BRIDGED BICYCLIC COMPOUNDS

a thesis

presented to the University of Glasgow

for the degree of

Doctor of Philosophy

by

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"If it be true that.... the Formes of Divers Bodys be but the result of the determinate size, figure, motion and connection, and such-like mechanical Affections of their component Corpuscles; it will seeme to follow, that since the Occult qualitys of Bodys are resolved to flow from their Formes, they likewise may be deduced from the same Eminent and Obvious Principles; by which if they could be explicated, they would no longer be Occult Qualitys."

Robert Boyle (1627 - 1691).

There are many people without whom this research could not have been done and described.

I have been privileged to study under the supervision of Dr. G.L. Buchanan. His interest and enthusiasm, and his unfailing concern for the progress of both the subject and its students, have been an inspiration.

My sincerest thanks are due to Professor R.A. Raphael, who gave me the opportunity to undertake this research, and to the Carnegie Trust for the Universities of Scotland, whose generosity has been instrumental in keeping body and soul together.

The expertise of many members of the technical staff of the Department has been invaluable, and I extend to them my gratitude for their services.

Finally I must mention my fellow research students. Stimulating discussion, both on and outwith the subject of study, is a vital part of education, and in this respect our laboratory is not lacking. I thank my colleagues for their assistance, their opinions, and not least their sense of humour. It has been a privilege to know them.

SUMMARY

This thesis is concerned with certain aspects of the application of Bredt's Rule in bridged bicyclic compounds.

The reported monodecarboxylation of bicyclo[2,2,2]-octane-2,5-dione-1,4-dicarboxylic acid (1) to give bicyclo-[2,2,2]octane-2,5-dione-1-carboxylic acid (2) has been found to be genuine, and the structure of the product has been confirmed by synthesis. Bicyclo[2,2,2]octan-2-one-1-carboxylic acid (3) has also been prepared, and (2) and (3) have been shown to be resistant to decarboxylation.

The decarboxylation of (1) has been found to proceed with racemisation, and conclusions have been drawn concerning the mechanism of the reaction.

The Cope elimination has been shown to be unsatisfactory in generating the strained alkene bicyclo[2,2,2]oct-1-ene.

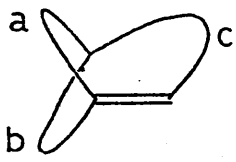
Two synthetic approaches to bicyclo[4,3,1]decane-2,9-dione, a key intermediate for the study of isomeric "anti-Bredt" alkenes, were unsuccessful, as were attempts to prepare a derivative of the [5]-metacyclophane system.

INTRODUCTION

"Auf Grund unserer Vorstellungen über die Lage der Atome im Raum kann in den Systemen der Camphan- und Pinanreihe, sowie in ähnlich konstituierten Verbindungen ..... von den Brückenköpfen eine Kohlenstoffdoppelbindung nicht ausgehen."

Since its first statement thus[1] in 1924, Bredt's Rule has been fundamentally important as a principle of molecular structure in bridged bicyclic compounds. Bridgehead double bonds have for fifty years been regarded as stereochemical outlaws, and large numbers of them lurking in the literature have been hunted down[2] and done to death.

No mean effort has been devoted to determining the smallest size of ring system which will accommodate such a so-called "anti-Bredt" double bond, for the phrase "ähnlich konstituierten Verbindungen" was never intended to cover all bridged structures; and this research has spawned two generalisations of the problem. The first was made in 1950 by F.S. Fawcett, who suggested[3] that a bicyclo[x,y,z]alkene, with the double bond at the bridgehead and x,y and z all greater than zero, would be isolable if (x + y + z) (i.e. "S") were 9 or more, and detectable if S were 7 or more. This idea, as Fawcett himself realised, was not quite adequate to explain all the experimental findings, and was weak in its predictive capacity.



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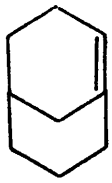

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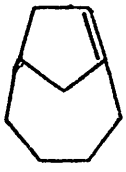

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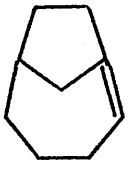

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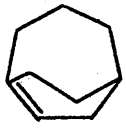

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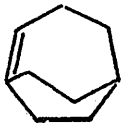

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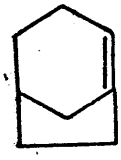

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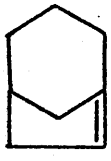

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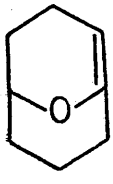
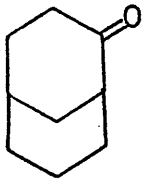


(9)

The more recent, and less empirical, hypothesis is that of J.R. Wiseman, who drew a comparison[4,5] between the double bonds in "anti-Bredt" olefins and those arranged in a trans fashion in monocyclic systems. This structural relationship becomes clear on consideration of the generalised molecule (1). The double bond, which is common to rings ac and bc, must be cis substituted in one (ac, as drawn) and trans in the other (bc). It is therefore plausible that the olefins (2), (3) and (4) should be isolable, being essentially bridged trans-cyclooctenes[6], while (5), (6), (7) and (8) should be at least detectable as reaction intermediates, by analogy with trans-cycloheptene[7]. In support of this hypothesis Wiseman and his co-workers have prepared an impressive succession of compounds, including (2)[4,5], (3) and (4)[8], (5) and (6)[9], and (7)[10]; and recently also the oxygen analogue (9)[11]. These compounds were prepared by reactions under kinetic control, and exhibit more or less the properties predicted for them. Bicyclo[3,3,1]non-1-ene (2), the mixture of isomeric bicyclo[4,2,1]non-1-enes (3) and (4), and 9-oxabicyclo[3,3,1]non-1-ene (9) were isolated, while the other three were characterised only as adducts or dimers.

Bicyclo[3,3,1]non-1-ene (2) was simultaneously prepared[12,13] by J.A.Marshall, using a different, but still irreversible, route.

Two pieces of evidence led Marshall to believe that



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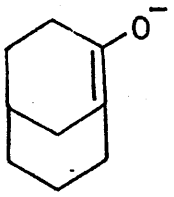

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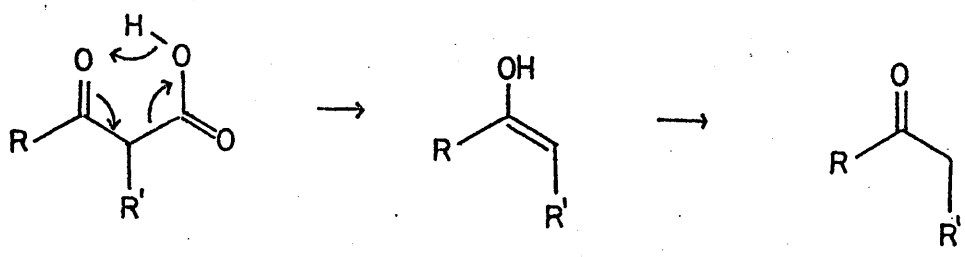
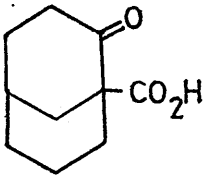


Fig. 1



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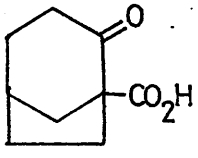

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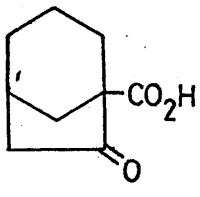

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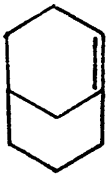


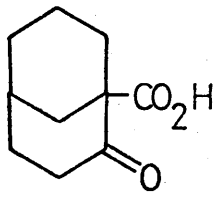
(2)

this compound might be capable of discrete existence. Firstly, the ketone (10) had been shown[14] to exchange its bridgehead proton on boiling with NaOD in D_2O, a reaction which presumably occurs via the enolate form (11). Secondly, there was a body of compelling evidence from studies of the decarboxylation of β-keto acids.

The presently accepted mechanism of this reaction[15] was propounded in 1941 by F.H. Westheimer and W.A. Jones (and is henceforth referred to as the "Westheimer mechanism"). The process (fig. 1) is concerted and involves a six membered cyclic transition state as in the "ene" reaction, the immediate product being the enol form of the decarboxylated ketone.

In the case of a bicyclic acid such as (12), such an enol will incorporate a double bond at the bridgehead, contrary to Bredt's Rule; and in agreement with prediction such acids are more stable than their monocyclic or acyclic counterparts. However, (12) does decarboxylate, while even (13) and (14) can be persuaded to part with carbon dioxide, albeit with some difficulty. Marshall argued[12,13] that these findings pointed to the feasibility of a double bond existing at the bridgehead in ring systems of this size, and prepared bicyclo[3,3,1]non-1-ene (2) to prove the validity of his reasoning.

These decarboxylations are interesting for another reason. In 1963, four years before the Wiseman hypothesis was published, J.P. Ferris and N.C. Miller prepared[16]



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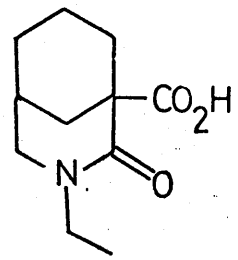

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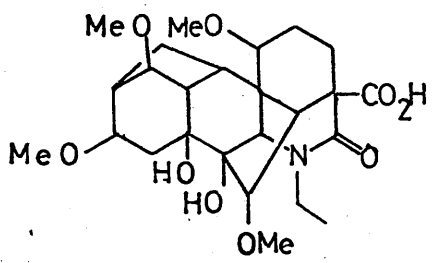

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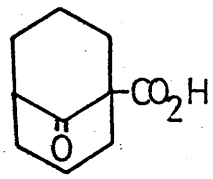

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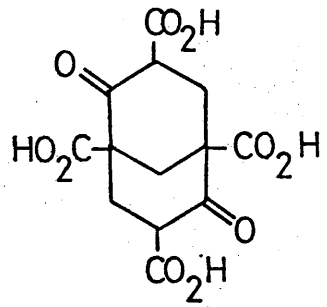

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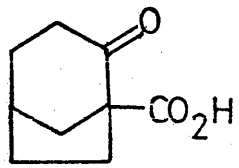

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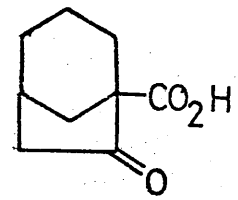


(14)

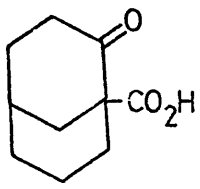
compounds (12) and (15) as models for comparison with lycoctonamic acid (16). This substance decarboxylates with surprising facility compared with other known [3,3,1] β-keto acids, for example (17) and (18).

On the basis of their results with (12) and (15), Ferris and Miller proposed that in bicyclic β-keto acids decarboxylation was not concerted but went by way of a bridgehead carbanion. This species, they argued, would be stabilised by overlap of the bridgehead orbital with the p orbitals of the adjacent carbonyl group. Such overlap is dependent on the dihedral angle between the carbonyl and carboxyl groups in the starting material, and Ferris and Miller were able to show that as the C=O/ $-CO_2H$ dihedral approached 90° (and hence the orbital dihedral (θ) in the carbanion approached 0°) the decarboxylation temperature (T) decreased.

Subsequently they synthesised (13) and (14), and showed[17] that for these and (12), $\cos\theta$ was inversely proportional to T. The fact that the nitrogen-containing compounds (15) and (16) do not fit the graph they ascribed to "the intrinsic difference between the ketone carbonyl and the lactam carbonyl".

Their idea does, of course, also explain the total resistance of (17) to decarboxylation, since here the orbital dihedral (θ) would be 90°.

However, Wiseman's hypothesis accounts for this and the other observations in a much more satisfactory manner without invoking special non-concerted mechanisms. It is



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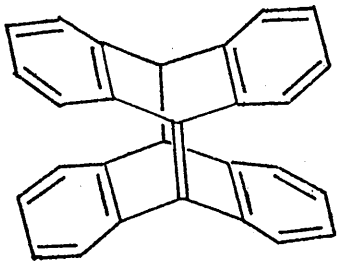

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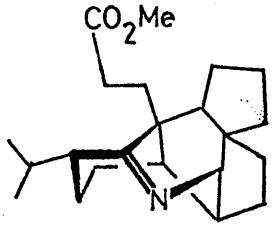

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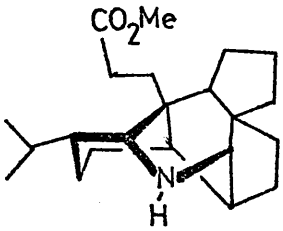

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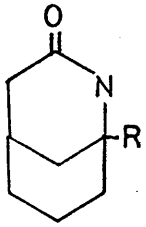

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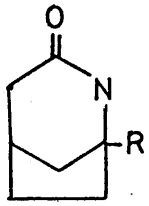
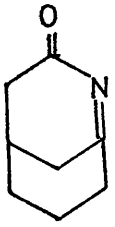
(24) R = OAc



(23) R = H

(25) R = OAc



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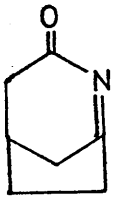

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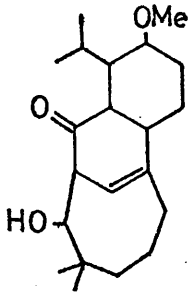

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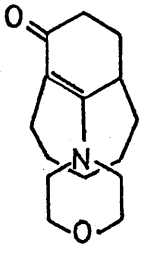

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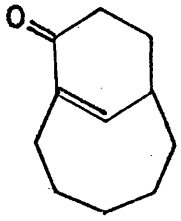

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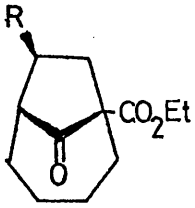
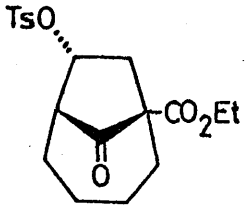


(31) R = OTs

(35) R = Cl



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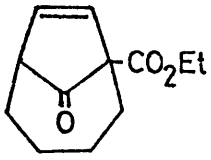

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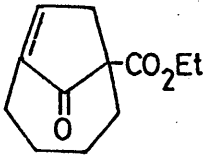


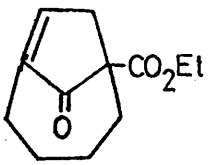
(34)

perhaps a little ironic that the decarboxylation of (12) should be used as evidence first for the non-existence of bridgehead double bonds, and then, somewhat more convincingly, for precisely the opposite.

Approaches to "anti-Bredt" olefins of the trans-cyclooctene type have been made by a number of groups. N.M. Weinshenker and F.D. Greene in 1968 reported[18] the synthesis of 9,9'-dehydrodianthracene (19), while the "anti-Bredt" imine (20) was isolated[19] by M. Toda et. al. from the lead tetraacetate oxidation of the amine (21). This group went on to investigate the course of the same reaction on the model compounds (22) and (23); and on obtaining the acetates (24) and (25) respectively, they proposed [20] the intermediacy of the imines (26) and (27).

Other instances include compound (28), postulated[21] as an intermediate by R.C. Cambie and co-workers, while isolation of the enamine (29) was reported[22] by J.R. Hargreaves, P.W. Hickmott and B.J. Hopkins. The parent enone (30) has been synthesised[23] in this Department by G.L. Buchanan and G. Jamieson.

A particularly remarkable example was reported[24,25] by W. Carruthers and M.I. Qureshi, who found that either of the tosylates (31) and (32) gave, on elimination in collidine, not only the $\beta\gamma$-enone (33) but also the $\alpha\beta$ isomer (34); similar treatment of the chloride (35) gave exclusively (34). This must surely be the thermodynamically less stable of the two enones, for the degree of



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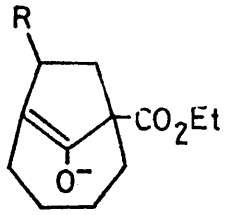

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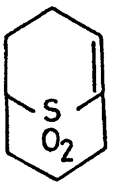

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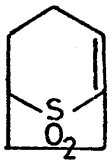

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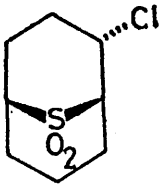

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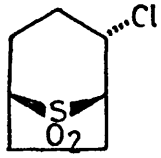

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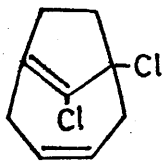

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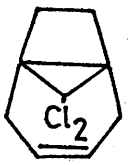

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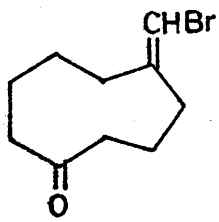

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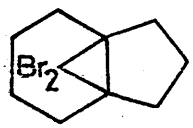

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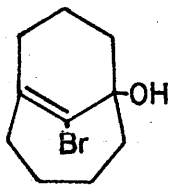


(45)

conjugation will be minimal. Presumably the formation of (34) results from the greater acidity of the bridgehead proton, compared with the one at C(8); and the authors suggest that the anion (36) might be an intermediate. One would expect, however, that this bridged trans-cycloheptene would be of high energy, and it is surprising that kinetic control apparently still predominates.

Sulphur-containing bridged bicyclics have for some time been known[26] to be somewhat more sterically accommodating than their all-carbon analogues. L.A. Paquette in 1969 suggested[27] the sulphones (37) and (38) as intermediates in the reactions of (39) and (40), respectively, with potassium tert-butoxide; and Wiseman has recently trapped[28] (37) from such an elimination.

In addition to those already mentioned[9,10,17,20,25] several other trans-cycloheptenes have been invoked. P. Warner et. al. suggested[29] (41) as the immediate product from the rearrangement of (42). Compound (41) is not isolated, but dimerises in a $[\pi^2_s + \pi^2_a]$ sense, or in the presence of furan forms adducts of the bridgehead double bond. C.B. Reese and M.R.D. Stebles have obtained (43) by rearrangement of (44), and postulate[30] (45) as an intermediate.

In discussions about small trans-cycloalkenes and "anti-Bredt" compounds, it must be borne in mind that the double bond in these molecules possesses a most

unusual stereochemistry; one must for example guard against treating trans-cyclohexene (46) as a normal olefin. Calculations on this molecule, performed by N.L. Allinger and J.T. Sprague, indicate[31] that the strain is 42 Kcal/mole greater than that of the cis isomer, and that the C - C = C - C dihedral angle is closed from 180° to 85°. Distortion of this type seems unlikely to be accommodated by classical means, and in fact the same calculations indicate considerable rehybridisation of the "olefinic" carbon atoms. The effect of this introduction of s character into the atomic orbitals making up the π bond is to decrease the dihedral angle between them but at the same time to cause them to lean away from one another along the line of the bond. A compromise between these opposing trends represents the equilibrium situation.

The conversion barrier between the trans and cis forms of cyclohexene has been calculated at not more than 12.9 Kcal/mole, and so isomerisation of trans to cis will be rapid at room temperature. It follows that only when trapping reactions are faster than this process, or when the isomerisation is hindered by the presence of an atomic bridge, will trans-cyclohexene be detectable.

Allinger has also applied his method to trans-cycloheptene and trans-cyclooctene, and has found similar, though naturally less severe, distortions - dihedrals of 125° and 149°, and strain energies (relative to cis

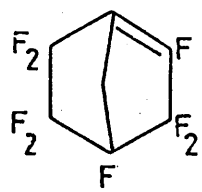
isomers) of 20 and 12 Kcal/mole, respectively. The bridgehead double bond in bicyclo[3,3,1]non-1-ene(2) was calculated to possess 13 Kcal/mole of strain. Such calculated values as can be compared with experimental findings showed excellent agreement.

It would be difficult to argue that trans-cyclo-octene does not contain a conventional double bond. Numerous examples have been isolated and in all cases the spectroscopic properties and reactivities have been more or less as expected on the classical model.

Trans-cycloheptenes are rarer, few actually having been isolated, but some, including the mixture of (5) and (6), have been spectroscopically examined at low temperatures, and once again show the features expected.

No example of a trans-cyclohexene has been isolated. The species was first suggested[32,33] as an intermediate in photosensitised addition of hydroxy compounds to cyclohexenes, and it was considered that it might resemble the triplet in geometry, though electronically a singlet. S.F. Campbell, R. Stephens and J.C. Tatlow observed[34-37] that 1-lithioundecafluorobicyclo[2,2,1]heptane (47) forms a mixture of stereoisomeric adducts (48) on heating with furan, and suggested that (49) was initially produced. The same authors found evidence for this intermediate also in the pyrolysis of sodium undecafluorobicyclo[2,2,1]-heptane-1-carboxylate (50).

The species (49) is a bridged trans-cyclohexene, and



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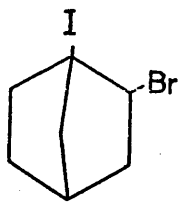

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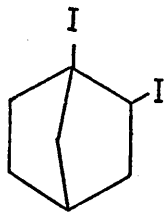

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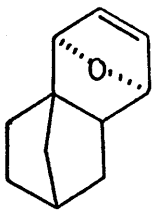

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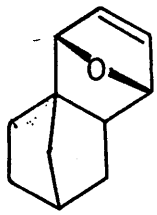

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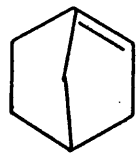

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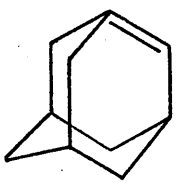

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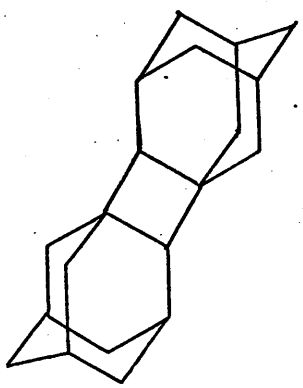

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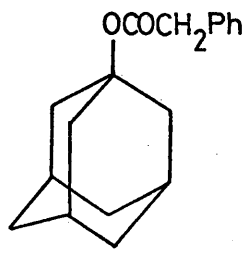


(58)

in referring to it the authors use the terms "bridgehead olefin" and "diradical" interchangeably. The reactions observed for (49) could be explained equally well in terms of either.

In the parent hydrocarbon series R. Keese and E.-P. Krebs found[38,39] that 1-iodo-2-bromobicyclo[2,2,1]heptane (51) or 1,2-diiodobicyclo[2,2,1]heptane(52) reacted with butyllithium in the presence of furan, forming the adducts (53) and (54) in constant ratio, together with three hydrocarbons of formula $C_{14}H_{20}$. The stereochemistry of the starting halide (exo or endo) made no difference, and it was proposed that the reaction occurred by way of initial lithium-iodine exchange at the bridgehead, followed by elimination to give 1-norbornene (55). Keese and Krebs were undecided whether this species was a singlet or a triplet, but considered that a good deal of rehybridisation took place.

The fleeting existence of the much-sought-after adamantene (56) was postulated[40] by M.A. McKervey, who reacted 1,2-diiodoadamantane with butyllithium and isolated an almost quantitative yield of the dimer (57). J.E. Gano and L. Eizenberg have recently invoked[41] adamantene in the photolysis of 1-adamantyl phenylacetate (58). The reaction, carried out in the presence of methanol, gave a 1% yield of 1-methoxyadamantane.

Study of molecular models suggests that adamantene ought to be even more strained than 1-norbornene; consid-

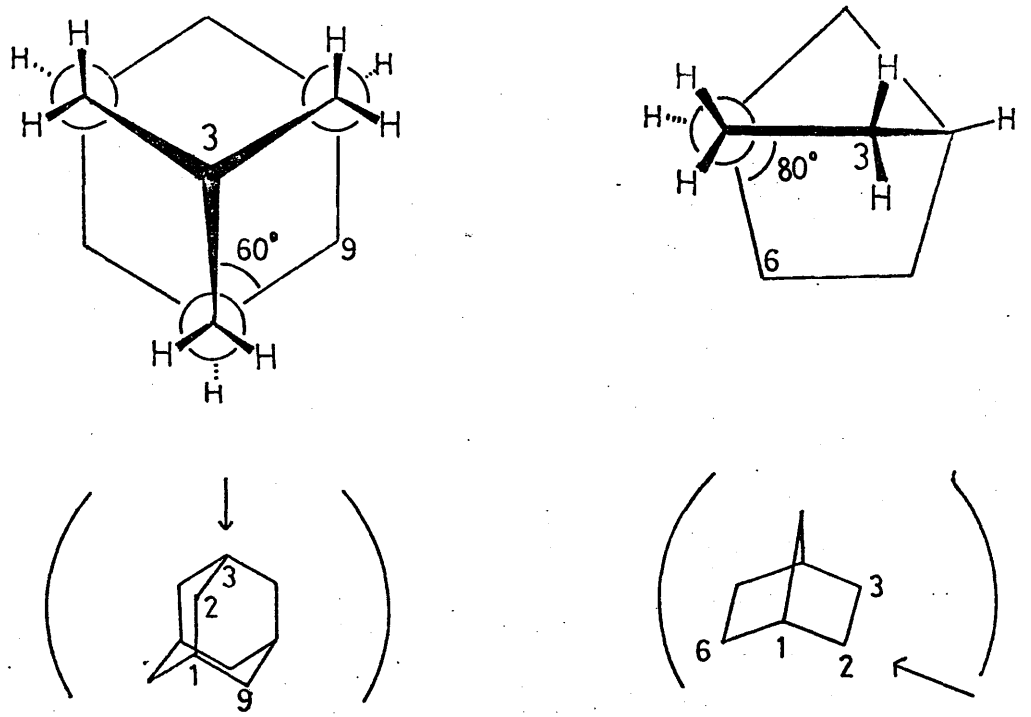
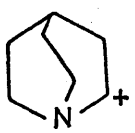


Fig. 2

(56)



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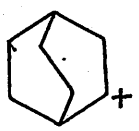

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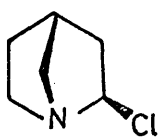

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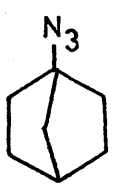
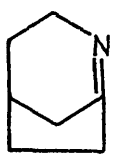


(62)

(63)



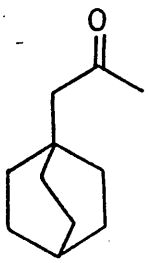
(64)

erable distortion of this very rigid framework being necessary to obtain orbital overlap, even with rehybridisation. The $C_9 - C_1 - C_2 - C_3$ dihedral angle in adamantane (see fig. 2) is 60^o, while the $C_6 - C_1 - C_2 - C_3$ dihedral angle in norbornane is $80^o - 85^o$ (as measured on a model). The latter figure compares with Allinger's calculated C - C = C - C dihedral for trans-cyclohexene of 85^o. It seems extremely unlikely that the formulation (56) is anything like a true representation of "adamantene".

Apparent mesomeric effects involving the lone pairs on bridgehead nitrogen atoms have been observed by C.A. Grob[42] and by P.G. Gassmann[43]. The former found the 2-quinuclidinium cation (59) to be significantly more stable than its carbon analogue (60), while the latter observed apparent N-participation in the solvolyses of several azanorbornanes such as (61).

There have also been several unsuccessful attempts to generate trans-cyclohexenes, by a variety of routes. J.O. Reed and W. Lwowski studied[44] the decomposition of the 1-azidonorbornane system (62), which, if it occurs by the normal mechanism, will produce the strained imines (63) or (64). They found, however, that concerted bridge migration and addition of alcohol took place, avoiding these intermediates. Reduction or hydrolysis of the resultant amino ethers provided evidence that (64) was accessible, while (63) was not.

