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SYNTHESIS AND REACTIVITY OF SOME BICYCLIC
AND TRICYCLIC MEDIUM RING SYSTEMS

A Thesis

Presented to the University of Stirling
for the degree of Ph.D.

by

RODNEY STEPHEN HENRY

March 1976

(Awarded December 1976)

Approved, March 1977

I am grateful to Professor W. Parker for his continued support and advice during these researches.

My thanks are also due to Dr. P. and Dr. J. Murray-Rust for performing X-ray crystallographic studies.

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I should also like to thank Mrs. N. Gibson of Food Industries Limited for her skill and patience in typing this thesis.

Finally, my gratitude is expressed to the North Atlantic Treaty Organisation for a maintenance award for three years.

The Intellect : "Apparently there is colour, apparently sweetness,
apparently bitterness, actually there are only atoms
and the void".

The Senses : "Foor Intellect, do you hope to defeat us, while
from us you borrow your very evidence. Your victory
is in fact your defeat".

Democritus (ca. 420 B.C.)

To my Mother and Father

ABSTRACT

In connection with a broader interest in transannular hydride shifts and bridgehead reactivity in bridged bicyclic and tricyclic systems, a synthetic route to hitherto unavailable 3,7 disubstituted bicyclo(3,3,2) decanes is described. Bridging of the readily available Meerwein ester to its corresponding double homologue was followed by regio-specific decarboxylation to achieve unprecedented 1,8 disubstitution in the homo-adamantane skeleton. Subsequent degradative stages afforded 7-exo-methylene bicyclo(3,3,2)decan-3-one. X-ray crystallographic structural elucidation of an intermediate, 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecane, confirmed the complete regio-specificity of the decarboxylation and showed that the preferred ground state conformation of the compound has an almost C_{2v} symmetry with its ethano bridge virtually eclipsed (dihedral angle 2°).

Exo-7-hydroxy-bicyclo(3,3,1)nonan-3-one was synthesised by ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-exo-3 ol. The ketol undergoes a degenerate base catalysed rearrangement via a specific 1,5 transannular hydride shift. The presence of epoxide by-products from the ozonolysis is rationalised on steric grounds.

Attempts to prepare specifically ^{18}O labelled, and optically active, 1-methyl bicyclo(3,3,1)nonan-3,7-dione by ozonolysis of the corresponding labelled (^{18}O , 75%) exo-methylene ketone resulted in almost complete label loss. This observation is discussed in terms of recent mechanistic theory relating to ozonolysis of olefins. Similar results from ruthenium tetroxide oxidative cleavage are also discussed.

The bis-trimethyl ammonium iodide of 1,5 diamino bicyclo(3,3,1)nonane has been synthesised and preliminary attempts made to identify the olefinic products formed during the pyrolysis of its di-hydroxide.

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SECTION I

A synthetic route to 3,7 disubstituted bicyclo(3,3,2) decanes

INTRODUCTION

The incentive to undertake the research described in this section of the thesis arose from work performed at Glasgow, Stirling and elsewhere in recent times, on two aspects of bridged medium ring chemistry, viz. transannular hydride shifts and bridgehead reactivity.

(A) Transannular Hydride Shifts

For almost fifty years^{1,2} it has been known that the chemistry of medium alicyclic ring compounds, that is to say those containing between eight and eleven atoms, differ markedly from those of small and large rings. Even the problem of their preparation in yields of more than a fraction of a per cent was not resolved until 1947 when the acyloin cyclisation was developed³. Examination of molecular models shows immediately that multiple conformations are available to the medium ring and that its size is such that a situation always exists where two non-adjacent carbon atoms are forced into close proximity with one another, giving rise to an inevitable strained situation. Such 'transannular' interactions included as a component of the collective 'I' (for internal) strain described by Brown⁴, give rise to a group of properties unique in relation to other types of cyclic compounds; namely the influence through space of functional groups remote from the reaction site during various chemical changes at that site.

A highly typical member of the series, and an intensely studied one, is cyclooctane, which has figured prominently in a thorough review of transannular interactions in medium rings by Cope and McKervey⁵. It shows the multiple conformation properties apparent from the model above and indeed much controversy is to be found in the literature surrounding the attempt to establish the preferred ground state. A number of alternatives have been suggested at various times including a boat chair⁶, butterfly⁷, saddle⁸, stretched crown⁹ and crown¹⁰. More recently X ray analysis has

provided good evidence for the boat chair conformation^{11,12} although from a consideration of strain energy minimisation calculations by Hendrickson and Wiberg^{13,14} together with NMR evidence by Anet¹⁵, current reasoning would seem to indicate that no distinct conformation is preferred and that a mobile equilibrium of these exists, at least in solution where crystal packing forces are not a factor.

Another characteristic feature of the cyclooctyl system is its enhanced solvolytic reactivity accompanied by a tendency towards producing elimination rather than substitution products. In such processes the driving force for the greater reactivity is seen as owing to the relief of steric strain in the reaction centre proceeding from a tetrahedral sp^3 to the sp^2 trigonal cation. Indeed a number of reactions characterises the series in this way^{16,17}. Conversely the borohydride⁴⁷ reduction of cycloalkanones ($sp^2 \rightarrow sp^3$) is slow when compared with the solvolysis rates for the corresponding tosylates^{16,17}. Strain, inherent in all ring systems, was described by Brown⁴ to be consisting of a number of inter-related contributions. He described the total '1' strain as incorporating angle, torsional, bond length and transannular constraints on ideal geometry and further that the latter type features prominently in medium rings.

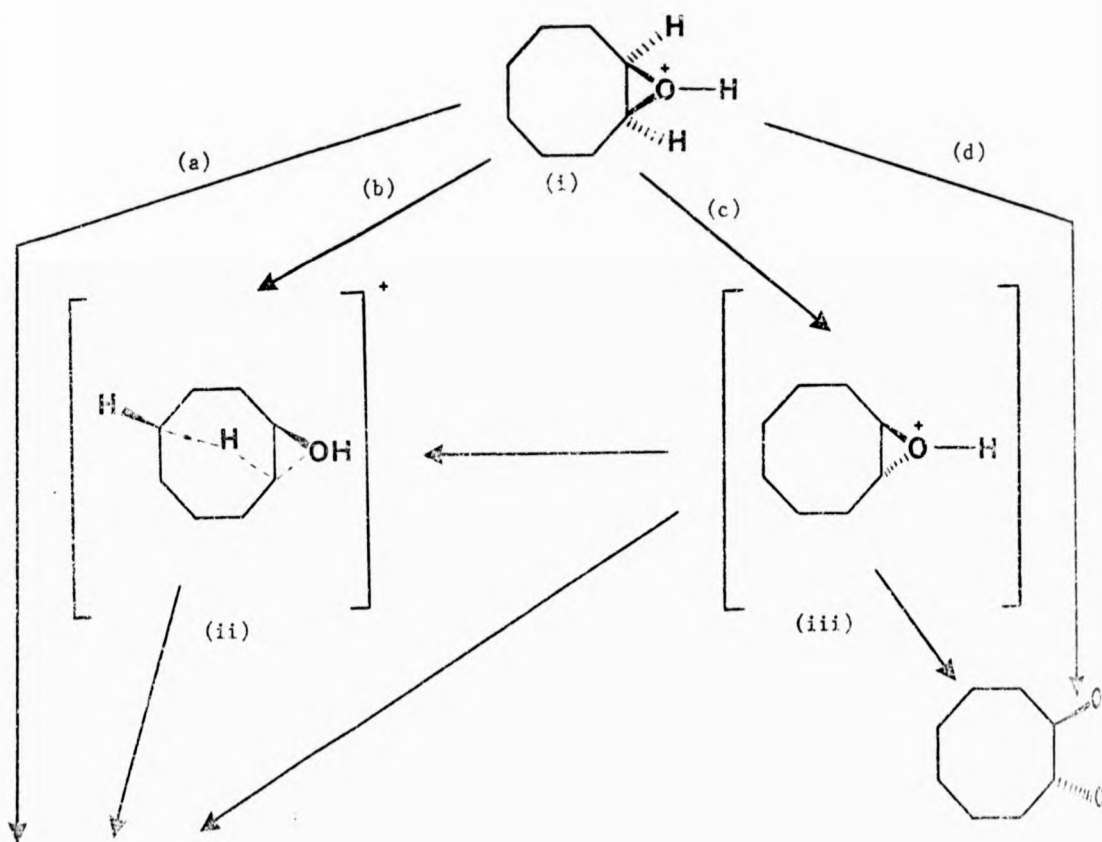
Perhaps a more striking consequence of strain is the propensity of medium ring systems to undergo transannular intramolecular hydride shifts during solvolysis. The general phenomenon of hydride shifts was originally described in the classical work of Bartlett et al.¹⁸ who demonstrated that transfer could occur from a non-activated C-H group although such a shift did not successfully compete with solvent capture at the carbonium ion reaction site when the migrating hydride was not adjacent to the site and when the carbonium ion was not continuously regenerated during the course of the reaction. In 1952 however Fieser¹⁹

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SCHEME I



Transannular products

cis cyclooctane 1,4 diol (2)

cyclooct-3-ene-1-ol

cyclooct-4-ene-1-ol

1,4 epoxy cyclooctanone

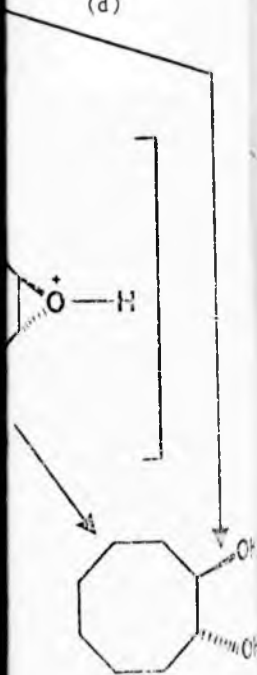
1,5 epoxy cyclooctanone

endo-cis-bicyclo(4,2,0)octan-7-ol

and Cope²⁰ independently reported results relating specifically to the cyclooctyl system which were unprecedented at that time.

Cope's initial work²⁰ described the formolysis of cis cyclooctene oxide (1) during which, in addition to the normal elimination and substitution products, a number of species was detected whose appearance could only be explained by transannular processes having taken place; e.g. after hydrolysis of the formate esters the major abnormal product was cis-cyclooctane-1,4-diol (2). An illustration of the product distribution is found in Scheme I accompanied by a summary of possible routes which would account for it. From the initial protonated form (i) of the cis olefin oxide (1), mechanism (a) is a completely concerted process whereby hydride transfer occurs simultaneously with solvent attack at C5 or C3 and ring opening at C1. Route (b) illustrates a rate determining formation of the intermediate non-classical ion (ii) which is able to collapse in one of two ways to transannular or normal products. This pathway is also able to give the observed results by means of a 1,3 or 1,5 hydride shift. Pathway (c) has as its rate determining step the slow formation of the classical ion (iii) which by virtue of retaining some of its tetrahedral character by partial bonding is able to afford the cis stereospecificity demanded of paths (a) and (b) and indicated in the major product cis-cyclooctane-1,4-diol (2). Route (d) is a conventional trans ring opening by attack at C1 or C2 to give normal products only. Hence the product distribution listed may be arrived at by a combination of two, three and four routes. In addition to the primary work on cis cyclooctene oxide (1) Cope et al. studied the solvolysis of this compound in a number of different carboxylic acids and demonstrated a striking dependence of the extent of transannular product formation on the acid strength, which in turn can be associated with the diminishing nucleophilicity of the acid as its strength increases²¹.

(d)

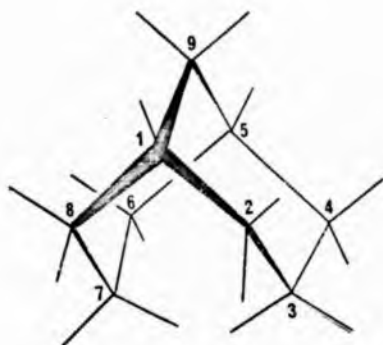


For example in trifluoroacetic acid, transannular processes occur to the extent of 100% whereas buffered acetolysis results in a figure of only 24%. The same author in a further report, again using cis cyclooctene oxide (1), provided evidence to the effect that the major product of formic acid solvolysis discussed in detail above arose from a combination of 1,3 and 1,5 hydride shifts respectively occurring at 39% and 61% of the transannular processes²². This result was arrived at by a thorough piece of work involving deuterium labelling of (1) followed by stepwise degradation of the product to adipic acid and associated locating of deuterium content and position.

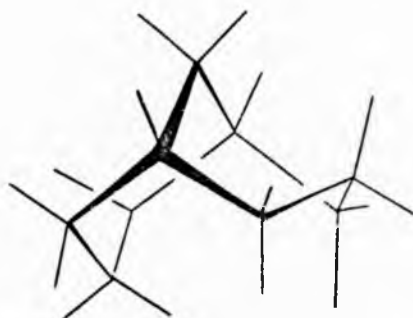
In an attempt to establish if a non-classical ion situation was involved Prelog and Borcic^{23,24} compared the solvolysis rates of 5,5,6,6-tetradeuterio-cyclodecyl-tosylate (3) and its unlabelled parent (4) and although $\frac{k_H}{k_D} = 1.08$ was established, no difference was observed in the ratio of transannular to normal products as would have been the case if hydride were participating in the rate determining step. On the basis of this evidence participation was dismissed for the cyclooctane case. However, it has been suggested that this work could be suspect since the method of synthesising the labelled compound (3) could involve a scrambling of deuteria²⁵.

The placement of a methano bridge across the positions C1, C5 of cyclooctane may be envisaged as a formal derivation of the bicyclo(3,3,1) nonane system. This results in a drastic restriction of the abundant conformations available to the former monocyclic series. Indeed, molecular models demonstrate that there are only four possibilities. It will serve here simply to list them together with their major strain components since they have already been adequately discussed²⁶. Three-dimensional

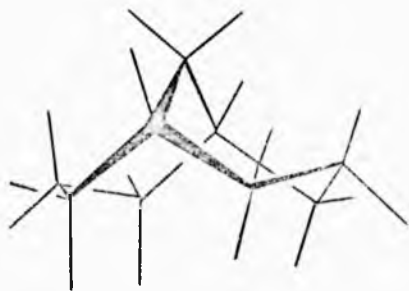
FIG. I



1. Twin Chair



2. Boat Chair



3. Twin Boat



4. Twin Twist Boat

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ml

reproductions of the Drieding model representation of the four alternatives are shown in Fig. I.

1. Twin Chair

There is only one serious non-bonded interaction due to the endo C3,C7 hydrogens necessarily approaching to within a distance of approx. 0.8 \AA in ideal chairs.

2. Boat Chair

Severe interactions between C3,C6 and C8 and to a lesser extent between C7 and C9.

3. Twin Boat

The flagpole interactions C3,C9 and C7,C9 cannot readily be relieved by flexing due to the onset of further hindrance in the endo face of the molecule namely C2,C8 and C4,C6.

4. Twin Twist Boat

Achieved by conformational rotation from the twin boat example and viewed as a mode of relieving exo face flagpole interactions, this conformation results in unfavourable C2,C6 and/or C4,C8 constraints.

From a consideration of all these factors the conclusion drawn, reinforced by X-ray and spectroscopic evidence, was that bicyclo(3,3,1)nonane resides preferentially in the twin chair conformation.²⁷ The associated premise, that C3,C7 interactions should be markedly apparent in this system prompted interest.

Eakin and Parker²⁸ reflected on the fact that C3,C7 hydride shifts had previously been reported in the bicyclo(3,3,1)nonane system for reactions performed in strongly acidic conditions and commented that it might be of interest to examine the solvolysis of exo 3-bicyclo(3,3,1)



air



1st Boat

nonan-toluene-p-sulphonate (5) under conditions of buffered acetolysis thereby removing the previously powerful thermodynamic and equilibrative driving force for the observed hydride shift²⁹. The relieving of the severe transannular non-bonded interactions between C3 and C7 is accommodated in the bicyclo nonane system by the easing apart of these centres thereby flattening the chairs²⁶ and interest in the above solvolysis was to observe if a hydride shift between C3 and C7 would occur with its associated transition state involving the approach of these centres during migration. In the event a shift of 4% in the major product bicyclo(3,3,1)non-2-ene (6) showed the reluctance of the system to undergo transannular hydride shift under kinetically controlled conditions. A rate enhancement factor of some 1,200 times that of cyclohexyl tosylate can be considered as demonstrating the steric acceleration afforded by the relief of strain upon ionisation at C3 but the extremely low extent of shift was considered to rule out participation by the migrating hydrogen as a rate enhancement factor. Previously Cope had demonstrated a transannular hydride shift of 50% during the buffered acetolysis of 1,2,2,8,8 penta-deuterio cyclooctyl brosylate (7)³⁰. The olefinic and solvent-capture products both arise from a specific 1,5 transannular hydride shift and this example illustrates clearly the conformational constraints imposed by the methano bridge in the bicyclic case resulting in a shift of only 4%.

7-exo-methylene-bicyclo(3,3,1)nonan-3-one (8) prepared originally by Stetter in 1963³¹ and latterly via a British patent involving the base catalysed cleavage of 1,3 dibromo adamantane (9)³² provided a convenient starting material for the same group to seek the results of similar solvolytic experiments on the homologous 7-exo-methyl-bicyclo(3,3,1)nonan-3-exo-tosylate (10). In this case a shift of 55% was observed

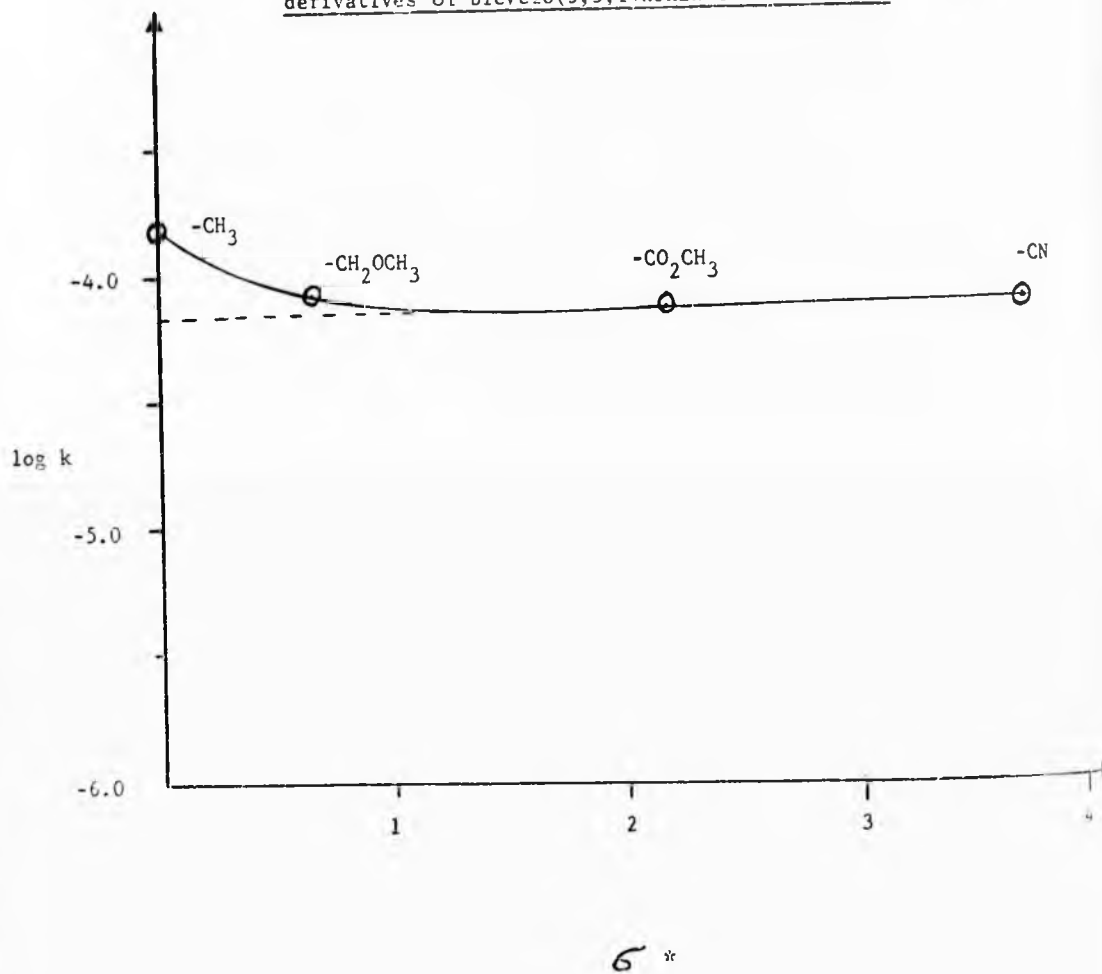
in the major transannular product, 3-methyl-bicyclo(3,3,1)nonan-3-ene³³ (11), arousing particular interest because the possibility was again raised of transannular hydride participation in the rate determining step, thus enhancing the reaction rate. These authors maintain that this premise is invalid since under identical conditions the labelled analogue exo-7-methyl-7-deuterio-bicyclo(3,3,1)nonan-3-exo-tosylate (12) showed no deuterium isotope effect³³. The enhanced transannular shift in this instance as compared with the nor²⁸ case was rationalised as a thermodynamic preference for the tertiary carbonium ion at C7.

Marvel has examined the solvolysis of bicyclo(3,3,1)nonan-exo-2,3 oxide (13)³⁴ and compared it with the earlier results of Cope on the formolysis of cis-cyclooctene oxide (1)²⁰. His results showed a remarkable difference from those of the tosylate solvolysis in which transannular reactivity is dramatically reduced in comparison with the cyclooctyl homologue. In Marvel's case formolysis showed only a slightly greater tendency of the monocyclic reactant to undergo transannular reactions. This difference between the tosylate and epoxide behaviour in the same bicyclic system caused Marvel to reflect that factors other than steric strain govern intramolecular hydride shift in such systems during solvolysis. Particularly, the ratio of the rate of transannular hydride shift versus the rate of collapse to normal products may be significant and governed by other conformational factors introduced by, in this case, the presence of a substituent at C3 after ring opening of the epoxide moiety.

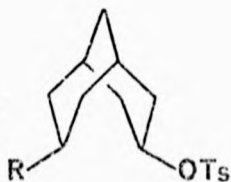
Much more recently Ourisson has demonstrated a kinetic proof of (C-H) participation in the solvolysis of 7-substituted-bicyclo(3,3,1)non-3-yl tosylates³⁵. A series of 7-substituted derivatives of the type (14) ($R=CN, CO_2CH_3, CH_2OCH_3, CH_3$) was synthesised and the rates of solvolysis using identical conditions for each one were placed in a

FIG. II

Taft-Hammet analysis of the solvolysis of 7-substituted derivatives of bicyclo(3,3,1)nonan-exo-3-tosylate



Acetolysis of



R = -CN

-CO₂CH₃

-CH₂OCH₃

-CH₃

stituted
e

Taft-Hammet plot. The derivatives containing the electron withdrawing groups ($R=CN, CO_2CH_3$) form a linear plot as would be expected from the results since no hydride shift could be found in the products. A departure from linearity was observed with the other two groups ($R=CH_2OCH_3, CH_3$) resulting in k_{CH_3} being four times greater than the value extrapolated from the linear part of the curve. This result, seen more clearly in Fig. II, is concordant with 75% transannular products instead of the 55% value observed and previously mentioned³³, and the discrepancy was accounted for by Ourisson who postulated the intermediate structures (15) and (16) having competitive breakdown modes for transannular and normal products. That is to say it is still not clear whether a synchronous transfer, non-classical intermediate, or indeed a combination of both pathways is involved. Further work was performed by the same author on a similar series of derivatives of the type (17) ($R=CN, CO_2CH_3, CH_2OCH_3, CH_3$) with the difference that the geminal dimethyl groups on the bridge block both rings securely into a twin chair conformation and should thus result in increased participation and reaction rate enhancement³⁶. This was found to be the case and in the solvolysis of exo-7-methyl-9-dimethyl-bicyclo(3,3,1)nonan-exo-3-tosylate (17) ($R=CH_3$) k_{CH_3} was indeed four times larger than that of the nor compound (100% hydride shift).

The insertion of an ethano bridge across the C1,C5 positions of cyclo-octane gives the bicyclo(3,3,2) decane series of compounds. From spectroscopic and kinetic evidence strong arguments were proposed for the preferred conformation being, as in the bicyclo(3,3,1)nonane case, a deformed twin chair^{37,38}. However, a considerably greater degree of flexibility is open to this molecule and it may be appreciated that prohibitive strain is incurred in the symmetrical twin chair conformation by eclipsing of the hydrogens in the ethano bridge and by a particularly

-CN



4

-CN

-CO₂CH₃

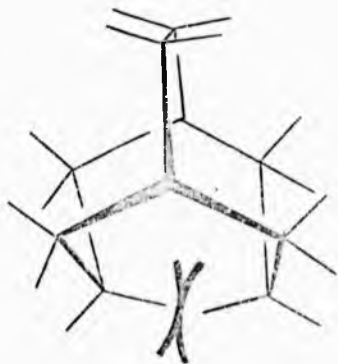
-CH₂OCH₃

-CH₃

FIG. III



Bridge staggered



Bridge eclipsed

sev
in
all
res
tha
geo
wit
of
487
so
go
It
of
sy
su
hy
th
it
de
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d
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s
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severe C3,C7 interaction between the endo hydrogens which actually touch in a Drieding model (Fig. III). Rotation about the C9,C10 bond axis alleviates both of these situations and it is believed that the molecule resides in this staggered twin chair conformation³⁸. It can be shown that on ionisation of say a tosylate at C3, the resulting trigonal geometry at this centre would enable the C7 endo hydrogen to approach, without strain, to a position exactly equidistant between C3,C7 by means of the molecule twisting to an eclipsed bridge situation. In the event 48% hydride shift was observed in the elimination product from the solvolysis of bicyclo(3,3,2)decan-exo-3-tosylate (18)³⁷.

Hence it is apparent that our knowledge of the factors and parameters governing the mechanism of transannular hydride shift is far from complete. It occurred to us that it would be instructive to attempt the synthesis of suitable 3,7 disubstituted derivatives of the bicyclo(3,3,2)decane system, similar to those of Ourisson in the lower homologues but more suitable templates than the latter series for pursuing the sought-after hydrogen participation in the rate determining steps. It might be expected that the non-classical ion (19) could more easily exist as a stabilised intermediate in the decane case and further, 7,7 di-deuterio bicyclo(3,3,2)decan-exo-3-tosylate (20) may exhibit a distinct kinetic isotope effect.

(E) Bridgehead Reactivity

A second and unrelated reason for devising a synthesis of 3,7 disubstituted bicyclo(3,3,2)decanes arose from the extensive work of Schleyer and others on bridgehead reactivity in polycyclic systems^{39 - 45}. Interest in this subject was originally precipitated by Bartlett in 1939 with the observation that bridgehead substituents of small bridged ring systems were virtually inert to solvolytic displacement⁴⁶. The important concept born here is that if widely differing reactivities characterise different bridgehead situations,

then there exists the facility of the provision of models to determine various effects of strain on reactivity. Schleyer has defined the general concept of strain⁴⁰. The ideal tetrahedral orientation of the four bonds about a carbon atom having sp^3 hybridisation is seldom realised; i.e. when the four groups attached to the carbon in question are different in identity, interactions between them result in a deviation from the ideal tetrahedral angle of $109^\circ 28'$ and the molecule is said to be strained. When this fundamental example is applied to the complex structures of bridged bicyclic and polycyclic systems, where deviations far from the ideal are usual, it should be realised that the internal strain may be considerable. A means of obtaining predictable information on the solvolytic reactivity of molecules is provided by such systems because they present rigid templates in which the difference in strain energy between ground and transition states can be ascertained from quantitative conformational analysis. Schleyer⁴² argued that if the energy of the transition state in a solvolysis reaction at a bridgehead were the same as that of the carbonium ion or proportional to it, then providing entropy effects were negligible during solvolysis, the energy difference between ground and transition state/carbonium ion should be proportional to the rate of solvolysis. The first attempt at a quantitative approach to the determination of steric strain in molecules generally was instituted by Westheimer⁴⁸. The total internal strain was taken as a summation of various components viz. the equation :-

$$E_{\text{total strain}} = E_{\text{bond length strain}} + E_{\text{bond angle strain}} + E_{\text{torsional strain}} + E_{\text{non-bonded interaction strain}}$$

Hendrickson^{49,50} later employed these terms using a computer technique and successfully obtained good agreement between empirical and calculated

FIG. IV

Calculated v. experimental relative rate constants for the solvolysis
of bridgehead bromides

System	Energy Diff. (Calc.) k/cal.	Rel. Rate Constants (calc.) 25°	Rel. Rate Constants (exptl.) 25°
t. butyl	2.85	0.22	1.0
3-homoadamantyl (24)	9.23	4.65	0.46
1-adamantyl (23)	10.16	4.6×10^{-5}	1.2×10^{-3}
1-bicyclo(2,2,2)octyl (21)	12.93	1.8×10^{-6}	2.4×10^{-7}
1-norbornyl (22)	20.39	3.1×10^{-12}	2.0×10^{-12}
1-homoadamantyl (26)	7.76	7.0×10^{-4}	-
1-bicyclo(3,3,1)nonyl (25)	3.10	0.12	-
1-bicyclo(3,2,1)octyl	12.44	3.3×10^{-6}	-

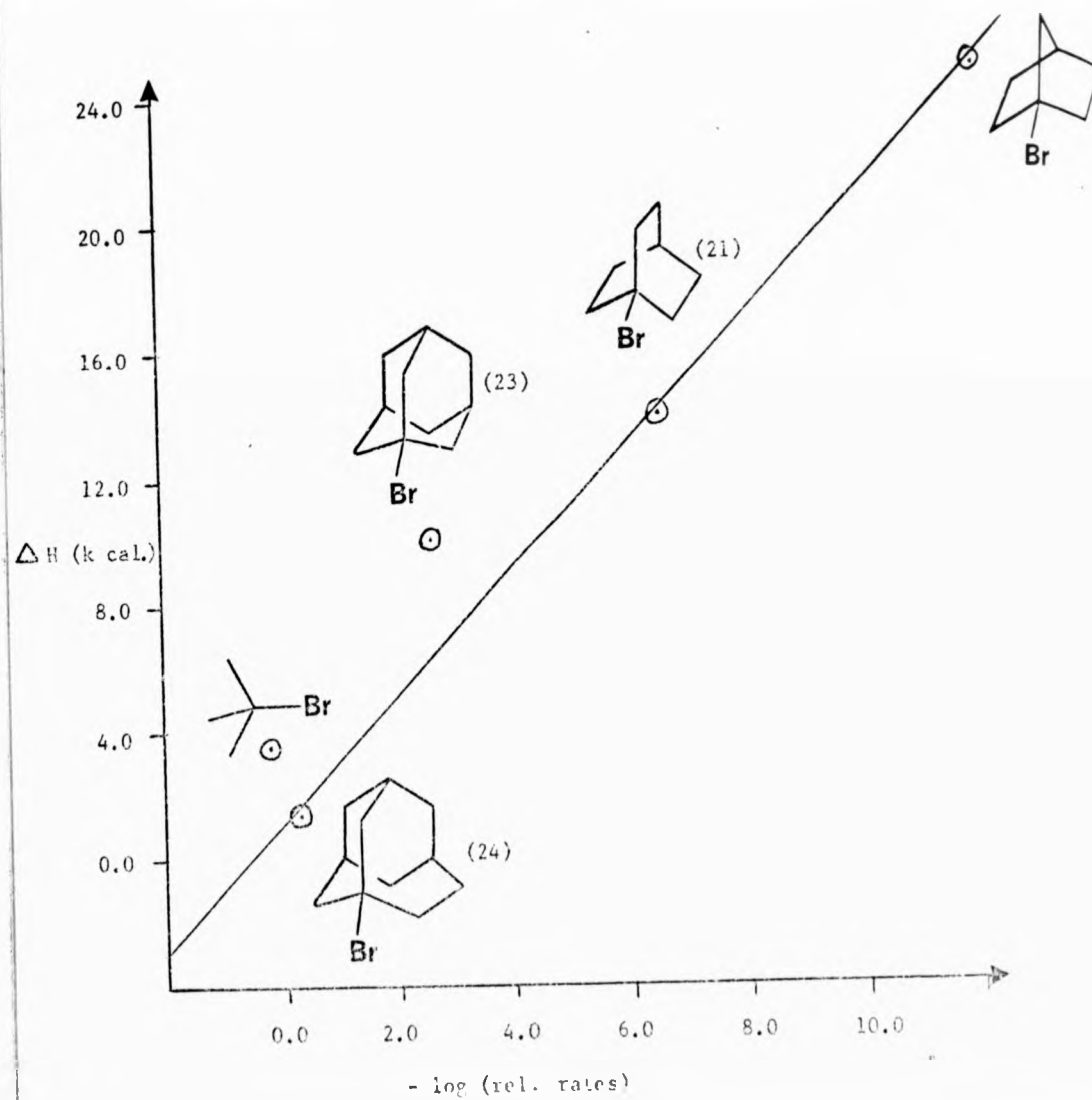
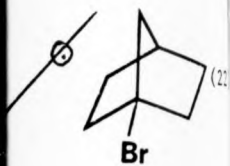
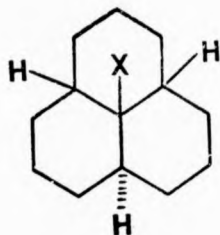


FIG. V

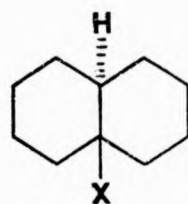
Bridgehead systems studies by 1972



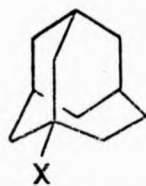
(a)



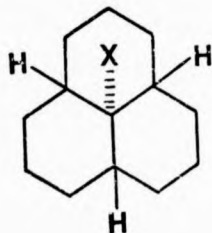
(b)



(c)



(d)



(e)



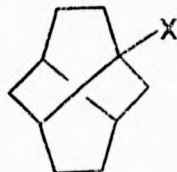
(f)



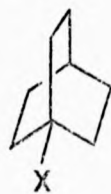
(g)



(h)



(i)



(j)



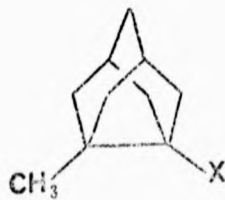
(k)



(l)



(m)



(n)



(o)



(p)

values for the energy difference between the boat and chair forms of cyclohexane. Subsequently, Schleyer exploited the technique to relate the observed and calculated solvolysis rates of a number of bridgehead bromides⁴¹. These were 1-bromo-bicyclo(2,2,2)octane (21), 1-bromo-bicyclo(2,2,1)heptane (22), 1-bromo-tricyclo(3,3,1,1^{3,7}) decane (23), and 3-bromo-tricyclo(4,3,1,1^{3,8})undecane (24). Reasonably good agreement between observed and calculated values was obtained and some of this data is summarised in Fig. IV. In a later paper by the same author⁴², improved parameters were employed to result in even better agreement for a large and wide ranging number of bridgehead systems a-p (Fig. V). These included 'harder' non-bonded potentials and improved values for bond angles. Also, correlation between tosylate and bromide solvolysis rates was explained and the influence of torsional strain in particular was illustrated by the anomalous experimental v. calculated results on example 1 (Fig. V). Interestingly, in the period between his initial work and later publications^{41,42}, experimental data on the hitherto unknown bicyclo(3,3,1)non-1-yl (25)^{39,45} and tricyclo(4,3,1,1^{3,8})undecan-1-yl⁵¹ (26) systems became available and was shown to be in close agreement with the calculated values found in the later report. Amongst the sixteen examples considered by Schleyer above were the three tricyclic systems, tricyclo(3,3,1,1^{3,7})decan-1-yl (23), tricyclo(4,3,1,1^{3,8})undecan-1-yl (26) and tricyclo(4,3,1,1^{3,8})undecan-3-yl (24). A fourth member can be seen as completing these examples in tricyclo(4,4,1,1^{3,8})dodecan-1-yl (27). At the start of this research, the system was unknown but a simple route can be drawn up to obtain it from 7-exomethylene-bicyclo(3,3,2)decan-3-one (28). Eakin and Parker⁵² prepared tricyclo(4,3,1,1^{3,8})undecan-3-acetate (29) by the solvolytic rearrangement of 7-cyclopropyl-bicyclo(3,3,1)nonan-exo-3-tosylate (30) which itself was obtained via a Simmons-Smith reaction on 7-exomethylene-bicyclo(3,3,1)nonan-exo-3-ol (31).

The latter alcohol is formed in 17% yield by the lithium aluminium hydride reduction of 7-exomethylene-bicyclo(3,3,1)nonan-3-one (8) the remaining 83% being the endo epimer (32)²⁶. Such a process applied to the bicyclic decyl homologue (33) would give tricyclo(4,4,1,1^{3,8})dodecan-1-acetate (34) and information relating to the bridgehead reactivity of this tricyclic structure would clearly be of interest in relation to Schleyer's work. Similar solvolytic conditions to those in the above report have been applied to the olefin tosylate (35) resulting in ring closure to adamantyl acetate⁵² and it may be appreciated that identical treatment of 7-exomethylene bicyclo(3,3,2)decan-3-one (28) should provide a convenient access to 1-substituted tricyclo(4,3,1,1^{3,8})undecane derivatives of which there is only one report in the literature⁵¹.

Quite apart from consideration of reactivity aspects, a pursuit of tricyclo(4,4,1,1^{3,8})dodecane (36) is highly desirable in that it is a bis homologue of adamantane (97) and while not possessing "the fearful symmetry" of the latter it nevertheless, by virtue of being constructed of all seven numbered rings, has an intriguing symmetry in its own right. Unlike its tricyclic decane relative, however, this structure, far from being rigid, is very flexible and it is of considerable interest to speculate on its preferred ground state conformation. The two ethano bridges may bear three relationships to one another as extreme cases. Both bridges may be eclipsed, both may be staggered or a third case of one staggered, and one eclipsed is possible.

Any situation intermediate between the first and second cases is possible. Recent evidence has been presented by three authors independently to suggest that the barrier to rotation from one 'skew butane' position to another in the ethano bridge of homo adamantane may not be very large.

For example, Braun and Hornstra⁵³ have shown by X-ray crystallography that the dihedral angle between the carbonyl groups in tricyclo(4,3,1,1^{3,8})undecan-4,5-dione (37) is $11^{\circ} 9'$, which in terms of the adverse steric interactions normally encountered between groups of this type, is an abnormally low value. Nordlander⁵⁴ and Schleyer⁵⁵ have presented evidence for the phenomenon by virtue of the extent of hydrogen bonding in tricyclo(4,3,1,1^{3,8})undecan-4,5-diol (38), while Schleyer⁵⁶, from an analysis of coupling constants in the 220 MHz n.m.r. spectrum of the hydrocarbon, concluded a dihedral angle of 0° . The question which should now be asked is, with the increased mobility possessed by the dodecane, can it reside with both bridges eclipsed or will it necessarily take up the low symmetry with both bridges staggered?

In an attempt to answer some of these questions, a programme was devised to synthesise suitable 3,7 disubstituted derivatives of bicyclo(3,3,2)decane.

DISCUSSION

In marked contrast to the lower homologue, bicyclo(3,3,1)nonane, there was, at the outset of this project, relatively little in the literature dealing with the corresponding bicyclic decane, and what small amount of work had been carried out provided no obvious starting point for access to the required specific substitution. In 1956 Alder⁵⁷ described the deaminative ring expansion of endo-6-aminomethyl-bicyclo(3,2,2)nonan-hydrochloride (39) to yield, allegedly, an epimeric mixture of bicyclo(3,3,2)decan-exo and endo-3-ols (40). Ten years later Doyle⁵⁸ performed a rigorous re-examination of Alder's work since he required bicyclo(3,3,2)decan-exo-3-ol (41) for kinetic studies involving transannular hydride shifts as already described in this text³⁷. It was demonstrated that a 10 component mixture was produced consisting mainly of a mixture of epimeric bicyclo(3,3,2)decan-exo- and endo-2-ols (42). This route was therefore quickly dismissed as a source of the exo-3-ol (41) and eventually Doyle successfully carried out a Demjanow-Tiffeneau reaction on 9-aminomethyl-bicyclo(3,3,1)nonan-2-ene (43). Previously⁵⁸, bicyclo(3,3,1)nonan-2-ene (6) had been stereoselectively hydroborated to a mixture of exo-2- and exo-3-ols (44) and (45) and he subsequently synthesised the exo-3-ol (41) in a similar way. Before arriving at this approach however, an attempted ring expansion of bicyclo(3,3,1)nonan-9-one-2-ene (46) with diazomethane had failed. A possible reason for this could have been the choice of conditions since in 1971 Schleyer⁴³ had successfully employed an in situ diazomethane generation method to make 9-bicyclo(3,3,2)decanone (47) from 9-bicyclo(3,3,1)decanone (48). Almost at the same time Leonard^{59,60} ring expanded bicyclo(3,3,1)nonan-2-ene-9-one (46) and the saturated ketone (45) with similar successful results.

