SYNTHETIC STUDIES IN THE SESQUITERPENE FIELD.

ROBERT RAMAGE

THESIS

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SUMMARY.

Part I:

The synthesis of (±) cuparene and (±) cuparenic acid was achieved starting from 3-methylcyclohex-2-enone. A Friedel Crafts reaction with toluene gave 3-methyl-3-p-tolylcyclohexanone. The mono-furfurylidene derivative of this ketone was bis-alkylated to give 2-furfurylidene-5:6:6-trimethyl-5-p-tolylcyclohexanone which was subjected to ozonolysis, cyclization, and reduction to give (±) cuparene which was then oxidized to (±) cuparenic acid.

Two unsuccessful synthetic approaches to cuparene are also described. Acid treatment of an α - ketol, 3:3 dimethyl-2-hydroxy-2-p-tolylcyclopentanone, brought about a novel 1:2-hydride shift leading to 4:4-dimethyl-5-p-tolylcyclopentenone.

The mechanism of enol-chloride formation of unsymmetrical cyclohexan-1:3-diones is also discussed.

Part II:

A novel approach to the spiro-[5:4]-decane system encountered in acorone was undertaken by 1:4 addition of acetylenic Grignard reagents to the cyclohexylidene malononitrile system. The ethynyl dinitriles, so formed, were found to undergo basic internal hydration.

Construction of the spiro system was effected by an internal Michael cyclization of ethyl 5-(4-methyl-3-oxo-

[over]

cyclohexenyl)-3-oxo-hexanoate. The product of this cyclization was elaborated to the gross structure of acorone.

I wish to express my thanks to Professor R. A. Raphael and Dr. W. Parker for their help and advice during the past three years. Their interest and guidance have been a constant source of encouragement to me

I also wish to thank the Department of Scientific and Industrial Research for a maintenance award. My thanks are also due to Mr. J. M. L Cameron and Dr. R. I. Reed of Glasgow University for microanalyses and mass spectrometric determinations. It is also a pleasure to acknowledge the help given by Mr. G. Milmine.

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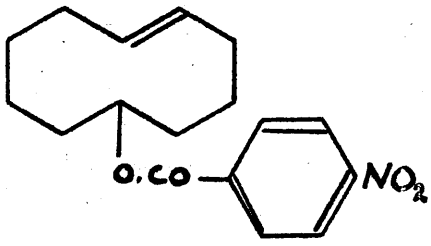

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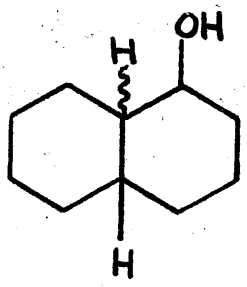

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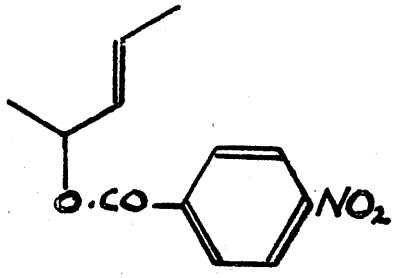

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INTRODUCTION.

In recent years structural investigations in the sesquiterpene field have furnished a series of compounds which, although of intrinsic interest, also, constitute a challenge to the present theory of sesquiterpene biogenesis.[1,2] According to this theory, the carbon skeleton of most sesquiterpenes can be derived from the farnesol chain* by enzyme-catalysed cyclizations. The mechanism of these cyclizations may be considered to involve displacement of the allylic hydroxyl, or a derivative thereof, by the π - electrons of one of the double bonds to give the carbonium ions (7 - 12), via the non-classical ions (4 - 6). Confirmation of the existance of such double bond - hydroxyl interactions is to be found in the relative rates of solvolysis[3] of <u>trans</u> - 5 - cyclodecen - 1 - yl p - nitrobenzoate (13) and $\alpha:\gamma$ - dimethylallyl p-nitro benzoate (14). It was found that (13) solvolysed ten times more rapidly than (14) to give a mixture of <u>cis</u> and <u>trans</u> decal - 1 - ol (15).

* Although natural farnesol is a complicated mixture of double bond isomers, it is assumed that the central double bond in the farnesol precursor is <u>trans</u>. The allylic double bond may be <u>cis</u> (1) or trans (2), since isomerization is possible via anionotropic rearrangement of nerolidol (3).

There are two possibilities for each of the biogenetic cyclizations, but the steric and electronic stabilities of the alternatives will determine which cation is preferred. Consideration of each cyclization will serve to illustrate the genesis of apparently unrelated sesquiterpenes, in particular those sesquiterpenes whose structures have been determined since the noteworthy publication of Hendrickson. In fact, it is our contention that the time is now ripe for a new classification of sesquiterpenes based on the well - tested theory of their biogenesis. (See chart.)

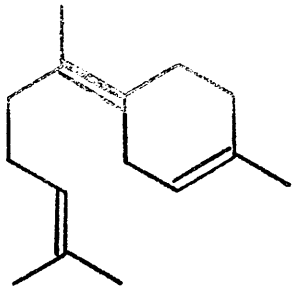
Sesquiterpenes derivable from (7).

Only in the cyclization of cis farnesol (1) can the central double bond participate giving rise to either (7) or (8) ; the former being favoured on steric and electronic grounds. Indeed, all the monocyclic 6 - ring sesquiterpenes[4], with the exception of the elemane type, have a carbon skeleton corresponding to the ion (7). One of the most ubiquitous sesquiterpenoid hydrocarbons, α -bisabolene* (16) may be formed by deprotonation of the cation (7).

The cadinane** class of sesquiterpenes is thought to be derived from cyclization of bisabolane - type precursors.

* The in vitro conversion of nerolidol to bisabolene has been accomplished[5].

** This form of nomenclature is that suggested by Sorm[6].



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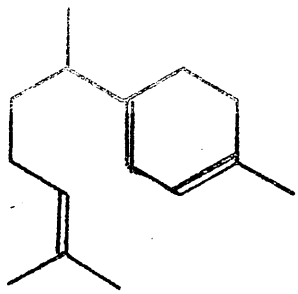

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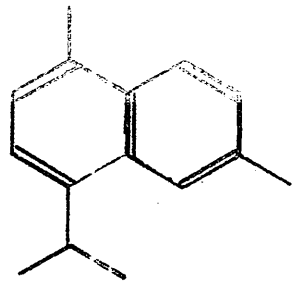

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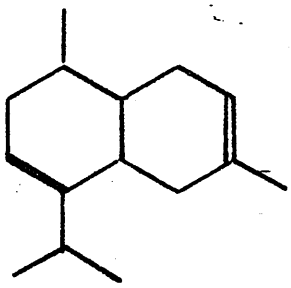

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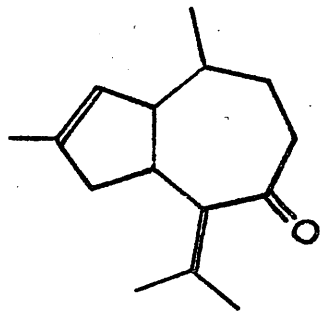

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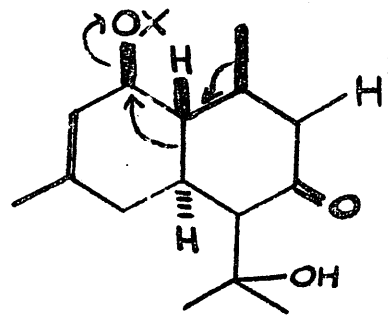

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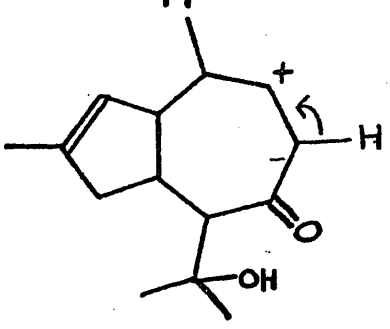

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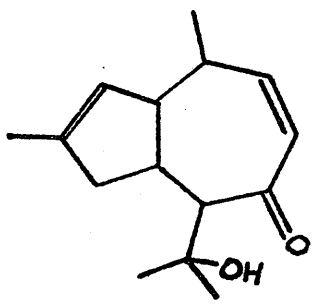

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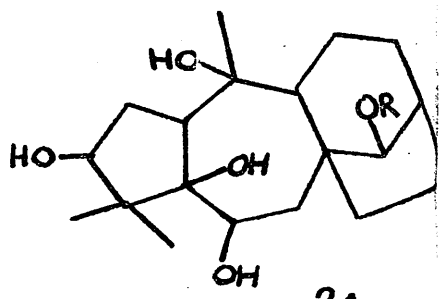

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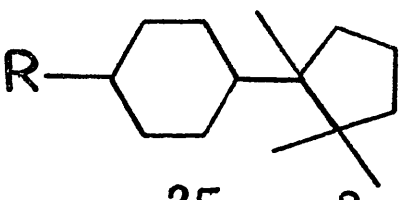
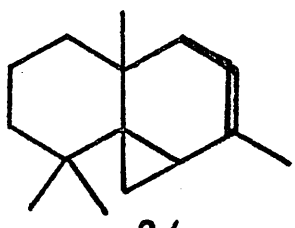


25 a, $R = CH_3$

b, R = COOH



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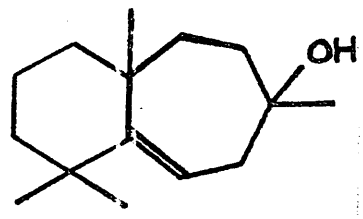

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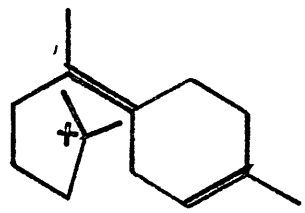

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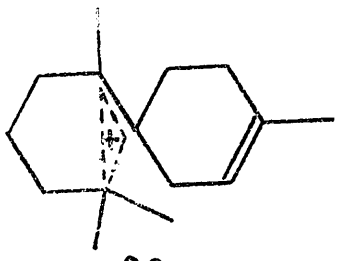
Sulphur dehydrogenation of zingiberene[7] (17) yields cadalene (18) and treatment of (17) with hydrogen chloride furnishes the dihydrochloride of iso - zingiberene[8] (19). Internal cyclisation of a cadinane precursor could obviously give rise to the copane tricyclic system.

The non - isoprenoid hydroazulene, zierone[9,10] (20) is the only member of its class of sesquiterpenes, which can be considered to be derived from a cadinane progenitor, such as (21). Displacement of the allylic oxygen function in (21), followed by migration of the central C - C bond with concomitant methyl migration would lead to the ion (22), and hence the $\alpha\beta$ - unsaturated ketone (23). The sesquiterpene would be formed by reduction of the more polar double bond followed by dehydration of the tertiary alcohol. The novel diterpene, grayanotoxin[11] (24) may be derived from the normal phyllocladene class by a ring A contraction of the above type.

Taxonomic investigations by Erdtman[12] have produced four new sesquiterpenes of unusual constitution, viz ; cuparene (25a), cuparenic acid (25b), thujopsene (26), and widdrol (27). Since both thujopsene and cuparene have been shown to occur together in nature, it is meaningful that the biogenetic theory predicts a common progenitor. Protonation of the trisubstituted acyclic double bond in bisabolene (16) would afford the tertiary carbonium ion (28), which could interact with the exocyclic double bond to yield



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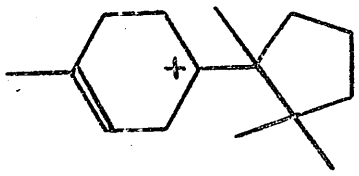

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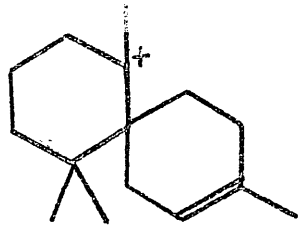

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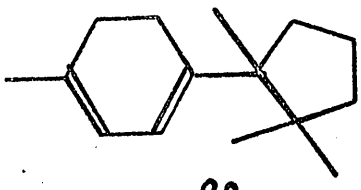

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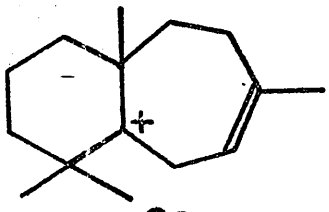

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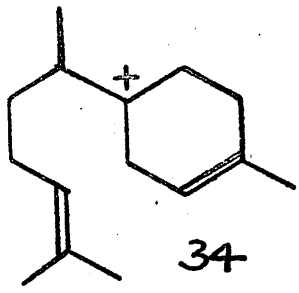

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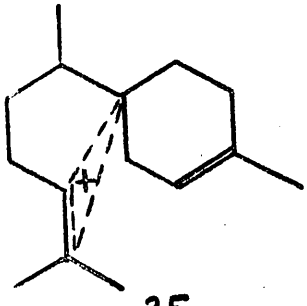

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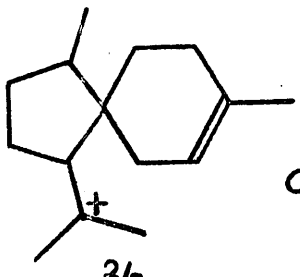

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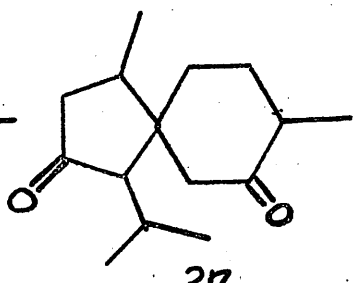

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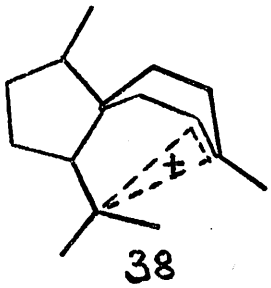

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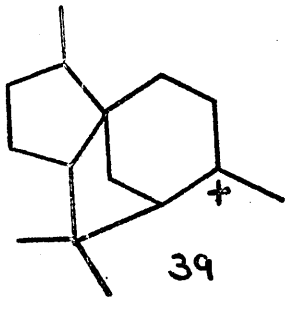

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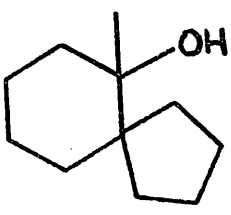
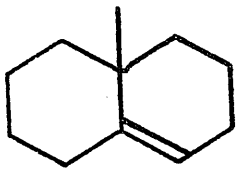


(i)



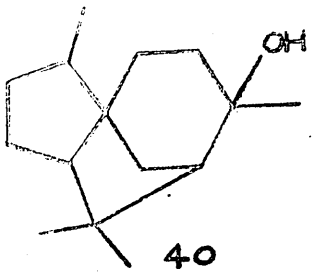
(ii)

the tertiary ions (30) and (31), presumably via the non-classical ion (29). Deprotonation of (30) would then give the sesquiterpene cuprenene[13] (32) which is the precursor of both cuparene (25a) and cuparenic acid (25b). The spiro carbonium ion (31) could rearrange[+] to furnish (33) from which both thujopsene (26) and widdrol (27) are derivable.

The carbonium ion (34) may be formed from (7) by a 1 : 2 hydride shift, which is permissible since both (7) and (34) are tertiary carbonium ions. In (34) the positive charge can only be neutralized by interaction with the acyclic double bond to give the electronically more stable bicyclic ion (36), via the bridged cation (35). It is then proposed that (36) is elaborated to the sesquiterpene, acorone (37)[*]. Subsequent interaction of (36) with the cyclic double bond would yield (39). The alternative tricyclic carbonium ion, formed from the intermediate (38), would be a secondary cation which could not be favoured unless there was some steric inhibition to the formation of (39). Solvent attack or deprotonation

[+] A close analogy of this rearrangement is the acid-catalysed solvolysis of the tertiary alcohol[14] (i) to give (ii).

[*] Rearrangement of a spiro system of the acorane type would result in the formation of the cadinane and laserpitane skeletal classes.



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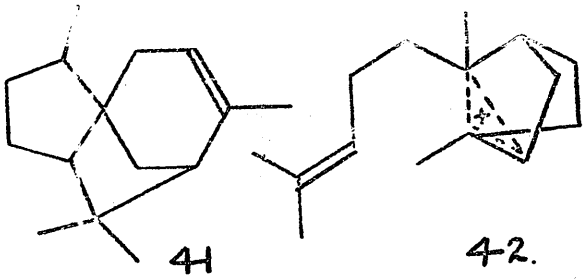

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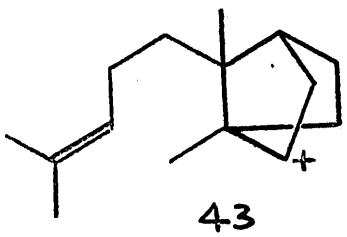

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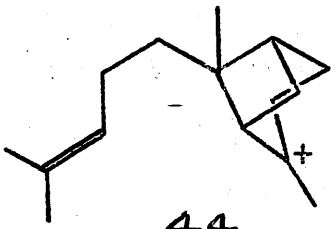

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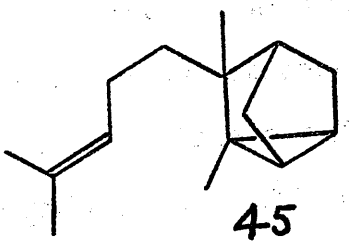

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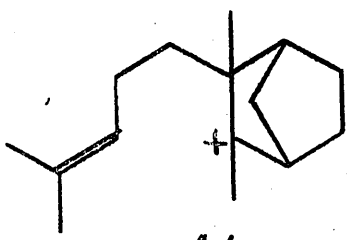

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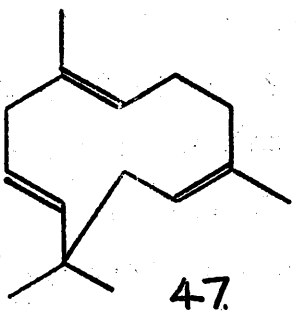

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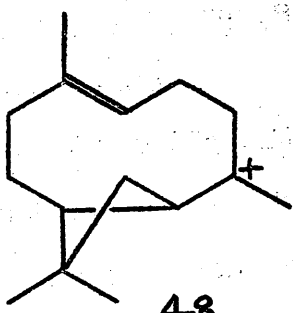

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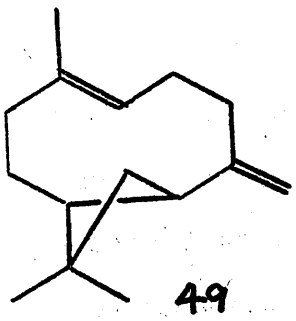

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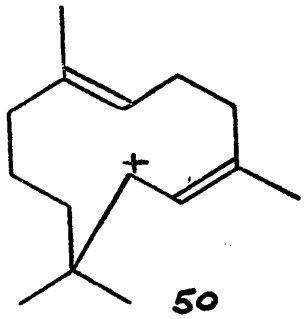
of (39)furnishes cedrol (40) or cedrene (41) respectively.

Interaction of the cyclic double bond with the cation (7) yields the bicyclic ion (43), rather than (44), via (42), i.e. steric considerations superseding the electronic control of cyclization. Further cyclization of (43) would furnish α - santalene (45). A Wagner-Meerwein bond migration in (43) would lead to the more stable carbonium ion (46) from which β -santalene may be obtained by deprotonation.

Sesquiterpenes derivable from (10).

Another group of sesquiterpenes may be obtained from the alternate cyclization of cis farnesol (1) involving the terminal double bond. Such a cyclization could give either (9) or (10) ; however the former is much more strained than the 11-ring carbonium ion and thus preference for the secondary ion infers steric rather than electronic control of the cyclization. Deprotonation of (10) affords not only the gross structure of the sesquiterpene, humulene (47), but also assigns the orientation of each double bond.

Double bond - carbonium ion interaction in (10) can only occur with the $\Delta^{2,3}$ bond, since the hydrogen atoms at C.1 shield the $\Delta^{6,7}$ bond from the positive centre. This interaction leads to the tertiary ion (48) which, by loss of a proton, yields caryophyllene (49), correct in stereochemical detail. Hendrickson[2] has pointed out that this is a direct consequence of the unique conformation of



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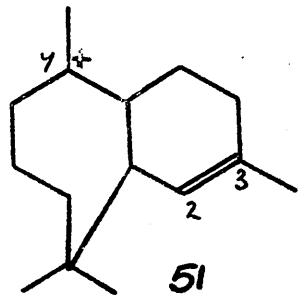

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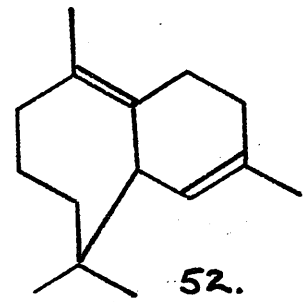

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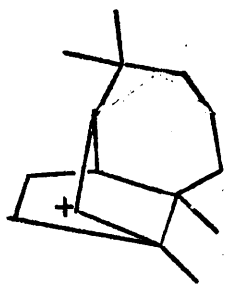

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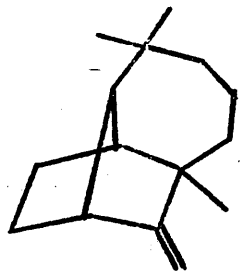

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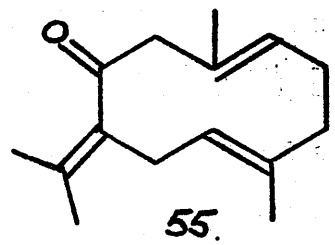

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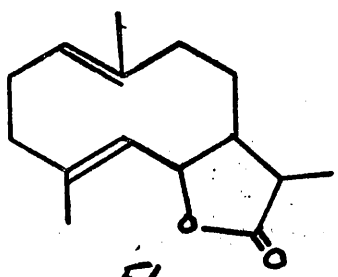


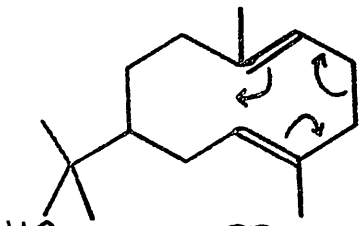
56.

the ion (10).

A 1 : 3 - hydride shift in (10) would eliminate the shielding effect of the hydrogen atoms at C.1 described above, thus allowing interaction between the newly formed cation at C.1 and the $\Delta^{6,7}$ bond to give (51) via (50). Deprotonation then yields himachalene[12] (52). The proximity of the positive charge at C.7 and the $\Delta^{2,3}$ bond in (51) should lead to the formation of a C.2 - C.7 bond. Although this is to be preferred on electronic grounds, it would lead to a highly strained four membered ring in a tricyclic system. Thus the preferred ion would be (53) which, after bond migration and deprotonation, gives the structure assigned to longifolene (54) by X-ray methods[15] and by synthesis[16].

