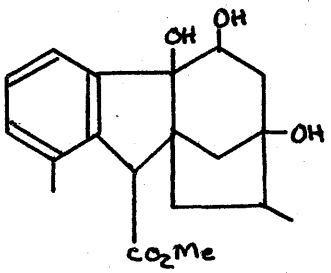

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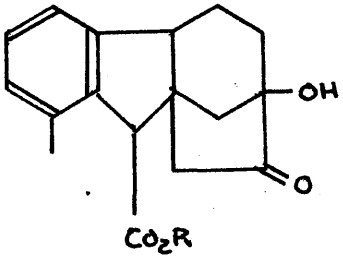

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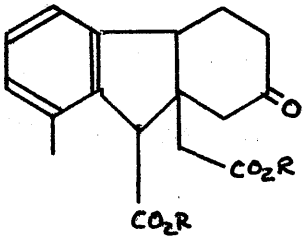

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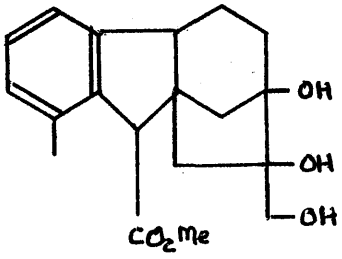

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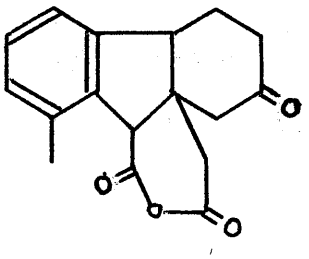


(29)

Table 5 - Ultraviolet Absorption Maxima

	λ_{max}	log ε
(22)	259,264,273,287,297	2.47,2.51,2.35,1.28,1.25
(23)	260,264,273	2.18,2.24,2.88
(24)	250,259,268,290,300	3.98,4.13,4.07,3.50,3.46

catalytic hydrogenation and its non-crystalline methyl ester gave a crystalline diol (25) with osmium tetroxide. Further evidence for the structure of allogibberic acid was obtained from oxidation and dehydrogenation experiments[25] and is described below.

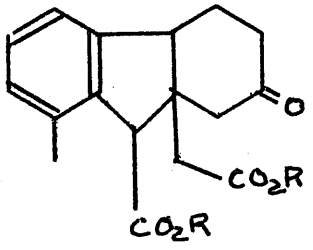
Ozonolysis of allogibberic acid furnished, in addition to formaldehyde, the monobasic ketol (26; R = H) and a dibasic keto-acid (27; R = H). The corresponding esters (26; R = Me) and (27; R = Me) were obtained when methyl allogibberate was ozonised. Oxidation of methyl allogibberate with zinc permanganate, or via the glycol (28) followed by fission with sodium bismuthate[28], gave the same products as ozonolysis while treatment of the ketols (26; R = H and R = Me) with sodium bismuthate yielded the corresponding keto-acids (27; R = H and R = Me). The keto acid (27; R = H) formed an anhydride (29) from which it could be recovered by mild alkaline hydrolysis.

The ketols (26; R = H and R = Me), which showed reducing properties and were cleaved by sodium bismuthate, were assigned α-ketol structures by Mulholland.[25] In

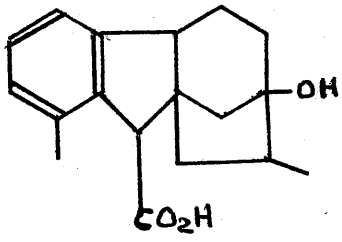
agreement with the evidence described above the ketols were stable to bismuth oxide and acetic acid[29] and therefore contained a tertiary hydroxyl group. The infrared spectra of the ketols in solution (Table 6) showed a high-frequency band at ca. 1750 cm^{-1} (five membered ring ketone), the frequency having been raised (cf. gibberone 1745 cm^{-1} in CCl_4) by the presence of an adjacent hydroxyl group.[30] Oxidation of the ketol (26; R = H), without loss of carbon atoms, to the dibasic keto-acid (27; R = H) indicated that the tertiary hydroxyl group was situated in a saturated six-membered ring. The dimethyl ester of this acid showed bands in the infrared at 1712 cm^{-1} (six-membered ring ketone) and 1739 cm^{-1} (ester-carbonyl).

Table 6 - Infrared Absorption Maxima (cm^{-1}) in Solution

Compound	Solvent	CO bands
(26)(R = H)	Dioxan	1751, 1734
(26)(R = Me)	$CHCl_3$	1749, 1739 (sh)
	CCl_4	1750
	Dioxan	1752, 1736
(27)(R = H)	Dioxan	1735 (broad)
(27)(R = Me)	$CHCl_3$	1739, 1712
(29)	Dioxan	1813, 1766, 1726
Succinic anhydride	$CHCl_3$	1871, 1791
Glutaric anhydride	$CHCl_3$	1815, 1767



(27)



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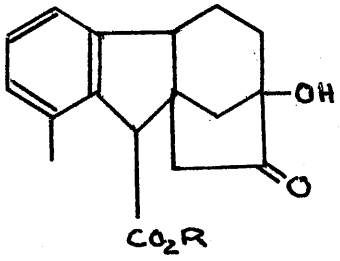
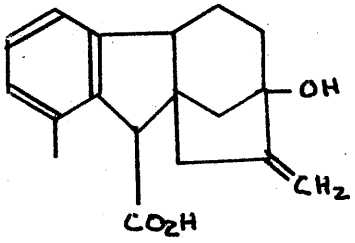
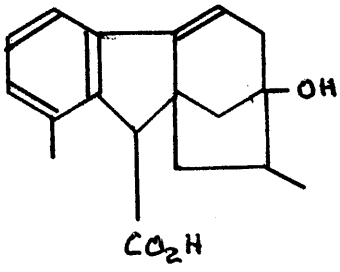


(26)



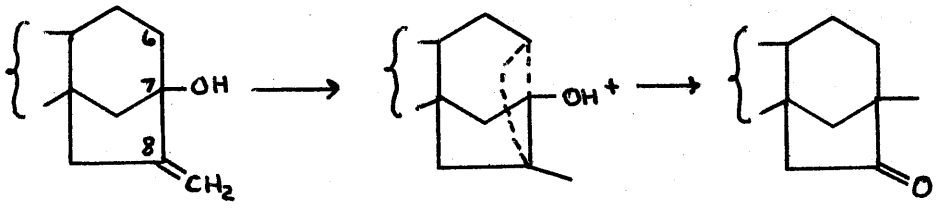
(22)



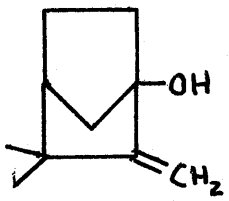
(24)

Dehydrogenation of the dibasic acid (27; R = H) and of dihydroallogibberic acid (23) with selenium established the position of the tertiary hydroxyl group and hence one point of attachment of the five-membered ring on the hexahydrofluorene skeleton of the ketol (26) and allogibberic acid.[25] Thus while allogibberic acid, like gibberic acid, gave mainly 1:7-dimethylfluorene (5) (gibberene), dihydroallogibberic acid did not. The latter, and more readily the keto acid (27; R = H), gave as a main product a fluorenol whose structure was established as 7-hydroxy-1-methylfluorene (13) by comparison with a specimen prepared by unambiguous synthesis.[31] Sumiki et al.[32] have also isolated the fluorenol (13) from gibberellin A_1 methyl ester (methyl α-dihydrogibberellate) by ozonolysis and dehydrogenation essentially as described above for allogibberic acid.

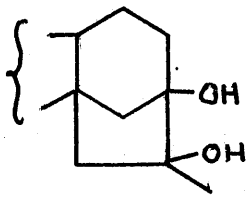
In the dehydrogenation of the acid (27; R = H) to the fluorenol (13) all the non-skeletal carbon atoms were eliminated except the aromatic C-methyl group. Thus it was concluded that the second point of attachment of the five-membered ring in the ketol and in allogibberic acid was angular as in (26) and (22) respectively.[25] The alternative angular position could not accommodate a five-membered ring D or explain the formation of the dehydro-derivative (24) of dihydroallogibberic acid. Moreover the infrared spectrum



(22) (30) (1)



(31)



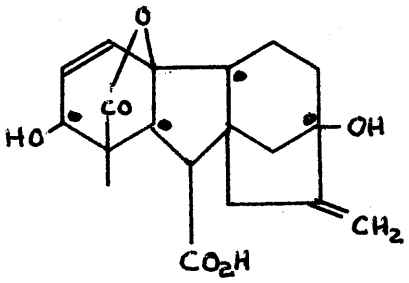
(32)

of the anhydride (29) (Table 6) showed it to contain a six-membered anhydride ring. Since methyl allogibberate can be converted to methyl gibberate by boiling dilute hydrochloric acid, Mulholland suggested that the carboxyl group in each of these acids occupied the same position.[25] The six-membered ring anhydride from (27; R = H) was therefore assigned the structure (29).

The evidence outlined above established the structure (22) for allogibberic acid.

Allogibberic acid - Gibberic acid Transformation

It has been suggested[17,25] that the isomerisation of allogibberic to gibberic acid could be explained by a Wagner-Meerwein rearrangement; (22)⟶(30)⟶(1). This explanation was analogous to the conversion of 1-hydroxycamphene (31) to camphor.[33] During the course of his investigations on the biosynthesis of gibberellic acid (p. 73) Birch reported evidence, based on Kuhn-Roth oxidations of compounds biosynthesised from (1 - ^{14}C) - acetate, which implied migration of the methylene carbon atom from C_8 to C_7. It was suggested that this could occur as a consequence of preliminary hydration followed by pinacol-pinacolone rearrangement of the resulting glycol (partial structure 32).[34,35] Since this sequence, which involved a carbonium ion at a bridgehead position, seemed mechanistically improbable, Birch re-examined his earlier



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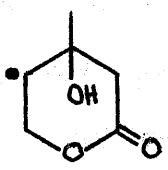

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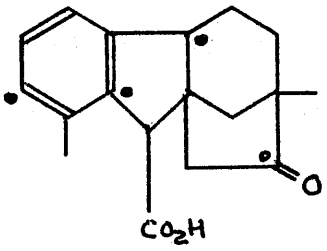

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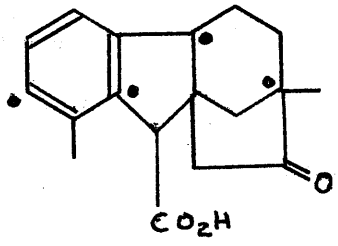

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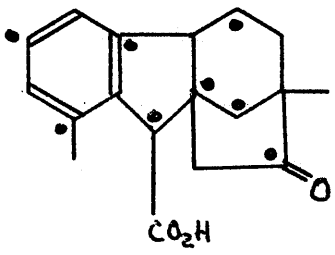

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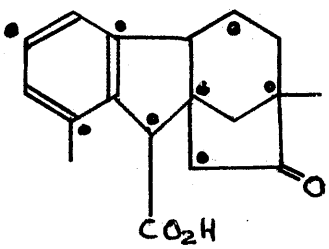
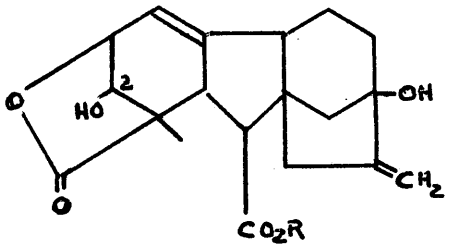


(38)

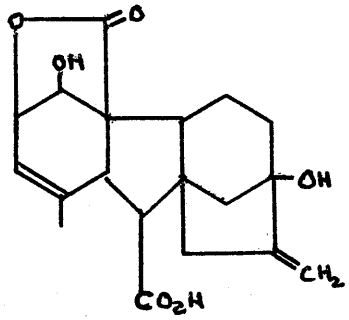
experimental findings. Thus by degrading labelled gibberellic acid (33), obtained from (4 - ^{14}C) - mevalonic lactone (34), Birch isolated gibberic acid and demonstrated, by dehydrogenation and oxidation experiments, that it possessed the labelling pattern as shown in (35).[36] This was in agreement with the migration of C_6 to C_8 and conflicted with the alternative mechanism (C_8 to C_7) which would give the pattern shown in (36). Repetition of the earlier work on the degradation of (1 - ^{14}C) - acetate-derived gibberic acid showed that gibberic acid did not possess the ^{14}C distribution (37) as reported but distribution (38) which was in agreement with the results outlined above. This confirmation of the Wagner-Meerwein mechanism also verified the stereochemistry assigned to allogibberic and gibberic acid in this region (see "Stereochemistry" p. 52).

Gibberellic acid

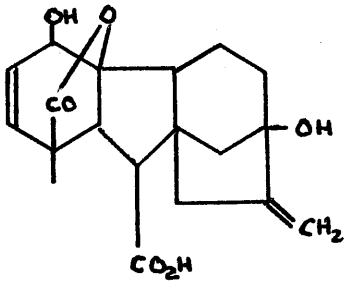
Having elucidated the structures of both allogibberic and gibberic acid Cross et al. turned their attention to the structure of gibberellic acid. They had previously suggested (p. 6) that the acid possessed a non-benzenoid tetracyclic dihydroxylactonic structure.[7] Of the two hydroxyl groups one was considered to be secondary since methyl tetrahydrogibberellate could be oxidised to a ketone $C_{20}H_{26}O_6$ while the other hydroxyl


O
2
HO
OH
O
CH2
CO2R

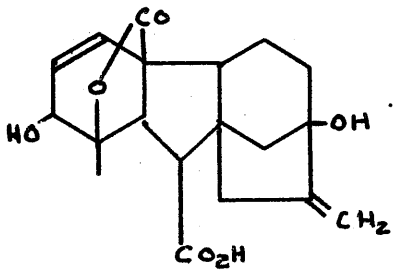
(39)


O
O
OH
OH
CH2
CO2H

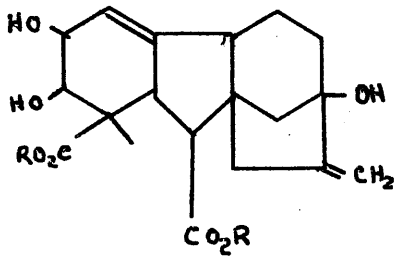
(40)


OH
O
CO
OH
CH2
CO2H

(41)


CO
O
HO
OH
CH2
CO2H

(42)

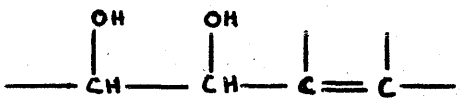

HO
HO
RO2C
OH
CH2
CO2R

(43)

group was assigned a tertiary nature because of the failure to prepare a ditosylate. The position of the carboxyl group was assumed to be the same as in gibberic acid (and, therefore, allogibberic acid) since methyl gibberellate could be converted to methyl gibberate. Of the two double bonds in gibberellic acid one was shown to be present as a terminal methylene group since ozonolysis of its methyl ester furnished formaldehyde. These facts led Cross et al. to suggest that the conversion of gibberellic to allogibberic acid involved only the aromatisation of ring A and consequently concluded that ring A accommodated the five-ring lactone, the secondary hydroxyl group, and a double bond.[17]

On the basis of the evidence outlined so far Cross et al. proposed tentative structures (39; R = H) and (40) for gibberellic acid and noted that the non-isoprenoid alternative structures (41) and (42) were not excluded by their evidence.[17]

In 1958, the I.C.I. workers (Cross et al.) published further work on the structural elucidation of gibberellic acid which, in their opinion, established that structure (39) was correct.[37] Thus periodate oxidation of the dimethyl ester ($C_{21}H_{28}O_7$)(43; R = Me) of the amorphous acid ($C_{19}H_{24}O_7.H_2O$)(43; R = H), obtained by opening the lactone ring of gibberellic acid by mild alkali,



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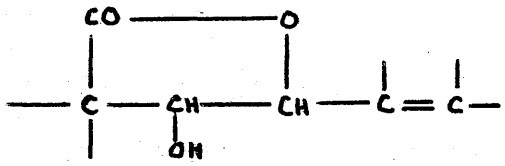

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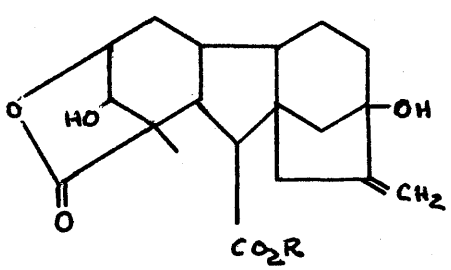

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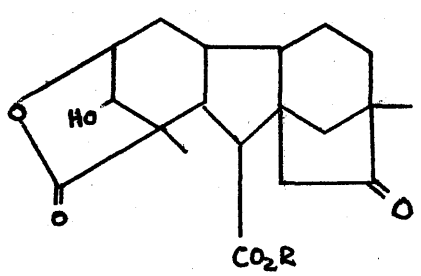
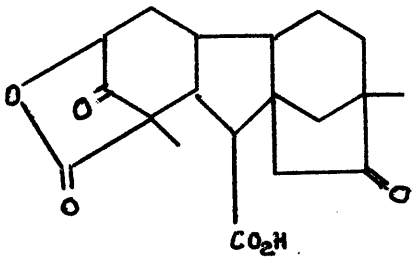


(47)

furnished a compound $C_{21}H_{26}O_7$ while oxidation with manganese dioxide in chloroform yielded a ketol $C_{21}H_{26}O_7.H_2O$ (λ_{max} 240 mu; ε 17,000 - $R_2C = CHR$). Reduction of the ketol with sodium borohydride regenerated the ester $C_{21}H_{28}O_7$ which was therefore assigned the partial structure (44). Accordingly the partial structure (45) was assumed to be present in methyl gibberellate (and hence in gibberellic acid) and could be accommodated in ring A in either of two ways to give structures (39) or (40). The nuclear magnetic resonance (NMR) spectra of methyl gibberellate and its derivatives and hydrogenation products excluded structure (40) for gibberellic acid. Thus methyl gibberellate showed a sharp, strong peak at a chemical shift (σ) value of + 4.15 which was attributed to a methyl attached to a saturated carbon atom (present in (39) but not in (40)). Moreover the alternative structure (41) was further invalidated by the absence of a similar sharp peak in the vicinity of σ + 3, usually diagnostic of the Me-C=C- group. As a final proof of structure Cross et al. provided evidence which conclusively established the position of the secondary hydroxyl group in gibberellic acid.[37] Treatment of methyl α-dihydrogibberellate (46; R = Me) with acid gave the keto-acid (47; R = H) which was oxidised in acetone by chromic oxide-sulphuric acid to a diketo acid $C_{19}H_{22}O_6$(presumably (48)).[38] Dehydrogenation



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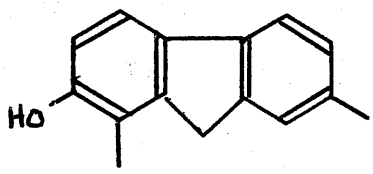
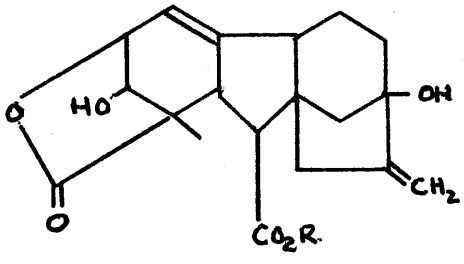
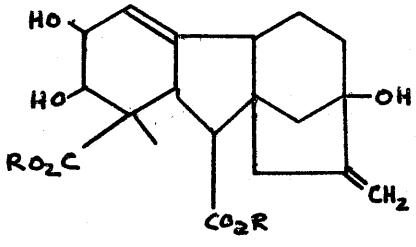


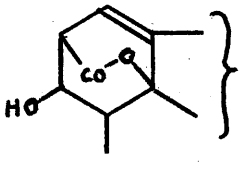
(49)



(39)



(43)

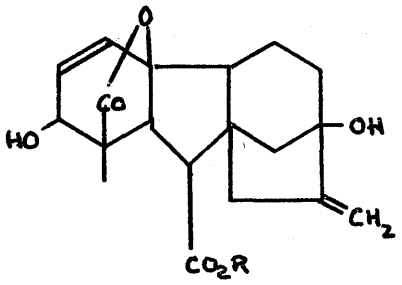


(50)

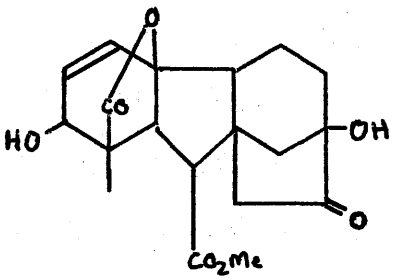
of this with selenium gave 2-hydroxy-1:7-dimethylfluorene (49) identical with a synthetic specimen.[44]

Simultaneous with the publication[37] of the structure (39; R = H) for gibberellic acid there appeared in the literature a paper by Sumiki et al.[39] which reached the same conclusion regarding the position of the secondary hydroxyl group in ring A. The latter workers, however, criticised structure (39) since they had found that reduction of methyl gibberellate and methyl α-dihydrogibberellate by lithium aluminium hydride gave the compounds $C_{19}H_{30}O_5$ and $C_{19}H_{32}O_5$ respectively, which in contrast with the acid (43; R = H) described above, did not react with periodate. They concluded, therefore, that the acid (39; R = H) was not a simple hydrolysis product of gibberellic acid and that a molecular rearrangement had occurred during its formation. Sumiki et al., therefore, proposed that gibberellic acid possessed the ring A structure (50) and presented structural arguments in its favour.[40,41]

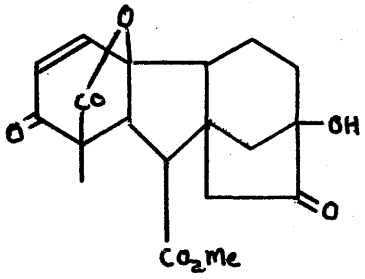
In answer to the criticism outlined above Cross et al. provided evidence which in their opinion substantiated structure (39; R = H) and explained the stability of its reduction products to periodate.[37] Relactonisation of the acid (43; R = H) followed by methylation did not yield methyl gibberellate but gave an


O
CO
HO
OH
CH2
CO2R

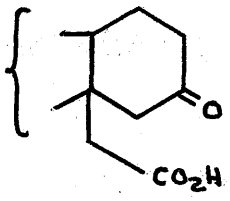
(51)


O
CO
HO
OH
O
CO2Me

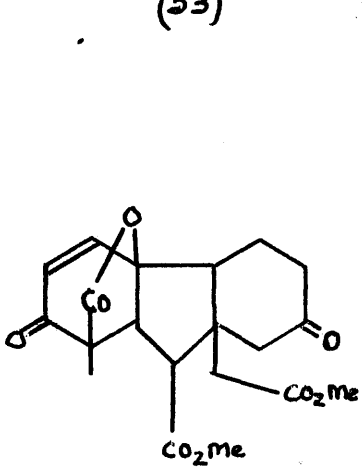
(52)


O
CO
O
OH
O
CO2Me

(53)


O
CO2H

(54)

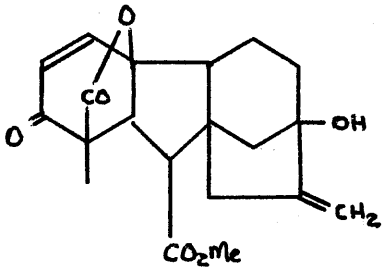

O
CO
O
O
CO2Me
CO2Me

(55)

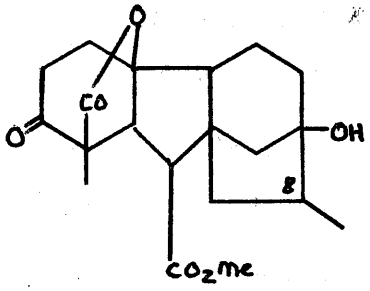
isomer (m.p. 174°) which could also be obtained directly from methyl gibberellate by the action of 0.01N sodium hydroxide. Cross et al. suggested that this isomer was the 2-epimeric alcohol by analogy with the 2-epimerisation of methyl α-dihydrogibberellate which had been shown to take place under identical conditions. Thus they concluded that gibberellic acid did not undergo molecular rearrangement on mild alkaline hydrolysis but that epimerisation did take place giving a cis-1:2-diol. The stability of the reduction products of methyl gibberellate and methyl α-dihydrogibberellate to periodate was explained by postulating either cyclic ether structures or products with trans-disposed oxygen functions in ring A.

Finally in 1959, further work by Cross et al. demonstrated that gibberellic acid had the structure (51; R = H) and, in agreement with the suggestion by the Japanese workers, admitted that a rearrangement occurred during the formation of the acid (43; R = H).[42]

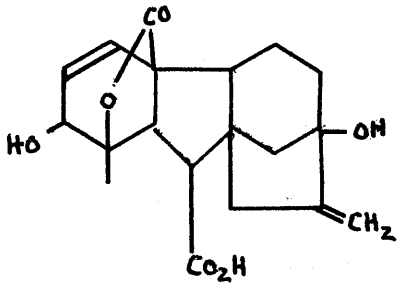
Thus ozonolysis of methyl gibberellate furnished a ketol $C_{19}H_{22}O_7$(52) which, with chromic oxide in chloroform, gave the ketone $C_{19}H_{20}O_7$(53)(λ_{max} 229 mu, ε 7,050). The methyl ester of the acid (54), derived from the ketol (52), on oxidation with manganese dioxide in chloroform also furnished a ketone $C_{20}H_{22}O_8$(55)(λ_{max} 229 mu, ε 7,500). The ultraviolet spectra of these compounds indicated the presence



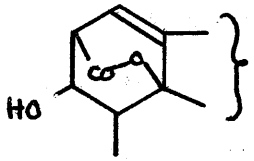
(56)



(57)



(58)

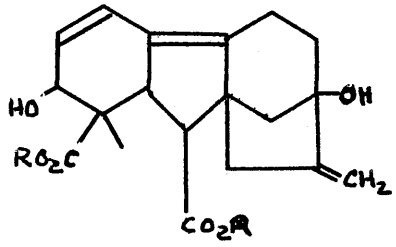


(50)

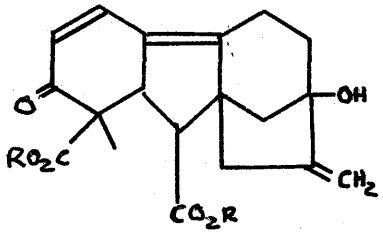
of an enone group and this prompted the I.C.I. workers to re-investigate the oxidation of methyl gibberellate with manganese dioxide. Previously a manganese dioxide preparation had left methyl gibberellate unchanged. Further study, however, resulted in a more active preparation of this reagent which was found to oxidise methyl gibberellate to an α,β-unsaturated ketone, $C_{20}H_{22}O_6$, (56)(λ_{max} 228 mu, ε 9,700). Hydrogenation of this ketone gave a saturated ketone (57) which was also obtained, together with the previously described 8-epimer,[17] by chromic acid oxidation of the mixed methyl tetrahydrogibberellate derived from methyl gibberellate by hydrogenation. It was concluded, therefore, that no rearrangement had taken place during the formation of the ketone (56) from methyl gibberellate and that the latter was an allylic alcohol.[42]

The above evidence when considered with the earlier work,[37] which established the position of the secondary hydroxyl group, was quite inconsistent with the ring A structure (50) advanced by the Japanese workers[41] and left only two possible structures for gibberellic acid, namely (51) and (58).

