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REACTIONS OF SUBSTITUTED CYCLOPENTENYL AND RELATED ESTERS

BY

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

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DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1969

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

REACTIONS OF SUBSTITUTED

CYCLOPENTENYL AND RELATED ESTERS

submitted by Cyril Levine, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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A. F. Casy

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Paul Haberfield
External Examiner

Date Spring 1969

TO MY WIFE AND DAUGHTER

A C K N O W L E D G E M E N T S

The author wishes to express his deep indebtedness to his research supervisor, Dr. Karl R. Kopecky, without whose encouragement and patient assistance this work could not have been accomplished.

Gratitude is also due to the author's many fellow graduate students, and, in particular, to Messrs. Thomas Gillan, Cedric Mumford, Michael Hall, (Dr.) Joseph Grover and (Dr.) Symalarao Evani for many helpful discussions; to Professors D. Darwish, R. J. Crawford, J. S. Martin, and others, for answering many knotty questions at inopportune moments, and to the other members of the staff (academic and non-academic) and graduate students for helping to make the author's stay at this University a most pleasant one, though somewhat longer than initially anticipated.

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Finally, the author's gratitude goes to his wife, Patricia, for her selfless devotion and constant delight in his achievments, without which the last three years of his work would have been unbearably frustrating.

A B S T R A C T

In an attempt to confirm the findings of Stork (15, 16) that, in the S_N2' reaction, the entering nucleophile attacks the allylic system on the same side of the plane of the double bond as that from which the leaving group departs, the reactions of 5,5-dimethylcyclopent-2-en-1-yl esters (6, X = OCOR) with selected nucleophiles under quite severe conditions were investigated. It was found that this system is surprisingly unreactive to bimolecular nucleophilic displacement, and that, in cases where reaction did occur, a simple nucleophilic displacement with rearrangement was not obtained - possible exceptions to this statement being reactions with cyanide and thiocyanate ions.

To test the proposition that this lack of reactivity might be due to some abnormal feature of this system, the rates of solvolysis (in 80% ethanol) of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate, cyclopent-2-en-1-yl p-nitrobenzoate, and cis-2-methylhex-4-en-3-yl p-nitrobenzoate were determined. The hoped-for very large rate difference between the two cyclic esters did not eventuate; the experimental rate ratio of approximately 1:25 between the 5,5-disubstituted and unsubstituted

esters is considered to be quite insufficient to account for the lack of reactivity towards bimolecular nucleophilic displacement of the 5,5-disubstituted ester.

It is shown that the observed solvolysis rates for these two esters and for the acyclic ester are compatible with each other and with previously-observed results, and that, therefore, these three esters behave as normal allylic esters. This is also confirmed by product studies. The lack of reactivity towards bimolecular nucleophilic displacement of the 5,5-dimethylcyclopent-2-en-1-yl system is incompatible with these solvolytic results and with previously-published work on allylic systems.

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L I S T O F F I G U R E S

CHAPTER I

S_N2' REACTIVITY OF THE 5,5-DIMETHYLCYCLOPENT-2-EN-1-YL SYSTEM

Introduction

The chemistry of allylic compounds presents many interesting features not to be found in the reactions of saturated systems. Both types undergo normal bimolecular nucleophilic substitution by the well-understood S_N2 mechanism. The possibility of a new mechanism, in allylic systems, which would involve bimolecular nucleophilic displacement with concomitant three-carbon rearrangement (Figure I) - the so-called S_N2' reaction - was initially raised many years ago (1-3).

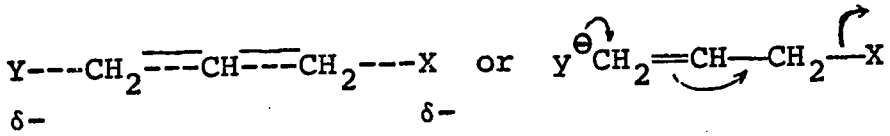


Figure I

Bimolecular nucleophilic displacement in an allylic system (S_N2' reaction)

The history of the protracted, and eventually successful, search for examples of this reaction has been adequately reviewed elsewhere (4-7). The validity of the S_N2' assignments made in many of the investigations cited in references (4-7) has very recently been called into question in an important series of papers by Bordwell and coworkers (8-12). These papers will be discussed later in this Chapter (see the Results section); in the interim,

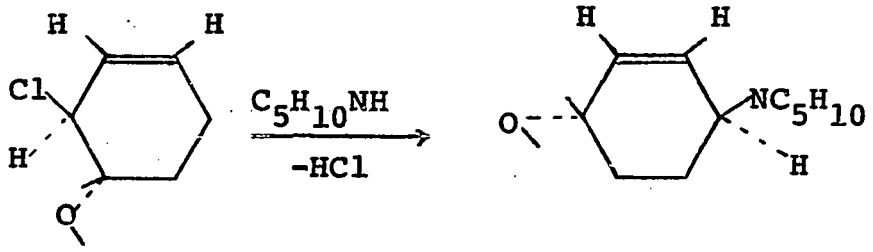
the existence of the general type of mechanism depicted in Figure I - i.e., bimolecular attack of the nucleophile on carbon atom 3 of an allylic system with synchronous departure of a leaving group from carbon atom 1 and attendant electronic rearrangement - will be treated as accepted.

The aspect of the S_N2' reaction which originally prompted the present investigation is its stereochemistry, and, in particular, the stereoelectronically-preferred relationship between the entering and leaving groups. Many years ago, it was predicted (13), following an earlier suggestion (3), that, in complete analogy with the explanation for the fact that bimolecular reaction at a saturated carbon atom (S_N2) always leads to inversion of configuration, the corresponding substitutions with three-carbon rearrangement would occur with the entering and leaving groups cis- to each other. This prediction has quite recently been given quantum-mechanical support (14).

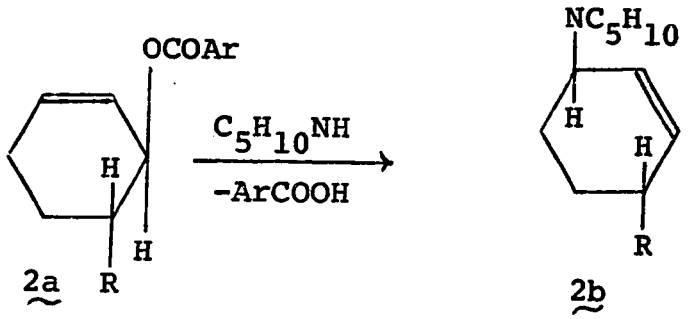
Experimental support was provided in 1956 by Stork and co-workers (15-16). They showed that S_N2' reaction of α-chlorocodide (1a, partial structure) with piperidine occurred with the introduction of the piperidino-grouping cis- to the displaced chloride to produce 1b.

It was also shown that trans-6-alkylcyclohex-2-en-1-yl 2',6'-dichlorobenzoates (2a) reacted with, for example, piperidine as in [2] to give products 2b, in which

the cis- relationship between entering and leaving groups had again held.

[1] 

1a 1b

[2] 

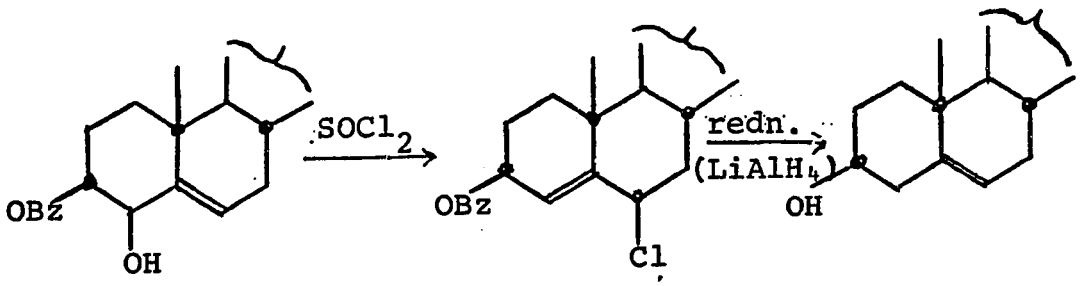
2a 2b

R = CH_3, i-C_3H_7, t-C_4H_9

Ar = 2,6-dichlorophenyl

Similar results were also obtained when malonic ester anion was used as nucleophile.

Subsequent experimental support for Stork's work has been sparse. Ireland and co-workers (17) have shown that the product of the reaction between thionyl chloride and 4β-hydroxycholesteryl benzoate (3a) is 6β-chloro-3β-benzoyloxy-4-cholestene (3b), and that 3b is reduced by lithium aluminum hydride exclusively to cholesterol (3c), as shown in Scheme I.



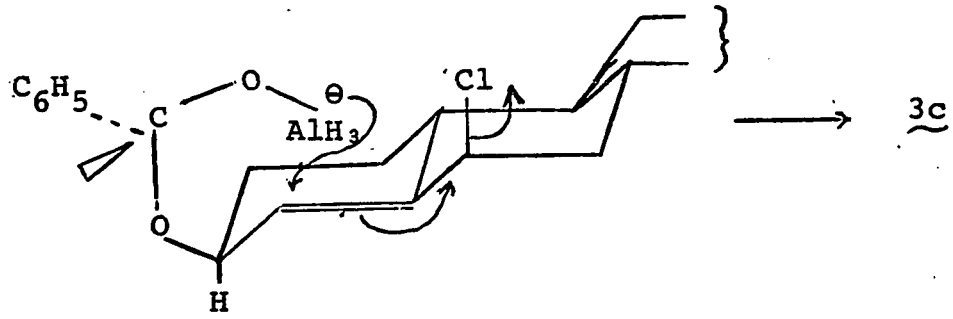
3a 3b 3c

Scheme I

The stereospecifity of the hydride reduction was shown to be due to an intramolecular S_N2' reaction sequence by repetition of the reduction with lithium aluminum deuteride, which was shown to introduce D exclusively into the 4β position.

The authors (17) depict the conversion 3b → 3c as occurring by the attack of a complex hydride ion on the C_4-C_5 double bond of 3b from the side of the molecule cis- to the departing chloride ion, as in Equation [3].

[3]



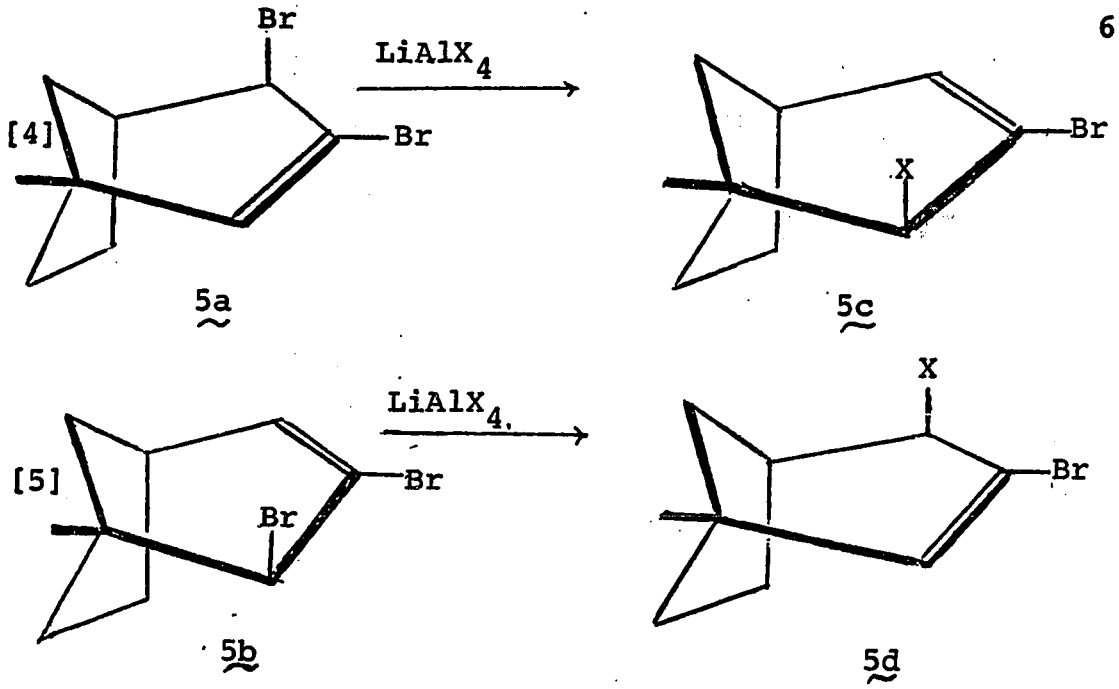
In our view, this work does not offer unequivocal support for Stork's work (15-16). It would seem that compound 3b is constituted in such a manner as to force attack by a complexed hydride ion from the top side for

simple steric reasons, formation of the required cyclic transition state from the bottom side being prevented by the axial hydrogen at C-3. More meaningful results might have been obtained if the chlorine had been equatorial, or the benzoyloxy-grouping axial.

In our view, also, Stork's work (16) is open to question, since his non-rigid cyclohexenyl systems are by no means free of possible steric effects, as inspection of models of his three possible transition states (ref. 16, p.4614) clearly shows. This view has also been expressed by Park and co-workers (18).

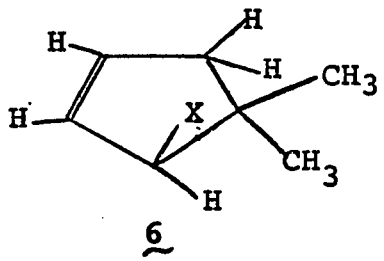
Very recently, support for Stork's work has been offered by Jefford and co-workers (19). Expanding on an earlier communication (20), they have shown that exo-1-methyl-3,4-dibromobicyclo[3.2.1]octene-2 (5a), and its allylic isomer, exo-1-methyl-2,3-dibromobicyclo[3.2.1]-octene-3 (5b) are reductively debrominated by lithium aluminium hydride or deuteride to give the allyic rearrangement products, 5c and 5d respectively (X = H or D) with the indicated stereochemistry.

Jefford and co-workers (19) adduce evidence to show that these reactions occur by exclusive S_N2' attack of hydride (deuteride) on the exo-face of 5a and 5b. Since 5a and 5b are both set up in such a way that steric hindrance to approach by a nucleophile from either the exo-or endo- side would appear to be approximately equal,



this work would seem to circumvent our objections, expressed above, and give resounding support to Stork (15-16). We are not in entire agreement with this view; further discussion is, however, reserved for a later part of this Chapter (see the Results section).

The present research was initially prompted by the desire to re-investigate the stereochemistry of the S_N2' reaction in a system chosen so as to avoid possible steric effects. For this purpose, the 5,5-dimethylcyclopent-2-en-1-yl system (6) was selected.



6

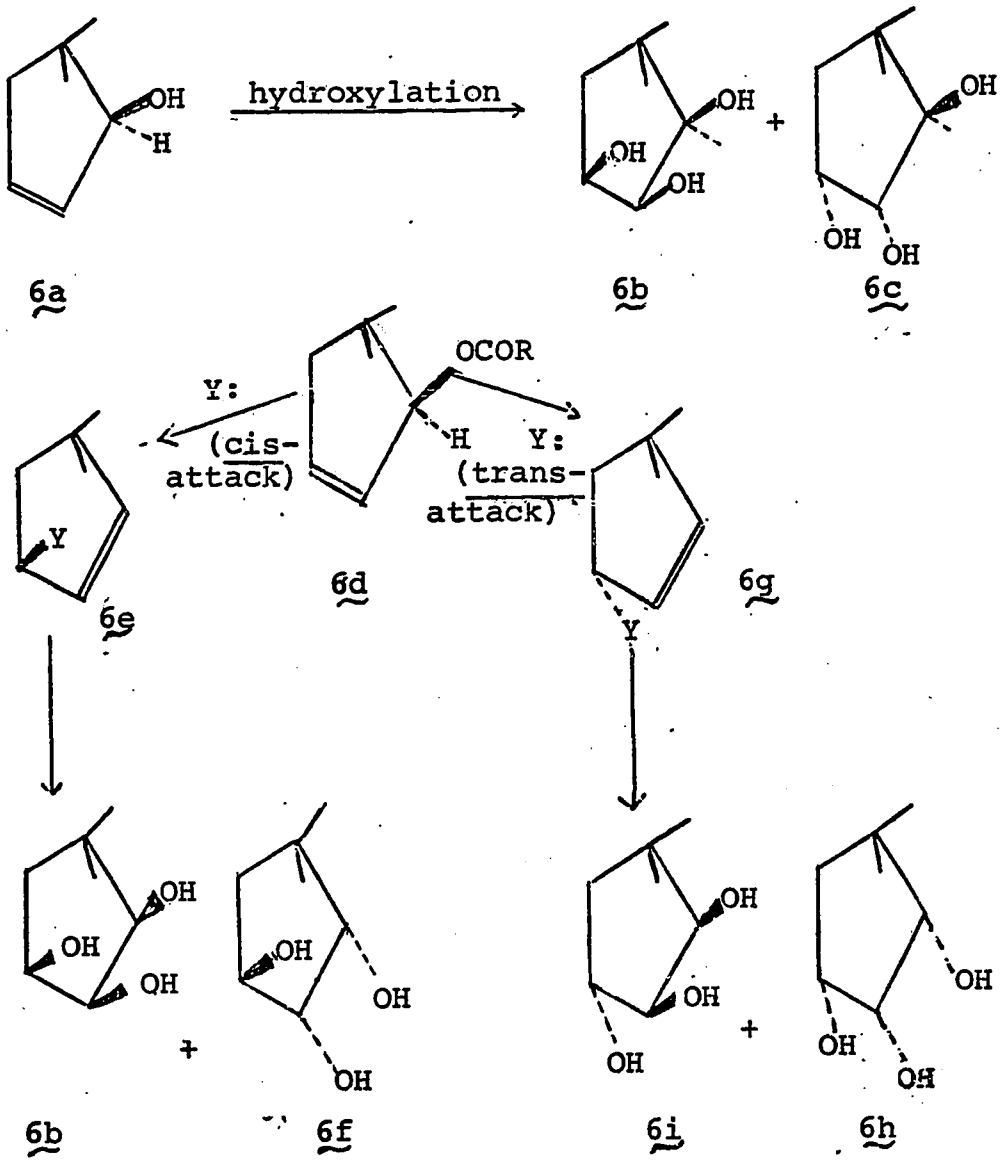
It was considered, firstly, that a gem-dimethyl grouping in the 5-position should present equal hindrance to a nucleophile approaching from either above or below the plane of the double bond, and, secondly, that the rigid conformation of such a system leads naturally to the three-carbon triangular co-planar transition state, as proposed by Young (13). Jefford's system (19-20), of course, fulfils both conditions, but the system 6 would appear to be intrinsically simpler in design.

The intention was to resolve 5,5-dimethylcyclopent-2-en-1-ol (6, X = OH), prepare a suitable ester (6, X = OCOR), perform the S_N2' reaction with selected nucleophiles, and, finally, to correlate the stereochemistry of products and starting materials, according to the general Scheme II.

As shown, starting alcohol of configuration 6a will, on cis-hydroxylation, give a mixture of two optically-active triols, 6b and 6c. Cis- attack by nucleophile Y on the corresponding ester 6d will give 6e, which could be converted to a mixture of two triols, one of which, 6b, will be identical to one of the triols from starting material, and the other, 6f, will be a new compound. Trans- attack on 6d will give 6g, from which could be derived two triols, one of which, 6h, will be of opposite configuration to 6b, while the other, 6i, will be of

opposite configuration to the new triol, 6f. Random attack, would, of course, give racemic products.

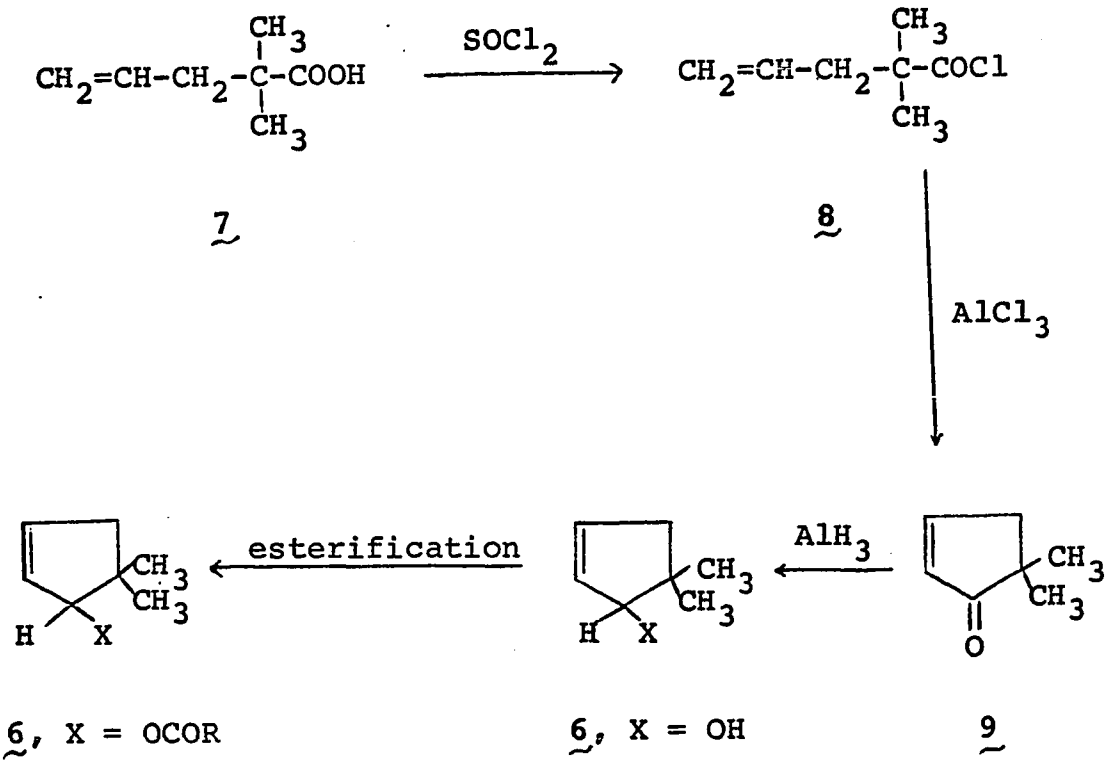
By some such scheme, the problem under investigation could have been solved. However, as will appear, the present research never reached this stage.



Scheme II

Synthesis

The series of compounds, 6, required for our research into the stereochemistry of the S_N2' reactions, was synthesised as shown in Scheme III, below:



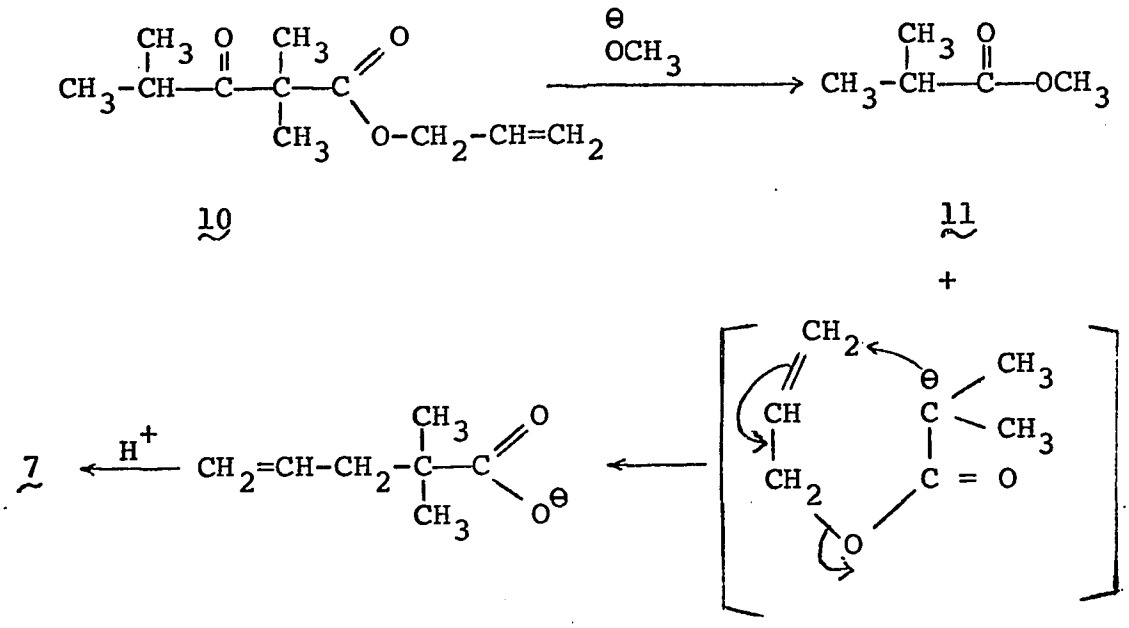
SCHEME III

Synthesis of the 5,5-dimethylcyclopent-2-en-1-yl system

At various times during the course of this research, 2,2-dimethylpent-4-enoic acid, 7, was prepared by: saponification (21) of the corresponding nitrile (22); silver oxide oxidation (23) of the corresponding aldehyde

(24); and base-catalysed rearrangement (25) of allyl isobutyrate (26). The method of choice, however, proved to be one developed during the present research.

This method was based on the observation by Hasek and co-workers (27) that allyl 2,2,4-trimethyl-3-oxopentanoate, 10, underwent scission by methoxide ion to a mixture of methyl isobutyrate, 11, and the anion of 7. The latter arose, as shown in Scheme IV, by Claisen-type rearrangement of allyl isobutyrate anion, as already observed by Brannock (25).

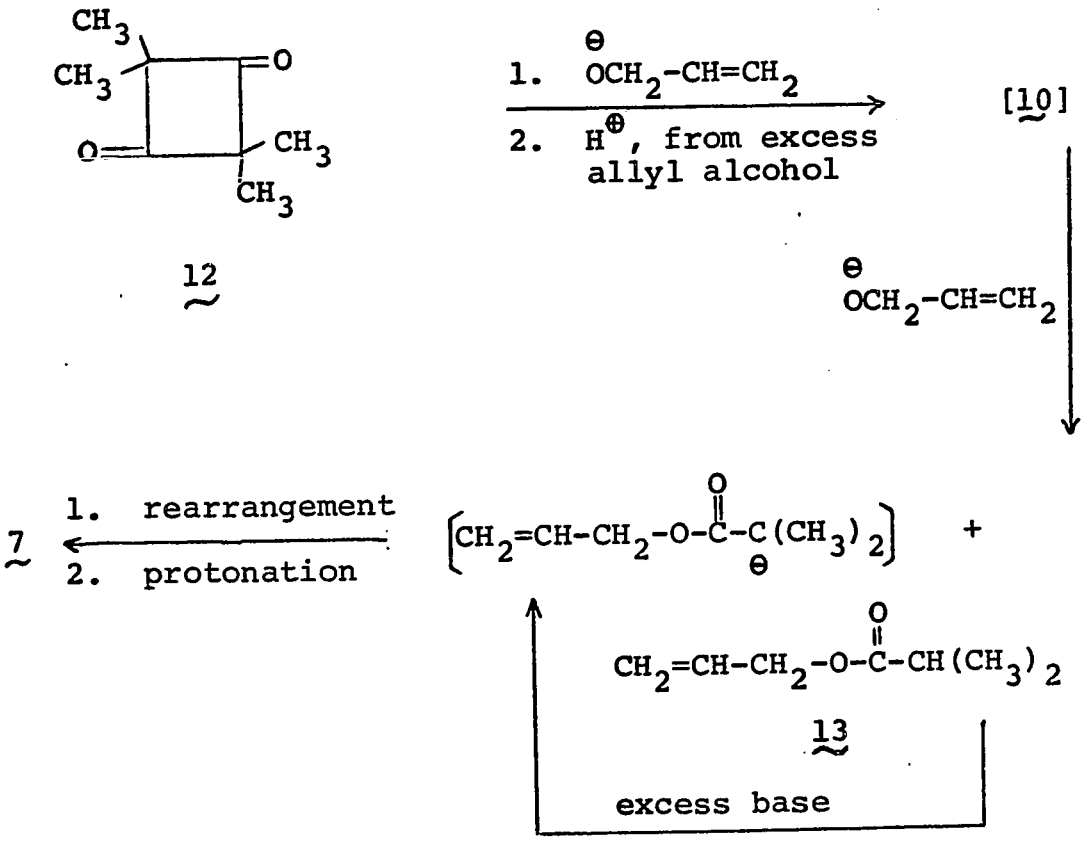


SCHEME IV

Hasek's route (27) to 2,2-dimethylpent-4-enoic acid, 7.

Since 10 was obtained (27) in high yield by reaction between allyl oxide anion and dimethylketene dimer (2,2,4,4-tetramethylcyclobutane-1,3-dione, 12), an obvious

modification seemed to be to attack 10, preferably in situ, with additional allyloxide anion, rather than methoxide as in Scheme IV. Under these conditions, 10, should be cleaved to one molecule of allyl isobutyrate, 13, and one of allyl isobutyrate anion; the latter would promptly rearrange as before, excess base would convert 13 to its anion, and the ultimate result would be the formation of two moles of 7 from one mole of 12.



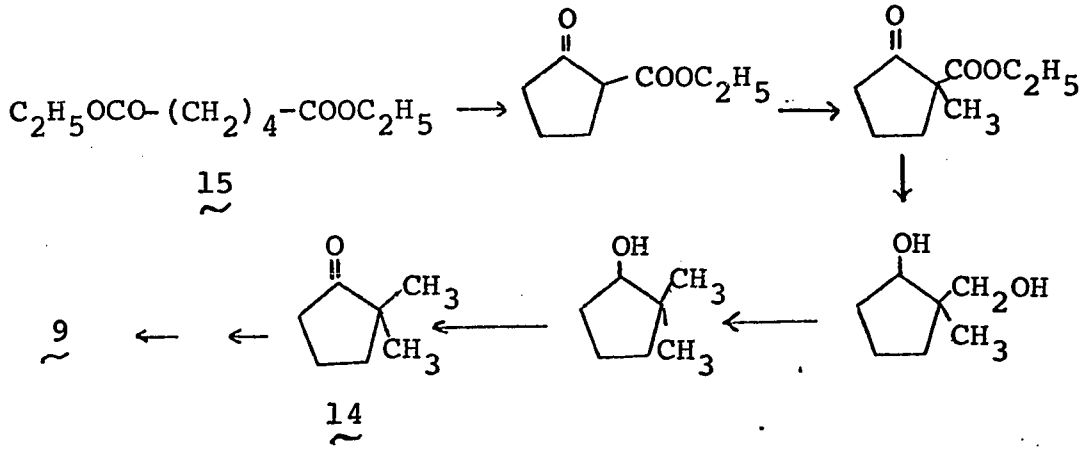
SCHEME V

Proposed modification of Hasek's route (27) to 7

This, in fact, proved to be a practical procedure; 7 was consistently obtained in approximately 65% yield.

Conversion of 7 to 5,5-dimethylcyclopent-2-en-1-one, 9, was effected by cyclization of the acid chloride, 8, using anhydrous aluminum chloride in refluxing methylene chloride-nitromethane. Yields were in the range 30-52%.

After the present route had been worked out, Shirahama and co-workers reported (28) the physical properties of 9; their synthesis, which is not yet readily available in the general literature, proceeds (29) through 2,2-dimethylcyclopentanone, 14, as the key intermediate. They obtain 14 by a series of steps commencing with diethyl adipate, 15.



SCHEME VI

Shirahama's route (29) to 9

Ketone 14 is more conveniently available by other routes (30, 31); nevertheless, we feel that the present synthesis of 9, Scheme III, offers advantages in simplicity and ease of manipulation over any route proceeding through 14.

Significant quantities of other, higher-boiling, products were found to be produced in the present synthesis. Inspection of the crude cyclization product by gas-liquid chromatography (GLC) disclosed two peaks eluting a considerable time after the peak due to 9. These two components could be separated from all lower-boiling materials, but not from each other, by simple distillation - B.P. 186-8°/700 mm. The yield of this high-boiling fraction was approximately 50%.

The two major components of this fraction - accompanied by two other trace components - were in the ratio 1.2-1.8:1; in the total cyclization product, the more abundant of these two was about 0.3-0.6 times as abundant as 9, based on peak areas. The two compounds under discussion could not be separated by GLC or column chromatography; however, the more abundant component was isolated as a white, low-melting solid by prolonged freezing at -20°, decantation of the supernatant liquid, repeated thawing and freezing of the crystals, and finally, distillation under reduced pressure.

The compound obtained in this manner was deduced to be 3-chloro-2,2-dimethylcyclopentanone, 16, on the following grounds:

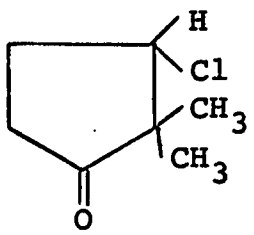
The presence of chlorine was signalled, both by a positive Beilstein test, and by the mass spectrum, in which two parent peaks were obtained at $\frac{m}{e}$ 146 and 148, in the ratio of approximately 3:1, corresponding to the natural $Cl^{35}:Cl^{37}$ abundance ratio.

The analysis was correct for $C_7H_{11}OCl$.

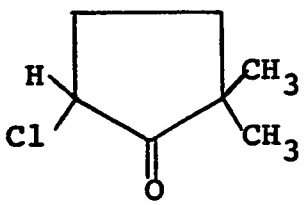
The infrared spectrum (CCl_4) showed carbonyl absorption at 1745 cm^{-1} and gem-dimethyl at 1365, 1385 cm^{-1}.

The nuclear magnetic resonance (n.m.r.) spectrum was as follows: multiplet, showing fine splitting, centre τ 5.83, 0.96H, methine proton; complex multiplet, τ7.4-8.0, 3.82H, methylene protons; two singlets, separation 1Hz, τ8.92, 6.00H, methyl protons.

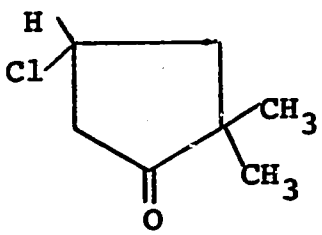
The above data are consistent only with a monochlorodimethylcyclopentanone structure. In order to distinguish between the three possible alternatives, 16, 17 and 18, the following additional evidence is put forward:



16



17



18

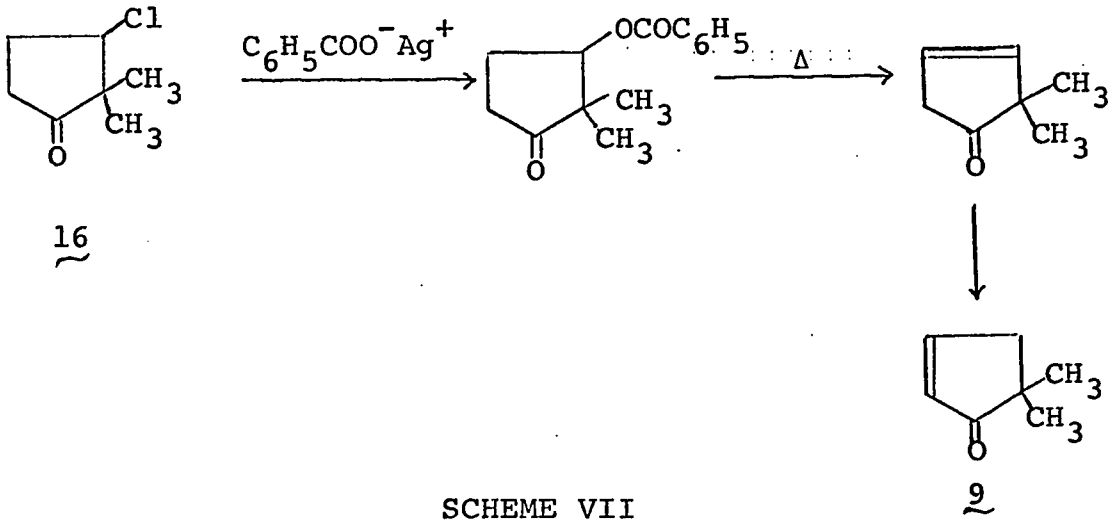
The α-chloroketone, 17, would be expected to be a strong lachrymator (32), whereas the parent compound possesses a pleasant, camphor-like odor. The chlorine in 17 is expected to be quite susceptible to displacement (32); the present compound, however, was virtually unaffected by treatment with silver acetate in refluxing ethanol for 24 h. (33, 34), or in glacial acetic acid at 110° for 40 h. (35, 36).

The β-chloroketone, 18, would be expected to suffer easy loss of hydrogen chloride when treated with base (32). Refluxing the present compound in dimethylaniline for 20 h. failed to effect dehydrochlorination, as could be seen on direct inspection of the crude reaction mixture by GLC; similar treatment with a solution of potassium t-butoxide in refluxing t-butanol for 24 h., on the other hand, destroyed the chloroketone but failed to generate 5,5-dimethylcyclopent-2-en-1-one,

9. Instead, one of the trace peaks in the GLC, previously mentioned as occurring together with the two high-boiling products presently under discussion, became quite intense. The nature of these latter changes was not investigated.

When the present compound was heated with silver benzoate in boiling (235°) benzoic acid for 8.5 h., and the product worked up, inspection of the crude material by GLC showed that the chloroketone had been destroyed to the extent of 51%; the products obtained were 9 (25%), and a completely new compound which eluted from the GLC much later than either of the previously major components (33%). The yields here were estimated by relative peak areas, and hence are only approximate.