Attempts to bring about Norrish Type II or McLafferty



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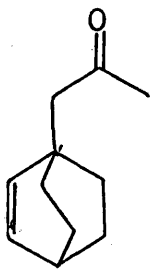

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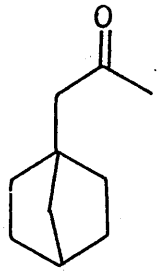

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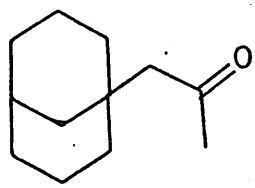

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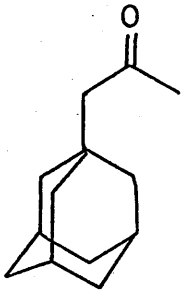

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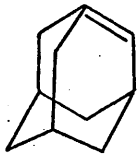

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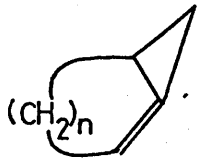

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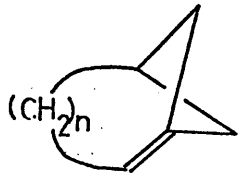

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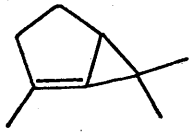

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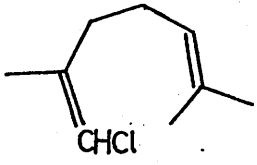

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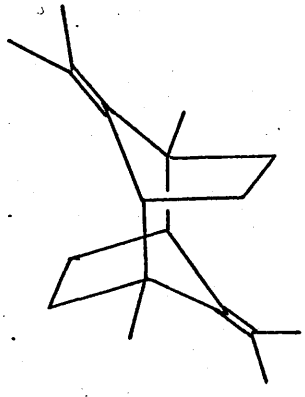

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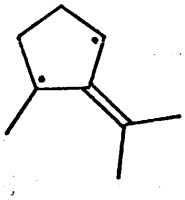

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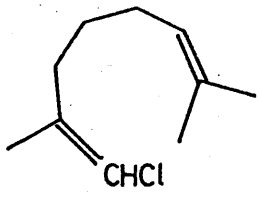

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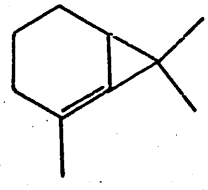


(77)

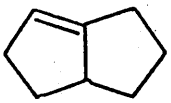
rearrangement of the 1-acetonyl substituted bridged bicyclic systems (65) - (69) were made by R.R. Sauers and co-workers[45]. Similar approaches to adamantene (56) were made from (69) by N.J. Turro[46]. In all cases such reactions would give rise to bridgehead olefins, and in no case did such reactions occur.

Many other, older examples are cited in the 1950 review by Fawcett[3].

G. Köbrich and co-workers have examined an interesting sideline on Bredt's Rule. Köbrich has suggested that the strain existing in fused bicyclic systems of the general formula (70) might be comparable, in nature and magnitude, to that in the formally "anti-Bredt" compounds (71).

Synthesis directed at (72) by carbenoid cyclisation[47] of (73) gave among the products (74) which could be formed from (72) via the diradical (75). Analogous reaction of (76) gave[48] the desired olefin (77), which was remarkably stable (half-life 70 hours) and showed little tendency to undergo cycloadditions.

These findings are very interesting. While fused bicyclic compounds have been declared[3] to be outwith the scope of the Rule, the Wiseman hypothesis provides a link between fused and bridged systems of this type. Compounds (77) and (72) can be regarded as a trans-cycloheptene and a trans-cyclohexene respectively. Since, on this basis, (77) does not show the expected properties, it



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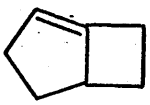

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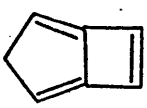


(80)

(7)

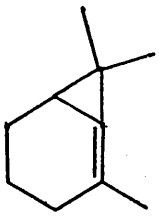
may be that this analogy is not a very good one. However, examination of models of larger fused systems is revealing.

There is no doubt that bicyclo[3,3,0]oct-1(2)-ene (78) can be regarded as trans-cyclooctene with a trans-annular bond. Similarly bicyclo[3,2,0]hept-1(2)-ene (79) is derived from trans-cycloheptene. Derivatives of both systems have been isolated. The parent olefins (78) and (79) are both quite stable[49,50], while even (80),(formally a transannularly bonded trans, trans, cis-cycloheptatriene) is stable[51] for several days at 0°.

A study of molecular models helps to explain this apparently anomalous stability.

Trans-cycloheptene in a flat conformation suffers from severe transannular interactions involving the inwardly directed hydrogen atom attached to the double bond. In the real molecule this strain is delocalised and distributed by the adoption of an alternative conformation, involving a certain amount of twist of the double bond, and angle strain throughout the molecule.

In either of the bicyclic systems (7) or (79), however, the molecule has much less conformational choice open to it. The double bond in the "atomic-bridged" compound (7) is held in a twisted conformation, with consequent localisation of strain at a reactive site; whereas that in the "valence-bridged" compound (79) is held more or less planar, while the strain is concentrated in the relatively unreactive cyclobutane.



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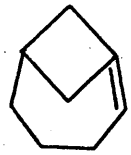

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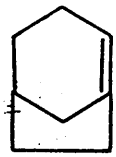

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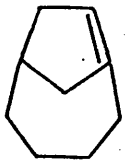

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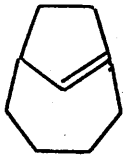

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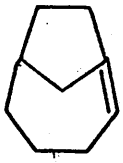

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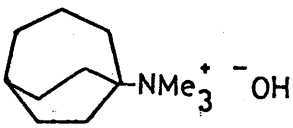

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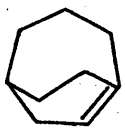

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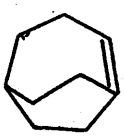

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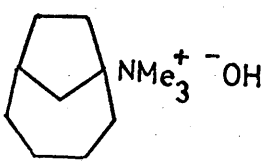
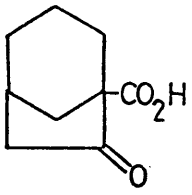


(84)

This distinction may well explain the relative stabilities of fused and bridged bicyclic bridgehead olefins; though rigid application of the Wiseman hypothesis leads to expectation of the same properties for both types.

Köbrich's claim that the double bonds in (77) and (81) should exhibit similar strain cannot be tested until a derivative of (81) is made; but the isomer (7) is certainly much more reactive than (77), probably for the reasons outlined above.

Wiseman's hypothesis[5] neatly explains the difference in strain energy between bridgehead olefin isomers such as (3) and (82), the former being derived from trans-cyclooctene and the latter from trans-cycloheptene. It does not, however, discriminate between (3) and (4), which are both trans-cyclooctenes. Wiseman has produced evidence[9] that the more abundant of the two products from Hoffmann elimination of the quaternary ammonium hydroxide (83) is also the more reactive, and hence, by inference, the more strained; but it is not known whether this is (5) or (6). He has also shown that (3) is formed in greater amount than (4) from (84). By fitting these two pieces of evidence together one can draw a conclusion about the relative energies of (3) and (5) compared, respectively, with (4) and (6), but in so doing one is making some unjustified assumptions. Wiseman made no assertions on this basis, but from a study of molecular models concluded that (4), where the double bond is endocyclic in the



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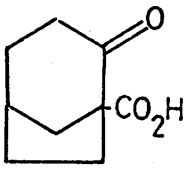

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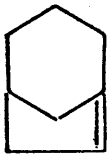

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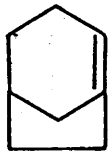

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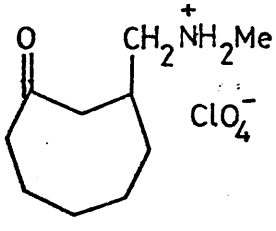

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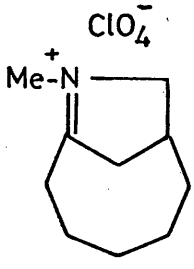

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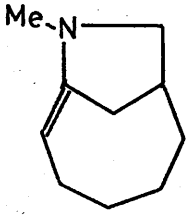

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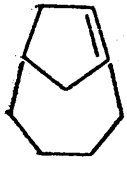

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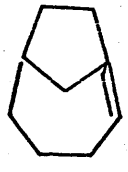


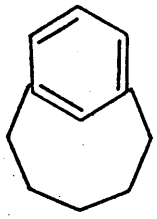
(4)

larger ring, was less strained than (3).

Further evidence comes from the work of Ferris and Miller, who found[17] that the keto acid (15) was somewhat more resistant to decarboxylation than was its isomer (14). This suggests that the olefin (8) is more strained than (7); once again, the placing of the double bond wholly within the larger ring (in this case six-membered rather than five-membered) seems to lead to lower total energy.

The acceptance of this as a general rule is militated against by the findings of H. Newman and T.L. Fields, who studied the cyclisation of compounds such as (85) under apparently equilibrating conditions. They found[52] that (85) cyclised to give the salt (86), rather than the enamine (87). These results are, however, open to more than one interpretation. A recent communication, of which J.R. Wiseman is a co-author, reports[53] that photoelectron spectroscopy, used as a technique for examining trans-cycloalkenes, failed to discriminate, in terms of strain energy, between (3) and (4).

Very little research has been carried out to determine the relationship, with respect to strain and molecular deformation, between "anti-Bredt" compounds and bridged aromatic systems. Many such systems are known[54], with a wide variety of structures and substituents, but in the majority it is difficult to apply Bredt's Rule in any meaningful sense. Some cyclophanes, however, do bear



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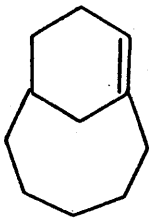

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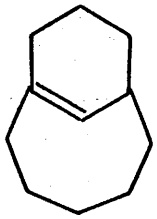

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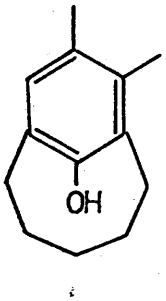

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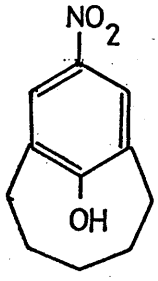

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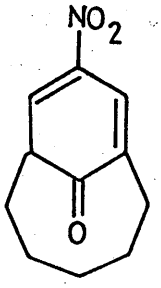
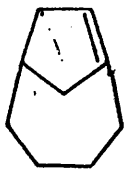


(93)

an obvious resemblance to simpler "anti-Bredt" structures. Bicyclo[5,3,1]undeca-1,7,8-triene, or [5]-metacyclophane (88), can perhaps be regarded as a resonance-stabilised combination of the olefins (89) and (90), derivatives of which have been prepared[23] in this Department. The [5]-metacyclophane system is represented among known compounds only by the phenol (91), which was synthesised[55] by Prelog before 1950 in his classical work on Bredt's Rule. Prelog also prepared the nitrophenol (92), but found[56] that it existed in the tautomeric form (93). Aromatisation involves, on the one hand, an increase in strain due to more exacting steric requirements, and on the other a degree of stabilisation due to resonance. Apparently the nature of the substituents controls the position of the tautomeric equilibrium.

Thus, at the time of commencement of this work, there presented themselves several aspects of the chemistry of bridged bicyclic compounds, into which research appeared necessary and promised fruitful results. In planning the work described in this thesis, three principal aims were adopted.

I. To cast more light on J.R. Wiseman's rationalisation of Bredt's Rule, and in particular to seek further examples of "anti-Bredt" compounds related, according to Wiseman's hypothesis, to <u>trans</u>-cyclohexene.



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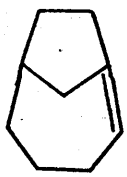

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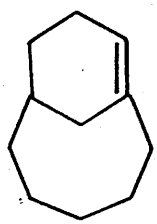

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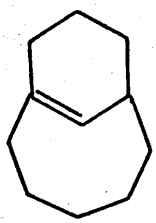

(90)

II. To investigate the factors governing the relative strain existing between isomeric olefin pairs of the general type (3) and (4), where Wiseman's hypothesis fails to discriminate.

III. To study the [5]-metacyclophane system, with particular regard to the way in which the strain in the parent compound and its derivatives is accommodated; and to compare the properties of [5]-metacyclophane with those of derivatives of the bicycloundecenes (89) and (90).

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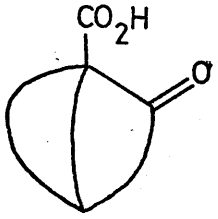
DISCUSSION

PART I

INVESTIGATIONS IN THE BICYCLO[2,2,2]OCTANE SYSTEM



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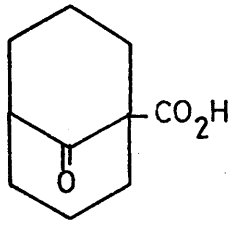

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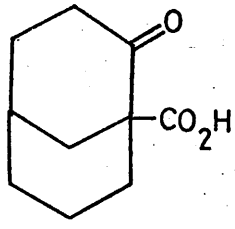

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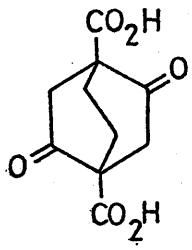
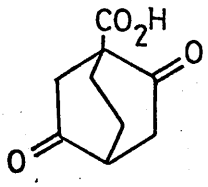


(4)

The decarboxylation of bicyclic β-keto acids of the general type (1) has often been used as a probe into the scope of Bredt's Rule. The Westheimer mechanism[1], producing in such cases a bridgehead enol intermediate, is qualitatively supported by the available data, and the reluctance of these compounds to undergo decarboxylation is well documented.

F.S. Fawcett, in his review in 1950, pointed out[2] two anomalies in the findings up to that date. The first of these was that while bicyclo[3,3,1]nonane derivatives of the form (2) were in all cases completely resistant to decarboxylation, those of the form (3) would undergo loss of carbon dioxide relatively easily. Fawcett suggested correctly that the stability of bridgehead double bonds in this system was dependent upon whether they were contained in the "[1]-branch" or a "[3]-branch",but concluded that with the available information it did not seem profitable to try to define the Rule in such detail.

The other anomaly was more puzzling. In 1939 P.C. Guha had reported[3] that bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid (4) was stable to decarboxylation when its diethyl ester was (a) heated to 200° with dilute hydrochloric acid in an autoclave or (b) refluxed with 50% sulphuric acid. Loss of one mole of carbon dioxide did, however, occur when the free diacid (4) was heated to 270°-280° under reduced pressure, giving an unspecified yield of a monocarboxylic acid, $C_9H_{10}O_4$, m.p. 216° - 217°. Guha



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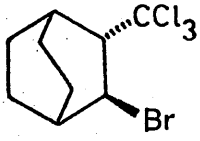
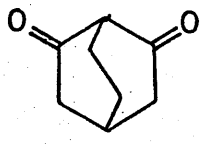


(6)



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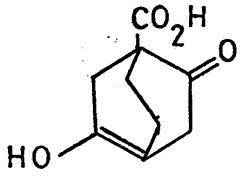
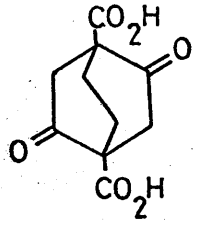


(8)



(4)

assumed it to be the product of straightforward mono-decarboxylation, namely bicyclo[2,2,2]octane-2,5-dione-1-carboxylic acid (5).

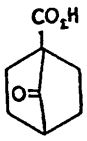
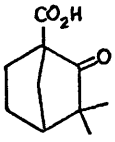
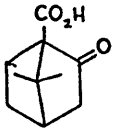
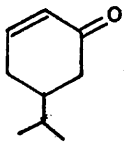
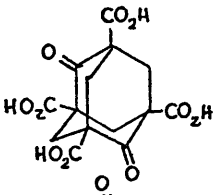
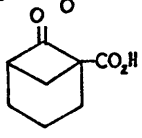
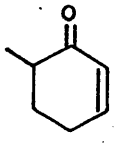
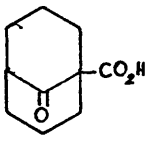
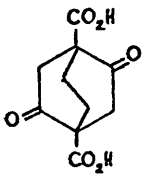
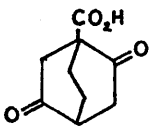
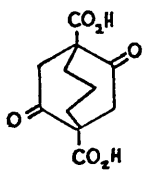
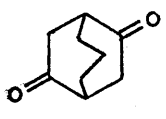
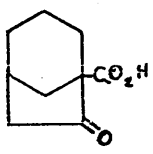
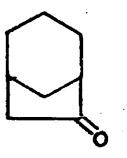
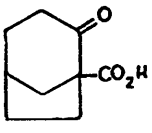
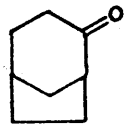
The apparent production of a bridgehead double bond in the bicyclo[2,2,2]octane system was in sharp disagreement with both Bredt's Rule and the other available data. All other attempts to detect "anti-Bredt" reactive intermediates in this system have met with failure. For example, the 2-bromo-3-trichloromethylbicyclo[2,2,2]octane (6) fails[4] to eliminate HBr, and in bicyclo[2,2,2]octane-2,6-dione (7) no exchange of the bridgehead proton (via the enol) can be detected[5]. Fawcett, in his rationalisation of Bredt's rule in terms of an "S-number", came to the conclusion that reactive intermediates with S equal to 7 were the smallest "anti-Bredt" olefins possible.

Guha's example apparently involves the intermediate enol (8), for which S = 6. Fawcett's comment was "further work is needed to determine the applicability of the Rule in such cases."

J.P. Ferris and N.C. Miller considered[6] Guha's acid (4) in formulating their ideas about the mechanism of decarboxylation, but dismissed it as an unsuitable example for their purposes.

In the light of the Wiseman hypothesis[7,8] the enol (8) can be seen to be a bridged trans-cyclohexene. In a survey of known decarboxylations (see table) this example is unique. Other compounds which would produce trans-

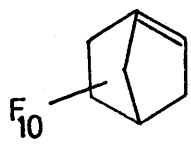
DECARBOXYLATION OF BICYCLIC β-KETO ACIDS

Acid	Temperature	Product	"enol ring" size	Note	Ref.
	not at 500°		5	1	9
	not at 310°		6	2	10
	above 315°		6	2	11
	not at 346°		6	3	12
	350°		6	4	13
	not at 240°		6	5	14
	280°		6	4	3
	240°		7	6	15
	320°		7	4	16
	260°		7	4	16

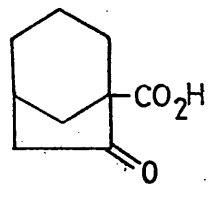
NOTES ON DATA IN TABLE

1. Sublimes at 500° with charring.
2. Distils at 310° at atmospheric pressure.
3. Melts without decomposition at 346°.
4. On heating alone.
5. On heating alone or in quinoline.
6. On heating in quinoline.

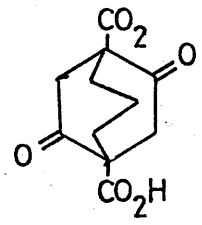
(Data taken in part from ref. 8)



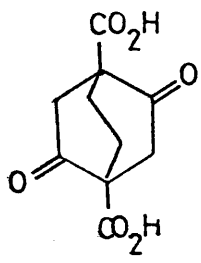
(9)



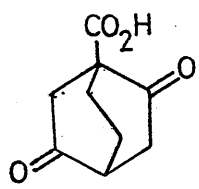
(10)



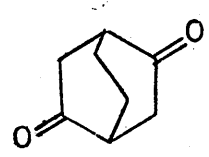
(11)



(4)



(5)



(12)

cyclohexenes on decarboxylation either rearrange in preference or fail to react at all. Only Guha's acid appears to undergo straightforward decarboxylation.

We considered the reaction worthy of further investigation, on the following threefold basis.

1. It is the only recorded case of decarboxylation without rearrangement apparently involving a trans-cyclohexene intermediate. At the time of commencement of our work "perfluoronorbornene" (9) was the only example of a trans-cyclohexene-type "anti-Bredt" compound.[17]

2. The reaction occurs at an anomalously low temperature. Compare (10) which requires a temperature of 320° to effect decarboxylation.

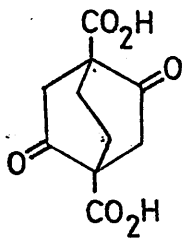
3. Only one mole of CO_2 is lost. Compare (11) in the table.

We considered three possibilities.

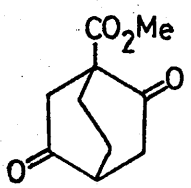
1. The decarboxylation of (4) occurred with rearrangement, and Guha's proposed structure for the product was wrong.

2. The decarboxylation occurred to give both (5) and (12), though only (5) was detected.

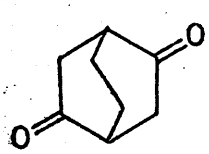
3. The decarboxylation occurred to give one product of the



(4)



(13)



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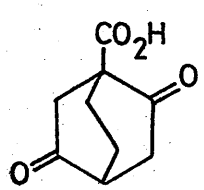


(5)

structure assigned to it by Guha.

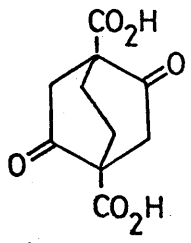
There were ample grounds for speculation; firstly the structure assignment was based on a roughly correct elemental analysis before the days of spectroscopic techniques; and secondly there has been some precedent for suspicion of inaccuracy in Guha's publications. A synthesis of thujane described[18] by him in 1937 was repeated[19] by W.G. Dauben in 1958, and several structural assignments were shown to be in error.

The reaction was repeated with some difficulty by a colleague (R. Taylor) and is described in detail in his Ph.D. dissertation.[20] A brief outline will be useful.

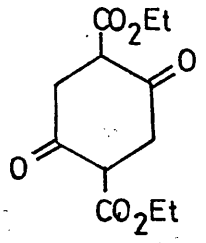
Pyrolysis of the diacid (4) gave a semi-crystalline yellow distillate composed of two identifiable compounds, one of which was the starting material. The other was an acid of m.p. 216° whose methyl ester showed the spectroscopic properties expected for (13).

Taylor also prepared a sample of the dione (12) and compared this with the very small neutral fraction of the pyrolysate. Searching g.l.c. examination revealed no trace of (12) resulting from decarboxylation of (4).

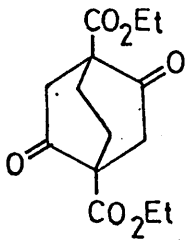
We then set about synthesising a sample of the dione-monoacid (5) for comparison purposes. The most practicable route appeared to be some sort of controlled degradation of the diacid (4), and we regarded the Hunsdiecker reaction as the most likely method for removal of one carboxyl



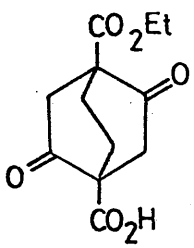
(4)



(14)



(15)



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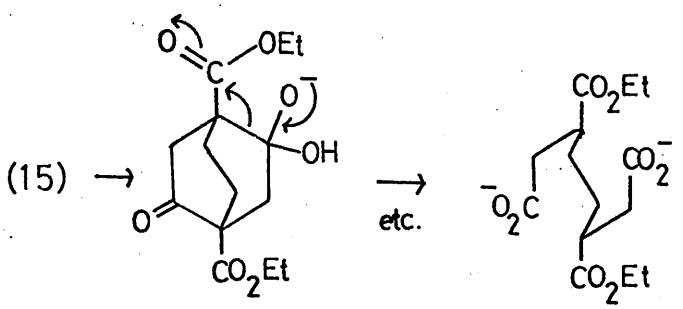
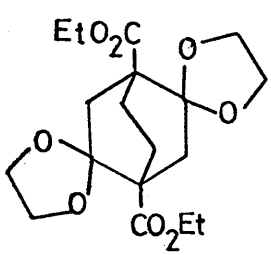
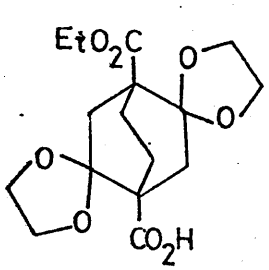


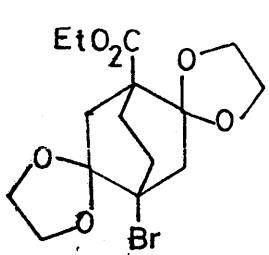
Fig. 1



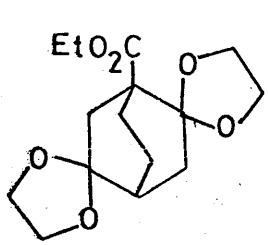
(17)



(18)



(19)



(20)

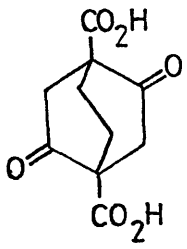
group.

Diacid (4) is prepared from diethyl succinyl succinate (14) via the diester (15) which is hydrolysed in acid[3]. If we could partially hydrolyse (15), to give the half-acid ester (16), we would have effected the necessary distinction between the identical carboxyls of (15). Clearly the best method of hydrolysis would be using one equivalent of base. Guha himself, however, had demonstrated[3] the tendency of the ester (15) to undergo base-catalysed cleavage of the α-β bond (see fig. 1).

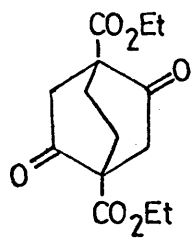
It was therefore necessary to protect the β-keto ester function, and to this end the diester (15) was converted to its bis-acetal (17) with ethylene glycol. Hydrolysis using one equivalent of potassium hydroxide in ethanol gave as the acidic portion of the product a white crystalline solid which after recrystallisation showed the properties expected for the half-acid ester (18).

The Hunsdiecker reaction was carried out by the method of M.J.S. Dewar[21] using red mercuric oxide and the free carboxylic acid in 1,2-dibromoethane, and gave after chromatography a moderate yield of the crystalline bis-acetal bromo ester (19).

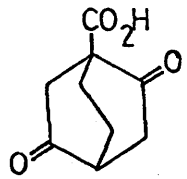
Hydrogenolysis of this compound, using Raney nickel as catalyst and ethanol as solvent, proceeded smoothly and in high yield to give a clear oil having similar infra-red absorption, but different chromatographic properties, to the starting material. It is assumed to be the bis-acetal ester (20).


CO2H
O
O
CO2H

(4)


CO2Et
O
O
CO2Et

(15)


CO2H
O
O

(5)

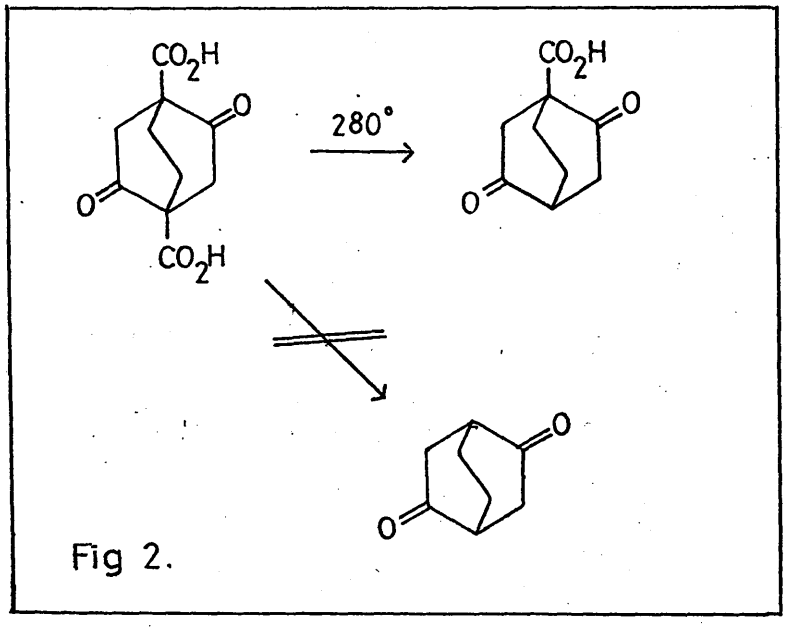
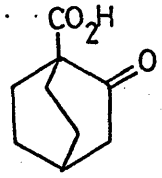

CO2H
O
O
CO2H
280°
CO2H
O
O
O
O

Fig 2.


CO2H
O

(21)

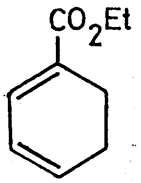
This product was not further characterised, but was hydrolysed directly by overnight reflux in acid solution. This gave a crystalline product, identical (melting point/ mixed melting point) to the material obtained by pyrolysis of the diacid (4).

Both samples were treated with diazomethane and the resulting methyl esters compared by i.r., n.m.r., mass spectrometry, and g.l.c. They were identical in all respects.

Since the foregoing interconversion of (15) to (5) involved no stage at which molecular rearrangement could take place, Guha's report was shown to be correct. Bicyclo-[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid undergoes thermal monodecarboxylation, producing up to 50% of bicyclo-[2,2,2]octane-2,5-dione-1-carboxylic acid as the sole identifiable product, and in particular no trace of bicyclo-[2,2,2]octane-2,5-dione. (fig. 2)

As the next step in elucidating the mechanism of the reaction we decided that examination of the properties of the "parent" β-keto acid, bicyclo[2,2,2]octan-2-one-1-carboxylic acid (21), would be useful. A search of the literature revealed that this was not a known compound, and synthetic approaches were considered.