In a 1968 patent application, Smith, Kline and French Laboratories⁶¹ have reported the preparation of a number of bicyclo(3,3,2)decane derivatives via carbonium ion rearrangement processes. A Koch-Haaf reaction on 1-hydroxymethyl-bicyclo(3,3,1)nonane (49) yielded bicyclo(3,3,2)decane-1-carboxylic acid (50) while 6-acetamido-bicyclo(3,3,2)decane (51) was prepared from a Ritter reaction on 2-hydroxymethyl-bicyclo(3,2,2)nonane (52) and 9-bicyclo(3,3,2)decanol (53) was obtained from a deaminative ring expansion of 9-aminomethyl-bicyclo(3,3,1)nonane (54). The patent also discussed a synthesis of bicyclo(3,3,2)decane-exo- and endo-3-ols (40) but with no reference to starting materials.

In 1963 the first of a number of reports^{62,63,64} by Schroeder appeared on the chemistry of bullvalene giving bicyclo(3,3,2) decanes substituted in both rings. Bullvalene itself (55) is a 2,6-dihydro-bicyclo(3,3,2)deca-triene from which catalytic hydrogenation afforded the parent bicyclic hydrocarbon (56) whereas sodium-liquid ammonia reduction results in 2,6,9-bicyclo(3,3,2)deca-triene (57). If the latter reaction is carried out at elevated temperatures, an additional compound (C₁₀ H₁₄) is formed which has tentatively been assigned the structure bicyclo(3,3,2)deca-2,6-diene (58)⁶². Treatment of bullvalene with bromine or sulphuryl chloride yields respectively 4,8-dibromo- (59) and 4,8-dichloro-bicyclo(3,3,2)deca-2,6,9-triene (60)^{63,64}. An isolated example of the bicyclic system containing functionality in both rings but with no accompanying detail of synthesis appeared in 1959 in connection with the use of a nuclear induction spectrometer. The compound in question is 1,6,6-trimethyl-bicyclo(3,3,2)decane-9-ene-3-one⁶⁵ (61).

In conformational studies using e.s.r. spectroscopy, Russell has specifically studied bicyclo(3,3,2)decane-9,10-semidione (62)⁶⁶. Apart from controversial conclusions being drawn regarding the preferred conformation of the system as being boat chair, this report is of

additional interest because it is one of the rare occasions on which the acyloin reaction has been used to prepare such bridged systems. Previous work by Russell⁶⁸ seems to indicate that the semidione (62) was obtained from an acyloin ring closure of 1,5-dicarboethoxy-cyclooctane (63).

In 1968 Graham⁶⁹ reported that the acid catalysed cyclisation of 1,5-bis-methylene-cyclooctane (64) afforded a mixture of 1-chloro-bicyclo(3,3,2)decane (65) and 1-bicyclo(3,3,2)decanol (66). This is a surprising result since treatment of the bis-methylene compound (64) with bromine is known to produce 1-bromo-5-bromomethyl-bicyclo(3,3,1)nonane (67)⁶⁹. The spurious nature of Graham's result was later highlighted by Schleyer's⁴³ unambiguous synthesis of both 1-chloro- and 1-hydroxy-bicyclo(3,3,2)decane (65) and (66) by bridgehead functionalisation of the parent hydrocarbon. In ensuing private communication, Graham conceded that his hydroxy compound could not be 1-hydroxy-bicyclo(3,3,2)decane (66). This problem has been finally resolved in these laboratories, primarily as a consequence of an improved synthesis of 1,5-bis-methylene-cyclooctane (64). Bishop⁷⁰ has found that a double Wittig reaction on cyclooctane-1,5-dione (68) affords (64) in good yield, the starting material, 1-hydroxy-5-ketocyclooctane (69) being readily available. Acid catalysed cyclisation resulted in chloro and hydroxy compounds whose nmr spectra were inconsistent with Graham's structural assignments. Instead, it was found that the compounds were 1-hydroxy-5-methyl-bicyclo(3,3,1)nonane (70) and 1-chloro-5-methyl-bicyclo(3,3,1)nonane (71). These results are consistent with those of the above bromine addition⁶⁹.

Finally, a synthesis of the bicyclo(3,3,2)decane system has been reported which is the result of a sigmatropic rearrangement of cycloheptatrienyl-propargyl-ether (72). This thermally allowed process gives

SCHEME II

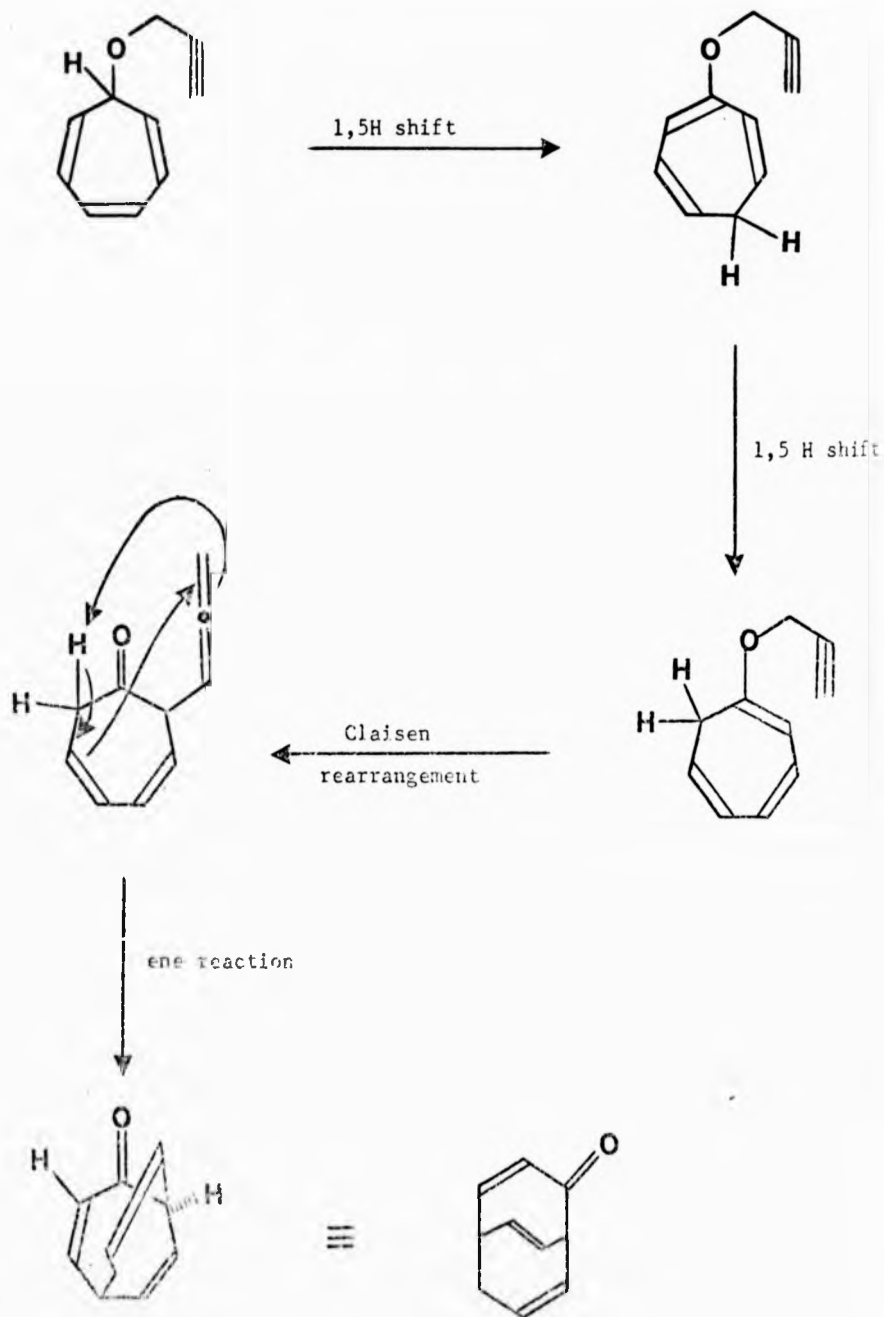


TABLE I

Trifluoroacetylolysis of Epoxides

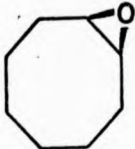


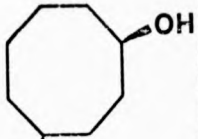

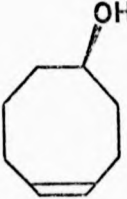
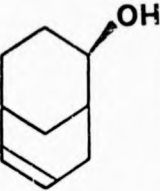
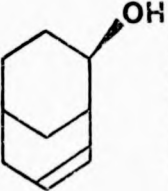
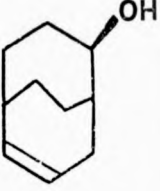
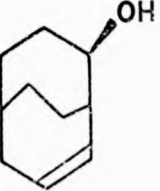
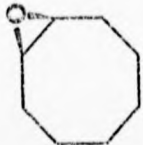
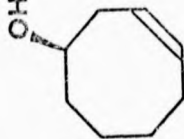
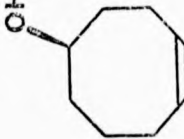
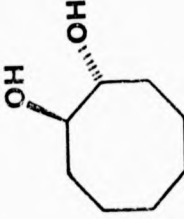
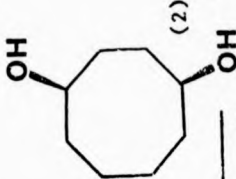

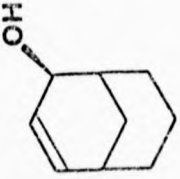
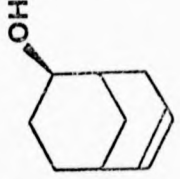
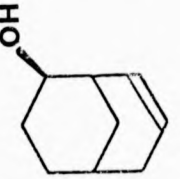
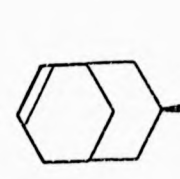
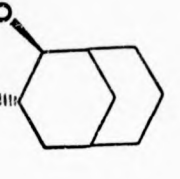
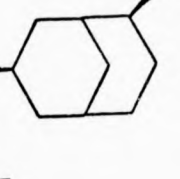

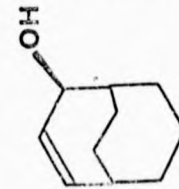
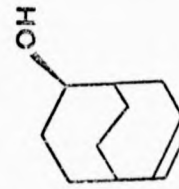
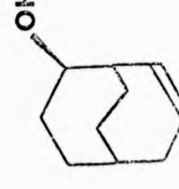
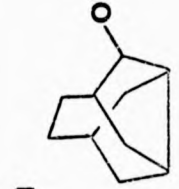
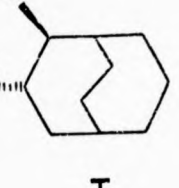
 <p>(1)</p>	 <p>(13)</p>	 <p>(75)</p>	
 <p>(2)</p>  	<p>45%</p> <p>30.5%</p> <p>3.5%</p>	 	<p>80%</p> <p>20%</p>   <p>70%</p> <p>30%</p>

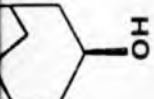






TABLE II
Acetolysis of Epoxides

 (1)	 7.5%  2.5%  71%  9% others 3%
 (13)	 21%  23%  3%  46%  5%  27% others 6%
 (75)	 6.5%  17.5%  1.5%  17%  20% others 6%

bicyclo(3,3,2)decan-3,7,9-triene-2-one (73)⁷¹ and is more clearly illustrated in Scheme II.

Following the report by Marvel³⁴ in which he described the results of the solvolysis of bicyclo(3,3,1)nonan-2,3-cis-oxide (13) it had become clear that factors more complex than those originally supposed should be taken into consideration to explain transannular processes and particularly those of hydride shift in bridged medium ring systems. From Doyle's work bicyclo(3,3,2)decan-2-ene (74) had become available and hence Hafter⁷² was able to prepare bicyclo(3,3,2)decan-2,3-cis-oxide (75) routinely. Hence it seemed productive to perform similar experiments and compare the results of the trifluoro acetolysis and buffered acetolysis of this compound with Marvel's results³⁴. A further point of interest from such an operation would be that one should expect to obtain the first examples of specific functionality in both rings of the bicyclic decane; and further, it would be advantageous to consolidate the evidence available³⁷ for the propensity of the bicyclic decane to exhibit enhanced transannular activity as compared with its lower homologue, since there was at this time only one previous example in the literature, namely that by Doyle³⁷, already well discussed here. Subsequently Hafter⁷² was able to demonstrate a marked increase of transannular activity in the bicyclic decyl oxide in comparison with the two lower homologues, thereby providing more evidence for the strain-flexibility hypothesis governing the approach of the transannularly reacting centres. He rigorously identified all the products by G.L.C. and synthesis of authentic samples and his results for both trifluoro acetolysis and buffered acetolysis are shown in Tables (I) and (II) together with those from the two lower homologues.

A solution relating to the intriguing question of the extent, if any, of hydride participation in the rate determining step, was unfortunately no nearer from these results and hence a need for specific 3,7 functionality in order to obtain a series of compounds in the nature of those prepared

others	6%
	20%
	17%
	1.5%
	17.5%
	23.5%
	6.5%
	(75)

by Ourisson³⁵ was apparent. This prompted Malochich⁷³ to devise a synthetic route to bicyclo(3,3,2)decan-3,7-dione (76), and one was selected after an examination of the plentiful literature describing the synthetic methods available for the bicyclo(3,3,1)nonane system⁷⁴⁻⁷⁹, viz. the double Michael addition of 1,3 dicarbomethoxy acetone (77) with the abnormal Reimer-Tiemann product (78). The product was 2,4 dicarbomethoxy 9-methyl-9-dichloromethyl (3,3,1)nonan-3,7-dione (79) and Malochich⁷³ reasoned that an obvious procedure would be to employ the homologous cycloheptadienone (80) with the same alkylating compound (77) but found that only mono alkylation took place (81). The second ring closure addition could not be made to occur and in hindsight this is not particularly surprising when it is realised that the bicyclo(3,3,1)nonyl example (79) involves the formation of a second six-membered ring as opposed to a seven-membered one on cyclisation to the bridged system. In an alternative approach, reaction of cycloheptadienone (80) with two molecules of malonic ester resulted in the successful formation of the double Michael product (82), which was converted by routine procedures to the diester ketone (83). Several methods of cyclisation were then attempted. Standard alkoxide procedures failed completely and similarly with a ketal function replacing the carbonyl group no bicyclic product was obtained. This lead Malochich⁷³ to consider that the two side chain groups were substituted trans to each other on the seven-membered ring. A final attempt by pyrolysis of the barium salt also failed and hence this approach was abandoned. It should be mentioned in passing that a publication has appeared⁸⁰ at the time of writing in which a similar cyclisation has been achieved on the benzo-diester dione (84) to yield 5,6,8,9 tetrahydro 5,9 propano (70)-benzocycloheptene 7,11 dione (85), thus illustrating the effectiveness of a conformational anchor in facilitating cyclisation. It is noteworthy that the Stirling group has

recently been unable to perform the same cyclisation on the diester derivative (86)⁸¹.

Before leaving this approach entirely it should be pointed out that the use of the acyloin condensation may be applicable here. It can be repeated that this reaction has been demonstrated historically to be the only successful way of closing acyclic compounds to form a medium ring. Hence if Malochich's failures were due to classical medium ring conformational constraints and not the trans disposition of substituents in the diester (83) then an acyloin reaction on a similar derivative (87) should not fail to yield the hydroxy diones (88) and (89). Lengthy manipulation of these compounds would be required, however, to achieve conversion to our desired specific 3,7 functionality, and indeed the type of substitution pattern in (88) and (89) is not far removed from that already made available by Hafter⁷².

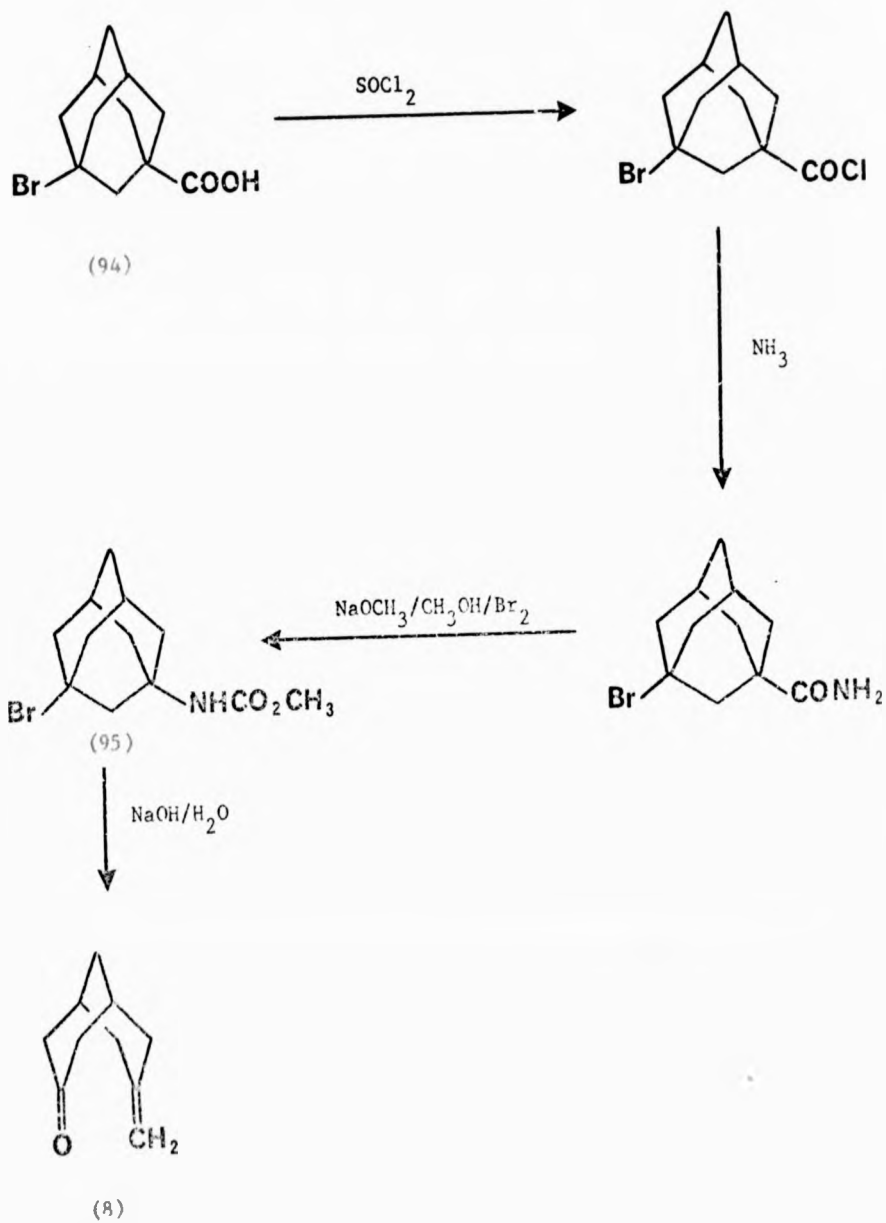
Hence, although a few examples of functionality in both rings are now to hand for the bicyclic decane, none of these is suitable for the specific purposes discussed earlier in this text and obviously a fresh appraisal of the synthesis was required.

A number of reports in the literature provided a starting point for the construction of a projected route to 3,7 disubstitution in the form of 7-exomethylene bicyclo(3,3,2)decan-3-one (28) as follows :-

1. In work pertaining to pharmacological agents, Humber et al.⁸² have reported the direct insertion of an ethano bridge across 1,4-dicarboethoxy-cyclohexane-2,5-dione (90), thereby affording a convenient and high yield (85%) route to 1,4-dicarboethoxy-bicyclo(2,2,2)octan-2,5-dione (91). Although this compound had previously been prepared

SCHEME III

(H. Stetter and J. Mayer, Chem. Ber., 92, 2664, (1959).



independently by Roberts et al.⁸³ and Guha⁸⁴, both authors used sodium alkoxide as base and obtained very poor yields. Humber's⁸² success was attributed to the use of sodium hydride as proton abstracting base.

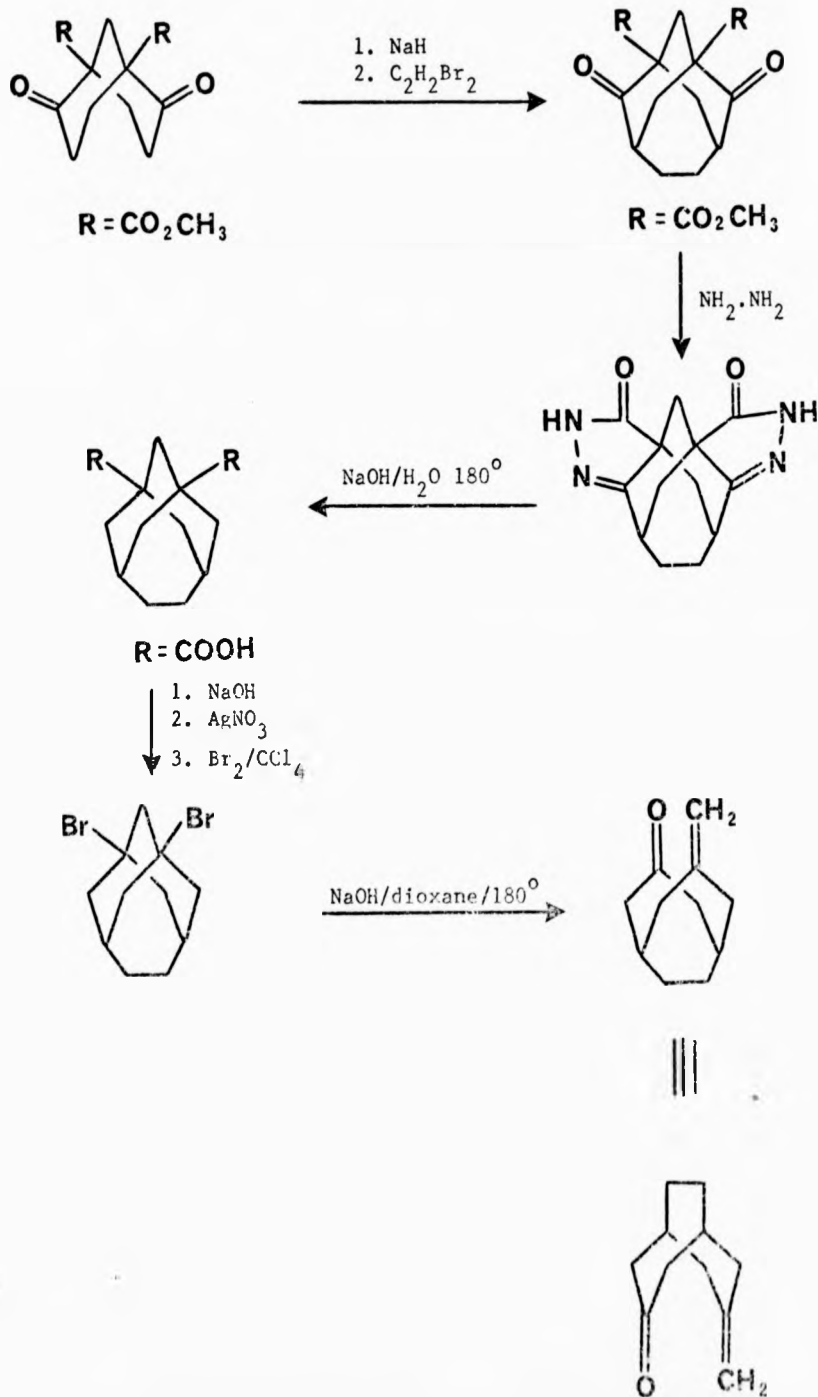
2. More recently, Vogt⁸⁵ has used a similar approach to the homoadamantyl system in the form of 3,6-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (92) from 3,7-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (93) in 40% yield.
3. In a converse manner there are three publications which describe a preparatively useful degradative route to bicyclo(3,3,1)nonanes by means of the base catalysed ring opening of a tricyclic system, namely 1,3-disubstituted adamantanes. The first report appeared by Stetter in 1963³¹ when he performed the sequence of reactions from 1-bromoadamantane-3-carboxylic acid (94) to the bromo urethane compound (95) shown in Scheme (III). Subsequent treatment of (95) with base afforded, in good yield, 7-exomethylene-bicyclo(3,3,1)nonan-3-one (8). It is immediately apparent that the acquisition of the bicyclic decyl homologue of this compound (28) would constitute the precise goal of this project. Stetter's sequence was repeated by McKervey⁸⁶ on the methyl homologue (96) in a novel study of optical activity in the system but prior to this a much more convenient access to the exomethylene ketone (8) had been given by a Gulgy

959).

COCl

CONH₂

SCHEME IV



patent in 1964³² which employed the direct ring opening by high pressure/temperature base catalysed cleavage of 1,3-dibromoadamantane, (9) itself obtainable in one step and in high yield from adamantane (97)⁸⁷.

4. In the original Meerwein paper⁷⁵, describing the preparation of 1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107), it was demonstrated that in addition to facile decarboxylation of the corresponding acid at the 3,7 centres, the tetraester itself could be converted into 1,5-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (98) by heating with water in a sealed tube.

Accordingly, the commencement of actual practical work was initiated along the projected route illustrated in Scheme IV. Having achieved the first bridging step, the remainder of the route is refreshing in its simplicity, until the penultimate key precursor, 1,8-dibromo-tricyclo(4,3,1,1^{3,8})undecane (99) at which point an analogous cleavage using the Geigy patent method³² can be predicted to produce 7-exomethylene-bicyclo(3,3,2)decan-3-one (28) with no conceivable complication. Steps 2 and 3 to afford respectively tricyclo(4,3,1,1^{3,8})undecan-1,2;8,7-bis-pyrazolone (101) and tricyclo(4,3,1,1^{3,8})1,8-dicarboxylic acid (102) are examples of classical preparative organic chemistry and should proceed in high yield. Indeed, Landa⁸⁸, in a communication, has described the quantitative preparation of bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) from the corresponding bicyclo(3,3,1)nonan-1,2;5,6-bis-pyrazolone (104) via a modified Wolff-Kishner reaction. Further.

Meerwein⁷⁵ had already prepared the bis pyrazolone (104) from the diester dione (98) in quantitative yield as one of a series of bicyclo nonane derivatives, thereby establishing the conditions for an exactly similar process using 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8}) undecan-2,7-dione (116). Step 4, a classical Hunsdiecker reaction, is hardly worthy of comment save that Prelog⁸⁹ had thus obtained 1,3-dibromoadamantane (9) from adamantane-1,3-dicarboxylic acid (105).

Attention then turned to the problem of inserting an ethano bridge across the C3,C7 positions of the diester dione (98). In spite of the fact that Vogt⁸⁵ and Humber⁸² had both used alkylation techniques employing the active protons α to the carbonyl groups of β keto esters it was reasoned that the α protons of the diester dione (98) would be acidic enough to allow double sodium salt formation and hence bridging with 1,2 dibromoethane. In the event, treatment of (98) with sodium hydride followed by heating with 1,2-dibromoethane, even for lengthy reaction times gave only the starting material. This disappointing but not altogether unexpected result prompted a more careful examination of the literature to reveal some interesting and independent observations by Corey⁹⁰, Cram⁹¹ and Bloomfield⁹². The use of dimethyl sodium by these authors was the first realisation that this species is a highly powerful aprotic base evidenced by success in improving yields in alkylation alpha to a ketone⁹². Accordingly treatment of (98) with dimethyl sodium prepared by the method of Cram appeared to indicate that sodium salt formation was taking place. This was followed by treatment with 1,2-dibromoethane, but again only starting material was recovered, the remaining material being an intractable oil. The reaction was repeated a number of times under different conditions with virtually the same result and so at this stage of events the prospect of performing a nucleophilic

displacement of 1,2-dibromoethane with the dianion of (98) was dismissed.

A second route involved enamine alkylation. Prominent workers in the field, Stork and Szmuszkowicz^{93,94,95}, have reviewed this area extensively. The main advantage of the method is that it does not require strong base to obtain an enolate anion which is subsequently alkylated together with side reactions including dimerisation and double alkylation. Hence the dual attractiveness of enamine alkylation is the ability to react under mild conditions with the electrophilic alkylating agent without a catalyst, and the impossibility of further reaction once alkylation has taken place. In this light it seemed reasonable that treatment of the bis pyrrolidino enamine (106) with 1,2-dibromoethane could be successful in providing an adequate yield of 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (116).

In the event, the diester dione (98) was treated with pyrrolidine using a routine procedure to give a light brown oil which was assigned the structure of the bis enamine (106) by analysis of its highly characteristic infrared spectrum. On heating this product with 1,2-dibromoethane, for 48 hours at 100^o an oily product was recovered whose infrared spectrum was identical with that of the starting bis enamine (106). Subsequent decomposition in mineral acid disappointingly confirmed these observations with only recovery of the starting dione diester (98). Several repeat experiments with differing reaction conditions were then performed producing similar negative results.

At this point it seemed clear that no success was to be obtained in bridging the diester dione (98) and so a third approach was adopted. Meerwein ester (107) can be seen as falling into the same class of compounds used separately by Vogt⁸⁵ and Humber⁸² for ethano bridge insertions and it seemed that an identical operation, performed on Meerwein ester, should

TABLE III

Decarboxylation data for bridgehead β -keto acids

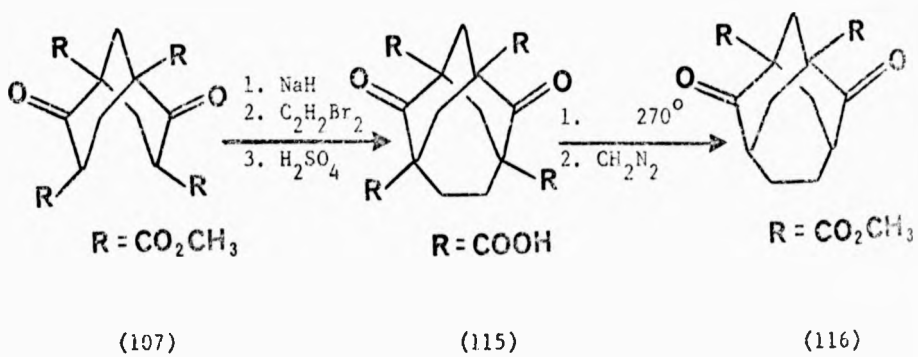
Compound									
Decarboxylation temp. °C	Not at 500	350	Not at 310	280	Not at 240	Not at 346	240		
Enol Ring Size	5	6	6	6	6	6	7		
Orbital dihedral angle deg.	90	90	90	Ca. 90	90	90	80		
Compound									
Decarboxylation temp. °C	260	320	220	240	145	220 110	132		
Enol Ring Size	7	7	7	7	8	8	8		
Orbital dihedral angle deg.	50	60	65	65	30	30	30		

result in similar yields of 1,3,6,8-tetracarboxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108). Such a course of action was, of course, always obvious during the design of the synthesis, but had been set aside on account of the expected difficulties in the removal of functionality at C3 and C6. Nevertheless, further consideration of this problem now became of clear importance.

Simultaneously, in 1967 Wiseman⁹⁶ and Marshall⁹⁷ published independent syntheses of bicyclo(3,3,1)nonene (109), the most flagrant violation of Bredt's rule to date relating to isolable compounds. In the subsequent full paper Wiseman⁹⁸ listed a large number of β -keto bridgehead acids together with decarboxylation data and these are illustrated in Table III. He argued that the criterion governing ease of decarboxylation and in some cases preventing it altogether, depended on the minimum dihedral angle which can be attained by the Π orbitals of the developing incipient double bond forming in the transition state at the bridgehead. If the minimum angle is as high as 80°, decarboxylation is still a possibility but this value would seem to be a limiting one from the examples recorded. Reference to Table III shows clearly that a considerable differential of decarboxylation temperatures exists across a range of different types of acids. Of particular relevance are three examples, bicyclo(3,3,1)nonan-2-one-carboxylic acid (110); tricyclo(3,3,1,1^{3,7})decan-2,6-dione-1,3,5,7-tetracarboxylic acid (111); and tricyclo(4,3,1,1^{3,8})undecan-2,7-dione-3,6-dicarboxylic acid (112). The bicyclic (110) decarboxylates easily at 145° while in contrast the adamantane keto acid (111) will not do so even at 340° and a cursory examination of Brieding models shows that this data is in accord with a limited ability for Π orbital overlap in the former case in contrast to a complete incapacity for it in the latter. The homoadamantyl dione (112) decarboxylates smoothly at 270°⁸⁵ and can be considered as falling somewhere between (110) and (111) on the basis of the criteria

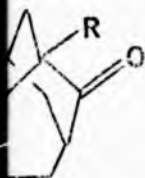
Decarboxylation temp. °C	260	320	220	240	145	220 110	132
	7	7	7	7	8	8	8
Enol Ring Size	7	7	7	7	8	8	8
Orbital dihedral angle deg.	50	60	65	65	30	30	30

SCHEME V



above. A close examination of the molecular model of tricyclo(4,3,1,1^{3,8})undecan-2,7-dione-1,3,6,8-tetracarboxylic acid (113) shows that this compound should decarboxylate selectively at a similar temperature to the Vogt example (112)⁸⁵ leaving the carboxylate functions at C1,C8 intact. Hence it was argued that indeed it would be possible to remove the two ester groups required to bring about the bridging but which were superfluous for the later steps. With regio-selective decarboxylation thus justified the projected route (Scheme IV) was altered as far as the diester dione (116) to that shown in Scheme V. The conditions of Vogt⁸⁵ and Humber⁸² were duplicated by using Meerwein ester (107) as the substrate. Treatment of (107) in 1,2-dimethoxyethane with a 1.5 molar equivalent of sodium hydride was accompanied by gaseous evolution and the appearance of a characteristic pink colour⁸². After removal of the solvent, 1,2-dibromoethane was added and the mixture heated at 140° for 12 hours. A light orange gummy product was obtained which on trituration yielded 1,3,6,8-tetracarbomethoxy tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) in 12% yield. No more crystalline material was obtained on further trituration and the oil itself could not be resolved by chromatographic techniques. The identity of the new compound was established from routine physical data particularly, integration of its 60 MHz n.m.r. spectrum. The parameters of temperature and time were studied in a large number of experiments and it quickly became apparent that the reaction temperature was critical. Further, reaction time was significant and when the reaction was run at 110° for 12 hours yields of product rose reproducibly into the region of 40%, and it was when this maximum figure had been arrived at that an unexpected bonus accrued.

When something of the order of 15 reactions had been performed during optimisation the expense of 1,2-dimethoxyethane solvent became a factor and it was decided to substitute 1,4-dioxane. Subsequent experiments using the



R = CO₂CH₃

(116)

previously established high yield conditions but retaining dioxane in the alkylation stage at 50:50 v/v with 1,2-dibromoethane achieved satisfactory yields of $> 60\%$. The lower limit of reaction time was then established at 8 hours since in addition to the product, quantities of starting material began to be obtained on trituration, at the same time as reduced yields of product being observed. At this stage these yields were considered as optimum. Interestingly, while Humber⁸² recorded yields in the region of 85% for the bridging of 1,4-dicarbo-ethoxy-cyclohexyl-2,5-dione (90), Vogt⁸⁵ was only able to obtain 40% yield using identical conditions on 3,7-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (93). These observations would seem to indicate conformational factors coming into play. It is, in fact, slightly surprising that Vogt's and our bridging reactions proceed as efficiently as indicated since one would expect a preponderance of attack at the exo face of the molecule in its dianionic form (114), a process which would preclude the following intramolecular bridging cyclisation. In addition, the well reported²⁷ C3,C7 endo transannular non-bonding interactions of the system should be taken into account. These are not present in the dianion (114) but are immediately re-introduced on the substitution of an endo species, in this case a halo-ethyl group, and clearly, this should be thermodynamically unfavourable. The experimental evidence, however, clearly demonstrates that bridging is reasonably facile, although it may be that the difference in yields between these and the monocyclic case is a result of the factors discussed here.

The tetra ester dione (106) hydrolysed in a mixture of glacial acetic and hydrochloric acids in an uneventful manner save for a slight difficulty in isolation of the product, bicyclo(4,3,1,1^{3,8})undecan-2,7-dione-1,3,6,8-tetracarboxylic acid (113) which was eventually obtained

in 98% yield by removal of solvents and hydrogen chloride at 100° under reduced pressure. The identity of the product was assumed from the following evidence. Its infrared spectrum was consistent with that of a typical carboxylic acid, there being no starting material bands present and esterification with diazomethane produced a material which was identical in all respects with 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108). Tricyclo(4,3,1,1^{3,8})undecan-2,7-dione-1,3,6,8-tetracarboxylic acid (113) decarboxylated smoothly at 270° and crystallisation of the product yielded tricyclo(4,3,1,1^{3,8})undecan-2,7-dione-1,8-dicarboxylic acid (115) in 94% yield. Again, infrared spectroscopy showed it to be a characteristic carboxylic acid and the corresponding dimethyl ester was unambiguously assigned the identity 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (116) from determination of routine physical and spectroscopic data.

In passing, a small amount of the tetra-acid dione (113) was slowly heated to a temperature of 330° and the resulting product examined for the presence of neutral material. None was found but it should be well worth while to carry out a more rigorous study to determine if the C1, C8 positions are completely inert thermally.

The next step in the synthesis of 1,8-dibromo(4,3,1,1^{3,8})undecane (99) demanded the reduction of the two carbonyl groups at C2, C7. Meerwein⁷⁵ and Landa⁸⁸ had shown that treatment of the pyrazolone (104) with base in a sealed reactor afforded a quantitative yield of the corresponding diacid (103). Hence treatment of 1,8-dicarbomethoxy tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (116) with hydrazine hydrate resulted in an immediate exothermic reaction with the formation, in high yield, of a crystalline solid, readily identified as tricyclo(4,3,1,1^{3,8})undecan-1,2;8,7-bis pyrazolone (101) (78%), from indicated spectroscopic and elemental analytical data. This derivative was too insoluble in all

the common solvents for an nmr spectrum to be obtained. On subjecting (101) to Landa's⁸⁸ conditions a material was recovered which was incompletely reacted, showing infrared bands corresponding to both carboxylic acid and pyrazolone functional groups being present. When the reaction was repeated at higher temperatures and longer reaction times, complete conversion to acidic material was effected. The clean crystalline product recovered from these latter reactions was notably insoluble in any common solvent including water with the exception, of course, of sodium hydroxide solution. As a result, an nmr spectrum was not determined. The infrared spectrum was again highly characteristic, for the expected product (102) however and was very similar to its relative, bicyclo(3,3,1)nonane-1,5-dicarboxylic acid (103). The new compound was characterised spectroscopically and analytically as its dimethyl ester.

The mode of synthesis at this stage was completely consistent with the structural assignments made but the possibility of ambiguity in resultant substitution pattern due to non regioselective decarboxylation could not be totally disregarded and hence an X-ray crystallographic structure analysis of 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecane (100) was undertaken. Additionally, the recent interest in the conformation of the flexible ethano bridge of the homoadamantane skeleton 53-56 has been mentioned in the introduction and it seemed that such an analysis could shed light on this inquiry. The results from the successful crystal structure determination are dealt with in the appendix but suffice to say here that they confirm entirely the correctness of the structural assignment of the diester (100).

The Hunsdiecker reaction, well established in the literature for 40 years, has been reviewed several times^{99,100,101}. Mechanistically, it involves the formation of an acyl hypohalite from the silver salt of a carboxylic acid which subsequently decomposes via a free radical pathway

SCHEME VI

Classical Hunsdiecker reaction

(D.D. Tanner and N.J. Bunce, Acyl Hypohalities. Chapter of The Chemistry of the Carbonyl Halides. (Edited by S. Patai) Wiley Interscience (1971).



to the corresponding alkyl halide, CO_2 and silver halide, (See Scheme VI). Although high yields are often recorded¹⁰⁰, silver carboxylates are notoriously unstable thermally and the reaction itself is known to be inhibited by trace amounts of water. These two observations are unfortunately in direct opposition to one another since the silver salts must be thoroughly dried by heating in vacuo. Nevertheless, the reaction was attempted on bicyclo(3,3,1)nonan-1,5-dicarboxylic acid disilver salt (117), a "test bed" molecule since it was readily available whereas at an early stage of this work tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) was certainly not! Treatment of (117) with bromine in carbon tetrachloride yielded a volatile highly crystalline solid with a characteristic oil of wintergreen type of odour generally associated with moderate molecular weight alkyl halides. The neutral product readily sublimed to give colourless crystals, but in only 10% yield based on the expected dibromide. Infrared analysis showed bands in the C-halogen region although not particularly characteristic of C-Br stretch and indeed the mass spectrum revealed that the product was in fact a mixture of dibromo and chlorobromo compounds. There was no mass spectral evidence of polyhalogenated material. The halogen scrambling between carbon tetrachloride solvent and the product was not surprising since the effect has been reported on a number of occasions. Vogt⁸⁵ had noted the occurrence in the degradation of tricyclo(4,3,1,1^{3,8})undecan-2,7-dione-3,6-dicarboxylic acid (112), and similarly in the bicyclo(2,2,2)octan-1-carboxylic acid (118) case, Stock¹⁰² reported the corresponding bridgehead chloride (119) among the products. This is interpreted as providing evidence for the participation of the species K^{\cdot} in the reaction which in turn is able to produce Cl^{\cdot} radicals in solution. Apart from the disadvantage of being unable to isolate a single pure compound in this instance (the components were unresolved on T.L.C.) the occurrence of

The Chemistry

AgBr

Br

CO_2

RCO_2

this mixture was not an insurmountable obstacle to the later steps of the synthesis since, for example, McKervey¹⁰³ has shown that 1,3-dichloroadamantane (120) can readily replace the corresponding dibromide (9) in the base induced fragmentation of the latter of 7-exo-methylene-bicyclo(3,3,1)nonan-3-one (8). The low yield was a more serious problem and when no improvement could be achieved after several modifications in reaction conditions, an alternative decarboxylative reaction was sought.

