THE PREPARATION AND REACTIVITY OF SOME BICYCLO (3,3,1) NONANE DERIVATIVES

T H E S I S

presented to the University of Glasgow

for the degree of PhD.

by

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GENERAL INTRODUCTION.

Since Whitmore's[1] brilliant paper advancing a hypothesis concerning the occurrence of electron-deficient intermediates in organic chemical reactions, the study of processes involving carbonium ions as reaction intermediates has enlarged to a remarkable extent. Only thirty years ago, such intermediates were proposed on theoretical grounds with almost no experimental evidence, whereas recently the efforts[2] of Olah and his co-workers have produced very informative nuclear magnetic resonance spectra of carbonium ions, stabilised in antimony pentafluoride solution. Once the concept of carbonium ions had been accepted, the rates of reactions involving these species and the nature and stereochemistry of products resulting from such reactions could be examined with reference to the steric and electronic effects involved. Thus, today, the S.N.1. mechanism and the various factors which can affect solvolyses in general are well understood[3]. Over the last two decades, the phenomenon of "neighbouring group participation"[3, 4] in such reactions has been extensively studied, mainly by the group led by Winstein.

Neighbouring group participation is said to take place when a functional group distant from the reaction

site influences the reaction by stabilising a transition state or intermediate, by becoming bonded or partially bonded to the reaction centre. Normally such participation causes a marked increase in rate over that expected by analogy for such a reaction, and the neighbouring group is said to provide "anchimeric assistance"[5] to ionisation. This increased rate is often extremely difficult to verify, since it is necessary to have an estimate of the rate in the absence of such assistance. Substrate and product stereochemistry are often critical indications of the operation of participation in solvolytic reactions. Processes involving participation are associated, in quite a large number of cases, with the presence of oxygen, sulphur or nitrogen atoms, but the following discourse will deal only with carbon participation. In particular, in this discussion, we will be concerned with alkyl or σ-participation and double bond or π-participation.

Alkyl or σ- Participation.

Alkyl participation, causing anchimeric assistance and stereospecificity of product formation was first thoroughly studied in the monoterpene field by Nevell, DeSalas and Wilson in their investigation of

the camphenehydrochloride - isobornyl chloride rearrangement[6]. Winstein, however, in work on a suitable model series where conclusions could be drawn much more confidently, put the subject of alkyl participation on a sound theoretical and experimental footing.

In his work on the solvolysis of norbornyl compounds, he has shown that exo-norbornyl derivatives (1; Bs = $SO_2C_6H_4Br$) solvolyse at a rate very much faster than the corresponding endo-compounds (2)[7]. (in the case of the brosylates, the titrimetric rate ratio is 350.). Product analysis showed that both exo - and endo-brosylates solvolysed to give exo products exclusively. To explain this, Winstein proposed that the exo compound (1) ionised directly to give the bridged ion (3) which, being more stable than the classical ion by virtue of delocalisation of charge, lowered the activation energy, increasing the rate over that expected. The endo-brosylate (2) solvolysed to give a classical ion-pair (4) (Winstein's representation), which could subsequently rearrange to give the bridged ion (3) or could itself react to form products. Of the acetate fraction (greater than 95% of products) from both the exo- and endo-norbornyl acetolyses, the exo-acetate (5) is present to the

extent of at least 99.98%[8], the limit of analytical accuracy. An intermediate of type 3 would preclude solvent attack on the endo face giving exclusively exo products.

To obtain more information about the intermediate, Winstein solvolysed optically active norbornyl derivatives. Exo-norbornyl brosylate solvolysed with less than 0.05% retention of optical activity whereas the endo-brosylate retained, in its products, 3 - 13% of the optical activity[8]. The polarimetric rate ratio (1600) was even larger than the titrimetric one, indicating internal return. These results corroborated the postulate of a symmetrical ion being formed directly from the exo-brosylate, while a fraction of the endo-brosylate passes through a non-symmetrical intermediate (4).

π - Route to the Norbornyl Cation.

The norbornyl cation (3) which Winstein proposed as the intermediate in solvolysis of exo-norbornyl derivatives can be formulated as a resonance hybrid of three canonical forms (3 a - c). In a formal sense, products could be perceived to arise from the attack of solvent on the bicyclic canonical forms (3 a and b), but no monocyclic

products from attack on 3 c had ever been isolated. These considerations led to the conclusion that if structure 3 c could be independently generated it ought to lead to products derived from 3 a and b. Lawton[9] and Bartlett and Bank[10], independently, provided dramatic verification of this. Lawton, carried out the acetolysis of the crystalline 2(Δ^3-cylopentenyl) - ethyl p - nitrobenzenesulphonate (6; N_S = $SO_2C_6H_4NO_2$) at 60°, found that it solvolysed 95 times faster than the saturated analogue and that it gave exo-norbornyl acetate (5) as the sole product. Bartlett and Bank solvolysed the corresponding liquid tosylate and obtained similar results. This was a very strong indication that the ion formed from 6 was identical to that formed in solvolysis of exo-norbornyl derivatives and that it could be formulated as 3. This was the first demonstration of duality (σ and π) in generation of the same non-classical ion; several other examples have since been demonstrated.

Le Ny acetolysed Δ^3 - cyclohexenylmethyl tosylate (7)[11], finding a rate increase over the saturated analogue and obtaining endo - 2 - bicyclo (3, 2, 1) octyl acetate (8), through the intermediacy of 9. Goering and Sloan[12] then solvolysed endo - 2 - bicyclo -

(3, 2, 1) octyl tosylate (10) obtaining 8, again via cation 9, this time generated by a σ-route.

Walborsky[13], and Goering and Sloan[12] have shown that ~~both~~ bicyclo (2,2,2) octyl tosylate (11) and exo-2-bicyclo (3,2,1) octyl tosylate (12) both solvolyse in acetic acid to give the same mixture of products, namely bicyclo (2,2,2) octyl acetate (13) and exo-2-bicyclo (3,2,1) octyl acetate (14). Both of these solvolyses consist of σ-routes to the non-classical cation 15. Winstein then considered it possible to obtain this same cation by means of a π- route from 2-(Δ^3 - cyclohexenyl) ethyl tosylate (16).[14] In the event he obtained, as in the σ- route, 13 and 14 along with a little monocyclic acetate.

These examples are interesting because two isomeric bridged non-classical ions have been formed by both σ and π - routes and there has been no stereochemical leakage from one to the other; in fact both ions have apparently retained their stereochemical integrity.

Homologues of the Norbornyl System.

On kinetic and steric grounds it is now becoming evident that the bridged bicyclo (2,2,1) heptyl system is a special case. Berson[15], by his ring

expansion method (17→18 and 19), has obtained evidence that classical cations can, and do, exist in the bicyclo (3,2,1) octyl system, one which until this time had been thought to be ruled exclusively by non-classical ions (see above). The 2 - norbornylcarbinyl cations (endo and exo) were obtained by deamination of the corresponding amines (20,21; X = NH_2) or acetolysis of the brosylates (X = OBs). The products, their percentages, and percentage racemisation are shown in Scheme A.

Scheme A also shows the reaction mechanism which Berson proposes for the solvolyses. This complex scheme involving a large number of discrete intermediates is, according to Berson, the simplest possible explanation of his experimental results. In the endo case, for example, the resulting equatorial 2 - bicyclo (3,2, 1) octanol (22a and b) is partially, but not totally, racemised and has a different percentage racemisation than its epimer, axial 2 - bicyclo (3,2,1) octanol (23 a and b). These results cannot be explained by involving only classical or non-classical ions because 24a alone would have given optically pure 22 and 23 while symmetrical 25 (the non-classical ion of Le Ny), would have given (by

exclusive α - attack) completely racemic 22.
Similarly if it were simply an equilibrium between 24a and 24b both 22 and 23 would have been formed with the same percentage racemisation. Using the same type of arguments, the products from exo-2-norbornylcarbinyl substrates (21; X = NH_2 or OB_S) were rationalised as shown in Scheme A. In the endo solvolysis a small, but significant quantity (7% in deamination) of bicyclo (2, 2, 2) octanol (26) was obtained. Berson believes this to be due to a slow leak connecting the exo and endo rearrangement paths. This could occur at the classical cation stage (24 $\rightleftharpoons$ 27), provided this reversible chair-boat conformational isomerisation were slow enough to provide partial insulation between the two systems so that only a small percentage actually does leak. Berson is therefore postulating that isomeric classical ions, in their subsequent reactions, can exhibit a high degree of specificity dependent on their precise mode of formation. A possible explanation of this specificity of reaction is shown by ions 30 and 32. These are the ions formed from exo - and endo - norbornyl - carbinyl systems. In 30 the vacant p-orbital in the 2 - position is almost parallel to the C_1 - C_7 bond with the result that this bond is

delocalised giving 28. A similar criterion can be invoked to give 25 (from 32).

The important aspect of these mechanisms is that a) a classical ion has been postulated in the bicyclo - (3,2,1) octyl system and that b) it is separated from its carbon-bridged, non-classical counterpart by an energy barrier roughly equal in magnitude to that necessary for reaction with solvent and that the non-classical ion is not very much (if any) more stable than the classical one since its rate of reversible interconversion with the latter is large enough to compete readily with capture by solvent. This, of course, is in very sharp contrast with the (2,2, 1) heptyl system in which the non-classical ion is much more highly favoured, and the classical ion (formed from 2 - endo derivatives) is very rapidly converted to the non-classical ion.

A recent communication[16] describing collaborative work between the Institut de Chemie des Substances Naturelles, Gif and this department reports a reinvestigation of the solvolysis of Δ^4 - cycloheptenylcarbinyl brosylate (see above). This was found to be not quite as simple and uncomplicated as had been imagined. Acetolysis of 33 (X = OBs) gave

93% endo - 2 - bicyclo (3,2,1) octyl acetate (34;X = OAc), 4% exo - acetate (35; X = OAc) and 3% of an acetate which the authors assumed to be bicyclo (2,2,2) octyl acetate. This is extremely interesting since it is in good agreement with Berson's work in that the major product - forming intermediate is probably (9) but there must be some of the classical ion (36) formed to account for the exo - acetate and also a leak to the isomeric series (24 ⇌ 27 Scheme A) to account for the bicyclo (2,2,2) octyl compound formed.

Continuing to a homologue of the above case, we find the trends toward classical ion formation becoming more pronounced. Cope acetolysed[17] Δ^4 - cyclo-octenylcarbinyl tosylate (37; X = OTs) obtaining mainly the equatorial 2-bicyclo (3,3,1) nonyl acetate (38; X = OAc), some axial isomer and bicyclo (4,2, 1) nonyl product. The formation of the equatorial compound in high yield seemed to be an indication that a non-classical ion (39) was responsible. Grave doubts have since been cast on this assumption.[16] Felkin, on acetolysing Δ^4 - cyclo-octenylcarbinyl brosylate, (37; X = OBs) obtained 91% of the endo-acetate (38; X = OAc), 8% of the exo-acetate (40; X = OAc) and 1% of an unidentified acetate. If, as Cope suggests,

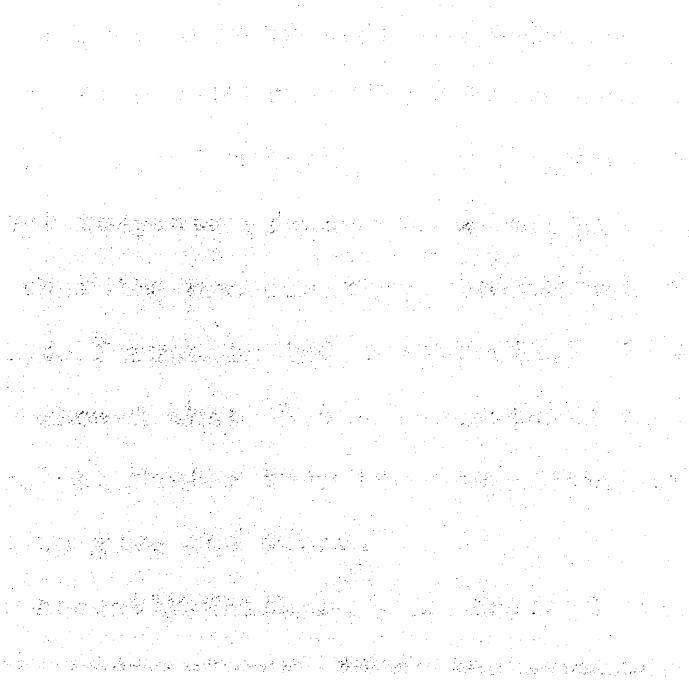
the non-classical cyclo-octenylcarbinyl cation (39) is the major product - forming intermediate in this solvolysis, then, solvolysis of endo - 2 - bicyclo (3,3, 1) nonyl brosylate (38; X = OBs) ought to give the same intermediate and therefore the sameproducts.

The acetolysis of 38 (X = OBs) was duly carried out and the products shown to be 45% endo-acetate (38; X = OAc), 46% exo-acetate (40; X = OAc), along with two other acetates (8% and 1%). This result seems to preclude the possibility of 39 playing a major role in the acetolysis of 37 and 38. The products from Δ^4 - cyclo-octenylcarbinyl brosylate (37; X = OBs) and from endo - 2 - bicyclo (3,3,1) nonyl brosylate (38; X = OBs) can be plausibly explained by invoking classical ions which are protected to some extent by the leaving group. In the cyclo-octenylcarbinyl case (41), double bond participation across the ring to give classical ion 42 would leave the endo face virtually clear for attack by solvent, giving a large (but not total) percentage of endo product. Similarly, were the endo-brosylate (38; X = OBs) to ionise to classical ion 43, the endo side would be partially blocked by the leaving group causing a large proportion of exo-acetate to be formed.

This is an interesting suggestion, since, as Felkin points out, there is no reason to suppose that the bridged non-classical ion 39 would be any more readily formed than the classical ion 44. The double chair conformation has been shown to be preferred by the bicyclo (3,3,1) nonane system[18] although this is strained due to 3, 7 - methylene interaction making both rings flatter than in cyclohexane. The formation of a classical cation in the 2 - position would cause one of the rings to flatten and allow the other to adopt a more perfectly staggered conformation thus reducing strain in forming the intermediate. In the bridged ion, however, the 3, 7 - methylene interaction is relieved at the expense of distortion of both six-membered rings. In the bicyclo (3,2, 1) octyl system, this situation is reversed since an eclipsing interaction between 6, 7 - hydrogens is relieved in going to the symmetrical bridged ion 9 and yet Derson has shown that there is little difference in stability between 9 and its classical counterpart 36. It would therefore seem feasible that the classical 2 - bicyclo (3,3, 1) nonyl cation is more stable than the non-classical one.

Thus it is possible that as ring size increases, the importance of classical ions as reaction intermediates

tends to increase. The bicyclo (3,2,1) octyl system may well be the dividing line between the 'domains' of the classical and non-classical ion. As further rigorous investigation of carbonium ion behavour in other bicyclic ring systems is accomplished, a greater understanding of the factors controlling the formation of classical and non-classical ions in specific cases may be gained.



Double Bond or π - Participation.

There are many known examples of π - participation in the literature[3,4]. One of the earliest and surely one of the most striking was the one discovered by Shoppee[19], and later studied in detail by Winstein[20], involving π - participation in solvolysis of cholesteryl tosylate (45). Shoppee found that substitution reactions of cholesteryl derivatives gave products whose configuration was the same as that of the starting compound (45→46). Treatment of cholesteryl compounds in buffered solvents gave i-steroids, also with the β - configuration (45→47)[20]. Since cholesteryl tosylate also solvolysed faster than cholestanyl tosylate (factor of 40 at 70°) Winstein proposed that the non-classical ion 48 was the intermediate formed in the solvolysis. Later work by Shoppee[21] showed that 3 β - cholesteryl derivatives also solvolyse faster than the 3 α - compounds which eliminate to give the diene.

More recently, Whitham[22], in order to verify whether the unsymmetrical 48 or the symmetrical 49 was the true intermediate formed, solvolysed the tosylate of 3 β - hydroxymethyl - A - norcholest - 5 - ene (50) in aqueous acetone buffered with potassium acetate.

This gave a mixture of alcohols (51 and 52) in the same ratio as that formed in the solvolysis of cholesteryl tosylate under the above conditions. He concluded from this that symmetrical ion 49 was a better representation of the intermediate than was 48.

Probably the most famous example of double bond participation was found when anti - 7 - norbornenyl tosylate (53) was solvolysed[23]. Acetolysis of 53 produced exclusively anti - 7 - norbornenyl acetate (54) with a rate 10^{11} times faster than that observed for the saturated analogue. Winstein proposed that 55 was a suitable representation of the intermediate formed and that the remarkable rate increase was due to the developing charge being stabilised by delocalisation with the double bond in the symmetrical manner shown. Such a situation restricts nucleophilic attack to that side of the molecule remote from the double bond.

Some time later[24] Winstein published the rate and product analysis for acetolysis of syn - 7 - norbornenyl tosylate (56). He found that although the rate for the syn - tosylate was slower than for the anti - tosylate by a factor of 10^7, it was faster than for the saturated tosylate by a factor of 10^4. Here also there is marked anchimeric assistance. The product

obtained from solvolysis proved to be bicyclo (3,2,0) hept - 2 - en - 4 - ol (57). Winstein explained these results by postulating methylene participation by the anti - 5 - membered ring giving rise to a stabilised allylic cation (58).

Introduction of another double bond into the norbornene skeleton served to increase the charge delocalisation in the cation and so, also the rate of solvolysis. The rate of solvolysis of 7 - chloronorbornadiene (59) in aqueous acetone is faster than that of 7 - chloronorbornene by a factor of 750[25]. The intermediate cation (60) forms a stable fluoroborate whose structure has been investigated by nuclear magnetic resonance spectroscopy[26]. The results obtained support an unsymmetrical non-classical structure such as 60.

Other investigations of the steric requirements necessary for overlap between a double bond and a developing homoallylic carbonium ion have been accomplished. Roberts, on solvolysing exo - norbornenyl chloride (61; X = Cl) and exo - norbornyl chloride (62)[27], found that the latter was the more facile. This led him to believe that if a non-classical ion such as 63 was the intermediate in

solvolysis of 61, then stabilisation of charge by delocalisation of π - electrons was less effective than stabilisation by delocalisation of σ - electrons as in the norbornyl cation (3). He reversed this decision, however, when he found that the rate ratio for solvolysis of exo - and endo - norbornenyl chlorides (61 and 64; X = Cl) was exo/endo = 150 in 80% ethanol at 85°, whereas the ratio for exo - and endo - norbornyl chlorides (62 and 65) is only about 70[28]. Winstein obtained an exo/endo rate ratio of 7000 for the exo - and endo - norbornenyl brosylates (61 and 64; X = OBs) (the exo/endo rate ratio for the norbornyl brosylates is 350). Solvolysis of both 61 and 64 (X = OBs), in acetic acid, supplied mainly tricyclic material (66), and exo - norbornenyl acetate (61; X = OAc)[28]. The exo/endo rate ratio and the product composition are strong evidence for postulating a non-classical cation of type 63 as intermediate in the solvolysis of exo-norbornenyl brosylate (61; X = OBs). The similarity of products from endo - norbornenyl brosylate (64; X = OBs) would indicate that after ionising to give the classical ion 67, this then degenerated to the same non-classical intermediate (63) obtained in the exo-brosylate

solvolysis.

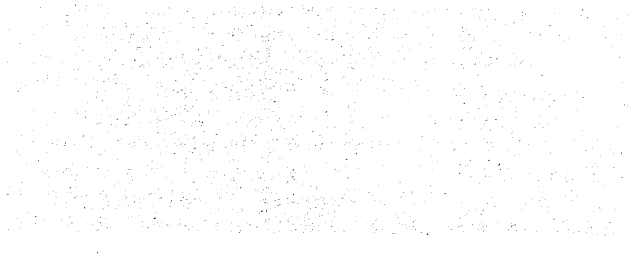
Using labelled (C^{14}) exo - and endo - norbornenyl brosylates, Roberts[30] demonstrated that rearrangement of the initially formed intermediate from solvolysis of exo - norbornenyl brosylate took place (less than 50% in acetic acid). This strongly indicates a slow equilibration of 63 with its enantiomorph 68.

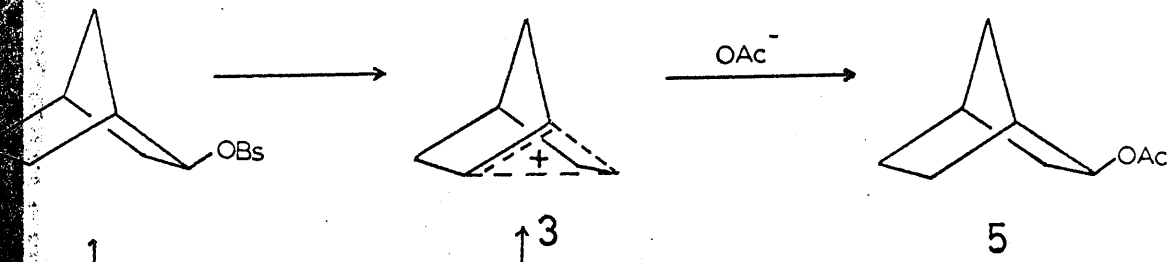
De Puy has studied[31] a pair of structurally related yet chemically different homoallylic cations. Acetolyses of endo - and exo - 7 - isopropylidenenorborn - 5 - en - 2 - yl tosylates (69 and 70) showed that both are anchimerically assisted, each producing a different intermediate. Endo - 7 isopropylidenenorborn - 5 - en - 2 - yl tosylates (69) (2000 times faster than endo - norbornenyl tosylate) furnished the endo - acetate (71) exclusively. The exo - tosylate (70) also acetolysed rapidly (slightly faster than exo-norbornenyl brosylate 61) and supplied 72 only. De Puy considered that the intermediates formed could be represented as 73 and 74 and that these ions, though structurally similar, were not interconvertible.

A discussion of participation in carbonium ion reactions in a text such as this must be highly selective, since the number of examples is so large and the

interpretations frequently at variance with one another. No attempt has been made to discuss the current controversy[8,32] over the detailed nature of bridged ions and, for simplicity, the more popular representations, based on Winstein's ideas and used by most of the investigators in these fields are used throughout.

The following two sections deal with the preparation and reactivity of some derivatives of the bicyclo-(3,3,1) nonane system and our attempts to correlate the results of carbonium ion reactions in this semi-rigid framework with those discussed above, and with other pertinent investigations.





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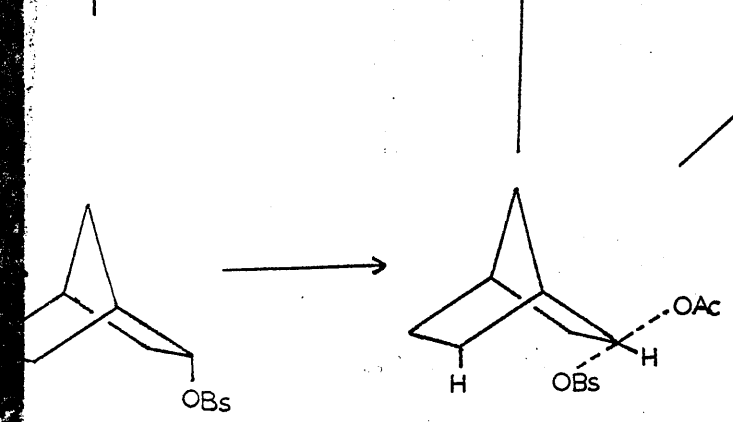

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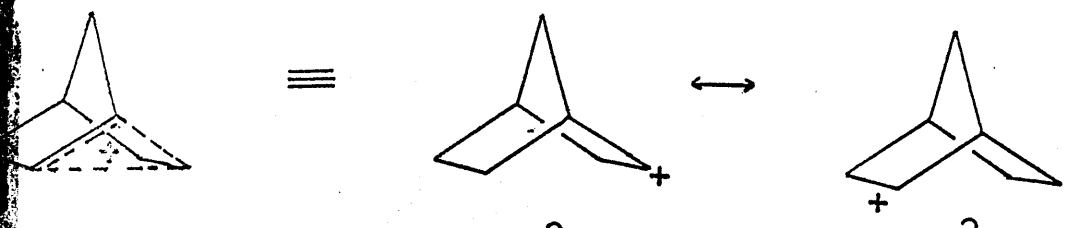
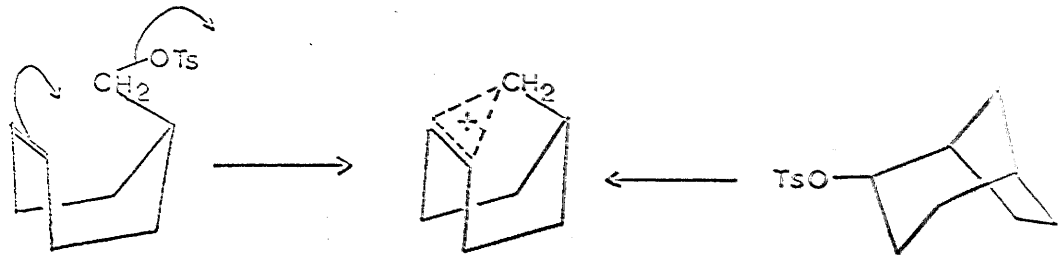


3 3a 3b

6 3c



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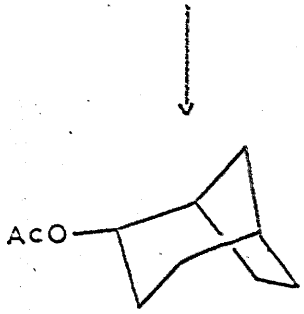

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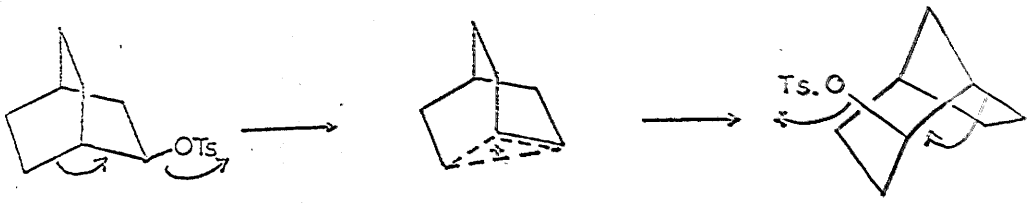

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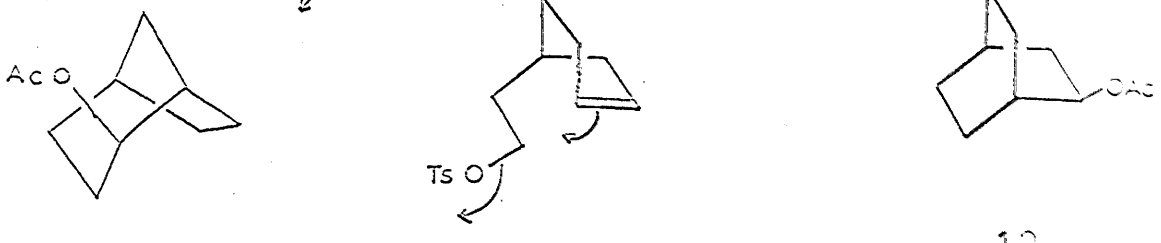

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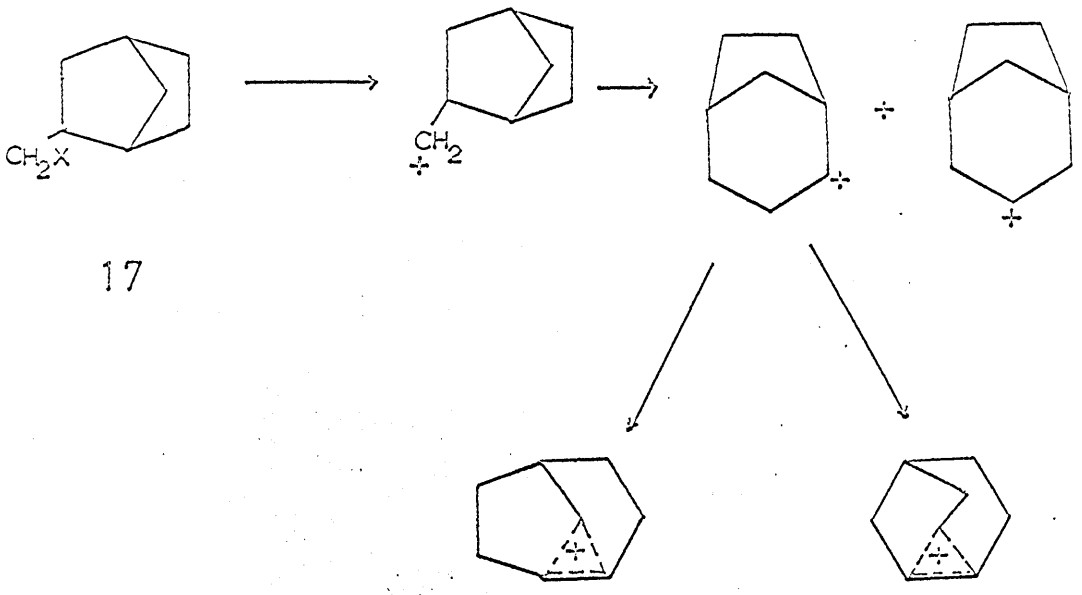

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Scheme A

	Endo Solvolysis		Exo Solvolysis	
	ol°	ol° Racemised	ol°	ol° Racemised
23	9	50	35-40	45
22	3	90	35-40	6
26	7	—	3	—

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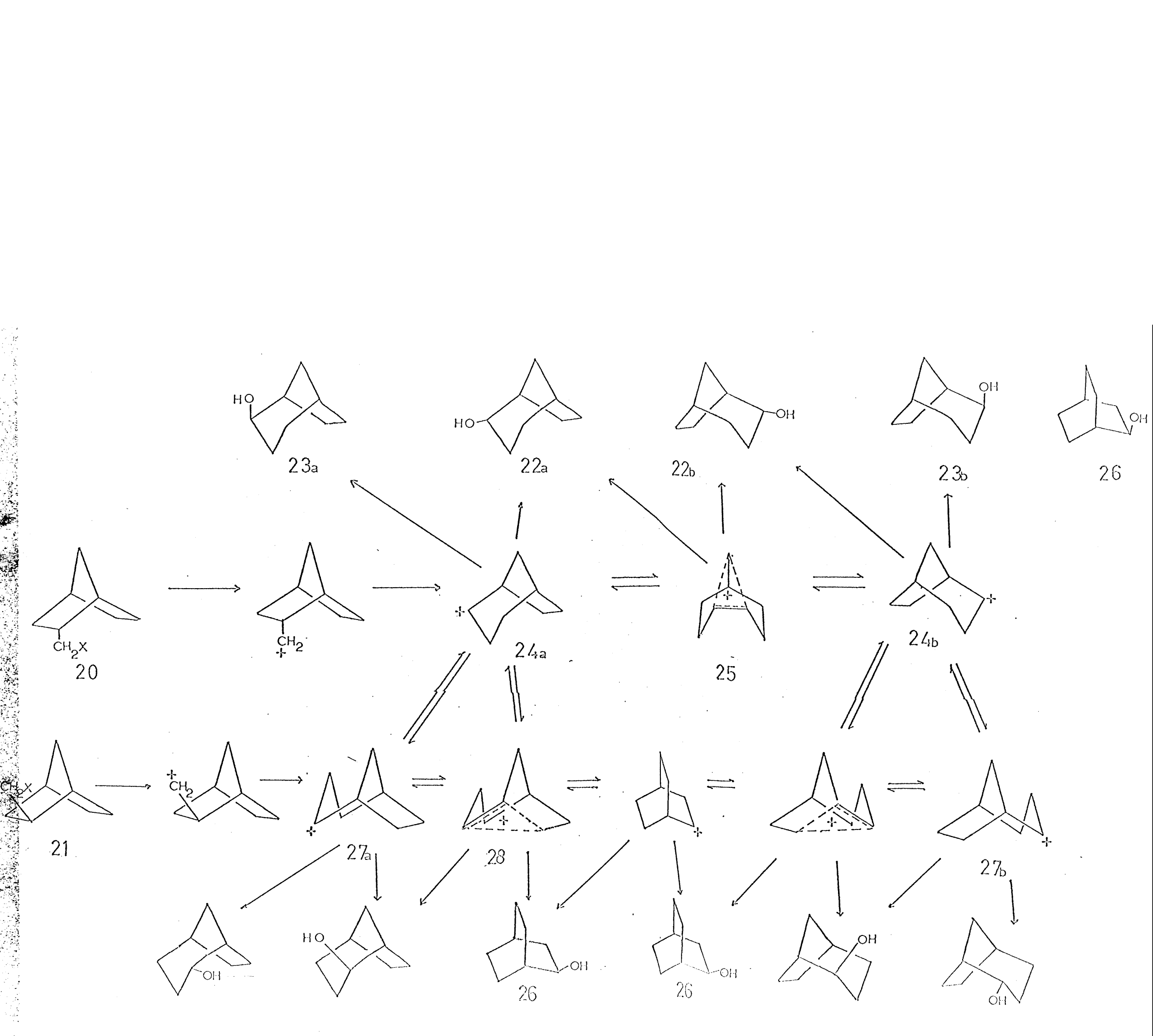
HO
23a
HO
22a
OH
22b
OH
23b
OH
26
CH2X
20
CH2
24a
25
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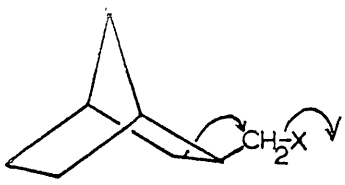

