SYNTHETIC APPROACHES

TO THE GIBBERELLINS

A T H E S I S

Presented to the University of Glasgow

for the degree of Master of Science

by

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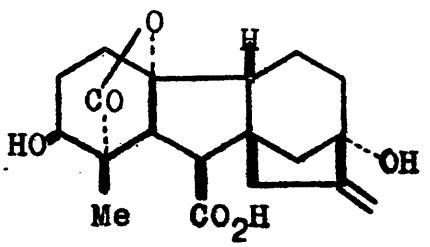
HISTORICAL REVIEW OF THE GIBBERELLINS.

Introduction

In 1926, Kurosawa[1] demonstrated that cell free filtrates from cultures of the fungus Gibberella fujikuroi produced in healthy seedlings the symptoms characteristic of "Bakanae", a soil borne disease in rice which caused the plants to elongate, eventually wither and die. Eighteen years later Yabutu[2] isolated a colourless crystalline compound - Gibberellin A - from cultures of G. fujikuroi, and found that this had plant growth promoting properties. The original publications from the University of Tokyo on the chemistry of this compound have been reviewed.[3] The exact composition of Gibberellin A is not quite certain.[4]

Gibberellic acid was first isolated by Curtis and Cross[5] in 1954. To date the structures of eleven gibberellins together with a tentative structure for a twelfth have been reported. Several others have been isolated but as yet no structures have been assigned. G. fujikuroi together with G. moliforme has proved a veritable mine of gibberellins. Phaseolus vulgaris (bean seed), P. multiforus (scarlet runner bean, Echinocystis macrocarpus (wild cucumber), and Zea mays (sweet corn) are rich sources of plant gibberellins.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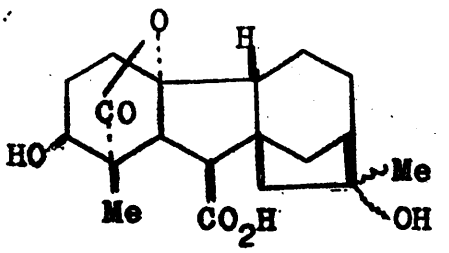
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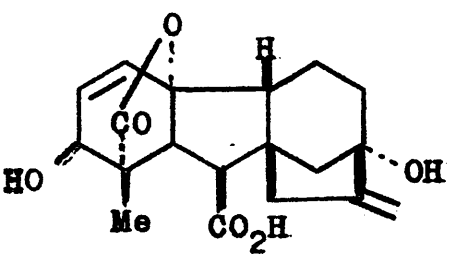
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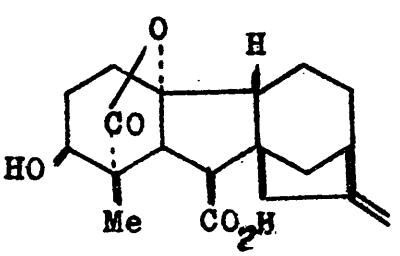
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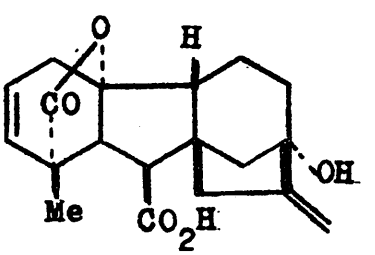
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(5)

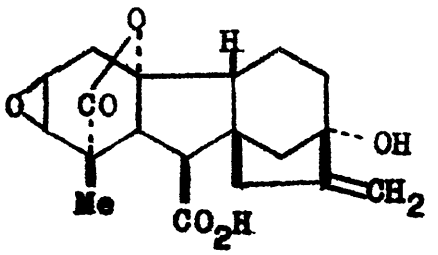
Gibberellin A[1] (1) was first isolated from *G. fujikuroi*[6] and later from *P. multiforus*[7] and *P. vulgaris*.[8] It was shown to be a dihydro derivative of gibberellic acid.

Gibberellin A[2] (2) has also been isolated from *G. fujikuroi*[10] but as yet not from higher plants. A structure, correct in all but the lactone ring, was proposed by Kitamura and his coworkers.[11] The position of the lactone in the gibberellins was not finally established till later.[12]

Gibberellin A[3] (Gibberellic Acid) (3) was first isolated from *G. fujikuroi*[5] and has also been isolated by Jones and his colleagues from *Hordeum vulgare*[13] and several other higher plants.[14] The evidence for its now accepted structure has been excellently reviewed by Grove.[4]

Gibberellin A[4] (4) was isolated from *G. fujikuroi*[15] and later found in *E. macrocarpus*.[16] A structure equivalent to (4) was put forward by the Japanese workers.[11] This again had the lactone ring wrongly located.

Gibberellin A[5] (5) has not yet been isolated from a fungus. It was first isolated by MacMillan and his collaborators[7] from *P. vulgaris* and the structure (5) proposed.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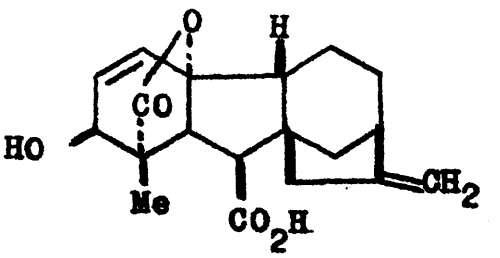
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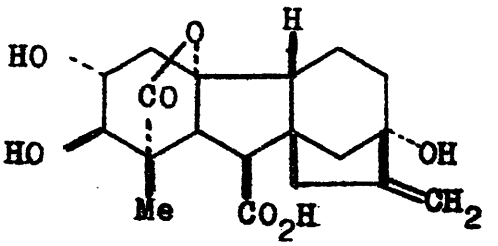
CH2
CO2H

(7)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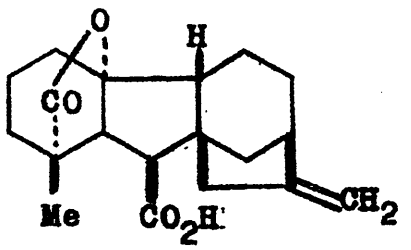
CO
HO
OH
Me
CO2H
CH2

(8)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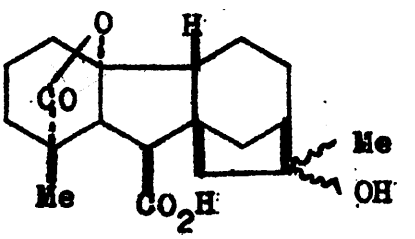
CH2

(9)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CO2H

(IO)

Gibberellin A_6 (6) like A_5 has only been isolated from P. vulgaris.[17] It was shown to have the structure (6).[17]

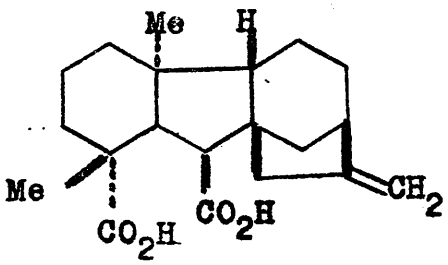
Gibberellin A_7 (7) was isolated from G. fujikuroi[18,19], and later from E. macrocarpus.[16] The structure was proposed by the Imperial Chemical Industries group.[18,19]

Gibberellin A_8 (8) was isolated together with A_6 from P. vulgaris by MacMillan and his colleagues[17] who also proposed the structure.

Gibberellin A_9 (9) was isolated from G. fujikuroi.[18,20] It is structurally the simplest of the gibberellins having no hydroxyl groups nor double bonds save the exocyclic methylene.

Gibberellin A_{10} (10) is reported by Cross, Galt and Hanson[21] to have been isolated from G. fujikuroi during attempts to isolate radioactive gibberellins from fermentations containing radioactive gibberellin A_9. They have advanced (10) as a probable structure since the same product is obtained by treating A_9 with hot mineral acid.

Gibberellin A_{11} has not yet been officially reported, though it seems likely it is "a dehydrogibberellin A_9 of uncertain structure",[21] isolated with gibberellin A_{10} during radioactive feedings of gibberellin A_9 to G. fujikuroi.



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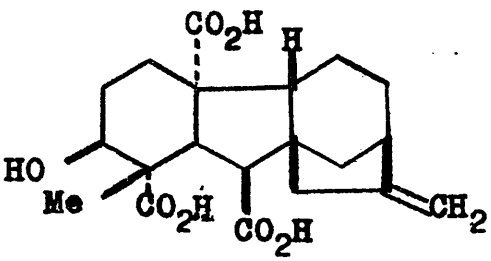

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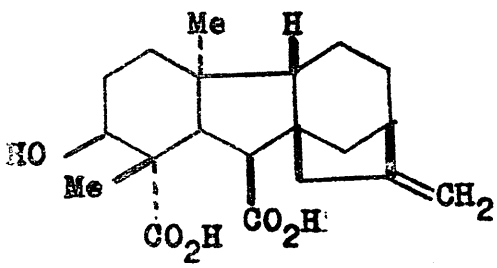

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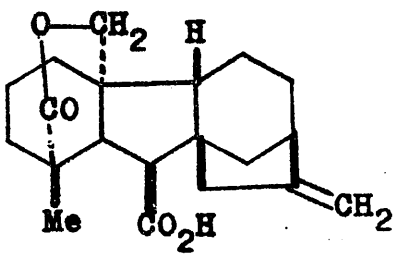

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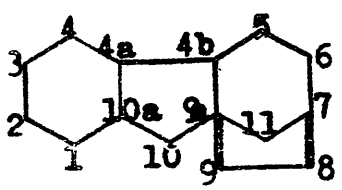

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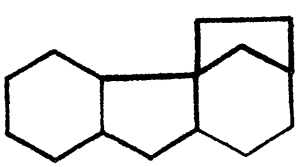


(16)

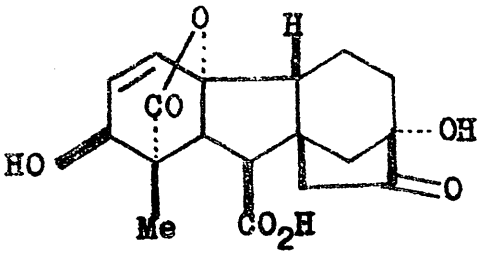
Gibberellin A_{12} (11) has recently been reported and structure (11) proposed.[22] This, the first C_{20} gibberellin to be isolated, is tetracyclic and must be a gibberellin (i.e. have the basic gibbane carbon skeleton) as it has five pendant carbon atoms.[21] It exhibits the same highly specific biological characteristics as the C_{19} gibberellins, and the implications of this will be discussed later.

Gibberellin A_{13} (12), a C_{20} triacid from G. fujikuroi has also recently been reported by Galt,[23] who also proposed its structure (12). It is probably identical with fujic acid previously isolated by Sternberg[24] from the same source though wrongly characterised.

Several other C_{20} gibberellins have been reported[21] and tentative structures have been advanced for two of these, (13) and (14).

Nomenclature

Gibberellins all have the basic gibbane carbon skeleton (15) numbered as shown. If the $C_{8,9}$ bridge is inverted (i.e. α orientated) the compound is then a 7α-gibbane. Compounds with the bridge at C_{4b-6} are isogibbanes (16). Gibberellic acid (3) is then 2β, 4aβ, 7α-trihydroxy-1β-methyl-8-methylenegibb-3-ene-1α-10β-dicarboxylic acid 1 → 4a lactone. Gibberellic acid



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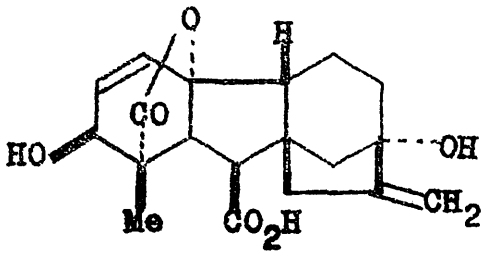

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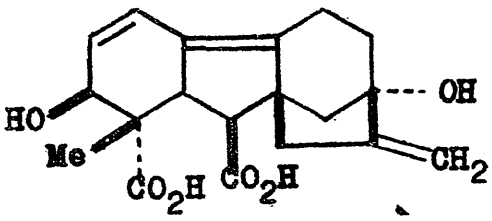

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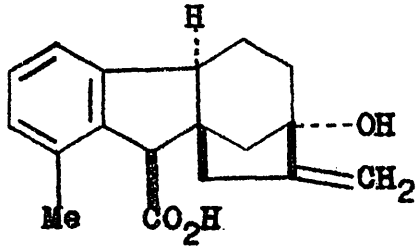

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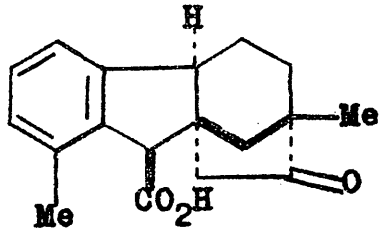

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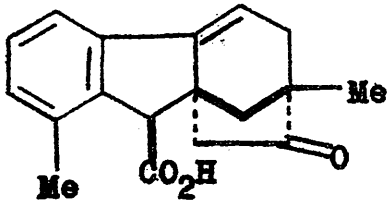

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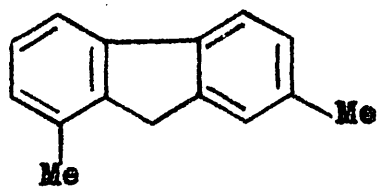

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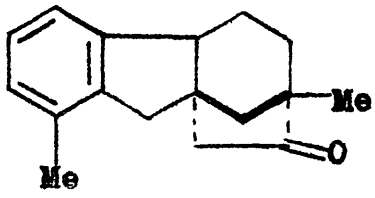

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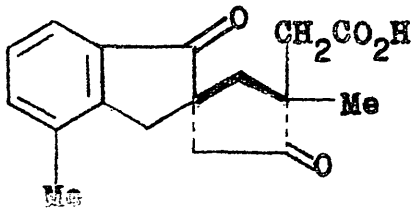

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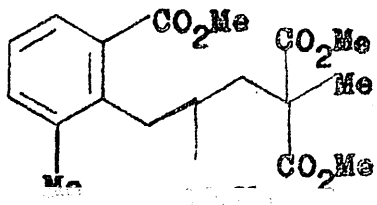


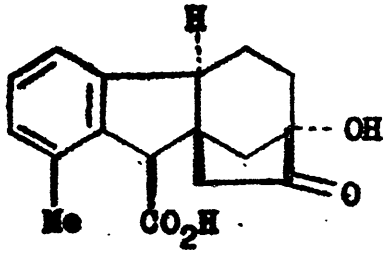
(24)

nor-ketone is the 8-oxocompound (17). Allogibberic (18) and gibberic acid (19) are the trivial names retained for degradation products where ring A is aromatic. The prefix epi within this class of compounds signifies that the 4b hydrogen atom is β orientated. Seco-ring D derivatives are named as fluorenes.

Structure

The basic chemistry and relationship of the gibberellins have been excellently reviewed by Grove[4] and since that review the Imperial Chemical Industries group have published a series of papers on the derivatives of gibberellins.[25]

A brief outline of the main degradation products of gibberellic acid is given in Chart (I). On treatment with dilute mineral acid gibberellic acid (3) affords allogibberic acid (18) via the intermediate gibberellenic acid (20). On further treatment with hot mineral acid both allogibberic and gibberellenic acid afford gibberic acid (19) which on dehydrogenation over palladium-charcoal affords gibberone (21), also obtainable by oxidation of gibberic acid to dehydrogibberic acid (22) and subsequent decarboxylation. Gibberone was further degraded to the tetramethyl ester (24) via a second order rearrangement of the 2'-oximino derivative of the spirodiketo-acid (23) followed by hydrolysis and



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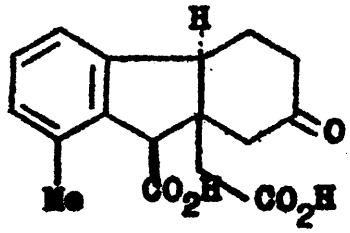

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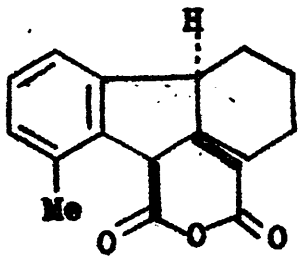

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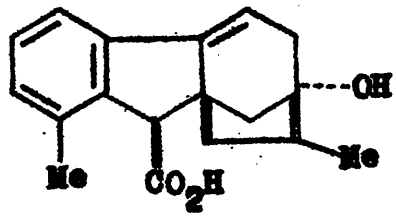

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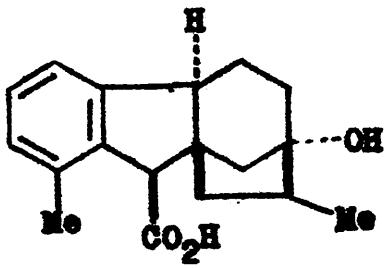

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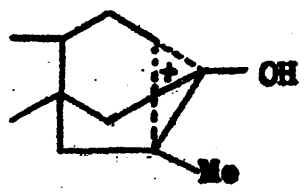


~~(30)~~ (32)

methylation. Selenium dehydrogenation of both gibberic and allogibberic acids furnished gibberene (25) which was shown to be 1,7-dimethylfluorene by unambiguous synthesis.[26]

Stereochemistry.

(i) Allogibberic Acid (18).

Cleavage of the allogibberic acid nor-ketone (26) with sodium bismuthate gave the keto diacid (27). The derived anhydride (28) on hydrolysis afforded the original keto diacid (27) implying that the two carbon bridge must be cis to the carboxyl at C_{10}. The stereochemistry at C_{4b} was elucidated from the evidence below.[27] Catalytic hydrogenation of dehydrodihydroallogibberic acid (29) will take place from the least hindered side of the molecule i.e. on the side remote from the two carbon bridge and carboxyl group. Since hydrogenation afforded dihydroallogibberic acid (30) it follows that the hydrogen at C_{4b} is trans to the carboxyl. This requires rings B and C to be trans fused. Thus the two carbon bridge is β-orientated as is the carboxyl, and the C_{4b} hydrogen is α-orientated.

(ii) Gibberic Acid (19).

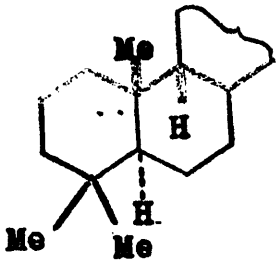
Since the acid catalysed conversion of allogibberic acid (18) to gibberic acid goes via a Wagner-Meerwein rearrangement involving the carbonium ion (32), the only difference in stereochemistry must be that of the 8,9 bridge

which is thus α-orientated.

(iii) The Gibberellins.

The hydroxyl at C_2 was shown to be axial as it underwent facile epimerisation to the more stable equatorial configuration.[25h] This implies that the hydroxyl must be oppositely orientated to the 1 → 4a-lactone. Stork and Newman[31] from optical rotatory dispersion measurements assigned an α-orientation to the lactone basing their conclusions on the Hudson-Klyne lactone rule.[32] Edwards and his co-workers[33] cited examples of terpenes in which the rotational change on opening the lactone violated the Hudson-Kyne rule leading these workers to favour a β-orientation of the lactone ring in gibberellins and a 2α-hydroxyl function. The configuration at C_2 and hence that of the lactone was determined independently by Masamune[34] using a modification of the Prelog-Mackenzie[35] atrolactic method. These results favoured the 2β-hydroxyl-α-lactone configuration.

