SYNTHETIC APPROACHES TO TRICYCLIC COMPOUNDS

THESIS

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SUMMARY

Synthetic routes to the tricyclo$(5,3,1,1^{2,6})$dodecane and tricyclo$(5,1,0,0^{3,5})$octane systems have been investigated. Routes to the former class have involved double Michael additions to 4,4'-dimethoxycyclohexa-2,5-dienone, and attempted preparation of a bis δ-enol-lactone from diethyl succinylsuccinate, but no tricyclic compounds were produced.

Since approaches to the latter system, involving carbene additions to 3,3',6,6'-tetramethoxycyclohexa-1,4-diene gave a novel rearrangement to hydroquinone dimethyl ether, 1,2,4-trimethoxy benzene and a pentamethoxy biphenyl, the tricyclo$(5,1,0,0^{3,5})$octan-2,6-dione has been synthesised by reaction of 4,4'-dimethoxycyclohexa-2,5-dienone with an ylid reagent.

A reported violation of Bredt's rule involving monodecarboxylation of bicyclo(2,2,2)octan-2,5-dione-1,4-dicarboxylic acid to bicyclo(2,2,2)octan-2,5-dione-1-carboxylic acid has been proved genuine, but the other expected decarboxylation product, bicyclo(2,2,2)octan-2,5-dione has not been detected.

I wish to express my gratitude and sincere appreciation to Dr.G.L.Buchanan and Prof.R.A.Raphael F.R.S. for their continued encouragement and assistance during the last three years, and also to the latter for the opportunity to carry out this research.

I also wish to thank Mrs.F.Lawrie and her staff for recording high resolution infra-red absorption spectra; Mr.J.M.L.Cameron B.Sc. and his staff for micro-analyses; Mrs.S.J.Hamilton, Mr.J.Gall and Mr.A.Heizmann for recording proton magnetic spectra, Mr.A.Ritchie for recording mass spectra and the technical staff of the department for various large scale preparations.

The work described in this thesis was carried out during the tenure of maintenance awards from the James Fleming Scholarship Fund and the Science Research Council, and to these bodies I should like to express my gratitude.

Postgraduate Lectures Attended by R.Taylor.

Session		Units
1968-69	Newer Aspects of N.M.R. Spectroscopy	1
"	Kinetics of Organic Reaction Mechanisms	1
"	The Year in Organic Chemistry	1
"	Organic Literature Seminars	3
1969-70	Organic Photochemistry	1
"	The Enzymically-catalysed Hydrolysis of Esters and Amides	1
"	The Year in Organic Chemistry	1
"	Organic Literature Seminars	3
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"	Modern Methods of Protein Structure Investigation	1
"	The Year in Organic Chemistry	1
"	Organic Literature Seminars	3
	Total	18

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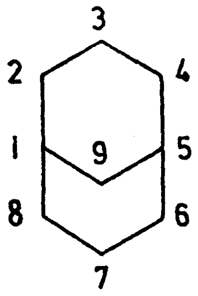
PART 1a

SYNTHETIC APPROACHES TO THE TRICYCLO$(5,3,1,1^{2,6})$DODECANES.



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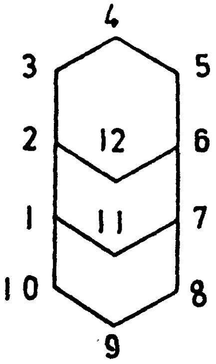

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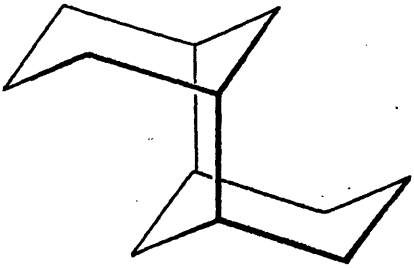

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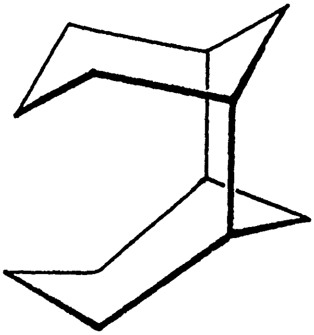

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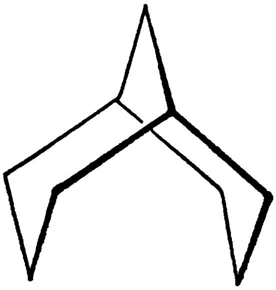
INTRODUCTION

Many important chemical principles have been illustrated by the study of bridged ring systems. Indeed, problems of a completely different nature e.g. those of structure and reactivity or of synthesis have been solved using the chemistry that is peculiar to a bridged ring system.

One of the systems which has been widely studied is bicyclo(3,3,1)nonane (1). Compounds of this class have provided the chemist with a continuous stream of interesting results, and it is to be expected, as a logical extension that the related tricyclo(5,3,1,$1^{2,6}$)-dodecane (2) will reflect this interesting chemistry. That this has not yet proved correct is due solely to the lack of success encountered in logical attempts to synthesise (2).

It should be noted that the tricyclododecane (2) in plan conceals the existence of two configurational isomers (3) and (4). A figure of the molecule in perspective reveals that they differ in the trans and cis substitution of the central ring which will be in a chair conformation (3) or a boat (4).



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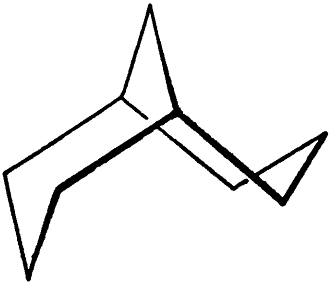

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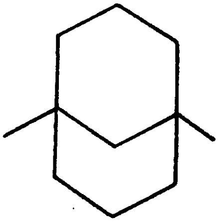

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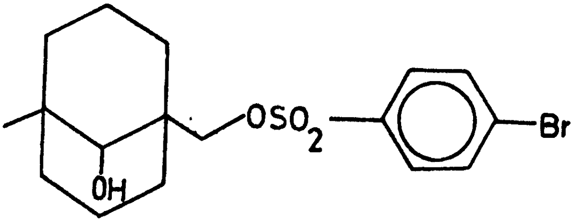

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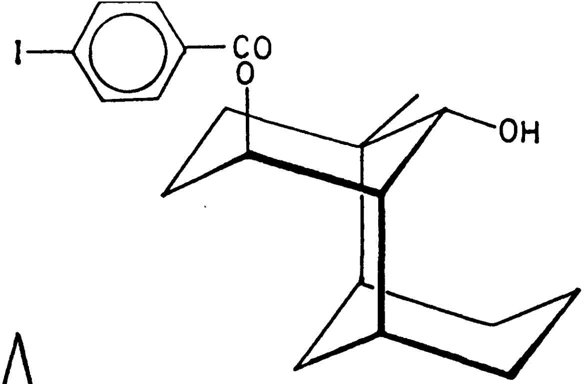
The conformation adopted by bicyclo(3,3,1)nonane was in doubt for many years. In 1922, Meerwein[1] preferred the chair-chair conformation (5), but doubts were cast on this because of the severe C(3)-C(7) endo hydrogen interaction and the chair-boat conformation (6) became favoured[2]. More recent studies by physical methods have proved Meerwein correct viz. :- Infra-red spectroscopy[3] of (7) in solution and solid state shows unusual absorptions at 1490 and 2990 cm^{-1} which have been unambiguously attributed to the C(3)-C(7) hydrogen interactions. Further, X-ray analysis[4] shows that (8) adopts the chair-chair conformation in the crystal. The C(3)-C(7) endo hydrogen interaction is relieved by distorting the valency angles resulting in a flattening of the rings, carbon atoms 3 and 7 'splaying outwards'.

The problems posed by this type of conformational argument are probably obvious in the tricyclododecanes; e.g. in the isomer (3) will the non-bonded interactions of the hydrogen atoms on C(4), C(9), C(11) and C(12) force one of the outer rings into a boat conformation ? How will (4) relieve the obvious non-bonded interactions between C(11) and C(12) hydrogens, and similarily between those hydrogens on C(4) and C(9) ? It would seem naively that lessening of one interaction would increase the other.



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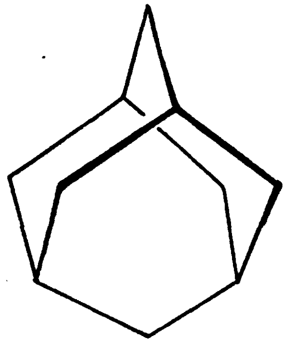

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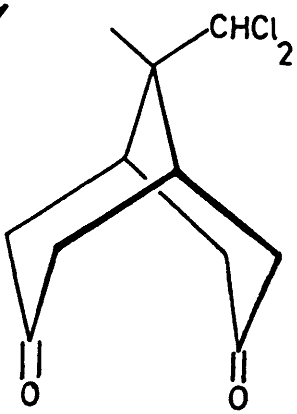

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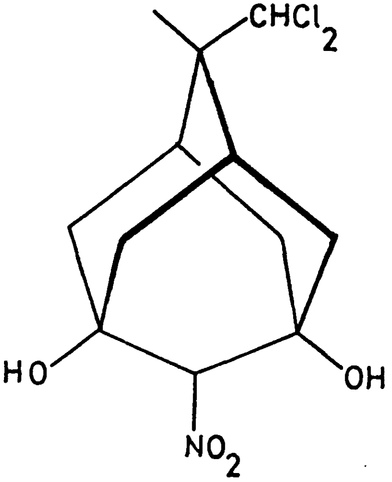

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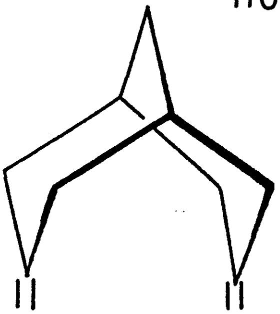

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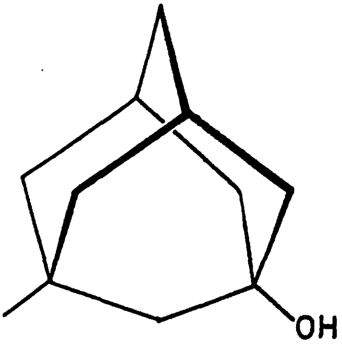

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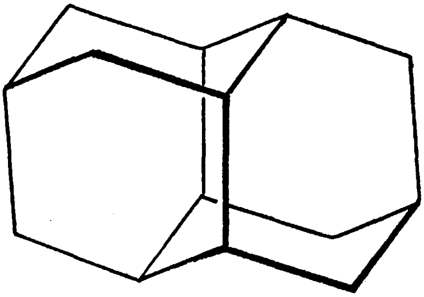

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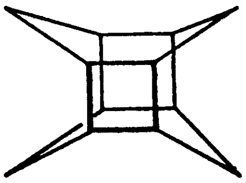
The answer to one of these questions has already been partly provided. It has been found by X-ray crystallographic analysis[5] that the tricyclic alcohol (9) adopts an all chair conformation which is especially surprising in view of the obvious interaction between the C(12) hydroxyl and the C(9) endo hydrogen. The pathway by which this molecule relieves its strain is very similar to that of bicyclo-(3,3,1)nonane itself. This is the only evidence of a structural nature available concerning the tricyclododecanes and unfortunately it is only applicable to the crystal. Undoubtedly much work remains to be carried out in this field.

The synthetic utility of bicyclo(3,3,1)nonane has been clearly demonstrated. The relation between it and adamantane (10) is readily seen, and several examples of the conversion of bicyclo(3,3,1)nonanes to adamantanes exist; e.g. a) the dione (11) gives (12) by a double aldol reaction with nitromethane[6], and b) the bis methylene compound (13) is ring closed under various conditions giving for example (14) by treatment with sulphuric acid[7].

Similar reactions of suitably substituted tricyclododecanes, structurally akin to (3) could be expected to give compounds of the congressane[8] (15) class. The



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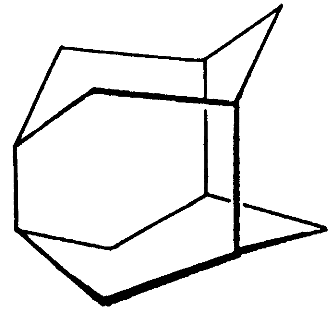

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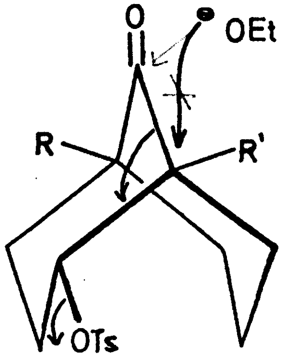

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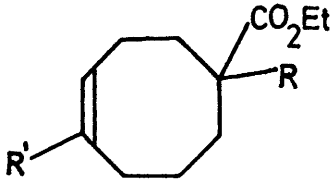

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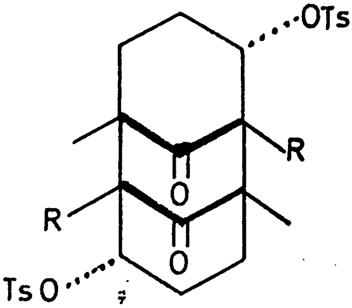

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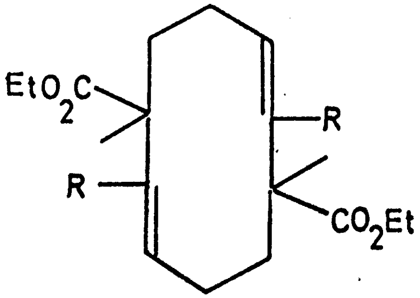

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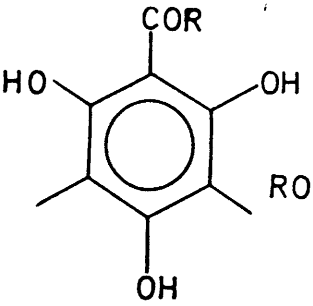
relation of (4) to the theoretically interesting asterane[9] (16) and pentacyclododecane (17) is readily seen, and again it is hoped that these would be available via appropriately substituted tricyclododecanes.

Another pathway of synthetic utility available to bicyclo(3,3,1)nonanes is found in a bridge fission reaction encountered in a 2-(endo)-substituted compound[10]. This particular substitution renders available a fragmentation reaction e.g. (18) giving (19), possible only because of the antiperiplanar geometry of the 2-(endo)- substituent with respect to the C(1)-C(9) bond, giving an eight -membered ring. Since medium sized rings are so difficult to form, it is hoped to extend this to a double bridge fission carried out on a tricyclododecane e.g. (20), giving a ten-membered ring compound (21).

Several syntheses of tricyclo(5,3,1,$1^{2,6}$)dodecanes have been reported to date, and without exception they exhibit no control over which configurational isomer is produced (i.e. type (3) or (4)). Indeed in all but one example, no attempt is made to determine the nature of the product with regard to this configurational isomerism.

Most reports concern the fortuitous union of two heavily substituted aromatic rings, e.g. on the oxidative



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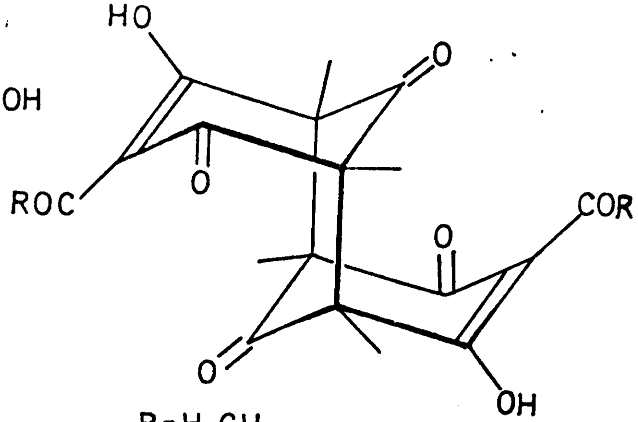
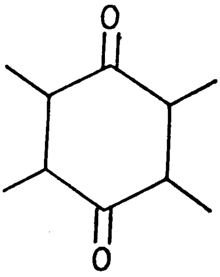


$R = H, CH_3$ 23



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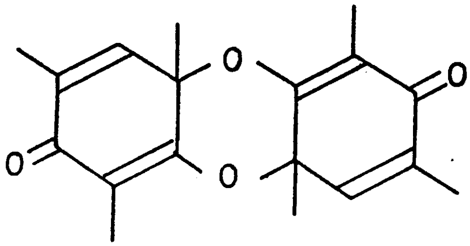

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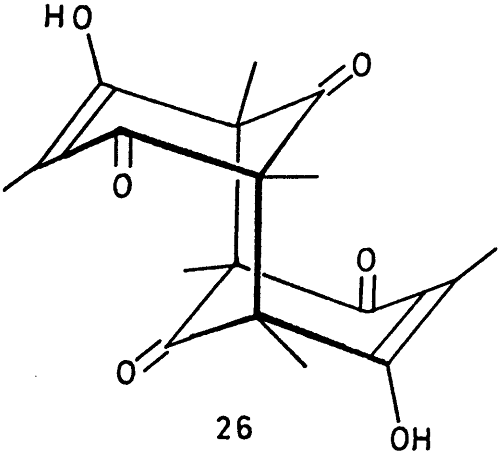

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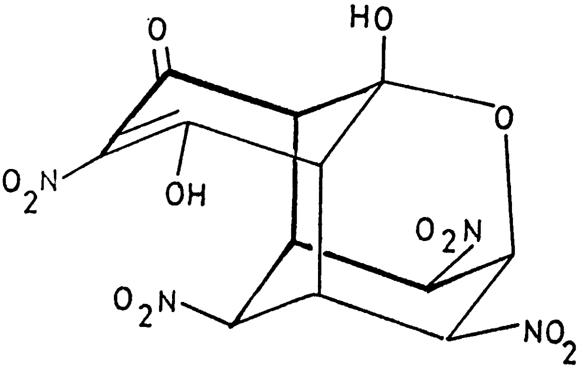

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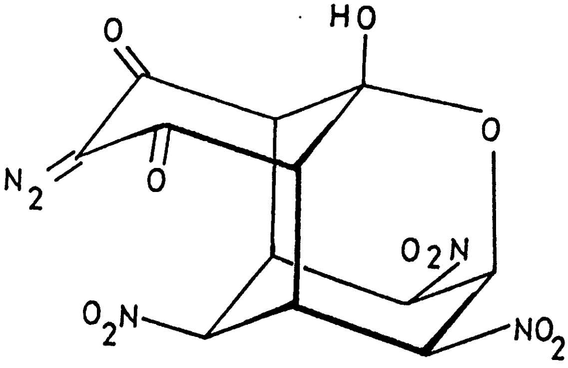

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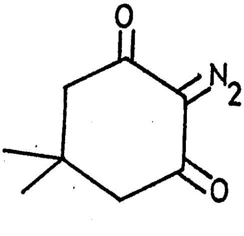

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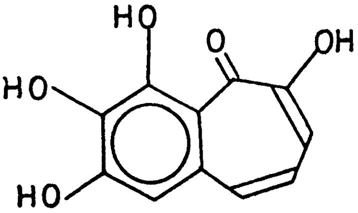
dimerisation of some acyl substituted phenols, Erdtman et al[11] reported that the acyl phloroglucinol (22) on treatment with ethanolic ferric chloride gave an 85% yield of a dimer of proposed structure (23). Treatment of the dimer with palladium on carbon in ethanol gave 100% yield of the acyl phloroglucinol (22). While the spectroscopic evidence is not incorrect, the best evidence for the structure (23) is its degradation by hydrogen peroxide to (24). It is difficult to conceive of another structure for the dimer which takes account of this and the other evidence given. These findings led Erdtman to reinvestigate the structure of 'cedrone', the oxidative dimeric product from 2,4,6-trimethyl phloroglucinol. In 1934, he had proposed the structure (25) for cedrone[12], but in a reinvestigation in the light of the results discussed earlier the tricyclododecane (26) is now favoured[13].

Severin has claimed several syntheses of tricyclo-$(5,3,1,1^{2,6})$dodecanes. Reaction of 1,3,5-trinitrobenzene with nitrophloroglucinol gave[14] a compound of proposed structure (27). This is corroborated by formation of several derivatives and comparison of their U.V. spectrum with a corresponding derivative of dimedone, e.g. the diazo compounds (28) and (29). Several similar syntheses



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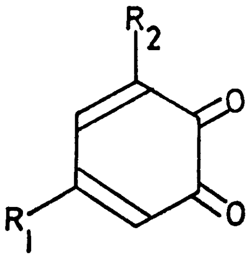
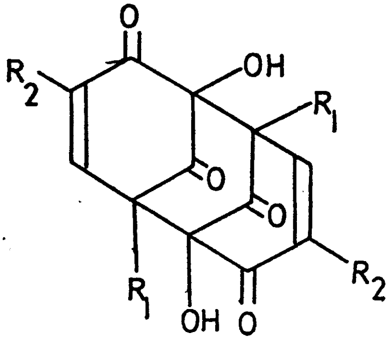


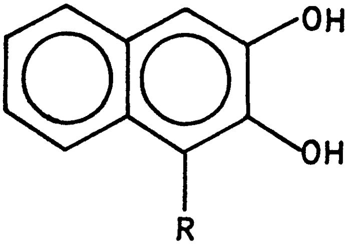
31a $R_1 = R_2 = H$

b $R_1 = R_2 = Et$

c $R_1 = Et$ $R_2 = H$



32a, b, c



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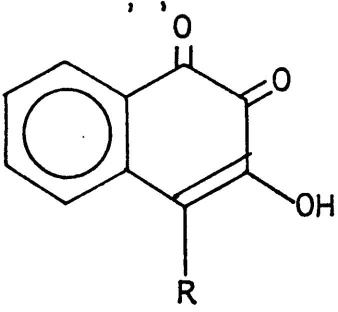

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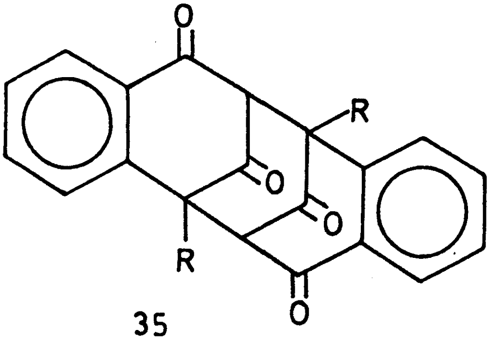

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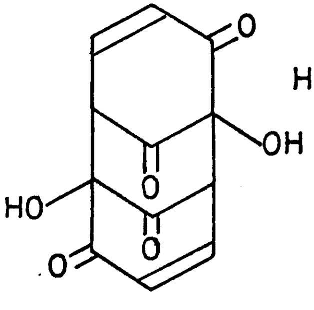

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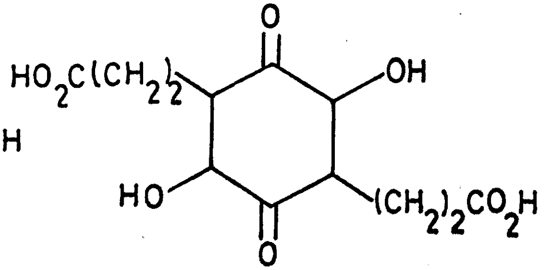

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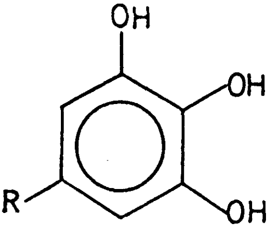
have been claimed by the same author[15].

In 1906, Perkin and Steven reported[16] the formation of a colourless dimer obtained from pyrogallol by oxidation with amyl nitrite in acetic acid in an attempt to prepare the dye purpurogallin (30). By boiling in water the colourless dimer is converted into purpurogallin.

More recently Teuber[17] has investigated the oxidation of some 3-hydroxy orthoquinones e.g. the reaction of (31c) with potassium nitrosodisulphonate, and has proposed the structure (32c) for the product obtained. Similar compounds were obtained from the reaction of (33) with potassium nitrosodisulphonate[18] giving (35) through the intermediacy of (34). Although these dimers were significantly more stable than Perkin's, the similarity caused Teuber to reinvestigate the oxidation of the hydroxyquinone (31a) with amyl nitrite. He has now proposed[19] the structure (36) for the dimer based on chemical and spectroscopic evidence. The chemical evidence is most compelling in that hydrogenation gave a tetrahydro derivative, which, on base treatment gave the dione (37), subsequently air oxidised to the p-quinone.

Although these findings seem sound, some English workers have published results which are not in complete agreement with those of Teuber. These refer to the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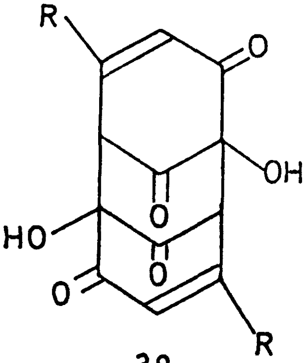
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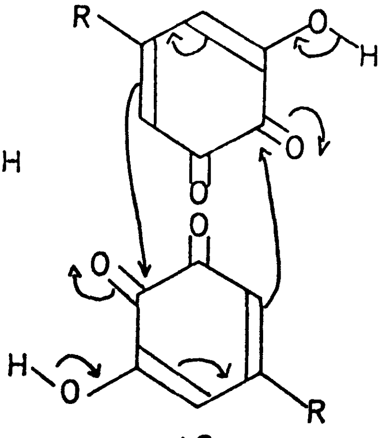
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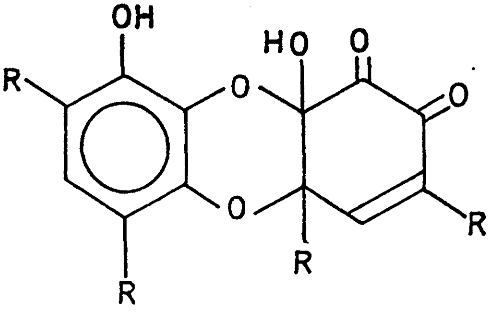
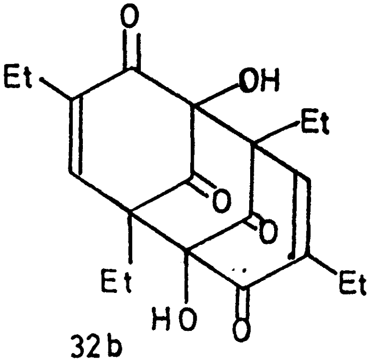
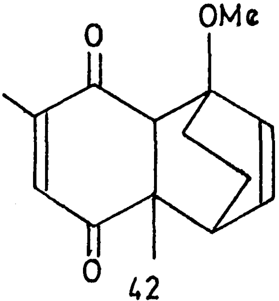

41, R=Bu^t, Et


32b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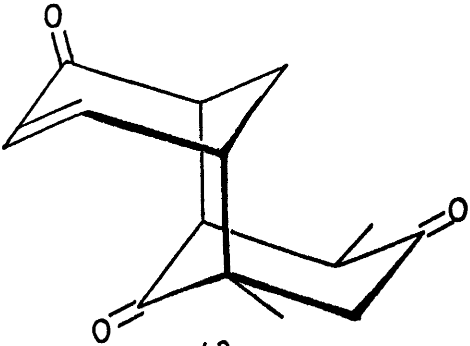
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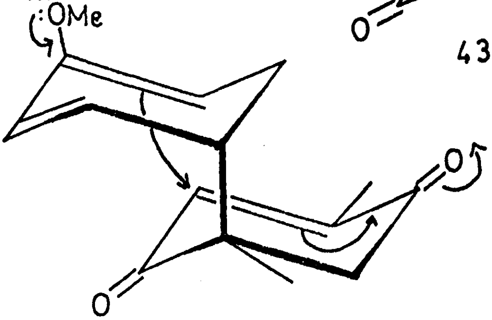
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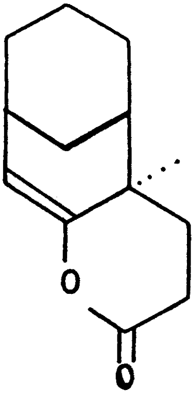
dimerisation of 4,6-diethyl and 4,6-di t-butyl pyrogallol under the action of potassium iodate. While they found[20] that 4-alkyl pyrogallols under treatment with potassium iodate gave tricyclododecane type structures, e.g. (38) giving (39) by the mechanism shown in (40), they considered that the dimers formed from the above 4,6-dialkyl pyrogallols possessed structures of type (41). This is based on the spectroscopic properties of the di t-butyl dimer, and the structure of the diethyl compound is claimed by analogy. However Teuber has proposed[19] structure (32b) for the dimer of 4,6-diethyl pyrogallol by analogy with the dimer from pyrogallol, and the problem of the structure of the 4,6-diethyl pyrogallol dimer is still not resolved.

One further example of a fortuitous synthesis has been reported by Birch[21]. Rearrangement of the Diels-Alder adduct (42) of 2,5-dimethyl p-benzoquinone and 2,3-dihydroanisole in 0.3N hydrochloric acid gave a compound $C_{14}H_{16}O_3$. The structure, based on good spectroscopic evidence, was given as the tricyclic compound (43), and the proposed mechanism is shown in (44) i.e. a Michael attack initiated by an enol ether.

One 'logical' synthesis of a tricyclo$(5,3,1,1^{2,6})$-



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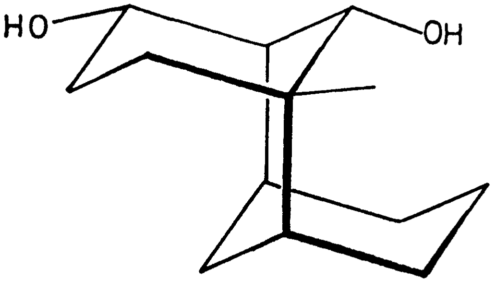

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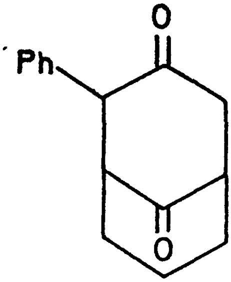

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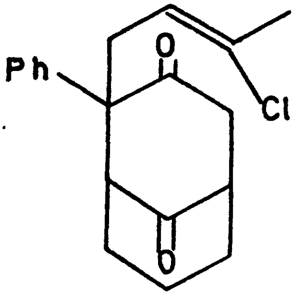

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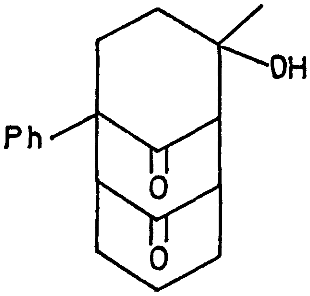

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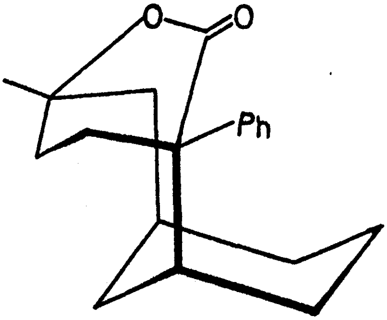

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dodecane has, to date, been reported, and indeed this is the only case in which the structure of the product has been rigourously determined. Following the success of the route to bicyclo(3,3,1)nonanes by reductive cyclisation of a δ-enol lactone[22], the Glasgow group[23] synthesised the enol lactone (45) which, on treatment with lithium aluminium hydride gave the tricyclic diol (46). Preparation of a derivative suitable for X-ray crystallographic analysis unambiguously established the nature and stereochemistry of the product.

In this light, one other example of an attempted synthesis is very interesting. Recognising the usefulness of the Wichterle[24] procedure for the preparation of bicyclo(3,3,1)nonanes, Buchanan and Lawson[25] envisaged an extension of this as a means of synthesising a tricyclo($5,3,1,1^{2,6}$)dodecane. Thus they prepared (48) by treatment of the phenyl dione (47) with 1,3-dichloro-but-2-ene. However, attempted cyclisation of (48) did not give the expected product (49), but (50) derived from a complex rearrangement.

It is clear from the foregoing survey that there is a general lack of methods available for the logical synthesis of tricyclo($5,3,1,1^{2,6}$)dodecanes, suitably substituted so as to render possible conformational, reactivity and synthetic studies of the type mentioned earlier in this thesis. It will be the purpose of the work described in the first part of this thesis to establish synthetic procedures leading to the desired tricyclic skeleton. Further, since no example of a tricyclic molecule of type (4) has been reported, methods will be investigated which will lead to two isomeric tricyclododecanes in order to study and compare the reactivity of the two configurational isomers.