The α,β-unsaturated ketone, 9, probably arises by prior, slow displacement of chloride by benzoate, pyrolysis of the benzoate, and tautomerisation, thus:

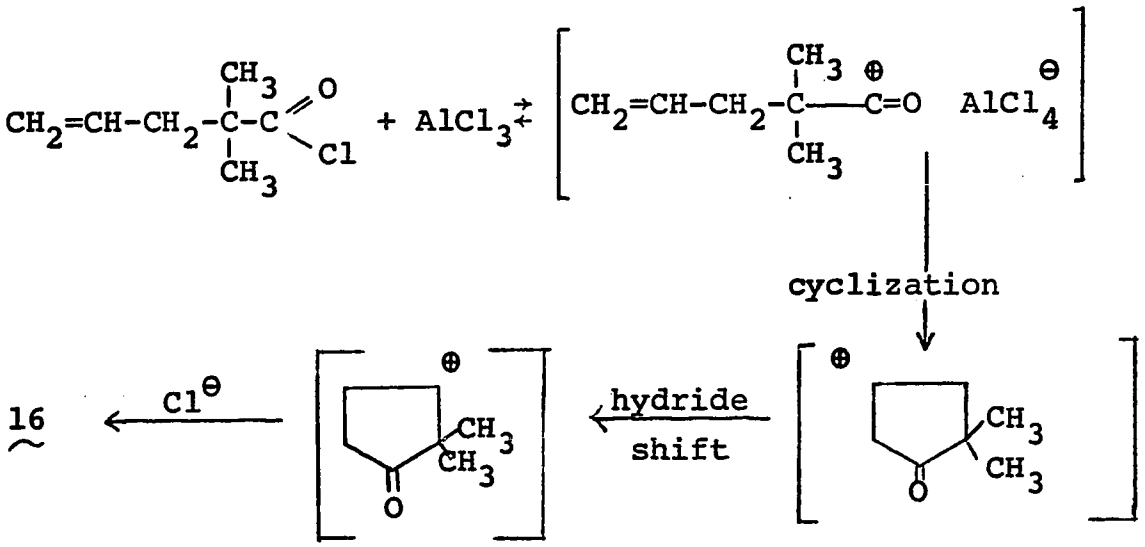


16 9

SCHEME VII

The nature of the new compound referred to above is not known.

The above data would appear to conclusively rule out 17 and 18 as possible structures for the chloroketone, which is, therefore, assigned the structure 16. The occurrence of compounds such as 16 as significant by-products in acylation reactions of this kind is well-known (37, 38). Hydride transfers appear to be involved in the mechanism (38).



SCHEME VIII

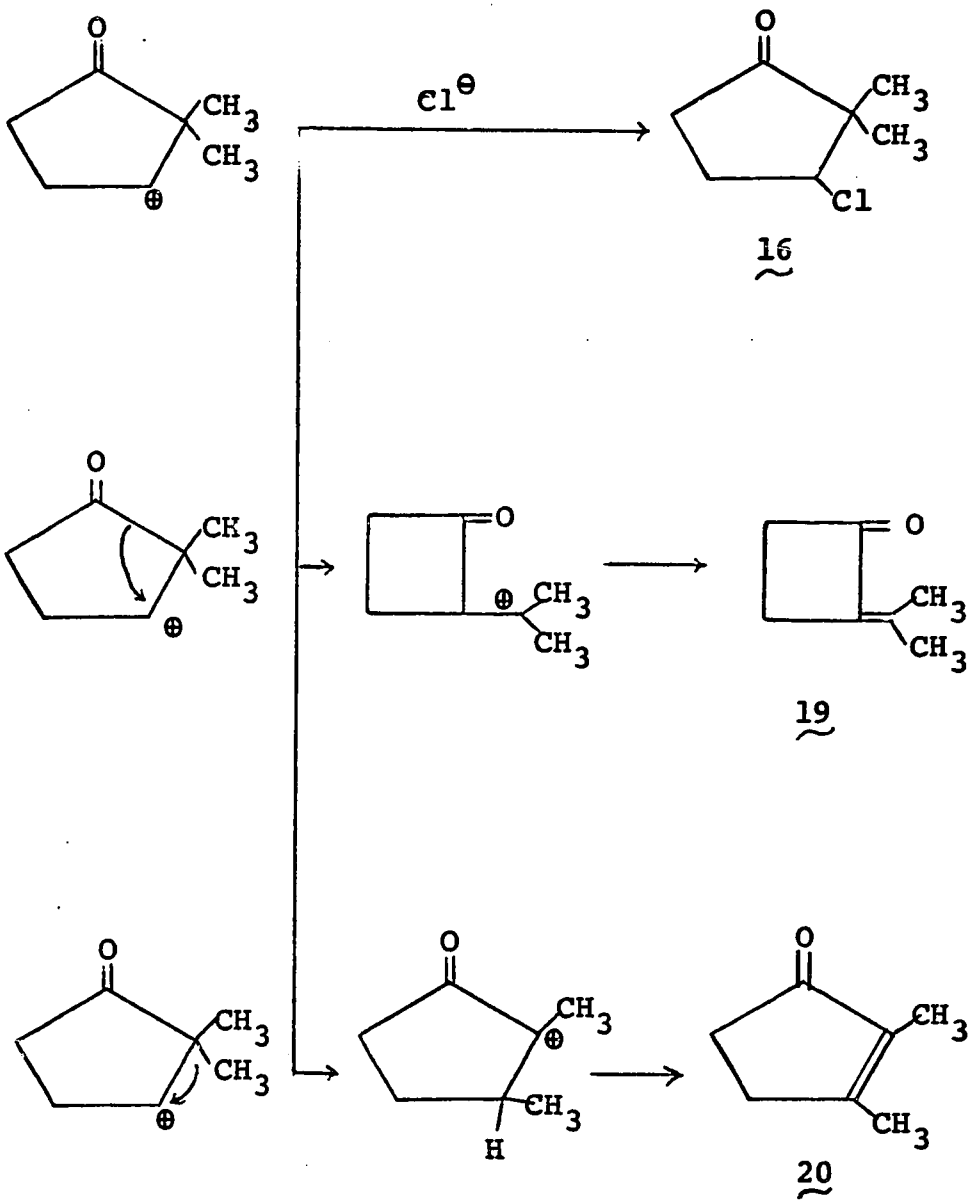
Mechanism of formation of 16

The n.m.r. spectrum of the crude high-boiling mixture contains, in addition to peaks attributable to 16, a broad, slightly perturbed singlet at τ 7.97, and

a slightly broader singlet, showing at least 7 shoulders, at τ 8.40. These peaks are in the ratio 1:1; if they are presumed to represent methyl protons, it can be shown, by direct analysis of the integration, that exactly 4.0 protons are hidden under the τ7.4-7.9 multiplet of 16. The minor component can therefore be presumed to contain 10 protons, distributed thus: τ7.4-7.9, 4.0 H; τ 7.97, 3.0 H; τ 8.40, 3.0 H.

The infrared spectrum of the crude mixture contains, besides those peaks previously attributed to 16, a very strong carbonyl band at 1695 cm^{-1}, strong olefinic carbon-carbon stretch at 1650 cm^{-1}, but no olefinic carbon-hydrogen stretch, in agreement with the absence of olefinic protons in the n.m.r. spectrum. The compound under discussion is thus a ketone containing only fully-substituted double bond(s).

Two compounds which could be envisaged as possibly arising as byproducts in this cyclization and which might fit the n.m.r. spectrum are 2-isopropylidene-cyclobutanone 19, and 2,3-dimethylcyclopent-2-en-1-one, 20. These could arise from the same intermediate carbonium ion which gives rise to 16, although it is admitted that the carbonium ion α-to the carbonyl group, postulated for the formation of 20, would be highly unstable.



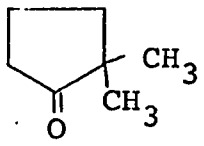
SCHEME IX

Formation of 16, 19 and 20 from the same carbonium ion

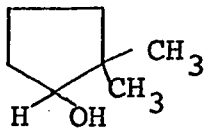
The possibility that the compound under discussion is 19 is ruled out on the infrared evidence, as 19 has been reported (39) to show carbonyl absorption at 1745 cm^{-1} and olefinic carbon-carbon stretch at 1680 cm^{-1} (vs. 1695 and 1650 cm^{-1}, respectively, for our compound).

The published infrared and n.m.r. data (40) for 20 fit our compound well: infrared, 1656 and 1701 cm^{-1}; n.m.r., τ7.7 (multiplet, CH_2), 7.97 and 8.39 (singlets, methyls). However, the spectrum of the crude mixture exhibits broadening of the methyl peaks, and additional fine structure, which would not be expected of 20, and which are not mentioned in ref. (40). Consequently, an absolutely definite identification of this compound cannot be given.

Considerable difficulty was experienced in finding a suitable method for the reduction of 9 to 5,5-dimethylcyclopent-2-en-1-ol(6, X = OH). The method of choice proved to be the use of aluminum hydride in ether (41). All other procedures which were tried gave significant amounts of non-olefinic products, namely 2,2-dimethylcyclopentanone, 14, and 2,2-dimethylcyclopentanol, 21.



14



21

These two products undoubtedly arise by initial 1,4-reduction of 9 to give 14, subsequent 1,2-reduction of which gives 21.

The reduction procedures which were tried included the following; the mode of reduction observed is given in brackets, and refers to initial reduction only, further reduction to 21 being mentioned in the discussion of the individual reagent:

a) Sodium borohydride (1, 4): This reagent, in 2-propanol solution, or in methanol or diethylene glycol dimethyl ether (diglyme) in the presence of sodium hydroxide solution, gave 21 almost exclusively.

b) Lithium tri-t-butoxyaluminum hydride (1,4): Again, exclusive 1,4-reduction was observed. However, presumably due to the slower reduction of 14 by the bulky reagent, significant quantities of 14 were always found in the products. Indeed, at -78°, 14 could be obtained pure, and in high yield.

c) Dibutyltin dihydride (1,4): This reagent was selected for trial because it had been alleged (42-45) to reduce carbonyl groups by direct hydrogen transfer and not through a metal-organic intermediate, thus giving exclusive 1,2-reduction. Attempted reduction of 9 by the method of Reference (42) yielded a crude product which was shown, by GLC to consist of 60% 21, 15% 14, and the remainder, a mixture of 6 (X = OH) and unreacted 9. The occurrence of 1,4-reduction with this reagent has since been corroborated elsewhere (46,47), although significant amounts of 1,4-addition of $H\text{-}Sn(C_4H_9)_2H$ are usually obtained; it is not known if such was the case in the reduction of 9, as such an adduct from 9 would have a very high B.P. and be retained on the GLC column.

d) Aluminum isopropoxide (1,4): Although the Meerwein-Pondorff-Verley procedure has occasionally been observed to yield some 1,4-reduction (48), there are other cases in which reagents such as those mentioned above, give mostly 1,4-reduction, while aluminum isopropoxide gives exclusive 1,2-reduction (49). In the present work, reduction of 9 gave 21, con-

taminated with only very small amounts of 14; no trace of 6 (X = OH) was observed. To the best of the author's knowledge, this represents the first example of exclusive 1,4-reduction by this reagent.

e) Lithium aluminum hydride (1,2 + 1,4): Results with this reagent were somewhat contradictory. In general, considerable amounts of 1,2-reduction were obtained under various conditions, though always accompanied by 1,4-reduction. The latter was much lessened when older samples of reagent, presumably containing partly hydrolysed or oxidised species, were used.

f) Aluminum hydride (1,2): Using Jorgenson's procedure (41), 9 could be consistently reduced to 6 (X = OH) in high yields, accompanied by a maximum of 8%, but usually 0-1% of saturated products.

It should be noted here that reduction of 9 by either sodium borohydride or lithium tri-t-butoxyaluminum hydride affords a very convenient entry into the 2,2-dimethylcyclopentyl system, superior in convenience to any previously published route, such as described in (30) or (31).

Reduction of 9 to 6 (X = OH) having been successfully achieved, the next problem was the selection of a suitable ester for the projected S_N2' reactions. Stork's use of 2,6-dichlorobenzoate as a leaving group in his system (16) necessitated quite drastic conditions for his displacement reactions. It appeared that phenylmethanesulfonate, $-OSO_2CH_2C_6H_5$, would be a more suitable leaving group, since displacement ought to be realisable under relatively mild conditions. In order to test this suggestion, the preparation of the phenylmethanesulfonate of a suitable model alcohol was undertaken, with a view to checking its S_N2' reactivity; if this part of the work were successful, the same could be done with 6, X = OH.

The model allylic alcohol chosen was 4,4-dimethylpent-1-en-3-ol, 22. Attempts to prepare 22 by the reaction between t-butylmagnesium bromide and acrolein, according to Green (50), failed completely:

[6] $$CH_2{=}CH{-}CHO \xrightarrow[2.\ H_3O^+]{1.\ t\text{-}C_4H_9MgBr} \not\longrightarrow CH_2{=}CH{-}\underset{\displaystyle OH}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}{-}C(CH_3)_3$$

22

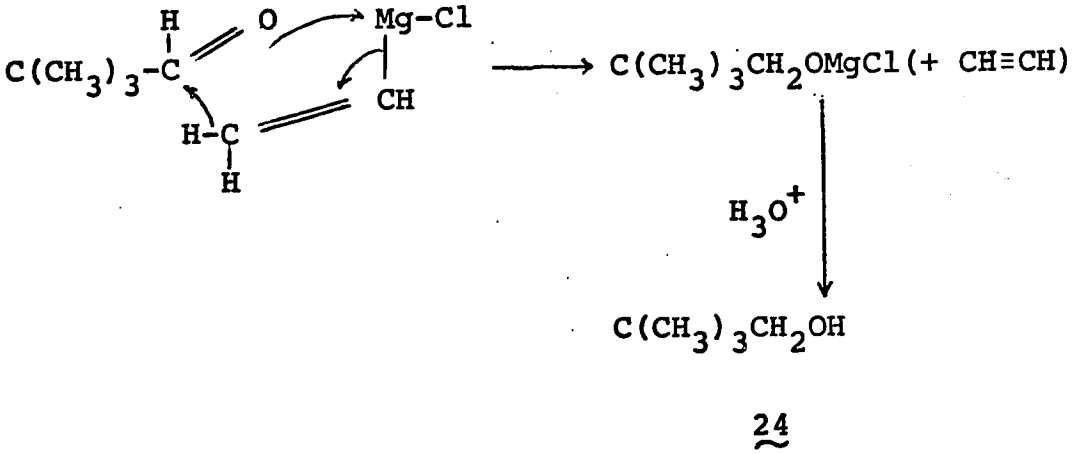
This result, at first rather disconcerting, was later confirmed by other workers (51).

The approach to 22 which proved successful was that given in Equation [7]:

[7] $C(CH_3)_3CHO$ $\xrightarrow[2.\ H_3O^+]{1.\ CH_2=CH-MgCl}$ 22

23

The reaction between pivalaldehyde, 23, (52), and vinyl magnesium chloride (53) afforded 20 in 20% yield. An unexpected by-product, obtained in approximately 5-7% yield, was 2,2-dimethylpropanol (neopentyl alcohol, 24). As far as the author is aware, this is the first case of apparent reduction of a substrate by a vinyl Grignard reagent:

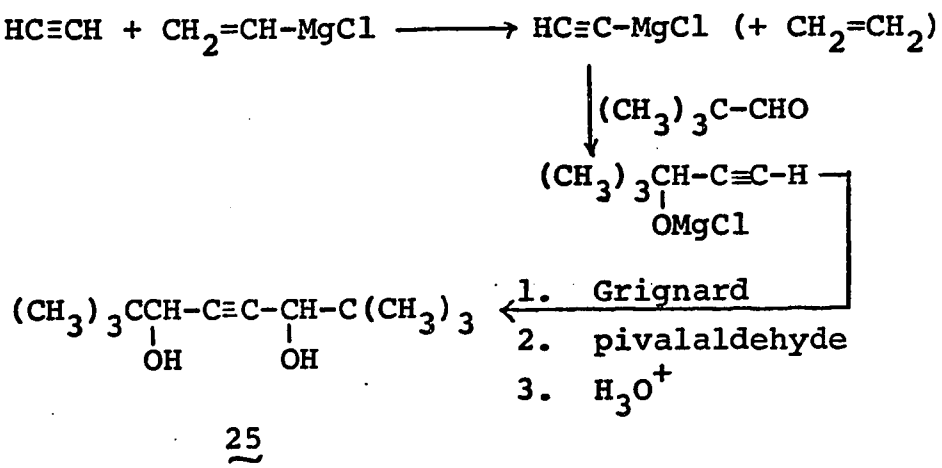


24

SCHEME X

Reduction of pivalaldehyde by vinyl Grignard reagent

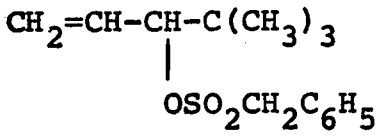
Acetylene, shown as a byproduct in Scheme X, would most likely react further with Grignard reagent, as follows:



SCHEME XI

The acetylenic diol 25 is expected to be very high-boiling and will thus remain in the distillation residue after the desired alcohol, 22, is removed; no search for 25 was made. Ethylene, projected as a by-product above, was not noticed, but could easily have been missed, if it evolved reasonably slowly.

With 22 on hand, the preparation of its phenylmethanesulfonate, 26, was undertaken.



26

When phenylmethanesulfonyl chloride (54,55) was allowed to react with 22 in carbon tetrachloride, using triethylamine as base (56), a 40% yield of 26 could be obtained. This proved to be a very labile compound at room temperature, but could be kept several months in a closed vial at -20°.

Preliminary results on the S_N2' reactivity of 26 were quite encouraging (see the next Section of this Chapter) so that attention was next shifted to the preparation of 5,5-dimethylcylopent-2-en-1-yl phenylmethanesulfonate (6, X = $OSO_2CH_2C_6H_5$). However, repeated attempts to prepare this ester, under a wide variety of conditions, and at temperatures as low as -30°, failed. These attempts were all monitored by n.m.r., and in no case was a spectrum seen which could be clearly attributed to the desired ester, although excellent evidence was obtained for its transitory existence. The type of result which was obtained can best be indicated by reference to

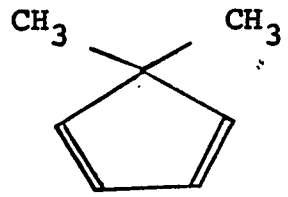
a specific example:

A mixture of 6, X = OH (approximately 10^{-3} mole) and an equimolar amount of phenylmethanesulfonyl chloride, suspended in carbon tetrachloride (3 ml), was added to a solution of triethylamine (5% excess) in carbon tetrachloride (2 ml) at -25 to -30°C. After storage at -25° overnight, a sample was submitted for 100 mHz n.m.r., and the following peaks were seen: a sharp singlet at τ 2.65, superimposed on a multiplet, τ 2.60-2.75; a sharp singlet at τ 3.90; a complex multiplet at τ 4.20-4.40; multiplet (six lines in the approximate ratio of 1:2:2:2:2:1), τ 5.05-5.20; quartet, further split, τ 5.4-5.65; two perturbed singlets, τ 5.80 and 5.90; and a very complex methylene-methyl region, incorporating several multiplets, and, in particular, at least four different kinds of methyl peaks, all over the region τ 7.68-9.05. The integrated intensities over these regions were in the ratio 19:17.5:34:7:6.5:5.5:217.

There are two things to note here, firstly, the phenyl:olefin ratio is inverted, from the 5:2 expected in the ester, to approximately 1:2 (considering only the region from τ 4.2-4.4). This indicates the removal of phenyl from the solution by an unwanted side reaction. An important consequence of this is that the proportion of the τ 4.2-4.4 region ascribable to the

olefin protons in the desired ester is quite small.

Secondly, the strong singlet at τ 3.90, and a methyl peak at τ 8.82, are ascribable with some certainty to 5,5-dimethylcyclopentadiene, 27, on the basis of Wilcox's reported spectrum (57): two peaks in the neat liquid in the ratio of 2.9:2, at +3.95 and -0.93 ppm., relative to methylene chloride. Although Wilcox's results were reported under different conditions to those used here, extrapolation to our conditions is quite simple.



27

Compound 27 is, of course, anticipated to be a decomposition product of the desired ester (6, X = $OSO_2CH_2C_6H_5$). The present assignment is also supported by the observation that, as the n.m.r. tube was permitted to warm to 25°, the peak at τ 3.90 (and also that at τ 8.82) grew rapidly in intensity, vs. the τ 4.2-4.4 and phenyl peaks, from its initial ratio of approximately 1:2:1, to a final ratio of approximately 1:1:0.4, after a total elapsed time of approximately 40 min. in the n.m.r.

spectrometer.

Essentially similar results were obtained under a variety of conditions, except that, in general, in reactions commenced at temperatures higher than -30°, 5,5-dimethylcyclopentadiene, 27, was not so important a product, and, on occasion, was not seen at all. Even in these cases, however, the olefin vs. phenyl ratio was always too high, the methyl region was too complex, and there were no peaks ascribable to either the benzylic or the methine protons of the desired ester. These observations can be reconciled as follows:

The presence of 27 in the reaction mixture at -30°, together with the absence of the desired ester, would indicate that this ester was formed, initially, but subsequently decomposed very rapidly. This decomposition would also liberate phenylmethanesulfonic acid, which, in the absence of excess triethylamine, could protonate unesterified alcohol (6, X = OH). This protonated alcohol would then decompose to more 27, seen to increase as the temperature rises. The absence of 27 when the reaction is started at higher temperatures may tentatively be ascribed to Diels-Alder reaction between 27 and intermediate sulfene (56).

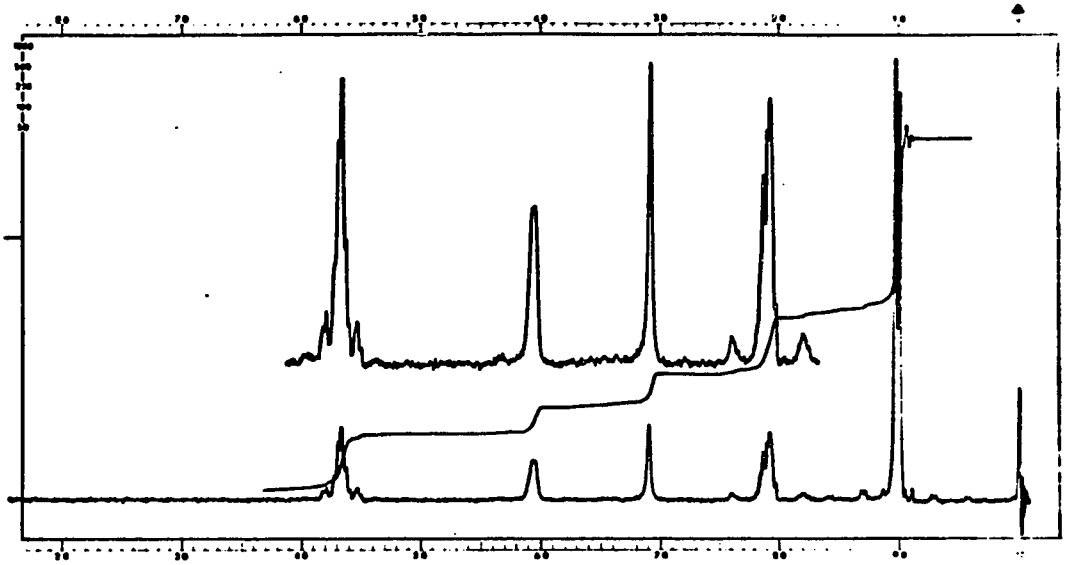
Since the phenylmethanesulfonate of 6 was obviously too unstable for our purposes, the synthesis

of other esters of the 5,5-dimethylcylopent-2-en-1-yl system was next investigated, and the p-nitrobenzoate, 3,5-dinitrobenzoate and 2,6-dichlorobenzoate were successfully prepared.

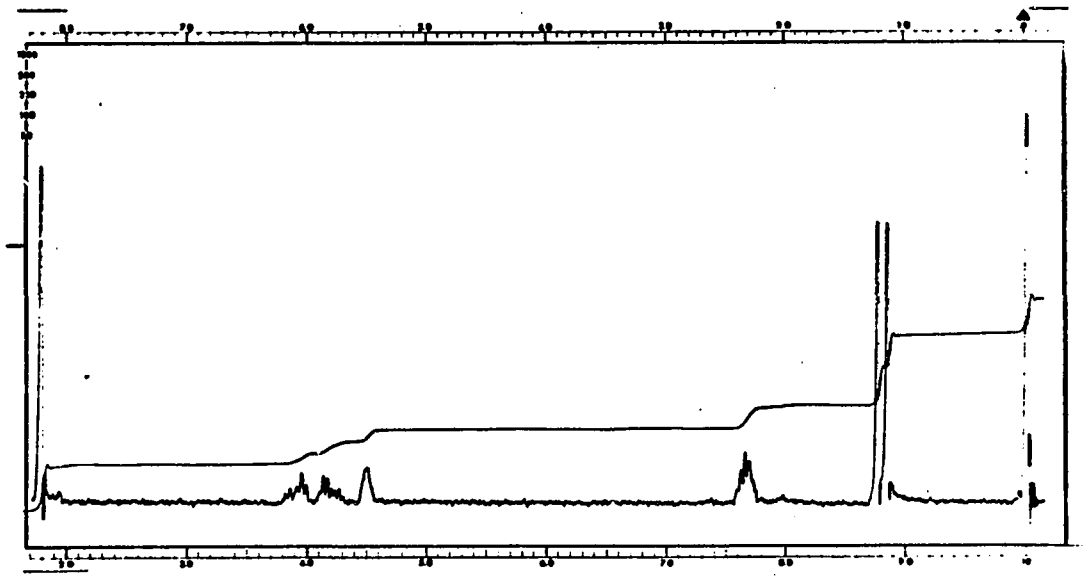
The p-nitrobenzoate (6, X = $OCOC_6H_4(4\text{-}NO_2)$) and the 3,5-dinitrobenzoate (6, X = $OCOC_6H_4(3,5\text{-di-}NO_2)$) were prepared, in yields of up to 60%, and 36% respectively, by the reaction of 6, X = OH with the appropriate acid chloride, in the presence of base. When the same procedure was tried for the 2,6-dichlorobenzoate case, however, no ester was obtained. The only isolable product was assigned the structure of 2,6-dichlorobenzoic anhydride, on the following spectral evidence: the n.m.r. spectrum showed only aromatic protons, while the infrared spectrum showed two strong peaks at 1820 and 1760 cm^{-1}, which are diagnostic of an acid anhydride (58).

The desired 2,6-dichlorobenzoate (6, X = $OCOC_6H_4(2,6\text{-di-}Cl)$) was successfully synthesised, in up to 71% yield, by reaction of 2,6-dichlorobenzoyl chloride (16) with the anion of 5,5-dimethylcyclopent-2-en-1-ol (i.e., 6, X = $O^{\ominus}$) in tetrahydrofuran solution.

The n.m.r. spectrum of the p-nitrobenzoate is given in Figure 2, and that of the 2,6-dichlorobenzoate in Figure 4.

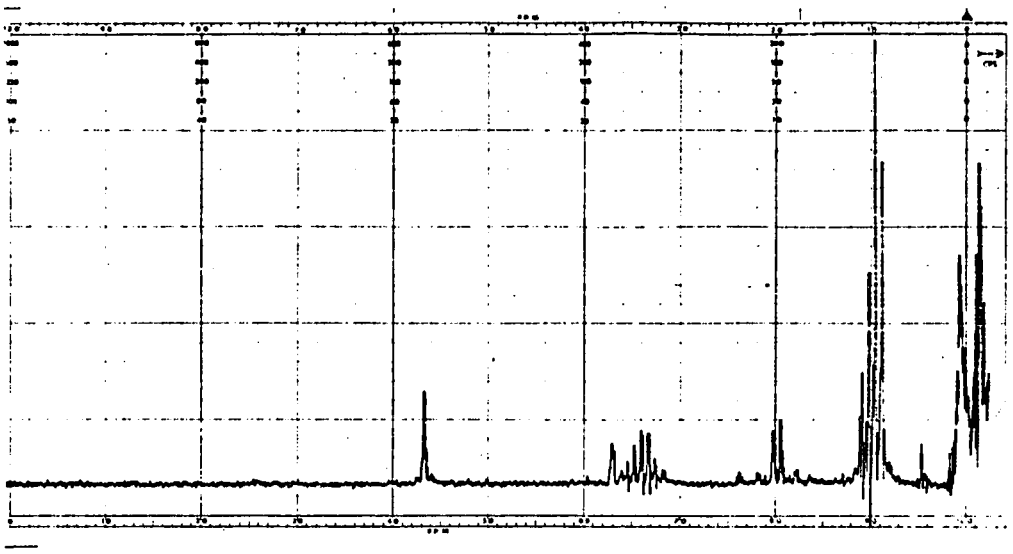


(a) 5,5-DIMETHYLCYCLOPENT-2-EN-1-OL
(6, X = OH) (CCl_4)

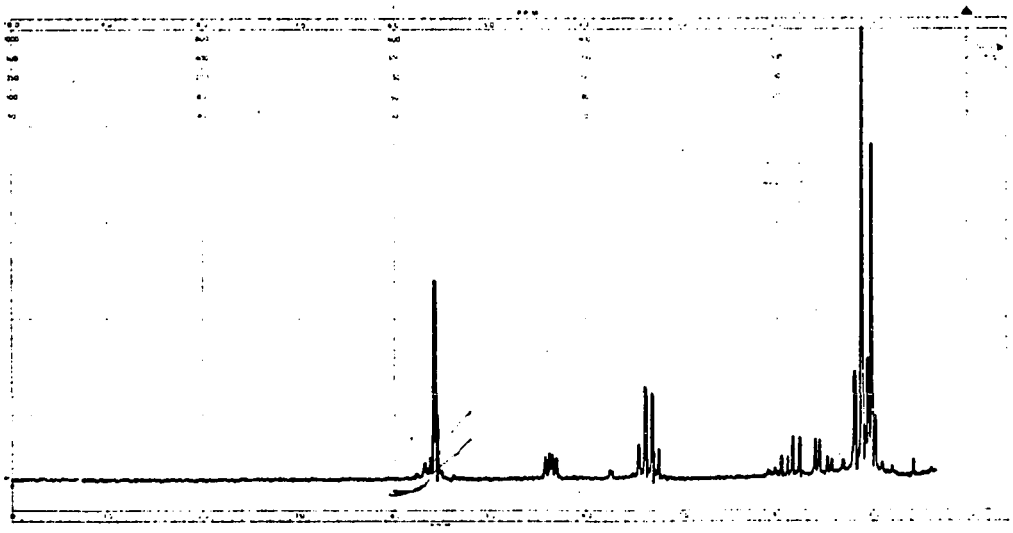


(b) 5,5-DIMETHYLCYCLOPENT-2-EN-1-YL p-NITROBENZOATE
(6, X = $OCOC_6H_4(4\text{-}NO_2)$) (CCl_4)

Figure 2

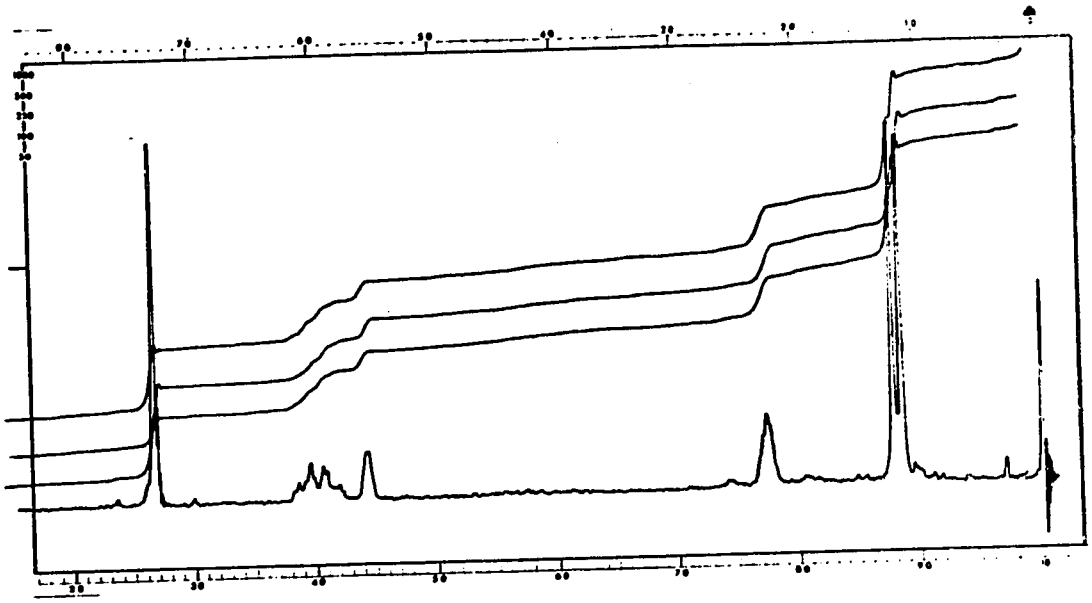


(a) 5,5-DIMETHYLCYCLOPENT-2-EN-1-YL ETHYL ETHER ($CDCl_3$)

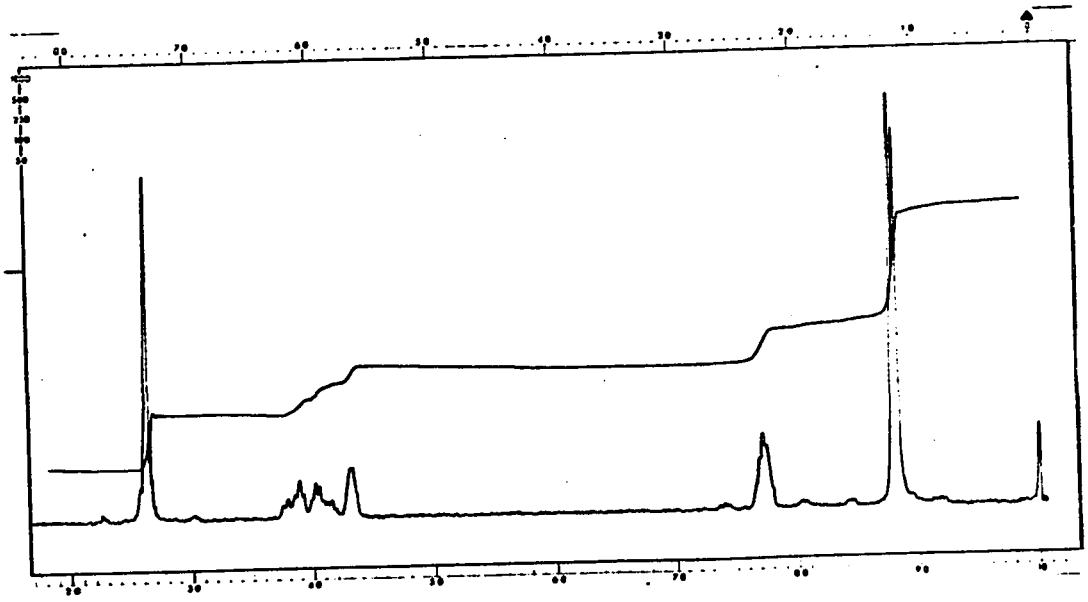


(b) 4,4-(+5,5-)DIMETHYLCYCLOPENT-2-EN-1-YL ETHYL ETHER ($CDCl_3$)

Figure 3



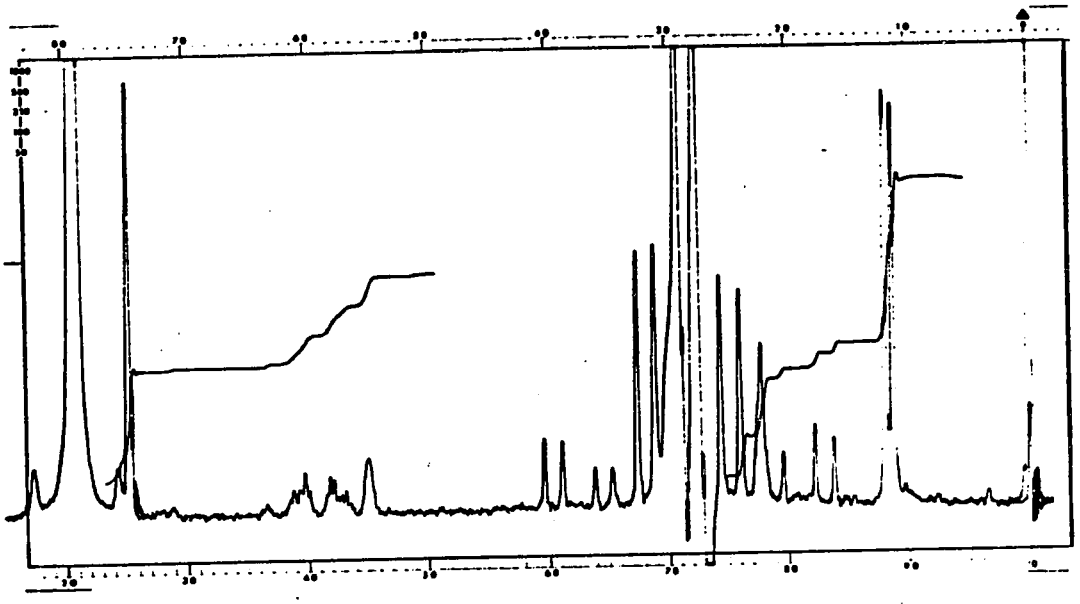
(a) in carbon tetrachloride



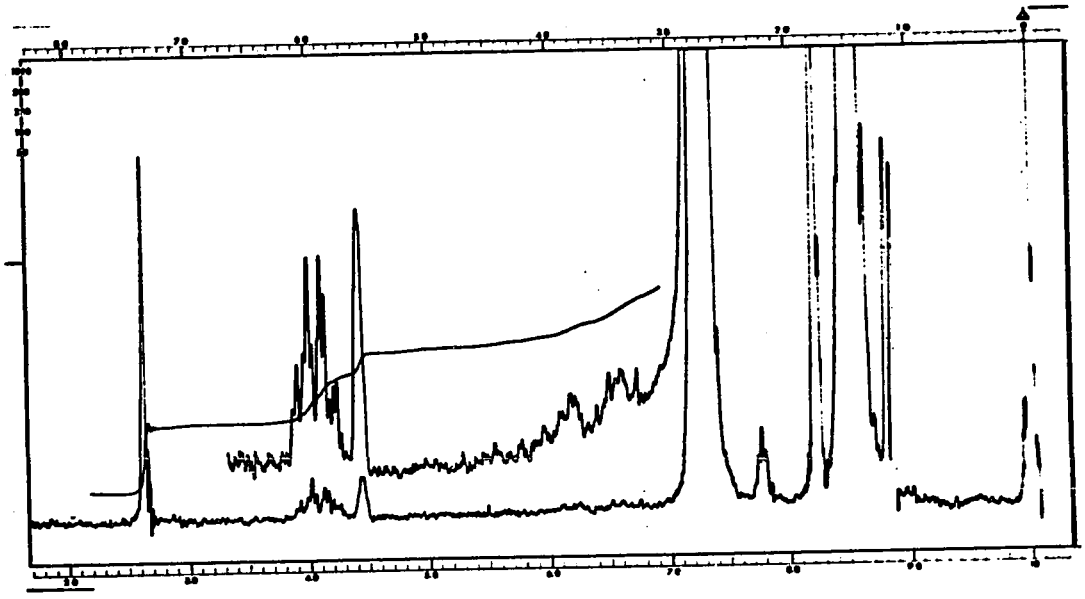
(b) in chloroform-D

Figure 4

Spectra of 5,5-dimethylcylopent-2-en-1-yl 2',6'-dichlorobenzoate



(c) in dimethylformamide

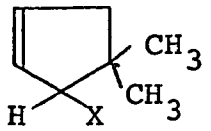


(d) in piperidine

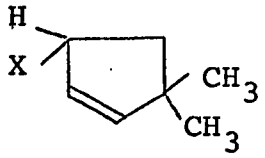
Figure 4

5,5-Dimethylcyclopent-2-en-1-yl
2',6'-Dichlorobenzoate

These two esters, and also the 3,5-dinitrobenzoate (details of which are in the Experimental section of this Chapter), evidently have very similar spectra, as regards both the chemical shifts of the protons in the non-aromatic part of the molecule, and even the degree of spin-spin splitting within each peak. It is, therefore, virtually certain that all of these possess the same gross molecular structure. In order to show that this structure was, in fact, 6, and not its allylically-rearranged alternative, 6', some n.m.r. double resonance experiments were carried out.