Aldridge and his colleagues[36], assuming the configuration of the C_{10a} hydrogen to be β cited the ready dehydration of gibberellic a cid to gibberellin A_5[7a] together with the base catalysed rearrangement of the Δ^3 -1→4a-lactones to the Δ^4-1→3 lactones[37] as strong evidence for the 2β hydroxyl 1 → 4aα-lactone system. These workers discounted the alternative 2α-hydroxyl-β-lactone system since these


Me
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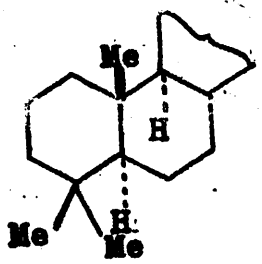
Me
Me

(35)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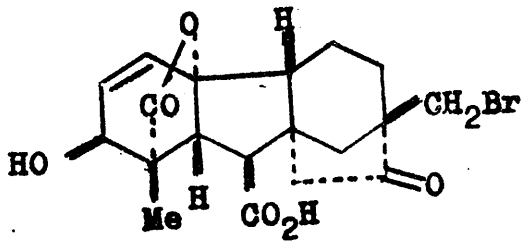
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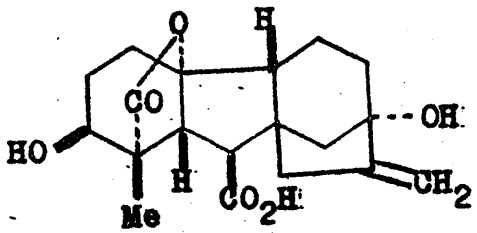
CO2H

(37)


O
H
CO
OH
HO
CH2
Me
H
CO2H

(3)

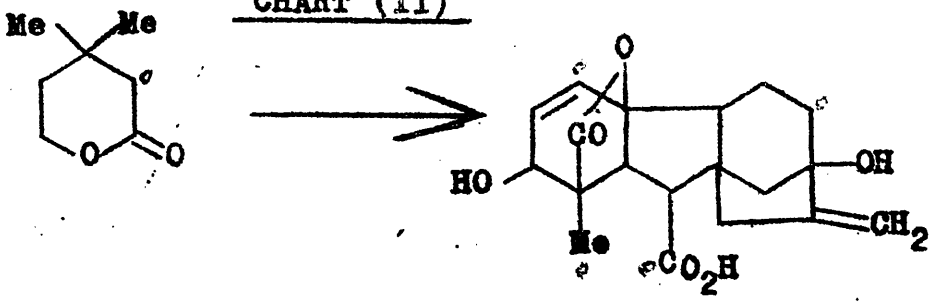
rearrangements would involve highly strained transition states.

The evidence for the assignment of a β orientation to the hydrogen at C_{10a} comes from both optical rotatory dispersion studies [38,39] and measurement[40] of the coupling observed between the C_{10a} and C_{10} hydrogens in the nuclear magnetic resonance spectra of methylacetyldihydro- and methylacetyltetrahydro gibberellate.

Bourn and Cross[41] formally proved the configuration at C_{10} using optical rotatory dispersion arguments. The orientation of ring D was shown to be β as in allogibberic acid.[29]

The evidence in favour of a 4bα hydrogen was based on optical rotatory dispersion studies by both Stork and Newman[31] and Grove and his coworkers.[38] However this evidence was not conclusive. The 4b hydrogen atom if α orientated would lead to a "trans-syn" (35) rather than the "trans-anti" (36) backbone to be expected by analogy with other diterpenes. This together with other aspects of the biogenesis (discussed below) prompted Scott and his colleagues[42] to perform an x-ray analysis of the bromo-derivative (37) obtained by treating methyl gibberellate with pyridine perbromide, a transformation known to invert the 8,9 bridge but not to affect the stereochemistry at C_{4b}. The stereochemistry

CHART (II)



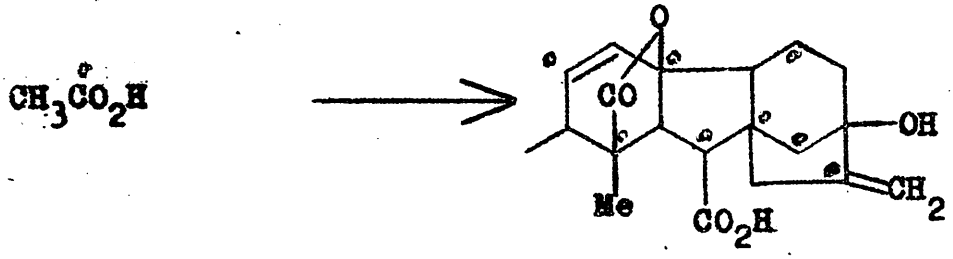
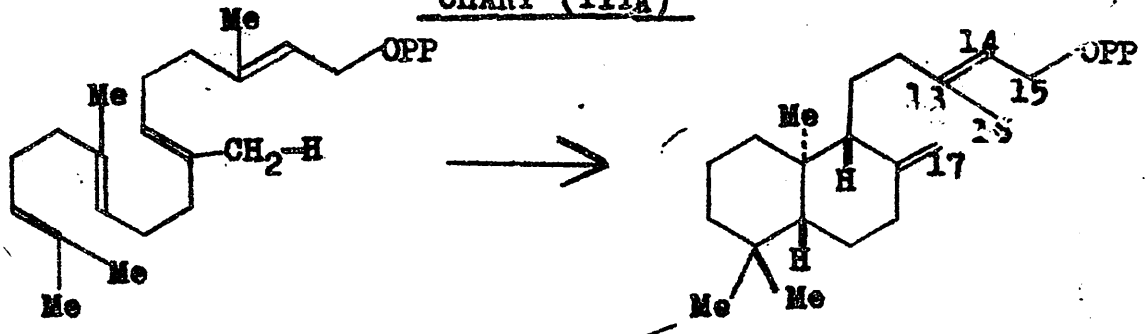
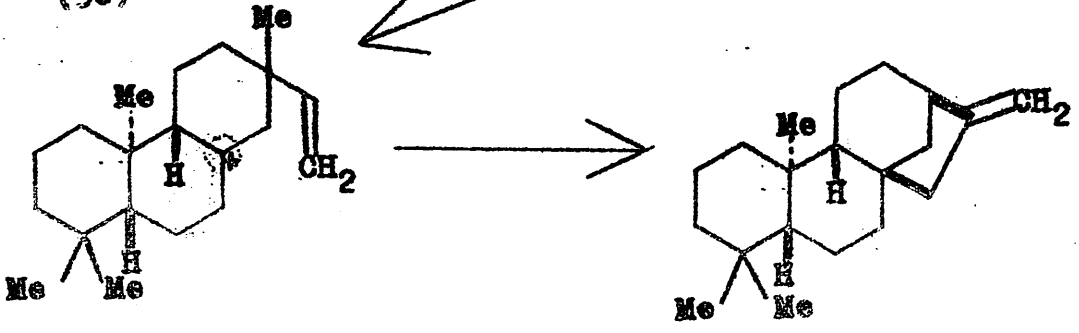


CHART (III$_A$)



(38)

(39)



(40)

of (37) implies that gibberellic acid is as in (3), a finding later confirmed by other workers.[36,41]

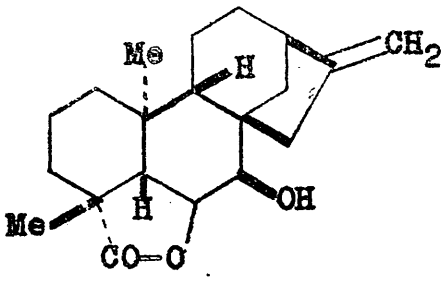
The stereochemical relationships of gibberellins A_1 - A_9 have been reviewed[4] and the later gibberellins were related to gibberellic acid during structural determination.

Biogenesis of Gibberellins

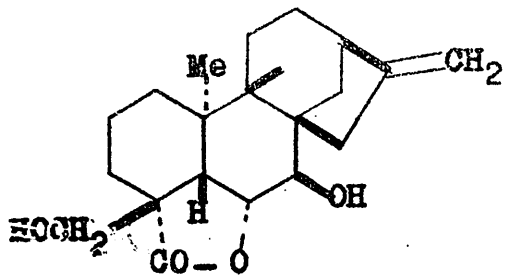
Cross and his associates[43] first suggested the structural and genetic relationship of the gibberellins to diterpenes. Birch[44] showed that ^{14}C labelled acetic acid and 2 - ^{14}C mevalonic acid lactone were incorporated into gibberellic acid produced by G. fujikuroi. Degradation of the labelled gibberellic acid gave the results shown (Chart II).

It is reasonable to assume that the biogenesis of gibberellins proceeds according to the Biogenetic Isoprene Rule.[45] Once the correct stereochemistry had been established it was evident that the gibberellin skeleton, hitherto regarded as abnormal[46] did indeed possess the "trans anti" backbone of normal diterpenes and the biogenetic scheme discussed below and represented in Chart IIIA was proposed.[46]

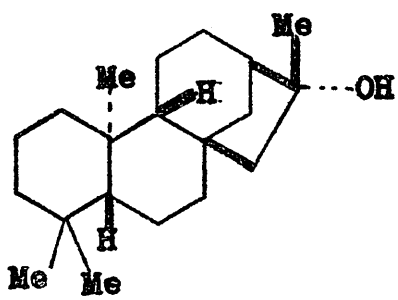
All trans cyclisation of the geranylgeranyl precursor (38) affords the bicyclic intermediate (39) which embodies the stereochemistry at $C_{5,9,10}$ of all bicyclic diterpenes. Formation of rings C and D now takes place according to


Me
H
CH2
OH
Me
H
CO—O

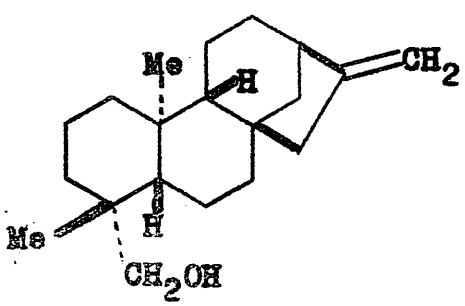
(41)


Me
CH2
OH
H
CO—O

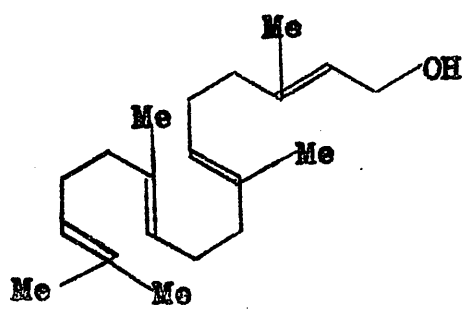
(42)


Me
Me
H
OH
H
Me
Me

(43)


Me
H
CH2
Me
H
CH2OH

(44)


Me
OH
Me
Me
Me
Me

(45)

a scheme proposed by Wenkert[47] in which the B/C ring fusion and orientation of rings C and D depend on the stereochemistry at C_{13}. This leads to the tetra cyclic intermediate (40) which has been shown to have the structure and stereochemistry of (-) kaurene.[48]

Radioactive (-) kaurene has been incorporated into gibberellins in G. fujikuroi fermentations to the extent of 5·7 %.[49] Other evidence cited below lends further credence to this hypothesis.

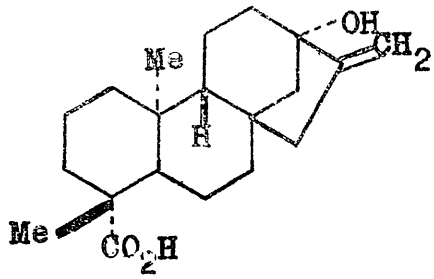
Further investigation of the metabolites in G. fujikuroi [21-23] led to the isolation of a number of new compounds. Some of these are C_{20} gibberellins and some have the basic skeleton of (-) kaurene. Among the (-) kaurene derivatives which have been isolated are (-) kaurene (40) itself; 7-hydroxykaurenolide (41); 7,18-dihydroxy-kaurenolide (42) and kauranol (43). E. macrocarpus has been shown to be a relatively rich source of gibberellins.[50] Graebe and his coworkers[51] using 2-^{14}C labelled mevalonic acid lactone have been able to isolate radioactive (-) kaurene and (-) kauren-19-ol (44) from this source along with radioactive geranylgeraniol (45). The same workers have shown that (-) kaurene and (-) kauren-19-ol were incorporated into gibberellic acid in washed suspensions of Fusarium moliforme.

Phinney and his colleagues have demonstrated that (-) kaurene[52] and (-) kauren-19-ol[53] will stimulate leaf sheath elongation in seedlings of Z.mays, an effect qualitatively indistinguishable from that produced by exogenous gibberellins.

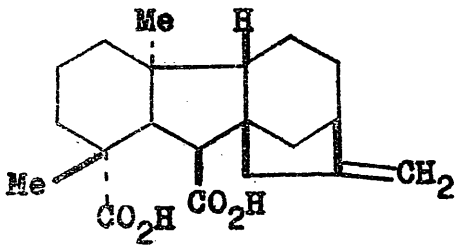
It has also been shown[51] that radioactive geranylgeraniol is not incorporated into the kaurenes or gibberellins isolated from E. macrocarpus. This, however is understandable on the basis of irreversibility of the transformation of geranylgeranyl pyrophosphate to geranylgeraniol. 7-hydroxylkaurenolide (41) might be expected to be a precursor since the carbon skeleton has the correct stereochemistry and it is oxygenated at position 7. It was found, however, that this compound was not incorporated.[21] A possible reason for this is discussed later.

From the above evidence it seems likely that the biogenesis of gibberellins follows the normal diterpenoid pathway and (-) kaurene and certain kaurenolides act as precursors.

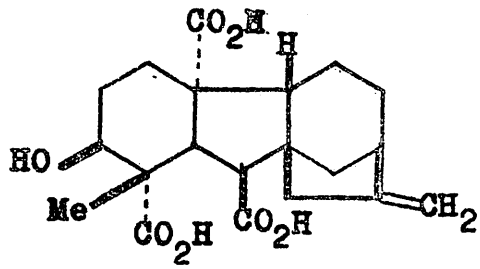
As will be realised the plant gibberellins and fungal gibberellins need not necessarily evolve via the same biogenetic pathway and it is desirable at this juncture to examine any evidence on this point. As Brian[54] points out, diterpenoids are well known secondary metabolic products of higher plants,


OH
CH2
Me
H
Me
CO2H

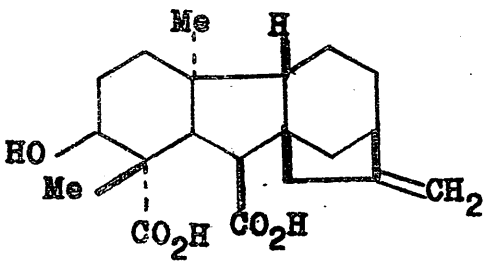
(46)


Me
H
Me
CH2
CO2H
CO2H

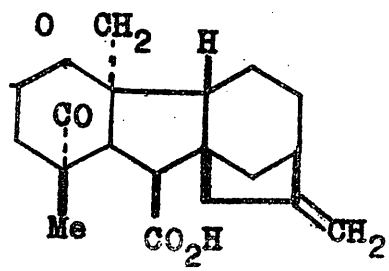
(11)


CO2H
H
HO
Me
CO2H
CO2H
CH2

(12)


Me
H
HO
Me
CH2
CO2H
CO2H

(13)

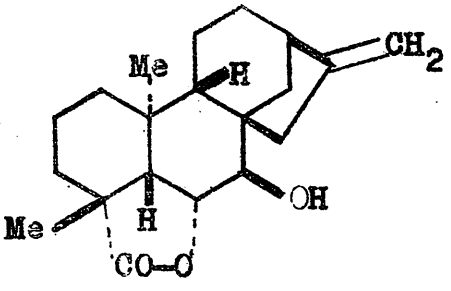

O
CH2
H
CO
Me
CO2H
CH2

(14)

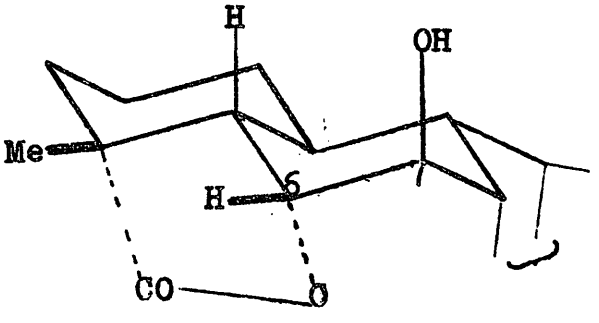
(-) kaurene itself being first isolated from the wood of the Kauri pine. Ruddatt and Lang[55] have found that the diterpenoid steviol (46) exhibits gibberellin-like activity. At least four gibberellins are known to be common to both plants and fungi, A_1, A_3, A_4, and A_7,. In view of these facts coupled with the complexity of the gibberellin molecule it is inherently probable that the two do have a common biogenesis.

The problem now remaining is the conversion of kaurene to gibberellin. There are three modifications.necessary (a) oxidation at C_{19} (b) contraction of ring B. (c) oxidation and loss of the C_{20} carbon atom. It seems likely that (a) may precede (b) as no ring contracted compound has het been isolated which is not oxidised at C_{19}. The isolation of compounds like gibberellin A_{12} (11), gibberellin A_{13}(12), and diacid (13) and the δ -lactone (14) suggests that ring contraction takes place prior to oxidation and decarboxylation at C_{10}.

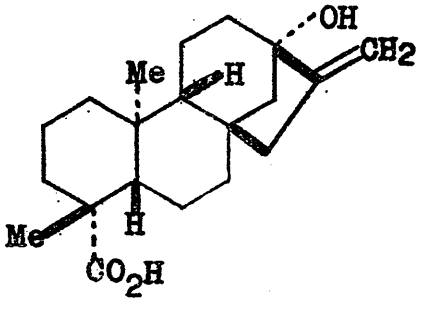
Oxidation at C_{19} probably proceeds by the usual microbiological mechanism. The mechanism of demethylation at C_{10} would seem to be analogous to the lanosterol to chlolesterol sequence[56] as this would lead to a $C_{10}\alpha$ hydrogen and thence by the usual stereoselective bond insertion process of biological hydroxylation to a $C_{10}\alpha$ hydroxyl. Confirmatory



(41)



(41)



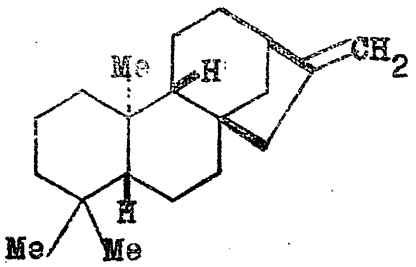
(46)

evidence for this postulate is the isolation from G.fujikuroi of the lactone (14)[21] and gibberellin A_{13} which have the C_{20} carbon atom at the oxidation level of an alcohol and an acid respectively.

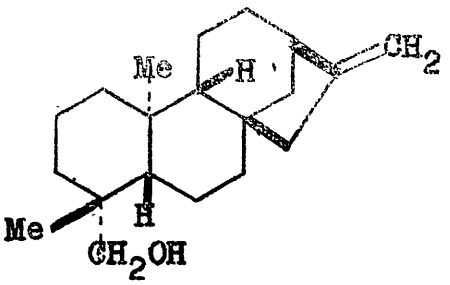
The mechanism of ring B contraction is still under review. From the tracer studies of Birch et al[44] (Chart II) it is evident that it is C_7 which is extruded. If this takes place via a 1:2 shift rather than a benzilic acid type rearrangement then 7-hydroxykaurenolide (41) could not be a precursor of the gibberellins since it has the hydroxyl group β (axially) orientated and not α(equatorially) orientated as required for such a shift.