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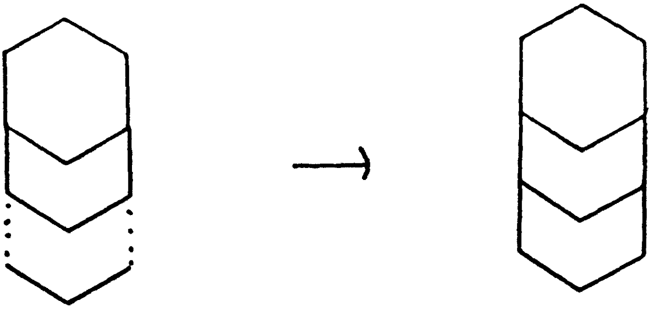

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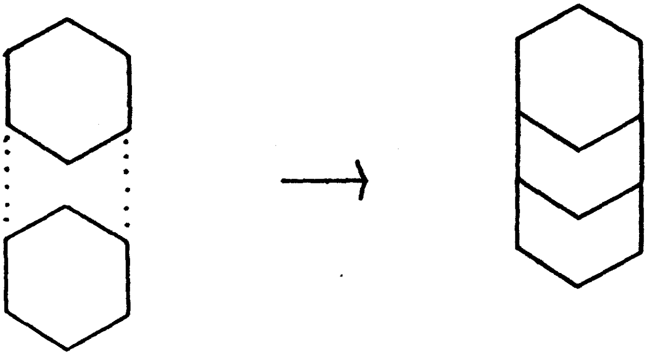

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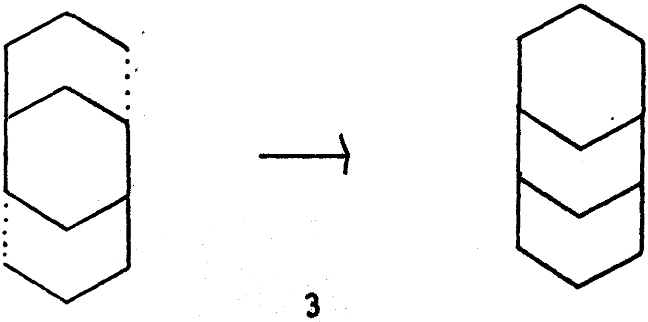

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DISCUSSION

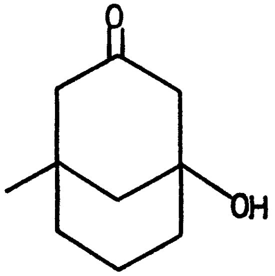
In planning new synthetic routes to tricyclo-(5,3,1,$1^{2,6}$)dodecanes, three methods of forming the desired skeleton were available.

a) Further bridging of a bicyclo(3,3,1)nonane by a three carbon unit as shown in (1).

b) 1,3-union (by a logical process) of two substituted cyclohexane derivatives as in (2).

c) Cyclisation of a 1,4(or 1,3)-disubstituted cyclohexane as in (3).

The relative merits of the three methods are rather difficult to assess; however since several examples of a synthesis of the first type have been reported, with varying degrees of success, it was decided to attempt firstly a method of type (b). Although this type of formation is exemplified by almost all the known syntheses of tricyclododecanes, i.e. those involving the union of two heavily substituted aromatic rings, it was decided to attempt a synthesis based on sound mechanistic grounds rather than simply mixing two compounds, which could theoretically react in several ways, in the presence of an oxidising agent. The method of joining the two moieties



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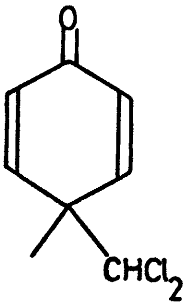

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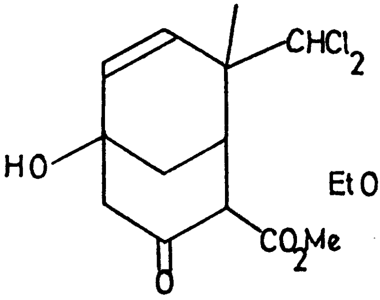

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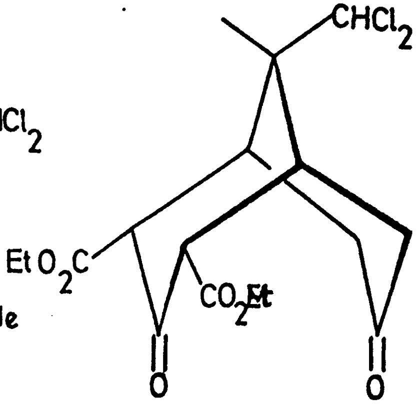

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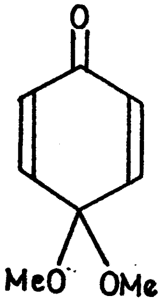
together which was selected was the Michael reaction.

The Michael reaction has never been used in the synthesis of a tricyclododecane, but it has been used in the preparation of bicyclo(3,3,1)nonanes, and it was hoped that this use would be capable of extension to a tricyclo$(5,3,1,1^{2,6})$dodecane. Rabe[1] has described an early synthesis of bicyclo(3,3,1)nonanes by reaction of ethyl acetoacetate with 3-methylcyclohexenone to give (4) by an initial Michael reaction, followed by an aldol condensation, and similarily Wenkert[2] has described the formation of (6) by reaction of the dienone (5), the abnormal Riemer-Tiemann product of p-cresol, with ethyl acetoacetate, again by an initial Michael and subsequent aldol condensation. It is quite possible therefore that these syntheses of bicyclo(3,3,1)nonanes could be extended to produce tricyclo$(5,3,1,1^{2,6})$dodecanes by replacing the β-keto ester, acetoacetic ester with one such as 2-carboethoxycyclohexanone.

Of more interest was the report of Stetter[3] concerning the double Michael reaction of the dienone (5) with diethyl acetone-1,3-dicarboxylate giving the bicyclic compound (7). It was hoped that this process could be extended to the synthesis of tricyclododecanes by simply



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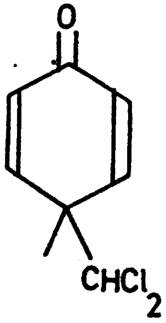

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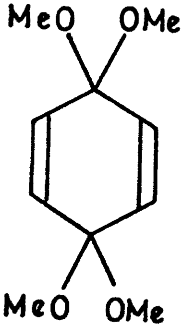

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replacing dicarboethoxyacetone by 2,6-dicarbomethoxycyclohexanone. Further it was envisaged that the tricyclododecanes so produced would be amenable to some of the studies mentioned in an earlier part of this thesis, since there was available a ready source of the dimethoxy-dienone (8) as starting material. Obviously bicyclic and tricyclic compounds formed from this dienone would be capable of being elaborated further due to the presence of a protected carbonyl group in the position formerly occupied by a methyl and dichloromethyl groups in the compounds formed from (5).

The dienone (8) was obtained by half hydrolysis of the bis acetal* (9) in water, the isolation of (8) in good yield (70%) being made possible by the retardation of the rate of hydrolysis of the second acetal by the electron withdrawing carbonyl group at C(4) in the dienone (8)[4]. This slowing down of the rate of hydrolysis of (8) to p-benzoquinone relative to the rate of hydrolysis of (9) to (8) permits the isolation of the dienone (8) if the reaction is carried out under certain stringently observed conditions.

It was originally intended that, prior to attempting the double Michael condensation of the dienone (8) and

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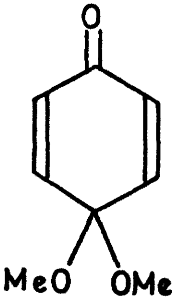
* We thank I.C.I. (Mond Division) for a generous gift of this material.



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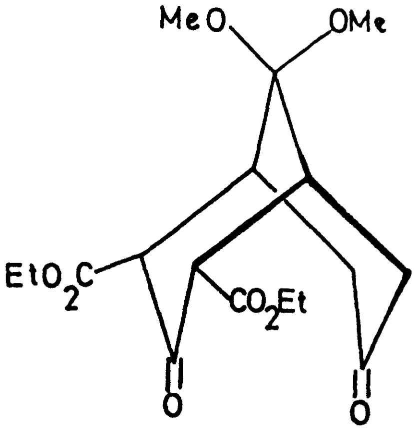

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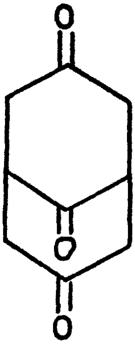

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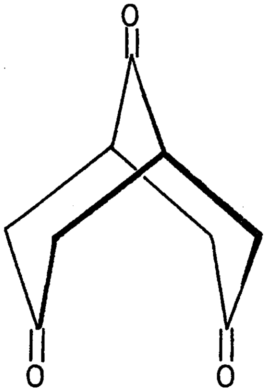
2,6-dicarbomethoxycyclohexanone, the usefulness of the dienone (8) as an electrophile in a double Michael reaction would be investigated by carrying out a series of experiments designed to produce bicyclo(3,3,1)nonanes rather than the tricyclo(5,3,1,$1^{2,6}$)dodecanes.

To this end, the dimethoxy-dienone (8) and diethyl acetone-1,3-dicarboxylate were reacted in ethanol containing a catalytic amount of sodium ethoxide, giving in 77% yield a sole compound, $C_{17}H_{24}O_8$, whose analytical and spectral data were in accordance with the proposed structure (10), with the exception of some unusual findings in the N.M.R. spectrum. These abnormalities do not in any way conflict with the proposed structure of the product of the double Michael reaction, but they will be discussed later since they are shown by some compounds which occur later in the text.

It was envisaged at this time that, prior to attempted extension of this reaction to the formation of a tricyclo(5,3,1,$1^{2,6}$)dodecane, the structure of the compound (10), obtained by Michael reaction be corroborated by degradation to the bicyclo(3,3,1)nona-3,7,9-trione (11), as yet an unknown compound, but one which would be readily converted to a known compound e.g. bicyclo(3,3,1)nonane



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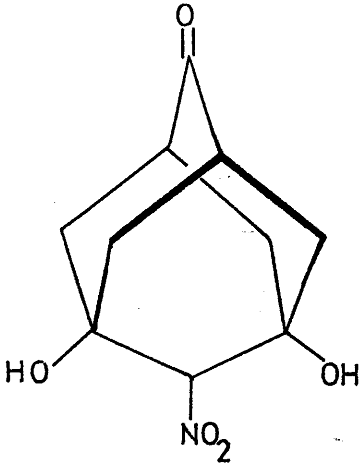

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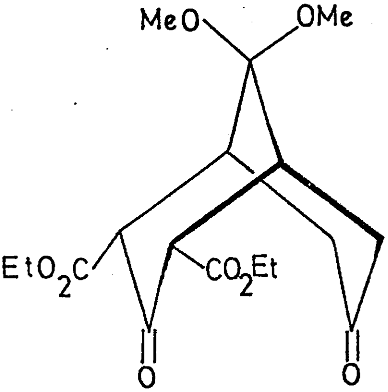

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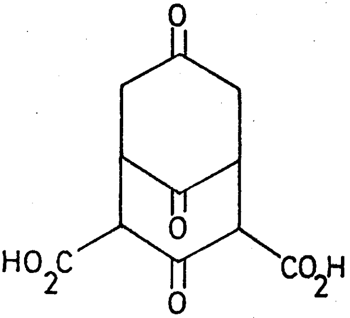

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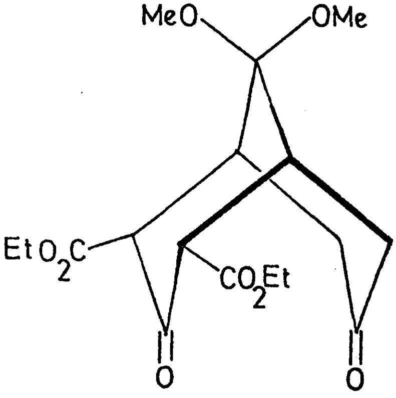
itself. It was also hoped that (11) would be a useful precursor of substituted adamantanes e.g. the nitro ketone (12) which might arise from a double aldol condensation with nitromethane, and thus provide a route to adamantane derivatives of a type not yet known. However the degradation of (10), apparently facile on paper, proved to be impossible in our hands. Several methods of ketonic cleavage of the β-keto ester functions were attempted.

Refluxing (10) in an ethanolic caustic soda solution caused the solution to rapidly turn black, and after a reflux period of two hours, on acidification and extraction only a small amount of brown residue was obtained. On refluxing an ethanolic hydrochloric acid solution of (10) for 16 hours, a very poor yield of the triketo-diacid (13) was obtained, as evidenced by the disappearance of the resonances in the N.M.R. spectrum at 6.7τ to 7.0τ due to the methoxyl protons of the acetal and those at 5.8τ and 8.8τ due to the protons of the two ethyl ester moieties, and the presence of a strongly bonded hydroxyl, typical of a carboxylic acid in the infra-red spectrum. However attempted decarboxylation of this product e.g. by refluxing in quinoline containing copper bronze, or by distilling the compound under vacuum from an intimate mixture of



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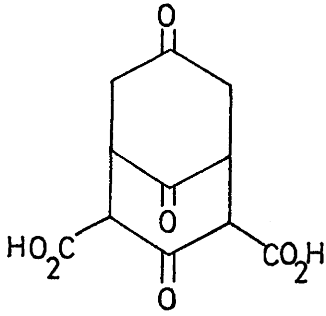

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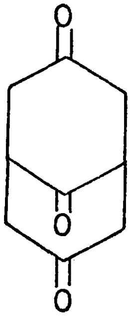

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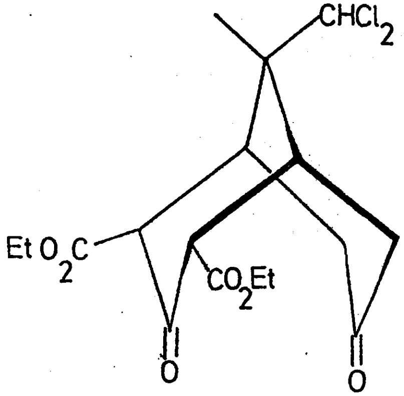

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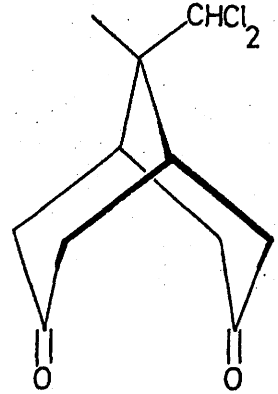

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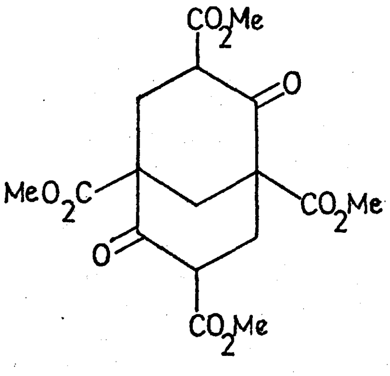

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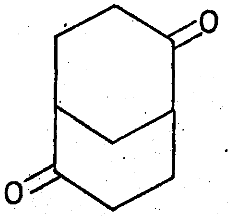

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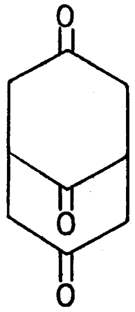
itself and ground glass yielded no recognisable product. In fact the major component isolated from the latter method seemed to possess a carboxylic acid function as shown by the typical infra-red absorption of this functional group.

Although it had been assumed that the double Michael product was the β-keto ester (10), the stability of the hydrolysis product (13) was anomalous. Indeed its resistance to decarboxylation was sufficient to raise doubts about the structure of the β-keto ester. For this reason it became imperative to pursue the degradation to (11) or to bicyclo(3,3,1)nonane.

Two methods of ketonic cleavage of (10) which seemed promising in view of literature reports on successful cleavages carried out on similar compounds were investigated. Stetter[3] reported the hydrolysis and decarboxylation of the Michael product (7) by a mixture of glacial acetic acid and concentrated sulphuric acid to the dione (14), and Meerwein[5] carried out the hydrolysis of the tetraester (15) to (16) by heating the compound with water in a sealed tube at 220°. Unfortunately, subjection of the β-keto ester (10) to either of these conditions gave in each case a low yield of a mixture of several components, none of



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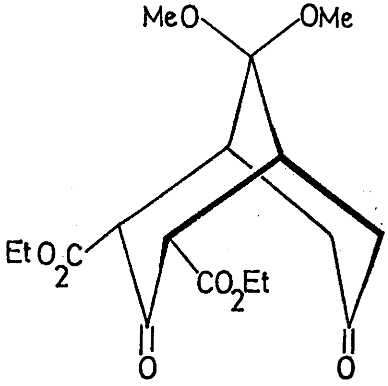

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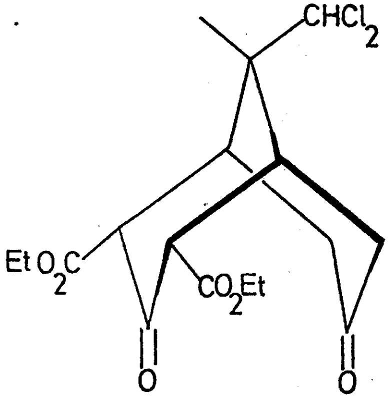

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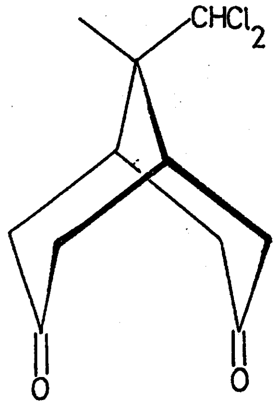

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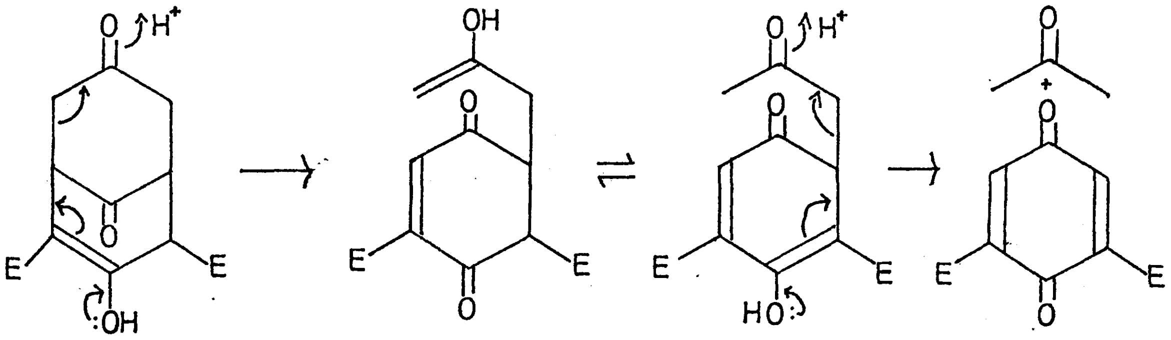
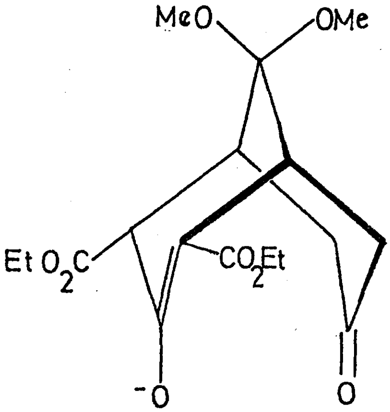
which was recognisable as the desired trione (11). In fact hydrolysis by Stetter's method produced a great deal of darkening in the solution on reflux, and it was found that this darkening could not be stopped by carrying out the reaction under an atmosphere of nitrogen.

One other method attempted was that of Chang et al[6] whereby β-keto esters are cleaved in a ketonic fashion by anhydrous sodium iodide or calcium iodide in refluxing ethylene glycol to the ketone, carbon dioxide and the corresponding alkyl iodide. Reaction of the β-keto ester (10) under these conditions produced the dissappointing result obtained previously i.e. rapid darkening of the solution followed by isolation of a low yield of several unrecognisable products.

On consideration of the results of this series of attempted ketonic cleavages, it seemed likely that the β-keto ester (10) was undergoing decomposition in the basic or acidic media to which it was subjected. Of particular interest to these results is the report of Stetter[3] mentioned earlier whereby the β-keto ester (7) is converted to the dione (14) by refluxing in a mixture of glacial acetic and sulphuric acids. Comparison of the two β-keto esters (7) and (10) indicated that the only



SCHEME 1 E = CO_2Et



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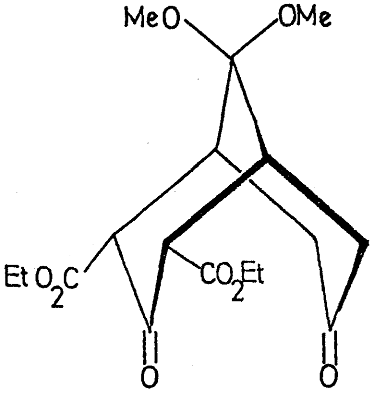

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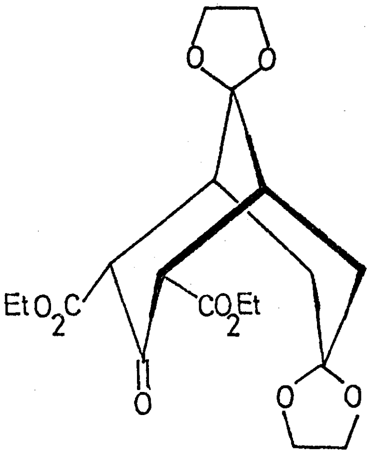

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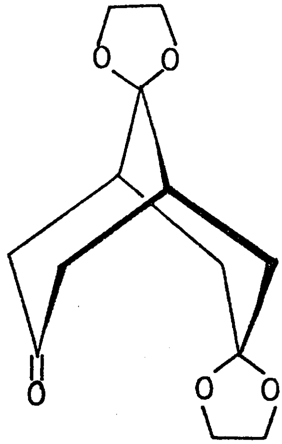
real difference between them was the presence of an acetal grouping in basic solution, or a carbonyl grouping in acidic solution at C(9), rather than a methyl and dichloromethyl groups. It was difficult to see how either of these functional groups could induce some form of degradation. It was thought more likely that the carbonyl group at C(7) could act as an electron withdrawing centre thereby facilitating the degradation outlined in Scheme 1 in acidic solution. A similar mechanism is operative in basic media, initiated by the enolate anion (17). The test of this postulate would then be removal of the electron withdrawing facility at C(7) for example by acetalisation of the carbonyl group to thwart the proposed undesired degradation.

Reaction of the β-keto ester (10) with excess ethylene glycol in the presence of p-toluene sulphonic acid in refluxing benzene gave the bis ethylene acetal (18), resulting from acetalisation of the 7-keto group and transacetalisation of the 9-keto function. The establishment of a positive reaction to ferric chloride and an infra-red absorption spectrum typical of a β-keto ester identifies the structure of the product as (18). Refluxing this compound in 4N caustic soda solution produced in this



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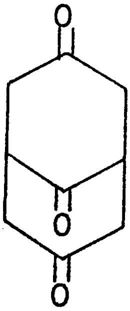

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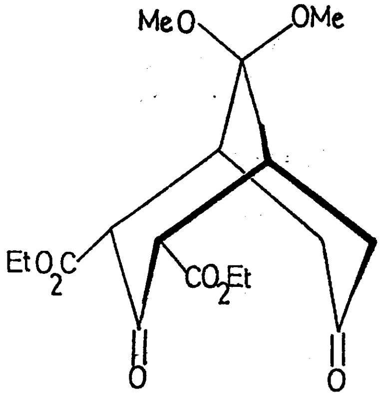

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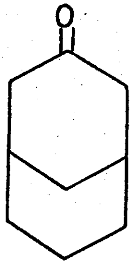

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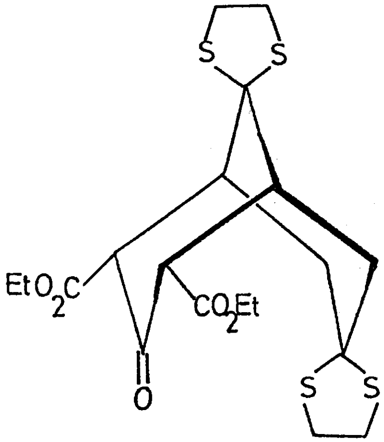

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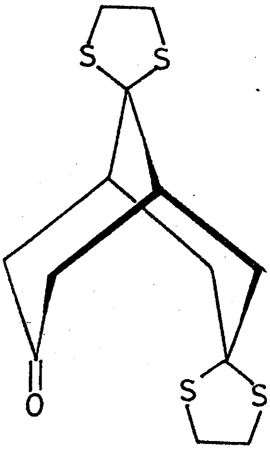

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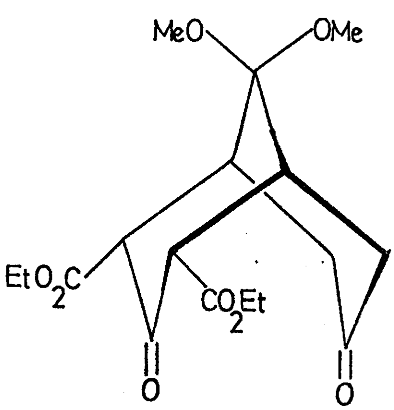
case a very clean reaction, with no blackening observed, and the gratifying result of a 70% yield of the bis decarbethoxylated ketone (19), with analytical and spectral data completely in accordance with the structure (19). Unfortunately attempted acidic hydrolysis of the bis ethylene acetal (19) did not give any of the desired trione (11), but resulted in the production of a very polar compound as shown by t.l.c..This polar product, seemingly polymeric in nature, was probably derived from ring closure initiated by aqueous acid to form an oxa-adamantane species, which have been shown to undergo polymerisation[7].

Following the failure to degrade the β-keto ester (10) to bicyclo(3,3,1)nona-3,7,9-trione, it was decided to transform (10) to the known ketone bicyclo(3,3,1)nonan-3-one (20). This was accomplished by reaction of the β-keto ester (10) with ethane-1,2-dithiol and boron trifluoride etherate in chloroform over a prolonged period. Column chromatography of the resultant mixture afforded the bis thioacetal (21) which was successfully converted to the decarbethoxylated product (22) by basic reflux, and the latter by desulphurisation with Raney nickel in absolute ethanol to bicyclo(3,3,1)nonan-3-one (20),



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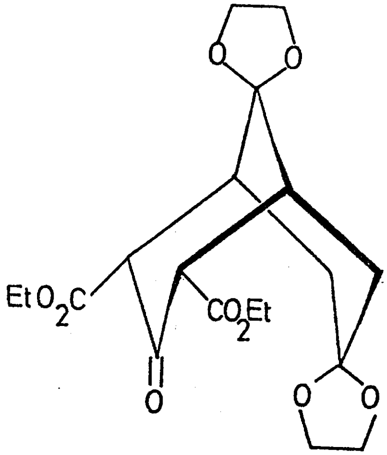

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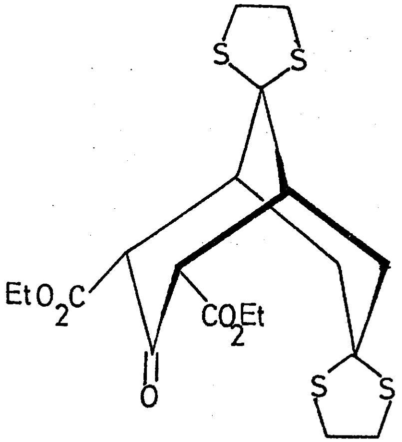

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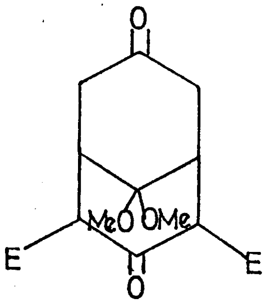
identical with an authentic sample by gas chromatography coinjection on several columns, and by comparison of their mass spectral breakdown pattern. By this method the nature of the product (10) obtained from the initial double Michael reaction was unambiguously established.

One intriguing feature of the N.M.R. spectra of the β-keto esters (10), (18) and (21) is worthy of note. Each of these compounds exhibits in its N.M.R. spectrum two resonances due to the carboethoxyl groupings i.e. a doublet of quartets at 5.8τ and a doublet of triplets at 8.85τ, these resonances i.e. the two triplets or two quartets being in the ratio 1:1. In addition the C(9) methoxyls of (10) resonate at three different frequencies in the ratio of 2:1:1. Running the N.M.R. spectrum in various solvents does not cause the two carboethoxyl resonances to coalesce, nor the methoxyl resonance to become two singlets as would be expected for these compounds. In fact in solvents such as d_6-benzene or d_6-dimethyl sulphoxide, the reverse is observed in that the carboethoxyl resonances become more complex, and those of the methoxyl group still show as a 2:1:1 series of singlets.

These phenomena can be explained by postulating the



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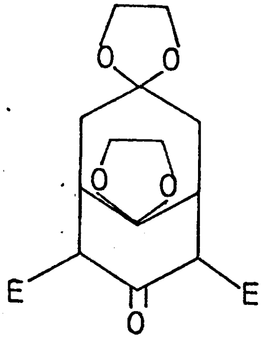

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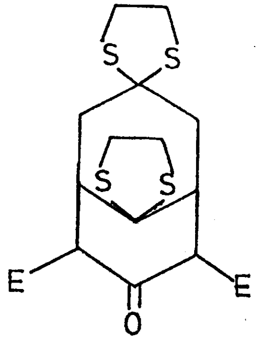

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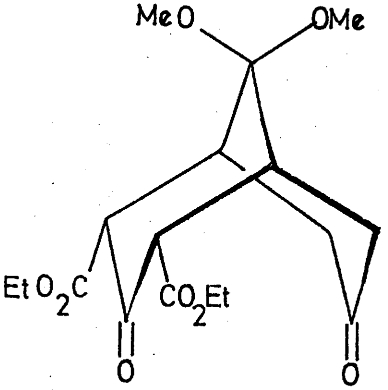
E = CO_2Et



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existence of two separate species in solution, but any explanation of how these might arise must take account of the following observations.

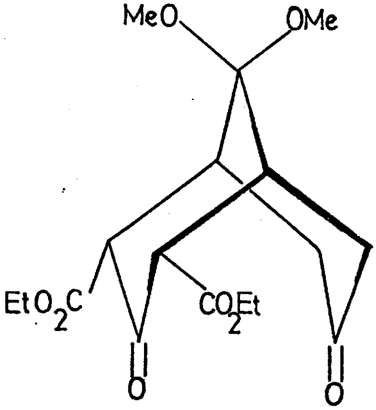
1) The carboethoxyl regions of the spectra are such that they show the presence of <u>two types</u> of carboethoxyl signals in the ratio of 1:1.

2) The methoxyl signals (a 2:1:1 three peak signal, but assumed to be a 1:1:1:1 four singlet signal with two peaks being accidently equivalent.)

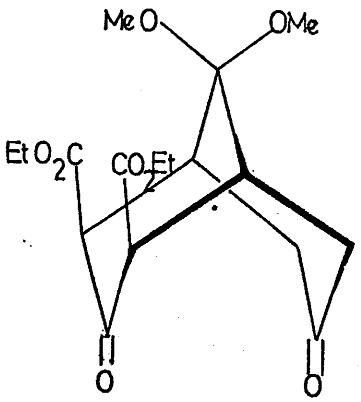
3) All compounds under study (10), (18) and (21) were found to be chromatographically completely homogeneous.

Several explanations of how two species might arise are possible. Although none seem entirely plausible, they are as follows.

