RECENT STUDIES ON THE SYNTHESIS OF HOMOCYCLIC SYSTEMS

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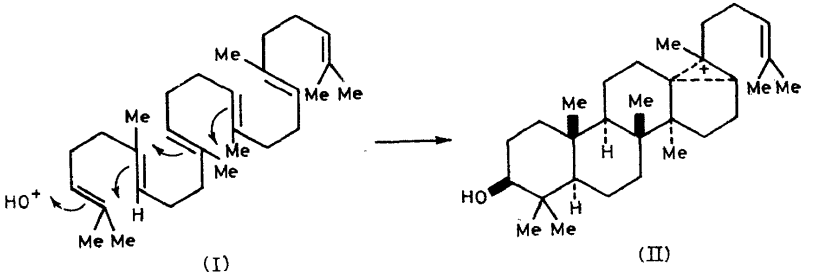
This paper constitutes a report of results that have been obtained in a new programme of study which has been under way for some time in our laboratory. The ultimate aim of this research is to develop a laboratory method of simulating the cyclization processes that are involved in the biosynthesis of the polycycloisoprenoids such as the tetra- and penta-cyclic triterpenoids as well as the steroids. This programme is only in its preliminary stages, and our results thus far are limited almost exclusively to relatively simple systems.

It has been unequivocally established[1] by the work of Bloch, Cornforth, Tavormina, Woodward and others that the biosynthesis of lanosterol and, in turn, of cholesterol from mevalonic acid involves an intermediary open-chain polyolefin, namely squalene (I), which undergoes cyclization and rearrangement. It seems probable that the vast number of polycyclic triterpenoids occurring in nature are also derived from squalene. In 1955 both Stork[2a] and Eschenmoser[3] proposed a stereo-rational theory for the biogenesis of most of the known members of this group of natural pro-



ducts. This theory is based on the assumption that the process is initiated by attack of an external electrophile (for example, HO^+) on squalene (I), and that this attack is attended by cationic cyclizations involving *trans* additions to the olefinic bonds. If the internal olefinic bonds have the *trans* configuration as in squalene, and if the cyclization is synchronous†, the process is expected to yield the *trans-anti* configuration of the ring junctures. One such mode of concerted cyclization is shown above and is postulated to lead to a

† Non-classical carbonium ion intermediates (see ref. 3) would serve as well to preserve the stereochemical integrity of the process, and this alternative possibility is recognized in using the term " synchronous ".

polycyclic cation (II) which may be regarded as the precursor of a number of the tetra- as well as penta-cyclic triterpenoids. The configuration of lanosterol and of the steroids, on the other hand, suggests that, in their biosynthesis, the concerted process is interrupted at a bicyclic stage. The stereo-electronic course of the concerted process is illustrated in *Figure 1.* If

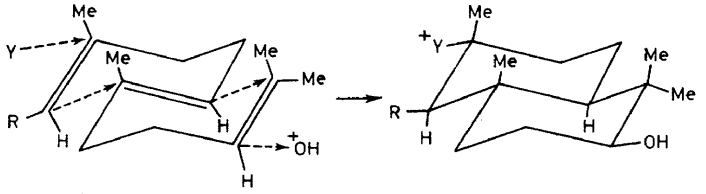
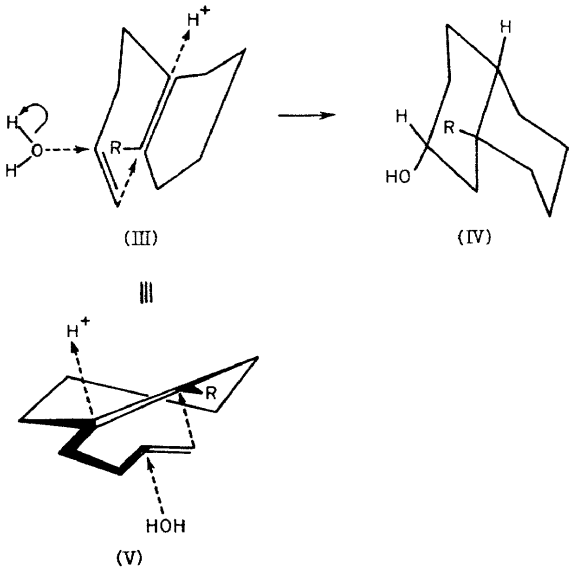


Figure 1

the nucleophile Y is an external species, such as the solvent, the cyclization process is interrupted with the formation of two rings; on the other hand, if Y represents an appropriately juxtaposed olefinic bond in the side chain R, the cyclization process may continue further to give *trans-anti-trans* fused rings.

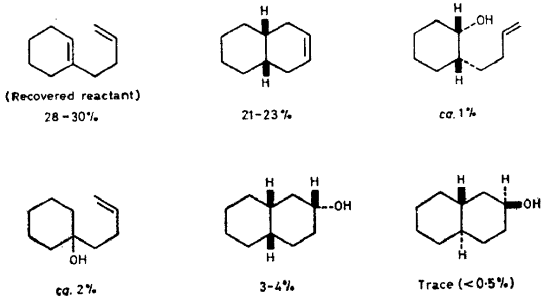
A corollary to the principle described above is that a synchronous protonation and cyclization of a monocyclic diene, like 3-butenyl-1-cyclohexene (III) will produce exclusively a *cis*-fused ring system (IV). The process is



depicted in formulae (III)–(V), water being used as the nucleophile for convenience. Formula (V) is equivalent to (III) in a different perspective. The simple system has already been examined by Linstead and his collaborators who studied the cyclization of the diene (III) (R = H)[4] with a mixture of sulphuric and acetic acid. After saponification, the crude *cis-syn-β*-decalol (IV) (R = H) was isolated in 12·5 per cent yield. (A 25 per