McKillop¹⁰⁴ has reported the high yield preparation of several aliphatic bromides from their corresponding thallos carboxylates, whose ready purification and stability has been noted¹⁰⁵. In this modified decarboxylative bromination, inorganic products are formed which indicate that an interplay between the Tl^I and Tl^{III} oxidation states takes place, thus forming the metal halide species Tl_2Br_4 ($Tl^I(Tl^{III}Br_4)$). Stoichiometry required by this analysis demands a thallos salt; bromine ratio of 1 to 1.5 and using these proportions, the East Anglian group reported yields of the corresponding alkyl bromide as being improved from 30% to 90%¹⁰⁴. Although all of McKillop's examples dealt with monocarboxylic acids it seemed that these highly successful procedures could be applied to our dicarboxylic examples. Thallos ethoxide is easily prepared in ethanolic solution¹⁰⁶ and McKillop's technique involves adding the ethoxide to a solution of the appropriate carboxylic acid in light petrol. In our case this was impossible due to the extraordinary insolubility of the diacids. Instead, the finely powdered diacid (103) in its stoichiometric quantity was added in small portions to the thallos ethoxide in ethanol, resulting in precipitation of a heavy solid. When this material was isolated dry it quickly darkened into an amorphous form which defied attempts at crystallisation. When several similar experiments failed to yield a crystalline salt and gave only the same result, this procedure was discarded.

SCHEME VII

Cristol and Firth modified Hunsdiecker reaction

(S.J. Cristol and W.C. Firth, J. Org. Chem., 26, 280, (1961).

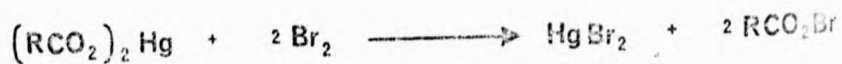
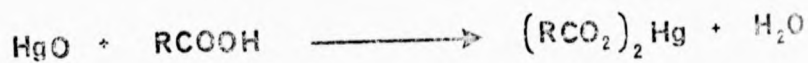


Then as for classical Hunsdiecker reaction (Scheme VI).

SCHEME VIII

Mercury Salt Pathway for modified Hunsdiecker reaction

(N.J. Bunce, J. Org. Chem., 37, 664, (1972).



Then as for classical Hunsdiecker reaction (Scheme VI).

(1961).
Br₂O
H₂O
Scheme VI).

Attention moved to a modification of the Hunsdieker reaction originally employed by Cristol and Firth in 1961¹⁰⁷ with remarkable success, viz. the treatment of carboxylic acids with bromine and mercuric oxide in refluxing carbon tetrachloride, bromo-trichloromethane or 1,2-dibromoethane to give the alkyl bromide directly, (e.g. stearic acid \longrightarrow heptadecylbromide 90%). The method is remarkable in that trace quantities of water do not adversely affect the reaction (cf. Hunsdiecker¹⁰⁰). Indeed as shown in the postulated mechanism, also supported by Ziebarth¹⁰⁸ (Scheme VII) it is a product of the reaction. The brominating species was originally thought to be bromine monoxide which reacted with the acid to form the acyl hypohalite followed by subsequent decomposition in the normal manner.

tion
Hg + H₂O
+ 2 RCO₂Br
Scheme VI).

The solubility problem of our diacids proved troublesome when bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) was subjected to these Cristol-Firth conditions viz.¹⁰⁷ the addition of bromine in carbon tetrachloride to a stirred slurry of the diacid in the same solvent. No mercuric oxide was taken up and only starting material was recovered. Recalling that both diacids (103) and (102) were very slightly soluble in 1,2-dibromoethane a second experiment was performed using this solvent at 100°. The reaction products were a mixture of starting material, contaminated with a small amount of a neutral compound (ν max. 1732 cm⁻¹). In the event that a refluxing reaction mixture was important to remove azeotropically any water from the reaction a further experiment was performed using carbon tetrachloride/1,2-dibromoethane (1:1) as the solvent system. On this occasion uptake of mercuric oxide was observed together with gas evolution and a small yield (15% based on dibromide) of neutral organo-halogen material was obtained whose infrared spectrum was identical with that of the chloro-bromo mixture obtained from the Hunsdiecker reaction (vide supra). The corresponding mass spectrum was

very similar, indicating a mixture of chloro- and bromo-dihalide moieties and the recurrence of an impurity with adsorption at (ν max. 1732 cm^{-1}) in the infrared was noted. It readily separated from the bridgehead dihalo components by adsorption chromatography but was not identified here or at any other stage in the project since effort was concentrated on obtaining adequate yields of the bridgehead dihalo species. In a thorough investigation, Bunce¹⁰⁹, has reported on the relationship between the Hunsdiecker and Simonini reactions. The latter refers to the formation of symmetrical esters during a Hunsdiecker reaction depending on the conditions used and is concluded as involving a nucleophilic attack of excess silver carboxylate on the already formed alkyl halide. Competition from the Simonini process is typical in Hunsdiecker type reactions where iodine is used as the halogen, the iodide ion being an excellent leaving group, such that in some cases the products are exclusively symmetrical esters. The effect is less commonly observed for the bromine case, but examples do exist, particularly for tertiary acids, although generally excluding bridgehead types. For example, silver pivalate affords only traces of t-butyl bromide with bromine. The only product apart from starting material is t-butyl pivalate. Using this observation and the fact that the decarboxylative bromination of pivalic acid can only be achieved by reactions not involving silver salts e.g. the decarboxylation of pivaloyl hypohalite with bromine oxide, Bunce¹⁰⁹ concluded that the Simonini reaction pathway involves a metal salt/alkyl halide interaction in ester formation. In the field of bridgehead carboxylic acids he commented on the appearance of only the bridgehead iodide (121) from a Hunsdiecker reaction on 7,7-dihydro-1,2-dioxabicyclo(2,2,1)heptan-1-carboxylic acid (122)¹⁰⁹ with iodine as halogen, but that ester formation was exclusive in the homologous bicyclo(2,2,1)heptan-1-carboxylic acid (123)¹⁰².

SCHEME IX

(N.J. Bunce and N.G. Murray, Tetrahedron, 27, 5323 (1971))

Anchimeric assistance to halogen bond breaking during a Walden S_{N2} inversion introducing S_{NI} character.



(1971).
S_{N2} inversion
Ag X
Ag X

The rationale presented for this exaggerated difference in behaviour of these two bridgehead compounds lies in the inertness of the norbornane bridgehead to nucleophilic substitution of iodide by silver carboxylates while the bicyclo-octyl system is more flexible and is able to accommodate such a process. This work discusses the question of bridgehead reactivity extremely loosely, however, and seems not to take account of the impossibility of Walden-type nucleophilic processes taking place as demanded by the reaction pathway postulated and shown in Scheme IX. Bunce¹⁰⁹ does give provision, however, for ester formation being allowed to take place via a carbonium ion (S_{N1}) attack and cites an examples where this is certainly the case¹¹⁰, hence it must be supposed that this is the mechanism followed in bridgehead cases. It is therefore not surprising that one should find Simonini esters appearing in the products from our modified Hunsdiecker reaction on bicyclo(3,3,1)nonan- acid (103). However, returning to the Cristol-Firth¹⁰⁷ and Ziebarth¹⁰⁸ mechanisms an anomaly exists since these postulate a mechanism precluding the formation of a mercury salt at all; this intermediate being necessary for Simonini ester formation¹⁰⁹.

During the time that these studies were being undertaken at Stirling, Bunce¹¹¹ and Cason¹¹² independently published examinations of the Cristol-Firth mechanism with particular reference to the stages between the starting carboxylic acid and the formation of the free radical R'. In short, the Cristol-Firth and Ziebarth mechanistic arguments were disproved by painstaking and thorough work. The new work provided compelling evidence against the involvement of bromine monoxide as the positive brominating species. Bunce¹¹¹ concluded that this could not be the case from the observation that pivalic and phenyl acetic acids give virtually no yield of the corresponding bromides in the mercury oxide

reaction but significant amounts of them when preformed bromine monoxide is used. Cason¹¹² noted that excellent yields of the alkyl halides are obtained at reflux temperatures at which bromine monoxide would be extremely unstable and would not be expected to be present except transiently and in minute amounts. The joint conclusion reached^{111, 112} was that a metal salt is indeed formed with mercury oxide to result in the currently accepted mechanism shown in Scheme VIII. Cason¹¹² also mentioned that the original Hunsdiecker papers had rejected preformed mercury salts as inferior to their silver counterparts without any experimental evidence, stating that the former salts were insoluble in carbon tetrachloride. However, these results refer to the cold and as already mentioned Cason attained superlative yields of the required bromides from mercuric salts at reflux temperatures. In addition, Cason noted that when a mercury oxide/bromine reaction was performed under conditions of continuous azeotropic distillation of carbon tetrachloride, then even higher yield resulted, a fact which returns to our low yield problem at hand. Using this information, the degradation of (103) was again attempted using a 1:1 carbon tetrachloride/1,2-dibromoethane solvent system, with carbon tetrachloride distilling out of the system at the same rate as the bromine/carbon tetrachloride mixture was introduced. Recall that these conditions are slightly different from the initial Cristol-Firth¹⁰⁷ procedure tried here (Page 32) in that previously the system was maintained at reflux. A product was formed, which after separation of neutral carbonyl material was present in 75% yield based on bicyclo(3,3,1)nonan-1,5-dibromide (124). In addition, the amount of the by now familiar Simonini product was reduced. The corresponding (102) was subjected to the above conditions and gave what appeared to be an incredible 95% yield based on tricyclo(4,3,1,1^{3,8})undecan-1,8-dibromide (99). The suspect nature of this result

was soon confirmed, however, when the associated mass spectrum revealed that the product was polyhalogenated consisting mainly of tetrahalogenated material of an indeterminate chlorobromo mixture with some evidence for pentahalogenation! It is ironic to note in passing here that early in the sequence bridgehead reactivity was observed aiding in the decarboxylation of tricyclo (4,3,1,1^{3,8})undecan-1,3,6,8-tetracarboxylic acid-2,7-dione (113)^{96,97,98} and now here seemed to be manifesting itself again, this time proving to be a serious problem in the later steps.

Happily, at this juncture, Bunce¹¹³ provided an explanation of the unusual behaviour by reporting the potent reactivity of bromine mercuric oxide mixtures. He observed that when some carboxylic acid chlorides and mercuric oxide are treated with bromine, no decarboxylation products are observed, although bromine is consumed. In subsequent control experiments, bromine was shown to be virtually unreactive towards tetrachloroethane but when mercuric oxide was introduced, bromo tetrachloroethane was formed in a vigorous reaction and hence it became clear that bromine and mercuric oxide form a highly reactive brominating agent. Indeed, cyclohexane was found to react vigorously at reflux while 2,2,3,3-tetramethyl-butane was readily converted to its corresponding monobromide. The high reactivity of primary and secondary centres to the new reagent was demonstrated but tertiary positions were found to be relatively unaffected as evidenced by the virtual lack of 2-bromo-2,3-dimethyl-butane in the products of a reaction on 2,3-dimethyl butane. The reaction was subsequently shown to involve bromine monoxide as the reactive brominating agent on the basis that this compound when used as a preformed reagent has a very similar reactivity to the mercuric oxide bromine reagent. Its thermal instability is accounted for by the departure from stoichiometry of the reaction¹¹³. Although it has been mentioned that tertiary centres are not so reactive to these conditions,

it should be recalled that the bridgehead position C3,C6 in the diacid (102) might be expected to be since Schleyer describes a parallel reactivity of carbonium ion and free radical mechanisms at a given bridgehead in his extensive work on this subject⁴⁰.

Bridgehead positions being a special case amongst tertiary centres in terms of their reactivity, it seemed we were faced with two reactions, both of a free radical nature which were proceeding by wholly different and competitive mechanisms viz. in the homo adamantane diacid (102) on the one hand, irreversible hydrogen atom abstraction was taking place at C3,C6¹¹³ and on the other the modified Hunsdiecker mechanism was operating at the carboxylic sites C1,C8 via the now accepted mercury salt mechanism (Scheme VIII)^{111,112}.

Prior to this no attempt had been made to restrict the amount of bromine added to the system, mercuric oxide being added in a slight stoichiometric excess. It now became necessary to achieve selectivity between these two reactions.

The homoadamantane 1,8-dicarboxylic acid (102) was treated in the same way that had proved successful for its bicyclic relative (103) except that the precise stoichiometric quantity of bromine was added to effect double decarboxylation with the simultaneous distillation of carbon tetrachloride from the system. A yield of organohalogen material was obtained which could be calculated as a 75% yield based on exclusive dibromination. The product sublimed only with difficulty, however, and although its infrared spectrum illustrated a well-defined C-halogen region, the mass spectrum showed trihalogenated material to be present together with some dihalide. The mixture was homogeneous to T.L.C., and could not be separated by adsorption chromatography. This result, although disappointing, was informative in that it illustrated the

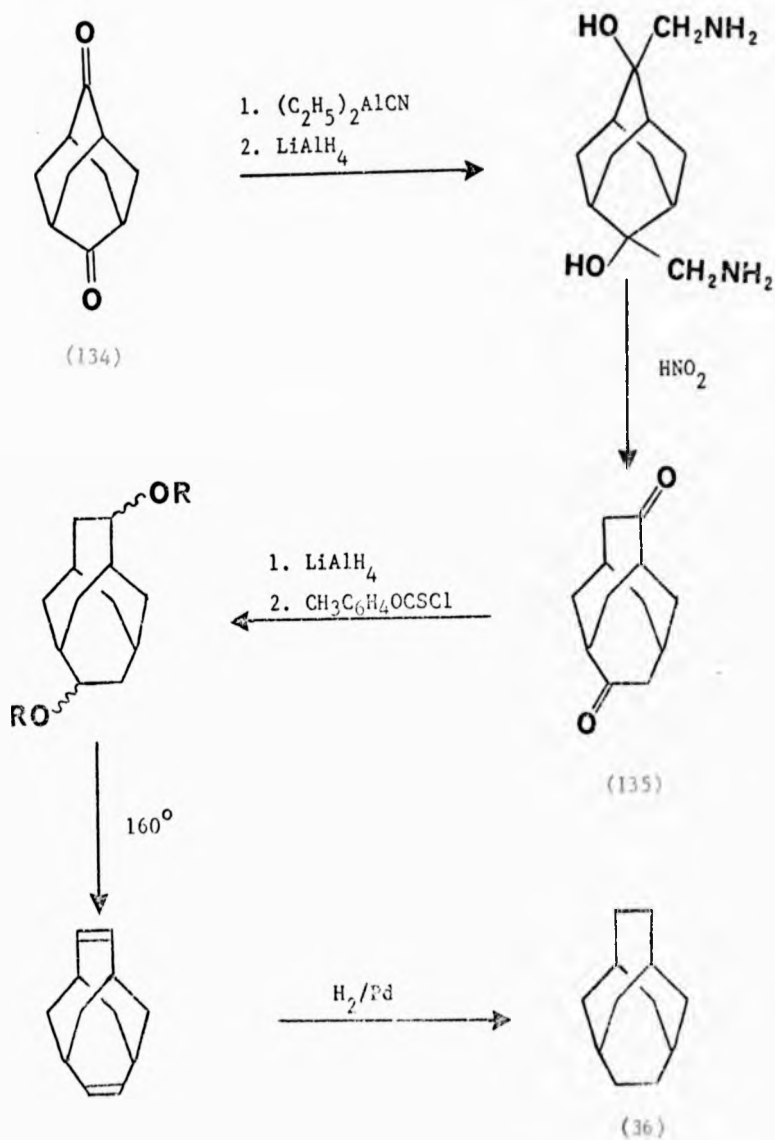
selectivity which could be achieved by controlling the amount of bromine used and hence a final reaction was performed using an excess of tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) but a deficit of bromine. Workup in the usual way yielded a colourless crystalline neutral material which readily sublimed. The infrared spectrum was very similar to that of the above trihalo mixture but the mass spectrum clearly showed that only dihalo material was present.

This dihalo mixture (125) (R = Br, R' = Cl, Br) was subjected to the identical conditions for the base catalysed fragmentation of 1,3-dibromo adamantane (9)³² and on workup a colourless crystalline material was obtained which readily sublimed and possessed a camphoraceous odour highly typical of oxygenated bicyclo(3,3,2)decane compounds^{72,76}. The product, homogeneous to T.L.C., was assigned the structure 7-exomethylene-bicyclo(3,3,2)decane-3-one (28) on the basis of spectral and analytical data. The 58% yield for the fragmentation was calculated, making the assumption that the dihalo mixture (125) contained equal amounts of dibromo- and chlorobromo compounds.

A ready and obvious chemical structure proof was seen in degradation to the parent hydrocarbon (56), the latter being readily available. Indeed, Stetter had confirmed the structure of the lower homologue in exactly this way³¹. 7-exomethylene-bicyclo(3,3,2)decane-3-one (28) was ozonised using standard procedures¹¹⁴ to yield the corresponding dione in 38% yield. Spectral and analytical data were consistent with bicyclo(3,3,2)decane-3,7-dione (76). Wolff-Kishner reduction of (76) afforded a non-polar material with an odour identical to bicyclo(3,3,2)decane (56) although comparison of its infrared spectrum with that of an authentic sample of bicyclo(3,3,2)decane (56) was inconclusive due to the fingerprint regions being extremely weak, a not surprising occurrence in view of the symmetry involved. Both compounds were subjected to G.C.H.S. analysis after which

an interesting anomaly came to light. The two mass spectra were very similar yet fundamentally different. Bicyclo(3,3,2)decane (56) exhibits a parent ion M^+ $m/e = 138$ and a subsequent fragmentation pattern virtually identical with that of the Wolff-Kishner product except that the latter shows M^+ $m/e = 136$ as a parent ion and all the fragment ions appear at a corresponding two mass units lower than in the authentic hydrocarbon. Several attentive re-runs of the unknown spectrum clearly demonstrated that no errors of mass assignment had been made and the the Wolff-Kishner hydrocarbon was indeed not bicyclo(3,3,2)decane (56). Taking into account the evidence provided earlier by the X-ray crystal structure elucidation of (100) and the subsequent reaction mechanisms involved in the later steps it was not seriously doubted that the exomethylene ketone (28) was other than as assigned. An obvious explanation lies in ring closure during the Wolff-Kishner reduction to form tricyclo(3,3,2,0^{3,7})decane (126) and indeed there are precedents for anomalies occurring in the Wolff-Kishner reduction involving ring closure albeit; not of this precise nature^{115,116}. Since this work was completed, Dr. I. Watt at Stirling⁸¹ has observed that the bis carboxylic acid chloride (127) when treated with a catalytic amount of chlorocarbonyl bis (triphenylphosphine)rhodium at 250°, converted smoothly to specifically the bis bridgehead chloride (128) in 70% yield. ¹³C n.m.r. analysis of (128) exhibited a five-line signal consistent with the structural assignment. Treatment of (128) with the Geigy conditions³² afforded 7-exomethylene-bicyclo(3,3,2)decan-3-one (28) in 53% yield. Regarding the complete confirmation of the structure (28) Watt has succeeded in preparing the exo alcohol (129) and has demonstrated that it readily cyclises to 1-homoadamantanol⁸¹ (130) identical in all respects with an authentic sample supplied by Majerski¹¹⁷. As mentioned previously

SCHEME X



(U. Gerlach, *Helv. Chim. Acta.*, 55 2962 (1972))

H₂
NH₂
Fohlisch et. al.⁸⁰ have published a synthesis of 5,6,8,9-tetrahydro-5,9-propano-(7H)-benzocycloheptene-7,11-dione (85) which was cyclised to the derivative (131), thereby illustrating the first example of 3,7 transannular interactions in a bicyclo(3,3,2) system having specific 3,7 functionality. It is noteworthy that attempts by the Stirling group to use this method for a preparation of the non-benzenoid system from the compound (88) have failed⁸¹.

It is convenient to mention in the concluding paragraphs of this discussion the independent publications by three authors^{118,119,120} describing the synthesis of the tricyclo(4,3,1,1^{4,9})dodecane system. All of these reports appeared during the course of this work, the first being a short communication by Stepanova¹¹⁸. From rearrangement studies in the adamantane series Stepanova had at his disposal 1-methylamino-homoadamantane (132) and subsequent deaminative ring expansion resulted in the formation of the bridgehead alcohol (133). Although he prepared a number of other bridgehead derivatives Stepanova acquired no conformational data on the new skeleton. One year later a number of derivatives of the dodecane were prepared by Gerlach¹¹⁹ starting from adamantane-dione (134). Entry to the system was achieved with the dione (135) following the route of deaminative ring expansion shown in Scheme X. Gerlach did perform a ¹³C n.m.r. spectral analysis on the hydrocarbon (36) reflecting that Bridging models indicate the D_{2d} symmetry (both bridges eclipsed) not to be the lowest energy conformation as would be expected. However, the S₄ symmetry situation with both ethano bridges staggered presents an identical situation regarding the environmental equivalence of four pairs of carbon atoms relating to ¹³C n.m.r. In both these symmetries the four ethano bridge carbons are equivalent as are the four bridgeheads and the four methano bridge methylenes. Three equal intensity signals were duly found, but of course gave no clue as to a preferred conformation. Gerlach proceeded to study

the ^{13}C n.m.r. of the dione (135) and acquired data which seemed to indicate that, in this compound at least, equilibration occurs between one all staggered form and the other. In each of the staggered conformations of the dione each carbon is environmentally different but when equilibration takes place, a pair wise interchange of carbons takes place. That this is the case was borne out by the ^{13}C n.m.r. spectrum having three peaks of equal intensity and not six. On this evidence therefore it would seem that the most recent Schleyer data⁶⁷ on ethylene bridged bicyclic and tricyclic molecules which indicates that no particular conformational preference seems to be observed, is vindicated. Schleyer had concluded that the substituents on the ring system are responsible for providing the steric requirements resulting in conformational preferences and not the skeleton itself. Majerski has also synthesised the same derivatives as Gerlach by a virtually identical route¹²⁰.

An interesting co-publication by the Princeton and Stirling groups has appeared¹²¹ during the preparation of this thesis. "Manxane", bicyclo(3,3,3) undecane (137), previously synthesised by Doyle¹²² was predicted as having greatly enhanced bridgehead reactivity from empirical force field calculations. 6.8 k.cal./mole should be relieved in proceeding from the parent hydrocarbon (137) to the corresponding bridgehead cation (138). In the event values of $k = 4.71 \times 10^{-2} \text{ sec}^{-1}$ (20.3°) and $2.57 \times 10^{-1} \text{ sec}^{-1}$ (20.2°) were observed during the solvolysis of the bridgehead chloride in respectively aqueous acetone and aqueous ethanol. This remarkable result shows that this bridgehead system, in addition to being the most reactive of all bridgeheads studied, is much more reactive even than *t*-butyl in the same solvents as a consequence of the relief of exaggerated bond angle strain in forming an sp^2 centre at the bridgehead.

In conclusion it may be said that the work described in this section is for all practical purposes the first route into bicyclo(3,3,2)decane substituted in both rings from readily available starting materials.

Experimental

General

The following is applicable to the experimental parts of Sections II and III also.

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Mass spectra were determined by the Physico-Chemical Measurements Unit (P.C.M.U.) at Aldermaston on an AEI M.S.9 Spectrometer. Routine infra-red spectra were measured on Perkin-Elmer 157G and 457 spectrophotometers in CCl_4 solution unless otherwise stated. Routine nuclear magnetic resonance spectra were measured on a Perkin-Elmer R10 (60 MHz) spectrometer using tetramethylsilane as internal reference unless otherwise stated. Microanalyses were carried out at Oxford by Dr. F.B. Strauss and his staff. Thin layer chromatography was carried out on baked Kieselgel G plates, which were developed with methanol/sulphuric acid spray and visualisation at 140° . Alumina for chromatography was Camag. type H, deactivated with 5% w/w water.

1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107)

A mixture of dimethyl malonate (792g.; 6.00 mol.), paraformaldehyde (135g.; 4.50 mol.), piperidine (12ml.) and benzene (1,200ml.) were heated at reflux under a Dean-Stark attachment for 8 hours. During this time 78.9ml. of water, 97% of the theoretical were collected. Benzene was removed by distillation under reduced pressure and the residue was dissolved in absolute methanol (450ml.). This mixture was added rapidly to a stirred solution of sodium methoxide prepared from sodium (97.8g.; 4.25g. atom) and absolute methanol (1,200ml.) and the resulting solution stirred and heated gently at reflux for seven hours, more solvent being added as necessary to facilitate stirring. After cooling the solvent was removed under reduced pressure and the residue dissolved in ice-water (1,500ml.). The aqueous solution was extracted with ether (3 x 500ml.) and the crude product was precipitated by bubbling carbon dioxide through the aqueous phase. The precipitate was collected at the pump, washed with water, air-dried and then combined with benzene (900ml.) and residual water removed from the system by azeotropic distillation followed by rapid filtration of the hot solution. The dione tetraester (385g. 67%) crystallised in colourless needles m.p. 159-162° (lit. 163-164°).

1,5-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (96)

1,3,5,7-Tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107) (10.00g., 0.026 mole.) was placed in a thick walled glass tube along with enough water to occupy the same volume as the solid admitted. The tube was then sealed and placed in a Carius furnace, pre-heated at 220° for 90 minutes. The tube, together with its outer steel protective casing, was removed from the furnace and allowed to cool to the ambient temperature. The compressed carbon dioxide was released by heating the narrow sealed joint

of the tube with an oxygen flame until the molten glass was opened by the pressure from within. The reaction mixture consisted of an upper aqueous phase with an organic oil (pale brown) at the bottom of the tube. Crystallisation was achieved readily by shaking the tube violently after which a colourless crystalline solid was deposited. The product was filtered at the pump, washed once with water (30ml.) and air dried to yield 1,5-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (98) (5.2g. 72%) m.p. 186-187° (lit. 187-188°).

Attempted bridging of 1,5-dicarbomethoxybicyclo(3,3,1)nonan-2,6-dione (98) using sodium hydride and 1,2-dibromoethane

(a) A solution of 1,5-dicarbomethoxybicyclo(3,3,1)nonan-2,6-dione (98) (55.26g.; 0.21 mole) in dry 1,2-dimethoxy ethane (450ml.) was added dropwise over 30 minutes to a stirred slurry of sodium hydride (25.4g. of a 60% suspension in oil; 0.66 mole) in dry 1,2-dimethoxyethane (450ml.). Gaseous evolution was observed during the addition but no pink colouration appeared. 1,2-dimethoxyethane was distilled from the system until (500 ml.) had been collected after which 1,2-dibromoethane (900ml.) was added portion-wise while distillation and stirring were continued. After three-quarters (675ml.) of the 1,2-dimethoxyethane had been collected, the distillation temperature rose to 130° at which point 1,2-dibromo ethane itself was distilling as an azeotrope. The system was arranged for reflux and heated with stirring at 120° for 48 hours, then filtered hot and the inorganic solids washed once with chloroform (100ml.). The filtrate was then evaporated under reduced pressure to yield a light orange gum which was subsequently triturated with methanol to yield a colourless crystalline solid (47.2g.), subsequently shown to be identical in all respects with the starting material. The remaining gum (3.2g.) could not be crystallised and was unresolved by T.L.C. analysis. Chromatography on Camag type 'R' alumina returned the gum unchanged.

(b) Conditions identical to those in Experiment (a) were followed until the removal of 1,2-dimethoxy ethane. Distillation was then continued with a simultaneous addition of 1,2-dibromoethane maintaining a total reaction volume of (900ml.). When pure 1,2-dibromoethane began to distill at 150° the system was arranged for reflux with heating and stirring continued for 48 hours. The hot reaction mixture was filtered and inorganic solids washed once with chloroform (100ml.). A similar brown gum (49.0g.) was isolated on removal of the solvents. Trituration with methanol produced a preponderance of starting material (45.2g.). The residual gum (3.1g.) was similarly unresolved by chromatography.

(c) Experiment (a) was repeated using identical conditions except that a prolonged reaction time (72 hours) was employed during the alkylation stage. The results obtained were virtually identical with those of Experiments (a) and (b). Trituration with methanol yielded starting material (48.4g.) and the same intractable orange gum (2.8g.).

Attempted bridging of 1,5-dicarbomethoxybicyclo(3,3,1)nonan-2,6-dione (98) with 1,2-dibromoethane using dimethyl sodium as base

(a) Dimethyl sulphoxide was prepared pure and dry by fractional distillation from calcium hydride.

A solution of 1,5-dicarbomethoxybicyclo(3,3,1)nonan-2,6-dione (98) (2g.; 0.0074 mole) in dry DMSO (30ml.) was added dropwise to a stirred solution of sodium hydride (0.60g. of a 60% suspension in oil; 0.015 mole) in DMSO (30ml.) at the ambient temperature. An immediate colour change from colourless to pale yellow was noted and an exothermic evolution of hydrogen observed. After five minutes a clear yellow solution resulted which was cooled to the ambient temperature and 1,2-dibromoethane (9.4g.; 0.05 mole) added dropwise with stirring over 30 minutes and the

reaction mixture set aside overnight. The mixture was then poured into water (200ml.) resulting in precipitation of a brown quasi-crystalline material. The mixture was extracted with methylene chloride (3 x 100ml.) and the organic phase dried ($MgSO_4$). Removal of solvents under reduced pressure yielded a semi-solid gum which was triturated with methanol to yield a starting material (1.92g.). Evaporation of the filtrate yielded a residue which was not resolved by T.L.C. analysis or adsorption chromatography.

(b) Experiment (a) was repeated using identical conditions except that the reaction mixture was heated at 140° for eight hours. An identical work-up procedure afforded a residue which was unresolved by T.L.C. analysis and was not further purified.

Attempted bridging of the bis-pyrrolidino enamine of 1,5-dicarbomethoxy bicyclo (3,3,1)nonan-2,6-dione (106) with 1,2-dibromoethane

Pyrrolidine (5.60g., 0.08 mole) was added to a solution of 1,5-dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (98) (5.4g., 0.02 mole) in benzene (50ml.). The mixture was boiled under reflux using a Dean-Stark trap until no further separation of water could be observed (16 hours).

Removal of the solvent together with excess amine by evaporation under reduced pressure gave a light brown oil (7.52g.) ν_{max} . (CCl_4) 2256, 2880, 1725, 1627, 1439, 1368, 1344, 1327, 1225 (broad) 1106 and 1086 cm^{-1} . The infrared spectrum is consistent with the formation of the bis enamine of 1,5-dicarbomethoxy bicyclo(3,3,1)nonan-2,6-dione (106).

The bis enamine (106) (6.8g., 0.018 mole) was dissolved in 1,2-dibromoethane (40ml.) and heated at 120° overnight. Removal of solvent under reduced pressure yielded a light brown oil whose infrared spectrum was identical with that of the starting bis enamine (106). The crude product was decomposed by boiling with dilute sulphuric acid to yield the starting

material 1,5-dicarbomethoxy bicyclo(3,3,1)nonan-2,6-dione (98) (4.6g.).

1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108)

(a) A solution of 1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107) (100g., 0.26 mole) in dry 1,2-dimethoxyethane (750ml.) was added to a stirred slurry of sodium hydride (31.20g. of a 60% dispersion in oil; 0.78 mole) in dry 1,2-dimethoxy ethane (750ml.) over 30 minutes. The mixture was stirred at 60° for 40 minutes after which 1,2-dimethoxyethane (1L) was distilled from the system. 1,2-dibromoethane (1L) was added dropwise to the reaction mixture with continued stirring while distillation continued. An azeotrope of the two solvents appeared to distil at 130° and at this point the system was arranged for reflux and the reaction continued at 130° for 12 hours. The mixture was then filtered hot and the inorganic residue washed twice with chloroform (2 x 100ml.). Evaporation of solvent under reduced pressure gave a light brown gum which was readily triturated with methanol to give a colourless crystalline solid. The crude product was collected at the pump and a second crop obtained from the mother liquor in the same manner. The two crops were combined and re-crystallised from ethanol in needles to yield 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108), (30.1g., 28%)

m.p. 253 - 254° (Found: C, 55.33; H, 5.49. $C_{19}H_{22}O_{10}$ requires C, 55.6; H, 5.4%); M^+ 410; ν_{max} . 1745, 1715, 1262, 1071, 1031, 958 and 932 cm^{-1} . n.m.r. τ_H (CDCl₃) 6.17 (12H, s), 7.17 (4H, s), 7.53, 7.67, 7.73, 7.79 (6H, m).

(b) A solution of 1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107) (100g., 0.26 mole) in dry 1,2-dimethoxyethane (750ml.) was added to a stirred slurry of sodium hydride (31.20g. of a 60% dispersion in oil; 0.78 mole) in 1,2-dimethoxyethane (750ml.) over one hour. The mixture was stirred at 60° for one hour after which 1,2-dimethoxy ethane (1L) was distilled from

the system. 1,2-dibromoethane was then added slowly to the reaction mixture with continued distillation and stirring until pure 1,2-dibromoethane distilled (2.5L). Stirring was continued and the mixture heated at reflux for 12 hours, filtered and the inorganic residues washed with chloroform as above. The reaction was then worked-up in the usual manner to give 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) (12.9g, 12%).

(c) The procedure of experiment (b) was followed as far as the distillation of 1,2-dimethoxyethane. After 700ml. of this solvent had been removed, 1,2-dibromoethane (750ml.) was added to the stirred mixture and the system fitted for reflux and heated at 110° for 12 hours. Work-up as before gave 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) (43.7g, 41%).

(d) A solution of 1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107) (100g., 0.26 mole) in dry 1,2-dimethoxyethane (750ml.) was added to a stirred slurry of sodium hydride (31.20g. of a 60% dispersion in oil; 0.78 mole) in 1,2-dimethoxyethane (750ml.) over 30 minutes. The mixture was stirred at 60° for 2 hours after which 1,2-dimethoxyethane (1L) was distilled from the system. 1,2-dibromoethane (750ml.) was then added to the mixture and the system arranged for reflux, heated and stirred at 130° for 72 hours and then worked up in the normal way to yield 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (27.3g., 25%).

(e) 1,3,5,7-tetracarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (107) (100g, 0.26 mole) in dry dioxane (750ml.) was added over 30 minutes with stirring to a mixture of sodium hydride (18.72g., 0.78 mole; 31.20g. of a 60% dispersion in oil) and dry dioxane (750ml.). The mixture was stirred at 60° for 40 minutes and dioxane (1L) then distilled from the system. 1,2-dibromoethane (1L) was added slowly to the reaction mixture and stirring continued for 12 hours while the system was heated at 110°. The mixture was

then filtered hot and the inorganic residue washed twice with chloroform (2 x 100ml.). Evaporation of solvent under reduced pressure gave a light brown gum which was readily triturated with methanol to give a colourless solid. The crude product was collected at the pump and a second crop obtained from the mother liquor in the same manner. The two crops were combined and recrystallised from ethanol in needles to yield 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) (68.34g., 64%).

Acid Hydrolysis of 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108)

To a solution of 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) (50g., 0.12 mole) in glacial acetic acid (500ml.) was added hydrochloric acid (170ml.) and water (170ml.) and the mixture heated at reflux for 15 hours, cooled and solvent removed under reduced pressure. The light brown residue was dried in vacuo over phosphorous pentoxide to yield colourless crystalline crude 2,7-dioxo-tricyclo(4,3,1,1^{3,8})undecan-1,3,6,8-tetracarboxylic acid (113) (42.30g., 98%) based on complete conversion.

ν_{max} (mull). 3500-2300, 1700 (broad), 1270, 1115, 1063, 1022 and 933 cm^{-1} . n.m.r. - absence of $-\text{OCH}_3$ signals.

The compound was characterised as its tetramethyl ester. The crude acid (1.0g.) in diethyl ether at 0° was treated dropwise with an ice-cold ethereal solution of diazomethane until no more evolution of gas could be observed and the solution had turned yellow. Excess diazomethane was destroyed by the dropwise addition of glacial acetic acid, and the mixture was evaporated to dryness under reduced pressure giving a lightly discoloured solid. Recrystallisation of the product from ethanol in needles yielded 1,3,6,8-tetracarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (108) (1.10g., 94%).

based on complete conversion. m.p. 253-254°. The identity of the product was confirmed by the comparison of its infrared and n.m.r. spectral data with that of an authentic sample.

Attempted Exhaustive Decarboxylation of 2,7-dioxo-tricyclo(4,3,1,1^{3,8})

1,3,6,8-tetracarboxylic acid (113)

2,7-dioxo-tricyclo(4,3,1,1^{3,8})1,3,6,8-tetracarboxylic acid (113) (2.0mg.) was placed between two microscope slides and slowly heated to 270° on a Kofler melting point apparatus. The first decarboxylation was observed to take place at 240° accompanied by a collapse of the crystal structure to a frothing fluid mass. At 270° the material resolidified and heating was continued until at approximately 330° a further frothing less vigorous than the first took place with a blackening of the material. The residual substance was ground into a powder and extracted with ether (3 x 10ml.). The combined organic phase was washed with sodium hydroxide solution (N, 3 x 10ml.) water (4 x 10ml.) and dried (MgSO₄). Removal of solvent under reduced pressure yielded no organic material.

1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecan-2,7-dione (116)

2,7-dioxo-tricyclo(4,3,1,1^{3,8})undecan-1,3,6,8-tetracarboxylic acid (113) (38.00g.) crude from the previous experiment was placed in a 500ml. round bottomed flask and the system evacuated to a 0.9 Torr. The flask was heated in an oil bath at 270° for 40 minutes. During the first 20 minutes the solid appeared to melt and froth after which it gradually re-solidified to a whitish-grey granular material. This residue was dissolved in dioxane (250ml.) and the solution cooled in ice-salt. A solution of diazomethane in diethyl ether at 0°, containing 10% more than the theoretical amount, was added dropwise with swirling over 30 minutes and the mixture stirred for a further hour. After this time excess diazomethane was destroyed by

the dropwise addition of glacial acetic acid. The solution was evaporated to dryness under reduced pressure to give a dark brown solid. The crude product was recrystallised from ethanol in needles to give 1,8-dicarbomethoxy-tricyclo(4.3.1.1^{3,8})undecan-2,7-dione (116) (25.72g., 81%) m.p. 251-253°. (Found: C, 60.97; H, 5.97. $C_{15}H_{18}O_6$ requires C, 61.22; H, 6.16%); ν max.: 1748, 1718, 1464, 1375, 1353, 1293, 1142, 1105, 1027, and 976 cm^{-1} . n.m.r. τ_H 6.18 (6H, s), 6.85 (2H, s broad), 7.23, 7.33, 7.42, 7.58, 7.67 (6H, m), 8.03 (4H, s broad).

Tricyclo(4,3,1.1^{3,8})undecan-1,2;7,8-bis-pyrazolone (101)

1,8-dicarbomethoxy-tricyclo(4,3,1.1^{3,8})undecan-2,7-dione (116) (30g., 0.10 mole) was treated dropwise with hydrazine hydrate (40ml.) and the mixture thoroughly stirred until solution had been achieved. The mixing was vigorously exothermic and on cooling the product was precipitated from the solution to the extent that a moist solid resulted. This was diluted with water, filtered at the pump, and the precipitate washed once with ice-cold water followed by suction drying. The resulting highly crystalline colourless solid was recrystallised from ethanol in needles to yield tricyclo(4,3,1.1^{3,8})undecan-1,2;7,8-bis-pyrazolone (101) (20.08g, 78%) m.p. 336-337° (decomp), (Found: C, 60.18; H, 5.50; N, 21.56. $C_{13}H_{14}O_2N_4$ requires C, 60.46; H, 5.46; N, 21.69%); ν max.: 3503, 3225, 2755, 1700 (sh), 1678, 1618, 1327, 1285, 1203, 1157, 1113, 1055, 1012, 905, 783 and 741 cm^{-1} . An n.m.r. spectrum was not obtained for this compound due to its insolubility in all common solvents.

Tricyclo(4,3,1.1^{3,8})undecan-1,8-dicarboxylic acid (102)

Tricyclo(4,3,1.1^{3,8})undecan-1,2;7,8-bis-pyrazolone (101) (20g., 0.077 mole) was placed in a calorimetric bomb charged with powdered sodium hydroxide (20g.).

The solids were well mixed and water (14ml.) then added, the sealed mixture heated at 210° for 15 hours and after cooling the resulting white plug dissolved in water (300ml.). The solution was brought to pH 1 with hydrochloric acid and the precipitated product was left overnight at 0° and then filtered at the pump, washed with water (100ml.) and acetone (3 x 50ml.). The colourless solid was then recrystallised from dioxane to yield tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) (15.30g., 82%) m.p. $316-317^{\circ}$; ν max. (mull) 3600-2400, 1725, 1392, 1290, 1258 1219 and 908 cm^{-1} . No n.m.r. spectrum is available for this compound due to its extreme insolubility in all solvents investigated; it was characterised as its dimethyl ester.