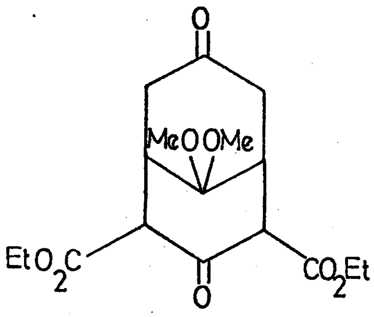
a) Two compounds can be obtained from the Michael reaction differing in stereochemistry around C(2) and C(4). The expected product of the Michael reaction would be that isomer bearing both carboethoxyl groups in an endo configuration i.e. (23), since the reaction conditions are such that the product of thermodynamic control would be obtained. In order to explain the above factors, especially the first, the mixture of species must contain 50% of the di-endo substituted compound at C(2) and C(4),


MeO
OMe
EtO$_2$C
CO$_2$Et
O
O

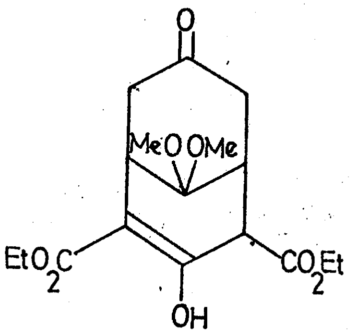
23


MeO
OMe
EtO$_2$C
CO$_2$Et
O
O

24


O
MeO OMe
EtO$_2$C
O
CO$_2$Et

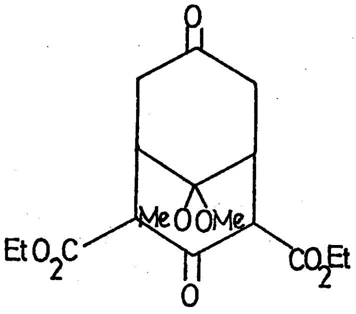
10


O
MeO OMe
EtO$_2$C
OH
CO$_2$Et

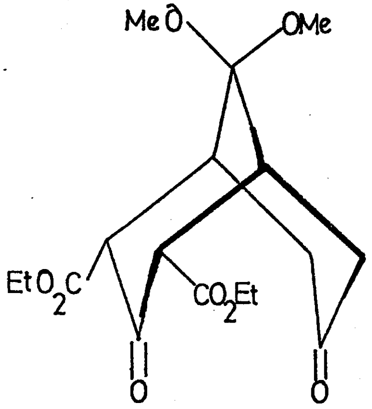
25

(23) and 50% of the di-exo (24). Consideration of the possible non-bonded interactions expected in the di-exo (24) leads to the conclusion that it is extremely unlikely that it would be a product obtained from a reaction which is under thermodynamic control.

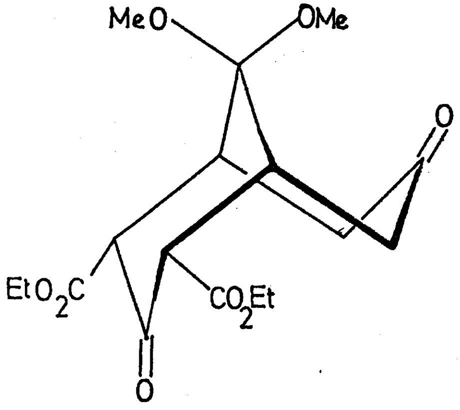
b) Two compounds will undoubtedly be present which differ only in that they are tautomers i.e. (10) and (25), and indeed the infra-red spectrum of (10) indicates that there is a large percentage of the enolised form (25) present from the strong absorptions at 1658 and 1618 cm^{-1} due to the H-bonded carbonyl of the ester grouping and the double bond of the enol respectively. However in order to achieve a solution to the problem of the different carboethoxyl resonances, the assumption must be made that (10) is more or less completely enolised thereby giving two different types of carboethoxyl resonances, one due to the grouping with non hydrogen-bonded carbonyl and the other due to one which is bonded. Unfortunately this explanation is not satisfactory since the signals observed for the methoxyl groups demand an approximately 50:50 mixture of tautomers. It was also found that addition of pyridine[8] to the N.M.R. solution did not cause the signals in question to coalesce as would be


O
MeO OMe
EtO2C
CO2Et
O

10


MeO
OMe
EtO2C
CO2Et
O
O

23

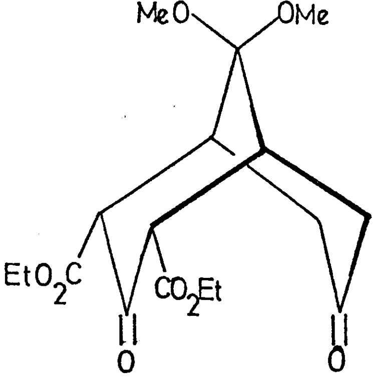

MeO
OMe
O
EtO2C
CO2Et
O

26

expected, since pyridine catalyses the tautomerism and should therefore speed it up relative to the N.M.R. time scale.

c) A solution which explains the observed facts, but which is not really acceptable concerns the conformational ambiguity of the bicyclo(3,3,1)nonane system i.e. the existence of chair-chair and chair-boat forms. If (10) were to exist as a 50:50 mixture of the two conformational isomers (23) and (26), then the N.M.R. spectra would be expected to appear as they do, assuming that the rate of interchange of the two conformers is slower than the N.M.R.relaxation time. However this explanation would conflict with all known facts concerning the conformation of bicyclo(3,3,1)nonane derivatives[9] which indicate that the preferred conformation is the chair-chair form. The only situation in which a chair-boat would possibly contribute would be in a molecule bearing C(7) and C(9) keto functions in order to eliminate non-bonded interactions from the 'bowsprit' positions of the boat cyclohexane.

An attempt was made to examine this third possibility experimentally by recording the N.M.R. spectra under temperature programming conditions in the hope that



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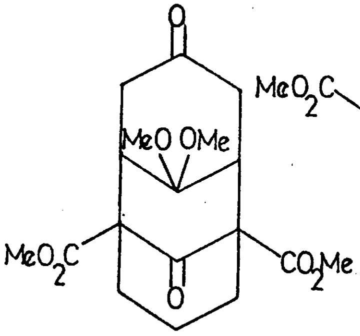

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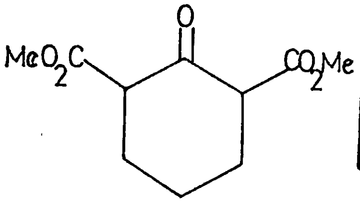

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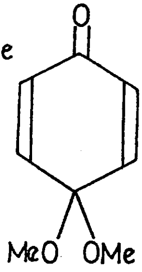

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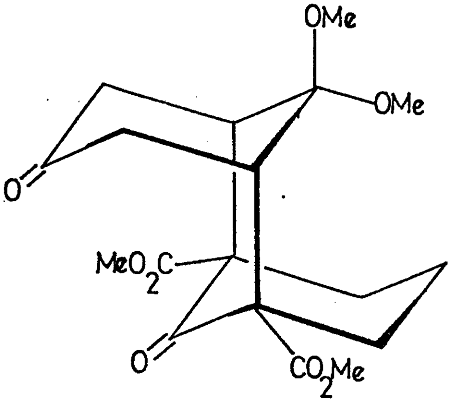

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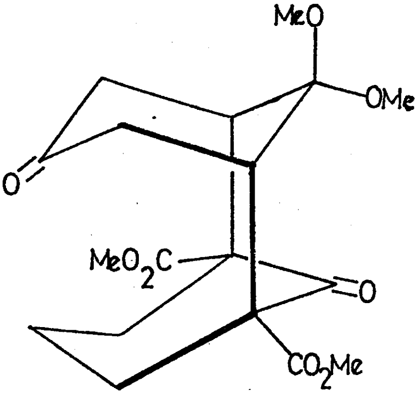

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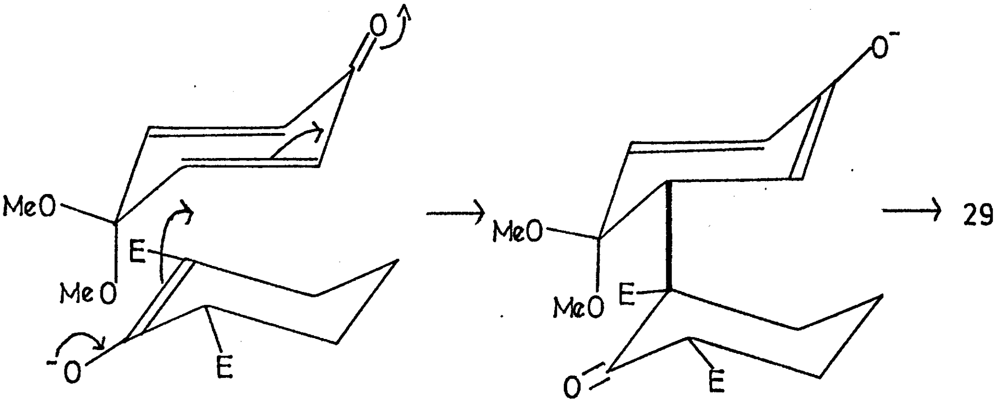
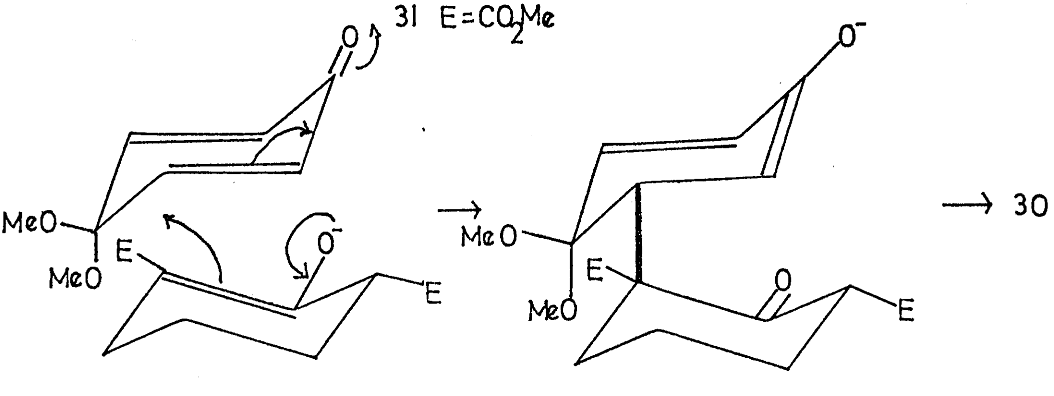


31 E=CO$_2$Me

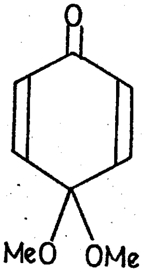


32 E=CO$_2$Me

coalescence of the signals might occur at higher temperature. Over a range of temperature from 30 to 160° the N.M.R. spectra proved essentially invariant and hence it is difficult therefore to pinpoint one specific factor which determines these peculiar N.M.R. spectra.

Following the establishment of the successful course of the Michael reaction in the formation of the bicyclo-(3,3,1)nonane (10), it was now hoped that the reaction would be extended to the synthesis of a tricyclo$(5,3,1,1^{2,6})$-dodecane such as (27) by condensation of dimethyl cyclohexan-2-one-2,6-dicarboxylate (28) with the dimethoxy dienone (8). Although this reaction precluded any stereochemical control as to which of the two configurational isomers (29) or (30) is produced, it is possible to obtain either isomer as shown in figures (31) or (32).

In the event, an attempted Michael condensation of (8) and (28) was carried out in methanol containing a catalytic amount of sodium. After stirring for 24 hours at room temperature, no new compound was detected by t.l.c., and the reaction mixture was therefore refluxed for a further 16 hours resulting in the formation of one new compound and the disappearance of the dienone (8). The new compound,



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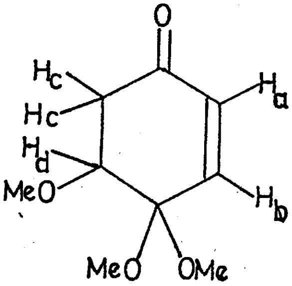


33

a clear oil satisfactorily analysed for $C_9H_{14}O_4$. Examination of the infra-red spectrum revealed absorptions at 1690cm^{-1} and 1620cm^{-1} indicating the presence of an enone grouping, although the relative intensites of the two absorptions compared to those of the corresponding absorptions of the dienone (8) indicated the presence of an enone rather than a dienone grouping. The N.M.R. spectrum was suitably analysed as follows :-

3x3H singlets at 6.5τ to 6.53τ due to the three methoxyl groups: a 2H doublet at 7.2τ due to the two hydrogens H_c: a quintuplet at 6.16τ due to H_d, and an AB quartet with further splitting of the lower half, centred on 3.62τ.

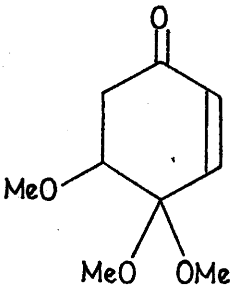
Double resonance experiments were carried out as follows :-

a) Irradiation at the 7.2τ doublet reduced the quintuplet at 6.16τ to a doublet.

b) Irradiation at the 6.16τ quintuplet effected the reduction of the 7.2τ doublet of the two H_c hydrogens to a singlet, and also removed the further small coupling of the lower half of the olefinic hydrogens AB quartet.

c) Irradiation at 3.2τ, the centre of the lower half of the AB quartet reduced the signal at 6.16τ due to H_d to a triplet.

These decoupling studies are all in accordance with



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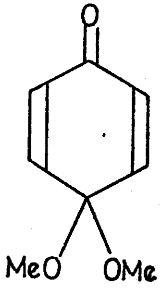

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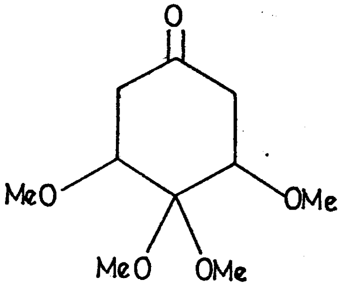

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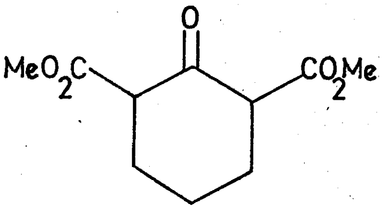

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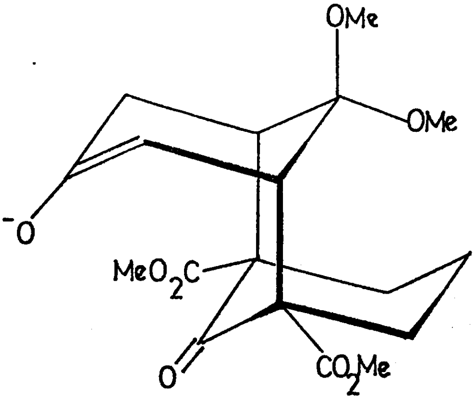
the proposed structure (33). Further attempts to characterise the structure of the compound as (33) by mass spectrometry produced the rather surprising determination of a molecular ion at m/e 218 rather than the expected m/e 186 for the compound $C_9H_{14}O_4$. Repetition of the mass spectral determination on pure material consistently gave the same result, which seems to indicate the presence of the tetramethoxy compound (34), and, in each case, no peak at m/e 186 was observed, although there was present an ion at m/e 154 (corresponding to the molecular ion of the dienone (8)). It was also noted that a sample of the trimethoxyenone (33) decomposes on standing to a mixture of two compounds, one of which as shown by g.l.c. is the dienone (8). It would seem therefore that a disproportionation of the enone (33) to a mixture of the dienone (8) and the tetramethoxy ketone (34) is occuring, and this is probably accelerated in the mass spectrometer giving rise to a molecular ion at m/e 218, with no ion observed at m/e 186.

In view of this synthetic result, it was decided to attempt the double Michael condensation of (8) and (28) using very strong, but non-nucleophilic bases since the enone (33) must arise from a Michael attack by methoxide



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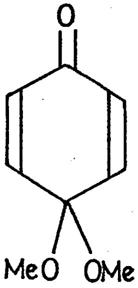

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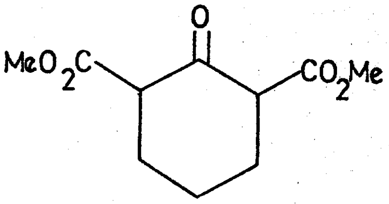

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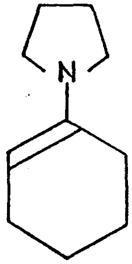
anion. Accordingly several Michael reactions were attempted using the following sets of basic media, the base being present in catalytic amount.

1) Lithium diisopropylamide[10], formed from butyl lithium and diisopropylamine, in ether.
2) Sodium hydride in benzene.
3) Butyl lithium in ether.
4) Sodium t-amylate in benzene.
5) 1,5-diazobicyclo(4,3,0)non-5-ene[11] in ether.

Unfortunately none of these reactions was successful as indicated by chromatographic analysis.

The failure to carry out this reaction can probably be explained by considering factors involving steric hindrance in that the enolate anion derived from condensation e.g. (35) is so severely strained and congested by non-bonded interactions, possibly involving the methoxyl groups, that the reverse reaction, forming the dienone (8) and the enolate anion of (28) is the preferred pathway rather than protonation of the enolate anion (35) to give the tricyclic product.

One other method of tricyclo$(5,3,1,1^{2,6})$dodecane synthesis briefly attempted, which again exerts no stereochemical control as to which configurational



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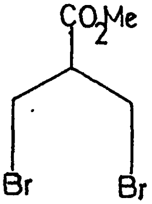

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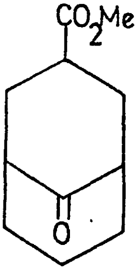

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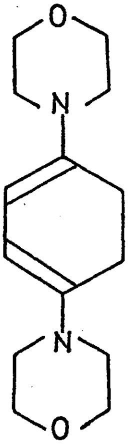

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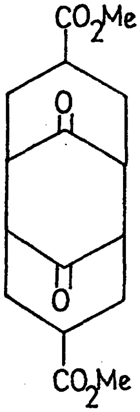

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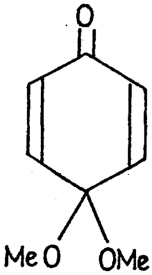

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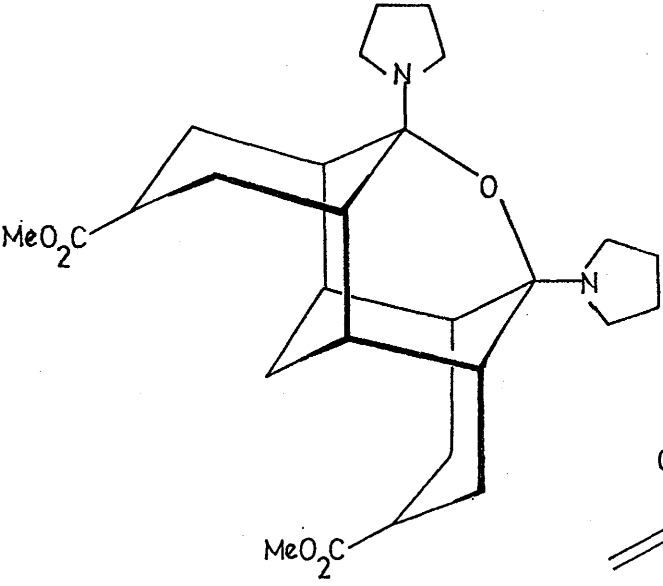

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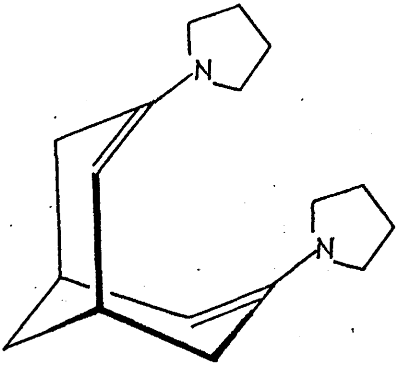

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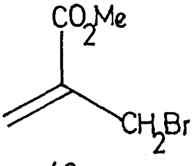

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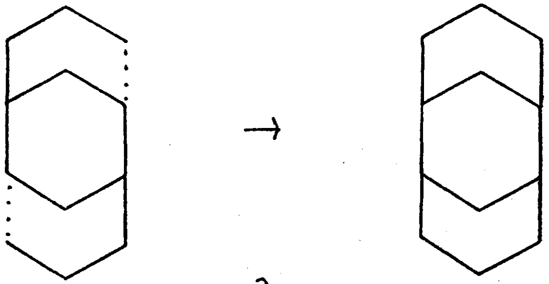
isomer is produced, was suggested by recent publications by McEuen et al[12] concerning the synthesis of bicyclo(3,3,1)nonanes e.g. (38) from 1-pyrrolidino-cyclohexene (36) and the dibromo ester (37). It was planned that, by a similar experimental method, condensation of the bis morpholino enamine of cyclohexan-1,4-dione (39) with two equivalents of the dibromo ester (37) would give the tricyclic compound (40). An attempt to carry out this reaction using triethylamine as base in dry acetonitrile was made, but no recognisable product was obtained. It is probable that this reaction could be carried out in the light of a recent publication by Stetter[13] describing the synthesis of the pentacyclic compound (41) by reaction of the bis enamine (42) with two equivalents of the bromomethyl acrylic ester (43).

Since approaches to the desired tricyclic molecules utilising the union of two functionalised cyclohexane derivatives had proved ineffectual, it was decided to approach the tricyclic system by a different method, although various other modifications of the approach so far discussed are still possible, e.g. the reaction of the dienone (8) with β-keto esters such as ethyl acetoacetate in an initial Michael and subsequent aldol



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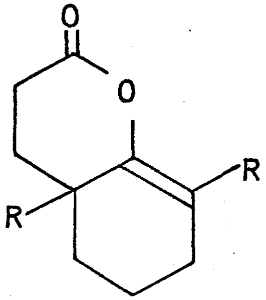

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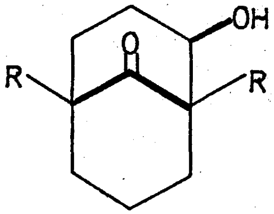

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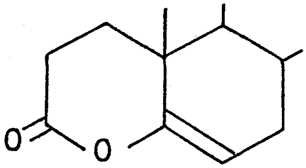

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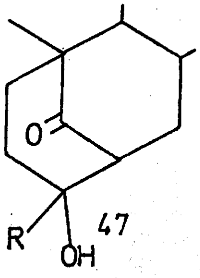

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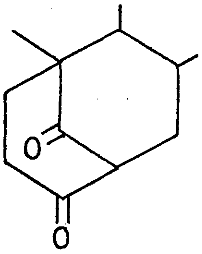

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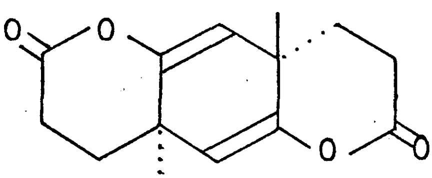
sequence to form bridged compounds. However, it was felt that considerable effort should be expended in developing a synthesis which would lead to either configurational isomer.

Of the three general methods of tricyclododecane formation described earlier in this thesis, that which is most amenable to a stereospecific synthesis is undoubtedly type C as illustrated in (3), since it should be possible to synthesise the necessary cis or trans 1,3 or 1,4 disubstituted cyclohexane, and thus control the stereochemistry of the tricyclododecane produced from it.

It remained only to choose the method of cyclisation of the two side chains to the six-membered ring, and for this there were available all the methods of production of a bicyclo(3,3,1)nonane by cyclisation of a propionate substituted cyclohexane. The method chosen was one which has been of great use in the synthesis of bicyclo(3,3,1)-nonanes, the cyclisation of a δ-enol-lactone. Several examples of the conversion of δ-enol-lactones to bicyclononanes exist, e.g. the reduction of (44) by complex hydride[14] to (45), and the reaction of (46) with a Grignard reagent in a 'Fujimoto' reaction[15] to give (47), or its photochemical transformation[16] to (48). So it was



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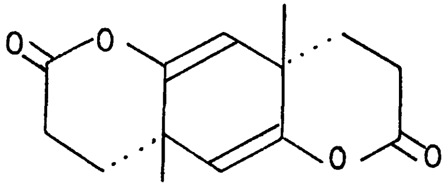

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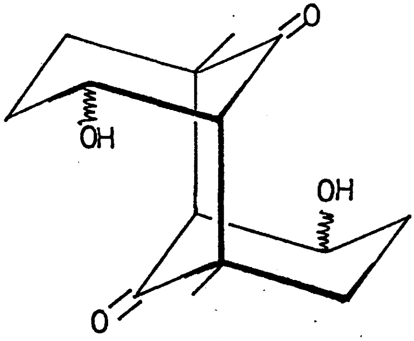

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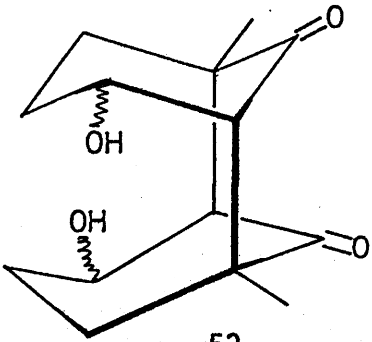

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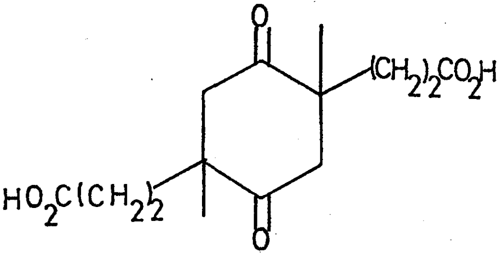

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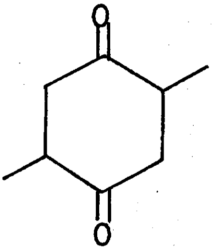

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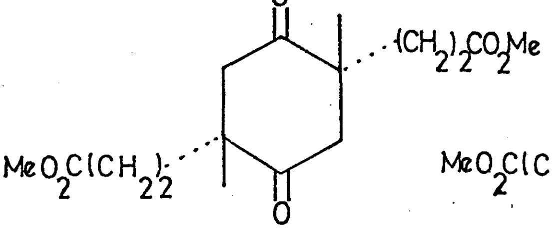

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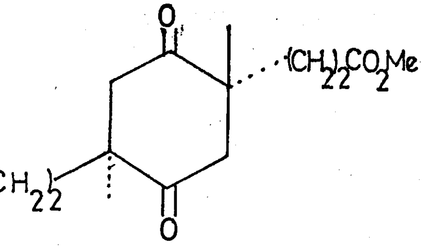

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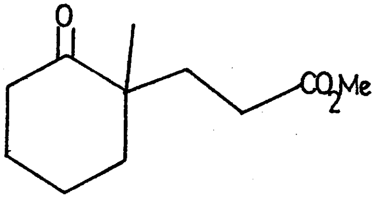
with hope that a synthesis of the two isomeric enol lactones (49) and (50) was approached, since there was a good chance that the desired cyclisations, of (49) to (51) and (50) to (52), could be effected by one of the above mentioned methods. It was also thought that the photochemical cyclisation reaction might be particularily suitable for the conversion of the isomer (50) to the more strained tricyclododecane (52).

The first approaches to the synthesis of the necessary intermediate, the diketo-diacid (53) involved Michael additions of 2,5-dimethylcyclohexa-1,4-dione (54) to two different electrophiles, acrylonitrile and methyl acrylate. It was realised that no stereochemical control exists in these reactions in that the two propionate groupings introduced will bear no predictable stereochemical relation to each other, but it was hoped that both isomers e.g. (55) and (56) from reaction with methyl acrylate, might be produced and that separation of these might be effected by chromatographic methods.

Attempted cyanoethylation of (54) using the standard conditions[17] i.e. an excess of ketone and Triton B as base produced no new compound, the starting dione being reisolated from the reaction mixture. Addition to methyl



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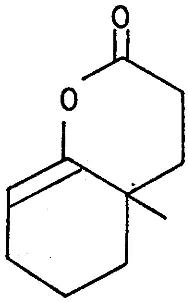

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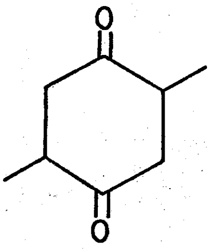

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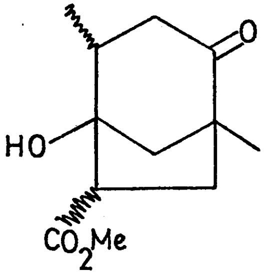
acrylate proved a more promising method. The conditions employed for this were those described by House[18] for the reaction of methyl acrylate and 2-methylcyclohexanone which gave a mixture of the keto ester (57) and the enol lactone (58) under the catalytic influence of potassium t-butoxide. Reaction of the dione (54) and methyl acrylate under these conditions gave a mixture of four new components, two being major and the other two minor. Separation of the two major components was effected by column chromatography giving one as a clear viscous gum, and the other as a crystalline solid. Although the former did not give the expected micro-analytical figures, mass spectral determinations gave the same parent ion at m/e 226 for each compound, and this corresponded with the analytical data obtained for the crystalline compound i.e. $C_{12}H_{18}O_4$.

It was obvious from this data that the compounds isolated were isomeric, and that they had been produced by condensation of the dione (54) with only one molecule of methyl acrylate instead of the desired two molecules. It was now, however, necessary to determine the structure of the two isomeric condensation products. Assuming that condensation had taken place with one molecule of methyl



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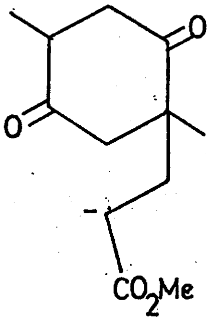

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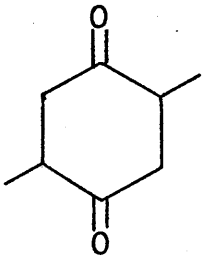

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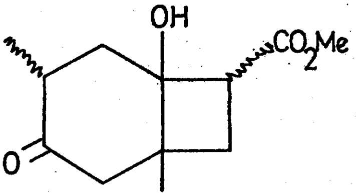

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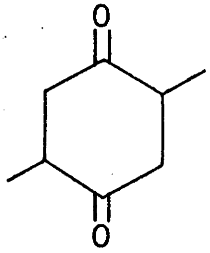
acrylate, giving in the N.M.R. spectrum of each a three proton siglet at ca. 6.25τ, the other noticeable features of these spectra were, in each, the presence of two non-equivalent aliphatic methyl resonances at ca. 8.9τ, and a multiplet from 6.8τ to 8.4τ integrating for nine protons, with a reduction to eight on the addition of deuterium oxide. In addition, the infra-red spectra showed the presence of a hydroxyl grouping ($3550cm^{-1}$) which failed to oxidise with Jones reagent, indicating its tertiary nature, and a ketone group ($1705cm^{-1}$).

This evidence suggests the structure (59) for the isomeric condensation products, and it can be readily seen that this will arise from aldol condensation of the carbanion (60), first formed by Michael reaction of one molecule of methyl acrylate with the dione (54). Although the aldol condensation can take place on two different carbonyl groups giving (59) or (61), it was thought more likely that the former structure represented the product since formation of a five-membered ring is greatly favoured over four-membered ring formation. The presence of four components in the reaction mixture can also be explained on the basis of the structure (59), since there are two asymmetric centres at C(2) and C(7)



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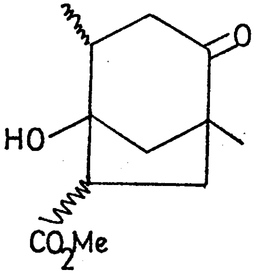

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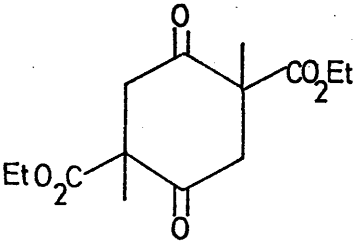
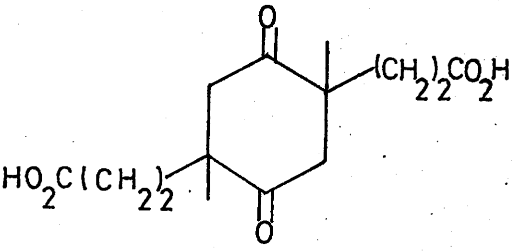
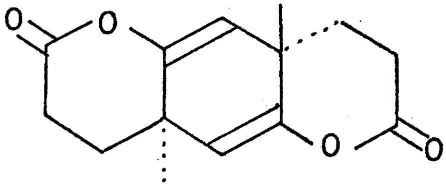


62 a-trans
b-cis



53a-trans
b-cis



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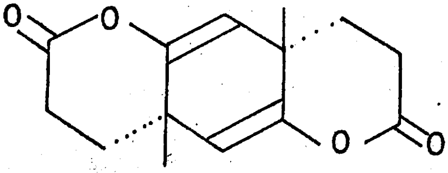

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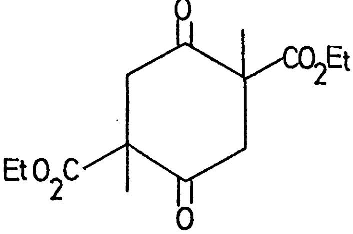
giving rise to four isomeric aldol condensation products.