6



6'

X = OCOR

If one were to irradiate the methine proton, in the general structure 6, and observe the methylene protons, one should see very little change, if any; coupling through five bonds is expected to be very small. Similar irradiation of the methine proton in 6' should lead, on the other hand, to near-total collapse of the methylene region.

The 3,5-dinitrobenzoate was chosen for examin-

ation. At 100 mHz, the methylene region consists, essentially, of 4 groups of multiplets: a quartet, further split, at τ 7.40; a second quartet at τ 7.58; a multiplet at τ 7.69; and a multiplet at τ 7.84. Irradiation of the methine causes the two quartets to collapse to triplets (further split), and the two multiplets to smooth out somewhat. The coupling which is eliminated appears to be approximately 0.4 Hz. The minor effect of irradiation proves that the general structure 6 is applicable to the 3,5-dinitrobenzoate, and by extension, to the p-nitrobenzoate and 2,6-dichlorobenzoate.

It should be pointed out here that the phenylmethanesulfonate of 6 is, by analogy, expected to exhibit a n.m.r. spectrum similar to those of the three esters discussed above, as regards the alicyclic portion of the molecule. The absence of such a spectrum in any of the experimental results obtained on attempted synthesis of this phenylmethane sulfonate, fully supports what has already been written about the instability of this compound.

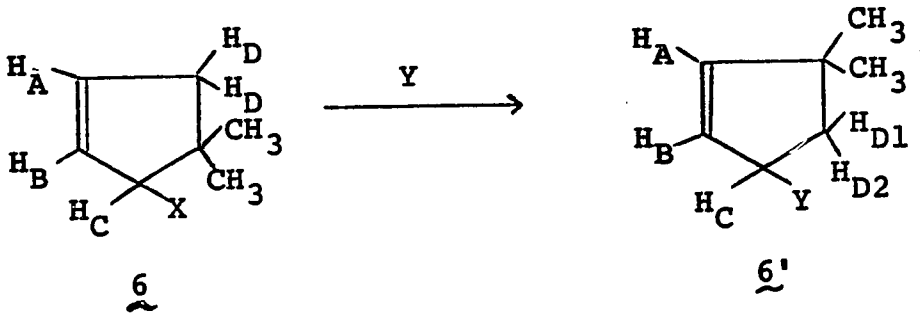
Results of Attempted S_N2' Reactions in System 6

Once a suitable route to the esters of system 6 had been evolved, as described in the previous Section, attention was shifted to assessment of the reactivity of this system towards nucleophilic displacement. Based on the results of previous investigators (4-7), little difficulty was anticipated in achieving the desired S_N2' reactions; more support for this optimism was obtained when strong indications of a successful S_N2' reaction in the closely-related 4,4-dimethylpent-1-en-3-yl (t-butylvinylcarbinyl) system were observed (see later). Therefore, a number of trial experiments were carried out, involving the use of selected nucleophiles with one or more of the esters of system 6. The results obtained were quite disappointing; thiourea, tetra-n-butylammonium acetate and diethylmalonate anion failed to give any displacement, whereas reactions with piperidine and thiophenoxide anion apparently took a different course. Cyanide and thiocyanate ions were the only nucleophiles which may have effected S_N2' reactions; the evidence is, however, not convincing.

All of the trial experiments discussed below were monitored by n.m.r. spectroscopy, since it was considered that the spectra to be expected from the S_N2'

products could be predicted with some precision. The justification for this statement is as follows:

Consider structure 6 being converted by a nucleophile Y to a rearranged product, 6':

[8] 

6 6'

In structure 6, H_A is adjacent to methylene protons, H_D, whereas H_B is allylic to them. In structure 6', both olefinic protons are homoallylic to the methylene protons. Hence, in going from 6 to 6', the H_A-H_D coupling (which, in all the compounds 6 prepared in this study, is approximately 2-3 Hz), will vanish, and any coupling with H_D which remains will be vanishingly small (59). The olefinic region in 6' will thus be considerably simplified, as regards the spin-spin splitting pattern; there may also be a slight chemical shift difference, both of these effects being somewhat dependent on the difference in electronegativity between X and Y (ref. (59), pp.49,85).

The methine proton in 6 is coupled to H_B, with

J_{BC} being approximately 2-3 Hz, (see ref. (59), p.87, and the present work), and to H_A, with J_{AC} vanishingly small (ref. (59), pp.87,108). In structure 6', however, there will be in addition, a larger coupling with the methylene protons H_D; also, since the protons H_D are now adjacent to an asymmetric centre, they will be more magnetically non-equivalent than in 6, (ref. (60), p.224), and there will be a possibility of two separate H_C-H_D coupling constants being involved. In other words, protons H_C, H_{D1} and H_{D2} will form a 3-spin system, most probably of either the ABX or AMX type, dependent on the chemical shifts and coupling constants involved. These 3-spin systems will give complex, but readily-recognizable patterns, which have been adequately described in the literature (ref. (59) p.46; ref. (60), p.225; ref. (61), p.88).

An example of this is seen in Figure 3. The lower spectrum is that of the product obtained on ethanolysis of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate (6, X = $OCOC_6H_4(4\text{-}NO_2)$) (for details, see Chapter 2). Analysis of the spectrum clearly shows the product to consist of 88% of 4,4-dimethylcyclopent-2-en-1-yl ethyl ether (6', Y = OC_2H_5) and 12% of the 5,5-isomer (6, X = OC_2H_5), the spectrum of which is also given in Figure 3. In the lower spectrum the methine quartet at

τ 5.63 and the methylene group at τ 8.05-8.58 clearly form a 3-spin system of the type just discussed. It so happens that this particular case is amenable to analysis as an AMX pattern, and the following coupling constants can be derived: J_{D1-D2} = 13 Hz, J_{CD1} = 7 Hz, J_{CD2} = 5 Hz.

The final appearance (including the chemical shifts) of the spectrum of each compound 6, will vary somewhat with the electronegativity of Y as compared to that of X; that it will not be affected very much, is strongly suggested by Tables (3-2) and (3-3) of reference (59)(p.53). The relatively small effect to be expected from the use of different solvents in the trial nucleophilic displacement reactions to be described below, is pointed up in Figure 4, where the spectrum of 5,5-dimethylcyclopent-2-en-1-yl 2,6-dichlorobenzoate (6, X = $OCOC_6H_4$(2,6-di-Cl)) in each of a range of solvents of varying polarity (and hydrogen-bonding capability) is presented.

Some special remarks about individual nucleophiles are warranted at this point:

In order to avoid the possible occurrence of solvolysis reactions, tetra-n-butylammonium acetate was required to be as free as possible of both acetic acid and water of crystallization. For this purpose, the well-known hydrate (62) was dehydrated in two stages;

firstly, by solution in 98% ethanol and drying over #3A molecular sieves, to a composition corresponding closely to a semihydrate ($(\underline{n}\text{-}C_4H_9)_4N^+OCOCH_3^-$); and then, by solution in carbon tetrachloride and drying over #4A molecular sieves, to what was apparently a decihydrate ($(\underline{n}\text{-}C_4H_9)_4N^+OCOCH_3^-$). This decihydrate, which, despite protracted effort, could not be further dehydrated, was used in the trial nucleophilic displacements discussed below, in Table 1, and in the Experimental section, and is the compound which is referred to, in what follows, as tetra-n-butylammonium acetate or TBA.

A solution of 4,4-dimethylpent-1-en-3-yl phenylmethanesulfonate, 26, in carbon tetrachloride, was allowed to react with a solution of a 20% excess of tetra-n-butylammonium acetate (TBA) in carbon tetrachloride for 10 min. at room temperature, after which a sample was taken for n.m.r. evaluation. A second sample was taken after the mixture had been allowed to stand overnight at room temperature, and a third, after the mixture had been heated 5 h. at 40-45°. The following observations were made:

1) A doublet at τ5.30 (J = 8 Hz) in the spectrum of 26, assigned to the methine proton, was seen to progressively disappear, while a new doublet (poorly-resolved) (J = 5.5 Hz) progressively appeared at τ 5.60. The most

likely assignment for this peak is the allylic methylene group in the rearranged acetate,

$$\begin{array}{l} CH_2\text{-}CH{=}CH\text{-}C(CH_3)_3 \\ | \\ OCOCH_3 \end{array}$$

2) The original acetate peak of TBA at τ 8.32, progressively disappeared, and a new peak at τ 8.0 gradually appeared. This was assigned to the allylic acetate group in the above molecule.

While the above evidence is not conclusive, the inference is strong that 26 was reacting by the S_N2' route. By analysis of the integrations, it was inferred that approximately 50% reaction had occurred by the time the third sample was taken.

The apparent observation of reaction by the S_N2' route in the 4,4-dimethylpent-1-en-3-yl system is in accord with the work of de la Mare, et al. (63), who observed that the corresponding chloride reacted exclusively S_N2' with ethoxide ion, but is in sharp contrast with the results reported by Kushibab (64). He found no simple reaction between either the corresponding methanesulfonate or p-nitrobenzoate, and piperidine, pyridine or thiophenoxide ion. This discrepancy is most curious, and this system could well bear re-investigation.

Selected, representative results obtained in the trial nucleophilic displacements using system 6 and

the list of selected nucleophiles given at the start of this Section are presented in Table I and amplified in the Experimental section.

The case of cyanide and thiocyanate ions deserves special comment. The results obtained with these nucleophiles can be interpreted as indicating the occurrence of S_N2' reactions, but the evidence is not convincing. By the time these results were obtained, it was already evident that there was something peculiar about the reactions of system 6 and that our attention should be shifted to solvolyses in this system. Therefore, the cyanide and thiocyanate results were not investigated further.

It is evident, from Table I and the Experimental section, that unexpected difficulties were met in achieving S_N2' reactions in the 5,5-dimethylcyclopent-2-en-1-yl system. This system is, fundamentally, not so very different to that of Stork (16), and he apparently obtained clean S_N2' reactions under conditions no more stringent than those used in the present work.

Such difficulties were, in fact, unprecedented, until the very recent appearance of work of Bordwell, et. al. (8-12). This work will now be discussed in some detail, followed by a discussion of some work by Jefford (19,20) which bears on the question of the stereochemistry

T A B L E I

REPRESENTATIVE TRIAL NUCLEOPHILIC DISPLACEMENTS IN SYSTEM 6

TBA - Tetrabutylammonium acetate
pNB - p-Nitrobenzoate of 6
dNB - 3,5-Dinitrobenzoate of 6
dCB - 2,6-Dichlorobenzoate of 6
DMF - Dimethylformamide
DEM - Diethylmalonate anion
Th - Thiourea

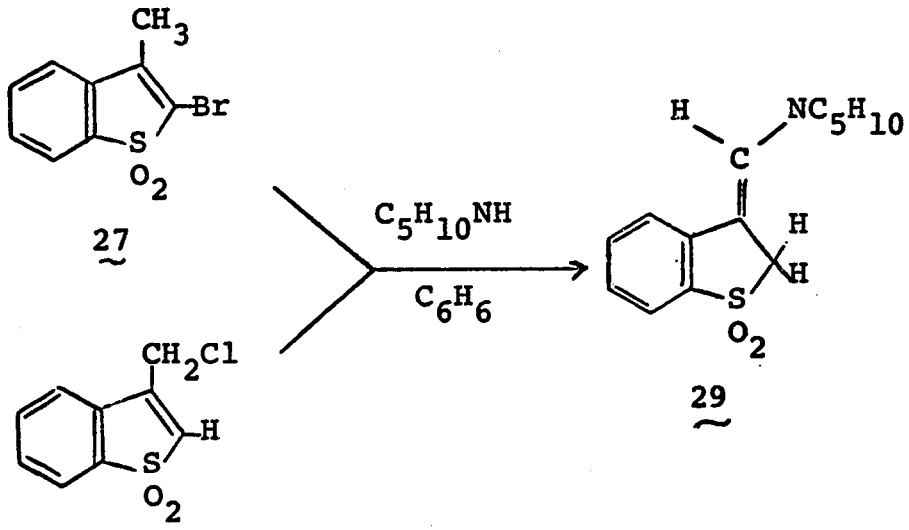
Nucleophile (Moles x 10^4)	Ester (Moles x 10^4)	Solvent (Ml.)	Time h.	Temp	Results obtained
TBA(7.7)	pNB(6.7)	CCl_4(3)	23 then15	Room Reflux	N.m.r. spectra at various times showed no effect on ester, but destruction of TBA
TBA(4.2)	dCB(3.2)	C_6H_5Cl(3)	20	Reflux	Spectrum after H_2O extraction showed no effect on ester, but destruction of TBA
Th (6.4)	dNB(5.0)	acetone(3)	20	Reflux	Solvent evaporated - recovered material identical to mixture of starting materials

Nucleophile (Moles x 10^4)	Ester (Moles x 10^4)	Solvent (Ml.)	Time h.	Temp	Results obtained
Th. (86)	dCB (37)	DMF (25)	40	100°	Only starting materials recovered
$SC_6H_5^-$ (36)	dNB (35)	DMF (70)	2.5	110°	Recovered material showed no S_N2' product
Piperidine	dCB (5.0)	Piperidine(0.5)	20	130°	Spectrum of ester disappeared. New spectrum doesn't fit S_N2' product
DEM (10)	dCB (3.8)	DMF (1)	36	100°	Spectra at various times showed no change
$CN^{\ominus}$ (4.3)	dCB (4.0)	DMF (1)	3	Reflux	Ester spectrum disappearing. New spectrum fits S_N2', except no ABX (AMX) system
$SCN^{\ominus}$ (3.9)	dCB (3.9)	DMF (1)	3	Reflux	Ester spectrum disappeared. Results similar to $CN^{\ominus}$

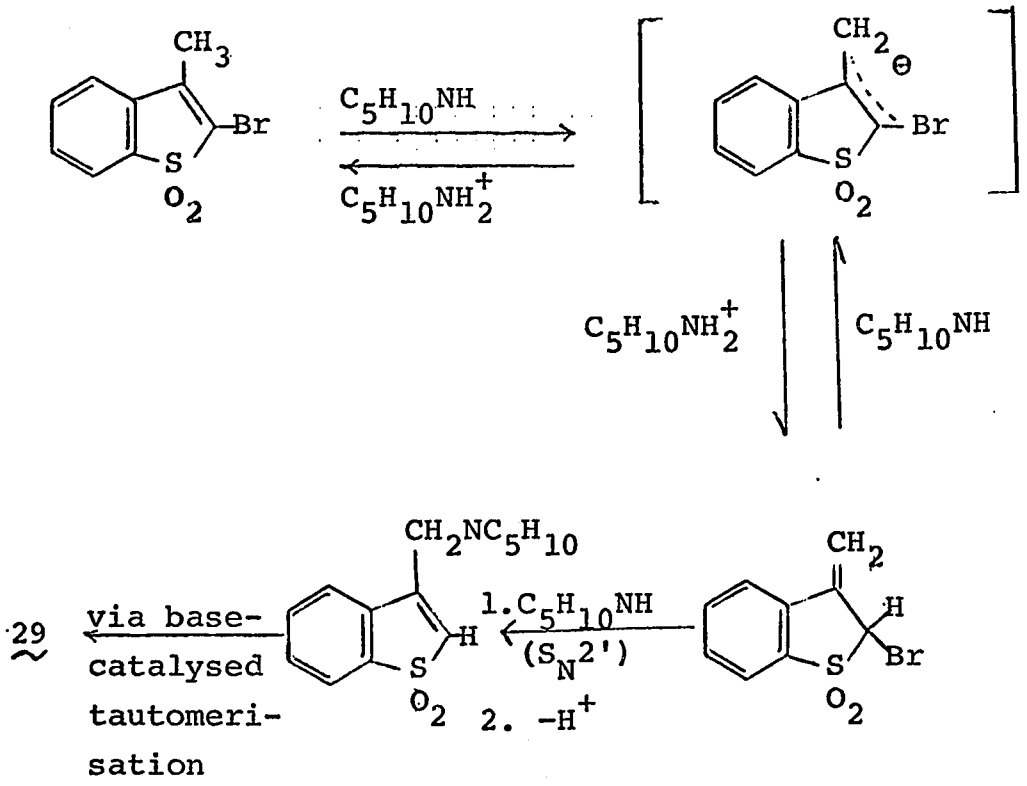
of the S_N2' reaction, and then by some remarks on the bearing of these investigations on the present work.

Bordwell and co-workers have shown (8-12) that, contrary to an earlier paper from the same source (65), 2-bromo-3-methylbenzo[b]-thiophene 1,1-dioxide, 27, and 3-chloromethylbenzo[b]-thiophene 1,1-dioxide, 28, react with piperidine in benzene to give the same product, 29.

[9]



The transformation of 27 to 29, which proceeds analogously with morpholine and thiophenoxide ion (both of which, like piperidine, are basic nucleophiles) but not with thiourea, a neutral nucleophile, is shown to proceed by the following mechanism:



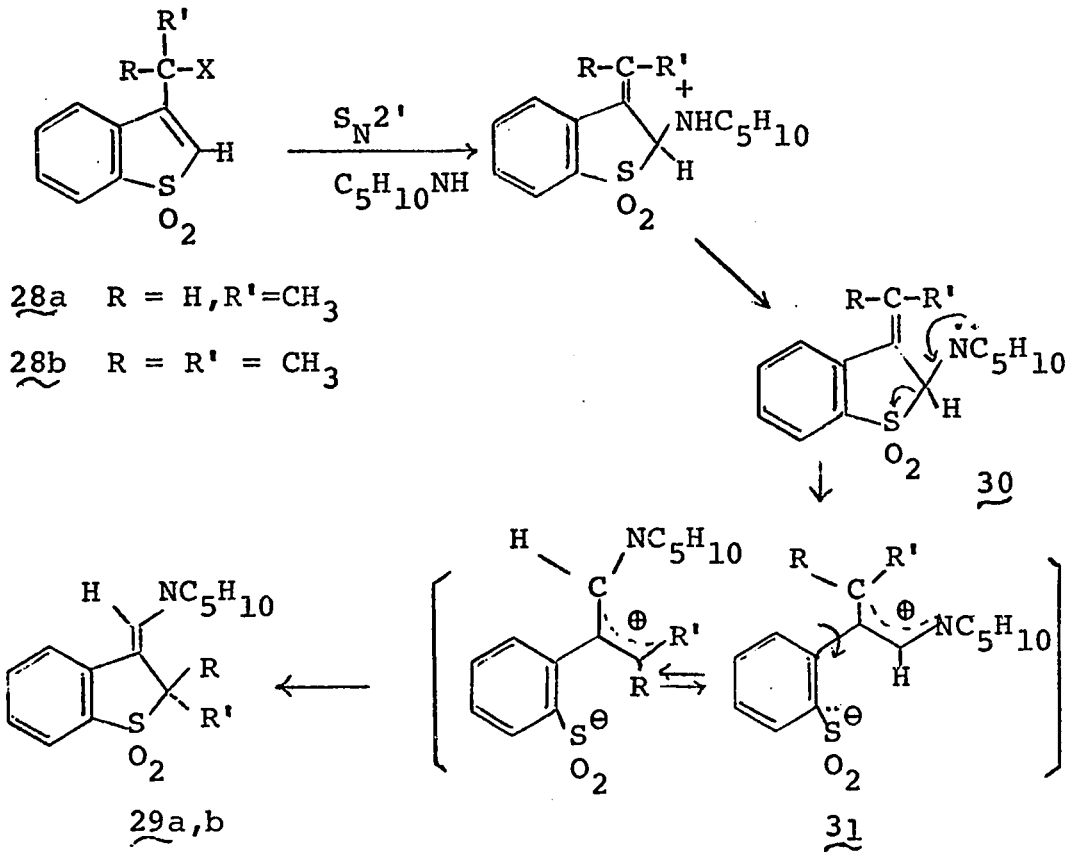
SCHEME XII

Of these steps, the final base-catalysed tautomerisation is rate-determining (as regards product formation); in the presence of a stronger base, such as methoxide, the S_N2' step becomes rate-controlling.

The lack of reaction of 27 with thiourea may be due to the inability of thiourea to promote the initial base-catalysed tautomerisation, or it may be explained by

the reluctance of thiourea to behave as nucleophile in a true S_N2' process (see later for amplification of this latter statement). The fact that thiophenoxide behaves as a successful S_N2' nucleophile with 27, but not in the reactions to be discussed below, militates against the latter explanation.

The transformation of 28 to 29 is of considerably greater interest. Bordwell and co-workers (8) show that the mechanism for the case of substituted analogues of 28 proceeds by the following steps:



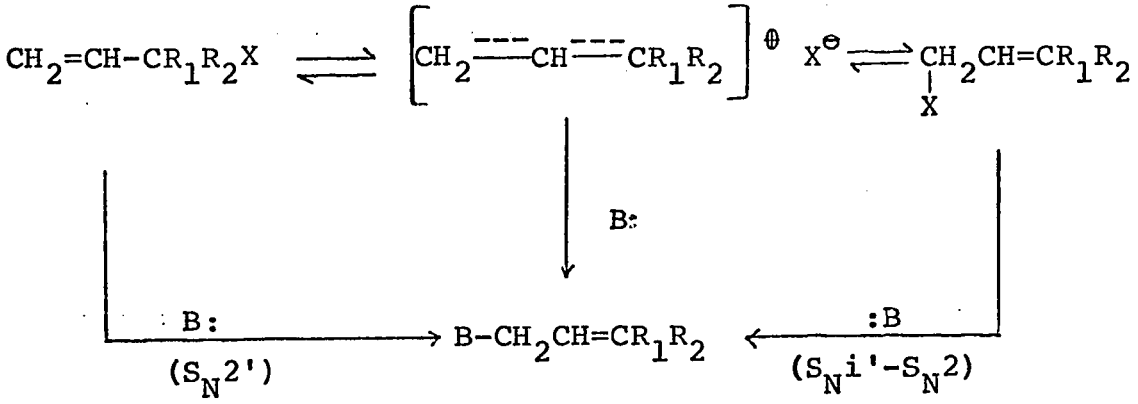
SCHEME XIII

For case 28a, the secondary halide, the S_N2' step is rate-determining for halide-ion release, while the cleavage of the intermediate 30 to the dipolar ion 31 is rate-determining for product formation; in case 28b, the tertiary halide, the S_N2' step is rate-controlling for both processes.

Compounds 28a and 28b are very reactive towards the secondary amines, piperidine and morpholine, behaving as shown in Scheme XIII. Compound 28a (X = Cl) reacts with bromide ion by the S_N2 mechanism, giving 28a (X = Br); 28b is unaffected by bromide ion. Compound 28a also reacts with thiophenoxide ion by the S_N2 mechanism; 28b appears to behave likewise. Both 28a and 28b are inert to thiourea, a nucleophile which would appear to be several orders of magnitude more powerful than secondary amines as a nucleophile in "S_N2'" reactions (as judged by the results of Young et al. (66) and Table I of ref. (12)). Similarily, 28a and 28b appear to be unaffected by alkoxide ions or tertiary amines. Clearly, these facts are contrary to previous reports on the S_N2' reaction (4-7,12), and require an explanation.

It is the view of Bordwell (12) that all previous results on the S_N2' reaction can be explained by invoking a mechanism in which either prior rearrangement of the substrate occurs and is followed by a rate-

controlling S_N2 reaction (the S_Ni'-S_N2 pathway) or rapid formation of an ion-pair takes place, followed by selective nucleophilic attack on the γ-carbon. The mechanistic possibilites are summarised in Scheme XIV.



SCHEME XIV

Now, the conditions which have to be met before a given allylic displacement reaction can be designated as S_N2' have been stated as follows (7): (a) the reaction must be first-order in both nucleophile and substrate; (b) the normal substitution product does not rearrange under the reaction conditions, and (c) the substrate does not rearrange prior to reaction with the nucleophile. Conditions (a) and (b) are readily met experimentally, although, as de la Mare points out (ref. (6), p.36),

demonstration that the normal substitution product does rearrange, does not necessarily mean it was actually formed in the reaction. Condition (c) is rather more difficult to meet, as S_Ni' reactions are known to occur very readily (7,67).

There are several possible situations with regard to prior rearrangement of substrate. There will be an equilibrium involved, in which a significant proportion of rearranged substrate may or may not be present; as Bordwell points out (12), the equilibrium will usually lie significantly on the side of rearranged substrate, particularly if, as in Scheme XIV, a tertiary system is rearranging to a primary. The situations which may occur are: (1) there is a slow equilibration, followed by fast reaction with nucleophile, and (2) there is a fast equilibration, followed by slow reaction with nucleophile. In case (1), second-order kinetics will not be observed, so that, if condition (a) is met, this situation may be discounted at once. In case (2), both rearranged and unrearranged substrate should react with nucleophile at the same rate. This latter test seems to have been employed quite infrequently; indeed, the present writer could find only one example (66).

The most frequently used procedure for determining whether or not prior rearrangement of substrate

has occurred, has been to interrupt the displacement reaction before completion (13), or react substrate with insufficient nucleophile (68), then, in either case, to isolate unreacted substrate and check for presence of rearranged substrate. This procedure will work provided that there is, indeed, a significant proportion of rearranged substrate present at equilibrium; this may not always be the case. The best way to check this point would be to subject the substrate to reaction conditions in the absence of the nucleophile. Again, this seems to have been done only rarely, as in the work of Stork (16); however, even here, reaction conditions were not duplicated exactly, as no salts were added to bring ionic strength to the actual reaction conditions.

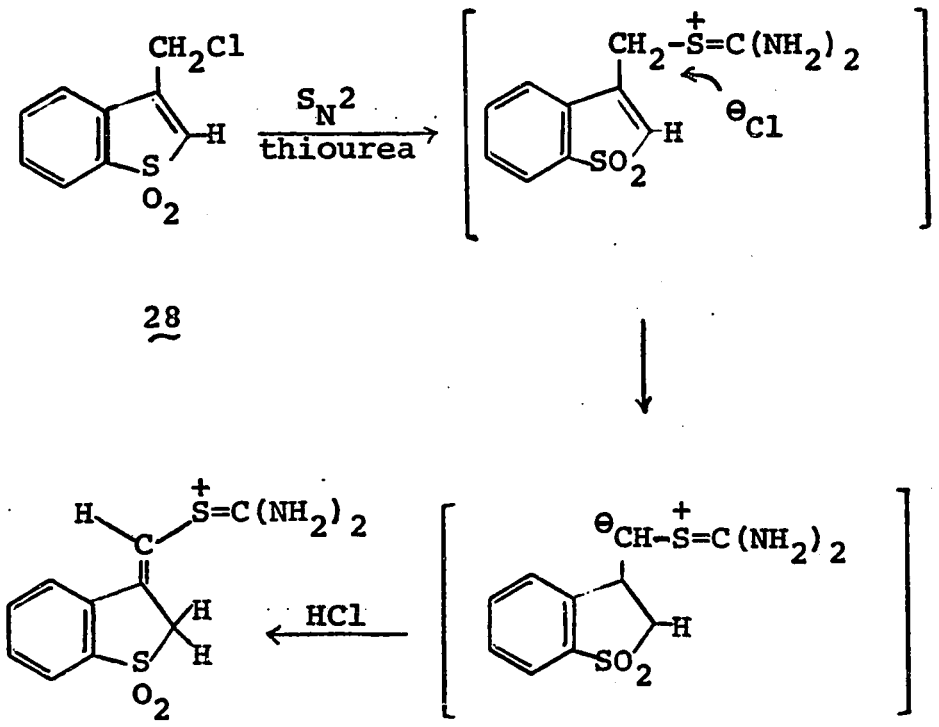
Bordwell's objections (12) to previous S_N2' assignments are, therefore, well taken, and his further arguments, which are outlined below, merit serious consideration.

Bordwell's primary system 28 could form the observed products by analogy with Scheme XIII, or by reacting by the S_N2 mechanism, followed by tautomerisation (see below for amplification of this statement). The secondary and tertiary systems 28a and 28b must, however, proceed by Scheme XIII, and the question of the intimate mechanism of the rearrangement step now arises.

Bordwell shows (12) that these systems solvolyse far too slowly to permit the S_Ni'-S_N2 pathway to occur; this is, of course, expected, because of the presence of the highly electron-withdrawing sulfone grouping, which must greatly inhibit carbonium ion formation. This means that a true S_N2' mechanism must be operative here.

Now, for the S_N2' process to occur, the nucleophile has to overcome a large energy barrier in approaching the π-bond. This barrier is very large, even for powerful bases (12); non-basic nucleophiles (thiourea, bromide ion) will, therefore, experience very great difficulty in initiating S_N2' reactions, even in Bordwell's system, in which the double bond is made more electrophilic than usual by the sulfone grouping. The case of negatively-charged nucleophiles, such as ethoxide, will be even worse.

The fact that the primary system 28 reacts with thiourea, thiophenoxide and other nucleophiles with which systems 28a and 28b do not react must mean, on the basis of what has been written above, that system 28 reacts by a different mechanism. This can only be by the S_N2 mechanism, followed by tautomerisation:



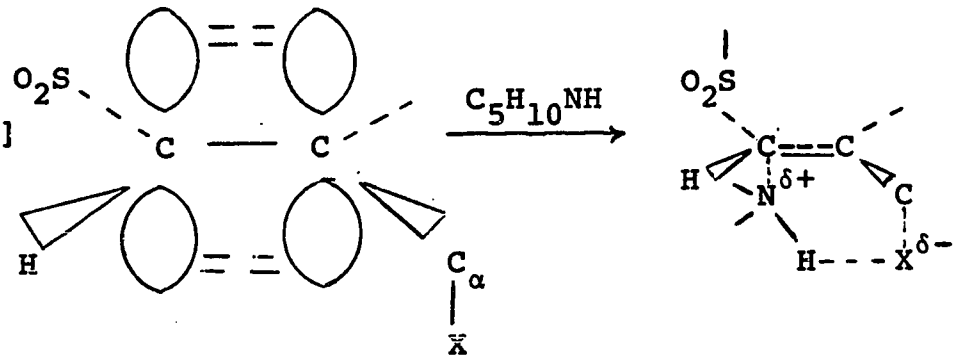
SCHEME XV

The view expressed above as the mode of reaction of 28 is contrary to Bordwell's own statement in ref. (12), but is, in the present writer's view, more in harmony with the observed facts. If 28 actually does react as in Scheme XV, Bordwell's views as to the structure of the S_N2' transition state and the synchronous nature of the reaction (69) must be discounted; in any case, these views were predicated on incorrect structural

assignments.

The successful S_N2' reactions of 28a and 28b with piperidine and morpholine must, then, be ascribed to some special property of these nucleophiles. This can only be their ability to assist reaction through hydrogen bonding, by delocalising the positive charge developing on the nitrogen atom.

[10]

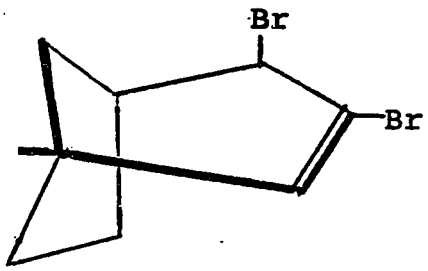


28a or 28b S_N2' transition state

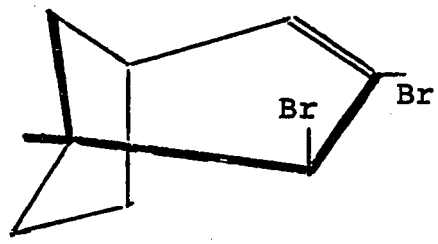
The present writer is in substantial agreement with the conclusions derived from this very important work by Bordwell, et al. (apart from the question of the mode of reaction adopted by the primary system 28), and also agrees that the earlier-assigned S_N2' reactions require reappraisal. The significance of Bordwell's work as regards the present research is dicussed a little

further ahead.

The work of Jefford, et al (19,20) is also of some relevance. As already briefly outlined in the Introduction to this Chapter, these workers have investigated the course of the reductive bromination of compounds 5a and 5b.

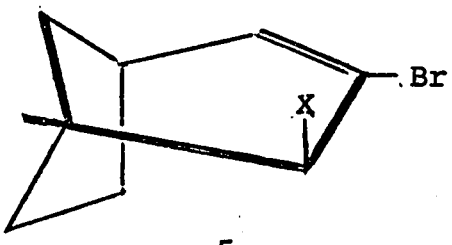


5a

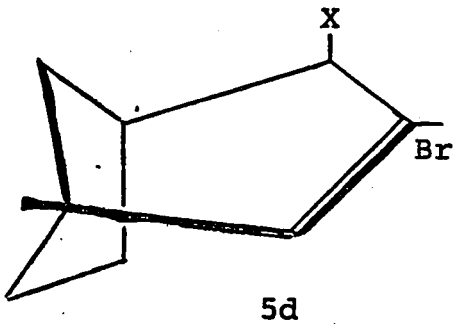


5b

These compounds 5a and 5b are synthesised by Jefford in a non-separable 80:20 mixture, the composition of which can be altered to 90:10 in refluxing o-dichlorobenzene. Both of these mixtures are reduced to the same mixture of products 5c and 5d, and always in the same ratio of 86:14, whether lithium aluminum hydride (X = H) or lithium aluminum deuteride (X = D) is used.



5c



5d

Moreover, the hydride (or deuteride) is introduced exclusively exo, as shown.

Jefford, et al also show that reactions of 5a and 5b under carbonium-ion-producing conditions produce quite different ratios of products; for example, treatment of either mixture of 5a and 5b with aqueous silver nitrate produces a 50:50 mixture of the exo-allylic alcohols (5c and 5d, X = OH).

Two different mechanisms could explain these reductive debromination results: either 5a reacts exclusively S_N2' on its exo-face to produce 5c and a minor, concurrent mechanism involves ionisation of both compounds and random attack on the carbonium ion to give 5c and 5d, or both 5a and 5b react S_N2'. The first of these alternatives is ruled out by Jefford (19) on the basis that $LiAlH_4$ and $LiAlD_4$ produce identical product proportions. The S_N2' component of the reaction should suffer a primary isotope effect, but not the S_N1' component; hence, different product proportions should be observed. The present writer accepts this argument.

Jefford then asserts that his results are best explained by prior equilibration of both the 80:20 and 90:10 5a:5b mixtures to 86:14, followed by exclusive S_N2' attack on the exo-face of both 5a and 5b. Since these compounds appear to be so constituted as to make

approach of hydride from the exo- or endo-side equally feasible, we would appear to have here a case of pure stereoelectronic control of the S_N2' reaction, lending support to the previously-asserted (3,15,16) cis-relationship of the entering and leaving groups. There are, however, some objections which one may raise.

Jefford himself states (19) that, during reduction, the metal hydride undoubtedly co-ordinates with the allylic bromine, and that it cannot be decided whether delivery of hydride occurs internally, from the co-ordinated metal hydride, or externally. If any degree of co-ordination does occur prior to hydride delivery, it would seem that the delivery would be constrained to come from the exo-side of the molecule, because that is where the co-ordinated complex is located.

The evidence as to the different product composition obtained from 5a and 5b under carbonium-ion-producing conditions does seem to rule out the intervention of free carbonium ions in the reductive debromination of 5a and 5b. However, the present writer feels a good case can be made for the intervention of ion-pair intermediates.

The postulated isomerisation of 5a to 5b (and vice-versa), which is required to account for production of the same product ratio from both starting mixtures,

most probably occurs through formation and recombination of ion-pair intermediates (ref. 5, p.721), although, since it is not shown whether or not the equilibration occurs in the absence of the hydride, catalysis on the surface of the hydride may be partly responsible. Some degree of electrophilic catalysis by lithium ion may also be occurring, as has been postulated (ref. 5, p.722) to account for the exchange isomerisation reaction between α- and λ-methylallyl bromide and radioactive lithium bromide (70).

Given the postulated ion-pair intermediates, it is only necessary to postulate further, that these intermediates will be trapped by the highly nucleophilic hydride ion before separation can occur, attack occurring at the less-shielded site on the positively-charged partner.

The stereospecificity of the reaction is adequately accounted for by a similar argument to that advanced by Jefford (19) to account for the corresponding stereospecificity of the hydrolysis reaction, namely, the preferential formation of a quasi-axial bond, due to better overlap with the p-orbitals of the double bond (ref. (19), p.2923).

Based on the above arguments, Jefford's work (19,20) cannot be accepted as unequivocal support for the

work of Stork (15,16).

Returning now to the present research, the question now arises as to why most, if not all, of the nucleophiles which were tested, failed to give the desired S_N2' reactions. The evidence of Bordwell, et al. (8-12), just discussed, indicates that piperidine is a favored nucleophile for the S_N2' reaction, yet it does not work here. Thiourea, thiophenoxide, etc. will work if the S_Ni'-S_N2 pathway is open to the substrate, but not if it is forced to adopt the S_N2' synchronous-displacement route. In our system, the S_Ni'-S_N2 pathway is certainly available, as solvolysis does occur (see Chapter 2), though possibly at a prohibitively slow rate in the non-aqueous, relatively non-polar solvents used in this segment of the work. Nevertheless, several powerful nucleophiles do not react in our system. Hence, another explanation must be sought, and the following is tentatively put forward:

The transition state of the S_N2' reaction (13) would require all five carbon atoms of our system 6 to become co-planar, or very nearly so. In order for this to occur, as the carbon atom bearing the leaving group is proceeding from sp^3 towards sp^2 hybridisation, the methine hydrogen will be moving, from an angle of approximately 60° to the C_α-C_β-C_λ plane, in an attempt to

be within this plane. During this movement, there will be severe steric interaction with the gem-dimethyl grouping, which is simultaneously being twisted in the opposite sense. The attainment of the required transition state may thus involve a rather high activation energy.

