The Stereochemistry of the S_N2' Reaction.

Alexander A. Dobbie

A thesis presented to the University of Glasgow

for the degree of Ph.D.

Department of Chemistry

University of Glasgow

October, 1976.

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

I wish to take this opportunity to express my sincere gratitude to Prof. K. H. Overton for his advice and encouragement during the course of this work. I would also like to thank my colleagues and the Staff of the Department of Chemistry for making my stay there an enjoyable one.

Alexander A. Dobbie

October, 1976.

To SHARON and LYNSEY.

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SUMMARY

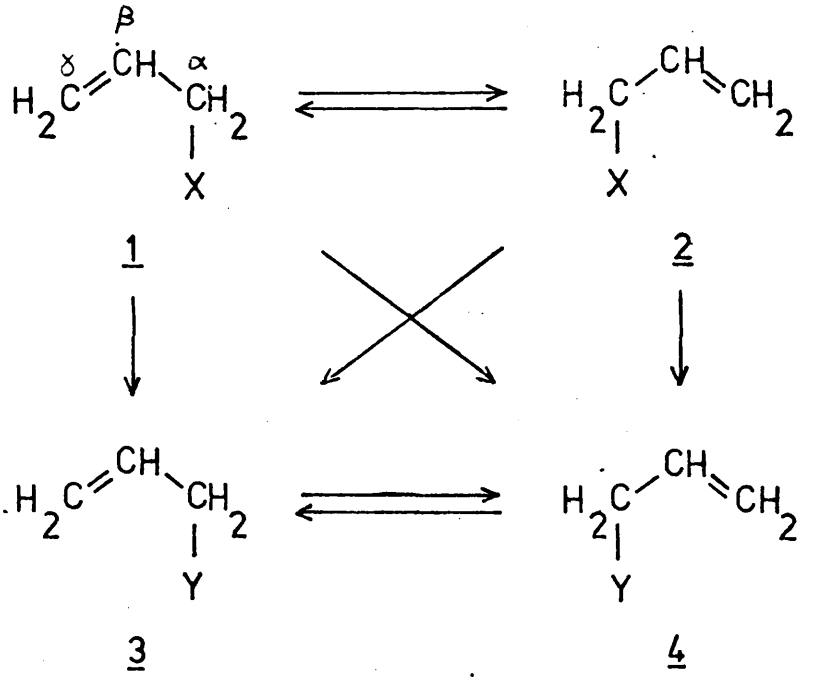
In an attempt to determine the preferred stereochemistry of the S_N2' reaction of cyclohex-2-en-1-yl systems, it was desired to study the reactions of the cis and trans 6-alkyl cyclohex-2-en-1-yl 2,6-dichlorobenzoates (81, 82, 83; 39, 40, 41) with piperidine. Problems encountered in the preparation of these superficially simple compounds forced the curtailment of this exercise, however, and only the trans 6-isopropyl ester (40) was successfully obtained in a pure state. Attempts were made to find other 6-alkyl cyclohex-2-en-1-yl derivatives which would be suitable substrates for reaction with piperidine. These were found in the cis and trans 3,5-dinitrobenzoates (84, 85), and the cis p-nitrobenzoate (87).

Analysis of the reactions of these compounds with piperidine was complex - the esters reacted by substitution (S_N2, S_N2') and aminolysis, and were subject to isomerisation, by epimerisation and allylic rearrangement, during the course of reaction. However, it did eventually prove possible to establish that the S_N2' reaction, when involved, proceeded only in syn fashion, regardless of the initial configuration of the substrate. The configuration of the S_N2' products (229, 43) was confirmed by their comparison, after hydrogenation, with authentically prepared N-(4-alkyl cyclohexyl) piperidines (195, 196).

The complexity of the reacting system precluded full kinetic analysis, but it was possible to determine approximate initial rates for the syn S_N2' reactions of the cis and trans 3,5-dinitrobenzoates (84, 85) with piperidine.

The implications of these findings are discussed.

INTRODUCTION.



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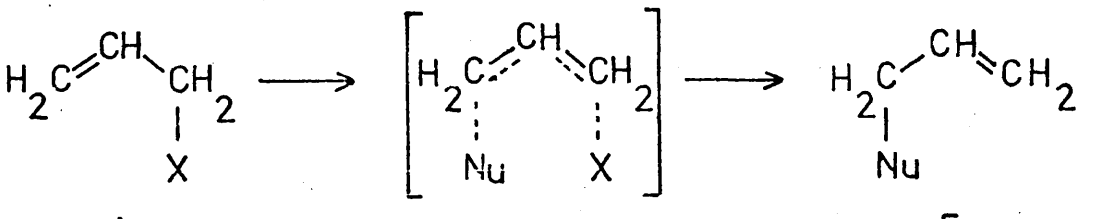


1 5

1. The S_N2' reaction.

The intrinsic structural simplicity of the allylic framework (1) masks a complexity of chemical behaviour which has puzzled, and fascinated organic chemists for many years.

The presence of the double bond in the β,γ-position confers enhanced substitutional reactivity upon displaceable groups in the allylic position (α). This simple reactivity enhancement is overshadowed, however, by the ease with which allylic systems undergo rearrangement (1→2; 3→4). Thus, in practice, allylic systems undergo substitution reactions with varying amounts of concomitant rearrangement.

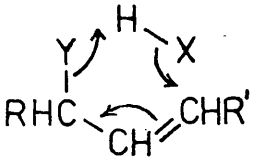
The simple, or "normal", substitution of an allylic system is designated an S reaction (1→3; 2→4). In this, no rearrangement accompanies the substitution reaction.

The substitution plus rearrangement, or "abnormal" substitution, reaction of an allylic system is designated S' (1→4; 2→3). Here, substitution is attended by total rearrangement and the product has the "incoming" substituent (Y) attached to a carbon atom two removed from that which bore the "outgoing" substituent (X).

Such substitution reactions may be either nucleophilic or electrophilic, designated by the subscripts N and E, respectively, and may involve either a unimolecular or bimolecular transition state, designated by the suffixes 1 and 2, respectively.

Thus, the S_N2' reaction is defined as "bimolecular nucleophilic substitution with allylic rearrangement" (1→5).

In general, the S_N2' reaction is not competitive with "normal" S_N2 reaction in allylic systems and study of the S_N2'



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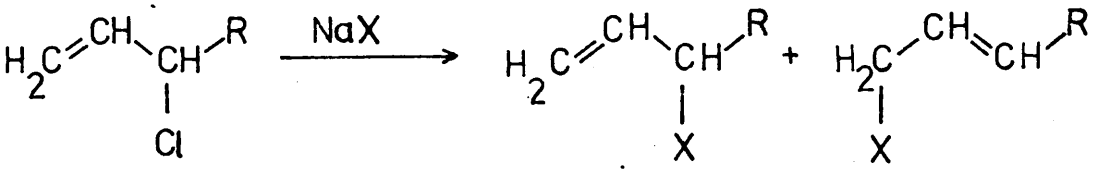


7 8 9

X = $CH(CO_2Et)_2$

a. R = Me	90%	10%
b. R = Et	77%	23%

reaction, therefore, requires that its rate be enhanced relative to S_N2 reaction. This is commonly accomplished by decreasing the rate of S_N2 reaction by the use of steric "blocking groups" on the α-position of the allylic system, although, as will be demonstrated later, methods which involve increasing the rate of S_N2' reaction by stabilisation of that reaction's transition state have also been employed.

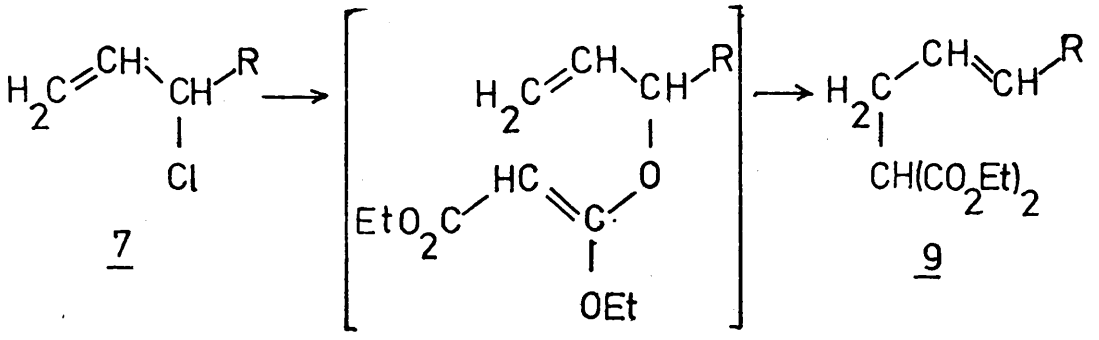
2. History.

The earliest suggestion of an S_N2'-like mechanism was made in 1928 by Burton[1], in considering a cyclic variant of the S_N2' reaction in which an allyl system is attacked by an H-X molecule (6).

The credit for the modern postulate of the S_N2' reaction is jointly given, however, to Hughes[2], Winstein[3], and Bergmann[4], who, working independently, made their proposals a decade after Burton's original suggestion and, as it turned out, more than a decade before the reaction was experimentally demonstrated.

This "first authentic example" of the S_N2' reaction was reported in 1949 by Kepner, Winstein, and Young[5] (7 → 8 + 9), following a period in which attempts to find an example of the S_N2' reaction had proved to be fruitless[6,7,8,9], leading to the proposition[10] by Catchpole, Hughes, and Ingold, in 1948, that the S_N2' reaction was non-attainable because of shielding of the γ-carbon atom by the electrons of the π-bond.

This "first example" was not readily accepted, however, especially by the English group of workers in this field, who


H2C
CH
CH
R
Cl
7
EtO2C
HC
C
O
OEt
10
CH(CO2Et)2
9

based their objections on a suggestion by Dewar[11] that the "abnormal" product (9) may have been formed by O-alkylation of the diethylmalonate ion, followed by Claisen rearrangement of the resulting vinyl ether (10).

This objection was overruled by Winstein[12], and DeWolfe and Young[13], on the basis that the intermediate ketene acetal (10) would be more likely to react with the alcoholic solvent to form an ortho ester rather than the "abnormal" product (9), and by Stork and White's demonstration[14] that O-alkylation, followed by rearrangement, did not occur in the reactions of other allylic systems with diethylmalonate anion. However, the English school did not unreservedly accept this evidence and remained unconvinced.[15,16,17]

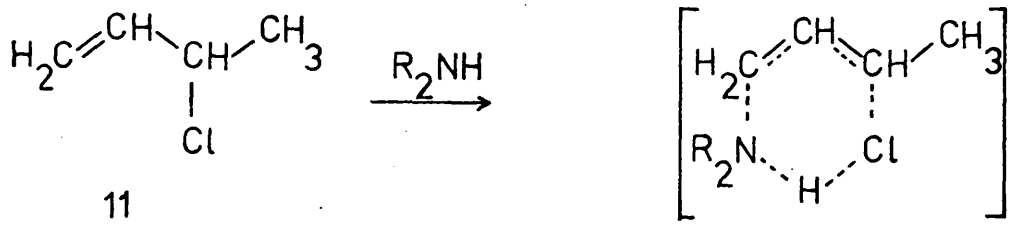
Progress was rapid after this initial controversy and soon many "examples" of the S_N2' reaction were reported. Many of these, however, failed to satisfy the criteria demanded by DeWolfe and Young[13], and Kepner, Winstein and Young[5], for a reaction to be designated S_N2', viz.

"1. The rate of the reaction must be proportional to the concentration of both the substituting reagent and the compound being substituted (usually this implies second-order kinetics).

2. The reaction must give isolable amounts of abnormal substitution products.

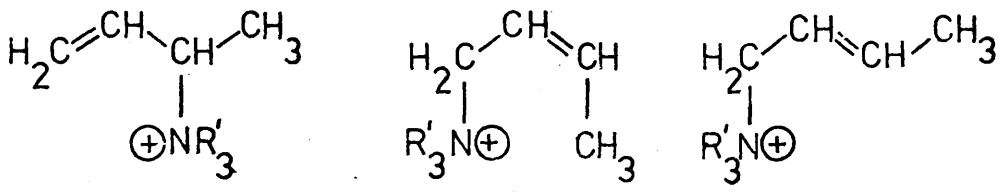
3. It must be demonstrated that neither the starting material nor the normal substitution product undergo rearrangement under the conditions of the reaction."

Several examples were, fortunately, shown to fulfil these criteria. England and Hughes[18] studied the bromide exchange reactions of α- and γ-methyl allyl bromides with radioactive lithium bromide and showed that the S_N2' reaction was involved,



11 12 13

R = CH_3CH_2



14 15 16

30% 7% 63%

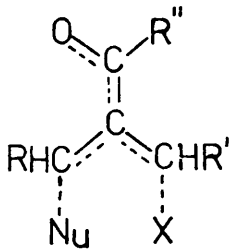
R′ = CH_3

while De la Mare and Vernon[19-23] published a series of papers on S_N2' reactions of allylic chlorides having sterically hindered α-carbon atoms.

"Abnormal" substitution reactions using amines as nucleophiles were reported by Jones, Lacey and Smith[24] and by Young, Webb and Goering[25] who, in 1951, described a study of the reaction of diethylamine with α-methyl allyl chloride (11→13). The observed increase in the S_N2'/S_N2 ratio, compared with reactions using other nucleophiles, caused them to ponder upon the possibility that hydrogen bonding between the incoming and departing groups could be involved.

Because of the possibility of hydrogen bonding in this[25] and other related systems[14], England and Hughes[18], and Ingold[26] preferred to consider such reactions as S_Ni' (substitution by intramolecular rearrangement of an intermediate compound) but, considering the intrinsically weak character of a hydrogen bond when compared with the covalent bonds normally associated with S_Ni' reactions, it would appear to be subjective whether such reactions should be considered as S_Ni' or as cyclic variants of the S_N2' reaction. Indeed, it has been shown[27,28] that hydrogen bonding is not a necessary requirement for S_N2' reaction of allylic chlorides with amines since this mechanism accounted for 70% of the products from reaction of α-methyl allyl chloride (11) with trimethylamine (11→ 14 + 15 + 16).

The initial flurry of activity on the S_N2' reaction in the late 1940's and early 1950's culminated, in 1956, in Stork and White's apparent demonstration of the syn relationship between entering and departing groups in the S_N2' reaction of substituted cyclohex-2-en-1-yl 2,6-dichlorobenzoates with



17

piperidine[14]. (This subject is discussed fully in INTRODUCTION 3. Stereochemistry p. 12)

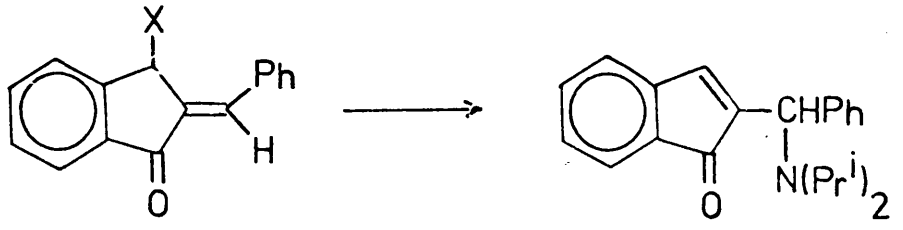
Thus, by the mid-1950's, the S_N2' reaction had been well established and its stereochemistry determined. This led to a lack of interest in further studies, which was to last for about ten years. Indeed, during this period, the major works were review articles summarising the early history of the reaction.[13,17,29,30,31]

Interest was revived in the late 1960's and, since then, several groups of researchers have been active in this field. Perhaps inevitably, the rebirth of interest was accompanied by a renewal and extension of the controversy surrounding the reaction mechanism.

The approach of Cromwell and his co-workers to the study of the S_N2' reaction was founded on the concept of making it competitive with "normal" S_N2 reaction by stabilising its transition state. This is in contrast to the majority of the early studies in which steric hindrance of the S_N2 reaction was employed to render the S_N2' reaction observable.

His aim was achieved by the use of a β-carbonyl substituent on the allylic system, the rationale being that the developing negative charge on the β-carbon atom of the allylic system, in the transition state, could be delocalised over the β-carbonyl system as well as the leaving group, thereby stabilising the transition state (17).

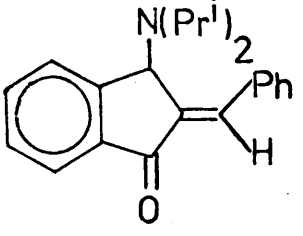
Products arising from S_N2'-like reactions were observed in many of these studies,[32-42] and several of the systems considered were subjected to full product and kinetic analyses.[34,35,37,39,40]



18 X = Br

21 X = Cl

19



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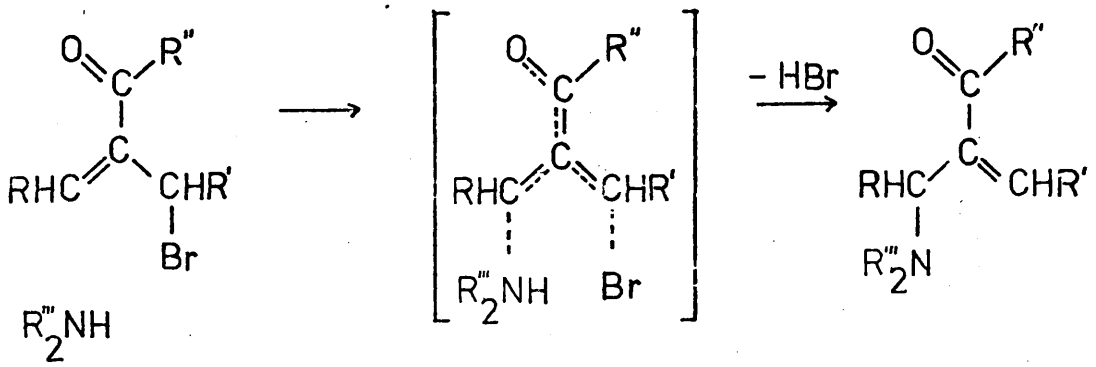


22 23 24

R, R', R'' = alkyl, phenyl

R''' = alkyl, H

Typical is the reaction of 3-bromo-2-benzal-1-indanone (18) with di-isopropylamine, in acetonitrile.[34]

The reaction was shown to fulfil the criteria for classification as an S_N2' reaction,[5,13] viz.

1. It was shown to be kinetically first order in amine and first order in substrate (18).

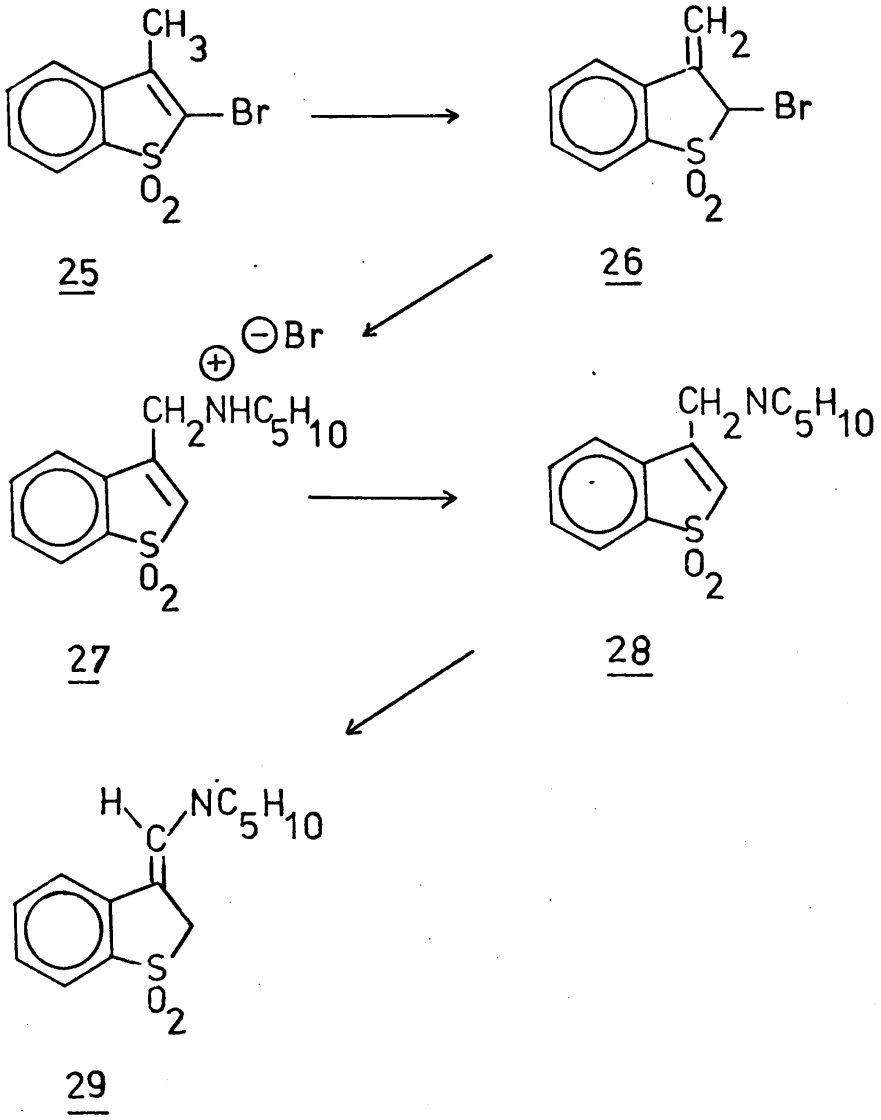
2. "Abnormal" product was isolated.

3. It was shown that both the starting material (18) and the "normal" substitution product (20) did not rearrange under the reaction conditions.

However, caution must be exercised in designating this, and the other similar reactions investigated by Cromwell, as S_N2' because studies of an analogous system (21)[34] (in which Br has been replaced by Cl) showed a ratio $k_{Br}/k_{Cl} = k_{18}/k_{21} =$ 3.7 (at 30°C), whereas the expected ratio for a concerted, synchronous S_N2' reaction would be much higher[43] (~40-50).

The dichotomy between the observed and expected values suggests a transition state which is only partially influenced by the nature of the departing group, a situation explained by the probability that the β-carbonyl substituent, by absorbing some of the developing negative charge in the transition state, perturbs the simple, synchronous S_N2' process.

Cromwell suggested that the β-keto allyl system must be considered in its entirety and not as a combination of discrete allylic bromide and enone moieties, each reacting independently. Thus, such reactions are, perhaps, best described as highly perturbed S_N2'-like processes in which bond-breaking is running slightly ahead of bond-making, in a concerted reaction. (22→ 23→ 24).


CH3
Br
S
O2
25
CH2
Br
S
O2
26
⊖Br
⊕
CH2NHC5H10
S
O2
27
CH2NC5H10
S
O2
28
H
C
NC5H10
S
O2
29

A similar approach to facilitation of the S_N2' reaction was utilised by Bordwell and his co-workers who employed a sulphonyl substituent to stabilise the transition state of the reaction.

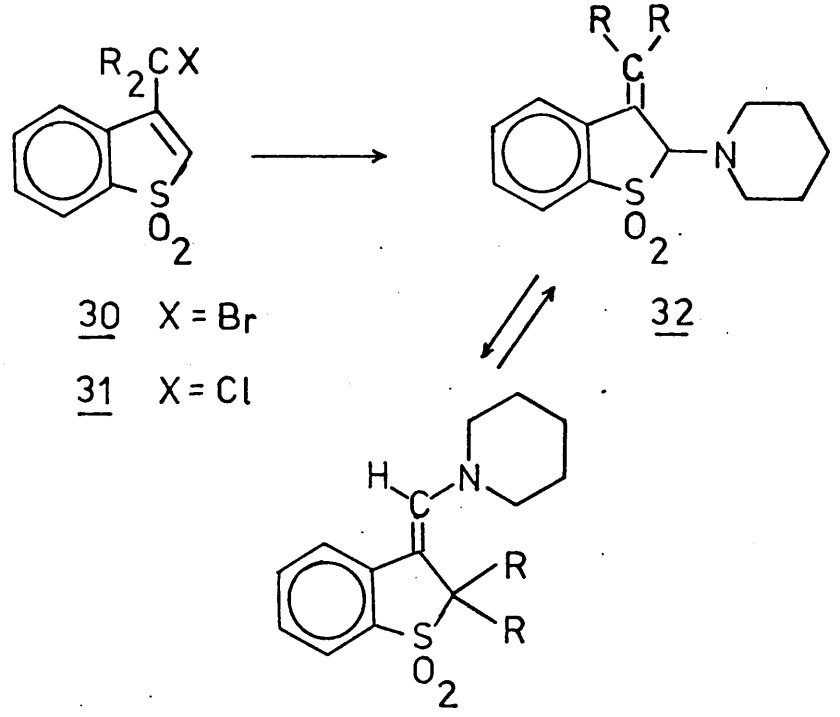
Thus, Bordwell, Hemwall and Schexnayder showed[44,45,46] that 3-methyl-2-bromobenzo-[b]-thiophene 1,1-dioxide (25) reacted with piperidine to give a product (29), formed by a process involving an S_N2'-like reaction (26→ 27).

They suggested that the sulphonyl group facilitated the S_N2' reaction of this, and other systems[47], for the following reasons:-

1. Electron-withdrawal by the sulphonyl group increases the susceptibility of the vinyl carbon atom to nucleophilic attack and, by the same token, decreases the tendency of the allylic system to react via an allylic carbonium ion mechanism.
2. The presence of the sulphonyl group may facilitate the S_N2' reaction by delocalisation of the developing negative charge on the β-carbon atom in the transition state. The sulphonyl group may accept this excess electron density via the conjugated aromatic ring, c.f. Cromwell's use of a β-carbonyl substituent to delocalise the developing negative charge on the β-carbon atom in other S_N2'-like reactions.

Bordwell and Schexnayder[47] were, however, dubious about the designation of reactions as S_N2' without what they regarded as adequate authentication and this led Bordwell,[48] in 1970, to question the very existence of the S_N2' reaction, concluding that, "there appear to be no unambiguous examples of the S_N2' concerted mechanism," and that, "the concerted S_N2' reaction mechanism may well be a myth."

His arguments were based upon the assertion that not all of



30 X = Br

31 X = Cl

32

33

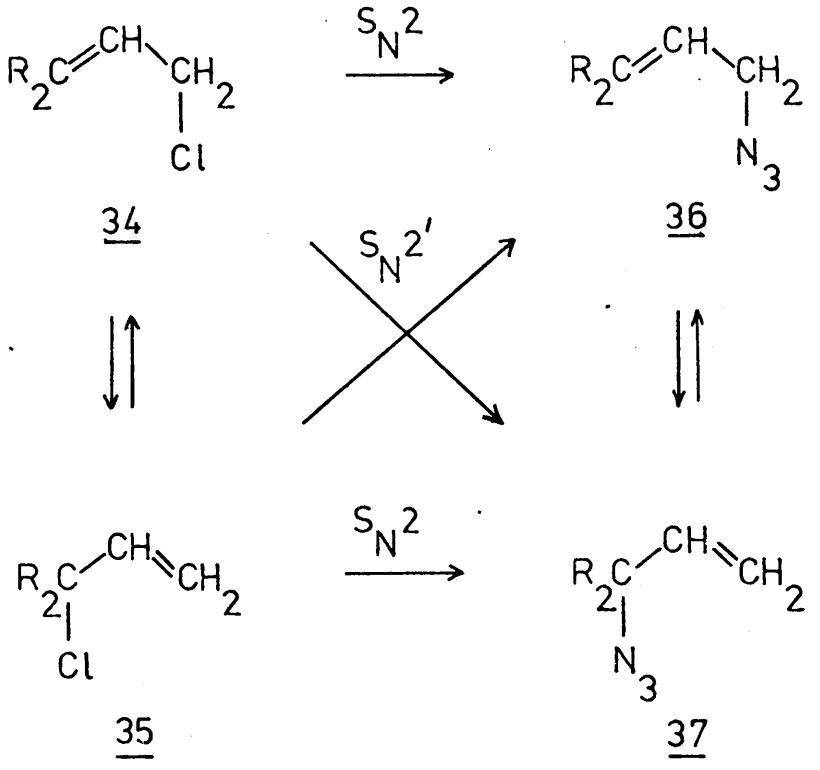
R = CH_3

the other possible mechanistic routes to the observed products in supposedly S_N2' reactions could be eliminated.

