SOLVOLYTIC STUDIES

IN THE

BICYCLONONANE FIELD

THESIS

Presented to the University of Glasgow

for the Degree of Ph.D.

by

Alexander Ballingall Penrose

1969

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

TO RAY

SUMMARY

Cis- and trans-3-allylcyclohexanol have been synthesised and the kinetics and products of buffered acetolysis of the corresponding tosylates investigated. No double bond participation was observed either in the solvolysis products or in the kinetic behaviour.

Exo- and endo-2-bicyclo(3,3,1) nonanol, exo- and endo-6-bicyclo (3,2,2) nonanol and exo- and endo-2-bicyclo(4,2,1) nonanol have been synthesised (the latter two in insufficient epimeric purity for study) and the kinetics and products of buffered acetolysis of the corresponding tosylates have been studied. Interesting kinetic behaviour has been uncovered here and explanations for this are outlined in the text. An exciting non-classical/classical ion interplay has been observed and with the evidence obtained to date, it appears that in this series of isomeric bicyclononyl p-toluenesulphonates, which represents three Wagner/Meerwein related pairs of tosylates, the extent of neighbouring carbon-carbon bond participation and non-classical behaviour varies greatly throughout this series.

Thermodynamic parameters are extensively employed as supporting evidence for the proposed intermediacy of a flexible 'twin-twist boat' conformation in the solvolysis of endo-2-bicyclo(3,3,1) nonyl tosylate, and proposals are outlined for future experiments designed to provide more information on the nature of this intermediate.

ACKNOWLEDGEMENTS

I wish to express my thanks to Dr. W. Parker for his help and advice throughout the past three years; his interest and guidance have been a constant source of encouragement to me.

I would also like to thank Dr. S.R. Logan for his many helpful contributions to the kinetic aspects of this thesis.

My thanks are also due to Mr. J. Gall, Mr. J. Lennon and Miss S.J. Price for nuclear magnetic resonance spectra, to Mr. J.M.L. Cameron and his staff for micro-analyses, to Mrs. F. Lawrie and her staff for high resolution infra-red spectra, and finally to Mr. G. Milmine and his staff for technical assistance, all at Glasgow, and finally to Mr. B. Thorman for nuclear magnetic resonance spectra and to Mr. R. Graham for technical assistance at the New University of Ulster, Coleraine.

To Professors R.A. Raphael and M.F. Grundon I would also like to extend my gratitude for their continued interest during the course of this work, both at Glasgow and Coleraine.

Finally, I am grateful to the Science Research Council for a maintenance award for three years.

CONTENTS

SECTION I.

Preparation and Reactivity of cis- and trans- 3-Allyl-cyclohexanol Derivatives:- A Potential π-Route to the 3-Bicyclo (3,3,1) nonyl Cation.

SECTION II.

Solvolytic Inter-relationships in the Bicyclononane Series:- Potential σ-Routes to Non Classical Ions.

---oOo---

SECTION I.

Preparation and Reactivity of *cis*- and *trans*-3-Allylcyclohexanol Derivatives:- A Potential π -Route to the 3-Bicyclo (3,3,1) nonyl Cation.

INTRODUCTION

In a wide variety of cases, substituents on a molecule may influence a reaction of that molecule by stabilising a transition state or intermediate by becoming wholly or partially bonded to the reaction centre. Winstein[1] called this type of behaviour neighbouring group participation and if the transition state of a reaction is stabilised in this way, an increased reaction rate relative to some suitable model compound generally results, and the neighbouring group is then said to provide anchimeric assistance.

In terms of double bond participation, the generation of a non classical species by the interaction of a double bond and a developing carbonium ion has been described[2] as a π -route to the mesomeric ion. In contrast to the exo-2-bicyclo (2,2,1) heptyl[3], exo-2-bicyclo (3,2,1) and bicyclo (2,2,2) octyl[2], and endo-2-bicyclo (3,2,1) octyl[4] systems, there is a paucity of information relating to bridged ions in the bicyclo (3,3,1) nonane system, and, in particular, π -routes to such species. During a rigorous examination of products and rates of reaction associated

with possible σ- - and π -routes to the same system, Bartlett et.al.[5] found that the distribution and nature of the cyclised products formed, in 18% yield, by the acetolysis of (1) were fully compatible with the intermediacy of (2), and indeed a similar product pattern is uncovered from corresponding treatment of either 9-bicyclo (3,3,1) nonyl (3) or exo-4-cis-hydrindanyl p-toluenesulphonate (4)[6]. Hence, the solvolysis of (1) represents an authenticated π -route to the 9-bicyclo (3,3,1) nonyl cation.

The buffered acetolysis of the cyclo-octenylcarbinyl arenesulphonates (5; R = OTs or OBs) has been reported[7-10] to proceed with an enhanced rate and to afford endo-2-bicyclo (3,3,1) nonylacetate (6; R = OAc) as the major product. Cope et.al.[7] have taken this result to indicate that the reaction proceeds mainly through the unsymmetrical intermediate (7) i.e. the endo-2-bicyclo (3,3,1) / endo-2-bicyclo (4,2,1) nonyl non classical ion*, and thence by positionally selective, stereospecific solvent capture to the endo-2-acetate (6; R = OAc). It has been pointed out[8], however, that acetolysis of (6; R = OBs) might then be expected to proceed

through the same intermediate (7) and hence afford predominantly the starting acetate (6; R = OAc). In the event, acetolysis of (6; R = OBs) gave a mixture of (6; R = OAc) and (8) in the ratio 1:1, and the result has been explained by invoking the classical 2-bicyclo (3,3,1) nonyl cation as the major product-forming intermediate in the solvolysis of both (5) and (6) (R = OBs).

Marvell et.al.[11] have examined the solvolytic behaviour of 3-(3-cyclohexenyl)-propyl p-toluenesulphonate (9) but could find neither kinetic nor product distribution evidence for the intermediate (10), i.e. the exo-2-bicyclo (3,3,1) / endo-6-bicyclo (3,2,2,) nonyl non classical ion*.

An apparent π -route to the 9-oxabicyclo (3,3,1) nonyl 3-cation has been the subject of a preliminary communication by Riemann and his co-workers[12] who found that treatment of (11) with formic acid gave the bicyclic alcohol (12), of undetermined stereochemistry, in high yield. It should be noted that if a bridged ion is involved in such a reaction it could possess stereostructure (13) or (14). These ions

are produced simply by allowing the tetrahydropyranyl cation to interact with two different conformations of the allyl side chain.

Accordingly, the preparation of the cis- and trans-3-allylcyclohexyl esters (15) and (16) (R = OTs) was undertaken to permit an investigation of their solvolytic behaviour, since the stereochemistry of 3-substituted bicyclo (3,3,1) nonanes produced in this reaction might reflect a preference for the intermediacy of the carbocyclic equivalents of (13) or (14).

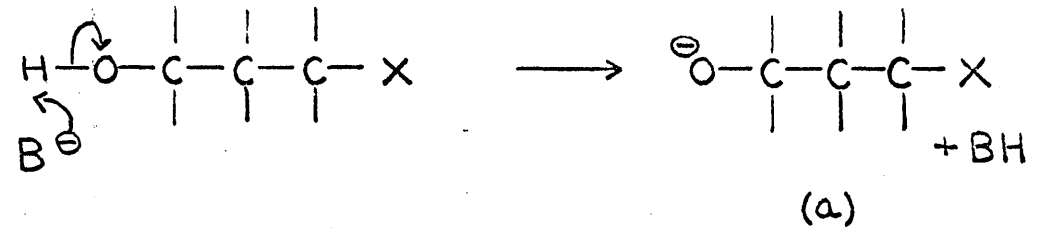
*The whole question of σ-routes to the non classical bicyclo (3,3,1) nonyl cations will be dealt with in Section II of this thesis.

DISCUSSION

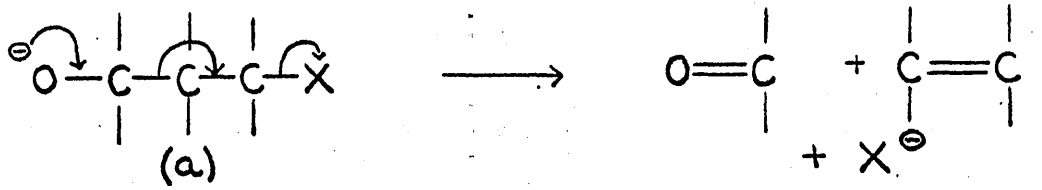
Initial attempts to prepare the obvious precursor, 3-allylcyclohexanone (17) by conjugate 1,4 addition to cyclohex-2-enone of either allylmagnesium bromide or allyl lithium failed, the sole isolable product being the corresponding 1,2 adduct.

The synthetic approach which eventually proved successful was based on the work of Henbest and Clayton[13] in which they described the reactions of cyclohexane-1,3-diol monoarenesulphonates with various metal alkoxides. These workers proposed that reactions of the type (i) and (ii) should clearly be promoted, at the expense of 1,2 elimination , by bases which efficiently generate the necessary intermediate alkoxide ion (a).

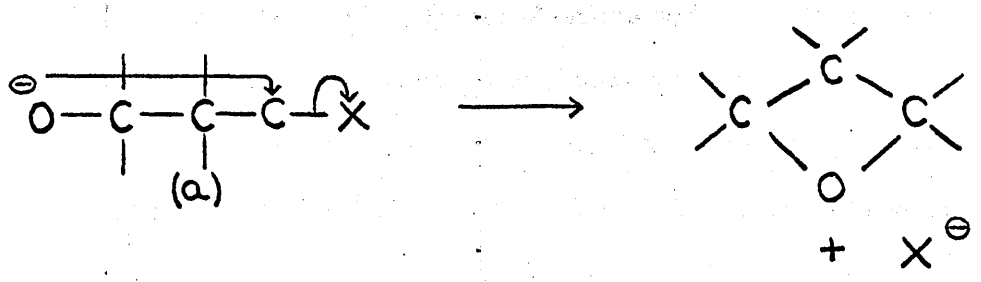
The formation of this ion by alkoxides in alcohol solutions is an equilibrium process, the position of which will depend on the relative acid strengths of the hydroxysulphonate and the solvent alcohol. And since the acidities of alcohols decrease in the order primary > secondary > tertiary[14],



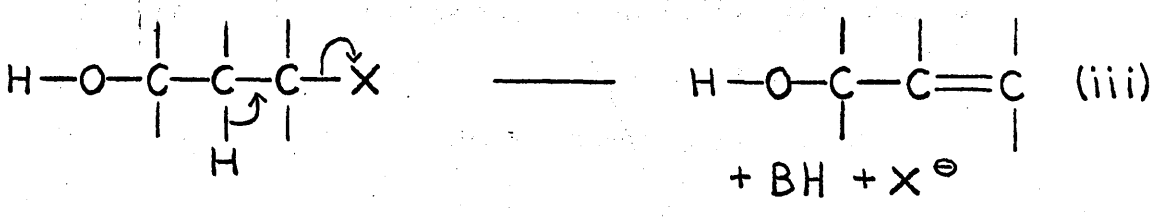
(a)



(a) (i)



(a) (ii)



(iii)

(1,2 elimination)

B^- = Alkoxide Anion

X = Arenesulphonate

a tertiary alcohol should most completely generate the required anion of the starting material.

With this evidence before us, it was concluded that base treatment of the mono p-toluenesulphonates of the bicyclic diols (18) should yield, at least in part, the required 3-allylcyclohexanone (17).

Fortunately 1-hydroxybicyclo (3,3,1) nonan-3-one (19) was a readily-available compound in our laboratories, the preparation being based on the original work of Rabe[15].

Treatment of cyclohex-2-enone with ethyl acetoacetate and sodium methoxide in refluxing methanol, followed by hydrolysis with aqueous potassium hydroxide gave the desired ketol (19). Sodium borohydride reduction of (19) would be expected to proceed by hydride delivery from the less hindered exo-face of the molecule, and the hygroscopic diol thus obtained exhibited in the ^{1}H n.m.r. spectrum a carbinyl proton signal at τ 6.25 (1H, multiplet; half-band width 27 c./sec.). After crystallisation, the diol could be obtained 100% pure as judged by g.l.c. analysis, and was

assigned the 3-endo-hydroxyl configuration (20; R = OH) on the basis of the above mechanistic considerations and spectral comparisons[16].

The mono p-toluenesulphonate ester of the diol (20; R = OH) was prepared by reaction with p-toluenesulphonyl chloride in anhydrous pyridine, care being taken to ensure that the diol was thoroughly dry, and then treated with potassium t-butoxide in dry t-butanol. The product proved to be an 87:13 mixture of the fission product (17) and the elimination product(s) (21) respectively. When sodium ethoxide in ethanol is used as the base, the product ratios change from 87:13 in favour of (17) to 52:45 respectively[17]. This is of course, to be expected on the basis of the relative alcohol acidities, as proposed by Henbest and Clayton[13].

It has also been suggested[13] that the fission reaction described above requires trans-antiparallel arrangement of the C_1-C_2 and C_3 - OTs bond, and that such reactions do not necessarily depend on the additional coplanarity of the alkoxide anion. The boat-chair conformation [16] depicted in (22) fulfils the above stereoelectronic requirements, and

so the high yield of (17) from (20; R = OTs) is to be expected. In conformer (23), however, the disposition of the tosylate group with respect to the surrounding bonds is such as to favour 1,2 elimination. Thus, since elimination products are found, we must invoke both (22) and (23) as product forming intermediates, but we can conclude that on the basis of the Curtin-Hammett Principle, the transition state for fragmentation is energetically more favourable than that for elimination.

With the preparation of 3-allylcyclohexanone (17) now completed, stereoselective reduction of the ketone was examined. Huckel and co-workers[18] have reported that lithium aluminium hydride reduction of 3-methylcyclohexanone gave cis-3-methylcyclohexanol in 94% yield, and corresponding treatment of (17) produced this cis-alcohol (15; R = OH) in 92% yield. Preparation of the epimeric trans-alcohol (16; R = OH) by direct reduction methods was unsuccessful[17], but application of Chang and Blickenstaff's[19] epimerisation procedure to cis-3-allylcyclohexyl tosylate (15; R = OTs) and lithium aluminium hydride reduction of

the resulting formate gave the trans-alcohol (16; R = OH) in 65% yield, free from the cis-isomer.

Cis- and trans-3-n-propylcyclohexanol (24) and (25) (R = OH) were prepared for comparison purposes from the known[20] 3-n-propylcyclohexanone by analogous methods.

The physical characteristics of the cis- and trans-3-allyl cyclohexanols (15) and (16) (R = OH) and cis- and trans-3-n-propylcyclohexanols (24) and (25) (R = OH) are displayed in Table I and provide strong support for the configurational assignments made above. The ν_{O-H} and ν_{C-O} infrared absorption frequencies are in accord with those found for axial and equatorial alcohols of fixed configuration, and in the p.m.r. spectrum an axial carbinyl proton on a cyclohexane ring is known to resonate at higher fields and to have considerably larger half-band widths than its configurational epimer[21]. These generalisations are in agreement with the data of Table I.

With the configurations of the various alcohols now established, the solvolytic studies were carried out using

	n_D/Temp.	τ (CHOH)	$W_{\frac{1}{2}}$	ν C-OH ($cm.^{-1}$)	ν O-H ($cm.^{-1}$)
24 R = OH	1.4623/19	6.58	21	1039	3625
25 R = OH	1.4646/19	6.05	9	976	3629
15 R = OH	1.4745/18	6.55	18	1037	3623
16 R = OH	1.4792/22	6.05	9	981	3629

Table I.

sodium acetate buffered acetic acid as solvent. Should the allyl grouping participate in the solvolysis, with resulting cyclisation, then the 3-bicyclo (3,3,1) nonyl cation (26) will be formed. Collapse of this ion to products can occur in various ways:-

a) Solvent capture at position 3.

b) Elimination of an adjacent proton to form olefin.

c) 1,2 Hydride shift followed by (a) and/or (b).

Thus in addition to the unrearranged system, cyclisation could lead to the bicyclic products (27), (28) and (29). Authentic samples of all these compounds were fortunately available in our laboratories, and using these and the acetates (15) and (16) (R = OAc), capillary g.l.c. conditions were devised which permitted unambiguous detection of both the uncyclised and the possible cyclisation products.

Kinetic studies were carried out using the sealed ampoule technique. The acetic acid used was dried over and distilled from boron triacetate and the sodium acetate buffer was fused before use. At appropriate intervals of time, ampoules were removed from the thermostated oil bath, immersed in

liquid nitrogen to prevent further reaction and allowed to come to room temperature. The ampoules were then opened and the rate of the reaction followed using the ultraviolet spectrometric method of Swain and Morgan[22]. From the data thus acquired, the first order rate constants were calculated using the well-known equation that for a first order reaction the rate constant k is given by:-

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

where $t_{\frac{1}{2}}$ is the reaction half-life period and can be obtained from the graph of Log. (% unchanged tosylate) v. time.

The cis- and trans-3-allylcyclohexyl tosylates (15) and (16) (R = OTs) respectively, were solvolysed for roughly ten half-lives in buffered acetic acid at 100°. The solvolysis mixture was then worked up in the usual way and the products analysed by g.l.c. The results are shown in Table 2, and it can be seen that no bicyclic products were formed. In both cases a mixture of four acetates was formed along with two olefins. The same two

	15 R = OAc	16 R = OAc	Other[a] Acetates	34[b]
15 R = OTs	2	20	1	77
16 R = OTs	4.4	4	1.6	90
	24 R = OAc	25 R = OAc	Other[c] Acetates	Olefins[d]
24 R = OTs	1.5	13.0	0.5	85
25 R = OTs	6.0	2.5	1.5	90

a) Two other acetates were obtained in the ratios 1:1 and 4:1 from (15) and (16)(R = OTs) respectively.

b) The same two olefins were obtained from (15) and (16) (R = OTs) in the ratios 3:2 and 2:1 respectively.

c) Two other acetates were obtained in the ratios 2:1 and 70:1 from (24) and (25) (R = OTs) respectively.

d) The same two olefins were obtained from (24) and (25) (R = OTs) in the ratios 3:1 and 4:1 respectively.

Table 2.

olefins were formed from each tosylate, with neither of these being bicyclo (3,3,1) nonan-2-ene (29) as shown by cross injection experiments. If the carbonium ion (26) had been formed, then by analogy with the work of Eakin et.al.[23] one would expect to find (29) since it is by far the major product of solvolysis of either of the two epimeric tosylates. (30).

The bulk of the acetate fraction in each case was composed of products arising from solvent capture of the 3-allylcyclohexyl cation (31). The minor acetates have not yet positively been identified, but they do not correspond to the expected bicyclic products. However, from their g.l.c. behaviour it is possible that they are the acetates (32) or (33) arising from 1,2 hydride shifts in the cation (31), an effect which we have encountered frequently in our solvolytic excursions in the bicyclononane field and which Whiting et.al. have discovered in a large number of cyclohexyl solvolysis experiments.[24]

A by-product which is generally formed in the Chang[19] epimerisation reaction is an olefin or olefins arising from

1,2 elimination of the tosylate group. From the g.l.c. analysis it was found that the same olefins were obtained from either solvolysis of the epimeric 3-allylcyclohexyl tosylates (15) and (16) (R = OTs) or from elimination in the Chang reaction of dimethylformamide on the cis-tosylate (15; R = OTs). Thus it was tentatively concluded that the olefinic solvolysis products were composed of the olefins (34).

In view of the absence of cyclised products it could be argued that there is no participation by the double bond during solvolysis. However, this effect could be operative without necessarily producing bicyclic products, particularly in the stereochemically favourable trans-system (16; R = OTs). This situation, however, is usually characterised by a significant rate enhancement and products exhibiting retention of configuration when compared to the corresponding dihydro series. It can be seen from Tables 2 and 3 that trans-3-allylcyclohexyl tosylate (16; R = OTs) has in fact a smaller rate constant that its saturated analogue, and in addition, the acetate ratios for each configurational pair of

	15 R = OTs	16 R = OTs	24 R = OTs	25 R = OTs
$T^{o}C$	80.3	80.3	80.3	80.3
$10^{5}k$	4.44	6.56	5.86	10.3
$k_{rel.}$	1.00	1.47	1.32	2.32

Table 3.

tosylates (15) and (24) (R = OTs) and (16) and (25) (R = OTs) are very similar. Indeed the overall picture arising from solvolysis rates and product distribution is one of unassisted solvolysis in the 3-allylcyclohexyl system to the complete exclusion of the potential π - assisted reaction. The double bond in fact exhibits a rate retarding effect on solvolysis which is consistent with the inductive effect of a non-participating double bond in the vicinity of a reaction centre.

Bartlett and his group[25-28] at Harvard have carried out a definitive examination of the structural features which influence the degree of participation by a double bond during solvolysis. When this work is supplemented by that of Wilcox[29], Winstein[2], Marvell[11], Youssef[31] and Closson[32], a pattern emerges for the solvolysis of primary arenesulphonates with a double bond in a five or six membered ring as illustrated in Table 4; i.e. participation is most effective for a chain of six carbon atoms with 1,2 disubstituted double bond at one end and a solvolysable function at the other.

In addition to the stereospecific polyene cyclisations

Arenesulphonate	Ref.	% Product	
		With Participation	Without Participation
2-(3-cyclopentenyl) ethyl	3(a)	100	0
3-(3-cyclopentenyl) propyl	28	0	92-100
2-(2-cyclopentenyl) ethyl	32	0	100
3-(2-cyclopentenyl) propyl	32	58	42
2-(2-cyclohexenyl) ethyl	31	0	100
3-(2-cyclohexenyl) propyl	5	18	82
3-cyclohexenylmethyl	29	0	100
2-(3-cyclohexenyl) ethyl	2	80	20
3-(3-cyclohexenyl) propyl	11	0	95
4-(3-cyclohexenyl) butyl	11	0	96

Products of Acetolysis of Primary Arenesulphonates with Double-bonds in five- or six-membered rings.

Table 4.

invoked both in steroid and triterpenoid biogenesis[33] and total stereospecific steroid sytheses[34], this 'rule of six' seems to have wider application in that cyclo-oct-4-enyl brosylate[35], cyclohept-4-enylcarbinyl brosylate[4], cyclo-oct-4-enylcarbinyl brosylate and tosylate[7-10], cis- and trans-cyclodec-5-enyl[36] p-nitrobenzoates and 5-hexenyl p-nitro benzenesulphonate[27] all give cyclic products on acetolysis. A recent interesting illustration of this rule is provided by Coates and Bertram[37] who subjected the isomeric tricyclic tosylates (35) and (36) to buffered formolysis and found that the isomer (35) was unaffected while (36) underwent smooth cyclisation thus providing a α -route to the atiserine system (37).

In this context we are therefore forced to seek an explanation for the lack of double bond participation in the solvolysis of allylcyclohexyl system. Schaefer and Higgins[38] have rationalised the lack of participation in the solvolysis of trans-3-vinylcyclopentyl bromide (38) (an apparent alternative α -route to the 2-bicyclo (2,2,1) heptyl ion) on three counts; a secondary to secondary carbonium ion change as compared with the primary to

secondary transfer in the 2-(3-cyclopentenyl) ethyl tosylate (39); unfavourable p-to α-orbital overlap in the vinylcyclopentyl cation as compared with the cyclopentenylethyl case and finally on the grounds that a classical norbornyl cation would, of necessity, result from the trans-3-vinylcyclopentyl bromide (38).

In our case the carbonium ion change is a secondary to secondary one and either of the transition states leading to the non classical species (40) and (41) is already experiencing the adverse non bonded interactions which are inherent in the bicyclo (3,3,1) nonane system. We must therefore conclude that the reported ring closures to bicyclo (3,3,1) nonanes of certain 3-allylcyclohexyl systems viz. (11), (42)[39] and (43)[40] must all proceed by a two-step process initiated by unassisted ionisation rather than a true intramolecular displacement by the double bond.

EXPERIMENTAL

Melting points were determined on a hot-stage Kofler apparatus and are corrected. Routine infrared spectra were measured on a Unicam SP 200 instrument, the Unicam SP 100 double-beam infrared spectrophotometer equipped with an SP 130 sodium chloride prism grating double monochromator being used to determine high-resolution spectra. Routine ^{1}H n.m.r. spectra were measured in carbon tetrachloride solution, using tetramethylsilane as internal reference, on a Perkin-Elmer 60 Mc.instrument, and high-resolution spectra on a Varian 100 Mc. instrument.

Thin-layer chromatoplates were prepared from Merck 'Kieselgel G'; preparative plates were 1 mm. thick. Analytical gas-liquid chromatography was performed with a Pye Argon Chromatograph and Perkin-Elmer F 11. Light petroleum refers to the fraction boiling between '40 and 60°. Solutions in organic solvents were dried over anhydrous magnesium sulphate.

1-Hydroxybicyclo(3,3,1)nonan-3-one (19)

Ethyl acetoacetate (8.12 g.) and cyclohex-2-enone (5 g.) were added to a solution of sodium methoxide prepared by the dissolution of sodium (1.20 g.) in dry methanol (75 ml.). After the mixture had been boiled under reflux for 72 hr. a solution of potassium hydroxide (7.28 g.) in water (20 ml.) was added, and heating under reflux continued for a further 12 hr. The methanol was removed by evaporation and the aqueous residue thoroughly extracted with methylene chloride (5 x 10 ml.). The combined organic extracts were washed with hydrochloric acid (4N; 2 x 10 ml.), brine (2 x 10 ml.), saturated sodium hydrogen carbonate solution (2 x 10 ml.) and brine (3 x 10 ml.), and dried. Removal of solvent afforded a tacky solid which on crystallisation from ether gave the ketol (19) (4.0 g.) as a crystalline solid, m.p. 192-193°, ν_{max} (CCl_4) 3613, 1725, 1711 and 1081 $cm.^{-1}$ (Found: C, 70.1; H, 8.9. $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%). G.l.c. retention time (10% P.E.G.A., 150°, 48 ml./min.) 27.4 min., (1% Ap.L, 125°, 44 ml./min.), 4.8 min.

Endo-bicyclo(3,3,1)nonane-1,3-diol (20; R = OH)

Sodium borohydride (3.2 g.) was added to a cold (-10°) stirred solution of the ketol (19) (6.5 g.) in methanol (100 ml.). After 30 min. the cooling bath was removed and the mixture stirred at room temperature for 16 hr. Sufficient hydrochloric acid (4N) was added to bring pH to 6, and the mixture was evaporated to dryness. The solids thus obtained were dissolved in water (20 ml.) and the resulting solution was extracted with methylene chloride for 72 hr. in a continuous-extraction apparatus. The organic layer was separated, dried and evaporated, thus affording a pale yellow solid which on crystallisation from light petroleum (b.p. 60-80°)-ethyl acetate gave the diol (20: R = OH) (5.3 g.) as a crystalline solid, m.p. 212-214°, ν_{max} (CCl_4) 3623, 3609, 1124, 1108, 1084, 1035, 990 and 968 cm.$^{-1}$, τ ($CDCl_3$) 6.24 (1H);(complex multiplet, $W_{\frac{1}{2}}$ 27 c./sec.) (Found: C, 69.0; H, 10.2 $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%). G.l.c. retention time (2% P.E.G., 20 M, 150°, 35 ml./min.) 27.5 min.; product not less than 95% homogeneous by g.l.c.

Monotoluene-p-sulphonate (20; R = OTs)

Toluene-p-sulphonyl chloride (1.3 mol.) and the requisite diol (1.0 mol.) were dissolved in a minimum volume of anhydrous pyridine and the mixture kept at 0° for 48 hr. The mixture, still at 0°, was diluted with ten times its volume of brine and extracted with four portions of ether. The combined ether extracts were washed with hydrochloric acid (4N), brine, sodium hydrogen carbonate solution, and finally brine. After drying and solvent removal, the unstable ester was afforded as a mobile oil. Infrared and t.l.c. characteristics of the product indicated almost complete conversion of the diol into monotoluene-p-sulphonate. All attempts to induce the latter liquid to crystallise failed.

3-Allylcyclohexanone (17)

A solution of (20; R= OTs) (2.00 g.) in anhydrous t-butyl alcohol (10 ml.) was added to a freshly prepared solution of potassium (0.30 g.) in t-butyl alcohol (30 ml.). After heating at 75° for 20 min. the mixture was diluted with brine

(100 ml.), and the t-butyl alcohol removed by evaporation. The aqueous residue was extracted with ether (3 x 20 ml.) and the combined extracts were washed with brine (6 x 20 ml.) and dried. Evaporation of the solvent gave a pale yellow oil, which on fractional distillation, afforded the allyl-ketone (17) (0.46 g.) as a limpid oil, b.p. 30-31°/0.06 mm., n_D^{21} 1.4691, ν_{max} (CCl_4) 3077, 1716, 1640, 991 and 913 cm.$^{-1}$, τ 4.27 (1H; complex multiplet), 4.90 (1H; singlet), and 5.12 (1H quartet with spacings of 3 c./sec.) (Found: C, 77.9; H, 10.3. $C_9H_{14}O$ requires C, 78.2; H, 10.2%). G.l.c. retention time (25% Ap.L, 150°, 32 ml./min.) 13.0 min., (10% P.E.G.A., 100°, 55 ml./min) 12.0 min.

cis-3-Allylcyclohexanol (15; R = OH)

Lithium aluminium hydride (0.01 g.) in anhydrous ether (10 ml.) was added to a stirred solution of the allyl-ketone (17) (0.04 g.) in anhydrous ether (10 ml.), and the mixture stirred at room temperature for 30 min. After the cautious addition of water (40 ml.) and separation of the organic phase, the aqueous layer was extracted with ether (3 x 5 ml.).

The combined extracts were washed with brine (6 x 10 ml.) and dried. Removal of solvent and distillation afforded cis-3-allylcyclohexanol (15; R = OH) (0.035 g.) as a colourless liquid, b.p. 88-90°/2 mm., n_D^{18} 1.4745, ν_{max} (CCl_4) 3623, 3077, 1640, 1094, 1037, 1015, 992 and 912 $cm.^{-1}$, τ 6.55 (1H; complex multiplet, $W_{\frac{1}{2}}$ 18 c./sec., base-line width 38 c./sec.) and 4.27-5.12 (3H; complex multiplets as in allyl-ketone (17)). G.l.c. retention time (10 % P.E.G.A., 100°, 55 ml./min.) 16.2 min.; steric purity 92% (Found: C, 76.8; H, 11.5 $C_9H_{16}O$ requires C, 77.1; H, 11.5%). The corresponding acetate (15; R = OAc) was prepared by treatment with acetic anhydride-pyridine in the usual manner, to give a mobile liquid, n_D^{20} 1.4573, ν_{max} (CCl_4) 3073, 1735, 1640, 1245, 992 and 915 $cm.^{-1}$ (Found: C, 72.3; H, 9.9 $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%).

p-Toluenesulphonates of cis- and trans-3-allylcyclohexanols (15) and (16) (R = OTs)

A mixture of p-toluenesulphonyl chloride (1.1 mol.) and the allyl alcohol (1.0 mol.) was dissolved in a minimum

quantity of anhydrous pyridine and kept at 0° for 24 hr. Brine was added to the mixture which was then extracted with portions of pentane. The combined extracts were washed copiously with brine and dried. Removal of solvent afforded in each case a mobile oil whose t.l.c. and infrared characteristics indicated almost complete conversion of the allyl alcohol into its corresponding p-toluenesulphonate ester. Neither (15) nor (16) (R = OTs) could be induced to crystallise.

Trans-3-allylcyclohexanol (16; R = OH)

A solution of the cis-ester (15; R = OTs) (0.98 g.) in aqueous dimethylformamide (10%; 30 ml.) was heated at 78° for 70 hr. with a boiling ethanol vapour jacket. The mixture was diluted with water and extracted with ether (5 x 5 ml.). The combined extracts were washed with saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulphate. After drying, the ether solution was evaporated to small bulk and treated with lithium aluminium hydride (0.25 g.). After 30 mins., water was added (20 ml.) and the ether layer separated. The aqueous layer was extracted

with ether (3 x 5 ml.) and the combined ether extracts washed with brine and dried. Removal of solvent afforded an oil (0.62 g.) which by t.l.c. and infrared spectroscopy showed the presence of traces of unreacted tosylate as well as the expected olefinic and hydroxylic products. The oil was chromatographed on silica and afforded the trans alcohol (16) as a colourless oil (0.19 g.), b.p. 75-78°/0.8 mm., n_D^{22} 1.4792 ν_{max} (CCl_4) 3629, 1641, 1054, 996, 981 and 913 cm.$^{-1}$ τ 6.05 (1H; complex multiplet, $W_{\frac{1}{2}}$ 9 c./sec., base-line width 16 c./sec.) and 4.27-5.12 (3H; complex multiplets as in allyl ketone (17)). (Found: C, 77.1; H, 11.5; $C_9H_{16}O$ requires C, 77.1; H, 11.5%). G.l.c. retention time (10% P.E.G.A., 100°, 55 ml./min.) 14 min.

The corresponding acetate (16; R = OAc) was prepared by treatment with acetic anhydride-pyridine in the usual manner, to give a water clear liquid, ν_{max} (CCl_4) 3070, 1730, 1637, 1230, 985 and 909 cm.$^{-1}$. (Found: C, 72.3; H, 9.75; $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%).

Buffered Acetolysis of (15) and (16) (R = OTs)

The toluene-p-sulphonates were heated in sealed ampoules

in buffered acetic acid for ca. ten half-lives at 100°, with an approximately 1.2M excess of sodium acetate relative to toluene-p-sulphonate. Toluene-p-sulphonate concentrations were of the order of 40 mg./25 ml. of buffer solution. The sodium acetate was fused before use, and the acetic acid dried over and distilled from, boron triacetate.