Sesquiterpenes derivable from (12).

The cyclization of trans - farnesol by an ionic mechanism may give rise to ions (11) or (12) but steric, as well as electronic, requirements favour the tertiary ion (11). Deprotonation, followed by oxidation of (11) gives the structure of germacrone[17] (55). In fact all the sesquiterpene 10 - membered ring lactones, e.g. costunolide (56) may be derived from (11). All of these can undergo transannular cyclizations furnishing compounds of the cadinane, eudesmane and guaiane types thereby providing an alternative biogenetic pathway to these sesquiterpenes.



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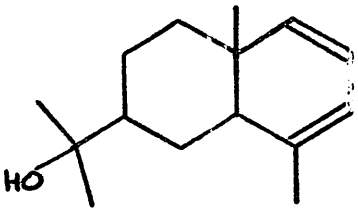

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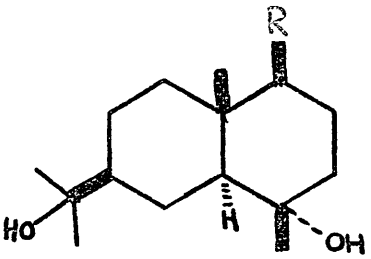

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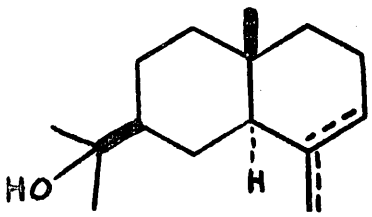

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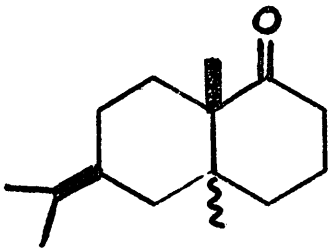

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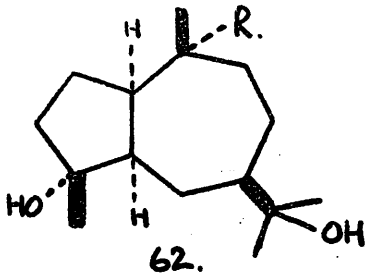
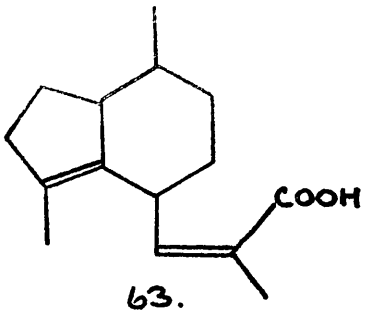


62.

Neutralization of (11) by solvent attack, followed by an internal cyclization and ring fission yields β - elemol[18] (58) via (57). Models of (57) show that both double bonds are ideally positioned for internal cyclizations yielding bicyclic structures. These cyclizations may be either simple acid - catalysed or oxidative in nature. If, during cyclisation, both double bonds are polarized according to the Markownikoff Rule then the product would be expected to be (59) with R = H for the acid - catalysed cyclization, or R = OH for an oxidative mechanism. The product (51), R = H is the obvious precursor of eudesmol[19] (60) and has the correct stereochemistry of the eudesmane group in all known cases[20]. The maaliane class may be derived from the eudesmane type by cyclization.

Jatamansone[21] (61) is the only known representative of its class of sesquiterpenes which could arise from a precursor, such as (59, R = H), by migration of the 4 - methyl group to the angular position.

Polarization of one double bond in (57) in an anti-Markownikoff manner would lead to the formation of the guaiane - type structure (62) which is thought to be the progenitor of the aromadendrane, patchoulane, and valerane types of sesquiterpenes. The aromadendrane and patchoulane classes arise by some form of cyclization, whereas valerenic



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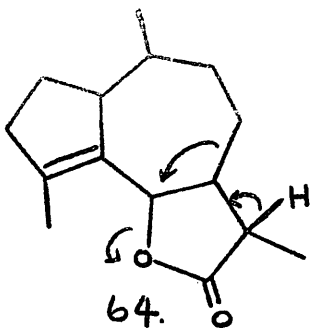

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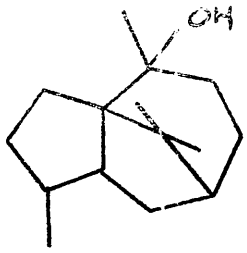

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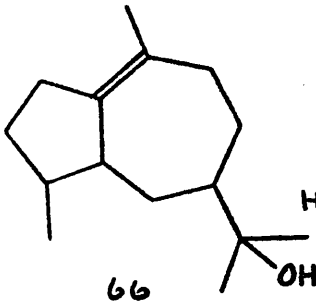

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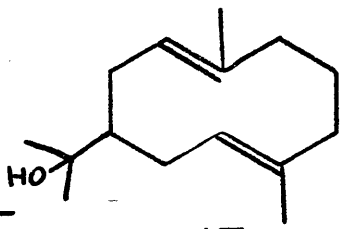

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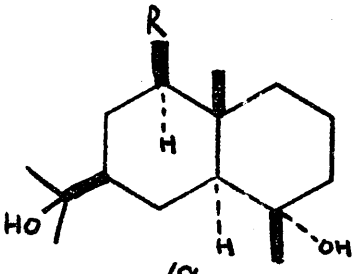

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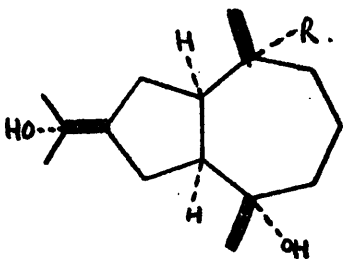

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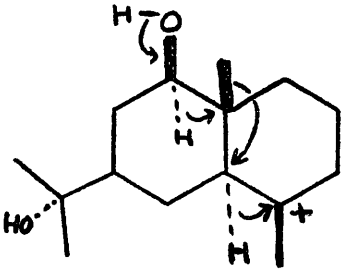

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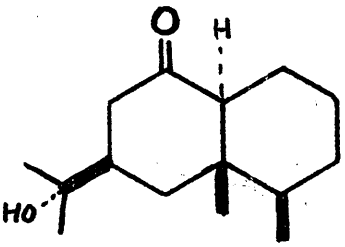

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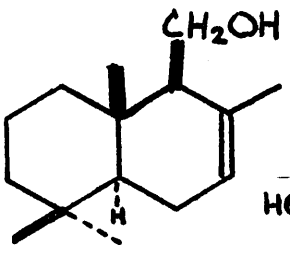

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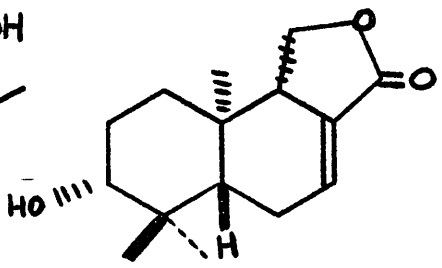


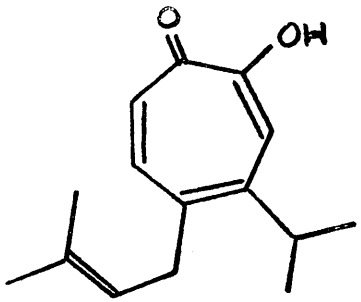
73.

acid[22] (63) could be derived by ring contraction of the guanolide (64). Patchouli alcohol[23] (65) may be derived by an ionic cyclization of bulnesol[24] (66), if the latter has the 7 β - isopropyl configuration, which is indeed predicted from the biogenetic consideration outlined above.

Similar concerted cyclizations could occur with the isomer (67), formed by double bond migration in (57) to give the structures (68) and (69). Consideration of (68, R =OH) reveals the presence of the correct stereochemistry for a multi - group rearrangement leading, via (70), to the ketol (71), which has both the general structure and correct stereochemistry of the known eremophilanes[25]. The structure (69) is the obvious antecedent of the vetivane and tricyclovetivane sesqui - terpenoids.

Concerted cyclization of trans - farnesol.

Trans - farnesol may also undergo a concerted acid or oxidative cyclization akin to that found in the biogenesis of the higher terpenes[26]. The sesquiterpenes, drimenol[27] (72) and iresin[28] (73) are two examoles of such cyclizations ; in fact, racemic drimenol has been formed in vitro by the acid - catalysed cyclization of trans - farnesol[29].



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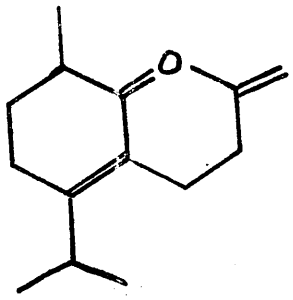

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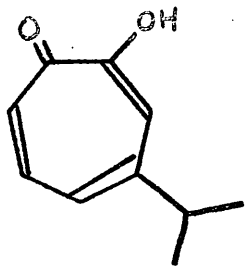

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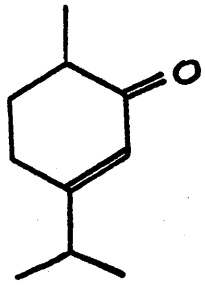
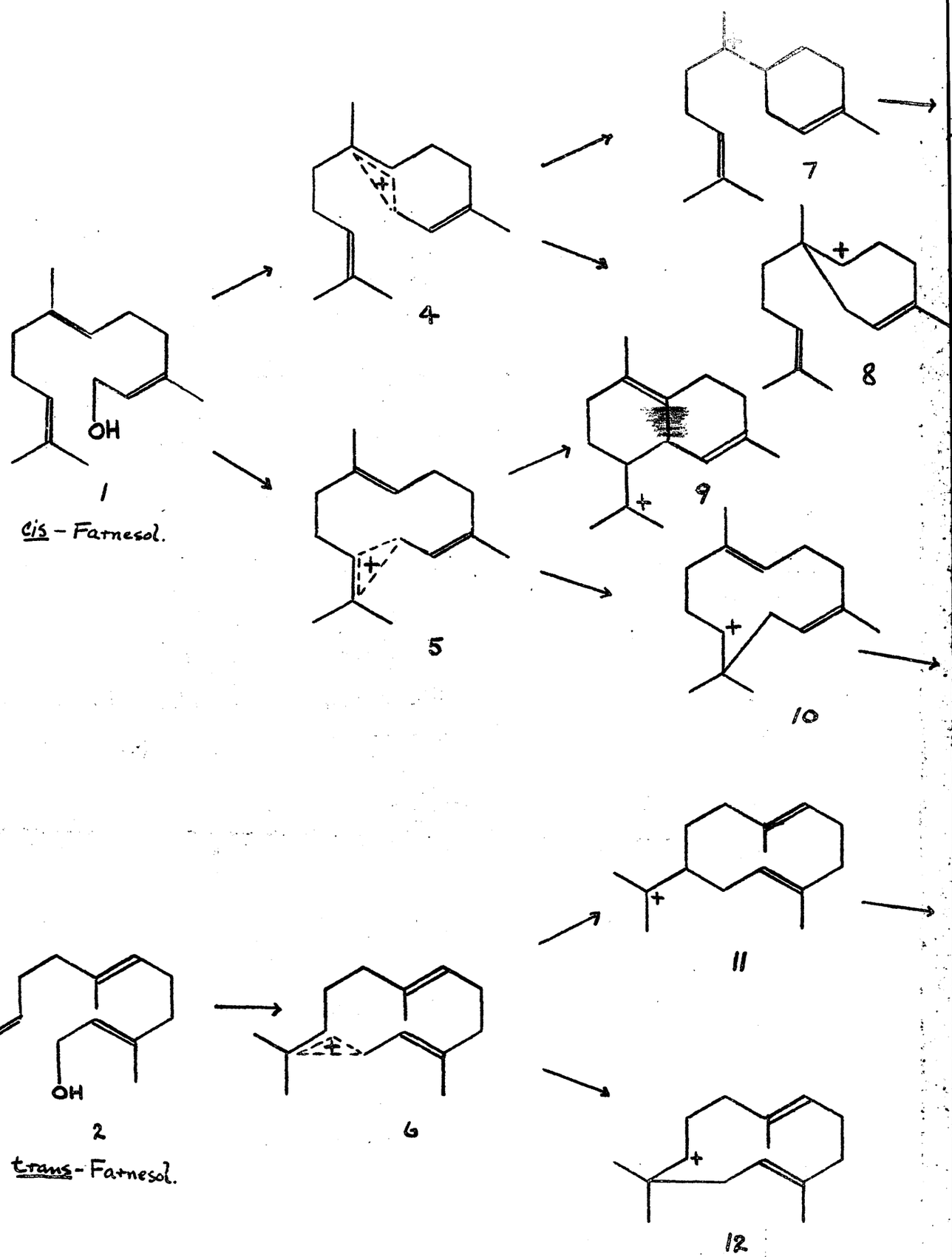


77.

Two sesquiterpenes, nootkatin[30] (74) and calacone[31] (75), which do not conform to the above classifications may be considered to be derived from the simple monoterpenes, β - thujaplicin (76) and carvenone (77) by the addition of a mevalonate unit at a later stage in the biogenesis[32].



Monocyclic

Bisabolane.

Bicyclic

Cadinane

Zietane.

Widdrane

Cupatane.

Acotane.

Laset pitane.

β-Santalane.

Tricyclic

Copane.

Thujopsane

Cedrane.

α-Santalane.

Humulane.

Himachalane.

Caryophyllane.

Longifolane.

Germacrane.

Eudesmane

Etemophilane.

Maaliane.

Elemane.

Jatamansane.

Vetivane.

Tricyclovetivane.

Guaiane.

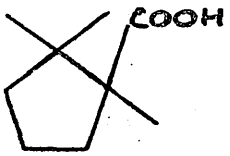
Valerane.

Aromadendrane.

Patchoulane.

PART I.

The Synthesis of (±) Guparene.



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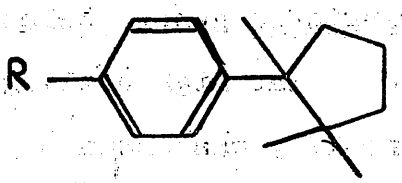


25, a $R = CH_3$

b $R = COOH$.

HISTORICAL.

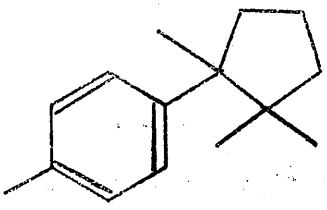
In 1958, Erdtman and Thomas[33] isolated two sesqui - terpene hydrocarbons, widdrene and"widdrene II", from the heartwood of Chamaecyparis thujoides, Biota Orientalis and various Widdringtonia genera belonging to the natural order Cupressaceae. The high boiling, dextrarotatory fraction, "widdrene II", was shown to contain about 60 per cent of an aromatic hydrocarbon, which was named cuparene, the structure of which was elucidated by Enzell and Erdtman[34].

The infrared and ultraviolet absorption spectra of the sesquiterpene showed the presence of a 1 : 4 disubstituted benzene nucleus ; in fact, the ultraviolet absorption was identical to that of p -tertbutyltoluene. The mass spectrum of cuparene not only confirmed the molecular weight of 202 but also showed a fragmentation pattern corresponding to the loss of four successive carbon atoms and a main peak due to the cleavage of a p -tolyl fragment.

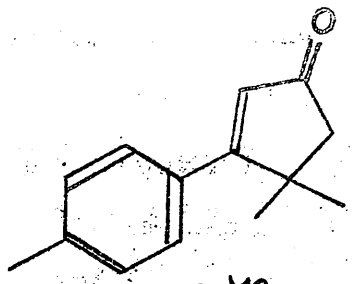
Oxidation of cuparene with dilute nitric acid yielded terephthalic acid ; thus confirming the presence of a 1 : 4 disubstituted benzene nucleus. Treatment of cuparene with ozone followed by alkaline hydrogen peroxide furnished D (+) - camphonanic acid (78). Erdtman and Thomas had earlier[33] reported the presence of a para - substituted benzoic acid, "acid III", in the Widdringtonia genus. Chromic

acid oxidation of cuparene afforded an acid, which was identical with "acid III" and the name cuparenic acid was proposed for this latter compound.

On the basis of these oxidative degradations, Erdtman and Enzell were able to propose the structures (25a) and (25b) for cuparene and cuparenic acid respectively. These formulations have now been verified by synthesis[35,36] of the racemic sesquiterpenes.



25a.



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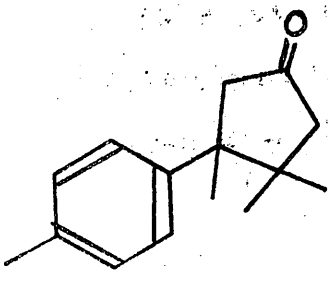

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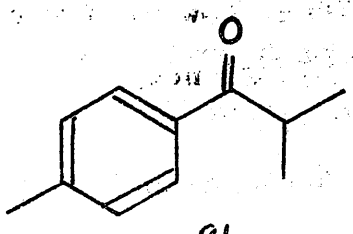

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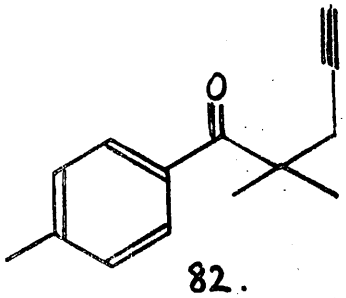

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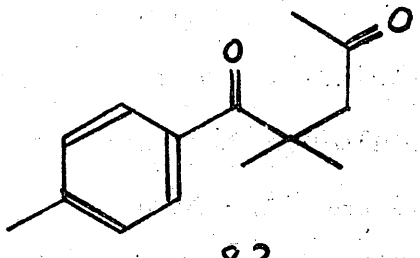

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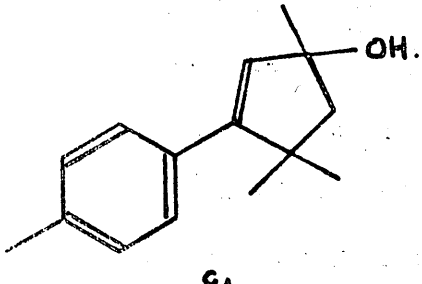


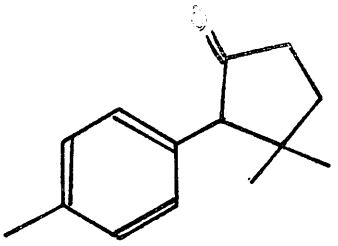
84.

DISCUSSION.

The synthesis of cuparene (25a) presents an interesting problem because of the high degree of substitution in the cyclopentane moiety which creates the maximum steric congestion possible in a tetrasubstituted five-membered ring.

The first approach envisaged the formation of the cyclopentenone (79), which on treatment with methyl - magnesium iodide, should give the cyclopentanone (80) by conjugate addition. Subsequent reduction of the carbonyl group in (80) would then afford (±) cuparene (25a). Alkylation of p -methylisobutyrophenone (81) with propargyl chloride furnished the ethynyl - ketone (82) which was smoothly hydrated[37] to the 1 : 4 diketone (83). This diketone was cyclized with aqueous potassium hydroxide to give 4 : 4 - dimethyl - 3 - p - tolylcyclopent - 2 - enone (79) which was treated with methylmagnesium iodide in the presence of 5 mole per cent cuprous chloride[38]. The product from this reaction was that resulting from a 1 : 2 attack of the Grignard reagent, viz. structure (84). The occurrence of a hydroxyl infrared absorption at 3350cm^{-1}, coupled with the disappearance of the phenyl - conjugated cyclopentenone band at 1680cm^{-1}, served to confirm this.

It was then decided to attempt the synthesis of 3 : 3 -



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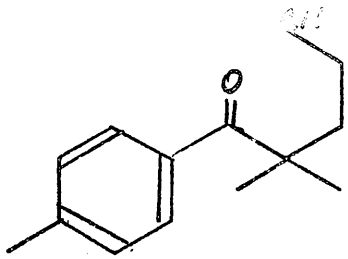

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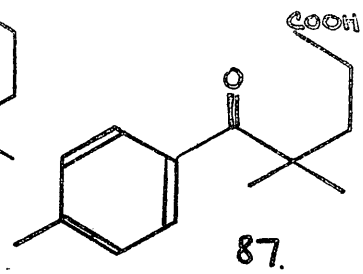

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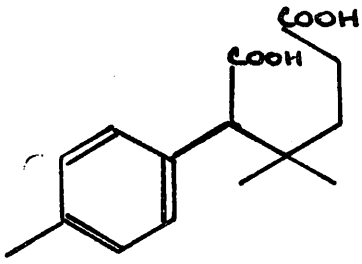

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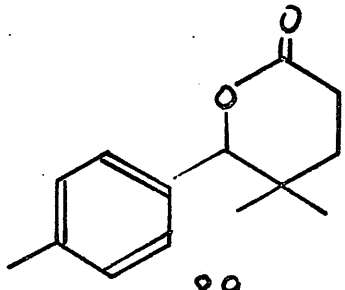

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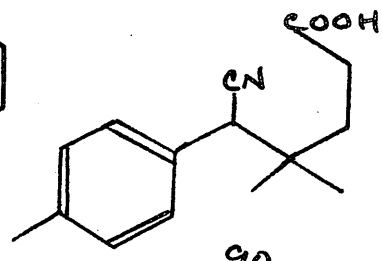

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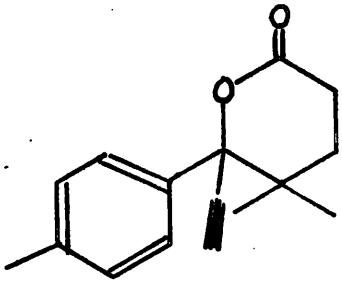

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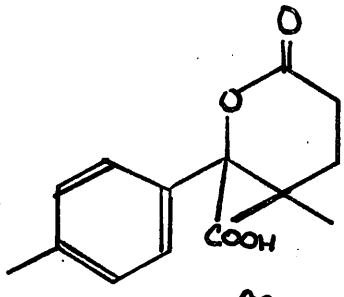

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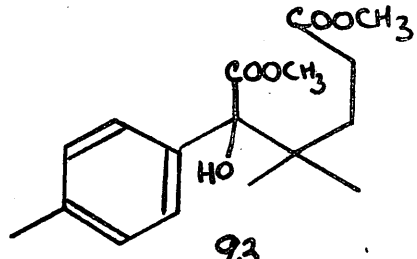

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dimethyl - 2 - p - tolylcyclopentanone (85) which could plausibly be expected to undergo facile methylation at the doubly activated position α to the carbonyl group. Cyanoethylation[39] of (81) followed by basic hydrolysis of the resulting keto - nitrile (86) gave the crystalline δ - keto - acid (87). It was hoped to convert this material into a substituted adipic acid (88) by introduction of a benzylic carboxyl group. The obvious method of achieving this is by conversion of the ketone function of (87) into the corresponding cyanhydrin[40]. All attempts at this reaction failed. Selective reduction of the ketone in (87) then gave the δ - lactone (89) which, however, did not yield the cyano - acid (90) by treatment with potassium cyanide [41].