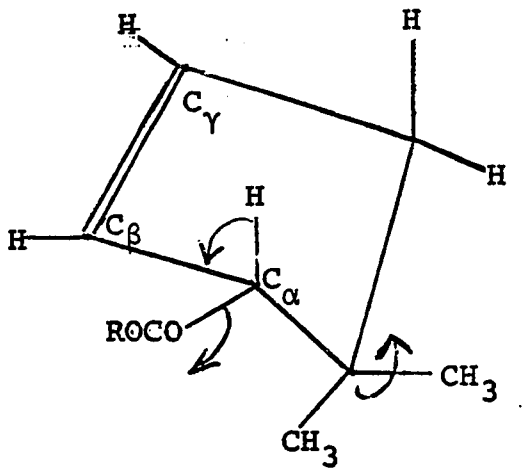
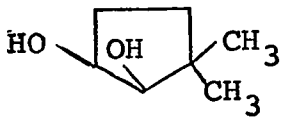


Figure 5

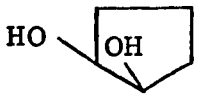
The 5,5-dimethylcyclopent-2-en-1-yl system proceeding towards a planar transition state

This effect will certainly be accentuated by two other factors, namely, steric hindrance to departure of the leaving group, and steric hindrance to the incoming nucleophile. In the first case, as the carbon bearing

the leaving group is becoming sp^2, the steric hindrance between the C-OCOR and the gem-C-CH_3 may well become considerable, particularly if bond-breaking has not proceeded very far at the transition state. That this interference may well be quite important is suggested by the results of Ford (71). He found that in cis-5,5-dimethylcyclopentan-1,2-diol (32) as opposed to the parent diol (33) ring puckering had to occur in order to relieve eclipsing between C_1-OH and C_5-CH_3.



32



33

This was shown by the tightening of the OH--OH hydrogen bond in 32, as seen in the infrared spectrum, and by the increased stability of the boric acid complex over that from 33.

Steric hindrance to departure of the leaving group will also be reflected in hindrance to solvation of this group. This will, of course, not be the case in solvents which solvate anions poorly, such as CCl_4.

The second factor, hindrance to entrance of the

nucleophile, by the leaving group and the gem-dimethyl grouping, will be of major importance only if bond-making has proceeded reasonably far at the transition state, but nevertheless will still play a part, even in cases where this is not so. Evidently, however, this factor will be of smaller importance, the less the steric size of the nucleophile, and, of those nucleophiles tried, cyanide and thiocyanate anions in dimethylformamide will have the smallest effective bulk. This is because (a) the anions will not be solvated in dimethylformamide (72) and (b) both of these ions are linear. This may explain why these ions possibly did succeed in effecting displacement.

It is evident that all of these factors, with exception of the one discussed in the last paragraph, will be operative in determining the rates of unimolecular solvolyses in our system 6, since the transition state for such solvolyses also requires complete flattening of the molecule (before a carbonium ion can be formed). Steric hindrance to entrance of the nucleophile (solvent) would also become of importance if the solvolysis should partake of any S_N2' character. Therefore, it became of interest to determine the rates and activation parameters of solvolyses in this system 6, and Chapter 2 of this thesis is concerned with those experiments.

Experimental

Melting-points and boiling-points are uncorrected. Refractive indices were measured on a Bausch and Lomb Abbe-3L Refractometer. Infrared spectra were recorded on Perkin-Elmer model 421 and model 337 spectrophotometers, and only characteristic absorption bands are cited. Nuclear magnetic resonance (n.m.r.) spectra were determined with Varian analytical spectrometers, models A-60, A-60A and HR-100, with tetramethylsilane (TMS) as internal standard. Gas-liquid chromatography (GLC) was carried out on a Perkin-Elmer Vapor Fractometer using their column P (diethylene glycol polysuccinate), or, in the work to be described in Chapter 2 of this thesis, on an Aerograph 202 gas chromatograph, using a column containing 20% SE-30 on Chromosorb W. All quantitative GLC analyses were made with suitable calibrated internal standards. Mass spectra were obtained on A.E.I. MS-2-H or MS-90 mass spectrometers.

2,2-Dimethylpent-4-enoic acid (7)

Two three-necked round-bottom flasks, one 1-litre and one 3-litre, were each fitted with a mechanical stirrer, a constant pressure dropping-funnel, a reflux condenser surmounted by a drying-tube, and a thermometer.

A suspension of sodium hydride (Metal Hydrides, Inc., 10 g 56.7% suspension, or 5.67 g, 0.26 mole as NaH) in diglyme, pre-purified by the procedure of Brown (73) (200 ml) was prepared in the 1-litre flask and cooled to 20°, with continuous stirring. Allyl alcohol, pre-dried over molecular sieves, (207 g, 3.6 moles) was added over a 20 min. period, the temperature being kept below 30°. When the solution of allyloxide anion was clear and red, and hydrogen evolution had ceased, the internal temperature was lowered to 10°, and tetramethylcyclobutanedione, 12 (250 g, 1.79 mole), was added in small portions down the condenser, at such a rate as to keep the internal temperature below 30°; the addition time was approximately 45 min.

The resultant solution was stirred 1 h., transferred to the dropping-funnel on the 3-litre flask, and added to a suspension of sodium hydride (160 g suspension, 90.7 g, 3.69 moles NaH) in diglyme (450 ml), stirred at 110°. Addition over a 1 h. period was at such a rate as to keep the internal temperature in the range 120-140° without external heating or cooling; a cooling bath was, however, at hand at all times, to moderate the reaction, if required. The mixture was finally heated to 140° for 1 hr., then permitted to cool to room temperature with continuous stirring.

Excess sodium hydride was destroyed by the cautious, dropwise addition of water; more water was added, the solution was extracted with ether (3 x 200 ml) and the aqueous layer was acidified by pouring onto a mixture of ice and concentrated hydrochloric acid (450 ml), stirring being continuous and the temperature being kept below 10°. The resultant oil was extracted into pentane (500 ml), the water layer extracted twice more with pentane (2 x 300 ml), and the combined pentane extracts shaken with ice-water (2 x 300 ml), then dried over anhydrous magnesium sulfate. The solvent was removed by atmospheric pressure distillation through a Vigreux column, and the residue was fractionally distilled under vacuum. Forerun amounting to 60 g was collected in the temperature range 30-104°/16.6 mm; the final fraction boiled at 104-109°/16.6 mm, and amounted to 299 g, 2.34 moles (65.4%). n_D^{28} = 1.4301. Reported: B.P. 104-108/ 20 mm (21); n_D^{25} = 1.4318 (74). The infrared spectrum (CCl_4) showed absorption bands at 3600-2400 (OH, S), 3080 (vinylic CH, S) and 1680 cm^{-1} (carbonyl, V.S.). The n.m.r. spectrum (CCl_4) showed peaks at τ -1.6 (s, carboxyl proton), 4.25 (m, vinylic CH), 4.90 (m vinylic CH_2), 7.70 (d, allylic CH_2) and 8.72 (s, methyl protons) in the ratio 1.01:2.00:2.02:6.00, required 1:2:2:6.

2,2-Dimethylpent-4-enoyl chloride (8)

A mixture of 7 (263 g, 2.1 moles) and thionyl chloride (530 g, 4.5 moles) was prepared in a 2-litre round-bottom flask equipped with a reflux condenser and a drying tube. After a short induction period, the reaction commenced, and was permitted to proceed for 5-6 h. without external heating, until evolution of hydrogen chloride had almost ceased. Refluxing the mixture 0.5 h. then completed the reaction. The excess thionyl chloride was then removed under moderate vacuum on the bath, and the product was distilled in vacuo. Yield 250 g, 1.71 mole (83%). B.P. 70-72.5°/50mm, n_D^{26} = 1.4403. Reported (74): B.P. 69°/50 mm, n_D^{25} = 1.3995. The reason for the discrepancy in refractive indices is not known.

The infrared spectrum (CCl_4) showed vinylic CH at 3080 cm^{-1} (M) and olefinic carbon-carbon stretch at 1640 cm^{-1}. The carbonyl region consisted of peaks at 1790 and 1770 cm^{-1}, both very strong, and overlapping into one broad band. This carbonyl doubling is ascribed to Fermi resonance (75), with the overtone of a very strong band at 885 cm^{-1}.

The n.m.r. spectrum (CCl_4) showed peaks at τ 4.15 (m, vinylic CH), 4.90 (m, vinylic CH_2), 7.58 (d, allylic

CH_2) and 8.68 (s, methyl protons), in the ratio 0.94:1.88: 1.88:6.00, required 1:2:2:6.

5,5-Dimethylcyclopent-2-en-1-one (9)

Anhydrous aluminum chloride (160 g, 1.20 mole) was slowly added, with stirring, to 250 ml nitromethane, in a 5-litre three-necked flask fitted with a stirrer, a reflux condenser, a constant-pressure dropping funnel, and a drying-tube. The resultant suspension was diluted with methylene chloride (900 ml) and heated to reflux. A solution of 8 (181 g, 1.23 mole) in methylene chloride (1100 ml) was added dropwise to the refluxing suspension over a period of 10 h., and the mixture was then refluxed a further 2 h.

The mixture was allowed to cool and was then hydrolysed by careful pouring into a stirred mixture of ice and concentrated HCl. The organic layer was set aside, the aqueous layer extracted with methylene chloride (2 x 400 ml) and the combined organic layers washed in succession, with saturated brine, saturated sodium bicarbonate solution and saturated brine (2 x 400 ml each), then dried over anhydrous magnesium sulfate. The bulk of the methylene chloride was removed by distillation at atmospheric pressure through a Vigreux column, and the remaining solution was subjected to distillation through

a Nestor-Faust annular teflon spinning-band column. Residual solvent was collected at 36° head temperature, nitromethane at 99-103°, and a small intermediate fraction at 103-145°/700 mm.

The major fraction, which was 99 + % pure 9, (GLC) distilled at a head temperature which was somewhat variable from run to run, according to the reflux ratio and the boil-up rate, but which generally was in the range 150-152°/700mm. Reported (28): 150-154°, pressure unspecified. Yield, 71 g, 0.65 mole (52%). The ultraviolet spectrum had λ_{max} at 219 mμ (log ε = 3.48, cyclohexane). n_D^{25} = 1.4550. The infrared and n.m.r. spectra were essentially identical to those reported by Shirahama (28).

3-Chloro-2,2-dimethylcyclopentanone, 16

After removal of 9 from the crude cyclisation product (see last paragraph), distillation was continued, and a fraction distilled over at 186-188°. Yield, 55 g. This material was seen by GLC to consist of 2 major and 2 minor components (see the Synthesis section of this Chapter). Storing in the freezing compartment of a refrigerator (at approximately -11°) for a period of 5-6 months produced a small crop of crystals. The supernatant liquid was decanted from the crystals and discarded; the

crystals were then melted and refrozen. The decantation, freezing and thawing process was repeated twice more, after which the remaining crystals were purified by vacuum distillation. B.P. 95-7°/30 mm; M.P. (Anschutz thermometer): 16.8-17.0°. Yield, 5 g. Analysis, calcd. for $C_7H_{11}OCl$: C 57.35; H 7.59. Found: C 57.41; H 7.80.

The n.m.r. spectrum (CCl_4) showed 5 lines (further split), centre τ 5.83 (methine proton); complex multiplet, τ 7.4-8.0 (methylene protons): two singlets, separation 1 Hz., τ 8.92 (methyl protons), ratio 0.96:3.82:6.00, required 1:4:6. The infrared spectrum showed absorption bands at 1745 (carbonyl, V.S) and 1365 and 1385 cm^{-1} (gem-dimethyl, M). These spectra are fully consistent with the assigned structure (see the Synthesis section of this Chapter).

Attempted dehydrochlorination of 16

(1) A 5.5 g sample of crude high-boiling cyclisation product, containing approximately 65% of 16 (by relative peak areas) was refluxed 20 h. in dimethylaniline (20 ml, 3.5 equivalents). Direct inspection by GLC showed no change in the proportion of 16.

(2) A 6 g sample of crude high-boiling cyclisation product was refluxed 24 h. in a solution of potassium metal (5 g, 0.12 mole) in t-butyl alcohol (50 ml), after

which the solution was acidified and extracted into ether. After drying over anhydrous magnesium sulfate, inspection of the ether extract by GLC showed complete disappearance of 16, but no appearance of 5,5-dimethylcyclopent-2-en-1-one, 9. Instead, a previously minor peak was now of major importance.

Attempted displacement of chloride from 16

(1) A mixture of crude high-boiling cyclisation product (1.1 g, containing 61% of 16 by GLC) and silver acetate (2.04 g, 0.12 mole) was refluxed in 98% ethanol (7 ml) for 24 h. on a steam-bath. After cooling, the supernatant liquid was inspected by GLC, and no change in the proportion of 16 was seen. The mixture was filtered and distilled; at 68°/35 mm, 0.429 g of material was recovered, the n.m.r. and infrared spectra of which were virtually completely superimposable on those of 16.

(2) A mixture of high-boiling cyclisation product (4.5 g) silver benzoate (9 g, 0.04 mole) and benzoic acid (35 g) was refluxed at 237-241° for 8.5 h. After cooling overnight under a drying tube, the contents were permitted to react with saturated sodium bicarbonate solution. After the aqueous solution was definitely alkaline, the entire bulk was stirred with ether for some time; the solid was then filtered off, thoroughly

washed with saturated sodium bicarbonate and triturated with ether.

The total filtrate was transferred to a separatory funnel, the ether layer removed, and the water layer extracted several times with ether. The combined ether layers were then washed with saturated brine and dried over magnesium sulfate; the solvent was then carefully removed by distillation through a Vigreux column. Inspection of the residue by GLC gave the following results. (Yields are calculated from relative peak areas): the proportion of 16 had dropped from 74.8% to 24.1%; 5,5-dimethylcyclopent-2-en-1-one, 9, was now present to the extent of 24.7%; a new peak, eluting much later, was present to the extent of 33.1%. The proportion of the minor ketonic component of the high-boiling cyclisation product remained unchanged at 18%.

5,5-Dimethylcyclopent-2-en-1-ol (6, X = OH)

A suspension of lithium aluminum hydride (5.28 g, 0.14 mole) in anhydrous diethyl ether (500 ml) was prepared in a 2-litre three-necked flask, fitted with a constant-pressure dropping-funnel, mechanical stirrer, reflux condenser and drying tube. The suspension was stirred and cooled to 0°, and anhydrous aluminum chloride

(6.00 g, 0.05 mole) was cautiously added in small portions, and with continuous stirring, the reaction being permitted to moderate after each addition. Total addition time was approximately 15 min.

The mixture was then allowed to warm to room temperature, and a solution of 8 (27.7 g, 0.25 mole) in anhydrous ether (500 ml) was added over 1 h., with external cooling as required. The resultant mixture was permitted to stir overnight at room temperature and was hydrolysed by the cautious, dropwise addition of saturated ammonium chloride solution, with continuous stirring and cooling, until the salts had coagulated.

The supernatant solution was decanted through a Buchner funnel, under suction, and the coagulated salts were thoroughly washed by trituration and decantation with ether. The combined ether solution was dried over sodium sulfate, the solvent was largely removed by distillation at atmospheric pressure through a Vigreux column and the remainder was subjected to fractional distillation in vacuo. B.P. 65.5-66.5°/20 mm. Yield, 23 g, (0.21 mole, 82%), n_D^{25} = 1.4598. The infrared spectrum (CCl_4) showed bands at 3590 (M, free OH), 3340 (broad, M, bonded OH), 3040 (M, olefinic carbon-hydrogen stretch) and 1610 cm^{-1} (W, olefinic carbon-carbon stretch). The n.m.r. spectrum (CCl_4) showed peaks at τ4.30 (m,

olefinic protons), 5.95 (s, methine proton), 6.90 (s, hydroxyl proton), 7.88 (m, methylene protons), and 8.95 (two singlets, methyl protons), in the ratio 1.96:0.98: 0.98:2.00:6.00, required 2:1:1:2:6. A satisfactory elemental analysis could not be obtained; however, based on the spectra, the method of synthesis, and the results with the esters (see below) the structure of this compound appears secure.

2,2-Dimethylcyclopentanone (14)

A solution of 9 (3.0 g, 0.027 mole) in purified tetrahydrofuran (35 ml) was added dropwise to a stirred solution of lithium tri-t-butoxyaluminum hydride (76) (13.8 g, 0.055 mole) in tetrahydrofuran (45 ml) at -78°, contained in a 250 ml three-necked flask fitted with a mechanical stirrer, constant-pressure dropping-funnel, and cold-temperature thermometer. Addition time was approximately 1 h., and the solution was then stirred 2 h. at -78° and 16 h. while warming to room temperature. The excess hydride was then decomposed, and the complex hydrolysed, by the slow addition, with stirring and cooling, of a solution of Rochelle salt (sodium potassium tartrate, 234 ml of a solution of 150 g Rochelle salt in 300 ml water).

Two layers slowly separated; the upper layer was extracted into pentane. A quantitative yield estimate by GLC at this point gave a result of 77%; only one peak other than solvent could be seen. The solution was then dried, the solvent removed and the residue distilled in vacuo. The product had B.P. 65°/70 mm, $n_D^{25} = 1.4306$. Reported (57): B.P. 140-143° (745 mm); $n_D^{22.5} = 1.4312$. Yield 2.0 g, 0.018 mole (66%). The n.m.r. spectrum disclosed that the product was pure 14: τ 7.7-8.3 (m, methylene protons) and 9.0 (s, methyl protons), ratio 5.90:6.00, required 6:6. The infrared spectrum showed carbonyl stretch at 1740 cm^{-1} (V.S.) and the gem-dimethyl doublet at 1360 and 1380 cm^{-1} (S).

2,2-Dimethylcyclopentanol (21)

A solution of sodium borohydride (2.32 g, 0.061 mole) in isopropyl alcohol (40 ml) was prepared in a 250 ml. three-necked flask fitted with a mechanical stirrer, constant-pressure dropping funnel, and reflux condenser surmounted by a drying tube. To this solution was added a solution of 9 (3.2 g, 0.029 mole) in isopropyl alcohol (30 ml) at the reflux point, over a 40 min. period. The mixture was refluxed a further 4 h., cooled, water (125 ml) added, heated back to reflux and kept there 8 h. The product was extracted into pentane,

(2 x 100 ml) the pentane layer washed twice with ice-water (2 x 50 ml) and dried over magnesium sulfate. Inspection by GLC (with ethylbenzene as an internal standard) indicated a yield of 86% of a single product. Removal of the solvent followed by distillation gave 2.65 g, 0.023 mole (80%) of a product which boiled at 70°/27 mm. n_D^{25} 1.4518. M.P. of p-nitrobenzoate 91-92°. Reported (51): B.P. 151-2°, n_D^{20} 1.4532, M.P. of p-nitrobenzoate 90°. The identity of this product as 21 is confirmed by the spectra: the n.m.r. spectrum showed peaks at τ6.35 (m, hydroxyl plus methine protons), τ 8.1-8.7 (m, methylenes) and τ 9.1 (s, methyls) in the ratio 1.86:5.89:6.00, required 2:6:6. The i.r. spectrum (CCl_4) shows bands at 3400 (broad, OH), 2960 and 2880 (aliphatic CH stretch) and 1365 and 1385 cm^{-1} (gem-dimethyl).

Attempted preparation of 5,5-dimethylcyclopent-2-en-1-yl phenyl-methanesulfonate (6, X = $OSO_2CH_2C_6H_5$)

A mixture of 6, X = OH (0.12 g, 0.00103 mole) and phenylmethanesulfonyl chloride (0.20 g, 0.00103 mole) in carbon tetrachloride (3 ml) was added in 3 portions to a solution of triethylamine (0.11 g, 0.00107 mole) in carbon tetrachloride (2 ml) at -25 to -30°C. The mixture, in a 10 ml round bottom flask, was shaken several times

and stored at -20° overnight. N.m.r. spectra at 100 mHz were then taken at -30°, and as the mixture warmed to 25°, the peaks seen were: a sharp singlet at τ 2.65, superimposed on a multiplet, τ 2.60-2.75; a sharp singlet at τ3.90 (increasing with time and temperature); a complex multiplet at τ 4.20-4.40; a six-line multiplet at τ 5.05-5.20; a quartet, further split, at τ5.40-5.65; two perturbed singlets at τ 5.80-5.90; and a very complex methylene-methyl region, including a peak at τ 8.82 which increased with time and temperature, over the range τ 7.68-9.05. Integration over these regions was 19:17.5:34:7:6.5:5.5:217.

Interpretation of these results is discussed in the Synthesis section of this Chapter.

5,5-Dimethylcyclopent-2-en-1-yl p-nitrobenzoate (6, X = $OCOC_6H_4(4\text{-}NO_2)$)

A solution of 6 (X = OH) (27.9 g, 0.25 mole) in dry pyridine (350 ml), contained in a 1 litre three-necked flask fitted with a drying tube and a thermometer, was magnetically stirred and cooled to -5° in an ice-salt bath. Recrystallised p-nitrobenzoyl chloride (46.8 g, 0.25 mole) was added, in small portions, over 15 min., the temperature being kept in the range -5 to 0°C. The cooling bath was removed, stirring was allowed to continue

while the mixture warmed spontaneously for 1 h., then for a further 3 h. at room temperature. The mixture was then poured into ice water (200 ml), stirred well and filtered. The solid was washed well by trituration with ice-water and dissolved in ether (500 ml); the ether solution was then washed twice with ice-water (200 ml each time) dried over anhydrous sodium sulfate and the solvent removed in a rotary evaporator.

The residual solid was recrystallised several times from n-pentane at -11°. Yield, 37.5 g (0.14 mole, 58%). The analytical sample melted at 66.3-67°. Analysis for $C_{14}H_{15}NO_4$: C 64.36; H 5.79; N 5.36. Found, C 64.13; H 5.74; N 5.36. The infrared spectrum (CCl_4) showed bands at 3060 (M, olefinic carbon-hydrogen stretch) and 1732 cm^{-1} (V.S., ester carbonyl). The n.m.r. spectrum (CCl_4, see Figure 2) showed peaks at τ1.80 (s, phenyl protons), 3.77-4.0 and 4.1-4.33 (m, olefinic protons), 4.50 (m, methine proton), 7.67 (m, methylene protons) and 8.85 (two singlets, separation 4.7 Hz methyl protons), in the ratio 3.95:1.89:1.00:2.00:6.00, required 4:2:1:2:6.

5,5-Dimethylcyclopent-2-en-1-yl 3',5'-dinitrobenzoate (6, X = $OCOC_6H_3$(3,5-di-NO_2))

A solution of triethylamine (4.0 g, 0.04 mole) in carbon tetrachloride (200 ml) was prepared in a 1 litre

three-necked flask fitted with a reflux condenser, drying tube and constant-pressure dropping funnel. This solution was magnetically stirred, and to it was rapidly added a suspension of 3,5-dinitrobenzoyl chloride (7.7 g, 0.034 mole) in a mixture of 6 (X = OH) (3.75 g, 0.034 mole) and carbon tetrachloride (125 ml). Addition occupied approximately 10 min., and no attempt was made to control the temperature. Stirring was allowed to continue overnight.

The mixture was filtered under suction, the solid was washed well with carbon tetrachloride, and the combined organic solution was concentrated in a rotary evaporator. The resultant red oil crystallised on addition of pentane; the crystals were then filtered under suction and dissolved in pentane. The pentane solution was then cooled to -11° and the resultant crystals filtered, washed and again recrystallised from pentane at -11°. The solvent was then removed from the crystals by allowing them to stand overnight in a vacuum desiccator over paraffin wax.

Yield, 3.65 g (0.012 mole, 36%). M.P. 71-72°. Analysis, calcd. for $C_{14}H_{14}N_2O_6$: C 54.90; H 4.61; N 9.15. Found: C 54.87, H 4.57, N 9.25. The infrared spectrum (CCl_4) exhibited bands at 3070 (M, olefinic C-H stretch), and 1730 cm^{-1} (V.S., ester carbonyl). The n.m.r. spectrum (CCl_4) showed peaks at τ 0.92 (m, phenyl protons), 3.7-4.0

and 4.0-4.35 (m, olefinic protons), 4.48 (m, methine proton), 7.60 (m, methylene protons) and 8.78 (two singlets separation 3 Hz, methyl protons) in the ratio 3.00:2.20: 0.92:2.00:6.00, required 3:2:1:2:6.

5,5-Dimethylcyclopent-2-en-1-yl 2',6'-dichlorobenzoate (6, X = $OCOC_6H_3$(2,6-di-Cl))

Tetrahydrofuran was purified by allowing it to stand 2-3 days over solid potassium hydroxide, then distilling from lithium aluminum hydride. 2,6-Dichlorobenzoyl chloride was synthesised by the method of Stork (16), with the single modification that, owing to inability to control the oxidation of 2,6-dichlorobenzaldehyde by potassium permanganate if Stork's conditions were followed, this oxidation was carried out under high-speed stirring in a Morton (creased) flask. Under these conditions it was found that permanganate could be added quite rapidly to the suspension of the aldehyde in water.

A 250 ml three-necked flask was fitted with a reflux condenser surmounted by a delivery tube for gas collection, a mechanical stirrer, a constant-pressure dropping funnel and a thermometer. A suspension of sodium hydride (8.5 g of 56.7% suspension or 4.8 g, 0.2 mole NaH) in tetrahydrofuran (100 ml) was prepared in

this flask, stirred and brought to the reflux point. A solution of 6 (X = OH) (4.36 g, 0.039 mole) in tetrahydrofuran (10 ml) was added to this suspension at such a rate as to maintain gentle reflux. The hydrogen collected amounted to a yield of 89%.

A drying-tube was fitted in place of the gas delivery-tube, the mixture was cooled to -11°, and a solution of 2,6-dichlorobenzoyl chloride (16) (8.15 g, 0.039 mole) in tetrahydrofuran (30 ml) was added over 25 min., the temperature being kept below -8°. Stirring was allowed to continue overnight, with no attempt to keep the temperature low. The mixture was filtered, the precipitated sodium chloride washed well by trituration with tetrahydrofuran, and the red filtrate (plus washings) was dried over anhydrous sodium sulfate and the solvent distilled under water-pump vacuum.

The oily residue readily crystallised on addition of n-hexane. More hexane was added, and the suspension was thoroughly shaken and refiltered. The solid obtained in this way was, apparently, the hitherto-unreported 2,6-dichlorobenzoic anhydride, as could be seen from the spectra: the n.m.r. spectrum (CCl_4) disclosed only aromatic protons, and the infrared spectrum (CCl_4) showed two strong peaks at 1820 and 1760 cm^{-1}, diagnostic of an acid anhydride (58). Yield, 1.36 g,

0.0037 mole (19.5%) M.P. 154-155° (dec.), after three recrystallisations from n-hexane.

The desired ester was recovered from the hexane filtrate (above) by evaporation, and recrystallised at low temperatures from more n-hexane. Yield 7.90 g, 0.027 mole (71%). M.P. 56-57°. The infrared spectrum (CCl_4) showed peaks at 3060 (W, olefinic carbon-hydrogen) and 1735 cm^{-1} (ester carbonyl, V.S.). The n.m.r. spectrum (CCl_4) showed peaks at τ2.63 (s, phenyl) 3.55-3.96 and 3.96-4.25 (m, olefinic protons), 4.32 (m, methine proton), 7.75 (m, methylene protons) and 8.81 (two singlets, methyl protons, in the ratio 3.12:1.92:0.96:1.92:6.00, required 3:2:1:2:6. Analysis, calcd. for $C_{14}H_{14}O_2Cl_2$: C 58.97; H 4.95; Cl 24.86. Found: C 59.86; H 5.18; Cl 24.57. The reason for the poor analysis is not known; however, the structure of this ester is considered to be secure, based on the method of synthesis, and on the spectra.

4,4-Dimethylpent-1-en-3-ol, 22

Vinyl magnesium chloride was prepared as follows (53): a 2 litre three-necked flask was fitted with a mechanical stirrer, a thermometer, an acetone-dry ice condenser and a constant-pressure dropping funnel. A solution of vinyl chloride (58 g, 0.93 mole) (gas pre-scrubbed with sodium hydroxide solution) in THF (200 g) was

prepared, and a small amount of it was added, from the dropping funnel, to magnesium turnings (30 g, 1.29 mole), slightly wetted with 1,2-dibromoethane, in the three-necked flask. A vigorous reaction soon set in. After a short time, sufficient tetrahydrofuran was added to permit easy stirring, the mixture was heated to 43°, and the remainder of the vinyl chloride solution was added dropwise for over 1 h., during which time the temperature slowly rose to 47°. After addition was over, the temperature was raised to 60°, by continued careful heating, over a 1.5 h. period.

The mixture was kept at 60° for 15 min., then cooled to -10°. A solution of pivalaldehyde (52) (75 g, 0.87 mole) in tetrahydrofuran (150 ml) was added over 1.5 h., keeping the temperature near -10°. After addition was over, stirring at -10° was continued for a further 15 min., then the mixture was heated to 45° for 15 min., cooled, and quenched by pouring onto ice-cold saturated ammonium chloride solution. The aqueous mixture was extracted with pentane (2 x 200 ml) the organic layer was washed with water (2 x 250 ml) and saturated brine (250 ml), then dried over anhydrous potassium carbonate. The solvent was stripped by distillation at atmospheric pressure through a spinning-band column, then by raising the temperature slowly, residual

tetrahydrofuran was removed next.

At 107-108° (head temperature) it was noted that a solid was crystallising in the condenser. This was removed, by temporarily shutting down the cold water, and was found to melt at 50.5-51.5°. It was easily shown to be 2,2-dimethylpropan-1-ol (neopentyl alcohol), from the following spectral evidence: the infrared spectrum showed peaks at 3600 (free OH, S), 3350 (broad, bonded OH, V.S.), 1360 (V.S.) and 1390 cm^{-1} (M) (gem-dimethyl), while carbonyl and olefinic carbon-carbon stretch were completely absent. The n.m.r. spectrum (CCl_4) showed peaks at τ 6.07 (broad s, disappearing on D_2O exchange, hydroxyl proton), 6.8 (s, methylene protons) and 9.1 (s, t-butyl protons) in the ratio 1.00:2.00:9.00, as required. The yield of this by-product was 3.7 g, 0.042 mole (4.5%).

The desired alcohol distilled at a B.P. of 128-129°/700 mm. n_D^{25} = 1.4286. Reported (63): B.P. 131°/760 mm, n_D^{25} = 1.4282. Yield 15.5 g (0.14 mole, 16%). A considerable amount of residue was left.

The infrared spectrum of this alcohol showed peaks at 3605 (free OH, M), 3470 (broad, bonded OH, M), 3080 (olefinic carbon-hydrogen stretch, M) and 1390 and 1360 cm^{-1} (gem-dimethyl, S). The n.m.r. spectrum (CCl_4) showed peaks at τ 3.9-5.1 (m, vinyl protons), 6.38 (d,

methine, proton), 7.40 (s, hydroxyl proton) and 9.12 (s, t-butyl protons), in the ratio 3.17:1.00:1.00:8.58, required 3:1:1:9.

4,4-Dimethylpent-1-en-3-yl phenylmethanesulfonate 26

The synthesis of phenylmethanesulfonyl chloride, by chlorination of S-benzylisothiouronium chloride, was, in this work, found to be not, by any means, as clean as claimed (54, 55). Yields were approximately 30%, as against reported (55) yields of 81% and, contrary to the previous work (54, 55), considerable amounts (as much as 30%) of material insoluble in hot chloroform were obtained. This material was not examined.

A suspension of 22 (0.224 g, 0.002 mole) and phenylmethanesulfonyl chloride (0.374 g, 0.002 mole) in carbon tetrachloride (10 ml) was prepared in a 25 ml round bottom three-necked flask fitted with a magnetic stirrer, a constant-pressure dropping-funnel and a drying-tube. This suspension was stirred at room temperature, and a solution of triethylamine (0.414 g, 0.004 mole) in carbon tetrachloride (5 ml) was added dropwise over approximately 10 min. Stirring was continued 1 h., then the mixture was filtered through a Buchner funnel under suction. (In this, and in all subsequent operations, all apparatus was rinsed with isopropylamine just before

use). The precipitated triethylamine hydrochloride was washed by trituration with CCl_4, and the organic solution was concentrated in a rotary evaporator.

The residual red oil solidified when cooled to -11°, then remained solid at room temperature. This solid was dissolved in a little n-pentane; addition of more pentane deposited a very dark oil, which was rejected. The supernatant pentane solution was cooled to -11° and the resultant white crystals were isolated by filtration at -5° under a blanket of dry nitrogen. After four crystallisations from pentane, using the same procedure, the yield of slightly yellow needles was 0.223 g (0.00082 mole, 42%). M.P. 38.5-39.5°. This compound was found to be very unstable, decomposing within 10 min. at room temperature; it could, however, be kept at least 1 year at -11° in a sealed vial.

Analysis, calcd. for $C_{14}H_{20}O_3S$: C 62.66; H 7.51. Found C 62.13, H 7.41. The analytical sample was kept at -11° until just before analysis, but still decomposed before duplicates could be run. An infrared spectrum was not obtained; the n.m.r. spectrum showed peaks at τ 2.59 (s, phenyl protons), 3.95-4.85 (m, vinyl protons), 5.30 (d, methine proton), 5.77 (s, benzyl protons) and 9.10 (s, t-butyl protons), in the ratio 5.02: 3.04:1.00:2.12:9.13, required 5:3:1:2:9.

Tetrabutylammonium acetate (TBA)

The hydrate of TBA was prepared according to McMullan and Jeffrey (62). M.P. 14.7-14.9°. Reported M.P. (62): 15.1°.

A solution of TBA-hydrate (164 g) in 98% ethanol (total volume approximately 350 ml) was allowed to stand 7 days over Linde Molecular Sieves #3A (approximately 200 g). The solvent was stripped in a rotary evaporator, first using a water-pump and then a vacuum pump, and evaporation was permitted to continue overnight at 45° and 7 mm. The resultant dark, viscous oil readily crystallised on cooling, with the evolution of much heat.

A portion of this solid was transferred, under nitrogen, to a melting-point tube, the other end of which was then sealed. M.P. 45-48°. A rough Karl Fisher titration indicated a maximum water content of 0.5%; integration of the n.m.r. spectrum, which in CCl_4 solution, showed the water peak at τ 3.1, gave a water content of 3%, which the writer considers more reliable. This corresponds quite well to a composition of TBA.1/2 H_2O - the "semi-hydrate" referred to in the Synthesis section of this Chapter.

No further water could be removed by repetition of the above process. The following was, however, fairly successful:

A solution of TBA-semihydrate in carbon tetrachloride was allowed to stand 7 days over Linde Molecular Sieves #4A, then treated as above, except that the final pumping-out was done at the temperature of a hot water-bath. The resultant solid was extraordinarily hygroscopic so all subsequent operations were done under nitrogen. M.P. 70-72°. Karl Fisher titration again showed 0.5% water. Integration of the n.m.r. spectrum (which showed the water peak at τ 2.1) gave a water content corresponding to the composition $10TBA \cdot H_2O$ - the "decihydrate" referred to in the Synthesis section. This compound is referred to below simply as "tetrabutylammonium acetate (TBA)".

Reaction of 4,4,-dimethylpent-1-en-3-yl phenylmethanesulfonate, 26, with tetrabutylammonium acetate (TBA)

A solution of 26 (0.205 g, 0.00077 mole) in carbon tetrachloride (2 ml) was prepared by removing the previously weighed vial containing 26 from the refrigerator, permitting it to warm to room temperature, opening it and rapidly adding the solvent. This solution was cooled to 0° and added to a solution of TBA (0.265 g, 0.00088 mole) in CCl_4 (2 ml), over a period of 5 min., with magnetic stirring. After 10 min. at 0°, a portion of the solution was removed and placed in a pre-cooled n.m.r. tube; a spectrum was taken as rapidly as possible.

A second spectrum was run after the tube had remained overnight at room temperature, and a third, after the tube had been heated 5 h., at 40-45°. The following changes in the n.m.r. of the mixture took place during this period: the doublet ascribed to the methine proton in 26, at τ 5.3 (J = 8 Hz), progressively diminished in intensity, while a new doublet appeared at τ 5.6 (J = 5.5 Hz). This new doublet is almost certainly ascribable to the methylene protons of the expected product, $CH_3COO-CH_2-CH=CH-C(CH_3)_3$. As well as this, a new peak at τ 8.0 gradually replaced the original tetrabutylammonium acetate peak at τ 8.35, the new peak being assigned to the acetate grouping in the product. Other peaks in the spectrum were less definite. This was, however, considered as encouraging evidence for the occurrence of the desired S_N2' reaction in this system.

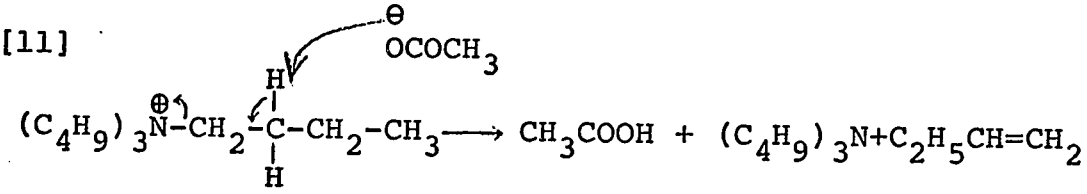
Reaction of TBA with 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate (6, X = $OCOC_6H_4(4-NO_2)$)

(1) A mixture of TBA (0.265 g, 0.00077 mole) and 6, X = $OCOC_6H_4$ $(4-NO_2)$ (0.175 g, 0.00067 mole) in carbon tetrachloride (3 ml) was magnetically stirred in a stoppered vial for 23 h. at room temperature, then an n.m.r. spectrum was run. Others were run after the solution was refluxed (for 1.5 h., and then overnight),

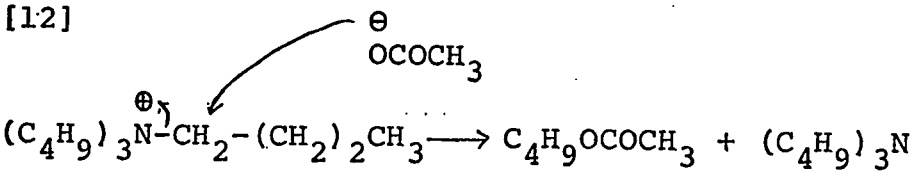
and again after extraction of the organic layer with water, followed by drying over sodium sulfate.