The Diels-Alder reaction seemed the most attractive proposition for the construction of the bicyclooctane skeleton. Addition of a suitable dienophile to ethyl cyclo-



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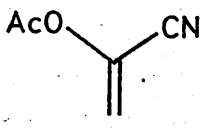

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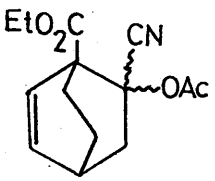

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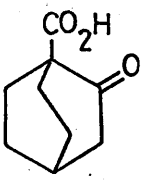
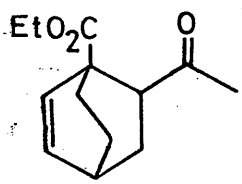


(21)



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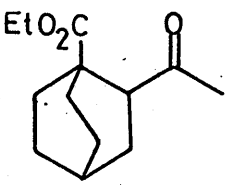

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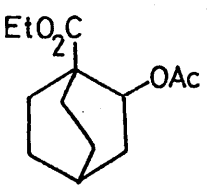


(27)

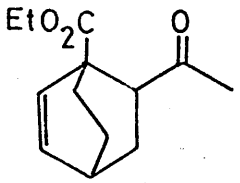
hexa-1,3-diene-1-carboxylate (22) would give the ring system substituted at one of the bridgeheads. At least one Diels - Alder reaction of this diene has been shown[22] to give mixtures of structural isomers, differing in the orientation of addition, but consisting predominantly of "head - to - head" isomers.

Addition of 1-acetoxyacrylonitrile (23) to the diene (22) might therefore be expected to produce predominantly (24). This would be easily converted to the desired acid (21) by hydrogenation and hydrolysis.

The reaction of (23) and (22), however, gave a complex mixture from which four components could be separated by thin layer chromatography. None showed infra-red absorption corresponding to the nitrile group, and accordingly this approach was dropped.

The next candidate as dienophile was methyl vinyl ketone. This would give the acetyl-substituted bicyclo-octene (25) which could be hydrogenated to the saturated compound (26). Baeyer-Villiger oxidation of this would be expected to take place with migration of the secondary carbon (i.e. the bicyclic system) to produce the acetate (27). Conversion of this compound to the desired acid (21) is fairly obvious.

In practice the synthesis was not quite so straightforward. The Diels - Alder reaction, using neat reagents in a sealed tube, gave a clean mixture of products on thin layer chromatography. Distillation of the product yielded



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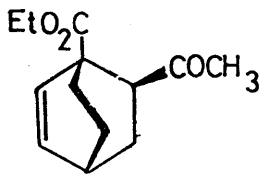

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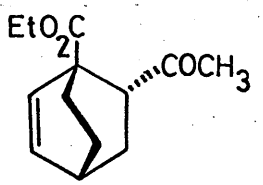

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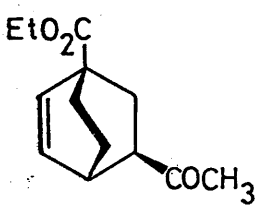

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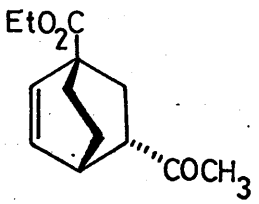
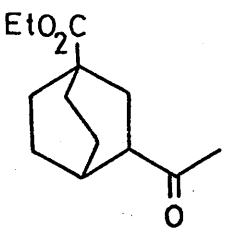


(31)



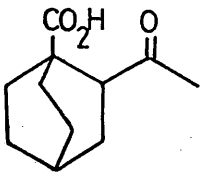
(32)

a clear colourless liquid which on examination by g.l.c. appeared to contain four compounds, in the approximate ratio 1 : 10 : 1 : 2 (in order of increasing retention time). The infrared spectrum of this material showed two carbonyl peaks in the positions expected for those in the keto ester (25). The n.m.r. spectrum showed a singlet at 7.99τ and the triplet and quartet typical of an ethyl ester. However, slight shoulders at about 1/3 peak height appeared on the downfield side of these signals.

From these data we concluded that there had been formed a mixture of all four possible isomers (28) - (31). If this were the case, hydrogenation of the double bond would remove the exo - endo distinction and give a mixture of only two compounds.

Hydrogenation over palladium on carbon gave in almost quantitative yield a mixture which on g.l.c. appeared as two peaks in the ratio 4 : 1 (in order of increasing retention time). N.m.r. showed a similar pattern to that produced by the starting material, minus the olefinic protons and with the bridgehead proton (no longer allylic) shifted upfield. The same shoulders as before appeared on the signals.

One obvious question presented itself; which isomer, (26) or (32), was the major one? Methods of separating the major component out of the mixture were sought. Chromatography was ineffective, as was fractional distillation. We decided to hydrolyse the mixture, to give the keto acids



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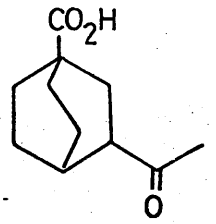

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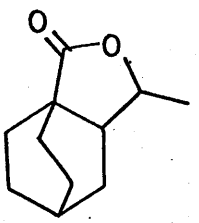

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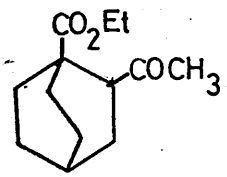

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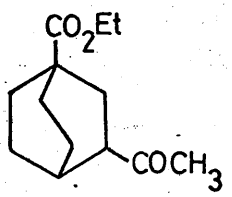

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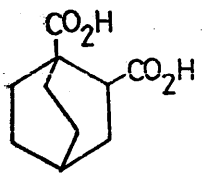

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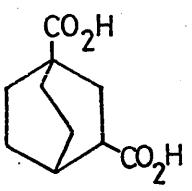


(37)

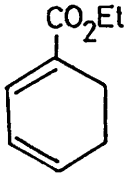
(33) and (34), and to investigate the possibilities of fractional crystallisation. Basic hydrolysis gave a crystalline product whose n.m.r. spectrum showed a singlet at 7.87τ with a shoulder on its downfield side.

Crystallisation of this material from ethanol gave a first crop of sharp-melting crystals in 55% yield. Evaporation of the mother liquors and fractional crystallisation from benzene/petroleum ether gave two more, smaller, batches of crystals.

The first and second fractions showed clean singlets at 7.87τ in the n.m.r. Treatment with ethereal diazomethane and examination by g.l.c. showed that the first and largest fraction was greater than 95% pure and corresponded to the major component of the mixture. The second and third fractions contained both components.

It was now necessary to determine which compound was which. Attempts to form the γ-lactone (35) by borohydride reduction of the keto esters (26) and (32) gave no satisfactory results, and we therefore considered the possibility of relating our product to a known compound.

Bicyclo[2,2,2]octane-1,2-dicarboxylic acid (36) and bicyclo[2,2,2]octane-1,3-dicarboxylic acid (37) have been prepared[22] as a 4 : 1 mixture by J. Kazan and F.D. Greene, and these workers were able to assign each compound its structure quite unequivocally. If it were possible to effect degradation of the keto acids (33) and (34) by the iodoform reaction there would be produced (36) and (37) which could be compared with the mixture obtained by the



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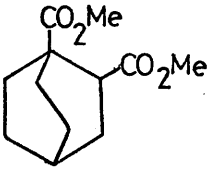

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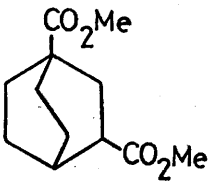

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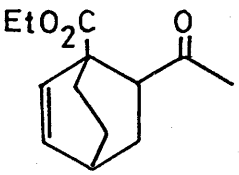

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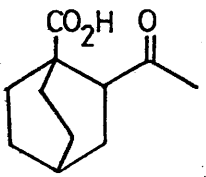

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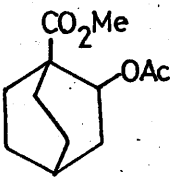

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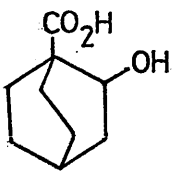


(41)

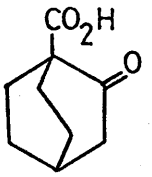
method of Kazan and Greene.

Diels - Alder reaction of the diene (22) and ethyl acrylate, hydrogenation, hydrolysis and esterification with diazomethane produced a 4 : 1 mixture (by g.l.c.) of the dimethyl esters (38) and (39). Iodoform reaction of our crystalline keto acid, and of the mother liquor for comparison, followed by methylation and examination by g.l.c. revealed that fraction 1 corresponded to the 1,2-disubstituted compound (38), while the mother liquor contained a mixture of 1,2- and 1,3-disubstituted material.

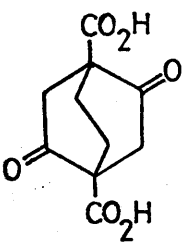
We thus showed that Diels - Alder reaction of the diene (22) with methyl vinyl ketone produces a 4 : 1 preponderance of the "head - to - head" oriented isomer (25).

In order that the Baeyer - Villiger oxidation step could be monitored directly by t.l.c., the acid (33) was converted to its methyl ester. Treatment with buffered trifluoroperacetic acid gave complete conversion (on analysis by t.l.c.) to the acetate (40), which was then hydrolysed to the hydroxy acid (41). As additional proof of structure, the solution infra-red spectrum of the methyl ester of this compound exhibited a broad absorption between 3650 and 3350 cm^{-1}, and carbonyl peaks at 1735 and 1712 cm^{-1}, indicating weak intramolecular hydrogen bonding between the hydroxyl group and the ester carbonyl. Such bonding would not be possible in the 3-hydroxy isomer.

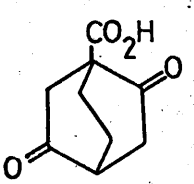
Chromic acid oxidation of the hydroxy acid (41) gave



(21)



(4)



(5)

the desired bicyclo[2,2,2]octan-2-one-1-carboxylic acid (21).

We were now in possession of samples of three bicyclo-octane β-keto acids, (4), (5) and (21), and set about deriving conditions for parallel experiments on decarboxylation.

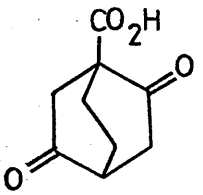
Pyrolysis of the diacid (4) had been carried out under two sets of conditions.

(A). The diacid was placed in the bottom of a sublimation tube, which was heated in a block under low vacuum. The products distilled up to the cold part of the tube.

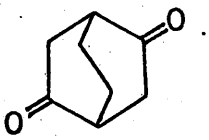
(B). The diacid, dissolved in tetrahydrofuran, was dropped through a vertically mounted hot tube in a nitrogen flow at atmospheric pressure. The products were collected in a cold trap.

Taylor had obtained[20] decarboxylation of (4) using both methods, but we found that the use of the latter resulted in a great deal of charring, even with degassed solvents and rigorous exclusion of oxygen. Results from the first method, however, were easily reproducible, and yields were acceptable.

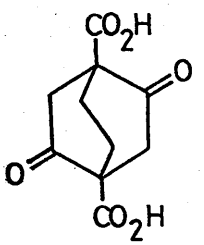
However, application of method (A) to the keto acids (5) and (21) resulted merely in sublimation of the acids at temperatures below 280°. Method (B) was more satisfactory, though charring again occurred with (5); (21) was



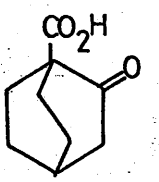
(5)



(12)



(4)



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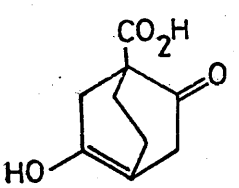


(8)

recovered at temperatures up to 430°, and no neutral products were observed. The products of pyrolysis of (5) contained no trace of the dione (12).

Since neither method was particularly suitable for all three acids, we investigated other procedures. Our requirement was to heat all three to the same temperature for the same length of time, to recover all the products and examine them.

Sealed tubes seemed to be one likely answer. Solutions of the three acids in tetrahydrofuran were placed in Carius tubes which were flushed with nitrogen, sealed and heated to 315° for 30 minutes.

Gross recovery of material was better than 95% in all cases. The product from the dione-diacid (4) was a black tar in which a very small yield of the dione-monoacid (5) could be found. It was significant, however, that none of the starting material survived. In the parallel experiment on the dione-monoacid (5), it was recovered in 37% yield as the only identifiable product, the remainder of the material being again tarry and polymeric.

Under the same conditions the "parent" keto acid (21) was recovered fairly cleanly in 84% yield, with no neutral products; and no trace of the dione (12) was found among the products of pyrolysis of either (4) or (5).

These data we regard as conclusive evidence that conditions which bring about monodecarboxylation of bicyclo-[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid (5) have no

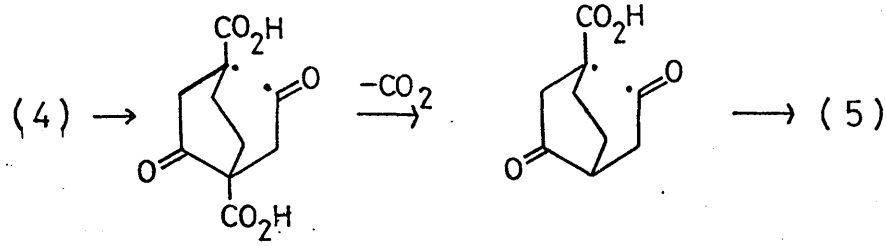


Fig. 3

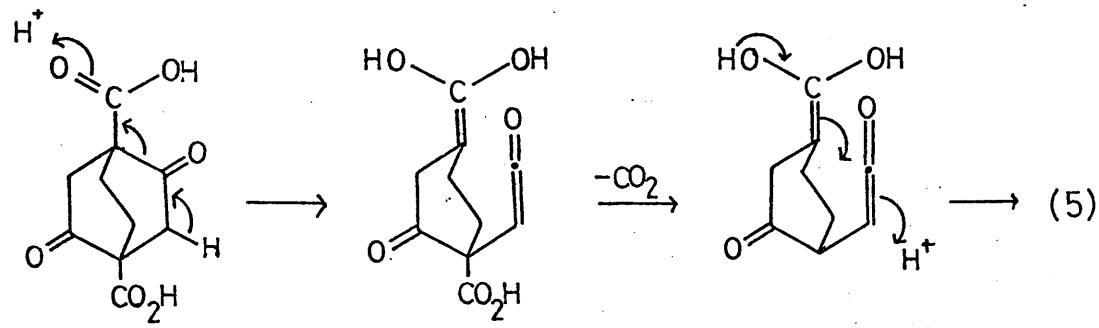


Fig. 4

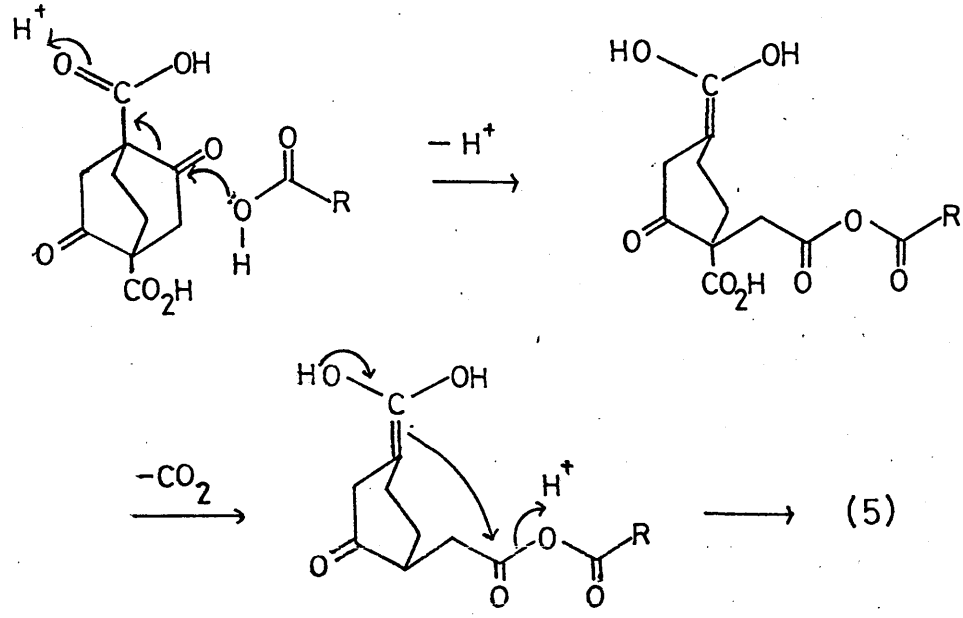


Fig. 5

effect on either bicyclo[2,2,2]octane-2,5-dione-1-carboxylic acid (5) or bicyclo[2,2,2]octan-2-one-1-carboxylic acid (21); and we have evidence that the latter compound is stable, at least for a short time, at 430° C. It follows that decarboxylation, at temperatures below 300°, of bridgehead β-keto acids in the bicyclo[2,2,2]octane system, is not a general phenomenon.

Why does (4) decarboxylate once, and only once? Three types of mechanism can be envisaged.

(a) The straightforward Westheimer mechanism, with the bicyclooctane skeleton remaining intact throughout and the bridgehead enol (8) as an intermediate. This pathway is unlikely to be followed since there appears to be no good reason on this basis why (5) and (21) should not likewise decarboxylate.

(b) Initial cleavage of one bond to open the bicyclic skeleton. The weakest bonds in the ring system would be expected to be those between the bridgeheads and the carbonyl carbons, and if one of these were to break, there would be produced a monocyclic β-keto acid. This species would readily undergo decarboxylation, and reversal of the original cleavage process would yield the observed product (5).

Such a process could occur in several ways, including (i) simple homolytic cleavage of the α-β bond,

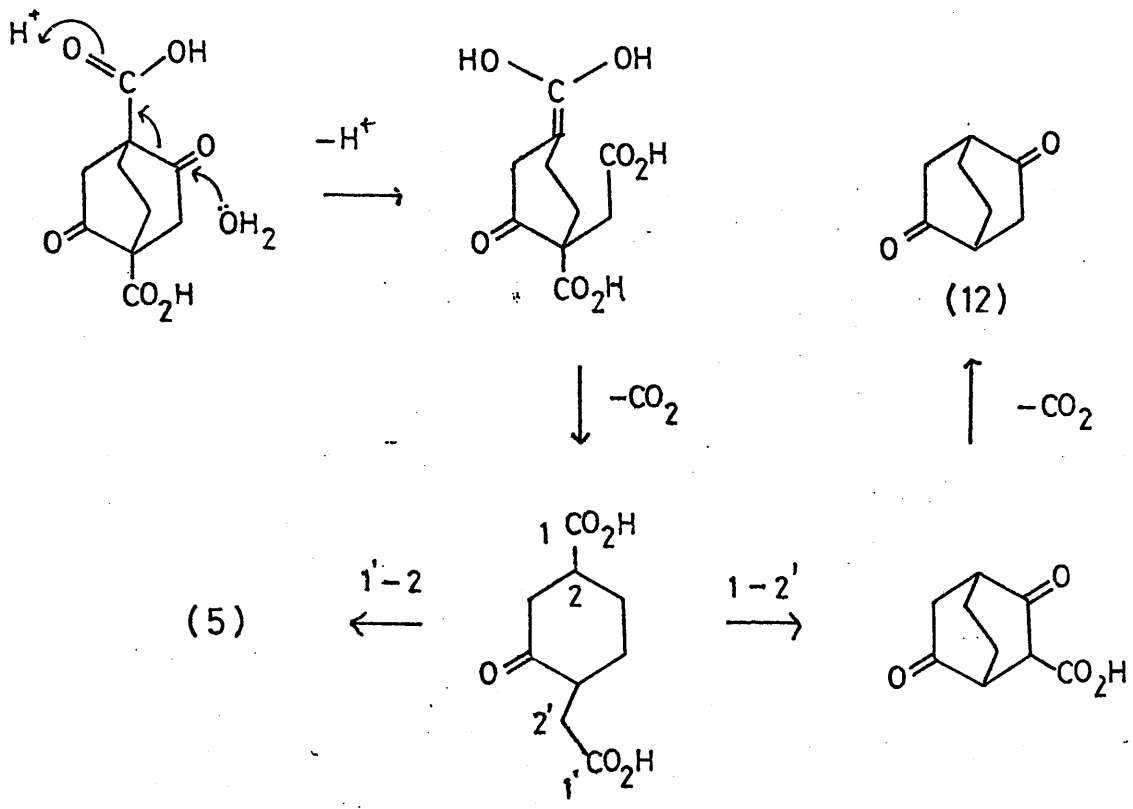

H+
O
OH
C
O
OH2
CO2H
-H+
HO
OH
C
CO2H
CO2H
O
O
(12)
-CO2
-CO2
1 CO2H
2
2'
1' CO2H
1'-2
1-2'
(5)
O
CO2H

Fig. 6

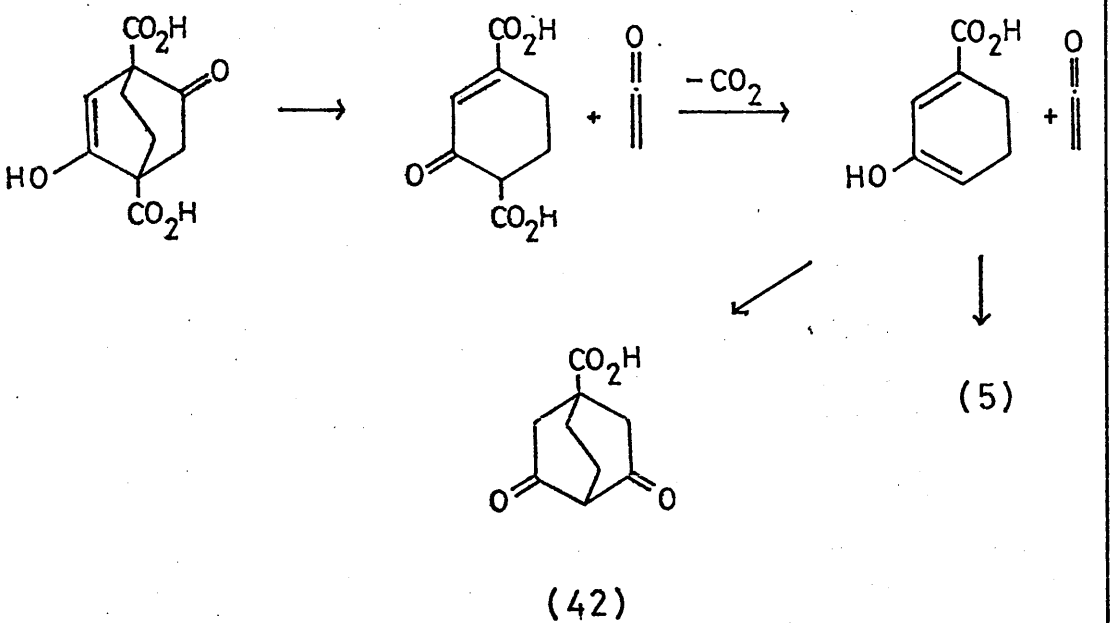
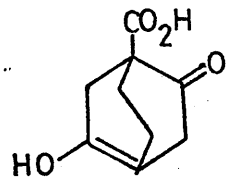

CO2H
O
HO
CO2H
CO2H
O
CO2H
-CO2
CO2H
O
HO
(5)
CO2H
O
O
(42)

Fig. 7

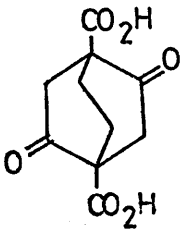
giving a diradical (fig. 3); (ii) loss of a proton α to one of the carbonyl groups, with cleavage to form a ketene (fig. 4); or (iii) attack by a second molecule of acid on one of the carbonyl groups, with cleavage to form an anhydride (fig. 5). One variant is, however, disallowed. Attack of water in an analogous fashion (fig. 6) might produce a diacid which has two modes of cyclisation open to it. Perhaps one of these is favoured to the exclusion of the other, but it seems unlikely, and the failure to detect the dione (12) is significant.

(c) Initial cleavage of two bonds in a retro-Diels-Alder fashion, followed by loss of carbon dioxide from the "diene" fragment (fig. 7). This we feel is improbable, for two reasons; (i) the extremely reactive and volatile ketene has to remain nearby for long enough to recombine after decarboxylation, and (ii) recombination must take place wholly in the correct orientation. While such exclusively mono-oriented cycloadditions are not by any means unknown, our own experience, and that of Kazan and Greene[22], suggests that it is unlikely with a carboxy-substituted diene. It is noteworthy that the γ-keto acid (42) is not observed among the products of the reaction.

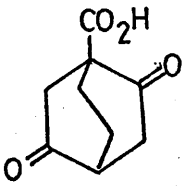
To sum up, the evidence at this point suggested that



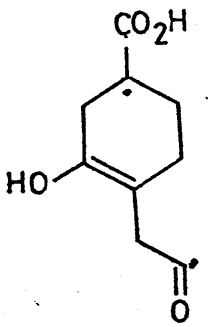
(8)



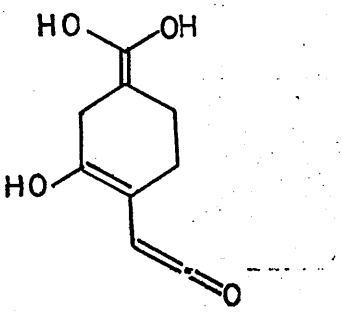
(4)



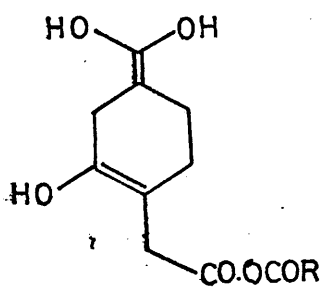
(5)



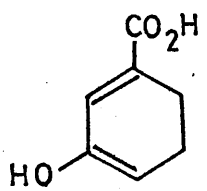
(43)



(44)



(45)



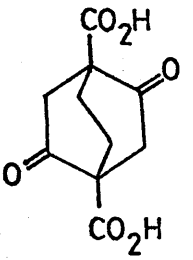
(46)

a one-bond-cleavage mechanism (one of the variants under (b), above) was the most probable, purely on account of the improbability of the alternatives. However, it was not possible expressly to rule out the intermediacy of the "anti-Bredt" enol (8). Since our aim was to determine whether or not this species was produced in the reaction, we sought means of distinguishing mechanism (a) from the others.

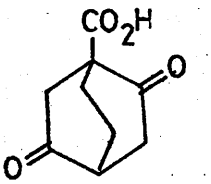
One convenient method became clear on consideration of the symmetry properties of the molecules of the diacid (4) and the monoacid (5). Neither is superimposable on its mirror image. It would therefore be possible to carry out the decarboxylation using optically active diacid (4), and to compare the optical purity of the product with that of the starting material.

Decarboxylation of resolved material by the straightforward Westheimer route (mechanism (a)) involves no stage at which total or even partial racemisation can take place. Indeed, since interconversion of the enantiomers can only occur (formally) by inversion at both bridgeheads, it is clear that so long as the bicyclic skeleton remains integral, optical purity will be preserved in full.

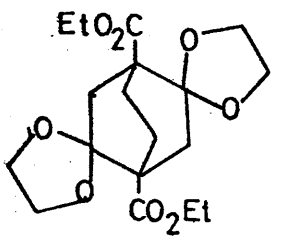
On the other hand, any mechanism involving bond cleavage in the skeleton carries with it the possibility of racemisation. The alternative processes discussed under (b) and (c) above each incorporate intermediates ((43)-(46)) which have no asymmetric centres (inversion of radical



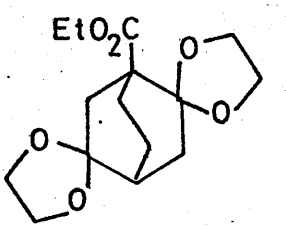
(4)



(5)



(17)



(20)

centres such as that in (43) being a rapid process).

It follows that reaction by these mechanisms, or by any other which involves cleavage of the skeleton to produce an achiral intermediate, will cause complete racemisation.