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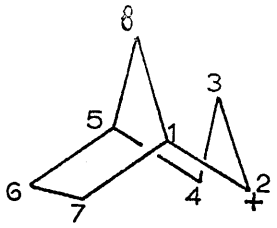

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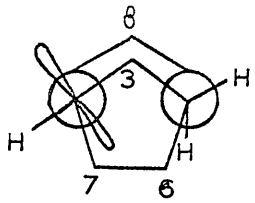

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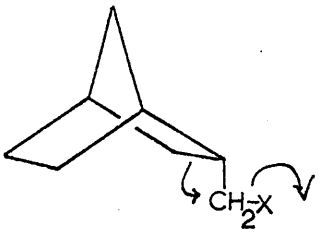

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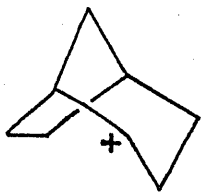

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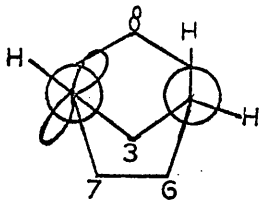

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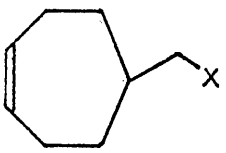

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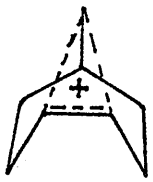

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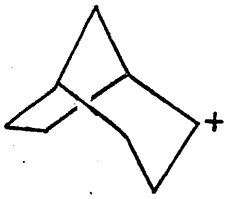

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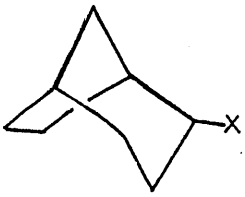

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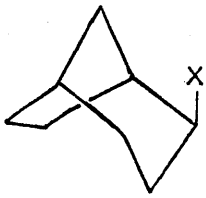

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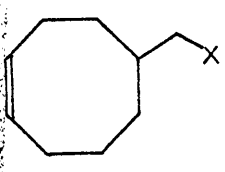

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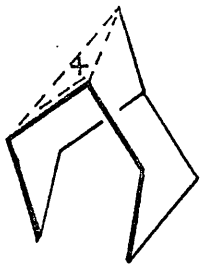

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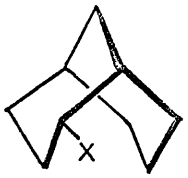

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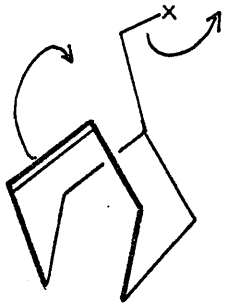

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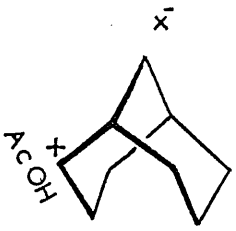

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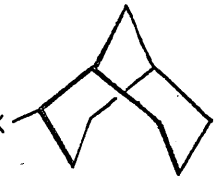

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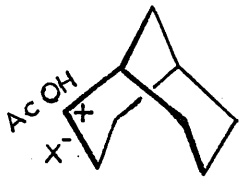

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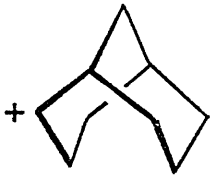

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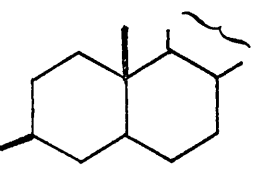

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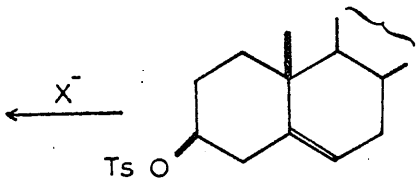

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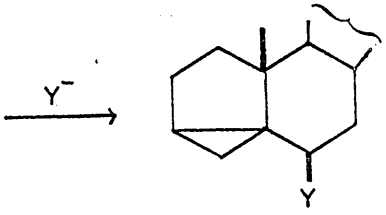

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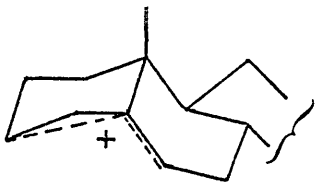

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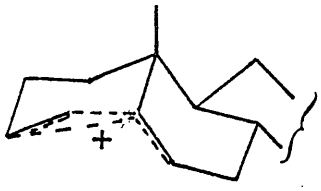

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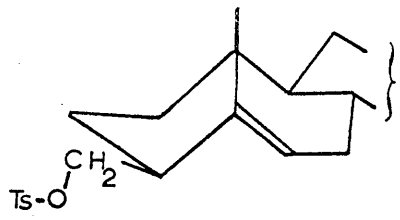

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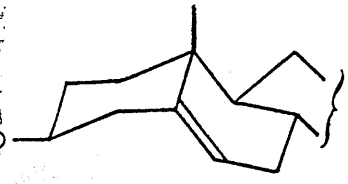

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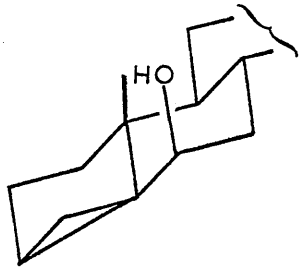

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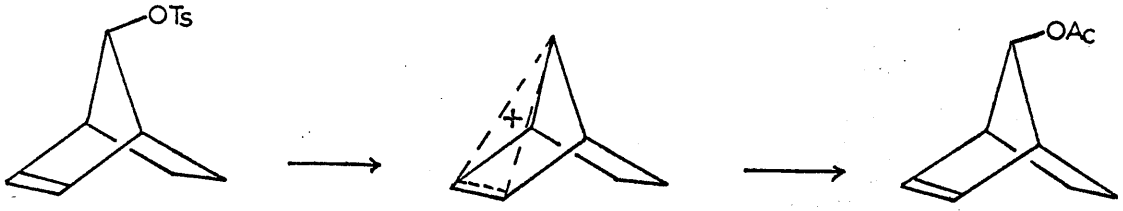

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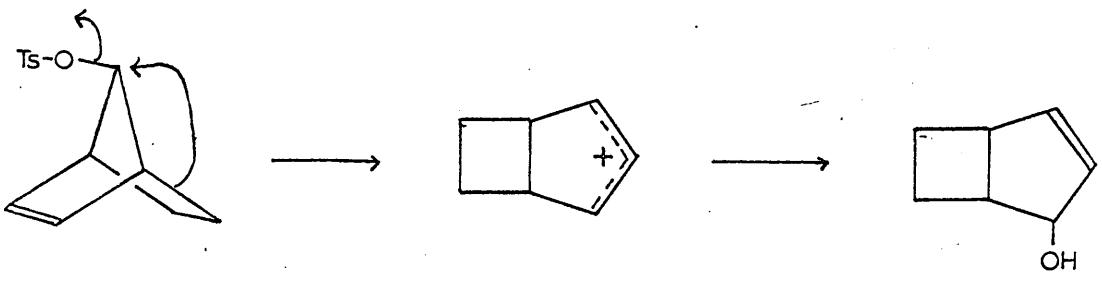

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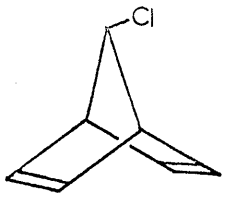

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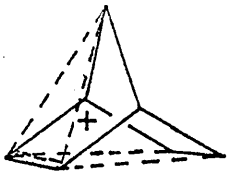

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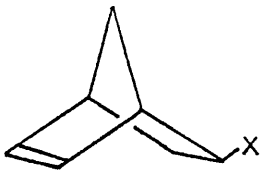

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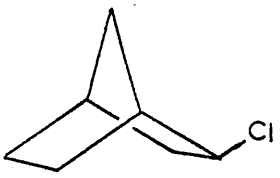

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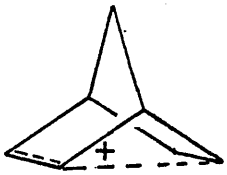

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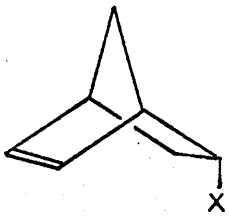

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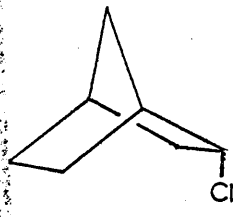

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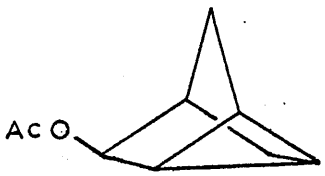

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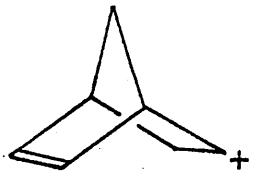

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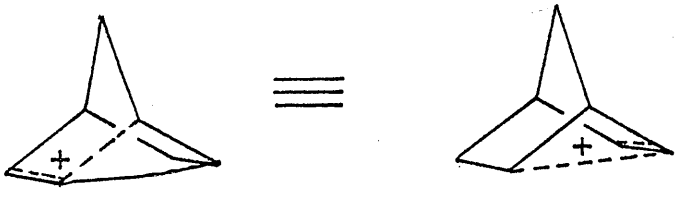

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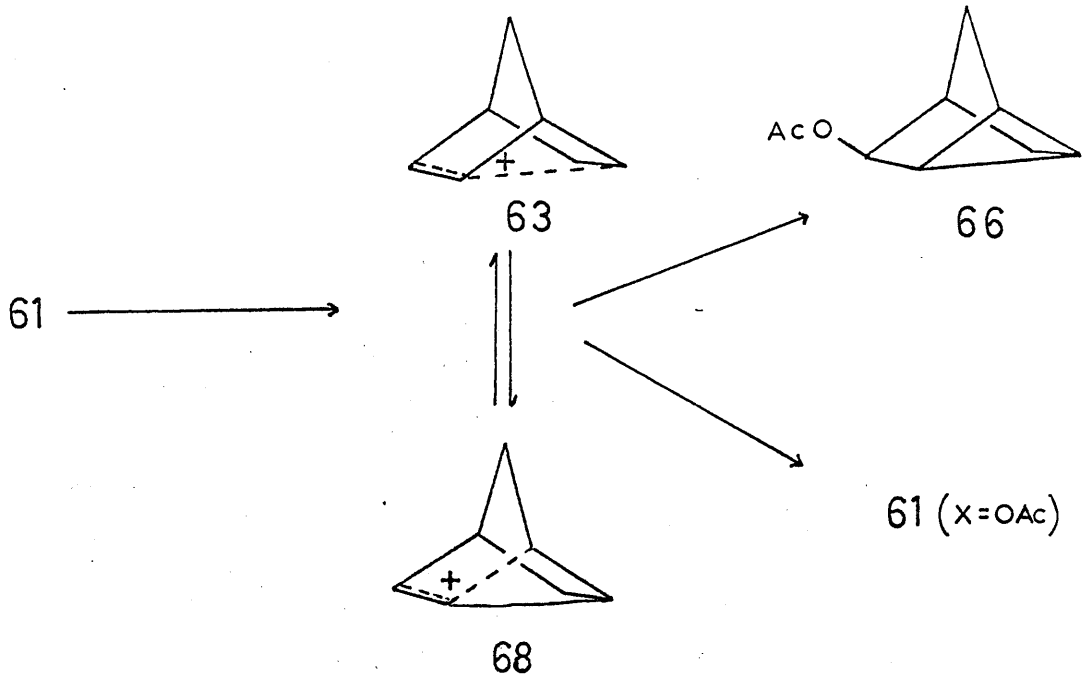
AcO
63
66
61
61 (X=OAc)
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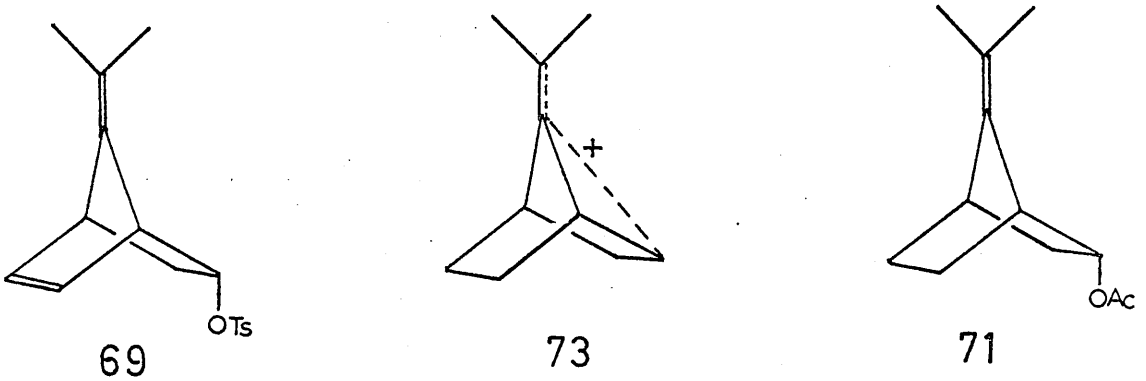
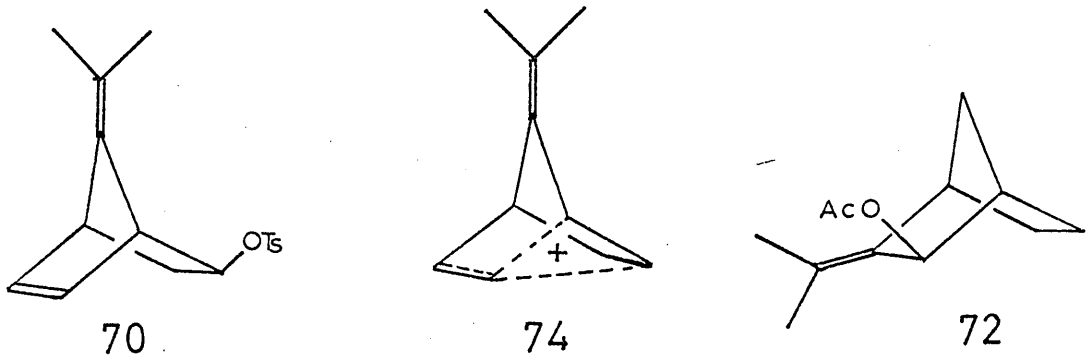

OTs
OAc
69
73
71


OTs
AcO
70
74
72

SECTION I PART I.

Solvolyses of Equatorial and Axial 1,5 - Dimethyl - bicyclo (3,3,1) nonan - 2 - yl Toluene - p - sulphonates.

For some years, a group of workers, in this department, were engaged in the synthesis of clovene (75)[33]. Because 1 - carbethoxy - 5 - methylbicyclo (3,3,1) non - 2 - en - 9 - one (76) was a basic intermediate in this synthesis, large stocks of this compound were prepared. This unsaturated keto-ester (76) was obtained from an acid-catalysed aldol-dehydration of 3 - (1 - carbethoxy - 2 - oxo - 3 - methylcyclohexyl) - propionaldehyde (77) with concentrated sulphuric acid[34]. It was noted that the unsaturated keto - ester (76) was not the only compound obtained but that certain rearranged products were also formed, namely, 7 - methylindan - 4 - carboxylic acid (78) and ethyl 2 - acetobicyclo (3,3,0) oct - 1 (2)- ene - 5 - carboxylate (79).

The mechanism for formation of the rearranged products 78 and 79 presented the investigators with an intriguing problem. When this work was published the mechanisms shown in Schemes B and D were postulated to

explain the production of each of the rearranged compounds. In the formation of the aromatic acid (78; scheme B), the initial step was proposed as protonation of the carbonyl group of 76, after this had been formed by aldol closure of 77 to 80, and dehydration of the latter. Indeed, it has been shown, that treatment of the unsaturated keto- ester (76) with sulphuric acid gives rise to the aromatic acid 78[35]. The remainder of the mechanism consisted of two Wagner - Meerwein rearrangements, a dehydration step, and finally hydrolysis of the aromatic ester in concentrated sulphuric acid. There seemed no apparent reason for the final ester hydrolysis, when the ester groups on 76 and 79 remained intact and Martin[36] proposed the alternative mechanism seen in scheme C. Adoption of the ketene intermediate (81) explains the formation of the aromatic acid and not the ester, more satisfactorily.

The mechanism to obtain the conjugated enone-ester (79; Scheme D) depends on loss of hydroxyl from the aldol product (82) and then an acyl migration with concommitant or subsequent attack by water taking place, to give 83. A retro-aldolisation and realdolisation of the β -hydroxy-ketone system in another way would

then form the conjugated enone-ester(79).

The ketols (80) could be formed by acid treatment of keto-aldehyde (77) with dilute mineral acid, but the mixture formed could not be separated into the axial and equatorial epimeric compounds[37]. The interesting possibility that each of the rearrangement products 78 and 79 could be derived separately from one of the C - 3 epimers, was obviously worthy of consideration. For example, the acyl migration in 82 would seem to be more favoured if the hydroxyl group were equatorial, and therefore in a trans-antiparallel disposition with respect to the migrating bond (see 84). The epimeric 2 - hydroxy - 1, 5 - dimethylbicyclo (3,3,1) nonan - 9 - ones (85 and 86; R = H) had been prepared, in these laboratories, in pure form by Martin[36], and the tosylates of these alcohols (85 and 86; R = Ts) were both solid and readily obtained in a high degree of purity. (The synthesis of these compounds is discussed in detail in the Introduction to Part II of this section). For these reasons, the dimethyl compounds were obviously more suitable than derivatives of 80, as the materials for a more subtle attack on the stereochemical aspects of the

rearrangement. In addition, replacement of the ester grouping with its attendent electronic effects, by a methyl was expected to simplify the explanation of results obtained.

DISCUSSION.

It was expected that solvolyses of the crystalline epimeric tosylates of the 2 - hydroxy - 1,5 - dimethyl-bicyclo (3,3,1) nonan - 9 - ones (85 and 86; R = Ts) under mild controlled conditions, would provide more useful information on the rearrangement paths, than the drastic (e.g. concentrated sulphuric acid) conditions applied heretofore. The solvent chosen for the solvolytic studies was acetic acid, for several reasons. It is, by far, the most popular solvolytic medium and use of the same solvent would simplify correlation of our results with those of other workers. Since the original aldol - dehydration [34] (77⟶76 + 78 + 79) was carried out with concentrated sulphuric acid and since the postulated mechanism (Scheme B) for the formation of the indan-carboxylic acid (78) included a protonation step, it appeared to us advisable to use a protic, polar solvent if we were to produce substantial rearrangement.

The tosylates, 85 and 86 (R = Ts), were carefully purified by recrystallisation and then acetolysed individually by heating them in glacial acetic acid solution under reflux. Care was taken in the work-up procedures that no volatile components would be lost.

Such acetolyses produced complex mixtures which posed an interesting problem in separation. Since the keto-acetates 85 and 86 (R = Ac) were expected to be formed, these were individually prepared before the solvolytic experiments were begun, for identification purposes. To alleviate the task of separating a mixture of these keto-acetates into its components, the relative detector responses to each in gas-liquid chromatographic analysis was obtained. This allowed rapid and accurate quantitative analysis of mixtures of these keto-acetates.

Treatment of both 85 and 86 (R = Ts) with acetic acid, in the manner described, gave mixtures containing the same five compounds, though in different proportions. Because of the differences in molecular weight between the keto-acetates, 85 and 86 (R = Ac), and the other olefinic products, a suitable gas-liquid chromatographic separation could only be obtained by temperature-programmed gas-liquid chromatography (g.l.c.). A fine separation of the five compounds was obtained using 5% Q.F.1. as stationary phase, temperature programmed from 100 - 175° (3° per minute). Full g.l.c. details of all compounds discussed are supplied in Appendix A.

A partial separation of the mixture was

accomplished by careful column chromatography on alumina. The mixture was separated, in order of increasing polarity, into : i) a hydrocarbon oil, homogeneous under several sets of g.l.c.conditions, and subsequently assigned the formula 87, on evidence outlined below; ii) the known 1,5 - dimethylbicyclo (3,3,1) non - 2-en - 9 - one (88), and iii) a mixture of three compounds, two of which were the keto-acetates 85 and 86 (R = Ac) discussed above, while the third was later identified as Δ^1 - 2 - aceto - 5 - methylbicyclo (3,3,0) octene (89). By analogy with the products formed from sulphuric acid treatment of the keto-aldehyde (77)[34], the formation of the conjugated enone (89) had been expected in the solvolytic reactions described. Attempts to separate the conjugated enone (89) from the mixed keto-acetates (85 and 86; R = Ac) by various chromatographic methods including thin-layer and column chromatography met with little success.

Hydrolytic experiments on the mixture of keto-acetates (85 and 86; R = Ac) and the conjugated enone (89) in acidic and basic media in an attempt to convert the keto-acetates (85 and 86; R = Ac) to the ketols (85 and 86; R = H) leaving the conjugated

enone (89) accessible to chromatographic separation were quite unsuccessful resulting mainly in the destruction of the conjugated enone (89), the compound we wished to preserve. The 9 - oxo function of 1, 5 - dimethyl-bicyclo (3,3,1) nonane derivatives was known to be extremely hindered [36], whereas that of the conjugated enone (89) was not. Consequently, treatment of the mixture with semicarbazide acetate resulted in the formation of the crystalline semicarbazone of the conjugated enone (89) easily separated from the unchanged keto-acetates (85 and 86; R = Ac). An analogous separation technique had been used to separate 79 from 76 in earlier work [34]. G.l.c. analysis of the remaining keto-acetates showed that semicarbazone formation had completely removed the conjugated enone (89). The conjugated enone (89) could be regenerated from the semicarbazone by treatment with dilute sulphuric acid. With the separation of the hydrocarbon (87) and the enone (89), elucidation of their structures could then begin.

Since treatment of 77 with sulphuric acid had given the aromatic acid 78 [34], we had expected, by analogy, to obtain the hydrocarbon 90 (4, 7-dimethylindane). Comparison of the hydrocarbon from solvolysis, with an

authentic sample of 4, 7 - dimethylindane [38] (90) by g.l.c. and infra red (i.r.) showed them to be quite different. The hydrocarbon from the solvolysis exhibited C- H deformation bands in the i.r. at 709 and 769 cms^{-1}, characteristic of 1,2,3 - trisubstituted benzenes, and the i.r. spectrum was almost superimposable with that of 4 - methyl indane (91). The nuclear magnetic resonance (n.m.r.) spectrum (see formula 92) exhibited absorption at τ = 8.73 (3H, doublet; J = 7 c.p.s.) indicating the presence of a secondary methyl, a singlet at 7.81 (3H) assigned to the methyl on a benzene ring, multiplets at 7.3 and 6.83 (2H and 1H respectively) assigned to benzylic protons and a multiplet (2 H) at 8.37, for the two aliphatic protons. Finally a multiplet at 3.06 (3H) indicated the presence of aromatic protons. The combined spectral evidence, and the limitations set by its mode of formation pointed to the structure of the hydrocarbon from the solvolyses as being 1,4 - dimethylindane (87). An authentic specimen of 1,4 - dimethylindane was synthesised by the method of Elsner and Parker [39]. Benzylic mono.-bromination of o-xylene (93) furnished the o-tolylmethyl bromide (94). Alkylation of diethyl malonate with 94 produced the substituted malonic ester

(95), which was hydrolysed and decarboxylated to give ω - (o - tolyl) - propionic acid (96).

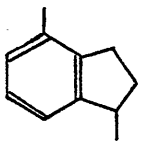
Normal closure of the aromatic acid (96) with polyphosphoric acid gave the methylindanone (97). Treatment of 97 with methyl magnesium iodide gave a tertiary alcohol which readily dehydrated during isolation to give 1, 4 - dimethylindene (98). This was readily reduced to the desired 1,4 - dimethylindane (87), which proved to be identical in all respects with the aromatic hydrocarbon isolated from the acetic acid treatment of both tosylates 85 and 86 (R = Ts).

The second compound eventually identified as the conjugated enone (89) separated from the keto-acetates (85 and 86; R = Ac) as the semicarbazone, and regenerated from the latter, exhibited absorption in the i.r. (1670 cms^{-1}) and ultraviolet (u.v.) ($\lambda_{max.}$ 252 mμ ; ε = 10,100) characteristic of a conjugated enone system. The n.m.r. spectrum (see fig. 99) showed no vinylic proton signals and two singlet methyl absorptions at τ = 8.91 and 7.85. The signal for the methyl adjacent to the carbonyl group in the conjugated enone-ester (100; τ , 7.80). Thus, on the basis of the spectral properties outlined, and by analogy with the formation of enone (79) in the acid-

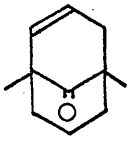
catalysed aldol-dehydration of keto-aldehyde (77), the structure 89 was assigned to the conjugated enone obtained from solvolysis of 85 and 86 (R = Ts) with acetic acid. Confirmation of this was obtained by catalytic hydrogenation of the conjugated enone (89) to 104 and subsequent synthesis of an identical ketone from the enone-ester (79) by the route indicated (79 - 104)[36].

Proof of the structure of enone (89) completed the identification of all five products from acetic acid treatment of tosylates (85 and 86; R = Ts), and the relative proportions of the products from each are shown in Table 1. A glance at the results will show that the axial keto-tosylate (85; R = Ts), gave very much less rearranged material than the equatorial keto-tosylate (86; R = Ts). The total amount of rearranged material (87 + 89) comes to 9% from 85 (R = Ts), yet is 46% from 86 (R = Ts). It is obvious 87 and 89 are formed in the latter case, at the expense of bicyclic olefin-ketone (88). In other words, solvolysis of the axial keto-tosylate (85; R = Ts) favours simple β - elimination (see formula 105), giving mainly the olefin-ketone (88), presumably because a proton on C - 3 is in a favourable trans-antiparallel configuration with respect

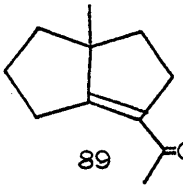
Table 1



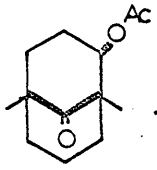
87



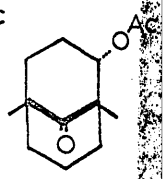
88



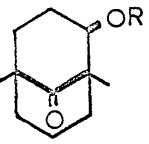
89



85(R=Ac)



86(R=Ac)



HOAc →

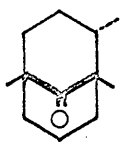
4 %

68 %

5 %

5 %

18 %



HOAc →

20 %

19 %

26 %

23 %

12 %

to the leaving group.

What at first sight might seem a second process favoured by the particular stereochemistry of the leaving group in 85 (R = Ts), would be a concerted rearrangement as shown in (106), since the C_1 - C_8 bond is trans-antiparallel to the leaving group. This, however, would give rise to a bicyclo (3,2,2) nonane (107) having a carbonium ion adjacent to an already electron-deficient carbonyl carbon. That this situation is unlikely, is borne out by the absence of products with the skeleton of 107, from the solvolysis of 85 (R = Ts).

The third possibility, that of complete ionisation of 85 (R = Ts) to 108 thereby nullifying the importance of the stereochemistry of the leaving group in the substrate (85; R = Ts) seems to play some part, since rearranged products are obtained, although to a lesser extent than from 86 (R = Ts). Solvent capture by 108 obviously competes with rearrangement and the proportions of acetates with retained and inverted stereochemistry are discussed later.

The solvolysis of the equatorial keto-tosylate (86; R = Ts) can be discussed in the same way. There is no possibility of favourable trans- β -elimination

of a proton from C - 3, because of the equatorial disposition of the leaving group on C - 2. A conformational change to the boat-chair 109, which would have a pseudo-axial leaving group, is unlikely, in view of our knowledge[18,40] of the conformational aspects of the bicyclo (3,3,1) nonane system. It is not surprising, therefore, that concerted β - elimination is less important in product formation from 86 (R = Ts) than from 85 (R = Ts), 19% and 68% respectively. On the other hand, the C_1 - C_9 bond is suitably placed with respect to the leaving group, for acyl migration (see formula 110), and indeed, this process (followed by further changes discussed below) can account for the high proportion of rearranged material obtained from 86 (R = Ts).

Ionisation to 108 and subsequent solvent capture can lead to the acetates (85 + 86; R = Ac), as also happens in solvolysis of 85 (R = Ts).

Inspection of the quantities and ratios of the keto-acetates formed on solvolysis of each of the keto-tosylates shows nothing untoward. The axial keto-tosylate (85; R = Ts) has produced more equatorial than axial keto-acetate (3·6: 1) while from the equatorial keto-tosylate (86; R = Ts) the proportions

are reversed (1: 1·9). This is perfectly normal in cations considered to be "classical", since examples of classical ions which are partially (sometimes almost totally) shielded by the leaving group are common[3] (111 and 112), and a specific example has already been quoted in bicyclononane chemistry[16].

Although, in general, the above results of acetic acid solvolysis could be accommodated in the known patterns of carbonium ion behaviour, we were somewhat surprised that such deep-seated rearrangements as could give rise to compounds 87 and 89 were still found to occur. We had hoped to obtain <u>primary</u> rearrangement products, in order to explain how 78 and 79 were formed from 77 in sulphuric acid.

We therefore decided to repeat the above solvolyses, in anhydrous acetic acid containing sodium acetate[41], conditions which are, in any case, more standard for acetolyses. Solvolyses of 85 and 86 (R = Ts) with dry acetic acid/sodium acetate produced quite different results to those obtained with glacial acetic acid as solvent. Both 85 and 86 (R = Ts) gave six compounds (g.l.c. analysis on 5% Q.F.1; temperature programmed from 100 - 175° at 3°/min.), none of which corresponded to either 87 or 89 in g.l.c.

mobility. The components appeared to be two eliminated products (i.e. olefin-ketones) and four keto-acetates. A partial separation of the mixtures could be obtained by chromatography on alumina giving i) 1,5 - dimethylbicyclo (3,3,1) non-2-en-9-one (88), ii) a new olefin-ketone ($\nu_{C=O}$, 1738) , and iii) a mixture of four other compounds (keto-acetates) two, of which were 85 and 86 (R = Ac).

The least polar compound formed (88), needed no investigation. Next in order of polarity was a colourless oil, with a mass spectral parent at 164 and which analysed correctly for an elimination product ($C_{11}H_{16}O$). An exhaustive search of gas-liquid chromatographic conditions and stationary phases was finally successful in producing a <u>partial</u> separation of this oil into two components (golay apiezon 'L' capillary). Catalytic hydrogenation of the suspected double bond isomers, afforded an oil ($C_{11}H_{18}O$) (homogeneons by g.l.c.) whose i.r. spectrum exhibited <u>no</u> double bond absorption but a carbonyl absorption at 1733 cm^{-1} (CCl_4). The olefin mixture, tentatively assigned as (113 + 114), exhibited absorption in the i.r. at 1738 cm^{-1} (CCl_4), 893 (exomethylene) and 816 (trisubstituted double bond) (CS_2). The n.m.r.

spectrum (see formula 113 + 114) was consistent with 113 and 114 being present in the ratio of 2·7: 1. Assuming this ratio in analysis of the spectrum, isomer (113) showed signals at 4.50 (broad multiplet, 1 vinyl H) and signals at 8.21 (vinyl CH_3) and 9.02 (tertiary CH_3). The exomethylene isomer (114) exhibited a narrow multiplet at 5.27 (2 vinyl H) and a single methyl signal at 8.97.