1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecane (100)

Finely ground tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) (2.00g., 0.008 mole) was added to an Erlenmeyer flask charged with diethyl ether (30ml.). The slurry was cooled in ice-salt, stirred, and an ice-cold ethereal solution of diazomethane added dropwise until a homogeneous solution containing no solid had occurred, and the yellow colour of excess diazomethane had become apparent. Glacial acetic acid was then added dropwise until the solution became colourless. Removal of solvent under reduced pressure gave a colourless solid which recrystallised from a very small amount of light petrol in prisms to yield 1,8-dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecane (100) (2.17g., 97%) m.p. $188-189^{\circ}$ (Found: C, 67.48; H, 8.17. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%; M^+ m/e 266; ν max. (CCl₄) 1730, 1461 (sh), 1451, 1435, 1268, 1225, 1190, 1163, 1090 (sh), 1074 and 1027 cm^{-1} . n.m.r. τ _H 6.36 (6H, s), 8.21 (16H, s broad)

Unsubstituted Reaction on bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103)

Powdered bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (4.2g., 0.02 mole) was treated with the theoretical amount of sodium hydroxide solution (N; 40ml.) and the mixture stirred to achieve solution. A further drop of the sodium hydroxide solution was added so that the pH of the mixture rose to 14. Freshly prepared silver nitrate solution (N; 26.5ml.) was added dropwise with stirring to result in a heavy precipitate of the bis silver salt which was filtered at the pump and washed with water (3 x 50 ml.). The product was dried primarily in air by suction during one hour after which it was transferred to a drying pistol at $100^{\circ}/0.5\text{mm.}$ for 48 hours. The product (8.1g., 96%) had discoloured during this period becoming at first brown and latterly a light grey. The dry silver salt was added to dry carbon tetrachloride (50ml.) and with vigorous stirring, a solution of dried bromine (6.4g., 0.04 mole) in dry carbon tetrachloride (50ml.) was added dropwise over one hour while the reaction mixture was heated at 80° . During this time water was rigorously excluded from the system. The mixture was heated and stirred for a further two hours when most of the bromine had disappeared. The mixture was filtered hot and the precipitate washed once with carbon tetrachloride (25ml.). The organic filtrate was washed with sodium hydroxide solution (N, 2 x 50ml.) to remove any monobrominated diacid, water (3 x 50ml.), and dried (MgSO_4). Removal of solvent under reduced pressure yielded a green-brown crystalline solid with an "oil of wintergreen" type of odour indistinguishable from that of 1,3-dibromoadamantane (9); (0.56g., 10%) based on 1,5-dibromo bicyclo(3,3,1)nonane (124) H^+ m/e. No parent ion present, base peak m/e 121; fragments at m/e 201, 203 (1:1 doublet), m/e 157, 159 (3:1 doublet).

are consistent with the product being a mixture of 1-chloro-5-bromobicyclo(3,3,1)nonane (136), ($R = Cl, R' = Br$) and 1,5 dibromo-bicyclo(3,3,1)nonane (124). ν_{max} . (CS_2) 3000, 2948, 2896, 2865, 1469, 1453, 1351, 1295, 1183, 1057, 1040, 966, 888 and 693 cm^{-1} . The yield of 10% rises to a maximum of 11.8% if the chloro-bromo compound (136), ($R = Cl, R' = Br$) was present exclusively.

Attempted Preparation of 1.5-Dithallium (I) bicyclo(3,3,1)nonan-dicarboxylate

Thallic ethoxide was prepared as follows:

Filings of thallium metal (5g., 0.025g. atom) were placed in a soxhlet thimble and continuously extracted with dry refluxing ethanol for 72 hours. The ethanol was removed by distillation under reduced pressure to yield thallic ethoxide as a colourless oil, (4.5g., 72%).

A solution of thallic ethoxide (10.0g., 0.04 mole) in ethanol was added dropwise to a stirred slurry of finely ground bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (4.32g., 0.02 mole) in ethanol (200ml.) at 50° . A heavy white precipitate appeared immediately and stirring was continued for 30 minutes. The precipitate was then filtered and washed with water (3 x 20ml.) and dried by suction for one hour. During this time the precipitate darkened considerably and acquired a gelatinous appearance. The product (8.23g.) failed to recrystallise from ethanol or aqueous ethanol and continued to darken until it was dark grey in colour. The infrared spectrum at this stage was consistent with amounts of the starting acid in the unidentified product.

Attempted brominative decarboxylation of bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) employing the conditions of Cristol and Pirth.

Carbon tetrachloride (50ml.) was added to a mixture of finely ground

bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (5.00g., 0.024 mole) and red mercuric oxide (7.80g., 0.036 mole) and then stirred and heated at reflux while bromine (11.80g., 0.074 mole) in carbon tetrachloride was added dropwise over one hour. Bromine did not appear to be taken up during the addition but the orange colour of the solution disappeared slowly over three hours of continued reflux. The mixture was filtered hot and the filtrate washed with sodium hydroxide solution (N, 100ml.), water (3 x 100 ml.) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded no organic material. The aqueous phase was not examined but the precipitate, clearly containing largely unchanged diacid (103) and mercuric oxide was taken up in sodium hydroxide solution (N, 50ml.), filtered and the filtrate acidified with sulphuric acid. The precipitate was collected at the pump, washed with water (3 x 100ml.) and dried by suction to yield a colourless crystalline material (4.2g.) identical in all respects with the starting material (84% recovery).

Attempted brominative decarboxylation of bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) using the conditions of Cristol and Firth¹⁰¹ and 1,2-dibromoethane as solvent.

1,2-dibromoethane (50ml.) was added to a mixture of finely ground bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (5.00g., 0.024 mole) and red mercuric oxide (7.80g., 0.036 mole) and the mixture heated at 100° while bromine (11.80g., 0.074 mole) in 1,2-dibromoethane (100ml.) was added over one hour. A small amount of gaseous evolution was apparent during the addition although mercuric oxide did not appear to be consumed. Reaction was continued at 100° with stirring for a further three hours after which the mixture was filtered hot and the filtrate washed with sodium hydroxide solution (N, 100ml.) and the precipitation of mercury salts noted. After filtration the organic phase was washed with water

(3 x 100ml.) and dried (MgSO_4). Removal of solvent under reduced pressure yielded a small amount of green-brown neutral material (0.012g.)

ν_{max} . (CCl_4) 3000, 2948, 2896, 2865, 1732 (weak), 1487, 1469, 1453, 1440 and 693 cm^{-1} . The infrared spectrum is consistent with a neutral compound mixture contaminated with a small amount of carbonyl compound. T.L.C. analysis revealed two components when visualised with $\text{MeOH}/\text{H}_2\text{SO}_4$, r.f. 0.91 and 0.52 respectively.

The crude product sublimed at $100^\circ/0.5\text{mm}$. to yield a colourless crystalline material which was homogeneous to T.L.C. analysis showing only the fast running spot above, and whose infrared spectrum was very similar to that of the Hunsdiecker product, (see page 52) but with the carbonyl stretching peak at 1732 cm^{-1} absent. M^+ m/e No parent ion, base peak m/e 121 and fragments m/e 201, 203 (1:1 doublet); m/e 157, 159 (3:1 doublet) suggest an identical product mixture as in 1,5-dibromo and 1-chloro-5-bromo bicyclo(3,3,1)nonanes (124) and (136), ($R = \text{Cl}$, $R' = \text{Br}$).

Low yield brominative decarboxylation of bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) using modified Cristol-Firth¹⁰¹ conditions

Carbon tetrachloride (25ml.) and 1,2-dibromoethane (100ml.) were added to a mixture of finely ground bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (6.20g., 0.0295 mole) and red mercuric oxide (6.37g., 0.0295 mole) and the mixture stirred and heated at reflux while bromine (19.20g., 0.12 mole) in carbon tetrachloride (100ml.) was added over one hour. The reaction was continued at reflux with stirring for a further three hours, after which the mixture was filtered hot and the filtrate washed with sodium hydroxide solution (N, 2 x 50 ml.). Precipitation of a substantial quantity of mercury salts was noted which caused difficulty in separating the organic phase, this being achieved by leaving overnight. The organic phase was further washed with water (3 x 50ml.), brine (1 x 25ml.) and dried (MgSO_4). Evaporation of solvent under reduced pressure yielded a light green crystalline solid (1.35g.) which was adsorbed on *Cambiosorb 'B'* alumina from benzene and eluted with the

same solvent to yield a colourless crystalline solid which readily sublimed at 120° mm. to afford the product free from oxygenated material (1.24g. 15%) based on 1,5-dibromo-bicyclo(3,3,1)nonane (124). T.L.C. analysis with methylene chloride as eluent revealed only one component when visualised with MeOH/H₂SO₄ r.f. 0.90 and the infrared spectrum was very similar to that of the product obtained from the classical Hunsdiecker experiment (page 52).

High yield brominative decarboxylation of bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) using conditions of Cason.

Carbon tetrachloride (50ml.) and 1,2-dibromoethane (50ml.) was added to a mixture of finely ground bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (103) (3.3g., 0.018 mole) and red mercuric oxide (3.89g., 0.018 mole) and stirred and heated until CCl₄ began to distil, at which point a solution of bromine (11.52g., 0.072 mole) in carbon tetrachloride (200ml.) was added dropwise at such a rate as to be equal to that with which CCl₄ was distilling out of the system. When the addition was complete (approx. 2 hours) the mixture was filtered while hot and the precipitate washed once with carbon tetrachloride (25 ml.). The filtrate was washed with sodium hydroxide solution (N, 3 x 50ml.), water (4 x 50ml.) and brine (50ml.). The solution was then dried (MgSO₄) and solvent removed under reduced pressure to yield a green-brown crystalline solid. Infrared spectral analysis indicated a carbonyl impurity at ν_{\max} 1732 cm⁻¹. The crude product was eluted from Camag-type 'H' alumina with benzene to yield a colourless crystalline solid which was homogeneous to T.L.C. and which sublimed readily at 120° /mm. to give the product (3.79g., 75%) based on 1,5-dibromo-bicyclo(3,3,1)nonane (124). T.L.C. analysis revealed only one component with methylene chloride as eluent and MeOH/H₂SO₄ visualisation, r.f. 0.68. M^+ m/e no parent ion, base peak m/e 121;

fragments at m/e 201, 203 (1:1 doublet); m/e 157, 159 (3:1 doublet). The infrared spectrum was identical with that of the product from the classical Hunsdiecker experiment (page 52).

Attempted brominative decarboxylation of tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102)

Finely ground carbon tetrachloride (25ml.) and 1,2-dibromoethane (25ml.) were added to a mixture of tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) (300mg., 0.00126 mole) and red mercuric oxide (272mg., 0.00126 mole) and the system arranged for distillation. The reaction mixture was stirred and heated until carbon tetrachloride began to distil from the system at which point bromine (600mg., 0.0050 mole) in carbon tetrachloride (50ml.) was added dropwise at the same rate as carbon tetrachloride distilled from the system. When the addition was complete, (approx. 2 hours) the mixture was filtered hot and the precipitate washed once with carbon tetrachloride (25ml.). The filtrate was washed with sodium hydroxide solution (N,3 x 25ml.), water (4 x 25ml.) and brine (25ml.). Removal of solvent under reduce pressure yielded a green-brown crystalline solid (423 mg.), ν_{max} 1732 cm^{-1} . T.L.C. analysis revealed two components with methylene chloride eluent and MeOH/H₂SO₄ visualisation r.f. 0.88, r.f. 0.55 (weak). The product was eluted from Canag type 'H' alumina with benzene to yield a colourless crystalline solid, homogeneous to T.L.C., which would not sublime (368mg., 95%) based on tricyclo(4,3,1,1^{3,8})undecan-1,8-dibromide (99). M⁺ m/e no parent ion. Fragments at m/e 539, 541, 542, 544, 546, 548; m/e 461, 463, 465, 467, 469; m/e 337, 339, 340, 341 are consistent with a pentabromo-tricyclo(4,3,1,1^{3,8})undecane and unspecified chloro-bromo mixtures ν_{max} (CS₂) 2958, 2932, 2830, 1347, 1226, 1311, 1303, 1114, 972, 958 (sh), 950, 937, 833, 830, 820, 806, 770, 754, 733, and 695 cm^{-1} .

Attempted selective brominative decarboxylation of tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102)

This experiment was carried out in a manner identical with the above except for the quantity of bromine used (403mg., 0.00252 mole). The colourless crystalline product was chromatographed in the same way to yield a product homogeneous to T.L.C. which sublimed only partially and with difficulty 150°/0.1mm, (291 mg., 75%) based on 1,8-dibromo-tricyclo(4,3,1,1^{3,8})undecane (99). M⁺ m/e no parent ion, fragments at m/e 339, 341, 343, 345 and m/e 183, 185 (3:1 doublet) are consistent with 1-chloro-3,6-dibromo tricyclo(4,3,1,1^{3,8})undecane (137) and isomers. ν max. (CS₂) 2929, 2860, 1314, 1293, 1245, 1204, 1022, 976, 957, 930, 925, 803, 787, 718 and 692 (strong) cm⁻¹.

Selective brominative decarboxylation of tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102)

Tricyclo(4,3,1,1^{3,8})undecan-1,8-dicarboxylic acid (102) (1.00g., 0.0042 mole) was finely ground and thoroughly mixed with mercuric oxide (0.9g., 0.0042 mole). 1,2-Dibromoethane (25ml.) and carbon tetrachloride (50ml.) were added and the mixture heated and stirred such that carbon tetrachloride distilled and was collected at approx. 3 drops per second. After 15 minutes the residual water in the flask had azeotroped onto the coils of the condenser and the level of carbon tetrachloride was recharged from a dry reservoir. Bromine (0.75g., 0.0047 mole) in carbon tetrachloride (dry, 30ml.) was added dropwise to the reaction mixture at the same rate as carbon tetrachloride was distilling from the system. During the course of the reaction, additional water was observed to condense on the coils of the condenser. After the addition, distillation of carbon tetrachloride and recharging were continued until no trace of

bromine was apparent in the reaction mixture or distillate. The hot mixture was filtered and the residue washed with carbon tetrachloride (2 x 20ml.). The combined filtrates were washed with sodium hydroxide (2N, 3 x 50ml.), water (3 x 50ml.), brine (1 x 50ml.), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a light green-brown solid, (0.49g.). The crude product was eluted from grade I Camag-type 'H' alumina with benzene to give a colourless crystalline solid homogeneous to T.L.C. analysis (0.45g. 35%) based on 1,8-dibromo-tricyclo(4,3,1,1^{3,8})undecane (99) M^+ m/e 306, 308, 310 (1:3:1 triplet), fragments at m/e 227, 229, (1:1 doublet) and m/e 183, 185 (3:1 doublet, base peak) are consistent with a mixture of 1-chloro-8-bromo-tricyclo(4,3,1,1^{3,8})undecane (125) (R = Cl, R' = Br) and 1,8 dibromo-tricyclo(4,3,1,1^{3,8})undecane (99). ν_{max} . (CS_2) 2976, 2935, 2904, 2890 (sh), 2835, 1350, 1312, 1294, 1244, 980, 956, 925, 810, 799, 789, 726 (sh), 719, 703, and 692 cm^{-1} .

7-exomethylene-bicyclo(3,3,2)decan-3-one (26)

The above mixture of 1,8-chloro-bromo, and 1,8-dibromo-tricyclo(4,3,1,1^{3,8})undecanes (125) (R = Cl, R' = Br) (R = Br, R' = Br) (500mg.) in dioxane (10ml.) was placed in a calorimetric bomb (capacity 50ml.), sodium hydroxide solution (10ml., N) added and the mixture heated at 170-180° for 12 hours. The resulting light brown homogeneous solution was extracted with ether (3 x 40ml.), the combined organic extracts washed with water (6 x 40ml.), brine (40ml.) and the organic layer dried ($MgSO_4$). Removal of solvent under reduced pressure yielded a slightly discoloured crystalline solid smelling characteristically of the bicyclo(3,3,2)decane systems. The product was sublimed at 100°/0.5mm to give a highly crystalline colourless solid. Recrystallisation from light petrol yielded

pure 7-exomethylene bicyclo(3,3,2)decan-3-one (28) as needles, (185mg., 56%) based on the starting material being an equimolecular mixture of (129) (R = Cl, R' = Br) and (129) (R = Br, R' = Br), m.p. (sealed tube) 159.5 - 160.5°; M^+ m/e 164 (Found: C, 79.99; H, 9.65. $C_{11}H_{16}O$ requires C, 80.35; H, 9.82%); ν_{max} . (CCl_4) 3080, 1690, 1640 and 907 cm^{-1} ; n.m.r. τ_H (CCl_4) 5.28 (2H, s), 7.5 - 7.59 (10H, s(broad)), 8.06 (4H, s).

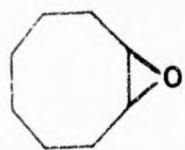
Bicyclo(3.3.2)decan-3,7-dione (76)

7-exomethylene-bicyclo(3,3,2)decan-3-one (28) (80mg., 0.5 m.mole) in freshly distilled, dry methylene chloride (20ml.) and pyridine (0.5ml.) was cooled in an acetone- $CO_2(s)$ bath. A slow stream of ozonised oxygen was passed through the solution until it turned blue, at which point the ozone flow was disconnected and pure oxygen passed through the reaction mixture until it became colourless. The reaction mixture was then allowed to warm to ambient temperature and set aside overnight. A precipitate of pyridine-N-oxide was observed at the bottom of the reaction flask. The solution was filtered and solvents removed under reduced pressure to yield a green syrupy oil. The crude product was adsorbed on Camag type 'H' alumina from light petrol/ether and eluted with ether to give a colourless crystalline solid which was homogeneous to T.L.C. analysis. The product was then sublimed at $100^\circ/0.5\text{ mm}$ to yield a highly crystalline colourless solid, bicyclo(3,3,2)decan-3,7-dione (76) (50.4mg., 38%), m.p. (sealed tube) 248-250°; (Found: M^+ , 166.0985. $C_{10}H_{11}O_2$ requires M^+ , 166.0994). ν_{max} . (CCl_4) 1704, 1420, 1410, 1344, 1290, 1215 and 1165 cm^{-1} ; n.m.r. τ_H ($CDCl_3$) 7.57 (10H, s), 7.91 (4H, s).

Wolff-Kishner reduction of bicyclo(3,3,2)decan-3,7-dione (76)

Bicyclo(3,3,2)decan-3,7-dione (20mg., 0.12 m. mole) and hydrazine hydrate (2.0ml.) were added to a solution of sodium (10mg., 0.44 mg atom) in diethyl ether (5.0ml.) and the solution placed in a sealed tube. The mixture was

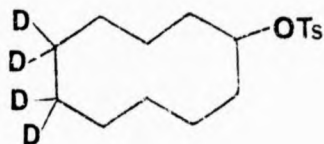
warmed for 90 minutes and then heated at 200° for 12 hours. After cooling the tube was opened and the reaction mixture extracted with pentane (3 x 10ml.). The pentane solution was washed with water (2 x 10ml.) and dried (MgSO_4). The pentane was evaporated at atmospheric pressure to yield a crystalline solid (3.8mg.) with a characteristic odour similar to that of an authentic sample of bicyclo(3,3,2)decane (56). M^+ m/e 136. An authentic sample of (56) gave M^+ m/e 138. The data is consistent with the product being tricyclo (3,3,2,0^{3,7})decane (126).



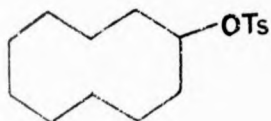
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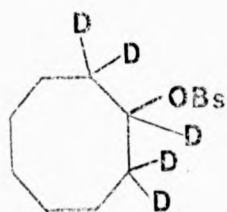


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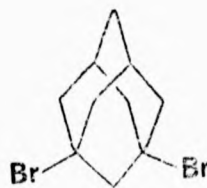
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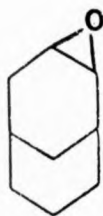
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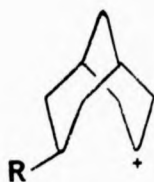
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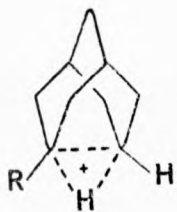
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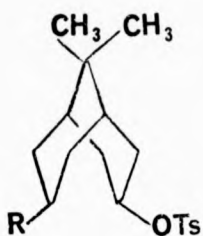
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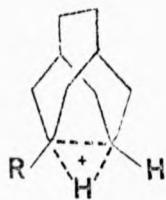
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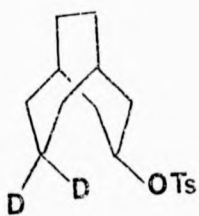
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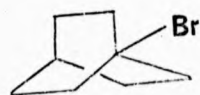
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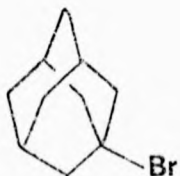
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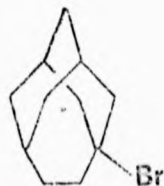
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24



25



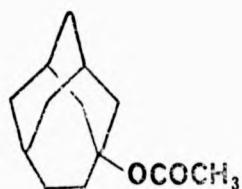
26



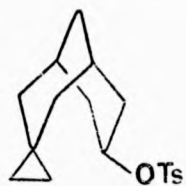
27



28



29



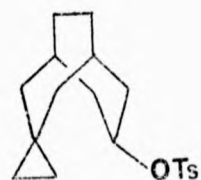
30



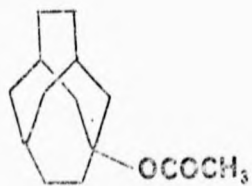
31



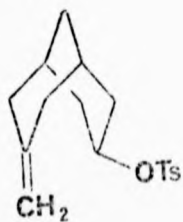
32



33



34



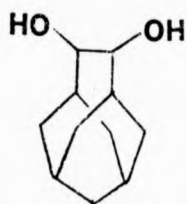
35



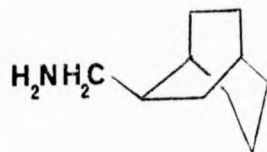
36



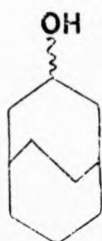
37



38



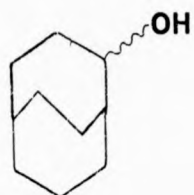
39



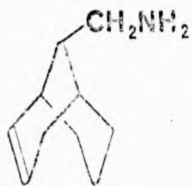
40



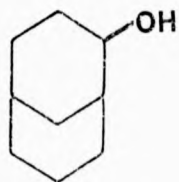
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42



43



44



45



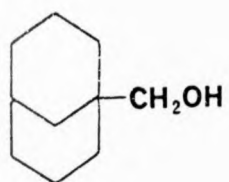
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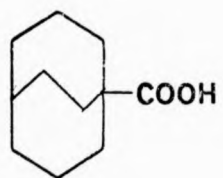
47



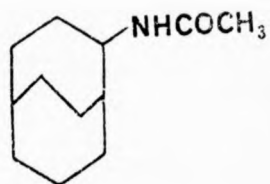
48



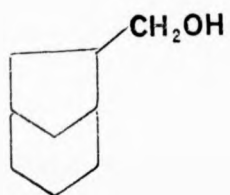
49



50



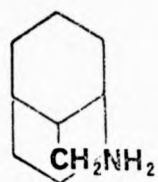
51



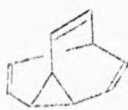
52



53



54



55



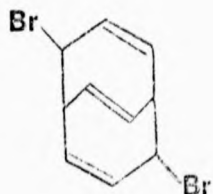
56



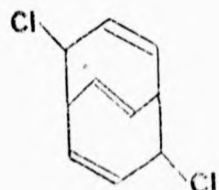
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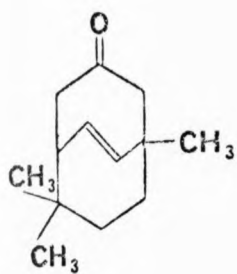
58



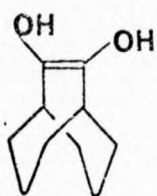
59



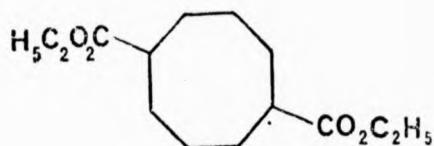
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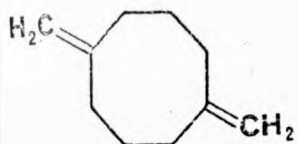
61



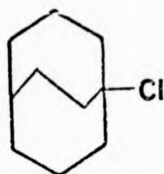
62



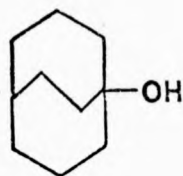
63



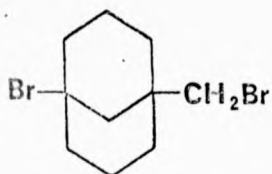
64



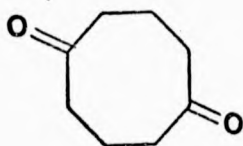
65



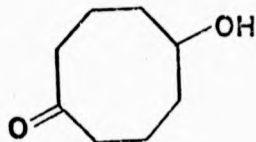
66



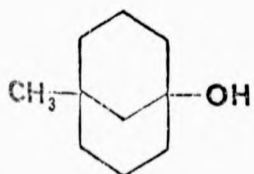
67



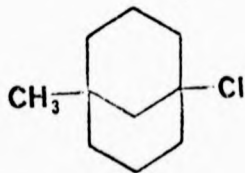
68



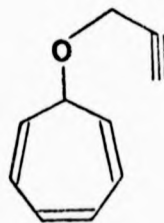
69



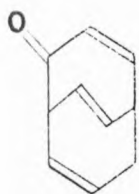
70



71



72



73



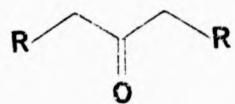
74



75

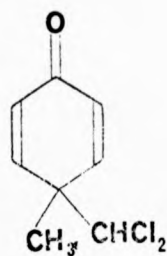


76

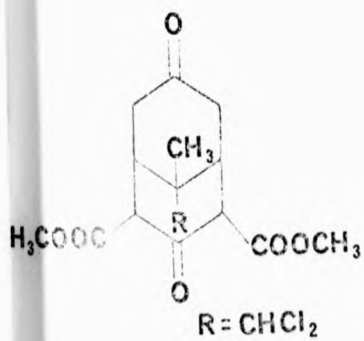


R = COOCH₃

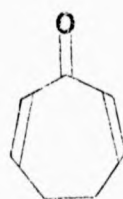
77



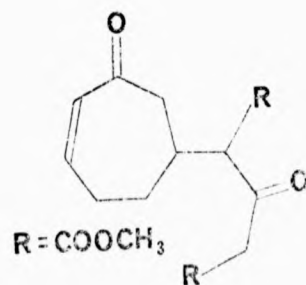
78



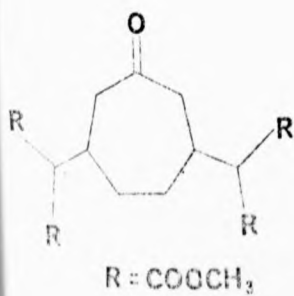
79



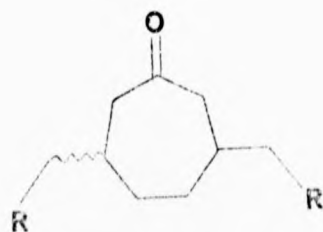
80



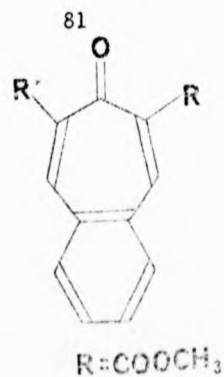
81



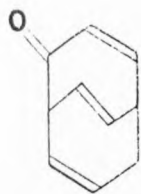
82



83



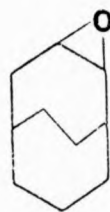
84



73



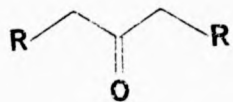
74



75

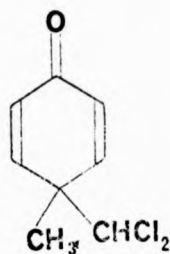


76

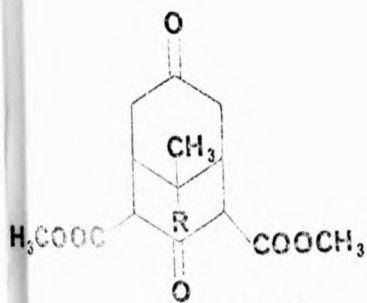


R = COOCH₃

77

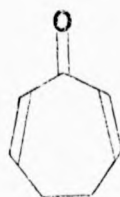


78

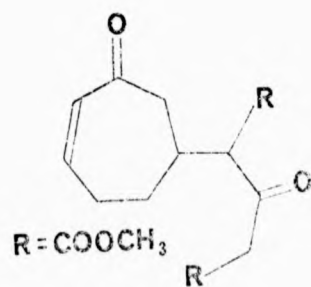


R = CHCl₂

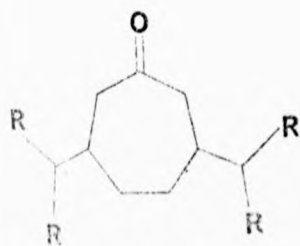
79



80

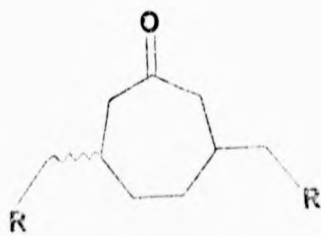


81



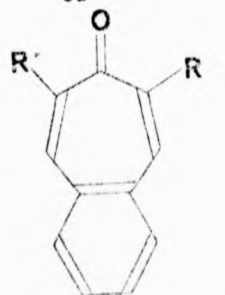
R = COOCH₃

82



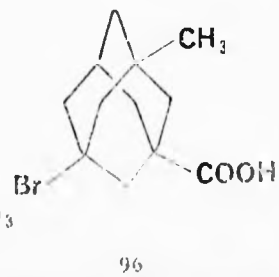
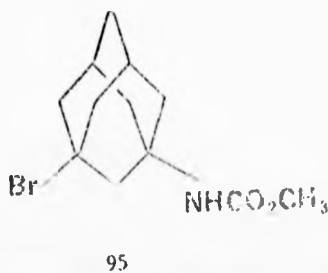
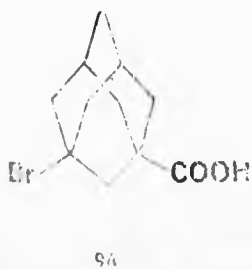
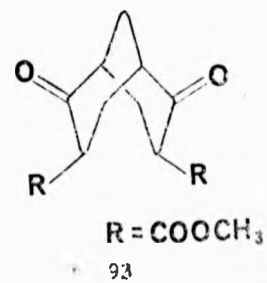
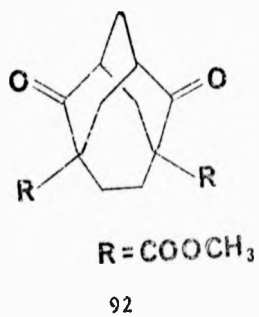
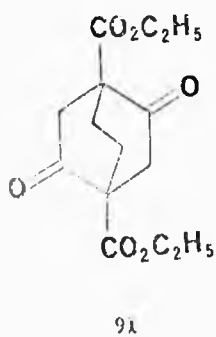
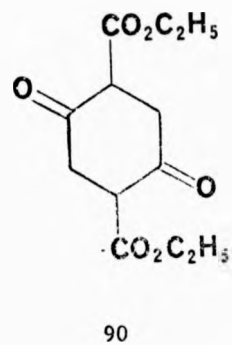
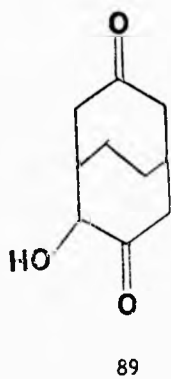
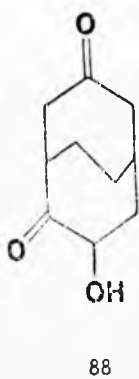
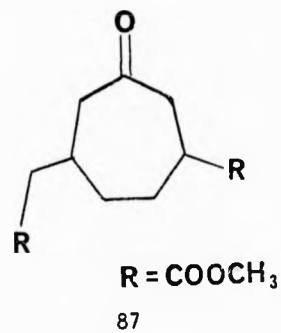
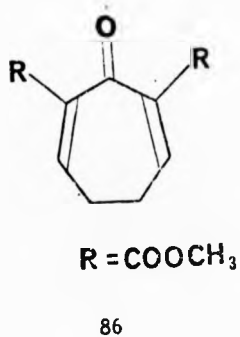
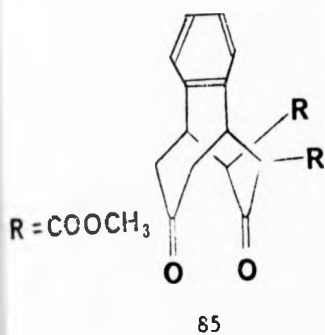
R = COOCH₃

83



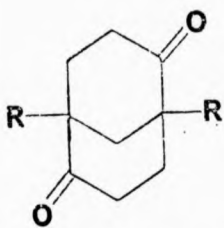
R = COOCH₃

84



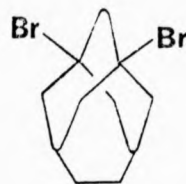


97

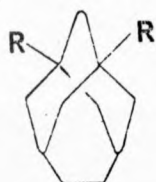


$R = \text{COOCH}_3$

98

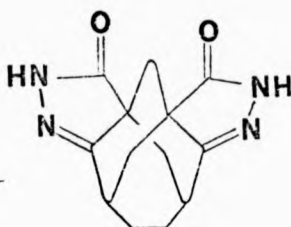


99

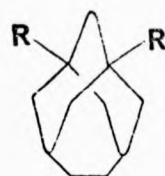


$R = \text{COOCH}_3$

100

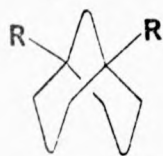


101



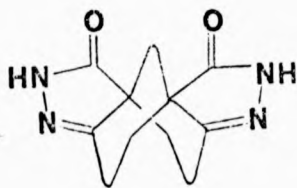
$R = \text{COOH}$

102

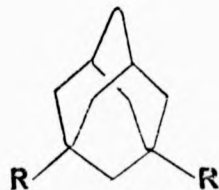


$R = \text{COOH}$

103

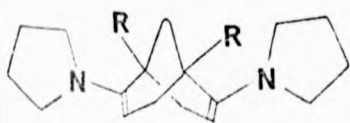


104



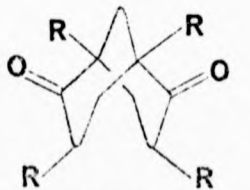
$R = \text{COOH}$

105



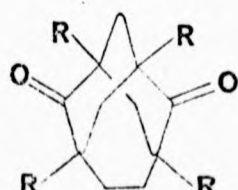
$R = \text{COOCH}_3$

106



$R = \text{COOCH}_3$

107



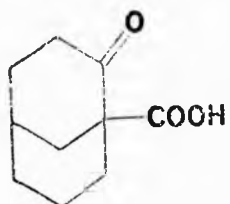
$R = \text{COOCH}_3$

108

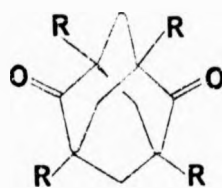
X



109

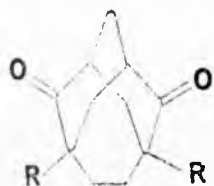


110



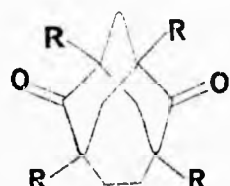
R = COOH

111



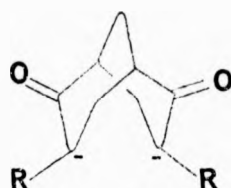
R = COOH

112



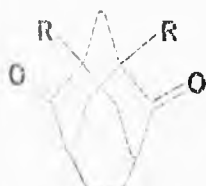
R = COOH

113



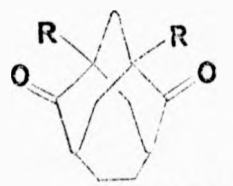
R = COOCH₃

114



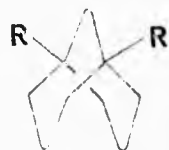
R = COOH

115



R = COOCH₃

116



R = COOAg

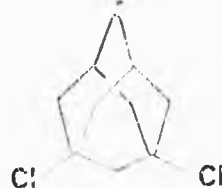
117



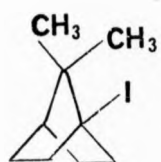
118



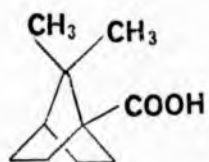
119



120



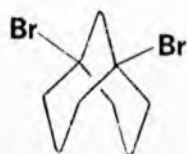
121



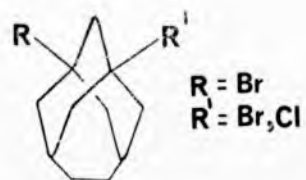
122



123



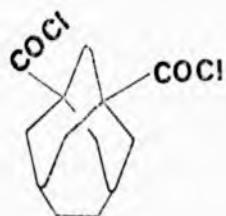
124



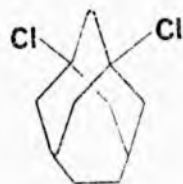
125



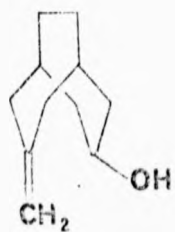
126



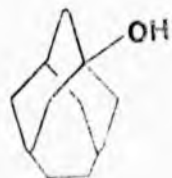
127



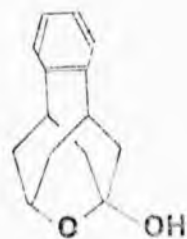
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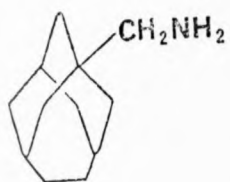
129



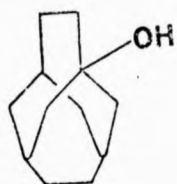
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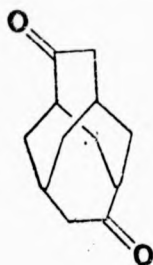
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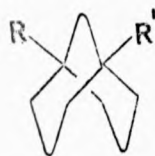
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SECTION II

Use of Optically Active Bicyclo(3,3,1)nonanes as Substrates
for Mechanistic Studies

(A) Transannular Hydride Shifts

Introduction

From a long standing interest in the chemistry of bridged bicyclic medium ring systems, and particularly their transannular interactions¹, interest was aroused at Stirling in acquiring the activation parameters for 3,7 intramolecular hydride shifts. An indication of the energy barriers involved, for example, would be expected to throw light on the enquiry of their effect on solvolytic reaction rates (see Section I).

Although transannular hydride migrations in bicyclic systems generally have been known for a considerable time², the means of estimating their activation parameters was unavailable and the assignment of values purely a matter for conjecture. Hence in 1964 when Schleyer *et al.* were able to acquire the activation data for a 1,2 transannular hydride shift in the norbornyl system^{3,4} their report was unique. The means of acquiring the data had arisen out of studies carried out by Olah. When certain alkyl fluorides are dissolved in antimony pentafluoride itself or as a mixture with liquid sulphur dioxide, the resulting cation SbF_6^- salts are indefinitely stable for example even the *t*-butyl cation has been prepared⁵. From the same treatment of 2-norbornyl fluoride (1) the corresponding cation was produced and its stability demonstrated when only norbornyl-*exo*-2-ol (2) was recovered on hydrolysis⁶. Examination of the variable temperature ^1H n.m.r. of the 2-norbornyl cation (3) by Schleyer and Olah³ revealed a single band at ambient temperatures due to rapid redistribution of the positive charge within the bicyclic skeleton. Below -60° the single line separates into three bands of area 4:1:6 and on warming collapses again to the original unit signal. Repeated warming and cooling to achieve the same effect was possible and these authors interpreted the phenomenon as the "freezing out" of a 1,2 intramolecular hydride shift below -60° on the n.m.r. time scale.

