Aspects of

Bicyclo (3,3,1) nonane

Chemistry

THESIS

presented to the University of Glasgow

for the degree of Ph.D.

by

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1969

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To

MUM and DAD.

SUMMARY

SECTION I

A study of the solvolytic behaviour of exo- and endo- 1,5-dimethylbicyclo (3,3,1) nonan-9-one-2-yl tosylates revealed a stereochemical control in product formation which can best be explained in terms of ion-pair intermediates. Evidence for an acyl migration during solvolysis was found.

SECTION II

A 2,6- hydride shift was discovered during the deuteration of exo-2-hydroxybicyclo (3,3,1) nonan-6-one. Studies of other possible 2,6-interactions in the bicyclo (3,3,1) skeleton, (i.e. homoenolisation between C_2 and C_6, synthesis of twistane derivatives from 2,6- disubstituted bicyclo (3,3,1) nonane compounds and reactivity of 6-hydroxy-2-cations) were also initiated. Finally the influence of a keto group at C_6 and C_9 on the solvolytic rate constant of the epimeric-2-tosylates was also studied and evidence found to support the current ideas regarding the influence of polar groups on ionisation of tosylates.

ACKNOWLEDGEMENTS

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Εἰδέναι μὲν μηδὲν πλὴν αὐτὸ τοῦτο εἰδέναι

Socrates,

Diogenes Laertius, Bk. ii, sec. 32.

SUMMARY

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CONTENTS

SECTION I

The Solvolytic Behaviour of exo- and endo 1,5 Dimethylbicyclo (3,3,1) nonan-9-one-2-yl Toluene-p-sulphonates

Introduction 1

Discussion 3

Experimental 10

SECTION II

2,6- interactions in the Bicyclo (3,3,1) nonane Skeleton

Introduction 15

Discussion 22

Experimental 43

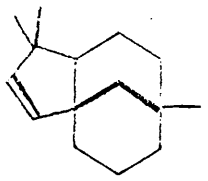
APPENDIX I

Stereochemistry of Bicyclo (3,3,1) non-2-yl Derivatives 71

APPENDIX II

Rate Constants for Buffered Acetolysis of Alkyl Tosylates 73

References 75



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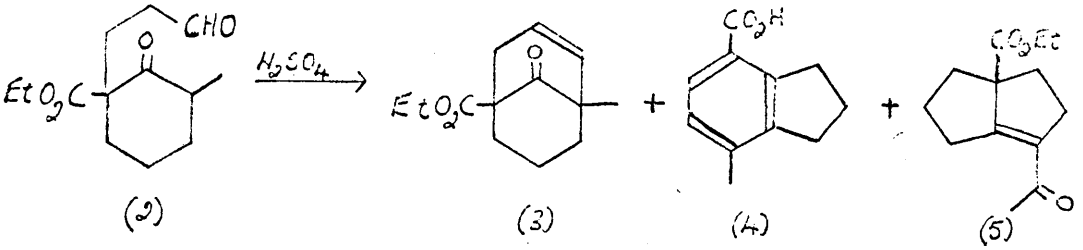

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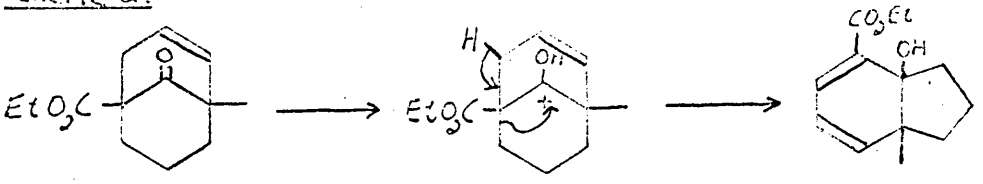

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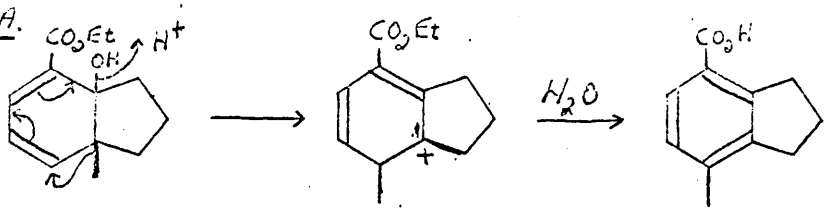

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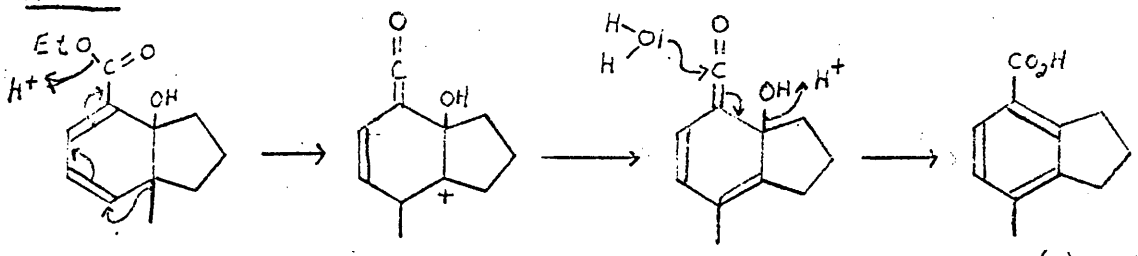

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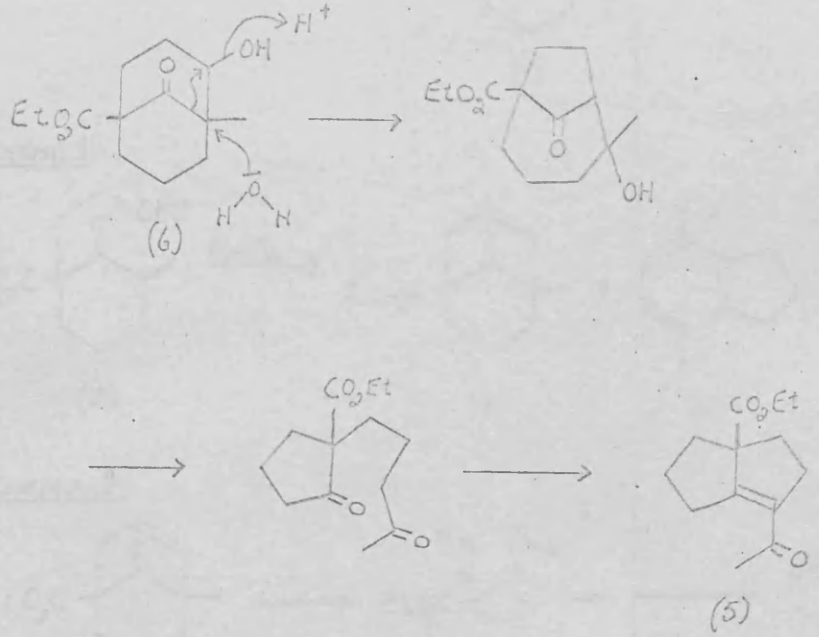


SECTION I

The Solvolytic Behaviour of exo- and endo- 1,5 Dimethylbicyclo (3,3,1) Nonan - 9 - One - 2 - yl Toluene - p - Sulphonates.

Introduction

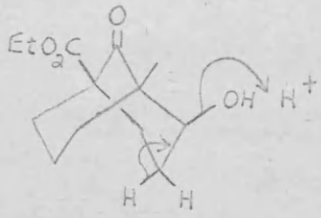
The work described in this section arose from a reaction encountered at Glasgow during the synthesis of clovene (1)[1].

Sulphuric acid treatment of 3 - (1 - carbethoxy - 2 - oxo - 3 - methylcyclohexyl) propionaldehyde (2) gave the desired bicyclo-keto-ester (3) accompanied by 7 - methylindan - 4 - carboxylic acid (4) and ethyl 2 - acetobicyclo (3,3,0) oct - 1 (2) - ene - 5 - carboxylate (5)[2] in an overall yield of 50%, (scheme 1)[3].

Since the pure keto-ester (3) is slowly converted to (4) by acid[4], two variants of a general mechanism of formation have been suggested (scheme 2). Martin[5] has pointed out that since (3) and (5) are isolated with the carboethoxyl group non-hydrolysed, Path B is a preferred mechanism for the formation of the aromatic acid (4).

The initial aldol product (6) has been prepared and shown to give a similar product distribution on acid treatment thus providing the rationale for the formation of (5) illustrated in scheme 3.

At this time it was recognised that the ketol (6) can exist in two epimeric forms (7) and (8) which might provide a stereoelectronic control of the relative production of (4) and (5).



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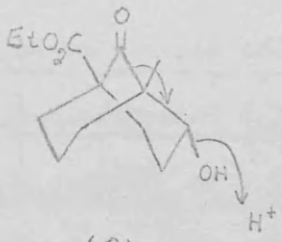

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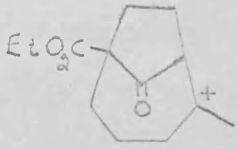

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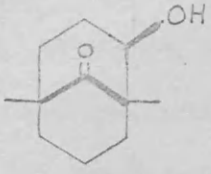

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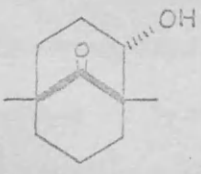


(11)

The preferred conformation of the bicyclo (3,3,1) nonane framework is twin chair[6]. Hence the axial-ketol (7) has a facile trans-antiparallel dehydration mechanism available (encouraged by removal of the severe C_3-C_7 non-bonded interactions) for production of (3) and hence (4). In contrast, bond alignment in the equatorial - ketol (8) is ideal for the concerted removal of the protonated hydroxyl group and acyl shift leading to the tertiary cation (9) which by solvent capture etc. (scheme 3) leads to the enone ester (5). Unfortunately the mixture of ketols (7) and (8) obtained by dilute acid treatment of (2) proved impossible to separate. However stereoselective routes[7] then became available for the related ketols (10) and (11) and so it was decided to study their behaviour in terms of the above proposals.

TABLE 1.

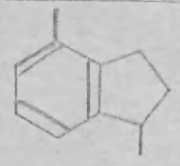
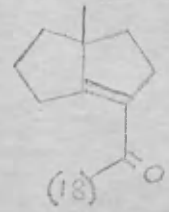
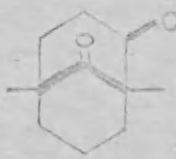
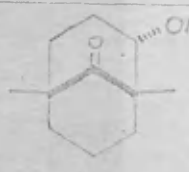
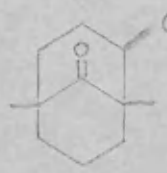
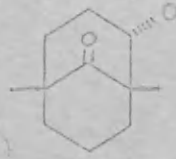
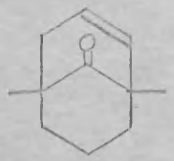
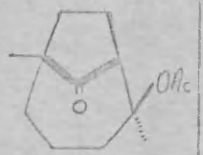
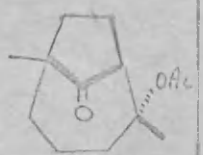
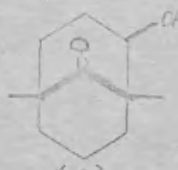
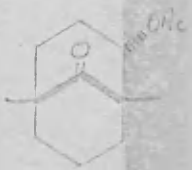
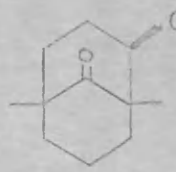
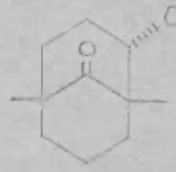
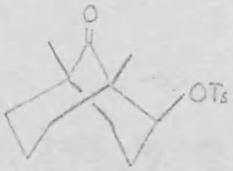
	 (16)	 (17)	 (18)	 (19)	 (20)
 (12) $\xrightarrow{HOAc}$	4%	68%	5%	5%	18%
 (13) $\xrightarrow{HOAc}$	20%	19%	26%	23%	12%

TABLE 2.

	 (14)	 (21)	 (22)	 (23)	 (19)	 (20)
 (12) $\xrightarrow[HOAc]{NaOAc}$	75%	7%	4%	<1%	1%	12%
 (13) $\xrightarrow[HOAc]{NaOAc}$	8%	51%	12%	4%	24%	<1%



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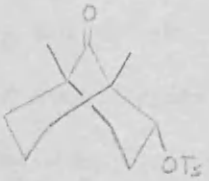
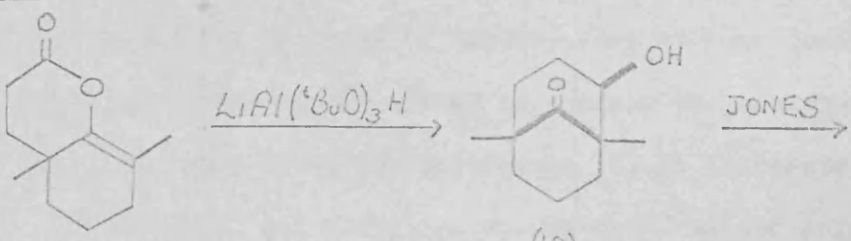


(13)

SCHEME 4.



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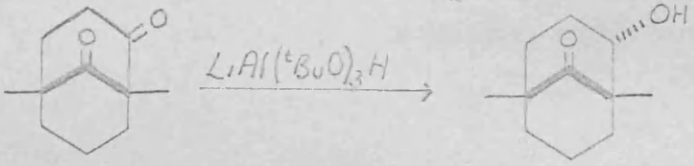


(15) (11)

DISCUSSION

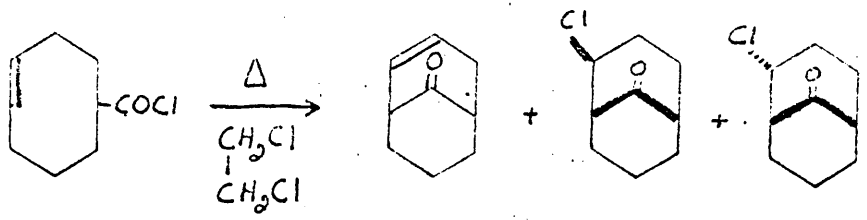
Because of the severe reaction conditions employed and the apparently key role played by 9 - oxobicyclo (3,3,1) nonyl - 2 - cation(s) in these deep-seated rearrangements described in the Introduction, it was decided to study the formation and behaviour of such species under milder and more informative conditions viz the acetolysis of the exo- and endo- keto-tosylates (12) and (13).

Lithium aluminium tri-t-butoxy hydride reduction of the enol-lactone (14) gave the exo- ketol (10) which was then oxidised to the 2,9,- dione (15) and subsequently reduced with the same reagent to give the endo- ketol (11) both ketols being formed with high stereospecificity[7] (scheme 4).

The solvolyses of the corresponding tosylates were then examined in unbuffered and buffered (NaOAc) acetic acid and the major part of products structure proof was carried out by Dr. T. Stewart[8]. The complete product distributions for acetolysis and buffered acetolysis of (12) and (13) are shown in Tables 1 and 2 respectively.

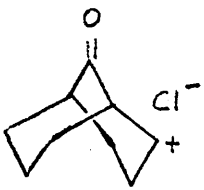
The structures of the conjugated ketone (18) and the aromatic hydrocarbon (16) were confirmed by partial and total synthesis respectively[8]. The structure of the non-conjugated enone (21) could be inferred from spectroscopic evidence and was confirmed by synthesis as follows. Erman and Kretschmar[9] have reported that heating cis - Δ^4 - cyclooctene - 1 - carboxylic acid chloride (24)

Scheme 5.



(24) (25) (26) (27)

5% 41% 16%



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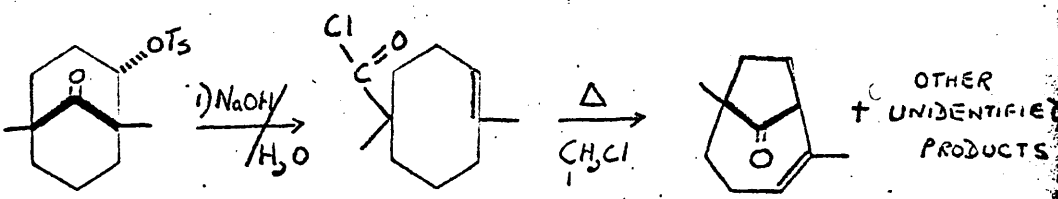
Scheme 6.

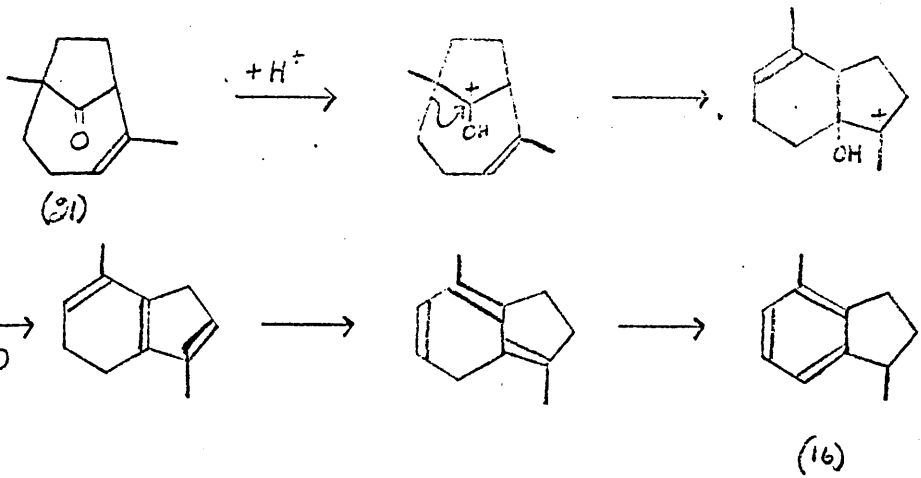


(13) (29) (21)

in ethylene chloride gave bicyclo (3,3,1) non - 2 - en - 9 - one (25), exo- 2 - chlorobicyclo (3,3,1) nonan - 9 - one (26) and the corresponding endo- epimer (27) (scheme 5). These workers rationalised these findings in terms of double bond participative removal of the acyl halide ion resulting in the formation of a 9 - oxobicyclo (3,3,1) nonyl - 2 - cation in the form of an ion pair with chloride ion (28). They did not detect any of the corresponding bicyclo (4,2,1) chloroketone and/or keto olefin, i.e. of the two possible secondary carbonium ions, the 2 - bicyclo (3,3,1) nonyl cation was preferred over the 2 - bicyclo (4,2,1) isomer. If the choice was between a secondary bicyclo (3,3,1) non - 2 - yl cation and a tertiary bicyclo (4,2,1) non - 2 - yl cation it was thought the tertiary one might be preferred. Hence 1,5 - dimethyl - cis - Δ^4 - cyclooctene - 1 - carboxylic acid chloride (29) was prepared from endo- 9 - oxo - 1,5, - dimethylbicyclo (3,3,1) non - 2 - yl tosylate (13) as shown (scheme 6) and heated in ethylene chloride. Only one keto-olefin was formed which had identical spectral and physical properties to those of the rearranged ketone (21) and markedly dissimilar to 1,5 dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (17). The structure of the acetates (22) and (23) were arrived at [8] by relating them to the bicyclo (4,2,1) keto-olefin (21) through an elegant series of reactions.

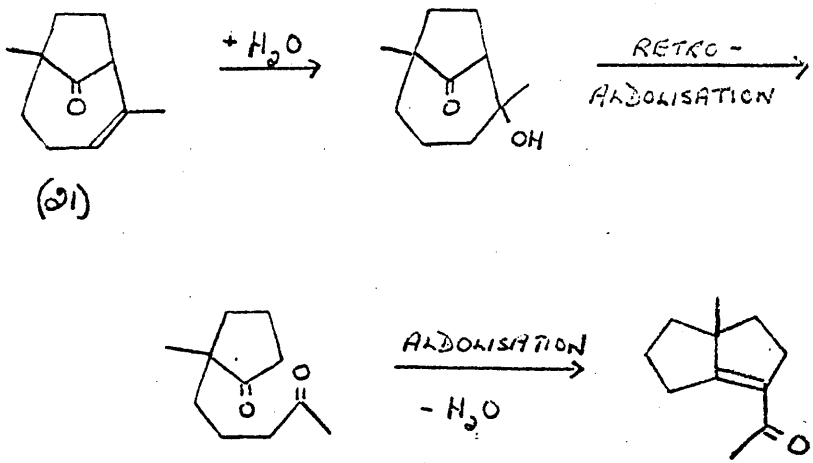
Two salient points emerge from the results shown in Table 1; the higher percentage of rearranged products from (13) than (12) and the formation of an aromatic hydrocarbon (16) whose substitution

SCHEME 7.



(21) (16)

SCHEME 8.



(21) (18)

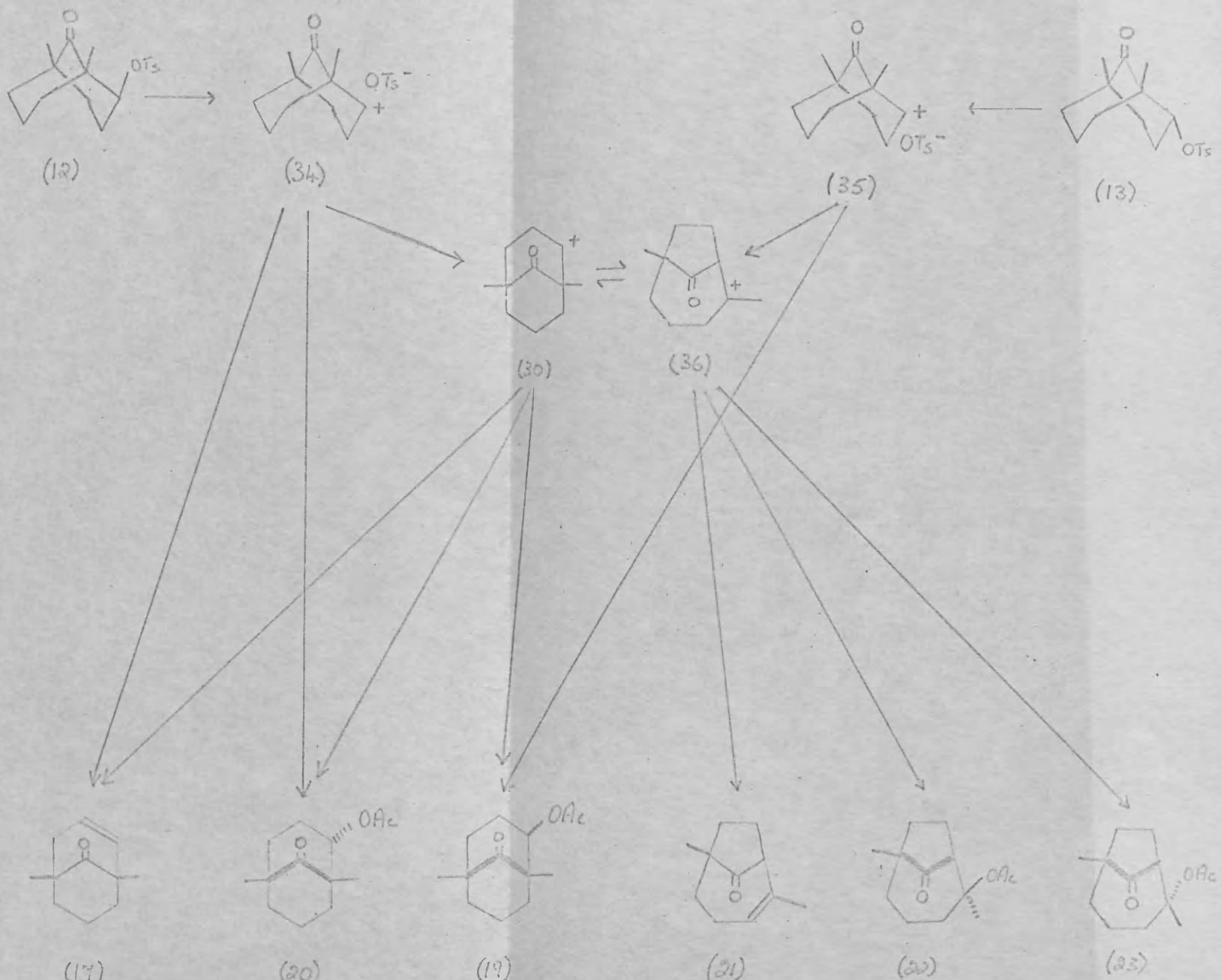
pattern (1,4 dimethyl) differs from that to be expected from earlier work described in the Introduction (viz, 4,7 - disubstituted). The results from the buffered acetolysis of (12) and (13) are even more informative; e.g. the virtual absence of rearranged products from (12) ($>$ 90% bicyclo (3,3,1) nonane carbon skeleton); the extent ($>$ 65%) of rearrangement accompanying the solvolysis of (13); the absence of aromatic products but the appearance of a new carbon skeleton i.e. the bicyclo (4,2,1) nonane system.

