REVIEWS

The Thermal Cyclisation of Unsaturated Carbonyl Compounds

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This review describes the wide synthetic uses of thermal cyclisation reactions of unsaturated carbonyl compounds as a method for the formation of carbon-carbon σ-bonds. Details of the mechanisms are mentioned first in order to evaluate the scope and limitations resulting from geometrical and thermodynamical aspects of the reaction. Syntheses of various systems, in particular bicyclic and bridged compounds, applications of the method in the steroid and terpenoid fields, and some applications to other more highly unsaturated systems are discussed.

Dieser Übersichtsartikel beschreibt umfassend die synthetische Anwendung von thermischen Cyclisierungsreaktionen ungesättigter Carbonylverbindungen zur Bildung von Kohlenstoff-Kohlenstoff σ-Bindungen. Zunächst werden die Reaktionsmechanismen eingehend erörtert um Anwendungsbereich und Grenzen, die sich aus geometrischen und thermodynamischen Gesichtspunkten der Reaktion ergeben, abzuschätzen. Es werden die Synthesen verschiedener Verbindungen, besonders von bicyclischen und überbrückten Systemen, Anwendungen der Methode auf Steroide und Terpene sowie auf höher ungesättigte Systeme abgehandelt.

The reactivity of the carbonyl group in intra- and intermolecular reactions can be regarded in various different ways depending on the nature of the reactive centre and the energy sources.

In basic or acidic media, the reactions of carbonyl compounds frequently involve either an enolate intermediate or the enolic tautomer. Such phenomena are the basis of a great variety of reactions used for cyclisation: Michael addition, aldol condensation, cycloalkylation, etc. The polarisability of the C=O group may also be responsible for a new base-catalysed cyclisation which leads to tertiary cycloalkanol derivatives, starting from δ- or ε-iodo (or bromo) ketones in the presence of the nickel tetraphenylporphine dianion[1].

In the case of stepwise free radical cyclisations, the carbonyl group is involved at least in two well-known different ways: either by accepting a γ-hydrogen leading to a 1,4 diradical intermediate which then cyclises to a cyclobutanol derivative[2]; or by stabilising a free radical centre in the α-position which can subsequently lead to cyclic C_5 and C_6 compounds by intramolecular attack on an unsaturated centre situated in the δ-position[3,4,5].

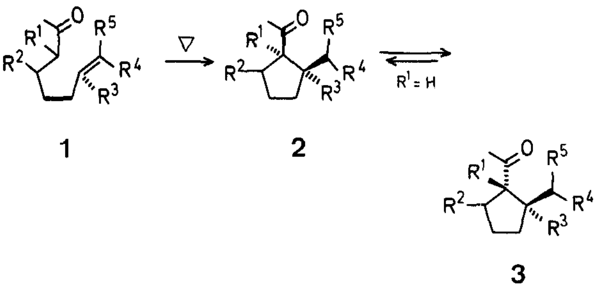
Another class of intramolecular reactions of the carbonyl group is the thermal reaction of unsaturated carbonyl compounds. Such compounds are able to undergo considerable changes in structure, under relatively mild thermal conditions, by intramolecular hydrogen displacement leading to ring closure[6].

The type of process reported in this article is, in fact, an intramolecular variant of the general intermolecular "*ene*" reaction, a process defined earlier by Alder[7] and recently well reviewed by Hoffmann[8]. As is usually the case, this class of six electron process, which here involves an enol hydrogen shift, follows a concerted route and the stereospecificity of the reaction, i.e. the ring size and the stereochemistry of the different groups present or formed in the ring closure reaction, is the main aspect of the reaction to be considered.

1. The Reaction

1.1. Mechanistic Aspects

The most significant example of the thermal behaviour of unsaturated carbonyl compounds is represented by the thermal cyclisation of the oct-7-en-2-one system in which four carbon atoms separate the two unsaturated termini. Oct-7-en-2-one (**1**; R^1 to $R^5 = H$), heated in a sealed tube or in the vapour phase at around 350°, is converted smoothly and quantitatively into a mixture of *cis*- and *trans*-2-methylacetylcyclopentanes (**2** and **3**) in the equilibrium ratio 7:93[9,10,11].



1 **2** **3**

When an alkyl group is present in the α-position of the starting compounds ($R^1 = CH_3$, for instance), the same cyclisation occurs and gives quantitatively a single non-epimerisable product, *trans*-1,2-dimethylacetylcyclopentane (**2**; $R^2 - R^5 = H$, $R^1 = CH_3$) in which the methyl group formed by the cyclisation process and the acyl group assume a *cis*-configuration.

Thermal cyclisation still occurs with aryl-substituted aliphatic ketones (**1**, for instance, with $R^1 = C_6H_5$ instead of CH_3), with more highly alkyl-substituted aliphatic or alicyclic ketones, and with ketones substituted by functional groups, for example: **1**; $R^1 = R^5 = COOC_2H_5$.

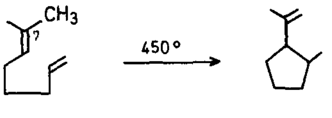
The process clearly results from two consecutive and distinct steps: the formation of the enol intermediate, generated catalytically by 1,3-hydrogen displacement at elevated temperature, followed by hydrogen shift from the enol group to the terminal double bond with simultaneous formation of the $\alpha,\varepsilon,\sigma$-bond.

In this case, where the formation of a C_5 ring is invariably observed, independent of the degree of substitution, the alkyl group generated in the ring closure process must initially be *cis* with respect to the acyl group. The formation of the *trans*-isomer in all cases of thermal cyclisation of α-unsubstituted-ε-unsaturated aliphatic carbonyl compounds is the consequence of the subsequent enolisation towards the ring, which occurs in the final cyclic compound under the conditions of the reaction and leads mainly to the thermodynamically more stable *trans*-isomer.

Other cases of formation of *trans*-isomers have been observed in the aliphatic and alicyclic series which are not due to this factor. Such results arise from the different allowed orientations of the two olefinic sites in the transition states, a question which will be discussed in Section 1.5.

Arguments for unimolecularity of the reaction might be based upon kinetic measurements and determination of Arrhenius parameters. This has not been clearly achieved in the case of the carbonyl compounds (although a first order rate constant has been reported in one case)[10], because the reactant is the site of two different reactions, both of which are obviously kinetically controlled: (i) enolisation, which depends on different factors such as catalytic conditions (here the nature of the glass vessel, for example) and the effects of temperature and pressure; (ii) a type of thermal concerted 1,5-hydrogen shift.

Fortunately a similar process occurs when the enolic hydrogen atom is replaced by an allylic one[12,13,14]; such a *cis*-cyclisation has been claimed for instance in the case of the 1,6-dienes **4** bearing a methyl group at the 7 position. Although this thermally induced cyclisation reaction requires vigorous conditions, the reaction seems to be unaffected by the introduction of radical initiators or inhibitors and a first order rate constant is observed.



4 **5**

In this case, the thermodynamic data reported show that the reaction is endothermic towards the C_5 ring formation and the entropy is one of the lowest known for a unimolecular process[12,20].

Other evidence reported which establishes the mechanism of this cyclisation of ε-unsaturated car-

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[1] E. J. Corey, I. Kuwajima, *J. Amer. Chem. Soc.* **92**, 395 (1970).

[2] P. J. Wagner, G. S. Hammond, *Advan. Photochem.* **5**, 21 (1968).

[3] M. Julia, M. Maumy, *Bull. Soc. Chim. France* **1965**, 434; **1968**, 1603.

[4] R. Dulou, Y. Chretien-Bessieres, H. Desalbres, *C. R. Acad. Sci., Paris* **258**, 603 (1964).

[5] J. P. Montheard, *C. R. Acad. Sci., Paris* **266**, 577 (1965).

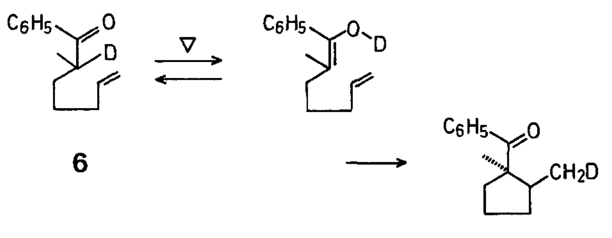
[6] J. M. Conia, *Bull. Soc. Chim. France* **1968**, 3057.

[7] K. Alder, M. Schumacher, *Fortschr. Chem. Org. Naturstoffe* **10**, 1 (1953).

[8] H. M. R. Hoffmann, *Angew. Chem.* **81**, 597 (1969); *Angew. Chem. Internat. Edit.* **8**, 556 (1969).

[9] F. Rouessac, P. Le Perchec, J. M. Conia, *Bull. Soc. Chim. France* **1967**, 818.

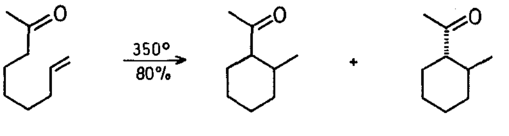
bonyl compounds has been obtained from experiments with labelled compounds. For instance, in reactions of α-deuteriated ketones such as **6**, the deuterium shift to the terminal carbon atom gives rise to a deuteriomethyl group in **7**, clearly indicating the participation of an enol intermediate[10].



6 **7**

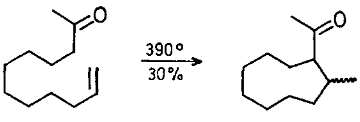
1.2. Chain Length Requirements

From the general considerations of the mechanistic aspect of this reaction it can be expected that the cyclisation of unsaturated carbonyl compounds will occur when the geometry of the system favours a six electron cyclic process, involving the participation of an enol intermediate and the alkenic centre situated in the hydrocarbon chain. This condition is obviously readily obtained when four carbon atoms separate the two unsaturated centres. By increasing the chain length, for example when five carbon atoms are between the alkenic site and the carbonyl group, the cyclisation reaction is again observed in the same range of conditions (350°/1 h)[15,16] and the product with a six-membered ring is formed in good yield. This is depicted in the scheme below by the thermal cyclisation of non-8-en-2-one which, as an α-unsubstituted system, leads to a mixture of the *cis* and the *trans* isomers **9** and **10**, in approximately equal amounts.



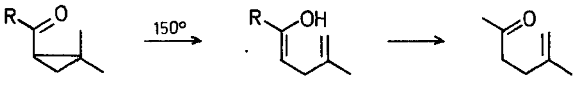
8 **9** **10**

Investigations of medium-sized ring synthesis have also been reported[15,16]; for example, 2-methylacetylcyclononane (**12**) is obtained from dodec-11-en-2-one (**11**), but the reaction needs a higher temperature (around 390°), the yield is considerably lower (around 30%), and the reaction gives other unidentified side products. It might be argued that it becomes more and more difficult for the reactant to achieve a rigid transition state—i.e. the gain in entropy should be practically negligible—when the length of the carbon side chain increases.



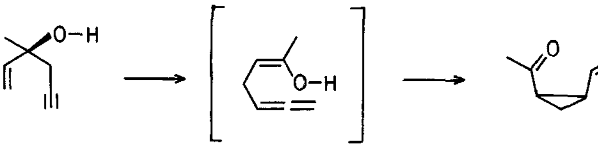
11 **12**

Intramolecular hydrogen transfers are also thermally induced between the aliphatic allylic enol and cyclopropyl carbonyl systems[17,18,19]. But in this case, the reverse reaction takes place and a ring opening is always observed when *cis*-2-methyl-(or alkyl)-cyclopropyl carbonyl compounds (**13**; R = H, alkyl, aryl, OR, etc.) are submitted to thermal conditions (**13**→**14**→**15**). Kinetic measurements have been made at 150°; they show an activation energy parameter of 33 Kcal/mole, a value in agreement with the energy demand for a concerted 1,5-hydrogen shift[20]. The reversible character of this process has been nicely demonstrated by using labelled allylacetophenone derivatives[18,19].