The order of hydroxylation of the gibberellins is not known though bridgehead hydroxylation is thought to occur late in the pathway since no intermediate has been isolated with this structural feature. However steviol (46) may be such an intermediate in the plant gibberellins.[55] Hydroxylation could occur after the basic skeleton has been formed. If this is so, gibberellin A_9 might be expected to act as a precursor for the other gibberellins. However addition of radioactive Aq to a fermentation of G.fujikuroi did not lead to the isolation of any radioactive gibberellins except gibberellin A_{10}[21], formed by hydroxylation of the

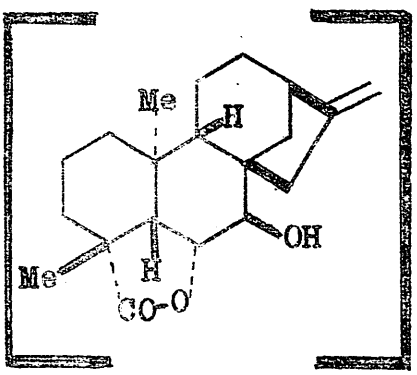
CHART IIIB



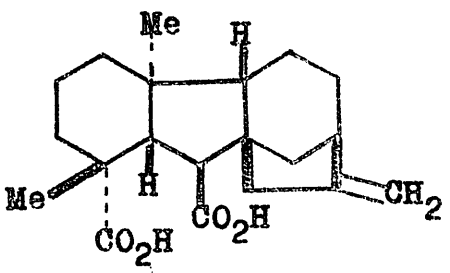
(40)



(44)



(41)



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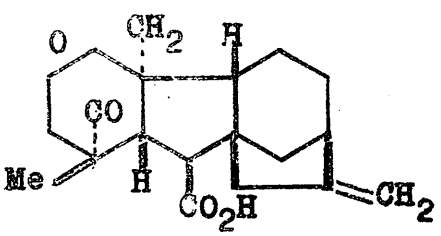

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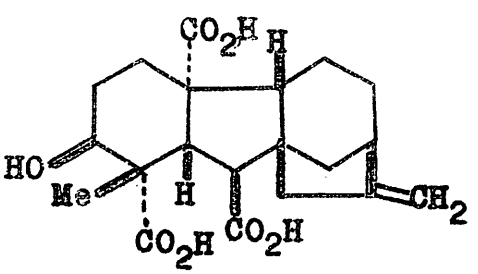


(12)

8-methylene substituent, and "a dehydro-gibberellin Aq".[21,49]

At present there is little or no evidence on the order of production of the gibberellins. A possible pathway for the transformation from kaurene to the gibberellins is suggested in Chart IIIB. This hypothetical scheme has been formulated on the basis of compounds isolated from both plant and fungal sources.

The first step is probably the oxidation of kaurene to kauren-19-ol isolated from E. macrocarpus[51]. Although 7-hydroxykaurenolide (41) is not an intermediate[21] it seems logical to assume that further oxidation would produce something similar to it. Contraction of ring B would afford gibberellin A_{12} (11)[22] and subsequent oxidation at C_{20} followed by lactonisation or even direct lactonisation of gibberellin A_{12} would furnish the δ-lactone (14) reported to have been isolated from G. fujikuroi[21]. Further oxidation would afford gibberellin A_{13} (12) which on decarboxylation and lactonisation would lead to the C_{19} gibberellins.

The Biological and Physiological Aspects of the Gibberellins

It is now generally accepted that the gibberellins are a most important group of plant hormones, having highly specific effects on their growth and morphenogenesis. The responses of plants to gibberellins cannot be elicited by

any other group of compounds natural or synthetic.

Only very small quantities of gibberellins are available but recently improved methods of fermentation have been reported both for gibberellic acid[57] and radioactive gibberellins.[58]

Only a brief account of some of the responses of plants to gibberellins can be given here but these have been excellently reviewed elsewhere.[4,54,59]

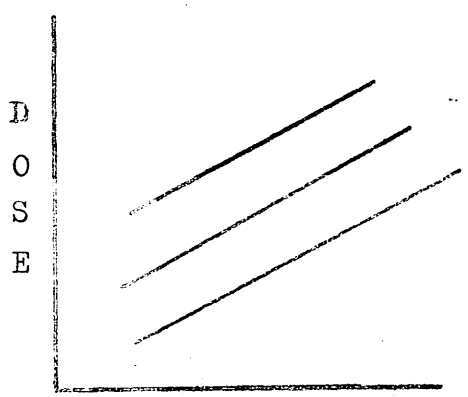
In plants whose growth is independent of day length or temperature gibberellins although having no effect on the number of nodes, increase the length of those internodes actually extending at the time of application[60]. In general genetically dwarf plants show the greatest response. Increases in both cell number[61] and cell size[62] are involved. Some plants can be induced to bolt and flower without a period of cold treatment which they would normally require,[63] A gibberellin will similarly replace the long day requirements of some plants[64] and terminate dormancy due to short days[65]. Gibberellins can arrest autumnal leaf fall and development of autumn foliage colours.[66]

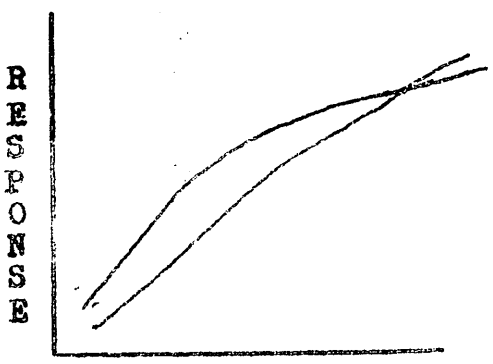
They also have wide ranging effects on both the time of production and quality of certain fruits, a matter of no small economic interest, and their uses in agriculture have been reviewed elsewhere.[67] They are of interest to the

Relative Potencies of Nine Gibberellins

Gibberellin	Maize			Pea	Lettuce
	d-1	d-3	d-5		
A_1	3	3	3	2	3
A_2	2	2	2	3	2
A_3	3	3	4	3	4
A_4	3	3	3	3	4
A_5	2	4	4	2	3
A_6	2	2	2	1	2
A_7	3	4	4	3	4
A_8	0	0	0	0	0
A_9	1	4	3	0	4

CHART IV Fig 1





brewing industry as they accelerate the germination of barley.[68]

Gibberellins may be applied externally by spraying the plant with a solution of the desired gibberellin. Thus if sufficient hormone were available it would be relatively easy to treat large areas of crops. An added advantage is that they are of negligible mammalian toxicity,[69] an important consideration if they are to be used in agriculture.

As to the mode of biological action, this has been reviewed excellently by Brian[54,59] and others, and a few of the more stimulating observations are set out below.

Not unexpectedly the gibberellins are not all equally active. However the order of activity within the gibberellins varies with nature of the bioassay. This high degree of specificity is a striking feature in the biological action of the gibberellins. A_7 is highly active in all or most bioassays while A_5 and A_9 vary from almost complete inactivity to very high activity depending on the bioassay (Chart IV fig I).

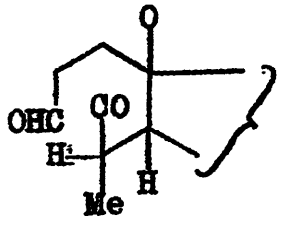
The dose: response relationship is generally linear and in some cases the regression lines for all the gibberellins are parallel, as qualitatively represented in Chart IV fig 2. In a few assays however the lines are not parallel and some studies do not even give a linear dose: response relationship.

The relative activity of the gibberellins depends on the time which elapses between treatment and measurement of the response. In comparing the activities of A_5 and A_3 in the dwarf pea assays, it is found if the response is measured a week after treatment A_5 is much less active than A_3. If we delay measurement for a further three weeks the two gibberellins appear to exhibit equal activity. This is because A_5 has a more prolonged effect on peas than A_3 (Chart IV fig 3).

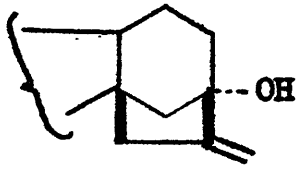
It may be that only some of the gibberellins, or even only one, are intrinsically active and that others need to be transformed into this species. A_7 may be such an active species, A_5 and A_9 those which must undergo metabolic transformation to A_7. The fact that the dose -response regression lines are parallel for the various gibberellins is analogous to the results expected from using different dilutions of one species. This and the differences in the time: course of action of distinct gibberellins suggests that a metabilic conversion mechanism is involved. It has been suggested that the varying order of activity within the gibberellins and bioassay to bioassay (Chart IV fig 1) contradicts this theory, but it may be that some plants are more able than others to carry out the required metabolic transformations.

The high specificity could possibly be better accounted for by a "receptor-shape" theory i.e. the activity of the gibberellin being dependent on its ability to fit into a receptor surface on the plant cells. It is reasonable to suppose that the shape of such receptor sites would vary from plant to plant. It is also worthy of note that the gibberellins which exhibit consistently high activity are A_4, A_7 and A_9, i.e. those which lack the bridgehead hydroxyl group. On the basis of present knowledge it is impossible to decide between the two theories and it may well be that a hybrid of both is involved, such as metabolic conversion of an unsuitable species to one which is a suitable shape.

There is still practically no evidence about the physiological mode of action. It has been suggested[54] that gibberellins exercise a highly specific control on protein synthesis encouraging the synthesis of some enzymes, like the hydrolytic ones whilst retarding the formation of others like the peroxidases. The overall result is an increase in the protein level - an event closely related to cell mitoses. Much work still remains to be done in this field.



(47)



(48)

General Chemical reactions of the Gibberellins.

Some of the more important reactions encountered with gibberellins are reported below

(i) 2β(ax)-Hydroxgibbane1→4a-lactones undergo epimerisation in dilute alkali to 2α(eq)hydroxy1→4a-lactones via a retroaldol intermediate[37] (47).

(ii) In dilute alkali 2β(ax)hydroxygibb-3-ene1→4a-lactones undergo an allylic rearrangement to gibb-4-ene1→3-lactones without concomitant epimerisation of the hydroxyl substituent[37]

(iii) In the 1→4a-lactone series catalytic reduction of a 3-ene precedes that of the 8-methylene group. In the 4-ene 1→3-lactone series hydrogenolysis of the lactone is accompanied by reduction of the 4-4a double bond[37]

(iv) 2-hydroxyl groups are smoothly oxidised to ketones only in cases where the 8-methylene substituent has been reduced or eliminated[12a]. Reduction of 2-keto compounds with alkali metal hydrides affords the more stable 2(eq) isomer[37]

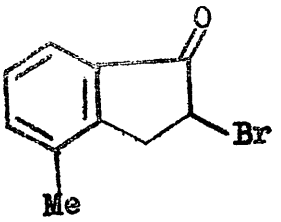
(v) In gibbanes 2(ax)-hydroxyls are readily eliminated directly or as the p-toluene sulphonate esters to give gibb-2-enes[7a].

(vi) Compounds with the C/D partial structure (48) undergo a Wagner Meerwein rearrangement in acid to give the corresponding 7-methyl-8-oxo-7αgibbane.[29] Compounds not possessing the 7-hydroxyl add the elements of water to the

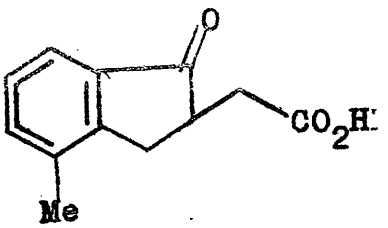
8-methylene group under these conditions.

(vii) In the hydrogenolysis of degradation products with ring A aromatic a carbomethoxyl at C_{10} determines the steric course of the reduction directing it trans.

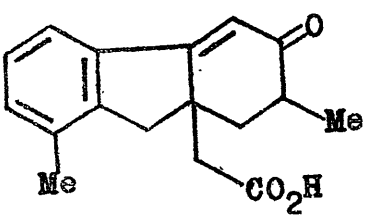
CHART V



(49)



(50)



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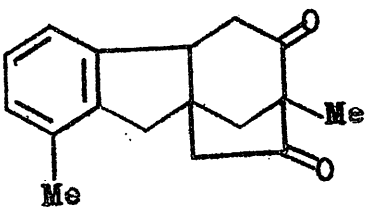

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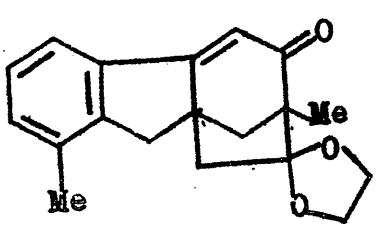

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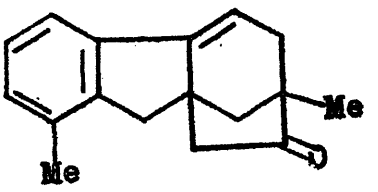

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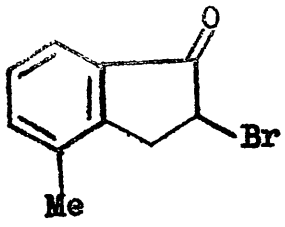
CHART V



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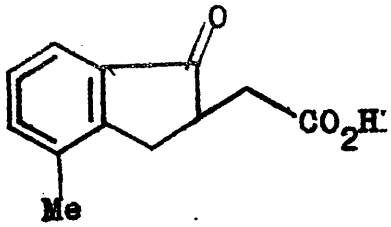

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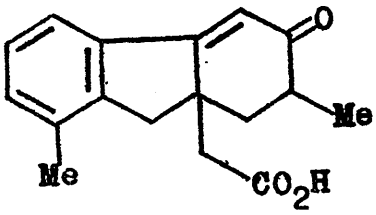

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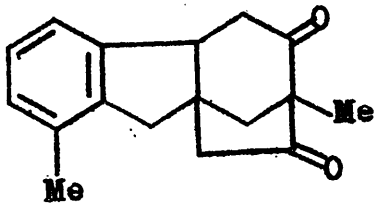

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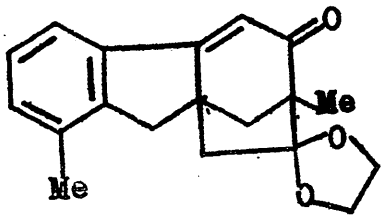

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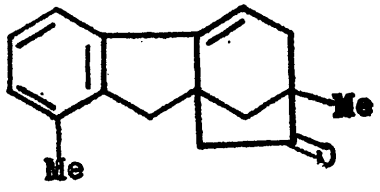

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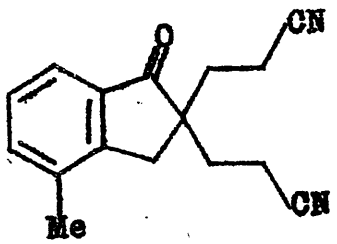
CHART VI



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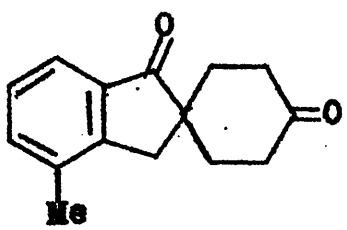

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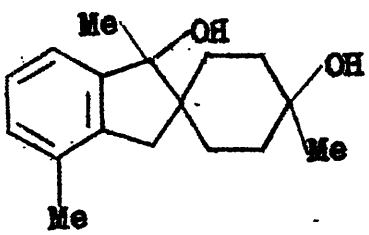

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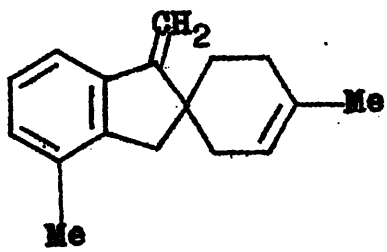

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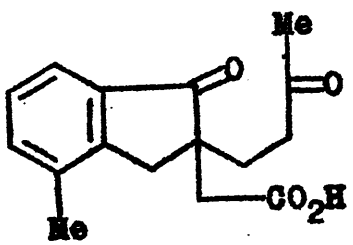

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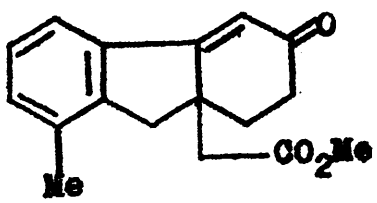


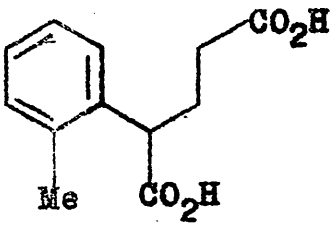
(59)

Raphael's synthetic scheme is shown on Chart VI. Dicyancethylation of 4-methylindan-1-one yielded the dinitrile (54). The corresponding diester after cyclisation and hydrolysis gave the required spirodione (55). Treatment of this diketone with methyl magnesium iodide furnished a diol (56) which was dehydrated to the diene (57). Careful ozonolysis afforded the expected diketo-acid (58) which was in turn converted to the tetrahydrofluorenone (59). The corresponding 2-hydroxymethylene derivative on methylation and hydrolysis gave the keto-ester (51) identical in all respects with that obtained by Loewenthal.

Loewenthal and Malhotra have also been successful in synthesising gibberic acid.[72] The synthesis was stereospecific throughout and is summarised in Chart VII.

The glutaric acid (60) was obtained from o-tolyl acetonitrile by condensation with diethyl carbonate, cyanoethylation, acid hydrolysis and decarboxylation. The corresponding anhydride was cyclised to the keto-acid (61), the furfurylidene derivative of which on ozonolysis, methylation and cyclisation afforded the β-keto-ester (62). Alkylation of this with ethyl bromoacetate and hydrolysis, decarboxylation and methylation furnished the desired keto-diester (63). In a manner analogous to the gibberone synthesis this keto diester was condensed with isopropenyl methyl ketone,

CHART VII



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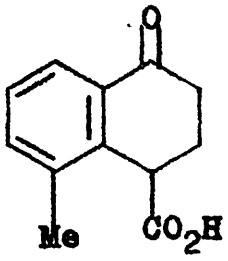

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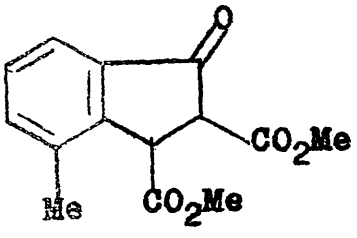

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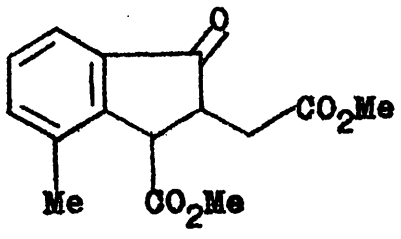

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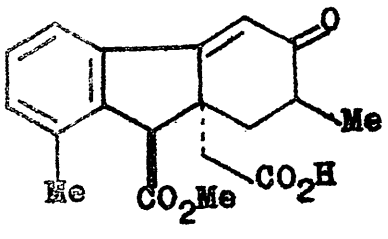

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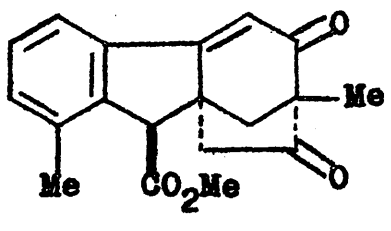

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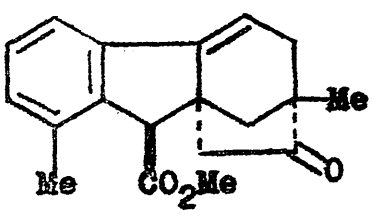

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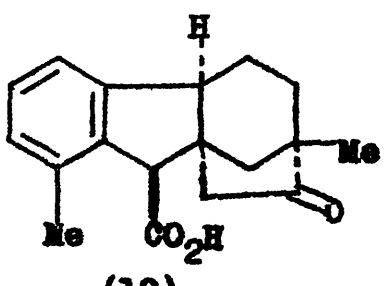

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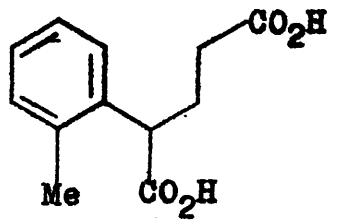
CHART VII



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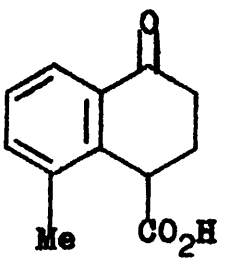

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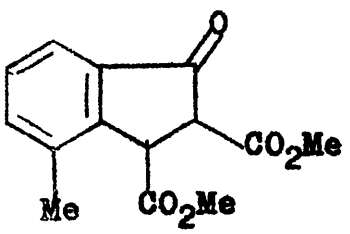

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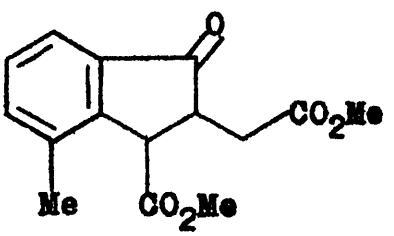

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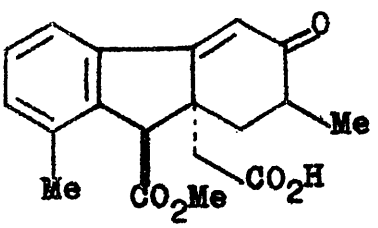

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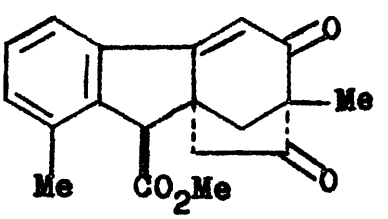

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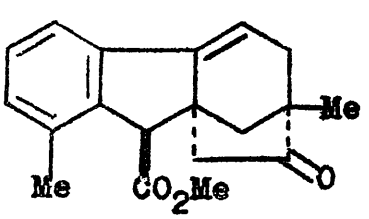

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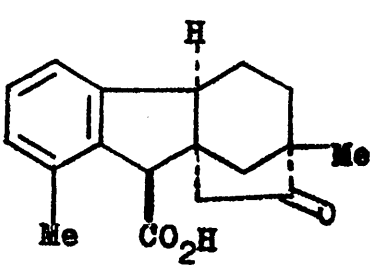
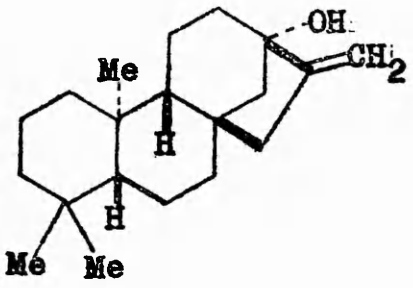


(19)

providing the half ester (64) of the required enone diacid. The derived dimethyl ester on cyclisation with boron trifluoride etherate afforded exclusively the desired enedione (65) which readily furnished a monoketal. Huang-Minlon reduction and removal of the protecting group gave the expected conjugated enone (66) which on catalytic reduction and hydrolysis yielded only gibberic acid (19). The stereospecificity of the hydrogenation was in agreement with findings discussed earlier which showed that hydrogen was introduced on the side remote from the carbomethoxyl group.