We therefore decided to prepare a resolved sample of the diacid (4), to subject it to decarboxylation at 280° and to examine the optical activity of the product (5) or a derivative. To obtain a measure of the optical purity of the product, relative to that of the starting material, it would be necessary to prepare a sample of the monoacid (5) from resolved diacid (4) by a route which involved no possibility of racemisation. Fortunately the degradative sequence already described met this requirement. Base treatment is carried out on the protected β-keto ester (17), the Hunsdiecker and subsequent hydrogenolysis reactions are stereospecific, and acid hydrolysis of (20) is unlikely to bring about ring opening and re-closure.

The diacid (4) had been resolved by Guha[23] as part of his structure proof for this compound. In a very detailed experimental section he reported that five recrystallisations from water of the bis-brucine salt of (4) effected complete separation of the dextrorotatory enantiomer of the diacid.

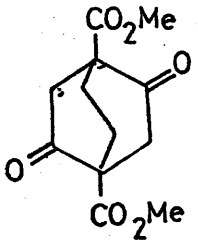
In following Guha's procedure, we found that the use of the recommended quantity of water in the initial salt-formation step resulted only in a good yield of recrystallised

brucine, and no salts were isolated. Several variations were tried, including rigorous purification of materials, and eventually a satisfactory method was devised. Portion-wise addition of an intimate mixture of diacid and brucine to 60% of the recommended quantity of boiling water, over a period of about an hour, followed by slow cooling, gave a reasonable yield of the salt; though it actually began crystallising out of the boiling solution before all the material had been added, and hot filtration was not possible. Despite the appalling aspect of this preparation, we found that a sizeable degree of resolution had been effected even at this stage.

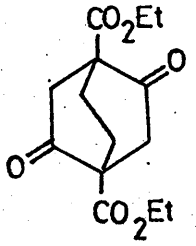
Two recrystallisations of the salt, in a much more orthodox manner, afforded material from which could be recovered the diacid (4) of rotation similar to that reported by Guha[23].

The diacid, thus resolved, was pyrolysed using method (A) (sublimation tube, low vacuum), which we had found to be the most practicable for preparative purposes. The product (5) was isolated and purified as its methyl ester (13). Solutions of this material in a variety of solvents failed to rotate the plane of polarised light to an observable extent.

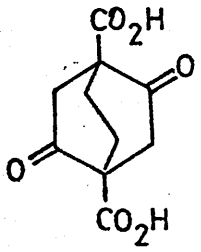
A resolved sample of this compound was then prepared as outlined above, with one minor modification in the route. It was naturally desirable to maximise the yield of (13), and since the diacid (4) could be converted virtually


CO2Me
O
O
CO2Me

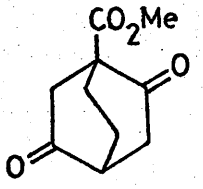
(47)


CO2Et
O
O
CO2Et

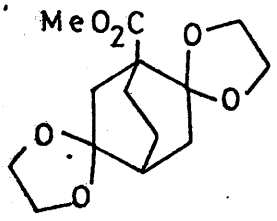
(15)


CO2H
O
O
CO2H

(4)


CO2Me
O
O

(13)


MeO2C
O
O
O
O

(48)

quantitatively to the dimethyl ester (47) by treatment with diazomethane, we decided to proceed from this compound rather than from the diethyl ester (15). A "dummy run" using the (relatively plentiful) racemic diacid (4) showed that all reactions could be carried out in yields at least equivalent to those in the ethyl ester series.

On obtaining by this means a sample of optically active ester (13) we found that it, too, failed to show an observable rotation. We concluded that compound (13) had a specific rotation so low that we could not measure it. (In fact, with the quantities of material available to us, a specific rotation of less than $\pm 4^{o}$ would not have been measurable in our apparatus.) Our previous observation, that the product of thermal decarboxylation of active diacid (4) was "inactive", was thus rendered meaningless.

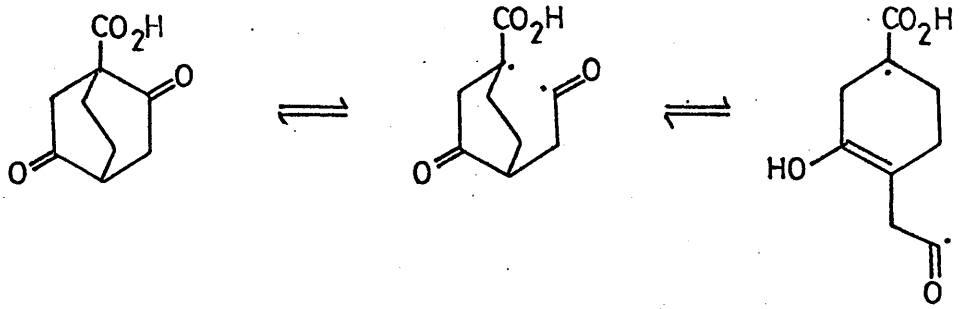
However, the ester (13) absorbs weakly in the ultraviolet (λ_{max}^{EtOH} = 290 nm, ϵ = 150; 215 nm, ϵ = 600), and we hoped that observable circular dichroism would be associated with this absorption. Samples of the ester (13), prepared from optically active diacid (4), by (a) thermal decarboxylation and (b) stepwise chemical degradation, as above, were rigorously purified and examined with a view to detection of this phenomenon. To our satisfaction, sample (b) gave rise to a significant curve ($\Delta\epsilon$ = + 0.62 at 289 nm, - 0.58 at 214 nm), while sample (a) showed no circular dichroism whatsoever.

As a check that the final degradation step (the acid

hydrolysis of the bis-acetal ester (48)) did not cause any racemisation, a sample of the active diketo-monoacid (5) was heated in dilute acid for nine hours, then recovered, esterified and re-examined. The c.d. curve of its methyl ester was virtually unchanged ($\Delta\epsilon$ = + 0.68 at 290 nm, - 0.57 at 217 nm).

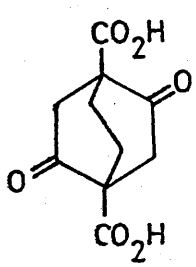
Bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid (4) thus decarboxylates with complete racemisation. This is strong evidence for the opening and re-closing of the bicyclic skeleton in the course of the reaction, and indeed only one possibility remains to be excluded.

It may be argued that we have not shown that racemisation occurs <u>during</u> the reaction; that it is possible that the product (5) is formed <u>via</u> the enol (8) and racemises afterwards. However, in making this suggestion, it is necessary to propose a mechanism for the racemisation of (5). For the reasons already given (see page 35), this mechanism must involve a ring-opened intermediate. Owing to the structural similarity of (4) and (5), it is difficult to conceive of any likely cleavage process in (5) which will not occur with equal facility in (4); that is to say that if (5) undergoes thermal racemisation, (4) will be subject, under the same conditions, to ring-opening to give a monocyclic β-keto acid. This will, in all probability, be the species which actually decarboxylates, thus avoiding the high energy intermediate (8). Conversely, if (4) undergoes ring-opening, it is likely that (5) (and indeed (21))

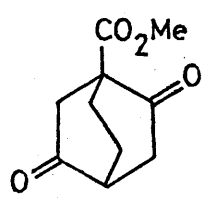


(5) (43)

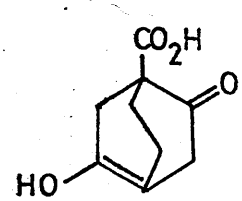
Fig. 8



(4)



(13)



(8)

will react similarly, and this leads to the possibility of racemisation of (5).

A sample of optically active dione-monoacid (5) was pyrolysed under the reaction conditions, with one slight modification. Since heating of (5) under low vacuum resulted only in sublimation of the acid at temperatures below 280°, vacuum was not applied until a temperature of 290° had been reached; this being the point by which most of the product had distilled out from the pyrolysis of the diacid (4).

Treatment of the product with diazomethane gave the ester (13). This sample showed a c.d. curve with $\Delta\epsilon = +0.44$ at 290nm and - 0.43 at 216 nm, representing approximately 28% racemisation.

This is only to be expected. Choosing mechanism (b) (i) (page 33) to illustrate the point, cleavage of (5) (fig. 8) would give a cyclohexanone which could racemise <u>via</u> its enol form. In the case of the diacid (4), decarboxylation provides a driving force for formation of the enol, but when the second carboxyl group is absent, enolisation would be expected to be a slower process. Hence partial, but not complete, racemisation occurs. The same considerations apply to the other alternative mechanisms outlined in category (b) on pages 33 - 34.

We therefore postulate;

(i) that monodecarboxylation of bicyclo[2,2,2]octane-2,5-

dione-1,4-dicarboxylic acid occurs with concomitant loss of optical activity;

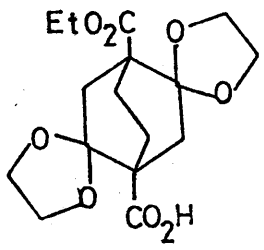
(ii) that initial cleavage of the bicyclic skeleton produces a monocyclic intermediate, this being the species which actually decarboxylates, presumably by the Westheimer mechanism; and

(iii) that it is not necessary to invoke the intermediacy of the strained enol (8) in the reaction.

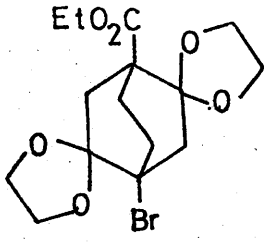
It is difficult to formulate an experiment to determine the mechanism of the reaction more precisely. The "radical" mechanism (fig. 3, facing p.33) might give rise to adducts with radical-trapping reagents, while loss of deuterium label from the 3- and 6-positions in the diacid (4) might point to the "ketene" mechanism (fig. 4).

Further investigations of this type would be difficult and might well prove futile. The conditions of the reaction and the acidic nature of the compounds involved, might render labelling experiments meaningless, and at the least they would be unlikely to give clear-cut results. Addition of other compounds (such as radical-trapping agents) could in itself cause a change of mechanism. It is even possible that more than one mechanism is operative.

Our conclusion, however, based on the above postulates, is that this reaction does not provide evidence for the existence of a bridgehead double bond in the bicyclo[2,2,2]-octane system.



(18)



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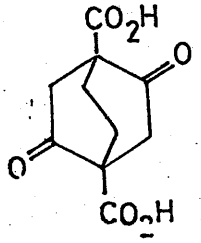
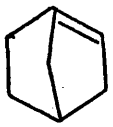


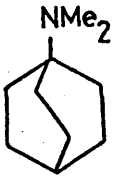
(4)

These results, and the conclusion drawn from them, were published in the form of a short communication[24]. Subsequently there appeared a paper by a French group, describing[25] the syntheses of several derivatives of the bicyclo[2,2,2]octane system, including the bis-acetal half acid ester (18) and the bis-acetal bromo ester (19). These compounds, and the others described, were prepared for a purpose completely unrelated to the theme of our work. The authors also report (without comment) the repetition of the decarboxylation of the diacid (4) "comme l'indique P.C. Guha". They did not, however, convert 1,4-disubstituted systems to 1-monosubstituted systems by any other means. They give almost no spectral data, but the melting point they report for (18) agrees to within 3^{o} with ours. The bromo compound (19) they obtained as a liquid.

(49)



(50)



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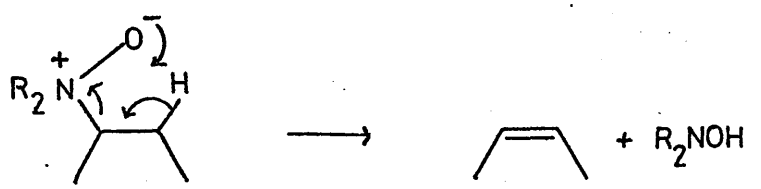
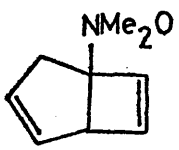


Fig. 9



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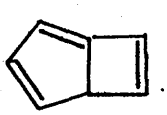

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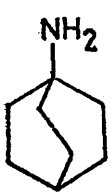

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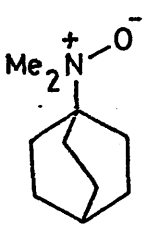


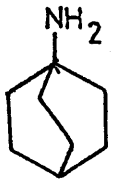
(55)

To complement the foregoing studies on decarboxylation, we decided that an approach to bicyclo[2,2,2]oct-1-ene (49) would be a worthwhile undertaking. Despite the attention paid to the bicyclo[3,2,1]octane, norbornane and adamantane systems, and the successes achieved, the olefin (49) has not been prepared, nor has any attempt been published. Examination of models suggests that the double bond in (49) would be distorted to a similar extent to that in 1-norbornene (50).

We decided to aim at N,N-dimethyl-1-aminobicyclo[2,2,2]-octane (51), and to attempt either Hoffmann or Cope elimination of the appropriate derivatives. The latter route seemed the more worthwhile for investigation, since it had not previously been used to prepare "anti-Bredt" olefins. Additionally, Wiseman's observation that the Hoffmann elimination fails in the bicyclo[3,2,1]octene case was published[26] while this project was in its early stages. We therefore planned a Cope elimination as the last step.

This reaction, the pyrolytic elimination of tertiary amine oxides, has been shown[27] to give olefins in good yield from a wide variety of starting materials (fig. 9). In particular, pyrolysis of the amine oxide (52) gave[28] the trans-cycloheptene (53).

The bridgehead primary amine (54) is known, as are its N,N-dimethyl derivative (51) and the amine oxide (55), all being important as antiviral agents, and unfortunately, as a result, most of the data on them are under patent[29,30].



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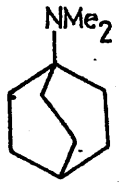

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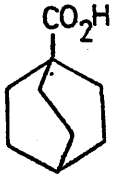
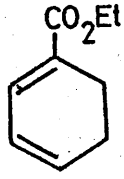


(56)



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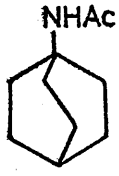


(57)

Brief abstracted methods for the preparation of (54) and the oxidation of (51) are given in Chemical Abstracts. C.A. Grob has also prepared[31] several related compounds, including the hydrochloride of the primary amine (54), but since the route was rather indirect we decided to use the method described in the patent abstract[29].

Bicyclo[2,2,2]octane-1-carboxylic acid (56) was prepared by the standard literature method[32], i.e. addition of maleic anhydride to the diene (22), followed by hydrogenation, hydrolysis of the anhydride moiety and removal of the resulting carboxyl groups with lead tetraacetate.

Attempted conversion of this material to the amine (54) by a Schmidt reaction (sodium azide/sulphuric acid)[29] proved unproductive in our hands, and an alternative was sought. The four-stage Curtius reaction used by Wiseman[8] for the preparation of bridgehead amines from the corresponding carboxylic acids was the obvious choice. Application of a similar procedure to the acid (56) resulted in an overall 53% yield of the primary amine (54). The ready reaction of this compound with atmospheric carbon dioxide prevented accurate analysis; however, Grob has described[31] the preparation of the N-acetyl derivative (57). Reaction of our amine with acetic anhydride gave crystals of melting point similar to that given by Grob for the amide (57).

Methylation of the amine by the Clark-Eschweiler method gave the tertiary amine (51), which was purified by distillation. Reaction of this material with hydrogen peroxide

in methanol gave the amine oxide (55) as a waxy solid, probably a hydrate. The same substance was also obtained by oxidation of (51) with m-chloroperbenzoic acid in chloroform, the immediate product being an oil which solidified on contact with the air.

Pyrolysis of the amine oxide was carried out at 430° under reduced pressure in a flow of helium. Yields were extremely low, but results were reproducible. T.l.c. examination of the product (ethyl acetate/petroleum ether, 1 : 9) showed :-

(a) some very polar material

(b) a component of R_f 0.2

(c) two components of $R_f \sim 0.8$

Isolation of the least polar fractions (c) by preparative t.l.c. gave only trace quantities. Mass spectral examination revealed that neither compound corresponded to the desired olefin (49) or a dimer. One of the compounds gave a molecular ion at m/e 273, while the other showed no peak identifiable as the parent. The latter showed no fragments of significant abundance at m/e 108 or 109 (bicyclooctane minus one or two mass units), and since the yield of these compounds was less than 0.5% they were not further investigated.

Gas-liquid chromatography of the crude product showed it to be a complex mixture of at least sixteen compounds in all, the major one (60 - 90% by g.l.c.) corresponding to fraction (b) above. This compound could be isolated, in

quantities of less than 1 mg, by preparative t.l.c. Co-injection on g.l.c. demonstrated that the tertiary amine (51) was not among the products, and that none of the peaks on the trace corresponded to the amine oxide (55).

Experiments were also carried out with a bleed of furan vapour into the tube, in the hope of detecting adducts of the bridgehead olefin, but results with furan were in fact very similar to those without.

We regarded combined gas chromatography/mass spectrometry to be the best, indeed the only possible, means of investigating the product. The results were interesting though disappointing. Mass spectra were recorded at eight points on the g.l.c. trace. Not surprisingly, certain peaks tended to recur, common instances being those at m/e 110, 109, 97, 96, 81, 79, 71, 70, 69, 67 and 55, some or all of which were of high abundance in most of the spectra. Comparison of these values with those commonly found for bicyclo[2,2,2]octane systems is interesting. The parent compound, bicyclo[2,2,2]octane, gives a mass spectrum[33] with significant peaks at m/e 110, 81, 79, 69, 68, 67 and 55. This strongly suggests that the integrity of the bicyclic skeleton has been preserved in the products recovered.

It was not possible to make structural assignments for all the products. However, a prominent component of the mixture (~10% by g.l.c.) showed a molecular ion at m/e 126, and we speculated that it might be the bridgehead alcohol (58). Co-injection on g.l.c. with an authentic sample and

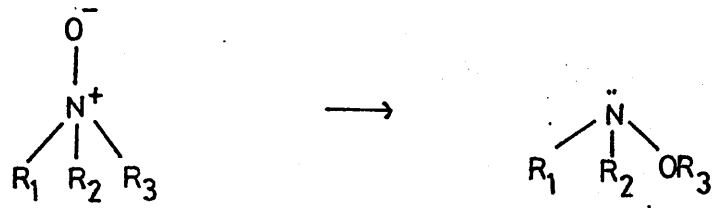
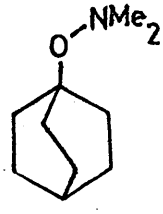


Fig.10



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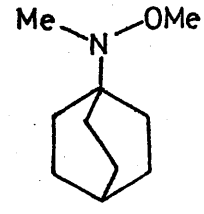

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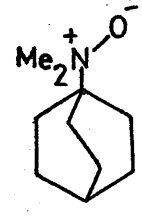
(49)



(55)

comparison of mass spectra indicated that this was indeed the case.

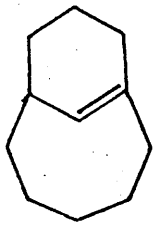
The major component of the product mixture (60 - 90% by g.l.c.) gave rise to a molecular ion at m/e 169, and fragments at 154 ($M^+ - CH_3$), 140 ($M^+ - C_2H_5$, cf. bicyclo-[2,2,2]octane) and 109 (bicyclooctyl). This led us to believe that instead of elimination, the Meisenheimer rearrangement[34] had taken place, to give rise to an O-alkyl hydroxylamine (fig. 10). Two such processes are possible, involving migration of (a) a methyl group, or (b) the bicyclic system. Methyl migration in this type of rearrangement is unusual, and perhaps the production of bicyclo[2,2,2]-octan-1-ol implies the intermediate formation of the N,N-dimethyl compound (59). Another, much lesser, component of the product mixture also showed a molecular ion at m/e 169, however, and it is possible that both migrations in fact occur, producing (60) as well as (59). It must be stressed that the product examined constituted a yield of less than 5% from the amine oxide.

In any case, as far as the production of bicyclo[2,2,2]-oct-1-ene (49) is concerned, the pyrolysis of the amine oxide (55) was totally unsuccessful. No products were obtained which corresponded to either the olefin (49) or a dimer.

DISCUSSION

PART II

APPROACHES TO THE BICYCLO[4,3,1]DECANE SYSTEM



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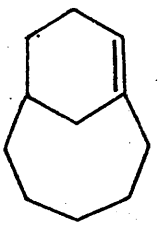

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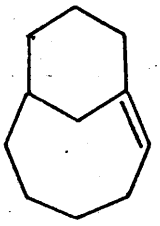

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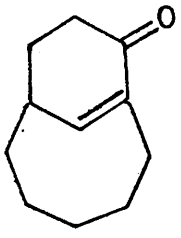

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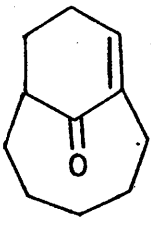

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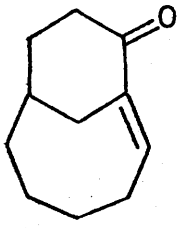


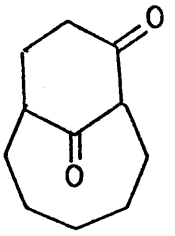
(66)

We next turned our attentions to the second of our aims as set out in the introduction.

For a given bicyclo[x,y,z] system containing a double bond with one terminus at a bridgehead position, what is the relationship between the strain in the system and the size of the "branch" in which the double bond lies? Is it true to say, as has been implied[35], that the bigger the "branch", the less strained the olefin?

Considering as an example the bicyclo[5,3,1]undecenes (61), (62) and (63), derivatives of the first two have been made[36] in this Department, and exhibit the comparative properties which one would expect by application of the Wiseman hypothesis. The "[1]-branch" olefin (61) is considered as a bridged trans-cyclooctene, while the "[3]-branch" isomer (62) can be regarded as a derivative of the much less strained trans-cyclodecene. The enone (64) was indeed found[36] to be considerably more reactive than its isomer (65).

But what of the "[5]-branch" compound (66)? So far it is unknown. In fact, in such bridged bicyclic compounds, where x>y>z, functionality at C-2 (i.e. in the largest bridge, next to the bridgehead) is rare. This is due, at least in part, to the commonly employed means of preparing these compounds. Almost all the bicyclo[5,3,1]undecanes and bicyclo[4,3,1]decanes in the literature (to cite but two systems as examples) have been made by bridging a pre-formed and suitably substituted cyclooctane or cycloheptane



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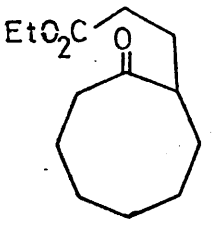

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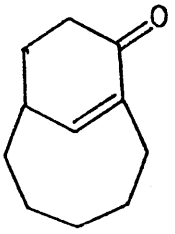

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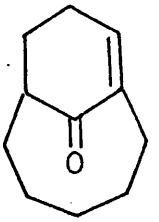

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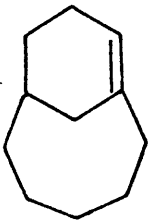

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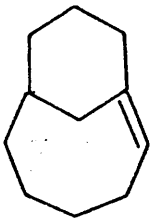

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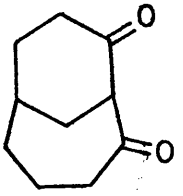

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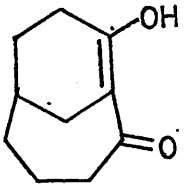

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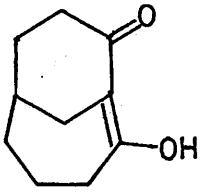

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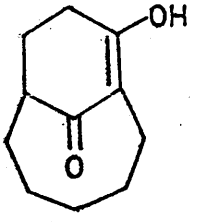


(72)

respectively. Functionality in the incipient "[1]-branch", in order to achieve cyclisation, is almost universal, and cyclisation very often results in some substituent next to the bridgehead in the "[3]-branch".

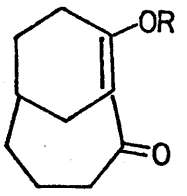
J.A. Marshall's synthesis of the dione (67) is an archetypal example - the incipient 11-carbonyl group is necessary for cyclisation of the keto ester (68), while the cyclisation itself produces the 10-carbonyl.[37] The syntheses of the enones (64) and (65) also exemplify the principle; both were made from cyclooctanone.

Our first task in this line of research was to choose a bicyclic system for study. Our aim was the synthesis of a key compound from which we could make derivatives of isomeric "peripheral anti-Bredt" olefins (e.g. (62) and (63)), preferably by some kind of competitive reaction.

The choice fell upon the bicyclo[4,3,1]decane system, and in particular upon bicyclo[4,3,1]decane-2,9-dione (69), for the following reasons.

(1) This compound might be expected to exist, at least to some extent, in the enol forms (70) and/or (71). These enols are bridged trans-cyclononenes, and as such would probably not be prohibitively strained. The dione (67) has been found[36] to exist partly in its enol form (72).

(2) The alternative positions of the double bond in these enols (cis in either a six- or a seven-membered ring) are likely to be different enough to cause a difference



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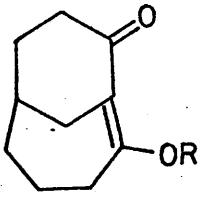
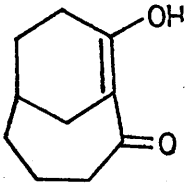


(74)

(R = Me or Ac)



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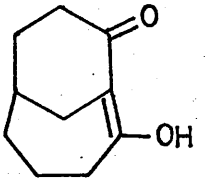

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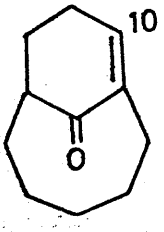

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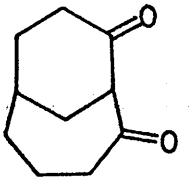


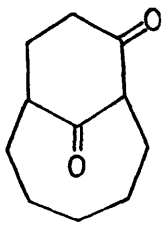
(69)

in energy, yet possibly not so different that one will exist to the exclusion of the other. It might be possible to distinguish the two spectroscopically.

(3) Trapping of these compounds as their enol ethers or enol acetates (73) or (74) might give information about the position of the equilibrium between them, and hence their relative energies. Not too much stress could be placed on this, however, since one enol might react faster than the other; but study of models suggests that the hydroxyl groups in (70) and (71) are equally accessible.

(4) Elaboration of the enol derivatives (73) and (74) (for example by reaction at the carbonyl group) might provide a compound which could be examined by X-ray diffraction or other means to gain information about the nature of the deformation of the double bonds. One important aspect of this study is the fact that all four of the substituents on the double bond would be detectable by X-ray methods, and we could thus distinguish bending and twisting distortions of the bond. This contrasts with the X-ray structure analysis of a derivative of (65), in which the position of the olefinic hydrogen at C-10 could not be accurately determined.[38]

We therefore considered possible synthetic approaches to the dione (69). The nearest analogies in the literature



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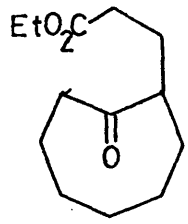

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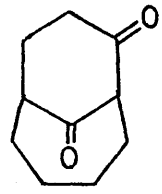

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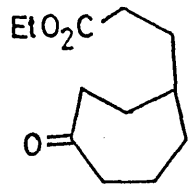

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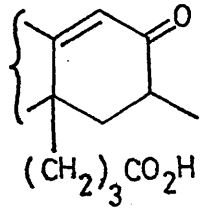

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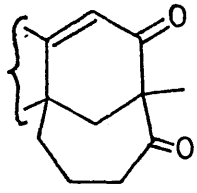

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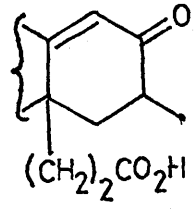

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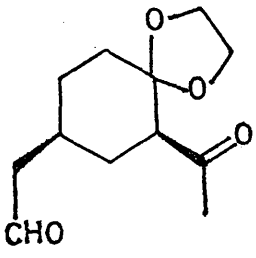

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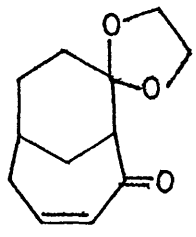

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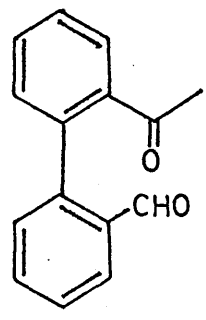

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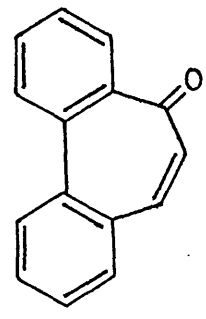

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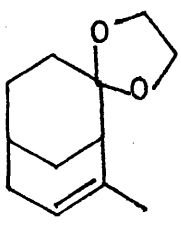

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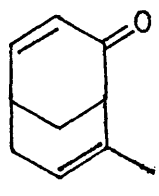

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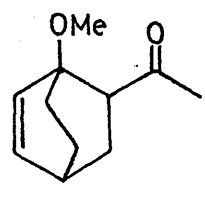

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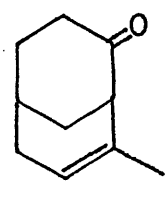

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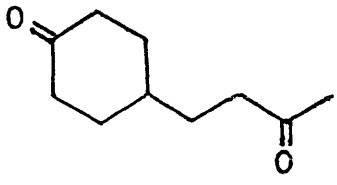

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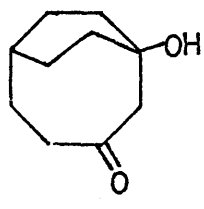

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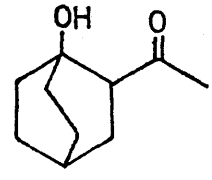


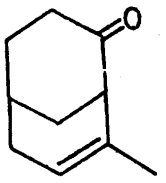
(90)

were the diones (67) (prepared[37] by base-catalysed cyclisation of the keto ester (68)) and (75) (prepared[39] by addition of acryloyl chloride to 1-morpholinocycloheptene). The latter route could not be readily modified to suit our purposes, while the analogous precursor for the former, the keto ester (76), would not be easy to synthesise.