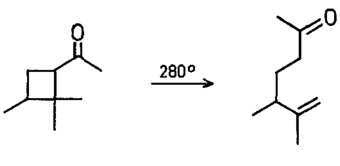
13 **14** **15**

The existence of a thermal equilibrium between γ-unsaturated aliphatic carbonyl compounds and the corresponding cyclopropyl ketone suggests that the reaction will go exclusively in the direction of cyclisation, if the nature of the hydrogen acceptor, which becomes a hydrogen donor when the cyclic compound is formed, does not satisfy the condition required for the reverse ring opening reaction. Such conditions occur in the case of the reaction of the allenic enol **17**, formed by heating methylvinylpropargylmethanol (**16**), which is converted into 1-acetyl-2-vinylcyclopropane (**18**)[21,22]. For the different thermal behaviour of the corresponding ene-allenol, see ref.[23].



16 **17** **18**

In the cyclobutane series, when an acyl function and an alkyl group are attached to the ring in a *cis*-configuration, the ring opening process is also favoured, but the question of the reversibility of the process has not been settled[15,16], e.g. the reaction **19**→**20**.



19 **20**

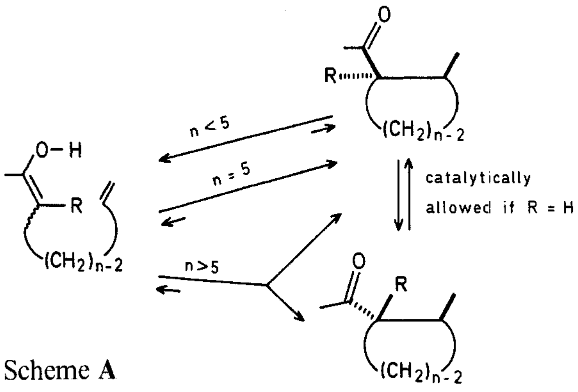
According to the microscopic reversibility principle[24], whatever the direction of the reaction is, it seems reasonable to consider the hydrogen displacement formally as a 1,5-hydrogen shift in both directions accompanied by the formation or the cleavage of one σ-bond. In fact, if the ring opening reaction, such as **13**→**15** and **19**→**20**, can be considered as a true 1,5-suprafacial hydrogen shift, the ring closure reaction is more closely related to the intramolecular ene-reaction which also involves a cyclic 6-electron process but with a different spatial arrangement of the two reactive centres (see Section 1.5.).

In addition to the reversible character of the process, strongly supported by the results shown in the cyclopropane series, at least one other factor may affect the stereochemistry of the cyclisation: the spatial arrangement of the two reactive centres, which mainly depends on the configuration at the enol centre and the various steric effects arising from the chain in the ground state.

In the thermal reaction of oct-7-en-2-one (**1**; $R^1=H$) the equilibrium *cis-trans* mixture is obtained, but no simple conclusion can be reached concerning the importance of each factor, because subsequent enolisation of the cyclic product would modify the product ratio. However, with 3-methyloct-7-en-2-one (**1**; $R^1=CH_3$) the results are more clear, since only the *trans*-1,2-dimethyl-1-acetylcyclopentane is formed which suggests only one spatial arrangement.

Moreover, such a result excludes a possible hydrogen exchange between a cyclic *trans*-C_5-structure and the open chain compound in a retro-ene type reaction by direct suprafacial displacement, a result which has been experimentally verified and is understandable, due to the very unfavourable configuration of the alkyl and acyl group for a planar framework.

The general scheme is as shown in Scheme **A**.



Scheme **A**

As the reaction should follow the endothermic route, the result will be a ring closure for $n \geqslant 5$ and a ring opening process for $n=3,4$[6,15]. The best results are obtained for the C_5 ring formation ($n=5$) but the reaction is still suited enough for the formation of various C_6 systems ($n=6$), particularly in the bicyclic series (cf. Section 2).

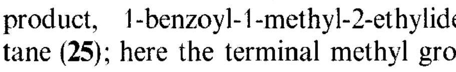
1.3. Nature of Hydrogen Acceptors and Donors

The examples so far reported have been exclusively concerned with the thermal cyclisation reactions of olefinic ketones, but the same reaction has been observed satisfactorily with various other groups as acceptors and donors of hydrogen atoms.

ε-Alkynic ketones

Carbonyl compounds containing an alkynic bond seem *a priori* less favourable as precursors for cyclisation; strain increase is expected by the participation of a triple bond in the transition state and by the presence of a double bond in the final cyclic product. However this is largely compensated for by the difference in dissociation energy between alkynic and alkenic bonds. Several examples of thermal cyclisation of octynones have been reported[25,34].

Oct-7-yn-2-one (**21**) under mild thermal conditions (3 h, 260°) reacts quantitatively to give a mixture of conjugated and *endo*-unconjugated 1-acetyl-2-methylcyclopentenes (**22** and **23**) (in the ratio 85:15). A different result is observed when the α-hydrogen atom is replaced by a methyl substituent which prevents reconjugation after cyclisation: phenyl 1-methylhex-5-ynyl ketone, on heating at 350° reacts to give exclusively and quantitatively 5-benzoyl-1,5-dimethylcyclopentene, but again with no trace of the isomer with the *exo* double bond, which nevertheless must be the primary product of the cyclisation. In fact, the *exo-endo* isomerisation is a well known phenomenon even in hydrocarbon series, particularly from *exo*-methylene substrates.



21 **22** **23**

The study of an alkynic ketone substituted on the triple bond[25] confirms the fact. For example phenyl 1-methylhept-5-ynyl ketone (**24**), heated in a sealed tube at 300° for 2.5 h, is converted into a single product, 1-benzoyl-1-methyl-2-ethylidenecyclopentane (**25**); here the terminal methyl group stabilises the *exo*-double bond. It can therefore be concluded from this result that the alkyne bond enters directly into the cyclisation process without any alkyne-allene isomerisation; other examples will be given below.

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[10] P. Le Perchec, F. Rouessac, J. M. Conia, *Bull. Soc. Chim. France* **1967**, 830.

[11] F. Rouessac, R. Beslin, J. M. Conia, *Tetrahedron Lett.* **1965**, 3319.
F. Rouessac, J. M. Conia, *Tetrahedron Lett.* **1965**, 3313.

[12] W. D. Huntsman, T. H. Curry, *J. Amer. Chem. Soc.* **80**, 2252 (1958).

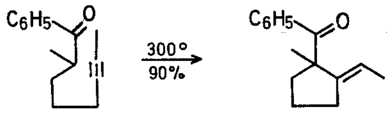
[13] W. D. Huntsman, V. C. Solomon, D. Eros, *J. Amer. Chem. Soc.* **80**, 5455 (1958).

[14] H. Pines, N. E. Hoffmann, V. N. Ipatieff, *J. Amer. Chem. Soc.* **76**, 4412 (1954).

[15] J. M. Conia, F. Leyendecker, *Bull. Soc. Chim. France* **1967**, 830.

[16] J. M. Conia, F. Leyendecker, C. Dubois-Faget, *Tetrahedron Lett.* **1966**, 129.

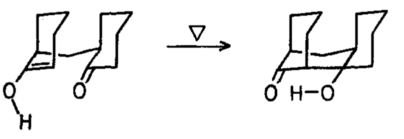
[17] R. M. Roberts, R. G. Landolt, *J. Amer. Chem. Soc.* **87**, 2282 (1965).



24 **25**

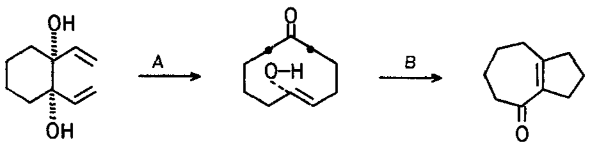
Mono- and Dicarbonyl Compounds

Intramolecular thermal aldolisation reactions include examples of C_5 and C_6 ring formation by hydrogen shift. Aliphatic diketones such as 1,5-dibenzoylpentane and 1,4-dibenzoylbutane undergo ring closure reactions under similar thermal conditions; another interesting example is reported[26]: pyrolysis of the dione **26** leads to the β-ketol **27**.



26 **27**

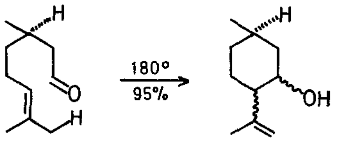
Usually the ketol intermediate is not isolated, the reaction being followed by dehydration. It has been proposed that the same scheme is applicable to transannular cyclodehydration reactions[27,28,29] e.g. **28**→**29**→**30**.



28 **29** **30**

Reaction A: Cope and monoketonisation
Reaction B: Enol hydrogen shift and dehydration

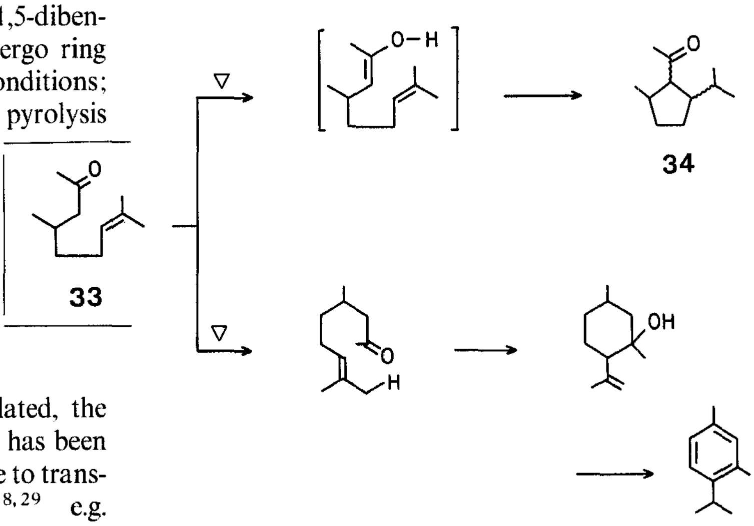
The carbonyl function is also involved as a reactive acceptor centre when allylic hydrogens are present in the side chain. The thermal cyclisation reaction of (+)-β-citronellal (**31**)[30,31,32], into the four C_6 isopulegol isomers **32** has been reported, a reaction used as an industrial method in the synthesis of e.g. (−)-menthol.



31 **32**

Because enolisation is a slow process in the vapour phase, the reaction is completely directed toward the hydrogen shift from the allylic methyl group to the carbonyl group as acceptor; no cyclopentane ring formation by hydrogen shift from a hypothetical enolic intermediate to the C=C double bond has been detected.

A similar example has been examined[34] using the methyl ketone **33** corresponding to aldehyde **31**. The results are quite different since the reaction was effected by a different technique (sealed tube) where the effect of pressure and the nature of glass is known to favour the formation of the enol intermediate. On heating up to 350°, the ketone **33** shows two competitive processes, where both allylic and enolic hydrogen shifts are involved leading to C_5 and C_6 ring formation, namely products **34** and **35**.

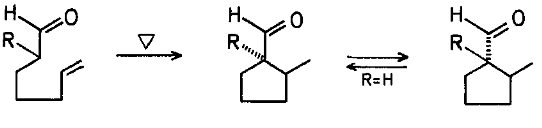


33 **34** **35**

ε-Unsaturated Aldehydes

Unsaturated aldehydes behave similarly to unsaturated ketones; thermal cyclisation occurs in the same range of temperatures, but reactants and products are more sensitive to such thermal conditions and the starting compounds must be used in a high degree of purity. Both heptenal and octenal structures have been investigated[34,35,36].

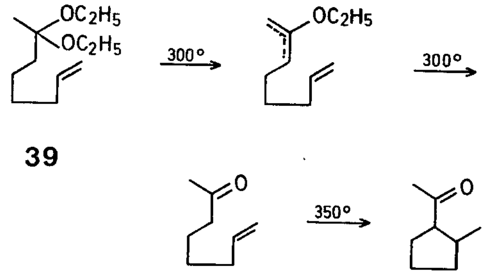
Only the *cis*-product is obtained from the α-substituted aldehyde (**36**; $R=CH_3$). In the octenal series, the reaction fails and degradation products are formed, even under mild conditions.