The final spectrum disclosed no peaks which could not be attributed to the starting ester, other than a very minor peak at τ 8.05. This peak, in the spectra of the mixture at the various stages of treatment, was seen to gradually increase at the expense of the τ 8.35 peak of TBA, together with the appearance of intense, broad absorption at approximately τ 8.5, and of additional complexities in the methyl region. The τ 8.05 can be attributed, either to acetic acid, arising from β-elimination [11], or to n-butyl acetate, arising from de-alkylation [12]:

[11]



[12]



No distinction between these alternate mechanisms was made.

(2) A mixture of TBA (0.41 g, 0.00012 mole) and 6, X = $OCOC_6H_4$-(4-NO_2) (0.31 g, 0.0011 mole) in chlorobenzene (3 ml) was refluxed 3 h., then a portion submitted for a n.m.r. analysis. The solution was allowed to cool overnight, then thoroughly extracted with water; the organic layer was then dried and a second sample inspected by n.m.r. spectroscopy.

Once again, the spectra obtained are compatible with no reaction having occurred, other than (in this case, virtually complete) destruction of the TBA. The occurrence of a triplet at τ6.0 would seem to tend to confirm the presence of n-butyl acetate, this peak being attributable to the methylene protons adjacent to the acetate grouping.

Reaction of TBA with 5,5-dimethylcyclopent-2-en-1-yl 3',5'-dinitrobenzoate

Refluxing of samples of the 3,5-dinitrobenzoate of 6 with excess TBA in carbon tetrachloride and in chlorobenzene for periods of 20 h., followed by extraction with water, yielded solutions the n.m.r. spectra of which disclosed results essentially identical to those discussed above - i.e., no displacement of the dinitro-

benzoate moiety occurred, but the TBA was decomposed.

Reaction of TBA with 5,5-dimethylcyclopent-2-en-1-yl 2',6'-dichlorobenzoate

Exactly similar results to the above were obtained when a sample of the 2,6-dichlorobenzoate of 6 was heated 24 h. at 90° in a sealed n.m.r. tube with a solution of excess TBA in carbon tetrachloride.

Reaction of thiourea with esters of system 6

(1) A mixture of thiourea (0.049 g, 0.00064 mole) and the 3,5-dinitrobenzoate of 6 (0.154 g, 0.000503 mole) in acetone (3 ml) was refluxed 20 h. Evaporation of the solvent gave a recovery of 86% of material, the n.m.r. spectrum of which, in acetone-d_6, was completely compatible with a mixture of the two starting materials, and could be exactly reproduced by superimposing the two starting spectra.

(2) The same result was obtained when either the p-nitrobenzoate or the dichlorobenzoate of 6 was used, under identical conditions.

(3) When a sample of the dinitrobenzoate was refluxed in diglyme with excess thiourea for 1 h., the solution cooled, diluted with water, extracted into ether and the solvent evaporated, the n.m.r. of the

product disclosed again mostly starting materials. In this case, the development of small traces of extra peaks, such as low-field olefinic resonance, could not be reconciled with the expected rearranged isothiouronium salt, and can probably be ascribed to decomposition.

(4) A mixture of the dichlorobenzoate of 6 (1.04 g, .0037 mole) and thiourea (0.65 g, 0.0086 mole) was heated at 100° for 40 h. in purified dimethylformamide (DMF) (25 ml). On cooling and addition of ether, (50 ml), no precipitation occurred, so that this solution was extracted with water (3 x 50 ml) and the water layer back-extracted once with ether (50 ml). The combined organic solution was dried over anhydrous sodium sulfate and the solvent removed. There remained a yellow liquid, which, on examination by n.m.r., contained ether, DMF, a little thiourea, and starting dichlorobenzoate. The latter, by direct integration, was present in 50% yield. A small amount of solid which had been deposited on evaporation of the ether was thiourea, as disclosed by n.m.r. spectroscopy.

The extracts (above) were evaporated at room temperature to a yellow oil. Addition of carbon tetrachloride precipitated more thiourea. The carbon tetrachloride solution was seen to contain a preponderance of starting material by n.m.r. inspection. The

conclusion is that reaction with thiourea under these conditions is exceedingly slow, if it occurs at all.

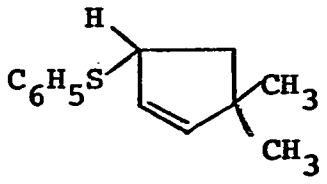
Reaction of thiophenoxide ion with esters of system 6

(1) A mixture of the 3,5-dinitrobenzoate of 6 (0.917 g, 0.00299 mole) and thiophenol (0.39 g, 0.0036 mole) in dimethylformamide (50 ml) was added to a suspension of sodium hydride (0.085 g, 0.0036 mole as NaH) in DMF (20 ml) stirred at 110°, in a 250 ml three-necked flask fitted with a mechanical stirrer, reflux, condenser and thermometer. After 2.5 h. at 100-110°, the mixture was cooled, poured into ice-water and extracted with pentane (3 x 125 ml). The extracts were dried over Na_2SO_4 and the solvent removed. The residue amounted to 1.035 g (approximately 80% recovery). The n.m.r. spectrum showed, besides residual DMF, a vast preponderance of methyl absorption (8.8, s and 9.1, m), with comparatively insignificant amounts of phenyl olefin or methylene protons.

(2) Samples of both the p-nitrobenzoate and the 3,5-dinitrobenzoate of 6 were heated 3.5 h. at 105-110° with a 20% excess of potassium thiophenoxide in DMF, the KSC_6H_5 having been separately prepared by the reaction between KOH and thiophenol in methanol solution, followed by evaporation of the solvent and excess

thiophenol.

The 3,5-dinitrobenzoate had apparently reacted to a greater extent, since the reaction mixture became much darker and there was solid present, which was not the case for the p-nitrobenzoate. Inspection of the total reaction solutions by n.m.r. showed that the olefin-methine region of the ester was in the process of collapsing to a sharp singlet (τ 4.2) superimposed on broad absorption, the methyl peaks were being replaced by singlets displaced upfield by approximately τ 0.2 to τ 9.0 and the phenyl peaks were in the process of being replaced by considerably more complex absorption displaced upfield by as much as τ 1.6 to τ 2.5. These are changes which could perhaps be reconciled with the expected product



except that (a) the phenyl region integrates to far too much vs. the olefin-methine region and (b) the total methyl region integrates to almost as great an excess over the olefin-methyl region (2.58:1, not 2:1).

These results are, in toto, incompatible with the expected S_N2' reaction having occurred.

Reaction of piperidine with 5,5-dimethylcyclopent-2-en-1-yl 2',6'-dichlorobenzoate

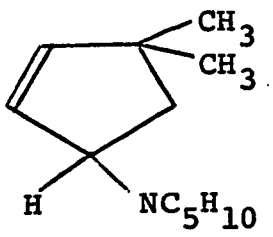
A sample (0.14 g) of the dichlorobenzoate of 6 was dissolved in piperidine (0.5 ml), a few drops of tetramethylsilane (TMS) added, and the solution transferred to a n.m.r. tube which was sealed. The spectrum of this mixture showed peaks at τ 2.68 (s, phenyl protons), 3.9-4.35 (m, olefin protons), 4.47 (unresolved m, methine proton), 7.78 (essentially t, methylene protons) and 8.85 (two singlets, methyl protons).

The tube was heated 20 h. at 130° (in a metal bath) and a new n.m.r. spectrum run. This showed: appearance of a sharp singlet superimposed on the original methine; a new quartet at τ 2.97, approximately equivalent to one proton; a decrease in the original phenyl singlet from 3 protons to 1.2 (vs. the olefinic region); and the appearance of a precipitate.

Heating the tube contents for a further 20 h. at 130° in an air oven caused very striking changes indeed. The peak at τ 4.5 was now extremely intense; the original phenyl peak had virtually disappeared, being replaced by a singlet at τ 2.55, superimposed on a

complex multiplet at τ 2.5-3.1; there was a new triplet at τ 6.25; the methylene and methyl peaks had very nearly disappeared.

These changes are impossible to reconcile with the desired product:



Reaction of diethylmalonate anion with 6, X = $OCOC_6H_3$ (2,6-di-Cl)

The anion of malonic ester was generated from 0.1 g of the ester and excess sodium hydride in DMF (1 ml). The solution was decanted into a n.m.r. tube containing a solution of the dichlorobenzoate of 6 (0.11 g, 0.00038 mole) in DMF (1 ml). The contents of the tube were thoroughly mixed and a spectrum taken. The tube was sealed and heated 16 h. at 100°, when a second spectrum was run, and again for a further 20 h., when a third spectrum was taken.

All three spectra were essentially identical -

i.e. diethyl malonate anion did not cause displacement under these conditons.

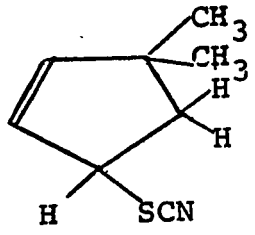
Reaction of cyanide and thiocyanate anions with 5,5-dimethylcylopent-2-en-1-yl 2',6'-dichlorobenzoate

(1) A sample of the dichlorobenzoate was refluxed overnight in acetone solution with an equivalent amount of potassium thiocyanate. Inspection of the solution by n.m.r. spectroscopy showed no reaction, nor was any seen to have occurred after the solution had been transferred to a sealed n.m.r. tube and heated at 95° for 6 h. The sole difference between this latter spectrum and the first, was the occurrence of a small new peak, located at τ 0.1 upfield from the original phenyl peak.

After 24 h. further heating at 95°, the spectrum had collapsed completely. There was now a singlet at τ 3.25 (displaced upfield τ0.1 from the original phenyl peak), a broad singlet at τ 4.05, and a close doublet at τ 4.45, these peaks being in the ratio 1:0.85:1. If the τ 4.05 is assumed to be water (not checked), the other two peaks are correct for the anticipated products, (4,4-dimethylcyclopent-2-en-1-yl thiocyanate and potassium 2,6-dichlorobenzoate), provided the further assumption is made that the τ 4.45 peak comprises both olefin and methine protons (i.e. is equivalent to 3 protons). The spectrum, however, seems too simple. See

below, and the discussion in the previous Section of this thesis.

(2) Separate samples of the dichlorobenzoate of 6 were refluxed 3 h. in dimethylformamide solution with potassium cyanide (5% excess) and potassium thiocyanate (equivalent amount) respectively. The n.m.r. spectra showed that the ester structure had completely (thiocyanate case) or partially (cyanide case) disappeared. In the thiocyanate spectrum, the original phenyl singlet at τ2.55 had been replaced by a new singlet at τ2.65; the olefin-methine region had collapsed to a close doublet at τ3.85, and the methyl doublet at τ8.85 had been replaced by a singlet at τ8.90. The ratio was 5:2:4, which can be understood if the excess phenyl is ignored, and if the τ3.85 doublet is assumed to comprise three protons - i.e. the olefin and methine protons - of the expected product. However, as explained in the previous Section of this thesis, this spectrum, despite the integration, seems too simple for the desired structure:



The methine proton should be the X-part of an ABX (or AMX) spectrum, and should show strong coupling to the methine protons, which themselves should be strongly coupled to each other. That this is not so may be purely fortuitous; on the other hand, the product may not have the structure above.

CHAPTER 2

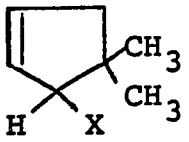
SOLVOLYSIS OF THE 5,5-DIMETHYLCYLOPENT-2-EN-1-YL AND RELATED SYSTEMS

Introduction

The solvolytic behaviour of allylic systems has long been a subject for intensive research (for reviews see (5-7), (77)). Much has been learned about the intimate details of such reactions, largely due to the researches of Sneen, et al. (78-80) and of Goering and his co-workers (see esp. (81-85)). Briefly, the situation may be summarised thus: the solvolysis of allylic systems seems to proceed through discrete ion-pair intermediates, which may undergo internal return to give unrearranged or rearranged starting material, or may proceed to products via dissociated carbonium ions. Some evidence has recently appeared (86) that very simple allylic systems such as allyl or α-methylallyl chlorides may react with solvent (or nucleophile) at the ion-pair stage.

These considerations were, however, only of indirect concern to the present investigation. As explained in the previous chapter, it was tentatively postulated that solvolysis of the 5,5-dimethylcyclopent-2-en-1-yl system might be unusually slow, relative to suitable reference compounds, and that this fact might be

useful in explaining the curious lack of S_N2' reactivity of this system. For this purpose, a preliminary study of the solvolysis of system 6, and certain related ones, was undertaken. The related systems chosen for study were the unsubstituted cyclic analogue of 6, the cyclopent-2-en-1-yl system, 34, and the open-chain analogue of 6, the cis-2-methylhex-4-en-3-yl system, 35.



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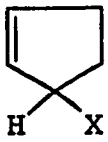

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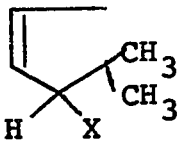

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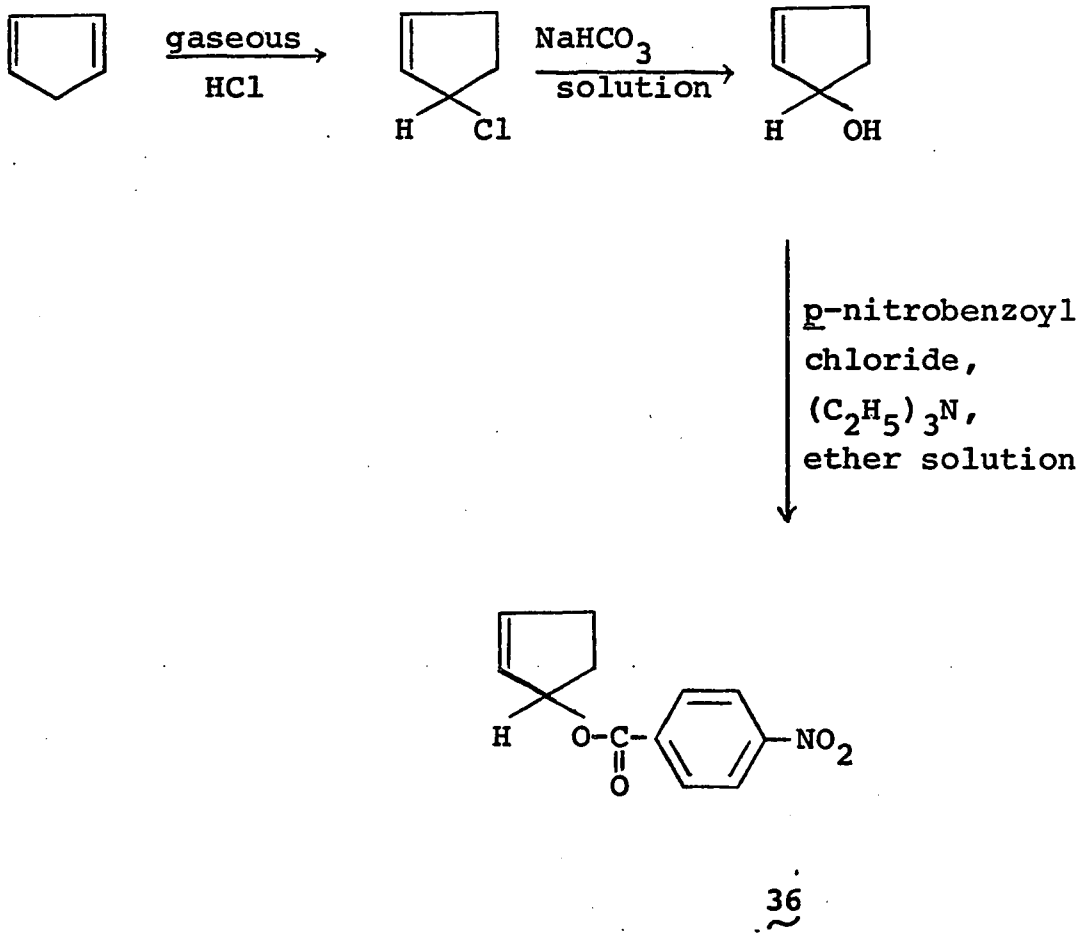
The leaving group X was chosen to be p-nitrobenzoate, in each case.

The result of this preliminary solvolytic study can be stated briefly: the 5,5-dimethylcyclopent-2-en-1-yl system does not seem to undergo solvolysis at an unusually slow rate, nor does the solvolysis of this system seem to present any unusual features. Thus, the lack of S_N2' reactivity of system 6 still requires an explanation.

Synthesis of required compounds

The synthesis of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate (6, X = $OCOC_6H_4(4\text{-}NO_2)$) has already

been described. Cyclopent-2-en-1-yl p-nitrobenzoate, 36, which seems not to have been previously reported, was prepared by the following sequence, starting with cyclopentadiene, and proceeding without isolation of the two intermediates. The yield was approximately 15% overall (from dicyclopentadiene):



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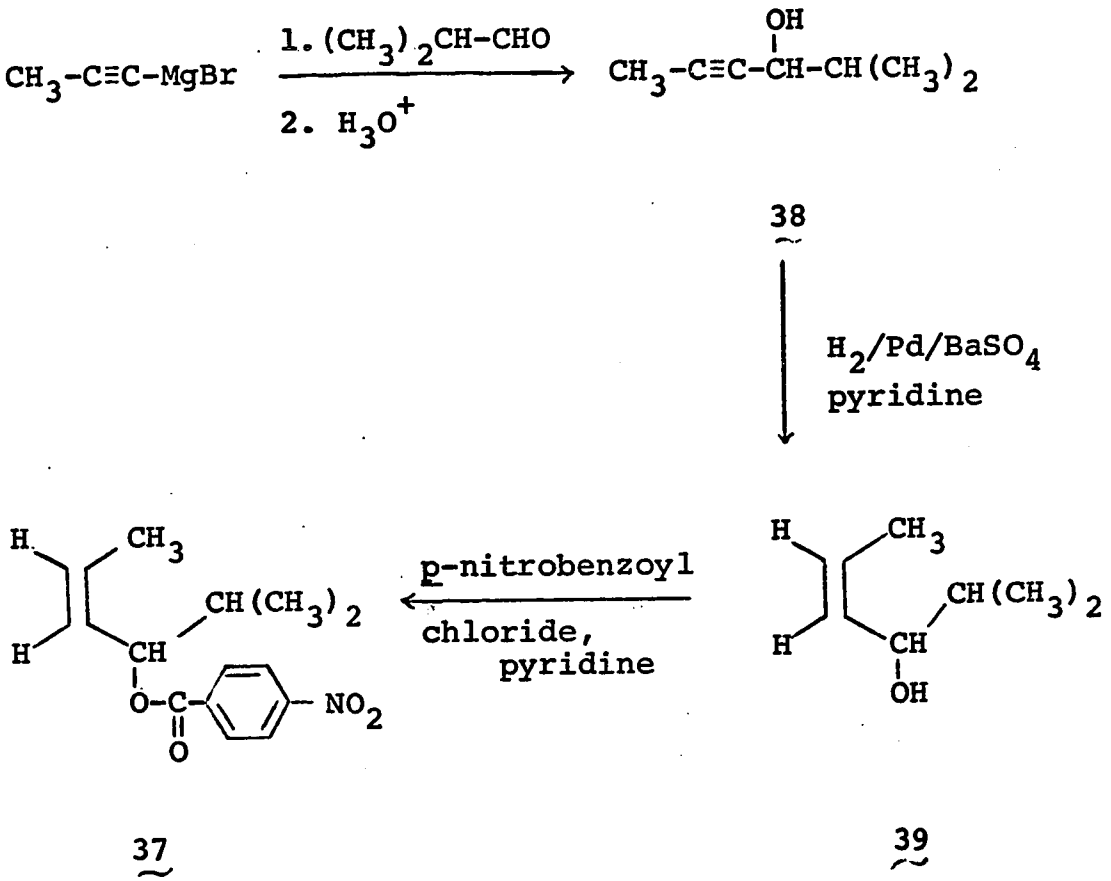
SCHEME XV

The synthesis of cis-2-methylhex-4-en-3-yl p-nitrobenzoate, 37, was accomplished by the following route:



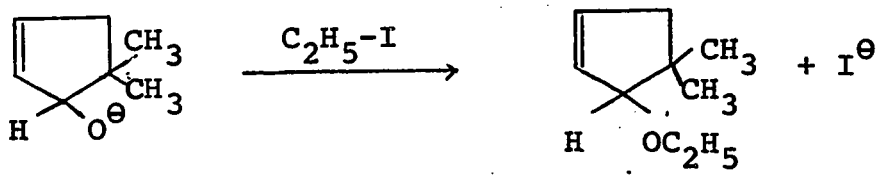
SCHEME XVI

The first intermediate, 2-methylhex-4-yn-3-ol, 38, was prepared from methylacetylene magnesium bromide and isobutyraldehyde according to the procedure of Favorskaya, et al. (87). Some experimental difficulties were encountered; these will be presented in the Experimental section (q.v.). The next step, the controlled

semi-hydrogenation of 38 to cis-2-methylex-4-en-3-ol, 39, was achieved by dissolving 38 in pyridine and using palladium on barium sulfate as a catalyst, at room temperature and approximately 40 psi pressure. This procedure, in effect a slight modification of that due to Heilmann and co-workers (88), was the one of choice in this system, in spite of the fact that a 30-40 h. induction period was encountered.

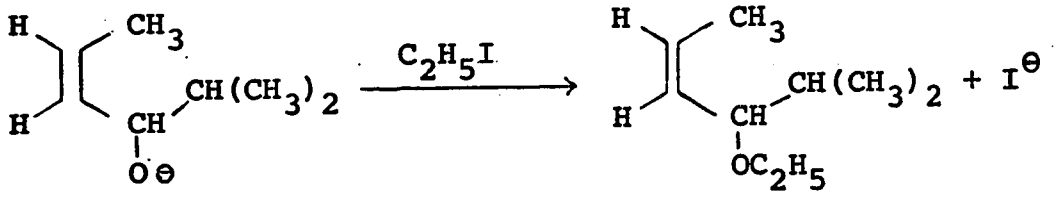
The esterification step was performed without isolation of 39; the pyridine solution was simply filtered from catalyst and the acid chloride added directly.

The compounds which were anticipated to be the major products of ethanolysis of these systems without accompanying rearrangement were synthesised in the following ways: 5,5-dimethylcyclopent-2-en-1-yl ethyl ether (6, X = OC_2H_5), and cis-2-methylhex-4-en-3-yl ethyl ether, 40, were prepared by reaction of the respective alcoholate anions with ethyl iodide:

[11] 

6, X = OC_2H_5

[12]



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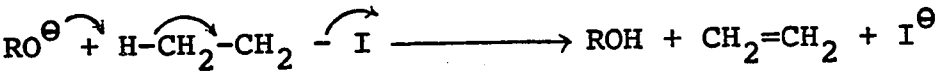
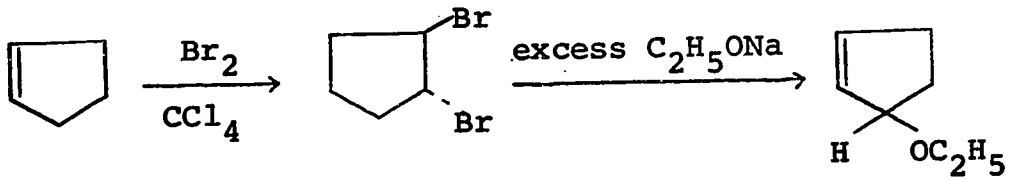
In both cases the base used for preparation of the anion (sodium hydride) and the alkylating agent, ethyl iodide, both had to be in very considerable excess, otherwise the yields and conversions were seriously reduced by elimination of hydrogen iodide from the ethyl iodide by the alcoholate anion:

[13] 

Cyclopent-2-en-1-yl ethyl ether, 41, was synthesised by the following sequence, due to Levina and co-workers (89):



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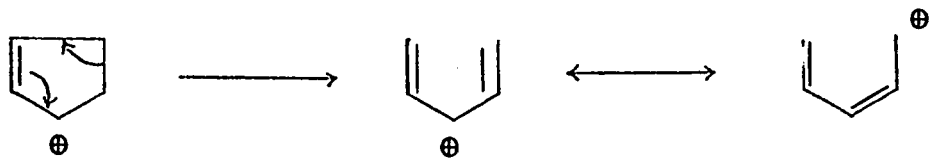
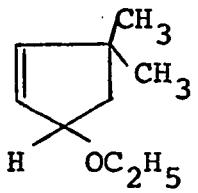
SCHEME XVII

It was difficult to predict what products might arise from these systems by ethanolysis with rearrangement. In the case of the cyclopent-2-en-1-yl system, rearrangement without skeletal disruption would, of course, lead to the same compound, 41, as solvolysis without rearrangement, and a distinction could only have been made by some labelling procedure, such as putting a deuterium atom in the methine position of the ester. This was not considered worthwhile. Similarly, synthesis of the products which might arise by electrocyclic ring opening (Eq. [14]) of the carbonium ion was not undertaken; as it transpired, these compounds were not needed.

[14] 

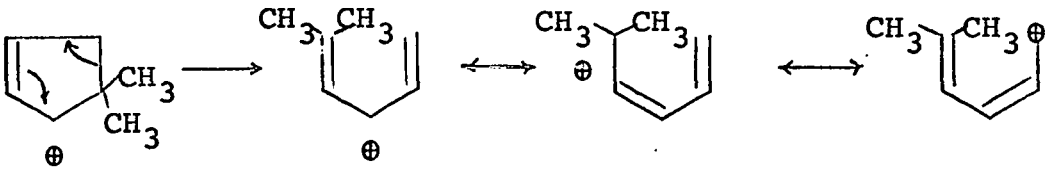
In the case of the 5,5-dimethylcyclopent-2-en-1-yl system, the product anticipated from solvolysis with rearrangement, but without skeletal disruption, was 4,4-dimethylcyclopent-2-en-1-yl ethyl ether (6', Y = OC_2H_5).



6', Y = OC_2H_5

As explained in the Section of Chapter 1 dealing with nucleophilic displacements in System 6, it was anticipated that derivatives of the 6' ring system, such as this ether, could easily be recognised from their n.m.r. spectra. This turned out to be the case with this ethyl ether, whose spectrum is given in Figure 3, and a separate synthesis of this compound was not developed.

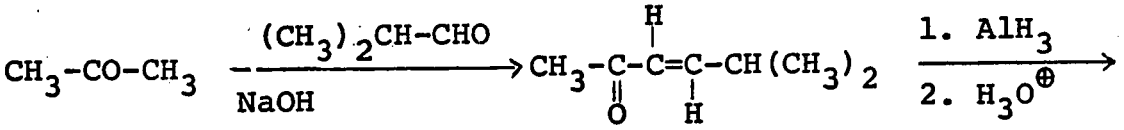
The products which might have arisen from System 6 by solvolysis with skeletal disruption, were also not prepared, in spite of the fact that formation of such products seemed, a priori, quite likely, due both to possible relief of steric strain in going from the cyclopentenyl cation to the pentadienyl cation, and to stabilisation of the latter ion by the gem-dimethyl grouping. [15]



It seemed that formation of any products derived from the pentadienyl cation could easily be recognised from the presence of vinyl methylene proton signals in the n.m.r. spectrum (the primary carbonium ion resonance structure shown above was not thought to be likely to give rise to products). As it transpired, the formation of

such open-chain compounds could be discounted from the examination of the products of this solvolysis.

It was considered that the cis-2-methylhex-4-en-3-yl system could solvolyse with rearrangement to give either cis- or trans-5-methylhex-3-en-2-yl ethyl ether (or possibly both). As it happened, however, the major product was the trans-ether, 42, a fact which will be commented upon later. The synthesis of this ether was accomplished by the following route:



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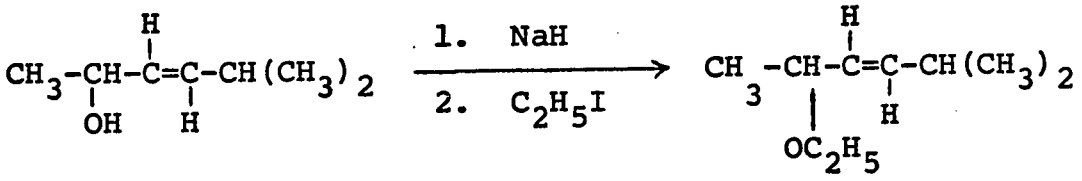


44 42

SCHEME XVIII

The first intermediate, trans-5-methylhex-3-en-2-one (trans-isobutylideneacetone, 43) was prepared by the procedure of Heilmann, et al. (88). Some experimental difficulties will be commented on later. The reduction step, patterned after the procedure previously developed for 5,5-dimethylcyclopent-2-en-1-one, 9, led to a mixture of products, which was refined by recrystallisation of the p-nitrobenzoate, 45. This was then hydrolysed to the allylic alcohol, 44, and this was converted to the ether, 42, by base and ethyl iodide, as already discussed for the isomeric ether. Experimentally, it proved very difficult to obtain 42 pure by distillation, so that it was obtained by preparative GLC in sufficient quantity and purity for the purpose of comparison with solvolysis product; see the next Section.

Note, however, that not one of the compounds in this trans-series was obtained pure despite repeated recrystallisation of the p-nitrobenzoate, 45. The reason is not known.

Kinetics - methods and results

For the initial solvolytic work, 80% acetone-water was chosen as the medium. Samples of each p-nitrobenzoate were weighed out and dissolved in sufficient 80% acetone to make approximately 0.05M solutions. Small

portions of these solutions were charged into ampoules, which were then sealed and inserted into a heating bath thermostatted at 80.05±0.03°C. From time to time, ampoules were removed, equilibrated to 25.0°C, and broken open; aliquots were then removed by means of pre-calibrated automatic pipettes (approximately 5 ml. in volume), drained into 50 ml. distilled water. 8 drops of phenolphthalein indicator added, and titration carried out against approximately 0.05M sodium methoxide solution to a pink end-point. The base, pre-standardised in the usual manner, against potassium hydrogen phthalate, was delivered from a 5 ml. automatic burette.

It should be remarked at this point that the author found the phenolphthalein end-point in this system to be unsatisfactorily diffuse and unstable, and that reasonably reproducible results could only be achieved by titration to quite an intense pink color. Control experiments indicated that p-nitrobenzoic acid itself was quantitatively titratable under these conditions. The diffuse nature of the end-point in this aqueous acetone system, presumably due to the presence, in suspension, of unsolvolysed ester, was considerably reduced, though not eliminated, by draining the aliquots into methanol, rather than distilled water, thus keeping unsolvolysed ester in solution.

Even with this improvement, however, the author experienced considerable difficulty in achieving reproducible end-points over an extended period of time, such as was required for the solvolysis of cis-2-methylhex-4-en-3-yl p-nitrobenzoate. This, the author feels, accounts for the somewhat less satisfactory results with this ester, as compared to those with cyclopent-2-en-1-yl and 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoates.

It is apparent from Table 2 (see below) that the results obtained in aqueous acetone were not too precise. No attempt to refine the results by repetition was made, however, as it seemed that a better procedure would be to find a solvent medium in which the open-chain p-nitrobenzoate would solvolyse sufficiently fast to improve the reproducibility of the results.

One trial run in 65% dioxan-water at 100° was made. It was found that, under these conditions, cis-2-methylhex-4-en-3-yl p-nitrobenzoate solvolysed at an initial rate corresponding to $k = 4.74 \times 10^{-6}$ sec^{-1}, but that this rate climbed rapidly until, at a titration value corresponding to 83% solvolysis, the rate constant was 7.00×10^{-6} sec^{-1}. Further, the titration continued to increase until, at between 2 and 3 "half-lives", the theoretical infinity titration was already exceeded by 4%.

Table 2

SOLVOLYSES OF ALLYLIC p-NITROBENZOATES

IN 80% ACETONE AT 80.05±0.03°C

Allylic p-nitrobenzoate	$k \times 10^7$, sec^{-1}
cis-2-Methylhex-4-en-3-yl	approx. 1.0[a]
5,5-Dimethylcyclopent-2-en-1-yl	42.5[b]
Cyclopent-2-en-1-yl	1090[c]

[a] One run only, followed to 68% completion. Continuous rise in k, from 9.7-14.4 x 10^{-8} sec^{-1}

[b] One run only, k = (4.25±0.27) x 10^{-6} sec^{-1}. Followed to 88% solvolysis (7 points)

[c] Mean of 2 runs, k = 1.04 (±0.04), 1.13 (±0.03) x 10^{-4} sec^{-1}. Both followed to ca. 90% solvolysis

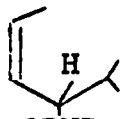
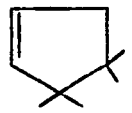
These observations, coupled with an increasing yellow color in the solution, showed that the solvent was undergoing an acid-producing decomposition, as already observed by Sneen (78). It is interesting to note that Zinck (90) apparently observed no such side-reaction, even though he used 70-85% dioxan at 120-140° in his investigation.

Finally, 80% ethyl alcohol-water was chosen as the solvolytic medium. It was found that none of the three esters under investigation were sufficiently soluble in this medium to enable solutions much above 0.03M in strength to be prepared. The base used for titration was changed to approximately 0.03M sodium hydroxide solution , and the indicator to α-naphtholbenzein. This indicator has a green end-point, which proved to be more reproducible than that of phenolphthalein, but still not entirely satisfactory over the extended period needed for the open-chain ester.

The following table summarises the results obtained from solvolyses of the three p-nitrobenzoates in 80% ethanol-water at 80.05±0.03°C and 100.0±0.03°. The values for cyclopent-2-en-1-yl p-nitrobenzoate, which solvolysed at an unmanageably fast rate at 80°, are extrapolated from the values found at 70.0±0.02° and 50.0±0.03°.

Table 3

SOLVOLYSIS OF ALLYLIC p-NITROBENZOATES IN 80% ETHANOL (PNB = $COC_6H_4-NO_2$)

Ester		k, sec^{-1}, at indicated temperature			
		50°	70°	80°	100°
	1.			$(6.39\pm0.19)\times10^{-7}$	$(5.20\pm0.12)\times10^{-6}$
	2.			$(6.24\pm0.32)\times10^{-7}$	$(5.27\pm0.10)\times10^{-6}$
	Mean			$(6.32\pm0.40)\times10^{-7}$	$(5.24\pm0.16)\times10^{-6}$
	1.			$(2.02\pm0.09)\times10^{-5}$	$(1.51\pm0.02)\times10^{-4}$
	2.			$(2.03\pm0.05)\times10^{-5}$	$(1.62\pm0.02)\times10^{-4}$
	Mean			$(2.02\pm0.09)\times10^{-5}$	$(1.57\pm0.08)\times10^{-4}$
	1.	$(2.34\pm0.04)\times10^{-5}$	$(1.99\pm0.01)\times10^{-4}$		
	2.	$(2.36\pm0.06)\times10^{-5}$	$(1.95\pm0.05)\times10^{-4}$		
	Mean	$(2.35\pm0.07)\times10^{-5}$	$(1.97\pm0.07)\times10^{-4}$	$[5.23\times10^{-4}]$	$[3.16\times10^{-3}]$

All the values for k given in Table 3 are means of duplicate runs of satisfactory precision and reproducibility. It will be noted again that the scatter within runs is worse for the open-chain case than for the two cyclic esters. This is again attributed to the author's personal difficulty in achieving reproducible end-points over a period of many weeks, rather than any trends inherent in the solvolysis mechanism (see later for an amplification of this statement).

All solvolytic runs in ethanol-water involved at least seven points and were followed to at least 80% completion. The values of the first-order rate constant, k, were calculated from the usual expression, $k = \frac{2.303}{t} \log \frac{V_\infty - V_o}{V_\infty - V_t}$, where t = elapsed time in seconds from the zero reading, V_o = zero titration (ml.), V_t = titration at time t, and V_∞ = theoretical titration at $t = \infty$. As required by this first order equation, graphs of log $(V_\infty - V_t)$ *vs.* t were substantially linear, over the range examined in each run; deviations from linearity were of a random nature, since they could not be reproduced from run to run, and must again be ascribed to the author's subjective difficulty in achieving reproducible end-points over an extended period.

The instantaneous values of k within each run were averaged; the average deviation of each individual

point from this average k_t was computed, and any point further than arbitrarily-chosen three times the average deviation from the mean was rejected from the computation. Refinement of the data was continued in this way until a suitably precise result emerged. In no case were more than two points rejected.

It will, of course, be observed that only a very small number of kinetic runs was made during this work; further, no runs were made with added salts present, and none of the compounds was resolved, to enable polarimetric rates to be run. This is because elucidation of fine, mechanistic points was not within the scope of this investigation; such points as are required to be made in the Discussion (see later) are based on analogy with existing data.

The activation parameters for these three solvolyses were calculated from the following equations (91):

[16] $$E_a = \frac{4.576\ T_2T_1(\log k_2 - \log k_1)}{T_2 - T_1}$$

[17] $$\Delta H^{\ddagger} = E_a - RT$$

[18] $$\Delta S^{\ddagger} = 4.576 \left(\log k - 10.753 - \log T + \frac{E_a}{4.576T}\right)$$

Here, E_a = activation energy, cal/mole

$\Delta H^{\ddagger}$ = activation enthalpy, cal/mole

$\Delta S^{\ddagger}$ = activation entropy, e.u.

k = specific rate constant, sec^{-1}, at T°K

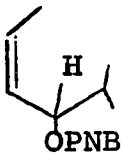
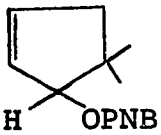
R = Universal Gas Constant = 1.98 cal/mole degree

Table 4

ACTIVATION PARAMETERS - SOLVOLYSES OF ALLYLIC

p-NITROBENZOATES IN 80% ETHANOL

PNB = $COC_6H_4NO_2$

Ester	E_a Kcal/mole	$\Delta H^{\ddagger}$ Kcal/mole 80°	$\Delta S^{\ddagger}$ e.u. 80°
	27.8±1.1	27.1±1.1	11±3
	26.7±1.1	26.0±1.1	7±3
	23.3±0.6	22.6±0.6	10±2

Selected examples of the individual kinetic runs given in Table 3 are presented in tabular and graphical form at the end of this Thesis. The errors given in Table 4 have been derived by computing the activation parameters for the three solvolyses, using the individual rate constants at the extremes of the ranges quoted in Table 3, and then averaging the values so found.