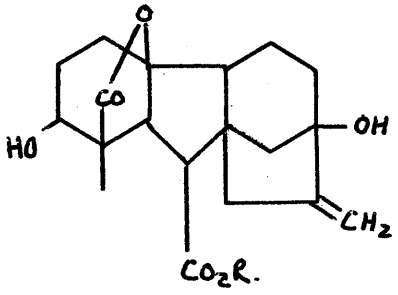
The structure (58) did not accommodate the formation, in dilute acid, of gibberellenic acid $C_{19}H_{22}O_6$ which was assigned the heteroannular diene structure (59; R = H) on the basis of its ultraviolet spectrum



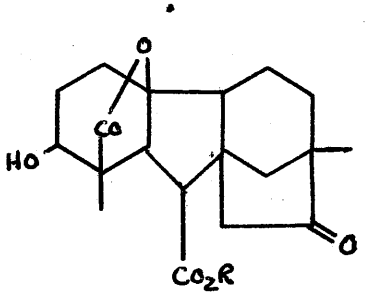
(59)



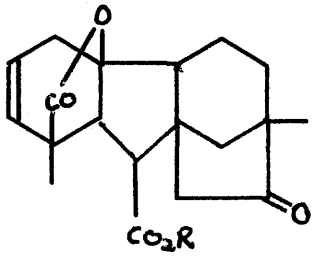
(60)



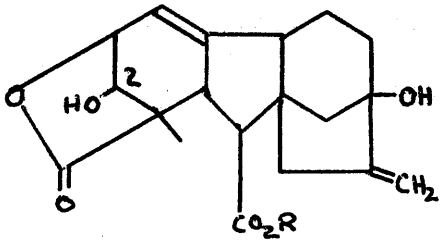
(61)



(62)



(63)



(39)

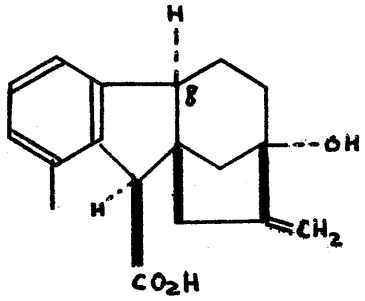
(λ_{max} 253 mu, ϵ 21,400) and by the fact that its dimethyl ester (59; R = Me) furnished a dienone $C_{21}H_{24}O_6$ (60; R = Me) (λ_{max} 309 mu, ϵ 16,500) on oxidation with manganese dioxide.[42] Cross et al. therefore concluded that gibberellic acid had structure (51; R = H) and α-dihydrogibberellic acid (gibberellin A_1) the structure (61; R = H).

Further confirmation for these structures was obtained in the following way. Treatment with collidine of the toluene-p-sulphonate of the keto ester $C_{20}H_{26}O_6$ (62; R = Me), obtained from methyl α-dihydrogibberellate (61; R = Me) with acid, gave the anhydro-compound (63; R = Me). This reaction was consistent with the structure (62; R = Me) but impossible with the alternative structure (47).

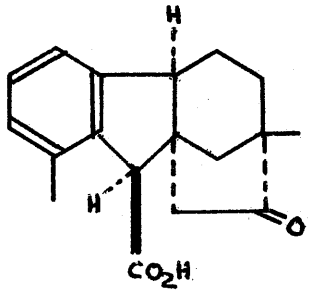
Having admitted that a rearrangement had occurred during the formation of the acid (43) Cross et al.[42] then concluded that the structure of the isomer (m.p. 174°C.) of methyl gibberellate (p.45) was (39; R = Me) which had previously been assigned[37] to methyl gibberellate. This isomer which was previously considered to be the 2-epimer of methyl gibberellate was not oxidised by manganese dioxide. Moreover a comparison of the nuclear magnetic resonance spectra of methyl gibberellate and the isomer (m.p. 174°C.) indicated that these esters were not epimers.

The results of more detailed studies on the

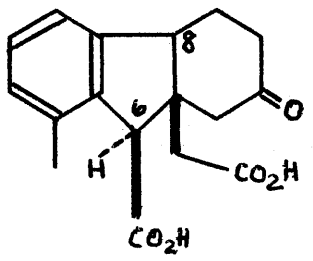
chemistry of gibberellic acid and its degradation products have recently been reported in the literature.[43-46]



(64)



(65)



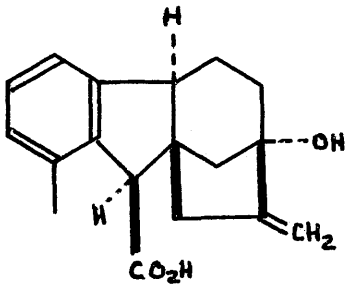
(66)

(b) Stereochemistry

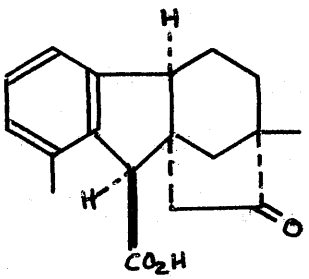
With the establishment of the structure (51; R = H) for gibberellic acid[42] the problems of stereochemistry, biogenesis and synthesis remained to be solved. Before the publication of the revised structure of Cross et al., Stork and H. Newman published the results of their work on the stereochemistry of allogibberic and gibberic acid. These results permitted the assignments of stereochemistry as shown in (64) and (65) respectively.[47] They arrived at their conclusions in the following way.

It was first established that the carboxyl group in allogibberic acid was cis to the two-carbon bridge of the bicyclo-(1,2,3)-octane system. This followed from the fact that the diacid (66) was known to give an anhydride (p.30). Stork and Newman demonstrated that the C_6 epimer of (66) gave the same anhydride as (66) when refluxed with acetic anhydride and, since this behaviour was compatible only with a cis relationship of the two acid groups in (66),[48,49] concluded that the C_6-carboxyl and the two-carbon bridge were cis to each other.

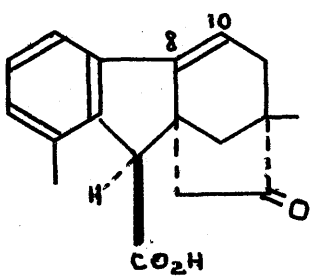
The mechanism of the rearrangement of allogibberic to gibberic acid (p.35) required that the two-carbon bridge in gibberic acid had the opposite configuration from that which it occupied in allogibberic acid. This mechanistic consideration was compelling but, since the evidence was



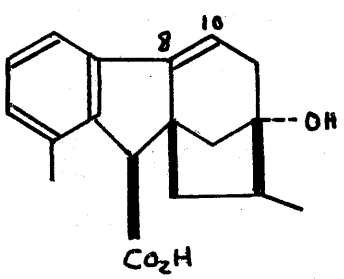
(64)



(65)



(67)

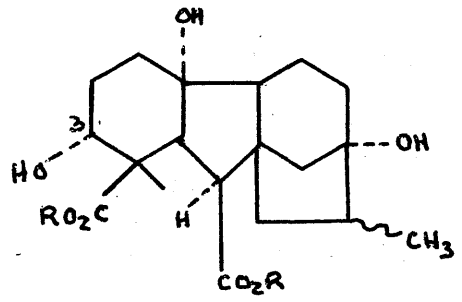


(68)

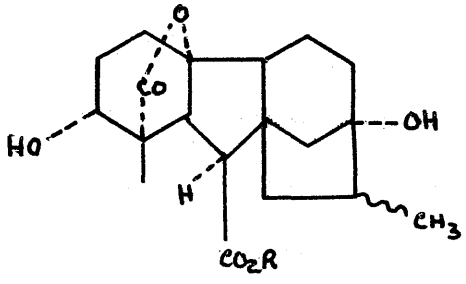
contradictory,[34] Stork and H. Newman conclusively established this point by demonstrating that the rotatory dispersion curve of (65) was the mirror image of that of the ketone obtained by ozonolysis of (64).

This "inversion" of the two-carbon bridge led to the conclusion that the B/C junction was cis in one member of the gibberic-allogibberic acid pair and trans in the other. In support of this catalytic hydrogenation of the $\Delta^{8,10}$-olefins derived from (65) and from the dihydro-derivative of (64)((67) and (68) respectively) resulted in the regeneration of the stereochemistry of C_8 present in the parent substance. Stork and H. Newman suggested that catalytic hydrogenation of these bicyclo-octane systems had thus produced a cis B/C junction in one case and a trans junction in the other, i.e. the reduction had taken place cis to the two-carbon bridge in one substance and trans in the other. They concluded, therefore, that since reduction takes place trans to the two-carbon bridge in only one of the two cases it must be that in which both the carboxyl and the bridge are on the same side of the plane. Since such a trans reduction regenerated the original stereochemistry, allogibberic acid was assigned the structure (64).[47]

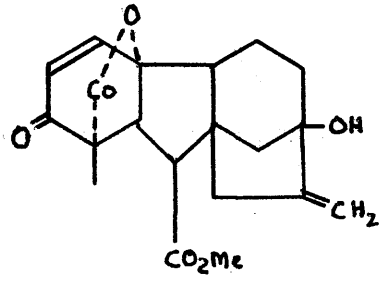
The structures (64) and (65) represent the relative stereochemistry of the four asymmetric centres in these molecules. Stork and H. Newman showed that it also



(69)



(70)



(71)

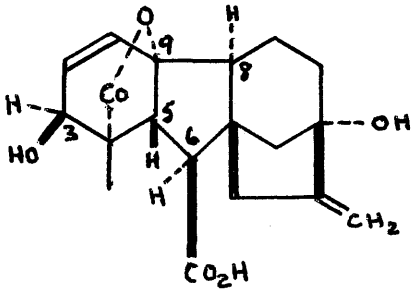
represented the absolute stereochemistry.[47] Thus the keto acid (66) which has been shown to have a trans B/C fusion, had a rotatory dispersion curve which possessed the same sign of the cotton effect as cholestanone or the related (+)-trans-8-methylhydrindanone.[50] The absolute stereochemistry of (64) and (65) was thus established.

In a later paper Stork and H. Newman extended their results on the stereochemistry of allogibberic acid to that of gibberellic acid.[51] First of all the relationship of the lactone ring to the β-oriented two-carbon bridge of ring D was deduced from the demonstration that the lactone was α-oriented. Tetrahydrogibberellic acid on treatment with 20% sodium hydroxide solution for eighteen hours yielded a diacid (69; R = H) whose dimethyl ester had $[\alpha]_D^{EtOH}$ -40.3°. By refluxing the diacid for two hours with ethyl acetate containing a drop of concentrated hydrochloric acid they obtained a lactonic acid (70; R = H) isomeric with tetrahydrogibberellic acid. The lactonic acid methyl ester (70; R = Me) had $[\alpha]_D^{EtOH}$ +34.4°. That the lactonic acid (70) possessed the same lactone ring system as gibberellic acid was shown in the following manner. Oxidation of methyl gibberellate with manganese dioxide gave the corresponding ketone (71)(λ_{max} 228 mu, ε 7,500). Reduction of this unsaturated ketone with platinum oxide in acetic acid gave a substance identical

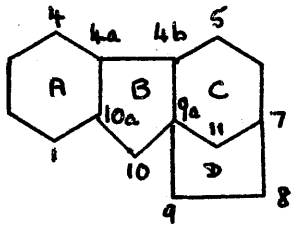
(infrared, mixed m.p.) with (70; R = Me). This established that (70; R = H) differed from tetrahydrogibberellic acid ONLY at the C_3 hydroxyl group. The large positive rotation difference between the lactonic ester (70; R = Me) and the conformationally related diester (69; R = Me) established the α-orientation of the lactone ring.[52]

The assignment of β-orientation to the C_5 hydrogen atom was based on the following reasoning. It was argued that if the C_5 hydrogen were α, C_6 would be axial to ring A and the C_6 carboxyl group, which is known to be β, would have the less stable of the two possible orientations. Base hydrolysis of the methyl ester of tetrahydrogibberellic acid followed by relactonisation gave the same 3-epi-tetrahydrogibberellic acid (70; R = H) obtained from hydrolysis of the acid itself. Since (70; R = H) had the original orientation of the carboxyl group, no epimerisation had taken place and it was concluded that C_6 was equatorially linked to ring A.

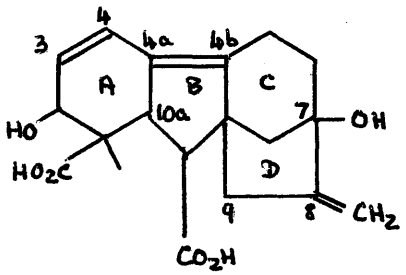
The observation (quoted above) that the 3-epi configuration of (70; R = H) was formed on catalytic hydrogenation of the 3-ketone from gibberellic acid implied α-stereochemistry for the 3-epi series (adsorption from the β-side, trans to the lactone). As a consequence of this Stork and H. Newman assigned a 3β-hydroxyl group


O
H
9
8
H
Co
5
3
6
H
H
HO
OH
CH2
CO2H

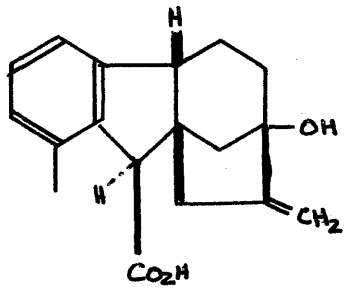
(72)


4
4a
4b
5
A
B
C
10a
9a
11
7
1
10
D
9
8

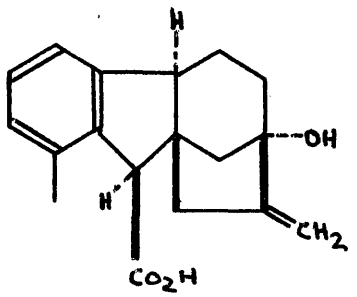
(73)


4
3
4a
4b
A
B
C
7
HO
10a
OH
HO2C
D
9
8
CH2
CO2H

(74)


H
OH
H
CH2
CO2H

(75)

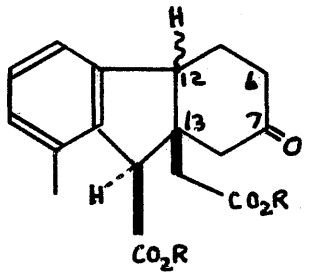

H
OH
H
CH2
CO2H

(64)

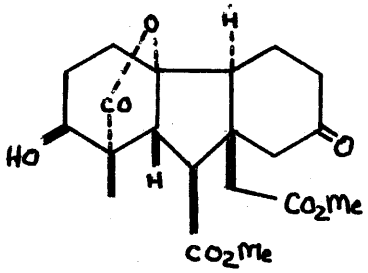
to gibberellic acid.[51] The same conclusion was reached by Cross et al. who noted that the base epimerisation of C_3 implied axial⟶ equatorial transformation (presumably via dealdolisation-realdolisation).[37]

Finally Stork and H. Newman provided strong but not rigorous evidence for the α-orientation of the C_8 hydrogen in gibberellic acid (as in allogibberic acid).[51] They showed that there was a close correspondence in shape and intensity of the rotatory dispersion curve from the seco keto esters derived from the oxidation of ring D of methyl allogibberate and of the acetate of methyl α-dihydrogibberellate ($[\alpha]_{314}^{CH_3OH}$ +1070 in both cases). Gibberellic acid was therefore assigned the stereochemistry (72).[51]

The same conclusions regarding the stereochemistry of gibberellic acid were reached by Cross et al. whose results were published simultaneously.[53] The nomenclature adopted by the latter workers was based on the fully substituted tetracyclic system (73) to which they assigned the trivial name, gibbane. Gibberellenic acid (74)[42] with hydrazine hydrate yielded allogibberic acid (64) and its C(4b)-epimer epiallogibberic acid (75) (the latter compound was convertible to epigibberic acid[7] with acid). Studies of anhydride formation of the keto acids (76; R = H) obtained from compounds (64) and (75)



(76)



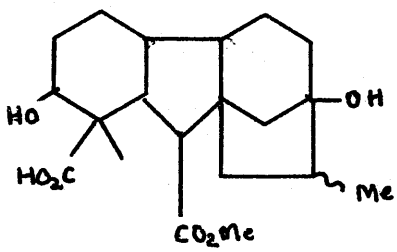
(77)

by ozonolysis, and of the optical rotatory dispersion (O.R.D.) curves of the corresponding esters (76; R = Me) led Cross et al. to assign the absolute configurations (64) and (75) to allogibberic and epiallogibberic acid respectively. The O.R.D. curves of a number of related keto-acids and esters of type (76) all showed positive Cotton effect curves[54] in accordance with the predictions of the Octant rule[55] for such structures.

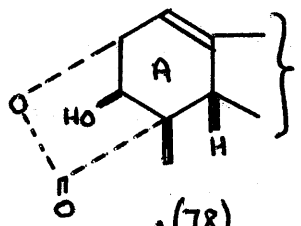
Several compounds enantiomeric at C(13) (fluorene numbering) were prepared from (76; R = Me) by an intramolecular Claisen-type condensation at C(6) followed by fission of the C_6-C_7 bond. These compounds gave negative Cotton effect curves.

The O.R.D. curve for the keto-ester (77) obtained by ozonolysis of methyl Δ^{1}-dihydrogibberellate was almost identical with the curve for the keto-ester (76; R = Me, C(12α)) derived from allogibberic and significantly different from that for the keto-ester (76; R = Me, C(12β)) obtained from epiallogibberic acid. Gibberellic acid therefore has the same <u>trans</u> B/C ring junction as allogibberic acid.

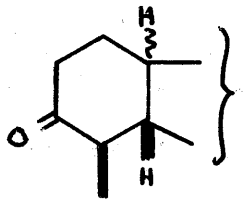
Catalytic hydrogenolysis of methyl gibberellate and of the ester (78), produced by its alkali-induced isomerisation, gave the same acid (79) showing that epimerisation of the 2-hydroxyl substituent (cf. methyl



(79)



(78)

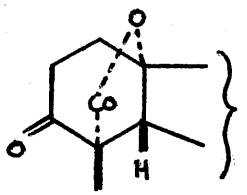


(80)

α-dihydrogibberellate[37]) did not occur during the isomerisation. Since hydrogenolysis of the lactone ring of (78) preceded reduction of the Δ^4-ethylenic bond, which must then have taken place *trans* to the liberated carboxyl group, Cross et al. concluded that the formation of (79) from methyl gibberellate involved inversion of configuration at C(4a).[53]

Oxidation and decarboxylation of the acid (79) yielded a ketone (80) the O.R.D. curve of which showed a negative Cotton effect in agreement with a β-hydrogen at C(10a). This led to the assignment of the configurations 4aα, 10aβ (*trans*, antipodal to a 3-oxo-5α-steroid) or 4aβ, 10aβ (*cis*, curve similar in sign and amplitude to that of a 3-oxo-5β-steroid) for the ketone. Cross et al. stated that the latter was the more probable configuration (i.e. *cis*), C(4a) being inverted in methyl gibberellate.[53] Moreover, the nuclear magnetic resonance spectrum of methyl acetylgibberellate showed that the protons at C(10) and C(10a) were *trans*, thus confirming the stereochemical assignment at C(10a).

Having assigned a β-hydrogen at the 10a position Cross et al. were left with a choice between two possible configurations at the A/B ring junction in gibberellic acid. This was resolved by an examination of the ring A ketone (obtained by oxidation of methyl tetrahydro-



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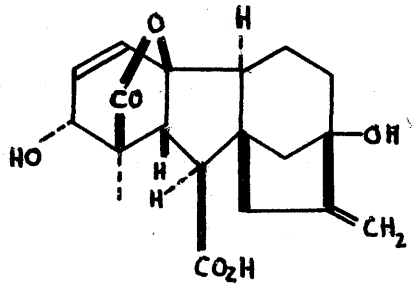
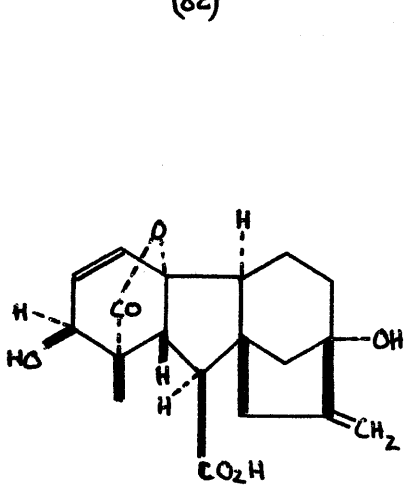


(82)



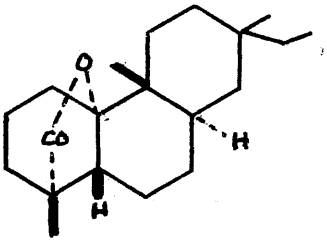
(72)

gibberellate) which showed a strong positive Cotton effect consistent with the absolute configuration (81). This conclusion agreed with that of Stork and Newman.[51]

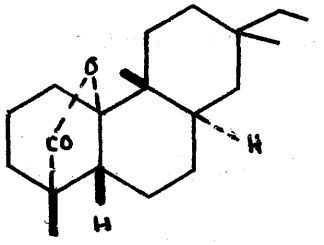
The assignment of an axial configuration to the ring A hydroxyl substituent in methyl α-dihydrogibberellate was also proposed by Cross et al.[53] This configuration was supported by the formation of a ring A anhydro compound and by sodium borohydride reduction of the ketone (81) which gave predominantly the C(2) epimer of methyl tetrahydrogibberellate.

The evidence outlined above led Cross et al. to propose that the trans-syn-trans structure (72) represented the absolute configuration of gibberellic acid.[53] They have also commented on the strained cis-fused A/B structure (82) which more readily explains the rearrangement of methyl gibberellate to the ester (78) and the formation of gibberellenic acid (74) from gibberellic acid by trans elimination. They concluded, however, that this structure was inconsistent with the O.R.D. results and with the facile closure and stability of the lactone ring in methyl α-dihydrogibberellate.

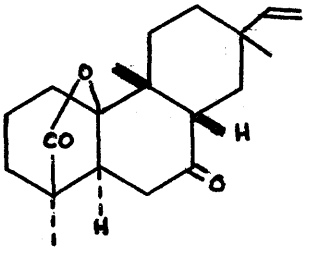
Recently, however, Edwards et al. have assigned a β-orientation to the lactone ring of gibberellic acid and have drawn attention to the fact that comparison of the rotational changes on ring opening of diterpenoid



(83)



(84)



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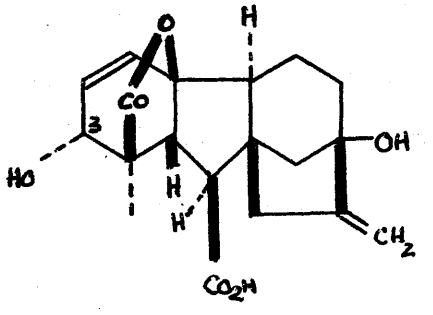


(86) (≡ 82).

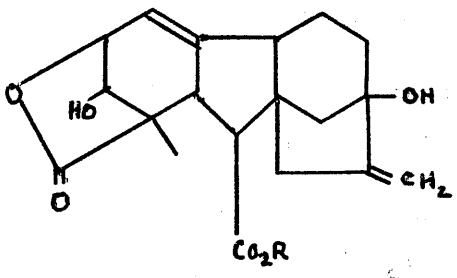
lactones of known configuration with that of 3-epitetrahydrogibberellic acid leads them to this conclusion.[56]

Thus dihydroisopimaric γ-lactone (83)[57] was opened with sodium hydroxide in triethylene glycol at 150°C. The resulting hydroxy-acid had $[\alpha]_D$ +40° whence $\Delta_D = [\alpha]_D(\text{lactone}) - [\alpha]_D(\text{acid}) = -130°$. Le van Thoi and Ourgaud[58] had reported $[\alpha]_j$ -17° for the γ-lactone from dihydropimaric acid (84) and $[\alpha]_j$ +33° for the corresponding hydroxy-acid making $\Delta_j = -50°$. Edwards et al. therefore emphasised that the Δ value for α-oriented γ-lactones was large and negative.

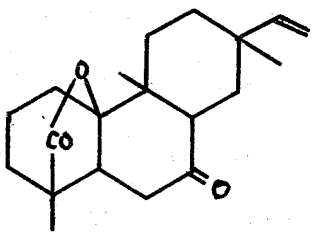
By comparison the Δ_D values for the opening of β-oriented γ-lactone rings of isorosenonolactone (85)[59,60] to methyl isorosenonate and of dihydroisorosenonolactone to methyl dihydroisorosenonate are +36° and +52° respectively.

Since the Δ_D for the conversion of 3-epitetrahydrogibberellic acid[51] to the corresponding methyl ester is +74° it was concluded that the ring A stereochemistry of gibberellic acid was as shown in (86). In addition Edwards et al. have concluded that the 3-hydroxyl group was α-oriented in gibberellic acid and β-oriented in 3-epitetrahydrogibberellic acid.