However, his criticisms were later refuted, for some examples at least,[20,21,23] by De la Mare and Vernon.[49] In their rebuttal of Bordwell's attack, they made incidental use of a study by Eberhardt, McKee and Fry,[50,51] who showed that, in the reaction of diethylamine with α-methyl allyl chloride (11), significant kinetic isotope effects were observed for all three carbon atoms of the allyl system ($^{12}C:^{14}C$) and for the chlorine ($^{35}Cl:^{37}Cl$). Thus, bonding changes at all the atoms of the reacting system were implicated in the rate-determining step, suggesting a concerted process. This reaction is, indeed, one of the examples which Bordwell was very reluctant[48] to classify as S_N2'.

The controversy continued, however, - writing in "Organic Reaction Mechanisms", Stevens stated[52], "the paper by De la Mare and Vernon[49] refuting Bordwell's attack on the S_N2' process is convincing, which Bordwell's attack never was," while Jefford, Sweeney, Hill and Delay[53] concurred with Bordwell that, "the myth concerning *syn*-facial S_N2' displacements should not be perpetuated and that such processes should henceforth be regarded as S_Ni'."

Bordwell returned to the fray in 1972, when, with Mecca,[54,55] he showed that the halides (30,31) reacted with piperidine to produce the enamine (33) via the "abnormal" substitution product (32). Kinetic examination of these reactions and of the k_{Br}/k_{Cl} ratios obtained (25/1 for reaction in dimethylformamide, 26/1 for reaction in methanol) prompted the authors to propose that the data obtained were best explained by an ion-pair



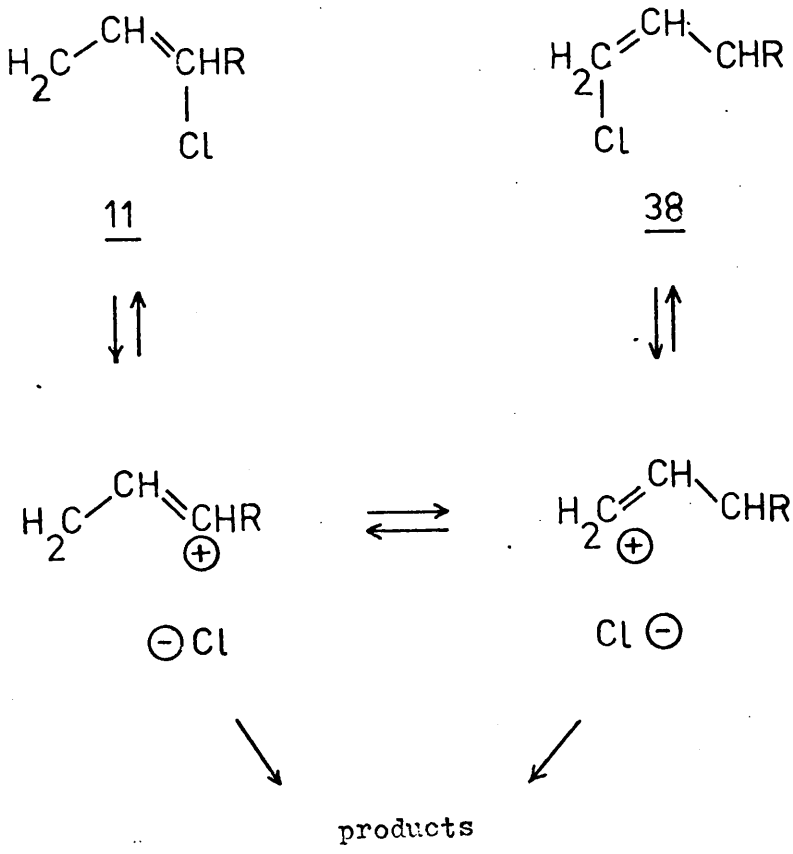
R = CH_3

mechanism, rather than a concerted S_N2' mechanism, although they did concede that a concerted S_N2' process could not be eliminated. Indeed, their rejection of the S_N2' mechanism was based upon external observations,[48,56] rather than evidence accruing from this particular experiment.

A valuable ally for Bordwell's idea of "ion-pair" rather than "concerted" S_N2' reactions, was found in Sneen, a champion of nucleophilic reactions occurring via ion-pairs.

Sneen and Bradley suggested[57] that the considerable volume of kinetic data obtained from a study of the reaction of α,γ-dimethyl allyl chloride in ethanol (in the presence or absence of added nucleophiles) was best explained by an ion-pair process, in which the intermediacy of discrete, distinct, allylically-related ion-pairs was implicated. They further proposed that such a mechanism allowed the interpretation of the long-standing problem of the "product spreads" observed in the solvolyses of other allylically-related chlorides, viz. that these "product spreads" were a result of the indiscriminate behaviour of relatively high-energy intermediates (ion pairs) towards added nucleophile or solvent or further ionisation (to solvent-separated ion pairs).

In a subsequent paper, Sneen and Kay[58] described the competitive reaction of the primary, γ,γ-, and tertiary, α,α-dimethyl allyl chlorides (34, 35) with solvent and with sodium azide. Both substrates were shown to undergo kinetically second-order reactions with sodium azide, that of the tertiary allylic chloride being either S_N2' reaction or bimolecular nucleophilic attack at a tertiary carbon, a process envisaged by the authors as occurring via a rate-determining displacement



R = Me

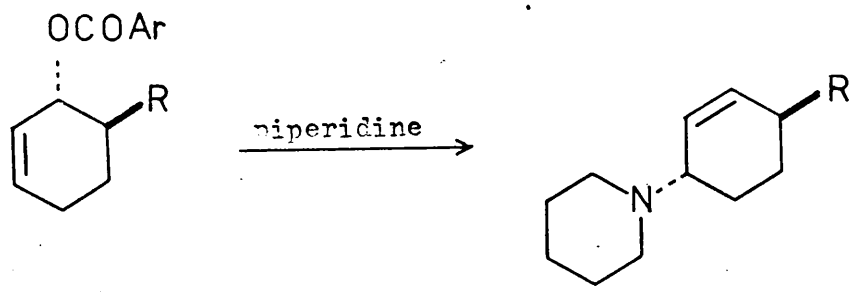
on a pre-formed ion-pair.[59] Because the products (36, 37) of the reaction were unstable under the reaction conditions, and equilibrated at a rate comparable to their rate of formation,[60] the authors were unable to distinguish between the S_N2' pathway (35→ 36) and the $S_N2/$ rearrangement pathway (35→ 37→ 36).

In an attempt to unify the diverse reactions of simple allylic compounds, Sneen and Carter[61] proposed that an ion-pair mechanism was operative in the competitive reactions of ∝- and γ-methyl allyl chlorides (11, 38) with solvent, and with added nucleophile (phenoxide ion).

They suggested that such a mechanism would replace the "traditional S_N2' mechanism" which requires unprovoked attack of a nucleophile at the γ-carbon, since it would provide provocation for that attack, thereby making the S_N2' reaction "intellectually satisfying."

In summary, the history of the S_N2' reaction has been a tale of controversy, which seems certain to continue for some time. Regarding the recent "ion-pair" S_N2' versus "synchronous, concerted" S_N2' argument , it appears likely that the truth will be found somewhere between these two extremes, since neither can satisfactorily account for all of the results obtained from reactions which have been shown to fulfil the criteria for classification as S_N2'.

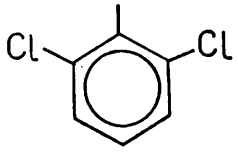
Thus, Bordwell's and Sneen's arguments for "ion-pair" S_N2' mechanisms, although explaining much of the data obtained, do not satisfactorily account for the low activation energies and high negative activation entropies encountered in many S_N2' reactions[62] (criteria normally taken to be indicative of a concerted process[63,64]), nor for the kinetic isotope effects observed by

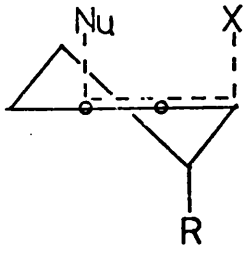


	R
39	Me
40	Pr^i
41	Bu^t

	R
42	Me
43	Pr^i
44	Bu^t

Ar =





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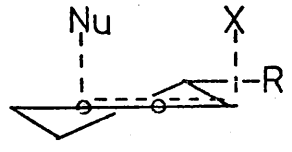

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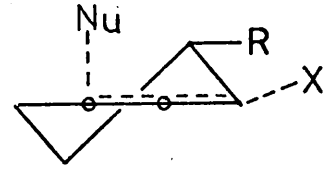


C

Fry.[50,51]

In contrast, the concept of a fully synchronous, concerted process is unable to explain the appearance of the "product spreads" observed in many solvolytic reactions of allylic halides,[61] although it does account for the low activation energies, high negative activation entropies, and kinetic isotope effects mentioned above.

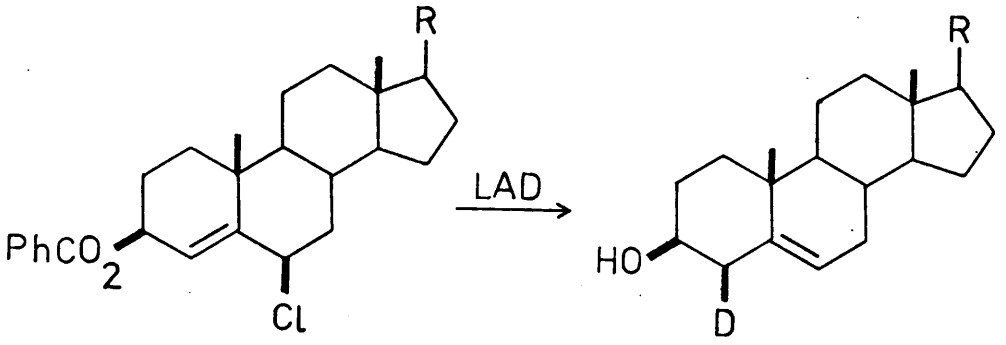
3. Stereochemistry

The first suggestion of a stereoelectronic preference in the S_N2' reaction was made by Young, Webb, and Goering,[24] who postulated that the incoming and departing substituents should bear a syn relationship to one another, a stereochemical course later supported experimentally by Stork and White [14] in their demonstration that piperidine approached syn to the departing 2,6-dichlorobenzoate anion in the S_N2' reaction of piperidine with the trans 6-alkyl cyclohex-2-en-1-yl 2,6-dichlorobenzoates (39, 40, 41).

In a similar experiment using diethylmalonate anion[14] (see p. 4), syn attack was again observed, although this time the S_N2' reaction was accompanied by "normal" S_N2 reaction.

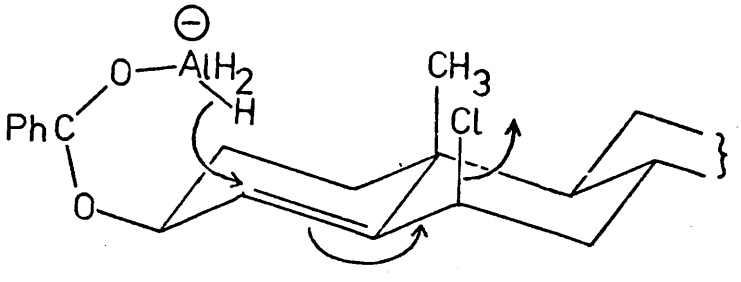
Of the three possible conformations of the transition state of the reaction (A, B, C), the authors favoured C, although in this case the C-O bond to be broken is in the least favourable conformation for interaction with the developing π-bond system.[65]

Reservations about the conclusions reached by Stork and White have been raised[26,48] because of the possibility that the syn



45 47

R = C_8H_{17}



46

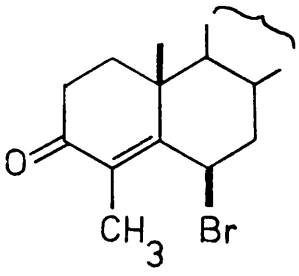
stereochemistry observed was not a result of a stereoelectronic requirement for syn attack in an S_N2' reaction but, instead, was simply the result of an energetic preference caused by hydrogen bonding between the incoming piperidine and departing dichlorobenzoate anion, a factor which is possible only in syn approach.

In spite of this, the conclusion by Stork and White has, generally, been accepted and has come to be widely regarded as the "definitive work" on the stereochemistry of the S_N2' reaction. This statement is supported by the fact that, of the 67 references[66] to their results,[14] during 1964-75, more than 95% unreservedly accepted their conclusion as being the required stereoelectronic course of the S_N2' reaction.

The publication of their work also marked the end of the early period of the history of the S_N2' reaction (see p. 5) and, since then, most of the stereochemical studies have been concerned with hydride attack on allylic systems and with other related S_N2'-like reactions. Formally, such reactions should be classified as S_Ni' but for the purposes of determining the preferred stereoelectronic course of the S_N2' reaction, they may be used as valid examples of a special class of S_N2' reactions.

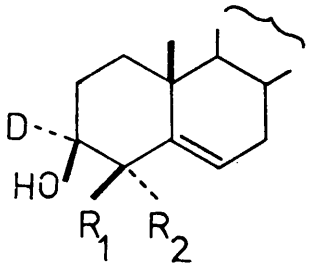
Several S_N2'-like reactions in the steroid field have been studied from a stereochemical viewpoint.

In 1959, Ireland, Wrigley, and Young[67] demonstrated the syn relationship of hydride and chloride in the reductive dechlorination of 6β-chloro-cholest-4-en-3β-yl benzoate (45) with lithium aluminium hydride (LAH) via the intermediacy of a species (46) in which the aluminohydride was complexed to the carbonyl oxygen. The stereochemistry at C-4 was determined by use of



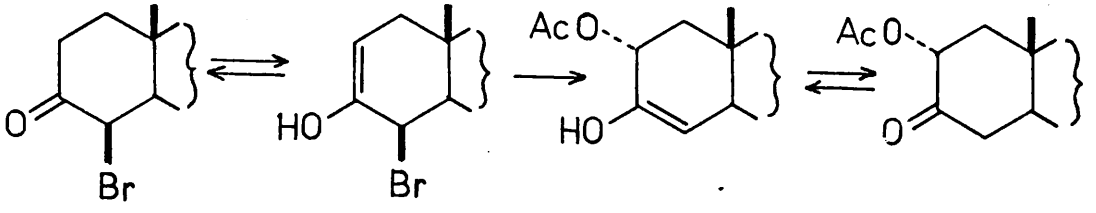
48

LAD →

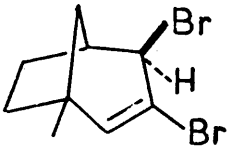


49 D CH_3

50 CH_3 D

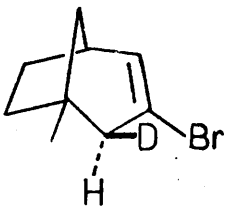


51 52 53 54

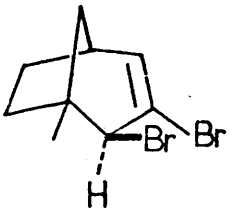


55 90%

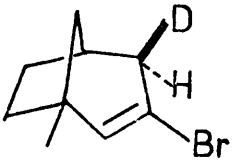
LAD →



57 84%



56 10%



58 16%

lithium aluminium deuteride (LAD).

In an analogous system, 6β-bromo-4-methyl cholest-4-en-3-one (48), Knapp and Schroepfer[68] demonstrated that, depending on the amount of LAH (LAD) used, products corresponding to both syn and anti S_N2'-like reactions were obtained (49, 50).

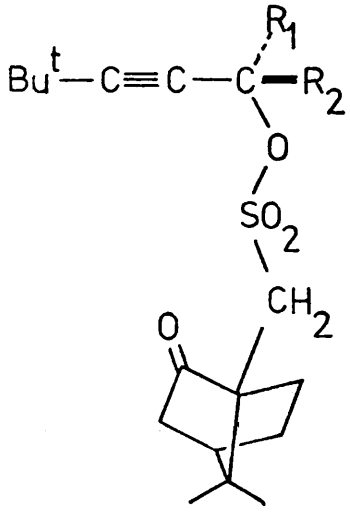
In studies on the acetolysis of 4β-bromo-5β-cholestan-3-one (51), Satoh and Takahashi[69,70] postulated what they believed to be the first example of an S_N2' reaction in which the nucleophile ard leaving group bore an anti relationship (52→53). They ascribed the stereochemistry of this reaction to conformational factors which permit anti attack more readily than syn attack.

Studies of the stereochemical course of reductive dehalogenation in bicyclic compounds have been reported.

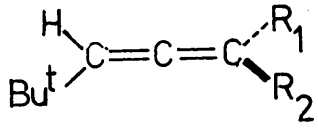
Jefford, Mahajan, and Gunsher[71] demonstrated the syn-faciality of entering hydride (deuteride) and departing bromide in the reactions of exo 1-methyl-3,4-dibromo bicyclo(3,2,1)oct-2-ene (55) and its allylic isomer (56) with LAH and LAD.

In a subsequent paper,[53] Jefford, Sweeney, Hill, and Delay demonstrated that analogous bicyclic systems, also, reacted with nucleophiles in a syn-facial manner, but concluded that this syn-faciality was a result of an S_Ni' reaction, via an intermediate species in which the reducing agent was complexed to the departing halide ion, rather than an S_N2' reaction which, they proposed, may, for theoretical reasons,[72] proceed in either syn or anti fashion. The reason for the syn-facial S_Ni' reactions observed in their studies was suggested to be not only steric hindrance to anti S_Ni' reaction, but also a stereoelectronic preference[73] for a syn cyclic S_Ni' mechanism.

An anti S_N2' mechanism has been claimed, by Borden and Corey,[74]

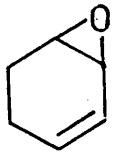


LAH →



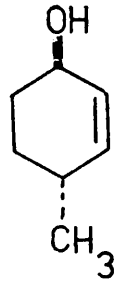
	R_1	R_2
59	H	Bu^t
60	Bu^t	H

	R_1	R_2
61	H	Bu^t
62	Bu^t	H



63

Li $CuMe_2$ →



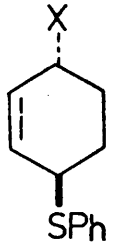
64

to be operative in the LAH reduction of the propargylic derivatives (59, 60), forming allenic compounds (61, 62). They demonstrated that reaction with the bulky species tri-tert.butoxy lithium aluminium hydride $(Bu^tO)_3LiAlH$ led only to reduction of the carbonyl group of the camphor moiety, thereby indicating that prior ionisation of the compound to an acetylenic cation was not the preferred pathway for the transformations (59→61, and 60→62). Their results indicated that the reaction was proceeding by a kinetically second-order route in which optically active allene was produced by an S_N2'-like reaction involving an anti relationship of nucleophile and leaving group.

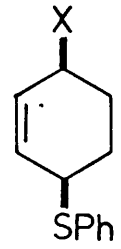
In an interesting footnote, the authors noted, "Stork and White have found, in contrast, that in a cyclic system with very different nucleophiles and leaving group, the S_N2' reaction proceeds in a predominantly trans* fashion. We are undertaking experiments to determine the stereochemical preference of this reaction in an acyclic system with the same nucleophiles and leaving groups as used by these authors." However, no account of this work has appeared, to date.

An anti S_N2'-like mechanism has been employed to explain the production of trans 4-methyl cyclohex-2-en-1-ol (64) from the reaction of 1,3 cyclohexadiene mono-epoxide (63) with lithium dimethyl cuprate.[75,76]

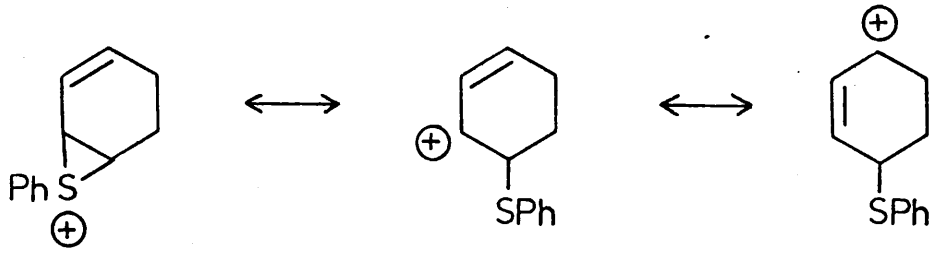
* The use of the term "trans" is in error; Stork and White demonstrated that the nucleophile and leaving group were syn related, i.e. starting from trans 6-alkyl cyclohex-2-en-1-yl esters (39, 40, 41) they obtained N-(trans 4-alkyl cyclohex-2-en-1-yl) piperidines (42, 43, 44).



65

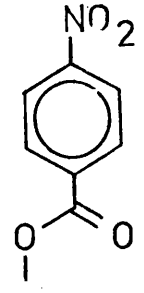


66



67 68 69

X =



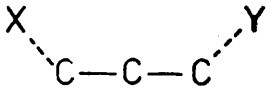
Milaszewski[77] has presented evidence for the operation of an anti S_N2' mechanism in the solvolyses of the phenylthio-substituted p-nitrobenzoate esters (65 and 66) in 2,2,2 trifluoroethanol.

It was proposed that the reaction occurred by an intramolecular S_N2'-like (S_Ni') mechanism (65,66→67), giving the species (68, 69) which were trapped by solvent. Product analysis suggested that both the trans (65) and cis (66) epimers were reacting by the same pathway, while kinetic studies demonstrated the involvement of both the sulphur and the double bond in the rate-determining, ionisation step. The degree of sulphur participation in the rate-determining step was found to be 96% for the trans isomer (65) and 83% for the cis isomer (66). Coupling of these figures with the relative rates for the reactions (k_{65} = 1.4; k_{66} = 0.27) led Milaszewski to the conclusion that the stereochemistry of the S_N2' reaction could be either anti (as in 65) or syn (as in 66) and that there was a 6:1 preference for sulphur to participate in an anti fashion.

In summary, therefore, the stereochemistry of the S_N2' reaction, like the very existence of the reaction , appears to be in some doubt and further studies to dispel some of this doubt would be welcomed.

4. Theoretical studies.

The first theoretical studies of the S_N2' reaction to use a molecular orbital (MO) approach were performed by Fukui and Fujimoto[78,79] who, in a general application of MO theory to the



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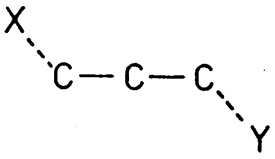

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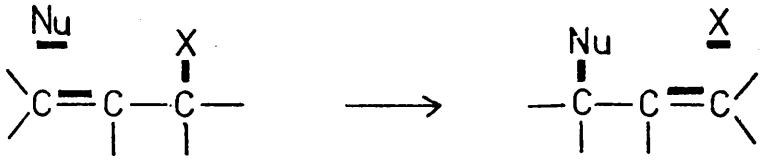


72

73

rationalisation of the stereoselectivity observed in certain non-cyclic reactions of planar, conjugated systems, concluded that, for the specific case of a 1,3 non-cyclo-interaction (of which the S_N2' reaction is an example), the syn mode of interaction should be energetically favoured relative to the anti mode, i.e. that the S_N2' reaction should exhibit a stereoelectronic preference for syn entry of nucleophile and departure of leaving group.

This conclusion was supported by Drenth[80] who, by use of a simple Hückel MO treatment, demonstrated that the syn transition state (70) was of lower energy than the corresponding anti transition state (71).

In a qualitative approach, analogous to Woodward and Hoffmann's treatment of sigmatropic reactions[81], Anh[72] considered the transition state of the S_N2' reaction as an allylic cation interacting with two anions, X and Y. As in a sigmatropic reaction,[81] the most important interactions are those between the lowest unoccupied molecular orbital (LUMO) of the allyl cation and the highest occupied molecular orbitals (HOMO) of the anions, X and Y. Depending upon the relative timing of the bond-making and bond-breaking processes, he concluded that the reaction could proceed either in syn fashion (for a concerted reaction in which bond-breaking is running ahead of bond-making), or in anti fashion (for a fully synchronous process).

In a further extension of the Woodward-Hoffmann Rules,[82,83,84] Mathieu,[85] and Rassat[86] suggested that the stereochemistry of non-cyclic, concerted reactions could be determined by consideration of the parity (oddness or evenness) of the number of electron pairs involved in the reaction. Thus, in the S_N2' reaction, which involves 3 electron pairs, syn stereochemistry is to be

preferred (72→ 73).

Another qualitative approach was employed by Liotta,[87] who applied his "orbital distortion technique"[88] to resolving the dichotomy between the syn stereochemistry demonstrated by Stork and White[14] for the reaction of piperidine with allylic 2,6-dichlorobenzoates (39, 40, 41) and the anti stereochemistry demonstrated by Rickborn,[75] and Johnson[76] for the reaction of 1,3 cyclohexadiene mono-epoxide (63) with lithium dimethyl cuprate. He concluded that the S_N2' reaction should, indeed, have syn stereochemistry and that the work of Rickborn, and of Johnson, was best explained by the assumption[89] that the first step involved a one-electron transfer from the reagent to the substrate to form a radical anion intermediate whose conformation was the cause of the subsequent anti stereochemistry of attack by the alkyl group.

In the first quantitative attempt to determine the stereochemistry of the S_N2' reaction by theoretical calculations, Yates, Epiotis, and Bernardi[91] used ab initio and semi-empirical methods to show that the stereochemistry was determined by non-bonded interactions and electrostatic factors, rather than by an inherent electronic requirement for a particular stereochemistry. Thus, they proposed that the stereochemistry of the S_N2' reaction could be externally controlled by suitable manipulation of the electronic and steric properties of the nucleophiles and allylic substrates employed, and that, in particular, neutral nucleophiles would favour syn attack, while charged nucleophiles would favour anti attack.

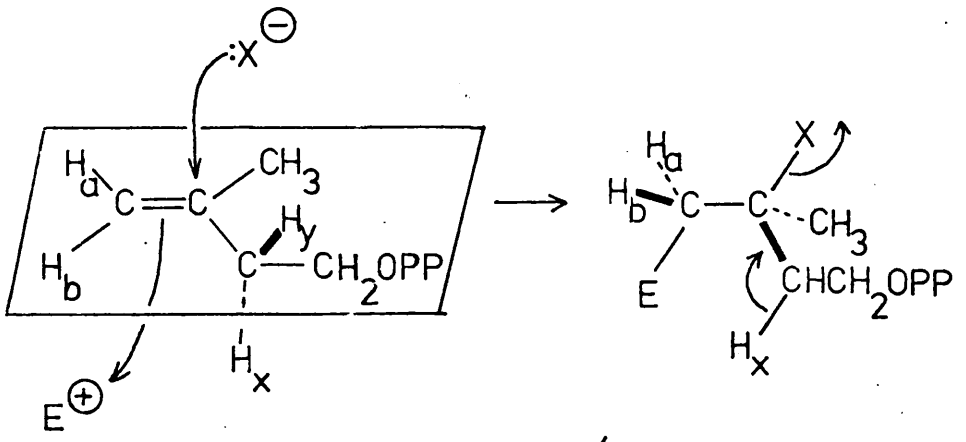
5. Introduction to this study

Consideration of the results already obtained regarding the stereochemistry of the S_N2' reaction leads, almost inevitably, to the conclusion that the requirement demonstrated by Stork and White for S_N2' reactions to occur in *syn* fashion[14], must, now, be regarded with some degree of doubt. Thus, any study which will reinforce, or contradict, the work of Stork and White would be welcomed as a means of determining whether there really is a preferred stereoelectronic course for the S_N2' reaction - it is to this objective that the work described in this thesis is directed.