After solvolysis, the solutions were poured into ice-water and extracted with n-pentane. The extracts were washed with sodium hydrogen carbonate solution and brine, and dried, ($MgSO_4$). The dried pentane extracts were injected into the gas chromatograph.

cis-3-n-Propylcyclohexanol (24; R = OH)

A solution of 3-n-propylcyclohexanone (10.0 g.) prepared by the method of Woods et al.,[20] in anhydrous ether (50 ml.) was added drop-wise to a stirred suspension of lithium aluminium hydride (1.4 g.) in anhydrous ether (50 ml.). After stirring for 2 hr., water (10 ml.) and then hydrochloric acid (2N; 20 ml.) were added, and the ethereal layer was separated. The aqueous phase was extracted with ether (3 x 10 ml.) and the combined ether phases were washed with

saturated sodium hydrogen carbonate solution (3 x 10 ml.) and brine (3 x 10 ml.) and dried. Removal of solvent gave a pale yellow oil which on distillation yielded the cis-alcohol (24; R = OH) (9.2 g.) as a water clear liquid, b.p. 58-59°/0.35 mm., n_D^{19} 1.4623, ν_{max} (CCl_4) 3625, 1108, 1048, 1039, 1013 and 945 cm.$^{-1}$ τ 6.58 (1H complex singlet, $W_{\frac{1}{2}}$ 21 c./sec., base-line width 37 c./sec.). G.l.c. retention time (10% P.E.G.A., 100°, 63 ml./min.) 6.60 min.; 94% steric purity by g.l.c. The corresponding liquid acetate was prepared, n_D^{20} 1.4429, ν_{max} (CCl_4) 1733, 1245, and 1027 cm.$^{-1}$ (Found: C, 71.7; H, 10.8. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.95%).

The corresponding toluene-p-sulphonate was prepared as a mobile liquid free from starting alcohol.

trans-3-n-propylcyclohexanol (25; R = OH)

A solution of cis-3-n-propylcyclohexanol (0.60 g.) and p-bromobenzenesulphonyl chloride (0.85 g.) in anhydrous pyridine (2 ml.) was kept at 0° for 48 hr. and then swamped with brine (10 ml.). The mixture was extracted with

pentane (5 x 5 ml.) and the combined organic extracts were washed with brine (6 x 10 ml.). Removal of the solvent afforded the p-bromobenzenesulphonate (1.4 g.) as a clear mobile oil. Trituration with light petroleum gave the product as a white crystalline solid, m.p. 56-57°.

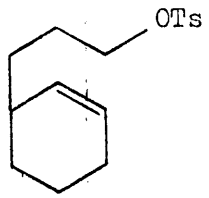
The ester thus obtained was dissolved in aqueous dimethylformamide (10%; 100 ml.) and held at 72° for 96 hr. The mixture was diluted with brine (250 ml.) and extracted with ether (5 x 10 ml.) The combined extracts were washed with saturated sodium hydrogen carbonate solution (2 x 10 ml.) and brine (5 x 10 ml.), and dried.

After evaporation to small bulk (20 ml.) the ethereal solution was added drop-wise to a stirred suspension of lithium aluminium hydride (0.30 g.) in anhydrous ether (25 ml.). After stirring for 30 min., water (10 ml.) and then hydrochloric acid (2N; 20 ml.) were added. After separation of the ethereal layer, the aqueous phase was extracted with ether (3 x 10 ml.) and the combined extracts were washed with saturated sodium hydrogen carbonate solution (4 x 10 ml.) and then dried. Evaporation of solvent afforded a pale yellow oil which on distillation gave the trans-alcohol (0.42 g.) as a clear liquid,

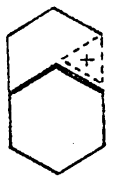
b.p. 75-76°/0.6 mm., n_D^{19} 1.4646, ν_{max} (CCl_4) 3629, 1053, 1036, 1012 and 976 cm.$^{-1}$, τ 6.05 (1H; complex multiplet, $W_{\frac{1}{2}}$ 9 c/sec., base-line width 18 c./sec.) (Found: C, 75.7; H, 12.8. $C_9H_{18}O$ requires C, 76.0; H, 12.75%). G.l.c. retention time (10% P.E.G.A., 100°, 63 ml/min.) 5.80 min.

The corresponding acetate was prepared as a clear liquid n_D^{20} 1.4431, ν_{max} (CCl_4) 1734, 1240 and 1021 cm.$^{-1}$ (Found: C, 71.85; H, 10.95%).

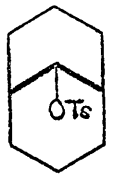
The corresponding toluene-p-sulphonate was a clear oil which could not be induced to crystallise.



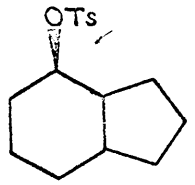
1



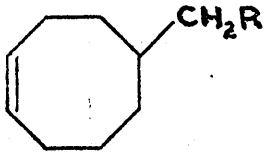
2



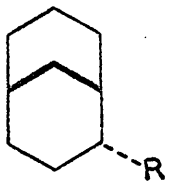
3



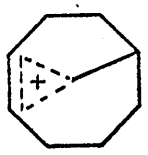
4



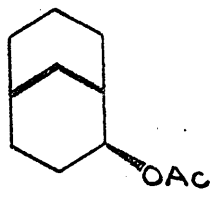
5



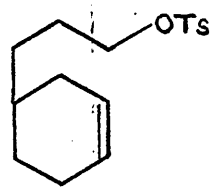
6



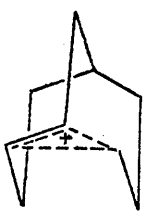
7



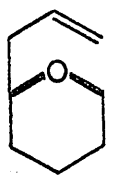
8



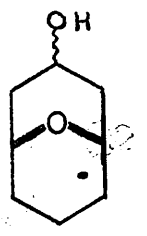
9



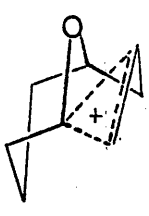
10



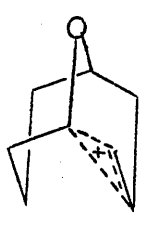
11



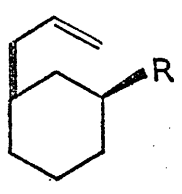
12



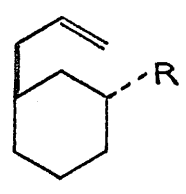
13



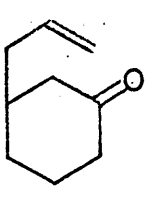
14



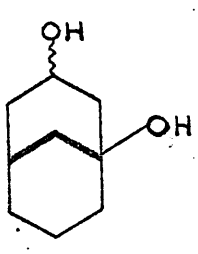
15



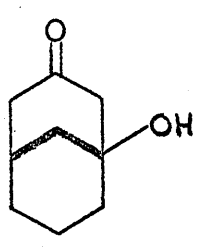
16



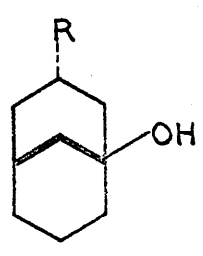
17



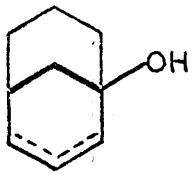
18



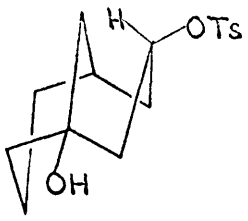
19



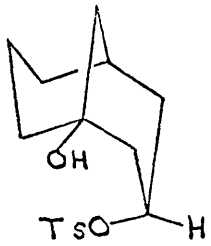
20



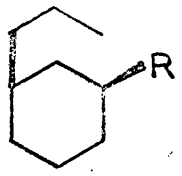
21



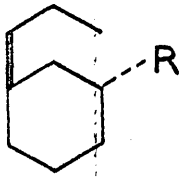
22



23



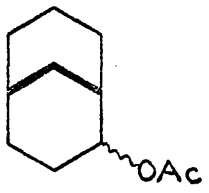
24



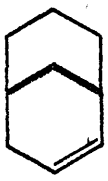
25

26

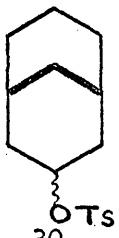
27



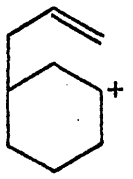
28



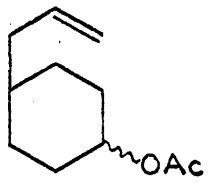
29



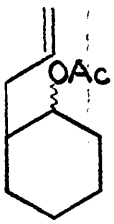
30



31

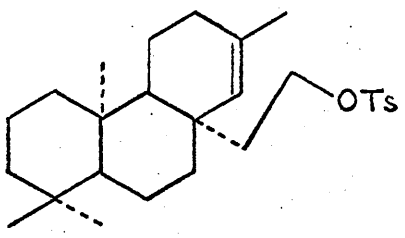


32

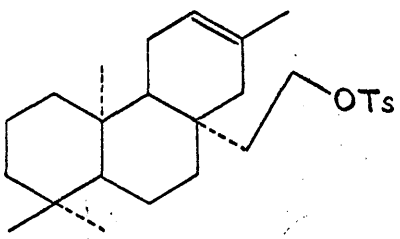


33

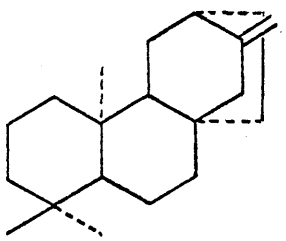
34



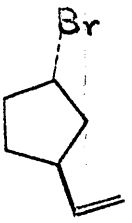
35



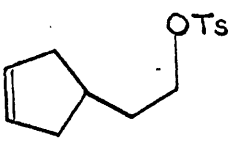
36



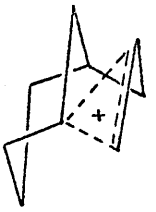
37



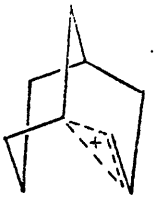
38



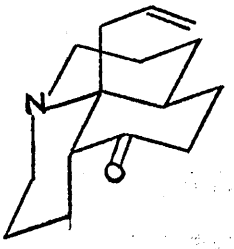
39

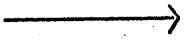


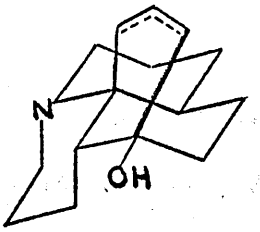
40



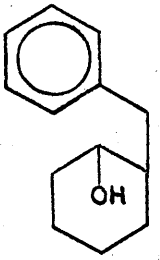
41

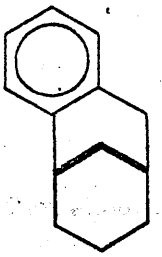






42





43

REFERENCES

1. S. Winstein and R.E. Buckles, J. Amer. Chem. Soc., 64, 2780, 1942.

2. S. Winstein and P. Carter, J. Amer. Chem Soc., 83, 4485, 1961.

3. a) R.G. Lawton, J. Amer. Chem. Soc., 83, 2399, 1961.

   b) P.D. Bartlett and S. Bank, J. Amer. Chem Soc., 83, 2591, 1961.

4. G. Le Ny, Compt. rend., 251, 1526, 1960.

5. P.D. Bartlett, E.M. Nicholson and R. Owyang, Tetrahedron, 1968, Suppl. 8, Part II, 399.

6. C.S. Foote and R.B. Woodward, Tetrahedron, 20, 687, 1964.

7. A.C. Cope, D.L. Nealy, P. Scheiner and G. Wood, J. Amer. Chem. Soc., 87, 3130, 1965.

8. H. Felkin, G. Le Ny, C. Lion, W.D.K. Macrosson, J. Martin and W. Parker, Tetrahedron Letters, 157, 1966.

9. M. Hanack, W. Kaiser, W. Kraus and W. Rothenwöhrer, Tetrahedron Letters, 1705, 1966.

10. K.H. Baggaley, J.R. Dixon, J.M. Evans and S.H. Graham, Tetrahedron, 23, 299, 1967.

11. E.N. Marvell, D. Sturmer and R.S. Knutson, J. Org., Chem., 33, 2991, 1968.

12. F. Bohlmann, H.J. Schultz and J. Riemann, Tetrahedron Letters, 1704, 1964.

13. R.B. Clayton, H.B. Henbest and M. Smith, J. 1982, 1957.

14. McEwan, J. Amer. Chem. Soc., 58, 1124, 1936.

15. P. Rabe, Ber., 37, 1671, 1904; 76B, 979, 1943.

16. W.D.K. Macrosson, J. Martin and W. Parker, Tetrahedron Letters, 2589, 1965.

17. W.D.K. Macrosson, Ph.D. Thesis; Glasgow, 1967.

18. W. Hückel, M. Maier, E. Jordan and W. Seeger, Annalen, 616, 46, 1958.

19. F.C. Chang and R.T. Blickenstaff, J. Amer. Chem. Soc., 80, 2906, 1958.

20. G.F. Woods, P.H. Griswold, B.H. Ambrecht, P.I. Blumenthal and R. Plapinger, J. Amer. Chem. Soc., 71, 2028, 1949.

21. E.L. Eliel, M.H. Gianni and T.H. Williams, Tetrahedron Letters, 741, 1962.

22. C.G. Swain and C.R. Morgan, J. Org. Chem., 29, 2097, 1964.

23. M.A. Eakin, J. Martin and W. Parker, Chem. Commun., 298, 1968.

24. N.C.G. Campbell, D.M. Muir, R.R. Hill, J.H. Parish, R.M. Southam and M.C. Whiting, J. (B), 355, 1968.

25. P.D. Bartlett, S. Bank, R.J. Crawford and G.H. Schmid, J. Amer. Chem. Soc., 87, 1288, 1967.

26. P.D. Bartlett and G. Dann Sargent, J. Amer. Chem. Soc., 87, 1297, 1967.

27. P.D. Bartlett, W.D. Closson and T.J. Cogdell, J. Amer., Chem. Soc., 87, 1308, 1967.

28. P.D. Bartlett, W.S. Trahanovsky, D.A. Bolon and G.H. Schmid, J. Amer. Chem. Soc., 87, 1314, 1967.

29. C.F. Wilcox Jr. and S.S. Chibber, J. Org. Chem., 27, 2332, 1962.

31. A.A. Youssef and S.M. Sharaf, J. Org. Chem., 33, 2581, 1968.

32. W.D. Closson and G.T. Kwiatkowski, J. Amer. Chem., Soc., 86, 1887, 1964.

33. R.B. Clayton, Quart. Revs., Vol. XIX, No. 2, 1965, p. 168 and references therein.

34. W.S. Johnson, N.P. Jensen, J. Hooz and E.J. Leopold, J. Amer. Chem. Soc., 90, 5872, 1968 and references therein.

35. A.C. Cope, P.E. Peterson and J.M. Grisar, J. Amer., Chem. Soc., 82, 4299, 1960.

36. H.L. Goering and W.D. Closson, J. Amer. Chem. Soc., 83, 3511, 1961.

37. R.M. Coates and E.F. Bertram, Chem. Commun., 797, 1969.

38. J.P. Schaefer and J. Higgins, J. Org. Chem., 32, 553, 1967.

39. H. Dugas, R.A. Ellison, Z. Valenta, K. Wiesner, and C.M. Wong, Tetrahedron Letters, 1965, 1279.

40 J.W. Cook and C.L. Hewett, J. Chem. Soc., 1936, 62.

SECTION II.

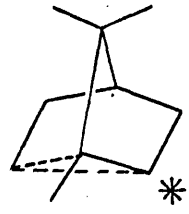
Solvolytic Inter-relationships in the Bicyclononane Series:- Potential σ-Routes to Non Classical Ions.

INTRODUCTION

In a publication by C. L. Wilson[1] in 1939 on the rearrangement of camphene hydrochloride into isobornyl chloride, the following statement appeared:-

"Although the intermediate is represented as having the camphene structure, it is possible that it is mesomeric between this and the corresponding isobornyl structure.

.....One condition..... would seem to be that, whatever the structure of the ion, the stereochemical identity of the carbon marked with an asterisk must be preserved."



Although the veracity of this statement was not tested at the time, the implications therein represented the planting of a seed, which some ten years later, was to appear as a slender sapling which in the next twenty years would flourish

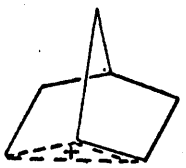
and grow into a powerful and fruitful tree.

The sapling was, of course, the preliminary communication of Winstein and Trifan[2] on the nature of the cationic intermediate formed during the solvolytic ionisation of the norbornyl system (1), and the tree and its fruits are the ever-widening field of carbonium ion chemistry and the techniques and concepts which have arisen as a result of Wilson's original suggestion.

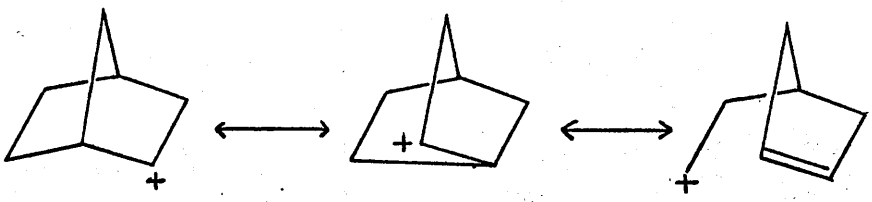
From both stereochemical and kinetic evidence Winstein and Trifan[2] proposed the intermediacy of the symmetrical three-centred carbonium ion (2) during the acetolysis of the brosylate (1; R = OBs). This type of electron deficient ion, formed by the interaction of the σ-electrons of a carbon-carbon bond with an adjacent carbonium ion has been called by Ingold[3] a " synartetic ion ". However, this terminology has been superceded by the name "non classical ion", defined[4] as an ion having delocalised bonding σ-electrons in its ground state. Winstein's proposal of a non classical intermediate fired the interest of a host of workers, some agreeing with the existence of

these species, others disagreeing. And even to-day the Brown-Winstein controversy over non classical ions still rages.

However, whether one considers the intermediate as being the non classical species (3) or in terms of the three limiting structures (3a-c) of the valence bond notation, the fact remains that this field of study has resulted in many elegant contributions to the theory of valency.



3



3a 3b 3c

In principle, there are several ways in which non classical carbonium ions can be formed e.g.

a) Direct solvolysis of arenesulphonates - σ -route.

b) Olefin participation in solvolysis - π -route.

c) Ring expansion routes. (See Fig. I).

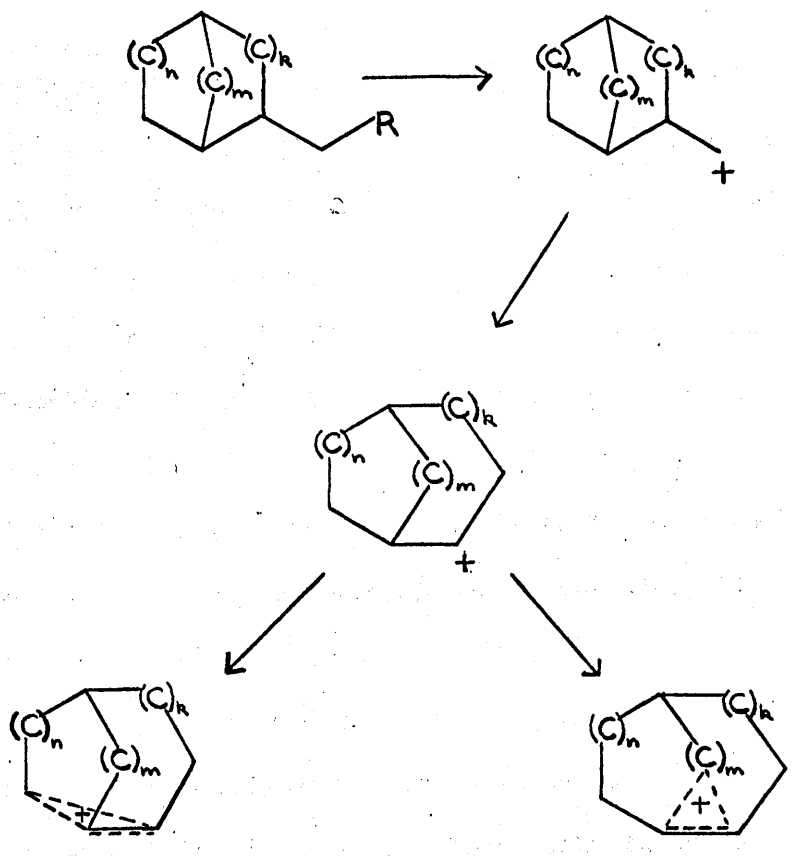
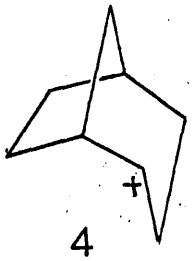
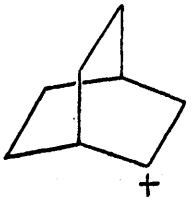


Fig. I

The 2-bicyclo (2,2,2)/(3,3,1) octane cations (4) and (5) have been extensively studied by various workers using all three of these approaches.



4



5

There are two main points to be remembered about (4) and (5). Firstly, there are two epimeric tosylates which can give rise to ion (4) - the endo-(equatorial) tosylate (6; R = OTs) and the exo-(axial) tosylate (7; R = OTs), whereas in the case of the ion (5) there is only one such tosylate (8; R = OTs) due to the symmetry properties of the bicyclo (2,2,2) octane ring system. Secondly, from consideration of the stereochemically favoured Wagner/ Meerwein shifts in the three isomeric tosylates, it can be seen that the exo-(3,2,1) and the (2,2,2) octane systems are related by migration of bonds (i), whereas a corresponding shift of the appropriate bond (ii) in the endo-tosylate (6; R = OTs) leads only to an enantiomeric

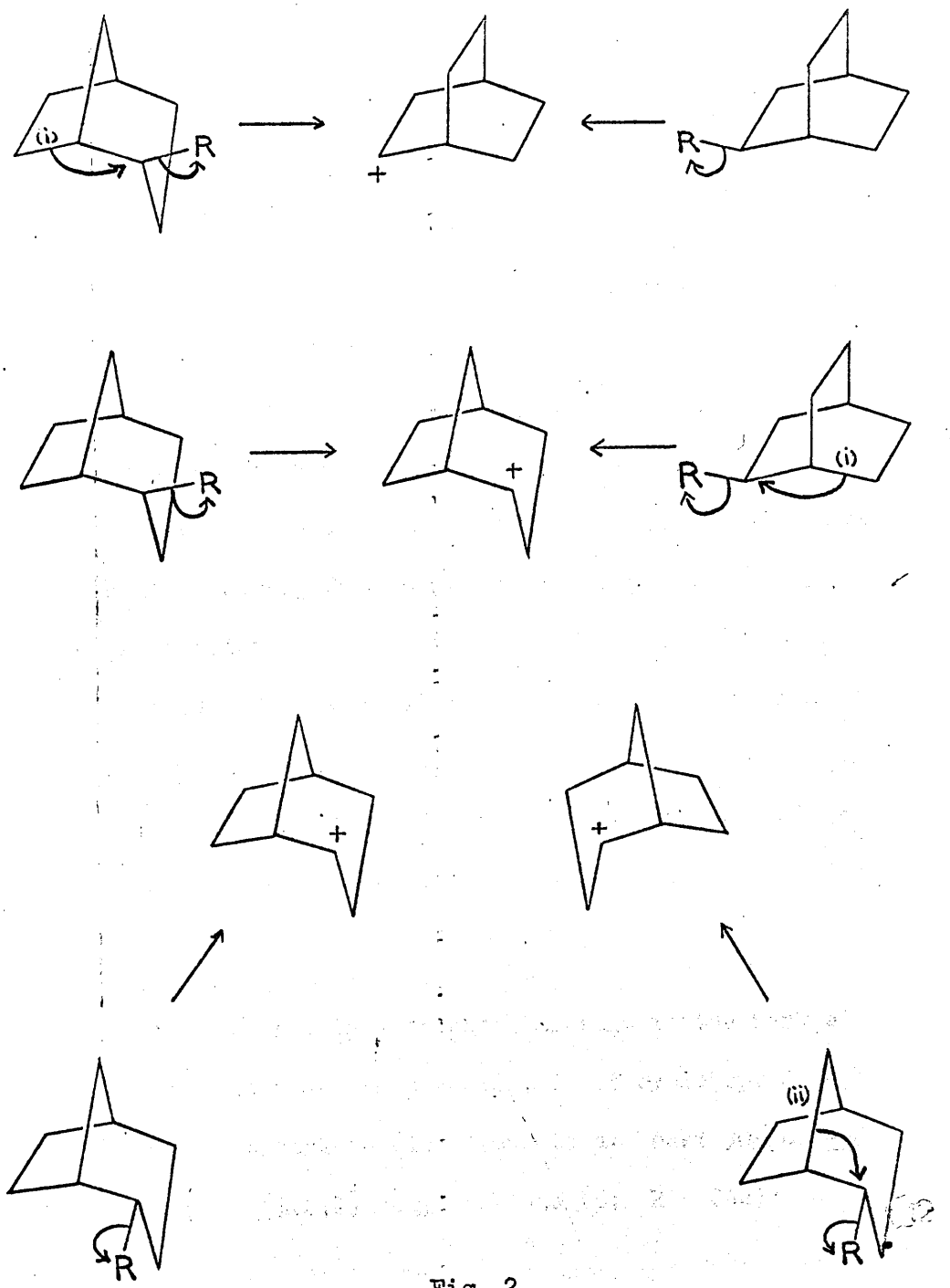


Fig. 2

structure. (See Fig. 2).

Goering and Fickes[5] examined the solvolytic behaviour of all three of the esters (6), (7) and (8) (R = OTs), both from a kinetic and a product distribution standpoint. They found that by far the major product of buffered acetolysis of endo-2-bicyclo (3,2,1) octyl tosylate (6; R = OTs) was the corresponding endo-acetate (6; R = OAc); and when optically active substrate was used, the products were at least 99% racemic. Hence, Goering formulated the major product forming intermediate as the non classical ion (9). The necessary direction of solvent attack on this ion, together with its symmetry properties, adequately account for the observation of almost total retention of geometrical configuration and racemisation of the major product.

Support for this proposal appears in the work of Le Ny[7] who found that acetolysis of cyclohept-4-enyl carbinyl brosylate (10) leads to at least 90% of endo-2-bicyclo (3,2,1) octyl acetate (6; R = OAc); a

result expected from a non classical intermediate, i.e. very similar, if not identical, products from σ- and π - routes, with the small variation observed in the amount of the major product (6; R = OAc) being possibly due to the different locations of the counter ion in the two pathways. This latter effect must be small, however, since both routes lead to more than 90% <u>endo</u>-acetate (6; R = OAc).

On the other hand, the Wagner/Meerwein related <u>exo</u>-2-bicyclo (3,2,1) octyl and 2-bicyclo (2,2,2) octyl tosylates exhibit strikingly different solvolytic behaviour. Under a variety of solvolysis conditions, each tosylate gives the same binary mixture of compounds, e.g. a 45:55 mixture of the acetates (7) and (8) (R = OAc) respectively, is obtained from acetolysis. In addition, when optically active substrates are employed (7) and (8) were found to retain a substantial amount of optical activity.

These observations were explained by invoking the non classical species (11) as the major product forming intermediate. This ion is unsymmetrical and would be

expected to lead to optically active and, in a geometric sense, configurationally pure products.

As with the case of the endo-2-tosylate (6; R = OTs) there is π-route support for the non classical ion (11) being an intermediate. Winstein and Carter[8] found that the major product of acetolysis of 2-(3-cyclohexenyl) ethyl tosylate (12; R = OTs) was again a binary mixture of the acetates (7) and (8) (R = OAc), in the ratio 46:54 respectively.

The fact that a small amount of the epimeric exo-(3,2,1) acetate (7; R = OAc) and its (2,2,2) isomer (8; R = OAc) is produced during acetolysis of (6; R = OTs) has been rationalised by Goering in terms of interconversion of the non classical ions (9) and (11) probably via the classical ions (13) and (14). This leakage or crossover is virtually negligible in the reverse direction, with very little, if any, endo-(3,2,1) product being formed from the exo-(3,2,1)/(2,2,2) system.

That there is leakage from one carbonium ion system to another is supported by evidence from the deamination

reactions of exo- and endo-2-norbornyl carbinylamines (15) and (16) i.e. the ring expansion route described in Fig. I above.

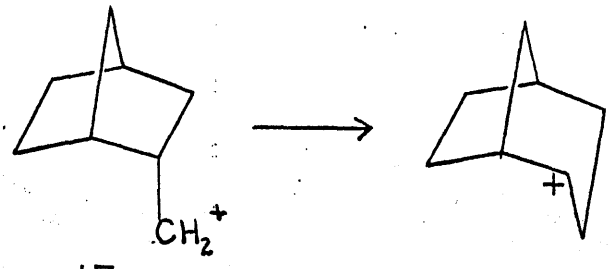
Berson and co-workers[9,10] have found that these epimeric amines are related to two different carbonium ion systems since the product distribution from each is quite different. A "memory effect" seems to be operative here in that the endo-amine (16) gives rise to a product distribution similar to that from the endo-tosylate (6; R = OTs) whereas deamination of the exo-isomer leads to a mixture of alcohols similar to that obtained from solvolysis of (7) and (8) (R = OTs).

It was also found that of the 80% endo-(3,2,1) alcohol (6; R = OH) formed from optically active amine (16), at least 80% of its optical purity had been lost, whereas the exo-(3,2,1) and (2,2,2) alcohols (7) and (8) (R = OH) had retained 90% and 50% respectively of the initial optical purity of (15).

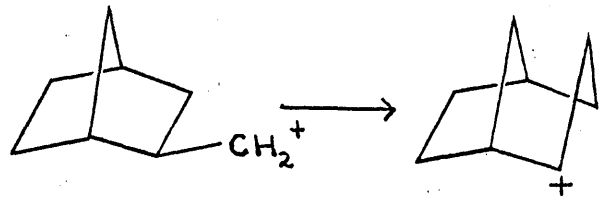
Thus the solvolytic behaviour of the various bicyclic

derivatives can be explained on the basis of one or other of the non classical ions (9) and (11) being the major product forming intermediate, approach to them being possible via σ-, π - and ring expansion routes. It is perhaps noteworthy that, in contrast to the norbornyl system, Brown has never challenged this formulation.

However, any complete mechanistic description of these reactions must take account of the significant deviations in optical purity detected in the products and also the small amounts of additional products formed, neither of which would arise if the intermediate in the reactions was solely one of the non classical ions (9) and (11). In the case of the ring expansion deamination reactions, the non classical species cannot be formed directly from the substrates since the latter do not fulfil the stereoelectronic trans-anti-parallel bond arrangement requirement, but must arise after the initial formation of the classical carbonium ions 17 and 18.



17



18

This has led the Wisconsin Group[9,10] to produce the somewhat complex but nevertheless essential mechanistic schemes shown in Fig.3.

Berson[10] has pointed out that unlike the 2-norbornyl system, the energy difference between (9) and (11) and their classical counterparts may not be very high, and has provided compelling evidence that such classical

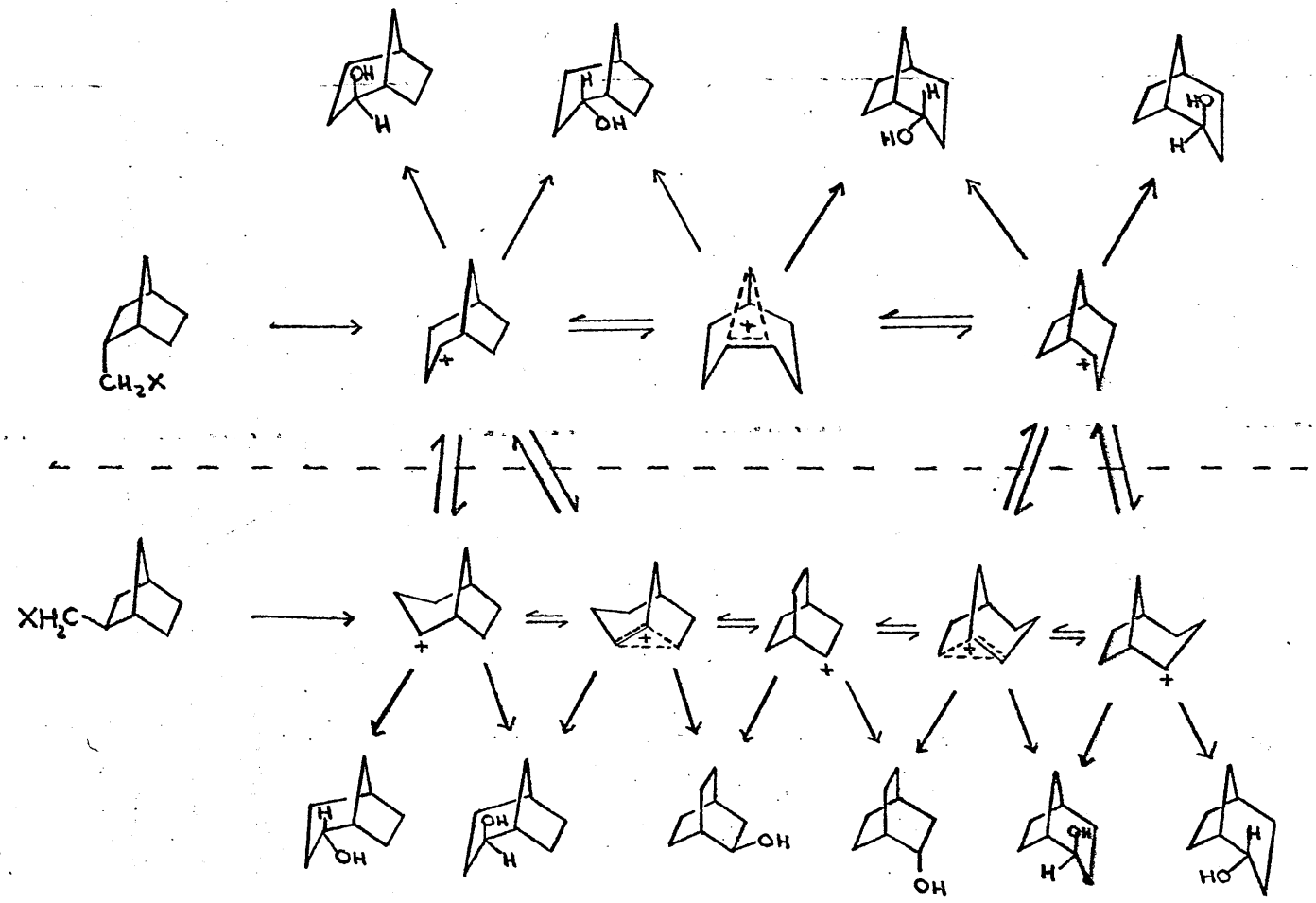


Fig. 3.

species do exist as detectable intermediates during these reactions. In summing up the results from the norbornyl and bicyclo-octane systems discussed above he has also speculated that perhaps the reactivities of bicyclic non classical ions may fall into a graded series, and that norbornyl represents that extreme of behaviour in which the non classical ion is sovereign, with its classical counterparts becoming more and more important as the ring systems increase in size.

