Studies on Bredt's Rule.

THESIS

presented to the University of Glasgow
in part fulfilment of the requirements
for the degree of Doctor of Philosophy

by

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October, 1978.

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Acknowledgements

I should like to thank most sincerely my supervisor, Dr. G.L. Buchanan, for his guidance and friendship during the course of this research, and Professor G.W. Kirby for allowing me to undertake this work in the University of Glasgow Chemistry Department.

The friendship of my fellow research workers has contributed much towards making my stay in these research laboratories a pleasurable one during the last three years and to them I am grateful.

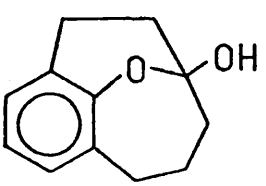
I am indebted to the members of staff who supply the technical services for their assistance and to Mrs. Rae Miller and Maria Pita who performed the onerous tasks of typing and proof-reading the thesis respectively.

The provision of a maintenance award by the Science Research Council is gratefully acknowledged.

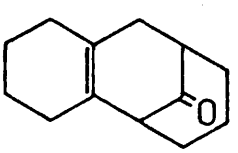
Summary

The object of the first part of this thesis was to determine whether a bridgehead double bond is more stable when located in the larger or smaller bridge of a bicycle. For this purpose a unique Bredt compound (A) was prepared. This is the only verified example of an aromatic ring located on two bridges of a bicycle. The compound was examined (^{1}H n.m.r., ^{13}C n.m.r., u.v. and Raman) for evidence of bond-fixation (Mills-Nixon effect) within the aromatic ring. An x-ray analysis was not possible, but other workers have made available molecular mechanics calculations on (A). Although there was spectroscopic evidence that the benzene ring is non-planar and molecular mechanics calculations show that some bonds are unusually short, there was no indication that it is other than aromatic. On the basis of the calculations, it would appear that, contrary to published evidence, the bridgehead double bond is more stable when located in the smaller bridge. The preferred conformation of the molecule, as deduced spectroscopically, was in agreement with that calculated for (A).

The second part of the thesis describes an attempt to use ring annulation-scission methods to synthesise macrocycles from available five and six membered rings. The necessary tricyclic (B) and benzo-tricyclic (C) precursors were obtained, but various attempts to cleave the bridges of these compounds proved more difficult than expected. Thus, the amide derived from (B) by Beckmann rearrangement of its oxime, could be hydrolysed, but rapidly recyclised on standing.



(A)



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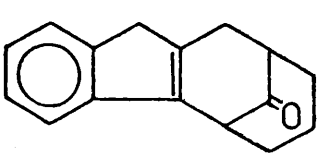

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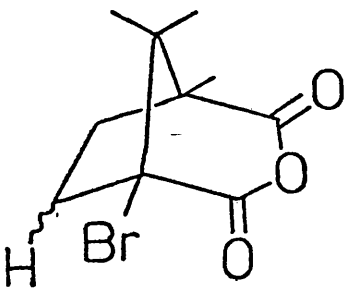
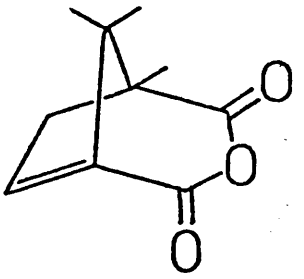
INTRODUCTION TO PART 1

A SHORT REVIEW OF BREDT'S RULE



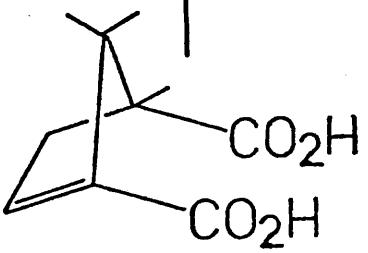
(1)

$-HBr$



(4)

$-H_2O$



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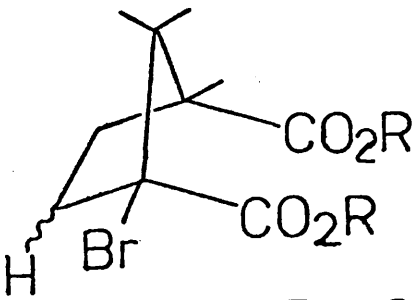
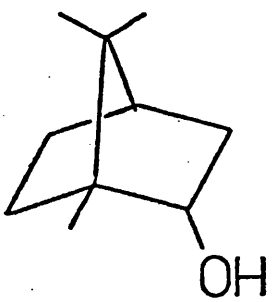


(2) $R = C_6H_5$



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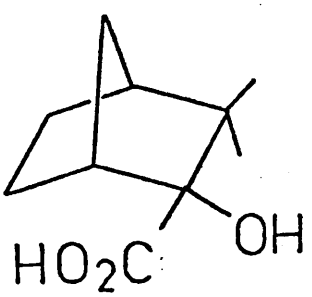


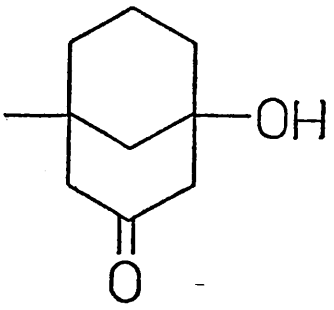
(6)

Since the first announcement by Julius Bredt of the rule which now bears his name, Bredt compounds and the Bredt rule have been the subject of much investigation by many researchers. As a consequence, a wealth of knowledge has been accumulated in this specialised field which is that of highly strained polycyclic hydrocarbons containing a double bond at the bridgehead position.

The published work includes several reviews set against a background of numerous papers and communications which have appeared over a period of more than half a century. The purpose of this introduction is to describe briefly the more important milestones in the development of this interesting field of chemistry up to the present day.

Although the first formal statement of Bredt's rule was made in 1924[1] there were several similar observations made previous to this by Bredt and other workers. In 1902 Bredt, Houben and Levy[2] compared the relative ease of dehydrohalogenating the α-halocamphoric acid derivatives (1) and (2). It was found that the anhydride (1) could not be dehydrobrominated whereas the corresponding dicarboxylic ester (2) could be readily dehydrobrominated. Also, the unsaturated dicarboxylic acid (3) was found to be incapable of forming an internal anhydride (4) whereas saturated analogues underwent this cyclisation readily. The difficulty in forming (4) was correctly attributed by Bredt to the stereochemical nature of the compound.

In 1903 Wagner and Brykner[3] again put forward stereochemical reasons for the formation of tricyclic derivatives upon dehydration of isoborneol (5) and camphenilic acid (6), suggesting that the formation of a double bond at a carbon atom common to two pentamethylene rings is disfavoured. In 1908 Rabe[4] reported the unusual resistance of the β-hydroxyketone (7) to dehydration. He offered steric reasons as the explanation saying ".... the bicyclic system offers great



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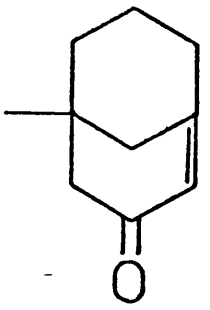

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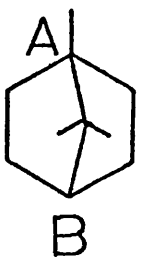

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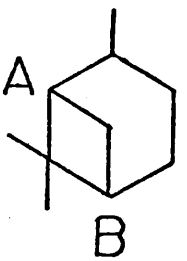

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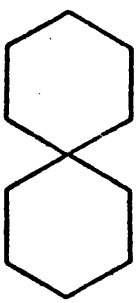
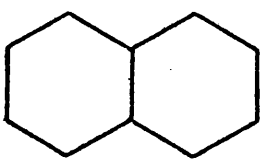
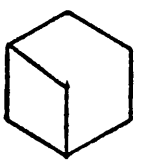


(11)
SPIRO



(12)
FUSED



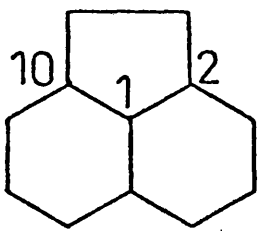
(13)
BRIDGED

resistance to the formation of a double bond in the 1,2 position". (as in (8)).

Subsequent investigations, particularly by Bredt and co-workers, provided compelling evidence in a general sense of the type of compound in which a double bond cannot occur. The formal statement of the rule came in 1924[1] : "On the basis of our conceptions of the positions of atoms in space, in the systems of the camphane (9) and pinane (10) series, as well as in similarly constituted compounds, a carbon double bond cannot occur at the branching positions A and B of the carbon bridge (the bridgeheads)". Soon after, Bredt realised two things : firstly that the rule need not be restricted to compounds of the camphane and pinane series and similarly constituted compounds, and secondly that stable bridgehead double bonds were indeed possible if only the bridge were large enough. Accordingly, in 1927 he modified his rule[5]. Since then the rule has been restated and extended several times to allow for circumstances apparently unforeseen by Bredt at the time. These events will be discussed elsewhere in this introduction.

Bicyclic systems can be grouped into the types illustrated by formulae (11), (12) and (13). In the past structures such as (11) and (12) were always excluded from Bredt's rule. In its original form Bredt's rule also made no mention of heterocyclic systems. However it is now accepted that similar geometric constraints must apply to these systems except in cases where elements below the first row of the periodic table are present (such as sulphur). The rule has also been applied to systems in which the double bond is part of an aromatic ring[6].

Tricyclic systems in which all of the rings are not mutually contiguous can be treated as substituted bicyclic compounds. If there are three mutually contiguous rings however there may be a question as to whether the rule applies, since the criterion of the



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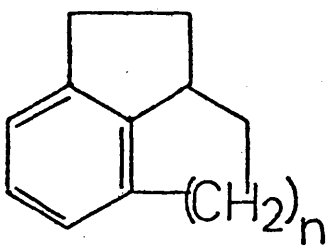
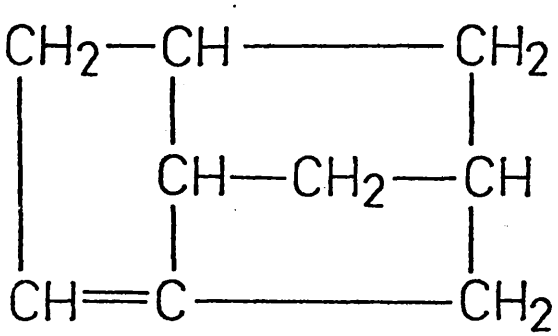


(15) a) n = 1

b) n = 2



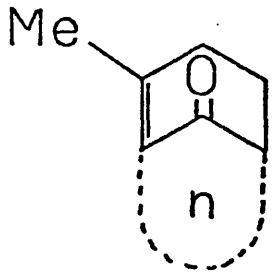
(16)

number of atoms in common needs qualification.

Bredt[7] regarded perhydroacenaphthene (14) and similarly constituted structures as bridged-ring considering, for example, C_1 as a bridge across the eleven membered ring containing C_2 and C_{10}, while Patterson[8] on the other hand considered (14) to be a fused-ring with three ortho fusions among the three rings. Hückel[9] included the ring system (15a) in a discussion of Bredt's rule. Compounds of this type which have bridgehead double bonds are known where the rings are larger, for example, tetrahydroacenaphthene (15b), and these larger ring homologues appear to be reasonably unstrained.

As in the case of bicyclic systems the ring size is the determining factor in tricyclic systems although the critical value in deciding the feasibility of a bridgehead double bond may be slightly different. Fawcett[10] suggests than an approximate criterion to decide whether the rule permits or forbids a bridgehead double bond in a tricyclic structure is to consider the smallest bicyclic analogue from which it can be regarded as being derived by incorporation of an additional bond or bridge. The presence of this additional bond or bridge would not be expected to reduce the amount of strain. Thus a compound having the structure (16) might be considered as being derived from bicyclo [3.2.1]-5-octene by adding a carbon bridge. According to the rule this structure is therefore prohibited.

In the years following Bredt's publication[1] the concept was widely adopted by researchers working with bridged ring systems and was found to be an invaluable aid to excluding erroneous structures which could look entirely plausible on paper. In fact a large number of structures which had been assigned previous to Bredt's rule were re-examined and had to be corrected. This aspect of Bredt's rule



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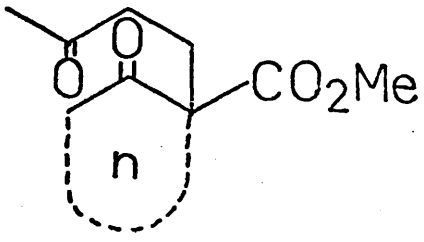
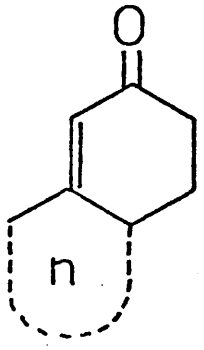


(17)

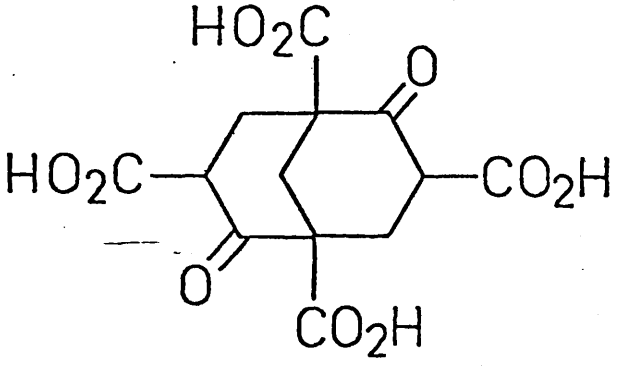
acid or base →

+



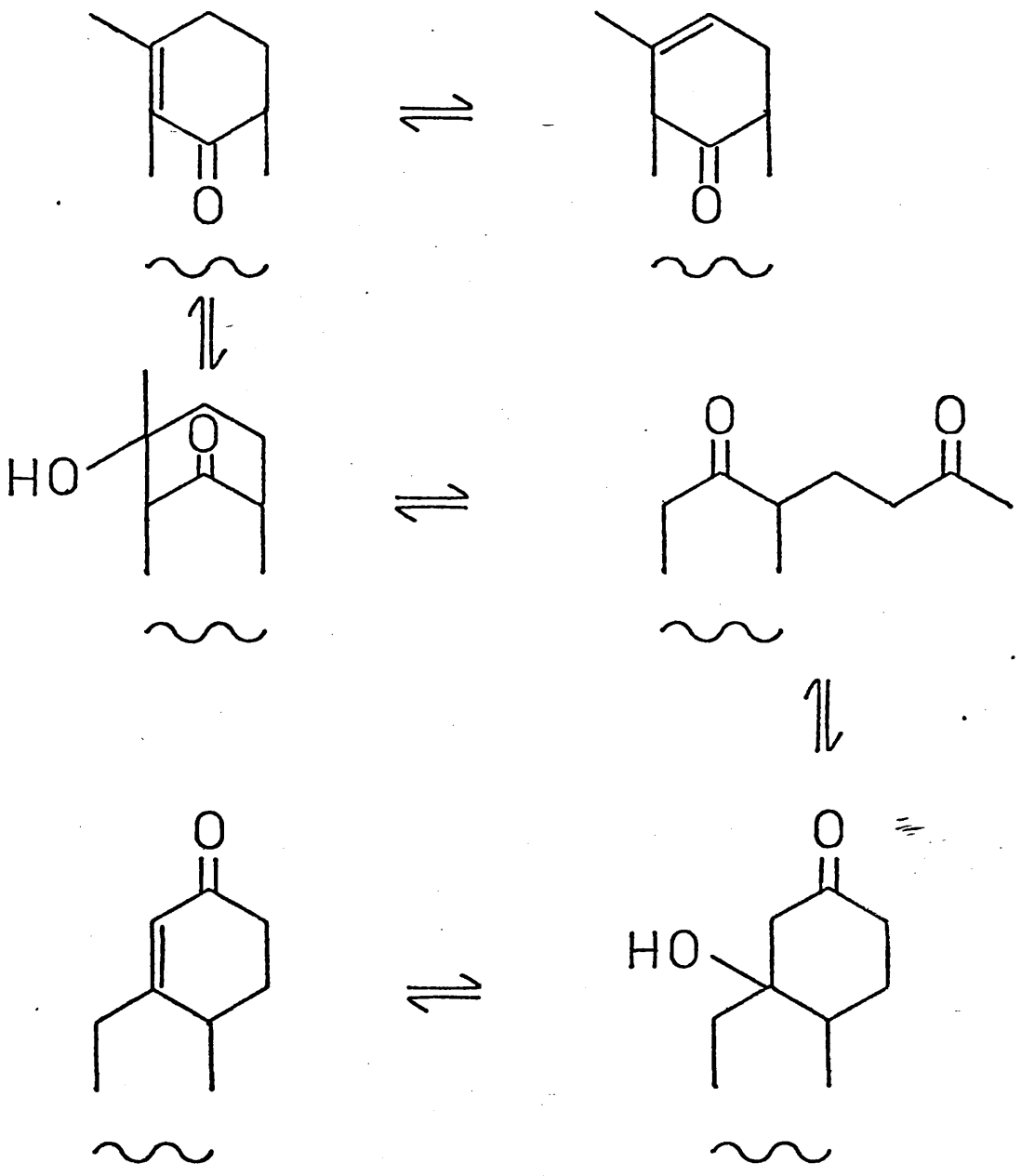
(19)

n = Total number of carbon atoms in ring



(20)

Scheme 1

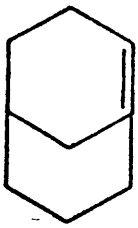


has been presented by Fawcett[10] in great detail.

A natural consequence of Bredt's rule was that efforts be made to locate the exact limits of the rule. This task was pursued by Prelog and others. Prelog[6a, 11] studied the aldol condensation of (17) and found that the ratio of products (18) and (19) was a sensitive function of n. He concluded that bicyclo [5.3.1] undecane was the smallest system that could accommodate a bridgehead double bond.

Prelog's investigations, however, present two drawbacks. Firstly they relate solely to bridged cyclohexenones with the carbonyl group located in the smallest bridge and secondly all his experiments were carried out under equilibrating conditions which would yield only the thermodynamically preferred product. As Buchanan[12, 13] has pointed out, such cyclisations involve five equilibria (Scheme 1) interconverting structural isomers and double bond isomers. As a result the isolation of one product rather than another simply mirrors the difference in their free energies. It is entirely possible that different products might arise under conditions of kinetic control.

Fawcett[10] made significant contributions to the subject by re-expressing Bredt's rule in terms of S numbers and also by making the valuable distinction between isolable alkenes and transient intermediates containing a bridgehead double bond. He defined the strain number S in a bicyclo [x.y.z] alk-1-ene as $S = x + y + z$ (x, y and $z \neq o$) and so deduced from Prelog's results that $S = 9$ represents the smallest ring size where a bridgehead double bond can occur in an isolable compound. He concluded that "the tentative upper limit to the ring size for which the rule forbids such double bonds in isolable compounds is $S = 8$". At the same time he realised that for a transient reaction intermediate the limit might be as low as $S = 6$. He knew for example that the ketoacid (20) (which has an



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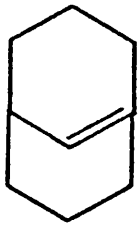

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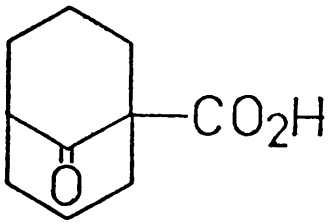

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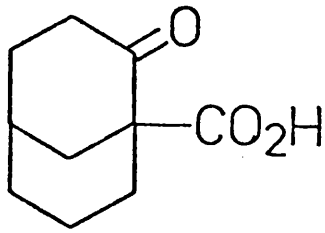

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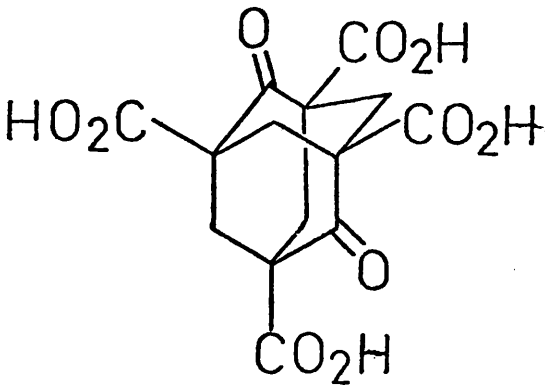

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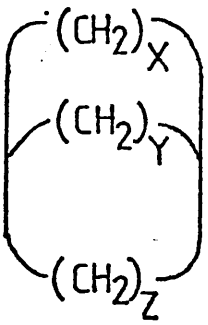

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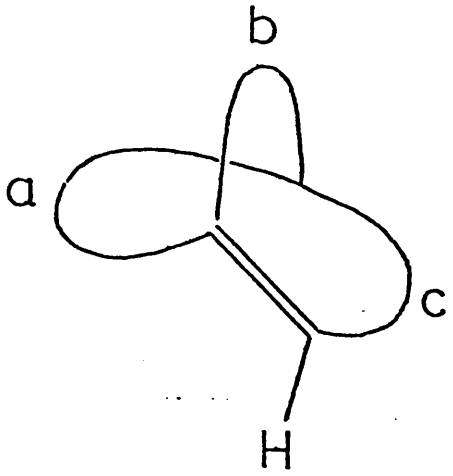

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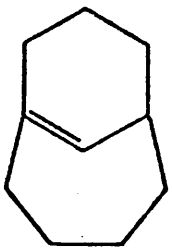

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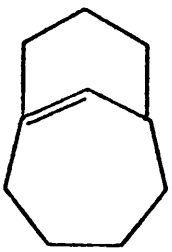

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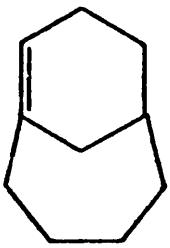

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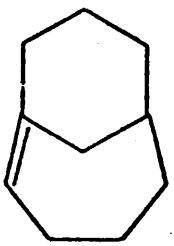
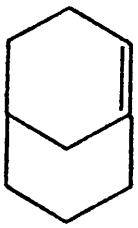


(31)

S number of 7) could be totally decarboxylated.[14]

At the time of Fawcett's proposals it was recognised that the stability of a bridgehead double bond depends on which branch of a bicyclic system it is contained. Yet Fawcett's S formula fails to differentiate isomeric alkenes such as (21) and (22) which have the same strain number (S = 7) but differ in strain energy. This difference is exemplified by the high stability[15] of the ∝-ketoacid (23) on the one hand and the ready decarboxylation of (24)[16] on the other, and also by the extreme resistance[17] of (25) to decarboxylation in contrast to the behaviour of (20).[14]

In 1967 a more fundamental approach to defining the limits of Bredt's rule was proposed by Wiseman.[18] He pointed out that a bridgehead double bond in any bicyclic alkene (26) is endocyclic to two of the rings, and must lie trans within one of these (ac in (27)). He postulated therefore that "the strain of bridgehead alkenes is closely related to the strain of trans-cycloalkenes". On this basis he predicted that since trans-cyclo-octene[19] is a highly reactive yet isolable compound, bridgehead alkenes which incorporate a trans-cyclo-octene should be isolable even if unstable. In a similar fashion he predicted that since trans-cycloheptene[20] has been prepared only as a transient reactive species, bridgehead alkenes which incorporate a trans-cycloheptene might be isolable and would be detectable as transient intermediates. This revision of Bredt's rule now allows one to predict that, for a given carbon skeleton, the double bond will be more stable if it is trans within the larger of the two rings to which it is endocyclic. Thus (28) (a trans-cycloheptene) should be more stable than (29) (a trans-cyclohexene). Also, (30) (a trans-cyclononene) should be more stable than (28). Wiseman's postulate is of no use in differentiating (30) and (31), however.



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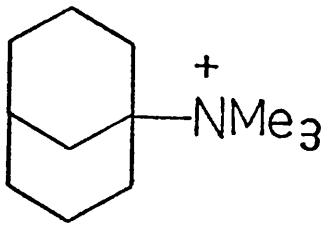

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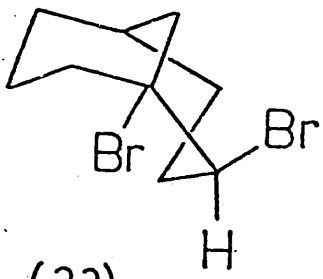

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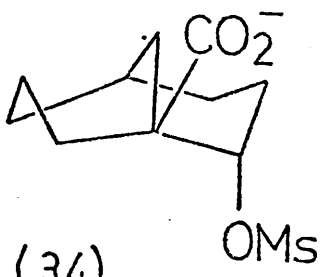

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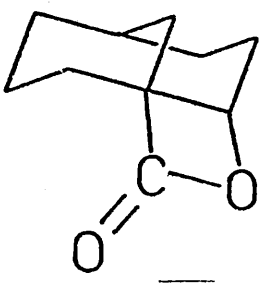

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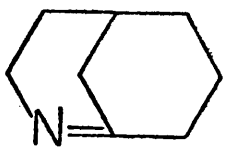

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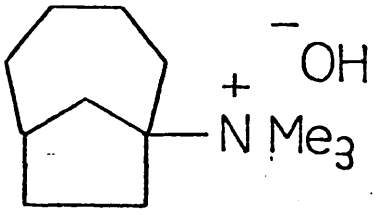

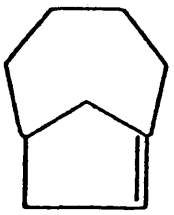

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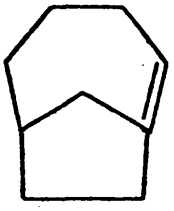

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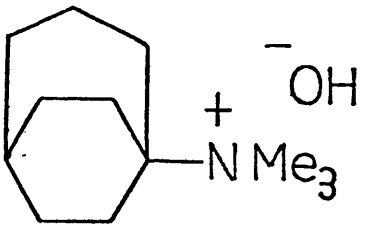

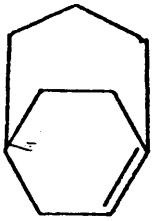

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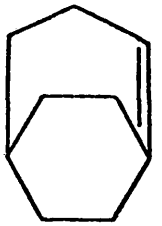

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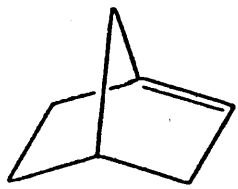

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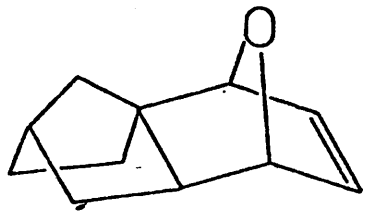
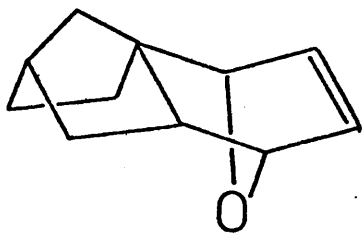


(42)



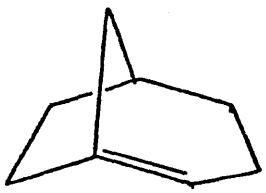
(43)

Since 1967 much effort has been expended in developing syntheses of bridged bicyclics containing bridgehead double bonds[21] particularly by Wiseman. Bicyclo [3.3.1] non-1-ene (21) was synthesised simultaneously in two laboratories *via* irreversible elimination reactions. Wiseman[18] obtained it from the quaternary ammonium salt (32) and from the 1, 2 dibromide (33) by the action of sodium t-butoxide. Marshall[22] used decarboxylative elimination of the *endo*-methane p-sulphonate (34) to prepare (21), obtaining the β-lactone (35) as byproduct. The aza analogue (36) is now also known.[23]

At this point it would be helpful to introduce a point of nomenclature. The bar (-) symbol is used to indicate in which bridge of a system the bridgehead double bond lies. So, for example, (38) may be called bicyclo [4.2.1] non-1(2)-ene or bicyclo [$\bar{4}$.2.1] non-1-ene and (37) may be called bicyclo [4.2.1] non-1(8)-ene or bicyclo [4.$\bar{2}$.1] non-1-ene.

The isomeric [4.$\bar{2}$.1] and [$\bar{4}$.2.1] systems[24] ((37) and (38)) and [3.$\bar{2}$.2] and [$\bar{3}$.2.2] systems[25] ((39) and (40)) were also synthesised shortly afterwards using the well-tried Hofmann elimination route. Compounds (37) and (38) are formed in the ratio 5:1 respectively and the preferential formation of the presumably less stable compound (37) has been attributed to the stereo-electronically favoured *syn*-elimination in the five membered ring.. The third possible olefin would contain a *trans*-cycloheptene and as such its non-occurrence is not unexpected. Olefins (39) and (40) dimerise rapidly and attempts to isolate the pure compounds failed.

In 1971 Keese and Krebs[26] reported the generation of 1-norbornene (41). By treating 1, 2-dihalogeno-norbornanes with butyl-lithium in the presence of furan two stereoisomeric adducts were obtained, which yielded the same 1,2 *exo*-norbornane dicarboxylic



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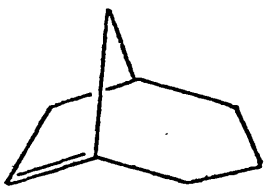

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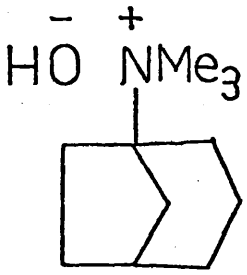

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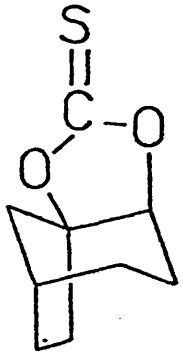

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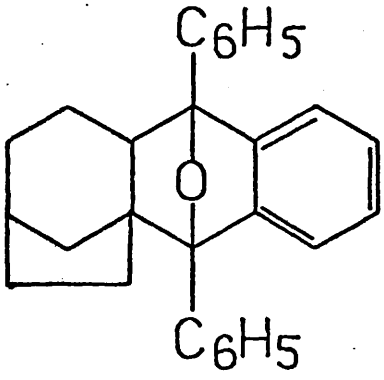

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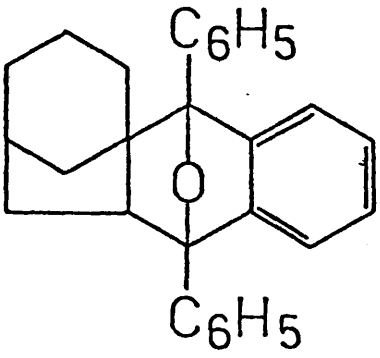

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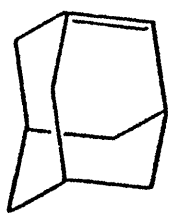

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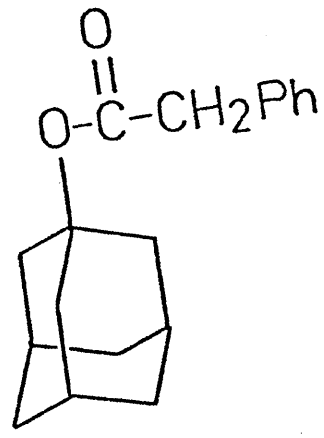

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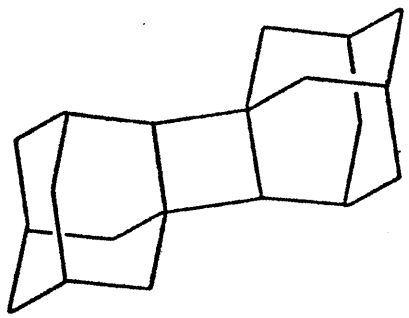

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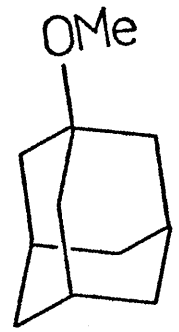

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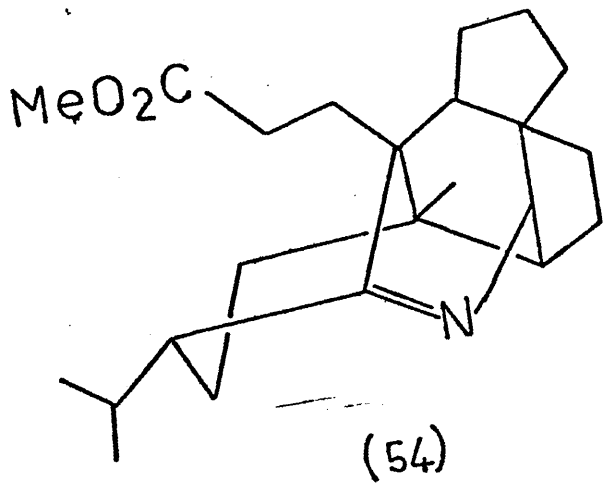
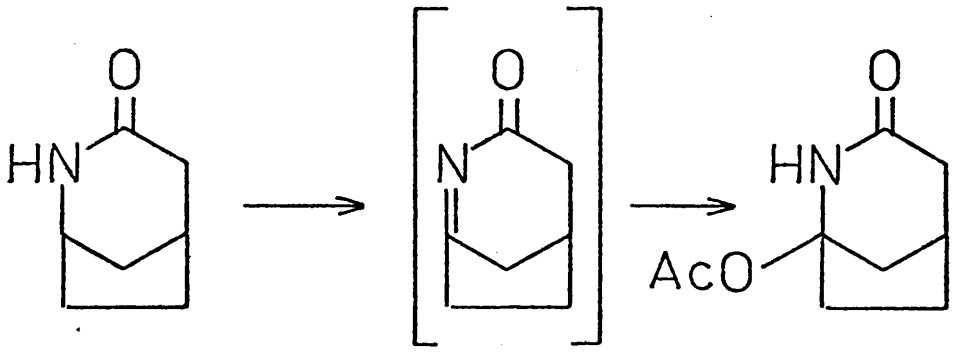
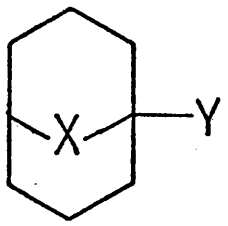
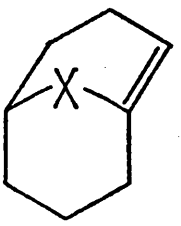


(54)



(55) (56)





(57) X = NMe, Y = Cl (60) X = NMe

(58) X = O , Y = OSO_2Me (61) X = O

(59) X = S , Y = OSO_2Me (62) X = S

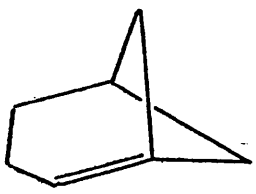
acid on oxidative degradation. These adducts must be (42) and (43). Irrespective of the nature or configuration of the halogens, the proportions of (42) and (43) remained constant and this is compelling evidence for the intermediacy of (41).

In 1972 the formation of the transient bridgehead olefins (44) and (45) in the bicyclo [3.2.1] octane ring system was disclosed.[27] The synthesis was accomplished via two routes involving in the first case the quaternary ammonium hydroxide (46) and in the second case the thionocarbonate (47). In both instances the olefins were trapped as their 1,3-diphenylisobenzofuran Diels-Alder adducts (48) and (49).

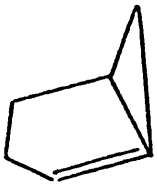
Adamantene (50) has also been generated as a transient intermediate both from 1,2-di-iodoadamantane by the action of butyl-lithium[28] and from the ester (51) by a photochemical Norrish type II fragmentation.[29] The former route yielded dimer (52) whilst the photochemically generated intermediate could be trapped with solvent to give for example (53) when methanol was used as solvent.

In its original form Bredt's rule made no mention of heterocyclic systems, however, as previously stated, the same geometric constraints must apply at least in cases where the heteroatom is in the first row of the periodic table. The smallest isolable example[23] is (54) which contains a trans-cyclo-octene and is formed by lead tetra-acetate oxidation of the corresponding dihydro-compound. A similar oxidation of amide (55) to (56) is believed[30] to involve a seven membered intermediate. No corresponding six membered case is known.

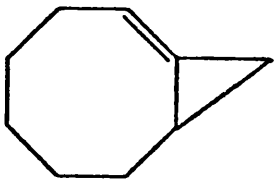
Bridgehead olefins having adjacent heteroatoms have also received some attention.[31] Compounds (57), (58) and (59), which may be prepared from 5-substituted cyclo-octanones, undergo base catalysed reaction to give the bridgehead olefins (60), (61) and (62) respectively.



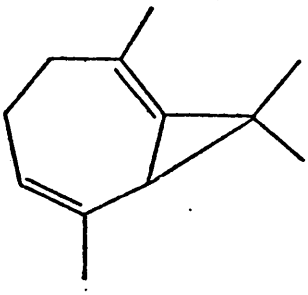
(63)



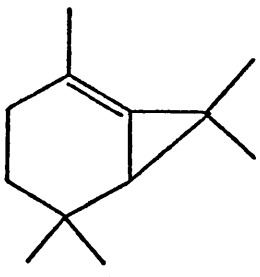
(64)



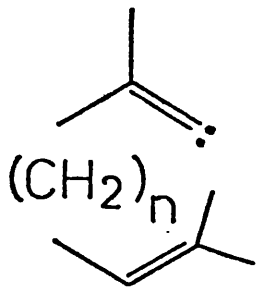
(65)



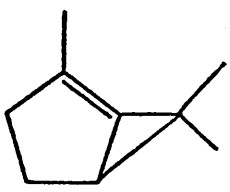
(66)



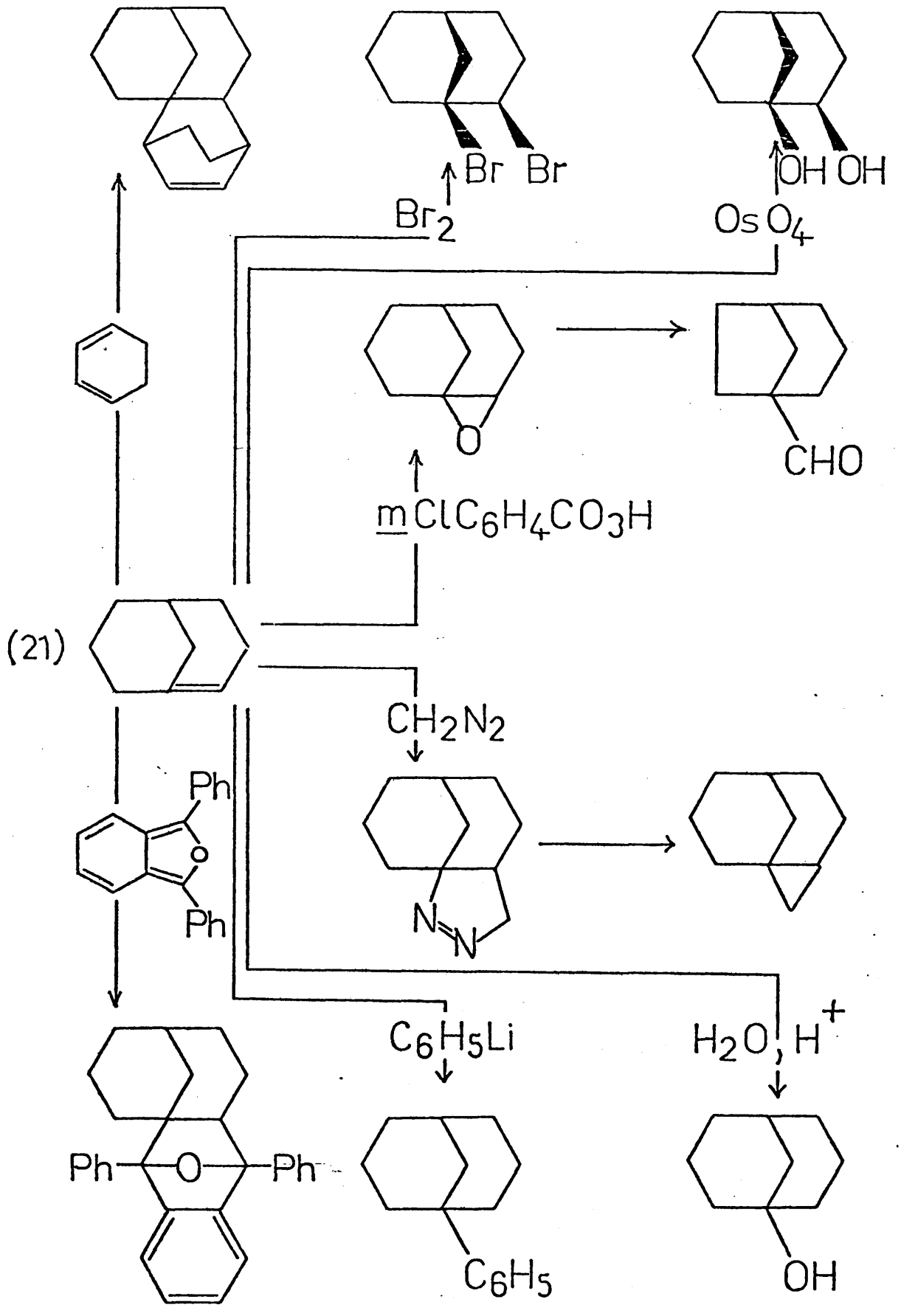
(67)



(68) n=3,4



(69)

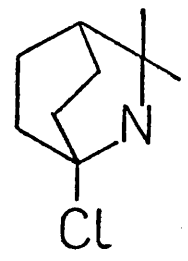

Br Br
Br_2
OH OH
OsO_4
O
CHO
$mClC_6H_4CO_3H$
(21)
CH_2N_2
Ph
O
Ph
N=N
C_6H_5Li
H_2O, H^+
Ph
O
Ph
C_6H_5
OH

These are formally bicyclo [3.3.1] non-1-enes in which the methylene bridge has been replaced by a heteroatom.

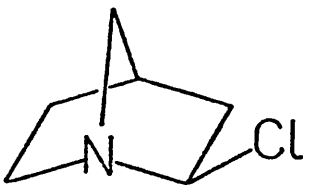
Fused bicyclic systems, previously excluded from Bredt's rule, have now been shown to be subject to similar restrictions as bridged bicyclic systems. Köbrich[32] has argued the case for including fused systems with "classical" Bredt compounds as follows. If a carbon atom bonded to two bridgeheads is removed from, say, bicyclo [3.1.1] hept-1-ene (63), which undoubtedly is a Bredt compound, the compound (64) is obtained. This might be expected to have a ring strain roughly comparable with (63) but where the twisting strain is slightly reduced and the deformation strain is slightly increased. Thus, if an [$\bar{x}$.1.1] or [x.$\bar{1}$.1] system is a Bredt compound, then the [$\bar{x}$.1.0] or [x.$\bar{1}$.0] system should also be considered as a Bredt compound. This seems reasonable if the strain is in fact related to the presence of a trans-cycloalkene as Wiseman has suggested.[18]

A stable trans-cyclononene (65) has been prepared from 9-bromo-bicyclo [6.1.0] nonane by elimination of hydrogen bromide and Köbrich has synthesised the analogues (66) and (67) which contain a trans-cyclo-octene and a trans-cycloheptene respectively. The preparation of (66) and (67) was accomplished via the appropriate vinyl carbene (68). Both were isolable though (67) slowly decomposed. Bicyclo [3.1.0] hexene (69) was formed but could be isolated only as its dimer. Attempts to synthesise the next lower homologue failed.

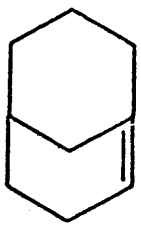
The physical and chemical properties of bicyclic compounds containing bridgehead double bonds have been studied. A case where the alkene was isolable is provided by that of the compound bicyclo-[3.3.1] non-1-ene (21).[18, 22] As the scheme opposite shows, reactions leading to saturation of the double bond take place readily. Adamantene and norborn-1-ene, being more highly strained, have only been trapped as adducts. However, the chemistry of the perfluoro-



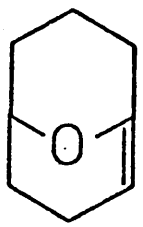
(70)



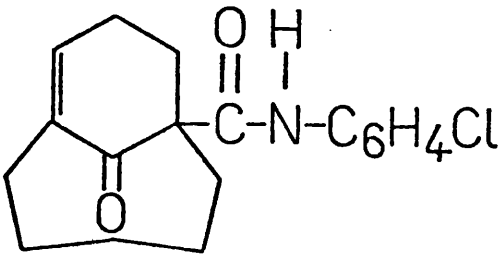
(71)



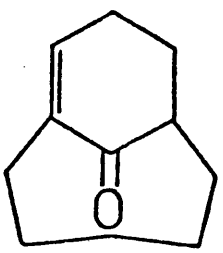
(21)



(61)



(72)



(73)

derivative of norborn-1-ene has been investigated[33, 34] and yielded a large number of interesting transformations.

The chemical behaviour of heterocyclic systems has also been studied.[31] Solvolysis studies[35] on (70) and (71) show that they react appreciably faster than their all-carbon analogues and this must involve some stabilization of the adjacent carbonium ion by p-orbital overlap from the nitrogen. In the cases of bridgehead olefins having adjacent heteroatoms it has been shown that the heteroatoms clearly influence the reactivity of the bridgehead double bond. For example, addition of acetic acid to (21) at 25°C is complete in under two minutes whilst the half reaction time for (61) is 68 hours. This is a result of constraining the heteroatom in a bridged bicyclic framework where the resonance of the heteroatom with the double bond has been inhibited while leaving the inductive effect essentially the same.

Crystallographic and spectroscopic analysis of Bredt compounds provides interesting data. A bicyclo [5.3.1] system (72) has been examined by x-ray crystallography[36, 37] and the strain in the system is seen to be present both in warping of the double bond and in bond angle deformation, particularly around the bridgehead position. The α,β-enone system is twisted out of ideal coplanar alignment and with conjugation thus inhibited the analogous enone (73) fails to add malonic ester under Michael conditions.[38] As regards the u.v. spectroscopy of these systems warping of the π-bond causes a bathochromic shift and a rise in ε max whilst poor overlap between two adjacent π-bonds (such as in (73)) leads to a drop in ε max but no change in λ max until the angle becomes severe whereupon there is a hypsochromic shift. An effect is also to be seen in the i.r. and n.m.r. spectra. A comparison of the i.r., u.v., and n.m.r. spectra of several alkenes and enones has been presented by Buchanan.[39]

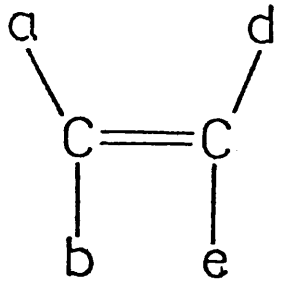


fig 1

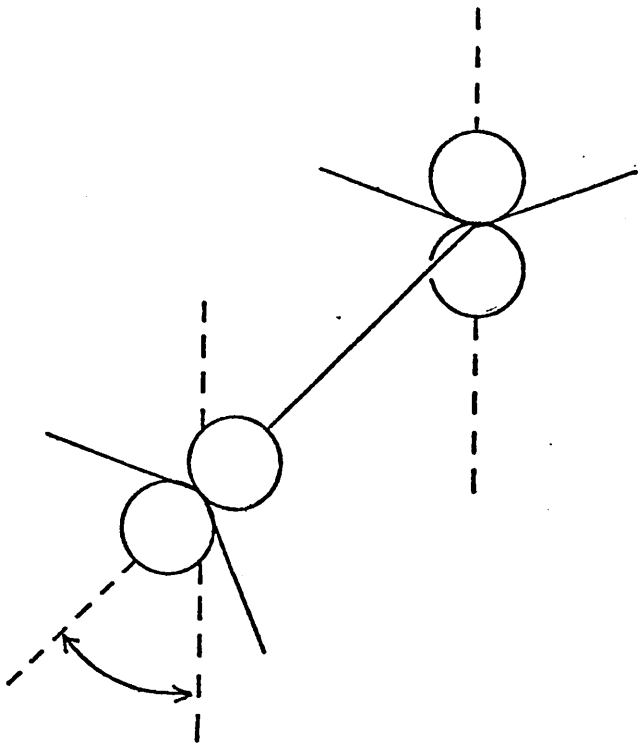
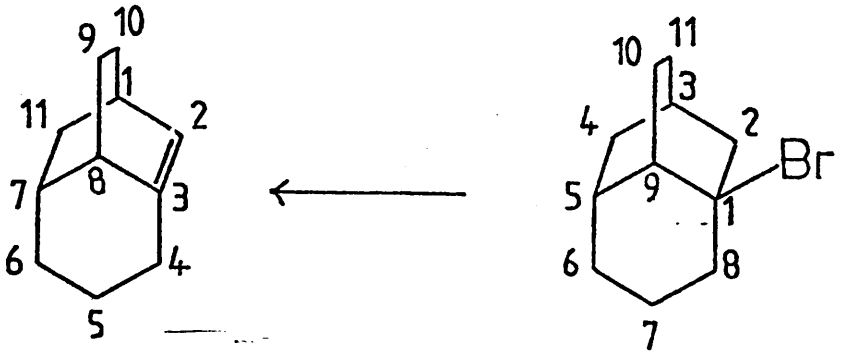
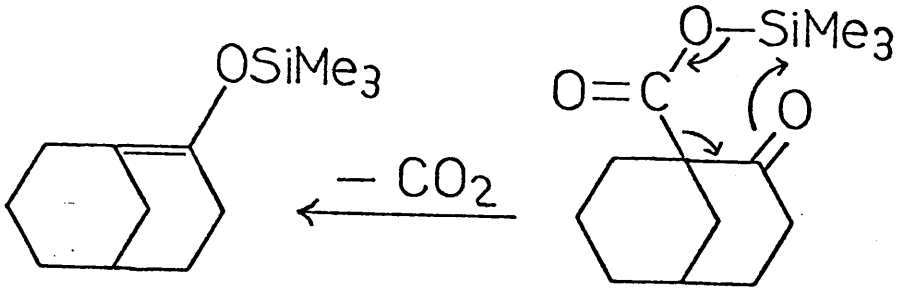


fig 2

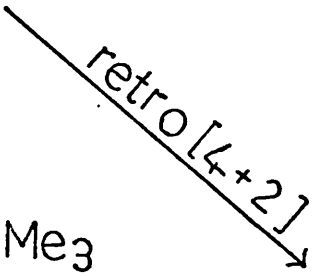


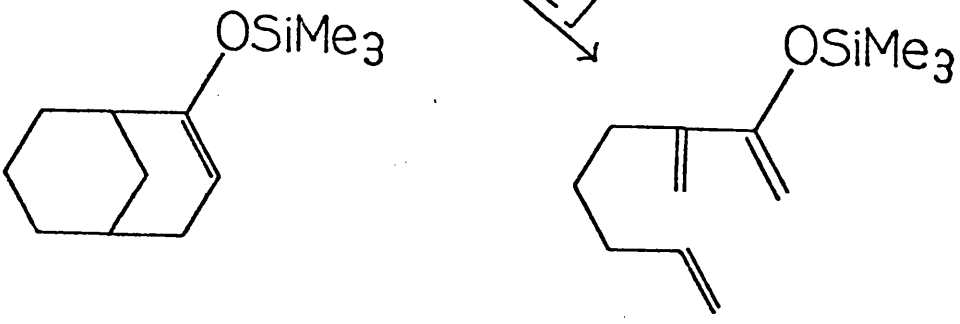
(74)

(75)

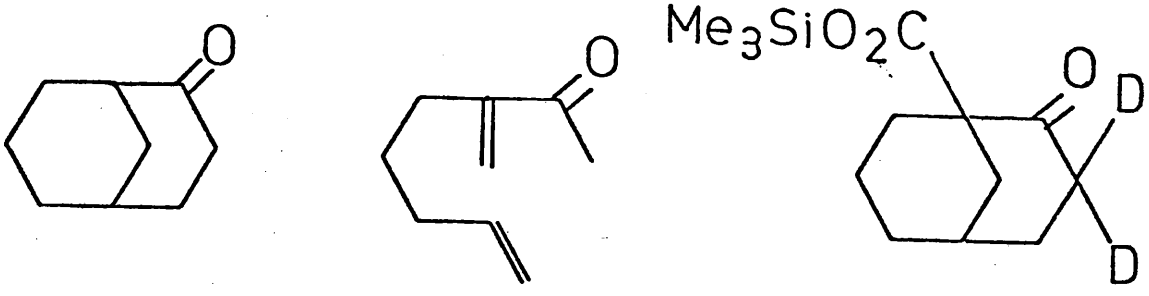


(76) (77)





(78) (79)



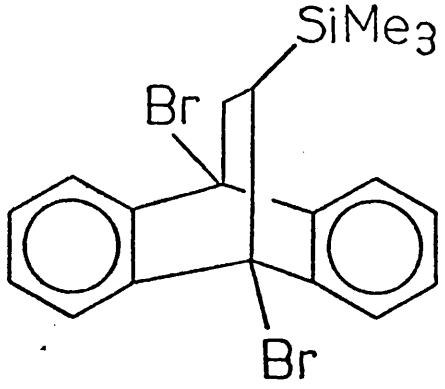
(80) (81) (82)

It is now clear that the instability of compounds containing bridgehead double bonds is due to the distortion of the double bond. The distortions are two-fold : a) In-plane deformations and b) Out-of-plane deformations. These are represented in figures I and 2 respectively. It should also be apparent from the foregoing discussion that the range of validity of Bredt's rule now encompasses bridged, fused and heteropolycyclic systems in which a double bond is located at a bridgehead position. The threshold between isolable and non-isolable alkenes may be different in each system.

Currently, the study of bicyclic bridgehead alkenes remains a topic of much interest. In 1975[40] synthesis of the tricycle (74) was reported. Prepared from (75) by dehydrobromination with sodium amide in refluxing toluene, the reaction was highly regio-specific giving neither 3(4)-ene nor 3(8)-ene. This was explained in terms of a planar cis-elimination of the 2-exo hydrogen and 1-bromine atoms. However the authors wrongly cite this as the first example of the formation of a Bredt compound in dehydrohalogenation of a bridgehead halide.[31d]

In 1976 Bloch[41] described evidence for the formation of a bridgehead trimethylsilyl enol ether (76) during the thermal decarboxylation of the ester (77). This report is of interest since the decarboxylation of some bicyclic β-ketoacids is suggested to proceed via strained bridgehead enols but the presence of these intermediates has never been shown. The products obtained from the thermolysis of (77) were the two enol ethers (78) and (79) and their hydrolysis products (80) and (81). Additional support for the intermediate formation of (76) was given by the thermolysis of the deuterium labelled keto-ester (82).

In 1977 the preparation[42] of (83), a derivative of (84),[43] was described. The generation of (83) was accomplished using fluoride



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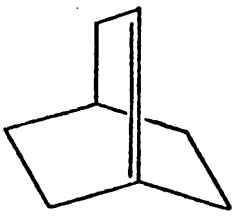
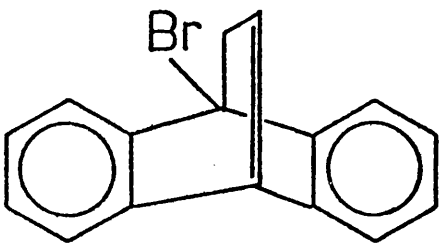
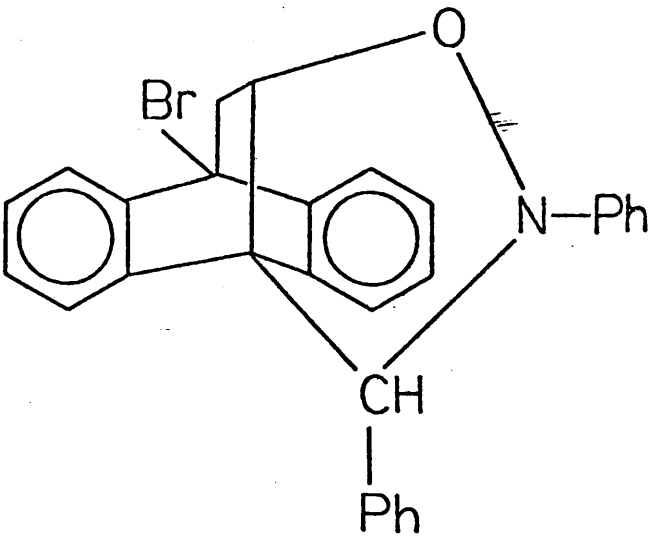


(84)



(83)



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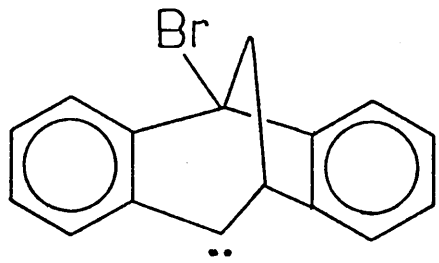
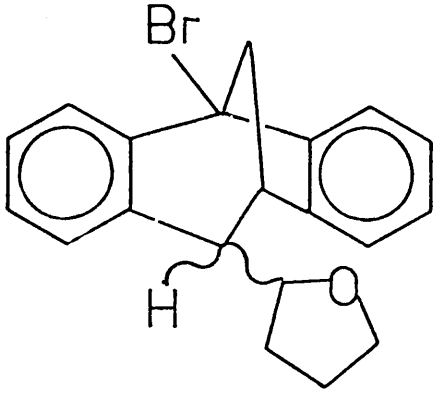


(87)



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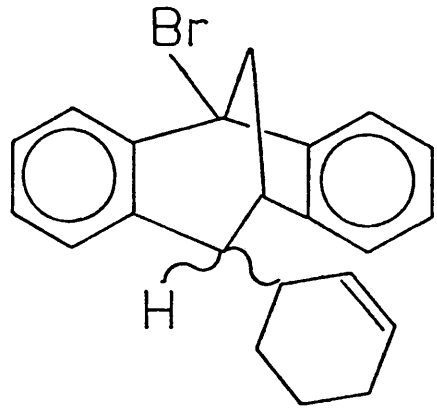

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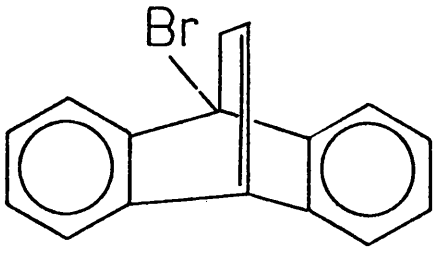
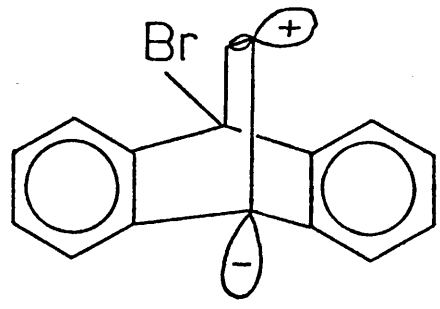


(83)



(83a)

ion-promoted elimination of β-halosilane from (85). Evidence for the formation of (83) was obtained by trapping it with C, N-diphenylnitrone to give the cyclo-adduct (86). Evidence for the intermediacy of the carbene (87), derived from the alkene (83) was obtained from the reaction of (85) in the presence of tetrahydrofuran and cyclohexene to give (88) and (89) respectively. The presence of (87) raises the question ever present in studies of strained alkenes: What is the nature of the double bond? Is it perhaps better represented in the ground state as a diradical or a C-ylide[26c] or is this merely a matter of semantics?[39] If (83) may be better represented by the dipole (83a) than by a diradical, the bicyclo [2.2.2] to [3.2.1] rearrangement can be understood since such rearrangements have been well documented in carbonium ion chemistry.

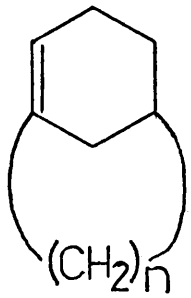
Looking to the future, studies on Bredt's rule will probably still concentrate on methods of synthesising the highly strained members of Bredt compounds and examining their physical and chemical properties. Yet there are unanswered questions amenable to study via larger ring olefins. For example, what is the relative stability of (90) and (91)? Wiseman's transcycloalkene hypothesis offers no help.

Köbrich has formulated three rules :

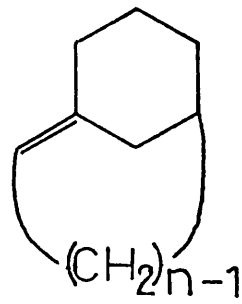
Rule A. For homologues with different S values, the ring strain varies inversely with S.

Rule B. For a given S, the ring strain varies inversely with the size of the larger of the two rings with respect to which the bridgehead double bond is endocyclic.

Rule C. For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.