Product studies - methods and results

Samples of each of the three p-nitrobenzoates under study were solvolysed in 80% ethanol, at a convenient temperature, for a period in excess of ten half-lives. In each case, the solvolysis solutions were poured into water, the organic solutions shaken with sufficient cold 5% sodium hydroxide solution to neutralise the p-nitrobenzoic acid, then dried over anhydrous sodium sulfate, and the major part of the solvent removed by careful distillation. The residual solutions were then inspected by GLC. The yield of the major product was then determined (by addition of a suitable internal standard), and then this major product was isolated by preparative GLC and compared with the anticipated product(s) by n.m.r. spectroscopy.

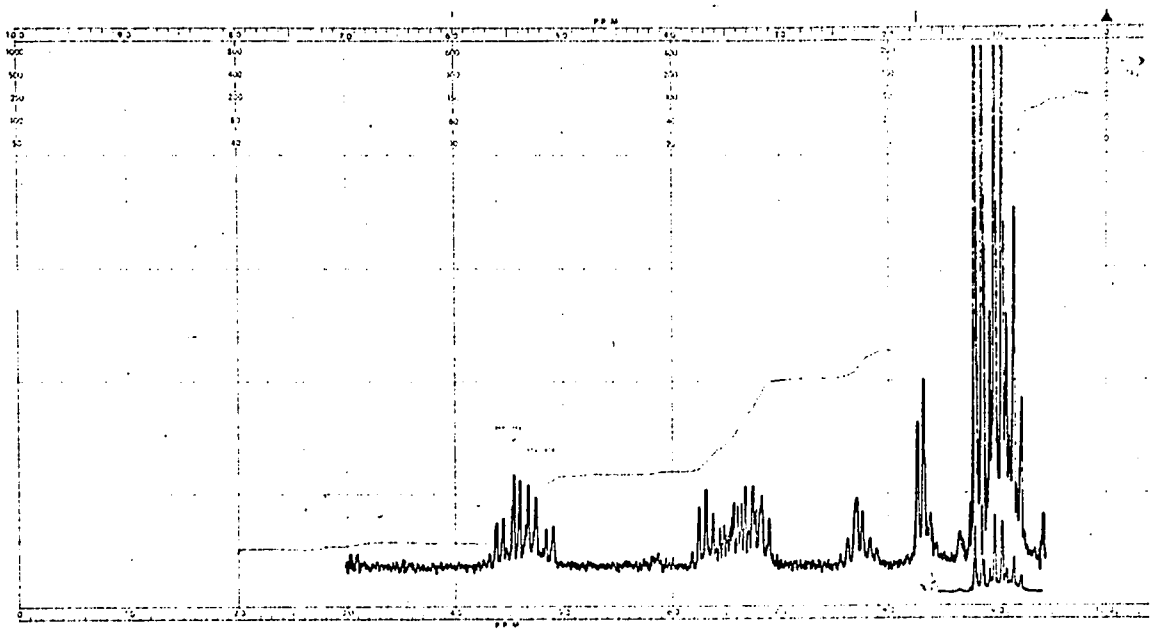
(a) cis-2-Methylhex-4-en-3-yl p-nitrobenzoate, 37: This ethanolysis apparently produced at least nine

products; six of these were present in trace amounts only, while the remaining three were present in the approximate ratio of 1:1:2, as judged by relative peak areas. Retention times of these three peaks were approximately 2, 2.5 and 5 minutes, respectively, under the conditions employed (SE-30 column, temperature 83°, flow 45 ml/min He). By using bromobenzene as internal standard, the yield of the major product was estimated to be 54%.

That this major product was not cis-2-methylhex-4-en-3-yl ethyl ether (40, the expected major product of ethanolysis without rearrangement) was easily shown by comparison of GLC retention times, which, though close, were not identical, on two different columns. Isolation of this material by preparative GLC and analysis of the olefinic part of the n.m.r. spectrum (Figure 6, spectrum A) showed that this material (though not entirely homogeneous - see later) was mostly a trans-olefinic ether. This was apparent from the magnitude of the H_A - H_B coupling constant (J_{AB} = 15.2 Hz) derived from the analysis of the olefin peaks, assuming that the 8 major visible peaks constituted the AB part of an ABX system.

The most likely trans-olefinic ether to be expected from this solvolysis would be trans-5-methylhex-3-en-2-yl ethyl ether, 42. This was synthesised as already described, and comparison of its spectrum

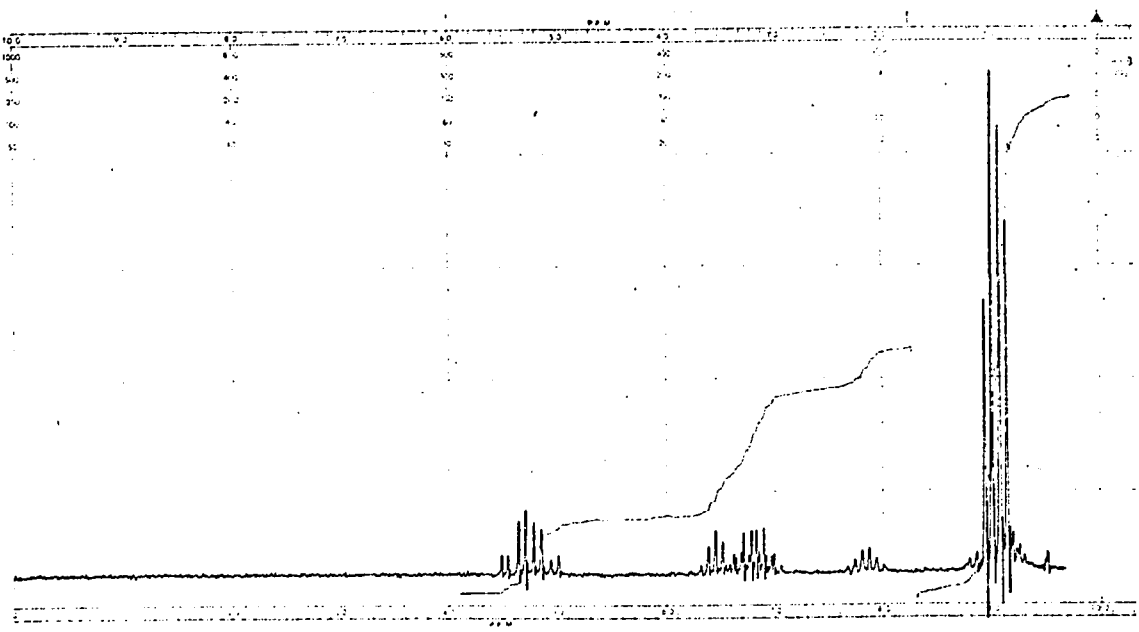
Spectrum A



Major product of solvolysis of

cis-2-methylhex-4-en-3-yl p-nitrobenzoate

Spectrum B

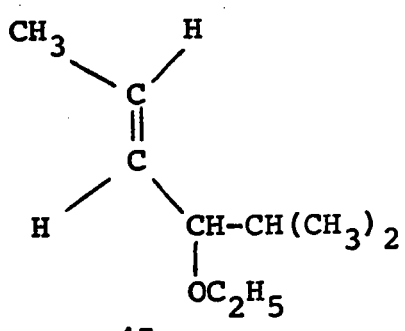


Authentic trans-5-methylhex-2-en-4-yl ethyl ether

Figure 6

(Figure 6, spectrum B) with that discussed above, as well as comparison of GLC retention times, which are identical, confirms that the chief product of this solvolysis is indeed 42.

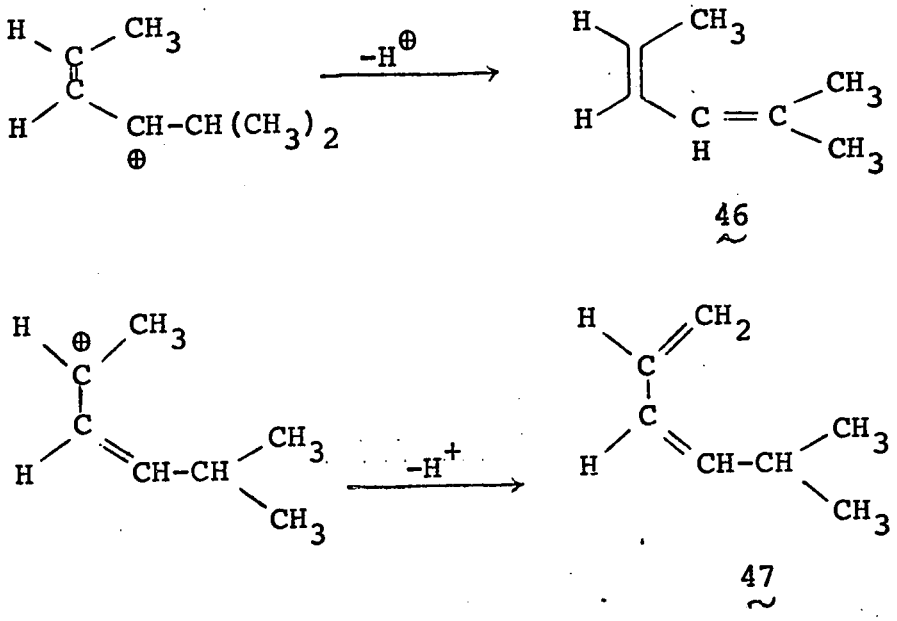
It is apparent from Figure 6 that the material isolated by GLC from the solvolysis product was not pure 42. This is shown by the additional splittings in the olefin region, the relative complexity of the τ6.5-7.0 region, the presence of additional peaks in the methyl region, and, above all, by the presence of additional peaks at approximately τ8.3. It is interesting to note that this is close to the chemical shift of the olefinic methyl group in cis-2-methylhex-4-en-3-yl ethyl ether, 40, (see Experimental section), although 40 was not detected (by GLC) among the solvolysis products. This suggested the possibility that the extra n.m.r. peaks mentioned above might be due to the presence of trans-2-methylhex-4-en-3-yl ethyl ether, 45:



45

This assignment could not, however, be reconciled with the integrated intensities of the various peaks (see Experimental section) so that the identity of the contaminant(s) remains uncertain.

The identities of the compounds represented by the other two major peaks in the GLC were not investigated. It seems probable, however, that significant quantities of dienes 46 and 47 may have been formed in this solvolysis (although the absence of vinyl methylene peaks in the n.m.r. spectrum militates against 47). The low retention times of these two GLC peaks is interesting in this regard.



SCHEME XIX

(b) 5,5-Dimethylcyclopent-2-en-1-yl p-nitrobenzoate: The ethanolysis of this compound produced three products, one of which greatly predominated (>90%, by GLC inspection). This major product had the same retention time as 5,5,-dimethylcyclopent-2-en-1-yl ethyl ether (6, X = OC_2H_5) under the conditions employed (SE-30 column, temperature 83°, flow 43 ml/mm He). Addition of cumene as an internal standard and determination of the yield of this major product gave figures of 99% and 94% in two separate experiments.

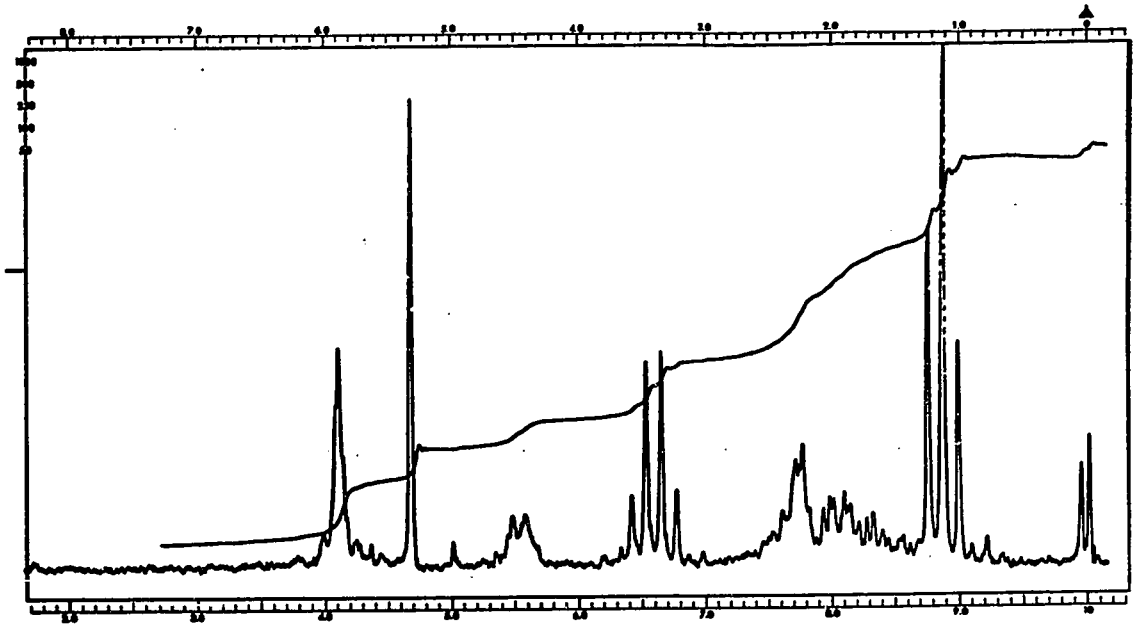
Isolation of this material by preparative GLC and inspection of its n.m.r. spectrum indicated quite clearly that it consisted of a mixture of 88% 4,4-dimethylcyclopent-2-en-1-yl ethyl ether (6', Y = OC_2H_5) and 12% of the 5,5-isomer. (See Figure 3). One of the minor peaks was tentatively identified as 5,5-dimethylcyclopent-2-en-1-ol (6, X = OH), from comparison of GLC retention times with authentic material; however, in view of the above-mentioned identity of retention times of the two ethers, this identification is by no means certain.

(c) Cyclopent-2-en-1-yl p-nitrobenzoate, 36: This solvolysis produced 4 products, one of which again greatly predominated (>90%). A quantitative yield determination gave a figure of 92%.

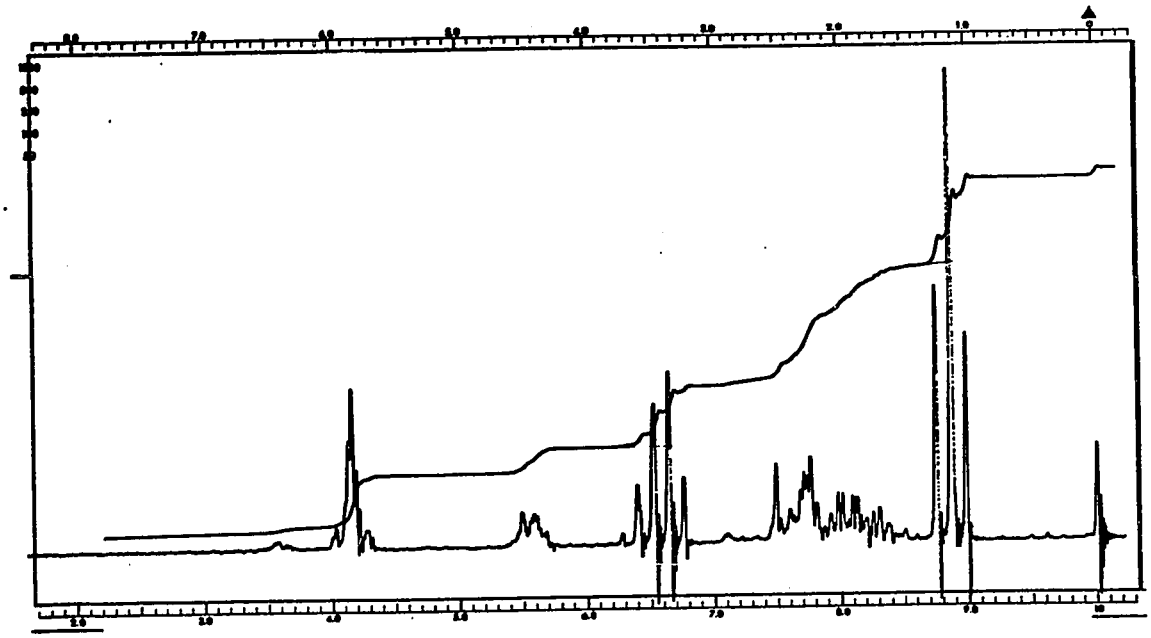
Comparison of the n.m.r. spectrum of the crude

product, still containing methylene chloride, with that of authentic, though crude, cyclopent-2-en-1-yl ethyl ether, 41, confirms that the major product of this ethanolysis is, indeed, as expected, this ether 41. (See Figure 7).

In order to search for any evidence of intramolecular rearrangement accompanying solvolysis (i.e. internal return), samples of the individual p-nitrobenzoates were solvolysed in 80% ethanol, at a convenient temperature, for 1-1 1/2 half-lives. The solvent was then evaporated off, and the residual mixture of p-nitrobenzoic acid and unsolvolysed ester was examined by n.m.r. spectroscopy. In initial work, the mixture was suspended in chloroform and filtered, the p-nitrobenzoic acid was washed well with chloroform, the solution was evaporated and the residual ester submitted for n.m.r. inspection. Repetition of this type of experiment, using n-pentane instead of chloroform gave no detectable difference in the n.m.r. spectrum of the unsolvolysed ester, thus ruling out fractionation during work-up (it is known that p-nitrobenzoic acid is insoluble in both n-pentane and chloroform). In the final stages of the work, the mixture of p-nitrobenzoic acid and unsolvolysed ester was submitted, as such, for n.m.r. inspection in deuterochloroform, and the technician leached the mixture



Crude product of solvolysis of cyclopent-2-en-1-yl p-nitrobenzoate (τ4.7 peak is CH_2Cl_2)



Authentic cyclopent-2-en-1-yl ethyl ether

Figure 7

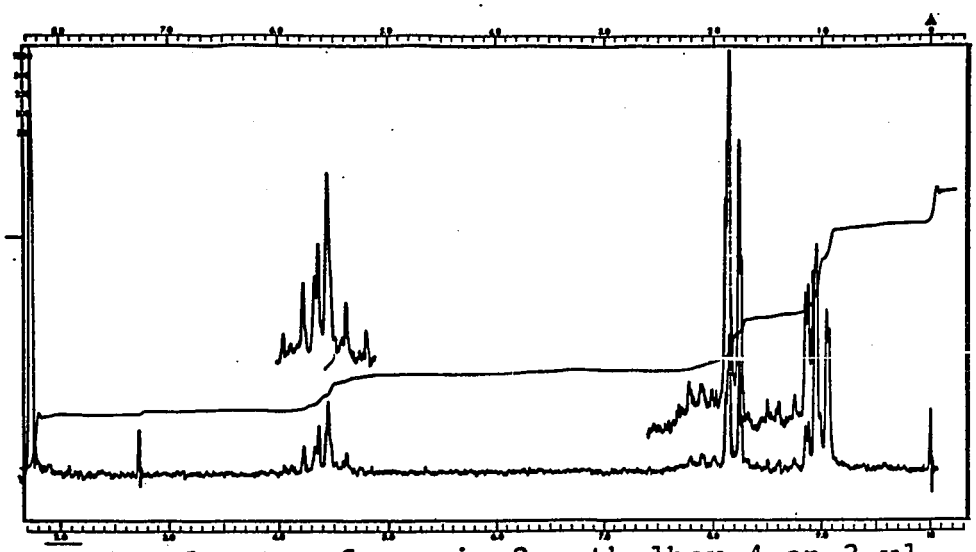
directly with the solvent.

a) cis-2-Methylhex-4-en-3-yl p-nitrobenzoate: Figure 8 displays the spectrum of the recovered, unsolvolysed ester from this interrupted solvolysis (upper spectrum), together with those of authentic starting material (middle spectrum) and of trans-5-methylhex-3-en-2-yl p-nitrobenzoate, the anticipated product of return with rearrangement (see later) (lower spectrum). It is clear that little or no intramolecular rearrangement has accompanied this solvolysis.

b) 5,5-Dimethylcyclopent-2-en-1-yl p-nitrobenzoate: The situation is different here. By comparison of the spectrum of recovered unsolvolysed ester (Figure 9, lower spectrum) with that of authentic starting material (upper spectrum) it is clear that some rearrangement must have occurred. (Compare the olefinic regions, and, more particularly the τ7.8-8.1 regions, notice, also, the broadening of the methyl peaks in the lower spectrum).

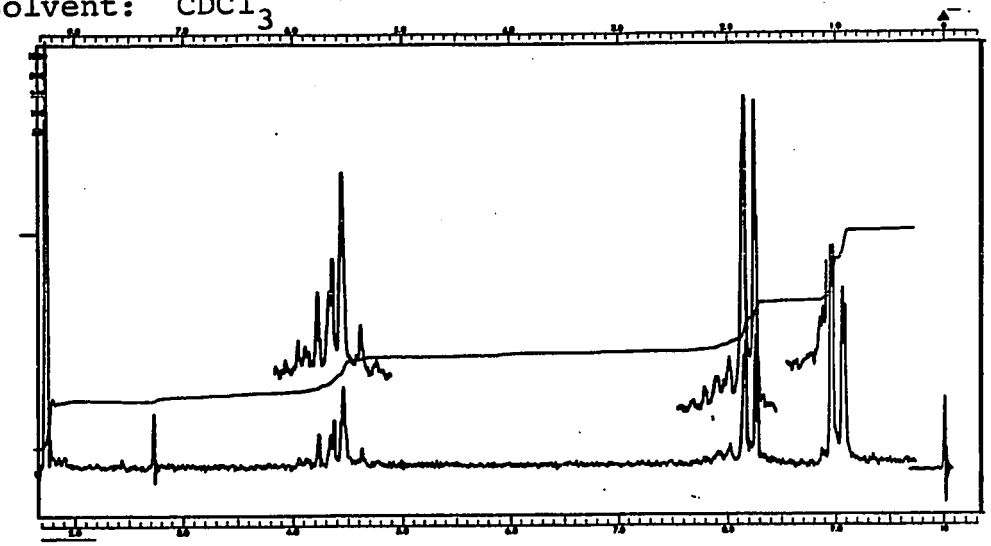
The absence of vinyl methylene (and vinyl methyl) signals in the lower spectrum rules out the occurrence of internal return involving a ring-opened intermediate ion (see Equation [15]). Therefore, the expected product of internal return is 4,4-dimethylcyclopent-2-en-1-yl p-nitrobenzoate (6', Y = $OCOC_6H_4(4\text{-}NO_2)$). This, by analogy with the spectrum of the corresponding

Solvent: $CDCl_3$



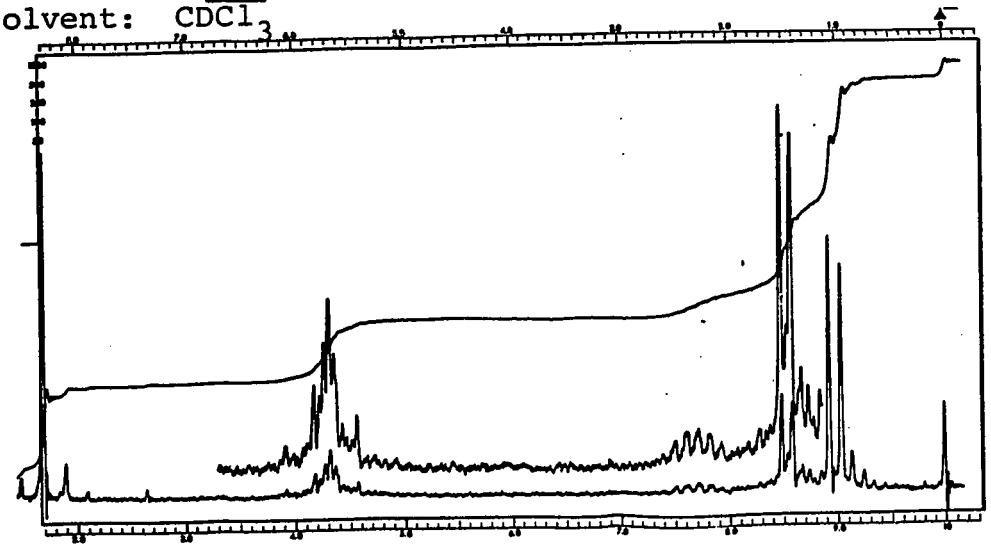
Unsolvolysed ester from cis-2-methylhex-4-en-3-yl p-nitrobenzoate

Solvent: $CDCl_3$



Authentic cis-2-methylhex-4-en-3-yl p-nitrobenzoate

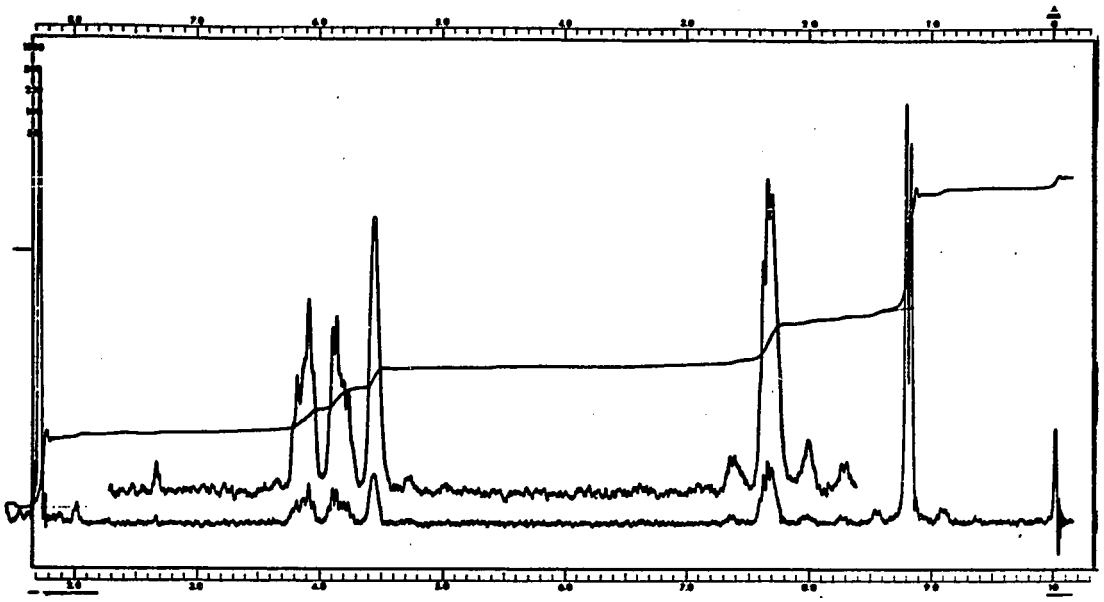
Solvent: $CDCl_3$



trans-5-Methylhex-2-en-4-yl p-nitrobenzoate

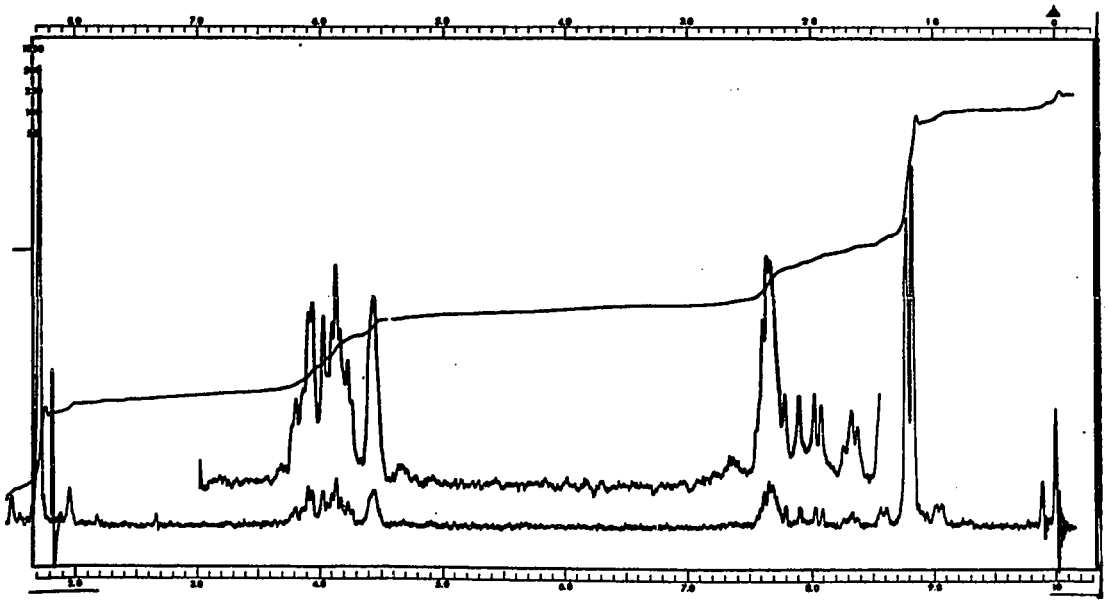
Figure 8

Solvent: $CDCl_3$



5,5-Dimethylcyclopent-2-en-1-yl p-nitrobenzoate

Solvent: $CDCl_3$



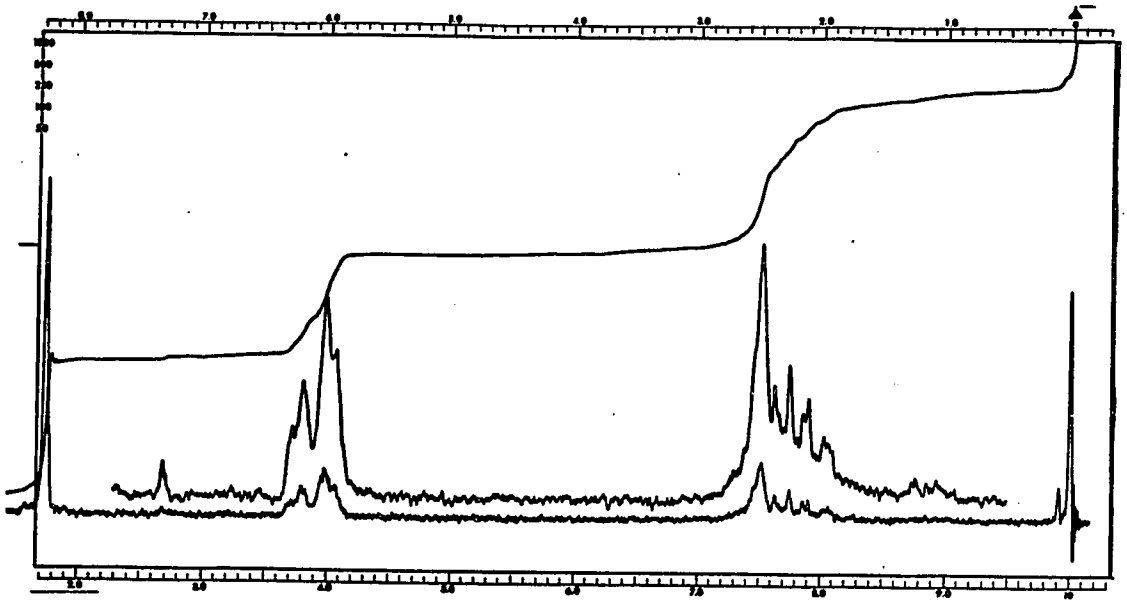
Recovered ester from interrupted solvolysis of above ester

Figure 9

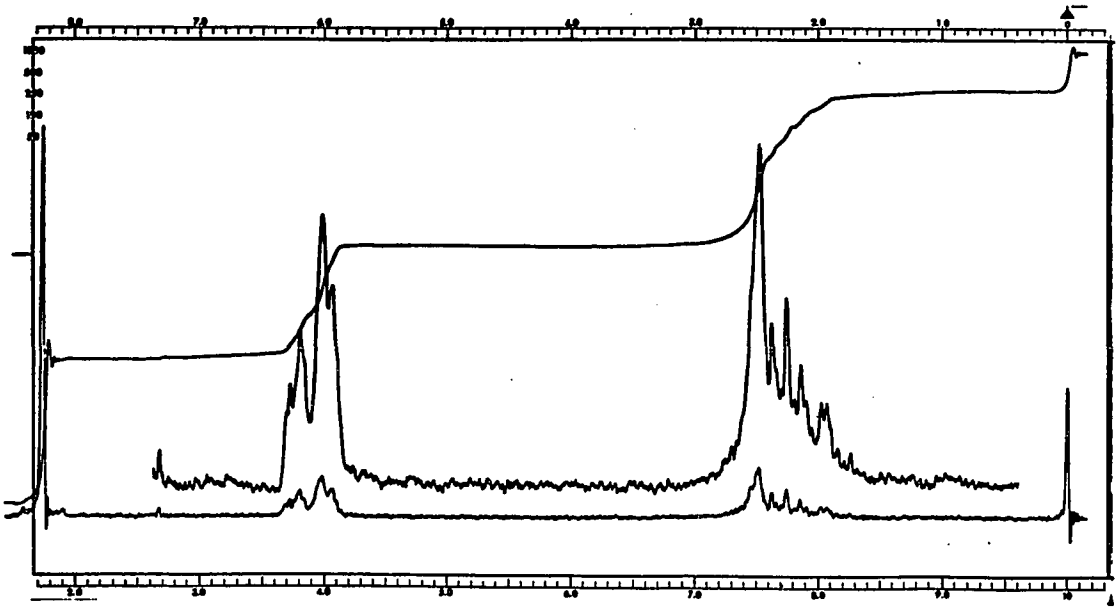
ether (see Figure 3, and the discussion in Chapter 1) is expected to display methylene resonance of the AB type (the X proton being the methine). A portion of this pattern is evident in the lower spectrum, τ7.8-8.1 region. On the assumption that this is indeed so and that the methine proton of the rearranged ester has been shifted downfield and lies under the olefin region (for justification, see the ethers in Figure 3), the n.m.r. spectrum of the recovered unsolvolysed ester can be easily analysed. The results indicate that, after one half-life, the recovered ester is 23.5% rearranged.

c) Cyclopent-2-en-1-yl p-nitrobenzoate: Here, as explained in the Introduction, internal return from the skeletally-unrearranged carbonium ion-pair is undetectable, without the presence of some label in the molecule. However, in order to see whether any return occurred from ring-opened carbonium ion intermediate (Equation [14]) the interrupted solvolysis of this p-nitrobenzoate was carried out.

The absence of vinyl proton signals in the n.m.r. spectrum of the recovered, unsolvolysed ester (see Figure 10, upper spectrum) rules out any significant ring-opening in this system. Comparison of this spectrum with the lower spectrum (authentic starting ester) confirms their identity.



Recovered unsolvolysed ester from solvolysis of cyclopent-2-en-1-yl p-nitrobenzoate ($CDCl_3$)



Authentic cyclopent-2-en-1-yl p-nitrobenzoate ($CDCl_3$)

Figure 10

Discussion

It is admitted that the present solvolytic study is only introductory in nature, and that a good many experiments remain to be done in these systems in order to elucidate a number of mechanistic points. However, the data presented herein, while fragmentary, is sufficient to enable certain conclusions to be drawn, with appropriate reservations.

It is quite apparent that the kinetic results described herein are concerned with the solvolysis step (i.e. appearance of product, or capture of dissociated carbonium ion, q.v.) and not with the ionisation step (i.e. formation of the intermediate ion-pair, q.v.), which is the step which, for the purposes of this investigation, was really of most concern. However, the small amount of internal return detected in this investigation will not affect our conclusions very much.

Now, it is essential to decide whether or not the systems under investigation, and, in particular, the 5,5-dimethylcyclopent-2-en-1-yl system, solvolyse in 80% ethanol by the S_N1 mechanism. Although no direct experimental evidence on this point was obtained in this present study, it is felt that a good case for the S_N1 mechanism can be made by relying on evidence from the literature.

It has previously been shown that α,γ-dimethyl-

allyl p-nitrobenzoate solvolyses via ion-pair intermediates in 80% aqueous acetone (93,94). It is also know that, in a given solvent, mechanisms shift closer to the S_N1 end of the range with increasing alkyl substitution at both the α- and γ-carbons (ref. (5), pp.699-702). Hence our open-chain system (α- isopropyl-γ-methylallyl-, or 2-methylhex-4-en-3-yl) will certainly solvolyse by an ionic mechanism, especially in 80% ethanol, which is more ionising than 80% acetone.

There appears to be no direct proof in the literature that cyclopent-2-en-1-yl derivatives solvolyse by an ionic mechanism; however, this system is the direct cyclic analogue of the α,γ-dimethylallyl system, and there would seem to be little reason for anticipating a mechanistic change in proceeding from an acyclic system to its cyclic analogue. Some evidence is presented below to show that the results obtained in this study on these two systems fit well with previous results, where corresponding mechanisms are strongly implicated.

By the same token, the 5,5-dimethylcyclopent-2-en-1-yl system - the cyclic analogue of the 2-methylhex-4-en-3-yl system - should also solvolyse by the S_N1 mechanism, particularly because of increased steric hindrance to S_N2 attack.

The above argument is considered to provide direct

confirmation of the operation of the S_N1 mechanism in the systems of present interest. Some support also comes from estimation of the Winstein-Grunwald m parameters (95) for each of the three solvolyses investigated. From the Winstein-Grunwald equation:

$$[19] \qquad \text{Log} \frac{k}{k_o} = mY$$

where k is the rate constant in 80% acetone (for our work), k_o is the rate constant in 80% alcohol, and Y is the solvent parameter for 80% acetone = -0.67 (ref. (91), Table VI, p.243), the following rough values for m may be calculated from the data in Tables 2 and 3:

cis-2-Methylhex-4-en-3-yl p-nitrobenzoate:1.2

5,5-Dimethylcyclopent-2-en-1-yl p-nitrobenzoate:1.0

Cyclopent-2-en-1-yl p-nitrobenzoate:1.0

Now, it seems to be generally agreed that these m values are a reasonably reliable guide as to the mechanism being followed. Reactions at the S_N2 end of the spectrum have m values in the neighborhood of 0.4, while those at the S_N1 end have m values of about 1.0 (ref. (5) p.699).