The impetus for the work to be reported originated from an apparent irregularity of behaviour in the enzyme-mediated biosynthesis of terpenoids and steroids. Two of the fundamental reactions in this process are the enzymic interconversion of isopentenyl pyrophosphate (74) to dimethyl allyl pyrophosphate (75) and the subsequent enzymic condensation of these isomers, producing geranyl pyrophosphate (76).

The isomerisation reaction has been shown to exhibit an *anti* relationship[92,93,94] between the electrophile (H_c) and the leaving group (H_x), while the formally analogous condensation reaction exhibited a *syn* relationship[94,95] of electrophile (dma-OPP) to leaving group (H_x).

Intuitively,[96,97] and from orbital symmetry arguments,[72,78,98] both of these formally S_E2' reactions should proceed in *anti* fashion. Cornforth and Popjak[95,96,97] neatly circumvented this apparent contradiction by their now famous postulate involving an unidentified nucleophile in the condensation reaction.



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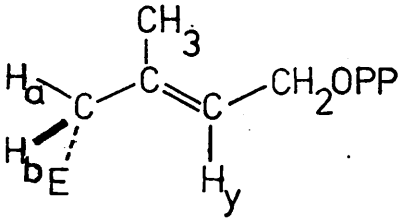

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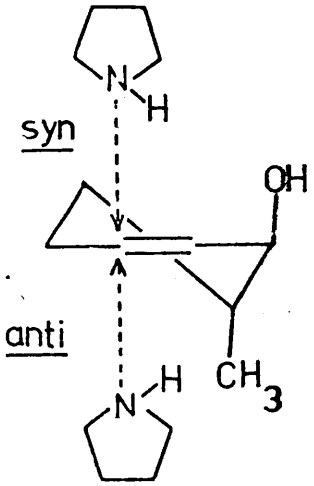
E = dma-OPP OPP = $OP_2O_6^{3-}$



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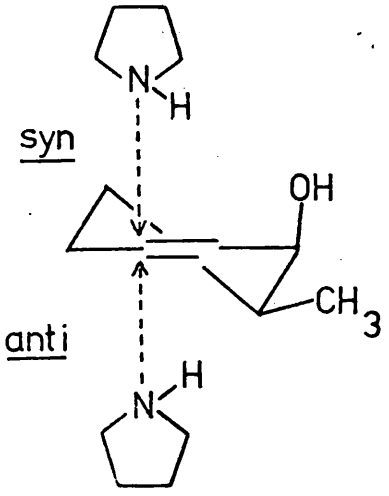


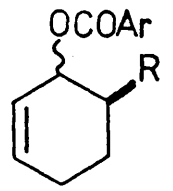
79

In this so-called "X-group mechanism", the nucleophile X and dimethyl allyl pyrophosphate (75) were added in anti fashion across the double bond of isopentenyl pyrophosphate (74), followed by a subsequent trans elimination of H_X and X.

No proof, other than the stereochemistry of the observed product (76) is available for the "X-group mechanism" however, and Cunningham and Overton[99] have, recently, suggested that S_E2' reactions observed in steroidal systems may proceed in either syn or anti fashion provided that the carbon to leaving group bond may attain a significant degree of coplanarity with the π-system. The stereoselectivity observed in their experiments is ascribed to steric, rather than stereoelectronic factors, a conclusion reinforced by quantitative, semi-empirical (INDO) molecular orbital calculations.[100]

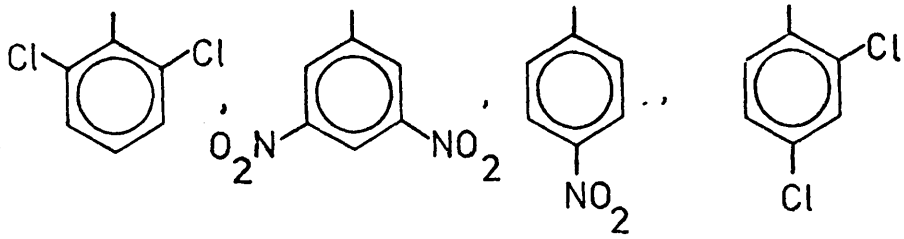
Extension of this theoretical approach to study of the stereochemistry of the S_N2' reaction suggested that steric factors may be dominant in that case, also. These studies appeared to indicate that, in the simple case of propene being attacked at C-3 by a hydride ion, either syn or anti stereochemistry was possible,[100] and that, in a model system (78)[101] for that studied by Stork and White,[14] the syn mode of attack was preferred[100] because of steric hindrance by the 6-alkyl group to anti attack. In the epimeric case (79), however, both modes of attack were predicted to be feasible[100] because the steric barrier to anti attack had been largely removed, since the 6-alkyl group was quasi-equatorial when the molecule was in the most favourable conformation for overlap of the C-O bond with the developing π-system.[65,99]

This thesis is a report of experiments performed in order to



80

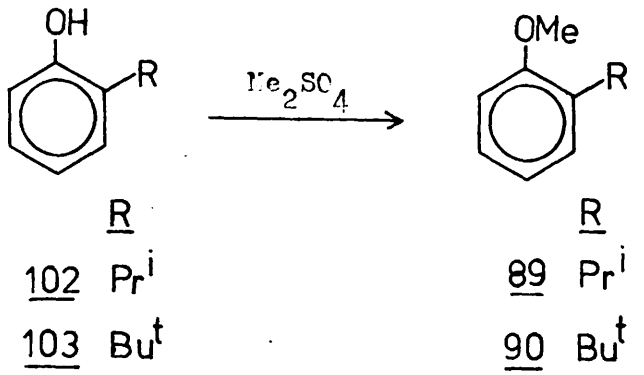
R = Me, Pr^i, Bu^t

Ar = 

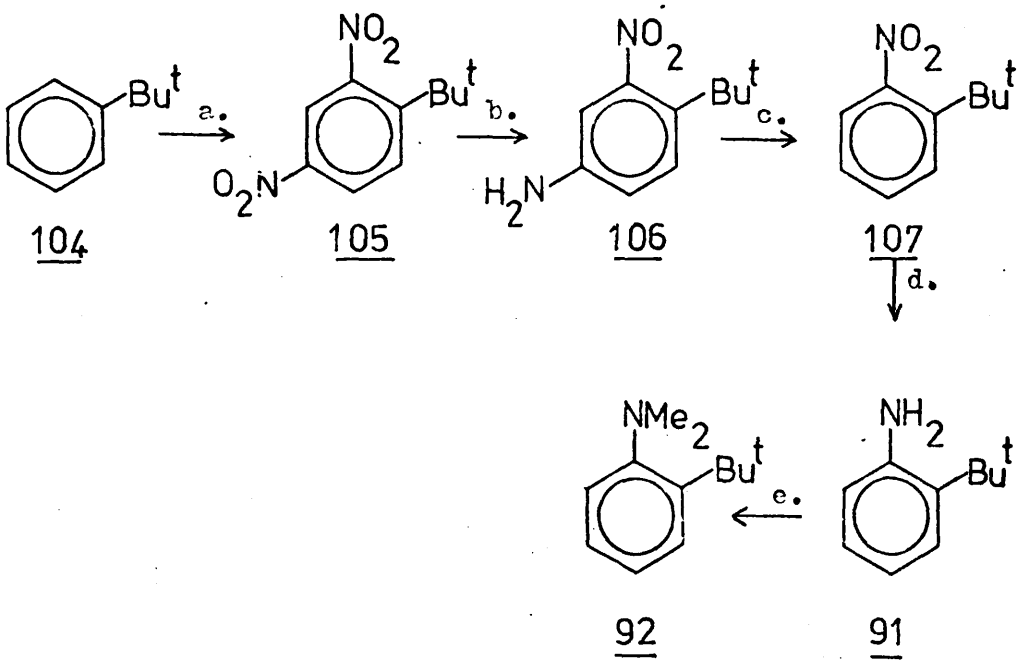
test the above prediction, regarding the stereochemistry of the S_N2' reaction.[14] In particular the present report will describe attempted syntheses of compounds of the general formula (80) and their subsequent reactions with piperidine.

DISCUSSION

Scheme 2. Preparation of anisoles and anilines



R		R	
102	Pr^i	89	Pr^i
103	Bu^t	90	Bu^t

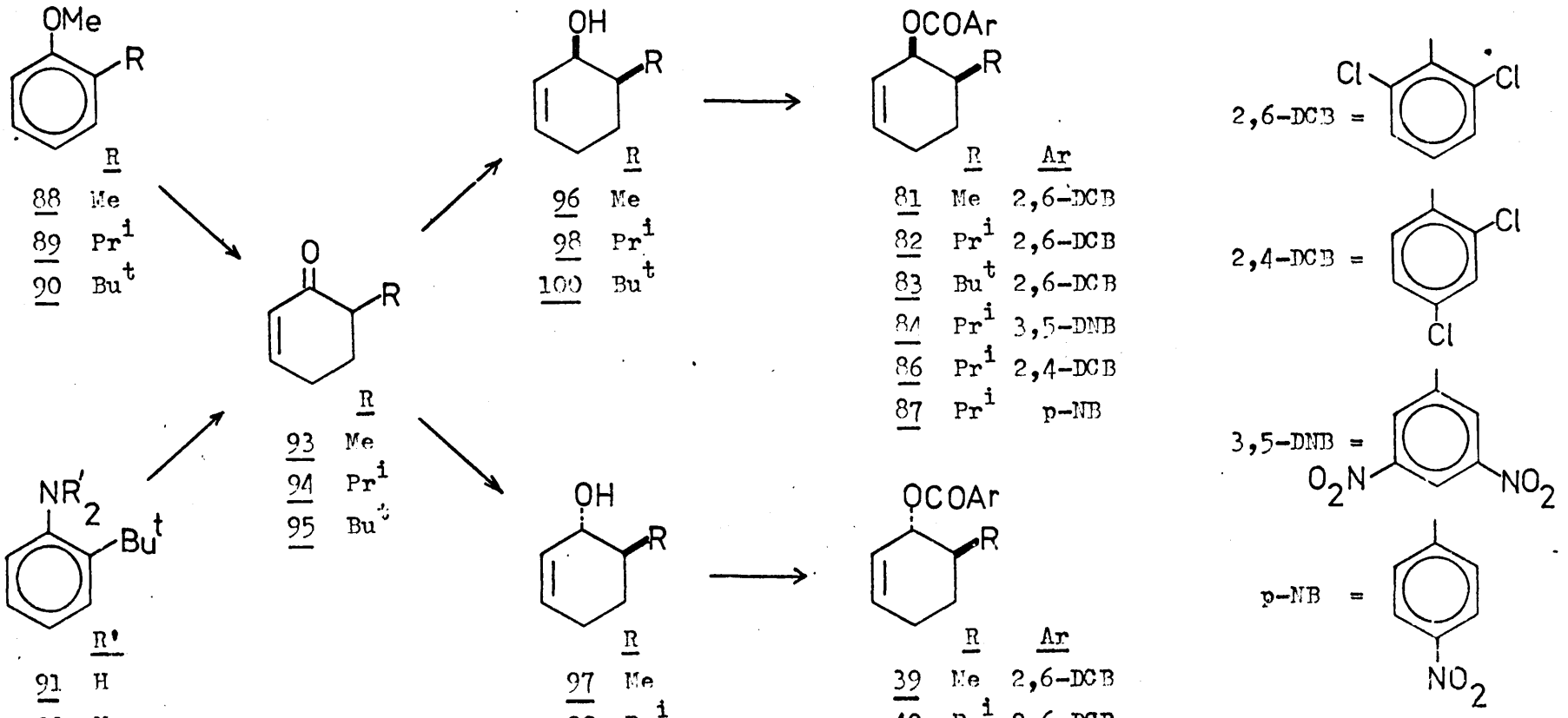


104 105 106 107 92 91

a. HNO_3/H_2SO_4 b. Na_2S/S_8 c. $HCl/NaNO_2$ then H_3PO_2

d. Fe/acetic acid e. MeI

Scheme 1. Synthetic route to allylic esters



Part A. Synthesis of allylic esters for use as substrates in study of the S_N2' reaction.

1. Summary.

Initially, it was intended to prepare the cis and trans 6-alkyl cyclohex-2-en-1-yl 2,6-dichlorobenzoates (39, 40, 41, 81, 82, 83) for use as substrates for the S_N2' reaction, since Stork and White[14] had already employed the trans epimers (39, 40, 41) for this purpose.

Difficulties encountered in the preparation of these esters, however, led to an expansion of this objective to include the synthesis of other displaceable ester derivatives, in particular the cis and trans 3,5-dinitrobenzoates (84, 85) and the cis 2,4-dichlorobenzoate (86) and p-nitrobenzoate (87).

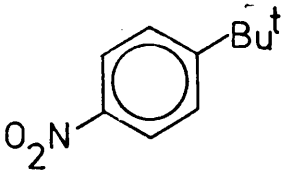
The synthetic route to these compounds is shown in Schemes 1 and 2, and will now be discussed.

2. Preparation of anisoles and anilines required as substrates for Birch reduction (Scheme 2).

Methylation[102] of 2-isopropyl phenol (102) and 2-tert.butyl phenol (103) produced the desired 2-alkyl anisoles (89, 90).

The aniline derivatives, 2-tert.butyl aniline (91) and its N,N-dimethylated analogue (92), were prepared from tert.butyl benzene (104) by known procedures:-

Nitration[103] of tert.butyl benzene (104) proved troublesome, producing a mixture of PLC-separable nitrated compounds,



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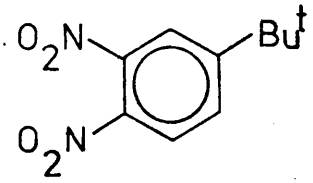

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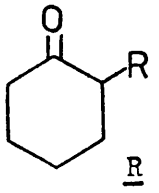
Table 1. Reported[102] yields of enones and ketones from Birch reductions.

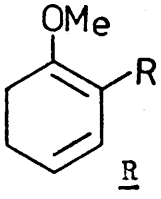
substrate		saturated ketone		enone	
		identity	%yield	identity	% yield
88	2-methyl anisole	110	17	93	52
89	2-isopropyl anisole	111	13	94	13
90	2-tert.butyl anisole	112	5	95	10
91	2-tert.butyl aniline	112	23	95	25
92	N,N-dimethyl 2-tert.butyl aniline	112	20	95	24



110 Me

111 Pr^i

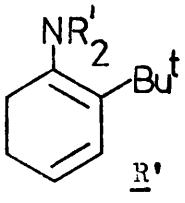
112 Bu^t



113 Me

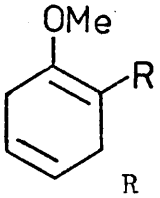
114 Pr^i

115 Bu^t



116 H

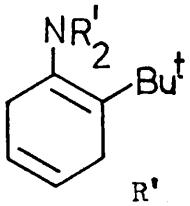
117 Me



118 Me

119 Pr^i

120 Bu^t



121 H

122 Me

including 4-nitro-tert.butyl benzene (108; 70%), 2,4-dinitro-tert.butyl benzene (105; 20%), and 3,4-dinitro-tert.butyl benzene (109; 2%). However, under more forcing conditions, it was possible to obtain 64% yield of the desired 2,4-dinitro-compound (105).

Removal of the 4-nitro group via selective reduction[103] to the 4-amino compound (106) and reductive deamination[103] produced the 2-nitro compound (107) which was reduced[104] to 2-tert.butyl aniline (91).

Attempted methylation of this by formylation/reduction[105] was not successful and the desired N,N-dimethyl 2-tert.butyl aniline (92) was subsequently prepared by treatment[106] of the aniline (91) with methyl iodide.

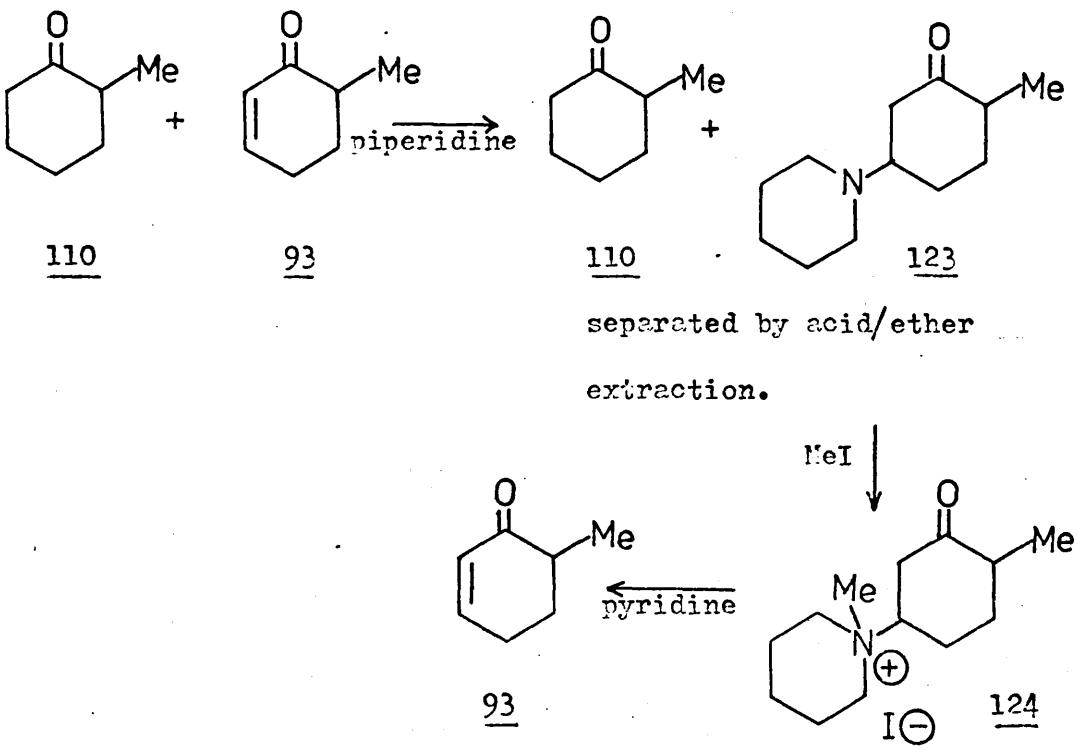
3. Birch reduction; preparation of 6-alkyl cyclohex-2-en-1-ones

Stork and White found[102] that Birch reduction of 2-alkyl anisoles (88, 89, 90) and 2-alkyl anilines (91, 92) yielded mixtures of the desired 6-alkyl cyclohex-2-en-1-ones (93, 94, 95) and the corresponding saturated ketones (110, 111, 112; Table1).

These unwanted saturated ketones were, presumably, formed by reduction of intermediate 1,3-cyclohexadienes (113-117), resulting from conjugation of the initially formed enol ethers (118, 119, 120) and enamines (121, 122). Such a process is known, for anisoles, to be dependent upon the acidity of the proton source employed.[107]

This study will show, in agreement with other reports[108-110] for similar systems, that the best conditions for obtaining

Scheme 3. Chemical separation of saturated and unsaturated ketones resulting from Birch reduction.



dihydro rather than tetrahydro products from Birch reduction involve the use of lithium, with tert.butanol as proton source, and tetrahydrofuran (THF) as co-solvent.

Thus, the procedure[110] adopted for the Birch reduction was a modification of that used by Stork and White[102], in the hope that an improved ratio of unsaturated to saturated ketones would result.

It was anticipated, wrongly, that Birch reduction of 2-tert.butyl anisole (90) would be unsatisfactory[102] and that the most suitable substrates for Birch reduction in the tert.butyl series would be the anilines (91,92).[102] As will be seen, however, this expectation was reversed for the reduction process chosen.[110]

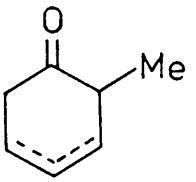
a. Results

(i) Methyl series

Birch reduction of 2-methyl anisole (88) and acid hydrolysis of the product produced a ketonic mixture, apparently containing the expected[102] saturated (IR: 1720cm^{-1}, νC=O) and unsaturated (IR: 1690cm^{-1}, νC=O α,β unsaturated) ketones (110, 93).

Isolation of 6-methyl cyclohex-2-en-1-one (93) from this mixture was, accordingly, pursued via the chemical separation method developed by Stork and White[102] (Scheme 3). This involved reaction of the mixture with piperidine, separation of the resulting piperidino-compound (123) from the inert saturated ketone (110), and subsequent regeneration of the desired 6-methyl enone (93) by base-catalysed elimination of the methiodide derivative (124).

However, the material recovered from this process was very



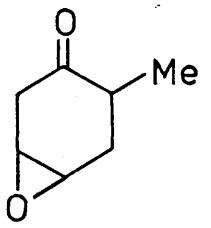
125

similar to the original mixture, showing IR absorptions at both 1690 and 1720cm^{-1}. This suggested that the β,γ unsaturated ketone (125) may be present since this compound would show IR absorption at 1720cm^{-1} and would be expected to react with piperidine, by prior isomerisation to its α,β analogue (93), to produce the piperidino-compound (123). Base-catalysed elimination of the quaternary methiodide would then lead to regeneration of an equilibrium mixture of the α,β and β,γ enones (93, 125).

Further investigation of the Birch reduction thus appeared appropriate. IR and Nmr examination of the products, before acid hydrolysis, from a second reduction showed the major component (74% by GLC) to be the expected 3,6 dihydro anisole (118).

On acid hydrolysis, ketonic mixture similar to that from the first reduction was obtained. This mixture was inseparable by TLC and column chromatography but GLC demonstrated the presence of four components (relative % : 2, 5, 15, 78) and Nmr identified the major component as the desired 6-methyl cyclohex-2-en-1-one (93). Attempts to identify the other components by further Nmr investigation, utilising double irradiation techniques, were unsuccessful, but GC-MS analysis showed the 5% component to be the expected [102] 2-methyl cyclohexanone (110), while the 15% component was shown to be isomeric with the desired enone (93). The UV spectrum of the mixture showed only the absorption expected for the major product (λ_{max}^{EtOH} 224nm, ϵ7350).

Assuming the major contaminant (15%) to be the previously proposed β,γ enone (125), unsuccessful attempts were then made to alter the ratio of this product to the desired enone (93) by treatment with base. The failure of this attempt suggested



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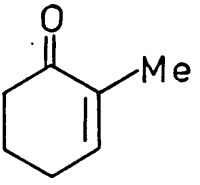
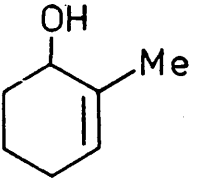


127



128

equilibration between the α,β and β,γ enones (93, 125) and a chemical separation method was, therefore, devised. It was hoped that selective epoxidation[111, 112] of the β,γ isomer (125) would lead to a mixture of the β,γ epoxide (126) and α,β enone (93) which would be more amenable to chromatographic separation than the parent mixture (93, 125). Results were disappointing, however, - instead of selective epoxidation, Baeyer-Villiger oxidation occurred, producing a mixture of lactones and this method was, consequently, abandoned.

Because of these failures, the chromatographic behaviour of the ketonic mixture was explored further. TLC and column chromatography on various grades of silica and alumina were unsatisfactory, either because no separation was achieved or, particularly with alumina, because the material applied to the column was not recovered in its original state. The only technique found to give a practicable separation was TLC on $AgNO_3$-impregnated silica. Although rather unwieldy on a large scale, this method eventually produced 66% recovery of apparently pure (by TLC and GLC) 6-methyl cyclohex-2-en-1-one (93) - or so it was thought!

For, although the IR, Nmr, MS and UV spectra of this material appeared to confirm its identity as the desired 6-methyl enone (93), it was later found to contain 16% of its 2-methyl isomer (127). This discovery was made after LAH reduction and separation of the alcohol products when 2-methyl cyclohex-2-en-1-ol (128) was identified, suggesting the presence of its enone precursor, 2-methyl cyclohex-2-en-1-one (127) as an inseparable impurity in the sample of supposedly pure 6-methyl cyclohex-2-en-1-one (93).

(ii) isoPropyl series

Birch reduction of 2-isopropyl anisole (89) produced a four component mixture, comprising starting material (89, 14%) and three products (relative %: 11, 14, 61). IR and Nmr analysis of the mixture identified the major component (61%) as the expected 3,6 dihydro anisole (119).

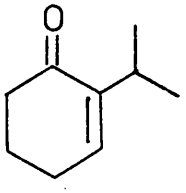
Acid hydrolysis gave a mixture shown to contain 2-isopropyl anisole (89, 14%) and four other components (relative %: 10, 2, 20, 54). Analysis of this mixture was complicated by the fact that the major impurity (20%) and the anisole (89; 14%) were inseparable on available GLC systems, but an estimate of the amount of anisole was obtained from Nmr. As in the methyl series, the mixture was seen to contain both saturated and unsaturated ketones (IR: 1720, 1690cm^{-1}) while its Nmr spectrum demonstrated that the major product was, indeed, the desired 6-isopropyl cyclohex-2-en-1-one (94).

TLC and column chromatography failed to separate the ketonic components of the mixture, but preparative GLC did effect a separation, albeit at high cost in labour and yield - only 38% recovery of the desired 6-isopropyl enone (94) was obtained.

Consequently, efforts were then directed towards improvement of the yield from Birch reduction and of the separation efficiency.

Repetition of the reduction, over a longer period, yielded a mixture containing only 2% of the starting material (89), which, by that time, could be separated from the major impurity on an improved GLC system, and an increased amount (69%) of the desired enone (94).

Other separation methods were investigated. Of these, "dry-column chromatography"[113] appeared to be the most promising and after extensive testing, was shown to be the method of choice.



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Using this method, 51%* recovery of the enone (94) was achieved and that in a very much shorter time than was required for preparative GLC.

The major impurities were also identifiable after separation by "dry-column chromatography" and were shown to be 2-isopropyl cyclohexanone (111, 14% of mixture) and 2-isopropyl cyclohex-2-en-1-one (129, 15% of mixture).

(iii) tert.Butyl series

Birch reductions of 2-tert.butyl aniline (91) and of its N,N-dimethylated analogue (92) were totally ineffective, yielding high recovery of starting materials and only traces of products.

This unexpected[102] discovery led to attempts being made to reduce 2-tert.butyl anisole (90) using the improved Birch reduction procedure[110], although Stork and White had found it to be an unsatisfactory substrate under their conditions.[102]

Birch reduction of this anisole (90) gave 95% yield, after acid hydrolysis, of a four-component mixture, comprising three products (relative %: 17, 18, 40) and starting material (90, 25%).

As in the methyl and isopropyl series, the mixture was seen to contain both saturated and unsaturated ketones (IR: 1720, 1685cm^{-1}). Nmr analysis of the mixture was more complex than before but it did prove possible to determine that the major component was the desired 6-tert.butyl cyclohex-2-en-1-one (95).

Although the three ketonic products were inseparable by "normal" TLC, the use of multiple development techniques resulted

* In practice, this figure was often further increased (by up to 20%) by rerunning partially separated mixtures.

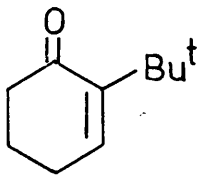

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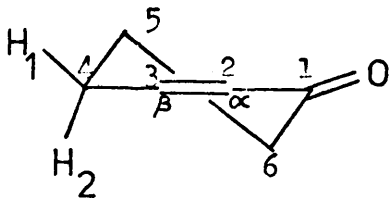
Figure 1.

a.