FIG. I

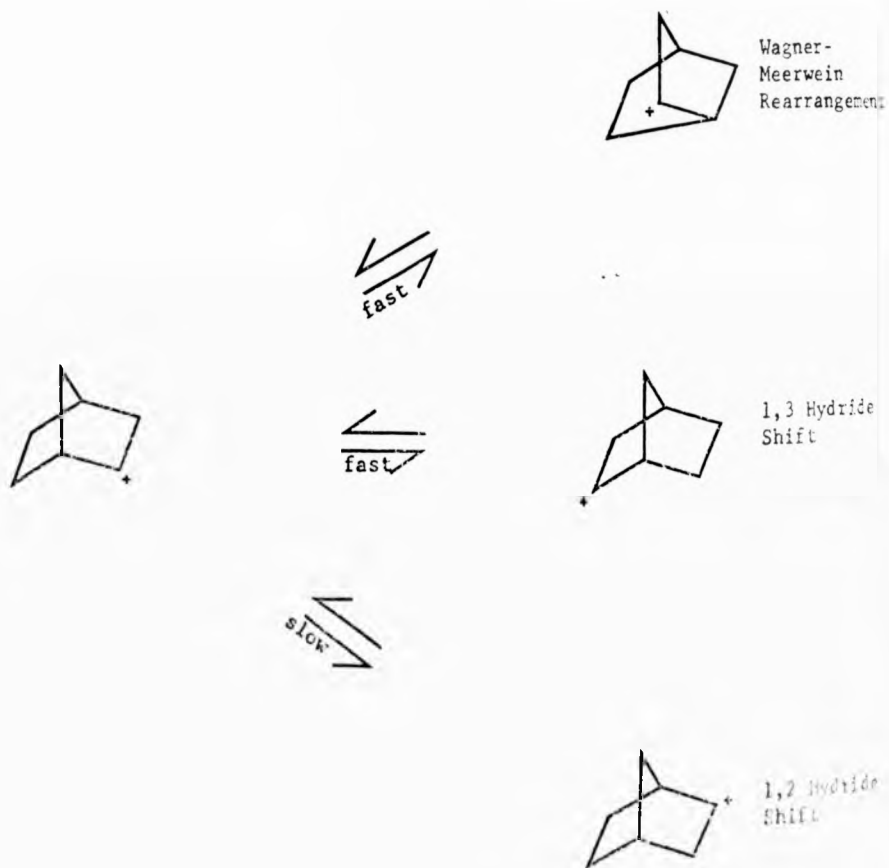
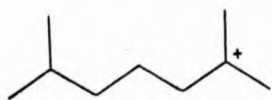
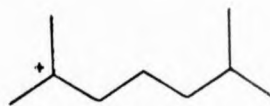


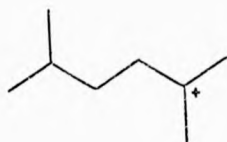
FIG. II



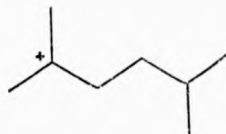
1,5 Hydride Shift



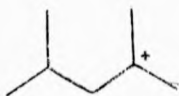
$\Delta E = 6 - 7 \text{ k. cal./mole.}$



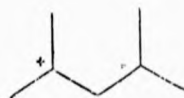
1,4 Hydride Shift



$\Delta E = 12 - 13 \text{ k. cal./mole.}$



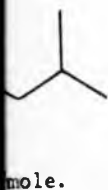
1,3 Hydride Shift



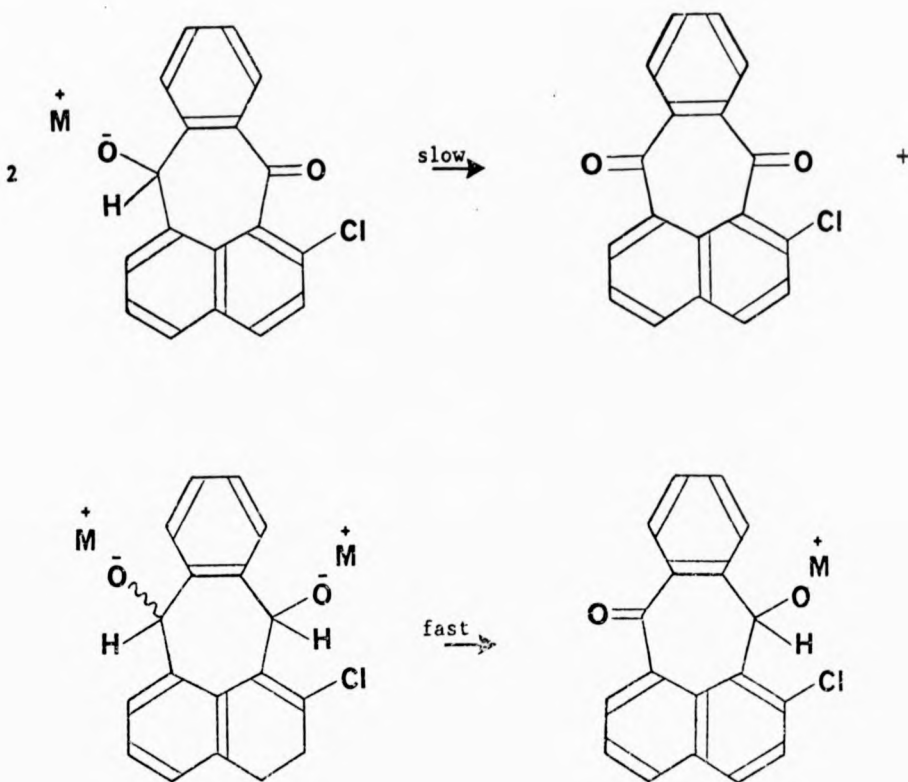
$\Delta E = 12.6 \pm 0.1 \text{ k. cal./mole.}$

A 1,3 transannular shift and Wagner-Meerwein rearrangement remained rapid even at low temperatures thus explaining the 3 - line signal. The three simultaneously operating rearrangement mechanisms are illustrated in Fig. I. In what was then a novel technique, a general computer programme was devised to analyse ¹H n.m.r. line shapes at varying temperatures from -60° to ambient which are a function of the rate of the 1,2 hydride shift. Thus a value of $\Delta H = 10.8 \pm 0.6$ k. cal./mole. with a pre exponential factor of $A = 10^{2.3} \text{ sec}^{-1}$ was obtained and with it the first indication of the energy barriers governing such shifts. At the time of commencing the experimental work described here, this report remained as the only recorded example in a cationic system. No information was available for other types, e.g. 1,3; 1,4; and 1,5 shifts, the latter of these being of interest because they are characteristic of the bicyclic systems studied by this group. Very recently, however, Saunders⁶ has obtained activation parameters for each of these types in tertiary aliphatic systems. Employing a molecular beam technique the 2,4 dimethyl-2-pentyl (4), 2,5 dimethyl-2-hexyl (5) and 2,6 dimethyl-2-heptyl (6) cations were formed at liquid nitrogen temperatures and activation values obtained from variable temperature ¹H n.m.r. spectroscopy; again by computing line shapes. The shifts were assumed to be respectively 1,3 (4); 1,4 (5); 1,5 (6) and the activation data may be found in Fig. II. The order of magnitude $1,4 \approx 1,3 > 1,5$ is taken as a reflection of the steric and conformational factors operative in the straight chain systems studied.

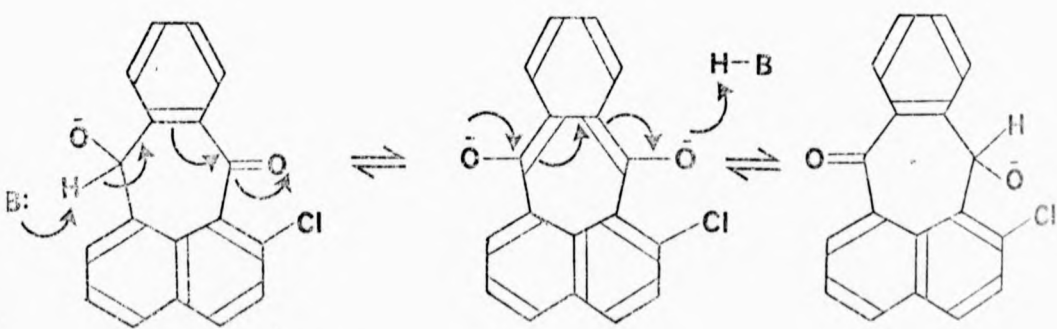
At the time of commencing the project, there was also a single report⁷ giving similar data for a base induced 1,4 transannular hydride shift. Lansbury and Sacva had carried out a variety of studies amongst which was included the evaluation of the energy barriers to ring inversion⁸ in the dihydropleidene system. These authors further found⁷ that the presence of chlorine at C1 in



SCHEME I



SCHEME II



1-chloro-7-hydroxy-12 (7H) pleidenone (7) enables the methine proton to be distinguished (^1H n.m.r.) from that at C12 in the isomer 1-chloro-12-hydroxy-7 (12H) pleidenone (8) such that they were able to follow the interconversion of the salt (9) to its isomer (10) in KOBU_t by the disappearance of the methine proton at C7. Values of $\Delta H_{321}^\circ = 24.5$ k. cal./mole. and $\Delta S_{321}^\circ = -1$ e.u. were calculated from the Arrhenius and Eyring equations. That the hydride shift was in fact a rate determining one was accounted for by the following evidence. Alternative mechanism (1) (Scheme I) requires second order kinetics for the intermolecular slow step and these are not observed. Mechanism (2) (Scheme II), a benzoin-ene process, was eliminated on observing complete label retention when deuterium is substituted at C7, and finally, a primary deuterium isotope, effect of $\frac{k_H}{k_D} = 3$ was noted.

In fact base induced rearrangements of this type are quite common. Acklin and Prelog⁹ noted the conversion of hydrindanone (11) to the ketol (12) by neutral alumina catalysis, an example of a 1,5 hydride shift, although no experimental proof was offered for the proffered intramolecular mechanism. When the alkaloid (13) was treated with alcoholic KOH the rearranged product (14) was obtained and again a 1,5 transannular hydride shift was invoked without experimental proof¹⁰. More recently, Wicha and Caspi¹¹, observing a similar effect on base treatment of 19-d-(19R)-19-hydroxy-19-methyl-5-androstane-3,17-dione (15) (R = H) which yielded 3-d-3-hydroxy-19-methyl-5-androstane-17,19-dione (16) (R = H), commented on the lack of experimental evidence concerning the nature of the previously assumed 1,5 transannular hydride shifts. Subsequently they labelled the methine hydrogen atom at C19 in (15) (R = D) and observed complete label retention in the rearranged product (16) (R = D) thus proving the transannular mechanism. Very recently a base induced intramolecular 1,4 hydride shift in the endo tricyclo (5,2,1,0) decyl ketol series has been

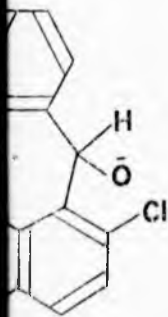
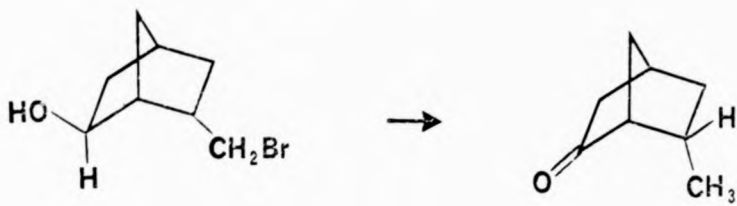


FIG. III



reported by Shepherd *et al.*¹² and Suginome and Kato¹³ have reported an alumina-induced intramolecular cyclisation of 3,4-seco-4-iodo-cholest-5-en-3-al (17) accompanied by hydride transfer. Finally, Gwynn¹⁴ has recorded an unusual 1,3 hydride shift in a norbornyl and 3,5-dihydro norbornyl systems shown in Fig. III.

Stevenson¹⁵ has shown that a transannular 2,6 hydride shift occurs in the base catalysed equilibration of *exo*-2-hydroxy bicyclo(3,3,1)nonan-6-one (18). Treatment of (18) in D₂O/NaOD resulted in an uptake of 8-deuteria to form 1,3,3,5,7,7 octadeuterio-*exo*-2-hydroxy bicyclo(3,3,1)nonan-6-one (19). The hydride shift was further deduced to be intramolecular from chemical evidence.

With this information to hand, it was considered that one method of obtaining the activation parameters for a 1,5 base induced transannular hydride shift would lie in a study of the rate of racemisation of optically active 1-methyl-3-*exo*-hydroxy bicyclo(3,3,1)nonan-7-one (20); this 3,7 shift is analogous to the 2,6 example¹⁵ and is possibly a more suitable choice in view of the known preference for the system to adopt a distorted twin-chair conformation in the ground state¹⁶. An optically active precursor was already available arising from the work of two groups who have examined optical activity in the adamantane skeleton when four different groups are substituted at each bridgehead of this symmetrical hydrocarbon. Applequist¹⁷ noted that extrapolation of the bonds joining such groups to the tricyclic skeleton results in coincidence at the centre of a tetrahedron and hence the substitution is analogous to that on a central carbon atom but elongated. He proceeded to perform a theoretical study on a number of derivatives with varying substitution. Prior to this, however, McKervey¹⁸ had repeated Stetters' route to 7-*exo*-methylene-bicyclo(3,3,1)-nonan-3-one (21) using

the homologous and optically active 1-methyl-3-bromo-adamantyl-5-carboxylic acid (22) as starting material, and obtained optically active 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-one (23). Hence it was anticipated that reduction of the carbonyl function and cleavage of the terminal methylene by routine methods would satisfactorily furnish the required ketol (20).

Discussion

In the interest of rapid establishment of conditions for the synthesis, and to ascertain if a 3,7 transannular hydride shift would take place as predicted, it was decided to use the lower homologue 7-exo-methylene-bicyclo(3,3,1)nonan-3-one (21) as a template because of its ready availability from 1,3 dibromoadamantane¹⁹. Recalling that lithium aluminium hydride reduction of olefin-ketone (21) yields an epimeric mixture of the endo and exo-3-ols (24) in which the exo isomer is present at only 17%, it was considered that the methyl olefin ketone (23) as derived from McKervey's synthesis¹⁸ was too valuable a commodity to use as starting material before conditions for the synthesis were established.

Accordingly, 7-exo-methylene bicyclo(3,3,1)nonan-exo-3-ol (25) was prepared in suitable quantities by standard procedures and cleavage of the terminal methylene group then attempted by ozonolysis. As part of different studies Eakin²¹ had attempted to prepare 7-exo-hydroxy-bicyclo(3,3,1)nonan-3-one (26) but failed to recover any product from the ozonolysis of 7-exo-methylene-bicyclo(3,3,1)nonan-exo-3-ol (25). A possible reason may have been the aqueous work-up coupled with a very water soluble product (*vide infra*). Eakin had employed the Conia²² conditions in which ozonide cleavage occurs *in situ* by reaction with pyridine. Excess pyridine and the resulting pyridine-N-oxide are washed from the system with aqueous acid. In our experiments, the olefin-alcohol (25) was ozonised using similar conditions but without an aqueous wash. Attempts to sublime the product from the residue were only partially successful and instead a crystalline solid was obtained by alumina column chromatography.

T.L.C. analysis indicated the product to be apparently a single compound containing a trace of a faster running impurity, but accompanying spectroscopic data was wholly inconsistent with it being the required ketol (26). In particular the ¹H N.M.R. spectrum was confusing but suggested a mixture of

two compounds present in approximately equal amounts. Contained in the spectrum were two separate ^1H multiplets which had splitting patterns typical²⁰ of the C3 endo methine signals belonging to a series of bicyclo(3,3,1)nonan-exo-3-ols. Three compounds were subsequently isolated by careful and lengthy adsorption chromatography. They were recovered in a 44:55:1 ratio with an overall yield of 68% by weight, and one of them easily identified as ketol (26). The other predominant compound containing a hydroxy group by infrared spectral data gave $\text{M}^+ m/e = 168$, $\text{C}_{10}\text{H}_{16}\text{O}_2$ and also exhibited a ^1H multiplet at 5.8τ consistent with an exo hydroxy group at C3. Sufficient quantities of the trace component were isolated during the course of the above chromatography to obtain the following data, viz :- the material was a carbonyl compound of molecular weight $\text{M}^+ m/e = 166$ but its ^1H n.m.r. spectrum gave no obvious structural clues.

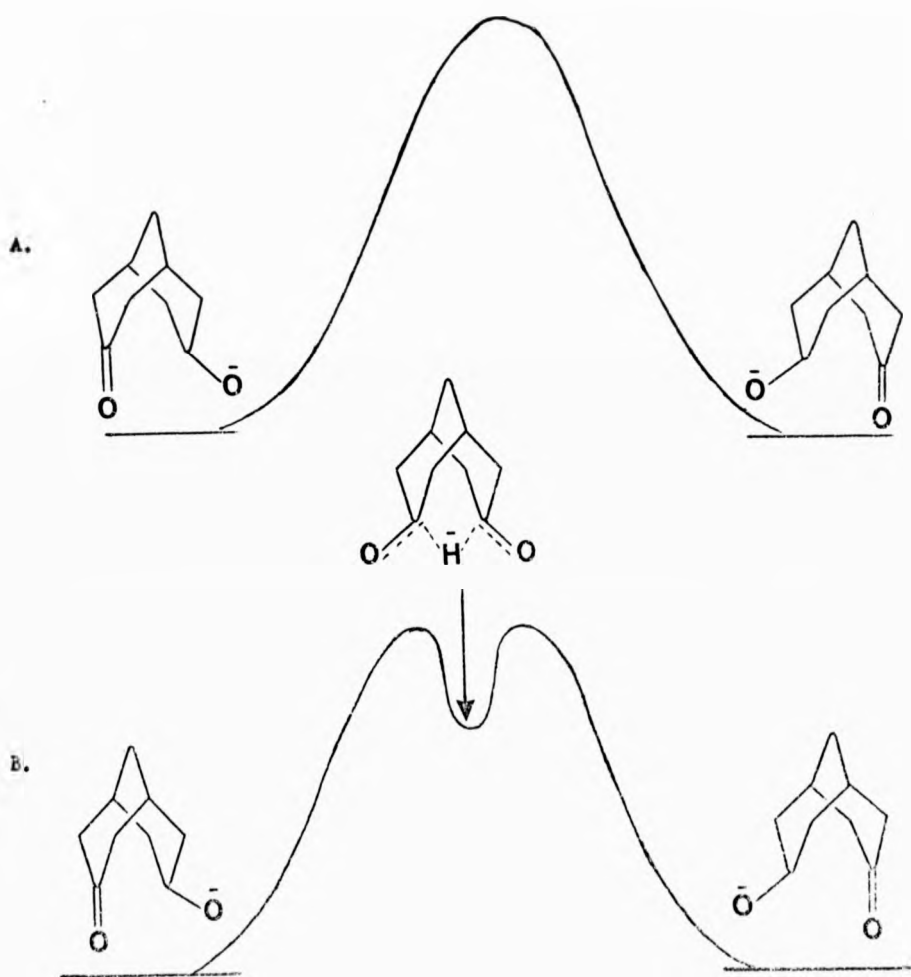
These results appeared strange especially when a similar ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-3-one (21) using identical conditions furnished only the dione (27) in 74% yield. Hence it was considered informative to include the endo olefin-alcohol (28) in an ozonolysis of this type, an experiment which was duly carried out with further intriguing results. T.l.c. analysis of the product showed it to consist of two distinct components with widely differing r.f.'s. From the observation that one of these had an identical r.f. and colour (by $\text{CH}_3\text{OH}/\text{H}_2\text{SO}_4$ visualisation) to the trace carbonyl compound found in the ozonolysis products of olefin-exo-alcohol (25) it was readily found to be identical in all respects with this compound. A logical assumption was that this material is an oxidation product of the unknown alcohol $\text{C}_{10}\text{H}_{16}\text{O}_2$ from the first ozonolysis, a fact which was subsequently proved by Jones chromic acid oxidation of the latter alcohol to a product identical in all respects with ketone $\text{M}^+ m/e 166$. The second component from the ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan

endo-3-ol (28) was identified as 1-hydroxy-2-oxa-adamantane (33) a not surprising observation in view of the fact that Bishop²³ has reported that the cyclooctyl lower homologue (29) exists entirely in its hemi-acetal form (30). Reference to the literature soon cast light on the identity of the unknown products. Bailey²⁴ has noted that there are a number of examples of partial cleavage of terminal methylenes during ozonolysis when one side of the double bond is sterically hindered and even more specifically Criegee²⁵ has reported that olefins of the general type (31) (R = mesityl, Ar = aryl) when ozonised in the presence of triethylamine gave the epoxide (32). Bailey²⁶ has carried out a further study using groups of varying steric size and it is clear that all three of the exo-methylene bicyclic compounds treated here (21), (25) and (28) fall into this class.

The ketone $C_{10}H_{14}O_2$ common to the two sets of ozonolysis products was shown to be exo-7-epoxy-methylene-bicyclo(3,3,1)nonan-3-one (34) by synthesis of an authentic sample. This compound has been independently prepared by two groups. During a study of 3,7 interactions in the bicyclo(3,3,1)nonane system arising out of photolytic process, Mori *et al.*²⁷ obtained it from 7-exo-methylene bicyclo(3,3,1)nonan-3-one (21) by treatment with hydrogen peroxide and benzonitrile while Stepanova²⁸ employed m.chloro perbenzoic acid on the same olefin-ketone (21). We used the latter method to prepare an authentic sample which was identical in all respects with the $C_{10}H_{14}O_2$ ketone isolated above.

7-exo-Hydroxybicyclo(3,3,1)nonan-3-one (26) was then treated with $D_2O/NaOD$ in a sealed ampoule for seven days and the product found to have incorporated up to 8-deuteria per molecule. Additionally, the multiplet at $\delta 6.2\tau$ in the 1H n.m.r. spectrum of (26) was observed to have collapsed to a broad singlet. This was taken as evidence for a transannular hydride shift.

FIG. IV



A. Classical ions - transition state, no intermediate.

B. Non-classical ion - stabilised intermediate.

More recently, further work has been carried out on the system by another member of the group. Watt²⁹ has succeeded in preparing the exo alcohol (25) by a stereospecific reaction using the Meerwein-Ponndorf - Verley reductive technique in good yield (60%) and has found that its ozonolysis using DMS is a clear cut reaction with apparently very little, if any, epoxide formation. This evidence makes the results described above assume further interest in mechanistic terms, and a discussion on the mechanism of ozonolysis in connection with other work is found in the following sub-section. Very recently Watt²⁹ has obtained the optically active 1-methyl-7-exo-hydroxy bicyclo(3,3,1)nonan-3-one (20) and carried out preliminary polarimetric studies, and found that the racemisation is too fast to follow even at low temperatures. These observations raise the question of the nature of the activation energy profile for the transannular hydride shift. That is to say, does it proceed in a synchronous manner as illustrated in A.Fig.IV or is anchimeric assistance from the migrating hydrogen atom operating as in case B. From the extremely rapid rate determined the latter seems likely and indeed the system may be depicted as residing in the stabilised non-classical³⁰ ionic form shown.

(B) Optical Activity due to Isotopic Substitution

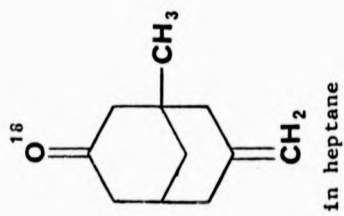
Introduction

The requirement for McKerverys optically active olefin ketone (23)¹⁸ (vide supra) caused us to become involved in a separate project in co-operation with two other groups, namely those headed by Prof. L.J. Oosterhoff at Leiden, Netherlands and Prof. G. Snatzke at Bonn. The phenomenon of optical activity due entirely to isotopic substitution had been little studied. In 1949 the first example appeared³¹ with the synthesis of 2,3-dideuterio-p-menthane (35) and since that time a number of examples have been reported involving deuterium^{32,33}. Very few compounds exhibiting the phenomenon by virtue of ¹⁸O are available however, and indeed prior to this joint project, there were only three examples to be found in the literature³⁴⁻³⁶. Cotton³⁷ introduced the concept of optical rotatory dispersion (O.R.D.) and circular dichroism (C.D.) in 1895 and at the present date a vast amount of work has been carried out by means of their use in structural elucidation. However, no Cotton effect had ever been reported for a compound rendered optically active by isotopic substitution. An attraction of such compounds for theoretical studies lies in the relatively small perturbation of symmetry imparted by the small mass differences between isotopes. More particularly ketones can be considered as ideal substrates because the absorption bands associated with them have low molar extinction coefficients, i.e. the electronically forbidden $n \rightarrow \pi^*$ transition. This enables concentrated solutions to be used in order to obtain measurable CD values since it should be realised that in, for example, replacing hydrogen by deuterium, the effective rotation is 500 times smaller than for replacement with a methyl group.

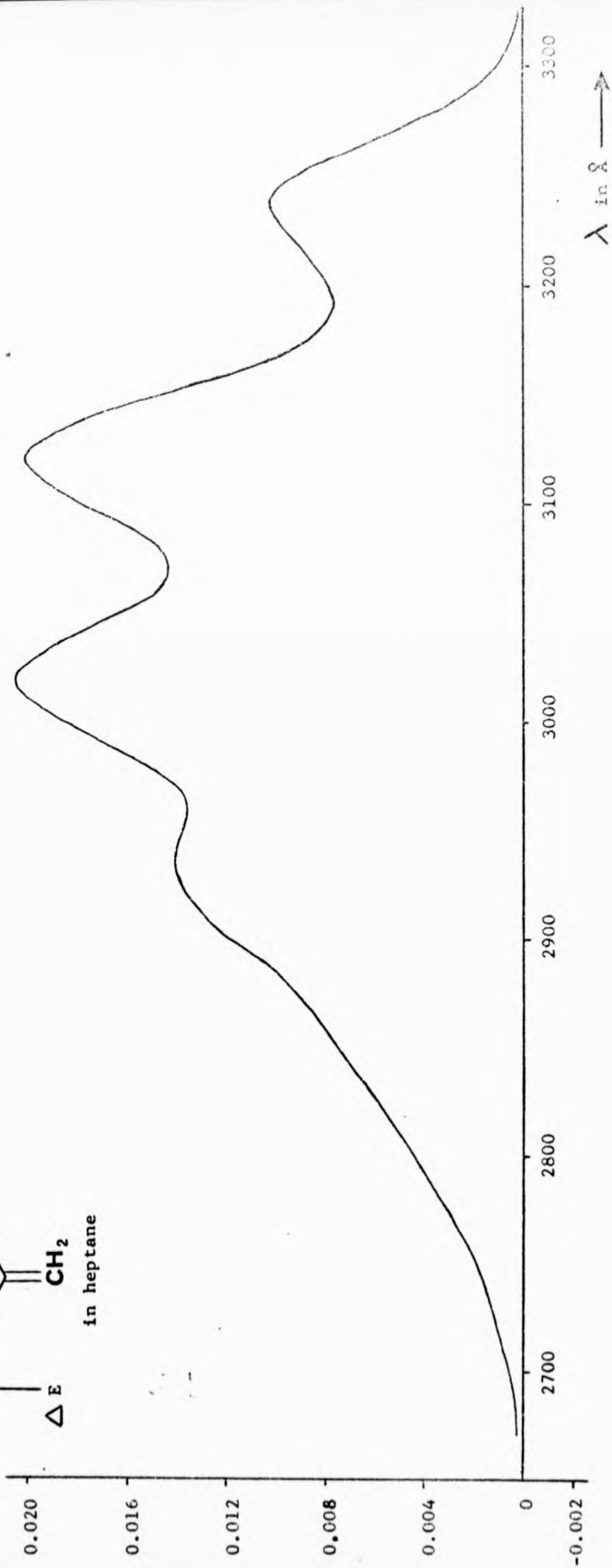
Given these requirements, the Stirling and Leiden groups set out to synthesise a number of diketones having asymmetry by virtue of containing one ¹⁶O and one ¹⁸O atom, the parent twin ¹⁶O diketones having a plane of

symmetry. Such a choice of compounds was arrived at because although satisfactory small perturbations can be achieved in optically active mono-ketones by labelling one of the antipodes with ^{18}O enormous difficulty is associated with the synthesis. Following successful execution of these tasks, Professor Snatzke was to carry out C.D. measurements on sophisticated instrumentation at Bonn while Professor Oosterhoff was to perform theoretical treatment of the results. At the time of writing, the Dutch group have successfully carried out syntheses of 1,2 diones containing one ^{18}O atom and reported the first C.D. measurements on such compounds^{38,39}. (1R)-(2- ^{18}O)- α -fenchocamphorone quinone (36) was synthesised by selenium dioxide oxidation of ^{18}O labelled optically active α -fenchocamphorone (37). Ketone (37) was labelled by hydrolysis of its hydrazone with H_2^{18}O . Predicting that the water formed in the oxidation of ketone (37) to dione (36) would exchange the label, the reaction was carried out in the presence of acetic anhydride to bind water. Initial difficulties in label loss were overcome when it was realised that the acetic anhydride itself was being consumed by selenium dioxide. When a reduced amount of the oxidant was employed, (36) was obtained with a specific label and having suffered a label loss of only 14.67% from an initial ^{18}O content of 62.72%. Although small, measurements of C.D. were possible in the wavelength range 250-520 nm and a definite fine structure observed. More recently, this group has also published a synthesis of (1R)-(1- ^2H)- α -fenchocamphorone quinone (38) and measured a small but fine structured C.D.⁴⁰. Optical activity is again entirely due to isotopic substitution, in this case by deuterium.

FIG. V



ΔE ↑



Discussion

The task undertaken at Stirling was to attempt the synthesis of other types of dione which could exhibit asymmetry by virtue of containing one ^{16}O and one ^{18}O atom. Initially, a suitable example was seen in 1-methyl-bicyclo(3,3,1)nonan-3,7-dione (39) which could be prepared from McKervey's ^{18}O olefin ketone (23). H_2^{18}O enriched at $> 98\%$ was purchased from Yeda Scientific Co., Israel and used to label (23). Two possibilities presented themselves as methods for inserting an ^{18}O label into the olefin ketone (23). On the one hand a technique similar to that of the Dutch group³⁹ could be employed by using labelled water as the hydrolytic medium in the formation of the ketone from a precursor. In the present case, this would entail hydrolysis of the urethane (40). On the other hand, the ketone itself could be labelled by hydrolytic exchange in a basic medium exclusively consisting of $\text{H}_2^{18}\text{O}/\text{Na}^{18}\text{OH}$. The first method was tried without success. The expense of H_2^{18}O demanded that very small quantities only could be used and hence a situation of large excesses of aqueous sodium hydroxide solution was not available. Instead, the reaction was carried out using a 2 molar excess only of H_2^{18}O over the urethane (40) and no products were isolated from the reaction mixture. Attention turned therefore to the second method and optically active ketone (23) itself was treated with $\text{H}_2^{18}\text{O}/\text{Na}^{18}\text{OH}$ in dry dioxane in a sealed ampoule. From several runs it was found that adequate incorporation of label was achieved only with reaction times of not less than 7 days. Mass spectroscopy indicated approximately 75% enrichment with ^{18}O and shift of the associated carbonyl infrared from 1720 cm^{-1} to 1690 cm^{-1} was observed. A C.D. measurement was carried out on this compound (41) and is illustrated in Fig. V.

A suitable method was now required to cleave the terminal methylene to carbonyl functionality without label loss or racemisation. Completely

anhydrous ozonolysis appeared to be the method of choice since the techniques were already available from the work described in the previous subsection. An advantage of this method over the selenium oxide oxidations of the Dutch group³⁹ was seen to lie in the fact that water is not generated during the reaction and would not be a factor in causing exchange of label. In addition, the conditions had already been established (vide supra) for the preparation of bicyclo(3,3,1)nonan 3,7-dione (27) in which an aqueous work-up was not involved.

Accordingly, the labelled optically active olefin ketone (41) was ozonised in a mixture of redistilled and rigorously dried methylene chloride and pyridine, the product being isolated by sublimation. Unexpectedly mass spectroscopy indicated that a virtually complete loss of label in the dione had occurred. Immediately suspect was the meticulousness with which water had been excluded from the reaction since Kokke had noted³⁹ label loss with the presence of water produced in similar reactions. Hence, a further six reactions were carried out in which it was certain that adventitious moisture could not have been present; in each case identical results were obtained namely an exasperating residual label content of < 2% in the product 1-methyl bicyclo(3,3,1)nonan-3,7-dione (39). In fact dione (39) containing an adequate enrichment of label was never obtained during these researches. However, this label loss is itself of considerable interest and merits a discussion here of recent views on the mechanism of ozonolysis.

Questions as to whether ozonolysis of olefinic double bonds proceeds by a free radical or ionic mechanism were originally answered by Criegee when he observed that no polystyrene was present in the ozonolysis products of styrene⁴¹. That the initial attack of ozone on the double bond is electrophilic in nature was originally suggested by Wibaut^{42,43} and evidence has become available to support this⁴⁴. Indeed all these to date on the mechanism of ozonolysis agree with the 1925 proposal by Staudinger⁴⁵

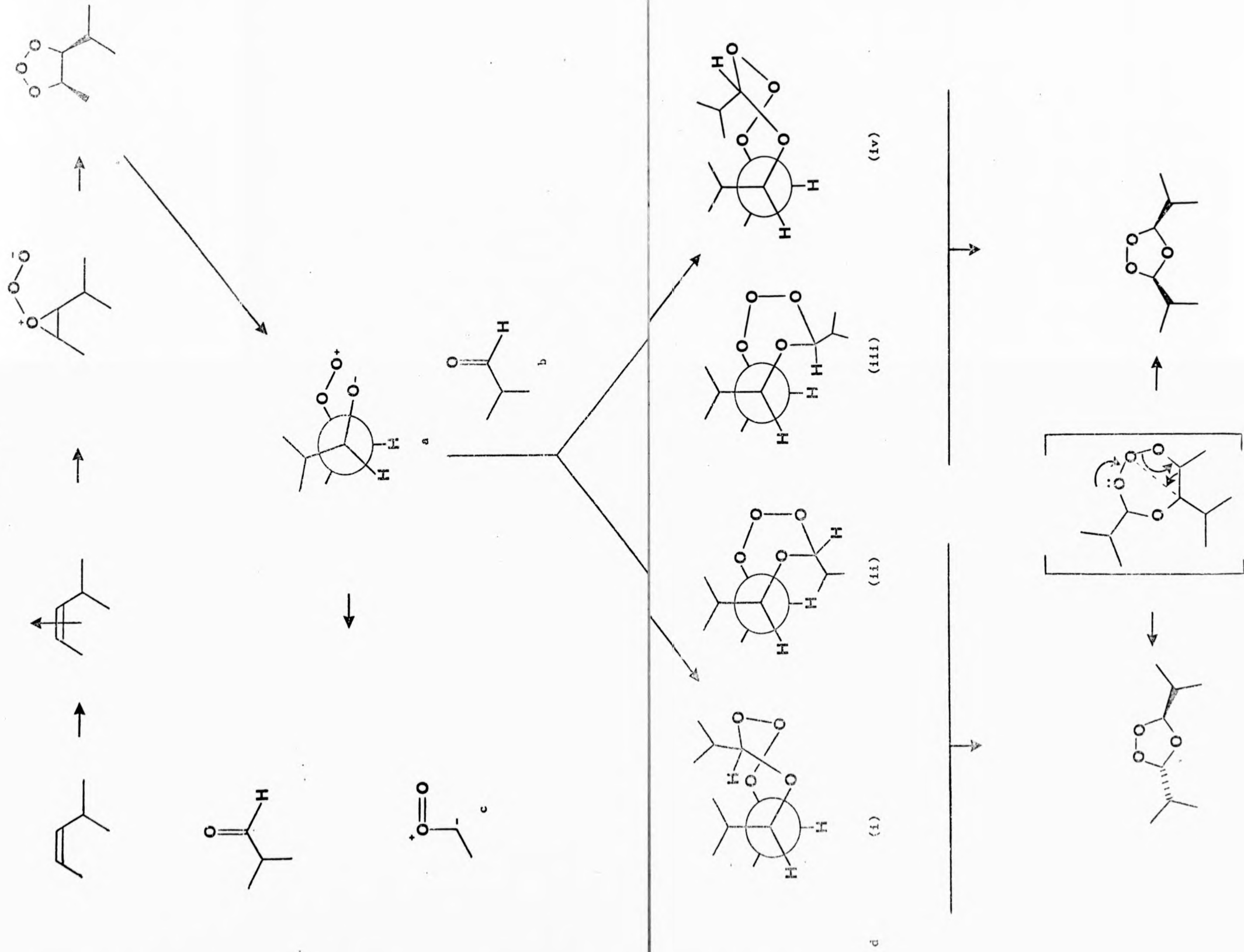
that an initial adduct (molozonide) is formed which then is converted by some pathway into the normal ozonide. While Staudinger preferred the structure (42)⁴⁵ for the initial adduct, Bailey *et al.*⁴⁶ have observed that the ¹H n.m.r. spectrum of the initial adduct of trans-di-*t*-butylethylene has a single methine resonance which is consistent with a 1,3 dipolar cycloaddition to give the less strained 1,2,3, trioxolane moiety (43). Different initial adducts^{26,47,48} have been proposed to account for cases in which epoxides^{25,26,47,49} are amongst the products of ozonolysis. These are the three membered Π and Σ complexes (44) and (45) which then form the epoxide by subsequent elimination of molecular oxygen²⁶. The open Zwitterion (46) has also been proposed²⁶ for cases where closure to (44) or (45) is prevented by steric constraints. The oxygen evolved from such intermediates on epoxide formation should have singlet multiplicity⁵⁰ and in a related case the product oxygen has indeed been shown to undergo typical singlet oxygen reactions⁵¹. These concepts and experimental evidence bear directly on the results of the ozonolysis experiments described in the preceding subsection.

Subsequent extensive work by Criegee^{41,52} resulted in a general proposal for the overall mechanism of ozonolysis. The initial adduct (47) was said to undergo synchronous decomposition to a Zwitterion (48) and carbonyl compound (49) and the two fragments subsequently recombined to form the normal ozonide⁵². This mechanism has been extremely useful in accounting for most of the observed experimental data. Criegee further strengthened his proposal with the observation that when a foreign aldehyde, *i.e.* one non-derivable from the olefin being ozonised, is added to the reaction mixture a new ozonide was formed which incorporated the added aldehyde⁴¹. The related premise that "cross" ozonides (*i.e.* a symmetrical ozonide from an unsymmetrical olefin) should be present was not proved until later when Riesbus⁵³ and Privett⁵⁴ independently found the three expected ozonide pairs in the ozonolysis of methyl oleate. Criegee attributed his failure to find cross ozonides in the

ozonolysis of heptene-3 to the inability of the Zwitterion and carbonyl components to escape a solvent cage in which they recombined⁴¹. In fact this is now attributed to the olefin concentration used and Story *et al.*⁵⁵ have since obtained the cross ozonides from butene-2, pentene-2, and hexene-3. Ozonides are capable of existing as cis/trans stereo chemical pairs and before the discovery of "cross" ozonide formation, Schröder⁵⁶ had already reported the interesting observation that the cis/trans distribution in parent ozonides was not identical from starting cis and trans olefins as demanded by the simple Creigee proposals. Further examples followed⁵⁷ but in 1966 the intriguing observation by Story *et al.*⁵⁸ that the cis/trans distribution in "cross" ozonides was a function of starting olefin geometry demanded a complete reappraisal of the original Creigee postulates. Story and co-workers continued to examine this phenomenon and tabulated the cis/trans "cross" ozonide distribution from the ozonolysis of a number of cis and trans olefins as a function of substituent bulk⁵⁷. A marked trend was found in the case of cis olefins which tended to give more cis ozonide as the substituents increased in size. A similar although less definite trend was found for trans olefins⁵⁷. Cis olefins gave higher yields of ozonide, which has been interpreted by Greenwood⁵⁹ as a function of the relative stabilities of the initial adducts. Nucleophilicity of the solvent was also found to be a parameter⁶⁰ in governing ozonide yield and stereo chemical distribution as was the concentration of starting olefin⁶⁰.

From all of this data, Story proposed a working hypothesis in the form of an intramolecular mechanism for ozonide formation involving an "aldehyde interchange" pathway which includes a foreign aldehyde in a 7-membered transition state which subsequently collapses to yield the ozonide^{47,48,61}. The mechanism gives provision for stereo selective cis ozonide formation in the case of a cis olefin and is more clearly illustrated in Fig.VI.

FIG. VI

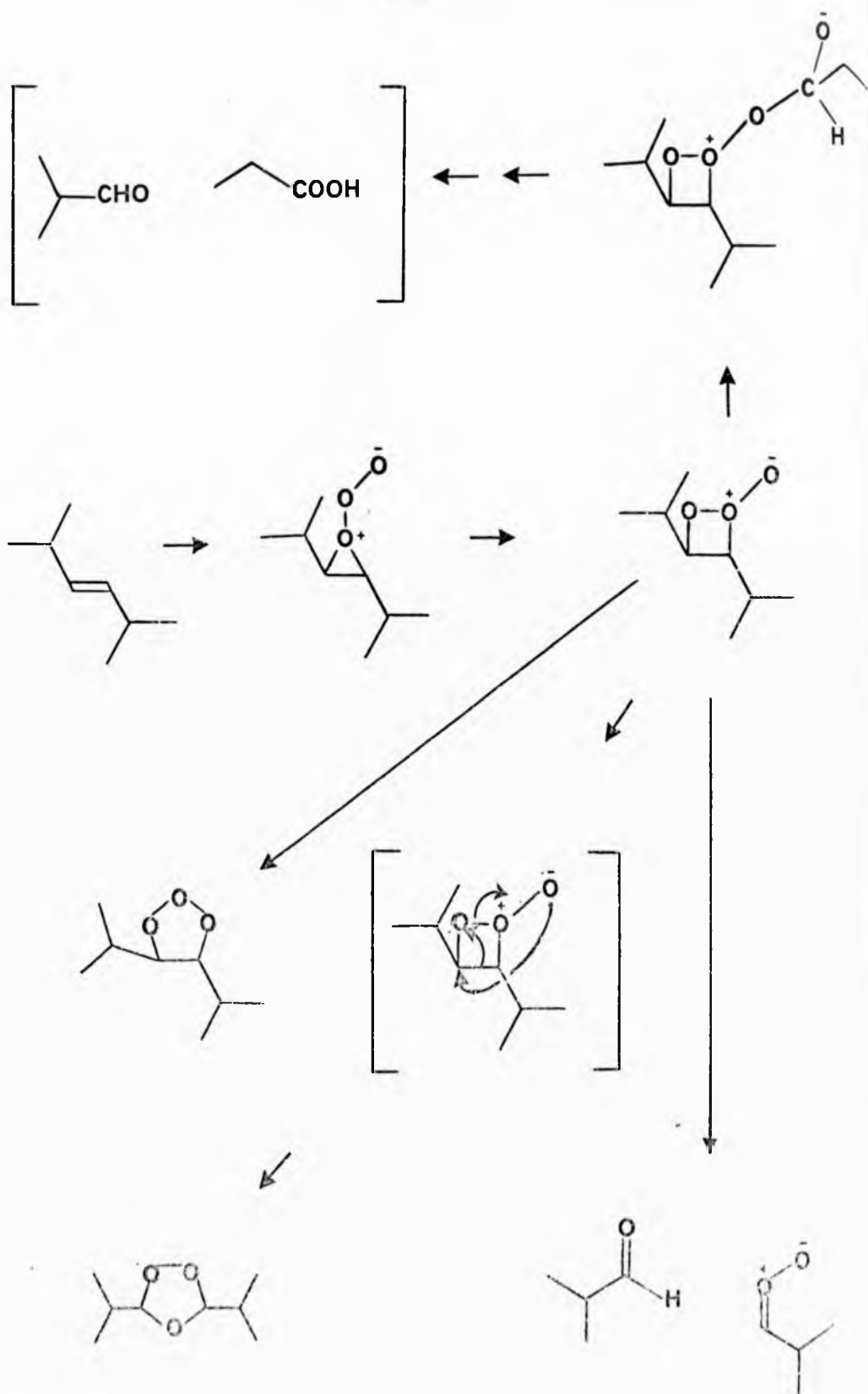


The initial adduct may be 1,2,3 trioxolane structure or a complex which can itself rearrange to the former. Heterolysis to the Zwitterion (a) (Fig. VI) now enables insertion of the added aldehyde (b) to produce any of four possible conformers (d) (i)-(iv). From this example it can be seen that (d) (iii) will be preferred since it has only H-H non-bonded interactions. Collapse of (d) conformers to the cross ozonide will result in a predominance of the cis stereo isomer if (d) (iii) is the major conformer. Story is at pains to point out that the mechanism is only a postulate⁵⁷ and should be taken as complementing the Criegee Zwitterion pathway provision for which is given in Fig. VI.