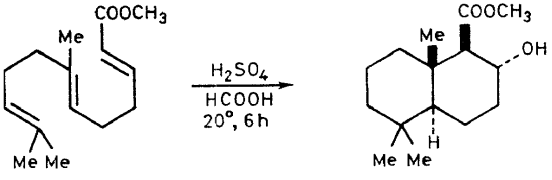
cent yield of this decalol was obtained on cyclization of the precursor of the diene, Δ^3-butenylcyclohexanol, with added acetic anhydride to assist dehydration.) Similarly the homologous diene (III) (R = CH_3) afforded (IV) (R = CH_3)[5] as the only pure product that was isolated (in unspecified yield). Now it is possible that in both of these cases the *cis*-decalin derivative did represent the major cyclization product; however, it was not demonstrated that the residual reaction product did not contain significant amounts, or even possibly a preponderance, of the *trans*-isomers. Therefore, we have repeated the work of Linstead with butenylcyclohexene and, by taking advantage of vapour phase chromatographic techniques that are described below, have made a quantitative analysis of the products (*Table 1*). The

Table 1. Products from treatment of butenylcyclohexene with acetic and sulphuric acid according to Linstead



product was composed of approximately 29 per cent starting material, 22 per cent of octalin fraction which was not the Δ^2-*trans* isomer and, therefore, is regarded as *cis*-fused material†, about 2 per cent of 1-(Δ^3-butenyl)cyclohexanol, 1 per cent of *cis*-2-(Δ^3-butenyl)cyclohexanol, 3–4 per cent of *cis-syn*-2-decalol, and less than 0·5 per cent of *trans-anti*-2-decalol. In addition there was an unidentified peak corresponding to 2–2·5 per cent of alcoholic material. The remainder of the product evidently was water-soluble (probably sulphate esters). Our failure to obtain as high a yield of the *cis*-decalol as reported by Linstead may be due to small differences in conditions which resulted in the formation of *cis*-octalins† at the expense of the alcohol. In any case, it is clear from our study that the Linstead cyclization is highly stereoselective, if not stereospecific, and the mechanistic interpretation of Stork[2a] may be regarded as reasonable.

Now attention is turned to the problem of simulating the proposed synchronous all-*trans* cyclization of open-chain polyenes with the ultimate

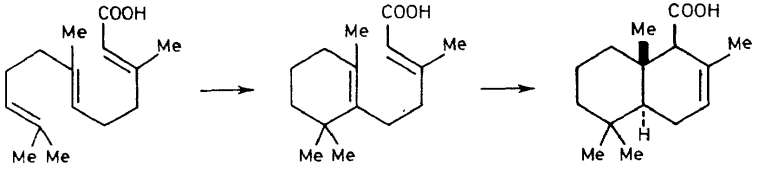


(VI) (VII)

† *Note added in proof*
More recent work shows that this material is not an octalin, but rather a cyclic ether, probably 2-methyl-5,5-pentamethylene-tetrahydrofuran.

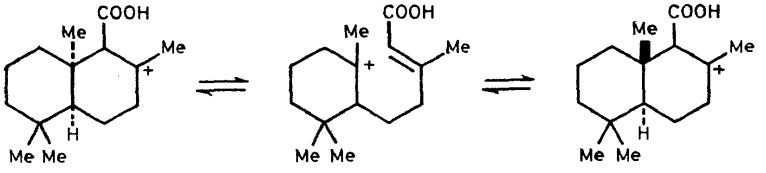
hope of applying the methods to a laboratory synthesis of natural products. Our work up to the present has served mainly to demonstrate that this will be a difficult goal to reach, and at best we have been able only to disclose some possible clues to the solution of the problem.

There has been relatively little previous work that is pertinent†. Eschenmoser and his collaborators[7] have reported the acid-catalysed cyclization of *trans*-desmethylfarnesic ester (VI) to yield a single *trans*-fused decalin derivative (VII) in 60–70 per cent yield. Seemingly this is an example of the process in question; however, Stork and Burgstahler[2a], working in the farnesic acid series (see formula VIII), showed that under mild conditions the process proceeded only to the monocyclic stage, formula (IX), and that the monocyclic diene on further treatment was converted into the *trans*-fused bicyclic substance (X)[2b]. This result suggests that the Eschenmoser case is



(VIII) (IX) (X)

similarly a two-stage cyclization‡. The most striking feature of the Stork work is that the cyclization of the monocyclic diene proceeds stereochemically in a manner exactly *opposite* from that expected on the basis of Linstead's butenylcyclohexene case which gives mainly the *cis*-decalin derivative. A possible interpretation of this enigma is that the unknown *cis* product, shown in the protonated form in formula (XI), is actually formed initially as



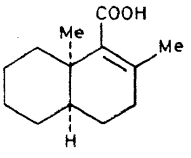
(XI) (XII) (XIII)

in Linstead's case, but that under the conditions of reaction the *cis* is converted to the more stable *trans* isomer (XIII) through an equilibrium established *via* the ring-opened carbonium ion (XII). Such a ring-opening process falls into the class of a well-known type of cationic fragmentation reaction, and its activation energy might be lowered (with respect to comparable ring-opening in the Linstead case) because, in the protonated forms, (XI) and (XIII) of the bicyclic acids, there would be a stabilizing

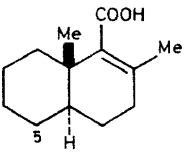
† Cyclization experiments like that with farnesylacetic acid,[6] cannot be regarded as relevant because the *trans*-fused product was isolated in very low yield, and it was not demonstrated that the remainder of the reaction product did not contain a preponderance of *cis*-material.

‡ Eschenmoser[8] has indeed shown that (VII) is the major product produced on cyclization of the monocyclic diene ester, an observation that is consistent with (but does not prove) the premise.

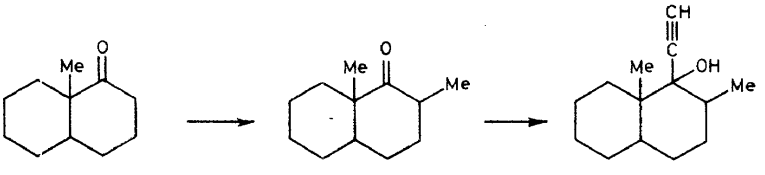
effect resulting from having the positive charge removed to a position that is more remote from the electron-deficient carbon of the carboxyl group. The *cis*-fused bicyclic acids were not found either by Eschenmoser or Stork so that there has been no way of finding out if it was indeed convertible to the *trans*-isomer by acid treatment.