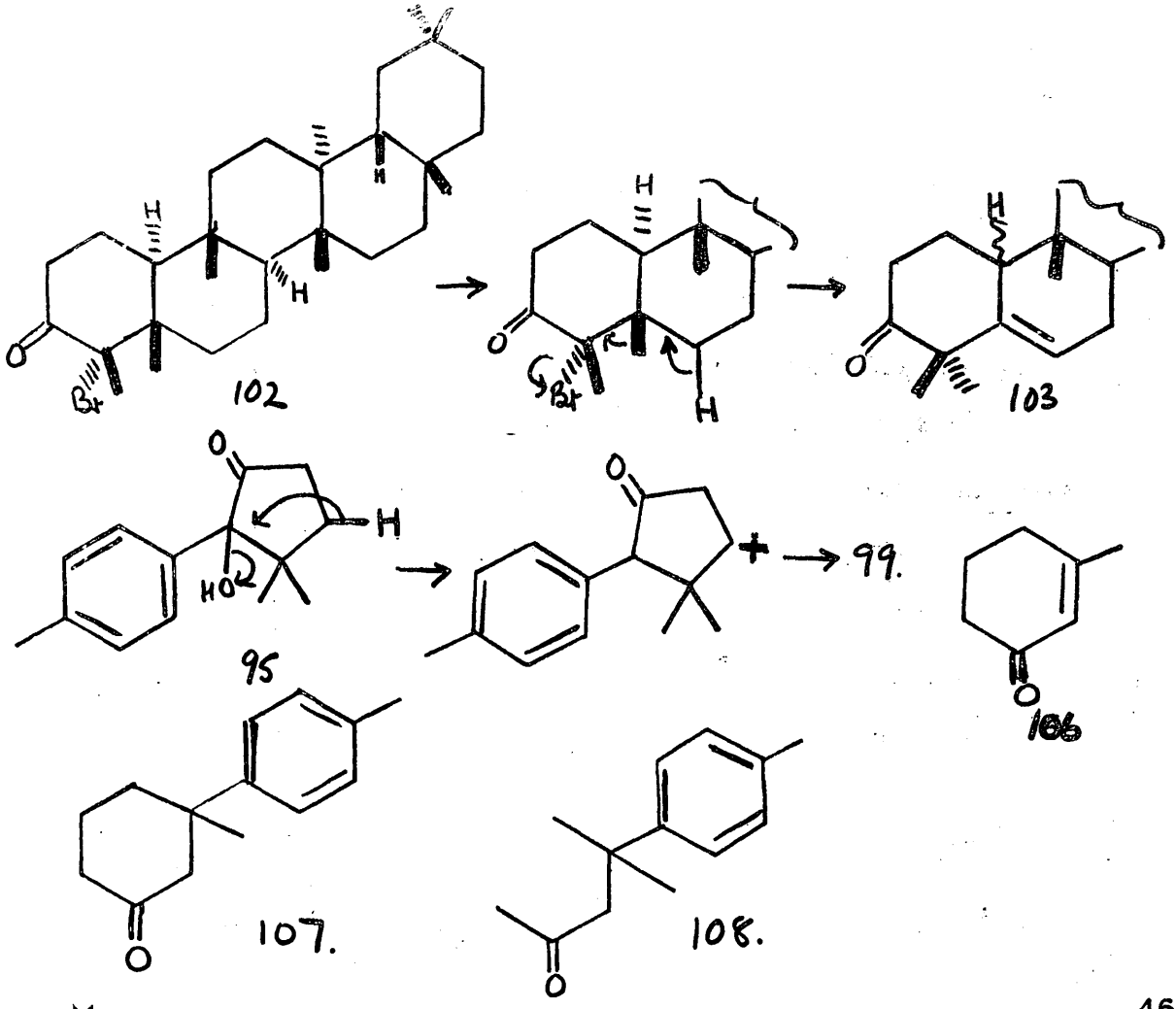
Treatment of (87) with sodium acetylide in either liquid ammonia or dimethylformamide[42] gave the corresponding ethynyl - alcohol which gave the acetylenic - lactone (91) on treatment with acetic anhydride and fused potassium acetate. Ozonolysis[43] then afforded the lactone - carboxylic acid (92) together with some keto - acid (87) formed by further oxidation of (92). Since attempted hydrogenolysis either of the lactone - acid (92) or its methyl ester produced variable and unsatisfactory results, it was decided to remove the benzylic hydroxyl at a later stage in the synthesis. Alcoholysis and esterification of (92) led to the hydroxy - diester (93) which, on

Dieckmann cyclization should furnish the ketol (95), after hydrolysis and decarboxylation of the intermediate β - keto - ester (94).

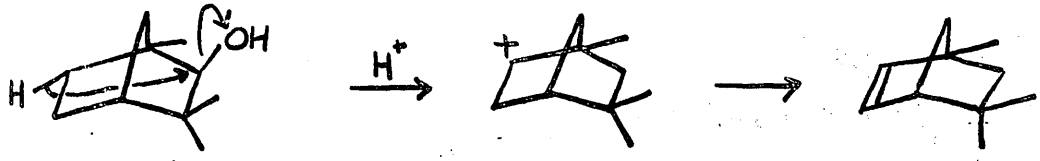
In order to find conditions for the hydrogenolysis of a system similar to (95), it was decided to use the hydroxy - keto - ester (96) as a model. This was formed in one step from (91) using the hydration technique of Raphael[37]. Hydrogenolysis at room temperature under 5 atmospheres pressure yielded the keto - ester (97).

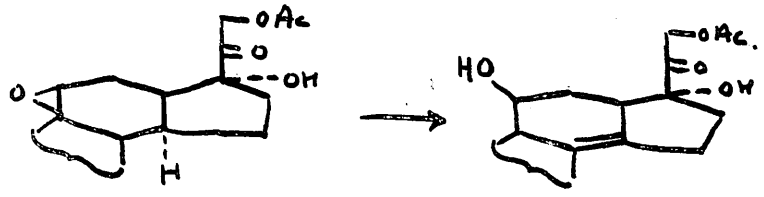
Having found conditions which would probably convert (95) to the desired cyclopentanone (85), the cyclization of (93) was undertaken. The intermediate β - keto - ester (94) was identified by the positive ferric chloride test and infrared spectrum. Hydrolysis and acid - catalysed decarboxylation of (94) did not yield the expected α- ketol (95). In fact, the compound isolated proved to be a conjugated cyclopentenone, which was thought to be either 4 : 5 - dimethyl - 5- p - tolylcyclopent - 2 - enone (98) or 4 : 4 dimethyl - 5 - p - tolylcyclopent - 2 - enone (99).

The former structure could be derived from (95) by the mechanism shown opposite. Two analogies of such a mechanism are to be found in the triterpene field, e.g. the formation of iso - α - amyradienonylacetate (101) from the 12 - keto - α -amyrin derivative (100) on treatment with selenium dioxide[44]; the rearrangement proceeding via the α- ketol as shown, and also the formation of



* 1:3 Hydride shifts were postulated as long ago as 1924[46] by Meerwein. A close analogy to the formation of (99) is the acid-catalysed dehydration of fenchol[47] (104), which is thought to involve the mechanism shown. Another example of a 1:3-hydride shift is the acid-catalysed opening of the oxide (105).



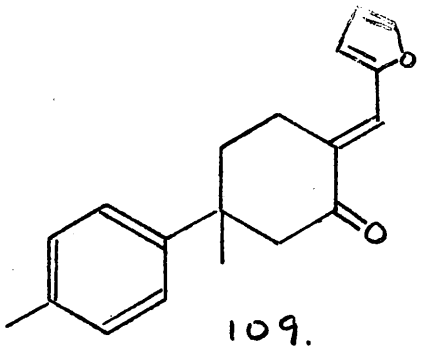


alnusenone (103) from α - bromofriedelin[45] (102). Both of these are examples of a methyl migration induced by a transient positive charge residing α to a carbonyl group.

Nuclear magnetic resonance measurements have shown, however, that the correct structure is in fact (99). The simplest explanation involves a 1 : 3 - hydride shift* neutralizing the temporary positive charge on the α - carbon atom. Deprotonation would then afford the cyclopentenone (99).

The successful synthesis of cuparene was achieved using the readily accessible 3 - methylcyclohex - 2 - enone[49] (106) as starting material. A Friedel - Crafts reaction with (106), toluene and aluminium chloride gave 3 - methyl - 3 - p - tolylcyclohexanone (107). Rigorous proof of the 1 : 4 orientation of the benzene nucleus in such a reaction had been obtained, in the analogous reaction between mesityl oxide and toluene, by oxidation of the product, 4 - methyl - 4 - p - tolylpentan - 2 - one (108) to give terephthalic acid[50]. Confirmation of the 1 : 4 disubstituted pattern in (107) was given by the infrared spectrum which exhibited a peak at 825cm^{-1} ; known to be typical of such a system.

Introduction of the gem - dimethyl grouping at the sterically hindered 2 - position in (107) was accomplished



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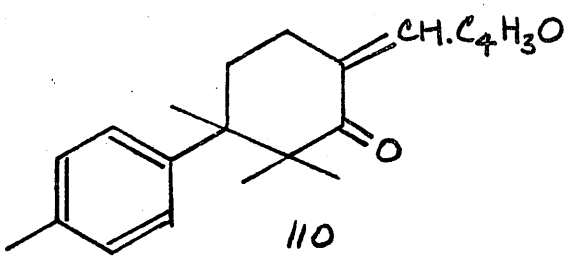

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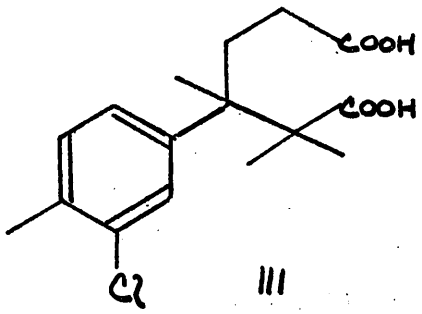

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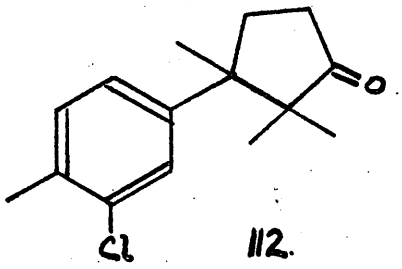


112.

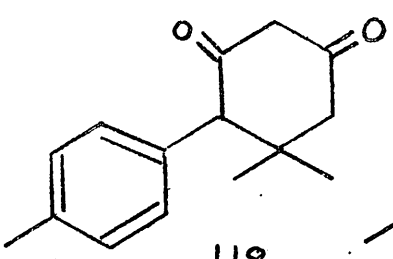
chlorine. This would seem to indicate the presence of the halogen in the aromatic nucleus. The aromatic chlorination was due to attack by Cl^+ derived from hypochlorous acid which would be formed from the mixture of hydrochloric acid and hydrogen peroxide used to decompose the ozonide.

The fact that the "open diester" (111) readily yielded a β - keto - ester which gave a positive $FeCl_3$ test and then the cyclopentanone (112), afforded proof of the structure of the furfurylidene derivative (109). If the furfurylidene derivative of 3 - methyl -3 - p - tolylcyclo hexanone had the structure (113), ozonolysis of the dimethyl compound (114) would furnish a ditertiary acid whose diester could not undergo a Dieckmann cyclization since there is not an active hydrogen atom α - to an ester function.

A second ozonolysis of (110), using a catalytic amount of 6N sulphuric acid, yielded the desired diacid (115) whose dimethyl ester cyclized smoothly in the presence of potassium tertbutoxide[51] in benzene to give the β - keto - ester (116). Hydrolysis and decarboxylation of the crude product gave 3 - p - tolyl - 2 : 2 : 3 -trimethylcyclopentanone (117) which had the expected molecular weight of 216.

Huang - Minton reduction of (117) then gave an oil which proved to be identical in infrared, ultraviolet and mass spectra with the natural sample of D(+) cuparene. Both natural and synthetic samples had the same retention times on

vapour phase chromatography. Oxidation of synthetic cuparene afforded racemic cuparenic acid, the infrared spectrum of which was superposable with that of natural D(+) cuparenic acid.



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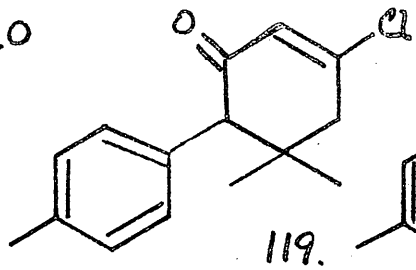

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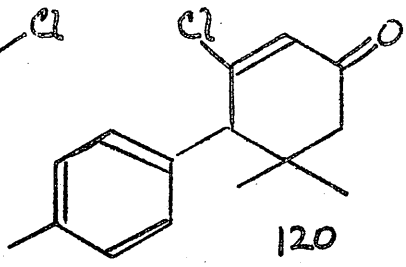

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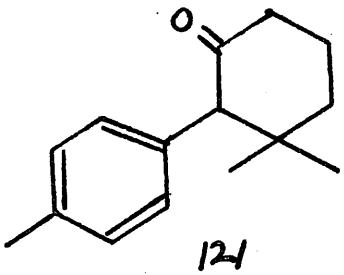

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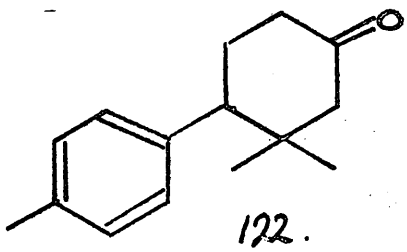

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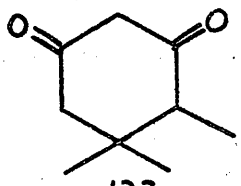

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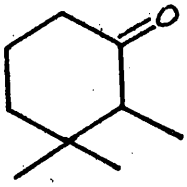

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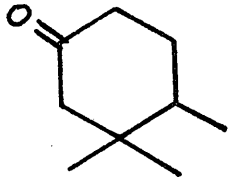

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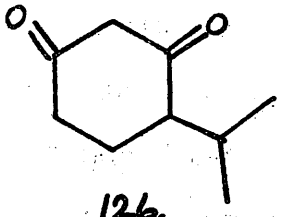

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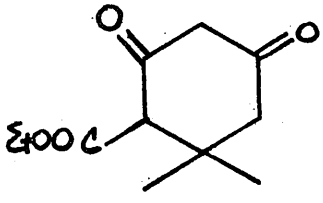

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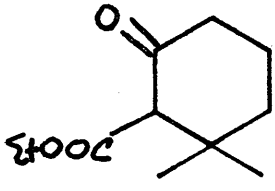

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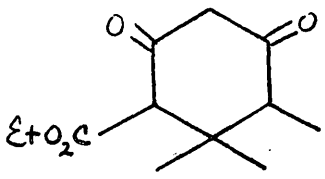
ADDENDUM.

While examining alternate synthetic routes to cuparene, a useful precursor seemed to be 5 : 5 - dimethyl - 4 - p - tolylcyclohexan - 1 : 3 - dione (118) which was readily prepared[52] from ethyl p-tolylacetate and mesityl oxide. However, treatment of (118) with phosphorus trichloride gave two isomeric enol - chlorides (119) and (120), as witnessed by the formation of two ketones (121) and (122) on hydrogenation.

Crossley and Renouf[53] have shown that 4 : 5 : 5 - trimethylcyclohexan - 1 : 3 - dione (123), on similar treatment, gave a mixture of 2 : 3 : 3 - trimethylcyclo - hexanone (124) and 3 : 3 : 4 - trimethylcyclohexanone (125), whereas, Steiner and Willhalm[55] have shown that 4-carbethoxy-5 : 5 - dimethylcyclohexan - 1 : 3 - dione (127) gave only one product, viz. 2 - carbethoxy - 3 : 3 - dimethyl - cyclohexanone (128) on hydrogenation of the enol - chloride. Also, Favre and Schinz[56] could only isolate 2 - carbethoxy -

* It has been reported[54] that 4 - isopropylcyclohexan - 1 : 3 - dione (126) gave only one ketone, 2 - isopropyl - cyclohexanone, on treatment with phosphorus trichloride followed by hydrgenation, however, the isolation procedure d id not preclude the presence of 4 - isopropylcyclohexanone.



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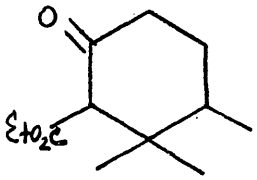

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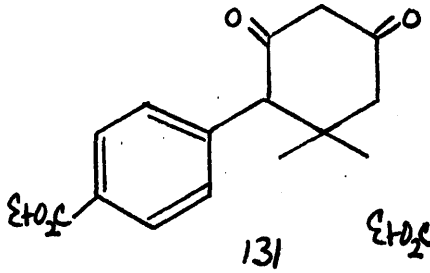

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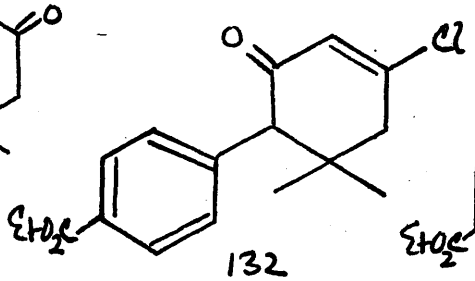

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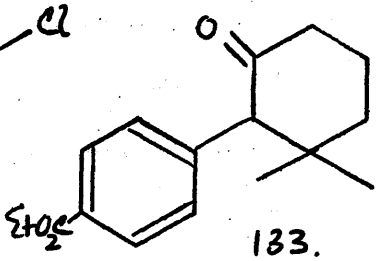


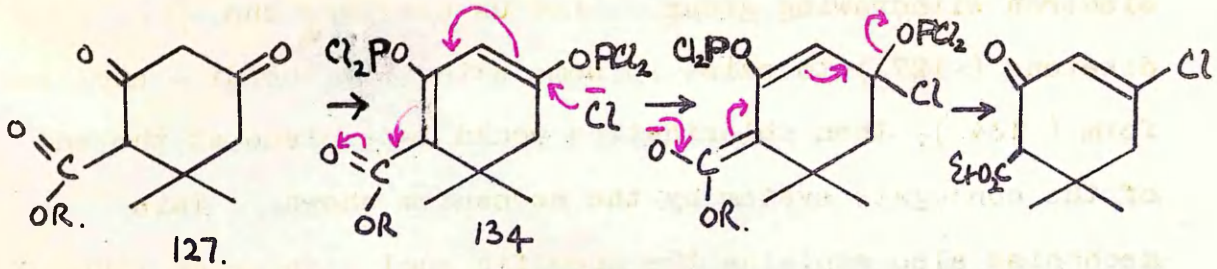
133.

3 : 3 : 4 - trimethylcyclohexanone (130) from the diketone (129). N.B. Thus it would appear that an ester function has a directing influence when it is para to one of the carbonyl groups in a cyclic β - diketone. There are three possible explanations for this :-

(i) The bulky ester group in a compound similar to (127) could result in the exclusive attack of phosphorus trichloride at the exposed carbonyl function and hence, lead to only one enol - chloride. However, the formation of a mixture of ketones from (123) is in disagreement with this since the steric requirements of a methyl group and a carbethoxyl group would be expected to be of the same order of magnetude.

(ii) Some type of intramolecular chelate may exist in the β - keto - ester system of (127) and (129) which would direct the attack of phosphorus trichloride to the non - chelated carbonyl. This explanation is invalidated by the fact that treatment of 4 - (p - carbethoxyphenyl) - 5 : 5 - dimethylcyclohexan - 1 : 3 - dione (131) with phosphorus trichloride followed by hydrogenation gave only 2 - (p - carbethoxyphenyl)- 3 : 3 - dimethylcyclohexanone (133) via (132). In fact, this is also conclusive proof that the reaction is not sterically controlled since both (131) and (118) have the same steric requirements with respect to attack by phosphorus trichloride.

(iii) The third explanation makes use of the ester as an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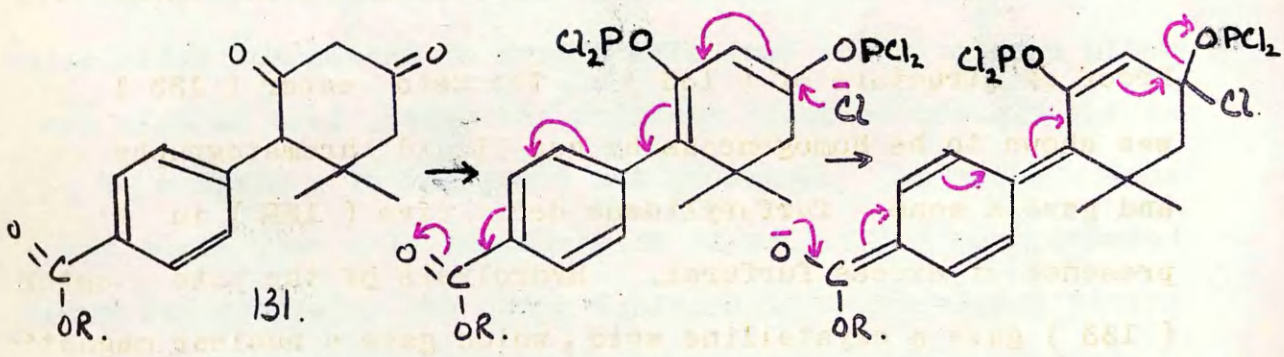
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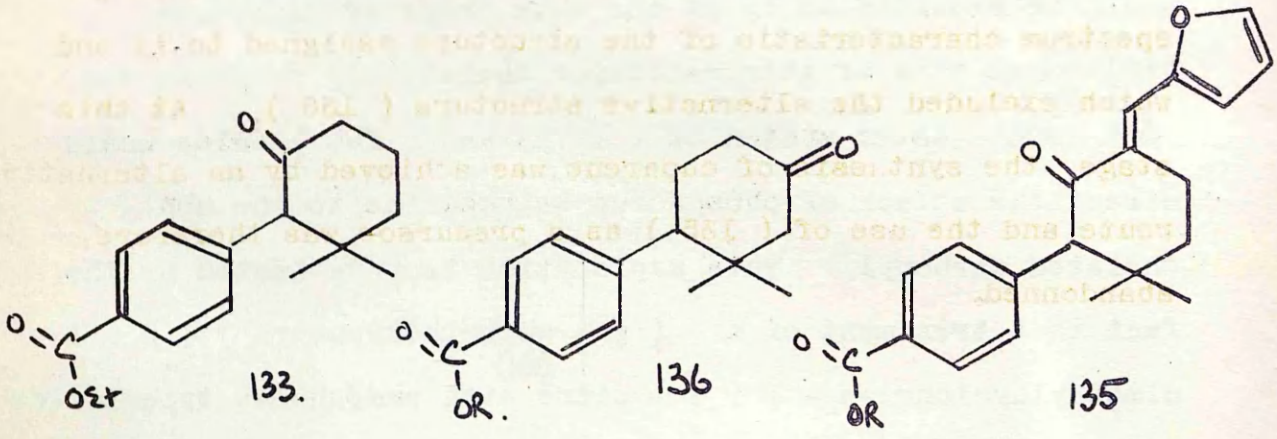
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electron withdrawing group. Let us consider the β - diketone (127) to exist to some extent in the di - enolized form (134), then chlorination would take place at the end of the conjugate system by the mechanism shown. This mechanism also explains the specific enol - chloride found on treating (131) with phosphorus trichloride (see opposite.)