It therefore seemed important to examine the solvolytic behaviour of the next higher bridged ring series i.e. the bicyclononyl system.

From the point of view of trans-anti-parallel σ-bond displacement, Wagner/Meerwein participative interrelationships in this series do not seem improbable, since the bond alignments are at least as good as those in the bicyclo-octane series.

If non classical ions solely were involved, then for substituents adjacent to the ring junctions the following relationships would hold:- (see Fig. 4)

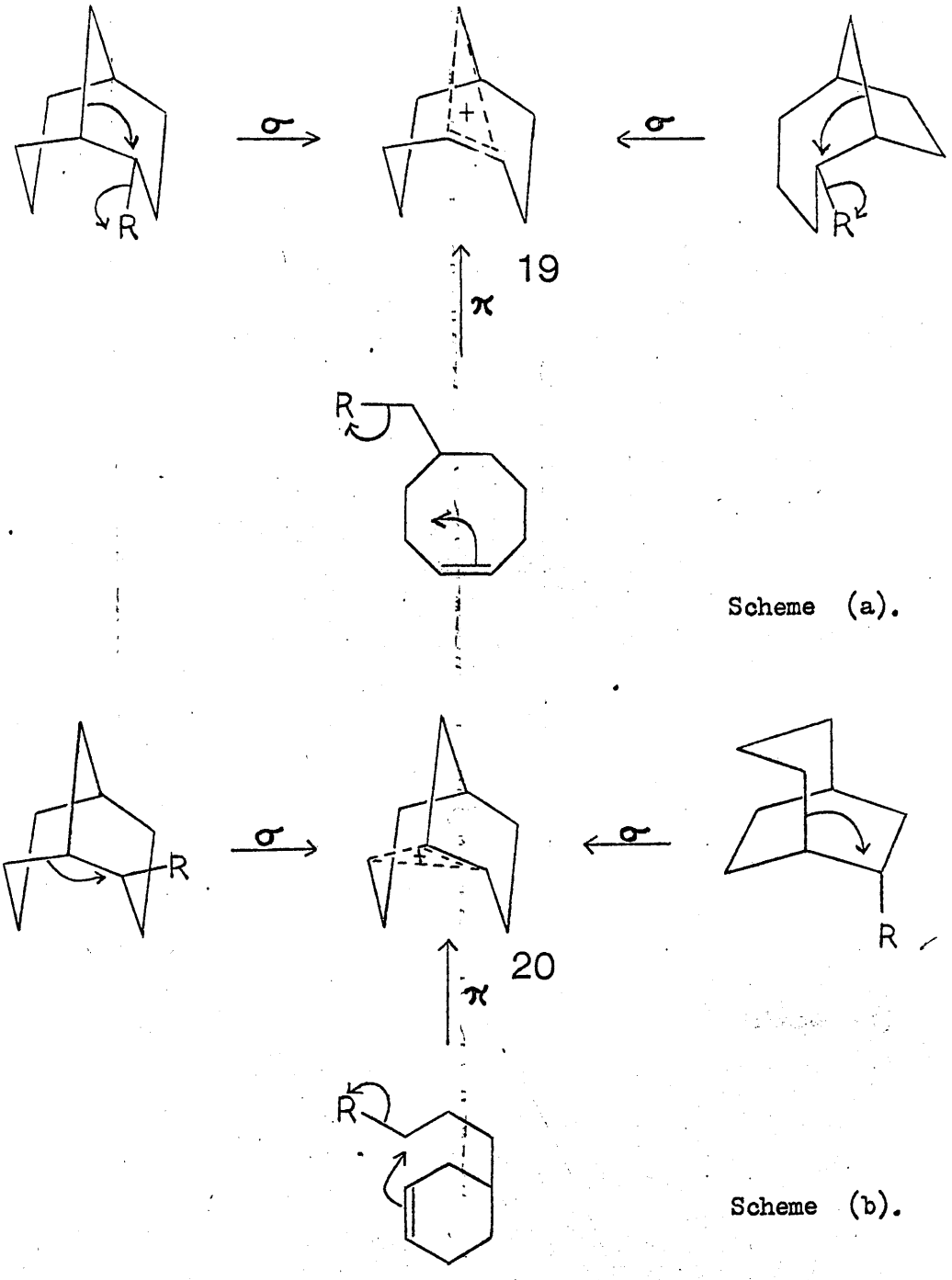
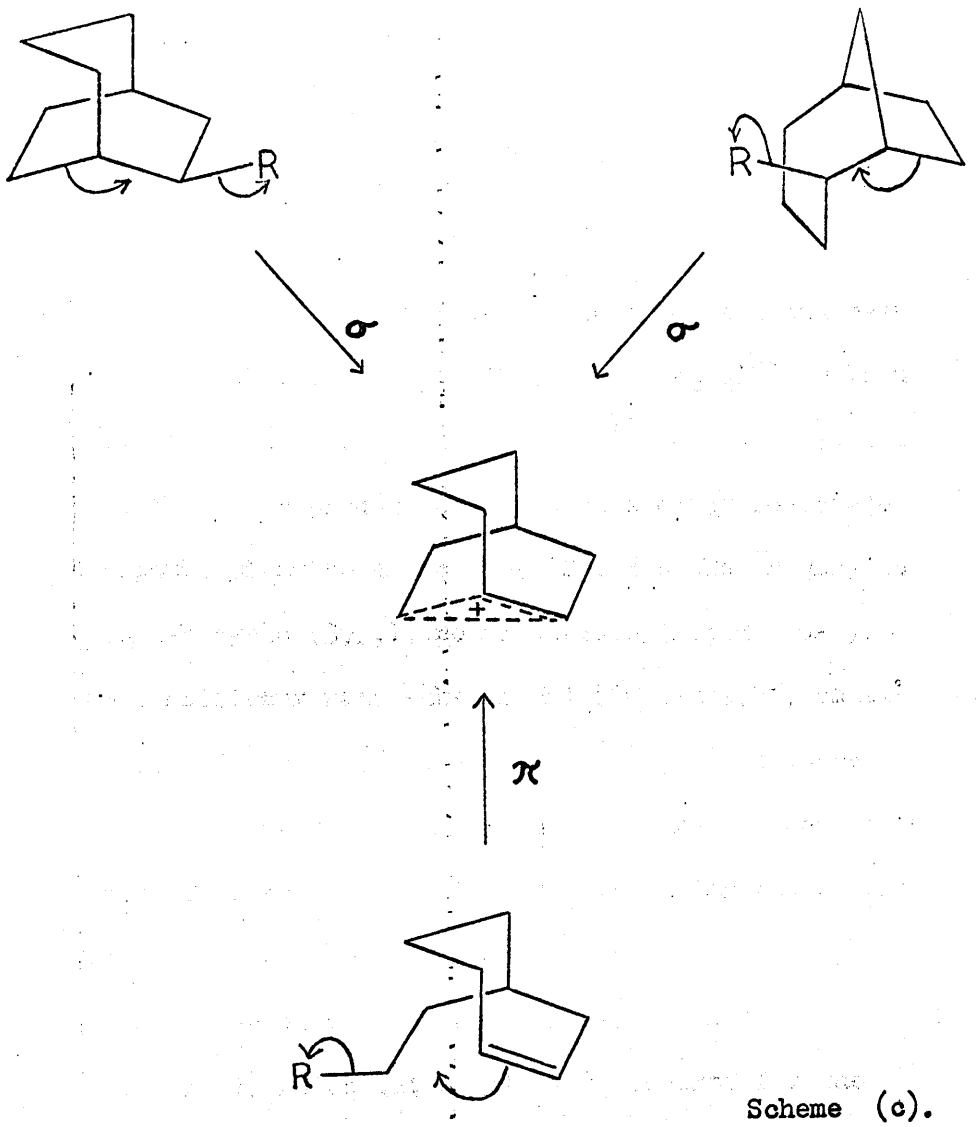


Fig. 14



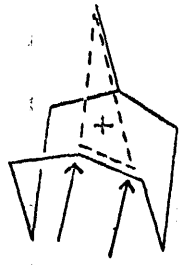
Scheme (c).

Fig. 4

In other words, three different unsymmetrical non classical ions can be formulated as arising from solvolysis of the Wagner/Meerwein related 2-bicyclo (3,3,1); 2-bicyclo (4,2,1) and 6-bicyclo (3,2,2) nonyl derivatives.

A literature survey revealed that a start had been made in this problem, Cope et.al.[11], Hanack et.al.[12], Felkin et.al.[13] and belatedly Graham et.al.[14] have all reported that the major product of acetolysis of cyclo-oct-4-enylcarbinyl arenesulphonates (22; R = OTs or OBs) is endo-2-bicyclo (3,3,1) nonyl acetate (23; R = OAc). The significant rate enhancement (70 times)[13], small amounts of olefin (10%) and the high product stereospecificity observed in the reaction are all characteristic of carbonium ion reactions involving non classical intermediates. Hence Cope[11] suggested that the intermediate species was the non classical ion(19) (cf. Ref. 7) which satisfactorily accounts for the formation of the endo-acetate (23; R = OAc), even although one would have expected the latter to be accompanied by a substantial amount of the isomeric endo-2-bicyclo (4,2,1) acetate (24; R = OAc) on the

basis of the statistically equal chance of backside attack by solvent at the two positions shown on the non classical carbonium ion (19). To date, the largest amount of



19

(24; R = OAc) detected is only 18%[14] and even here its stereochemistry has only been inferred.

Marvell[15] has attempted a α-route entry to the mesomeric ion (20) of scheme (b) (see Fig.4) by solvolysis of 3-(3-cyclohexenyl)-propyl p-toluenesulphonate (25) but could find neither kinetic nor product distribution evidence for the ion (20).

The solvolysis of the brosylate (26; R = OBs) has been described by Schaefer[16], however the study was concerned with the kinetics rather than the products of the reaction. Schaefer[17] has also examined the solvolytic

behaviour of the 6-bicyclo (3,2,2) nonyl p-nitrobenzene sulphonates (27; R = ONs). However, since the substrate was known to be impure and its stereochemical assignation inconclusive, the intrinsic value of the results must be measured with some care.

In view of this paucity of information relating to the solvolytic behaviour of the various participants in the schemes (a), (b) and (c) shown in Fig.4, we decided to unambiguously synthesize exo- and endo-2-bicyclo (3,3,1) nonyl tosylates (26) and (23) (R = OTs), exo- and endo-2-bicyclo (4,2,1) nonyl tosylates (28) and (24) (R = OTs) and exo- and endo-6-bicyclo (3,2,2) nonyl tosylates (29) and (30) (R = OTs) respectively and to study their solvolytic behaviour in the light of schemes (a), (b) and (c). (See Fig. 4).

DISCUSSION

The first hurdle to be surmounted in the solution of the problem was the synthesis of the three epimeric pairs of tosylates (23) and (26), (24) and (28) and (29) and (30) (R = OTs) described in the introduction to this section.

A common feature in the envisaged synthetic routes to the three isomeric ring systems was the involvement of ketones as key intermediates. Unambiguous syntheses were devised for the preparation of the ketones (31), (32) and (33) from which we hoped, by suitable choice of reducing agents, to obtain the alcohols (23), (24), (26) and (28)-(30) in high epimeric purity. As will become evident in the text, however, this was only partially successful and several modifications had to be made to the syntheses.

The route to bicyclo (3,3,1) nonan-2-one (31) was based on the work of Stork *et.al*[18] who had shown that condensation of acrolein with the pyrrolidine eneamine of cyclohexanone (34) in dioxan solution gives the bicyclic keto amine (35) in high yield. Application of the modification of Hanack[19] to this reaction resulted in a yield of 65% of the desired

product (35). Thus in one reaction we have already formed one of the desired ring systems, and in addition have achieved substitution at the required 2-position. The keto group in (35) was removed by Wolff-Kishner reduction to give the saturated amine (36) again in good yield.

Hauck and Leonard[20] have shown that mercuric acetate oxidation of a tertiary amine results in direct formation of the related eneamine, and treatment of (36) with mercuric acetate in aqueous acetic acid, followed by hydrolysis of the intermediate (presumably the eneamine 37) with dilute hydrochloric acid led to the formation of the ketone (31) in 40% yield after chromatographic purification.

With this ketone now available in substantial quantity, its reduction was investigated. In accord with the findings of Graham et.al[14], treatment of (31) with lithium aluminium hydride in anhydrous ether yielded an alcohol which by g.l.c. analysis was not less than 96 - 98% epimerically pure. The pure epimer was obtained by crystallisation

from pentane, and was identical in all respects with an authentic sample of endo-2-bicyclo(3,3,1) nonanol (23; R = OH). The p.m.r. spectrum exhibited a complex multiplet integrating for one proton and centred at τ 6.14 with a half-band width of 17 c./sec. - a value consistent with an axial carbinyl proton and hence with an equatorial hydroxyl group[21].

Brown[22] has found that in the hydride reduction of bicyclic ketones, the direction of reduction is controlled by steric factors in rigid sterically congested ketones. Thus it would appear that from the above results, the exo-face of the 2-ketone (31) must be much more exposed than the endo-face. For this reason it is unlikely that reagents which have been known to give high yields of axial alcohols e.g. complex boranes[23] would do so in the case of the ketone (31), and alternative routes to the exo-alcohol (26; R = OH) had to be sought.

It is known[24] that hydroboration of 2-bicyclo (3,3,1) nonene (38) proceeds exclusively from the exo-face of the

molecule and gives rise to approximately equal amounts of exo-2- and exo-3-bicyclo (3,3,1) nonanols (26) and (39) (R = OH) respectively. Since this would mean an upper limit of around 50% for the yield of the desired alcohol, this route was not further considered.

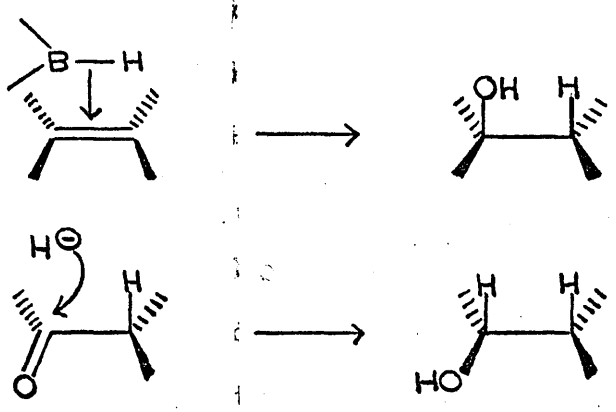
Chang and Blickenstaff[25] have shown that treatment of tosylates with dimethylformamide gives rise to the respective epimeric formate in appreciable yields, accompanied by olefinic products formed by β - elimination. Since the endo- (3,3,1) tosylate (23; R = OTs) was available in substantial quantities, this reaction seemed a suitable method of obtaining exo-2-bicyclo (3,3,1) nonanol (26; R = OH). The tosylate (23; R = OTs) was therefore heated at 78°C in 10% aqueous dimethylformamide solution, and the product reduced with lithium aluminium hydride to convert the formate to the corresponding alcohol. Chromatography afforded the required exo-alcohol (26; R = OH) identical with that obtained by hydroboration of the olefin (38). Unfortunately, the alcohol was accompanied by the formation of large amounts of the olefin (38) and

the best yields of (26; R = OH) were of the order of 40 - 45%. In addition the epimeric purity of the desired alcohol was not always totally reproducible.

Graham et.al.[14] have shown that lithium aluminium hydride reduction of the exo-epoxide of 2-bicyclo (3,3,1) nonene (38) leads exclusively to exo-2-bicyclo (3,3,1) nonanol, and this preparation was found to be eminently superior to the others described above. The olefin (38) was obtained from the endo-tosylate (23; R = OTs) either by buffered acetolysis or by elimination using sodium ethoxide in ethanol. Treatment of the olefin (38) with m-chloroperbenzoic acid in chloroform gave the desired exo-epoxide (40) which was opened stereospecifically with the lithium aluminium hydride to give the exo-alcohol (26; R = OH). The p.m.r. spectrum of (26; R = OH) displayed a signal at τ 6.11 whose half-band width of 8 c./sec. is consistent with a carbinyl proton of equatorial disposition[21] and confirms the exo-hydroxyl configuration.

With the successful synthesis of the epimeric bicyclo (3,3,1) nonanols completed, our attention was focused on the bicyclo (3,2,2,) nonyl ring system.

The synthetic route was based on the reasoning that in a case where steric effects markedly influence the direction of attack of diborane on a symmetrical cyclic olefin, to the extent that one of the two possible epimeric alcohols is produced exclusively, or at least greatly predominates, then it might feasibly be expected that hydride reduction of the ketone corresponding to these alcohols will be governed by these effects in a similar manner to the hydroboration reaction, and hence these two reactions would give rise to alcohols of opposite stereochemistry.

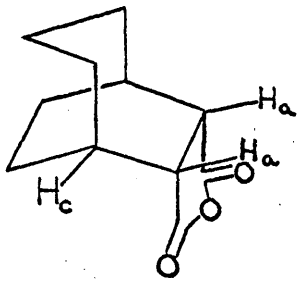


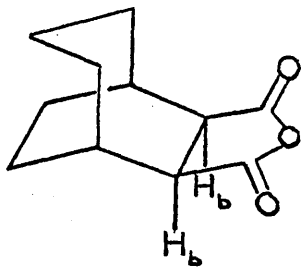
It was therefore decided to prepare 6-bicyclo (3,2,2) nonene (41) and 6-bicyclo (3,2,2) nonanone (33) and to investigate their behaviour in the light of the above reasoning.

Being a typical (n,2,2) bicyclic ring system, the obvious synthetic approach was via a Diels-Alder condensation.

Musso and Biethan[26] have shown that the required olefin (41) can be obtained by oxidative bis-decarboxylation of the acid (43) which was prepared on a large scale in the following manner.

Birch reduction of cyclohepta (1,3,5) triene[27] by lithium in liquid ammonia gave the corresponding conjugated diene in high yield. Diels-Alder reaction of this diene with maleic anhydride gave an adduct which had been shown[28], by chemical transformation, to have the endo- configuration (44). In this ring system, stereochemical assignments for these 'locked' 1,2 disubstituted structures can also be made on the basis of their magnetic resonance spectra. It has been found[29] that the p.m.r. signal for H_a is a sharp singlet, whereas





that for H_b is a highly complex multiplet. An examination of models supports this finding in that the dihedral angle between H_a and H_c is approximately 80° which corresponds to a coupling constant, J_{ac} of less than 0.5 c./sec.[30]

Hydrogenation of the adduct (44) over Adam's catalyst, PtO_2, gave the corresponding saturated system (45) in extremely high yield, and this was cleaved in a very facile manner by reaction with dilute potassium bicarbonate solution to give the bis-endo-dicarboxylic acid (43). Treatment of (43) with lead tetracetate in anhydrous pyridine at 67± 2°, according to the method of Cimarusti and Wolinsky[31], resulted in bis-decarboxylation to give the olefin (41) as a distressingly volatile, waxy solid in 56% yield after chromatography. This olefin (41) was then subjected to hydroboration in the hope that one of the two possible hydroxylic products (27; R = OH) would be formed exclusively or nearly so. Reaction of (41) with diborane in tetrahydrofuran, followed by oxidation with 30% hydrogen peroxide solution and chromatography of the product, gave a mixture of two alcohols, in which one of the components predominated to the extent

of 95-98% as judged by g.l.c. analysis.

Jones[34] oxidation of the alcohol mixture produced a solid ketone whose elemental analysis and spectral properties were consistent with the structure (33) i.e. 6 -bicyclo (3,2,2) nonanone. The reduction of (33) by various metal hydrides was then investigated.

Lithium aluminium hydride in anhydrous ether reacted with (33) to give a mixture of alcohols in the ratio 87:13 which is in total agreement with the results found by Schaefer[17] for this reaction. The major component of this mixture was identical in g.l.c. retention time to the minor component in the products of hydroboration of (41) and vice versa. In an effort to increase the selectivity of reduction, the reagent was changed to the much more bulky lithium aluminium tri-tertiary-butoxy hydride. Unfortunately, no reduction occurred whatsoever, even after a prolonged period of time.

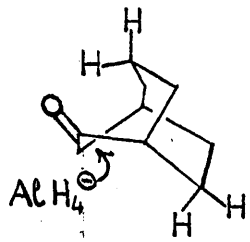
Brown[22] has found that the complex hydride lithium aluminium tri-methoxy hydride is at least as reactive as

lithium aluminium hydride but is also considerably more stereoselective in carbonyl reduction reactions. Therefore, in a final attempt, the ketone (33) was treated with this tri-methoxy hydride in anhydrous ether and to our great relief gave a hydroxylic product which by g.l.c. was composed of at least 98% of one of the two desired epimers (27; R = OH).

Thus our hopes had been realised in that the hydroboration and hydride reduction reactions had in fact reacted to give alcohols of opposite stereochemistry, and, if not exclusively, in at least sufficient preponderance to allow epimeric purification e.g. by crystallisation techniques. The fact still remained however, that although the two epimers (29) and (30) (R = OH) had now been prepared, the question of their respective configurations was still unanswered.

Schaefer[17] has proposed that the major alcohol from lithium aluminium hydride reduction of (33) is the alcohol (29; R = OH) (which we shall call exo-). This assignment is based on the argument that from inspection

of Dreiding models, there is a preferred conformation for the ketone (33), in which non bonded interactions are minimised. In this conformation (42) the endo-face of the molecule is the more exposed and hydride attack from this direction would therefore lead to the exo-alcohol (29; R = OH). However, since both epimers are



42

formed, albeit in considerably unequal amounts, this argument was not considered by us to be a sufficiently watertight basis on which to assign the configurations to the alcohols (29) and (30) (R = OH). In our opinion, this configurational decision could only be reached by preparation of one or other of the two alcohols (29) and (30) (R = OH), or a derivative thereof, in a series of stereochemically unambiguous reactions, and thence by comparison of this alcohol, of known configuration, with

the products from hydroboration and hydride reduction. We resolved, therefore, to prepare the endo-alcohol (30; R = OH).

Hartmann et.al.[32] have prepared the epimeric acids (47) and separated them by means of the iodolactonisation method, and this procedure formed the basis of our synthetic scheme.

Cyclohepta-1,3-diene and ethyl acrylate were heated in a sealed tube and gave rise to the ethyl esters (46) which, on hydrolysis with sodium hydroxide in aqueous methanol, produced the corresponding acids (47). Treatment of the sodium salts of these acids with iodine and potassium iodide resulted in the formation of the iodolactone (48) from the endo- epimer (50), while leaving the corresponding exo-acid (49) unchanged, and thus allowing a facile separation of the two acids. That the iodolactone was the γ-lactone (48) and not the alternative possibility, a δ-lactone, was evident from the carbonyl stretching frequency, $\nu_{C=O}$ 1799 cm.$^{-1}$

Having separated the two acids in this way, the endo-

epimer (50) was cleanly regenerated from the iodolactone (48) by treatment with zinc and acetic acid. The corresponding saturated compound (51) was obtained on catalytic hydrogenation of (50) over Adam's catalyst.

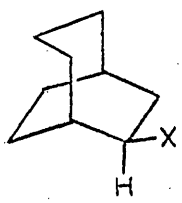
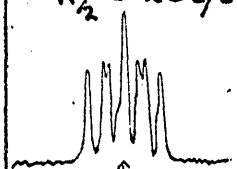
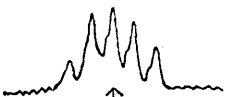
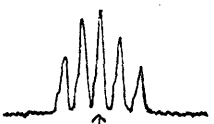
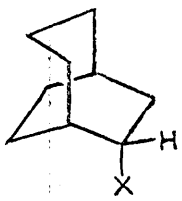
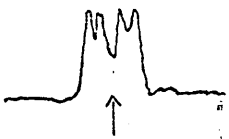
Thus, by these transformations, we have a bicyclo (3,2,2) nonyl derivative, substituted at the required position, and of known stereochemistry.

Treatment of (51) with two equivalents of methyl lithium in ether solution afforded the methyl ketone (52) as a colourless oil. Baeyer-Villiger oxidation of the ketone (52), using trifluoroperacetic acid as oxidant, produced (after removal of unchanged starting material as the corresponding semicarbazone) an acetate, which must have the structure (30; R = OAc) since this reaction is known[33] to proceed with retention of configuration and a cycloalkyl group has a greater migratory aptitude than a methyl group in these peracid oxidations.

The acetates of the two alcohols from hydroboration of (41) and complex hydride reduction of (33) were then

prepared, and their chromatographic and spectral properties compared to those of the Baeyer-Villiger product above. It was found that the acetate of the predominant (> 95%) alcohol formed by hydroboration of the olefin (41) was identical in infrared and p.m.r. spectra, and in g.l.c. behaviour to the Baeyer-Villiger product, and was therefore assigned the endo-configuration (30; R = OAc). The carbinyl region of their p.m.r. spectra was the deciding factor here, since the two epimers differ markedly both in the position and multiplicity of signal in this part of the p.m.r. spectrum, as shown in Fig. 5.

In addition, the relative half-band widths of these carbinyl proton signals are in qualitative agreement with those expected[21] for configurationally fixed axial and equatorial carbinyl hydrogens on carbon bearing oxygen. However, since we are dealing here with a cyclohexane ring in a 'boat' conformation, where we have dihedral angles about the centre in question which differ from those in a 'chair' conformation, and lead only to 'pseudo' equatorial and axial proton configurations, the difference in $W_{\frac{1}{2}}$ is explicably smaller than that in a fixed 'chair' cyclohexyl system.

	X = OH	X = OTs	X = OAc
	$W_{1/2}$ = 20c/s  τ 6·11	$W_{1/2}$ = 20c/s  τ 5·28	$W_{1/2}$ = 20c/s  τ 5·11
	$W_{1/2}$ = 16c/s  τ 5·95	$W_{1/2}$ = 15·5c/s  τ 5·17	$W_{1/2}$ = 16c/s  τ 5·00

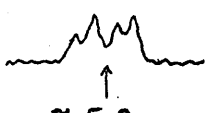
Hydroboration	Baeyer/Villiger
 τ 5·0	 τ 5·0

Fig. 5.

It was therefore concluded that hydroboration of (41) gives almost exclusive endo- addition to form (30; R = OH) and complex hydride reduction of (33) results in the formation of (29; R = OH) to the virtual exclusion of the alternative product (30; R = OH).

Having successfully prepared four of the six required alcohols, there only remained the problem of the bicyclo (4,2,1) nonyl system, and this, unfortunately proved to be the least successful part of the synthetic work.

A literature survey showed that very little work had been carried out on this basic skeleton, and, in particular, the information concerning 2-substituted derivatives was, to say the least, scant. As with the previous syntheses, a ketone (in this case (32)) was an important intermediate in our route. Although this compound was known[35] in the literature, when our work commenced, its synthesis was long and involved, and we therefore resolved to seek an alternative route to (32).

Since the ketone (53) was readily accessible by combination of the Stork[18] reaction and mercuric acetate oxidation[20],

as in the 2-bicyclo (3,3,1) nonanone synthesis described above, we decided to synthesise (32) by a Tiffeneau/ Demjanov[36] ring expansion of (53).

Treatment of the pyrrolidine eneamine of cyclopentanone (55) with acrolein in dioxan solution resulted in the formation of the extremely oxygen-labile keto-amine (54). The corresponding amine (56) was obtained by a Wolff/ Kishner reduction, and on treatment with mercuric acetate in aqueous acetic acid, followed by hydrolysis with dilute hydrochloric acid, was converted in reasonable yield to bicyclo (3,2,1) octan-2-one (53).

Reaction of (53) with potassium cyanide and acetic acid gave the corresponding cyanohydrin (57) as a waxy solid which was extremely difficult to separate from the parent ketone and, as a result, was very difficult to purify. This difficulty has also been encountered by Vaughan and Caple[37] in their preparation of (57). The cyanhydrin was acetylated with acetic anhydride in pyridine to yield the acetate (58) as a colourless oil. This compound was also difficult to purify since any attempt at distillation resulted in its decomposition with the formation of the

ketone (53). Lithium aluminium hydride reduction of the cyanoacetate (58) gave the hydroxyamine (61) as an extremely hygroscopic solid, which liquified immediately on exposure to the atmosphere.

The ring expansion reaction of (61) with nitrous acid proved to be yet another unsuccessful stage in a synthetic sequence fraught throughout with difficulties of separation and purification. The bulk of the reaction product consisted of two ketonic components in the ratio of approximately 3 : 1 as evidenced by g.l.c. analysis. The major component proved to be the desired ketone (32) by g.l.c. comparison with an authentic sample prepared by oxidation of a mixture of the corresponding alcohols[38] and it was inferred that the minor component was the other possible ring expansion product the 3-ketone (62). Chromatographic separation of (32) and (62) was achieved only with difficulty and at great expense to the yield of the desired 2-ketone, and fractional crystallisation of the corresponding semicarbazone mixture proved equally uneconomic.

This route was therefore abandoned and an alternative sought. An interesting point about the last stage of the

sequence is, however, the close resemblance of the product distribution to that found by Roberts and Gorham[39] in the corresponding ring expansion of the hydroxy-amine (63). These workers obtained the ketones (64) and (65) in the ratio 85:15 respectively.

Berson[9,10] has uncovered some interesting results in this field, in that deamination of the exo- and endo-norbornylamines (15) and (16) leads to quite different product distributions in each case. At first sight this dependence of product distribution on the stereochemistry of the starting material seems somewhat unusual, since, in each case there are two possible bonds which can migrate to the CH_2^+ grouping. When one considers the results of Berson with those of Roberts and Gorham[39] and ourselves it would appear an interesting problem to investigate the relationship between the stereochemistry of hydroxyamines such as (61) and their behaviour in a Tiffeneau/Demjanov ring expansion.

The synthesis of (32) which was ultimately successful was based on the work of Graham et.al.[14]. These workers found that the required ketone (32) is formed from treatment of the keto-tosylate (72) with sodium hydroxide in

aqueous methanol. Unfortunately, only the later stages in the synthesis of (72) were outlined in this work, but this difficulty was easily overcome by utilising the results of Cope et.al.[40] who had synthesised the hydroxy-tosylate (70) from the bicyclic ketone (67). Since this latter compound was readily available in our laboratories, combination of the work of Cope with that of Graham - which requires only oxidation of the hydroxy-tosylate (70) to the keto tosylate (72) - seemed to us a most convenient route to the ketone (32).

Catalytic hydrogenation of bicyclo (3,3,1) non-2-ene-9-one (66) afforded the corresponding dihydro derivative (67). From this compound, Cope[40] had obtained the bicyclic lactone (68) by Baeyer/Villiger oxidation using peracetic acid as oxidant. However, trifluoroperacetic acid was found to be a far superior reagent for this reaction both in terms of yield and speed. The lactone (68) thus obtained was treated with lithium aluminium hydride in tetrahydrofuran and the resulting cis-diol (69) reacted with slightly more than one molar equivalent of p-toluenesulphonyl chloride in anhydrous pyridine. In

spite of the small excess of p-toluenesulphonyl chloride employed, the desired mono-tosylate (70) was contaminated with a small amount of the ditosylate (71). Due to the lability of tosylate groups, however, no further purification of (70) was attempted and the crude material was carried on to the next stage of the reaction. Jones[34] oxidation of the crude mono-tosylate (70) proceeded smoothly at 0°C to yield the keto-tosylate (72) still contaminated with the ditosylate (71). These latter compounds could be separated by preparative t.l.c. but this procedure was only carried out on a sample quantity. The crude keto-tosylate (72) was treated with sodium hydroxide according to the method of Graham[14] and afforded the required ketone (32) as a volatile waxy solid which could be purified by chromatography or as the corresponding semicarbazone derivative[14].

From our experience with 6-bicyclo (3,2,2) nonanone (33), we anticipated some difficulty in the reduction of (32) due to the high conformational mobility of these systems relative to the rigid bicyclo (3,3,1) nonan-2-one. Unfortunately this proved to be the case, and to such an

extent that even lithium aluminium trimethoxy hydride gave insufficient stereoselectivity for our purposes. Catalytic hydrogenation[41], lithium in liquid ammonia[41], lithium aluminium hydride and lithium aluminium tri-tertiarybutoxy hydride all proved unsatisfactory, the latter giving a 65:35 mixture of the epimers (73) and finally lithium aluminium trimethoxy hydride reduction of (32) resulted in a 76:24 epimeric mixture.

The mixed p-toluenesulphonates (74) were prepared from the product of trimethoxy hydride reduction, but even after four crystallisations and regeneration of the parent alcohols by the method of Closson et. al.[42], which does not involve epimerisation of the alcohols, there still remained an 87:13 mixture of the epimers (73).

Thus, although synthesis of the desired ring systems had been successful, the bicyclo (4,2,1) alcohols (73) were of insufficient epimeric purity for our purposes. The remaining alcohols (23), (26), (29) and (30) (R = OH), which could be obtained as pure epimers, were converted to the corresponding p-toluenesulphonate esters and their kinetics and products of buffered acetolysis investigated.

The first order rate constants and respective thermodynamic parameters for the solvolysis of the epimeric 2-bicyclo (3,3,1) nonyl tosylates (23) and (26) (R = OTs) are shown in Table I.

The first striking feature about these results is the large rate difference observed for the solvolysis of the two tosylates ($k_{exo} / k_{endo} = 260$ at 25°C) over that expected for what, at first sight, would appear to be fixed equatorial and axial tosylates in a chair cyclohexyl system (the 4-t-butylcyclohexyl tosylates differ only by a factor of three in acetolysis rate at 50°C, the cis-epimer (axial tosylate) being the faster of the two. (See Table 2.)

The first order rate plots for these solvolyses were linear to at least 80 - 90% reaction, and this strongly suggests that no skeletal rearrangement, such as ion-pair return, occurs during these reactions.