A more detailed account of the stereochemical studies on epiallogibberic and epigibberic acid has recently been reported in the literature.[61,62]



(39)



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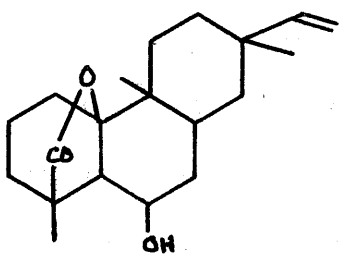

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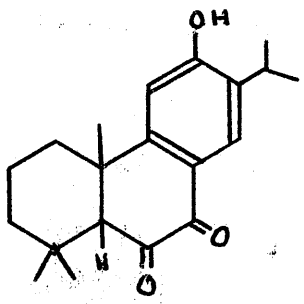
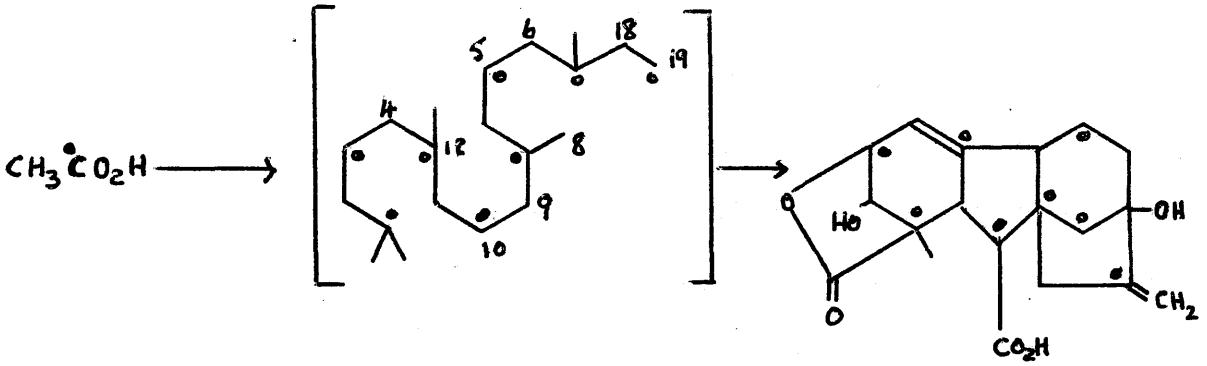


(89)

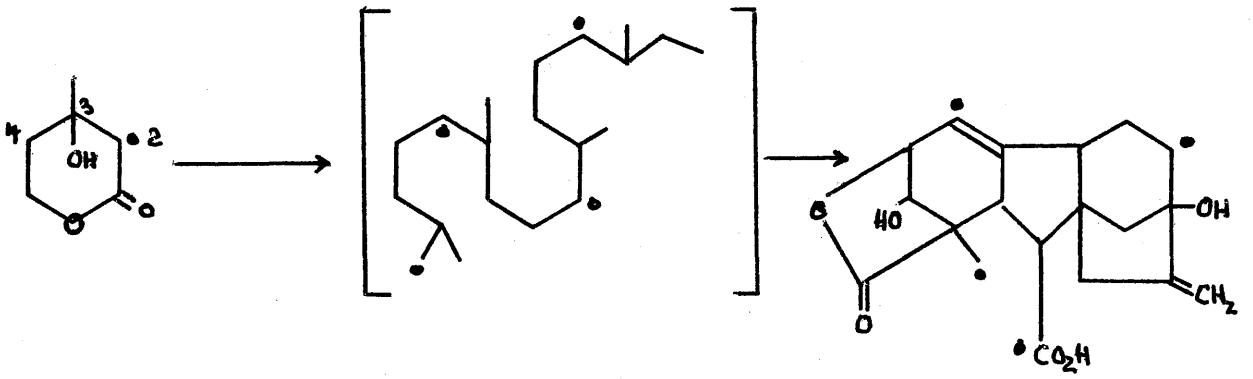
(c) Biogenesis

After the erroneous assignment of structure (39; R = H)[37] for gibberellic acid speculation arose concerning its biogenesis. In 1958-9, Birch produced evidence which indicated that gibberellic acid was biosynthesised by a variant of the diterpene resin acid process.[34,35] This involved, besides oxidation, a number of additional steps for which there were biochemical or laboratory analogies. The various steps included (a) oxidative loss of the methyl group attached to the 12-position; (b) ring contraction of ring 3 with extrusion of a carbon atom and formation of a cyclopentane carboxylic acid unit, and (c) rearrangement of ring C resulting in the generation of a phyllocladene-type of bridged-ring structure.

Step (a) was considered to be analogous to the loss of the angular group attached to the 14-position in the lanosterol-cholesterol conversion.[63] In view of the occurrence of diterpenes with oxygen substituents in the 9- or 10-positions or both (e.g. rosenonolactone (87),[64] rosololactone (88)[65] which occur together, and xanthopherol (89)[66]) Birch suggested that step (b) proceeded via a 9:10-dioxygenated intermediate and listed ways in which this could be transformed to a cyclopentane carboxylic acid unit. These included; (i) a benzil-benzilic acid type of rearrangement leading to a



(90a) (39a)

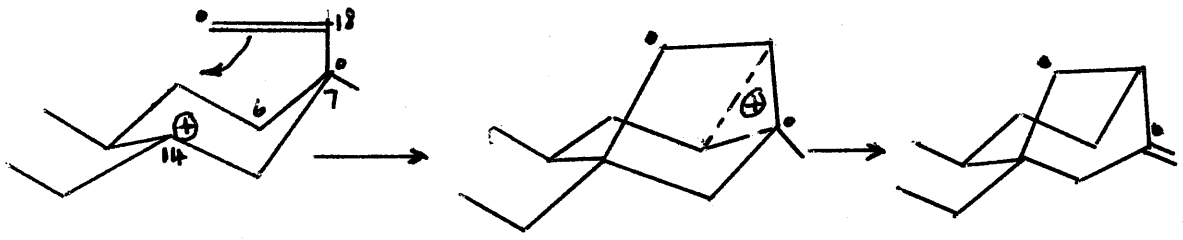


(91) (90b) (39b)

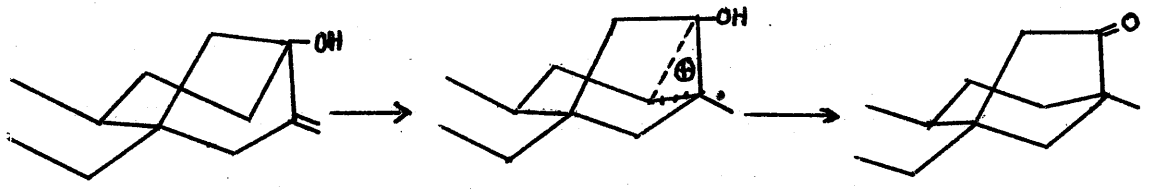
1-hydroxycyclopentane carboxylic acid; (ii) a Faworski-type rearrangement of an esterified 2-hydroxyketone leading directly to a cyclopentane carboxylic acid, and (iii) rearrangement of a diesterified diequatorial cyclohexane-1:2-diol of a type observed to convert an 11-acetoxy (or tosyloxy)-12-tosyloxy (or acetoxy-) steroid into a C-norsteroid[67] from which a cyclopentane aldehyde would result. Finally, step (c) was analogous to the acid-catalysed transformation of rimuene to phyllocladene.[68]

By degrading labelled gibberellic acid obtained from growth media containing either $CH_3{}^{14}CO_2H$ or (2-^{14}C)-mevalonic lactone (91) Birch was able to show that the degradations were in quantitative agreement with the labelling patterns shown in (39a) and (39b) and with the formation of gibberellic acid from 4 molecules of mevalonic lactone or 12 molecules of acetic acid. The degradation methods were essentially those used in the structure determination.

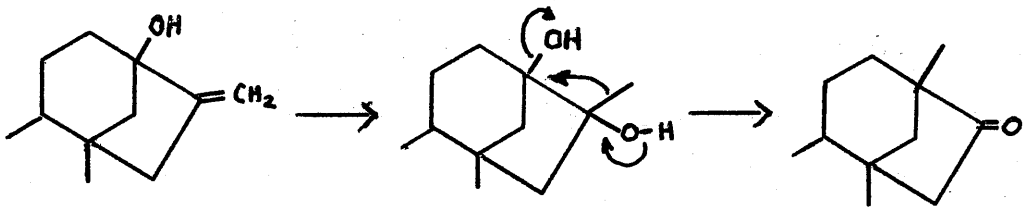
Reference to the predicted labelling patterns (90a) and (90b) in the diterpene precursor showed clearly that the lactone carbonyl carbon atom was derived specifically from the 3-position of mevalonic lactone and that the carboxylic carbon of gibberellic acid arose specifically from the 9-position of the diterpenoid precursor. In addition the degradations indicated that



(92) (93)



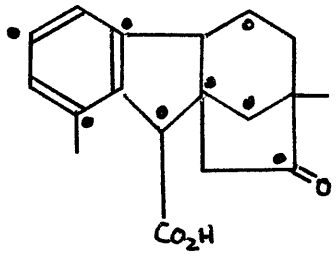
(94) (95)



(96) (97)

the formation of the phyllocladene ring system occured through the migration of C_6 from C_7 to C_{18} as in the sequence (92)⟶(93). Thus the original methyl group (becoming = CH_2 in the final product) remained attached to a labelled carbon atom if $CH_3{}^{14}CO_2H$ was the precursor. This view of the mechanism of formation of the bridged ring system was in accord with the views expressed by Wenkert in the case of the analogous phyllocladene system.[69]

As a result of his initial degradational studies on labelled gibberellic acid, Birch[34,35] also obtained information regarding the rearrangements of gibberellic acid which questioned the validity of the Wagner-Meerwein mechanism, (94)⟶(95), proposed by Cross et al.[17] for the gibberellic-gibberic acid transformation (p. 35). By degrading gibberellic acid (39a), derived from $CH_3{}^{14}CO_2H$, Birch obtained gibberic acid to which he assigned the labelling pattern (37) on the basis of further degradational experiments. Thus it was suggested that the transformations involved preliminary hydration of the exomethylene double bond followed by a pinacol-pinacolone rearrangement (96)⟶(97). Since the latter sequence involved a carbonium ion at a bridgehead and as such was mechanistically improbable, Birch examined the rearrangement further. Repetition of the earlier work, however, showed that gibberic acid did not possess the ^{14}C-



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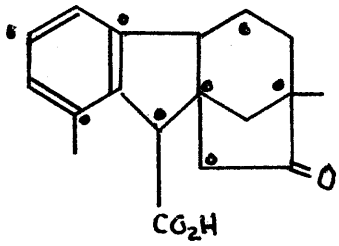

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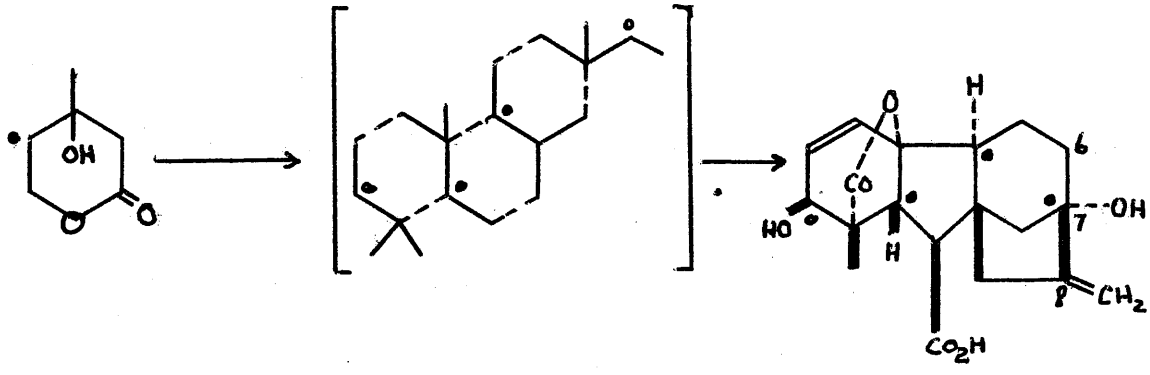
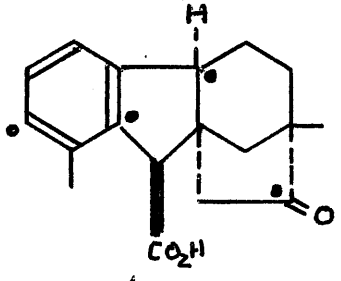


(34)

(98)



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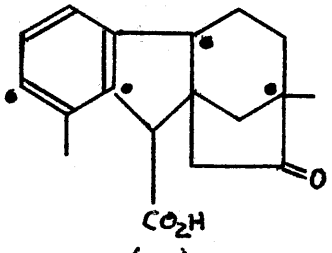

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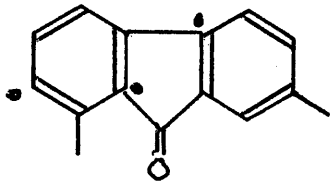


(100)

distribution (37) but distribution (38) which was in agreement with the Wagner-Meerwein mechanism of rearrangement. Further confirmation for the latter was obtained by degrading gibberellic acid (98) obtained from (4-^{14}C)-mevalonic lactone (34).[36] Thus Birch was able to show that the gibberic acid obtained from (98) had the labelling pattern (99) in agreement with the migration of C_6 to C_8. In addition, dehydrogenation and oxidation of (99) furnished (100) and indicated that the loss of the D-ring bridge had involved the loss of one of the four labelled atoms. The alternative mechanism of methylene carbon migration would have given gibberic acid with the labelling pattern (36) which, on dehydrogenation and oxidation, would have retained its four labelled atoms.

This confirmation by Birch of the Wagner-Meerwein mechanism has also verified the stereochemistry assigned to the compounds in this region.

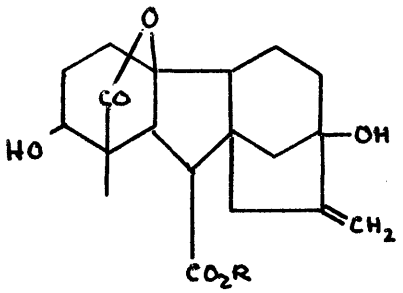
(d) **The Gibberellins**

In addition to gibberellic acid (gibberellin A_3) the fungus Gibberella fujikuroi produces other monobasic acid compounds (gibberellin A_1, A_2 and A_4). Those which closely resemble gibberellic acid in biological properties and chemical structure are collectively known as the gibberellins. At the present time the naturally occuring gibberellins consist of a group of tetracyclic lactonic carboxylic acids. All have one or more hydroxyl substituents and the majority have one or more ethylenic bonds present in or attached to the tetracyclic system; there is no evidence that either of these structural features is essential to biological activity. The gibberellins can now be regarded as a new class of natural plant-growth hormones.

Takahashi et al.[6] working with strains of the fungus different from those of the I.C.I. workers and using a medium with a higher nitrogen carbon ratio obtained a mixture, "gibberellin A", from which they isolated gibberellin A_1, $C_{19}H_{24}O_6$, gibberellin A_2, $C_{19}H_{26}O_6$, and gibberellin A_3 (gibberellic acid). Using the same medium as the Japanese workers but a different strain of G. fujikuroi Stodola et al.[5] obtained a mixture which they separated[70] by chromatography on Celite into gibberellin A_1, and gibberellin X (gibberellic acid). Gibberellin A_1 has

also been isolated from immature bean seed (Phaseolus multiflorus). Recently Macmillan et al.[71] have isolated another plant-growth promoting acid from the same source and, since it is very similar in biological properties and chemical structure to the fungal gibberellins, they have named this compound gibberellin A_5.

Gibberellic acid, gibberellin A_1, and gibberellin A_2 have been shown by hydrogenation experiments to contain two, one and no double bonds respectively.[6,73] Kitamura et al. considered the possibility that the gibberellins A_1 and A_2 might be reduction products of gibberellic acid but their evidence is somewhat inconclusive.[74] However Grove et al. have shown that gibberellin A_1 is a dihydro derivative of gibberellic acid.[75] Thus careful, partial hydrogenation of methyl gibberellate (uptake 0.94 mol.) furnished a mixture from which an acidic and neutral fraction were isolated. Crystallisation of the latter gave a mixture of methyl dihydrogibberellates $[\alpha]_D$+55° which was separated into α- and β-isomers, $[\alpha]_D$ +46° and $[\alpha]_D$+74° respectively. The former was identical with gibberellin A_1 methyl ester and with methyl α-dihydro-gibberellate. Grove et al. also provided evidence which indicated that methyl α-dihydrogibberellate (gibberellin A_1) was formed by reduction of the ring A double bond in gibberellic acid.[8] Thus ozonolysis furnished formaldehyde



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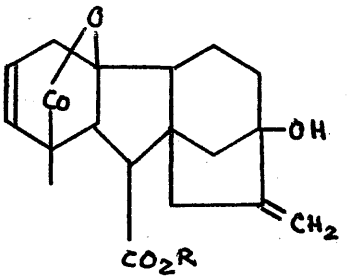

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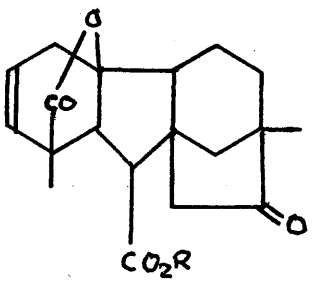

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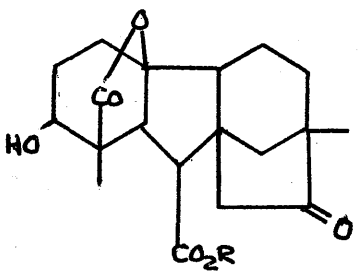

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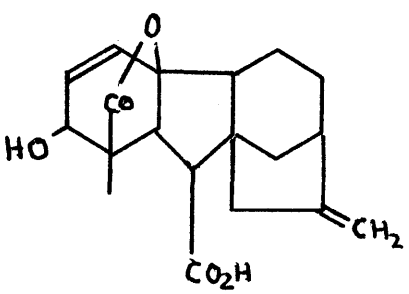


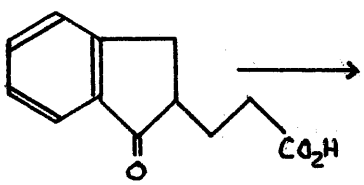
(102)

(a fact previously reported by Seta et al.[32]) which indicated that the terminal methylene group in ring D was still present in methyl ∝-dihydrogibberellate (gibberellin A_1). Gibberellin A_1 may therefore be assigned the structure (61; R = H). The structures of gibberellin A_2 and gibberellin A_4 remain to be elucidated.

Gibberellin A_5, $C_{19}H_{22}O_5$, has recently been assigned the structure (101; R = H). Hydrogenation of the ester (101; R = Me) furnished a tetrahydro derivative and the absence of hydrogenolysis products suggested that there was no double bond allylic to the lactone hydroxyl function as in gibberellic acid.[42] Acid catalysed rearrangement of the acid (101; R = H) furnished the keto acid (63; R = H). Similar treatment of ∝-dihydro-gibberellic acid (gibberellin A_1) (61; R = H) with dilute hydrochloric acid gave the analogous ketone (62; R = H) which indicated that the acids (101; R = H) and (61; R = H) have the same C/D ring structure.[37] Treatment of the toluene-p-sulphonate of (62; R = Me) with collidine furnished an unsaturated ester identical with (63; R = Me) while hydrolysis gave the corresponding acid (63; R = H). It was concluded, therefore, that only structure (101; R = H) for gibberellin A_5 was consistent with these results.[72]

Recently the structure (102) has been assigned

to gibberellin A_7 which is yet another metabolic product of the fungus Gibberella fujikuroi.[76]



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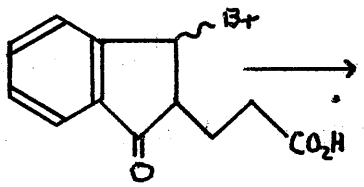

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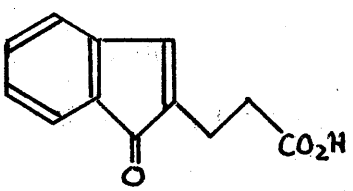

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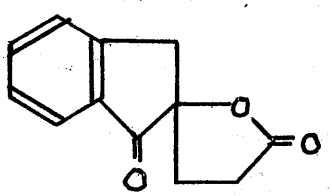


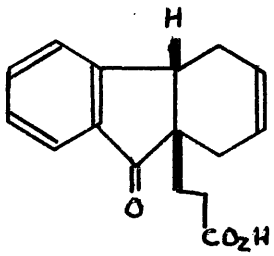
(106)

(2) Synthetic Routes to Degradation Products

As yet there has been no recorded synthesis of gibberellic acid or any of its immediate degradation products. Recently, however, House and his co-workers at the Massachusetts Institute of Technology have published the results of their preliminary studies on synthetic approaches to the degradation products of gibberellic acid.[77,78,79] The essential details of their findings are outlined below.

After a fairly extensive study of the preparative routes to 2-substituted indenones, House devised a synthesis of 2-(2-indenonyl)-propionic acid (105) which he regarded as an important starting material for his projected syntheses.[77] Thus the propionic acid (103) was first obtained by the cyclisation of α-benzyl glutaric acid in the presence of anhydrous hydrogen fluoride as previously described by Ansell and Hey.[80] Reaction of the indanone (103) with N-bromsuccinamide afforded a mixture of bromo-acids (assigned the structure (104)) which reacted readily with γ-collidine to form the desired indenone (105) (15% overall yield) and an isomeric neutral compound (36% yield). The latter was assigned the γ-lactone structure (106) from an examination of its spectral properties.

Having achieved the synthesis of the required



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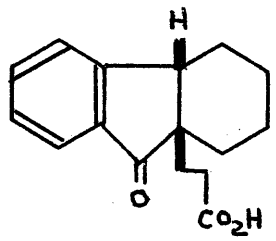

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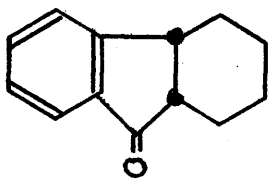

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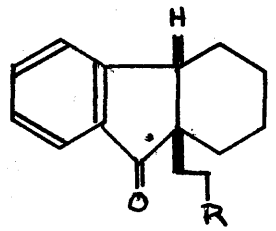
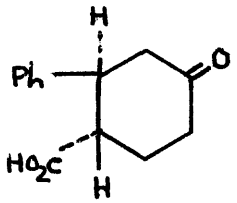
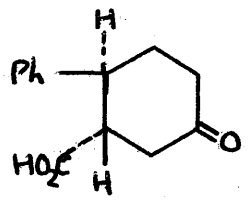


(110) (R = CN)
(111) (R = CO_2Me)



(114)

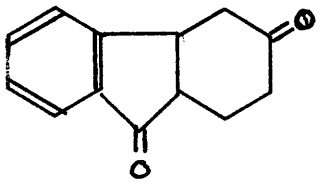


(115)

indenone (105), House then investigated methods of preparing cis-hexahydrofluorenone derivatives and succeeded in synthesising the cis-keto-acid (108) by two alternative routes.[78] One route involved a Diels-Alder reaction between (105) and butadiene. The resulting unsaturated cis-keto-acid (107), obtained in 58% yield, was hydrogenated with 10% palladium-charcoal to yield the desired hexahydrofluorenone derivative (108).

The alternative route to (108) involved direct substitution of hexahydrofluorenone (109) and, since previous routes[81,82,83] to this compound were not entirely satisfactory, House et al. devised an alternative synthesis. Reaction of cis- or trans-hexahydrofluorenone with either acrylonitrile or methyl acrylate afforded the cis-ketones (110) and (111) both of which could be hydrolysed to the cis-keto acid (108).

Further studies by House et al. have demonstrated the possibility of using 2-ethoxy-1:3-butadiene for preparing hexahydrofluorenones in ring C.[79] Their studies were initiated primarily with a view to obtaining preparative routes to hexahydrofluorenones with oxygen substituents at position 2. Using ethyl trans-cinnamate as dienophile a mixture of two isomeric keto acids (114) and (115) were obtained and, as expected from previous studies, the predominant component was the adduct (114).



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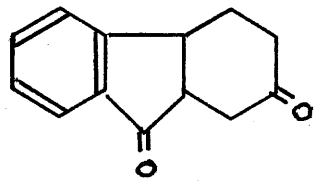

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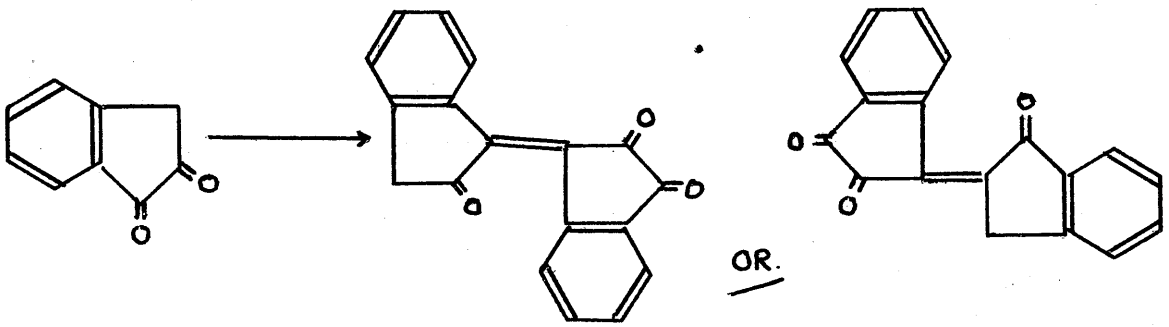
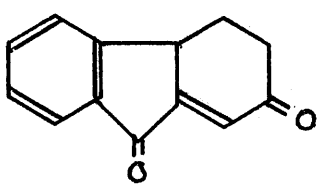


(116) (118) (119)



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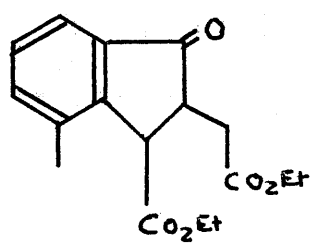


(120)

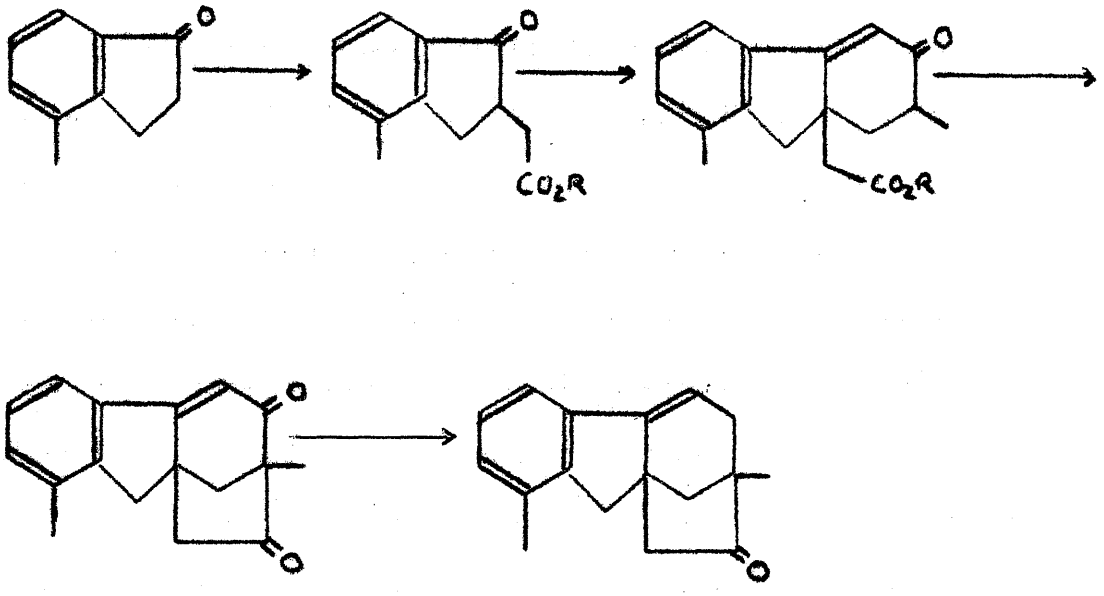
Both acids on cyclisation with polyphosphoric acid afforded the diketones (112) and (113) respectively. An alternative route to (112) was then explored using indenone ethylene ketal as dienophile. According to the probable mechanism[84] of the Diels-Alder reaction this route was expected to yield a derivative of the diketone (113) as a major product in the reaction. However the sole product, isolated in ca. 25% overall yield, was found to be cis- hexahydrofluorene-3:9-dione (112).