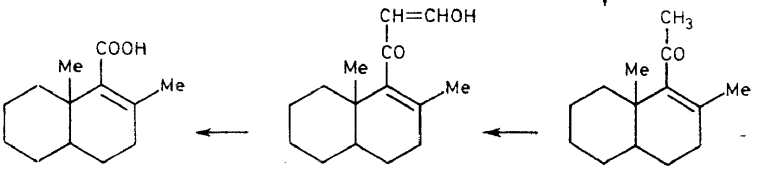
(XIV)



(XV)



(XVI) (XVII) (XVIII)



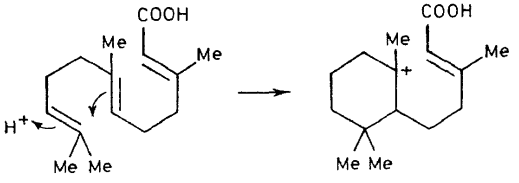
(XXI) (XX) (XIX)

In order to test this hypothesis, we undertook the preparation of the *cis* and *trans* bicyclic acids (XIV) and (XV) by an unequivocal synthesis. Note that the acid (XV) is related to the cyclization product obtained by Stork except that it lacks the *gem* dimethyl group at the 5 position. The acids (XIV) and (XV) were synthesized respectively from the known *cis* and *trans*-9-methyldecalones. The steps were the same for both series and are summarized in the accompanying non-stereochemical formulae. The methyldecalone (XVI) was converted, by alkoxide-catalysed condensation with ethyl formate, into the hydroxymethylene derivative which, on catalytic hydrogenation in ethanol over palladium on carbon in the presence of hydrochloric acid, was transformed into the 2,9-dimethyldecalone (XVII). In both the *cis* and *trans* series this ketone failed to react with cyanide to form

the cyanohydrin. However, it did react nicely with ethynylmagnesium bromide to give the acetylenic alcohol (XVIII) which, on treatment with 90 per cent formic acid, was transformed smoothly into the unsaturated ketone (XIX). In the *cis* series this ketone was exceedingly unreactive, failing to give a 2,4-dinitrophenylhydrazone, or a furfurylidene derivative on treatment with furfural. A number of attempts to degrade the ketone to the acid, for example by alkaline hypobromite, failed. Finally, it was discovered that the ketone (XIX) would undergo condensation with ethyl formate to produce the hydroxymethylene derivative (XX). Ozonolysis of this derivative followed by treatment with periodic acid afforded the desired unsaturated acid (XXI).

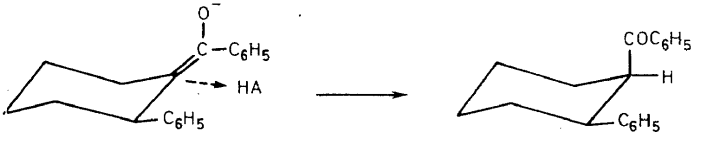
The acids (XIV) and (XV) were thus in hand for testing the interconversion hypothesis. Each was treated with boron trifluoride etherate in benzene under the conditions reported by Stork for converson of monocyclic to bicyclic material. After esterification with diazomethane the products were analysed by vapour phase chromatography, and it was found that there had been no interconversion. The interconversion failed even under prolonged treatment with the acidic reagent. If it is assumed that the acid (XV) constitutes a satisfactory model of Stork's acid, then our interconversion hypothesis is invalid.

In view of these findings we are forced to adopt an alternative interpretation of the stereochemical course of Stork's cyclization, namely that the

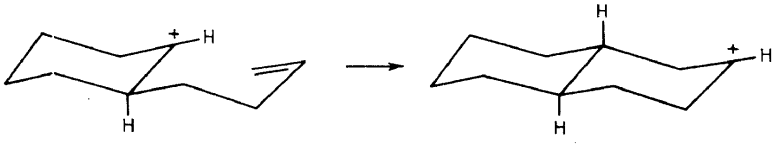


(VIII) (XXII)

conjugated olefinic bond of farnesic acid (VIII), because of delocalization of the π-electrons by the carboxyl group, is such a poor nucleophile that it does not react synchronously, *i.e.*, the process occurs in steps with the intermediacy of the tertiary carbonium ion (XXII). The possibility of such a stepwise process has already been suggested by Eschenmoser[8]. If this interpretation is correct, it follows that a free monocyclic carbonium ion, like (XXII), will undergo cyclization so as to produce preferentially a *trans*-fused ring system. It is not unreasonable to expect that a nucleophile would prefer to make an equatorial rather than axial attack on a cyclohexyl cation. Indeed such a process has considerable geometrical similarity to the case of the protonation of the enolate of 2-phenylbenzoylcyclohexane (XXIII) to give the less stable *cis*-isomer (XXIV)[9], which constitutes an example of a rate-controlled reaction involving an sp^2 carbon in the cyclohexane ring where the attacking group prefers the equatorial approach. Similarly, in the hypothetical carbonium ion (XXV) an equatorial attack by the olefinic bond would give the *trans*-fused system (XXVI). If this behaviour is general, then the biosynthesis of natural products from squalene



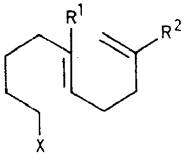
(XXIII) (XXIV)



(XXV) (XXVI)

might be equally satisfactorily rationalized as occurring in steps rather than synchronously†.

Now to turn to our own cyclizations: before undertaking a plan of study, we decided not to employ the acid-catalysed approach that had been used by previous workers, because treatment of polyenic systems with acid would in most cases be non-selective, bringing about the indiscriminate generation of cationic centres, resulting in competing reactions to give a variety of products. We have, therefore, been directing our attention to systems in which the cationic centre can be generated at a specific site and under conditions which are not acidic enough to effect competing protonation of the olefinic bonds. Accordingly one of the approaches that we selected for study was the generation of incipient cationic sites by solvolysis reactions.