36 **37** **38**

Potential Carbonyl Compounds

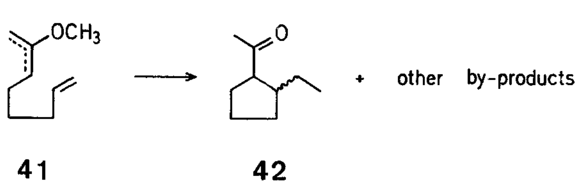
Acetals, enol ethers, and enol acetates are thermal precursors of ketones by elimination reactions more or less related to a 1,5-hydrogen shift. Thus, ketones are formed at 200° from enol acetates, at 300° from enol ethyl ethers, and at higher temperatures, via the enol ethers, from diethylacetals[38]. Consequently, if the temperature is high enough, the cyclic structure is obtained from the regenerated ketone[38], e.g. the reaction of the diethylacetal **39** to give the cyclopentane **40**.



39

40

It should be noted that methyl enol ethers are unable to undergo an elimination as from **39** and advantage has been taken of this in an attempt to carry out cyclisation by an alkyl group shift (here CH_3). Actually when the mixture of the methyl enol ethers **41** (three isomers) of oct-7-en-2-one is heated to around 350°, a new cyclic ketone is formed, 1-acetyl-2-ethylcyclopentane (**42**)[38].

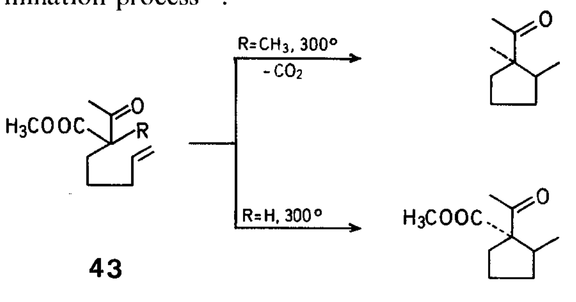


41 **42**

However, it has been recently established that such a methyl shift involves a homolytic process[39]. Concerning a related 1,3-alkyl shift, see ref.[40].

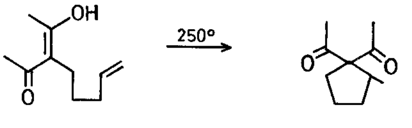
Unsaturated β-Ketoesters and β-Diketones

It has been shown that the presence of a methyl ester group on a C=C double bond does not prevent the thermal cyclisation of ε-ethylenic ketones, such a group being retained in the reaction. If this group is located α to the carbonyl group of an unsaturated ketone such as **43** (R = H) the same cyclisation occurs. But if no hydrogen atom is present at the α-position, e.g. **43** (R = CH_3), cyclisation still occurs, but with preliminary loss of the ester group involving the participation of the acyl group in a multicentre elimination process[38].



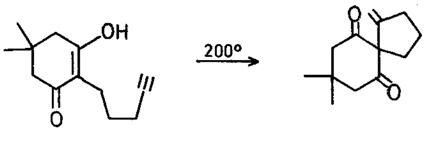
43

The pronounced enol character of β-diketones allows cyclisation at temperatures as low as 200–250°, as for example with compound **44**.



44 **45**

In the case of an acetylenic β-diketone, such a still lower temperature avoids the *exo→endo* migration of the double bond of the product quantitatively obtained e.g. **47** from **46**[41,42].



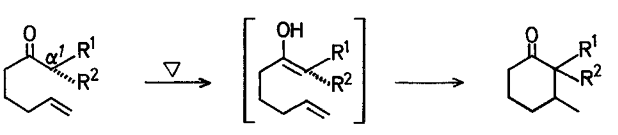
46 **47**

1.4. Orientation Phenomenon: "α'-Thermocyclisation"

In the different cases already examined the new C—C bond formed between the α and ε carbon atoms of a ε-ethylenic ketone (or the α and ζ carbon atoms of a ζ-ethylenic ketone) entails the previous generation of the α-enol intermediate.

It has been found recently[43,44] that the cyclisation reaction still occurs if the formation of the enol intermediate is oriented or forced into the opposite side: the α' carbon atom. These "α'-thermocyclisations" then lead to cycloalkanones.

An illustration of such a directive effect is the thermal synthesis of various cyclohexanones from aliphatic δ-ethylenic ketones (e.g. **48** to **49**). The reaction proceeds more easily when R^1, R^2 substituents are present. For example, when $R^1 = R^2 = H$, 3-methylcyclohexanone (**49**, $R^1 = R^2 = H$) is obtained in 35% yield by heating **48** at ~380° for 16 h, while the same cyclisation reaction takes place in 80% yield at 350°/4 h when $R^1 = R^2 = CH_3$, and in 90% yield at 300°/2 h with $R^1 = C_6H_5$, $R^2 = H$.



48 **49**

In such a system the α-cyclisation has no chance to take place since it would lead to a cyclobutyl ketone which is known to undergo the reverse process. In fact, when *cis*-2-methylacetylcyclobutane **50** is heated, 3-methylcyclohexanone is formed via, of course, the ring opened ketone.

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[18] R. M. Roberts, R. N. Greene, R. G. Landolt, E. W. Heyer, *J. Amer. Chem. Soc.* **89**, 1404 (1967).

[19] D. E. McGreer, N. W. K. Chu, R. S. McDaniel, *Chem. Commun.* **1964**, 415.

[20] M. R. Willcott, R. L. Cargil, *Thermal Unimolecular Rearrangements*, distributed at the Karlsruhe Symposium, 1969.

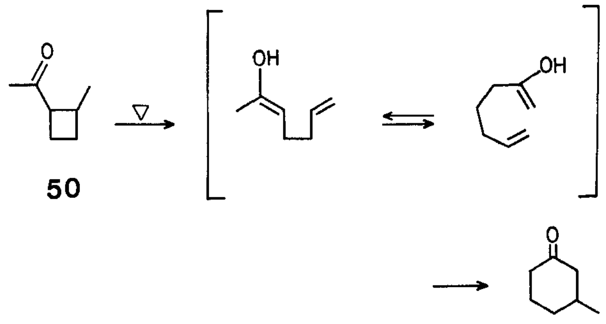
[21] J. W. Wilson, S. A. Sherrod, *Chem. Commun.* **1968**, 143.

[22] A. Viola, J. H. McMillan, *J. Amer. Chem. Soc.* **90**, 614 (1968).

[23] A. Viola, J. H. McMillan, *J. Amer. Chem. Soc.* **92**, 2404 (1970).

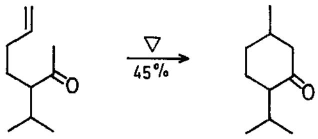
[24] A. T. Balaban, *Rev. Roumaine de Chimie* **12**, 875 (1967).

[25] F. Rouessac, P. Le Perchec, J. L. Bouket, J. M. Conia, *Bull. Soc. Chim. France* **1967**, 3554.



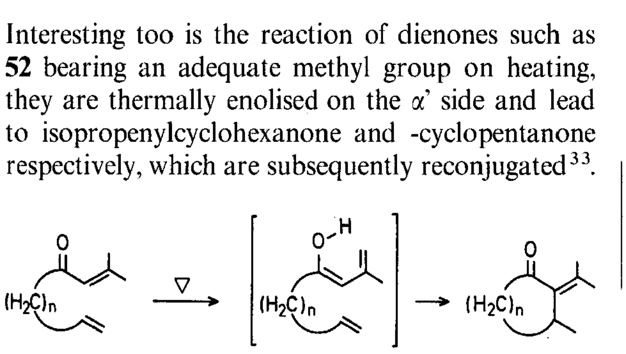
50

A nice illustration of this new synthesis of cyclohexanones is that of *dl*-menthone from 3-isopropylhept-6-en-2-one (**51**) (see Synthetic Applications, Sections 2)[43,44].



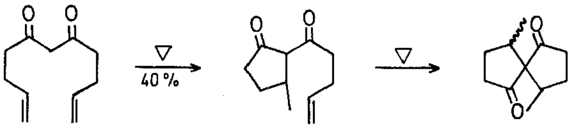
51

Interesting too is the reaction of dienones such as **52** bearing an adequate methyl group on heating, they are thermally enolised on the α' side and lead to isopropenylcyclohexanone and -cyclopentanone respectively, which are subsequently reconjugated[33].



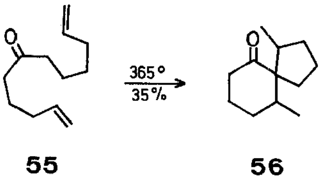
52

From the symmetrical aliphatic γ-ethylenic dione **53**, a double α'-thermocyclisation is possible with the formation of two C_5 rings; actually, as was foreseen, the spiro[4.4]dione (**54**) (two epimers) is formed via the monocyclic product[43,44].



53 **54**

Finally, as was foreseen, a double thermocyclisation reaction (α and α') has been observed with undeca-1,10-dien-6-one (**55**), a ketone ε-ethylenic on one side, δ-ethylenic on the other side. But it is not known which ring is formed first (from a common enol intermediate) in the process leading to **56**[43,44].

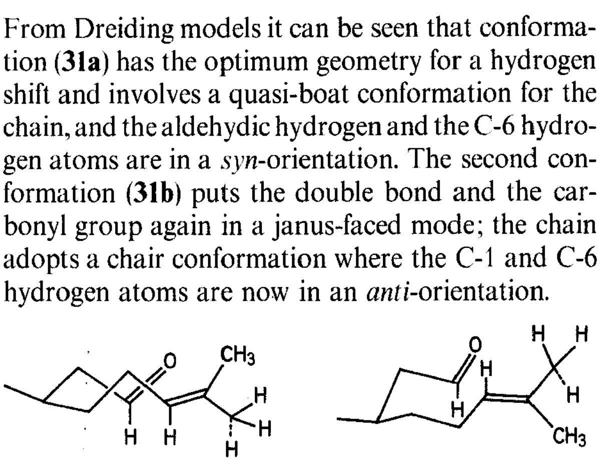


55 **56**

1.5. Stereochemistry and Geometry of the Transition State

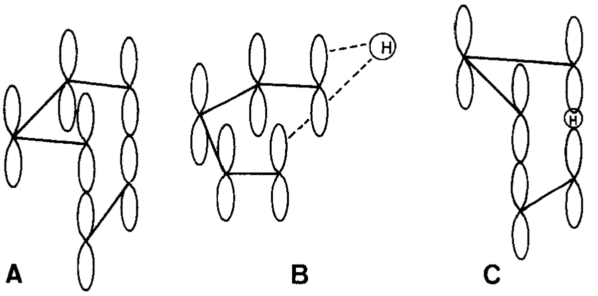
It should be born in mind that a stereospecific *cis*-cyclisation is usually found in the case of the participation of an enol intermediate from ε-unsaturated aliphatic carbonyl compounds, whatever the degree of substitution is on the chain, while different behaviour is noted when an allylic hydrogen shift is implicated. For example, the formation of the cyclohexane ring from (+)-β-citronellal (**31**→**32**) gives a 1:4, *cis:trans* ratio (hydroxyl and isopropenyl) and, in the same way, the linalols (3-hydroxy-3-methylocta-1,6-diene) have been shown, under the same conditions, to give the four possible cyclopentane stereoisomers in 4:1 *cis:trans* ratio[32].

From Dreiding models it can be seen that conformation (**31a**) has the optimum geometry for a hydrogen shift and involves a quasi-boat conformation for the chain, and the aldehydic hydrogen and the C-6 hydrogen atoms are in a *syn*-orientation. The second conformation (**31b**) puts the double bond and the carbonyl group again in a janus-faced mode; the chain adopts a chair conformation where the C-1 and C-6 hydrogen atoms are now in an *anti*-orientation.



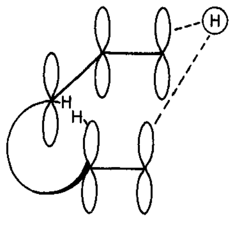
31a **31b**

Analysis of the different types of transition states in such cyclic six electrons processes has been excellently discussed and classified into three different limit states[8] (Scheme **B**). These are the Diels Alder addition (Formula **A**), the 1,5 hydrogen shift (Formula **B**) (a variant of the pericyclic $\pi_s^2+\pi_s^2+\sigma_s^2$ process) and the ene reaction (Formula **C**), where bonding in the transition state is maximised in each case differently; both of the latter could *a priori* represent the transition state of the thermal cyclisations discussed in this review.