It was subsequently found to be impossible to effect the desired double Michael condensation of (54) and methyl acrylate by varying the reaction conditions, e.g. by increasing the relative proportion of methyl acrylate. Presumably the formation of the isomers of (59) exemplifies the extremely facile process of an intramolecular condensation reaction giving a cyclic compound which is essentially strain free.

Following the failure to react the dione (54) with two molecules of methyl acrylate in the desired manner, it was decided to approach the synthesis of the diketo -diacid by a different method. Since the precursor of 2,5-dimethylcyclohexan-1,4-dione (54), the methylated[19] diethyl succinylsuccinate (62) was readily available, and was known to consist of a 3:1 mixture of the trans and cis isomers, it was envisaged that elaboration of the two carboethoxyl groupings of (62) to propionic acid side chains would furnish the required intermediate (53) which would give the enol lactones (49) and (50) on dehydration. Also if the elaboration of the carboethoxyl groupings to propionate groups could be accomplished without formation of an sp^2 centre alpha to the ketone groups, i.e. at C(2) or C(5), a starting mixture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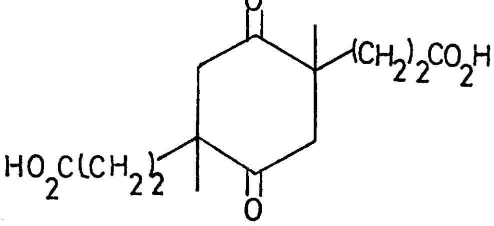
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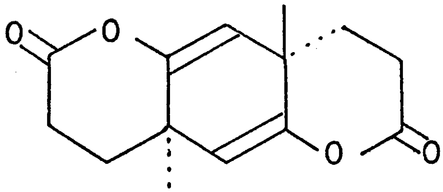
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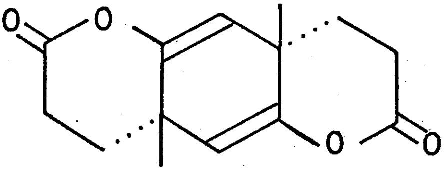
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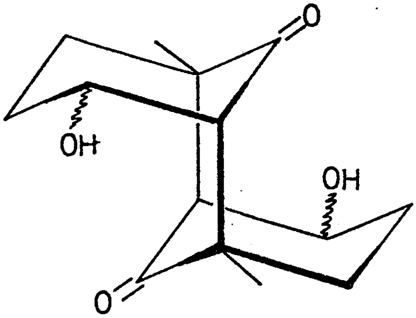
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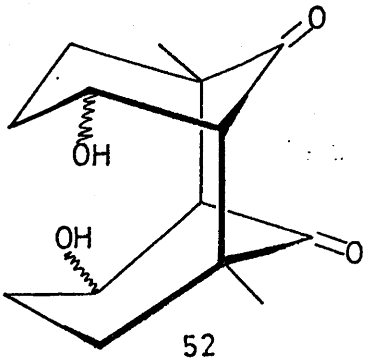
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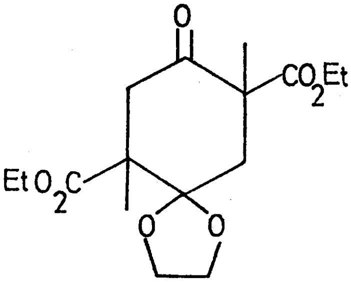
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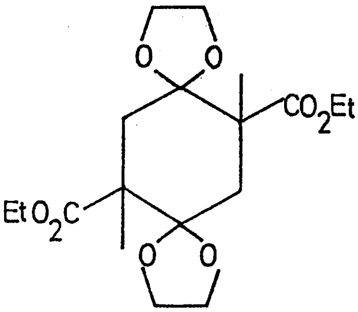
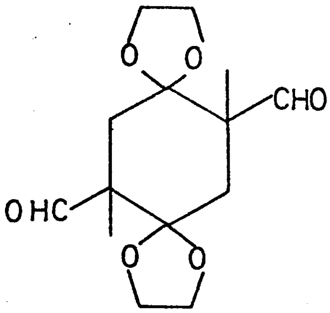

64

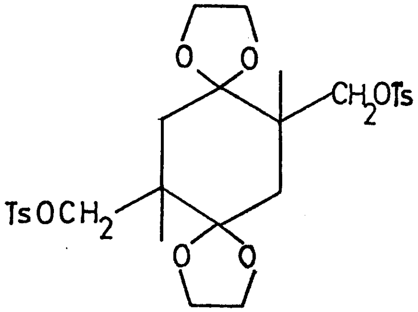
of the trans and cis diesters (62a) and (62b) would furnish a mixture, in the same proportions, of the trans and cis enol lactones (49) and (50), which would then on cyclisation give the two isomeric tricyclododecanes (51) and (52).

The synthetic scheme employed to convert the diester (62) to the required diacid (53) is as follows. Preparation of the diethyl ester (62) was found to proceed in much greater yield than that of the literature method by employing the method developed for alkylation of β-keto esters by the Australian group[20]. Using this method, a product could be obtained which gave no colouration whatsoever with ethanolic ferric chloride solution, and which was shown to be a 3:1 mixture of the trans and cis isomers as found in the N.M.R. spectrum. The two compounds show resonances for the geminal methylene groups of the cyclohexane ring which occur at different frequencies.

Ketalisation of the diester (62) under forcing conditions gave a mixture of the mono ketal (63, 20%) and the bis ketal (64, 80%), separation of these being carried out by column chromatography. It was not possible to separate the cis and trans isomers of the bis ketal (64) by chromatographic means, and as a result, the 3:1



65a-trans
b-cis



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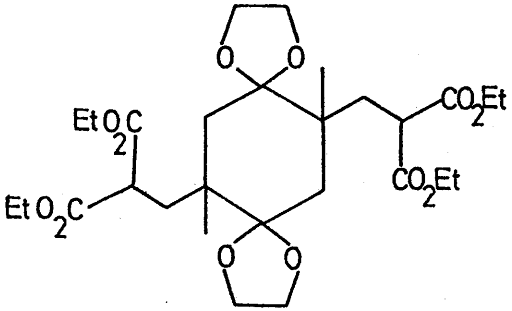

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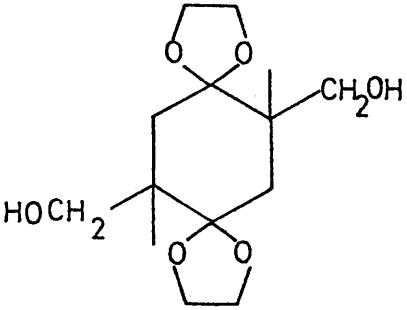
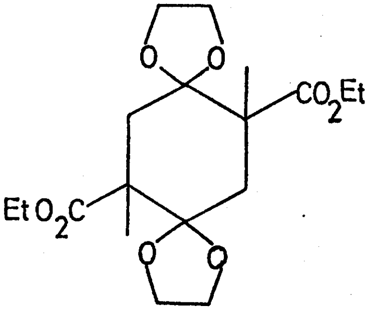


68a-trans
b-cis

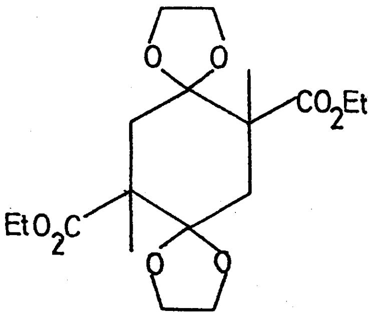


64

mixture of trans and cis isomers was used for subsequent transformations.

These transformations involved elaboration of the carboethoxyl groupings to ,propionic acid groups, either via a Wittig reaction of triethyl phosphonoacetate[21] with the dialdehyde (65), followed by catalytic hydrogenation, or via alkylation of diethyl malonate with the bis tosylate (66) to give (67), followed by hydrolysis and decarboxylation. In fact both of these routes were attempted. The latter was unsuccessful in that a mixture of products was obtained from the reaction of sodiodiethyl malonate and the bis tosylate in dimethyl formamide, and it was not possible to isolate any compound in reasonable yield which showed the expected spectroscopic characteristics. The transformation involving the Wittig reaction proved more successful.

Preparation of the dialdehyde (65) was attempted by two different methods, via reduction to the diol (68) and subsequent selective oxidation, and via direct reduction of the diester (64) with sodium aluminium hydride. Although this reagent has been reported[22] to reduce esters to aldehydes in good yield, it was not found to be effective at carrying out the desired



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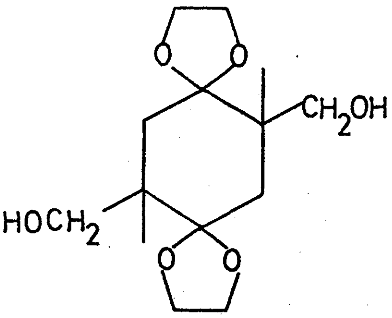

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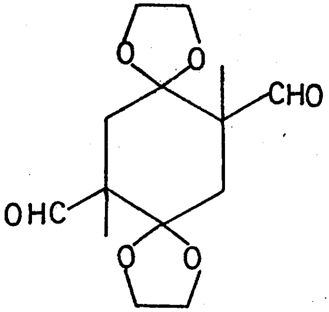
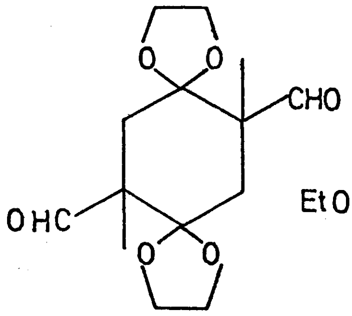


65a-trans
b-cis

reduction of (64) to (65) under various conditions. However the former route to the dialdehyde (65) involving non-selective reduction and then selective oxidation gave better results.

Reduction of the diester (64) to the diol (68) was carried out by excess lithium aluminium hydride, and it was found that the two isomeric cis and trans diols (68a and b) were separable by column chromatography, although it was not possible to characterise each unambiguously by their recorded spectral data. On oxidation to the dialdehydes (65a and b) this characterisation was possible. Oxidation of the diol was attempted by three different methods. The first was a low temperature Jones reaction, the production of the dialdehydes being monitored by t.l.c., but it was difficult to achieve yields of greater than 20% by this method. Collin's[23] reagent, the second method, gave after chromatographic purification on average 35% yield of the dialdehyde, and the third, and most successful oxidation, by dicyclohexyl carbodiimide, dimethyl sulphoxide and pyridinium trifluoroacetate[24] gave a 43% yield of the dialdehydes (65a and b)

At this stage it was possible to characterise the



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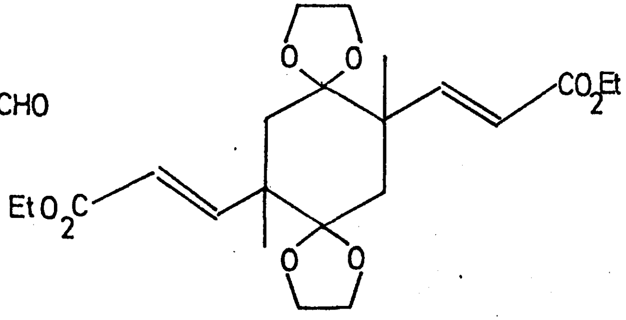

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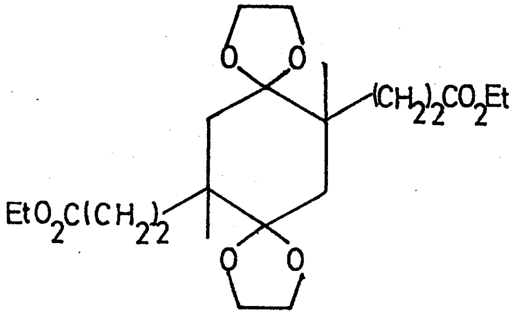
a - trans

b - cis



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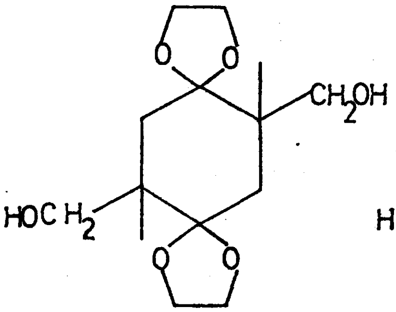

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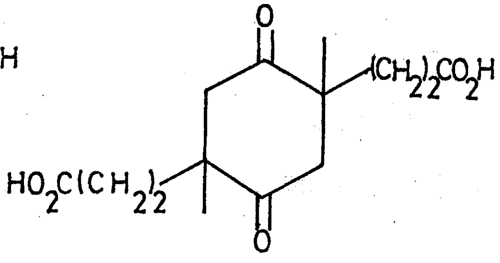
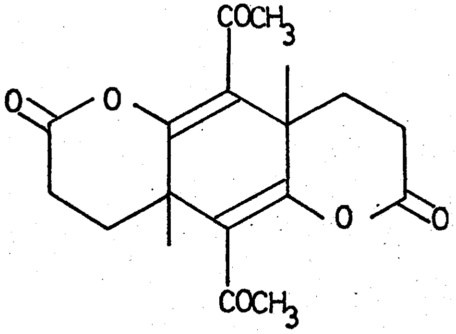


53

cis and trans dialdehydes (65a and b) since the trans dialdehyde exhibits a simple N.M.R. spectrum, the two methyl groups resonating as a six proton singlet at 8.9τ and the cyclohexane methylene groups giving a single AB quartet centred on 8.02τ. On the other hand, the cis dialdehyde shows in the N.M.R. two three proton singlets at 8.86τ and 8.93τ, and two overlapping AB quartets for the cyclohexane geminal methylene hydrogens between 7.6τ and 8.3τ. Therefore, at this stage in the synthesis of two isomeric tricyclododecanes two of the major goals were achieved, i.e. separation and characterisation of the isomeric series.

The remainder of the synthetic scheme was quite easily accomplished by reaction of the pure cis dialdehyde (65b) with triethyl phosphonoacetate according to the Wadsworth-Emmons procedure[21]. This gave (69b) which was reduced to (70b), and hydrolysed to the diketo-diacid (53b). A similar sequence carried out on the mixture of stereoisomeric dials (65a and b) gave a mixture of stereoisomeric diketo-diacids (53a and b). Although the stereoisomeric diols (68a and b) could be separated, the process was tedious and wasteful, and so initially, all attempted enol lactonisations of the diketo-diacid (53)



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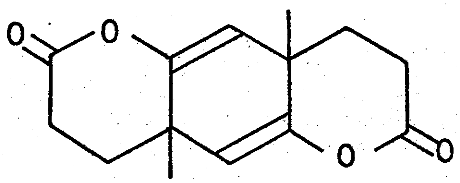
were carried out on this mixture of stereoisomers.

Enol-lactonisation was attempted by two different methods, refluxing the diketo-diacid in acetic anhydride containing a trace of anhydrous sodium acetate[25], or stirring the diketo-diacid briefly in ethyl acetate containing acetic anhydride and a catalytic amount of perchloric acid[26], but neither was successful. On every occasion the major component of the reaction mixture showed infra-red absorptions at 1620cm^{-1} and 1705cm^{-1}, ultra-violet absorption at 250nm., little or no olefinic hydrogen in the N.M.R. spectrum and a singlet in the latter at 7.6τ corresponding to the three protons of an acetyl group. This would suggest that acetylation of the double bonds of the enol-lactone had taken place giving the bis enone (71).

It was possible to obtain a component of the reaction mixture, by t.l.c. separation, which showed the expected spectroscopic characteristics of an enol-lactone, i.e. infra-red absorptions at 1680cm^{-1} and 1760cm^{-1} and a singlet in the N.M.R. at 4.8τ, but this was obtained in rather poor yield, and in general the separation of the components of this mixture was very difficult to achieve. An N.M.R. of the crude reaction mixture showed that the



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integration of the singlet at 7.6τ due to the acetyl group was on average 65-70% of that of the singlet at 8.8τ due to the tertiary methyl groups, indicating that only a small yield of the desired bis enol-lactone (72) would be available. In all variations of the enol-lactonisation which were attempted, e.g. by varying the amount of sodium acetate in the first method, or by shortening the reaction time in the second method, it was impossible to obtain a reaction mixture whose N.M.R. spectrum showed the singlet at 7.6τ to be less than half, by integration, of the singlet at 8.8τ.

In view of this disappointing result, and in the light of other factors, e.g. the amount of time available, the poor yields obtained in some of the synthetic steps and the progress being made in the work described in other sections of this thesis, the work on a synthesis of tricyclo(5,3,1,$1^{2,6}$) dodecanes was at this point discontinued.

EXPERIMENTAL

The remarks prefacing this experimental section are also applicable to all other sections of this thesis which describe experimental procedure.

All melting points were recorded on a Kofler block and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam SP. 200 spectrophotometer. Solution infra-red spectra were recorded on the Perkin-Elmer 225 and 257 and the Unicam SP. 100 double beam spectrometers.

Ultra-violet absorption spectra, measured on a Unicam SP. 800 spectrophotometer, refer to solutions in ethanol unless otherwise stated.

Nuclear magnetic resonance spectra were obtained on the Varian HA 100, the Varian AT 60 and the Perkin-Elmer R 10 spectrometers, using 0.3 molar solutions with tetramethylsilane as internal standard.

Mass spectral determinations were recorded on an AEI MS12 mass spectrometer.

Gas-liquid chromatography (g.l.c.) was carried out on a Pye Argon and Perkin-Elmer F11 Gas chromatographs.

Thin layer chromatography (t.l.c.) was carried out on chromatoplates prepared by the method of Stahl using Kieselgel G (Merck) for analytical separations, and Kieselgel HF_{254} (Merck) for preparative.

Column chromatography was carried out using Woelm grade III basic alumina or Spence grade H silica gel as indicated.

Petrol refers to that fraction of petroleum ether boiling between 60° and 80°.

Preparation of 4,4'-dimethoxycyclohexa-2,5-dienone (8)

3,3',6,6'-Tetramethoxycyclohexa-1,4-diene (9, 5g.) was dissolved in water (500ml.) and the solution stirred at 37° in a water bath. After 4 hours, the solution was extracted with ether (400ml.), the ether dried and removed to give 4.1g. of crude product. Column chromatography of the mixture on alumina gave starting material (650mg.) and 4,4'-dimethoxycyclohexa-2,5-dienone (8, 3.1g.), uncontaminated with p-benzoquinone.

IR. (l.film) cm^{-1} :- 1695(s), 1650(s), 1120(s), 1050(s), 980(s), 880(m).

N.M.R. ($CDCl_3$) :- 3.55τ (quartet, J=10Hz.) -4H, 6.68τ (singlet) -6H.

g.l.c. on 1% APL at 150° gave the following retention times

3,3',6,6'-tetramethoxycyclohexa-1,4-diene	2.50 mins.,
4,4'-dimethoxycyclohexa-2,5-dienone	4.40 mins..

Michael condensation of 4,4'-dimethoxycyclohexa-2,5-dienone (8) with diethyl acetone-1,3-dicarboxylate.

Diethyl acetone-1,3-dicarboxylate (170mg.) in dry ethanol (10ml.) was added dropwise to a solution of sodium (5mg.) in ethanol (25ml.). After stirring at room temperature for one hour, a solution of 4,4'-dimethoxycyclohexa-2,5-dienone (8, 130mg.) in ethanol (5ml.) was added dropwise. The solution was stirred at room temperature for 21 hours and subsequently at 50° for one hour. The ethanolic solution was boiled down, the residue dissolved in ether (50ml.), the ether washed with 2N HCl (20ml.) and saturated brine (2 x 25ml.), dried and the solvent removed giving 260mg. of oily product which t.l.c. (30% EtOAc/petrol) showed to be largely one new component.

Preparative t.l.c. gave diethyl 9,9'-dimethoxybicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7-dione (10, 186mg.). m.pt. 106 - 107° Found C 57.31 H 6.53

$C_{17}H_{24}O_8$ requires C 57.30 H 6.79

IR. (CCl_4) cm^{-1} :- 2830(m), 1752(m), 1720(s), 1658(s), 1618(s), 1230(s), 1057(s) and 953(m).

N.M.R. (CCl_4) :- 5.81τ (doublet of quartets) -4H,
6.68τ (singlet) -3H,
6.81τ and 6.91τ (singlets) -3H,
6.3τ - 8.2τ (multiplets) -8H,
8.71τ (doublet of triplets) -6H.

M.S. Parent ion at m/e 356, important breakdown peaks at m/e 252, 250, 221, 219, 167, 165, 101 and 85.

Attempted hydrolysis of diethyl 9,9'-dimethoxybicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7-dione (10) with ethanolic hydrochloric acid.

Diethyl 9,9'-dimethoxybicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7-dione (10, 350mg.) was refluxed in a mixture of 6N HCl (20ml.) and ethanol (40ml.) for 16 hours. After removal of the ethanol, the aqueous solution was extracted with ether (100ml.), the ether washed with water until acid free washings were obtained, dried and removed to give 75mg. of oily product.

The infra-red spectrum (l.film) of the crude product indicated the presence of a carboxyl grouping, and the N.M.R. showed no bands at 6.7 - 7τ or at 5.8τ and 8.8τ. t.l.c. indicated the presence of a very polar component which gave, on staining, a colour with ferric chloride solution.

Attempted decarboxylation of the above product.

50mg. of the product obtained from the previous experiment were sublimatively distilled from powdered glass. The resulting white crystalline solid became oily on standing.

Infra-red (CCl_4) of the oily product showed bands at 3610, 3500, 3222 (broad), 1765, 1680 and 1635cm^{-1}, indicating the possibility of an unsuccessful decarboxylation.

Attempted decarboxylation of bicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7,9-trione (13) with copper/quinoline

Bicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7,9-trione (13, 120mg.) was dissolved in redistilled quinoline (25ml.) and copper bronze (500mg.) added. The resultant mixture was refluxed 1 hour, cooled, filtered, dissolved in ether (100ml.), the ether extracted with 6N HCl (3x100ml.), dried and boiled down giving 35mg. of crude product shown by t.l.c. in 20% ethyl acetate in petrol to consist of at least five components.

Attempted hydrolysis of (10) with base

The bicyclic β-keto ester (10, 200mg.) was added to 4N sodium hydroxide solution (50ml.) and the solution refluxed for 3 hours. The solution rapidly became dark brown in colour, and on extraction with ether before and after acidification with 6N HCl, only a few mg. of brown residue were recovered.

Attempted hydrolysis of (10) with water.

The bicyclic β-keto ester (10, 350mg.) and water (0.35ml.) were heated together in a sealed tube at 200° for 20 minutes. Ether extraction of the reaction mixture gave only 20mg. of material shown by t.l.c. (30% EtOAc

/petrol) to consist of at least five components.

Attempted hydrolysis of (10) with glacial acetic acid and concentrated sulphuric acid

Diethyl 9,9'-dimethoxybicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7-dione (10, 500mg.) was added to a mixture of glacial acetic acid (20ml.) and conc. sulphuric acid (2ml.), and the solution refluxed under nitrogen for 10 hours. Acetic acid was removed under reduced pressure and water (20ml.) added to the aqueous residue. Ether extraction of the aqueous solution gave only 10mg. of product, shown by t.l.c. (30% EtOAc/petrol) to be mainly one compound.

IR. (CCl_4) cm^{-1} :- 2957(m), 2923(s), 2862(m), 1740(w), 1255(s), 1090(s), 1005(s).

Reaction of the β-keto ester (10) with anhydrous calcium iodide.

Calcium iodide (500mg.) was heated to 450° under nitrogen for 2 hours. On cooling under nitrogen, the β-keto ester (10, 90mg.) and ethylene glycol (2ml.) were added and the mixture stirred under nitrogen at 140° for 2 hours. On cooling, water (10ml.) was added, the aqueous layer extracted with ether (40ml.) and the ether dried and removed giving 42mg. of crude product. Preparative t.l.c. (30% EtOAc/petrol) gave two components, A (12mg.) and B (9mg.).

A IR. (CCl_4) cm^{-1} :- 2924(s), 2854(m) and 1740(m).

B IR. (CCl_4) cm^{-1} :- 2920(s), 2850(m) and 1743(m).

Acetalisation of diethyl 9,9'-dimethoxybicyclo(3,3,1)-nonane-2,4-dicarboxylate-3,7-dione (10) with ethylene glycol.

The β-keto ester (10, 300mg.), p-toluene sulphonic acid (50mg.) and ethylene glycol (1ml.) were refluxed in dry benzene (50ml.) for 24 hours in a flask equipped with a water separator. The solution, on cooling, was added to ether (100ml.) and the combined organic solutions extracted with saturated sodium bicarbonate solution (2 x 100ml.), water (2 x 100ml.) and brine (100ml.). The solution was then dried and the solvent removed to give 315mg. of crude product from which was separated by t.l.c. (30% EtOAc/petrol), diethyl bicyclo(3,3,1)nonane-2,4-dicarboxylate-7,7',9,9'-bisethylenedioxy-3-one (18, 263mg.) as a clear oil. Found C 57.50 H 6.63

$C_{19}H_{26}O_9$ requires C 57.28 H 6.58.

IR. (CCl_4) cm^{-1} :- 2988(s), 2875(s), 1750(m), 1725(s), 1660(s), 1620(s), 1190(s), 1124(s), 1046(s) and 942(m).

N.M.R. ($CDCl_3$) :- 5.8τ (quartet) -4H, 5.98τ (singlet) -4H,
6.2τ (doublet of triplets) -4H,
7.2τ - 9.0τ (multiplets) -8H,
8.81τ (triplet) -6H.

Reaction of the bis acetal (18) with base.

The bis acetal (18, 1.10g.) was added to 4N caustic soda solution (150ml.) and the solution refluxed for 2 hours. On cooling, the basic solution was extracted with ether (200ml.), the ether washed with brine (2 x 100ml.), dried and the solvent removed giving bicyclo-(3,3,1)nonane-7,7',9,9'-bisethylenedioxy-3-one (19, 620mg.), recrystallised from petrol as white needles, m.pt. 93°.

Found	C 61.58	H 7.26
$C_{13}H_{18}O_5$ requires	C 61.41	H 7.14

IR. (CCl_4) cm^{-1} :- 2953(m), 2880(m), 1720(s), 1386(m), 1146(s), 1084(m), 1036(s) and 948(m).

N.M.R. ($CDCl_3$) :- 6.0τ(singlet) -4H, 6.2τ (triplet) -4H,
7.5τ, 7.83τ and 8.4τ (multiplets) -10H.

MS. Parent ion at m/e 254, other significant peaks at m/e 155, 154, 141, 127, 114, 113, 112, 100 and 99.

Reaction of diethyl 9,9'-dimethoxybicyclo(3,3,1)nonane-2,4-dicarboxylate-3,7-dione (10) with ethane-1,2-dithiol.

A solution of the β-keto ester (10, 2g.), ethane-1,2-dithiol (6ml.) and boron trifluoride etherate (5ml.) in chloroform (100ml.) was refluxed for 4 days. On cooling, the chloroform solution was washed with saturated sodium bicarbonate solution (10 x 100ml.) and brine (2 x 100ml.), the solution dried and the solvent removed giving 2.3g. of crude product which was chromatographed on alumina yielding, as the major component, the 7,9-bisthioacetal of diethyl bicyclo(3,3,1)nonane -2,4-dicarboxylate-3,7,9-trione (21, 914mg.).

IR. (n.mull) :- 2980(m), 2892(m), 1745(s), 1720(s), 1680(m), 1625(m), 1180(s), 960(m) and 750(s).

N.M.R. ($CDCl_3$):- 5.8τ (doublet of quartets) -4H,
6.8τ (doublet of triplets) -4H,
6.9τ (singlet) -4H,
6.4τ - 7.8τ (series of multiplets) -8H,
8.78τ (doublet of triplets) -6H.

Reaction of the bisthioacetal (21) with base.

The bisthioacetal (21, 250mg.) was added to 4N sodium hydroxide solution (50ml.) and the resulting solution refluxed for 6 hours. On cooling, the basic solution was extracted with ether (100ml.), the ether washed with brine (2 x 250ml), dried and boiled down giving the 7,9-bisthioacetal of bicyclo(3,3,1)nona -3,7,9-trione (22, 96mg.) after purification by preparative t.l.c. (50% EtOAc/petrol).

IR. (n.mull) :- 2930(s), 2870(m), 1705(s), 1425(m) and 754(s).

N.M.R. ($CDCl_3$) :- 6.82τ (singlet) -4H,
6.84τ (triplet) -4H,
7.12τ, 7.50τ and 7.81τ (series of multiplets) -10H.

M.S. :- Parent ion at m/e 318. Other significant peaks at m/e 290, 258, 225, 197, 187, 165, 131, 123 97 and 71.

Raney nickel desulphurisation of the 7,9-bisthioacetal of bicyclo(3,3,1)nona-3,7,9-trione (22)

W-2 grade Raney nickel (a large excess) was added in small portions to a solution of the bisthioacetal (22, 150mg.) in 95% ethanol (25ml.). After stirring and refluxing for 4 hours, the suspension was filtered through Celite, and the ethanol removed giving bicyclo(3,3,1)nonan-3-one (20), identical with an authentic sample by g.l.c. coinjection on several columns and by mass spectral comparison.

IR. (n.mull) :- 2970(s), 1710(s), 1462(m) and 1140(s) cm^{-1}.

M.S. :- Parent ion at m/e 138, important breakdown peaks at m/e 123, 81, 67, 54 and 41.

Attempted acidic hydrolysis of the bis acetal (19)

The bis acetal (19, 25mg.) was dissolved in a mixture of dioxan (10ml.) and 6N HCl (10ml.) and the solution refluxed for 36 hours. t.l.c. in benzene/dioxan

/acetic acid (90 : 25 : 4) indicated that all the starting material had been consumed and that one major component was produced. Preparative t.l.c. in the above solvent system gave only 5mg. of a very polar compound.

IR. (l.film) cm^{-1} :- 3460(s), 2985(s), 1130(s).

Preparation of dimethyl cyclohexanone-2,6-dicarboxylate (28)

This was prepared by the method of Stiles[27] and obtained as white plates from methanol m.pt. 142 -143°.

IR. (n.mull) cm^{-1} :- 1720(s), 1652(s), 1413(m), 1213(s).

N.M.R. ($CDCl_3$) :- 6.24τ (singlet) -6H,
6.4τ - 6.6τ (multiplet) -2H,
7.6τ -8.4τ (multiplet) -6H.

Attempted Michael reaction of dimethyl cyclohexanone -2,6-dicarboxylate (28) and the dienone (8).

The diester (28, 214mg.) was added to a solution of sodium (23mg.) in methanol (20ml.) under an atmosphere of nitrogen. After stirring for 1 hour at room temperature, the dienone (8, 150mg.) in methanol (5ml.) was added and the mixture stirred overnight. After 16 hours at room temperature, t.l.c. (30% EtOAc/petrol) showed only the presence of starting materials.

The mixture was refluxed a further 16 hours, poured into water (50ml.) and extracted with ether (100ml.). The ether was washed with brine (50ml.), dried and the solvent removed giving 280mg. of crude mixture, shown by t.l.c. to contain the diester (28), no dienone (8) and one new component. Preparative t.l.c. afforded this component 4,4',5-trimethoxycyclohex-2-en-1-one (33, 107mg.) as a clear oil, further purified by distillation.

Found	C 57.84	H 7.55
$C_9H_{14}O_4$ requires	C 58.05	H 7.58

IR. (l.film) cm^{-1} :- 2987(m), 2870(w), 1690(s), 1630(w) 1135(s), 1094(s) and 998(m).

N.M.R. ($CDCl_3$) :- 3.62τ (quartet) -4H,
6.16τ (quintet) -1H,
6.5τ, 6.51τ and 6.53τ (singlets) -9H,
7.2τ (doublet) -2H.

M.S. Parent ion observed at m/e 218. No peak observed at m/e 186. Other significant peaks at m/e 187, 155, 154, 128, 113, 99, 95, 59, 55 and 41.

Further attempted Michael reactions of the diester (28) and the dienone (8).

In a series of five experiments, the dicarbomethoxy cyclohexanone (28, 100mg.) was added to the following basic solutions under an atmosphere of nitrogen.

A A solution of lithium diisopropylamide, formed from butyl lithium (0.25mmole) and diisopropylamine (25mg.), in ether (5ml.)

B A solution of sodium hydride (6mg.) in benzene (5ml.)

C A solution of butyl lithium (0.25mmole) in ether (5ml.).

D A solution of sodium t-amylate (0.25mmole), formed from sodium hydride (6mg.) and t-amyl alcohol(22mg.), in benzene (5ml.).