An early objective was to examine the solvolysis of systems like that shown in the formula above with the view to determining what factors would promote the stereoselective formation of *trans* bicyclic product. The problem is complex, and some of the factors which would be expected to influence the course of the reaction are (*i*) the solvent, (*ii*) the nature of the leaving group X, (*iii*) the nucleophilicity of the internal olefinic bond as it is affected by the nature of R^1, (*iv*) the nucleophilicity of the terminal olefinic bond as affected by the nature of R^2, and (*v*) the preferred ground state conformation of the substrate.

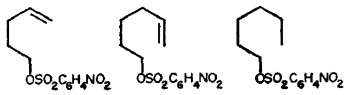
Before undertaking this study we felt it necessary to establish some ground rules with simple systems capable of forming monocyclic substances. Questions to be answered were: what conditions of solvolysis would favour

† Such a process would involve carbonium ion intermediates which, however, are not long-lived enough to deprotonate reversibly as this would lead to *cis*-fused rings as well as to deuterium incorporation from D_2O.

cyclization rather than direct substitution? Do we have to be concerned with the possibility of 5-membered competing with 6-membered ring formation?

Bartlett[10] with Clossen has recently obtained some information on these points in a study of the acetolysis of 4-pentenyl *p*-nitrobenzenesulphonate and of 5-hexenyl *p*-nitrobenzenesulphonate, summarized in *Table 2*.

Table 2. Acetolysis experiments (0·035M NaOAc in HOAC)



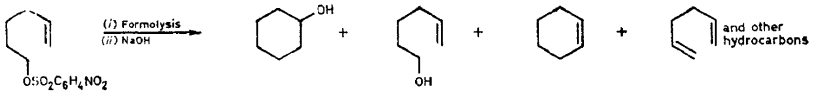
Relative rates	0·7	1·5	1
Yield of cyclic acetate	0%	25%	
Yield of non-cyclic acetate	—	60%	

Incidentally Bartlett in his article gives an excellent review of previous work on related solvolyses. Of particular interest is the fact that the hexenyl compound shows a 50 per cent rate acceleration relative to the n-hexyl ester; therefore the olefinic bond definitely assists the solvolysis. The yield of cyclohexyl acetate under the conditions indicated was 25 per cent and of direct displacement product, namely 5-hexenyl acetate, was 60 per cent. The pentenyl ester in contrast underwent solvolysis somewhat more slowly than the saturated ester, and gave no cyclic material. Therefore the 6-membered ring cyclization is definitely preferred to the 5-membered ring process. Bartlett and Clossen also noted that the yield of cyclohexyl acetate decreased with increased concentration of sodium acetate, and conversely the yield increased to 34 per cent when the sodium acetate was omitted; however, in this latter case considerable reaction of solvent with the olefinic bond resulted due to protonation by the strong acid (*p*-nitrobenzenesulphonic acid) liberated in the reaction. For our aims, therefore, it was obviously essential to employ a buffered medium which would minimize this undesirable side reaction.

The work of Winstein[11] and his collaborators has shown that formic acid is more effective than acetic acid in promoting the anchimerically assisted process in the solvolysis of phenylethyl tosylate. It was, therefore, not surprising to find that solvolysis of hexenyl *p*-nitrobenzenesulphonate in formic acid and sodium formate was about twice as fast as of hexyl *p*-nitrobenzenesulphonate. Moreover there was a marked improvement in yield of cyclic material (see *Table 3*). The solvolysis of a 0·02M solution of the substrate in 100 formic acid containing 2 mole-equivalents of sodium formate was 96 per cent complete after 3 h at 75°. The product of this run (no. 1, *Table 3*), after saponification, was analysed quantitatively by vapour phase chromatography over a Craig succinate column and was shown to contain 52 per cent of cyclohexanol, 24 per cent of hexenol, 4 per cent of cyclohexene and about 20 per cent of other hydrocarbons including any 1,5-hexadiene. A somewhat higher yield (68 per cent) of cyclohexanol was obtained when 98 per cent (instead of 100 per cent) formic acid was used. In this case (run 2) the yields of other products were: hexenol, 26 per cent;

cyclohexene, 5 per cent; and other hydrocarbons, about 2 per cent. As the solvent was diluted further with water, the yield of direct substitution product was increased at the expense of cyclic product. Thus, in formic acid containing 10 per cent water (run 3) the yields of cyclohexanol and hexenol

Table 3. Yields of products of solvolysis of 0·02M 5-hexenyl *p*-nitrobenzenesulphonate at 75° for 3 hours in formic acid containing 2 mole-equivalents of sodium formate



Run	*% of water in solvent*	(%)	(%)	(%)	(%)
1	0	52	24	4	*ca.* 20
2	2	68	26	5	*ca.* 2
3	10	50	35	6	*ca.* 7
4	40	30	58	1	*ca.* 3

were 50 and 35 per cent respectively; and in 40 per cent water (run 4), 30 and 58 per cent respectively.

The olefinic bond was shown to be inert to these solvolysis conditions inasmuch as 1,5-hexadiene was largely unaffected by the treatment. These results also demonstrate that cyclization of the *p*-nitrobenzenesulphonate does not proceed *via* the diene. Under our preferred solvolysis conditions, pentenyl *p*-nitrobenzenesulphonate gave only the product of direct substitution. 6-Heptenyl *p*-nitrobenzenesulphonate underwent formolysis at approximately the same rate as the n-hexyl ester. The failure of the olefinic bond to participate in the solvolysis was reflected also in the nature of the

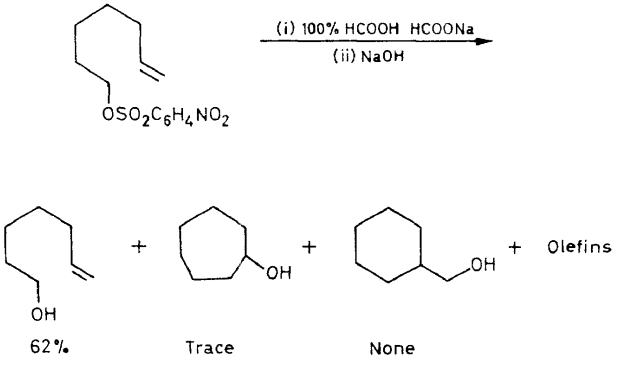


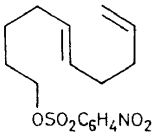
Figure 2

product which was composed mainly (62 per cent yield) of heptenol (*Figure 2*). A small amount (about 1 per cent) of cycloheptanol, but no cyclohexyl carbinol, was detected. A substantial hydrocarbon fraction was produced, and this may contain cyclized olefins, but the matter has not yet been resolved.