Scheme **B**

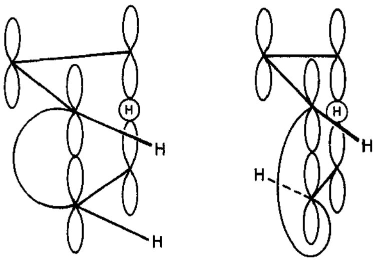
At first glance, in intramolecular concerted cyclisation the optimum orientation for a planar framework is not possible due to the obvious total steric interference arising from the two inward olefinic hydrogen atoms (Structure **D**, Scheme **C**) and particularly when alkyl groups are present in these positions.



D

Scheme C

The only favoured placement must be the intramolecular spatial arrangements **E** and **F** of the two π systems (Scheme **D**).



syn-**E** *anti*-**F**

Scheme **D**

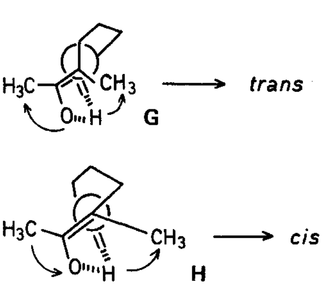
The arrangements **E** and **F** referring to the optimisation of allylic resonance should be regarded as another variant of the symmetry allowed 1,5-hydrogen shift in the sense of the Woodward-Hoffmann rules[46,47,48]. Such geometry leads to the conclusion that the stereochemistry of the new bond formed should not be taken as a criterion of the concertedness of the reaction (i.e. both *cis* and *trans* configurations are allowed). The transition states in a thermal cyclisation of an ε- or ζ-unsaturated ketone are of the same type.

Other geometries can be regarded as possible, for example a boat-like structure where the π-bonds are faced and parallel, but it would not be worth while to examine such arrangements in detail since the final results should be very similar to those obtained with states (**E**) and (**F**).

Under kinetic control, when a C_5 ring will be formed (from ε-unsaturated ketones), models clearly predict that the best orientation among the different states, at the stage of the enol intermediate, for maximum overlapping, without any perturbation due to steric interactions or torsional effects, is when the 3- and 7-H (i.e. α and ε) are in a *syn*-position (**E**). In contrast the *anti*-position seems less favoured, particularly if a boat-like structure for the transition state and a *cis*-configuration at the enol olefinic centre are taken into account.

A rational analysis may be done by considering the respective values of bond scission energies[$\Delta_{O-H} = 102 \pm 2$ Kcal (H-enol case) and $\Delta_{C-H} = 98 \pm 1$ Kcal (H-allylic case)] which are almost equivalent and presumably not fully compensated during the shift process involving the formation of a new H—C bond.

In the C_5 series it can be seen from the figure below that the formation of the C_5-*trans* isomer requires more O—H (or C—H) bond breaking (**G**) than that of the *cis*-derivative (**H**); in (**G**) the migration origin and terminus are moving away from each other when compared with (**H**)[48a].



Scheme **E**

In fact, these effects are small compared with the energy barrier of the cyclisation process but, in the case of unsaturated carbonyl compounds, are important only because the reaction is kinetically controlled by the keto-enol equilibrium. This seems to be the main reason to consider in interpreting the lack of stereoselectivity in the cyclisation by H-allylic shift of compounds like linalol which contrast with the stereospecific H-enol shift cases presented.

However, from examination of the models, the same consideration in the C_6 ring series (from ζ-unsaturated ketones) leads to quite different conclusions. The two *syn*- and *anti*-configurations appear to be practically free of strain; the only slight difference arises from the different conformations adopted by the C_6 chain where an eclipsing effect seems to favour a *trans*-cyclisation.

In summary, it can be difficult to predict the stereochemistry of the new σ-bond formed in the thermal cyclisation of unsaturated compounds when strong, non-bonded or torsional strain effects are involved during the process, a conclusion which will be particularly illustrated in the bicyclic series.

2. Synthetic Applications

The thermal cyclisation of γ- and δ-ethylenic aliphatic ketones (into cycloalkanones), of ε- and ζ-ethylenic aliphatic ketones (into cycloalkyl ketones), of

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[26] N. S. Barbulescu, G. Nadita, M. N. Tilichenko, *Zh. Obshch. Khim.* **33**, 4027 (1963).
J. A. Miller, M. H. Durand, J. E. Dubois, *Tetrahedron Lett.* **1965**, 2831.

[27] E. N. Marvell, W. Walley, *Tetrahedron Lett.* **1969**, 1337.

[28] E. N. Marvell, T. Tas, *Tetrahedron Lett.* **1969**, 1341.

[29] P. Leriverend, E. Brown, J. P. Barnier, J. M. Conia, *Bull. Soc. Chim. France* **1968**, 2630.
E. Brown, P. Leriverend, J. M. Conia, *Tetrahedron Lett.* **1966**, 6115.
P. Leriverend, J. M. Conia, *Tetrahedron Lett.* **1970**, 1040.

cycloalkanones and acylcycloalkanes substituted by an unsaturated side chain (into bi- and polycyclic ketones) and of various dienones has been investigated in order to test the usefulness of such intramolecular processes in synthesis.

2-Methylacetylcyclopentanes:

Method A (see page 18): not used.

Method B: Oct-7-en-2-one (1 g) was heated in a sealed tube at 370° for 30 min. G.L.C. and N.M.R. analysis of the colourless reaction product showed that it consisted of an equilibrium mixture of *cis*- (7%) and *trans*- (93%) 2-methylacetylcyclopentane.

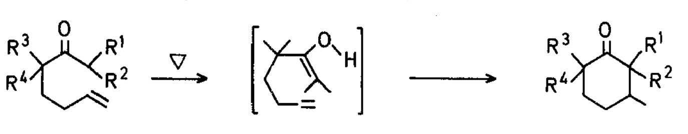
Method C: Oct-7-en-2-one was heated at 370° for 2.5 h in the static vapour phase apparatus described in Figure 1, page 18, and gave exactly the same result.

Method D: Using the gas flow process apparatus described in Figure 2, page 19, oct-7-en-2-one (11 g) was heated in the flask at 170° and atmospheric pressure and then entrained into the furnace at 440° during 12 h using a nitrogen flow of 8 ml/min. Distillation of the pyrolysate gave the same mixture of *cis*- and *trans*-2-methylacetylcyclopentanes.

2.1. Cycloalkanones

Cyclohexanones have been obtained from reactions of δ-ethylenic ketones enolisable in the α'-position[43] i.e. in good yield when suitable substituents are present in that position. (See Table 1). The presence of substituents on the other side (in α position) does not favour cyclisation. However an interesting result is the easy formation of *dl*-menthone from ketone **51** (see p. 7).

Table 1. Thermal Cyclisation of some δ-Ethylenic Ketones

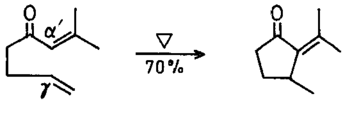


57

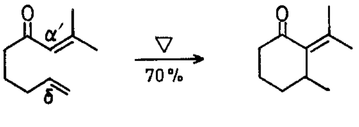
57	R^1	R^2	R^3	R^4	Reaction Conditions temp/time	Method[a]	Yield (%)
a	H	H	H	H	380°/16 h	v.p.	35
b	CH_3	H	H	H	350°/ 8 h	s.t.	60
c	CH_3	CH_3	H	H	350°/ 4 h	s.t.	80
d	$-(CH_2)_5-$		H	H	350°/ 5 h	s.t.	60
e	C_6H_5	H	H	H	300°/ 2 h	s.t.	90
f	H	H	CH_3	H	400°/16 h	v.p.	20
g	H	H	CH_3	CH_3	370°/ 6 h	v.p.	0
h	CH_3	CH_3	CH_3	CH_3	420°/ 4 h	v.p.	0

[a] v.p. is vapour phase; s.t. is sealed tube

α'-Enolisation can be initiated by a 1,5-hydrogen shift such as in the ketones **58** and **60** where another double bond is present in α'-position; cyclisation occurs from either γ-[**58**→**59**] or δ-[**60**→**61**] ethylenic ketones[33].



58 **59**



60 **61**

2-Isopropylidene-3-methylcyclohexanone (61):

2-Methylnona-2,7-dien-4-one (**60**; 0.57 g; λ_{max}(ethanol) = 239 nm, ε = 10800) was introduced following the general procedure described on page 18 into a static vapour phase apparatus (Figure 2) and heated at 370° for 3 h. At the end of the reaction the product had collected in the receiver; yield: 0.51 g. G.L.C. and N.M.R. analysis showed that this consisted of 2-isopropylidene-3-methylcyclohexanone (**61**); yield: 85%; λ_{max}(ethanol) = 252 nm, ε = 5300, and unidentified light fragments.

2,2,3-Trimethylcyclohexanone (49; $R^1 = R^2 = CH_3$):

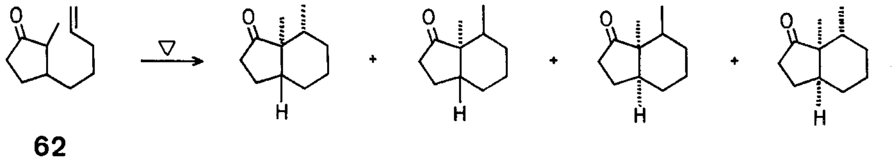
2-Methyloct-7-en-3-one (**48**; 1.0 g)—prepared by reaction of pent-4-enyllithium and lithium 2-methylpropanoate—was heated for 5 h at 350° in a 2 ml degassed sealed pyrex tube. The mixture was allowed to cool and G.L.C. and N.M.R. analysis of the product showed that it consisted of 2,2,3-trimethylcyclohexanone (**49**); yield: 80% and unidentified light fragments.

2.2. Hydrindan-1-ones

Hydrindanes and related systems have been studied because of their direct implications in the steroid chemistry field[49]. The various factors governing the relative stabilities of the *cis* and the *trans* isomers have received great attention. It appears that for hydrindane itself the *cis-trans* thermodynamic data ($\Delta H = 1.07$ Kcal, $\Delta S = 2.3$ e.u. (at 522 °K) favour the *trans*-fused configuration at room temperature but the *cis* one at elevated temperature[50]. Concerning hydrindanones, the relative stabilities depend on the position of the carbonyl group; the *cis*-configuration is usually the more stable in the case of the hydrindan-1- and -4-ones[51]. This question has led many authors to attempt a stereoselective approach to the synthesis of 17-keto-steroids having either the *cis* or *trans* C/D ring fusion.

Because of the readily available starting material, 3-(pent-4-enyl)-cyclopentanone, the thermal cyclisation process of carbonyl compounds seems ideally suited for the synthesis of such hydrindanones.

In fact, when 2-methyl-3-(pent-4-enyl)-cyclopentanone (**62**) is heated at 350° for 90 min, cyclisation occurs quantitatively and the four possible stereoisomers, expected from the general reaction pathway, of 7,7a-dimethyl-hydrindan-1-ones (**63**) are obtained[52].

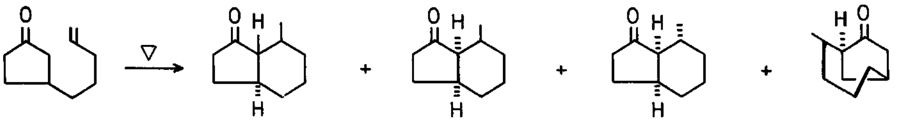


62

63a (43%) **63b** (2%) **63c** (21%) **63d** (34%)

The product ratio of such unepimerisable ketones is directly related to the optimum geometry involved in the enolic state and the reaction is not at all a stereospecific process. The chain is long enough to allow the approach of the two reactive centres on either side of the ring. From models the markedly favoured orientation seems to be the one which leads to the *cis* fused junction (i.e. on the same side on the ring plane) but this is not substantiated by the resultant *cis*/*trans* ratio (55:45). However, concerning the stereochemistry of the methyl group formed in the process the results are in good agreement with what could be expected: (**d**) is favoured over (**c**) due to the repulsion in (**c**) between the 2-CH_3 and the 4'-H atom; the same situation is found for the (**a**)/(**b**) ratio but where (**b**) looks the worst orientation of the two π-bonds.