Schaefer[16], in a kinetic investigation of the acetolysis of the corresponding brosylates (23) and (26) (R = OBs), has also found a large difference in solvolysis rate with

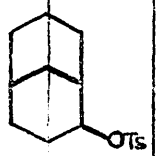
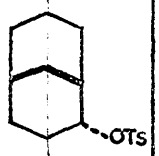
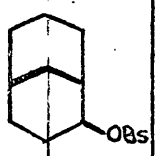
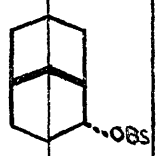
ROTs	T°C	k sec.$^{-1}$	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$ [d]
	48.9 58.9 68.5	1.26×10^{-4} 3.96×10^{-4} 1.18×10^{-3}	24.0	-1.9	24.6
	49.3 [c] 62.5 [c] 80.3	1.10×10^{-6} 6.15×10^{-6} 6.79×10^{-5}	29.5	+5.4	27.9
	-	-	26.9 26.4	-8.5 +8.3	29.5 [a] 23.9 [b]
	-	-	26.6 26.1	-0.9 -1.2	26.9 [a] 26.5 [b]

Table I.

a) Schaefer's reported parameters. (Ref. 16)

b) Our values using Schaefer's rate data.

c) These values are for unbuffered acetolysis as found by Hanack et.al. (Ref. 19)

d) Calculated for 298°K.

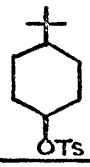
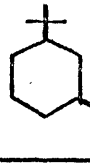
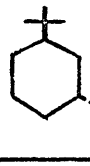
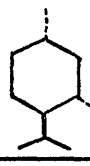
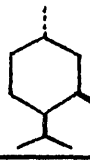
ROTs	k. sec.$^{-1}$ [c]	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$ [d]
 a	0.148 x 10^{-5}	28.1	+1.7	27.6
 a	0.491 x 10^{-5}	26.7	-0.5	26.9
 a	0.142 x 10^{-5}	27.5	-0.5	27.7
 a	0.510 x 10^{-5}	26.6	-0.6	26.8
 b	1.28 x 10^{-6}	29.9	+7.1	27.8
 b	9.9 x 10^{-5}	24.6	-0.7	24.8

Table 2.

a) Reference 49.

b) Reference 48.

c) Measured at 50°C.

d) Calculated for 298°K.

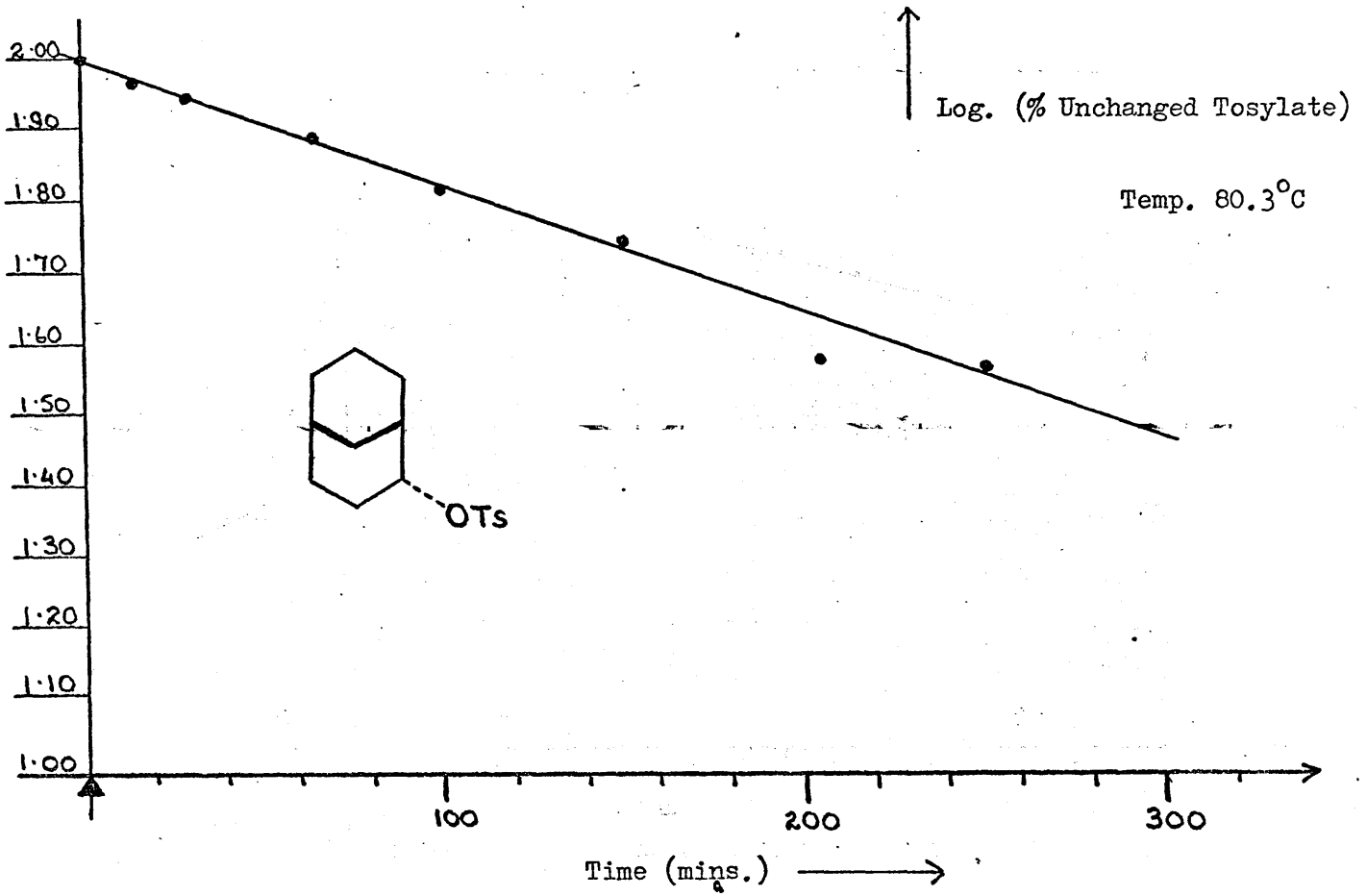

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
Log. (% Unchanged Tosylate)
Temp. 80.3°C
OTs
100
200
300
Time (mins.)

Fig. 6.

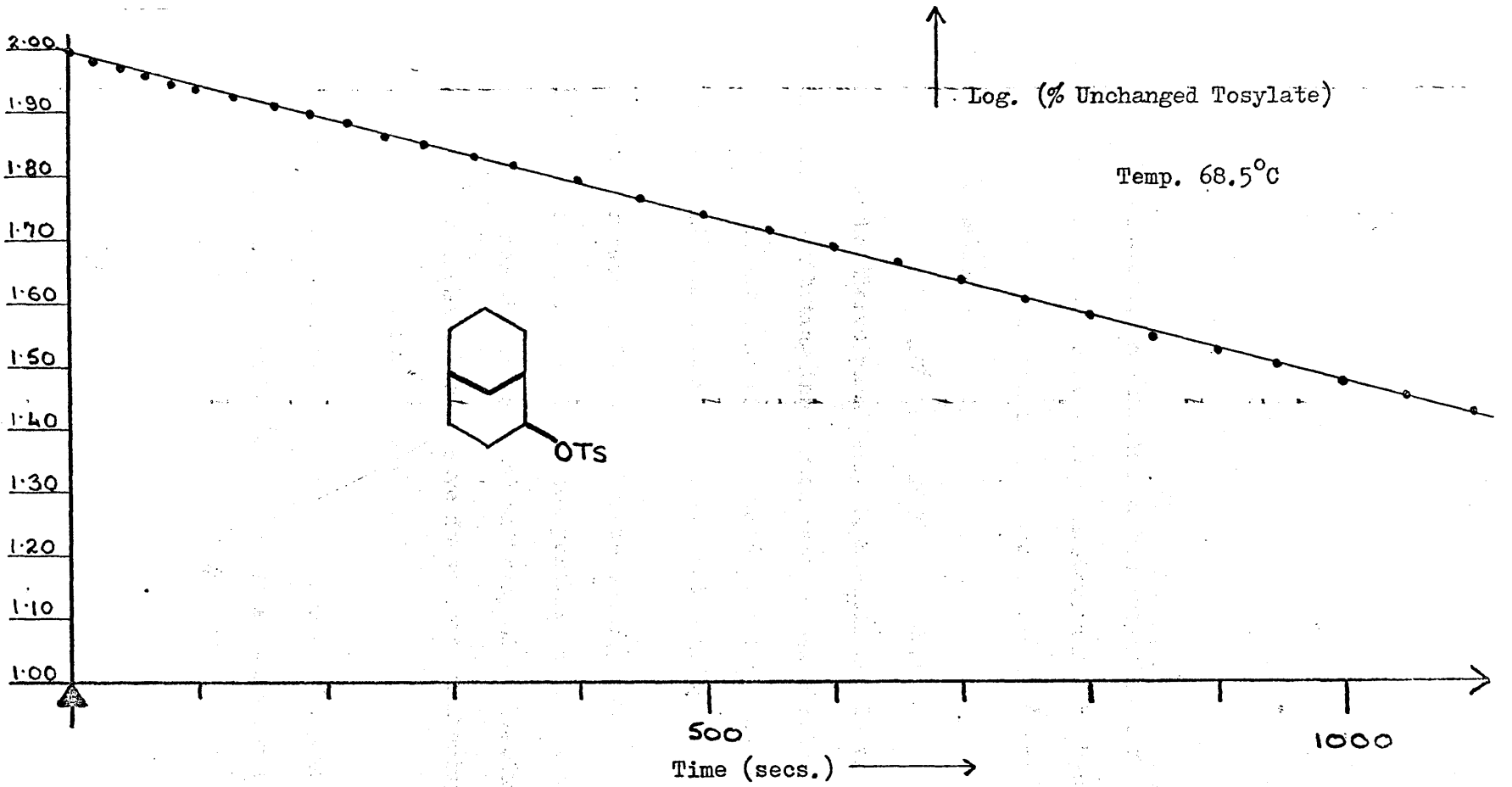

Log. (% Unchanged Tosylate)
Temp. 68.5°C
2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
OTs
500
1000
Time (secs.)

Fig. 7.

$k_{exo} / k_{endo} = 75$ at 25°C. Apart from this qualitative similarity in acetolysis rate, however, Schaefer's thermodynamic parameters differ greatly from those which we have obtained (see Table I).

Unfortunately, computation of his published data does not result in the activation parameters which he has reported, and insertion of his values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ in the equation

$$\Delta G^{\neq} = \Delta H^{\neq} - T \Delta S^{\neq}$$

leads to the thermodynamically impossible result that the brosylate exhibiting the faster rate of solvolysis, (26; R = OBs) does so via a transition state which has a higher $\Delta G^{\neq}$ value than its slower-solvolysing epimer!

Even correcting for this obvious error, however, the results of Schaefer still do not parallel ours, in that his values for the entropy and enthalpy of activation differ from those which we have found both in absolute and relative magnitude (see Table I).

It is pertinent to note that for each of the pairs of tosylates shown in Table 2, the epimer which is assumed

to have an equatorially disposed sulphonate grouping in its ground state conformation exhibits the higher enthalpy of activation than its axial counterpart in acetolysis, and the same holds true for the entropy values. These results are in accord with our own findings, and for this reason, among others, we view the results of Schaefer with some dubiety.

It is also relevant to note that in his explanation of the difference in reactivity of the two brosylates (23) and (26) (R = OBs), Schaefer makes no reference whatsoever to the activation parameters, (a common feature of many publications in this field) but uses an argument based wholly on the rate difference between the two brosylates being due to steric hindrance to ionisation of the endo-brosylate (23; R = OBs). Here again we differ from this author in that we have utilised the $\Delta S^{\neq}$ and $\Delta H^{\neq}$ to a large extent, and place great importance on their relevance and interpretation from a mechanistic viewpoint.

Another finding which is of some importance to this

work is that Graham et.al.[14] have shown by equilibration studies that the epimeric 2-bicyclo (3,3,1) nonanols differ in ground state free energy by 0.6 K.cal/mole at 88°C. Assuming that the corresponding tosylates do not differ greatly in relative ground state stability from this value, then we still have to explain a difference of some 2.5 K.cal/mole of free energy of activation to account for the relative reactivities of these two tosylates. The mechanistic implications of this and the respective thermodynamic parameters will be discussed more fully later in the text.

A kinetic examination of the 6-bicyclo (3,2,2) system proved to be extremely interesting. As can be seen from the graphs, (Figs. 8 and 10) the first order rate plots deviate markedly from linearity in the solvolysis of both epimers, and this immediately suggests the possibility of molecular rearrangement. The thermodynamic parameters are listed in Table 3. Let us consider first the endo-case (30; R = OTs).

As shown in the graph, the initial rate constant drifts downwards till about 50% reaction, after which it

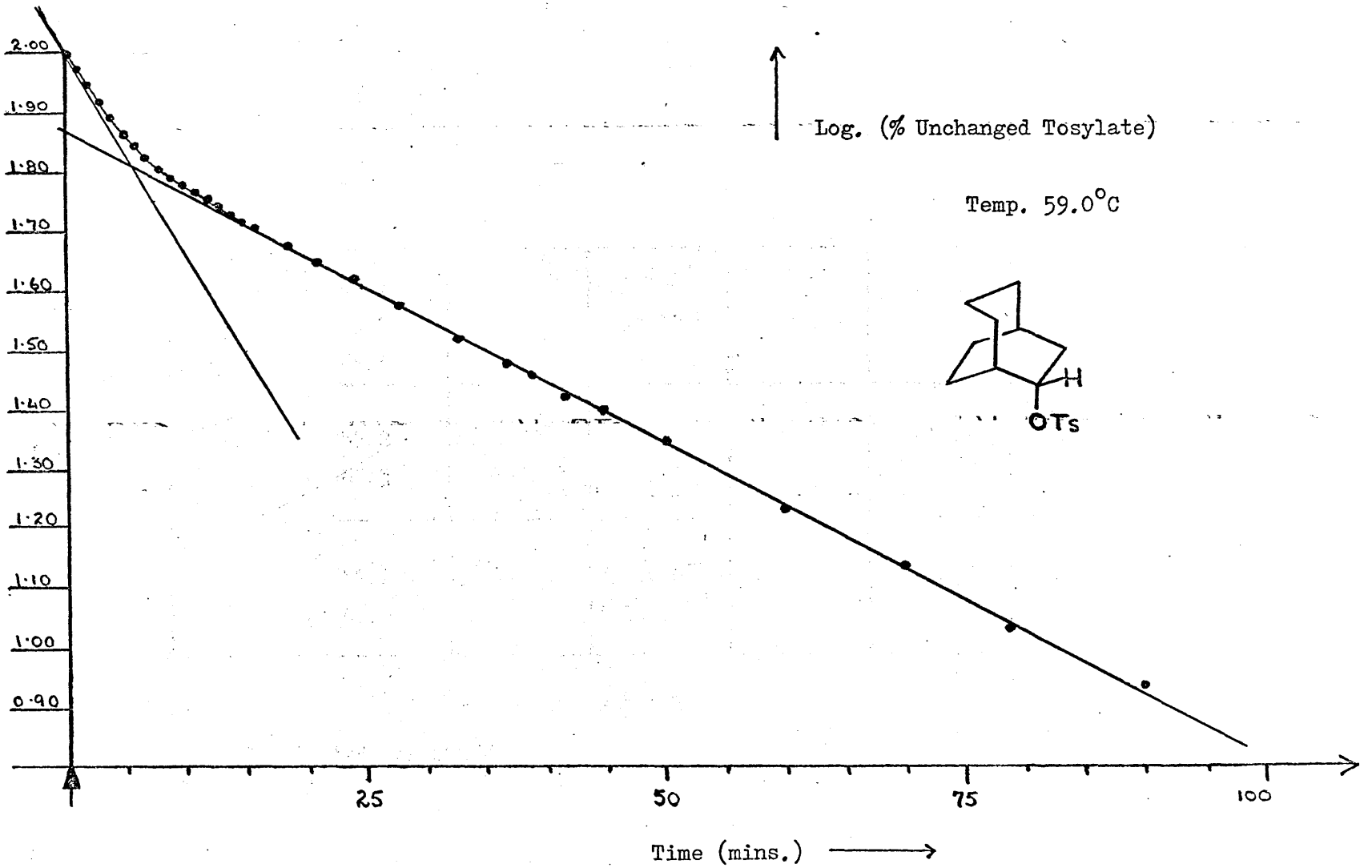

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
0·90
Log. (% Unchanged Tosylate)
Temp. 59.0°C
H
OTs
25
50
75
100
Time (mins.)

Fig. 8

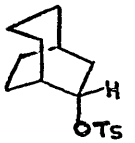
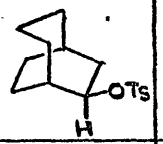
ROTs	Temp. °C	$k_{initial}$ [b]	k_{final} [b]	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$ [a]
	49.7 59.0 68.6	5.86×10^{-4} 1.28×10^{-3} 2.35×10^{-3}	-	15.6	-24.96	23.1
-	49.7 59.0 68.6	-	1.3×10^{-4} 4.02×10^{-4} 1.15×10^{-3}	24.6	- 0.2	24.7
	59.2 68.5	1.12×10^{-4} 2.78×10^{-4}	-	21.2	-13.1	25.1
-	59.2 68.5	-	2.08×10^{-4} 5.25×10^{-4}	21.7	-10.2	24.8

Table 3.

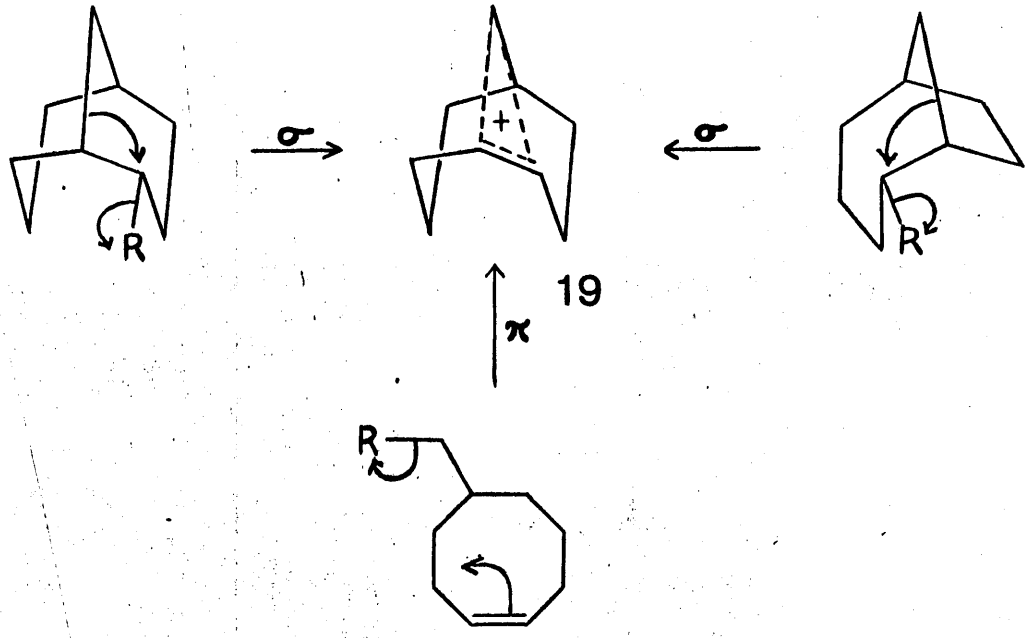
a) Calculated for 298°K.

b) Measured in $sec.^{-1}$.

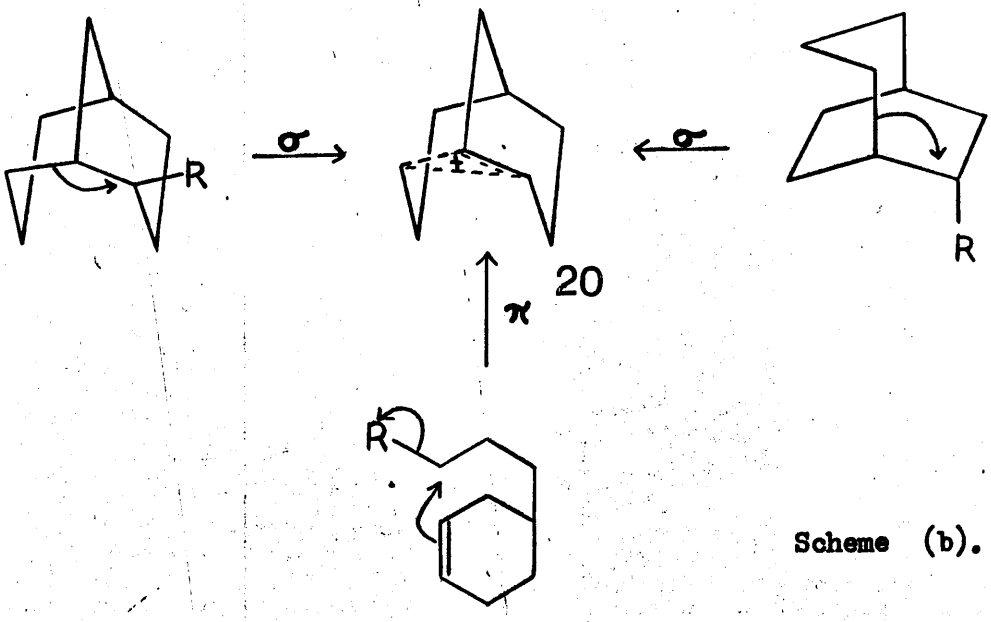
steadies to a constant value for the remainder of the reaction. The initial rate constants were obtained from the limiting tangent to the curved part of the graph at time t = zero.

The straight part of the graph can be interpreted in two ways; either we are observing a rearrangement of one species to another exclusively, or we have an equilibrium rearrangement set up which reaches its steady state after 50% reaction. The salient feature about the values of the final rate constants found is that they are almost identical to those obtained for the solvolysis of exo-2-bicyclo (3,3,1) nonyl tosylate (26; R = OTs). This is, of course, mirrored in the entropy and enthalpy values as shown in Tables I and 3. These results are in themselves extremely exciting, since the exo-(3,3,1) tosylate (26; R = OTs) and the endo- (3,2,2) tosylate (30; R = OTs) are a Wagner/Meerwein related pair via the non-classical species (20) (see Fig. 4).

Thus from the rate data found, and from the fact that the exo-(3,3,1) tosylate (26; R = OTs) shows no deviation from linearity in its first order rate plots, it would appear that the endo-(3,2,2) system has in fact

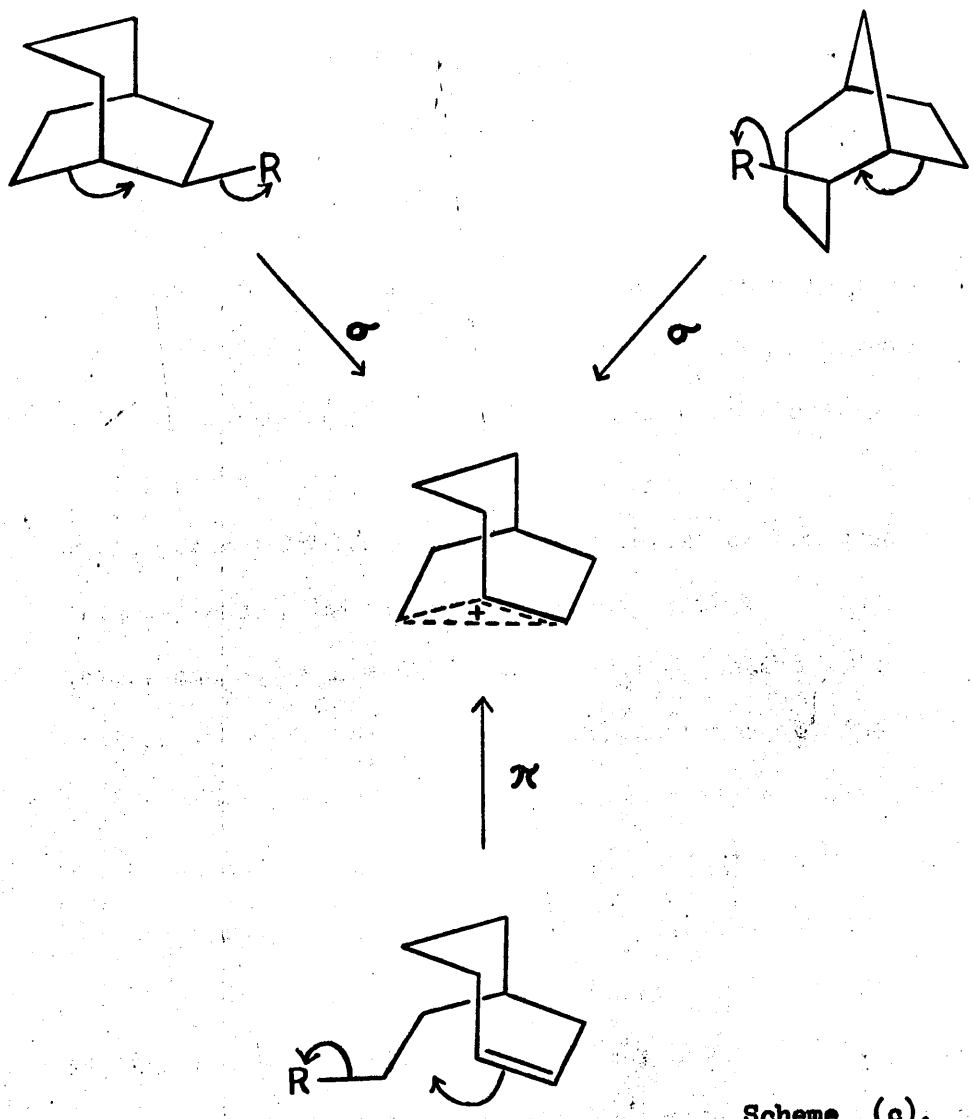


Scheme (a).



Scheme (b).

Fig. 4



Scheme (c).

Fig. 4

rearranged, if not exclusively, at least to an extremely high degree, to the related exo-2-bicyclo (3,3,1) nonyl tosylate.

In an effort to glean more information on this rearrangement, a preparative solvolysis was interrupted after approximately 50% reaction, i.e. on the steady part of the graph. The unsolvolysed tosylate was obtained by pouring the solvolysis mixture into water and extraction with pentane. The extract was washed with water and dried, and after removal of most of the pentane by evaporation at low temperature, the tosylate was obtained by crystallisation at -20°C. The material thus obtained was identical by infrared and n.m.r. spectroscopy to an authentic sample of exo-2-bicyclo (3,3,1) nonyl tosylate (26; R = OTs). It did however display a melting point which was some 20° below that of (26; R = OTs). Solvolysis of this material under conditions identical to those from which it was obtained resulted in perfect first order behaviour (see Fig. 9) and a rate constant of 3.96×10^{-4} sec.$^{-1}$ at 59°C which is identical to that for exo(3,3,1) tosylate - 3.96×10^{-4} sec.$^{-1}$ at 58.9°C (see Table 4).

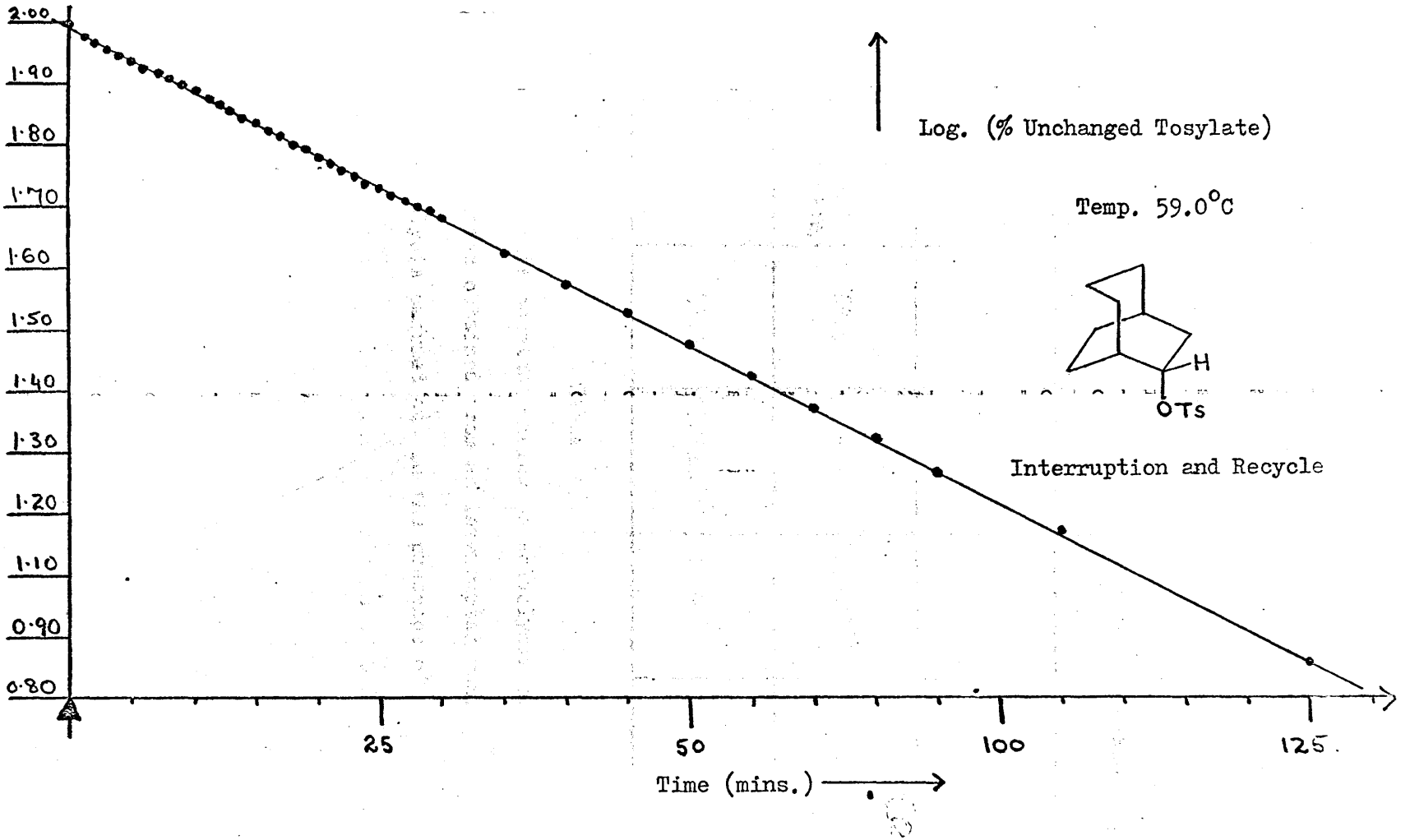

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
0·90
0·80
Log. (% Unchanged Tosylate)
Temp. 59.0°C
H
OTs
Interruption and Recycle
25
50
100
125
Time (mins.)

Fig. 9.

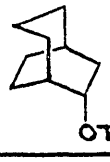
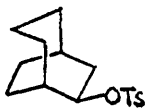
ROTs	T°C	k [a] sec.$^{-1}$	k (sec.$^{-1}$) [b]	
			initial	final
	59.1	-	1.44×10^{-3}	5.02×10^{-4}
-	59.0	3.96×10^{-4}	-	-
	68.5	-	3.98×10^{-4}	7.22×10^{-4}
-	58.9	2.06×10^{-4}	-	-

Table 4.

a) These rate constants refer to solvolysis of tosylates obtained from an interrupted run.

b) Solvolysis carried out in the presence of approximately 1.2 molar equivalents of $LiClO_4$

A sample of the tosylate from the interrupted solvolysis was cleaved to the corresponding alcohols by the method of Closson et.al.[42]. G.l.c. analysis of this material showed it to be at least 95% exo-2-bicyclo (3,3,1) nonanol (26; R = OH). Another component, which was not endo-6-bicyclo (3,2,2) nonanol (30; R = OH), but which has not yet been positively identified, accounted for the remaining 5% of the product.

A sample of endo-6-bicyclo (3,2,2) nonyl tosylate (30; R = OTs) was solvolysed at 59° in the presence of approximately 1.2 molar equivalents of lithium perchlorate (see Fig. 12). This resulted in an increase in both the initial and final rate constants, as shown in Table 4, which is probably due to the positive salt effect of the lithium perchlorate. From a consideration of the magnitude of this salt effect with respect to the concentration of lithium perchlorate, coupled with the results of Winstein et.al.[43] it is probable that this is a 'normal' salt effect.

Thus we have uncovered an exciting phenomenon in this bicyclo-(3,2,2) nonyl system in that the endo-tosylate

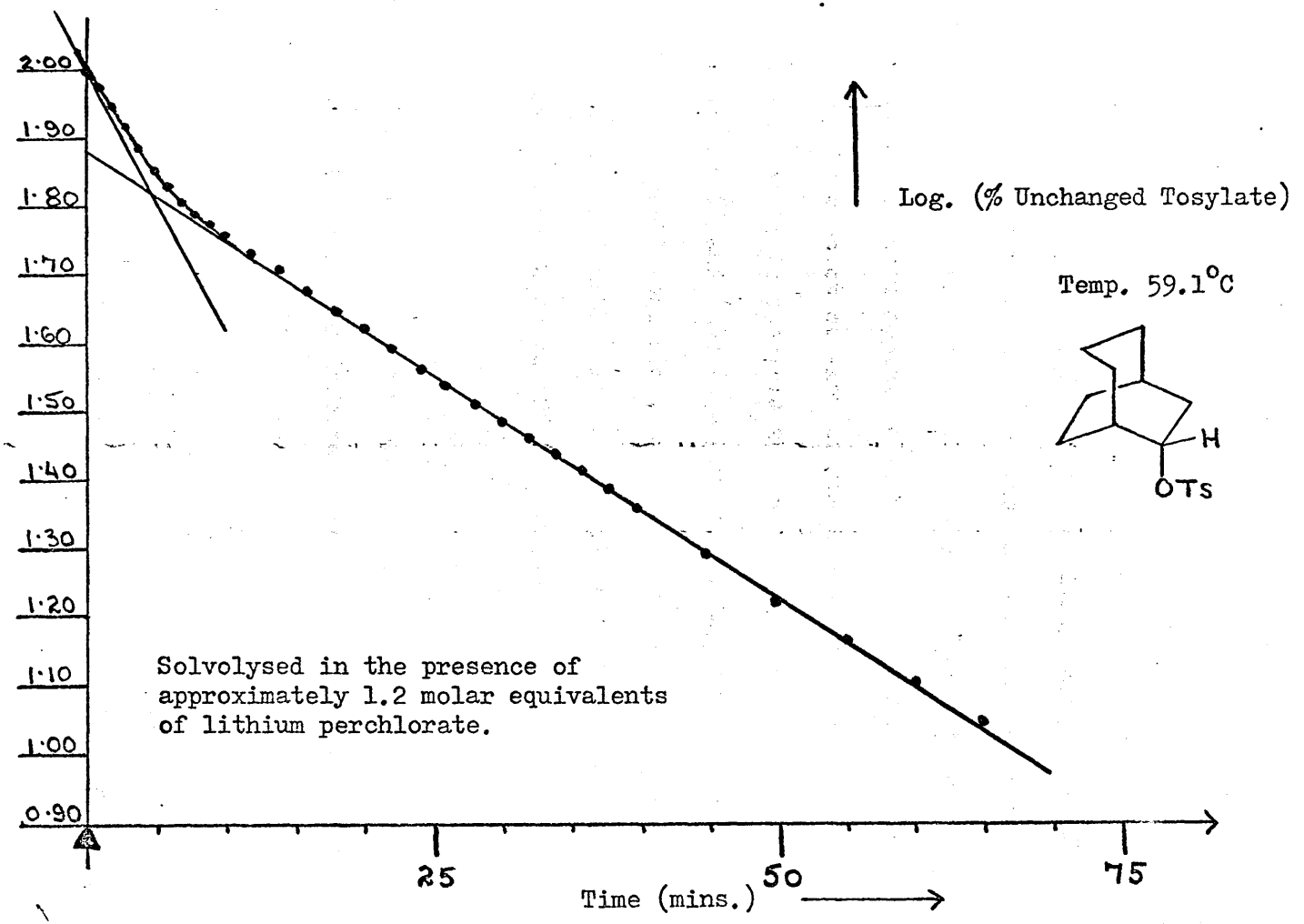

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
0·90
Log. (% Unchanged Tosylate)
Temp. 59.1°C
H
OTs
Solvolysed in the presence of
approximately 1.2 molar equivalents
of lithium perchlorate.
25
50
75
Time (mins.)