Our attention was now turned to the more pertinent case of the solvolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulphonate (XXVII). This substance was prepared as shown in the accompanying formulae by the condensation of 1,4-bromochlorobutane with the monosodio derivative of 1,5-hexadiyne

$$Cl(CH_2)_4Br + NaC{\equiv}C(CH_2)_2C{\equiv}CH \longrightarrow Cl(CH_2)_4C{\equiv}C(CH_2)_2C{\equiv}CH \longrightarrow$$

$$HO(CH_2)_4C{\equiv}C(CH_2)_2C{\equiv}CH \longrightarrow HO(CH_2)_4CH{\equiv}CH(CH_2)_2CH{\equiv}CH_2$$

(XXVII) 

$OSO_2C_6H_4NO_2$

$p\text{-}O_2NC_6H_4SO_2Cl$, NaOH

m.p. 40–42°

to give 1-chloro-5, 9-decadiyne which was hydrolysed to the corresponding alcohol. Reduction with sodium in liquid ammonia under appropriate conditions afforded the *trans* dienol which was converted, on treatment with *p*-nitrobenzenesulphonyl chloride and aqueous sodium hydroxide, into the crystalline *p*-nitrobenzenesulphonate.

The solvolysis of a 0·02M solution of the ester in 80 per cent formic acid containing 2 mole-equivalents of sodium formate was 96 per cent complete after 1 h at 75°. It is noteworthy that this reaction is slightly faster than the solvolysis of the hexenyl ester already discussed, which was only 74 per cent completed under identical conditions. This behaviour may be a reflection of the stronger nucleophilicity of the internal olefinic bond. The products of the solvolysis experiments were hydrolysed with alkali and analysed by vapour phase chromatography on a Craig succinate column. A typical chromatogram is reproduced in *Figure 3*. When the chromatography was

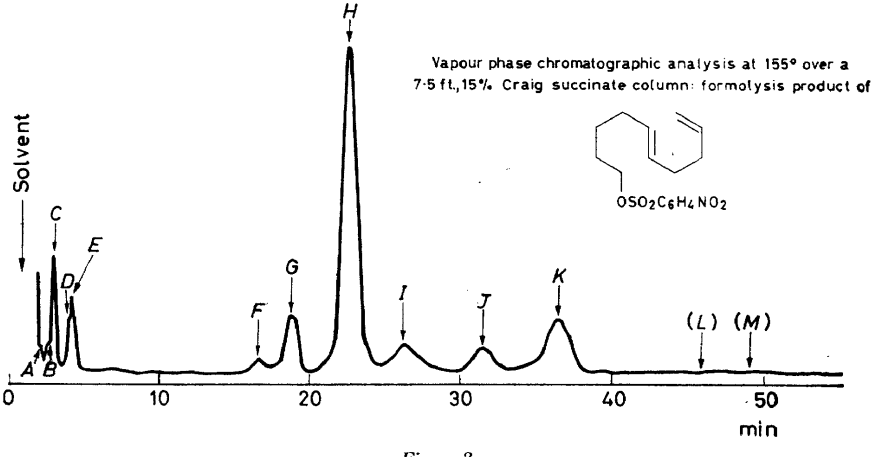
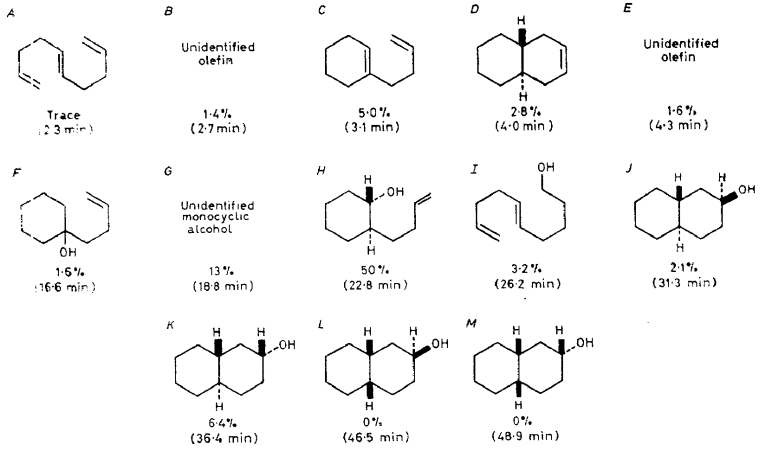


Figure 3

carried out at 100° instead of 155°, the hydrocarbon fraction (peaks *A–E*) was nicely resolved. Thus at least 11 products were detected, 9 of which have been provisionally identified by peak enhancement experiments†.

Table 4. Yields (and retention times) of products of solvolysis of 0·02M 5,9-decadienyl *p*-nitrobenzenesulphonate at 75° in 80% formic acid containing 2 mole-equivalents of sodium formate



The yields of products for the experiments under consideration are given under the structures in *Table 4*. Considering the rather bewildering array of products produced and the very poor yield of bicyclic material, it might be concluded that this type of approach to the synthesis of polycyclic compounds is doomed to failure. One encouraging aspect, however, is the fact that a relatively large proportion of mono(carbo)cyclic material (formula *H* in *Table 4*) was formed. It might be anticipated, therefore, that yields of bicyclic material could be improved by decreasing the nucleophilicity of the solvent which is responsible for the interruption of cyclization at the monocyclic stage. The situation might also be improved by increasing the nucleophilicity of the terminal olefinic bond with an appropriate substituent, *e.g.*, a methyl group at C–9. The simple unsubstituted system, indeed, probably represents one of the most unsatisfactory substrates imaginable. It is, accordingly, a good case for learning the kinds of side reactions to be dealt with and for determining what kinds of external factors favour cyclization. Such a study may be likened to using a 200 lb. instead of a 2 lb. weight in order to test the strength of a man.