E A solution of 1,5-diazo bicyclo(4,3,0)non-5-ene (24mg.) in ether (5ml.).

After stirring for 2 hours under nitrogen, to each reaction was added the dienone (8, 100mg.) in the appropriate solvent. t.l.c. analysis of each reaction was carried out after stirring at room temperature for 36 hours, and subsequently after heating the reaction mixtures to reflux for 12 hours. In each case, no new spot was detected by t.l.c.. On working up the reactions by pouring into water (20ml.), extracting with ether (50ml.), drying and removal of the ether, no new component was detectable by t.l.c..

Preparation of diethyl bis(hydroxymethyl)malonate.

This was prepared by the procedure of Welch[28] by condensation of formaldehyde and diethyl malonate, and obtained as a chunky crystalline solid from diisopropyl ether m.pt. 52 - 53°.

Preparation of β,β'-dibromoisobutyric acid.

This compound was prepared by the action of 48%

hydrobromic acid on diethyl bis(hydroxymethyl)malonate according to the procedure of Ferris[29].

m.pt. 100 - 102° (water).

Esterification of β,β'-dibromoisobutyric acid.

This was carried out by the method of McEuen[12], and the methyl ester obtained as a clear liquid.

b.pt. 60 - 62° at 0.4 mm..

IR. (CCl_4) cm^{-1} :- 1740(s), 1440(m),1337(m) and 1025(s).

N.M.R. (CCl_4) :- 6.30τ (singlet) -3H, 6.34τ (doublet) -4H
6.82τ (quintuplet) - 1H.

Preparation of 1,4-dimorpholinocyclohexa-1,3-diene (39).

Cyclohexan-1,4-dione (112mg.) and morpholine (174mg.) were refluxed together in dry benzene (50ml.) in a flask equipped with a water separator. After 2 hours, the benzene was removed giving the crude bis enamine (39) as shown by the absence of an absorption at 1720cm^{-1} in the infra-red spectrum.

Attempted condensation of the bis enamine (39) and the bromo ester (37).

To a solution of the entire yield of bis enamine from the above experiment and triethylamine (202mg.) in dry acetonitrile (25ml.) was added, under nitrogen, the dibromo ester (37, 520mg.) in acetonitrile (10ml.).

The entire solution was refluxed for 13 hours under nitrogen, 5ml. of 5% aqueous acetic acid added, and reflux continued for another hour. On cooling, an equal volume of water was added, and the aqueous solution extracted with ether (100ml.). The ethereal solution was washed with 5% HCl (50ml.), saturated sodium bicarbonate solution (50ml.)& saturated brine (50ml.), dried and the solvent removed giving 140mg. of crude product. Preparative t.l.c. of this product gave no component which seemed to be the expected diester (40).

Preparation of diethyl succinylsuccinate.

This was prepared by a modification of the procedure in Organic Reactions 1 , 283 according to conditions worked out by Lawson[30].

The diethyl succinylsuccinate was obtained as pale yellow needles, m. pt. 126 - 127°.

IR. (CCl_4) cm^{-1} :- 1668(s) and 1624(m).

N.M.R. ($CDCl_3$) :- 5.72τ (quartet) -4H,
6.82τ (singlet) -4H,
8.67τ (triplet) -6H.

Methylation of diethyl succinylsuccinate.

To a suspension of sodium hydride (530mg.) in a mixture of dimethyl formamide (15ml.) and benzene (15ml.) was added diethyl succinylsuccinate (2.5g.) in solution in a mixture of dimethyl formamide (50ml.) and benzene (50ml.). The mixture was refluxed for 2 hours under nitrogen giving a deep pink suspension of the disodio salt. To this was added, as quickly as possible, methyl iodide (10ml.) and the resulting mixture refluxed a further 2 hours, after which time the solution had become clear and yellow. On cooling, this was poured into water (500ml.), the aqueous solution extracted with ether (500ml.) and the ethereal extract washed with 2N HCl (2 x 200ml.) and water (3 x 200ml.). Drying and removal of the solvent gave 2,5-dimethyl-2,5-dicarboethoxycyclohexan-1,4-dione (62, 2.55g.) as a 3:1 mixture of the trans and cis isomers.

IR. (n.mull) cm^{-1} :- 3000(s), 1730(s), 1247(s), 1209(s) and 1115(s).

N.M.R. (CCl_4) :- 5.8τ (doublet of quartets) -4H,
7.02τ (doublet of quartets) -4H,
8.6τ (singlet) -6H,
8.8τ (doublet of triplets) -6H.

<u>Acidic hydrolysis of 2,5-dimethyl-2,5-dicarboethoxycyclohexan-1,4-dione (62)</u>.

The dimethyl diethyl succinylsuccinate (62, 2.5g.) was refluxed for 16 hours in 6N H_2SO_4 (60ml.). On cooling, the solution was saturated with sodium chloride and extracted with chloroform (75ml.). The chloroform extract was washed with water (50ml.), dried and the solvent removed giving 900mg. of crude product which, on recrystallisation from ether,gave 2,5-dimethylcyclohexan-1,4-dione (54, 520mg.) as a 3:1 mixture of the trans and cis isomers.

IR. (n.mull) cm^{-1} :- 1705(s), 1154(m), 878(m) and 800(m).

N.M.R. ($CDCl_3$) :- 6.8τ - 8.0τ (multiplet) -6H,
8.82τ and 8.90τ (singlets) -6H

Attempted cyanoethylation of the dione (54).

To a solution of the dione (54, 200mg. = 4x excess) in dioxan (25ml.) were added two drops of Triton B. After stirring under nitrogen for 2 hours, acrylonitrile (50mg.) was added dropwise, and the resulting solution stirred at room temperature for 72 hours. The solution was poured into 2N HCl (25ml.) and extracted with ether (100ml.). Drying and removal of the solvent afforded 230mg. of product, shown by t.l.c. (40%EtOAc/petrol) to consist only of the starting dione (54).

On repeating the above procedure and further refluxing the solution for 16 hours, an identical result was obtained.

Reaction of the dione (54) with methyl acrylate.

Potassium (40mg.) was added to,dry t-butanol (20ml.)

under nitrogen, and the solution stirred for 30 minutes, after which time all the potassium had dissolved. The dione (54, 6oomg.) in t-butanol (10ml.) was added, followed by methyl acrylate (720mg.) in t-butanol (0.5ml.) over a period of 30 minutes. After stirring for 90 minutes at room temperature, the reaction mixture was poured into 2N H_2SO_4 (30ml.), the acidic solution extracted with ether (50ml.), the ether washed with brine (20ml.), dried and the solvent removed giving 720mg. of crude product, shown by t.l.c. (40% EtOAc/petrol) and g.l.c. to contain no starting material and four new components, two major and two minor.

g.l.c. on 1% SE30 at 175° gave the following retention times :- 7.25 and 8.3 mins. for the major components and 8.9 and 9.6 mins. for the minor components.

Column chromatography on alumina gave pure samples of the two major components.

Component A a viscous oil retention time 8.3mins.

Found	C 62.57 H 7.86
$C_{12}H_{18}O_4$ requires	C 63.70 H 8.02
IR. (l.film) cm^{-1}	:- 3550(m), 2990(m), 1735(s), 1705(s). 1204(s) and 1053(m).
N.M.R. ($CDCl_3$)	:- 6.23τ (singlet)

:- 6.8τ - 8.2τ (multiplet) -9H, one of which is exchangeable,
8.8τ (singlet) -3H,
8.85τ (multiplet) -3H.

M.S. :- Parent ion at m/e 226. Other significant peaks at m/e 195, 155, 140, 123, 112, 97, 95, 87, 69 and 55

Component B m.pt. 140 -150^{o}, retention time 7.25 mins.

Found C 63.58 H 7.99

$C_{12}H_{18}O_4$ requires C 63.70 H 8.02

IR. (n.mull) cm^{-1} :- 3545(s), 2990(s), 1735(s), 1706(s), 1452(m), 1371(m), 1213(s) and 1050(m).

N.M.R. ($CDCl_3$) :- 6.23τ (singlet) -3H,
6.8τ - 8.2τ (multiplet) -9H, one of which is exchangeable,
8.87τ (singlet) -3H,
8.95τ (multiplet) -3H.

M.S. :- Parent ion at m/e 226. Other significant peaks at m/e 195, 194, 155, 140, 123, 97, 95, 87, 69 and 55.

Acetalisation of 2,5-dimethyl-2,5-dicarboethoxycyclohexan-1,4-dione (62) with ethylene glycol.

A solution of the diester (62, 5g.), p-toluene sulphonic acid (2.5g.) and ethylene glycol (15ml.) in benzene (150ml.) was refluxed for 60 hours using a Dean and Stark apparatus to effect separation of the water formed. On cooling, the solution was poured into ether (250ml.) and the combined organic solutions washed with saturated sodium bicarbonate solution (2 x 100ml.) and water (2 x 100ml.). Drying and removal of the ether gave 6.1g. of a mixture of the mono ethylene acetal and the bis ethylene acetal of the starting material in approx. 1:3 as shown by t.l.c. (40% EtOAc/petrol).

Column chromatography on silica gel gave the mono acetal (63, 1.5g.) and the bis acetal (64, 4.4g.).

Mono acetal (63) a viscous oil

IR. (l.film) cm^{-1} :- 2995(m), 1730(s), 1710(m), 1303(m), 1241(s), 1112(s), 960(w) and 880(w).

N.M.R. ($CDCl_3$) :- 5.83τ (doublet of quartets) -4H,
5.97τ (multiplet) -4H,
6.7τ - 8.4τ (multiplet) -4H
8.67τ (singlet) -6H,
8.71τ (doublet of triplets) -6H.

Bis acetal (64) a white crystalline solid m.pt. 114 -117°.

Found	C 57.87 H 7.36
$C_{18}H_{28}O_8$ requires	C 58.05 H 7.58

IR. (CCl_4) cm^{-1} :- 2995(m), 2890(m), 1730(s), 1256(s), 1112(s), 1040(s), 998(m) and 960(m).

N.M.R. ($CDCl_3$) :- 5.83τ (doublet of quartets) -4H,
6.12τ (singlet) -8H,
7.80τ (quartet) -4H,
8.63τ (singlet) -6H,
8.74τ (doublet of triplets) -6H.

The identity of the mono ethylene acetal (63) was established by its conversion to the bis acetal (64) on treatment with ethylene glycol/p-toluene sulphonic acid in refluxing benzene for 16 hours.

Reduction of the bis acetal (64) by lithium aluminium hydride.

Lithium aluminium hydride (2.5g.) was added in small portions to a solution of the bis acetal (64, 10g.) in tetrahydrofuran (100ml.). The resulting solution was refluxed for 16 hours and then cooled to room temperature. Ethyl acetate was added dropwise until effervescence ceased, followed by careful addition of water until the white precipitate became granular. The precipitate was filtered and washed with ethyl acetate (200ml.) and all organic solvents were removed from the filtrate under reduced pressure. The resulting aqueous solution was extracted with chloroform (150ml.), the chloroform extract dried and boiled down giving 5.7g. of crude product. t.l.c. (60% EtOAc/petrol) showed the presence of only two new components.

These were separated by column chromatography on alumina giving the cis diol (68b, 1.03g.) and the trans diol (68a, 3.38g.).

Cis diol m.pt. 152 -162°. Found C 58.32 H 8.39

$C_{14}H_{24}O_6$ requires C 58.46 H 8.22

IR. (n.mull) cm^{-1} :- 3390(s), 1138(s), 1055(s), 1045(s) 1010(s) and (976).
No absorption between 1500 - 2000cm^{-1}.

N.M.R. ($CDCl_3$) :- 6.02τ (singlet) -8H, 6.4τ (singlet) -4H, 7.3τ (broad singlet) -2H -exchangeable, 8.2τ (quartet, J = 14Hz.) -4H, 8.9τ (singlet) -6H.

M.S. Parent ion at m/e 288. Other significant peaks at m/e 257, 227, 183, 171, 146, 130, 126, 113, 99, 83, 69 and 55.

<u>Trans diol</u> m.pt. 91 - 95°. Found <u>C</u> 58.22 <u>H</u> 8.15

$C_{14}H_{24}O_6$ requires <u>C</u> 58.46 <u>H</u> 8.22

IR. (CCl_4) cm^{-1} :- 3550(s), 2993(s), 1471(m), 1422(m) 1220(s), 1198(S), 1052(s) and 1000(m).

N.M.R. ($CDCl_3$) :- 6.1τ (singlet) -8H, 6.47τ (singlet) -4H, 7.6τ (broad singlet) -2H -exchangeable, 8.2τ (quartet, J = 14Hz.) -4H, 9.02τ (singlet) -6H.

M.S. Parent ion at m/e 288. Other significant peaks at m/e 257, 227, 171, 146, 130, 113, 99, 83, 69 and 55.

<u>Reaction of the trans diol (68a) with p-toluene sulphonyl chloride in pyridine</u>.

The trans diol (68a, 288mg.) and p-toluene sulphonyl chloride (450mg.) were dissolved in dry pyridine (5ml.) and the solution kept at 0° for 1 week. After this time, the solution was poured on ice-water (50ml.) and left to stand for 30 minutes. The resulting white precipitate was filtered off and dried under vacuum. Infra-red analysis of this showed the absence of hydroxyl absorptions and the presence of the typical sulphonate ester absorptions at 1170 - 1200 cm^{-1} indicating the likelyhood of the formation of the bis tosylate (66).

Attempted alkylation of diethyl malonate with the bis tosylate (66).

Diethyl malonate (160mg.) was added to a suspension of sodium hydride (50mg.) in a mixture of benzene (15ml.) and dimethyl formamide (15ml.). After stirring for 1 hour under an atmosphere of nitrogen, the bis tosylate (66, 314mg.) dissolved in dimethyl formamide (5ml.) was added over a period of 15 minutes. The resulting solution was heated at 60° for 16 hours, and after this time t.l.c. (40% EtOAc/petrol) showed only the presence of the starting bis tosylate (66).

Subsequent attempts to effect the alkylation proved unsuccessful in that raising the reaction temperature resulted in the production of several products, none of which seemed to be the desired tetraester (67).

Attempted quantitative Jones Oxidation of the diol mixture (68a and b).

To a mixture of the diols (68a and b; 288mg.) in acetone (25ml.) was added dropwise, at ice temperature, Jones reagent (.58ml. of 8N). As soon as the addition was complete, the solution was poured into water (20ml.) and this combined solution extracted with ether (100ml.). The ether was dried and boiled down giving 160mg. of crude product. t.l.c. (40% EtOAc/petrol) showed the presence of the dialdehyde (65), but also a significant amount of another component, probably the intermediate half-oxidised hydroxy-aldehyde. Preparative t.l.c. gave 67mg. of this component.

IR. (n.mull) cm^{-1} :- 3600(m), 1710(s), 1205(m), 1152(s), 1055(s), 1040(s) and 972(s).

N.M.R. ($CDCl_3$) :- 0.3τ (singlet) -1H,
6.06τ (multiplet) -8H,
6.3τ (broad singlet, sharpening to a doublet on addition of D_2O) -2H,
7.5τ (broad singlet) -1H exchangeable,
7.97τ (multiplet) -4H,
8.9τ and 8.95τ (singlets) -6H.

Attempted monitoring of the Jones oxidation of the diols (68a and b) by thin layer chromatography.

Jones reagent (8N) was added dropwise to a solution of the diols (68a and b, 700mg.) in acetone (30ml.). The reaction was monitored by t.l.c., analytical plates being run (40% EtOAc/petrol) after the addition of every 2 drops of Jones reagent. As soon as acidic material started to appear on t.l.c., water (30ml.) was added and the solution extracted with ether (100ml.). Drying and removal of the ether gave 500mg. of crude product.

Column chromatography on alumina gave the mixture of dialdehydes (65a and b, 300mg.) and the intermediate hydroxyaldehyde (45mg.).

The identity of the hydroxyaldehyde was further established by its oxidation, by Collin's reagent to the mixture of dialdehydes (65a and b).

Preparation of Collins reagent.

This was prepared by the method of Collins, Hess and Frank[23], and obtained as deep red crystals which were stored in vacuo over phosphorous pentoxide.

Collins oxidation of the diols (68a and b).

The two diols were oxidised separately under identical conditions, viz. :-

Collin's reagent (6g.) was added to a solution of the diol (575mg.) in methylene chloride (150ml.) which, prior to use, had been eluted through grade I basic alumina. After addition of barium hydroxide (500mg.), the suspension was stirred under nitrogen for 30 minutes, and the solvent then removed. The brown residue was extracted with ether (3 x 200ml.) and the ethereal extract washed with water (2 x 200ml.), 2N HCl (200ml.) and brine (2 x 100ml.). Drying and removal of the solvent gave the dialdehyde (65, 170mg.) which was purified by preparative t.l.c. (40% EtOAc/petrol).

Cis dialdehyde (65b) m.pt. 165°. Found C 59.00 H 7.15

$C_{14}H_{20}O_6$ requires C 59.14 H 7.09.

IR. (n.mull) cm^{-1} :- 2720(w), 1710(s), 1201(m), 1119(s), 1040(s), 1032(s) and 970(s).

N.M.R. ($CDCl_3$) :- 0.3τ (singlet) -2H, 6.05τ (triplet)-8H
8.0τ and 8.05τ (quartets) -4H,
8.3τ and 8.7τ (singlets) -6H.

Trans dialdehyde (65a) m. pt. 110 - 115°.

IR. (CCl_4) cm^{-1} :- 2750(w), 1725(s), 1467(s), 1140(m), 1124(m), 1043(m), 1026(m) and 975(m).

N.M.R. (C_6D_6) :- 0.2τ (singlet) -2H,
6.70τ (broad singlet) -8H,
8.02τ (quartet) -4H,
8.9τ (singlet) -6H.

Pfitzner-Moffat oxidation of the diol (68b).

A solution of the diol (68b, 144mg.), dicyclohexylcarbo-di-imide (616mg.), pyridine (.08ml.) and trifluoroacetic acid (.04ml.) in a mixture of dimethyl sulphoxide (5ml.) and benzene (10ml.) was left to stand at room temperature for 16 hours. Ethyl acetate (25ml.) was then added, and the dicyclohexyl urea which precipitated out was filtered off. The ethyl acetate solution was washed with water (3 x 20ml.), dried and boiled down giving 580mg. of residue, which was shown by t.l.c. to contain the dialdehyde (65b), dicyclohexyl urea , and dicyclohexylcarbo-di-imide.

Column chromatography on alumina gave the dialdehyde (65b, 68mg.).

Attempted reduction of the diester (64) by sodium aluminium hydride.

A solution of sodium aluminium hydride (14.5mg.) in tetrahydrofuran (10ml.) was gradually added to a solution of the diester (64, 144mg.) in tetrahydrofuran (10ml.), under an atmosphere of nitrogen, and between -45° and -65°. After stirring for 6 hours at this temperature, the reaction mixture was poured into excess cold sodium bisulphite solution (50ml.). The aqueous solution was extracted with ether (50ml.), the ether dried and removed giving starting diester (64, 110mg.). Acidification and ether extraction of the aqueous layer gave none of the expected dialdehyde (65).

Preparation of triethyl phosphonoacetate.

This was prepared by refluxing equimolar quantities of ethyl bromoacetate and triethyl phosphite, and obtained as a clear liquid, b.pt. 109° @ 0.80 mm..
IR. (l.film) cm^{-1} :- 3040, 1740, 1290, 1058 and 996.

Reaction of the dialdehyde (65b) with triethyl phosphonoacetate.

Triethyl phosphonoacetate (230mg.) in benzene (5ml.) was added slowly under nitrogen to a suspension of sodium hydride (25mg.) in benzene (10ml.). After vigorous evolution of hydrogen, the resulting clear pale yellow solution was stirred at room temperature for 1 hour. The dialdehyde (65b, 130mg.) in benzene (5ml.) was then added over a period of 15 minutes, and the entire mixture then stirred 2 hours at room temperature. The benzene solution was poured into 2N HCl (25ml.), washed with brine (10ml.), dried and boiled down giving 212mg. of crude product, from which the product (69b, 108mg.) was obtained by preparative t.l.c. (40% EtOAc/petrol).

m.pt. 142°. Found $\underline{C}$ 62.17 $\underline{H}$ 7.34

$C_{22}H_{32}O_8$ requires $\underline{C}$ 62.25 $\underline{H}$ 7.60.

IR. (n.mull) cm^{-1}:- 2985(s), 2920(s), 1715(s), 1658(m), 1195(s), 1130(m), 1040(m), 1008(m) and 970(m).

N.M.R.(CCl_4) :- 3.6τ (quartet) -4H, 5.82τ (quartet) -4H, 6.03τ (singlet)-8H, 8.2τ (singlet) -4H, 8.8τ (triplet) -6H, 8.84τ (singlet) -6H.

M.S. Parent ion at m/e 424. Other important breakdown peaks at m/e 327, 253, 187, 172, 157, 100 and 87.

Catalytic hydrogenation of the diunsaturated diester (69).

The diester (69, 200mg.) in ethanol (50ml.) containing excess 10% palladium on carbon was stirred under one atmosphere of hydrogen until no further uptake of hydrogen was observed. Filtering through glass paper and removal of ethanol by boiling gave the saturated diester (70, 197mg.).

IR. (l.film) cm^{-1} :- 2995(s), 2923(s), 1735(s), 1152(s), 1046(s) and 972(m).

N.M.R. ($CDCl_3$) :- 5.85τ (quartet) -4H,
6.13τ (singlet) -8H,
7.8τ - 8.4τ (multiplets) -12H,
8.78τ (triplet) -6H,
9.00τ (singlet) -6H.

Acidic hydrolysis of the saturated diester (70).

The diester (70, 150mg.) was dissolved in ethanol (5ml.) to which was added 6N hydrochloric acid (50ml.). The entire solution was refluxed for 24 hours, cooled, and extracted with ether (100ml.). The ethereal extract was then extracted with saturated sodium bicarbonate solution (50ml.), this in turn acidified with 6N HCl, and the resulting aqueous solution extracted with ether (100ml.). This ethereal extract was dried, and the ether removed giving 67mg. of crude product, whose N.M.R. in $CDCl_3$ indicated the absence of ethyl ester and ethylene acetal protons.

N.M.R. ($CDCl_3$) :- 3.0τ (broad singlet) -2H exchangeable,
7.2τ - 8.4τ (series of multiplets) -12H,
8.85τ and 8.87τ (singlets) -6H.

The above data is consistent with the proposed diacid structure (53).

Attempted enol-lactonisation of the diacid (53).

The diacid (53, 50mg.) was refluxed in acetic anhydride (5ml.), to which had been added a trace of anhydrous sodium acetate. After refluxing for four hours, the entire solution was dissolved in toluene (50ml.) and the toluene solution boiled down, giving a residue which was dissolved in ether (50ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (2 x 10ml.), saturated brine (15ml.), dried and boiled down giving 35mg. of crude mixture, shown by t.l.c. to consist of at least three components. Infra-red analysis indicated the presence of an enone function due to absorptions at 1620 and 1705 cm^{-1}, in addition to the expected absorptions at 1680 and 1760 cm^{-1}.

Preparative t.l.c. partially separated the three components, giving three fractions, all of which showed a large peak in the N.M.R. at 7.6τ, due to the presence of an acetyl group. In addition, each fraction showed an ultra-violet absorption at 250nm..

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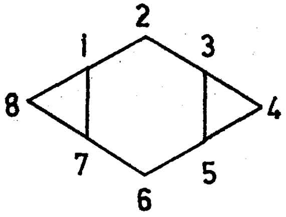
PART 1b

SYNTHETIC APPROACHES TO THE TRICYCLO(5,1,0,$0^{3,5}$)OCTANES.



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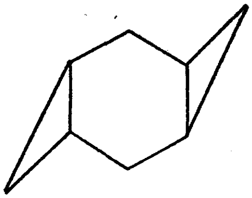

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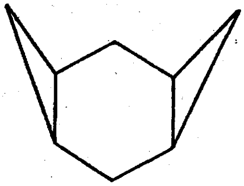


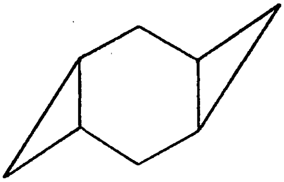
3

INTRODUCTION

In recent years, the exploration of the chemistry of small-ring compounds has greatly intrigued the organic chemist. The stimulus for this increased activity is probably due to several factors, e.g. the present availability of a large number of methods of formation of these compounds, the increasing interest in the unusual reactivity possessed by them because of their high strain energy, and also the success with which the rules for the conservation of orbital symmetry[1] can be applied to the reactions of many of these compounds.

One such system which has been studied, for some but not all of the reasons cited above, is the tricyclo-$(5,1,0,0,^{3,5})$octane (1). Compounds of this class are of interest for several reasons, the synthetic challenge presented in the preparation of them, the potential conformational variance in either the anti (2) or syn (3) isomers, and the unusual reactivity conferred on them by constraints of strain or of stereochemistry.

The synthesis of compounds of the tricyclo$(5,1,0,0^{3,5})$-octane class is normally achieved by the addition of two moles of a carbene, or a carbenoid, to a



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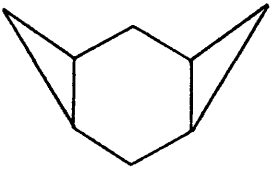

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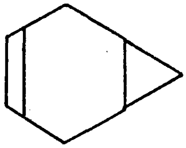

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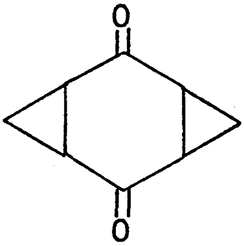

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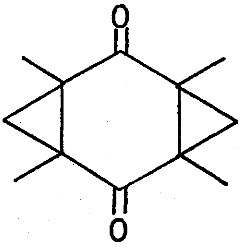

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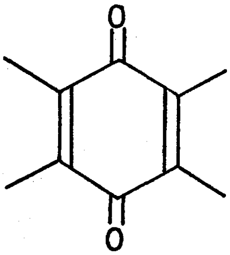

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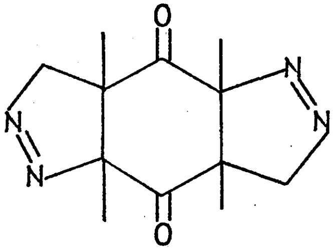

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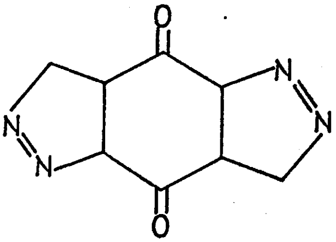

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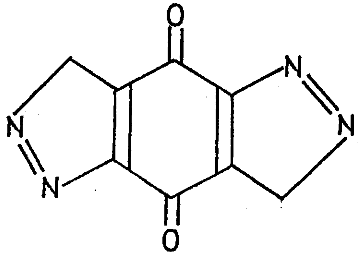

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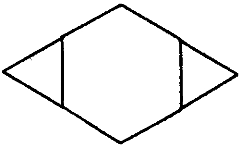
cyclohexa-1,4-diene, e.g. the two isomeric parent compounds (2) and (3) have been prepared[2] by a stepwise reaction of cyclohexa-1,4-diene with Simmons-Smith reagent, via the intermediate bicyclo(4,1,0)heptene (4). However this method is limited by the availability of suitable cyclohexa-1,4-dienes, and a survey of the literature reveals that all tricyclooctanes prepared by this general method lack oxygenated functionality at C(2) and C(6). In particular, at the time of commencement of this work, no synthesis of the potentially interesting tricyclo($5,1,0,0^{3,5}$)octan-2,6-diones (5) existed. An example of the preparation of tricyclooctanes akin to (5) exists[3], i.e. the thermolytic preparation of the tricyclooctandione (6) from the bis pyrazoline (8), prepared by addition of two moles of diazomethane to duroquinone (7), but substitution of p-benzoquinone for duroquinone in the above reaction sequence[4], although giving the bis pyrazoline (9), was unsuccessful, since (9) was readily converted to (10), thereby precluding any thermolysis or photolysis of (9) to (5)

The availability of 'bishomoquinone' (5) would facilitate further studies in the tricyclooctane field, in particular in the areas of stereochemistry, and



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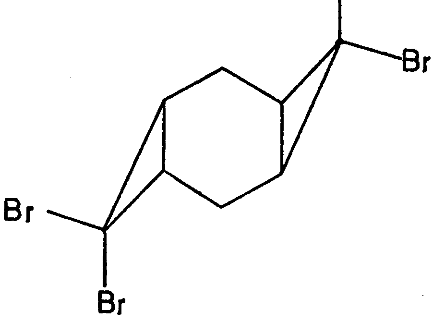

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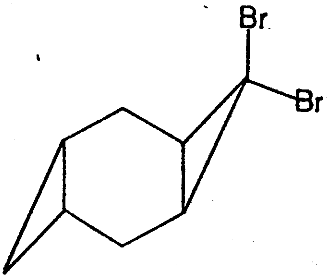

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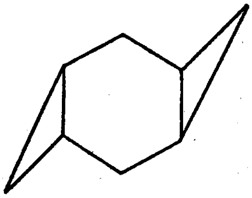

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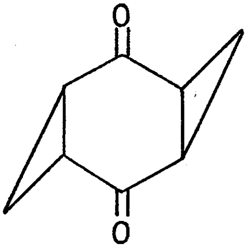

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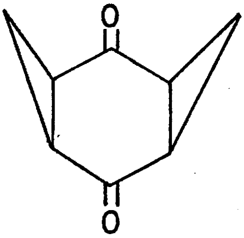

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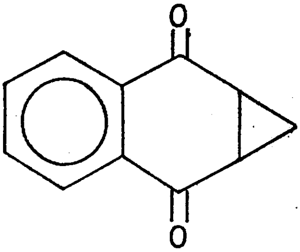

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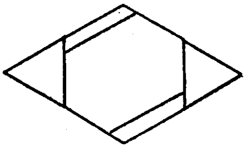
synthesis and reactivity.

Little is known concerning the conformation of either isomer of (1), the only determination which has been carried out having been done by Winstein[5], who studied the conformation of the tetrabromide (11), the dibromide (12), and the parent hydrocarbon (2) by dipole moment measurements. These indicated that, in all three cases, the preferred conformation is one in which the central six-membered ring is flat. Construction of molecular models vindicated these findings, since it is seen from these that a flat six-membered ring minimises any non-bonded interactions in the molecule.

Further studies on this subject would certainly be possible if the two isomeric bishomoquinones (13) and (14) were available, since a choice of the method of examination of the conformation would then be possible; e.g. a spectroscopic or dipole moment measurement, or a determination of the crystal structure, it being expected that both (13) and (14) are crystalline.

A related system which has been studied[6] by the last method is the homonaphthoquinone (15). This has provided interesting results in that the two carbon-oxygen bonds are non-collinear. This is probably caused by the



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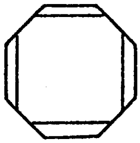

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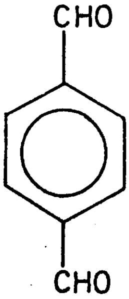

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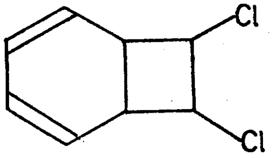

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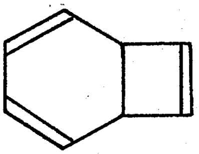

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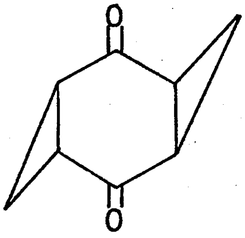

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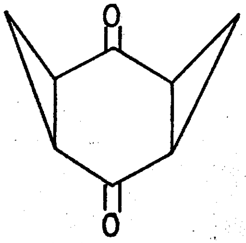

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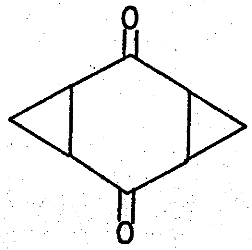
distortion at carbon atoms 2 and 3 due to their fusion to a three-membered ring. Distortions of this kind would be expected in the molecular structure of bishomoquinone.

Conversion of bishomoquinone to other tricyclooctanes of potential interest should also be possible; e.g. the diene (16), proposed[7] as an intermediate in the oxidation of cyclooctatetraene (17) with hypochlorous acid in alkali, the product being (18). It is obvious that this reaction does not parallel that of cyclooctatetraene with e.g. sulphuryl chloride[8] to give the dichloride (19) by chlorination of the cyclobutene double bond of the valence isomeric bicyclo(4,2,0)octatriene (20), since the diene (16) cannot be derived simply by a valence isomerism, but must arise by some type of hydrogen shift. Nevertheless, the preparation of (16) represents some considerable synthetic challenge, which may be met by utilising bishomoquinone as an intermediate.