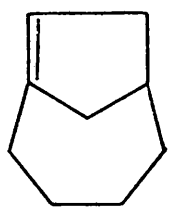


(90)



(91)

n > 3



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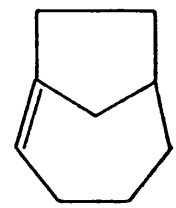

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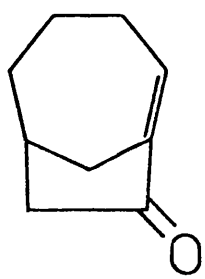
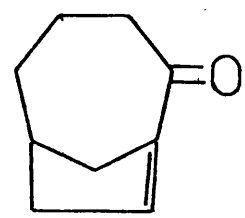


(92)



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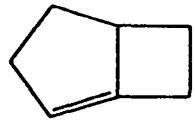
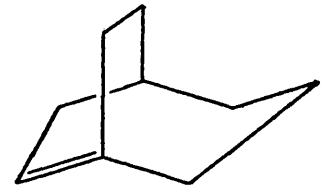


(94)



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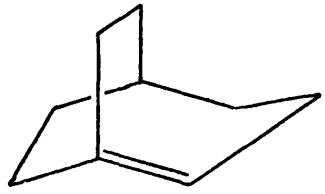

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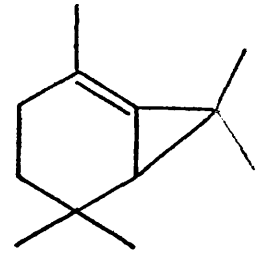
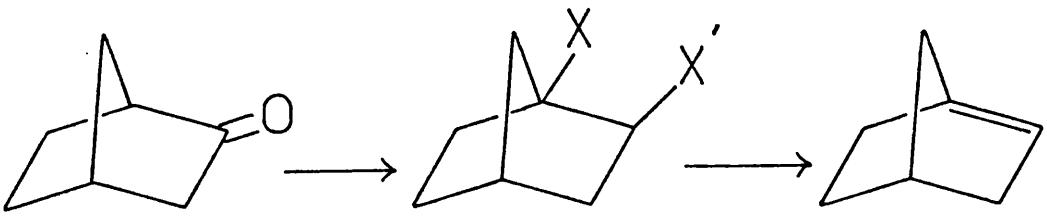
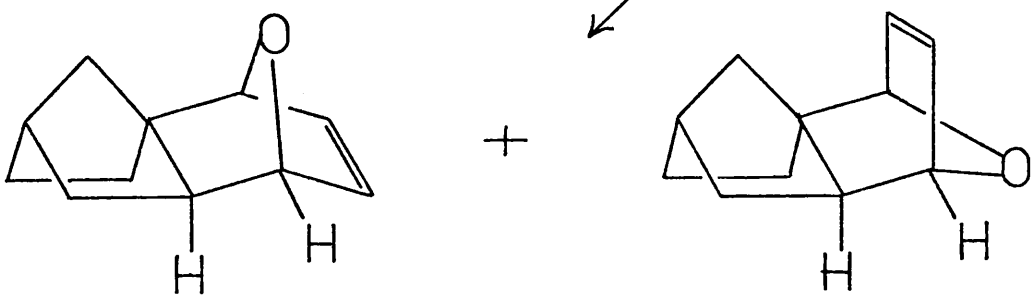


(67)

Scheme 2



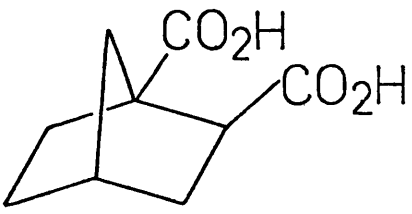
(96) $X = X' = Br$ $X = X' = J$ (41)



1. $O_3/CH_2Cl_2/-70^\circ C$

2 $CrO_3/CH_3COOH/H^+$

$70-75^\circ C$



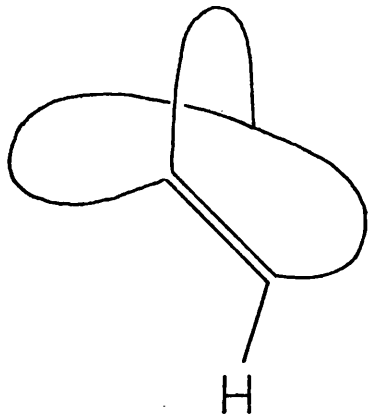
(95)

On the basis of Rule C therefore we would say that (90) is more strained than (91). Wiseman[24] had reached the same conclusion from a study of models but a PE-spectroscopic investigation was inconclusive.[44] In 1977 a paper describing molecular mechanics calculations arrived at the opposite conclusion[45] and recent estimations of the relative strain in (37) and (38) support this, namely that the double bond is more strained when it is located in the larger bridge.[46] An attempt to shed further light on the problem was made by Carruthers.[47] He had hoped to obtain an answer through a comparison of the properties of (92) and (93) but unfortunately was unable to synthesise the latter isomer.

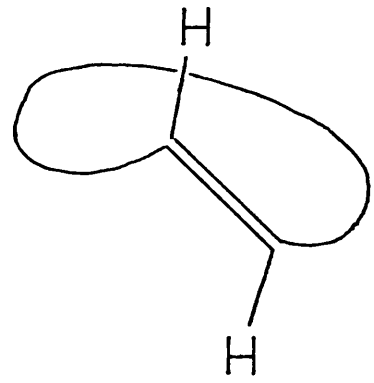
There are also anomalies to be explained in the case of, for instance, (94), (39), (40) and (67). Here, although all of the compounds incorporate a trans-cycloheptene, (94) is much more stable than any of the others.

The remaining facet of Bredt's rule which is still largely unexplored is the use of bridgehead olefins in synthesis. One example of this is to be seen in the synthesis of (95) from (96) via 1-norbornene (41).[26a] The synthesis was carried out as shown in Scheme 2.

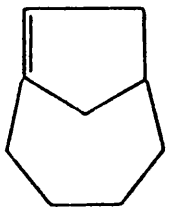
PART 1



(27)



(97)



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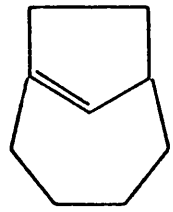

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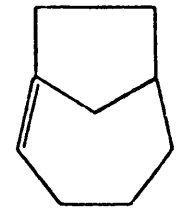

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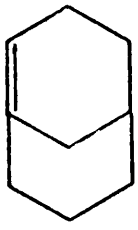

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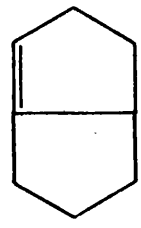

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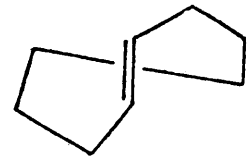

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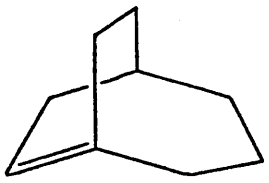

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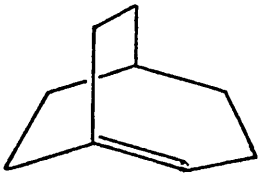

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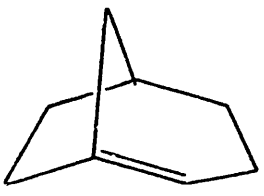

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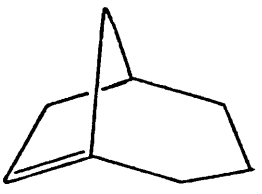

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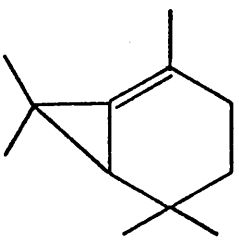

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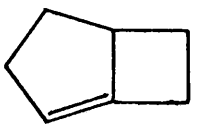
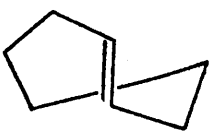


(94)



(101)

Bredt's Rule and the Mills-Nixon Effect.

Wiseman's redefinition[18] of Bredt's rule[10, 21a, 32, 39], in which the strain inherent in a bridgehead double bond (27) is related to the strain in the corresponding trans-cycloalkene (97), does itself need to be qualified or restated in more fundamental terms if it is to allow all of the double bond isomers within any given bridged bicyclic molecule, for example (37), (98) and (38), to be compared. The hypothesis indicates that (98) is more strained than either (37) or (38), however the energy relationship between (37) and (38) is not clear. Neither is it possible, on the basis of Wiseman's hypothesis, to distinguish between (37), (38), (21) and (99), though all of them are trans-cyclo-octenes, nor to compare them with trans-cyclo-octene itself (100).

Such experimental evidence as is available suggests that such isomers will not be equally strained. Thus, in the trans-cycloheptene series, (39) and (40) both dimerise at room temperature but at different rates;[25] (44) and (45) are also unisolable[27] while (67) has a half-life of approximately 70 hours at room temperature[48] and (94) appears to be far more stable than any of the others.[49] Trans-cycloheptene itself (101) has only been detected as a transient intermediate.[20]

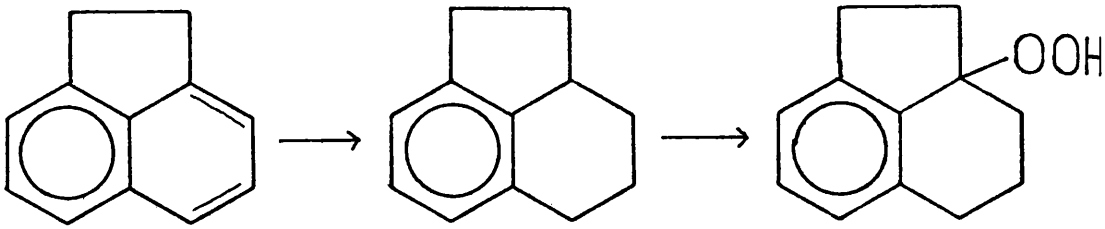
From the above data we may at least conclude :

1. Bridgehead double bonds in a bicyclo [x.y.o.] system, for example (94) and (99), are less strained than in a bicyclo [x.y.z.] system ($z \neq o$), for example (21) and (40).
2. Bridgehead double bonds in bridged systems differ in strain depending on whether they are located in the smaller or the larger bridge, as in (39) and (40).

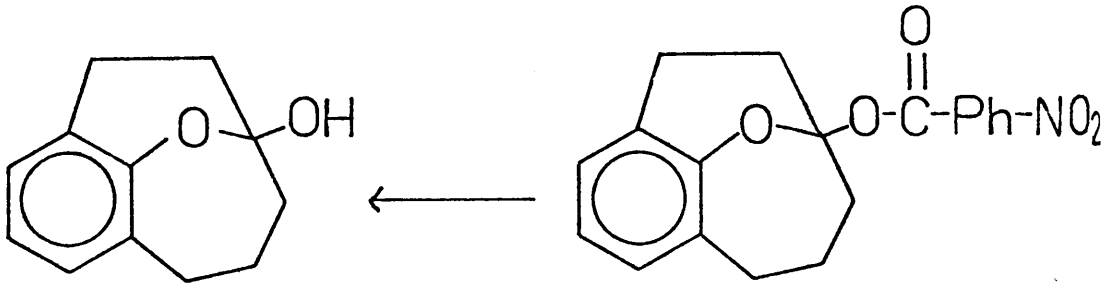
The purpose of our investigation was to clarify this latter point.

At the outset of this work Köbrich[32] and Wiseman[24] had independently arrived at the conclusion that a double bond located in the smaller

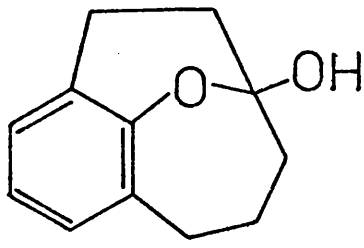
Scheme 3



(102) (15b) (103)



(105) (104)



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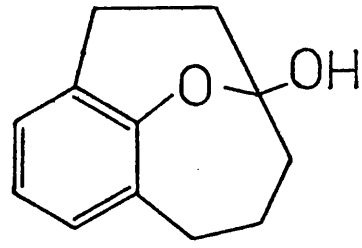

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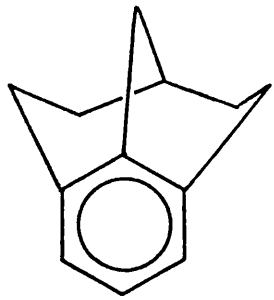
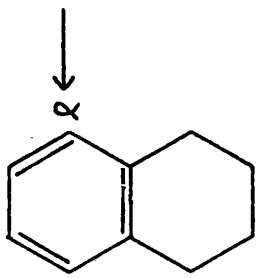
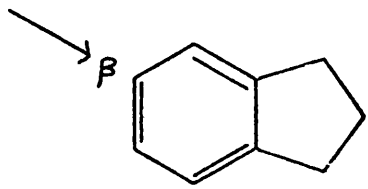


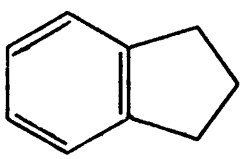
(106)



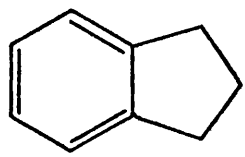
(107)



(108)



(108a)

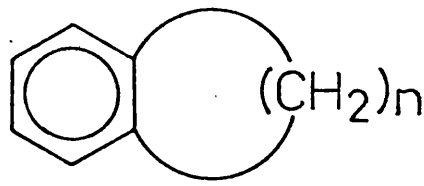


(108b)

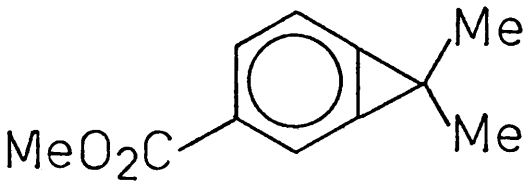
bridge will be the more strained one. Since the start of this work, however, Burkert[45], using molecular mechanics calculations, has arrived at the opposite conclusion. Recent estimations of the relative strain in (37) and (38) support this, i.e. that a double bond located in the larger bridge will be more strained.[46]

The present work describes an investigation of the bridged bicyclic hemiacetal (105) which had been obtained by Treibs[50] by the route shown in Scheme 3. An examination of molecular models indicates that the aromatic ring in (105) is severely strained and our objective was to investigate the possibility of bond fixation within the aromatic ring. Apart from (106)[51], which is symmetrical, compound (105) is the only known example of an aromatic ring located on two bridges of a bridged bicycle. The structure of (106) is completely unsubstantiated in that no structural evidence has been provided apart from an u.v. spectrum which, a little surprisingly, shows much fine structure. Compound (105) is therefore a unique Bredt compound in that the two contributing Kekulé structures (105a) and (105b) require a bridgehead double bond. Moreover, these structures will have different energies. It was hoped that a significant difference in energies between the Kekulé "isomers" would be reflected in a degree of bond localisation. In turn, it was hoped that this would shed light on the question as to whether a bridgehead double bond is more strained when located in the larger or smaller bridge of a bicycle.

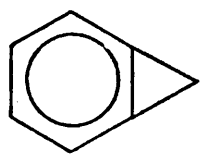
The concept of bond localisation originated in 1930 when Mills and Nixon[52] explained the predominant α substitution in (107) and β substitution in (108) in terms of the bond-fixated structures shown. At the time there was a search for confirmation of the effect using such physical and chemical techniques as were available but no firm evidence was obtained and the topic lost popularity. In 1946 Coulson and Higgins[53] published calculations to show that structure (108a) was



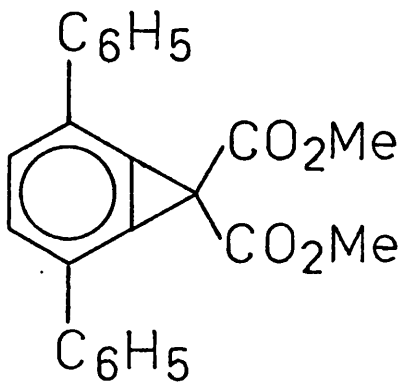
(109) n = 1 – 4



(110)



(111)



(112)

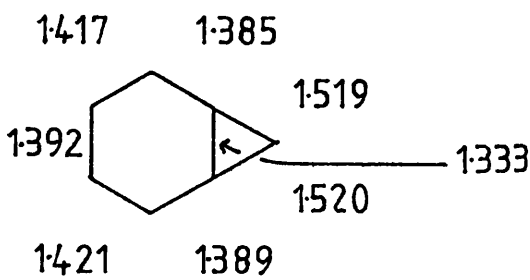


fig 3

Bond lengths (Å)

preferred rather than (108b) which contradicts the conclusion arrived at by Mills and Nixon. It was some 25 years till the next theoretical study was made on the geometries of benzocycloalkenes[54]. These semi-empirical calculations predict bond localisation in (109) and in vindication of Mills and Nixon concluded that in the case of indane structure (108b) contributes more to the hybrid than (108a). The reduced reactivity of the α position in (108) has been explained both in terms of strain[55] and hybridisation[56].

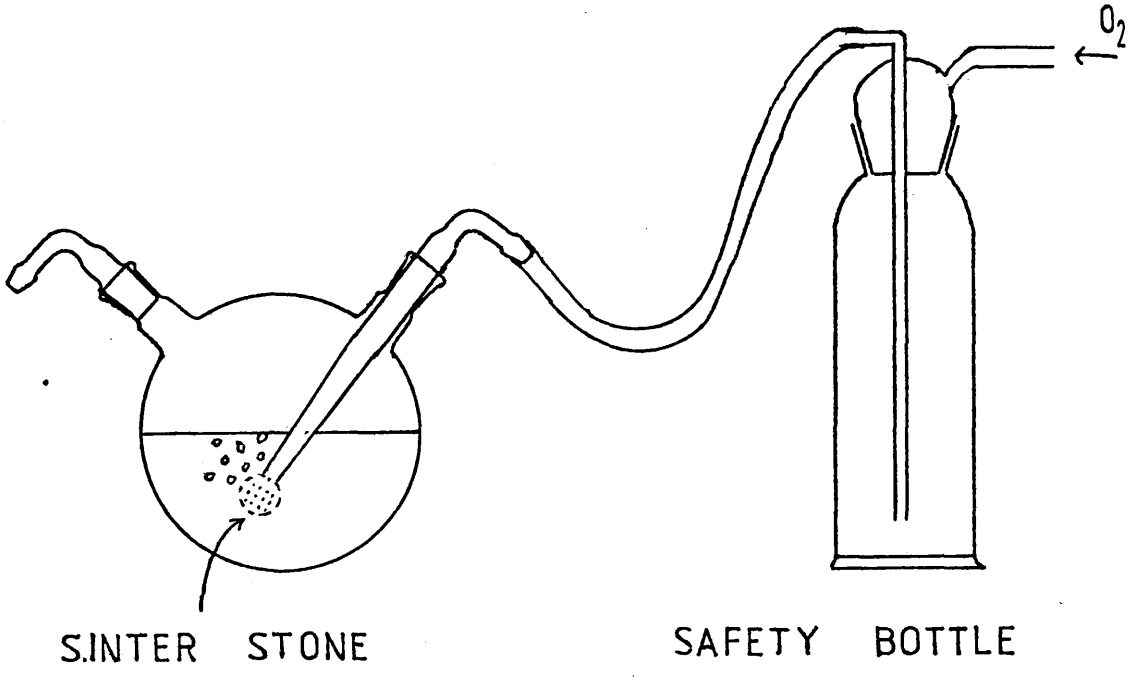
More recently, with the synthesis of molecules more strained than (108), and with the availability of modern techniques with which to examine them, there has been a reawakening of interest in the Mills-Nixon effect. The first substituted benzocyclopropene (110) was reported in 1964[57] and the parent compound (111) appeared in the literature in the following year[58]. X-ray data (see figure 3) on the substituted benzocyclopropene (112)[59] are not, however, readily interpretable in terms of bond-fixated structures. Although bond C_{1-6} is almost as short as a carbon-carbon double bond, bonds C_{2-3} and C_{4-5} are long, that is, there are three consecutive short bonds and not an alternating system as expected by the Mills-Nixon hypothesis. Neither is the decreased aromaticity associated with bond fixation evidenced by the observed diamagnetic ring current of (111) which would indicate a normal aromatic system.

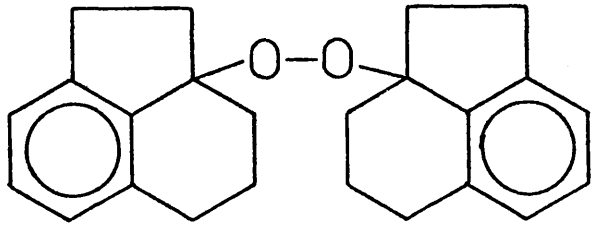
The strain in (111) is wholly due to in-plane distortion of the aromatic ring by the cyclopropene moiety. The effect of out-of-plane distortion on bond fixation has not been previously investigated and this is the type of ring distortion which is likely to be found in (105)

Synthesis of Hemiacetal (105).

Tetrahydroacenaphthene (tetraphthene) (15b) was readily obtained in almost quantitative yield by the hydrogenation of acenaphthene (102) over Raney nickel catalyst[60]. The hydrogenation was carried out at

Fig 4





(113)

Fig 5

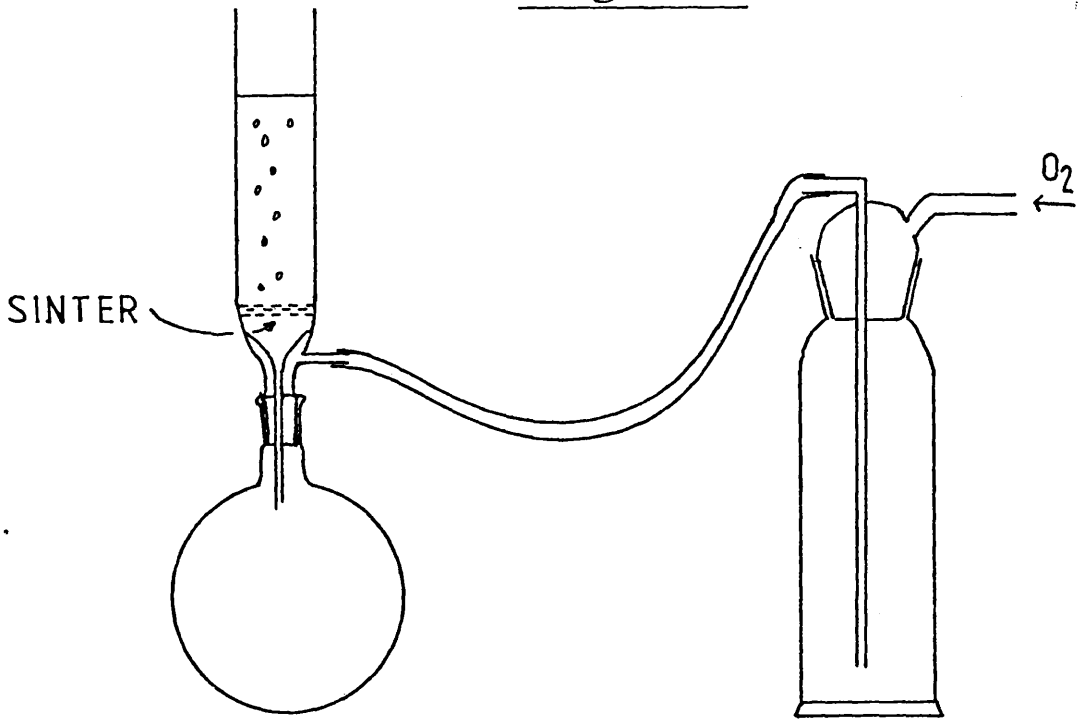
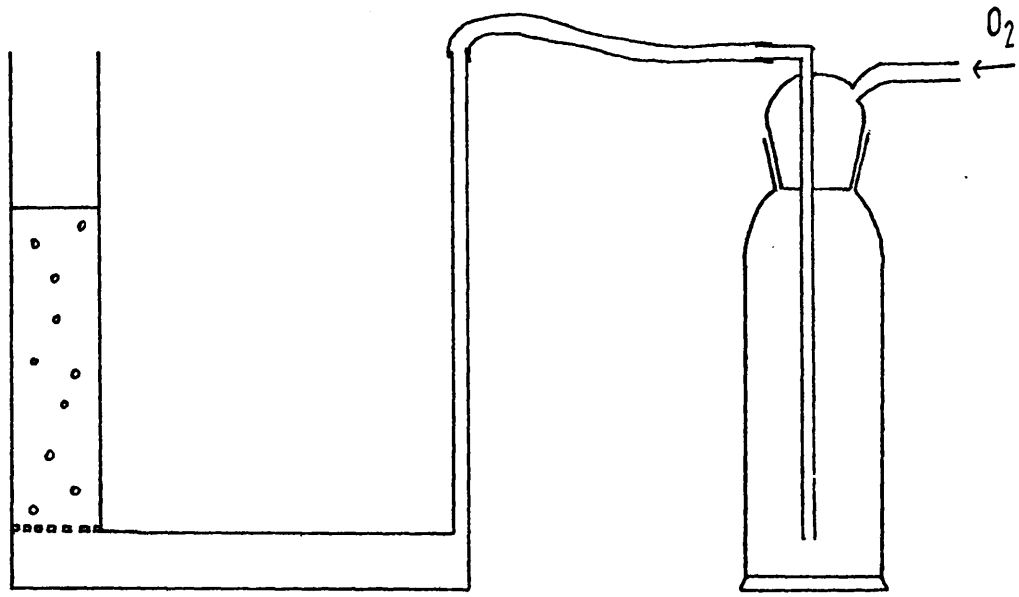


Fig 6

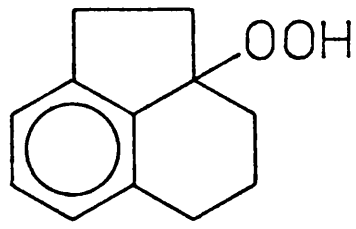


high pressure and temperature in the fashion of Treibs[50] although it is possible to carry out the reduction at atmospheric pressure[61]. After purification the m.s., i.r., and n.m.r. evidence obtained was consistent with a reduction of (102) to (15b) without the formation of decahydroacenaphthene.

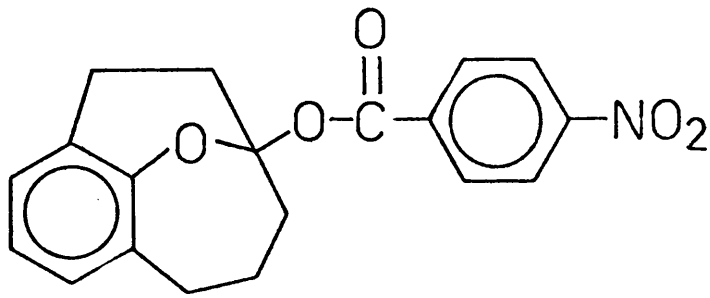
The product (15b) was then oxygenated for 100 hours in an all-glass apparatus (figure 4) at room temperature. Work-up of the product of this reaction (see experimental section for details) yielded a thick gum (crude hydroperoxide (103)). Partial crystallisation of this gum gave material which was identified as the symmetrical peroxide (113). The m.s. showed a parent ion at m/e 346 with a significant ion at m/e 173 due to cleavage of the oxygen-oxygen bond. The i.r. and n.m.r. evidence was consistent with structure (113).

As the initial yield of crude product from the autoxidation was low (ca.5%), the isolation of a significant portion of it as symmetrical peroxide was a disappointment and attempts were made to increase the yield of the hydroperoxide (103). Firstly, an improved method of introducing the O_2 was tried using the apparatus shown in figure 5. This had no effect on the reaction. Secondly, it is known that autoxidation of hydrocarbons may be facilitated by the use of transition metal catalysts. To this end $Co(acac)_3$ and subsequently finely divided cobalt metal were used in trace quantities in repeat reactions but again the yield of (103) was not improved. Finally, an all-quartz apparatus, such as depicted in figure 6, was used. However, no significant effect on the reaction was observed. It was evident at this point that there was not much room for improvement of the reaction conditions. It was therefore decided to use the apparatus depicted in figure 5 for any further autoxidation reactions.

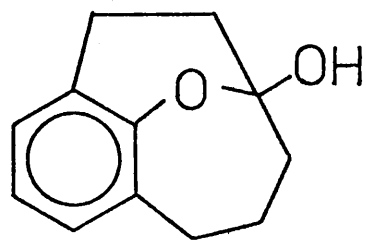
The hydroperoxide (103), now separated from symmetrical peroxide (113), could still not be crystallised and was used in the form of a



(103)



(104)



(105)

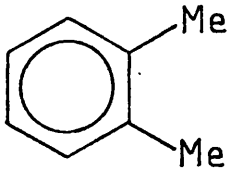
gum without further purification to prepare the ester (104). Treatment of (103) with p-nitro-benzoyl chloride in dry pyridine at room temperature for 1 hour followed by work-up yielded the p-nitrobenzoate (104) in a crude form which could not be crystallised by the literature procedure[50] and a new work-up method was derived. This involved either plate chromatography or dry column chromatography and did give the desired crystalline p-nitrobenzoate, m.p. 108-109°C (lit.[50] m.p. 108-109°C). The mass spectrum showed a parent ion at m/e 339. Infra-red spectroscopy showed ν_{co}^{ccl4} 1745, 1730 and the ^{1}H n.m.r. had two signals in the aromatic region. One signal at δ 8,3 (s, 4H) was assigned to the protons of the para-disubstituted benzene ring and the other at δ 7.05 (m, 3H) was assigned to the protons of the trisubstituted benzene ring.

It was proposed that high resolution ^{1}H n.m.r. and ^{13}C n.m.r. spectra should be obtained on (104) in addition to an x-ray analysis. In the event however no crystals of (104) could be prepared that were suitable for x-ray analysis (they are twinned needles[62]) and an attempt to reduce and simultaneously acetylate the $-NO_2$ function failed to yield a clear product.

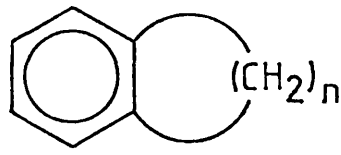
The hydrolysis of the ester (104) to the hemi-acetal (105) was now carried out in the hope that crystals of this compound would be more acceptable for x-ray analysis. Hydrolysis by the literature method[50] gave the hemiacetal as colourless prisms (n-pentane) m.p. 75-76°C (lit[50] m.p. 76.5-77.5°C). The mass spectrum showed a parent ion at m/e 190, the i.r. showed ν_{OH}^{ccl4} 3600, 3560-3200 and the ^{1}H n.m.r. had one exchangeable proton signal at δ 3.9.

Significantly, there is a signal at ca. δ 0.85 which is assigned to one of the protons adjacent to the bridgehead which is tucked under the aromatic ring.

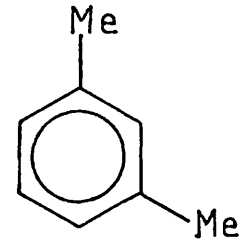
A preliminary examination of (105) for x-ray crystallography



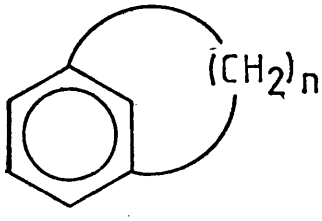
(114)



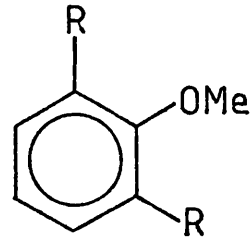
(115) a) n=1
b) n=2



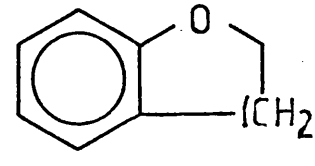
(116)



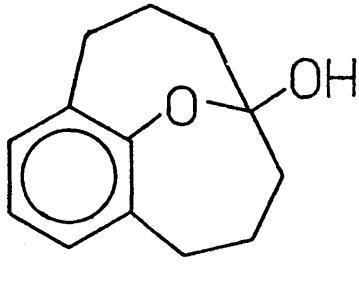
(117) a) n=6
b) n=7
c) n=8
d) n=10



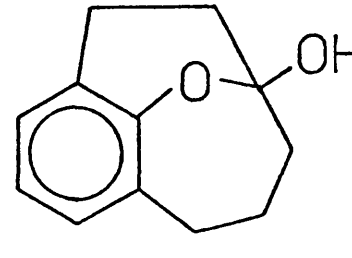
(118) a) R=H
b) R=Me
c) R=i-Pr
d) R=t-Bu
e) R=Et



(119) a) n=2
b) n=3



(120)



(105)

revealed that the crystals are disordered[62], however Treib's hemiacetal can usefully be compared spectroscopically with several model compounds. In some cases the necessary spectroscopic data were to be found in the literature, but in other cases it was necessary to synthesise the compounds prior to obtaining the spectra. Compounds (114)-(120) were chosen as models for comparison with (105). The synthesis of (118b), (119a) and (119b) was routinely carried out and is described in the experimental section. In addition to the spectroscopic investigation, molecular mechanics calculations were carried out for structure (105) and this aspect of the work will be described in the following section.

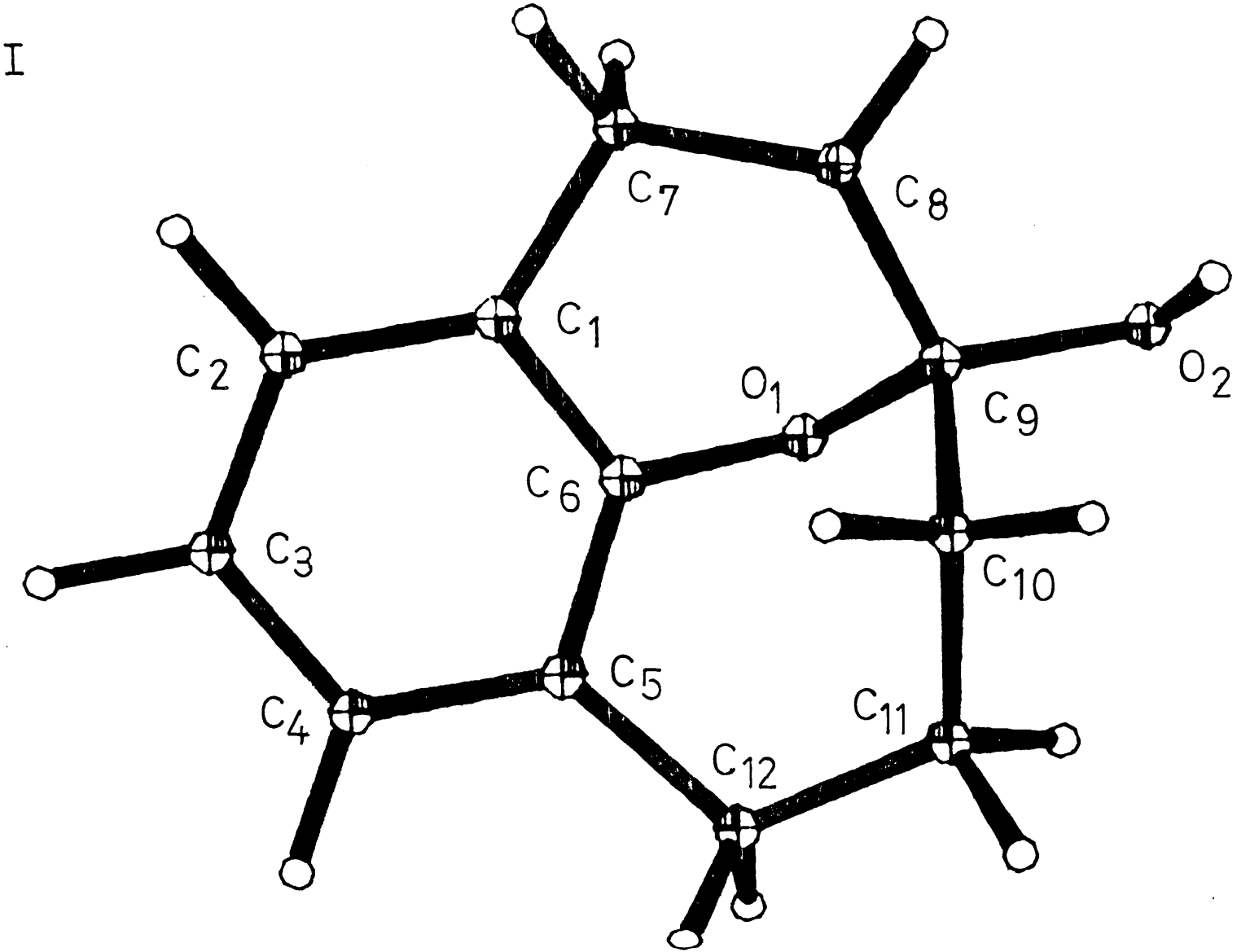
Molecular Mechanics Calculations.

Molecular mechanics calculations have been performed, in recent years, on an increasing number and type of organic molecules and have been most useful in the interpretation and understanding of various experimental results. The elucidation of molecular conformation, thermodynamic properties, reaction mechanisms and kinetics have been undertaken as well as the interpretation of spectroscopic results.

At present, high precision calculations are only possible for a limited range of compounds embracing alkanes[63], alkenes[64] and carbonyl compounds[65] though useful, but less reliable calculations have been performed on compounds such as alkynes[66], sulphur containing compounds[67], sesquiterpenes[68] and peptides[69] using ad-hoc force fields.

For the purposes of molecular mechanics calculations, the molecule is treated as an isolated ensemble of static nucleii held together by elastic linkages. The first requirement is therefore a set of three dimensional atomic co-ordinates which describe, at least approximately, the arrangement of the nucleii in space. No real molecule is strain free, the difference in energy between the hypothetical strain free

105 I



105 II

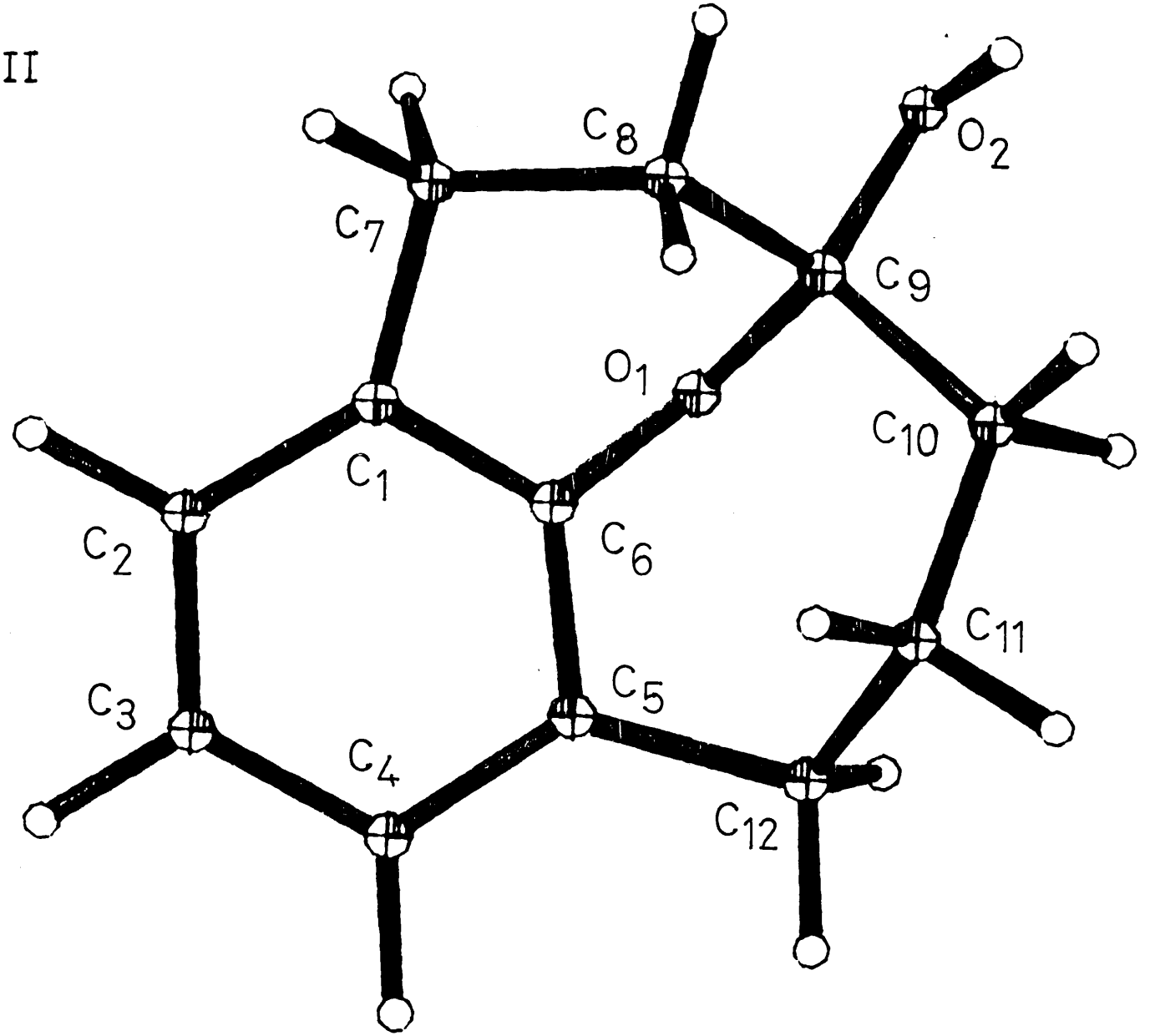
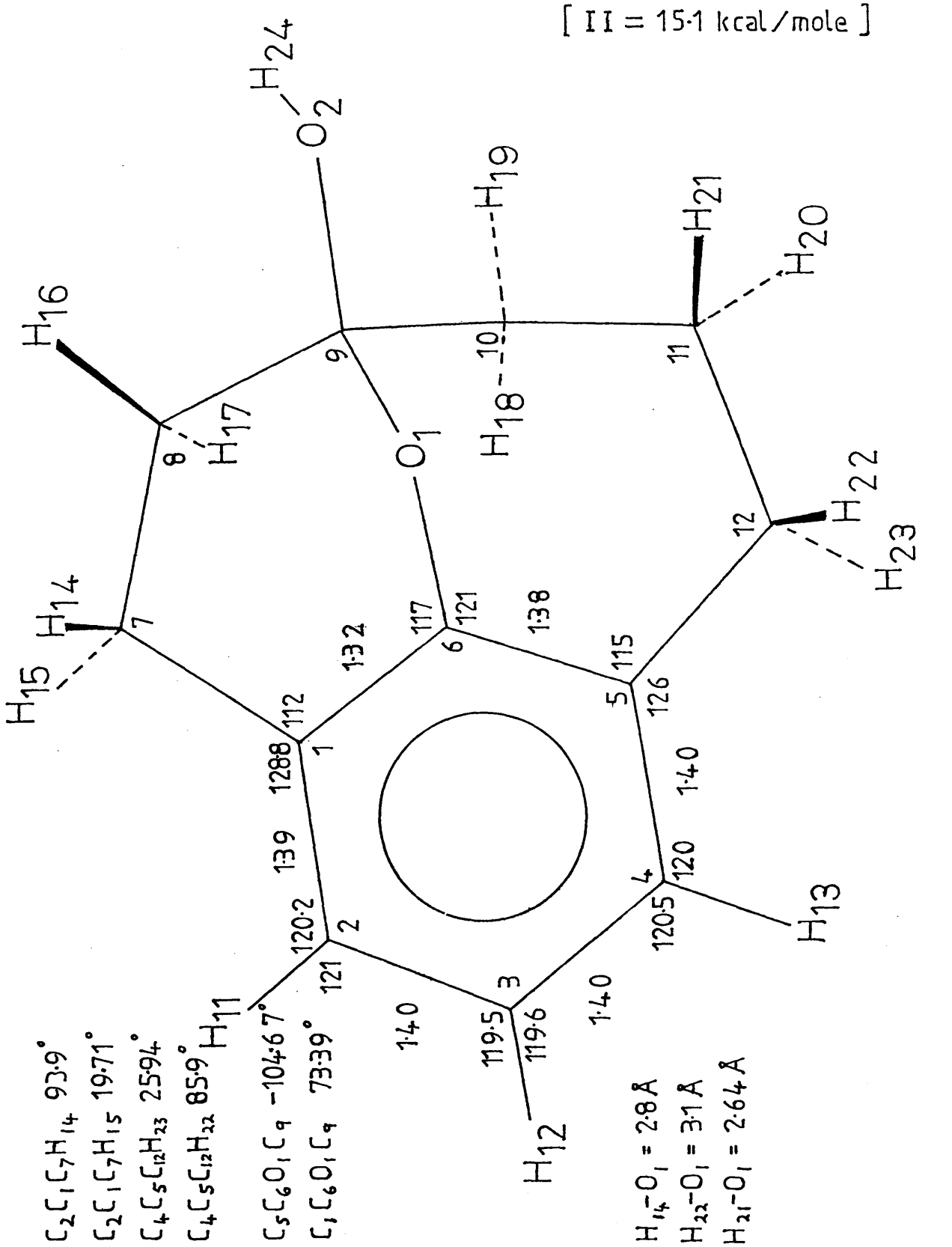


Fig 7

Conformer I (total P.E. 13·6 kcal/mole

[II = 15·1 kcal/mole]



Torsion ∠ $C_2C_1C_7H_{14}$ 93·9°

$C_2C_1C_7H_{15}$ 19·71°

$C_4C_5C_{12}H_{23}$ 25·94°

$C_4C_5C_{12}H_{22}$ 85·9°

$C_5C_6O_1C_9$ −104·67°

$C_1C_6O_1C_9$ 73·39°

H_{14}–O_1 = 2·8 Å

H_{22}–O_1 = 3·1 Å

H_{21}–O_1 = 2·64 Å

molecule and its real counterpart being its potential energy. In the context of molecular mechanics calculations this has become known as the steric energy. Molecular mechanics calculations minimise the steric energy of a given molecular structure by systematically adjusting its geometry. The entity which enables the steric energy of a molecule to be calculated as a function of its geometry is known as a force field.

The steric energy, V_s, is partitioned into the sum of a series of components, with each contributor expressing potential energy in terms of an easily visualised molecular deformation from the strain free situation. In general, V_s may be written as :

$$V_s = V_{(l)} + V_{(\theta)} + V_{(w)} + V_{(r)} + V_{(q)} + V_{(PiPj)}$$

where $V_{(l)}$ represents the molecular potential energy due to bond stretching from strain free values and $V_{(\theta)}$, $V_{(w)}$, $V_{(r)}$ and $V_{(q)}$ are the corresponding terms for angle bending, bond torsion, non-bonded interactions and coulombic interactions respectively. $V_{(PiPj)}$ arises from cross terms where the energy is a function of two or more of the previous molecular dimensions. When the steric energy has been reduced to its minimum value there should be a very close correspondence between the real and calculated structures.

From a study of molecular models it is clear that the hemiacetal (105) can adopt the two conformations (105I) and (105II). Energy minimisation calculations, which were carried out by Mr. C. Morrow of this department, lead to the conclusion that the former is preferred by about 1.5 Kcal. mole^{-1}. The calculations on conformer I^{70} give bond lengths and angles as shown in figure 7. These results show that the aromatic ring is distorted in a number of ways. The aromatic carbon-carbon bonds lengths are normal (1.38 - 1.40Å) except for $C_1 - C_6$ which is as short as an olefinic carbon-carbon double bond (1.32Å);

Fig 8

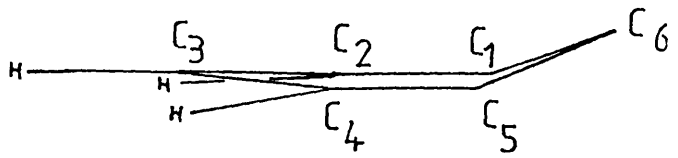
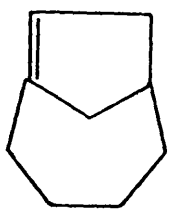
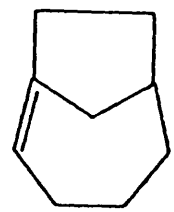


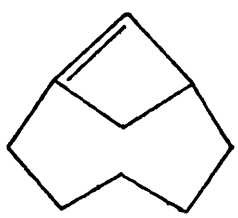
Fig 9



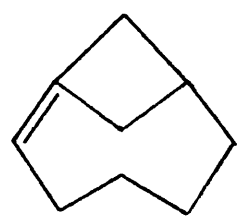
(37)



(38)



(121)



(122)

NOMENCLATURE OF BENZENE BANDS.

180 nm. band	200 nm. band	260 nm. band	ref.
$A_{Ig} \longrightarrow E_{Iu}$	$A_{Ig} \longrightarrow B_{Iu}$	$A_{Ig} \longrightarrow B_{2u}$	25
E_I	E_2	B	26
——	K	B	27
A	B	C	28, 29
Primary(second)	Primary(first)	Secondary	30
——	Principal	——	31
β	P	α	32
I_B	I_{L_a}	I_{L_b}	33

Table I

Solvent	Absorption maxima nm.
Heptane	234 239 244 249 255 261 269
Alcohol	—— 238 243 248 255 261 268

Table 2

the ring is folded about an axis through C_1 and C_5 so that C_6 is tilted almost 20° out of the plane of $C_2C_3C_4$ (see figure 8); there is also a minor distortion at C_3 so that the C_3-H bond subtends angles of approximately 2.5° to 3.3° with the C_2-H and C_4-H bonds respectively (figure 9).

It is interesting to note that the shortest carbon-carbon bond in the aromatic ring is located in the smaller bridge. This is in agreement with the results of Burkert[45]. From a comparison of the double bond isomeric pairs (37), (38) and (121), (122) he concluded, in contrast to Kobrich's Rule C (see Introduction, p11), that in both cases the isomer with the double bond in the smaller bridge proves to be the less strained one. It is also in agreement with molecular mechanics calculations carried out in this department[71] on a group of seventeen bridged bicyclic olefins, sixteen of which are bridgehead olefins.

U.V. Spectroscopy.

Benzene exhibits two intense absorption bands at about 180nm. (ε max c.a. 47,000) and 200nm (ε max c.a. 7,000) and a weak absorption band around 260nm (ε max c.a. 220)[72]. All three bands are associated with the π electron system of benzene. The two intense bands are ascribed to transitions to dipolar excited states while the weak band is ascribed to the forbidden transition to a homopolar excited state. Different nomenclatures have been used to describe the three bands (see Table 1). We will use the terminology A, B, C to describe the 180, 200 and 260 nm. bands respectively. In the case of benzene the C band centred around 260nm exhibits a completely resolved vibrational structure with well defined absorption maxima in solution spectra as shown in Table 2. The C band possessing the fine structure is referred to as the "benzenoid absorption". As may be seen from Table 2 the band is not sensitive to changes in solvent.

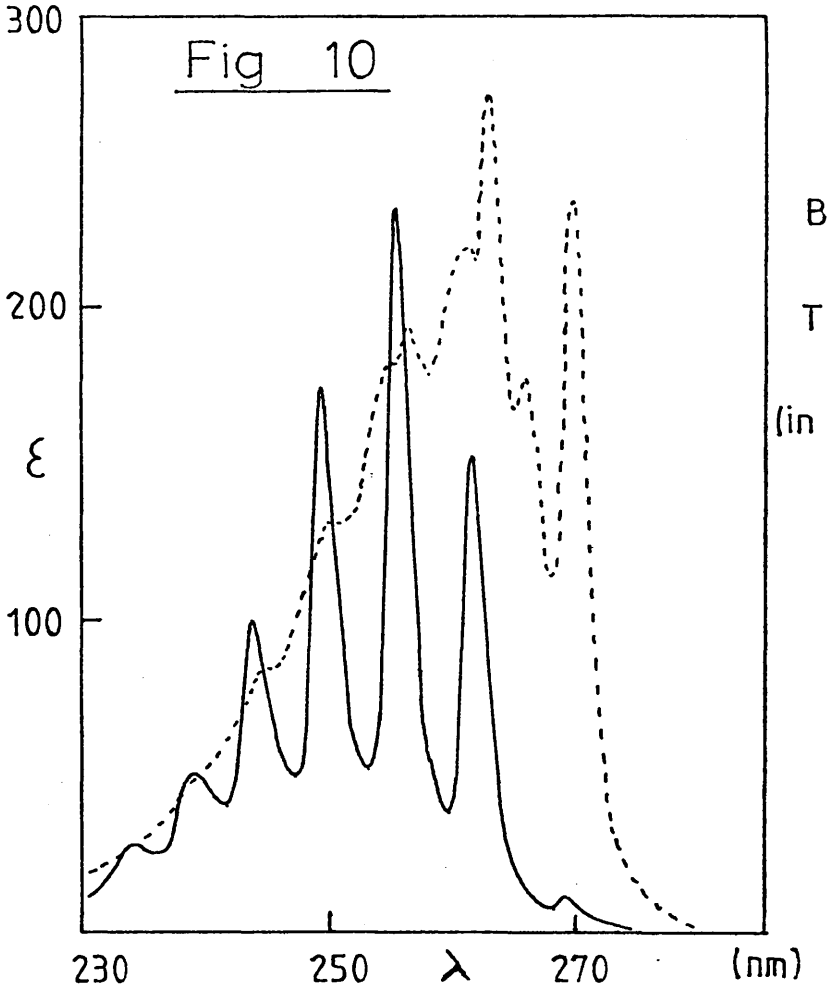


Fig 10
300
200
100
ε
230
250
λ
270
(nm)
Benzene (——)
Toluene (----)
(in cyclohexane)

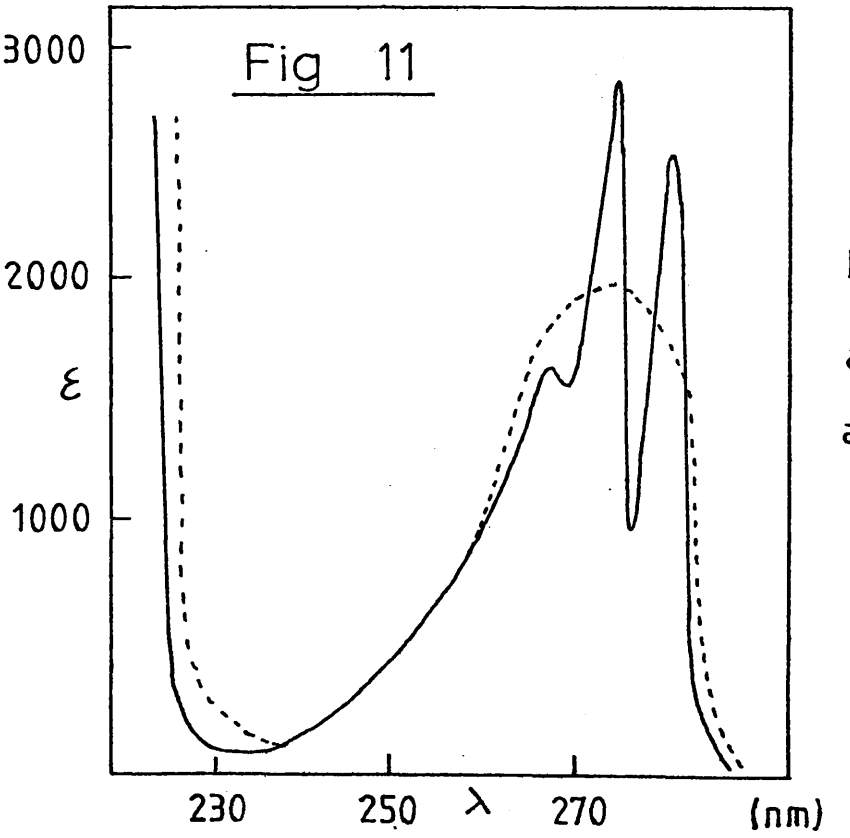


Fig 11
3000
2000
1000
ε
230
250
λ
270
(nm)
Phenol in hexane (——)
and
alcohol (-----)

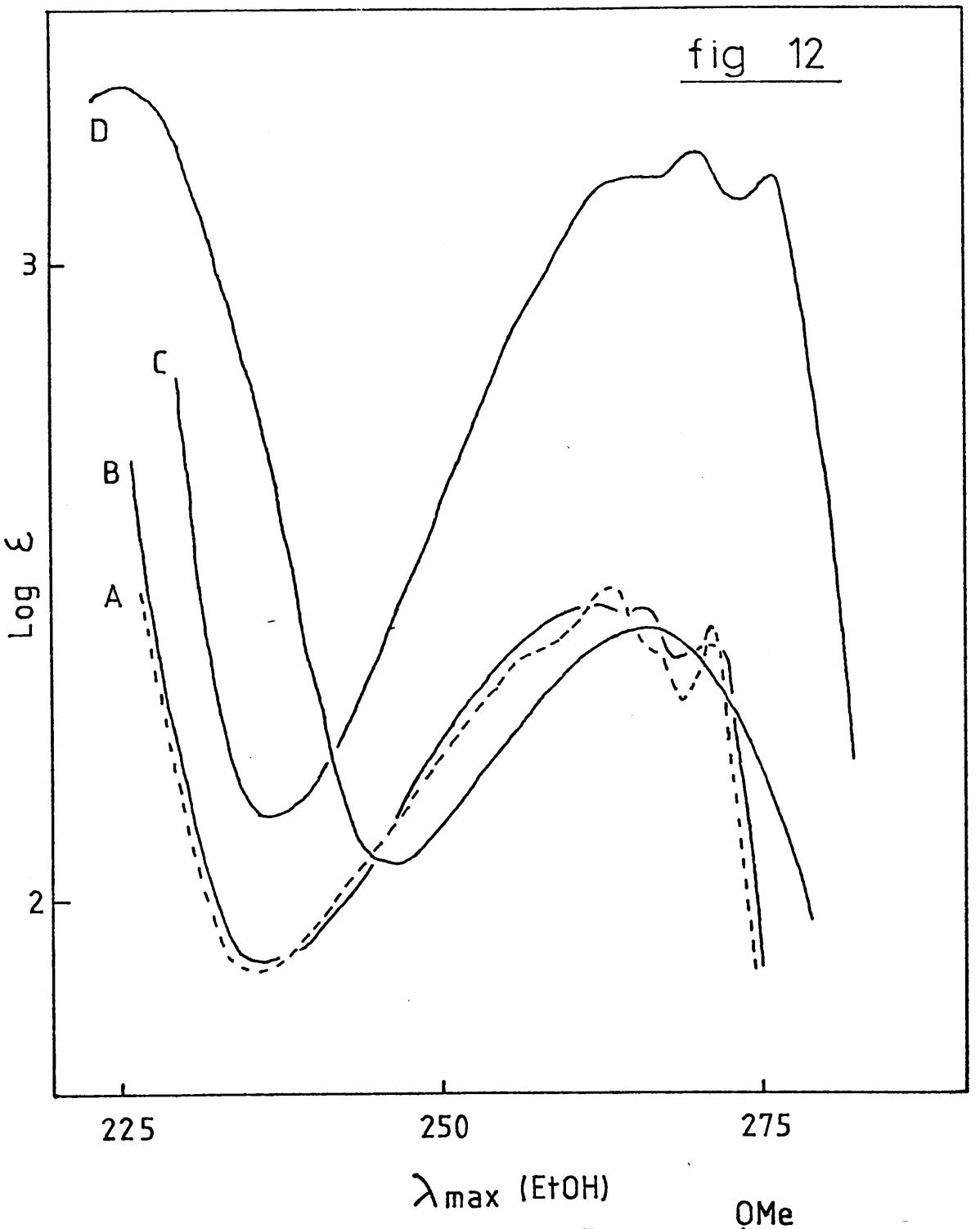
Clearly, any interpretation of the spectrum of the hemiacetal (105) must take account of the following factors :

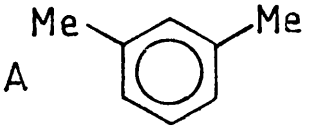
1. The presence of the o-alkyl auxochrome.
2. The presence of the two alkyl groups and their position relative to the o-alkyl group.

All three bands of the u.v. spectrum of benzene are affected by substitution but since the B and C bands occur in the wavelength range normally accessible to most spectrophotometers they are of greater interest than the A band. Both bands are shifted to longer wavelengths upon substitution which is supposed to perturb the benzene ring both by resonance and inductive effects[78,82-84]. A substituent with positive inductive effect lowers the ionisation energy of the substituted benzene, one with negative inductive effect increases it. Resonance effects lower the ionisation energy of the molecule which is manifested in terms of wavelength shifts. Both resonance and inductive effects intensify the bands, but the former apparently cause greater changes in spectra[78, 83].