Proof of structure of (133) : The keto -ester (133) was shown to be homogeneous by gas-liquid chromatography and gave a mono - furfurylidene derivative (135) in presence of excess furfural. Hydrolysis of the keto - ester (133) gave a crystalline acid , which gave a nuclear magnetic spectrum characteristic of the structure assigned to it and which excluded the alternative structure (136). At this stage the synthesis of cuparene was achieved by an alternative route and the use of (135) as a precursor was therefore, abandonned.

EXPERIMENTAL.

Ultraviolet absorption spectra refer to ethanol solutions, unless stated otherwise, and were measured with a Unicam S.P. 500 spectrophotometer. Infrared spectra were determined for natural films and nujol mulls on the Perkin - Elmer infracord spectrophotometer and Perkin - Elmer 13 spectrophotometer.

Melting points (corrected) were determined on a Kofler block. Boiling points are uncorrected.

The alumina used for chromatography (Spence , type H) was acid - washed and activated and graded according to the method of Brockmann and Schodder[99].

Gas - liquid chromatography was carried out on a Pye " Argon Chromatograph " with 46" X 1/5" columns of 5 % Apiezon L on Celite 545 (120 - 150 mesh).

Molecular weights were determined on the Metropolitan Vickers M.S.2 mass spectrometer.

p - Methylisobutyrophenone (81).

p - Toluamide (17g) was added slowly to a solution of isopropylmagnesium bromide (from magnesium, 15.6g) in dry ether (300ml). More ether (200ml) was then added, the reaction mixture refluxed, with stirring, under nitrogen for 40 hours, and the Grignard complex then decomposed at 0°C with dilute sulphuric acid. The ether layer was washed with sodium hydrogen carbonate solution, water and dried. Removal of the solvent and distillation of the residual oil gave p - methylisobutyrophenone (12g) as a colourless liquid, b.p. 128 - 130° / 23m.m; n_D^{23} 1.5185, Vmax (film) 1675cm^{-1} (aromatic ketone).

α- Propargyl - p - methylisobutyrophenone (82).

A mixture of p - methylisobutyrophenone (14g) and sodamide (3.9g) in toluene (120ml) was heated under reflux for 2 hours. Propargyl chloride (7.4g) was added dropwise to the stirred mixture held at 0°C and the reaction mixture refluxed for 6 hours, then washed with water, dried and the solvent removed. Distillation of the residual oil gave α- propargyl - p - methylisobutyrophenone as a colourless oil b.p. 84° / 0.1m.m; n_D^{22} 1.5296 (Found : C, 84.10; H, 8.35. $C_{14}H_{16}O$ requires C, 83.95; H, 8.05 %).

Vmax. (film) 3280cm^{-1} (ethynyl), 1675cm^{-1} (aromatic ketone), 1360 - 1380cm^{-1} (gem dimethyl). The corresponding 2 : 4-dinitrophenylhydrazone crystallized from methanol as plates m.p. 114-5° (Found : C, 63.05; H, 5.40. $C_{20}H_{20}O_4N_4$ requires C, 63.15; H, 5.30 %).

2 : 2 - Dimethyl - 1 - p - tolylpentan - 1 : 4 - dione (83).

A mixture of α - propargyl - p - methylisobutyrophenone (2g), mecuric oxide (400mg), trichloroacetic acid (10mg.) and boron trifluoride etherate (0.2ml) in methanol (10ml) was shaken for 2½ hours. The mixture was poured into dilute sulphuric acid, extracted with ether, and the combined ether extracts washed with dilute sodium carbonate solution, water and dried. Removal of the solvent gave 2 : 2 - dimethyl - 1 - p - tolylpentan - 1 : 4 - dione (1.5g) as an oil b.p. 92° / 0.02 m.m; n_D^{26} 1.5163 (Found : C, 76.75; H, 8.10. $C_{14}H_{18}O_2$ requires C, 77.05; H, 8.30 %). Vmax (film) 1705cm^{-1} (methyl ketone), 1675cm^{-1} (aromatic ketone). The corresponding bis - 2 : 4 dinitrophenylhydrazone recrystallized from methanol : chloroform as prisms m.p. 207 - 208° (Found : C, 53.80 ; H, 4.0 ; N, 19.0 $C_{20}H_{22}N_4O_5$ requires C, 53.80 ; H, 4.50 ; N, 19.40 %).

4 : 4 - Dimethyl - 3- p - tolylcyclopent -2 - enone (79)

A solution of 2 : 2 - dimethyl - 1 - p - tolylpentan - 1 : 4 - dione (1.5g.) in aqueous methanolic potassium hydroxide solution (30ml, 5%) was refluxed for 6 hours

under an atmosphere of nitrogen. The cooled solution was acidified with 6N hydrochloric acid and extracted with ether. The organic layer was washed with sodium carbonate solution, brine and dried. Removal of the solvent gave 4 : 4 - dimethyl - 3- p - tolylcyclopent - 2 - enone (1.2g) as an oil ; Vmax (film) 1675cm^{-1} (phenyl conjugated cyclopentenone). The corresponding 2 : 4 dinitrophenyl - hydrazone crytallized from acetic acid in deep red prisms m. p. 223°- 4°(Found : C, 63.15 ; H, 5.30 ; N,14.75 . $C_{20}H_{20}N_4O_4$ requires C,62.85 ; H,5.45 ; N,14.90 %). λ max 400mμ, ε = 24,000.

Attempted preparation of 3:3:4 Trimethyl-4-p-tolylcyclopentanone(80

Cuprous chloride (25mg) was added to a solution of methylmagnesium iodide (from magnesium, 200mg.) in dry ether (40ml). A solution of 4 : 4 - dimethyl - 1 - p - tolylcyclopent - 2 - enone (1g.) in ether (20ml) was then added and the mixture refluxed for 1 hour followed by 16 hours stirring at room temperature. The Grignard complex was decomposed with saturated ammonium chloride solution (40ml) and the ether layer washed with water and dried. Removal of the solvent gave a viscous oil (900mg.) Vmax (film) 3400cm^{-1} (hydroxyl) with no absorption in the region 1800cm^{-1} - 1700cm^{-1} .

A solution of the above oil (900mg) in benzene containing p - toluene sulphonic acid (50mg) was refluxed

for 1 hour, cooled washed with water, and the solvent evaporated. The residue was absorbed on alumina (I) from petroleum ether. Elution with petroleum ether gave a hydrocarbon oil (800mg), λ max 320 mμ ε=4,000.

4:4 - Dimethyl - 5 - oxo - 5 - p - tolylvaleric acid (8%).

A mixture of Triton B, 40% w/w (15g), p - methylisobutyrophenone (30g.), and acrylonitrile (42.5g.) in benzene (700ml) and tertbutanol (1400ml) was stirred, under nitrogen, at 50°C for 50 hours. After removal of the solvent, the dark residue was extracted with ether (1000ml) followed by methylene chloride (1000ml). Filtration of the organic extracts through charcoal and subsequent removal of the solvents afforded a yellow oil (37g.) which was heated with aqueous potassium hydroxide solution ; 20% (200ml) for 8 hours. The aqueous solution was extracted with ether then acidified. The acid - layer was extracted with ether and the organic layer was washed with brine and dried. Removal of the solvent gave an oil (28g.), which solidified on standing. Crystallization from petroleum ether (60° - 80°) : benzene afforded 4 : 4 - dimethyl - 5 - oxo - 5 - p - tolylvaleric acid as prisms m.p. 71.5° - 72.5° (Found : C, 71.70 ; H, 7.85 $C_{14}H_{18}O_3$ requires C, 71.75 ; H, 7.75 %). Vmax (CCl_4 solution) 1715cm^{-1} (carboxyl), 1675cm^{-1} (aromatic ketone).

4:4 - Dimethyl - 5 - p - tolyl - δ - valerolactone (89).

A solution of 4:4 - dimethyl - 5 - oxo - 5 - p - tolylvaleric acid (200mg) and sodium borohydride (25mg) in aqueous dioxane (25ml.) was allowed to stand overnight at room temperature. The solution was acidified with 3N hydrochloric acid and the solvent removed in vacuo. Water was then added and the aqueous solution extracted with ether, which was washed with water and dried. Removal of the solvent gave 4:4 - dimethyl - 5 - p - tolyl - δ -valerolactone (160mg.) which crystallized from petroleum ether (60°-80°) in fine needles m.p. 97° (Found : C, 76·90; H, 8·00. $C_{14}H_{18}O_2$ requires C, 77·05 ; H, 8·30 %). Vmax (CCl_4 solution) 1750cm^{-1} (δ - lactone), 1050cm^{-1} (C - O).

Attempted preparation of 4:4-dimethyl -5-p-tolyl valeric acid (90).

Potassium cyanide (150mg.) and 4:4 - dimethyl - 5 - p - tolyl - δ - valerolactone (150mg.) were heated at 270° C in a sealed tube for 5 hours. The cooled mixture was dissolved in water and extracted with ether. No cyano - acid was isolated from acidification of the aqueous alkaline layer. The starting material was isolated from the neutral ether layer in quantitative yield.

4:4-Dimethyl-5-ethynyl-5-p-tolyl-δ -valerolactone (91).

Method (a): Sodium acetylide was formed by saturating a suspension of sodamide (900mg.) in dry dimethylformamide

(40ml) with acetylene; the mixture being held at - 20°C. To this was added 4 : 4 - dimethyl-5-oxo-p - tolylvaleric acid (2g.) in dimethylformamide (10ml) and the solution stirred at -20°C for 1 hour. After standing overnight at room temperature, the solution was poured into ice-water (200ml) and acidified with 6N sulpnuric acid giving a white precipitate, which was collected.. This material crystallized from petroleum ether (60-80°) to give 4 : 4 - dimethyl - 5 - ethynyl - 5 - hydroxyl - 5 - p - tolylvaleric acid as prisms m. p. 126-8°, Vmax (nujol) 3500cm^{-1} (hydroxyl), 3300cm^{-1} (ethynyl), 1705cm^{-1} (carboxyl).

The acid was refluxed for 2 hours with acetic anhydride (20ml) containing fused potassium acetate (700mg), then poured into water and extracted with ether. The organic layer was washed with brine, dried and the solvent evaporated in vacuo to yield a gum which was absorbed on silica (20g.) from petroleum ether (60-80°) : benzene (1 : 1). Elution with benzene gave 4 : 4 - dimethyl - 5 - ethynyl - 5 - p - tolyl - δ - valerolactone (680mg.) which crystallized from petroleum ether (60-80°) in prisms m. p. 97-98°C (Found : C, 79.30 ; H, 7.70 ; $C_{16}H_{18}O_2$ requires C, 79.30 ; H, 7.50 %). Vmax. (CCl_4 solution) 3300cm^{-1} (ethynyl), 1750cm^{-1} (δ -lactone). Method (b) : 4 : 4 - Dimethyl - 5 - oxo - 5 - p - tolyl - valeric acid (11.5g.) in ether (50ml) was added slowly

to a solution of sodium acetylide (from sodium, 3·5g.) in liquid ammonia (250ml) and stirred for 6 hours with acetylene passing through the solution. After a further 6 hours stirring, ammonium chloride (20g) was added and the ammonia allowed to evaporate. The residue was then worked up as in method (a) to give the ethynyl - lactone (8·5g.).

4:4-Dimethyl-5-carboxy-5-p-tolyl-δ-valerolactone (92).

Ozone was passed through a solution of 4 : 4 - dimethyl - 5 - ethynyl - 5 - p - tolyl - δ - valerolactone (1·1g.) in "Analar" ethyl acetate (60ml) at -70°C for 5 hours. The solvent was then removed below 50°C in vacuo and the ozonide decomposed with a mixture of glacial acetic acid (10ml) and water (4ml). After standing at room temperature for 14 hours, most of the acetic acid was removed and ether added. The ethereal layer was extracted with sodium hydrogen carbonate solution and the alkaline aqueous layer acidified with 6N hydrochloric acid. Ether extraction followed by washing with water, drying and removal of solvent yielded a viscous gum (1·04g) which furnished 4 : 4 - dimethyl - 5 - carboxy-5- p - tolyl - δ - valerolactone as a white solid (400mg.) on trituration with a mixture of petroleum ether and benzene. The acid recrystallized from petroleum ether : ethyl acetate in prisms m.p. 170°-173°; Vmax (KCl disc) 1750cm^{-1} (δ-lactone), 1710cm^{-1} (carboxyl).

The residual oil from trituration was esterified with excess ethereal diazomethane and the resulting ester absorbed on silica from benzene : petroleum ether60° - 80° (1 : 4). Elution with benzene : petroleum ether (1 : 2) afforded 4 : 4 - dimethyl - 5 - methoxycarbonyl - 5 - p - tolyl - δ - valerolactone, which crystallized from petroleum ether in prisms m. p. 101 - 102° (Found : C, 69·55 ; H, 7·30 ; $C_{16}H_{20}O_4$ requires C, 69·30 ; H, 7·05 %). Vmax (CCl_4 solution) 1750cm^{-1} (δ - lactone), 1735cm^{-1} (ester).

Methyl-5-acetyl-4:4-dimethyl-5-p-tolylvalerate (97).

A solution of 4 : 4 - dimethyl - 5 - ethynyl - 5 - p - tolyl - δ - valerolactone (1·27g.) in methanol (15ml) was added slowly to a mixture ofmercuric oxide (500mg.) trichloroacetic acid (20mg.), boron trifluoride etherate (0·2ml) and methanol (1ml) and the mixture was shaken for 18 hours at room temperature. After removal of most of the methanol, 6N sulphuric acid (5ml) was added, the aqueous suspension extracted with ether and benzene and the organic extracts washed with water then dried. Removal of the solvent gave a gum, which on trituration with methanol furnished a solid (725mg) m. p. >200° which proved to be the mercury salt of the hydroxy - keto - acid corresponding to (97), Vmax (nujol) 1600cm^{-1} (carboxylate ion). An aqueous solution of this salt on treatment with ammonium

sulphide solution gave a black precipitate of HgS. The methanolic mother liquor, on evaporation gave methyl 5 - acetyl - 4 : 4 - dimethyl - 5 - hydroxy - 5 - p - tolyl - valerate as a viscous gum (825gm), Vmax (film) 3450cm^{-1} (hydroxyl) ; Vmax (CCl_4 solution) 1735cm^{-1} (ester), 1705cm^{-1} (aliphatic ketone).

A solution of the ketol - ester (96) (825mg) in methanol (150ml) was hydrogenated for 24 hours at a pressure of 5 atmospheres using 10% palladium on charcoal (300mg) as catalyst. Removal of the solvent yielded a gum (400mg) which was adsorbed on alumina (III) from benzene : petroleum ether(60° - 80°) 1 : 5. Elution with benzene afforded methyl 5 - acetyl - 4 : 4 dimethyl - 5 - p - tolylvalerate (160mg), which crystallized from pentane in prisms m. p. 75.5 - 76.5 (Found : C, 74.05 ; H, 8.45 , $C_{17}H_{24}O_3$ requires C, 73.90 ; H, 8.75 %). Vmax (CCl_4) 1735cm^{-1} (ester), 1710cm^{-1} (ketone).

Dimethyl 2-hydroxy-3:3-dimethyl-2-p-tolyladipate (93).

A solution of 4 : 4 dimethyl - 5 - carboxy - 5 - p - tolyl - δ - valerolactone (92), (2.9g) in methanol (80ml), which had previously been saturated with hydrogen chloride, was allowed to stand overnight at room temperature. Water was added and most of the methanol removed in vacuo. The aqueous solution was extracted with ether and the ethereal

layer extracted thoroughly with sodium hydrogen carbonate solution. Acidification of the alkaline layer followed by the usual isolation procedure gave an acid which was esterified by diazomethane to yield dimethyl 2 - hydroxy - 3 : 3 - dimethyl - 2 - p - tolyladipate (93), (2.3g) as a thick oil b.p. 154 /0.2m.m ; n_D^{24} 1.5120 (Found : C, 66.20 ; H, 7.60. $C_{17}H_{24}O_5$ requires C, 66.20 ; H, 7.85 %). Vmax (film) 3450cm^{-1} (hydroxyl), 1730cm^{-1} (ester).

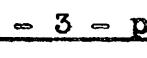
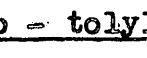
Dieckmann cyclization of dimethyl 2-hydroxy-3:3-dimethyl-2-p-tolyladipate. (93)

Dimethyl 2 - hydroxy - 3 : 3 - dimethyl - 2 - p - tolyladipate (1.8g) in tertbutanol (10ml) was added to tertbutanol (50ml) containing potassium tertbutoxide (from potassium 1.8g) and the whole refluxed under nitrogen for 30 hours. Removal of the solvent followed by addition of benzene and acidification with 6N sulphuric acid yielded, after normal isolation procedure, a yellow oil, which gave a positive ferric chloride test (wine colour), Vmax (film) 3500cm^{-1} (hydroxyl), 1730cm^{-1} - 1750cm^{-1} (ester - cyclopentanone).

A solution of this oil in a mixture of glacial acetic acid (15ml), concentrated hydrochloric acid (5ml) and water (1ml) was refluxed under nitrogen for 4 hours. The solvent was removed and water added. Ether extraction

was followed by washing the organic layer with saturated sodium hydrogen carbonate solution, water, and drying. Removal of the ether gave an oil which was absorbed on alumina (III) from petroleum ether : benzene; 10 : 1. Elution with petroleum ether : benzene ; (5 : 1) gave a solid which sublimed to furnish prisms m. p. 52° (Found : C, 83·85 ; H, 8·45. $C_{14}H_{16}O$ requires C, 83·95 ; H, 8·05), mass spectrometric molecular weight 200 ($C_{14}H_{16}O$ requires 200), Vmax (CCl_4) 1715cm^{-1} (cyclopentenone) ; λ max 219mμ ε = 20,000. Nuclear magnetic resonance (of italicized protons) :

9·27τ, 8·65τ [$CH_3-C<^{R}_{R}$] ; 7·67τ [$\phi-CH_3$] ; 6·60τ [$\phi-CH<^{CO}_{C}$] ;

3·87τ, 3·78τ [] ; 2·52τ, 2·44τ []

3 - Methyl - 3 - p - tolylcyclohexanone (107).

3 - Methylcyclohex - 2 - enone (36g) was added dropwise to a stirred suspension of aluminium chloride (120g) in toluene (150ml) held at 0°C and the stirring continued for a further 16 hours at room temperature. The reaction mixture was poured on ice and thoroughly extracted with ether. The organic layer was washed with water (6x50ml), dried and the solvent removed to give an oil, which on distillation afforded 3 - methylcyclohex - 2 - enone (15g) and a pale yellow oil (15g), which was absorbed on silica from petroleum ether. Elution with petroleum ether gave a hydrocarbon (3g) and 3 - methyl - 3 - p - tolylcyclo - hexanone was eluted with benzene and redistilled to give a

colourless oil (11.5g) b.p. 101°/ 0.5m.m n_D^{22} 1.5365 (Found : C, 82.70 ; H, 8.85 . $C_{14}H_{18}O$ requires C, 83.10 ; H, 8.95 %). Vmax (film) 1710cm^{-1} (ketone), 1600-1520 cm^{-1} (aromatics) , 820cm^{-1} (1 : 4 - disubstituted benzene nucleus.).

2-Furfurylidene-5-methyl-5-p-tolylcyclohexanone (109).

Furfural (10ml) was added to a solution of 3 - methyl - 3 - p - tolylcyclohexanone (16g) in a mixture of ethanol (100ml) and aqueous sodium hydroxide 15% (40ml). After 1 minute the solution became cloudy and a red oil was precipitated. The reaction mixture was poured into water (750ml) after 2 hours and extracted with ether. The organic layer was washed with water and dried. Evaporation of the solvent furnished a yellow gum (22g), which was not purified further. Vmax (film) 3100cm^{-1} , 1600cm^{-1} , 750cm^{-1} (characteristic of a furfurylidene derivative). λ_{max} 333mμ .

2-Furfurylidene-5-p-tolyl-5:6:6-trimethylcyclohexanone (110).

2 - Furfurylidene - 5 - methyl - 5 - p - tolylcyclo - hexanone (22g) in tertbutanol (100ml) was added to potassium tertbutoxide (from potassium, 25g) in tertbutanol (400ml). After 20 minutes at 40°C, methyl iodide (150ml) was added and the reaction mixture stirred overnight at room temperature, under nitrogen. The reaction mixture filtered and the solvent evaporated. The residue was extracted with

ether, washed with water and dried. Removal of the solvent yielded a gum(22g), which on trituration with petroleum ether : pentane gave a solid (4.6g). Recrystallization from methanol afforded 2 - furfurylidene - 5 - p - tolyl- 5 : 6 : 6 : trimethylcyclohexanone (2.6g) as prisms m.p. 146-8° (Found : C,81.75 ; H,7.80. $C_{21}H_{24}O_2$ requires C,8.80 ; H,7.85 %). Mass spectrometric molecular weight 308 ($C_{21}H_{24}O_2$ requires 308). Vmax 1670cm^{-1} (enone) 1600 - 1540cm^{-1} (aromatics), 1380 - 1360cm^{-1} (gem dimethyl). λMax 323mμ, ε=10,000.

Residue from the alkylation was recycled to give di- alkylated furfurylidene derivative (2g).

Chloro- α: α: β -trimethyl- β -p-tolyladipic acid (lll).

A solution of 2 - furfurylidene - 5 - p - tolyl - 5 : 6 : 6 - trimethylcyclohexanone (340mg) in ethyl acetate (25ml) was ozonized at -78°C until the solution became blue. The solvent was removed below 40°C to give a yellow gum which was treated with acetic acid (10ml), 30% hydrogen peroxide (2ml) and 6N hydrochloric acid (0.5ml). After standing overnight, the solvent was evaporated in vacuo and sodium hydrogen carbonate solution added. The neutral material was separated by ether extraction, then the aqueous layer acidified and ether extracted. The organic layer was washed with water, dried and the solvent removed to give a solid (290mg) which crystallized from aqueous

methanol in cubes m.p. 225-229° (Found : C, 61.85 H, 7.25 $C_{16}H_{21}O_4Cl$ requires C, 61.45 ; H, 6.70 %). Vmax (nujol) 1700cm^{-1} (carboxyl) ; positive Beilstein test for chlorine.