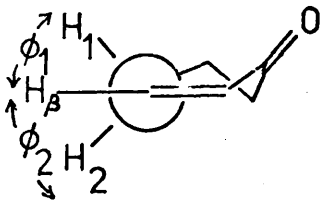


C-1,2,3,4 coplanar

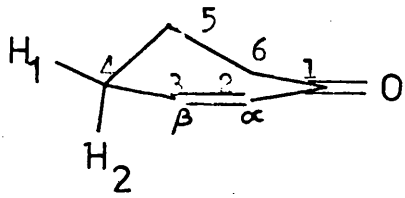
C-5, and O above plane

C-6 below plane

View along C-3 to C-4.



b.



C-1,2,3,4,6, and O are coplanar.

C-5 out of plane.

View along C-3 to C-4.

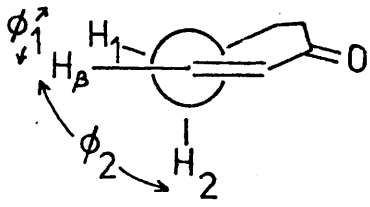
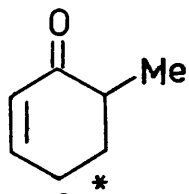
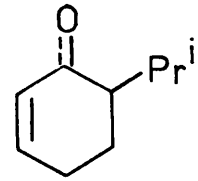
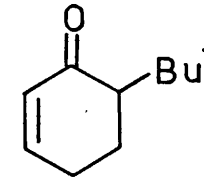


Table 2. Analysis of 6-alkyl cyclohex-2-en-1-ones.

	 93 *	 94	 95
IR (cm^{-1})	1690	1690	1685
Nmr (δ)	6.93 (1H, d of t of d, J=10,4,1Hz.) 5.95 (1H, d of t, J=10,2Hz.)	6.88 (1H, d of t of d, J=10,4,1Hz.) 5.95 (1H, d of t, J=10,2Hz.)	6.80 (1H, d of t of d, J=10,4,1Hz.) 5.91 (1H, d of t, J=10,2Hz.)
MS (M^+)	110	138	152
UV $\lambda_{max.}^{EtOH}$	224nm. (ϵ 7350)	225nm. (ϵ 9000)	225nm. (ϵ 8000)
% yield	43	30	25
GLC	97+%	99+%	97+%

* Contains approximately 16% of its 2-methyl isomer (127)

in a partial separation, which was exploited by chromatogramming the mixture on a silica gel column.

Extensive testing led to a practicable method for separating the ketonic components which, in order of elution, were shown to be 2-tert.butyl anisole (90), 2-tert.butyl cyclohexanone (112), 2-tert.butyl cyclohex-2-en-1-one (130) and 6-tert.butyl cyclohex-2-en-1-one (95). Using this method, the desired enone (95) was recovered in 66% yield.

Repetition of the Birch reduction under different conditions produced a mixture containing 35% of this enone (95), of which 58% was recoverable, using the method above.

b. Analysis of 6-alkyl cyclohex-2-en-1-ones

The relevant spectroscopic and analytical data of the 6-alkyl cyclohex-2-en-1-ones (93, 94, 95) formed by Birch reduction are shown in Table 2.

The enones (93, 94, 95) exhibited very similar IR, Nmr and UV spectra. Particularly significant were the Nmr signals due to the vinyl protons. H_β appeared to lower field than H_α, as expected[114]. They were vicinally coupled (J = 10 Hz.) and H_β had additional vicinal coupling to the two protons at C-4 (J = 4Hz.) and a further, smaller coupling, presumably via a "W" configuration to one of the protons on C-5 (J = 1Hz.),[115] while H_α had additional allylic coupling to the two protons at C-4 (J = 2Hz.).

The fact that the coupling of the two protons at C-4 to either H_α or H_β produced a triplet suggested that the C-4 protons were symmetrically disposed about the plane formed by C-2, C-3 and C-4. This would be expected[116, 117] for the monoplanar "half-chair" conformation (Figure 1a) in which the carbonyl and double bond

do not lie in the same plane, but would not be possible[116, 117] for the 1, 2 diplanar or "envelope" conformation (Figure 1b) where the carboryl and olefinic groups are coplanar. In the "envelope" conformation, the vicinal coupling of H_β to H_2 would be negligible[117] since the dihedral angle (ϕ_2) between them is approximately 90° while the coupling to H_1 would be appreciable,[117] ($\phi_1 \sim 30°$). Thus, coupling of H_β to the protons at C-4 would produce a doublet for this conformation, while for the "half-chair" a triplet would be expected since $\phi_1 \approx \phi_2$ in that conformation. Conversely, the allylic coupling of H_α to H_1 would be negligible[118] in the "envelope" conformation ($\phi_1 \sim 30°$) while that to H_2 would be appreciable[118] ($\phi_2 \sim 90°$), thus producing a doublet for this conformation but a triplet in the "half-chair" ($\phi_1 \approx \phi_2$).

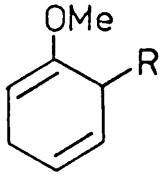
Thus, the observation of triplets for the coupling of H_α and H_β to the protons at C-4 suggests that the preferred conformation of the enones (93, 94, 95), in solution, resembles the "half-chair" rather than the "envelope".

The conformation of cyclohex-2-en-1-ones in solution has been a matter of debate[119], for some studies have shown that the carbonyl and conjugated olefinic bond are not normally coplanar[120, 121] (Figure 1a) while others[122, 123, 124] have favoured the coplanar structure (Figure 1b) on the basis of microwave,[122] Nmr,[123] and circular dichroism[124] analysis.

c. Conclusions

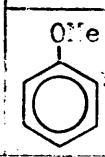
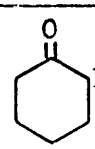
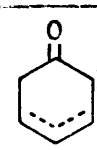
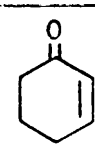
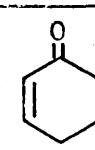
Summaries of the results obtained from the various Birch reductions are given in Tables 3 and 4.

(i) The isolated yields of 6-alkyl cyclohex-2-en-1-ones (93, 94,



R	
131	Me
132	Pr^i
133	Bu^t

Table 3. Summary of results from Birch reductions of 2-alkyl anisoles.

Substrate	Product distribution (%)					recovery of 6-alkyl enone %	yield %	reported yield[102] %
								
88[a] R=Me	-	5	15	13[d]	65[d]	66[f]	43	52
89[a] R=Pr^i	14[e]	10	-	20[e]	54	38[g]	17	13
89[b] R=Pr^i	2	14	-	15	69	51[h]	30	
90[a] R=Bu^t	25	17	-	18	40	66[j]	25	10
90[c] R=Bu^t	28	18	-	19	35	58[j]	19	

a. Standard conditions[110] b. Longer reaction time c. Higher concentration of substrate d. Analysis after LAH reduction e. Analysis by n.m.r. f. separated by $AgNO_3$-impregnated t.l.c. g. Separated by prep. g.l.c. h. Separated by dry-column chromatography[113] j. Separated by column chromatography.

Table 4. Distribution of ketonic products from Birch reduction.*

a. ratio of unsaturated to saturated ketones.

b. ratio of 6-alkyl to 2-alkyl enones.

Substrate	a. Col. 1	a. Col. 2	a. Col. 3	b.
88 R=Me	93:7	94:6	75:25	83:17
89 R=Pr^i	84:16	88:12	50:50	73:27
90 R=Bu^t	70:30	77:23	67:33	69:31

* All values reported refer to standard conditions[110]

Col. 1 = 6-alkyl enone/saturated ketone

Col. 2 = 6- and 2-alkyl enones/saturated ketone

Col. 3 = reported ratio[102] of enone/saturated ketone

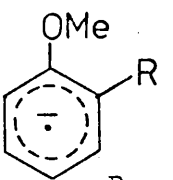
95) are seen to be superior to those obtained by Stork and White[102] for the iscpropyl and tert.butyl series, thus justifying the choice of reduction procedure[110] (Table 3).

(ii) Similarly the ratio of unsaturated to saturated ketone has been improved for each of the series (Table 4a). Direct comparison with the results obtained by Stork and White[102] (Col. 3) is hampered, however, by the difficulty of knowing which of the values (Col. 1 or 2) corresponds to their result (Col. 3) since it is possible that the 2-alkyl cyclohex-2-en-1-ones (127, 129, 130), although undetected, may have been present in their samples of 6-alkyl cyclohex-2-en-1-ones (93, 94, 95) and may therefore, have been unwittingly included in the reported[102] ratios of unsaturated to saturated ketones.

The observed decrease in this ratio (as determined from this study, Table 4, Cols. 1,2) as the size of the alkyl group increases is presumably related to either the ease of conjugation of the intermediate 1,4-dienes (118, 119, 120) or to the ease of reduction of the resulting 1,3-dienes (113, 114, 115) or to both.

(iii) The formation of the 2-alkyl cyclohex-2-en-1-ones (127, 129, 130), although unexpected according to the work of Stork and White,[102] is, in fact, in agreement with results obtained by Smith,[107] who, using sodium, with ethanol as proton source, found that 2-methyl (88) and 2-isopropyl anisole (89) produced mixtures containing the 2-alkyl cyclohex-2-en-1-ones (127, 129) in addition to their 6-alkyl isomers (93, 94) and saturated ketones (110, 111).

The reason for the occurrence of 2,5-reduction to give the enol ethers (131, 132, 133) from which the 2-alkyl enones (127, 129, 130) were formed appears[110] to be related to selectivity in the addition of the first proton to the initial radical



R

134 Me

135 Pr^i

136 Bu^t

anions (134, 135, 136). Whether this is directed exclusively, or only partly, by the charge distribution[125] is still a matter of debate[126-131] and is unlikely to be settled until an experimental method can be devised to decide which proton is added first.

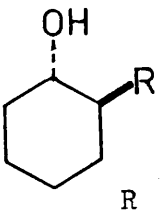
The observed decrease in the ratio of 6-to 2-alkyl enones as the size of the alkyl group increases (Table 4b) may be associated with the greater electron-releasing effect of the alkyl group to the para (C-5) rather than the ortho (C-3) position,[132] thereby leading to an increased amount of 2,5 reduction as the ability of the alkyl group to supply electrons increases.

(iv) Although evidence for its presence is circumstantial, the proposed formation of the β,γ-enone (125) from reduction of 2-methyl anisole (88) is not entirely unexpected since it has been demonstrated[133] that the equilibrium ratio of α,β and β,γ isomers of some 4-alkyl cyclohex-2-en-1-ones is 70:30,[133] although for cyclohex-2-en-1-one, itself, the ratio is 99:1.[134]

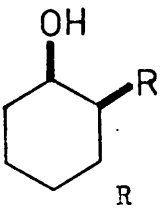
4. Reduction of 6-alkyl cyclohex-2-en-1-ones: preparation of 6-alkyl cyclohex-2-en-1-ols.

The objective of this section of work was to prepare the 6-alkyl cyclohex-2-en-1-ols (96-101) by reduction of their enone precursors (93, 94, 95).

Initially, efforts were directed towards the separation of the alcoholic products from non-selective reduction processes, but emphasis later shifted, because of separation problems, towards stereo- and regioselective reduction. When disappointing results



R	
137	Me
138	Pr^i
139	Bu^t



R	
140	Me
141	Pr^i
142	Bu^t

were obtained there, the circle was completed by returning attention to the improvement of the available separation methods.

a. Product analysis

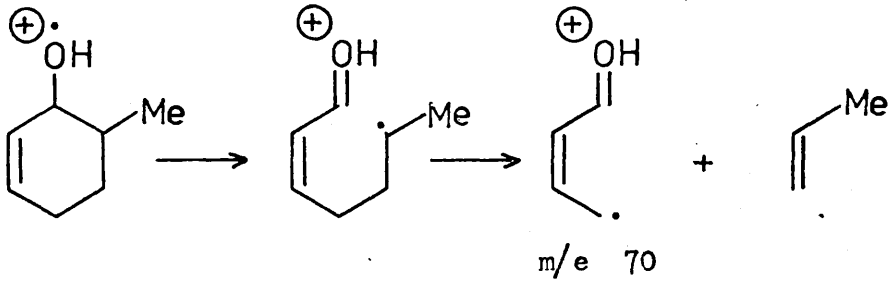
The various reductions of the enones (93, 94, 95) produced complex mixtures of products, whose analysis was complicated by difficulties in their physical separation and by the failure of GLC, the main analytical technique employed, to distinguish all of the components. Potentially the most serious of these complications was the failure of GLC to separate, in the isopropyl and tert.butyl series, the trans saturated alcohols (138, 139) from the corresponding cis unsaturated alcohols (98, 100). This problem was circumvented, however, by two facts: i) the cis saturated alcohols (141, 142) were estimable by GLC and ii) the ratio of cis to trans saturated alcohols could be determined from appropriate reduction of the corresponding saturated ketones (111, 112), thereby permitting estimation of the amount of trans saturated alcohols (138, 139). In practice, however, this problem was seldom as serious as had been feared since the amounts of saturated alcohols (138, 139, 141, 142) formed were generally slight. (<5%)

In spite of these and other difficulties, it eventually proved possible to identify, though not necessarily isolate, the products of the reductions by a combination of analyses of the product mixtures, themselves, and of separated and partially separated components.* Techniques of particular value for the analysis of

* The detailed analysis of the 6-alkyl cyclohex-2-en-1-ols (96-101) is given later (p. 39).

Scheme 4. Fragmentation of methyl cyclohex-2-en-1-ols

a. 6-methyl



m/e 70

b. 2-methyl

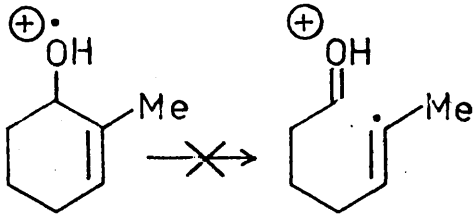
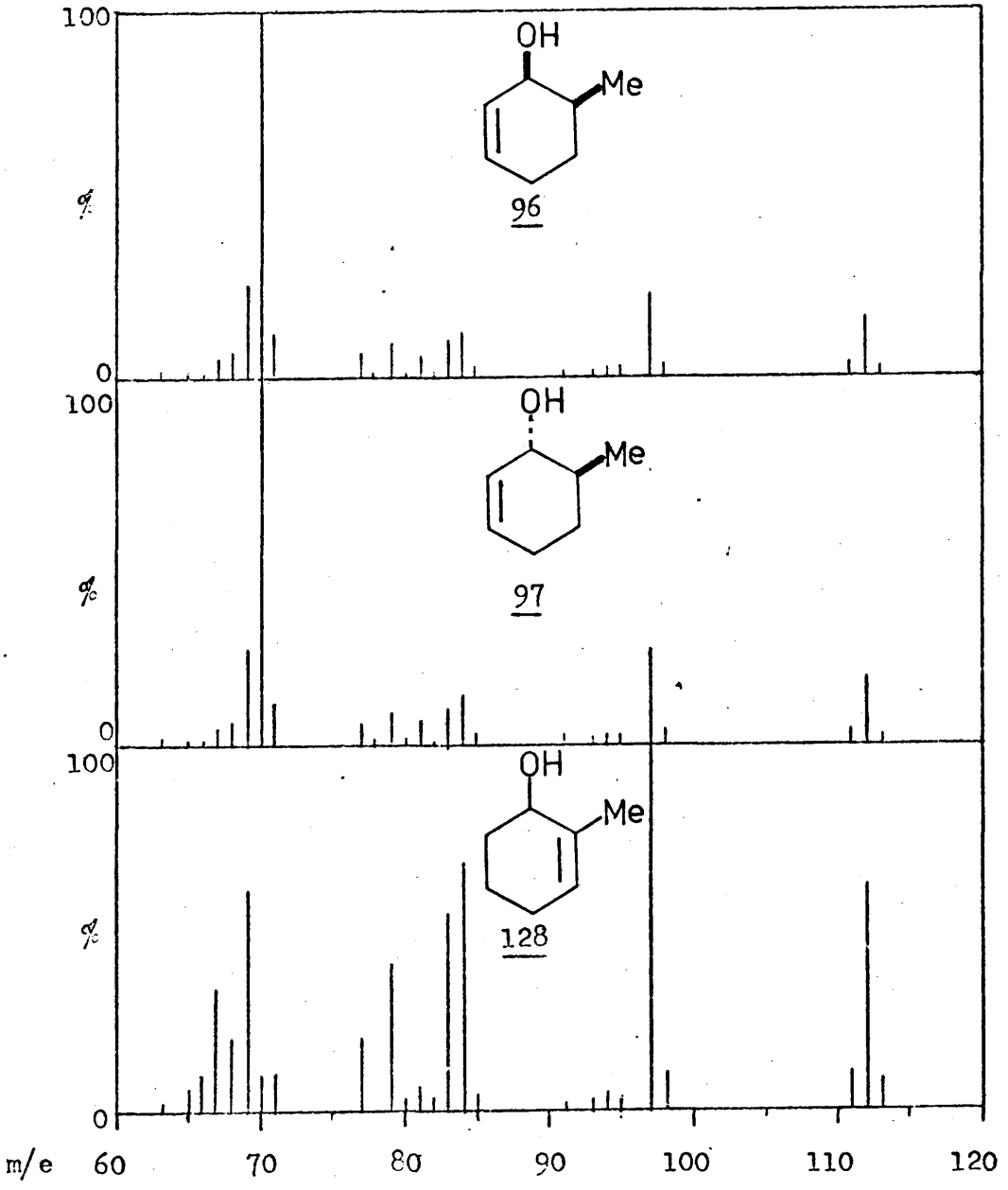


Figure 2. MS of methyl cyclohex-2-en-1-ols



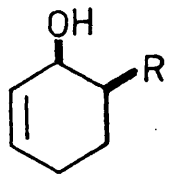
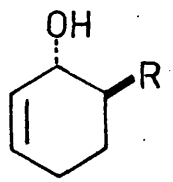
non-separated components were GLC co-injection with authentic materials [enones (93, 94, 95), saturated ketones (110, 111, 112), cis saturated alcohols (140, 141, 142) and trans saturated alcohols (137, 138, 139)] when these became available, and GC-MS.

The GC-MS analysis of the reduction products from the apparently pure 6-methyl enone (93) is worthy of note since this detected the unexpected presence of three isomeric allylic alcohols (96, 97, 128). Differentiation of the structural isomers as 6-methyl (96, 97) or 2-methyl (128) was straightforward since the cis and trans 6-methyl alcohols (96, 97) showed virtually identical fragmentation patterns while that of their 2-methyl isomer (128) was quite different (Figure 2). Their major difference was the lack of a base peak at m/e 70 in the latter, attributable to the fact that, unlike its 6-methyl isomers (96, 97), the 2-methyl alcohol (127) will not undergo α-cleavage followed by propene loss because of the already high electron density on the methyl-bearing carbon (Scheme 4).

b. Separation of products

Extensive efforts to separate the product mixtures were fraught with difficulty. It proved almost totally impossible to obtain a separation of the epimers of the methyl and isopropyl allylic alcohols (96, 97; 98, 99) from one another by TLC or column chromatography on various grades of silica or alumina, although some success was achieved in separating these allylic alcohols (96-99) from the other components of the product mixtures. Of particular value in this context was the use of TLC on $AgNO_3$-impregnated silica , which allowed a separation of the 6-methyl alcohols (96, 97) from their 2-methyl isomer (128) and from the

Table 5. Preparative GLC separation of allylic alcohols.

R						
	compound no.	recovery %	purity %	compound no.	recovery %	purity %
Me	96	21	86	97	27	93
Pr^i	98	16	98+	99	60	99+
Bu^t	100	29	96	101	29	88

saturated analogues (137, 140).

The only liquid chromatographic separation of the allylic epimers achieved was in the tert.butyl series (100, 101), 21% recovery of the cis epimer (100, 96% pure) being realised on a silica column, while 75% recovery of 97% pure alcohol (100) was obtained by multiple development PLC. However, neither method successfully yielded high recovery of the minor component, the trans alcohol (101) - in fact, only 27% recovery of only 58% pure alcohol (101) could be achieved.

Similarly, efforts to separate the alcohol epimers (96-101) via their 2,6-dichlorobenzoate derivatives (39, 40, 41, 81, 82, 83) were frustrated. (see later p.47)

The only separation method to be successfully used at that time was preparative GLC. Although compromise had to be reached between the attainment of reasonable recovery and a reasonable degree of purity, it was possible to obtain sacrificially small quantities of each of the allylic alcohol epimers (96-101) (Table 5).

The obviously unsatisfactory separations so far obtained prompted further study of the reduction processes themselves with a view to achieving a higher degree of stereoselectivity, thereby lessening the separation problem. For several reasons, particularly availability of the enones (93, 94, 95), further investigation was largely restricted to the isopropyl series. The results obtained were disappointing, however, the desired degree of stereoselection being only partially attainable in the absence of conjugate reduction (see later - pp. 42-46, Table 9).

Accordingly further chromatographic experiments were undertaken, utilising the techniques of "dry-column chromatography"[113] and PLC on highly activated silica layers but these, too, were to no avail.

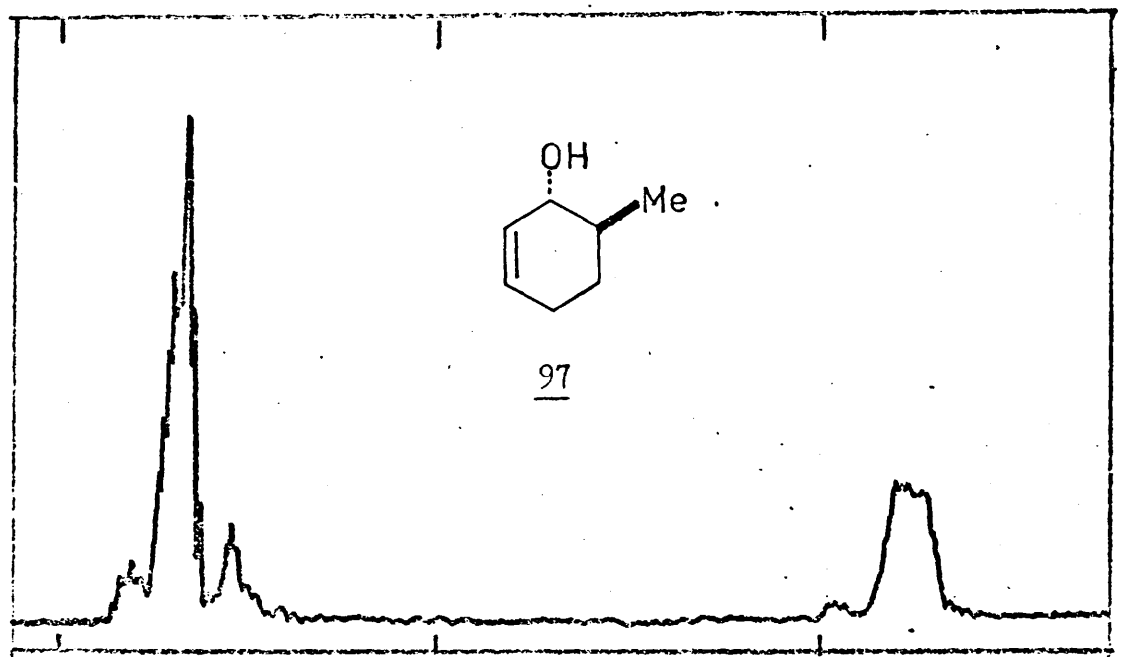
The separation of suitable derivatives, other than the 2,6-dichlorobenzoates (40, 82) was pursued, exploiting the fact that with different reducing agents it had been found possible to alter the ratio of cis to trans alcohols (98, 99) from ~1:2 (ex LAH) to ~3:1 (ex di-isobutyl aluminium hydride, DBAH). From these two different mixtures of alcohols, two mixtures of the corresponding 3,5-dinitrobenzoates (84,85) were prepared in high yield. Very slow fractional crystallisation from hexane afforded the cis ester (84) from the cis-rich mixture and the trans ester (85) from the trans-rich mixture. Monitoring of the recrystallisation procedure, by LAH reduction of the ester mixtures* and GLC analysis of the resulting allylic alcohols (98, 99), allowed the recombination and recrystallisation of appropriate fractions from the mother liquors, a factor which increased the overall recovery of the cis and trans esters (84, 85) to 68% and 60%, respectively.

By that time, the pure trans allylic alcohol (99), isolated by preparative GLC, had already been converted in 15% yield (see later p. 47) to its 2,6-dichlorobenzoate derivative (40). Thus, it seemed, the final requirement in the isopropyl series was to convert the cis 3,5-dinitrobenzoate (84), via hydrolysis and re-esterification, to the cis 2,6-dichlorobenzoate (82).

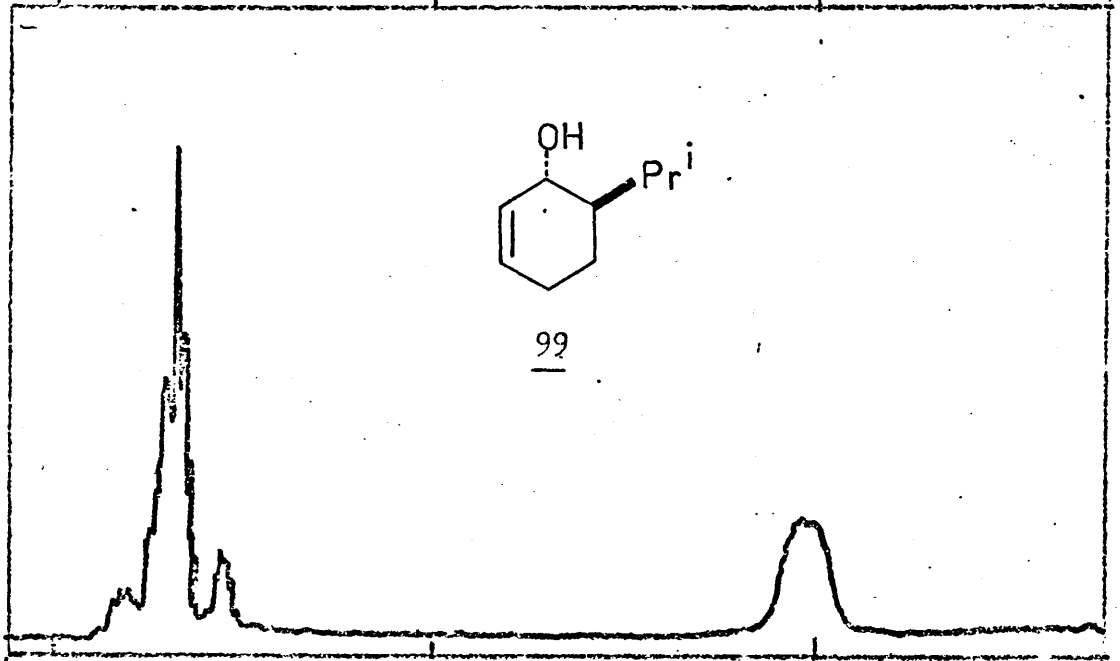
In practice, this final stage was not satisfactorily accomplished - a fact which was to have more than the obvious significance. For, as it happened, the 3,5-dinitrobenzoate derivatives themselves, (84, 85) were later found to be suitable substrates for study of the S_N2' reaction. By the time this was

* The esters (84, 85) could not be directly analysed.