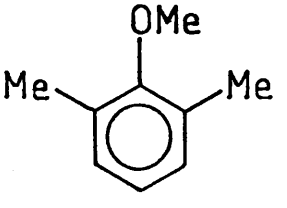
Matsen, Robertson and Chouke[85] found that alkyl substitution intensifies and shifts the C band of benzene to longer wavelengths (see figure 10). Of all the alkyl groups, the methyl group causes the greatest intensification and wavelength shift, the effect decreasing as the hydrogens of the methyl group are replaced. This has been attributed to C-H hyperconjugation though objections have been raised to this interpretation[86]. Substitution of benzene with polar groups containing unshared electrons (auxochromes like - OH or - NH_2) shifts the absorption bands to longer wavelengths and also intensifies them. The effect is shown in figure 11 for phenol. In general, the fine structure of the C band disappears in polar solvents through solvent-solute interactions when the substituents are polar groups. The effect of auxochromes on the benzene bands is explained in terms of

fig 12

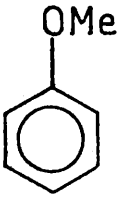




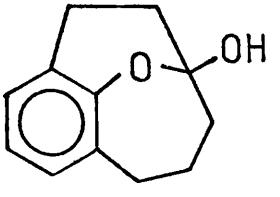
A



B



C



D

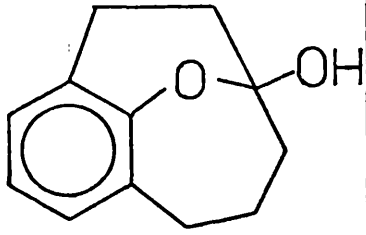
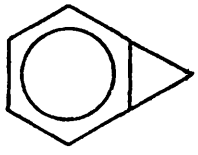
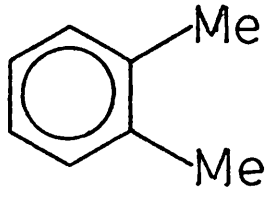
Compound	λ_{max} (logε)	Solvent	Ref.
 (105)	224 (3.39) 265.5 (2.55) 223 (3.2) 265.5 (2.43)	no solvent given EtOH	50 Exptal.
 (111)	252 (2.7) 258 (3.0) 264 (3.2) 270 (3.4) 277 (3.3)	C_6H_{12}	58
 (114)	252 (2.2) 256 (2.3) 263 (2.4) 267 (2.3) 272 (2.3)	C_7H_{16}	89

Table 3

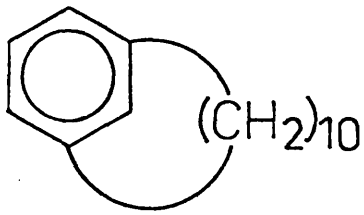
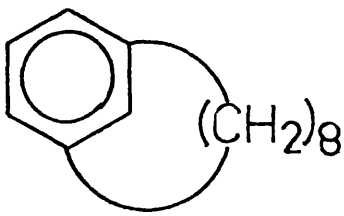
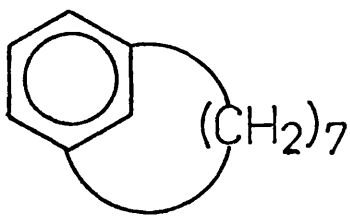
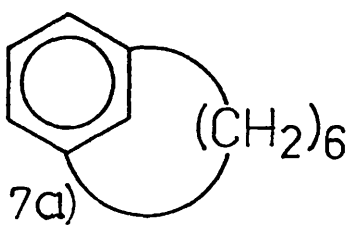
Compound	λ_{max} (logε)	Solvent	Ref.
 (117d)	215 (3.88) 256 (2.57) 263 (2.55) 273 (2.44)	C_6H_{14}	90
 (117c)	266 (2.4)	C_6H_{14}	92
 (117b)	203 (4.5) 218 (3.95) 271 (2.40)	C_6H_{14}	90
 (117a)	209 (3.88) 223 (3.59) 280 (2.48)	C_6H_{14}	90

Table 4

the interaction of the unshared electrons with the benzene nucleus. Braude calls this interaction π-p conjugation[87].

Moreover, from a study of molecular models and from the results of the molecular mechanics calculations (vide supra), three stereochemical phenomena must be taken into account :

1. In-plane distortion of the aromatic ring.
2. Out-of-plane distortion of the aromatic ring.
3. Reduced p-π orbital overlap between the aromatic ring and the oxygen atom.

The spectrum of (105) shows a superficial resemblance to that of anisole but is less intense. It resembles more closely those of m-xylene and 2,6 - dimethylanisole (see figure 12) but significantly, it lacks the fine structure present in either one of them.

In-plane "pinching" as exemplified by cyclopropabenzene (111) is known to distort the bond angles and bond lengths of the benzene ring[58, 88] but the u.v. spectrum shows no lack of fine structure and is all but identical with that of o-xylene (see Table 3). The inference is that the bond angle and bond length changes associated with this strained ring system cannot be disrupting the aromatic chromophore to any great extent.

Out-of-plane bending is well illustrated[90] by the m-cyclophanes (117). As the strain increases with shortening of the bridge, the u.v. spectrum differs increasingly from that of m-xylene. The C band coalesces into a single broad absorption and moves to longer wavelengths (see Table 4). A lack of fine structure is characteristic of the spectra of aromatic rings that are warped out of planar conformation[91]. The effect may be due to the fact that the vibrational and electronic wave functions are no longer separable, that is, when the rings are badly warped vibrations will vary the warping and thus also vary the electronic energy. This will cause a loss of

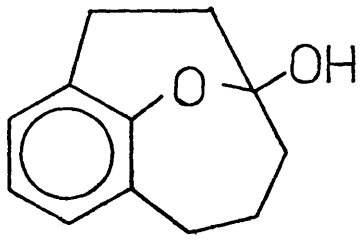
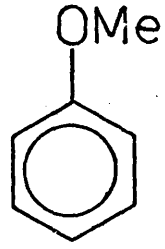
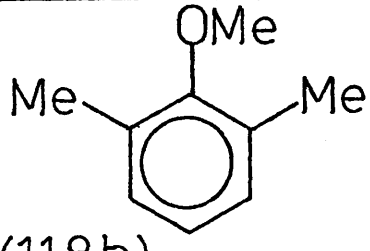
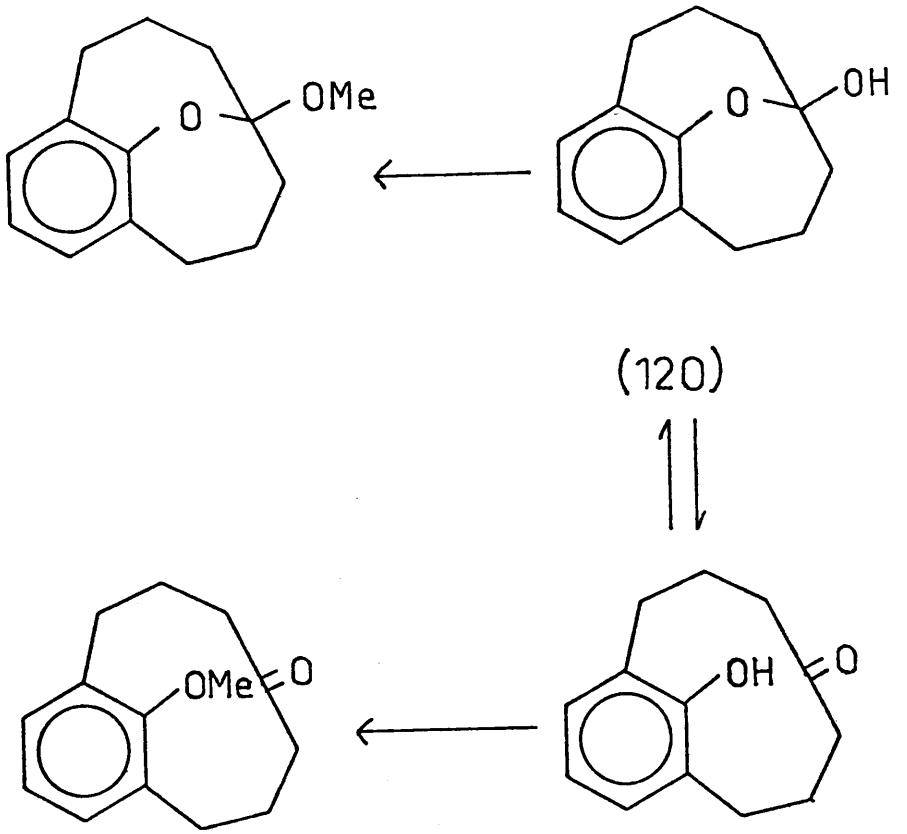
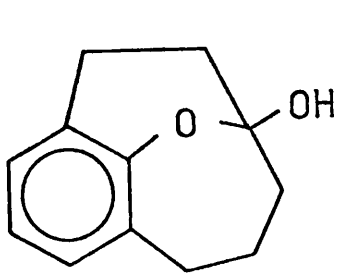
Compound	λ_{max} (logε)	Solvent	Ref.
 (105)	224 (3.39) 265.5 (2.55)	no solvent given	50
	223 (3.2) 265.5 (2.43)	EtOH	Exptal.
 (118a)	220 (3.9) 224 (3.8) 265 (3.I4) 27I (3.32) 277.5 (3.32)	C_6H_{I2}	93
	226 (3.0) 264 (3.04) 270 (3.07) 276 (3.03)	EtOH	Exptal.
 (118b)	265 (2.49) 268 (2.53) 272.5 (2.48)	C_6H_{I4}	94

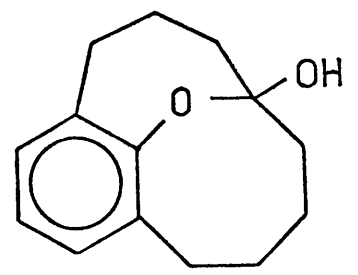
Table 5 (p.t.o.)



(120)



(105)



(123)

fine structure. The shift to longer wavelengths is also characteristic of the spectra of bent benzene rings[91]. The first excited state of benzene by necessity must have more antibonding and less bonding interactions than the ground state. When the benzene ring is bent, all interactions are affected by about the same amount, so that the ground state and excited states become closer in energy and the band moves to longer wavelengths.

The u.v. spectroscopic consequences of reduced p- π orbital overlap between an aromatic ring and an oxygen atom have been systematically studied[93] for the cases of 2,6 - disubstituted anisoles (118) by varying the size of R. As R increases in bulk from H to isopropyl the longest wavelength absorption is lost, but the C band continues to show fine structure, with the most intense band drifting slightly to shorter wavelengths. However, the intensity of this band is insensitive to changes in steric hindrance beyond R=Me (see Table 5). Change of solvent, from hydrocarbon to ethanol, has remarkably little effect as is illustrated by two of the cases in Table 5. The data recorded for 2,6 - di-t-butylanisole is anomalous and the original authors[93] offer no explanation.

In view of the fact that out-of-plane bending and the poor p- π overlap phenomena induce opposing effects on the position of the C band, no useful conclusions can be drawn from the λ max of (105). However, the value of ε max is consistent with Treibs structure and the absence of fine structure suggests that the aromatic ring is non-planar. Significantly, the u.v. absorption of the ring homologue (120) (λ_{max}^{EtOH} 263 (2.6) ; 284 (2.06) nm) shows two maxima in the C band[96] and unlike (105) compound (120) exists in equilibrium with the keto-phenol tautomer and gives derivatives of both tautomers[96]. Another ring homologue (123) has been prepared[97] and this also gives derivatives of both tautomers. However, no u.v. data have been

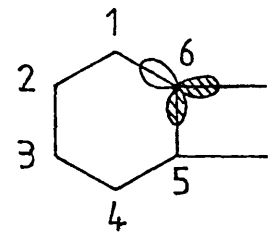


Fig 13

Shaded orbitals have increased p-character — hence unshaded orbital has higher s-character.

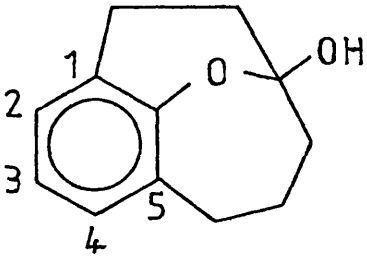
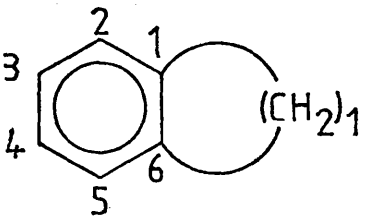
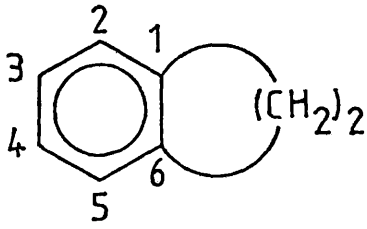
Compound	δ Ar-H	J (Hz.)	Ref.
 (105)	δ_3 6.9 δ_2 7.0	$J_{2,3}$ 5	Exptal.
 (115a)	7.I2 δ_2 7.I5 δ_3 7.I9	$J_{2,3}$ 6.04 $J_{2,4}$ 0.33 $J_{2,5}$ I.85 $J_{3,4}$ 7.63	58 98
 (115b)	δ_2 6.90 δ_3 6.76 6.97	$J_{2,3}$ 7.36 $J_{2,4}$ I.0 $J_{2,5}$ I.03 $J_{3,4}$ 7.79	98 99

Table 6 (p.t.o.)

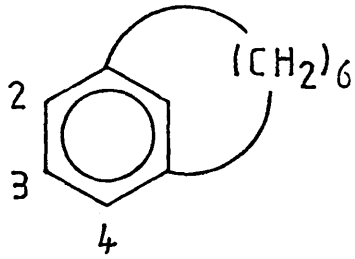
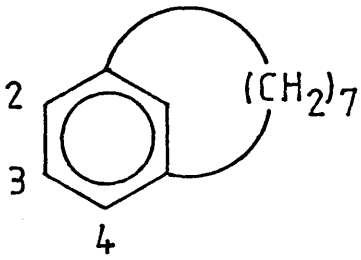
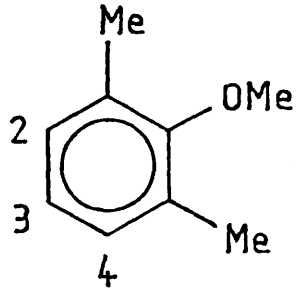
Compound	δ Ar-H	J (Hz.)	Ref.
 (117a)	δ_3 6.8I δ_2 7.09		90
 (117b)	δ_3 6.92 δ_2 7.I7		90
 (118b)	δ_3 6.98 δ_2 7.06	$J_{2,3}$ 7.5	Exptal.

Table 6 (contd.)

published for this compound.

^{1}H n.m.r. Spectroscopy.

The n.m.r. behaviour of strained molecules such as (105) can be explained by postulating that two electronic effects are operating simultaneously[54]. Firstly, in the case of the bridgehead carbons, the atomic orbitals used to construct the ring which is strained have higher p character, hence the remaining orbital has higher s character (figure 13). The ortho-carbon is thus bound to an orbital of higher electronegativity and as the size of the fused ring decreases the electronegativity of this ortho-carbon should increase. The expected effect of this would be to decrease the shielding of the attached proton, shifting the resonance to lower field. Working against this, however, is the perturbation of the ring current resulting in a decrease in the diamagnetic anisotropy of the molecule and a consequent shifting of the proton resonance to higher field.

The 90 and 220 MHz n.m.r. spectra of (105) show a tightly coupled aromatic multiplet at ca. δ 7, two deshielded benzylic protons at δ 3.45 and δ 3.13, an -OH proton at ca. δ 4 which disappears on shaking with D_2O, a one proton quartet at δ 2.15 and two three proton multiplets at δ 2.4 and δ 1.6 ; most strikingly there is a one proton high field multiplet at δ 0.85.

The chemical shift of the aromatic protons in (105) is not significantly different from those recorded for related strained or unstrained molecules (see Table 6). On the other hand, the aromatic proton-proton coupling constants in (105) and (118b) are markedly different.

In the case of 2,6 - dimethylanisole (118b), the 90 MHz spectrum shows an aromatic multiplet at δ 6.95 and two singlets at δ 3.7 and δ 2.35. The aromatic multiplet was sharpened by irradiating at δ 2.25 and the resulting pattern was identified as that of an AB_2

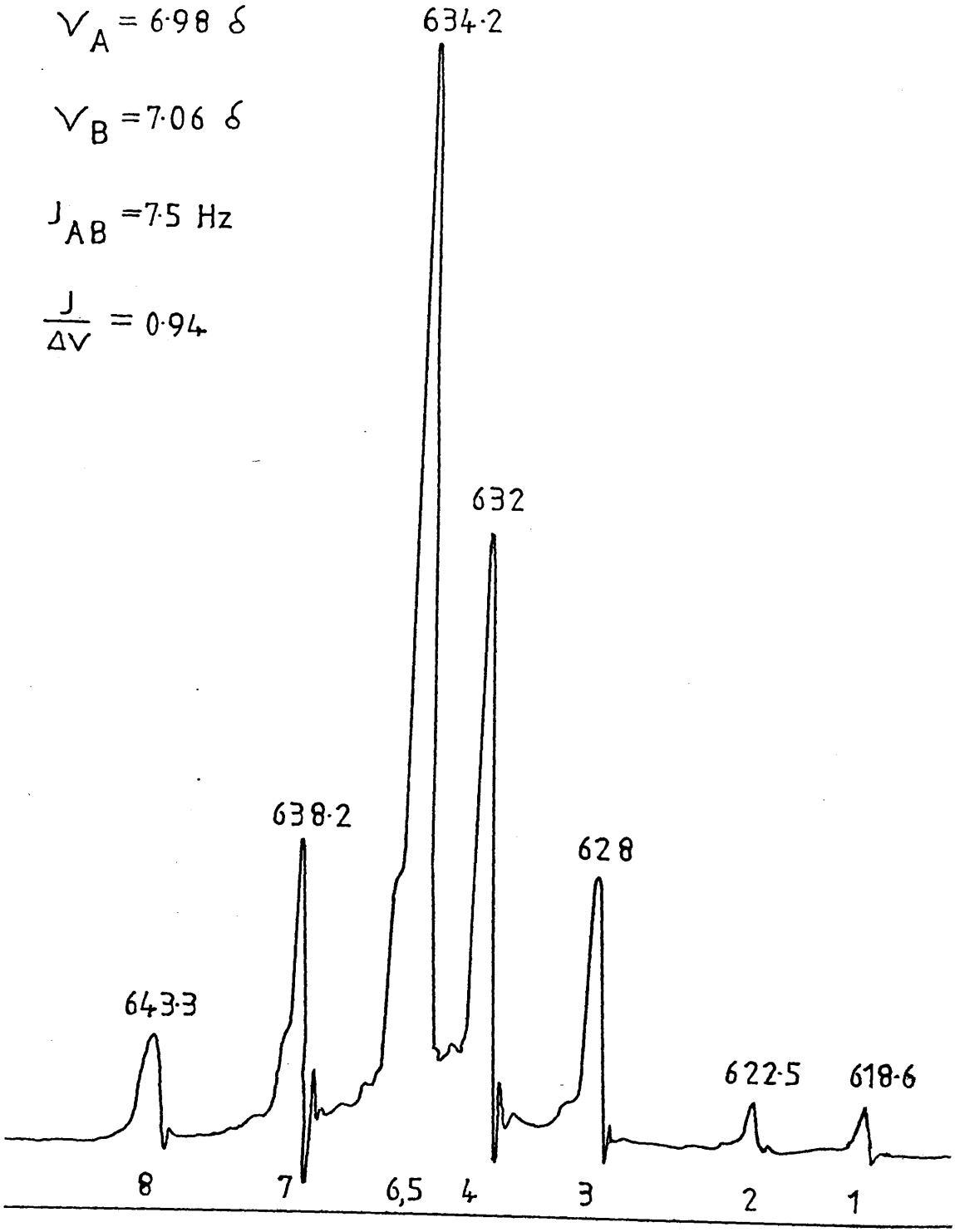
Fig 14

$\nu_A = 6{\cdot}98\ \delta$

$\nu_B = 7{\cdot}06\ \delta$

$J_{AB} = 7{\cdot}5$ Hz

$\frac{J}{\Delta\nu} = 0{\cdot}94$



SWEEP RANGE 100 Hz

AT 90 MHz

METHYLS DECOUPLED ($H_2 = 2{\cdot}25$ (+))

system (see figure 14) and analysed by the method described below[100]. In an AB_2 system there is one chemical shift difference $\Delta\nu$, two equal coupling constants J_{AB}, and a third J_{BB}, not necessarily equal to J_{AB}. In the limit of the AX_2 case, one would expect a triplet for A and a doublet for X, a total of five transitions. As $\Delta\nu$ decreases, the magnetic field begins to mix energy states appreciably resulting in a splitting of levels which are degenerate when $J/\Delta\nu$ is small. Each line of the doublet splits into two, as does the centre line of the triplet, making a total of 8 lines. There is also a ninth transition, called a combination line, which is usually difficult to see but may be detectable if $J/\Delta\nu$ is large. The coupling J_{BB} has no effect on the spectrum and so the AB_2 system may be characterised by the single parameter $J_{AB}/\Delta\nu$. In particular :

1. The chemical shift of nucleus A, ν_A, is always given by line 3.
2. The chemical shift of nucleus B, ν_B, is given by the mean of lines 5 and 7.
3. The coupling constant J_{AB} is obtained <u>via</u> the calculation :

$$J_{AB} = I/3 \left\{ (\nu_8 - \nu_6) + (\nu_4 - \nu_I) \right\}$$

(where ν_n is the chemical shift of the nth line of the pattern).

Analysis of the spectrum of (118b) gave $\nu_A = \delta\ 6.98$; $\nu_B = \delta\ 7.06$ and $J_{AB} = 7.5$ Mz.

For the hemiacetal (105), a similar sharpening of the δ 7 multiplet was achieved in the 90 MHz spectrum by irradiating successively at δ 3.45 and δ 3.13. The resulting spectrum had the characteristic appearance of an AB_2 system and was analysed by the same method as used for (118b) to give $\nu_A = \delta\ 6.9$; $\nu_B = \delta\ 7.0$ and $J_{AB} = 5$ Mz. Since coupling constants are independent of the applied magnetic field whereas chemical shifts are field dependent, at 220 MHz, the same aromatic multiplet lies closer to an AX_2 system in appearance. A scale-expanded spectrum in which the "extra" benzylic couplings have

Fig 15

AS AB_2

ν_A = 6·909 δ

ν_B = 6·988 δ

J_{AB} = 4·666 Hz

$\frac{J}{\Delta\nu}$ = 0·27

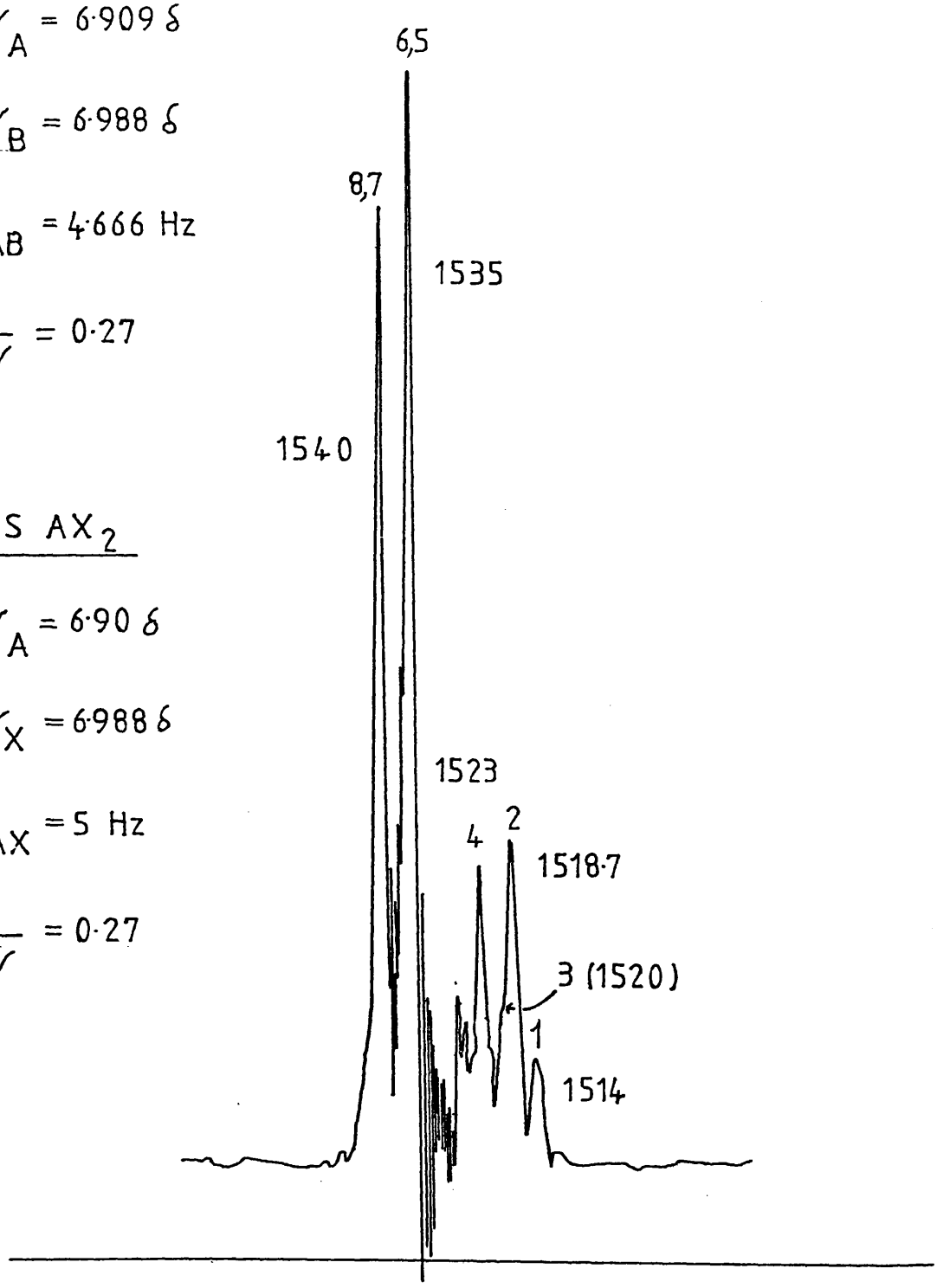
AS AX_2

ν_A = 6·90 δ

ν_X = 6·988 δ

J_{AX} = 5 Hz

$\frac{J}{\Delta\nu}$ = 0·27



SWEEP RANGE 500 Hz

AT 220 MHz

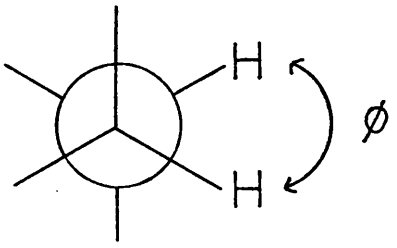
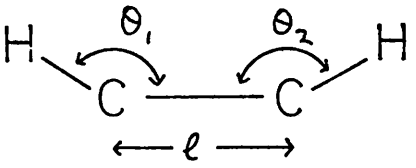


Fig 16

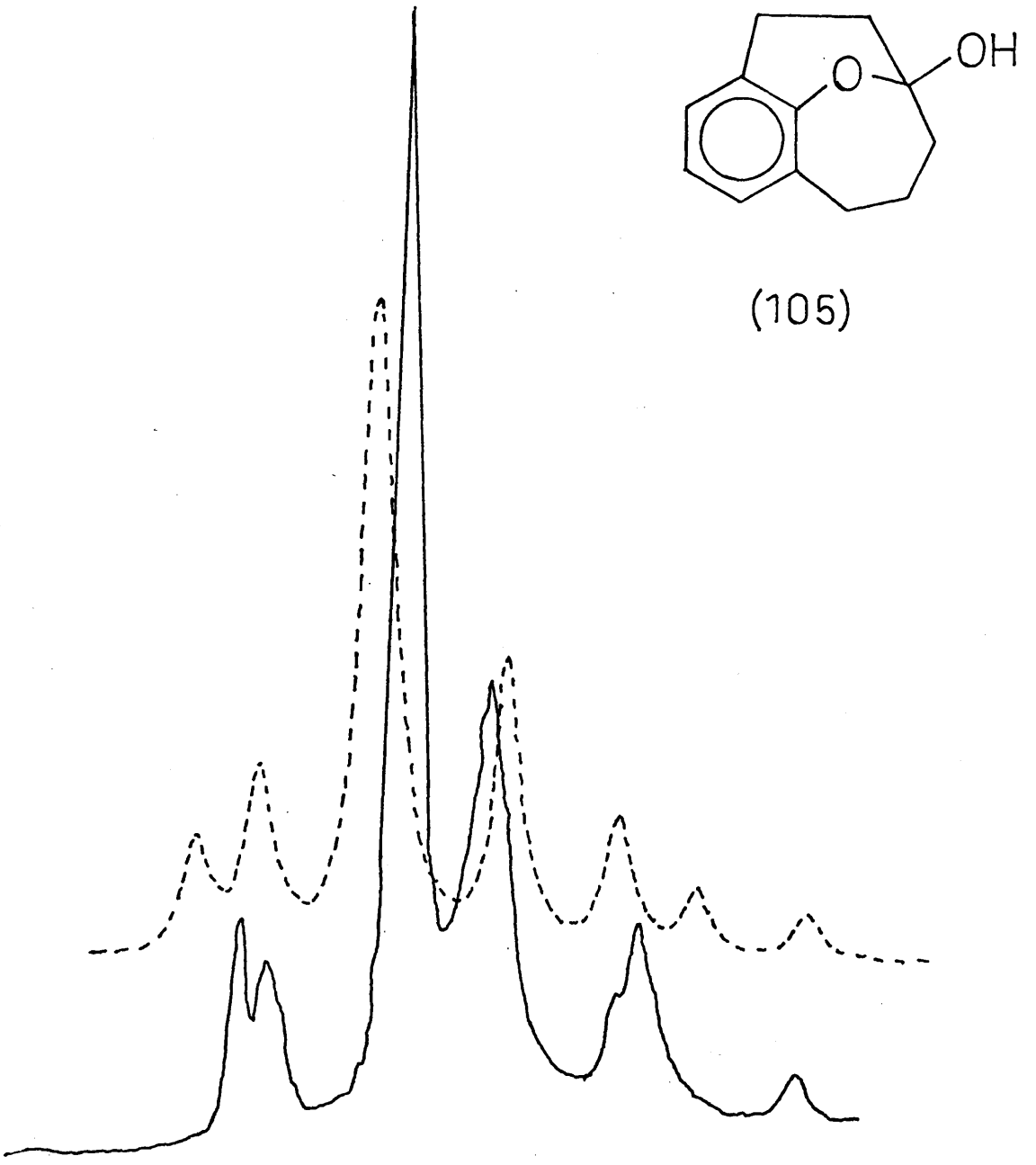


Variation of vicinal coupling constants with ϕ, θ_I, θ_2, and ℓ

Fig 17

OBSERVED SPECTRUM (100 Hz at 90 MHz)
(———)

SIMULATED SPECTRUM
(------)



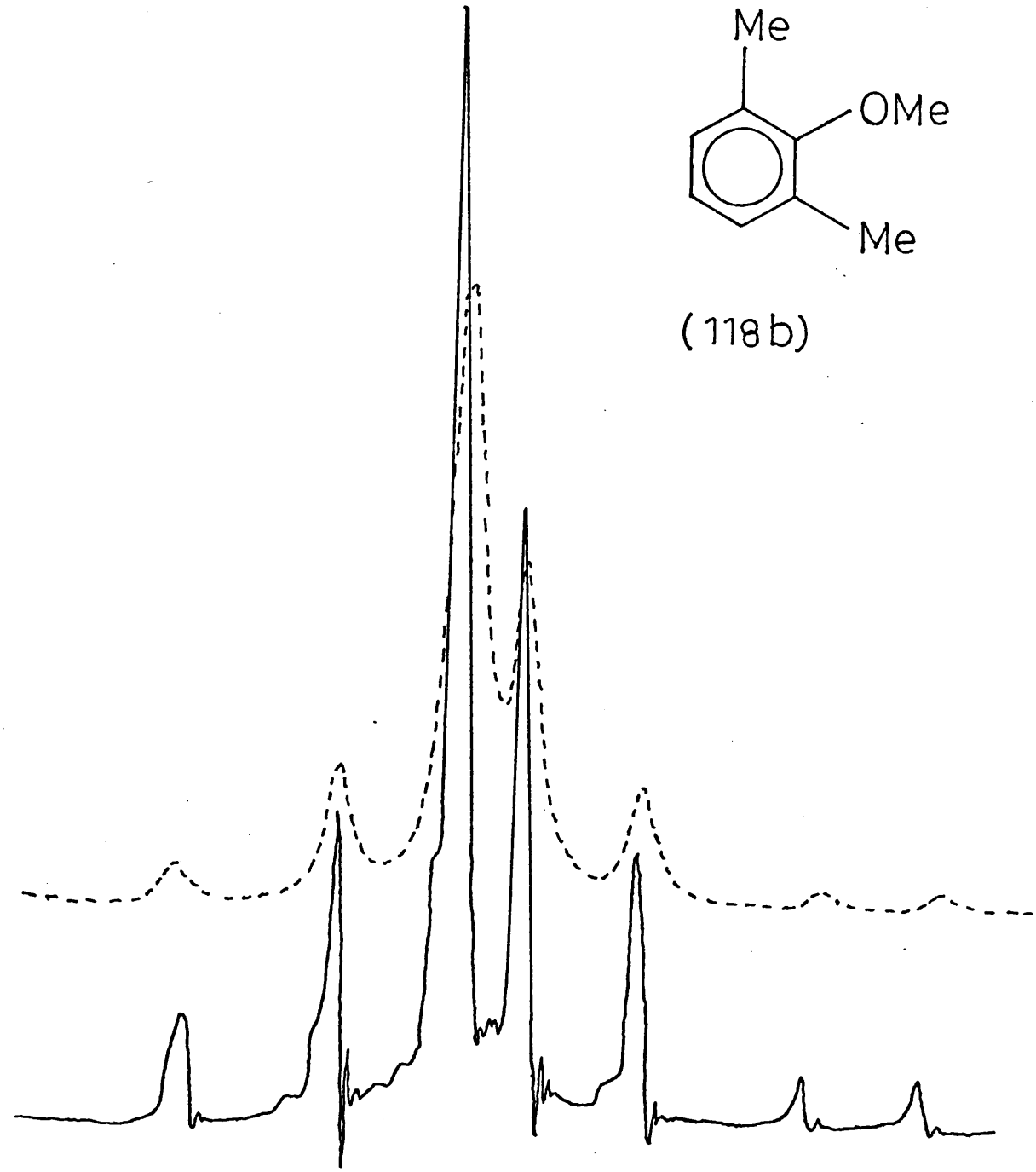
(105)

Fig 18

(METHYLS DECOUPLED)

OBSERVED SPECTRUM (100 Hz at 90 MHz)
(———)

SIMULATED SPECTRUM
(- - - - -)



(118b)

not been eliminated is shown in figure 15. Analysis as an AB_2 system gives $\nu_A = \delta\ 6.91$; $\nu_B = \delta\ 6.99$ and $J_{AB} = 4.67$ Hz whilst analysis as an AX_2 system gives $\nu_A = \delta\ 6.9$; $\nu_B = \delta\ 6.99$ and $J_{AX} = 5$ Hz. ($J/\Delta\nu = 0.27$).

There seems to be no doubt that the aromatic ortho coupling in (105) is close to 5 Hz and unusually low. The fact that the aromatic protons appear at δ 7 as an AB_2 system implies that there is little or no bond localisation between C_2, C_3, and C_4 and this is in agreement with the calculated data reported above. The fact that the ortho coupling constant is so low is less readily explained. Vicinal coupling constants vary inversely with the size of the dihedral angle ϕ, the size of the two angles θ_1 and θ_2 and with the length of the carbon-carbon bond (ℓ)[98, 101] (see figure 16). However, the calculated data indicate that although the benzene ring is slightly distorted at C_3 and C_6, the bond lengths C_2-C_3 and C_3-C_4 are normal and the variation in bond angles is too small to be significant (see figures 7 and 9).

The computer simulation of the spectrum of (105) using the data calculated above was attempted using a SIMEQ-II-16/3 programme[102]. These attempts were unsuccessful in exactly matching the experimentally obtained spectrum. It is worth noting, however, that the spectrum of 2,6-dimethyl-anisole (118b), which should be a classical AB_2 system, could not be simulated either using this programme. Figures 17 and 18 show the results of these attempts. It is doubtful, in the light of the programme's failure to simulate the spectrum of (118b), if any reliance may be placed on this programme.

As regards the one-proton, high field multiplet at δ 0.85, from molecular models this signal is assigned to a proton located under the edge of the aromatic ring in one of the conformations discussed above or an average value derived from equilibration between these conformations. Although similar equilibration

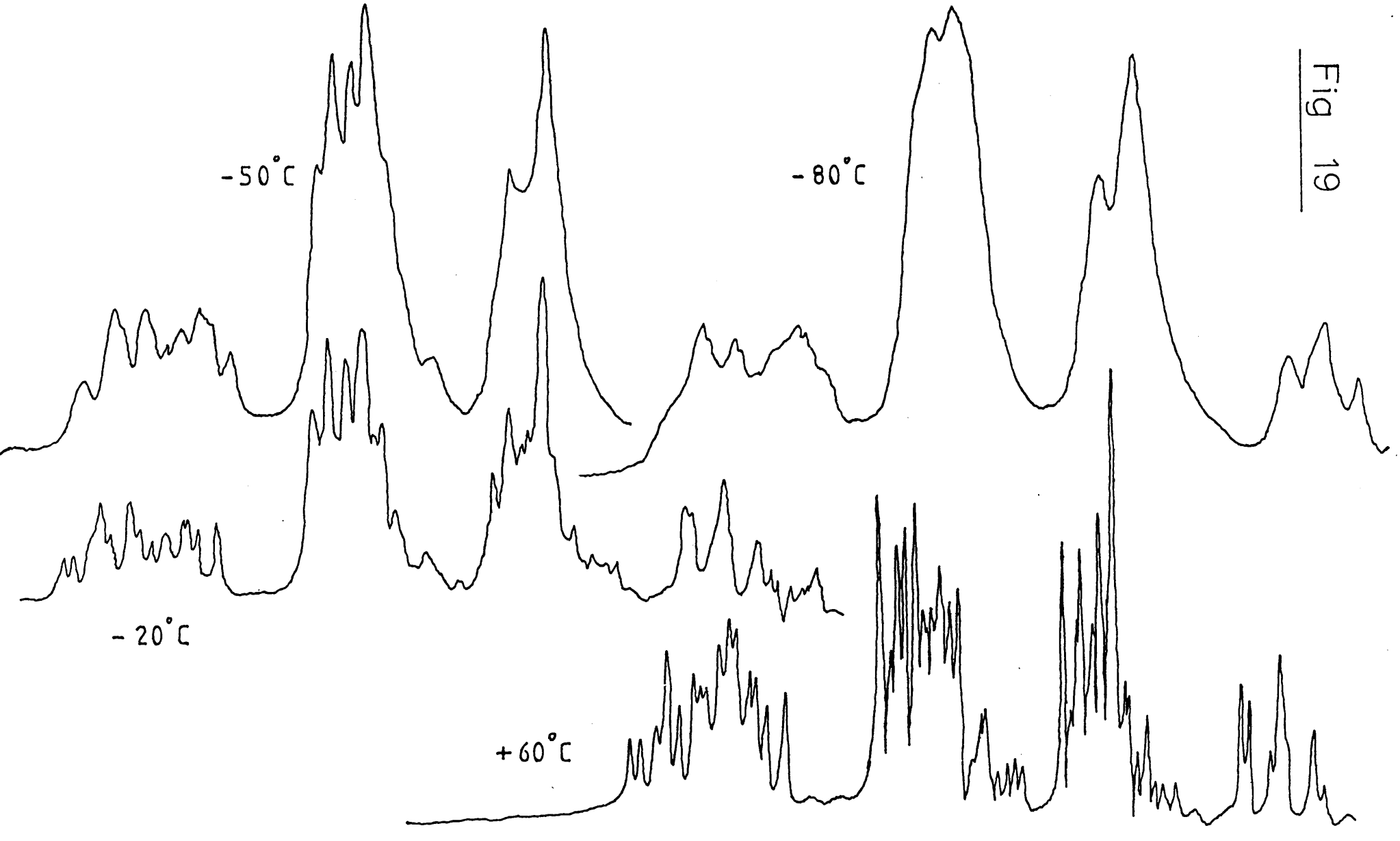


Fig 19

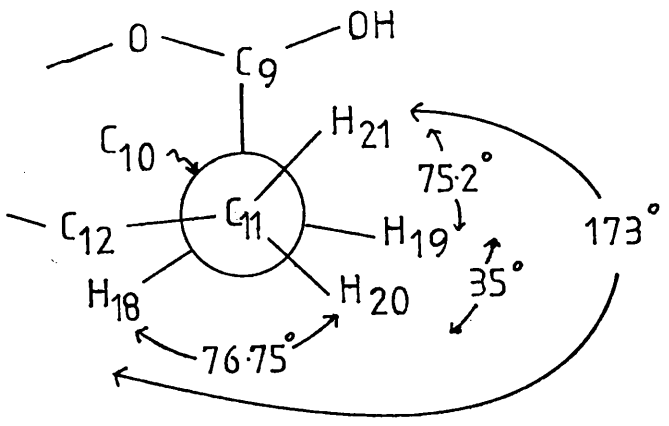

O
C9
OH
C10
H21
75·2°
C12
C11
H19
173°
35°
H18
H20
76·75°

Fig 20

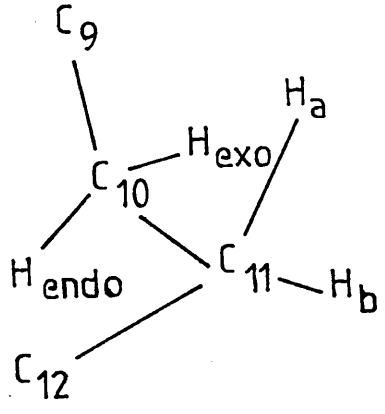
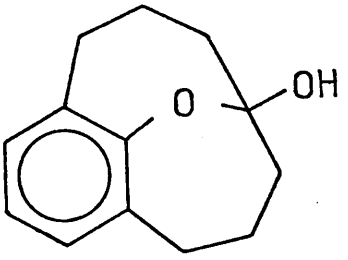
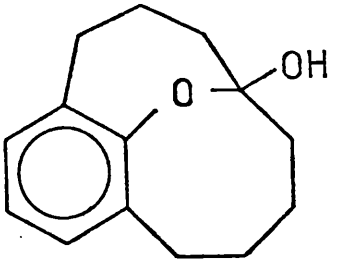

C9
Ha
Hexo
C10
Hendo
C11
Hb
C12

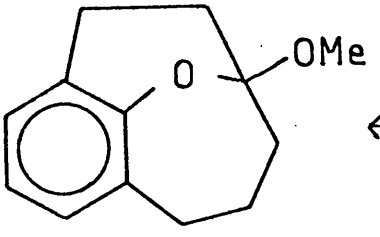
Fig 21



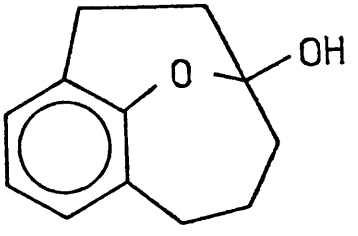
(120)



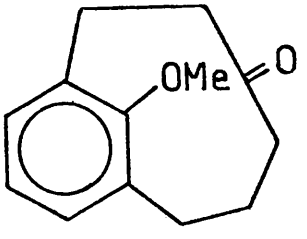
(123)

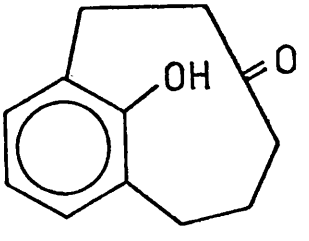


(124)



(105)

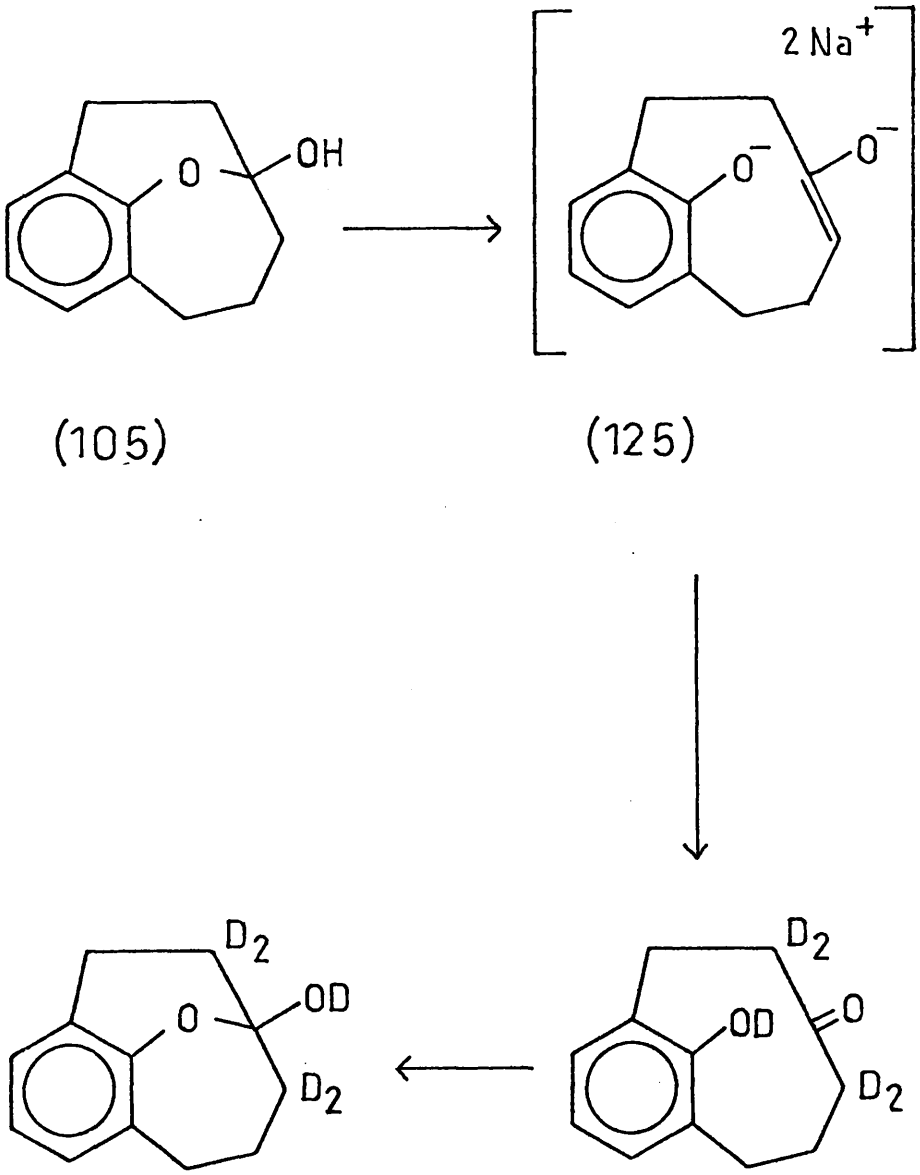




between conformational isomers has been observed in certain m-cyclophanes[90] this latter possibility has been discounted on the grounds that the chemical shift and splitting pattern of the shielded proton remain unaltered, apart from broadening, between -80°C and +100°C (see figure 19). This is evidence that the hemiacetal (105) is locked in one conformation. The shielded proton represents the X component of a multi-spin system - in conformer I a four spin system and in conformer II a six spin system. In principle, a choice between these alternatives could be made from an analysis of the coupling constants, but no reliable assignment can be made solely on the X component. However, it is significant that irradiation at δ 0.83 induces deep-seated changes in the δ 1.6 multiplet but not in the benzylic signals at δ 3.4 or δ 3.13. This indicates that the high field proton is not adjacent to a benzylic centre and therefore favours conformer I (105I).

It is also significant that the calculated geometry of this conformer shows that the endo-C_{10}-H subtends angles of 77° and 173° with the C_{11} protons (figure 20). Thus, if we assume that one of these couplings will be very small, we might treat the high field multiplet as a perturbed quartet arising from a geminal coupling with exo-C_{10}-H and quasi-axial coupling with Ha (figure 21). At 220 MHz, the high field multiplet shows apparent couplings of 15 Hz and 12 Hz, each being further split by a small coupling of about 3 Hz. This is consistent with conformation I and the balance of evidence suggests that this is indeed the preferred conformation.

An attempt was made to confirm the assignment of the high field proton by a selective deuteration experiment. As mentioned above, in contrast to the ring homologues (120)[96] and (123)[97] the hemiacetal (105) is reported not to be in equilibrium with its keto-phenol tautomer, as it gives only the one derivative (124)[50]. However, there



(105) (125)

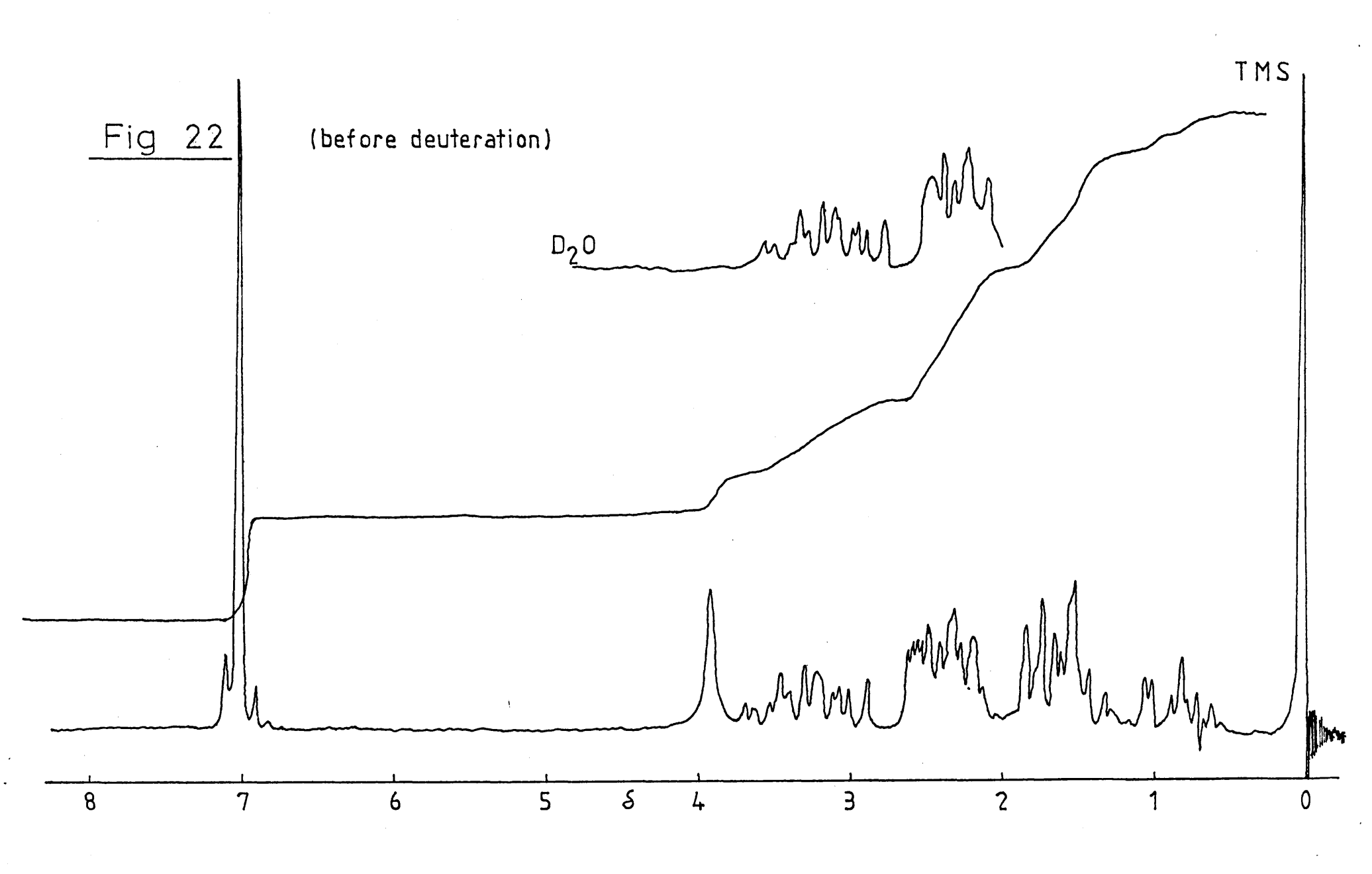


Fig 22
(before deuteration)
TMS
D_2O
8
7
6
5
δ
4
3
2
1
0

Fig 22 (after deuteration)

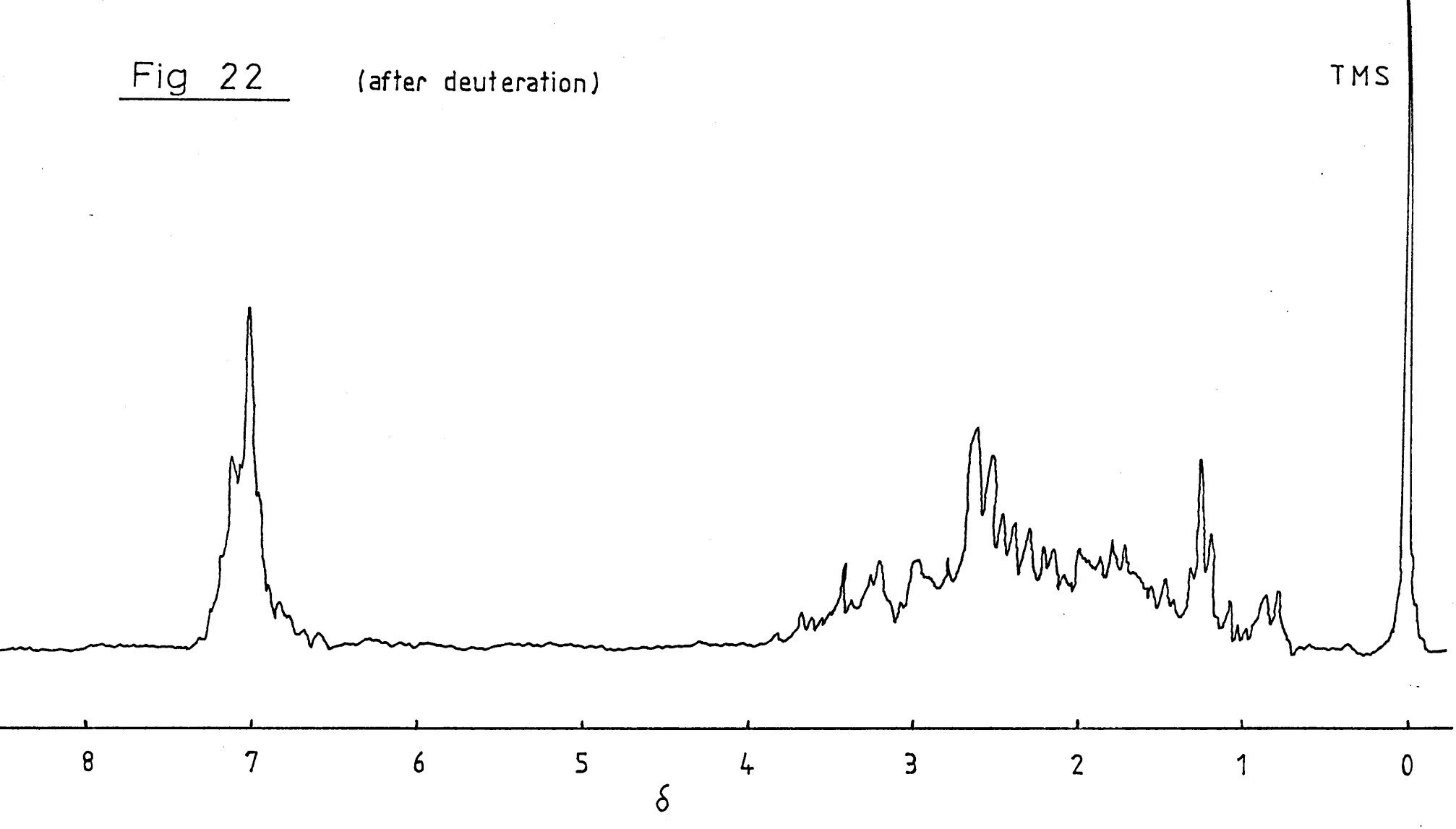


Fig 23 (before deuteration)

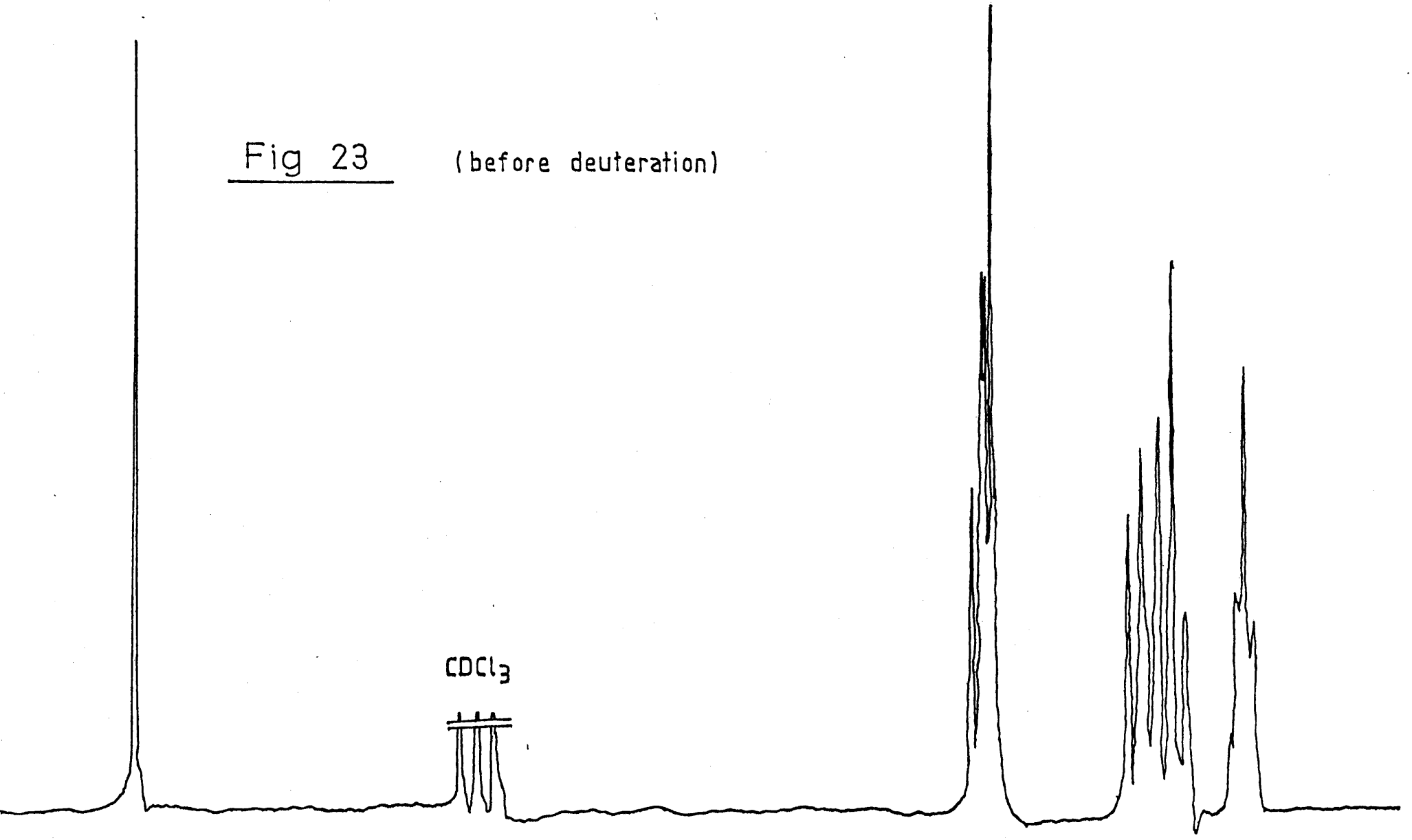
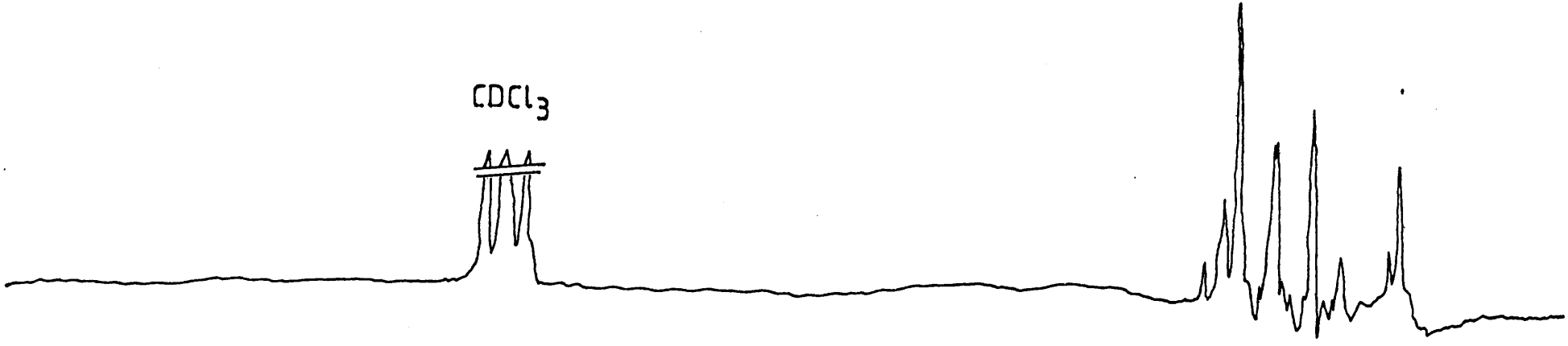


Fig 23 (after deuteration)



may in fact be an equilibrium, albeit severely biased towards the hemiacetal form (105), and the absence of a derivative of the keto-phenol form may be due to steric reasons. It was proposed therefore that, subject to there being such an equilibrium, if (105) were refluxed with sodium deuteroxide in D_2O for several days, then the protons α to the carbonyl in the keto-phenol tautomer would become replaced with deuteriums. This would necessitate the formation of dianions such as (125). In turn, this would mean that the protons α to the carbon carrying both oxygens in the ring-closed form (105) would become replaced with deuteriums (in addition, of course, to the deuteration of the -OH function).