The diacid (230mg), on treatment with diazomethane, afforded the diester as a gum (240mg).

Chloro-2:2:3-trimethyl-3-p-tolylcyclopentanone (112).

Dimethyl chloro - α : α : β - trimetnyl - β - p - tolyl - adipate (230mg) and sodium hydride (excess) in dry ether (60ml) containing ethanol (0.5ml) was stirred at 0°C for 1 hour and allowed to attain room temperature. After stirring for 48 hours, ethanol and 6N hydrochloric acid (20ml) were added. The ethereal layer was washed with water and dried. Removal of the solvent gave a red gum (185mg) ; positive ferric chloride test.

A solution ofthe gum in acetic acid (10ml), concentrated hydrochloric acid (5ml) and water (1ml) was refluxed, under nitrogen, for 1 hour followed by removal of the solvent below 40° C. Methanol (20ml) and 5% sodium hydroxide (15ml) were added and the mixture refluxed for 1 hour. Most of the alcohol was then removed and water (50ml) added. The ethereal solution was washed with water and dried, then evaporated to give a gum (80mg) which was absorbed on alumina (III) from benzene : petroleum ether ; (1 : 4). Elution with benzene ; petroleum ether (1 : 1), gave a solid which crystallized

from aqueous methanol as prisms m.p. 66-69° (Found : C, 71.55 ; H, 7.10. $C_{15}H_{19}OCl$ requires C, 71.85 ; H, 7.60). Vmax (CCl_4) 1740cm^{-1} (cyclopentanone), 1360 - 1380cm^{-1} (gem dimethyl) Mass spectrometric molecular weight 250 ($C_{15}H_{19}OCl$ requires 250). All fragments from mass numbers 250 to 150 contain chlorine (double peaks), which suggests the chlorine is situated in the aromatic ring. The ketone gives a positive Beilstein test for chlorine.

α : α : β-Trimethyl-β-p-tolyladipic acid (115).

Ozone was passed through a solution of 2 - furfurylidene - 5 - p - tolyl - 5 - : 6 : 6 - trimethylcyclohexanone (1g) in ethyl acetate (100ml) at -78°C until the solution became blue. The solvent was removed *in vacuo* at 40°C and a mixture of glacial acetic acid (10ml), 30% hydrogen peroxide (2ml), 6N sulphuric acid (6 drops), was added to the residue. After standing overnight the solvent was again removed and saturated sodium bicarbonate solution added. The aqueous solution was worked up as in the previous case to give α : α : β - trimethyl - β - p - tolyladipic acid (740mg) which crystallized from dilute methanol in prisms m.p. 222-224°. (Found : C, 68.80 ; H, 7.75. $C_{16}H_{22}O_4$ requires C, 69.05 ; H, 7.95 %). Vmax (nujol) 1705cm^{-1} (carboxyl), 825cm^{-1} (1 : 4 disubstituted benzene). The mass spectrum showed no molecular ion due to bond rupture between the two

quaternary carbon atoms, thus, the higher mass number was found to be 191 (required 191).

Diazomethane treatment of the diacid afforded the diester, which was not purified further.

2:2:3-Trimethyl-3-p-tolylcyclopentanone (117).

A solution of dimethyl $\alpha:\alpha:\beta$ - trimethyl - p - tolyladipate (1.9g) in benzene (50ml) was added to potassium tertbutoxide (from potassium, 7g) in benzene (500ml). The mixture was refluxed under nitrogen for 6 hours followed by stirring at room temperature for 11 hours. After acidification with dilute sulphuric acid, the benzene layer was washed with water and dried. Removal of the solvent furnished an oil (1.7g) which gave a positive ferric chloride test (purple). Vmax (film) 1750cm^{-1} (cyclopentanone), 1730cm^{-1} (ester).

The β - keto - ester (1.7g) was dissolved in acetic acid and refluxed with concentrated hydrochloric acid (10ml) water (2ml), under nitrogen, for 4 hours. The solvent evaporated under reduced pressure and the residue heated at 100°C in a solution of methanol (30ml) and 4N sodium hydroxide solution (25ml). After the solvent had been removed, water was added and the whole extracted with ether. The ethereal solution was washed with water and dried. Removal of the solvent gave an oil (1.07g), which was

adsorbed on alumina (III) from benzene : petroleum ether 60°- 80° (1 : 5) gave 2 : 2 : 3 - trimethyl - 3 - p - tolylcyclopentanone (950mg). Vmax (film) 1742cm^{-1} (cyclopentanone), 1385cm^{-1}, 1380cm^{-1}, 1360cm^{-1} (C-methyl pattern), 825cm^{-1} (1 : 4 disubstituted benzene). Mass spectrometric molecular weight 216 (required 216). The ketone gave a semicarbazone, which crystallized from aqueous methanol in prisms m. p. 212 - 215° (Found : C, 70·25 ; H, 8·20 ; N, 15·30. $C_{16}H_{23}ON_3$ requires C, 70·30 ; H, 8·50 ; N, 15·35 %).

(±) Cuparene, (25a).

100% Hydrazine hydrate (2ml) was added to diethylene glycol (40ml) and ethylene glycol (10ml) containing 2 : 2 : 3 - trimethyl - 3-p - tolylcyclopentanone (800mg.) The temperature was kept at 184° C for 1½ hours then cooled to 70 C when sodium (1g) in diethylene glycol (20ml) was added. The reaction mixture was refluxed (192°) for 4¼ hours and poured into ice-water. Extraction with 40° - 60° petroleum ether, followed by evaporation of the solvent afforded an oil (790mg), which was adsorbed on alumina (III) from petroleum ether. Elution with petroleum ether gave an oil (300mg) (Found : C, 88·90 ; H, 10·85 . $C_{15}H_{22}$ requires C, 89·05 ; H, 10·95 %). The infrared ultraviolet and mass spectra of synthetic (I) and natural D (+) -cuparene were identical. Both the synthetic and natural hydrocarbons had the same retention time on gas -

liquid chromatography.

(±) Cuparenic acid (25b).

The oxidation of (±) cuparene (150mg) was accomplished by the method of Erdtman and Enzell. A crystalline acid (25mg) was obtained which crystallized from 40 -60° petroleum ether in prisms m. p. 151 - 154°. (Found : C, 77.35 ; H, 8.35 . $C_{15}H_{20}O_2$ requires C, 77.55 ; H, 8.65 %). The infrared spectrum (KCl disc) was identical to that of D (+) - cuparenic acid.

4:4- Dimethyl-5-p-tolylcyclohexan-1:3-dione (118).

Mesityl oxide (8.5g) was added to a solution of ethyl p - tolylacetate (15.5g) in ethanol (40ml) containing sodium ethoxide (from sodium, 2.27g) and the solution refluxed for 4 hours. Most of the ethanol was removed in vacuo and water added. The aqueous solution was extracted with ether (2 X 25ml) then acidified to give an oily suspension which yielded a solid (10g) on standing. Crystallization from benzene : petroleum ether gave 4 : 4 - dimethyl - 5-p - tolylcyclohexan - 1 : 3 - dione as prisms m.p. 152°-154°. (Found : C,78.15 ; H,7.80 . $C_{15}H_{18}O_2$ requires C,78.25 ; H, 7.90 %). Vmax (nujol) 1680cm^{-1} (enone), 1600cm^{-1} (enol double bond). λ max 259mμ , ε= 16,000 ; in base, λ max 285mμ , ε= 26,000.

4-(Carbethoxyphenyl)-5:5-dimethylcyclohexan-1:3-dione (131).

Mesityl oxide was added to diethyl homoterephthalate (22g) in anhydrous ethanol (150ml) containing sodium ethoxide (from sodium, 2.2g) and the solution refluxed for 5 hours. After standing at room temperature for 12 hours, most of the ethanol was removed and ether extracted. The aqueous layer was acidified to yield an oil which solidified at 0°C. Trituration of the solid with ether (10ml) afforded 4 - (p - carbethoxyphenyl)-5 :5 - dimethylcyclohexan -1 : 3 - dione (18 g.) which crystallized

from aqueous ethanol as the monohydrate m.p. 75°-80°. (Found : C,66·55 ; H,7·30. $C_{17}H_{22}O_5$ requires C,66·65 ; H,7·25 %). Vmax (CCl_4) 1700cm^{-1} (aromatic ester) ; Vmax (nujol) 1605cm^{-1} (enol double bond). λ max 250mμ ε = 22,600 ; in base λ max 242mμ ε=15,700, 283mμ ε=26,000

Action of phosphorus trichloride on 4:4-dimethyl-5-p-tolylcyclohexan 1 : 3 - dione. (118)

A mixture of 5 : 5 - dimethyl - 4 - p - tolylcyclo - hexane - 1 : 3 - dione (2·5g) and phosphorus trichloride (2·5g) in anhydrous, ethanol - free chloroform (80ml) was refluxed for 3 hours followed by removal of the solvent *in vacuo*. Ether was added to the residue, then ice -water and the ethereal layer washed with ice - cold 2% potassium hydroxide solution (100ml), water and dried. Removal of the solvent gave the enol - chloride (1·3g) as a viscous gum. Vmax (film) 1670cm^{-1} (enone), 1600cm^{-1} (double bond). λ max 238mμ, ε=10,000.

Reduction to give a mixture of 3:3-dimethyl-2-p-tolylcyclo-hexanone and 3:3-dimethyl-4-p-tolylcyclohexanone

A solution of the above enol - chloride (1·3g) in methanol (50ml), containing pyridine (1ml), was hydrogenated for 15 hours in the presence of 5% palladium on calcium carbenate (500mg), after which the suspension

was filtered, stripped of solvent, and water added. The ether extract was washed with 6N hydrochloric acid, water and dried. Removal of the solvent gave an oil which was adsorbed on alumina (III) from petroleum ether 40°-60°. Elution with petroleum ether 60°- 80° afforded a crystalline compound (300mg), which crystallized from aqueous ethanol in prisms m. p. 56-61°. Sublimation at 75°/ 1·35 X 10^{-4} mm raised the m. p. to 62°-64° (Found : C, 83·70 ; H, 8·90 . $C_{15}H_{20}O$ requires C, 83·30 ; H, 9·30 %). Vmax (KCl disc) 1705cm^{-1} (saturated cyclohexanone), 825cm^{-1} (1:4 disubstituted benzene nucleus). Vapour phase chromatography showed a mixture of two isomers.

Action of phosphorus trichloride on 4-(carbethoxyphenyl)-5:5-dimethylcyclohexan-1:3-dione. (131).

The enol - chloride was prepared from 5 : 5 - dimethyl 4 - (p - carbethoxyphenyl) cyclohexan 1 : 3 - dione (8.6g) using phosphorus trichloride (4ml) in chloroform (80ml) by the method described above. This yielded enol - chloride (4·3g) as a viscous gum. Vmax (film) 1710cm^{-1} (benzoate), 1670cm^{-1} (enone), 1610cm^{-1} (double bond). λ max 242mμ ε= 24,000.

2-(p-Carbethoxyphenyl)-3:3-dimethylcyclohexanone (133).

The above ester enol - chloride (132) was hydrogenated as before to give 3 : 3 - dimethyl - 2 - (p - carbethoxy -

phenyl) cyclohexanone as a gum which sublimed at 145° / 0.005mm. Vmax (film) 1710cm^{-1} (benzoate + saturated ketone). λ max 238mμ , ε=16,000. Vapour phase chromatogram on Pye - argon using a 5% Apiezon column at 190°C exhibited only one peak R_t = 60 minutes.

The ester was hydrolysed by base to give 3 : 3 - dimethyl - 2 - (p - carboxyphenyl)- cyclohexanone , which crystallized from aqueous ethanol in prisms m. p. 149-151°

(Found : C, 72.85 ; H, 7.15 . $C_{15}H_{18}O_3$ requires C, 73.15 ; H, 7.35 %). Nuclear magnetic resonance (of italicized protons) : 9.57τ, 9.63τ [$>C(CH_3)$] ; 6.9 [R-CO.CH.$(CH_3)_2$.ϕ]. Ratio of methylene protons α to carbonyl function, to methylene protons not adjacent to carbonyl function was found to be 2 : 4.

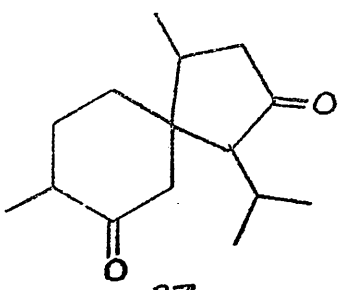
2-(p-Carbethoxyphenyl)-3:3-dimethyl-6-furfurylidene cyclo - hexanone.(135).

A solution of sodium ethoxide (from sodium, 100mg) in ethanol (10ml) was added to 2 - (p - carbethoxy - phenyl) - 3 : 3 - dimethylcyclohexanone (1g.) in ethanol (5ml). Excess furfural (0.8ml) was added to the red - orange solution and the mixture allowed to stand at room temperature. After 20 minutes crystals precipitated and water (10ml) added after 2 hours, then the precipitated

filtered off. Crystallization from aqueous methanol gave 2 - (p - carbethoxyphenyl) - 3 : 3 - dimethyl - 6 - furfurylidenecyclohexanone (830mg.) as needles m. p. 135°-136°. (Found : C, 74·95 ; H, 6·90 . $C_{22}H_{24}O_4$ requires C, 74·95 ; H, 6·85 %). Mass spectrometric molecular weight 352 (required 352) λ max 238mμ, ε = 8,000, 333mμ ε = 13,5000.

PART II

Approaches to the Synthesis of Acorone.



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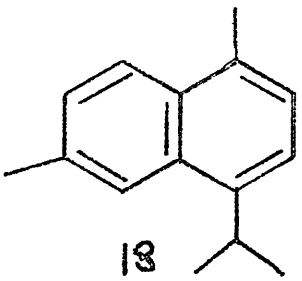

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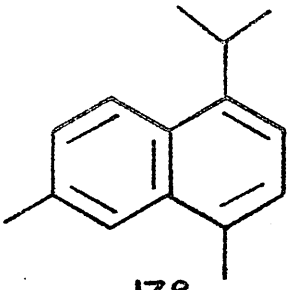

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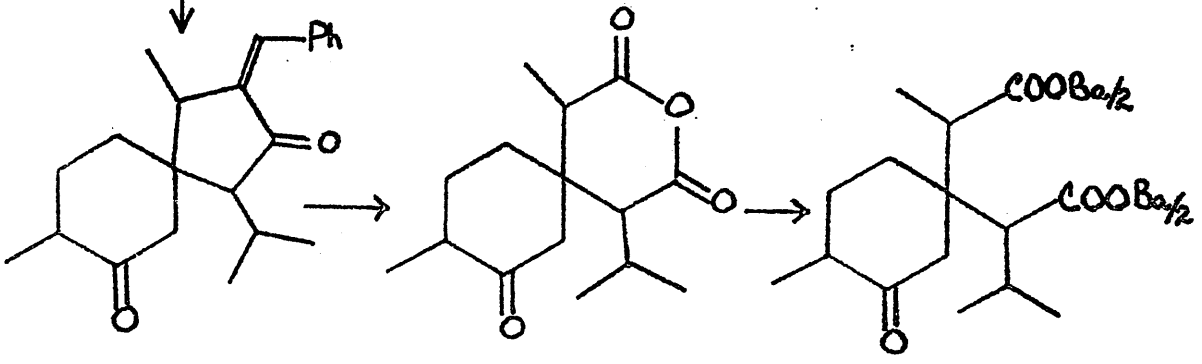
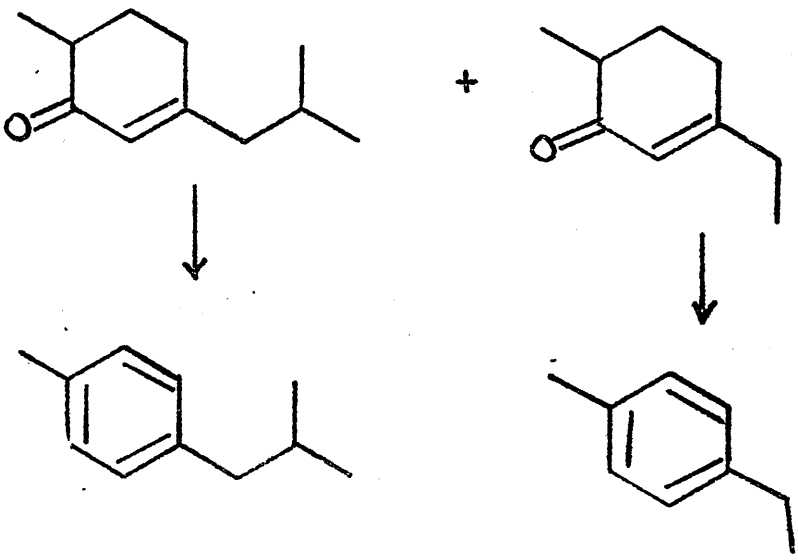


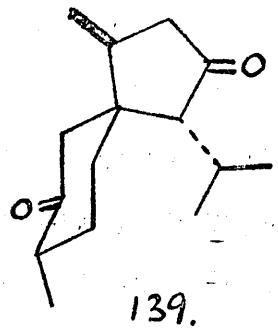
$C_2H_5.COOH$ + $(CH_3)_2.CH.CH_2.COOH$



HISTORICAL.

In 1947, Soorm and Herout[57,58] isolated two new isomeric sesquiterpenes during an investigation into the terpenic constituents of the essential oil of sweet flag (Acorus calamus L). Chromatography on alumina afforded a dextrarotatory ketone, which was named acorone, $C_{15}H_{24}O_2$; m.p. 101° - 102° and its laevorotatory isomer, isoacorone, m.p. 96° - 97°. Later work showed, by the same school, the presence of a third isomer, neoacorone, m.p. 83° - 84°. All three isomers, on treatment with alkali, furnished the same equilibrium mixture of two parts of acorone to one part of isoacorone.

The structure of acorone (37) was deduced from the following observations. Acorone formed a di - semicarbazone and was found to contain no olefinic double bonds ; hence a bicyclic structure was indicated. The spiro nature of the bicyclic system was suggested by reduction of acorone to the diol, followed by dehydration and sulphur dehydrogenation to give a mixture of 1 : 7 - dimethyl - 4 - isopropylnaphthalene (138) and cadalene (18). This type of rearrangement of a 4 : 5 spiro system to a decalin is well authenticated[60]. The infrared indicated the presence of a cyclohexanone and a cyclopentanone. Preferential reduction and ketalization of the C.6 ring carbonyl function showed that the cyclopentanone was much



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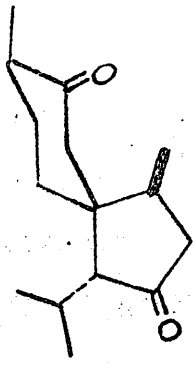

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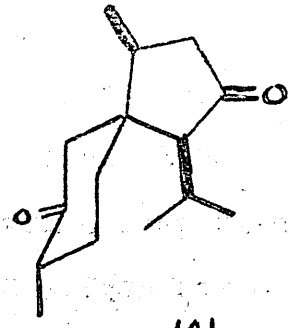

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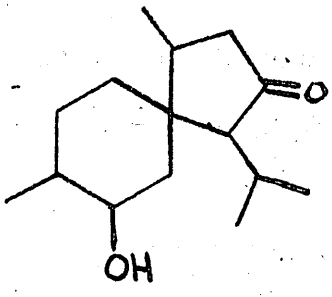


142.

more sterically hindered. The degradative evidence (shown opposite) substantiated the gross structure (37). Acorone gave a mono - benzylidene derivative, which was ozonized to give a diacid. Pyrolysis of the barium salt gave a mixture of isovaleric acid, propionic acid, 3 - isobutyl - 6 - methylcyclohexenone and 3 - ethyl - 6 - methylcyclohexenone. The enones were characterized as the corresponding aromatic hydrocarbons p - isobutyl - toluene and p - ethyltoluene. Although the position of the carbonyl in the five - membered ring was not rigorously proved, structure (37) was favoured because of the sterically hindered nature of the cyclopentanone ; it is also more compatible from a biogenetic standpoint.

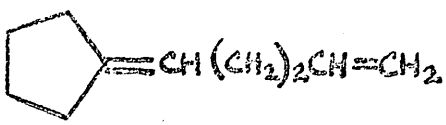
Recent work[61] on the stereochemistry of the three isomers has led to the formulations (139), (140), (141) for acorone, isoacorone and neoacorone respectively. The molecular rotation difference between the hydroxy - ketone (142) and the 1 : 5 - diketones (37) was found to be of the same order of magnitude in all three cases, but, in the case of isoacorone the molecular rotation difference had the opposite sign to that of acorone and neoacorone. This suggested that, the methyl group adjacent to the cyclohexanone carbonyl group had the same configuration in acorone and neoacorone, but was opposite to that in isoacorone. Support for this was given by the rotatory

dispersion curves of acorone and isoacorone, which were found to be mirror images of each other.

The dipole moments of the three isomers differed from each other to such an extent that it was possible to make use of this evidence for further detailed stereochemical study. Calculation of the dipole moment of the acorone structure (139) led to a value of 4·87 D which compared favourably with the observed value of 5·11 D. The observed values for isoacorone and neoacorone were 2·39 D and 4·39 D respectively.

It was found that the hydroxy - ketone (142) from acorone and isoacorone did not isomerize by treatment with methanolic potassium hydroxide, whereas the neoacorone hydroxy - ketone underwent epimerization. This suggested, that the configuration of the isopropyl group was the same in acorone and isoacorone but opposite to that in neoacorone. The problem of the relative configuration of the methyl and isopropyl groups is still unsolved, although it does seem probable that, in acorone and isoacorone, the two groups are <u>trans</u> to each other.