Such a pair of double bond isomers would have been formed, presumably, from the tertiary carbonium ion 116. An attempt was made to equilibrate the mixture (113+ 114), through the carbonium ion (116), to the more stable trisubstituted compound 113. Treatment of the mixture with toluene - p - sulphonic acid in ether under anhydrous conditions did, in fact, cause the exomethylene absorption at 893 cm^{-1} in the i.r. to fall, compared with the trisubstituted absorption at 876 cm^{-1}, but total elimation of absorption at 893 cm^{-1} could not be attained. Nevertheless, the experiment proved that 114 was converted to 113, since no other products were formed (g.l.c.)

Of the mixture of four keto-acetates, two, as has already been said, were 85 and 86 (R = Ac) by g.l.c. retention times, while the others were tentatively

assigned the structures 117 and 118, containing rearranged skeletons corresponding to those of olefin - ketones (113 + 114). Attempts to separate these four keto-acetates were quite unsuccessful, since column-and thin-layer-chromatography would not provide a pure sample of the rearranged keto-acetates either singly or together. Preparative scale g.l.c. (1% Q.F.1., 10' x $\frac{3}{8}$", 120°) separated the rearranged from the non-rearranged keto-acetates, but, unfortunately, the rearranged compounds tended to pyrolyse at the exit-tube of the instrument, behaviour not unexpected of tertiary acetates.

Incidental indications that the rearranged keto-acetates were thermally unstable (preparative g.l.c.) led us to attempt preparative pyrolysis of the mixture of four keto-acetates in the hope of isolating keto-olefins 113 and 114 and 88, a mixture which would have been readily identified. Pyrolyses proved fruitless, however, because even at atmospheric pressure the keto-acetates distilled unchanged.

One other method (shown in Scheme E) remained open to us. Due to the (suspected) tertiary nature of the acetoxyl groups in the rearranged keto-acetates (117 + 118) the parent ketols (122) would be

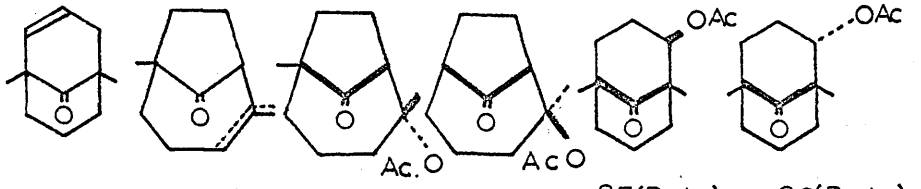
resistant to mild oxidation. Thus, if the mixture of keto-acetates was treated with lithium aluminium hydride and then oxidised, a mixture (121 + 122) should be obtained from which the known dione (121) could be easily separated leaving the mixed ketols (122) which could then be converted to the mixed olefin - ketones (113 + 114), establishing their relationship in this way.

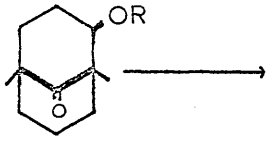
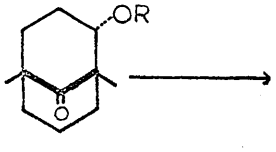
In the event, this sequence proved gratifying. Reduction of the mixture of keto-acetates supplied a gross mixture of diols. Oxidation under acidic conditions was to be avoided because of the danger of dehydrating the tertiary alcohols or of causing further extensive rearrangements.[42] Oxidation under Sarett conditions (chromium trioxide in pyridine) was first tried and discarded because it was found to be very slow (the 9-hydroxyl of 1,5-dimethyl bicyclo (3,3,1) nonane compounds is hindered), resulting in incomplete oxidation, and also causing some measure of dehydration of the tertiary ketols (122) giving the olefin-ketones (113 + 114) as well as the desired products.[43] Oxidation under Snatzke conditions (chromium trioxide in dimethylformamide) was found to proceed beautifully giving no dehydration and a very

clean reaction product containing only 121 and 122. After removing the known dione (121) by chromatography, the remaining mixture of tertiary ketols was treated with phosphorus oxychloride in pyridine to effect dehydration. A good yield of the olefin-ketones (113 + 114) was obtained, identical by i.r. and g.l.c. retention time with a sample from solvolysis. This series of transformations showed that the skeleton of the rearranged keto-acetates was the same as that of the olefin-ketones (113 + 114) and that the acetoxyl group was, in fact, in a tertiary position.

Attempts to degrade the olefin-ketones (113 + 114) to the keto-ester (124) by the route indicated (113 - 124) have been set in progress but, due to lack of material, have not yet been completed. The mixture of olefin-ketones (113 + 114) was ozonised using an oxidative work-up technique (hydrogen peroxide in acetic acid). Separation of the acidic fraction and esterification (diazomethane), gave a mixture of compounds (t.l.c.) one of which gave a colouration with ferric chloride (required β - diketone system). Separation of this enolic compound furnished a small quantity of an oil whose mass spectral parent (P = 242) was too large for the desired diketo-ester (123, R = Me; P = 226). The

Table 2



	88	113+114	118	117	85(R=Ac)	86(R=Ac)
	42%	23%	10%	5%	2%	18%
	2%	48%	14%	8%	28%	<1%

mass spectral parent and breakdown (Scheme F) indicated the ozonolysis product to be the lactone 125. This may have been formed by Baeyer-Villiger oxidation conditions during work-up of the desired β -diketo-acid (123; R = H). Work is progressing to degrade the olefin - ketone mixture (113 + 114) using osmium tetroxide/sodium metaperiodate, rather than ozonolysis, in the initial stages.

The ratios of products (Table 2) show some interesting features. The acetate fraction was estimated purely on peak areas (i.e. considering the g.l.c. detector to have an equivalent response to equal concentrations of all four isomeric keto-acetates). Of the non-rearranged keto-acetates (85 and 86; R = Ac), the same effect found on solvolysis with glacial acetic acid is found here, namely that the equatorial keto-tosylate (86; R = Ts) has produced more axial keto-acetate while the axial keto-tosylate (85; R = Ts) has produced the reverse. The ratio of rearranged keto-acetates (2: 1) is, however, approximately the same from both tosylate solvolyses, a strong indication that they are formed from the same carbonium ion, in both cases. They must both have been

formed from cation 116 obtained by migration of the C_1 - C_9 bond (acyl). It would then seem fair to assume that the more abundant keto-acetate will be that formed by attack of nucleophile on C_1 in a direction anti to the migrating C_1 - C_9 bond (see formula 126). This would mean the more abundant rearranged keto-acetate is 118 in which the acetoxyl group is in a position trans to the carbonyl bridge.

The formation of the mixed olefin-ketones (113 + 114) on solvolysis of 85 and 86 (R = Ts) in anhydrous conditions, with none of the extreme rearranged compounds (87 and 89) was a strong indication that 116 was a true intermediate in the formation of 87 and 89. If this were so, then formation of 116 from 113 + 114 in conditions which were not anhydrous ought to supply the rearranged products (87 and 89). In the event, treatment of the olefin-ketones (113 + 114) with a small quantity of toluene - p - sulphonic acid in refluxing benzene gave a mixture, which, by g.l.c. mobilities consisted of 87 and 89 and, interestingly, the olefin-ketone 88 (see Scheme G). Obtention of the latter (88) demonstrates that the process leading to intermediate 116, is a reversible one. Treatment of

113 + 114 with toluene - p - sulphonic acid in benzene under anhydrous conditions however also gave the mixture described. Similar treatment of 113 + 114 with glacial acetic acid produced no similar rearrangements and the olefin-ketones were recovered unchanged.

It had been proposed[34] that the aromatic acid (78) was formed from the olefin-keto-ester (76) by an initial protonation step and, in fact, 76 had been converted to 78 by treatment with sulphuric acid. To ascertain if this were an important step in the above formation of the aromatic hydrocarbon (87), the olefin-ketone (88) was treated first with glacial acetic acid and finally with toluene - p - sulphonic acid in benzene, but no change in the olefin-ketone (88) was observed by g.l.c. analysis, indicating that the dimethyl indane (87) as well as the conjugated enone (89) is formed from bicyclo (4,2,1) nonane intermediates. The dimethyl olefin - ketone (88) was treated with sulphuric acid to ascertain if a hydrocarbon (90), equivalent to the original aromatic acid (78) could be obtained, but only polymeric, intractable material was recovered from this treatment.

Our thoughts then turned to rationalisation of the

various results described above. The main problem seemed to us to be the conversion of the bicyclo (4,2,1) nonane olefin-ketones (113 + 114) or cation (116) to the dimethyl indane (87). In this, an oxygen function had to be removed and, the only obvious way to do this, under solvolytic conditions, was by protonating the carbonyl, forming a hydroxyl (113 ⟶ 127), and removal of the hydroxyl at some later step. Protonation of a carbonyl requires a strong acid, and yet, in solvolysis with glacial acetic acid the rearrangement had proceeded to completion (i.e. to extreme rearrangement products 87 and 89). Treatment of 113 + 114 with glacial acetic acid, however, produced no change (g.l.c. analysis) indicating that acetic acid itself was not strong enough to protonate the carbonyl group of (113 + 114). The production of 87 by treatment of 113 + 114 with toluene-p-sulphonic acid in benzene indicates the need for a strong acid in producing the species, 127, and a plausible route from 127 to 87 has been devised (see below). It would appear that toluene - p - sulphonic acid, liberated from tosylates (85 or 86; R = Ts) during acetic acid treatment is responsible for the necessary protonation. This is borne out by the

absence of 87 when buffered medium is used for solvolysis.

The series of experiments discussed above and summarised in Scheme G also indicate that the presence of water (in glacial acetic acid) has no effect on the initial protonation of 113 + 114 to give 127. Scheme H includes one possible mechanism, involving a Wagner-Meerwein shift, in the protonated species 127, and subsequent dehydration and deprotonation to produce 87.

A similar protonation argument can be invoked to obtain 89 from 113 + 114 as presented in Scheme H. The species 116 which can arise either during unbuffered solvolysis of 85 and 86 (R = Ts) or in that of 113 + 114 with toluene - p - sulphonic acid/benzene, but not from acetic acid treatment of 113 + 114, is regarded as the necessary first step in formation of 89. Scheme H includes a pathway from 116 to 89, involving formation of tertiary carbinol 128, which could undergo retroaldolisation and realdolisation in another sense to give 89, after a final and expected dehydration. The presence of water, necessary for formation of 89 is obvious in the glacial acetic acid solvolyses; under

the "anhydrous" conditions (anhydrous toluene - p - sulphonic acid/benzene), enough water is present, either incidentally or liberated in formation of 87, to allow formation of 128. In any case, the transformations (116⟶89) need involve only catalytic amounts of water.

Two recent publications of Gassman and Marshall[44,45] are of immediate interest in connection with the above work. These authors solvolysed the tosylates of exo - and endo - 2 - hydroxybicyclo (2,2,1) - heptan - 7 - one (129 and 130; R = Ts) and supply details of both rates and products . They found endo - tosylate (130; R = Ts) to solvolyse faster than exo-tosylate (129; R = Ts) and the products (of acetolysis) from both to contain endo - keto-acetate (130; R = Ac). This is the first norbornyl system to have an exo/endo solvolysis rate ratio of less than unity and to have produced a substantial quantity of products with the endo configuration.

The authors believe the carbonyl dipole would inhibit the formation of a delocalised structure, due to the build up of positive charge in the intermediate (131). They, therefore, came to the conclusion that both the exo - and endo - keto - tosylates (129 and 130; R = Ts)

solvolyse to give the same classical cation (132) and that the endo - compound reacts a little faster because of steric overcrowding due to the C_6 endo - hydrogen (133)[46] interacting with the leaving group.

One of three possible reasons given by these authors as to why the endo - ketonorbornyl tosylate (130; R = Ts) solvolyses faster than the exo - epimer (129; R = Ts) was of great interest to us in the present context. A concerted bond cleavage (134) in the endo - epimer could provide an acyl carbonium ion (135) but this contingency was discarded, because all the products observed, had the 7 - ketonorbornane skeleton.[47] Soon afterwards, Hanack published some findings on the treatment of diazonorcamphor (136) with acid. His products from this and subsequent reactions are shown in Scheme I.

Because of the formation of Δ^3- cyclohexene - carboxylic acid (137) there is little doubt that in Hanack's case (slightly different conditions), the acyl carbonium ion (135) is formed. In our own case (the solvolysis of 85 and 86; R = Ts), bond migration does, in fact, take place in very similar circumstances. This leaves us with the interesting possibility of 138 being an intermediate between the

bicyclo (3,3,1) nonyl and bicyclo (4,2,1) nonyl skeletons. Although no attempt was ever made to isolate a possible acidic product (139) from solvolysis of either 85 or 86 (R = Ts), a careful examination of the material balance between tosylates 85 and 86 (R = Ts) and the neutral products from solvolysis of these (87% from 86, R = Ts and 90% from 85, R = Ts) would require that any quantity of olefin - acid (139) formed would be well below 10% of the total reaction product.

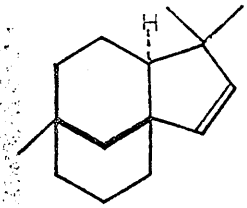
Scheme H shows the conclusions we have arrived at in the solvolysis of 85 and 86 (R = Ts). We have inserted the acyl carbonium ion (138) as a possible intermediate in the rearrangement between the 9 - oxobicyclo (3,3,1) nonane and 9 - oxobicyclo (4,2,1) nonane systems. The steps indicated with dotted lines are the paths which, from an inspection of the product analysis, are possible but for which there is no direct evidence. For example to explain the formation of 88 from the equatorial tosylate (86; R = Ts), one can postulate either direct ionisation of the tosylate (86; R = Ts) to the cation (108), or from 116 (possibly via 138) a conversion shown to be possible above.

We set out in this work, to investigate the stereochemical implications of the reaction of 77 with concentrated sulphuric acid and to attempt to verify or refute those mechanisms (described above) postulated for the formation of 78 and 79 on treatment of 77 with concentrated sulphuric acid. Drawing a parallel between the sulphuric acid cyclisation and our solvolytic experiments, we can say that most of the rearrangement does, in fact, proceed from the equatorial epimer (84) and that this is due to the trans-antiparallel nature of C_5 - C_9 bond (84) with respect to the tosylate leaving group.

In the task of verification of the postulated mechanisms we have been partially successful. We feel that we have now supplied evidence which substantiates the route suggested for the formation of the conjugated enone-ester (79). On the subject of the proposed route to the aromatic acid (78; see Scheme B) we are not in a position to comment, since, we could find no trace of 90 (the compound analogous to 78) in the products from our solvolytic experiments. For this, there are two possible reasons; i) that the reaction sequence taking place in sulphuric acid medium cannot be duplicated under simple solvolytic conditions, or ii)

that the ester group in 77 is critically important in the formation of an aromatic compound with the substitution pattern of 78 (see Scheme C).

Considering that the cation 141 must be an intermediate in the formation of the conjugated enone - ester (79), there is a possibility that a divergent path from 141 giving 140 (Scheme J) (analogous to that found in solvolyses above) might have applied in the sulphuric acid treatment of 77. One obvious drawback, however, in the route to 140 shown in Scheme J is that one of the intermediates (142) contains a cation bearing a carbethoxyl group, a situation which cannot be a favourable one, and would seem to preclude formation of 140 from 77.



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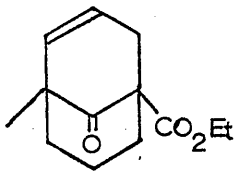

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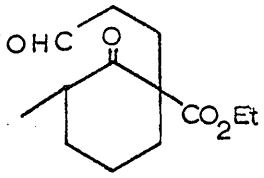

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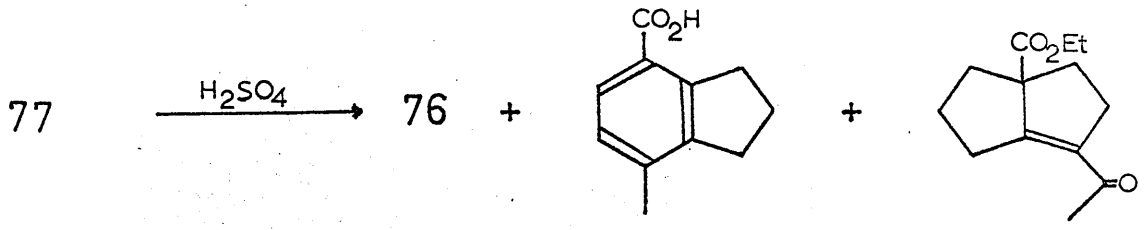

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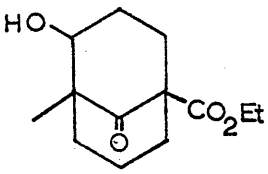

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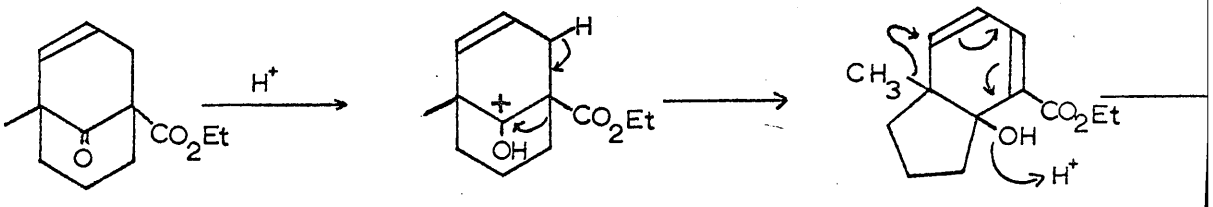
Scheme B



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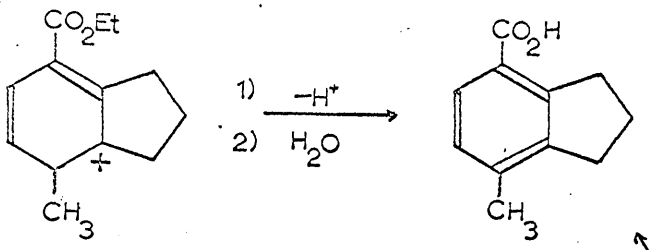

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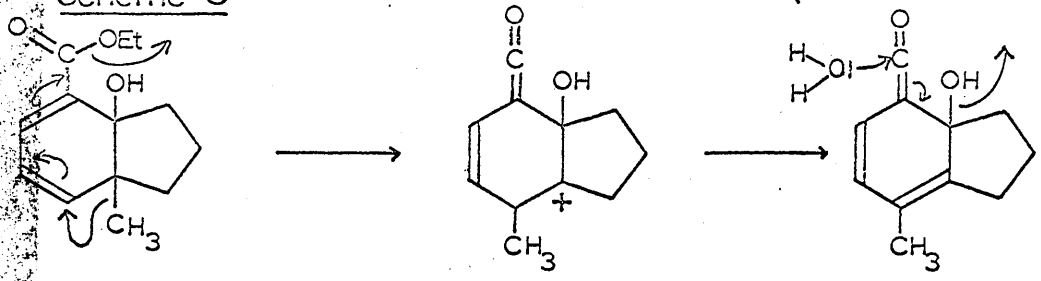
Scheme C



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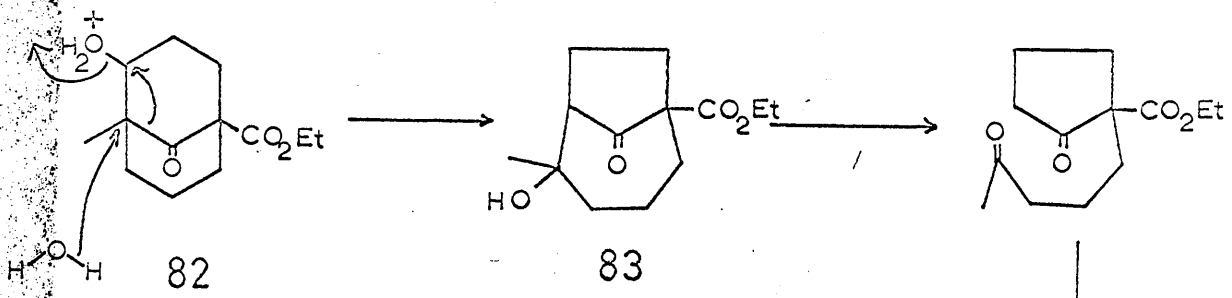
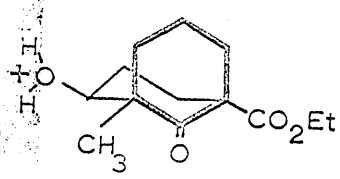
Scheme D





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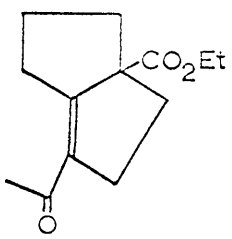

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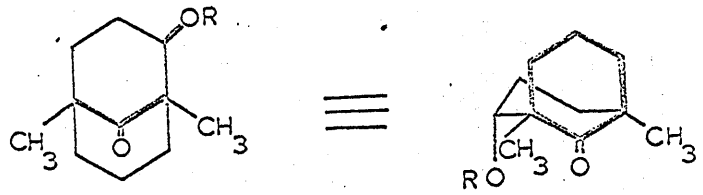

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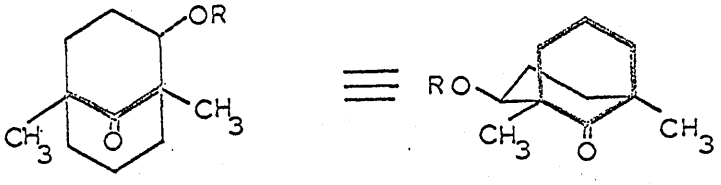

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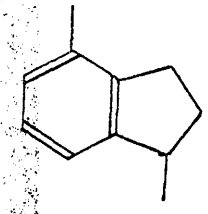

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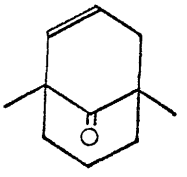

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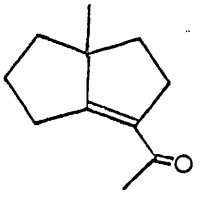

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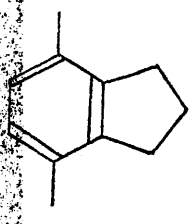

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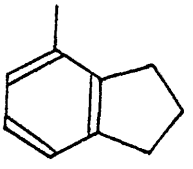

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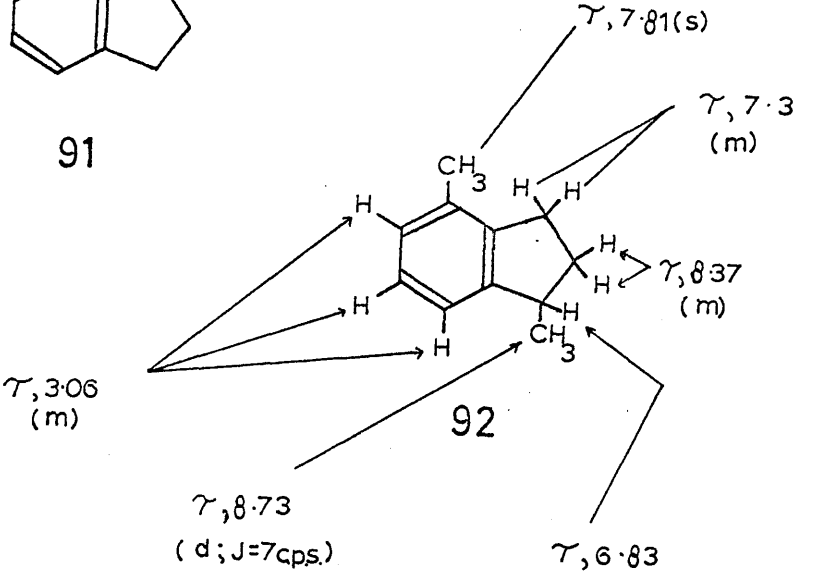

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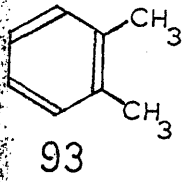

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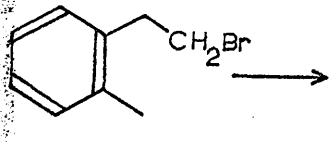

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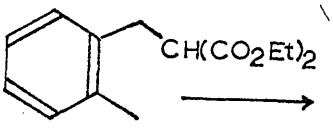

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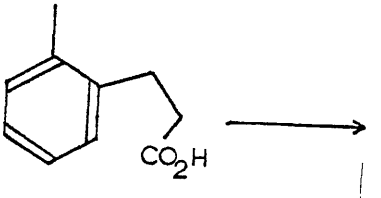

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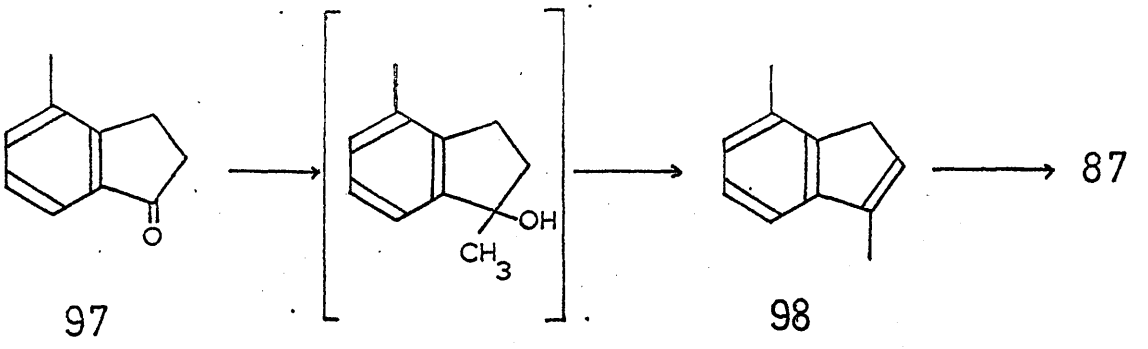

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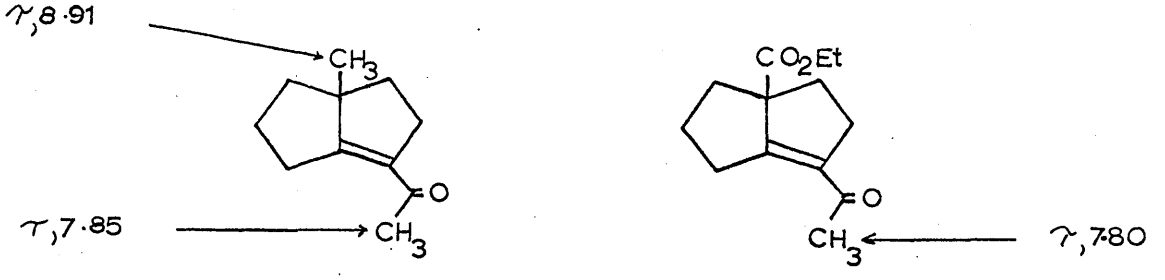

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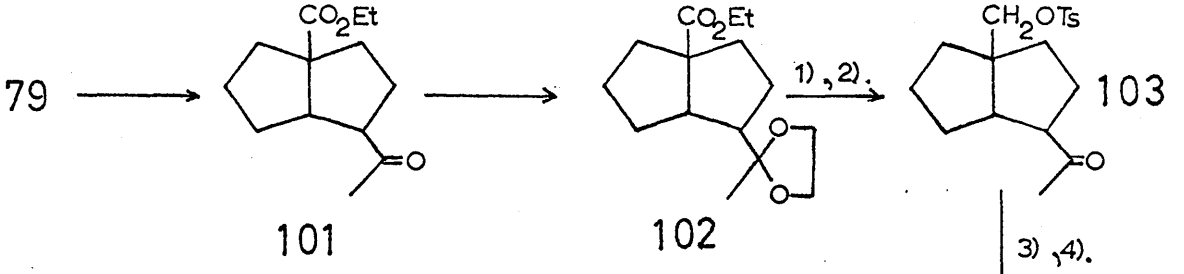

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3) = $LiAlH_4$

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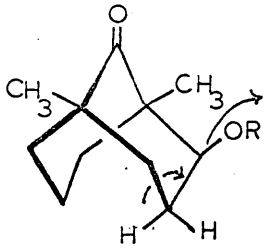

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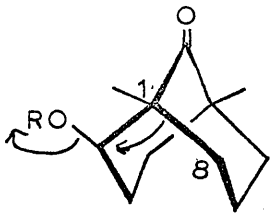

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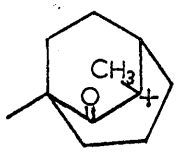

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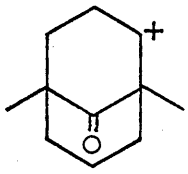

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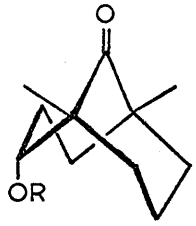

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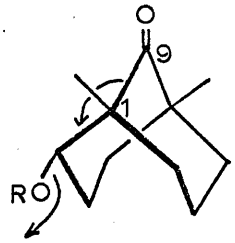

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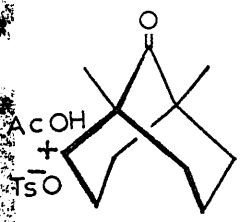

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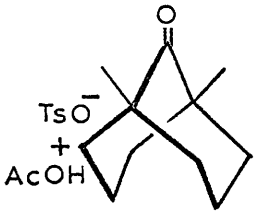

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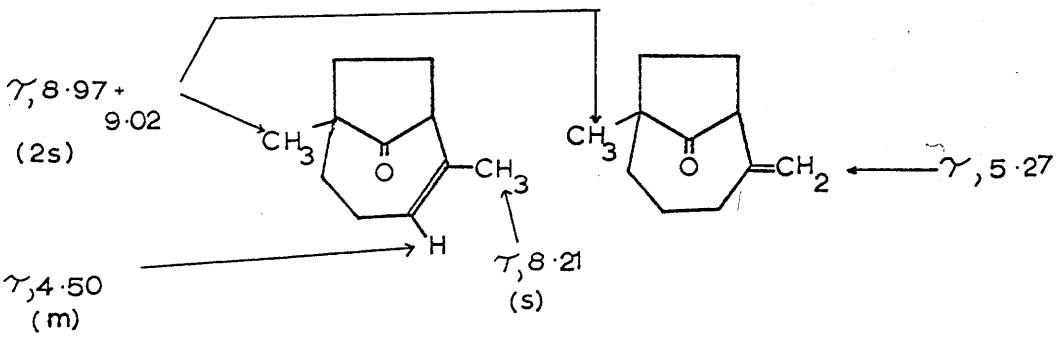

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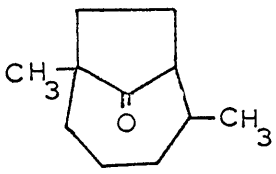

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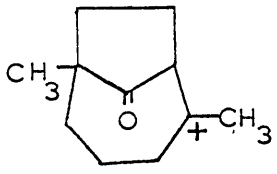

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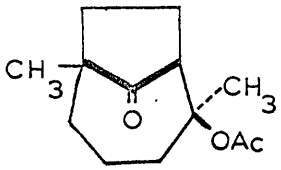

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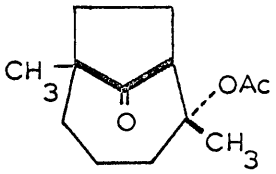

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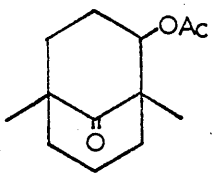
Scheme E



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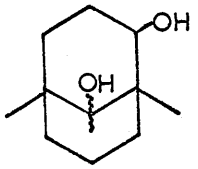

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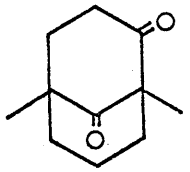

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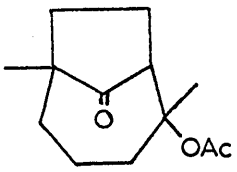