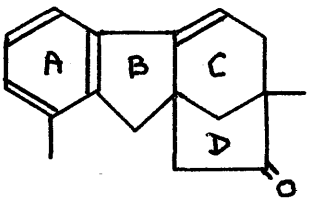
House et al.[79] have also studied the condensation of 1,2-indanedione (116) with methyl vinyl ketone as a possible preparative method for the enedione (117). The product obtained, however, proved to be the aldol-condensation product (118) or (119). This product could also be obtained when the dione (116) was treated with pyridine.

Thus House's original intention of obtaining a hexahydrofluorenone with an oxygen substituent in position 2 remains to be realised.

Recently we have obtained information that Professor G. Stork and his co-workers at Columbia University, New York, are engaged on synthetic approaches to the degradation products of gibberellic acid and that they have succeeded in preparing the indanone-diester (120).[85]

At the time of writing we have been informed[86] that Loewenthal, at the Israel Institute of Technology, has successfully synthesised the racemic form of gibberone. The synthesis, which is essentially a four-step process, is outlined below and will be the subject of a forthcoming communication.





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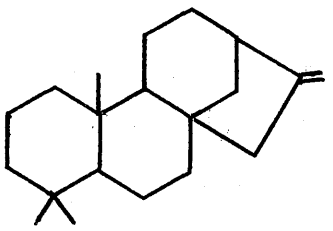

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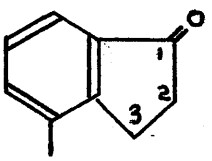


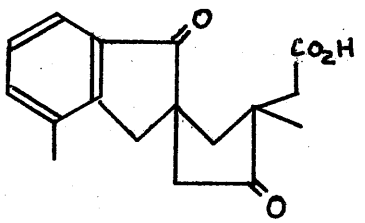
(122)

THEORETICAL

(1) Synthetic Approaches to Gibberone

A consideration of the structure of gibberone (12)[11] has prompted us to formulate possible synthetic routes to this compound. It is our opinion that the synthesis of gibberone presents a challenge to the organic chemist in that it is related to the wider problem presented by the synthesis of compounds having a basic structural similarity to phyllocladene (121).

Thus we devised a synthetic route which, it was hoped, would surmount the problem presented and which would provide us with some control over the stereochemistry of the final product. The starting material in our projected route was 4-methylindan-1-one (122).[87-91] The latter compound was considered to be eminently suitable in this respect since it contained a correctly substituted aromatic ring A fused to a five-membered ring ketone capable of further elaboration. In addition, the preparative routes[87-91] available to this starting indanone were facile and took place in fairly high overall yield. Thus Doebner condensation of o-tolualdehyde with malonic acid.[91,] gave the corresponding cinnamic acid. Hydrogenation of a solution of the latter in sodium hydroxide using 5% palladium-charcoal as catalyst gave an almost quantitative yield of o-methyldihydro-



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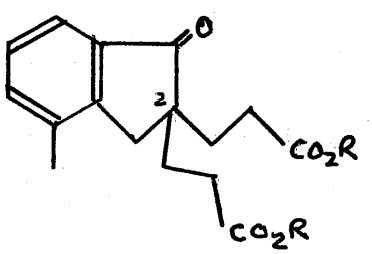
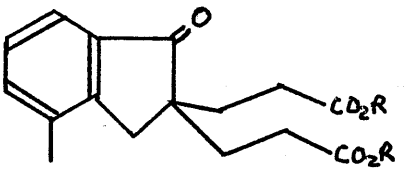


(123)

cinnamic acid which underwent polyphosphoric acid cyclisation at 100°C. to furnish the desired indanone (122).

Many synthetic pathways, based on reasonable literature analogies, were scrutinised before a final decision was made about the way in which our starting indanone was to be elaborated. Some preliminary experiments were performed on some of these pathways and will be described later. In the event, the choice of route was based on its practicability and by the fact that it might also provide us with a means of synthesising the diketo-acid (15), obtained by ozonolysis of gibberone.[11] The essential feature of this route was the addition, to the indanone framework, of a spiro-ring which could be cleaved in such a way as to provide us with appendages capable of forming the basis of the rings C and D of gibberone. The way in which we attempted to achieve this objective is described in the sequel.

When 4-methylindan-1-one (122), in dry benzene solution, was treated with acrylonitrile in the presence of Triton B at room temperature, dicyanoethylation took place, as expected, at C_2. The crude oily reaction product thus obtained was hydrolysed, almost quantitatively, with 15% potassium hydroxide solution to the crystalline keto-diacid (123; R = H) whose infrared spectrum (nujol) showed peaks at 1720 cm^{-1} (indanone carbonyl) and 1700 cm^{-1}



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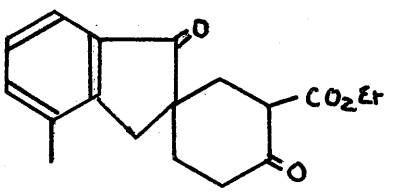

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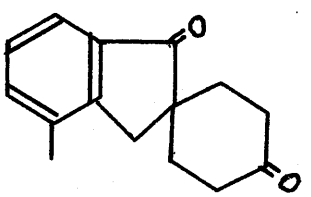
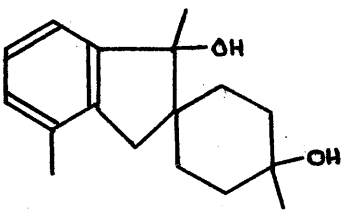


(125)

(carboxyl). No attempt was made to increase the yield in the cyanoethylation reaction but we have little doubt that this could be accomplished by using more forcing conditions or by employing the modified conditions described by Woodward.[92] Fischer-Spier esterification of the diacid (123; R = H) yielded the corresponding diethyl ester (123; R = Et) which, on Dieckmann cyclisation using sodium sand, provided us with the crystalline spiro-β-keto-ester (124). The infrared spectrum of (124) showed peaks at 1720 cm^{-1} (ester and indanone), 1670 cm^{-1} ($\alpha:\beta$-unsaturated ketone) and 1615 cm^{-1} (enol double bond) while the ultraviolet spectrum exhibited absorption maxima at 250-252 mu (ε 26,200) and 295-300 mu (ε 3,080). The spiro-β-keto-ester (124) was regarded as a key intermediate in the projected synthesis of gibberone and its degradation product (15). Subsequent acid hydrolysis, with concomitant loss of carbon dioxide, resulted in the formation of the crystalline spiro-diketone (125)(ν_{max} 1720 cm^{-1}, indanone and cyclohexanone: λ_{max} 250-255 mu (ε 12,700) and 295-300 mu (ε 3,080)).

With regard to the synthesis of gibberone, we were now faced with the problem of devising a method for cleaving the six-membered ring ketone of (125) in such a way as to provide us with a means of constructing rings C and D of gibberone. The method used was based on the



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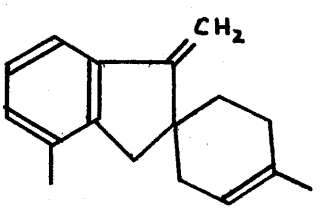


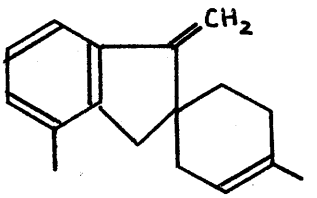
(127)

initial reaction of excess methylmagnesium bromide with the spiroketone (125). In this way the colourless diol (126) was obtained, whose infrared spectrum showed a peak at no carbonyl absorption in the region 1600-1800 cm^{-1}. The ultraviolet spectrum exhibited an absorption maximum at 265 mu (ε 430). Dehydration of this crude diol was effected by refluxing with p-toluene-sulphonic acid in dry benzene and resulted in the formation of a viscous brown semisolid product. The infrared spectrum of the latter showed the absence of hydroxyl bands and the presence of a styrene double bond (1630 cm^{-1}). Chromatography of the crude reaction product on alumina, using petroleum ether (b.p. 60-80°) as eluant, provided us with the colourless, crystalline spiro diene (127) whose spectral properties (ν_{max} 1635 cm^{-1}, styrene double bond: λ_{max} 255 mu (ε 15,500), 290 mu (ε 3,940) and 300 mu (ε 3,520)) were consistent with the assigned structure. Further elution of the column with ether provided a yellow viscous oily material which did not exhibit styrene absorption in the infrared and whose structure remains to be elucidated. It may be noted that during one dehydration experiment a much larger proportion of p-toluene-sulphonic acid was used and, in this case, work up in the usual manner furnished a colourless gum which failed to crystallise and whose infrared spectrum possessed only aromatic peaks

in the region 1600-1800 cm^{-1}. The ultraviolet spectrum of this product, however, exhibited absorption bands identical to those shown by (127) but with their intensity very much reduced. This product, which was not investigated further, is regarded at this preliminary juncture as an acid-catalysed rearrangement product of the diene (127).

In connection with the aforementioned dehydration we were cognizant of the fact that an alternative mode of dehydration was possible to furnish the di-exo diene (128). The evidence we possessed at this stage in our synthesis, namely, spectral properties and elemental analysis, did not permit an unequivocal exclusion of this structural possibility. It was our opinion, however, based on literature analogy[93] and on the rather meagre evidence of a peak at 790 cm^{-1} in the infrared spectrum of the dehydrated product, that our diene possessed the structure (127). This was later confirmed by the subsequent cleavage experiments.

Thus we assumed for the present the diene structure (127) and proceeded to consider the various methods, available in the literature, which had been employed for the cleavage of ethylenic systems to oxygenated products.[94-99] Of these, ozonolysis seemed the most suitable for our present purpose. In point of fact, ozonolysis of pure crystalline diene in ethyl acetate at -80°C.,



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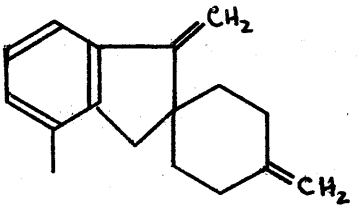

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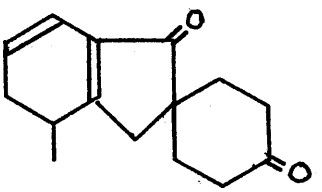

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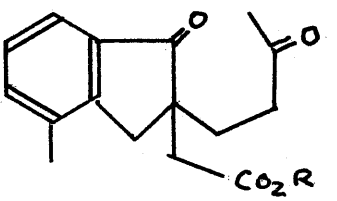
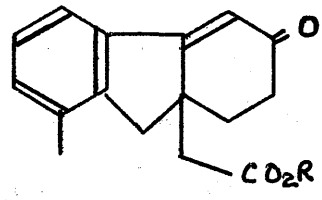


(129)

followed by oxidative hydrolysis, furnished a 75% yield of crude acidic material which resisted our attempts at crystallisation. The formation of this acidic product (129; R = H), in the yield indicated, further confirmed the structure (127) assigned to the starting diene since the alternative di-exo structure (128) would have provided us with the non-acidic spiro-diketone (125). Esterification of the diketo-acid (129; R = H) with diazomethane gave a product whose infrared spectrum in carbon tetrachloride solution showed peaks at 1735 cm^{-1} (ester carbonyl) and 1715 cm^{-1} (indanone carbonyl) in agreement with the assigned structure (129; R = Me). Moreover, the ultraviolet spectrum, which exhibited absorption maxima at 250 mu (ε 7,200) and 295 mu (ε 1,390), was typical of an indanone-type compound.[100] The spectral properties outlined above for the esterified ozonolysis product led us to conclude that we had effected cleavage of the spiro-diketone (125) in the desired manner and that the diketo-ester (129; R = Me) obtained would provide us with entry into the proper tricyclic series.

The "obvious" way in which this could be accomplished was by internal aldol condensation of (129; R = Me). A wide choice of acidic and basic condensing agents is available in the literature for effecting such condensations.[101-105] In the event, treatment of



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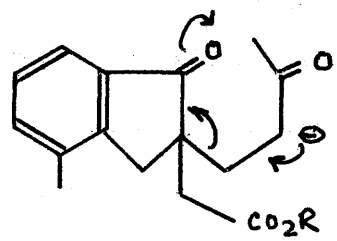
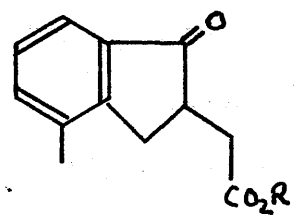


(131)



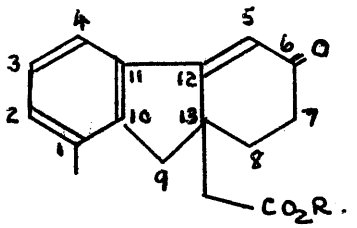
(132)

(129; R = Me) with 1% sodium methoxide in a nitrogen atmosphere furnished a red semisolid acidic product which, on trituration with ether, gave a yellow crystalline compound having an infrared spectrum (1705 cm^{-1}, carboxyl; 1665 cm^{-1}, cyclohexenone; 1625 cm^{-1}, styrene double bond) consistent with the desired enone-acid structure (130; R = H). This was subsequently confirmed when esterification with diazomethane yielded the crystalline methyl ester (130; R = Me) which exhibited the expected spectral properties, (ν_{max} 1735 cm^{-1}, ester; 1670 cm^{-1}, cyclohexenone; 1630 cm^{-1}, styrene double bond : λ_{max} 238 mu (ε 8,300) and 300 mu (ε 19,500)), and whose elemental analysis provided us with final proof of structure.

It may be noted that esterification of the red gum, obtained as a by-product in the cyclisation reaction, afforded a viscous oil which resisted our attempts at crystallisation and whose infrared spectrum in carbon tetrachloride solution (1735 cm^{-1}, 1715 cm^{-1}) was reminiscent of that of the starting diketo-ester. We concluded, therefore, that either the aldol condensation had not proceeded to completion or that, more likely, some dealdolisation had occurred. In addition, we were also aware of the fact that a retro-Michael reaction could have occurred, (see (131) and arrows), to furnish the indanone-ester (132) possessing spectral properties

similar to (129). The former explanations seemed to be invalidated, however, when re-treatment of the crude esterified by-product with either 1% sodium methoxide or p-toluene-sulphonic acid in benzene failed to produce further quantities of the tricyclic enone-acid or ester. Chromatography of this by-product on alumina enabled us to obtain a yellow viscous oil free from traces of enone ester but, as yet, we have been unable to characterise this material conclusively.

The disappointingly low yield in the cyclisation reaction and the rather obscure nature of the side-product(s) (vide infra) prompted us to consider other condensing agents for the aldol condensation. When the diketo-acid (129; R = H) was treated with potassium hydroxide in aqueous dioxan[102] no solid enone acid was obtained and the infrared spectrum of the reaction product indicated that the desired cyclisation had not proceeded to any significant extent. Successful cyclisation of (129; R = H) was accomplished, however, using 1% sodium ethoxide but the yield of tricyclic material did not warrant a change to these conditions. In order to prevent any retro-Michael reaction or dealdolisation occurring during the cyclisation, we then resorted to acidic conditions. Prolonged treatment of the diketo-ester (129; R = Me) in benzene with p-toluene-sulphonic acid[101],



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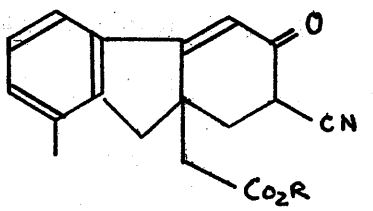

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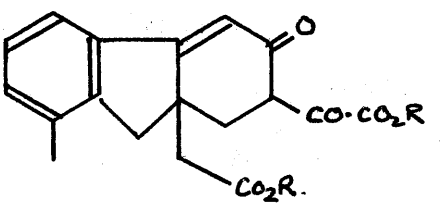
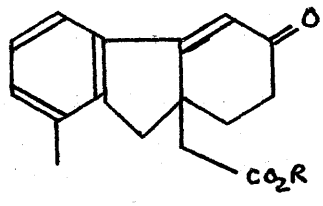


(134)

however, failed to provide us with more than a trace of tricyclic material. Beyond this no further variation of the cyclisation conditions was attempted.

We return now to the main synthetic pathway. In the tricyclic ketone (130; R = Me), the presence of the 12:5-double bond, with the attached quaternary centre, C_{13}, makes possible the unambiguous introduction of substituents at C_7. It will be noted that, while constructing ring C by the steps outlined above, we had made part-provision for the construction of ring D by having the required carbomethoxymethyl side chain already built into the tricyclic system. A consideration of the structure of gibberone enforced the "obvious" conclusion that the substituents required at C_7 were a methyl and a carbomethoxy group or its equivalent. The latter group would then be required to undergo Dieckmann cyclisation with the angular carbomethoxy group to furnish ring D.

In the event, we envisaged a reaction scheme involving the preparation of the β-keto-nitrile (133; R = Me) since we considered that the preparative route to this compound would be more facile than the introduction of the carbomethoxy group via the pyrolytic decarbonylation of the glyoxalate derivative (134; R = Me)[106]. Moreover, the steric requirements of the nitrile function are small. Before describing the specific means whereby



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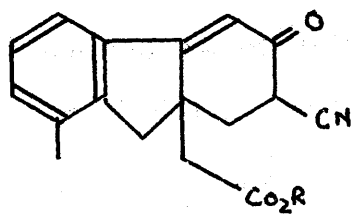

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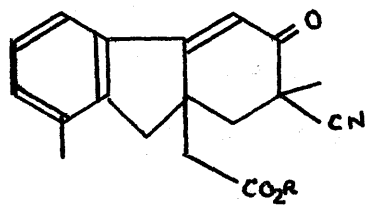
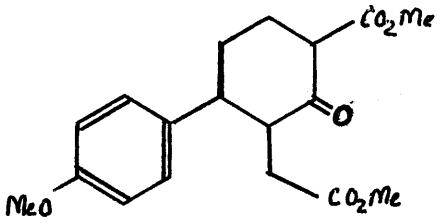


(135)

this objective could be realised, let us consider, for the moment, the stereochemical implications of our synthetic pathway.

The introduction of methyl and nitrile groups at C_7 poses the stereochemical question of whether the nitrile function (or the ester derived therefrom) will then undergo Dieckmann cyclisation with the angular carbomethoxymethyl group. The requirements for success in this latter reaction are a cis relationship of these two groups and thus we envisaged a reaction sequence which would satisfy this requirement. Construction of the molecular model of the tricyclic ketone (130; R = Me) demonstrated that this compound was essentially planar, with the carbomethoxymethyl group projecting above or below the plane. The reaction sequence contemplated for the preparation of the C-methylated β-keto-nitrile (135; R = Me) involved the preliminary formation of the unsubstituted cyano-ketone (133; R = Me). C-methylation of this enolic system would be expected to involve attachment of the methyl group to the side of the molecule opposite to that occupied by the angular carbomethoxymethyl function. A cis relationship between these two groups would be assured. It is probably of interest to note that in the total synthesis of estrone one step involved the C-methylation of the keto-diester (136). The



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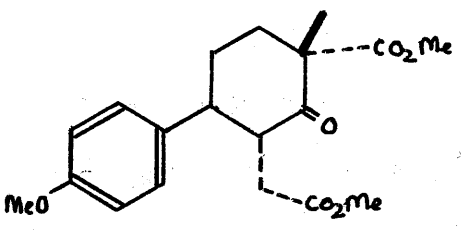

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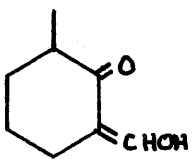

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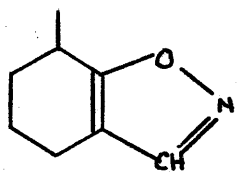

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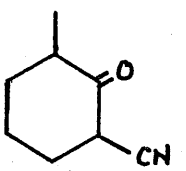
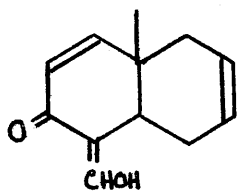


(140)

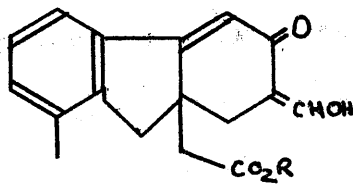
resulting compound (137) possessed the stereochemistry indicated.[107]

During their elegant studies on the total synthesis of steroids, W. S. Johnson and his co-workers evolved a facile procedure for preparing C-methylated β-keto-nitriles from substituted cyclohexanones**.[108,109] We considered this procedure to be eminently suitable for the preparation of the desired intermediate (135; R = Me). In order to obtain comparative spectra and to test the practicability of Johnson's method on a small scale, a series of model reactions was carried out using 2-methyl-cyclohexanone as starting material. Thus the hydroxy-methylene derivative (138) was prepared without difficulty and underwent smooth conversion to the isoxazole (139). Treatment of (139) with sodium methoxide resulted in the formation of 2-methyl-6-cyano-cyclohexanone (140). It may be noted that the assignment of structure in this model series was based to a large extent on the characteristic and predictable infrared spectra of the products. The fairly high overall yield and the practical facility

** The specificity of this procedure prompted Johnson to suggest its use in distinguishing chemically between the presence of six-membered and five-membered ring ketones in natural products.[108]



(141)



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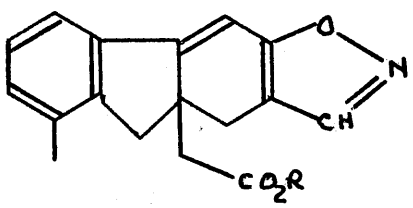

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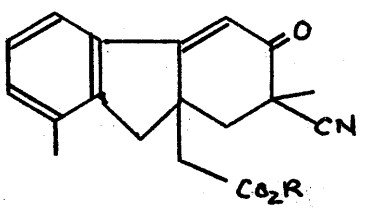
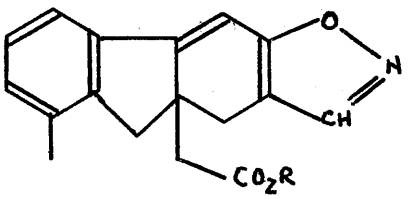


(135)

encountered in this series of model reactions encouraged us in our further enquiries.

Accordingly an attempt was made to prepare the hydroxymethylene derivative of the enone-ester (130; R = Me) using the conditions prescribed by Woodward for the preparation of the steroid intermediate (141).[102] The crude reaction product thus obtained gave a dark brown colouration with alcoholic ferric chloride solution and exhibited the expected spectral properties (ν_{max} 1740 cm^{-1}, ester; 1670 cm^{-1} 1640 cm^{-1}, β-diketone : λ_{max} 238 mu (ε 7,350) and 300-305 mu (ε 12,800)). Subsequent treatment of the crude hydroxymethylene derivative (142; R = Me) with hydroxylamine hydrochloride furnished an oil which was assigned the isoxazole structure (143; R = Me) on the basis of its ultraviolet (238 mu, ε 7,200 and 320 mu, ε 11,700) and infrared spectrum (1730 cm^{-1}, ester; 1630 cm^{-1}, styrene double bond and C=N) and by its failure to give a positive ferric chloride test. Cleavage of the substituted isoxazole (143; R = Me) in the desired manner was then accomplished by treatment with sodium methoxide/methyl iodide and resulted in the formation of the crystalline C-methylated β-keto-nitrile (135; R = Me). Confirmatory evidence for this structure was provided by its ultraviolet and infrared spectrum (λ_{max} 240 mu, ε 8,150 and 302-310 mu, ε 20,300 : ν_{max} 2250 cm^{-1}, nitrile; 1740 cm^{-1},



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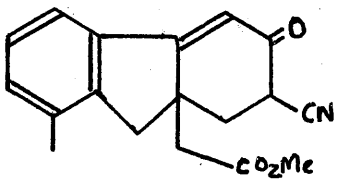

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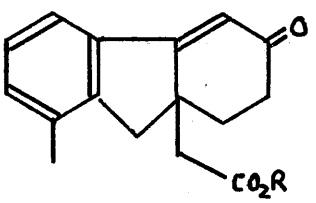

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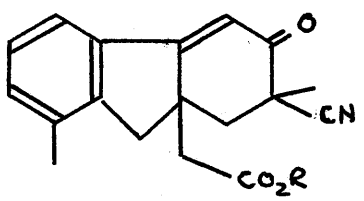
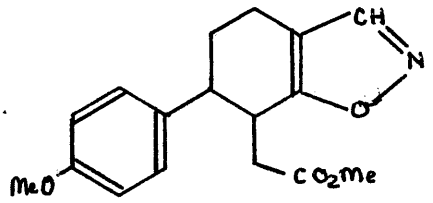


(135)

ester; 1675 cm^{-1}, cyclohexenone; 1640 cm^{-1}, styrene double bond). The presence of the very weak nitrile band in the latter is probably due to the "quenching effect" of the oxygenated functions in the molecule.[110] It may be noted that, prior to the above cleavage reaction, a preliminary investigation into the effect of sodium methoxide on the isoxazole (143; R = Me) had resulted in the formation of a solid acidic product. Subsequent esterification of this material with diazomethane furnished a crystalline alkali-soluble ester whose infrared spectrum in carbon tetrachloride solution, (2250 cm^{-1} 2200 cm^{-1}, nitrile; 1735 cm^{-1}, ester; 1670 cm^{-1}, cyclohexenone; 1620 cm^{-1}, styrene double bond), was consistent with the expected β-keto-nitrile structure (133; R = Me). In the event, the isolation of this compound became unnecessary due to the "in situ" alkylation/esterification procedure later employed (p.109). Nevertheless, apart from confirming the general validity of introducing a nitrile function adjacent to the carbonyl group in (130), the unsubstituted β-keto-nitrile (133; R = Me) later assumed the mantle of importance when a comparison of its melting point and solubility with that of (135; R = Me) provided us with the first indication that we had in fact obtained the C-methylated β-keto-nitrile.