Similar keto ester cyclisation in the opposite sense, with the six-membered ring preformed, was discounted, since the acid (77) fails to cyclise to (78) under conditions which effect cyclisation[40] of (79).

The method chosen was that of cyclisation of the ketoaldehyde (80). Hopefully this would yield the enone (81); analogy for this conversion is provided by the cyclisation of (82) to (83)[41]. Synthesis of the key intermediate (80), of the correct stereochemistry, could best be accomplished by cleavage of a bicyclic system; oxidative cleavage of the bicyclo[3,3,1]nonene derivative (84) leading, at least on paper, to the desired ketoaldehyde (80).

The dienone (85) has been synthesised[42] by rearrangement of the bicyclo[2,2,2]octene (86). However, the authors describe the reaction as being "difficult to reproduce". The desired ketone (87), however, can be visualised as arising from cyclisation of the diketone (88), with dehydration of the first-formed aldol to give the less strained $\beta\gamma$ double bond. Cyclisation of (88) could also give rise to (89) or (90), but since dehydration is



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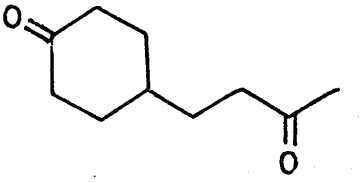

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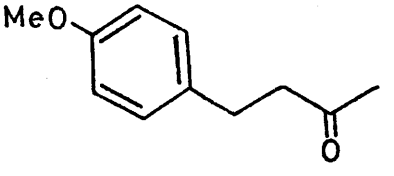

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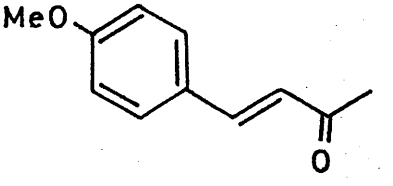

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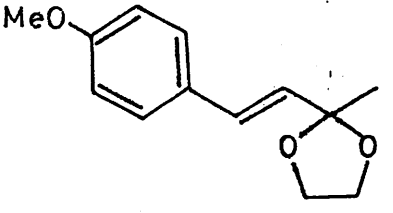

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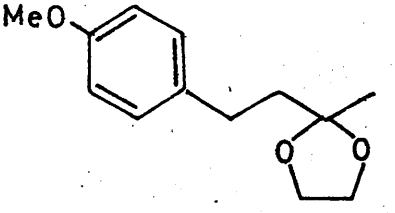

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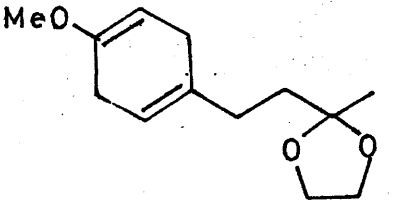

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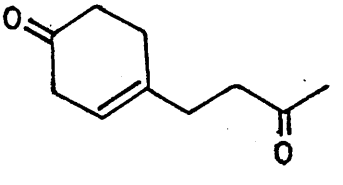

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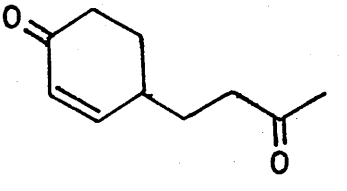


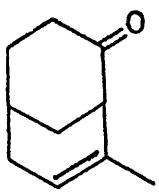
(97)

unfavourable, the [3,3,1] system (87) would be the preferred product. Somewhat surprisingly the dione (88) is unknown, but it is not difficult to imagine its formation from the known p-methoxyphenyl butanone (91) by metal - ammonia reduction.

Anisalacetone (92) was prepared by the standard literature method. It was necessary to protect the ketone group from the conditions required to reduce the aromatic ring, but formation of the acetal (93) did not occur cleanly. Hydrogenation of (92) to (91) and subsequent protection to give (94) was much more successful.

Reduction of the acetal (94), using lithium in ammonia, was carried out in high yield, affording the enol ether (95). This material could readily be hydrolysed, to either the $\beta\gamma$enone (96), or the $\alpha\beta$enone (97), depending on conditions. Catalytic hydrogenation gave the dione (88), purified by distillation.

Cyclisation of this compound was attempted using several sets of conditions, including concentrated sulphuric acid, ethanolic potassium hydroxide, toluene-4-sulphonic acid in benzene and hydrochloric acid in methanol, the last-named being the most fruitful method. The enone (87) was obtained in 57% yield after chromatography. The structure of this compound was confirmed by its spectra; it showed absorption in the i.r. at 1712 cm^{-1} (C=O), 1670 cm^{-1} (C=C) and 905 cm^{-1} (trisubstituted double bond), λ_{max}^{EtOH} 300 nm (ϵ = 340), and n.m.r. signals at 8.33τ (3H, narrow



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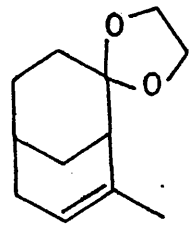

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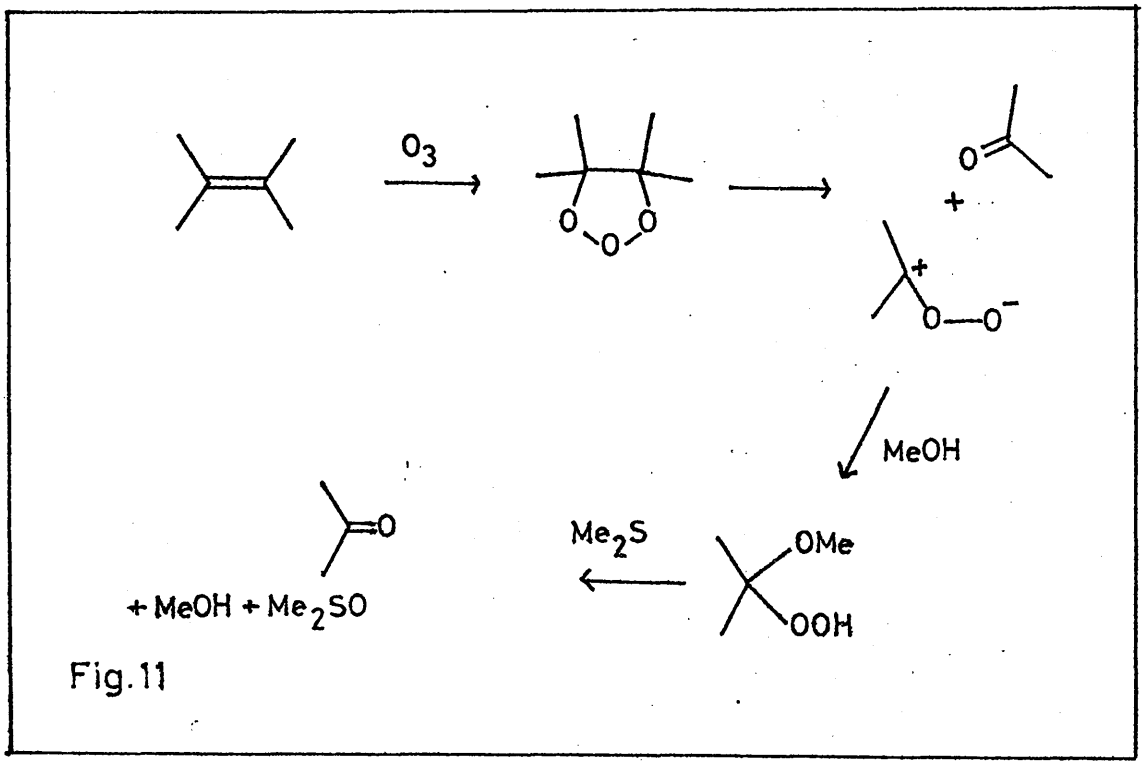
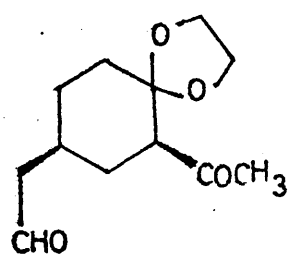


Fig.11



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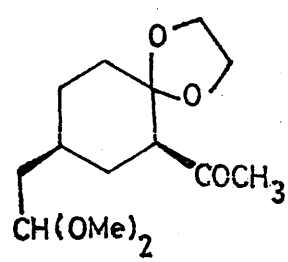


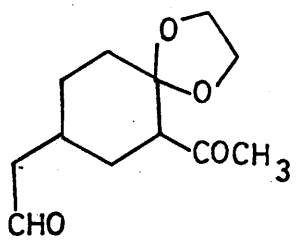
(98)

multiplet) and 4.32τ (1H, multiplet). On irradiation at the former frequency, the latter signal reduced to a broad doublet, while simplification of the methyl signal occurred on irradiation at 4.32τ. The olefinic proton signal also sharpened on irradiation between 7.0 and 7.5τ.

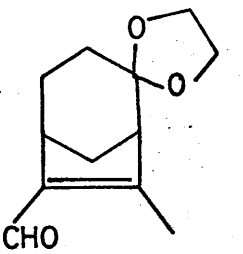
Reflux of a solution of the enone (87) in benzene containing an excess of ethylene glycol and a trace of toluene-4-sulphonic acid gave the acetal (84) in high yield. Ozonolysis of this compound was first attempted using ethyl acetate as solvent and a reductive workup by catalytic hydrogenation. This procedure, however, failed to give any of the desired ketoaldehyde (80), only acidic material being isolated, and alternatives were sought.

The method of J.J. Pappas et. al.[44] was next tried. In this procedure, (fig. 11) methanol is used as solvent, producing an intermediate hydroperoxide which is reduced to the carbonyl compound by treatment with dimethyl sulphide. Ozonolysis of (84) in this way gave a compound which appeared from its spectra to be the dimethyl acetal (98) of the desired keto aldehyde. Attempts to selectively hydrolyse the dimethyl acetal function were abortive.

In an attempt to prevent such acetal formation during the workup of the ozonolysis product, a small amount of triethylamine was added to the dimethyl sulphide, ensuring that the solution was kept basic. This had the desired effect, and the ketoaldehyde (80) was successfully isolated. It proved to be a somewhat labile compound, though



(80)



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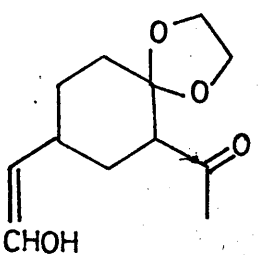

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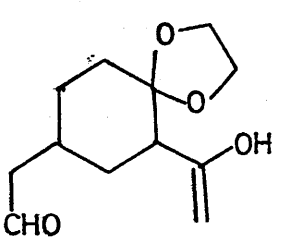

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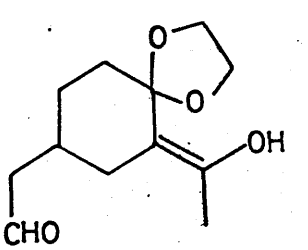


(102)

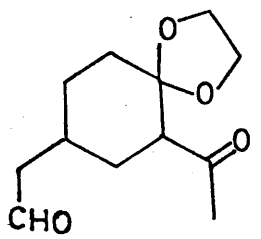
crystalline, and decomposed slowly on exposure to the air.

Cyclisation was first attempted using a dilute solution of the ketoaldehyde (80) in methanolic sodium methoxide. Formation of a less polar compound was detected by t.l.c., and on workup and chromatography this material was isolated. In fact it was the only significant product, and was identified by its i.r. and n.m.r. spectra as the bicyclo[3,2,1]octene aldehyde (99).

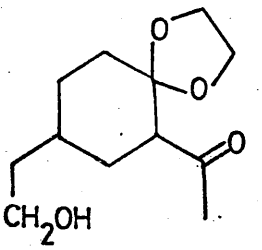
This observation indicates the intermediacy of the enol (100) (or the corresponding enolate), and cyclisation to give a five-membered ring must result either from the greater stability of this enol compared with (101) and (102) or from the rapidity of formation of five- compared with seven-membered rings.

The most obvious alteration in experimental conditions, to effect cyclisation to a cycloheptenone *via* (101), would be to use acid catalysis rather than base. While it is difficult to predict which would be the most stable enol, it is reasonable to suggest that a change in the pH would have some effect on the equilibria involved. However, toluene-4-sulphonic acid in benzene failed to bring about any reaction of the ketoaldehyde (80).

A commonly used device to increase or change the specificity of "active methylene" reactions is the use of an intermediate enamine. Catalysis by amines, such as pyrrolidine, may well occur *via* a transient enamine, and if this were to form on the ketone group of (80), rather



(80)



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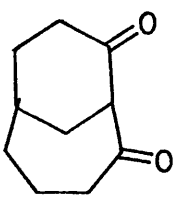

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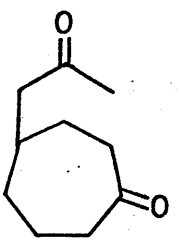

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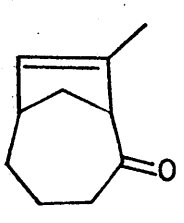

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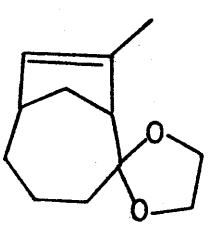

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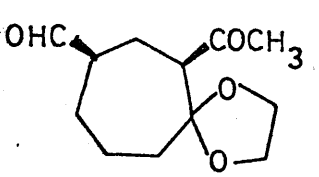

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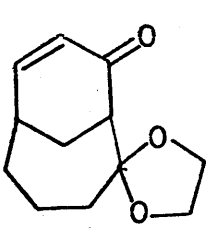


(108)

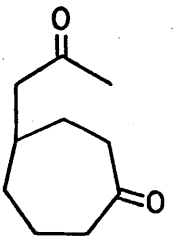
than on the aldehyde, this method would stand a fair chance of producing the desired cyclisation. However, reaction of (80) with pyrrolidine/acetic acid led only to polymeric products.

We next attempted to change the reacting conformation of the molecule, by the use of magnesium ethoxide as catalyst. The enols would be expected to co-ordinate to magnesium, thus possibly leading to different relative positions of the reacting groups in the transition state and a different product. Once again, however, only tarry polymers were obtained.

As a final stratagem, we attempted selective reduction of the aldehyde group of (80), since base treatment of the tosylate of the keto alcohol (103) would, we hoped, produce a cycloheptanone. Treatment of (80) with one equivalent of sodium borohydride afforded, after chromatography, a compound whose spectra suggested that it might be the desired keto alcohol (103), but the low yield precluded further investigation and made the route impracticable.

We had come across yet another instance of the phenomenon noticed and described by Burns[45]; one which is fairly commonly encountered in the pursuit of chemistry.

In the search for alternative methods of synthesis of the dione (69), the exactly analogous route (104) - (108) was considered, since the cyclisation step involves the favoured formation of a six-membered ring, but in this



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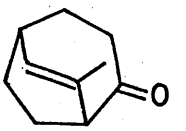

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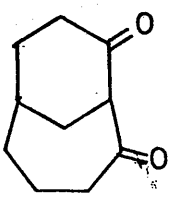

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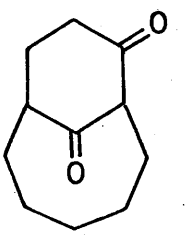

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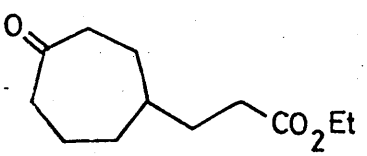
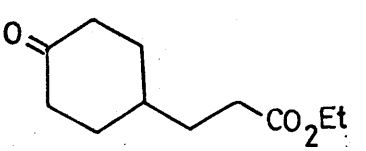


(76)



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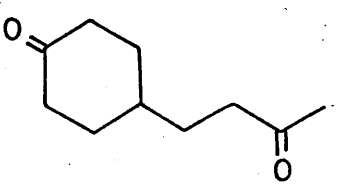

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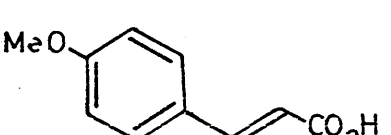

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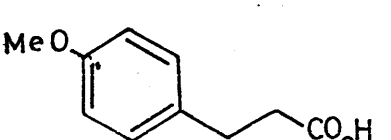

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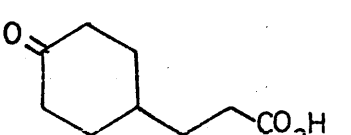


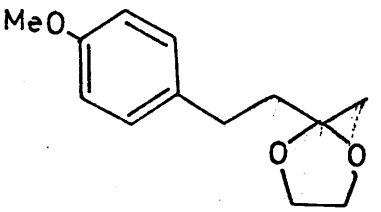
(113)

case the alternative mode of cyclisation of the dione (104) to the bicyclo[3,2,2]nonane derivative (109) is available, and might be expected to compete significantly. This sequence was therefore ruled out.

We finally decided to attempt synthesis of (69) by a similar route to that used by Marshall[37] for preparation of (67). This would require synthesis of the keto ester (76) as a key intermediate, and we envisaged that this compound could be made by ring expansion of its six-membered homologue (110) using diazomethane[46]. Since compound (110) is symmetrical with respect to the ketone group, such ring expansion could give only one product, the desired cycloheptanone (76).

Synthesis of (110) by an exactly analogous method to that used to prepare the dione (88), we regarded as presenting no problems. Hydrogenation of p-methoxycinnamic acid (111) and metal-ammonia reduction of the resulting acid (112), followed by trivial functional group manipulation, would give the desired keto ester (110). In fact the acid (113) is a known compound[47], but its preparation involved a high-pressure hydrogenation step, and we hoped to avoid the technical difficulties of this process by the use of the Birch reduction.

The dihydrocinnamic acid (112) was prepared from (111) by the standard literature method[48]. This compound proved difficult to reduce cleanly using lithium in ammonia. Use of conditions similar to those which effected smooth



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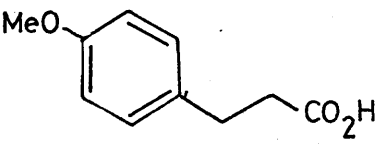

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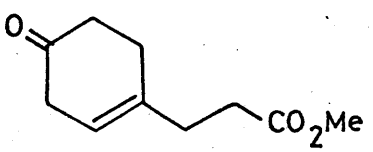

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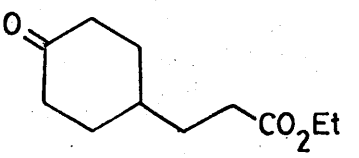

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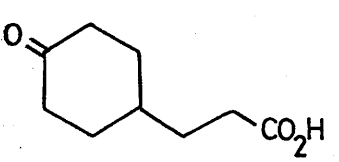


(113)

reduction of the acetal (94) gave mixtures of products with a variety of uninformative spectral properties. In an effort to improve the performance of the reaction, the sodium salt of the acid (112) was prepared by reaction of the acid with sodium hydride, and this material, suspended in tetrahydrofuran, was used as substrate in the reaction in place of the free acid. Tert-butanol was used as proton source. Workup and hydrolysis, followed by treatment of a sample of the crude product with diazomethane, and chromatography, afforded a compound which showed the spectral properties expected for the enone ester (114).

The Birch reduction did not, however, go to completion. Hydrogenation of the crude hydrolysed product gave a mixture of acids which on esterification and separation by t.l.c. gave about 35% of the desired keto ester (110), and about 25% of the ethyl ester of the starting material (112).

It was not possible to crystallise the acid (113) from the oily product resulting from hydrogenation, but a sample isolated by gel filtration and purified by sublimation had a melting point which correlated well with that reported for this compound[47].

Ring expansion of the keto ester (110) was attempted by the method of E. Muller et. al.[49], using diazomethane and boron trifluoride etherate, but only starting material was recovered. Generation of diazomethane in situ gave better results. A product isolated in 30% yield showed a lowering of the ketone carbonyl absorption frequency in the i.r.,

suggesting the formation of a larger ring. Somewhat surprisingly, however, the mass spectrum of this material indicated that not only had addition of (CH_2) taken place, but also, to a substantial extent, addition of (C_2H_4). This is unusual, since cycloheptanones are normally somewhat less reactive towards diazomethane than are cyclohexanones.[46]

A pilot cyclisation of this material by Marshall's method[37] gave very disappointing results. The product, on t.l.c., was largely very polar and polymeric, and no individual compounds could be isolated.

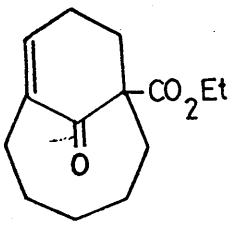
At this point the cumulative effect of the low yield of the Birch reduction, the impure nature of the product of ring expansion and the failure of the cyclisation reaction began to render this approach not so much a "synthesis" as a "mode of formation", and not a very good one at that. It was accordingly abandoned.

No further investigations in the bicyclo[4,3,1]decane system were made; however, the properties of the dione (69) remain an interesting study, and its synthesis a worthwhile aim of research.

DISCUSSION

PART III

APPROACHES TO THE [5]-METACYCLOPHANE SYSTEM



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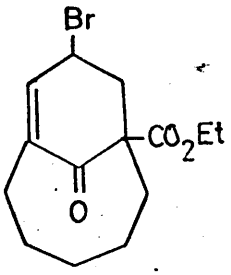

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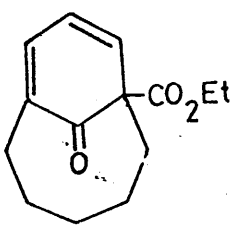

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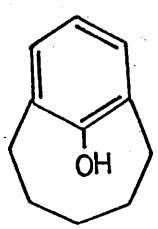

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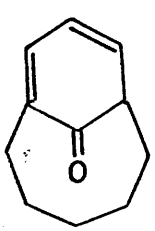

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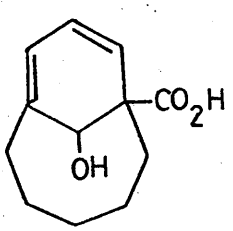

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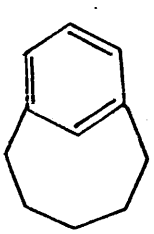


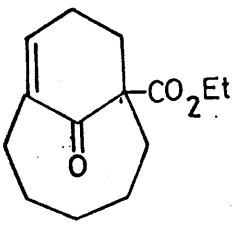
(121)

In planning a synthesis of the [5]-metacyclophane system we considered that a suitable approach would be the aromatisation of a pre-formed bicyclo[5,3,1]undecane derivative. An ideal starting material appeared to be the enone ester (115), the synthesis of which has been described by E.W. Warnhoff *et. al.*[50] Since this method had been used in our laboratory to prepare this compound[51], we had all the necessary materials at hand.

As an approach to the parent system, we planned the following sequence of reactions. Allylic bromination of the enone ester (115) would be expected to give the bromo compound (116). This species could then be dehydrobrominated, yielding the dienone ester (117). This compound is in the same oxidation state as the phenol (118), and hydrolysis and decarboxylation might give (118) either in this form or that of the keto tautomer (119). Hydrolysis of (117), followed by reduction of the 11-keto function, would give the hydroxy acid (120), and we hoped that decarboxylative fragmentation of the tosylate of this compound would lead to the parent [5]-metacyclophane (121).

However, the enone ester (115), on reaction with N-bromosuccinimide, gave a mixture separable with difficulty (by t.l.c.) into two fractions. N.m.r. and i.r. spectra of both were similar to those of the starting material, but g.l.c. indicated that both fractions were in fact complex mixtures.

Allylic oxidation was next attempted. The enone ester



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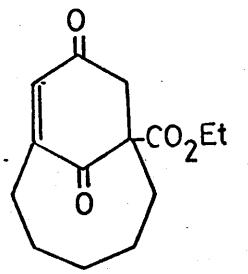

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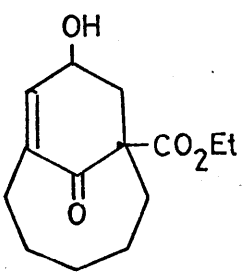

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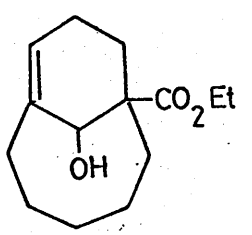

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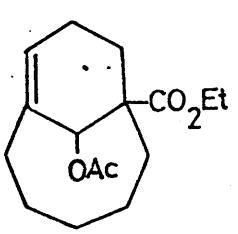

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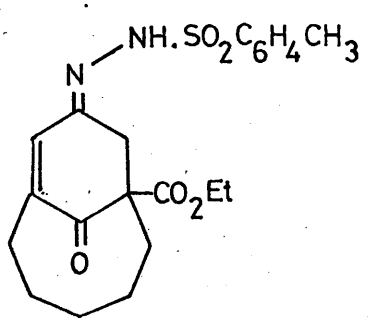


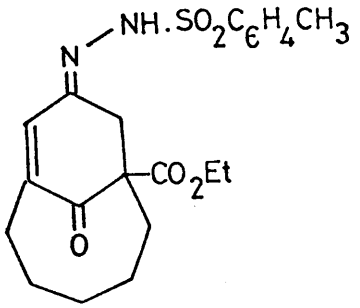
(126)

(115) was treated with sodium chromate in acetic acid / acetic anhydride, and monitoring by t.l.c. showed the slow formation of a more polar product, which on isolation was identified as the desired ene-dione ester (122). Interestingly, this compound was detected (by t.l.c.) among the decomposition products of a sample of the enone ester (115) left open to the air for two months.

We hoped that it would be possible to effect partial reduction of the ene-dione ester (122) to give the allylic alcohol (123), but results were disappointing. Both sodium borohydride and lithium aluminium hydride gave mixtures containing very polar material, suggesting that both ketone groups and the ester function were reduced, despite the hindered environment of the 11-ketone group.

To circumvent this problem we attempted to carry out reduction in a "stepwise" fashion. The enone ester (115) was reduced (by the method of G. Jamieson[51]) to the allylic alcohol (124). However, chromate oxidation of this compound gave only the enone ester (115), and reaction with acetic anhydride/pyridine (to protect the 11-hydroxy group) failed to give the acetate (125), presumably due to steric factors.