The experiment was carried out using a reaction mixture 0.25M in (105) and 1.0M in NaOD. After 38 hours at 100°C under an atmosphere of nitrogen, charring of the mixture became noticeable and the reaction was stopped and worked-up using CO_2 gas to neutralise the solution. The mass spectrum of the product showed a parent ion at m/e 195 which is an increase of 5 a.m.u. over that of the starting material. There was some (M + 4), (M + 3), (M + 2) and (M + 1) but no signal at all corresponding to (105). It was expected that the ^1H n.m.r. spectrum of this deutero-compound would resolve the question of which proton was under the ring and concomitantly in which conformation compound (105) existed. If our assignment was correct then there would be no high field signal in the deutero-compound. However, there was a high field multiplet in the spectrum. Figure 22 shows the spectra before and after deuteration. The ^{13}C n.m.r. spectrum of the product was obtained and this showed the absence of signals assigned from the ^{13}C spectrum of (105) as being due to C_7, C_9, and C_{12} (see figure 23). In addition, the product from the deuteration experiment was not crystalline and showed a carbonyl absorption in the i.r. spectrum. On the possibility that the product had somehow remained in the keto-phenol

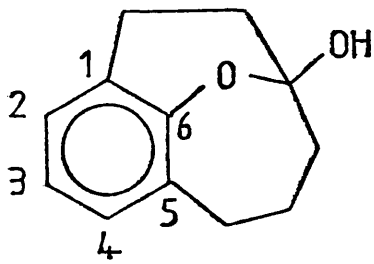
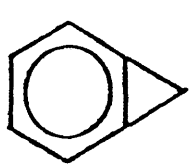
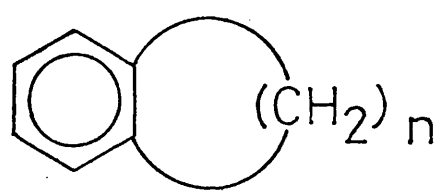
Compound	$\delta^{13}C_x$ (p.p.m.)	$^{1}J_{CH}$ (Hz.)	Ref.
 (105)	C_1 136.1 C_2 (124.1) C_3 124.9 C_4 (126.1) C_5 136.1 C_6 155.1	 (158.9) 158.8 (159.0)	Exptal.

Table 7



(111)



(126) n = 2–4

form, a drop of DCl was added and the spectra rerun. There was no change in any of the spectra. It must be assumed therefore that the treatment with base had somehow caused a change in the skeleton of (105) in addition to replacing five hydrogen atoms by five deuterium atoms.

^{13}C n.m.r. Spectroscopy:

Chemical shifts in ^{13}C n.m.r. are sensitive to changes in hybridisation and electron density whilst C-H coupling constants ($^{1}J_{C-H}$) are particularly sensitive to hybridisation changes. There was therefore every prospect that the spectrum of (105) would reflect any double bond localisation or loss of aromatic character associated with distortion of the benzene ring as indicated by the molecular mechanics calculations and by the u.v. spectroscopic results.

^{13}C n.m.r. spectroscopy has been used in the case of cyclopropabenzene (111) to provide evidence for bond fixation. Although the resonance of the six membered ring protons in the normal aromatic region indicates that the diamagnetic ring current is not disturbed to any significant extent when compared with that of normal aromatic molecules, the ^{13}C-H coupling constants for the methylene protons, determined as 178 ± 2 Hz, is comparable with the value measured for 1 - methyl cyclopropene (172 Hz)[103]. This can be taken to reflect similar bond angles at C_3 and C_7 in cyclopropene and benzocyclopropene respectively[103, 104]. ^{13}C n.m.r. studies have been undertaken on the homologous compounds (126)[88b].

The spectrum of (105) shows C_9 at δ 102.8, two benzylic carbons at δ 38.7 and δ 39.4, two alicyclic carbons at δ 25 and δ 27.2, and one high field signal at δ 19.47 which is assigned to C_{10} shielded by the aromatic ring current. The aromatic signals are as listed in Table 7. The assignments were made using noise, off-resonance and gated decoupled spectra. Carbon atom C_3 was

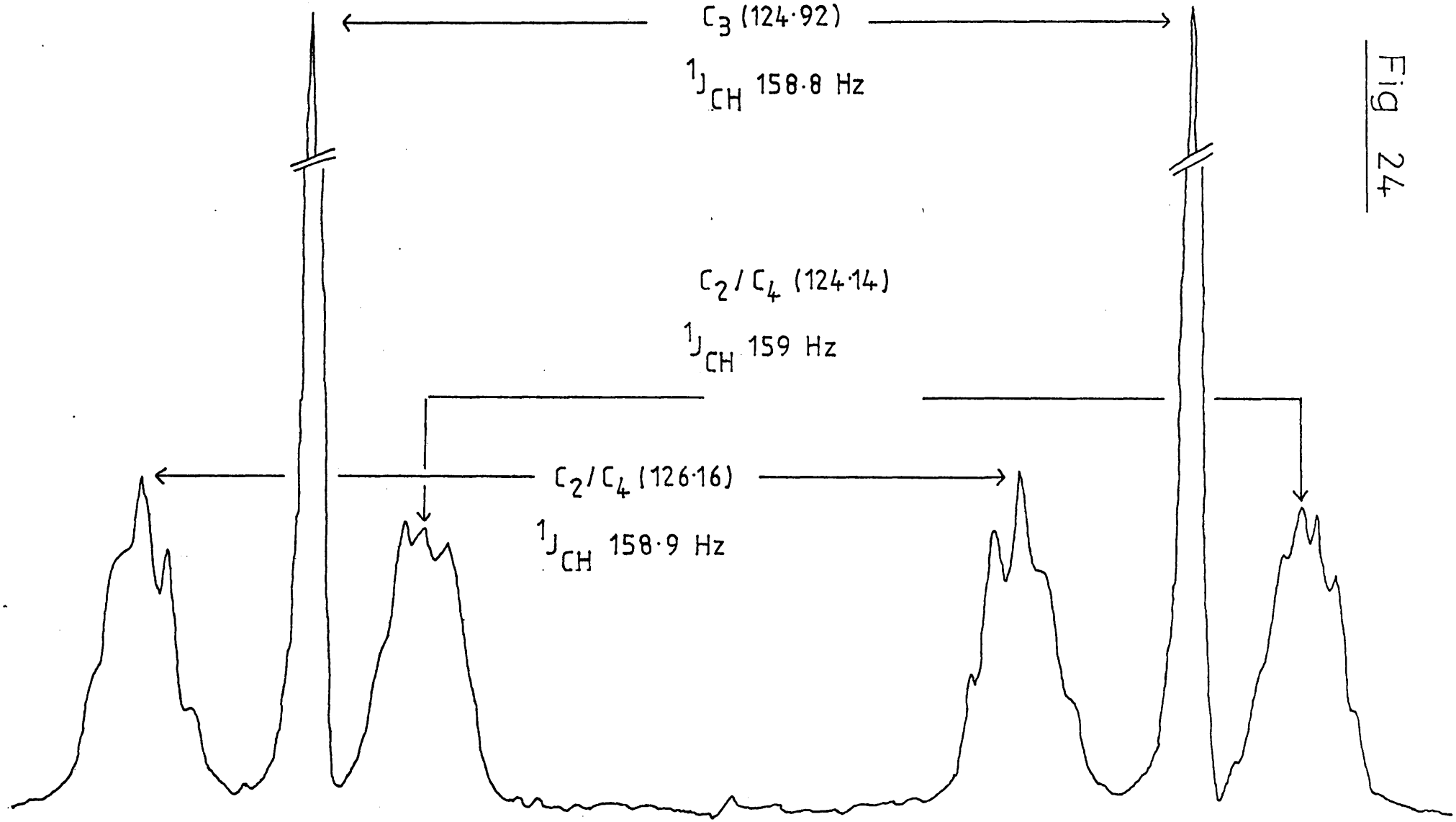

C3 (124·92)
1JCH 158·8 Hz
C2 / C4 (124·14)
1JCH 159 Hz
C2 / C4 (126·16)
1JCH 158·9 Hz

Fig 24

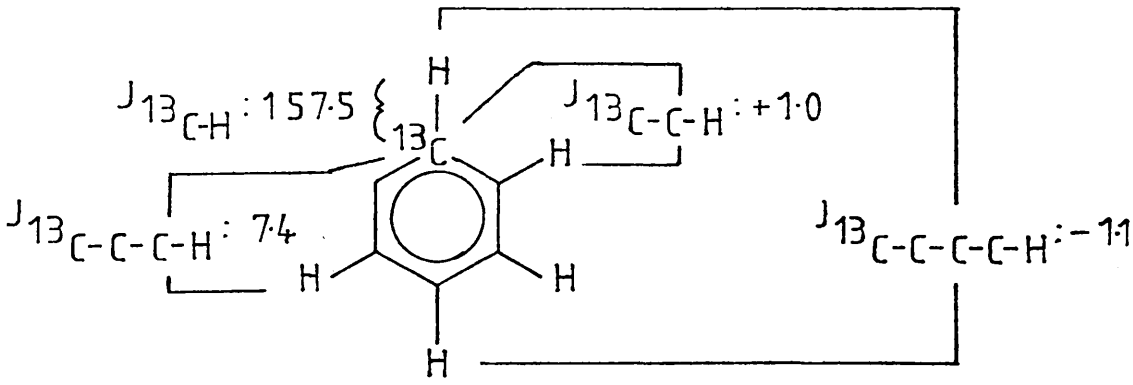


Fig 25

Compound	^{13}C (p.p.m.) of benzylic and alicyclic carbons
(II9a)	24.875, 22.403
(II9b)	34.460, 32.522, 26.308
(I05)	39.4I6, 38.7I5, 27.202, 24.998

Table 8

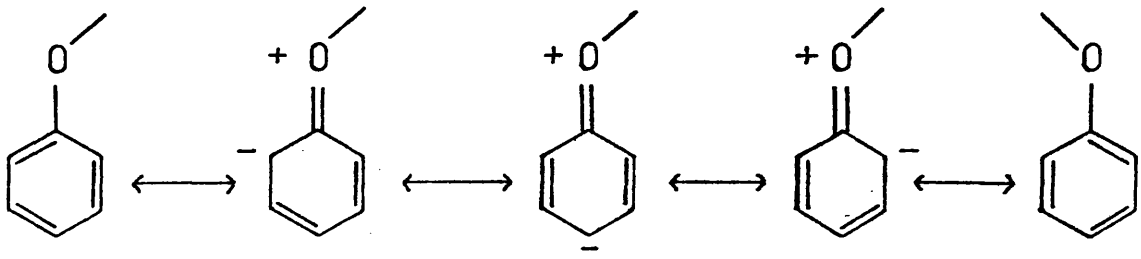
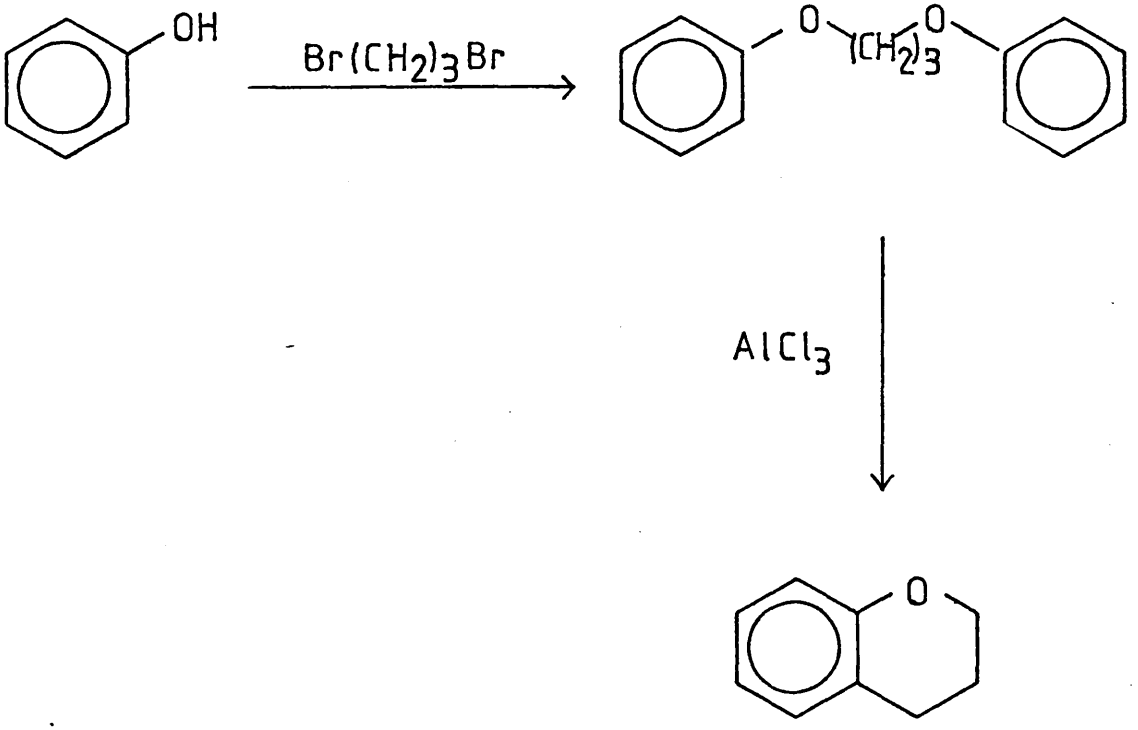
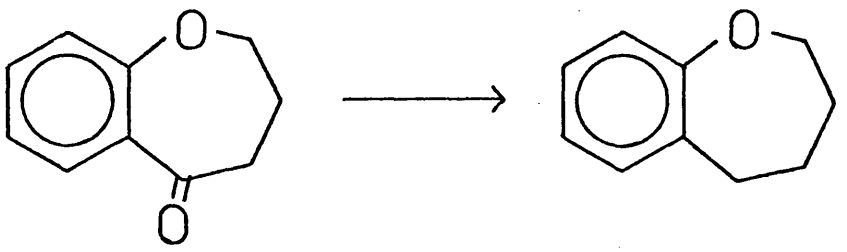


Fig 26

Scheme 4



(119a)



(127) (119b)

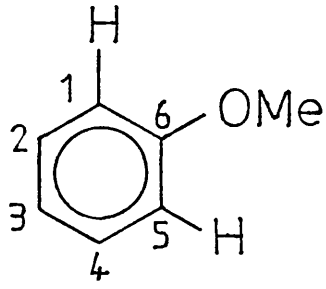
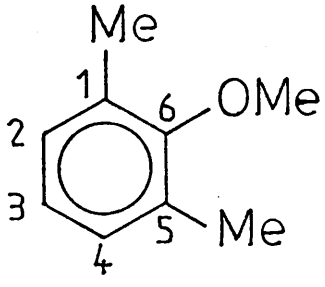
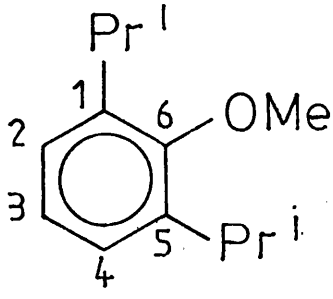
Compound	$^{13}C_x$ (p.p.m.)	$^{1}J_{CH}$ (Hz.)	Ref.
 (118 a)	C_1 113.8 C_2 128.9 C_3 120.1 C_4 128.9 C_5 113.8 C_6 159.2	156 158 162 158 156	107 and 108
 (118 b)	C_1 129.3 C_2 127.6 C_3 122.6 C_4 127.6 C_5 129.3 C_6 156.2		107
 (118 c)	C_1 141.4 C_2 123.9 C_3 123.3 C_4 123.9 C_5 141.4 C_6 154.7		107

Table 9

identified from the gated decoupled spectrum (figure 24) on the assumption that $^{2}J_{C-H}$ will be very small. The various J_{C-H} couplings in benzene are shown in figure 25.[105]

It was thought that comparison spectra of (119a) and (119b) might allow an unambiguous assignment of the two benzylic and the two alicyclic carbons (δ 25 and δ 27.2). Compound (119a) was synthesised according to the method of Deady, Topson and Vaughan[105], (see Scheme 4), whilst it was possible to prepare (119b) by Wolff-Kishner reduction of (127), a sample of which was available. Details of these preparations are included in the experimental section. As may be seen from Table 8 the results obtained did not in fact allow such an assignment to be made.

Comparison spectra of anisole and two 2,6 - disubstituted anisoles (see Table 9) illustrate the effect of reducing the effective overlap of the aromatic π system with the non-bonding p electrons on the oxygen atom. The ^{13}C chemical shifts for anisole can be reasonably interpreted in terms of conjugative electron release by the oxygen atom.(figure 26). Contributions from these resonance forms will increase the electron density at the ortho- and para - positions relative to benzene and thus increase the shieldings. In the 2,6 - dialkyl derivatives deshielding effects are observed at the para carbon. For an extensive series of anisoles Dhami and Stothers[109] have shown that the magnitude of this deshielding is dependent on the size of the ortho groups. It is reasonable to conclude that there is steric interference of the ortho substituents with the methoxy function, such that electron release by the oxygen atom is substantially reduced. The most populated conformatiom of these hindered molecules is likely to be one in which the $O-CH_3$ group deviates from coplanarity with the aryl ring.

A similar interpretation may be made for the spectra of (105)

and so it would be expected that the hemiacetal would fit into this series unless the distortion of the ring brought about distortion of the aromatic character. No such effect could be detected. The chemical shift and C-H coupling constant data are all normal for a phenyl ether in which there is little delocalisation of the nonbonding electrons on the oxygen atom into the benzene ring. An empirical correlation of the chemical shift of the C_4 carbon of disubstituted anisoles with the average angle of twist (θ) of the phenyl ring from the reference plane has been made[107], the reference plane being the C_{Ar}-O-CH_3 plane. Assuming complete absence of conjugation at $\theta = 90^\circ$, the value of $\cos^2\theta$ should be proportional to the extent of conjugation present. Assigning chemical shift values of 120.1 at $\theta = 0^\circ$ and 125.3 at $\theta = 90^\circ$ for C_4 we arrive at the equation :

$$\cos^2\theta = \frac{125.3 - \delta}{125.3 - 120.1}$$

(where δ = C_4 chemical shift in p.p.m.)

Applying this relationship to the case of (105) gives a value of $\theta = 74^\circ$ which is startingly close to that derived from the force field calculations (73.4°) (see figure 7). This contrasts with the case of cyclopropabenzene in which aromatic bond length abnormalities lead to $^1J_{C-H}$ values of 168.5 and 159 Hz[88b].

Conclusions:

The hemiacetal (105), originally prepared by Treibs, has been re-synthesised and much corroborative evidence obtained to support the structure proposed by him for the compound. In spite of the evidence from u.v. spectroscopy that the benzene ring is non-planar, and from molecular mechanics calculations that some bonds are abnormally short, we have been unable to detect any evidence that the ring is other than aromatic in nature. As in the case of other small

ring-annelated benzenes, it represents one more example of the resilience of the aromatic delocalised π system in the face of bond distortion.

GENERAL EXPERIMENTAL

AND ABBREVIATIONS

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. All boiling points are uncorrected. Microanalyses were carried out by Mrs. W. Harkness and her staff.

Routine mass spectra were recorded by Mr. A. Ritchie on an AEI-GEC MS12 instrument. Accurate mass measurements were obtained from an AEI-GEC MS902 instrument.

Infra-red spectra were recorded on a Perkin Elmer 225 grating spectrophotometer by Mrs. F. Lawrie and her staff or on a Perkin Elmer 257 spectrophotometer.

All ultra-violet spectra were recorded, using ethanol as solvent, either on a Pye Unicam SP800 spectrophotometer or a Perkin Elmer 550 spectrophotometer.

Routine ^{1}H n.m.r. spectra were obtained from a Varian T-60 (60 MHz.) spectrometer and a Perkin Elmer R32 (90 MHz.) spectrometer. High resolution ^{1}H n.m.r. spectra were obtained from a Varian HA 100 (100 MHz.) spectrometer by Mr. J. Gall and from a Varian HR 220 (220 MHz.) spectrometer, courtesy of P.C.M.U. (Harwell). ^{13}C n.m.r. spectra were recorded by Dr. D.S. Rycroft on a Varian XL 100-12 FT NMR spectrometer. All n.m.r. spectra were recorded using deuteriochloroform as solvent with tetramethylsilane as internal standard or using deuterium oxide as solvent with 3-(trimethylsilyl)-1-propanesulphonic acid sodium salt hydrate as internal standard.

Kieselgel GF_{254} or HF_{254} (Merck) was used for preparative thin layer chromatography which was carried out on 20 x 20 x 0.2 cm. glass plates coated with a 1 mm. thickness of silica. Kieselgel G (Merck) was used for analytical thin layer chromatography which was carried out on 1 x 3 in. microscope slides coated with a 0.5 mm. thickness of silica. Analytical and preparative t.l.c. plates were viewed under an ultra-violet lamp (254 and 350 nm.). Analytical plates were develcped with iodine vapour and/or spraying the plates with a solution of ceric

ammonium sulphate and then heating the plates to approximately 150°C. The ceric ammonium sulphate solution was prepared by dissolving ceric ammonium nitrate (5g.) in concentrated sulphuric acid (50 ml.) and making the volume up to 500 ml. with water.

Alumina used for column chromatography refers to the grade I neutral variety (Woelm), and made up to grade II or III as indicated by the addition of 3 or 6% water prior to use. Silica gel columns used the 0.05 - 0.2 mm. silica gel (Merck) "for column chromatography". Silica gel columns for dry-column chromatography used silica gel (Woelm) "for dry-column chromatography".

The solvents used for chromatography are expressed as a percentage volume e.g. 30% ethyl acetate-light petroleum is equivalent to ethyl acetate and light petroleum in a volume ratio of 3:7. Light petroleum refers to the fraction boiling in the range 60-80°C. All dilute mineral acids and bases were 6N aqueous unless otherwise stated.

In cases where the products were isolated "by solvent extraction", the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent ; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous magnesium sulphate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

The following abbreviations and symbols have been used throughout the text.

t.l.c.	thin layer chromatography
R_f	In t.l.c. $\frac{\text{distance travelled by compound}}{\text{distance travelled by mobile phase}}$
i.r.	infra-red
$cm.^{-1}$	reciprocal centimeter
ν	frequency (in cm^{-1})
u.v.	ultra-violet
nm.	nanometer
λ	wavelength (in nm.)
ε	molar extinction coefficient
n.m.r.	nuclear magnetic resonance
p.p.m.	parts per million
δ	chemical shift value (in p.p.m.)
J	coupling constant
m.s.	mass spectrum
M^+	molecular ion
m/e	mass to charge ratio
PE	photo-electron
m.p.	melting point
b.p.	boiling point
mm.	millimeters of Hg ($\equiv$ Torr)
s	singlet
d	doublet
t	triplet
q	quartet
qu	quintet
m	multiplet
e	envelope
b	broad
dd	doublet of doublets
sh	shoulder

*	eg 6.31* ; this refers to a signal in the n.m.r. spectrum which disappears on addition of D_2O to the solution.
P	page number
aq.	aqueous
W./V.	weight by volume e.g. 5% W./V. means a solution of 5g. in 100 ml. of solvent.

PART I

EXPERIMENTAL

2a, 3, 4, 5 - Tetrahydroacenaphthene (15b)

Acenaphthene (102) (115 g., 0.75 mole) which had been once recrystallised from ethanol (m.p. 94-95°C) was placed in a steel bomb of total capacity 2 litres, and enough ethanol added to bring the total volume of the suspension to 1500 ml. Raney nickel catalyst[60] (8 g.) was then added and hydrogen introduced to a pressure of 70 atmospheres. The temperature of the bomb was raised slowly as the solution was stirred. At 100°C the hydrogenation became rapid and slightly exothermic, raising the temperature to 120°C. After about 15 minutes the temperature settled to 110°C and stirring was continued at this temperature for an additional half hour. The mixture was siphoned out of the bomb and the catalyst was removed by filtration through a pad of Celite. Evaporation of the solvent yielded the crude product which was distilled to give a colourless liquid (109 g., 0.69 mole, 92%) ; b.p. 82-84°C/1.0 mm. (lit.[110,111] b.p. 249.5°C/719 mm. and 113.5-114°C/10 mm.) ; ^{1}H n.m.r. δ 0.9-2.4 (6H ; e), 2.4-3.4 (5H ; m) and 6.6-7.2 (3H ; m) ; i.r. $\nu_{max.}^{ccl_4}$ 3040, 3020, 2940, 2850 and 1605 $cm.^{-1}$; m.s. m/e 158 (M^{+}), 141, 130, 115, 91 and 77.

2a, 3, 4, 5 - Tetrahydroacenaphthene-2a-hydroperoxide (103)

Tetrahydroacenaphthene (15b) (40 g., 0.25 mole) was oxygenated for 100 hours in an all-glass apparatus (see figure 4) at room temperature. The resulting oil was dissolved in light petroleum (125 ml.) and extracted into aqueous methanol by shaking twice with 90% methanol-water (25 ml). The extracts were concentrated on a rotary evaporator after which extraction[112] into ether and base wash yielded an oily residue. The residue was triturated with n-pentane and after 24 hours at 0°C, the solvent was decanted off, leaving a thick gum of crude hydroperoxide (1.8 g). Partial crystallisation of this gum gave

material which was identified as the symmetrical peroxide (113) m.p. (n-pentane) 193-194°C (lit.[50] m.p. 187°C) ; ^{1}H n.m.r. δ 1.0-2.2 (6H ; m), 2.2-3.6 (14H ; m) amd 6.9-7.4 (6H ; m) ; i.r. $\nu_{max.}^{KBr}$ 3060, 3040, 3010, 2975, 2940, 2920, 2865, 2840, 2820, 1605, 1590, 895 and 850 cm.$^{-1}$; m.s. m/e 346 (M^{+}), 174, 173, 158, 157, 129, 128, 115, 91, 77, 65, 63 and 51. Attempts to increase the yield of crude hydroperoxide (103) were made using different apparatus (see figures 5 and 6) and using transition metal catalysis. In all cases the outcome of the reaction was nearly identical with the result obtained using the initially chosen reaction conditions. The crude hydroperoxide remaining (380 mg.) after partial crystallisation of the symmetrical peroxide in this reaction was combined with crude hydroperoxide obtained from other runs and used to prepare the ester (104) without further purification.

p-Nitro-benzoate of the Hemiacetal (104)

Crude hydroperoxide (103) (680 mg., 3.6 m.mole) in dry pyridine (2 ml.) was added to a suspension of p-nitrobenzoyl chloride (630 mg., 3.7 m.mole) in dry pyridine (2 ml.) at 5°C with stirring. The mixture was allowed to stir for 1 hour at room temperature. Ice-cold dilute sulphuric acid was then added till the pH was ca. 4 and a gummy solid was precipitated. Extraction[112] into ether and base wash yielded the crude p-nitro-benzoate which could not be purified by the literature procedure. Purification was however possible using either of two methods :

a) Preparative t.l.c. of a portion of the crude product (400 mg.) on five plates using 50% chloroform-ethyl acetate as eluant gave a band with Rf 0.6 which fluoresced green in u.v. light and afforded the p-nitrobenzoate (104) as crystals m.p. 105°C. Re-crystallisation from light petroleum yielded pure ester (104)

(140 mg.) m.p. 108-109°C (lit.[50] m.p. 108-109°C).

b) The remainder of the crude product (1.7 g.) in 50% chloroform - light petroleum was poured onto a column of dry silica[113] (29 g.) and eluted with the same solvent mixture. The first 125 ml. of eluant afforded the p-nitrobenzoate (104) (480 mg.) as crystals m.p. 103°C. Recrystallisation from light petroleum yielded the pure ester (104) (450 mg.) m.p. 108-109°C (lit.[50] m.p. 108-109°C).

Combining the material obtained from a) and b) gave a total yield of p-nitrobenzoate (104) (590 mg., 1.7 m mole, 48%) ^{1}H n.m.r. δ 0.7.3.8 (10H ; e), 6.9-7.2 (3H ; m) and 8.3 (4H ; s) ; i.r. ν_{max}^{ccl4} 3040, 3020, 2960, 2940, 2890, 2860, 2850, 1745, 1730, 1610, 1525 and 1350 cm.$^{-1}$; m.s. m/e 339 (M+), 322, 309, 293, 284, 249, 209, 189, 172, 150 and 120.

p-Acetamido-benzoate of the Hemiacetal.

The p-nitrobenzoate (104) (90 mg., 0.27 m mole) and Pd/c (10%, 190 mg.) in acetic anhydride (5 ml.) and acetic acid (1 ml.) were hydrogenated at N.T.P. The uptake (ca. 70 ml) exceeded the theoretical uptake (ca. 20 ml.) and continued after 1 hour. Work-up afforded a colourless gum which was shown by t.l.c. (50% ethyl acetate/light petroleum) to contain one main product and two minor products. Preparative t.l.c. using the same solvent system allowed isolation of the main product which had Rf 0.37. The product was a glass and could not be crystallised. The ^{1}H n.m.r. spectrum which was weak did however show new aromatic signals at δ 7.6 and δ 8.0.

Hemiacetal (105)

Hydrolysis of the ester (104) to the hemiacetal (105) was carried out according to the published procedure.[50] The p-nitrobenzoate (104)

(34 mg., 0.10 m mole) was suspended in methanol (2 ml.) and treated with potassium hydroxide (12 mg.) in a 33.3% water-methanol solution (3 ml.). The mixture was stirred at room temperature overnight. After stirring, water (15 ml.) was added and the mixture extracted[112] with ether to give a semi-solid (31 mg.). Recrystallisation from n-pentane yielded the pure hemiacetal (105) (18 mg., 0.1 m mole, 94%) m.p. 75-76°C (lit.[50] m.p. 76.5-77.5°C). Subsequent preparations were carried out using 220 mg. and then 251 mg. of the ester (104) and combining the products led to a total yield of the hemiacetal (105) (247 mg., 1.3 m mole, 90.9%) ^{1}H n.m.r. δ 0.85 (1H ; m), 1.2-2.0 (3H ; m), 2.0-2.7 (4H ; m), 2.8-3.8 (2H ; m), 3.9* (1H ; s) and 7.0 (3H ; m) ; i.r. $\nu_{max.}^{ccl4}$ 3600, 3560-3200 (3440), 3040, 3020, 2950, 2930, 2890, 2860, 2845, 1255, 1240, 1075, and 1060 cm.$^{-1}$; u.v. $\lambda_{max.}^{EtoH}$ 265.5, 223 nm. (log ε 2.43, 3.2) ; ^{13}C n.m.r. 155.138 (s), [2x] 136.137 (s), 126.138 (d), 124.900 (d), 124.089 (d), 102.829 (s), 39.416 (t), 38.715 (t), 27.202 (t), 24.998 (t) and 19.468 (t) p.p.m. ; Raman $\nu_{max.}^{Powder}$ 1612 and 1592 cm.$^{-1}$; m.s. m/e 190 (M+), 162, 135, 115 and 92.

m-2-Xylenol methyl ether (118b)

This compound was prepared by the method of Rowe, Bannister and Storey.[114] A solution of m-2-Xylenol (6.1 g., 0.05 mole) and sodium hydroxide (2 g.) in water (20 ml.) was boiled under reflux and dimethyl sulphate (5 ml.) was added in one portion. The mixture was then refluxed for a further 3 hours. After cooling, the oil was separated and the aqueous layer extracted with ether (3 x 10 ml.). The oil and ethereal extracts were combined and washed with dilute sodium hydroxide, dried over magnesium sulphate, filtered and concentrated on a rotary evaporator. The residue was fractionally distilled to give pure m-2-xylenol methyl ether (118b) (6.0 g., 0.044 mole, 88%) b.p.

182-184°C/760 mm. (lit.[114] b.p. 182-183°C/760 mm.) ^{1}H n.m.r. δ 2.2 (6H ; s), 3.6 (3H ; s) and 6.85 (3H ; s); i.r. $\nu_{max.}^{ccl4}$ 3070, 3040, 3025, 2990, 2940, 2860, 2820, 1590, 1260 and 1020 cm.$^{-1}$; u.v. $\lambda_{max.}^{EtoH}$ 226, 264, 270, 276 (log E 3.0, 3.04, 3.07 and 3.03).

1,3-Diphenoxypropane (128)

This compound was prepared by the method of Deady, Topson and Vaughan.[106] 1,3-dibromopropane (17.5 g., 0.087 mole) was added dropwise to a stirred solution of phenol (37.5 g., 0.4 mole) and sodium hydroxide (11.75 g., 0.3 mole) in water (50 ml.). The mixture was refluxed for 3 hours and then cooled whilst being stirred. The product was filtered off and washed with 3% aqueous alkali and then with water. Recrystallisation from ethanol gave 1,3-diphenoxypropane (128) (15.75 g, 0.07 mole, 79%) m.p. 57-58°C (lit.[106] m.p. 60°C) ^{1}H n.m.r. δ 2.25 (2H ; qu ; J 6.5 Hz.), 4.2 (4H ; t ; J 6.5 Mz) and 6.8-7.6 (10H ; m) ; i.r. $\nu_{max.}^{ccl4}$ 3100, 3070, 3040, 3030, 2960, 2940, 2880, 1600, 1585, 1285, 1240, 1060, 1040 and 1030 cm.$^{-1}$; m.s. m/e 228 (M+), 135, 134, 119, 107, 79, 77, 65, 51, 41 and 39.

Chroman (119a)

This compound was prepared by the method of Deady, Topson and Vaughan.[106] To a stirred slurry of 1,3-diphenoxypropane (128) (12 g., 0.053 mole) in anhydrous benzene (100 ml.) was added anhydrous aluminium chloride (9.08 g., 0.068 mole). The mixture was refluxed for 4 hours, cooled and poured onto ice (100 g.). Concentrated hydrochloric acid was added and the benzene layer was separated. The aqueous layer was extracted with ether (3 x 30 ml.) and these extracts combined with the benzene fraction. The combined organic layers were washed with 3% aqueous alkali, then water and finally

dried. The solvents were removed by distillation after which fractionation of the residue furnished chroman (119a) (6.15 g., 0.046 mole, 86.6%) b.p. 92-96°C/12 mm. (lit.[106] b.p. 96-100°C/16 mm.) ^{1}H n.m.r. δ 1.85 (2H ; qu ; J 6 Hz.), 2.6 (2H ; t ; J 6 Hz.), 4.0 (2H ; t ; J 5 Hz.) and 6.5-7.1 (4H ; m) ; i.r. $\nu_{max.}^{ccl4}$ 3080, 3040, 3025, 2980, 2950, 2940, 2900, 2880, 2860, 2850, 1610, 1585, 1265, 1225, 1070 and 1010 cm.$^{-1}$; ^{13}C n.m.r. 154.963, 129.789, 127.182, 122.172, 120.085, 116.702, 66.339, 24.875 and 22.403 p.p.m. ; m.s. m/e 134 (M+), 107, 94, 91 and 77.

Homochroman (119b)[115]

A solution of homochroman-5-one[116] (127) (4 g., 0.025 mole), potassium hydroxide (4.25 g., mole) and hydrazine hydrate (100%, 8 ml.) in diethylene glycol (10 ml.) was heated under reflux for 2 hours. Water was drained from the condenser and the temperature allowed to rise to 200°C. The residue was refluxed for a further 4 hours, cooled, diluted with water and extracted[112] with light petroleum to give a colourless liquid with an aniscle-like odour. Distillation yielded the pure homochroman (119b) (1.5 g., 0.01 mole, 40.5%) b.p. 95-96°C/1.5 mm. (lit. b.p.[115] 60°C/0.2 mm) ^{1}H n.m.r. δ 1.4-2.2 (4H ; m), 2.6-3.0 (2H ; m), 4.0 (2H ; t ; J 5 Hz.) and 6.8-7.4 (4H ; m) ; i.r. ν_{max}^{ccl4} 3070, 3020, 2930, 2860, 2840, 1605, 1580, 1280, 1235, 1080, 1045 and 1030 cm.$^{-1}$; ^{13}C n.m.r. 160.470, 135.636, 130.379, 127.299, 123.394, 121.253, 73.541, 34.460, 32.522 and 26.308 p.p.m. ; m.s. m/e 148 (M+), 133, 119, 107, 91 and 78.

Deuteration of Hemiacetal

Deuterium oxide (10 ml) was degassed by placing the liquid under a pressure of 1 mm. Hg for 12 hours. Clean, dry sodium metal (23 mg)

was then added, under a N_2 atmosphere, to a 1 ml. portion of this deuterium oxide. After the metal had dissolved, the hemiacetal (105) (47.5 mg) was added to the solution to give a mixture which was 0.25 molar in hemiacetal and 1.0 molar in deuterium oxide. The mixture was then refluxed (oil bath temperature ca. 105°C) under nitrogen for 38 hours whereupon significant charring of the material was noted and the reaction stopped. After cooling, CO_2 gas generated from Drikold was bubbled into the reaction mixture to neutralise the solution. It was found necessary to add more D_2O (6 ml) at this stage. The product was extracted with chloroform to yield a semi-solid which could not be crystallised. This crude material was purified by preparative t.l.c. on a 5 x 20 mm. precoated alumina plate (Merck F_{254} type T) using 30% ethyl acetate - light petroleum as eluant. The purified material could still not be crystallised. ^1H n.m.r. δ 0.85-4.0 and 6.8-7.3 ; i.r. $\nu_{max}^{CCl_4}$ 3600, 3540-3200 (3400), 3020, 2950, 2925, 2850, 1705, 1650 and 1460 $cm.^{-1}$; ^{13}C n.m.r. 129.917, 127.629, 126.909, 126.157, 124.135, 30.592, 29.708, 27.341, 27.158, 24.814 and 19.263 p.p.m. ; m.s. m/e 195 (M^+), 194, 193, 192, 191, 165, 164, 139, 121, 71 and 57.

A drop of DCl added to the solutions produced no change in either ^1H or ^{13}C n.m.r. spectrum.

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102. This programme was written by :
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and,
Dr. M.J.A. de Bie, Utrecht University, Laboratory of Organic Chemistry, Department of Instrumental Analysis.

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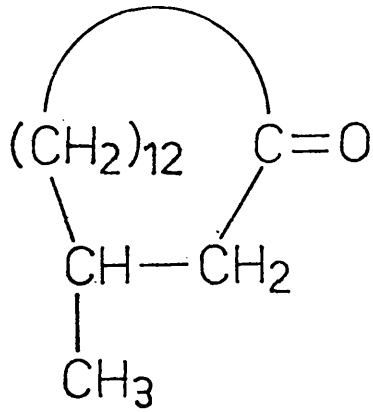
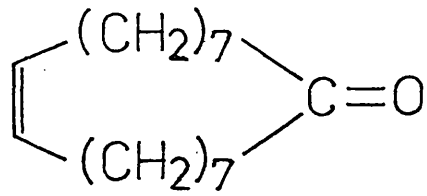
INTRODUCTION TO PART 2.

A SHORT REVIEW OF SYNTHETIC APPROACHES TO MEDIUM - AND LARGE - SIZED RINGS



(1)



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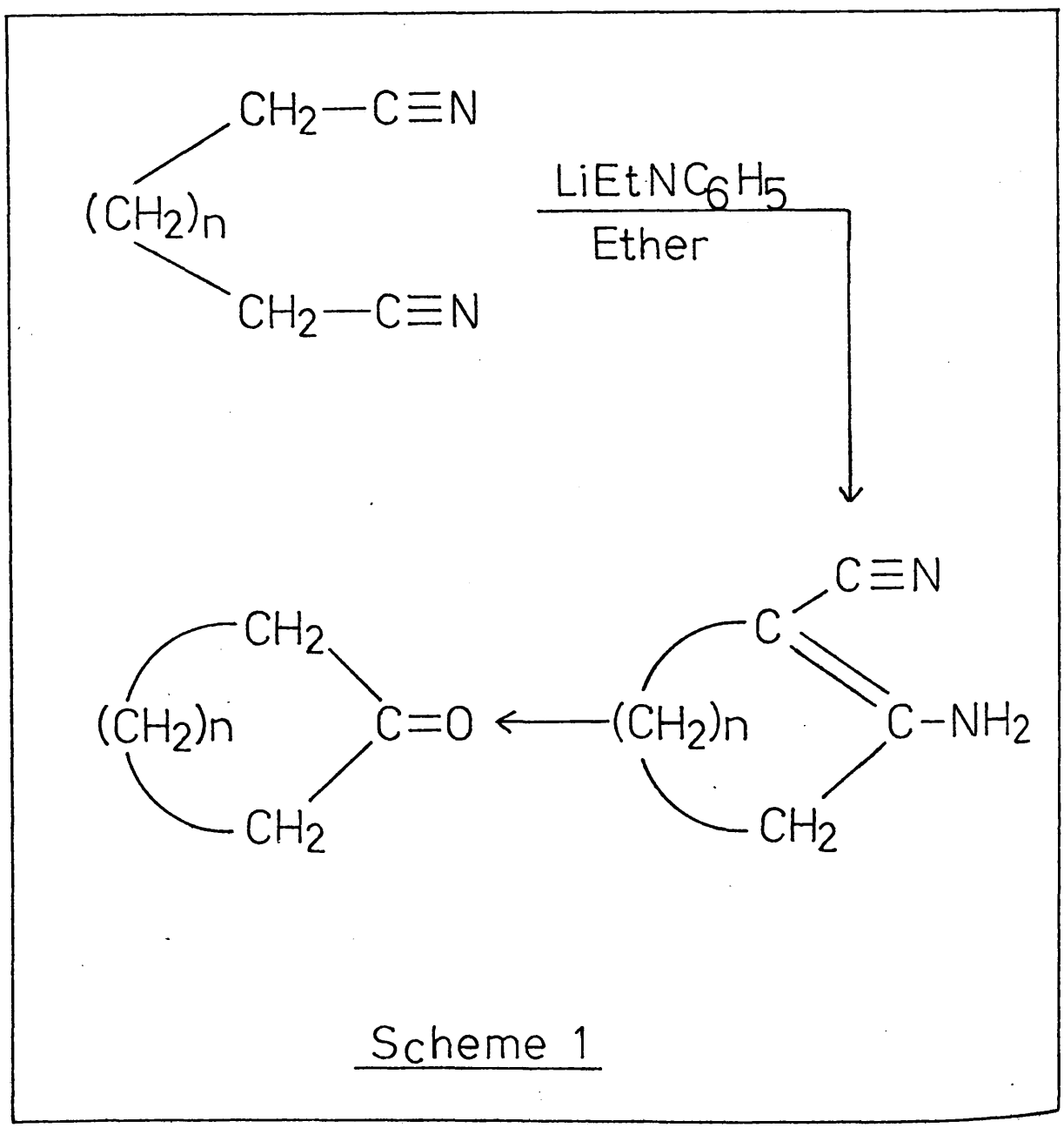
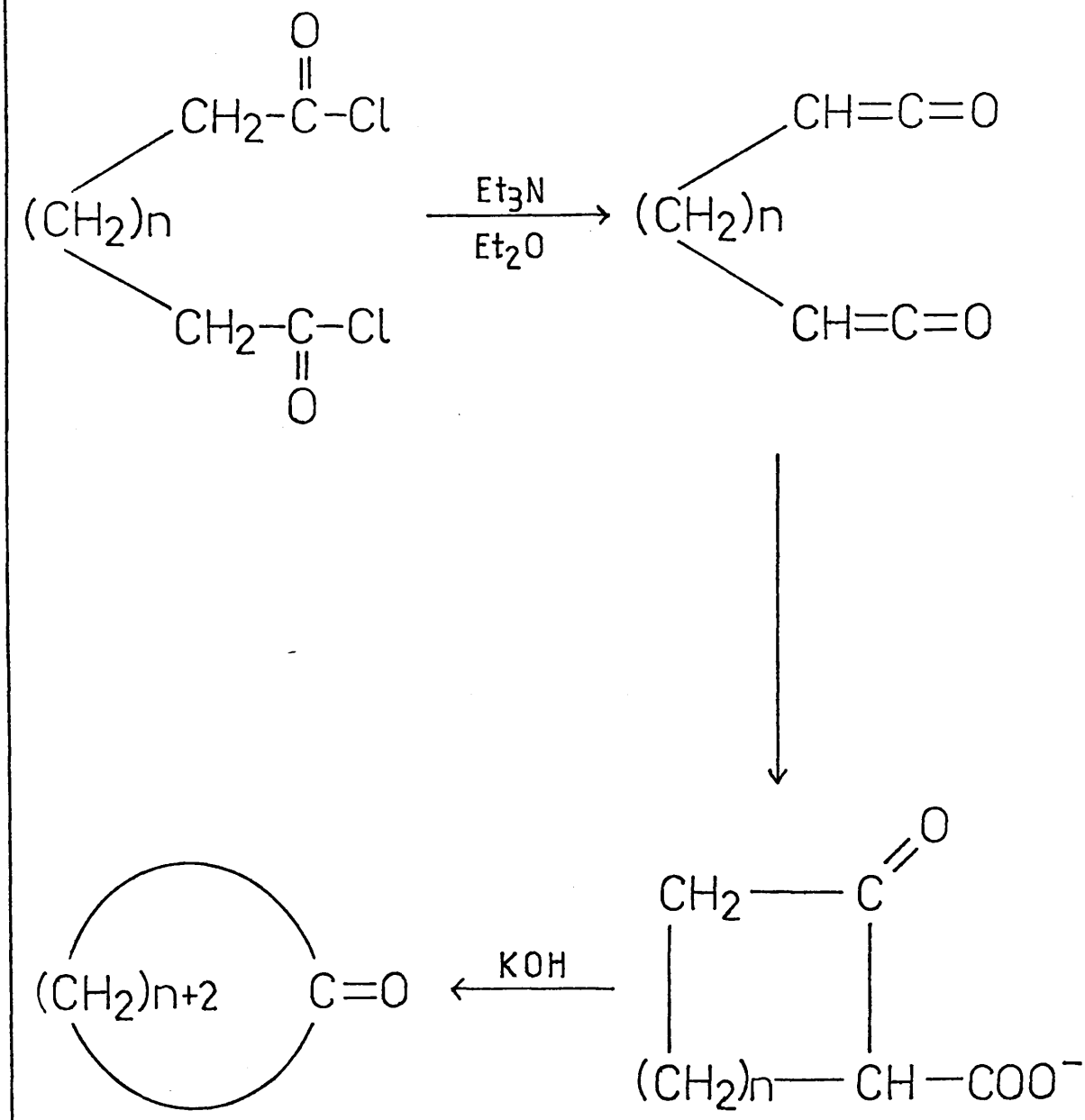

CH2—C≡N
(CH2)n
CH2—C≡N
LiEtNC6H5
Ether
C≡N
C
C-NH2
CH2
(CH2)n
CH2
C=O
(CH2)n
CH2

Scheme 1


CH2-C-Cl
(CH2)n
CH2-C-Cl
Et3N
Et2O
CH=C=O
(CH2)n
CH=C=O
CH2
C
(CH2)n
CH
COO⁻
KOH
(CH2)n+2
C=O

Scheme 2

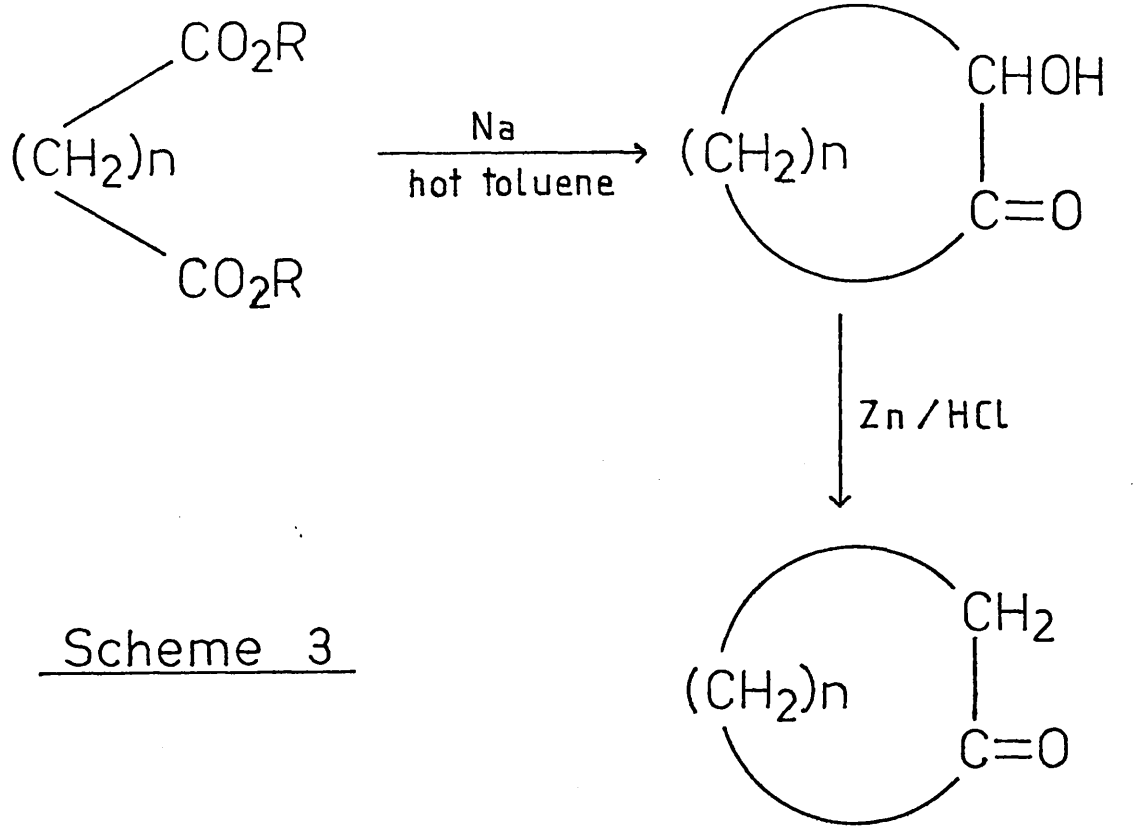
The purpose of this introduction is to outline some of the different synthetic approaches which have been used to prepare compounds containing medium - and large - sized rings and in particular the macrocyclic alkanes, ketones and lactones (macrolides). Other types of macrocyclic compounds such as the naturally occurring porphyrins and the non-naturally occurring crowns, cryptates and cyclophanes will not be discussed.

Synthetic approaches to medium - and large - sized rings* date back to 1926 with the first synthesis of macrocyclic compounds by Ruzicka and co-workers[1] in low yield through pyrolysis of heavy metal salts of long chain carboxylic acids. This established the large ring structures for the musk ketones muscone (1) and civetone (2)[2], both of which had earlier been isolated from natural sources[3, 4].

Ruggli's observation[5] that intramolecular ring closure is favoured under conditions of high dilution was applied by Ziegler[6] in 1933 to synthesise muscone and other macrocyclic ketones in high yield. The yields of even-membered ring ketones were especially high (scheme 1). In 1942 the high dilution technique was extended by Hunsdiecker who used ω-halo-β-ketoesters to synthesise both muscone and civetone[7]. A few years later Blomquist developed a synthesis of macrocyclic ketones, again at high dilution, via cyclisation of diketenes generated in situ from acid chlorides[8] (scheme 2).

Up to this time all of the synthetic methods suffered from two serious disadvantages in that it was necessary to use a) a long-chain

* In general, large rings are considered to be those containing 12, 13 or more atoms, while medium rings fall in the range of 8 to 12 atoms.



Scheme 3

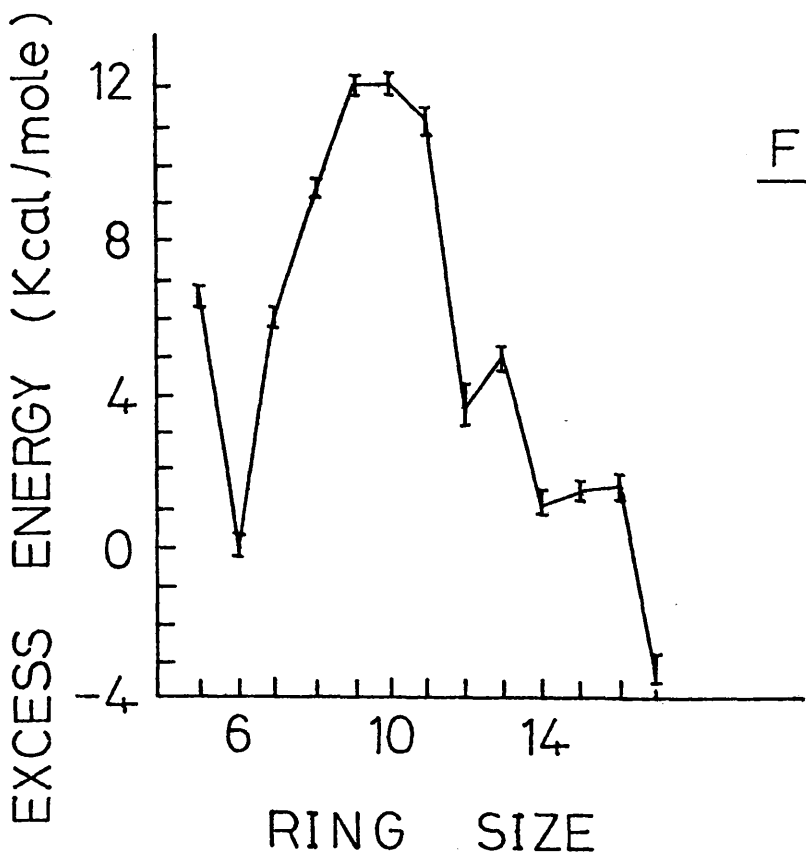
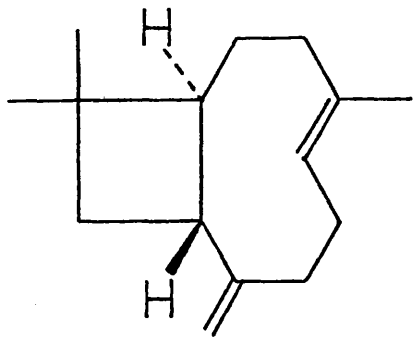
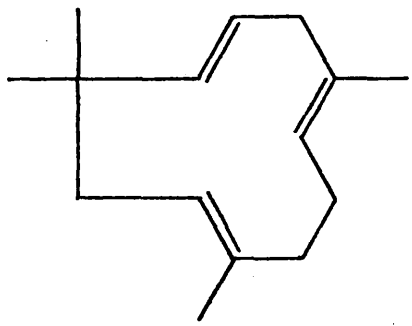


Fig 1



(3)



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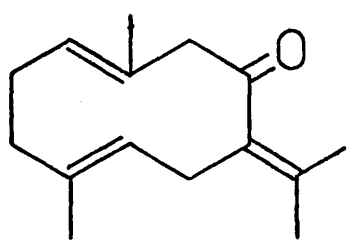
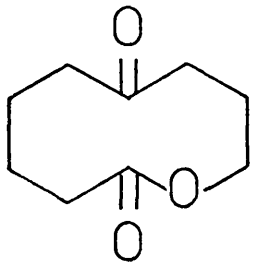


(5)

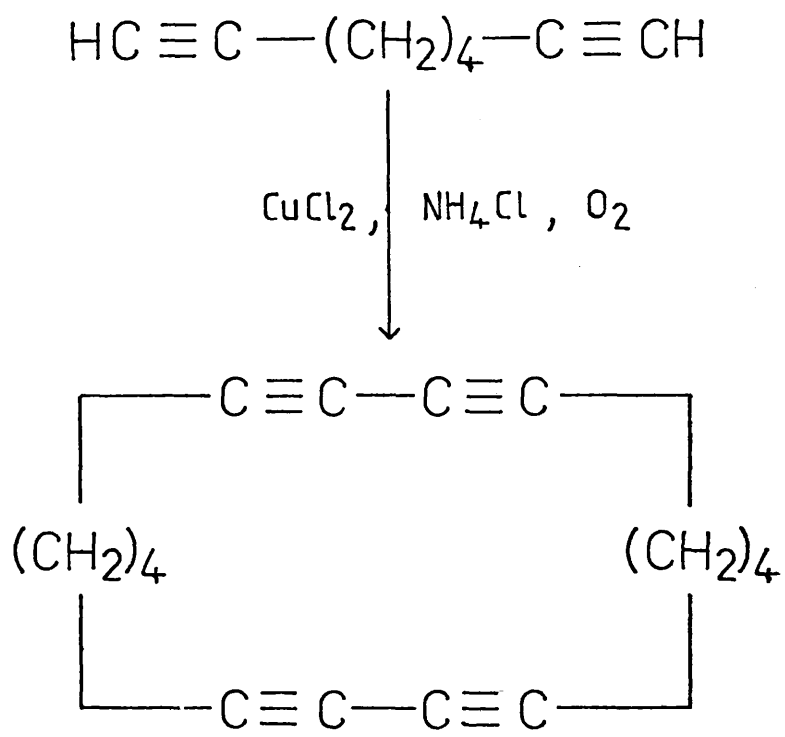
difunctional precursor and b) high dilution conditions for the cyclisation. This latter disadvantage was overcome in 1947 when Prelog[9] and Stoll[10] independently introduced the "acyloin" condensation[11]. This provided the first feasible route to medium-sized carbocyclic rings and served to stimulate interest in this area of research. High dilution is not a requirement for the acyloin condensation since the reaction takes place via chemisorption of an α, ω - diester onto the surface of molten sodium. This favours formation of the acyloin and hence the ketone in high yield (Scheme 3). Further stimulus was provided by the discovery in 1949 of medium-sized rings in nature by Sorm[12] from his studies on the nature of caryophylene (3). Since then many other sesquiterpenes have been isolated and shown to contain similar ring systems, for example, humulene (4) and germacrone (5).

Medium - and large - sized rings show no regular interdependence of properties and ring size[13, 14] (see figure 1). The strain in these rings was initially attributed to Pitzer strain, Baeyer strain and intra-molecular overcrowding across the ring (transannular strain) or I-strain[15]. By replacing an sp^3 carbon with an sp^2 carbon the I-strain is reduced by increasing the C-C-C angles in the ring. There is therefore a driving force for tetrahedral centres to be converted to trigonal centres. The reverse, conversion of an sp^2 centre to an sp^3 centre, is disfavoured since this leads to a smaller C-C-C bond angle and hence an increase in strain.

Much of the chemistry of medium - and large - sized rings is governed by conformation[16] which often brings opposite sides of the ring into close proximity. For instance, hydroxylation of cis-cyclodecene with performic acid gave only the 1,6 - diol (thought to be cis[17]), while trans-cyclodecene gave the stereoisomeric 1,6 - diol. Such transannular interactions[18] do not occur in the larger

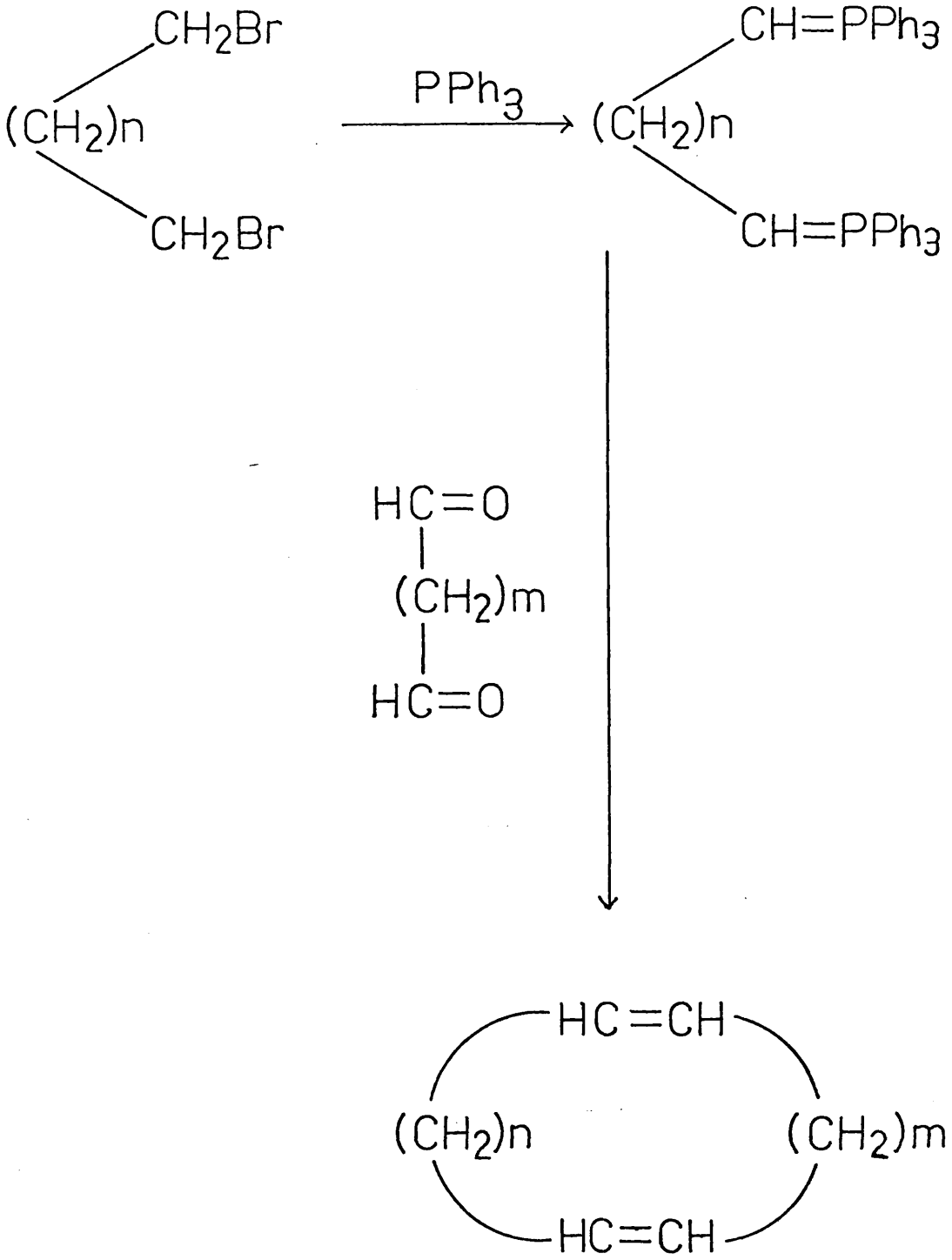


(6)



Scheme 4

Scheme 5


CH2Br
(CH2)n
CH2Br
PPh3
CH=PPh3
(CH2)n
CH=PPh3
HC=O
(CH2)m
HC=O
HC=CH
(CH2)n
(CH2)m
HC=CH

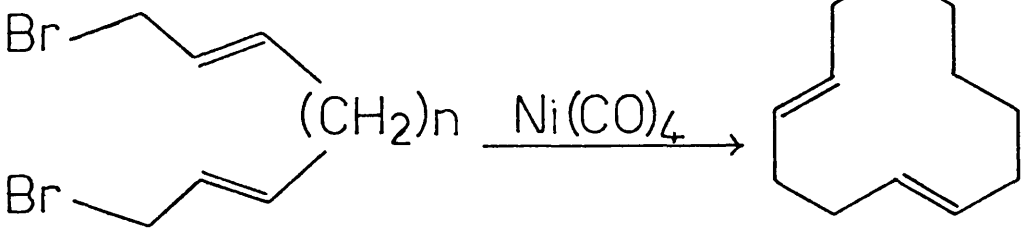
cycloalkane systems, as they are more spacious. Cyclododecene, for example, gives the expected 1,2-diols[19]. Again, reduction of ketone function in the nonanolide (6) is extremely difficult. This is attributed to the conformation of the ring which "surrounds" the carbonyl carbon and hinders attack of the reducing agent. Dunitz[20] and co-workers have investigated cyclononane and cyclodecane derivatives by x-ray methods in an attempt to elucidate their conformations.