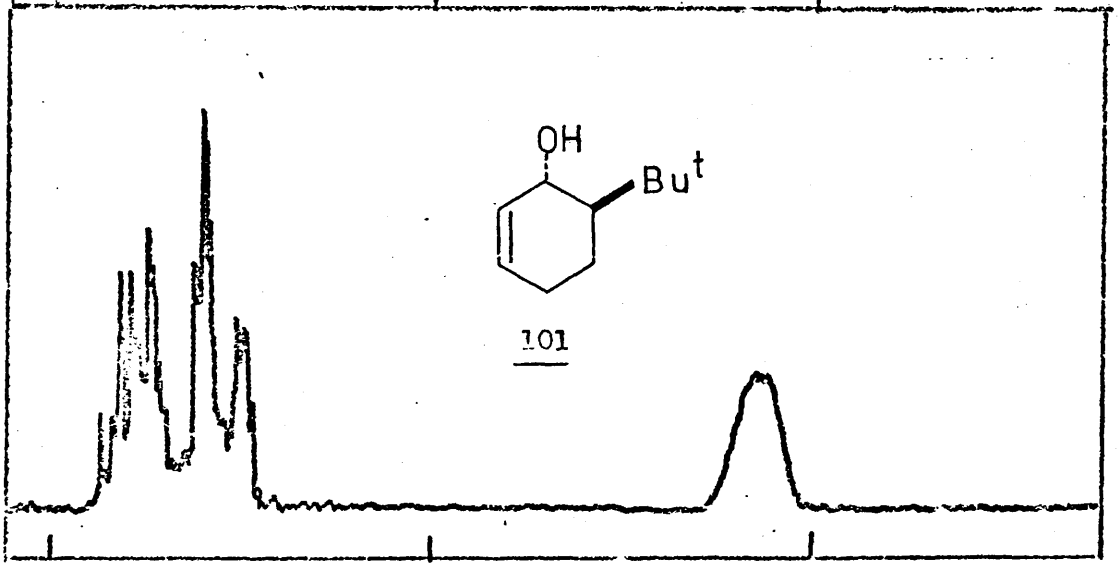
Figure 3b. Partial Nmr spectra of trans 6-alkyl cyclohex-2-en-1-ols.



97



99



101

δ 6.0 5.0 4.0

Figure 3a. Partial Nmr spectra of cis 6-alkyl cyclohex-2-en-1-ols.

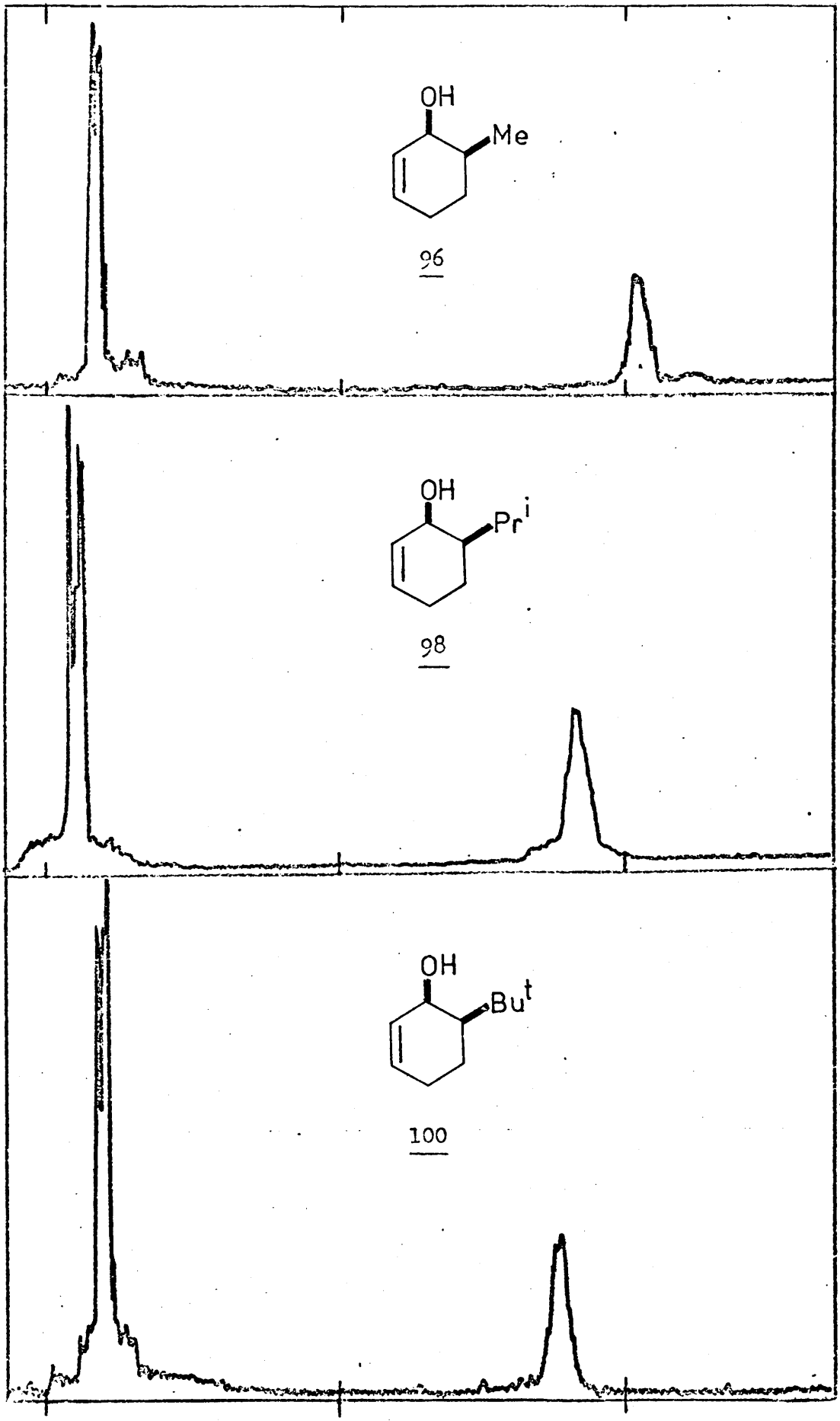
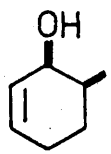
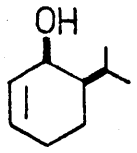
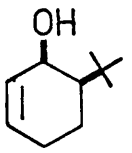
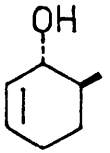
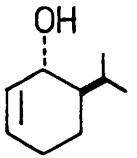
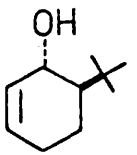


Table 6. Analysis of cis and trans 6-alkyl cyclohex-2-en-1-ols

	 96	 98	 100	 97	 99	 101	
IR	3400 vs 3030 m 985 vs	3620 m * 3020 m 1050, 910 s	3620. m * 3020 m 985 m	3400 vs 3030 m 1060-1015	3600 m * 3020 m 1040 s	3600 m * 3020 m 1040-1020 s	O-H C-H alkene C-O, O-H
Nmr	5.83 (2H) 3.96 (1H), $w_{\frac{1}{2}}$=8Hz.	5.88 (2H) 4.16 (1H), $w_{\frac{1}{2}}$=8Hz.	5.82 (2H) 4.24 (1H), $w_{\frac{1}{2}}$=8Hz.	5.67 (2H) 3.77 (1H) $w_{\frac{1}{2}}$=14Hz.	5.71 (2H) 4.07 (1H), $w_{\frac{1}{2}}$=14Hz.	5.63 (2H) 4.16 (1H), $w_{\frac{1}{2}}$=16Hz.	vinyl H CHOH
MS	112	140	154	112	140	154	M^+
GLC	86%	98+%	96%	93%	99+%	88%	

* CCl_4 solution

discovered, however, almost all of the precious cis 3,5-dinitrobenzoate (84) had been hydrolysed to the alcohol (98) and used in attempted preparation of the cis 2,6-dichlorobenzoate (82)!

Consequently, some of the studies of the S_N2' reaction of the cis 3,5-dinitrobenzoate (84) had to be performed using cis ester (84) contaminated with up to 11% of its trans epimer (85), this being the highest degree of stereochemical purity obtainable from the few remaining samples of mother liquors of the original recrystallisations.

c. Analysis of 6-alkyl cyclohex-2-en-1-ols : proof of stereochemistry.

The spectroscopic and analytical data for the alcohols are shown in Table 6.

The configuration of the alcohols was assigned as cis or trans on the basis of their Nmr spectra and confirmed by hydrogenation of the allylic epimers (96-101) and comparison of the resulting saturated alcohols (137-142) with authentic materials. Further confirmation was afforded, in the isopropyl series, by the melting-points of the trans 2,6-dichlorobenzoate (40)[14] and trans 3,5-dinitrobenzoate (85).[102]

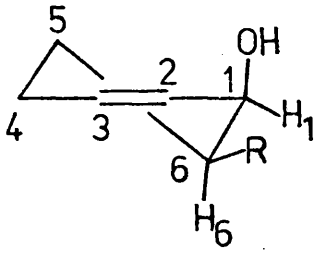
Nmr showed the three cis alcohols (96, 98, 100) to have very similar spectra (Figure 3a) which were quite different from those of their trans epimers (97, 99, 101) (Figure 3b).

In particular, the vinyl and carbinol resonances of the cis and trans epimers were very distinctive. (Figures 3a, 3b). The spectra of the cis alcohols (96, 98, 100) exhibited narrow ($w_{\frac{1}{2}} \doteq 5$Hz) signals for the vinyl protons while those of the trans epimers (97, 99, 101) were broader, more complex resonances.

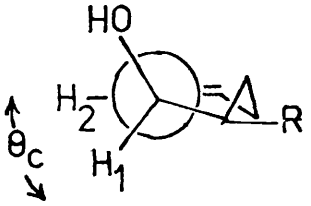
Figure 4. Coupling constants and dihedral angles; 6-alkyl cyclohex-2-en-1-ols. (96-101)

cis

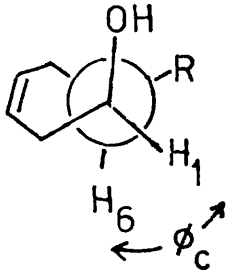
a.



b.

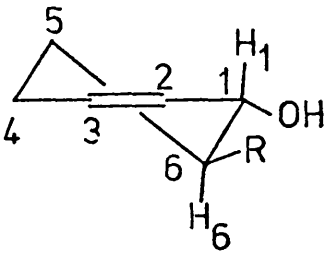


c.

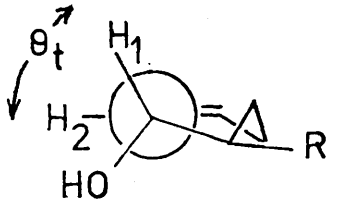


trans

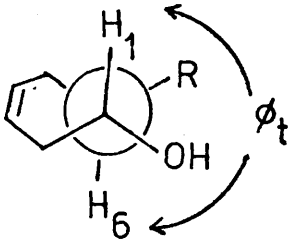
a.



b.

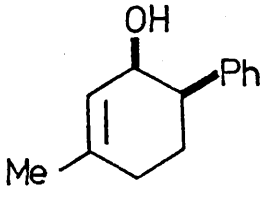


c.

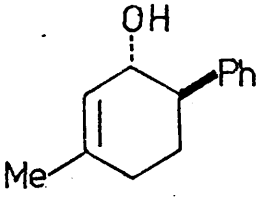


b. view from C_1 to C_2.

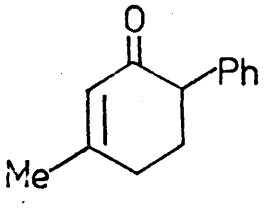
c. view from C_1 to C_6.



143



144



145

The chemical shifts of the vinyl protons were consistently to lower field for cis, the chemical shift differences between the epimers being 16, 17, and 19Hz. for the methyl, isopropyl and tert. butyl series, respectively.

Similar distinctions between the epimers were noted for the carbinol protons, the chemical shift differences in this case being 20, 9 and 8Hz respectively, while the differences in signal width were more pronounced ($w_{\frac{1}{2}}$ = 8Hz for cis, $w_{\frac{1}{2}}$ = 14-16Hz for trans). The difference in the half-band widths ($w_{\frac{1}{2}}$) of the carbinol protons is rationalised by reference to Figure 4. The carbinol proton H_1 is vicinally coupled to H_6 and H_2 and allylically coupled to H_3. The magnitude of the coupling constants is dependent upon the relevant dihedral angle (θ,ϕ) between the coupled protons.[117] Because of the geometric constraints placed upon the cyclohexenol system by the double bond, the coupling constants $J_{1,2}$ and $J_{1,3}$ will be little different for the cis and trans epimers (Figure 4b, $\theta_c \approx \theta_t$) but the magnitude of $J_{1,6}$ will be considerably greater for the trans than for the cis epimer (Figure 4c, $\phi_c \neq \phi_t$) and the half-band width of the carbinol proton will consequently be greater for the trans epimer, as found.

This analysis of the signals due to the carbinol protons is in qualitative agreement with results from the corresponding saturated alcohols (137-142, p.54) where δ(cis CHOH) has been found to lower field than δ(trans CHOH) and $w_{\frac{1}{2}}$ (cis CHOH) has been found to be smaller than $w_{\frac{1}{2}}$ (trans CHOH) and is in general agreement with similar studies in other cyclohexanol systems.[135, 136]

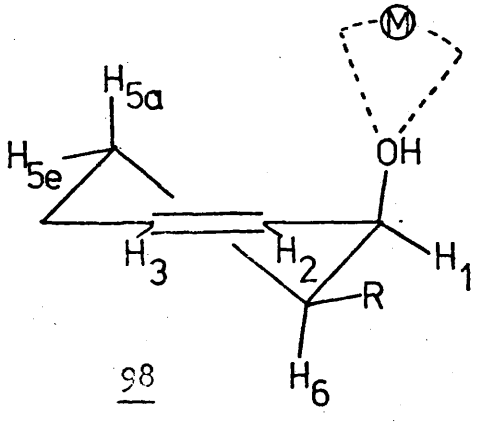
The overall analysis apparently contradicts Nmr study[137] of the hydride reduction products (143, 144) from 6-phenyl, 3-methyl cyclohex-2-en-1-one (145), where the carbinol proton of

Table 7. LIS for the protons of cis and trans 6-isopropyl cyclohex-2-en-1-ol (98, 99).

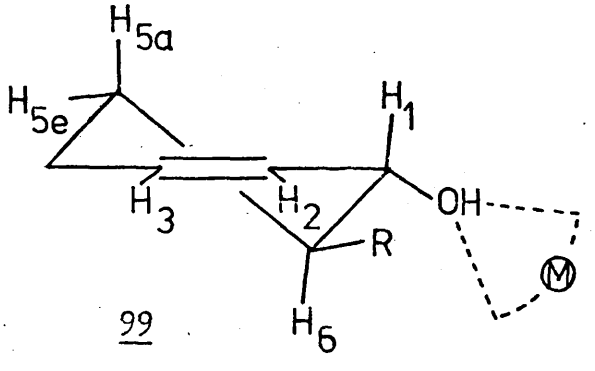
	cis*		trans*	
[lanthanide]	0.2M	0.4M	0.2M	0.4M
H_1	4.5	10.2	6.3	13.5
H_2	1.8	3.9	3.5	7.5
H_3	0.8	1.8	1.3	2.7
H_{5a}	2.7	5.8	1.8	3.8
H_6	1.7	3.7	4.4	9.3

*all LIS are expressed in p.p.m. downfield from the original position of the proton concerned.

Figure 5. Spatial relationship of protons H_{5a} and H_6 to lanthanide ion.



98



99

Ⓜ = lanthanide ion R = isopropyl

the trans epimer (144) was found to lower field than that of the cis epimer (143) and the trans vinyl proton was found to exhibit no coupling while the cis proton gave rise to a 3.7Hz doublet.

Further configurational confirmation was obtained from extensive studies of lanthanide-shifted spectra of the isopropyl alcohol epimers (98, 99) coupled with double irradiation techniques. Unfortunately, signal broadening masked the coupling information being sought but it did prove possible to identify the majority of the protons by combinations of decoupling experiments, although reliable coupling constants could not be obtained. The most significant information to emerge from this study was, in fact, the magnitude of the lanthanide-induced shifts (LIS) of the various protons (Table 7).

For alcohols, the oxygen-lanthanide bond length has been estimated to be 2.5-3.0Å [138,139,140] and the angle C-O-lanthanide to be 115-140° [138,139,140] Using these values, a comparative assessment of the LIS for the protons of the cyclohex-2-en-1-ol system can be made by study of molecular models, since the magnitude of the LIS is known to exhibit both distance[141] and angular dependence[142] upon the relative spatial disposition of the lanthanide ion and the proton. Obviously, such estimates will vary with rotation about the C-O bond, making some of the predictions difficult. However, the LIS of protons H_{5a} and H_6, although different for the different rotamers, will still show the same qualitative relationship viz. that in the cis alcohol (98) H_{5a} will be appreciably further shifted downfield than in the trans alcohol (99) since, in the former, it is nearer the lanthanide, while for H_6, the reverse will apply (Figure 5). The correlation between these predictions and the observed results (Table 7)

References from Table 9, overleaf.

a. analysis by GLC — TML = $LiAl(OMe)_3H$

b. non-separable by GLC — AIP = $Al(Pr^iO)_3$

c. solvent: ether — Selec = $Li(\underline{sec}.butyl)_3BH$

d. solvent: THF — K Sel = $K(\underline{sec}.butyl)_3BH$

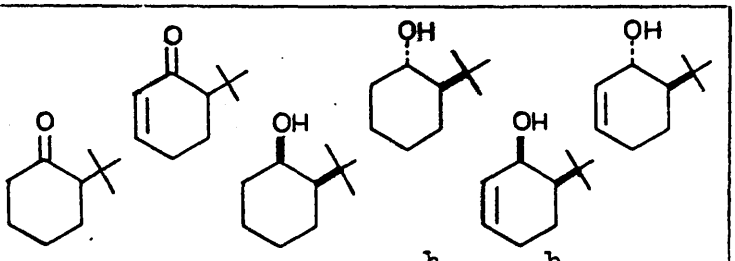
e. solvent: isopropanol

f. solvent: ether/THF

g. inverse addition of reducing agent to substrate.

* these reductions also produced unidentified compounds (~10%)

Table 10. Product distribution[a] from reduction of 6-tert.butyl cyclohex-2-en-1-one (95).

Reducing agent		Time	Temp.						
name	equiv.	min.	°C	112	95	142	139[b]	100[b]	101
LAH[c]	4.0	60	0	9	-	9	70		12
"	8.0	10	25	3	-	3	69		25
"	4.0	10	25	2	-	3	71		24
"	3.8	20	25	2	-	3	76		19
DBAH[c]	1.5	10	0	-	-	6	77		17
"	1.5	10	25	-	-	5	81		14

a. analysis by GLC

b. non-separable by GLC

c. solvent: ether

Table 9. Product distribution[a] from reduction of 6-isopropyl cyclohex-2-en-1-one (94).

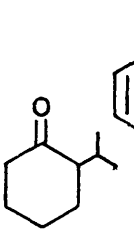
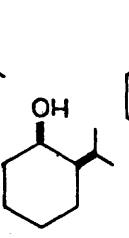
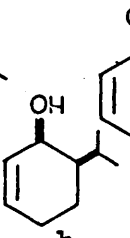
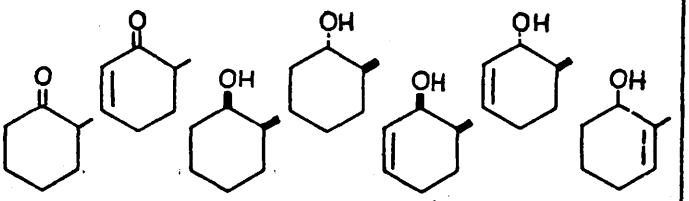
Reducing agent		Time	Temp.						
name	equiv.	min.	°C	111	94	141	138[b]	98[b]	99
LAH[c]	10.0	20	-40	5	14	-	25		56
"	12.0	20	0	1	-	2	30		67
"	6.0	20	25	1	-	2	31		66
"	3.0	20	25	2	-	-	34		63
"	1.5	20	25	5	-	-	40		55
DBAH[c]	1.5	20	-70	2	-	2	49		47
"	1.5	20	0	1	-	-	57		42
"	1.5	20	25	2	-	2	58		38
"	1.1	20	25	2	-	1	68		29
"	1.05	20	25	2	-	4	74		20
DBAH[d,*]	1.5	20	0	8	-	9	49		33
"	1.5	20	40	4	-	16	53		25
"	1.5	20	60	6	-	4	57		23
TML[d]	20.0	20	-70	-	99+	-	-		-
"	20.0	20	0	44	20	6	25		5
"	20.0	20	25	41	-	3	43		13
AIP[e]	18.0	3h	97	-	96	-	-		4
"	"	18h	"	18	46	-	21		15
"	"	21h	"	3	38	1	46		12
Selec[f]	0.95	20	-78	95	5	-	-		-
" [g]	0.95	20	-78	93	5	-	2		-
"	25.0	20	0	-	-	99+	-		-
"	25.0	20	25	-	-	99+	-		-
K Sel[f]	1.25	20	25	74	1	25	-		-

Table 8. Product distribution[a] from reduction of 6-methyl cyclohex-2-en-1-one[b] (93).

Reducing agent		Time	Temp.							
name	equiv.	min.	°C	110	93	140	137	96	97	128
LAH[c]	5.0	30	0	-	——	4[d]	——	29	53	14
"	2.3	30	0	2	——	10[d]	——	28	42	18
"	8.0	30	25	-	——	5[d]	——	26	52	17
"	4.0	30	25	-	——	4[d]	——	25	54	17
$NaBH_4$[e]	12.0	60	25	1	——	54[d]	——	13	22	10
"	8.0	60	25	-	——	44[d]	——	22	22	14

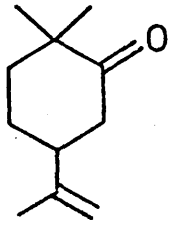
a. analysis by GLC

b. contained approximately 16% of the 2-methyl isomer (127)

c. solvent: ether

d. non-separable by GLC

e. solvent: THF



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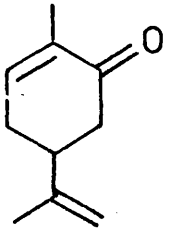

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provides further support for the configurational assignment.

d. Conclusions

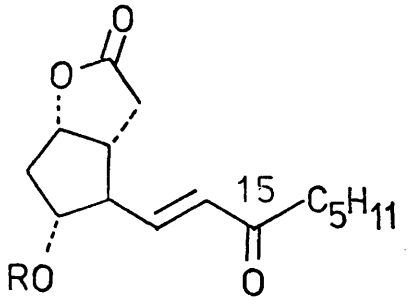
(i) Regiochemistry of reduction processes.

The results obtained from the various reductions are summarised in Tables 8, 9, 10.

As can be readily seen, conjugate 1,4 reduction was a minor pathway, except for those reductions employing the "soft" borohydride reagents, $NaBH_4$, Li(sec.butyl)$_3$BH[143] and K(sec. butyl)$_3$BH[144], and those involving very large excesses of reagent, e.g. Li(OMe)$_3$AlH.

Such a result is in qualitative agreement with the suggestion[145] that, in the reactions of enone systems, the ratio of 1,2 to 1,4 addition is dependent upon the "softness" or "hardness"[146] of the reducing species. Since the β-carbon atom of an enone system is "softer" than the carbonyl carbon,[147] addition of "soft" reagents will occur preferentially at the β-carbon.

In this context, it was hoped that, although K(sec.butyl)$_3$BH had produced only 1,4 reduction of the isopropyl enone (94), the analogous Li reagent would, by the "symbiotic effect",[148] be somewhat "harder" and might, therefore, perform 1,2 reduction. In the event, such a hope was unfounded since, even with inverse addition of a deficiency of Li(sec.butyl)$_3$BH, only 1,4 reduction occurred, producing the saturated ketone (111). Such a regioselective reduction of the conjugated double bond has obvious synthetic utility and, indeed, this was demonstrated[149] shortly afterwards by the production of a 98% yield of 2-methyl 2,3 dihydrocarvone (146) from carvone (147) by reductive alkylation



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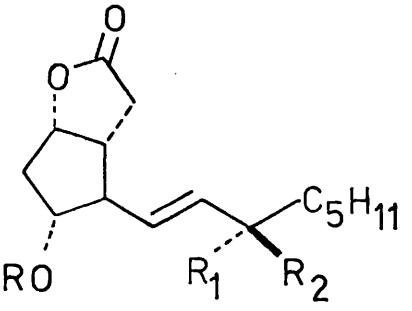
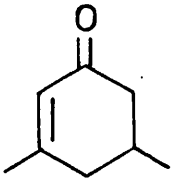


149	OH	H	15S
150	H	OH	15R

R = p-phenyl-C_6H_4CO



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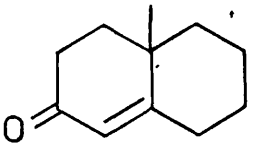

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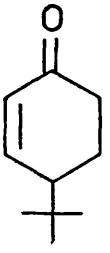

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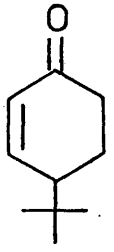

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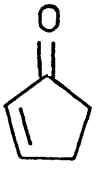

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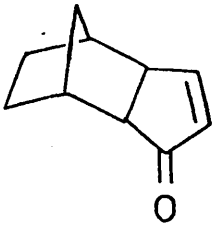


156

using K(sec.butyl)$_3$BH and methyl iodide.

The observation of 1,4 reduction with these trialkyl borohydride reagents is not universal, however - the prostaglandin intermediate (148) possessing an acyclic α,β-enone system has been reduced[150] in 1,2 fashion by Li(sec.butyl)$_3$BH yielding a 78:22 mixture of the 15S and 15R epimers (149, 150). This apparent contradiction is ascribed to steric sensitivity of the reduction process, as suggested by the fact that the β-substituted enones (151, 152) gave exclusive 1,2 reduction[149] although the β-unsubstituted enones (147, 153, 154) gave 1,4 reduction.[149]

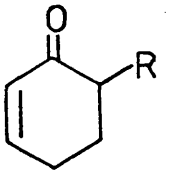
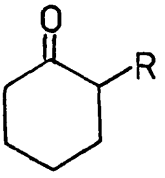
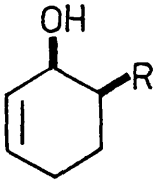
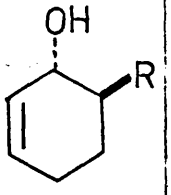
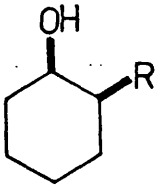
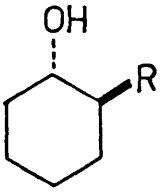
The behaviour of the different aluminohydride reagents as regards the regioselectivity of the reduction process is not so readily rationalised, although the absence of 1,4 reduction with LAH, itself, was expected since 1,4 reduction of enones by LAH is normally unimportant unless the double bond is conjugated both to the carbonyl and another electron-withdrawing group[151,152] or is in a strained ring.[153,154]

The substantial amount of 1,4 reduction found with Li(OMe)$_3$AlH is apparently out of step with the predictions made from the "hard-soft acid-base" principle[145,146] and with experimental observations made for cyclopent-2-en-1-one (155)[154] and 5,6 dihydro-endo-dicyclopentadien-1-one (156),[154] where saturation of the double bond was less prevalent using Li(OMe)$_3$AlH than with LAH itself.

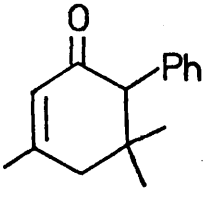
The utility of DBAH as a regioselective 1,2 reducing agent for cyclopent-2-en-1-one (155) has already been demonstrated[155].

In this study, reduction of the enones (94, 95) by DBAH in ether proceeded in 1,2 fashion but reduction of enone (94) in

Table 11. Stereochemistry of reduction by LAH[a].

substrate						
products	 cis	 trans		 cis	 trans	
R	no.	%	no.	%	no.	%	no.	%
Me	96	31	97	69	140	30	137	70
Pr^i	98	35	99	65	141	40	138	60
Bu^t	100	74	101	26	142	47	139	53

a. all reductions in ether, at 25°C, with analysis by GLC.