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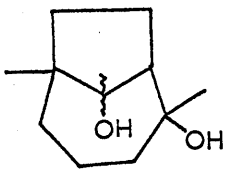

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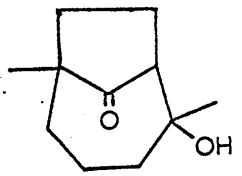

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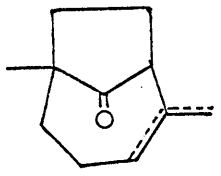

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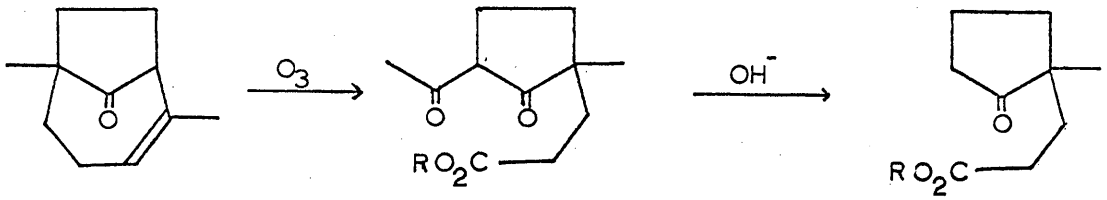

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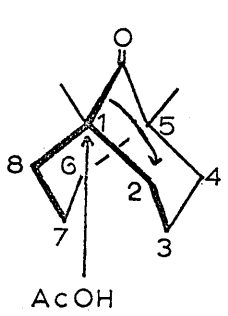

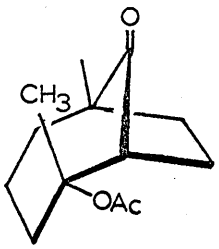

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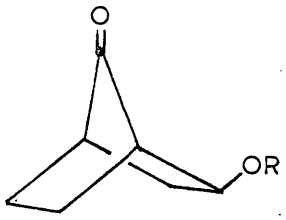

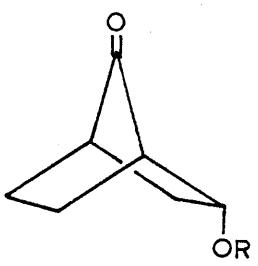

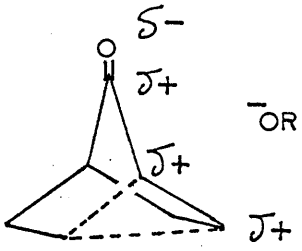

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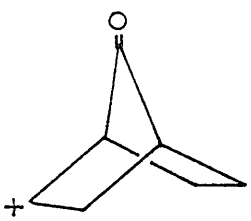

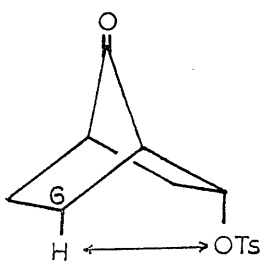

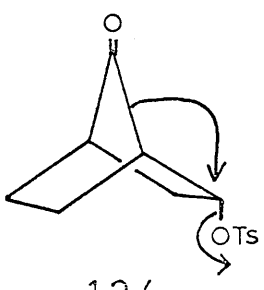

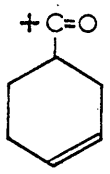

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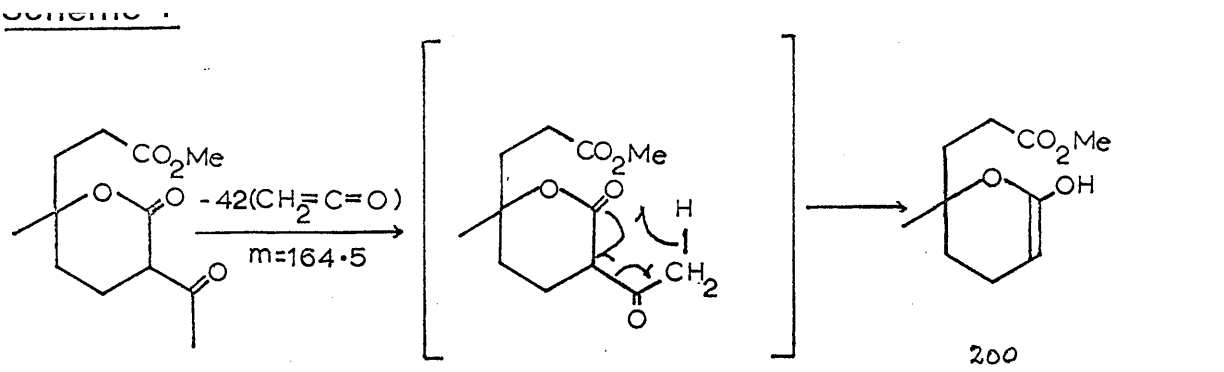
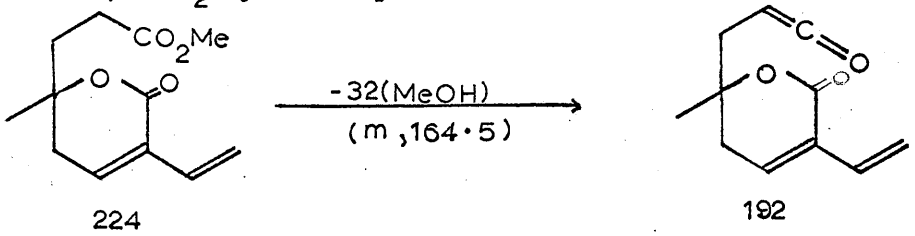


125 (P = 242)

↓ -18(H_2O) [m, 207·3]



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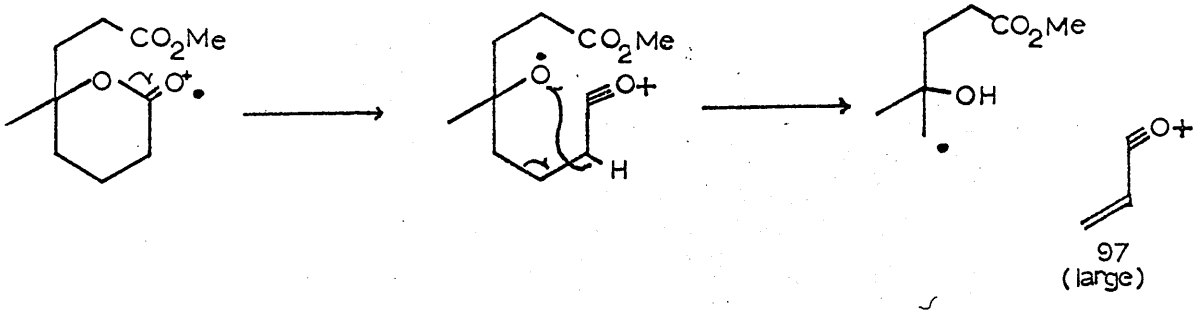
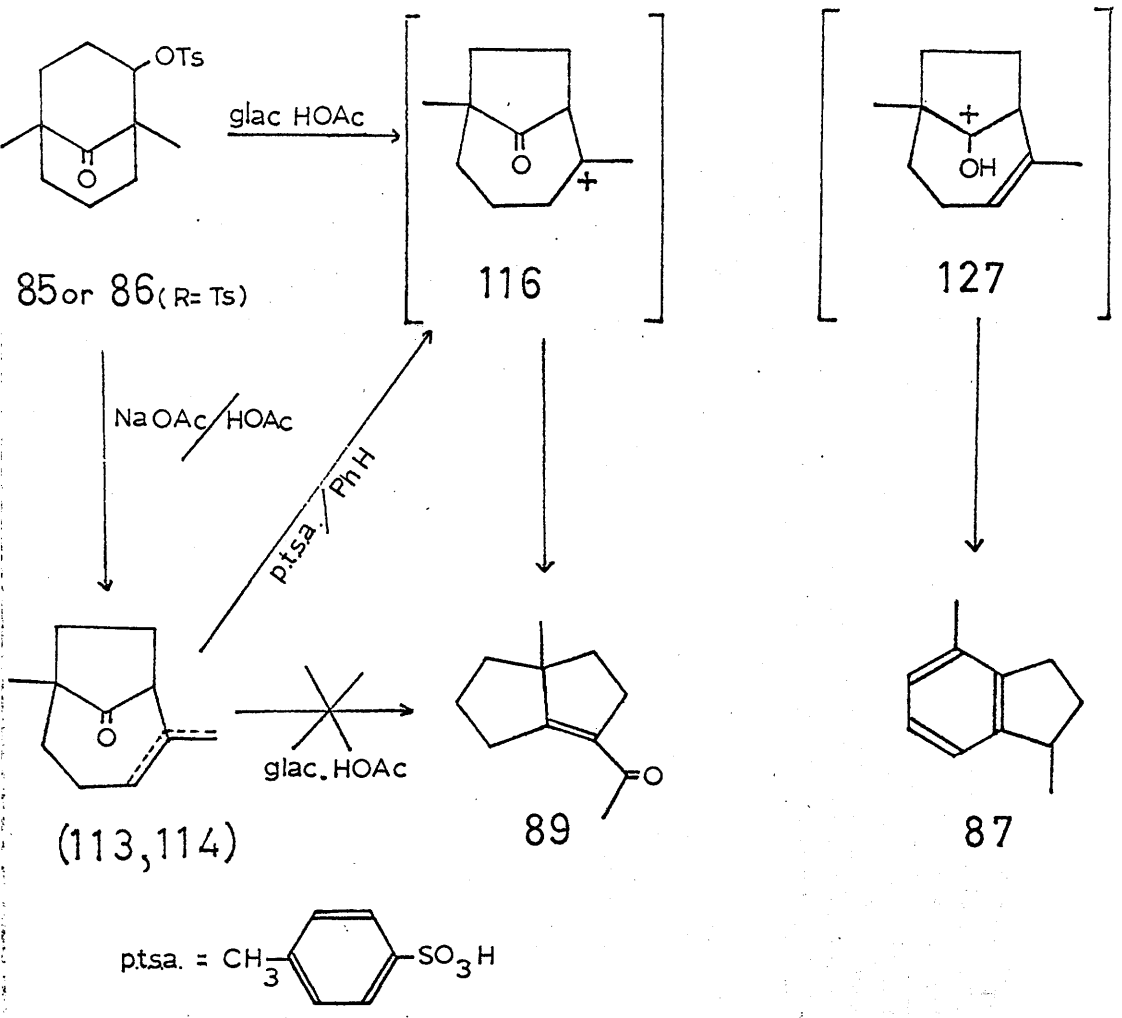
192

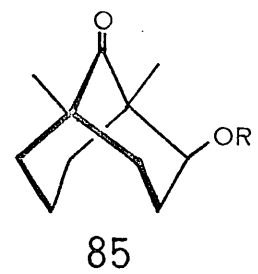


97
(large)

m = metastable


OTs
glac HOAc
85 or 86 (R= Ts)
116
127
OH
NaOAc / HOAc
p.t.s.a. / PhH
glac. HOAc
(113, 114)
89
87
p.t.s.a. = CH3 SO3H

cheme H



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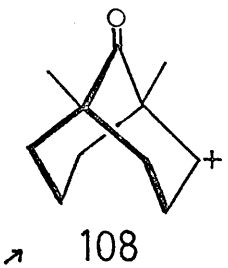

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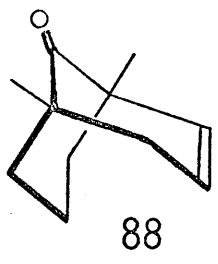

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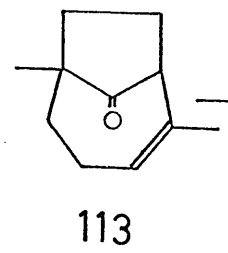

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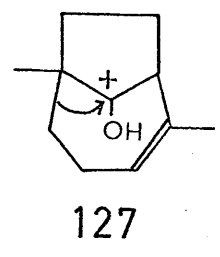

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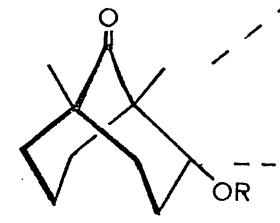

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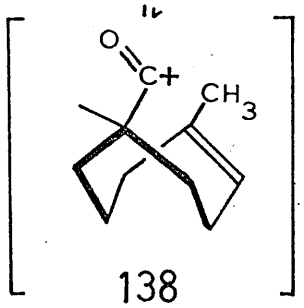

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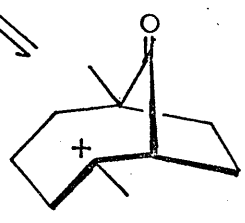

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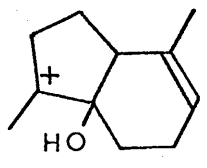

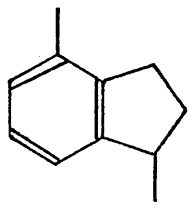

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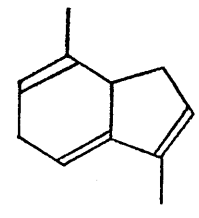

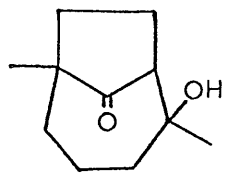

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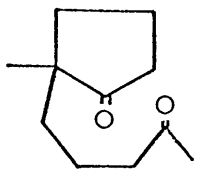
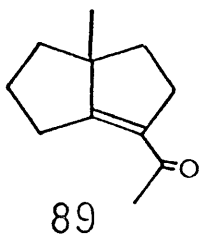


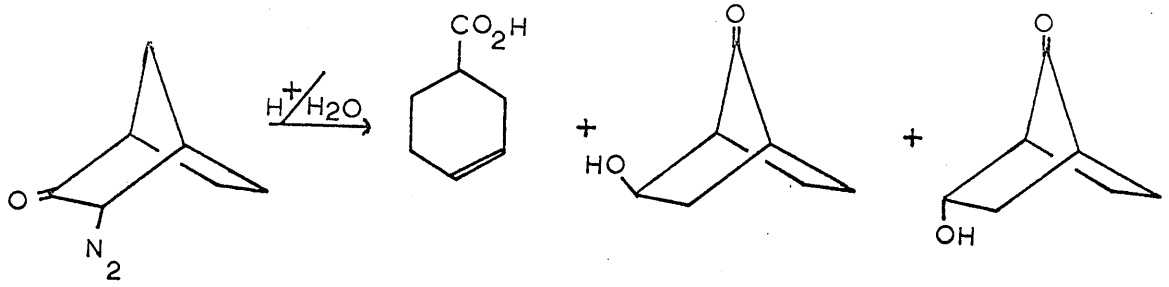


89

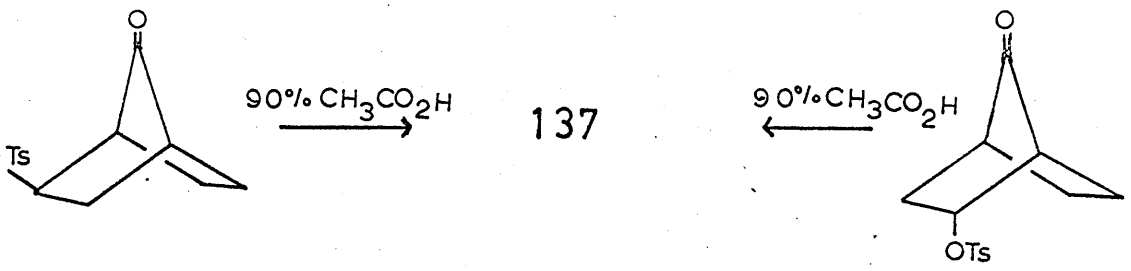
$-H^+$

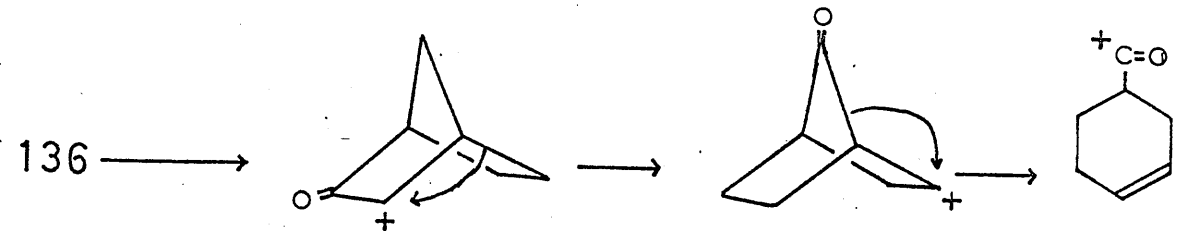
H^+

H_2O



136 137





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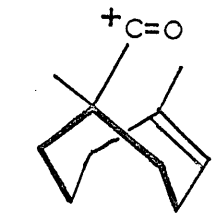
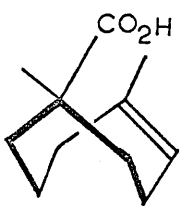
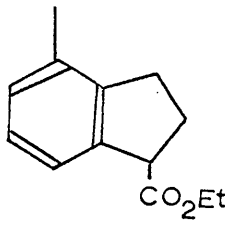
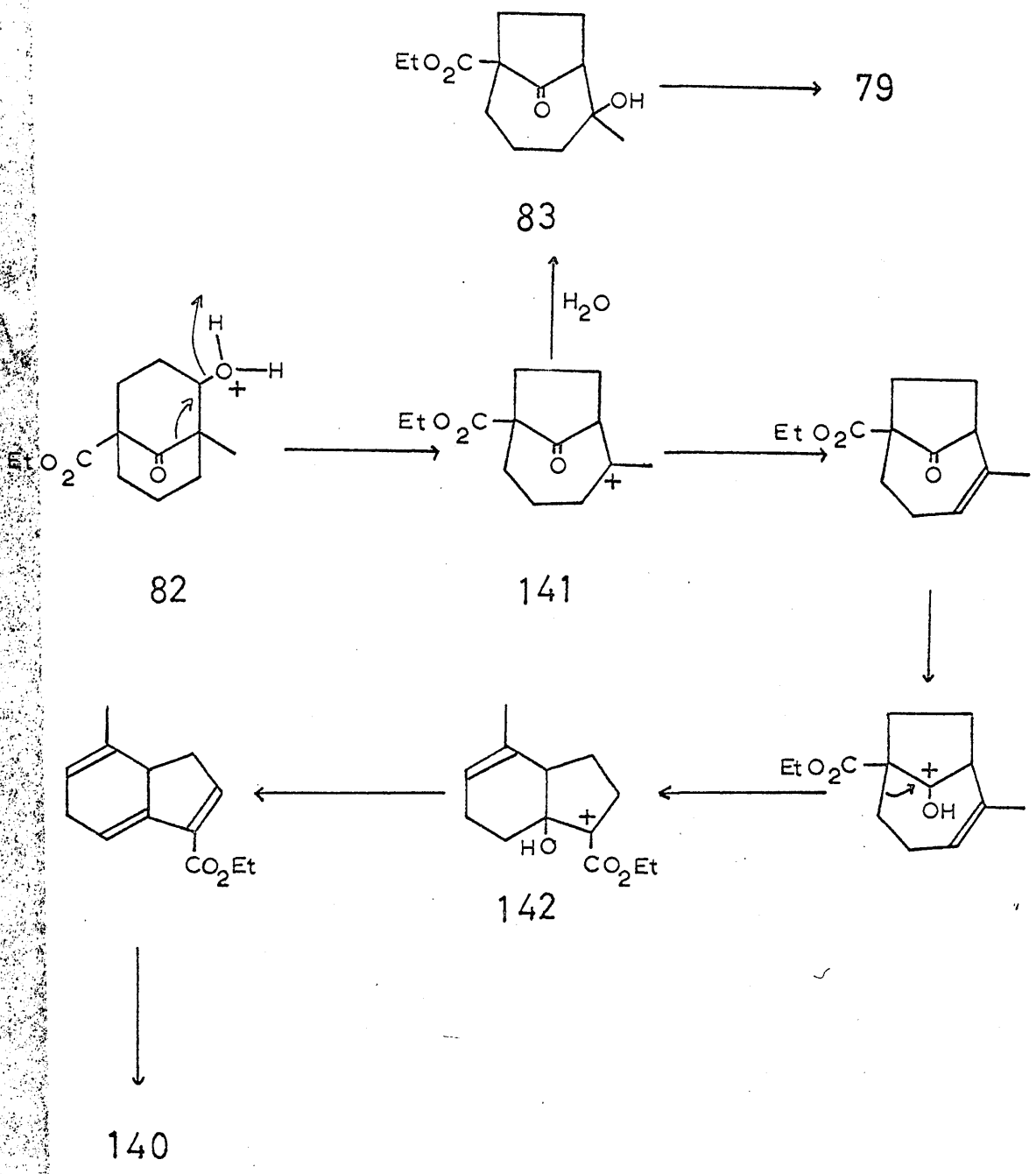






138 139 140

Scheme J


EtO2C
OH
79
83
H2O
H
O
H
EtO2C
82
141
EtO2C
EtO2C
OH
HO
CO2Et
CO2Et
142
140

EXPERIMENTAL. *

Melting points, unless otherwise stated, were recorded on a Kofler block and are corrected; boiling points are uncorrected. The adsorbents used for chromatography were either Woelm Grade I alumina or chromatographic silica gel. Light petroleum refers to the fraction of b.p. 40 - 60°. All organic extracts were dried with anhydrous magnesium sulphate and thin-layer chromatoplates were prepared[48] from Merck's 'Kieselgel G'.

Analytical gas-liquid chromatograms were run on the Pye-Argon Chromatograph while capillary g.l.c. was carried out on the Perkin Elmer Fractometer (P.E.451). Temperature - programmed analytical g.l.c. was accomplished on a Pye 104 instrument. The Aerograph 'Autoprep' A - 700 model was used for preparative g.l.c. separations.

Mass spectra were determined on an A.E.I. M.S.9. spectrometer. Ultraviolet absorption spectra

* The comments on experimental procedure in the preamble to the section below also apply to the experimental parts of Section I Part II and of Section II.

were measured using an automatic Unicam S.P. 800 instrument. Routine infrared spectra were measured on a Unicam S.P. 200 instrument; where high resolution is specified, spectra were recorded linearly in cm^{-1} as percentage transmission with a Unicam S.P.100 double - beam infrared spectrophotomer equipped with an S.P. 130 sodium chloride prism - grating double monochromator operated under vacuum. Proton magnetic resonance spectra were measured using carbon tetrachloride as solvent, unless otherwise stated, with tetramethylsilane as internal reference on a Perkin - Elmer 60 Mc/s spectrometer.

Equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Toluene - p - sulphonate (86; R = Ts).

Equatorial 9 - oxo - 1,5 - dimethylbicyclo - (3,3,1) - nonan - 2 - yl toluene - p - sulphonate (86; R = Ts) was prepared by the method of Martin[36].

Axial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Toluene - p - sulphonate (85; R = Ts).

Axial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl (85; R = Ts) was also prepared by the method of Martin[36].

Anhydrous Acetic Acid.

The anhydrous acetic acid used in the solvolytic experiments was dried by the method of Winstein[49], from glacial acetic acid (A.R.). The fraction b.p. 118° - 120° was collected and used.

Acetolysis of Equatorial 9 - Oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Toluene - p - sulphonate (86; R = Ts) in Glacial Acetic Acid.

Equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1)-nonan - 2 - yl toluene - p - sulphonate (86; R = Ts;1 g.) was dissolved in glacial acetic acid (A.R.; 20 ml) and heated under reflux (120°) for 5 hours. The volume of acetic acid was reduced to approximately 5 ml. by gentle heating under reduced pressure. A saturated solution of brine (15 ml.) was then added and the aqueous mixture extracted with ether (3 x 75 ml.). The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent at 50° under reduced pressure gave a red oil (0.49g.). The oil was adsorbed on grade I neutral alumina (20g.) from light petroleum. Elution with the same solvent gave 1,4 - dimethylindane (87) as a colourless oil (0.093 g, 20%), identical with authentic 1,4 - dimethylindane by i.r. and n.m.r. spectra and by g.l.c. retention time (golay capillary apiezon 'L' column)

Further elution with light petroleum supplied 1,5 - dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (88) as a colourless oil (0.086g, 19%) identical with an

authentic sample by i.r.spectrum and g.l.c. retention time (5% O.F.1. stationary phase).

Elution with ether-light petroleum (1:9) furnished a yellow oil (0.274 g) which, by g.l.c. analysis was a mixture of three compounds. The oil was treated, in the cold, with a solution of semicarbazide acetate and left for 12 hours. The resulting crystalline semicarbazone (0.173g) was filtered at the pump and washed well with ether. Recrystallisation from ethanol afforded the semicarbazone as needles m.p. 212 - 214° (dec.). (Found: C, 65.15; H, 8.5; N, 18.9, $C_{12}H_{19}N_3O$ requires C, 65.1; H, 8.65; N, 19.0%)

After removing the semicarbazone, the filtrate and washings were combined and extracted thoroughly with ether. The ethereal extract was washed with brine and dried. Removal of solvent gave a yellow oil (0.157g 35%) which consisted of a mixture of equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl acetate (86; R = Ac) and axial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl acetate (85; R = Ac) in the ratio of 1: 1.89 analysed by g.l.c. on 5% O.F.1 stationary phase at 150°.

The semicarbazone obtained above was shaken in a separating funnel with ether and sulphuric acid (2N).

The sulphuric acid layer was removed and the ethereal layer washed with brine, saturated sodium hydrogen carbonate solution and dried. Removal of the solvent gave Δ¹-2 - aceto - 5 - methylbicyclo (3,3,0) - octene (89) as a colourless oil; $\lambda_{max.}$ 252 mμ ε = 10,100, $\nu_{max.}$ (film) 1670 cm.

Acetolysis of Axial 9 - Oxo - 1,5 - dimethylbicyclo - (3,3,1) nonan - 2 - yl Toluene - p - sulphonate (85; R = Ts) in Glacial Acetic Acid.

The method was identical to that used above, supplying a red oil (0.52 g.). Separation of the oil in a manner similar to that described above gave (i) 1,4 - dimethylindane (87; 0.022 g, 4%), (ii) 1,5 - dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (88; 0.35 g. 68%), (iii) the semicarbazone of [illegible]-2- - aceto - 5 - methylbicyclo (3,3,0) octene (0.038 g.) and (iv) mixture of equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl acetate (86; R = Ac) and axial 9 - oxo - 1,5 dimethylbicyclo (3,3,1) nonan - 2 - yl acetate (85; R = Ac) (0.166 g. 23%) in the ratio of 3.64 : 1 by g.l.c. analysis.

1, 4 - Dimethylindane (87).

1,4 - Dimethylindane was prepared by the method of Elsner and Parker[39] giving 1,4 - dimethylindane (87) as a colourless oil, b.p. 103 - 104°/35 mm. n_D^{23} 1.5242 ν_{max} (CS_2) 769,709 cm^{-1} (Literature, b.p. 89°/13 mm. n_D^{23} 1.5253).

Acetolysis of Equatorial 9 - Oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Toluene - p - sulphonate (86; R = Ts) with Anhydrous Acetic Acid/ Sodium Acetate.

Equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl tosylate (86; R = Ts, 1g.) was dissolved in dry acetic acid (40 ml.) containing fused sodium acetate (0.49g) and heated to 100° under anhydrous conditions for 7 hours. The mixture was cooled and to it was added saturated brine solution (100 ml.) and the resulting mixture extracted thoroughly with ether (3 x 75 ml). The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent, under reduced pressure at 50° supplied a yellow oil (0.55g.). The oil was adsorbed on grade I neutral alumina (22 g.) from light petroleum. Elution with the same solvent gave 1,5 - dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (88; 0.01 g. 2%) identical with authentic.

Elution with ether - light petroleum (1: 200) furnished Δ^4 -1,5 - dimethylbicyclo (4,2,1) nonen - 9 - one (113) and 1-methyl - 5 - exomethylenebicyclo (4,2,1) nonan - 9 - one (114) in the ratio of 2.7: 1

(by n.m.r. integration) as a sweet smelling colourless oil (0.23g, 48%) b.p. 91°/12 mm; ν_{max} (CCl_4) 1738, 899,816 cm^{-1}, τ, 4.50 (broad multiplet), 5.27 (narrow multiplet), 8.21 (singlet), 8.97 and 9.02 (singlets). (Found, C,80.41; H, 9.64 $C_{11}H_{16}O$ requires C. 80.44; H, 9.82%). A partial separation of this oil into its components was obtained on a 50 m. golay capillary apiezon 'L' column at 154°.

Elution with ether-light petroleum (1:9) gave a mixture of four keto-acetates (85, R = Ac: 86, R = Ac: 117: 118 = 3.5: 0: 1: 1.75, by g.l.c. analysis) as a yellow oil (242 mg. 50%). Analysis of the acetate mixture was carried out at 150° on a 5% Q.F.1. stationary phase.

Acetolysis of Axial 9 - Oxo - 1,5 - dimethylbicyclo - (3,3,1) nonan - 2 - yl - Toluene - p - sulphonate (85; R = Ts) with Anhydrous Acetic Acid/Sodium Acetate.

The axial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl toluene - p - sulphonate (85; R = Ts, 1 g.) was solvolysed and worked up as described above giving a yellow oil (0.46 g.). An identical separation technique separated the oil into i) 1,5 - dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (88; 0.172 g, 42%), ii) mixture of olefin - ketones (113 + 114; 0.097 g, 23%) and iii) mixture of four keto-acetates (85, R = Ac: 86, R = Ac: 117: 118 = 1:9 : 2.5 : 5) as a yellow oil (0.146g.)

Hydrogenation of Double Bond Isomers (113 + 114).

The mixture of isomers (113 + 114; 0.05g) in ethyl acetate (10 ml.) was hydrogenated over 10% palladium - charcoal (0.01g.) for 24 hours at room temperature. Removal of catalyst by filtration through celite 535 followed by removal of the solvent gave an oil (0.045g.) which exhibited no double bond absorption in the i.r. $\nu_{max}(CCl_4)$ 1733 cm^{-1}.

The 2,4 - dinitrophenylhydrazone crystallised as yellow needles from ethanol m.p. 141 - 142° (Found: C, 59.15; H, 6.20; N, 16.50 $C_{17}H_{22}N_4O_4$ requires C, 58.95; H, 640; N, 16.48%).

Axial 9 - Oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Acetate (85; R = Ac).

Axial 2 - hydroxy - 1,5 - dimethylbicyclo (3,3,1) nonan-9-one (85; R = H, 1 g.) was dissolved in acetic anhydride (5 ml.) to which was added dry pyridine (0.3 ml.). The solution was left 12 hours and then poured into brine and allowed to stand for 1 hour. The mixture was extracted thoroughly with ether and the ethereal extract washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent afforded a colourless oil (1.1g).

Sublimation of the oil under high vacuum supplied an analytical sample of axial 9 - oxo - 1,5 dimethylbicyclo (3,3,1) nonan - 2 - yl acetate (85; R = Ac) as colourless needles m.p. 52 - 53°; ν_{max}(mull) 1735, 1715, 1230 cm^{-1} τ , 4.91 (1 proton, half-height width = 7 c.p.s. assigned to carbinyl proton). (Found: C, 69.58; H, 9.19 $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%)

Equatorial 9 - Oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 - yl Acetate (86; R = Ac)

Treatment of equatorial 2 - hydroxy - 1,5 - dimethylbicyclo (3,3,1) nonan - 9 - one (86; R = H) with acetic anhydride/pyridine in the manner described above for the epimeric compound (85; R = H) supplied equatorial 9 - oxo - 1,5 - dimethylbicyclo (3,3,1) nonan - 2 yl - acetate (86; R = Ac) as a colourless oil which on sublimation gave an analytical sample; ν_{max} (film) 1735, 1710, 1240, τ , 5.31 (1 proton - triplet, J = 9 c.p.s., half- height width = 20 c.p.s., assigned to carbinyl proton). (Found: C, 69.34; H, 8.79; $C_{13}H_{20}O_3$ requires C,69.61; H, 8.99%).

Treatment of Isomers (113 + 114) with Toluene - p - sulphonic acid in Benzene under Anhydrous Conditions.