It is apparent from the foregoing discussion that medium - and large - sized rings can be of much interest to both physical and organic chemists. However, this introduction will concern itself solely with synthetic aspects of these ring systems.

In 1956, some 9 years after the development of the acyloin condensation, Sondheimer successfully applied the oxidative coupling of terminal diacetylenes[21] to the preparation of macrocyclic compounds[22]. Eglinton and Galbraith, at about the same time, also generated large ring compounds from the oxidative coupling of α, ω - diynes at high dilution[23]. The Sondheimer synthesis, though characterised by low yields, was the first macrocyclic synthesis to obviate the need for both high dilution conditions and difficult to obtain long-chain difunctional precursors. Scheme 4 is illustrative[22a, c].

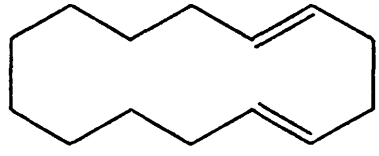
A number of syntheses for particular macrocyclic compounds have been developed, a few have some general applicability while others are clearly restricted to certain special cases. One example of a synthesis which should have some general applicability is that of the use of the Wittig reaction to generate macrocyclic systems[24] as depicted in Scheme 5. The reaction has also been employed for the preparation of macrocyclic ketones[25].

Corey[26] has approached the problem of cyclisation of long chain

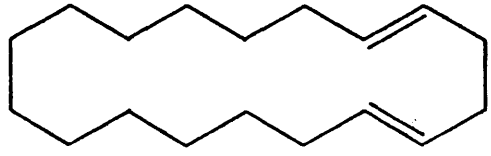


n=6 ; 59 %

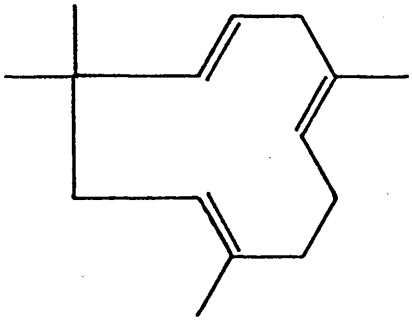
Scheme 6



n=8 ; 70-74 %



n=12 ; 76-84 %



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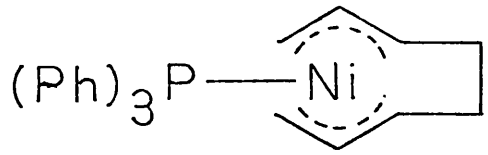

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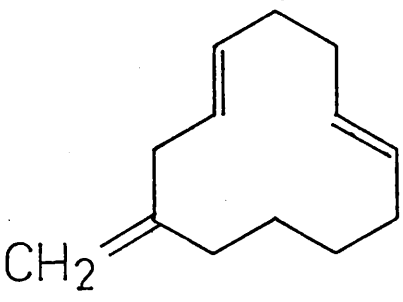
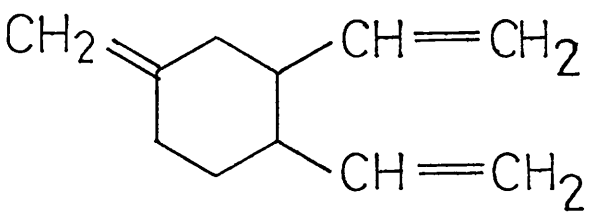


(8)



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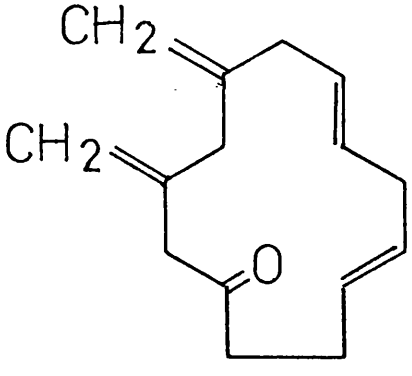

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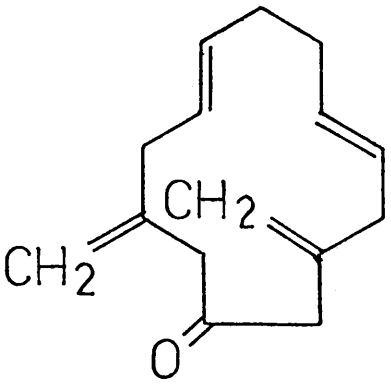
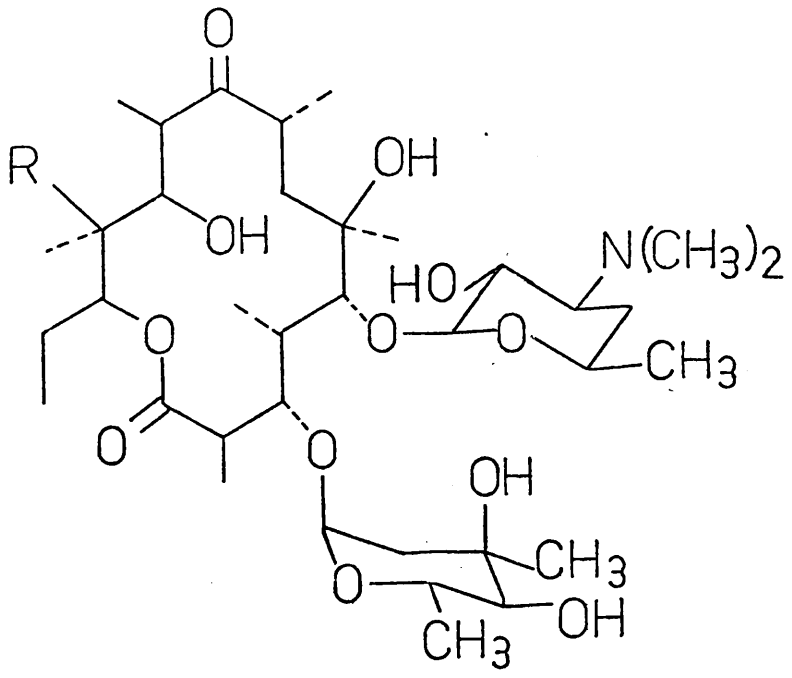


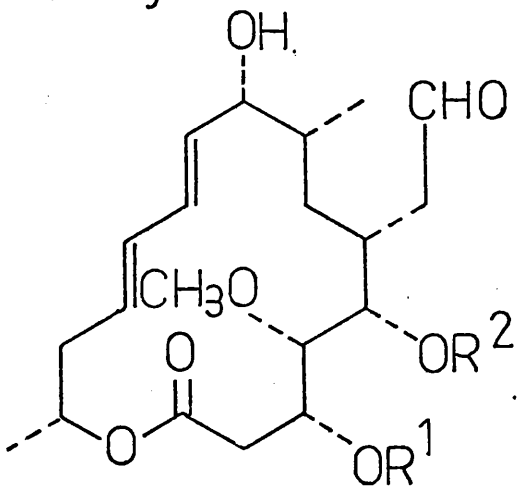
(11)



(12)

R=OH, Erythromycin A

R=H , Erythromycin B

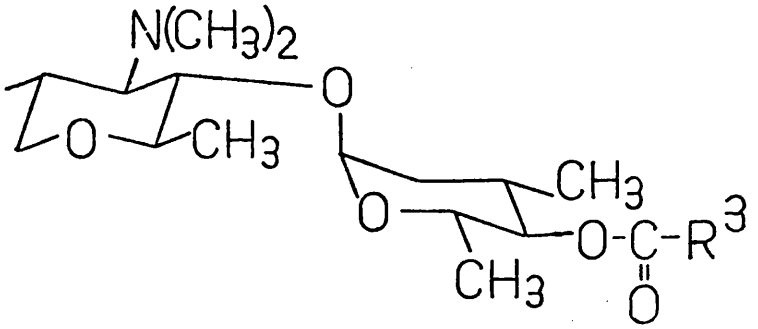


(13)

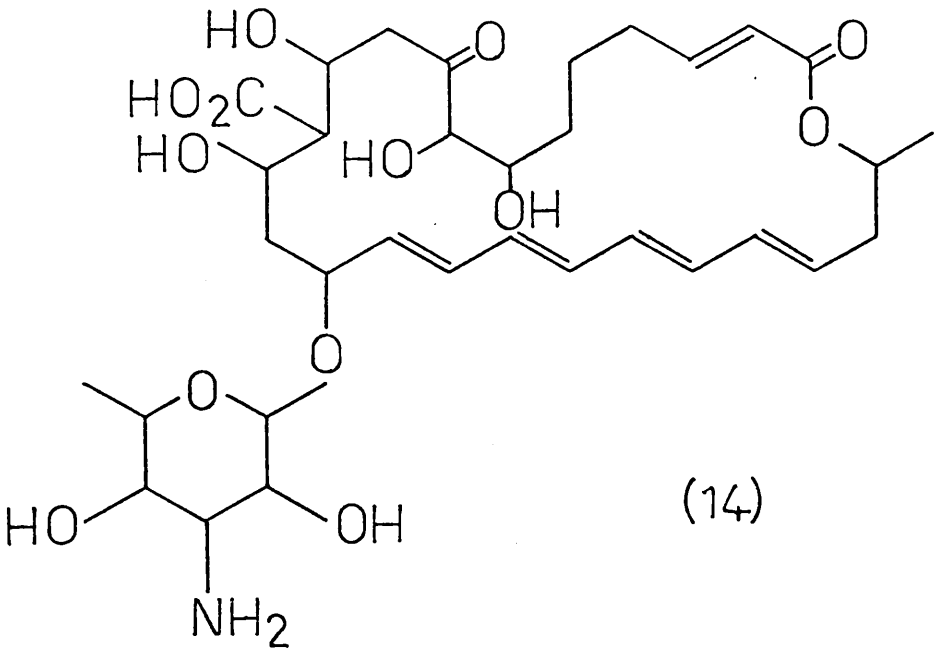
Leucomycins

R^1 = H, Acetyl

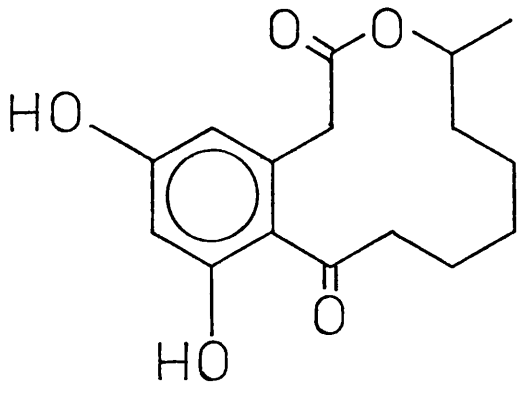
R^2 =



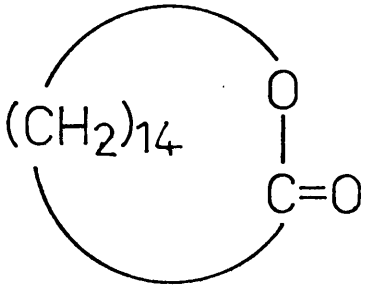
R^3 = Acetyl , propionyl , iso-valeryl , iso-butyl


HO
HO2C
HO
HO
O
O
O
OH
O
O
HO
OH
NH2

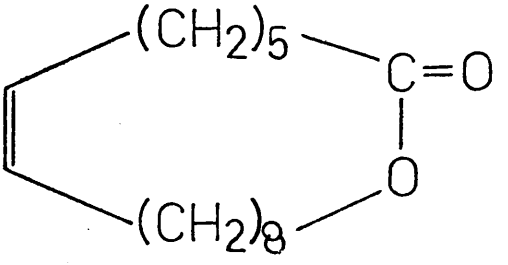
(14)


O
O
HO
O
HO

(15)

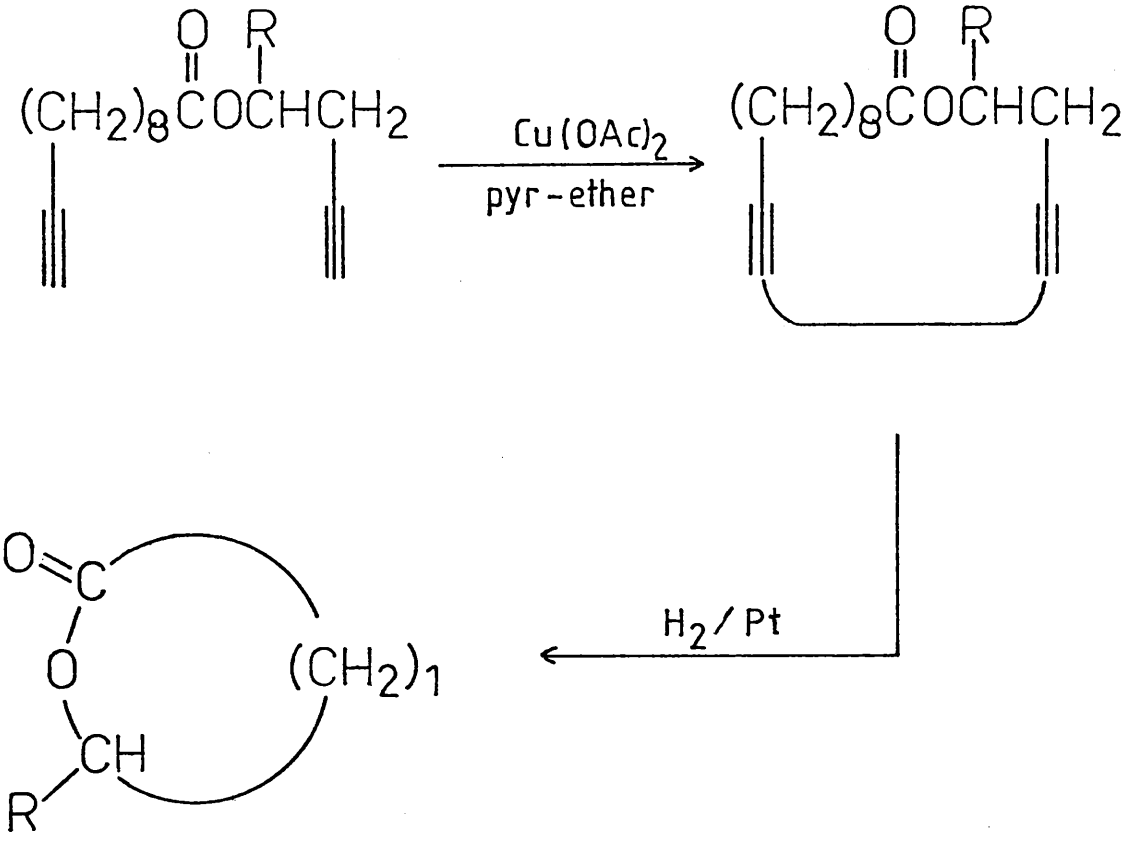

(CH2)14
O
C=O

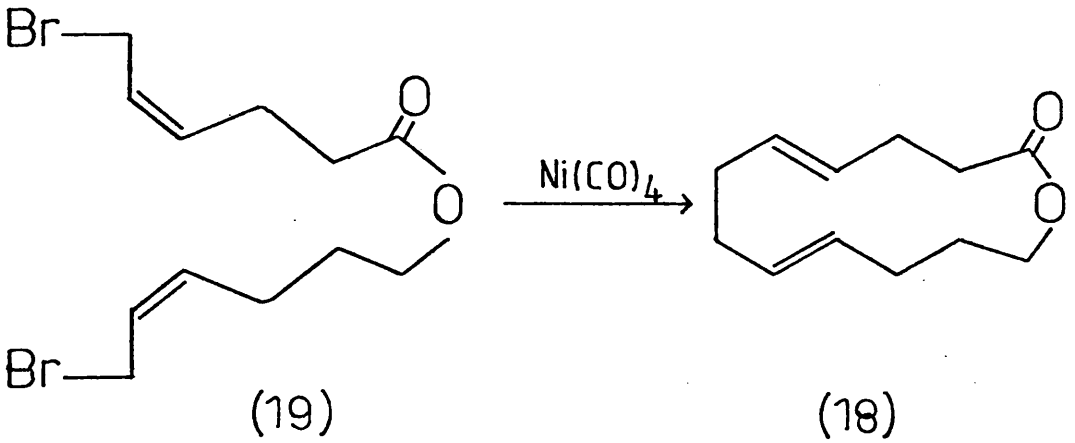
(16)


(CH2)5
C=O
O
(CH2)8

(17)

Scheme 7





(19) (18)

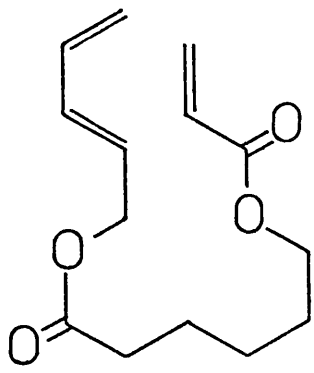
Scheme 8

molecules in a novel way. Allylic dibromides may be cyclised, under high dilution conditions, to cyclic olefins using nickel carbonyl as catalyst (Scheme 6). This method has been developed and applied to the total synthesis of humulene (4)[26] and the potential applicability of the method to the synthesis of other natural products has been noted[26].

Very recently, α,ω-octadienediylnickel (7) has been used to prepare a series of cyclic alkenes and keto-alkenes[27]. As an example, treatment of (7) with allene at low temperature followed by overnight treatment with CO gave a mixture of (8) - (11).

Macrolides[28] are an important group of macrocyclic compounds, many of which are biologically active. They contain numerous asymmetric centres and have many conformational possibilities about 12-, 14- or 16-membered lactone rings. There are usually a variety of substituents including one, two or three glycoside units. Total absolute configurations have been assigned to several macrolides including erythromycin (12) and the leucomycins (13). The stereochemical studies have been the subject of a review by Celmer[29]. However, not all macrolides possess 12-, 14- or 16-membered rings, pimaricin (14), for example, has a ring of 26 atoms; nor do they all possess antibiotic activity, as for example curvularin (15). There are also macrocyclic lactones such as exaltolide (16) and ambrettolide (17) whose main feature is an odour much prized in perfumery.

The Sondheimer synthesis (see p 55) has been extended to the synthesis of macrolides[30] as shown in Scheme 7. The allylic dibromide-nickel carbonyl coupling reaction (see above) has also been successfully applied to the synthesis of macrocyclic lactones[31]. The example shown in Scheme 8 is the synthesis of E,E - cyclo-



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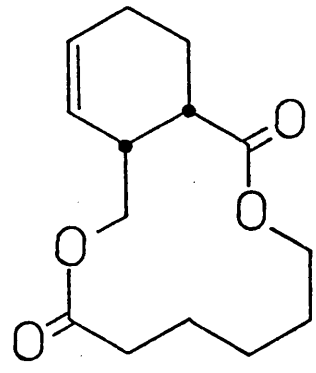

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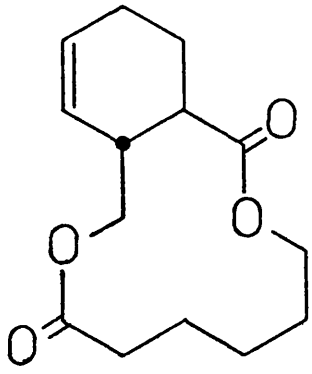

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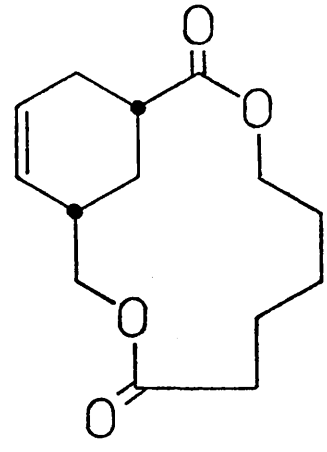
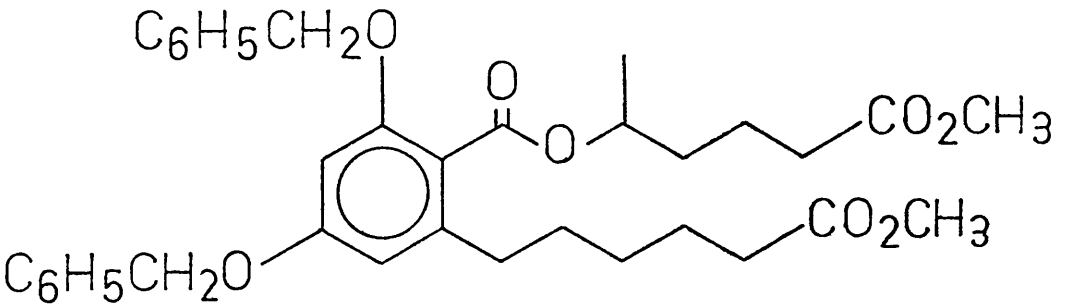
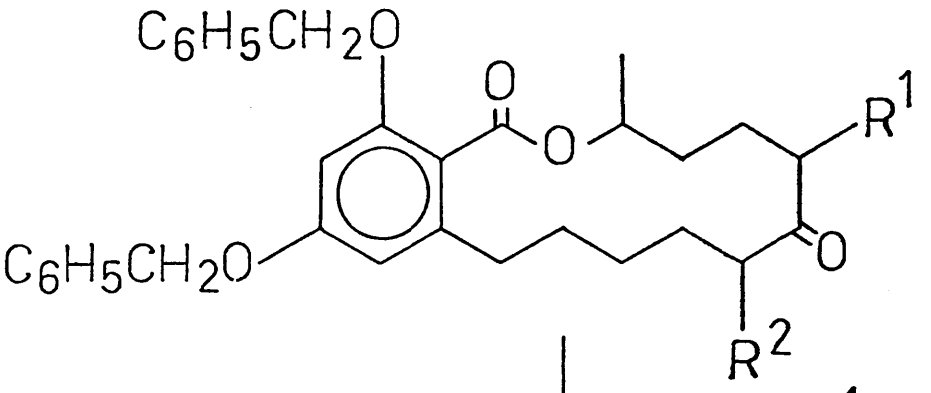
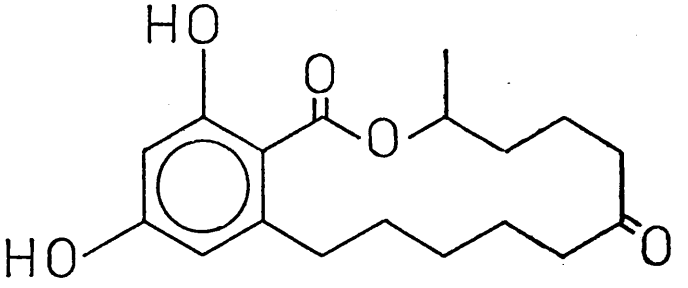


(23)





R^1=H ; R^2= CO_2Me
R^1= CO_2Me ; R^2=H
R^1=H ; R^2=H



(24)

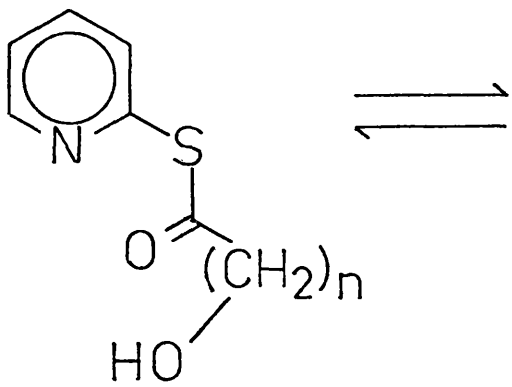
Scheme 9

dodeca-5,8-dienolide (18) from the Z,Z-dibromoester (19). Bicyclic macrolactones have been prepared via an intramolecular version of the Diels-Alder reaction[32]. Thus, slow addition of the open-chain diester (20) to refluxing benzonitrile gave in high yield a mixture of three intra-molecularly formed Diels-Alder products (21)-(23). The high temperatures(ca.190°C) and the non-stereoselective nature of the reaction are obvious limitations of the method for the construction of complex, naturally occurring macrolides. The Dieckmann condensation has been applied by Hurd and Shah[33] to the preparation of the macrolide antibiotic zearalanone (24). The route used is as depicted in Scheme 9.

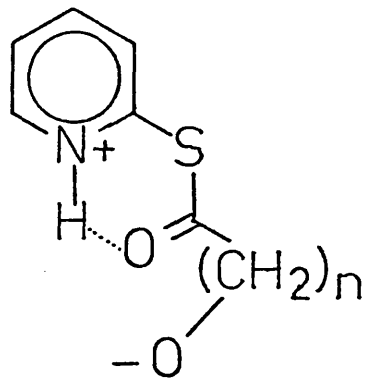
All of the methods mentioned in the previous paragraph use high dilution conditions. Apart from dilution, ease of cyclisation is dependent on several structural factors which influence the conformation of the chain, and hence the probability of a suitable conformation occurring which favours cyclisation. Replacement of a methylene group by an oxygen atom, which diminishes conformational strain due to replacement of a tetravalent atom by a divalent atom, or introduction of a rigid group, such as an acetylenic bond or an aromatic ring, which decreases mobility, results in an increased yield of macrocyclic compound. The influence of substituents on cyclisation of medium rings has been studied by Friedman[34] and Blomquist[35].

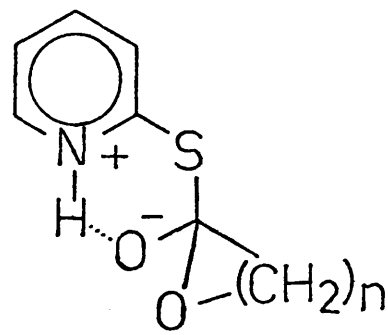
Of all the macrolide-forming reactions, the lactonisation of long open-chain hydroxy acids is the most direct and general method. Most of the procedures for macrolide synthesis therefore involve -C(=O)-O- bond formation by internal esterification of hydroxy acid precursors. Both entropy and polymerisation factors tend to disfavour this however. In 1974 Corey[36] reported a new efficient and mild lactonisation procedure for the synthesis of macrolides.

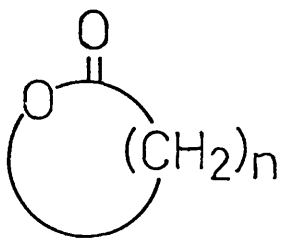
Scheme 10



(25)

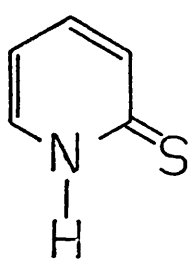


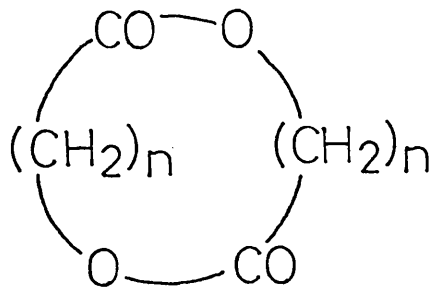




(26)

+





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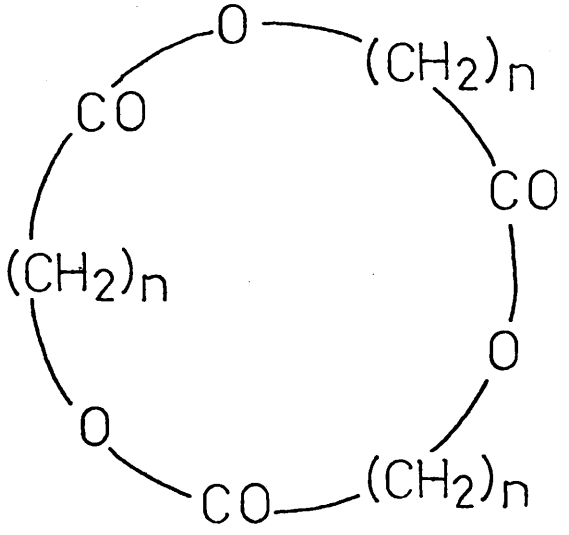
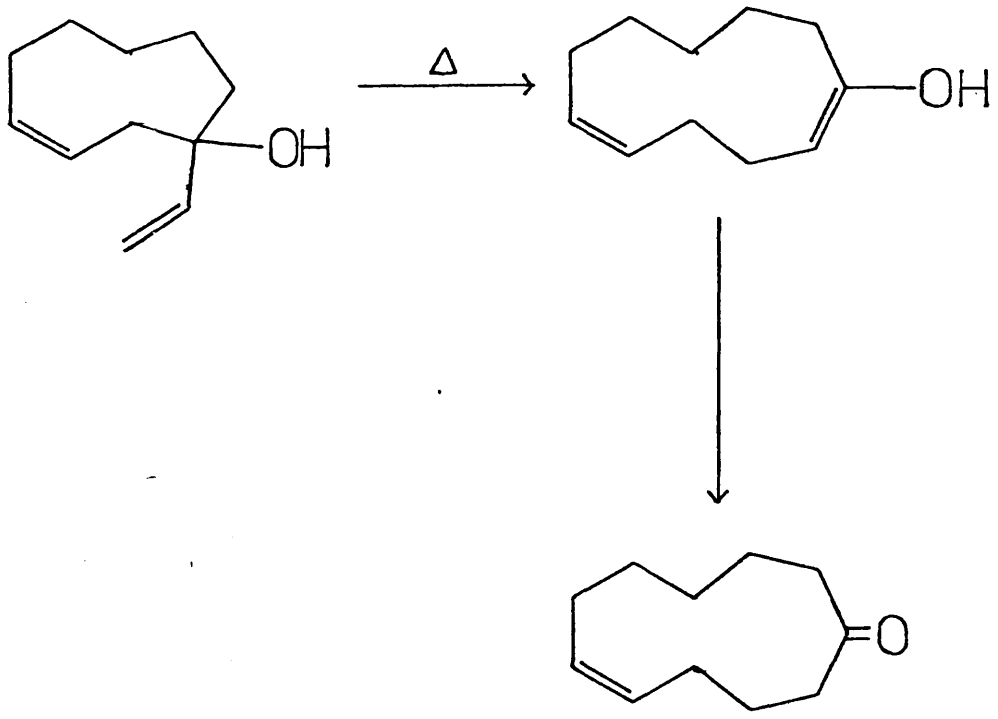


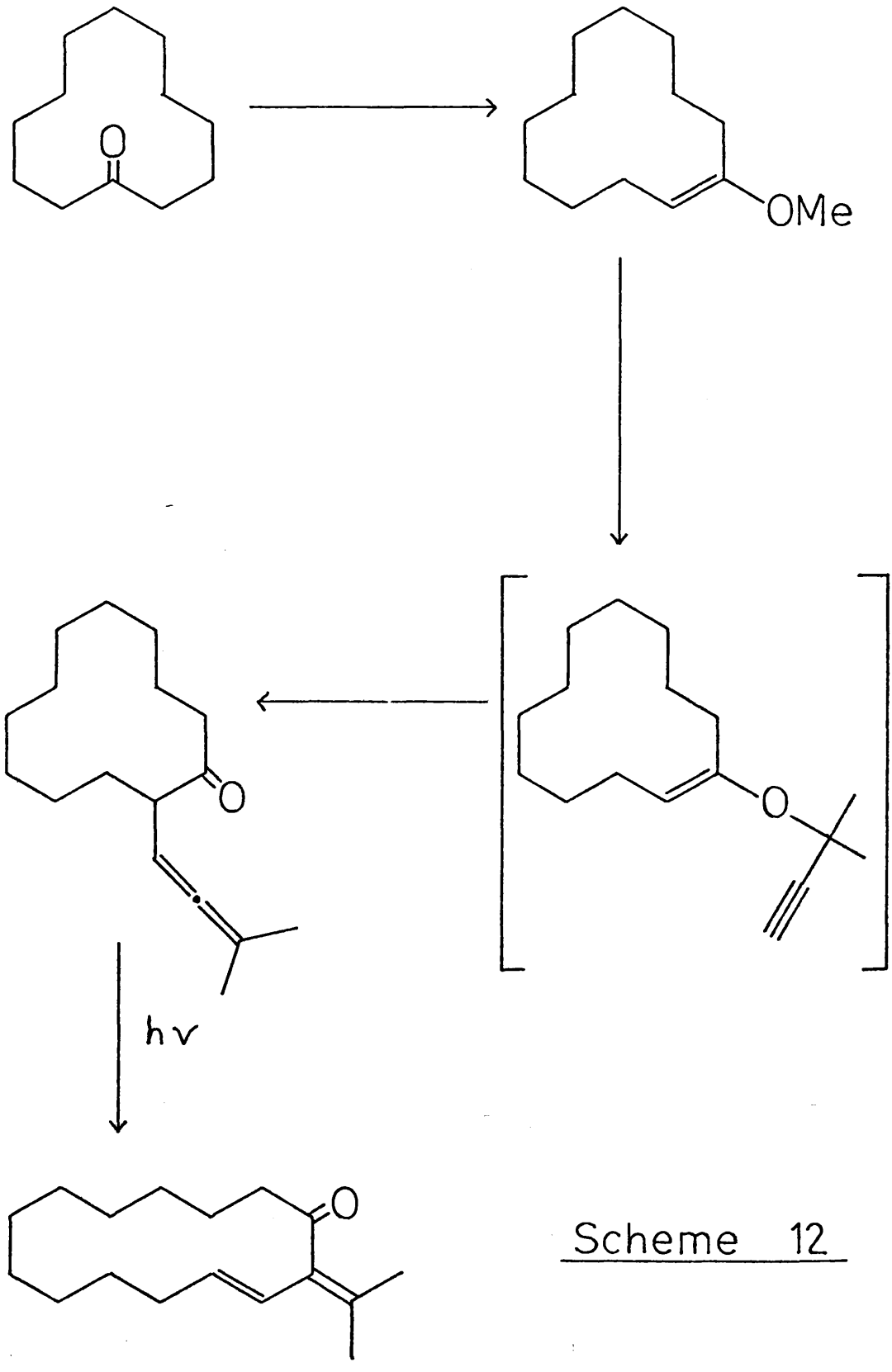
(28)

The technique involves the simultaneous activation of both carboxyl and hydroxyl groups of a hydroxy acid for mutual reaction by utilising a carboxyl derivative which favours proton transfer from hydroxyl to carboxylic oxygen. The idea is illustrated for the specific case of a 2-pyridinethiol ester of a hydroxy acid (25) in Scheme 10. The formation of medium and large ring lactones via internal esterification of hydroxy acids by this method is highly effective and yet mild enough to be used with complex and polyfunctional substrates. In addition to the lactones (26), dimeric cyclic diesters (dilides) (27) and trimeric cyclic triesters (trilides) (28) are also formed in varying amounts. This "double activation" method has been widely used[37] to synthesise macrocyclic lactones including those in the prostaglandin[38] and polyether[38] antibiotic series. Mechanistic studies have attempted to extend the method to other thiol esters[40]. Closely related methods have been developed by Masamune[41] and Mukaiyama[42].

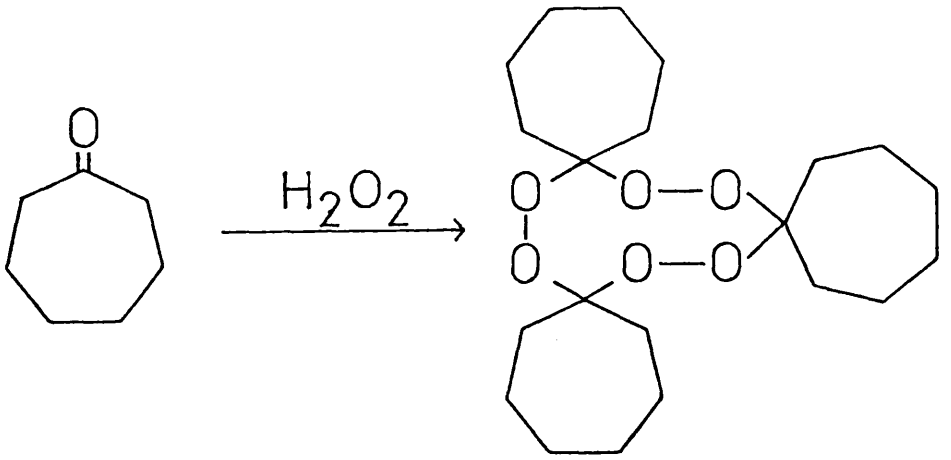
All of the syntheses mentioned above involve the cyclisation of long chain compounds. The problems encountered in this approach to macrocycles and some of the attempts to surmount these difficulties have been discussed. A second method of synthesis of medium and large ring compounds involves ring enlargement of smaller cyclic compounds, and many such methods of ring enlargement are known[43]. These reactions usually offer ring expansion by only one or two carbon atoms and have little general applicability to the synthesis of complicated macrocyclic ketones and lactones, and in particular to the synthesis of the macrolide antibiotics with their multiplicity of substituents and asymmetric centres. However, with the increasing availability of certain medium and large ring compounds, these ring expansion reactions



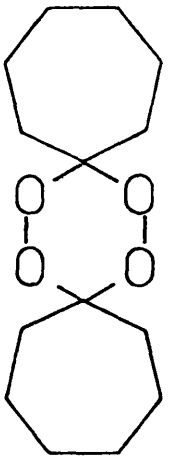
Scheme 11



Scheme 12

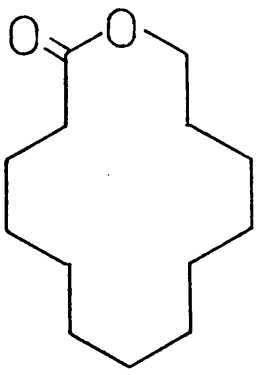


(29)

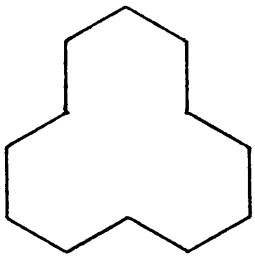


(30)

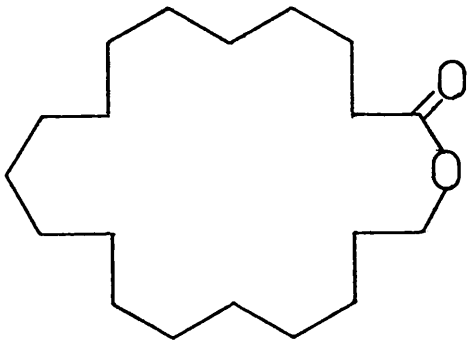
Scheme 13



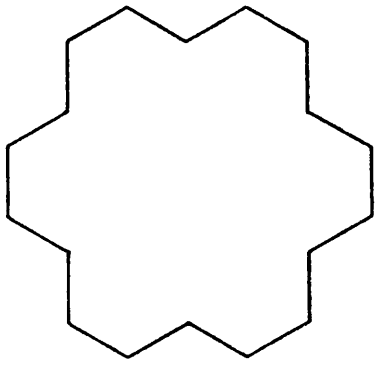
(31)



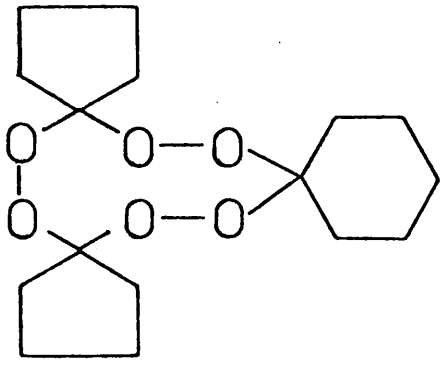
(32)



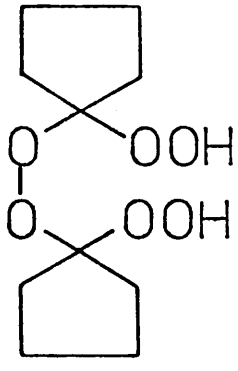
(33)



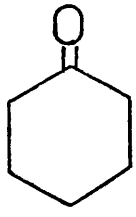
(34)



(35)



(36)



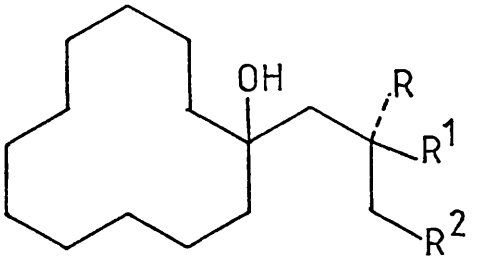
(37)

assume a greater importance as may be seen from the examples given below.

The reaction of diazomethane on cyclic ketones gives a one carbon ring expansion and has been known for some time. The two carbon ring expansion of Thies[44] is more recent (see Scheme 11). A disadvantage is the low yields commonly obtained by the method.

A photochemical method of ring enlargement (Scheme 12) has been published by Cookson[45]. It is specific for ketone synthesis and gives high yields. However it suffers from the limited application of any photochemical method in that it will not be feasible when a complicated ketone containing photochemically sensitive groups is required.

Story[46] has developed a method of synthesis of a large number of macrocycles (C_8-C_{33}) through treatment of small ring ketones. The basic route is shown in Scheme 13. Cycloheptanone, for example, is heated with hydrogen peroxide under acid conditions to give initially trimeric peroxide (29) then the dimer (30). Decomposition of the peroxides, either photochemically or thermally in refluxing decane, yields the macrolide (31) and cycloalkene (32) and the macrolide (33) and cycloalkane (34) from the dimer and trimer respectively. The dimer/trimer ratio is dependent on the temperature of the ketone-hydrogen peroxide reaction. The cycloalkanes are formed in 10 to 40% yield and the corresponding lactones in 10 to 25% yield. It is possible to synthesise mixed peroxides such as (35) by first obtaining the 1,1' - dihydroperoxy-dicycloalkyl peroxides, for example (36) followed by reaction at low temperatures with a cycloalkanone such as (37) in propionic acid as solvent and perchloric acid as catalyst. This synthetic method is evidently one of some general applicability which makes available many macrocyclic systems hitherto unobtainable.

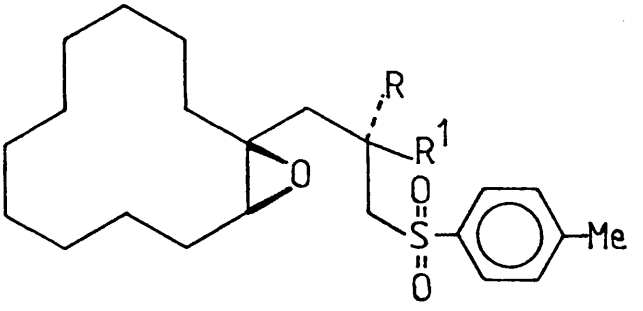


(38)

R = H R = Me

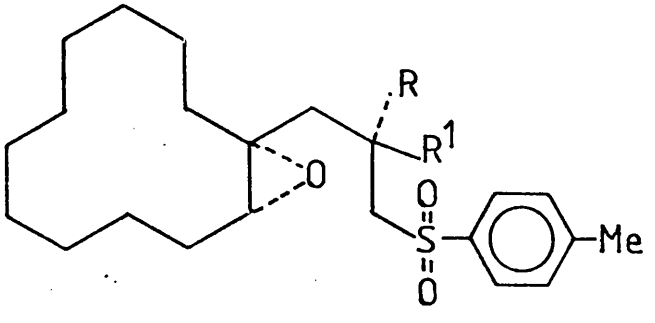
R^1 = Me R^1 = H

R^2 = OH R^2 = OH



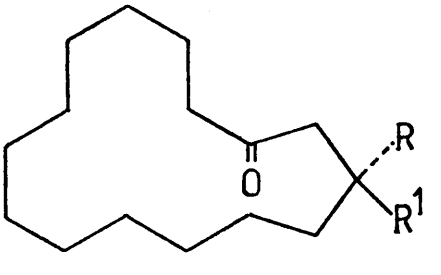
(39) R = H R^1 = Me

(40) R = Me R^1 = H



(41) R = H R^1 = Me

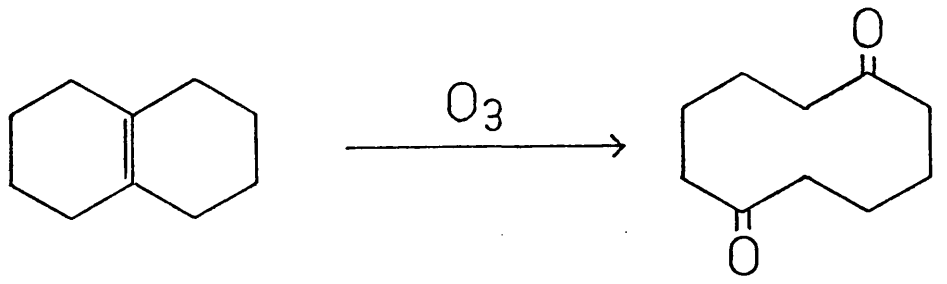
(42) R = Me R^1 = H



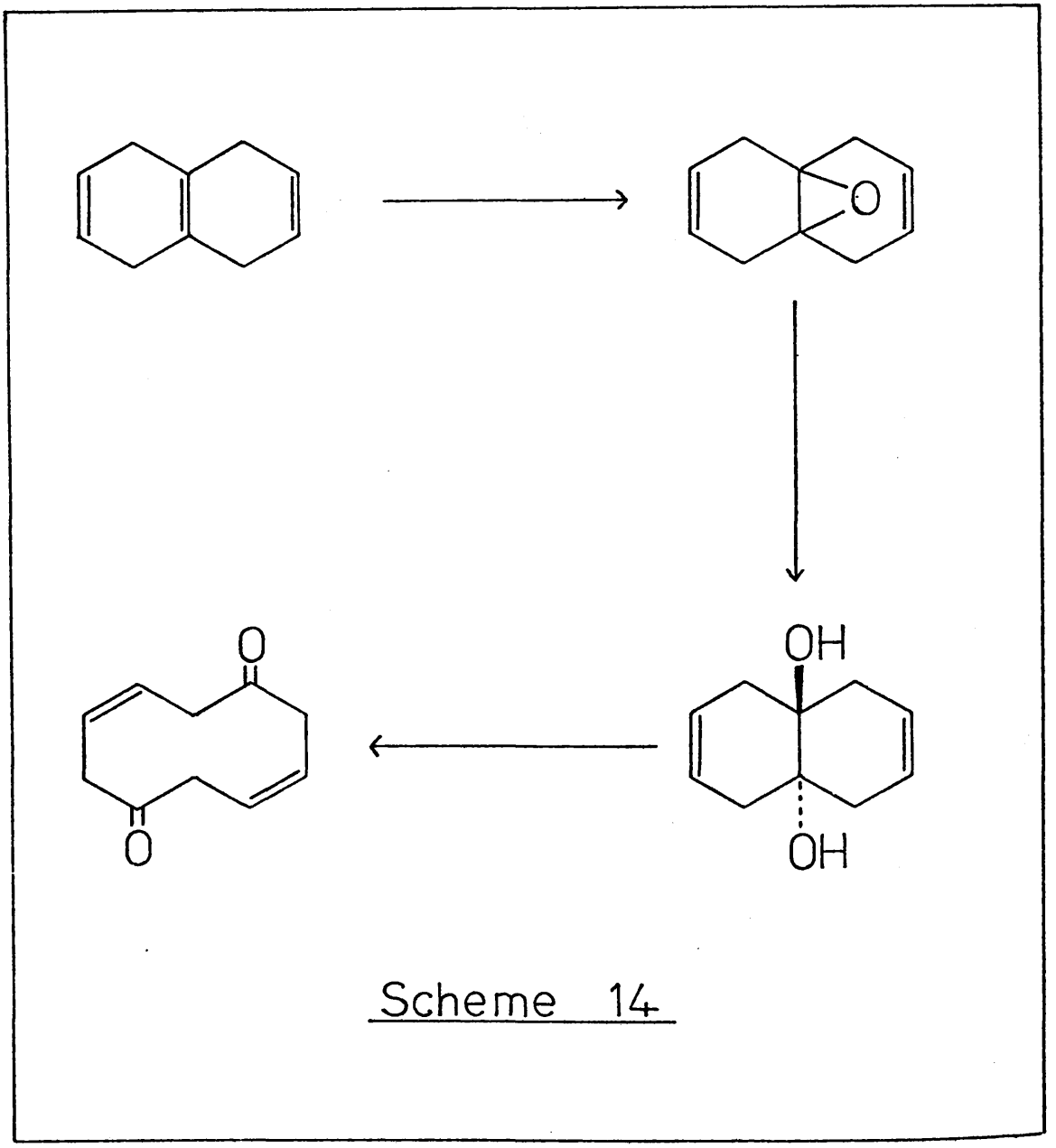
(43)

(R) R = Me R^1 = H

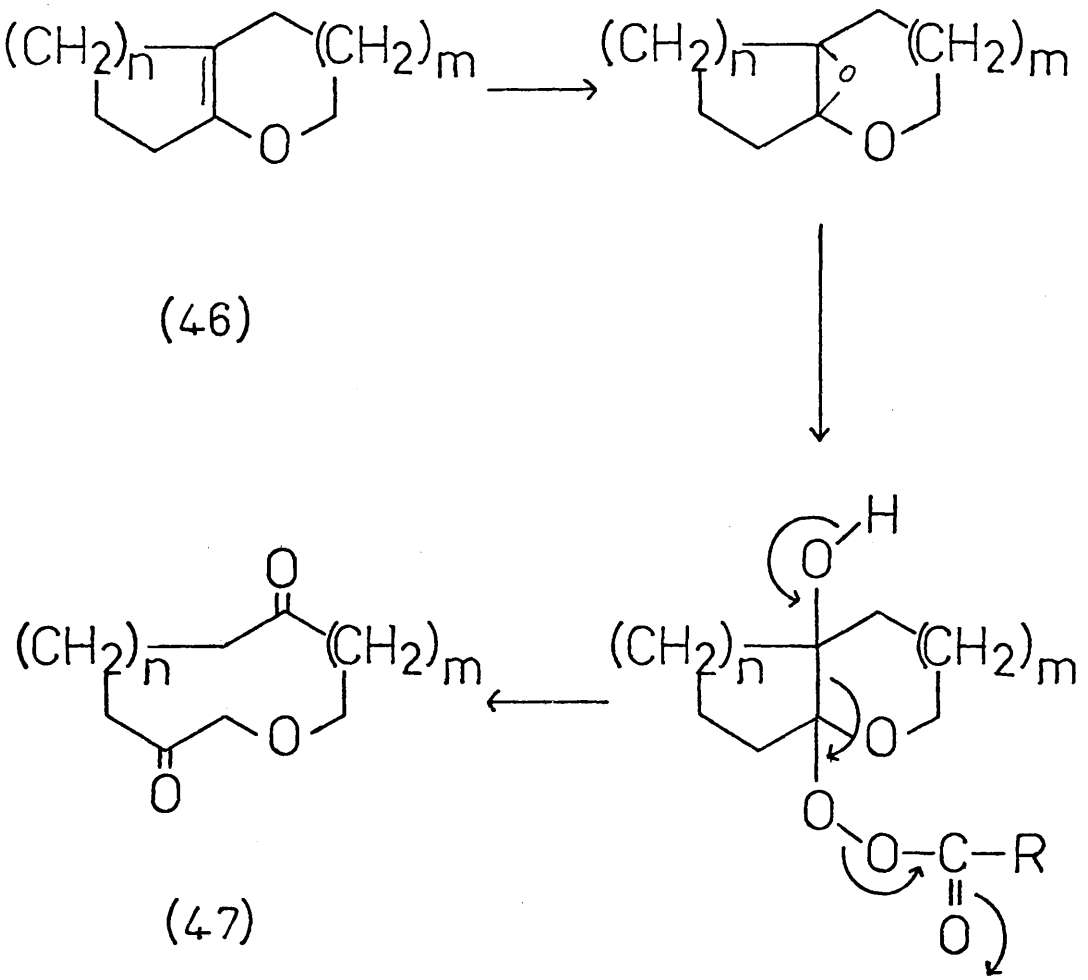
(S) R = H R^1 = Me



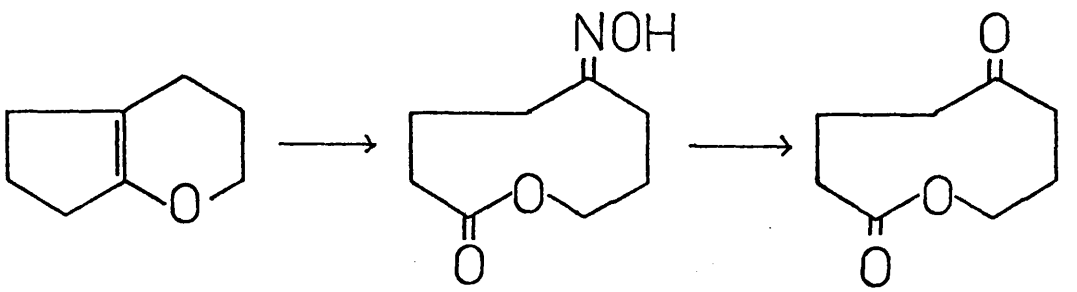
(44) (45)



Scheme 14



Scheme 15



(46) n=m=1

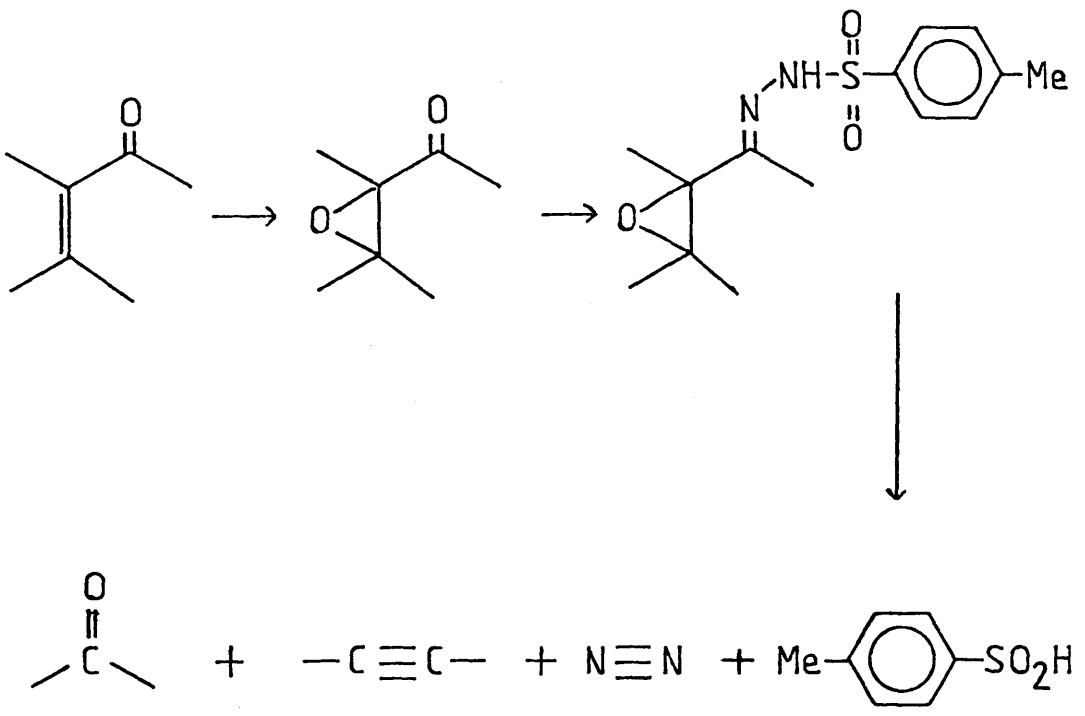
(47) n=m=1

Considerable effort will be required, however, to extend the technique to the synthesis of substituted species.

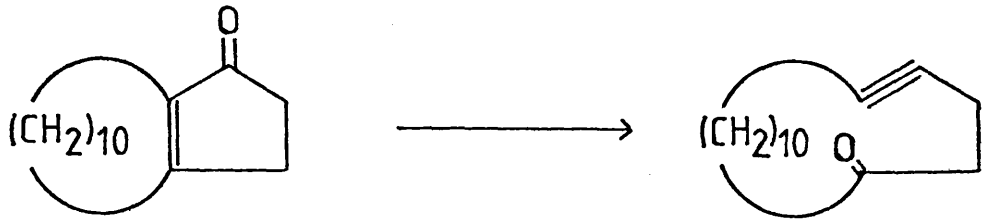
Recently[47], (R)- and (S)- muscone have been synthesised *via* an epoxy-sulphone cyclofragmentation reaction. Grignard reaction of the bromo compounds (R)- and (S)- $Br\text{-}CH_2\text{-}CH.Me\text{-}CH_2\text{-}OCH_2\text{-}Ph$ with cyclododecanone, followed by hydrogenolysis gave the enantiomeric diols (38) which were treated with $(4\text{-}Me\text{-}C_6H_4\text{-}S)_2$ and PBu_3, then oxidised, to give the corresponding hydroxy sulphones (38) ($R^2 = SO_2\text{-}C_6H_4\text{-}Me\text{-}4$). These were dehydrated and epoxidised to give the epoxy-sulphones (39)-(42). Cyclisation of (39)-(42) followed by hydrogenation gave the chiral muscones (R)-(43) and (S)-(43).

The remaining approach to medium and large size ring compounds involves ring annulation-scission methods. In bicyclic compounds where there is a carbon-carbon double bond at the ring fusion, macrocyclic compounds can be obtained by ozonolysis followed by hydrolysis of the ozonide. For example, ozonolysis of octalin (44) yields cyclodecan-1,6-dione (45)[48]. Cleavage of a transannular carbon-carbon double bond has also been effected by the use of perbenzoic acid, followed by hydrolysis and cleavage of the glycol[49] (see Scheme 14).