Mori[73] and his coworkers have used this specificity in an elegant synthesis of the C_{4b}-β-epimer, epigibberic acid (67) (Chart VIII).

Hydrolysis of the half ester (64) afforded the corresponding trans diacid which was converted to the anhydride (68). Treatment of this anhydride with boron trifluoride-etherate gave the 10-α-carboxy-diketone (69). Conversion of the corresponding methyl ester to the monoketal as before and subsequent catalytic hydrogenation afforded the hydroxy-ketal (70) with the required stereochemistry at C_{4b}. Oxidation with chromium trioxide in pyridine regenerated the C_6 keto group. Huang-Minlon reduction of the derived monoketal and subsequent acid hydrolysis effected removal of the C_6-ketone, deketalisation and hydrolysis with



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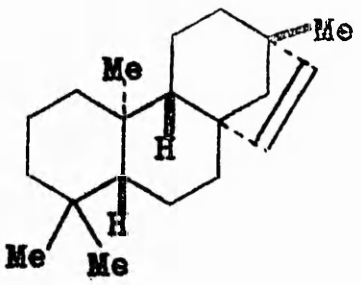

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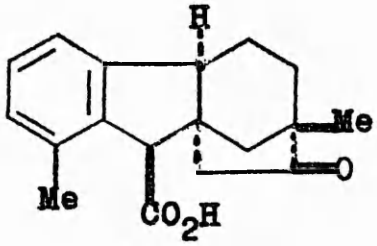

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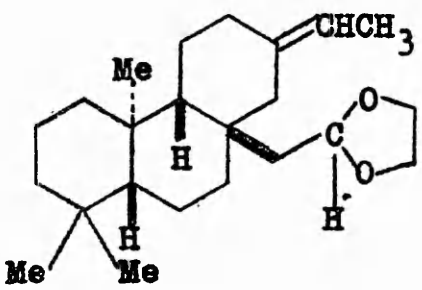
CHART X



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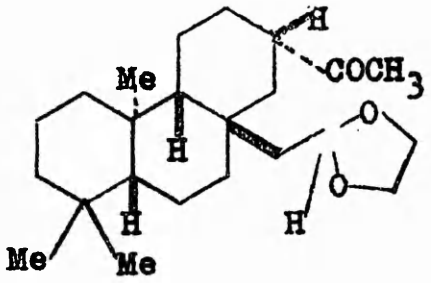

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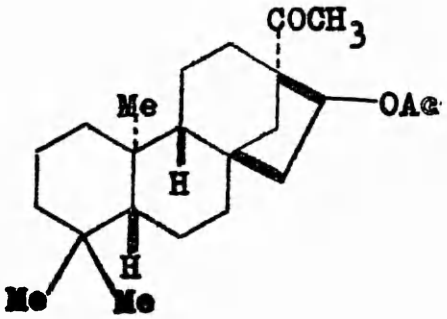

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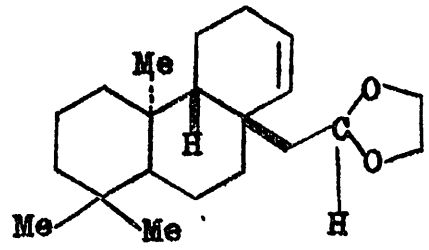
CHART IX



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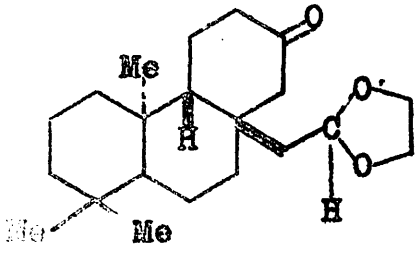

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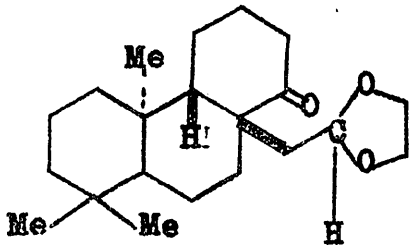

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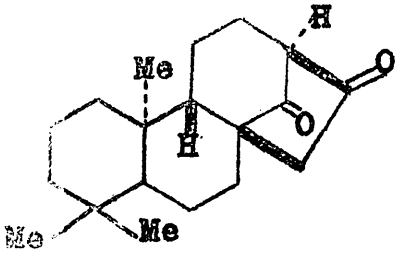

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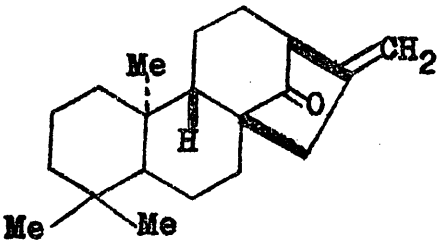

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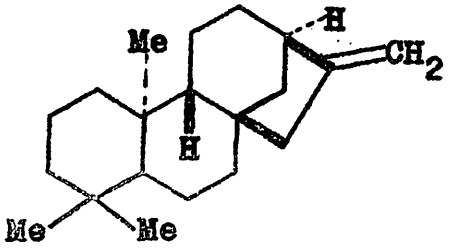


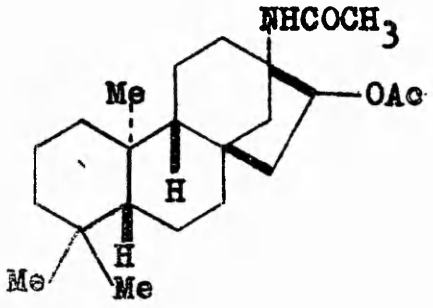
(40)

concomitant inversion of the C_{10}-carbomethoxyl affording racemic epigibberic acid (70).

Progressing a little further to the non-aromatic gibberellin structures, the meticulous contributions of Ireland and his coworkers are worthy of note. They have produced a successful stereospecific synthesis of (±) kaurene[74] (40), outlined in Chart (IX), starting from the tricyclic acetal (71) prepared from m-methoxy-benzaldehyde. Hydroboration and Jones oxidation of this acetal gave a mixture of the 13-keto- and 14-keto-acetals. The 14-keto compound (72) on treatment with mineral acid and subsequent oxidation smoothly furnished the dione (73) which underwent a Wittig condensation in the presence of methylene triphenylphosphorane affording the desired exomethylene-ketone (74) in high yield. Wolff-Kishner reduction of this ketone gave kaurene (40) in excellent yield.

The same workers have also synthesised (±) hibaene[75] (84) from the tricyclic acetal (71). The C/D ring structure of (±) hibaene being similar to that of gibberic acid (19), they decided to synthesise hibaene via a Wagner-Meerwein rearrangement of the intermediate (82) in which the C/D ring structure and B/C fusionare identical to that of the 7-hydroxy gibberellins. The sequence is summarised in Chart (X). The 13-keto-acetal (75) was derived from the acetal (71) as previously

CHART X



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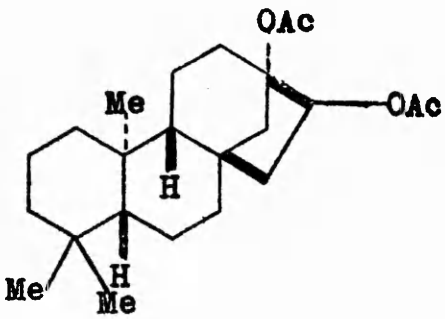

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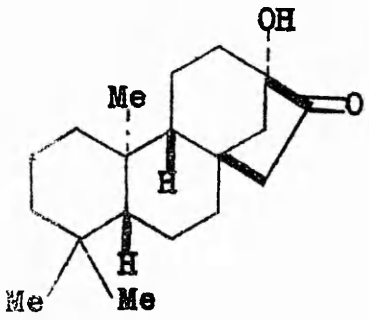

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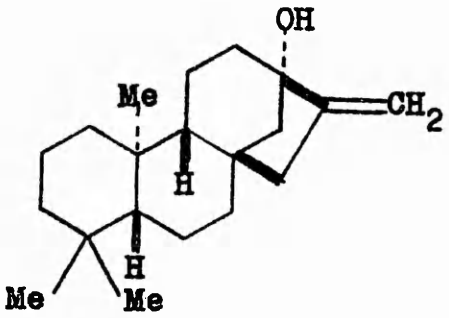

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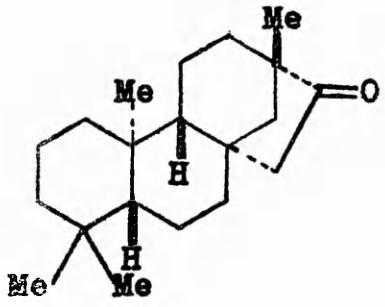

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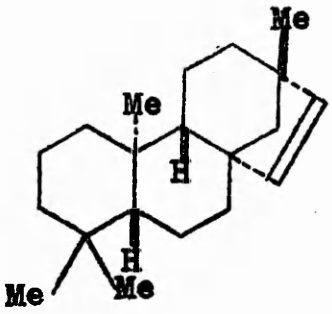

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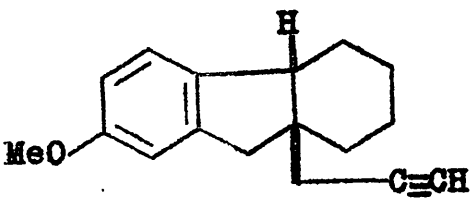
CHART XI



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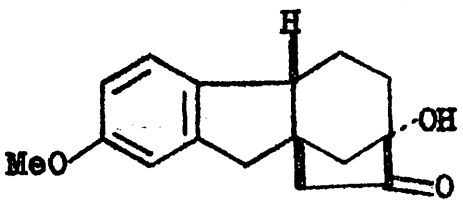
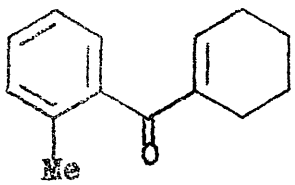


(86)

mentioned. This on Wittig condensation with ethylene-triphenylphosphorane afforded the olefin (76) which on hydroboration, oxidation and subsequent equilibration with base yielded the 13β-acetylacetal (77). Regeneration of the aldehyde with concomitant cyclisation was achieved with mineral acid and the resulting alcohol then converted to the corresponding acetate (78) in high yield. Baeyer-Villiger oxidation furnished only small amounts of the diacetate (80) but warming the oximinotosylate of the acetate (78) in dioxane-water and treatment of the amidoacetate (79) so derived with acetate buffered nitrogen dioxide afforded the desired diacetate (80) in 90% yield. Hydrolysis and oxidation gave the acyloin (81) which on condensation with methylene-triphenylphosphorane furnished the bridgehead alcohol (82). Rearrangement of this hydroxyolefin in acid afforded as expected the ketone (83) which on subsequent reduction and dehydration provided (±) hibaene (84).

Model compounds having the correct C/D ring structure and stereochemistry have been synthesised from ethynyl ketones. By treating the tricyclic ethynyl ketone (85) with sodium in liquid ammonia, Stork[76] obtained the tetracyclic bridgehead alcohol (86) albeit in poor yield (Chart XI). He points out that when a five membered ring is fused 1:2 cis to a six membered ring as in the ketone (85) then the cyclohexane

CHART XII



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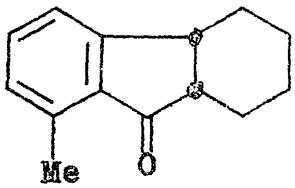

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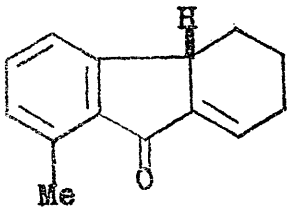

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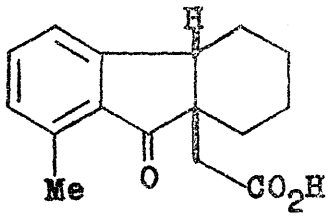

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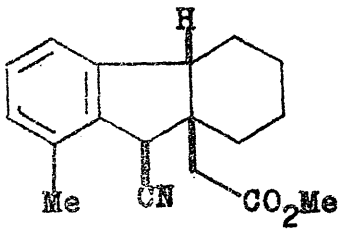

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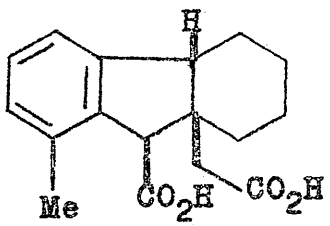

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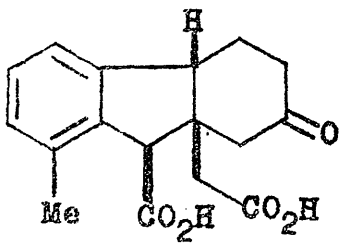

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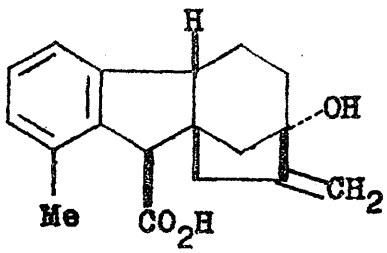


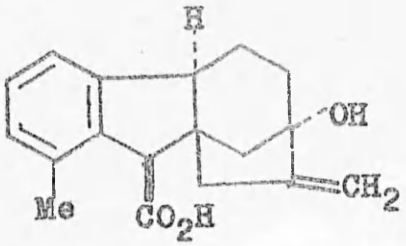
(87)

moiety will prefer to exist in the boat conformation. This being so subsequent cyclisation should afford the 3;2;1 bicyclo-octane having the six membered ring still in the boat conformation, as required in ring C of the gibberellins.

House has studied a number of perhydroindane and hexahydrofluorene systems with a view to synthesising gibberellins.[77-79] The major part of this work was however based on the assumption that the 4b hydrogen was α-orientated which has since been shown not to be the case.

Epiallogibberic acid (87) on sodium bismuthate cleavage affords a keto diacid (88). From the corresponding dimethyl ester House[77] was able to obtain the tricyclic diacid (89) by desulphurisation of the derived ethylene thioketal. He then proceeded to synthesise this key degradation product (Chart XII). Condensation of o-tolylmagnesium bromide with 1-cyanocyclohexene afforded 1-cyclohexenyl-o-tolylketone (90) which on cyclisation gave the 8-methyl-hexafluorenone (91). Bromination and dehydrobromination furnished the exocyclic conjugated ketone (92) as the major product. This on alkylation with ethyl bromoacetate followed by saponification yielded the desired keto acid (93). After catalytic hydrogenation and methylation, a one carbon unit was added at C_9 via the action of sodium cyanide on the derived bromide. Hydrolysis of the nitrile (94) gave the diacid (89), identical in all respects with the degradation product of epiallogibberic acid.

CHART XIII



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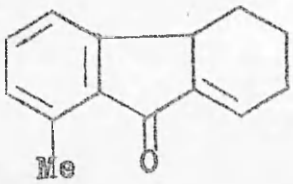

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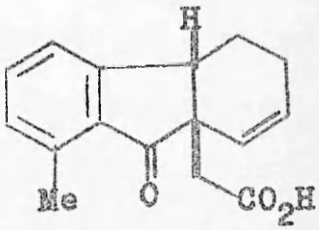

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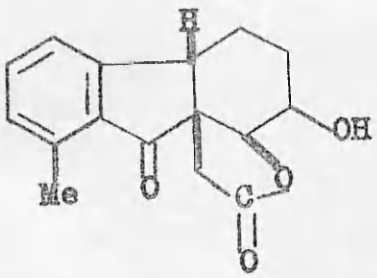

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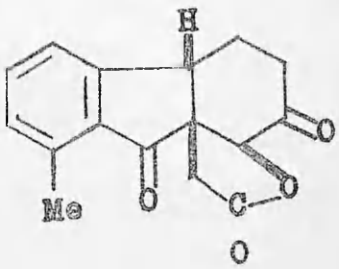

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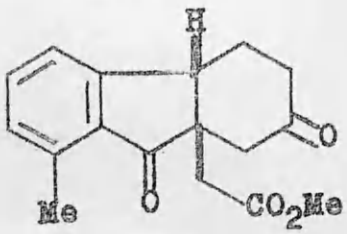

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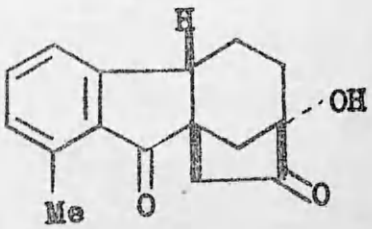

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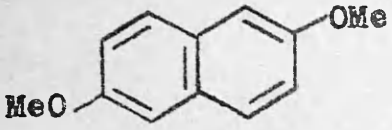
CHART XIV



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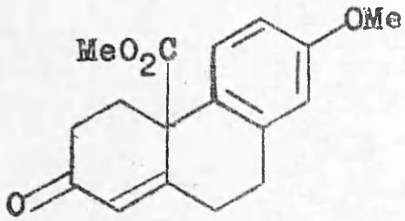

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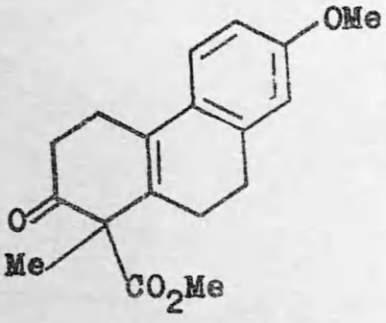

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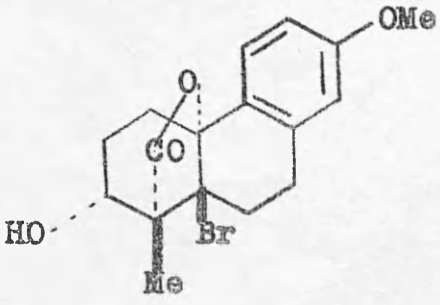

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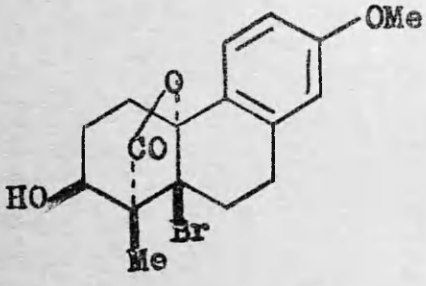

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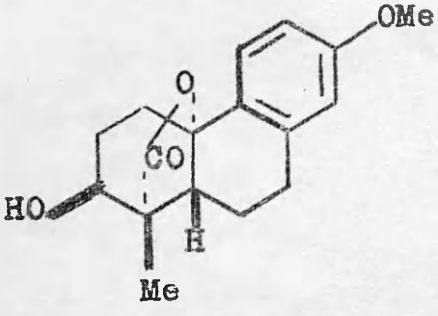
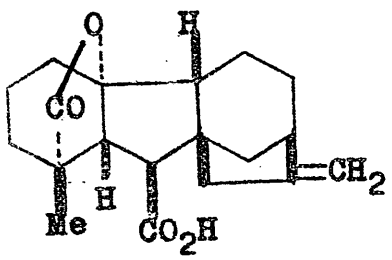


(104)

House has made an unsuccessful attempt to synthesise allogibberic acid (18) (Chart XIII), starting from the keto acid (93).[78] Methylation and treatment of the derived enone ester with peracetic acid afforded an epoxide which on subsequent cleavage with perchloric acid furnished the hydroxy lactone (95). Oxidation gave the dione lactone (96) which with chromous chloride in pyridine to open the lactone ring gave the required tricyclic diketo ester (97). However attempts to effect an internal acyloin condensation to the desired hydroxy diketone (98) met with little success due mainly to competition from the carbonyl at C_9.