The more thermally sensitive 3-(pent-4-enyl)-cyclopentanone (**64**) has been heated with water in order to accelerate the rate of enolisation and also to avoid resinification by working in an emulsion. This ketone heated with an equal amount of water at 350° for 2.5 h gives in 56% yield the four stereoisomeric 7-methylhydrindanones (**65**).



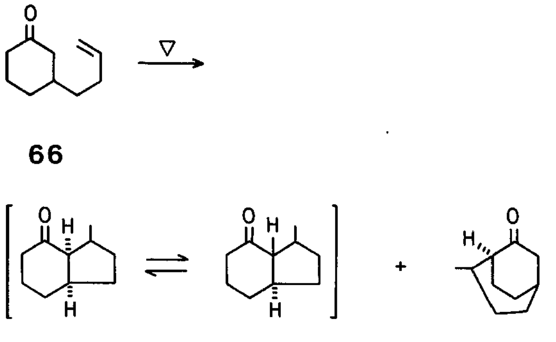
64 **65a** (23%) **65b** (17%) **65c** (52%) **65d** (18%)

Here it is not possible to establish a correlation between the transition states and the final products because of subsequent enolisation towards the fused 7a-position. In fact, the three hydrindanones are formed in the proportion expected from their respective stabilities. But α'-enolisation is now found to occur from the starting compound, which no longer has a methyl group in the α-position, and leads to a new class of compounds, possibly obtained by α'-thermal cyclisation (see p. 6), e.g. bicyclo[4.2.1]nonan-7-one (**65d**).

2.3. Hydrindan-4-ones

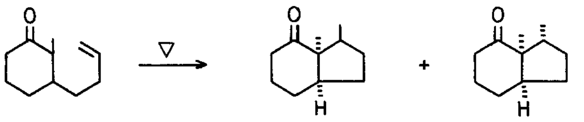
Both 3-alkenyl cyclohexanones (**66** and **69**), when heated at 350° for 1 hour, lead quantitatively to the expected cyclic products[53].

From **66**, two types of compounds are formed: the 3-methyl-*cis*- and -*trans*-hydrindan-4-ones (an equilibrium mixture 80/20) and the product of α'-thermocyclisation: 4-methylbicyclo[3.2.2]nonan-6-one (**68**).



67a (66%) **67b** (17%) **68** (17%)

The corresponding α-methylated ketone **69** undergoes the cyclisation under the same conditions (350°, 1 h) but now only two non-epimerisable *cis* products are formed: **70a** and **70b**. In contrast to the thermal behaviour of the 2-methyl pent-3-enyl-cyclopentanone, no *trans*-fused ring is observed. This is of course a direct consequence of the difference in the chain length. However α'-cyclisation is still observed (see **68**) in the cyclohexyl series, a reaction involving an intermediate with an axial side chain.



69 **70a** (70%) **70b** (30%)

An application of the process has been reported in the total synthesis of oestratrienone derivatives[54]. The reaction sequence necessitated the introduction of the adapted alkenyl chain into a rigid tricyclic system in a stereospecific way, in order to build the D-ring of the steroid skeleton.

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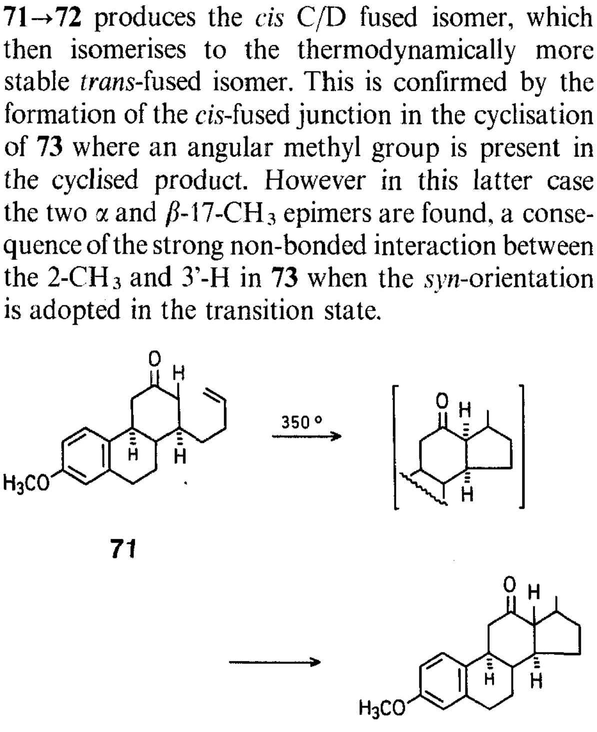
[30] K. H. Schulte-Elte, G. Ohloff, *Helv. Chim. Acta* **50**, 153 (1963).

[31] V. Grignard, U. J. Doeuvre, *C. R. Acad. Sci., Paris* **190**, 1164 (1930).

Using a reaction scheme described by Ziegler[55] two phenanthrone esters have been prepared and then converted by a five step sequence into the 1-(but-1-enyl)-phenanthr-3-ones with the B/C *trans-anti-trans* configuration and having a 1-β-butenyl side chain (**71**; **73**)[58].

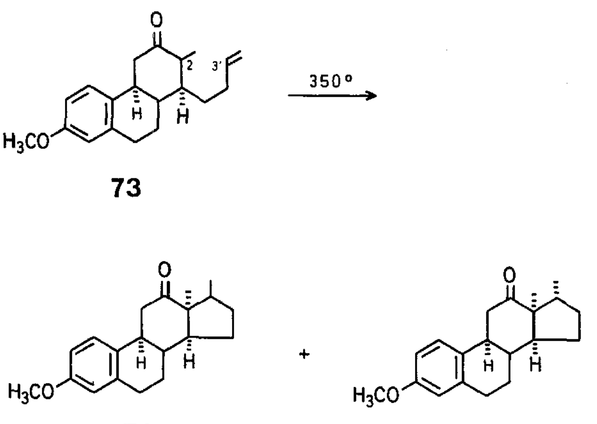
When compounds **71** and **73** are heated at 350°, using the sealed tube technique they reveal a remarkable thermal behaviour, that is they lead to the tetracyclic structures **72** and **74a** and **74b**, respectively, in good yield.

By analogy with the result observed in the bicyclic series, it is clearly assumed that the transformation **71**→**72** produces the *cis* C/D fused isomer, which then isomerises to the thermodynamically more stable *trans*-fused isomer. This is confirmed by the formation of the *cis*-fused junction in the cyclisation of **73** where an angular methyl group is present in the cyclised product. However in this latter case the two α and β-17-CH_3 epimers are found, a consequence of the strong non-bonded interaction between the 2-CH_3 and 3'-H in **73** when the *syn*-orientation is adopted in the transition state.



71

72

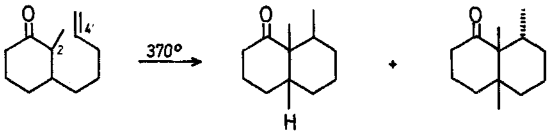


73

74 a **74 b**

2.4. *cis*-Decalones

In this series the relative stabilities of the *cis*- and the *trans*-9-methyldecal-1-one have already been shown to favour the *cis*-fused isomer at equilibrium. The thermal cyclisation applied to 2-methyl-3-(pent-4-enyl)-cyclohexanone (**75**) is a convenient way to confirm this observation. The two decalones are obtained from **75** at 370° in low yield (25%). Each has a *cis*-fused ring with either the α- or the β-configuration at the 8-position: the observed ratio (**76a**): (**76b**) (1:3) is again understandable, through the two spatial arrangements of the reactive centres[56].

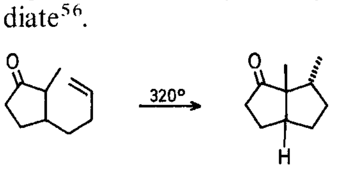


75 **76a** **76b**

From models, the *syn*-orientation (see scheme E) involves a boat conformation for the side chain in addition to the 2-CH_3, 4'-H interaction, while the *anti*-orientation is better achieved with a half-chair conformation for the side chain.

2.5. *cis*-Perhydropentalenones

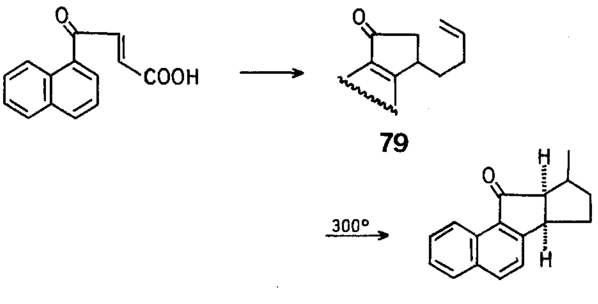
The cyclisation process has been applied to the preparation of *cis*-perhydropentalenone compounds (**78**). The reaction of the 2-substituted but-3-enyl cyclopentanone leads quantitatively, and uniquely, to *trans*-3,3a-dimethyl-*cis*-hydropentalenone (**78**), as expected from the geometry of the dienol intermediate[56].



77 **78**

Starting from β-naphthoylacrylic acid, benzo[6.7]indanone (**79**), with a butenyl group in the 3-position, has been prepared[57].

In the same range of thermal conditions as used before, cyclisation is found to give as the sole product in 88% yield the 11-keto-C-norsteroid **80** with the C/D *cis*-fused junction with the C—CO bond and the CH_3 group *cis*- to each other.



79

80

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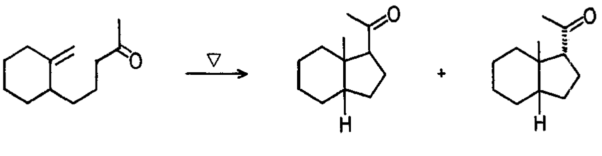
[32] H. Strickler, G. Ohloff, E. Kovats, *Helv. Chim. Acta* **50**, 759 (1967).

[33] M. Bortolussi, R. Bloch, J. M. Conia, *Tetrahedron Lett.* **1973**, 2499.

[34] R. Bloch, P. Le Perchec, F. Rouessac, J. M. Conia, *Tetrahedron* **24**, 5971 (1968).

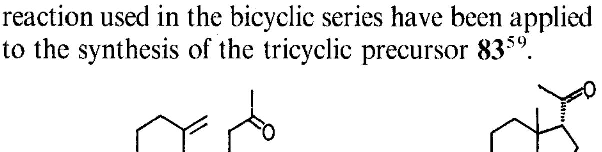
2.6. 3a-Methyl-3-acetyl-*cis*-hydrindanes

As a model for the pregnanones and related compounds attention has been paid to the 3a-methyl-3-acetyl-*cis*-hydrindane system[58]. From **81** heated at 355° for 1.5 h, two ketones (**82a** and **82b**) are obtained in the thermodynamically controlled ratio 9:1, both having the required 3a-methyl-3-acetyl-*cis*-hydrindane structures. From models, it appears that the cyclisation of **81** necessitates having the side chain in an axial conformation.



81 **82a** (90%) **82b** (10%)

The same sequence has been applied to synthesis 3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (**84**) already investigated by Nagata[61] and Djerassi[62]. The reaction used in the bicyclic series have been applied to the synthesis of the tricyclic precursor **83**[59].

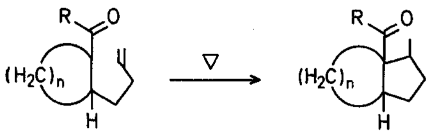


83 **84**

However, the thermal reaction of **83** gave quite unsatisfactory results. By contrast with the result encountered in the bicyclic series, 75% of **83** undergoes the *exo-endo*-migration of the double bond then leading to a non-cyclisable ketone and only 12% of the recovered material had the expected tetracyclic steroid structure with the *cis* C/D junction which was obtained as a mixture of the 17-α- and -β-stereoisomers **84**. The main reason for this is that the predominant configuration of **83** has the side chain in the equatorial position and therefore cannot undergo cyclisation[59].