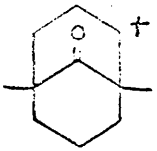
The results[8] of two control experiments are worthy of comment at this stage. The keto-olefin (21) was unaffected by refluxing acetic acid but could be converted into a mixture of (16), (17), and (18) by treatment with p - toluene sulphonic acid in benzene whereas the bicyclo (3,3,1) non - 2 - en - 9 - one (17) was unaffected by either of these reaction conditions.

These findings coupled with those shown in Tables 1 and 2 point to 1,5 - dimethylbicyclo (4,2,1) non - 4 - en - 9 - one (21) as playing the key role in the production of 1,4 - dimethylindane (16) and the conjugated ketone (18), presumably by the pathways illustrated in schemes 7 and 8 respectively.

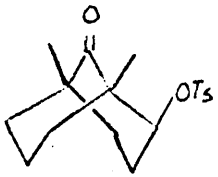
With the initial question of the source of (16) and (18) resolved, an equally interesting question arises from an examination of Table 2 i.e. what is the nature of the intermediate(s) in the buffered acetolysis of (12) and (13)? The striking difference in

Scheme 9.





(30)



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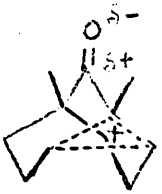

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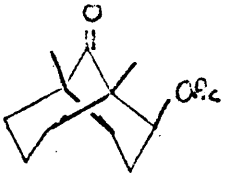

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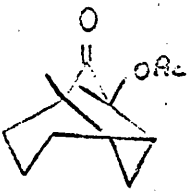

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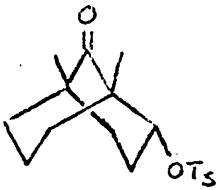

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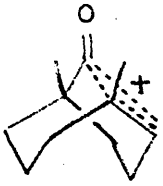


(33)

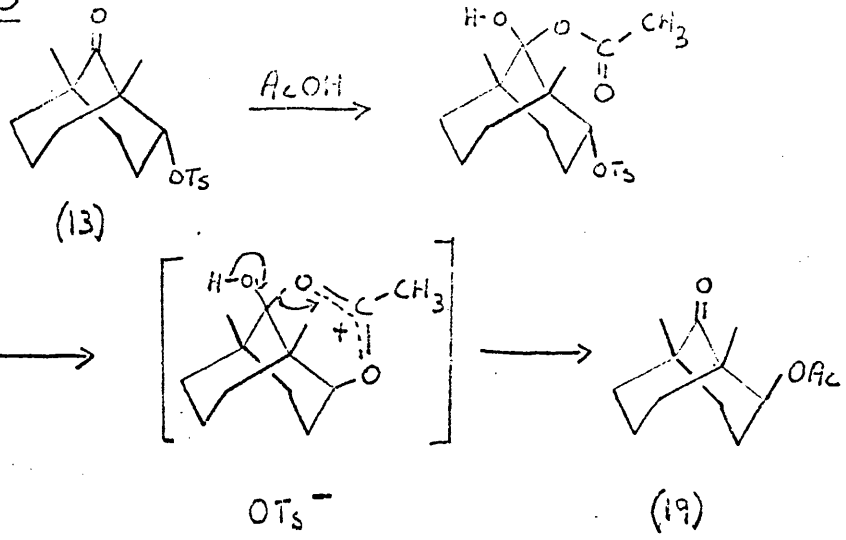
products arising from (12) and (13) mitigates against the intermediacy of a common classical carbonium ion (30). On the other hand an explanation of these different product distributions as arising from two different non-classical ions as the reaction intermediates falls down on several points. The non-classical ion derivable from (12) possesses the unlikely structure (31) and would demand the production of exo- 2 - acetate (19) and perhaps even a little of the bicyclo (3,2,2) nonyl acetate (32). No trace of (32) has been found and the major bicyclo (3,3,1) nonyl - 2 - acetate formed is endo- (exo/endo = $<1/12$).

Similarly the corresponding non-classical ion related to (13) i.e. (33) does not explain the relatively high inversion of configuration in the recovered bicyclo (3,3,1) non - 2 - yl acetates. (exo/endo = $>24/1$).

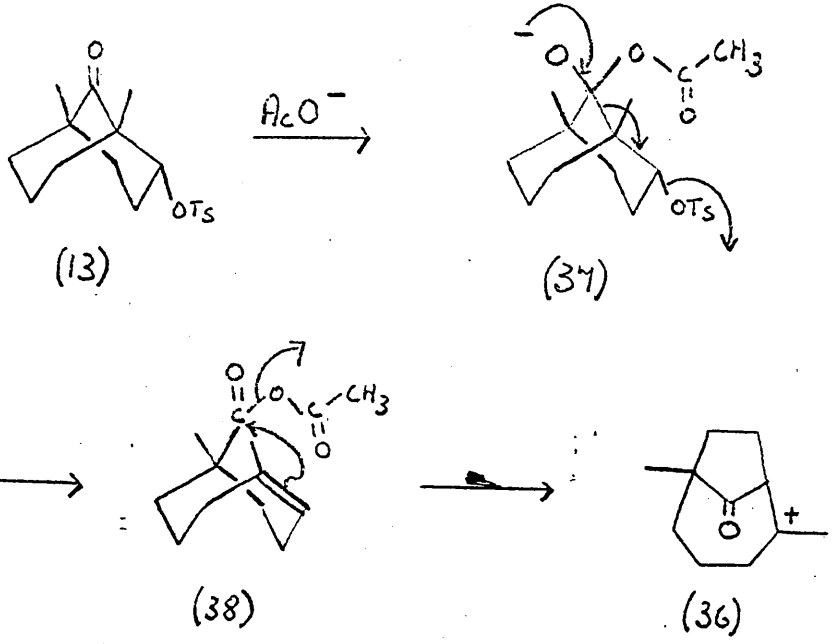
However, an argument couched in terms of intimate ion pair/ classical carbonium ion equilibrium does seem to account for all the observed facts (scheme 9).

Ionisation of (12) to the intimate ion pair (34) and subsequent reaction either by loss of the stereochemically favoured endo- C_3 proton (which also relieves the quite substantial C_3-C_7 methylene interaction) or acetate ion capture (from the endo- face of C_2) would explain the overall product distribution if there was a small leakage from the ion pair (34) to the classical - 2 - cation (30).

SCHEME 10



SCHEME 11



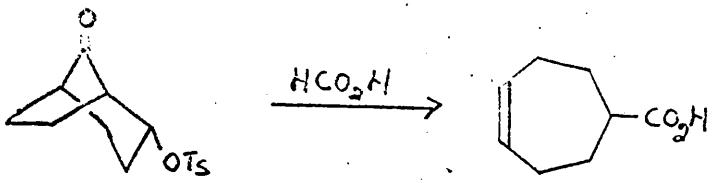
The corresponding intimate ion pair (35) formed from (13) could suffer solvent capture (leading to inverted acetate) or a stereoelectronically favoured acyl shift to give the bicyclo (4,2,1) nonyl - 5 - cation (36) and thence the major products. Here again a leakage to (30) from either the ion pair (35) or the (4,2,1) cation (36) would explain the small amounts of (17) and (20) encountered.

This mechanistic picture certainly seems to be an acceptable one for the exo- 2 case and is probably valid for the endo- 2- epimer. However several alternative schemes must be considered for the latter tosylate.

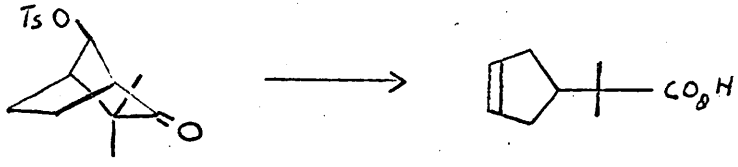
(i) [10] The addition of acetic acid to (13) and subsequent neighbouring group participation by the carbonyl of the acetate would result in the production of inverted acetate (19) (scheme 10). However this pathway does not explain the formation of bicyclo (4,2,1) nonyl compounds and hence would require another pathway to operate at the same time.

(ii) A variant of (i) involves the addition of acetic acid as in (i) or acetate ion attack leading to an intermediate (37) which then undergoes a facile fragmentation to the cyclooctenyl mixed anhydride (38) which in turn recyclises to the bicyclo (4,2,1) nonyl cation (36) by intramolecular displacement of acetate ion from the mixed anhydride moiety by the trisubstituted double bond (scheme 11).

SCHEME 12

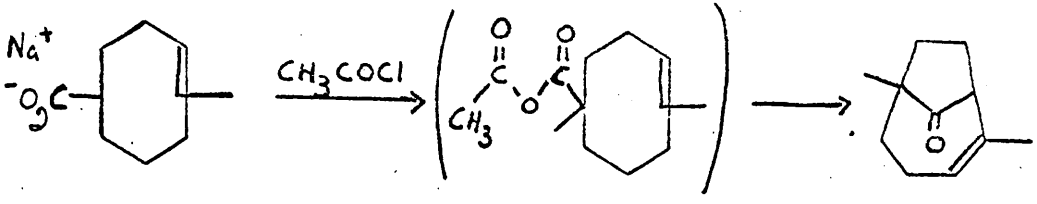


SCHEME 13



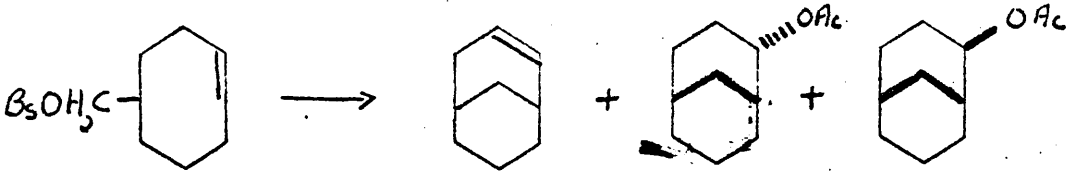
(39) (40)

SCHEME 14.



(41)

SCHEME 15.



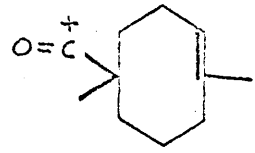
(42) (43)

14% 45% 3% + 4%

The above fragmentation reaction finds numerous analogies in the recent literature both in the bicyclo (3,3,1) nonane ring system [7, 11] and other bridged ring systems [12-18]. An example [13] is shown in scheme 12 but a particularly relevant example [18] is shown in scheme 13 where the acid (40) is obtained in high yield from the keto-tosylate (39) by acetolysis. It is noteworthy that the product balance from solvolysis of (13) is virtually complete which suggests that if this pathway is operating the mixed anhydride must be extremely reactive towards buffered acetolysis.

There are also many examples of such transannular cyclisations [9, 19-23], and the closure of a cyclooctenyl acid chloride has already been reported in this thesis (page 4).

An attempt was therefore made to prepare the mixed anhydride and subject it to the appropriate solvolysis conditions. The sodium salt (41) of the cyclooctenyl acid was made and treated with acetyl chloride as in scheme 14. In the infra-red spectra of the product there was evidence of some anhydride but also of some bicyclo (4,2,1) keto-olefin (further substantiated by gas-liquid chromatography). Therefore the anhydride if it was formed was certainly very unstable and hence our attempt to subject it to solvolysis conditions failed. Although this might be taken as evidence for the fragmentation/cyclisation mechanism such a process would demand the formation of endo- 2 - acetate (20), by analogy [21] with the solvolysis of cis - Δ^4 - cyclooctene - 1 - methyl brosylate (42) which gives mainly endo- bicyclo (3,3,1) non - 2 - yl acetate (43) (scheme 15).



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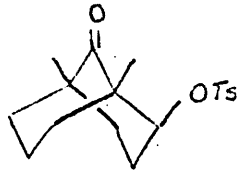

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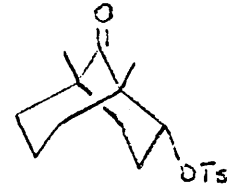

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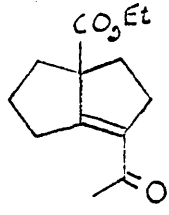

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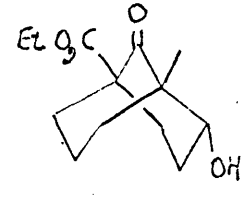

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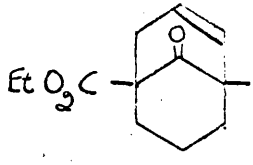

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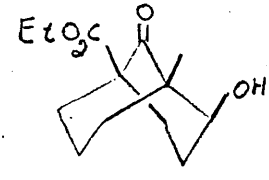


(4)

It is perhaps of interest to note that the rate constant for buffered solvolysis of (13) was virtually unaffected by addition of a tenfold excess of sodium acetate.

(iii) A third variant on this general theme is to propose a fragmentation to an acylium ion [12] (44) but for similar reasons it would not account for the product distribution.

Hence until we can prepare the mixed anhydride and check the product distribution (if any), the ion pair mechanism seems worthy of consideration for the solvolysis of both (12) and (13).

In an effort to clarify the mechanisms of solvolyses the first order rate constants for buffered acetolysis of (12) and (13) were measured and will be discussed later in the thesis.

The explanation of the results of unbuffered and buffered acetolysis leaves us in a position to comment on the reaction which provided the starting point for this work (scheme 1). Notwithstanding the difference in conditions it seems that the enone ester (5) would arise from one (8) of the initially formed ketols whereas the olefin (3) would come from the other (7). As no comparably substituted indane was found during solvolysis we cannot comment directly but if the proposed mechanism is correct then it arises from ketol (7) via the olefin (3).

EXPERIMENTAL.*

Melting points were recorded on a Kofler block and are uncorrected. Boiling points are also uncorrected. Light Petroleum refers to the fraction b.p. 40-60°. All organic extracts were dried with anhydrous magnesium sulphate and thin-layer chromatoplates were prepared from Merck's "Kieselgel G'.

Analytical gas-liquid chromatograms were run on the Perkin Elmer F 11 instrument. Mass spectra were determined on an A.E.I./ M.S. 902 instrument. Ultraviolet absorption spectra were run on a recording Unicam S.P. 800 instrument. Routine infra-red spectra were run on a Unicam S.P. 200 or a Perkin Elmer 157 instrument. All infra-red data reported are from high resolution spectra in carbon tetrachloride record on a Perkin Elmer 220 instrument unless otherwise stated. Proton magnetic resonance spectra were measured using carbon tetrachloride as solvent, unless otherwise stated, with tetramethyl silane as internal standard in a Perkin Elmer 60 MC/S spectrometer.

* The comments here are also applicable to the experimental part of Section 2.

Axial and Equatorial 9-oxo-1,5-dimethylbicyclo (3,3,1) nonan-2-yl toluene-p-sulphonates (12) and (13)

These were prepared without difficulty by the method of Martin[5].

Anhydrous Acetic Acid

The anhydrous acetic acid was obtained by refluxing glacial acetic acid with boron triacetate and then distillation, the fraction b.p. 118° - 120° being collected.

Buffered Acetolysis of axial and equatorial 9-oxo-1,5-dimethylbicyclo (3,3,1) nonan-2-yl toluene-p-sulphonates

For preparative work the solvolyses were carried out by the method of Stewart[8], the products being separated by column chromatography. To determine the accurate product analysis the following procedure was adopted.

The tosylate (37 mg.), sodium acetate (25 mg., 1.1 molar equivalents) and anhydrous acetic acid (6 ml.) were heated in a sealed ampoule at 80°C for ten half-lives at that temperature. The products were recovered by partitioning between pentane (10 ml.) and brine (5 ml.) the aqueous solution being washed with pentane several times (2 x 5 mls.). The combined organic layers were washed with saturated sodium bicarbonate solution (4 x 5 ml.), brine (2 x 5 ml.) and dried. Careful removal of solvent at 5° under reduced pressure left a pale yellow oil which was analysed using gas liquid

chromatographic methods.

The conditions employed were temperature programming from 100°-175° at 3°/min on a 6' 5% Q.F.1 column. The following retention indices were found.

1,5-dimethylbicyclo (3,3,1) non-2-ene-9-one (17) 1540,

1,5-dimethylbicyclo (4,2,1) non-4-ene-9-one (21) 1640,

acetates of 1,5-dimethylbicyclo (4,2,1) nonan-9-one (22) 2033,

(23) 2070,

endo-acetate of 1,5-dimethylbicyclo (3,3,1) nonan-9-one (20) 2125,

exo-acetate of 1,5-dimethylbicyclo (3,3,1) nonan-9-one (19) 2170.

1,5-dimethylbicyclo (4,2,1) non-4-ene-9-one. (21)

Equatorial 9-oxo-1,5 dimethylbicyclo (3,3,1) non-2-yl tosylate (13)(168 mg.) was refluxed with 1N. sodium hydroxide solution (1.5 ml.) and water (2 ml.) for 30 mins. Solvent was removed under reduced pressure and benzene (2 ml.) and oxalyl chloride (1 ml.) were added and left stirring for 4 hrs. Removal of solvent left a brownish white solid which was heated in ethylene dichloride for 10 mins. and then solvent removed. Chromatography of the pet. ether solubles on grade III neutral alumina gave one ketoolefin (15 mg.) identical in gas liquid chromatographic properties (6' 1½% Q.F.1 and 6' 3% OV22 columns) to the suspected bicyclo (4,2,1) ketoolefin (21) obtained from solvolysis. The infra-red spectrum was superimposable with that of the ketoolefin (21) obtained from solvolysis. ν_{max} (film)(S.P. 200) 3090, 1735, 1656, 830 cm^{-1}.

Attempted preparation of 1,5-dimethyl-cis-Δ^4-cyclooctene-1-carboxylacetyl mixed anhydride (38)

a) A mixture of benzene (5 ml.) and dioxan (10 ml.) were refluxed under a Dean and Stark water separator for 30 mins. Fused sodium acetate (11 mg.) was added and reflux continued. After 1 hr. equatorial 9-oxo-1,5-dimethylbicyclo (3,3,1) non-2-yl tosylate (13)(50 mg.) was added and reflux continued for a further three days. Thin layer chromatography and infra-red spectroscopy showed that little if any reaction had occurred.

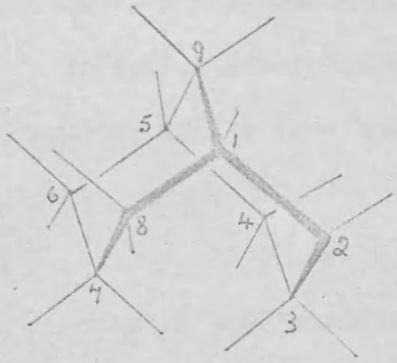
b) Ethyl 1,5-dimethyl-cis-Δ^4-cyclooctene-1-carboxylate (40 mg.),

obtained from equatorial 9-oxo-1,5-dimethybicyclo (3,3,1) non-2-yl tosylate (13) by fragmentation using sodium ethoxide in ethanol, was hydrolysed using refluxing .35 N aqueous sodium hydroxide (1 ml.) for 30 min. The solvent was removed and the salt refluxed in benzene (3 ml.) with acetyl chloride (0.1 ml.) for 1 hr. After removal of solvent the infra-red spectrum of the ether solubles showed some anhydride and some olefin perhaps bicyclo (4,2,1) ketoolefin.

ν_{max} (film) (S.P. 200) 1810 (W), 815 (W) cm.$^{-1}$

c) 1,5-dimethyl-cis-Δ^4-cyclooctene-1-carboxylic acid (140 mg.), obtained by hydrolysis of its ethyl ester, was dissolved in ethanol (5 ml.) and 4N sodium hydroxide solution added till the solution was just red to phenolphthalein. One drop of dilute hydrochloric acid was added and the solution was evaporated to dryness under vaccuum. The sodium salt was suspended in benzene (3 ml.) and acetyl chloride (0.1 ml.) added and the mixture stirred overnight. The infra-red spectrum of the product showed it to contain some anhydride and some bicyclo (4,2,1) ketoolefin.

ν_{max} (film) (S.P. 200) 1810, 835 cm.$^{-1}$



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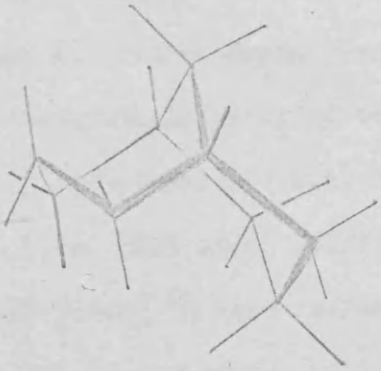

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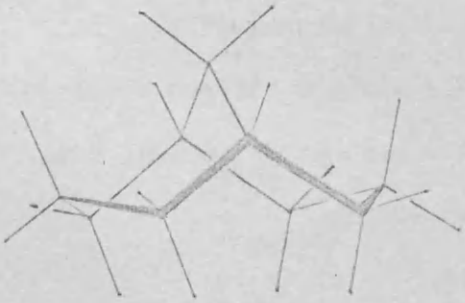

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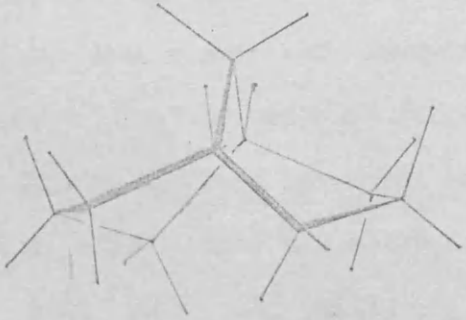


(48)

SECTION 2

2,6 - Interactions in the Bicyclo (3,3,1) nonane Skeleton.

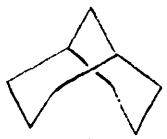
Introduction

From a study of molecular models one might surmise that there are four candidates for the preferred conformation of the bicyclo (3,3,1) nonane skeleton i.e. (45) to (48).

In the "twin-chair" conformation (45) there is serious interaction between the endo- hydrogens on C_3 and C_7. From Dreiding models the H-H internuclear distance is only 0.8Å, the C_3-C_7 distance being 2.52Å. That this is relieved at the expense of the ideal chairs was shown first by Martin et al [6a] and all later work [6c,d,e] has confirmed this finding.