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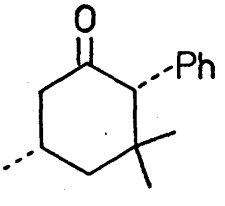


158

THF produced substantial amounts (>15%) of 1,4 reduction. This solvent dependence is probably due to complex formation between DBAH and THF,[156] and thus reductions in the two solvents cannot be directly compared, since the nature of the reducing species is different.

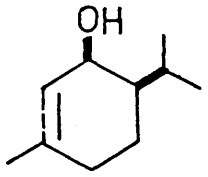
d. Conclusions

(ii) Stereochemistry of reduction processes

The stereochemistry of the reductions by LAH is in general agreement with Barton's rule,[157] the amount of quasi-axial (cis) alcohol increasing as the steric hindrance to axial approach of hydride increases i.e. as the size of the 6-alkyl group increases (Table 11).

The stereochemical results obtained from the LAH reductions of the methyl and isopropyl enones (93,94) closely resemble those from the reductions of the corresponding saturated ketones (110, 111) (Table 11), in agreement with a study of the LAH reductions of the 6-phenyl enone (157) and its saturated analogue (158) from which it was concluded that the double bond exhibited little effect on the stereochemistry.[158]

Reduction of the 6-tert.butyl enone (95), however, showed a marked increase in stereoselectivity relative to its saturated analogue (112) and to its methyl and isopropyl homologues (93, 94). The formation of the cis allylic alcohol (100) as major reduction product (Table 11) demonstrates, in contrast to the immediately preceding discussion, the hazards of predicting the stereochemical outcome of an enone reduction from results for the corresponding saturated ketone. For, attractive as this may be, the different geometries[159,160,161] of the two systems require that such a



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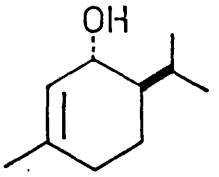

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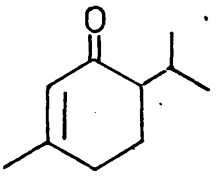

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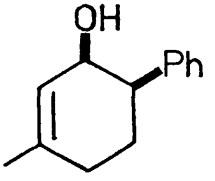

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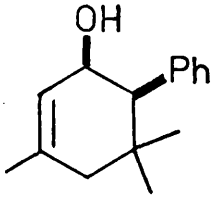

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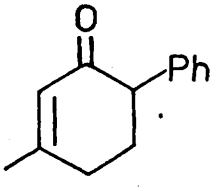

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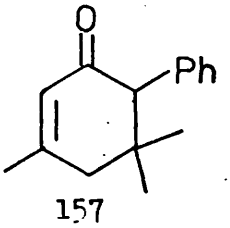

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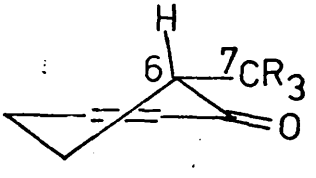
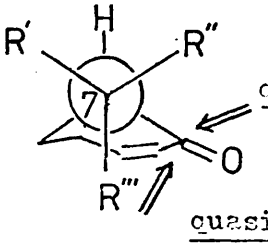
Figure 6. Conformation of the alkyl group in the 6-alkyl cyclohex-2-en-1-ones (93, 94, 95).





view along C_7–C_6

quasi-equatorial approach

quasi-axial approach

	R′	R″	R‴	
a.	H	H	H	(93)
b.	Me	Me	H	(94)
c.	Me	Me	Me	(95)

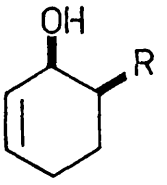
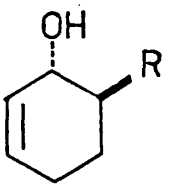
prediction be made with caution, as evidenced by this study, and even more strikingly, by several results from the steroid field.[161-165]

Similarly, rationalisation of the stereochemistry observed in 1,2-hydride addition to an enone system may be difficult, requiring, at the very least, knowledge of the conformations of the substrate[120-124] and product and of the direction of approach of the anion. Indeed, the commonly employed assumption[166] that an anion approaches a carbonyl group along an axis passing through the trigonal carbon and perpendicular to the plane of the substituents of the carbonyl has recently been disputed by theoretical studies.[167,168,169]

The result obtained from LAH reduction of the isopropyl enone (94) (Table 11) is, in fact, in close agreement with the 36:64 ratio of cis : trans allylic alcohols (159, 160) from LAH reduction of piperitone (161).[170] Similarly, the result from reduction of the tert.butyl enone (95) is not unprecedented since cis alcohols (143, 162) were the major products from LAH reduction of the 6-phenyl enones (145, 157), a result rationalised by steric factors.[171]

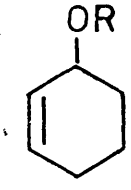
The observed sharp increase in stereoselectivity on going from the isopropyl to tert.butyl enone (Table 11) illustrates the special effect of a tert.butyl substituent as a steric "blocking group". Both methyl and isopropyl groups in the enones (93, 94) can adopt a lowest energy conformation in which their hindrance to quasi-axial approach of hydride approximates to a 1,3-diaxial H interaction (Figure 6a,b) while the minimum hindrance offered by a tert.butyl group approximates to a 1,3-diaxial H-methyl interaction (Figure 6c), thus leading to a decrease in quasi-axial

Table 12. Variation in the stereochemistry of allylic alcohol products with change of reducing agent.[a]

	Substrate	Reducing agent[b]	 cis	 trans
1	93	LAH	31	69
2	93	$NaBH_4$	50	50
3	94	LAH	35	65
4	94	TML[c]	77	23
5	94	DBAH	70	30
6	95	LAH	74	26
7	95	DBAH	85	15

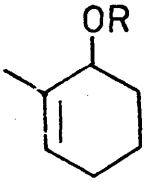
a. analysis by GLC b. ether; 25°C

c. TML = $LiAl(OMe)_3H$; solvent, THF; 25°C



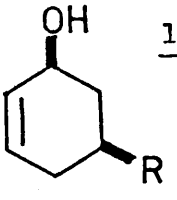
163 R=H

165 R=Ac



164 R=H

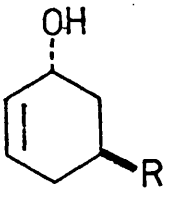
166 R=Ac



167 Bu^t

171 Me

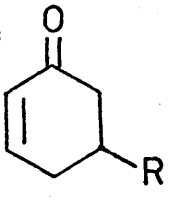
173 Ph



168 Bu^t

172 Me

174 Ph



169 Me

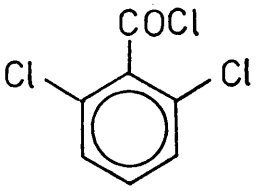
170 Ph

attack.

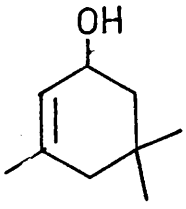
The increase in the cis : trans alcohol ratio as the steric bulk of the reducing species was increased (Table 12, entries 1-4) is in qualitative agreement with results obtained in cyclohexanone systems.[172,173] Similarly, the increase in amount of cis alcohol formed with DBAH relative to LAH was not unexpected since the analogous AlH_3 has been shown to produce a greater amount of quasi-axial alcohol than LAH in enone reductions.[154,171,174]

One surprising feature to emerge from this study was that, for the isopropyl series at least, the cis alcohol (98) appeared to be thermodynamically favoured over its trans epimer (99), as evidenced by the increase in the ratio of cis : trans alcohols (98:99) as reaction temperature was increased or amount of hydride was decreased, particularly for reduction by DBAH in ether and, less markedly, for LAH (Table 9). This unexpected result was confirmed by Meerwein-Ponndorf-Verley reduction,[175] which demonstrated that the ratio of cis : trans alcohols (98:99) increased with time.

This finding is, in fact, in agreement with ^{13}C Nmr studies[176,177] of conformational preference in cyclohex-2-en-1-ol (163), 2-methyl cyclohex-2-en-1-ol (164) and their acetates (165, 166), which proposed that the quasi-axial orientation of the hydroxy- or acetoxy- groups was preferred by 0.97-1.60 $Kcal.mole^{-1}$. Available results from equilibrium studies of 5-substituted cyclohex-2-en-1-ols appear to contradict one another, however - for the cis and trans 5-tert.butyl cyclohex-2-en-1-ols (167, 168), a quasi-equatorial preference of 0.4$Kcal.mole^{-1}$ is suggested,[178] while study of the Meerwein-Pondorf reductions of the 5-methyl and 5-phenyl enones (169, 170)



171



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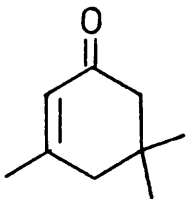


173

and subsequent equilibration of the resulting alcohols (171, 172 : 173, 174) demonstrated[179] that the quasi-axial orientation of the hydroxyl group was favoured by a factor of 2 (≡ 0.4Kcal.mole^{-1} [180]).

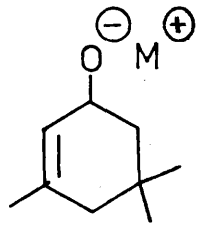
5. Esterification : preparation of 6-alkyl cyclohex-2-en-1-yl esters.

a. 2,6-dichlorobenzoate esters

Unexpectedly, this final stage of the proposed synthetic route (Scheme 1) to the 2,6-dichlorobenzoates (39, 40, 41, 81, 82, 83) proved to be the most troublesome. Indeed, only one of these desired esters, the trans 6-isopropyl ester (40) was ever "successfully" prepared, and that was in only 15% yield, a result in marked contrast to Stork and White's report[14] of the 70-80% yields of trans esters (39, 40, 41) achieved by treatment of the corresponding alcohols (96, 99, 101) with 2,6 dichlorobenzoyl chloride (171) in pyridine.

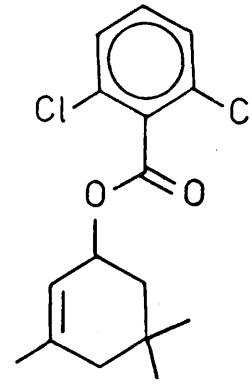
Not surprisingly, initial esterification attempts employed this method[14] with either stereochemically pure alcohol or mixtures of the alcohol epimers (96-101) as substrates. In no case was a yield greater than 15% achieved nor, despite extensive efforts, was any separation of ester epimers realised.

Alteration of the reaction conditions failed to affect this situation and studies were, accordingly, undertaken to investigate the improvement of this method, using a model compound, 3, 5, 5 trimethyl cyclohex-2-en-1-ol (172), obtained from reduction of the corresponding enone (173). The best yield obtained from this

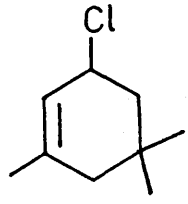


174 M=Li

177 M=Na



175



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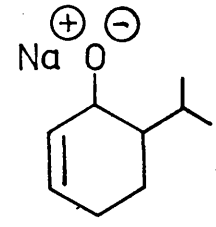

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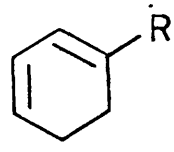
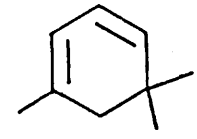


179 R=Me

180 R=Pr^i

181 R=Bu^t



182

alcohol under the conditions employed by Stork and White[14] was 8% but changes in the reaction time, temperature and work-up procedure succeeded in increasing this to 53%. However, application of these conditions to the esterification of the 6-alkyl substrates (96-101) failed to improve upon the abysmal results previously obtained and this esterification method was consequently abandoned.

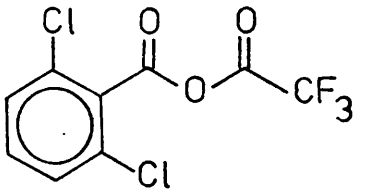
Using the model compound (172), a search was made for other esterification methods.

(i) Under a variety of conditions, pre-formation of the lithium alcoholate (174) by treatment of the alcohol (172) with n-butyl lithium before reaction with 2,6-dichlorobenzoyl chloride (171) produced mixtures containing the desired ester (175) but also, as major product, the allylic chloride (176)*

(ii) Equally unsuccessful were attempts to encourage esterification by preformation of the analogous sodium alcoholates[182] (177, 178) of the model compound (172) and cis 6-isopropyl alcohol (98), respectively.

(iii) Acid-catalysed esterification via the medium of an ion-exchange resin (IER)[183] was extensively investigated since it appeared that a probable reason for the low yields obtained by other methods was that the allylic alcohols and/or esters were undergoing base-catalysed elimination to form the dienes (179-182), which may polymerise under the reaction conditions. Such an explanation would account for the large quantities of intractable tars formed in the esterification reactions, particularly those

* A similar method has, in fact, been used as a general synthesis of allylic chlorides.[181]



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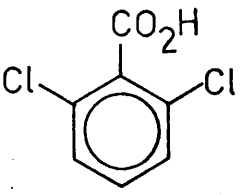

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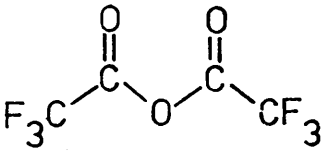

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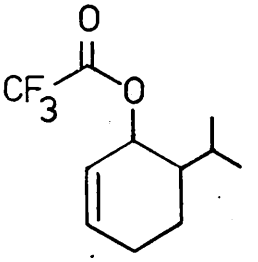
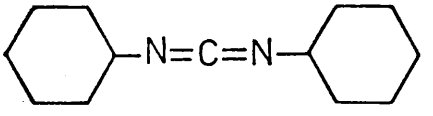


186



187

at elevated temperatures.

This study established optimum reaction conditions, under which 36% yield of pure ester (175) was obtained, and demonstrated that the esterification reaction appeared to be in competition with decomposition of the alcohol (172) and ester hydrolysis.

However, under these optimum conditions, the cis 6-isopropyl alcohol was not esterified, but elevation of the reaction temperature produced 37-44% yields of mixtures, comprising the desired ester (82) and an unidentifiable impurity (ratio 2:1). However, no physical separation of this impurity could be achieved, while attempts to avoid its formation by employing different DERs or solvents were also unsuccessful.

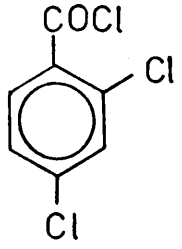
By that time, in fact, it had become apparent that the model alcohol (172) was not sufficiently similar in its reactivity to the 6-alkyl substrates (96-101) to justify its further use. Later studies were, therefore, restricted to the 6-alkyl substrates, in particular the cis 6-isopropyl alcohol (98).

(iv) Attempts to prepare the ester (82) by reaction of the alcohol (98) with the mixed anhydride (183) formed from 2,6-dichlorobenzoic acid (184) and trifluoroacetic anhydride (185)[184] were unsuccessful, the major product in each case being the allylic trifluoroacetate (186).

(v) Similarly, promotion of esterification by dicyclohexyl-carbodiimide (187)[185] failed, only traces of ester (82) being formed even after extended reaction times.

b. Other esters

It appeared that the primary cause for the failures noted above was steric repulsion between the 6-alkyl group of the



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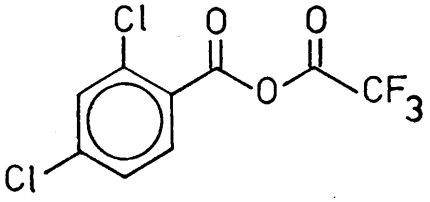

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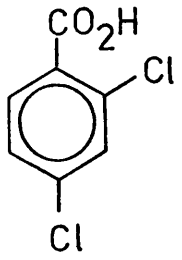

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cyclohexenol and the chlorine substituents on the aromatic ring of the benzoylchloride, since the absence of either of these factors had been shown to permit esterification, e.g. the relative ease of formation of the 2,6-dichlorobenzoate (175) from the 6-unsubstituted alcohol (172) and of the 3,5-dinitrobenzoates (84, 85) from the 6-isopropyl alcohols (98, 99).

Thus the preparation of cis 6-isopropyl cyclohex-2-en-1-yl 2,4-dichlorobenzoate (86) was investigated in the hope that steric strain would be sufficiently lowered in this ester to allow its formation.

On treatment of the alcohol (98) with 2,4-dichlorobenzoyl chloride (188) in pyridine, under various conditions, a 3:1 mixture of ester (86) and unidentifiable impurity was obtained. The impurity, shown to contain the 2,4-dichlorobenzoyl moiety and approximately 6 aliphatic protons (IR, Nmr.), was inseparable from the ester (86) by extensive chromatography or crystallisation or by preferential hydrolysis under mildly alkaline conditions.

Similar results were obtained when the sodium alcoholate (178)[182] was reacted with 2,4-dichlorobenzoyl chloride (188), while treatment of the alcohol (98) with the mixed anhydride (189)[184] of 2,4-dichlorobenzoic acid (190) and trifluoroacetic anhydride (185) produced only the trifluoroacetate (186).

Consequently, it was decided to waive the condition[14] that a suitable group for displacement by piperidine would, of necessity, possess substituents on the aromatic ring capable of sterically "blocking" nucleophilic attack by piperidine at the carbonyl carbon.

Once this had been accepted, the problems of esterification vanished - the preparation of the cis p-nitrobenzoate ester (87)

was readily accomplished while the cis and trans 3,5-dinitrobenzoates (84, 85) had already been successfully prepared.

Trial experiments demonstrated that these compounds would react with piperidine by displacement of the ester group in addition to straightforward attack at the carbonyl, and the stage was, therefore, finally set for a study of the stereochemistry of the S_N2' reaction to be commenced, albeit with substrates (40, 84, 85, 87) different from those originally envisaged (39, 40, 41, 81, 82, 83).

Part B. Synthesis of authentic N-(alkyl cyclohexyl) piperidines.

Before the stereochemistry of the S_N2' reaction could be determined, it was necessary to devise an analytical method which would unambiguously assign the configuration of the reaction products. This was achieved by GLC comparison of the amine products*, after hydrogenation, with the corresponding, authentic saturated amines.

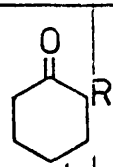
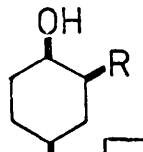
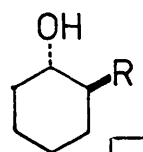
In practice, the synthesis of the authentic amines (191-198) was completed before it was realised that esters of only 6-isopropyl cyclohex-2-en-1-ol (98, 99) would be available as substrates for the S_N2' reaction. As a consequence of this only the isopropyl amines (195, 196) were used for the purpose for which they were intended.

It was planned to prepare saturated analogues of the products which would be formed by either S_N2 or S_N2' displacements of the esters by piperidine, but this proved possible for only the methyl series (191-194). For the isopropyl and tert.butyl series only the amines corresponding to hydrogenation of the possible S_N2' products could be obtained (195, 196 : 197, 198).

Preparation of each of the epimers in a stereochemically pure state was unnecessary since if either epimer could be identified then the other was necessarily assigned, also. Consequently, only the trans epimers (192, 194, 196, 198) were prepared stereochemically pure, the cis epimers (191, 193, 195, 197) being identified from

* Stork and White[14] assigned the stereochemistry of the products by m.p. and mixed m.p. comparison of derivatives of the amine products, after hydrogenation, with authentic materials.

Table 14. Distribution[a] and analysis of products from hydride reductions of alkyl cyclohexanones.

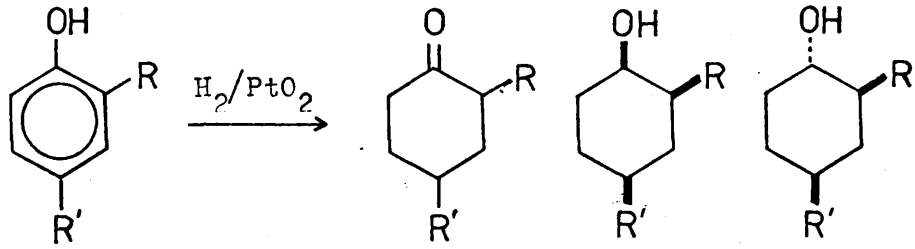
							IR	Nmr		GLC			IR	Nmr		GLC
Hydride	R	R'		T°C		%	ν C–O, δ O–H	δ CHOH	W½	R.i.		%	ν C–O, δ O–H	δ CHOH	W½	R.i.
LAH	Me	H	110	25	140	30[b]	980	3.7	8	1390	137	70[b]	1050	3.0	21	1390
"	H	Me	–	–	200	–	965	3.9	8	1400	202	–	1050	3.4	22	1415
"	Pr^i	H	111	25	141	40	960	4.0	8	1510	138	60	1050	3.3	22	1540
"	H	Pr^i	205	25	201	16	960	3.9	8	1595	203	84	1050	3.4	22	1625
"	Bu^t	H	112	25	142	47	960	4.1	8	1545	139	53	1050	3.3	22	1570
"	H	Bu^t	206	25	207	12	955	3.9	8	1480	208	88	1060	3.4	22	1520
Select.	Me	H	110	0	product ratio			99:1 cis:trans								
"	H	Me	204	-78	"			91:9 "								
"	Pr^i	H	111	-78	"			>99:<1 "								
"	H	Pr^i	205	-78	"			97:3 "								
"	Bu^t	H	112	0	"			>99:<1 "								
"	H	Bu^t	206	-78	"			98:2 "								

a. analysis by GLC

b. inseparable by GLC – analysis by Nmr.

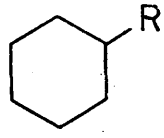
Select. = $Li(sec.butyl)_3BH$

Table 13. Product distribution[a] from hydrogenation of phenols.



Substrate	Pressure	%	%	%	R	R'
102	20 atm.	23	64	13	Pr^i	H
199	40 atm.	5	48	47	H	Pr^i
102	50 atm.	46	46	8	Bu^t	H

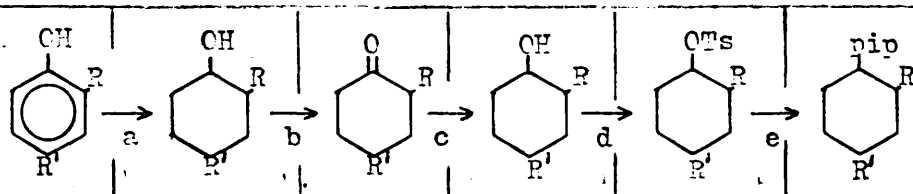
a. analysis by GLC



221 R=Pr^i

222 R=Bu^t

Scheme 5. Synthetic route to authentic N-(alkyl cyclohexyl) piperidines.



R	R'		cis	trans		cis	trans	cis	trans	cis	trans
Me	H	-	-	-	110	140	137	209	210	191	192
H	Me	-	200	202	204	200	202	211	212	193	194
Pr^i	H	102	141	138	111	141	138	213	214	-	-
H	Pr^i	199	201	203	205	201	203	215	216	195	196
Bu^t	H	103	142	139	112	142	139	217	218	-	-
H	Bu^t	-	-	-	206	207	208	219	220	197	198

OTs = toluene-p-sulphonate

pip = piperidyl

a. H_2/PtO_2/acetic acid/25°C

b. Jones oxidation

c. LAH or Selectride*

d. toluene-p-sulphonyl chloride/pyridine

e. piperidine

* reductions by LAH produced mixtures of the cis/trans epimers while Selectride reduction gave the cis epimer.

epimer mixtures.

The synthetic route to these compounds is shown in Scheme 5.

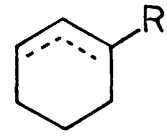
Hydrogenation of the phenols (102, 199, 103) produced mixtures of alcohols (141, 138 : 201, 203 : 142, 139) and ketones (111 : 205 : 112) (Table 13), contaminated with varying amounts of the alkyl cyclohexanes (221, 222) formed by hydrogenolysis of the C-O bond. From the 2-alkyl phenols (102, 103) the major alcoholic products were the cis epimers (141, 142), as expected,[186] while, from 4-isopropyl phenol (199), the cis and trans alcohols (201, 203) were formed in approximately equal amounts. The concomitant hydrogenolysis reaction was an inevitable and expected consequence of the choice of PtO_2 as catalyst.[187] It could have been minimised by use of Ruthenium at high temperature and pressure[188] but suitable apparatus was not available.

The cyclohexanones (110-112, 204-206) were either readily available or were obtained by Jones oxidation of the corresponding alcohol/ketone mixtures, and were subsequently divided into two fractions, of which one was reduced by LAH to produce a mixture of cis and trans alkyl cyclohexanols (Table 14) while the other was stereoselectively reduced by Li(sec.butyl)$_3$BH[143] to produce the cis epimer (Table 14).

The stereochemical assignment of these alcohols, upon which the remainder of the synthesis depended was rigorously and unambiguously defined by the following considerations:

(a) Li(sec.butyl)$_3$BH is known[143] to reduce 2- and 4-alkyl cyclohexanones with very high stereoselectivity to the axial (cis) alcohols. Conversely, the major products from the corresponding LAH reductions are expected[157] to be the equatorial (trans) alcohols.

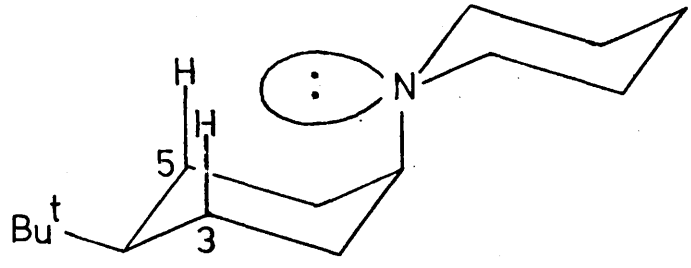
(b) IR: The observation of the νC-O, δ O-H band at 955-980cm^{-1}



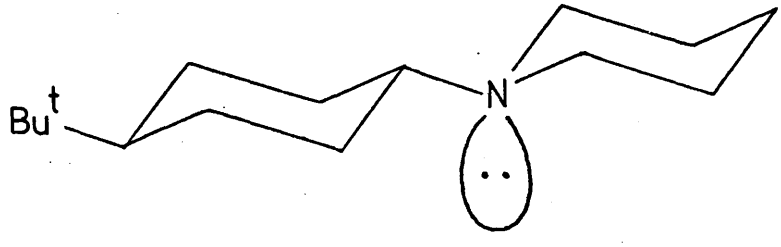
223 $R=Pr^{i}$

224 $R=Bu^{t}$

Figure 7. N-(4-tert.butyl cyclohexyl) piperidines.



cis (197)



trans (198)

for cis and 1050-1060cm^{-1} for trans has previously been recorded[189] .(Table 14).

(c) Nmr: The chemical shifts of the cis carbinol protons were consistently to lower field than for the trans epimers and the half-band widths of the former were consistently much smaller ($w_{\frac{1}{2}}$ = 8Hz.) than for the trans epimers ($w_{\frac{1}{2}}$ = 21-22Hz.), in agreement with other studies.[135,136] (Table 14)

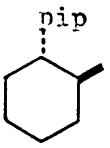
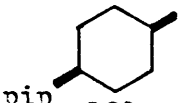
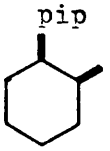
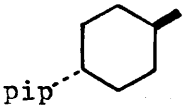
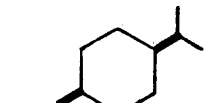
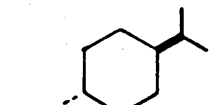
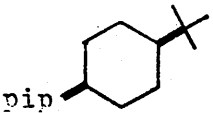
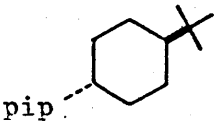
(d) GLC: The retention indices of the cis alcohols were consistently smaller than for the trans epimers on a polar column (Carbowax 20m), as previously reported.[190,191] (Table 14)

Tosylation and subsequent displacement of the toluene-p-sulphonate group by piperidine was successfully accomplished except in the sterically hindered 2-isopropyl and 2-tert.butyl series, where elimination to the corresponding olefins (223, 224) occurred either upon tosylate formation or subsequent attempted displacement.