As a result of the stereochemical arguments



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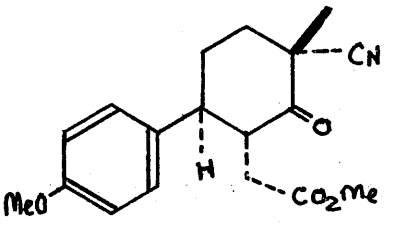
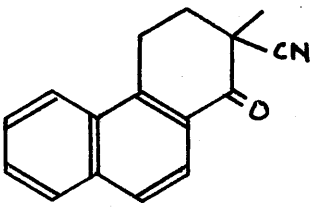


(145)



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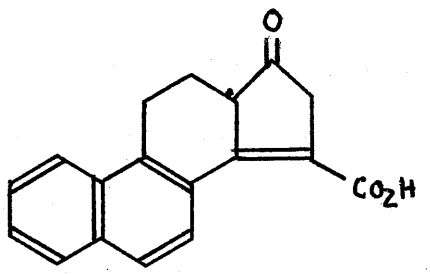

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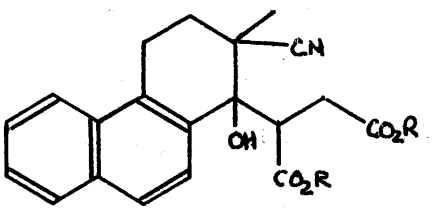

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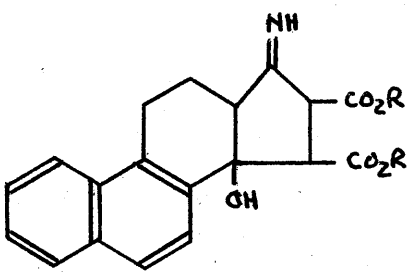
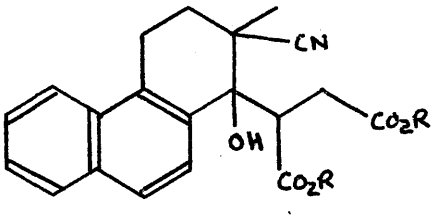


(149)

outlined above (p.105) and in view of the recent stereochemical conversion of the isoxazole (144) to (145),[111] we were confident that the nitrile and carbomethoxymethyl functions of (135; R = Me) possessed the required cis relationship and that entry into the proper tricyclic stage of our synthesis had been achieved with complete stereochemical control. The two remaining steps in our projected synthesis, namely, the construction of ring D and the reductive removal of the C_6 ketone, now awaited accomplishment. The way in which we intended to realise these final objectives and the underlying principles involved, are described in the sequel.

During his studies on the total synthesis of equilenin, Johnson and his co-workers[108,109] constructed ring D of this compound by a series of synthetic steps one of which is particularly relevant to the present discussion. Thus by treating the methylated β-keto-nitrile (146) with methyl succinate and potassium tert-butoxide the unsaturated keto-acid (147) was obtained. Obviously this remarkably facile one-step process had involved the usual Stobbe condensation of a ketone with a succinic ester followed by a cyclisation of the Dieckmann type and alkaline fission of the methoxycarbonyl group. The intermediates in this reaction were thus assigned the structures (148; R = Me) and (149; R = Me).



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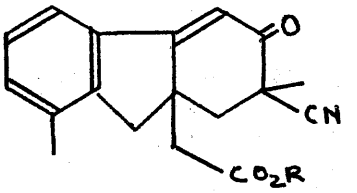

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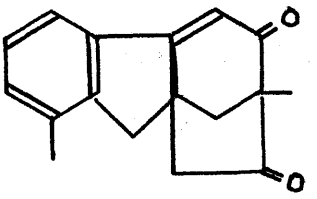

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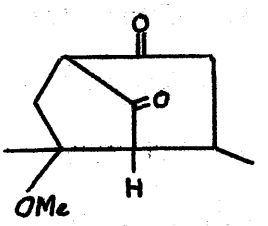
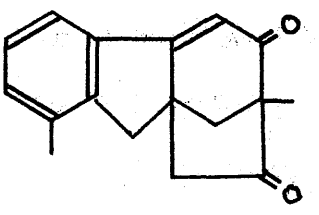


(151)

The striking structural analogy between our C-methylated β-keto-nitrile (135; R = Me) and the intermediate (148; R = Me) prompted us, therefore, to speculate on whether the former compound would, under these conditions, provide us with the desired tetracyclic diketone (150) by a similar one-step process. In the event, when the C-methylated β-keto-nitrile (135; R = Me) was treated with potassium tert-butoxide a crystalline product was obtained whose infrared spectrum (1766 cm^{-1}, cyclopentanone; 1677 cm^{-1}, cyclohexenone; 1622 cm^{-1}, styrene double bond) was compatible with the tetracyclic diketone structure (150). A comparably high wave number (1768 cm^{-1}) has recently been assigned to the five-membered ring ketone in (151), a degradation product of delphinine.[112] In this case it has been suggested that dipole-dipole interaction of both carbonyl groups, due to the rigid structure of (151), could reasonably account for this shift to higher wave number.[112] We consider that a similar explanation is equally applicable in the case of the rigid tetracyclic diketone structure (150).

Further confirmation for the presence of the enone chromophore in our product was provided by the ultraviolet spectrum which exhibited absorption maxima at 238 mu (ε 6,850), 300-302mu (ε 15,400) and 330 mu (ε 14,600). The presence of the band at 330 mu (not



(150)

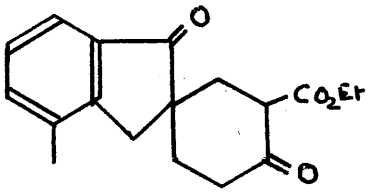
present in the starting material) could be explained in terms of π-electron interaction between the chromophore and the carbonyl group in the five-membered ring. Unfortunately our supply of reaction product at this stage (3.8 mg., impure) prevented us from confirming the structure (150) by elemental analysis.

At this time, however, we received information that Loewenthal had succeeded in synthesising gibberone (see p. 87) and that the penultimate compound in his synthesis was the tetracyclic diketone (150).[86] Although obtained by a completely different route, the physical properties of this compound were similar to those of our impure reaction product (Table 1).

Table 1

	Diketone (150)	Reaction Product
m.p.	207°C.	204-207°C.
U.V.	238 mu (ε 7,400)	238 mu (ε 6,850)
	300 mu (ε 19,000)	300-302 mu (ε 15,400)
	330 mu (ε 15,300)	330 mu (ε 14,600)
I.R.($CHCl_3$) ..	1742 cm^{-1}	1766 cm^{-1}
	1661 cm^{-1}	1677 cm^{-1}
	1621 cm^{-1}	1622 cm^{-1}

The exact nature of this reaction product awaits elucidation.



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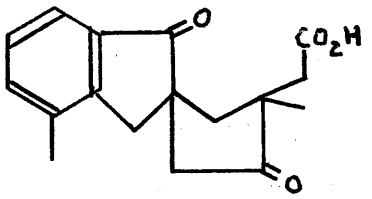

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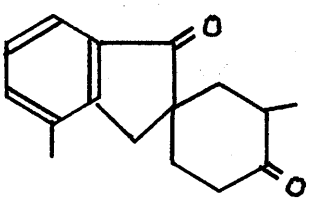
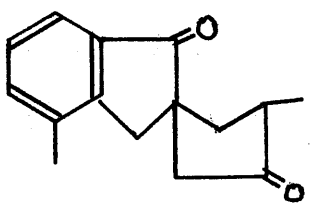
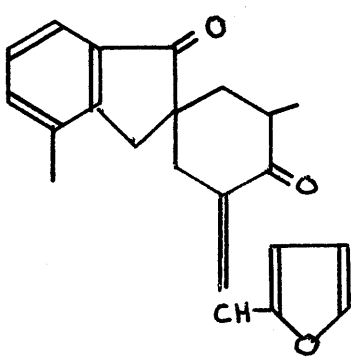


(152)



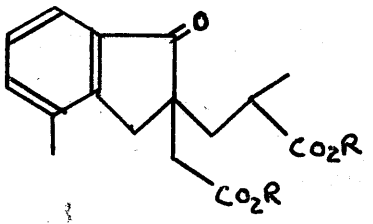
(153)



(154)

As indicated previously, the main synthetic pathway to gibberone involved the important intermediate (124). The potential synthetic utility of this compound became evident to us when we were considering synthetic avenues to the diketo-acid (15). Most of these involved the preliminary preparation of the methylated spiro-diketone (152) from which, it was hoped, the corresponding nor-compound (153) could be readily prepared by conventional ring-contraction methods. Accordingly, methylation of the spiro-β-keto-ester (124) with methyl iodide in the presence of sodium furnished a neutral product which on subsequent acidic hydrolysis and decarboxylation furnished the crystalline methylated spiro-diketone (152). Two conventional methods of ring contraction were then chosen to test the general validity of our synthetic route and we investigated these by a series of small-scale experiments.

When the methylated spiro-diketone (152) was treated with freshly distilled furfural in the presence of sodium hydroxide[113] a yellow gum was obtained which resisted our attempts at crystallisation but whose ultraviolet spectrum (250 mu, ε 13,000 and 325-330 mu, ε 17,500) was consistent with that of the furfurylidene derivative (154). Furfurylidene derivatives of cyclic ketones normally exhibit ultraviolet absorption at 324 mu (ε 20,000).[113] Ozonolysis of the furfurylidene derivative,



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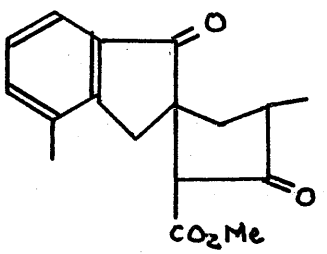

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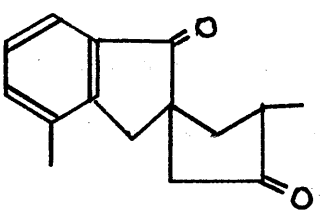
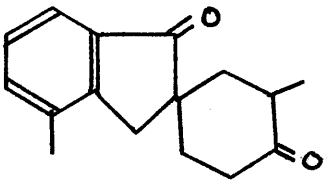


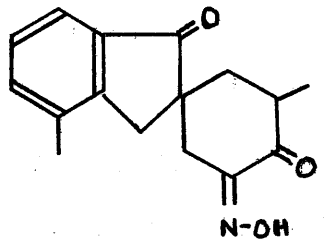
(153)

followed by oxidative hydrolysis, furnished an acidic product which exhibited characteristic indanone absorption in the ultraviolet (λ_{max} 250-255 mu (ε 9,200) and 295 mu (ε 1,800)). Although crystallisation of this acidic product seemed possible, no attempt was made to purify it during this preliminary investigation. Esterification with diazomethane furnished the corresponding dimethyl ester (155; R = Me) which, on Dieckmann cyclisation using sodium sand, furnished a viscous oil. The β-keto-ester structure (156) was assigned to this compound on the basis of its infrared spectrum (1720 cm^{-1}, indanone and ester; 1665 cm^{-1} cyclopentenone; 1620 cm^{-1}, enol double bond) and by the fact that it gave a purple colouration with alcoholic ferric chloride solution. Subsequent acidic hydrolysis and decarboxylation furnished a neutral compound whose infrared spectrum was consistent with the methylated nor-spiro-diketone structure (153). Chromatography of the crude product on alumina, using benzene-petroleum ether (b.p. 60-80°) as eluant, provided a colourless mobile oil whose infrared (1745 cm^{-1}, cyclopentanone; 1715 cm^{-1}, indanone) and ultraviolet spectrum (252 mu (ε 12,300) and 298-300 mu (ε 2,200)) were in full agreement with the assigned structure. Final confirmation for the latter was provided by elemental analysis.

Preliminary results of investigations into the



(152)



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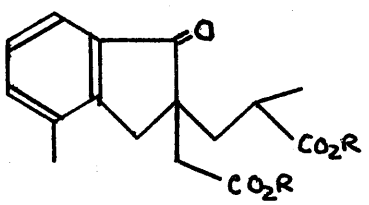

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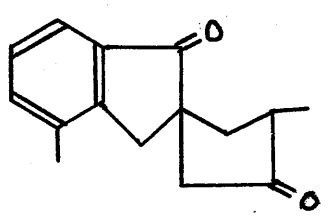

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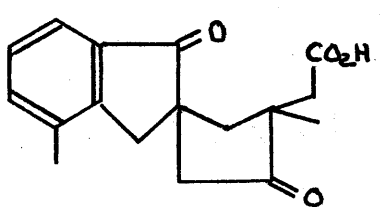
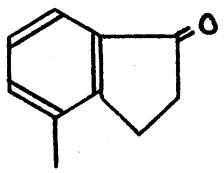


(15)

validity of another ring-contraction method were also obtained. Thus, parallel with the series of experiments outlined above, an attempt was made to prepare the oximino compound (157) by treating (152) with butyl nitrite and sodium methoxide.[22,114] Beckmann rearrangement of the crude product, followed by alkaline hydrolysis, furnished an acidic compound which was esterified with diazomethane. The infrared spectrum of this impure ester in carbon tetrachloride solution was identical with that of the keto-diester (155; R = Me). The overall success of the furfurylidene method of ring-contraction, however, made the further investigation of this latter approach unnecessary.

With the preparation of the methylated nor-spiro-diketone (153) we came within one stage of our final objective. As yet, however, no attempts have been made to complete the synthesis although methods of incorporating the carboxymethyl group into the methine position of the cyclopentanone ring have been considered in detail. We presume that this could be accomplished by the preliminary introduction of a suitable blocking group[101,115,116] prior to reaction with ethyl bromoacetate or its equivalent. Subsequent removal of the blocking group and hydrolysis of the ester function would then provide the desired diketo-acid (15). Resolution, of course, would be



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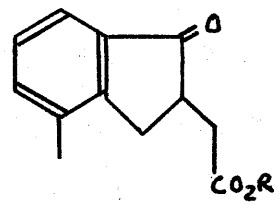

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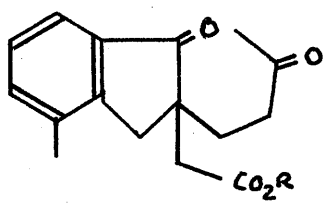

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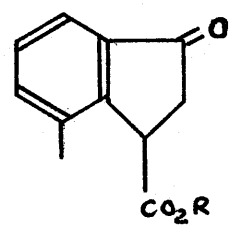
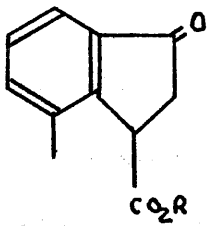


(158)

required at some suitable stage in the synthesis.

We conclude this section on the synthetic approaches to gibberone with an account of some miscellaneous experiments which were intended to lead directly or indirectly to the indanone ester (132). One of the more conventional ways of building the gibberone framework would seem to involve the initial preparation of this compound using 4-methylindan-1-one (122) as starting material. A Michael reaction, using methyl vinyl ketone or its equivalent,[117,118] would then be expected to yield the diketo-ester (129) and the remainder of the synthesis would then follow the lines already indicated. This mode of approach occurred to us very early in our work since it followed closely the synthetic route originally envisaged to gibberic acid. It was perhaps inevitable, however, that, due to the success we experienced in our other synthetic scheme (vide infra), very little experimental effort was expended on this conventional route.

Direct attempts to introduce a carbethoxy group into (122), using ethyl chloroacetate and sodamide or sodium as condensing agents, provided us with unchanged indanone. A similar failure to introduce this group directly into the indanone ester (158; R = Et) (p.146) then prompted us to consider indirect methods of achieving our objective. It may be noted, however, that no



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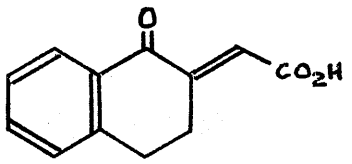

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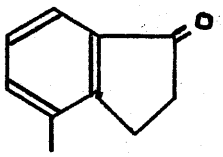

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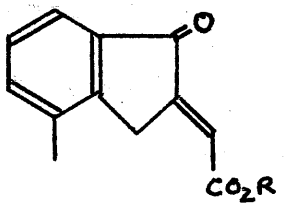

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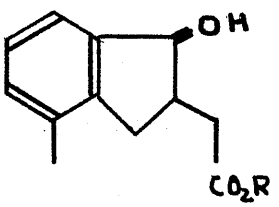
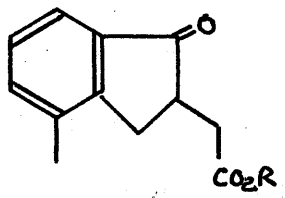


(161)

attempt was made to utilise the elegant enamine method of preparing alkylated cyclic ketones[119] since we felt that our previous failure to prepare the pyrrolidine or morpholine enamine of (158; R = Et) (p.148), and the reported general failure of indanones to provide these intermediates,[120] made the possibility of success remote.

Recently, however, Newman has devised an elegant procedure for preparing 2-carboxymethylene-α-tetralone (159) and has alluded to its general applicability.[121] In point of fact, when the indanone (122) was treated with tartaric acid, in the presence of sodium periodate, smooth conversion to the corresponding carboxymethylene derivative (160; R = H) occurred. Subsequent catalytic hydrogenation of (160; R = H), using 5% palladium-charcoal as catalyst, followed by esterification of the non-ketonic acidic product, furnished a neutral compound which was assigned the hydroxy-ester structure (161; R = Me) on the basis of its ultraviolet (λ_{max} 265 mu, ε 320) and infrared spectrum (3150 cm^{-1}, hydroxyl; 1720 cm^{-1}, ester). This was later confirmed by elemental analysis. Attempts to remove the unsaturated centre in (160; R = H) by partial hydrogenation provided a non-homogeneous product whose infrared spectrum showed peaks at 3500 cm^{-1} (hydroxyl), 1760 cm^{-1} (w)(γ-lactone) and 1725 cm^{-1} (carboxyl and indanone carbonyl). We considered, there-



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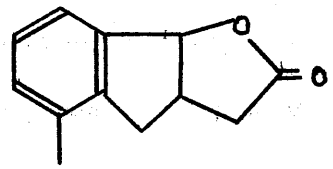

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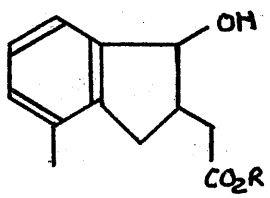

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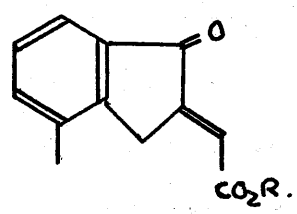
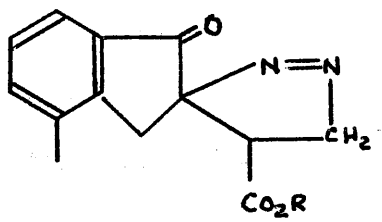


(160)

fore, that the product was a mixture of the required keto-acid (132; R = H) and the lactone (162) derived from the completely hydrogenated hydroxy-acid (161; R = H). That the majority of the reaction product contained an intact indanone carbonyl group was confirmed by the weak intensity of the lactone peak and also by the characteristic ultraviolet spectrum (λ_{max} 250 mu, ε 9850 and 295 mu, ε 1,840). Although these attempts to achieve partial hydrogenation seemed promising, we decided to investigate an alternative and less ambiguous means of selectively reducing the unsaturated centre.

Thus it occurred to us that the unsaturated keto-ester (160; R = Me) might well behave as a 1:4-dicarbonyl compound and that reduction with zinc and acetic acid, (widely used for the conversion of ene-1:4-diones to the corresponding saturated 1:4-diketones), would furnish the saturated keto-ester (132; R = Me). Unfortunately, however, when (160; R = H) was treated with diazomethane a non-acidic crystalline material was obtained whose infra-red spectrum was singularly inconsistent with the expected structure (160; R = Me). Specifically the spectrum failed to show signs of the unsaturated linkage although the indanone carbonyl and ester functions appeared to be intact. Further confirmation for the presence of the indanone carbonyl was provided by the ultraviolet spectrum



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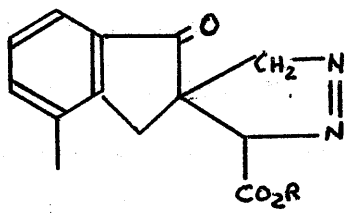

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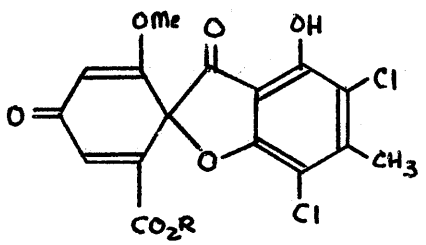

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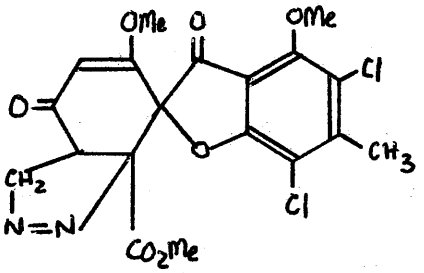

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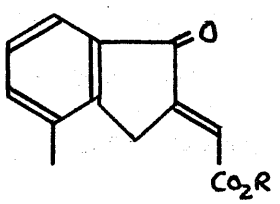


(160)

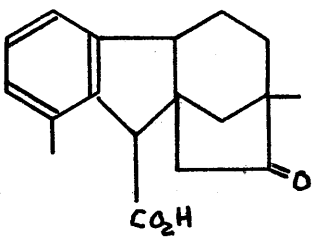
(λ_{max} 260 mμ, ε 13,200 and 300 mμ, ε 2,580) which was typical of compounds belonging to this class.[100] Our failure to obtain the methyl ester of (160; R = Me) in this way was finally substantiated by elemental analysis which alluded to a more complex structure.

The simplest and most logical explanation of the facts outlined above can be provided in terms of the alternative pyrazoline structures (163; R = Me) and (164; R = Me). It would seem, therefore, that treatment of (160; R = H) with diazomethane involves preliminary esterification followed by addition of diazomethane across the ene-1:4-dione system. A completely analogous reaction is the conversion of erdin (165; R = H) or geodin (165; R = Me) to the pyrazoline (166).[122] Further experimental evidence will be required, of course, before a final choice between the structures (163; R = Me) and (164; R = Me) can be made.

It may be noted, however, that our failure to obtain the methyl ester (160; R = Me) did not invalidate the projected reduction of the latter with zinc and acetic acid. On the contrary, the fact that the unsaturated keto-acid (160; R = H) behaved as an ene-1:4-dione in the above reaction augured well for the success of the reductive step. The difficulties associated with the use of diazomethane could obviously be removed by Fischer-Speir

esterification and further work in this direction is anticipated. Alternatively it may be possible to reduce the free acid (160; R = H) with zinc and acetic acid.

In addition, many of the synthetic methods available in the literature[123,124] for the introduction of a carbomethoxymethyl function into the 2-position of cyclic ketones remain to be investigated.



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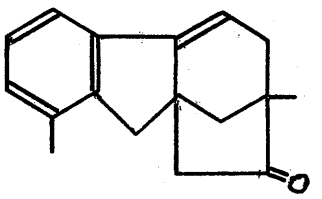


(12)

(2) Synthetic Approaches to Gibberic Acid

The close structural similarity of gibberic acid (1) and gibberone (12) leads one to the obvious conclusion that the problems presented by the synthesis of either of these compounds are, for the most part, common. It would seem, therefore, that the ideas on which the main synthetic route to gibberone was based (p. 89) would be applicable with scant modification to the synthesis of gibberic acid. Historically, however, our investigations into synthetic approaches to gibberic acid were carried out prior to our interest in a synthesis of gibberone and thus the synthetic approaches outlined below bear little relationship to those in section 1 (p. 89).

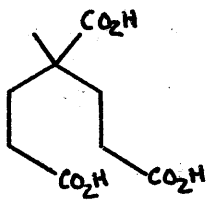
Although several different synthetic routes to gibberic acid have been investigated we shall, for the purpose of clarity, confine ourselves to the two main lines of approach on which the majority of our practical work has been based. These are named arbitrarily as follows:-

A. Coumarin route.

B. Indanone route.

Each of these are dealt with in the sequel.