Corey and Barcza[80] have attempted to syntehsise the gibberellins from naphthalene derivatives. These attempts are summarised in Chart XIV. Reduction, hydrolysis and α-carbomethoxylation of 2:6-dimethoxy-naphthalene (99) followed by annulation with methyl vinyl ketone afforded the tricyclic enone (100) which on saponification, decarboxylation, α-carbomethoxylation and α-methylation gave the ketone (101). Reduction of the carbonyl group followed by saponification and bromolactonisation of the resulting acid furnished the desired bromolactone (102). The hydroxyl group had an α-orientation but the lactone underwent an oxidation-reduction cycle affording a β-hydroxyl group (103). Acetylation and debromination gave the tricyclic lactone (104) which has the

ring A partial structure of the corresponding acetyl derivatives of gibberellins A_1, A_2, and A_4. Attempts to cleave ring B and form rings C and D have as yet been unsuccessful.



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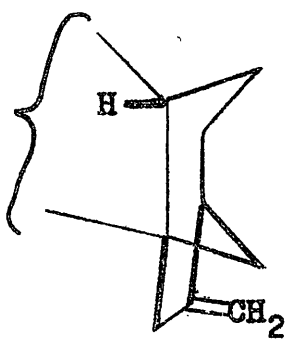

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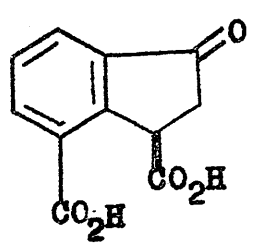


(126)

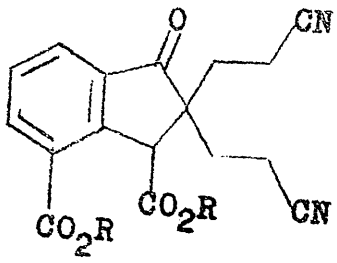
Theoretical Discussion

Gibberellin A_9 (9) is structurally the simplest member of the gibberellin family, having no double bonds or hydroxyl groups in ring A and no bridgehead hydroxyl at C_7. Nevertheless this important biological species, presents interesting problems for the organic chemist, particularly the stereochemical aspect, since it possesses several asymmetric carbons and a 3:2:1 bicyclooctane system with the cyclohexane ring held in the boat conformation (9).

To attempt a synthesis of gibberellin A_9 from a 3:2:1 bicyclooctane intermediate by building on rings A and B is probably inadvisable as such an intermediate would be liable to uncontrollable rearrangement unless the reaction conditions were seriously limited.

It was decided to attempt a synthesis of gibberellin A_9 via a suitably substituted indane derivative. 3-Keto-indane-1,7-dicarboxylic acid (126) was considered to be a desirable starting material for the synthesis for several reasons:-

1. It had a carboxyl at C_1 which could eventually become the carboxyl at C_{10} in gibberellin A_9
2. It also possessed a carboxyl group at C_7 from which the 1 → 4a lactone could possibly be generated. It seemed imperative that any



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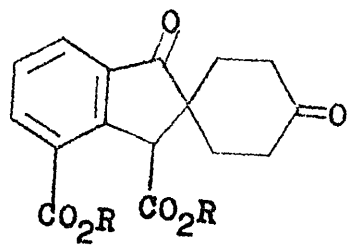
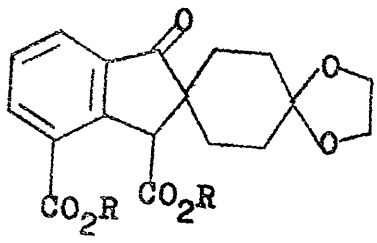


(128)

R = protecting group

e.g. t-butyl



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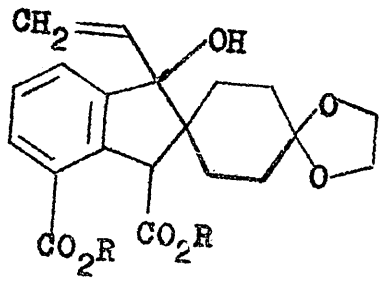

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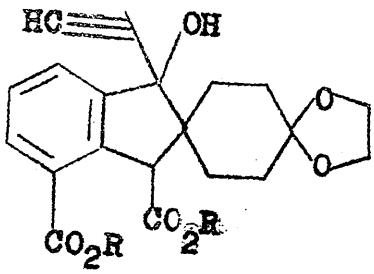

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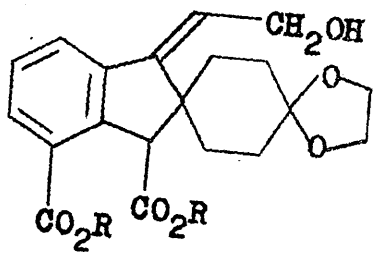

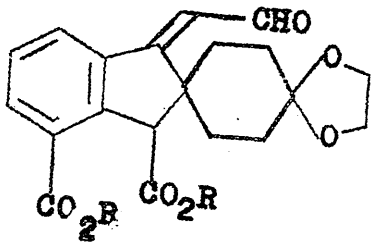

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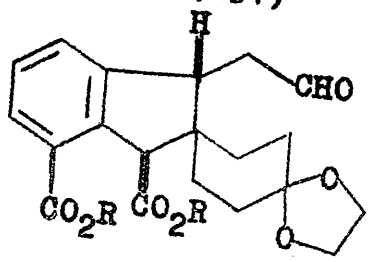
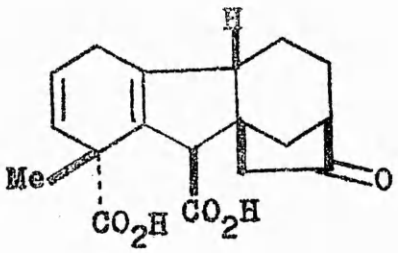


(133)

starting material should possess such a carboxyl group since although numerous methods of introducing a carboxyl group into an aromatic ring existed, these are almost exclusively limited to bimolecular electrophilic substitution reactions, with resultant uncertainty about the site of introduction.

3. The carbonyl at C_3 provided a basis for elaboration at C_2 and C_3 to rings C and D of A_9.

The projected scheme envisaged dicyanoethylation of the indanone (or suitably protected derivative) to the dinitrile (127). Cyclisation of the dinitrile could afford the spirodiketone (128), the six membered ring of which would later be modified to ring D of gibberellin A_9. It was hoped that the difference in reactivity of the two carbonyls in the spirodiketone (128) would allow the cyclohexanone carbonyl to be ketalised in preference to the carbonyl of the indanone. Thereafter Grignard condensation of the monoketal (129) with either ethynylmagnesium iodide or vinylmagnesium bromide should afford respectively the ethynylcarbinol (130) or the vinylcarbinol (131). Rearrangement of the ethylnylcarbinol[81] (130) under basic conditions should afford the unsaturated aldehyde (132) which on hydrogenation might yield the aldehyde (133). Base rearrangement of the vinylcarbinol (131) could give the alcohol (134) which on hydrogenation



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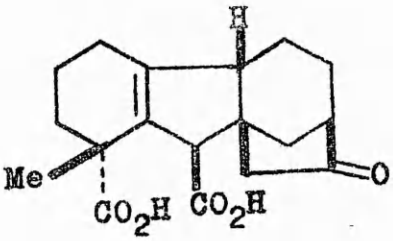

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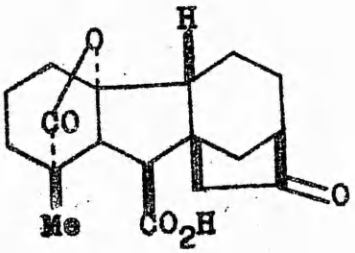

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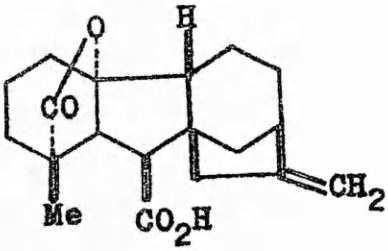

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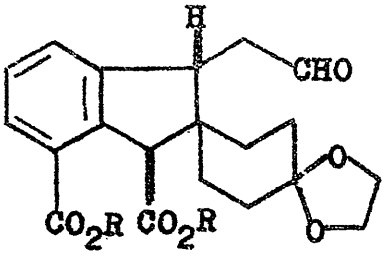

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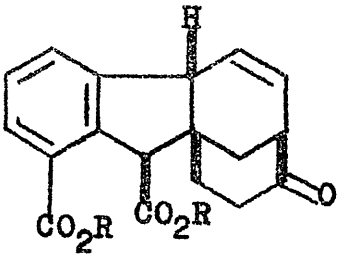

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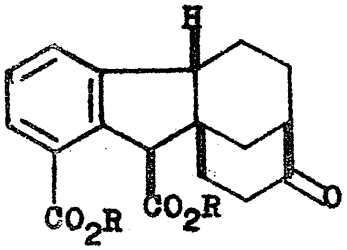

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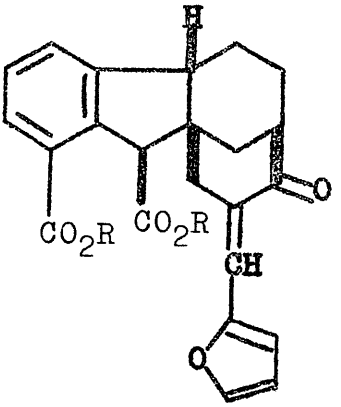

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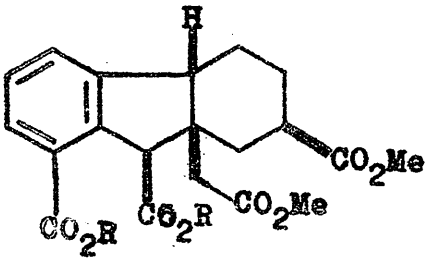

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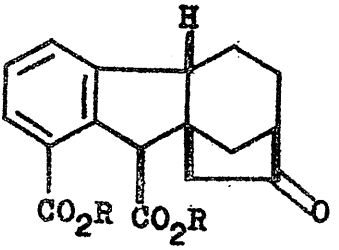
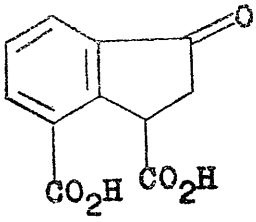


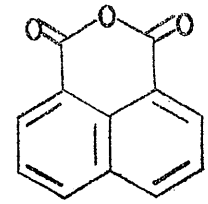
(139)

and oxidation would also give the aldehyde (133). One advantage of both these methods of inserting the two carbon unit at C_3 of the indanone (C_{4b} of gibberellin A_9) is that each involves hydrogenation at C_3, with some possibility of stereochemical control at this centre. Assuming the carboxyl function at C_1 to be β (absolute configuration) the required stereochemistry of the aldehyde (133) is as shown.

Mild acid hydrolysis of the aldehyde (133) regenerating the carbonyl function should leave the molecule free to cyclise under basic conditions affording, after dehydration, the tetracyclic ketone (135). This on hydrogenation would be expected to give the desired bicyclic intermediate (136). Treatment with furfural in the presence of sodium hydroxide should yield the furfurylidene[82] (137) which on ozonolysis and methylation would afford the dimethyl ester[83] (138). Dieckmanncyclisation of the diester and decarboxylation of the resulting β-keto ester should give the unsaturated gibbane (139). The stereochemistry of this intermediate would follow from the stereochemistry of the aldehyde (133), the C_{8-9} bridge being cis to the hydrogen at C_{4b} and ring C being in the boat conformation. If epimerisation were to take place at C_7 of the seco-derivative (138) without epimerisation at C_{9a} then cyclisation would not take place.



(126)



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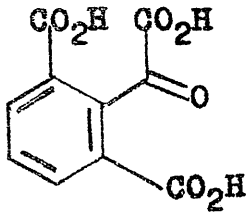
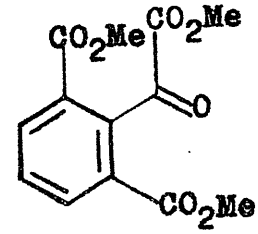
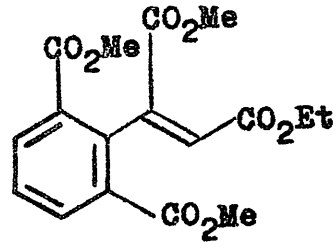


(151)



(152)



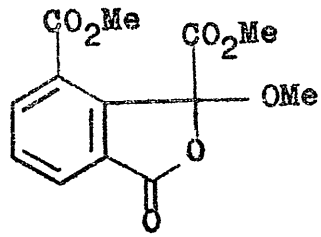
(143)

One possible method of modifying ring A of the gibbane (139) to that of gibberellin A_9 might be via the intermediate (140) - a possible saponification product of reductive methylation of the gibbane. If selective reduction of the disubstituted double bond could be accomplished affording the β-γ unsaturated acid (141), this could possibly undergo iodolactonisation[84] to the 1 → 4a lactone (142). Introduction of the exocyclic methylene in the usual way via a Wittig condensation would then afford racemic gibberellin A_9 (9)

The desired starting material was therefore 3-keto-1:7-dicarboxyindane (126). A plausible route to this compound appeared to be the Reformatsky condensation of the known[85] keto triester (152) with ethyl bromoacetate, subsequent reduction to the tetra-ester (143) and Dieckmann cyclisation and hydrolysis to the desired keto diacid.

Oxidation of naphthalic anhydride (150) in alkaline potassium permanganate gave 2:6-dicarboxyphenylglyoxyllic acid (151) which on methylation with diazomethane afforded the crystalline trimethyl ester (152) in 85% overall yield.

In the light of further studies indicating the apparent unreactivity of the ketone in this keto ester (152) it was deemed expedient to substantiate the structure proposed for this compound by Graebe and Bossel[85] and



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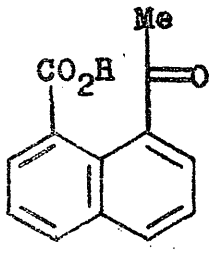

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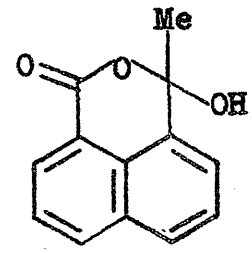

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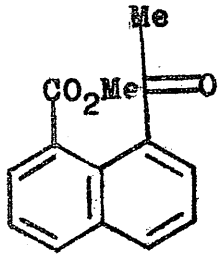

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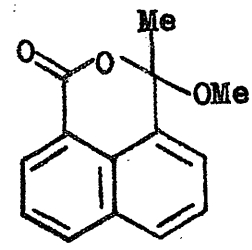
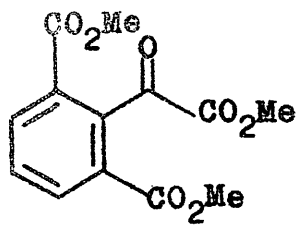


(147)

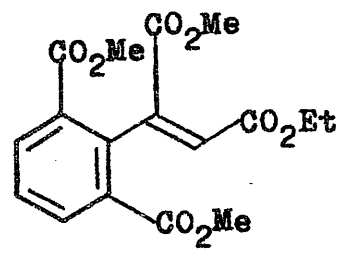
accepted here. Thus a broad band in the i.r. at 1732 $cm.^{-1}$ could be assigned a composite band for the aromatic carbomethoxyls and the α-keto ester system, but a weak band at 1764 $cm.^{-1}$ is not readily explained on the basis of this structure but may be an overtone.

An alternative formulation for the compound, having the tautomeric pseudo-ester structure (144) warranted careful examination. Lansbury and Bieron[86] having studied such ring chain tautomerism in 8-acetyl-1-naphthoic acid (145) concluded that this acid existed in the cyclic pseudo-acid form (146). Diazomethylation afforded the pseudo-ester (147) 3H singlet peaks at 6·80 and 8·13 τ in the n.m.r. being assigned to the methoxyl group and the methyl attached to the doubly oxygenated carbon respectively. Esterification of the pseudo-acid with methanolic hydrogen chloride afforded the isomeric open chain keto ester (148) showing resonances at 6·14 ($-CO_2-C\underline{H}_3$) and 7·38 τ ($-C-C\underline{H}_3$).

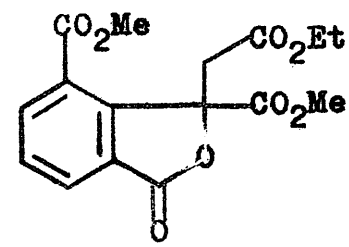
Surprisingly esterification of the dicarboxyphenylglyoxyllic acid (151) with methanolic hydrogen chloride gave a product identical with that obtained by diazomethylation. A 2H doublet centred at 1·68 τ (J = 8 c.p.s.) and a 1H triplet centred at 2·31 τ (J = 8 c.p.s.) in the n.m.r. of both products is completely in accord with the open-chain structure having two equivalent aromatic protons (A_2B system).


CO2Me
O
CO2Me
CO2Me

(152)


CO2Me
CO2Me
CO2Me
CO2Et
CO2Me

(143)

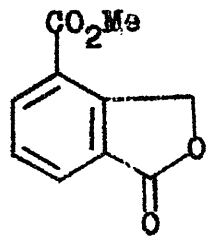

CO2Me
CO2Et
CO2Me
O
O

(149)

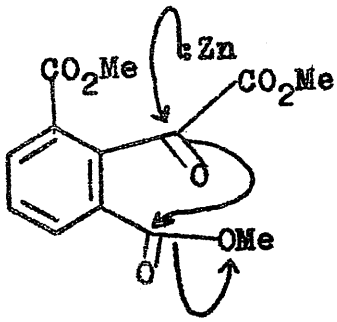
The aromatic regions of later compounds having the alternative γ-lactone ring system are markedly different from that of the triester (vide infra.). Again, as expected, only two methyl resonances are discernible in the n.m.r. at 6·05 (3H, $-\overset{O}{\overset{\|}{C}}-CO_2\underline{CH}_3$) and 6·1 τ (6H, $\phi-CO_2\underline{CH}_3$), unresolved even in benzene solution, 6·4 (3H) 6·6 τ (6H).

Numerous attempts to attach a two carbon unit to the ketone group of the glyoxyllic ester (152) using a large excess of purified zinc and ethyl bromoacetate failed completely to give any of the expected condensation product (143). Significantly attempts to carry out the reaction with a zinc free ethereal solution of the zinc-ethyl bromoacetate complex led to quantitative recovery of the starting material, whereas a new compound, m.p. 112-114°, was formed in small yields in the normal reaction. This compound was later obtained in high yield by simply refluxing the glyoxyllic ester (152) with zinc and acetic acid.