Evidence for the new mechanism has been presented from labelling experiments^{62,63,64}. If ^{18}O labelled added aldehyde is employed then the labelled oxygen must by definition appear in the ether bridge of the normal ozonide for the Criegee pathway while if the new aldehyde interchange mechanism is followed it will be found in the peroxy bridge of the normal ozonide. Following experiments to determine which ozonide oxygen is lost on lithium aluminium hydride reduction, Story et al.⁶³ have examined the corresponding alcohols from reduction of the ozonides of trans di-isopropylethylene ozonised in the presence of labelled acetaldehyde. The results suggested that 32% of the ozonide was formed by a route placing ^{18}O in the ether bridge and 68% with ^{18}O in the peroxy bridge.

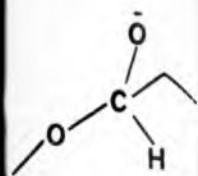
The proposal by Story and co-workers of aldehyde or carbonyl participation in the transition state for ozonide formation enables us to propose a rationale for the virtual complete loss of ^{18}O label in the above ozonolysis of optically active labelled 1-methyl-7-exomethylene bicyclo(3,3,1)nonan-3-one (41). Relating the 7-membered ozonide forming transition state to this case, one can consider an intramolecular variation of the aldehyde interchange

FIG. VII



mechanism. In terms of the Story hypothesis, the 1,2,3 trioxolane (50) is first formed and may be followed by ring closure to the nor-bicyclo(3,3,1) nonane system (51), which is also a Story type seven membered transition state containing ^{18}O . Collapse to the normal ozonide (52) places ^{18}O exclusively in the ether bridge and the subsequent reductive cleavage of the ozonide by pyridine must be regiospecific either to place ^{18}O in the formaldehyde fragment or pyridine-N oxide. Such a process accounts for complete removal of ^{18}O label. This mechanism is not identical to the Story "aldehyde interchange" pathway it being sterically impossible for the latter to operate intramolecularly in this system; 7- membered transition state (51) once formed, however, is a typical Story one.

In 1971 Story *et al.* introduced a "new and unifying concept" for the mechanism of ozonolysis^{65,66} which has since become the subject of vigorous controversy⁶⁷⁻⁶⁹. The concept followed an observation that the ozonolysis of certain aliphatic olefins in the presence of increasing concentrations of added aldehyde curtails ozonide formation and at high concentrations prevents it altogether⁶⁵. The added aldehyde in the case of ethylidene cyclohexane (53) was propionaldehyde and at concentrations $> 4\text{M}$ in pentane the only products found were cyclohexanone acetaldehyde and propionic acid. The yields suggested stoichiometry of ozonide cleavage with the propionaldehyde being oxidised in a Baeyer-Villiger fashion. Similar results were obtained when (53) was ozonised in cyclohexanone. No ozonide was formed but the products were δ -hexanolide and acetaldehyde. To accommodate these results, Story⁶⁶ laid down a unifying rationale intended to encompass all aspects of the mechanism of ozonolysis and this is illustrated in Fig. VII. The trioxolane structure was no longer considered to be the initial adduct and is replaced by the δ complex. This may now give an epoxide directly for the cases already discussed or more normally rearrange to the Staudinger molozonide. The molozonide now becomes the key intermediate which can be



reduced by added aldehyde (when this is present in excess) to yield the dioxetane which then readily breaks down directly to the carbonyl products. When added aldehyde is not in excess the molozonide is not trapped and can follow three different pathways to the products via respectively the 1,2,3, trioxolane, direct rearrangement to normal ozonide, or cleavage to Criegee type Zwitterion and carbonyl fragments.

In a subsequent paper Story reports the isolation of dioxetane intermediates from the ozonolysis of several olefins⁷⁰. In particular ethylidene cyclohexane (53) ozonised in the "Baeyer-Villiger" solvent pinacolone yielded on low temperature solvent removal, a residue whose ¹H n.m.r. spectrum was consistent with the dioxetane (54). Lithium aluminium hydride reduction afforded ethylidene cyclohexane glycol (55) in addition to cyclohexanol and ethanol.

Recently Story's work has been the subject of vigorous attack by a number of workers. For example Bailey has consistently supported the concept of a modified Criegee mechanism to explain cross ozonide cis/trans distributions being a function of olefin geometry. Prior to his recent report, this author has published an alternative interpretation. In 1968 he⁷¹ maintained that all the ozonolysis data available at that date could be explained in terms of syn and anti Zwitterions. Such conformers would react with a carbonyl to produce different cis/trans ratios in the ozonide. Bailey also maintains that different distributions of syn and anti Zwitterions are possible depending on the conditions, and Murray, a co-worker with Story, admits that interconversion between syn and anti conformers may not be rapid at the low temperatures associated with ozonolysis experiments⁵⁷. Hence in a strongly worded 1973 publication⁶⁸ Bailey "refutes" the Story "unifying concept" and maintains that his modification of the Criegee mechanism still provides the most adequate interpretation of the Criegee mechanism. Such an emphatic disagreement with

Story's results is justified by the fact that Bailey's work involves a careful re-examination of the conditions previously⁷⁰ claimed to yield the dioxetane (54) in the ozonolysis of ethylidene cyclohexane (53) and concludes that it is not formed, an observation reinforced by the simultaneous and independent publication by Kopecky⁶⁷ *et al.* of an almost identical study. At about the same time, Kerur⁶⁹ reported a failure to find the 6-hexanolide product in excess of 1% yield when Story's experiments were repeated. However, Murray⁷² has recently described the photo-oxidative cleavage of 1-naphthyl-phenyl diazomethane (56), a process known to produce Criegee type carbonyl oxide Zwitterions, in the presence of acetaldehyde and benzaldehyde from which amounts of 1-(1-naphthyl)-1-phenyl-1-propene (57) and 1-(1-naphthyl)-stilbene (58) ozonides were obtained. Of special interest in this case is the comparison of the cis/trans ozonide ratio (0.75) with that of the cis/trans ratios of the cross ozonides from the ozonolysis of cis and trans 1-(1-naphthyl)-1-phenyl-1-propene (59) and (60) which were respectively 1.08 and 0.78. Murray interprets this result as supporting the concept of a pathway other than the Criegee mechanism operating in the case of the cis olefin ozonolysis consistent with the Story aldehyde interchange mechanism. A subsequent communication by this tenacious worker⁷³ described further use of the photo-oxidative technique to follow the fate of an ¹⁸O tracer placed in the ozonide from diphenyl diazomethane (61) and ¹⁸O labelled benzaldehyde. It was shown that ¹⁸O is indeed confined to the ether bridge of the ozonide when an exclusive Criegee pathway is followed, thus negating an assertion by Fliszar⁷⁴ that oxygen exchange is possible between Zwitterion and carbonyl components. It should be recalled that exclusive location of ¹⁸O in the ether and peroxy bridges during the operation of respectively the Criegee pathway and the aldehyde interchange mechanism was a pre-requisite to justify earlier ¹⁸O labelling work which indicated an alternative pathway to the Criegee mechanism.

Hence, at the time of writing in spite of the emergence of a considerable number of recent results⁶⁵⁻⁷⁴, many questions remain to be answered before the precise nature of the mechanism of ozonolysis can be stated. It is maintained here that the complete loss of ¹⁸O label during the ozonolysis of 1-methyl 7-exo-methylene bicyclo(3,3,1)nonan-3-one (41) constitutes a valuable addition to the available data since an intermolecular pathway could only account for a limited loss of label, scrambling being an alternative. Although it seems clear from the recent evidence that dioxetane intermediates are not formed in the presence of excess added aldehyde^{67,68} there appears to be no objection to the aldehyde interchange pathway itself proceeding from a 1,2,3 trioxolane initial adduct and it may be said that the result described here provides support for it.

Returning briefly to the formation of epoxides in the ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-exo-3-ol (25) and 7-exo-methylene bicyclo(3,3,1)nonan-endo-3-ol (28) and the unusual result of the corresponding olefin-ketone (21) yielding only dione (27), an explanation may be offered. Olefin ketone (21) may not be as sterically crowded as the alcohols (25) and (28) to initial ozone attack in that its carbonyl bearing carbon atom at C3 is sp² hybridised and hence the familiar transannular steric interactions are not present to preclude formation of the initial adduct. The simultaneous oxidation of the alcohol group at C3 during ozonolysis of (28) together with the almost total absence of this during the same treatment of (25) are easily attributed to the already well documented²⁴ propensity of ozone to oxidise alcohols to their corresponding carbonyl compounds. The different configuration of the alcohol groups between (25) and (28) can account for the selectivity observed.

In conclusion it should be mentioned that work is proceeding at Stirling both on finding a successful synthesis of selectively labelled diones and also to determine the fate of the lost ^{18}O label from 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-(^{18}O)-one (41). Particularly ozonolysis of the labelled acetates (62) seems to be attractive and it is expected that the results will be reported in due course.

As a footnote it is interesting to include here the results of a further single experiment. ^{18}O labelled (75%) 1-methyl-7-exomethylene bicyclo(3,3,1)nonan-3-one (41) was oxidised with ruthenium tetroxide in dry carbon tetrachloride to yield the corresponding dione (39) in 80% yield^{75,76}. The ruthenium tetroxide was prepared immediately before use by oxidation of black ruthenium dioxide with sodium metaperiodate in aqueous solution⁷⁷. The method involved shaking a slurry of the dioxide in aqueous solution with carbon tetrachloride so that the yellow ruthenium tetroxide was taken up in the organic phase as it formed. The organic phase was then quickly filtered through a plug of anhydrous magnesium sulphate and used immediately. This experiment is of note because the product dione (39) was almost completely devoid of label a fact which is not readily explicable. It is not possible to draw conclusions from this unexpected result since only one experiment was carried out. However, a factor which may be pointed to is the exclusion of moisture. The rapid passage of the carbon tetrachloride solution through magnesium sulphate is probably inefficient in removing all moisture and an oxygen exchange equilibrium catalysed by formic acid arising from oxidation of the formaldehyde cleavage fragment is likely to be operating. However, such complete exchange via this mechanism is at least surprising in view of the preceding discussion. An intramolecular transition state of the type described in the ozonolysis mechanism is not possible and other

pathways resulting in removal of ^{18}O into the ruthenium dioxide product are not immediately obvious. Hence further study of this reaction is currently in progress.

Experimental

1,3 dibromoadamantane

Adamantane (32.7 g., 0.24 mole) was added in portions to a mixture of dry bromine (120 ml., 2.4 mole), distilled from phosphorous pentoxide, boron tribromide (6 ml.) and aluminium foil (2.0 mg.). Addition of the adamantane was carried out under rigorously anhydrous conditions, the system being maintained under a constant stream of nitrogen terminating in a sodium hydroxide trap. When the addition was complete, the mixture was boiled at reflux for two hours after which time the effluent gases were neutral to universal pH paper. The cooled mixture was poured into a stirred two component system of ice water (200 ml.) and carbon tetrachloride (350 ml.) and excess bromine destroyed by the portionwise addition of sodium metabisulphite, the temperature being maintained below 40°. The phases were separated and the aqueous layer extracted with carbon tetrachloride (3 x 150 ml.). The combined organic phase (800 ml.) was washed with water (800 ml.), sodium bicarbonate solution (10%, 800 ml.), brine (800 ml.), and dried (MgSO₄). Removal of solvent under reduced pressure yielded a light yellow crystalline solid (65.2 g.). Pure 1,3 dibromoadamantane was obtained by recrystallisation of the product from methanol 63.5 g., 90% m.p. 112-113°, lit. 112-113°. ν_{max} (CCl₄) 2929, 2916, 2868, 1339, 1317, 1292, 1236, 1104, 1026, 1000, 984, 958, 939, 823, 778, 701 cm⁻¹. n.m.r. τ_{H} 7.12 (2H, s), 7.68 (10H, s), 8.26 (2H, s).

7-exo-methylene-bicyclo(3,3,1)nonan-3-one (21)

A solution of 1,3 dibromoadamantane (50 g., 0.17 mole) in dioxane (500 ml.) was placed in an unstirred autoclave of capacity 2000 ml. and sodium hydroxide solution (N, 500 ml.) added. The sealed autoclave was heated at 180° for 24 hours and then allowed to cool to ambient temperatures. Dioxane was removed completely from the resulting light

brown solution by distillation under reduced pressure to yield an aqueous slurry of solid organic material. The slurry was extracted with ether (4 x 200 ml.) and the combined organic phase washed with water until the washings were neutral (4 x 500 ml.), brine (500 ml.) and dried (MgSO_4). Removal of solvent under reduced pressure yielded a light brown crystalline solid 21.2 g. The product was sublimed at 1 mm/100° to give highly crystalline 7-exo-methylene bicyclo(3,3,1)nonan-3-one (21) 19.2 g. 75%. m.p. 163-4°. lit. 160-4°. n.m.r. τ_{H} 5.26 (2H, s), 7.71 (10H, s), 8.08 (2H, s).

Lithium aluminium hydride reduction of

7-exo-methylene-bicyclo(3,3,1)nonan-3-one (21)

A solution of 7-exo-methylene-bicyclo(3,3,1)nonan-3-one (1.30 g., 0.008 mole) in dry ether (50 ml.) was added dropwise over 30 minutes to a stirred slurry of lithium aluminium hydride (0.33 g., 0.011 mole) in dry ether (25 ml.). After the addition the mixture was boiled at reflux for two hours and on cooling a saturated solution of sodium sulphite added dropwise until the excess hydride had been destroyed. Water (50 ml.) was added and the ether layer decanted off. The aqueous slurry was further extracted with ether (3 x 50 ml.) and the combined organic phase washed with water (3 x 50 ml.), brine (50 ml.) and dried (MgSO_4). Removal of solvents under reduced pressure yielded a colourless oil which quickly crystallised to a highly odiferous volatile solid (1.28 g.). This product was eluted from a Camag type 'H' alumina column with ether/light petrol to yield the faster running 7-exo-methylene bicyclo(3,3,1)nonan-endo-3-ol (28) 1.00 g., 77%.

ν_{max} . (CCl_4) 3516, 2928, 1457, 1442, 1431, 1411, 1113, 1087, 1054, 956, 898 cm^{-1} . n.m.r. τ_{H} 5.10 (2H, s), 6.34 (1H, unresolved m), 7.3 - 8.8 (13H, m), followed by 7-exo-methylene bicyclo(3,3,1)nonan-exo-3-ol (25), 0.2 g., 16%. ν_{max} . (CCl_4) 3626, 3378, 2984, 2925, 2858, 2833, 1655, 1640, 1462, 1444, 1427, 1383, 1351, 1280, 1257, 1172, 1120, 1047, 963, 927, 888 cm^{-1} . n.m.r. τ_{H} 5.32 (2H, s), 5.55 (1H, 9 line m), 7.5 - 9.1 (13H, m).

Ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-exo-3-ol (25)

7-exo-methylene bicyclo(3,3,1)nonan-exo-3-ol (25) (1.0g; 0.0067 mole) in freshly distilled dry methylene chloride (30 ml.) and dry pyridine (1.5 ml.) was cooled to -70° . A slow stream of ozonised oxygen was passed through the solution until it turned blue, at which point the ozone was disconnected and pure oxygen passed through until the blue colour had been discharged. The mixture was allowed to warm up to ambient temperatures by leaving overnight after which a precipitate of pyridine -N-oxide had collected at the bottom of the vessel. The mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The resulting light green syrupy oil was eluted from a short column of Camag type 'H' alumina with methylene chloride to yield a colourless crystalline solid 0.92 g. This product was homogeneous to T.L.C. save for a trace component at high r.f. (0.83). The major components were superimposed in a single spot at r.f. 0.54. Separation was achieved by chromatography from Camag type 'H' alumina with benzene/methylene chloride, a large number of very small fractions being taken. This also resulted in isolation of the trace material (7 mg.) which was subsequently identified as exo-7-epoxymethylene bicyclo(3,3,1)nonan-3-one (34) (vide infra authentic sample), m.p. $258-260^{\circ}$, lit. $258-260^{\circ}$. M^+ m/e 166, ν_{\max} . (CS_2) 3072, 2940, 2918, 2881, 1722, 1407, 1354, 1346, 12.85, 1237, 1222, 1204, 1171, 1119, 1108, 1090, 1008, 985, 934, 883, 846, 817, 800, 772, cm^{-1} . n.m.r. τ_H 7.1 - 8.4 (12H, m), 8.5 - 9.2 (2H, m). A zone of pure 7-exo-epoxy-^{methylene}bicyclo(3,3,1)nonan-exo-3-ol (vide infra Jones oxidation) was eluted secondly, 0.396 g., 35%. M^+ m/e Found 168.1150, $C_{10}H_{16}O_2$ requires 168.1145. ν_{\max} . ($CHCl_3$) 2981 (sh), 2920, 2846, 1420, 1346, 1045, 980 (sh), 973. n.m.r. τ_H 5.76 (1H, m), 7.27 (2H, s), 7.45 - 8.9 (13H, m). A two component zone followed and finally

pure 7-exo-hydroxy-bicyclo(3,3,1)nonan-3-one (26) was collected 0.27 g., 27%. m.p. 151 - 152°. M^+ m/e. Found 154.0994, $C_9H_{14}O_2$ requires 154.0994. ν_{max} ($CHCl_3$) 3623, 2953, 2835, 1718, 1703, 1450, 1416, 1356, 1320, 1283, 1236, 1175, 1124, 1033 cm^{-1} . n.m.r. τ_H 6.22 (1H, m), 6.8 (1H, s), 7.52 (6H, s), 7.7 - 8.9 (6H, m); D_2O shake removes singlet at 6.8 τ

Ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-endo-3-ol (28)

7-exo-methylene bicyclo(3,3,1)nonan-endo-3-ol (28) (1.5g; 0.01 mole) in freshly distilled dry methylene chloride (45 ml.) and dry pyridine (2.25 ml.) was cooled to -70°. A slow stream of ozonised oxygen was passed through the solution until it turned blue. The ozone was disconnected and pure oxygen passed through until the blue colour had been discharged. The mixture was allowed to warm up to ambient temperatures overnight after which time a precipitate of pyridine-N-oxide had collected at the bottom of the vessel. The mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The resulting light green syrupy oil 1.54 g. showed two distinct components by analytical t.l.c. at respectively r.f. 0.81 (brown) and 0.51 (blue) together with an unresolved material at the baseline - presumably Py-N-oxide. This product was eluted from a Camag type 'H' alumina column with methylene chloride to yield exo-7-epoxymethylene-bicyclo(3,3,1)nonan-3-one (34) 0.64g., 39.4%. m.p. 259 - 260°, lit. 258 - 260°. Infrared and 1H n.m.r. spectral data were identical with the trace (7 mg.) product from the previous experiment. Further elution yielded the slower running component which was identified as 1-hydroxy-oxa-adamantane (33) by comparison with an authentic sample 0.63 g., 42%. m.p. 247 - 248°, lit. 248.5° n.m.r. τ_H ($CHCl_3$) 5.67 (1H, m unresolved), 6.07 (1H, s), 7.5 - 9.00 (12H, m). D_2O shake removes singlet at 6.07 τ

Ozonolysis of 7-exo-methylene bicyclo(3,3,1)nonan-3-one (21)

7-exo-methylene bicyclo(3,3,1)nonan-3-one (21) (5.20 g., 0.035 mole) was submitted to conditions identical with those of the preceding two experiments as far as the isolation of a similar syrupy green oil, 4.52 g. Elution from Camag type 'H' alumina yielded bicyclo(3,3,1)nonan-3,7-dione (27) 3.82 g., 74% as the only product. m.p. 255 - 256°, lit. 254 - 255.5° n.m.r. τ H 7.17 (2H, s), 7.41 and 7.49 (10H, d), 7.76 (2H, s).

Preparation of an authentic sample of ^{methylene}exo-7-epoxy bicyclo(3,3,1)nonan-3-one (34)

m-chloroperbenzoic acid (85%, 15.0 g., 0.074 mole) in dry methylene chloride (150 ml.) was added dropwise during 40 minutes to a stirred solution of 7-exo-methylene bicyclo(3,3,1)nonan-3-one (21) (7.5 g., 0.05 mole) in dry methylene chloride (150 ml.). The solution was stirred for a further two hours after which time a saturated solution of aqueous sodium metabisulphite was added until the excess oxidant had been destroyed. The organic phase was separated and washed with saturated sodium bicarbonate solution (3 x 100 ml.) water (100 ml.) and dried (MgSO₄). The solvent was removed by evaporation under reduced pressure to yield a colourless crystalline solid 7.20 g. Pure 7-exo-epoxymethylene-bicyclo(3,3,1)nonan-3-one (34) crystallised in needles from ethanol 6.8 g., 82%. m.p. 258 - 259°, lit. 258 - 260°. Infrared and n.m.r. spectral data are identical with those of the common product from the ozonolysis of alcohols (25) and (28) above.

Jones Oxidation of 7-exo-epoxymethylene-bicyclo(3,3,1)nonan-3-ol

Jones reagent (5 ml.) was added during 15 minutes to a stirred solution of 7-exo-epoxymethylene-bicyclo(3,3,1)nonan-3-ol (2.5 g., 0.015 mole) in ether (25 ml.) maintained at 0° with an ice bath. Stirring at 0° was continued for 90 minutes after which granular anhydrous potassium carbonate (25 g.) was

added and stirring continued for a further 20 minutes. The organic phase was filtered from the mixture and the solids washed once with ether (50 ml.). The combined organic phase was washed once with water (25 ml.) and dried (MgSO_4). Removal of solvent by evaporation under reduced pressure yielded a colourless crystalline solid 2.12 g. The product was recrystallised from ethanol in needles to yield pure 7-exo-epoxymethylene-bicyclo(3,3,1)nonan-3-one (34) 1.97 g., 79%. m.p. 259 - 260°, lit. 258 - 260°. Infrared and ^1H n.m.r. spectral data are identical in all respects with those of the product obtained in the previous experiment.

^{18}O isotopic labelling of 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-one (23)

A glass ampoule of capacity (10 ml.) dried by heating in an oven at 100° overnight was charged with H_2^{18}O (500 mg., 99% isotopic purity, ex Yeda Scientific Ltd., Israel). A piece of clean sodium metal (50 mg., 2.2 mg. atom) was admitted and as soon as solution had been achieved, 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-one (23) (200 mg., 1.22 m. mole) in anhydrous dioxane (5 ml.) was added. The ampoule was sealed and heated at 90° for 7 days. After opening the homogeneous solution was diluted with dry ether (20 ml.) and the aqueous phase separated. Solvents were removed under reduced pressure and the oily product distilled at 110°/0.5 mm. to yield a clear oil 92 mg. ν_{max} . (film) 1675 ($\text{C} = ^{18}\text{O}$), 1707 ($\text{C} = ^{16}\text{O}$) cm^{-1} . M^+ m/e 164 and 166. Corrected for natural abundance of ^{18}O in a "cold" sample, an enrichment of 75% in ^{18}O was calculated from the parent ion peak relative intensities.

Ozonolysis of ^{18}O labelled 1-methyl-7-exo-methylene bicyclo(3,3,1)
nonan-3-one (41)

Labelled 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-one (41) from the previous experiment (100 mg., 0.61 m.mole) was ozonised in rigorously dried methylene chloride and pyridine using the procedure described above. The system was maintained under a blanket of dry nitrogen throughout the reaction. The product was isolated by removal of solvents under reduced pressure followed by sublimation at $100^{\circ}/0.5$ mm. to yield a colourless crystalline solid, 1-methyl-bicyclo(3,3,1)nonan-3,7-dione (39), 69 mg. Infrared and ^1H n.m.r. spectral data were identical with those of an authentic sample of unlabelled dione. M^+ m/e 166 and 168. A residual enrichment in ^{18}O of $< 2\%$ above natural abundance was calculated from the parent ion peak relative intensities.

Ruthenium tetroxide cleavage of ^{18}O labelled 1-methyl 7-exo-methyiene
bicyclo(3,3,1)nonan-3-one (41)

To a slurry of ruthenium dioxide (100 mg., 0.8 m.mole) in aqueous sodium metaperiodate (10%, 12 ml.) was added redistilled carbon tetrachloride (15 ml.). The mixture was shaken vigorously in a separatory funnel until all of the black ruthenium dioxide solid had been oxidised and the tetroxide product extracted into the organic phase to give a bright yellow homogeneous solution. The aqueous phase was separated and the remaining solution of ruthenium tetroxide in carbon tetrachloride dried by quickly passing through a plug of anhydrous magnesium sulphate. The dried solution was used immediately by adding dropwise to a stirred solution of ^{18}O labelled 1-methyl-7-exo-methylene bicyclo(3,3,1)nonan-3-one (41) (100 mg., 0.61 m.mole, 75% enrichment), in dry carbon tetrachloride (15 ml.). Immediate reaction was apparent by the precipitation of black ruthenium dioxide. After the

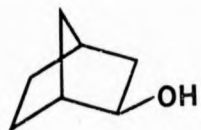
addition (15 minutes) the mixture was stirred for a further three hours, and then filtered and the precipitate washed with dry carbon tetrachloride (15 ml.). The combined organic phase was evaporated under reduced pressure to yield a colourless crystalline solid 81 mg. The product was sublimed at $100^{\circ}/0.5$ mm. to yield a highly crystalline material whose infrared and ^1H n.m.r. spectral data were identical with those of an authentic sample of unlabelled 1-methyl bicyclo(3,3,1)nonan-3,7-dione. M^+ m/e 166 and 168. A residual enrichment of $< 2\%$ was calculated from the parent ion peak relative intensities.

7-exo-hydroxy-bicyclo(3,3,1)nonan-3-one d8

A glass ampoule of capacity 10 ml. was dried by heating overnight in an oven. The ampoule was charged with deuterium oxide (2.5 ml.) and clean sodium metal (25 mg., 1.1 mg. atom) admitted. When solution had been achieved, 7-exo-hydroxy-bicyclo(3,3,1)nonan-3-one (26) (100 mg., 0.65 m. mole) in dry dioxane (2.5 ml.) was added. The ampoule was sealed and heated at 90° for 7 days. On cooling the contents were removed and continuously extracted with benzene for 48 hours. The organic phase was washed with deuterium oxide (3 x 3 ml.) and dried (MgSO_4). Removal of solvent under reduced pressure yielded a colourless crystalline solid which was sublimed at $100^{\circ}/0.5$ mm. to yield deuteriated 7-exo-hydroxy-bicyclo(3,3,1)nonan-3-one, 62 mg. n.m.r. τ_{H} singlet at 6.05 τ remains after D_2O shake. M^+ m/e 162, 161, 160. d6 2.1%, d7 12.3%, d8 85.6%. Number of deuteria per molecule = 7.835.



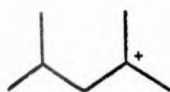
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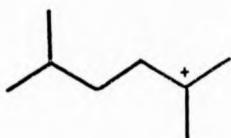
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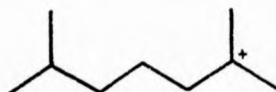
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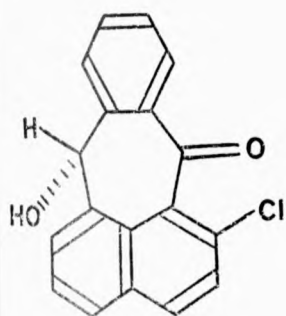
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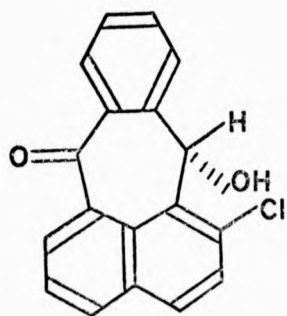
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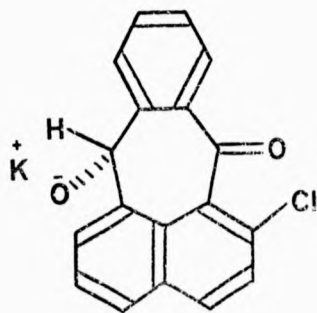
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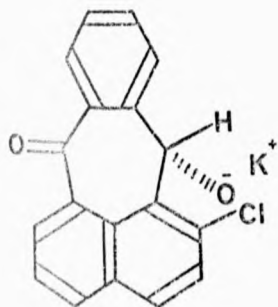
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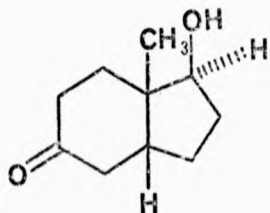
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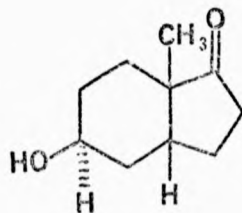
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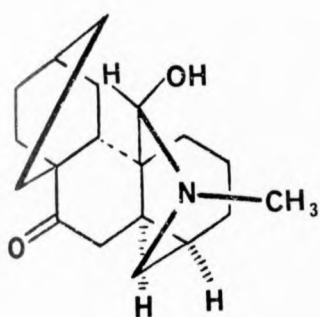
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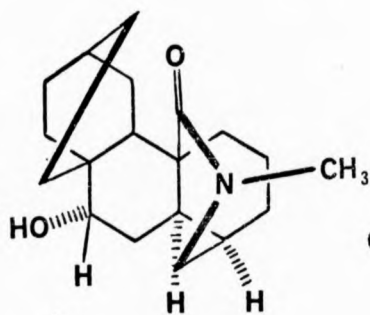
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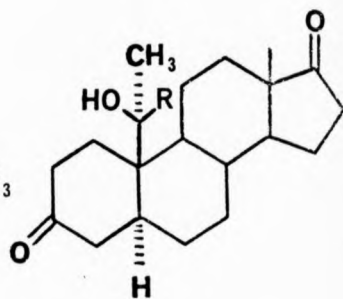
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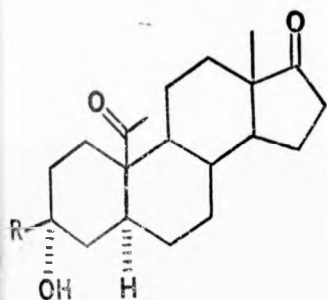
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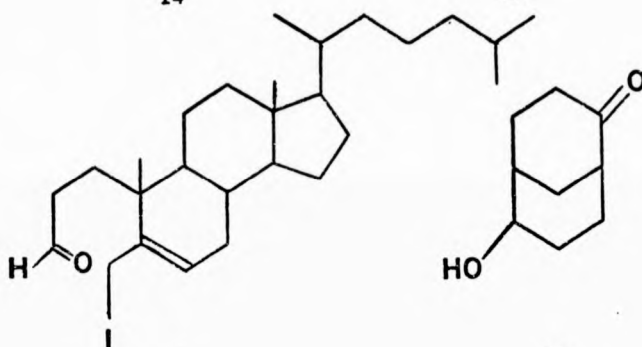
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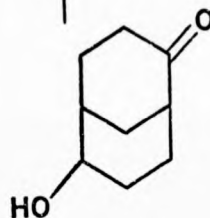
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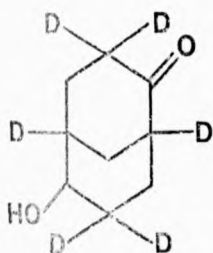
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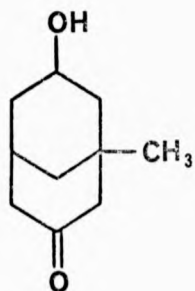
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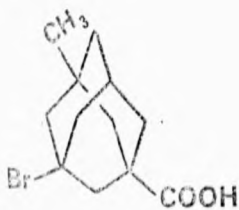
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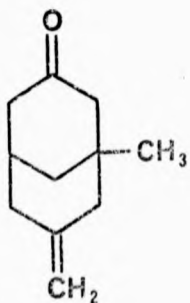
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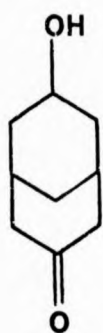
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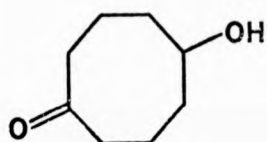
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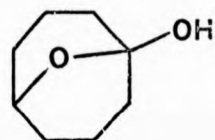
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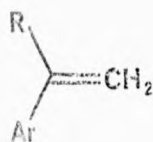
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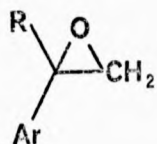
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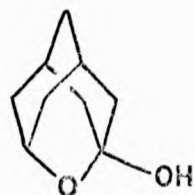
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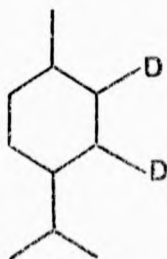
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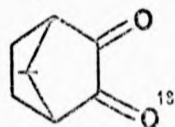
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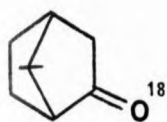
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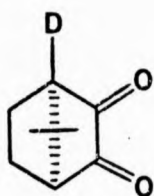
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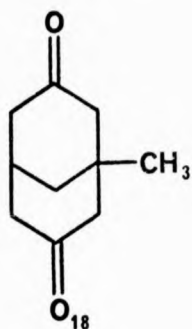
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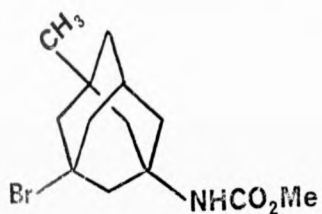
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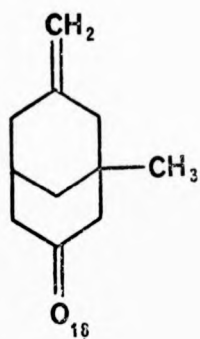
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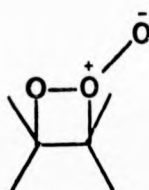
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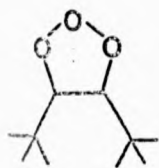
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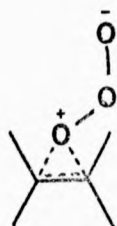
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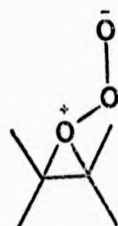
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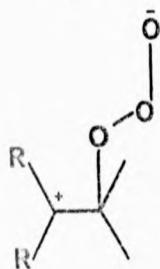
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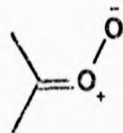
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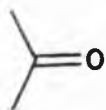
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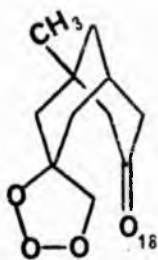
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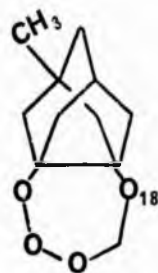
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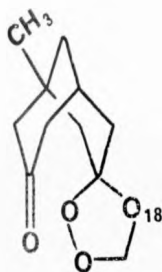
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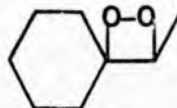
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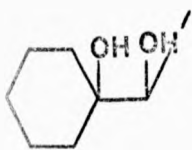
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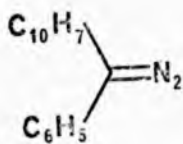
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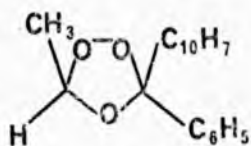
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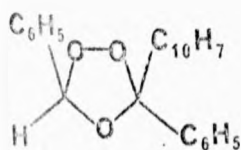
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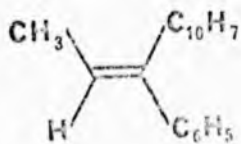
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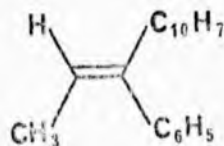


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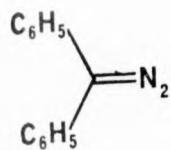


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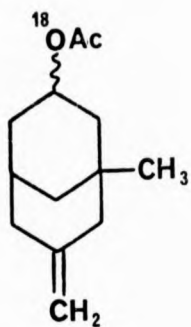
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SECTION III

Bredt's Rule - Attempted synthesis of bicyclo(3,3,1)nonan-1(2); 5(6)-diene

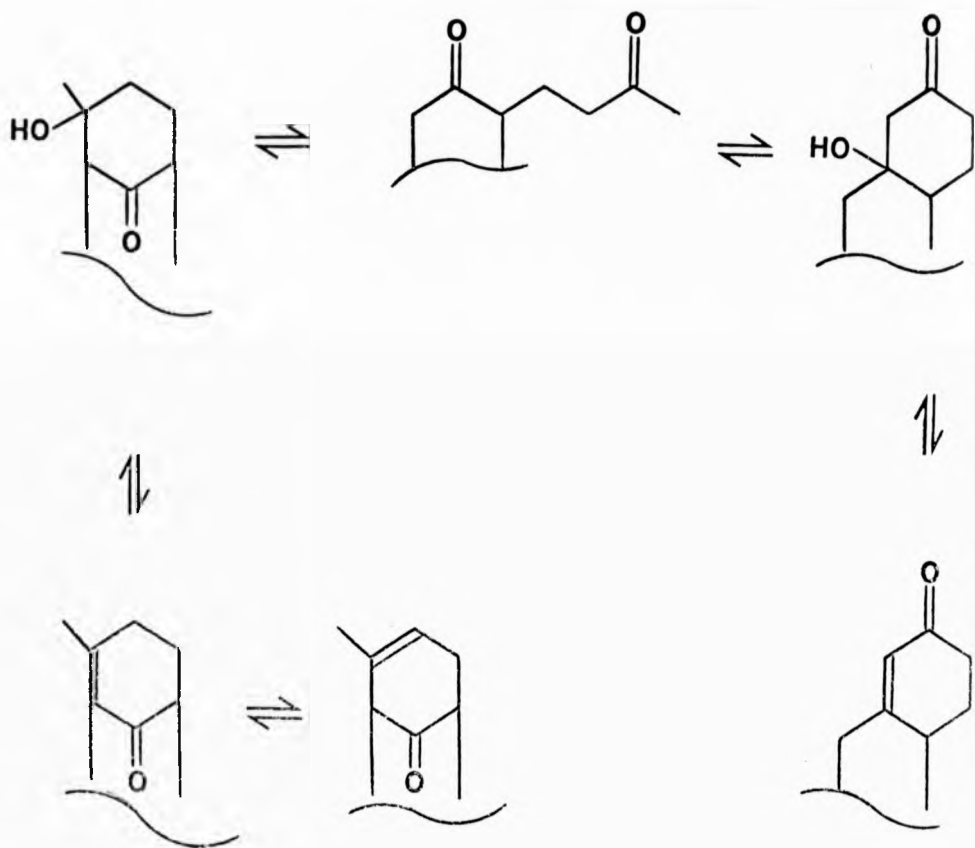
INTRODUCTION

This section describes an incomplete investigation into the possibility of obtaining the title compound itself as an isolable entity, or trapped derivative. Largely instrumental in the decision to initiate the project was the ready availability of a suitable starting material, bicyclo(3,3,1) nonan-1,5-dicarboxylic acid (1) arising out of the studies described in Section I.

Bredt's rule in its original formulation served as an exclusion criterion for the existence of certain unsaturated compounds. Laid down in 1924^{1,2} it states that "in systems of the camphane and pinane series (2), (3) and related compounds, the branching points of the carbon bridges cannot be involved in a double bond". Bredt interpreted the effect correctly as being due to ring strain incurred by the attempt to form a double bond at the bridgehead which would of necessity be required to accommodate the resulting sp^2 hybridisation. Of course the validity of the rule becomes blurred in higher homologues and beyond a certain ring size "anti-Bredt" olefins are quite stable. It is in the intermediate range of bicyclic and polycyclic systems that interest has been shown since Bredt's original rigid statement and at the present date the statement has ceased to be a definite rule and instead becomes a guideline in the wider context of ring strain.