A. The basic idea of this route was the synthesis of a suitably substituted coumarin which, on alkaline cleavage and subsequent cyclisation, would furnish a



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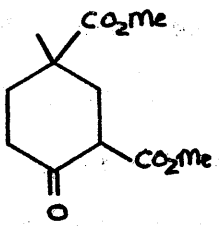

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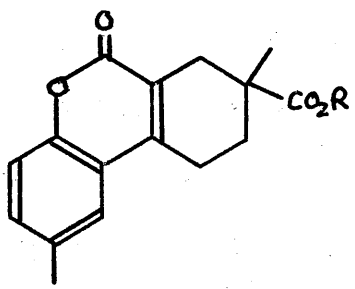

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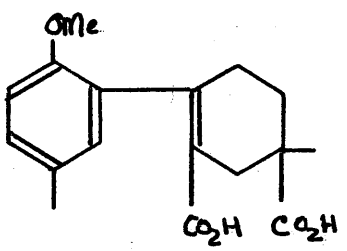
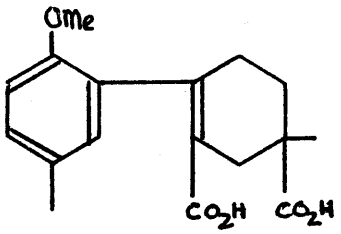


(170)

tricyclic intermediate capable of further elaboration. One of the most elegant methods of preparing coumarins consists of allowing phenols to react with β-keto-esters under strongly acidic conditions (Pechmann reaction).[125-128] Accordingly, γ-carboxy-γ-methyl-pimelic acid (167)[129] was prepared and its trimethyl ester, on cyclisation with sodium hydride in ether[130] at 0°C., furnished 2:4-dicarbomethoxy-4-methylcyclohexanone (168)[129] which was used without purification. Treatment of (168) with p-cresol in the presence of 80% (v/v) sulphuric acid at room temperature afforded a colourless crystalline compound whose ultraviolet spectrum (λ_{max} 275 mu, ε 10,025 and 318 mu, ε 6,130) exhibited the characteristic absorption bands normally associated with coumarins.[131,132] Coumarin itself exhibits absorption bands at 278 mu (ε 10,500) and 310 mu (ε 6,000) in the ultraviolet.[133] Consequently, we assigned the structure (169; R = Me) to this product and this was confirmed by elemental analysis. Cleavage of (169; R = Me) with dimethyl sulphate and alkali[134] resulted in the formation of the unsaturated methoxy-diacid (170) whose ultraviolet spectrum (λ_{max} 285-288 mu, ε 2,530) did not exhibit the normal styrene absorption bands. This initially surprising fact, however, is not without precedent since the anomalous ultraviolet spectra of compounds possessing the styrene chromophore in a



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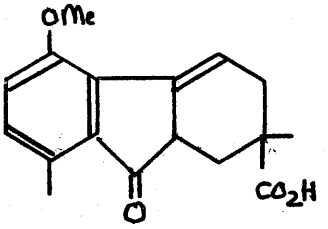

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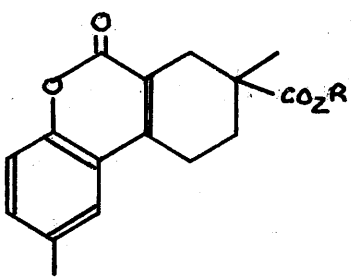

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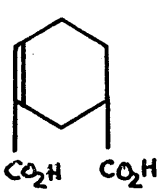

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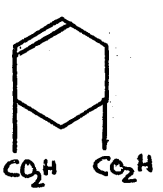

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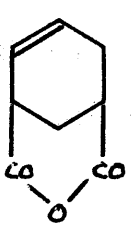
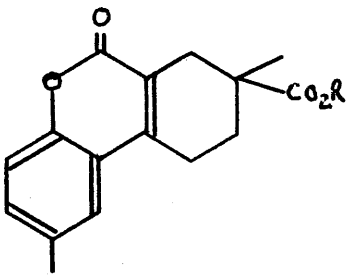


(175)

similar environment have been reported in the literature.[131] Carlin has provided evidence which suggests that the anomaly is due to steric inhibition of π-electron overlap.[135]

At this juncture it was hoped that cyclisation of (170), with concomitant double shift, would provide us with the desired tetrahydrofluorenone (171). However, treatment of (170) with either concentrated sulphuric acid or polyphosphoric acid merely yielded the coumarin acid (169; R = H). Further confirmation for this latter structure was provided by the fact that an identical product was obtained by simple alkaline hydrolysis of the coumarin-ester (169; R = Me). Analogous instances are known of suitably substituted unsaturated methoxy-acids undergoing this somewhat unusual conversion to a coumarin with elimination of methanol.[136,137] An attempt was also made to cyclise the unsaturated diacid (170) via its anhydride. Treatment of (170) with acetic anhydride/ acetic acid furnished a crude product whose infrared spectrum contained the characteristic twin anhydride peaks (1810 cm^{-1}, 1725 cm^{-1}). The double bond shift associated with the formation of this anhydride is of course necessitated by Bredt's rule and is analogous to the conversion of (172), (173) and (174) to the anhydride (175).[138] Attempted Friedel-Crafts cyclisation of the



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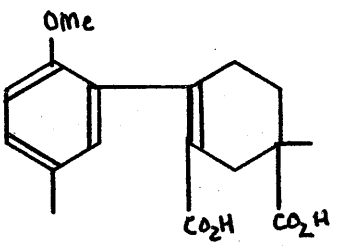

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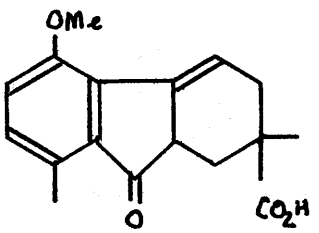

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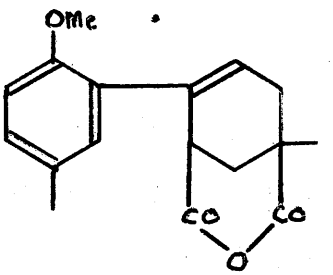

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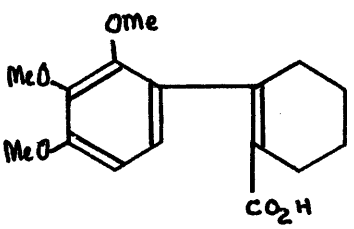

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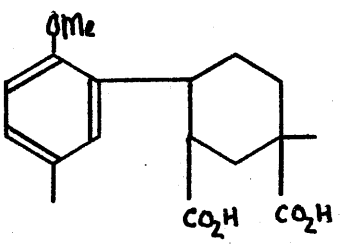
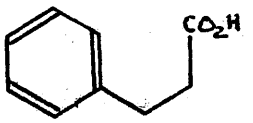


(178)

anhydride (176) using stannic chloride, however, failed to yield the desired keto-acid (171). Instead this mode of cyclisation again provided us with the coumarin-acid (169; R = H).

Since the double bond in the alicyclic ring of (170) was assumed to be a major contributory factor in directing the above cyclisations towards the coumarin rather than the tetrahydrofluorenone (171), it was decided that reductive removal of this tetrasubstituted double bond was essential. Unfortunately catalytic hydrogenation using Adams' catalyst with ethyl acetate, acetic acid or ethanol as solvent, failed —— a fact not without precedent in similar compounds. Loewanthal, faced with this same difficulty in the case of the unsaturated acid (177), reverted to the reductive technique of lithium/liquid ammonia with considerable success.[136] This prompted us, therefore, to attempt the same technique on (170). As a result of this a compound was isolated whose melting point was depressed by admixture with starting material or with the coumarin-acid (169; R = H). The structure (178) was assigned to this product on the basis of spectral properties (ν_{max} 1710 cm^{-1}, carboxyl ; λ_{max} 280 mu, ε 2,300) and elemental analysis.

With the preparation of (178) and the consequent removal of any possibility of coumarin formation a series



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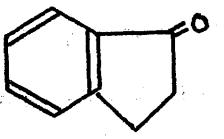

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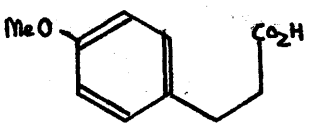

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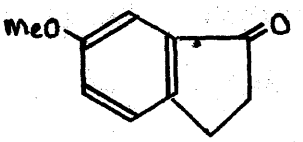

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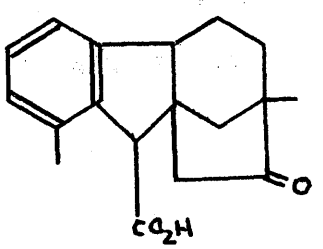
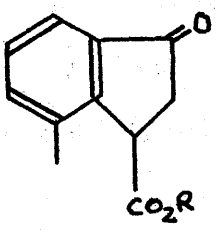


(1)

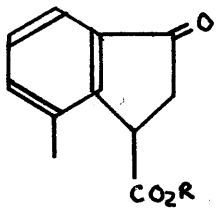


(158)

of meaningful cyclisations could now be undertaken. Unfortunately, however, our attempts to cyclise (178) using either concentrated sulphuric acid or polyphosphoric acid as cyclodehydrating agents, failed. This failure is not altogether surprising, however, when one considers that similar cyclisations, involving electrophilic attack meta to a methoxyl group, have proved difficult to achieve, e.g. β-phenylpropionic acid (179) can be cyclised to (180) in 73% yield while, under the same conditions, the yield for the conversion of the p-methoxy-acid (181) to (182) is only 3%.[139]

At this stage we abandoned our efforts to obtain a suitable tricyclic intermediate via coumarin-type compounds. It may be noted that, in addition to the undesirable electronic effects associated with the methoxyl group (vide infra), the eventual presence of this group in the final product and the possible difficulties associated with its removal were other fundamental objections to this synthetic approach.

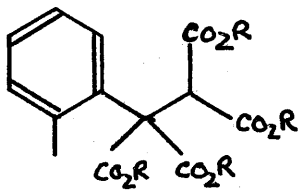
B. As the name implies, the basic theme of this synthetic approach to gibberic acid (1) involved the preliminary preparation of a suitably substituted indanone. We considered that 3-carbethoxy-4-methylindan-1-one (158; R = Et) would be eminently suitable in this respect since



(158)

$(EtOOC)_2C=C(COOEt)_2$

(183)



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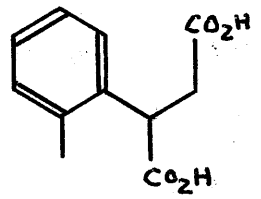

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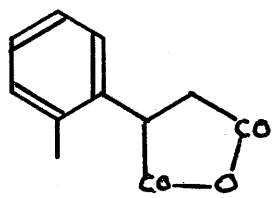
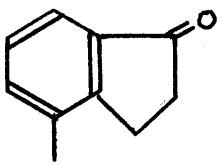


(186)

it contained the essential features of rings A and B of gibberic acid. In addition the presence of an active methylene group at C_2 rendered (158; R = Et) potentially capable of further elaboration. The preparative route which was devised to this compound is described in the sequel.

1:4-addition of the grignard reagent, prepared from o-bromotoluene, to tetraethyl ethylene tetra-carboxylate (183)[140,141] resulted in the formation of the tetra-ester (184; R = Et) which, on alkaline hydrolysis and thermal decarboxylation, afforded o-tolylsuccinic acid (185). Subsequent cyclodehydration of (185) with polyphosphoric acid at 140°C. yielded a mixture of starting material and the desired indanone-acid (158; R = H) (ν_{max} 1720 cm^{-1}, indanone; 1690 cm^{-1}, carboxyl : λ_{max} 250 mu, ε 10,040 and 295 mu, ε 1,930) which were separated by silica chromatography. The overall yield of (158; R = H) in the cyclisation stage was 44% and attempts to augment this by the alternative use of hydrogen fluoride or concentrated sulphuric acid as cyclo-dehydrating agents, met with failure. The ethyl ester (158; R = Et) was prepared in the usual way. It may be noted that although the substituted succinic acid (185) readily formed an anhydride (186) no attempt was made to utilise this intermediate for the preparation of the



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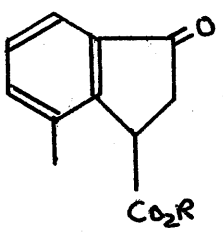
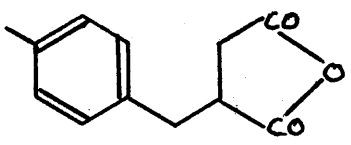


(158)



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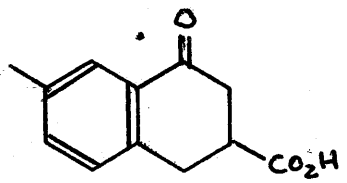

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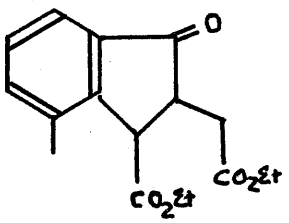

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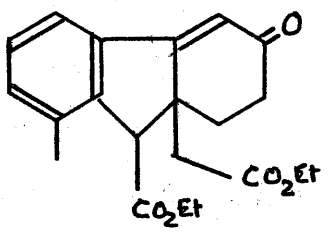
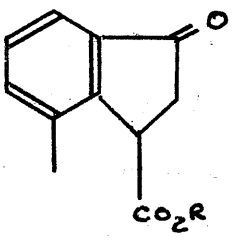


(189)

indanone-acid (158; R = H). The analogous conversion of the anhydride (187) to (188) in 66% yield[142] augured well for the success of this mode of preparation but it was felt that the overall yield in this two-step process could not be expected to exceed 44%. Since the termination of this work, however, an interesting paper has appeared purporting to a new route to indanones of this general type.[143] This would seem to indicate that the conversion of 4-methylindan-1-one (122) to (158; R = H) could be achieved with little difficulty. Further work on this possibility is anticipated.

Although the above method of preparing the indanone-ester (158; R = Et) was laborious on a large scale, several possible routes to the tetracyclic system of gibberic acid were investigated. The most conventional and straightforward of these synthetic approaches envisaged the initial preparation of the keto-diester (120) from which, it was hoped, the important tricyclic intermediate (189) could be obtained by the well-known Robinson annelation reaction.[117,118] Unsuccessful attempts to prepare (120) by treatment of (158; R = Et) with ethyl bromoacetate in the presence of sodamide or sodium ethoxide as condensing agents, however, soon prompted us to consider indirect methods of achieving our objective. Of these, the elegant enamine method of preparing



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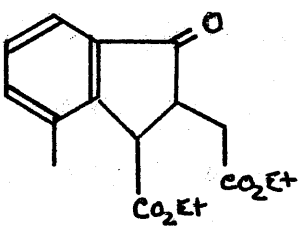

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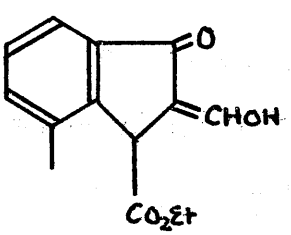
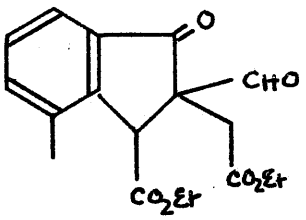


(190)

alkylated cyclic ketones[119] seemed the most promising. Once again, however, our efforts were thwarted by the failure of (158; R = Et) to form either a morpholine or pyrrolidine enamine. This rather surprising result has also been experienced by Stork and his co-workers who have recently obtained (120) by an independent route.[85] It has also been claimed that indanones in general fail to form enamine derivatives.[120]

Although we had by no means exhausted the many methods available in the literature for the introduction of a carboalkoxymethyl group into the 2-position of cyclic ketones,[123,124] the failure of the attempts described above led us to consider the preparation of derivatives of the indanone-ester (158; R = Et) which would possess enhanced reactivity at C_2. An attempt was therefore made to prepare the hydroxymethylene compound (190) by treating (158; R = Et) with ethyl formate and sodium ethoxide.[21,104] The crude reaction product, which resisted our attempts at crystallisation, was assigned the structure (190) on the basis of its characteristic infrared spectrum (1730 cm^{-1}, ester; 1670 cm^{-1} 1630 cm^{-1}, β-diketone). The enolic nature of this product was also confirmed by a positive ferric chloride colour test and by its ability to give a complex with saturated cupric acetate solution. Unfortunately, the attempted C-alkylation of (190) using



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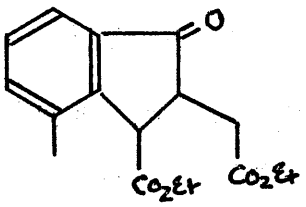

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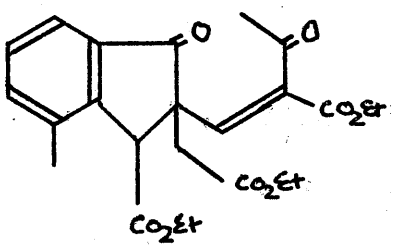

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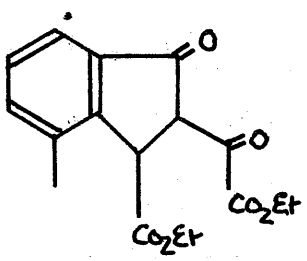

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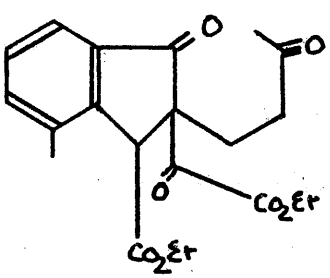

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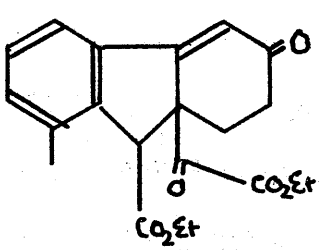
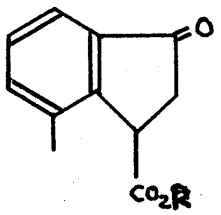


(195)

ethyl bromoacetate and sodium ethoxide failed to yield the required product (191). C-alkylation of β-diketones using methyl iodide[144] or propargyl bromide[145] are well-known reactions but it is interesting to note that O-alkylation predominates when ethyl or propyl bromide is used.[144,146] The latter compounds, like ethyl bromoacetate, react by an S_N2 mechanism and this may constitute a possible explanation for the failure of our alkylation experiment. It may be noted that a successful synthesis of (191) would have enabled us to obtain (120) by base-catalysed removal of the formyl group.[145] Alternatively, condensation of (191) with acetoacetic ester, in a manner reminiscent of that employed in synthetic steroidal work,[147] could have provided us with the highly important compound (192).

The failure of these attempts to prepare (120) and the appearance, at this time, of an interesting paper by Newman on the preparation of bicyclic compounds from monocyclic β-diketones[105] led us to consider an alternative synthetic approach. This envisaged the preparation of the ethoxalyl derivative (193) followed by Michael addition of methyl vinyl ketone (or its Mannich base) to yield (194) or its ring-closed product (195). Accordingly, the indanone-ester (158; R = Et) was treated with diethyl oxalate and sodium methoxide and a smooth conversion to



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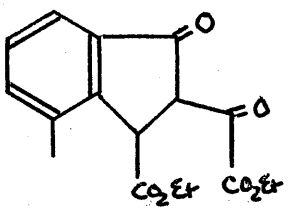

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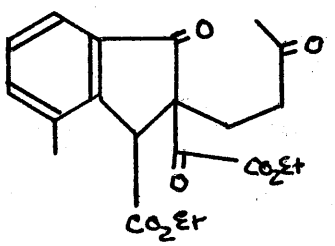

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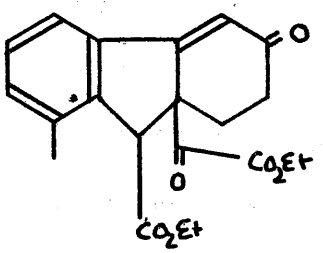

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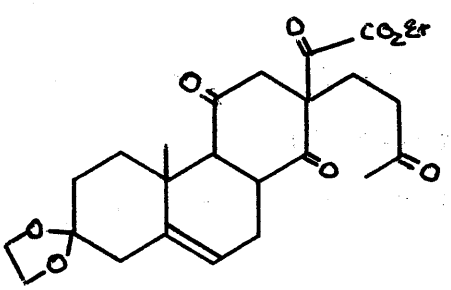

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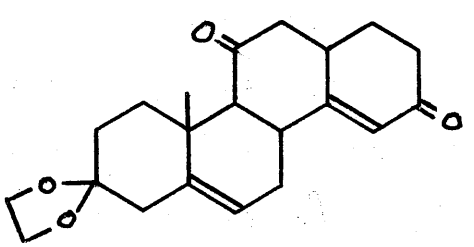
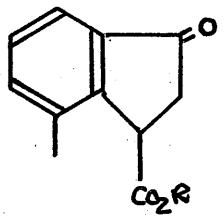


(197)

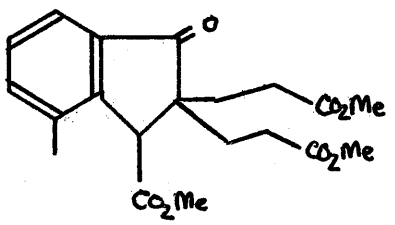
(193) achieved. Unfortunately, from our attempts to prepare the Michael addition product (194) only starting could be isolated. It is interesting to note, however, that even if a successful synthesis of (194) had been achieved its ring closure to (195) was questionable when one considers that the analogous cyclisation of (196) to (197) was only realised at the expense of the elimination of the ethoxalyl function.[148]

It is perhaps relevant at this stage to describe some preliminary enquiries which were undertaken at a much later date as a direct result of our investigations into the synthetic approaches to gibberone. The general validity of the main synthetic scheme outlined in this latter section (p. 89) seemed theoretically possible and thus we envisaged a synthesis of gibberic acid which was basically identical to that described for gibberone except with respect to starting material. The indanone ester (158; R = Et) seemed especially suited for this latter purpose.

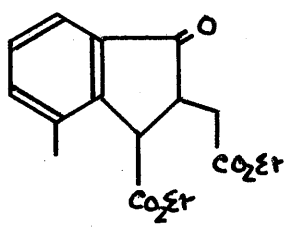
In the event, an attempt to achieve dicyanoethylation of (158; R = Et) resulted in the isolation of a crude reaction product, the infrared spectrum of which exhibited the expected nitrile absorption band at 2250 cm^{-1}. Subsequent alkaline hydrolysis of this crude reaction product, followed by silica chromatography of the acidic



(158)



(198)



(120)

mixture obtained, yielded the crystalline indanone acid (158; R = H) and an acidic oil which resisted our attempts crystallisation. The latter material, on esterification with diazomethane, furnished an ester which also failed to crystallise. Chromatography of this esterified product on alumina followed by short-path distillation under reduced pressure, yielded a colourless oil which was assigned the structure (198) on the basis of its infrared spectrum (1735 cm^{-1}, ester; 1715 cm^{-1}, indanone carbonyl) and elemental analysis. We feel confident that the rather low yield experienced in the cyanoethylation step could be overcome by suitable modification of the reaction conditions. Although further experimental work has still to be undertaken on this synthetic approach the isolation of (198) seems to substantiate its general validity. The remainder of the synthesis would, of course, follow the lines previously indicated in section 1 (p. 89).

It is also anticipated that further experimental effort will be expended on a suitable preparation of the keto-diester (120) since many relevant synthetic ideas, reported in the literature, have yet to be tested.

EXPERIMENTAL

(1) o-Methylcinnamic acid

This was obtained in 75% yield by the method described by Bachmann.[91]

o-Methyldihydrocinnamic acid

The following modifications were made to the method previously reported.[91] A solution of o-methylcinnamic acid (20 g.) in 10% sodium hydroxide (120 ml.) containing 5% palladium-charcoal (3 g.) was hydrogenated until the theoretical amount of hydrogen had been absorbed (2 hours). Filtration, followed by acidification of the cold filtrate with dilute hydrochloric acid, yielded a white solid which was filtered off and dried. Crystallisation from petroleum ether (b.p. 60-80°) yielded colourless plates (18.5 g., 91%) m.p. 102-104°C. (lit. m.p.104°C.)

4-Methylindan-1-one (122)

This was obtained by modification of the method previously described.[91] A mixture of o-methyldihydrocinnamic acid (8 g.) and polyphosphoric acid (150 g.) was stirred vigourously for three hours at 100°C. The viscous red syrup which resulted was added, with stirring, to iced water (400 ml.) and a yellow solid precipitated. The aqueous mixture was extracted with benzene and ether and the organic extracts washed with sodium bicarbonate

solution, water and dried ($MgSO_4$). Evaporation of the solvent yielded a crude yellow solid which, on crystallisation from petroleum ether (b.p. 60-80°C.), gave (122) (5.5 g., 79%) as pale yellow prisms m.p. 98-101°C. (lit. m.p. 96°,[87] 99-100°,[90] 103-104°C.[88]).

Keto-diacid (123; R = H)

Acrylonitrile (2.2 g.) was added slowly, at room temperature, to a stirred solution of the indanone (122) (3 g.) and Triton B (300 mg.) in dry benzene (30 ml.). Stirring was continued for 16 hours and the deep brown benzene solution was then washed with water. Evaporation furnished a viscous oil which was refluxed for 8 hours with 10% potassium hydroxide solution (100 ml.). The alkaline solution was cooled, filtered, and extracted with benzene. Acidification of the ice-cold aqueous layer yielded an off-white solid which was collected by filtration and dried (4.5 g., 75%). Crystallisation from hot water gave (123; R = H) as colourless plates m.p. 160-164°C. (Found: C, 65.98; H, 6.23; $C_{16}H_{18}O_5$ requires C, 66.19; H, 6.25). The infrared spectrum (mujol) showed peaks at 1720 cm^{-1} (indanone carbonyl) and 1700 cm^{-1} (carboxyl).

The diethyl ester (123; R = Et) was obtained in the usual way as a viscous oil and was used without purification. The infrared spectrum showed bands at

1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl).

Spiro-β-keto-ester (124)

The crude keto-diester (123; R = Et) (21.6 g.) was added dropwise, over one hour, to a stirred and gently refluxing mixture of sodium sand (1.44 g.) and dry benzene (175 ml.). Stirring and refluxing was maintained for a further 12 hours. The orange reaction mixture was then cooled and shaken with ice-cold dilute hydrochloric acid. After separating the benzene layer, the aqueous layer was extracted with ether and the organic extracts combined, washed with sodium bicarbonate solution, water and dried ($MgSO_4$). Evaporation of the solvent yielded a yellow solid which was dissolved in a minimum amount of ethanol, boiled with charcoal, and filtered. On cooling, the ethanolic solution deposited colourless needles (11.2 g.) m.p. 129-133°C. A further crop (2 g.) was obtained by concentration of the solution and the addition of a small quantity of water. Total yield, 13.2 g., 70%. Recrystallisation from 95% ethanol gave (124) as colourless needles m.p. 131-133°C. (Found: C, 71.78; H, 6.84; $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71). The infrared spectrum (carbon tetrachloride) showed peaks at 1720 cm^{-1} (s) (ester and indanone carbonyl), 1670 cm^{-1} (s) (chelated ester carbonyl) and 1615 cm^{-1} (w) (enol double bond) while the ultraviolet spectrum exhibited absorption maxima at

250-252 mu (ε 26,200) and 295-300 mu (ε 3,080).

Spiro-diketone (125)

A mixture of the spiro-β-keto-ester (124) (10 g.), glacial acetic acid (40 ml.), concentrated hydrochloric acid (10 ml.), and water (6 ml.) was refluxed, under nitrogen, for 5 hours. The cooled solution was added, with stirring, to ice and water (150 ml.) and the white solid obtained removed by filtration and dried (7 g., 92%). Crystallisation from aqueous ethanol gave colourless prisms m.p. 123-126°C. (Found: C, 79.18; H, 7.19; $C_{15}H_{16}O_2$ required C, 78.92; H, 7.06). The infrared spectrum (carbon tetrachloride) had a peak at 1720 cm^{-1} (broad) (superimposed indanone and cyclohexanone) and the ultraviolet spectrum showed bands at 250-255 mu (ε 12,700) and 298 mu (ε 2,420).