2.7. Angular Acyl-bicyclic Compounds

The application of the thermal cyclisation to 1-formyl and 1-acylcycloalkanes having a convenient unsaturated side chain in the 2-position has been reported. For example, in this manner, the all-*cis*-3a-acylhydrindanes (**85**; R = H or CH_3;n = 4) and the all-*cis*-3a-acylperhydropentalenes (**85**; n = 3) have been obtained in high yield[36].

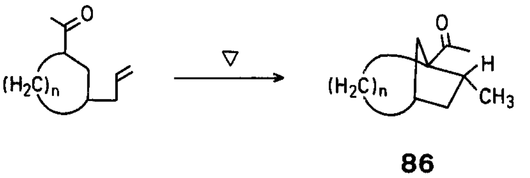


85

2.8. Bridged Compounds

As has already been pointed out, bridged carbonyl compounds may sometimes be the main products in the thermal cyclisation of 3-alkenylcycloalkanones.

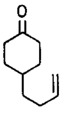
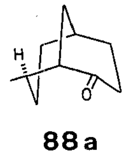
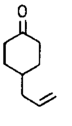
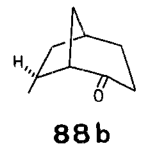
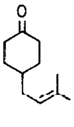
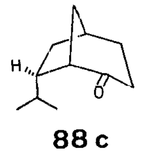
An unequivocal route to bridged compounds involves heating acylcycloalkanes bearing an appropriate side chain in the 3-position. From 3-alkyl acetylcyclopentane or -cyclohexane, for instance, the corresponding 1-acetylbicyclo[n.2.1]alkanes (**86**; n = 2 or 3) are obtained in very good yields. Only the stereoisomer with the methyl group *cis* with respect to the acetyl group appears to be formed[9].



86

The thermal behaviour of a variety of 4-alkenyl substituted cyclohexanones has been reported[63]. Models show that such ketones **87**, with at least an allyl chain length, must be able to undergo the thermal cyclisation; this has been fully confirmed (see Table 2). On the other hand the experiments in this field show the importance of the technique (sealed tube process or vapour phase process) used.

Table 2. The Thermal Cyclisation of 4-Alkenyl- and 4-Alkynylcyclohexanones[63]

Substrate	Conditions	Product	Yield (%)
 **87a**	V, sealed tube	 **88a**	100
 **87b**	V, vapour phase	 **88b**	60
 **87c**	V, sealed tube	 **88c**	60

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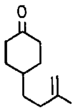
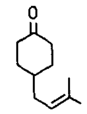
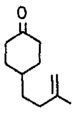
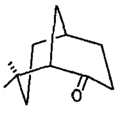
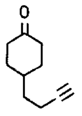
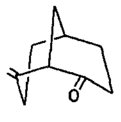
[35] R. Bloch, J. M. Conia, *Tetrahedron Lett.* **1967**, 3409.

[36] R. Bloch, J. L. Bouket, J. M. Conia, *Bull. Soc. Chim. France* **1969**, 489.

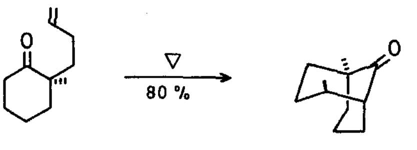
[37] M. Bortolussi, R. Bloch, J. M. Conia, *Tetrahedron Lett.* **1973**, 4171.

[38] P. Le Perchec, F. Rouessac, J. M. Conia, *Bull. Soc. Chim. France* **1967**, 822.

Table 2. continued

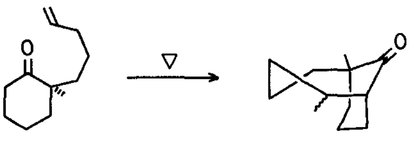
Substrate	Conditions	Product	Yield (%)
 **87d**	V, sealed tube	 **87c**	—
 **87d**	V, vapour phase	 **88d**	95
 **87e**	V, vapour phase	 **88e**	85

Bridged carbonyl compounds are obtained by heating cycloalkanones bearing an unsaturated chain in the position α to the carbonyl group and an alkyl substituent in the same position thus forcing the enolisation towards the α'-position and promoting α'-thermal cyclisation[41,43] (see p. 6). 2-Methyl-2-(but-3-enyl)-cyclohexanone (**89**) and 2-methyl-2-(pent-4-enyl)-cyclohexanone (**91**) undergo such a cyclisation in good yield.



89 **90**

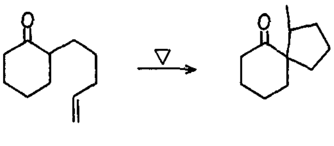
From **89** only one 1,4-dimethylbicyclo[3.3.1]nonan-9-one stereoisomer **90** is formed, the only one geometrically allowed, while **91**, having a long enough chain, leads to both of the 1,5-dimethyl[4.3.1]decan-10-ones (**92**).



91 **92**

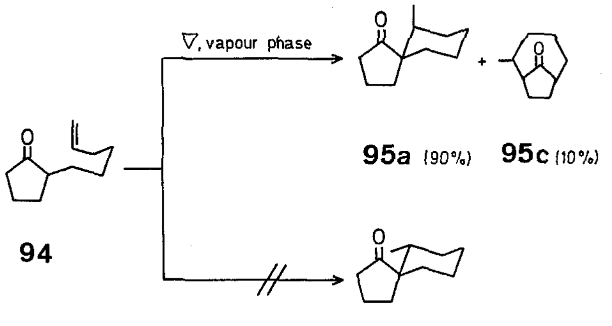
2.9. Spiro Compounds

In a same way, substituted 2-alkenylcycloalkanones are cyclised into spiro compounds, e.g.: (**93**) in 100% yield. As in the aliphatic series, the *cis*-configuration (CH_3 and C—CO) is obtained, when a cyclopentane ring is formed.

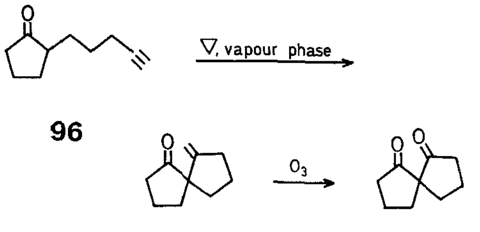


93

This is a good and simple way to spiro-ketones. The ring size C_5 or C_6 of the starting ketone has no influence on the result. But the chain length is important; hex-ω-enyl ketones, such as **94**, lead to two products: *cis*-6-methyl-spiroketone (**95a**) [with no trace of the epimeric ketone (**95b**)] and the resulting compound (**95c**) of α'-thermocyclisation[41].



The reaction can be applied to corresponding 2-alkynylcycloalkanones and the resulting double bond maintained in the *exo* position. This represents a good synthetic approach to spirodiketones.



3,3-Dimethyl-6-methylenespiro[4.5]decane-1,5-dione (47):

The liquid pentynylation product of dimedone (**46**; 1 g) was heated in a 2 ml pyrex tube at 235° for 30 min. The tube was allowed to cool to room temperature, a solid product was thus obtained and was recrystallised from water/methanol; yield: 0.9 g (90%); m.p. 89–90°. This sole product was the spirodione **47**.

I.R.: $\nu_{C=O}$ = 1710 and 1685 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ=0.87 (s, CH_3), 1.17 (s, CH_3), 4.94 and 5.08 ppm (2 t, $=CH_2$, J=2.0 Hz).

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[39] U. Schirmer, J. M. Conia, *Tetrahedron Lett.* **1974**, 3057.

[40] K. B. Wiberg, B. I. Rowland, *J. Amer. Chem. Soc.* **77**, 1159 (1955).

[41] F. Leyendecker, G. Mandville, J. M. Conia, *Bull. Soc. Chim. France* **1970**, 549.

[42] G. Mandville, F. Leyendecker, J. M. Conia, *Bull. Soc. Chim. France* **1973**, 963.

[43] G. Moinet, J. Brocard, J. M. Conia, *Tetrahedron Lett.* **1972**, 4461.

[44] J. Brocard, G. Moinet, J. M. Conia, *Bull. Soc. Chim. France* **1973**, 1711.

[45] W. Oppolzer, E. Pferminger, R. Keller, *Helv. Chim. Acta* **56**, 1807 (1973).

3. Thermal Cyclisations of Diethylenic Carbonyl Compounds

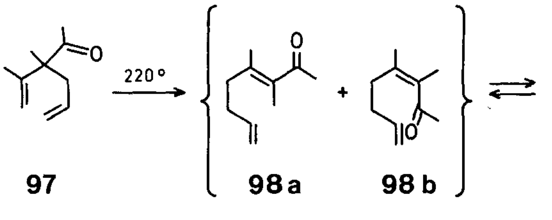
3.1. Conjugated α-Ethylenic Ketones bearing another ε- or ζ-Double Bond

3.1.1. Reactions Involving Enol Hydrogen Shift

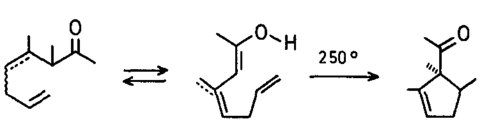
Interesting results directly related to the thermal cyclisation of enones have been reported concerning the thermal behaviour of compounds with the allylvinylacyl structures 97[64,65,66,67,68]. Under mild thermal conditions two different types of rearrangements may be observed.

At a temperature below 220° a Cope rearrangement takes place leading to a *cis-trans* mixture of α and ε-diethylenic ketones **98a** and **98b** accompagnied by the unconjugated isomer **99** in a ratio determined by the equilibrium constant[65].

As the temperature is raised to 250° a single new compound, 3-acetyl-2,3,4-trimethyl-cyclopentene (**100**), is quantitatively formed from **99** (the overall yield can reach 80%).



97 **98a** **98b**

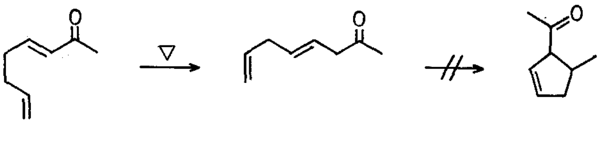


99 **99a** **100**

3-Acetyl-2,3,4-trimethylcyclopentene (100):
3-Isopropenyl-3-methylhex-5-en-2-one (**97**; 10 g), prepared by methylation and subsequent allylation of mesityl oxide[64,65], was heated under reflux under nitrogen for 8 h and then distilled under vacuum to remove resinous products. The distillate (9 g) was introduced into a 20 ml annealed pyrex tube (wall thickness 0.3 mm) and heated again at 240° for 12 h. The mixture was allowed to cool and a second distillation gave the cyclopentenyl ketone **100**; yield: 7–8 g; b.p. 60°/20 torr; oxime m.p. 82°.
I.R.: $\nu_{C=O} = 1700\ \mathrm{cm}^{-1}$.
^{1}H-N.M.R. (CCl_4): $\delta = 0.98$ (d, CH_3, $J = 7$ Hz), 1.14, 1.67, 2.00 (3 s, 3 CH_3), and 5.80 ppm (s, =CH).

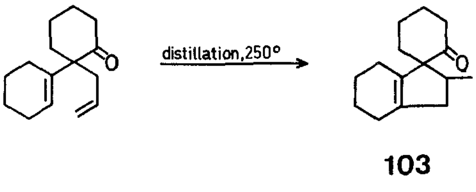
The formation of the enolic intermediate which is responsible for both the loss of conjugation and the cyclisation is now obtained with participation of the 4-methyl group of **98b** for instance (and possibly of the vicinal CH_2 in the side chain of **98a**) in a thermally allowed 1,5-hydrogen shift. The difference (~100°) between the temperature of this cyclisation and that of the corresponding ε-monoethylenic ketones should be noticed.

Obviously in the absence of the 4-methyl group, as in **101**, keto-enol tautomerisation leads to the *trans*-octa-4,7-dien-2-one (**102**) which is unable to undergo the ring closure since the *trans-cis* isomerisation which would permit the approach of the two reactive centres cannot occur under such conditions[69].