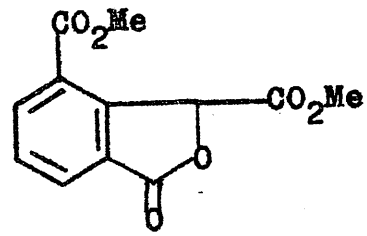
This product shows a complex carbonyl region in the i.r. with bands at 1790, 1780, 1757, 1740, and 1724 $cm.^{-1}$, which initially was thought to be in accord with the structure (149) which would result from Reformatsky condensation followed by lactonisation. In an attempt to open the lactone ring and concomitantly effect a Dieckmann



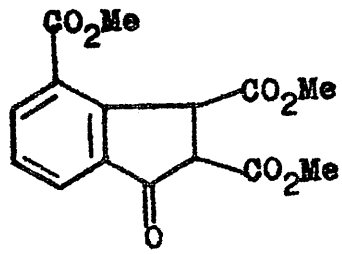
(154)



(152)



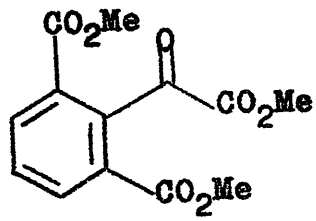
(153)



(155)

condensation, the compound was refluxed with methanolic sodium methoxide. This gave in fairly good yield, not the expected product (155) but a far simpler compound, m.p. 180-181°, possessing but one aromatic carbomethoxyl ($\nu_{max.}$ 1725 $cm.^{-1}$; 3H singlet at 6·0τ) and a γ-lactone ($\nu_{max.}$ 1768 $cm.^{-1}$) 2H singlet at 4·40τ(φ-CH_2-O-C(=O)-). The resonances of the three aromatic protons agreed with an ABC system showing a 2H quartet centred at 1·75 τ (J = 8 c.p.s.) and a 1H triplet centred at 2·32 τ (J = 8 c.p.s.) both showing further slight coupling. These findings were completely in accord with the 4-carbomethoxyphthalide structure (154) assigned to this compound.

This evidence taken with n.m.r. data on the previous compound showed that the structure proposed was in error, that the Reformatsky condensation had not indeed taken place, and the product was in fact due to reductive lactonisation. The 3:4-dicarbomethoxyphthalide structure (153), which dould arise by attack of an electron pair from the zinc on the carbonyl of the glyoxyllic ester (152) followed by intramolecular lactonisation and elimination of a methoxyl group, was fully supported by the n.m.r. data. The aromatic region is similar to that of the carboxyphthalide (154), 2H quartet centred at 1·75 (J = 8 c.p.s.), and 1H triplet centred at 2·30 τ (J = 6 c.p.s.), and is markedly different from the



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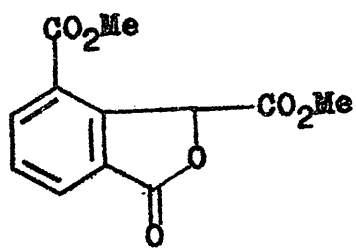
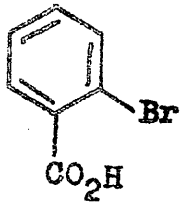


(153)

same region in 2:6-dicarbomethoxyphenylglyoxyllic acid methyl ester (152). The two 3H singlets at 6·05 and 6·20 τ are ascribed to the aromatic methyl ester (φ-$CO_2C\underline{H}_3$) and aliphatic ester (φ-$\underset{\underset{O}{|}}{C}H(CO_2C\underline{H}_3)$) respectively. A 1H singlet at 3·84 τ is due to the benzylic proton on a carbon also bearing oxygen and an ester group (φ-$C\underline{H}(CO_2CH_3)$). The fact that the compound is obtained in high yield by zinc and acetic acid reduction of the triester, convincingly confirms the structure (153) assigned to it.

Alternative methods of adding a two carbon unit to the ketone of the triester were all characterised by a singular lack of success. From attempted condensations of the triester (152) with malononitrile and with ethylcyano-acetate only starting material was recovered. Attempted condensation of the glyoxyllic ester (152) with the Wittig salt from triphenyl phosphine and ethylbromoacetate proved fruitless. Such Wittig salts are known to lead to very stable phosphobetaines,[87] stabilised by the β-carbethoxyl group. Attempts using sodium metal as the base in boiling xylene[88] led to poor yields of a mixture of at least seven products. Attempts to promote condensation between the triester (152) and ethoxyethyne in the presence of boron trifluoride etherate[89] led only to quantitative recovery of crystalline triester.



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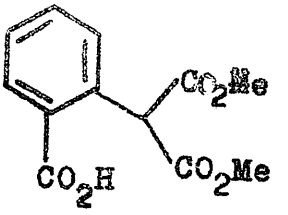

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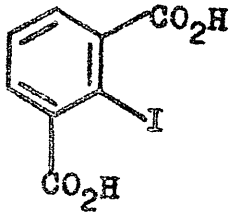

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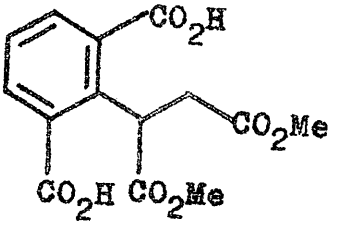

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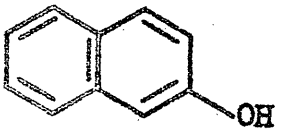

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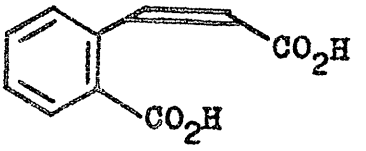

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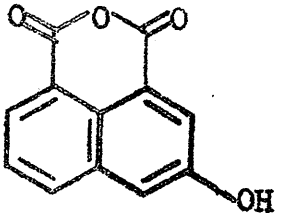

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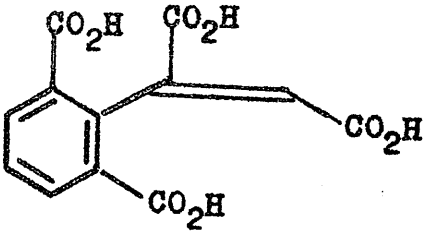
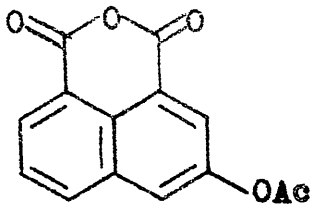


(163)

Hurtley[90] has reported that a halogen ortho to an aromatic carboxyl group will undergo nucleophilic displacement under the catalytic influence of copper or copper acetate. Thus condensation of o-bromobenzoic acid (156) and diethyl malonate with sodium methoxide and copper acetate afforded o-carboxyphenylmalonate (157) in moderate yield. This compound had the expected n.m.r. spectrum ($CDCl_3$ soln) with signals at 0·4 (multiplet, 1H, o-$CO_2\underline{H}$) and 4·2 τ (singlet, 1H, o-$C\underline{H}(CO_2Et)_2$).

If this reaction could be developed using 2:6-dicarboxyiodobenzene (158) with a succinic ester then cyclisation of the product (159) should provide a route to the required indanone dicarboxylic acid (126). However attampts to effect such a condensation between o-bromobenzoic acid and dimethyl succinate using either sodium methoxide or potassium t-butoxide as base led to quantitative recovery of the starting materials, while condensation with 1:1:2-tircarbomethoxyethane gave an intractable mixture of products.

β-Naphthol (160) on oxidation with 40% peracetic acid afforded o-carboxy-cis-cinnamic acid (161).[91] Attempts to promote similar oxidative cleavage of 3-hydroxynaphthalic-1:8-anhydride (162) to o:o'-dicarboxyphenylfumaric acid (163)



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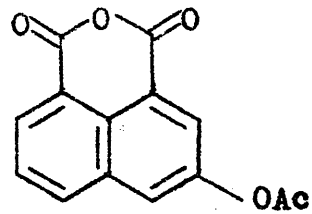

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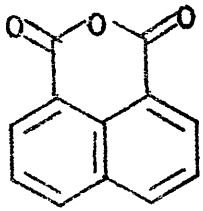

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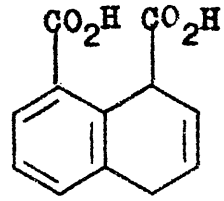

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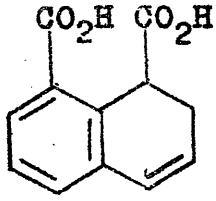

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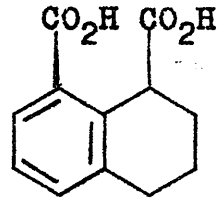

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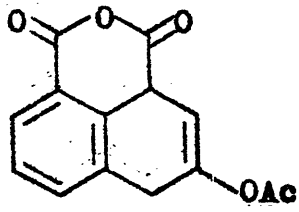

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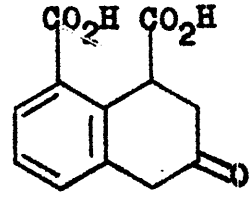


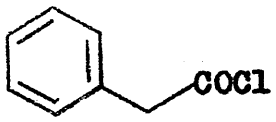
(167)

failed due to the facile preferential acetylation of the 3-hydroxyl group affording the insoluble 3-acetoxynaphthalic-1:8-anhydride (164).

It was reported[92] that sodium amalgam reduction of naphthalic-1:8-anhydride (150) in sodium carbonate solution gave "a mixture of dihydro products". If the 2:3-dihydro product (165) could be isolated from the reaction this could possibly afford a route to the desired dicarboxyindanone (126). In the event the only insoluble products were 1:4-dihydro-naphthalic-1:8-dicarboxylic acid (105) and 1:2:3:4-tetrahydro-naphthalic-1:8-dicarboxylic acid (106). The structures of these two products were elucidated from u.v. and n.m.r. data on the corresponding dimethyl esters (vide infra).

Attempts to effect a similar reduction of 3-acetoxy-naphthalic-1:8-anhydride (164) to the 1:4-dihydro compound (166) were unsuccessful, leading only to hydrogenolysis to 3-hydroxynaphthalic-1:8-anhydride (162) which itself was unreactive and failed to reduce to the β-tetralone (167).

As previously indicated it was considered imperative to have a carboxyl group present at C_7 of the indanone starting material since the methods for introducing carboxyl groups into aromatic rings generally involved electrophilic substitution with consequent uncertainty about the position of attack. Fortunately Smith and Kan have recently developed



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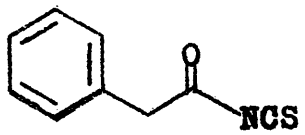

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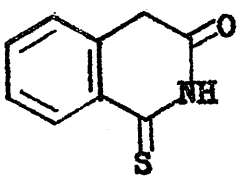

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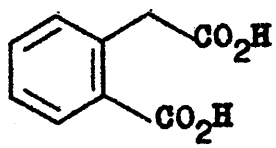

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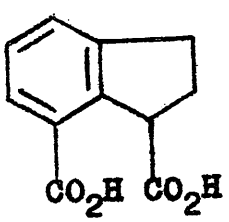

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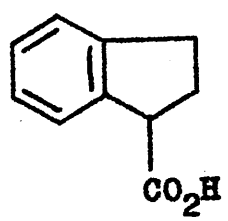

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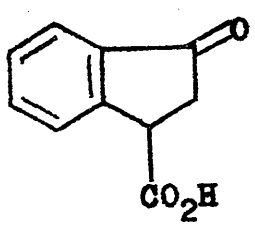

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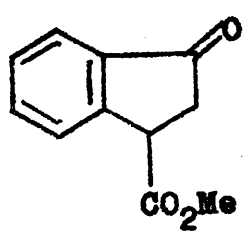
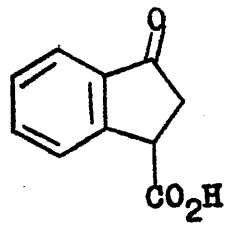


(172)

a novel method for substituting a carboxyl function into the ortho-position of the aromatic nuclei of substituted benzoic and phenylacetic acids.[93] This involved conversion of phenylacetic acid to its acid chloride (168) which on treatment with lead thiocyanate gave phenylacetylisothiocyanate (169). Intramolecular Friedel-Crafts cyclisation of the isothiocyanate with aluminium chloride in carbon disulphide or s-tetrachloroethane afforded 1-thio-1:3-[2H:4H]-isoquinolinedione (170) which on base hydrolysis gave homophthalic acid (171).

This reaction sequence should allow the insertion of a carboxyl function at the correct position in ring A of an aromatic gibberellin A_9 intermediate, using the carboxyl group present in ring B. As will be more fully discussed later, 1-carboxyindane (119) was converted to 1:7-dicarboxyindane (123) with little difficulty using this method. This insertion process precludes the necessity of using as starting material an indanone with carboxyl groups both in the five membered ring and in the benzene nucleus.

A new starting material, 3-carboxyindan-1-one (107) was readily obtained via Friedel-Crafts cyclisation of phenylsuccinic anhydride.[91] Diazomethylation or treatment with methanol-sulphuric acid under Clinton-Laskowski conditions gave the methyl ester (172). $\nu_{max.}(CHCl_3)$, 1740 ($-CO_2Me$),



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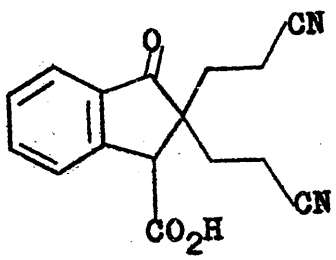

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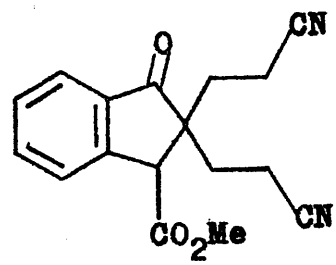

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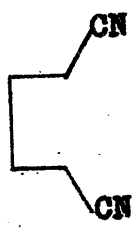

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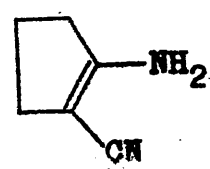
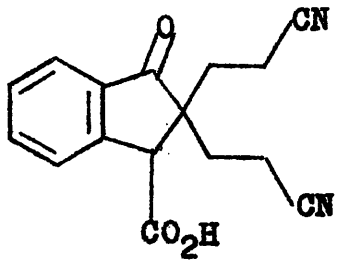


(174)

1717 cm.$^{-1}$ (ketone). The n.m.r. spectrum was in agreement with the expected structure, 5·8 (1H, quartet, ω-C<u>H</u>(-CH_2-)-CO_2Me), 6·2 (3H, singlet, $-CO_2C\underline{H}_3$) and 7·1 τ (2H, triplet, ω-CH-C<u>H</u>$_2$-CO-).

Treatment of the indanone carboxylic acid (107) with acrylonitrile and 1·2 moles of Triton B catalyst in peroxide free dioxan, conditions developed by Baldwin for cyanoethylation of fluorene, afforded 2:2-di-(w-cyanoethyl)-3 carboxyindan-1-one (108) in good yield, which with diazomethane quantitatively afforded the methyl ester (109).

Attempts were made to cyclise the dinitrile directly. Thorpe[95] reported the cyclisation of adiponitrile (173) to the enamino nitrile (174) in the presence of methanolic sodium methoxide. Under the conditions both the dinitrile acid (108) and the dinitrile ester (109) failed to cyclise. This agreed with the reports of Baldwin[96] who failed to cyclise 9:9-dicyanoethylfluorene under these conditions and with those of Thomson[97] who failed to repeat Thorpe's original cyclisation. Baldwin using potassium t-butoxide in t-butanol did succeed in cyclising 9:9-dicyanoethylfluorene, but this was probably due to the enamino nitrile being insoluble in t-butanol, for others[98] report that unless the enamino nitrile is insoluble in the reaction media,



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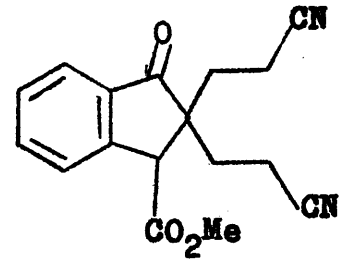

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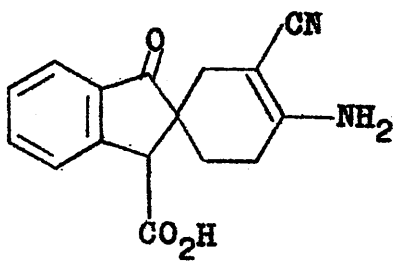

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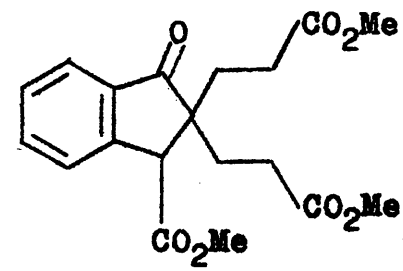

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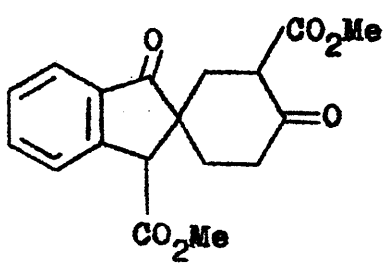

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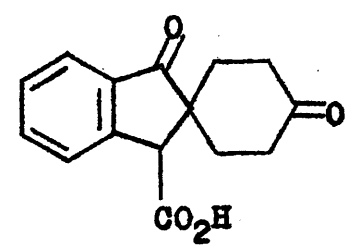
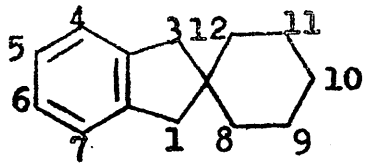
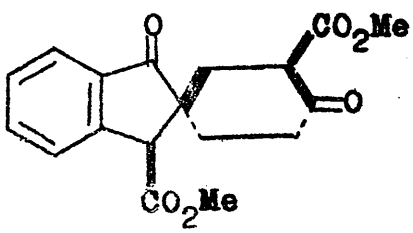


(112)

dimerisation occurs. Treatment of the dinitrile ester (109) with potassium t-butoxide in t-butanol afforded an intractable mixture of products, while the dinitrile acid (108) under similar conditions failed to react due to insolubility of the potassium salt in t-butanol. Attempted cyclisation of the acid (108) to the enamino nitrile (175) using sodium hydride in dimethylsulphoxide[99] gave, quantitatively, the starting material.

Refluxing the acidic dinitrile (108) in methanolic hydrogen chloride smoothly afforded the trimethyl ester (110) in good yield. Dieckmann cyclisation of the triester (110) with sodium methoxide in benzene[100] gave two products one of which dissolved in 10% sodium bicarbonate. The non-acidic product gave a positive purple colouration with alcoholic ferric chloride solution and u.v. evidence indicated that it was a β-keto ester. A bicarbonate solution of the acidic product on acidification with 6N hydrochloric acid afforded a carboxylic acid which on diazomethylation furnished a methyl ester. This methyl ester gave a grey colouration with ferric chloride and was less polar than the neutral β-keto ester on t.l.c. examination using 40% ethyl-acetate-petrol solution. Both products on acid hydrolysis afforded an identical diketo acid (112).