Martin found that a flexed "twin-chair" conformation is adopted in the crystalline state and infra-red data suggests it is also the preferred conformation in solution. The C_3-C_7 distance was found from the X-ray analysis to have lengthened to 3.06Å resulting in a H-H distance of 1.8Å. The easing apart of these two centres is accomplished by distortion of the internal bond angles at C_2, C_3, C_4 and C_6, C_7, C_8, which have an average value of 114°, whereas the angles around C_1, C_5, and C_9 remain close to the tetrahedral value, being on average 110°. All future reference to a "twin-chair" conformation will unless otherwise stated refer to this flexed "twin-chair" conformation.

Another method of relieving the C_3, C_7 interaction is found in



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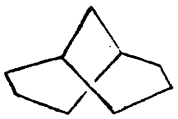

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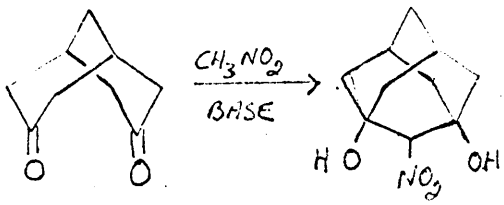
SCHEME 16



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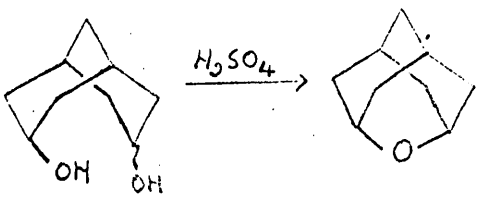

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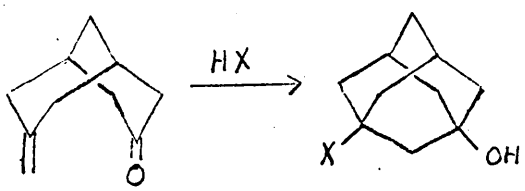

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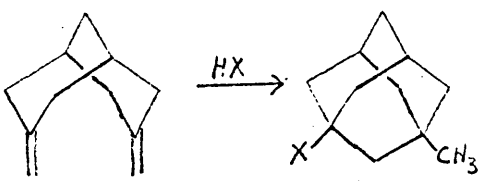

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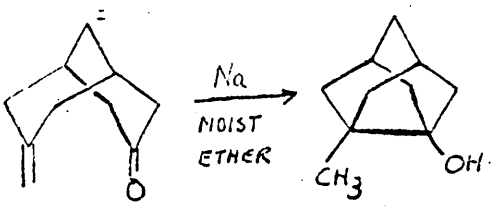


(53) (54)

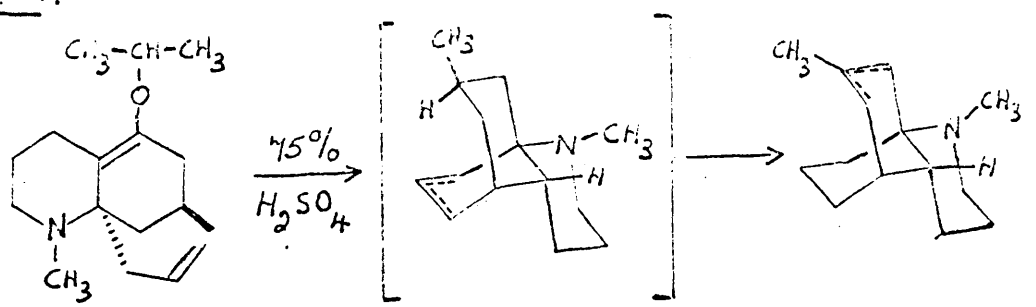
the "chair-boat" conformer (46). Several new interactions are also introduced i.e. a C_7, C_9 - hydrogen "flagpole" interaction (from a model, an H-H distance of 1.9Å) and C_3, C_6 - and C_3, C_8 - endo- hydrogen interactions (the H-H distance from a model being 1.9Å). These and the resulting C_1, C_8 and C_5, C_6 eclipsing interactions cannot be relieved by twisting of the boat due to the constraint of the other ring.

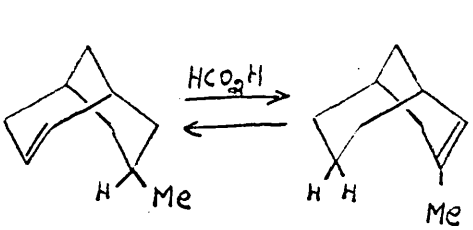
Forming both rings into a boat to give the "twin-boat" conformer (47) introduces two "flagpole" interactions (C_3, C_9 and C_7, C_9). Similarly eclipsing interactions between four pairs of carbon atoms are also introduced (C_1, C_2; C_4, C_5; C_5, C_6; and C_8, C_1). Two new hydrogen interactions in which the H-H distance is 2Å result at C_2, C_8 and C_4, C_6.

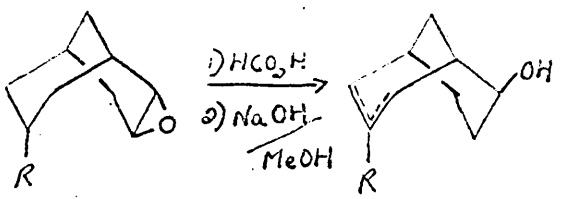
Rotation to relieve the interactions present in (47) result in the fourth conformer, the "twin-twist-boat" (48). Together with the somewhat lessened barriers experienced in the "twin-boat" a new interaction, that of the endo- hydrogens on C_2 and C_6 is found (from a model the H-H distance is 1.85Å).

Transannular reactions involving the two centres (C_3 and C_7) seen to be interacting in the "twin-chair" conformer have now been established. For example the first one, studied by Stetter and Tacke[24] involved the 3,7- dione (49) and diol (51) reacting to give adamantane derivatives, (50) and (52). (scheme 16). Stetter in later work[25] studied new syntheses of adamantane derivatives, (54)

SCHEME 17:

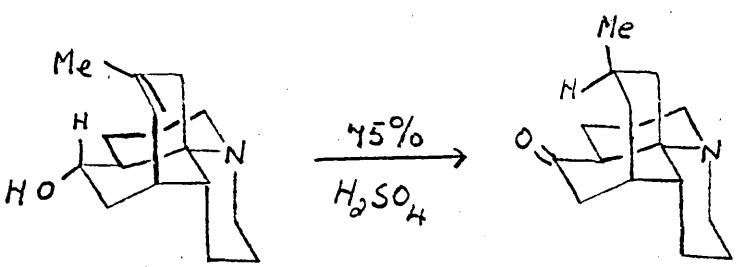




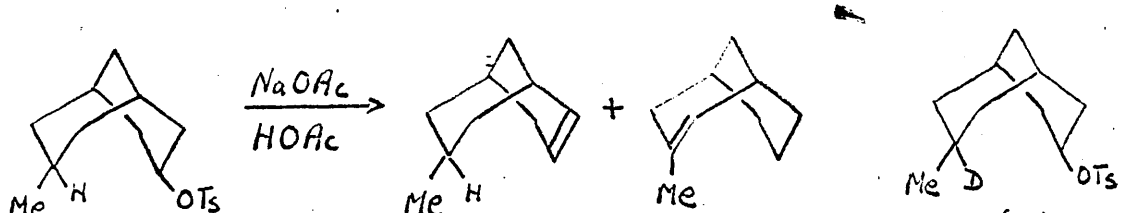


(58) R=H (60) R=H

(59) $R=CH_3$ (61) $R=CH_3$



SCHEME 18.



(62) (63) (64) (65)

44% 55%

and (56), from the 3-keto-7-exomethylene(53) and 3,7- diexomethylene (55) bicyclo (3,3,1) nonyl compounds. He showed that the diene formed stable π complexes with metal salts. Eakin, Martin and Parker[26] have also found a ring closure reaction between C_3 and C_7 in the 3-keto-7-exomethylene compound (53) when it is treated with sodium in moist ether. On this occasion a noradamantane, 3-hydrexy-7-methyl (57), was formed involving a direct bond between C_3 and C_7.

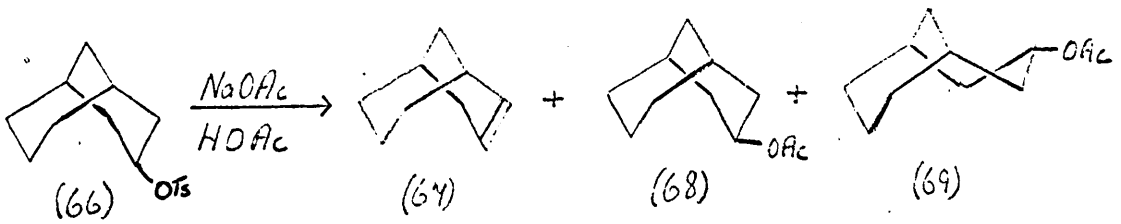
In scheme 17 are shown the cases[27-30] of hydride shift between C_3 and C_7 which have been found. In the work of Graham and co-workers[30] it was found that the presence of an oxygenated function at C_9 stopped the reactions (58) ⟶ (60) and (59) ⟶ (61) from occurring. No satisfactory explanation was put forward but the result did not seem to negate that C_3, C_7 hydride shift had occurred in the reaction.

All these preceding attempts have involved equilibrating conditions and from the evidence not much comment can be made on the relative stabilities of the possible transition states.

Eakin et al[31] studied the solvolytic behaviour of exo, exo-7-methylbicyclo (3,3,1) non-3-yl tosylate (62). In it from the relative proportions of disubstituted (63) and trisubstituted olefin (64) it was considered about 55% hydride shift had occurred. But interestingly the k_H/k_D ratio for acetolysis of the tosylate (62) and its deutero analogue (65) was unity suggesting that the hydride being transferred played no part in the rate determining step (scheme 18).

An attempt[32] has been made to determine the extent of C_3, C_7

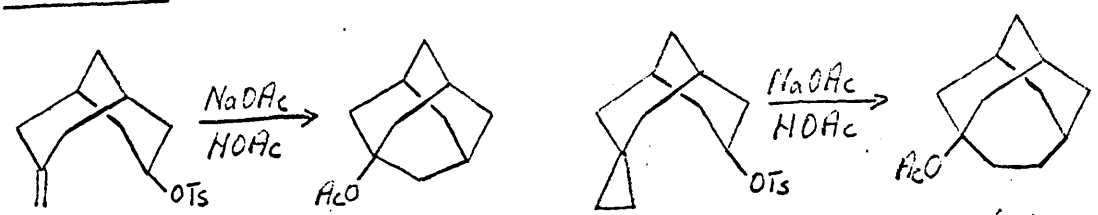
SCHEME 19



(66) (64) (68) (69)

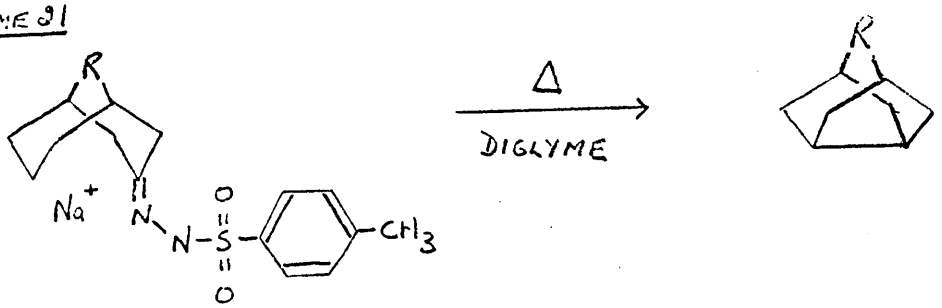
91% 3·6% 5·4%

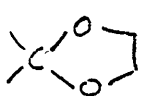
SCHEME 20



(70) (71) (72) (73)

SCHEME 21



R = $\overset{\cdot\cdot}{N}-CH_3$, $\overset{\cdot\cdot}{C}H_2$, 

hydride shift under kinetically controlled conditions during the acetolysis of exo-3-bicyclo (3,3,1) nonyl tosylate (66) (scheme 19). In the major product, bicyclo (3,3,1) non-2-ene (67), less than 5% hydride shift has been found. Work is in progress[33] to determine the percentage hydride shift in the minor products, exo-3-acetate (68) and endo-3-acetate (69).

These last two pieces of work suggest that under kinetic control the conformation of the C_3 carbonium ion and the transition state leading to it may not be twin-chair but in fact be twin-twist-boat.

Another example of reaction between C_3 and C_7 has been found by Eakin, Martin and Parker[34] in the acetolysis of the olefinic tosylate (70) and the cyclopropyl tosylate (72). The rates of reaction were also measured and showed the expected rate enhancement over the parent exo- bicyclo (3,3,1) non-3-yl tosylate (66) (scheme 20).

Formation of a noradamantane skeleton has been reported in two cases[35,36] where carbene insertion has occurred between C_3 and C_7 (scheme 21).

Many of the above reactions appear to be occurring through a transition state similar to that of the ground state conformer. Intermediacy of other conformers must be considered but as yet no comprehensive quantitative relationship between the four possibilities has been produced. From an examination of models and the non-bonded interactions therein the conformers (45-48) may be arranged in a relative stability order of "twin-chair" of lowest energy, followed

(45)

TWIN-CHAIR

(46)

CHAIR-BOAT

(47)

TWIN-BOAT

(48)

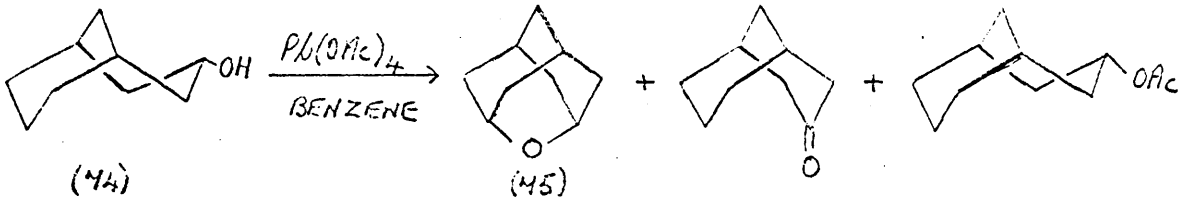
TWIN-TWIST-BOAT.

by "twin-twist-boat" and "chair-boat" of comparable value with "twin-boat" having the highest relative energy, although this qualitative picture has very little observed or calculated quantitative basis.

As a result of calculations carried out on bicyclo (3,3,1) nonane itself Marvell et al[37] have calculated a ΔH^{o} value 3.7 kcals/mole as a measure of the stability of the "twin-chair" conformation with reference to the "chair-boat". An experimental ΔG^{o} value from the same authors of 2.5 kcals/mole (362°K) supports the previous figure although suggests it is a little high. To examine the corresponding conformational preference of bicyclo (3,3,1) nonan-2-one they also performed calculations on the bicyclo (3,3,1) non-2-yl cation giving the ΔH^{o} of the "twin-chair" as 2.7 kcals/mole more stable than the "chair-boat" conformer (sp^2 carbon in the boat ring). This analogy of a carbonium ion to a carbonyl group is not very satisfactory and they suggest that an examination of 1,4-cyclohexanedione is more relevant. Here it can be shown that the introduction of a ketone group to replace a methylene group reduces the energy difference between boat and chair by a factor of approximately 3 kcals/mole. Hence taken with the ΔG^{o} figure of 2.5 kcals/mole in the saturated compound it may well be that bicyclo (3,3,1) nonan-2-one marginally prefers to exist in the "chair-boat" conformation (the ketone group being in the boat ring).

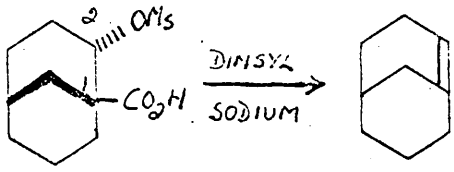
From this short examination of the energetics of the bicyclo (3,3,1) nonyl system it can be seen that the various conformers

SCHEME 22

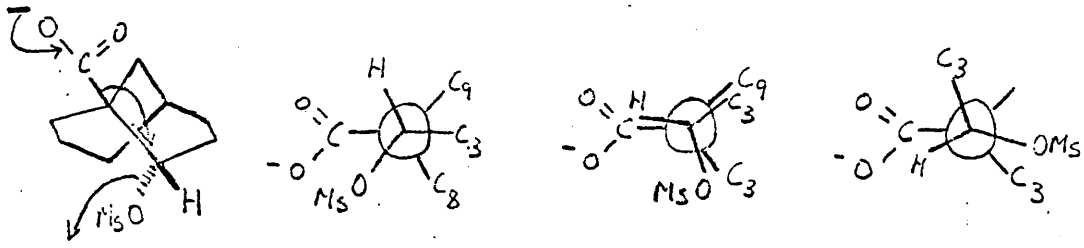


(74) (75) (89%) 6% 4·4%

SCHEME 23.

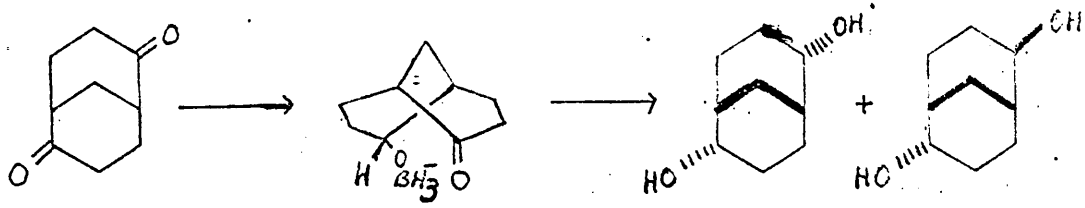


(76) (77)



(78) (79) (80) (81)

SCHEME 24



(82) (83) (84) (85)

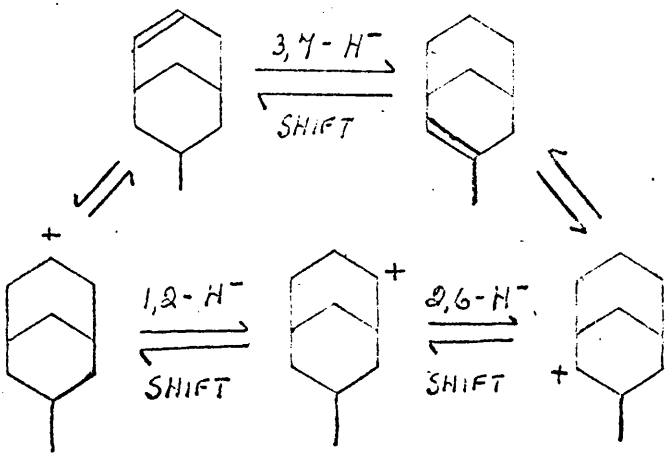
can easily be of comparable energy.

In the case where the evidence[38,39,40] tends to support a "chair-boat" conformation in the ground state of endo- bicyclo (3,3,1) nonan-3-ol (74), its reported[40] oxidation with lead tetraacetate gives predominately oxaadamantane (75) which obviously requires the "twin-chair" conformation in the transition state. (scheme 22).

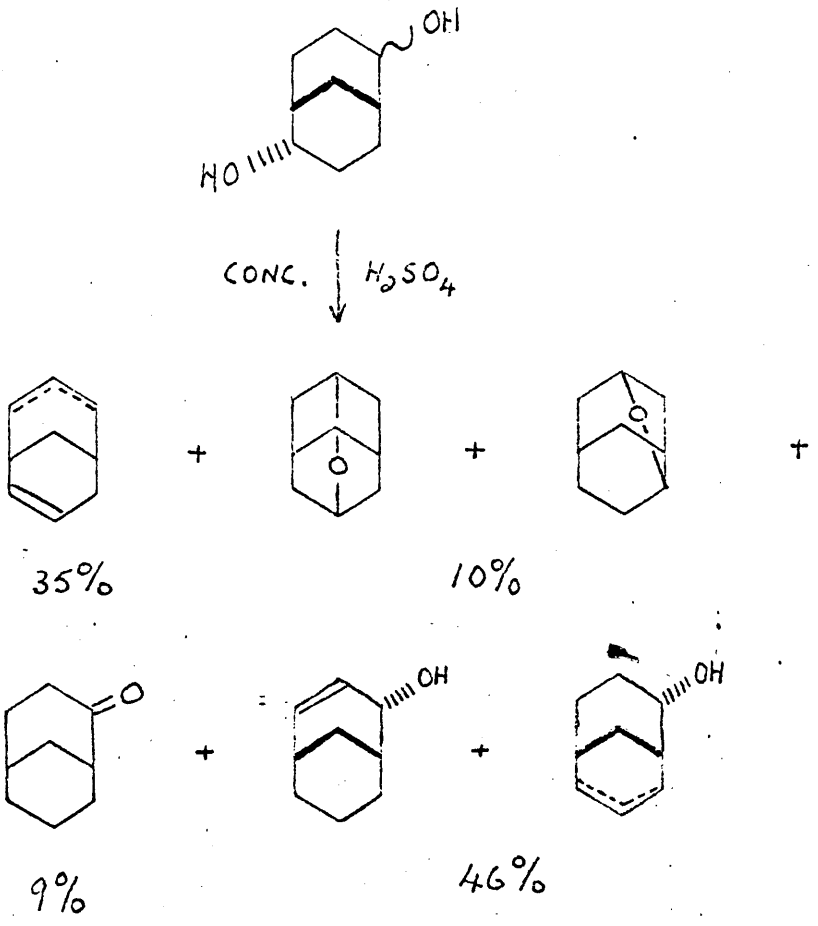
Indirect evidence for the intermediacy of the "twin-twist-boat" conformer during reaction has como from two studies. In the formation of bicyclo (3,3,1) non-1-ene (76) from the mesylate of endo-2-hydroxybicyclo (3,3,1) nonane-1-carboxylic acid (77) Marshall and Faubl[41] pointed out that the best bond alignment for the base induced fragmentation would occur in the "twin-twist-boat" conformation (78) (scheme 23). This is clarified by looking at a Newman projection diagram of the situation along the bond between C_2 and C_1 in the three conformations "twin-chair" (79), "chair-boat" (80) (the boat containing the mesylate group) and "twin-twist-chair"(81).

Schaefer and Honig[42] obtained two alcohols from sodium borohydride reduction of bicyclo (3,3,1) nonan-2,6-dione (82). Without any further evidence or their stereochemistry proved these alcohols were assumed to be endo, endo- 2,6 diol (84) and exo, endo- 2,6-diol (85). The rationale for the formation of the exo, endo- epimer was that the initially formed alkoxyborohydride (83) (produced by preferential[43] exo- attack of hydride) assumed the "twin-twist-boat" conformation before reduction of the second carbonyl group (scheme24).

SCHEME 25.



SCHEME 26



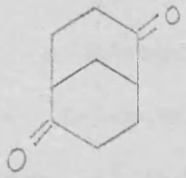
These postulates of "twin-twist-boat" transition state conformations in reactions involving 2- (and 2,6-) substituted bicyclo (3,3,1) nonanes coupled with the recent evidence[44,45,46] pointing to simple cyclohexyl derivatives reacting with "twist-boat" transition states prompted a number of questions.

(i) Is it possible to have C_2, C_6 transannular reactions? e.g. an alternative scheme for the intereonversion of (86) and (87) could involve 2,6- hydride shift (scheme 25).

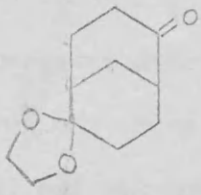
(ii) In suitably substituted compounds is it possible for substitution on C_6 to affect reactions at C_2 i.e. is their neighbouring group participation between C_6 and C_2?