The mixture of Δ^4 - 1,5 - dimethylbicyclo (4,2,1) nonen - 9 - one (113) and 1 - methyl - 5 - exomethylene-bicyclo (4,2,1) nonan - 9 - one (114) (10 mg.) obtained from the solvolyses described above was heated under reflux in benzene (5 ml.) containing toluene - p - sulphonic acid (2 mg.) for 4 hours. The solution of toluene - p - sulphonic acid in benzene had been carefully dried by heating for 4 hours the solution under reflux in a sohxlett apparatus containing calcium hydride.

The benzene solution was cooled and poured into saturated sodium hydrogen carbonate solution. The mixture was extracted thoroughly with ether and the ether extract then washed with brine and dried. Removal of solvent gave a yellow oil (9 mg.); ν_{max} film 1740 (w), 1710 (s), 1670 (s). G.l.c. analysis of this oil showed it to contain 1,4 - dimethylindane (87), 1,5 - dimethylbicyclo (3,3,1) non - 2 - en - 9 - one (88), a little starting olefin - ketone mixture (113 + 114) and Δ^1 - 2 - aceto - 5 - methylbicyclo 3,3,0) octene (89).

Treatment of Isomers (113 + 114) with Toluene - p -

sulphonic acid in Benzene.

The olefin-ketones (113 + 114) were treated in an identical manner to that described above, this time, however, no attempt was made to remove water from the solution beforehand (The sulphonic acid used was a hydrated form).

A similar work - up and analytical technique showed that the above treatment also produced rearrangement giving a mixture of the same four compounds described above.

Treatment of Isomers (113 + 114) with Glacial Acetic Acid.

The olefin-ketones (113 + 114, 10 mg.) were heated under reflux in glacial acetic acid solution for 12 hours. The solution was taken up in ether and this was washed with saturated sodium hydrogen carbonate solution and dried. Removal of solvent gave the olefin-ketones (113 + 114, 9 mg.) as an oil, identical with starting material by i.r. spectrum and g.l.c. retention time.

Reduction of Keto - acetates (85, R = Ac + 86, R = Ac + 117 + 11

The mixed acetates (85 + 86, R = Ac + 117 + 118; 1.12g.) in anhydrous ether (15 ml.) was added to a suspension of lithium aluminium hydride (0.43 g.) in ether (15 ml.) over 1 hour. The mixture was then refluxed for 24 hours and cooled. Saturated ammonium sulphate solution was added until no further reaction took place and then the precipitated aluminium salts were filtered off using Celite 535. The ethereal layer was separated, washed with brine and dried. Removal of solvent gave a colourless oil (0.83 g.); ν_{max} (film) 3500, 1636, 1650 cm^{-1}, containing several diols (119 120).

Oxidation of Diol Mixture.

The diol mixture (119 120; 0.35g.) in dry dimethylformamide was treated with chromium trioxide (1.4g). To the mixture was added two drops of concentrated sulphuric acid and the resulting solution allowed to stand at room temperature for 16 hours. To the solution was added a mixture of ether and water (1: 1; 40 ml.). The ethereal layer was separated, washed well with water to remove dimethylformamide and dried. The solvent was removed giving a pale yellow oil (0.33g.) which contained three compounds (by t.l.c).

The oil was adsorbed on silica gel (13 g.) from light petroleum. Elution with ether-light petroleum (1:3) gave 1,5 - dimethylbicyclo (3,3,1) nonan - 2, 9 - dione (121) identical with an authentic sample. Elution with ether-light petroleum (3:7) supplied a mixture of the epimeric 5 - hydroxy - 1,5 - dimethylbicyclo (4,2,1) nonan - 9 - ones (122) as an oil (0.14 g.); ν_{max} (film) 3500, 1725.

Dehydration of Ketols (122).

The ketol mixture (0.05g.) obtained above was dissolved in dry pyridine (5 ml.) and to the solution was added phosphorus oxychloride (1 ml.). The mixture was left for 1 hour at room temperature, poured into a mixture of ice and water, and extracted thoroughly with ether. The ethereal layer was washed with brine, hydrochloric acid (IN), brine and dried. Removal of solvent gave a colourless oil (0.03g.) identical to the mixed olefin - ketones (113 + 114) by i.r. and g.l.c. retention times.

Ozonolysis of Isomers (113 + 114).

The mixture of olefin-ketones (113 + 114; 0.1g.) in ethyl acetate (10 ml.) was cooled to -70° and ozone was passed through the solution for 3 hours. To the

solution was added hydrogen peroxide (30%; 1 ml.) and glacial acetic acid (1 ml.) and the resulting solution was stirred for 12 hours. The mixture was then extracted thoroughly with ether and the ethereal extract washed with dilute ferrous sulphate solution, brine and dried. Removal of the solvent gave a brown acidic oil (0.065g.) which was treated with excess diazomethane. The resulting neutral oil (0.063g.) on examination by t.l.c. revealed the presence of four compounds, one of which, gave a colouration with ferric chlorides. Separation of this compound by preparative t.l.c. supplied a yellow oil (0.014g.); ν_{max} (film) 1735, 1640 cm^{-1}, mass spectral parent = 242 (breakdown, Scheme F). The lactone structure 125 was tentatively assigned to this oil.

SECTION I PART II

Reductive Rearrangement of Enol-lactones and Synthetic Routes to Bicyclo (3,3,1) nonane Derivatives

Because of the general interest in homoallylic participation (see general introduction) and our own interest in the reactivity of derivatives of the conformationally interesting[18,40] bicyclo (3,3,1) nonane system, a study of the solvolytic behaviour of syn- and anti- bicyclo(3,3,1)non-2-en-9-yl tosylates (143 and 144; R=T_s) was initiated. In order to undertake such a task, however, an efficient synthesis of the alcohols (143 and 144;R=H) was required. When this work was started, no such route existed although a synthetic scheme to obtain syn- and anti-9-hydroxy-1,5-dimethylbicyclo-(3,3,1)non-2-ene(145 and 146;R=H) had been developed in this laboratory[50].

This route (147→85;R=H) consisted initially of cyanoethylating 2,6-dimethyl-2-carbethoxycyclohexanone(147) to give 148. Basic hydrolysis of the nitrile-ester afforded the keto-acid 149 in one step. Lactonisation of the keto-acid, 149 gave the dimethyl enol-lactone, 150. This lactone, on treatment with lithium hydridotri-t-butoxyaluminate[51] was converted, in excellent yield (>90%), to the bicyclic ketol

(85;R=H) with the stereochemistry shown. Conversion of the ketol to the tosylate 85 (R=Ts) and subsequent treatment of this with sodium ethoxide furnished the unsaturated ketone 88 in good yield. Reduction of the carbonyl of the unsaturated ketone (88) furnished the epimeric alcohols 145 and 146 (R=H).

Oxidation of the ketol (85), gave the dione, 151, which, on reduction with the complex hydride supplied a liquid mixture of ketols in which the equatorial 2-hydroxy-1,5-dimethylbicyclo (3,3,1)nonan-9-one(86;R=H) was in preponderance[36]. Treatment of the mixture with toluene-p-sulphonyl chloride provided the equatorial keto-tosylate (86;R=Ts) as a crystalline solid. This series of preparations supplied us with the epimeric keto-tosylates studied in Part I of this section (see above).

The reaction converting the enol-lactone(150) to the bridged bicyclic ketol (85;R=H), was discovered in these laboratories and its high yield and formation of the thermodynamically less stable ketol made it interesting and potentially useful as a synthetic procedure. It was decided at an early stage in this work to attempt to synthesise 9-oxobicyclo(3,3,1)non-2-ene(158) by a method analogous to that described above for the 1,5-dimethyl analogue(~~10~~ (88)), and, 'en passant', to gain more information about the general usefulness of the reduction of δ -enol-lactones with lithium hydridotri-t-butoxyaluminate. Again it was not at all clear how this reductive rearrangement proceeds, and we were interested

in gaining some insight into the mechanism of the transformation. The route proposed is shown in figures 152—158.

DISCUSSION

From the Michael addition of the pyrollidine enamine of cyclohexanone(153) to ethyl acryllate, a good yield (80%) of ethyl 3-(2-oxocyclohexyl)propionate(154) was obtained as reported by Stork[52]. Acidic hydrolysis of this ester furnished 3-(2-oxocyclohexyl)-propionic acid (155) whose melting point (60-62°) was identical to that reported earlier[53]. Treatment of 155 with acetic anhydride-sodium acetate furnished an oil, presumably the same as that obtained by Shusherina[53] to which had been assigned the tetrasubstituted enol-lactone structure 159. In our hands, thin-layer chromatographic analysis showed it to be a mixture of two compounds. The less polar compound, a colourless oil, was identified as $\Delta^{1,6}$-2-oxabicyclo(4,4,0)-decen-3-one(159) mainly on the basis of its n.m.r. spectrum which exhibited no absorption in the region τ ,4-6, indicating the absence of olefinic protons. The more polar compound, a crystalline solid (m.p. 42-43°) exhibited a narrow, one proton, multiplet at τ ,4.73 in its n.m.r. spectrum and was identified as $\Delta^{1,10}$-2oxabicyclo(4,4,0)decen-3-one(160) The enol-lactones 159 and 160 were formed in a ratio of 4:1; both were unstable in air, hydrating partially in a few hours to keto-acid, 155. Basic hydrolysis of each enol-lactone at room temperature gave 3-(2-oxocyclohexyl)-propionic acid (155) in a few minutes.

The more abundant enol-lactone (159) was treated with a

slight excess (1.3 moles) of lithium hydridotri-t-butoxyaluminate at -70° under nitrogen[50]. Work-up with acid furnished 3-(2-oxocyclohexyl)-propionaldehyde(161) contaminated with another compound of very similar thin-layer chromatographic mobility. Careful chromatography on silica gel separated a pure sample of 161 but not its contaminant. The structure 161 was assigned to the major product from infra red evidence (ν_{max},1732,1715) from formation of a bis-dinitrophenylhydrazone and from comparison with the physical properties of 161 prepared later by Cope[54]. The formation of keto-aldehyde (161) was not wholly unexpected from such a reduction since Parham and Huestis[55] had obtained a similar product from an analogous lactone. Reduction of dihydrocoumarin(162) gave the hemiketal(163) which, with acid work-up afforded the phenolic aldehyde(164).

The contaminant was later separated as an oil which, on standing, deposited a crystalline solid.Recrystallisation from pentane afforded an alcohol (m.p.65-75°). This alcohol decomposed even on warming in petroleum ether to give two different, less polar, compounds. These were separated by preparative t.l.c. into a dehydration product (ν_{max} 1688,1157 cms^{-1}), and a keto-alcohol (ν_{max} 3600,1708 cms^{-1}), both, of which, on standing reverted to the original alcohol (m.p.65-75°). Distillation of the alcohol with a small crystal of iodine supplied the dehydration product alone. The structure 166 was assigned to this alcohol and structures 167 and 168 to its

decomposition products. Compounds 166 - 168 arise from over-reduction of 159 since reduction of $\Delta^{1,6}$-2-oxabicyclo(4,4,0)decen-3-one(159) with excess lithium aluminium hydride also gave 2-oxabicyclo(4,4,0)decan-1-ol(166) as the only product in this case, in a reaction analogous to that of Shusherina[56] in reducing 169 to give 170.

Subsequently, the reduction was considerably simplified when $\Delta^{1,6}$-2-oxabicyclo(4,4,0)decen-3-one(159) was reduced with one equivalent of lithium hydridotri-t-butoxyaluminate and the only product was the keto-aldehyde (161), obtained in yields up to 80%. Until Cope's recent synthesis of 161[54], the above was the most efficient method of preparing this compound.

Complex hydride reduction of $\Delta^{1,10}$-2-oxabicyclo(4,4,0)decen-3-one(160) which is more closely related to the dimethyl enol-lactone(150) (the double bond in both compounds is exo to the lactone ring) afforded a poor yield of neutral material (38%) which consisted mainly of three compounds, none of which was the keto-aldehyde (161). Separation of these on silica gel identified the least polar compound as 166. The two more polar compounds could not be separated by column chromatography. Preparative t.l.c. supplied the more polar of these in a pure state and this was identified as axial 2-hydroxybicyclo(3,3,1) nonan-9-one(157;R=H), while the less polar compound, though not obtained pure at this stage was subsequently assigned the epimeric structure (171;R=H). The ketols, as their acetates,

were examined by quantitative g.l.c. analysis (the parent ketols could not be separated) and found to be in the ratio (157;R=H): (171;R=H)=19:1.

Attempts to improve the yield of ketols 157 and 171(R=H) (15% total) by modifying the reduction conditions were completely ineffective. Use of equimolar amounts of complex hydride and enol-lactone (160) did not prevent the formation of 166. The solvent, tetrahydrofuran, fell under immediate suspicion and it was found that unless it was dried over potassium hydroxide pellets for a few days and then distilled from lithium aluminium hydride, even the above yields were not achieved. Next, the complex hydride[51] was prepared a) as the solid and b) in solution just before use; both gave essentially the same results, although the solid complex hydride gave better reproducibility. Prior filtration of the complex hydride reagent solutions did not improve the yields in any noticeable way. Variations of temperature and time were equally ineffective. Any unchanged enol-lactone would be expected to hydrolyse to keto-acid (155) during the work-up and indeed in the product, large amounts (30-50%) of this acid were invariably recovered.

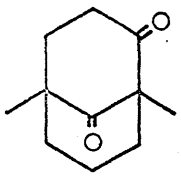
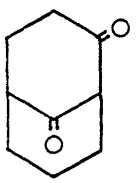
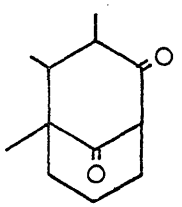
Stereochemistry of Ketols 157 and 171(R=H).

In the elucidation of the stereochemistry of the various bicyclic derivatives formed, n.m.r. was used very effectively. According to Musher[57], the half-band width of the signal for

TABLE 3

Compound	Carbinyl Proton	τ	$W^{\frac{1}{2}}$ c/s.
85 (R=H	e	6.12	6
(R=Ac)	e	4.91	7
86 (R=H)	a	6.45	21
(R=Ac)	a	5.31	20
157 (R=H)	e	5.75	8
(R=Ac)	e	4.87	8
(R=Ts)	e	4.90	6
171 (R=H)	a	6.05	16
(R=Ac)	a	5.03	20
181 (R=H)	e	5.85	7
(R=Ts	e	5.08	7
182 (R=H)	a	6.15	20
(R=Ts)	a	5.56	21

Table.4.

Compound		ν1	ν2	Δν (cm^{-1})
	Hexane	1712	1741	29
	CCl_4	1707	1737	30
	$CHCl_3$	1701	1729	28
151	CH_3CN	1702	1728	26
	Hexane	1717	1741	24
	CCl_4	1713	1739	26
	$CHCl_3$	1708	1729	21
173	CH_3CN	1712	1732	20
	Hexane	1711	1738	29
	CCl_4	1707	1734	30
	$CHCl_3$	1700	1729	28
183	CH_3CN	1702	1729	26

The equatorial ketol was characterised as its p-nitrobenzoate (171;R=$C_7H_4NO_3$,m.p.111-113°). The ketol, on treatment with toluene-p-sulphonyl chloride in pyridine gave an unstable tosylate which was converted by treatment with ethoxide to ethyl Δ^4-cyclo-octene-carboxylate (174), identical with a sample synthesised by the method of Stork[60], in its i.r. spectral properties and in gas chromatographic retention times (using two different stationary phases). This can be envisaged as arising from a ring-opening process represented in formula 175, previously substantiated in these laboratories[36,58].

Jones oxidation (chromium trioxide in dilute sulphuric acid)[61] of both the axial and equatorial ketols (157 and 171;R=H) gave the same unstable dione(173). The carbonyl stretching frequencies for dione, 173, in a number of solvents can be found in Table 4. Table 4 also lists the carbonyl stretching frequencies of 1,5-dimethylbicyclo(3,3,1)nonan-2-9-dione(151)[36,40] and the steroid dione 183 (see below) It will be seen that the band separation is virtually solvent independent and is diagnostic of this type of non-enolisable β-diketone system.

It had been hoped that, as with reduction of the dimethyl dione (11)[36], a large preponderance of the equatorial ketol (171;R=H) would be formed. In the event, reduction of the dione gave a mixture of four ketols (g.l.c. of acetates) in which the equatorial ketol was present to the extent of about 50%. This can easily be understood since one would expect less specific

attack of hydride on the 2-oxo function in 173 than in 151 where the 9-oxo function is more hindered.

The ketol melting at 169-171°(157;R=H) was reduced with complex hydride to give a mixture of diols of quite different thin-layer chromatographic mobilities and which exhibited intramolecular hydrogen bonding at high dilution in the infra red. The less polar diol (the hydrogen bonded compound) was separated and assigned the structure 176 because, of the four possible diols in the 2- and 9- positions (176-179), only 176 would exhibit intramolecular hydrogen bonding. The equatorial ketol (171;R=H), on reduction, afforded a mixture of two diols which showed no hydrogen bonding at high dilution in the infra red, confirming the equatorial disposition of the hydroxyl function in 171(R=H).

In the reduction of the trisubstituted enol-lactone(160) therefore, cyclisation to give mainly axial 2-hydroxybicyclo(3,3,1) nonan-9-one(157;R=H) does, in fact, take place, albeit in poor yield. Although the preponderance of bicyclic products is very heavily toward the thermodynamically less stable ketol (157;R=H), it is not complete. The reduction of Martin on the dimethyl enol-lactone(150) was therefore repeated to ascertain whether or not, reduction gave exclusively axial ketol (85;R=H). In the event, a good yield (90%) of crystalline product was obtained from the reaction. This was acetylated (the ketols were not separable by g.l.c.) and g.l.c. analysis of the mixed acetates showed it to contain the axial and equatorial 2-hydroxy-1,5-

dimethylbicylo(3,3,1)nonan-9-ones(85:86;R=H) in the ratio of 19 : 1 .

Thus far, it seemed that in order for the reductive rearrangement of δ-enol-lactones to give bicyclic products, the enol double bond must be exocyclic to the lactone ring. In the case of the heavily substituted dimethyl enol-lactone (150) the yields were excellent whereas for the unsubstituted lactone (160) they were much poorer. It was therefore deemed worthwhile to investigate the reduction of moderately substituted enol-lactones, firstly to check the "exo-double bond" requirement, and secondly to provide us with more information as to the importance of the degree of substitution on the course of the reaction. It also occurred to us that we might be able to relate our results to those of Fujimoto[62] and Woodward[63] on the reaction of steroidal enol-lactones with Grignard reagents (see below) and we therefore chose Turner's lactone(180)[64] whose substitution pattern was intermediate between the two cases (150 and 160) which we had studied. The C_{19} methyl of the lactone (180) forces the enol double bond to take up the exocyclic position desired and provides the "intermediate" substitution required.

Turner's lactone(180), on reduction with lithium hydridotri-t-butoxyaluminate was converted smoothly and in good yield (72%) to the mixed ketols (181 and 182;R=H). Neither the ketols nor their acetates could be separated by g.l.c. using three different stationary phases, but separation by preparative t.l.c.

was successful, allowing the isolation of the ketols (axial: equatorial=16:1). Oxidation of the mixture with Jones reagent[61] gave a single diketone (183)[65]. The stretching frequencies of the carbonyls of 183 in different solvents, are shown in Table 4. As in 1,5-dimethylbicyclo(3,3,1)nonan-2,9-dione(151) the band separation of the carbonyl groups is virtually solvent independent characteristic of a non-enolisable β-diketone system.

Reduction of the dione (183) with complex hydride furnished a mixture of ketols (181 and 182;R=H), this time with the equatorial compound (182;R=H) in excess (axial:equatorial=1:7). Due to steric factors, which will be discussed later, the central carbonyl in the steroid bicyclic dione (183) is particularly inaccessible (possibly even more than in the dimethyl dione, 151) and the above reduction is specific to the 2-oxo function.

Table 3 lists the n.m.r. absorptions and half-band widths of the signals of the carbinyl protons of the steroid bicyclic derivatives prepared. Both 181 and 182 (R=H) could be separately oxidised to dione 183. Reduction of the axial ketol (181;R=H) with complex hydride produced a diol mixture showing weak intra-bonded hydroxyl absorptions in the i.r. Reduction with lithium aluminium hydride, however, produced a mixture of diols with quite different t.l.c. mobilities in approximately equal amounts. The hydrogen bonded diol (184) (the less polar compound) was separated and characterised (m.p. 200-202°). Reduction of the equatorial ketol (182;R=H) gave a mixture of diols (with similar t.l.c.

mobilities), exhibiting no internal hydrogen bonding in the infra red. Tosylation of 181(R=H) was very slow and gave a poor yield of the unstable tosylate (181;R=Ts). If the alcohol (181;R=H) with toluene-p-sulphonyl chloride or the tosylate (181;R=Ts) were heated in pyridine, a dehydration product, which could not be obtained pure, was formed. Spectral evidence - absorption at 1726 and 700 $cms.^{-1}$ in the infra red, a mass spectral parent ion of molecular weight 370, and absorption at τ,4.35 in the n.m.r. (broad multiplet), all indicated the structure 185. The equatorial steroid keto-tosylate(182;R=Ts) on the other hand, was formed smoothly and in high yield.

The above examples have shown the immediate usefulness of the complex hydride reductive rearrangement as a synthetic procedure, and the method has now been used several times in these laboratories to prepare a large range of bicyclic compounds. Because of the inactivity of the reagent to carboxylic esters, it may be used with impunity in systems containing these groups. For example, as models in a projected synthesis of lycopodine (186) the enol-lactones 187 and 189 have been treated with complex hydride and have given, in good yield, the bicyclic compounds 188 and 190 respectively[66]. The enol-lactone reduction route was found to be especially useful in the preparation of 188, since standard acid- or base-catalysed aldol closures of 191 were quite useless, the ketal being unstable to acidic conditions, and the 1,5-dicarbonyl system undergoing a

retro-Michael degradation in base. Yet another example of its use is in the conversion of 192 to 193[67], a diol derivative in the tricyclo(5,3,1,1,^{2,6}) dodecane system, whose interesting conformational aspects are being currently investigated in these laboratories. In this case, the methyl substituent was incorporated in the 2-position of 192 in order to fulfil the necessary requirement of having an exocyclic enol double bond and lithium aluminium hydride was used in place of complexed reagent. Only one example of reduction of an enol-lactone whose parent keto-acid is not a cyclohexanone derivative but a cycloheptanone derivative has come to our attention. The lactone 194 was converted to the ketol 195 smoothly and in good yield[68], the ketol being of use as an intermediate in a projected synthesis of allohimachalol(196).

Finally, there have been two references in the recent literature to reductive cyclisations of enol-lactones. The first, by Mazur[69] concerned the cyclisation, using complex hydride, of certain steroid enol-lactones (197) to the bicyclic ketols (198) for comparison purposes. The second, by Fujimoto[65] reported the treatment of Turner's lactone (180) with lithium aluminium hydride from which he obtained a diol 199. Oxidation furnished a dione (183) melting at 113-114°(identical with our value). The stereochemistry of the hydroxyls of the diol is unknown to him, although he reports that no internal hydrogen bonding was apparent. We suggest that the stereochemistry is that shown in

200, caused by hydride of the ketol aluminate (201) attacking the bridgehead carbonyl group stereospecifically to give 200.

Treatment of either axial or equatorial 2-hydroxy-1,5-dimethylbicyclo(3,3,1)nonan-9-one (85 or 86;R=H), with methanolic potassium hydroxide gave an identical mixture of ketols (g.l.c. analysis of the acetylated product mixture showed the ratio, equatorial:axial=1.8:1). This equilibration presumably took place via the open keto-aldehyde (202;R=CH_3) giving a predominance of the thermodynamically more stable epimer.

Any mechanism proposed for the reductive rearrangement must, therefore, explain the production of the thermodynamically less stable epimer exclusively (the small amount of equatorial ketol formed, we believe, is due to some technical fault, possibly a little moisture in the reaction), as well as the stereochemistry the enolic double bond must have, before rearrangement takes place. That the rearrangement does not follow a course which first forms the keto-aldehyde (202;R=CH_3 or H) which is then cyclised under the reaction or work-up conditions is evident because 202(R=H) is formed in, and is stable to, the conditions of the reduction of the tetrasubstituted nor-methyl enol-lactone (159).

It is generally agreed that the first step in hydride reduction is attack on the carbonyl moiety by hydride ion giving the aluminate (203). Since we cannot postulate an acid-catalysed aldol cyclisation, this only leaves an explanation based on intramolecular rearrangement. A mechanism of the type

shown in 204 including, essentially, a four-centre transition state is not an appealing one for two reasons: the distance between carbons 3 and 10 is rather large for subsequent bond formation, and there is no apparent reason why a rearrangement of this type should give axial ketol exclusively.

A mechanism which does satisfy our requirements has, as its first step (after hydride attack), a transfer of the trialkyl aluminium residue from the oxygen on carbon-3 to the enolic oxygen (2) on carbon -1(205), giving 206. It is important that the bond between the enolic oxygen and the carbon originally bearing the carbonyl group should be broken without allowing the enol to "ketonise" since re-enolisation would cause a common intermediate to be formed in reducing 159 and 160, giving the same products from both. Examination of models shows that 206 is capable of rearranging in the cyclic manner shown, to give exclusively the axial aluminate (207).

In the reduction of 160, the formation of substantial amounts of 208(R=H) was a serious problem, whereas, reduction of 150 forms none of the equivalent compound 208($R=CH_3$).

Assuming that 150 and 160 both give bicyclo(3,3,1)nonane derivatives by the same mechanism, then it is apparent that there is a marked difference in the rates of cyclisation of 206 ($R=CH_3$) and 206(R=H). The dimethyl compound may cyclise rapidly to relieve steric crowding in the highly substituted intermediate 206($R=CH_3$). In 206 (R=H) however, no such crowding is apparent,

causing this intermediate to have an appreciably longer life-time than the dimethyl analogue (206;R=CH_3) so that attack by excess hydride giving 208 (R=H) is a process which could compete with the cyclisation process.

The configurations of steroidal bicyclic compounds obtained from ring-closure by the enol-lactone method are of special interest. In the reductive cyclisation of Turner's lactone (β -series of steroids), the stereochemistry of the starting enol-lactone is represented by 209. Ring closure between carbons-3 and 6 must proceed as shown (path a), so that the ring residue C_1-C_3 is axially fused to ring B; path b is impossible if a bicyclo(3,3,1)nonane moiety is to be formed. This places ring B of the product (210) in a boat configuration. Were such a reduction carried out on the enol-lactone of the α-series (211) then the twin-chair steroid (212) would be the expected product. Realisation of the difference in stereochemistry of the rearranged β- and α- enol-lactones (210 and 212) and the apparent similarity of reaction and products between Grignard reagents and complex hydride on δ-enol-lactones[62,63] has prompted investigation in these laboratories into the mechanism and stereochemistry of the Grignard reaction on δ-enol-lactones. Although this reaction has been studied by Fujimoto[62b] in a suitable model series (213), the exact composition of the products (reaction of the enol-lactone, 213 with phenyl magnesium bromide caused mono-addition and formation of a ketol, 214;

treatment with methyl magnesium bromide caused bis-addition and a mixture of diols, 215) was not determined. We feel that there is every likelihood that the product of mono-addition of Grignard reagent could have the hydroxyl axially disposed as in 216.

We also feel that a suitable explanation for a seeming anomaly in the steroid synthesis[63] is now at hand. Woodward, on treating the enol-lactone 217 (β-series) with methyl magnesium halide obtained the mono-adduct (218) which could be converted smoothly to the enone 219, with base. On treating 220 (α-series) with the same reagent, however, he obtained a poor yield (10%) of mono-adduct (221) and a large quantity of di-adduct (222). We believe that these results are due to the configurations of the bicyclic derivatives formed viz., the boat-chair configuration of 218 and the chair-chair configuration of 221. In 218, the central carbonyl is relatively hindered by the adjacent methyl, the hydroxyl (or the methyl) in the 3-position (steroid numbering) and the steroid rings B,C and D. Hydride reductions of the dione 183 and the ketol 181(R=H)(see above) lend weight to the assertions of steric hindrance of the central carbonyl. The former, on reduction with complex hydride, reduced only the 3-carbonyl, whereas the latter was reduced with difficulty and, using complex hydride, gave mainly the non-hydrogen bonded diol (223)(attack of hydride from the least hindered side). In 221, however, the central carbonyl is not hindered by rings B, C and D as was that of 218 above, but instead, has a face open to

attack by a second mole of Grignard reagent. We feel that this may well be the reason for bis-addition in the α-series.

Work is now progressing to gain more information about the Grignard rearrangement and to ascertain if the above is indeed a suitable explanation for the "anomaly".

Returning to our original objective of an efficient synthetic route to the unsubstituted bicyclo(3,3,1)nonane skeleton we became interested in a cyclisation technique[70] used to obtain the bicyclo(3,2,1)octyl moiety of giberellin derivatives (225). Cyclisations of the anhydride (224) with boron trifluoride in tetrahydrofuran and acetic acid furnished the dione 225. We thought, therefore, that a similar reaction on the mixed anhydride of 3-(2-oxocyclohexyl)-propionic acid (155) and carbonic or acetic acids (226) might supply the bicyclic dione (173). Formation of the anhydride of 155 and acetic acid, (226;R=CH_3), by the method of Inouye[71] failed because an attempted conversion of 155 to the acid chloride (227), with oxalyl chloride gave, instead, the enol-lactones (159 + 160)

The mixed anhydride of 155 and carbonic ester (226;R=OEt) was successfully prepared by the method of Wieland[72](ν_{max} 1820,1770, 1710). Distillation of this material, however, converted it smoothly to 154, the ethyl ester of 3(2-oxocyclohexyl)-propionic acid. Because of this, subsequent attempts to cyclise the anhydride were carried out on impure material. On treating the mixed anhydride (226;R=OEt) with boron trifluoride in both

tetrahydrofuran and acetic acid, the mixed enol-lactones (159 + 160) were obtained. Cyclisations of this type were abandoned.

It was obvious that reduction of the trisubstituted enol-lactone, $\Delta^{1,10}$-2-oxabicyclo(4,4,0)decen-3-one(160), with complex hydride, was unsuitable as a synthetic route to the bicyclo (3,3,1)nonane skeleton. In the first place, the exo-enol-lactone (160) was formed as the minor product of a mixture with 159, and even after separation, its conversion to 2-hydroxybicyclo (3,3,1)nonan-9-one (157;R=H) proceeded to the extent of only 15%.

The tetrasubstituted enol-lactone (159) could, however, be obtained in fair yield and reduction of 159, with complex hydride, gave keto-aldehyde(161) in good yield. It was decided to attempt to cyclise 161 in an aldol fashion to give the epimeric mixture of ketols (157 + 171;R=H). In reductions of the exo-enol-lactone (160) our efforts were mainly concerned with the formation of the axial ketol (157;R=H), the epimer which we knew would, as its tosylate, be converted smoothly to the olefin-ketone (158) with ethoxide. Cyclisations of 161, we thought, would give mixtures of 157 and 171(R=H) in which the thermodynamically more stable ketol (171;R=H) would be in preponderance. To convert this mixture to enone we proposed to convert the mixture of ketols (157+171;R=H) to thermally unstable esters such as carbonates, xanthates or acetates and subsequently to pyrolyse the mixture. Such pyrolyses are known to proceed through cyclic mechanisms (228), a neighbouring hydrogen

atom in a cis-configuration, being essential for smooth pyrolysis. Inspection of models of suitable esters of the epimeric 2-hydroxy-bicyclo(3,3,1)nonan-9-ones (229+230) reveals the presence of a hydrogen atom in a cis-relationship on the 3- position in both cases.

Cyclisation of 161 was attempted with several basic and acidic reagents, although, because of the strong possibility of retro-Michael reactions on the 1,5-dicarbonyl system of the keto-aldehyde (161), basic reagents were not favoured. Cyclisation with methanolic potassium hydroxide gave a complex mixture of products from which a 25% yield of a mixture of the ketols (157+171;R=H) contaminated with another compound (of identical t.l.c. mobility) could be separated by chromatography. Other catalysts tried included triethylamine in benzene, pyridine, pyridine and toluene-p-sulphonyl chloride, concentrated sulphuric acid, hydrochloric acid in dioxan and hydrochloric acid in acetic acid. The closures were attempted at a variety of temperatures and, because of the susceptability of 161 to oxidation, under an atmosphere of nitrogen. All the cyclisation media listed, met with some success but this was, in the main, limited. Unlike the other reagents, concentrated sulphuric acid was intended to cyclise keto-aldehyde 161 to ketols (157+171;R=H) and dehydrate these, giving olefin-ketone (158) in one reaction (See Introduction to Part I Section I). The olefin-ketone (158) was, in fact, obtained from treatment of 161 with sulphuric acid but in

poor (12%) yield, and contaminated with polymeric product. The two most successful cyclisation agents were hydrochloric acid in acetic acid and in dioxan. The former gave a good yield (80%) of very clean cyclised material of which, unfortunately, a large part (~ 60%) was the acetates of the epimeric bicyclic ketols (157+171;R=A_c). Attempts to convert the keto-acetates to the ketols by hydrolysis with methanolic hydrochloric acid met with a complete lack of success.