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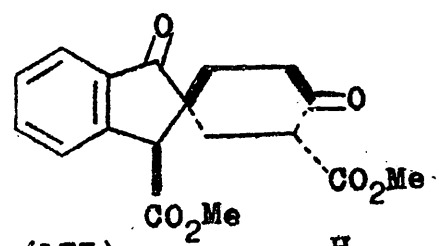

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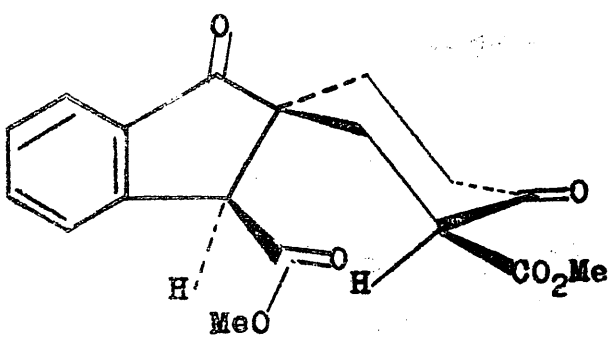

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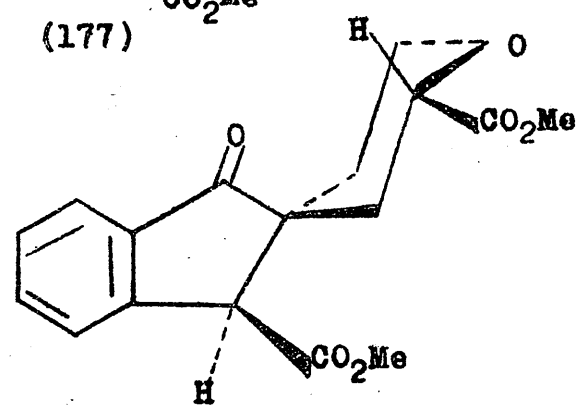

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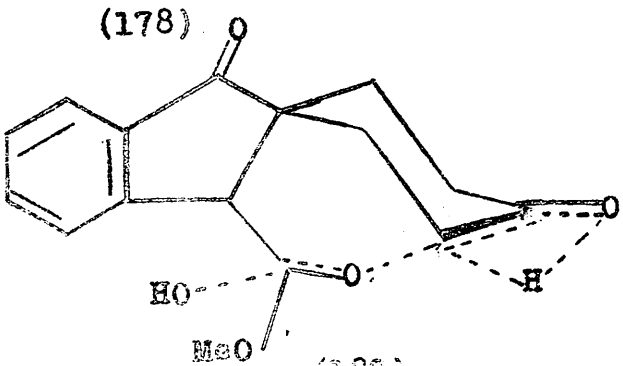

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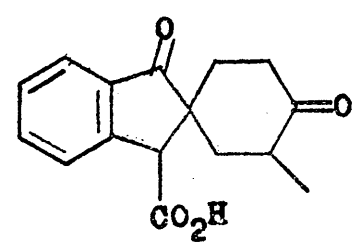
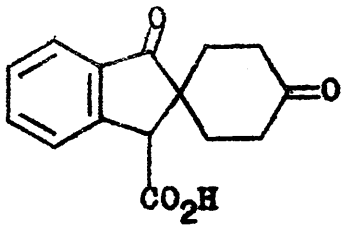


(112)

From the Dieckmann cyclisation of the triester (110) two geometric isomers were expected, one having the two methyl ester groups cis to each other (176) the other having these methyl ester groups trans to each other (177). Each of these isomers can be epimeric at C_9, the carbon α to the ketone. Assuming that the cyclohexanone ring exists in the chair conformation and that the bulky ester group would prefer to occupy the least hindered equatorial position, the preferred conformation of the two cis epimers are as shown in figures (178) and (179). In one of these conformations (178) the acidic α hydrogen at C_9 is hindered by the ester group at C_1 and the possibility exists that participation of this neighbouring ester group may facilitate attack by the hydroxide ion and subsequent removal of the acidic α-hydrogen, via the intermediate (180). Such a mechanism would furnish a β-keto ester carboxylic acid (181) and would account for the behaviour of the bicarbonate soluble cyclisation product. The neutral product is, then, probably the trans-β-keto-diester (177) and the acidic product is probably the cis-β-keto-diester (176).

As indicated above, hydrolysis of either of the two Dieckmann products afforded the spiro-diketo acid (112) which on diazomethylation gave the spiro-diketo ester (113). The structure proposed for the spiro-diketo ester (113)



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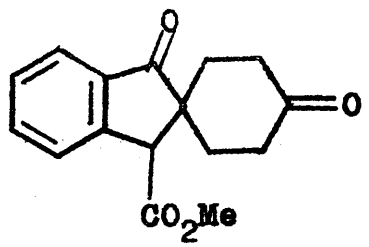
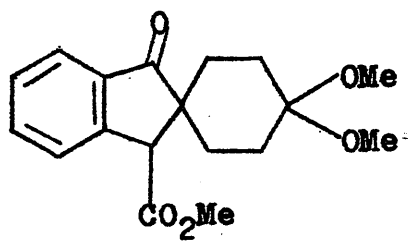
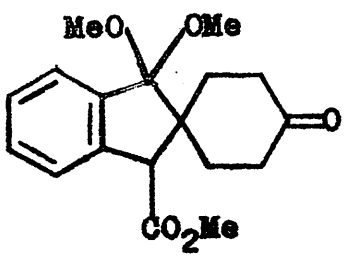


(113)



(182)



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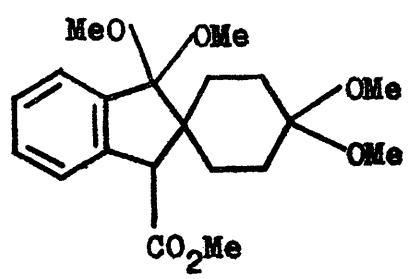
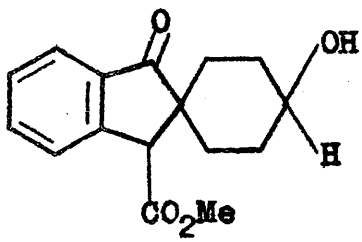


(184)

was confirmed by i.r., n.m.r. and analysis. A 4H singlet in the n.m.r. of a carbontetrachloride solution of the spiro-ester (113) can be explained as the superimposition of the methyl ester and benzylic hydrogen (φ-C<u>H</u>-$CO_2C\underline{H}_3$). In the n.m.r. of a benzene solution of the spiro-ester (113) this 6·4 resonance is resolved into two resonances, a 3H singlet at 6·65 (φ-CH-$CO_2C\underline{H}_3$) and a 1H singlet at 6·80 τ (φ-C<u>H</u>-CO_2CH_3).

Numerous attempts to selectively ketalise the cyclohexanone carbonyl of the spiro-diketone proved singularly unsuccessful. Under the standard conditions of refluxing the compound with ethylene glycol and a catalytic amount of <u>p</u>-toluenesulphonic acid in benzene and azeotroping any water formed, only starting materials were recovered. Attempts with excess ethylene glycol with and without benzene[98] or with 1 mole of <u>p</u>-toluenesulphonic acid gave similar results. Refluxing the diketone with ethyl orthoformate and <u>p</u>-toluenesulphonic acid[101] also proved fruitless and attempted exchange dioxolanation[102] using the 1:3-dioxolane of methyl ethyl ketone also gave only starting materials. Attempts to form the dimethyl ketal of the cyclohexanone both by direct ketalisation with methanol and exchange ketalisation with 2:2 dimethoxy propane[103] led to a complex mixture of mono and diketals, (182), (183) and (184) respectively.



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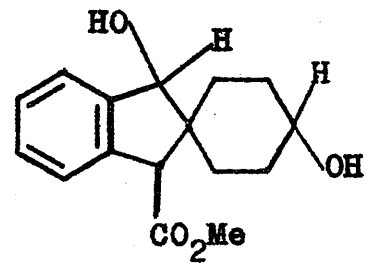

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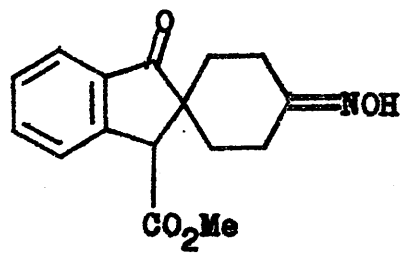
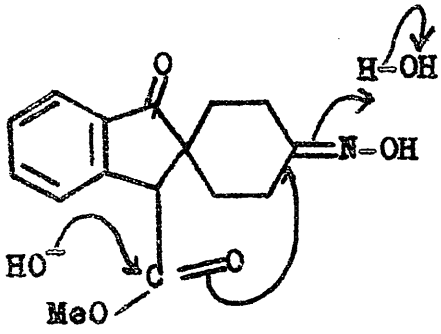


(116)

Reduction of the spiro-diketone either as the acid (112) or as the ester (113) with sodium borohydride afforded a complex mixture of alcohols. There were two major components of the mixture and repeated preparative t.l.c. allowed complete separation of one of these, alcohol A (114) and partial separation of the other, alcohol B (115). The absence of any adsorption in the i.r. of alcohol A at 1735 $cm.^{-1}$ indicated that the cyclohexanone carbonyl had been reduced. The presence of a molecular ion at m/e 274 in the mass spectrum suggests that alcohol A is the mono-ol (114). The i.r. of alcohol B (contaminated with a trace of alcohol A) is characterised by the absence of any adsorption at 1735 $cm.^{-1}$ and by the almost complete disappearance of any adsorption at 1717 $cm.^{-1}$ (indanone carbonyl). This suggests that alcohol B is the diol (115). Even though alcohol A represented selective protection of the cyclohexanone carbonyl against nucleophilic attack, at that position, such a method did not appear to warrant inclusion in a synthetic scheme due to the difficulty of purification.

Treatment of the spiro-diketo ester (113) with hydroxylamine hydrochloride and sodium acetate afforded the expected oxime (116) which was thermally unstable. Attempts to purify this oxime regenerating it from a 5% sodium bicarbonate solution at 0° with 3N hydrochloric acid, led to



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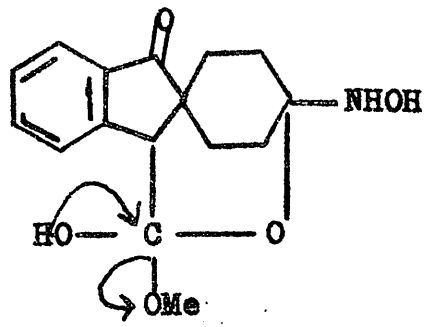

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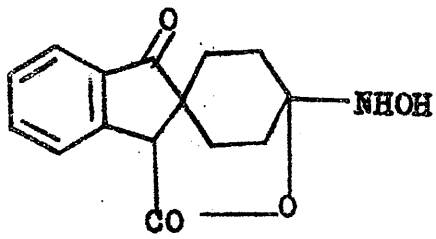

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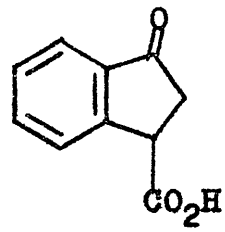

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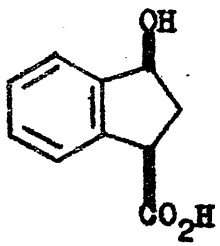

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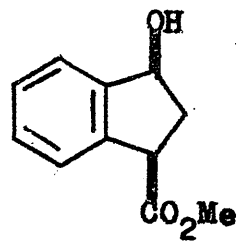
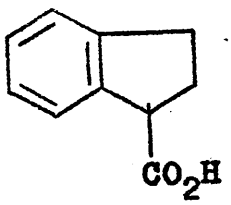


(118)

formation of a compound m.p. 145-150°. This compound was extremely insoluble in common solvents and in contrast to the oxime which exhibits a sharp absorption at 3592 $cm.^{-1}$ in the i.r., this compound has a broad adsorption at 3350 $cm.^{-1}$. It did not react with diazomethane. This compound may possibly be the lactone (185). Such a compound could be formed via the interaction of the oxime group with the neighbouring methyl ester, giving the hemiketal (186) which on subsequent acidification would furnish the lactone (185).

1-Carboxy-3-keto-indane(107) on sodium borohydride reduction in the presence of sodium bicarbonate afforded a mixture of hydroxy acids, probably epimers at C_3. Fractional crystallisation gave cis-1-carboxy-3-hydroxy-indane (117) as the major component of the mixture (85%). Diazomethylation afforded the corresponding hydrindol methyl ester (118). The i.r. of this ester shows evidence of intramolecular hydrogen bonding between the hydroxyl and the carbonyl of the ester with carbonyl adsorptions at 1728 and 1742 $cm.^{-1}$

As indicated previously a key step in the synthetic route is the introduction of a carboxyl group into the correct position in the benzene nucleus of an aromatic ring A intermediate, to permit elaboration to the 1 → 4a lactone of the gibberellins. It was proposed to



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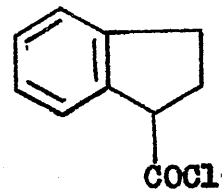

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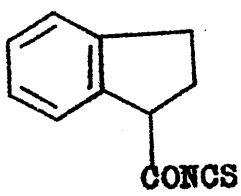

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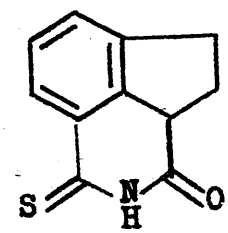
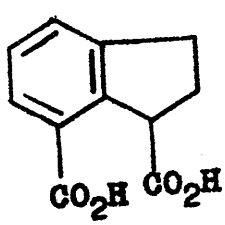
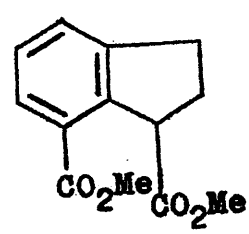


(188)



(123)

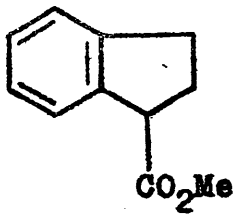


(189)

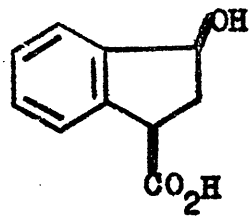
employ the ortho-selective insertion procedure of Smith and Kan.[93]

Conversion of 1-carboxy indane (119), obtained by Clemmensen reduction[104] of 1-carboxy-3-keto-indane (107) to isothiocyanate (122) was accomplished with little difficulty via the acid chloride (121). Cyclisation of the isothiocyanate in the presence of aluminium chloride and subsequent hydrolysis gave the desired diacid (123), which on diazomethylation afforded the [illegible]-diester (189). The n.m.r. spectrum of the diester (189) revealed an aromatic A_2B system, with a 1H split singlet at 2·25 and a 2H multiplet at 2·75 τ. The n.m.r. also indicated the presence of two methyl esters with resonances at 6·2 (3H singlet φ-$CO_2\underline{CH}_3$) and 6·4 τ (3H singlet, φ-CH-$CO_2\underline{CH}_3$). Smith and Kan have since reported[105] that cyclisation of isothiocyanates to thio-isoquinolines can be accomplished using much milder conditions than were used in this cyclisation. The use of these new conditions should afford better yields of much purer isoquinolines and would possibly allow isolation and characterisation of the thio-isoquinoline intermediate of this reaction (188).

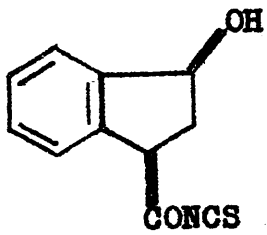
Preliminary attempts to cyclise the hydroxyisothiocyanate (190) derived from cis-1-carboxy-3-hydroxy-indane (117), gave a product which on hydrolysis, diazo-



(120)



(117)



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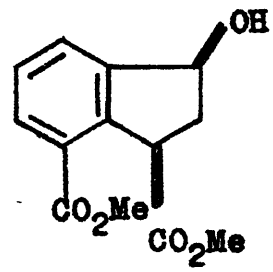

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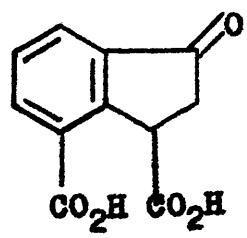

(126)

methylation, and preparative t.l.c. isolation had a n.m.r. spectrum in agreement with that expected for 1:7-dicarbomethoxy-3-hydroxyindane (187). The aromatic region of the spectrum was that of an A_2B system - a split 1H singlet at 2·3 and a 2H multiplet at 2·8 τ. There were also two 3H singlets at 6·2 (ϕ-$CO_2\underline{CH}_3$) and 6·4 τ (ϕ-CH-$CO_2\underline{CH}_3$), indicating the presence of both an aromatic and an aliphatic carbomethoxyl group. Jones oxidation and hydrolysis of this hydroxy diester (187) should afford 1:7-dicarboxy-3-keto indane (126), the original proposed starting material for this synthesis of gibberellin A_9.

It is hoped that these researches have in some measure substantiated the general validity of the proposed approach to the gibberellin skeleton and have provided at least a slender foundation for future work on the construction of the fascinating molecules of the gibberellin family.

1. Petrol or petroleum ether refers to that fraction of petroleum ether boiling between 40°-60°
2. Grade III* alumina refers to Spence Grade H alumina deactivated with 5% $^{W}/_{W}$ of a solution of 1 part glacial acetic acid to 9 parts water
3. Thin layer chromatograms (t.l.c.) were carried out on plates coated with a layer, 0.1 mm thick, of kieselgel G (Merck) suspension.
4. Preparative t.l.c. was carried out on plates coated with a layer, 0.8 mm thick, of kieselgel H (Merck) suspension.
5. Mass spectra were obtained using a Metropolitan Vickers M.S.9. spectrometer
6. Infra-red solution spectra were obtained using a Unicam S.P. 100 spectrometer and spectra of liquid films and nujol mulls were obtained using a Unicam S.P.200 spectrometer.
7. Ultra-violet spectra were obtained using a Unicam S.P. 800 A spectrometer
8. Nuclear Magnetic Resonance (n.m.r.) spectra were obtained using a Perkin-Elmer R.10 spectrometer.

2:6-Dicarboxyphenylglyoxyllic acid (151)

A slurry of naphthalic anhydride (150) (40·1 g.; 0·2 moles; m.p. 274-275°) in 25% aqueous potassium hydroxide (100 ml.) was diluted to 1 litre and refluxed with stirring for 4 hrs., during which time potassium permanganate (195 g.; 1·22 moles) was added to the reaction mixture via a Soxhlet attachment. Stirring and heating were continued for a further 2 hrs. after the addition was complete and the solution then cooled. Ethanol (150 ml.) was added and stirring and heating recommenced for another ½ hr. The cooled solution was filtered through celite 525, and the filtrate acidified with 6N sulphuric acid (100 ml.) and extracted thoroughly with ether. The dried ethereal extracts on evaporation gave the triacid (151) as a colourless amorphous solid, m.p. 223-230° (46·9g., 98%), $\nu_{max.}$(nujol) 1695 (aromatic carboxyl), 1730 (keto acid carboxyl), 1745 $cm.^{-1}$ (ketone).

Methyl 2:6-dimethoxycarbonylphenylglyoxyllarte (152)

A solution of the triacid (151) (2·5 g., 1·1 m.moles) in methanol (10 ml.) was allowed to stand with an excess of ethereal diazomethane for 2 hrs. Evaporation gave a semi-solid residue which on crystallisation from methanol gave the trimethyl ester (152) as colourless prisms m.p. 145-147° (2·58 g., 87%), homogeneous on t,l.c. (Rf 0·75 in 30%

ethylacetate/petrol). Recrystallisation from methanol afforded colourless prisms m.p. 147-148° (Found: C, 55·5; H, 4·1. $C_{13}H_{12}O_7$ requires: C, 55·7; H, 4·3%). $\nu_{max.}$($CHCl_4$) 1724 (aromatic ester), 1732 (keto ester), and 1764 $cm.^{-1}$(ketone). $\lambda_{max.}$ 205; 282; 291 mμ (log. ε, 4·5; 2·7; 2·6) n.m.r. ($CDCl_3$) 1·68 (2H doublet J, 9 c.p.s.) 2·31 (1H quartet J, 9 c.p.s.); 60·5 (3H singlet) and 6·1 τ (6H singlet); n.m.r. (benzene) 6·4 (3H singlet) and 6·6 τ (6H singlet).

3:4-Dicarbomethoxyphthalide (153)

A mixture of the glyoxyllate trimethyl ester (102) (0·34 g., 1·2 m.moles) in acetic acid (10 ml.) was refluxed with zinc (1·21 g., 20·0 m.moles) for 3 hrs. The solution was cooled, taken up into ethylacetate (75 ml.) and washed with brine (6 x 25 ml.). The ethylacetate extracts were dried and evaporated yielding the phthalide (153) as a greyish semi-solid. Crystallisation from ethylacetate afforded 3:4-dicarbomethoxyphthalide as prisms m.p. 112-114° (200 mg., 66%). (Found: C, 57·4; H, 4·2. $C_{12}H_{10}O_6$ requires: C, 57·6; H, 4·0%), $\nu_{max.}$($CHCl_3$) 1724 (aromatic ester), 1740 (aliphatic ester) 1757 (lactone carbonyl) 1780 and 1790 $cm.^{-1}$ (Fermi resonance); n.m.r. ($CDCl_3$) 1·75 (2H split quartet); 2·3 (1H triplet J, 6 c.p.s.); 3·8 (1H singlet); 6·05 (3H singlet); 6·2 τ (3H singlet).