Since acorone belongs to the spiro [5 : 4] decane system, it was decided to investigate the known routes to this skeletal type. The parent hydrocarbon spiro [5 : 4] decane may be obtained by acid - cyclization of the diene[62] (143), followed by hydrogenation of the



143

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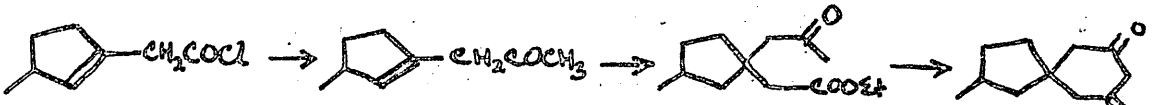
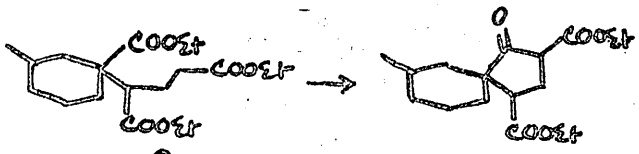
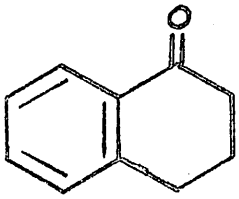
(A)



(B)





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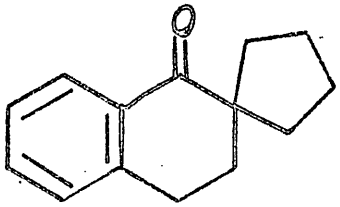

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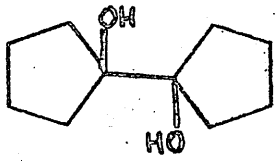

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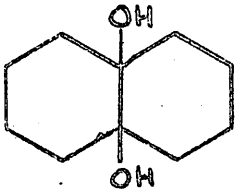

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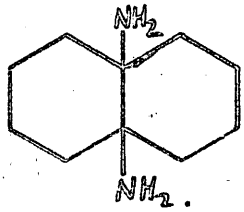

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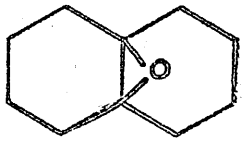

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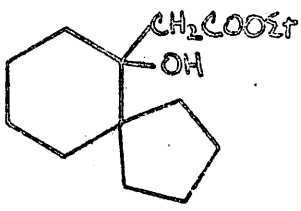

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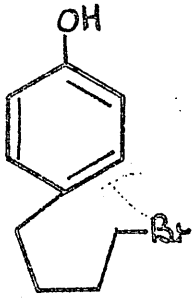

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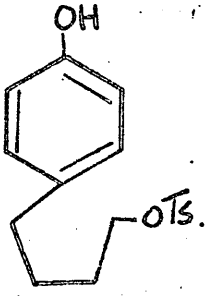

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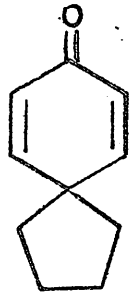

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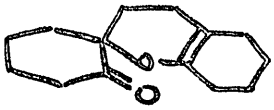


155

156

157.

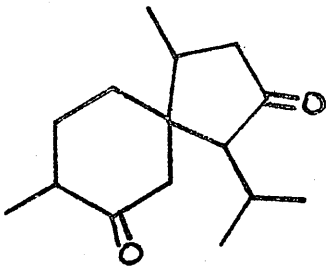
unsaturated spiro compound (144).

Perhaps the most common method of construction involves either an internal Claisen ester condensation , or a Dieckmann condensation (see examples A[63] and B[64]).

Alkylation of the tetralone[65] (145) with an $\alpha:\omega$ - dibromide leads to the spiro system (146). Pinacolic rearrangement of the ditertiary alcohols[66] (147) and (148), or the action of nitrous acid on the diamine[67] (149), also yields a 5 - keto - spirane. A similar type of rearrangement may be observed in the Reformatski reaction of zinc and ethyl bromoacetate on the oxide (150), which leads to the abnormal product[68] (151).

4 : 4 - Spirocyclohexa - 2 : 5 - dienones (154) may be prepared from p - (W - halogenoalkyl) phenols[69] (152) or p - (W - tosylalkyl) phenols[70] (153). This method is only applicable when the tosylate is primary, because of the high rate of elimination in the case of secondary or tertiary derivatives.

The action of suphuric acid on the dimer of 2 - methylenecyclohexanone (155) leads to the interesting dispiramoid ketone[71] (158) ; the reaction proceeding via (156) and (157).



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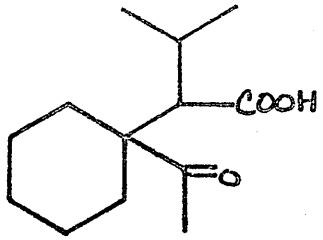

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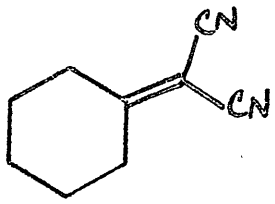
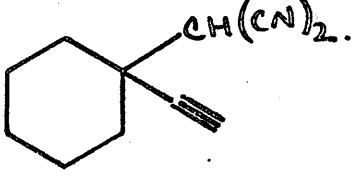
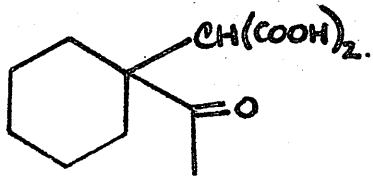


160 a.



161 a.



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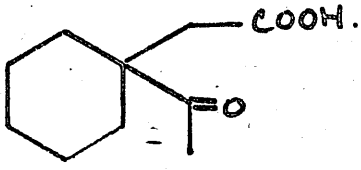


163.

DISCUSSION.

The synthesis of acorone (37) presents an interesting problem, because of the large number of asymmetric centres in the molecule and, also, because of the heavily substituted nature of the spiro - [5 : 4] - decane system.

The Approach by Acetylenic Precursors.

As a model experiment to examine the feasibility of this method of constructing the spiro - centre in acorone (37), it was decided to synthesize the keto - acid (159). The quaternary centre in (159) was formed by 1 : 4 addition[72] of ethynylmonomagnesium bromide to cyclohexylidene - malononitrile (160a) giving the ethynyl - dinitrile (161a).

Basic hydrolysis of (161a) was accompanied by intramolecular hydration of the triple bond to give the keto - malonic acid (162) which was subsequently decarboxylated to give the γ- keto - acid (163).

This acid (163) had been reported[73] as a crystalline solid, but our product would not crystallize. It was thus obviously desirable to confirm the validity of the literature report. The Indian workers reported a m.p. 123° for 1 - ethylcyclohexylacetic acid formed by Clemmenson reduction of their keto - acid. It was decided to synthesize 1 - ethylcyclohexylacetic acid by an unambiguous method. Conjugate addition of ethylmagnesium bromide to

160

a ; R' = H

b ; R' = Ph.CO.O–

c ; R' = –OH

d ; R' = 

161

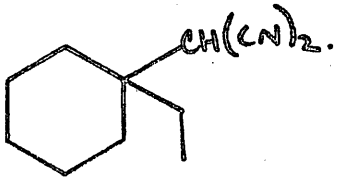
a ; R' = H , R'' = H

b ; R' = Ph.COO , R'' = H

c ; R' = H , R'' = Ph

d ; R' = H , R'' = C_6H_{13}

e ; R' = H , R'' = 



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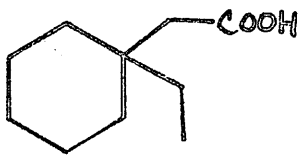

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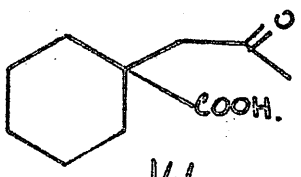

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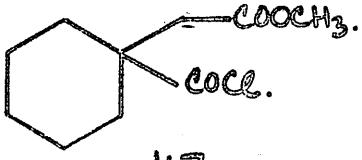

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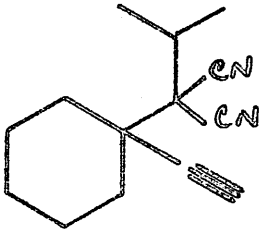

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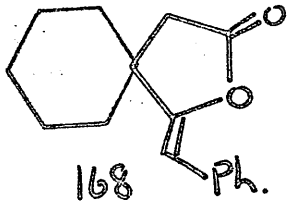

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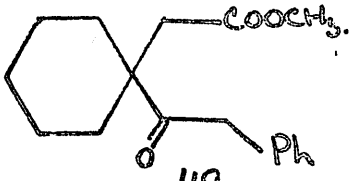

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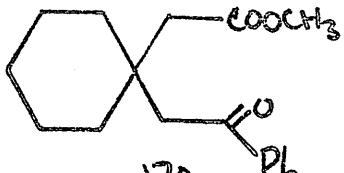

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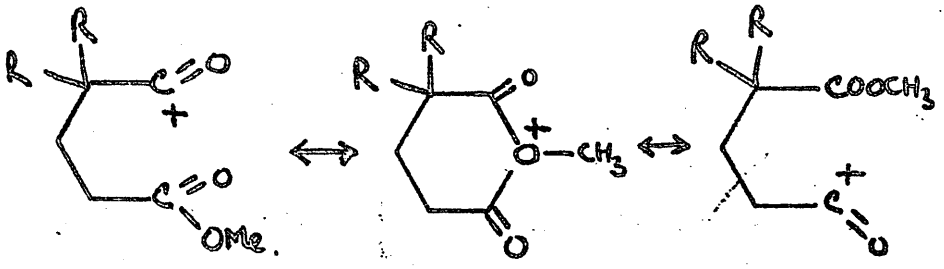


(160a) afforded the saturated dinitrile (164) which, on hydrolysis, furnished 1 - ethylcyclohexylacetic acid (165) as a viscous gum which would not crystallize.

It is thus possible that the compound reported as being 1 - acetylcyclohexylacetic acid (163) was in fact, the isomeric keto - acid (166). There is some justification for this claim since the earlier method of preparing 1 - acetylcyclohexylacetic acid (163) involved the reaction of methylzinc iodide on the ester - acid chloride (167). Such unsymmetrical ester - acid chlorides as known[74] to rearrange in presence of Lewis acids e.g. aluminium chloride or magnesium chloride, possibly by the mechanism[75] shown. This results in the nucleophilic attack occurring at the least hindered acylium ion, i.e. primary.

The ethynyl - dinitrile (161a) was treated with isopropyl iodide and sodium ethoxide to give (175), which was hydrolysed to furnish the desired keto - acid (159).

A series of such conjugate Grignard additions was carried out in order to examine this procedure as a general synthetic route (see opposite). Alkaline hydrolysis of (161c) followed by thermal decarboxylation and esterification gave a mixture of the enol - lactone (168) and the keto - ester (169), which were separated by chromatography. The failure to isolate the benzoyl - ketone (170) is indicat of internal hydration proceeding via γ - enol lactone and not a δ - enol lactone intermediate. An interesting

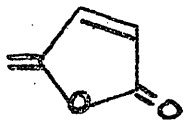
$CH_3.CH=^{c}CH.C\equiv C.C\equiv C.C\equiv C.CH=^{c}CH.COOH.$

171

$CH_3.C\equiv C.C\equiv C.C\equiv C.C\equiv C.CH=^{c}CH.COOH.$

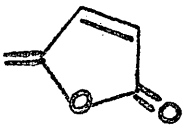
172

$CH_3.CH=^{c}CH.C\equiv C.CH=$



173

$CH_3.C\equiv C.C\equiv C.CH=$



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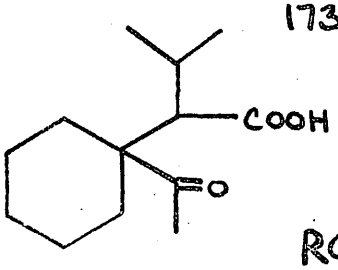

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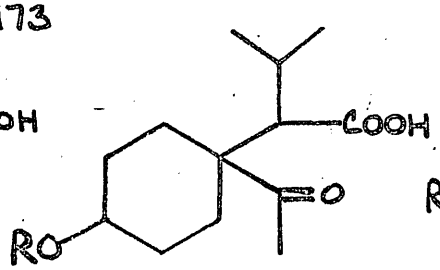

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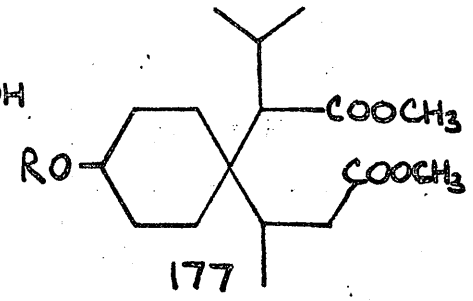

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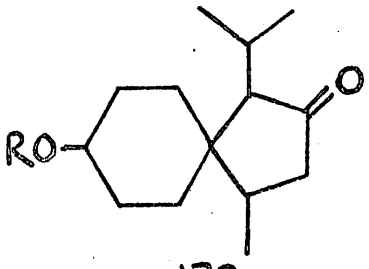

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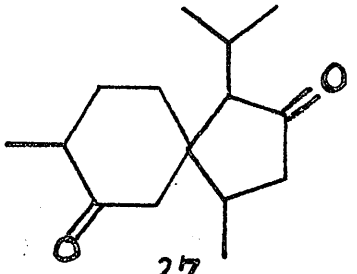

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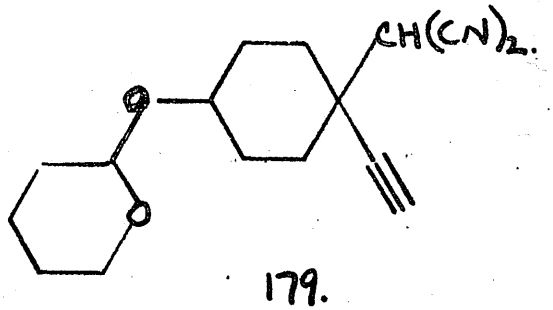
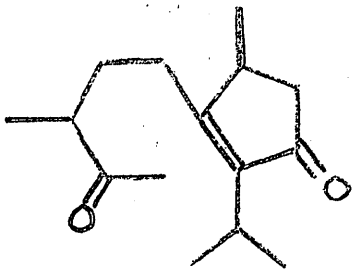


179.

analogy for this is the lactonization [76] of the naturally occurring polyacetylenic acids (171) and (172) at pH7.6 to give the corresponding γ - enol lactones (173) and (174).

It was then decided to repeat the successful synthesis of the model acid (159) using a 4 - oxygenated cyclo - hexylidene malononitrile in order to obtain a compound of the type (176). Such a compound when subjected to a Reformatski reaction with ethyl bromoacetate, followed by dehydration and hydrogenation would furnish the diester (177). Dieckmann cyclization and decarboxylation of this diester would then give the spiro - cyclopentanone (178), which could then be elaborated by standard procedures to the required acorone type structure (37).

To this end, we prepared 4 - benzoyloxycyclo - hexylidenemalononitrile (160b) and also 4 - tetrahydro - pyranyloxycyclohexylidenemalononitrile (160d) via 4 - hydroxycyclohexylidenemalononitrile (160c). The conjugate addition of ethynylmonomagnesium bromide to (160b) gave 4 - benzoyloxy - 1 - ethynylcyclohexylmalononitrile (161b) as a mixture of epimers, which were separated by careful chromatography on alumina (III). When the preparation of (179) was attempted by this method, no pure product could be isolated, although there was spectroscopic evidence for the presence of (179) in the crude reaction product.



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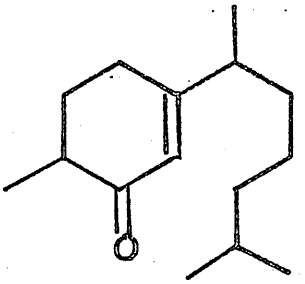

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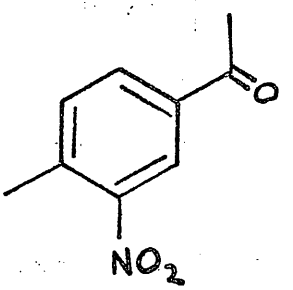

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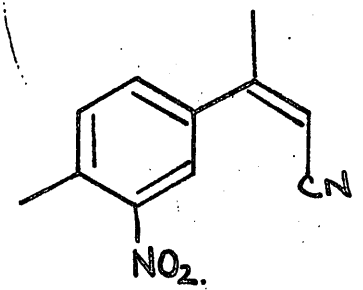

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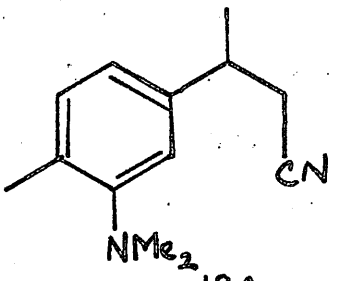

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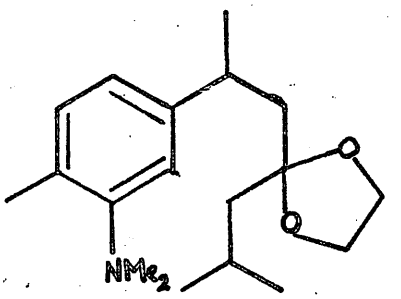


185

Due to the low yield encountered at this stage it was decided to abandon this route in favour of an alternative approach to the spiro [5 : 4] decane system.

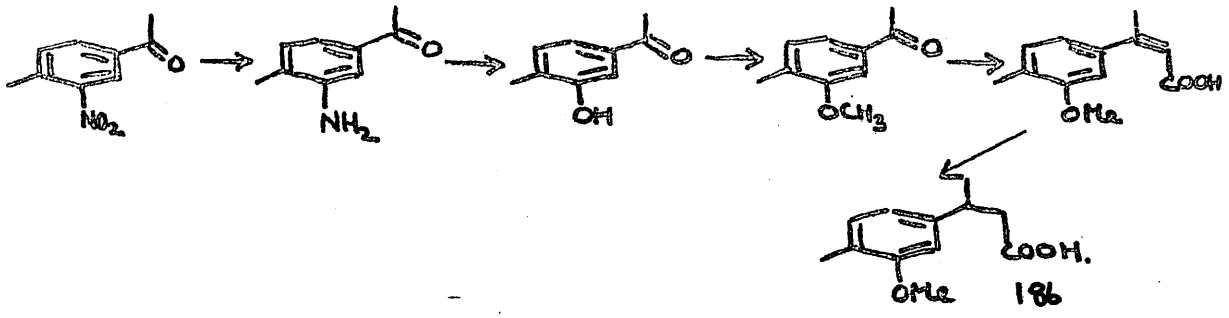
Approach by an Intramolecular Michael Condensation.

Since acorone (37) is a 1 : 5 - diketone, such a structure could be formed by internal cyclization of a suitably substituted enedione*. There are two enediones (180) and (181), which could plausibly give acorone directly on cyclization. The more accessible cyclohexenone (181) was chosen as the key precursor in this synthesis.

4 - Methyl - 3 - nitroacetophenone[80] (182) was condensed with cyanoacetic acid, followed by thermal decarboxylation of the resultant cyano - acid, to give the α: β - unsaturated nitrile (183)[81] in poor yield. Reduction of the double bond in this latter compound with concomitant reductive methylation[82] of the nitro - group afforded the dimethylamino - nitrile (184). It was hoped to convert this compound into (185) by reaction with isobutylmagnesium bromide followed by ketalization. Metal - ammonia reduction[83] of (185) would then be expected to give (181). However, this approach was discontinued owing to the low yield from the Knoevenagel reaction between

* Several beautiful examples of this type of reaction occur in the work of Woodward[77], Corey[16], Buchi[78], Barton[79].

Route to 4;β -dimethyl-3-methoxy dihydrocinnamic acid (186).



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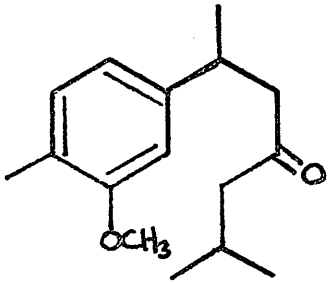

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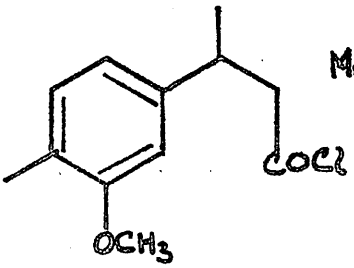

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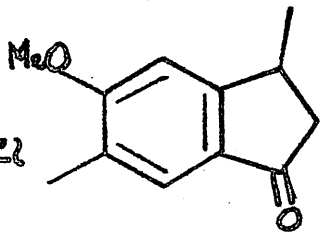

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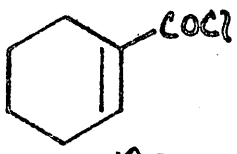

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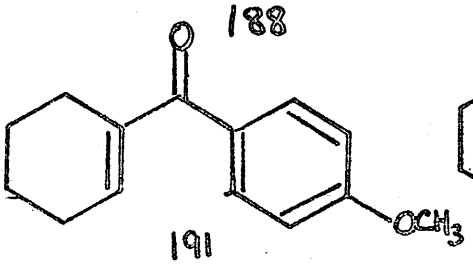

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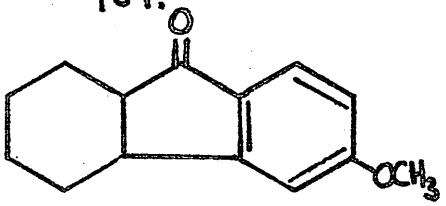

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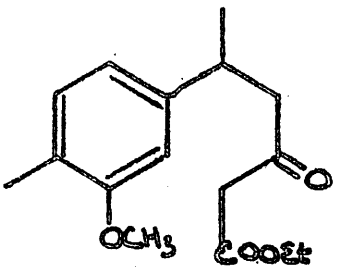

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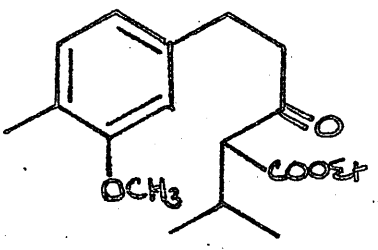


194.

(182) and cyanoacetic acid.

4 - Methyl - 3 - nitroacetophenone was converted by standard methods into 4 : β - dimethyl - 3 - methoxy - dihydrocinnamic acid (186)[84], which was converted to the ketone (187) by three methods.

(i) The reaction between the acid chloride (188) and diisobutylcadmium gave the expected ketone (187) in poor yield, the major product being the indanone (189). In the formation of organo - cadmium derivatives from Grignard reagents, there is formed an equimolar quantity of MgX_2 and it is this Lewis acid which probably brought about the internal Friedel Crafts reaction leading to (189). An interesting analogy for this is to be found in the reaction between the acid chloride (190) and the cadmium compound derived from m - bromoanisole[85]. The products from this reaction were (191) and the hydrofluorenone (192).

(ii) Condensation of the acid chloride (188) with sodio - tertbutylethyl malonate, followed by acid - catalysed loss of isobutene and carbon dioxide led to the formation of the β - ketoester (193). Alkylation of this with isopropyl bromide and potassium tert - butoxide gave (194) which on hydrolysis and decarboxylation furnished the ketone (187).

(iii) The best overall yield was obtained using the technique devised by Bowman[86]. The acid chloride (188) was condensed with dibenzyl isopropylmalonate and resulting dibenzyl

ester (195) hydrogenolysed to give the β - ketomalonic acid, which smoothly decarboxylated to the desired ketone (187).