The next route considered for preparation of the dienone (117) was the Bamford-Stevens reduction of the mono-(tosylhydrazone) of the ene-dione (122). It proved easily possible to prepare the hydrazone (126) from (122), but once again all attempts to obtain the dienone (117) were in vain. Reaction of the hydrazone (126) with sodium



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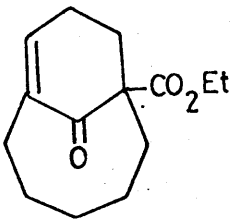

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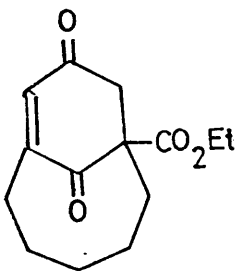

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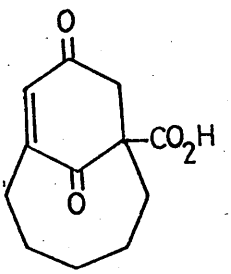

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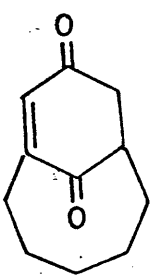

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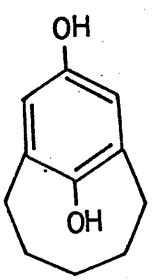

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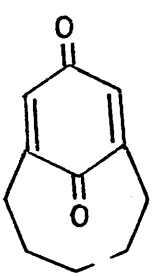


(130)

in ethylene glycol[52] resulted in isolation, in low yield, of a more polar compound which appeared from its n.m.r. spectrum to have lost the ethyl ester function of the starting material, but showed very little in the way of signals due to olefinic hydrogen. The i.r. was uninformative, showing peaks at 1705 and 1670 cm^{-1} but also O-H absorption at 3450 cm^{-1}. It is possible that trans-esterification with ethylene glycol took place, but no further examination of this material was made.

Using the method of H. Dannenberg and H.J. Gross[53], reaction of the hydrazone (126) with sodium hydride in toluene gave two compounds in tiny quantities. Both showed ν_{max} 1740 and 1695 cm^{-1}, but the yield was such as to preclude further investigation. Using this method with diethylene glycol dimethyl ether as solvent, a complex mixture of at least six components (by t.l.c.) was obtained.

Research on this line was hampered by the poor reproducibility of the oxidation of (115) to (122), and finally time prevented further progress. However, an investigation of the product(s) of decarboxylation of the ene-dione acid (127) would be a worthwhile exercise. Decarboxylation should occur with moderate ease, giving the ene-dione (128). It would be interesting to examine the equilibrium between this form and the hydroquinone tautomer (129); while it might also be possible to prepare the quinone (130) by this route.

EXPERIMENTAL

EXPERIMENTAL SECTION

Melting points were measured on a Kofler hot stage and are uncorrected. Infra-red spectra were obtained using Perkin-Elmer 225 and 257 and Pye Unicam SP1000 instruments, and ultraviolet spectra were measured on a Unicam SP800 spectrophotometer. Nuclear magnetic resonance spectra, of 0.3 molar solutions in deuterochloroform, were obtained on Varian T-60 (60 MHz) or HA-100 (100MHz) spectrometers. Optical rotations were determined with the aid of a Hilger and Watts microptic photoelectric polarimeter, and mass spectra were measured on an A.E.I. M.S.12 instrument. Combined gas chromatographic - mass spectrometric analysis was carried out using an LKB 9000 unit.

A Perkin-Elmer F11 chromatograph was used for g.l.c. measurements. Thin layer chromatography was carried out using Kieselgel G (Merck) for analytical purposes and Kieselgel H_{F254} for preparative work. Solutions used in chromatography are described as percentage combinations; for example "20% ethyl acetate/petrol" refers to a mixture of ethyl acetate and petrol in the proportions 20 : 80. "Petrol", in this and other contexts, refers to the fraction of light petroleum boiling between 60^{o} and 80^{o}.

Solutions were dried over anhydrous magnesium sulphate, and solvents were removed on a rotary evaporator at reduced pressure.

Diazomethane

All operations involving the preparation and use of this substance were carried out in a well-ventilated fume cupboard.

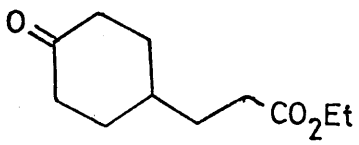
Diazomethane was prepared from bis-(N-methyl-N-nitroso)-terephthalamide, available commercially as a 60% dispersion in mineral oil ("Nitrosan"). Decomposition of this material was achieved by warming a mixture of "Nitrosan", ether, ethanol and 4N sodium hydroxide solution, in the proportions 1g : 10 ml : 5 ml : 5 ml. The resultant ethereal solution of diazomethane was distilled into a cooled receiver. Esterification of carboxylic acids was carried out by slowly adding this solution to a solution of the acid in ether or ethyl acetate at 0^{o} until a permanent yellow colour persisted. The mixture was allowed to stand at room temperature for 30 minutes, and anhydrous magnesium sulphate was then added to catalyse the decomposition of excess diazomethane. When the solution became colourless it was filtered and the solvent removed in vacuo.

Abbreviations

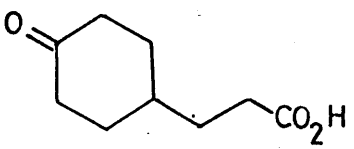
a.b.t.		air bath temperature
b.		broad
d.		doublet
d.d.		double doublet
m.	(in n.m.r.)	multiplet
m.	(in i.r.)	medium (intensity absorption)
q.		quartet
s.	(in n.m.r.)	singlet
s.	(in i.r.)	strong (intensity absorption)
t.		triplet
w.		weak (intensity absorption)

Acknowledgements

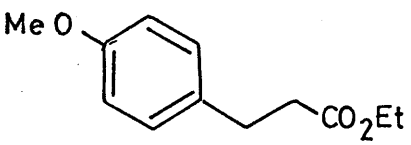
Thanks are due to Professor W. Klyne and Dr. P.M. Scopes, of Westfield College, for measurements of circular dichroism, and to Dr. C.J.W. Brooks and his group for g.c./m.s. analysis. For microanalyses, we are indebted to J.M.L. Cameron ("take it away, there's a hair in it"), Fiona Cowan, and their assistants; for n.m.r. spectra, to Andy Haetzman and Jim Gall ("doesn't dissolve in chloroform at all"); for i.r. measurements, to Mrs. Freida Lawrie ("these cells cost forty pounds a pair"), Sylvia Cathcart and Jeanette MacSwan; and for mass spectra, to Tony Ritchie ("if there's anything in there, we'll find it") and Margaret Laing.



(110) p.105



(113) p.105



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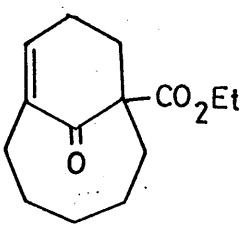

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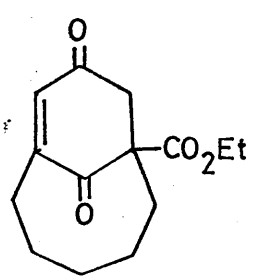

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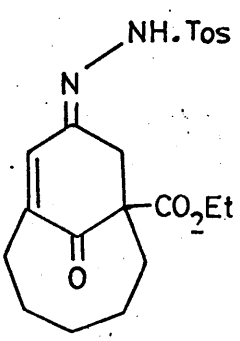

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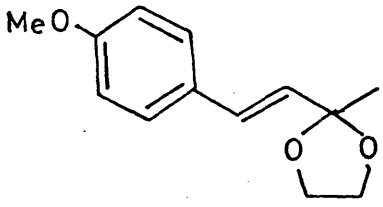

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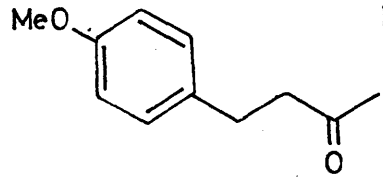

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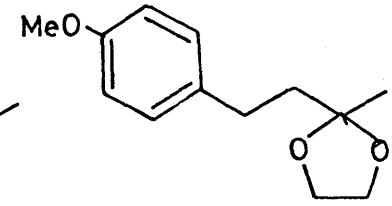

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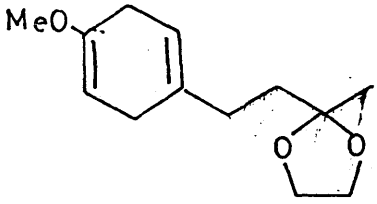

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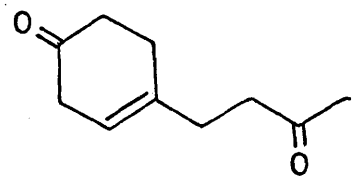

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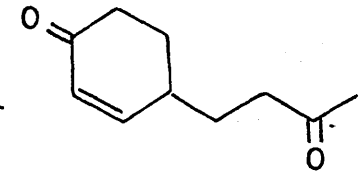

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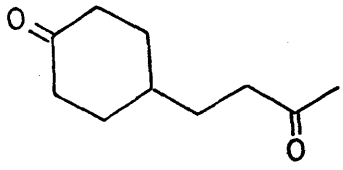

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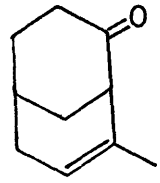
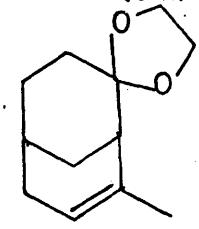
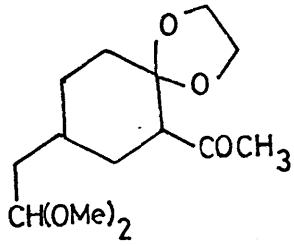


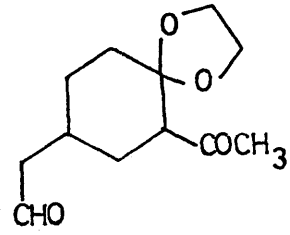
(87) p.96



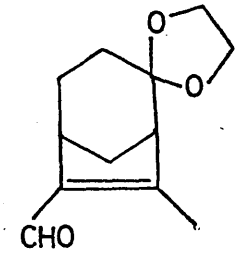
(84) p.98



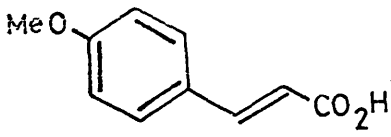
(98) p.99



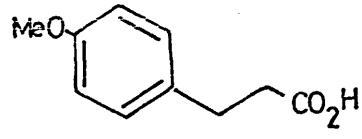
(80) p.99



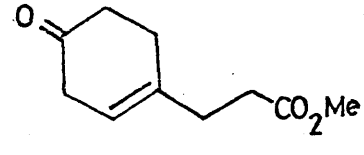
(99) p.100



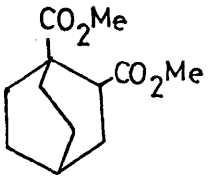
(111) p.102



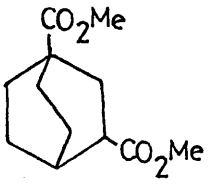
(112) p.103



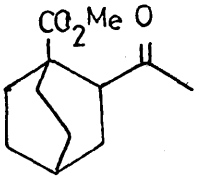
(114) p.104



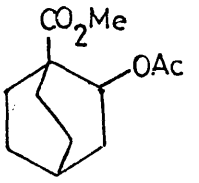
(38) p.73



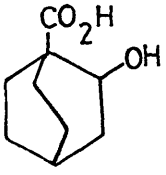
(39) p.73



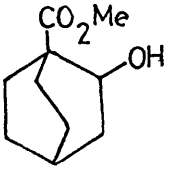
(133) p.74



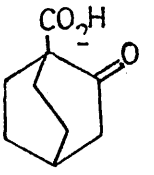
(40) p.74



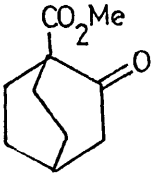
(41) p.75



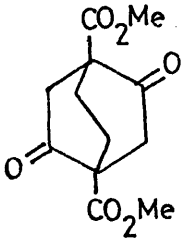
p.76



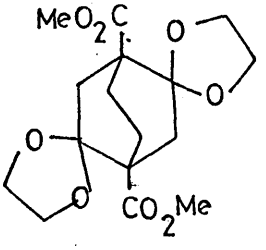
(21) pp. 76, 78 - 80.



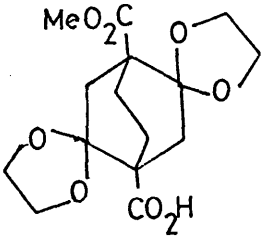
(134) pp.77, 80.



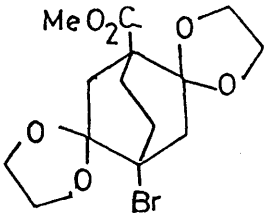
(47) p.81



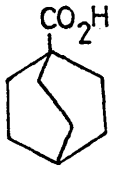
(135) p.82



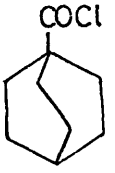
(136) p.83



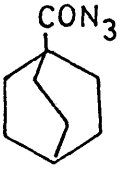
(137) p.83



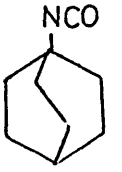
(56) p.85



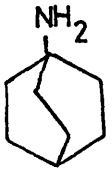
(138) p.85



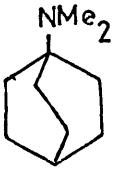
(139) p.85



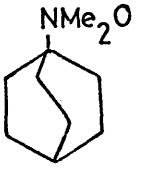
(140) p.85



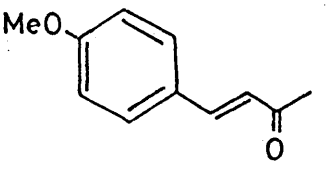
(54) p.85



(51) p.87

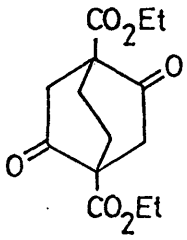


(55) pp.87-90

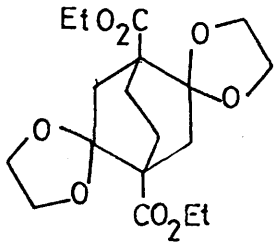


(92) p.91

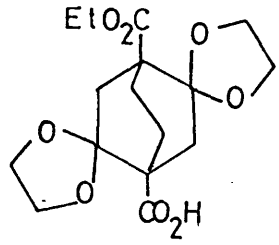
COMPOUNDS REFERRED TO IN EXPERIMENTAL SECTION



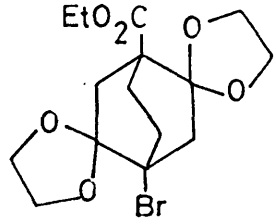
(15) p.65



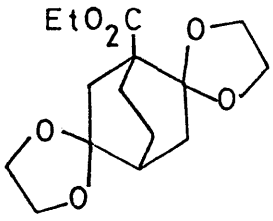
(17) p.65



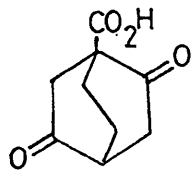
(18) p.65



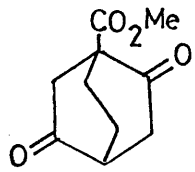
(19) p.66



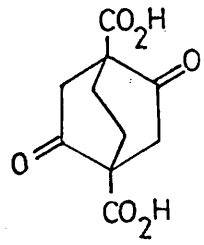
(20) p.67



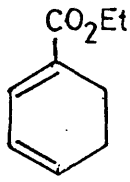
(5) pp.67,78-80



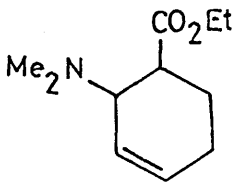
(13) pp.68, 79, 80, 84.



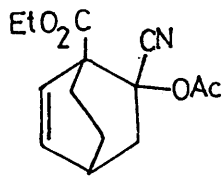
(4) pp.68,77-82, 84.



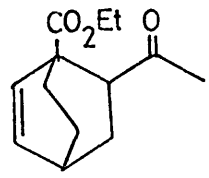
(22) p.69



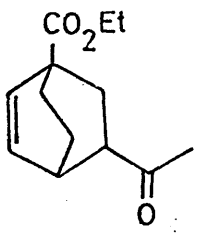
(131) p.69



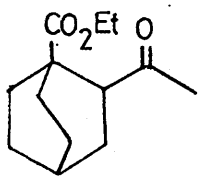
(24) p.69



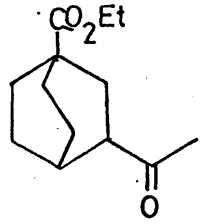
(25) p.69



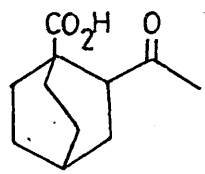
(132) p.69



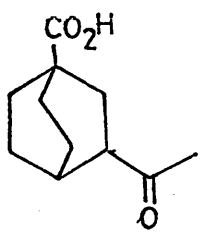
(26) p.70



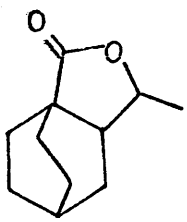
(32) p.70



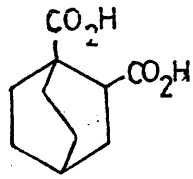
(33) p.71



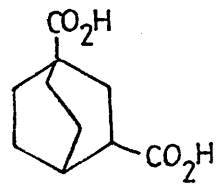
(34) p.71



(35) p. 72



(36) p.73



(37) p.73

2,5-bis(ethylene acetal) of diethylbicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylate (17)

This compound was prepared by the method of Holtz and Stock[54]. In a typical preparation the yield was 85% from (15), m.p. 82° - 84° (lit. 85°).

i.r. ν_{max} (Nujol) 1720 (s), 1165 (m), 1075 (s), 1055 (s) cm^{-1}

n.m.r. τ 8.75 (6H, t, J=7Hz), 8.5 - 7.3 (8H, series of multiplets appearing as roughly symmetrical five line signal), 6.1 (8H, m), 5.85 (2H, q, J = 7 Hz).

2,5-bis(ethylene acetal) of 1-ethoxycarbonylbicyclo [2,2,2]-octane-2,5-dione-4-carboxylic acid (18).

A solution of the diester (17) (1g, 2.7 mmole) and potassium hydroxide (0.154 g, 2.7 mmole) in absolute ethanol (3.7 ml) was refluxed for 16 hours. It was then poured into water and the aqueous solution extracted with ethyl acetate (2 x 20ml). On drying and evaporation the ethyl acetate extracts afforded the starting material (17) (280 mg).

The aqueous solution was then acidified to pH 5 with 1N sulphuric acid in brine, and extracted with chloroform (3 x 20 ml). The chloroform extracts were dried and evaporated to yield a white crystalline solid (385 mg, 43%) which was recrystallised from benzene/petrol as prisms, m.p. 142°.

Found C 55.92% H 6.55%

$C_{16}H_{22}O_8$ requires C 56.14% H 6.48%

i.r. ν_{max} (CCl_4) 1770 (m), 1728 (s), 1700 (s), 1070 (s) cm^{-1}.

n.m.r. τ 8.76 (3H, t, J = 7Hz), 8.5 - 7.4 (8H, envelope), 6.0 (8H, m), 5.85 (2H, q, J = 7Hz), 1.0 (1H, b.s.).

m.s. m/e (M^+) 342; other major peaks at m/e 296, 269, 222, 195, 171, 143, 135, 127, 125, 107, 99, 79 & 59.

2,5-bis(ethylene acetal) of 1-ethoxycarbonyl-4-bromobicyclo-[2,2,2]octane-2,5-dione (19).

A stirred mixture of the half acid ester (18) (2.22g, 6.5 mmole), red mercuric oxide (1.00g, 4.6 mmole) and 1,2-dibromoethane (22 ml) was heated to 75°, and bromine (1.04g, 6.5 mmole) in 1,2-dibromoethane (9 ml) was added over 15 minutes. The mixture was stirred and heated at 75° for 12 hours. It was then cooled and filtered, and the solids were washed with ether and benzene. The solution was washed with dilute sodium bisulphite solution, dilute sodium hydroxide solution, and brine, and finally dried. Removal of solvent afforded a colourless oil (1.83 g). Chromatography on alumina (Spence grade "H") gave the white crystalline bromide (19) (1.09 g, 45%). A sample further purified by sublimation (120° - 130° (a.b.t.)/0.05 mm Hg) had m.p. 62°.

Found C 47.70% H 5.57%

$C_{15}H_{21}O_6Br$ requires C 47.74% H 5.57%

i.r. ν_{max} (CCl_4) 1728 (s), 1245 (s), 1160 (s), 1045 (s), 947 (m) cm^{-1}.

n.m.r. τ 8.76 (3H, t, J = 7Hz), 8.4 - 7.0 (8H, envelope), 6.2 - 5.8 (10H, m).

m.s. m/e (M^+) 376/378; other major peaks at m/e 331/333, 303/305, 297, 225, 211, 184, 179, 171, 151, 125, 112, 89 and 79.

2,5-bis(ethylene acetal) of ethyl bicyclo[2,2,2]octane-2,5-dione-1-carboxylate (20).

To a solution of the bromide (19) (200 mg) and sodium (100 mg) in absolute ethanol (10 ml) was added Raney nickel (grade $W2^{55}$, one large spatula). The mixture was stirred in an atmosphere of hydrogen for 3 hours at room temperature and atmospheric pressure. After uptake of 12.2 ml of hydrogen (theor. 11.9 ml) t.l.c. indicated complete conversion to a more polar product. The catalyst was then filtered off and washed with water and ethanol. The combined filtrate was poured into water and extracted with ether (2 x 10 ml). The ether extracts were dried and evaporated to yield a colourless oil (148 mg, 98%), pure by t.l.c.

i.r. ν_{max} (neat) 1720 (s),1245 (s), 1035 (s), 940 (w) cm^{-1}.

Bicyclo[2,2,2]octane-2,5-dione-1-carboxylic acid (5).

The product of the previous stage (140 mg) was dissolved in ethanol (5 ml) and 5N hydrochloric acid (25 ml) was added. The solution was refluxed for 14 hours, then cooled and extracted with ethyl acetate (2 x 25 ml). The ethyl acetate extracts were washed with brine, dried and evaporated to yield white crystals (70 mg, 75%) which were recrystallised from water to m.p. 214° - 216° (decomp.).

Found C 59.27% H 5.74%

$C_9H_{10}O_4$ requires C 59.34 % H 5.53%

i.r. ν_{max} (Nujol) 3400 - 2500 (m), 1745 (s), 1250 (s) cm^{-1}.

m.s. m/e (M^+) 182; other major peaks at m/e 165, 154, 140, 137, 119, 110, 109, 91, 85, 81 and 79.

A mixed melting point determination of a mixture of this material and a sample prepared by pyrolysis of the diacid (4) showed no depression of the melting point.

Methyl bicyclo[2,2,2]octane-2,5-dione-1-carboxylate (13).

Treatment of the acid (5) with diazomethane gave the methyl ester (13), which was purified by sublimation to m.p. 119° - 121°.

i.r. ν_{max} (CCl_4) 2952 (m), 2918 (w), 2880 (w), 1751 (s), 1735 (s), 1450 (w), 1435 (w), 1401 (w), 1246 (s), 1230 (m), 1059 (m), 1042 (m) cm^{-1}.

n.m.r. τ 8.5 - 7.2 (7H, series of multiplets), 7.03 (2H, d, lower half of AB quartet, peaks further split into doublets, J = 20 and 2 Hz), 6.23 (3H, s).

m.s. m/e (M^+) 196; other major peaks at m/e 181, 165, 137, 119, 109, 81, 79, 55, and 53.

u.v. λ_{max}^{EtOH} 215 nm (ϵ = 600), shoulder at 290 nm, (ϵ = 150).

Retention time on g.l.c. (1% APL, 150°), 5.6 minutes.
(5% QF-1, 150°), 3.0 minutes.

R_f (40% ethyl acetate/petrol) = 0.4.

A sample of the compound obtained by decarboxylation of diacid (4) was similarly methylated andthe product compared with the foregoing. The chromatographic properties (thin layer and vapour phase) of the two samples were identical, and their spectra superimposable.

Ethyl cyclohexa-1,3-diene-1-carboxylate (22).

This compound was prepared by the method of Grob, Ohta, Renk and Weiss[32]. In a typical preparation the yield was 50% from (131), b.p. 94° - 100°/ 15 mm Hg.

i.r. ν_{max} (neat) 3030 (w), 1700 (s), 1270 (s), 1215 (s), 1080 (s) cm^{-1}.

Attempted preparation of ethyl 2-acetoxy-2-cyanobicyclo-[2,2,2]oct-5-ene-1-carboxylate (24).

The diene ester (22) (130 mg), 1-acetoxyacrylonitrile (200µl) and hydroquinone (2 mg) were placed in a Carius tube which was flushed with nitrogen and sealed. The tube and contents were heated in an oven at 150° for 36 hours.

The tube was then opened and the volatiles removed in vacuo. Ether extraction of the residue afforded a brown mobile oil (226 mg) which appeared on examination by t.l.c. (40% ethyl acetate/petrol) to contain four major components of R_f's 0.4, 0.5, 0.7 and 0.8. Preparative chromatography yielded four fractions (32 mg, 19 mg, 44 mg and 13 mg), none of which showed i.r. absorption between 2700 and 1800 cm^{-1}. N.m.r. suggested that all four were in fact mixtures.

Ethyl 2-acetylbicyclo[2,2,2]oct-5-ene-1-carboxylate (25) and ethyl 3-acetylbicyclo[2,2,2]oct-5-ene-1-carboxylate (132).

The diene ester (22) (10 g, 0.066 mole), methyl vinyl ketone (9.03g, 0.13 mole, freshly distilled) and hydroquinone (5 mg) were placed in a Carius tube which was

flushed with nitrogen and sealed. The tube and contents were heated in an oven at 140° for 18 hours.

The product was a clear colourless liquid which appeared on examination by t.l.c. to contain a major component of R_f 0.2 (10% ethyl acetate/petrol). Fractional distillation gave the mixture of keto esters (25) and (132) (13 g, 90%.)

i.r. ν_{max} (CCl_4) 3050 (w), 2976 (w), 2940 (m), 2865 (w), 1730 (s), 1716 (s), 1250 (s), 1173 (s), 1076 (s) cm^{-1}.

n.m.r. τ 8.77 & 8.73 (triplets, 3H altogether, J = 7 Hz for both, ratio ~3:1), 8.8 - 7.6 (6H, envelope), 7.99, 7.91 & 7.88 (singlets, 3H altogether, ratio ~6:1:1), 7.3(1H, m), 6.76 (1H, d.d., J = 11 & 6 Hz), 5.90 & 5.86 (quartets, 2H altogether, J = 7 Hz for both, ratio ~3:1), 3.85 (1H, d.d., J = 8 & 6 Hz), 3.38 (1H, broad d., J = 8 Hz).

g.l.c. (5% QF-1, 130°) - four peaks, retention times 2.5, 3.3, 4.6, and 5.7 minutes, ratio 1 : 10 : 1 : 2.

Ethyl 2-acetylbicyclo[2,2,2]octane-1-carboxylate (26) and ethyl 3-acetylbicyclo[2,2,2]octane-1-carboxylate (32).

The mixture of keto esters (25) and (132) (12.6 g) was dissolved in tetrahydrofuran (30 ml) and palladium on carbon powder (10% w/w, 200 mg) was added. The mixture was stirred in an atmosphere of hydrogen at room temperature and atmospheric pressure until the calculated amount (1500 ml)

had been taken up. It was then filtered and the solvent was removed in vacuo, affording a mixture of the keto esters (26) and (32) as a clear colourless liquid (12.5 g, 95%).

i.r. ν_{max} (CCl_4) 2935 (m), 2876 (w), 1735 (s), 1715 (s), 1245 (s), 1065 (s) cm^{-1}.

n.m.r. τ 8.83 &8.81 (triplets, 3H altogether, J = 7 Hz for both, ratio ~4:1), 8.8 - 7.8 (10H, envelope), 7.93 & 7.91 (singlets, 3H altogether, ratio ~4:1), 7.1 - 6.7 (1H, m), 5.95 & 5.93 (quartets, 2H altogether, J = 7 Hz for both, ratio ~4:1).

g.l.c. (5% QF-1, 100°) - two peaks, of retention times 3.3 and 5.8 minutes, ratio 4:1.

2-acetylbicyclo[2,2,2]octane-1-carboxylic acid (33) and 3-acetylbicyclo[2,2,2]octane-1-carboxylic acid (34).

A solution of the ketoesters (26) and (32) (12.0 g) and potassium hydroxide (10 g) in aqueous ethanol (10% v/v, 110 ml) was refluxed for 2 hours. It was then cooled, acidified with concentrated hydrochloric acid, and extracted with ether (3 x 50 ml). The combined ether extracts were dried and evaporated, and the residue was recrystallised from ethanol, yielding as fraction (1) the keto acid (26) as prisms (5.7 g, 55%, m.p. 164° - 167°).