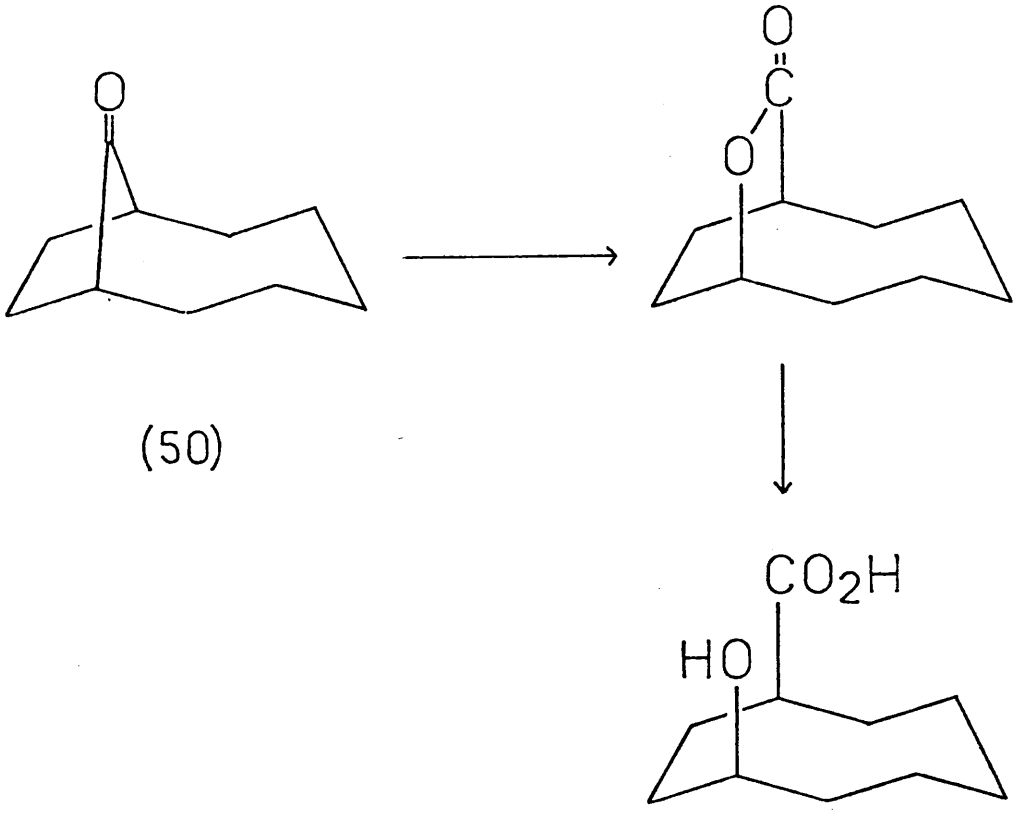
The concept of cleaving fusion bonds of bicyclic structures to create larger rings[50] has been successfully applied to the synthesis of macrocyclic lactones. A reaction which generates a large ring from a bicyclic system and at the same time creates a lactone functionality is the oxidative cleavage of bicyclic enol ethers with the double bond at the ring fusion. Borowitz[51] *et al.* have reported the synthesis in good yield of several ketolactones (47) of various sizes ranging from 10- to 16- membered from the enol ethers (46). *m*-Chloroperbenzoic acid (as shown in the scheme), ozone followed by



Scheme 16

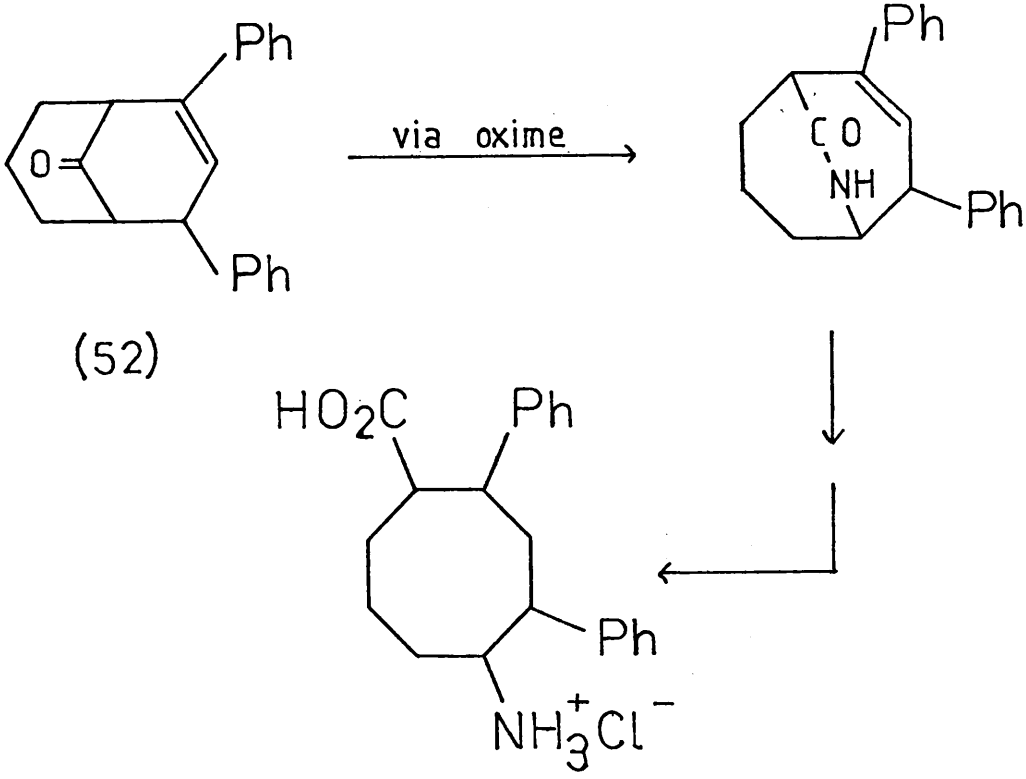


(48) (49)



(50)

(51)



(52)

(53)

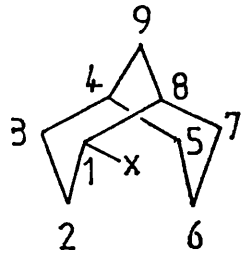
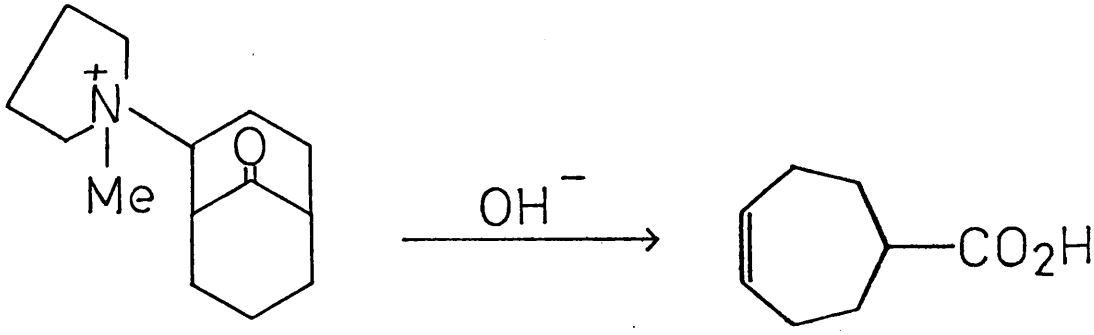
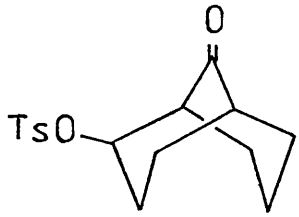


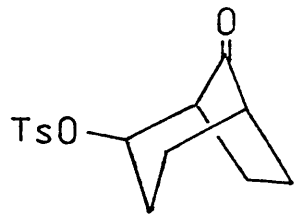
Fig 2



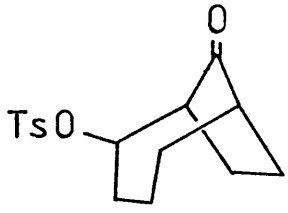
(54) (55)



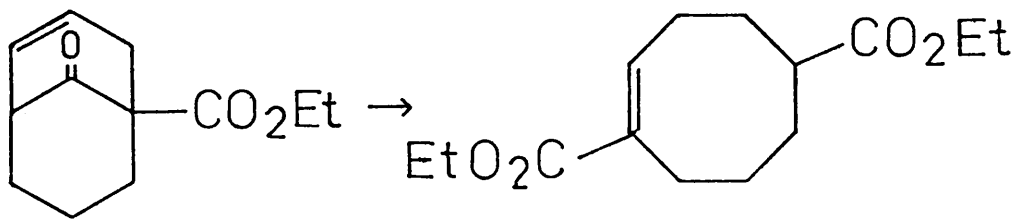
(56)



(57)



(58)



(59) (60)

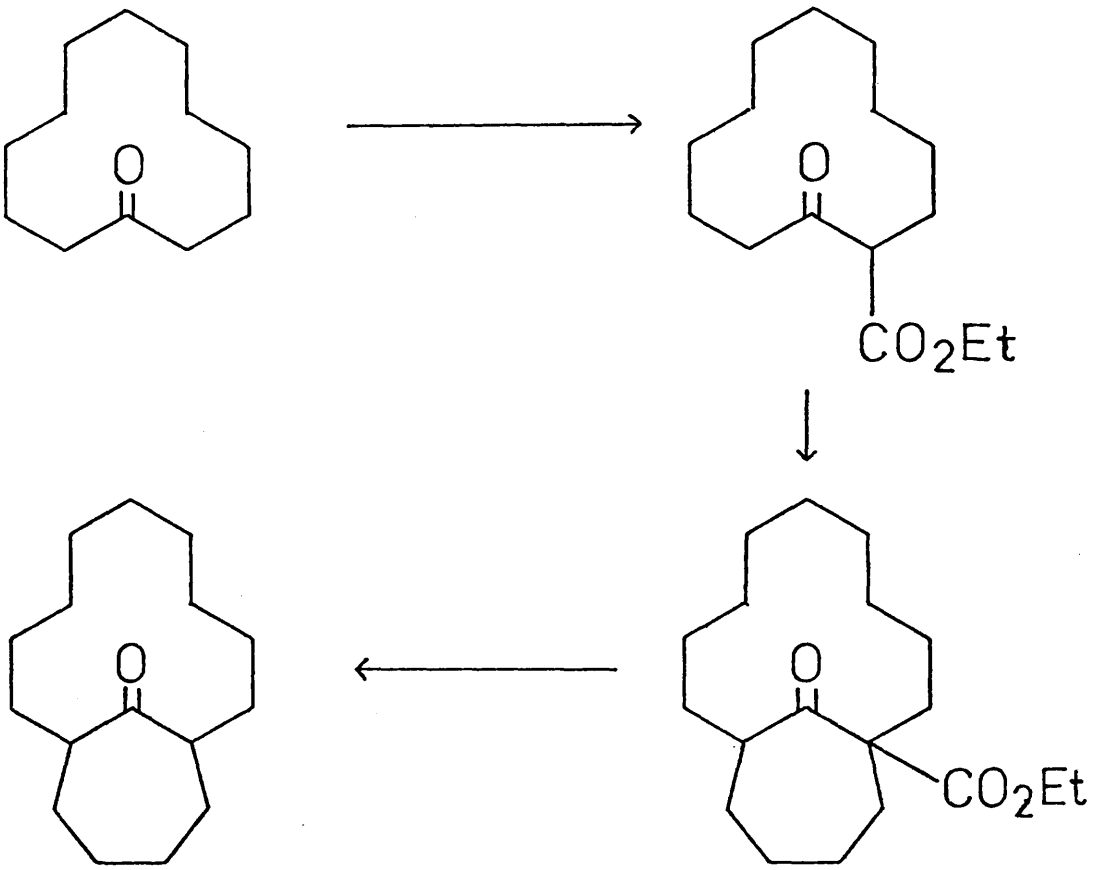
zinc-acetic acid, or chromic acid may be used to effect the cleavage of (46) to (47). The same cleavage of (46) to (47) (n=m=1) was effected by Mahajan[52] using n-butyl nitrite followed by acid hydrolysis of the resulting oximelactone (Scheme 15).

Eschenmoser[53] has developed a synthesis of macrocycles from bicyclic enones. The method involves a heterolytic fragmentation of α,β-epoxy-toluene-p-sulphonylhydrazones, obtainable from the enones as shown in Scheme 16. The technique has general applicability[54], one example being the synthesis of cyclopentadec-4-yn-1-one (49) from bicyclo [10.3.0] -pentadec-14-en-1-one (48).

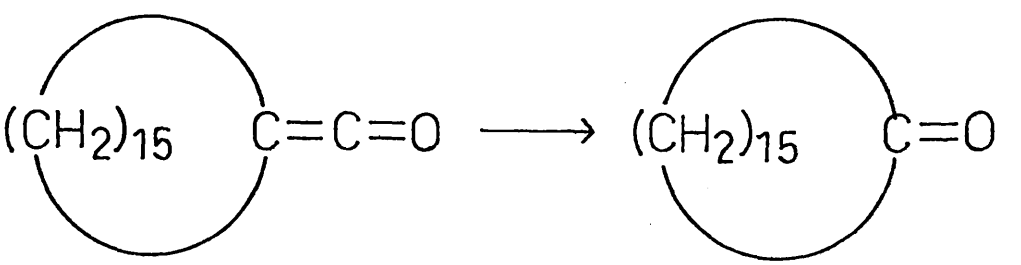
Bicyclic compounds having a carbonyl bridge have been converted to medium sized monocycles via Baeyer-Villiger[55] and Beckmann[56] reactions. In an example of the former, bicyclo [5.2.1] dec-10-one (50) was transformed into 4-hydroxycyclononanecarboxylic acid (51) whilst in the latter case, the bicyclic ketone (52) was converted to the amino-acid hydrochloride (53).

Bridge fission in the bicyclo [3.3.1] nonanes and related compounds has been the subject of a review by Buchanan[57]. Fission reactions in these systems utilise the fact that a 1-(endo)-substituent has the antiperiplanar geometry with respect to the C(1)-C(9) bond (see figure 2) which is essential to a smooth fragmentation reaction. The reaction was first demonstrated by the transformation of (54) to (55), but has been more extensively studied on the analogous tosylates (56)-(58) giving a series of cycloalkene carboxylic acids from the appropriate bicyclo [3.3.1] nonane, bicyclo [3.2.1] octane and bicyclo [4.2.1] decane derivatives. Bridge scission has also been effected by a retro-Claisen reaction, as in the conversion of (59) to (60), in which bridge opening is accompanied by migration of the double bond.

Scheme 17

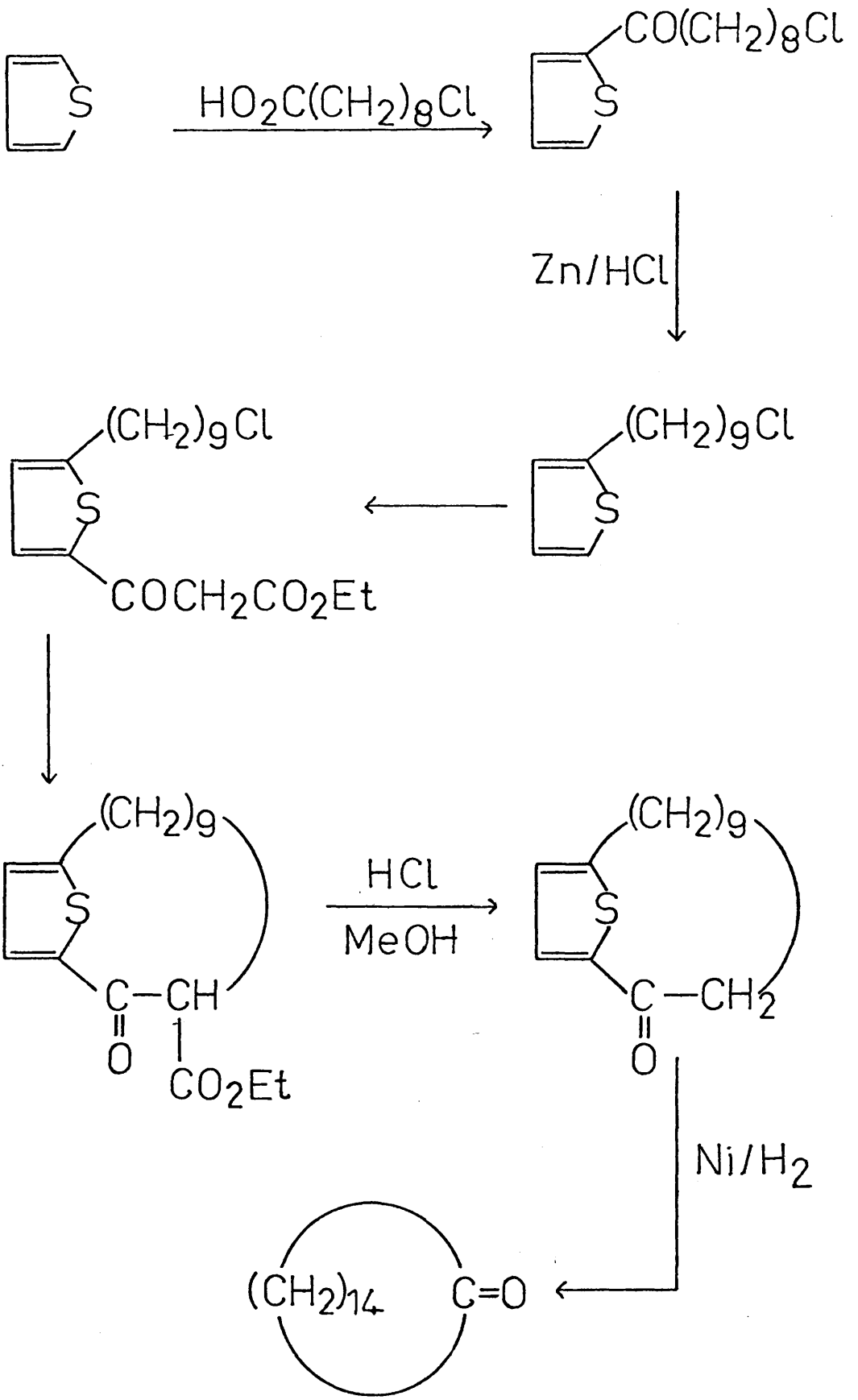


(61)

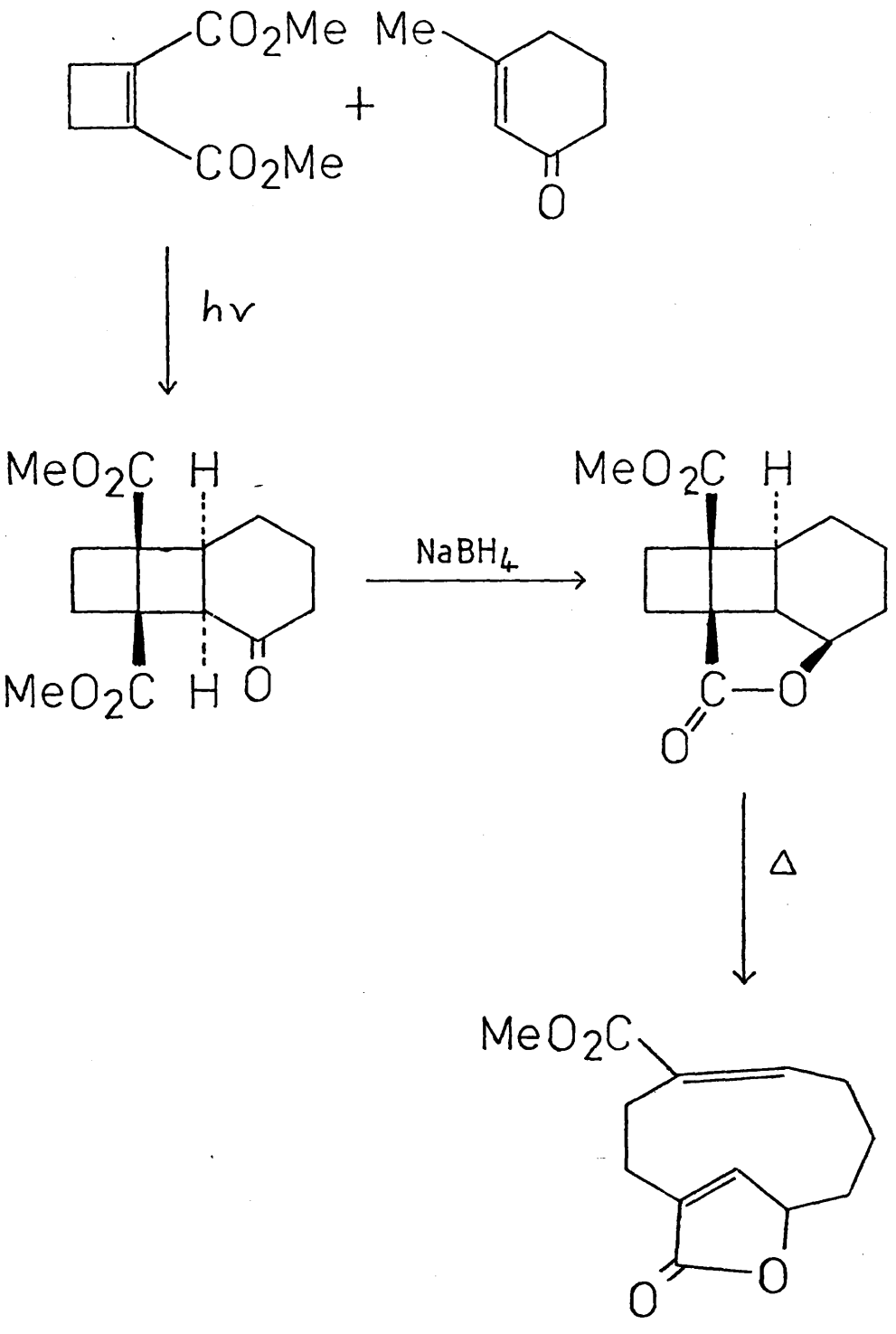


(62)

Scheme 18

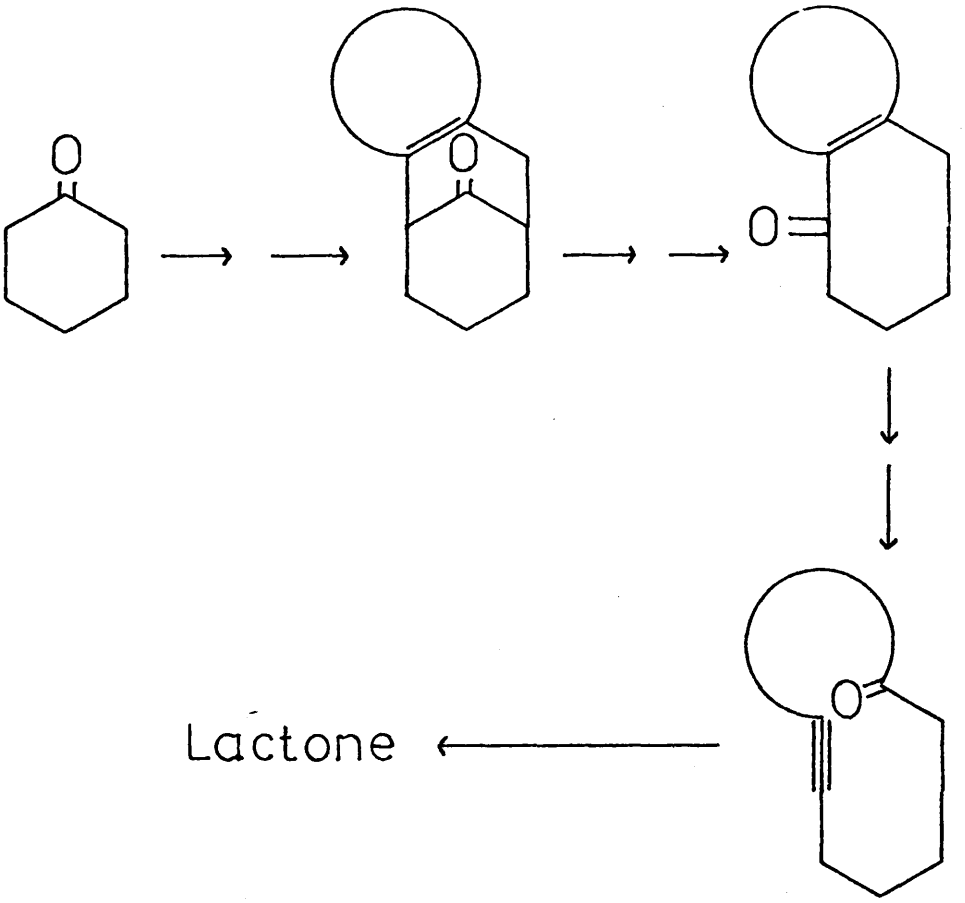

S
HO2C(CH2)8Cl
CO(CH2)8Cl
Zn/HCl
(CH2)9Cl
COCH2CO2Et
HCl
MeOH
CO2Et
Ni/H2
(CH2)14
C=O

Scheme 19

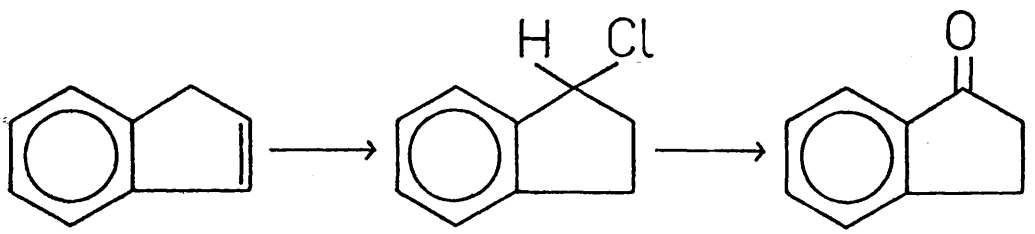

CO2Me
Me
+
CO2Me
O
hν
MeO2C H
MeO2C H O
NaBH4
MeO2C H
C—O
O
O
Δ
MeO2C
O
O

The cleavage of bicyclic ketones has been accomplished photochemically. Nozaki[58] synthesised cyclo-pentadecanone (62) in 20-30% yield *via* a three carbon ring enlargement of the bicyclic compound (61) (see Scheme 17). Desulphurisation of sulphur bridged bicycles has also been used to produce macrocycles[59] and is illustrated in Scheme 18. Finally, the cleavage of carbon-carbon single bonds must be mentioned. A recent example[60] of the application of this method is shown in Scheme 19.

PART 2

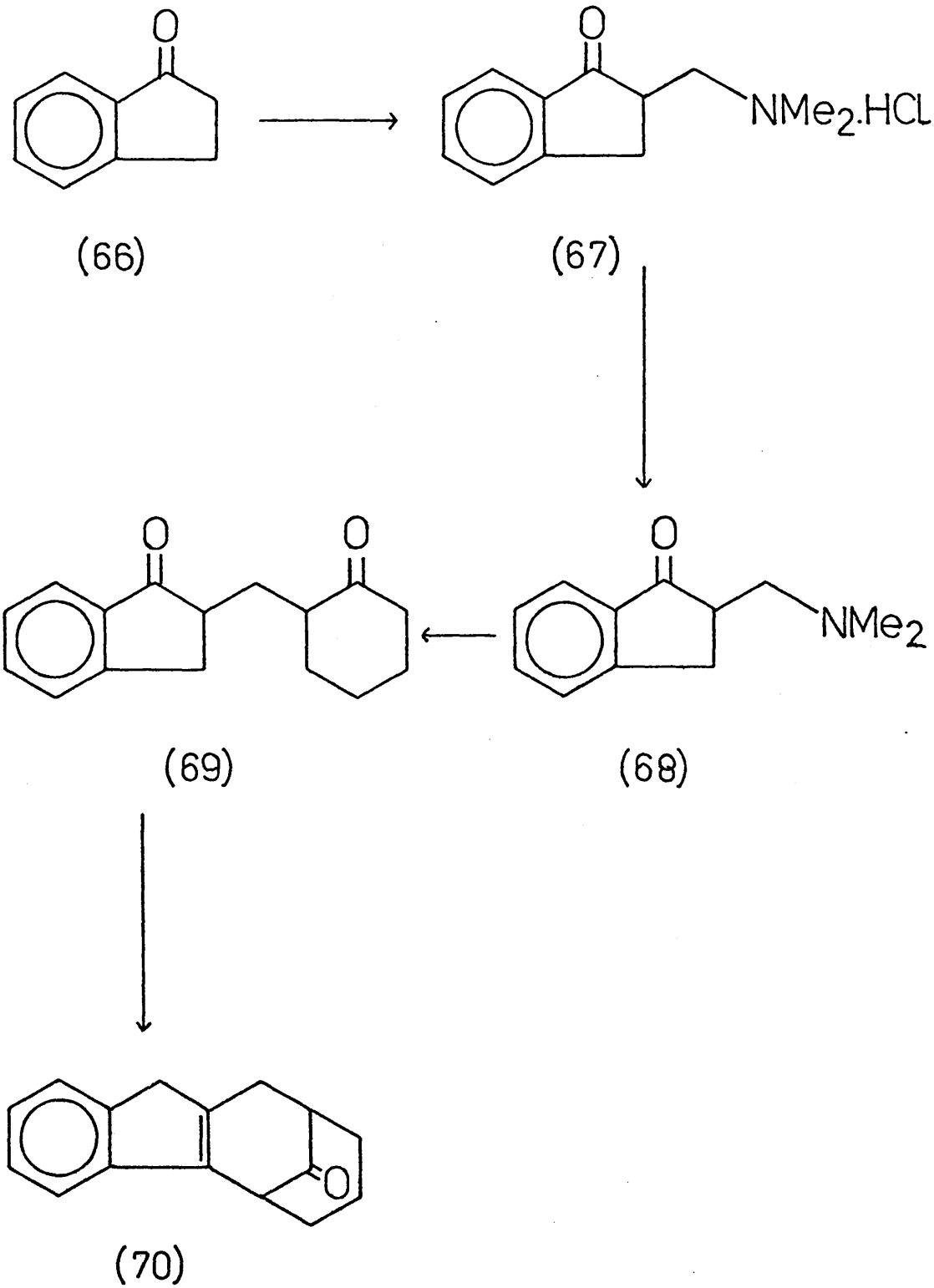


Scheme 20

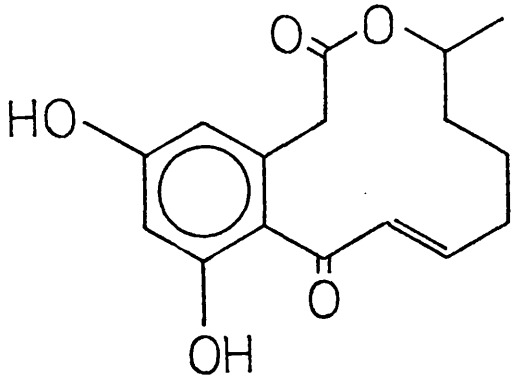


(63) (64) (65)

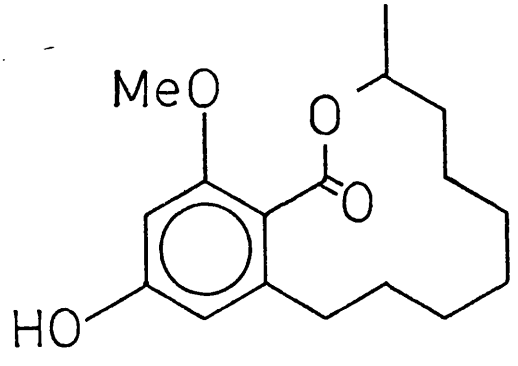
Scheme 21



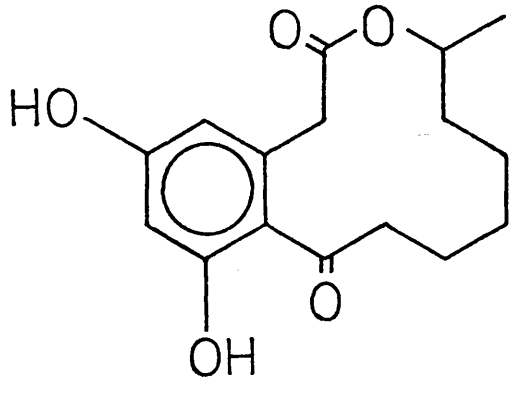
Scheme 22



(71)



(72)



(15)

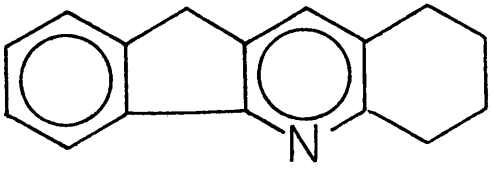
It is apparent from the introduction to Part 2 that the synthesis of medium and large ring compounds may be effected using cyclisation of long chain precursors, ring expansion of smaller cyclic compounds or ring annulation-scission methods. The object of the work to be described here was to extend the ring annulation-scission method of preparing large rings and macrocyclic lactones using available 5- or 6- membered rings (see Scheme 20).

Indanone (65) may be prepared quite easily from indene (63)[61] by the route shown in Scheme 21 and cyclohexanone is readily available. It was proposed, therefore, to use these two materials to synthesise (70) using the route shown in Scheme 22. This benzotricyclic compound (70) embodies all the features necessary for ring opening. Moreover, the aromatic ring should introduce reactivity into the molecule whilst increasing the molecular weight, thus giving, in all probability, solids, which are easier to handle.

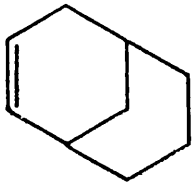
Aromatic macrolides are known in nature, some examples being α,β - dehydrocurvularin (71)[62], lasiodiplodin (72)[63] and curvularin (15).[64] If (70) proved to be a useful synthetic precursor to macrocyclic lactones, a wide range of these aromatic macrolides could be synthesised by suitable modification of starting materials.

Following the preparation of indanone (66)[61], the Mannich[65] base hydrochloride, [2-(N,N-dimethyl-aminomethyl)-indan-1-one hydrochloride (67)] was prepared by refluxing indanone (66) with paraformaldehyde and dimethylamine hydrochloride.[66] The i.r. spectrum showed absorptions at 2780-2300 $cm.^{-1}$ (ammonium band) and 1710 $cm.^{-1}$ (conjugated C = O), while the n.m.r. spectrum showed signals at δ 3.1 (6H ; s), assigned to the two N-methyl groups, and at δ 7.3-8.0 (4H ; m), assigned to the aromatic protons.

Liberation of the Mannich base (68), from its hydrochloride (67) proved difficult, due, presumably, to the solubility of the free base

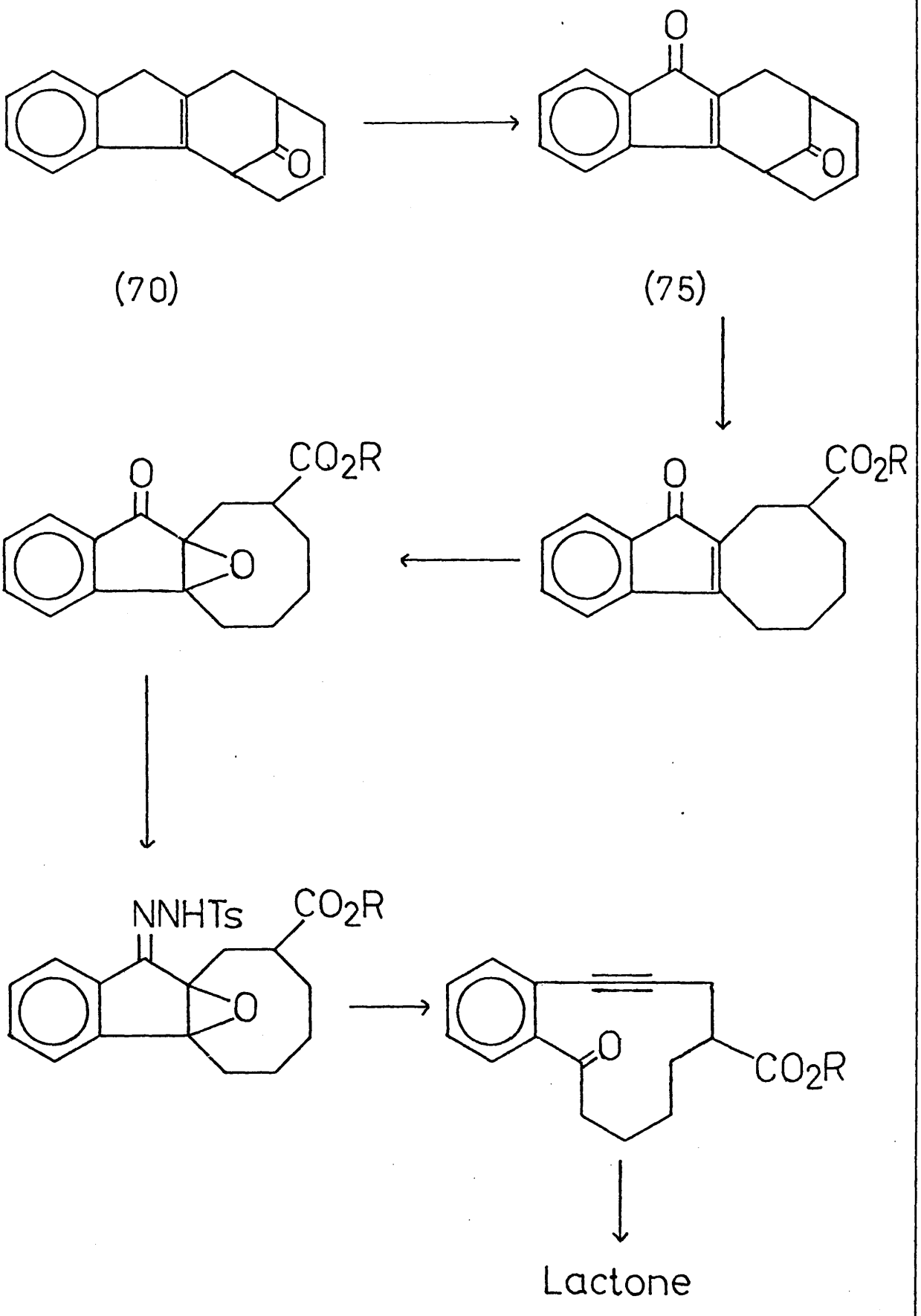


(73)



(74)

Scheme 23



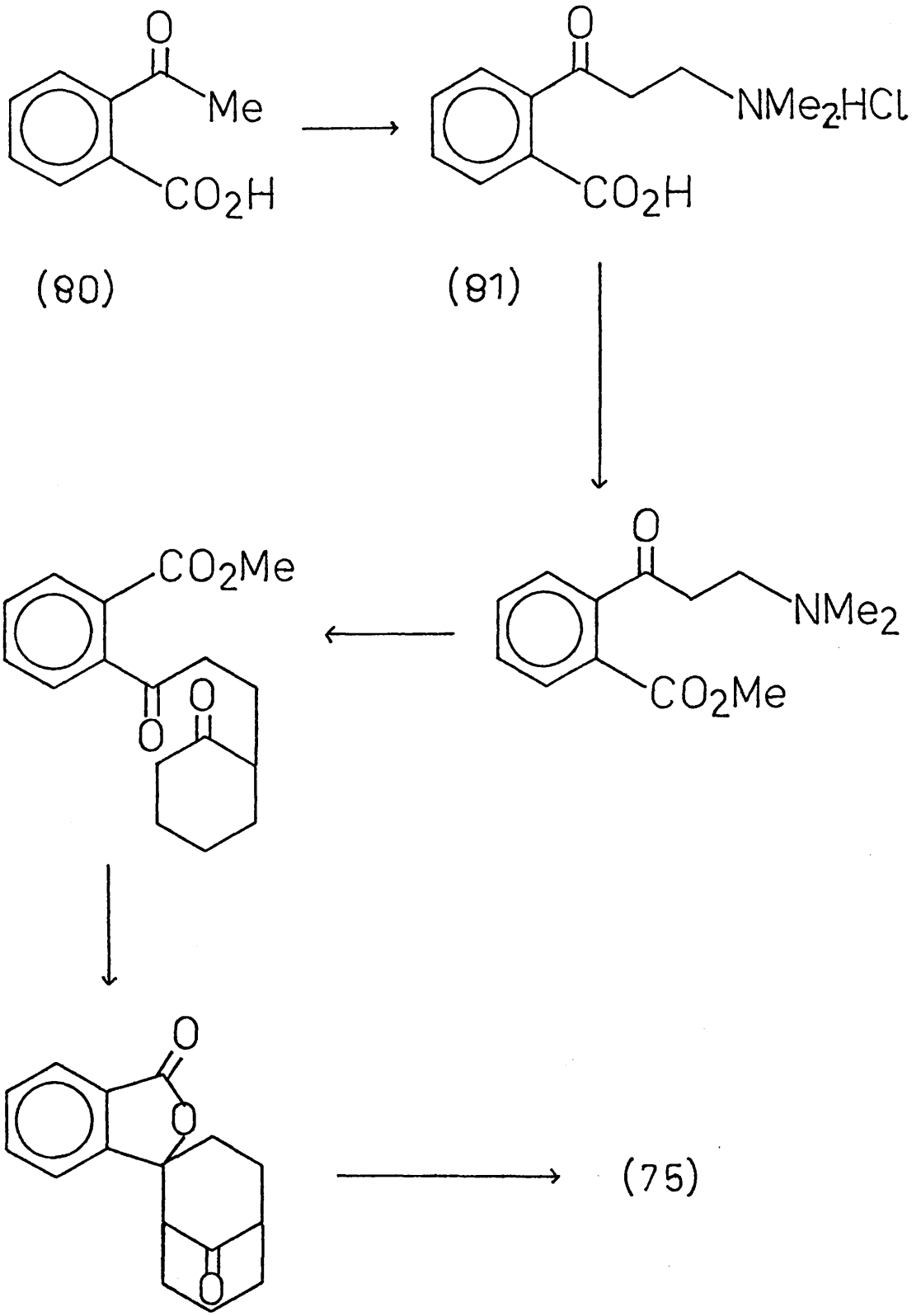
in the water used initially to dissolve the hydrochloride. After several modifications, the best results were obtained by dissolving the Mannich base hydrochloride (67) in a minimum amount of water and neutralising this solution with 0.88 ammonia, followed by salting-out and extraction of the free Mannich base (68) with ether. The i.r. spectrum of the crude Mannich base (68) showed absorptions at 1715 $cm.^{-1}$ (conjugated C = O), 1610 and 1590 $cm.^{-1}$ (conjugated aromatic ring) and 1210 $cm.^{-1}$ (C - N stretch) while the n.m.r. spectrum showed signals at δ 2.3 (6H ; s) assigned to the two N-methyl groups, and δ 7.2-8.0 (4H ; m), assigned to the aromatic protons.

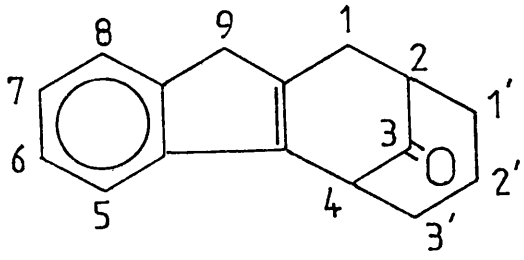
The crude Mannich base (68) was then subjected to thermal-Michael[67] conditions with cyclohexanone to give the expected product, 2-(2^{1}-oxo-cyclohexyl)-indan-1-one (69) as a clear yellow oil. The i.r. spectrum showed absorptions at 1715 $cm.^{-1}$ (C = O) and at 1610, 1590 $cm.^{-1}$ (conjugated aromatic ring), while the n.m.r. spectrum showed a ratio of aromatic to aliphatic protons 2 : 7. There was no fine structure visible in the methylene "envelope". The mass spectrum had a parent ion at m/e 242, and the preparation of the derivative (73) confirmed the structure as (69).

The cyclisation of the diketone (69) has previously been studied[68] and the best procedure, based on the work of Allan and Wells,[69, 70] involves the use of Amberlite IR-120 (H) resin in water. The product (70) obtained from this reaction showed absorptions in the i.r. at 1730 and 1720 $cm.^{-1}$ (c.f. ν_{CO} 1733 and 1725 $cm.^{-1}$ in the bicyclononenone (74)[71]). The n.m.r. spectrum had signals at δ 7.0-7.5 (4H ; m) due to the aromatic protons, δ 3.5 (1H ; m) due to the proton on C-4 and δ 3.4 (2H ; s) due to the indene methylene protons. The mass spectrum gave a parent ion at m/e 224.

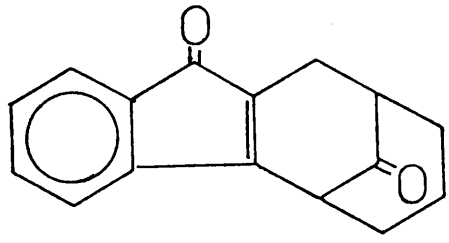
The proposed route to the macrocycle was now to be as shown in Scheme 23 using (70) as the starting material. Since C-9 of

Scheme 24

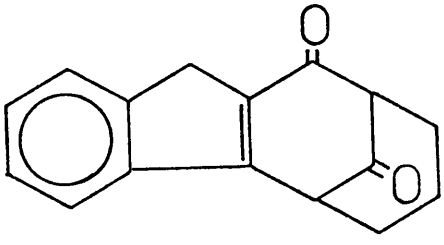




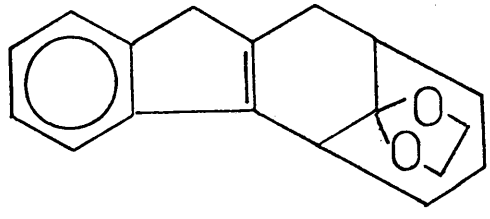
(70)



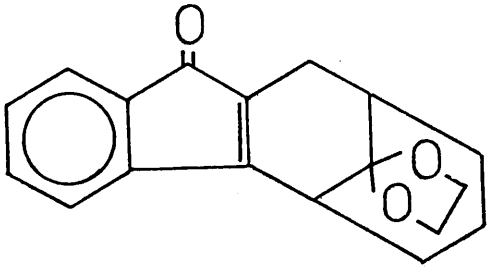
(75)



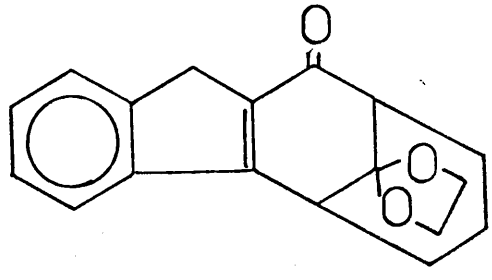
(76)



(77)



(78)

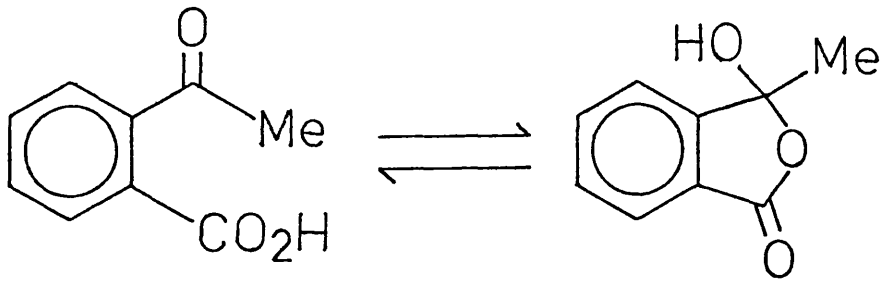


(79)

ketone (70) is both benzylic and allylic, whereas C-1 is only allylic, it was thought that oxidation would occur preferentially at C-9. The oxidation of (70) had previously been studied[72] and several reagents had been used in the attempt to prepare (75). These included anhydrous sodium chromate, lead tetraacetate, mercuric acetate, N-bromo-succinimide, chromium trioxide in pyridine (Collins' reagent), sodium dichromate and selenium dioxide. Only with selenium dioxide in acetic acid had it been possible to obtain (75) and then only in 25% yield. Despite several attempts using both sodium dichromate (reported[72] to give the allylic oxidation product (76)) and selenium dioxide, it was impossible to prepare either (75) or (76) from the ketone (70). Instead, in each case, several products were obtained and separated by t.l.c.; none of these products had the required molecular weight or n.m.r. characteristics.

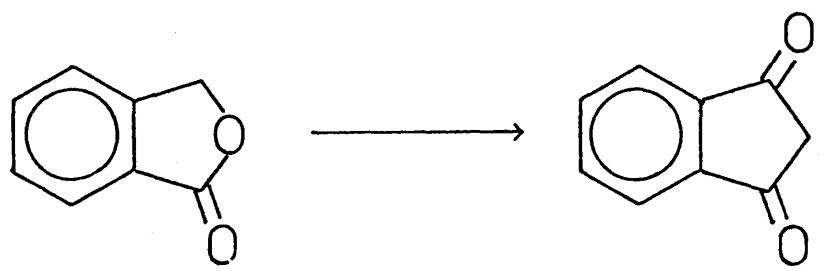
Refluxing the ketone (70) with ethylene glycol and toluene-p-sulphonic acid in benzene gave an almost quantitative yield of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (77). The i.r. spectrum showed the absence of ketone absorption, while the n.m.r. spectrum showed a signal at δ 3.8 (4H ; m) due to the acetal function. The mass spectrum had a parent ion at m/e 268. Attempts to oxidise the acetal (77) to either (78) or (79) similarly met with failure.

As the route from the vinylogous-β-diketone (75) to the macrocycle seemed so promising (see Scheme 23) other methods of preparing (75) were sought. One such method is depicted in Scheme 24. However it was not possible to prepare the Mannich base hydrochloride (81) of o-acetyl benzoic acid (80). This may be due to the existence of (80) in the form of the pseudo-acid (82). The i.r. spectrum of (80) shows absorptions at 3600-2300, 1730, 1615

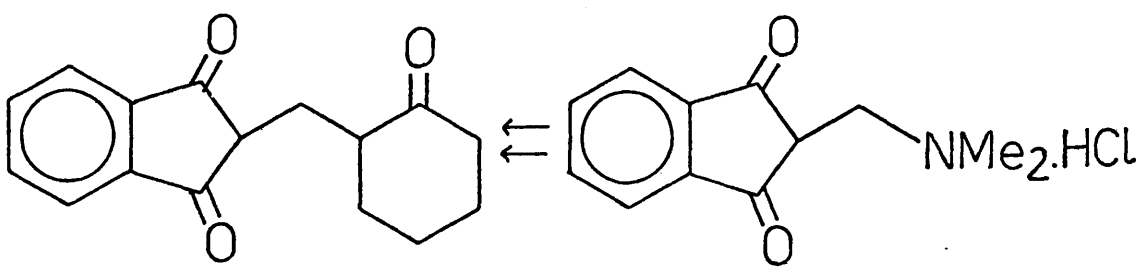


(80) (82)

Scheme 25



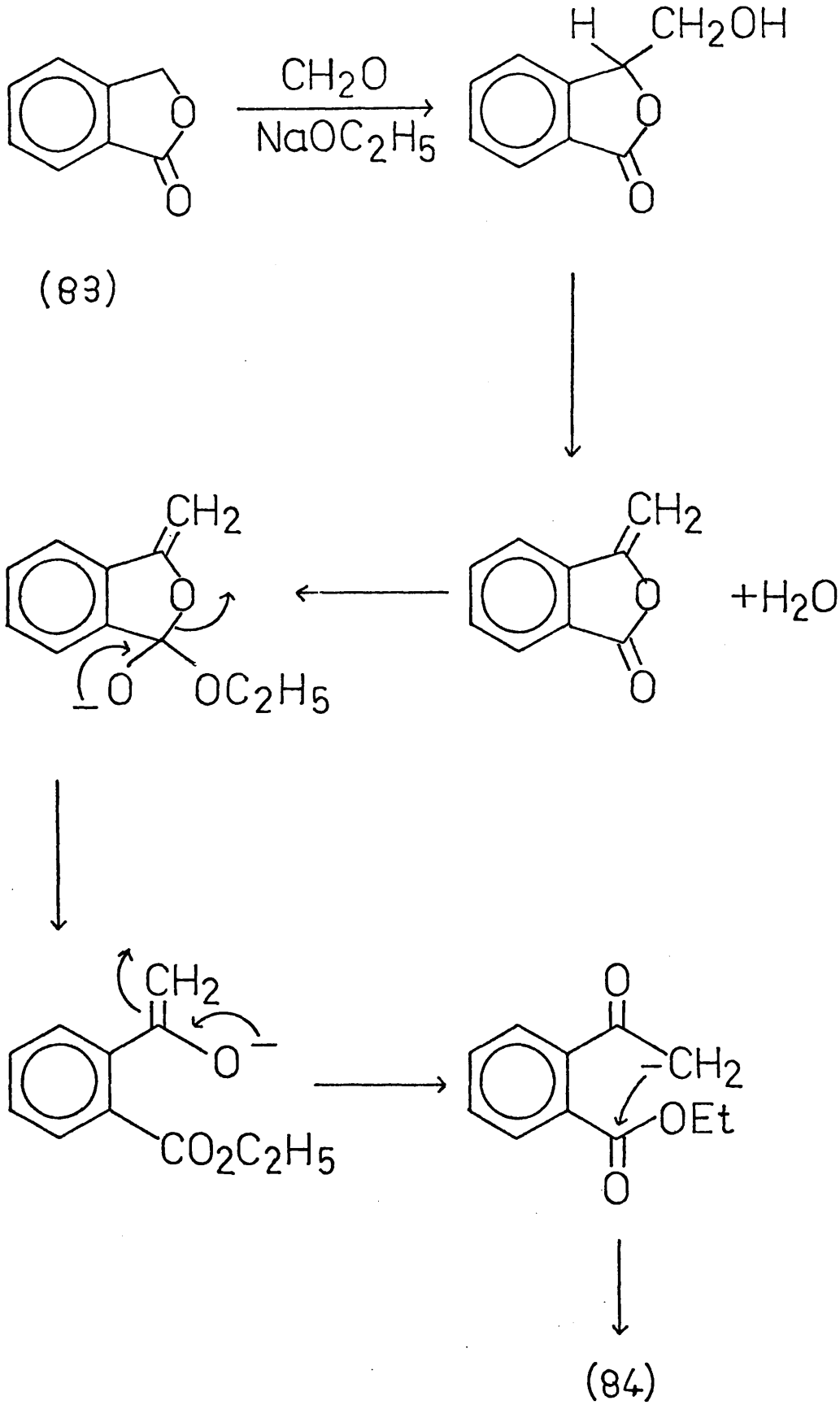
(83) (84)



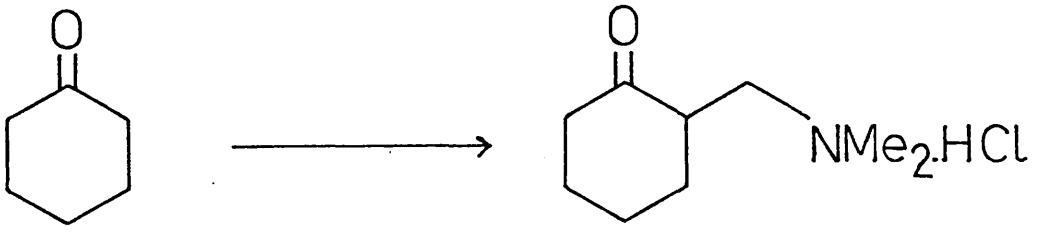
(88) (85)

(75)

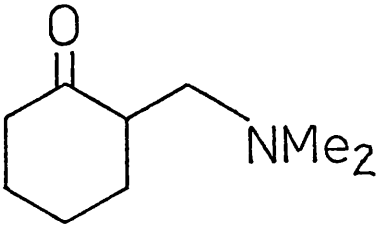
Scheme 26



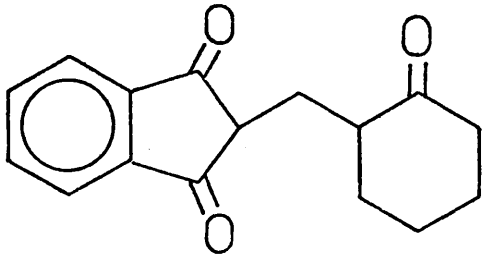
Scheme 27



(86)



(87)



(88)

(75)

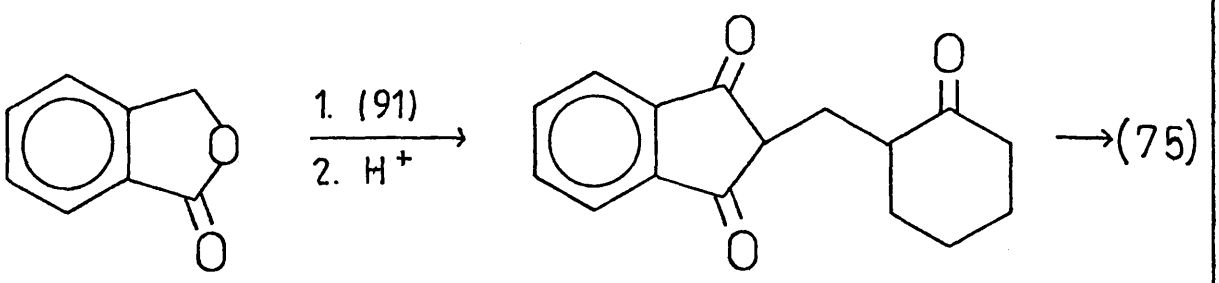
and 1600 $cm.^{-1}$ while the n.m.r. spectrum has signals at δ 2.0 (3H ; s), δ 5.9 (1H ; s), which disappears on addition of D_2O, and δ 7.4–8.0 (4H ; m).

Another possible route to (75) is shown in Scheme 25. Indan-1,3-dione (84) was prepared from phthalide (83) by the literature procedure[73] whose mechanism is outlined in Scheme 26. This compound showed absorptions in the i.r. at 1750, 1715, 1690 and 1600 $cm.^{-1}$, while the n.m.r. had signals at δ 3.2 (2H ; s) and δ 7.8–8.1 (4H ; m). However, the preparation of the Mannich base hydrochloride (85) of indandione failed. Instead, an amorphous solid, insoluble in most organic solvents, was obtained. A literature search revealed that the Mannich condensation had previously been attempted with indan-1,3-dione[74] and dimedone[75] and had failed to give the expected product in each case.

By modifying Scheme 25 a new approach to (75) was attempted. This involved condensing the Mannich base (87) of cyclohexanone with indan-1,3-dione (84) (see Scheme 27). The Mannich base hydrochloride (86) of cyclohexanone, prepared using formalin and dimethylamine hydrochloride[76], showed i.r. absorptions at 2700–2280$cm.^{-1}$ (ammonium band) and 1700 $cm.^{-1}$ (C = O), and n.m.r. signals at δ 2.9 (3H ; s) and δ 2.8 (3H ; s) assigned to the two N-methyl groups. As in the case of indanone, the free Mannich base of cyclohexanone was obtained by treatment of the Mannich base hydrochloride with 0.88 ammonia. It showed i.r. absorptions at 1715 $cm.^{-1}$ (C = O) and 1210 $cm.^{-1}$ (C–N stretch) and n.m.r. signals at δ 2.2 (6H ; s) assigned to the two N-methyl groups. Subjection of this crude Mannich base (87) to thermal-Michael conditions[67] with indan-1,3-dione failed however to yield the desired product (88).

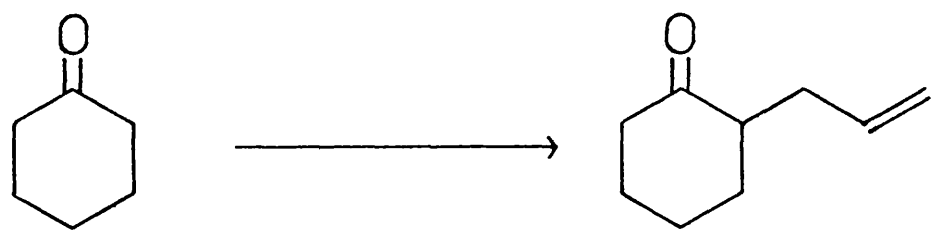
A further modification of the basic route shown in Scheme 25

Scheme 28

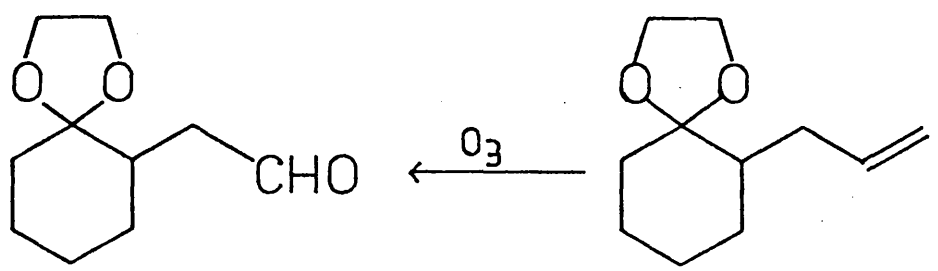


(83) (88)

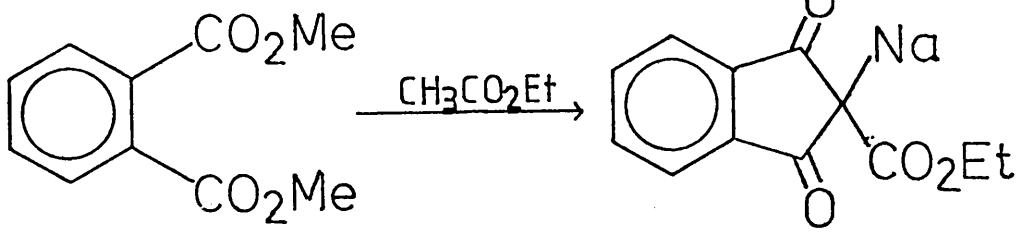
Scheme 29



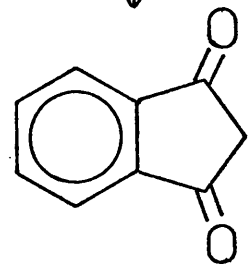
(89)



(91) (90)

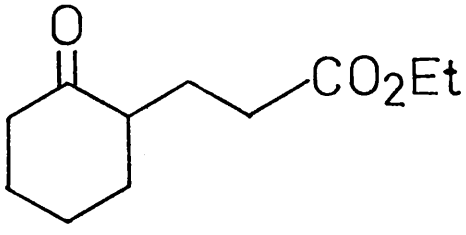


(92)

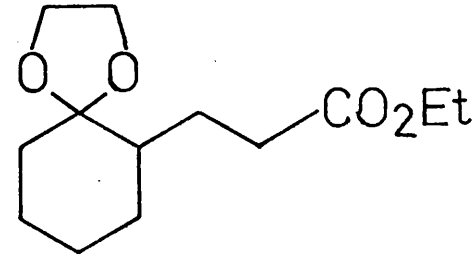


(84)

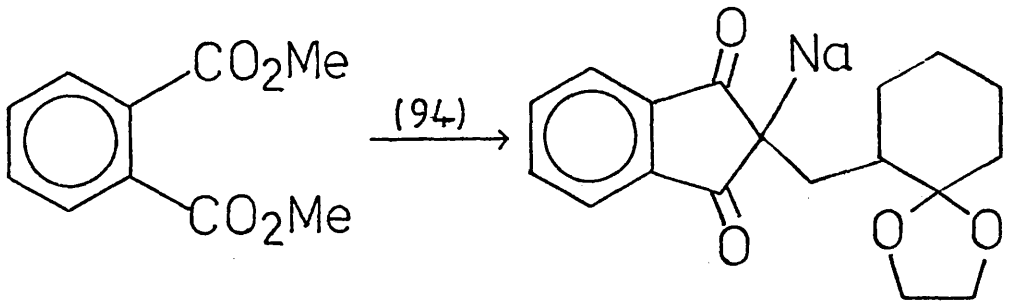
Scheme 30



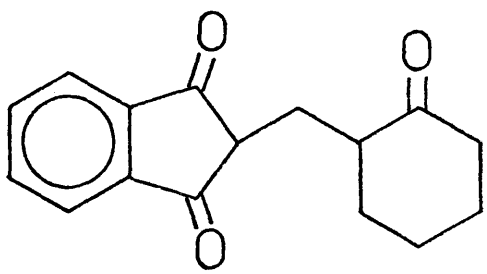
(93)



(94)



(95)



(88)

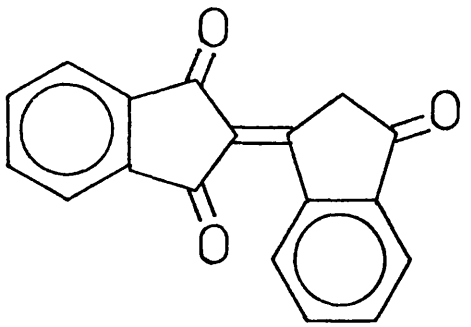
Scheme 31

was now attempted. This involved using phthalide again but this time instead of formaldehyde, as in Scheme 25, the aldehyde (91) was employed. It was hoped that this would allow the formation of (88) directly in one pot (see Scheme 28).