Fig. 12.

(30; R = OTs) rearranges almost exclusively on acetolysis to the Wagner/Meerwein related tosylate (26; R = OTs). In addition, the lithium perchlorate result suggests that the rearrangement occurs via internal ion-pair return, and together these findings are highly suggestive of the intermediacy of the non-classical species (20). Approach to this species from the (3,3,1) tosylate (26; R = OTs), however, would appear to negate its occurence, at least from the point of view of the kinetic behaviour. Nevertheless it is possible that we have an equilibrium between (26) and (30) (R = OTs) but this equilibrium lies very much to one side, so much so as to be virtually indistinguishable from a specific 'one-way' rearrangement of (30; R = OTs) to (26; R = OTs).

It is pertinent to note at this juncture that our interpretation of the above results is not without precedent. In 1964, Schleyer informed Winstein and Holness that their reported results[44] on the solvolysis of the α- and β-nopinyl brosylates (75) and (76) were in error, and that they had actually been studying the solvolysis of the corresponding rearranged endo-camphenilyl and apobornyl

brosylates (77) and (78). Schleyer had based this information on the discrepancy between the calculated[45] and observed first order rate constants for the solvolysis of (75) and (76).

As a result of this, Winstein and Freidrich[46] reinvestigated the problem and confirmed Schleyer's findings. By special techniques, these workers succeeded in preparing β - nopinyl brosylate (76) - the α - epimer was too reactive to be isolated - and found that on solvolysis it rearranged extensively to the related apobornyl brosylate (78), with the latter making up the residual ester after 53% solvolysis. To explain this behaviour, Winstein and Friedrich[46] postulated the mechanistic scheme shown in Fig. 11.

These workers also concluded that the conversion of (76) to (78) is apparently irreversible. This is of course essentially the result which we have found for the relationship between the esters (30) and (26) (R = OTs).

It is noteworthy also that the results of Winstein and Friedrich are in themselves an excellent measure of the

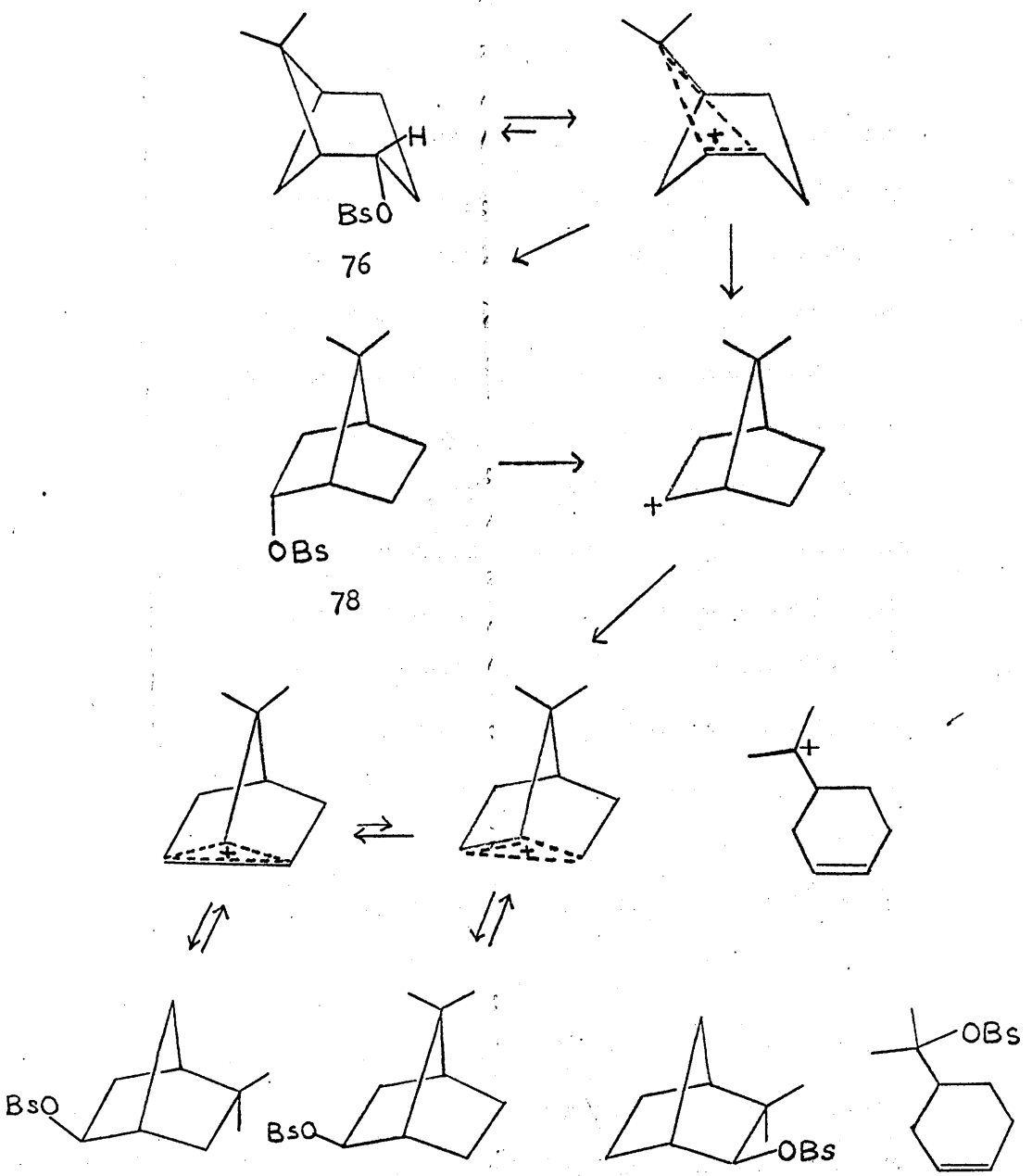


Fig. 11.

importance and validity of Schleyer's scheme[47] for the estimation of solvolysis rate constants.

The large negative value for the initial $\Delta S^{\neq}$ for solvolysis of the endo-tosylate (30; R = OTs) is worthy of some comment regarding its magnitude and sign. In these acetolysis reactions, ions, and therefore charges, are being created. The formation of charges results in orientation of solvent dipoles and hence leads to an increase in the order of the system. Therefore in a solvolysis reaction where we have simple ionisation and no drastic conformational changes in or leading to the transition state, we would expect $\Delta S^{\neq}$ to be negative, since entropy reflects the amount of disorder in a system. A perusal of the literature shows that, with one or two exceptions, normal values for the entropy of activation in these solvolyses are of the order of -5 to -0.5 e.u.[48,49,50]

From the initial value for the endo-tosylate (30; R = OTs) of -24.7 e.u., we must conclude that there is a large degree of ordering of the system during solvolysis, and we are left with the question of why this should be so. On

the basis of the reasoning above, ionisation could account for at least -5 e.u., but this still leaves -20 e.u. to be explained. A possible reason for the remainder can be found if one considers the n.m.r. spectrum of each of the epimeric alcohols (29) and (30) (R = OH).

By measuring the dihedral angles about the carbinyl protons and converting these to the corresponding Karplus[30] J. values, the best fit between the calculated and observed carbinyl proton signals is to be found, in each case, when the six membered ring adopts an eclipsed boat conformation. However, as evidenced from models, this is a considerably strained system, with the preferred skeletal conformation in each case being one of two extreme twisted boat conformations. Thus it seems reasonable to conclude that the six membered ring is in rapid equilibrium between two twisted boat conformations, the average of which, as far as the n.m.r. time scale is concerned, is the eclipsed boat form. If one also makes the reasonable assumption that the three-carbon bridge is flipping back and forth, then we have a system of considerable mobility. However, models show that there is one conformation of the endo-tosylate which is most favoured for Wagner/Meerwein

participation, and from the kinetic results it would appear that this participation occurs to a large extent.

Now, by adopting this favoured conformation, we place a severe restriction on the mobility of this system; and since this is another way of saying that the order of the system has increased, then we have markedly reduced the entropy of the transition state relative to the ground state. This mechanism therefore would make $\Delta S^{\neq}$ even more negative than the -5 e.u. which we could expect for reasons given above, thus the value of -24.7 e.u. takes on a more realistic meaning than a first glance would suggest.

The first order rate constants and activation parameters for the acetolysis of exo-6-bicyclo (3,2,2) nonyl tosylate (29; R = OTs) are illustrated in Table 3. As with the case of the epimeric endo-tosylate (30; R = OTs) an examination of the rate plots (see Fig. 10) provides us with the interesting result that the graphs are not linear, and that the initial rate constant increases throughout the first 50% of the reaction, after which time it reaches a constant value. As before, this immediately suggests that a skeletal

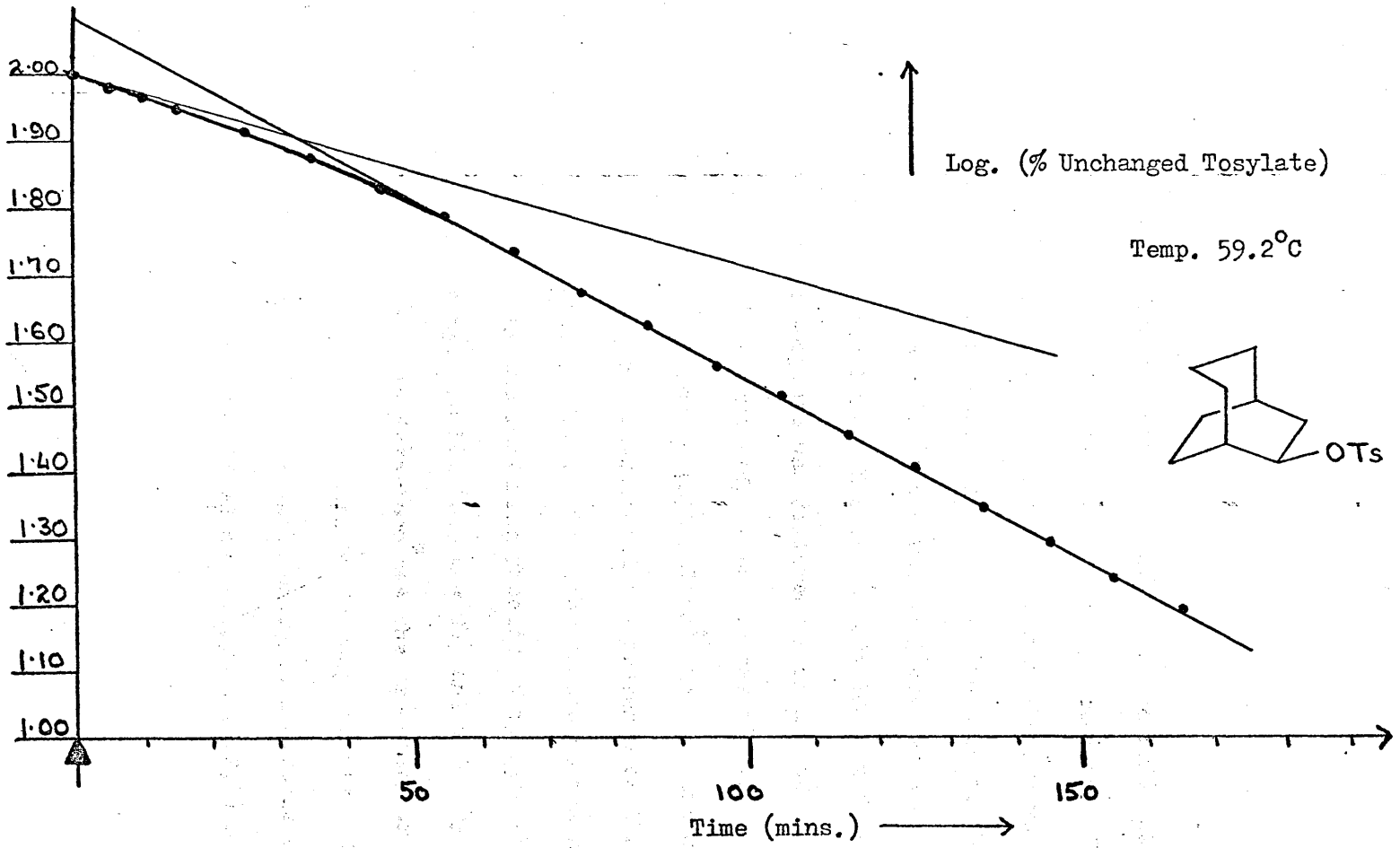

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
Log. (% Unchanged Tosylate)
Temp. 59.2°C
OTs
50
100
150
Time (mins.)

Fig. 10.

rearrangement of the exo-tosylate (29; R = OTs) to some species which has a faster rate of solvolysis, is taking place.

A preparative scale solvolysis was carried out and interrupted after approximately 50% reaction. The unreacted tosylate was obtained from the solvolysis mixture in the manner described above for the case of the endo-epimer (30; R = OTs), and was subjected to a similar examination. Infrared spectroscopy indicated that this unreacted tosylate was different from any of the tosylates we had yet encountered. A sample was cleaved to the parent alcohols with sodium naphthalene[42] and the products analysed by g.l.c. This showed the presence of three components in the ratio 55:38:7. The minor component was not identified but the two remaining products were exo-6-bicyclo (3,2,2) nonyl alcohol (29; R = OH) and a 2-bicyclo (4,2,1) nonanol which by inference* has the exo-configuration (28; R = OH) in the ratio 55:38 respectively. Jones[34] oxidation of these alcohols produced a mixture of two ketones only, identified as 2-bicyclo (4,2,1) nonanone (42%) (32) and 6-bicyclo (3,2,2) nonanone (33) (58%).

* See Appendix E.

Now if one neglects the unidentified peak (7%) in the alcoholic cleavage products, the remaining components are in the ratio 41:59 in favour of exo-6-bicyclo(3,2,2) nonanol (29; R = OH); and since the 7% unidentified material does not correspond to either the 2-bicyclo (4,2,1) nonanols, the 6-bicyclo (3,2,2) nonanols or the 2-bicyclo (3,3,1)nonanols, and gives no new ketone on oxidation, it is tentatively assumed that this is an impurity.

Thus it appears that the exo-6-bicyclo (3,2,2) nonyl tosylate (29; R = OTs) rearranges under these conditions to an equilibrium mixture of exo-2-bicyclo (4,2,1) nonyl tosylate (28; R = OTs) and exo-6-bicyclo (3,2,2)nonyl tosylate (29; R = OTs) in the ratio 41;59 respectively.

The fascinating feature of this observation is, of course, that these two tosylates are related as a Wagner/ Meerwein pair via the non-classical species (21) (see Fig.4).

A sample of this tosylate mixture obtained from the interrupted solvolysis was re-solvolysed under the normal acetolysis conditions. Perfect first order kinetic

behaviour was observed (see Fig. 13) thus indicating that we have a constantly-maintained equilibrium mixture of tosylates which would be expected on the basis of the non-classical species (21) being a common intermediate between the two tosylates comprising the equilibrium mixture. In addition it was shown (Fig. 14 and Table 4) that solvolysis of (29; R = OTs) in the presence of approximately 1.2 molar equivalents of lithium perchlorate exhibited a positive salt effect which, by a similar argument to that used for the case of the endo- (3,2,2) tosylate (30; R = OTs), is strongly suggestive of internal ion pair return.

Thus it appears from the above results that exo-6-bicyclo (3,2,2) nonyl tosylate (29; R = OTs) partially rearranges, by internal ion pair return to the Wagner/Meerwein related exo-2-bicyclo (4,2,1) nonyl tosylate - a result which is most conveniently explained by invoking the intermediacy of the non-classical species (21).

Unfortunately our attempts to prepare the required bicyclo (4,2,1) nonyl tosylates were only partially successful, and they could not be obtained in sufficient epimeric

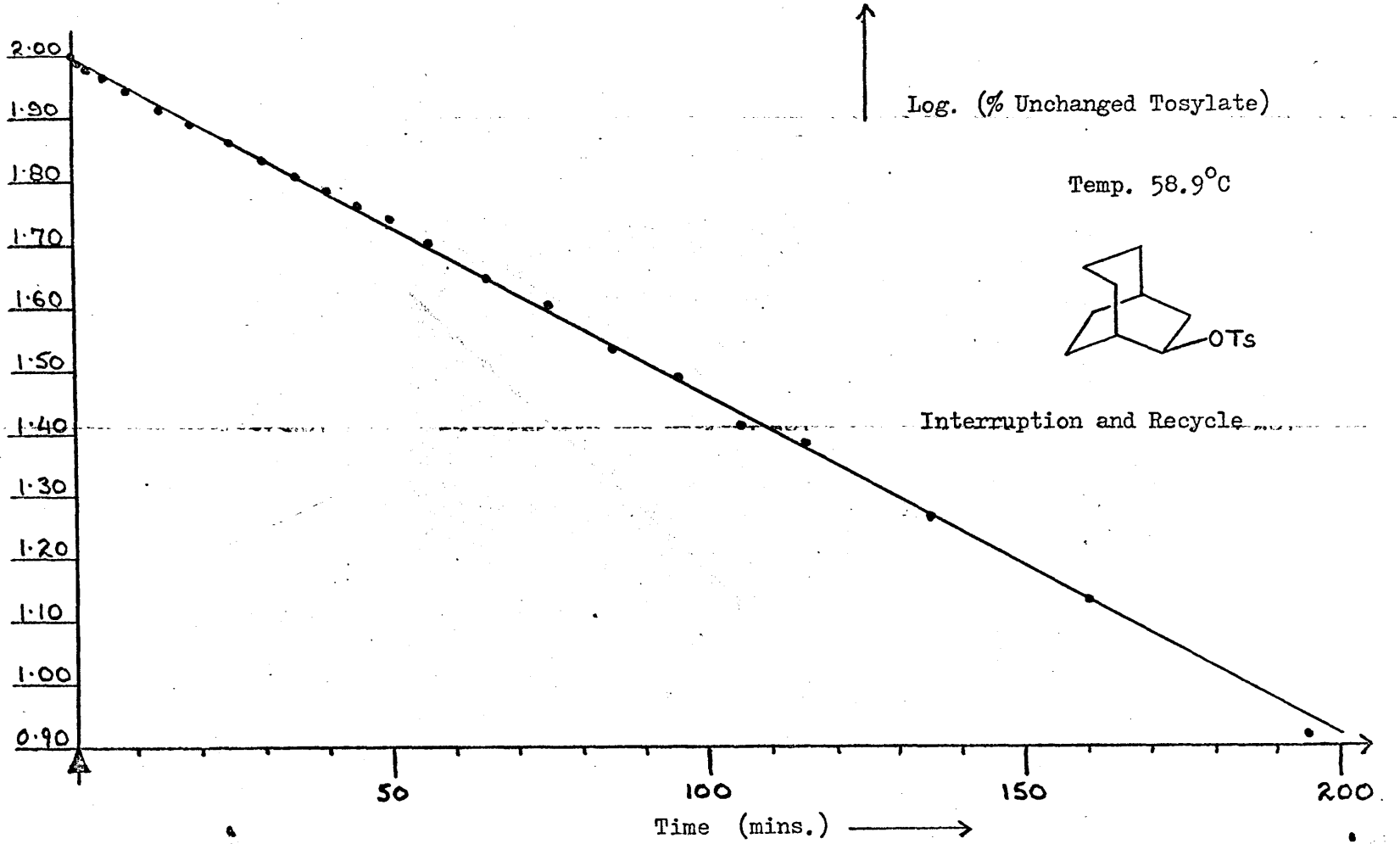

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
0·90
Log. (% Unchanged Tosylate)
Temp. 58.9°C
OTs
Interruption and Recycle
50
100
150
200
Time (mins.)

Fig. 13.

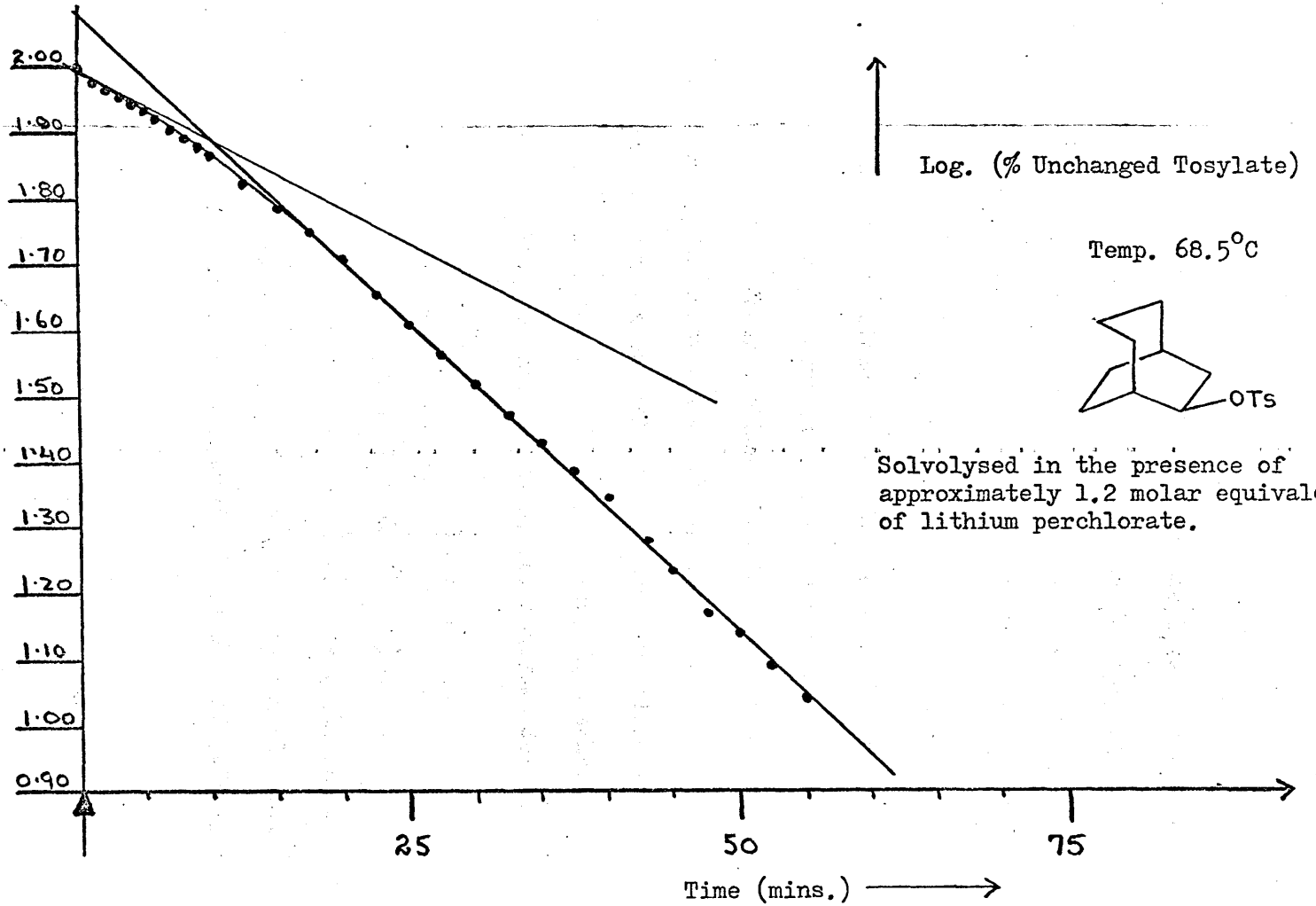

2·00
1·90
1·80
1·70
1·60
1·50
1·40
1·30
1·20
1·10
1·00
0·90
25
50
75
Time (mins.)
Log. (% Unchanged Tosylate)
Temp. 68.5°C
OTs
Solvolysed in the presence of approximately 1.2 molar equivalents of lithium perchlorate.

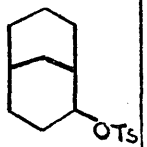
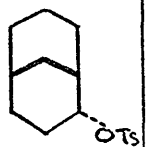
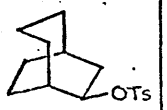
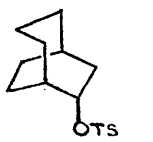
Fig. 14.

purity to merit the kinetic investigation so necessary to our mechanistic argument.

As with the case of the endo-tosylate (30; R = OTs) one can give qualitative arguments for the magnitude and sign of the entropies of activation for solvolysis of (29; R = OTs), again based largely on conformational considerations.

Having described the kinetic results, let us now examine the products of buffered acetolysis of the various tosylates. These are described in Tables 5,6,7 and 8. Table 5 was constructed from a combination of cross injection experiments on both the acetates and alcohols (obtained by hydride reduction of the acetates) from solvolysis and Table 8 combines all of the g.l.c. analyses detailed in Tables 5,6 and 7.

Solvolysis of endo-2-bicyclo (3,3,1) nonyl tosylate (23; R = OTs) gave a mixture of olefins (67%) and acetates (33%). By cross injection experiments the olefinic fraction was shown to consist solely of 2-bicyclo (3,3,1) nonene (38) (see Tables 5 and 7).

ROTs	23	26	24	28	29	30	82	83
	20.5	44.2	?	?	?	?	15.1	?
	37.7	47.6	2.2	-	-	-	9.3	3.7
	8.3	10.0	?	56.7	?	14	-	-
	10.4	43.9	?	?	?	?	6.2	?

This table was constructed from a combination of g.l.c. analyses of solvolysis acetates and the alcohols derived from them, and takes no account of the amounts of olefin formed (see Appendix D.).

Table 5.

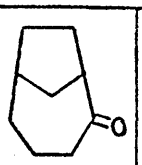
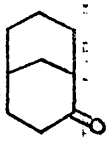
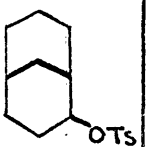
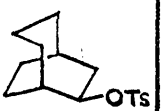
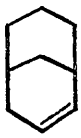
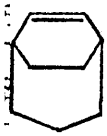
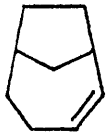
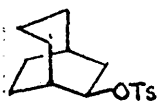
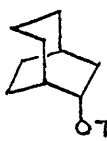
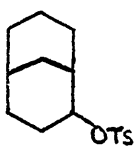
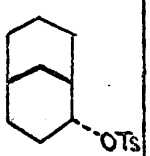
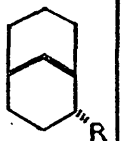
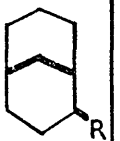
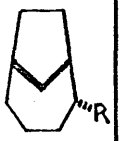
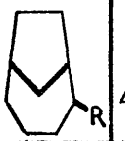
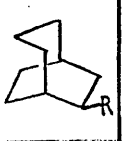
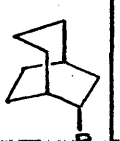
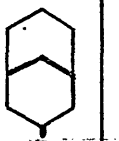
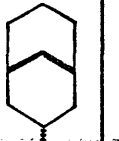
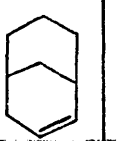
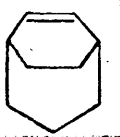
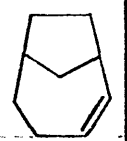
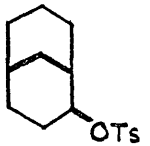
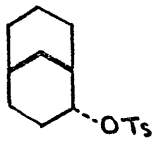
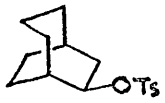
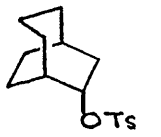
ROTs	Relative Ketone Percentages			
–				
	-	66.5	18.1	15.3
	66.1	21.4	-	9.1

Table 6.

ROTs			
	-	15	10
	>95	-	-
	>95	-	-
	67	-	-

Olefinic Solvolysis Products (total).

Table 7.

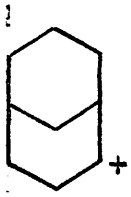
ROTs											
	1.0	2.2	?	?	?	0.75	0.75	0.15	>95	-	-
	12.4	15.7	0.7	-	-	-	3.0	1.2	67	-	-
	6.2	7.5	7.1	42.5	1.3	10.5	-	-	-	15 ?	10*
	0.52	2.2	?	?	?	?	0.3	?	>95	-	-

Total Solvolysis Products. Question marks indicate insufficient peak distinction for accurate analyses to be carried out. (See Appendix D.).

* See Appendix D.

Table 8.

In scheme (a) of Fig. 4, we see that the endo-2-(3,3,1) and endo-2-(4,2,1) tosylates are a Wagner/Meerwein related pair via the species (19). As shown in the kinetic results, however, no rearrangement of (23; R = OTs) is suggested by the rate plot. (See Fig. 6). This finding is supported by the product analysis which shows (Tables 5,8) that 85% of the total acetate product consists of almost equal amounts of the epimeric 2-bicyclo (3,3,1) nonyl acetates (23) and (26) (R = OAc) with a slight preference for inversion of configuration. Now if (19) was a major product forming intermediate, one would expect both retention of configuration i.e. (23; R = OAc) to predominate, and the formation of substantial amounts of the related endo-2-(4,2,1) acetate (24; R = OAc). In fact less than 1.3 % of the latter was formed, and even this figure represents only an upper limit. These results would suggest that the major product forming intermediate is the classical cation (79) and that the non-classical



79

ion (19) plays only a minor (if any) role in the product formation.

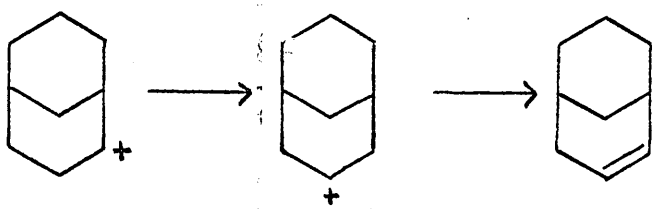
With reference to the publication by Eakin et.al.[51] the formation of 3% of exo-3-bicyclo (3,3,1) nonyl acetate from (23; R = OTs) is very interesting. These workers found that solvolysis of the epimeric 3-bicyclo (3,3,1) nonyl tosylates give the following results. (See Table 9).

ROTs	exo-3 acetate	endo-3 acetate	Olefin (38)
exo-3	3	2	95
endo-3	6.6	2.8	90.6

Table 9.

If one considers these results as a measure of the partitioning of the cation (80) between olefin (38) and 3-acetate (81) then application of the partition ratios of Table 9 to the exo-3-(3,3,1) acetate (82) observed in

the acetolysis of the tosylate (23; R = OTs) (3%) would predict the formation of 43-95% of 2-bicyclo (3,3,1) nonene (38) from the 3-cation (80). Thus, of the 67% of (38) which is in fact formed, it is possible that at least 43% arises as a result of 1,2 hydride shift from (79) to (80) rather than simple elimination of a proton from (79) to form olefin.



79 80 38

Since no account has been taken of the endo-3-(3,3,1) acetate (83) this figure of 43% hydride shift represents a lower limit.

Unfortunately, due to insufficient epimeric purity, the related 2-bicyclo (4,2,1) nonyl tosylate (24; R = OTs) was not investigated, so no definite conclusion can be drawn regarding the alternate σ-route of scheme (a) (Fig.4).

The products from acetolysis of exo-2-bicyclo (3,3,1) nonyl tosylate (26; R = OTs) are markedly different from those of its epimer (see Tables 5 - 8). Firstly, it can be seen that not less than 95% of the total product is 2-bicyclo (3,3,1) nonene (38). In view of the well known C_3-C_7 endo-hydrogen interaction present in the twin chair ground state conformation[52] of the bicyclo (3,3,1) nonane skeleton, formation of a large amount of olefin is reasonable, since this removes the severe 3-7 interaction and affords substantial strain relief. The epimeric endo-tosylate (23; R = OTs), however, yields only 67% olefin, and although one can argue on stereo-electronic grounds that axial tosylates give rise to more olefin on solvolysis than do their corresponding equatorial epimers, nevertheless the endo- and exo-2-(3,3,1) tosylates (23) and (26) (R = OTs) in twin chair conformations are experiencing the same 3-7 nonbonded interaction strain which should be relieved to the same extent in both epimers on formation of the olefin (38), and one might feasibly expect the amount of olefin from each to be much more similar than results indicate.

When one includes the observation that there is a marked difference in solvolysis rate between these 2-bicyclo (3,3,1)

nonyl tosylates, (far in excess of the normal axial: equatorial rate ratio), and also that the product distributions exhibit marked variations (see Tables 5 - 8), it becomes clear that the sequence of events leading to products can not be the same for both cases. Before this point is further discussed, however, let us consider the products of acetolysis of (26; R = OTs) in terms of the initial scheme (b) (see Fig. 4).