The first systematic study to establish the limiting point of the rule was carried out by Prelog *et al.*³ who investigated a series of aldol condensation ring closures on the general compound (4) and noted a transition in the series at $n = 5$. Ring closure in this case afforded (5) in addition to the "anti-Bredt" compound (6) whereas at $n < 5$ the "anti-Bredt" compound was no longer obtained. This work corresponds to only one series, namely bicyclo(x,3,1)alkanes and all the experiments were performed under equilibrating conditions yielding only the thermodynamically preferred

SCHEME I



products. In fact it is now known that in cyclisations of this type, a complex of equilibria are set up simultaneously^{34,35} (Scheme I). Subsequently Fawcett⁴ considered it more useful to classify "anti-Bredt" types as bicyclo(x.y.z)alkenes being characterised by having an S number where $x + y + z = S$. The limiting value of the rule could now be sought in terms of the S value which enables several compounds of different types to exist within the same group with the implication that compounds having a common S number would be similarly strained.

However, a given S value does not give a complete picture of the situation as illustrated by the following pairs of examples. The "anti-Bredt" structures (7) and (8) contain a double bond within a 1-carbon bridge and both have $S = 8$ (1-olefins with $S = 7$ are now known: vide infra); yet evidence from their attempted construction with Fieser models indicates that it is extremely unlikely they could exist at least within the confines of the formal sp^2 hybridised 120° planarity of the conventional olefinic double bond. Alternatively the two olefins (9) and (10) both have the same S value ($S = 7$) and as such are indistinguishable by the Fawcett criteria, yet keto acid (11) decarboxylates smoothly⁵ to bicyclo(3,3,1) nonan-2-one (14) at 145° , while its isomer (12) is thermally stable⁶. Hence the S value is of use only when a series of homologues of similar structure are considered.

Kobrich⁷ has recently expanded the S value treatment so that a number of further rules should now be considered which treat the principles involved in terms of general ring strain, viz :-

1. Ring strain varies inversely with S.
2. With S constant, ring strain is inversely proportional to the size of the ring containing the double bond.

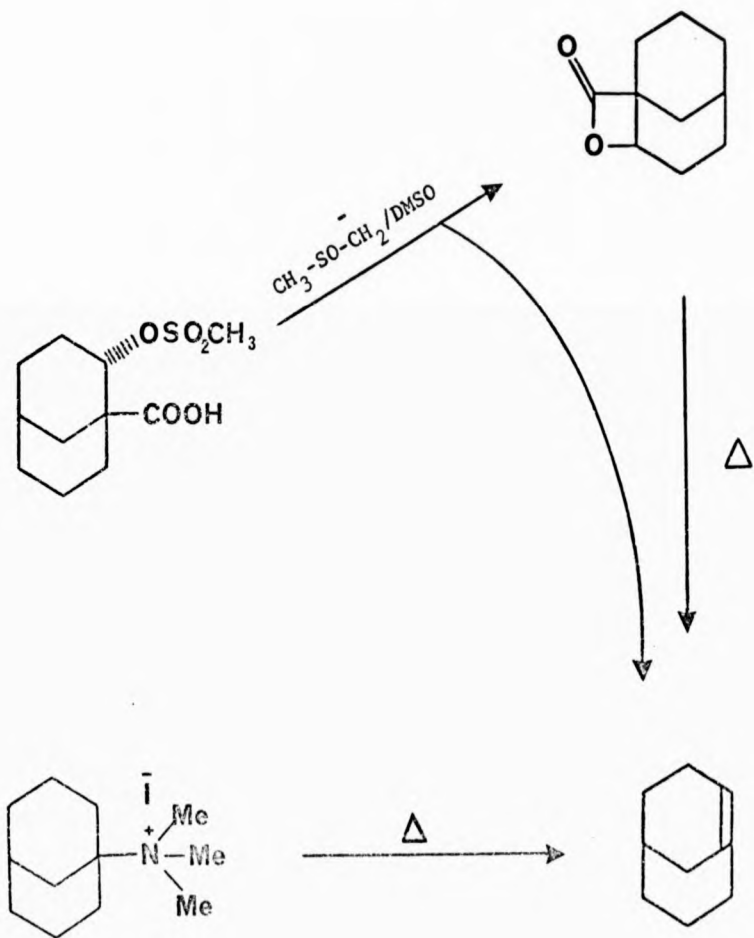
3. For a variable S value, ring strain is inversely proportional to the size of the bridge containing the double bond.

The improved treatment enables a cataloguing of stabilities of bridgehead olefins within a particular S group which may be more or less stable than examples in higher and lower groups. For example, the new treatment can classify bridgehead olefins with the double bond contained in a 1-carbon bridge separately as being the most unstable except when the S values becomes large.

However, even this new interpretation is incomplete as noted in a very recent review by Buchanan⁸, who points out that Wiseman⁹ in describing the synthesis of bicyclo(3,3,1)nonan-1(2)-ene (10) viewed bicyclic 1-olefins as bridged trans cycloalkenes. The latter author perceived that in any bicyclic olefin (13) the double bond is endocyclic to two of the rings and hence must be trans in one of them. From this situation it is at once apparent that strain in such a system is very similar to that in trans cycloalkenes, for example bicyclo(3,3,1)non-1(2)-ene (10) is a bridged trans cyclooctene. Indeed the fact that trans cyclooctene is an isolable entity was one of the factors that encouraged Wiseman to attempt his synthesis of (10). Further incentive was afforded by the uptake of 3 deuteria per molecule in the base catalysed exchange of bicyclo(3,3,1)nonan-2-one (14) with D₂O¹⁰, verifying transient existence of the enol form (15); and also by the facile decarboxylation of keto-acid (11)⁵.

Wiseman states that bridgehead bicyclic alkenes which incorporate a trans cyclooctene should be isolable, although reactive, compounds while those incorporating a trans cycloheptene should at least be detectable as transient intermediates. This treatment enables a distinction to be made between (16) and (17), the latter being less stable by virtue of being a trans cyclohexene. This distinction is unavailable from the Kobrich treatment. On the other hand, it should be pointed out that Wiseman's interpretation is

FIG. 1



Synthesis of bicyclo(3,3,1)non-1-ene.⁽²⁾

J.R. Wiseman, *J. Amer. Chem. Soc.*, 89, 5966, (1967).

J.A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, 92, 948, (1972).

unable to distinguish the two olefins (18) and (19) while Kobrich's treatment can.

In a report published simultaneously with Wiseman's⁹ synthesis of (10) from the corresponding bridgehead quaternary ammonium hydroxide (Fig. 1) Marshall¹¹ has also prepared (10) by two different routes also depicted in Fig. 1. and at about the same time a mixture of bicyclo(4,2,1)non-1-ene (20) and bicyclo(4,2,1)non-6-ene (21) ($S = 7$) was isolated from the pyrolysis of the bridgehead quaternary ammonium salt (22)¹². In fact a number of analogs of bicyclo(3,3,1)nonan-1(2)-ene (10) containing hetero-atoms have appeared since the original reports by Marshall¹¹ and Wiseman⁹. The oxa derivative¹⁴ (23) ($X = O$; $R = H, Me$) and the sulphones (24)¹⁵, (25) are all reported to be stable at room temperature and interestingly, (23) and (24) adopt the Z configuration as does the parent hydrocarbon (10). Surprisingly the sulphone (25) is reported as being isolated in the E configuration¹⁵. The aza analog (26) is now also known¹³. These examples ($S = 7$) constitute, at the time of writing, the lower limit for stable and isolable bridgehead olefins. Wiseman has added further comment to this in terms of the trans cyclo-octene/trans cycloheptene boundary to stability¹⁶. Both olefins (72) and (73) ($S = 7$) were obtained transiently, as evidenced by adduct formation, via the Hofmann elimination route. Of greater interest, however, was the fact that the olefins themselves survived long enough for n.m.r. spectra to be obtained.

Nevertheless, a considerable number of short lived intermediates have been detected, both in the $S = 7$ and $S = 6$ series, for example a single bridge 1-olefin intermediate has been suggested for the rearrangement of the dichloro-cyclopropane (27) to the dimer (28) namely the "anti-Bredt" dichlorodiene (29)¹⁷. In this area of single bridge 1-olefins, surely the most strained "anti-Bredt" situation of all is found in the proposal that adamantene (30), a formal derivative of bicyclo(3,3,1)non-1(9)-ene (9), is an

intermediate in two different reactions^{18,19}. Alkyl lithium treatment of 1,2 di-iodo and 1-bromo-2-iodo adamantanes (32) ($X_1 = I$; $X_2 = I, Br$) gives the head to tail dimer (33); attempted trapping experiments of (30) with furan having proved unsuccessful¹⁸. A Norrish type II fragmentation on photolysis in methanol of 1-adamantyl-phenyl acetate (34) or its 2-isomer (35) resulted in subsequent solvent capture of (30) to yield 1-methoxyadamantane (36)¹⁹. When the reaction was carried out in glycol and deuterio methanol, the products were respectively the trapped derivatives (37) and (38)¹⁹. These examples are consistent with the necessary severe twisting of the p-orbital in (30) which would prevent a supra-supra 4 + 2 cycloaddition as observed by the failure to obtain furan adducts. On the other hand, such twisting leads towards the symmetry required for a $\pi 2s + \pi 2a$ cycloaddition consistent with the results^{18,19}. Adamantene (30) is assumed to have its π electrons completely decoupled¹⁸.

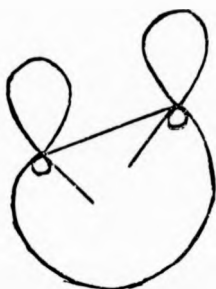
In the $S = 6$ series, examples of bridgehead aza bicyclo olefins have been postulated as intermediates. The carbenium ion (39) is known to be present in the mechanistic pathway of the thermolysis of O-tosyl-2 quinuclidinyl phenyl ketoxime (76)²⁰. The reaction is faster than with its all carbon analog which decomposes exclusively by Beckmann rearrangement and this has been explained by resonance stabilisation which includes the bridgehead olefin ion (40). Photolysis of 1-azido-norbornane (41) in methanol gives two ring expansion products (42) and (43) in roughly equal amounts. These could arise from methanol addition to the corresponding "anti-Bredt" intermediates (44) and (45)²¹. Intermediacy of bicyclo(3,2,1) oct-1(2)ene (46) ($S = 6$) during the thermolysis of 2,4-dioxatricyclo(6,2,1,0¹⁵),3-thiene (47) has been demonstrated by a trapping experiment using 1,3-diphenyl-iso-benzofuran²². Both stereo-isomers of the Diels-Alder adducts (48) were obtained and the authors also isolated (0.3% yield) the

adducts (49) corresponding to the less stable bicyclo(3,2,1)oct-1(7)ene (50)²² from pyrolysis of the bridgehead quaternary ammonium hydroxide (51). The silver salt rearrangement of the dibromo-cyclopropane (52)²³ is thought to proceed through the bicyclo(4,3,1)decyl moiety (53) the latter being an S = 8 situation and containing a double bond in a methano bridge.

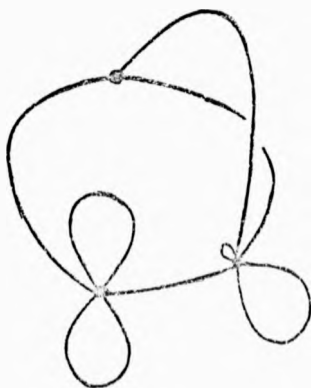
In view of the fact that there is no firm evidence for the existence of trans cyclohexene, recent reports describing the intermediacy of 1-(2)norbornenes (S = 5)²⁴⁻²⁸ are of considerable interest; incidentally, this is the bicyclic system expressly forbidden by the original Bredt's rule. For ten years it has been known that the fluorinated anion (54) obtained from 1 H-undecafluoronorbornane (55) decomposes rapidly at ambient temperatures to an intermediate which behaves as the olefin (56), as evidenced by trapping experiments²⁴. More interestingly, in 1971, Keese and Krebs²⁸ have described the preparation of the parent hydrocarbon (57) from butyl lithium treatment of the 1,2 vicinal dihalide (58) ($X_1 = X_2 = \text{Br}, i$) in the presence of furan. Both stereo-isomers of the adduct (59) were obtained in proportions which remained constant regardless of which halogen was used or of configuration, thus demonstrating the presence of a common intermediate assumed to be (57). In terms of the Wiseman interpretation this intermediate incorporates a trans cyclohexene and is the first recorded example.

The foregoing discussion does not embrace all the literature to date relating to "anti-Bredt" compounds or intermediates. For example, as argued cogently by Buchanan⁸ and Kobrich⁷ in two recent reviews, fused ring systems of the general type (60) while not belonging formally to the bridgehead examples cited here, are nevertheless governed by the same criteria of ring strain. These authors have provided a comprehensive coverage of the general subject of "anti-Bredt" compounds and offer good points of reference. What has emerged from recent work is the new concept of a limiting range for Bredt's rule which, from experimental evidence, now lies

FIG. II



Trans-cyclo octene



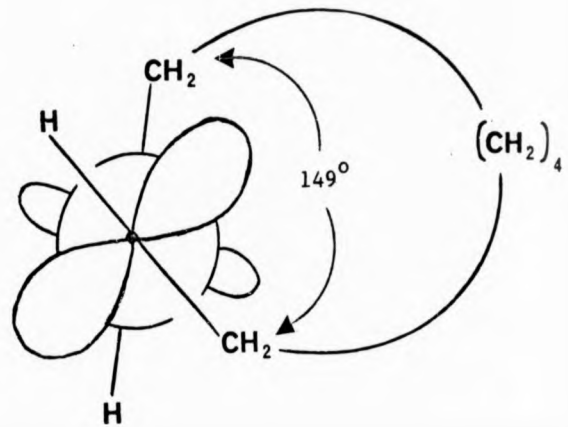
Norborn-1(2)-ene

between bridged trans cyclo-octenes and trans cyclo heptenes from the Wiseman⁹ standpoint and within bridgehead olefins with $S = 7$ in Kobrich's modified Fawcett interpretation⁷. As a result it now becomes possible to present a case for the plausibility of bicyclo(3,3,1)nonan-1(2);5(6)-diene (63) being an isolable entity.

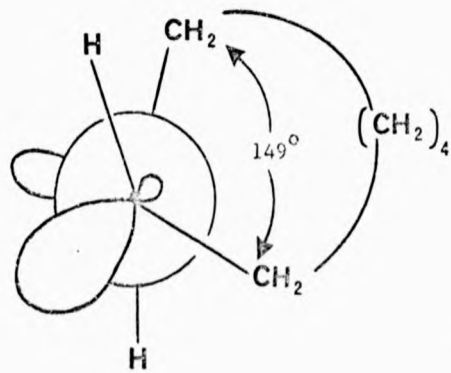
It is extremely unlikely that an olefinic double bond of the conventionally accepted type is present in "anti-Bredt" species, particularly the more strained ones. Substance is given to this by the complete incapacity of Fieser and Dreiding molecular models to accommodate many of the structures. For optimum overlap the dihedral angle between the valences on the remaining three σ bonds of each carbon containing the double bond must be 0 or 180° . In a 90° situation where no overlap can occur, bonding is not possible and a diradical or C-ylide results. Recall that a diradical is postulated for the intermediate adamantene (30) (vide supra)^{18,19}. Bond deformation with consequent change in hybridisation has been suggested to explain certain other examples. In the case of trans cyclo-octene, Mock²⁹ has suggested that strain could be accommodated by extension of the p-orbitals above the plane of the ring accompanied by a subsequent reduction in electron density in the lobes beneath the plane and also a bending downwards of the hydrogen bearing valences (Fig. II). If this modification is applied to bridgehead olefins the change in hybridisation is likely to be more pronounced at the bridgehead which is more susceptible to shearing forces. Also shown in Fig. II is a proposal by Keese and Krebs^{28,30} to account for the transient C_8H_{12} norbornene (57) in which the bridgehead orbital more or less retains sp^3 hybridisation while the adjacent carbon possesses a formal p-orbital. Some overlap is possible and a $\text{C}=\text{C}$ bond order of half the value for that of ethylene has been calculated, this formulation being

FIG. III

A.



B.

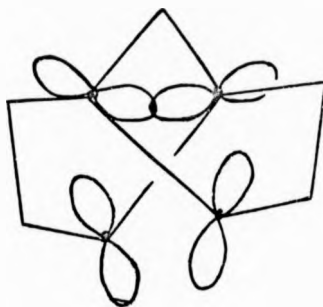


energetically more favourable than the proposal for trans cyclo-octene. Buchanan⁸ summarises ring strain in bridgehead "anti-Bredt" olefins by speaking of a "spectrum of strain" increasing with the lessening size of the incorporated trans cyclo-alkene such that it becomes immaterial whether one talks of double bonds or diradicals but rather that the existence of an "anti-Bredt" situation is governed by the means of surmounting the activation barrier to it, coupled with a suitable means of detection.

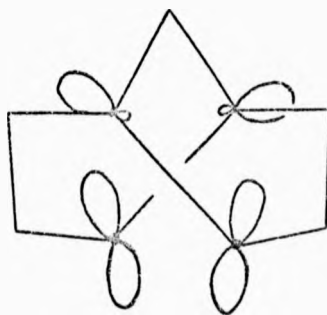
In drawing comparisons between trans cyclo-octene and the bridged bicyclo(3,3,1)nonan-1(2)-ene (10), it is pertinent to consider recent X-ray structural evidence on the former. Two groups^{31,32} independently investigated the Cu^I and Pt^{II} complexes of the olefin and found it to reside in the twist conformation (61) in preference to the chair form (62). This is of interest since methano bridging of this conformation results in the bicyclic (10). The X-ray results further indicate a warping out of plane of the pair of allylic carbons adjacent to the double bond to give a dihedral angle of 134°. If it is assumed that the complexed (61) accurately represents the conformation of the parent hydrocarbon, then comparison with energy minimisation calculations carried out by Allinger are informative³³. These indicate a preference for the twist conformation over the chair by 2.43 k. cal./mole and show a dihedral angle of 149° about the double bond. If this were achieved merely by rotation about the π bond (Fig. IIIA) the p-orbital dihedral angle would be 31° and the overlap reduced corresponding to a predicted low value for the dipole-moment which is in fact quite large (0.82D). To accommodate this, rehybridisation of the p-orbitals in the way already described^{38,30} (Fig. II, IIIB) with out of plane bending enables more overlap to take place. An energetic compromise between strain relief acquired in

FIG. IV

Bicyclo(3,3,1)nonan-1(2); 5(6)-diene



Without rehybridisation



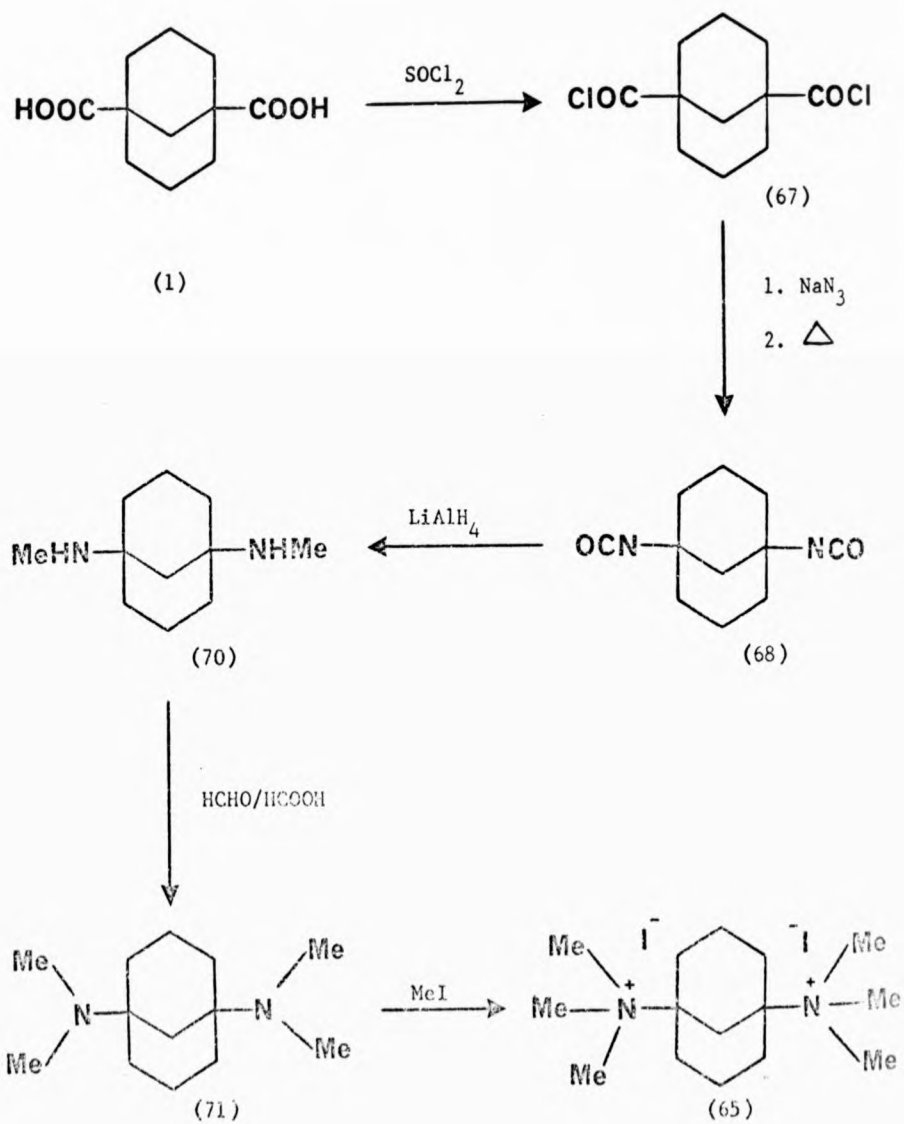
With rehybridisation

this way and increased repulsion between the lobes of p-orbitals as they assume more s character with rehybridisation, has been calculated as resulting in a dihedral angle of 16.3° from which a dipole moment of 1.2D can be calculated⁸. Similar calculations applied to bicyclo(3,3,1)nonan-1(2)-ene (10), for which as yet there is no X-ray evidence, support a similar situation but with more twisting about the double bond giving a dihedral angle of 138° ³³.

These theories of strain relief by rehybridisation resulting in less electron density in the p-orbital lobes projecting into the ring are intrinsic to support for the concept of bicyclo(3,3,1)nonan-1(2); 5(6)-diene (63) being an isolable entity. If the p-orbitals in these structures were essentially unchanged then the dual backside projection into the ring from positions C1 and C5 in (63) would certainly result in a prohibitive non-bonding interaction (Fig. IV). With the reduced endo-cyclic electron densities from rehybridisation^{28,29,30} it is reasonable to assume that a stable situation may be possible. Certainly the molecule is accommodated by molecular models. Trans, trans 1,5 cyclo-octadiene (64) is readily assembled using Fieser models and the subsequent placing of a methano bridge across the positions C1, C5 is surprisingly easy. While the limitations of models are well known in that only bond angle and torsional strains are represented, the accommodation of non-bonded strain presented here as an additional factor seems to support a definite case for the diene (63) being isolable. If this is the case then it may well occupy a unique position in the spectrum of "anti-Bredt" bridgehead olefins as encompassed by the Wiseman and Kobrich criteria. It is a double trans cyclo-octene and therefore much more strained than trans cyclo-octene itself and yet may be less so than the "forbidden" trans cycloheptene situation. It is also an S = 7 compound and hence it may be reasonable to speculate that if it is

isolable then this diene would lie at the threshold of isolable - non isolable "anti-Bredt" compounds. In the following text a synthesis of the bis-trimethyl
nonane
ammonium iodide of 1,5 diamino bicyclo(3,3,1)(65) is described along with preliminary attempts to identify the product(s) from the pyrolysis of its corresponding di-hydroxide.

FIG. V



RESULTS

Bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (1) was obtained in plentiful supply from Meerwein ester (66) by routine literature methods, and the synthesis of the bis-trimethyl ammonium iodide of 1,5 diamino bicyclo(3,3,1)nonane (65) accomplished via the route indicated in Fig. V. The extreme insolubility of the diacid (Section I) did not on this occasion cause any problem since it was converted to its diacid chloride (67) by gradual uptake in refluxing thionyl chloride during the first step Curtius reaction. Subsequently bicyclo(3,3,1)nonan-1,5-bis-isocyanate (68) was isolated in good yield as a pale-brown oil, infrared spectroscopy being the evidence taken. Initially hydrolysis of the bis isocyanate (68) was tried in an attempt to obtain bis 1,5 amino bicyclo(3,3,1)nonane (69) as the Step 3 product, but when the reaction was carried out in either acid or base precipitation of a colourless solid resulted whose physical texture is best described as 'plastic'. The material was insoluble in a number of common solvents and in particular was not taken up by dilute mineral acid. Although not investigated further it is virtually certain that this material was polymeric in nature. On standing in an open vessel the bis isocyanate (68) was seen to decompose, possibly polymerising from catalysis by atmospheric moisture. The problem was resolved by treating the isolated bis isocyanate (68) immediately with anhydrous lithium aluminium hydride to yield the secondary amine 1,5-bis-methyl-amino-bicyclo(3,3,1)nonane (70). Although eventually obtained in 65% yield, the isolation of this compound was not uneventful since in the first experiments no product was obtained by ether extraction of the basified reaction mixture although a characteristic fishy amine smell persisted in the reaction mixture. The bis amine (70) has an enormous affinity for water since only when a continuous solvent extraction was

carried out with benzene on an aqueous slurry containing a massive excess of sodium hydroxide was the product isolated. Bis-1,5-dimethyl-amino-bicyclo(3,3,1)nonane (71), was prepared in 71.5% yield by standard procedures, although this amine too could only be isolated satisfactorily by continuous solvent extraction. Methyl iodide treatment of the tertiary amine resulted in highly crystalline quaternary ammonium salt needing little further purification and crystallised readily from ethanol. The two amines (70) and (71) and the final quaternary ammonium salt (65) were easily identified by their ^1H n.m.r. spectra. Hence, the diiodide (65) was obtained from diacid (1) in 43% yield in a routine manner save for some minor complications arising out of the double functionality.

A number of pyrolysis experiments were then carried out on the bis-quaternary ammonium hydroxide (74) using a cooled receiver to collect the product. At 180° the reaction was carried out using a high vacuum system such that the products underwent short path distillation and were collected in an n.m.r. tube cooled with liquid nitrogen. When the contents of the tube were allowed to attain ambient temperature, at atmospheric pressure, trimethylamine distilled off and the residue consisted of liquid which rapidly polymerised, characterised by a highly penetrating odour. When a compromise was sought in which most of the trimethylamine had been removed but volatilisation and polymerisation had been kept to a minimum prior to the addition of spectrograde solvent, the resultant ^1H n.m.r. spectrum reproducibly showed a signal at 4.3τ which was not the shape expected for bicyclo(3,3,1)non-1(2)-ene (10) as reported by Wiseman⁹ and Marshall¹¹. Another feature of the spectrum was a sharp N-methyl singlet at 8.3τ . It has not yet proved possible to tell whether the latter signal arises from residual trimethylamine in the sample or whether an N-methyl group is a constituent part of the molecule giving rise

to the olefinic absorption. The latter possibility, i.e. 5-di-methyl-amino bicyclo(3,3,1)non-1(2)-ene (75) would arise from Hoffmann elimination on one side of the molecule (65) and base-induced nucleophilic displacement of methanol from the other (c/f Wiseman's original synthesis of (10)⁹). Obviously additional pyrolysis and pyrolysis/trapping experiments are required but at least the necessary 1,5-disubstitued precursors are now available.

It should be noted that recently at Stirling, attempts have been made to treat the bis quaternary ammonium iodide (65) with sodium hydroxide to bring about the desired double elimination. However, the product proved to be 5-exo-methylene cyclooctanone (31) arising from a fragmentation reaction and subsequent hydrolysis of the intermediate olefinic enamine.

Experimental

Bicyclo(3,3,1)nonan-1,2; 5,6-bis-pyrazolone

1,5 dicarbomethoxy-bicyclo(3,3,1)nonan-2,6-dione (20 g., 0.075 mole) was treated dropwise with hydrazine hydrate (30 ml.). Solution was achieved immediately accompanied by a vigorous exothermic reaction. The mixture was allowed to stand overnight after which the product had crystallised. The product was collected by suction filtration, washed once with ice cold water, and dried in air. Bicyclo(3,3,1)nonan-1,2; 5,6-bis-pyrazolone crystallised in needles from ethanol (13.82 g., 82%). m.p. 304 - 306°, lit. 305°.

Bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (1)

Bicyclo(3,3,1)nonan-1,2; 5,6-bis-pyrazolone (18 g., 0.078 mole) was placed in a calorimetric bomb charged with powdered sodium hydroxide (18 g.). The solids were well mixed and water (13 ml.) added. The sealed mixture was heated at 190° for ten hours and then cooled. The resulting white solid plug was dissolved in water (250 ml.) and the solution acidified to pH 1 by dropwise addition of concentrated hydrochloric acid. A colourless crystalline solid precipitated from the mixture which was cooled at 0 - 10° overnight. The product was collected by suction filtration and washed three times with ice cold water (3 x 50 ml.). The damp solid was air dried to yield bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (1) (12.35 g., 75%). m.p. 216 - 217°, lit. 215 - 217°.

Bis 1,5 bicyclo(3,3,1)nonan-isocyanate (68)

Bicyclo(3,3,1)nonan-1,5-dicarboxylic acid (1) (12g. 0.056 mole) was treated with freshly distilled thionyl chloride (60 ml.) and the stirred mixture boiled at reflux. The insoluble diacid gradually dissolved and a clear yellow solution was obtained after six hours. Refluxing was continued overnight and the solution then cooled, excess thionyl chloride removed by distillation under reduced pressure, and the crude product obtained as a moist pale brown crystalline solid, from which the last traces of thionyl chloride were removed by co-distillation with benzene under reduced pressure to yield a dry pale brown crystalline solid 14.02 g. ν max. 1788 cm^{-1} .

This crude diacid chloride (13.10 g.) was immediately dissolved in redistilled acetone (20 ml.) and the solution added dropwise with stirring to an ice cooled solution of sodium azide (60.00 g., 0.92 mole) in water. A precipitate separated from the mixture as soon as the addition was commenced. Stirring was continued overnight and then methylene chloride (120 ml.) was added to the slurry dissolving the precipitate. The organic phase was separated and the remaining acetone/aqueous phase extracted once with methylene chloride (50 ml.). The combined organic phase was dried (MgSO_4), solvent removed by distillation under reduced pressure and the residue dissolved in benzene (200 ml.). The solution was heated at 60 - 70° until evolution of nitrogen had ceased (six hours). Solvent was removed by distillation under reduced pressure to yield a light brown oil, (9.72 g.) ν max. 2,250 vs cm^{-1} , transparent at 1788 cm^{-1} .

Attempted preparation of 1,5 diamino bicyclo(3,3,1)nonane (69)

The crude bis isocyanate from the previous experiment (8.3 g.) was treated with boiling sodium hydroxide solution (10%, 100 ml.) for three hours. During

this time an amorphous white precipitate separated. On cooling, the solid (8.0 g.) was collected by suction filtration and had an appearance and texture best described as plastic. The product was completely insoluble in water, chloroform, benzene, ethanol, methanol and 2M sulphuric acid. It was therefore assumed to be polymeric in nature and not investigated further.

Bis-1,5-methylamino-bicyclo(3,3,1)nonane (70)

The crude bis isocyanate (68) as obtained above (12.34 g.) was dissolved in dry ether (100 ml.) and the solution added dropwise to a stirred slurry of lithium aluminium hydride (7.5 g., 0.25 mole) in dry ether (50 ml.). The mixture was boiled under reflux overnight and on cooling excess hydride was destroyed by the dropwise addition of saturated sodium sulphite solution. The organic layer was then decanted, the aqueous phase extracted with ether (2 x 50 ml.) and the combined organic phase was washed with water (3 x 50 ml.) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded a small amount (0.2 g.) of a volatile crystalline solid having a characteristic fishy odour. The product was purified by sublimation under reduced pressure and characterised as bis-1,5-methylamino bicyclo(3,3,1)nonane (70). ν_{max} . (CCl_4) 3000, 2932, 2855, 2803, 1480, 1456, 1437, 1420, 1353, 1302, 1163, 1125, 1097, 1047 cm^{-1} . n.m.r. τ_H (CCl_4) 7.71 (6H, s), 7.9 - 9.0 (14H, m), 9.3 (2H, s). Singlet at 9.3 τ removed by D_2O .

The remaining available product was recovered as follows. Sodium hydroxide pellets were added to the aqueous phase until a viscous slurry had been achieved and the mixture was continuously extracted with benzene for three days. The organic phase was then separated, dried ($MgSO_4$) and solvent removed under reduced pressure to yield a gelatinous and hygroscopic solid which was purified by sublimation ($90^\circ/1mm$) to yield a highly crystalline colourless solid (8.5 g. 72% from diacid (1)) whose infrared and n.m.r.

spectra were identical with those of the small sample obtained above.

Bis 1,5-dimethylamino bicyclo(3,3,1)nonane (71)

Bis 1,5 methylamino bicyclo(3,3,1)nonane (70) (6 g., 0.033 mole) from the above experiment was dissolved in a mixture of aqueous formaldehyde (60 ml., 37%) and formic acid (60 ml.). The solution was then heated on a steam bath for 48 hours with additional formaldehyde (60 ml.) being added after 24 hours. The solution was cooled and sodium hydroxide pellets added until a viscous slurry was achieved. The mixture was then continuously extracted with refluxing benzene for 72 hours after which the organic phase was separated and dried ($MgSO_4$). Removal of solvent by distillation under reduced pressure at 0° yielded a crude gelatinous solid 4.5 g. which was extremely hygroscopic and would not sublime. ν max. (film) 3100, 3080, 3043, 2992, 2940, 2873, 2826, 2784, 1467, 1365, 1354, 1310, 1253, 1237, 1210, 1180, 1150, 1100, 1087, 1047, 1003, 975, 950, 926, 904, 840, 819, 682 cm^{-1} n.m.r. τ_H (CCl_4) 7.81 (12H, s), 7.9 - 9.1 (14H, m). This material was used directly for the following experiment.

The bis-trimethyl ammonium iodide of 1,5 diamino bicyclo (3,3,1)nonane (65)

Methyl iodide (7.1 g., 0.05 mole) was added dropwise with stirring to a solution of 1,5-bis-dimethylamino bicyclo(3,3,1)nonane (71) (2.0 g., 0.01 mole) in ether (25 ml.). Cloudiness developed immediately and the mixture was kept at $0 - 10^\circ$ for 24 hours. The crystals were collected by suction filtration and washed with ether (2 x 10 ml.) yield: 4.35 g., 93%. A sample of pure bis-trimethyl ammonium iodide of 1,5 diamino bicyclo (3,3,1)nonane (65) was obtained by crystallisation from ethanol in needles, m.p. $260 - 261^\circ$ (Found: C, 36.15; H, 6.50; N, 5.45. $C_{15}H_{32}N_2I_2$ requires C, 36.45; H, 6.55; N, 5.65%). n.m.r. τ_H (D_2O). Internal reference HOD at 5.04 τ . 5.07 (18H, s), 7.5 - 8.3 (14H, m).

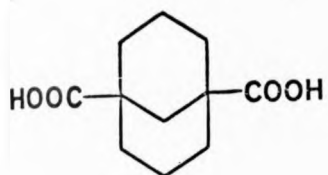
Pyrolysis of (3,3,1)nonane
the bis-trimethyl ammonium hydroxide of 1,5 diamino bicyclo (74)

(a) Silver oxide (0.3 g., 1.2 mmole) was added to a solution of the bis-trimethyl ammonium iodide of 1,5 diamino bicyclo(3,3,1)nonane (65)

(0.10 g., 0.2 m. mole) in water (2 ml.). After one hour the solution was filtered and solvent removed from the filtrate by distillation under reduced pressure until the solution volume was small. The remaining water was removed by leaving the solution under high vacuum for one hour after which the resulting light brown solid was left over P_2O_5 in vacuo overnight. The dry product was placed in a 10 ml. round bottomed flask which was connected to a vacuum line arranged such that short path distillation was possible into an n.m.r. tube to which a standard joint had been fitted. The system was evacuated to 0.1 mm/Hg and the flask heated at 180° . The pyrolysate distilled and was collected in the n.m.r. tube at liquid nitrogen temperatures. Vacuum was released from the system and the tube stoppered while it was allowed to warm up to ambient temperatures. The stopper was then removed and the tube warmed at 40° until evolution of trimethylamine had ceased. The residue was a clear colourless oil which evaporated from the tube at a visible rate to fill the entire laboratory with a distinctive odour. Simultaneously the remaining oil became cloudy and gradually began to deposit solid (presumably polymeric material) around the edges of the tube. Immediately this process began to occur, spectrograde CCl_4 was added and an 1H spectrum determined. n.m.r. τ_H 4.2 - 4.5 (unresolved m), 7.7 - 9.3 (unresolved m), 7.85 (s). The olefinic multiplet did not integrate for 2 protons against the rest of the spectrum.

(b) A further experiment was carried out using identical conditions and quantities with the exception that spectrograde CCl_4 was charged to the receiver prior to pyrolysis. After collection of the pyrolysate, the n.m.r. tube was removed from the system and sealed while still under vacuum. The

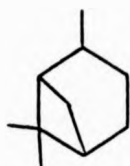
tube was immediately transferred to the n.m.r. probe and a spectrum run as soon as temperature equilibration had been achieved. Although a stronger spectrum was obtained, the line shapes were largely identical to those of the experiment (a) spectrum and resolution of the olefinic signal was not improved. Integration was not possible due to a massive signal at 7.85τ from unreleased trimethylamine.