Found C 67.25% H 8.24%

$C_{11}H_{16}O_3$ requires C 67.32% H 8.22%

i.r. ν_{max} (CCl_4) 1758 (m), 1745 (m), 1717 (s), 1705 (s) cm^{-1}.

n.m.r. τ 8.8 - 7.5 (11H, envelope), 7.87 (3H, s), 6.97 (1H, m), -0.73 (1H, b.s.)

m.s. no molecular ion seen; major peaks at m/e 179 (M^+ - 17), 150, 135, 125, 120, 107, 93, 91 and 79.

After separation of the crystals the remainder of the solvent was removed, giving an oil which was fractionally crystallised from benzene/hexane. This procedure gave two further fractions, (2) (0.8 g) and (3) (1.2 g).

Samples of fraction (1) and of a mixture of fractions (2) and (3) were treated with diazomethane.

g.l.c. (5% QF-1, 130°) - (1) one peak, retention time 2.6 minutes (2)/(3) two peaks, retention times 2.6 and 4.7 minutes, ratio 1.5 : 1.

Attempted preparation of the γ-lactone (35).

The mixture of keto esters (26) and (32) (208 mg, 0.9 mmole) was dissolved in ethanol (12 ml) and sodium borohydride (250 mg, 6.8 mmole) was added. The solution was stirred at 0° for one hour, poured into water and extracted with ether. After workup the extracts afforded a clear oil (196 mg) which on t.l.c. (20% ethyl acetate/petrol) appeared to contain two major components of R_f 0.2 and 0.3, and these were isolated by preparative chromatography. Both showed carbonyl absorption, the latter showing bands in the 1760 - 1780 cm^{-1} region, but also strong O-H bands at 3100 - 3600 cm^{-1}.

Dimethylbicyclo[2,2,2]octane-1,2-dicarboxylate (38) and dimethylbicyclo[2,2,2]octane-1,3-dicarboxylate (39)

The mixture of acids (36) and (37) (4:1) was prepared by the method of Kazan and Greene[22]. Treatment of this mixture with ethereal diazomethane gave (38) and (39).
g.l.c. (5% QF-1, 130°) - two peaks, retention times 2.4 and 3.6 minutes, ratio 4:1.

"Iodoform reaction" of the keto acids (33) and (34).

The mother liquors from crystallisation of the keto acids (33) and (34) were evaporated to give a yellowish solid. This material (40 mg) was dissolved in a mixture of dioxan (2 ml) and aqueous sodium hydroxide (4N, 2 ml), and a solution of iodine and potassium iodide (2.5 g iodine/5g potassium iodide/20 ml water) (6 ml) was added. The mixture was allowed to stand at room temperature for 10 minutes, and a yellow precipitate was observed.

The solution was then poured into water (50 ml) containing sodium thiosulphate (1 g) and 5N hydrochloric acid (3 ml). The mixture was extracted with ether and the ether solution with 4N sodium hydroxide solution. The basic aqueous phase was acidified and re-extracted with ether. On drying and evaporation the ether extracts afforded a yellowish solid residue (25.9 mg, 66%).

Treatment with ethereal diazomethane and examination by g.l.c. (5% QF-1, 130°) showed two peaks, retention times 2.4 and 3.6 minutes, ratio 1:2.

A similar procedure carried out on fraction (1) of crystals of the keto acid (33) (40 mg) gave as immediate product 26.6 mg, 68%, of solid material. Treatment with ethereal diazomethane and examination by g.l.c. (5% QF-1, 130°) showed one peak, retention time 2.4 minutes.

Methyl 2-acetylbicyclo[2,2,2]octane-1-carboxylate (133)

Treatment of the keto acid (33) (5.3 g) with diazomethane in the usual manner gave the ester (133) (5.4 g, 97%) as a colourless liquid.

i.r. ν_{max} (neat) 1735 (s), 1712(s), 1270 (s), 1090 (s) cm^{-1}.

n.m.r. τ 8.8 - 7.7 (11H, envelope), 7.87 (3H, s), 7.3 - 6.7 (1H, m), 6.40 (3H, s).

g.l.c. (5% QF-1, 130°) - retention time 2.6 minutes.

R_f (20% ethyl acetate/petrol) = 0.4.

Methyl 2-acetoxybicyclo[2,2,2]octane-1-carboxylate (40).

Trifluoroacetic anhydride (10.2 ml) was added over 30 minutes to a stirred mixture of methylene chloride (10 ml) and 90% hydrogen peroxide (1.6 ml) at 0°.

Anhydrous sodium dihydrogen phosphate (16 g) was added to a solution of the ester (133) (5.6 g) in dry methylene chloride (48 ml). To this mixture at 0° was added with stirring over one hour the solution of trifluoroperacetic acid prepared as above. The reaction mixture was stirred at 0° for a further two hours and was then allowed to come to room

temperature. Constant monitoring by t.l.c. (20% ethyl acetate/petrol) indicated the slow formation of a new compound of R_f 0.45. After three hours' stirring at room temperature, conversion appeared to be complete. Methylene chloride (100 ml) was then added and the mixture washed with sodium bicarbonate solution (2 x 30 ml). The organic layer was dried and evaporated, affording the acetate (40) as a clear liquid (6.0 g, 95%, b.p. 100°(a.b.t.)/0.1 mm Hg.).

Found C 63.53% H 7.83%

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

i.r. ν_{max} (CCl_4) 1740 (s), 1735 (s), 1238 (s), 1070 (m), 1025 (m) cm^{-1}.

n.m.r. τ 8.8 - 7.6 (11H, envelope), 8.00 (3H, s), 6.38 (3H, s), 4.80 (1H, d.d., J = 11 & 3 Hz).

g.l.c. (5% QF-1, 130°) - one peak, retention time 2.5 mins.

2-hydroxybicyclo[2,2,2]octane-1-carboxylic acid (41).

A solution of the acetate (40) (5.9 g) and potassium hydroxide (6g) in aqueous ethanol (10% v/v, 90 ml) was refluxed for $1\frac{3}{4}$ hours. It was then cooled, poured into water and extracted with ether. The aqueous phase was acidified and extracted with ethyl acetate (3 x 30 ml). After washing with brine, drying and evaporation the ethyl acetate extracts afforded the crystalline hydroxy acid (41) (4.0 g, 95%). A sample purified by sublimation had m.p. 110° - 111.5°.

Found C 63.56% H 8.20%

$C_9H_{14}O_3$ requires C 63.51% H 8.29%

i.r. ν_{max} (Nujol) 3500 - 2500 (s), 1705 (s), 1300 (s), 1045 (s) cm^{-1}.

n.m.r. τ 8.9 - 7.6 (11H, envelope), 5.82 (1H, d.d., J = 9 & 3 Hz), 3.1 (2H, b.s.)

The methyl ester of this compound was prepared by treatment with diazomethane, and was isolated as a clear oil.

i.r. $\nu_{max}(CCl_4)$ 3650 - 3350 (m), 1735 (s), 1712 (s), 1240 (s), 1068 (s), 1037 (s) cm^{-1}.

n.m.r. τ 8.8 - 7.6 (11H, envelope), 7.00 (1H, b.s.), 6.33 (3H, s), 5.95 (1H, d.d., J = 9 & 3 Hz). The signal at 7.00τ disappeared on shaking with D_2O.

g.l.c. (5% QF-1, 130°) - one peak, retention time 1.0 min.

Bicyclo[2,2,2]octan-2-one-1-carboxylic acid (21).

A solution of the hydroxy acid (41) (4.0 g) in acetone (100 ml) was cooled to 0°. Jones reagent (8N) was added dropwise until a permanent orange colour persisted. The solution was then concentrated in vacuo and poured into water. After extraction with ether (3 x 15 ml) the combined extracts were washed with brine and dried. On removal of half of the ether in vacuo, the keto acid (21) crystallised as platelets, m.p. 146°.

i.r. ν_{max} (CCl_4) 3400 - 2500 (s), 1760 (s), 1730 (s), 1707 (s), 1293 (s), 1274 (s) cm^{-1}.

n.m.r. τ 8.5 - 7.5 (9H, series of multiplets), 7.61 (2H, d, J = 3 Hz), 0.00 (1H, b.s.).

m.s. m/e (M^+) 168; other major peaks at m/e 167, 150, 149, 139, 123, 122, 79 and 55.

The methyl ester of this compound was prepared by treatment with diazomethane. On sublimation it was obtained as needles, m.p. 62.5° - 64.5°.

Found C 65.56% H 7.62%

$C_{10}H_{14}O_3$ requires C 65.92% H 7.74%

i.r. ν_{max} (CCl_4) 1757 (s), 1731 (s), 1164 (s), 1028 (m) cm^{-1}.

n.m.r. τ 8.5 - 7.5 (9H, envelope), 7.66 (2H, d, J = 3 Hz), 6.30 (3H, s).

m.s. m/e (M^+) 182; other major peaks at m/e 154, 137, 126, 79, 55 and 53.

g.l.c. (5% QF-1, 130°) - one peak, retention time 2.5 mins.

PYROLYSES OF KETO ACIDS (4), (5) AND (21).

Method (A)

The diacid dione (4) (65mg) was placed in a small sample tube, which was loosely plugged with glass wool and inserted in a sublimation tube. The tube was heated in a block to 300°, the temperature being increased from 260° at a rate of approximately 1 - 2° /minute, under reduced

pressure (200 mm Hg). Between 280° and 290° the product distilled up to the cold part of the tube as a yellow oil, which slowly became semi-crystalline. The crude product was washed out with ethyl acetate. Extraction with dilute sodium bicarbonate solution separated the acidic portion of the product which was recovered (by acidification and re-extraction) and esterified with diazomethane.

g.l.c. (5% QF-1, 150°) - major peak (80 - 90%) retention time 3.0 minutes.

The neutral material, on examination by g.l.c., showed no peak corresponding to the dione (12).

A similar procedure applied (a) to the dione monoacid (5) and (b) to the simple keto acid (21) resulted in sublimation of the acids (checked by m.p./mixed m.p.) at temperatures around 200°.

Method (B)

A Pyrex glass tube, 70 cm x 1 cm, was mounted so as to pass vertically through a 60 cm long oven. A loose packing of glass wool, 20 cm in length, was positioned within the hot part of the tube. A U-tube immersed in an acetone-Drikold bath was attached to the outlet.

The tube was heated to 310° - 315° and allowed to equilibrate with a slow flow of oxygen-free nitrogen. A degassed solution of the diacid (4) (200 mgs) in tetrahydrofuran (20 ml) was dropped through the hot tube over a

period of 15 minutes, and the nitrogen flow was maintained for a further hour. The product (68 mgs) was divided into acidic and neutral fractions as before, and the acidic fraction treated with diazomethane.

Neutral fraction (less than 1 mg).

g.l.c. (1% APL, 100°) - four main peaks, retention times 4.0, 4.9, 7.7 and 8.8 minutes.

Under the same conditions the dione (12) had retention time 6.4 minutes.

Acidic fraction.

g.l.c. (5% QF-1, 150°) - several peaks, including one of retention time 3.0 minutes (corresponds to (13)).

A similar procedure applied to the dione monoacid (5) resulted in a very low yield of recovered products, while starting with the simple keto acid (21), it was recovered unchanged (mp/mixed mp). In one run with the oven at 430° the same result was observed.

Method (C)

The diacid (4) (49 mg) was dissolved in tetrahydrofuran (2 ml) in a Carius tube. The tube was flushed with nitrogen, sealed and heated in an oven at 315° for 30 minutes. It was then opened and the brownish, charred contents examined by t.l.c. (40% ethyl acetate/petrol). No component of $R_f > 0$ was observed.

The total recovered material (49 mg, 100%) was treated

with diazomethane and chromatographed. Most of the product was extremely polar. Two fractions were isolated in very low yield, but neither was further investigated.

In another, similar, run the neutral and acidic materials were separated as before, and the neutrals examined by g.l.c. The absence of a peak corresponding to the dione (12) was noted. On methylation and g.l.c. examination the acidic fraction showed one peak, corresponding to the dione ester (13).

A similar procedure applied to the monoacid dione (5) (49 mg) in t.h.f. (2 ml) resulted in recovery of 47 mg (95%) of crude product. This material, on examination by t.l.c., showed no component of $R_f > 0$. Diazomethane treatment and preparative t.l.c. afforded the dione ester (13) (18 mg, 34%), identical (i.r., g.l.c., t.l.c.) to an authentic sample.

In another run the neutral material was initially separated and examined by g.l.c. No peak corresponding to the dione (12) was observed.

A similar procedure applied to the simple keto acid (21) (51 mg) in t.h.f. (2 ml) resulted in recovery of 50 mg (98%) of crude product. No component of $R_f > 0$ was seen on t.l.c. Diazomethane treatment and preparative t.l.c. afforded the keto ester (134) (42 mg, 84%), identical (i.r., g.l.c., t.l.c., n.m.r.) to an authentic sample.

No neutral products whatsoever could be detected on g.l.c.

Resolution of bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid (4).

An intimate mixture of the diacid (4) (8g, 0.035 mole) and brucine (28g, 0.07 mole) was added portionwise over one hour to boiling water (1100 ml). The mixture was left to cool and the resulting brownish needles (21.8g, 60.5%) filtered off. This material was recrystallised twice from boiling water, with filtration of the hot solution through Celite;

(a) 1000 ml water, recovered 12g

(b) 800 ml water, recovered 7.6g.

Recovery of resolved diacid (4)

The salt was dissolved in 5N hydrochloric acid (250 ml) and the solution extracted with ethyl acetate (3 x 100 ml). Drying and evaporation of the extracts afforded the diacid (4), which was recrystallised from ethanol as platelets (2.8 g, 78%, m.p. 300°(decomp.))

$[\alpha]_D^{25}$ = + 22.95° (H_2O, c = 0.13) (lit.[23] + 23.85°).

Dimethyl bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylate (47) (racemic).

Treatment of the diacid (4) with diazomethane in the usual manner afforded the diester (47) in 98% yield. A sample purified by sublimation (150°(a.b.t.)/1 mm Hg) had m.p. 148° - 150°.

Found C 56.67% H 5.52%

$C_{12}H_{14}O_6$ requires C 56.69% H 5.55%

i.r. ν_{max} (CCl_4) 1753 (s), 1735 (s), 1280 (m), 1245 (m), 1072 (s) cm^{-1}.

n.m.r. τ 8.1 - 7.3 (4H, series of multiplets), 7.25 (2H, d, J = 20 Hz), 6.87 (2H, d.d., J = 20 & 2 Hz), 6.2 (6H, s).

m.s. m/e (M^+) 254; other major peaks at m/e 222, 195, 135, 107, 89 and 59.

crude optically active material showed m.p. 143° - 144°, $[\alpha]_D^{25}$ = + 17.7° (acetone, c = 0.3).

This material was converted to the dione acid by exactly analogous reactions to those used for the diester (15). Details of the intermediates will be given.

2,5-bis(ethylene acetal) of dimethyl bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylate (135).(racemic)

Sublimed at 120° (a.b.t.)/1 mm Hg, m.p. 100° - 102°.

Found C 56.26% H 6.42%

$C_{16}H_{22}O_8$ requires C 56.14% H 6.48%

i.r. ν_{max} (CCl_4) 1734 (s), 1265 (s), 1072(s) cm^{-1}.

n.m.r. τ 8.5 - 7.3 (8H, envelope), 6.36 ($_6$H, s), 6.1 (8H, m).

m.s. m/e (M^+) 342; other major peaks at m/e 297, 239, 211, 171, 157, 111, 103, 86 and 79.

crude optically active material showed m.p. 87° - 91°, $[\alpha]_D^{25}$ = + 40.0° (acetone).

2,5-bis(ethylene acetal) of 1-methoxycarbonylbicyclo[2,2,2]-octane-4-carboxylic acid (136) (racemic)

Sublimed at 180° (a.b.t.)/0.2 mm Hg, m.p. 126° - 130°.

found C 54.83% H 6.33%

$C_{15}H_{20}O_8$ requires C 54.88% H 6.14%

i.r. ν_{max} (CCl_4) 1770 (m), 1730 (s), 1700 (s), 1250 - 1260 (m), 1070 (s) cm^{-1}.

n.m.r. τ 8.5 - 7.3 (8H, envelope), 6.32 (3H, s), 6.1 - 5.9 (8H, m).

m.s. m/e (M^+) 328; other major peaks at m/e 296, 284, 283, 269, 253, 225, 197, 157, 111 and 86.

crude optically active material had m.p. 118° - 125°, $[\alpha]_D^{25}$ = + 38.7° (acetone, c = 0.06).

2,5-bis(ethylene acetal) of methyl 4-bromobicyclo[2,2,2]-octane-2,5-dione-1-carboxylate (137) (racemic).

Sublimed at 130° (a.b.t.)/0.3 mm Hg, m.p. 116° - 120°.

found C 46.26%, H 5.31%

$C_{14}H_{19}O_6Br$ requires C 46.3% H 5.24%

i.r. ν_{max} (CCl_4) 1732 (s), 1245 (m), 1160 (s), 1045 (s) cm^{-1}.

n.m.r. τ 8.4 - 7.1 (8H, envelope), 6.32 (3H, s), 6.2 - 5.7 (8H, m).

m.s. m/e (M^+) 364/362; other major peaks at 283, 211, 151, 125, 112 and 79.

crude optically active material had m.p. 95° - 100°, $[\alpha]_D^{25}$ = + 45.5° (acetone, c = 0.03).

Methylbicyclo[2,2,2]octane-2,5-dione-1-carboxylate (13) (optically active).

This material, after purification by t.l.c. and sublimation, had m.p. 70° - 72° and showed no observable rotation at the D line when dissolved in benzene, chloroform or ethyl acetate. A solution in methanol (0.0032 M) showed circular dichroism, $\Delta\epsilon$ = + 0.62 (289 nm) and - 0.58 (214 nm).

Pyrolysis of optically active bicyclo[2,2,2]octane-2,5-dione-1,4-dicarboxylic acid (4).

Method (A) was used. The diacid (4) (56.7 mg, $[\alpha]_D^{25}$ = + 23°) after pyrolysis and treatment with diazomethane, gave 34 mg of recovered material, from which the ester (13) was isolated by preparative t.l.c. (18.8 mg, 33%). This material was further purified by sublimation (110° (a.b.t.) /0.15 mm Hg) to give 16.6 mg of t.l.c./g.l.c. pure (13), m.p. 118° - 120° (m.p. of racemic (13) = 119° - 121°)

Solutions of this material (0.15 M) in chloroform, ethyl acetate and benzene showed no observable net rotation. A solution in methanol (0.004 M) showed no observable circular dichroism.

Bicyclo[2,2,2]octane-1-carboxylic acid (56).

This compound was prepared by the method of Grob, Ohta, Renk and Weiss[32], being obtained as needles, m.p. 140° - 142° (lit. 140.5° - 142°).
i.r. ν_{max} (Nujol) 3300 - 2400 (s), 1700 (s), 1275 (s) cm^{-1}.

1-aminobicyclo[2,2,2]octane (54).

A solution of the acid (56) (495 mg, 3.2 mmole) in thionyl chloride (1 ml) was refluxed for two hours. The excess thionyl chloride was then removed in vacuo, affording the acid chloride (138) as a clear oil, ν_{max} (neat) 1790 cm^{-1}.

This material was dissolved in acetone (1 ml) and this solution was added dropwise with stirring to a saturated aqueous solution of sodium azide (1.25 g, 19 mmole). The mixture was stirred for 15 hours at room temperature, then extracted with methylene chloride (20 ml). On drying and evaporation the methylene chloride extracts afforded the azide (139) as an oil, ν_{max} (neat) 1710 and 2150 cm^{-1}. Use of a water bath at 60° to evaporate the solvent led to partial rearrangement to the isocyanate (140), evidenced by the appearance of an i.r. band at 2270 cm^{-1}.

The crude azide was dissolved in benzene (10 ml), and the solution refluxed for 12 hours. Removal of solvent gave the isocyanate (140) as a waxy, volatile solid, ν_{max} 2270 cm^{-1}.

A mixture of this material and 5N hydrochloric acid

(20 ml) was refluxed for 24 hours, and was then cooled and extracted with ether. The aqueous phase was made basic by addition of potassium hydroxide pellets, and extracted with methylene chloride (3 x 10 ml). The methylene chloride extracts, after drying and evaporation, afforded a solid residue which was sublimed (100°(a.b.t.)/60 mm Hg)) to give the primary amine (54) as a white waxy solid, m.p. 100° - 110° (lit[29] 141° - 142°), reactive with CO_2.

i.r. ν_{max} (CCl_4) 3660 (w), 3360 (w), 1575 (s), 1450 (s), 1345 (s), 1125 (m), 875 (s).

n.m.r. τ 9.0 - 8.0 (envelope)

m.s. m/e (M^+) 125; other major peaks at m/e 110, 97, 96, 82, 79, 70 and 69.

A sample of this material (5 mg) was dissolved in a mixture of pyridine (1 drop) and acetic anhydride (4 drops) and the solution heated in a closed tube at 60° - 70° for 20 minutes. The excess reagents were then evaporated in a nitrogen stream and the residue extracted with ethyl acetate. Evaporation of the ethyl acetate extracts and recrystallisation of the residue from petrol gave needles, m.p. 134° - 136° (lit[32] m.p. of N-acetyl-1-aminobicyclo[2,2,2]-octane = 135° - 136°).

N,N-dimethyl-1-aminobicyclo[2,2,2]octane (51).

The primary amine (54) (170 mg) was dissolved in a mixture of 40% aqueous formaldehyde (1 ml) and 90% aqueous formic acid (1 ml) and the solution heated at 100° for 24 hours, after which time a further 1 ml of formaldehyde solution was added. After a total of 43 hours' heating, the solution was cooled and poured into water. The resulting solution was made basic and extracted with ether (3 x 10 ml). On drying and evaporation the ether extracts afforded the tertiary amine (51) as a colourless liquid (80 mg, 39%, b.p. 110° - 120° (a.b.t.)/0.7 mm Hg).

i.r. ν_{max} (neat) 2860(s), 2830 (m), 2790 (s), 1260 (m), 1080 (s), 960 (s) cm^{-1}.

n.m.r. τ 8.43 (13H, b.s.), 7.80 (6H, s).

g.l.c. (1% SE-30, 70°) - one peak, retention time 5.1 minutes.

N,N-dimethyl-1-aminobicyclo[2,2,2]octane N-oxide (55).

(1) A solution of the tertiary amine (51) (75 mg, 0.5 mmole), 30% hydrogen peroxide (50 μl, 0.6 mmole) and methanol (100 μl) was stored at room temperature for 24 hours. Platinum oxide (5 mg) was then added and the mixture left for a further 24 hours. It was then filtered, and removal of solvent gave the amine oxide (55) as a waxy solid, m.p. 183° - 185°.

i.r. ν_{max} (Nujol) 970 cm^{-1}.

n.m.r. τ 8.6 - 7.8 (13H, envelope), 6.95 (6H, s); also

peaks at 5.2τ and 6.3 τ, the latter disappearing on shaking with D_2O.

m.s. m/e (M^+) 169; other major peaks at m/e 153, 139, 138, 124, 110, 96, 83, 82, 68 and 67.

Picrate; crystallised as platelets from ethanol, m.p. 203° - 206° (decomp.).

	found C	48.43%	H	5.59%	N 14.32%
$C_{16}H_{22}N_4O_8$	requires C	48.24%	H	5.57%	N 14.06%

(2) The tertiary amine (51) (384 mg, 2.5 mmole) was dissolved in chloroform (2 ml) and the solution cooled to 0°. A solution of m-chloroperbenzoic acid (430 mg, 2.5 mmole) in chloroform (5 ml) was added dropwise with stirring over a period of 15 minutes. The mixture was stirred for three hours, then applied to a column of alumina (Woelm basic, activity grade 1, 20g). The column was washed with chloroform to remove traces of amine, and elution with 25% methanol/chloroform gave the amine oxide (55) as an oil which on exposure to the air slowly formed waxy crystals identical (i.r./n.m.r.) to the above.

PYROLYSIS OF THE AMINE OXIDE (55).

Pyrolyses were carried out in a Pyrex glass tube 70 cm x 1 cm, mounted horizontally in a furnace 60 cm long, and packed with 3mm glass beads. A U-tube, immersed in liquid nitrogen, was connected to the outlet end of the tube.

(1) The furnace was equilibrated at 430° with a slow bleed of helium. The amine oxide (55) (70 mg) was sublimed into the hot part of the tube at a pressure of 1mm Hg. A yellowish oily product was observed to collect in the U-tube. After sublimation of all the substrate the pyrolysis was allowed to run, with slow helium bleed at 1 mm Hg, for one hour more. The contents of the U-tube were then washed out with ether and examined by t.l.c. (10% ethyl acetate/petrol). Components of R_f 0.2 and 0.8 (the latter being two spots, partially superimposed) were observed, as well as polar material of R_f 0. The total yield was about 10 mg, of which about 8 - 9 mg was very polar.

g.l.c. (1% APL, 80°) - peaks of retention times 0.9, 1.1, 1.3, 3.2, 4.2, 8.6, 9.7, 13.0 and 14.8 minutes, as well as several other minor ones. The component of retention time 13.0 minutes appeared to constitute 60 - 90% of the mixture. Co-injection (on 1% SE-30 at 70°)indicated that the tertiary amine (51) was not present in the mixture. Under these conditions the amine oxide (55) did not run on g.l.c.

Preparative t.l.c. allowed isolation of the component of R_f 0.2 and co-injection demonstrated that it corresponded to the compound of retention time 13.0 minutes.

(2) The pyrolysis was run as before, but with a fine-nozzle dropping funnel fitted into a side-arm on the inlet

1.	2.	3.	4.
I	1.4	not clear	100(17), 87(100), 75(48), 71(26), 57(100), 56(52), 55(34).
II	4.8	126(34)	133(5), 97(43), 84(19), 79(12), 70(32), 69(28), 67(15), 56(25), 55(100).
III	6.0	124(63)	97(7), 96(70), 95(18), 82(50), 81(100), 79(10), 77(10), 69(10), 68(69), 67(75), 55(37).
IV	6.4	140(30)	111(25), 98(15), 97(20), 96(64), 83(42), 81(29), 70(33), 69(62), 67(24), 57(30), 56(36), 55(100).
V	7.8	not clear	136(20), 110(28), 109(45), 96(11), 95(44), 93(11), 81(100), 69(32), 68(33), 67(66), 55(51).
VI	10.6	169(11)	136(15), 121(15), 110(11), 109(100), 93(26), 81(31), 79(11), 67(84), 59(54), 55(33).
VII	14.0	169(60)	154(11), 140(55), 138(12), 126(11), 113(41), 110(20), 109(29), 96(8), 83(24), 82(16), 81(20), 79(11), 70(7), 69(12), 68(100), 67(37), 56(25), 55(58).
VIII	20.6	183(30)	154(42), 138(10), 126(8), 110(24), 109(38), 83(30), 82(14), 81(20), 79(17), 70(10), 69(16), 68(100), 67(37), 56(20), 55(50).

end of the pyrolysis tube. Furan (2 ml) was placed in this funnel and the tap manipulated so as to give a constant bleed of furan vapour through the tube during the pyrolysis. Ether extraction and evaporation gave the same products as above, and no significant new components were seen on t.l.c. or g.l.c.

Gas Chromatographic - Mass Spectrometric Analysis of the Product.

The ether extract from pyrolysis (1) was chromatographed in 60% ethyl acetate/petrol and all material of $R_f > 0$ was recovered. G.c./m.s. analysis of this material gave the results opposite.

Column 1 - component number

2 - retention time (minutes) on 2% SE-30 at 100°

3 - m/e value of molecular ion, with % abundance

4 - m/e values of major fragments, with % abundances.

Component II accounted for 10% of the mixture, and component VII for 80%, all others less than 5% each. An authentic sample of bicyclo[2,2,2]octan-1-ol had retention time 4.8 minutes and showed mass spectral peaks at m/e 126 (14), 133 (14), 97 (33), 85 (12), 79 (7), 77 (10), 70 (54), 69 (7), 67 (7) and 59 (100).

We are grateful to Professor C.A. Grob for supplying this sample.