Application of Schleyer's[47] rate correlation scheme to (26; R = OTs) predicts a rate enhancement of 11 times over that for cyclohexyl tosylate. The observed rate enhancement is 107 times, and we therefore must conclude that there is substantial anchimeric assistance of some form to ionisation of the exo-2-(3,3,1) tosylate. From the nature of the rate plots, however, (see Fig. 7) it seems unlikely that Wagner/Meerwein participation with resulting skeletal rearrangement is taking place, and the observation of only 0.75% of the related 6-bicyclo (3,2,2) nonyl product suggests that the non-classical species (20), if it is at all intermediate in the solvolysis of (26; R = OTs), plays only a very minor part in the

formation of the acetolysis products. The formation of such a large amount of olefin (>95%) is in itself contradictory to the existence of an all-carbon 3-centre non-classical intermediate[53], a characteristic feature of the latter being fairly high acetate : olefin ratios in acetolysis.

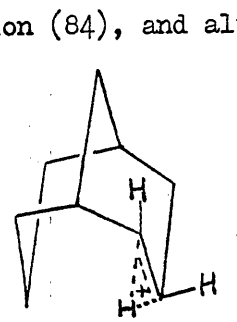
As with the endo-epimer (23; R = OTs) the bulk of the acetate fraction (65%) is again composed of acetates arising from solvent capture at the 2-position of the bicyclo (3,3,1) nonyl ring system, this time in favour of retention of configuration, (exo:endo = 2:1, cf. endo-epimer (23; R = OTs). Retention of configuration, of course, favours the non-classical intermediate (20), but this is offset by the formation of a maximum of 15% of the acetate products (0.75% of the total product) as the related endo-6-(3,2,2) acetate (30; R = OAc).

The remainder of the acetate products (approximately 20%) is made up of the 3-bicyclo (3,3,1) nonyl acetates (81). If one applies the same treatment to the exo-acetate (82) as was carried out on that from the endo-tosylate (23; R = OTs), it can be seen that hydride shift can only account for the formation of 11 - 24% of the olefin (38)

as opposed to 43-95% in the endo-case. This difference again is suggestive of a duality of solvolytic mechanism in the epimeric 2-bicyclo (3,3,1) nonyl tosyaltes (23) and (26) (R = OTs).

Irrespective of this latter point, however, it would appear that solvolysis of (26; R = OTs) does not represent an effective σ -route to the non-classical ion (20), see schome (b) Fig. 4. Nevertheless we still have to account for the observed anchimeric assistance.

An examination of models shows that in the twin chair form of the exo-tosylate (26; R = OTs), the C_3 - endo-hydrogen is trans-anti-parallel to the C-OTs bond and is, therefore perfectly aligned to participate in the ionisation of the tosylate grouping. Thus it seems reasonable to conclude that although there is no participation by the C_1-C_8 bond, assistance to ionisation by the endo-C_3 hydrogen is a feasible alternative. This participation will give rise to the bridged ion (84), and although Cram[54] has stated



84

that capture of such a species takes place from the same side as the participating proton, it is possible that due to the special stereochemical features of the bicyclo (3,3,1) nonyl ring system, solvent approach from this direction is sterically prohibited (cf. exo- attack of diborane on 2-bicyclo (3,3,1) nonene). Supporting evidence for this proposal is the observation of mainly exo- capture at position 3 in the products of acetolysis of (26; R = OTs).

The other possible σ-route to the non-classical species (20) from the endo- (3,2,2) tosylate (30; R = OTs) proved to be extremely interesting. As described above, kinetic studies indicated extensive rearrangement of (30; R = OTs) to the related tosylate (26; R = OTs) and this was confirmed by the products. Again at least 95% of 2-bicyclo (3,3,1) nonene (38) was formed to the total exclusion of the isomeric 6-bicyclo (3,2,2) nonene (41) (the latter being stable under the acetolysis conditions). The acetate fraction was composed of the same acetates as those from the exo-(3,3,1) tosylate (26; R = OTs), the ratios, however, being different.

If the non-classical species (20) were a major product forming intermediate, then one would expect almost equal amounts of the Wagner/Meerwein related acetates (26) and (30) (R = OAc) to be formed. On the other hand, if all of the endo-6-tosylate (30; R = OTs) rearranges to the (3,3,1) system, we would expect the product analysis to mirror that from (26; R = OTs). An inspection of the relative acetate product ratios, however, (Tables 5 and 8) would at first sight suggest a combination of these two mechanisms since the only difference between the acetates from solvolysis of the two tosylates is that the g.l.c. peaks for the Wagner/Meerwein related pair from the (3,2,2) tosylate (30; R = OTs) have increased in size. However, the presence of at least 95% of rearranged olefin would suggest that (20) is a minor contributor to product formation[53], and that most of the products arise after rearrangement i.e. from the (3,3,1) tosylate (26; R = OTs).

In view of these results, the most reasonable scheme which is consistent with the available data is shown in Fig. 15. From both kinetics and products it seems certain that k_3 is very small in comparison to k_2, and from the

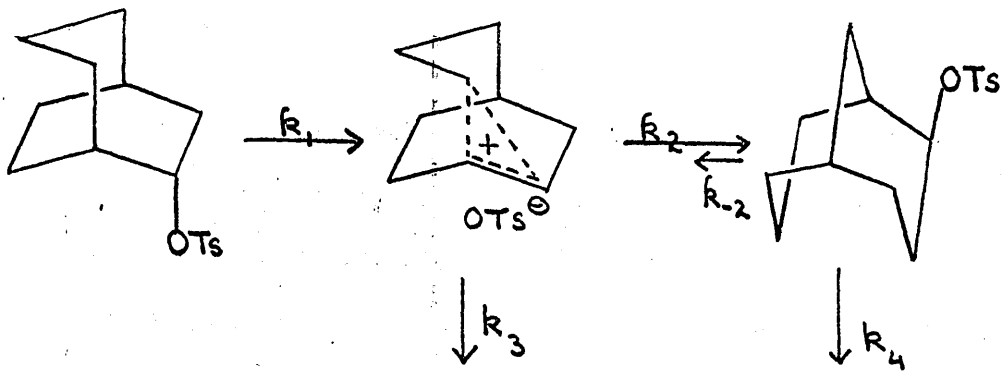


Fig. 15

results on the exo-(3,3,1) tosylate k_{-2} would appear to be negligible in comparison to k_2.

Let us now consider scheme (c) of Fig. 4. As with the case of scheme (a) we could only attempt to approach the postulated intermediate (21) from one direction due to the (4,2,1) tosylate (28; R = OTs) being of insufficient epimeric purity for study.

The kinetic studies have shown that the exo-(3,2,2)

tosylate (29; R = OTs) undergoes solvolytic rearrangement, giving rise to an equilibrium mixture of the Wagner/ Meerwein related tosylates (28) and (29) (R = OTs) in the ratio 41:59 respectively. The products of solvolysis are shown in Tables 5 - 8, and the first striking feature of these is the low percentage of olefinic products (25%). By conversion of the acetates to the corresponding alcohols and ketones, a fairly comprehensive g.l.c. analysis could be carried out on the products.

The major acetolysis product (42.5%) is exo-2-bicyclo (4,2,1) nonyl acetate (28; R = OAc). If the non-classical ion (21) were an important intermediate here then formation of this acetate would be expected, by virtue of the necessary direction of solvent attack on (21). In addition, the kinetic results and high acetate:olefin ratio (3:1) all point towards the intermediacy of a non-classical ion, namely (21) (see Fig. 4).

A possible objection to this is that very little, if any, exo-6-bicyclo (3,2,2) nonyl acetate (29; R = OAc) is formed, which would appear to disagree with the formation of (21).

However, apart from this point, the remaining results are most adequately accounted for in terms of the non-classical species (21) being the major product forming intermediate in the solvolysis of (29; R = OTs).

Since it is with the bicyclo (4,2,1) and bicyclo (3,2,2) nonyl systems that most of the g.l.c. separation difficulties arise, one cannot be absolutely clear-cut on the outcome of these solvolyses. It is the opinion of the author that when totally unambiguous g.l.c. conditions have been achieved, and the pure epimeric (4,2,1) alcohols obtained, the interplay of classical/non-classical behaviour thus revealed will prove this series of compounds to be one of the most interesting studied to date.

At the present time, it is only possible to make a summary of the results obtained in terms of Fig. 4. Thus the <u>endo</u>- 2-bicyclo (3,3,1) nonyl tosylate (23; R = OTs) behaves in true classical manner, with no evidence of participation either in rate or products of solvolysis. For reasons given above, nothing can, as yet, be said regarding the alternative σ -route to (19) i.e. from (24; R = OTs).

On the other hand, exo-2-bicyclo (3,3,1) nonyl tosylate (26; R = OTs) although not exhibiting any C_1-C_8 bond participation with subsequent formation of (20), behaves in a manner best explained in terms of the non-classical hydrogen-bridged ion (84). The observed behaviour of the Wagner/Meerwein related endo-6-bicyclo (3,2,2) nonyl tosylate (30; R = OTs) is best explained in terms of the scheme shown in Fig. (15) in which the non-classical species (20) may well be an intermediate, but must be extremely short-lived in relation to the rate of rearrangement to (26; R = OTs) and as such allows only a small amount of leakage to products.

Finally, the behaviour of exo-6-bicyclo (3,2,2) nonyl tosylate (29; R = OTs) is best explained in terms of the non-classical species (21) being the major product forming intermediate, but at the moment nothing can be said about the alternative σ-route from (28; R = OTs).

On a final perusal of the results to date one is immediately reminded of a statement by Berson[10]:-

"In particular, there is now a strong implication that reactivities of bicyclic non-classical ions may fall into a graded series."

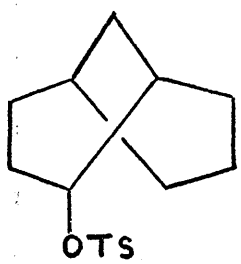
Berson, of course, was referring to reactivity within a

homologous series of bicyclic ring systems. In our case, the graded series actually lies within a group of isomeric Wagner/Meerwein related bicyclononyl tosylates.

There remains, however, one result which is of further interest. This is the observation of the large rate difference (260 times at 25°) between the epimeric 2-bicyclo (3,3,1) nonyl tosylates (23) and (26) R = OTs. Schaefer[16] has attributed similar behaviour in the corresponding brosylates to steric inhibition to ionisation of the endo-brosylate, by virtue of the fact that as the C-OBs bond lengthens and the 2-position attains sp^2 hybridisation, the OBs^- moiety is forced into close proximity with the endo-C_7 hydrogen. It is likely, however, that Schaefer means the endo-C_8 hydrogen, since the C_7 hydrogen is too far away to have any steric effect on the 2-position, but the C_8 hydrogen effectively constitutes a 1,3 diaxial interaction. At any rate, Schaefer's conclusion is that the endo-2 tosylate (23; R = OTs) solvolysis rate is slow due to this steric inhibition. This is of course essentially Brown's argument for the solvolytic behaviour of the norbornyl system. We feel that Schaefer is in error, here,

however, since a Schleyer[47] rate calculation indicates that the exo-tosylate (26; R = OTs) is in fact anchimerically assisted whereas the endo-tosylate (23; R = OTs) solvolyses normally. It is our contention that the answer to this problem is to be found in the thermodynamic parameters (see Table I). As stated in the kinetic discussion, for these solvolysis reactions one expects $\Delta S^{\neq}$ to be negative. This is, of course, the case for the exo-tosylate (26; R = OTs). The endo-tosylate, (23; R = OTs) however, differs strikingly here in that $\Delta S^{\neq}$ = +5.4 e.u. In other words, in going to the solvolytic transition state, the system has become less ordered!

To explain this finding, we propose that the endo-tosylate (23; R = OTs) is solvolysing in the flexible twin twist boat conformation (85). The increased ring mobility in going from



85

a rigid twin chair ground state conformation to the flexible

twin twist boat conformation is manifested in a large entropy increase which is sufficient to compensate for the normal loss of entropy, due to solvent ordering as a result of charge creation.

Support for this proposal can be found in Brown's results[50] on the solvolysis of a series of monocyclic arenesulphonates. As can be seen from Table 10, the $\Delta S^{\neq}$ values for acetolysis of the C_5-C_9 ring tosylates are, with one exception, almost constant (-4.1 to -5.7 e.u.). The exception is, of course, cyclohexyl tosylate for which $\Delta S^{\neq}$ values of -0.5 to +0.6 are quoted in this publication. Thus the activation entropy for acetolysis of cyclohexyl tosylate is some 4 e.u. above that for homologous ring systems. This increased entropy is again explicable if cyclohexyl tosylate solvolyses in flexible twist boat form.

Additional support for the reaction of cyclohexyl tosylates in flexible non-chair forms is to be found in the detailed product studies of Whiting et.al. on the solvolysis of various substituted cyclohexyl tosylates[56,57] and in the elegant deuterium isotope work of Shiner and Jewitt[58], and Sicher et.al.[59].

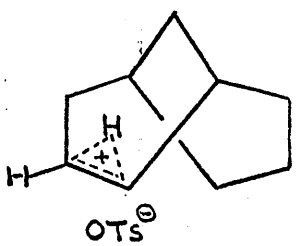
Tosylate	$\Delta H^{\neq}$ [a]	$\Delta S^{\neq}$ [b]
Cyclopentyl	24.1	-4.2
Cyclohexyl	27.3	-0.5
Cycloheptyl	23.3	-5.7
Cyclo-octyl	22.3	-4.5
Cyclononyl	22.5	-4.2

Table 10.

a) Measured in K. cal/mole.

b) Measured in entropy units

In a twist boat cyclohexyl tosylate, models indicate that one of the β-protons becomes trans antiparallel to the tosylate grouping and by selectively replacing these protons by deuterium it has been shown[58,59] that only the trans antiparallel deuterium atom has a large isotope effect. This of course suggests hydrogen participation to ionisation. Thus in our system we might expect the transition state geometry to be as shown (86). However,



86

this is the sort of participation to which we have attributed the rate enhancement in the exo-tosylate (26; R = OTs), so why is there still a large difference in rate?

The answer can again be found in the thermodynamic parameters. The exo-tosylate can form the ion (84) without structural change, whereas the endo-tosylate must 'flip' to the twin twist boat form. This 'flipping' requires

energy, and this energy should be reflected in the enthalpy of activation. This is, of course, the case as shown in Table I, there being a difference of 5.5 K.cal. in the $\Delta H^{\neq}$ values for (23) and (26) (R = OTs). Thus although hydrogen bridged ions are visualised as playing a major role in product formation in each case, the higher activation enthalpy in the endo- solvolysis results in a much slower acetolysis rate.

In this context it is heartening to see that the $\Delta H^{\neq}$ value for cyclohexyl tosylate, like the $\Delta S^{\neq}$ value, is higher than that for the homologous ring systems shown in Table 10.

Also of considerable importance to this argument are the results of le Noble et.al.[55]. These workers carried out some extremely interesting research on the activation volumes for certain cyclic and bicyclic arenesulphonates. Among these are the values for cyclopentyl, cyclohexyl and cycloheptyl (see Table 11), and it can be seen that cyclohexyl tosylate displays no abnormal activation volume for solvolysis. This is, of course, consistent with our mechanism since chair and twist boat forms would not be expected

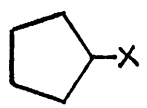
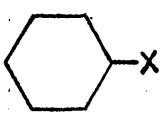
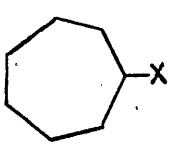
X = OTs	Temp. °C	Solvent, wt % acetone	$\Delta V^{\neq}$, cm^3/mole
	40.00	70.0	-17.0
	40.00	70.0	-17.5
	40.00	70.0	-17.7

Table 11.

to differ appreciably in volume, and in addition we propose the same type of charged intermediate in each case (84) and (85) and so the charge distribution effects on activation volume will be similar in each case.

Thus we feel that in the light of the kinetic results, the $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta V^{\neq}$ values, and the deuterium isotope effects outlined above, we must conclude that this is compelling evidence for the intermediacy of twist-boat or flexible conformations in the solvolysis of equatorially substituted arenesulphonate groups in a cyclohexyl ring system.

On consideration of the evidence presented above in support of our argument, it would appear both important and interesting to examine the solvolytic behaviour of suitably deuterated analogues of the 2-bicyclo (3,3,1) tosylates (23) and (26) (R = OTs) and in the event of the necessary apparatus becoming available, to carry out activation volume experiments in these bicyclic systems.

---oOo---

EXPERIMENTAL

All melting points were recorded on a Kofler block and are corrected, however the melting behaviour of these bicyclic compounds is most unusual in that the collapse of the crystal into a mosaic may take place at a temperature much below that at which only liquid is present. Because of this and a marked dependence on the rate of heating, accurate and reproducible melting points are difficult to obtain and the agreement with literature values is invariably poor. For these reasons only a few melting points are included in this section and structure confirmation is based on elemental and spectral analyses rather than on correlations with melting points recorded in the literature.

The absorbants used for column chromatography are commercial 'Woelm' alumina (basic or neutral) and silica. Thin-layer chromatoplates were prepared from Merck's 'Kieselgel G.' Analytical Gas-Liquid chromatograms were obtained on Pye-Argon and Perkin Elmer F 11 chromatographs, the latter being used when capillary columns were employed.

Nucleur magnetic resonance (n.m.r.) spectra were measured, using deuteriochloroform as solvent and tetramethylsilane as internal reference, on a Perkin Elmer R 10 60 Mc./sec. spectrometer with high resolution spectra being recorded on a Varian 100 Mc./sec. instrument.

Routine infrared spectra were recorded on Unicam SP 200 and Perkin Elmer 157 spectrometers; where high resolution is specified, spectra were recorded using a Unicam SP 100 double-beam infrared spectrophotometer equipped with an SP 130 sodium chloride prism-grating double monochromator operated under vacuum, and a Perkin Elmer 225 high resolution instrument.

Ultra-violet spectra were measured using a Unicam SP 800A instrument fitted with the SP 825 series 2 programme controller which was extensively used in the kinetic studies.

Unless otherwise stated, infrared spectra were recorded in carbon tetrachloride solution.

p-Toluenesulphonate esters were prepared by treatment of the alcohol (1 m.) with p-toluenesulphonyl chloride (1.05 m.) in anhydrous pyridine (0.8 ml/m.mole) at 0°C for 24 h. The resulting mixture was then poured into ice-water and extracted with pentane. The combined extracts were washed copiously with water, then with saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulphate. Solvent removal generally afforded viscous oils from which any residual traces of pyridine were removed under high vacuum at room temperature. The resulting materials were purified by crystallisation from ether-pentane at -20°.

Acetates were prepared by allowing the alcohol to stand for 12-15 h. at room temperature with an excess of acetic anhydride in anhydrous pyridine. The resulting solution was poured into water and extracted with portions of pentane. The combined extracts were then washed with dilute, ice-cold hydrochloric acid, saturated sodium bicarbonate solution and dried. Careful removal of solvent yielded volatile oils, which were purified by micro-distillation techniques suitable for quantities of liquid of the order of 20-300 mg.

p-Toluenesulphonates were converted to the corresponding alcohols by treatment with sodium naphthalene anion radical in tetrahydrofuran solution[42]. The reactions were carried out by injecting a fairly concentrated solution of the tosylate into a stirred tetrahydrofuran solution containing 2-6 equivalents (ca. 0.3M) of sodium naphthalene under nitrogen. Completion of the reaction, indicated by disappearance of the intense green colour of the anion radical generally occurs within a few seconds at room temperature. If more than 6 equivalents of anion radical is used the colour change may not occur; less than two equivalents may result in incomplete cleavage. The alcohol may then be isolated by usual techniques such as liquid chromatography or the mixture may also be directly analysed by gas chromatography after drying with magnesium sulphate.

Cyclohepta-1,3-diene[27]

Cyclohepta-1,3,5-triene (18.5 g., 0.2 m.) was added dropwise with stirring over 20 mins. to a solution of lithium (2.8 g.)(0.4 m.) in liquid ammonia (200 ml.) at -78°. The ammonia was then allowed to evaporate at room temperature, and the diene removed under high vacuum at room temperature and collected in an acetone-dricold trap as a colourless oil, which on distillation at atmospheric pressure gave a water clear liquid (14.3 g., 78%) b.p. 120-122° (lit.[27] 121-122°), n_D^{20} 1.4969 (lit., 1.4969), $\nu_{max.}$ 3050, 1612, 697 $cm.^{-1}$.

Endo-bicyclo (3,2,2) nonan-8-ene-6,7-dicarboxylic acid anhydride (44)

Cyclohepta-1,3-diene (79 g., 0.84 m.) was treated with maleic anhydride (89 g., 0.91 m.) in boiling o-xylene (500 ml.) containing a small amount of hydroquinone. After refluxing for 10.5 h. the xylene was removed at the pump to yield a yellow oil which crystallised on cooling. The resulting pale yellow solid was crystallised from ether to

yield the anhydride as colourless crystals (125 g., 78%), m.p. 108-110, $\nu_{max.}$ (high resolution) 3054, 1877, 1787, 1241, 1228, 1084, 954, 924 cm.$^{-1}$, τ 3.79 (2H) multiplet, 6.6 (2H) singlet, 6.99 (2H) complex multiplet. (Found: C, 69.1; H, 6.45. $C_{11}H_{12}O_3$ requires C, 68.75; H, 6.30%).

Endo-bicyclo (3,2,2) nonan-6,7, dicarboxylic acid anhydride (45)

The olefin anhydride (44) (60 g., 0.31 m.) was hydrogenated over Adam's catalyst, PtO_2, (0.53 g.) in glacial acetic acid (350 ml.). Reaction was complete after 3.25 h. and the catalyst was then removed by filtration and the solvent removed under reduced pressure to yield the saturated anhydride (45) as a colourless crystalline solid (59.3 g., 98%) m.p. 150-152°, $\nu_{max.}$ (high resolution) 1875, 1788, 1242, 1220, 1083, 949, 922 cm.$^{-1}$ τ 6.78 (2H) singlet, 7.48 (2H) complex multiplet, (Found; C, 67.85, H, 7.45. $C_{11}H_{14}O_3$ requires C, 68.00; H, 7.25%).

Endo-bicyclo (3,2,2) nonan-6,7-dicarboxylic acid (43)

The anhydride (45) (60 g., 0.30 m.) was stirred on the

steam bath with 20% (w/v) aqueous potassium bicarbonate solution (310 ml.) till all acid had dissolved. The solution was then cooled and concentrated hydrochloric acid (54.86 ml.) was added dropwise with stirring. The resulting precipitate was filtered at the pump and washed with a little water. The residue was then dried under high vacuum at room temperature to give (43) as an amorphous white solid which was not further purified since any attempt at crystallisation resulted in reclosure to the starting anhydride (45). $\nu_{max.}$ (nujol) 1711, 1226, 916 cm.$^{-1}$.

6-Bicyclo (3,2,2) nonene (41)

Endo-bicyclo (3,2,2) nonan -6,7- dicarboxylic acid (43) (4.66 g., 0.022 m.) was dissolved in anhydrous pyridine (60 ml.) through which oxygen had been bubbled for 20 mins. The solution was maintained at 65$\pm$ 2^{o} in an oil bath and dry, freshly crystallised lead tetra-acetate (15 g., 0.034 m.), was added with stirring. There was immediate effervescence which had completely subsided after about 20 mins. The resulting solution was then cooled to 0^{o} and acidified,

under pentane, with 6 N nitric acid. The layers were separated and the aqueous layer extracted further with three portions of pentane. The combined extracts were washed with saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulphate. The pentane was carefully removed by distillation up a vigreux column, leaving a yellow oil which was adsorbed on Grade I neutral alumina from pentane. Elution with pentane afforded the required olefin (41) as a very volatile, colourless, waxy solid (1.5 g., 56%). A sample purified by sublimation had $\nu_{max.}$ 3050, 1640, 933, 705 cm.$^{-1}$, τ 3,92 (2H) multiplet; 7.64 (2H) multiplet. (Found: C, 88.75; H, 11.15. C_9H_{14} requires C, 88.45; H, 11.55%).

Hydroboration of the olefin (41)

A solution of 0.8M diborane in tetrahydrofuran (8 ml., 0.0064 m.) was added dropwise with stirring over 15 mins., to a solution of the olefin (41) (3 g., 0.025 m.) in anhydrous ether (20 ml.); the reaction being carried out

at room temperature. After stirring for 24 h., 3N NaOH (11.5 ml.) and 30% H_2O_2 (11.5 ml.) were added and the mixture was stirred at room temperature for a further 4 h. The organic layer was separated and the aqueous layer extracted with ether (3 x 10 ml.). The combined organic extracts were then washed with brine (1 x 10 ml.), saturated ferrous sulphate solution (4 x 5 ml.), brine (1 x 10 ml.), saturated sodium bicarbonate solution (2 x 10 ml.) and finally brine (2 x 10 ml.) and dried ($MgSO_4$). The solvent was removed to yield a waxy solid (3.27 g.) which adsorbed on Grade III neutral alumina (90 g.) from pentane. Elution with ether-pentane gave the required alcohol as a colourless solid, (1.84 g., 53.5%). G.l.c. analysis showed the alcohol to be 95-98% epimerically pure. After sublimation, a sample had $\nu_{max.}$ 3665, 1009 cm.$^{-1}$, τ 5.95 (1 H) multiplet ($W_{\frac{1}{2}}$ = 16c./sec.), 8.30 (1 H) singlet. (Found: C, 77.30; H, 11.55. $C_9H_{16}O$ requires C, 77.10; H 11.50%).

The acetate was prepared from acetic anhydride-pyridine in the usual manner. $\nu_{max.}$ (CCl_4) 1732, 1246, 1019, 977 cm.$^{-1}$,

τ 5.0 (1H) multiplet; $W_{\frac{1}{2}}$ = 16 c./sec., 7.99 (3H, singlet). (Found: C, 72.25; H, 9.85. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%). The corresponding tosylate was prepared and after crystallisation from ether-pentane the colourless needles had m.p. 63-64.5°, $\nu_{max.}$ (CCl_4) 1599, 1187, 1176, 1097, 951, 926, 904, 863 cm.$^{-1}$, τ 2.17 (1 H) doublet, J = 8.5c./sec., 2.66 (1H) doublet, J = 8.5 c./sec., 5.17 (1H) multiplet, $W_{\frac{1}{2}}$ = 15.5 c./sec., 7.56 (3H) singlet. (Found: C, 65.05; H, 7.50. $C_{16}H_{22}O_3S$ requires C, 65.25; H, 7.55%).

Exo-and Endo-6-carbethoxy-bicyclo (3,2,2) non-8-ene (46)

Cyclohepta-1,3-diene (14.1 g., 0.15 m.), freshly distilled ethyl acrylate (15.8 g., 0.158 m.) and hydroquinone (0.35 g.) were sealed in an evacuated tube and heated at 175-180° for 46 hours. The tube was then cooled and opened and the resulting oil distilled under reduced pressure. The fraction boiling in the range 118-124°/10 mm. was collected (13.7 g., 47%). This material was used, without further purification, for the next stage of the synthetic sequence $\nu_{max.}$ 1730 cm.$^{-1}$

Saponification of the mixed esters (46)

A suspension of the esters (46) (10.7 g., 0.055 m.) in 50% aqueous methanol (65 ml.) containing sodium hydroxide (2.86 g., 0.071 m.) was refluxed for 3 h. The resulting solution was then diluted with water and extracted once with ether. The aqueous layer was then acidified with 6N sulphuric acid and thoroughly extracted with ether. The combined ether extracts were washed thoroughly with water, then with brine, dried over anhydrous magnesium sulphate and the solvent removed to yield the epimeric acids (47) as a waxy solid. Treatment of this material with animal charcoal gave a colourless solid (8.79 g., 96%). This mixture of epimeric acids was carried on to the next stage of the synthesis without further purification. $\nu_{max.}$ 1697 $cm.^{-1}$

Separation of exo- and endo-6-carboxybicyclo (3,2,2) non-8-ene by the Iodolactone method

To a suspension of the acids (47) (8.8 g., 0.053 m.) in water (40 ml.) was added 50% aqueous sodium hydroxide

solution until all of the solid had dissolved. Solid sodium bicarbonate was then added to saturation, followed by a solution of iodine (20.83 g., 0.156 m.) and potassium iodide (20 g., 0.121 m.) in water (70 ml.) and the mixture then stirred at 25-30° for 2.5 h. The reaction mixture was then decolourised by the addition of solid potassium metabisulphite and throughly extracted with four portions of ethyl acetate. The combined extracts were washed with potassium metabisulphite solution (2 x 15 ml.) and brine (2 x 20 ml.) and dried ($MgSO_4$).

Removal of solvent gave the iodolactone (48) as a pale yellow solid (12.5 g., 81%). Crystallisation from diethyl ether afforded colourless crystals m.p. 91-92.5°, $\nu_{max.}$ 1799, 1194, 1143, 1114, 973, 945 $cm.^{-1}$, τ 4.89 (1H) doublet, J = 6 c./sec; 5.25 (1H) doublet, J = 5.4 c./sec. (Found: C, 40.90; H, 4.45. $C_{10}H_{13}O_2I$ requires C, 41.10; H, 4.50%).

Endo-6-carboxybicyclo (3,2,2) non-8-ene (50)

A suspension of the iodolactone (48) (12.5 g., 0.043 m.)

and zinc powder (8.32 g., 0.13 m.) in glacial acetic acid (200 ml.) was refluxed for 45 mins. The mixture was then diluted with water and filtered free from the inorganic solids. The filtrate was then extracted with pentane (5 x 50 ml.), and the combined extracts washed with thiosulphate solution (1 x 25 ml.), water (4 x 20 ml.) and brine (1 x 25 ml.) and dried. Removal of solvent yielded an oil which crystallised on standing to give the endo-acid (50) (6.85 g., 96%). A sample was recrystallised from pentane, m.p. 73.5 - 75°, $\nu_{max.}$ 3055, 1704, 1289, 1222, 938, 703 cm.$^{-1}$, τ -0.32 (1H) multiplet, 3.78 (2H) multiplet. (Found: C, 72.30; H, 8.60. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.45%).

Endo-6-carboxybicyclo (3,2,2) nonane (51)

The olefin acid (50) (6 g., 0.036 m.) was hydrogenated over Adam's catalyst (0.5 g.) in glacial acetic acid (40 ml.). Reaction ceased before the theoretical amount of hydrogen had been used up and more catalyst (0.18 g.) was added. After stirring overnight, the reaction was complete and the

catalyst was removed by filtration. Evaporation of solvent and decolourising with animal charcoal gave the saturated acid (51) (5.6 g., 92%) as a colourless crystalline solid. Sublimation afforded material of m.p. 68-74°, $\nu_{max.}$ 1704, 1222 cm.$^{-1}$, τ -1.16 (1H) ($-CO_2H$). (Found: C, 71.40; H 9.70. $C_{10}H_{16}O_2$ requires C, 71.40; H 9.60 %).

Endo-6-bicyclo (3,2,2) nonyl methyl ketone (52)

To a solution of the endo-acid (51) (4.94 g., 0.029 m.) in anhydrous ether (50 ml.) was added an approximately 1.9 M solution of methyl lithium in ether (37 ml., ~ 70 mm.) with stirring over 25 mins. A white precipitate formed almost immediately but had completely disappeared five minutes after addition was complete. Saturated ammonium chloride solution was then added and the layers were separated. The aqueous layer was extracted twice with ether and the extracts combined and washed with saturated ammonium chloride solution (1 x 20 ml.), water (2 x 10 ml.) and brine (1 x 20 ml.). After drying ($MgSO_4$), the solvent was removed to yield an oil (4.9 g.). A semicarbazone was

prepared and recrystallised from methanol, m.p. 178.5°-179.5°, (Found: C, 64.60; H, 9.60; N, 18.70. $C_{12}H_{20}ON_3$ requires C, 64.55; H, 9.50; N, 18.80%). A sample of the ketone (52) was regenerated from the semicarbazone and had $\nu_{max.}$ 1712, 1169 $cm.^{-1}$, τ 7.86 (CH_3-CO-) singlet.

Baeyer / Villiger oxidation of ketone (52)

To a suspension of 90% H_2O_2 (2.5 ml.) in methylene chloride (15 ml.) was added trifluoroacetic anhydride (15 ml.) dropwise with stirring. A portion of this per-acid solution (17 ml.) was added dropwise to the crude ketone (52) (4.2 g., 0.0253 m.) in methylene chloride (15 ml.), containing potassium dihydrogen phosphate (6.7 g.) and di-potassium hydrogen phosphate (20 g.), with stirring over 40 mins. The mixture was then stirred for a further 0.5 h. at room temperature, then refluxed for 1 hour. The inorganic solids were filtered of and stirred with ether (30 ml.) for 45 mins., and the ether and methylene chloride extracts were combined and washed with saturated sodium carbonate solution and brine and dried. G.l.c. analysis

of the crude extract showed only about 45% conversion to acetate. The solvent was removed to yield an oil whose p.m.r. spectrum showed signals corresponding to both the ketonic (τ 7.86, singlet) and acetate (τ 7.99, singlet) methyl groups. The acetate and ketone were separated by means of the semicarbazone of the ketone, and gave the acetate as a pale yellow oil (1.95 g., 42%). A sample of this oil was purified by mioro-distillation. This latter material was identical by n.m.r. and infrared spectroscopy and g.l.c. retention time to the acetate of the alcohol obtained from hydroboration of 6-bicyclo (3,2,2) nonene (41). $\nu_{max.}$ 1732, 1246, 1019, 977 cm.$^{-1}$, τ 5.0 (1H, multiplet; $W_{\frac{1}{2}}$ = 16 c./sec.), 7.99 (3H, singlet).

Bicyclo (3,2,2) nonan-6-one (33)

To an ice-cold stirred solution of endo-6-bicyclo (3,2,2) nonanol (30; R = OH) (1.42 g., 0.01 m.) in anhydrous acetone (10 ml.) sufficient 8N Jones[34] reagent was added dropwise with stirring at 0°C to maintain the brown colouration. After stirring for 15 mins., the

reaction was poured into water and extracted with pentane (4 x 15 ml.). The combined extracts were washed with saturated sodium bicarbonate solution and brine and then dried ($MgSO_4$). The solvent was removed to yield the ketone (33) as a colurless solid (1.31 g., 92%) virtually pure by infrared analysis.

A sample purified by sublimation had $\nu_{max.}$ (CCl_4) 1716 $cm.^{-1}$, τ 7.52 (1H) multiplet, 7.73 (3H) singlet. (Found: C, 78.35, H, 10.35. $C_9H_{14}O$ requires C, 78.25; H, 10.20%).