The most interesting feature of this solvolysis is the fact that the bicyclic material consisted exclusively of *trans*-decalin derivatives, *D*, *J* and *K*‡. This finding is promising from the point of view of obtaining the desired

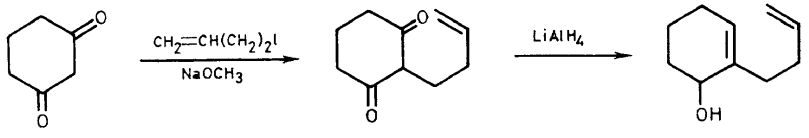
† I should like to take this opportunity to thank Professor William Dauben of the University of California for supplying us with pure specimens of all four isomeric forms of the β-decalols for identification purposes.

‡ When the solvolysis mixture was spiked with the two epimeric *cis*-decalols, they were easily resolved with higher retention times than any of the other components (see *Figure 3*).

stereochemical result, and it may represent a *bona fide* example of simulation of the basic features of the cyclization step in the biosynthetic process.

The concerted bicyclization should be favoured if, in the ground state, the substrate is coiled helically so that the double bonds are juxtaposed for ring closure. van Tamelen[12] has devized an ingenious scheme for effecting a coiling of squalene so that only the ends are exposed to attack by an oxidizing agent. His trick was to employ a solvent system containing a high enough concentration of water so that the hydrocarbon was almost out of solution and hence coiled by intramolecular " self-solvation ", a phenomenon that has been well recognized in polymer chemistry. In an effort to apply this principle to the present case, the solvolysis was conducted in 50 per cent formic acid in which the ester is sparingly soluble. The only major difference in the result of this change, however, was that the yield of product of direct substitution *I* (*Table 4*) was increased to 14 per cent. An attempt to carry out the solvolysis on the adsorbed surface of alumina following the method of Herz[13] afforded no cyclic material; only the product *I* of direct substitution was formed. It may be noted that the major effect of changing the solvent to acetic acid was to increase the yield of direct substitution product *I* to 30 per cent, an expected effect in view of Bartlett's results in the hexenyl series[10].

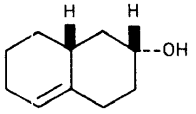
Now attention is turned to another study in which we have begun an examination of systems that are expected to be intrinsically more susceptible to ionization than those involving primary *p*-nitrobenzenesulphonates just described. One of a number of potential candidates is the allylic system which was expected to serve as a progenitor of relatively stable (allylic), and hence easily generated, cationic sites†. One further advantage of the allylic system is that the competing direct substitution reaction promoted by attack of solvent on the allylic cation is potentially (under appropriate conditions) reversible. Instead of being irreversibly eliminated by direct substitution, as in the solvolysis of the primary *p*-nitrobenzenesulphonates, this cationic site thus may be continuously regenerated until it finally reacts essentially completely with the olefinic bond.



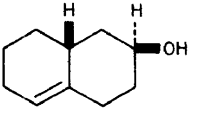
(XXVIII)

The first, and simplest, system to be examined was 2-(Δ^3-butenyl)-Δ^2-cyclohexenol (XXVIII) which was readily prepared by alkylation of dihydroresorcinol with butenyl iodide, followed by reduction with lithium aluminium hydride. The product (XXVIII), which was purified *via* the crystalline 3,5-dinitrobenzoate, m.p. 62·5–64°, proved to be extremely susceptible to cyclization. Indeed on dissolution in anhydrous formic acid at room temperature, essentially all of the starting material had reacted in less than 5 minutes as estimated by thin layer chromatography. After 5·5

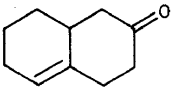
† A precedent for this type of cyclization is found in the conversion of *S*-(−)-linalool into *R*-(+)-terpineol[14].



(XXIX)



(XXIXa)



(XXIXb)

minutes, the reaction mixture was made alkaline so as to convert any formates into the corresponding alcohols. This product was then analysed by vapour phase chromatography on a Craig succinate column, which indicated the following composition:

92 per cent *syn*†-$\Delta^{1,9}$-6-octalol (XXIX), 6 per cent *anti*†-octalol (XXIXa), and 2 per cent olefins

The absolute yield of the octalol (XXIX), determined by quantitative peak enhancement experiments, was 80 per cent. The actual yield, therefore, is between 80 and 92 per cent.

Evidence for the structure and configuration of the *syn* and *anti* octalols (XXIX) and (XXIXa) was provided as follows. The fraction containing a mixture of these alcohols was separated by preparative gas chromatography, and one of the components was isolated as the crystalline 3,5-dinitrobenzoate, m.p. 118–119·5°, the compositional analysis of which was compatible with the formula $C_{17}H_{18}O_6N_2$. Oxidation of the alcohol mixture with Jones reagent gave a single (by gas chromatography) ketone, namely $\Delta^{1,9}$-6-octalone (XXIXb), characterized as the 2,4-dinitrophenylhydrazone, m.p. 172–174°. The n.m.r. spectrum of this derivative was entirely consistent with the presumed structure. Since there was absorption for one, and only one, ethylene proton, and since the double bond did not move into conjugation with the hydrazone residue, the structure of the octalone must be that represented by (XXIXb). Reduction of this ketone with lithium aluminium hydride gave a mixture of epimeric alcohols which exhibited gas chromatographic behaviour identical with that of the alcohols produced in the cyclization reaction. The preponderant epimer obtained in the reduction corresponded to that in the cyclization, and it showed a higher retention time on gas chromatography than the less preponderant isomer. The former alcohol is therefore considered to be the substance (XXIX) with a pseudo equatorial hydroxyl group, and the latter isomer is regarded as the epimer (XXIXa).