1-(4'-methoxyphenyl)but-1-en-3-one (anisalacetone) (92)

This compound was prepared by the method of Drake and Allen[43]. Crystallisation from methanol yielded yellow platelets, m.p. 72.5°- 73.5° (lit. 73° - 74°).

i.r. ν_{max} (Nujol) 1650 (s), 1620 (s), 1595 (s), 1240 (s), 1175 (s), 835 (m), 810 (m) cm^{-1}.

n.m.r. τ 7.7 (3H, s), 6.2 (3H, s), 3.45 (1H, d, J = 16 Hz), 3.12 (2H, d, J = 9 Hz), 2.55 (two superimposed doublets, 1H, J = 16 Hz & 2H, J = 9 Hz).

3-ethylene acetal of 1-(4'-methoxyphenyl)but-1-en-3-one (93).

A solution of the enone (92) (10 g), ethylene glycol (15 g) and toluene-4-sulphonic acid (50 mg) in benzene (125 ml) was refluxed in a water separator for three hours. It was then cooled, washed with sodium bicarbonate solution and brine, dried and evaporated. T.l.c. of the resulting pale brown oil (40% ethyl acetate/petrol) showed it to be a complex mixture with a major component of R_f 0.5. Preparative t.l.c. of the oil (120 mg) afforded this compound (34 mg), identified as the acetal (93).

i.r. ν_{max} (neat) 1600 (s), 1510 (s), 1245 (s), 1190 (s), 1030 (s), 850 (m), 810 (m) cm^{-1}.

n.m.r. τ 8.43 (3H, s), 6.20 (3H, s), 6.03 (4H, b.s.), 4.00 (1H, d, J = 16 Hz), 3.30 (1H, d, J = 16 Hz), 3.12 (2H, d, J = 9 Hz), 2.64 (2H, d, J = 9 Hz).

The bulk of the material was distilled (b.p. 100° - 110°/0.2 mm Hg) and gave a semicrystalline product (3 g).

T.l.c. showed it to be a complex mixture, and i.r. and n.m.r. indicated the presence of both (92) and (93), as well as some impurities.

1-(4'-methoxyphenyl)butan-3-one (91).

Palladium on carbon powder (5% w/w, 500 mg) was added to a solution of the enone (92) (50 g) in tetrahydrofuran (100 ml). The mixture was stirred in an atmosphere of hydrogen at room temperature and atmospheric pressure for 7 hours, after which time the theoretical amount of hydrogen had been taken up. The solution was then filtered and the solvent removed *in vacuo*, affording the ketone (91) as a clear liquid (46 g, 90%) b.p. 99° - 108°/0.09 mm Hg.

i.r. ν_{max} (neat) 1710 (s), 1600 (s), 1512 (s), 1245 (s), 1035 (s), 825 (s) cm^{-1}.

n.m.r. τ 7.95 (3H, s), 7.6 - 7.2 (4H, m), 6.25 (3H, s), 3.25 (2H, d, J = 9 Hz), 2.90 (2H, d, J = 9 Hz).

3-ethylene acetal of 1-(4'-methoxyphenyl)butan-3-one (94).

A solution of the ketone (91) (25 g), ethylene glycol (25 g) and toluene-4-sulphonic acid (100 mg) in benzene (250 ml) was refluxed for 6 hours with constant water separation. It was then cooled, washed with saturated sodium bicarbonate solution and brine, and dried. Removal of the solvent gave the acetal (94) as a clear liquid (28 g, 90%) b.p. 120° - 130° (a.b.t.)/0.05 mm Hg.

Found C 70.43% H 8.30%

$C_{13}H_{18}O_3$ requires C 70.24% H 8.16%

i.r. ν_{max} (neat) 1605 (s), 1510 (s), 1250 (s), 1180 (s), 1040 (s), 865 (s), 850 (s), 830 (s) cm^{-1}.

n.m.r. τ 8.65 (3H, s), 7.5 - 7.1 & 8.3 - 7.9 (symmetrical multiplets, each 2H), 6.25 (3H, s), 6.05 (4H, s), 3.15 (2H, d, J = 9 Hz), 2.85 (2H, d, J = 9 Hz).

m.s. m/e (M^+) 222; other major peaks at m/e 207, 177, 161, 150, 135, 134, 121 & 87.

3-ethylene acetal of 1-(4'-methoxycyclohexa-1',4'-dienyl)-butan-3-one (95).

A solution of the acetal (94) (73 g, 0.33 mole) in dry ether (100 ml) was added with stirring to redistilled liquid ammonia (1 litre). Lithium metal (12 g, 1.7 mole) in small pieces was added over a period of 20 minutes, and the resulting two-phase mixture was stirred under reflux (dry ice condenser) for one hour further. Absolute ethanol (90 ml) was then added with extreme caution, and the ammonia was allowed to evaporate.

The residue was dissolved in ice water and extracted with ether (3 x 300 ml). The ether extracts were washed with saturated sodium bicarbonate solution and brine, dried and evaporated. The crude product (67.3 g, 90%) showed one spot on t.l.c. (20% ethyl acetate/petrol, R_f = 0.45) and was identified as the enol ether (95), obtained as a clear oil.

i.r. ν_{max} (neat) 1700 (m), 1670 (s), 1220 (s), 1075 (s), 790 (s). cm^{-1}.

n.m.r. τ 8.70 (3H, s), 8.6 - 7.6 (6H, m), 7.27 (2H, b.s.), 6.45 (3H, s), 6.05 (4H, s), 5.40 (1H, m), 4.60 (1H, m).

u.v. λ_{max}^{EtOH} = 211 nm, changing to 207 & 223 nm on addition of 3 drops 5N HCl.

Hydrolysis of the enol ether (95).

(a). The enol ether (95) (55 g) was stirred for 45 minutes at room temperature in a 0.2N solution of hydrochloric acid in aqueous ethanol (50% v/v, 500 ml). T.l.c. showed the formation of a much more polar compound. The solution was neutralised with sodium bicarbonate and extracted with ether (3 x 300 ml). On drying and evaporation the ether extracts afforded impure 4-(3'-ketobut-1'-yl)cyclohex-3-enone (96) (45 g, 91%) as a colourless liquid.

i.r. ν_{max} (neat) 1715 (s), 1170 (m), 800 (w) cm^{-1}.

n.m.r. τ 7.85 (3H, s), 8.2 - 7.0 (10H, envelope), 4.55 (1H, m).

R_f 0.2 (40% ethyl acetate/petrol).

(b). The enol ether (95) (65 g) was refluxed for 90 minutes in a 1N solution of hydrochloric acid in aqueous ethanol (50% v/v, 200 ml). Extraction with ether as before and workup afforded an oil, which was distilled to give three fractions. Each of these appeared, on examination by t.l.c.,

to be a mixture, and from the third fraction (b.p. 104° - 109°/0.25 mm Hg) there could be isolated by preparative t.l.c. 4-(3'-ketobut-1'-yl)cyclohex-2-enone (97) , as a colourless liquid.

i.r. ν_{max} (neat) 1715 (s), 1680 (s), 1170 (m), 980 (m), 760 (w) cm^{-1}.

n.m.r. τ 7.80 (3H, s), 8.4 - 7.0 (9H, envelope), 4.00 (1H, d.d., J = 10 & 2 Hz), 3.15 (1H, d, J = 10 Hz, broadened by smaller couplings).

4-(3'-ketobut-1'-yl)cyclohexanone (88).

The impure enone (96) (40 g) was dissolved in tetrahydrofuran (100 ml) and palladium on carbon powder (5% w/w, 200 mg) was added. The mixture was stirred in an atmosphere of hydrogen at room temperature and atmospheric pressure until the uptake stopped. Filtration and evaporation of solvent gave a colourless oil (41 g) which showed no i.r. absorption at 800 cm^{-1}. Distillation of this material afforded a fraction (25.8 g, 65%, b.p. 103° - 108°/0.25 mm Hg) which corresponded on t.l.c. to the major component of the crude product mixture, and was identified as the dione (88).

Found C 71.27% H 9.47%

$C_{10}H_{16}O_2$ requires C 71.39% H 9.59%

i.r. ν_{max} (CCl_4) 1720 (s), 1714 (s), 1335 (m), 1160 (m) cm^{-1}.

n.m.r. τ 7.80 (3H, s), 8.7 - 7.2 (13H, envelope)

m.s. m/e (M^+) 168: other major peaks at m/e 150, 125, 122, 111, 110, 58 and 55.

R_f 0.3 (40% ethyl acetate/petrol).

G.l.c. (5% QF-1, 120°) - one peak, retention time 7.2 mins.

Cyclisation of the dione (88).

(a). The dione (88) (150 mg) was added dropwise to concentrated sulphuric acid (10 ml) at 0°, and the solution stirred under nitrogen for 40 minutes. It was then poured into ice water and extracted with ether. Workup and evaporation of the extracts produced an oil (62 mg) identical (g.l.c./t.l.c./i.r.) to the starting material.

(b). A solution of the dione (88) (114 mg) and potassium hydroxide (0.75 g) in ethanol (5 ml) was stirred for 18 hours at room temperature. Examination by t.l.c. of the reaction mixture showed only starting material present.

(c). A solution of the dione (88) (190 mg) and toluene-4-sulphonic acid (200 mg) in benzene (10 ml) was refluxed for 30 minutes with constant water separation. T.l.c. showed the formation of a mixture containing a less polar compound similar to that produced by method (d).

(d). The dione (88) (2.0 g) was added to a mixture of concentrated hydrochloric acid (25 ml) and methanol (25 ml), and the solution was refluxed gently for 30 minutes. It was

then cooled, poured into ice water and extracted with ether. The ether extracts were washed with brine, dried and evaporated to give a yellow oil, which appeared on examination by t.l.c. (20% ethyl acetate/petrol) to contain one major component of R_f 0.7. G.l.c. (5% QF-1, 120°) showed the appearance of a new peak with retention time 3.3 minutes, and disappearance of the starting material.

Chromatography of the crude product on Spence alumina (Grade H) gave, on elution with 5% ethyl acetate/petrol, a distinctive-smelling liquid which was identified as 2-methylbicyclo[3,3,1]non-2-en-8-one (87) (0.9 g, 57%, b.p. 70° (a.b.t.)/15 mm Hg).

Found C 79.81% H 9.54%

$C_{10}H_{14}O$ requires C 79.96% H 9.39%

i.r. ν_{max} (CCl_4) 1712 (s), 1670 (w), 1225 (m), 1115 (m), 905 (m) cm^{-1}.

n.m.r. τ 8.33 (3H, m, J_{obs} = 2 Hz), 8.2 - 7.0 (10H, envelope), 4.32 (1H, m).

Irradiation at 8.33τ reduces the signal at 4.32 τ to a broad doublet, J_{obs} = 3 Hz, while irradiation at 4.32τ simplifies the signal at 8.33τ. The olefinic proton signal also sharpens on irradiation at 7.0 - 7.5 τ.

m.s. m/e (M^+) 150; other major peaks at m/e 132, 117, 106, 93 and 91.

u.v. λ_{max}^{EtOH} = 300 nm (ϵ = 340).

7-ethylene acetal of 2-methylbicyclo[3,3,1]non-2-ene-7-one (84).

A solution of the ketone (87) (2.0 g, 13.3 mmole), ethylene glycol (2.0 g) and toluene-4-sulphonic acid (10 mg) in benzene (100 ml) was refluxed for 3 hours with constant water separation, then cooled, washed with saturated sodium bicarbonate solution and brine, and dried. Removal of solvent gave the acetal (84) (2.1 g, 86%) as a clear colourless liquid, b.p. 100° (a.b.t.)/15 mm Hg.

Found C 73.90% H 9.41%

$C_{12}H_{18}O_2$ requires C 74.19% H 9.34%

i.r. ν_{max} (CCl_4) 1185 (m), 1110 (s), 1085 (m), 1040 (m) 1030 (m), 950 (m), 925 (m), 900 (m) cm^{-1}.

additionally ν_{max} (neat) 810 (m), 790 (m).

n.m.r. τ 8.8 - 7.4 (13H, envelope) (methyl resonance centred on 8.2 τ), 6.05 (4H, b.s.), 4.46 (1H, m).

m.s. m/e (M^+) 194; other major peaks at m/e 183, 165, 150, 132, 117, 106, 99 and 91.

Ozonolysis of ethylene acetal (84).

(1). The acetal (84) (42 mg) was dissolved in ethyl acetate (5 ml) and the solution was cooled to -78°. A stream of ozone-enriched oxygen was bubbled through the solution until a blue colour developed. Nitrogen was then passed through the solution as it was allowed to warm to 0°. Palladium on carbon powder (5% w/w, 5 mg) was added and the mixture stirred in an atmosphere of hydrogen until the

uptake stopped. The solution was then filtered and the solvent evaporated. The residue, on examination by t.l.c. and i.r., appeared to contain mostly acidic material.

(2). The acetal (84) (1.0 g) in methanol (100 ml) was treated as above, but after warming to 0^{o}, dimethyl sulphide (10 ml) was added, and the solution stirred at room temperature for 90 minutes. The volatile materials were then removed in vacuo and the residue extracted with pentane (2 x 20 ml). The pentane extracts were washed with brine, dried and evaporated to give an oily residue (1.07 g) containing dimethyl sulphoxide and a compound of R_f 0.6 on t.l.c. (60% ethyl acetate/petrol). This material was isolated by preparative t.l.c., and was assigned the structure (98).

i.r. ν_{max} (neat) 2835 (m), 1705 (s), 1135 (s), 1070 (s) cm^{-1}.

n.m.r. τ 8.8 - 8.0 (9H, envelope), 7.76 (3H,s), 7.1 (1H, m), 6.70 (6H, s), 6.10 (4H, b.s.), 5.55 (1H, b.t., J = 5 Hz).

(3). The acetal (84) (1.47 g) in methanol (100 ml) was treated with ozone as above. The solution was allowed to warm to room temperature with nitrogen bubbling, and dimethyl sulphide (15 ml) and triethylamine (0.5 ml) were added. After stirring for three hours the volatile materials were removed in vacuo. The residue was partitioned between ice water and ether and the ether extracts dried and evaporated

to give an oily residue (410 mg, 25%).

i.r. ν_{max} (neat) 2745 (m), 1725 (s), 1712 (s), 1070 (s) cm^{-1}.

T.l.c. (60% ethyl acetate/petrol) indicated one major component of R_f 0.5, and this compound was isolated by preparative t.l.c. and identified as the ketoaldehyde (80). A sample purified by sublimation slowly crystallised, and had m.p. 64° - 65.5°.

i.r. ν_{max} (CCl_4) 2710 (m), 1728 (s), 1716 (s), 1094 (m), 1062 (m).

n.m.r. τ 8.8 - 7.9 (7H, envelope), 7.75 (3H, s), 7.8 - 7.4 (2H, m), 7.2 - 6.8 (1H, m), 6.10 (4H, b.s.), 0.25 (1H, t, J = 1.5 Hz).

m.s. m/e (M^+) 226; other major peaks at m/e 198, 183, 169, 141, 140, 127, 113, 99 and 86.

Cyclisation of the ketoaldehyde (80).

(1). A solution of the ketoaldehyde (80) (200 mg, 0.9 mmole) in methanol (30 ml) was degassed by bubbling nitrogen through it and was then added dropwise to a solution of sodium methoxide made up by dissolving sodium metal (1.0 g) in degassed methanol (50 ml). The solution was refluxed under nitrogen for one hour, boiled down to 20 ml, and poured into water. Extraction with ether (2 x 20 ml), followed by drying and evaporation of the ether extracts, afforded a yellow oil (170 mg) which appeared on analysis by t.l.c. (40% ethyl acetate/petrol) to contain one major component of R_f 0.6. This material was isolated by preparative t.l.c. and was

identified as the 2-ethylene acetal of 7-methylbicyclo-[3,2,1]oct-6-en-2-one-6-carbaldehyde (99).

Found C 69.08% H 7.79%

$C_{12}H_{16}O_3$ requires C 69.21% H 7.74%

i.r. ν_{max} (neat) 2750 (w), 1660 (s), 1120 (s) cm^{-1}.

n.m.r. τ 8.33 (4H, b.s.), 8.03 (2H, m), 7.72 (3H, s), 7.45 (1H, m), 6.95 (1H, m), 6.02 (4H, b.s.), - 0.1 (1H, s).

m.s. m/e (M^+) 208; other major peaks at m/e 136, 120, 99, 93, 91, 86, 79, 77 and 65.

(2). A solution of the ketoaldehyde (80) (100 mg) and toluene-4-sulphonic acid (30 mg) in benzene (10 ml) was refluxed under nitrogen with constant water separation. After four hours, t.l.c. analysis of the reaction mixture indicated that only the starting material was present.

(3). A solution of the ketoaldehyde (80) (100 mg), pyrrolidine (2 drops) and acetic acid (2 drops) in benzene (5 ml) was refluxed under nitrogen with constant water separation for 40 minutes. The reaction mixture was worked up by washing with sodium bicarbonate solution and brine, drying and evaporating. The crude product appeared on t.l.c. to contain at least six components, and most of the product was of a very polar nature. Preparative t.l.c. yielded only traces of material.

(4). Magnesium ethoxide (25 mg) was added to a solution of the ketoaldehyde (80) (25 mg) in dry ether (1 ml). The mixture was stirred at room temperature for 1½ hours. T.l.c. indicated that no reaction was occurring and the mixture was then refluxed under nitrogen for 30 minutes. No change was observed. Dry ethanol (1 ml) was then added, the ether allowed to boil off and the mixture refluxed for 25 minutes. The product was a complex mixture, largely very polar, which was not further investigated.

Reduction of the ketoaldehyde (80).

The ketoaldehyde (80) (70 mg, 0.3 mmole) was dissolved in dry ethanol (5 ml) and a solution of sodium borohydride (3 mg, 0.08 mmole) in dry ethanol (2 ml) was added dropwise over 10 minutes at room temperature. After stirring for a further 10 minutes the solution was poured into water. Extraction with ether and the usual workup afforded a mixture from which a component of R_f 0.3 (60% ethyl acetate/petrol) could be isolated by preparative t.l.c. Yield 12 mg (17%).

i.r. ν_{max} (neat) 3400 (s) cm^{-1}.

n.m.r. τ 8.8 - 8.0 (10H, envelope), 7.8 (3H, s), 7.1 (1H, b.m.), 6.3 (2H, b.t., J = 6.5 Hz), 6.1 (4H, b.s.).

P-methoxycinnamic acid (111).

This compound was prepared by the method of Wiley and Smith[56] and had m.p. 174° - 175° (lit. 175°).

3-(4'-methoxyphenyl)propionic acid (112).

This compound was prepared by the method of Schwenk, Papa, Whitman and Ginsberg[48] from (111), and had m.p. 100° (lit.[57] 104°).

i.r. ν_{max} (Nujol) 3300 - 2300 (m), 1705 (s), 1610 (m), 1515 (s), 1250 (s), 1220 (s), 1180 (s), 1037 (m).

Reduction of the acid (112).

(1). A solution of the acid (112) (1.0 g) in dry tetrahydrofuran (20 ml) was added to redistilled liquid ammonia (100 ml). Lithium metal (1.0 g, 25 equivalents) in small pieces was added over a period of 10 minutes. The solution was stirred for 30 minutes more, and absolute ethanol (15 ml) added dropwise. The ammonia was then allowed to evaporate, and the residue was partitioned between ice water and ethyl acetate. The aqueous phase was acidified and extracted twice with ethyl acetate, and on drying and evaporation these extracts afforded a yellow oil (1.05 g) which showed ν_{max} 3500 - 2500, 1715 cm^{-1}.

A sample of this material was treated with diazomethane, and t.l.c. of the product indicated that it comprised at least five compounds. Preparative chromatography afforded two fractions ((a) and (b)). Both showed singlets at 6.3τ in the n.m.r. The more polar (a) also gave rise to a broad singlet (~4H) at 2.8 τ, while (b) appeared to have an impurity giving rise to an AB quartet around 3τ. Both showed

carbonyl absorption in the i.r., (a) at 1710 - 1740, and (b) a narrower band at 1740 cm^{-1}.

(2). A solution of the acid (112) (1.0 g, 5.5 mmole) in dry tetrahydrofuran (20 ml) was treated with sodium hydride (60% suspension in benzene, 0.22 g, 5.5 mmole). The solvent was evaporated and the residual white amorphous mass resuspended in fresh t.h.f. (15 ml). This suspension was added to redistilled liquid ammonia (70 ml). Tertiary butanol (6.9 g) was then added, and lithium metal (0.45 g, 66 mmole) added in small pieces over a period of one hour. The mixture was stirred for 3 hours more, and methanol (4 ml) was added. The ammonia was allowed to evaporate, and the residue dissolved in water (60 ml). Chloroform (60 ml) was added , and the mixture stirred vigorously with ice cooling as the pH was lowered to 7 by addition of aqueous oxalic acid. The organic layer, after washing with water and brine, drying and evaporation, afforded an oil (1.3 g).

i.r. ν_{max} (neat) 3500 - 2500 (s), 1730 (s), 1710 (s), 1670 (m), 1610 (m), 1520 (m), 1220 (s), 770 (m) cm^{-1}.

This material was dissolved in methanol (50 ml) and 0.5N oxalic acid solution (5 ml) was added. The mixture was stirred for 10 minutes, and workup gave an oily product.

i.r. ν_{max} (neat) 3500 - 2500 (s), 1730 (s), 1710 (s), 1610 (w), 1520 (m), 1260 (m), 770 (m). cm^{-1}.

A sample treated with diazomethane and examined by

t.l.c. appeared to be a mixture, containing a major component (34%) which was isolated by preparative t.l.c. and appeared to be the enone ester (114).

i.r. ν_{max} (neat) 1740 - 1710 (s), 1205 (s), 1175 (s) cm^{-1}.

n.m.r. τ 7.55 (8H, b.s.), 7.15 (2H, m), 6.30 (3H, s), 4.50 (1H, m).

Ethyl 3-(cyclohexanon-4-yl)propionate (110).

The crude product of the Birch reduction (550 mg) was dissolved in ethyl acetate (20 ml) and palladium on carbon powder (5% w/w, 42 mg) added. The mixture was stirred in an atmosphere of hydrogen until the uptake stopped. It was then filtered and the solvent evaporated, giving an oil (560 mg) which showed ν_{max} 3500 - 2500 (s), 1740 - 1700 (s), 1610 (m), 1520 (m) and 1250 (s) cm^{-1}. A sample of this material chromatographed on Sephadex and sublimed had m.p. 67° - 69° (lit[47] m.p. of (113) = 65°).

The bulk of the crude material was dissolved in dry ethanol (20 ml) and concentrated sulphuric acid (10 drops) was added. The solution was refluxed for 14 hours, then poured into water and extracted with ether (3 x 20 ml). On workup the ether extracts afforded a yellowish mobile liquid which showed ν_{max} 1740, 1715, 1612, 1520, 1265, 1190 and 1045 cm^{-1}.

Preparative t.l.c. (40% ethyl acetate/petrol) gave two fractions, the more polar being the keto ester (110) (175 mg, 30%, b.p. 150° (a.b.t.)/25 mm Hg).

Found C 66.56% H 9.18%

$C_{11}H_{18}O_3$ requires C 66.64% H 9.15%

i.r. ν_{max} (neat) 1730 - 1705 (s), 1265 (m), 1195 (s), 1040 (m).

n.m.r. τ 8.8 (3H, t, J = 7 Hz), 8.8 - 7.4 (12H, envelope), 5.87 (2H, q, J = 7 Hz.).

The less polar band (125 mg) appeared to be a mixture containing the ester (141), evidenced by an AB quartet in the n.m.r. at 3.05 τ, and i.r. bands at 1735, 1610, 1520, 1260 and 1185 cm^{-1}.

Attempted ring expansion of the ester (110).

(1) A solution of the ester (110) (55 mg)(0.27 mmole) in dry ether (2 ml) was treated with a solution of boron trifluoride etherate (0.015 mmole) in dry ether (1 ml), followed by an ethereal solution of diazomethane (0.096M, 4 ml, 25% excess). The solution was stirred at 0° for 40 minutes, and was then washed with saturated sodium bicarbonate solution and brine, and dried. Removal of solvent gave the starting material (55 mg) unchanged (i.r., t.l.c.).

(2). The keto ester (110) (55 mg, 0.27 mmole) was dissolved in a mixture of ether (1 ml), ethanol (1 ml) and water (0.1 ml), and bis-(N-methyl-N-nitroso)terephthalamide (60% dispersion in oil, 250 mg) added. The mixture was cooled to 0° and a solution of sodium hydroxide in 50% aqueous ethanol (10%, 2.25 ml) added with stirring over a period of two

hours. The mixture was stirred for 12 hours, then acidified, poured into water and extracted with ether. Extraction of the ether with sodium bicarbonate solution, re-acidification and re-extraction with ether gave a white crystalline product which showed ν_{max} 3500 - 2500 and 1730 - 1690 cm^{-1}. Treatment with ethereal diazomethane followed by preparative chromatography gave an oil (14 mg).

i.r. ν_{max}(neat) 1737 (s), 1700 (s), 1265 (s), 1205 (s) 1180 (s) cm^{-1}.

n.m.r. τ 9.0 - 7.2 (envelope), 6.33 (s).

m.s. m/e (major peaks) 212, 198, 179, 170, 139, 138, 125, 111, 97, 95, 83, 81, 74, 69 and 67.

Peaks at m/e 212 and 198 in ratio approximately 2 : 1.

Ethyl bicyclo[5,3,1]undec-7(8)-en-11-one-1-carboxylate (115).

This compound was prepared by the method of Warnhoff, Wong and Tai[50], and was obtained as prisms, m.p. 50° - 53° (lit. 52° - 54°).

i.r. ν_{max} (Nujol) 1735 (s), 1695 (s), 1260 (s), 1105 (s) cm^{-1}.

n.m.r. τ 8.73 (3H, t, J = 7 Hz.), 9.0 - 7.0 (envelope, 12H), 5.81 (2H, q, J = 7 Hz), 3.78 (1H, b.m.)

t.l.c. (20% ethyl acetate/petrol) R_f 0.4

g.l.c. (5% QF-1, 150°) - one peak, retention time 3.0 minutes.

Ethyl bicyclo[5,3,1]undec-7(8)-en-9,11-dione-1-carboxylate (122).

The enone ester (115) (56 mg) was dissolved in a mixture of acetic anhydride (0.7 ml) and acetic acid (1.3 ml), and anhydrous sodium chromate (86 mg) was added. The mixture was heated at 50° for 16 hours, then poured into water. Extraction with ether and workup of the extracts afforded an oil (67 mg) which appeared on examination by t.l.c. to consist of one component, identified as the ene-dione ester (122).

i.r. ν_{max} (neat) 1732 (s), 1705 (s), 1678 (s), 1620 (w), 1250 (s), 1215 (s), 920 (m).

n.m.r. τ 8.68 (3H, t, J = 7 Hz.), 9.0 - 7.0 (10H, envelope), 7.22 (1H, d.d., J = 18 & 2 Hz.), 6.60 (1H, d, J = 18 Hz.), 5.73 (2H, q, J = 7 Hz.), 3.66 (1H, m).

g.l.c. (5% QF-1, 150°) - one peak, retention time 6.6 mins.

The 9-mono(toluene-4-sulphonylhydrazone) of this compound was prepared by refluxing for 30 minutes a solution in methanol of equimolar quantities of the ene-dione ester (122) and toluene-4-sulphonylhydrazine. On cooling, the hydrazone (126) crystallised, and recrystallisation gave needles, m.p. 201.5° - 203°.

Found C 61.14% H 6.42% N 7.23%

$C_{21}H_{26}N_2O_5S$ requires C 60.28% H 6.26% N 6.69%

i.r. ν_{max} (Nujol) 3260 (m), 1730 (s), 1692 (s), 1355 (s), 1165 (s) cm^{-1}.

n.m.r. τ 8.73 (3H, t, J = 7 Hz.), 9.0 - 7.0 (10H, envelope), 7.60 (3H,s), 7.33 (1H, b.d., J = 18 Hz.), 6.85 (1H, b.d. J = 18 Hz.), 5.85 (2H, q, J = 7 Hz.), 3.42 (1H, b.s.), 2.70 (2H, d, J = 9 Hz.), 2.15 (2H, d, J = 9 Hz.), 1.80 (1H, b.s.).

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