Preparation of Lithium Aluminium Tri-methoxy Hydride[22]

Tetrahydrofuran was dried by distillation from lithium aluminium hydride (L.A.H.) and to 150 ml. of the dried solvent was added L.A.H. (3.06 g., 0.081 m.). The suspension was stirred overnight at room temperature under an atmosphere of dry nitrogen. The mixture was then filtered under a slight nitrogen pressure through a 2 inch bed of celite in a sintered-glass cylinder, into a dry two-necked flask equipped with a drying tube. An active hydrogen analysis of the solution showed it to be 0.38M in L.A.H.

Exo-6-bicyclo(3,2,2) nonanol (29; R = OH)

To a stirred, ice-cold 0.38M solution of lithium aluminium hydride in tetrahydrofuran (THF) (35 ml., 13.3 mm.) was carefully added dry methanol (1.263 g., 39.5 mm.) in dry THF (2 ml.). A solution of the ketone (33) (1.31 g., 9.4 mm.) in dry THF (10 ml.) was then added at 0°C under nitrogen over 30 mins. The solution was then stirred at room temperature for 1 hour, after which t.l.c. showed the absence of ketone. After a further hour at room temperature, the excess hydride was destroyed with water, and the intermediate complex was then decomposed with a saturated solution of Rochelle salt. The layers were separated and the aqueous layer extracted three times with pentane. The combined extracts were washed with water and brine and dried. Removal of solvent afforded a colourless solid (1.203 g., 91%) whose infrared spectrum showed no carbonyl absorption band. After sublimation, a sample (at least 98% epimerically pure by g.l.c.) had $\nu_{max.}$ 3624, 1064, 1050 $cm.^{-1}$, τ 6.11 (1H, multiplet; $W_{\frac{1}{2}}$ = 20 c./sec.), 8.26 (1H; singlet)

(Found: C, 77.20; H, 11.40. $C_9H_{16}O$ requires C, 77.10; H, 11.50%).

The corresponding acetate (29; R = OAc) was prepared in the usual manner from acetic anhydride-pyridine. $\nu_{max.}$ 1742, 1728, 1243, 1040, 1020 cm.$^{-1}$, τ 5.11 (1H, multiplet; $W_{\frac{1}{2}}$ = 20 c./sec.), 7.98 (3H, singlet). (Found: C, 72.40; H, 9.90. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%).

The corresponding tosylate (29; R = OTs) was prepared in the usual manner, crystallised from ether-pentane as colourless crystals m.p. 57.5-59.5°, $\nu_{max.}$ 3045, 1595, 1097, 961, 930, 904, 863 cm.$^{-1}$, τ 2.12 (1H doublet, J = 8.5 C./sec.), 2.62 (1H doublet, J = 8.5 c/sec.), 5.28 (1H, multiplet, $W_{\frac{1}{2}}$ = 20 c./sec.), 7.55 (3H, singlet). (Found: C, 65.10; H, 7.50. $C_{16}H_{22}O_3S$ requires C, 65.25; H, 7.55%).

2-Pyrrolidinobicyclo (3,3,1) nonan-9-one (35)

This compound was prepared according to the method Hanack et.al.[19] $\nu_{max.}$ (film) 1714, 1490 cm.$^{-1}$.

2-Pyrrolidinobicyclo (3,3,1) nonane (36)

The keto-amine (35) (51.75 g., 0.25 m.), 100% hydrazine hydrate (75 g., 1.5 m.) and powdered potassium hydroxide (70 g., 1.25 m.) were added to diethylene glycol (500 ml.) and the mixture refluxed for 2 h. The apparatus was then set for downward distillation and pyrolysis started. After 3 h., the reaction flask was cooled and diluted with water (500 ml.) and thoroughly extracted with ether. The distillate was similarly treated, and the combined extracts were washed copiously with water, then brine and dried. The ether was removed at the pump to yield the amine (36) as a pale yellow oil (44.2 g., 91%) which was distilled under reduced pressure to give the amine (36) as a colourless oil (39 g., 81%) b.p. 104-106°/1.4 mm., n_D^{20} 1.5110, identical by i.r., n.m.r. to an authentic sample[24].

Bicyclo (3,3,1) nonan-2-one (31)

A mixture of the amine (36) (5 g., 0.026 m.), mercuric acetate (33 g., 0.1 m.) and aqueous acetic acid solution (5% AcOH) (150 ml.) was heated on the steam bath for 2.5 h.

Dilute hydrochloric acid was then added to pH 1 and the resulting mixture was heated for a further hour. The cooled reaction mixture was then filtered and the filtrate thoroughly extracted with 50% ether-pentane. The combined extracts were washed with saturated sodium bicarbonate solution (2 x 25 ml.), brine (1 x 30 ml.) and dried. Removal of the solvent afforded an oily solid which was chromatographed on Grade III neutral alumina to yield the ketone (31) as a colourless solid (1.4 g., 40%), identical by i.r. and n.m.r. to an authentic sample[24] $\nu_{max.}$ 2856, 2926, 1712, 1096 cm.$^{-1}$, τ 7.56 (3H) multiplet, (-CO-C<u>H</u> and -COC<u>H</u>$_2$).

The p-bromobenzenesulphonylhydrazone was prepared, m.p. 130.8-132°, (Found: C, 48.45; H, 5.25; N 7.50. $C_{15}H_{19}N_2O_2SBr$ requires C, 48.50; H, 5.15; N, 7.55%).

<u>Endo-2-bicyclo (3,3,1) nonanol</u> (23; R = OH)

2-Bicyclo (3,3,1) nonanone (31) (5 g., 0.036 m.) in anhydrous ether (25 ml.) was added dropwise, with stirring to a suspension of lithium aluminium hydride (1.05 g.,

0.028 m.) in dry ether (80 ml.) at room temperature. After addition was complete, the mixture was stirred for 1 h. at room temperature then refluxed for a further 1.5 h. The reaction was then cooled to 0°C and the excess hydride and intermediate complex both destroyed by the addition of excess 6N. sulphuric acid. The layers were then separated and the aqueous layer extracted with ether (3 x 20 ml.). The combined extracts were then washed with saturated sodium bicarbonate solution, brine and dried ($MgSO_4$). Removal of the solvent gave the alcohol (23; R = OH) as a colourless solid, at least 97% pure by g.l.c. Crystallisation from pentane afforded the pure epimer (23; R = OH) as colourless plates $\nu_{max.}$ (high resolution) 3624, 2984, 1496, 1067, 1035, 973, 955 $cm.^{-1}$, τ 6.14 (1H, multiplet; $W_{\frac{1}{2}}$ 17 c./sec.), 8.35 (1H, singlet). (Found: C, 77.05; H, 11.65. $C_9H_{16}O$ requires C, 77.10; H, 11.50%).

The corresponding acetate (23; R = OAc) was prepared as a colourless oil $\nu_{max.}$ 1737, 1242, 1027 $cm.^{-1}$, τ 5.02 (1H) multiplet, $W_{\frac{1}{2}}$ = 16 c/sec; 7.95 (3H) singlet. (Found: C, 72.30; H, 9.90. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%).

Treatment of the alcohol with p-toluenesulphonyl chloride - pyridine in the usual way, afforded the tosylate (23; R = OTs) which crystallised from ether-pentane as a colourless solid, m.p. 65.6-66.1°, $\nu_{max.}$ 3050, 1600, 1191, 1180, 973, 960, 938, 918, 868 $cm.^{-1}$, τ 2.67 (1H, doublet; J = 8.5 c./sec.) 2.18 (1H, doublet; J = 8.5 c./sec.), 5.30 (1H multiplet; $W_{\frac{1}{2}}$ = 25 c./sec.), 7.59 (3H, singlet). (Found: C, 65.40; H, 7.55. $C_{16}H_{22}O_3S$ requires C, 65.25; H, 7.55%).

Exo-2-bicyclo (3,3,1) nonanol (26; R = OH)

a) Epimerisation of endo-2-bicyclo (3,3,1) nonyl tosylate 23; R = OTs)

A solution of the tosylate (23; R = OTs) (4 g., 0.014m.) in dimethylformamide (90 ml.) and water (10 ml.) was heated in a constant temperature vapour jacket at 78° for 50 h. The solution was then poured into water and extracted with ether. The combined extracts were thoroughly washed with water then brine and dried. Lithium aluminium hydride was added to the dried solution and the mixture stirred at room temperature for 2 h. After working up the reaction in

the usual way, the solvent was removed to yield a colourless solid (1.8 g.) whose infrared spectrum showed bands at 3350 cm.$^{-1}$ (ν_{O-H}) and 715 cm.$^{-1}$ (cis-double bond). This solid was chromatographed on silica to yield the alcohol (26; R = OH) (0.8 g., 42%), bicyclo (3,3,1) non-2-ene (0.5 g., 30%) and a small amount of unchanged tosylate.

The alcohol could be obtained in at least 98-99% epimeric purity by crystallisation from pentane, as evidenced by g.l.c. analysis.

b) From 2-bicyclo (3,3,1) nonene

A solution of m-chloroperbenzoic acid (2.4 g.) in chloroform (30 ml.) was added dropwise to a stirred solution of 2-bicyclo (3,3,1) nonene (38) (1.2 g., 0.01 m.) in chloroform (7 ml.). Stirring was continued at room temperature for 45 h. during which time a white precipitate formed. Aqueous sodium sulphide solution (10%) was then added and the layers separated. The organic layer was washed with two further portions of the sulphide

solution, saturated sodium hydrogen carbonate solution (2 x 15 ml.) and brine (1 x 15 ml.) and dried.

The solvent was removed to yield a yellow oily solid (1.38 g.). A sample was purified by sublimation to yield a colourless waxy solid $\nu_{max.}$ 1170, 1097,1004, 965, 954, 881, 845 $cm.^{-1}$

The remainder was carried on to the next stage of the reaction without further purification.

A solution of the crude epoxide (40) (1.23 g.) in anhydrous THF (5 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (0.27 g.) in anhydrous THF (35 ml.). The reaction mixture was refluxed for 25 h., cooled, and the excess hydride destroyed with water. Dilute sulphuric acid was added and the layers were separated. The aqueous layer was extracted once with pentane, and the combined organic phases were washed with saturated sodium bicarbonate solution, brine and dried ($MgSO_4$).

The solvent was removed to yield a waxy solid (1.2 g.) which was adsorbed on Grade III neutral alumina from

pentane. Elution with ether-pentane yielded the alcohol as a colourless solid (0.8 g., 64.5%).

After sublimation this material was identical by i.r. and g.l.c. analysis to that from the epimerisation reaction above. $\nu_{max.}$ 3627, 2979, 1492, 1235, 1052, 998, 975, 956 cm.$^{-1}$, τ 6.11 (1H; multiplet, $W_{\frac{1}{2}}$ = 8 c./sec.) (1H). (Found: C, 77.25; H, 11.50. $C_9H_{16}O$ requires C, 77.10; H, 11.50%). Treatment of the alcohol with acetic anhydride-pyridine in the usual way, afforded the acetate (26; R = OAc) as a colourless oil $\nu_{max.}$ 1735, 1246. 1218, cm.$^{-1}$ τ 4.97 (1H) multiplet, $W_{\frac{1}{2}}$ = 7 c./sec; 7.94 (3H) singlet. (Found: C, 72.25; H, 9.80. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%).

The corresponding tosylate (26; R = OTs) was prepared in the normal fashion and crystallisation from ether-pentane yielded a colourless solid m.p. 51.5-53°, $\nu_{max.}$ 3045, 1597, 1189, 1178, 1102, 906 cm.$^{-1}$, τ 2.08 (2H) doublet, J = 8.5 c./sec., 2.58 (2H) doublet, J = 8.5 c./sec., 5.23 (1H) multiplet $W_{\frac{1}{2}}$= 7.5 c./sec., 7.54 (3H) singlet

2 -Pyrrolidine - bicyclo (3,2,1) octan-8-one (54)

Freshly distilled acrolein (70 ml.) in dioxan (70 ml.)

was added dropwise over 2 h. to a stirred solution of the eneamine (55) (137 g.) in dioxan (150 ml.)containing a small amount of hydroquinone, at 0^{0} C. The solution was stirred for a further 1 h. at room temperature, and the solvent was then removed at the pump. The residue was distilled under high vacuum and the fraction boiling in the range $120\text{-}127^{0}/1.3\text{-}1.5$ mm., was collected (109 g., 61%). $\nu_{max.}$ (film) 2800, 1740 $cm.^{-1}$

2-Pyrrolidine-bicyclo (3,2,1) octane (56)

The keto-amine (54) (57.9 g., 0.3 m.), 100% hydrazine hydrate (75 g., 1.5 m.), powdered potassium hydroxide (84 g., 1.47 m.) and ethylene glycol (600 ml.) were refluxed for 2.25 h. The apparatus was then set for downward distillation and pyrolysis started. After 3.5 h., the reaction flask was cooled and diluted with water (500 ml.) and thoroughly extracted with ether. The distillate was similarly treated and the combined extracts were copiously washed with water and brine and dried. Removal of solvent afforded a pale yellow oil, which was distilled under high vacuum. Collection of the fraction

boiling at 67-75°/0.08-0.1 mm., gave the amine (56) as a colourless oil (39.5 g., 74.5%).

Bicyclo (3,2,1) octan-2-one (53)

The amine (56) (4.5 g., 0.025 m.), 5% aqueous acetic acid solution (150 ml.) and mercuric acetate (25 g., 0.075 m.) were heated on the steam bath for 2 h. Dilute hydrochloric acid was then added to pH 1 and the reaction mixture was heated for a further hour on the steam bath, filtered and allowed to cool. The cooled filtrate was thoroughly extracted with 40-60° petrol and the combined extracts washed with saturated sodium hydrogen carbonate solution (2 x 25 ml.), brine and dried. The solvent was removed to yield an oily solid (1.8 g.). This was adsorbed on Grade I neutral alumina from pentane. Elution with ether-pentane yielded the ketone (53) as a colourless solid $\nu_{max.}$ 1720, 1097 cm.$^{-1}$, τ 7.29 (1H) multiplet.

2-Cyano-2-hydroxybicyclo (3,2,1) octane (57)

To a stirred solution of the ketone (53) (5.73 g., .046 m.) in absolute ethanol (170 ml.) and glacial acetic

acid (65 ml.) at 0°C was added potassium cyanide (60 g., 0.92 m.) in small portions over 25°. The resulting suspension was stirred at 0° for a further 30 mins., then overnight at 20°. The resulting yellow coloured mass was then poured into water and extracted with ether. The ether extract was washed with water and brine and dried ($MgSO_4$). Removal of solvent gave a reddish coloured oil (7.55 g.). Treatment with animal charcoal resulted in a colourless oily solid, whose i.r. spectra showed the presence of a carbonyl function. After two sublimations and crystallisation from pentane, a colourless solid was obtained. This latter material sublimed as a colourless waxy solid m.p. 113-116° $\nu_{max.}$ (film) 3440, 2280, 1120, 1085, 1060, 1005, 960, 940 $cm.^{-1}$ τ 7.12 and 7.19 singlets (C - OH). (Found: C, 71.20; H, 8.80; N, 9.10 $C_9H_{13}NO$ requires C, 71.50; H, 8.65; N, 9.25%).

2-Acetoxy-2-cyano-bicyclo (3,2,1) octane (58)

The above cyanohydrin (57) (6.3 g., 0.04 m.), acetic anhydride (10 g., 0.099 m.) and pyridine (8 g., 0.101 m.) were stirred at room temperature for 24 h. The solution

was then diluted with water and extracted with ether. The combined ether extracts were washed with ice-cold dilute hydrochloric acid, saturated sodium hydrogen carbonate solution and brine and dried. Removal of solvent gave a reddish oil (8.9 g.) which was chromatographed on silica to yield the cyanoacetate (58) as a pale yellow oil (7.9 g.). $\nu_{max.}$ 2285, 1754, 1370, 1232, 1213, 1190, 1042 cm.$^{-1}$. The ^{1}H n.m.r. spectrum displayed two different acetate methyl signals, due probably to the presence of the epimeric acetates, (59 and 60) at τ 7.9 and τ 7.95.

Distillation of the cyanoacetates was unsuccessful and resulted in the formation of the ketone (53) as shown by g.l.c. analysis.

2-Aminomethyl-2-hydroxybicyclo (3,2,1) octane (61)

The cyanoacetates (58) (3.4 g., 0.0176 m.) in anhydrous ether (30 ml.) were added dropwise to a stirred suspension of lithium aluminium hydride (2.9 g., 0.0763 m.) in anhydrous ether (100 ml.). The resulting suspension was stirred at room temperature for 1 h. and then refluxed for 2 h. Saturated sodium sulphate solution was added

and the layers were separated. The aqueous phase was further extracted with ether and the combined organic extracts washed with water, brine and dried. The solvent was removed to yield an oil (2.9 g.) $\nu_{max.}$ 3400, 1118, 1051, 1028 $cm.^{-1}$. The oil was distilled to yield the hydroxyamine (61) as an extremely hygroscopic solid (1.6 g., 58%) b.p. 81-82°/0.04 mm., τ 7.27, 7.46, 7.66, (all broad singlets removed by the addition of D_2O).

The low yield of the hydroxyamine is probably due to its hygroscopic properties resulting in high solubility in the aqueous phase during the extraction process.

Ring Expansion of the Hydroxy-amine (61)

A solution of sodium nitrite (2.1 g., 0.03 m.) in water (7 ml.) was added dropwise to the hydroxyamine (61) (3.5 g., 0.0227 m.) in acetic acid (1.75 ml.) and water (50 ml.) at 0°C. The mixture was stirred at 0° for 45 mins., then at 20° for 30 mins., and finally heated on the steam bath for 1 h. The reaction mixture was then cooled, diluted with water and extracted with ether. The organic

extract was washed with saturated sodium bicarbonate solution, brine and dried. Removal of the ether gave a yellow oil which, was adsorbed on Grade I basic alumina from pentane. Elution with ether-pentane gave a pale yellow oily solid (0.78 g.) which by g.l.c. analysis was composed of two main components in the ratio 3:1. The solid exhibited strong carbonyl absorption in the infra-red and was further purified as the semicarbazone derivatives, crystallisation of which afforded pale yellow crystals (0.81 g.)

The ketones were regenerated by shaking a suspension of the semicarbazones (0.46 g.) in 6N sulphuric acid and ether until all of the solid had dissolved (45 mins.). The layers were then separated and the organic phase washed with saturated sodium bicarbonate solution and brine and dried ($MgSO_4$). Removal of solvent gave the ketones (32) and (62) as a colourless waxy solid (0.3 g., 92%) in the ratio 7:1 as evidenced by g.l.c. analysis $\nu_{max.}$(mull) 1695 $cm.^{-1}$. Separation of the two ketones by column or thin-layer chromatography was only partially successful.

Bicyclo (3,3,1) nonan-9-one (67)

Bicyclo (3,3,1) non-2-ene-9-one (66) (10 g., 0.074 m.) in ethyl acetate (50 ml.) was hydrogenated over 5% palladium on charcoal. After the uptake of hydrogen was complete, the catalyst was filtered off and the solvent was removed at the pump to yield a colourless solid (9.6 g., 94%) identical by infrared and g.l.c. analysis with an authentic sample of the required ketone (67).

9-Oxabicyclo (3,3,2) decan-10-one (68)

Trifluoroperacetic acid was prepared by the slow addition of trifluoroacetic anhydride (25.4 ml.) to a stirred suspension of 90% hydrogen peroxide (4.2 ml.) in methylene chloride at room temperature.

To a stirred suspension of the ketone (67) (10.5 g., 0.076 m.) and dipotassium hydrogen phosphate (60 g.) in methylene chloride (60 ml.) was added the above per-acid solution (50 ml.) over 1 h. The resulting suspension was refluxed for a further hour and then the inorganic solids were filtered off and thoroughly extracted with

methylene chloride. The combined organic extracts were washed with 10% (w/v) sodium carbonate solution (1 x 25 ml.) brine (1 x 25 ml.), sodium carbonate solution (2 x 25 ml.) and finally brine (3 x 25 ml.) and dried. The solvent was removed to yield a colourless solid (10.4 g., 89%) virtually homogeneous by g.l.c. analysis, $\nu_{max.}$ 2984, 1729, 1485, 1469, 1394, 1280, 1169, 1033, 985 $cm.^{-1}$; τ 6.32 (1H, multiplet), 6.67 (1H, multiplet), (Found: C, 70.10; H, 9.15. $C_9H_{14}O_2$ requires C, 70.00; H, 9.20%).

Cis-5-hydroxycyclo-octanemethanol (69)

A solution of the above lactone (68) (6.8 g., 0.0441 m.) in anhydrous tetrahydrofuran (80 ml.) was added over 15 mins, to a stirred suspension of lithium aluminium hydride (4.23 g., 0.111 m.) in anhydrous tetrahydrofuran (150 ml.). The mixture was stirred at room temperature for 14.5 h. refluxed for 3 h. and stirred at room temperature a further 4 h. Water (4.2 ml.) and 15% sodium hydroxide solution were added, followed by more water (12.6 ml.) and the reaction stirred at room temperature for another 17.5 h. The inorganic solids were filtered off and the filtrate was dried over anhydrous $MgSO_4$.

The solvent was removed to yield a viscous oil (6.9 g., 100%), homogeneous by t.l.c. but containing traces of moisture as evidenced by infrared spectroscopic analysis $\nu_{max.}$(film) 3450 (broad), 1080, 1050, 1020 cm.$^{-1}$. A sample was purified by microdistillation, $\nu_{max.}$ (high resolution) 3641, 3626 cm.$^{-1}$. (Found: C, 68.05; H, 11.55. $C_9H_{18}O_2$ requires C, 68.30; H, 11.45%).

Cis-5-hydroxycyclo-octane-methanol mono p-toluenesulphonate (70)

A solution of the diol (69) (6.1 g., 0.0386 m.) and p-toluenesulphonyl chloride (7.37 g., 0.0387) in anhydrous pyridine (30 ml.) was held at 0°C for 1.25 h. The reaction mixture was then poured on to ice and dilute hydrochloric acid was added. The mixture was then extracted thoroughly with methylene chloride and the combined extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and finally brine and dried. Removal of the solvent afforded an oil (11.9 g., 98%). T.l.c. analysis indicated the absence of any starting diol, but also showed that some ditosylate (71) had been formed. The product was carried on to the next stage of the reaction without further purification.

5-Hydroxymethylcyclooctanone (72)

8N Jones[34] reagent was added to a stirred solution of the crude mono p-toluenesulphonate (70) (11.9 g., 0.0382 m.) in anhydrous acetone (100 ml.) at 0°C until the brown colouration just persisted. The reaction was then diluted with water and extracted thoroughly with ether. The combined extracts were washed with saturated sodium bicarbonate solution, brine and dried. Removal of the ether afforded a pale yellow solid (9 g., 76%). T.l.c. analysis of the product indicated the absence of any monotosylate but showed that there was a small amount of another compound, presumably some of the ditosylate (71) in the starting material. That this was indeed the case was shown by preparative t.l.c. of a sample which afforded the ketotosylate (72) as a crystalline solid $\nu_{max.}$ (nujol) 3080, 1689, 1596, 1169, 967, 956, 873, 827 and 672 cm.$^{-1}$; and the ditosylate (71) as an oil $\nu_{max.}$ (film) 1597, 1184, 1175, 1097, 965, 918, 825 and 672 cm.$^{-1}$. The main bulk of the product was not further purified.

2-Bicyclo (4,2,1) nonanone (32)

The crude keto-tosylate (72) (9 g.) methanol (225 ml.),

water (200 ml.) and sodium hydroxide (1.75 g.) were refluxed for 22 h. The resulting solution was acidified to Congo Red with 2N HCl, solid sodium chloride was added and the solution liberally extracted with ether. The organic axtract was washed with saturated sodium bicarbonate solution, brine and dried. The solvent was removed at the pump to yield an oil (4.5 g.) which displayed strong carbonyl absorption in the infrared. Chromatography on Grade I neutral alumina using ether-pentane as eluant afforded the ketone (32) (3 g., 75%) as a colourless, volatile, waxy solid which still contained an impurity. A sample purified by sublimation had $\nu_{max.}$ 1695, 1328, 1115, 964, 870 cm.$^{-1}$. (Found: C, 78.30; H, 10.20. $C_9H_{14}O$ requires C, 78.25; H, 10.20%).

Reduction of Bicyclo (4,2,1) nonan-2-one (32)

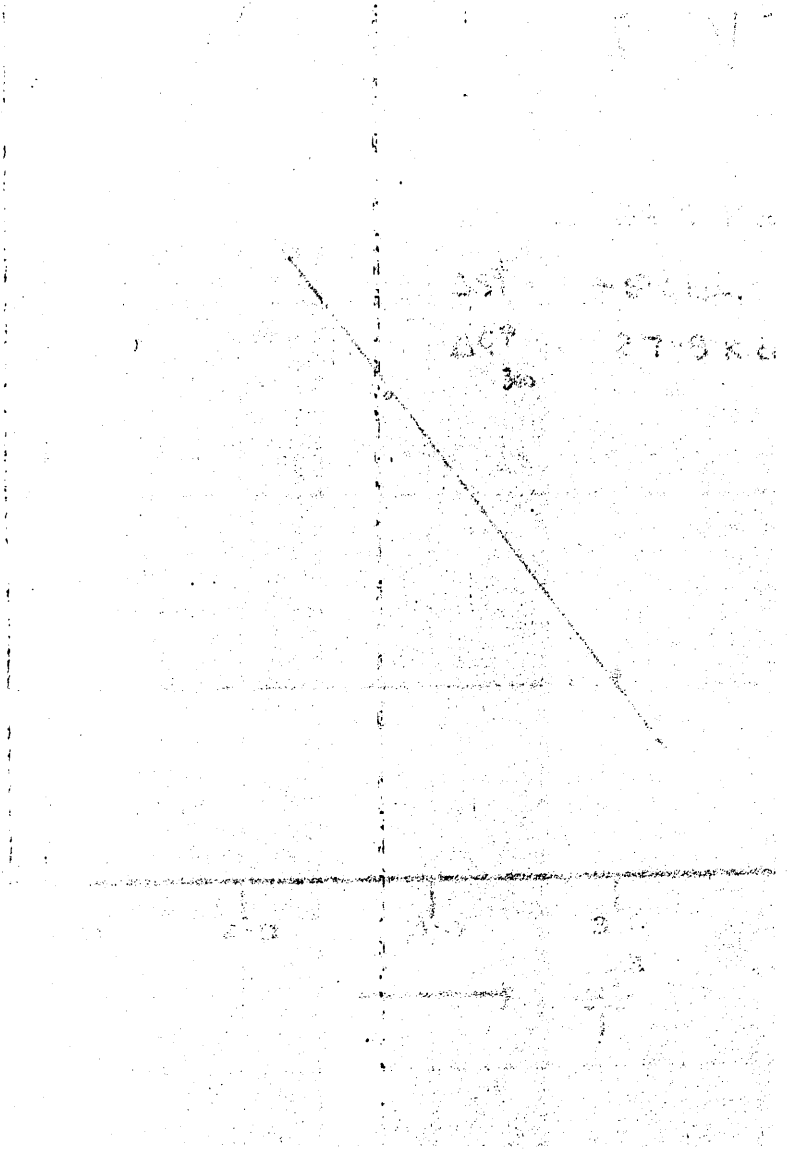
For this experiment, all apparatus and solvents were dried thoroughly before use.

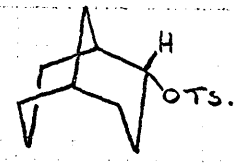
Dry methanol (3.058 g., 0.0956 m.) in tetrahydrofuran (3 ml.) was added dropwise to a stirred 0.38M solution of lithium aluminium hydride in tetrahydrofuran (84.25 ml.,

0.032 m.) at 0°. When addition was complete, a solution of the crude ketone (32) (3.14 g., 0.0228 m.) in tetrahydrofuran (25 ml.) was added over 30 mins. with stirring at 0°. After all of the ketone had been added, the reaction was stirred at room temperature for 12 h. The excess hydride was then destroyed with water and the intermediate complex decomposed with a saturated solution of Rochelle salt. The layers were separated and the aqueous layer extracted three times with pentane. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent afforded an oily solid (3.2 g.) which was adsorbed on Grade III neutral alumina from pentane. Elution with ether-pentane gave the alcohols (73) as a colourless crystalline solid (2.4 g., 79%) which showed strong hydroxyl absorption in the infrared. Capillary g.l.c. analysis showed the product to be a mixture of the two epimeric alcohols (73) in the ratio 76:24

The corresponding tosylates were prepared in the usual manner but even after four crystallisations from ether-pentane, followed by regeneration of the alcohols as described above, g.l.c. analysis still showed the presence of both epimers (73) in the ratio 87:13.

Similar treatment of (32) with lithium aluminium tri-tertiarybutoxy hydride produced the same alcohols (73), but in the ratio 65:35.

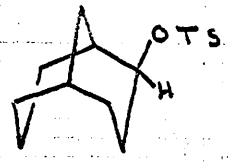




$\Delta H^{\ddagger}$ = 29·5 K.cal/Mole.

$\Delta S^{\ddagger}$ = +5·4 e.u.

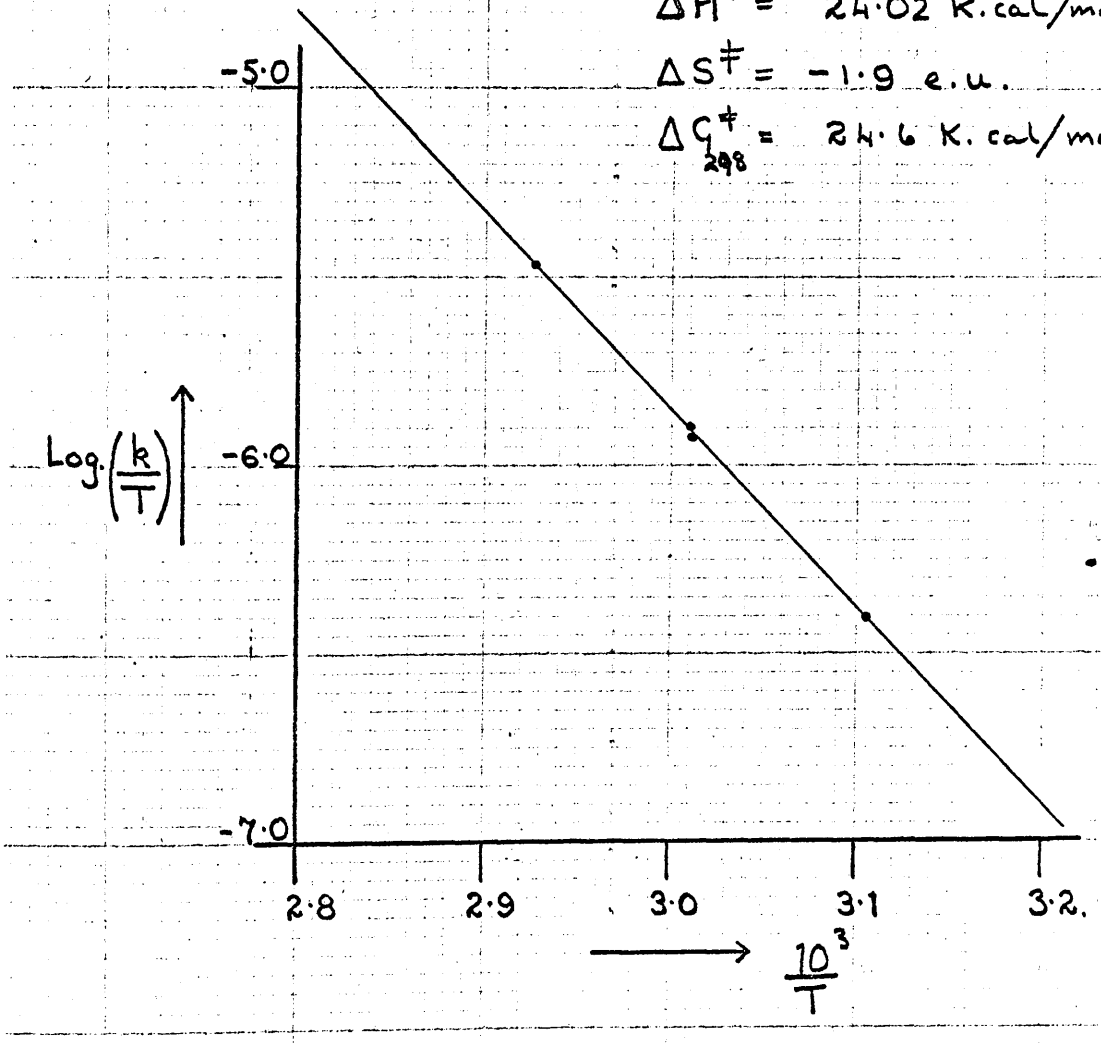
$\Delta G^{\ddagger}_{300}$ = 27·9 K.cal/mole.

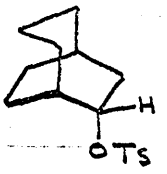


$\Delta H^{\ddagger}$ = 24·02 K. cal/mole.

$\Delta S^{\ddagger}$ = −1·9 e.u.

$\Delta G^{\ddagger}_{298}$ = 24·6 K. cal/mole.





Initial

$\Delta H^{\neq}$ = 15.64 K. cal/mole.

$\Delta S^{\neq}$ = − 24.96 en.