The m-values quoted above are only a qualitative guide, since, especially in 80% acetone, the experimental uncertainty in rate constants is probably somewhat higher

than one would like - chiefly due to the small number of experiments. However, the rate constants determined in this work would have to be in error by a factor of at least 10, and probably closer to 100, before an appreciable difference would be made to the quoted m values. This is considered quite unlikely, so that a fair degree of reliance may be placed on these values, preliminary though they may be, and subject to confirmation.

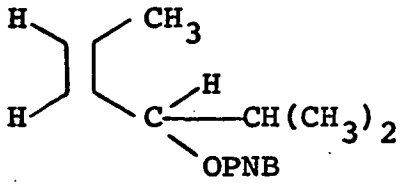
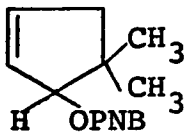
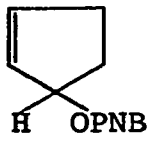
The following table gives the relative rates of solvolysis of the three esters of present interest.

There are not very many reports in the literature of comparisons in solvolysis rates between open-chain allylic compounds and their five-membered cyclic analogues. Cyclopentenyl chloride solvolyses 149 times as fast as α,γ-dimethylallyl chloride in pure ethanol at 30° (84); cyclopentenyl bromide solvolyses 210 times as fast as α,γ-dimethylallyl bromide in 80% aqueous ethanol at 0° (96); 2-phenylcyclopentenyl p-nitrobenzoate solvolyses 18 times as fast as β-phenyl-α,γ-dimethylallyl p-nitrobenzoate in 80% dioxan at 140° (90). Leaving aside for the moment the question of differences in solvent, temperature, leaving group and reference compound structure, it is clear that the present results adhere to the same trend, at least as regards the first and third of the esters in Table 5. Now, in order to be able to explain

Table 5

RELATIVE SOLVOLYSIS RATES IN 80% ETHANOL

PNB = $COC_6H_4NO_2$

Ester	Relative Rates			
	80°	100°	80°	100°
	1.0	1.0		
	32.1	30.0	1.0	1.0
	828	603	25.9	20.1

the lack of reactivity of the 5,5-dimethylcyclopent-2-en-1-yl system towards S_N2' displacements by the postulated steric hindrance in the transition state, one would have liked to have seen a very considerable reduction in solvolysis rate of this system over the unsubstituted case, preferably to a figure below the rate of the open-chain analogue, since, as has already been discussed, an even more hindered open-chain allylic system, the 4,4-dimethylpent-1-en-3-yl system, appears to undergo S_N2' displacement with no appreciable difficulty. The fact that the 5,5-dimethylcyclopent-2-en-1-yl ester solvolysed 30-32 times faster than its open-chain analogue (although slower than the cyclopent-2-en-1-yl analogue by a factor of 21-26), militates against this postulated dominant role of the steric effect.

The following estimate of expected solvolysis rates of cis-2-methylhex-4-en-3-yl and cyclopent-2-en-1-yl p-nitrobenzoates is quite crude, as will be subsequently emphasised. It nevertheless is considered to be sufficiently good to indicate that both esters are normal allylic compounds and the present results are not out of line with previous results.

It has been shown (94) that trans-α,γ-dimethylallyl p-nitrobenzoate solvolyses in 60% aqueous acetone at 79.6° with $k_t = 78.8 \times 10^{-3}\ h^{-1} = 2.19 \times 10^{-5}\ sec^{-1}$.

Taking Y for 60% acetone as 0.8 (91), and making the reasonable assumption that the m value for this ester is the same as that for cyclopent-2-en-1-yl p-nitrobenzoate found in the present work (viz, 1.0), application of the Winstein-Grunwald equation [19] (95) yields the following estimate for the rate constant of trans,α,γ-dimethylallyl p-nitrobenzoate in 80% ethanol at 80°:

$$k_t = 3.47 \times 10^{-6} \text{ sec}^{-1}$$

Now, the differences between trans-α,γ-dimethylallyl p-nitrobenzoate and cis-2-methylhex-4-en-3-yl p-nitrobenzoate are two-fold: firstly, the configuration about the double bond is different, and, secondly, the α-methyl group in the first ester becomes an α-isopropyl group in the second. No information about the possible influence of the first point on the solvolysis rate could be found, so it is ignored in what follows. As regards the second point, the following crude estimate of its effect can be made by utilising data quoted by Vernon (97) on relative solvolysis rates in 99.5% formic acid at 44.6°:

$CH_2 = CH\text{-}CH_2Cl$ 1.0

$CH_2 = CH\text{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{-}Cl$ 5670

$CH_2 = CH-\underset{\displaystyle C(CH_3)_3}{\underset{|}{CH}}-Cl$ 2520

Obviously, a reasonable place to put $CH_2=CH-\underset{\displaystyle CH(CH_3)_2}{\underset{|}{CH}}-Cl$ in this data would be 2/3 of the way from the second entry to the third (two hydrogens out of three have been replaced by two methyl groups):

$CH_2 = CH-\underset{\displaystyle CH(CH_3)_2}{\underset{|}{CH}}-Cl$ 3570

i.e. substitution of an α-isopropyl for an α-methyl group lowers the rate by a factor of $\frac{3570}{5670} = 0.63$. Now, making the rather tenuous assumptions that this rate diminution will be unaffected by a) the presence of a γ-methyl group, b) the change in solvent and temperature from 99.5% formic acid at 44.6° to 80% ethanol at 80°, and c) the change in leaving group from chloride to p-nitrobenzoate, the anticipated rate constant for our open-chain p-nitrobenzoate in 80% ethanol at 80° would be

$k_t = 0.63 \times 3.47 \times 10^{-6}\ sec^{-1}$

$= 2.18 \times 10^{-6}\ sec^{-1}$

This compares with an actually-observed rate constant of $6.32 \times 10^{-7}\ sec^{-1}$ - i.e. it is within a factor of 3.5 of experiment.

As to the above-noted assumptions: - there is

insufficient data in the literature to test the validity of assuming lack of effect of a γ-methyl group; Vernon (97) is of the opinion that ignoring solvent and temperature changes is a crude, but justified, aid to comparison of relative rates; and, finally, data on the effect of changing leaving group on relative solvolysis rates is meager. However, some data quoted by Streitweiser (98) indicates that such changes in leaving group do not have too serious an effect on observed relative solvolysis rates: cyclopentyl chloride solvolyses 5.2 times as fast as isopropyl chloride in 50% ethanol at 95°, while cyclopentyl tosylate solvolyses 6.1 times as fast as isopropyl tosylate in anhydrous ethanol at 50°. The relative rates for the corresponding cyclohexyl compounds vs the isopropyl compounds are 0.36 and 0.17:1, respectively. Such small effects as these will not invalidate our conclusions. Further confirmation can be obtained from data of Goering (84, 93, 94, 99): cis-5-methylcyclohex-2-en-1-yl p-nitrobenzoate solvolyses in 80% acetone at 99.72° with $k_t = 1.37 \times 10^{-2}\ h^{-1}$, while α,γ-dimethylallyl p-nitrobenzoate solvolyses in 90% acetone at 99.61° with $k_t = 22.5 \times 10^{-3}\ h^{-1}$, i.e. 1.6 times as fast as the ring compound (ignoring the minor differences in conditions). Also, α,γ-dimethylallyl chloride solvolyses in

pure ethanol at 30° with $k_t = 7.59 \times 10^{-5}$ sec^{-1}, whereas cis-5-methylcyclohex-2-en-1-yl chloride, under the same conditions, has $k_t = 2.15 \times 10^{-5}$ sec^{-1}, a rate ratio of 3.4. In other words, the major differences in temperature and solvent between the two sets of esters makes a difference of a factor of only 2 to the relative rates.

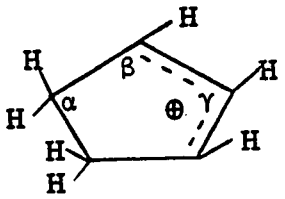
Reverting now to the estimation of the probable solvolysis rate of cyclopent-2-en-1-yl p-nitrobenzoate, we note again cyclopent-2-en-1-yl bromide solvolyses 210 times as fast as α,γ-dimethylallyl bromide in 80% ethanol at 0° (96). Using the rate diminution factor (deduced above) of 0.63 in going from the α,γ-dimethylallyl to the α-isopropyl-γ-methylallyl system (i.e. the 2-methylhex-4-en-3-yl system), we arrive at a figure of $\frac{210}{0.63} = 333$ for the expected relative solvolysis rate of cyclopent-2-en-1-yl bromide vs 2-methylhex-4-en-3-yl bromide. Finally, changing to p-nitrobenzoate will make an indeterminate, but small, difference in this relative rate. All things considered, the agreement with the observed rate ratio of 600-800 is surprisingly good, indicating that there is nothing unusual about the solvolysis of either 2-methylhex-4-en-3-yl or cyclopent-2-en-1-yl p-nitrobenzoate.

It is essential to stress once more that this estimate of the two solvolysis rates discussed above is very crude, depending to a considerable extent on ignoring

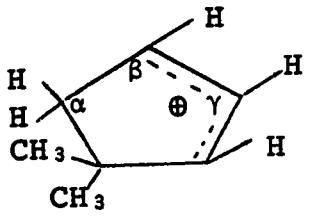
major differences in solvent, temperature, leaving group and so forth. It represents, however, the best estimate available, and its use is justified by the very reasonable agreement with experiment.

Consider now the case of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate. A very rough estimate of the anticipated difference in activation energies between this compound and cyclopent-2-en-1-yl p-nitrobenzoate may be made as follows:

Assume the solvolysis transition states for both cyclic esters resemble planar free carbonium ions. This is, of course, a crude approximation, but it is felt that resultant errors will tend to overestimate the energy differences.



A



B

Figure 11

Approximate representation of planar carbonium ions derived from Δ^2-cyclopentenyl esters

It may be shown that the angles involved in these ions are: $\alpha = 103.78°$, $\beta = 111.47°$, $\gamma = 109.50°$ (100). These angles are sufficiently close to the tetrahedral angle that the energy difference between hypothetical ions A and B may be approximated by the difference in non-bonded interactions.

Ion A contains 4 ethane-type H-H eclipsed interactions. Ion B contains 2 H-H and $2CH_3$-H butane-type interactions. Assigning values of 1 Kcal/mole and 1.8 Kcal/mole to these respective types - the former coming from the known rotational barrier of 3 Kcal/mole in ethane, and the latter from the 3.5 Kcal/mole energy difference between the eclipsed and staggered forms of n-butane (ref. (100), pp.29,31) - the energy difference between ions B and A becomes $(2 \times 1 + 2 \times 1.8) - (4 \times 1) = 1.6$ Kcal/mole. Granted that this is a very crude estimate, it ought, nevertheless, to represent a reasonable guess at the energy difference between the free, unsolvated ions B and A.

Transferring our attention to the respective transition states, which will include interactions involving both solvent and leaving group, these interactions will be more severe in case B than in case A, and the true energy difference will be somewhat higher than our crude estimate of 1.6 Kcal/mole.

Now, since the ground state energy of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate will undoubtedly be somewhat higher than that of its unsubstituted analogue, the transition state energy difference will have to be lowered by an amount equal to the ground-state energy difference, to arrive at the difference in activation energies for the two solvolyses. For proof, see below:

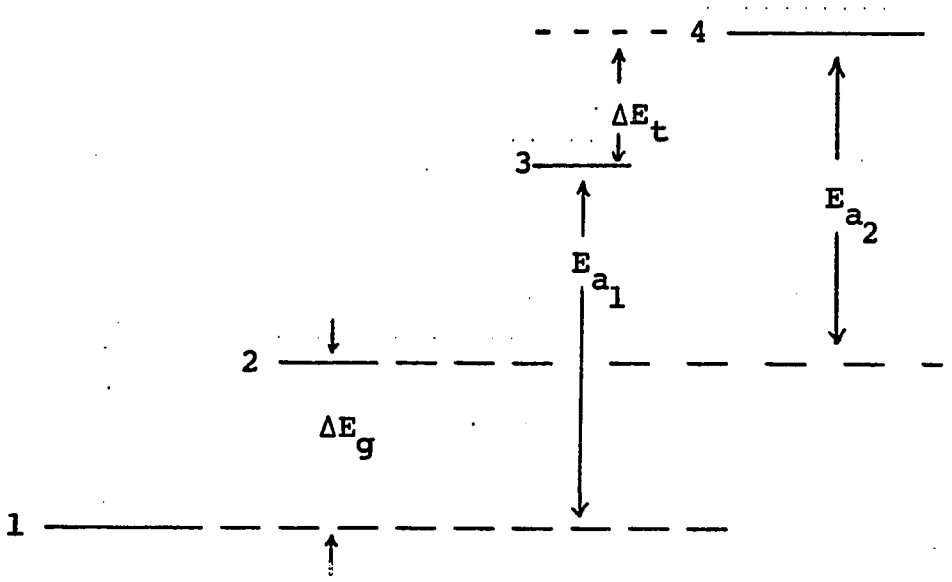


Figure 12

Energy level diagram for solvolyses of Δ^2-cyclopentenyl p-nitrobenzoates

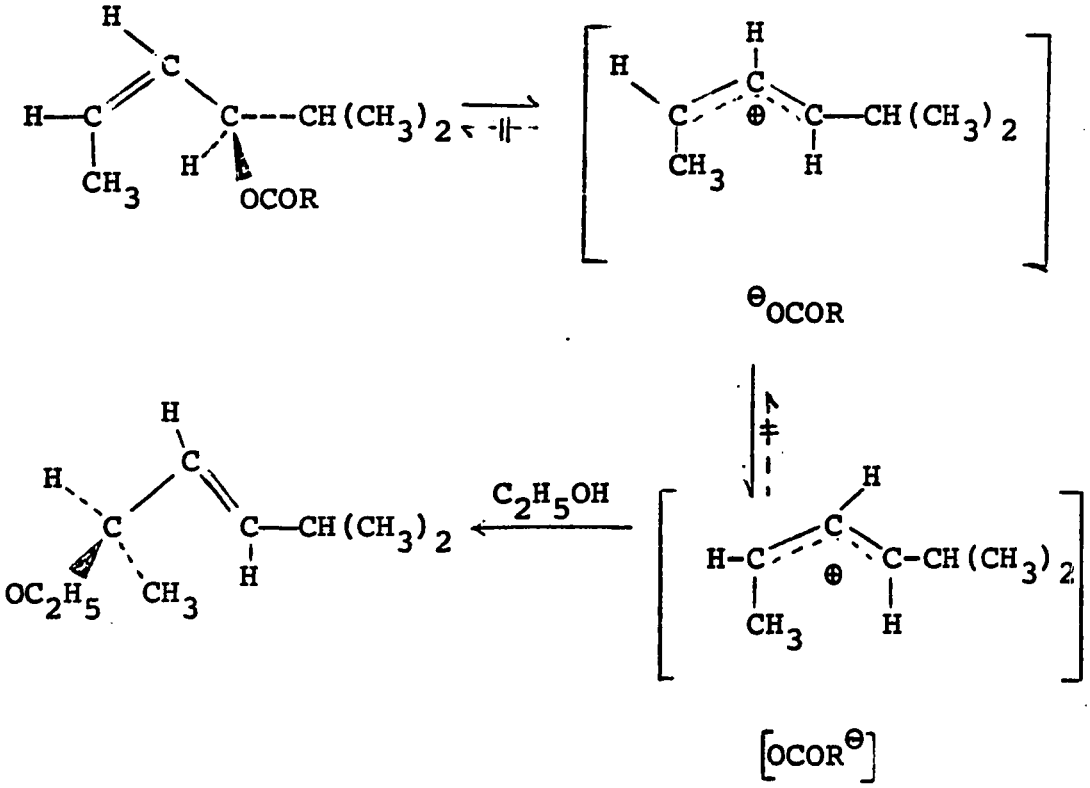
Here, 1,2 are the ground-state energy levels (the difference being ΔE_g), 3,4 are the transition-state energy levels (the difference being ΔE_t) and E_{a_1}, E_{a_2} are the respective activation-energies. We have, then, $E_{a_1} + \Delta E_t = E_{a_2} + \Delta E_g$, or $E_{a_2} - E_{a_1} = \Delta E_t - \Delta E_g$.

In view of the approximations pointed out in this discussion, the agreement between the calculated (1.6 Kcal/mole) and experimental (1.7-5.1 Kcal/mole) difference in activation energies is rather good, and suggests that the diminution in solvolysis rate, by a factor of 20-26, in proceeding from the cyclopent-2-en-1-yl system to the 5,5-dimethylcyclopent-2-en-1-yl system, is very largely steric in origin.

It follows, also, that, insofar as the transition state for the S_N2' reaction resembles that for unimolecular solvolysis, the observed rate diminution falls far short of accounting for the curious lack of S_N2' reactivity of the 5,5-dimethylcyclopent-2-en-1-yl system.

As far as the product studies reported herein are concerned, not too much information may be gleaned from the results. The observed formation of trans-5-methylhex-3-en-2-yl ethyl ether from cis-2-methylhex-4-en-3-yl p-nitrobenzoate can easily be rationalised on the basis of previous work: the intermediate ion-pair (78-85), arising from ionisation from the most stable conformation

of the ester (101), proceeds to dissociate to a free carbonium ion (93) which, while retaining its geometric configuration (101), is completely captured by the hydroxylic solvent (93) - thus, there is no external return (as well as no internal return from the ion pair) and no detectable disturbance in the kinetic plots.



SCHEME XX

Formation of trans-5-methylhex-3-en-2-yl ethyl ether from cis-2-methylhex-4-en-3-yl p-nitrobenzoate

In the case of the solvolyses of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate, the occurrence of 23% rearrangement in the unsolvolysed ester indicates internal return, since return from the disocciated carbonium ion would likely cause a detectable kinetic disturbance, which is not seen.

No speculation can be made about the occurrence or non-occurrence of internal return in the cyclopent-2-en-1-yl system, except that, if internal return occurs to the extent of 23% from the somewhat sterically-crowded 5,5-dimethylcyclopent-2-en-1-yl carbonium ion-p-nitrobenzoate anion ion pair, such internal return ought to be more extensive in the unsubstituted case.

The fact that internal return does occur in the substituted case may be taken as one more indication that the previously-advanced steric-crowding explanation for the lack of S_N2' reactivity in this system is totally inadequate.

One fact which follows from the present work is that neither the cyclopent-2-en-1-yl carbonium ion, nor the 5,5-dimethylcyclopent-2-en-1-yl carbonium ion is readily subject to electrocyclic ring opening, which would be, *a priori*, expected to be quite favorable. This observation is also supported by Zinck (90), who found 2-phenylcyclopent-2-en-1-ol to be the sole product of

solvolysis of the corresponding p-nitrobenzoate in aqueous dioxan. Zinck's study, and the present one, constitute the only product studies on solvolyses in Δ^2-cyclopentenyl systems.

Experimental

For the kinetic work reported herein, acetone and ethanol were both purified by methods reported by Fieser (103). The 80% solutions were prepared by mixing 80 volumes of the appropriate organic solvent with 20 volumes of carbon-dioxide-free water (distilled from potassium permanganate in an all-glass apparatus), both volumes being at 25.0° before mixing. Solutions of each ester in the appropriate mixed solvent were prepared by mechanical shaking and dilution to volume at 25.0°. Aliquots were removed by syringe and sealed in ampoules, these having been prepared from test-tubes which had been thoroughly cleaned with hot soap solution, then washed with tap water and distilled water, and dried in an oven. The sealed ampoules were then immersed in a properly-controlled and calibrated oil bath; three ampoules were removed from the bath after 7-10 minutes (to allow for temperature equilibration) and served as zero-time reference samples. These ampoules, as well as others which were removed, singly, from the bath from time to time, as

the solvolysis progressed, were quenched in ice-water, equilibrated to 25°, opened, aliquots removed by means of a pre-calibrated 5 ml. automatic pipette, drained into 50 ml methanol, and the solutions titrated with standardised, approximately 0.03 M, sodium hydroxide solution to the green end-point of α-naphtholbenzein (8 drops of 0.1% solution in anhydrous methanol). Blanks were run by the omission of ester solution and inclusion of an equal volume of solvent. The sodium hydroxide was frequently standardised against potassium hydrogen phthalate (104).

The data was treated according to the customary first-order equation, $k = \frac{2.303}{t} \log \frac{V_\infty - V_o}{V_\infty - V_t}$, and refined according to the procedure already explained. Selected sets of results were also treated graphically by plotting $\log (V_\infty - V_t)$ *vs.* t.

The selected individual experiments are given in detail in the final Section of this thesis.

Cyclopent-2-en-1-yl p-nitrobenzoate, 36:

Commercial dicyclopentadiene was cracked by dropping into hot paraffin oil, according to the procedure of Korach and co-workers (105). Cyclopentadiene (258 ml, 3.25 moles) was placed in a 500 ml measuring cylinder, cooled to -15°, and dry hydrogen chloride passed in until

the volume had increased to 318 ml; the data of Alder and Flock (106) would require a total volume of 329 ml, but this volume could not be reached. The temperature was kept below -10°.

The resultant crude solution of 3-chlorocyclopentene was hydrolysed (106) by slow addition (0.5 h) to well-stirred saturated sodium bicarbonate solution (800 ml) in a 4-litre beaker, the temperature being kept near 0°. After 2 h further stirring at 0°, evolution of carbon dioxide had ceased. The alkaline solution was then saturated with sodium chloride and thoroughly extracted with pure ether or n-pentane. (The use of commercial wash ether led to significant amounts of ethyl p-nitrobenzoate in the final product). The organic solution was then dried over anhydrous sodium sulfate and carried over directly to the next step.

The organic solution was transferred to a 3-litre 3-necked flask fitted with a thermometer, mechanical stirrer and reflux condenser. Triethylamine (180 ml, 132 g, 1.3 moles) was added, followed by slow addition of recrystallised p-nitrobenzoyl chloride (185.5 g, 1 mole) over a period of 0.5 h, keeping the temperature between 10° and 15°C. Stirring was allowed to continue overnight; the mixture was then filtered, the triethylamine hydrochloride washed well with dry ether, and the combined

organic solutions transferred to a rotary evaporator for removal of solvent.

The resultant dark liquid soon crystallised in the refrigerator. The solid cake was broken up, filtered, and recrystallised twice from n-pentane, then twice from ether-pentane (1:1). M.P. 79.5-80.2°. Yield 105 g (0.48 mole, 48% on acid chloride, 15% overall). Analysis, calcd. for $C_{12}H_{11}NO_4$: C 61.80; H 4.75; N 6.01. Found: C 61.93; H 4.76; N 6.12. The n.m.r. spectrum (CCl_4) showed peaks at τ1.75 (s, phenyl protons), 3.65-4.20 (complex m, olefinic and methine protons) and 7.35-8.15 (complex m, methylene protons), in the ratio 4.00:2.94:4.16, required 4.0:3.0:4.0. The infrared spectrum exhibited absorption at 1720 cm^{-1} (ester carbonyl, V.S.).

2-Methylhex-4-yn-3-ol, 38:

This compound was prepared in 89% yield from methylacetylene magnesium bromide and isobutyraldehyde according to the procedure of Favorskaya, et al. (87). This procedure calls for the addition of isobutyraldehyde to the Grignard reagent after the latter has separated into two layers. This did not occur for many hours after the preparation of the Grignard; it was also noted that 16 h. after this preparation, there was a powerful odor

of methylacetylene around the flask, due to gas evolution from the Grignard solution. A further charge of methylacetylene was added, the solution stirred 3 h. at 0°, and the isobutraldehyde then added according to directions, following which the mixture was permitted to stand 7 days, as the Russian workers call for. This may not be necessary, but the point was not investigated.

After workup, distillation yielded a small amount of solid product, not mentioned by Favorskaya (87), at 43°/37mm. The constitution of this was not investigated. The desired product boiled at 86-88°/37mm. n_D^{25} = 1.4517. Reported (87): B.P. 99°/90mm, n_D^{20} = 1.4510. The n.m.r. spectrum (CCl_4) showed peaks at τ5.95 (m, approximately 7 lines, methine proton), 6.49 (broad s, OH proton), 8.20 (d) and 7.90-8.50 (m) (acetylenic methyl group + isopropyl proton) and 9.10 (d, isopropyl methyl groups, J = 7 Hz) in the ratio 0.90:0.75:4.10:6.00, required 1:1:4:6. The infrared spectrum (CCl_4) showed no bands for olefinic carbon-carbon stretch.

cis-2-Methylhex-4-en-3-ol, 39:

The hydrogenation of 38 was carried out by dissolving 38 (34.6 g, 0.31 mole) in dry pyridine (100 ml), adding 0.575 g of 1.51% palladium oxide on barium sulfate, and hydrogenating at room temperature and

approximately 40 psi pressure in a Paar shaker apparatus. The expected pressure drop was 21.7 psi; the observed drop was 23.2 psi after 44 h.

The solution was filtered to remove catalyst, and then carried on to the esterification step (see below). The structure of the product was confirmed by saponification of its recrystallised p-nitrobenzoate, 37, (q.v.), by the following procedure: 37 (15 g, 0.057 mole) was stirred overnight with a solution of potassium hydroxide (7 g, 0.125 mole) in dry methanol (100 ml). The mixture was then filtered, the solid washed well with methanol, an equal volume of water added to the combined filtrate and washings, and the whole extracted with n-pentane (3 x 60 ml). The pentane solution was washed with water (1 x 75 ml), then dried over anhydrous sodium sulfate and the solvent largely removed by distillation at atmospheric pressure through a Vigreux column.

The residual solution was then subjected to distillation under reduced pressure. B.P. 66-68°/21 mm, n_D^{25} = 1.4399. Reported constants for the trans-isomer: B.P. 55-57°/18 mm (107); $n_D^{21.4}$ = 1.4377 (107); n_D^{17} = 1.4322 (108). The yield in this step was only 1.1 g (0.01 mole 17%), but an additional quantity was recovered by re-extraction of the aqueous alcoholic solutions with methylene chloride, then proceeding as before. The B.P.

this time was 60-62°/18 mm. Total yield, 4.1 g, 0.036 mole (63%).

The n.m.r. spectrum showed peaks at τ4.20-4.90 (complex m, not amenable to easy analysis, olefinic protons), 5.95 (t, further split, methine proton), 7.10, (s, hydroxyl proton), 8.40 (d, J = 7 Hz) and 8.00-8.90 (m) (olefinic methyl protons + isopropyl methine proton), and 9.15 (4 lines, isopropyl methyl protons), in the ratio 2.00:1.00:1.00:4.00:6.00, required 2:1:1:4:6. The infrared spectrum exhibits bands at 3520 (M, free OH), 3400 (M, bonded OH), 3018 (M, olefinic carbon-hydrogen stretch) and 1655 cm^{-1} (W, olefinic carbon-carbon stretch for a cis-disubstituted olefin, (ref. (92)), p.33).

cis-2-Methylhex-4-en-3-yl p-nitrobenzoate, 37:

The pyridine solution of 39 (prepared as described above, and assumed to contain 0.31 mole of 39) was transferred to a 500 ml 3-necked flask fitted with a thermometer, mechanical stirrer and reflux condenser. The solution was stirred and cooled to 0°, and recrystallised p-nitrobenzoyl chloride (57.5 g, 0.31 mole) added over a 20 min. period, keeping the temperature in the range 0-5°. After 2 h. additional stirring, the entire mixture was poured into ice-water, with stirring. The precipitated solid was filtered off, washed with ice-water and dissolved

in ether. The ether solution was washed with fresh water, dried over anhydrous sodium sulfate, decanted and evaporated to dryness.

The solid residue was dissolved in ether-hexane (5:100) and the solution was evaporated to incipient crystallisation. The small amount of white solid deposited at this point was isolated by filtration and discarded. The filtrate was evaporated to a low volume, cooled and refiltered. The solid was recrystallised at low temperature from the minimum amount of n-hexane. Yield, 30.5 g (0.12 mole, 37.4% from 38). M.P. 64.1-65°. Analysis, calcd. for $C_{14}H_{17}NO_4$: C 63.86; H 6.51; N 5.32. Found: C 63.77; H 6.50; N 5.45. The n.m.r. spectrum ($CDCl_3$) showed peaks at τ1.75 (s, phenyl protons), 4.05-4.65 (complex m, olefinic + methine protons), 8.25 (two d, 5 Hz apart) and 7.90-8.40 (complex m) (olefinic methyl protons + isopropyl methine proton) and 9.05 (two d, separation 7 Hz, isopropyl methyl protons) in the ratio 4.00:2.96:4.08:6.00, required 4:3:4:6. The infrared spectrum showed carbonyl absorption at 1715 cm^{-1} (VS): the olefinic carbon-carbon stretching band was not apparent.

5,5-Dimethylcyclopent-2-en-1-yl ethyl ether, 6 (X=OC_2H_5):

A suspension of sodium hydride (6.5 g NaH, 0.27

mole) in dry dimethylformamide was prepared in a 250 ml 3-necked flask, fitted with mechanical stirrer, constant pressure dropping funnel, and reflux condenser. To this was added a solution of 5,5-dimethylcyclopent-2-en-1-ol (6, X=OH) (5.73 g, 0.05 mole) in dimethylformamide (10 ml) at such a rate as to keep the very copious evolution of hydrogen under control

After gas evolution had ceased, the suspension was cooled to 0° and a solution of ethyl iodide (18 g 0.87 mole) in dimethylformamide (30 ml) was added over 15 min. with continuous stirring. Stirring was allowed to continue overnight; excess hydride was destroyed by the cautious additon of water, and the solution was extracted with n-pentane (3 x 100 ml). The combined organic layers were washed with water (2 x 150 ml) and dried over anhydrous sodium sulfate. The pentane was largely removed by distillation at atmospheric pressure, and the residual solution was subjected to distillation under vacuum. B.P. 58-58.5°/43 mm. $n_D^{28.5}$ = 1.4295. Yield 2.1 g, 0.015 mole (29%). Inspection by GLC disclosed that this material was at least 98% pure. A molecular analysis was not obtained; however, an accurate determination of molecular weight by mass spectrometry gave a result of 140.1200 (calcd. for $C_9H_{16}O$:140.1201). The n.m.r. spectrum (CCl_4) (Figure 3) showed peaks at τ4.25 (s,

slightly perturbed, olefinic protons), 6.20 (s, slightly perturbed, methine proton), 6.58 (q, showing some further splitting, methylene protons of ethyl group), 7.9 (essentially t, ring methylene protons), 8.75 (s) and 8.95 (three lines) (gem-dimethyl and ether methyl protons) in the ratio 2.09:1.00:2.09:2.00:9.78, required 2:1:2:2:9. The reason for the excess in the methyl region is not known. The infrared spectrum (CCl_4) showed three distinct peaks in the 1100 cm^{-1} region (1080, 1110, 1120, all VS) and olefinic carbon-hydrogen stretching at 3060 cm^{-1} (S).

cis-2-Methylhex-4-en-3-yl ethyl ether, 40:

As described previously, pure cis-2-methylhex-4-en-3-ol, 39, was prepared by saponification of the p-nitrobenzoate, 40. A solution of 39 (4.0 g, 0.035 mole) in purified tetrahydrofuran (30 ml) was added dropwise to a stirred suspension of sodium hydride (12 g NaH, 0.5 mole) in tetrahydrofuran (50 ml), contained in a 250 ml three-necked flask fitted with a stirrer, reflux condenser, drying-tube and constant-pressure dropping funnel. After addition (40 min) was over, the solution was refluxed 30 min, cooled to room temperature, and pure ethyl iodide (35 g, 0.22 mole) was added over a 15 min. period. Not much heat was evolved, but there was slow, steady evolution of gas.

Stirring was permitted to continue overnight. The solution was then refluxed for 1 h and cooled, and excess hydride was destroyed by cautious addition of water. Sufficient water was added to produce a clear solution, which was then extracted with methylene chloride (3 x 50 ml). The methylene chloride solution was then washed with water (50 ml), dried over anhydrous sodium sulfate, and the major part of the solvent removed by distillation at atmospheric pressure through a Vigreux column. The residue was then subjected to distillation in vacuo. B.P. 52-53°/35mm. n_D^{26} = 1.4148. Yield, 2.67 g, 0.019 mole (54.3%). The GLC showed excellent purity. Accurate molecular weight by mass spectrometry: 142.1358. Calcd. for $C_9H_{18}O$: 142.1358. The n.m.r. spectrum (CCl_4) showed peaks at τ4.10-5.00 (very complex m, about 18 different lines, not subject to ready analysis, olefin protons), 6.20-7.00 (very complex m, about 16 lines, ether methylene protons plus methine proton), 8.35 (two doublets. J = 1-2 Hz, separation 7 Hz), 8.8-9.25 (7 lines) and 8.10-9.50 (complex m) (altogether comprising the olefinic, ether and isopropyl methyl protons, plus the isopropyl methine proton) in the ratio 2.00:2.96:13.1, required 2:3:13. The infrared spectrum (CCl_4) shows two bands in the 1100 cm^{-1} region (1088, 1105, both VS), olefinic carbon-carbon stretch at 1655 cm^{-1} (W, cis-

disubstituted olefin), and olefinic carbon-hydrogen stretch at 3010 cm^{-1} (M).

Note: The complexity of the ether methylene region in the n.m.r. spectrum is undoubtedly caused by the magnetic non-equivalence of these protons, as they are situated very close to an asymmetric centre. That it is not due to fortuitous restricted rotation was shown by dissolving a sample of this compound in chlorobenzene and observing the n.m.r. spectrum at temperatures up to 100°C. No change in the methylene peaks could be seen.

Cyclopent-2-en-1-yl ethyl ether, 41:

Cyclopentanol (100 g, 1.16 moles) was dehydrated to cyclopentene with syrupy phosphoric acid, according to the procedure of Kogl (109). Yield 62.5 g, 0.92 moles (79%). trans-1,2-Dibromocyclopentane was then prepared according to Weinstock (110). Yield, 151 g (0.66 mole, 72%).

A solution of sodium (20 g, 0.87 mole) in absolute ethanol (410 ml) was prepared in a 2 litre 3 necked flask fitted with a stirrer, a reflux condenser, a drying tube and a constant-pressure dropping funnel. This solution was stirred and heated to near the boiling-point, and trans-1,2-dibromocyclopentane (75.6 g, 0.33 mole) was added over a 1.5 h. period. The violent reaction

mentioned by Levina (89) did not materialise; this reaction was smooth and readily controlled. After addition was over, the mixture was heated 16 h. on the steam-bath, then stirred for an additional 24 h.

The mixture was poured into an equal volume of water and extracted with ether (6 x 300 ml). The combined organic layers were washed with water (2 x 300 ml) and dried over anhydrous sodium sulfate. The bulk of the solvent was then removed at atmospheric pressure by distillation through a Vigreux column surmounted by a partial-reflux head. The residue was then distilled at atmospheric pressure; a large amount of material boiling from 78-80° was obtained, which doubtless was ethanol. The desired product distilled at a B.P. of 110-111°/ 700 mm. n_D^{25} = 1.4320. Reported (89): B.P. 120-121°/ 751 mm. n_D^{20} = 1.4426. The yield was only 2 g (0.018 mole, 5.4%). Although inspection by GLC did not show any serious impurity, the presence of bromine in this product was signalled by the fairly rapid development of a yellow color. Nevertheless, the spectra were satisfactory, and, in particular, the n.m.r. spectrum was sufficiently definitive for the purposes of this investigation. In CCl_4 solution, the n.m.r. spectrum showed peaks at τ4.15 (complex m, olefin protons), 5.55 (complex m, methine proton), 6.58 q, side-chain methylene protons), 7.50-8.40

(complex m, ring methylene protons) and 8.90 (t, methyl protons) in the ratio: 2.00:1.00:2.45:3.81:3.37, required 2:1:2:4:3. See Figure 7.

trans-5-Methylhex-3-en-2-one, 43:

A mixture of acetone (116 g, 2 moles) and 10% sodium hydroxide solution (340 ml) was prepared in a 1 litre 3 necked flask fitted with a mechanical stirrer, reflux condenser and constant-pressure dropping funnel. To this solution was added isobutyraldehyde (144 g, 2 moles) over 8-10 h., with no attempt made to control the temperature. The mixture was stirred for a further 36 h.; the upper layer was then separated, the aqueous layer extracted with methylene chloride (2 x 250 ml), the combined organic layers washed with anhydrous sodium sulfate, and the bulk of the solvent was removed by slow distillation at atmospheric pressure through a Vigreux column surmounted by a partial-reflux head. The residue was then subjected to distillation in vacuo. B.P. 73-80°/mm. $n_D^{24.8}$ = 1.4392. Reported (88) B.P. 60-63°/16 mm, n_D^{20} = 1.4463,giving upon redistillation the following fractions: B.P. 76.5°/5lmm, n_D^{20} = 1.4395, the non-conjugated isomer, 5%; B.P. 77-8°/5lmm, n_D^{20} = 1.4423, the conjugated isomer, 95%. Yield 99g (0.88 mole, 44%).

It is obvious that the physical constants found

here are rather too far from those for the desired, conjugated isomer. That this isomer was, indeed, the major product is confirmed by the spectra, which also show that there was present some acetone. No attempt was made to remove this before the next step.

The n.m.r. spectrum (CCl_4) showed the expected AB part of an ABX system for the olefin protons: lines 1 and 2, of equal intensity, centre τ3.12, separation 6.5 Hz; lines 3 and 4, intensity approximately 2, centre τ3.40, separation 6.5 Hz; lines 5 and 6, intensities 2.5 and 2, respectively separation 1 Hz, centre τ3.92; lines 7 and 8, intensities 1.2 and 1, separation 1 Hz, centre τ4.22. From this pattern, the coupling constant between the two olefinic protons is 16 Hz, confirming the trans-structure; the chemical shifts involved confirm the conjugated nature of the product.

As well as these peaks, the spectrum contains a very complex region from τ7.38-8.40, a sharp singlet τ7.85, and a doublet, separation 6.5 Hz, centre τ8.92. This whole region comprises the isopropyl methine, acetyl methyl and isopropyl methyl protons. The ratio of the olefin region to this complex region is 2.00:12.32, required 2:10. The excess in the second region is ascribed to acetone.