(iii) Is it possible that simple 2- derivatives could proceed via the "twin-twist-boat" conformation?

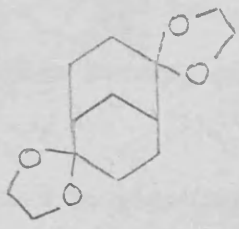
Schaefer[42] had re-examined the earlier work of Meerwein[47] on the dehydration of 2,6- diol(s). He obtained the results shown in scheme 26 and examined the products from the hexadeuterated diol(s). This led him to various conclusions involving the reactivity of the bicyclo (3,3,1) non-2-yl cation. It was felt that this was not satisfactory as the reaction conditions involved did not provide a subtle enough control of the reactive intermediates. This prompted us to prepare a series of 2,6- disubstituted derivatives which might shed light on the Schaefer propositions and also on the possible 2,6- interactions in the ring system.



(87)



(88)



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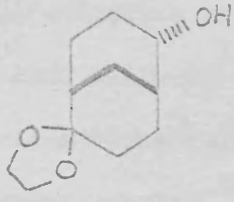
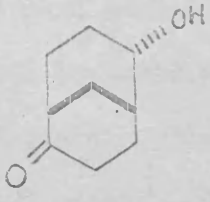


(90)



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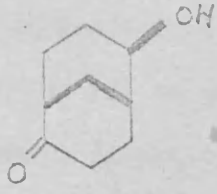


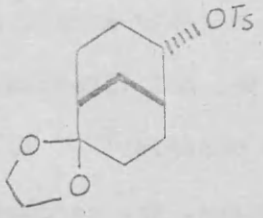
(92)

DISCUSSION

Since Meerwein's classic work on bicyclo (3,3,1) nonane compounds[48], the 2,6 diketone (82) has been readily available. For the present work it was prepared employing the modifications of Meerwein's method reported by Stetter[49] and Schaefer[42]. To permit selective manipulation of the 2 and 6 positions, the monoketal (88) was formed by treating the dione with 1.1 molar equivalent of ethylene glycol and a catalytic amount of p-toluenesulphonic acid in refluxing benzene under a Dean and Stark apparatus to remove the water being formed. The desired monoketal was readily separated from unreacted starting material and diketal (89) by column chromatography on alumina.

By analogy with the hydride reduction of bicyclo (3,3,1) nonan-2-one[43], lithum aluminium hydride reduction of the monoketal (88) gave preferentially the endo- hydroxyketal (90). That this stereochemical assignment is correct is substantiated by the proton magnetic resonance spectra of the corresponding acetate and tosylate (see Appendix 1). Deketalisation of (90) using p-toluenesulphonic acid in refluxing acetone[50] followed by column chromatography gave the endo- ketol (91) as a waxy solid.

The synthesis of the corresponding exo-ketol (92) proved to be a more difficult operation. Treatment[51] of endo-2-bicyclo (3,3,1) nonyl tosylate with 90% aqueous dimethylformamide for 68 hrs. at 78°C followed by lithium aluminium hydride treatment of the



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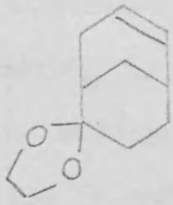

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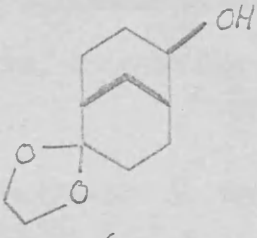

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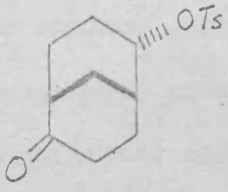

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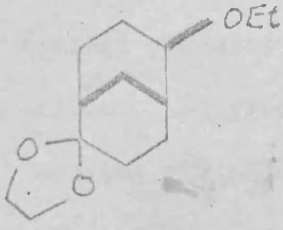
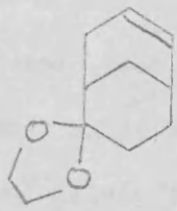


(97)

resulting mixture of olefin and formate results in an acceptable yield of the exo- alcohol[52]. The endo- ketal tosylate (93) proved to be remarkably resistant to this inversion procedure and after double the time about 80% of the tosylate still remained, the products being a mixture thought to include some resulting from deketalisation. Complete conversion to a mixture of olefin (94) and the exo- alcohol (95) was eventually achieved by treatment of the tosylate at 78°C for 96 hrs. with 90% aqueous dimethylformamide in the presence of 1.1 molar equivalents of sodium acetate, followed by lithium aluminium hydride reduction of the isolated olefin and ester mixture. That the water was a necessary reagent was shown by recovery of a large amount of unreacted tosylate from a reaction using a 5 molar excess of sodium acetate in 100% dimethylformamide at 78°C for 120 hrs. Attempts at inversion of the 2-tosylate had also been made on the 6-keto-endo-2-tosylate(96). Here treatment of the ketotosylate in 98% aqueous dimethylformamide at 78°C for 72 hrs. did not bring about any change. The ketotosylate was also returned substantially unchanged from two other treatments one involving 98% dimethyl-formamide at 100°C for 40 hrs. This lack of reactivity was also experienced in acetolysis of this tosylate and this will be discussed in a later section of the thesis.

As an alternative approach, the ketalolefin (94) was prepared from the corresponding tosylate (93) by refluxing under N_2 with sodium ethoxide in ethanol. Some of the corresponding ketal ethyl ether (97) (of unknown stereochemistry but presumed to be exo- from



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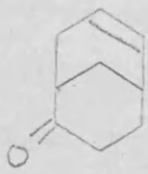

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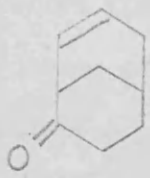

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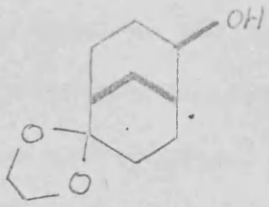

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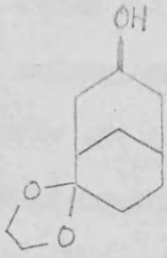

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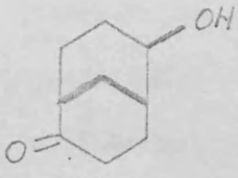

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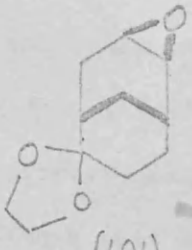
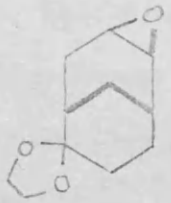


(101)

mechanistic considerations) was also formed but was readily removed by chromatography. That no rearrangement had taken place during the elimination was shown when the ketalolefin (94) was transformed to the ketoolefin (98) using p-toluene sulphonic acid in refluxing acetone. The ultraviolet spectrum of this compound (λ_{max}^{EtOH} 295 nm (ϵ19.8), λ_{max}^{hexane} 294 nm (ϵ19.8)) compared well to the value (λ_{max} 293 nm.(ϵ15)) quoted by Marvell et al[37] for the compound and was markedly dissimilar to the bicyclo (3,3,1) non-7-ene-2 one (99) value (λ_{max} 301 nm (ϵ198)) also from the same authors. This ketoolefin could also be hydrogenated to bicyclo (3,3,1) nonan-2-one identical in all respects with an authentic sample[54].

Hydroboration[55] of bicyclo (3,3,1) non-2-ene is known[39,43] to proceed by addition from the exo- (more exposed) face of the double bond, so hydroboration/oxidation of (94) was carried out to yield a mixture of alcohols (95) and (100) but it proved impossible to separate these by column chromatography.

The observation in the literature[56] that lithium aluminium hydride reduction of exo- 2,3 - epoxybicyclo(3,3,1) nonane gave the exo- 2-alcohol in high yield provided the third and happily successful route to the exo- ketol (92) series. Treatment of the ketal olefin (94) with m- chloroperbenzoic acid gave the exo- epoxide (101) which on careful treatment with lithium aluminium hydride gave the exo-2-hydroxyketal (95) in high yield (see Appendix 1 for proof of configurational assignment). In passing it should be mentioned that prolonged heating under reflux of the



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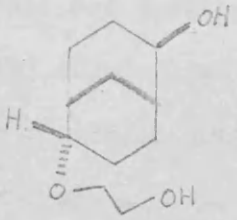
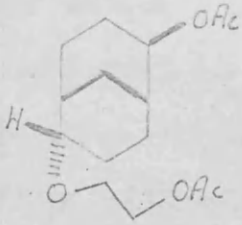


(102)



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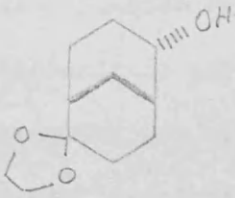
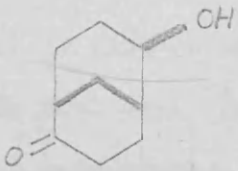
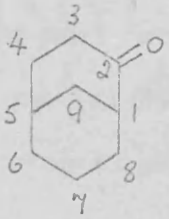


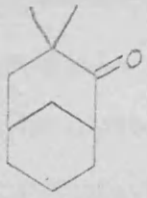
(90)



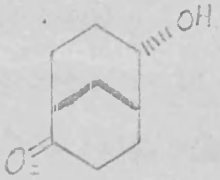
(92)



(104)



(105)



(91)

epoxide (101) with lithium aluminium hydride gave a product whose spectral properties etc. suggested a diol structure (102). Confirmation of this was found in the properties of its diacetate (103). This unexpected cleavage of the ketal moiety was also experienced when the endo-2-hydroxyketal (90) was treated under similar forcing conditions.

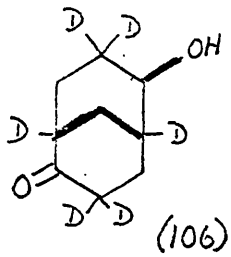
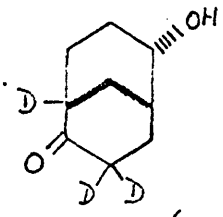
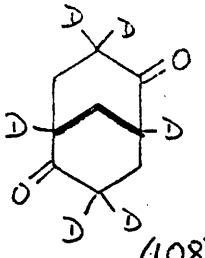
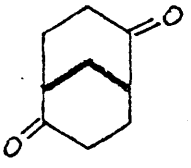
Deketalisation of the exo-2-hydroxyketal under the same exchange conditions as mentioned above gave the exo-2-ketol, (92) once again as a waxy solid (see Appendix 1 for proof of configurational assignment).

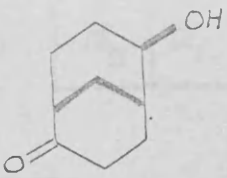
Schaefer and Lark[57] have reported that bicyclo (3,3,1) nonan-2-one incorporates up to 3 atoms of deuterium per molecule when heated at 95° in D_2O containing 0.1M NaOD and have shown that the exchangeable protons are those situated at C_1 and C_3 (104). Marvell and his coworkers[37] have measured the rate of exchange of the bridgehead proton in (105) using NaOMe/MeOD and found that at 100.8° this proceeds with a rate equal to 0.67×10^{-4} l./mole sec. They pointed to these results and Schaefer's as indicating that the rates of exchange of protons at C_3 and C_1 are comparable, hence giving strong indication (prior to its synthesis[41,58]) that bicyclo (3,3,1) non-1-ene should be a relatively stable entity.

It was therefore expected that the endo- ketol (91) should show at least an uptake of 3 deuteria when treated with NaOD/D_2O/ Dioxan and this was in fact the case (Table 3). The incorporation is clean cut and there is practically no more than 3 deuteria

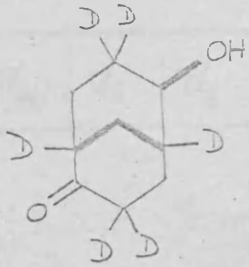
TABLE 3.

% DEUTERIUM CONTENT

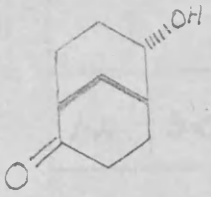
	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	D/MOL.
 (106)	0·4	0·9	1·1	2·8	9·2	29·7	55·1	0·6	5·33
 (104)	1·4	3·0	19·3	74·5	0·8	0·4	0·6	—	2·74
 (108)	2·0	0·3	2·0	5·2	14·9	38·0	37·6	—	4·95
 (82)	85·2	0·4	9·1	0·8	1·3	1·7	1·5	—	0·43



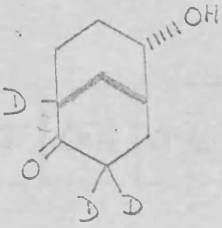
(92)



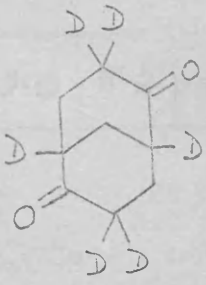
(106)



(91)



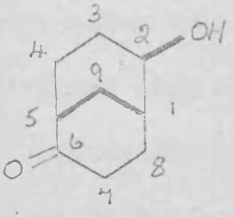
(107)



(108)

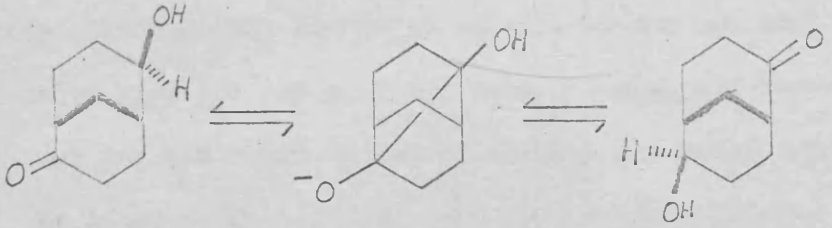
incorporated. (The workup procedure ensured that all -O-D was exchanged to -O-H before any measurements were made on the ketol). However on similar treatment the exo- ketol (92) incorporated 6 deuteria (Table 3). That the ketols were returned unchanged except for deuterium incorporation was shown by spectral and physical properties. In the infra-red spectrum of the deuterated exo-ketol (106) the C-O stretching vibrations which are different in position and intensity from the non-deuterated exo-ketol (92) superficially resembled those of the endo- epimer. As this was the only major difference in the infra-red spectra it was at first thought that epimerisation had taken place i.e. (91) to (92). This could be discounted however when it was found that the exo-ketol (92) was recovered uncontaminated by (91) on treatment with $NaOH/H_2O$/Dioxan. The change in infra-red spectrum on proceeding from exo-ketol (92) to the deuterated analogue (106) must arise from changes in the group frequencies involving the C-O bond and the surrounding C-D bonds. This is borne out by the fact that in proceeding from endo-ketol (91) to its deuterated analogue (107) no substantial change in the infra-red spectrum is observed, the difference between (106) and (107) being that in (106) the C-O bond is surrounded by C-D bonds.

The position of the "extra" deuterium atoms in the deuterated exo-ketol (106) was established by oxidising the deuterated ketol to the corresponding dione (108) (no. of D per molecule = 4.95, Table 3) and then treating this deuterated dione with sodium hydroxide in aqueous methanol. The resultant dione had virtually no deuterium

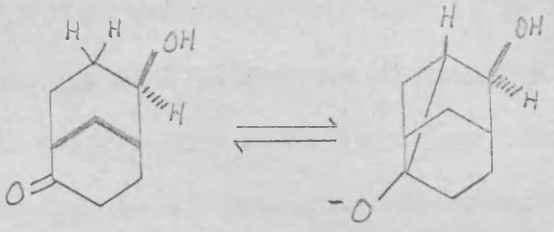


(92)

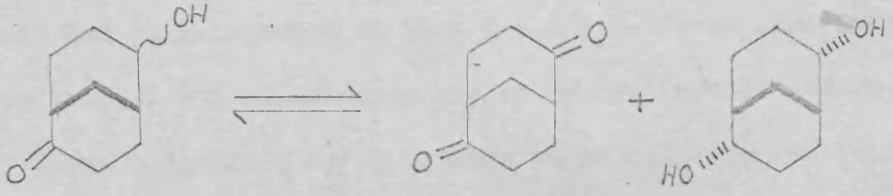
SCHEME 27.



SCHEME 28



SCHEME 29



(91) AND/OR (92) (82) (84)

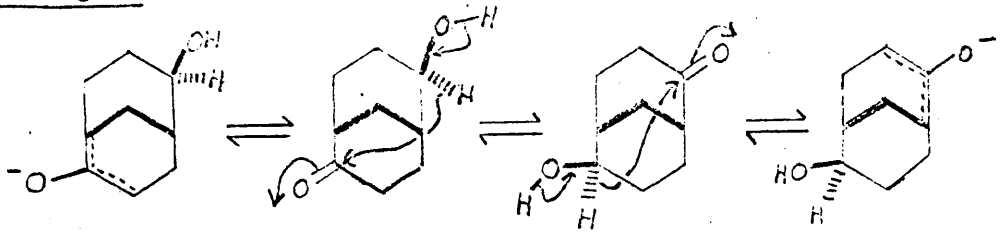
(No. of D per molecule, 0.43, Table 3) and that which it had could easily be explained in terms of percentage exchange which had taken place under the conditions. The extra deuteria are therefore located on C_1 and C_3 and hence a mechanistic pathway must be available to (92) which permits exchange of the protons on C_1 and C_3 in addition to those at C_5 and C_7.

A homoenolisation mechanism[59] would allow this extraordinary incorporation of deuterium although the experimental conditions used here are much less drastic than those required to bring about homoenolisation with camphenilone 59. A mechanism involving homoenolisation at C_2 (scheme 27) would however require the incorporation of 7 not 6 deuteria. Both the mass spectrum and p.m.r. spectrum (which shows a signal for 1 proton at the value expected for $>$ C<u>H</u>OH) of the deuterated <u>exo</u>-ketol (106) preclude the operation of this homoenolisation process.

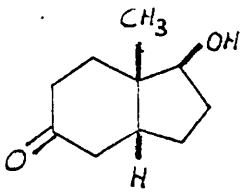
On the other hand a homoenolisation process involving C_3 is possible (scheme 28) but this would require the maximum number of deuteria incorporated to be 5. Hence this possibility can also be excluded.

An entirely different pathway invplving a bimolecular reduction/oxidation process (scheme 29) would also explain the incorporation. However this can be discounted since the <u>exo</u>-ketol (92) is not converted to the <u>endo</u>-epimer (91) under the experimental conditions and in addition no trace of either (91) or (92) could be detected in a control experiment using an equimolar mixture of dione (82) and diol (84)[42].

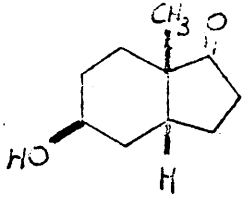
SCHEME 30.



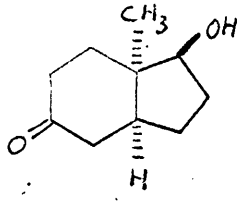
(92) (92)



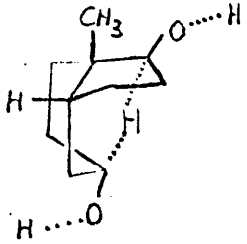
(109)



(110)



(111)



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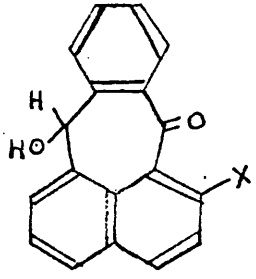
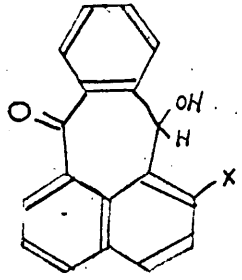


(113)



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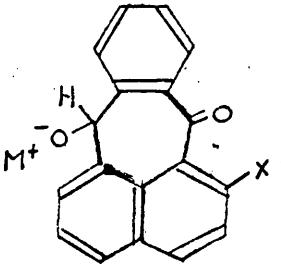


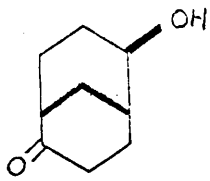
(115)

Hence the evidence to date is consistent with a stereospecific base induced intramolecular 2,6-hydride shift occurring in the exo-ketol (92) in addition to the normal keto-enol exchange process (scheme 30). It is noteworthy that two similar processes have been described in the recent literature.

Acklin and Prelog[60] have reported that (1S,8S)-1-hydroxy-8-methyl-cis-hydrindan-5-one (109) was isomerised to (5S,8S)-5-hydroxy-8-methyl-cis-hydrindan-1-one (110) by absorbing it on Grade I neutral alumina and eluting it with ether. The diastereoisomer of (109), (1S,8R)-1-hydroxy-8-methyl-cis-hydrindan-1-one (111), was returned unchanged from a similar treatment and so it was deduced that the conversion of (109) to (110) had taken place by an intramolecular 1,5-hydride shift involving the transition state depicted in (112).

Lansbury and Saeva[61] have unearthed a corresponding transannular hydride shift in 1- substituted 7- hydroxy -12(7H)-pleiadennones (113) which when treated with alkali metal t-butoxides in dimethylsulfoxide rearrange to 1- substituted-12-hydroxy-7(12H)-pleiadenones (114). In this instance, by using nuclear magnetic resonance spectroscopy, they have been able, for the first time, to obtain activation parameters for a hydride shift. The data show that the rate-determining transannular hydride transfer occurs in the initially formed alkoxide (115) and has an activation energy of approximately 24 kcal./mole. with a negligible entropy of activation.

By studying a suitably substituted exo-ketol (92) and th



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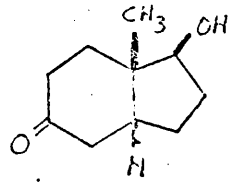

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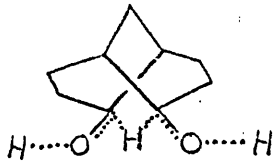

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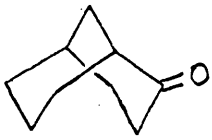

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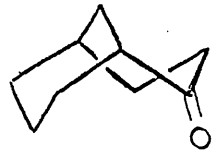

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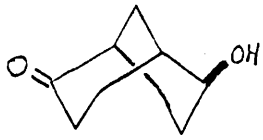
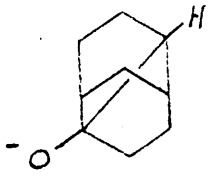
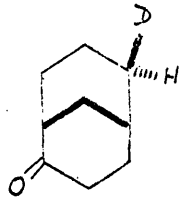


(119)

(120)



(121)



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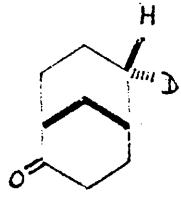

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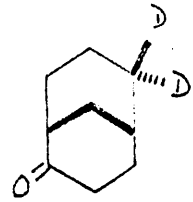


(124)

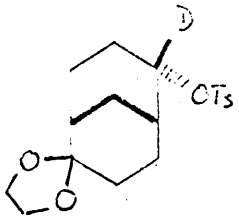
isomerisation found by Prelog[60] using infra-red spectroscopy it should be possible to obtain comparable thermodynamic data for the hydride shift of (92) and (109) and hence gain some insight into hydride shift as a function of molecular geometry for the first time.

However in terms of the original brief of this part of the thesis an interaction between C_2 and C_6 has been positively identified. This hydride shift demands as its most favourable geometry a twin-twist-boat conformation of the transition state (116).