Some other cyclization conditions were examined. With 0·08N perchloric acid in 80 per cent aqueous acetone at 75°, the reaction was about 90 per cent complete in 4·5 hours. The product composition was almost the same as that obtained in the experiment described above. Very similar results were also obtained on solvolysis of the 3,5-dinitrobenzoate of the butenylcyclohexenol (XXVIII) in either of the media mentioned above, but these reactions were considerably slower. Thus solvolysis in perchloric acid–aqueous acetone at 75° required 29 hours, and in formic–acetic acid (82:18)

† The terms *syn* and *anti* are used here to designate the stereochemical relationship between the hydrogen atom on the carbon bearing the substituent (usually hydroxyl) and the hydrogen atom in the nearest angular position.

at room temperature, 8 hours for about 90 per cent completion. When the solvolysis of the ester in formic–acetic acid was conducted at 75° for 2·3 hours, the gas chromatogram exhibited a new peak. After a reaction period of 4·7 hours, none of the $\Delta^{1,9}$-octalols remained, and only the peak corresponding to the new substance was present. This new product, therefore, is derived from both of the octalols. Since it showed no resonance for an ethylenic proton in the n.m.r. spectrum, it is tentatively regarded as the product resulting from migration of the olefinic bond of (XXIX) and (XXIXa) into the 9, 10 position.

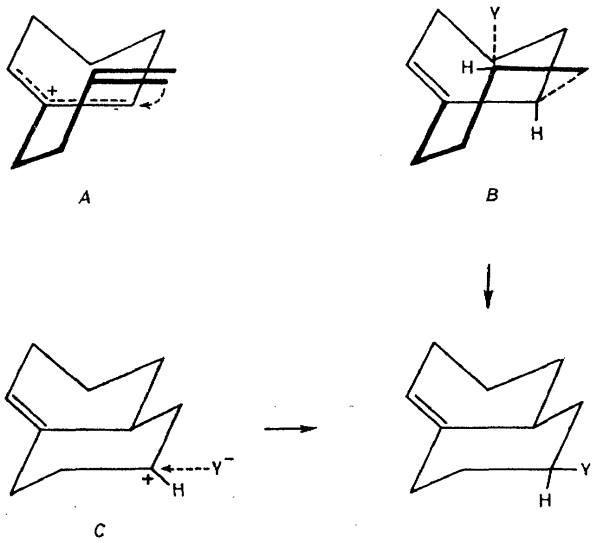
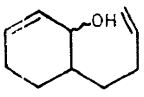


Figure 4

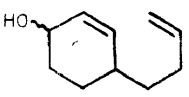
The stereoselective formation of the *syn* isomer (XXIX) in the cyclization may be rationalized as a rapid ionization to the allylic cation A (*Figure 4*) followed by a synchronous ring closure and attack by nucleophile as suggested by formula B. Alternatively the process could be stepwise, giving the intermediary cyclic secondary cation C which undergoes preferential equatorial attack by the nucleophile. It is possible that the cyclization occurs synchronously with the ionization of the allylic system, as is evidently the case in the linalool → terpineol conversion[14]. However, in the systems described below, evidence has been obtained which suggests (but does not prove) that the ionization step precedes cyclization.

We next undertook the examination of the cyclization of the butenylcyclohexanols (XXX) and (XXXI). This pair is of interest because, if ionization precedes cyclization, these substances would afford a common intermediate. The alcohols (XXX) and (XXXI) were prepared as follows. *o*-(Δ^3-Butenyl)-anisole (XXXII), obtained by coupling allyl magnesium bromide with *o*-methoxybenzyl bromide, was submitted to Birch reduction

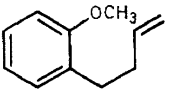
with lithium and ethanol in ammonia at −78°†. Mild acid hydrolysis of the resulting enol ether, followed by treatment with piperidine[15], gave the piperidyl ketone which was converted into the crystalline methiodide (XXXIII). On warming with pyridine this quaternary salt decomposed to



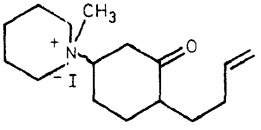
(XXX)



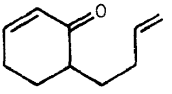
(XXXI)



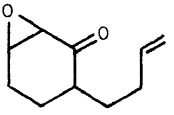
(XXXII)



(XXXIII)



(XXXIV)



(XXXV)

give 6-butenyl-Δ^2-cyclohexenone (XXXIV). Quantitative analysis of this product by n.m.r. spectroscopy demonstrated that the terminal vinyl group was intact to the extent of about 87 per cent. The remainder of the material was undoubtedly the dihydro compound resulting from partial reduction of the vinyl group. This contaminant evidently was not eliminated on recrystallization of the quaternary salt (XXXIII). It was, therefore, carried all the way through the series, as it was not expected to interfere with the cyclization experiments.

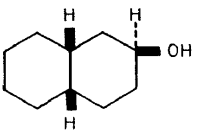
Treatment of the unsaturated ketone (XXXIV) with lithium aluminium hydride under conventional conditions resulted in considerable reduction of the conjugated olefinic bond as well as of the carbonyl group. After considerable experimentation a low temperature procedure was finally developed which, as shown by vapour phase chromatography, gave a product consisting of 81 per cent of a 2·3: 1 epimeric mixture of the desired dienol (XXX).

For the preparation of the isomeric butenylcyclohexenol (XXXI), the dienone (XXXIV) was converted, by the action of alkaline hydrogen peroxide, into the epoxy ketone (XXXV) (undoubtedly a mixture of epimers), which was submitted to the Wharton rearrangement[16]. Thus, treatment with hydrazine and acetic acid gave a product which, by quantitative vapour phase chromatographic and n.m.r. spectroscopic analysis, was shown to contain 71 per cent of the desired dienol (XXXI) as a 2·1: 1 epimeric mixture. This material was also used directly in the cyclization studies.

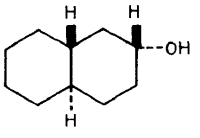
When the dienols (XXX) and (XXXI) were treated with formic–acetic acid (82:18) at room temperature, the reaction was about 90 per cent complete after 5 minutes. After 18 minutes the reaction mixture was

† B. W. Roberts, of our laboratory, has demonstrated that these mild conditions are required in order to minimize reduction of the terminal vinyl group.