The aldehyde (91) was prepared as shown in Scheme 29. The pyrrolidine enamine of cyclohexanone[77] was treated with allyl bromide to give 2-allylcyclohexanone (89). The i.r. spectrum showed absorptions at 1715 (C = O) and 1640 $cm.^{-1}$ (C = C) while there were signals in the n.m.r. at δ 1.0-2.8 (11H) and at δ 4.8 (1H ; m), 5.05 (1H ; m) and 5.7 (1H ; m) (olefinic protons). The mass spectrum gave a parent ion at m/e 138. Protection of the carbonyl group followed by ozonolysis and decomposition of the ozonide resulted in formation of the aldehyde (91). The i.r. spectrum showed absorptions at 1730 $cm.^{-1}$ (C = O) and 2720 $cm.^{-1}$ (C-H stretch of CHO) while the n.m.r. spectrum had signals at δ 3.9 (4H ; m) (acetal) and δ 9.66 (aldehydic proton). The reaction of phthalide with this compound however failed to produce the required triketone (88).

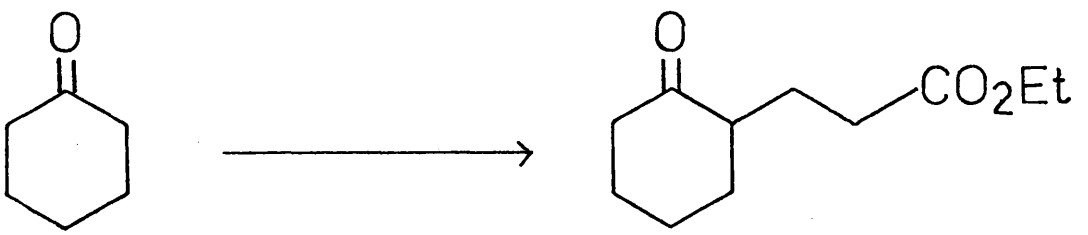
Indan-1,3-dione may also be prepared using dimethyl phthalate and ethyl acetate[78] (see Scheme 30). By analogy it was hoped that the reaction could be extended to the preparation of (88) by using the acetal (94) of the keto-ester (93) (see Scheme 31).

To gain experience in setting up and working up the reaction, the synthesis of the parent compound (84) was tried first according to the published procedure.[78] This gave initially the sodio-compound which has been represented[79] as (92). The i.r. spectrum of this compound (KBr disc) showed absorptions at 3700-2500 (3400), 1725, 1705, 1690, 1665, 1630 and 1615 $cm.^{-1}$ and the n.m.r. had signals at δ 1.4 (3H ; t), 4.3 (2H ; q) due to the ester function, and 7.5 (4H ; m) due to the aromatic protons. Treatment of (92)

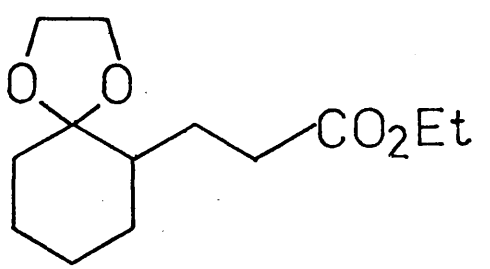


(96)

Scheme 32



(93)



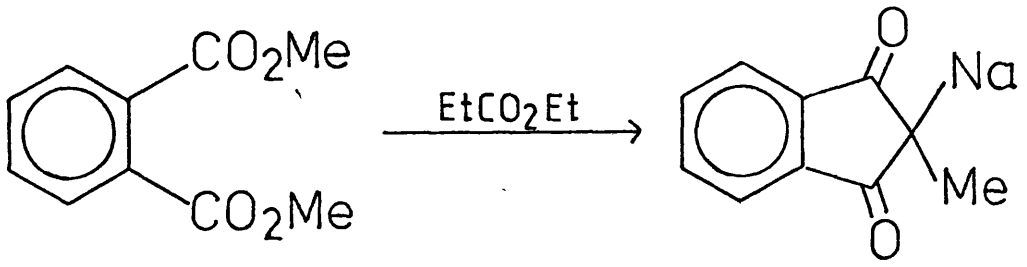
(94)

with acid furnished the dione (84) which was in all respects (m.p., m.s., i.r., and n.m.r.) identical with material previously prepared from phthalide (83) (see Scheme 25). In addition, a small amount of a biproduct, biindone (96), was obtained. The i.r. spectrum of this compound showed absorptions at 1725, 1690, 1680 and 1615 $cm.^{-1}$ while the n.m.r. spectrum had signals at δ 4.1 (2H ; s) and 7.7-8.1 (8H ; m).

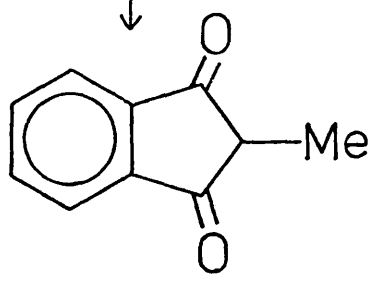
In order to attempt the reaction shown in Scheme 31 the synthesis of compound (94) was next carried out using the route shown in Scheme 32. The ester (93) was obtained by the published procedure[77] ; refluxing ethyl acrylate with the pyrrolidine enamine of cyclohexanone. The i.r. showed absorptions at 1740 (ester C = O) and 1720 $cm.^{-1}$ (ketone C = O), while the n.m.r. had signals at δ 1.2 (3H ; t) and 4.1 (2H ; q) due to the ester function. Protection of the ketone in the usual way gave (94) as a clear oil showing i.r. absorption at 1735 $cm.^{-1}$ (ester C = O) and the absence of any further absorption in this region indicated complete formation of the acetal (94). In the n.m.r., in addition to the signals at δ 1.25 (3H ; t) and 4.15 (2H ; q), due to the ester function, there was a signal at δ 4.0 (4H ; m) due to the methylene protons of the acetal ring.

This compound was now treated with dimethyl phthalate at 90-100°C. After ca. 5 minutes a deep brown colour developed but with only a little frothing of the mixture. After approximately 30 minutes, however, the reaction suddenly became very vigorous with some of the mixture filling almost half of the condenser. At this point the reaction was stopped and worked-up. Several products were obtained but none of them proved to be the desired compound. The material which was soluble in ether proved to be a mixture of starting materials and some other product which was not

Scheme 33

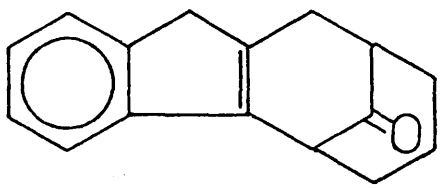


(97)

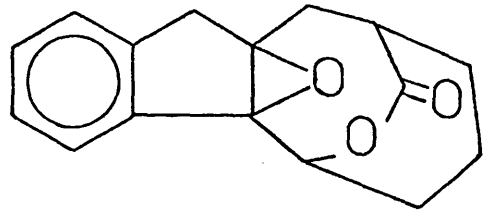


(98)

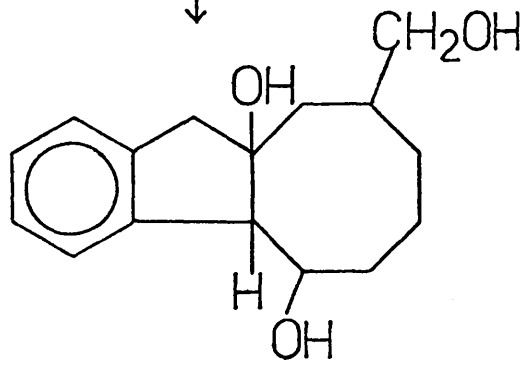
Scheme 34



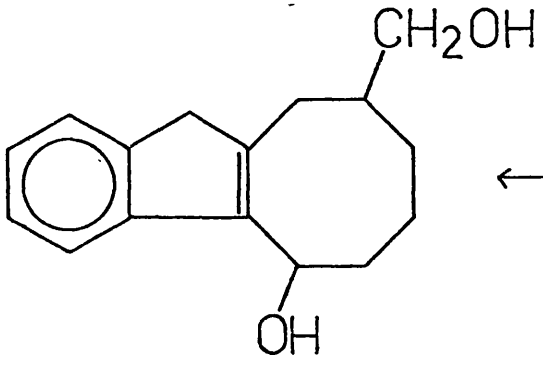
(70)



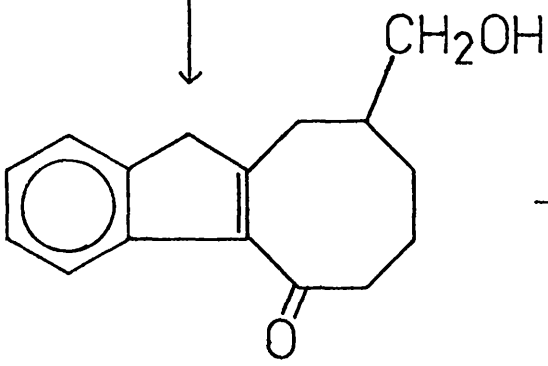
(99)



(100)



(101)



(102)

etc.

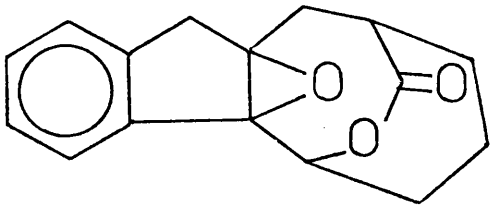
identified. The water-soluble material was found to have a melting point in excess of 330°C and from its n.m.r. spectrum was classed as inorganic. Addition of hydrochloric acid to the aqueous phase caused no precipitation and ether extractions of this acidified aqueous phase yielded only a trace of material.

As can be seen by comparing schemes 30 and 31, the reactions proceed along slightly different lines due to the fact that the ester (94) in Scheme 31 has an R group α to the ester function which, of course, is absent in the case of the ethyl acetate used in Scheme 30. It was decided to repeat the reaction with another ester which does have an R group α to the ester function. A literature search revealed that the reaction had been carried out using ethyl propionate[80] in place of ethyl acetate (see Scheme 33).

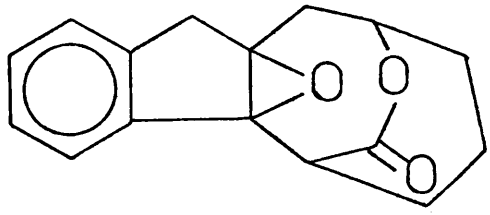
This reaction was carried out using the prescribed procedure[80] and the sodium salt (97) was obtained which, on treatment with acid, gave the dione (98). The i.r. spectrum had absorptions at 1755, 1720 and 1600 $cm.^{-1}$, while the n.m.r. spectrum showed signals at δ 1.4 (3H ; d), δ 3.1 (1H ; q) and δ 8.0 (4H ; m).

Having succeeded in this case, the reaction with (94) was repeated. On this occasion the reaction did not become vigorous and the mixture was heated for 4 hours. However, subsequent work-up failed to give the required material.

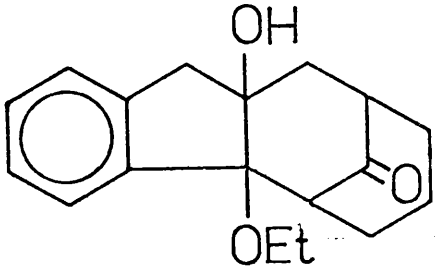
At this point it was felt that attempts to prepare the vinylogous-β-diketone (75) had been sufficiently explored and that perhaps it would be more profitable to concentrate on finding a way of using (70) to prepare a macrocycle without the intermediacy of (75). One such way is depicted in scheme 34. This involves the formation of a lactone by way of a Baeyer-Villiger reaction.[81] It was expected that the tetra-substituted double bond would also be epoxidised in this reaction to give the epoxy-lactone (99).



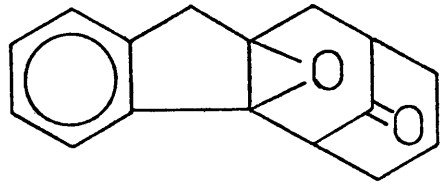
(99)



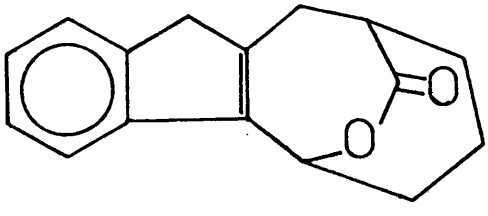
(103)



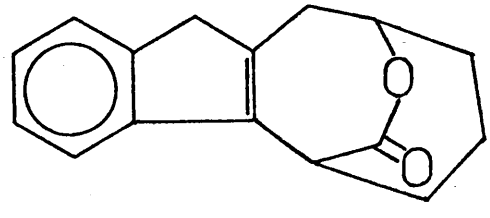
(104)



(105)



(106)



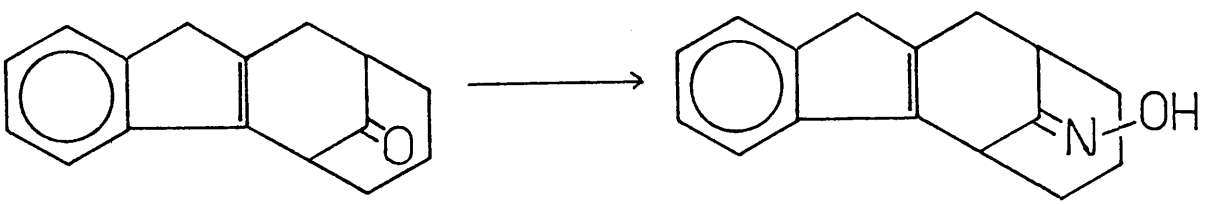
(107)

Treatment of (99) with a metal hydride should give the trihydroxy compound (100). Dehydration of the tertiary alcohol would reinstate the double bond allowing selective oxidation of the now allylic alcohol in (101) to give the keto-alcohol (102). This unsaturated ketone would be a suitable intermediate on which to perform the Eschenmoser ring fragmentation reaction (see Introduction to Part 2, p61). It was hoped that in the Baeyer-Villiger reaction some selectivity would be exhibited enabling the formation of lactone (99) rather than lactone (103).

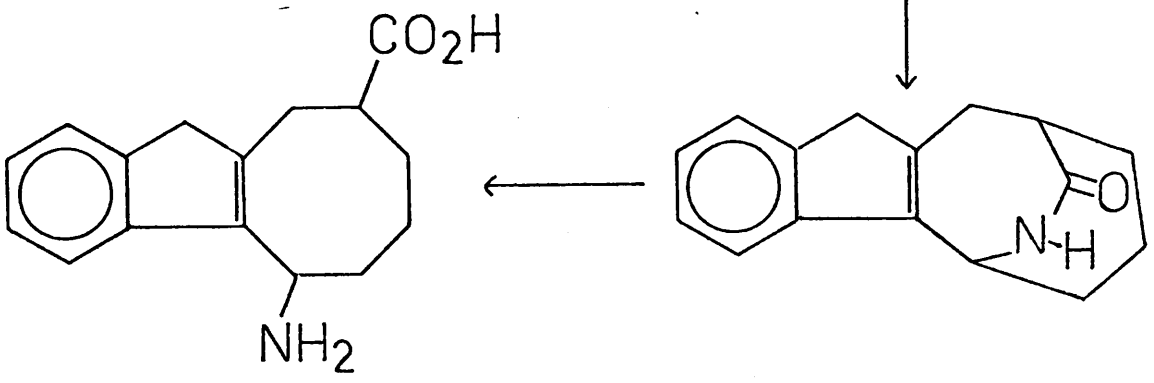
The Baeyer-Villiger reaction was tried initially using 2.1 equivalents of m-chloroperbenzoic acid in chloroform. After work-up, analytical t.l.c. showed the presence of several compounds and the crude material was chromatographed on silica using 30% ethyl acetate-light petroleum as eluant. The mass spectrum of the major product had a parent ion at m/e 286 and showed absorptions in the i.r. at 3540 and 1730 $cm.^{-1}$ The n.m.r. spectrum showed one exchangeable proton at δ 3.8 (hydroxyl) and further signals at δ 7.4 (4H ; m) (aromatics), δ 3.0 (2H ; q) and δ 1.1 (3H ; t). The material analysed for $C_{18}H_{22}O_3$ and was identified as the compound (104). The presence of a small amount of ethanol in the chloroform had apparently opened the epoxide.

The reaction was repeated using purified chloroform[82] and this time the major product had absorptions in the i.r. at 1730 (C = O) and 1610 $cm.^{-1}$ (aromatic ring) while the n.m.r. spectrum showed signals at δ 7.2 (4H ; m) due to the aromatic protons, and at δ 3.6 (2H ; s) due to the benzylic protons. The mass spectrum had a parent ion at m/e 240 and the material analysed for $C_{16}H_{16}O_2$ which corresponds to the epoxide (105). The absence of a one proton signal in the n.m.r. at ca. δ 5 or δ 6 excludes structure (106) or (107). There were still several biproducts formed in the

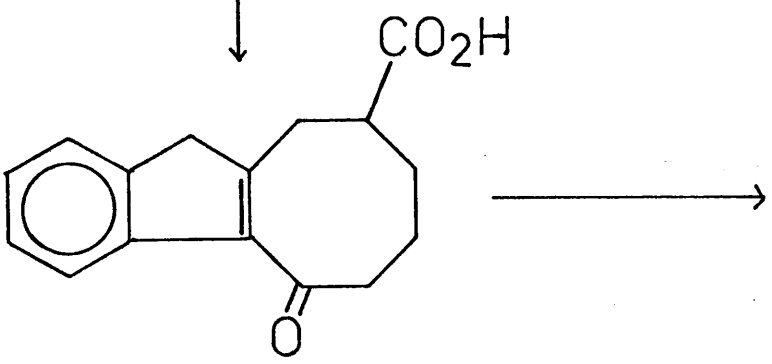
Scheme 35



(70) (109)

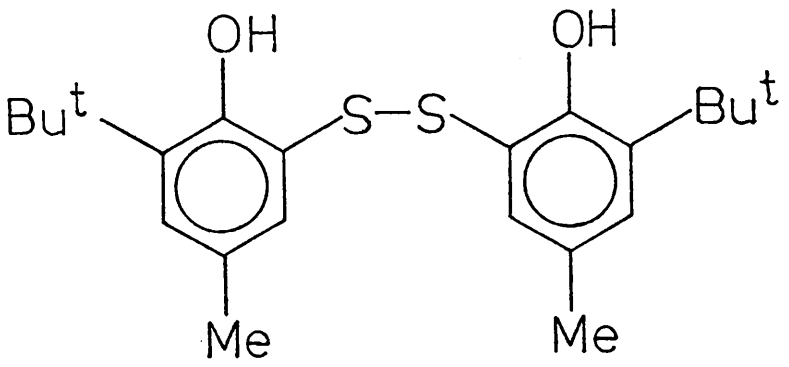


(111) (110)



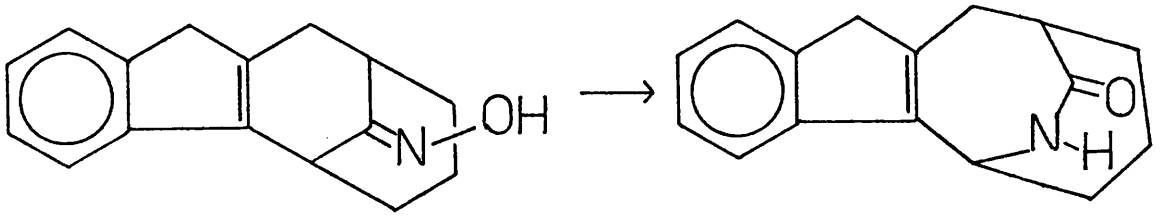
etc.

(112)

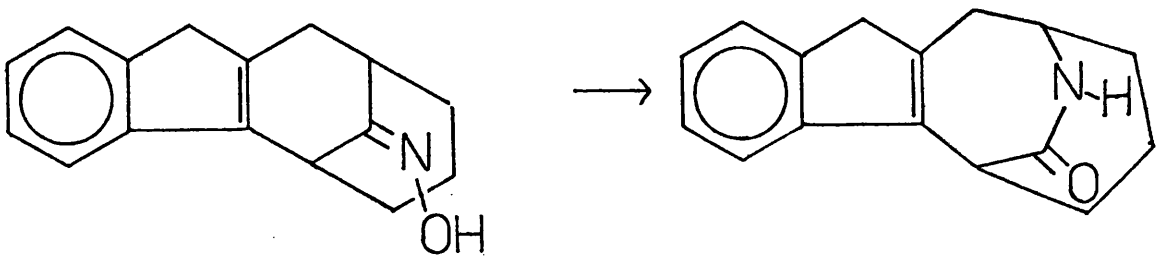


(108)

Scheme 36



(109) (110)



(113) (114)

reaction and again there was no evidence for the presence of any epoxy-lactone.

The reaction was repeated using methylene chloride as solvent and gave essentially the same results with 2.1, 3 and 5 equivalents of m-chloroperbenzoic acid. In all cases the epoxide (105) was the major product. The yield of epoxide was increased by using a radical scavenger.[83] The scavenger used was 2,2' thiobis (4 methyl 6 t-butyl phenol) (108).[84] The solvent chosen was ethylene dichloride and all subsequent reactions with this peracid were done in this solvent. Use of these conditions significantly reduced the amount of biproducts formed in the reaction[85] but still no epoxy-lactone (99) or (103) could be obtained. The use of peracetic acid gave similar results to those discussed above for m-chloroperbenzoic acid.

Unable to obtain a bridging lactone group, it was felt that a bridging lactam group might serve the same purpose. That is, if compound (110) could be prepared from the ketone (70) by way of a Beckmann rearrangement[86] of the oxime (109), it should be possible to prepare a macrocycle by the route shown in scheme 35. This involves cleavage of the lactam (110) to the amino-acid (111) or some derivative thereof, and conversion of the amine function to a ketone function. This would generate the desired α, β - unsaturated ketone necessary for the Eschenmoser reaction. It was expected that both oximes (109) and (113) would be produced from the ketone (70) but, as shown in scheme 36, oxime (109) would give lactam (110) while oxime (113) would give lactam (114). It was hoped that a separation would be possible at either the oxime or lactam stage in the synthesis.

Refluxing (70) with base and hydroxylamine hydrochloride yielded a product homogeneous on t.l.c. when ethyl acetate was used

Compound	^{13}C (p.p.m.) of α-carbons.
Ketone (70)	46.055 and 44.881
Oxime I	35.436 and 28.997
Oxime 2	36.306 and 27.993

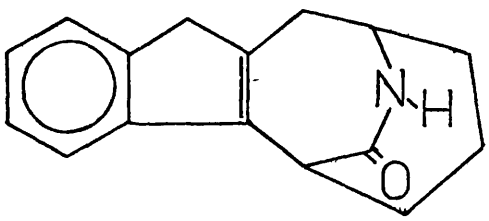
Table I

as eluant. However, with 30% ethyl acetate - light petroleum, two spots were visible when the plate was treated with iodine vapour. After separation by preparative t.l.c., both compounds gave a parent ion in the mass spectrum at m/e 239 and both compounds analysed for $C_{16}H_{17}N_1O_1$. The i.r. and n.m.r. spectra of the compounds were different, however. These must be the two oximes and it is convenient at this stage to designate them as oxime 1 (lower spot on t.l.c.) and oxime 2 (upper spot on t.l.c.). Oxime 1 showed absorptions in the i.r. at 3615 $cm.^{-1}$ (OH stretch), 3560-2600 (3250), 1745, 1670 (C = N stretch), 1630 and 1605 $cm.^{-1}$ (C = C) while the n.m.r. had signals at δ 6.9-7.5 (4H ; m), 4.6 (1H ; m), 3.2 (2H ; s). Oxime 2 showed absorptions in the i.r. at 3615 $cm.^{-1}$ (OH stretch), 3550-2500 (3280), 1740, 1720, 1670 (C = N stretch), 1630 and 1615 $cm.^{-1}$ (C = C) while the n.m.r. had signals at δ 7.6-6.9 (4H ; m), 3.9 (1H ; m), 3.8 (1H ; m) and 3.2 (2H ; s).

In ^{13}C n.m.r. the carbon resonances of aldo- and keto-oximes (>C = N-OH) appear in the region 145-163 p.p.m., such resonances being some 50 p.p.m. to higher field relative to the corresponding carbonyl resonances. When the substitution is asymmetrical, differences in the oxime carbon chemical shift are observed depending upon the conformation of the oxime N-OH moiety. Such conformational isomerism also has a profound effect on the chemical shift of the α-carbon. It was hoped that this latter effect would allow an identification of the oximes. The technique works well in the simple example of the oximes of butan-2-one.[87] ^{13}C n.m.r. spectra were obtained for the ketone (70) and its two oximes (109) and (113) (see Table 1). Unfortunately, as may be seen from this table, the chemical shifts of the α-carbons are quite similar in all three compounds and no precise assignment of the

Table 2

Lactam I			Lactam 2		
	calculated	observed		calculated	observed
NH-C-H	3.44	3.65	NH-C-H	4.29	4.4
CO-C-H	3.6I	3.97	CO-C-H	2.76	obscured



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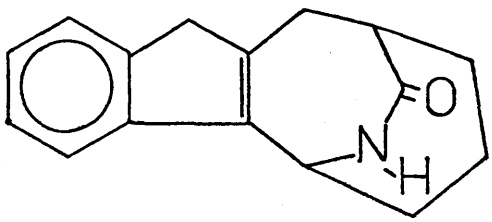


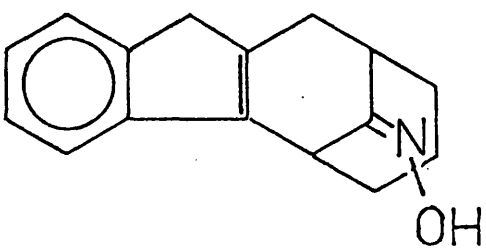
(110)

and therefore,

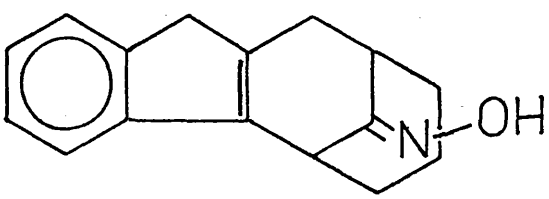
and therefore,

Oxime I

Oxime 2



(113)



(109)

chemical shifts to individual carbon atoms could be made. As a result, it was not possible to assign stereochemical structures to the two oximes.

Still uncertain of the identity of the two oximes, both were separately converted by the use of tosyl chloride/pyridine (Beckmann rearrangement) to the isomeric lactams (110) and (114). At this stage, of course, the identity of each lactam was still unknown and it is convenient at this stage to designate them as lactam 1 (derived from oxime 1) and lactam 2 (derived from oxime 2). Both lactams had identical Rf values on t.l.c. in a variety of solvent systems. Both had a parent ion in the mass spectrum at m/e 239, and both analysed for $C_{16}H_{17}N_1O_1$. As in the case of the oximes though, the two lactams gave different i.r., ^{1}H n.m.r. and ^{13}C n.m.r. spectra. Lactam 1 showed absorptions in the i.r. at 3300 (NH stretch), 3210, 1660 ("amide I band") and 1605 cm.$^{-1}$ (C = C) while the ^{1}H n.m.r. had signals at δ 7.5-7.0 (5H ; m), assigned as the aromatic protons plus the N-H proton, 4.0 (1H ; m) 3.7 (1H ; m) and 3.3 (2H ; s) due to the indene methylene protons. Lactam 2 showed absorptions in the i.r. at 3300 (NH stretch), 3205 and 1660 cm.$^{-1}$ ("amide I band"), while the ^{1}H n.m.r. had signals at δ 7.6-6.9 (5H, m) assigned to the aromatic protons plus the N-H proton, 4.4 (1H ; m) and 3.3 (2H ; s) due to the indene methylene protons.

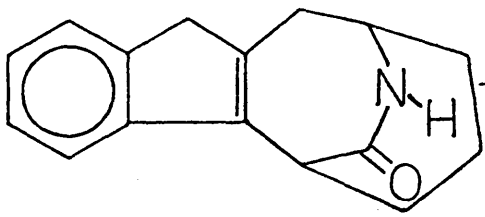
In the ^{1}H n.m.r. spectra of the two lactams, calculated values for the protons α to -NH and α to - C = O were obtained using Schoolery's rules.[88, 89] Comparison of these with experimentally obtained values (see Table 2) enabled an assignment of configuration to be made for each lactam, and therefore for each oxime, assuming the accepted mechanism of the Beckmann rearrangement. The δ values of the two methine protons, and their relative chemical shifts

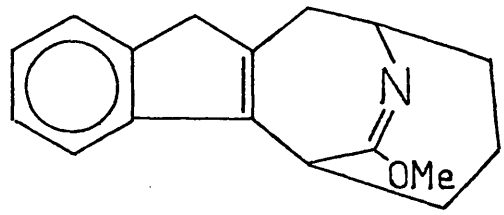
identify the lactams and therefore the oximes as the structures shown in the table. In each case the NH-C-H signals could be identified by its sharpening when the N-H proton was replaced by deuterium on addition of a small amount of D_2O to the sample.

Confirmation of the assignment was obtained by irradiation of the NH-C-H signal in each lactam. In lactam 1, this simplified the 2H allylic multiplet at δ 3.3 whereas in lactam 2 the 2H allylic multiplet at δ 3.3 was unchanged. Hence, lactam 1 is (114) and lactam 2 is (110).

It was discovered that if either oxime were refluxed in chloroform overnight the solution obtained then contained both oximes. This equilibration, far from being a disadvantage, proved to be highly advantageous, for after separation of the oximes the "wrong" isomer could be re-equilibrated to produce further amounts of the desired oxime. This meant that, in effect, virtually all of the ketone (70) could be transformed into either the lactam (110) or lactam (114), as required.

Equilibration of the oximes also takes place if the Beckmann rearrangement is carried out by poly-phosphoric acid (PPA) at 80°C, for the separate oximes each give a mixture of lactams. It was possible to convert each oxime to a single lactam using the PPA at room temperature but the use of this reagent at temperatures less than 80°C is troublesome. Replacing PPA by phosphorous pentoxide/methanesulphonic acid (1 : 10)[90] also resulted in the formation of both lactams from the single oximes when the reaction was carried out at 110°C. It was possible though, as before, to convert each oxime only to its correspoding lactam if the reaction was carried out at room temperature. In the light of these results it was decided to use the method originally chosen (TsCl/Py) to effect the Beckmann rearrangement in all subsequent





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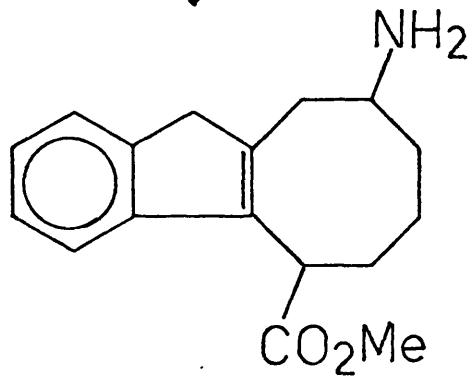
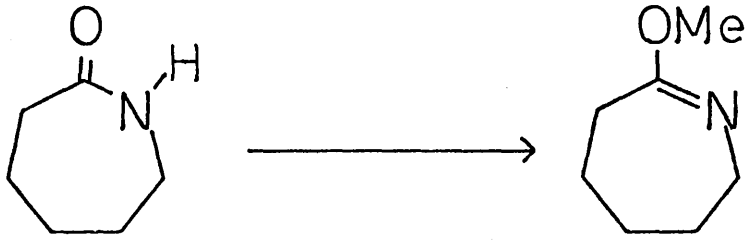
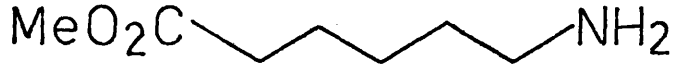


(115)

Scheme 37





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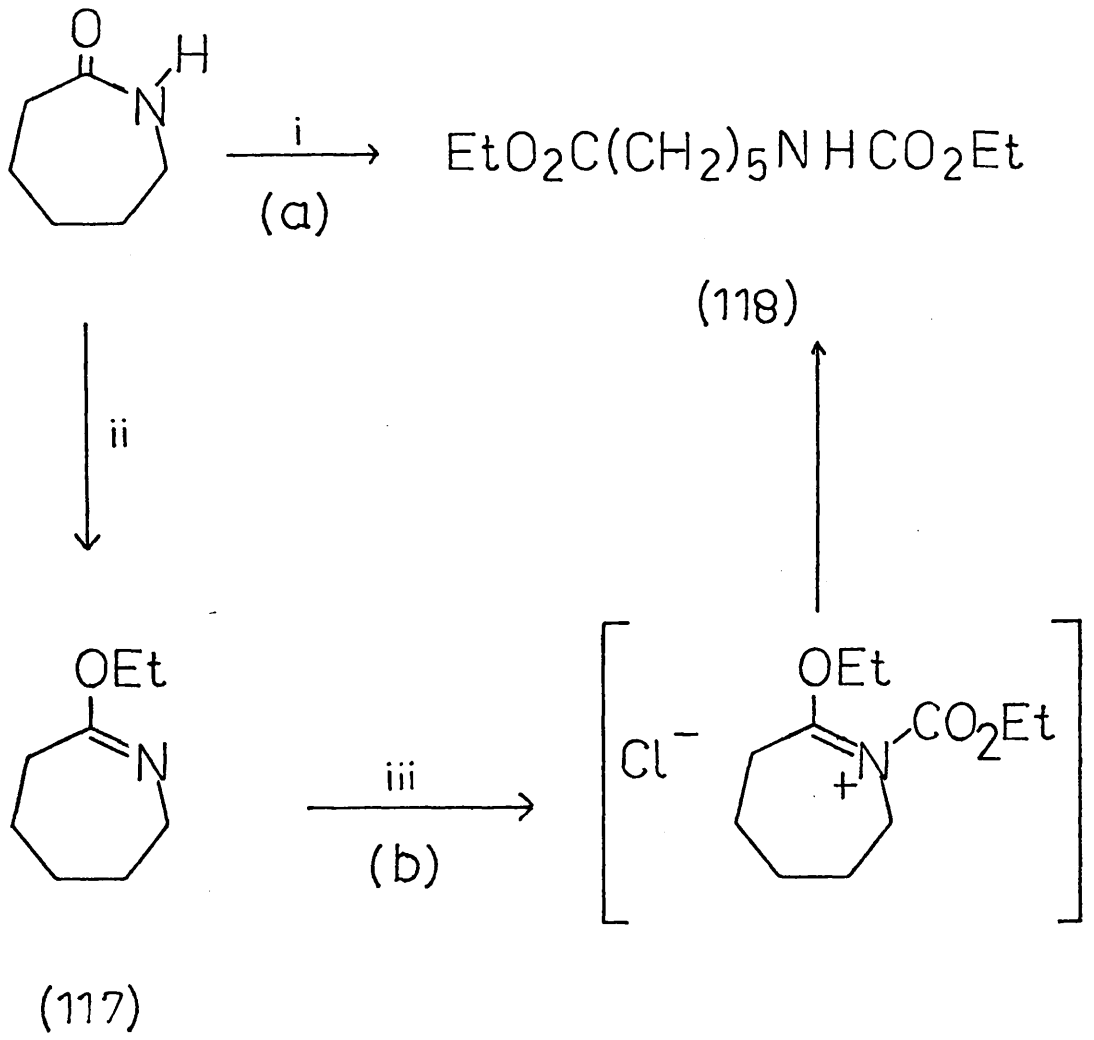
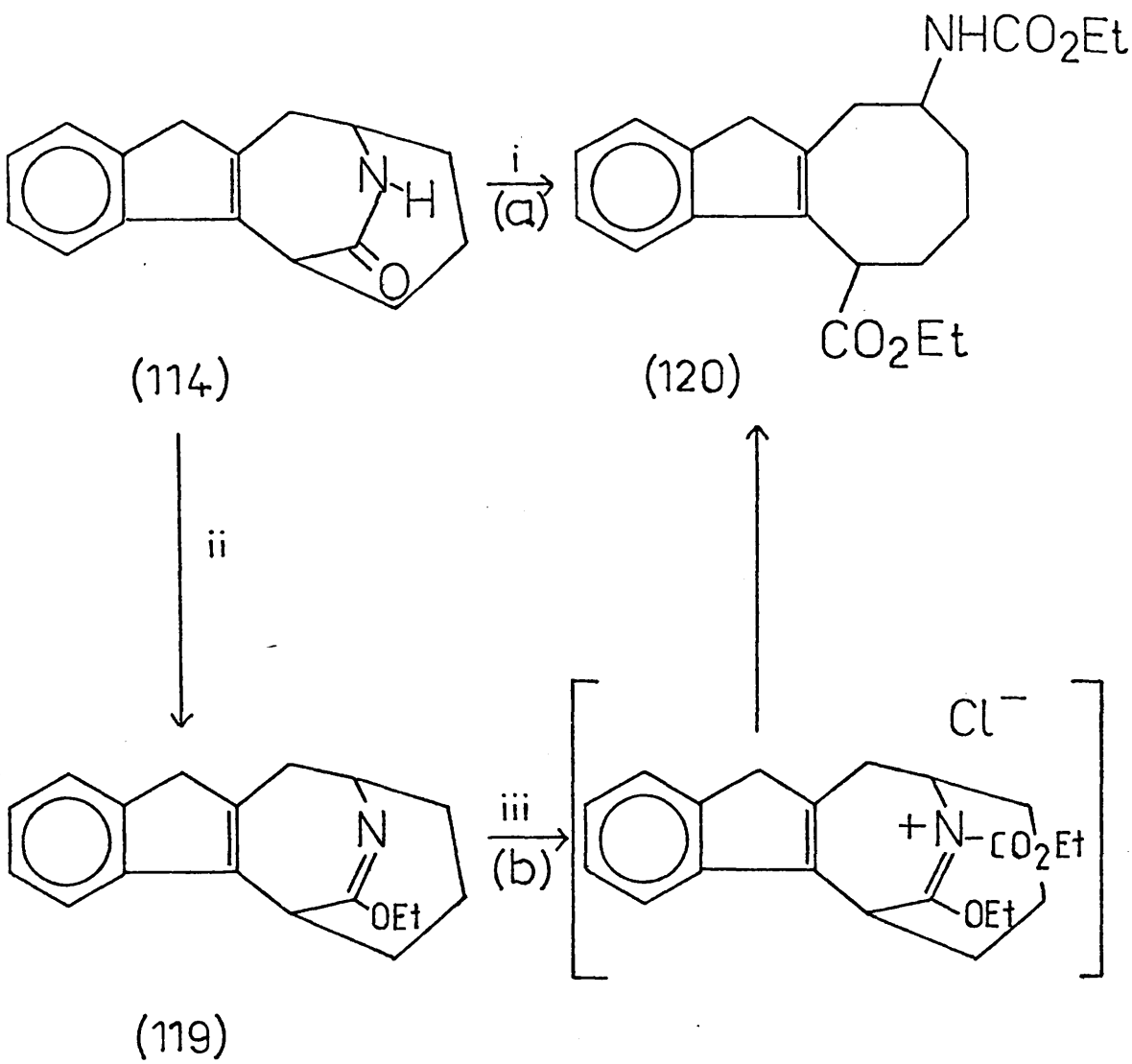


Scheme 38

REAGENTS: i) NaH, $CO(OEt)_2$

ii) $Et_3O^+BF_4^-$ (Meerwein's reagent)

iii) $ClCO_2Et$



Scheme 39

REAGENTS: i) NaH, $CO(OEt)_2$

ii) $Et_3O^+BF_4^-$ (Meerwein's reagent)

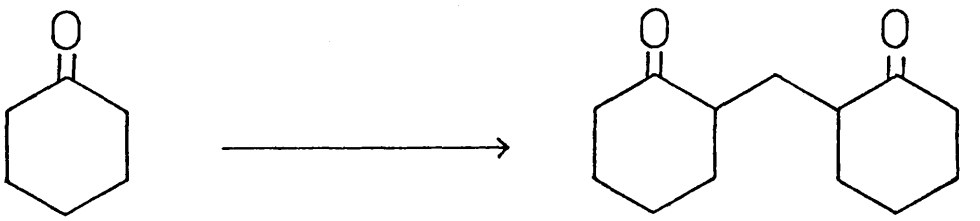
iii) $ClCO_2Et$

preparations of the lactams.

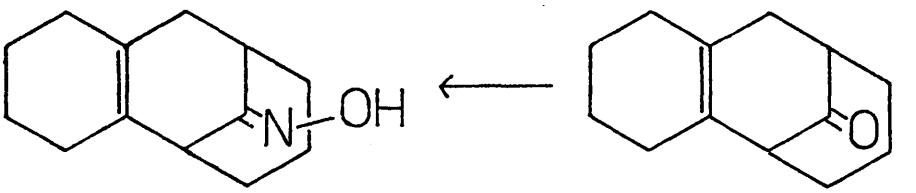
Having obtained lactam (110), a method of opening the -NH-CO- bridge to give the tricyclic compound (111) was required and there appeared to be several possible ways of doing this. The first method to be tried involved the use of PCl_5/pyridine/methanol[91] and was attempted initially using the lactam (114) (scheme 37) which had been prepared and was now of no further use in the synthetic approach to the macrocycle. This reaction failed to produce any identifiable product and it was decided that it would be prudent to investigate the various possible methods of cleaving the lactam bridge using a model compound such as caprolactam, which is readily available. It is notable that the attempt to prepare the amino-ester (116) from caprolactam using the PCl_5/pyridine/methanol[91] route failed.

The cleavage of the carbon-nitrogen bond in caprolactam has been accomplished by way of two methods which are in the literature[92] (see Scheme 38). Using the published procedures, it was possible to prepare the urethane-ester (118) by both routes (a) and (b) shown. An attempt to prepare urethane-ester (120) from lactam (114) was made using both routes (a) and (b) shown in scheme 39 but in both cases only starting material was recovered after work-up of the reactions.

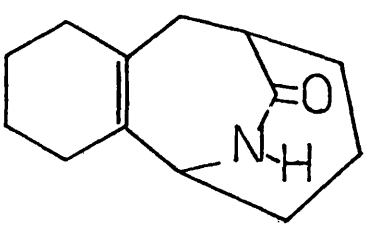
At this point it was decided that the cleavage of the lactam bridge of (110) and subsequent experimentation that no doubt would be needed to convert this product into an α,β -unsaturated ketone would probably require more material than could conveniently be made available. A suitable, readily available analogue was sought, therefore, on which to perform all of the initial experiments until a successful route through to the α,β -unsaturated ketone could be found. The successful reactions would then be applied to



(121)

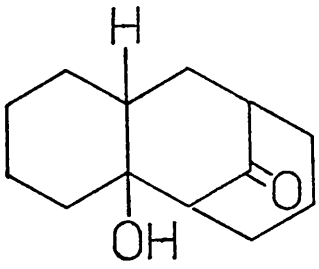


(123) (122)

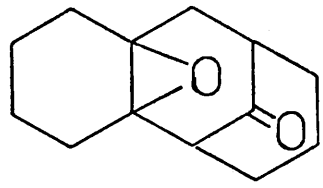


(124)

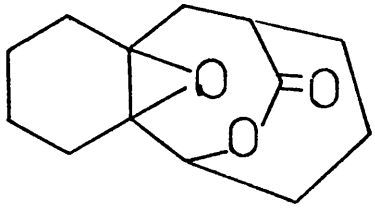
Scheme 40



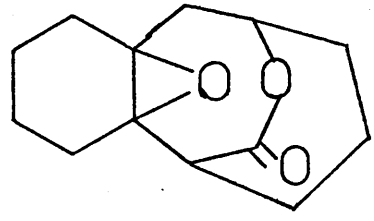
(125)



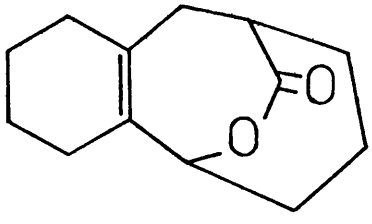
(126)



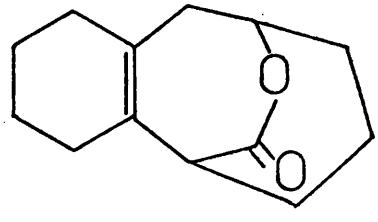
(127)



(128)



(129)



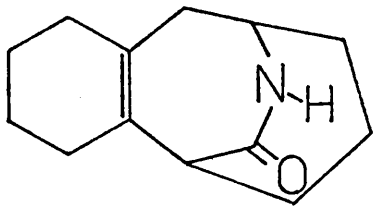
(130)

the lactam (110). The analogue chosen was compound (124) and it was proposed to prepare this molecule using the route shown in scheme 40. The ketone (122) was prepared as published[93] and furnished spectra and a derivative which identified it as (122). A little of compound (125) was also isolated from the reaction.

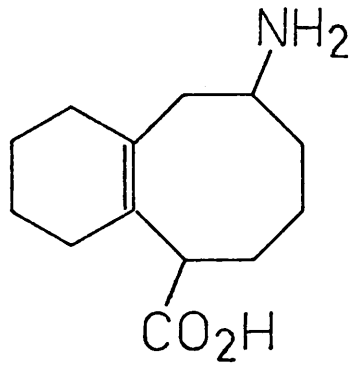
Before proceeding to the preparation of the oxime (123) it was decided to attempt the Baeyer-Villiger reaction using this compound (122). Under a variety of conditions, peracid oxidation led only to the epoxide (126) with no evidence for the formation of any epoxy-lactone (127) or (128). The mass spectrum of (126) had a parent ion at m/e 206 and the compound analysed for $C_{13}H_{18}O_2$. The i.r. spectrum showed absorptions at 1740 and 1725 $cm.^{-1}$ (C = O stretch), while the n.m.r. spectrum had an "envelope" at 1.2-2.8. As in the previous case,(p70), the absence of a 1H signal at ca. δ 5 or δ 6 excludes structure (129) or (130).

Refluxing (122) with base and hydroxylamine hydrochloride resulted in the formation of a product which differed from starting material on analytical t.l.c. However, in a variety of solvent systems, only one spot could be detected on the plate. The product showed a parent ion in the mass spectrum at m/e 205 and analysed for $C_{13}H_{19}N_1O_1$. The n.m.r. spectrum showed signals at δ 3.5 (1H ; m) and 2.8-1.0 (large envelope) while the i.r. spectrum had absorptions at 3610 (OH stretch), 3280, 1670 (C = N stretch) and 1580 $cm.^{-1}$ These data are consistent with structure (123) and apparently only one isomer is formed.

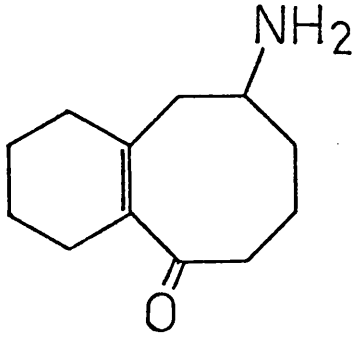
Treatment of the product from the above reaction with TsCl/ pyridine at room temperature produced a material which again was homogeneous on analytical t.l.c. but different from starting material. The product had a parent ion in the mass spectrum at



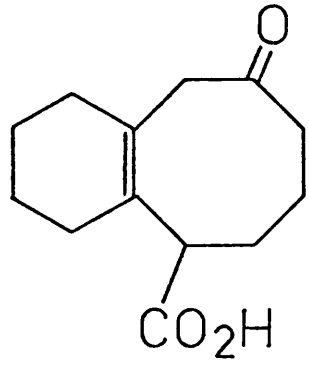
(132)



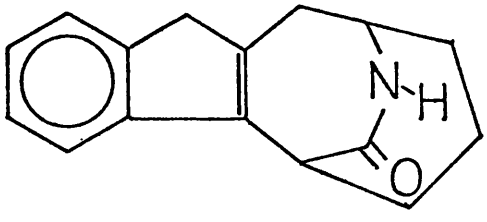
(133)



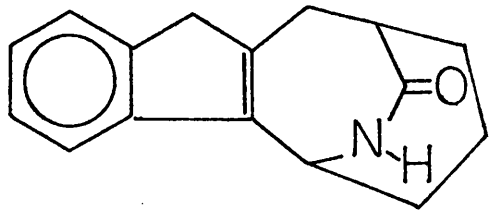
(134)



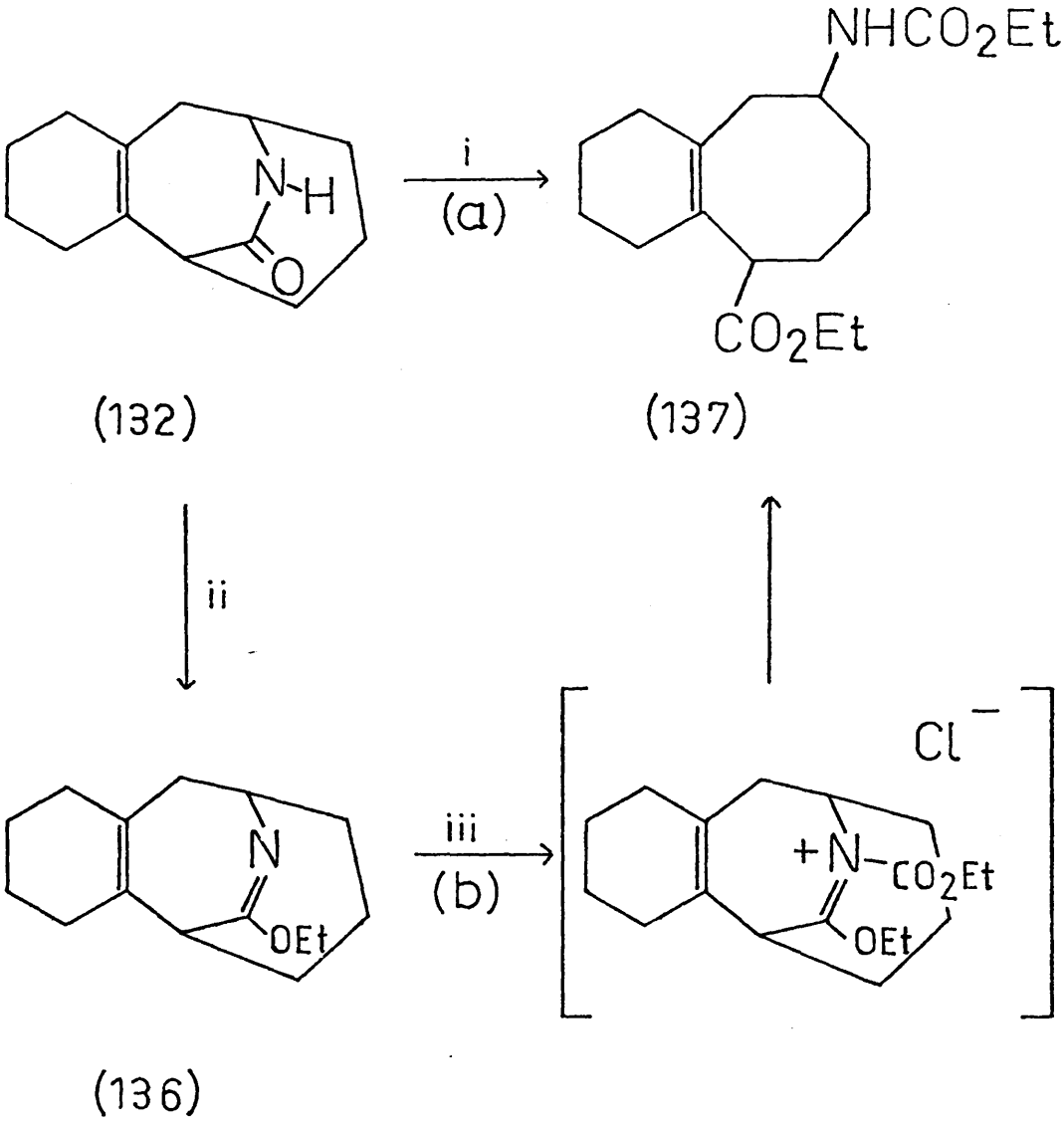
(135)



(114)



(110)



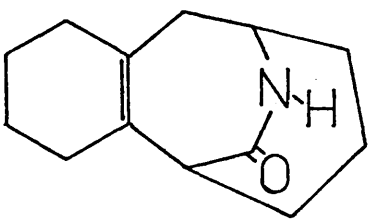
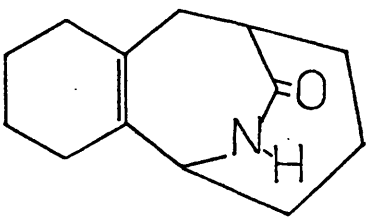
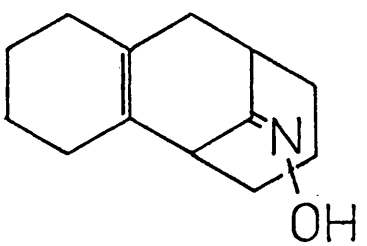
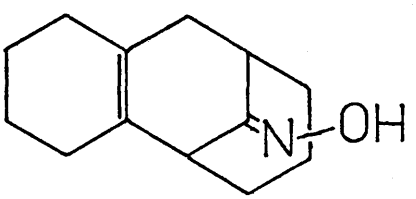
Scheme 41

REAGENTS : i) NaH , $CO(OEt)_2$

ii) $Et_3O^+BF_4^-$ (Meerwein's reagent)

iii) $ClCO_2Et$

Table 3

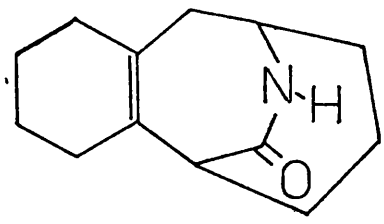
Lactam (I32) calculated		Lactam (I24) calculated		observed
NH-C-H	3.44	NH-C-H	4.29	3.0
CO-C-H	3.6I	CO-C-H	2.76	3.5
 (132)		 (124)		
 (131)		 (123)		

m/e 205 and analysed for $C_{13}H_{19}N_1O_1$. The i.r. spectrum showed absorptions at 3425, 3310 (NH stretch), 3210, 3100 and 1670 $cm.^{-1}$ ("amide I band"), while the n.m.r. spectrum had signals at δ 7.1 (1H ; s) assigned to the -N-H proton, 3.5 (1H ; m) and 3.0 (1H ; m). The ^{13}C n.m.r. spectrum showed the presence of only thirteen carbon resonances indicating that only one lactam had been produced in the reaction and confirming the suspicion that only one oxime had been formed from the ketone (122). Using ^{1}H n.m.r. in a manner similar to that used in the case of lactams (110) and (114) (see P.73), this lactam was identified as having the structure (132) (see Table 3). Assuming the normal trans-migration mechanism in the Beckmann rearrangement this means that only oxime (131) was produced from the ketone (122) with the complete absence of any (123).

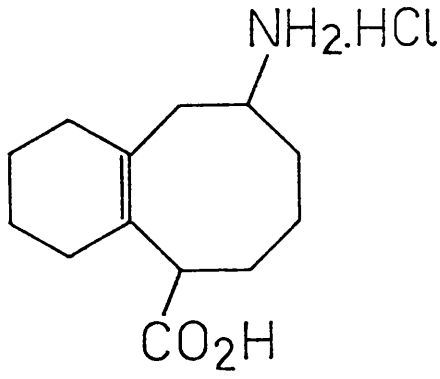
The aim had been to produce lactam (124) and use this compound as a model for lactam (110). Instead, the preparation had led to the isolation of the isomeric lactam (132). However, this compound is useful since either lactam (110) or (114) may be synthesised as required. The strategy to be followed now was to investigate the cleavage of the carbon-nitrogen bond of lactam (132) to give the amino-acid (133), or some derivative thereof. This compound could then be used to give either ketone (134) or ketone (135), after suitable manipulations on the carboxyl or amine functionalities respectively. Depending on the outcome of the above, either lactam (114) or (110) would be used for the rest of the synthesis.

The first attempts to open the lactam bridge of (132) were made using the two methods which had been successful in the case of caprolactam[92] (see Scheme 41). In both cases it was possible to isolate only unreacted starting material from the reactions.

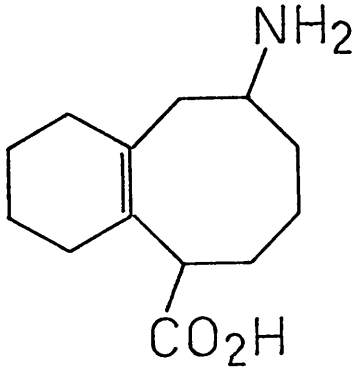
Cope[56] has successfully employed HCl to prepare amino-acid hydrochlorides from lactams. Using this method, lactam (132) was



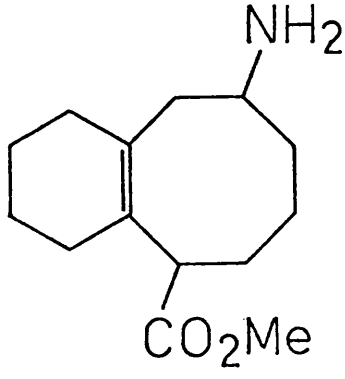
(132)



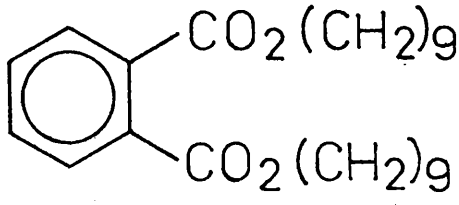
(138)



(133)



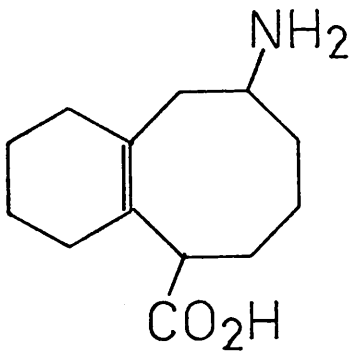
(139)



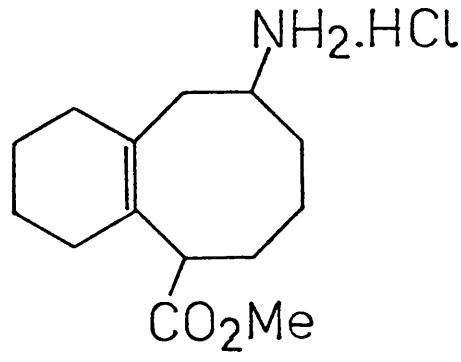
(140)

refluxed in a mixture of conc. HCl/water (2 : 3) for 24 hours. Careful neutralisation produced a turbidity in the solution but no precipitation and the free amino-acid had to be isolated using ion-exchange chromatography. After preparation of the column,[94] the aqueous solution of the amino-acid hydrochloride (138) was passed through the column and the neutral solution collected and evaporated to dryness. The high-melting solid showed a broad absorption at δ 0.8-4.2 in the n.m.r. spectrum (D_2O) while the i.r. spectrum (KBr disc) showed absorptions at 3400, 1650 and 1130 $cm.^{-1}$ This appears to identify the product as (133).