Corroboration of the configuration of the amine products was obtained from their Nmr spectra, in particular those of cis and trans N-(4-tert.butyl cyclohexyl) piperidine (197, 198) (prepared from the trans and cis tosylates (220, 219), respectively). These showed that, in addition to the five protons α to N, the cis epimer (197) had a further two low-field (δ>1.95) protons compared with trans (198), these being ascribed to the axial protons on C-3 and C-5 of the cyclohexane ring (Figure 7).

Attempts to obtain further configurational confirmation by study of lanthanide-shifted spectra of the amines (197, 198) were hampered by the failure of these amines to effectively complex with lanthanide ion. The most successful shift reagent used, Eu.(fod)$_3$, merely served to show that the trans epimer (198) could complex more easily (maximum shift = 2.2ppm) than the cis epimer (197)

Table 15. GLC retention indices of authentic tertiary amines.

	5% Carbowax 20M + 1% KOH	5% Carbowax 20M + 1% PEI	10% Carbowax 20M + 2% PEI
	T. 120°C	T. 90°C	T. 110°C
 192	1440	1310	1445
 193	1585	1350	1550
 191	1600	1365	1570
 194	1680	1390	1605
	T. 160°C	T. 110°C	T. 130°C
 195	1890	1520	1695
 196	2010	1610	1800
	T. 180°C	T. 130°C	T. 150°C
 197	1805	1555	1720
 198	2030	1670	1870

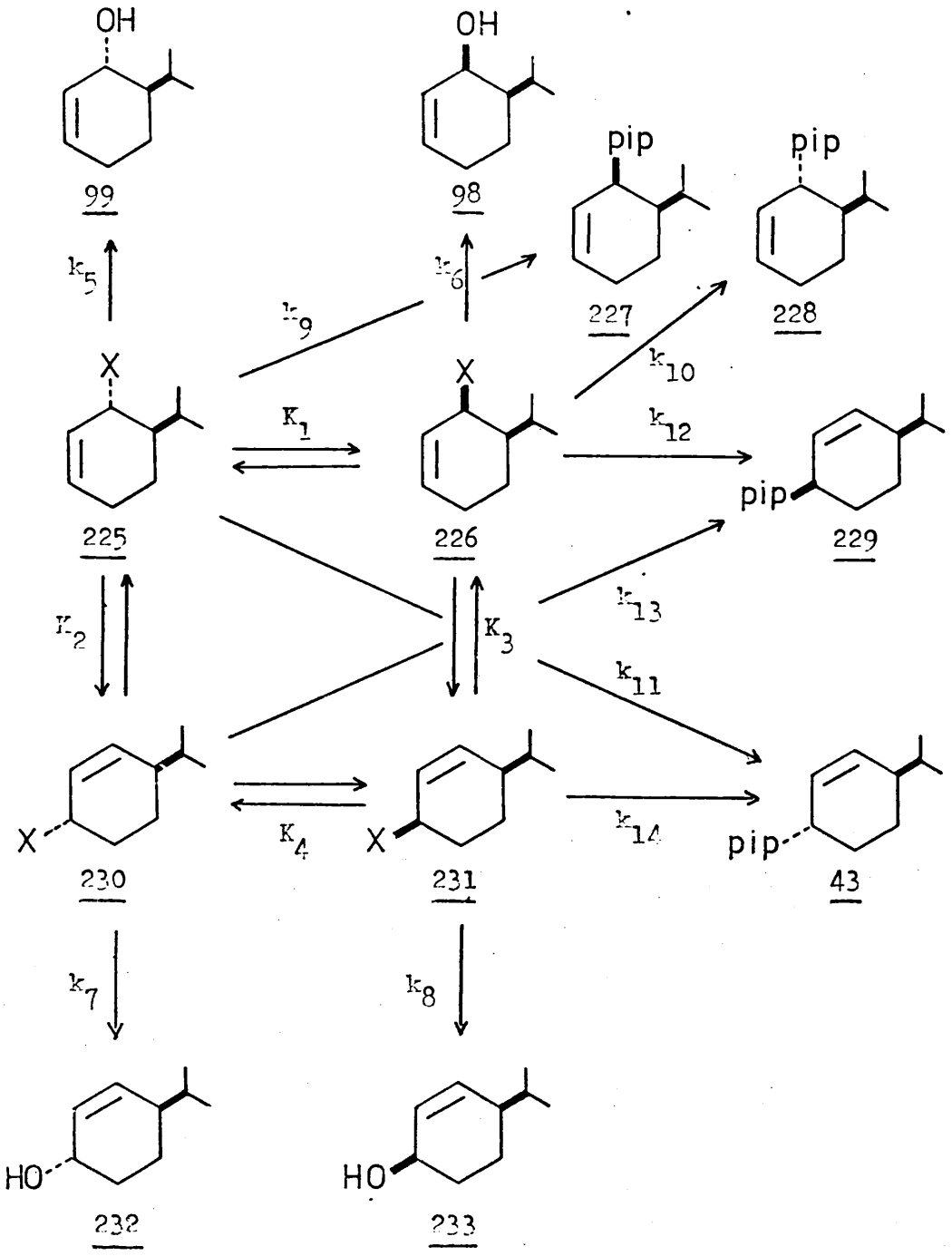
pip = piperidyl

(maximum shift < 0.5ppm) in accordance with the greater steric hindrance to complex formation in the latter (Figure 7).

GLC analysis of the amines on a variety of conventional columns was ineffective since the peaks observed were very badly "tailed", a feature common in the GLC analysis of amines.[192,193,194,195] This major analytical difficulty was overcome by the preparation and use of polar columns (5-10% Carbowax 20m) incorporating non-volatile bases (KOH, polyethyleneimine), a technique which proved invaluable.[193,195] Three separate columns of this type were prepared and each series of amines was studied on each column (Table 15).

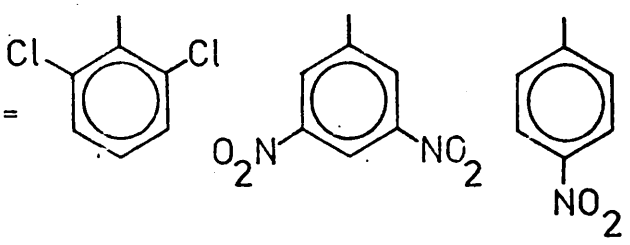
The results obtained demonstrated clearly the different characteristics of the three columns, a factor which was to be of significance in the comparison with authentic materials of the amines obtained from hydrogenation of the amine products from the S_N2' reaction.

Figure 8. Reactions of 6-isopropyl cyclohex-2-en-1-yl esters with piperidine.



pip = piperidyl

X = $ArCO_2$

Ar = 

Part C. Study of the stereochemistry of the S_N2' reaction.

1. Summary

It is demonstrated in the sequel that the 6-isopropyl cyclohex-2-en-1-yl esters* of general formulae (225, 226) react with piperidine by a variety of pathways (Figure 8).

a. "Normal" substitution ($k_{0,10}$) producing N-(6-isopropyl cyclohex-2-en-1-yl) piperidines* (227, 228).

b. "Abnormal" substitution ($k_{11,12}$) producing N-(4-isopropyl cyclohex-2-en-1-yl) piperidines* (229, 43).

c. Aminolysis ($k_{5,6}$) producing 6-isopropyl cyclohex-2-en-1-ols (99, 98).

d. Epimerisation (K_1) followed by reactions a, b or c above.

e. Allylic rearrangement ($K_{2,3}$) producing 4-isopropyl cyclohex-2-en-1-yl esters* of general formulae (230, 231). These, in turn, react by

(i) "normal" substitution ($k_{13,14}$) producing 4-amines (229,43).

(ii) aminolysis ($k_{7,8}$) producing 4-isopropyl cyclohex-2-en-1-ols (232, 233).

In addition to the reactions above, the esters are consumed by base-catalysed elimination to the diene (180) which polymerises under the reaction conditions while, over extended reaction times, the amine products are decomposed.

* Hereafter, these compounds will be abbreviated to

6-ester = 6-isopropyl cyclohex-2-en-1-yl ester

4-ester = 4- " " " "

6-amine = N-(6-isopropyl cyclohex-2-en-1-yl) piperidine

4-amine = N-(4- " " ") "

Figure 11. Mass spectra of 4- and 6-amines.

a. cis and trans N-(4-isopropyl cyclohex-2-en-1-yl) piperidines

b. cis and trans N-(6-isopropyl cyclohex-2-en-1-yl) piperidines

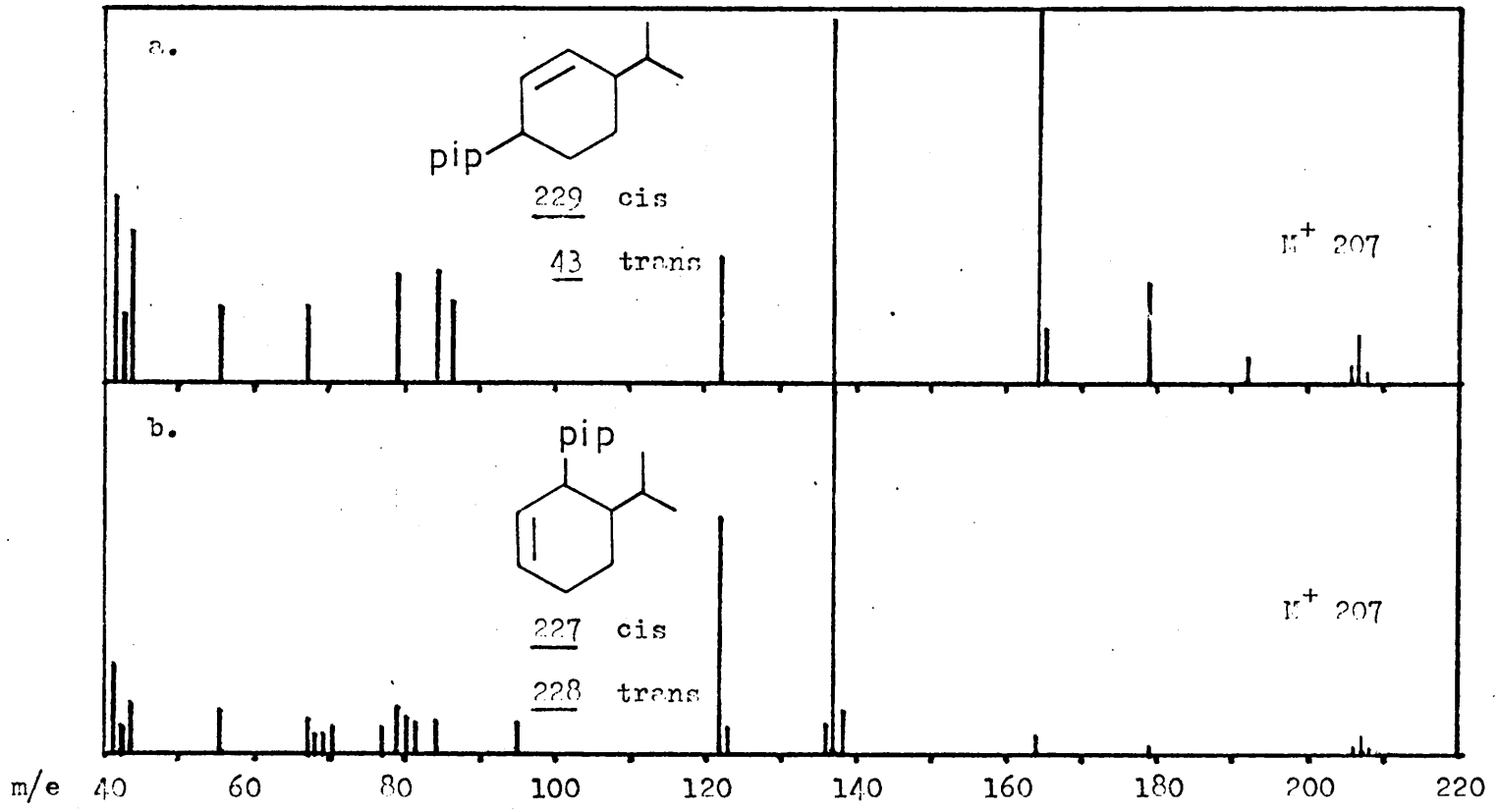
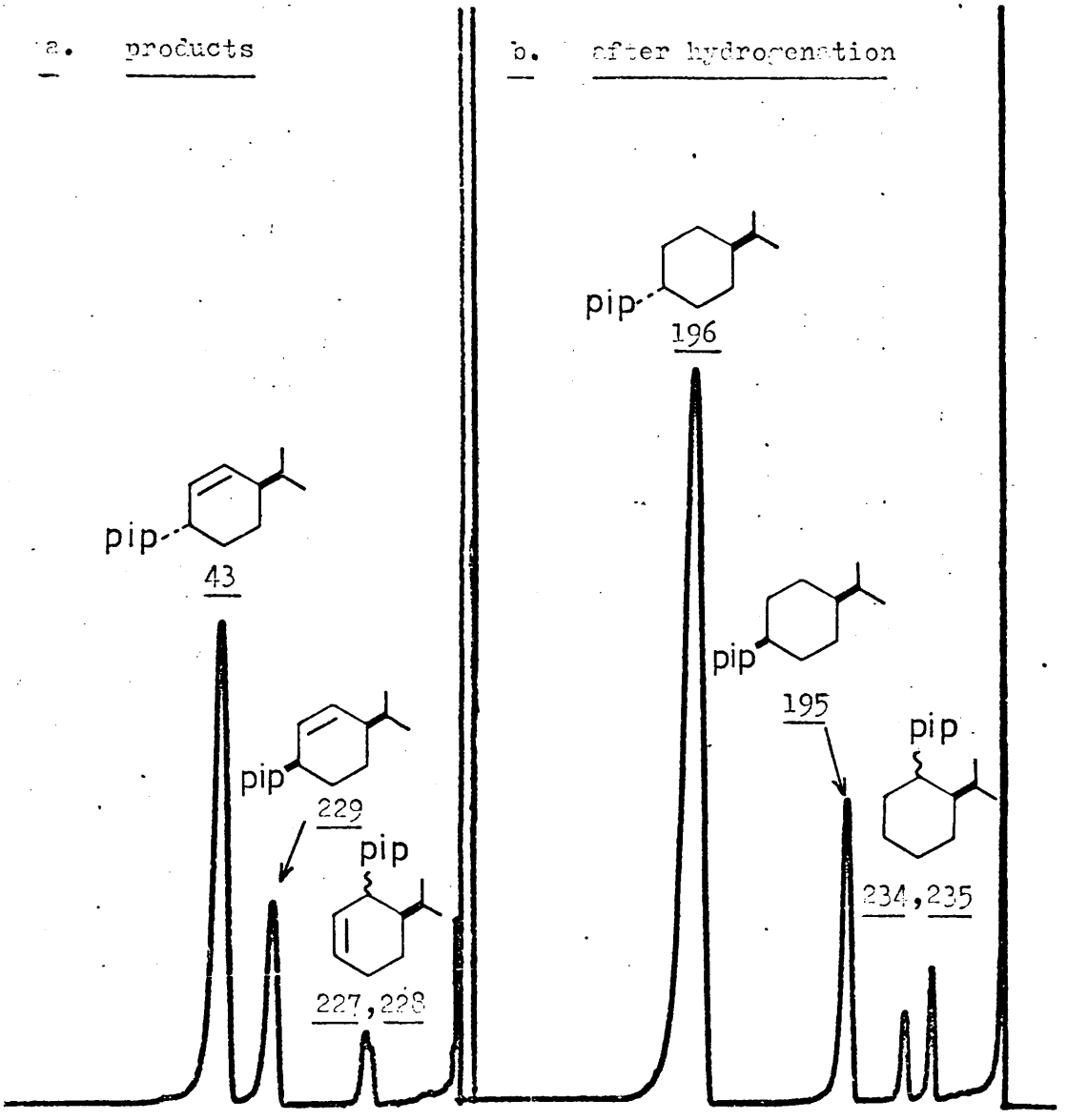
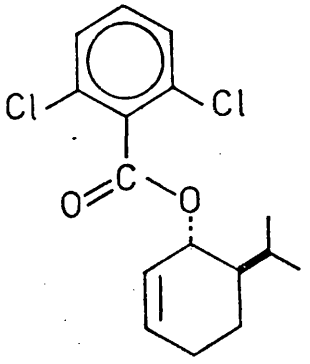


Figure 10. GLC analysis of the products from reaction of the 2,6-dichlorobenzoate (40) with piperidine.

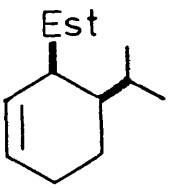


GLC conditions: 5% Carbowax 20M + 1% KOH; 130°C; nitrogen 20p.s.i.

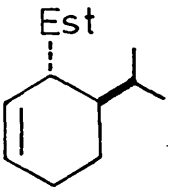


40

Figure 9. GLC analysis of the products from reactions of the 3,5-dinitrobenzoates (84, 85) with piperidine.

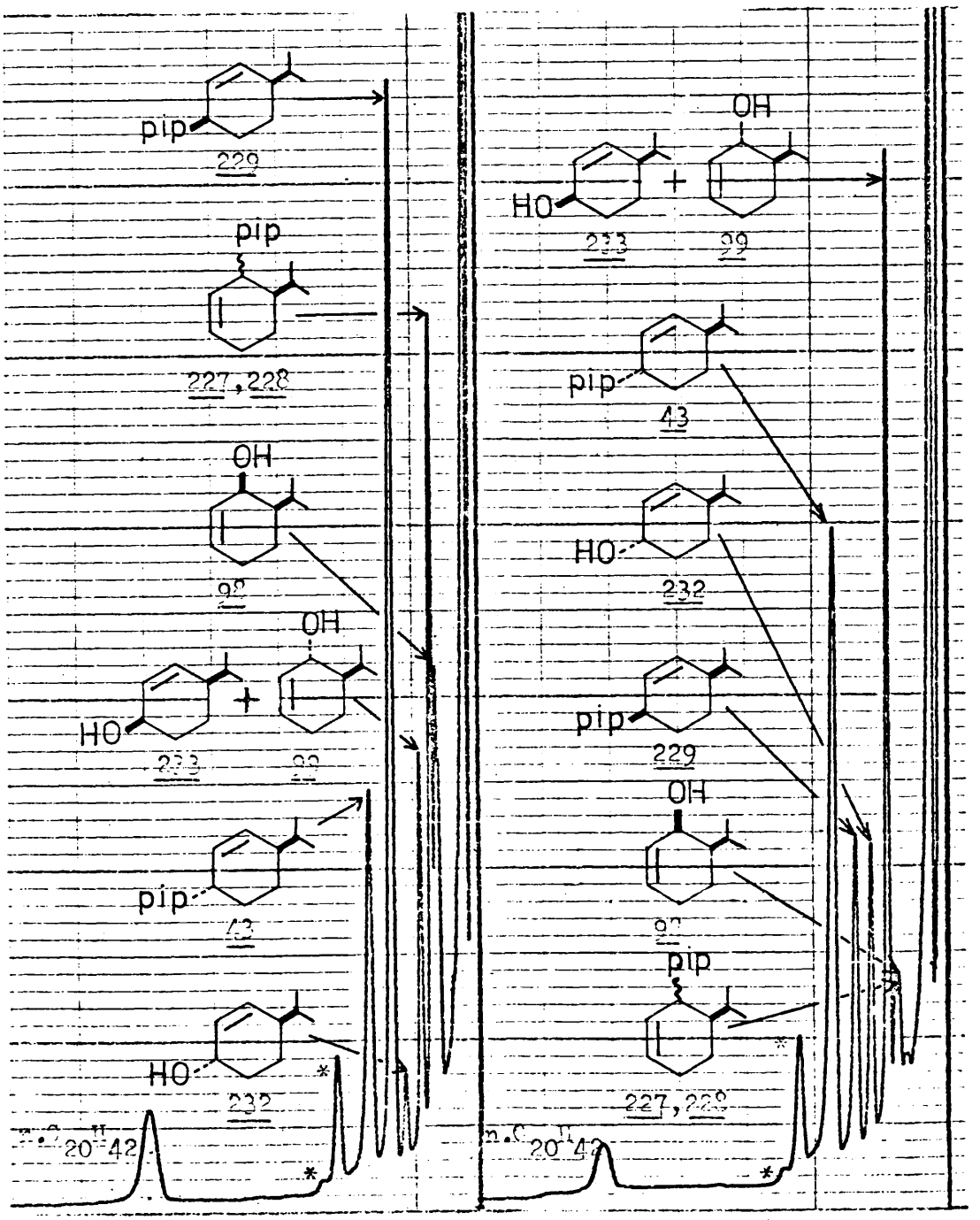


84



85

GLC conditions: 5% Carbowax 20M + 1% KOH; 150°C; nitrogen 20p.s.i.



* peaks due to decomposition products (M^+=113, 127)

2. Product analysis

The limited availability of ester substrates (40, 84, 85, 87) required that analysis be performed on a very small scale, while the complexity of the reacting system dictated that the analytical method must be sufficiently sensitive to detect even small amounts of minor products in multi-component mixtures.

GLC analysis on specially devised supports fulfilled these requirements admirably - not only did it serve to separate most of the products but it also identified them.

The efficiency of the GLC system is amply demonstrated by analysis of the products from the reactions of the cis and trans 3,5-dinitrobenzoate esters (84, 85) with piperidine (Figure 9), while the separation of the four possible amine products is clearly shown by the simpler analysis of the products from reaction of the trans 2,6-dichlorobenzoate (40) with piperidine (Figure 10a). In this latter case, steric hindrance from the chlorine substituents prevented aminolysis by piperidine, yielding a product mixture containing four amines only (227, 228, 229, 43).

GC-MS showed the four amines to be two pairs of stereoisomers (Figure 11), the 4-amines (229, 43) and 6-amines (227, 228). The stereochemistry of the 4-amines (229, 43) was assigned by hydrogenation and coinjection of the resultant saturated amines (Figure 10b) with authentic N-(4-isopropyl cyclohexyl) piperidines (195, 196) on three separate GLC columns.

The stereochemistry of the 6-amines (227, 228) could not be defined, however, as the appropriate, authentic saturated amines (234, 235) were not available.

GLC did not completely separate all of the allylic alcohols produced (98, 99, 232, 233), showing only three peaks, as the trans-6

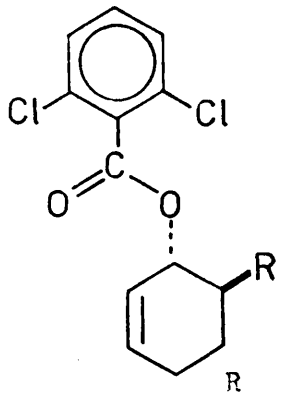
(99) and cis-4 unsaturated alcohols (233) were inseparable on all the systems used. The corresponding saturated alcohols (141, 138, 203, 201) obtained by hydrogenation were, however, separable, and were used to estimate the amounts of trans-6 and cis-4 alcohols (99, 233) present. The identity of the four alcohols was established by GC-MS and by co-injection of the saturated alcohols with authentic materials.

The 6-ester starting materials (225, 226) and their allylically rearranged 4-isomers (230, 231) were unsuitable for direct analysis by GLC and were determined by analysis of the allylic alcohol products (99, 98, 232, 233) obtained on reduction by LAH.

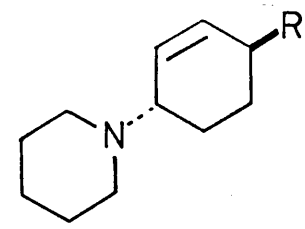
When the ratio of piperidine to products was high, as in the earlier stages of the reactions, the analysis was complicated by excessive "tailing", caused by piperidine, interfering with accurate estimation of the area of the product peaks. This problem was overcome by very careful washing of the analytical sample with a few microlitres of distilled water to selectively remove excess piperidine before GLC analysis. The selectivity was monitored by GLC analysis before and after washing.

Further analytical problems were caused by the presence of compounds apparently formed by decomposition of the amine products after extended reaction times (Figure 9). The identity of these compounds was not fully established although they were shown, by GC-MS, to have molecular weights of 113 and 127 and to contain piperidine.

Scheme 6. Reported[14] reaction of trans 2,6-dichlorobenzoate esters (39, 40, 41) with piperidine.

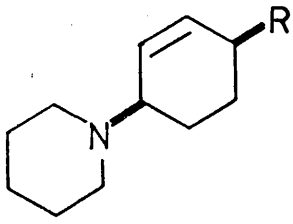


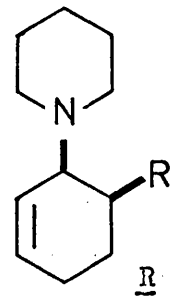
syn S_N2'

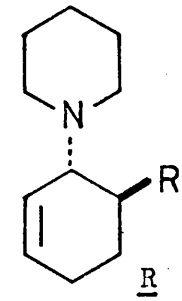


	R
39	Me
40	Pr^i
41	Bu^t

	R
42	Me
43	Pr^i
44	Bu^t







	R
236	Me
229	Pr^i
237	Bu^t

	R
238	Me
227	Pr^i
240	Bu^t

	R
239	Me
228	Pr^i
241	Bu^t

3. Trans substrates

a. Results

Stork and White reported[14] that the trans 2,6 dichlorobenzoates (39, 40, 41) reacted with piperidine to produce the trans 4-amines (42, 43, 44) in 60-73% yields (Scheme 6).

They claimed that:-

1. cis 4-amines (236, 229, 237) were not formed.
2. 6-amines (238, 239, 227, 228, 240, 241) were not formed i.e. "normal" substitution did not occur.
3. Rearrangement of esters did not occur during the reaction.
4. Reactions exhibited second order kinetics.

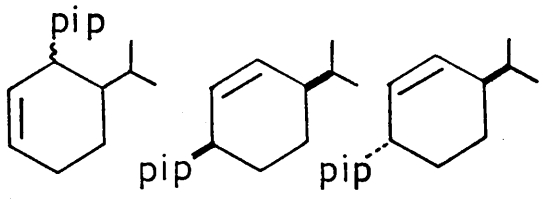
They concluded, on the basis of this evidence, that the trans 4-amines (42, 43, 44) were formed from the trans 6-esters (39, 40, 41) by the syn S_N2' mechanism.

This study will dispute claims 1, 2, and 3, above, but, as a result of further work with other displaceable ester groups, will uphold the conclusion that the S_N2' reaction, when involved, exhibits only syn stereochemistry.

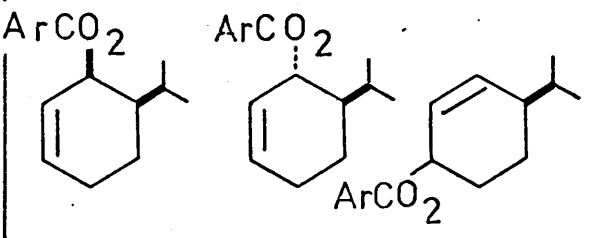
Unfortunately, the synthetic problems described earlier precluded full investigation of the S_N2' reaction of the substrates (39, 40, 41) employed by Stork and White,[14] but sufficient evidence was obtained from study of the available trans 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (40) to allow certain conclusions to be made and, importantly, to permit analogy with the more readily available and so more extensively studied trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenoate (85).