The carbonyl function in (187) was then protected by ketal formation giving (196), since metal - ammonia reduction would certainly reduce the ketone to the alcohol.

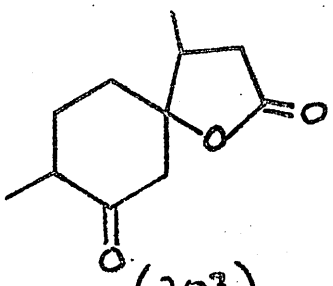
It is interesting to note that the substitution pattern in (196) is such that it defines uniquely which unsaturated ketone would result from metal - ammonia reduction. The orientation of proton addition was established by Birch's[87] work on the mechanism of this type of reduction. Addition of one electron to an aromatic ether (197) (or tertiary amine) results in the reversible formation of a radical ion (198), which in the presence of a proton donor e.g. ethanol, would lead to the irreversible addition of a proton at the position of greatest free charge density[88], i.e. meta - to the methoxyl in (198). Where there is an ortho - alkyl substituent, the first proton adds ortho - to the alkyl group and meta - to the methoxyl ; however, when there is a meta - alkyl substituent, the addition is such, that the proton avoids the position occupied by the alkyl group. It is at this stage, that the specificity of the reduction is decided. The radical (199) formed by addition of the first proton can then pick up another electron to give the ion (200), which is protonated to give

the 1 : 4 - dihydro compound.

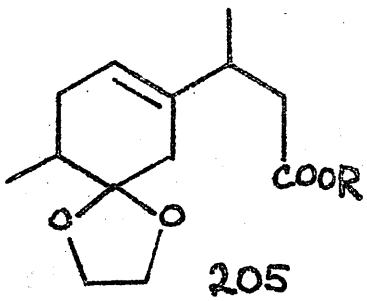
Birch reduction of (196) afforded the dihydro compound (201), which on treatment with mineral acid, yielded the enedione (181). This compound could not be induced to undergo an internal Michael reaction. The product of such attempts was an $\alpha\beta$ - unsaturated cyclohexenone, $C_{15}H_{22}O$ which was characterized as the 2 : 4 - dinitrophenylhydrazone. In order to effect the desired internal cyclization, the carbanion must form α - to the acyclic carbonyl fuction in (181), however, the formation of the $\alpha\beta$ - unsaturated ketone could only arise from an intramolecular aldol reaction. Thus, under basic conditions, the carbanion must have formed preferentially in the cyclohexenone moiety of (181). During early degradative work[58] on the structure of acorone Sorm and coworkers isolated a C_{10} - cyclohexenone produced by alkali treatment of acorone.

It was therefore decided to create a situation, which would ensure carbanion formation at the methylene adjacent to the saturated ketone i. e. activation of this methylene group by placing an electron - withdrawing carbethoxyl group at this position.

Lithium - ammonia reduction of the acid (186) gave the non - conjugated keto - acid (202), which was isomerized to the $\alpha\beta$ - unsaturated keto - acid (204, R=H) by treatment with fused potassium acetate[89] in refluxing



(203)



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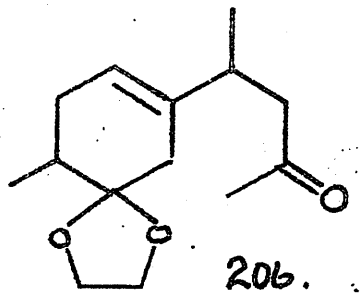

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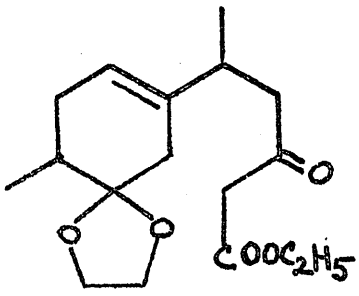

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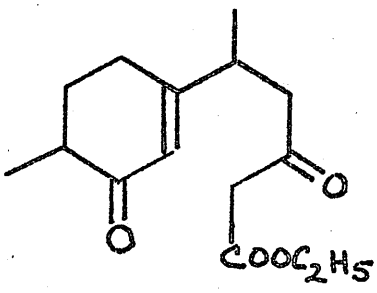

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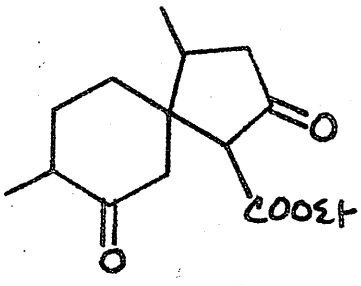

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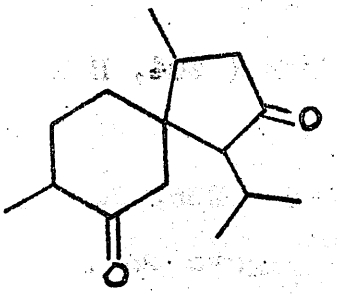

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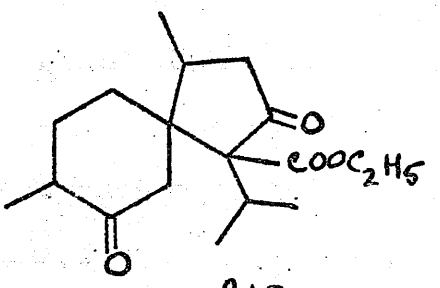
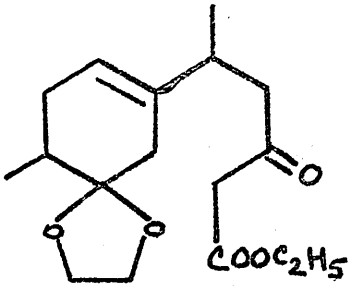


210.

amenable to spectroscopic examination, since the cyclo - hexenone chromophore in (208) diminished as the cyclization proceeded. During the course of the reaction a bathochromic shift of 6mμ was observed in the ultraviolet (in base), due to the formation of the monosubstituted β - keto ester (209). The reaction was found to have first order kinetics, since the ultraviolet maximum at 237mμ , due to the enone chromophore, decreased linearly with time. A dimerization mechanism was excluded by the mass spectrum of the product which gave a value of 266 for the molecular weight of (209).

The spiro β - keto ester (209) was then treated with isopropyl iodide and sodium ethoxide, but the yield of neutral material from this reaction was poor, probably due to the steric hindrance associated with the adjacent quaternary centre[93]. Hydrolysis and decarboxylation of this alkylated β - keto ester (210) gave a diketone which exhibited absorption maxima in the infrared at 1745cm^{-1} and 1710cm^{-1} (CS_2 solution). The carbonyl region was compatible with the structure (37) and the finger - print region was similar, although not identical to the naturally occurring isomeric acorones. Chromatographic separation of the complex mixture of stereoisomers was not possible due to the small quantity of the diketone available at this stage.

It is hoped to reverse the order of alkylation and



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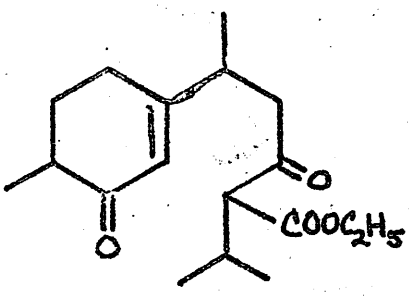

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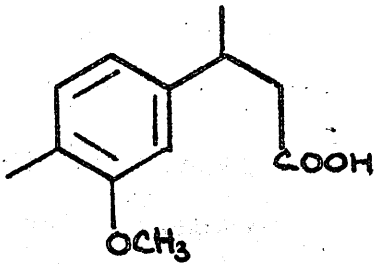

186.

cyclization to give a higher yield of the alkylated spiro β - keto ester (210). This would involve alkylating the ketal β - keto -ester (207), followed by deketalization to the en one alkylated β - keto ester (211), which should cyclize to (210). Another method of introducing the isopropyl group would involve the action of methyl - magnesium bromide on the bis ketal - ester of (209) followed by dehydration and reduction.

If separation of the above complex mixture of stereo - isomers proves impossible, the starting acid (186) could be resolved and the synthesis repeated with optically pure material of known absolute configuration[94] . Since acorone and cedrene are thought to be related biogenetically, it is reasonable to assume that the configuration of the C_1 methyl group in acorone is the same as the corresponding position in cedrene. Thus, knowing the absolute configuration of cedrene[23] we could decide which stereoisomer of (186) to use in the synthesis. This would mean that of the four asymmetric centres in the final product, one would be fixed and two others epimerizable with base to the most stable configuration, hence facilitating separation at the final step.

EXPERIMENTAL.

Cyclohexylidenemalononitrile, (160a).

This was prepared in the usual manner[96] by refluxing cyclohexanone (64·5g) and malononitrile (40g) with ammonium acetate (4·6g) and acetic acid (7·5g) in benzene. Isolation gave the required product (70·4g), b.p. 86°/ 2mm, n_D^{25} 1·5100, Vmax (film) 2230cm^{-1} (conjugate nitrile), 1595cm^{-1} (double bond), λ max 237mμ, ε=11,000.

4 - Benzoyloxycyclohexylidenemalononitrile. (160b).

A mixture of 4 - benzoyloxycyclohexanone (18g)[95] , malononitrile (3·3g), ammonium acetate (0·5g) and acetic acid (0·7g) in benzene (50ml) was refluxed for 15 hours using a Dean and Stark water separator. After the cooled reaction mixture had been washed with saturated sodium hydrogen carbonate and water, the benzene solution was dried and the solvent removed to give 4 - benzoyloxycyclo - hexylidenemalononitrile (10g) which crystallized from methanol in prisms m.p. 135°- 136° (Found : C,71·95 ;H,5·50 ; N,10·50 . $C_{16}H_{14}N_2O_2$ requires C,72·15 ; H,5·30 ; N,10·50 %). Vmax (nujol) 1720cm^{-1} (benzoate), 2230cm^{-1} (conjugated nitrile).

4 - Hydroxycyclohexylidenemalononitrile. (160c).

4 - Hydroxycyclohexanone[97] (25g), malononitrile (13·5g),

acetic acid (2·4g), ammonium acetate (1·54g) were reacted as in the previous experiments to yield 4 - hydroxy cyclohexylidenemalononitrile (22g), which crystallised from ether - light petroleum (40°-60°) in prisms m. p. 60° - 62°, b. p. 140° / 0·4mm (Found : C, 66·85 ; H, 6·35 ; N, 17·30 $C_9H_{10}N_2O$ requires C, 66·65 ; H, 6·20 ; N, 17·30 %). Vmax (film) 3450cm^{-1} (hydroxyl), 2230cm^{-1} (conjugated nitrile), λ max 237mμ ε = 11,000.

4 - Tetrahydropyranyloxycyclohexylidenemalononitrile (160d).

One drop of concentrated hydrochloric acid was added to a solution of 4 - hydroxycyclohexylidenemalononitrile (11g) in dihydropyran (20ml) held at 0°C. An exothermic reaction occurred and the reaction mixture was allowed to stand at room temperature for 16 hours, then heated at 60°C for 2 hours and again left for 16 hours. Ether (100ml) was added and the organic layer washed with sodium hydrogen carbonate solution, water and dried. Removal of the solvent afforded 4 - tetrahydropyranyloxycyclohexylidene - malononitrile (15g), which solidified to a crystalline mass. b. p. 167°/ 0·05mm. m. p. 61°. (Found : C, 68·10 ; H, 7·10 ; N, 11·60. $C_{14}H_{18}N_2O_2$ requires C, 68·25 ; H, 7·35 ; N, 11·35 %). Vmax (film) 2230cm^{-1} (conjugated nitrile). λ max 237mμ ε = 11,000.

1 - Ethynylcyclohexylidenemalononitrile. (16le).

A warm solution of ethylmagnesium bromide (from magnesium, 6.0g) in dry tetrahydrofuran (200ml), was transferred under nitrogen to a dropping funnel and added over 3 hours to a stirred saturated solution of acetone - free acetylene in tetrahydrofuran (500ml). Acetylene was passed through the solution during this addition and for a further hour. Freshly prepared cuprous chloride (5 mole %) followed by cyclohexylidenemalononitrile (7.5g) in dry tetrahydrofuran (100ml) was added over 3 hours to the ethynylmonomagnesium bromide solution held in a nitrogen atmosphere and the reaction mixture stirred for 20 hours at 20° C. The Grignard complex was then decomposed with excess saturated ammonium chloride solution. Ether extraction followed by washing with saturated sodium chloride solution, drying and removal of the solvent gave a red oil, λmax 257mμ, ε=1800, i.e. 16 % of starting material was present. An ethanolic solution of the crude oil was treated with potassium cyanide (1g) in a minimum volume of water and stirred for 4 hours. The reaction mixture was then poured into water, extracted with ether, etc. Removal of the solvent followed by distillation gave 1 - ethynylcyclohexylidenemalononitrile (4.2g), b.p. 74°/ 0.1mm., n_D^{25} 1.[illegible] (Found : C, 76.60 ; H, 6.75 ; N, 10.60 $C_{11}H_{10}N_2$ required C, 76.70 ; H, 7.00 ; N, 10.50 %). Uv ([illegible]) [illegible]

(ethynyl), 2270cm^{-1} (saturated nitrile) 2100cm^{-1} (acetylenic triple bond).

4 - Benzoyloxy - 1 - ethynylcyclohexylmalononitrile (161b).

4 - Benzoyloxycyclohexylidenemalononitrile (30g) in tetrahydrofuran (250ml) was added to a solution of ethynylmonomagnesium bromide (from magnesium, 12g ; prepared was in the previous experiment). Stirring was continued for 4½ hours at 4°C in an atmosphere of nitrogen. Decomposition of the Grignard complex and isolation of the product gave a dark red gum which was adsorbed on grade I alumina (900g) from benzene - light petroleum (40°-60°) (5 : 1). Elution with benzene - light petroleum (4 : 1) gave 4 - benzoyloxycyclohexylidenemalononitrile (5g). Elution with benzene afforded 4 - benzoyloxy 1 - ethynyl-cyclohexylmalononitrile (4.3g) which crystallized from carbon tetrachloride in prisms m.p. 129° - 130° (Found : C,73.75 ; H, 5.20 ; N, 9.80 $C_{18}H_{16}N_2O_2$ requires C,73.95 ; H,5.50 ; N,9.60 %). Vmax (KCl disc) 3300cm^{-1} (ethynyl C - H), 2270cm^{-1} (nitrile), 1720cm^{-1} ester. Further elution with benzene - chloroform (4 : 1) gave the isomer of 4 - benzoyloxy - 1 - ethynylcyclohexylmalononitrile (2.6g), which crystallized from methanol as prisms mp. 177° - 178°. (Found : C, 74.20 ; H,5.30 ; N,9.65 . $C_{18}H_{16}N_2O_2$ requires C,73.95 ; H,5.50 ; N,9.60 %).

1 - Phenylethynylcyclohexylmalononitrile. (161c).

Phenylacetylene (10.2g) in dry tetrahydrofuran (20ml) was added to a stirred solution of ethylmagnesium bromide (from magnesium, 2.4g) in tetrahydrofuran (250ml) and the reaction mixture heated under reflux for 2 hours. The cooled reaction mixture was then treated with cuprous chloride (5 mole %) followed by a solution of cyclohexylidene-malononitrile (7.5g) in tetrahydrofuran (25ml). After 4 hours heating under reflux the Grignard complex was decomposed with a saturated ammonium chloride solution. Extraction with ether, washing with water, drying and removal of the solvent gave a red viscous gum, which solidified on trituration with light petroleum (40° - 60°). to give 1 - phenylethynylcyclohexylmalononitrile (5g), which crystallized from light petroleum in needles m.p. 62° - 63°. (Found : C, 82.35 ; H, 6.40 ; N, 11.20 $C_{17}H_{16}N_2$ requires C, 82.20 ; H, 6.50 ; N, 11.30 %).

1 - Octynylcyclohexylmalononitrile. (161d.).

Oct - 1 - yne (11g) in dry tetrahydrofuran (50g) was added to a solution of ethylmagnesium bromide (from magnesium, 2.4g) in tetrahydrofuran (85ml) and the reaction mixture heated under reflux in an atmosphere of nitrogen for 20 hours. Cuprous chloride (5 mole %) was added to the reaction mixture chilled to 0° C followed by the slow addition of cyclohexylidenemalononitrile (9.0g)

in tetrahydrofuran. Stirring was continued for 18 hours at room temperature, then the solution was refluxed for 8 hours before being worked up as in the previous experiment to yield a viscous oil. Distillation gave a fore - run of cyclohexyliedenemalononitrile (1.0g) followed by 1 - octynylcyclohexylmalononitrile (7.0g) as a colourless oil, b.p. 112°/ 0.1mm ; n_D^{21} 1.4785 (Found : C,79.75 ; H,9.45 ; N,10.80 $C_{17}H_{24}N_2$ requires C,79.65 ; H,9.45 ; N,10.95 %). Vmax (film) 2260cm^{-1} (saturated nitrile) 2100cm^{-1} (C≡C).

1 - Tetrahydropyranyloxypropargylcyclohexylmalononitrile (16le).

3 - Tetrahydropyranyloxyprop - 1 - yne[98] (14g) in dry tetrahydrofuran (25ml) was added to a solution of ethylmagnesium bromide (from magnesium, 2.4g). The reaction mixture was then refluxed for 8 hours under nitrogen and chilled to 0° C. Cuprous chloride (5 mole %) was then added followed by the slow addition of cyclohexyl - idenemalononitrile (9g) in tetrahydrofuran (20ml). The reaction mixture was stirred for 4 hours at room temperature, then refluxed for 20 hours before being worked up in the usual way to give a dark red viscous gum. Distillation gave a fore - run of cyclohexylidenemalononitrile (4g) followed by 1 - tetrahydropyranyloxypropargyl - malononitrile (3g) as a colourless oil b.p. 140 / 0.05mm ;

n_D^{21} 1·4920 (Found : C,71·60 ; H,7·95 ; N,10·1 $C_{17}H_{22}O_2N_2$ requires C,71·30 ; H,7·75 ; N, 9·80 %).

1 - Acetylcyclohexylmalonic acid, (162).

1 - Ethynylcyclohexylmalononitrile (500mg) and 5% potassium hydroxide solution (20ml) were heated under reflux until ammonia ceased to be evolved. The reaction mixture was acidified with dilute hydrochloric acid , extracted with ether, and the organic layer washed with brine and dried. Removal of the solvent afforded 1-acetyl - cyclohexylmalonic acid (270mg), which crystallized from ethyl acetate - light petroleum (60°-80°) in prisms m.p. 124° - 6° (decomposition). (Found : C,57·85 ; H, 6·60 ; $C_{11}H_{16}O_5$ requires C,57·90 ; H, 7·05 %).

1 - Acetylcyclohexylacetic acid, (163).

1 - Acetylcyclohexylmalonic acid (250mg) was heated in vacuo at 130°C for 20 minutes to give 1 - acetylcyclo - hexylacetic acid (200mg) as a colourless gum b.p. 113°/0·1mm (Found : C,66·05 ; H,8·55 $C_{10}H_{16}O_3$ requires C,65·20 ; H,8·75 %).

Treatment with ethereal diazomethane furnished the corresponding methyl ester ; Vmax (film) 1735cm^{-1}(ester), 1705cm^{-1} (ketone). Semicarbazone crystallized from ethanol in prisms, m.p. 147°.

1 - Ethylcyclohexylmalononitrile. (164).

Cyclohexylidenemalononitrile (14g) in ether (20ml) was added slowly to ethylmagnesium bromide (from magnesium, 4.8g) in ether (100ml). The reaction mixture was refluxed for 1½ hours, and then stirred for 16 hours before being decomposed with ammonium chloride solution. Isolation, in the usual manner, gave 1 - ethylcyclohexylmalononitrile (9g) ; b.p. 152°/ 12mm ; n_D^{24} 1.4725 (Found :C,74.55 ; H, 9.30 ; N, 15.95 $C_{11}H_{16}N_2$ requires C,74.95 ; H,9.15 ; N,15.90 %). Vmax (film),2270cm^{-1} (saturated nitrile).

1 - Ethylcyclohexylacetic acid. (165).

A mixture of the dinitrile (164) (4.5 g) and concentrated hydrochloric acid (170ml) was vigouously refluxed for 70 hours, and then reduced to half bulk. The ether extract was washed with sodium hydrogen carbonate solution and the alkaline layer acidified, re - extracted, washed with water and dried. Removal of the solvent gave a gum (4g), which was triturated with light petroleum and filtered. Evaporation of the light petroleum, followed by distillation yielded 1 - ethylcyclohexylacetic acid as a colourless gum b.p. 86° - 8°/ 0.12mm ; $n_D^{24.5}$ 1.4693 (Found: C,70.35 ; H,10.40 $C_{10}H_{18}O_2$ requires C, 70.55 ; H,10.65 %). Vmax (film), 1700cm^{-1} (carboxylic acid).

Alkaline hydrolysis of 1-phenylethynylcyclohexylmalononitrile.

A mixture of 1 - phenylethynylcyclohexylmalononitrile (2·2g) and 20% potassium hydroxide solution (100ml) was refluxed, until ammonia ceased to be evolved. The solution was then acidified, extracted with ether and the organic layer was washed with water and dried. Removal of the solvent gave a gum, which was decarboxylated by heating in vacuo at 100°C for 2 hours. A portion of the product (1g) was esterified with ethereal diazomethane and the resulting ester adsorbed on grade III alumina from light petroleum (60° - 80°). Elution with light petroleum (60° - 80°)-benzene (5 : 1) yielded the γ - enol lactone (168) (200mg), which crystallized from n - hexane in needles m.p. 111° - 112·5° (Found : C, 79·05 ; H, 7·40 ; $C_{16}H_{18}O_2$ requires C, 79·30 ; H, 7·50 %). Vmax (KCl) 1800cm^{-1} (γ - enol lactone), 1670cm^{-1} (enol - double bond). λ max 256mμ ε=24,000.

Elution with light petroleum (60°-80°)-benzene (4 : 1) afforded the keto ester[169], (600mg) as a colourless oil, b.p. 120° / 0·05mm (bath temp.) ; n_D^{25} 1·5238 (Found : C, 74·20 ; H, 8·25 $C_{17}H_{22}O_3$ requires C, 74·40 ; H, 8·10 %). Vmax (film) 1730cm^{-1} (ester), 1710cm^{-1} (ketone).

1 - Ethynylcyclohexylisopropylmalononitrile, (175).

A solution of 1 - ethynylcyclohexylmalononitrile (2·3g)

and sodium ethoxide (from sodium, 0.33g) in dry ethanol (20ml) was refluxed for 3 hours, then chilled to -15° C. Isopropyl iodide (2.5g) was added and the reaction mixture heated under reflux for 16 hours. After removal of most of the ethanol, water was added and the solution extracted with ether. The ethereal extract was washed with water, dried and the solvent removed to furnish 1 - ethynylcyclohexylisopropylmalonic acid (900mg), which crystallized from petroleum ether (40° - 60°) in prisms m.p. 88° - 89° (Found : C, 78.80 ; H, 8.35 ; N, 13.25 ; $C_{14}H_{18}N_2$ requires C, 78.45 ; H, 8.45 ; N, 13.05 %).