The infrared spectrum shows bands at 1698 (carbonyl, α,β-unsaturated ketone, VS), 1675 (alkene, disub-

stituted, trans, VS), 1625 (apparently a small proportion of the non-conjugated olefin band, VS), and shoulders at 1640, 1650 and 1715 cm^{-1} (the latter seems to be the carbonyl of acetone).

trans-5-Methylhex-3-en-2-ol, 44:

This preparation was modelled on that previously developed for 5,5-dimethylcyclopent-2-en-1-ol. A suspension of lithium aluminum hydride (17 g, 0.45 mole) in dry ether (300 ml) was prepared in a 2 litre three-necked flask, fitted with a reflux condenser, mechanical stirrer, drying tube and constant-pressure dropping funnel. This suspension was cooled to -8°, and anhydrous aluminum chloride (19.7 g, 0.15 mole) was cautiously added, in small portions, over approximately 20 min.

After 15 min. additional stirring, the mixture was warmed to room temperature, and a solution of crude 43, prepared as described above (99 g, 0.88 mole) in dry ether (300 ml) was added over a 3.5 h. period. Stirring was then permitted to continue overnight. The mixture was decomposed by the cautious addition of water (17 ml), 15% sodium hydroxide solution (51 ml) and water (51 ml), in that order, with continuous stirring and cooling. The supernatant liquid was then decanted off, the solids washed well with ether, the combined ether fractions

dried over anhydrous sodium sulfate, and the major part of the solvent removed by distillation at atmospheric pressure. The residual solution was then subjected to distillation in vacuo. A large amount of forerun was collected from 30-78°/51 mm. The major fraction 4 boiled at 78-81°/51 mm. $n_D^{23.8}$ = 1.4293. There was a considerable amount of very high-boiling material left. Yield, fraction 4, 32.3 g, 0.28 mole (32%). Inspection by GLC showed three peaks, in the ratio 70:20:10 (the last having the same retention time as the starting ketone, 43).

Purification of 44 was performed by hydrolysis of the recrystallised p-nitrobenzoate, 45 (q.v.). This saponification was performed using 18.7 g (0.07 mole) 45, and potassium hydroxide (4.4 g, 0.09 mole) in refluxing methanol (100 ml) for 10 min., followed by work-up as for the saponification of 37 to 39.

B.P. 86-88°/74 mm. n_D^{24} = 1.4310.

Yield 5.7 g = 0.05 mole = 70%. This material still exhibited two close peaks in the GLC (approximate ratio 90:10). No attempt at further purification was made. The n.m.r. spectrum (CCl_4) showed peaks at τ4.55 (approximately 5 lines, olefin protons), 5.90 (broad t, methine proton), 6.80 (broad s, hydroxyl proton), 7.50-8.10 (7 lines, split into doublets, isopropyl methine proton), and 8.70-9.10 (t plus d, all methyl protons), in the ratio

2.00:1.00:1.00:1.20:13.20, required 2:1:1:1:10. The infrared spectrum (CCl_4) shows bands at 3620 (free OH, M), 3450 (broad, bonded OH, S), and 1670 cm^{-1} (olefin, disubstituted, trans, W). The nature of the impurity or impurities is not known.

trans-5-Methylex-3-en-2-yl p-nitrobenzoate, 45:

Fraction 4 from the distillation of 44 (see above; 32.3 g, 0.28 mole) was dissolved in dry pyridine (300 ml) in a 1 litre 3-necked flask fitted with thermometer, stirrer and reflux condenser. The solution was cooled to -10°, and recrystallised p-nitrobenzoyl chloride (52.5 g, 0.28 mole) added over 30 min., the temperature being kept below 0°. Stirring was allowed to continue overnight, and the mixture was then poured into ice-water. The resultant solid was filtered under suction, dissolved in ether, the ether solution washed with ice-water, dried over anhydrous sodium sulfate, and transferred to a rotary evaporator for removal of solvent. The recovered solid was recrystallised several times from n-hexane at -20°. Very careful workup was required to recover the product, due to its surprisingly high solubility. Yield, 18.7 g (0.07 mole, 25%). M.P. 47.7-48°. Analysis, calcd. for $C_{14}H_{17}NO_4$: C 63.86; H 6.51; N 5.32. Found: C 63.86; H 6.89; N 5.58.

The n.m.r. spectrum (Figure 8) ($CDCl_3$ solution), showed peaks at τ1.80 (s, phenyl protons), 3.90-4.60 (complex m, olefin + methine protons), 7.50-7.90 (complex m, isopropyl methine proton), 8.52 (d, methyl group attached to carbon bearing ester group), and 8.90 (d, isopropyl methyls) in the ratio 4.00:3.10:12.1 (the latter covering the last three quoted n.m.r. regions), required 4:3:10. Please note that the methyl region is again in excess, as for the previously-described compounds in this trans-series; note also that the above-quoted M.P. was sharp, and not improved by recrystallisation. The infrared spectrum ($CHCl_3$) showed bands at 1720 (carbonyl VS) and 1670 cm^{-1} (olefin, disubstituted, trans, W).

trans-5-Methylhex-3-en-2-yl ethyl ether, 42:

The "purified" 44 (5.7 g, 0.95 mole) was dissolved in dry dimethylformamide (30 ml) and added over 20 min. to a suspension of sodium hydride (4 g, 0.17 mole) in dimethylformamide (150 ml), contained in a 500 ml 3 necked flask fitted with a reflux condenser, stirrer and constant-pressure dropping funnel. Evolution of hydrogen was rapid and copious. The mixture was then heated to 80° for 1 h., cooled, and ethyl iodide (24 g, 0.15 mole) added over 1 h. There was again copious

evolution of gas. The mixture was then permitted to stand overnight, sufficient water cautiously added dropwise to produce a clear solution, then this was extracted with methylene chloride (3 x 150 ml). The combined extracts were washed with water (2 x 150 ml), dried over anhydrous sodium sulfate, and subjected to distillation at atmospheric pressure to remove the bulk of the solvent. When the remaining solution was subjected to distillation in vacuo, a fraction boiling at 56-63°/73 mm was obtained. This was shown to contain dimethylformamide plus a major portion of the desired product, with no 44 present. Later fractions contained higher proportions of dimethylformamide.

Since only enough 42 was required for an n.m.r. spectrum, the fraction rich in product was subjected to preparative GLC. With difficulty, the two closely-eluting product peaks (90:10 ratio) could be separated. The isolated product had $n_D^{25.3} = 1.4108$. An analysis was not obtained; the accurate molecular weight was 142.1358 (calcd. for $C_9H_{18}O$: 142.1358).

The n.m.r. spectrum (CCl_4, figure 6) showed peaks at τ4.50-5.00 (AB part of ABX; J_{AB} = 15 Hz; olefin protons); 6.40-7.00 (triplet + complex m, ether methylene protons + methine proton); 7.85 (m, isopropyl proton) and 9.10 (complex, m, methyl protons) in the ratio 1.95:3.50:1.00:12.50, required 2:3:1:12.

Solvolysis of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate

A solution of 5,5-dimethylcyclopent-2-en-1-yl p-nitrobenzoate (0.807 g, 3.09 millimoles) in 80% ethanol was diluted to 100 ml at 25° with 80% ethanol. One aliquot (25 ml) was sealed in one ampoule and heated for 18 half-lives at 100°. The remaining 75 ml was heated for one half-life at 100°.

Interrupted solvolysis:

The latter ampoule was opened after one half-life and the contents thoroughly evaporated. Now, this much solution originally contained 3/4 x 3.09 = 2.32 millimoles ester; we should therefore recover 1.16 millimoles ester (= 0.303 g) plus 1.16 millimoles p-nitrobenzoic acid (0.194 g). Theoretical recovery = 0.497 g. Actually recovered, 0.475 g (95.6%). This mixture of unsolvolysed ester and p-nitrobenzoic acid was submitted for n.m.r. inspection in $CDCl_3$ solution (Figure 9). The peaks are: τ1.75 (s, phenyl of original p-nitrobenzoate, Figure 9, lower spectrum), 1.83 (s, phenyl of rearranged ester), 3.8-4.3 (complex m, olefins of both esters plus methine of rearranged ester), 4.45 (broad s, methine of unrearranged ester), 7.65 (m, methylenes of unrearranged ester), tailing off into AB spectrum of

methylenes of rearranged ester (approximately τ8.0) and 8.85 (perturbed d, both types of methyl groups). The spectrum is amenable to analysis as follows: ratio, τ3.8-4.3 region: τ4.45 peak:methyl region = 23.8:7.8:62. Assume that τ4.45 peak is the methine of unrearranged ester, and that the methine signal of rearranged ester is buried under the olefin region.

Then 2 x 7.8 = 15.6 = that part of the olefin region due to olefin signals of unrearranged material. This leaves 23.8-15.6 = 7.2 to be due to 3 protons (olefin + methine) of rearranged material (1 proton = 2.4). This makes 2 x 7.2 = 14.4 of the 62 in the methyl region to be due to rearranged ester, leaving 62-14.4 = 47.6 to be due to unrearranged ester. This 47.6 will be equivalent to 6 protons, or 1 proton = 7.9, checking with our original assumption that 1 proton = 7.8 in the unrearranged material. Hence we have the ratio rearranged ester:unrearranged ester = 2.4:7.8 or amount of rearranged ester present = $\frac{2.4}{10.2}$ x 100 = 23.5%. The two phenyl peaks tend to confirm this analysis, being in the approximate ratio of 3:1 (peak heights, τ1.75 and 1.83 respectively).

Product analysis:

The 25 ml aliquot was heated for 18 half-lives cooled and opened. A 10 ml portion was set aside and the

remainder was poured into an equal volume of water and thoroughly extracted with methylene chloride (3 x 80 ml). The methylene chloride solution was washed with cold 5% potassium hydroxide solution (2 x 100 ml) then with saturated brine (1 x 100 ml) and finally dried over anhydrous sodium sulfate. The bulk of the solvent was removed by slow distillation through a Vigreux column, surmounted by a partial reflux head.

Submission of the remaining solution to GLC inspection disclosed three peaks (ratio approximately 90:5:5) eluting after methylene chloride. The major peak had the same retention time as 5,5-dimethylcyclopent-2-en-1-yl ethyl ether (SE-30, 83°, 43 ml/min He).

A weighed quantity of cumene was added to the 10 ml of the aqueous alcoholic solution which had been set aside. The areas of the GLC peaks due to the major solvolysis product and to cumene were computed, and the yield of the major was then derived from this data and from the relative areas obtained from an accurately-weighed mixture of 5,5-dimethylcyclopent-2-en-1-yl ethyl ether (assumed to have the same response factor, as well as the same retention time, as the major product) and cumene. The yield was determined to be 99%, and 94%, in two separate experiments.

Isolation of the major product and analysis of its n.m.r. spectrum showed it to consist of 88% 4,4-dimethylcyclopent-2-en-1-yl ethyl ether plus 12% of the 5,5-isomer. See Figure 3. The peak used for computation of relative proportions was the methine peak of the 5,5-isomer, which appears in both spectra in Figure 3.

Solvolysis of cis-2-methylhex-4-en-3-yl p-nitrobenzoate:

The method here was operationally similar to that described in the previous section. The major product, obtained in 54% yield, had the n.m.r. spectrum shown in Figure 6. The peaks are τ4.4-4.9 (AB of ABX system, further split, olefins of trans-5-methylhex-2-en-3-yl ethyl ether), 6.25-6.95 (t + m, ether methylenes plus methine, trans-ether, plus additional peaks), 7.75 (5 lines, isopropyl methine), 8.35 (approximate d, origin unknown), and 8.8-9.2 (very complex, methyl region). The ratio here is 30:41:12:23:172, and simple computation shows that this integration can't be reconciled with the theory that the τ8.35 peaks might be due to trans-2-methylhex-4-en-3-yl ethyl ether, as expressed in the Product Studies section of this Chapter.

In the interrupted solvolysis, comparison of the spectra of recovered, unsolvolysed ester (Figure 8, upper spectrum), authentic starting ester (Figure 8,

middle spectrum) and trans-5-methylhex-3-en-2-yl p-nitrobenzoate, the anticipated product of internal return with rearrangement (Figure 8, lower spectrum), confirms that little or no internal return has occurred.

Solvolysis of cyclopent-2-en-1-yl p-nitrobenzoate:

Interrupted solvolysis: Comparison of the spectra of recovered, unsolvolysed ester (Figure 10, upper spectrum) and starting ester (Figure 10, lower spectrum) confirms that no return from a ring-opened carbonium ion (Equation [14]) has occurred (absence of vinyl methylene signals).

Product Study: Comparison of the spectra of the crude solvolysis product (Figure 7, upper spectrum) and of crude cyclopent-2-en-1-yl ethyl ether, 41 (Figure 7, lower spectrum) confirms that the major product of this solvolysis is, indeed, 41. The yield was determined to be 92%.

Table 6

SOLVOLYSIS OF cis-2-METHYLHEX-4-EN-3-YL P-NITROBENZOATE IN 80% AQUEOUS ETHANOL AT 80.05° RUN A-3

Aliquot: 4.968 ml Titrant: NaOH (0.0349M)
Indicator: α-naphtholbenzein
Ester conc: 2.698×10^{-2}M. Theoretical V_∞: 3.837 ml

Time (10^4 sec)	Vt (ml)	log $(V_\infty - V_t)$	$10^7 k_t$ (sec^{-1})
0.000	0.020	0.5817	
0.843	0.034	0.5801	4.37*
15.68	0.392	0.5372	6.54
34.27	0.719	0.4939	5.90
51.65	1.061	0.4434	6.17
76.15	1.486	0.3713	6.36
102.2	1.852	0.2978	6.40
137.5	2.337	0.1761	6.79
173.6	2.622	0.0845	6.60
215.9	2.729	0.0444	5.73
276.2	3.042	$\bar{1}$.9004	5.68
413.1	3.292	$\bar{1}$.7364	4.71*
1350 (∞)	3.801		

* Omitted from average

$k_t = (6.24 \pm 0.32) \times 10^{-7}$ sec^{-1}

From graph, $k_t = 6.44 \times 10^{-7}$ sec^{-1}

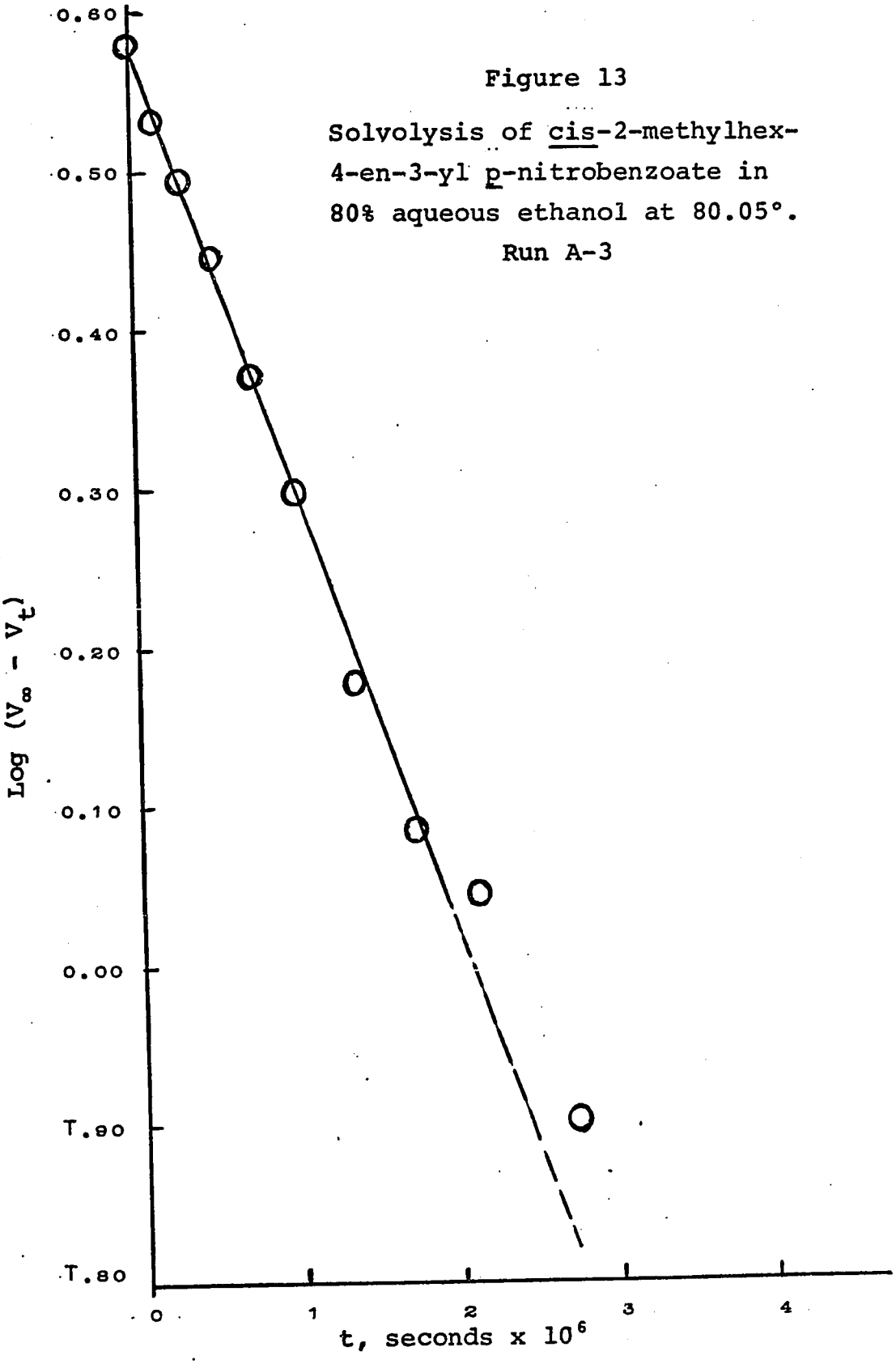


Figure 13

Solvolysis of cis-2-methylhex-4-en-3-yl p-nitrobenzoate in 80% aqueous ethanol at 80.05°. Run A-3

Table 7

SOLVOLYSIS OF cis-2-METHYLHEX-4-EN-3-YL P-NITROBENZOATE IN 80% AQUEOUS ETHANOL AT 100.0° RUN A-4

Aliquot: 5.019 ml Titrant: NaOH (0.0342 M)
Indicator: α-naphtholbenzein
Ester conc: 2.577×10^{-2} M Theoretical V_∞: 3.786 ml

Time (10^4 sec)	V_t (ml)	Log $(V_\infty - V_t)$	$10^6 k_t$ (sec^{-1})
0.000	0.024	0.5754	
0.4216	0.087	0.5681	3.99*
2.125	0.360	0.5348	4.40*
7.486	1.228	0.4079	5.15
9.166	1.471	0.3645	5.30
10.87	1.657	0.3281	5.24
16.30	2.217	0.1956	5.37
18.78	2.406	0.1399	5.34
27.07	2.855	$\bar{1}$.9689	5.16
34.18	3.076	$\bar{1}$.8513	4.88
142.6 (∞)	3.654		

* Omitted from average

$k_t = (5.20 \pm 0.12) \times 10^{-6}$ sec^{-1}

From graph, $k_t = 5.42 \times 10^{-6}$ sec^{-1}

Figure 14

Solvolysis of cis-2-methylhex-4-en-3-yl p-nitrobenzoate in 80% aqueous ethanol at 100.0°. Run A-4

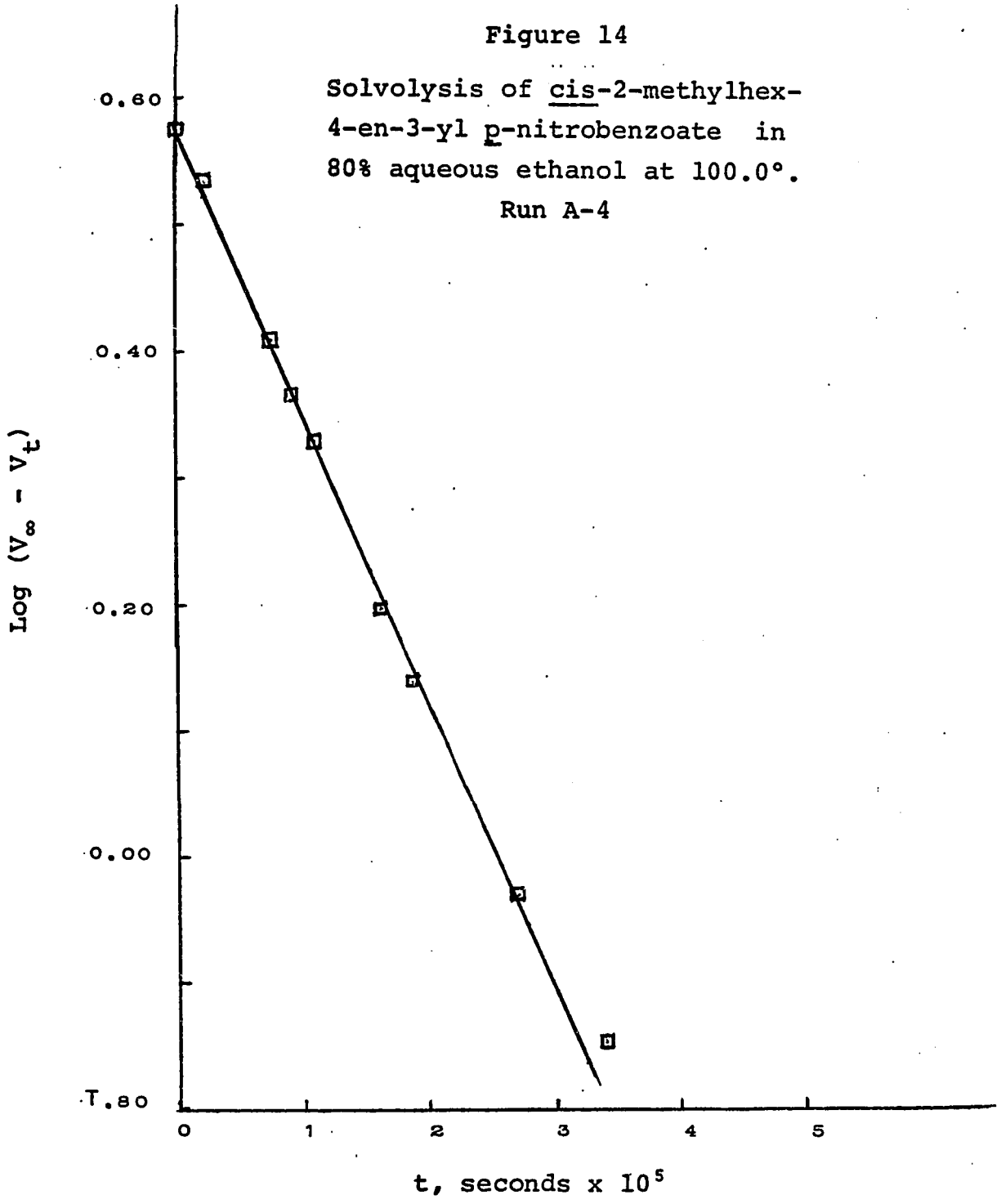


Table 8

SOLVOLYSIS OF 5,5-DIMETHYLCYCLOPENT-2-EN-1-YL P-NITROBENZOATE IN 80% AQUEOUS ETHANOL AT 100.0° RUN B-5

Aliquot: 5.019 ml Titrant: NaOH (0.0347 M)

Indicator: α-naphtholbenzein

Ester conc: 2.790×10^{-2} M Theoretical V_∞: 4.037 ml

Time (sec)	V_t (ml)	Log $(V_\infty - V_t)$	$10^4 k_t$ (sec^{-1})
0	0.262	0.5769	
1372	1.004	0.4818	1.60
2038	1.308	0.4360	1.59
2989	1.698	0.3691	1.60
3556	1.934	0.3228	1.64
4347	2.180	0.2688	1.63
5319	2.455	0.1993	1.64
6147	2.653	0.1412	1.63
7267	2.887	0.0607	1.64
8639	3.113	$\bar{1}$.9657	1.63
10231	3.390	$\bar{1}$.8109	1.73*
40750 (∞)	3.993		

* Omitted from average

$k_t = (1.62 \pm 0.02) \times 10^{-4}$ sec^{-1}

From graph, $k_t = 1.63 \times 10^{-4}$ sec^{-1}

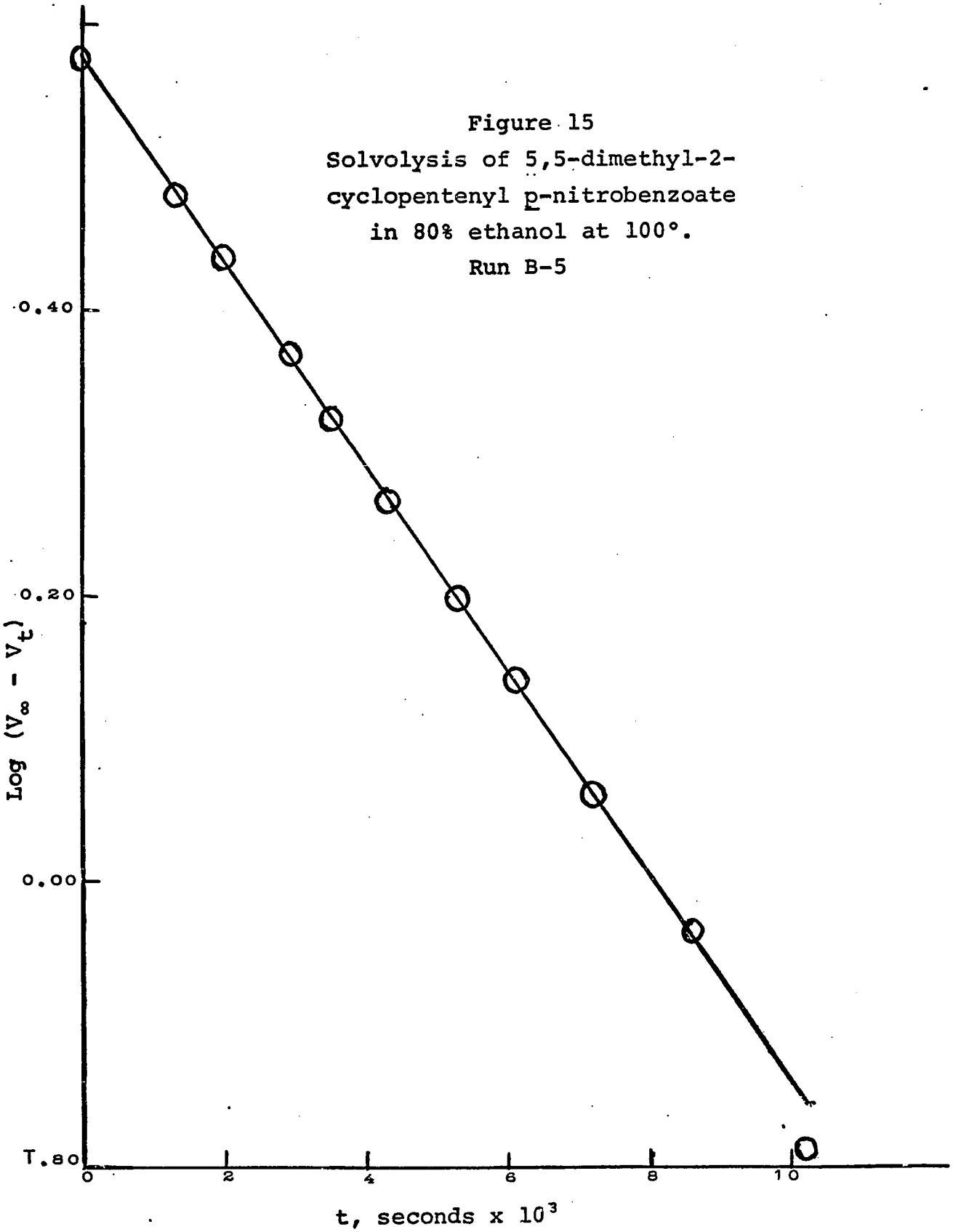


Figure 15
Solvolysis of 5,5-dimethyl-2-cyclopentenyl p-nitrobenzoate in 80% ethanol at 100°.
Run B-5

Table 9

SOLVOLYSIS OF CYCLOPENT-2-EN-1-YL P-NITROBENZOATE IN 80% AQUEOUS ETHANOL AT 70.0° RUN C-6

Aliquot: 4.968 ml Titrant: NaOH (0.0358 M)
Indicator: α-naphtholbenzein
Ester conc: 2.958×10^{-2} M Theoretical V_∞: 4.108 ml

Time (sec)	V_t (ml)	Log $(V_\infty - V_t)$	$10^4 k_t$ (sec^{-1})
0	0.315	0.5789	
688	0.805	0.5189	2.01
1459	1.294	0.4493	2.05*
2143	1.627	0.3947	1.98
2832	1.945	0.3351	1.98
3564	2.251	0.2688	2.00
4513	2.554	0.1914	1.98
5602	2.860	0.0962	1.98
6888	3.138	$\bar{1}$.9868	1.98
9014	3.463	$\bar{1}$.8096	1.97
11520	3.721	$\bar{1}$.5877	1.98
32750 (∞)	4.066		

* Rejected from average

$k_t = (1.99 \pm 0.01) \times 10^{-4}$ sec^{-1}

From graph, $k_t = 1.97 \times 10^{-4}$ sec^{-1}

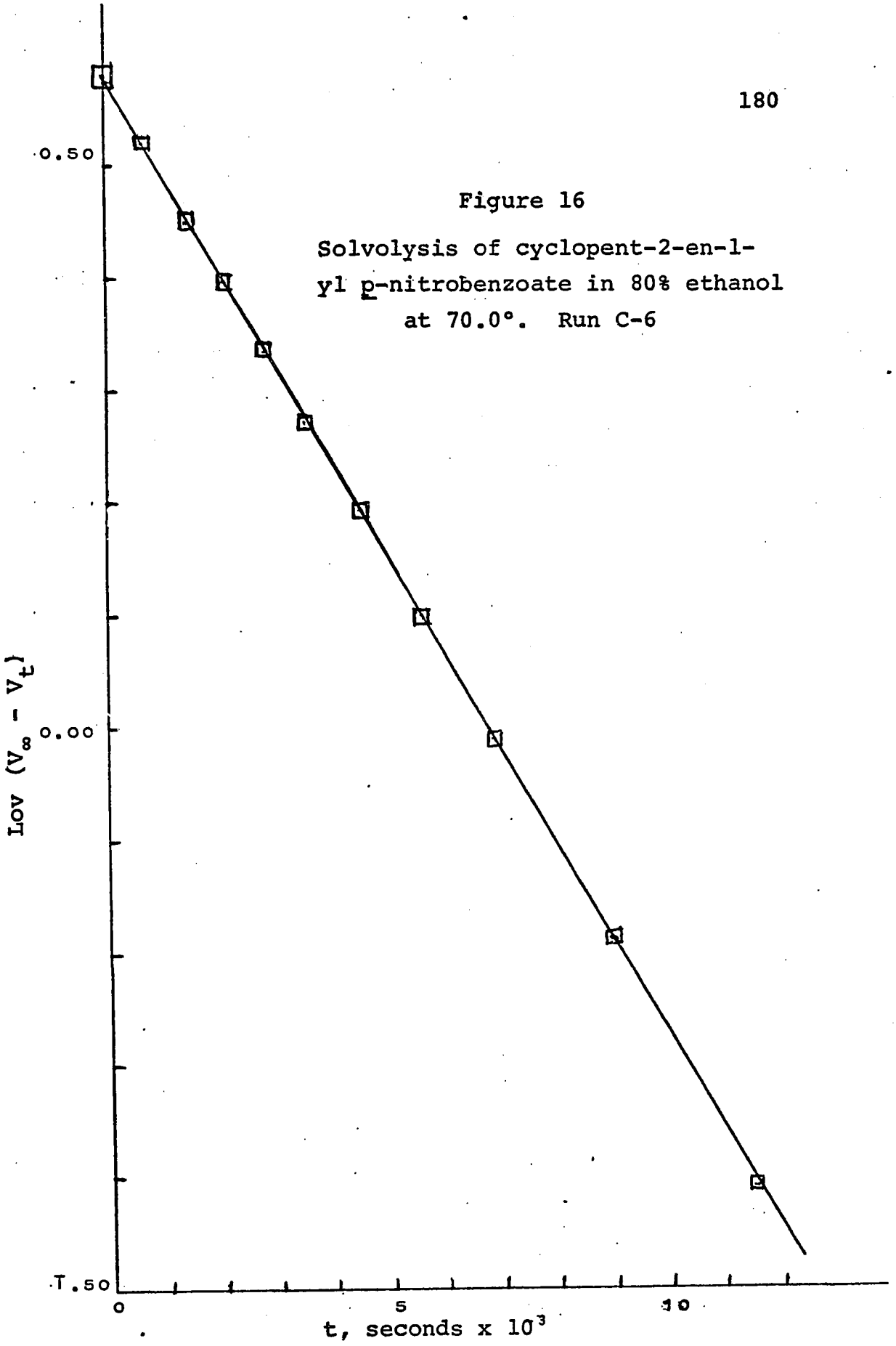


Figure 16

Solvolysis of cyclopent-2-en-1-yl p-nitrobenzoate in 80% ethanol at 70.0°. Run C-6

Table 10

SOLVOLYSIS OF CYCLOPENT-2-EN-1-YL P-NITROBENZOATE IN 80% AQUEOUS ETHANOL AT 70.0° RUN C-7

Aliquot: 4.968 ml Titrant: NaOH (0.0358 M)

Indicator: α-naphtholbenzein

Ester conc: 3.140×10^{-2} M Theoretical V_∞: 4.360 ml

Time (sec)	V_t (ml)	Log $(V_\infty - V_t)$	$10^4 k_t$ (sec^{-1})
0	0.414	0.5962	
1214	1.249	0.4929	1.96
1903	1.665	0.4306	2.00
2689	2.055	0.3626	2.00
3339	2.338	0.3058	2.00
4291	2.653	0.2322	1.95
5499	3.054	0.1158	2.01
6931	3.346	0.0060	1.96
8959	3.610	$\bar{1}$.8751	1.85
11758	3.903	$\bar{1}$.6599	1.83
32515 (∞)	4.283		

$k_t = (1.95 \pm 0.05) \times 10^{-4}$ sec^{-1}

From graph, $k_t = 1.97 \times 10^{-4}$ sec^{-1}

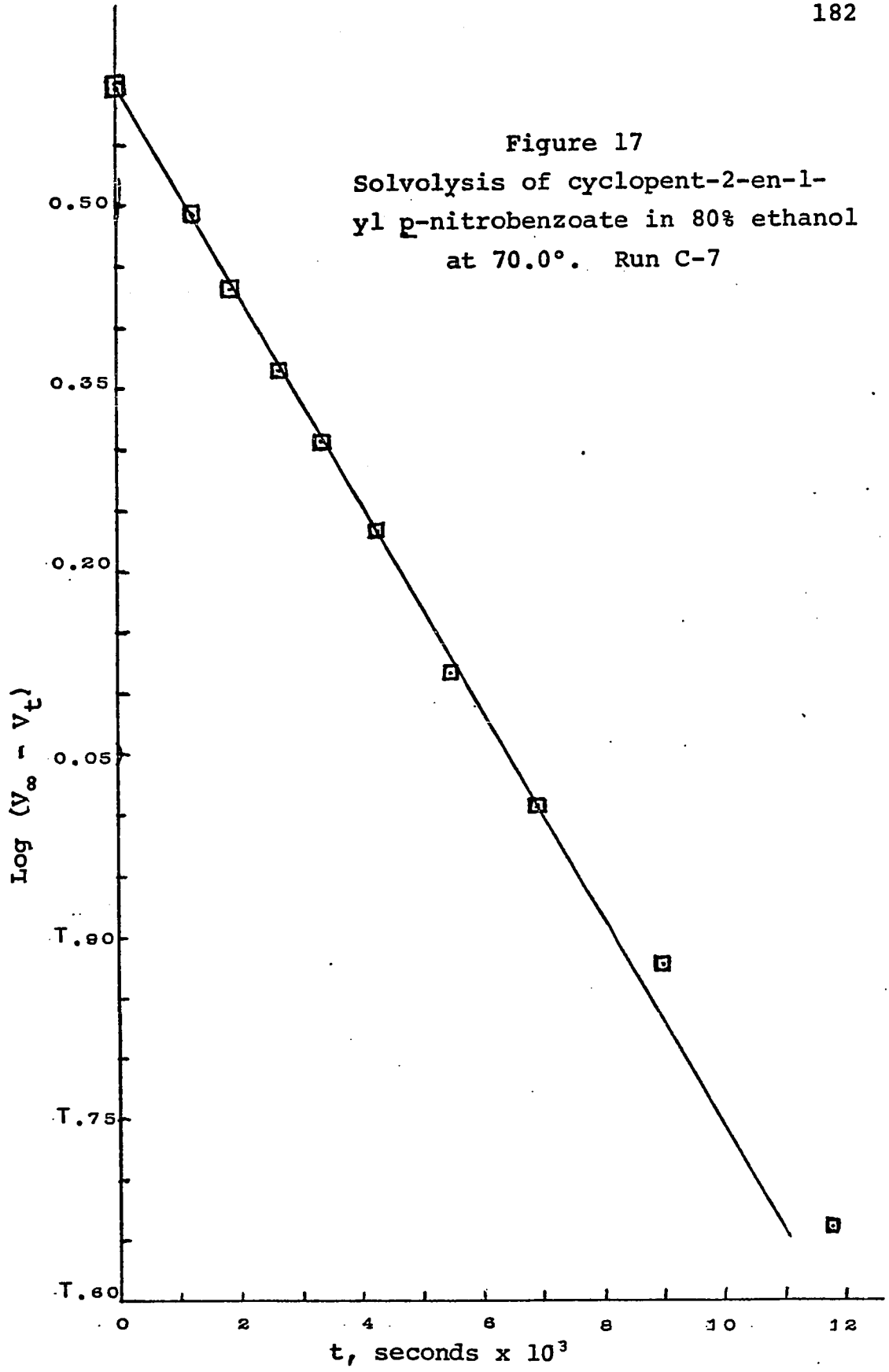


Figure 17
Solvolysis of cyclopent-2-en-1-yl p-nitrobenzoate in 80% ethanol at 70.0°. Run C-7

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