Marvell[37] has suggested that there may be very little difference between the twin-chair (117) and chair-boat (118) conformations in the ground state of bicyclo (3,3,1) nonan-2-one. By analogy one might surmise that the preferred ground state of the exo-ketol (92) would be either twin-chair (119) or chair-boat (120). Certainly from nuclear magnetic resonance data (see Appendix 1) the cyclohexanol part of this ring system seems to adopt a chair conformation. In any event the reaction coordinate for the exchange must involve a conformational change from either (119) or (120) to the twin-twist-boat of the transition state.

With this evidence in hand a series of interesting questions then came to mind.

Is it possible to bring about specific homoenolisation[59] involving C_2 and C_6 i.e. is formation of (121) a possibility? To examine this problem the monodeutero-ketones (122) and (123) and the dideutero-ketone (124) were required. The deutero-ketal tosylate (125) was readily obtained by lithium aluminium deuteride reduction



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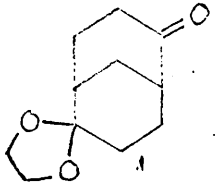
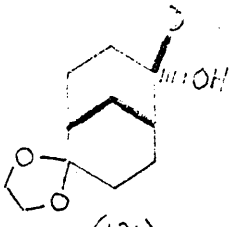


(88)



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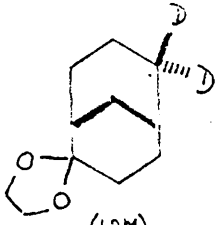
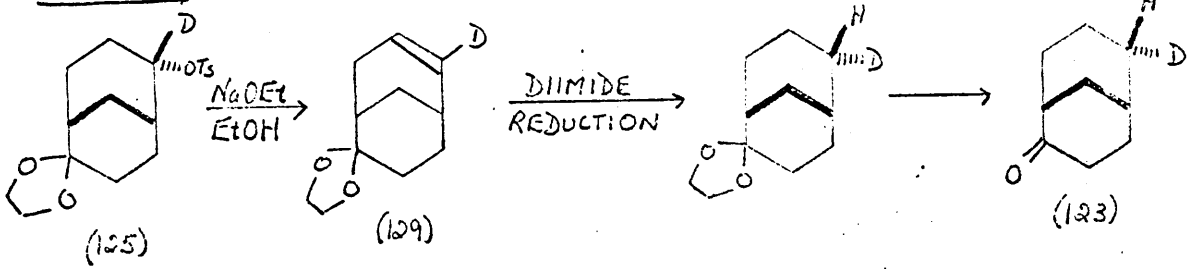


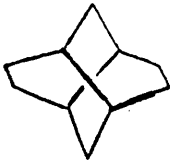
(124)

(128)

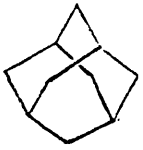
SCHEME 31.



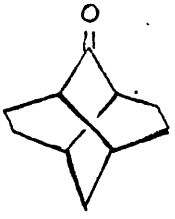
(125) (129) (123)



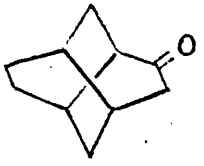
(130)



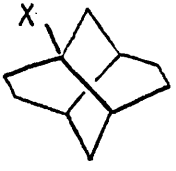
(131)



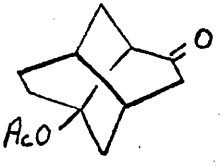
(132)



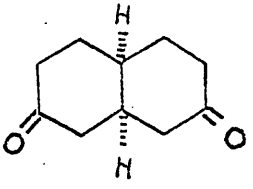
(133)



(134) X = -OH
-NH_2
-CO_2H



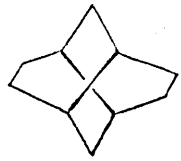
(135)



(136)

of ketalketone (88) and tosylation of the alcohol (126). However it proved impossible to convert (125) into the dideutero-ketal (127) with lithium aluminium deuteride in refluxing ether, tetrahydrofuran or dioxan. All of these reaction conditions are known to convert the simple endo-2-tosylate (128) into a separable mixture of bicyclo (3,3,1) nonane and bicyclo (3,3,1) non-2-ene. This negative evidence suggests a steric retardation to an S_N2 process on C_2 when C_6 is substituted (see later). An alternative synthetic approach to (123) involving a diimide reduction of the deutero-olefin (129) formed from the deutero-tosylate (125) remains to be examined but is illustrated in scheme 31.

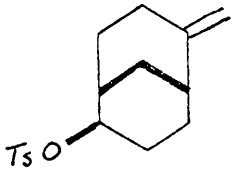
A further avenue for examining 2,6- interactions stemmed from the current interest in twistane chemistry. Twistane (130), tricyclo $(4,4,0,0^{3,8})$ decane, which is the twist-boat isomer of adamantane (131) was first synthesised by Whitlock[62] via twistan-2-one (132). Later Whitlock and Siefken[63] studied the rearrangement of twistane and its derivatives to adamantane and its derivatives. A new shorter synthesis of twistane was reported by Gauthier and Deslongchamps[64] who made it via twistan-4-one (133). 1-substituted derivatives (134) of twistane were formed by Deslongchamps and coworkers[65] from 8-acetoxytwistan-4-one (135)[66], which was synthesised in an analogous manner to twistan-4-one (133), by homoenolacetylation of a decalindione (136). Finally optically active twistane has been synthesised by Adachi, Naemura and Nakazaki[67] using a modified version of Whitlock's route[62] from



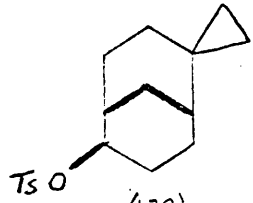
(134)

(70)

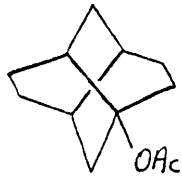
(72)



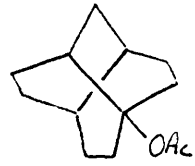
(138)



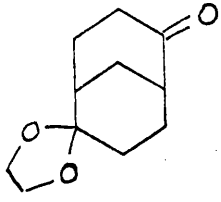
(139)



(140)



(141)



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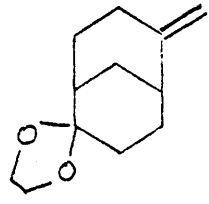


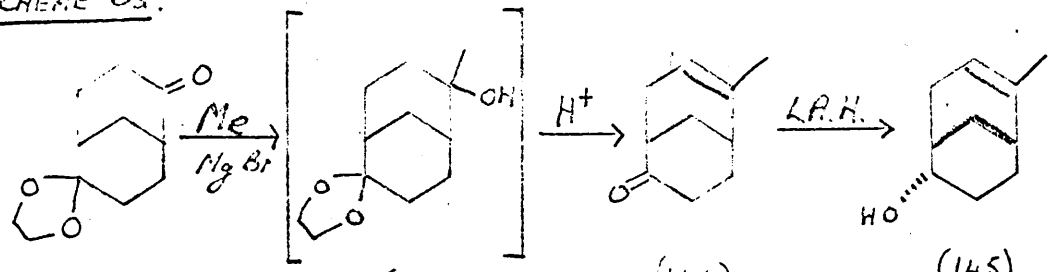
(142)

optically active precursors. (+)- Twistane has the absolute stereochemistry shown in (137) and a surprisingly large notation α_D^{22} + 414° (C, 0.489 in EtOH).

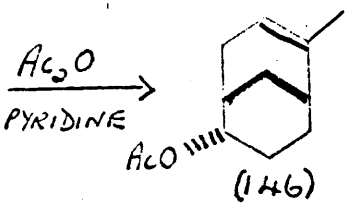
As has been described earlier (p.18) the 7-exo-methylene-3-tosylate (70) and the 7-cyclopropyl analogue (72) are known to undergo facile ring closure to adamantane and homoadamantane derivatives respectively. It was felt that the corresponding 2,6-substituted compounds (138) and (139) could well give rise on acetolysis to an interesting pair of twistane derivatives (140) and (141) particularly relevant to Schleyer's calculations and work on bridgehead reactivity[68]. As an initial attempt in the synthesis of (138) the conversion of the ketalketone (88) to the ketal-exo-methylene derivative (142) was attempted using triphenylphosphonium methylene ylid generated from triphenylphosphonium methylene bromide by either n-butyl lithium[69] or dimsyl sodium[70]. Neither method gave the desired olefin, the first one giving mainly starting material unchanged and the second starting material and a mixture of other compounds some of which may be olefinic (infra-red spectrum). An alternative method for the synthesis of exo-methylene compounds has been described by Cainelli et al[71]. Treatment of the ketalketone (88) with methylene magnesium iodide in the manner they describe failed to give the required exo-methylene compound; largely ketonic material being returned (infra-red spectrum).

In a final attempt to obtain an exo-methylene derivative endo-1-acetoxy-6-methylbicyclo (3,3,1) non-6-ene (146) was prepared from

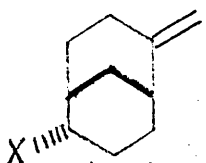
SCHEME 32.



(88) (143) (144) (145)

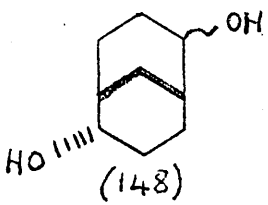


(146)

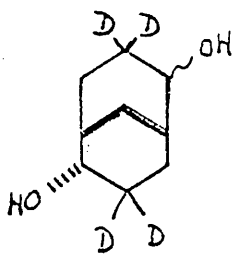


(147) X = -OH α-OAc

SCHEME 33

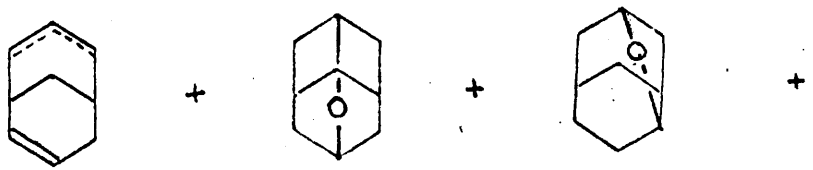


(148)

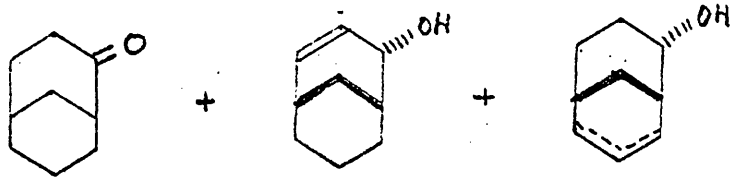


(149)

AQUEOUS H_2SO_4



35% 10%

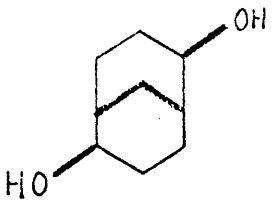


9% 46%

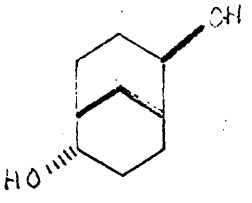
the ketalketone (88) as shown in scheme 32. After the initial Grignard the intermediate ketalalcohol (143) was simultaneously dehydrated and deketalised to give the keto olefin (144). This was transformed to the acetate (146) by acetylation of the alcohol (145) formed from lithium aluminium hydride reduction. Treatment of the acetate (146) with dry hydrogen chloride in ether at -70° followed by heating at 60° with potassium triethylmethoxide failed to give the exo-methylene derivative (147) (infra-red spectrum) although the structures of the products are not immediately obvious. This method had been used by Brown and Acharya[72] to prepare exo-methylene compounds from methylolefins in high yield.

As yet these reactions have not been performed on bicyclo (3,3,1) nonan-2-one and hence no relevant comment can be made on the lack of reactivity of the ketalketone. It is perhaps relevant though that bicyclo (3,3,1) nonan-3-one does not react with Grignard reagent and alkyl lithiums nor does it form an enamine[73] and that this has been attributed to steric compression caused by the C_3, C_7 proximity.

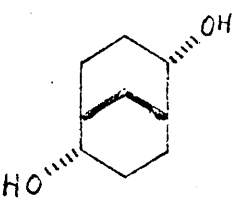
Schaefer[42] has reexamined the work of Meerwein[47] on the dehydration of bicyclo (3,3,1) nonan-2,6-diols (148) using sulphuric acid (scheme 33). From the deuterium content of the products from dehydration of the tetradeuterated bicyclo (3,3,1) nonan-2,6-diols (149) there is evidence to implicate C_1,C_2-, C_2,C_8-, and C_3,C_7-hydride shifts in the mechanistic pathways to the dehydration products.



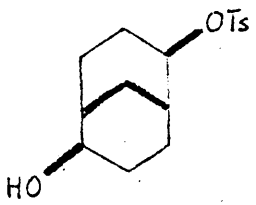
(149)



(85)



(84)



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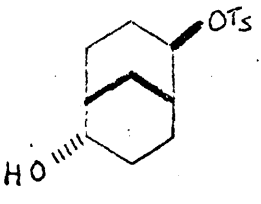

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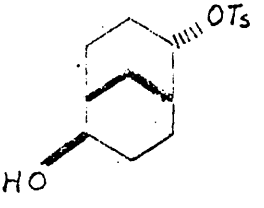

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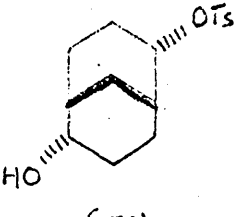

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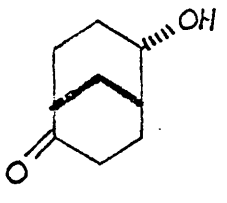
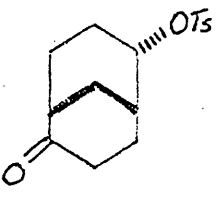
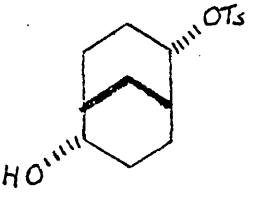


(91)



(96)



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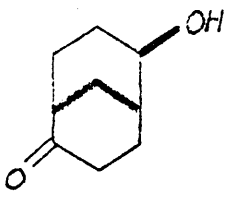
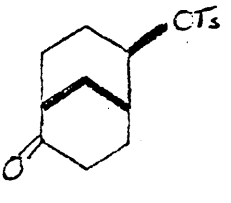
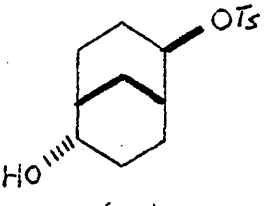


(92)



(154)



(151)

Our interest in 2,6- interactions prompted alternative explanations for the observations. It also seemed likely that more information would be forthcoming if these reactions were performed under controlled (solvolytic) conditions using pure stereoisomers rather than (a) working with an unspecified mixture of stereoisomers[42] and (b) using strong equilibrating conditions[42].

In this context it should be noted that bicyclo (3,3,1) nonan-2,6-diol can exist in three isomeric forms exo-, exo- (149) exo-, endo- (85) and endo-, endo- (84), and consequently to study all the possible variations of 2-tosylate orientation with a 6-hydrexyl group requires the syntheses of four tosylates.

viz. exo-6-hydroxy-exo-2-tosylate (150)

endo-6-hydroxy-exo-2-tosylate (151)

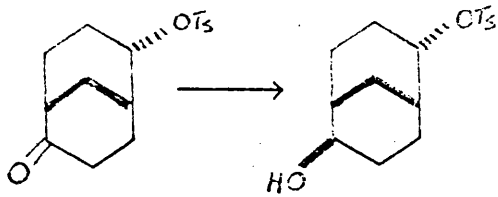
exo-6-hydroxy-endo-2-tosylate (152)

endo-6-hydroxy-endo-2-tosylate (153)

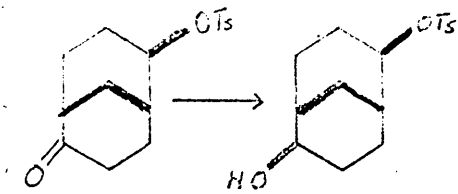
Accordingly, treatment of the endo-ketol (91) with p-toluenesulphonyl chloride in pyridine gave the corresponding keto-tosylate (96) and subsequent reduction with either sodium borohydride in tetrahydrofuran or lithium aluminium hydride in diethyl ether gave the endo-6-hydroxy-endo-2-tosylate (153) as a crystalline solid. Once again the proton magnetic resonance signal confirmed the stereochemical assignment (Appendix 1).

Corresponding treatment of the exo-ketol (92) with p-toluenesulphonyl chloride gave the keto -tosylate (154). Treatment of this derivative with lithium aluminium hydride gave,

SCHEME 34.

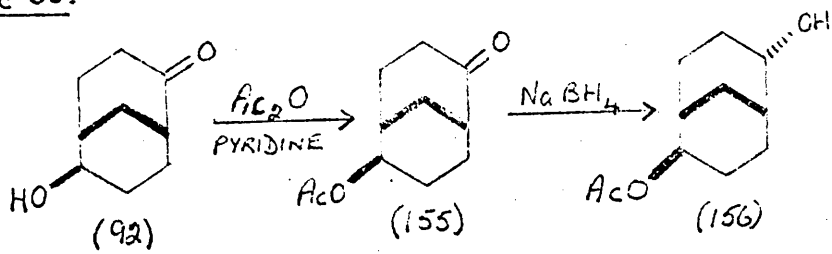


(96) (152)

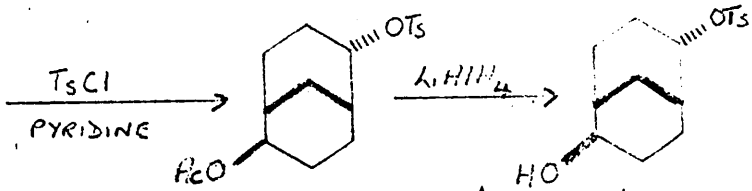


(154) (150)

SCHEME 35.

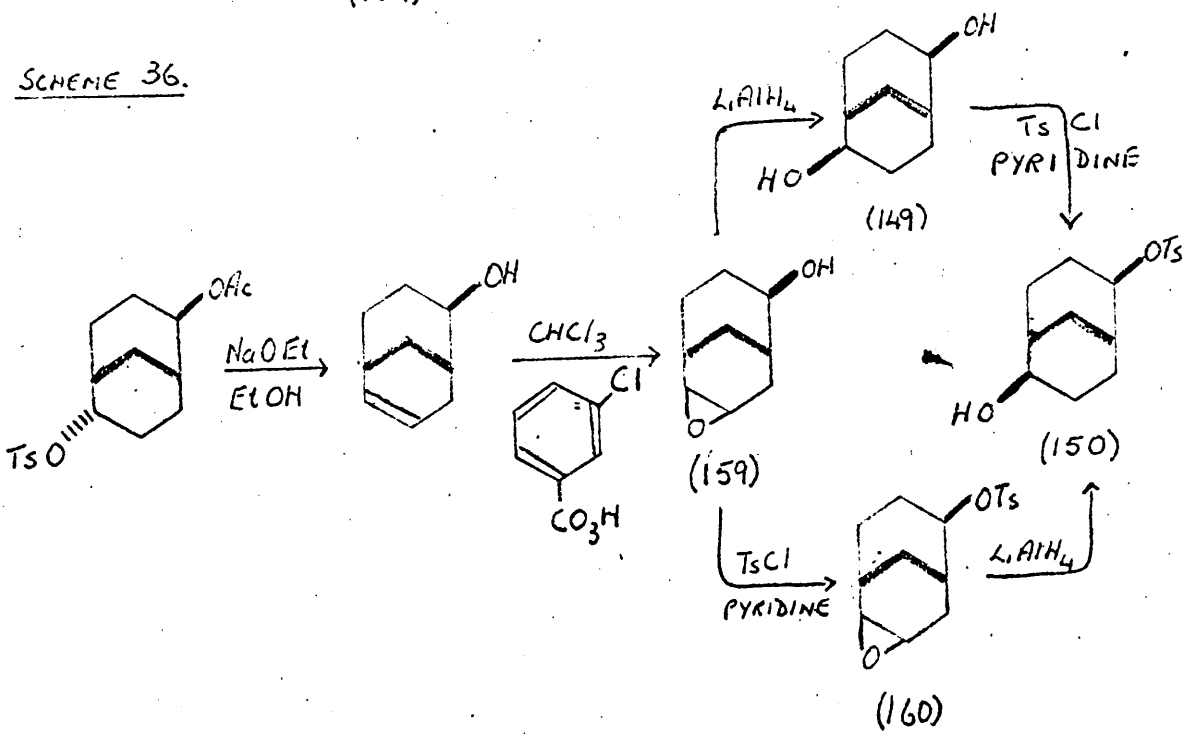


(92) (155) (156)



(154) (152)

SCHEME 36.



(149) (159) (150) (160)

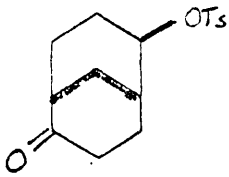
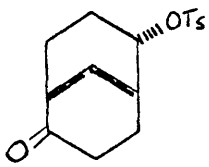
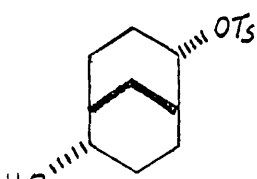
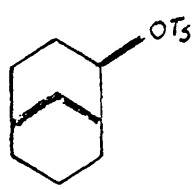
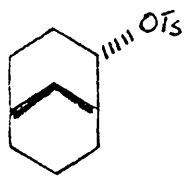
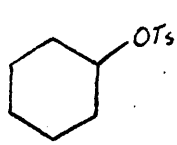
by infra-red spectroscopy, the corresponding endo-6-hydroxy-exo-2-tosylate (151) but as yet this has not been obtained as a crystalline solid.

A simple paper route to the remaining two 6-hydroxy-2-tosylates, (150) and (152) involves transformation of the ketonic group in the keto tosylates (154) and (96) respectively to the corresponding exo- hydroxy group (scheme 34). At the moment there is no known method of directly reducing bicyclo (3,3,1) nonan-2-one stereoselectively into exo-bicyclo (3,3,1) nonan-2-ol. An untested synthesis of (152) is shown in scheme 35. The ketol (92) should be readily converted to its acetate (155) which on sodium borohydride reduction would give exo-6-acetoxy-endo-2-hydroxybicyclo (3,3,1) nonane (156). Lithium aluminium hydride reduction of the tosylate (157) of this alcohol should give the desired exo-6-hydroxy-endo-2-tosylate (152). This step should not involve any great difficulty as endo-2-tosylates substituted at C_6 have been shown previously to resist these conditions.

The projected route to (150) is shown in scheme 36. Treatment of the previously discussed exo-6-acetoxy-endo-2-tosylate (157) with sodium ethoxide in ethanol will probably yield the hydroxy-olefin (158) whose epoxide (159) should also be readily prepared. At this stage two routes are available. The first involves lithium aluminium hydride reductions of the hydroxy-epoxide (159) to the exo-, exo- diol (149) whose mono-tosylate (150) should be readily formed. The second approach involves tosylation of the hydroxy-

REACTION RATE CONSTANTS AT 100°C

TABLE 4

	k, sec^{-1}	k_{rel}	REFERENCE
 (154)	2.36×10^{-4}	0·38	
 (96)	3.88×10^{-6}	0·0062	
 (153)	2.89×10^{-4}	0·46	
 (161)	2.11×10^{-2} a	34	46.
 (162)	6.14×10^{-4} a	0·99	76, 90.
	6.24×10^{-4} a	1	91.

a EXTRAPOLATED FROM LOWER TEMPERATURES.