α-(1 - Acetylcyclohexyl) - isovaleric acid. (159)

Sufficient ethanol was added to a mixture of 1 - (ethynyl) cyclohexylisopropylmalononitrile (600mg) and 30 % potassium hydroxide (25ml) to give a homogeneous solution, which was refluxed till no more ammonia was evolved The reaction mixture was acidified with dilute sulphuric acid and warmed at 100 for 20 minutes in order to effect decarboxylation of the intermediate malonic acid. The solution was extracted with ether, washed with brine and dried ($MgSO_4$). Removal of the solvent afforded α - (1 - acetylcyclohexyl) - isovaleric acid (575mg) which crystallized from ethyl acetate - light petroleum (60° - 80°) in prisms m.p. 108° - 109° (Found : C, 69.15 ; H, 9.55 ;

$C_{13}H_{22}O_3$ requires C, 69·00 ; H, 9·80 %).

4 - Methyl - 3 - nitroacetophenone (182).

This was obtained by the method described by Brady and Day [80].

4 : β - Dimethyl - 3 - nitro - cinnamonitrile (183).

A mixture of 4 - methyl - 3 - nitroacetophenone, cyanoacetic acid (6g), glacial acetic acid (2ml), and ammonium acetate (1·5g) in benzene (30ml) was heated under reflux for 10 hours. The cooled solution was washed with aqueous sodium hydrogen carbonate and water. Removal of the solvent gave a solid, which was decarboxylated at 140°/ 10mm to yield 4 : β -dimethyl-3-nitro-cinnamonitrile (1·1g), which crystallized from ethanol in needles m. p. 102° (Found : C, 65·25 ; H, 5·10 ; N, 14·05 $C_{11}H_{10}NO_2$ requires C, 65·35 ; H, 5·00 ; H, 13·85 %).
Vmax (nujol) 2210cm^{-1} (conj. nitrile), 1520cm^{-1} (nitro).

4 : β -Dimethyl-3-dimethylaminodihydrocinnamonitrile (184).

A solution of the cinnamonitrile (800mg) in ethanol (100ml), containing 30% formalin (3ml) and palladium on charcoal (5%), was hydrogenated at 5 atmospheres pressure for 48 hours. Filtration, and evaporation of the solvent was followed by the usual extraction procedure.

The crude product was adsorbed on grade H alumina from benzene - light petroleum (60° - 80°); (1 : 4). 4 : β - Dimethyl - 3 - dimethylaminodihydrocinnamonitrile (400mg) was eluted by benzene - light petroleum (60° - 80°); (1 : 1) as a colourless oil. (Found : C,76.70 ;H,9.15 ; N,13.85 $C_{13}H_{18}N_2$ requires C,77.15 ; H, 8.95 ; N,13.85 %). Vmax (film) 2240cm^{-1} (saturated nitrile), 1600 - 1570cm^{-1} (aromatics).

4 : β - Dimethyl - 3 - methoxydihydrocinnamic acid. (186).

This was obtained by the method described by Lindahl[84].

Reaction between 4: β -dimethyl-3-methoxydihydrocinnamoyl chloride/cadmium diisobutyl.

4 : β - Dimethyl - 3 - methoxydihydrocinnamic acid (1g) and oxalyl chloride (0.7ml) were allowed to stand for 4 hours in benzene (20ml). Removal of the solvent and residual oxalyl chloride afforded this acid chloride(188). Vmax (film) 1790cm^{-1} (acid chloride).

Dry cadmium chloride (1.76g) was added to a solution of isobutylmagnesium bromide (from magnesium, 0.46g) in ether (25ml). After 1½ hours reflux the ether was replaced by benzene (25ml). A solution of the acid chloride in benzene (20ml) was added 0°C to the benzene solution of the cadmiumdiisobutyl. The reaction

mixture was then heated under reflux for 1½ hours, followed by stirring at room temperature overnight. The complex was decomposed with N sulphuric acid, and the benzene solution washed with sodium hydrogen carbonate, brine and dried. Removal of the solvent gave an oil, which was adsorbed on grade III alumina from benzene - light petroleum (60° - 80°) (1 : 3). Elution with benzene - light petroleum (1 : 1) gave 2 - methyl - 6 - (m - methoxy - p - methylphenyl) - hept - 4 - one as an oil b.p. 110°/0.3mm. (Found : C, 77.05 ; H, 9.65 $C_{16}H_{24}O_2$ requires C, 77.35 ; H, 9.75 %). Vmax (film) 1705cm^{-1} (ketone). λmax 280mμ ε=1400.

Elution with benzene afforded 5 : 6 dimethyl 5 - methoxyindanone (520mg), which crystallized from light petroleum (40° - 60°) in prisms m.p. 90° - 92°. (Found : C, 75.85 ; H, 7.20 $C_{12}H_{14}O_2$ requires C, 75.75 ; H, 7.40 %). Vmax (CCl_4) 1706cm^{-1}, (KCl disc) 878cm^{-1} (1:2:4:5 substitutuon pattern). λ max 270mμ, ε 9000; 297mμ, ε 6000.

Ethyl 5-(m-methoxy-p-tolyl)-3-exohexanoate (193).

The acid chloride of 4 : β-dimethyl - 3 - methoxy - hydrocinnamic acid was prepared as described above.

Tert. butyl ethyl malonate (5.0g) in dry tetrahydrofuran (5ml) was added slowly to a stirred suspension of sodium hydride (1.4g) in tetrahydrofuran (40ml), and the reaction

mixture refluxed for 2½ hours. A solution of the acid chloride (from the acid, 4g) in dry tetrahydrofuran (20ml) was then added dropwise to the sodium enolate held at 0°C. After 6 hours reflux, the excess sodium hydride was decomposed by moist ether and acidified with dilute sulphuric acid. The ethereal layer was washed with sodium hydrogen carbonate solution, water and dried. Removal of the solvent gave an oil, which was dissolved in benzene containing p-toluene sulphonic acid (200mg). The solution was refluxed for 2 hours, then cooled and the above isolation procedure yielded the β - keto ester as a colourless oil (3.5g), b.p. 120° / 0.04mm n_D^{26} 1.5090. (Found: C, 68.80 ; H, 7.40 $C_{16}H_{22}O_4$ requires C, 69.05 ; H, 7.95 %). Vmax (film) 1735cm^{-1} (ester) 1715cm^{-1} (ketone) 1630cm^{-1} (chelated carbonyl).

Ethyl 5-(m-methoxy-p-tolyl)-2-isopropyl-3 oxohexanoate (194).

A solution of the β - keto ester (2.38g) in dry tert. butanol (10ml) was added to potassium tert.butoxide (from potassium, 410mg) in tert. butanol (25ml). After heating under reflux for 1 hour, the solution was stirred at room temperature for 4 hours. Isopropyl bromide (4ml) was added dropwise to the orange solution held at 0°C , followed by 12 hours reflux. The tert. butanol was replaced by benzene and the benzene solution washed with 6N

sulphuric acid, water and dried. Removal of the solvent followed by distillation gave ethyl 5 - (m - methoxy - p - tolyl) - 2 - isopropyl- 3 - oxohexanoate as a colourless oil (2.0g), b.p. 120°/0.01mm ; n_D^{21} 1.5036. (Found : C,70.85 ; H,8.60 . $C_{19}H_{28}O_4$ requires C,71.20 ; H,8.80 %).

2-Methyl-6-(m-methoxy-p-methyl)phenylheptan-4-one. (187).

A solution of the alkylated β - keto ester (1.8g) in a mixture of concentrated hydrochloric acid (2ml), glacial acetic acid (1oml), and water (5ml) was refluxed for 3 hours, then rendered alkaline with dilute sodium hydroxide solution. The crude product was isolated by the usual ether extraction procedure, and adsorbed on alumina (III) from light petroleum - benzene (5 : 1). Elution with light petroleum (60°-80°) - benzene (1 : 1) afforded an oil (0.5g) identical in all respects to 2 - methyl - 6 - (m - methoxy - p - methyl) phenylheptan - 4 - one prepared by the previous method.

Dibenzyl isopropylmalonate.

Isopropylmalonic acid was prepared by the method of Vogel[100]. A solution of the diacid (40g) in toluene (62ml) and benzyl alcohol (62ml) containing concentrated sulphuric acid (0.3ml) was heated under reflux for 2 hours ; the water produced being removed by continuous azeotropic

distillation. The cooled solution was washed with saturated sodium hydrogen carbonate solution, water and dried. Removal of the solvent followed by distillation yielded dibenzyl isopropylmalonate as a viscous oil (40g), b.p. 160° / 0.1mm ; n_D^{22} 1.5296.

2-Methyl-6-(m-methoxy-p-methyl)phenylheptan-4-one. (187).

The acid chloride of 4 : β - dimethyl - 3 - methoxy - hydrocinnamic acid was prepared as in previous experiments.

A solution of dibenzyl isopropylmalonate (32g) in dry tetrahydrofuran (60ml) was added slowly to a stirred suspension of sodium hydride (3.6g) in tetrahydrofuran (250ml). After 4 hours reflux, the mixture was chilled to 0°C and a solution of the acid chloride (from the acid, 20g) in tetrahydrofuran (70ml) was added slowly. The reaction mixture was refluxed with stirring in an atmosphere of nitrogen for 15 hours. Most of the solvent was removed in vacuo and ether (400ml) added. The excess sodium hydride was decomposed with moist ether and the ether layer washed with water and dried. Removal of the solvent gave the dibenzyl ester (195) as a yellow oil (45g).

A solution of this oil in ethanol (200ml) and ethyl acetate (100ml) was hydrogenated in presence of 10 % palladium on charcoal (4g). After 2¾ hours the solution was filtered and refluxed for 1 hour. The solvent was

removed in vacuo, and the residue heated to 170°C at 12mm pressure for 5 minutes. Ether was added to the cooled residue, and the ether washed with sodium hydrogen carbonate solution, water and dried. Removal of the solvent gave the ketone (187) as an oil (13g); b. p. 110° / 0.3mm.

4-Ethylenedioxy-2-methyl-6(m-methoxy-p-methyl)phenylheptane (196).

A solution of the ketone (17g) in a mixture of ethylene glycol (17ml) and benzene (500ml) containing β - naphthalene sulphonic acid (250mg), was refluxed for 50 hours. The water produced in the reaction was removed by continuous azeotropic distillation. The cooled solution was washed with sodium hydrogen carbonate and water. Removal of the solvent gave an oil, which was adsorbed on grade H alumina (400g). Elution with light petroleum (40° - 60°) gave the ketal as a colourless oil b. p. 108° -110° / 0.02mm ; $n_D^{19.5}$ 1.5049 (Found : C, 74.20 ; H, 9.45 $C_{18}H_{28}O_3$ requires C, 73.95 ; H, 9.65 %). Vmax (film) 1080cm^{-1}, 975cm^{-1} 950, 935cm^{-1} (ketal).

Enone ketone (181).

A solution of the ketal (196) (1.7g) in tetrahydrofuran (25ml) was added to liquid ammonia (120ml). Lithium (2.5g) - in strips - was added over 15 minutes to the homogeneous solution. After a period of 5 minutes

isopropanol (30ml) was added during 1 hour to the blue solution. Most of the ammonia was evaporated at 20°C, 10 minutes after the solution became white and water (250ml) was added. The ether extract was washed with water and dried. Removal of the solvent gave an oil which was dissolved in a solution of methanol (80ml) and 6N hydrochloric acid (20ml). The mixture was refluxed for 20 minutes, then most of the solvent removed. Water was added to the residue and the ether extract washed with sodium hydrogen carbonate, water then dried. Removal of the solvent gave (181) as an oil (1·7g) ; $n_D^{20·5}$ 1·4800 (Found: C, 75·95 ; H, 10 30 $C_{15}H_{24}O_2$ requires C, 76·20 ; H, 10 25%). Vmax (film) 1710cm^{-1} (ketone), 1680cm^{-1} (enone). λ max 237mμ ε = 16,600.

Attempted internal Michael reaction.

(i) A solution of the enedione (150mg) in tert butanol (15ml) containing potassium (15mg) was allowed to stand at room temperature for 15 hours then the solution was diluted with water and extracted with ether. The ether extract was washed with water and dried. Removal of the solvent gave a dark oil (140mg), which was adsorbed on alumina (III) from benzene - light petroleum (60°- 80°) ; (4 : 1). Elution with benzene - light petroleum (60°-80°) (1 :1) gave an oil. Vmax (film) 1670cm^{-1}

(enone), 1000cm^{-1} (double bond).

(ii) A solution of the enedione (50mg) in methanol (10ml) containing sodium methoxide (25gmg) was allowed to stand at room temperature overnight, then most of the methanol removed. Water was added to the residue and dried. Removal of the solvent gave the starting enedione.

(iii) A solution of the enedione (350mg) in ether (10ml), containing excess sodamide, was refluxed for 15 hours. Water was added and the ether layer washed with water and dried. Removal of the solvent gave the starting enedione.

(iv) A solution of the enedione (300mg) in tetrahydrofuran (15ml), containing excess sodium hydride, was refluxed with stirring for 2¾ hours. The organic layer was decanted and water added. The ether extract was washed with water and dried. Removal of the solvent gave a dark oil, which was adsorbed on grade III alumina from light petroleum (60°-80°)-benzene (4 : 1). Elution with light petroleum (60°-80°)-benzene (1 : 1) gave an oil. Vmax (film) 1670cm^{-1} (enone), 1600cm^{-1} (double bond). 2 : 4-Dinitrophenylhydrazone crystallized from n - butanol in prisms m.p. 157° - 158°. (Found : C, 63·05 ; H, 6·50 ; N, 13·75 $C_{21}H_{20}N_4O_4$ requires C, 63·30 ; H, 6·60 ; N, 13·75%). λ max 412 mμ, ε=15,000.

Methyl β-(3-oxo-4-methylcyclohexenyl)-butyrate. (204).

A solution of the acid (10g) in tetrahydrofuran (50ml) was added slowly to liquid ammonia (1000ml), followed by strips of lithium (12.75g), added as rapidly as possible without the reaction becoming too exothermic. Isopropanol (170ml) was added over ½ hour to the blue solution and the reaction mixture stirred for 5 hours. The ammonia was allowed to evaporate at room temperature leaving a residue which was dissolved in ice and 6N hydrochloric acid and extracted with ethyl acetate (8 X 100ml) after which the organic layer was washed with water and dried. Removal of the solvent afforded the enone acid (9.9g) as gum which on treatment with excess ethereal diazomethane yielded the corresponding ester (9.7g). This was adsorbed on silica from light petroleum -(60-60)- benzene (4 : 1). Elution with benzene gave methyl β- (3 - oxo - 4 - methylcyclohexenyl) - butyrate (204) as an oil (7.8g), b.p. 105 / 0.07mm. ; n_D^{25} 1.4865. Vmax (film) 1735cm^{-1} (ester), 1670cm^{-1} (enone). λmax 237mμ ε=15,500.

The enone ester furnished a semicarbazone m.p. 150° - 153°. (Found ; C,58.60 ; H,7.65 ; N,15.65 $C_{13}H_{21}N_3O_3$ requires C,58.40 ; H,7.90 ; N,15.90 %).

Methyl β-(5-ethylenedioxy-4-methylcyclohexenyl)-butyrate (205).

p - Toluenesulphonic acid (750mg) was added to a

solution of the enone ester (17g) in benzene (500ml) and ethylene glycol (20ml). The mixture was heated under reflux for 70 hours then cooled and the p - toluene sulphonic acid neutralized with sodium ethoxide, washed with water and dried. Removal of the solvent gave an oil, which was adsorbed on grade H alumina from light petroleum (60° - 80°).

Elution with light petroleum (40° - 60°) - benzene (3 : 1) gave an oil (13·7g), which on distillation afforded the ketal (11·3g) as an oil b.p. 170°/ 0·07 mm ; n_D^{23} 1·4812 (Found : C, 66·20 ; H, 8·55 ; $C_{14}H_{22}O_4$ requires C, 66·10 ; H, 8·70 %). Vmax (film) 1735cm^{-1} (ester) ; 1090cm^{-1} , 1080cm^{-1} , 1040cm^{-1} , 960cm^{-1} (ketal).

β - (5-Ethylenedioxy-4-methylcyclohexenyl)butyric acid, (205).

The ketal - ester (1·34g) was stirred at 100°C with N sodium hydroxide solution (17·82ml) for 45 minutes and the cooled, homogeneous solution neutralized with N hydrochloric acid (17·75ml) at 0 C . The ether extract was dried and evaporated to give the acid as a thick gum (1·32g). Vmax (film) 3200 - 2700cm^{-1} (bonded - OH) 1700cm^{-1} (carboxyl).

4-(5-Ethylenedioxy-4-methylcyclohexenyl)pentan-2-one (206).

A solution of lithium methyl (from lithium, 1·05g) and methyl iodide, 10g) in ether (150ml) was added during 5 minutes, in an atmosphere of nitrogen, to a stirred solution

of the ketal - acid (8g) in ether (150ml). The reaction mixture was refluxed for 1 hour, cooled, water added and the ethereal layer washed with water and dried. Removal of the solvent gave the methyl ketone (3g) as an oil $n_D^{24.5}$ 1.4835 (Found : C, 70.35 ; H, 9.35 ; $C_{14}H_{22}O_3$ requires C, 70.55 ; H, 9.30 %). Vmax (film), 1710cm^{-1} (saturated ketone).

The aqueous layer was acidified and the starting acid (5g) isolated by the normal procedure. Recyclization of the acid (1.9g) gave the methyl ketone (900mg).

Ethyl 5-(5 Ethylenedioxy-4-methyl)3-oxo-hexanoate. (207).

A solution of the methyl ketone in tetrahydrofuran was added to a mixture of sodium hydride, 50 % suspension in oil (0.7g), diethyl carbonate (1.7g) in refluxing tetrahydrofuran under an atmosphere of nitrogen. Vigorous effervescence was observed and the reflux continued for a further 3 hours. The excess sodium hydride was decomposed with moist ether and the ethereal layer washed with 4N sodium hydroxide, water and dried. Removal of the solvent gave the starting ketone (206) and hydrocarbon oil.

The alkaline layer was acidified with 4N sulphuric acid, extracted with ether, then the ether layer washed with sodium hydrogen carbonate solution, water and dried. Removal of the solvent yielded the β - keto ester (207) (1.04g)

as an oil b.p. 163 / 0.08mm ; n_D^{25} 1.4849. Vmax (film) 1750cm^{-1} (ester), 1715cm^{-1} (ketone), 1660 - 1640cm^{-1} (chelated carbonyl). The β - keto ester gave a wine colouration with alcoholic ferric chloride solution.

The starting ketone was recycled to yield β-keto ester (0.24g).

Ethyl 5-(4 methyl-3oxocyclohexenyl)-3-oxo-hexanoate. (208).

A solution of the ketal - β - keto ester (1.04g) in acetone (30ml) containing p - toluene sulphonic acid hydrate (90mg) was heated under reflux for 3 hours. The reaction was followed by the increase in ultraviolet absorption. After the reaction had reached completion, the acetone was removed, water added, and the ether extract washed with sodium hydrogen carbonate solution, water and dried. Evaporation of the ether in vacuo gave an oil (820mg), which proved to be the enone β - keto ester (208). b.p. 160°/ 0.08mm n_D^{24} 1.4932 (Found : C,67.50 ; H,8.60 , $C_{15}H_{22}O_4$ requires C,67.65 ; H,8.35 %). Vmax (film) 1750cm^{-1} (ester) 1715cm^{-1} (ketone) 1675cm^{-1} (enone). λ max 235mμ ε= 16,400. In base, λ max 239mμ ε=16,400, 276mμ ε= 20,200. The enone β - keto ester gave a wine colouration with alcoholic ferric chloride solution.

4-Carbethoxy-1;7-dimethyl spirodeca-3;6-dione. (209).

The enone β - keto ester (575mg) was added to 0.2N

potassium hydroxide in ethanol (39ml) and the cyclization followed by the fall in the ultraviolet absorption (in base) at 239mμ, with a concomitant shift from 276mμ to 282mμ. After 2 hours the solution was acidified with acetic acid and most of the solvent removed. The residue was taken up in ether and washed with sodium hydrogen carbonate solution, water, and dried. Removal of the solvent gave a colourless gum (500mg) b.p. 110°/ 0.05mm. (Found : C,68.95 ; H,8.60; $C_{15}H_{22}O_4$ requires C,67.65 ; H,8.35 %). The mass spectrometric molecular weight was 266 ($C_{15}H_{22}O_4$ requires 266). Vmax (film) 1750cm^{-1} (cyclopentanone) 1730 - 1700cm^{-1} (ester and cyclohexanone), 1650 - 1610cm^{-1} (chelated carbonyl). Neutral λmax 248mμ ε2500, base λmax 282mμ ε 14,000.

This β - keto ester gave an exceedingly strong purple colouration with alcoholic ferric chloride solution.

4-Carbethoxy-1:7dimethyl-4-isopropyl spirodeca-6:5dione (210).

The spiro β - keto ester (209) (490mg), in ethanol (18ml), was added to 0.65N sodium ethoxide solution (3ml) and the solution was kept at room temperature for 1 hour. Isopropyl iodide (2ml) was added and the reaction mixture heated under reflux for 16 hours. The solution was cooled, acidified, then most of the ethanol removed in vacuo and the residue dissolved in ether, which was washed with 4 N

sodium hydroxide solution, water and dried. Removal of the solvent yielded an oil (105mg) which gave no colouration with alcoholic ferric chloride solution. The oil was adsorbed on silica from light petroleum (60° - 80°). Elution with light petroleum (60° - 80°) - benzene (1:1) afforded the alkylated β - keto ester as an oil having no absorption at 282mμ in alkaline solution. Vmax (film) 1745 - 1710cm^{-1} (carbonyl.

1:7-Dimethyl-4-isopropyl spiro [5:4] decan 3:5-dione. (37).

A solution of the alkylated β - keto ester (60mg) in a mixture of acetic acid (10ml), concentrated hydrochloric acid (5ml) and water (1 ml) was refluxed for 2 hours in an atmosphere of nitrogen. The solvent was removed and the residue taken up in ether. The ethereal solution was washed with 4 N sodium hydroxide solution, water and dried. Removal of the solvent gave a gum (25mg). Vmax (C S_2) 1743cm^{-1} (cyclopentanone) 1710cm^{-1}(cyclohexanone). The infrared spectrum was similar, though not identical, to any of the naturally occurring acorones. Chromatography on grade V alumina (20g) failed to yield any crystalline isomers.

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