Therefore, there exist a number of reasons for attempting a synthesis of the tricyclooctandiones (13) and (14), and it will be the purpose of the work described in this section of the thesis to carry out this synthesis. It is also hoped that light may be shed on some other areas of tricyclooctane chemistry which have



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been mentioned, in the event of a successful route to (5) being established.

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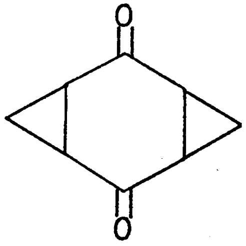

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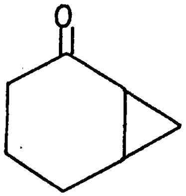

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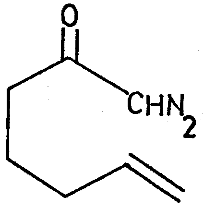

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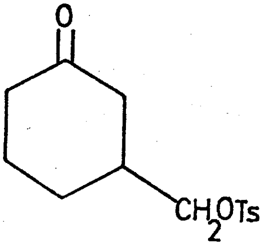

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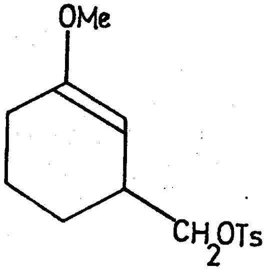

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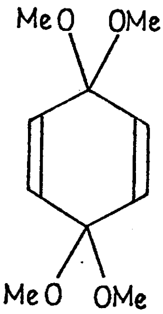

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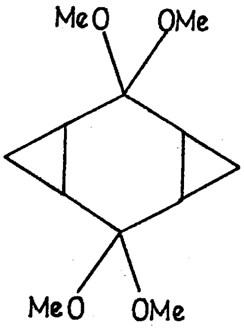

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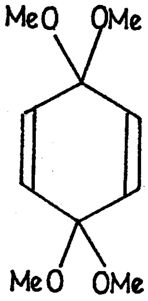
DISCUSSION

It is perhaps obvious that the method of choice for the synthesis of tricyclo(5,1,0,$0^{3,5}$)octan-2,6-dione (1) is suggested by the known preparations of bicyclo-(4,1,0)heptan-2-one (2). Several of these exist, e.g. copper catalysed intramolecular addition involving (3)[1], treatment of (4) with sodium hydride, or cyclisation of (5) in pyridine[2]. Although similar routes to (1) could be successful, the method initially attempted was prompted by the availability of a unique starting material, the tetramethoxy cyclohexa-1,4-diene (6)[3], used in the first part of this thesis. It seemed likely that this starting material would readily yield compounds of the tricyclooctane class e.g. (7) and (1), but the results produced from attempted conversion of (6) to (7) were both totally unexpected and unpredictable.

The reaction chosen for the addition of a carbene to the double bonds of (6) was the Simmons-Smith reaction[4], since this takes place under essentially neutral conditions, and the product obtained bears no halogen substituents in contrast to most of the other methods of carbene addition.



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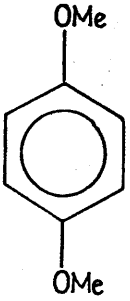

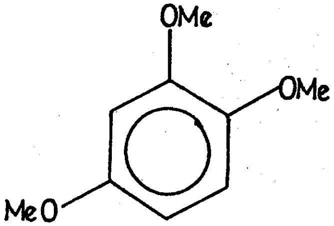

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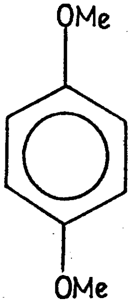
Reaction of the diene (6) with Simmons-Smith reagent gave a complex mixture of products, shown by t.l.c. and g.l.c. to consist of three major components, accompanied by a plethora of minor ones. Separation and purification of the three major components was accomplished by standard procedures, and the structures of two of these quickly became obvious as the dimethyl ether of hydroquinone (8) and 1,2,4-trimethoxy benzene (9). The other compound isolated analysed for $C_{17}H_{20}O_5$, and mass spectral determination was consistent with this, giving a parent ion at m/e 304. The I.R. showed absorptions assigned to an aromatic methyl ether, and the N.M.R. spectrum in $CDCl_3$ exhibited two types of protons, aromatic and methoxyl, in the ratio 1:3. From this information it was concluded that the compound was a pentamethoxy biphenyl, U.V. absorptions at 215nm. and 300nm. corroborating this assignment. However, determining which of the possible isomers of pentamethoxy biphenyl proved rather more difficult.

The N.M.R. spectrum in $CDCl_3$ proved impossible to interpret completely. Although each methoxyl group appeared non-equivalent since they all resonated at different frequencies, the aromatic region of the spectrum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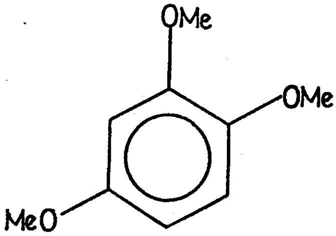
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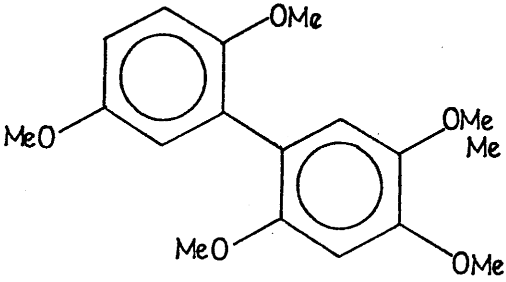
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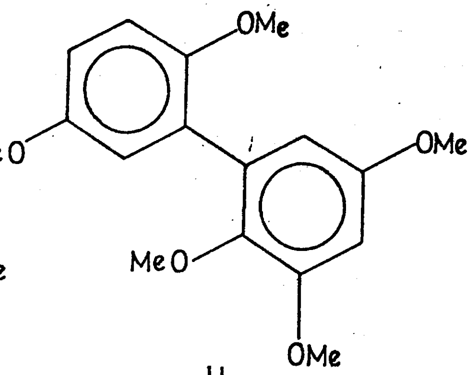
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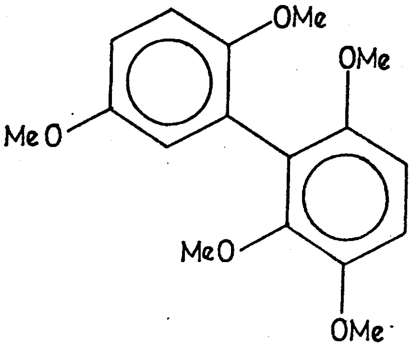
11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Me O
MeO
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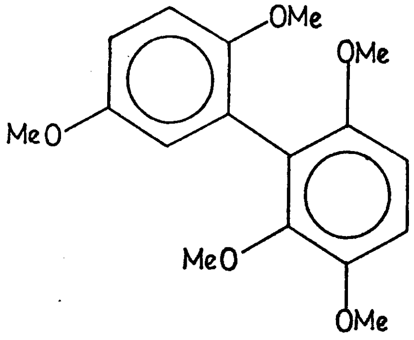
12

was singularily useless in the determination of the distribution of five methoxyls and five protons in the ten available positions.

To simplify the problem, it was postulated that the pentamethoxy biphenyl had arisen by union of the two aromatic compounds isolated from the reaction mixture i.e. (8) and (9). Since all the available positions of hydroquinone dimethyl ether are equivalent, there were three possible structures for the pentamethoxy biphenyl, (10), (11) and (12). Each of these should show in the aromatic region of the N.M.R., an AB quartet due to the two protons on the tetrasubstituted ring, and an ABC or ABX system for the three protons on the trisubstituted ring. If the spectrum is capable of analysis, differentiation should be possible because of the different size of the AB coupling constant arising from protons which are para (10), meta (11) or ortho (12).

Running the N.M.R. spectrum in d_6-benzene produced the best result, although this still did not give a first-order spectrum. However, the existence of an ABC system and an AB quartet was established. Unfortunately the coupling constant of the latter (1½Hz.) did not indicate unambiguously which of the three isomers was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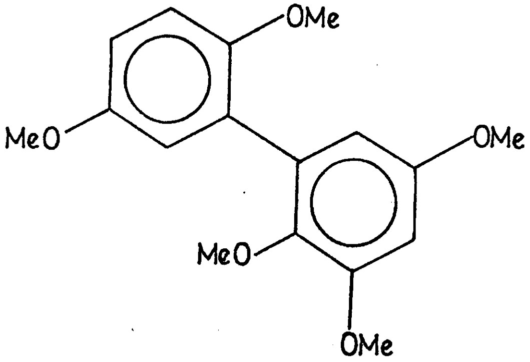
12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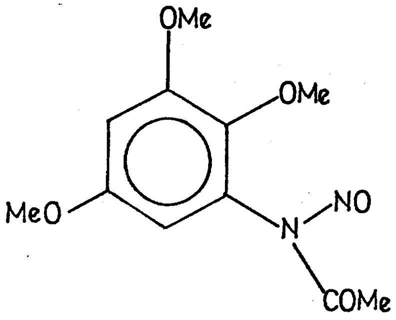
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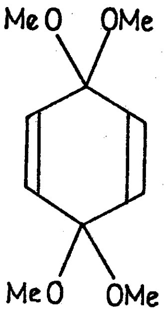
MeO
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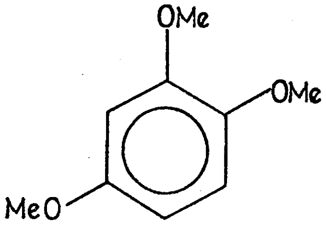
6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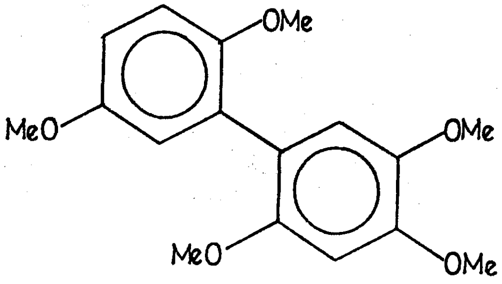
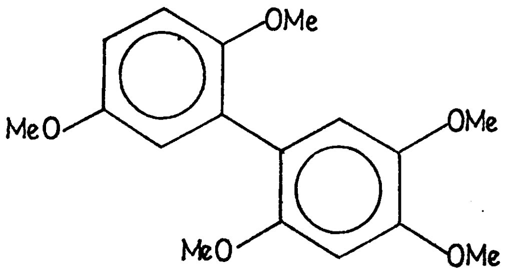

OMe
MeO
OMe
MeO
OMe

10

correct, although the field was narrowed since (12) would not give an AB coupling constant of 1½Hz., but one of ca. 8Hz., due to two ortho hydrogens.

Since the problem seemed incapable of solution by spectroscopic means, a synthetic solution was undertaken, and the goal of this was the synthesis of (11), since it seemed that 1½Hz. was more likely to be a meta hydrogen coupling constant rather than a para hydrogen coupling constant. The final synthetic step to (11), decomposition of the nitroso acetanilide (13) in hydroquinone dimethyl ether was being attempted when the existence of a note in the Journal of the American Chemical Society, unfortunately wrongly assigned in the cumulative index of Chemical Abstracts, was discovered.

This note[5] concerns the action of boron trifluoride etherate on the diene (6), reported to produce (9) and (10), although the structure (10) is based on an intuitive guess rather than concrete evidence. It was necessary, therefore, to establish the relationship between the biphenyl (10) isolated from this reaction, and that obtained from the Simmons-Smith reaction of (6). Repetition of the reaction involving (6) and boron trifluoride etherate and comparison of the two compounds



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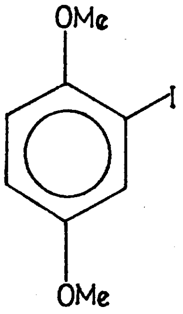

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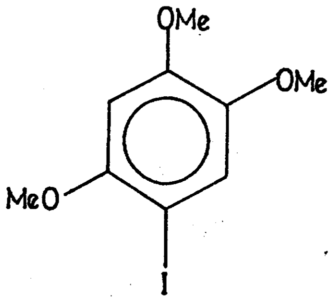

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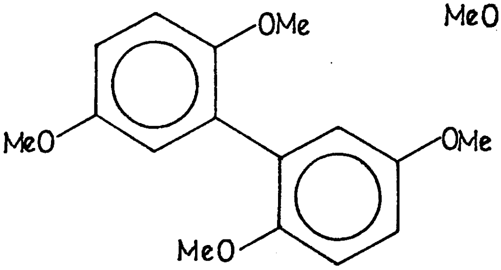

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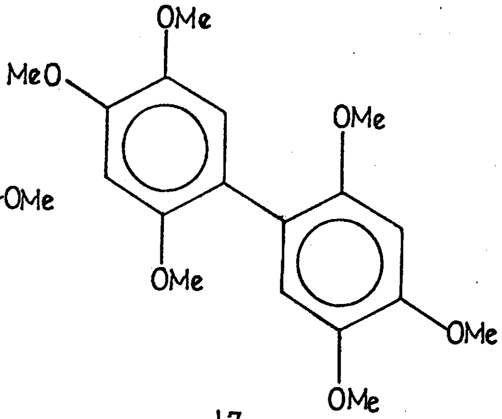

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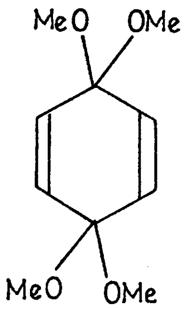

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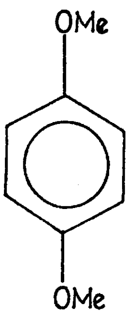

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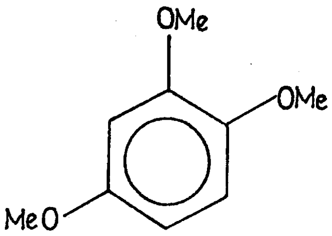

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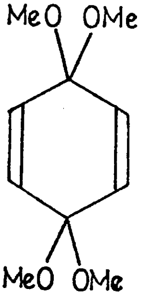
showed that they were identical in all respects. The actual structure of the pentamethoxy biphenyl was proved to be (10) by synthesis as follows.

An Ullmann reaction[6] of iodohydroquinone dimethyl ether (14) and 5-iodo-1,2,4-trimethoxy benzene (15) gave three compounds, a tetramethoxy biphenyl (16), a pentamethoxy biphenyl (10) and a hexamethoxy biphenyl (17) in the ratio 1:1:1. t.l.c. separation gave (10), identical in all respects with that obtained from treatment of (6) with boron trifluoride etherate or Simmons-Smith reagent.

The problem which now remained to be solved concerned the mechanism of the formation of 1,2,4-trimethoxy benzene (9) and the pentamethoxy biphenyl (10). The conditions of the Simmons-Smith reaction were investigated to determine whether it was necessary to have all the ingredients of the reaction present to form (8), (9) and (10), but the formation of these only took place if all the conditions for the Simmons-Smith reaction were fulfilled (viz. methylene iodide, zinc-copper couple, the alkene and a crystal of iodine added as described in reference 4). It was also found that the transformation could be effected by attempting to add dichloro carbene to (6), if the dichloro carbene was produced by



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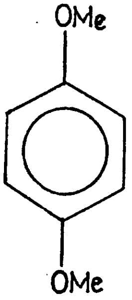

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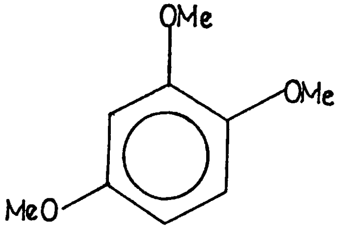

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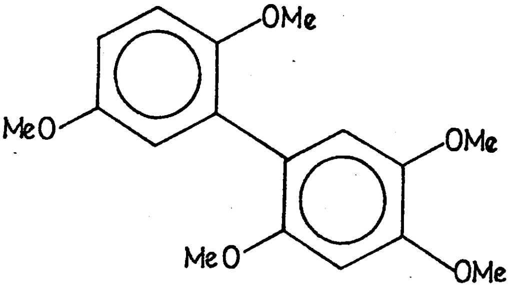

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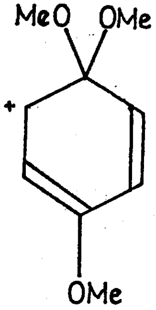

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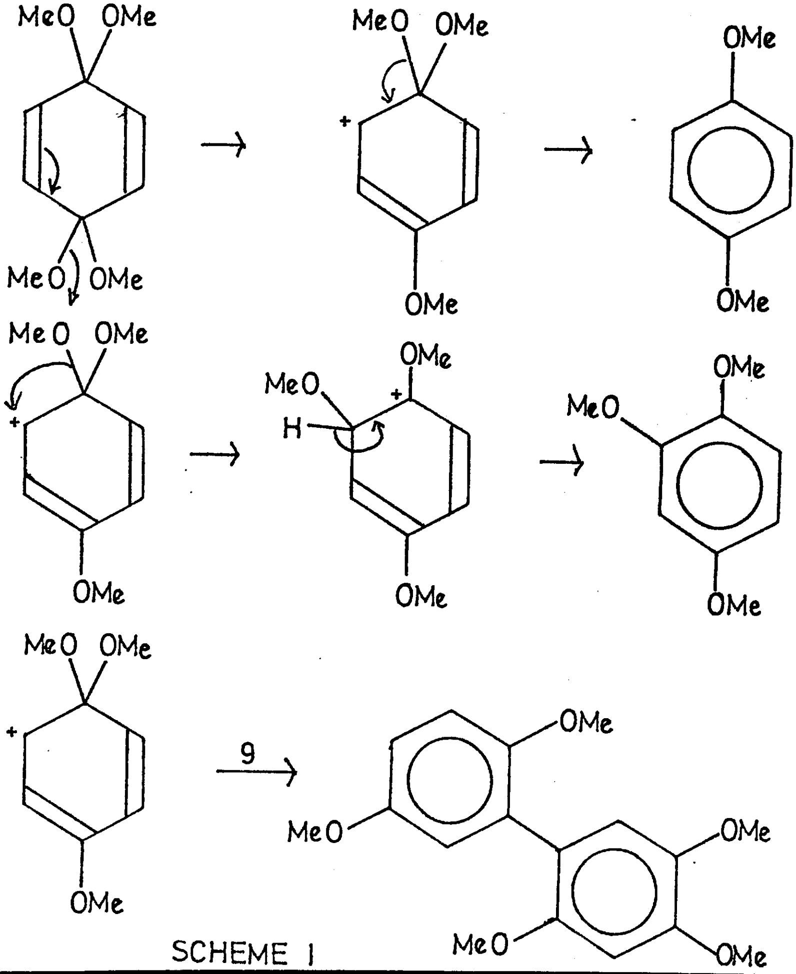
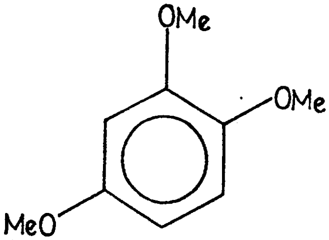


SCHEME 1

decomposition of sodium trichloroacetate[7]. Reaction of (6) with dibromo carbene produced under strongly basic conditions[8] did not promote formation of (8), (9) and (10). It appears that the one factor essential to the transformation of (6) to the above aromatic products is the presence of a carbene, in neutral conditions.

It would therefore seem that in these cases carbene is acting as a Lewis acid, taking a much longer time to promote a transformation that is carried out instantaneously by a strong Lewis acid, boron trifluoride etherate. Although acting as a Lewis acid is not a known property of carbenes, it does not seem impossible since carbenes are electron deficient species, and therefore fulfil the necessary condition for being a Lewis acid.

Assuming that the reaction is catalysed by a Lewis acid, a mechanistic scheme for the formation of the products (8), (9) and (10) can be readily drawn up as in Scheme 1. This particular pentamethoxy biphenyl is obtained since attack at the 5-position of 1,2,4-trimethoxy benzene is most likely when the carbonium ion (18) is electrophile. The facility with which the diene (6) is converted to 1,2,4-trimethoxy benzene is rather remarkable, since simply standing (6) in a flask for



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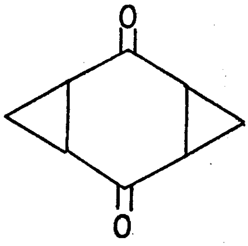

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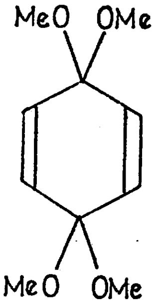

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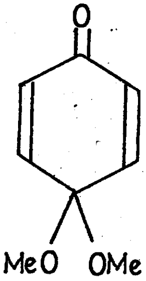

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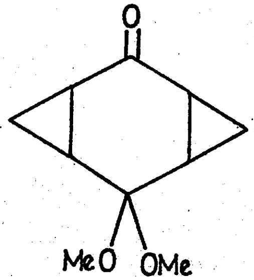
several months results in the production of (9).

Following this unexpected outcome, the projected synthetic scheme to the dione (1) required some modification. Several alternative routes to compounds of the tricyclo(5,1,0,$0^{3,5}$)octane class were explored, but these routes, starting from precursors other than the diene (6) were unsuccessful. The successful route eventually discovered arose from the diene (6), or rather the product of selective hydrolysis by water, the dimethoxy dienone (19).

Two methods exist for the conversion of enones to cyclopropyl ketones, and although the first attempted, reaction with Simmons-Smith reagent[9], gave a complex mixture of products, the second proved reasonably successful.

This second method involved reaction of the dienone (19) with dimethyl oxosulphonium methylide[10], generated by treatment of trimethyl oxosulphonium iodide with sodium hydride. Reaction of the ylid and the dienone (19) in dimethyl formamide for a period of 16 hours produced a mixture of two components, in a total yield of 20%. Although this yield is very low, it is not unexpectedly so, since the synthesis of cyclopropyl



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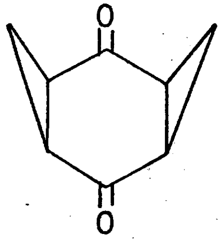
ketones from enones is not in general a high yield process.

Separation of the two components proved impossible, either by column chromatography on basic alumina, or by t.l.c. on silica. However it was possible to deduce that the formation of the dicyclopropyl ketone (20) had been carried out, since the N.M.R. spectrum of the reaction mixture showed no olefinic signals, and in addition to methoxyl groups, signals at 8τ and 9τ as expected for the cyclopropane protons of (20). The I.R. corroborated this, showing no alkene stretching absorption, with the carbonyl frequency occurring at 1690cm^{-1}.

Although it was not possible to separate the dicyclopropyl ketone (20) from the other product of the reaction, it was possible to convert (20) into the other component present. Indeed the transformation could be simply carried out by boiling the total product in ethanol containing animal charcoal, this latter fact being discovered in an attempt to remove a yellow impurity which possessed the same chromatographic characteristics as the two products.

This product, produced by attempted decolourisation of the crude mixture, and also present in small proportion



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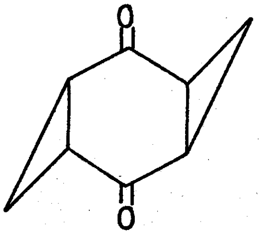

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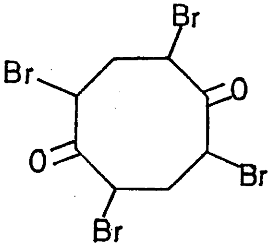
in the reaction mixture, satisfactorily analysed for $C_8H_8O_2$, and this was corroborated by mass spectral determination of the molecular ion at m/e 136. It seemed from this that a synthesis of bishomoquinone had been achieved. The I.R. and N.M.R. of the product were in accordance with this structural assignment, the former exhibiting carbonyl absorptions at 1710 and 1695cm^{-1}, and the latter a series of three resonances, 7.8τ, 8.15τ and 8.85τ in the ratio 2:1:1. Undoubtedly these are due to the four hydrogens alpha to the carbonyl, and the inside and outside hydrogens of the cyclopropane rings.

Although a synthesis of bishomoquinone had been carried out, it seemed that only one of the two isomers of that compound had been produced, since the compound a.) was chromatographically homogeneous, and b.) exhibited an N.M.R. spectrum which by its sharpness and simplicity indicated the unlikelyhood of the compound being a mixture of the syn (21) and anti (22) isomers. It was necessary therefore to establish which of the two isomers (21) and (22) had been produced.

In this determination help was provided since Dreiding had published[11] a synthesis of both isomers of bishomoquinone while this work was under way. This was



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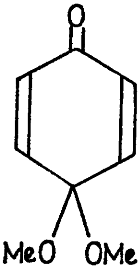

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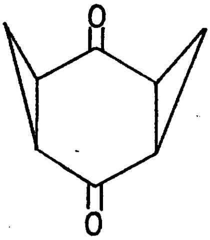

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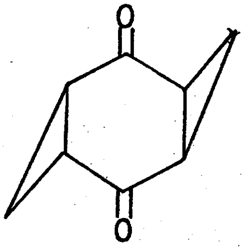

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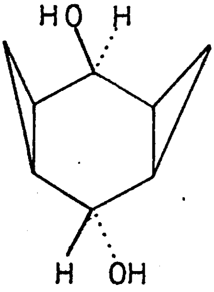

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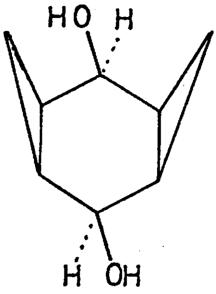

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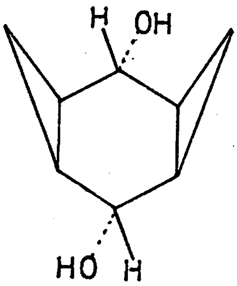

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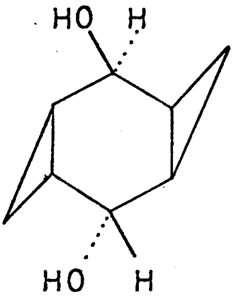

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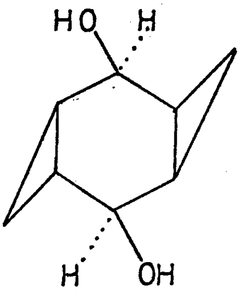

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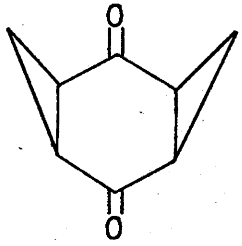
carried out by pyrolysis of two isomers of the tetrabromide (23) in the presence of excess copper powder. Each isomer of the tetrabromide produced a mixture of the isomeric bishomoquinones, the melting point of one of these being identical to that of the compound synthesised from the dienone (19). Comparison of a sample of bishomoquinone with one obtained from Prof. Dreiding by g.l.c. coinjection and mixed melting point determination established that they are identical in all respects.

From this evidence, the bishomoquinone synthesised was identical to that assigned the syn configuration by Dreiding. This assignment was made on the basis of the products of reduction of the diones by sodium borohydride, since the syn isomer gives rise to a mixture of a trans (24) and two cis diols (25) and (26), whereas the anti isomer (22) gives only a trans (27) and cis (28) diol. Identification of the two diones was carried out by examination of the carbinol proton ($C\underline{H}OH$) signals in the N.M.R. of the mixture of diols obtained from the borohydride reaction.

It was not possible, in our case, to extend the evidence for the assignment of anti or syn configuration since the resonances in the N.M.R. spectrum of (21) proved



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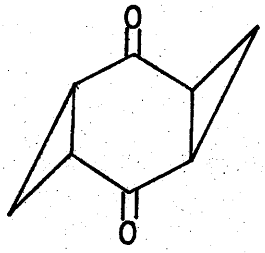

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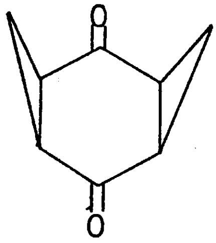
to be too close to permit decoupling studies. Indeed it was difficult to assign the two upper resonances to the outside and inside, or exo and endo hydrogens, of the methylene groups. This assignment was carried out on the basis of the vicinal coupling constants of the exo and endo hydrogens with the tertiary hydrogens. It was expected that the exo hydrogen coupling constant would be larger than that with the endo, since a cis cyclopropane coupling constant is larger than the trans[12]. Since the signal at 8.15τ has a smaller coupling than that at 8.85τ the former must be due to the endo hydrogens and the latter to the exo.

It is interesting that both syn and anti isomers of bishomoquinone exhibit two carbonyl absorptions, of equal intensity, in the I.R.. Perhaps this is an indication that the conformation of either is not a boat cyclohexane, since cyclohexan-1,4-dione, which has been shown to exist as a boat conformer[13], exhibits only one carbonyl absorption[14]. The probable cause of this carbonyl doublet is an interaction between the dipoles of the two carbonyls[15], and if this is so, the cyclohexane conformation in (21) and (22) should be such as to allow interaction of the dipoles, possibly



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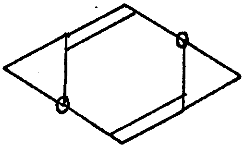

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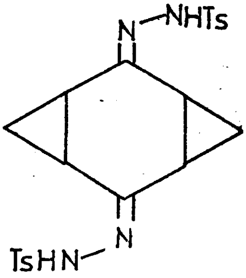

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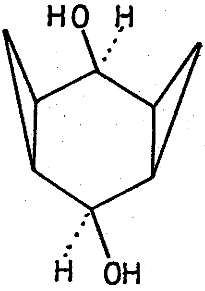

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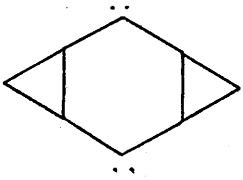

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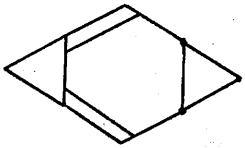

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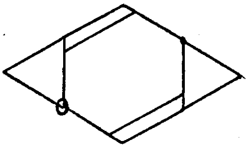

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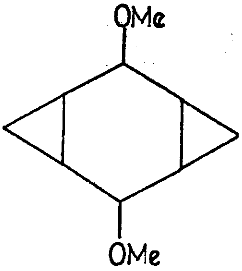

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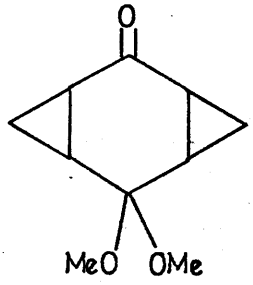
approaching a flat conformation rather than a boat.

Some preliminary investigations of the transformation of (21) to the diene (29) were attempted. These involved either reaction of the dione (21) with p-toluene sulphonyl hydrazine to give the bis tosyl hydrazone (30), or reduction to the diol (25), sulphonate ester formation and elimination.

The former route involving decomposition of the bis tosyl hydrazone (30) to give the bis carbene (31), which it is hoped will abstract two alpha hydrogens to give (29) is however entirely non-stereospecific, since either of the three isomeric dienes (29), (32) or (33) can be produced. The route involving reduction and elimination of (21) seems more profitable, since the major diol from reduction should be (25), with the correct stereochemistry for elimination of the bis sulphonate ester to the diene (29), (or possibly (32)).

Time allowed only initial attempts on this route to take place, and it was found that reduction of the dione (21) in aqueous methanol with sodium borohydride gave the dimethyl ether (34), presumably arising from boronate esterification of the diol, followed by solvolysis by methanol. This is not unexpected, since solvolyses of



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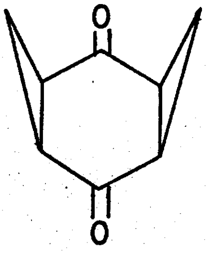

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2-substituted tricyclo(5,1,0,$0^{3,5}$)octanes have been found to be rapid[16], due to the stability of the bis cyclopropyl carbonium ion. Presumably this stability is the factor which causes the acetal (20) to hydrolyse so readily to (21), since the transition state for acetal hydrolysis is carbonium ion in nature.

EXPERIMENTAL

Reaction of 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6) with Simmons-Smith reagent.

Zinc-copper couple (20g.) and a crystal of iodine were added to anhydrous ether (150ml.), and the mixture stirred until the brown colour of the iodine disappeared. 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 5g.) and freshly distilled methylene iodide (15g.) were added and the mixture refluxed for 24 hours. After cooling and filtering, the organic solution was washed with saturated ammonium chloride solution (2 x 100ml.), saturated sodium bicarbonate solution (100ml.) and distilled water (2 x 100ml.). Drying and removal of the solvent afforded 3.2g. of crude oily product, which was shown by t.l.c. (30% EtOAc/petrol) to consist of several components, none of which was starting material.