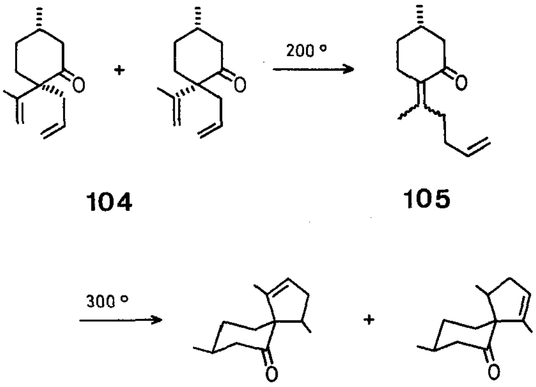
101 **102**

Cyclisation is easily achieved by the same sequence as from **97** in the alicyclic series, where spiro compounds are obtained. For example, 2-allyl-2-cyclohexenylcyclohexanone on distillation (250°) at ordinary pressure leads directly and quantitatively to the expected spiro-structure **103** but in this case the Cope intermediate has not been isolated[64,67].



103

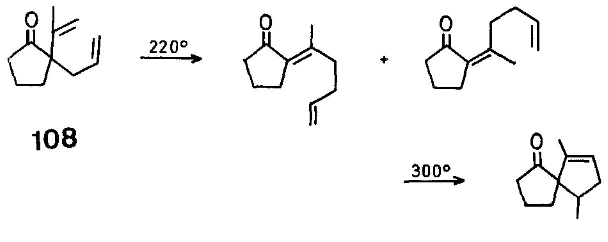
Optically active 2-allylisopulegones (**104**) have been also the subject of analogous work and their thermal cyclisation represents a convenient synthesis of spiro-[5.4]decen-6-ones. The formation of two diastereoisomers **106** and **107** is understandable since cyclisation is possible on both sides of the plane of the dienyl cyclohexenol formed by enolisation of the intermediate ketone **105**.



104 **105**

106 **107**

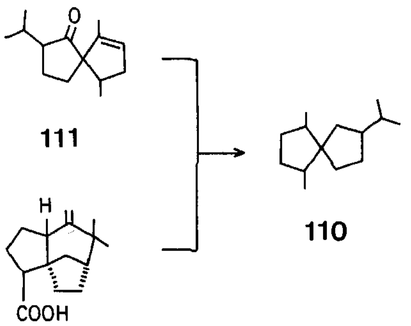
By starting from a 5-membered cycloalkanone, spiro-[4.4]nonen-6-one derivatives are also obtained, as illustrated by the conversion of **108** into **109**[64,67].



108

109

An application of this process is the structural determination of the tricyclic vetivene carboxylic acid (**112**); *this acid by a degradative method, leads to* a compound supposed to have the 1,4-dimethylspiro-[4.4]nonane structure (**110**). A sequence analogous to **108**→**109**, starting from an isopropyl-substituted ketone led to **111**, which was easily and efficiently converted into **110**[70].

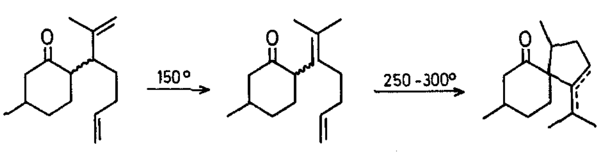


111

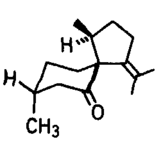
110

112

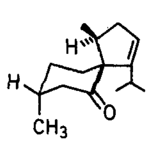
A simple route to optically active acorane derivatives has been given recently[71], which uses the thermal cyclisation of an easily available ketone, (+)-2-(1'-isopropenylpent-4'-enyl)-5-methylcyclohexanone (**113**) of known absolute configuration. Around 150°, this ketone undergoes a catalytically induced 1,3-hydrogen shift into the isopropylidene derivative **114**, which, at higher temperature (250–300°) leads to a mixture of four isomeric ketones with the acorane skeleton **115**. By spectroscopic examination and circular dichroism measurements of all the stereoisomers, it was established that the precise structure (absolute configurations and conformations) were **115a**, **b**, **c**, **d** all dextrorotatory; **a** and **b**: negative CD; **c** and **d**: positive CD.



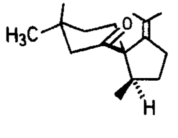
113 **114** **115**
(4 isomers)



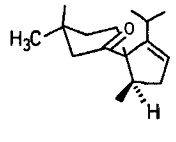
115 a



115 b



115 c

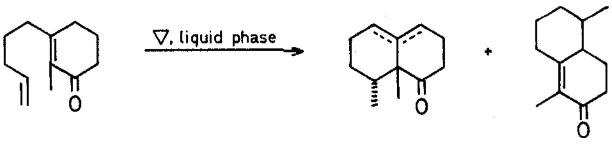


115d

The configuration of these four ketones are in good agreement with the geometry of the transition states *when a* C_5 *ring* is formed (methyl group formed and C—CO moiety in the *cis* configuration discussed before [see also **93**→**94**]) and with the possibility for the side chain to undergo cyclisation on both sides of the C_6 ring.

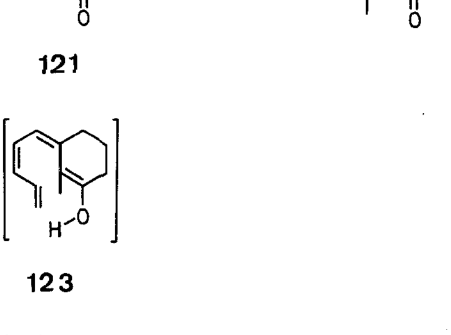
Attempts to prepare a member of the spiro[4.3]series from an alkylidenecyclobutanone did not achieve any satisfactory results[67,68].

Recently, other examples of thermal cyclisation of dienones have been pointed out[73,74], the formation of dimethyloctalones (**117**) and (**118**) from 2-methyl-3-(pent-4-enyl)-cyclohex-2-en-1-one (**116**). The striking feature is the unexpected formation, in the liquid phase, of a third octalone **119** as a main product. A competitive intermolecular hydrogen participation is proposed to explain its formation.



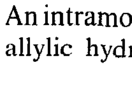
116 **117** and **118** **119**

On heating, trienones can also undergo cyclisation reactions. This has been shown for the trienones **120** and **121**[74]. In order to build the eremophilone system by using an electrocyclic intramolecular reaction, the authors found a stereoselective but not stereospecific process (in the sense of the Woodward-Hoffmann rules concerning the electrocyclic reaction). A probable explanation of this result is the formation of **122**, via a common tetraenol **123**, in an intramolecular ene reaction.



120 **122**

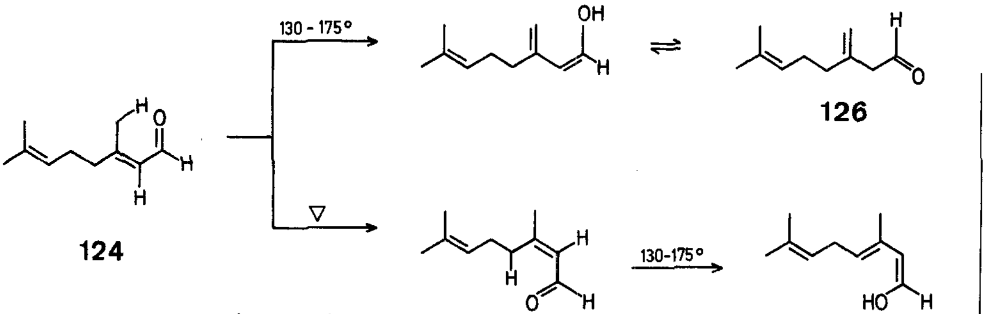
121



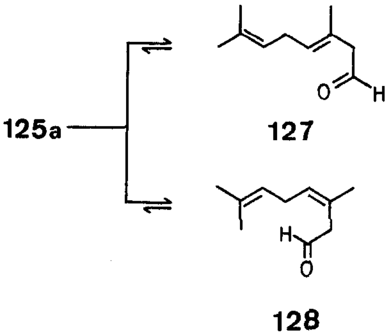
123

3.1.2. Reactions involving Allylic Hydrogen Shift

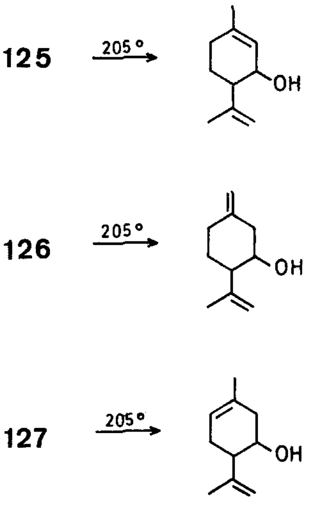
An intramolecular electron transfer process involving allylic hydrogen displacement towards a carbonyl group has been observed[72] in a thermal study of citral. In a beautiful piece of work, probably the first published concerning a comprehensive examination of the thermal behaviour of an unsaturated carbonyl compound, the author showed that geranial (*trans*-citral, **124**) and neral (*cis*-citral **125**) are thermally (130–175°) converted into the three unconjugated isocitrals (**126**, **127**, and **128**) via the corresponding enols.



125 **125a**



However, at 205°, the aldehydes **125**, **126**, and **128** undergo C_6 cyclisation by the facile migration of a terminal allylic hydrogen to the carbonyl group, leading to cyclohexenol derivatives. The aldehydes **124** and **127** do not behave similarly because of the *trans*-configuration of their central C=C bond.

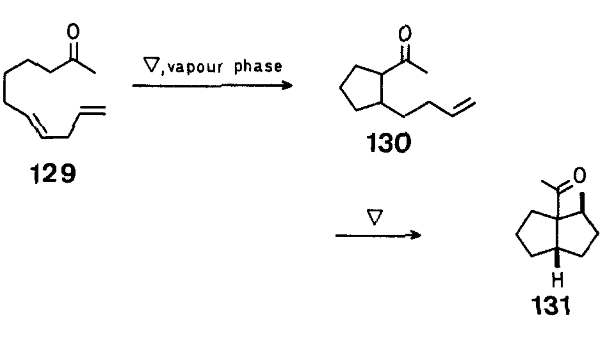


In summary, concerning the thermal behaviour of dienones and dienals, it can be seen that the reaction always involves compounds bearing a β-alkyl group which allows the thermal formation of the intermediate dienol by a 1,5-hydrogen shift and is geometrically restricted to compounds having the *cis*-configuration at the central double bond.

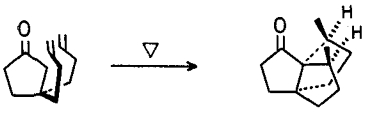
3.2. Double Cyclisations from Various Suitable Dienones

On heating, ketones bearing two double bonds in suitable positions can undergo two successive cyclisations; but the yields are not so good as with the corresponding mono ethylenic ketones.

For instance, ε- and θ-diethylenic ketone **129** is converted, via ε-monoethylenic ketone **130** to 4-acetylhydrindane (**131**)[60].



The symmetrical δ- and δ'-diethylenic diketone **53** leads to spiroketones **54** (two epimers)[60] (see page 7). Another type of spiroketone **56** is obtained by heating a δ-ethylenic (on one side) and ε-ethylenic (on the other side) ketone **55**. Two C_6 and C_5 rings are formed respectively, via a common enol and no monocyclic intermediate has been isolated[43] (see page 7). Finally, an interesting example of double cyclisation, because illustrating a simple route to propellanones, is that of 3,3-dibutenyl-cyclopentanone (**132**)[60].



132 **133**

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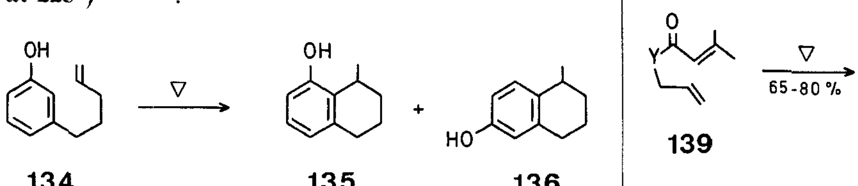
4. *Extensions to other Systems*

Now, knowing the mechanism of the thermal cyclisation reported in this review which involves an intramolecular hydrogen shift from a donor to an acceptor with the concerted formation of a σ-bond, it can be predicted that such a rearrangement will be applied to other systems. The main extensions so far reported concern the cyclisation of alkenylphenols and alkenyl-anilines and the heterocyclisation of esters and amides analogous to certain dienones.