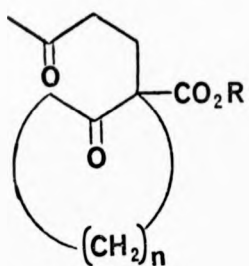
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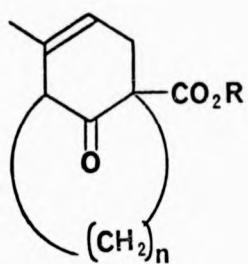
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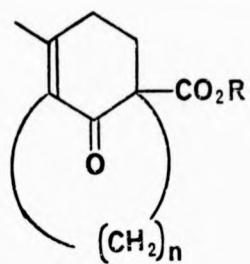
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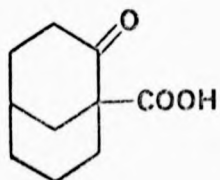
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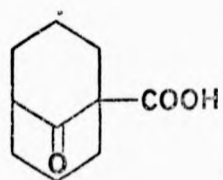
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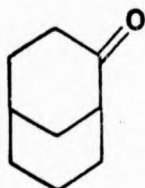
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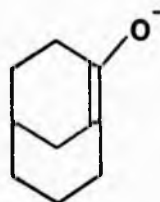
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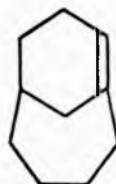
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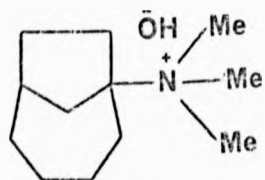
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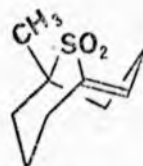
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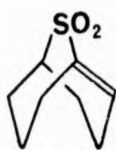
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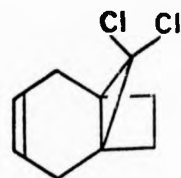
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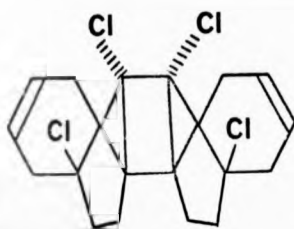
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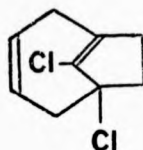
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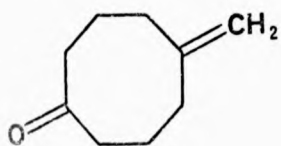
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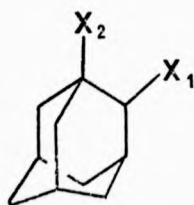
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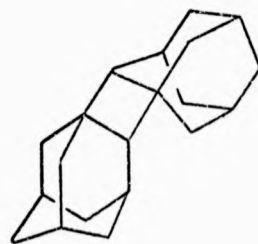
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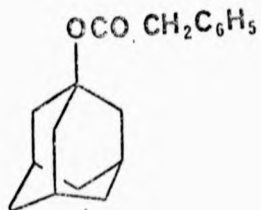
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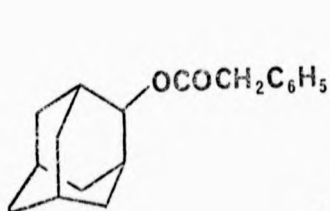
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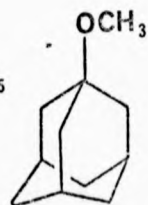
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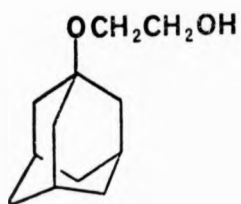
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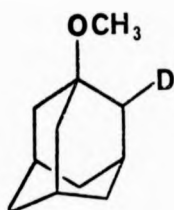
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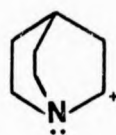
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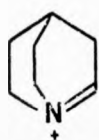
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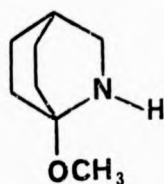
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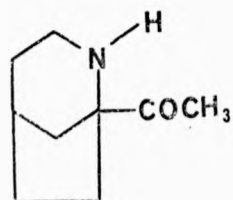
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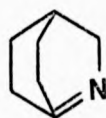
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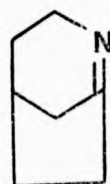
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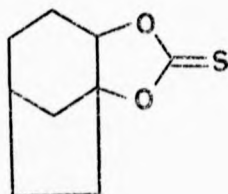
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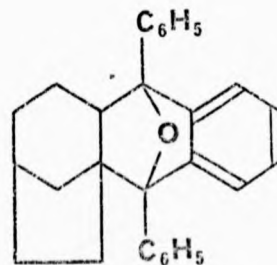
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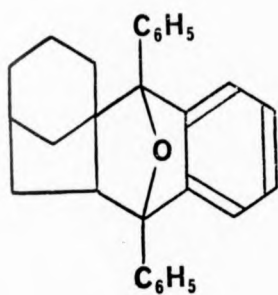
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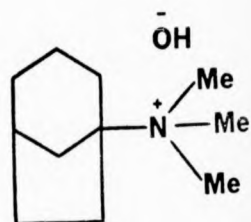
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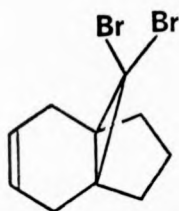
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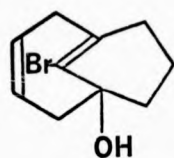
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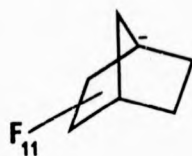
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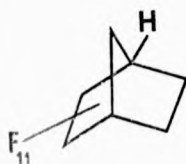
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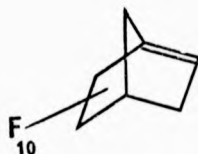
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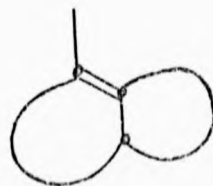
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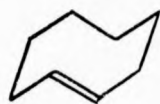
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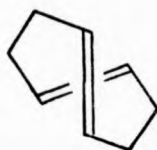
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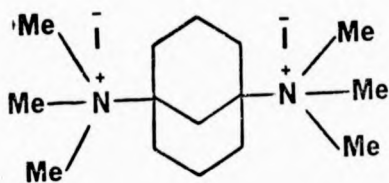
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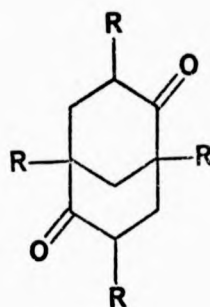
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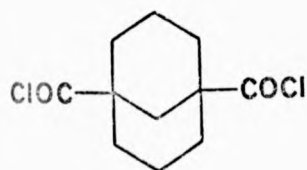


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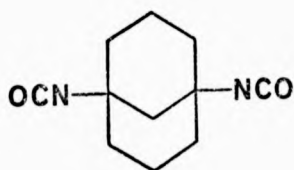


R=CO₂Me

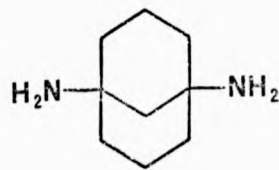
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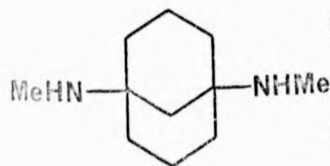
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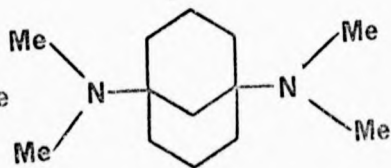
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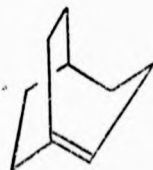
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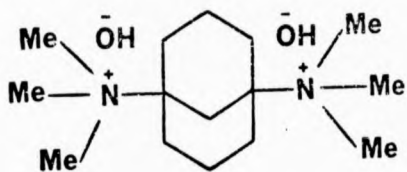
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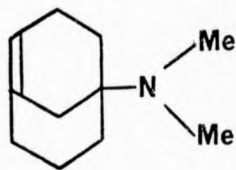
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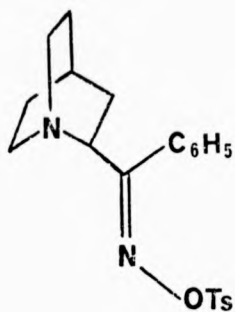
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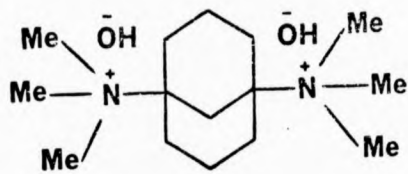
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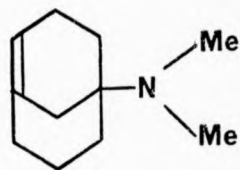
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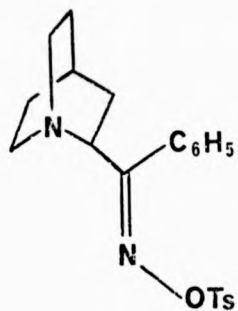
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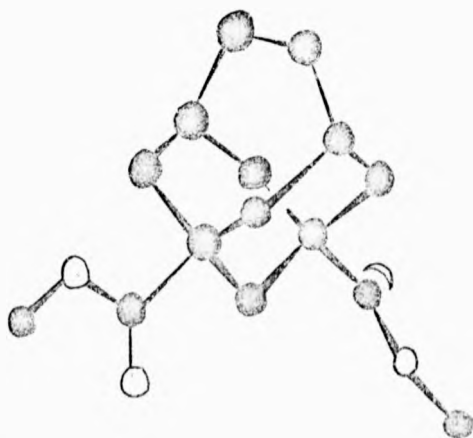
APPENDIX

X-ray crystallographic structural elucidation of
1,8 dicarbomethoxy-tricyclo(4,3,1,1^{3,8})undecane (100)

The slow recrystallisation of analytically pure 1,8 dicarbomethoxy tricyclo(4,3,1,1^{3,8})undecane (100) from light petrol yielded crystals suitable for the X-ray determination.

Data :- $C_{15}H_{22}O_4$ FT, triclinic $a = 6.81 (1)$, $b = 8.80 (1)$,
 $c = 12.10 (2) \text{ \AA}$;
 $\alpha = 104.3 (3)$, $\beta = 93.5 (3)$, $\gamma = 98.1 (3)^\circ$.

The molecule adopts an almost C_{2v} symmetry with its ethano bridge virtually eclipsed having a torsional angle of $2.0 (6)^\circ$. The results of this study have been published and for further details reference should be made to the accompanying communication reprinted from Acta Cryst. B 31 585 (1975).



● = carbon
○ = oxygen

1,8-Dicarboxymethyltricyclo[4,3,1,1^{3,8}]undecane

BY JUDITH MURRAY-RUST, PETER MURRAY-RUST AND RODNEY S. HENRY*

Department of Chemistry, University of Stirling, Stirling, Scotland

(Received 2 October 1974; accepted 4 October 1974)

Abstract. $C_{15}H_{22}O_4$, triclinic, $P\bar{1}$ (from structure analysis). $a=6.81$ (1), $b=8.80$ (1), $c=12.10$ (2) Å, $\alpha=104.3$ (3), $\beta=93.5$ (3), $\gamma=98.1$ (3)° from precession photography and diffractometer measurements. $Z=2$, $M=266.34$, $U=694.7$ Å³, D_m (floatation)=1.27, $D_c=1.273$ g cm⁻³. The structure, refined to $R=0.069$, consists of discrete molecules of nearly C_{2v} symmetry and

the ethylene bridge is eclipsed with a torsional angle of 2.0 (6)°.

Introduction. The crystals were irregular prisms and data were collected for layers $0kl$ to $6kl$ with a Hilger-Watts linear diffractometer (Mo $K\alpha$ radiation). 2947 reflexions were collected of which 1271 had intensities greater than 3σ . Lorentz and polarization corrections were applied (but none for absorption) and the layer scales were obtained from a Wilson plot. These were

* Present address: Food Industries Ltd, Bromborough Port, Cheshire, England.

Table 1. Atomic positions and anisotropic temperature factors ($\times 10^4$)

The expression used for the anisotropic temperature factor was $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	999 (6)	6909 (5)	-962 (3)	387 (40)	347 (10)	73 (3)	68 (8)	-41 (5)	36 (4)
O(2)	4062 (5)	7070 (5)	-164 (3)	309 (39)	270 (8)	63 (3)	81 (6)	8 (4)	17 (4)
O(3)	3706 (8)	5657 (6)	3526 (3)	696 (41)	438 (9)	94 (4)	405 (7)	80 (6)	106 (4)
O(4)	1923 (5)	6835 (4)	4812 (3)	363 (39)	200 (6)	70 (3)	121 (5)	36 (4)	64 (3)
C(1)	1685 (7)	7961 (5)	1093 (4)	242 (41)	120 (7)	56 (4)	1 (7)	-17 (5)	25 (4)
C(2)	-583 (7)	7898 (6)	1089 (4)	206 (41)	165 (8)	80 (4)	18 (8)	-19 (6)	42 (4)
C(3)	-1291 (7)	8402 (6)	2281 (4)	184 (39)	188 (9)	98 (4)	25 (8)	-12 (6)	62 (4)
C(4)	-1145 (8)	10204 (6)	2754 (5)	284 (41)	145 (9)	133 (6)	49 (8)	6 (7)	40 (5)
C(5)	918 (8)	11233 (6)	3031 (5)	347 (43)	135 (8)	108 (5)	45 (8)	7 (7)	27 (5)
C(6)	2774 (7)	10440 (6)	2792 (4)	273 (40)	121 (8)	74 (4)	-5 (8)	1 (6)	19 (4)
C(7)	3124 (7)	9304 (6)	3538 (4)	226 (40)	174 (9)	63 (4)	3 (8)	-19 (6)	22 (4)
C(8)	1891 (7)	7621 (5)	3082 (4)	199 (41)	136 (7)	58 (3)	30 (7)	0 (5)	33 (4)
C(9)	2379 (6)	6942 (5)	1844 (4)	218 (40)	136 (7)	61 (3)	16 (7)	-7 (5)	36 (4)
C(10)	2890 (7)	9652 (5)	1517 (4)	261 (41)	127 (7)	71 (4)	-15 (7)	1 (5)	39 (4)
C(11)	-348 (7)	7579 (6)	3120 (4)	206 (41)	182 (8)	91 (4)	45 (8)	23 (5)	62 (4)
C(12)	2161 (8)	7276 (5)	-109 (4)	303 (41)	120 (8)	60 (4)	13 (8)	-14 (6)	24 (4)
C(13)	4691 (9)	6401 (7)	-1260 (4)	394 (42)	214 (11)	67 (4)	42 (10)	31 (7)	21 (5)
C(14)	2645 (8)	6610 (6)	3814 (4)	280 (41)	192 (9)	80 (4)	117 (8)	12 (6)	47 (4)
C(15)	2590 (9)	5956 (7)	5590 (5)	401 (43)	195 (9)	90 (4)	68 (10)	-17 (7)	75 (4)
H(2a)*	-1112 (70)	6760 (67)	731 (48)	131	253	112	25	-18	55
H(2b)	-928 (72)	8643 (66)	577 (48)	131	253	112	25	-18	55
H(3)	-2779 (75)	7790 (69)	2060 (50)	204	257	128	47	-10	84
H(4a)	-1881 (81)	10394 (66)	3561 (58)	266	188	196	51	9	50
H(4b)	-1891 (81)	10591 (67)	2137 (59)	266	188	196	51	9	50
H(5a)	1307 (84)	11704 (68)	3856 (55)	320	205	157	74	18	33
H(5b)	1106 (83)	12121 (68)	2667 (55)	320	205	157	74	18	33
H(6)	4210 (79)	11372 (63)	3007 (47)	305	168	102	9	-5	23
H(7a)	2667 (77)	9826 (65)	4379 (47)	234	226	90	5	-25	36
H(7b)	4486 (76)	9217 (66)	3575 (47)	234	226	90	-5	-25	36
H(9a)	3938 (74)	6977 (60)	1821 (43)	224	181	81	46	-18	40
H(9b)	1449 (73)	5628 (65)	1477 (47)	224	181	81	46	-18	40
H(10a)	4336 (79)	9525 (62)	1337 (47)	272	174	96	-32	2	45
H(10b)	2479 (77)	10209 (61)	1003 (46)	272	174	96	-32	2	45
H(11a)	-685 (69)	8100 (66)	3885 (49)	146	262	124	43	23	93
H(11b)	-635 (71)	6345 (68)	2813 (49)	146	262	124	43	23	93
H(13a)	4434 (83)	7016 (69)	-1836 (53)	250	200	150	20	20	20
H(13b)	4082 (82)	5250 (69)	-1641 (54)	250	200	150	20	20	20
H(13c)	6073 (87)	6546 (68)	-1202 (54)	250	200	150	20	20	20
H(15a)	3912 (83)	6451 (67)	5831 (53)	250	200	150	20	20	20
H(15b)	2395 (82)	5030 (68)	5275 (54)	250	200	150	20	20	20
H(15c)	1877 (84)	6367 (70)	6273 (59)	250	200	150	20	20	20

* The anisotropic temperature factors of the hydrogen atoms were estimated from the temperature factors of the carbon atoms to which they were attached and were not refined.

later refined as parameters in the least-squares analysis. The statistics of the E values suggested the centrosymmetric space group, and the LSAM set of direct method programs (Main, 1971) were used to solve the structure. Apart from the trivial solution there were two sets with the same figure of merit, one of which was totally uninterpretable. The other revealed 15 peaks consistent with the assumed geometry of the molecule and two more were found from a difference synthesis based on this structure. However the model would not refine below $R=0.55$ and it was found necessary to shift the origin of the unit cell relative to the molecule by 0.74 Å, when all the remaining atoms could be found and the structure refined by standard least-squares techniques (8 cycles with a full matrix) to $R=0.176$. At this stage all the hydrogen atoms were found by difference synthesis and anisotropic temperature factors were introduced for the heavier atoms. Layer scales and the positions of the hydrogen atoms were also refined and the final R was 0.069 ($R = \sum |F_o| - |F_c| / \sum |F_o|$). * Unit weights were used and scattering factors were taken from *International Tables for X-ray Crystallography* (1968). The programs used were our adaptation of the CRYSTAL 69 system of Powell & Griffiths (1969). Atomic parameters are given in Table 1, the numbering of the non-hydrogen atoms in Fig. 1,

Table 2. Bond lengths (Å) (*e.s.d.* = 0.008 Å)

C(1)-C(2)	1.54	C(4)-C(5)	1.53	C(8)-C(14)	1.52
C(1)-C(9)	1.53	C(5)-C(6)	1.54	C(12)-O(1)	1.21
C(1)-C(10)	1.54	C(6)-C(7)	1.54	C(12)-O(2)	1.34
C(1)-C(12)	1.51	C(6)-C(10)	1.54	C(13)-O(2)	1.43
C(2)-C(3)	1.53	C(7)-C(8)	1.55	C(14)-O(3)	1.19
C(3)-C(4)	1.54	C(8)-C(9)	1.55	C(14)-O(4)	1.32
C(3)-C(11)	1.55	C(8)-C(11)	1.52	C(15)-O(4)	1.45

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30715 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

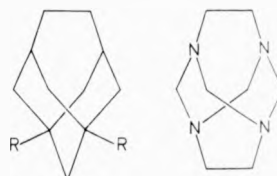
Table 4. Torsional angles in the hydrocarbon nucleus ($^{\circ}$) (*e.s.d.* = 0.5)

C(12)-C(1)-C(2)-C(3)	174.0	C(11)-C(8)-C(9)-C(1)	61.0
C(9) C(3)	56.0	C(7) C(1)	-64.0
C(10) C(3)	-65.8	C(14) C(1)	-178.6
C(1)-C(2)-C(3)-C(11)	-47.7	C(12)-C(1)-C(9)-C(8)	-179.7
C(1) C(4)	83.3	C(2) C(8)	-61.3
C(2)-C(3)-C(4)-C(5)	-66.3	C(10) C(8)	63.7
C(11) C(5)	63.3	C(12)-C(1)-C(10)-C(6)	-172.7
C(3)-C(4)-C(5)-C(6)	2.0	C(3) C(6)	66.5
C(4)-C(5)-C(6)-C(10)	63.3	C(9) C(6)	-55.7
C(4) C(7)	-66.0	C(9)-C(8)-C(11)-C(3)	-53.8
C(5)-C(6)-C(7)-C(8)	82.9	C(7) C(3)	67.9
C(10) C(8)	-47.9	C(14) C(3)	-172.7
C(6)-C(7)-C(8)-C(9)	56.4	C(8)-C(11)-C(3)-C(2)	46.5
C(6) C(11)	-66.7	C(8) C(4)	-84.7
C(6) C(14)	171.8	C(1)-C(10)-C(6)-C(7)	47.3
		C(1) C(5)	-83.4

Table 3. Bond angles ($^{\circ}$) (*e.s.d.* = 0.4 $^{\circ}$)

C(2)-C(1)-C(9)	109.4	C(7)-C(8)-C(9)	108.0
C(2)-C(1)-C(10)	114.0	C(7)-C(8)-C(11)	113.7
C(2)-C(1)-C(12)	108.8	C(7)-C(8)-C(14)	106.4
C(9)-C(1)-C(10)	108.7	C(9)-C(8)-C(11)	110.6
C(9)-C(1)-C(12)	108.2	C(9)-C(8)-C(14)	107.7
C(10)-C(1)-C(12)	107.7	C(11)-C(8)-C(14)	110.2
C(1)-C(2)-C(3)	114.1	C(1)-C(9)-C(8)	109.0
C(2)-C(3)-C(4)	114.3	C(1)-C(10)-C(6)	114.1
C(2)-C(3)-C(11)	111.6	C(3)-C(11)-C(8)	113.7
C(4)-C(3)-C(11)	113.9	C(1)-C(12)-O(1)	126.1
C(3)-C(4)-C(5)	118.8	C(1)-C(12)-O(2)	113.0
C(4)-C(5)-C(6)	119.1	O(1)-C(12)-O(2)	120.9
C(5)-C(6)-C(7)	113.9	C(8)-C(14)-O(3)	125.2
C(5)-C(6)-C(10)	114.2	C(8)-C(14)-O(4)	113.1
C(7)-C(6)-C(11)	111.3	O(3)-C(14)-O(4)	121.7
C(6)-C(7)-C(8)	113.8	C(12)-O(2)-C(13)	118.3
		C(14)-O(4)-C(15)	117.5

bond lengths in Table 2, bond angles in Table 3 and torsional angles in Table 4.



(I) R = H
(II) R = -COOMe

Discussion. The conformation of homoadamantane (II) is of considerable interest, for whilst a Dreiding model takes up a twisted (C_2) configuration, calculations suggest that the molecule has C_{2v} symmetry with the 4.5-bridge in an eclipsed arrangement (Gleicher & Schleyer, 1967). N.m.r. data on the hydrocarbon (Ligero, Schleyer & Ramey, 1969) and infrared data on the diol support the latter structure (Schleyer, Ligero & Ligero, 1969), and the crystal structure of the diol (Braun, Hornstra & Le...

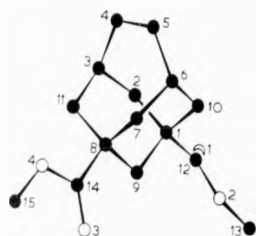


Fig. 1. The shape and numbering of the molecule. Solid circles represent carbon atoms, circles oxygen atoms. The numbers correspond to those used in Table 1.

1970), but there are no structural data for the hydrocarbon. We have shown that an analogous molecule (III) adopts a shape with planar ethylene bridges but with very pronounced vibration of C(4) and C(5) perpendicular to the plane of the bridge, suggesting that the energies of the planar and twisted bridge systems in (I) may be very similar (Murray-Rust, 1974). The crystal structure of the 1,8-disubstituted derivative (II) was undertaken to investigate this [and also to confirm it as the product of synthesis (Henry, Moodie, Parker & Watt, 1975)].

The structure consists of discrete molecules with no unusually short intermolecular contact distances (Table 5), and it is reasonable to assume that the configuration observed is close to that of minimum energy. The homoadamantane nucleus has almost C_{2v} symmetry and the torsional angle in the ethylene bridge is only 20° (6). The thermal ellipsoids of the two atoms in this bridge, C(4) and C(5), do not show any unusual anisotropic motion perpendicular to the bridge (the vibration of the ester groups is more pronounced by comparison) and the C_{2v} conformation would thus appear considerably more stable than C_2 arrangements with a torsional angle of about 60° (as predicted from

models). The bond lengths are normal, but although the angles in the nucleus are considerably larger than tetrahedral they are not unusual in this type of system (Murray-Rust, 1974; Murray-Rust & Murray-Rust, 1975; Murray-Rust & Smith, 1975).

Table 5. Intermolecular contact distances (\AA) less than 3.60\AA (*e.s.d.* = 0.008\AA)

C(13) \cdots O(3)	$\bar{x}, \bar{y}, 1-z$	3.24
O(3) \cdots C(1)	\bar{x}, \bar{y}, z	3.31
C(4) \cdots O(4)	$\bar{x}-1, 1-y, z$	3.55
O(4) \cdots C(15)	$\bar{x}-1, \bar{y}, z$	3.58
O(4) \cdots C(5)	$\bar{x}-1, 1-y, z$	3.58
O(1) \cdots C(5)	$\bar{x}-1, 1-y, z-1$	3.59

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0.4 $^\circ$)

C(9)	108.0
C(11)	113.7
C(14)	106.4
C(11)	110.6
C(14)	107.7
C(14)	110.2
C(8)	109.0
C(6)	114.1
C(8)	113.7
O(1)	126.1
O(2)	113.0
O(2)	120.9
O(3)	125.2
O(4)	113.1
O(4)	121.7
C(13)	118.3
C(15)	117.5

Table 3 and

adamantane (I) leading model calculations suggest with the 4.5 & Schleyer, on (Liggero, on the 4.5-er, Funke & of the 4.5- Leenhouts,

A Synthetic Route to 3,7-Disubstituted Bicyclo[3.3.2]decanes

By **Rodney S. Henry, W. Thomas Moodie, William Parker,*** and **C. Ian F. Watt**, Department of Chemistry,
University of Stirling, Stirling FK9 4LA

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PERKIN TRANSACTIONS I

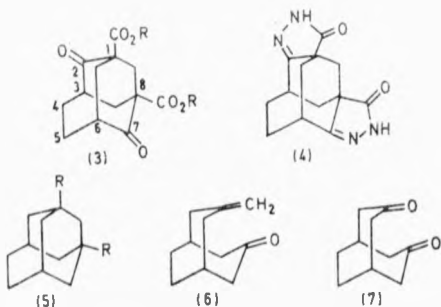
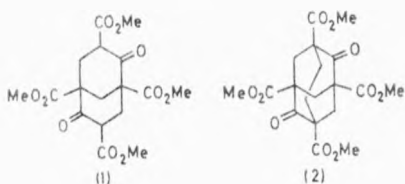
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A Synthetic Route to 3,7-Disubstituted Bicyclo[3.3.2]decanes

By Rodney S. Henry, W. Thomas Moodie, William Parker,* and C. Ian F. Watt, Department of Chemistry, University of Stirling, Stirling FK9 4LA

2,7-Dioxohomoadamantan-1,3,6,8-tetracarboxylic acid has been prepared in good yield from Meerwein's ester, and found to undergo specific 3,6-bisdecarboxylation. Wolff-Kishner reduction of the product gives homoadamantan-1,8-dicarboxylic acid. Treatment of the corresponding bis-acid chloride with chlorocarbonylbis(triphenylphosphine)rhodium gives 1,8-dichlorohomoadamantane, which is readily converted into 7-methylenebicyclo[3.3.2]decan-3-one in a base-induced fragmentation reaction.

In the course of our studies on the mechanism of transannular hydride migrations in bridged-ring systems¹



we had need of certain bicyclo[3.3.2]decanes functionalised at both the 3- and the 7-position. Synthetic routes² to this ring system are sparse, particularly those

¹ See M. P. Doyle and W. Parker, *Chem. Comm.*, 1970, 755, and references therein.

derivatives with specific functionality on both trimethylene bridges, so we have devised a new synthesis using the readily-available Meerwein ester³ (1) (tetramethyl 2,6-dioxobicyclo[3.3.1]nonane-1,3,5,7-tetracarboxylate) as starting material.

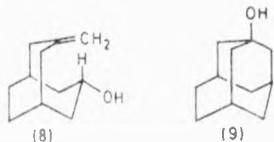
Treatment of the ester (1) with sodium hydride and 1,2-dibromoethane⁴ produced the dioxohomoadamantanetetracarboxylate (2) in good yield. Subsequent hydrolysis with aqueous acid gave the corresponding tetracarboxylic acid, which at 270–280° underwent

² (a) K. Alder, S. Hartung, and G. Hausmann, *Chem. Ber.* 1956, **89**, 1972; however see M. P. Doyle and W. Parker, *Tetrahedron Letters*, 1970, 945; (b) L. Wegmann, *Dechema Monograph*, 1959, **35**, 84; (c) G. Schroeder, *Angew. Chem. Internat. Edn.*, 1964, **3**, 481; G. Schroeder, R. Merenyi, and J. F. M. Oth, *Tetrahedron Letters*, 1964, 773; J. F. M. Oth, R. Merenyi, H. Roettke, and G. Schroeder, *ibid.*, 1968, 3941; (d) R. Aumann, *Angew. Chem. Internat. Edn.*, 1971, **10**, 188; (e) M. J. Goldstein, S. Tomoda, and G. Whittaker, *J. Amer. Chem. Soc.*, 1974, **96**, 3876; (f) K. B. Baggeley, W. H. Evans, S. H. Graham, D. A. Jones, and D. A. Jones, *Tetrahedron*, 1968, **24**, 3445; however see R. G. Humber and P. von R. Schleyer, *J. Org. Chem.*, 1971, **36**, 1198; (g) G. A. Russell and R. G. Keske, *J. Amer. Chem. Soc.*, 1970, **92**, 4460; (h) M. P. Doyle and W. Parker, *Chem. Comm.*, 1969, 319; (i) G. A. Russell and R. G. Keske, *J. Amer. Chem. Soc.*, 1970, **92**, 4460; (j) N. J. Leonard and J. C. Coll, *J. Amer. Chem. Soc.*, 1970, **92**, 6686; J. C. Coll, Del. R. Crist, M. de C. G. Barrio, and N. J. Leonard, *ibid.*, 1972, **94**, 7092; (k) H. Schmid, J. Szindely, and A. Pryde, Special Lectures, XXIIIrd International Congress of Pure and Applied Chemistry, Boston 28–30th July, 1971, Butterworths.

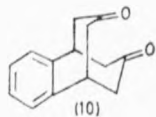
³ H. Meerwein, F. Kiel, G. Klosgen, and E. Schuch, *J. prakt. Chem.*, 1922, **104**, 161.

⁴ (a) L. G. Humber, G. Myers, L. Hawkins, C. Schmitt, and M. Boulterice, *Canad. J. Chem.*, 1964, **42**, 2852; (b) B. Vogt, *Tetrahedron Letters*, 1968, 1579.

smooth regiospecific decarboxylation⁵ to 2,6-dioxo-homoadamantane-1,8-dicarboxylic acid (3; R = H). The corresponding bispyrazolone (4) was then treated with strong alkali⁶ to give, after acidification, a dicarboxylic acid whose identification as (5; R = CO₂H) is fully supported by X-ray crystallographic analysis of the corresponding dimethyl ester.* Attempts to convert this system (5; R = CO₂H) into (5; R = halogen) by modified Hunsdiecker⁸ and Kochi reactions⁹ gave low yields and mixtures of products; however, when the mono-acid chloride (5; R = COCl) was treated with a catalytic amount of chlorocarbonylbis(triphenylphosphor)rhodium¹⁰ at 250°, a smooth reaction ensued, producing the desired bis-bridgehead chloride (5; R = Cl) in 67% yield. The ¹³C n.m.r. spectrum^{11,†} of the 1,8-dichlorohomoadamantane thus obtained showed the five-signal pattern expected. Subsequent treatment of (5; R = Cl) with aqueous sodium hydroxide¹² gave 7-methylenebicyclo[3.3.2]decan-3-one (6), which, either by oxidation with ruthenium tetroxide or by cyclolysis, is readily converted into the corresponding 3,7-dione (7). The expected transannular behaviour of these compounds is illustrated by the ready preparation of the *exo*-alcohol (8) and its cyclisation¹³ to homoadamantan-1-ol (9), identical with an authentic sample.¹⁴



Föhlisch¹⁵ and his co-workers have recently published a short synthesis of 5,6,8,9-tetrahydro-5,9-propanobenzocycloheptene-7,11-dione (10) which involved successive treatment of phthalaldehyde with dimethyl malonate dicarboxylate. The product from this double Aldol-double Michael reaction on hydrolysis and decarboxylation yielded (10). However, in our hands



it is not yet a practicable route to the simple non-benzenoid system.

* Apart from confirming the structure of (5; R = CO₂Me) the most significant finding from the X-ray crystallographic analysis (*R* factor 0.069) is that, in the solid state, the homoadamantane skeleton has virtual C_{2v} symmetry, e.g. the ethylene bridge shows torsion angle of -2° (cf. ref. 7) (R. S. Henry, J. Murray-Rust, and P. Murray-Rust, *Acta Cryst.*, in the press).

† We are indebted to the S.R.C.-supported ¹³C n.m.r. service operated by the Chemistry Department, University of Edinburgh, for these spectra.

⁵ (a) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, 1966, **88**, 3622; (b) J. R. Wiseman and W. A. Peltcher, *ibid.*, 1970, **92**, 1001; (c) O. Bottger, *Ber.*, 1937, **70B**, 314; (d) ref. 4b.

⁶ See ref. 3 and S. Landa, *Sci. Papers Inst. Chem. Tech. Prague*, 1964, 31; S. Landa and J. Kiefmann, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1005.

EXPERIMENTAL

I.r. spectra were recorded on Perkin-Elmer 157G and 457G spectrophotometers. N.m.r. were determined for solution in carbon tetrachloride or deuteriochloroform with a Perkin-Elmer R10 or R24 spectrometer (tetramethylsilane as internal standard). Mass spectra were determined by the P.C.M.U., Harwell.

Analytical g.l.c. was performed with a Perkin-Elmer F11 instrument (2 m stainless steel column of 5% FFAP on Chromosorb W (80–100 mesh); carrier gas, nitrogen; inlet pressure 20 lb in⁻²).

Tetramethyl 2,7-Dioxatricyclo[4.3.1.1^{3,6}]undecane-1,3,6,8-tetracarboxylate (2).—Sodium hydride (32 g of a 60% dispersion in oil) was washed free of oil with light petroleum and then stirred, under nitrogen, while a solution of Meerwein's ester³ (1) (100 g) in anhydrous dioxan (750 ml) was added dropwise. When hydrogen evolution had ceased, freshly-distilled 1,2-dibromoethane (750 ml) was added in portions; the mixture was then heated at 110° for 24 h and filtered warm. Removal of the solvent *in vacuo* and trituration of the resultant gum with methanol gave a crystalline product which was recrystallised from methylene chloride to give the *dione tetraester* (2) as white needles (67 g), m.p. 255–256° (Found: C, 55.35; H, 5.5. C₁₈H₂₂O₁₀ requires C, 55.6; H, 5.4%); *M*⁺ 410; *v*_{max} 1740, 1715, 1260, 1070, 1030, 957, and 930 cm⁻¹.

Dimethyl 2,7-Dioxatricyclo[4.3.1.1^{3,6}]undecane-1,8-dicarboxylate (3; R = Me).—A solution of the tetraester (2) (66.2 g) in acetic acid (300 ml), concentrated hydrochloric acid (100 ml), and water (100 ml) was heated under reflux for 16 h then evaporated to dryness *in vacuo*; the residue was then heated at 270–280° for 45 min, after which CO₂ evolution had ceased. The resultant crude dicarboxylic acid (3; R = H) was then converted by standard treatment with methanol-concentrated sulphuric acid into the *diester* (3; R = Me) (43 g), which crystallised from ethanol in needles, m.p. 254–255° (Found: C, 60.95; H, 5.95. C₁₈H₁₈O₆ requires C, 61.2; H, 6.15%); *v*_{max} (Nujol) 1742, 1717, 1288, 1140, 1100, 1020, and 970 cm⁻¹.

The corresponding *bispyrazolone* (4), prepared in quantitative yield by treatment of (3; R = CH₃) with hydrazine hydrate in the usual manner, crystallised from ethanol in needles, m.p. 336–227° (decomp.) (Found: C, 60.2; H, 5.5. C₁₈H₁₄N₄O₂ requires C, 60.45; H, 5.45%); *v*_{max} (Nujol) 3510, 3230, 1700, 1679, 1620, 1325, 1280, 1205, 1155, 1105, 905, and 740 cm⁻¹.

⁷ E. M. Engler, L. Chang, and P. von R. Schleyer, *Tetrahedron Letters*, 1972, 2526.

⁸ S. J. Cristol and W. C. Firth, *J. Org. Chem.*, 1961, **26**, 280; F. W. Baker, H. D. Holtz, and L. M. Stock, *ibid.*, 1963, **28**, 514; A. McKillop, D. Bromley, and E. C. Taylor, *ibid.*, 1968, **34**, 1172; N. J. Bunce, *ibid.*, 1972, **37**, 669; J. Cason and D. M. Walba, *ibid.*, 1972, **37**, 669; see also ref. 4b.

⁹ K. B. Becker, M. Geisel, C. A. Grob, and F. Kuhnen, *Synthesis*, 1973, 493.

¹⁰ K. Ohno and J. Tsuji, *J. Amer. Chem. Soc.*, 1968, **90**, 99.

¹¹ G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1276.

¹² A. R. Gagneux and R. Meier, *Tetrahedron Letters*, 1969, 1365; H. Hamill, A. Karim, and M. A. McKervey, *Tetrahedron*, 1971, **27**, 4317.

¹³ M. Eakin, J. Martin, and W. Parker, *Chem. Comm.*, 1965, 206.

¹⁴ J. Janjatović, D. Skare, and Z. Majerski, *J. Org. Chem.*, 1974, **39**, 651, and references therein; we thank Professor Majerski for a comparison sample.

¹⁵ B. Föhlisch, U. Dudek, I. Graessle, B. Novotny, E. Schupp, G. Schlaewiger, and E. Widmann, *Annalen*, 1973, 1839.

Tricyclo[4.3.1.1^{3,8}]undecane-1,8-dicarboxylic Acid (5; R = CO₂H).—The bispyrazolone (4) (35 g) was thoroughly mixed with powdered sodium hydroxide (35 g), water (22 ml) was added, and the mixture was heated in an autoclave (1500 ml) at 210° for 15 h. The cooled product was dissolved in water and acidified to pH 1 with aqueous hydrochloric acid, and the crude acid was filtered off, dried, and recrystallised from dioxan to give the *dicarboxylic acid* (5; R = CO₂H) as needles (23 g), m.p. 316–317°; ν_{\max} (Nujol) 3600–2400, 1715, 1390, 1290, 1260, and 1220 cm⁻¹.

The *dimethyl ester* (5; R = CO₂Me), prepared with diazomethane, gave white needles, m.p. 188–189° (Found: C, 67.5; H, 8.15. C₁₅H₂₂O₄ requires C, 67.65; H, 8.35%); δ_C (CDCl₃) 31.06, 32.98, 38.63, 38.95, 41.61, 51.74, and 178.17 p.p.m.

1,8-Dichlorotricyclo[4.3.1.1^{3,8}]undecane (5; R = Cl).—Oxalyl chloride (3 ml) was added to a stirred suspension of the dicarboxylic acid (5; R = CO₂H) (400 mg) in anhydrous benzene. The mixture was heated overnight under reflux, then the solvent and the excess of oxalyl chloride were removed *in vacuo*. The residual oil was then treated with chlorocarbonylbis(triphenylphosphine)-rhodium (70 mg) and slowly heated to 250°; gas evolution (presumably CO and HCl) was observed and a white solid sublimed into the neck of the flask. After 1 h at 250° the flask was cooled and the mixture and sublimate were dissolved in warm carbon tetrachloride and filtered through a short column of silica gel. Removal of the solvent left a white crystalline solid which was recrystallised from carbon tetrachloride to give the *bis-bridgehead dichloride* (5; R = Cl) (260 mg) as needles, m.p. (sealed tube) 159–160°; ν_{\max} (CS₂) 1355, 1315, 1299, 1248, 1207, 1170, 1070, 1061, 986, 957, 937, 931, 812, 800, and 720 cm⁻¹; δ_C (CDCl₃) 31.65, 32.56, 46.61, 56.00, and 69.06 p.p.m. The mass spectrum of the dichloride did not show a parent ion but the base peak corresponded to the loss of Cl⁻ (Found: *m/e*, 183.0939. C₁₁H₁₆Cl requires 183.0941).

7-Methylenebicyclo[3.3.2]decan-3-one (6).—A solution of the dichloride (5; R = Cl) (500 mg) in dioxan (10 ml) was heated at 170–180° for 12 h with aqueous (10%) sodium hydroxide (10 ml) in a stainless steel autoclave (50 ml). The cooled mixture was diluted with water and thoroughly extracted with pentane, and the combined organic extracts were dried and evaporated. The residue was sublimed (10 Torr) to give the *methylene ketone* (6) (200 mg), m.p. (sealed tube) 159–160°; *M*⁺ 164 (Found: C, 80.0; H, 9.65. C₁₁H₁₆O requires C, 80.35; H, 9.8%); ν_{\max} (CCl₄) 3080, 1690, 1640, and 907 cm⁻¹; δ_H (CCl₄) 2.1 (4H, apparent *t*, *J* 2.5 Hz), 2.31br (3H, s), 2.40 (3H, apparent *t*, *J* 4 Hz), 2.50br (s) and 2.57 (apparent *t*) (*J* 5 Hz, *J'* 6.5 Hz), and 4.87 (2H, *t*, *J* 2 Hz); δ_C (CDCl₃) 213.7, 144.5, 118.6, 49.56, 42.15, 30.67, and 29.43 p.p.m.

Homoadamantan-1-ol (9).—A mixture of the methylene ketone (6) (100 mg), aluminium isopropoxide (1 g), and toluene (10 ml) was heated to reflux and the toluene was

slowly distilled off through a Vigreux column. After 3 h, 2 ml of toluene had been removed and the mixture was then cooled and stirred for 1 h with aqueous 10% sodium hydroxide before separating the layers. The aqueous layer was further extracted with ether (2 × 5 ml), and the combined extracts were dried (Na₂SO₄) and evaporated to ca. 3 ml. The solution was applied to a short column of silica gel and eluted first with pentane to remove ca. 10 mg of toluene then with ether to provide a clear viscous oil (90 mg). This material had spectroscopic properties consistent with those of the expected methylene-*exo*-alcohol (8); ν_{\max} 3610 and 3470 cm⁻¹ (OH str.); δ_H (CCl₄) 4.6br (*s*, =CH₂) and 4.5 (multiplet partially obscured >CH-OH). However the integral of the n.m.r. spectrum suggested that this material also contained a non-olefinic component, possibly the cyclisation product (9). The crude material was therefore treated with toluene-*p*-sulphonyl chloride in pyridine, and the resultant crude toluenesulphonate was dissolved in *m*-sodium acetate in glacial acetic acid (10 ml) and kept for 24 h in a water-bath maintained at 40°. The mixture was then poured into water (50 ml) and extracted with ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, concentrated, and then added to a suspension of lithium aluminium hydride (200 mg) in ether (5 ml) and stirred for 1 h. The reaction was then quenched by cautious addition of saturated aqueous sodium sulphate. The ethereal solution was decanted, dried, and evaporated to give a white crystalline solid (40 mg), which was purified by g.l.c. and t.l.c. This was identified as homoadamantan-1-ol (9) by g.l.c. and i.r. comparison with an authentic sample.¹⁴

Bicyclo[3.3.2]decan-3,7-dione (7).—The methylene ketone (6) was ozonised by the method of Pappas *et al.*¹⁶ The solution was passed into a cooled (-80°) solution of 6 ml of methylene chloride (5 ml) and methanol (5 ml). The blue colour persisted. The mixture was then treated with nitrogen until the blue colour vanished, then the addition (at -80°) of dimethyl sulphide (1 ml). The mixture was set aside overnight at room temperature after which it gave a negative test for peroxides. It was evaporated under reduced pressure to leave a residue which was applied to a short column of silica gel. Extraction with chloroform then gave the *dione* (7) (42 mg), which crystallised from ether in needles, m.p. (sealed tube) 248–250°; ν_{\max} (CCl₄) 1704, 1420, 1410, 1344, 1270, 1215, and 1165 cm⁻¹; δ_H (CDCl₃) 2.25br (ca. 4H, s), 3.58br (ca. 8H, s) (Found: *M*⁺, 166.0999. C₁₀H₁₄O₂ requires *M*, 166.0994).

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¹⁴ J. J. Pappas, W. P. Keaveney, E. Gancher, and M. L. Huggins, *Tetrahedron Letters*, 1966, 4273.

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