Separation of these was achieved by column chromatography on silica gel using ethyl acetate / petrol as eluent.

The major component (1.25g.) was shown to be 1,2,4-trimethoxy benzene (9) Found C 64.17 H 7.20

$C_9H_{12}O_3$ requires C 64.27 H 7.19.

IR. (l.film) cm^{-1} :- 1601(m), 1510(s), 1220(s), 1200(s), 1150(s), 1025(s), 837(m) and 762(m).

N.M.R. ($CDCl_3$) :- 3.3τ - 4.0τ (ABX multiplet) -3H,
6.36τ, 6.42τ and 6.45τ (singlets) -9H.

M.S. Parent ion at m/e 168. Breakdown peaks at m/e 153, 125, 110, 95, 79, 69 and 52.

The least polar component was shown to be the dimethyl ether of hydroquinone (8), by comparison with an authentic sample.

The most polar component was shown to be a pentamethoxy biphenyl, m.pt. 120 - 121° Found C 66.89 H 6.65

$C_{17}H_{20}O_5$ requires C 67.09 H 6.62

I.R. (CCl_4) cm^{-1} :- 3000(m), 2952(s), 2937(s), 2915(m),
2837(s), 1500(s), 1469(s), 1222(s),
1212(s), 1047(s) and 1038(s).

U.V. absorptions at 215 and 300nm..

N.M.R. ($CDCl_3$) :- 3.2τ (multiplet) -3H,
3.23τ (multiplet) -1H,
3.41τ (singlet) -1H,
6.11τ - 6.40τ (series of five singlets)
- 15H.

M.S. Parent ion at m/e 304, and breakdown peaks at m/e 299, 258, 243, 231, 152, 126 and 115.

g.l.c. on 5% QF1, temperature programming from 30° to 220° at 4° per minute.

Component	retention time (mins.)	%
Hydroquinone dimethyl ether(8)	9.5	14
1,2,4-trimethoxy benzene (9)	15.7	63
Pentamethoxy biphenyl (10)	18.4	12

Investigation of the conditions of the Simmons-Smith reaction on the tetramethoxy diene (6).

a.) 3,3',6,6'-tetramethoxycyclohexa-1.4-diene (6, 100mg.) was refluxed for 24 hours in anhydrous ether (25ml.). t.l.c. (30% EtOAc/petrol) showed only the presence of starting material.

b.) 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 100mg.) and zinc powder (250mg.) were refluxed together in ether as in a. A similar result was indicated by t.l.c..

c.) 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 100mg.) and zinc-copper couple (250mg.) were refluxed together in ether as in a. Again t.l.c. indicated no conversion of (6).

d.) 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 100mg.), zinc-copper couple (250mg.) and methylene iodide (250mg.) were refluxed together in anhydrous ether (25ml.) for 24 hours. t.l.c. of the resulting solution showed only the presence of starting diene (6).

e.) 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 100mg.) and a crystal of iodine were refluxed together in ether (25ml.) for 24 hours. After this time, t.l.c. showed only the presence of starting material.

f.) 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 100mg.), zinc-copper couple (250mg.) and a crystal of iodine were refluxed together in anhydrous ether (25ml.) for a period of 24 hours. After this time, analysis of the reaction mixture by t.l.c. (30% EtOAc/petrol) or by g.l.c. (1% APL at 150°) indicated no other component to be present. On working up the reaction mixture in the normal manner for a Simmons-Smith reaction, only starting 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6) was isolated from the reaction mixture.

g.) It was also found, by g.l.c. analysis that merely storing the tetramethoxy diene (6) over a period of several months produced 1 - 2% of 1,2,4-trimethoxybenzene (9) in addition to much larger quantities of the hydrolysis product, the dienone (19).

Reaction of the tetramethoxy diene (6) with sodium trichloroacetate.

Sodium trichloroacetate was prepared by the method of Winston et al[17]. The resulting solid was dried at 50°/.1mm. for 24 hours.

A solution of 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 200mg.) and sodium trichloroacetate (1.65g.) in a mixture of tetrachloro ethylene (20ml.) and dry diglyme (5ml.) was refluxed for 2 hours at 130°. Excess solvent was then distilled off under water pump pressure, the residue dissolved in ether (50ml.), the ethereal solution washed with brine (25ml.) and dried. Removal of solvent gave 165mg. of crude product, shown by t.l.c. (30% EtOAc /petrol) to consist of approx. 10 components, some of which were minor.

Preparative t.l.c. gave 1,2,4-trimethoxy benzene (9, 70mg.), hydroquinone dimethyl ether (22mg.) and the pentamethoxy biphenyl (10, 25mg.), previously obtained from Simmons-Smith reaction on (6).

Action of boron trifluoride etherate on the diene (6).

This was carried out by the method of Weinberg[5], and the components of the crude product separated by t.l.c. (30% EtOAc/petrol) giving 1,2,4-trimethoxy benzene (9) and the pentamethoxy biphenyl (10), previously obtained from Simmons-Smith reaction on the diene (6). That the two pentamethoxy biphenyls obtained from this reaction and from attempted carbene additions to (6) are identical was established by chromatographic and spectroscopic analysis, and by a mixed melting point determination.

Mixture melting point 120^{o}.

Attempted reaction of the tetramethoxy diene (6) with dibromo-carbene.

Dry potassium t-butoxide, from potassium (90mg.) and t-butanol (50ml.) was prepared in situ by the method of Skattebøl and Solomon[18].

To the solid thus obtained was added, under nitrogen, 3,3',6,6'-tetramethoxycyclohexa-1,4-diene (6, 200mg.), followed by dropwise addition, with stirring and cooling, of a solution of bromoform (500mg.) in pentane (30ml.) over a period of 6 hours. The reaction mixture was then stirred overnight at room temperature, water (50ml.) added, and the solution neutralised with 6N HCl. Extraction of the aqueous solution with pentane (100ml.), drying and removal of the solvent gave 110mg. of crude product. t.l.c. (30% EtOAc/petrol) showed at least ten components, none of which was starting material. The I.R. (l.film) of the entire mixture indicated the possibility of the presence of an enone grouping due to absorptions at 1690 and 1640cm^{-1}. g.l.c. indicated that none of the products previously isolated from attempted 'neutral' carbene additions to the diene (6) was present in this reaction mixture.

Conversion of p-benzoquinone to 1,2,4-triacetoxy benzene.

This was carried out according to the reference[19] in Collective Organic Syntheses.

Conversion of 1,2,4-triacetoxy benzene to 1,2,4-trimethoxy benzene.

This was carried out by the procedure of Bargellini and Martegiani[20].

Preparation of 1-iodo-2,4,5-trimethoxy benzene.

This was carried out by iodination of trimethoxy benzene according to the procedure of Hughes et al[21].

Preparation of 1-iodo-2,5-dimethoxy benzene.

This was carried out by the procedure of Kaufmann and Fritz[22].

Ullmann reaction of 1-iodo-2,5-dimethoxy benzene (14) and 1-iodo-2,4,5-trimethoxy benzene (15).

A mixture of the iodo compounds, (14, 250mg.) and (15, 275mg.) was heated to 210°. To the heated mixture was added copper bronze (500mg.) in small portions. After the addition, the reaction mixture was maintained at 230° for 30mins.. On cooling, the residue was dissolved in ether (25ml.) and filtered. t.l.c. (30% EtOAc/petrol) showed the presence of three components.

Separation was effected by preparative t.l.c., and the middle component shown to be identical with the pentamethoxy biphenyl (10).

Reaction of 4,4'-dimethoxycyclohexa-2,5-dienone (19) with Simmons-Smith reagent.

Zinc-copper couple (2g.) and a crystal of iodine were added to anhydrous ether (150ml.) and the mixture stirred until the brown colour of the iodine had disappeared. 4,4'-dimethoxycyclohexa-2,5-dienone (19, 500mg.) and freshly distilled methylene iodide (1.5g.) were added, and the mixture refluxed for 72 hours. After filtering and cooling, the organic solution was washed with saturated ammonium chloride solution (2 x 100ml.), saturated sodium bicarbonate solution (100ml.) and distilled water (2 x 100ml.). Drying and removal of the solvent gave 386mg. of crude oily product, shown by t.l.c. (30% EtOAc/petrol) to contain at least ten components.

Preparation of trimethyl oxosulphonium iodide.

This was prepared according to reference 23 by refluxing dimethyl sulphoxide and methyl iodide together. The resulting solid was recrystallised from water and thoroughly dried, in vacuo, over phosphorous pentoxide.

Reaction of the dienone (19) with dimethyl oxosulphonium methylide.

Trimethyl oxosulphonium iodide (1320mg., 6mmoles) was added carefully to a suspension of sodium hydride (150mg., 6mmoles) in dry dimethyl formamide (30ml.). After stirring at room temperature for 1 hour, 4,4'-dimethoxycyclohexa-2,5-dienone (19, 308mg., 2mmoles) in dimethyl formamide (10ml.) was added over a period of 15 minutes. The resulting clear solution was stirred under nitrogen for 16 hours, after which time the total reaction mixture was poured into water (100ml.), and this aqueous solution extracted with chloroform (150ml.) The chloroform extract was washed thoroughly with water to get rid of dimethyl formamide, and then brine (100ml.).

Drying and removal of the chloroform gave only 96mg. of crude product, which t.l.c. showed to contain two compounds. It was not possible to purify the less polar component, i.e. to separate it from the more polar component, in order to carry out an elemental analysis, but suitable samples for spectroscopic analysis could be obtained by t.l.c. (50% EtOAc/petrol).

Less polar component (20).

I.R. (CCl_4) cm^{-1} :- 2978(s), 2862(s), 1690(s), 1380(m), 1348(m), 1118(m), 1050(s) and 931(m).

N.M.R. (CCl_4) :- 6.61τ and 6.62τ (singlets) -6H,
8.05τ (multiplet) -4H,
8.80τ (multiplet) -4H.

On attempting to remove a yellow impurity by boiling the total product in ethanol containing animal charcoal, the less polar component (20) was converted to the more polar component (21), purified by vacuum sublimation.

m.pt. 100 - 101°. Found C 70.93 H 6.22

$C_8H_8O_2$ requires C 70.58 H 5.92

IR. (CCl_4) cm^{-1} :- 2972(m), 2924(m), 1710(s), 1695(s), 1336(s), 1285(m), 1116(m) and 933(m).

N.M.R. ($CDCl_3$) :- 7.8τ (multiplet) -4H,
8.15τ (multiplet) -2H and
8.85τ (multiplet) -2H.

MS. Parent ion at m/e 136; other significant breakdown peaks at m/e 107, 91, 79, 68, 40 and 39.

Reaction of the dione (21) with sodium borohydride.

The dione (21, 80mg.) was dissolved in wet methanol (20ml.), sodium borohydride (excess) added. and the resulting solution stirred at room temperature for 12 hours. The methanol was removed under reduced pressure, and the residue dissolved in ether (100ml.). The ethereal solution was washed with brine (50ml.), dried and boiled down to give 67mg. of crude product which t.l.c. (40%EtOAc/petrol) showed to consist of one major component. This component was purified by preparative t.l.c.

IR. (CCl_4) cm^{-1} :- 3020(s), 2979(m), 2846(m), 2814(s), 1187(m), 1085(s), 1020(m) and 908(m).

N.M.R. ($CDCl_3$) :- 5.96τ (multiplet) -2H,
6.8τ (singlet) -6H,
8.83τ (multiplet) -4H and
9.58τ - 10.2τ (multiplet) -4H.

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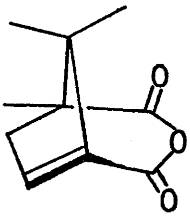
PART 2

DECARBOXYLATION STUDIES ON A BICYCLO(2,2,2)OCTANE β-KETO ACID.



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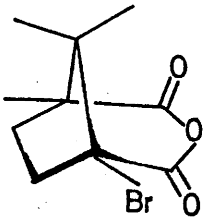

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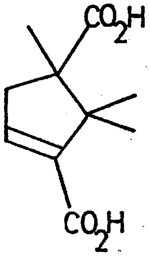

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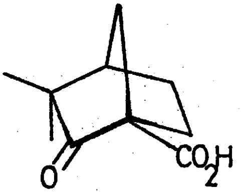

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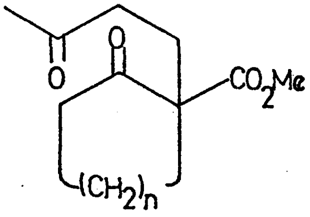
INTRODUCTION

Bredt's rule,[1] formulated in 1924, concerns the reluctance of bridged bicyclic molecules to accomodate a double bond at their bridgehead. The rule was proposed by Bredt in order to explain certain anomalous results encountered by him and other workers in exploring the chemistry of some camphane and pinane species; e.g. their inability to form the anhydride (1) by dehydrobromination of (2) or by cyclisation of the diacid[2] (3), and the failure of (4) to decarboxylate[3], and is stated as follows :-
"On the basis of our conceptions of the positions of atoms in space in the systems of the camphane and pinane series, as well as similarily constituted compounds, a carbon double bond cannot occur at the branching positions."

Several revisions of the rule since its initial statement have been proposed. The first of these came from Bredt himself when, in 1927, he conceded[4] that a double bond could be located at the bridgehead of a bridged bicyclic molecule if the rings were sufficiently large. This was later confirmed by Prelog who found[5] that bridgehead double bonds could be accomodated in a bicyclo(n,3,1) compound if n were



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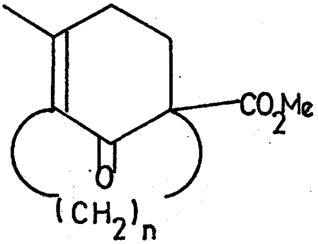

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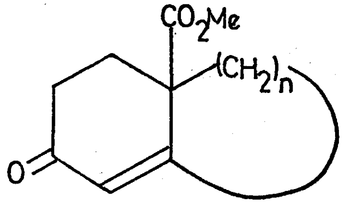

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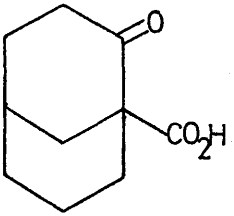

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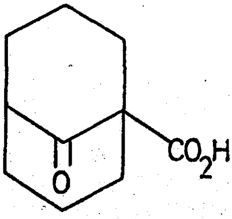

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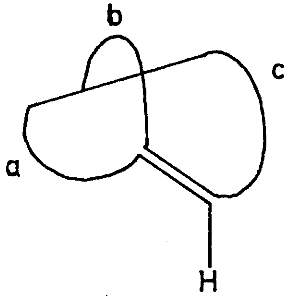
5 or greater by studying the cyclisation of the series (5, n = 4,5 and 6) to give either the bridged product (6) or the fused one (7). However the conditions employed by Prelog were equilibrating resulting in the formation of the product of thermodynamic control. Thus these results only demonstrate that some bridgehead alkenes are more stable than fused alkenes with which they are isomeric, and do not constitute a rigorous test of the possibility of preparing bridgehead alkenes.

The first serious attempt to define the limits of Bredt's rule was made by Fawcett[7] in the process of carrying out a review of the literature on the subject. Fawcett defined the S number as the sum x+y+z in a bicyclo(x,y,z) system in which neither x, nor y nor z is zero, and further tentatively proposed that bridged bicyclic systems with S = 8 should be isolable, and that transient species with bridgehead double bonds should be possible when S = 6.

However, it became apparent to Fawcett himself that this theory was inadequate in explaining many of the observed phenomena, e.g. the β-keto acid (8) decarboxylates readily[7] at 145°, whereas the isomer (9) resists decarboxylation[8] at 240°, yet both compounds have the same S number 7.



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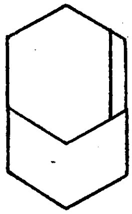

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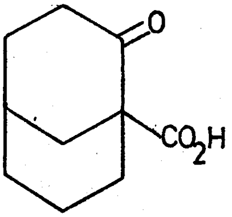

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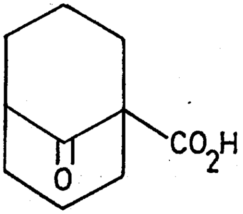

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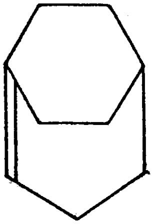

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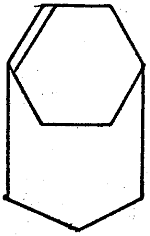

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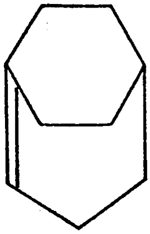
The most recent, and so far the best revision of Bredt's rule has been enunciated by Wiseman[9], who, on considering the general case of a bridged bicyclic molecule (10), observed that the double bond, which is exocyclic to ring ab, but endocyclic in rings ac and bc, must be cis in one ring, but trans in the other. On this basis he proposed that the strain in a bridgehead alkene is therefore closely related to the strain in the corresponding trans -cycloalkene. Thus since trans-cyclooctene has been shown to exist[10], bicyclo(3,3,1)non-1-ene (11) should be capable of existence, and this prediction has been vindicated by two independent syntheses of this bridgehead alkene[9,11]. The success in decarboxylating (8) and the failure to decarboxylate (9) can also be explained on the basis of Wiseman's postulate, since (8) will undergo more ready decarboxylation, giving a trans-cyclooctenol than will (9) which would give a trans-cyclohexenol, a species with much greater strain energy.

Wiseman has successfully extended his studies to include a bicyclic alkene in which the double bond is contained in a seven-membered ring[12] viz. the bicyclo(3,2,2)non-1-ene (12). Although this compound or its isomer (13) were not isolable, he was able to isolate the products of



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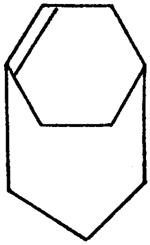

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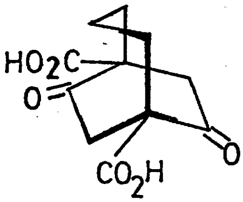

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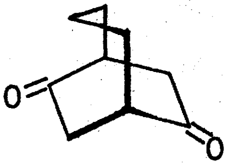

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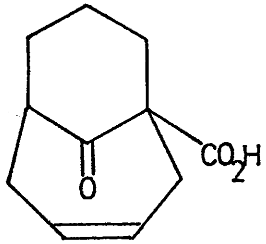

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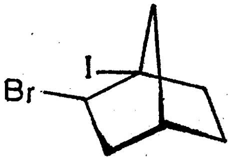

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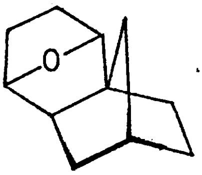
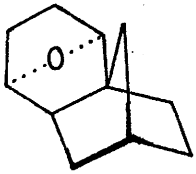


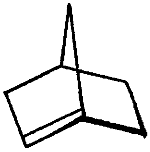
18a



18b

further reaction of the alkenes and thereby produce convincing evidence for the existence of (12) and (13) at low temperature. These results are in accordance with the Wiseman postulate since trans-cycloheptene has been detected as a transient species[13], but never isolated. In addition to the above, several examples of the decarboxylation of β-keto acids exist whereby the enol formed is a transient trans-cycloheptene e.g. (14) gives the dione (15)[14] at 240°, and the keto-acid (16) decarboxylates at a similar temperature[15].

When the case of an anti-Bredt alkene trans in a six-membered ring is considered, the situation is by no means as clear as the seven and eight-membered cases above. Trans-cyclohexenes have been postulated by Marshall[16] as transient intermediates in photosensitised ionic additions to cyclohexene double bonds, but this is the only case in which the intermediacy of such species has been discussed up to the time of completion of the work discussed in this thesis. Since that time, one such communication has been published concerning the existence of norborn-1-ene as an intermediate in the elimination of halogen from (17), induced by butyl lithium[17]. The products of the reaction in the presence of furan, (18a), (18b) and three isomeric



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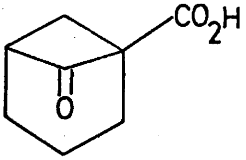

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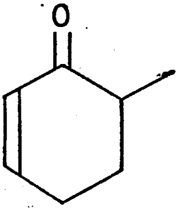

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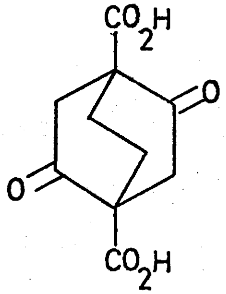

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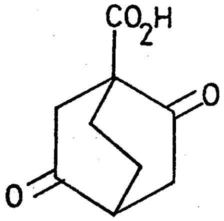
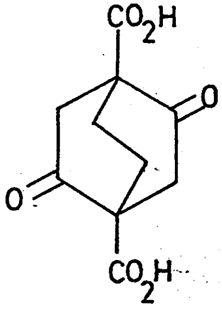


23

hydrocarbons of molecular formulae $C_{14}H_{20}$ are compelling evidence for the existence of bicyclo(2,2,1)hept-1-ene (19), if the existence of a diradical intermediate can be disproved.

Before the publication of this paper, two other unsubstantiated anti-Bredt cyclohexenes had appeared in the literature, both arising from the thermal decarboxylation of β-keto acids as transient intermediates. The acid (20) has been reported[18] to rearrange to (21) on heating at 350° although it is still not clear whether the rearrangement takes place before or after decarboxylation, and so it cannot be stated with authority that this reaction involves a trans-cyclohexenol intermediate.

The diacid (22) has been reported[19] to decarboxylate to (23), and if this occurs via the normal mechanism for decarboxylation of a β-keto acid, it is necessary to invoke a trans-cyclohex-1-ene-2-ol as the initially formed product. Unfortunately, the data on the acid (23) is very limited, consisting only of an analysis (roughly correct) and a melting point. Accordingly it was decided to reinvestigate this reaction in view of the need at that time to precisely define the limits of Bredt's rule. It was intended to characterise the decarboxylation product of (22), and, in



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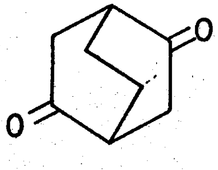

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the event of establishing the structure to be that proposed by Guha, to study the mechanism of the reaction and to look for the other obvious product of thermolysis of (22) i.e. the diketone (24)

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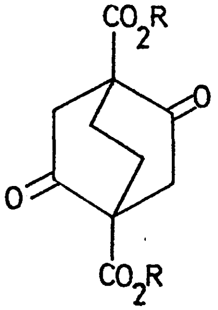
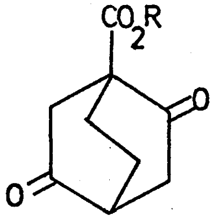


1a $R=H$

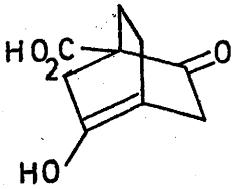
b $R=CH_3$

c $R=C_2H_5$



2a $R=H$

b $R=CH_3$



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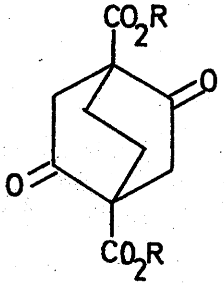
DISCUSSION

Since, at the time of commencement of this work, there were no substantiated examples in the literature of an 'anti-Bredt' alkene trans in a six-membered ring, it was hoped to answer several pertinent questions concerning this type of system by studying the decarboxylation of (1a) to (2a) reported by Guha[1]. Questions which it was hoped would be answered are, is this reported decarboxylation itself genuine ? ; if so, what is the mechanism of the process ? , and if the reaction pathway is concerted, what is the exact nature of the unfamiliar intermediate species (3) ?

In order to investigate the products of pyrolysis of (1a) at the temperature reported, it was decided firstly to attempt isolation of the compound reported by Guha (m.pt. 215°). Accordingly the pyrolysis was first studied by simply subliming the diacid (1a) at water pump pressure at 285°. When this was carried out, it was found that starting diacid sublimed from 230° onward at this pressure (circa 20mm.), even when the pyrolysis was carried out on an intimate mixture of either the diacid (1a) and ground glass, or the diacid and copper bronze. It was found that

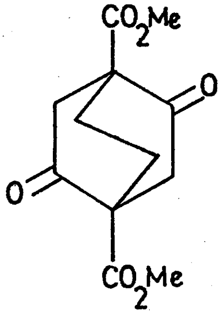


1a R=H

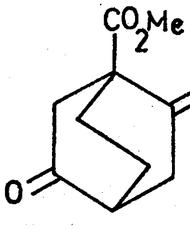
b R=CH_3

the only method by which some reaction took place was to carry out the pyrolysis at a pressure of ca. 200mm.. At this pressure, a yellow oil, which slowly crystallised distilled out at a temperature of 280°. g.l.c. analysis of the crude product, after treatment with diazomethane, showed the presence of two major components, one being the starting dimethyl ester (1b), and the other a new compound produced as 50% of the crude reaction product. A melting point determination on a sample of the acid obtained after acidic hydrolysis of the ester and recrystallisation showed that the compound had the same melting point as that isolated by Guha, and it was therefore probable that the compound isolated was that obtained by Guha.

An improvement on the method of pyrolysis was discovered whereby, on passing the diacid (1a) in tetrahydrofuran solution through a pyrolysis oven at 285° in a stream of nitrogen, one major product (90% of recovered material) was obtained, identical by g.l.c. comparison of the methyl esters and by melting point determination on the acid to that obtained by the previous method of pyrolysis. It was also found that very little, and sometimes no, starting diacid (1a) was present in the pyrolysis product when the reaction was carried out in this way.

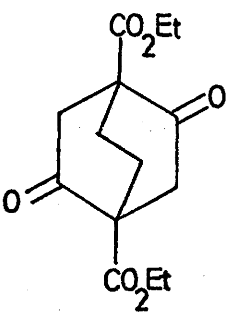


1b

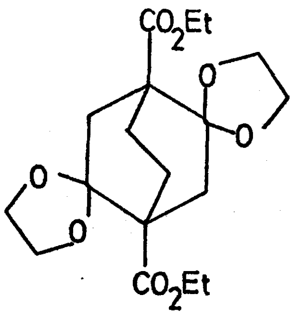


2b

It was now necessary to establish the structure of the isolated product, and to this end a sample of the methyl ester (2b) was purified by preparative t.l.c. and by sublimation. Mass spectral determination on this material gave a molecular weight of 196 in accordance with that expected for the ester (2b). Comparison of the N.M.R. and infra-red spectra of the two compounds (1b) and (2b) indicated their very close relation. In the infra-red, the only noticeable differences were the inversion of the relative intensities of the two bands at 1750cm^{-1} (ester carbonyl stretch) and 1735 cm^{-1} (ketone carbonyl stretch) and the expected changes in the C-O region (stretching) due to absence of a second carbomethoxyl grouping in (2b). The N.M.R. spectra showed a very close similarity, both compounds exhibiting an AB quartet, J = 20Hz., for the four hydrogens alpha to the ketone groupings, the bottom half of this quartet being further split (J = 1½Hz.) by w-coupling[2] with one of the hydrogens on the ethylene bridge. The only notable differences in the N.M.R. spectra were that the methyl ester integration differed as expected, and that there was present in the spectrum of (2b) a triplet at 7.23τ due to the resonance of the bridgehead hydrogen on C-4.



1c



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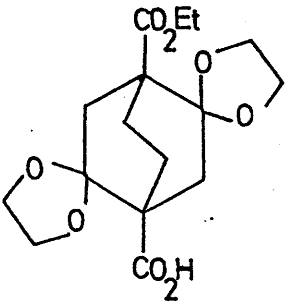

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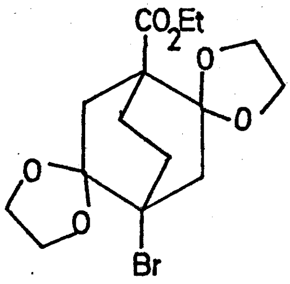

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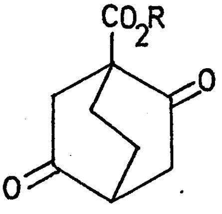
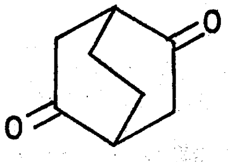


2a R=H
b R=Me



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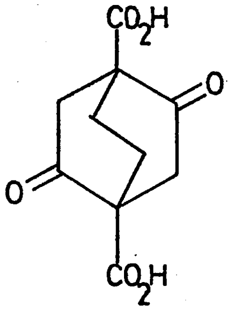
Structure (2a) was confirmed by direct comparison of the decarboxylation product with a sample synthesised by a colleague, using an unambiguous route. Details will be reported elsewhere^3, but the route used was as follows.

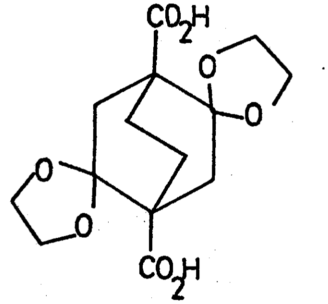
Acetalisation of (1c) gave (4b) which was converted to the bromide (6) by a Hunsdiecker^4 reaction on (5), obtained from (4b) by careful base hydrolysis. Reduction (Raney Nickel/hydrogen) and acidic hydrolysis gave the diketo-monoacid (2a), identical with the compound obtained by pyrolysis of (1a) by melting point and mixed melting point determinations and by g.l.c. coinjection of the methyl esters (2b).

In the light of this evidence, Guha's report is undoubtedly correct. The questions which now demand an answer are those concerning the nature of the intermediate and, linked with this, the mechanism of the decarboxylation process. If the mechanism is the accepted concerted pathway for thermal decarboxylation of a β-keto acid^5, the dione (7) should also be a product of the pyrolysis of (1a). It was decided therefore to synthesise (7) to enable a g.l.c. search for it to be carried out on the pyrolysis products.

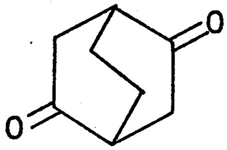
Some unsuccessful attempts were made to synthesise (7)


CO2H
O
O
CO2H

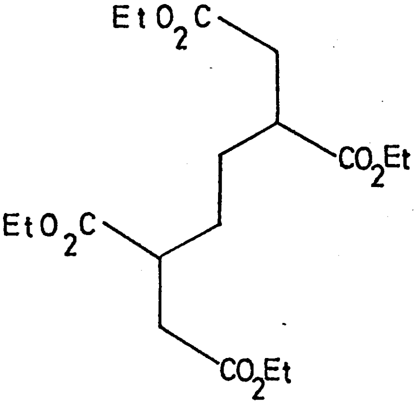
1a


CO2H
O
O
O
O
CO2H

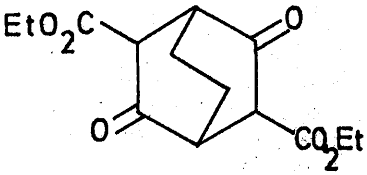
4a


O
O

7


EtO2C
CO2Et
EtO2C
CO2Et

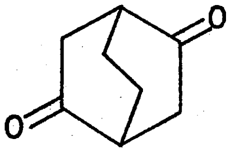
8


EtO2C
O
O
CO2Et

9

from (1a) or (4a) by a double Hunsdiecker reaction. This route would have been unambiguous, but poor yields made this route impracticable. However a synthesis of (7) has been reported by Guha[6], and although formal structure proof was never provided it was decided to repeat this synthesis.

The reported formation of (7) arises from a Dieckmann cyclisation of the tetraester (8) carried out by a suspension of sodium in benzene. The desired product (9) was extracted as a base soluble fraction which, on acidification, acidic hydrolysis and decarboxylation gave (7). It was decided to repeat this reaction using sodium hydride in a mixture of benzene and dimethyl formamide to effect the cyclisation, and when this was carried out, three new compounds were produced, each of which gave a positive ferric chloride test. Analysis of the infra-red and N.M.R. spectra indicated which component was most likely to be the desired β-keto ester (9), and after preparative t.l.c. separation this fraction , on acidic reflux, gave a neutral ketone, with spectra as expected and having the same melting point as that reported by Guha. Since no other product of one or two Dieckmann cyclisations of the tetraester (8) would completely decarbethoxylate, because



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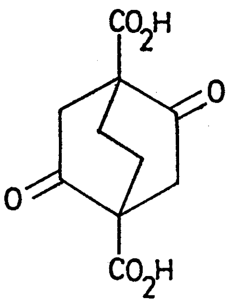
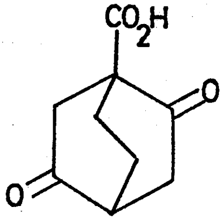


1a

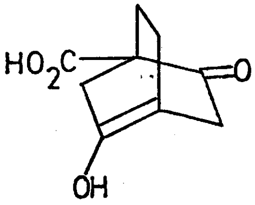


2a

of Bredt's rule or by virtue of the fact that ester groupings had no beta carbonyl function, the structure of the dione (7) is established.