The best yield (42%) of cyclised material was obtained by treating 161 with hydrochloric acid in dioxan at room temperature. The ketols (157+171) were, however, contaminated with another compound, as had been the mixture obtained by treatment of 161 with methanolic potassium hydroxide. The mixture of three products from cyclisation with hydrochloric acid/dioxan was treated with toluene-p-sulphonyl chloride in pyridine giving a mixture of three tosylate esters. Chromatography on silica gel supplied a pure sample of the most polar tosylate as a crystalline solid (m.p. 121-122°) identical by infra red and mixed melting point with 157 (R=Ts).

Of the remaining tosylates, one was suspected of being 171 (R=Ts). The mixture was therefore treated with sodium ethoxide for five minutes to convert 171 (R=Ts) to the olefin-ester (174), leaving the third tosylate untouched. The mixture of 174 and the third tosylate were easily separated and the olefin-ester was identified by infra red and g.l.c. comparison against

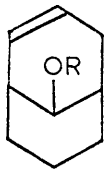
authentic olefin-ester. The third and unknown tosylate (m.p.127-128°) exhibited spectral properties (i.r.1712,1186,1175cm.-1 mass spectral parent, 444) consistant with its having a dimeric, unsaturated mono-keto-tosylate structure. Prolonged treatment of this tosylate with ethoxide gave the tosylate back unchanged, and the compound was not further investigated.

Cyclisation attempts were ceased after publication by Cope[54] of the synthesis of 161 and convertion of this to ketols (157+171; R=H). By a controlled Michael reaction of acrolein with the enamine of cyclohexanone, Cope obtained 161 and not the bicyclic amine (231) obtained by Stork[60] from this reaction. Treatment of 161 with hydrochloric acid (7N) at 0° in an atmosphere of nitrogen supplied a good yield of ketols (157+171;R=H) which Cope reported as being almost exclusively 171(R=H). In our hands, an identical cyclisation procedure furnished a mixture of ketols (77%), solid from the reaction mixture. Acetylation of this mixture and quantitative g.l.c. analysis showed the mixture to consist of axial: equatorial 1.1:1. Preparative t.l.c. separation of the mixed ketols confirmed this ratio. Cyclisation, by this method, supplied a very clean reaction product in which the epimeric ketols (157+171;R=H) were present, uncontaminated with the dimeric ketol we had obtained in cyclisations with methanolic potassium hydroxide or hydrochloric acid/dioxan. Ring closure of 161 with acid, by the method[54] of Cope, and subsequent t.l.c. separation of the mixture was used by us to obtain the equatorial

2-hydroxybicyclo(3,3,1)nonan-9-one (171;R=H) in a pure form (see above).

The mixed ketols (157+171;R=H) obtained by the Cope closure were converted to their carbonate esters (228;R=OEt) by means of ethyl chloroformate in pyridine. The mixture of carbonate esters, after purification by chromatography afforded, on pyrolysis at 300°, 9-oxobicyclo(3,3,1)non-2-ene (158) , in fair yield (51%).

The above method of obtaining the bicyclo(3,3,1) nonane skeleton was discarded in favour of the synthetic sequence of Foote and Woodward[59] to obtain 158 (described in SectionII). This sequence was published some time after the above work was started.



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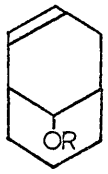

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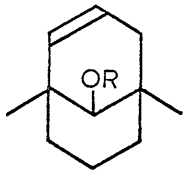

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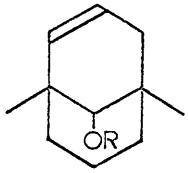

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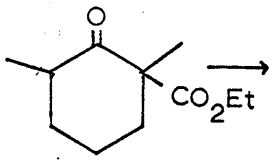

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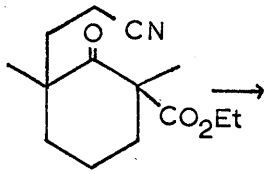

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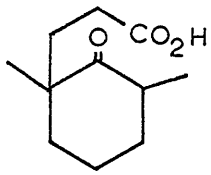

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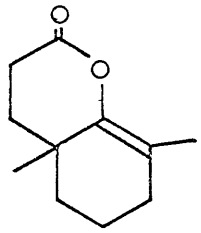

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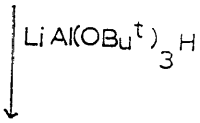

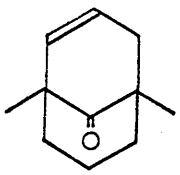

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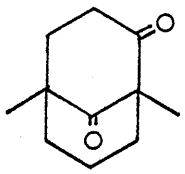

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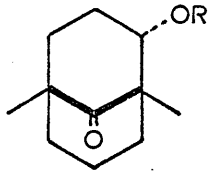

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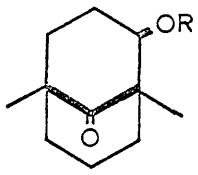

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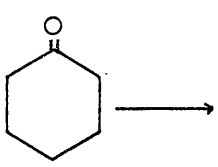

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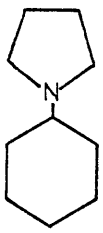

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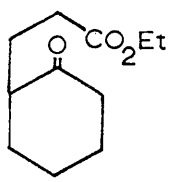

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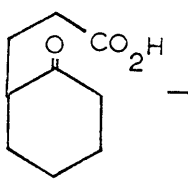

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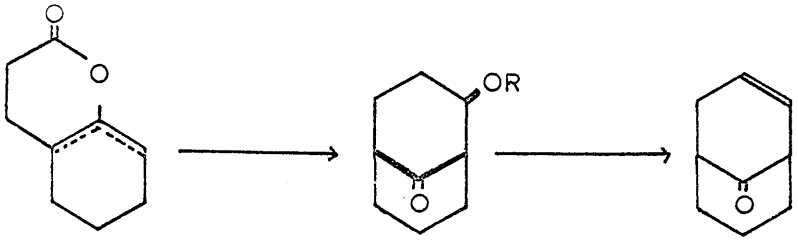

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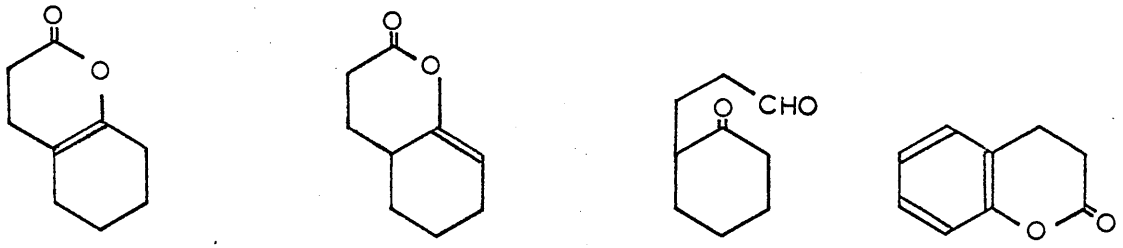

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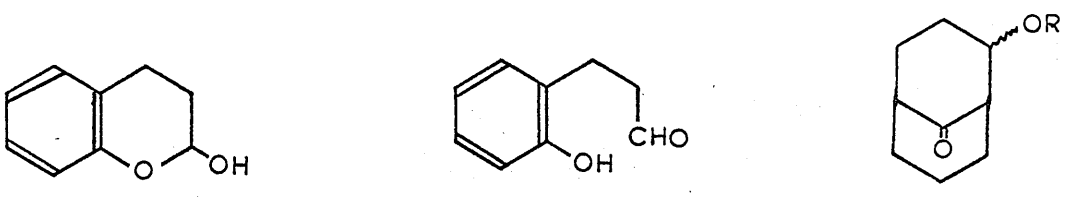

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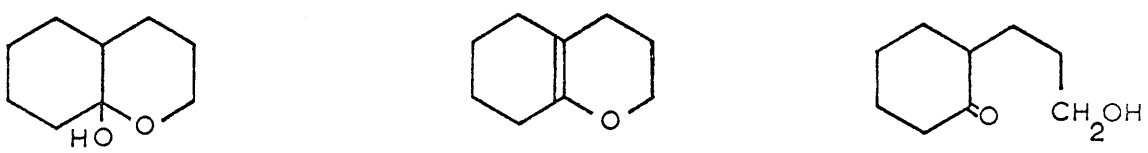

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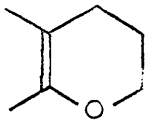

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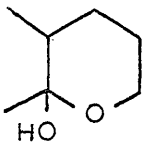

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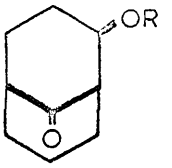

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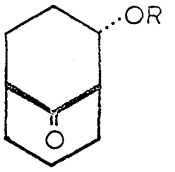

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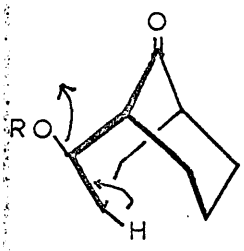

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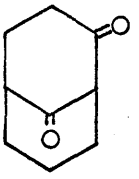

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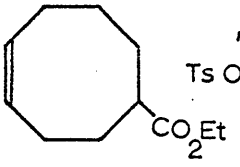

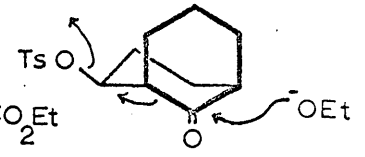

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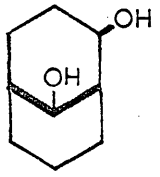

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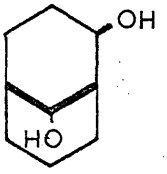

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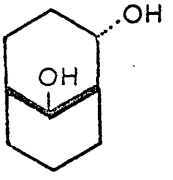

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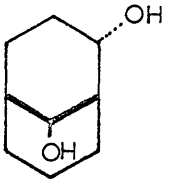

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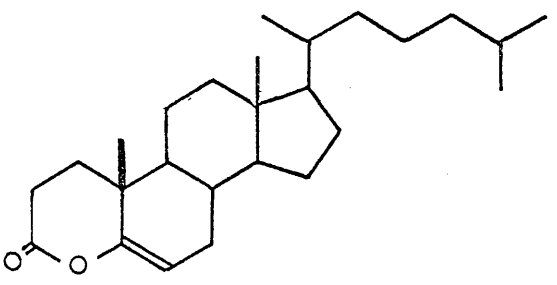

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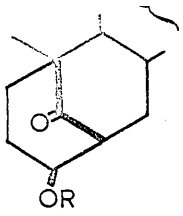

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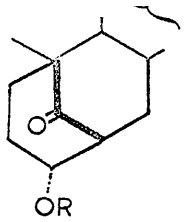

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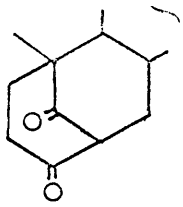

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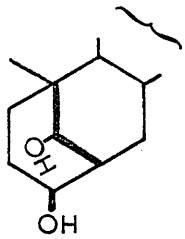

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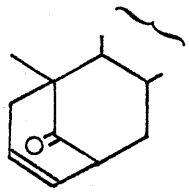

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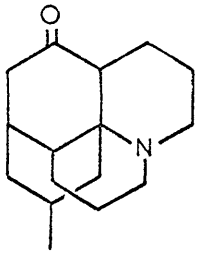

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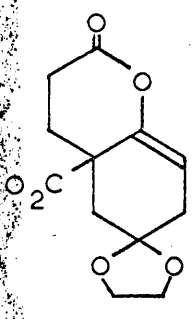

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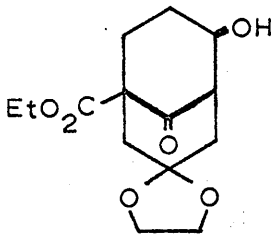

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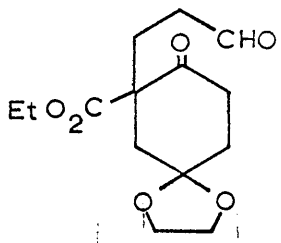

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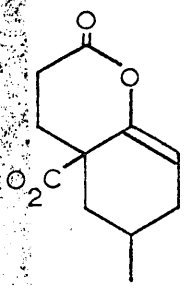

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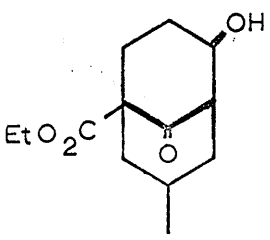

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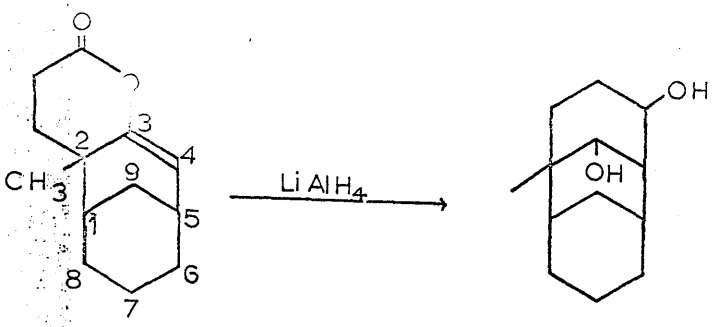

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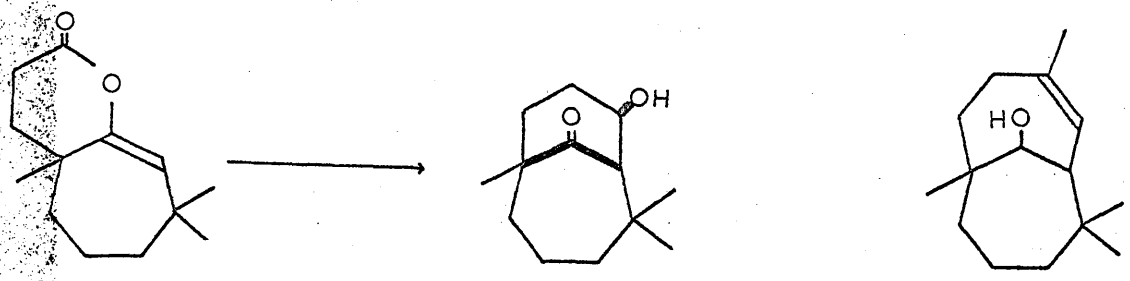

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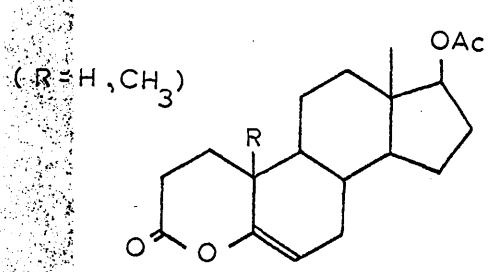

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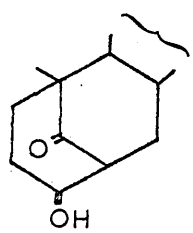

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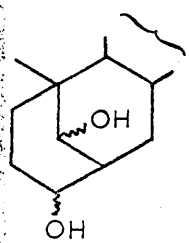

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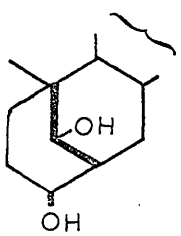

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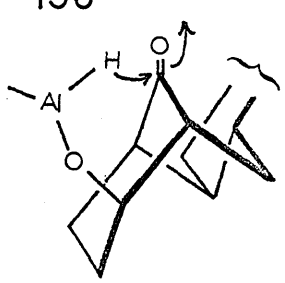

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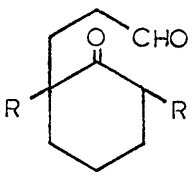

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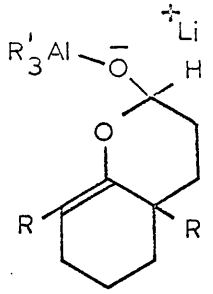

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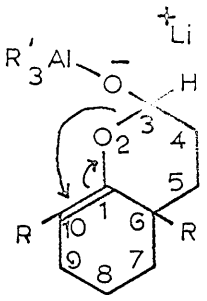

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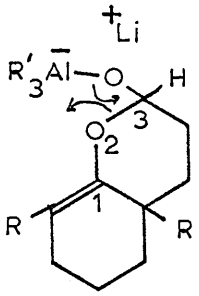

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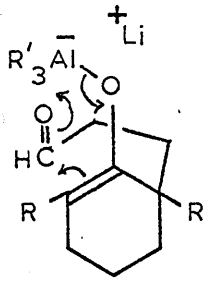

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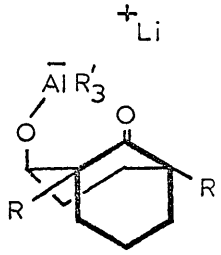

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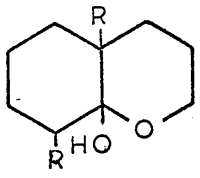

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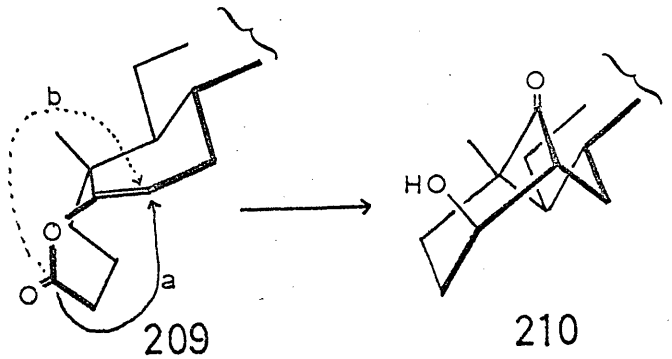

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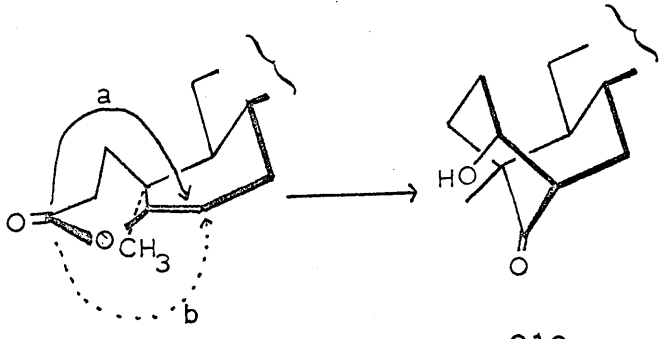

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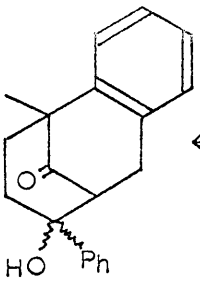

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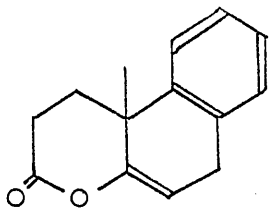

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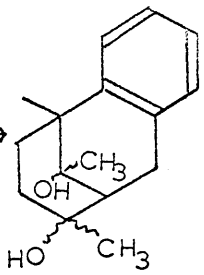

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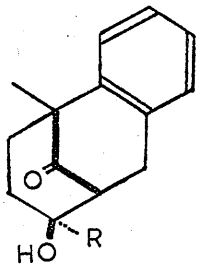

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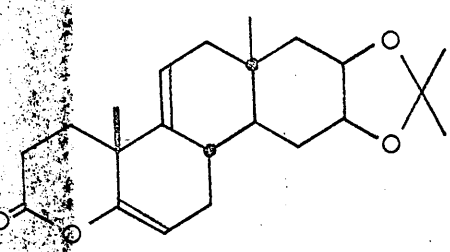

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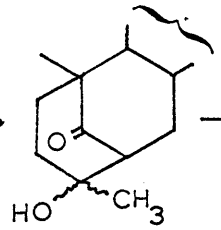

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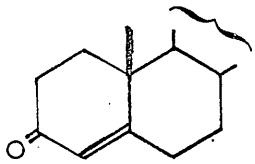

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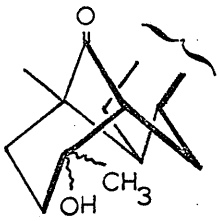

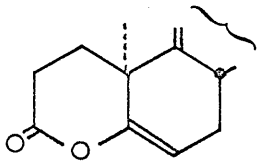

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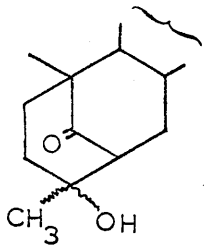

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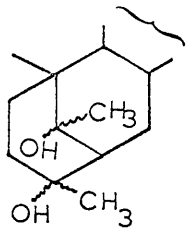

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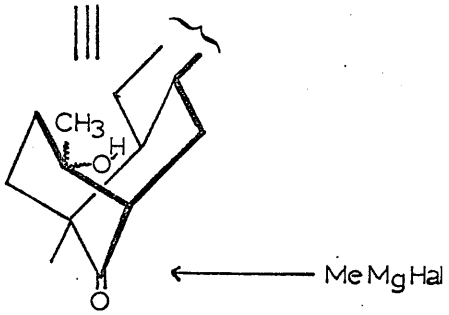

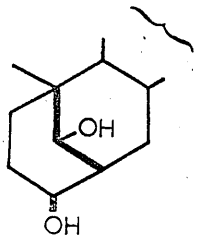

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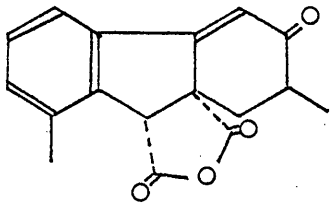

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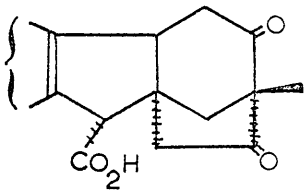

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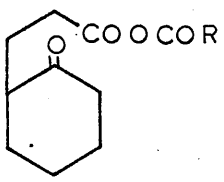

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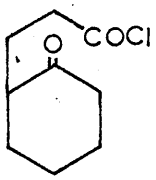

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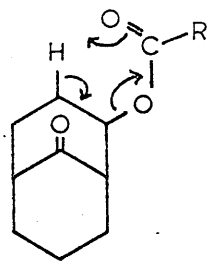

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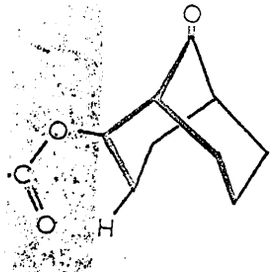

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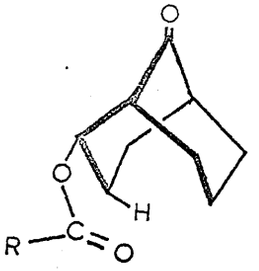

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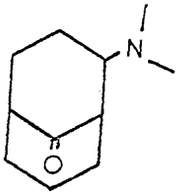

231

EXPERIMENTAL

Ethyl 3-(2-Oxocyclohexyl)-propionate (154)

Ethyl 3-(2-oxocyclohexyl)-propionate was prepared by the method of Stork[52]

3-(2-Oxocyclohexyl)-propionic acid (155)

Ethyl 3-(2-oxocyclohexyl)-propionate (154, 100g) was heated under reflux for 7 hours with hydrochloric acid (7N,1500ml). After cooling the reaction mixture, aqueous sodium hydroxide (6N,1l) was added to reduce the acidity, and the mixture was then extracted with ether (3 x 500 ml). The combined ethereal extracts were washed with sodium carbonate solution until the washings were basic and the sodium carbonate layer was then acidified and extracted thoroughly with ether (3 x 250 ml). The ethereal extract was washed with saturated brine solution and dried. Solvent removal gave a yellow oil (84g) which solidified on standing. Recrystallisation from light petroleum (60-80) gave 3-(2-oxocyclohexyl)-propionic acid (155) as plates m.p. 60-62° (Literature[53], m.p. 60-61°).

$\Delta^{1,6}$- and $\Delta^{1,10}$-2-Oxabicyclo (4,4,0) decen-3-one (159 and 160)

3-(2-Oxocyclohexyl)-propionic acid (155,10g) and freshly fused solium acetate (0.5g) in acetic anhydride (250ml) was heated under reflux for 4 hours. After removal of the acetic anhydride by azeotropic distillation with xylene under reduced pressure, the residual brown oil was taken up in ether (200ml) and washed with brine, saturated sodium hydrogen carbonate solution, brine and dried.

Removal of the solvent and distillation gave a water clear oil (7.4g), b.p. 87-89°/0.6 mm. n_D^{26} 1.5023 (Literature[53] n_D^{26} 1.5026). The oil was adsorbed on silica gel (220g) from light petroleum (60-80) and elution with ether-light petroleum (60-80) (1:4) gave $\Delta^{1,6}$-2-oxabicyclo (4,4,0) decen-3-one (159,5.2g), b.p. 86°/0.5 mm. n_D^{20} 1.5043; ν_{max}(CCl_4) 1772, 1709,1152,1115. (Fd: C, 70.37; H,7.91 $C_9H_{12}O_2$ requires C,71.05; H,7.95%).

Further elution with the same solvent gave first a mixture of compounds 159 and 160 (2.7g) and then $\Delta^{1,10}$-2-oxabicyclo (4,4,0) decen-3-one (160,1.3g) which was sublimed under high vacuum to give a white solid, m.p. 42-43°; ν_{max}(CCl_4) 1766,1683, 1150, τ 4.73 (1 proton multiplet). (Fd: C,70.55; H,7.65 $C_9H_{12}O_2$ requires C,71.05; H,7.95%)

Both $\Delta^{1,6}$-2-oxabicyclo (4,4,0) decen-3-one (159) and $\Delta^{1,10}$-2-oxabicyclo (4,4,0) decen-3-one (160), on treatment with aqueous sodium hydroxide in the cold and subsequent acidification, gave a keto-acid identical with 3-(2-oxocyclohexyl)-propionic acid (155) by melting point and mixed melting point.

3-(2-Oxocyclohexyl)-propionaldehyde (161)

A suspension of lithium hydridotri-t-butoxyaluminate (22.1g) in anhydrous tetrahydrofuran (150ml) was added dropwise, in a nitrogen atmosphere, over 2 hours to a stirred solution of $\Delta^{1,6}$-2-oxabicyclo (4,4,0) decen-3-one (159,12g) in tetrahydrofuran (75 ml) chilled to -70°. The reaction mixture was stirred at

room temperature for a further 15 hours, acidified with aqueous hydrochloric acid (6N, 25ml) and thoroughly extracted with ether (3 x 150 ml). The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent gave a pale yellow oil (10.7g), which, on distillation afforded 3-(2-oxocyclohexyl)-propionaldehyde (161, 8.0g), b.p. 86-89°/0.8mm. n_D^{23} 1.4743 ν_{max}(CCl_4) 2718, 1732,1715 cm.$^{-1}$ The 2,4-dinitrophenylhydrazone crystallised as needles from ethyl acetate, m.p. 199-200°, (Literature[54] b.p. 83-85°/0.7 mm. n_D^{25} 1.4743, 2,4-dinitrophenylhydrazone, m.p.193-195°)

1-Hydroxy-2-oxabicyclo (4,4,0) decane (166)

To a stirred suspension of lithium aluminium hydride (0.13g) in anhydrous ether (10 ml) was added dropwise a solution of $\Delta^{1,6}$-2-oxabicyclo (4,4,0) decen-3-one (159,0.5g) in anhydrous ether (20 ml) over 30 minutes. After the addition, the solution was heated under reflux for 2 hours and then cooled and carefully acidified with hydrochloric acid (6N). The ethereal layer was separated, washed with brine, saturated sodium hydrogen carbonate, brine and dried. Removal of solvent gave a yellow oil (0.48g) which solidified on standing. Recrystallisation from pentane afforded 1-hydroxy-2-oxabicyclo (4,4,0) decane (166) as colourless prisms m.p. 65-75° (dehydrates on warming); ν_{max}(CCl_4) 3590, 1077, 943. (Fd: C,68.50; H,9.9 $C_9H_{16}O_2$ requires C,69.19; H,10.32%)

Dehydration of 1-Hydroxy-2-oxabicyclo (4,4,0) decane (166)

Distillation of 1-hydroxy-2-oxabicyclo (4,4,0) decane (166) with a small crystal of iodine gave an unstable oil whose structure was tentatively assigned as $\Delta^{1,6}$-2-oxabicyclo (4,4,0) decene (167); ν_{max}(film) 1688 1157 cm^{-1}. On standing in air 167 readily hydrated to give the starting alcohol (166).

Reduction of $\Delta^{1,10}$-2-oxabicyclo (4,4,0) decen-3-one (160)

A solution of $\Delta^{1,10}$-2-oxabicyclo (4,4,0) decen-3- one (160,8.1g) in tetrahydrofuran (100 ml) was treated with lithium hydridotri-t-butoxyaluminate (18.7g) in tetrahydrofuran (100 ml) in the usual way. Normal work-up procedure afforded a neutral viscous oil (3.1g). Acidification of the sodium hydrogen carbonate washings gave 3-(2-oxocyclohexyl)-propionic acid (155, 3.8g). The neutral oil (3.1g) was adsorbed on silica gel (91g) from benzene - light petroleum (60-80) (1:1). Elution with ether-light petroleum (60-80) (3:2) afforded a yellow oil (1.70g) from which 1-hydroxy-2-oxabicyclo (4,4,0) decene (166) slowly crystallised. Recrystallisation from pentane afforded prisms m.p. 65-75° identical by i.r. spectrum with authentic 1-hydroxy-2-oxabicyclo (4,4,0) decane (see above).

Elution with ether gave a white semi-solid mixture of ketols (1.25g) which was separated by preparative t.l.c. giving pure axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157;R=H) which

crystallised from ethyl acetate - light petroleum (60-80) in prisms, m.p. 169-171° (sealed tube); $\nu_{max}(CCl_4)$ 3622,1731, 955 cm.$^{-1}$, τ , 5.75 (1 proton multiplet assigned to carbinyl proton; half-height width= 8 c.p.s). (Fd: C,70.15; H,8.70 $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%). A sample of the mixture of ketols from column chromatography was acetylated in the manner described below and the resultant mixture of keto-acetates was subjected to quantitative g.l.c. analysis on 10% apiezon "L" stationary phase at 150°. The acetates were present in the ratio, axial (157; R=Ac): equatorial (171; R=Ac)= 19:1.

Acetylation Procedure

In this section, several acetylations of pure compounds, or of mixtures, were carried out. The acetylation procedure used, was identical in all cases and is described below using the preparation of axial 9-oxobicyclo (3,3,1) nonan-2-yl acetate as an example. Careful control experiments showed it to cause no epimerisation in the systems examined.

A solution of axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157;R=H, 0.1g) in acetic anhydride (1 ml) containing dry pyridine (c.i ml) was left at room temperature for 12 hours. The solution was poured into water (10 ml) and left for 30 minutes. The resultant mixture was extracted thoroughly with ether (3 x 10 ml)

and the combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent gave a pale yellow oil (0.12g) which on distillation supplied axial 9-oxobicyclononan-2-yl acetate (157; (R=Ac) as a colourless oil, b.p. 110°-111°/0.04 m.m. n_D^{23} 1.4859; ν_{max} (film) 1720, 1703, 1235 cm.$^{-1}$, τ ,4.82 (1 proton multiplet assigned to carbinyl proton; half-height width= 8c.p.s). (Fd: C,66.85; H,7.85 $C_{11}H_{16}O_3$ requires C,67.32; H,8.22%)

Axial 9-Oxobicyclo (3,3,1) nonan-2-yl Toluene-p-sulphonate (157;R=Ts).