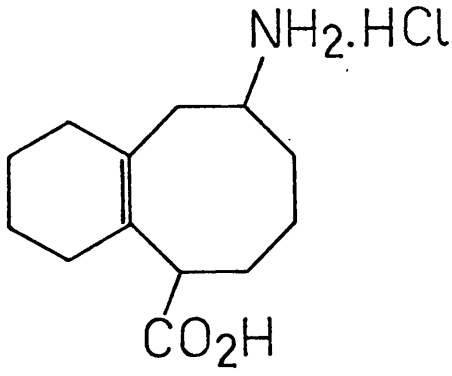
It was decided to attempt to make a suitable derivative of (133) to identify the product and the most obvious derivative to prepare was the amino-ester (139). After hydrolysis of the lactam (132) with HCl/H_2O, diazomethane was bubbled into the reaction mixture. It was expected that the HCl present would react first with the CH_2N_2 after which the amino-ester (139) would be produced. After extraction into chloroform, analytical t.l.c. showed the presence of one main spot and three other minor spots. Preparative t.l.c. on silica with 10% methanol/chloroform as eluant allowed isolation of the main product as a clear viscous oil, and the i.r. spectrum showed an absorption at 1730 $cm.^{-1}$ However, comparison with an authentic specimen of (140) proved that the compound isolated was in fact a plastisciser (dinonyl phthalate) which must have been leached out from the plastic tubing used in the experiment. Dispensing with the plastic tubing and using instead a long glass tube, the experiment was repeated. This time, after extraction of the crude product into chloroform, analytical t.l.c. showed one main spot and several other minor spots. Isolation of the major product gave an oil which showed absorptions at 1730 and 1670 $cm.^{-1}$ in the i.r. The n.m.r. spectrum



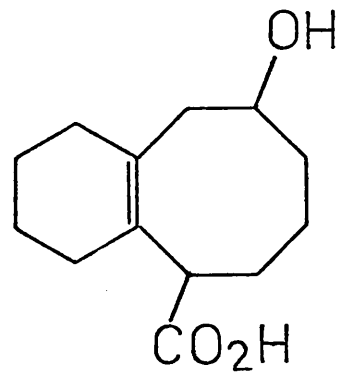
(133)



(141)



(138)

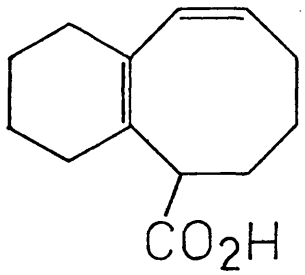


(142)

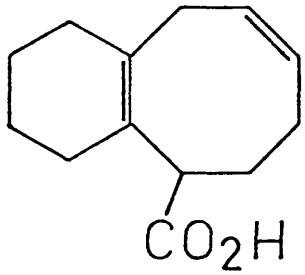
was not informative, having little fine structure. After a day or two, the sample was again examined spectroscopically and gave i.r. and n.m.r. spectra identical to that obtained for the lactam (132).

The use of methanol and thionyl chloride is recommended[95] for the esterification of amino-acids so the free amino-acid (133) was treated with such a mixture at 0°C. The temperature was then raised to 40°C and this temperature maintained for 2 hours. This should have produced the amino-ester hydrochloride (141). Careful neutralisation with sodium bicarbonate yielded a product which could be extracted into chloroform. The n.m.r. spectrum was very broad showing a large "envelope" at δ 0.8-3.0 and a signal at δ 8.4. The i.r. spectrum showed an absorption at 1730 $cm.^{-1}$ but also a broad absorption at 3500-2500 $cm.^{-1}$ The material could not be purified by chromatography and consequently better spectra could not be obtained and no structure can be assigned to this reaction product.

It was now decided to concentrate on the amine function. Attempts to diazotise the amino-acid hydrochloride (138) using $NaNO_2$/HCl at low temperature in an attempt to prepare the hydroxy-acid (142) resulted in the formation of many different products as indicated by analytical t.l.c. However, preparative t.l.c. led to the isolation of a colourless oil which was extracted into chloroform. It was possible to take up this material dilute sodium hydroxide and re-precipitate it by the addition of dilute hydrochloric acid. The i.r. spectrum showed absorptions at 3600, 3500-2500, 1750, 1710 and 1650 $cm.^{-1}$ while the n.m.r. spectrum had signals at δ 1.0-3.0, 3.7 and 6.4. This latter signal disappeared on addition of a small amount of D_2O to the sample. There were no signals to lower field. The mass spectrum had a parent ion at m/e 206 with the presence of small signals higher than this, including one at m/e 224. The material

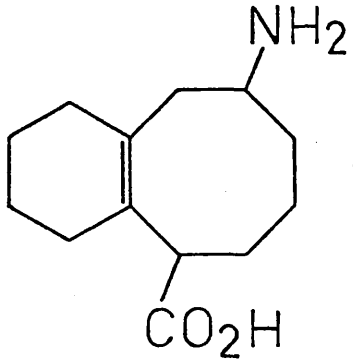


(143)

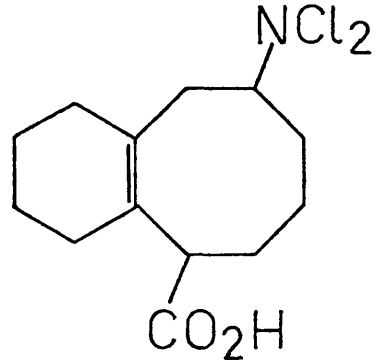


(144)

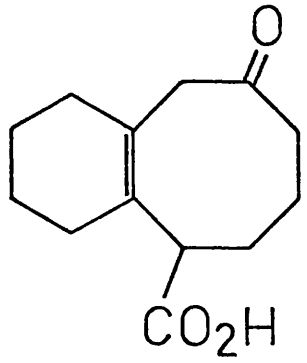
Scheme 42



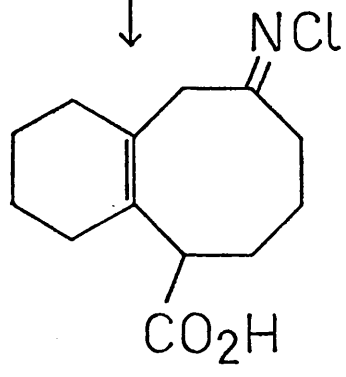
(133)



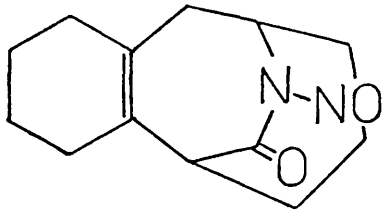
(145)



(147)

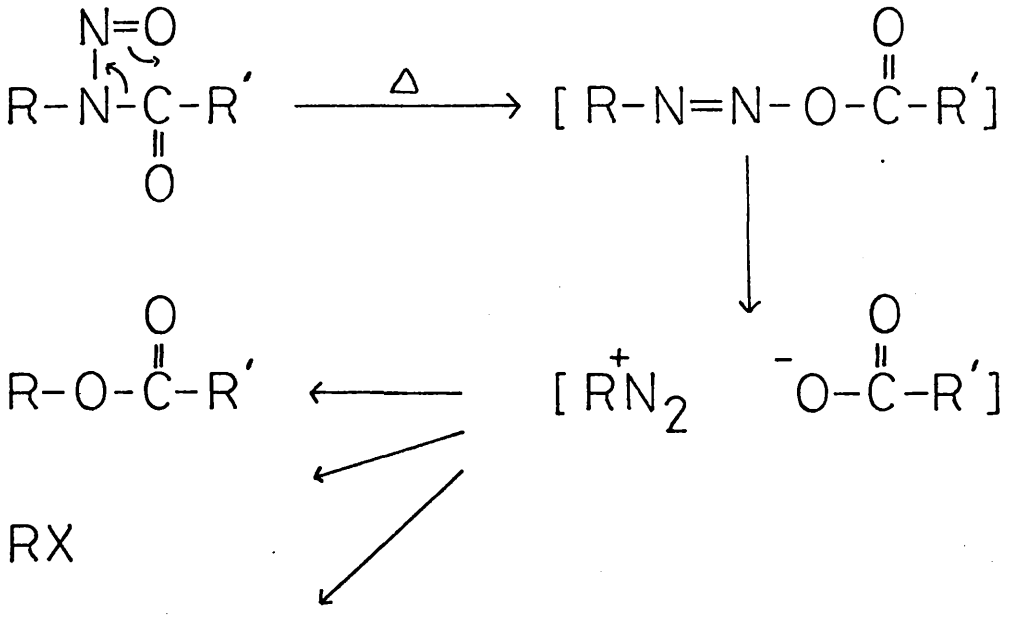


(146)



(148)

Scheme 43



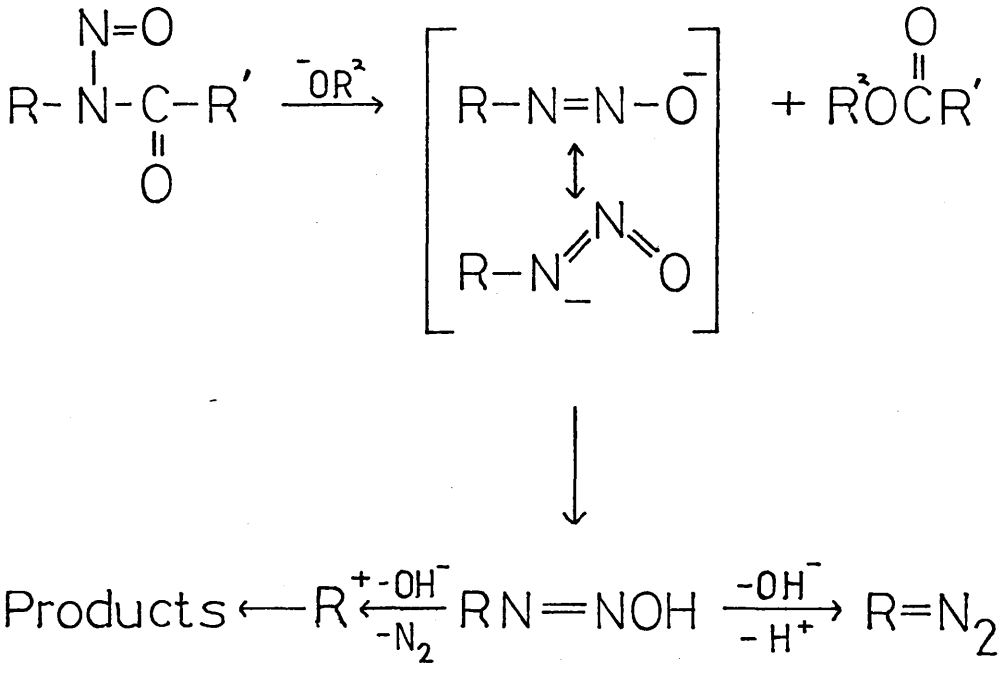
could not be purified sufficiently for a microanalysis to be obtained, and the spectra are confusing. Both structures (143) and (144) could fit the mass spectrum. The fact that the parent ion in the mass spectrum is even shows the lack of nitrogen in the compound. However the exchangeable proton at δ 6.4 is in an unusual position for a carboxylic -OH and is more suggestive of an alcoholic -OH group. Yet the material is soluble in base. Also, there are no olefinic protons visible in the n.m.r. spectrum. If the real parent ion in the mass spectrum is in fact at m/e 224, then the product could be the hydroxy-acid (142).

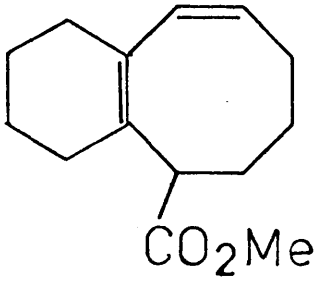
An attempt was made to prepare the keto-acid (147) directly from the amino-acid (133) (rather than *via* the hydroxy-acid (142)) by the *t*-butyl hypochlorite[96] route shown in scheme 42. The amino-acid (133) was added at 0°C to a solution of freshly prepared *t*-butyl hypochlorite[97] and then the mixture allowed to come to room temperature. However, after treatment with base followed by addition of water, it was not possible to isolate any identifiable product from this reaction.

It was noted that the lactam (132) would dissolve in boiling hydrochloric acid within *ca* 5 minutes. Upon adding $NaNO_2$ to the cooled solution a yellow precipitate was formed which could be extracted into ether. This material, as formed, was very pure and was identified as the N-nitrosolactam (148). It must be assumed that the lactam is reformed during the course of the reaction. The n.m.r. showed signals at δ 1.0-3.1 (16H ; m), 3.4 (1H ; m) and 5.3 (1H ; m) while the i.r. spectrum showed an absorption at 1730 $cm.^{-1}$ (C = O stretch) and 1520 $cm.^{-1}$ (N-NO stretch). The mass spectrum had a parent ion at m/e 234 and the compound gave an accurate mass measurement for $C_{13}H_{18}N_2O_2$.

Fragmentation of N-nitrosoamides[98] has been accomplished both by thermolysis and by treatment with base (see schemes 43 and 44). The

Scheme 44





(149)

N-nitrosolactam (148) was refluxed in benzene and then in xylene. In both cases it was recovered unchanged from the reaction solutions. Treatment of (148) with 30% methanolic KOH, however, did produce a product which was soluble in base. The n.m.r. showed signals at δ 1.2-2.8, 5.7 and a broad exchangeable signal at δ 8.0, while the i.r. spectrum had absorptions at 3540-2300, 1770, 1730 and 1700 $cm.^{-1}$ The mass spectrum had a parent ion at 206. This seems to be a mixture of olefin-acid and lactone.

Esterification with diazomethane yielded, after preparative t.l.c. a colourless oil which showed an absorption at 1730 $cm.^{-1}$ in the i.r. and signals at δ 1.0-2.6 and 3.7 (3H ; s) in the n.m.r. At 90 MHz., however, this signal at δ 3.7 which had been assigned as the methyl protons of the methyl ester was shown to consist of at least four sharp signals. This suggests that the product obtained actually consists of a mixture of closely related compounds.

In conclusion, attempts to prepare a macrocycle *via* ring annulation-scission reactions have been frustrated at several stages in the proposed synthesis. There were unexpected difficulties encountered in the oxidation of (70) to the vinylogous β-diketone (75) and later on, in performing a Baeyer-Villiger oxidation of (70). Having obtained the lactams, attempts to cleave the carbon-nitrogen linkage were bedevilled by facile recyclisation reactions and molecular rearrangements. Much more work would be necessary to find a reliable route from the lactams to the macrocycle.

PART 2

EXPERIMENTAL

Indan-1-one (66)

The method of Pacaud and Allen[61] was used to prepare (66) in 62% yield ; m.p. 39-41°C (lit.[61] m.p. 39-41°C), i.r. ν_{max}^{CCl4} 1720, 1610 and 1590 $cm.^{-1}$

2-(N,N-dimethylaminomethyl-indan-1-one hydrochloride (67)[66]

Indan-1-one (66) (50 g., 0.38 mole), paraformaldehyde (25 g., 0.83 mole) and dimethylamine hydrochloride (38 g., 0.46 mole) in absolute ethanol (250 ml.) and concentrated hydrochloric acid (6 ml.) were refluxed for 2 hours, cooled and poured into AnalaR acetone (1 litre). The solution was cooled overnight, and the amorphous white solid collected. The mother liquor was concentrated and poured into acetone to yield further white solid. The total yield of crude product was 95 g. and this was recrystallised from absolute ethanol/ acetone (1 : 4) to yield 2-(N,N-dimethyl-aminomethyl)-indan-1-one hydrochloride (67) (56.5 g., 0.25 mole, 66%), m.p. 145-148°C ; i.r. $\nu_{max.}^{KBr}$ 3680-3100, 3020, 2980, 2960, 2780-2300, 1710, 1610 and 1585 $cm.^{-1}$; ^{1}H n.m.r. (D_2O) δ 3.1 (6H ; s) and 7.3-8.0. (4H ; m).

2-(N,N-dimethylaminomethyl)-indan-1-one (68)

The Mannich base hydrochloride (67) (9 g., 40 m.mole) was dissolved in a minimum amount of water (4 ml.) and 0.88 ammonia (1 ml.) was added. A white precipitate formed immediately. The mixture was saturated with sodium chloride and extracted[99] with ether. This yielded the crude Mannich base, 2-(N,N-dimethylaminomethyl)-indan-1-one (68) (6.1 g., 0.03 mole, 81%) which was used in the next step without further purification. i.r. $\nu_{max.}^{CCl4}$ 1715 and 1210 $cm.^{-1}$; ^{1}H n.m.r. δ 2.3 (6H ; s) and 7.2-8.0 (4H ; m).

2-(2'-oxocyclohexyl methyl)-indan-1-one (69)

The indanone Mannich base (68) (6 g., 0.031 mole) and cyclohexanone (8.82 g., 0.09 mole) were refluxed together for 2 hours. Water (50 ml.) was then added, and the mixture neutralised by the addition of glacial acetic acid. The aqueous mixture was extracted[99] with ether and the excess cyclohexanone distilled off at reduced pressure. Fractionation of the residue gave the expected product, 2-(2'-oxocyclohexyl methyl)-indan-1-one (69) (5.4 g., 0.022 mole, 70%) as a clear yellow oil, b.p. 208-212°C/0.5 mm. ; i.r. ν_{max}^{CCl4} 1715 and 1610 $cm.^{-1}$; ^1H n.m.r. δ 1.0-3.7 (14H ; e) and 7.1-7.8 (4H ; m) ; m.s. m/e 242 (M^+), 145, 144, 131, 130, 129, 115, 103, 98, 91, 77, 67 and 55. Found : C,79.43 ; H,7.37. $C_{16}H_{18}O_2$ requires C,79.31 ; H,7.49%.

6,7,8,9-Tetrahydro-11H-indeno-[1,2-b]-quinoline (73)

A solution of the diketone (69) (100 mg) and ammonium acetate (100 mg) in glacial acetic acid (2 ml.) was refluxed for 30 minutes. The mixture was diluted with water and extracted[99] with ether. The ether extract was washed with base. The yield of the pyridine derivative (73) was (82 mg., 0.37 m. mole, 90%), m.p. 105-106°C ; i.r. ν_{max}^{CCl4} 1610 $cm.^{-1}$; ^1H n.m.r. δ 1.5-2.2 (4H ; m), 2.5-3.3 (4H ; m), 3.7 (2H ; s), 7.2-7.6 (4H ; m) and 7.9-8.2 (1H ; m) ; m.s. m/e 221 (M^+), 193, 165, 152, 102, 77 and 63. Found : C,86.87 ; H,6.78 ; N,6.33. $C_{16}H_{15}N_1$ requires C,86.84 ; H,6.83 ; N,6.33%.

2,4-propano-1,2,3,4-tetrahydrofluoren-3-one (70)[68]

2-(2'-oxocyclohexyl methyl)-indan-1-one (69) (4 g., 0.017 mole) and Amberlite IR-120 (H) resin[69, 70] (140 g.) in water (500 ml.) were refluxed, with rapid stirring to prevent bumping, for 90 hours. The resin was filtered off while hot, washed with hot water (250 ml.),

cooled and extracted[99] with ether. The aqueous phase was then extracted[99] with ether and the extracts combined. The crude product (4.2 g.) was chromatographed on silica (50 g.) using 30% ethyl acetate-light petroleum as eluant to yield a small amount of starting material (0.9 g.) and the cyclised (and *in situ* dehydrated) product, 2,4-propano-1,2,3,4-tetrahydro-fluoren-3-one (70) (2.7 g., 0.012 mole, 70.6%), m.p. 94.95°C ; i.r. $\nu_{max}^{CCl_4}$ 1730, 1720, 1630 and 1610 $cm.^{-1}$; ^1H n.m.r. δ 1.3-2.3 (6H ; e), 2.5-3.2 (3H ; m), 3.4 (2H ; s), 3.5 (1H ; m) and 7.0-7.5 (4 H ; m) ; ^{13}C n.m.r. 215.287 (s), 144.083 (s), 143.550 (s), 142.121 (s), 136.801 (s), 126.356 (d), 124.525 (d), 123.789 (d), 117.518 (d), 46.055 (d), 44.881 (d), 39.601 (t), 36.584 (t), 35.092 (t), 32.167 (t) and 17.671 (t) p.p.m. ; m.s. m/e 224 (M^+), 196, 181, 167, 165, 156, 153, 152, 128 and 115. Found : C,85.91 ; H,7.39 $C_{16}H_{16}O_1$ requires C,85.68 ; H,7.19%.

Attempted oxidation of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one (70)

a) with sodium dichromate dihydrate

The ketone (70) (224 mg, 1 m. mole) in glacial acetic acid (25 ml.) was added to a stirred solution of sodium dichromate dihydrate (590 mg., 2 m. mole) in glacial acetic acid (10 ml.) and heated at 60°C for 3 hours. The reaction was stopped by the addition of water (100 ml.), the mixture extracted[99] with ether and the combined extracts washed with base. Purification of the crude product (200 mg.) by preparative t.l.c. on silica with 50% ethyl acetate-light petroleum as eluant yielded starting material (40 mg.) and two other products, neither of which was the desired diketone (75) or (76).

b) with selenium dioxide in acetic acid

The ketone (70) (224 mg., 1 m. mole) in glacial acetic acid (25 ml.) was added to a refluxing solution of freshly sublimed selenium dioxide (220 mg., 2 m. mole) in glacial acetic acid (10 ml.) and the mixture refluxed for 30 minutes. The reaction mixture was flooded with water

(100 ml.) and extracted[99] with ether. The combined extracts were washed with base. The crude product (230 mg.) was purified by preparative t.l.c. on silica, with 50% ethyl acetate-light petroleum as eluant, to yield three products, all of which were light yellow oils. None of these products was the diketone (75) or (76) and they were not investigated further.

2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (77)

The ketone (70) (300 mg., 1.3 m. mole), ethylene glycol (90 mg., 1.43 m. mole) and toluene-p-sulphonic acid (20 mg.) were refluxed overnight in benzene (250 ml.) with a Dean and Stark water separator. The reaction mixture was cooled and the benzene removed. The crude material was extracted[99] into ether and washed with base. Purification of the crude product (420 mg.) on a column of silica (10 g.) using 10% ethyl acetate-light petroleum as eluant gave the pure product, 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (77) (326 mg., 1.2 m. mole, 91%) as a colourless oil. i.r. $\nu_{max}^{CCl_4}$ 1635 and 1605 $cm.^{-1}$ (no C = O band) ; ^1H n.m.r. δ 3.2 (2H ; s), 3.8 (4H ; m) and 6.8-7.5 (4H ; m) ; m.s. m/e 268 (M^+), 239, 167, 165, 153, 152, 141, 128, 115 and 99. Accurate mass measurement gave the mass as 268.1575 ; $C_{18}H_{20}O_2$ requires an accurate mass of 268.1582.

Attempted oxidation of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (77)

a) with sodium dichromate dihydrate

To sodium dichromate dihydrate (650 mg., 2.2 m. mole) in glacial acetic acid (20 ml.) was added the acetal (77) (300 mg., 1.1 m. mole) in glacial acetic acid (20 ml.) and the mixture refluxed for 2 hours. Water (50 ml.) was added to the cooled reaction mixture and the aqueous mixture extracted[99] with ether. The combined extracts were washed with

base. The crude product (350 mg.) was purified by t.l.c. using 30% ethyl acetate-light petroleum as eluant to give an orange oil (25 mg.) Spectroscopic analysis showed this to be neither (78) nor (79) and the product was not investigated further.

b) with selenium dioxide in acetic acid.

To freshly sublimed selenium dioxide (250 mg., 2.2 m. mole) in glacial acetic acid (20 ml.) was added the acetal (77) (300 mg., 1.1 m. mole) in glacial acetic acid (20 ml.) and the mixture refluxed for 4 hours. The cooled reaction mixture was poured into water (50 ml.) and extracted[99] with ether. The combined ether extracts were washed with base. The crude product (250 mg.) was purified by preparative t.l.c. on silica using 30% ethyl acetate-light petroleum as eluant. Two main products were isolated, but neither proved to be (78) nor (79).

Attempted preparation of the Mannich base hydrochloride (81) of o-acetyl benzoic acid (80)

o-Acetyl benzoic acid (80) (3.28 g., 0.02 mole), paraformaldehyde (1.2 g., 0.04 mole) and dimethylamine hydrochloride (2.1 g., 0.025 mole) were dissolved in absolute ethanol (50 ml.) and concentrated hydrochloric acid (1 ml.) was added. The mixture was refluxed for 2 hours, cooled and poured into AnalaR acetone (100 ml.) The solution was cooled overnight and the crystalline solid collected. This material was shown to be starting material (m.p., i.r. and n.m.r.)

Indan-1,3-dione (84)

The method of Shapiro, Geiger and Freedman[73] was used to prepare (84) from phthalide in 24% yield. m.p. 131-132°C (lit.[78] m.p. 131-132°C) ; i.r. $\nu_{max}^{CHCl_3}$ 1750, 1715, 1690, 1600 and 1570 $cm.^{-1}$; ^1H n.m.r. δ 3.2 (2H ; s) and 7.8-8.1 (4H ; m).

Attempted preparation of the Mannich base hydrochloride (85) of indan-1,3-dione (84)

The dione (84) (6 g., 0.04 mole), paraformaldehyde (2.5 g., 0.08 mole) and dimethylamine hydrochloride (4.1 g., 0.05 mole) were dissolved in absolute ethanol (100 ml.) and concentrated hydrochloric acid (2 ml.) was added. The mixture was refluxed for 2 hours, cooled and poured into AnalaR acetone (250 ml.). An amorphous solid was obtained, which was insoluble in most organic solvents and in water. It was therefore not the required product and was discarded.

2-(N,N-dimethylaminomethyl)-cyclohexanone hydrochloride (76)

This compound was prepared by the method of Mannich and Braun[76] in 80% yield. m.p. 155-157°C (lit.[76] m.p. 152°C) i.r. ν_{max}^{KBr} 2700-2280 and 1700 $cm.^{-1}$; ^1H n.m.r. (D_2O) δ 2.8 (3H ; s) and 2.9 (3H ; s)

2-(N,N-dimethylaminomethyl)-cyclohexanone (87)

The Mannich base hydrochloride (86) (6.8 g., 0.035 mole) was dissolved in a minimum amount of water (6 ml.) and 0.88 ammonia (1.5 ml.) was added. The mixture was saturated with sodium chloride and extracted[99] with ether. This furnished the crude Mannich base (87) (4.6 g., 0.030 mole, 86%) which was used in the next step without further purification. i.r. $\nu_{max}^{CCl_4}$ 1715 and 1210 $cm.^{-1}$; ^1H n.m.r. δ 2.2 (6H ; s).

Attempted preparation of 2-(2'-oxocyclohexyl methyl)-indan-1,3-dione (88)

The cyclohexanone Mannich base (87) (4.5 g., 0.029 mole) and indan-1,3-dione (84) (2.5 g., 0.017 mole) were refluxed together for 2 hours. Water (20 ml.) was added, and the mixture neutralised with glacial acetic acid. The aqueous mixture was extracted[99] with ether

and a solid product obtained which was identified as one of the starting materials, indan-1,3-dione (84) (2.1 g.)

2-Allylcyclohexanone[77] (89)

To a solution of the pyrrolidine enamine of cyclohexanone[77] (15.7 g., 0.095 mole) in acetonitrile (250 ml.) was added dropwise allyl bromide (14.5 g., 0.11 mole). After the addition was complete, the solution was refluxed overnight under an atmosphere of nitrogen. Most of the acetonitrile was removed and the residue diluted with water (50 ml.) and heated on a steam bath for 30 minutes. The resulting solution was cooled and extracted[99] with ether. Distillation under reduced pressure gave the expected product, 2-allylcyclohexanone (89) as a colourless oil, b.p. 46-52°C/0.8 mm. (lit[77] b.p. 94°C/16 mm.) ; i.r. ν_{max}^{CCl4} 1715 and 1640 $cm.^{-1}$; ^1H n.m.r. δ 4.8 (1H ; m), 5.05 (1H ; m) and 5.7 (1H ; m) ; m.s. m/e 138 (M^+), 109, 94, 79, 67, 54 and 41.

2-Allylcyclohexanone acetal (90)

The keto-olefin (89) (4.5 g., 0.032 mole), ethylene glycol (2.2 g., 0.035 mole) and toluene-p-sulphonic acid (25 mg.) were refluxed overnight in benzene (250 ml.) with a Dean and Stark water separator. The reaction mixture was cooled and the benzene removed. The crude material was extracted[99] into ether and washed with base. Purification of the crude product (4.2 g.) on a column of silica (50 g.) with 10% ethyl acetate-light petroleum as eluant gave the pure product, 2-allylcyclohexanone acetal (90) (4.1 g., 22 m. mole, 68%) as a colourless oil, b.p. 110-120°C/2-3 mm. ; i.r. ν_{max}^{CCl4} 1640 $cm.^{-1}$ (no C = O band) ; ^1H n.m.r. δ 3.95 (4H ; m), 4.9 (1H ; m), 5.1 (1H ; m) and 5.8 (1H ; m) ; m.s. m/e 182 (M^+), 139, 125, 99, 86 and 55. Accurate mass measurement gave the mass as I82.I3062 ; $C_{11}H_{18}O_2$ requires an accurate mass of I82.I30672 .

Preparation of the aldehyde (91)

Ozone was passed through a solution of 2-allyl-cyclohexanone acetal (90) (4 g., 0.022 mole) in methanol (25 ml.) at ca. -70°C (acetone/Drikold bath), until a dilute solution of bromine in acetic acid was no longer decolourised by the addition of a few millilitres of the reaction mixture. While still at -70°C, the system was flushed with nitrogen gas and dimethyl sulphide[100] (2 ml.) added. The solution was stirred at -10°C for 1 hour, then at ice bath temperature for 1 hour and finally at room temperature for 1 hour. The methanol was removed and the residue extracted[99] with ether to give the aldehyde (91) (2.8 g., 0.015 mole, 46%) as a colourless oil. i.r. ν_{max}^{CCl4} 1730 and 2720 $cm.^{-1}$; ^1H n.m.r. δ 3.9 (4H ; m) and 9.66 (1H ; m). The aldehyde (91) was used immediately.

Attempted preparation of 2-(2^1-oxocyclohexyl methyl)-indan-1,3-dione (88)

A mixture of the aldehyde (91) (1.9 g., 0.01 mole), phthalide (83) (1.34 g., 0.01 mole) and sodium ethoxide (0.55 g., 0.011 mole) in ethanol (40 ml.) was refluxed for 2 hours. Water (20 ml.) was added and the ethanol removed. The residue was diluted with ice water (50 ml.) and washed with ether (2 x 50 ml.). After acidification with dilute hydrochloric acid, the product could not be extracted into ether. However, it was extracted[99] into chloroform and subsequently shown to be predominantly one of the starting materials, phthalide (83).

Inden-1,3-dione (84)

This compound was prepared by the method of Gruen and Norcross[78]. Initially the sodio-compound, sodio-2-carbomethoxyindan-1,3-dione (92) was obtained (8.3 g., 80%) as yellow crystals, m.p. 307-310°C, i.r. ν_{max}^{KBr} 1725, 1705, 1690, 1665, 1630 and 1615 $cm.^{-1}$; ^1H n.m.r.

(D_2O) δ 1.4 (3H ; t ; J 7 Hz.), 4.3 (2H ; q ; J 7 Hz.) and 7.5 (4 H ; m).

On treatment with hydrochloric acid the dione (84) was obtained (4.23 g., 84%) and was identical (m.p., i.r., n.m.r.) to the product obtained earlier from phthalide. A small amount of a biproduct, biindone (96) was also obtained (420 mg., 0.09%), m.p. 208-211°C (lit.[101] m.p. 208-210) ; i.r. $\nu_{max}^{CHCl_3}$ 1725, 1690, 1680 and 1615 $cm.^{-1}$; ^1H n.m.r. δ 4.1 (2H ; s) and 7.7-8.1 (8H ; m) ; m.s. m/e 274 (M^+), 246, 222, 189, 177, 176, 151, 150, 121, 105, 104, 93, 71, 65 and 50.

2-Methyl indan-1,3-dione (98)

The method of Wislicenus and Kotzle[80] was used to prepare (98). Initially the sodio-compound, sodio-2-methyl indan-1,3-dione (97) was obtained as dark red crystals (5.6 g., 70%). Treatment with hydrochloric acid furnished the dione (98) (4.06 g., 83%), m.p. 84-85°C (lit.[80] m.p. 84-85°C) ; i.r. $\nu_{max}^{CCl_4}$ 1755, 1720 and 1600 $cm.^{-1}$; ^1H n.m.r. δ 1.4 (3H ; d ; J 7.5 Hz.) 3.1 (1H ; q ; J 7.5 Hz.) and 8.0 (4 H ; m).

Ethyl-3-(2-oxocyclohexyl)-propionate (93)

This compound was obtained by the published procedure[77] as a colourless oil (28.7 g., 72%), b.p. 125-130°C / 2 mm. (lit.[77] b.p. 98°C / 0.7 mm.) ; i.r. $\nu_{max}^{CCl_4}$ 1740 and 1720 $cm.^{-1}$; ^1H n.m.r. δ 1.2 (3H ; t ; J 7 Hz.) and 4.1 (2H ; q ; J 7 Hz.). m.s. m/e 198 (M^+), 153, 152, 125, 124, 98 and 55.

Ethyl-3-(2-oxocyclohexyl)-propionate acetal (94)

The keto-ester (93) (5.6 g., 0.028 mole), ethylene glycol (1.92 g., 0.031 mole) and toluene-p-sulphonic acid (25 mg.) were

refluxed overnight in benzene (50 ml.) with a Dean and Stark water separator. The reaction mixture was cooled and the benzene removed. The crude material was extracted[99] into ether and washed with base. Purification of the crude product (7.1 g.) on a column of silica (150 g.) with 20% ethyl acetate-light petroleum as eluant gave the pure product, ethyl-3-(2-oxocyclohexyl)-propionate acetal (94) (6.2 g., 0.026 mole, 91%) as a colourless oil, b.p. 126-128°C / 0.05 mm. ; i.r. ν_{max}^{CCl4} 1735 $cm.^{-1}$ (no ketone C = O band) ; ^{1}H n.m.r. δ 1.25 (3H ; t ; J 7 Hz.), 4.0 (4H ; m) and 4.15 (2H ; q ; J 7 Hz.) ; m.s. m/e 242 (M^+), 239, 237, 155, 113, 99, 86 and 55. Accurate mass measurement gave the mass as 242.15196 ; $C_{13}H_{22}O_4$ requires an accurate mass of 242.151799.

Attempted preparation of 2-(2'-oxocyclohexyl methyl)-indan-1,3-dione (88)

a) Dimethyl phthalate (8.75 g., 0.045 mole) was treated with 60% sodium hybride (5.4 g., 0.15 mole). While the mixture was being heated at 90-100°C (oil bath temperature), a slight excess of ethyl-3-(2-oxocyclohexyl)-propionate acetal (94) (12.1 g., 0.05 mole) was added. Hydrogen was evolved and within ca. 5 minutes a deep brown colour had developed. Heating was continued, but after approximately 30 minutes the reaction became very vigorous and had to be stopped. After cooling, the mixture was extracted[99] with ether. Examination of the ether fraction showed it to contain starting materials and a small amount of another product which was not identified. Evaporation of the aqueous fraction yielded a dark red amorphous solid which had a melting point in excess of 330°C. Addition of hydrochloric acid to an aqueous solution of this material caused no precipitation however, and ether extraction[99] of the acidified aqueous phase yielded only a trace

of material which was not the required product (i.r., ^{1}H n.m.r.).

b) The reaction was repeated on the same scale. This time the mixture did not become excessively vigorous as in the previous case and heating was continued for 4 hours. After cooling, the orange mixture was triturated with ether and a fine dark orange solid was obtained (5 g.). This material was dissolved in water but acidification followed by ether extraction[99] yielded only a small amount of material which was not the desired product (i.r., ^{1}H n.m.r.).

Attempted Baeyer-Villiger oxidation of (70)

a) with mcpba/CHCl3

The ketone (70) (450 mg., 2 m. mole) and m-chloroperbenzoic acid (730 mg., 4.2 m. mole) were refluxed in chloroform for 3 hours. After cooling, the solution was washed with 10% sodium sulphite, sodium bicarbonate (saturated) and water, then dried over $MgSO_4$, filtered and evaporated. Preparative t.l.c. of the crude product (650 mg.) on silica using 30% ethyl acetate-light petroleum as eluant allowed isolation of the major component which was identified as the alcohol (104) (405 mg., 1.68 m. mole, 84%), m.p. 159-161°C ; i.r. ν_{max}^{CCl4} 3540 and 1730 cm.$^{-1}$; ^{1}H n.m.r. δ 1.1 (3H ; t ; J 7 Hz.), 3.0 (2H ; q ; J 7 Hz.), 3.8* (1H ; s) and 7.2-7.7 (4H ; m) ; m.s. m/e 286 (M^+), 240, 224, 212, 171, 143, 141, 129, 128 and 115. Found : C, 75.32 ; H, 7.86. $C_{18}H_{22}O_3$ requires C, 75.49 ; H, 7.74%.

b) with mcpba/CHCl3

The ketone (70) (450 mg., 2 m. mole) and m-chloroperbenzoic acid (730 mg., 4.2 m. mole) were refluxed in purified[82] chloroform for 3 hours. The work-up procedure was as detailed in a) and preparative t.l.c. of the crude product (380 mg.) gave the pure

material (340 mg., 1.41 m. mole, 71%) as crystals m.p. 116-117°C which was identified as the epoxide (105), i.r. ν_{max}^{CCl4} 1730 and 1610 $cm.^{-1}$; ^1H n.m.r. δ 3.6 (2H ; s) and 7.2 (4H ; m) ; m.s. m/e 240 (M^+), 224, 212, 196, 181, 171, 167, 155, 153, 141, 128 and 115. Found : C, 79.97 ; H, 6.97 . $C_{16}H_{16}O_2$ requires C, 79.97 ; H, 6.71%.

c) mcpba / CH_2Cl_2

The ketone (70) (450 mg., 2 m. mole) and m-chloroperbenzoic acid (730 mg., 4.2 m. mole) were refluxed in purified methylene chloride for 3 hours. The work-up procedure was as detailed in a) and preparative t.l.c. of the crude product (400 mg.) gave the pure product (380 mg., 1.6 m. mole, 80%) as crystals m.p. 116-117°C. This product was identified as the epoxide (105) by comparison (m.p., i.r., n.m.r.) with the product obtained from b).

Essentially the same result was obtained when the reaction was repeated using 3 and then 5 equivalents of the peracid.

d) mcpba / CH_2Cl-CH_2Cl / radical scavenger.[83]

The ketone (70) (450 mg., 2 m. mole), m-chloroperbenzoic acid (730 mg., 4.2 m. mole) and 2,2[1] thiobis (4 methyl 6 t-butyl phenol)[84] (10 mg.) were refluxed in ethylene dichloride for 3 hours. The work-up procedure was as detailed in a) and preparative t.l.c. of the crude material (410 mg.) yielded the pure product (400 mg., 1.67 m. mole, 83%) as crystals m.p. 116-117°C. This compound was identified as the epoxide (105) by comparison (m.p., i.r., n.m.r.) with product obtained from b).

2,4-Propano-1,2,3,4-tetrahydrofluoren-3-one oximes (109) and (113)

The ketone (70) (896 mg., 4 m. mole), a five-fold excess of sodium hydroxide (800 mg., 20 m. mole) and a 50% excess of hydroxylamine hydrochloride (420 mg., 6 m. mole) were refluxed for 2 hours in an ethanol-water mixture (100 ml., 5:1). After cooling, the ethanol was

removed and the mixture extracted[99] with chloroform. Preparative t.l.c. of the crude product (1120 mg.) on silica (30% ethyl acetate-light petroleum) allowed isolation of the two isomeric oximes (109) and (113).

Oxime 1 (113) (472 mg., 1.98 m. mole, 49.5%), m.p. 153-155°C ; i.r. $\nu_{max}^{CCl_4}$ 3615, 3560-2600, 1745, 1670, 1630 and 1605 $cm.^{-1}$; ^1H n.m.r. δ 1.2-2.1 (6H ; e), 2.5-3.0 (4H ; m), 3.2 (2H ; s) ; 4.6 (1H ; m) and 6.9-7.5 (4H ; m) ; ^{13}C n.m.r. 163.544 (s), 143.895 (s), 143-780 (s), 142.993 (s), 136.198 (s), 126.162 (d), 124.068 (d), 123.612 (d), 117.605 (d), 39.717 (t), 35.891 (t), 35.436 (d), 34.247 (t), 29.412 (t), 28.997 (d) and 18.162 (t) p.p.m. ; m.s. m/e 239 (M^+), 222, 194, 180, 179, 165, 153, 152, 141, 129, 128 and 115. Found : C, 80.20 ; H, 6.93 ; N, 5.72. $C_{16}H_{17}N_1O_1$ requires C, 80.30 ; H, 7.16 ; N, 5.85%.

Oxime 2 (109) (276 mg., 1.15 m. mole, 28.75%), m.p. 54-56°C ; i.r. $\nu_{max}^{CCl_4}$ 3615, 3550-2500, 1740, 1720, 1670, 1630 and 1615 $cm.^{-1}$; ^1H n.m.r. δ 1.1-2.1 (6H ; e), 2.2-3.0 (3H ; m), 3.2 (2H ; s), 3.8 (1H ; m), 3.9 (1H ; m) and 6.9-7.6 (4H ; m) ; ^{13}C n.m.r. 163.894 (s), [2x] 143.710 (s), 142.592 (s), 137.462 (s), 126.184 (d), 124.085 (d), 123.642 (d), 117.489 (d), 39.697 (t), 36.306 (d), 34.228 (t), 33.355 (t), 30.907 (t), 27.993 (d) and 18.092 (t) p.p.m. ; m.s. m/e 239 (M^+), 222, 194, 180, 179, 165, 153, 152, 141, 129, 128 and 115. Found : C, 80.33 ; H, 7.11 ; N, 5.86. $C_{16}H_{17}N_1O_1$ requires C, 80.30 ; H, 7.16 ; N, 5.85%.

Beckmann rearrangement of oxime 1 (113)

Oxime 1 (113) (149 mg., 0.62 m. mole) and toluene-p-sulphonyl chloride (155 mg., 0.8 m. mole) in pyridine (8 ml.) were stirred overnight at room temperature. Water (10 ml.) was added and after neutralisation with dilute hydrochloric acid, the crude product was

extracted[99] into chloroform. Preparative t.l.c. on silica (ethyl acetate) of the crude product (180 mg.) gave the pure lactam (114) (130 mg., 0.54 m. mole, 87%), m.p. 262-264°C ; i.r. ν_{max}^{KBr} 3300, 3210, 1660 and 1605 $cm.^{-1}$; ^{1}H n.m.r. δ 1.4-2.2 (6H ; e), 2.2-3.1 (2H ; m), 3.3 (2H ; s), 3.7 (1H ; m), 4.0 (1H ; m) and 7.0-7.5 (5H ; m) ; ^{13}C n.m.r. 179.105, 145.366, 143.176, 142.190, 130.671, 126.399, 124.354, 123.422, 117.680, 47.630, 44.902, 42.350, 35.466, 34.178, 26.022 and 21.646 p.p.m. ; m.s. m/e 239 (M^+), 168, 167, 153, 128, 115 and 56. Found : C, 80.58 ; H, 7.06 ; N, 5.73. $C_{16}H_{17}N_1O_1$ requires C, 80.30 ; H, 7.16 ; N, 5.85%.

Beckmann rearrangement of oxime 2(109)

Oxime 2 (109) (119 mg., 0.50 m. mole) and toluene-p-sulphonyl chloride (115 mg., 0.6 m. mole) in pyridine (8 ml.) were stirred overnight at room temperature. The work-up procedure was as detailed above, and preparative t.l.c. of the crude product (150 mg.) gave the pure lactam (110) (110 mg., 0.46 m. mole, 92%), m.p. 254-256°C ; i.r. ν_{max}^{KBr} 3300, 3205 and 1660 $cm.^{-1}$; ^{1}H n.m.r. δ 1.5-2.2 (6H ; e), 2.2-3.2 (3H ; m), 3.3 (2H ; s), 4.4 (1H ; m) and 6.9-7.6 (5H ; m) ; ^{13}C n.m.r. 179.791, 144.255, 143.854, 141.870, 135.586, 126.315, 124.332, 123.583, 117.078, 46.867, 44.399, 42.068, 31,477, 29.921, 29.283 and 21.503 p.p.m. ; m.s. m/e 239 (M^+), 168, 167, 153, 128, 115 and 56. Found : C, 80.15 ; H, 6.88 ; N, 5.67. $C_{16}H_{17}N_1O_1$ requires C, 80.30 ; H, 7.16 ; N, 5.85%.

Beckmann rearrangement with PPA

a) At 80°C

Oxime 1 (113) (100 mg., 0.42 m. mole) and polyphosphoric acid (technical grade) (1.5 g.) were stirred at 80°C for 30 minutes. After

cooling, addition of ice-water (50 ml.) precipitated the crude product (75 mg.) which was purified by preparative t.l.c. on silica, with ethyl acetate as eluant, to yield a product (84 mg.) which was identified as a mixture of lactams (110) and (114) (^{1}H n.m.r.).

Oxime 2 (109) (100 mg., 0.42 m. mole) was similarly converted to a mixture of lactams (110) and (114) (76 mg.) by this method.

b) At room temperature

Oxime 1 (113) (100 mg., 0.42 m. mole) and polyphosphoric acid (technical grade) (1.5 g.) were left at room temperature overnight. After addition of ice-water (50 ml.), the precipitated crude product (91 mg.) was purified by preparative t.l.c. (ethyl acetate) to yield the lactam (114) (85 mg., 0.36 m.mole, 85%) by comparison with the product from the TsCl/Pyridine reaction.

Oxime 2 (109) (100 mg., 0.42 m. mole) was similarly converted to lactam (110) (81 mg., 0.34 m. mole, 81%) by this method.

Beckmann rearrangement with P_2O_5 / $MeSO_3H$[90]

a) At 110°C

Oxime 1 (113) (100 mg., 0.42 m. mole) and freshly prepared phosphorous pentoxide/methanesulphonic acid (1 : 10) (1.5 g.) were heated at 110°C for 1 hour. After quenching with saturated sodium bicarbonate, the precipitated crude product (76 mg.) was extracted[99] into chloroform and purified by preparative t.l.c. (ethyl acetate) to yield a product (80 mg.) which was identified as a mixture of lactams (110) and (114) (^{1}H n.m.r.).

Oxime 2 (109) (100 mg., 0.42 m. mole) was similarly converted to a mixture of lactams (110) and (114) (84 mg.) by this method.

b) At room temperature

Oxime 1 (113) (100 mg., 0.42 m. mole) and freshly prepared

phosphorous pentoxide/methanesulphonic acid (1 : 10) (1.5 g.) were left at room temperature overnight. After quenching with saturated sodium bicarbonate, the precipitated crude product (90 mg.) was extracted[99] into chloroform and purified by preparative t.l.c. to yield the lactam (114) (34 mg. 0.35 m. mole, 34%) by comparison with the product from the TsCl/pyridine reaction.

Oxime 2 (109) (100 mg., 0.42 m. mole) was similarly converted to lactam (110) (75 mg., 0.31 m. mole, 75%) by this method.

Attempted preparation of amino-ester (115)

The lactam (114) (120 mg., 0.5 m. mole), phosphorous pentachloride (156 mg., 0.75 m. mole) and pyridine (60 mg., 0.75 m. mole) were stirred in benzene (15 ml.) at 60°C for 2 hours. Methanol (30 ml.) was added and the mixture stirred for a further 24 hours at room temperature. Water was added and then the mixture evaporated to dryness. The residue was extracted[99] into ethyl acetate whereupon analytical t.l.c. showed the presence of several products. Two of these products were investigated but shown by ^{1}H n.m.r. not to be the required product.

Attempted preparation of amino-ester (116)

ε-Caprolactam (4 g., 0.035 mole) was treated as detailed above. After work-up of the reaction mixture, analytical t.l.c. showed the presence of many products and these were not investigated.

Ethyl 6-ethoxycarbonylaminohexanoate (118)

a) NaH/CO(OEt)2

The urethane-ester (118) was prepared according to the published procedure[92] in 35% yield. i.r. ν_{max}^{CCl4} 3350, 1725 (b) $cm.^{-1}$; m.s. m/e 231 (M^+), 186, 158, 140, 128, 112, 102, 88, 69 and 56.

b) Meerwein's reagent[101]/$ClCO_2Et$

After preparation of the imino-ether (117), the urethane-ester (118) was prepared according to the literature procedure[92] and identified by comparison with the product obtained from a).

Attempted preparation of urethane-ester (120)

a) $NaH/CO(OEt)_2$

Lactam (114) (150 mg., 0.62 m. mole) in benzene (25 ml.) was stirred with an excess of sodium hydride (24 mg., 1 m. mole) at room temperature for 3 hours. Diethyl carbonate (0.2 ml.) was then added. After 3 hours at room temperature, the reaction was stopped whereupon analytical t.l.c. showed the presence of starting material together with several other products. These products were not investigated.

b) Meerwein's reagent[101]/$ClCO_2Et$

After conversion of the lactam (114) (200 mg., 0.83 m. mole) to the imino-ether (119), the mixture was treated with ethyl chloroformate (0.3 ml.). After 3 hours at room temperature, analytical t.l.c. showed the presence of many products, including starting lactam (114), and these other products were not investigated.

Tricyclo (7,3,1,$0^{2,7}$) tridec-2^{7}-en-1^{3}-one (122)

This compound was prepared by the method of Julia and Varech[93]. The product was obtained in 72% yield, b.p. 162-172°C/12 mm. (lit.[93] b.p. 87°C/0.1 mm.); ν_{max}^{CCl4} 1740 (sh) and 1720 $cm.^{-1}$; m.s. m/e 190 (M^+), 162, 149, 148, 147, 133, 119, 115, 105, 91, 79 and 77. A semicarbazone derivative was prepared : m.p. 188-189°C (lit.[93b] m.p. 196°C).

A small amount of the cyclised, but undehydrated, product (125) was also obtained, m.p. 172-173°C ; ν_{max}^{CCl4} 3600, 3560-3220 and 1710 $cm.^{-1}$;

^{1}H n.m.r. δ 1.0-2.7 (including one exchangeable proton) ; m.s. m/e 208 (M^+), 111, 110, 98, 83, 72, 70, 67 and 55. Found : C, 75.26 ; H, 9.53. $C_{13}H_{20}O_2$ requires C, 74.96 ; H, 9.68%.

Attempted Breyer-Villiger oxidation of (122)

The ketone (122) (190 mg., 1 m. mole), m-chloroperbenzoic acid (365 mg., 2.1 m. mole) and 2,2' thiobis (4 methyl 6 t-butyl phenol)[84] (10 mg.) were refluxed in ethylene dichloride for 3 hours. After cooling, the solution was washed with 10% sodium sulphite, sodium bicarbonate (saturated) and water, then dried over $MgSO_4$, filtered and evaporated. Preparative t.l.c. of the crude product (150 mg.) on silica with 30% ethyl acetate-light petroleum as eluant gave the pure product which was identified as the epoxide (126) (120 mg., 0.58 m. mole, 58%), m.p. 82-84°C ; i.r. ν_{max}^{CCl4} 1740 and 1725 (sh) cm.$^{-1}$; m.s. m/e 206 (M^+), 190, 188, 161, 150, 137, 133, 119, 98, 91, 79, 67 and 55. Found : C, 76.00 ; H, 8.52. $C_{13}H_{18}O_2$ requires C, 75.69 ; H, 8.80%.

Tricyclo (7,3,1,$0^{2,7}$) tridec-2^7-en-13-one oxime (123)

The ketone (122) (190 mg., 1 m. mole), a five-fold excess of sodium hydroxide (200 mg., 5 m. mole) and a 50% excess of hydroxylamine hydrochloride (105 mg., 1.5 m. mole) were refluxed for 2 hours in an ethanol-water mixture (25 ml., 5 : 1). After cooling, the ethanol was removed and the mixture extracted[99] with chloroform. Preparative t.l.c. of the crude product (160 mg.) on silica (30% ethyl acetate-light petroleum) yielded the pure oxime (123) (140 mg., 68 m. mole, 68%) as a gummy solid, i.r. ν_{max}^{CCl4} 3610, 3560-3020 (3280), 1670 and 1580 cm.$^{-1}$; ^{1}H n.m.r. δ 1.0-2.8 (18H ; e) and 3.5 (1H ; m) ; m.s. m/e 205 (M^+), 188, 160, 146, 131, 117, 115, 105, 91, 79, 77, 65 and 51. Found : C, 75.91 ; H, 9.00 ; N, 7.10. $C_{13}H_{19}N_1O_1$ requires C, 76.06 ; H, 9.33 ; N, 6.82%.

Beckmann rearrangement of oxime (123)

The oxime (123) (144 mg., 0.7 m. mole) and toluene-p-sulphonyl chloride (155 mg., 0.8 m. mole) in pyridine (8 ml.) were stirred overnight at room temperature. Water (15 ml.) was added and after neutralisation with dilute hydrochloric acid, the solution was extracted[99] with chloroform. Preparative t.l.c. of the crude product (115 mg.) on silica (ethyl acetate) furnished the pure lactam (132) (110 mg., 0.54 m. mole, 76%) as crystals m.p. 158-160°C ; i.r. ν_{max}^{CCl4} 3425, 3310, 3210 and 1670 $cm.^{-1}$; ^{1}H n.m.r. δ 1.2-2.8 (16H ; e), 3.0 (1H ; m), 3.5 (1H ; m) and 7.1 (1H ; s); m.s. m/e 205 (M^+), 162, 148, 134, 119, 105, 91, 79, 77, 67, 65 and 56. ^{13}C n.m.r. 179.876, 132.245, 123.861, 54.097, 47.187, 39.138, 35.213, 32.045, 31.690, 25.964, 23.512, 22.506 and 21.944 p.p.m. Found : C, 76,06 ; H, 9.25 ; N, 7.02. $C_{13}H_{19}N_1O_1$ requires C, 76.06 ; H, 9.33 ; N, 6.82%.

Attempted preparation of urethane-ester (137)

a) $NaH/CO(OEt)_2$

Lactam (132) (152 mg., 0.74 m. mole) in benzene (25 ml.) was stirred with an excess of sodium hydride (100 mg., 4.1 m. mole) at room temperature for 3 hours. Diethyl carbonate (0.2 ml.) was then added. After 3 hours at room temperature, the reaction was stopped and analytical t.l.c. showed there to be many products present, including the starting lactam (132). The other products were not investigated.

b) Meerwein's reagent[101]/$ClCO_2Et$

Following the conversion of the lactam (132) (150 mg., 0.73 m. mole) to the imino-ether (134), the mixture was treated with ethyl chloroformate (0.2 ml.). After 3 hours at room temperature, analytical t.l.c. showed the presence of numerous products and these were not investigated.

5-Amino-2,3-tetramethylenecyclo-oct-2-ene carboxylic acid (133)

Lactam (132) (200 mg., 1 m. mole) was refluxed for 24 hours in hydrochloric acid (conc. HCl : H_2O, 2 : 3) (10 ml.). After cooling, careful neutralisation produced a turbidity, but no precipitation. After preparation of a column of Amberlite IR-4B ion-exchange resin[94], the aqueous solution was passed through the column and the neutral solution collected. Evaporation of the solution yielded the crude amino-acid (133) (148 mg., 0.66 m. mole, 66%) as a high melting solid, m.p. > 330°C ; i.r. ν_{max}^{KBr} 3400, 1650 and 1130 $cm.^{-1}$

Attempted preparation of amino-ester (139)

a) The lactam (132) (205 mg., 1 m. mole) was hydrolysed with ca. 15% aqueous hydrochloric acid. Diazomethane was then bubbled into the reaction mixture until a permanent yellow colouration was obtained. The excess diazomethane was then removed by flushing the solution with a stream of nitrogen gas. After extraction[99] into chloroform, analytical t.l.c. indicated one main product and three minor products. Preparative t.l.c. on silica (10% methanol-chloroform) allowed isolation of this major component which was identified as dinonyl phthalate (140) by comparison with an authentic sample.

b) The reaction was repeated using the lactam (132) (208 mg., 1 m. mole) in an all-glass apparatus. Preparative t.l.c. permitted isolation of a product (125 mg.), i.r. ν_{max}^{CCl4} 1730 and 1670 $cm.^{-1}$ The ^1H n.m.r. was not informative. This sample, after a day or so, gave spectra identical to that obtained from the lactam (132).

c) The lactam (132) (200 mg., 1 m. mole) was hydrolysed with ca. 15% hydrochloric acid and then passed through a column of IR-4B resin to give the free amino-acid (133). This product was then treated with methanol/thionyl chloride[95] at 0°C. The temperature

was then raised to 40°C and maintained at this for 2 hours. After neutralisation with sodium bicarbonate and extraction[99] of the mixture with chloroform, a product was obtained which could not be further purified by t.l.c. i.r. ν_{max}^{CCl4} 1730 and 2500-3500 cm.$^{-1}$; ^{1}H n.m.r. δ 0.9-3.0 (envelope) and 8.4. No structure could be assigned to this product.

5-Hydroxy-2,3-tetramethylenecyclo-oct-2-ene carboxylic acid (142)

Lactam (132) (200 mg., 1 m. mole) was hydrolysed with hydrochloric acid (conc. HCl : H_2O, 2 : 3) (10 ml.) and then cooled to 0°C. Treatment with sodium nitrite (200 mg.) resulted in the formation of many products (t.l.c.). Isolation of the main product yielded a colourless oil which could be extracted into dilute sodium hydroxide and reprecipitated by addition of dilute hydrochloric acid. This material was tentatively identified as the hydroxy-acid (142) (48 mg., 0.21 m. mole, 21%) ; i.r. ν_{max}^{CCl4} 3600, 3500-2500, 1750, 1710 and 1650 cm.$^{-1}$; ^{1}H n.m.r. δ 1.0-3.0, 3.7 and 6.4* ; m.s. m/e 206 (M^+ - 18).

Attempted preparation of 5-oxo-2,3-tetramethylenecyclo-oct-2-ene carboxylic acid (147)

The amino-acid (133) (100 mg., 0.5 m. mole) was added to a solution of freshly prepared t-butyl hypochlorite[97] (120 mg., 1.1 m. mole) at 0°C and the mixture then allowed to come to room temperature. Treatment with sodium methoxide, prepared from sodium metal (25 mg.) and methanol, was followed by addition of water. Analytical t.l.c. showed the presence of numerous products which were not separated.

N-nitrosolactam (148)

Lactam (132) (180 mg., 0.87 m. mole) was dissolved in boiling hydrochloric acid (conc. HCl : H_2O, 2 : 3) (5 ml.). When dissolution

was complete (ca. 5 minutes), the solution was cooled and a 10% solution of sodium nitrite was added. A yellow precipitate formed which was extracted[99] with ether. The crude product (140 mg., 0.59 m. mole, 69%) was very pure and needed no further purification. It was identified as the N-nitrosolactam (148). i.r. $\nu_{max}^{CCl_4}$ 1730 and 1520 $cm.^{-1}$; ^1H n.m.r. δ 3.4 (1H ; m) and 5.3 (1H ; m) ; m.s. m/e 234 (M^+), 204, 176, 162, 161, 150, 136, 134, 133, 119, 105, 93, 91, 79 and 67. Accurate mass measurement gave the mass as 234.13673 ; $C_{13}H_{18}N_2O_2$ requires an accurate mass of 234.13681.

Attempted preparation of 2,3-Tetramethylenecyclo-octa-2,4-diene carboxylic acid (I43)

a) Benzene/reflux

The N-nitrosolactam (148) (100 mg., 0.42 m. mole) was refluxed in benzene (5 ml.) overnight. After removal of the solvent, analytical t.l.c. showed only the presence of starting material.

b) Xylene/reflux

The N-nitrosolactam (148) (100 mg., 0.42 m. mole) was refluxed in xylene (5 ml.) overnight. After removal of the solvent, analytical t.l.c. showed only the presence of starting material.

Attempted preparation of 5-Hydroxy-2,3-tetramethylene-cyclo-oct-2-ene carboxylic acid (142)

The N-nitrosolactam (148) (240 mg., 1 m. mole) was treated at 0°C with a 30% methanolic KOH solution (4 ml.). The mixture was evaporated to dryness and extracted[99] with chloroform. This crude product (150 mg.) was extracted into dilute sodium hydroxide and reprecipitated by addition of dilute hydrochloric acid, as a mixture. i.r. $\nu_{max}^{CHCl_3}$ 3540-2300, 1770, 1730 and 1700 $cm.^{-1}$; ^1H n.m.r. δ 1.2-2.8 (envelope), 5.7 and 8.0* ; m.s. m/e 206.

Attempted preparation of 2,3-Tetramethylenecyclo-octa-2,4-diene carboxylic acid methyl ester (I49)

The crude product obtained above (150 mg.) was treated with diazomethane in ether until a permanent yellow colour persisted in the reaction mixture. The excess diazomethane was then removed by flushing the solution with a stream of nitrogen gas. The crude product was purified by preparative t.l.c. on silica (30% ethyl acetate-light petroleum) and yielded a colourless oil (140 mg.), i.r. $\nu_{max}^{CHCl_3}$ 1730 $cm.^{-1}$; ^1H n.m.r. (60 MHz.) δ 3.7 (3H ; s) ; ^1H n.m.r. (90 MHz.) δ 3.68, 3.69, 3.70 and 3.73 (total 3H). The product would therefore appear to be a mixture of closely related compounds.

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