On obtaining thus a sample of (7) it was now hoped to establish whether or not this compound was a product of pyrolysis of (1a). On carrying out a series of pyrolyses ranging in temperature from 280° to 360°, it was found that the neutral fraction of products, normally extremely small in bulk, contained no component corresponding to (7) on g.l.c. analysis. Two neutral products were consistently obtained, but the yield of these was such as to preclude any structural determinations on them.

The failure to observe the dione (7) in the product mixture has some serious implication on the mechanism of the first decarboxylation process. Another factor of interest in this respect is that it was found that carrying out the pyrolysis on an intimate mixture of the diacid (1a) and ground glass by the first pyrolysis method did not increase the proportion of (2a) in the product. Consideration of these two factors together must lead to some concern that the reaction pathway being followed in this pyrolysis is not the accepted mechanism for the decarboxylation of a β-ketoacid, i.e. a concerted process, but it is necessary



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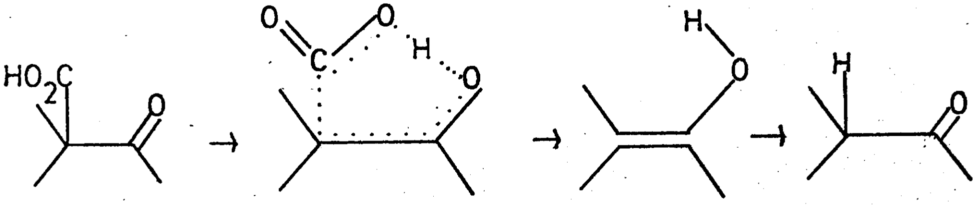
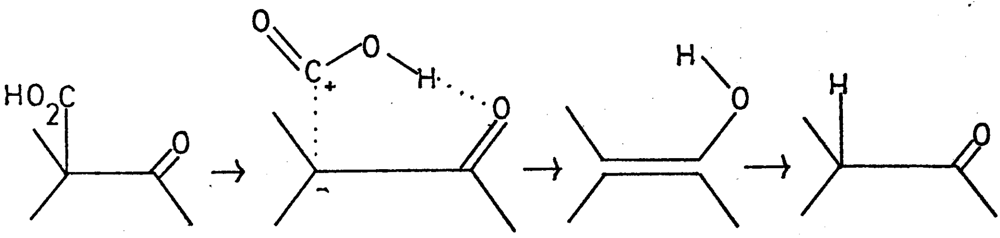


SCHEME 1



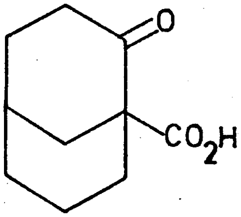
SCHEME 2

to invoke this type of mechanism if an 'anti-Bredt' alkene (3) is claimed as the reaction intermediate.

MECHANISTIC DISCUSSION

The accepted mechanism for the concerted decarboxylation of a β-keto acid[5] involves formation of the enol as depicted in Scheme 1, and this mechanistic pathway must of necessity be followed in order to produce an 'anti-Bredt intermediate. In the light of the two observations mentioned above, and in view of the excessive strain involved in the formation of the trans-cyclohexenol intermediate (3), some other mechanism may be operative e.g. radical or ionic rather than concerted.

Ferris and Miller[7] have proposed that the mechanism of decarboxylation of strained bicyclic β-keto acids does not follow a concerted pathway, but rather an ionic one as depicted in Scheme 2. The essential difference between the two mechanisms, concerted and ionic, is that in the concerted the carbon bearing the carboxyl group is sp^2 hybridised and the transition state is stabilised by overlap of the p-orbital of the sp^2 carbon atom bearing the carboxyl group and the p orbitals of the carbonyl group, whereas in the ionic case, the carbanionic centre will be sp^3 hybridised



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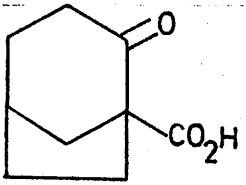

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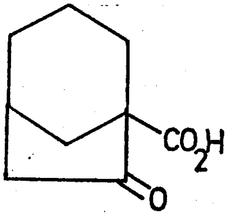
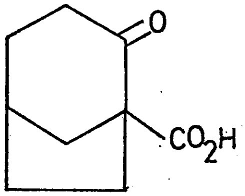


12

and the energy of the transition state will be determined by the angle between the sp^3 orbital of the developing carbanion and the p orbital of the carbonyl group, this angle controlling the degree of overlap between these orbitals. Ferris and Miller proposed this mechanism on the basis of their decarboxylation studies on various β-ketoacids (10), (11) and (12), since they found that the temperature necessary for complete decarboxylation was greater for (12) than (10) or (11), and greater for (11) than (10). This observation was explained on the basis that the orbital angle between the incipient carbanion and the carbonyl group also increased in this order, thereby explaining the increase in temperature, since increase in orbital angle destabilises the transition state by decreasing the overlap between the sp^3 orbital on the developing carbanion and the p orbitals of the carbonyl group.

Although this explanation fits the observed facts, it is unnecessary when the results are considered in the light of the Wiseman postulate[8]. This shows that the decarboxylation temperature differences are as would be predicted since the enol formed by decarboxylation of (10) will be a cyclooctenol but those formed by decarboxylation of (11) and (12) will be cycloheptenols. Thus the higher decarboxylation



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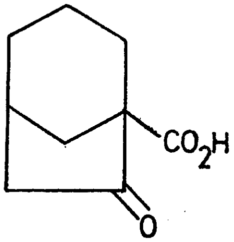

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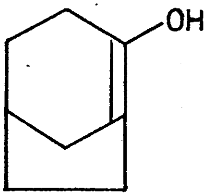

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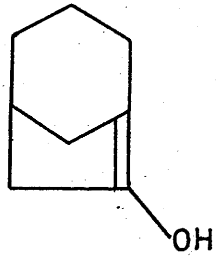

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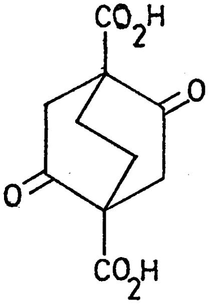
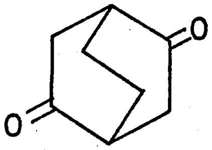


1a



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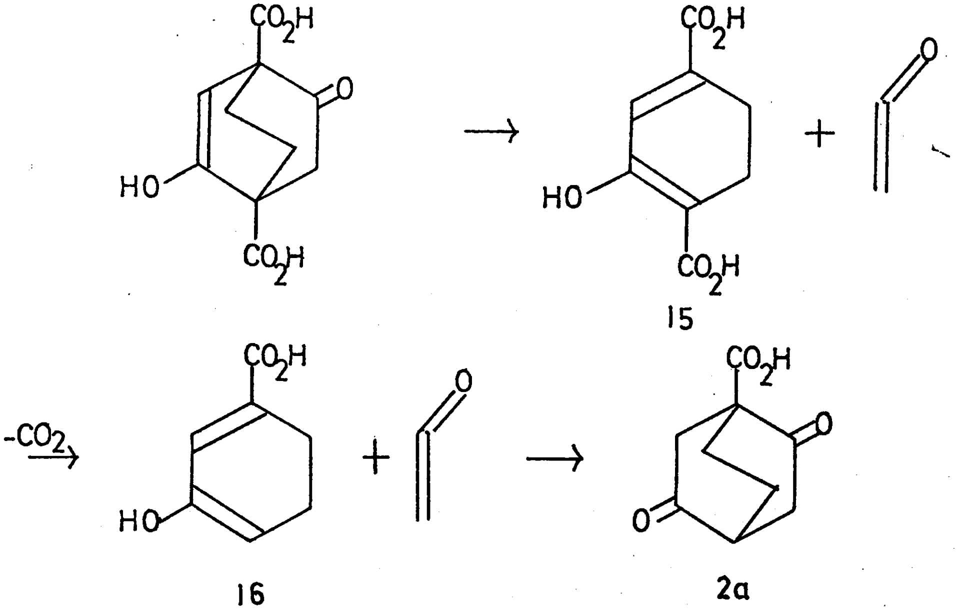
temperature necessary for (11) and (12) is due to the increase in strain in the transition states leading to trans-cycloheptenols rather than trans-cyclooctenols. The fact that (12) requires a higher decarboxylation temperature than (11) is due to the greater strain in the enol (14) compared with its isomer (13).

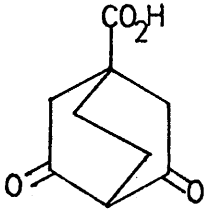
Thus it is not necessary to invoke any mechanism other than the concerted one to explain the observed facts on the decarboxylation studies carried out previously on bridged bicyclic β-ketoacids. That this can be extended to the case of a bridged ring system in which the alkene produced is trans in a six-membered ring does not necessary follow. The additional increase in strain encountered in this type of system may cause some change in the mechanism e.g. favouring a radical decarboxylation. It must be said however that the temperature required for decarboxylation of (1a) is not excessive.

The failure to observe the dione (7) in the reaction products leads to some speculation on the mechanism of the process i.e. that the first decarboxylation is facilitated by the presence of the second β-ketoacid function in the molecule. Two possible examples of this can be considered.

1.) A retro Diels-Alder reaction on the mono-enol form of



SCHEME 3



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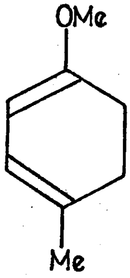

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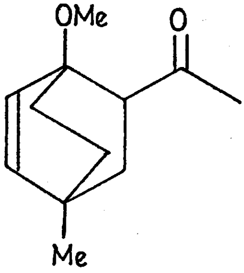
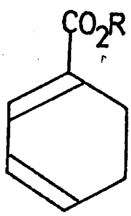
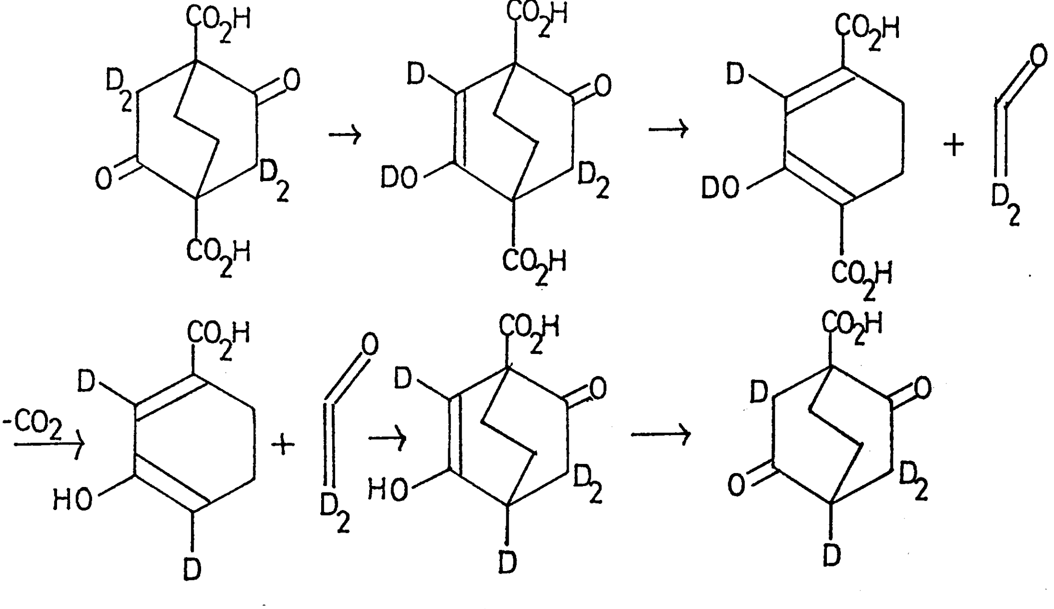


19

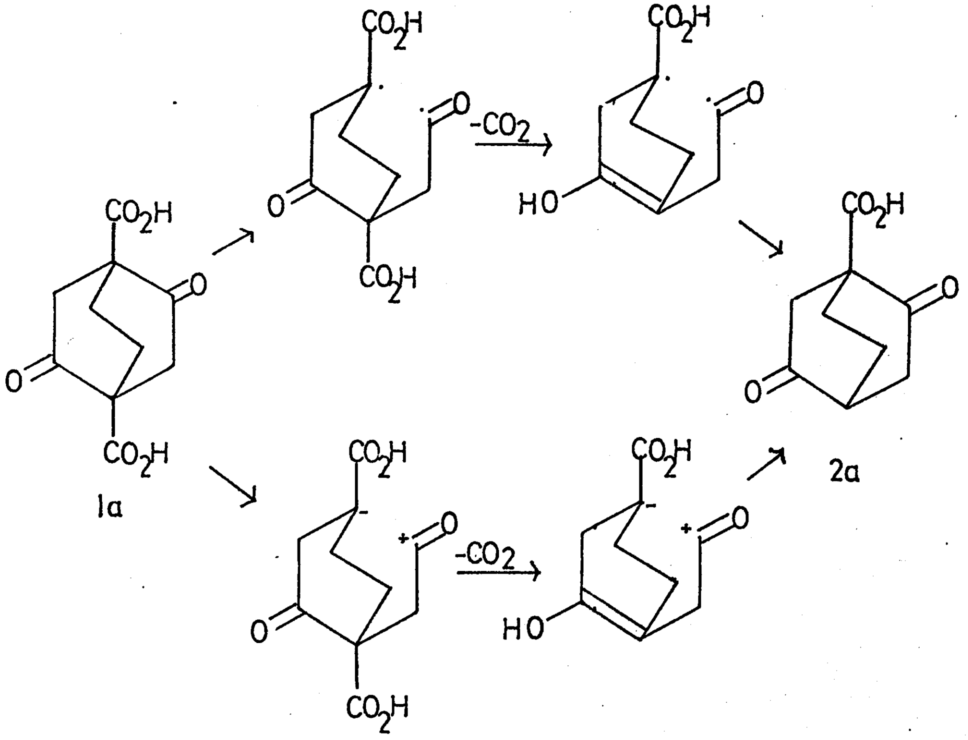


20

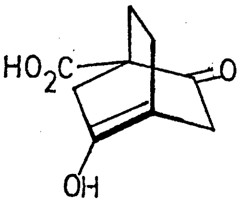
(1a), giving rise to a 1,2 dihydrobenzene and ketene as depicted in Scheme 3. The resulting dihydrobenzene (15) after decarboxylation can undergo a Diels-Alder reaction with ketene giving (2a). This mechanism would require a stereospecific Diels-Alder reaction between the cyclohexa-1,3-diene (16) and ketene giving no diketomonoacid of structure (17), but this is not an unknown occurrence in Diels-Alder reactions e.g. Birch[9] has carried out many Diels-Alder reactions on the dihydroanisole (18) giving exclusively the 1,2 disubstituted bicyclo(2,2,2)octene with a variety of dienophiles e.g. but-3-en-2-one giving the bicyclooctene (19). One factor which perhaps removes creedence from this argument is that cyclohexadiene derivatives of type (20) do not undergo completely stereospecific Diels-Alder reactions[10], but give a mixture of products, so the failure to detect the isomeric product (17) in the reaction products may indicate that the retro Diels-Alder mechanism is here inoperative. It could also be argued that ketene, when produced will be bound to the diene (15) by hydrogen bonding with the carboxyl group, thus ensuring a stereospecific Diels-Alder reaction. It would be perhaps possible to test this mechanism by pyrolysis of the tetradeuterio compound (21) giving (22)



SCHEME 4



SCHEME 5

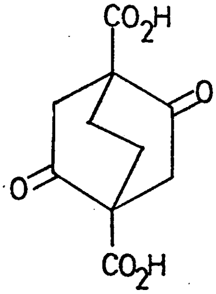


3

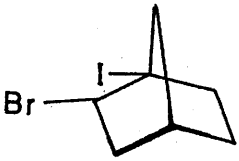
as depicted in Scheme 4.

2.) If by any process the bond between a bridgehead carbon and the carbonyl group on the β-position was subject to fission under the reaction conditions, by homolytic or heterolytic process, the resulting cyclohexane β-ketoacid could readily decarboxylate as in Scheme5. The final step in producing the product (2a) is merely reversal of the first step i.e. reformation of the bond originally broken. This mechanism would then fail to operate for the decarboxylation of the second β-ketoacid moiety, since any type of fission of the C(1)-C(2) bond in (2a) will produce a species which is not a β-ketoacid and which hence will not decarboxylate. Unfortunately it is difficult to devise an experiment which will clarify the situation as far as this type of mechanism is concerned.

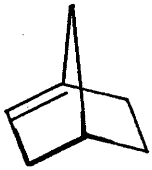
Discussion of the mechanism involved in the production of (2a) by decarboxylation of (1a) leads to further discussion concerning the nature of the intermediate trans-cyclohexenol (3) if the reaction pathway is concerted. The strain in 'anti-Bredt' alkenes is very similar to that in the corresponding trans-cycloalkene and this is accomodated by a torsional twist of the double bond[11], i.e. the overlapping p orbitals are twisted away from each other, increasing the dihedral angle between them from 0^o in the



1a



23



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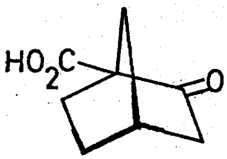

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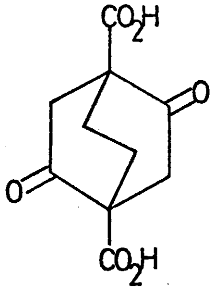
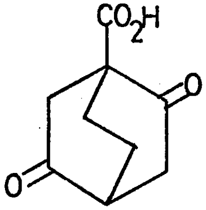
parallel case of the cis cyclohexene to an extent which depends on the ring size of the cycloalkene i.e. the smaller the trans-cycloalkene, the greater will be the dihedral angle. One fact which is obvious is that the degree of overlap between the p orbitals will decrease with decreasing ring size, and there will therefore be less π-bond character in the double bond itself. The degree of twisting necessary to form a trans-cyclohexene is quite remarkable, the dihedral angle between the two p orbitals being close to 90^{o}. In this situation there can be very little overlap between the two p orbitals, and the geometry closely resembles that of an orthogonal singlet diradical.

It will be very difficult to determine whether the proposed trans-cyclohexene intermediate, from decarboxylation of (1a) or from dehalogenation of (23) is a diradical or a discrete double bond. Perhaps an answer to this question could be obtained by electron spin resonance studies on the dehalogenation of (23) to (24). The reported formation of (24) is of great interest since it was found that the ketoacid (25) does not decarboxylate on heating, even at 500^{o}. Perhaps this failure to decarboxylate (25) has some implication on the mechanism of the dehalogenation of (23).

Despite the lack of evidence concerning the mechanism



1a



2a

of the decarboxylation of (1a) and the nature of the intermediate, what has been shown is that (2a) is the product of decarboxylation of (1a). Extensive studies are still necessary in order to prove conclusively the existence of an 'anti-Bredt' transcyclohexenol intermediate.

Preparation of Diethyl bicyclo(2,2,2)octane-1,4-dicarboxylate -2,5-dione (1c)

This was prepared by the method of Humber et al[12] by alkylation of diethylsuccinylsuccinate with ethylene dibromide. The product being obtained as a crystalline solid m.pt. 110°.

IR. (N.Mull) cm^{-1} :- 2987(s), 2800(s), 1730(s), 1176(m), 1080(s), 1023(m), 890(m).

N.M.R. ($CDCl_3$) :- 5.8τ (quartet)- 4H.
7.15τ (AB quartet, J=20Hz., the bottom half of which is further w-coupled J=1½Hz. -4H.
7.6τ-8.0τ (series of multiplets) -4H.
8.8τ (triplet) -6H.

g.l.c. retention time on 5% QF1 at 200° - 7.60 mins.

Acidic hydrolysis of diethyl bicyclo(2,2,2)octane-1,4-dicarboxylate-2,5-dione.

The diester (1c, 5.0g.) was dissolved in ethanol (10ml.) and this solution added to 6Nhydrochloric acid (150ml.). The resulting mixture was refluxed for 16 hours, cooled and extracted with ether (200ml.). The ether extract was in turn extracted with saturated sodium bicarbonate solution (100ml.), the bicarbonate solution acidified and extracted with ether (200ml.). The resulting ethereal extract was dried and the solvent removed giving the diacid (1a, 2.6g.) m.pt. 286° (decomp.) as reported.

N.M.R. (d_6-DMSO) :- 7.1τ (singlet) - 4H
7.83τ (singlet) -4H
No signal observed at 5.8τ or 8.8τ.

Esterification of the diacid (1a) with diazomethane

The diacid (1a, 100mg.) was added to an ethereal solution of excess diazomethane, and the resulting solution left to stand for one hour, after which time nitrogen had ceased to be evolved. Excess diazomethane was boiled off carefully in a fume cupboard, the resulting ethereal solution of the diester (1b) filtered through cotton wool and the solvent removed giving the dimethyl ester (1b, 105mg.)

IR (CCl_4) cm^{-1} :- 2952(m), 2851(w), 1753(s), 1737(s), 1450(w), 1435(w), 1401(w), 1280(s), 1247(s), 1170(m), 1072(s).

N.M.R. ($CDCl_3$) :- 6.2τ (singlet) -6H
7.12τ (AB quartet J=20Hz. the bottom half being further split by w-coupling J=1½Hz.) -4H
7.4τ -8.1τ (series of multiplets) -4H.

M.S. :- Parent ion at m/e 254
Important breakdown peaks at m/e 222, 195, 135, 107, 89 and 59.

g.l.c. retention time on 5% QF1 at 150° - 9.64 mins.

Pyrolysis of the diacid (1a) -Method 1.

The diacid (1a, 150mg.) was placed in a sublimation boat, in a sublimation tube and heated to 280° at ca. 18mm. pressure using a water pump. From 230°, white solid material sublimed out of the heating area. This material was treated with ethereal diazomethane and the products of this reaction subjected to g.l.c. analysis on 5% QF1 at 150°. This showed almost total retention of the starting diester (1b) Retention time -9.64 mins.

Modification A

The attempted pyrolysis was repeated under the same conditions as above using an intimate mixture of equal amounts of the diacid (1a) and ground glass. g.l.c. analysis of the product after treatment with ethereal diazomethane again indicated the presence of greater than 90% of the dimethyl ester (1b).

Modification B

The pyrolysis was repeated under the same conditions using an intimate mixture of equal amounts of the diacid (1a) and copper bronze. The product obtained was treated with ethereal diazomethane, and the resulting material subjected to g.l.c. analysis under the conditions stated for the previous two experiments. This indicated the presence of essentially pure starting material.

Modification C

The pyrolysis was carried out on the diacid (1a) in the experimental set-up described above, employing a pressure of circa 200mm.. Very little material sublimed out below 270°, the bulk of the material distilling out between 280° and 290° as a yellow oil, sections of which slowly crystallised. The product was treated with ethereal diazomethane, and the product of this esterification analysed by g.l.c. on 5%QF1 at 150°. This showed the presence of starting dimethyl ester (1b) (35%) and one new major component (50%) of retention time 3 mins., in addition to several minor components. The new component was purified by preparative t.l.c. in 40% ethyl acetate in petrol, and by sublimation.

IR. (CCl_4) cm^{-1} :- 2952(m), 2917(w), 2880(w), 2850(w), 1750(s), 1735(s), 1450(w), 1434(m), 1401(m), 1243(s), 1230(m), 1059(m), 1042(m).

N.M.R. ($CDCl_3$) :- 6.23τ (singlet) -3H
7.2τ (AB quartet, J=20Hz., the bottom half being further split by w-coupling J=1$\frac{1}{2}$Hz.) -4H,
7.23τ (triplet) -1H,
7.35τ -8.0τ (series of multiplets) -4H.

M.S. :- Parent ion at m/e 196,
Important breakdown peaks at m/e 181, 165, 137, 109, 81, 79, 59, 55, 53, 41 and 39.

A sample of the pyrolysis product, the diketoacid (2a) was recrystallised from water m.pt. 215°.

Mixed melting point with authentic synthetic material was established as 215°.

Pyrolysis Method 2

The diacid (1a, 200mg.) in tetrahydrofuran (10ml.) was dropped through a pyrolysis tube, containing a small plug of glass wool, at 285°, in a steady stream of nitrogen. The products were collected in a U-tube receiver, cooled to -78° in an acetone - dry ice bath. The tetrahydrofuran solution was boiled to dryness and the residue taken up in ether (100ml.). Extraction of the ether solution with saturated sodium bicarbonate solution (50ml.) left all neutral material in the ethereal layer. This material was isolated by drying and removal of the solvent giving only 1 - 2 mg. on average. The bicarbonate solution was acidified extracted with ether (100ml.), the ether dried and removed giving the acidic products of pyrolysis (105mg.). These were treated with an ethereal solution of diazomethane and subjected to g.l.c. analysis on 5% QF1 at 150°. The major product was shown by this to be identical to that obtained by the previous pyrolysis method and by synthesis. Retention time = 3 mins.. The neutral material was extremely small in bulk (1 -2%) and showed several components on g.l.c..

The following precautions were observed.

1.) Tetrahydrofuran was distilled from lithium aluminium hydride prior to use.

2.) Pyrolysis of tetrahydrofuran itself under the same conditions on g.l.c. analysis showed no component observed in the pyrolysis.

3.) All tetrahydrofuran solutions were thoroughly de-gassed with oxygen free nitrogen prior to pyrolysis.

Attempted Hunsdiecker reaction of bicyclo(2,2,2)octane -1,4-dicarboxylate-2,5-dione (1a)

To a mixture of bicyclo(2,2,2)octane-1,4-dicarboxylate -2,5-dione (1a, 102mg.) and red mercury oxide (129mg.) in 1,2-dibromoethane (10ml.) was added slowly a solution of bromine (132mg.) in 1,2-dibromoethane (3ml.). The resultant mixture was heated at 75^{o} for 12 hours. On cooling, the mixture was filtered and the solid residue washed with ether (150ml.). The resulting combined organic washings were washed with dilute sodium bisulphite solution (75ml.), dilute sodium hydroxide solution (20ml.) and water (100ml.) Drying and removal of the solvent gave only 30 mg. of crude product shown by t.l.c. in 30% ethyl acetate in petrol to consist of several non-polar components. It was also found that the infra-red spectrum of the crude product exhibited very little carbonyl absorption.

Acetalisation of Diethyl bicyclo(2,2,2)octane-1,4-dicarboxylate-2,5-dione (1c)

This was carried out by the method of Holtz and Stock[14], giving the desired product (4b), recrystallised from cyclohexane m.pt. 85-86°.

Basic hydrolysis of the bisacetal (4b)

The bisacetal (4b, 500mg.) was dissolved in ethanol (10ml.), and to this solution was added dilute sodium hydroxide solution (50ml.). The resultant mixture was refluxed for 12 hours and then cooled to ice temperature. The basic solution was carefully acidified to pH 5 with dilute hydrochloric acid, and the aqueous solution extracted with ether (150ml.), the ether dried and removed to give the bisacetal-diacid (4a, 260mg.)

Attempted Hunsdiecker reaction of the bisacetal-diacid (4a)

To a mixture of the bisacetal (4a, 130mg.)and red mercury oxide (129mg.) in 1,2-dibromoethane (10ml.) was added slowly a solution of bromine (132mg.) in 1,2-dibromoethane (3ml.). The resultant mixture was then heated at 75° for 12 hours, and on cooling the mixture filtered and the solid residue washed with ether (150ml.). The resulting combined organic washings were washed with dilute sodium bisulphite solution (75ml.), dilute sodium hydroxide solution (20ml.) and water (100ml.). Drying and removal of the solvent gave 50mg. of crude product from which could be separated by t.l.c. 23mg. of what seemed to be the desired bisethyleneacetal of 1,4-dibromo bicyclo(2,2,2)octane-2,5-dione.

IR. (CCl_4) cm^{-1} :- 2990(m), 2895(m), 2887(m), 1335(s), 1324(w), 1280(w), 1158(s), 1029(s), 950(s), 918(s).

Preparation of Tetraethyl butane-1,1',4,4'-tetracarboxylate

This compound was prepared by the method of Noyes and Kyriakides[13] by condensation of diethyl malonate and ethylene dibromide induced by magnesium amalgam, and obtained as a clear liquid b.pt. 210-230° at 10mm..

Preparation of hexaethyl hexane-1,2,2',5,5',6-hexacarboxylate

This was prepared by the method of Guha and Krishnamurthy[6] by condensation of tetraethyl butane-1,1',4,4'-tetracarboxylate with ethyl bromoacetate.

Preparation of Tetraethyl hexane-1,2,5,6-tetracarboxylate

The crude product from the above condensation, without purification was treated with dilute hydrochloric acid as described by Guha. The resulting tetraacid so obtained was refluxed overnight in 6% ethanolic hydrochloric acid giving the tetraester of the correct boiling range as described by Guha. b.pt. 195-205° at 2mm..

IR. (l.film) cm^{-1} :- 2987(s), 2926(m), 1730(s), 1443(m),
1370(m), 1170(s), 1025(s).

N.M.R. (CCl_4) :- 5.80τ and 5.82τ (quartets) - 8H
7.20τ - 8.0τ (series of multiplets) -6H
8.40τ (multiplet) - 4H
8.63τ (triplet) - 12H.

Attempted Dieckman cyclisation of tetraethyl hexane-1,2,5,6 -tetracarboxylate.

To a slurry of sodium hydride dispersion (100mg.) in dimethyl formamide (10ml.) was added a solution of tetraethyl hexane-1,2,5,6-tetracarboxylate (8, 375mg.) in dry benzene (10ml.) under an atmosphere of nitrogen. The resulting solution was refluxed for 16 hours under nitrogen and then poured into 2N hydrochloric acid (50ml.). Ether (100ml.) was added and the aqueous solution thoroughly extracted. The ethereal layer was then washed with water (2 x 75ml.) and brine (1 x 50ml.), dried and the ether removed giving a crude oily product (252mg.) shown by t.l.c. in 30% ethyl acetate in petrol to consist of three major components all of which gave a positive ferric chloride test.

Separation was effected by preparative t.l.c. giving the three components A (52mg.) , B(83mg.) and C(77mg.), all of which were characterised as β-keto esters by their reaction to ethanolic ferric chloride and by the presence of infra-red absorption bands at 1750, 1730, 1660 and 1618 cm^{-1}. From a comparison of the infra-red and N.M.R. spectra of the three components, it was concluded that component B was the desired product (9).

Component B

IR. (CCl_4) cm^{-1} :- 2982(m), 2937(w), 1750(s), 1732(s), 1657(s), 1616(m), 1300(m), 1230(s), 1154(m) and 1076(m).

N.M.R. (CCl_4) :- 5.82τ (doublet of quartets) -4H, 6.43τ, 6.95τ and 7.30τ (multiplets) -8H, 8.78τ (doublet of triplets) -6H.

Acidic hydrolysis and decarboxylation of diethyl bicyclo (2,2,2)octane-3,6-dicarboxylate-2,5-dione (9).

Component B from the previous condensation reaction was refluxed overnight in 6N HCl (20ml.). On cooling, the solution was extracted with ether (50ml.), the ethereal layer washed with brine (30ml.), dried and the ether removed giving a crude oily product (18mg.) which was purified by preparative t.l.c. (20% EtOAc/petrol) and by sublimation to give bicyclo(2,2,2)octan-2,5-dione (7mg.) as a white crystalline solid m.pt. 215°.

g.l.c. retention time on 1% APL at 150° = 1.32 mins.

IR. (CCl_4) cm^{-1} :- 2958(m), 2877(w), 1736(s), 1462(w), 1446(w), 1398(m), 1111(w), 1078(m), and 941(m).

Higher temperature pyrolyses of (1a)

Pyrolyses were carried out on the diketodiacid (1a) by method 2 over a range of temperatures from 280° to 360°. In each case the neutral fraction of the products was isolated as previously described and subjected to g.l.c. analysis on 1% APL at 100°.

Retention time for dione (7) = 6.32mins.

On each occasion, no peak was observed in the g.l.c. corresponding to the dione (7) . Four major products were consistently obtained at each temperature in total yield of less than 1%.

Retention times :- 4 mins., 4.96 mins., 7.73 mins. and 8.45 mins..

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