To a solution of axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157; R=H, 0.138g) in dry pyridine (2ml) was added toluene-p-sulphonyl chloride (0.17g). The reaction mixture was allowed to stand at room temperature for 5 days and was then extracted thoroughly with ethyl acetate (3 x 10 ml). The combined extracts were washed with hydrochloric acid (6N), brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent gave a yellowish solid (0.25g). Recrystallisation from methanol furnished axial 9-oxobicyclo (3,3,1) nonan-2-yl toluene-p-sulphonate (157; R=Ts) as colourless plates, m.p. 122-123°; $\nu_{max.}$(CCl_4) 1739, 1188, 1176, 929, 909 τ ,4.9 (1 proton multiplet assigned to carbinyl proton; half-height width = 6 c.p.s.). (Fd: C,62.65; H,6.65, $C_{16}H_{20}O_4S$ requires C,62.35; H, 6.55%)

9-Oxobicyclo (3,3,1) non-2-ene (158)

Sodium (0.035g) in dry ethanol (5 ml) was added to a stirred solution of axial 9-oxobicyclo (3,3,1) nonan-2-yl toluene-p-sulphonate (157; R=Ts, 0.25g) in ethanol (5 ml) at 60°. The solution was refluxed for 24 hours, cooled and acidified with acetic acid. Brine (10 ml) was added and the resultant mixture was extracted with light petroleum (2 x 10 ml). The remaining aqueous material was then extracted again with ethyl acetate (2 x 10 ml). Both organic layers were washed with brine and dried.

The petroleum extract, on careful evaporation at room temperature gave a yellow oil (0.085g) which was adsorbed on silica gel (3g) from light petroleum. Elution with ether-light petroleum (1:9) afforded 9-oxobicyclo (3,3,1) non-2-ene (158) as a clear yellow oil (0.06g) identical to an authentic sample prepared by the method of Foote and Woodward[59] by infra red spectrum and gas chromatographic retention time.

The ethyl acetate extract, on evaporation, gave the starting keto-tosylate (0.024g)

Equatorial 2-Hydroxybicyclo (3,3,1) nonan-9-one (171;R=H)

Treatment of 3-(2-oxocyclohexyl) propionaldehyde (161) with hydrochloric acid (7N) by the method of Cope[54] furnished a solid mixture of ketols which was separated by preparative t.l.c. into axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157; R=H) identical with that obtained above and equatorial 2-hydroxybicyclo (3,3,1) nonan-9-one (171; R=H) in a ratio of 157: 171 = 1.1:1 (by separation). Acetylation of the mixture obtained by closure and subsequent quantitative gll.c. showed the keto-acetates to be in the ratio 157 (R=Ac): 171 (R=Ac)= 1.18:1 which is in good agreement with the ratio obtained by separation.

The equatorial 2-hydroxybicyclo (3,3,1) nonan-9-one (171; R=H) was obtained as an oily unstable solid; ν_{max} (CCl_4) 3614,1719,1048 cm.$^{-1}$, τ , 6.05 (1 proton multiplet assigned to carbinyl proton; half-height width = 16 c.p.s.). The p-nitrobenzoate (171; R=$C_7H_4NO_3$) crystallised from light petroleum (60-80) as faintly yellow plates m.p. 111-113°. (Fd: C,63.52; H,5.76; N 4.31 $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.65; N, 4.62%).

Equatorial 9-oxobicyclo (3,3,1) nonan-2-yl acetate (171; R=Ac) was prepared in the usual manner and gave the acetate as an oil, b.p. 90°/06 mm. n_D^{22}= 1.4868, τ , 5.03 (1 proton multiplet assigned to carbinyl proton; half-height

width = 20 c.p.s) (Fd: C, 66.85; H, 7.85 $C_{11}H_{16}O_3$ required C,67.32; H, 8.22%).

Equatorial 9-Oxobicyclo (3,3,1) nonan-2-yl Toluene-p-sulphonate (171; R=Ts).

To a solution of 2-hydroxybicyclo (3,3,1) nonan-9-one (171;R=H, 0.05g) in pyridine (1ml) was added toluene-p-sulphonyl chloride (0.063g). The reaction mixture was heated at 90° for 1 hour and then left at room temperature for 48 hours. Normal isolation procedure gave 9-oxobicyclo (3,3,1) nonan-2-yl toluene-p-sulphonate (171; R=Ts) as an oil (0.045g) which could not be induced to crystallise; ν_{max} (film) 1715, 1170 cm.$^{-1}$

Treatment of Equatorial 9-Oxobicyclo (3,3,1) nonan-2-yl Toluene-p-sulphonate (171; R=Ts) with Ethoxide

Equatorial 9-oxobicyclo (3,3,1) nonan-2-yl toluene-p-sulphonate (171; R=Ts, 0.033g) was treated with sodium ethoxide in the manner described above for axial 9-oxobicyclo (3,3,1) nonan-2-yl toluene-p-sulphonate (157; R=Ts). The reaction mixture was heated at 60° for 5 minutes. During the addition and subsequent heating, a precipitate of the sodium salt of toluene-p-sulphonic acid was formed. Normal isolation techniques gave ethyl Δ^4-cyclo-octene-carboxylate (174, 0.014g) as a yellowish, sweet-smelling oil identical to an authentic sample prepared by the method of Stork[60]

by i.r. spectrum and g.l.c. retention time

Oxidation of Axial 2-Hydroxybicyclo (3,3,1) nonan-9-one (157;R=H)

A solution of axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157; R=H, 0.14g) in AnalaR acetone (7 ml) was stirred at 0°. A slight excess of Jones reagent[61] was added dropwise and the stirring continued for a further hour. The reaction mixture was poured into brine and extracted with ether. The ethereal extract was washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent gave a semi-solid oil (0.12g). Purification by preparative t.l.c. gave bicyclo (3,3,1) nonan-2,9-dione (173) as a low melting unstable solid. Sublimation under high vacuum afforded an analytical sample; $\nu_{max}(CCl_4)$ 1741, 1717 (Table 4 lists the carbonyl frequencies in different solvents). (Fd: C,70.70; H, 8.15 $C_9H_{12}O_2$ requires C,71.03; H, 7.95%).

Oxidation of Equatorial 2-Hydroxybicyclo (3,3,1) nonan-9-one (171; R=H)

Equatorial 2-hydroxybicyclo (3,3,1) nonan-9-one (171;R=H, 0.01g) was oxidised with Jones reagent[61] in the above manner. Identical isolation technique afforded an oil (0.009g) identical to bicyclo (3,3,1) nonan-2,9-dione (173) by i.r. spectrum and t.l.c. mobility.

Cis-Bicyclo (3,3,1) nonan-2,9-diol (176)

Axial 2-hydroxybicyclo (3,3,1) nonan-9-one (157;R=H, 0.066g) was treated with lithium hydridotri-t-butoxyaluminate (0.33g) in tetrahydrofuran (25 ml). After heating under reflux for 6 hours, the reaction was cooled, acidified with dilute hydrochloric acid (6N) and extracted with ether (3 x 15 ml). The The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent afforded a mixture of diols*. Separation of these by preparative t.l.c. gave cis-bicyclo (3,3,1)-nonan-2,9-diol (176) which crystallised from benzene-light petroleum (60-80) as colourless needles, m.p. 215-217° (sealed tube); ν_{max} (CCl_4, dilute solution) 3610, 3520 $cm.^{-1}$ (Fd: C,69.55; H,10.15 $C_9H_{16}O_2$ requires C,69.20; H, 10.30%).

Reduction of Equatorial 2-Hydroxybicyclo (3,3,1) nonan-9-one (171;R=H)

Equatorial 2-hydroxybicyclo (3,3,1) nonan-9-one (171;R=H, 0.01g) was reduced with complex hydride in the above manner. Identical work-up procedure supplied a mixture of diols (178 + 179, 0.009g), which exhibited no hydrogen-bonding at high dilution in the i.r.

*(176+177; 0.064g)

Reduction of Turner's Lactone (180)

A solution of Turner's Lactone (180; 1.87g) in dry tetrahydrofuran (50 ml) was treated with lithium hydridotri-t-butoxy aluminate (1.6g) in tetrahydrofuran (20 ml) in the manner described above. The semi-solid product (1.88g) was adsorbed on silica gel (75g) from benzene-light petroleum (60-80) (1:1). Elution with ether-light petroleum (2:1) separated a solid fraction (1:35g). By analytical t.l.c. it was evident that this was a mixture of two compounds. Separation by preparative t.l.c. supplied two pure ketols in a ratio of 16:1 by weight (neither the ketols nor their acetates could be separated by g.l.c. on several different stationary phases). Alternatively the more abundant ketol could be obtained pure by recrystallisation of the solid fraction from chromatography. The more abundant ketol, the axial steroid ketol (181;R=H) crystallised from light petroleum (60-80) as colourless needles, m.p. 183-185°; $\nu_{max}(CCl_4)$ 3606, 1715 cm.$^{-1}$, τ 5.85 (1 proton multiplet assigned to carbinyl proton; half-height width= 7 c.p.s.). (Fd: C, 80.30; H, 11.20 $C_{26}H_{44}O_2$ requires C, 80.35; H, 11.40%.

The less abundant ketol, the equatorial steroid ketol (182; R=H), obtained from preparative t.l.c. is described in detail below.

Toluene-p-sulphonate of Axial Steroid Ketol (181;R=Ts)

The axial steroid ketol (181; R=H, 0.07g) in dry pyridine (0.5 ml) was treated with toluene-p-sulphonyl chloride (0.04g) and left at room temperature for four weeks. The reaction mixture was poured on to brine and this was extracted thoroughly with ethyl acetate. The ethyl acetate extract was washed with hydrochloric acid (3N), brine, saturated sodium hydrogen carbonate solution, brine and dried. Careful removal of solvent at 40° supplied a semi-solid mixture (0.092g). Preparative t.l.c. of this mixture separated it into the toluene-p-sulphonate of axial steroid ketol (181;R=Ts, 0.042g) and the starting axial ketol (181;R=H, 0.046g). The toluene-p-sulphonate (181;R=Ts) resisted purification; ν_{max} (film) 1710, 1172 cm.$^{-1}$, τ , 5.08 (1 proton multiplet, assigned to carbinyl proton; half-height width= 7 c.p.s).

Steroid Olefin-ketone (185)

The axial steroid ketol (181;R=H, 0.086g) in pyridine (0.5 ml) containing toluene-p-sulphonyl chloride (0.035g) was heated at 90° for 11 hours and then left at room temperature for 36 hours. Identical isolation technique to that described above gave a yellowish semi-solid mixture containing starting ketol and a less polar compound. Preparative t.l.c. removed the ketol (181;R=H) from the less polar compound (0.039g) to which was assigned the olefin-ketone structure (185).

This was not obtained in a pure state; $\nu_{max}(CCl_4)$ 3030, 1726 (film) 699 cm.$^{-1}$, τ , 4.35 (wide multiplet assigned to the olefinic protons), mass spectral parent at 370 ($C_{26}H_{42}O$, molecular weight = 370)

Steroid Dione (183)

A solution of the axial ketol (181;R=H, 0.12g) in AnalaR acetone (10ml) was treated at 0° with a slight excess of Jones reagent[61] in the usual way. Normal isolation technique gave a crystalline product (0.118g). Recrystallisation from light petroleum supplied the dione (183) as needles, m.p. 111-112° (Literature[65], m.p. 113-114°). (Fd: C, 80.75; H, 10.80 $C_{26}H_{42}O_2$ requires C, 80.75; H, 10.95%).

Oxidation of Equatorial Steroid Ketol (182;R=H)

The equatorial steroid ketol (182;R=H, 0.01g) was treated with Jones reagent[61] in the usual manner. Standard isolation technique supplied the dione (183; 0.009g) identical to the sample obtained above by i.r. and t.l.c. mobility.

Equatorial Steroid Ketol (182;R=H)

A solution of the above diketone (183;92 mg) in tetrahydrofuran was treated with a suspension of lithium hydridotri-t-butoxyaluminate (67 mg) in tetrahydrofuran (2ml) and the reaction mixture heated under reflux for 2 hours. Normal acidic work-up (see above) gave a semi-solid mixture of ketols (181 and 182; R=H). Separation of these by preparative t.l.c. supplied the axial ketol (181; R=H; 10 mg), and a less polar ketol (70mg). Recrystallisation of this compound from ether-light petroleum afforded the equatorial steroid ketol (182; R=H), m.p. 165-167 (sealed tube); ν_{max} (CCl_4), 3606 1715 cm^{-1}, τ , 6.15 (1 proton multiplet assigned to the carbinyl proton; half-height width= 20 c.p.s.). (Found: C,80.01; H,11.19 $C_{26}H_{44}O_2$ requires C,80.35; H,11.41%)

The Toluene-p-sulphonate (182; R=Ts) of the equatorial steroid ketol was prepared in the usual manner and crystallised from light petroleum as colourless needles m.p. 165-167°; ν_{max} (CCl_4) 1722, 1188,1176 $cm.^{-1}$, τ ,5.56 (1 proton multiplet assigned to the carbinyl proton; half-height width= 21c.p.s.). (Found: C,73.05; H,9.10, $C_{33}H_{50}O_4S$ requires C, 73.05; H,9.30%)

Reduction of Axial Steroid Ketol (181; R=H)

A solution of the axial ketol (181; R=H, 0.11g) in anhydrous ether (10 ml.) was added dropwise to a suspension of lithium aluminium hydride (35mg.) in ether (5 ml.) and the mixture heated under reflux for 1 hour. Aqueous hydrochloric acid (6N;3ml.) was then added and the organic layer separated, washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. The solvent was removed giving a semi-solid mixture of diols. The diols were separated readily by preparative t.l.c. and the less polar compound was recrystallised from ethyl acetate - light petroleum (60-80) to give the cis-diol (184) as needles, m.p. 200-202° (sealed tube); ν_{max}(CCl_4, high dilution), 3611, 3512cm^{-1}. (Found: C,80.21; H,11.63 $C_{26}H_{46}O_2$ requires C, 79.94;H,11.87%).

The more polar diol, the non-hydrogen bonded diol (200), though obtained in an apparently pure state could not be induced to crystallise, and was not examined further.

Reduction of Equatorial Steroid Ketol (182;R=H)

A corresponding reduction of the equatorial ketol (182;R=H, 11mg.) gave a solid mixture of diols which exhibited no intra-molecular hydrogen bonding at high dilution in the infra red; ν_{max} (CCl_4 at high dilution), 3614cm.$^{-1}$.

Mixed Anhydride of 3-(2-Oxocyclohexyl)-propionic acid and Ethyl Carbonate. (226;R=OEt)

3-(2-Oxocyclohexyl) propionic acid (1g.) and triethylamine (3ml.) were dissolved in dry toluene (40ml.) and cooled to 0°. Ethyl chloroformate (1.5ml.) was added slowly to the solution and the mixture allowed to stand at room temperature for 12 hours. The mixture was again cooled to 0°, and the precipitated

triethlamine hydrochloride filtered off. Removal of solvent from the filtrate yielded the mixed anhydride (266;R=OEt,1.65g.) as a brown oil, ν_{max}(film) 1820, 1770 and 1710cm.$^{-1}$

Attempted Cyclisation of Mixed anhydride. (226;R=OEt)

The crude mixed anhydride (1.5g.) in dry tetrahydrofuran (40ml.) with boron trifluoride etherate (12ml.) was heated under reflux for 1 hour. The solution was cooled, and poured into brine. The resulting mixture was extracted with chloroform (2 x 30ml.) and the extract was washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent supplied the mixed enol-lactones (159 + 160) as a brown oil identical with an authentic sample by i.r. and t.l.c. mobility.

Cyclisation of 3-(2-Oxocyclohexyl)-propionaldehyde (161) with Hydrochloric Acid in Dioxan.

A solution of 3-(2-oxocyclohexyl)-propionaldehyde (161; 6.3g.) in dioxan (40ml.) and aqueous hydrochloric acid (6N;10ml.) was stirred at room temperature, under an atmosphere of nitrogen for 4 hours. The mixture was poured into brine and extracted with ether (3 x 100ml.). The combined ethereal extracts were washed with brine, saturated sodium carbonate solution, brine and dried. Removal of solvent furnished a brown oil (4.0g.).

The oil was adsorbed on silica gel (120g.) from ether-light petroleum (1:5). Elution with ether supplied the epimeric 2-hydroxybicyclo(3,3,1)nonan-9-ones (157 + 171;R=H) together

with another compound of identical thin-layer chromatographic mobility as a yellow oil (2.9g).

Treatment of Products from above Cyclisation with Toluene-p-sulphonyl Chloride.

The mixture from the above cyclisation (1.4g.) was treated with toluene-p-sulphonyl chloride (1.92g.) in pyridine (7ml.), heated on a steam-bath for 1 hour and left for 24 hours at room temperature. The reaction mixture was poured into brine and extracted thoroughly with ethyl acetate (3x100ml.). The combined extracts were washed with aqueous hydrochloric acid (6N), brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent at 50° under reduced pressure supplied a dark brown oil (2.1g.) containing three tosylate esters.

The oil was adsorbed on silica gel (84g) from benzene-light petroleum (1:1). Elution with ether-light petroleum (3:2) afforded a yellow oil (1.17g.) containing the two less polar tosylates. Elution with light petroleum (4:1) supplied an oil, which on trituration with ether gave axial 9-oxobicyclo-(3,3,1)nonan-2-yl tosylate (157;R=H,0.2g.) as a solid, which on recrystallisation, furnished plates, m.p. 122-123°, identical to an authentic sample by i.r. and mixed melting point.

Treatment of Mixed Toluene-p-sulphonate Esters with Ethoxide.

The mixed esters (0.67g.) obtained from chromatography above

was treated with sodium ethoxide in the manner described above for treatment of equatorial 9-oxobicyclo(3,3,1)nonan-2-yl tosylate with ethoxide. The reaction mixture was worked-up in the usual manner (using ether as the extracting solvent) and furnished a sweet-smelling yellow oil (0.48g). The oil was adsorbed on silica gel (15g.) from benzene-light petroleum (1:4). Elution with ether:light petroleum (1:9) supplied ethyl Δ^4-cyclo-octene-carboxylate identical with an authentic sample prepared by the method of Stork[60] by i.r. and g.l.c. mobility.

Elution with ether-light petroleum (1:1) supplied a colourless crystalline keto-tosylate (0.30g.) which, crystallised as prisms from methanol, m.p.127-128°; $\nu_{max}(CCl_4)$, 1712 1186, 1175 $cm.^{-1}$ Mass spectral parent, 444. The compound was not further investigated.

Ethyl, 9-oxobicyclo(3,3,1)nonan-2-yl carbonate (228;R=OEt)

Ethyl chloroformate (2ml.) was added dropwise to the epimeric 2-hydroxybicyclo(3,3,1)nonan-9-ones (165;R=H,0.34g.), (from cyclisation of 161 by method of Cope[54], described above) in dry pyridine at -10°. During the addition, pyridine hydrochloride was precipitated. The mixture was left 20 hours at 5°, and then acidified with a mixture of brine and aqueous hydrochloric acid (6N)(1:1). The mixture was extracted thoroughly with light petroleum (3 x 20ml.) and the combined extracts washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent at 50° under

reduced pressure furnished a pale yellow oil (0.49g.). The oil was adsorbed on silica gel (15g.) from light petroleum and elution with ether-light petroleum (1:1) supplied ethyl, 9-oxobicyclo(3,3,1) nonan-2-yl carbonate (228;R=OEt) as a colourless oil (0.31g), ν_{max}(film 1740,1720, 1280, 810cm.$^{-1}$.

9-Oxobicyclo(3,3,1)non-2-ene (158)

The carbonate esters obtained above (228;R=OEt,0.31g.) in silicone oil (M.S.550;1ml.) were heated to 300°. The vapours emitted were passed to a trap cooled in liquid nitrogen. Vigourous effervescence took place at first, but after one hour this had subsided. The cold trap was rinsed with ether and the resulting solution evaporated to give 9-oxobicyclo(3,3,1)non-2-ene (158;.10g.).

SECTION II

Homoallylic Participation in Bicyclo,(3,3,1) non-2-en-9-yl Derivatives.

The classic example of homoallylic participation, was reported by Winstein to occur in the solvolysis of 7- norbornenyl derivatives[23]. Because of the unusual stereochemistry of the norbornenyl system, the degree of symmetrical overlap between the π-electrons of the double bond and the developing carbonium ion is optimal, providing maximum anchimeric assistance to ionisation. There are, however, many other examples of homoallylic participation in which the relationship of the double bond with the developing ion is not quite as favourable for overlap (see General Introduction). Because of our interest in this subject and the availability of suitable bicyclo(3,3,1)non-2-en-9-yl derivatives we decided to find whether or not such participation would take place in this semi-rigid framework, where the double bond would appear to be less favourably oriented than in 53 for maximum overlap.

In the General Introduction, it was pointed out that there are indications, in bridged bicyclic systems that as the rings become larger than in the norbornyl system, the importance of non-classical ions as reaction intermediates becomes less. We felt that an investigation of homoallylic participation in the bicyclo(3,3,1)nonane system might allow us to comment on the above trends.

After this work had been started, two papers of immediate importance in this subject were published. The first, by Le Bel and Spurlock[73], concerned the solvolysis of syn- and anti- bicyclo(3,2,1)oct-2-en-8-yl tosylates (232 and 233;R=Ts), and homoallylic participation in solvolysis of the anti compound (233;R=Ts) was claimed. The other, by Foote and Woodward[59] described the solvolysis of 234,235, and 236 (R=Ts) in which 235 and 236 (R=Ts) were found to be anchimerically assisted by methylene participation from the anti six-membered ring.

The syn- and anti- 1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl methanesulphonates(mesylates) (145 and 146;R=Ms=SO_2CH_3) and the corresponding saturated mesylate(237;R=Ms) had been prepared by Martin[50], by methods outlined in the Introduction to Section I Part II, and were readily available to us. The substitution on the bridgeheads was an unnecessary if not an undesirable feature, although it appeared on inspection as if these would not affect participation of the type envisaged. At the time this work was started, the unsubstituted skeleton had not been synthesised and so a solvolytic study of 145 and 146 (R=Ms) was undertaken to ascertain if homoallylic participation did, in fact, take place in this system. For reasons which will become obvious, this was changed to an investigation of the corresponding nor-methyl compounds, the syn- and anti- bicyclo(3,3,1)non-2-en-9-yl tosylates (143 and 144;R=Ts)

TABLE 5

Rates of Ethanolysis of Mesylates in the 1,5-Disubstituted Bicyclo (3,3,1) nonane System

Mesylate (R=Ms)	$k \times 10^7 sec^{-1}$	Relative Rate
Cyclohexyl	1.9	1.0
Syn-1,5-dimethylbicyclo-(3,3,1) non-2-en-9-yl (145)	24.0	12.6
Anti-1,5-dimethylbicyclo-(3,3,1) non-2-en-9-yl (146)	25.4	13.4
1,5-Dimethylbicyclo-(3,3,1) nonan-9-yl (237)	214	113

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DISCUSSION

The amount of information obtained from analysis of the products of solvolysis of epimeric 1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl mesylates (145;R=Ms and 146;R=Ms) in acetic acid/sodium acetate was disappointing. Both compounds rearranged to give mixtures of the same three isomeric dienes. On standing the mixtures rapidly polymerised and also underwent hydroperoxidation. The hydrocarbon mixture was presumed to consist of three of the four dienes (238-241) which can be derived by simple Wagner-Meerwein migration and elimination (processes shown). Clearly nothing concerning possible double bond participation could be learned from a more rigourous examination of such a product mixture.

The rates of ethanolysis of 145,146 and 237(R=Ms) were measured in this department by Anderson[74] using a conductometric method and the results obtained are shown in Table 5. It will be noted that, to all intents and purposes, the rates for 145 and 146(R=Ms) are the same while that for 237 is faster by a factor of 8.7 at 25°. All three compounds solvolyse faster than cyclohexyl tosylate. This is quite different from both the norbornyl system[23] and the bicyclo(3,2,1)octyl system[73] where the saturated compounds solvolyse more slowly than cyclohexyl tosylate and is apparently due to a)methylene participation b) a larger C_1-C_9-C_5 angle than found in either 53 or 233 and c) to the heavy substitution at the bridgehead of 145, 146 and 237(R=Ms).

It would appear, from an examination of the rates, that anchimeric assistance to ionisation in 146(R=Ms) by the double bond does not definitely take place, since both unsaturated mesylates solvolyse at approximately the same rate. The saturated bicyclo(3,3,1)nonane skeleton (237) has severe non-bonded 3,7-methylene interactions[18], which do not exist in the unsaturated compounds 145 and 146. Apart from angle strain and inductive charges, relief of this strain may well be an additional driving force allowing the saturated compound (237) to solvolyse faster. It would appear in cases of the unsaturated mesylates that either no homoallylic participation was taking place or that both 145 and 146 (R=Ms) were being assisted, the first by methylene participation and the second by homoallylic participation to about the same extent.

Clearly, no further conclusions could be drawn with any degree of accuracy. The fact that the mesylates 145 and 146 (R=Ms), on solvolysis, gave only hydrocarbon products meant that little could be gained from separating and identifying the components of the mixtures. We suspected that the rearrangement to give hydrocarbons was due mainly to the substitution on the bridgehead positions which makes compounds of this type doubly neopentyl, therefore rearranging rapidly to give tertiary carbonium ions.

The rate results had interested us so much that we decided to turn our attention to the unsubstituted bicyclic compounds

143,144 and 236 (R=Ts). We felt that on solvolysis these would be less ready to rearrange, and, any conclusions we drew from them would be much more easily correlated with other pertinent investigations. There was, at this time, no adequate route to 143, 144 (R=H) or the olefin-ketone (158). Our attempts (Section I part II) to develop an efficient synthesis of this ketone ceased on publication[59] of such a scheme.

The synthesis (231→158) utilised a reaction discovered by Stork, namely treatment of cyclohexanone enamine (153) with acrolein to give the bicyclic keto-amine, 231. The authors then converted 231 to the ketal (242) and thence to the N-oxide (243). Pyolysis of 243 gave the olefin-ketal (244) which could be converted to the desired olefin (158) by hydrolytic treatment. This eminently satisfactory scheme has now been used successfully in this laboratory to prepare large quantities of 158.

Reduction of the olefin-ketone (158) with lithium aluminium hydride gave 143 (R=H)+ 144 (R=H) with the anti-olefin-alcohol in predominance. Separation on silica-gel showed the ratio to be approximately 144 (R=H):143 (R=H) = 5:1. The syn-olefin-alcohol structure (143;R=H) was assigned to the more polar alcohol m.p. 82-83°, mainly on i.r. evidence. As in the case of 145 (R=H)[40], the more polar compound exhibited internal hydrogen bonding at high dilution in the i.r., due to interaction between the π - electrons of the double bond and the hydrogen of the hydroxyl group. The other, less polar, compound m.p. 117-118

was assigned the epimeric structure (144;R=H). Both 143 (R=H) and 144 (R=H) could be oxidised back to ketone 158.

The reduction of the olefin-ketone 158 gave a mixture in which 144 (R=H) was in preponderance due to attack by hydride on the carbonyl from the least hindered side. It occurred to us that if the keto-amines 231 (epimeric pair) were reduced in this manner, attack from the least hindered side would supply a mixture containing mainly that amino-alcohol which, on subsequent formation of the N-oxide and pyrolysis would supply the syn-olefin-alcohol (143;R=H). In the event, this proceeded exceedingly well; reduction of the keto-amines (231) gave a mixture of amino-alcohols (245) which, after formation of the N-oxides and pyrolysis produced 143 (R=H) + 144 (R=H) in which 143(R=H) was present to an extent greater than 90% (g.l.c. analysis).

Both olefin-alcohols could be converted smoothly to the corresponding unsaturated tosylates (143+144;R=Ts) mp.117-118° and 67-69° respectively, and it was upon these that solvolytic studies were carried out. The work on these compounds is, at the moment, incomplete but some of the implications which can be drawn thus far have proved of interest.

The rates of acetolysis of 143(R=Ts) and 144(R=Ts) have been measured by Parker[75], and are shown in Table 6. The rate of acetolysis of 236(R=Ts), measured by Foote and Woodward[59], has been converted to the temperature at which our kinetic runs were

TABLE 6

Rates of Acetolysis of Tosylates in the Bicyclo (3,3,1) nonane system

Tosylate (R=Ts)	$k \times 10^5$ sec^{-1} *	Relative Rate
Cyclohexyl[76]	11.9	1
Syn-bicyclo (3,3,1)-non-2-en-9-yl (143)	4.14	0.35
Anti-bicyclo (3,3,1)-non-2-en-9-yl (144)	3.86	0.32
Bicyclo (3,3,1)-nonan-9-yl[59] (236)	31.3	2.6

* Acetolysis temperature = 80.78°

Figure 1

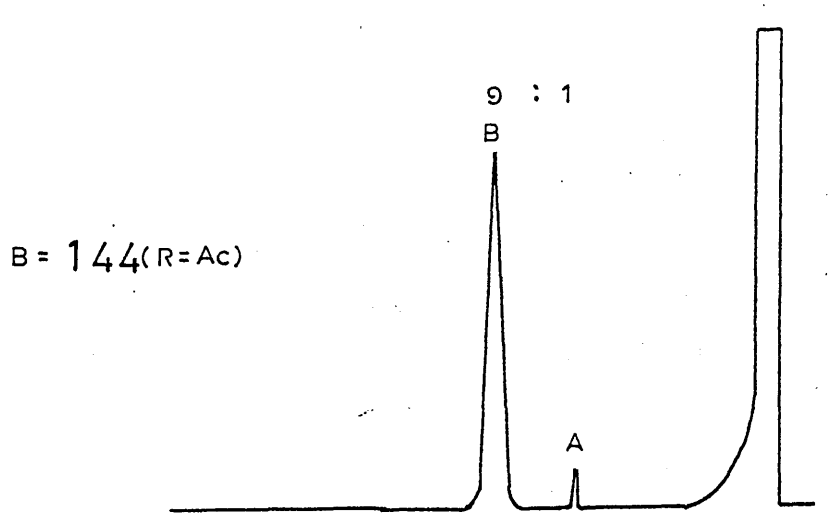
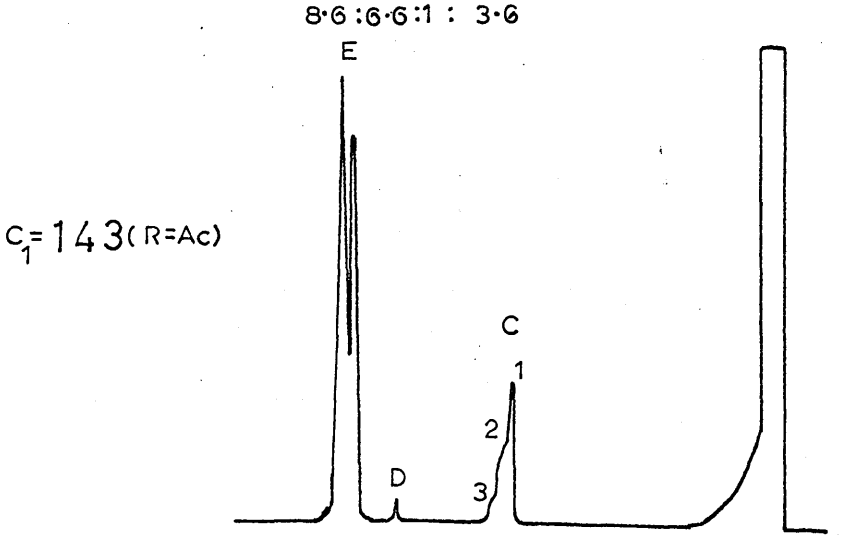


Figure 2



carried out, in order to compare the rates of saturated and unsaturated tosylates.

For the syn-, anti- and saturated tosylates (143;R=Ts) (144;R=Ts)(236;R=Ts), the relative rates were found to be 0.35, 0.32 and 2.6, relative to cyclohexyl tosylate. These results are remarkably consistent with the relative rates 12.6 : 13.4 : 113 found for the syn-, anti- and saturated 1,5-dimethyl substituted mesylates (145;R=Ms),(146;R=Ms) and (237;R=Ms). These rates will be discussed in detail after a description of the product analysis.