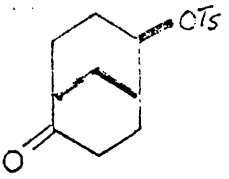
epoxide (159) and subsequent lithium aluminium hydride reduction of the tosylate (160) to exo-6-hydroxy-exo-6-tosylate (150).

As it was intended to solvolyse these hydroxy-tosylates, (150) to (153), rate studies were initiated on them to ensure that the acetolyses obeyed first order reaction kinetics. In this connection the lack of reactivity (to inversion and lithium aluminium hydride reduction) of 6-substituted-2-tosylates experienced earlier in the thesis prompted a rate study of such tosylates that were available.

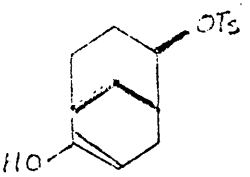
The rates of buffered acetolysis of the relevant compounds were found using spectrophotometric methods[74] (Appendix 2) and are shown in Table 4.

Immediately it can be seen that the presence of a keto group at C_6 decelerates the rate of acetolysis of the 2-tosylate in (154) and (96) with respect to the C_6- methylene derivatives (161) and (162). At 100° in the exo- series the keto/methylene rate ratio is 0.009 and in the endo- series 0.0063. This difference in deceleration is also manifested in the exo/endo rate ratios which for the methylene derivatives is 34.2 and the keto- derivatives is 60.8 both at 100°. (Because of the different Arrhenius dependence of the exo- and endo- epimers these differences would be much more marked at 25°.) Therefore the interaction of a 6-keto group has slowed the rate by a factor of approximately one hundredfold, the endo- epimer being retarded more than the exo- epimer.

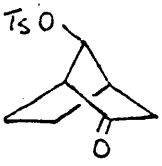
This retardation argues against the intermediacy of the enol form (163) in the solvolysis of exo-2-tosyloxybicyclo (3,3,1)



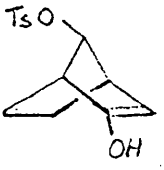
(154)



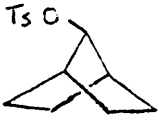
(163)



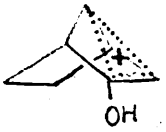
(164)



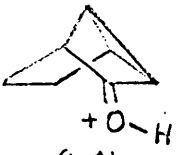
(165)



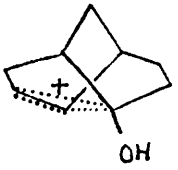
(166)



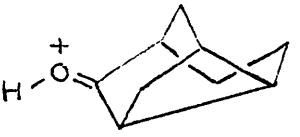
(167)



(168)



(169)



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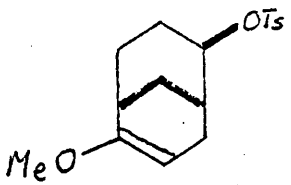

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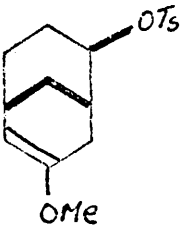
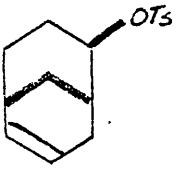
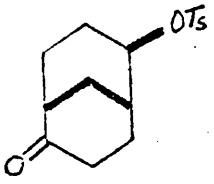


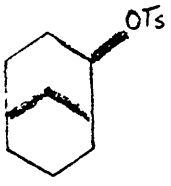
(172)



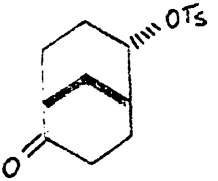
(173)



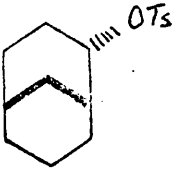
(154)



(161)



(96)



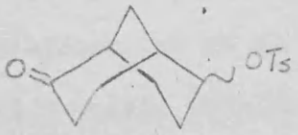
(162)

nonan-6-one (154), by analogy with the work of Gassman and Marshall[75]. They showed that in the solvolysis of (164) the enol form (165) was an intermediate, causing rate acceleration over (166) by a factor of 10^6. The acceleration was thought to be due to participation of the π electrons of the enol to give either a non-classical ion (167) or classical ion (168) as an intermediate. In our case the enol (163) would be expected to give either (169) or (170) and the fact that it does not seem to be involved may be a reflection of the difficulty of C_7-C_2 approach which (169) and (170) necessitate. In this context it would be interesting to study the reactivity of the exo-2-tosylates (171), (172) and (173). They would give some indication of the ability of $\Delta 6,7$ ethylenic moiety to participate and hence accelerate the solvolysis of exo-2-tosylates.

The difference of about hundredfold in reactivity of the keto tosylates, (154) and (96), from the simple methylene derivatives, (161) and (162), represents a difference in the free energy of activation, $\Delta(\Delta G_{373}^{\neq})$, of the solvolysis of about 3.5 kcal./mole. This is obtained from the relationship

$$\Delta(\Delta G_T^{\neq}) = (\Delta G_1^{\neq})_T - (\Delta G_2^{\neq})_T = 2.3\ RT \log (k_2/k_1).$$

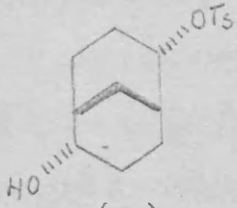
There are two extremes for an explanation of this factor. The first would account for the $\Delta(\Delta G^{\neq})$ as representing the lowering in free energy of the ground state in going from methylene tosylate to keto-tosylate. In the keto-tosylates the ground state



(174)

(175)

(176)



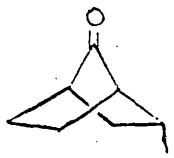
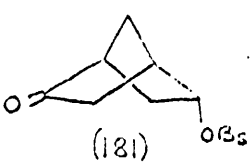
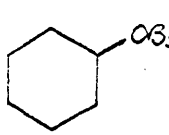
(153)

conformation of the cyclohexyl ring bearing the tosylate group is known to be chair (Appendix 1). Of the two available molecular conformations "twin-chair" (174) or "chair-boat" (175) neither seems to have much preference. As has been discussed earlier (P. 19) Marvell[37] has shown that the energy difference between the two should be very small. From Dreiding models the difference in non-bonded interactions of either of these conformations with the known "twin-chair" ground state conformation (176) of the simple methylene tosylates are not significant. Therefore the $\Delta(\Delta G^{\neq})$ of 3.5 kcal./mole cannot wholly be accounted for by a difference in ground state energy. This is also borne out by the fact that in endo-6-hydroxy-exo-2-tosyloxybicyclo (3,3,1) nonane (153), whose ground state energy would be of comparable value to that of the keto-tosylates, there is not such a marked rate difference the hydroxy/methylene ratio being only 0.47.

The second explanation for the rate and hence free energy difference involves the differences in transition state. The lengthening C_2 - OTs bond and its increasing dipole will begin to play a larger part. The interaction of this and the carbonyl dipole, which is easily polarised, because it involves π electrons, could cause a rise in energy of the transition state compared to the methylene derivative. It could be argued that the endo-hydroxy dipole would also cause this effect and it probably does but because of its smaller dipole (c.f. acetone, 2.9D, propan-2-ol, 1.7D) this interaction should be smaller.

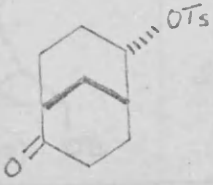
TABLE 5.

ACETOLYSIS RATE CONSTANTS AT 25°C

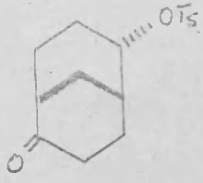
	k, sec^{-1}	$k_{rel.}$	REFERENCE
 (178)	4.32×10^{-8} a,b	0.25	10
 (179)	2.60×10^{-7} a,b	1.52	10
 (180)	8.5×10^{-9} a	0.050	44
 (181)	2.0×10^{-10} a	0.0012	44
 (182)	8.49×10^{-5} a	516	92
 (183)	2.52×10^{-4} a	1.5	92
	1.41×10^{-4} a	1.0	44

a EXTRAPOLATED FROM HIGHER TEMPERATURES

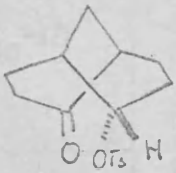
b CALCULATED FROM CORRESPONDING TOSYLATE USING A FACTOR OF 3 TO RELATE TOSYLATE TO BROSYLATE



(96)



(154)

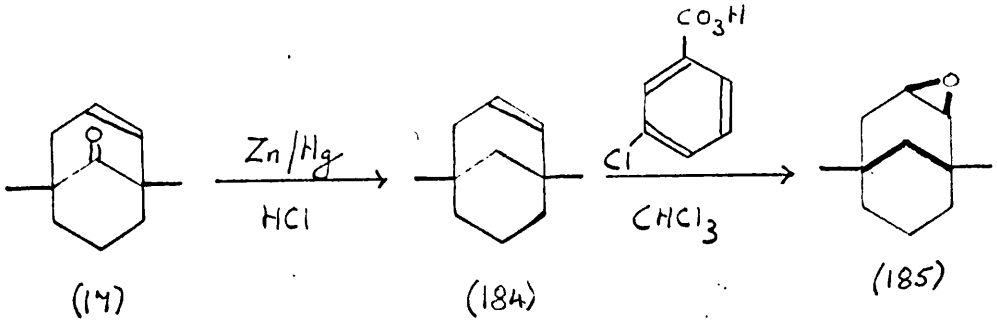


(174)

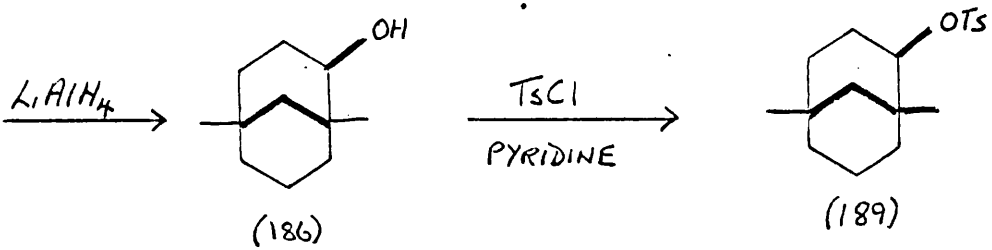
This explanation also accounts for the greater effect of the C_6- keto group on the endo- epimer (96) than on the exo- epimer (154). It is well documented now[44,45,46] that during solvolysis, axial and equatorial cyclohexyl tosylates react in different tranisition states the axial preferring the chair and the equatorial preferring the "twist-boat". The evidence[76] in the bicyclo (3,3,1) non-2-yl tosylates shows the same tendencies axial preferring "twin-chair" and equatorial "twin-twist-boat". In the "twin-twist-boat" (177) conformer of endo-2-tosyloxybicyclo (3,3,1) nonan-6-one (96) the keto group a departing tosylate group are brought into closer proximity than in the "twin-chair" conformation of the exo- epimer.

There is conflicting opinion in the literature with regard to the nature of the effect of polar groups on the acetolysis of tosylates.

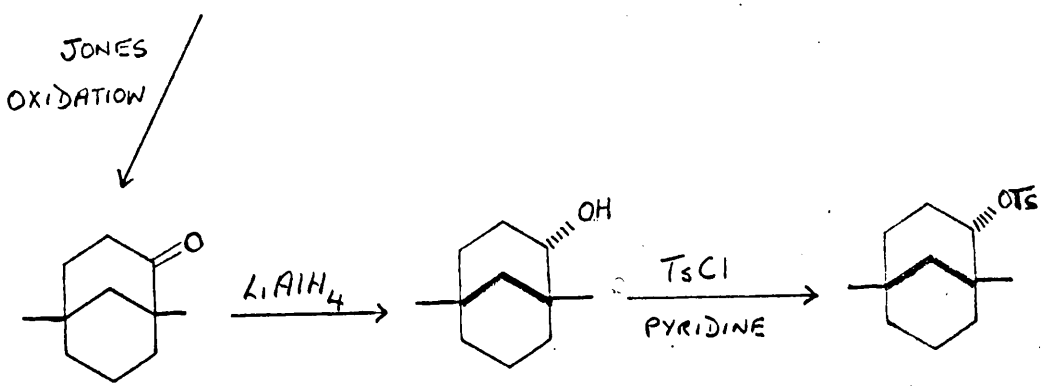
The results of work in the norbornanesare of interest here and the relevant rates are shown in Table 5. Gassman and Marshall[10] who studied the 7-keto-2-norbornyl system i.e. (178) and (179) discarded dipole-dipole interaction between the ketone and the carbon-tosyloxy grouping as the reason for retardation, preferring instead to use the loss of non-classicality as the argument for the slowing down of the exo- epimer (178). By way of contrast the evidence obtained from the 5-keto-2-norbornyl system i.e. (180) and (181) by Greaver and Gwynn[77] tend to support a dipole-dipole interaction being responsible for the substantial rate retardation. In the latter case no deactivation selective for the exo- epimer was found. In an



(14) (184) (185)



(186) (189)



(184) (188) (190)

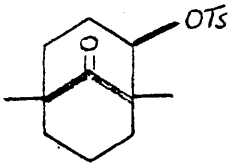
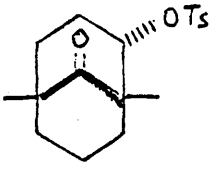
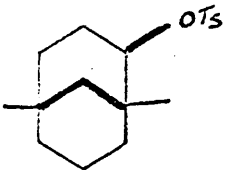
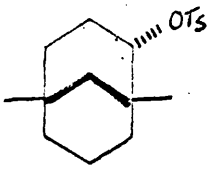
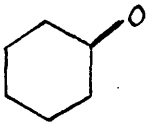
effort to clarify the picture Gassman and co-workers[78] have recently gathered together rate data for a variety of 7-substituted norbornyl tosylates and in the exo- cases have shown that there is a direct relationship between the rate constant and σ^* (polar substituent constant) for all the 7-substituents studied. This relationship held in the endo- cases where no other "abnormal" effects were present. The conclusion drawn was that the rate retardation was proportional to the inductive effect of the group, with the exo- tosylates being slightly more affected than the endo- epimers.

These studies in the norbornyl system have been involved with the non-classical ion/classical ion controversy[79,80] which exists in that system. Therefore any extension of their results to the bicyclo (3,3,1) system which is thought[20,22,76,81] to be classical in nature must be applied with care.

The work in section 1 on the 1,5-dimethylbicyclo (3,3,1) non-2-yl tosylates, (12) and (13), is relevant here and the rate data for the system is shown in Table 6. For comparitive purposes the simple 1,5-dimethylbicyclo (3,3,1) non-2-yl tosylates, (189) and (190), were required and their alcohols were synthesised by the routes shown in scheme 37. Clemmensen reduction of 1,5-dimethylbicyclo (3,3,1) non-2-ene-9-one (17), obtained from the solvolyses described in section 1, proceeded smoothly to give the olefin (184) which was readily converted to its epoxide (185) using m-chloroperbenzoic acid in chloroform. Lithium aluminium hydride

TABLE 6

ACETOLYSIS RATE CONSTANTS AT 80°C

	k, sec^{-1}	k_{rel}	REFERENCE
 (12)	6.61×10^{-5}	0.88	
 (13)	1.39×10^{-4}	1.86	
 (189)	4.82×10^{-3} a	105	
 (190)	2.92×10^{-4}	3.9	
	7.49×10^{-5} a	1	91

a EXTRAPOLATED FROM LOWER TEMPERATURES.

reduction of this epoxide gave exo-1,5-dimethylbicyclo (3,3,1) nonan-2-ol (185). Jones oxidation of (186) and lithium aluminium hydride reduction of the ketone (187) gave the desired endo- epimer (188).

A picture similar to that of the 6-ketotosylates pertains in the case of the 9-ketotosylates. The retarding effect of the keto group is revealed in the keto/methylene rate ratios. In the exo- series the ratio is 0.00845 whereas in the endo- epimers it is 0.48, both at 80°. The differential in the retardation effect of the exo- and endo- epimers is shown in the exo/endo rate ratio, which is 0.475 for the keto series and 26.8 for the methylene derivatives, (189) and (190).

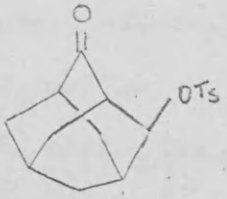
The replacement of a 9-methylene group by a 9-ketonic group should not affect the ground state energy of both exo- and endo- tosylates to any great degree. Hence the $\Delta(\Delta G^{\neq}_{353}o)$ for the activation free energies of acetolyses of (12) and (189), 3.37 kcal./mole, and (13) and (189), 0.52 kcal./mole, must be a reflection of the increased energy of the transition state of the keto tosylates, (12) and (13), as against the methylene tosylates, (189) and (190). A comparison between, (13) and (190), has to be treated carefully because the possibilities that (13) solvolyses by a different mechanism (P. 7) has not yet been discounted.

A comparable result has been reported for the simple endo-2-tosyloxybicyclo (3,3,1) nonan-9-one where the keto/methylene rate ratio at 62° is 0.195 representing a $\Delta(\Delta G^{\neq}_{335}o)$ of 1.09 kcal./mole.(13)

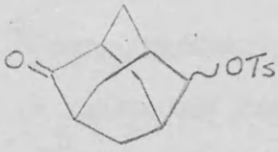
The results in the equivalent norbornane system, 7-keto, which have already been discussed show the same qualitative relationship as has been observed here.

These results in the bicyclo (3,3,1) nonane ring system which, as has already been said, does not show any tendency for formation of non-classical ions,[20,22,76,81] support in a positive manner the idea that the effect of polar groups on the solvolysis of tosylates can best be explained in terms of dipole-dipole interactions with due regard being given to direction, strength and intervening distance of the dipoles. Kwart and Takeshita[82] have already expressed this view in their study of some cyclohexyl tosylates substituted with polar groupings. The generally more marked effects seen in bicyclic compounds has been explained by Moriarty et al[83]. Their view is that the intervention of bulk solvent between the centres which would help to disperse the dipole-dipole forces is not very easy in bridged molecules which tend to be spherical.

A literature search reveals a relative paucity of information regarding dipole-dipole interactions in the solvolysis of secondary tosylates. With the results in the bicyclo (3,3,1) nonane system which seem to stem from classical carbonium ion behaviour and show a marked effect in reactivity by placing a ketone group at a distance from the reaction centre in hindsight one should probably have examined the solvolytic behaviour of keto-tosylates in a system free from non-classical behaviour yet with a geometry which is rigidly defined. The adamantane skeleton would provide an excellent



(191)



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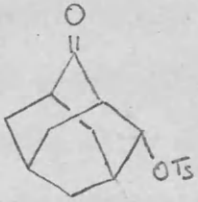
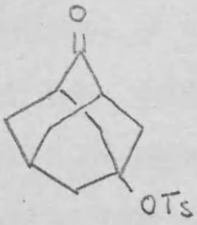


(193)



(194)

test bed for the study of these interactions e.g. (191) to (194). A careful study of the rates of reaction of these compounds would certainly check on Moriarty's comments[83] and also provide a basis for calculation of dipole-dipole interactions with regard to distance and orientation.

In this section although their nature has not always been completely understood evidence for 2,6-interactions has certainly been found. Because of the specific nature of this topic general application of our results is not possible but from it we have been led to consider more general ideas of dipole-dipole interactions, thermodynamic aspects of stereochemistry and conformational problems in the bicyclo (3,3,1) nonane ring system.

EXPERIMENTAL

The acetates and tosylates of alcohols were made as follows.

Acetate

A mixture of the appropriate alcohol (1 m.mole), acetic anhydride (0.8 ml.) and pyridine (0.8 ml.) were heated on a steam bath for 30 mins. The cooled solution was carefully poured into saturated sodium bicarbonate solution (5 ml.) and after mixing well allowed to stand for 30 mins. The combined ether extracts of this solution (3 x 5 ml.) were then washed with saturated sodium bicarbonate solution (3 x 5 ml.), brine (2 x 5 ml.) and dried. Removal of solvent left the acetate which was then purified usually by micro-distillation or sublimation.

Tosylate

The alcohol (1 m.mole) and p-toluenesulphonyl chloride (1.1 m.mole) were dissolved in pyridine (.8 ml.) and allowed to stand at 0° for 12 hrs. The solution was then poured into ice-cold very dilute aqueous hydrochloric acid (5 ml.) and extracted with ether (3 x 5 ml.). The combined ether extracts were washed with ice-cold dilute aqueous hydrochloric acid (3 x 5 ml.), saturated sodium bicarbonate solution (2 x 5 ml.), brine (1.5 ml.) and dried. Removal of solvent at 5° under reduced pressure gave the desired tosylate which was then purified by recrystallisation, often at low temperatures (e.g. -10°).

In some cases the tosylates were so unstable that dilute

aqueous hydrochloric acid could not be used. Here the ether extracts were washed well with water (10 x 5 ml.).

6-ethylenedioxybicyclo (3,3,1) nonan-2-one (188)

Bicyclo (3,3,1) nonan-2,6-dione (82) (3 g.) was refluxed with ethylene glycol (1.2 g.) and p-toluenesulphonic acid monohydrate (30 mg.) in benzene (30 ml.) under a Dean and Stark apparatus until no more water separated out (ca. 10 hrs.). The cooled organic layer together with ether washings of the reaction flask was washed with saturated sodium bicarbonate solution (3 x 10 ml.), brine (1 x 10 ml.) and dried and the solvent removed under reduced pressure to give a pale yellow oil (3.7 g.) which was adsorbed on Grade III neutral alumina from pet. ether. Elution with pet. ether gave 2,6-diethylenedioxybicyclo (3,3,1) nonane (89) as a colourless oil (1 g.).

ν_{max} film (S.P.200) 1110 cm.$^{-1}$

Elution with 10% ether/pet. ether gave 6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88) as a colourless oil (2.1 g.) which could be purified by sublimation (80°/5mm)

ν_{max} 1710, 1118 cm.$^{-1}$

τ 6.14 (4H,s).

(Found: C,67.00; H, 8.20. $C_{11}H_{16}O_3$ requires C,67.30; H,8.20%)

Elution with 50% ether/pet. ether gave bicyclo (3,3,1) nonan-2,6-dione (82) as a white crystalline solid (.5 g.) identical with

starting material by infra-red spectrum and gas liquid chromatographic properties (5% Q.F.1.).

Endo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (90)

6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88) (1 g.) was stirred in ether (15 ml.) with lithium aluminium hydride (0.2 g.) for 1 hr. Saturated sodium sulphate solution was added dropwise till all active hydrogen had been destroyed and the resulting precipitate was washed several times with ether. The combined ether extracts were dried and solvent was removed to give an oil (0.9 g.) which turned crystalline on standing. A pure sample of endo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (90) was obtained by recrystallisation (pet.ether/ethyl acetate) and subsequent sublimation (100°/0.5 mm.)

ν_{max} 3618, 2979, 1478, 1122, 1050 cm.$^{-1}$

τ 6.09 (5H,s), 8.36(s, removed by D_2O exchange).

(Found: C,66.50; H,9.35. $C_{11}H_{18}O_3$ requires C,66.85; H,9.15%).

The acetate of (90) was purified by distillation (70°/0.5 mm.)

ν_{max} 2980, 1731, 1482, 1245, 1238, 1105, 1046, 1030 cm.$^{-1}$

τ 5.19(1H,m, $W_{\frac{1}{2}}$ 21 c/s), 6.15(4H,s), 8.04(3H,s)

(Found: C,64.75; H,8.40. $C_{13}H_{20}O_4$ requires C,65.00; H,8.40%)

The tosylate (93) of ketalol (90) on recrystallisation from pet.ether/ethyl acetate had m.p. 103.5-105.5°.