Spiro-diol (126)

Methylmagnesium bromide was made by adding a solution of methyl bromide (20 ml.) in dry ether (25 ml.) to a stirred mixture of magnesium turnings (2 g.) and dry ether (10 ml.). Air was excluded from the reaction vessel by a slow stream of nitrogen and the loss of methyl bromide was prevented by using a methanol-drikold condenser (fitted with a silica gel tube to exclude moisture). After changing to a water condenser, a solution of crude spiro-diketone (125) (4.6 g.) in 50% ether-tetrahydrofuran

(100 ml.) was added dropwise to the stirred and gently refluxing Grignard reagent. Refluxing and stirring was continued for 3 hours after which time the Grignard complex was decomposed by careful addition of saturated ammonium chloride solution (80 ml.). The organic layer and the ether washings of the aqueous layer were washed with water and dried. Removal of the solvent gave (126) as a colourless gum (5.1 g., 97%) which was used without purification. The infrared spectrum (film) showed peaks at 3400 cm^{-1} (s)(broad)(hydroxyl) and 1600 cm^{-1} (aromatic) while the ultraviolet spectrum had an absorption maximum at 265 mu (ε 430).

Spiro-diene (127)

A solution of the crude diol (126) (5.1 g.) in dry benzene (150 ml.) containing p-toluene-sulphonic acid (400 mg.) was refluxed for 3 hours in a Dean and Stark apparatus. The deep red benzene solution was cooled, washed with sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a brown semisolid (4.3 g., 97%) which was chromatographed on alumina (grade 111). Elution with petroleum ether (60-80°) gave (127) as a white solid (2.8 g., 64%) which on crystallisation from petroleum ether (b.p. 60-80°) furnished white prisms m.p. 67-69°C. (Found: C, 90.67; H, 9.20; $C_{17}H_{20}$ requires C, 91.01;

H, 8.99). The infrared spectrum (carbon tetrachloride) showed peaks at 1635 cm^{-1} (styrene double bond) and 1600 cm^{-1} (aromatic) while the ultraviolet spectrum exhibited bands at 255 mu (ε 15,500), 290 mu (ε 3,940), and 300 mu (ε 3,520).

Anomalous dehydration of the diol (126)

A solution of the crude diol (126) (6.5 g.) in dry benzene (150 ml.) containing p-toluene-sulphonic acid (50 mg.) was refluxed for 4 hours in Dean and Stark apparatus. The yellow benzene solution which resulted was worked up in the manner described above and yielded a yellow gum (5.2 g.) whose infrared spectrum (film) showed peaks at 3300 cm^{-1} (hydroxyl), 1630 cm^{-1} (styrene double bond), and 1600 cm^{-1} (aromatic). Re-treatment of the yellow gum with p-toluene-sulphonic acid (1 g.) under the conditions described above, but using a shorter reflux time (2 hours), furnished a brown gum which was chromatographed on alumina (grade 111). Elution with petroleum ether (b.p. 60-80°) gave a colourless viscous oil which failed to crystallise. The infrared spectrum showed a peak at 1600 cm^{-1} (aromatic) while the infrared spectrum possessed bands at 257 mu (ε 3,180), 290 mu (ε 810), and 300 mu (ε 695).

Diketo-ester (129; R = Me)

A slow stream of ozone was passed through a

solution of the diene (127) (1 g.) in analar ethyl acetate (50 ml.) which was kept at -70°C. by means of a methanol-drikold bath. After 2 hours the blue ethyl acetate solution was allowed to attain room temperature and the ethyl acetate carefully removed under reduced pressure using a water bath kept at 50°C. The gummy yellow residue which remained was dissolved in glacial acetic acid (15 ml.) and to this was added 30% hydrogen peroxide (5 ml.) and dilute hydrochloric acid (2 drops). The solution was allowed to stand overnight at room temperature and then heated on the steam bath for a short time (10 minutes) to decompose excess hydrogen peroxide. Sodium bicarbonate solution was then added to the reaction mixture which had been concentrated to half its bulk by removal of acetic acid under reduced pressure. The alkaline solution was washed with ether, acidified with dilute hydrochloric acid, and finally extracted with ethyl acetate. Repeated washing with water and removal of the ethyl acetate (after drying: $MgSO_4$) yielded (129; R = H) as a pale yellow gum (1 g., 82%) which resisted our attempts at crystallisation. The infrared spectrum (film) showed peaks at 1700 cm^{-1} (broad)(indanone carbonyl, aliphatic carbonyl and carboxyl superimposed) and 1600 cm^{-1} (aromatic).

Treatment of the crude gum, obtained above, with ethereal diazomethane yielded the diketo-ester (129;

R = Me) as a viscous yellow oil (1 g., 97%) which was used without purification. The infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl) while the ultraviolet spectrum possessed bands at 250 mu (ε 7,200) and 295 mu (ε 1,390).

Tricyclic enone-ester (130; R = Me)

A solution of the diketo-ester (129; R = Me) (800 mg.) in sodium methoxide solution (100 ml., prepared from 1 g. sodium and 100 ml. methanol) was refluxed, under nitrogen, for 4 hours. The deep red solution was concentrated "in vacuo" to 30-40 ml., diluted with water (75 ml.), and acidified with dilute hydrochloric acid. The turbid solution which resulted was extracted with ethyl acetate, washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a red gum (600 mg.) which, on trituration with ether, gave the tricyclic enone-acid (130; R = H) as a yellow solid (250 mg., 33%). The infrared spectrum (carbon tetrachloride) showed peaks at 1730 cm^{-1} (sh)(ester), 1705 cm^{-1} (carboxyl), 1665 cm^{-1} (cyclohexenone), and 1625 cm^{-1} (styrene double bond). Repeated trituration with ether gave a white solid (m.p. 218-225°C.)but no further purification was attempted.

The corresponding methyl ester (130; R = Me) was obtained as a pale yellow solid by treatment of the enone-

acid (130; R = H) with ethereal diazomethane. Trituration of the solid ester with ether followed by crystallisation from petroleum ether (b.p. 60-80°), containing a trace of ethyl acetate, yielded (130; R = Me) as colourless prisms m.p. 109-111°C. (Found: C, 75.36; H, 6.26; $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71). The infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester), 1670 cm^{-1} (cyclohexenone), and 1630 cm^{-1} (styrene double bond) while the ultraviolet spectrum possessed bands at 238 mu (ε 8,300) and 300 mu (ε 19,500).

Attempted re-cyclisation of the crude by-product

Evaporation of the ether used for trituration of the crude enone-acid (130; R = H) yielded a red gum which, on esterification with ethereal diazomethane, gave a viscous red oil whose infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester), 1715 cm^{-1} (indanone carbonyl), and 1665 cm^{-1} (w)(cyclohexenone). Two attempts were made to obtain further quantities of tricyclic material from this crude oil and these are described in the sequel.

A. The crude oil (250 mg.) obtained above was refluxed with 1% sodium methoxide solution (50 ml.) for 3 hours in a nitrogen atmosphere. Work up in the usual way gave a red gum which was esterified with diazomethane. The red viscous oil (180 mg.) which resulted possessed peaks at

1740 cm^{-1} (ester), 1715 cm^{-1} (indanone carbonyl) and 1665 cm^{-1} (w)(cyclohexenone). Chromatography on alumina (grade 111) using petroleum ether (b.p. 60-80°)- benzene (1:1) as eluant provided a viscous yellow oil whose infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl). A small quantity of oily material was obtained from a later fraction and gave peaks at 1735 cm^{-1} (ester), 1715 cm^{-1} (indanone carbonyl), 1670 cm^{-1} (m)(cyclohexenone) and 1630 cm^{-1} (w)(styrene double bond). Attempts to obtain reasonably pure enone-ester from this small amount of oil were unsuccessful.

B. A solution of the crude oily by-product (200 mg.) in dry benzene (80 ml.) containing pure p-toluene-sulphonic acid (100 mg.) was refluxed for 2 hours in a Dean and Stark apparatus. Work up in the usual way (p.159) furnished a red oil whose infrared spectrum showed peaks at 1730 cm^{-1} (ester), 1670 cm^{-1} (w)(cyclohexenone), and 1630 cm^{-1} (w) (styrene double bond). Attempts to obtain the tricyclic enone-ester (130; R = Me) from this crude product, using crystallisation or chromatography on alumina, failed.

<u>Attempted cyclisation of the diketo-acid (129; R = H) and diketo-ester (129; R = Me)</u>

Several attempts were made to achieve a more efficient preparation of the tricyclic enone-ester (130;

R = Me) and the experimental details of these attempts are outlined below.

A. The impure diketo-acid (129; R = H) (1.2 g.) was dissolved in dry dioxan (35 ml.) and the solution cooled in ice. An ice-cold solution of potassium hydroxide (1 g.) in water (20 ml.) was added, the air was displaced by nitrogen, and the reaction mixture allowed to attain room temperature. The reaction mixture was then stirred for 3 hours, diluted with water, extracted with ether, acidified with dilute hydrochloric acid, and the aqueous layer finally extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a red gum (1.1 g.) which resisted our attempts at crystallisation. The infrared spectrum showed a broad peak at 1700 cm^{-1} (carbonyl and carboxyl).

Re-treatment of this product with sodium ethoxide solution, in the manner described below, provided the tricyclic enone-acid (130; R = H).

B. A solution of the impure diketo-acid (129; R = H) (1.2 g.) in 1% sodium ethoxide solution (100 ml.) was refluxed for 3 hours under nitrogen. The yellow turbid reaction mixture was allowed to stand at room temperature for 4 hours and then worked up as described on p.162. The tricyclic enone-acid (130; R = H) was thus obtained as a

pale yellow solid (250 mg., 22%). Esterification with ethereal diazomethane furnished the enone-ester (130; R = Me).

C. A solution of the diketo-ester (129; R = Me) (150 mg.) in dry benzene (80 ml.) containing p-toluene-sulphonic acid (25 mg.) was refluxed for 4 hours in a Dean and Stark apparatus. Work up in the usual way provided an oil whose infrared spectrum (1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl)) was identical with that of the starting material.

Re-treatment of this product with sodium methoxide, in the manner previously described (p.162), furnished the enone-ester (129; R = Me).

2-Formyl-6-methylcyclohexanone (138)

To a vigorously stirred suspension of powdered dry sodium methoxide[102] (430 mg.) in dry benzene (10 ml.) was added ethyl formate (590 mg., dried over potassium carbonate and freshly distilled) at room temperature. The mixture was stirred for 30 minutes and cooled in ice. A solution of 2-methylcyclohexanone (450 mg.) in dry benzene (10 ml.) was added in a thin stream to the stirred ice-cold suspension which was kept at 0°C. for a further 35 minutes. After stirring overnight at room temperature the yellow turbid mixture was diluted with benzene and ether and acidified with ice-cold dilute sulphuric acid.

The organic layer was combined with the ether washings of the aqueous layer, washed with wilute sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a mobile yellow oil (450 mg., 54%) which gave a deep red colouration with alcoholic ferric chloride solution. The infrared spectrum (carbon tetrachloride) showed peaks at 1700 cm^{-1} (m) and 1640 cm^{-1} (s)(broad)(β-diketone).

Isoxazole (139)

A solution of 2-formyl-6-methylhexanone (138) (400 mg.) in glacial acetic acid (15 ml.), containing hydroxylamine hydrochloride (300 mg.), was heated under reflux for 25 minutes. The cooled solution was diluted with water, extracted with ether and the ether extracts washed with sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of the ether under reduced pressure yielded a mobile yellow oil (300 mg., 76%) which gave no colouration with alcoholic ferric chloride solution. The infrared spectrum (film) of this product showed peaks at 1715 cm^{-1} (w)(trace cyclohexanone) and 1640 cm^{-1} (C=N).

2-Methyl-6-cyano-cyclohexanone (140)

A solution of the isoxazole (139) (300 mg.) in dry benzene (5 ml.) was added to an ice-cold solution of sodium (80 mg.) in dry methanol (2 ml.) and the resultant mixture was set aside, with occasional shaking, for 2 hours

at room temperature. After dilution with water, the clear yellow solution was extracted with ether and the ether layer washed with 0.5% potassium hydroxide solution. The alkaline layer, after acidification with dilute hydrochloric acid, was extracted with ether and the organic layer washed and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a mobile yellow oil (200 mg., 66%) whose infrared spectrum (film) showed peaks at 2250 cm^{-1} (nitrile) and 1710 cm^{-1} (cyclohexanone).

Formyl enone-ester (142; R = Me)

To a vigorously stirred suspension of powdered dry sodium methoxide[102] (450 mg.) in dry benzene (15 ml.) was added a solution of ethyl formate (600 mg.)(dried over potassium carbonate and freshly distilled) in dry benzene (5 ml.). The mixture was stirred for 40 minutes at room temperature under nitrogen and then cooled in ice. A solution of the enone-ester (130; R = Me) (1 g.) in dry benzene (35 ml.) was added dropwise to the stirred ice-cold suspension which was kept at 0°C. for a further 30 mimutes. More benzene (35 ml.) was added and the dark brown-green reaction mixture was left stirring overnight at room temperature.

The solution was diluted with water, ether, shaken with dilute sulphuric acid and the deep yellow organic layer separated off and dried. Removal of the solvent

yielded a red oil (900 mg., 81%) which gave a deep reddish-purple colouration with alcoholic ferric chloride solution and whose infrared spectrum (carbon tetrachloride) showed peaks at 1740 cm^{-1} (ester), 1670 cm^{-1} (sh)(cyclohexenone) and 1640 cm^{-1} (β-diketone, enol and styrene double bond). The ultraviolet spectrum exhibited absorption maxima at 238 mu (ε 7,350) and 300-305 mu (ε 12,800). In 0.1N alcoholic sodium ethoxide solution the ultraviolet spectrum showed bands at 232 mu (ε 7,900), 295 mu (ε 13,100) and 390-395 mu (ε 5,150).

Isoxazole (143; R = Me)

A solution of the formyl derivative (142; R = Me) (900 mg.) in glacial acetic acid (25 ml.), containing powdered hydroxylamine hydrochloride (900 mg.), was refluxed for 25 minutes under nitrogen. The deep red solution was cooled, diluted with water (200 ml.) and the pink turbid mixture extracted with ethyl acetate. The organic extracts were washed with water, shaken with charcoal, filtered and dried ($MgSO_4$). Removal of the solvent yielded a red oil (700 mg., 78%) which gave no colouration with alcoholic ferric chloride solution. The infrared spectrum showed peaks at 1730 cm^{-1} (ester) and 1630 cm^{-1} (w)(styrene double bond and C=N) while the ultraviolet spectrum exhibited absorption maxima at 238 mu (ε 7,200) and 320 mu (ε 11,700).

β-Keto-nitrile (133; R = Me)

A solution of the isoxazole (143; R = Me)(400 mg.) in dry benzene (7 ml.) was added, under nitrogen, to an ice-cold solution of sodium (130 mg.) in dry methanol 3 ml.) and the resultant mixture was set aside, with occasional shaking, for 1 hour at room temperature. After dilution with water, the solution was extracted with ether and the ether layer washed with 0.5% potassium hydroxide. The combined aqueous layers, after acidification with dilute hydrochloric acid, were extracted with ether and the organic extracts washed and dried. Removal of the solvent under reduced pressure yielded a yellow gum (250 mg., 62%) whose infrared spectrum (film) showed peaks at 2250 cm^{-1}, 2190 cm^{-1} (nitrile), 1710 cm^{-1} (carboxyl), 1660 cm^{-1} (cyclohexenone) and 1620 cm^{-1} (styrene double bond). Trituration of this acidic product with ether gave a pale yellow solid which was insoluble in carbon tetrachloride. Subsequent esterification with ethereal diazomethane furnished a yellow solid which, on trituration with ether, and repeated crystallisation from petroleum ether (b.p. 60-80°), containing a trace of ethyl acetate, gave (133; R = Me) as off-white prisms m.p. 139-142°C. The infrared spectrum showed peaks at 2250 cm^{-1}, 2200 cm^{-1} (nitrile), 1735 cm^{-1} (ester), 1670 cm^{-1} (cyclohexenone) and 1620 cm^{-1} (styrene double bond).

C-Methylated β-keto-nitrile (135; R = Me)

A solution of impure isoxazole (143; R = Me) (700 mg.) in dry benzene (18 ml.) was added, under nitrogen, to an ice-cold solution of sodium (150 mg.) in dry methanol (5 ml.). The resultant mixture was set aside, with occasional shaking, for 30 minutes at room temperature and then refluxed for 10 minutes. After cooling, methyl iodide (1 ml.) was added and the stirred solution was left for 1 hour at room temperature. Reflux was started and continued for 2 hours during which time an additional quantity of methyl iodide (0.5 ml.) was added. The cooled red solution was diluted with ether and benzene and the organic layer washed with water and dried. Removal of the solvent under reduced pressure gave a red oil (500 mg., 68%) which, on trituration with ether, yielded a yellow solid (250 mg., 34%) m.p.150-180°C. Repeated crystallisation from ethyl acetate gave (135; R = Me) as colourless plates m.p. 191-193°C. (Found: C, 73.82; H, 5.96; N, 4.58; $C_{19}H_{19}O_3N$ requires C, 73.76; H, 6.19; N, 4.53). The infrared spectrum showed peaks at 2250 cm^{-1} (nitrile), 1740 cm^{-1} (ester), 1675 cm^{-1} (cyclohexenone) and 1640 cm^{-1} (styrene double bond) while the ultraviolet spectrum exhibited absorption maxima at 240 mu (ε 8,150) and 302-310 mu (ε 20,300). Found: M (mass spectrometer), 309 Calc. for $C_{19}H_{19}O_3N$: M 309.

Attempted preparation of tetracyclic diketone (150)

To a cold solution of potassium (30 mg.) in dry tert-butanol (30 ml.) was added a solution of (135; R = Me) (20.25 mg.) in dry tert-butanol (2 ml.). The system was filled with nitrogen and the red solution was left stirring overnight at room temperature. After careful acidification with dilute hydrochloric acid, most of the tert-butanol was removed under reduced pressure (with minimum application of heat) and the gummy residue dissolved in benzene. The benzene solution was washed with water, sodium bicarbonate and dried ($MgSO_4$). Removal of the solvent under reduced pressure furnished a crude semisolid (9 mg., 54%) which, on trituration with ether and sublimation at atmospheric pressure, gave white prisms (6 mg., 36%) m.p. 204-207°C. (depressed on admixture with the starting nitrile). The solid product, which was sparingly soluble in ether and carbon tetrachloride, failed to give a positive reaction with either sodium bicarbonate or alcoholic ferric chloride solution. The infrared spectrum (chloroform) showed peaks at 1766 cm^{-1} (cyclopentanone), 1677 cm^{-1} (cyclohexenone) and 1622 cm^{-1} (styrene double bond) while the ultraviolet spectrum exhibited absorption maxima at 238 mu (ε 6,850), 300-302 mu (ε 15,400) and 330 mu (ε 14,600).

Methylated spiro-diketone (152)

A solution of the spiro-β-keto-ester (124) (6 g.) in dry benzene (30 ml.) was added dropwise to a stirred mixture of sodium sand (500 mg.) and dry benzene (5 ml.). After 30 minutes at room temperature the stirred mixture was refluxed for 1 hour under nitrogen. Methyl iodide (2 ml.) was added to the cooled yellow emulsion and the reaction mixture was stirred and heated under reflux for 8 hours. After cooling, the benzene layer was separated off and the aqueous layer diluted with water (30 ml.) and extracted with ether. The combined organic extracts were washed with 5% potassium hydroxide solution, water and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a viscous red oil (6 g., 95%) which gave no colouration with alcoholic ferric solution. The infra-red spectrum (film) of this crude product had a broad peak at 1710 cm^{-1} (ester, indanone carbonyl and cyclo-hexanone).

A mixture of the crude oil obtained above, glacial acetic acid (20 ml.), concentrated hydrochloric acid (8 ml.) and water (4 ml.) was refluxed, under nitrogen, for 6 hours. The cooled solution was added, with stirring, to ice and water (120 ml.) and the crude yellow solid obtained removed by filtration and dried (4 g., 86%). Crystallisation from aqueous methanol gave (152) as white

prisms m.p. 106-112°C. (2.3 g., 50%). Recrystallisation raised the m.p. to 112-114°C. (Found: C, 79.17; H, 7.64; $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49). The infrared spectrum showed a broad peak at 1710 cm^{-1} (indanone carbonyl and cyclohexanone) while the ultraviolet spectrum exhibited absorption maxima at 252 mu (ε 12,500) and 298-300 mu (ε 2,300).

Furfurylidene derivative of methylated spiro-diketone (154)

A mixture of the methylated spiro-diketone (152) (500 mg.), 95% ethanol (4 ml.), 15% sodium hydroxide solution (0.8 ml.) and redistilled furfural (0.3 ml.) was set aside for 2 hours at room temperature. No precipitate was observed and the dark red mixture was diluted with water, extracted with ether, and the organic extracts washed dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow gum (600 mg., 91%) which resisted our attempts at crystallisation. The ultraviolet spectrum exhibited absorption maxima at 250 mu (ε 13,000) and 325-330 mu (ε 17,500).

Keto-diester (155; R = Me)

A solution of the crude furfurylidene derivative (154) (600 mg.) in analar ethyl acetate (40 ml.) was ozonised at -70°C. for 30 minutes. The solution was allowed to attain room temperature and the ethyl acetate carefully removed under reduced pressure using a water

bath kept at 50°C. The gummy residue was dissolved in glacial acetic acid (5 ml.) and to this was added 30% hydrogen peroxide (2 ml.) and dilute hydrochloric acid (1 ml.). After standing overnight at room temperature the reaction mixture was diluted with water and sodium bicarbonate solution and finally extracted with ether. The ether extracts of the acidified aqueous layer were washed thoroughly with water and dried ($MgSO_4$). Removal of the solvent yielded a pale yellow acidic gum (400 mg., 73%) which was used without purification. The infrared spectrum showed a broad peak at 1700 cm^{-1} (broad)(indanone carbonyl and carboxyl) while the ultraviolet spectrum exhibited absorption maxima at 250-255 mu (ε 9,200) and 295 mu (ε 1,800).

The corresponding dimethyl ester (155; R = Me) was obtained in the usual way as a red oil (320 mg.) whose infrared spectrum showed peaks at 1735 cm^{-1} (ester) and 1710 cm^{-1} (indanone carbonyl).

Nor-spiro-β-keto-ester (156)

A solution of the impure diketo-ester (155; R = Me) (320 mg.) in dry benzene (30 ml.) was added dropwise, under nitrogen, to stirred and gently refluxing mixture of sodium sand (70 mg.) and dry benzene (20 ml.). Stirring and refluxing was maintained for a further 12 hours. The reaction mixture was then cooled, shaken with ice-cold

dilute hydrochloric acid, and the benxene layer separated off. The aqueous layer was extracted with ether and the organic extracts combined, washed with sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of the solvent yielded a red oil (230 mg., 79%) which gave a deep violet colouration with alcoholic ferric chloride solution. The infrared spectrum (carbon tetrachloride) showed peaks at 1720 cm^{-1} (indanone carbonyl and ester), 1665 cm^{-1} (chelated ester carbonyl) and 1620 cm^{-1} (enol double bond).

Methylated nor-spiro-diketone (153)

A mixture of the nor-spiro-β-keto-ester (156) (230 mg.), glacial acetic acid (8 ml.), concentrated hydrochloric acid (3 ml.) and water (1.5 ml.) was refluxed, under nitrogen, for 7 hours. The resultant solution was cooled, shaken with charcoal, filtered and added to ice and water (40 ml.). The turbid solution thus obtained was extracted with ether and the organic layer washed with sodium bicarbonate, water and dried. Removal of the ether under reduced pressure gave (153) as a red viscous oil (120 mg., 65%) which gave no colouration with alcoholic ferric chloride solution. Subsequent treatment with charcoal yielded a yellow oil which was chromatographed on alumina (grade 111). Elution with benzene-petroleum ether (b.p. 60-80°) (1:1) gave (153) as

a colourless viscous oil which was micro-distilled onto a cold finger by using an oil bath at 140-160°C. and a pressure of 0.4 mm. (Found: C, 78.41; H, 7.40; $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06). The infrared spectrum showed peaks at 1745 cm^{-1} (cyclopentanone) and 1715 cm^{-1} (indanone carbonyl) while the ultraviolet spectrum exhibited absorption maxima at 252 mu (ε 12,300) and 298-300 mu (ε 2,200).

Alternative preparation of keto-diester (155; R = Me)

The methylated spiro-diketone (152) (120 mg.) in dry methanol (0.5 ml.) was treated with a solution of sodium (30 mg.) in dry methanol (0.5 ml.). Butyl nitrite (0.1 ml.) was added and the reaction mixture was set aside, under nitrogen, for 2 days. The yellow solution was then diluted with water (2 ml.) and acidified carefully with 3N hydrochloric acid until maximum turbidity was obtained. Extraction with ether and evaporation of the washed and dried ether extract yielded (157) as a colourless gum which was heated at 120-130°C. with a mixture of p-toluene-sulphonyl chloride (150 mg.) and 10% sodium hydroxide solution (2 ml.). After cooling, the reaction mixture was diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. Evaporation of the washed and dried ($MgSO_4$) ether extracts yielded a yellow gum (75 mg.) which was heated under reflux for 4 hours

with 10% sodium hydroxide solution (5 ml.). The cooled alkaline solution was acidified, extracted with ether, and the combined extracts washed and dried. Removal of the solvent under reduced pressure yielded an acidic gum which was esterified with ethereal diazomethane. Work up in the usual way furnished a red oil whose infrared spectrum (1735 cm^{-1}, 1710 cm^{-1}) was identical with that of the keto-diester (155; R = Me) (p. 175).

Attempted preparation of 2-carbethoxymethyl-4-methylindan-1-one (132; R = Et)

A. To a stirred mixture of sodium sand (230 mg.) and dry benzene (10 ml.) was added a solution of 4-methylindan-1-one (122) (1.5 g.) in dry benzene (20 ml.). The system was filled with nitrogen and the reaction mixture was stirred for a further 2 hours at room temperature. To the dark red reaction mixture was added a solution of ethyl chloroacetate (2 ml.) in dry benzene (30 ml.) and the resultant solution was refluxed and stirred for 3 hours. After cooling, the reaction mixture was added to iced water (40 ml.) and the organic layer, after dilution with ether, was separated off and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a red semisolid which on crystallisation from petroleum ether (b.p. 60-80°) gave a pale yellow solid m.p. 96-100°C. The melting point was not depressed by admixture with the starting material.

B. A mixture of 4-methylindan-1-one (122) (1.46 g.), sodamide (450 mg.), and dry benzene (25 ml.) was refluxed and stirred under nitrogen for 8 hours. To the ice-cold dark red reaction mixture was added a solution of ethyl chloroacetate (2 ml.) in dry benzene (10 ml.). After refluxing and stirring for 4 hours the reaction mixture was worked up in the manner described above and a red semisolid was obtained. Trituration with ether followed by crystallisation from petroleum ether (b.p. 60-80°) yielded the starting indanone (122), identified by m.p. and mixed m.p.