Solvolysis of both tosylates (143 and 144;R=Ts) gave mixtures containing hydrocarbons and acetates in which the acetate fractions were present in amounts amenable to careful examination. The acetates of both product mixtures have been investigated (though not fully), while the hydrocarbon fractions have not been examined in detail. Attempts to separate the hydrocarbons from the acetates by distillation and preparative scale g.l.c. were unsuccessful. The hydrocarbons formed are extremely unstable and polymerise during distillation and at the metal exit-tube of the g.l.c. apparatus. From g.l.c. analysis, 144 (R=Ts) appeared to give only one hydrocarbon while 143 (R=Ts) produced at least three.

A fine analytical g.l.c. separation of the acetate fractions from both tosylates was obtained using a capillary carbowax column at 125°. Figures 1 and 2 are copies of the traces obtained.

Firstly we will consider the product from 144(R=Ts); g.l.c. analysis revealed the presence of only two acetates. There seemed to be no trace of syn- acetate (143;R=Ac). Since this was important and the degree of separation between syn- and anti- acetates (143;R=Ac and 144;R=Ac) was not large, the mixture was converted by lithium aluminium hydride to the parent alcohols. G.l.c. analysis of these confirmed the presence of two alcohols, neither of which was 143 (R=H). The two acetates were separated by preparative g.l.c. using a 25% Apiezon "L" stationary phase. The major component (B) was identical to anti-9-oxobicyclo (3,3,1) nonan-9-yl acetate (144;R=Ac) by i.r. spectrum and g.l.c. retention time. The less-polar acetate (A) from the preparative g.l.c. separation was homogeneous under several different sets of g.l.c. conditions. Treatment of this olefin-acetate with lithium aluminium hydride gave an olefin-alcohol which, on subsequent catalytic hydrogenation, supplied a saturated alcohol (homogeneous by g.l.c. analysis), with a relative retention time (20% T.C.E.P.) identical to that reported for cis-trans-hydrindan-4-ol(246). From what we know of carbonium ion migrations the two most likely structures for this acetate from the anti-solvolysis is 247(R=Ac) or 248(R=Ac). By analogy with the results of Le Bel and Spurlock, who obtained 249 from both 232(R=H) and 233(R=H), the most likely structure is 247 (vinyl migration). The other structure (methylene migration) cannot of course be discarded on the evidence.

In the solvolysis of 143(R=Ts) a larger number of compounds

was formed (see figure 2). The major components (the most polar compounds) appeared, by virtue of their similarity in g.l.c. behaviour, to be epimeric. An initial separation of this mixture by preparative-scale g.l.c. (10% Ucon Polar) separated the less polar mixture of compounds (C) from the two major components (E). The two more polar compounds were treated with lithium aluminium hydride supplying two olefin-alcohols. The pair of olefin-alcohols could then be oxidised to a single conjugated enone (ν_{max} 1676cm.$^{-1}$) which gave a dark red 2,4-dinitrophenyl-hydrazone. A tentative structure 250 was assigned to the conjugated enone, which, on reduction with lithium aluminium hydride gave two olefin-alcohols whose retention times were identical to those obtained from the initial reduction of the mixed acetates, showing the original pair of olefin-acetates were indeed epimeric. Structures 251(R=H) and 252(R=H) were therefore assigned to the alcohols from reduction of the acetates while structures 251 (R=Ac) and 252(R=Ac) were assigned to the acetates themselves.

Figure 2 shows three partially resolved peaks in the mixture from solvolysis of 143(R=Ts) (i.e. $C_{1,2,3}$). The largest peak, C_1, corresponded in retention time to the syn-olefin-acetate (143;R=Ac) while the second (C_2) was thought to be the anti-olefin-acetate (144;R=Ac). These three compounds were obtained together by preparative-scale g.l.c. Reduction of the mixture with lithium aluminium hydride gave a mixture of alcohols which on subsequent g.l.c. analysis gave three peaks, none of which

corresponded to the anti-alcohol(144;R=H). One of these had the same retention time as the syn-alcohol however. The structures of the other compounds is unknown to us at present. Because of the similarity in retention time of one of the unknown alcohols with 144(R=H), a small quantity of 144(R=H) could have been present.

Nothing more could be done on this work in the time available. Two developments are awaited, a) Professor C.S. Foote has kindly offered samples of 246, 253, 254 and 255 which will eventually be compared with hydrogenated solvolysis products, b) Professor N.A. LeBel is currently involved in the same problem, and we are awaiting information as to his progress.

Figures 1 and 2 also show the approximate ratios of the acetates formed, obtained by integration of the g.l.c. traces. The ratio of hydrocarbons to acetates is, at the moment, unknown, although the acetate fractions are larger than 50% in both cases.

The products of acetolysis of 143 and 144(R=Ts) indicate that both form different ions. On solvolysis of 144(R=Ts), the products consist of 144(R=Ac) and 247(R=Ac) (where the position of the double bond is in doubt), in the ratio of 9:1 respectively. The high proportion of non-rearranged material of retained configuration and the steric purity of 247 (R=Ac) are extremely unusual except in examples of non-classical ions [59,73]. The complete absence of 143(R=Ac) corroborates this view, since in solvolyses involving classical ions, predominant inversion is

normally found in the product. In this case also, attack on the 9-position from the direction of the double bond(256) would be expected, since this is the less-hindered side. Evidence such as this indicates that the classical bicyclo(3,3,1)nonen-9-yl cation (257) is not an important intermediate in solvolysis of 144 (R=Ts). It would seem, therefore, on examination of the products from 144 (R=Ts) that a form of protected or non-classical cation must be invoked to explain the products formed. Cation 258 would appear to be first formed and this would account for the lack of 143(R=Ac) in the products and the large proportion of non-rearranged material formed.

An explanation of the products from 143(R=Ts) is much less obvious. In this solvolysis, most of the acetate fraction is re-arranged material, mainly the epimeric allylic acetates 251 (R=Ac) and 252(R=Ac). The other rearranged compounds have not been identified. One other point of importance is that if 144(R=Ac) is formed at all, it is in extremely low concentration compared with 143(R=Ac). If the syn-tosylate (143;R=Ts) were solvolysing via the classical ion 257, a quantity of anti-acetate (144;R=Ac) at least comparable to that of 143(R=Ac) would have been expected by inversion.

On solvolysis of 235 (R=Ts) and 236 (R=Ts) Foote and Woodward have evidence for methylene participation. These compounds solvolyse with assistance and their product mixtures are mainly rearranged. In the mixture from solvolysis of 235 (R=Ts), a

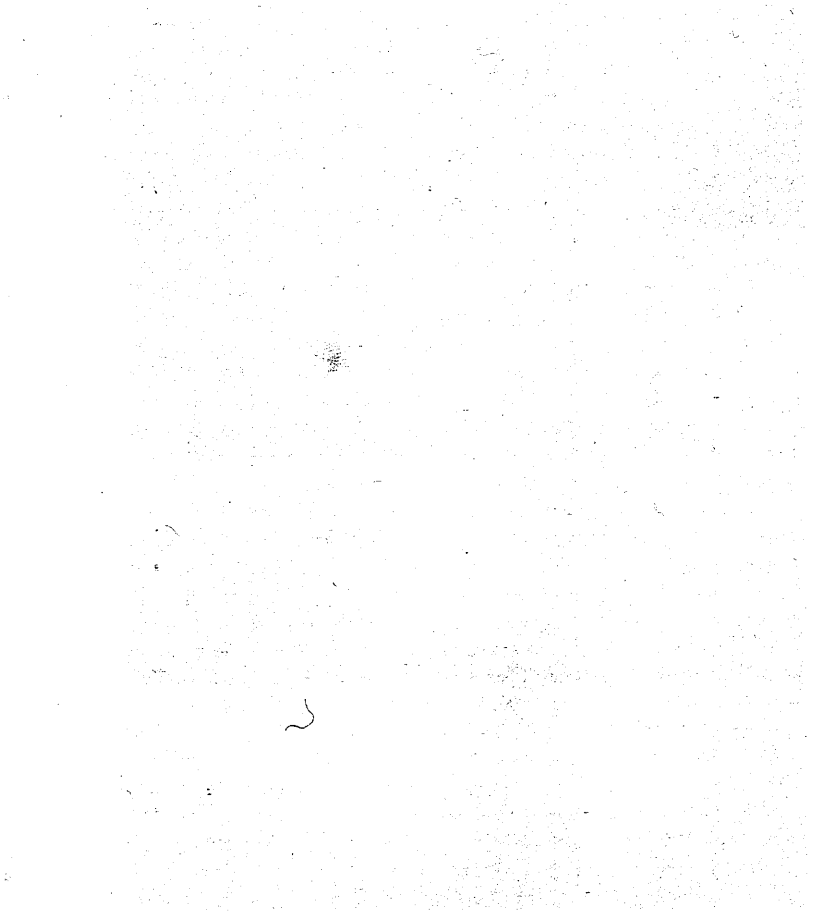
small amount of non-rearranged acetate was formed and this had the retained structure 235(R=Ac).

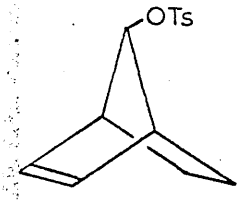
On solvolysis of 143 (R=Ts), a similar product mixture is obtained, and it would appear that 143 (R=Ts) might solvolyse with methylene participation. In this case, however, there are two methylene participations possible, the first, migration to give the allylic carbonium ion (259), stabilised by delocalisation (260) and therefore, probably favoured. The other migration giving 261 and subsequently 262 is presumably less favoured but may be responsible for some of the smaller components of the solvolysis product.

The rates of acetolyses of these compounds indicate that double bond participation is not exceptionally important as a rate-enhancing factor, and could be compared in its effect with methylene participation. The product analysis of the mixture from the anti-tosylate (144;R=Ts) however, would indicate that it does, in fact, occur. The faster rate of acetolysis of the saturated compound 236 (R=Ts) as compared with the syn- and anti-olefin-tosylates (143;R=Ts and 144;R=Ts) could arise from several factors including a) decreased angle strain at C_9, b) increased inductive effect (+ I), c) increased diaxial interactions and possibly because of the assistance due to relief of strain caused by the 3,7-methylene interaction

In conclusion, the syn- and anti- bicyclo(3,3,1)non-2-en-9-yl tosylates react to give vastly different mixtures obviously not

via the same intermediates. There are indications that both 143 (R=Ts) and 144 (R=Ts) react with participation and since both tosylates solvolyse at the same rate, this constitutes an example in which the anchimeric assistance to ionisation due to methylene and π-participation are equally important.





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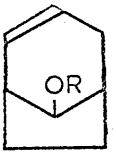

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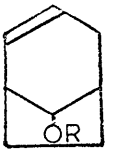

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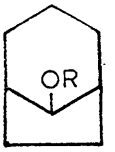

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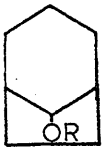

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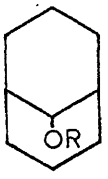

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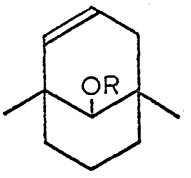

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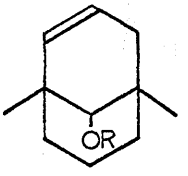

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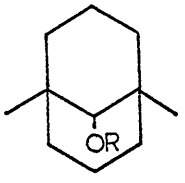

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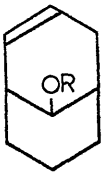

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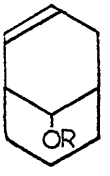

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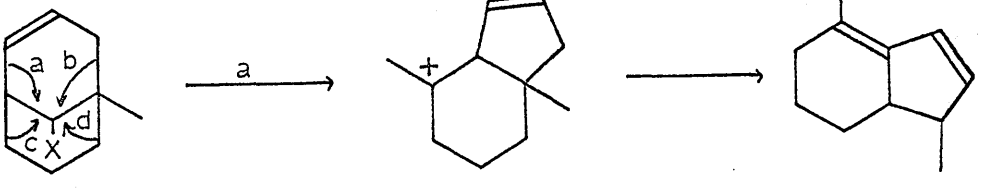

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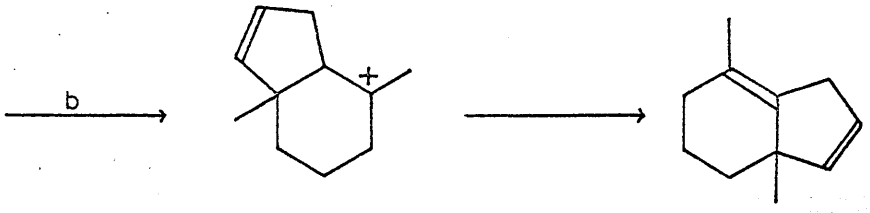

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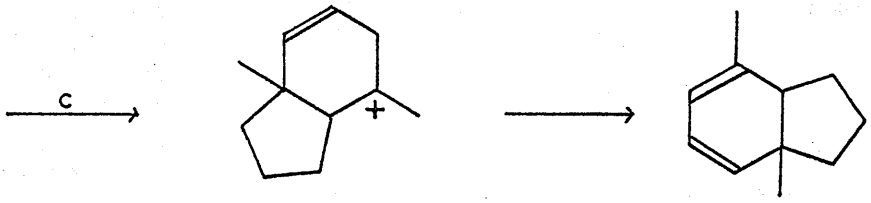

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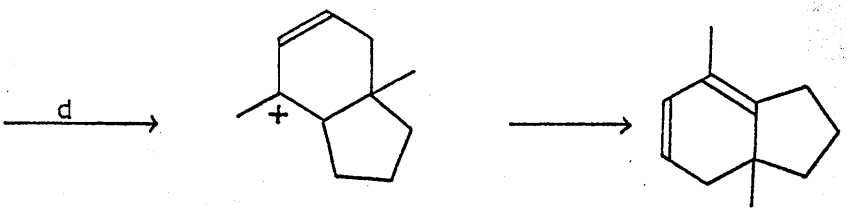

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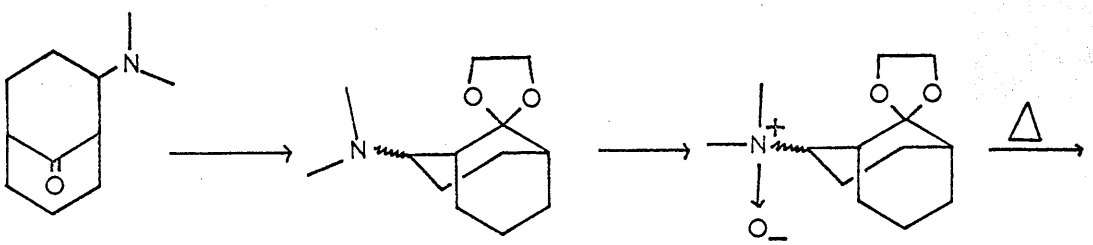

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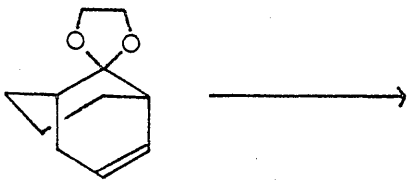

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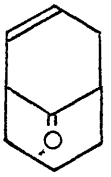

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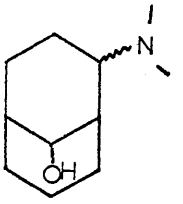

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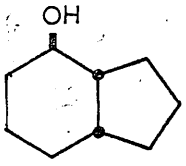

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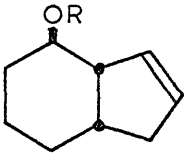

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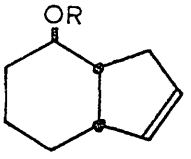

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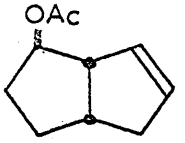

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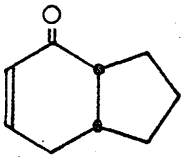

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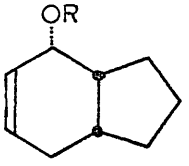

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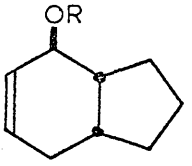

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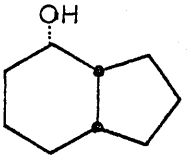

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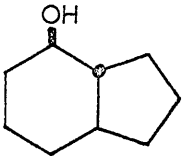

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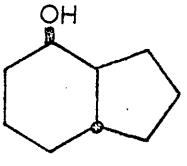

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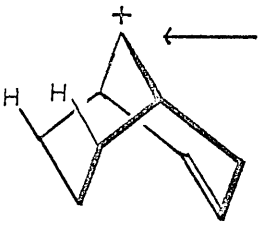

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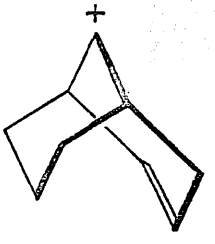

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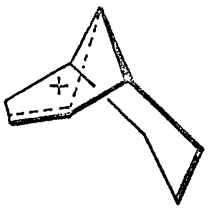

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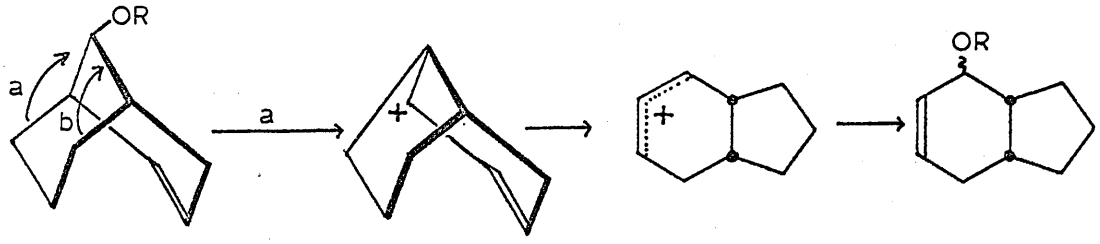
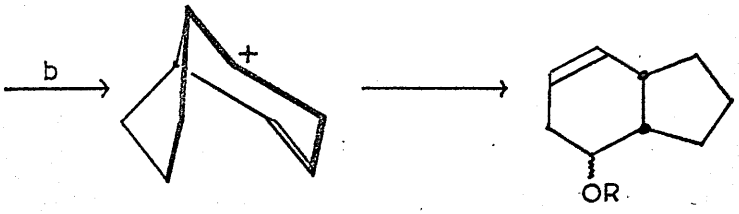


143 259 260 251+252



261 262

EXPERIMENTAL

Acetolysis of Syn-1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl Mesylate (145;R=Ms).

A solution of syn-1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl mesylate (145;R=Ms,0.4g.) and fused sodium acetate (0.53g.) in glacial acetic acid (10ml.) was heated under reflux for 3 hours and then poured into water and extracted with light petroleum (3 x 20ml.). The petroleum extract was washed thoroughly with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent at room temperature under reduced pressure gave a yellow mobile hydrocarbon oil (0.19g.); λ_{max} (EtOh) 245, 254, 265mμ Analysis of the oil on 10% apiezon 'L' at 90° showed the product to consist of at least three compounds.

Solvolysis of Anti-1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl Mesylate (146;R=Ms).

Anti-1,5-dimethylbicyclo(3,3,1)non-2-en-9-yl mesylate (146; R=Ms,0.4g.) was solvolysed in the manner described above. Identical isolation technique gave a yellow hydrocarbon oil (0.17g.) λ_{max}(EtOH) 246, 255mμ . G.l.c. analysis showed the product to consist of a mixture of the same three compounds found above.

Bicyclo(3,3,1)non-2-en-9-one (158)

Bicyclo(3,3,1)non-2-en-9-one(158) was prepared by the method of Foote and Woodward[59]; $\nu_{(max)}$ film 3050,1715, 700cm.$^{-1}$

Syn- and Anti-9-hydroxybicyclo(3,3,1)non-2-ene

(143;R=H + 144; R=H).

A solution of bicyclo(3,3,1)non-2-en-9-one (158;4g.) in anhydrous ether (40ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (1.5g.) in ether (20ml.). After the addition, the mixture was heated under reflux for 3 hours. The mixture was cooled and hydrochloric acid (6N;20ml.) was added slowly. The ethereal layer was separated, washed well with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of solvent gave a solid mixture of alcohols (4.1g.)

The mixture was adsorbed onto silica gel (120g.) from light petroleum. Elution with ether-light petroleum (3:7) gave anti-9-hydroxybicyclo(3,3,1)-non-2-ene (144;R=H) as a crystalline solid (2.17g.). Sublimation afforded an analytical sample, m.p. 117-118; ν_{O-H} (CCl_4) 3635cm.$^{-1}$ (Fd: C,77.95;H,10.2 $C_9H_{14}O$ requires C,78.21;H,10.21%).

Further elution with the same solvent gave firstly, a mixture of alcohols (0.94g.), and finally syn-9-hydroxybicyclo(3,3,1)non-2-ene (143;R=H) as a crystalline solid (0.49g.). Sublimation afforded an analytical sample, m.p.67-69°; ν_{O-H} (CCl_4) 3634, 3597cm.$^{-1}$ (high dilution). (Fd:C,77.85;H,10.2 $C_9H_{14}O$ requires C,78.21;H,10.21%).

9-Hydroxy-2-N-morpholinobicyclo(3,3,1)nonane (245).

A solution of 2-N-morpholinobicyclo(3,3,1)nonan-9-one (231; 200g.) in dry ether (500ml.) was added slowly to a stirred suspension of lithium aluminium hydride (13.8g.) in ether(500ml.). After the addition, the solution was heated under reflux for 4 hours and then cooled. Water was added slowly to the reaction mixture until no further effervescence took place. The precipitated aluminium salts were removed by filtration through Celite 535 and the residue washed thoroughly with ether. The washings and filtrate were combined and the ethereal layer was separated, washed with brine (3x) and dried. Removal of the solvent gave 9-hydroxy-2-N-morpholinobicyclo(3,3,1)nonane(245;182g,) as a viscous yellow oil. Distillation afforded an analytical sample, b.p. 132-133; ν_{max}(film) 3500cm.$^{-1}$ (Fd:C,69.55; H,10.26; N, 6.45, $C_{13}H_{23}NO_2$ requires C,69.29;H,10.29; N,6.22%).

N-oxide of 9-hydroxy-2-N-morpholinobicyclo(3,3,1)nonane

To a stirred solution of the amino-alcohol(245;140g.) in methanol (800ml.) at room temperature was added hydrogen peroxide (30%;600ml.) dropwise. The mixture was heated under reflux for 15 hours and then cooled. To it was added a little spent Adam's catalyst (0.5g.) and the solution was allowed to remain at room temperature for 48 hours. After removing the catalyst by filtration, most of the methanol/water was removed on the rotary evaporator giving the N-oxide as a soft yellow

glass (143g.)

Syn-9-hydroxybicyclo(3,3,1)non-2-ene (143;R=H).

The crude N-oxide (140g.) obtained above was pyrolysed carefully (temperature was raised slowly) at 140°0.3m.m. The pyrolysate was allowed to distil into a trap cooled in liquid nitrogen. The distillate was dissolved in ether and the ethereal solution was washed with hydrochloric acid (6N), brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent gave a dark, semi-solid mixture of alcohols (25g.). The mixture was adsorbed on silica gel (750g) from light petroleum and elution with ether-light petroleum (1:2) gave a colourless semi-solid mixture of syn-9-hydroxybicyclo(3,3,1)non-2-ene (143;R=H) and anti-9-hydroxybicyclo(3,3,1)non-2-ene (144; R=H) (21g.) in a ratio of 19:1. Further careful chromatography of this mixture provided the syn-olefin-alcohol (143;R=H) in a pure state.

Anti-bicyclo(3,3,1)non-2-en-9-yl Toluene-p-sulphonate (144;R=Ts)

Treatment of the anti-olefin-alcohol (144;R=H) with toluene-p-sulphonyl chloride in the usual manner supplied anti-bicyclo-(3,3,1)non-2-en-9-yl toluene-p-sulphonate (144;R=Ts) which crystallised from light petroleum as stout plates, m.p. 67-69°; ν_{max} (Mull) 1178cm.$^{-1}$ (Fd:C,65.5;H,6.55$C_{16}H_{20}O_3S$ requires C, 65.74; H, 6.90%)

Syn-bicyclo(3,3,1)non-2-en-9-yl Toluene-p-sulphonate (143;R=Ts)

Treatment of the syn-olefin-alcohol (143;R=H) with toluene-

p-sulphonyl chloride in the usual manner gave syn-bicyclo(3,3,1)-non-2-en-9-yl toluene-p-sulphonate (143;R=Ts) which crystallised from light petroleum (60-80) as needles, m.p.117-118°; ν_{max}(Mull) 1172cm.$^{-1}$ (Fd:C,65.73; H,6.67 $C_{16}H_{20}O_3S$ requires C, 65.74; H, 6.90%).

Anhydrous Acetic Acid.

The anhydrous acetic acid used for the ensuing solvolyses was dried by the method of Eichelberger[77].

Acetolysis of Anti-bicyclo(3,3,1)non-2-en-9-yl Toluene-p-sulphonate (144;R=Ts)

A solution of anti-bicyclo(3,3,1)non-2-en-9-yl-toluene-p-sulphonate (144;R=Ts,2g.) in anhydrous acetic acid containing fused sodium acetate(1.12g.) was sealed in an ampoule and maintained at 80° for 48 hours (10 half-lives). After a short time at 80° (1-3 hours) the solution became green in colour. This colour became steadily darker until the ampoule was cooled and opened. The solution was then poured into brine(100ml.) and the resulting mixture extracted thoroughly with isopentane(4x50ml.). The combined isopentane extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Careful removal of the solvent at 50° under reduced pressure gave a sweet-smelling red oil (1.34g.).

Temperature-programmed g.l.c. analysis on 2% 20M. polyethylene glycol (50-150° at 3°/min) revealed the presence of at least one hydrocarbon (diene) and two olefin-acetates. Subsequent

isothermal g.l.c. analysis of the acetates on a golay capillary carbowax column (50m) at 125° confirmed the presence of only two acetates (see Figure 1).

Separation of these acetates by preparative-scale g.l.c. on a 25% apiezon "L" stationary phase (12' x $\frac{3}{8}$" at 150°) supplied both acetates in a pure state. The slower compound, a colourless mobile oil, was identified as anti-bicyclo(3,3,1)non-2-en-9-yl acetate (144;R=Ac) by i.r. spectrum and g.l.c. retention time. The faster acetate, also a colourless mobile oil, $\nu_{max}(CCl_4)$ 3054,1738,1240 (film) 720cm.$^{-1}$, was found to be unstable on standing, decomping to a viscous polymeric mass. This was tentatively assigned the structure of Δ^2-cis-trans-hexahydrinden-4-yl acetate (247;R=Ac).

Acetolysis of Syn-bicyclo(3,3,1)non-2-en-9-yl Toluene-p-sulphonate (143;R=Ts).

The syn-bicyclo(3,3,1)non-2-en-9-yl toluene-p-sulphonate (143;R=Ts,2g.) was solvolysed in an identical manner to that described above for the anti-epimer (144,R=Ts). After 48 hours the solution was pale yellow in colour. Identical isolation technique gave a sweet-smelling red oil (1.22g.). Temperature-programmed g.l.c. analysis revealed the presence of at least three hydrocarbons and two acetates. Subsequent analysis on a golay capillary carbowax column showed there to be at least six compounds in the acetate mixture (Figure 2).

Partial separation of this mixture by preparative-scale

chromatography on a 10% Ucon Polar stationary phase ($10'x\frac{3}{8}''$) at 150° supplied the three least polar compounds ($C_{1,2,3}$) as a mixture and the two most polar compounds (E) together. One of the least polar compounds (C_1) was identified as syn-bicyclo-(3,3,1)non-2-en-9-yl acetate (143;R=Ac) by retention time comparisons of the acetate and alcohol obtained from reduction, while the two most polar compounds (E) were tentatively identified as the epimeric Δ^5-cis-hydrinden-4-yl acetates (251;R=Ac+252; R=Ac).

Reduction of Acetate (A) from the Solvolysis of the Anti-toluene-p-sulphonate.

The less polar acetate (A, 19mg.) in anhydrous ether (2ml.) was added to a suspension of lithium aluminium hydride (20mg.) in ether (2ml.) and the mixture was stirred at room temperature for three days. Water (4ml.) was slowly added to the mixture. The precipitated aluminium salts were removed by filtration through Celite 535. The residue was washed well with ether and the resultant washings combined with the filtrate. The ethereal layer was separated, washed with brine and dried. Removal of the solvent gave a colourless oil (11mg.) homogeneous on a 20% tris-(2-cyanoethoxy) propane (T.C.E.P.) stationary phase at 125°; ν_{max}(film) 3460,3100,720cm.$^{-1}$

Hydrogenation of the olefin-alcohol from Acetate (A).

The alcohol (5mg.) obtained above in ethyl acetate (5ml) was hydrogenated over 10% palladium-charcoal(1mg.) for 3 hours.

The catalyst was removed by filtration through Celite 535 and the filtrate was concentrated to give a yellow oil (4.6mg.) exhibiting no absorption characteristic of unsaturation in the i.r. The oil obtained was homogeneous on 20% T.C.E.P. (125°) and had a relative retention time of 87 (relative to bicyclo-(3,3,1)nonan-9-ol) which is identical to that reported[59] for cis-trans-hydrindan-4-ol (246).

Reduction of Acetates (E) from Solvolysis of the Syn-toluene-p-sulphonate.

A solution of acetates (E,70mg.) in anhydrous ether (10ml.) was added slowly to a stirred suspension of lithium aluminium hydride (40mg.) in ether (10ml.) and the reaction mixture was stirred at room-temperature for a further two days. An identical isolation technique to that described in the reduction of acetate (A) above, gave a yellow oil (52 mg.); ν_{max}(film) 3500,3050,750cm^{-1} G.l.c. analysis (20% T.C.E.P. at 125° flow-rate=48ml/min.) revealed the presence of two olefin-alcohols (Retention times, 32.4 and 34.8 mins,), assigned the epimeric structures of Δ^5-cis-trans-hydrinden-4-ol (252;R=H) and Δ^5-cis-cis-hydrinden-4-ol (251;R=H).

Oxidation of the Epimeric Δ^5-Cis-hydrinden-4-ols.(251;R=H+252;R=H)

The mixture of olefin-alcohols (40mg.) obtained above was treated with excess Jones reagent[61] in the usual manner giving a clear yellow oil (39mg.); ν_{max}(film) 3050, 1680, 1620cm.$^{-1}$, which formed a dark red 2,4-dinitrophenylhydrazone, crystallising

from ethanol as prisms, m.p.136-138°; λ_{max} (EtOH) 252, 376 (ε =). (Fd: C,5680;H,555 $C_{15}H_{16}O_4N_4$ requires C,56.96; H,5.10) The oxidation product was tentatively assigned the structure of Δ^5-cis-hydrinden-4-one (250).

Reduction of Δ^5-Cis-hydrinden-4-one (25)

The enone (29mg.) obtained above was treated with lithium aluminium hydride in the manner described for reduction of acetates (E). Similar work-up technique gave an oil (27mg.) which consisted of two olefin-alcohols with retention times (20% T.C.E.P., 125°) identical to those of the olefin-alcohols obtained on reduction of acetates (E).

APPENDIX A

Compound	Column	Temp. (°C)	Flow Rate (ml/min)	Ret. Time (or Ret. Index)
87	5% Q.F.1.	100-175 (3°/min)		1376
88	"	"		1484
113+114	"	"		1591
89	"	"		1684
118	"	"		2048
117	"	"		2084
86(R=Ac)	"	"		2164
85(R=Ac)	"	"		2208
87	"	100	30	3.6 min
88	"	"	"	9.4 "
89	"	"	"	30 "
113+114	"	"	"	16.7 "
85(R=Ac)	"	150	"	16.6 "
86(R=Ac)	"	"	"	14.7 "
118	"	"	"	10.8 "
117	"	"	"	11.2 "
157 (R=Ac)	10% Apl		40	16.1 "
171 (R=Ac)	"	"	"	17.3 "
143 (R=H)	10% PEGA	125	51	4.5 "
144 (R=H)	"	"	"	6.4 "
143 (R=Ac)	10% Apl	"	52	11.5 "
144 (R=Ac)	"	"	"	12.9 "
250	"	"	50	11.2 "
251+252 (R=H)	20% T.C.E.P	"	48	32.4; 34.8 "
				Relative * Retn. Time
247(R=H)	"	"		100
246(R=H)	"	"		86.5

* Relative retention times were noted using bicyclo (3,3,1)-nonan-9-ol as standard with its relative retention time taken as 100.

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