ν_{max} 1596, 1494, 1480, 1188, 1168, 1098 cm.$^{-1}$

τ 2.19 (2H,d, J 8.5c/s), 2.72(2H,d, J 8.5c/s), 5.42(1H,m,$W_{\frac{1}{2}}$ 22c/s), 6.20(4H,s), 7.58(3H,s).

(Found: C,61.35; H,6.90. $C_{18}H_{24}SO_5$ requires C,61.35; H,6.85%).

The deuterated analog (126) of (90) was prepared in a similar manner using lithium aluminium deuteride.

ν_{max} 3620,2980,2100,1487,1479,1126,1082,1060,1055,1034 cm.$^{-1}$

τ ($CDCl_3$) 6.1(4H,s), 8.1(s, removed by D_2O exchange).

(Found: c,66.30; H,9.35. $C_{11}H_{17}DO_3$ requires C,66.30; H,9.60%)

The tosylate (125) of this alcohol (126) was readily prepared.

ν_{max} 3028,2985,2180,1598,1495,1482,1190,1180,1105,925 cm.$^{-1}$

τ 2.16(2H,d,J 8.5c/s), 2.64(2H,d,J 8.5c/s), 6.1(4H,s), 7.55(3H,s).

(Found: C,61.20; H,7.00. $C_{18}H_{23}DSO_5$ requires C,61.15; H,7.15%).

Endo-2-hydroxybicyclo (3,3,1) nonan-6-one (91)

Endo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (90) (0.66 g.) was refluxed for 2 hrs. in acetone (40 ml.) containing p-toluenesulphonic acid monohydrate (20 mg.). The cooled solution was poured into a separating funnel with ether washings and washed with saturated potassium carbonate solution (2 x 10 ml.), brine (1 x 10 ml) and dried. The solvent was removed under reduced pressure, the residue dissolved in ether (25 ml.) and this ether layer washed with brine (1 x 5 ml.) and dried. Removal of solvent

gave a waxy solid (0.45 g.) which was absorbed on Grade III neutral alumina (18 g.) from 50% pet. ether/ether. Elution with ether gave endo-2-hydroxybicyclo (3,3,1) nonan-6-one (91) as a waxy solid (0.43 g.) which was further purified by sublimation (100°/0.5 mm.).

ν_{max} 3619, 1710, 1062, 1039 cm.$^{-1}$

τ 6.1(1H,m,$W_{\frac{1}{2}}$ 16c/s) 7.62(m) 7.85(m)

(Found: c,69.85; H,9.25. $C_9H_{14}O_2$ requires C,70.10; H,9.15%).

The tosylate (96) of the ketol was recrystallised from pet. ether/ethyl acetate, m.p. 83-84°.

ν_{max}(nujol mull)(S.P.200) 1709,1598,1498,1185 cm.$^{-1}$

τ 2.11(2H,d,J 8.5c/s), 2.55(2H,d,J 8.5c/s), 5.33(1H,m,$W_{\frac{1}{2}}$ 18c/s), 7.53(3H,s).

(Found: C,62.45; H,6.65. $C_{16}H_{20}SO_4$ requires C,62.30; H,6.55%).

Attempted inversion of endo-2-tosyloxy-6-ethylenedioxybicyclo (3,3,1) nonane (93).

(a) endo-2-tosyloxy-6-ethylenedioxybicyclo (3,3,1) nonane (93) (3.5 g.) was heated in 90% equeous dimethylformamide (100 ml.) at 78° for 184 hrs. The cooled solution was poured into water (150 ml.) and extracted with ether (1 x 200 ml., 2 x 100 ml.). The combined ether extracts were washed with water (4 x 50 ml.), brine (2 x 50 ml.) and dried.

The ether solution was filtered and stirred with lithium aluminium hydride (1 g.) for 15 mins. Saturated sodium sulphate solution was added dropwise until all active hydrogen had been destroyed. The resultant precipitate was washed several times with ether and the combined ether extracts dried. Removal of solvent gave a colourless oil (1.6 g.).

ν_{max} (film)(P.E.157) 3400,1650,1600,1498,1189,1175,1110,1100 $cm.^{-1}$

This oil was adsorbed one Grade I neutral alumina from pet. ether. Elution with 25% ether/pet. ether gave 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) (0.4 g.) whose infra-red spectrum was identical with an authentic sample.

Elution with 75% ether/pet. ether gave returned 2-hydroxy-6-ethylene ketal (93) (0.3 g.) whose infra-red spectrum was identical to starting material.

Elution with 0.5% methanol/ether gave an oil (0.2 g.) whose spectral data suggested that it was endo-2-hydroxybicyclo (3,3,1) non-6-ene.

ν_{max} (film)(P.E.157) 3400,3040,1060,705 $cm.^{-1}$

τ 4.32(2H,m), 6.35(1H,m,$W_{\frac{1}{2}}$ 18 c/s).

Elution with 1% methanol/ether gave an oil (0.6 g.) whose infra-red spectrum was almost identical to that of endo-6-hydroxy-endo-2-tosyloxybicyclo (3,3,1) nonane.

(b) The ketal tosylate (93) (6.5 g.) was heated with sodium

acetate (1.83 g.) in 90% aqueous dimethylformamide (200 ml.) for 96 hrs. at 78°C. A similar workup procedure as that used in (a) gave a colourless oil (2.6 g.) which was adsorbed on Grade III neutral alumina (100 g.) from pet. ether. Elution with the same solvent gave 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) as a colourless oil (1.11 g.) whose infra-red spectrum was identical to an authentic sample.

Elution with 50% ether/pet. ether gave exo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (95) as a colourless oil (1.4 g.) whose infra-red spectrum was identical to an authentic sample.

(c) The ketal tosylate (93) (0.35 g.) was heated with sodium acetate (0.4 g.) in 100% dimethylformamide (10 ml.) for 130 hrs. at 78°C. A similar workup procedure as that used in (a) furnished a pale yellow oil (0.24 g.) which by thin layer chromatography contained 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) (25%), starting material (50%) and the desired exo- alcohol (95) (25%).

Attempted inversion of endo-2-tosyloxybicyclo (3,3,1) nonan-6-one (96)

(a) Endo-2-tosyloxybicyclo (3,3,1) nonan-6-one (96) (0.3 g.) was heated in 98% dimethylformamide (25 ml.) for 72 hrs. at 78°. Thin layer chromatography of the reaction mixture showed that no change had taken place.

(b) The keto-tosylate (96) (0.3 g.) was heated in 98% dimethylformamide (25 ml.) for 7 days at 100°. Thin layer

chromatography of the reaction mixture showed that very little change had occurred.

(c) The keto-tosylate (0.3 g.) was heated with sodium benzoate (0.32 g.) in 98% dimethylformamide (25 ml.) for 48 hrs. at 100°. The cooled solution was poured into water (30 ml.) and extracted with ether (1 x 75 ml., 2 x 25 ml.). The combined ether extracts were washed with water (3 x 25 ml.) and dried and solvent was removed to give a pale yellow oil (0.29 g.). Thin layer chromatography and infra-red spectroscopy showed that very little change had occurred.

6-ethylenedioxybicyclo (3,3,1) non-2-ene (94)

Endo-2-tosyloxy-6-ethylenedioxybicyclo (3,3,1) nonane (93) (40 g.) was added to a solution of sodium (10 g.) in absolute ethanol (500 ml.) under dry nitrogen and the solution refluxed for ten days. The cooled reaction mixture was added to water (500 ml.) and extracted with pet. ether (1 x 500 ml., 3 x 150 ml.). The combined ether extracts were washed with water (2 x 50 ml.), brine (2 x 50 ml.) and dried. Removal of solvent gave a colourless oil (21 g.) which was adsorbed on Grade III neutral alumina (800 g.) from pentane. Elution with the same solvent gave 2-ethoxy-6-ethylene-dioxybicyclo (3,3,1) nonane (97) as a colourless oil (8.5 g.)

ν_{max} (film)(S.P.200) 1140-1080 $cm.^{-1}$

τ 6.2(4H,s), 6.63(2H,q,J 7c/s), 6.75(1H, mostly hidden by previous signal), 8.85 (3H,t, J 7c/s).

Further elution with pentane yielded 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) as a colourless oil (12 g.) which was purified by micro-distillation (60°/0.5 mm.)

ν_{max} (film)(S.P.200) 1650, 1120, 770, 725 cm.$^{-1}$

τ 4.33 (2H, unsym.d, J 4c/s) 6.13(4H,s)

(Found: C,73.20; H,9.15. $C_{11}H_{16}O_2$ requires C,73.30; H,8.95%)

Bicyclo (3,3,1) non-6-ene-2-one (98)

6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) (1.5 g.) was refluxed for 5 hrs. in acetone (50 ml.) containing p-toluenesulphonic acid monohydrate (30 mg.). The cooled solution was poured into a separating funnel with ether washings and washed with saturated potassium carbonate solution (2 x 10 ml.), brine (1 x 10 ml.) and dried. The solvent was removed at 5° under reduced pressure, the residue dissolved in ether (20 ml.) and this ether layer washed with brine (1 x 5 ml.) and dried. Removal of solvent at 5° under reduced pressure gave a pale yellow liquid (0.9 g.) which was adsorbed on Grade III neutral alumina (25 g.) from pentane. Further elution with this solvent yielded bicyclo (3,3,1) non-6-ene (98) as a mobile colourless oil (0.7 g.) which was further purified by micro-distillation (60°/0.5 mm.).

ν_{max} (P.E.157) 3040, 1710, 1100, 695 cm.$^{-1}$

λ_{max}^{EtOH} 295 nm (ϵ 19.8), λ_{max}^{hexane} 294 nm (ϵ 15)

τ 4.17 (2H, unsym d, J 4c/s)

(Found: C,79.40; H,9.00. $C_9H_{12}O$ requires C,79.30; H,8.90%).

Bicyclo (3,3,1) nonan-2-one

Bicyclo (3,3,1) non-6-ene-2-one (98) (30 mg.) was hydrogenated over 5% Pd/charcoal in ethyl acetate for 8 hrs. The solution was filtered through Celite 535 and the solvent removed at 5° under reduced pressure to give an oily solid (20 mg.) whose infra-red spectrum and gas liquid chromatographic behaviour (6% Q.F.1. and 2½% S.E.30) were identical with those of an authentic sample of bicyclo (3,3,1) nonan-2-one.

Hydroboration of 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94)

A 0.8 molar solution of diborane in tetrahydrofuran (20 ml.) was added under dry nitrogen over 1.5 hrs. to the ketal olefin (94) (9 g.) dissolved in tetrahydrofuran (50 ml.). After stirring for a further 2 hrs. water (ca. 2 ml.) was added dropwise with great care to destroy the active hydrogen. 3N sodium hydroxide solution (10 ml.) and 30% aqueous hydrogen peroxide solution (7.4 g.) was added and the mixture stirred for 1.5 hrs. at 40°. The solution was extracted with ether (1 x 100 ml., 2 x 50 ml.) and the combined ether extracts washed with saturated ferrous sulphate solution (4 x 20 ml.), water (1 x 20 ml.), brine (2 x 20 ml.) and dried. Removal of solvent gave a colourless oil (10.2 g.) which thin layer chromatography showed to be two spots of almost identical Rf at the position expected for a hydroxy ketal (cf. 90).

The oil (1.5 g.) was adsorbed on silica gel (60 g.) from 50% ether/pet. ether. Elution with 75% ether/pet. ether did not separate the two compounds.

Exo-2,3-epoxy-6-ethylenedioxybicyclo (3,3,1) nonane (101)

A solution of 85% m-chloroperbenzoic acid (2.4 g.) in chloroform (30 ml.) was added to 6-ethylenedioxybicyclo (3,3,1) non-2-ene (94) (2 g.) in chloroform (10 ml.) and left stirring for 15 hrs. at room temperature. 10% sodium sulphide solution was added dropwise until the reaction mixture gave no colouration with moist starch iodide paper. The chloroform layer was then washed with saturated sodium bicarbonate solution (4 x 20 ml.), brine (1 x 30 ml.) and dried and solvent removed to give a pale yellow oil (2.23 g.). A pure sample of exo-2,3-epoxy-6-ethylenedioxybicyclo (3,3,1) nonane (101) was obtained by thick layer chromatography with 40% ether/pet.ether as eluent followed by sublimation (80°/0.5 mm.)

$\nu_{max}(CCl_4)$(P.E.157) 1110, 1040 cm.$^{-1}$

τ 6.15(4H,s) 7.12(2H,m, $W_{\frac{1}{2}}$ 16c/s)

(Found: C,67.55; H,8.45. $C_{11}H_{16}O_3$ requires C,67.35; H,8.30%)

Exo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (95)

Exo-2,3-epoxy-6-ethylenedioxybicyclo (3,3,1) nonane (101) (0.98 g.) and lithium aluminium hydride (0.85 g.) were stirred in ether (50 ml.) for 7 days at room temperature. Saturated sodium sulphate solution was added dropwise till all the active hydrogen

had been destroyed. The precipitate was washed successively with ether and ethyl acetate and the combined organic layers were washed with brine (1 x 30 ml.) and dried and the solvent was removed under reduced pressure to give a colourless oil (0.8 g.) which was adsorbed on Grade III neutral alumina (30 g.) from 25% ether/pet. ether. Elution with 50% ether/pet.ether yielded exo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (95) as a viscous colourless oil (0.75 g.) which was further purified by micro-distillation (70°/0.5 mm.)

$\nu_{max}(CCl_4)$(P.E.157) 3630,1120,1100,1058,993 cm.$^{-1}$

τ 6.1(5H,s)

(Found: C,66.85; H,9.20. $C_{11}H_{18}O_3$ requires C,66.85; H,9.15%)

The tosylate of this alcohol has not yet been obtained as a crystalline solid.

The acetate was a colourless oil.

ν_{max}(film)(P.E.157) 1735,1250,1040 cm.$^{-1}$

τ 5.20(1H,m,$W_{\frac{1}{2}}$ 6c/s) 6.18(4H,s) 8.05(3H,s)

Endo-6-(2^1-hydroxyethyleneoxy)-exo-2-hydroxybicyclo (3,3,1) nonane (102)

The above reduction if carried out in refluxing ether for 4 days gave on the same workup an oil which was adsorbed on Grade III neutral alumina from ether. Elution with the same solvent gave the

dihydroxy-ether (102) which was further purified by sublimation (100°/0.5 mm).

ν_{max}(film)(P.E.157) 3360,1480,1105,1070,1050,978,950 cm.$^{-1}$

τ ($CDCl_3$) 6.1 to 6.7 (6H,m) 8.25(14H,m) becomes 12H,m after D_2O exchange).

(Found: C,66.10; H,10.25. $C_{11}H_{20}O_3$ requires C,66.00; H,10.05%)

The diacetate (103), a colourless oil, was purified by micro-distillation (90°/0.5 mm.)

ν_{max}(film)(P.E.157) 1735, 1250, 1040 cm.$^{-1}$

τ 5.18(1H,m,$W_{\frac{1}{2}}$ 7c/s), 5.87(2H, unsym.t,J 5c/s), 6.44(3H, unsym.t,J 5c/s), 8.00(3H,S) 8.02(3H,S)

(Found: C,63.60; H,8.60. $C_{15}H_{24}O_5$ requires C,63.35; H,8.50%)

Endo-6-(2^1-hydroxyethyleneoxy)-endo-2-hydroxybicyclo (3,3,1) nonane

Similar treatment to the last experiment of endo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (102) gave a colourless oil of identical thin layer chromatographic behaviour to the dihydroxyether (102).

ν_{max}(film)(P.E.157) 3400,1480,1115,1105,1060,1040,965,950, 910 cm.$^{-1}$

Exo-2-hydroxybicyclo(3,3,1) nonan-6-one (92)

Exo-2-hydroxy-6-ethylenedioxybicyclo (3,3,1) nonane (95) (0.72 g.) was refluxed for 2 hrs. in acetone (50 ml.) containing p-toluenesulphonic acid monohydrate (20 mg.). The cooled solution and ether washings were washed with saturated potassium carbonate solution (2 x 10 ml.) brine (1 x 10 ml.) and dried. The solvent was removed under reduced pressure, the residue dissolved in ether (25 ml.) and this ether layer washed with brine (1 x 5ml.) and dried. Removal of solvent gave a waxy solid (0.51 g.) which was adsorbed on Grade III neutral alumina (20 g.) from 50% ether/pet. ether. Elution with ether gave exo-2-hydroxybicyclo (3,3,1) nonan-6-one (92) as a waxy solid (0.49 g.) which was further purified by sublimation (100°/0.5 mm.)

$\nu_{max}(CCl_4)$(P.E.157) 3620,1710,1125,1050,970 cm.$^{-1}$

τ 6.05(1H,m,$W_{\frac{1}{2}}$ 6c/s) 6.91(1H,s, removed by D_2O exchange) 7.55(m), 7.80(m).

(Found: C,69.95; H,9.10. $C_9H_{14}O_2$ requires C,70.10; H,9.15%)

The tosylate (154) of this alcohol was recrystallised from pet. ether/ethyl acetate, m.p. 111-113°.

ν_{max}(mujol mull)(P.E.157) 3060,1700,1596,1494,1190,1175 cm.$^{-1}$

τ 2.12(2H, unsym. d, J 8.5c/s), 2.6(2H, unsym. d, J 8.5c/s), 5.3(1H,m,$W_{\frac{1}{2}}$ 7c/s), 7.53(3H,s)

(Found: C,62.50; 6.70. $C_{16}H_{20}SO_4$ requires C,62.30; H,6.55%).

Deuteration of endo-2-hydroxybicyclo (3,3,1) nonan-6-one (91)

The endo-ketol (91) (29 mg.) was heated with a solution of sodium (36 mg.) in dioxan (1.5 ml.) and deuterium oxide (1.5 ml.) in a sealed ampoule for 72 hrs. at 95°. The solvents were removed under reduced pressure and the residue washed with deuterium oxide (0.5 ml.) and then ether (3 x 5 ml.). The combined ether layers were then washed with deuterium oxide (2 x 0.5 ml.), brine (2 x 5 ml.) and dried and the solvent removed to give a waxy solid (ca. 25 mg.) which was adsorbed on Grade III neutral alumina (1 g.) from ether. Elution with the same solvent gave the deuterated endo-ketol (107) as a waxy solid (ca. 20 mg.) which was further purified by sublimation (100°/0.5 mm.). It had identical gas liquid chromatographic properties to starting material (6' 2½% S.E.30 and 6' 6% Q.F.1)

$\nu_{max}(CCl_4)$(P.E.157) 3640,2150,1705,1055,1031 cm.$^{-1}$

τ ($CDCl_3$) 6.11(1H,m,$W_{\frac{1}{2}}$ 18 c/s)

The mass spectrum was analysed [84] for deuterium content with the following results d_0, 1.4%; d_1, 3.0%; d_2, 19.3%; d_3, 74.5%; d_4, 0.8%; d_5, 0.4%; d_6 0.6%. No. of deuteria/molecule, 2.74.

Deuteration of exo-2-hydroxybicyclo (3,3,1) nonan-6-one (92)

Treatment, exactly the same as that for the endo-epimer (91), gave the deuterated exo-ketol (106)

$\nu_{max}(CDCl_3)$(P.E.157) 3650,2150,1705,1057 cm.$^{-1}$

τ ($CDCl_3$) 6.04(1H,s,$W_{\frac{1}{2}}$ 3c/s)

The mass spectrum was analysed[84] for deuterium content with the following results d_0, 0.4%; d_1, 0.9%; d_2, 1.1%; d_3, 2.8%; d_4, 9.2%; d_5, 29.7%; d_6, 55.1%; d_7, 0.6%; d_8, 0.2%. No. of deuteria/molecule, 5.33.

Treatment of exo-2-hydroxybicyclo (3,3,1) nonan-6-one (92) with sodium hydroxide in aqueous dioxan

The ketol (92) (29 mg.) was subjected to similar exchange conditions as before except ordinary water was used in place of deuterium oxide. A similar purification procedure gave a ketol which was identical in infra-red spectrum and gas liquid chromatographic properties (2½% S.E.30 and 6% Q.F.1) to starting exo-ketol (92)

$\nu_{max}(CCl_4)$(P.E.157) 3630, 1710, 1125, 1050, 970 cm.$^{-1}$

Hexadeuterated bicyclo (3,3,1) nonan-2,6-dione (108)

Hexadeuterated exo-2-hydroxybicyclo (3,3,1) nonan-6-one (106) (10 mg.) was treated in ice-cold acetone (1 ml.) with Jones reagent (3 drops). The solution was diluted with water (2 ml.) and extracted with ether (2 x 2 ml.). The combined ether extracts were washed with saturated sodium bicarbonate solution (2 x 1 ml.), brine (1 x 1 ml.) and dried and the solvent removed to give a solid

which was adsorbed on Grade III neutral alumina (0.5 g.) from ether Elution with the same solvent gave hexadeuterated bicyclo (3,3,1) nonan-2,6-dione (108) (6 mg.) which was further purified by sublimation (100°/0.5 mm.). It had identical gas liquid chromatographic properties to authentic dione (6% Q.F.1 and 2½% S.E.30)

$\nu_{max}(CCl_4)$(P.E.157) 2150,1710,1185,1115,1090 cm.$^{-1}$

The mass spectrum was analysed [84] for deuterium content. d_0, 2.0%; d_1, 0.3%; d_2, 2.0%; d_3, 5.2%; d_4, 14.9%; d_5, 38.0%; d_6, 37.6%. No. of deuteria per molecule, 4.95.

Exchange protonation of hexadeutero bicyclo (3,3,1) nonan-2,6-dione (108)

The dione (108) (3.6 mg.) was refluxed under nitrogen with 4N sodium hydroxide solution (1 ml.) and methanol (1.5 ml.) for 12 hrs. The solution was diluted with water (3 ml.) and extracted with ether (2 x 3 ml.). The combined ether extracts were washed with brine (2 x 2 ml.) and dried and the solvent removed to give a solid which was adsorbed on Grade III neutral alumina (0.25 g.) from ether. Elution with the same solvent gave the dione identical in gas liquid chromatographic properties to authentic dione (6% Q.F.1 and 2½% S.E.30).

The mass spectrum was analysed [84] for deuterium content. d_0, 85.2%; d_1, 0.4%; d_2, 9.1%; d_3, 0.8%; d_4, 1.3%; d_5, 1.7%;

d_6, 1.48%. No. of deuteria per molecule, 0.43.

Attempted equilibration of bicyclo (3,3,1) nonan-2,6-dione (82) and endo-endo-2,6-dihydroxybicyclo (3,3,1) nonane (84)

The dione (82) (15 mg.) and diol (84) (15 mg.) were heated with a solution of sodium (38 mg.) in dioxan (1.5 ml.) and water (1.5 ml.) in a sealed ampoule for 72 hrs. at 95°. Gas liquid chromatography (6% Q.F.1 and 2½% S.E.30) revealed that both compounds were still present and that no ketol either endo- (91) or exo- (92) was present.

Endo-, endo-2,6-dihydroxybicyclo (3,3,1) nonane (84)

Endo-2-hydroxy-bicyclo(3,3,1) nonan-6-one (91) (3.1 g.) was stirred for 30 mins. with lithium aluminium hydride (1 g.) in ether (25 ml.). The excess hydride was destroyed by dropwise addition of saturated sodium sulphate solution. Combined ether and ethyl acetate washings of the precipitate were washed with brine (1 x 10 ml.) and dried and the solvent removed to give a solid (2.8 g.) which was recrystallised from pet. ether/ethyl acetate to give endo-, endo-2,6-dihydroxybicyclo (3,3,1) nonane (84). A pure sample was obtained by sublimation (110°/0.5 mm.)