2-Carboxymethylene-4-methylindan-1-one (160; R = H)

To a cooled suspension of sodium periodate (4.28 g.), partly dissolved in concentrated sulphuric acid (0.4 ml.) and water (24 ml.), was added a solution of tartaric acid (3 g.) in water (6 ml.). After 5 minutes the ice bath was removed and the mixture was shaken mechanically for 25 minutes at room temperature. In order, 4-methylindan-1-one (122) (1.5 g.), sodium hydroxide (3 g.) in water (54 ml.), and ethanol (50 ml.) were added. After 14 hours at room temperature, the reaction mixture was heated to 60°C. for 10 minutes. The alkaline solution was cooled, diluted with water and extracted with ether. Acidification of the aqueous layer gave (160; R = H) as a yellow solid (1.4 g., 67%) which

was filtered off and dried. The infrared spectrum (nujol) of this crude material (m.p. 135-200°C.) showed peaks at 1710 cm^{-1}, 1680 cm^{-1} (indanone and carbonyl) and 1640 cm^{-1} (double bond) and the ultraviolet spectrum exhibited absorption bands at 255 mu (ε 10,030) and 285 mu (ε 7,600).

Trituration of the crude product with ether followed by crystallisation from methanol yielded white prisms m.p. 200-209°C. (decomp.) (Found: C, 71.63; H, 4.87; $C_{12}H_{10}O_3$ requires C, 71.28; H, 4.99).

Hydrogenation of 2-carboxymethylene-4-methylindan-1-one (160; R = H)

A. A solution of (160; R = H) (1.1 g.) in 1% potassium hydroxide (75 ml.) containing 10% palladium-charcoal (500 mg.) was hydrogenated to completion. Filtration, followed by acidification of the alkaline solution yielded a white solid (900 mg., 82%) which was esterified with ethereal diazomethane. Work up in the usual way furnished a pale yellow solid which gave no reaction with 2:4-dinitrophenylhydrazine reagent. Repeated crystallisation from petroleum ether (b.p. 60-80°) yielded 1-hydroxy-2-carbomethoxymethyl-4-methylindane (161; R = Me) as colourless needles m.p. 110-112°C. (Found: C, 70.68; H, 7.68; $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32). The infrared spectrum (nujol) showed peaks at 3150 cm^{-1} (broad) (hydroxyl) and 1720 cm^{-1} (ester) while the ultraviolet

spectrum exhibited an absorption maximum at 265 mu (ε 320).

B. A solution of (160; R = H) (800 mg.) in ethanol (100 ml.) containing 10% palladium-charcoal (400 mg.) was hydrogenated until 110 ml. of hydrogen had been absorbed (10 minutes). Filtration, followed by removal of the solvent under reduced pressure yielded a colourless oil (700 mg., 87%) which solidified to a white solid. Crystallisation from aqueous methanol (3 times) gave white prisms m.p. 124-134°C. This product reacted with sodium bicarbonate solution and gave a red 2:4-dinitrophenyl-hydrazone. The infrared spectrum (carbon tetrachloride) showed peaks at 3500 cm^{-1} (w)(hydroxyl), 1760 cm^{-1} (w) (γ-lactone) and 1725 cm^{-1} (carboxyl and indanone carbonyl) while the ultraviolet spectrum exhibited absorption maxima at 250 mu (ε 9,850) and 295 mu (ε 1,840).

Attempted preparation of 2-carbomethoxymethylene-4-methylindan-1-one (160; R = Me)

Treatment of the unsaturated keto-acid (160; R = H) (100 mg.) with ethereal diazomethane for 1 hour and work up in the usual way furnished a pale yellow solid (100 mg.) whose infrared spectrum (nujol) showed peaks at 1735 cm^{-1} (ester) and 1710 cm^{-1} (indanone carbonyl). Crystallisation of the yellow solid from ethyl acetate-petroleum ether (b.p. 60-80°) yielded the pyrazoline (163; R = Me or 164; R = Me) as white prisms m.p. 91-95°C.

The ultraviolet spectrum exhibited absorption maxima at 260 mu (ε 13,200) and 300 mu (ε 2,580). At the time of writing we await a more accurate final analysis for this compound.

(2) γ-Methyl-γ-carboxy-pimelic acid (167)

This was prepared by the method described in the literature.[129] The trimethyl ester was obtained in the usual way and was used without purification.

2:4-Dicarbomethoxy-4-methylcyclohexanone (168)

Anhydrous ether (150 ml.), containing dry methanol (7.5 ml.), was added slowly, with stirring, to sodium hydride (2.4 g.). A vigorous effervescence ensued and was allowed to subside. To this stirred ice-cold solution was added the trimethyl ester of (167) (26 g.) over a period of 20 minutes and the resultant reaction mixture was stirred at ice bath temperature for a further 18 hours. Dilute hydrochloric acid (approx. 100 ml.) was then added to the reaction mixture and the ether layer separated off, washed with 10% sodium carbonate solution, water and dried. Removal of the solvent under reduced pressure gave (168) as a pale yellow oil (20 g., 88%). The infrared spectrum (film) showed peaks at 1730 cm^{-1} (ester), 1665 cm^{-1} (chelated ester carbonyl) and 1620 cm^{-1} (enol double bond).

Coumarin ester (169; R = Me)

To a stirred ice-cold mixture of p-cresol (18 g.) and the cyclic β-keto-ester (168) (20 g.) was added 80% (v/v) sulphuric acid (200 ml.) in a thin stream. After 30 minutes the ice bath was removed and the mixture stirred for 24 hours at room temperature. The clear red

solution was added, with stirring, to ice water (600 ml.) and the pale yellow solid which precipitated was filtered off and dried. Crystallisation from methanol gave (169; R = Me) as white prisms (13 g., 52%) m.p. 144-148°C. Recrystallisation from methanol raised the m.p. to 152°C. (Found: C, 71.22; H, 6.12; $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34). The infrared spectrum (nujol) showed peaks at 1730 cm^{-1} (ester), 1700 cm^{-1} (coumarin) and 1620 cm^{-1} (w)(double bond) while the ultraviolet spectrum exhibited absorption maxima at 275 mu (ε 10,025) and 318 mu (ε 6,130).

Unsaturated methoxy-diacid (170)

A stirred mixture of the coumarin ester (169; R = Me) (8 g.) and 40% potassium hydroxide solution (130 ml.) was heated on the steam bath until dissolution was complete. Dimethyl sulphate (120 ml.) and 40% potassium hydroxide solution (270 ml.) were added separately and concurrently to this vigorously stirred solution over a period of 3 hours. The solution was left for a further 20 hours at room temperature and then cooled thoroughly. The straw-coloured solution was then filtered, slowly acidified with dilute hydrochloric acid, and the pale yellow solid which precipitated was filtered off and dried (7 g., 82%). Crystallisation from aqueous methanol gave a white solid (5.5 g., 65%) m.p. 172-178°C. Repeated crystallisation from aqueous methanol yielded white prisms

m.p. 173-178°C. (Found: C, 67.38; H, 6.43; OMe, 9.68; $C_{16}H_{16}O_4$ requires C, 67.09; H, 6.62; OMe, 10.20). The infrared spectrum (nujol) showed peaks at 1690 cm^{-1} (carboxyl), 1625 cm^{-1} (w)(double bond) and 1600 cm^{-1} (aromatic) while the ultraviolet spectrum exhibited an absorption maximum at 285-288 mu (ε 2,530).

Attempted cyclisation of the unsaturated diacid (170)

A. A mixture of the unsaturated diacid (170) (60 mg.) and polyphosphoric acid (20 g.) was stirred for 1 hour at 60°C. The dark green syrup was added, with stirring, to iced water (100 ml.) and the solution was extracted with a mixture of ether and benzene. After washing with water the organic extracts were dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a yellow solid (30 mg.) whose ultraviolet spectrum showed absorption maxima at 278 mu (ε 10,040) and 318 mu (ε 6,550). Crystallisation from methanol gave white prisms m.p. 218-223°C. undepressed by admixture with authentic coumarin acid (169; R = H).

B. A mixture of (170) (100 mg.) and concentrated sulphuric acid (20 ml.) was stirred for 1 hour at room temperature. The dark green mixture was added to ice water and the yellow solid which deposited was filtered off and dried (65 mg.). Crystallisation from ethyl acetate/petroleum ether (b.p. 60-80°) gave (169; R = H)

as white prisms m.p. 222-224°C. (Found: C, 70.66; H, 6.02; $C_{16}H_{16}O_4$ required C, 70.57; H, 5.92). The ultraviolet spectrum exhibited absorption maxima at 275 mu (ε 10,060) and 318 mu (ε 6,550).

Coumarin acid (169; R = H)

The coumarin ester (169; R = Me) (100 mg.) was heated for 1 hour on a steam bath with 4N sodium hydroxide solution (20 ml.) and methanol (2 ml.). The solution was cooled, filtered, and the filtrate acidified with dilute hydrochloric acid. A white solid deposited and was filtered off and dried (60 mg.). Crystallisation from methanol gave (169; R = H) as white prisms m.p. 221-224°C. (Found: C, 70.84; H, 6.24; $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92). The infrared spectrum (nujol) showed peaks at 1710 cm^{-1} (broad)(carboxyl and coumarin), 1630 cm^{-1} (w) (double bond) and 1600 cm^{-1} (aromatic) while the ultraviolet spectrum exhibited absorption maxima at 275 mu (ε 10,030) and 318 mu (ε 6,500).

Anhydride (176)

A mixture of the unsaturated diacid (170) (1 g.) and acetic anhydride (40 ml.) was refluxed for 4 hours. Removal of acetic anhydride under reduced pressure (1 mm.) yielded a yellow gum (950 mg.) whose infrared spectrum (film) showed peaks at 1810 cm^{-1}, 1725 cm^{-1} (anhydride), 1640 cm^{-1} (double bond) and 1600 cm^{-1} (aromatic). No

further purification of this material was attempted.

Attempted cyclisation of the anhydride (176)

A. The anhydride (176) (90 mg.) was treated with concentrated sulphuric acid (15 ml.) for 2 hours at room temperature. The dark green reaction mixture was added to ice water and the pale yellow solid which deposited was filtered off and dried (60 mg.). Crystallisation from ethyl acetate/petroleum ether (b.p. 60-80°) gave white prisms m.p. 218-222°C. The m.p. was undepressed on admixture with coumarin acid (169; R = H).

B. A mixture of the anhydride (176) (100 mg.), stannic chloride (200 mg.) and dry benzene (10 ml.) was set aside, with occasional shaking, for 15 minutes at room temperature. Concentrated hydrochloric acid and ether were added, the heterogeneous mixture shaken, and the organic layer separated off. After washing with 5% hydrochloric acid and water the ether layer was thoroughly washed with 5% sodium hydroxide solution. Acidification of the alkaline layer yielded a pale yellow solid which, on crystallisation from ethyl acetate/petroleum ether gave white prisms m.p. 220-224°C. The melting point was undepressed on admixture with coumarin acid.

Saturated methoxy-diacid (178)

A solution of the unsaturated diacid (170) (3 g.) in tetrahydrofuran (50 ml.) was added, with stirring, to

liquid ammonia (170 ml.). Lithium (0.7-0.8 g.) was added in small, freshly cut pieces until the reaction mixture remained blue for approximately 1 minute. The colour was then immediately discharged by adding powdered ammonium chloride. The reaction mixture was allowed to evaporate overnight and the white solid which remained was dissolved in water and the solution saturated with sodium chloride. After extraction with ether the ice-cold aqueous layer was acidified with dilute hydrochloric acid and the solid deposit filtered off and dried (1.4 g., 46%). Crystallisation from aqueous methanol yielded (178) as white prisms m.p. 210-214°C. (800 mg., 26%). Repeated crystallisation from aqueous methanol raised the m.p. to 212-215°C. (Found: C, 67.01; H, 6.98; $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24). The melting point was depressed on admixture with either the unsaturated diacid (170) or the coumarin acid (169; R = H). The infrared spectrum (nujol) showed a broad peak at 1710 cm^{-1} (carboxyl) while the ultraviolet spectrum exhibited an absorption maximum at 280 mu (ε 2,300).

Attempted cyclisation of the saturated diacid (178)

A. Treatment of the saturated diacid (178) (650 mg.) with polyphosphoric acid (60 g.) at 100°C. for 1.5 hours and work up of the deep red syrup in the usual way (p. 185), provided a deep yellow solid (400 mg.). Crystallisation

from aqueous methanol gave poorly-shaped crystals m.p.215-223°C. The melting point was not depressed on admixture with starting material.

B. Treatment of the saturated diacid (178) (50 mg.) with concentrated sulphuric acid (15 ml.) at 100°C. for 5 hours and work up in the usual way (p. 185) yielded only a trace of yellow solid. Trituration of the solid with ether gave a pale yellow solid whose m.p. 215-220°C. was undepressed on admixture with starting material.

Tetraethyl ethylene tetracarboxylate (183)

This was prepared by the method described in the literature.[140]

o-Tolyl-succinic acid (185)

Magnesium turnings (washed with ether and dried) (18 g.) were activated with a crystal of iodine. To the cooled turnings was added a solution of methyl iodide (0.5 ml.) in dry ether (100 ml.). A solution of o-tolyl bromide (129 g.) in dry ether (150 ml.) was then added dropwise to the stirred mixture and after effervescence had ceased the mixture was gently refluxed for a further 30 minutes. A solution of the tetra-ester (183) (47 g.) in dry ether (500 ml.) was added dropwise to the stirred Grignard reagent and the reaction mixture refluxed for 1 hour. Decomposition of the Grignard complex thus obtained was effected by carefully adding 25% ammonium

chloride (250 ml.) to the cooled mixture. Stirring was continued for 40 minutes after which time the ether layer was separated from the aqueous layer which contained much solid material. To this aqueous layer was added sufficient 10% acetic acid to dissolve the solid and the resultant solution was extracted thoroughly with ether. The combined ether extracts were washed with water and dried ($MgSO_4$). Removal of the ether under reduced pressure yielded a red oil. This was distilled under reduced pressure and the tetra-ester (184; R = Et) collected as a yellow oil b.p. 220-240°C./16 mm.(43 g., 71%).

The tetra-ester (184; R = Et) (43 g.) was refluxed with 25% potassium hydroxide solution (400 ml.) for 24 hours. The resultant solution was cooled, extracted with ether, and the aqueous layer acidified with 40% sulphuric acid. The turbid solution thus obtained was extracted with ether and the ether extracts washed and dried ($MgSO_4$). Removal of the solvent gave (184; R = H) as a pale yellow solid (22 g., 70%).

Decarboxylation was effected by fusing (184; R = H) at 165-175°C. On cooling, a red-brown solid was obtained which on crystallisation from ethyl acetate/petroleum ether (60-80°) yielded a pale yellow solid (8 g., 51%) m.p. 173-178°C. Recrystallisation from ethyl acetate/petroleum ether (60-80°) gave (185) as white prisms m.p. 181-182°C.

(Found: C, 63.17; H, 6.04; $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81). The infrared spectrum showed a broad peak at 1697 cm^{-1} (carboxyl).

3-Carboxy-4-methylindan-1-one (158; R = H)

A mixture of o-tolylsuccinic acid (185) (5 g.) and polyphosphoric acid (175 g.) was stirred vigorously for 70 minutes at 135°C. The dark coloured syrup which resulted was added, with stirring, to ice water (500 ml.) and the solution extracted thoroughly with ether. The ether extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a deep yellow solid (3.6 g.) m.p. 142-155°C. which was chromatographed on silica. Elution with benzene-ether (20:1) yielded a white solid (2.1 g., 46%) m.p. 154-157°C. which, on crystallisation from ethyl acetate/petroleum ether (b.p. 60-80°) gave (158; R = H) as white prisms m.p. 158-159°C. (Found: C, 69.11; H, 5.56; $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30). The infrared spectrum (nujol) showed peaks at 1720 cm^{-1} (indanone carbonyl) and 1690 cm^{-1} (carboxyl) white the ultraviolet spectrum exhibited absorption maxima at 250 mu (ε 10,040) and 295 mu (ε 1,930).

Further elution of the column with benzene-ether (10:1) yielded o-tolylsuccinic acid (500 mg.) m.p.176-180°C.

Fischer-Spier esterification of (158; R = H) gave 3-carbethoxy-4-methylindan-1-one (158; R = Et) in 82% yield.

Crystallisation from aqueous ethanol gave colourless needles m.p. 71°C. (Found: C, 71.55; H, 6.18; $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47). The infrared spectrum (nujol) showed peaks at 1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl).

o-Tolylsuccinic anhydride (186)

A mixture of o-tolylsuccinic acid (185) (650 mg.) and acetic anhydride (2 ml.) was heated under reflux for 1 hour. Removal of the acetic anhydride under reduced pressure furnished a yellow oil (400 mg., 67%) which, on distillation, yielded (186) as a colourless viscous oil 170-172°C./0.85 mm. (Found: C, 69.23; H, 5.60; $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30).

Attempted preparation of 2-carbethoxymethyl-3-carbethoxy-4-methylindan-1-one (120)

A. A mixture of the keto-ester (158; R = Et)(220 mg.), dry ether (15 ml.), and sodamide (800 mg.) was stirred under nitrogen for 45 minutes. Ethyl bromoacetate (0.5 ml.) was added and the reaction mixture refluxed for 3 hours. The cooled solution was diluted with water, acidified, and extracted with ether. After drying ($MgSO_4$), the ether was removed under reduced pressure and a red semisolid was obtained. Trituration with ether and crystallisation of the resultant solid (150 mg.) yielded starting material (identified by m.p. and mixed m.p.).

B. A mixture of the keto-ester (158; R = Et)(350 mg.), dry sodium methoxide[102] (350 mg.) and dry benzene (12 ml.) was stirred under nitrogen for 1.5 hours. A solution of ethyl bromoacetate (350 mg.) in dry benzene (10 ml.) was added to the mixture and stirring was continued for a further 4 hours. Water was added and the diluted mixture was extracted with benzene. The organic extracts, on evaporation, yielded a red oil which resisted our attempts at crystallisation. The crude reaction product was heated under reflux with 10% potassium hydroxide (50 ml.) and ethanol (3 ml.) for 35 minutes during which time the solution became very dark in colour. The cooled solution was acidified with dilute hydrochloric acid, extracted with ether, and the ether extracts washed dried. Removal of the solvent yielded a red oil from which no pure material could be isolated.

Attempted preparation of the pyrrolidine enamine of (158; R = Et).

A solution of the keto-ester (158; R = Et)(500 mg.) and redistilled pyrrolidine (0.8 ml.) in dry benzene (50 ml.) containing p-toluene-sulphonic acid (2 mg.) was refluxed in a Dean and Stark apparatus for 5 hours. Evaporation of the dark green solution gave a semisolid product which, on trituration with ether, gave a pale yellow solid (300 mg.). Crystallisation of the latter from aqueous ethanol yielded

the starting keto-ester, identified by m.p. and mixed m.p.

Attempted preparation of the morpholine enamine of (158; R = Et)

A solution of the keto-ester (158; R = Et)(420 mg.) and redistilled morpholine (250 mg.) in dry benzene (10 ml.) containing p-toluene-sulphonic acid (2 mg.) was refluxed for 21 hours. Work up in the usual way provided a semi-solid product from which starting material (300 mg.) was isolated by trituration with ether. This was identified by m.p. and mixed m.p.

The above experiment was repeated using a larger proportion of morpholine (1 g.). Once again, however, only starting material could be isolated.

2-Formyl-3-carbethoxy-4-methylindan-1-one (190)

The keto-ester (158; R = Et) (1.5 g.) in dry benzene (15 ml.) was added with shaking during 10 minutes to a stirred mixture of ethyl formate (1 g.), dry benzene (15 ml.), and dry powdered sodium methoxide (750 mg.) which was cooled in ice. The mixture was kept in ice for 30 minutes, then at room temperature overnight, and was then shaken with ice water. Ether was added and the combined aqueous layer and water washings of the organic layer were acidified with ice-cold dilute hydrochloric acid. The turbid solution thus obtained was extracted with benzene and ether and the combined organic extracts washed with water and dried. Removal of the solvent gave

the crude formyl derivative (190) as an orange solid (1.3 g., 77%). The latter material gave positive reactions with alcoholic ferric chloride solution and saturated cupric acetate solution. Trituration with ether gave a yellow solid (m.p. 90-95°C.) which resisted our attempts at crystallisation. The infrared spectrum (nujol) showed peaks at 1730 cm^{-1} (ester), 1670 cm^{-1}, 1630 cm^{-1} (β -diketone) and 1600 cm^{-1} (aromatic). The crude derivative obtained above was used for further work without purification.

Attempted preparation of 2-formyl-2-carbethoxymethyl-3-carbethoxy-4-methylindan-1-one (191)

A solution of the formyl derivative (190) (1 g.) in dry benzene (30 ml.) was added to a stirred mixture of powdered sodium methoxide (250 mg.) and dry benzene (5 ml.) kept under nitrogen. After 1 hour, a solution of ethyl bromoacetate (7.5 ml.) in dry benzene (15 ml.) was added and the yellow suspension was stirred under reflux for 48 hours. The reaction mixture was diluted with water and the separated benzene layer was combined with the ether washings of the aqueous layer. The total organic extracts were washed with ice-cold 5% potassium hydroxide solution (to remove enolic material), water and dried. Removal of the solvent yielded a red viscous oil (650 mg.) which gave a deep red colour with alcoholic ferric chloride solution.

The infrared spectrum showed peaks at 1730 cm^{-1}, 1670 cm^{-1}, and 1640 cm^{-1} (w). Repeated extraction of an ether solution of this oil with ice-cold 5% alkali followed by removal of the ether under reduced pressure yielded only a trace of oil. Acidification of the combined alkaline extracts provided an enolic product whose infrared spectrum was identical with that of the starting material.

2-Ethoxalyl-3-carbethoxy-4-methylindan-1-one (193)

The keto-ester (158; R = Et) (1 g.) in dry benzene (8 ml.) was added, with stirring, to a mixture of ethyl oxalate (1.5 g.), dry benzene (6 ml.) and powdered sodium methoxide[102] (500 mg.) which was cooled in ice. The mixture was kept in ice for 2 hours, refluxed for 2 hours under nitrogen, and then left overnight at room temperature. After dilution with water, the aqueous layer was separated and the benzene layer extracted with 2% sodium hydroxide solution. The total aqueous layers were acidified with dilute hydrochloric acid and the acidified solution was extracted with ether and benzene and the organic extracts washed with water and dried. Removal of the solvent yielded a crude yellow solid (1.2 g., 82%) which gave a red colour with alcoholic ferric chloride solution. Repeated crystallisation from aqueous ethanol gave (193) as pale yellow prisms m.p. 104-106°C. (Found: C, 63.75; H, 6.16; $C_{17}H_{18}O_6$ requires C, 64.14; H, 5.70). The

infrared spectrum (nujol) showed peaks at 1730 cm^{-1} (ester), 1715 cm^{-1}, 1670 cm^{-1} (β-diketone and ester) and 1600 cm^{-1} (aromatic) while the ultraviolet spectrum exhibited an absorption maximum at 320 mu (ε 13,700).

Attempted preparation of the Michael adduct (194)

A. A mixture of the ethoxalyl derivative (193) (350 mg.), 4-diethylamino-2-butanone[105] (200 mg.), pyridine (210 mg.) and dry benzene (10 ml.) was refluxed for 18 hours. The reaction mixture was cooled, diluted with benzene and washed with dilute hydrochloric acid, water, saturated sodium chloride solution and dried. Removal of the benzene under reduced pressure gave a yellow semisolid which gave a red colouration with alcoholic ferric chloride solution. No alkali-insoluble material could be obtained from this crude reaction product, which, on trituration with ether and crystallisation from aqueous ethanol, gave the starting ethoxalyl derivative (identified by m.p. and mixed m.p.).

B. To a stirred mixture of the ethoxalyl derivative (193) (700 mg.) and methyl vinyl ketone (1.5 ml.) was added a 25% solution of triethylamine in acetic acid (0.3 ml.). After a short time a red solution developed and was left overnight at room temperature. Most of the volatile matter was then evaporated off and a red semi-solid was obtained which gave a deep red colour with alcoholic ferric chloride solution. The semisolid product

was dissolved in ether and the ether solution extracted thoroughly with 5% sodium hydroxide solution. The alkaline layer was acidified, extracted with ether, and the ether extracts washed and dried. Removal of the solvent under reduced pressure yielded a yellow solid which, after crystallisation from aqueous ethanol, was identified as starting material (193) by m.p., mixed m.p., and by its infrared spectrum. Only a trace of alkali-insoluble material was isolated when the original ether layer was evaporated.

Keto-triester (198)

To a stirred mixture of the keto-ester (158; R=Et) (2 g.), Triton B, and dry benzene (20 ml.) was added a solution of acrylonitrile (1.1 g.) in dry benzene (10 ml.). The resultant mixture was stirred for 16 hours at room temperature, washed with water and the solvent removed under reduced pressure. A yellow viscous oil (2 g.) was obtained whose infrared spectrum (film) showed peaks at 2250 cm^{-1} (w)(nitrile) and 1710 cm^{-1} (broad)(ester and indanone carbonyl).

The yellow oil, obtained above, was refluxed with 10% potassium hydroxide solution (80 ml.) for 5 hours. The turbid solution was then shaken with charcoal and filtered. After acidification with dilute hydrochloric acid, the solution was filtered and the yellow filtrate extracted

with ethyl acetate. The ethyl acetate extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded an acidic semi-solid (1.8 g.) which was chromatographed on silica. Elution with benzene-ether (5:1) yielded the keto-acid (158; R = H) (600 mg.) m.p. 154-157°C. (m.p. undepressed on admixture with authentic keto-acid). Further elution with ether and methanol yielded a yellow gum (1 g.) which, on esterification with diazomethane, yielded a red viscous oil (1 g.) whose infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester) and 1715 cm^{-1} (sh) (indanone carbonyl). Chromatography on alumina (grade 111) using benzene-ether (20:1) as eluant yielded a pale yellow oil which, on micro-distillation onto a cold finger, gave (198) as a colourless viscous oil (Found: C, 64.25; H, 5.90; $C_{20}H_{24}O_7$ requires C, 63.82; H, 6.43). The infrared spectrum (carbon tetrachloride) showed peaks at 1735 cm^{-1} (ester) and 1715 cm^{-1} (indanone carbonyl).

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