4-Carbomethoxyphthalide (154)

The diester (153) (110 mg.; 0·4 m.mole) in methanol (3 ml.) was added to a methanolic (2 ml.) solution of sodium methoxide from sodium (0·1 g., 4·5 mg. atoms) and the solution refluxed. After 16 hrs. the monoester (154) separated from the solution as colourless needles, m.p. 178-180° (43 mg., 53%) which were removed by filtration and washed with cold methanol (2 ml.). Recrystallisation from methanol afforded 4-carbomethoxyphthalide as colourless needles, m.p. 180-181°. (Found: C, 62·8; H, 4·6. $C_{10}H_8O_4$ requires: C, 62·5; H, 4·2%). $\nu_{max.}$ ($CHCl_3$) 1725 (aromatic ester); 1768 (lactone carbonyl) and 1790 cm.$^{-1}$ (Fermi resonance). $\lambda_{max.}$ 230; 282; and 290 mμ (log. ε, 4·0; 3·4; 3·5). n.m.r. ($CDCl_3$) 1·75 (2H split quartet); 2·32 (1H triplet); 4·4 (2H singlet); 6·0 τ (3H singlet).

Reduction of naphthalic anhydride

4% Sodium-mercury amalgam (58 g., 0·1 g. atoms of sodium) was added to a suspension of naphthalic anhydride (4 g., 0·02 moles) and sodium carbonate (8·5 g.; 0·08 moles) in water (200 ml.). The solution was refluxed and after 30 minutes the anhydride dissolved completely. Heating was continued for a further 16 hrs. The cooled solution was acidified with 6N hydrochloric acid affording a mixture of reduction products as a colourless amorphous solid m.p. 260-268° (3·4 g.), $\nu_{max.}$ (nujol) 1705, 1710, 3480 (broad) cm.$^{-1}$.

Methylation of the reduction products

A portion of the crude reduction products (915 mg.) in methanol (10 ml.) was allowed to stand for 2 hrs. with excess ethereal diazomethane. Evaporation gave a colourless oil (910 mg.) which on t.l.c. with 10% ethylacetate/petrol gave two spots (Rfs 0·4 and 0·5). The oil was absorbed from 10% benzene/petrol onto grade III* alumina (30 g.). Elution with 30% benzene petrol afforded the 1:4 dihydro ester (105) as a colourless semisolid which crystallised from benzene/petrol as colourless prisms, m.p. 57-58° (620 mg., 50% overall from naphthalic anhydride), $\nu_{max.}$(nujol) 1710 (aromatic ester) and 1735 $cm.^{-1}$ (saturated ester) n.m.r. ($CDCl_3$) 2·1 (1H multiplet); 2·7 (2H doublet); 3·95 (2H doublet J, 6 c.p.s.); 4·9 (1H quartet); 6·15 (3H singlet); 6·30 (3H singlet); 6·55 τ (2H triplet J, 3 c.p.s.): mass spec., molecular ion at m/e = 242; t.l.c. Rf. 0·5 10% ethylacetate petrol.

Further elution with 90% benzene petrol afforded a colourless semisolid (170 mg.; 14% overall) probably the tetrahydro compound (106). This resisted further purification. Mass spec. molecular ions at m/e = 244 (tetrahydro compound) and m/e = 240 (naphthalic acid diester). No significant U.V. adsorption.

2.2-Dicyanoethyl-3-carboxyindan-1-one (108)

Freshly distilled acrylonitrile (40·2 g., 0·73 mole) was added slowly with stirring over a period of 1 hr. to a solution of the carboxyindanone (107), monohydrate (58·7 g. 0·33 moles) and Triton B (140 ml., 0·37 moles) in peroxide free dioxan (170 ml.). Stirring was continued at room temperature for 3·5 hrs. The solution was taken up into ethylacetate (500 ml.), washed with 6N hydrochloric acid (5 x 75 ml.) and extracted into 10% sodium bicarbonate (6 x 100 ml.). The bicarbonate extracts were acidified with 6N hydrochloric acid and extracted into ethylacetate. Washing with brine, drying and evaporation of these extracts furnished the dinitrile (108) as a pale yellow solid m.p. 155-158° (73·4 g., 86%). Crystallisation from methanol gave colourless microprisms m.p. 160·5-162°. (Found: C, 68·0; H, 4·9; N, 10·1. $C_{16}H_{14}N_2O_3$ requires: C, 68·1; H, 5·0; N, 9·9%), $\nu_{max.}$(nujol) 1675 (carboxyl); 1725 (benzylic ketone); 2280 (nitrile); and 3180 cm.$^{-1}$; n.m.r. (in CF_3CO_2H), 2·1 (multiplet, 4H), 5·4 (singlet, 1H) and a multiplet (8H) characterised by signals at 7·29, 7·38, 7·48, 7·56, 7·62 and 7·68 τ.

Esterification with diazomethane afforded the corresponding methylester (109) as a colourless oil, $\nu_{max.}$($CHCl_3$) 1716 (indanone) and 1741 cm.$^{-1}$ (methyl ester).

Hydrolysis and esterification of the dinitrile (108) to the trimethyl ester (110).

The dinitrile (46·6 g., 0·16 mole) was added to dry methanol (1·5 litres) saturated with dry hydrogen chloride (700 g.) and the solution stirred and refluxed for 12 hrs. The solution was evaporated to 200 ml. A little ammonium chloride separated out. Water (300 ml.) was added and the product extracted into ethylacetate (5 x 150 ml.). The extracts were thoroughly washed with 10% sodium bicarbonate (5 x 100 ml.) and brine (4 x 100 ml.), dried and evaporated giving the trimethyl ester (110) as a colourless, viscous oil, b.p. 210-212°, 0·4 mm. (50·5 g., 85%), $n_D^{23·5}$ 1·5288, $\nu_{max.}(CHCl_3)$ 1719 (indanone) and 1737 $cm.^{-1}$ (methyl esters), n.m.r.($CDCl_3$) expected aromatic multiplet centred at 2·4 τ, also signals at 5·92 (singlet, 1H), 6·2 (singlet, 3H), 6·4 (singlet, 6H). Mass spectral peak at m/e 362 (molecular ion)

Dieckmann cyclisation of the triester (110) to the β-keto ester (111)

The acid free triester (50·o g., 0·14 moles) in dry benzene (400 ml.) was added to dry sodium methoxide (from 9·7 g., 0·42 g. atoms of sodium) and the mixture refluxed under nitrogen for 2 hrs. The mixture was acidified with 5% hydrochloric acid and extracted into ethylacetate (5 x 200 ml.). Any acidic

material was extracted into 5% sodium bicarbonate (6 x 100 ml.) and the ethylacetate washed with brine. Evaporation of the dried solution gave the β-keto ester (111) as a light brown oil (29·4 g., 64%), $\nu_{max.}(CCl_4)$ 1675, 1720 and 1743 $cm.^{-1}$. The β-keto ester was shown to be contaminated with starting triester (10%) using t.l.c. (Rf, 60% ethylacetate/petrol, 0·45). A greyish purple ferric chloride colouration was obtained. Further purification proved impossible as the material decomposed on alumina and silica columns and at temperatures above 70°C. Repeated attempts to crystallise the viscous oil failed. $\lambda_{max.}$(EtOH) 210 and 248 mμ (log. ε, 4·71 and 2·40) $\lambda_{max.}$(EtOH + Dil. NaOH) 210, 247 and 288 mμ (log. ε, 5·40, 2·40 and 4·33).

The bicarbonate extracts were acidified with 6N hydrochloric acid (200 ml.) and extracted into ethylacetate (6 x 75 ml.). Washing with brine, drying and evaporation of these extracts afforded an acidic light brown oil (17·0 g., 36% based on a $C_{17}H_{16}O_5$ acid), $\nu_{max.}$(nujol) 1685, 1700, 1720 and 1740 $cm.^{-1}$, $\nu_{max.}(CCl_4)$ 1717 and 1743 $cm.^{-1}$. Treatment of the crude product with diazomethane afforded a mixture of methyl esters. t.l.c. examination revealed the mixture to contain a minor amount of starting triester (110) and an ester which gave a grey ferric chloride colouration (Rf 0·6; 60% ethylacetate/petrol).

Hydrolysis of the β-keto ester (111)

The β-keto ester (111) (29·1 g.; 0·088 moles) was refluxed for 1 hr. with glacial acetic acid (90 ml.), concentrated hydrochloric acid (180 ml.) and water (18 ml.). The cooled solution was taken up into ethylacetate (6 x 100 ml.) and the extracts thoroughly washed with brine. Drying and evaporation afforded the spiroacid (112) as a light brown solid m.p. 120-132° (20·8 g., 92%). $\nu_{max.}$(nujol) 1685, 1720 and 3200 cm.$^{-1}$ (broad).

Esterification to the Spirodiketo ester (113).

The crude acid (112) (20·8 g., 0·081 m.) in methanol (50 ml.) was allowed to stand with excess ethereal diazomethane for 2 hrs. The resulting solution was washed with brine, dried and evaporated, yielding the spirodiketo ester (113) as a pale yellow solid m.p. 84-87° (19·8 g., 91%). Crystallisation from methanol afforded colourless microprisms m.p. 89·5-91°C. (Found: C, 70·6; H, 5·9. $C_{16}H_{17}O_4$ requires: C, 70·3; H, 6·0%). $\nu_{max.}$($CHCl_3$) 1717, 1735 and 1741 cm.$^{-1}$ n.m.r. (CCl_4) signals at 2·3 (multiplet 4H), 6·4 (singlet 4H) and 7·8 τ (multiplet 8H) n.m.r. (benzene) resolves 6·4 signal into signals at 6·65 (singlet 3H) and 6·8 τ (singlet, 1H).

Hydrolysis and methylation of the Dieckmann Acidic Product.

Hydrolysis and esterification of the acidic product obtained from Dieckmann cyclisation of the triester (110) affords a product identical in all respects to the spirodiketo ester (113).

Reduction of the Spirodiketo ester (113).

Sodium borohydride (38 mg.; 1 m.mole) was added in small portions to a stirred solution of the diketone (113) (1·08 g.; 4·0 m.moles) in methanol (10 ml.) over a period of 10 mins. Stirring was continued for a further 15 mins. The complex was decomposed with 3N hydrochloric acid (10 ml.) and the products extracted into ethylacetate (4 x 15 ml.). Washing with brine drying and evaporation afforded a pale green oil (915 mg.). T.L.C. examination (40% ethylacetate/ petrol) revealed starting material (Rf 0·43) and two products Rf 0·72 and Rf 0·17. Distillation did not effect a separation. Preparative t.l.c. afforded the two products as colourless oils, unstable to distillation, The product Rf 0·17 (300 mg.) was possibly the monohydroxyl compound (114), $\nu_{max.}(CCl_4)$ 1715, 1741, 3586 and 3616 $cm.^{-1}$. Dilution had no effect on the positions or intensities of the hydroxyl absorptions, mass spec. molecular ion at m/e 274.

The product Rf 0·72 (320 mg.) was possibly the diol (115), $\nu_{max.}(CCl_4)$ 1718 (shoulder) 1742, 3468, 3581, and 3610 $cm.^{-1}$ no change on dilution.

Formation of the oxime (116) of the spirodiketo ester (113).

A mixture of hydroxylamine hydrochloride (412 mg., 5·9 millimoles) and sodium acetate (610 mg.; 6·1 millimoles) was dissolved in a minimum volume of water (2 ml.) and methanol (20 ml.) added to the solution. Sodium chloride was removed from the solution by filtration. The spirodiketo ester (113) (1·05 g. 3·9 millimoles) in methanol (5 ml.) was added to the hydroxylamine solution and refluxed for 1 hr. The solution was evaporated to 5 ml. and taken up into ethylacetate (30 ml.). The ethylacetate solution was washed with brine (3 x 15 ml.) dried and evaporated affording the oxime (116) as a light brown oil (1·10 gm., 100%) homogeneous on t.l.c. (Rf 0·45 in 60% ethylacetate/petrol). $\nu_{max.}(CCl_4)$ 1717, 1743 and 3592 $cm.^{-1}$ (sharp). The product was unstable to heat and purification was by preparative t.l.c. Mass spec. molecular ion at m/e 287.

The product was taken up into ethylacetate (15 ml.) and extracted into 5% aqueous sodium bicarbonate (3 x 10 ml.).

The bicarbonate extracts were carefully acidified with 3N hydrochloric acid at 0° and extracted with ethylacetate (3 x 10 ml.). The organic extracts were washed with brine (3 x 5 ml.), dried and evaporated affording a colourless solid m.p. 145-150°. $\nu_{max.}$(nujol) 1720, 1742, 3350 $cm.^{-1}$ (broad). mass spec. molecular ion at m/e 273. T.l.c. examination showed elongated spot at Rf 0·23 (60% ethylacetate/petrol).

Cis-1-carboxy-3-hydroxyindane (117).

Sodium borohydride (1·29 g., 0·03 moles) was added in portions, over 30 mins., to a stirred solution of the carboxyindanone (100) monohydrate (16·3 g., 0·082 moles) in 10% sodium carbonate (250 ml.). The solution was stirred for a further 30 mins., and washed with ethylacetate (2 x 100 ml.). The aqueous solution was acidified with 6N hydrochloric acid (250 ml.) and extracted with ether (4 x 250 ml.). The ethereal extracts were washed with brine, dried, and evaporated affording a mixture of carboxyhydrindols as a colourless solid (15·07 g., 97%) m.p. 117-132°. Fractional crystallisation from chloroform afforded the cis hydroxyacid (117) as fine needles (13·1 g., 85% overall) m.p. 131-133°. (Found: C, 67·25; H, 5.55 $C_{10}H_{10}O_3$ requires: C, 67·4; H, 5·65%).

Cis-1-carbomethoxy-3-hydroxyindane (118).

The cis-hydroxyacid (117) (1·78 g., 0·01 moles) in methanol (5 ml.) was allowed to stand with an excess of ethereal diazomethane for 2 hrs. The solution was dried and evaporated and the residue crystallised from chloroform/petroleum ether affording cis-1-carbomethoxy-3-hydroxyindane (118) as colourless needles (1·88 g., 100%) m.p. 95-97°. (Found: C, 68·4; H, 6·2. $C_{11}H_{12}O_3$ requires: C, 68·5; H, 6·3%). $\nu_{max.}$(in $CHCl_3$) 1728, 1742, 3498, 3590 and

3610 $cm.^{-1}$ (no change on dilution); mass spectral peaks at m/e 192 (molecular ion, M); 174 ($M-H_2O$); 160 ($M-CH_3OH$)

Indane-1-oic acid (119).

Concentrated hydrochloric acid (2·5 ml.) and water (73 ml.) were added to a mixture of mercuric chloride (1·0 g.) and granulated zinc (50 g.). The matrix was swirled for 1 minute and the supernatant liquors decanted. The keto acid (107) (13·5g.; 0·07 moles) in toluene (50 ml.) was added to the amalgamated zinc and refluxed for 6 hrs. with concentrated hydrochloric acid (90 ml.) and water (38 ml.). Further portions of concentrated hydrochloric acid (6 x 25 ml.) were added after 30 mins. and every hour thereafter. The cooled solution was neutralised with 6N sodium hydroxide and re-acidified with 6N hydrochloric acid till just acid to congo red paper. The solution was extracted with ethylacetate (6 x 100 ml.) and the extracts washed thoroughly with brine. The extracts were evaporated to 100 ml. and extracted with sodium bicarbonate (5 x 20 ml.). The bicarbonate extracts were acidified with 6N hydrochloric acid and extracted into ethylacetate (5 x 20 ml.). The extracts were washed thoroughly with brine, dried and evaporated, affording the desired indanoic acid (119) as a pale yellow oil (9·28 g., 84%) which was purified by dissolving in petroleum ether

(20-40° fraction) and subsequent evaporation. This afforded the acid (8·92 g., 79%) as colourless needles m.p. 54-57°C. Crystallisation from diethyl ether gave colourless needles m.p. 57-57·5° (lit value 54°).

Methyl indan-1-oate (120)

An excess of ethereal diazomethane was added to an ethereal solution (20 ml.) of the indanoic acid (119) (2·26 g., 1·23 m.moles) and the mixture left standing at room temperature for 1 hr. The solution was filtered, dried and evaporated, affording the corresponding methyl indanoate (120) (2·21 g., 97%) as a pale green oil b.p. 62-64° (0·5 mm.), $\nu_{max.}$ (in CCl_4) 1744 $cm.^{-1}$, n.m.r. (in CCl_4) signals at 2·9 (4H multiplet), 6·05 (1H, triplet, J = 8 c/s), 6·35 (3H, singlet), 7·0 (2H quartet) and 7·65 τ (2H multiplet).

Indan-1-oyl chloride (121)

Oxalyl chloride (2 ml.) was added to a solution of indanoic acid (2·52 g., 1·38 m.moles) in dry benzene (5 ml.) and the solution stirred for 1 hr. A further portion of oxalyl chloride (1 ml.) was added and stirring continued for a further period of ½ hr. The solution was evaporated to dryness leaving a brown oil. Distillation afforded the indanoyl chloride (121) (2·45 g., 91%) as a light brown oil b.p. 68-67° (0·07 mm.), $\nu_{max.}$ (liquid film) 1785 $cm.^{-1}$.

Indanoyl isothiocyanate (122)

A mixture of indanoyl chloride (0·92 g., 5·1 m. moles) and dry lead thiocyanate (725 mg., 5·1 m.moles) was stirred and refluxed in dry benzene (20 ml.) for 10 hrs. The cooled mixture was filtered twice to remove the traces of finely divided solid. The solvent was removed under vacuum and the residue distilled in vacuo just prior to use. This afforded the indanoyl isothiocyanate (121) as a light yellow liquid (755 mg., 75%) b.p. 62-64° (0·05 mm.), $\nu_{max.}$ (liquid film) 1720 and 2000 $cm.^{-1}$.

Indan-1;7-dicarboxylic acid (123)

The isothiocyanate (121) (735 mg., 3·6 m.moles) in S-tetrachloroethane (1 ml.) was added in two portions over a period of 5 mins. to a suspension at 0° of anhydrous powdered aluminium chloride (1·0 g., 8 m.moles) in S-tetrachloroethane (15 ml.). An orange complex formed and this was stirred at 0°C for 1 hr. The mixture was then refluxed for 2 hrs. The complex was cooled at 0° and carefully decomposed with 2N hydrochloric acid. s-Tetrachloroethane was removed by steam distillation leaving a black suspension of presumably 4:5 ethano-1-thio-1:3-(2H, 4H)-isoquinoline-dione (188). The isoquinoline or thiomide was removed by

filtration and taken up into dimethyl sulphoxide (30 ml.) and reprecipitated as a dark green amorphous solid by addition of water (200 ml.). The thiomide was added to a 25% solution of potassium hydroxide (70 ml.) and refluxed for 15 hrs. The cooled solution was filtered acidified with concentrated hydrochloric acid and extracted into ethylacetate (5 x 20 ml.). The acidic products were extracted into 10% sodium bicarbonate, the base extracts acidified with 6N hydrochloric acid and extracted with ethylacetate. The extracts were combined, washed thoroughly with brine dried and evaporated affording indane-1:7-dicarboxylic acid (123) (230 mg; 33%) as a brown oil. The oil was allowed to stand with excess ethereal diazomethane for 1 hr., the solution dried and evaporated affording the corresponding dimethyl ester (124) as a brown oil (270 mg.). This was almost homogeneous on t.l.c. examination (Rf. 0·6, 30% ethylacetate-petrol). A portion of this oil was purified on a preparative t.l.c. using 5% ethylacetate-petrol. This afforded 1:7-dicarbomethoxyindane as colourless prisms m.p. 84–86° (Found C, 66·8; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%) $\nu_{max.}$ (in $CHCl_3$) 1740 (aliphatic ester), 1722 $cm.^{-1}$ (aromatic ester) n.m.r. signal at 2·25 (1H, atomatic multiplet), 2·75 (2H, aromatic multiplet), 5·55 (1H multiplet), 6·2 (3H, aromatic ester), 6·4 (3H, aliphatic ester), 7·1 (2H, multiplet), 7·7 τ (3H, multiplet).

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