4.1. *m*-Alkenylphenols and *m*-Alkenylanilines

It has been shown that the thermal cyclisation of unsaturated β-diketones e.g. **44** and **46**, where the enol form is greatly stabilised, occurs at lower temperatures (200–250°) than those of the corresponding monoketones (~350°). In the same way, on heating, *m*-alkenylphenols easily undergo cyclisation although it implies the loss of aromaticity in the transition state.

For instance, depending on the conditions used, from *m*-pentenylphenol (**134**), it has been obtained either the one product of intramolecular ene reaction **135** (in the vapour phase at 350°) or the mixture of two products **135** and **136** (~50:50 in the liquid phase at 225°)[75,76,77].

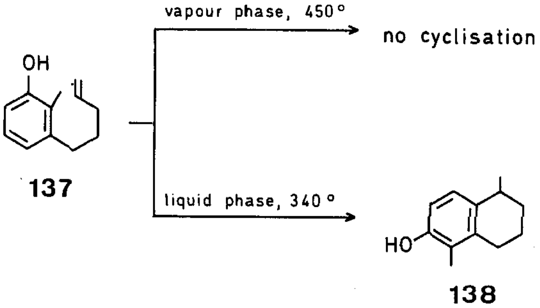


134 **135** **136**

	135	136
liquid phase:	50 %	50 %
vapour phase:	100 %	0 %

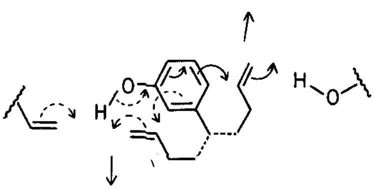
The thermal behaviour of the aniline corresponding to **134** (with an NH_2 instead of an OH group) is analogous, but the yields in the cyclisation products are lower[76].

Concerning the formation of **135** and **136** from phenol **134** in the liquid phase, evidence for the intermolecular participation of phenolic hydrogen in cyclisation has been obtained[76]. For example, phenol **137** does not cyclise even at 450° in the vapour phase, while it gives **138** exclusively, under mild conditions, in the liquid phase.



137 **138**

To rationalize the liquid phase reaction **134**→**135**+**136**, it is proposed that a type of bifunctional catalysis—i.e. two centres, the —OH and the C=C bond are simultaneously implicated in both of the processes leading to *ortho*- and *para*-cyclisations[76,77].

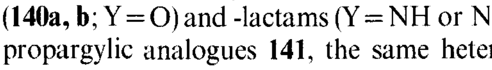


136

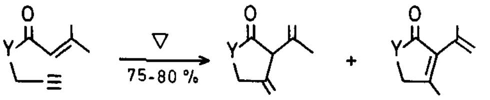
135

4.2. Heterocyclisations

γ-Lactones and γ-lactams have been recently prepared by heating great varieties of *O*- and *N*-allyl and -propargyl esters (**139** and **141**; Y=O) and amides (**139** and **141**; Y=NH or NR)[37]. In the same range of conditions used for the corresponding dienones (**139** and **141**; Y=CH_2) and only in the vapour phase, the thermal cyclisation is operating and leads to alkenyl- and alkenylidene-γ-lactones (**140a, b**; Y=O) and -lactams (Y=NH or NR). From propargylic analogues **141**, the same heterocyclisation occurs.



139 **140a** **140b**



141 **142a** **142b**

Concerning the possible two types of intramolecular ene reaction—i.e. is there allylic or enolic hydrogen shift?—the question is not yet entirely clear. But depending upon the nature of Y (CH_2, O, or NH) it seems that an enolic hydrogen shift **143** prevails with ketones, an allylic hydrogen shift **144** with amides, and both of them with esters.

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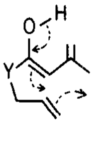
Besides, a recent work[45] has shown the interesting and facile thermal cyclisation of compounds **145** by allylic hydrogen shift into compounds **146** in the same range of temperatures.



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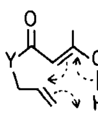

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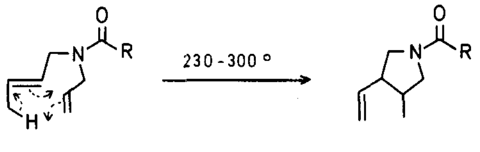

145 **146**

5. Experimental Aspects

The technique used must take into account the fact that the thermal cyclisation of unsaturated ketones requires initial enolisation of the keto group. When this occurs by a 1,3-hydrogen shift, the main effect on the rate of cyclisation is the catalytic activity arising from the glass vessel and from the intermolecular interactions between the ketone and its enol. When 1,5-hydrogen shift initiates the enol formation these effects are far less important.

Method A: *Simple heating* under nitrogen is only convenient for high boiling ketones (b.p. $\geq 300°/1$ torr) see for example compound **103**.

Method B: The sealed tube technique is suitable for small amounts of very pure samples when both products and reactants are stable under the reaction conditions, for example compounds **1**, **43**, **116**, and **137**. In some cases heating a dilute solution of the reactant in a high boiling hydrocarbon solvent gave satisfactory results; for example, heating a 10% solution of compound **55** in decalin at 400° for 16 h gave product **56** in 40% yield whereas heating of a neat sample gave only a 20% yield and no reaction occurred in the gas phase[60]. This method seems to be most suitable for reactions which must be carried out in the condensed phase.

Method C: The *static vapour phase technique* is generally useful for ketones which are sensitive to resinification. This process usually requires a higher temperature when carried out under vaccum (500 μl in a 500 ml glass reactor, 350–400°, contact time 2–15 hours). The apparatus used is described below in Figure 1.

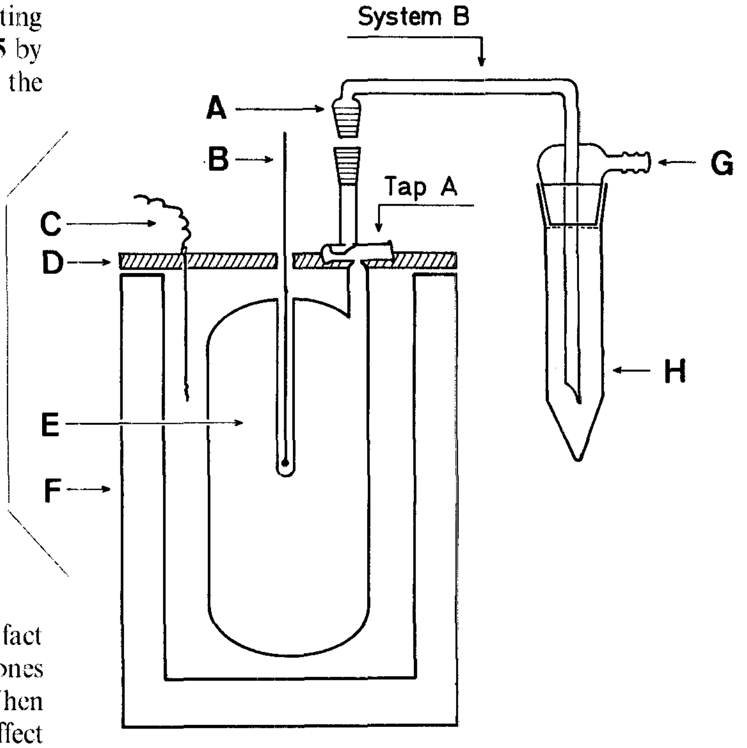

Figure 1. Apparatus for Vapour Phase Thermal Cyclisation by the Static Vapour Phase Technique

General Procedure:
The tap A is opened to the atmosphere and the reaction vessel E is heated to the desired temperature (thermometer **B** and thermocouple C) in the furnace F with insulated lid **D**. The vessel **E** is then evacuated via tap A. Tap A is closed and the starting material is introduced into the tube above tap A. Tap A is opened and the compound is allowed to pass into the vessel **E**, care being taken not to admit any air. After the desired reaction time system **B** is connected to the reactor at the joint **A**, evacuated through **G**, and the receiver **H** cooled in liquid nitrogen. Tap A is then opened and the product(s) condensed in the receiver H.

This method has been successfully used with, for example, the dienones **58**, **60**, **97**, **113**, **129**, **139**, **141**, the strained ketones **85**, **86**, **89**, **91**, and others.

Method D: The *gas flow process* has sometimes been used for preparation of large amounts of material when the reaction proceeds particularly easily, as for example with compounds **1**, **44**, **46**. The apparatus is described in Figure 2.

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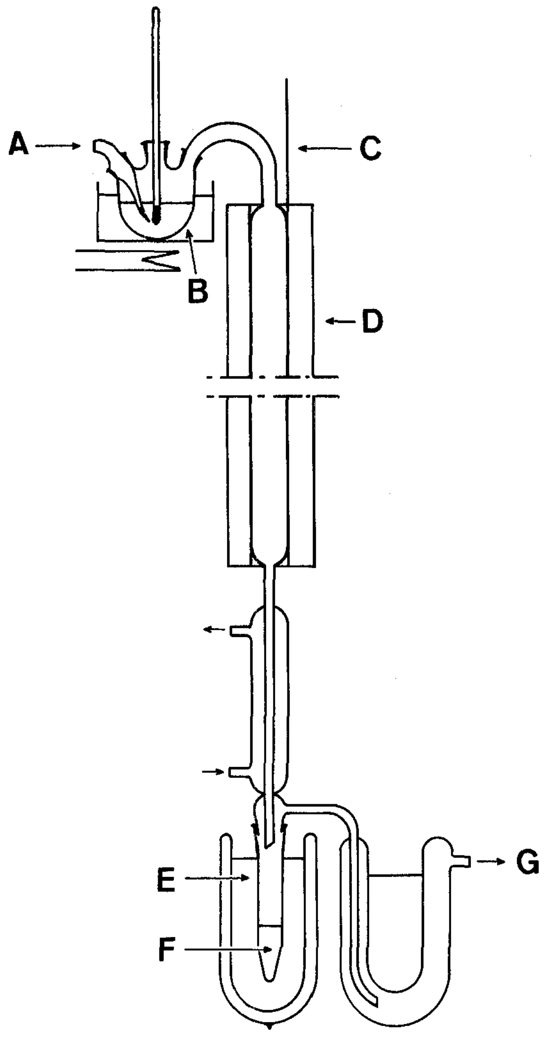

Figure 2. Apparatus for Thermal Cyclisation by the Gas Flow Process

General Procedure:
A three-necked flask equipped with a nitrogen inlet tube **A** and a thermometer is attached to a pyrex tube furnace **D** filled with helices. The compound is placed in the flask and heated at about 5–10° below its boiling point with the oil bath **B** under a controlled stream of nitrogen **A→G**. The compound is passed through the furnace at the desired temperature (thermometer **C**) and the product is collected in the receiver **F** cooled in a dry ice bath **E**.

The process can also be carried out at reduced pressure in the case of high boiling starting materials.

6. Conclusions

It appears clearly that the thermal cyclisation of unsaturated carbonyl compounds is a powerful and often simple synthetic tool in alicyclic chemistry and the scope and limitations now seem well established.

The reaction actually involves two successive and distinct steps: enolisation and cyclisation. From most of the starting compounds, enolisation occurs by a catalytically-induced 1,3-hydrogen shift; cyclisation occurs by a thermally allowed enol hydrogen shift, closely related to the intramolecular ene reaction.

The known transition state geometry allows one to predict in many cases, from molecular models, the success or the failure of an attempted thermal cyclisation and the stereochemistry of the cyclised ketone(s).

As yet the difficulty of working on a large scale often remains the weak point of the reaction. Sometimes it is not easy to achieve the first enolisation step thermally, and products due to allylic hydrogen shifts can be formed. Nevertheless this review clearly shows that the thermal cyclisation of unsaturated carbonyl compounds can be easily applied to the synthesis of many monocyclic, bi- and polycyclic, spiro or bridged carbonyl compounds, often with spectacular yields.

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