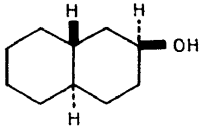
neutralized, and the product treated with excess lithium aluminium hydride to convert esters to alcohols. Vapour phase chromatography showed one major alcohol peak corresponding to a relative yield of 92 per cent of the same octalol from both of the dienols. The solvolysis product was hydrogenated over palladium-on-carbon in order to saturate the olefinic bonds,



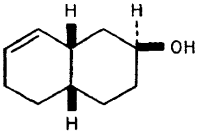
(XXXVI)



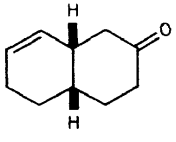
(XXXVII)



(XXXVIII)



(XXXIX)



(XL)

and then analysed by vapour phase chromatography. By quantitative peak enhancement experiments with the known β-decalols, it was possible to show that the absolute yield (corrected for the state of purity of starting material) of alcohols from the dienol (XXXI) was as follows: 56 per cent of *cis-anti*-β-decalol (XXXVI), 5 per cent of *trans-syn*-β-decalol (XXXVII), and 0 per cent of *trans-anti*-β-decalol (XXXVIII). The yields from the dienol (XXX) were: 68 per cent of (XXXVI), 10 per cent of (XXXVII) and 3 per cent of (XXXVIII). The deduction that the principal primary product of cyclization was $\Delta^{7,8}$-*cis-anti*-2-octalol (XXXIX) was confirmed by isolation of the octalol fraction *via* preparative gas phase chromatography. The n.m.r. spectrum of this fraction indicated absorption for two ethylenic protons showing that the double bond did not involve one of the bridgehead carbons. Oxidation of the octalol fraction with Jones reagent gave a ketone (XL) which was converted to a yellow (unconjugated) unsaturated 2,4-dinitrophenylhydrazone, m.p. 167–168°. The n.m.r. spectrum of this derivative also exhibited absorption for two ethylenic protons. The small yields of *trans*-decalols (XXXVII) and (XXXVIII) found after hydrogenation may indicate the formation of traces of the corresponding $\Delta^{7,8}$-octalols in the cyclization; however the *trans*-decalols might be artefacts due to bond migration or to isomerization at the allylic position during hydrogenation[17].

Considering the state of purity of the starting dienols, and the number of operations involved, before an analysis of products could be made, the yields of cyclic products are, within experimental error, the same from each isomeric dienol. This result constitutes evidence† for a common intermediate, namely the allylic cation D.

† Note that the result is a necessary, but not sufficient, condition for proof of the intermediacy of the allylic cation.

Of special interest is the high degree of stereoselectivity of the cyclization to give, unexpectedly, the *cis-anti*-octalol (XXXVI) in good yield. Formation of the *cis-anti* isomer precludes a concerted *trans*-addition of nucleophile to the olefinic bond which would lead to the *syn* series. The results, on the contrary, suggest a stepwise process with the intermediacy of a secondary bicyclic cation like E (*Figure 5*). Examination of Dreiding models suggests

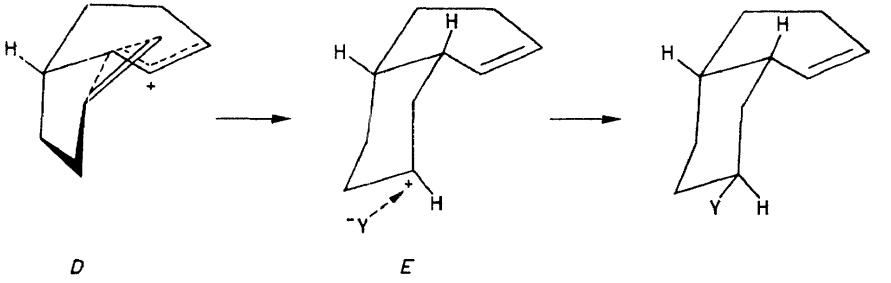


Figure 5

that when the allylic cation is in a conformation that would lead to a *cis*-fused product, *e.g.*, that represented by formula D, the bond angles permit better overlap of the empty orbital of the allylic cation with the π orbital of the terminal olefinic bond, than with conformations which would lead to *trans* ring fusion. Perhaps it is this stereo-electronic factor which is responsible for the preference of cyclization to form a *cis*-fused product, D→E. If the nucleophile makes a preferential equatorial attack on the intermediary bicyclic secondary cation, the latter must react in the conformation E, rather than in its flipped version, in order to yield the product found.

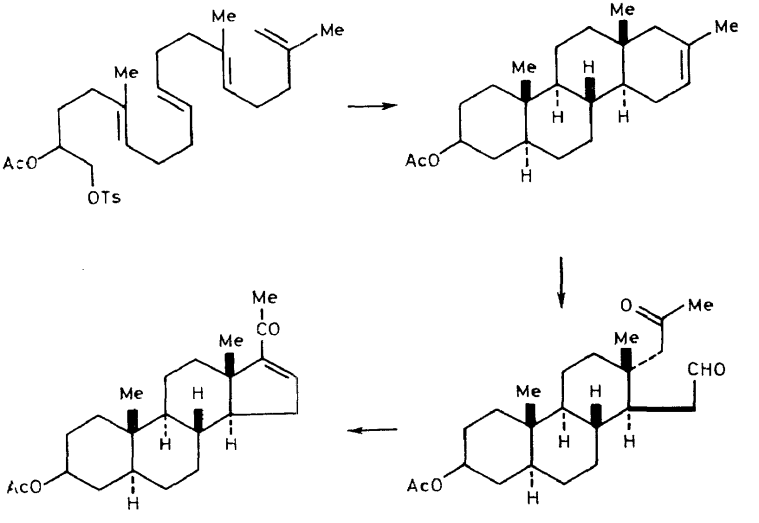


Figure 6. Proposed scheme

The foregoing represents a progress report on work that is essentially completed. We are currently in the process of examining more complex systems which afford the potential of producing three and four ring systems from acyclic substrates; the possibilities here are illustrated by the *speculative* scheme in *Figure 6*. We are also exploring other methods of generating cationic sites.

Finally I wish to express my appreciation to my co-workers. These collaborators, namely Denis M. Bailey, Russell A. Bell, Konrad O. Fitzi, Sharon L. Gray, Brian Jaques, William H. Lunn and Raymond Owyang, deserve the major credit for the work described in this paper.

I wish also to express thanks to the U.S. Public Health Service and the National Science Foundation for supporting the work reported in this article.

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