ν_{max} 3620, 2982 cm.$^{-1}$

τ ($CDCl_3$) 6.15(m, $W_{\frac{1}{2}}$ 16 c/s) 8.5(s, removed by D_2O exchange)

The solubility was not sufficient to enable integration period

τ (d_6- DMSO) 5.6(2H,d,J 5c/s removed by D_2O exchange) 6.4(2H,m, $W_{\frac{1}{2}}$ 19c/s) 7.5(2H,m)

(Found: C,69.25; H,10.50. $C_9H_{16}O_2$ requires C,69.20; H,10.30)

The diacetate of the diol was purified by sublimation (80°/0.5 mm.)

ν_{max} 2985, 1485, 1230, 1023 cm.$^{-1}$

τ 5.18(2H,m,$W_{\frac{1}{2}}$ 18 c/s) 8.03(6H,s)

(Found: C,64.70; H,8.25. $C_{13}H_{20}O_4$ requires C,65.00; H,8.40%).

Attempted preparation of 6,6-dideutero-2-ethylenedioxybicyclo (3,3,1) nonane (124)

(a) Endo-2-tosyloxy-2-deutero-6-ethylenedioxybicyclo (3,3,1) nonane (125) (5 g.) was refluxed with lithium aluminium deuteride (0.3 g.) in diethylether (35 ml.) for 48 hrs. An aliquot (1 ml.) was taken out and saturated sodium sulphate solution added dropwise till excess deuteride had been destroyed. The combined ether washings of the precipitate were washed with brine (1 x 2 ml.) and dried and the solvent removed to give a solid which was identical in infra-red spectroscopic and thin layer chromatographic properties to starting material. By addition/distillation the ether was replaced by tetrahydrofuran (35 ml.) and reflux continued for a further 33 hrs. The reaction mixture was worked up as before to give returned starting material.

(b) Endo-2-tosyloxy-2-deutero-6-ethylenedioxybicyclo (3,3,1) nonane (125) (0.1 g.) was refluxed with lithium aluminium hydride

(0.04 g.) in dioxan (10 ml.). Saturated sodium sulphate solution was added dropwise to the cooled reaction mixture until excess hydride had been destroyed. The combined ether washings of the precipitate were washed with water (3 x 10 ml.), brine (1 x 10 ml.) and dried and the solvent removed to give returned starting material shown by infra-red spectrum and thin layer chromatographic properties.

ν_{max}(Nujol mull)(S.P.200) 2225,1598,1498,1175,1125,1110 $cm.^{-1}$

Attempted Wittig on 6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88)

(a) The ketalketone (88) (0.61 g.) in ether (10 ml.) was added to a solution of triphenylphosphonium methylene ylid, formed by stirring a mixture of triphenylphosphonium methyl bromide (2.44 g.) and n-butyl lithium (1.3 ml. of 23% w/v in hexane) in ether (15 mls.) for 4 hrs. under dry nitrogen. The solution was refluxed for 12 hrs. under dry nitrogen. The cooled filtered solution was washed with brine (3 x 15 ml.) and dried and the solvent removed to yield slightly contaminated starting material (0.6 g.) from infra-red spectrum.

After addition of the ketal-ketone to the ylid it was found that replacing the ether by dry tetrahydrofuran and prolonging the reflux time to 48 hrs. did not effect the reaction, starting material being returned once again.

(b) Dimethylsulfoxide (1.5 ml.) was added under dry nitrogen to sodium hydride (0.19 g. of a 50% dispersion in oil which was washed

several times with n-pentane) and heated for 45 mins. at 70-75°. Triphenylphosphonium methyl bromide (1.07 g.) in warm dimethylsulfoxide (3 ml.) was added to the cooled solution of dimsyl sodium and the solution stirred for 10 mins. The ketone-ketal (88) (0.6 g.) in ether (0.5 ml.) was added and the solution stirred for 30 mins. at room temperature. An atmosphere of dry nitrogen was maintained above the reaction mixture throughout. The dimethylsulfoxide was removed at 40° under reduced pressure (1 mm.Hg) and the residue thoroughly extracted with ether. The combined ether extracts were washed with water (6 x 15 ml.), brine (1 x 15 ml.) and dried and the solvent removed to give an oil (0.55 g.) which from infra-red spectrum contained starting material and some olefinic material.

ν_{max} 1710, 1110, 760 cm.$^{-1}$

Attempted "Wittig" reaction on 6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88)

Attnonan-2-one (88)

nonan-2-one (88)

6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88) (0.2 g.) and methylene iodide (0.3 g.) in dry ether (15 ml.) were added over 2 hrs. to magnesium turnings (0.5 g.) in ether (5 ml.) and the solution refluxed under dry nitrogen for 80 hrs. Saturated ammonium chloride solution was added dropwise to the cooled solution till there was no more reaction on addition. The solution was then extracted well with ether and the combined ether extracts washed well with water (2 x 20 ml.), brine (1 x 10 ml.) and dried and the

solvent removed to give a fairly viscous pale yellow liquid whose infra-red spectrum showed that the material was mainly ketonic.

ν_{max} 3500,1710,1600,1498,1187,1175,1110,950,920,880,870,852, 825,802,795 cm.$^{-1}$

6-methylbicyclo (3,3,1) non-6-ene-2-one (144)

6-ethylenedioxybicyclo (3,3,1) nonan-2-one (88) (5.78 g.) in dry ether (15 ml.) was added to a solution of methyl magnesium iodide formed by adding methyl iodide (10 ml.) in dry ether (10 ml.) to dry magnesium turnings (0.83 g.) in dry ether (10 ml.) and allowing all the magnesium to dissolve. After refluxing for 18 hrs. saturated ammonium chloride solution was added dropwise to the cooled solution till there was no more reaction on addition. The solution was then extracted well with ether and the combined ether extracts washed with water (2 x 25 ml.), brine and dried and the solvent removed to give a pale yellow oil (5.4 g.). This oil was refluxed in acetone (50 mls.) containing p-toluenesulphonic acid monohydrate (30 mg.) for 2 hrs. The solution and ether washings were washed with saturated potassium carbonate solution (2 x 25 ml.) brine (1 x 10 ml.) and dried and the solvent removed. The residue was dissolved in ether (25 ml.), washed with brine (1 x 10 ml.) and dried and the solvent removed to give an oil which was refluxed in 50% aqueous sulphuric acid (30 ml.) for 3 hrs. The cooled solution was diluted with water (50 ml.) and extracted with ether (3 x 25 ml.). The combined ether extracts were washed with saturated sodium

bicarbonate solution (2 x 25 ml.), brine (1 x 25 ml.) and dried and the solvent removed to give an oil (2.2 g.) which was adsorbed on Grade III neutral alumina (100 g.) from pentane. Elution with the same solvent yielded 6-methylbicyclo (3,3,1) non-6-ene-2-one (144) as a colourless oil (1.8 g.) from which a pure sample was obtained by micro-distillation (70°/0.5 mm.).

ν_{max} 3012, 1710, 1680, 1100 cm.$^{-1}$

τ 4.5(1H, broad s, $W_{\frac{1}{2}}$ 9c/s) 8.26(s, with very small splittings)

(Found: C,79.70; H,9.35. $C_{10}H_{14}O$ requires C,79.95; H,9.40%)

Endo-2-hydroxy-6-methybicyclo (3,3,1) non-6-ene (145)

6-methybicyclo (3,3,1) non-6-ene-2-one (144) (1.53 g.) was stirred with lithium aluminium hydride (0.32 g.) in ether (15 ml.) for 30 mins. Saturated sodium sulphate solution was added dropwise till all active hydride had been destroyed and the resultant precipitate was washed well with ether. The combined ether washings were washed with brine (1 x 10 ml.), dried and solvent removed to give endo-2-hydroxy-6-methybicyclo (3,3,1) non-6-ene (145) as a colourless oil (1.5 g.) which could be purified by sublimation (80°/0.5 mm.)

ν_{max} 3620, 3004, 1059, 1042, 1021

τ 4.56(1H, broad s, $W_{\frac{1}{2}}$ 8 c/s), 6.42(1H, m, 18c/s),

7.93(s, removed by D_2O exchange) 8.39(s, with small splittings)

(Found: C,78.65; H,10.30. $C_{10}H_{16}O$ requires C,78.90; H,10.60%).

The acetate (146) of this alcohol was purified by micro-sublimation (70°/0.5 mm.)

ν_{max} 3004, 1732, 1238, 1025 cm.$^{-1}$

τ 4.58(1H, broad s, $W_{\frac{1}{2}}$ 9c/s), 5.33(1H,m,15c/s) 8.07(3H,s)

8.39(s, with small splittings)

(Found: C,74.25; H,9.35. $C_{12}H_{18}O_3$ requires C,74.20; H,9.35%).

Attempted isomerisation of endo-2-acetoxy-6-methylbicyclo (3,3,1) non-6-ene (146)

Endo-2-acetoxy-6-methybicyclo (3,3,1) non-6-ene (146) (0.4 g.) in ether (5 ml.) was saturated with dry hydrogen chloride gas at -70°. After removal of solvent at 0° the residue was mixed under dry nitrogen with a solution of potassium triethylmethoxide (4.5 mls. of a solution prepared by dissolving potassium (0.8 g.) in triethylmethanol (5.8 ml.) at 140° for 2.5 hrs.) and this solution kept at 60° for 12 hrs. in a stoppered flask. The infra-red spectrum of the crude material showed no bands at ca. 890 cm.$^{-1}$. Careful distillation afforded no fractions with bands at ca. 890 cm.$^{-1}$.

Endo-2-tosyloxy-endo-6-hydroxybicyclo (3,3,1) nonane (153)

(a) Endo-2-tosyloxybicyclo (3,3,1) nonan-6-one (96) (0.29 g.) was stirred with lithium aluminium hydride (0.07 g.) in ether (10 ml.) for 30 mins. Saturated sodium sulphate solution was added dropwise until all active hydrogen had been destroyed. The combined ether

extracts of the precipitate were washed with brine (1 x 10 ml.), dried and the solvent removed to give an oily solid (0.18 g.). Recrystallisation from pet. ether/ether afforded a pure sample of endo-2-tosyloxy-endo-6-hydroxybicyclo (3,3,1) nonane (153) m.p. 98°-100°.

(b) Endo-2-tosyloxybicyclo (3,3,1) nonan-6-one (96) (0.85 g.) was refluxed for 15 hrs. with sodium borohydride (0.12 g.) in tetrahydrofuran (30 ml.). After solvent had been removed under reduced pressure brine (30 ml.) was added and the solution extracted with ether (2.x 60 ml.). The combined ether layers were washed with brine (1 x 20 ml.), dried and the solvent removed to give a pale yellow oil (0.81 g.). Recrystallisation from pet. ether/ether afforded a pure sample of endo-2-tosyloxy-endo-6-hydroxybicyclo (3,3,1) nonane (153) m.p. 101°-102.5°

ν_{max} 3622,3035,2988,1598,1490,1188,1178 cm.$^{-1}$

τ 2.23(2H, unsym d, J 8.5c/s), 2.68(2H, unsym d, J 8.5c/s), 5.41(1H, m, $W_{\frac{1}{2}}$ 18c/s) 6.25(1H, m, $W_{\frac{1}{2}}$ 15c/s) 7.57(3H,s)

(Found: C,61.75; H,7.15. $C_{10}H_{22}O_4S$ requires C,61.90; H,7.15%).

Attempted preparation of exo-2-tosyloxy-endo-6-hydroxybicyclo (3,3,1) nonane (151)

The same procedure as in (a) above was employed on exo-2-tosyloxybicyclo (3,3,1) nonan-9-one (154) (0.25 g.). An oil

(0.18 g.) was obtained from which no solid tosylate could be isolated although the desired tosylate seemed to be the major product from both infra-red spectrum and thin layer chromatographic behaviour

ν_{max} (film)(P.E.157) 3400,3060,1650,1598,1185,1170 cm.$^{-1}$

1,5-dimethybicyclo (3,3,1) non-2-ene (184)

Zinc dust (20 g.), mercuric chloride (2 g.), water (10 ml.) and concentrated hydrochloric acid (1 ml.) were shaken together and the resulting amalgam washed with several successive amounts of water. Water (10 mls.) was added to cover the amalgan followed by 1,5-dimethybicyclo (3,3,1) non-2-ene-9-one (17) (2 g.) and concentrated hydrochloric acid (25 ml.) and the solution refluxed for 30 hrs. with stirring. The solution was decanted and the amalgam ether washed and the aqueous layer extracted with ether (2 x 10 ml.). The combined ether layers were washed with brine (1 x 10 ml.), saturated sodium bicarbonate solution (3 x 10 ml.) brine (1 x 10 ml.), dried and the solvent removed at 0°C in vacuo to leave 1,5-dimethybicyclo (3,3,1) non-2-ene (184) as a colourless oil (1.2 g.)

ν_{max} (film) (P.E.157) 700 cm.$^{-1}$

Exo-2,3-epoxy-1,5-dimethylbicyclo (3,3,1) nonane (185)

A mixture of 1,5-dimethylbicyclo (3,3,1) non-2-ene (184) (2.6 g.) and 85% m-chloroperbenzoic acid (4.1 g.) was stirred in

chloroform (60 ml.) for 15 hrs. at room temperature. 10% sodium sulphide solution was added dropwise until the chloroform solution no longer gave a black colouration with moist starch iodide paper. The chloroform layer was washed with saturated sodium bicarbonate solution (4 x 20 ml.), brine (1 x 30 ml.) and dried and the solvent removed at 10° under reduced pressure to give the desired epoxide (185) as an oil (2.65 g.)

ν_{max} 995, 923, 815 cm.$^{-1}$

Exo-2-hydroxy-1,5-dimethylbicyclo (3,3,1) nonane (186)

Exo-2,3-epoxy-1,5-dimethylbicyclo (3,3,1) nonane (185) (2.3 g.) and lithium aluminium hydride (1.8 g.) was refluxed in ether (25 ml.) for 12 hrs. Saturated sodium sulphate solution was added dropwise to the cooled solution until all the excess hydride had been destroyed. The combined ether washings were washed with brine (1 x 10 ml.), dried and the solvent removed at 0°C under reduced pressure to give an oil (2.0 g.) which was adsorbed from pentane onto Grade III neutral alumina. Elution with 10% ether/pet. ether yielded exo-2-hydroxy-1,5-dimethybicyclo (3,3,1) nonane (186) as an oil (1.2 g.) whose infra-red spectrum was identical to authentic material[5].

ν_{max}(film)(P.E.157) 3450,1485,1052,980,965,930 cm.$^{-1}$

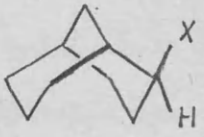
The tosylate (189) of this alcohol was recrystallised from ether/pet ether m.p. 103-105°.

Endo-2-hydroxy-1,5-dimethybicyclo (3,3,1) nonane (188)

Exo-2-hydroxy-1,5-dimethylbicyclo (3,3,1) nonane (186) (0.6 g.) in acetone (10 ml.) was treated at 0° with excess Jones reagent. The solution was poured into brine (10 ml.) and extracted with pentane (3 x 10 ml.). The combined pentane extracts were washed with water (3 x 10 ml.) saturated sodium bicarbonate solution (2 x 10 ml.) brine (1 x 10 ml.) and dried and the solvent removed to give an oil which was stirred in ether (10 ml.) with lithium aluminium hydride (0.3 g.) for 30 mins. The excess hydride was destroyed by dropwise addition of saturated sodium sulphate solution and the precipitate washed well with ether. The combined ether extracts were washed with brine (1 x 10 ml.), dried and the solvent removed to give an oil (0.5 g.) which was adsorbed on Grade III neutral alumina (20 g.) from pentane. Elution with 10% ether/pet. ether gave endo-2-hydroxy-1,5-dimethylbicyclo (3,3,1) nonane (188) as an oil (0.4 g.) whose infra-red spectrum was identical with an authentic sample[5]. The oil solidified to give colourless prisms m.p. 46-48° (LIT.[5] m.p. 48-50°)

ν_{max}(film)(P.E.157) 3400,1485,1060,1038,985,968,959 cm.$^{-1}$

The tosylate (190) of this alcohol was recrystallised from ether/pet. ether m.p. 98°-100°.



(195)

(196)

APPENDIX I

Stereochemistry of Bicyclo (3,3,1) non-2-yl Derivatives

The existence of the bicyclo (3,3,1) nonyl skeleton in the "twin-chair" conformer can be inferred from the presence of "abnormal" methylene bands in the infra-red spectrum[69,85]. These are only present when the C_3 and C_7 positions are unsubstituted and there are no sp^2 carbon atoms in the two three-carbon bridges. The frequencies of these interaction bands, found in a variety of compounds are approximately 2990 and 1490 $cm.^{-1}$

The presence of these bands in bicyclo (3,3,1) non-2-yl derivatives indicates that in the ground state it exists in the "twin-chair" conformation. Therefore in the exo-epimer (195) the carbinyl proton will be equatorial in a chair cyclohexane and in the endo-epimer (196), axial in a chair cyclohexane. From the Karplus equation[86,87] and analogy with other cyclohexane derivatives[88,89] an axial proton surrounded by two equatorial and one axial protons would be expected to have a larger half-band width of its p.m.r. signal than an equatorial proton similarly surrounded. This expected result was found in practice the two values being approximately 18 c/s for the endo-epimers i.e. axial proton and 6 c/s for the exo-epimers i.e. equatorial proton. The experimental values for each individual compound are shown in Table 7.

Table 4 CONT'D.

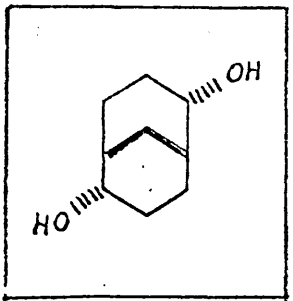
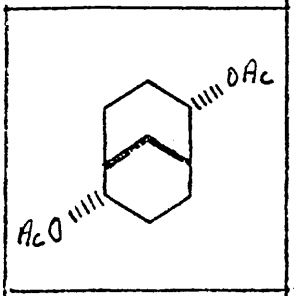
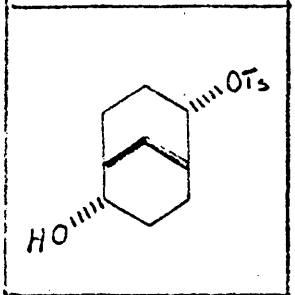
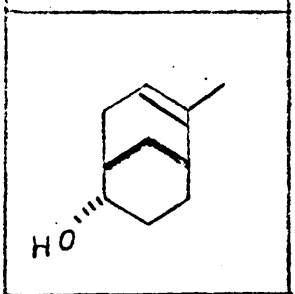
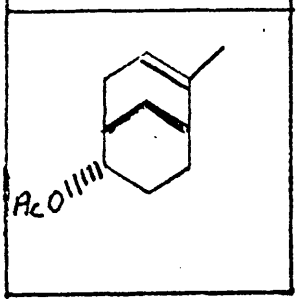
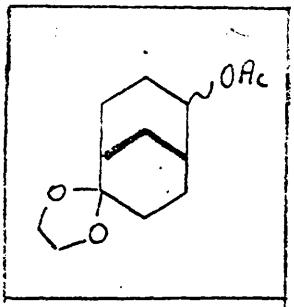
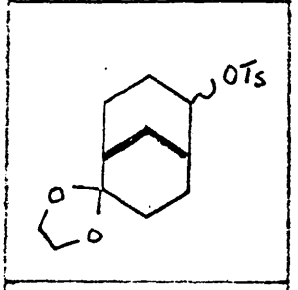
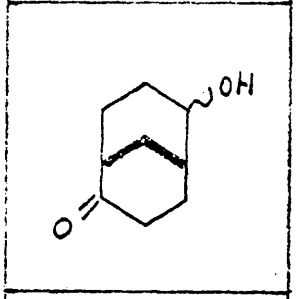
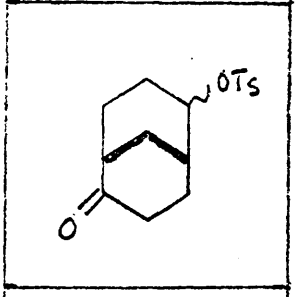
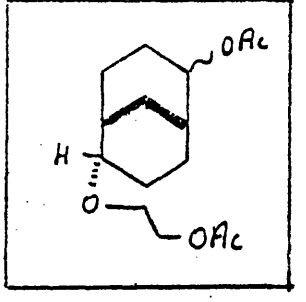
	ENDO		EXO		TWIN CHAIR IR BANDS
	τ	$W_{1/2}$ c/s	τ	$W_{1/2}$ c/s	
	6·15	16	—	—	✓
	5·18	18	—	—	✓
	5·41 6·25	18 15	—	—	✓
	6·42	18	—	—	—
	5·33	15	—	—	—

TABLE 1

	ENDO		EXO		
	τ	$W_{\frac{1}{2}}$ c/s	τ	$W_{\frac{1}{2}}$ c/s	MAIN CHAIR IR BANDS
	5·19	21	5·2	6	✓
	5·42	22	—	—	✓
	6·1	16	6·05	6	—
	5·33	18	5·3	7	—
	—	—	5·18	7	✓

During the course of reaction schemes in Section 2 changes were made to the bicyclo (3,3,1) nonane skeleton (i.e. introducing an sp^2 centre on one of the three-carbon bridges) which removed the abnormal bands without necessarily changing the conformation from "twin-chair". These changes did not affect the configuration of the 2-derivatives and hence from the half-band width comment could be made on the conformation of the cyclohexane ring containing C_2 i.e. if an endo-2-derivative had the same half-band width as other endo-2-derivatives whose conformation is known to be "twin-chair" then that endo-2-derivative must be contained in a "chair" cyclohexane. The half-band widths of such compounds are also shown in Table 7.

APPENDIX II

Rate Constants for Buffered Acetolysis of Alkyl Tosylates

The spectrophotametric method of Swain amd Morgan[74] was employed. It depends on the difference in absorption coefficient for bonded tosylate (λ_{max} 261 nm, ϵ , 671) and free tosylate anion (λ_{max} 261 nm, ϵ , 344), both these measurements being made in water. Hence during solvolysis the absorbance at 261 nm of thesolution falls at the same rate as acetolysis proceeds.

Where it was possible (up to 60°) the rates were by following the reaction in stoppered ultra-violet spectroscopy cells enclosed in a water-heated jacket kept at a constant known temperature using a thermostatically controlled water bath.

At higher temperatures (80° and 100°) the "ampoule" method was used. Here, after making up a stock solution of the tosylate in buffered acetic acid, aliquqts were put in sealed glass ampoules, which were immersed in a thermostatically controlled oil bath. At intervals the ampoules were removed and the reaction quenched by immersing the ampoule in liquid nitrogen. The aliquots were allowed to warm up to room temperature and their ultra-violet spectra run.

In both methods the infinity reading was obtained by allowing the reaction to proceed for approximately ten half-lives.

The plot of log (percentage unchanged tosylate) is time was

a straight line indicating first order kimetics. From the graph the half-life ($t_{\frac{1}{2}}$) of the reaction could be obtained. Hence the rate constant could be calculated from the relationship for first order reactions

$$k = 0.693/t_{\frac{1}{2}}.$$

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