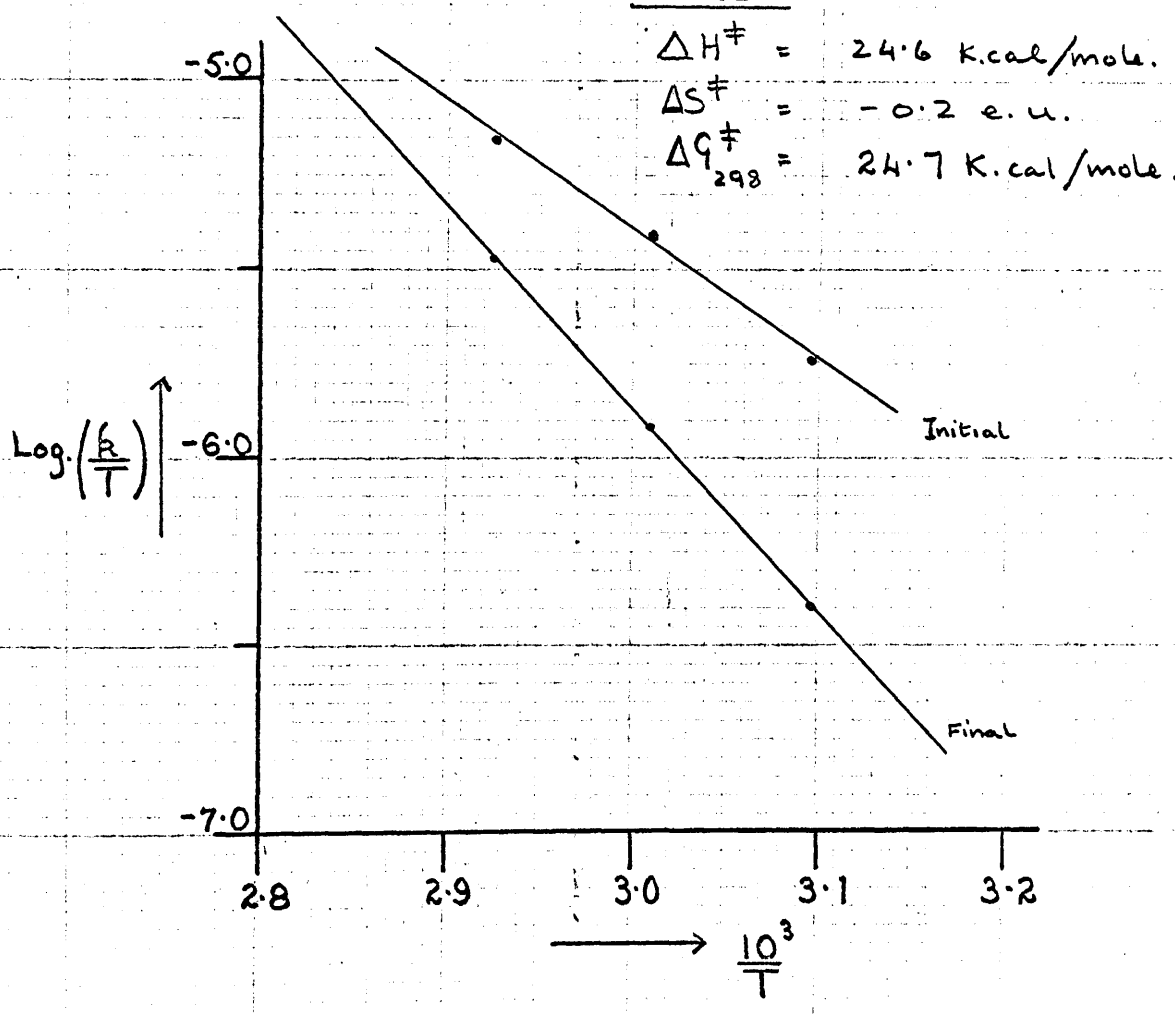
$\Delta G^{\neq}_{298}$ = 23.1 K.cal/mole

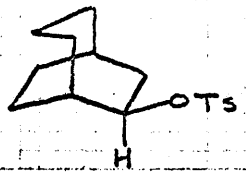
Final

$\Delta H^{\neq}$ = 24.6 K.cal/mole.

$\Delta S^{\neq}$ = − 0.2 e.u.

$\Delta G^{\neq}_{298}$ = 24.7 K.cal/mole.





Initial

$\Delta H^{\ddagger}$ = 21·18 K.cal/mole.

$\Delta S^{\ddagger}$ = −13·1 e.u.

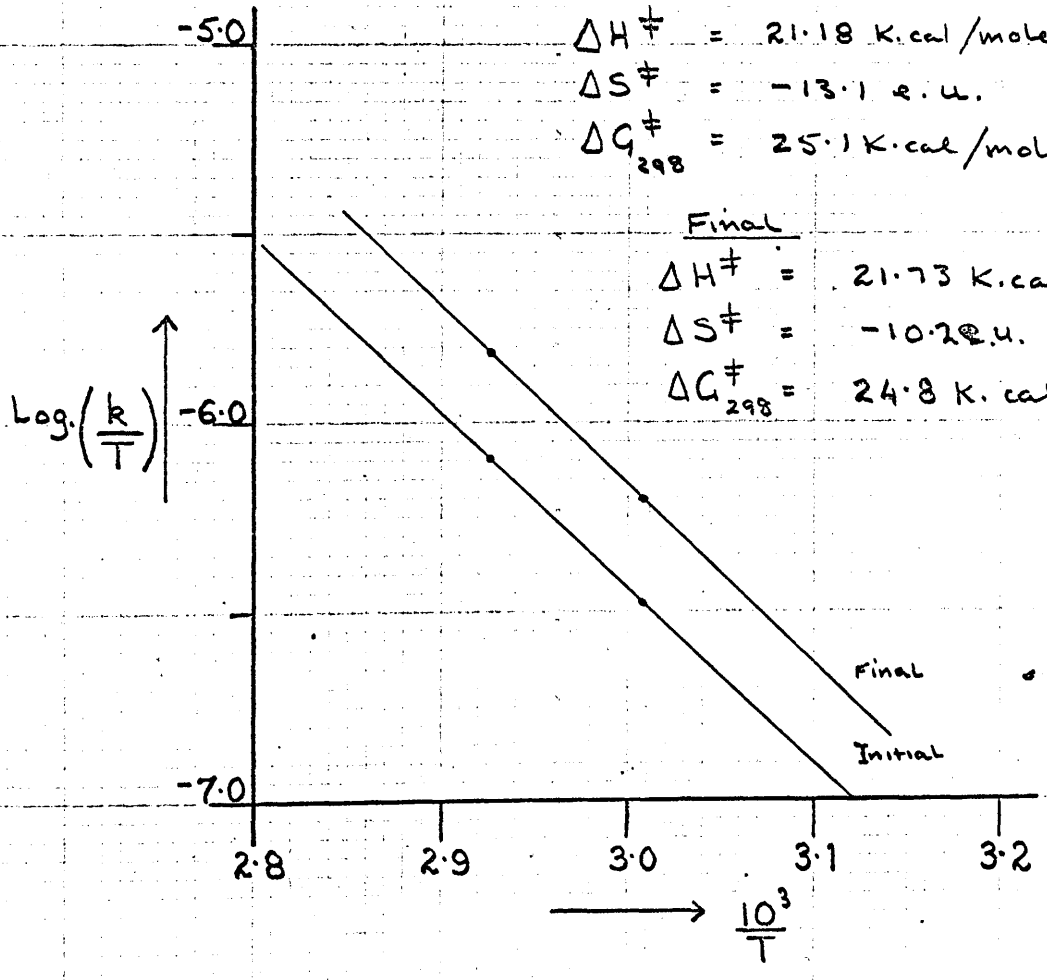
$\Delta G^{\ddagger}_{298}$ = 25·1 K·cal/mole.

Final

$\Delta H^{\ddagger}$ = 21·73 K.cal/mole.

$\Delta S^{\ddagger}$ = −10·2 e.u.

$\Delta G^{\ddagger}_{298}$ = 24·8 K. cal/mole



APPENDIX A.

Rate measurements were carried out using the ultra-violet spectroscopic method of Swain and Morgan[60]. In the case of endo-2-bicyclo (3,3,1) nonyl tosylate, which solvolysed considerably slower than the other tosylates, the sealed ampoule technique was used. At predetermined intervals of time, ampoules were withdrawn from the thermo-stated bath, and cooled in liquid nitrogen to prevent further reaction. The ampoules were then allowed to come to room temperature, opened and the u.v. spectrum measured over the range 240-300 mμ.

For the more reactive tosylates, the solvolysis reactions were actually performed inside 10mm u.v. cells fitted with p.t.f.e. stoppers which prevented any significant evap-oration during the time necessary for reaction. The tosylate (ca. 2 mg.) was placed in the cell which was then almost filled with a stock solution of fused sodium acetate in anhydrous acetic acid, and of such a concentration as to provide an approximately 1.2M excess of sodium acetate

relative to tosylate. The reference cell was filled with the buffer solution, and both cells were then placed in a special thermostated cell holder and the region 240-300 mμ was scanned at suitable intervals of time. It was also possible to follow the solvolyses by constantly measuring the absorption change at a single wavelength (262 mμ), the advantage of this and the previous method being that a large number of readings could be taken during any one run.

The decreasing optical density at 262 mμ was noted with time and the percentage unreacted tosylate (X) calculated for each reading. The half-life ($t_{\frac{1}{2}}$) for the reaction was then obtained by plotting log.(X) v. time and the first order rate constant (k) obtained from the equation:

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

To correct for the temperature gradient between the bath and the cell, the cell temperature was measured using a chromel-alumel thermocouple, and by means of this a calibration curve of bath temperature v. cell temperature was obtained. The maximum variation in bath temperature (at 70°C) was ± 0.15°C.

APPENDIX B.

The thermodynamic parameters were obtained from the equations:

$$\log\left[\frac{k}{T}\right] = \frac{-\Delta H^{\neq}}{2.303\ RT} + \frac{\Delta S^{\neq}}{2.303\ R} + \frac{1}{2.303} \cdot \log\left[\frac{k'}{h}\right] \qquad \text{(i)}$$

$$\Delta S^{\neq} = \frac{\Delta H^{\neq}}{T} + 4.575\left[\log\left[\frac{k}{T}\right] - 10.319\right] \qquad \text{(ii)}$$

both of which are readily derived from the standard rate equation:

$$k = \frac{k'T}{h} \cdot \exp.\left[-\frac{\Delta H^{\neq}}{RT} + \frac{\Delta S^{\neq}}{R}\right] \qquad \text{(iii)}$$

From equation (i) we can obtain $\Delta H^{\neq}$ from the gradient of the graph of $\log\left[\frac{k}{T}\right]$ v. $\frac{1}{T}$ and by substitution of $\Delta H^{\neq}$ in equation (ii) we can obtain $\Delta S^{\neq}$.

k' = Boltzmann's Constant = 1.38×10^{-16} erg/deg.

h = Planck's Constant = 6.625×10^{-27} erg second.

$\Delta S^{\neq}$ = Activation Entropy.

$\Delta H^{\neq}$ = Activation Enthalpy.

T = Absolute Temperature.

k = First order rate constant ($sec.^{-1}$).

APPENDIX C.

The first order rate constants for acetolysis of endo-2-bicyclo (3,3,1) nonyl tosylate (23; R = OTs) (at 49.3 and 62.5°C) are taken from the work of Hanack et.al.[19] and refer to unbuffered acetolysis. However, the presence of a 1.2M excess of buffer salt should only cause a slight positive salt effect which will be manifested in a small increase in $\Delta H^{\neq}$ and $\Delta S^{\neq}$. This of course would strengthen the argument put forward in favour of intermediacy of a flexible form in the acetolysis of (23; R = OTs).

APPENDIX D.

The initial product analyses on the acetates arising from solvolysis of the epimeric (3,3,1) tosylates were carried out using a 50 metre, 0.02" i.d., stainless steel capillary column coated with Carbowax 1540. Unfortunately circumstances prevented our using this column for the later analytical work and although a theoretically identical column was obtained, as well as another column of similar

dimensions, but different phase (Tris-cyanoethoxypropane) the performance could not be repeated and this, together with the fairly rapid column deterioration explains the inconsistencies which seem to arise in the product analysis. Hence, although compounds such as 2-bicyclo (3,3,1) nonene (38) and 6-bicyclo (3,2,2) nonene (41) or 2-bicyclo (4,2,1) nonanone (32) and 6-bicyclo (3,2,2) nonanone (33) could be separated without too much difficulty in the early stages of the work, this was not possible with the later product analyses.

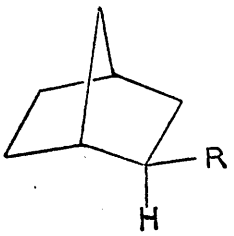
It should also be pointed out here that although 10% of the olefinic products from acetolysis of exo-6-bicyclo (3,2,2) nonyl tosylate is designated as 2-bicyclo (4,2,1) nonene, this has only been inferred and all that has been proved is that this 10% olefin in the products is definitely not (38) or (41).

APPENDIX E.

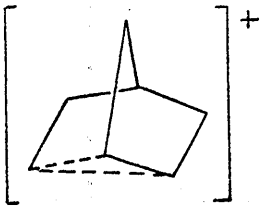
In the complex hydride reduction of 2-bicyclo (4,2,1) nonanone (32) the predominant alcohol of the two products is assumed to have the endo-configuration (24; R = OH)

since one would expect a hydride ion to attack from the less hindered exo-face of (32).

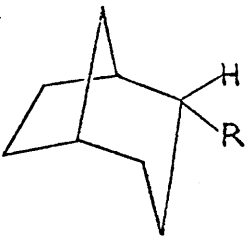
Since interrupted solvolysis of (29; R = OTs) gives rise to two alcohols, one of which is a 2-bicyclo (4,2,1) nonanol identical by g.l.c. behaviour to the minor product of hydride reduction of (32), it is inferred from the above reasoning that this (4,2,1) nonanol has the exo-configuration (28; R = OH). The fact, of course, that the alcohol in question has been formed by internal ion pair return from the tosylate (29; R = OTs) is strongly suggestive of our stereochemical assignations being correct.



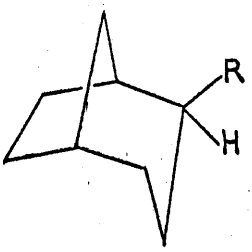
1



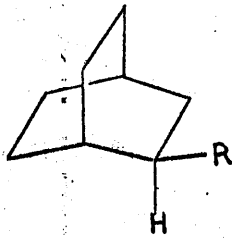
2



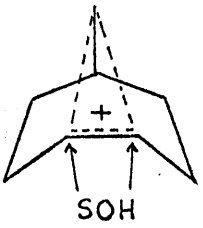
6



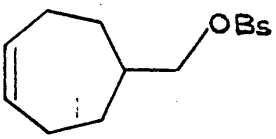
7



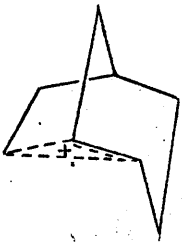
8



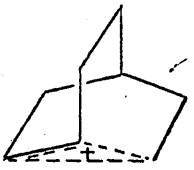
9



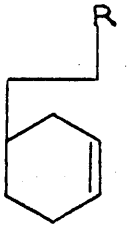
10



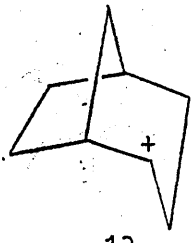
≡



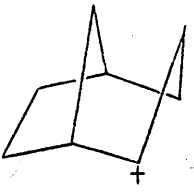
11



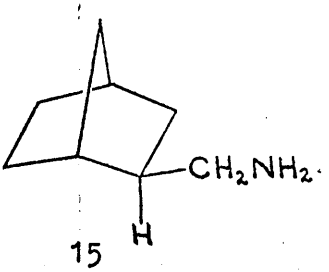
12



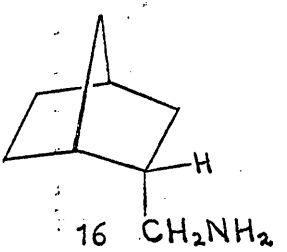
13



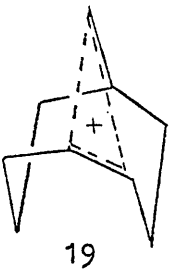
14



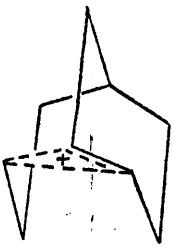
15



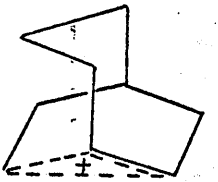
16



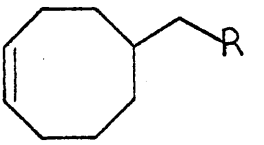
19



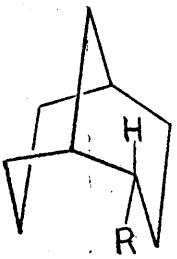
20



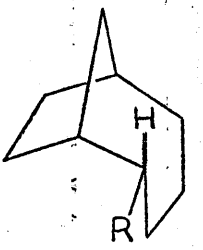
21



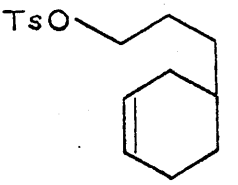
22



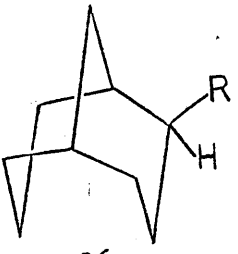
23



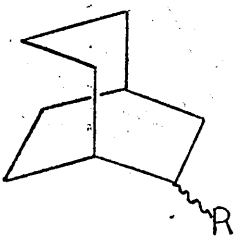
24



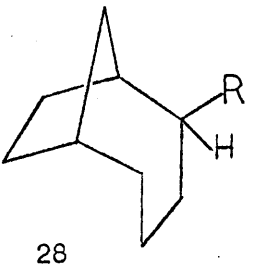
25



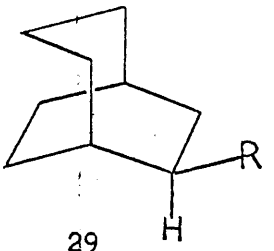
26



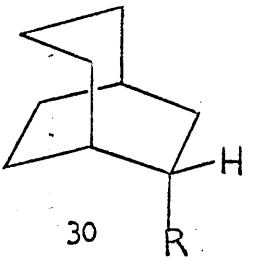
27



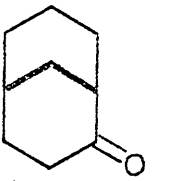
28



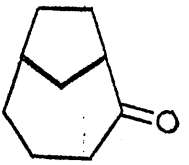
29



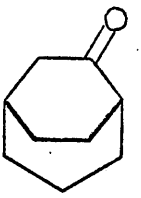
30



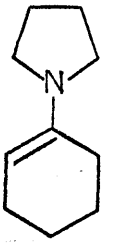
31



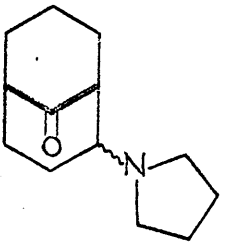
32



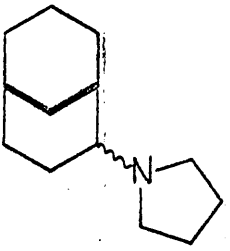
33



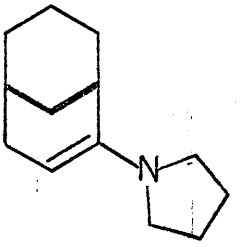
34



35

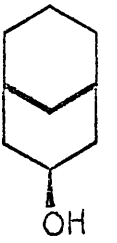


36

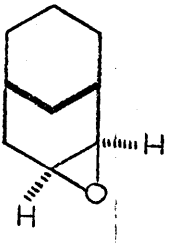


37

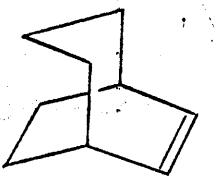
38



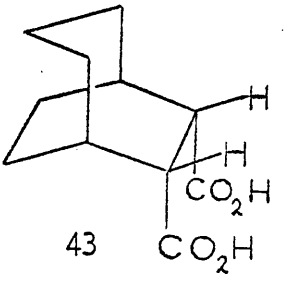
39



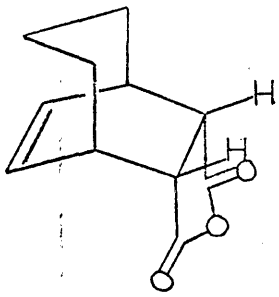
40



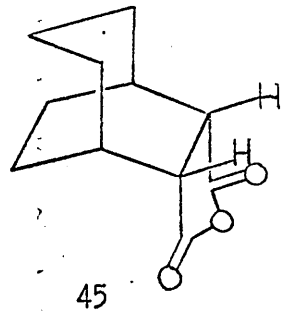
41



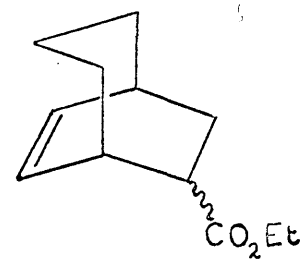
43



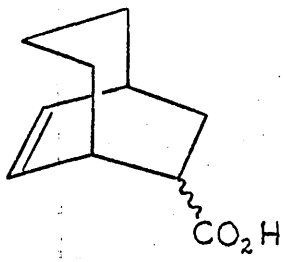
44



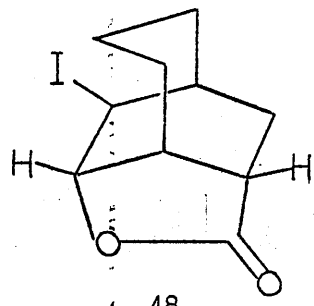
45



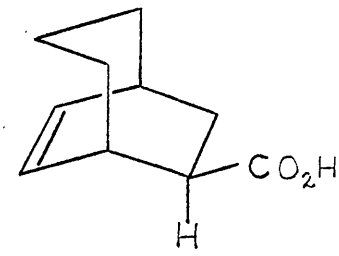
46



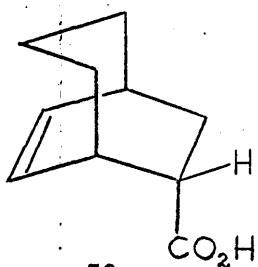
47



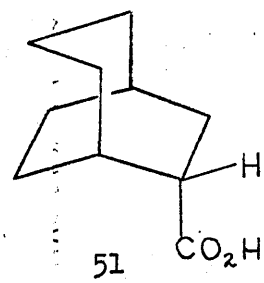
48



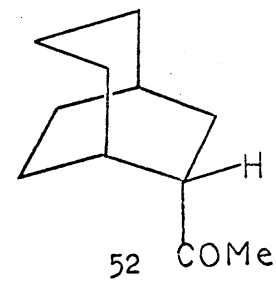
49



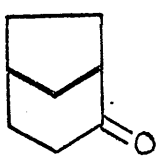
50



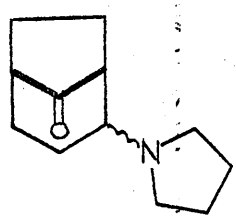
51



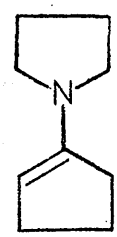
52



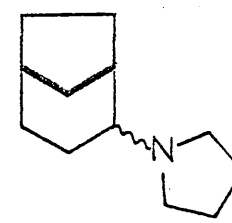
53



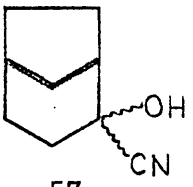
54



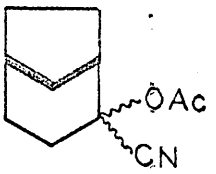
55



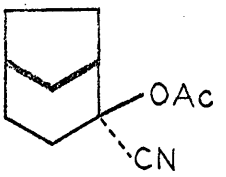
56



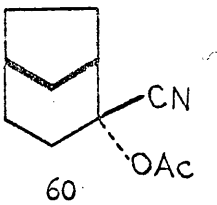
57



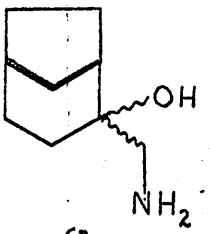
58



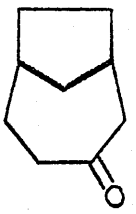
59



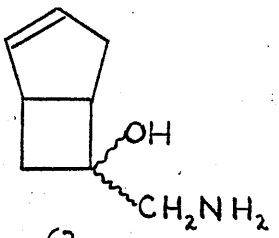
60



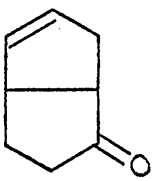
61



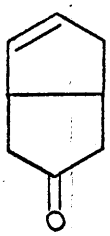
62



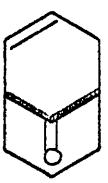
63



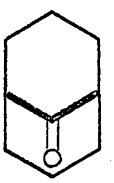
64



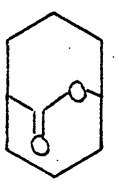
65



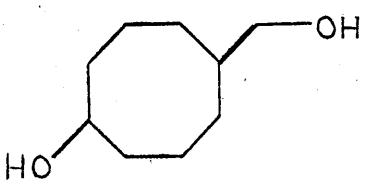
66



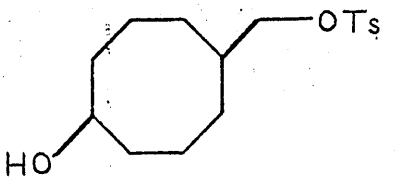
67



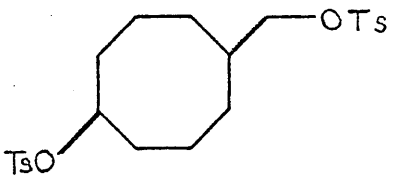
68



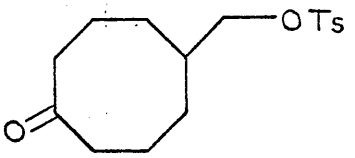
69



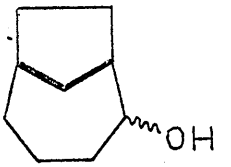
70



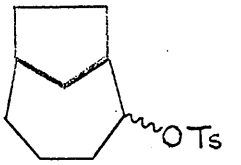
71



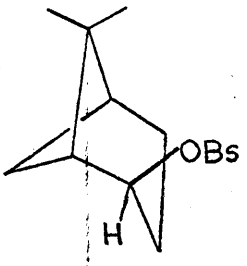
72



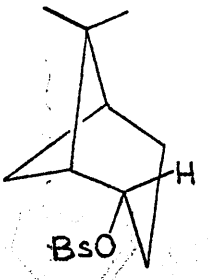
73



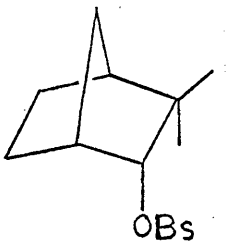
74



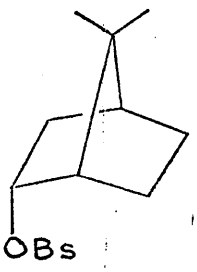
75



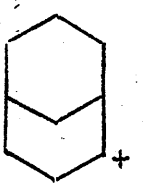
76



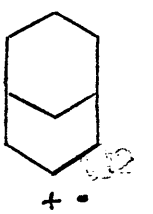
77



78

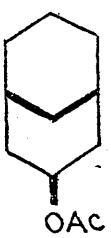


79



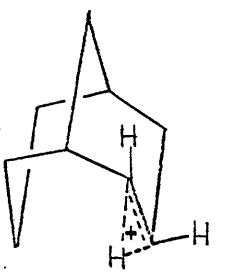
80

81

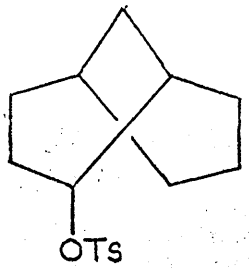


82

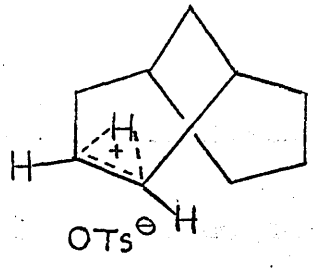
83



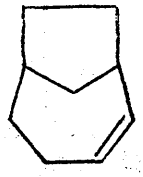
84



85



86



87

REFERENCES

SECTION II

1. T.P. Nevell, E. de Salas and C.L. Wilson, J, 1939, 1188.

2. S. Winstein and D.S. Trifan, J. Amer. Chem. Soc., 71, 2953, 1949.

3. F. Brown, Prof. E.D. Hughes F.R.S., Prof. C.K. Ingold F.R.S., and J.F. Smith Nature, 168, 65-67, 1951

4. P.D. Bartlett, 'Non Classical Ions', W.A. Benjamin Inc., New York, 1965.

5. H.L. Goering and G.N. Fickes, J. Amer. Chem. Soc., 90, 2848, 2856, 2862, 1968.

6. H.L. Goering and M.F. Sloan, J. Amer. Chem. Soc., 83, 1397-1401, 1992, 1961.

7. G. Le Ny, Compt. rend., 251, 1526, 1960.

8. S. Winstein and P. Carter, J. Amer. Chem. Soc., 83, 4485, 1961.

9. J.A. Berson and P. Reynolds-Warnhoff, J. Amer. Chem., Soc., 86, 595, 1964.

10. J.A. Berson and D. Willner, J. Amer. Chem. Soc., 86, 609, 1964.

11. A.C. Cope, D.L. Nealy, P. Scheiner and G. Wood, J. Amer. Chem. Soc., 87, 3130, 1965.

12. M. Hanack, W. Kraus, W. Röthenwöhrer and W. Kaiser, Tetrahedron Letters, 1705, 1966.

13. H. Felkin, G. Le Ny, C. Lion, W.D.K. Macrosson, J. Martin and W. Parker, Tetrahedron Letters 157, 1966.

14. S.H. Graham, K.H. Baggaley, J.R. Dixon and J.M. Evans, Tetrahedron, 23, 299, 1967.

15. E.N. Marvell, D. Sturmer and R.S. Knutson, J. Org., Chem., 33, 2991, 1968.

16. J.P. Schaefer, C.A. Flegal, J. Amer. Chem. Soc., 89, 5729, 1967.

17. J.P. Schaefer, L.S. Endres and M.D. Moran, J. Org., Chem., 32, 3963, 1967.

18. G. Stork and H.K. Landesman, J. Amer. Chem. Soc., 78, 5129, 1956.

19. M. Hanack, W. Kraus, W. Röthenwöhrer, W. Kaiser and G. Wentrup, Annalen, 703, 44, 1967.

20. N.J. Leonard and F.P. Hauck Jr., J. Amer. Chem. Soc., 79, 5279, 1957.

21. J.I. Musher, J. Amer. Chem. Soc., 83, 1146, 1961.

22. H.C. Brown and H.R. Deck, J. Amer. Chem. Soc., 87, 5620, 1965.

23. H.C. Brown and D.B. Bigley, J. Amer. Chem. Soc., 83, 3166, 1961.

24. W.D.K. Macrosson, Ph.D. Thesis, Glasgow, 1967.

25. F.C. Chang and R.T. Blickenstaff, J. Amer. Chem. Soc., 80, 2906, 1958.

26. H. Musso and U. Biethan, Ber., 100, 119, 1967.

27. K. Hafner and W. Rellensmann, Ber., 95, 2567, 1962

28. K. Alder and H. Mölls, Ber., 89, p. 1960, 1956.

29. A.M. Chalmers, Private Communication.

30. M. Karplus, J. Chem. Phys., 30:11 (1959).

31. C.M. Cimarusti and J. Wolinsky, J. Amer. Chem. Soc., 90, 113, 1968.

32. M. Hartmann, Annalen, 724, 102, 1969.

33.a) T.F. Gallagher and T.H. Kritchevsky, J. Amer. Chem., Soc., 72, 882, 1950.

b) R.B. Turner, J. Amer. Chem. Soc., 72, 878, 1950.

c) K. Mislow and J. Brenner, J. Amer. Chem. Soc., 75, 2318, 1953.

34. K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J., 39, 1946.

35. M. Hartmann, Z. Chem., 4, (12), 457, 1964.

36. P.A. Smith and D.H. Baer, Org. Reactions, Vol. 11, p. 157.

37. W.R. Vaughan and R. Caple, J. Amer. Chem. Soc., 86, 4928, 1964.

38. Kindly supplied by Prof. H. Felkin.

39. J.D. Roberts and W.F. Gorham, J. Amer. Chem. Soc., 74, 2278, 1952.

40. A.C. Cope and D.M. Gale, J. Amer. Chem. Soc., 85, 3743, 1963.

41. Prof. H. Felkin - Private Communication.

42. W.D. Closson, P. Wriede, S. Bank, J. Amer. Chem. Soc., 88, 1581, 1966.

43. A.H. Fainberg and S. Winstein, J. Amer. Chem. Soc., 78, 2767, 1956.

44. S. Winstein and N.J. Holness, J. Amer. Chem. Soc., 77, 3054, 1955.

45. P. von R. Schleyer, W.E. Watts and C. Cupas, J. Amer. Chem. Soc., 86, 2722, 1964.

46. E.C. Friedrich and S. Winstein, J. Amer. Chem. Soc., 86, 2721, 1964.

47. P. von R. Schleyer, J. Amer. Chem. Soc., 86, 1854, 1856, 1964.

48. S. Winstein, Betsy K. Morse, E. Grunwald, H.W. Jones, J. Corse, D. Trifan and H. Marshall, J. Amer. Chem., Soc., 74, 1127, 1952.

49. S. Winstein and J. Holness, J. Amer. Chem. Soc., 77, 5562, 1955.

50. H.C. Brown and G.Ham , J. Amer. Chem. Soc., 78, 2735, 1956.

51. M.A. Eakin, J. Martin, W. Parker, Chem. Commun., 298, 1968

52.a) M. Dobler and J.D. Dunitz, Helv. Chim. Acta, 47, 695, 1964

b) W.A.C. Brown, G. Eglinton, J. Martin, W. Parker and G.A. Sim, Proc. Chem. Soc., 57, 1964.

c) W.A.C. Brown, J. Martin and G.A. Sim, J. Chem. Soc., 1844, 1965.

d) I. Laszlo, Rec. Trav. Chim., 84, 251, 1965.

53. P.D. Bartlett, W.D. Closson and T.J. Cogdell, J. Amer., Chem. Soc., 87, 1308, 1965.

54. D.J. Cram and J. Tadanier, J. Amer. Chem. Soc., 81, 2737, 1959.

55. W.J. le Noble, B.L. Yates and A.W. Scaplehorn, J. Amer., Chem. Soc., 89, 3751, 1967, and references therein.

56. M. Pánková, J. Sicher, M. Tichý and M.C. Whiting, J. Chem. Soc. (B), 365, 1968.

57. N.C.G. Campbell, D.M. Muir, R.R. Hill, J.H. Parish, R.M. Southam and M.C. Whiting, J. Chem. Soc. (B), 355, 1968.

58. a) V.J. Shiner, Jr., and John G. Jewett, J. Amer. Chem., Soc., 86, 945, 1964.

b) V.J. Shiner, Jr., John G. Jewett, J. Amer. Chem. Soc., 87, 1382, 1383, 1965.

59. M. Tichý, J. Hapala and J. Sicher, Tetrahedron Letters, No.43, p. 3739, 1969.

60. C.G. Swain and C.R. Morgan, J. Org. Chem., 29, 2097, 1964.