Table 16.

(a) Products[a] from reaction of the trans 2,6-dichlorobenzoate (40) with piperidine.

reaction no.	temp. °C	time h.	solvent	 227,228[b] %	229 %	43 %
1	130	24	-	13	22	65
2	130	44	-	14	26	60
3	160	140	m-xylene	14	32	54
4	140	18	m-xylene	14	24	62
"	"	84	"	15	33	52

(b) Ester isomerisation[a] during reaction of the trans 2,6-dichlorobenzoate (40) with piperidine.

reaction no.	temp. °C	time h.	solvent	 82 %	40 %	242 %
4	140	0	m-xylene		99+	-
	"	84	"	6	62	32

a. analysis by GLC (esters analysed as alcohols, after LAH reduction)

b. the cis and trans epimers were not rigorously identified.

(i) trans 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (40).

When the trans 2,6-dichlorobenzoate (40) was heated with piperidine, in the absence of added solvent, under the conditions employed by Stork and White,[14] a mixture of amines resulted. (Table 16a, reaction 1). The expected[14] "abnormal" substitution product, the trans 4-amine (43, 65%) was accompanied by substantial amounts of its cis 4-epimer (229, 22%) and the "normal" substitution products, the 6-amines (227+228, 13%).

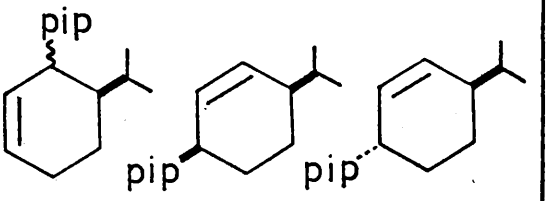
The appearance of both "normal" substitution products, cis and trans 6-amines (227, 228) was surprising, suggesting either that the trans 6-ester (40) was producing 6-amines by a non-stereospecific S_N1 process, or that partial epimerisation to the cis 6-ester was occurring, followed by S_N2 reaction.

The reaction was investigated under different conditions, variables being time, temperature, and the presence or absence of solvent (m-xylene). Surprisingly, this demonstrated (Table 16a) that the ratio of the isomeric 4-amines (229, 43) was dependent upon reaction conditions and varied during the course of reaction (Table 16, reaction 4).

If, as was initially thought, the cis and trans 4-amines (229, 43) were formed by anti and syn S_N2' reactions, respectively, from trans 6-ester (40) their ratio would remain constant during reaction and would be a measure of the ratio of the anti and syn rate constants. The observed non-constancy of the 4-amine ratio suggested that they were not formed by the same kinetic pathway (S_N2') from the same substrate (trans 6-ester (40)).

Analysis of the residual ester, after reaction, showed that, during the course of reaction, the trans 6-ester (40) had partially epimerised to the cis 6-ester (82) and, more significantly

Table 17. Comparison of the products[a] from reactions of the trans 2,6-dichlorobenzoate (40) with piperidine and the trans 3,5-dinitrobenzoate (85) with piperidine.

Ester substrate	Temp. °C	Time h.	Solvent	 227,228 %	229 %	43 %
2,6-DCB	140	18	m-xylene	14	24	62
(40)	"	84	"	15	33	52
3,5-DNB	145	18	"	8	16	76
(85)	"	90	"	9	30	61

a. analysis by GLC

allylically rearranged to the trans 4-ester (242) (Table 16b). The 62:32 ratio of trans 6-(40) to other esters (82, 242) was very similar to the ratio of trans 4- to cis 4-amines (43, 229) suggesting a link between the ester rearrangement and the observed stereochemistry of the 4-amines.

Unfortunately, further studies had to utilise another substrate, trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (85) as the supply of trans 2,6 dichlorobenzoate (40) had been exhausted. However, these confirmed and extended the initial results with the 2,6-dichlorobenzoate.

Sufficient information had already been obtained, however, to dispute claims 1, 2, and 3 made by Stork and White,[14] although, at that time, final judgement could not be passed on their conclusion.

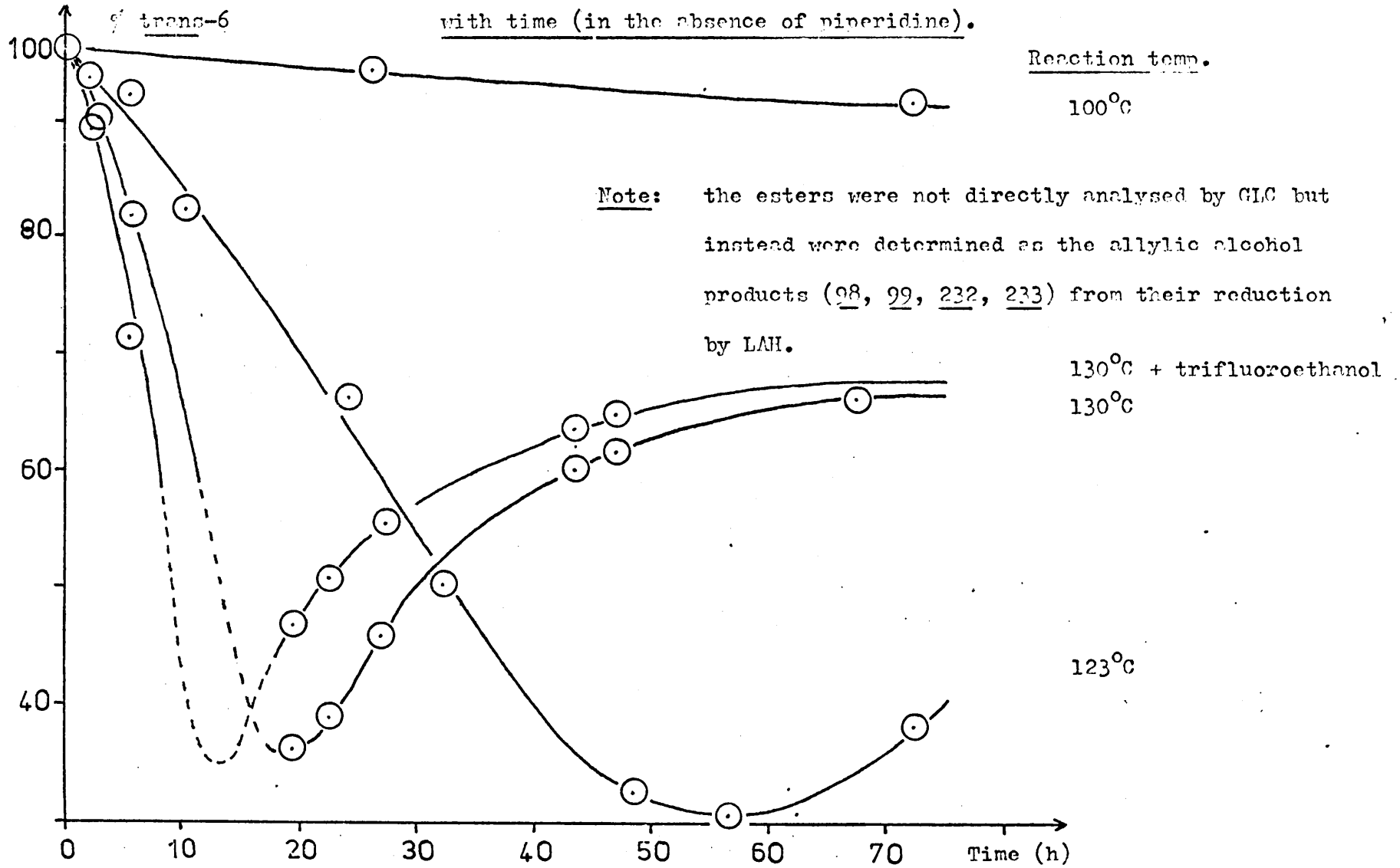
(ii) trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (85).

This substrate was less suitable for study of the S_N2' reaction than its 2,6-dichlorobenzoate analogue (40) because its reactions with piperidine produced a more complex mixture, products resulting from aminolysis also being formed.

Disregarding aminolysis, however, the trans 3,5-dinitrobenzoate (85) reacted similarly to the trans-2,6 dichlorobenzoate (40), yielding a mixture of "normal" and "abnormal" substitution products (Table 17). The amount of "normal" substitution was less than for the 2,6 dichlorobenzoate (40), presumably reflecting an increased steric barrier to nucleophilic attack by piperidine at the allylic position of the 3,5-dinitrobenzoate (85).

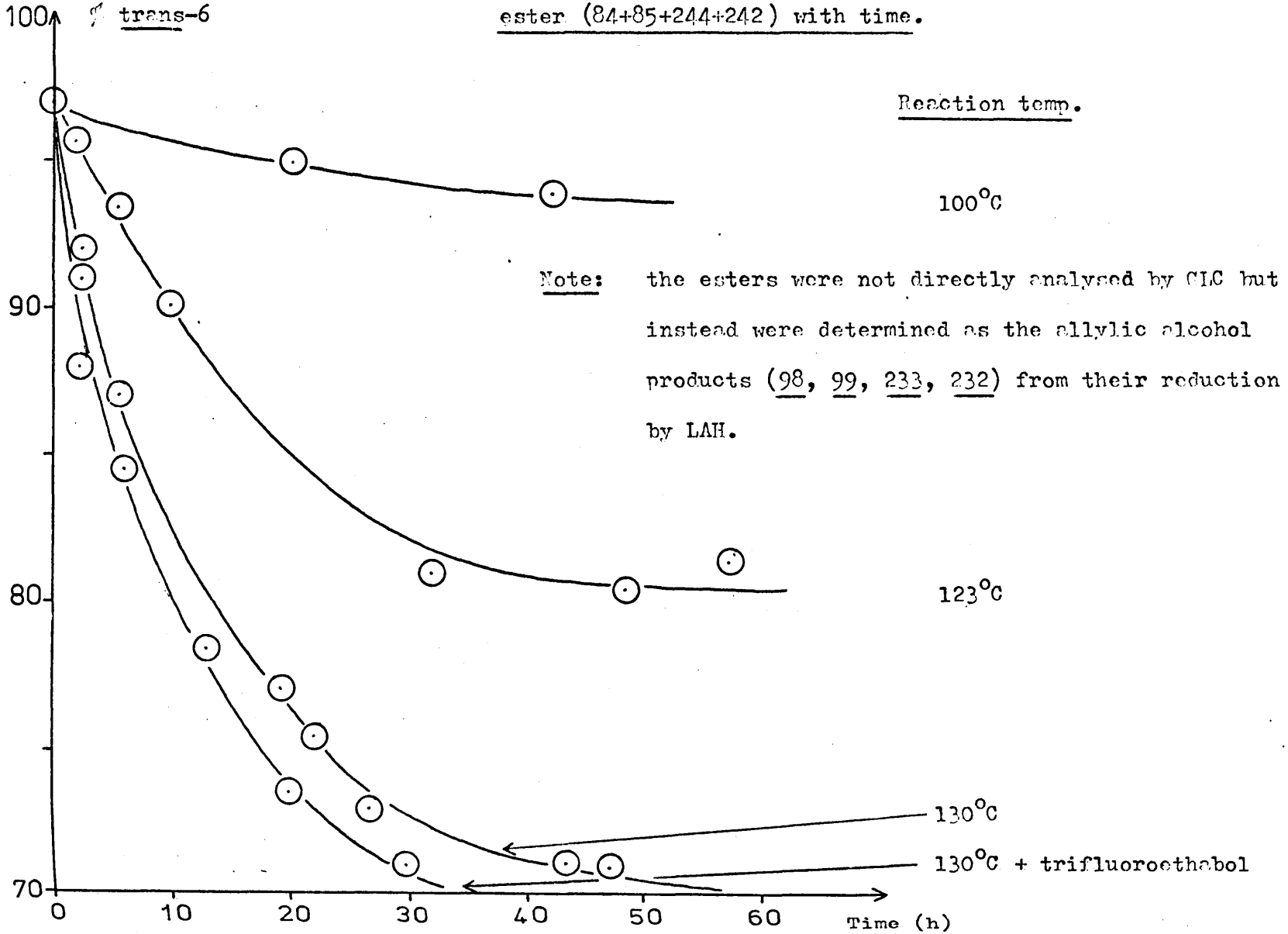
As before, the ratio of cis to trans 4-amines (229, 43) was not constant during the reaction, increasing with reaction time and also

Figure 15. Variation in the ratio of trans 6-ester (85) to total ester (84+85+244+242) with time (in the absence of piperidine).



Note: the esters were not directly analysed by GLC but instead were determined as the allylic alcohol products (98, 99, 232, 233) from their reduction by LAH.

Figure 14. LAH reduction: variation in ratio of trans 6-ester (85) to total ester (84+85+244+242) with time.



Note: the esters were not directly analysed by GLC but instead were determined as the allylic alcohol products (98, 99, 233, 232) from their reduction by LAH.

Figure 13. Aminolysis: variation in ratio of trans 6-alcohol (99) to total alcohol (98+99+232+233) with time.

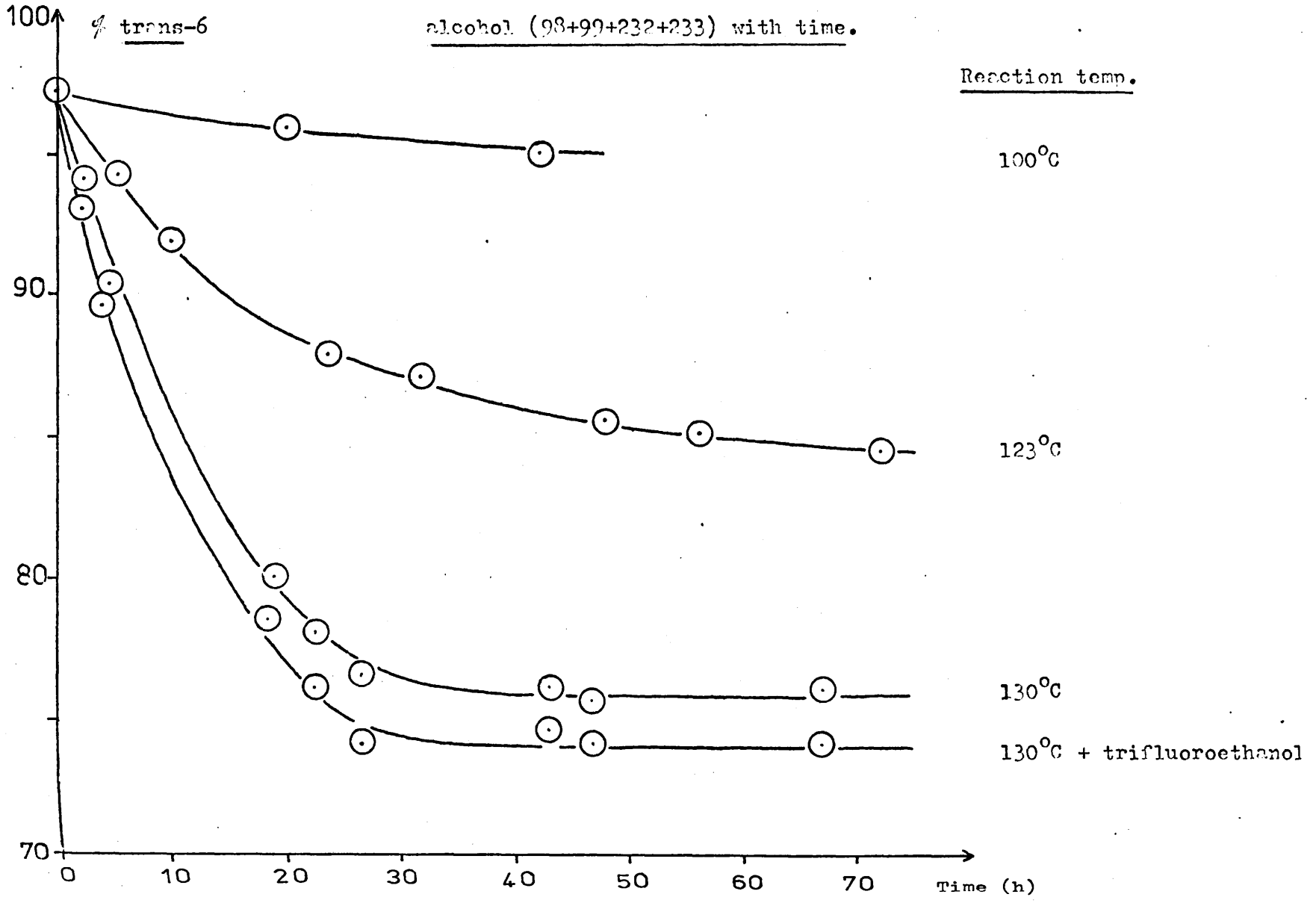


Figure 12. Variation in ratio of trans 4-amine (43) to total 4-amine (229+43) with time

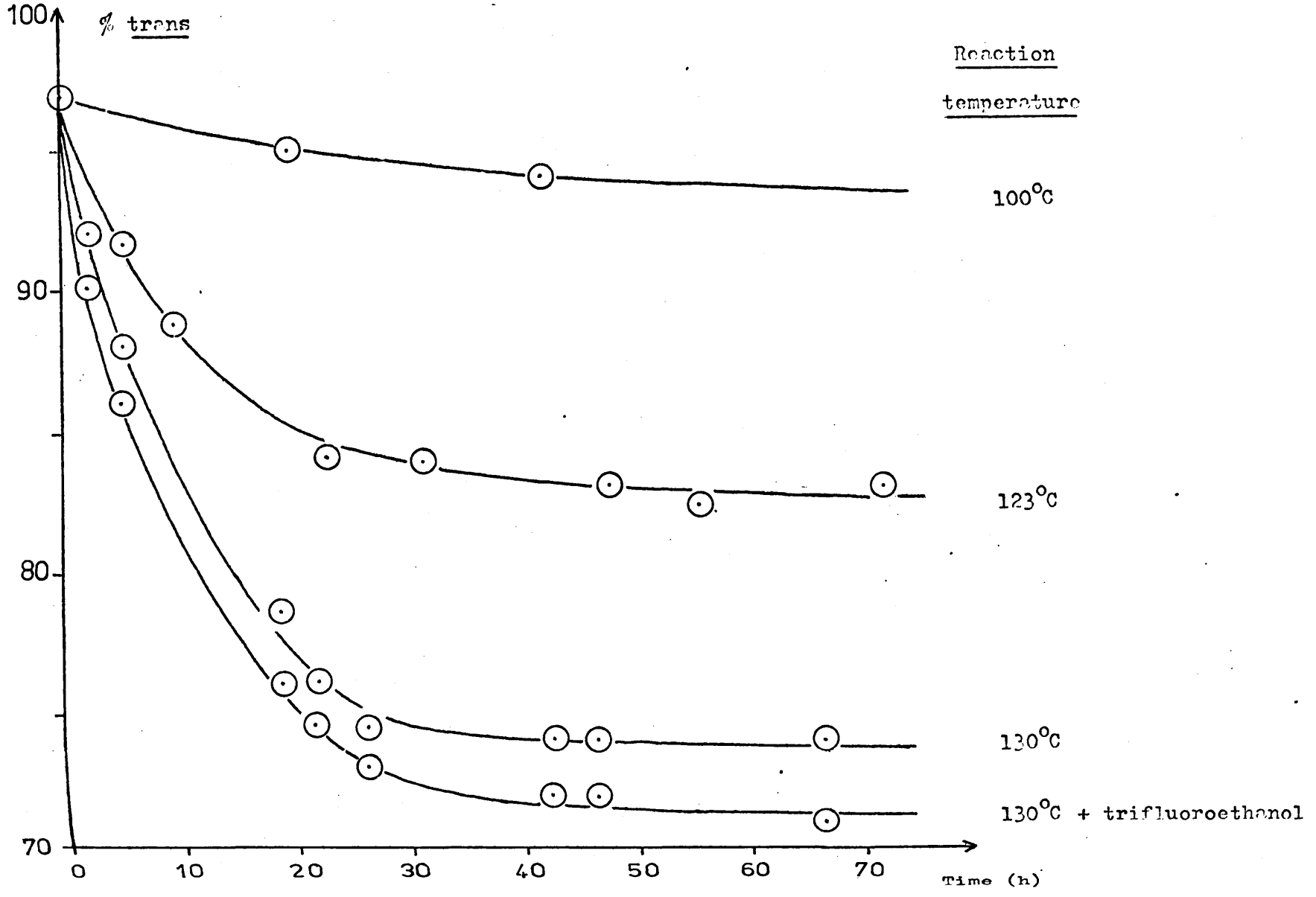
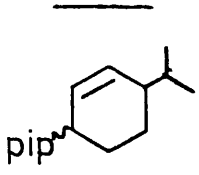
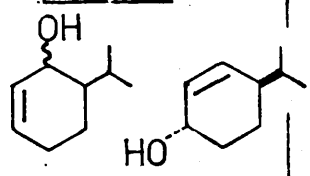
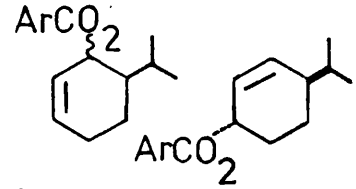


Table 18. Comparison of product distribution[a] and substrate isomerisation during reaction[b] of the trans 3,5-dinitrobenzoate (85)[c] with piperidine.

Time (h)	amines 		alcohols 			esters 		
	cis 229 %	trans 43 %	cis 98 %	trans 99 %	232 %	cis 84 %	trans 85 %	242 %
0	-	-	-	-	-	3	97	-
18	18	82	1	89	10	7	79	14
42	31	69	2	74	24	8	68	24
66	31	69	2	73	25	9	62	29
90	33	67	2	71	27	10	47	43

a. analysis by GLC

b. conditions: 145°C, m-xylene

c. analysed as the allylic alcohol products from LAH reduction

d. expressed as % of total 4-amines (229+43).

e. expressed as % of total alcohols (98+99+232) ex. aminolysis

f. expressed as % of total esters (82+40+242) as determined after LAH reduction.

with temperature. Analogy between the substitutional behaviour of the two ester systems (40, 85) is, therefore, valid and the qualitative conclusions to be drawn from a study of the 3,5-dinitrobenzoate (85) may reasonably be applied to the 2,6-dichlorobenzoate (40).

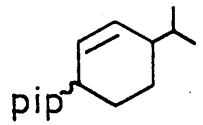
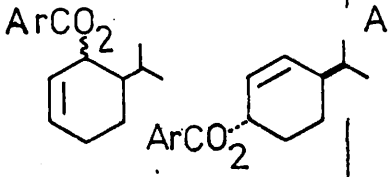
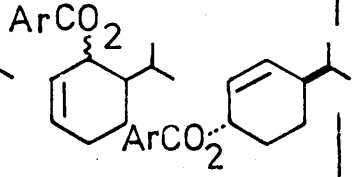
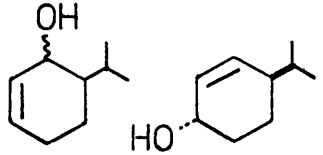
Initial experiments supported the previously inferred link between the stereochemistry of the 4-amine products (229, 43) and the ester epimerisation and rearrangement (Table 18). In addition, the distribution of the alcohol products from aminolysis was seen to alter during the reaction, the observed change reflecting the ester isomerisation, at least for the first forty hours of reaction (Table 18).

These relationships were explored further by studying the reaction of the trans 6-ester (85) with piperidine at different temperatures, in the dual hope of establishing the source of the 4-amines (229, 43) and of reducing, by lowering reaction temperature, the complication of ester isomerisation. In practice, this latter hope was dashed for, although ester isomeration was, indeed, reduced as the temperature was lowered, the ratio of aminolysis to substitution increased until aminolysis became the dominant reaction.

However, the relationship between 4-amine stereochemistry and ester isomerisation was clear. As reaction time or temperature varied, so did:-

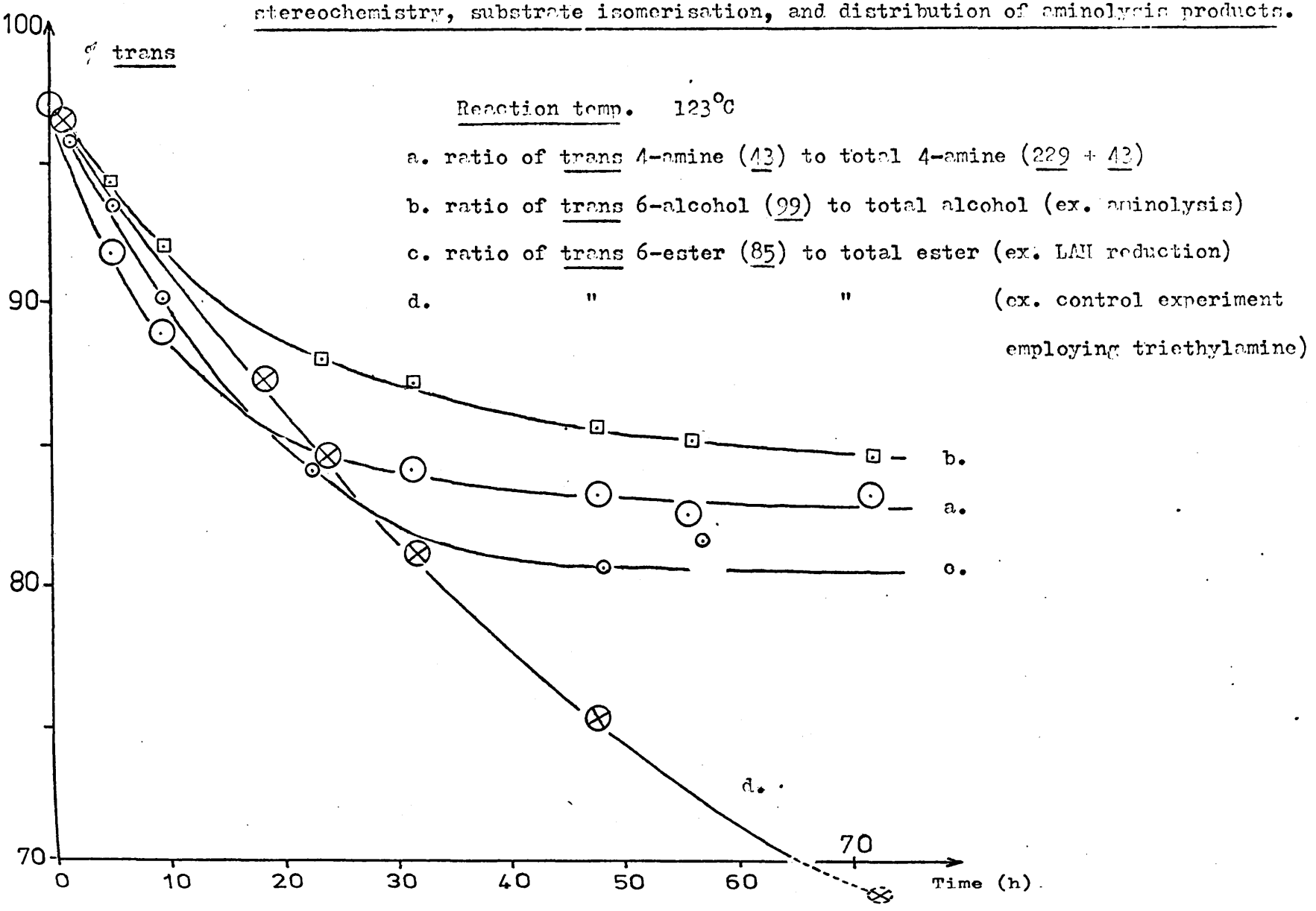
1. The ratio of cis/trans 4-amines (229, 43) (Figure 12).
2. The distribution of the alcohol products from aminolysis (Figure 13).
3. The ester composition, as determined after LAH reduction (Figure 14).

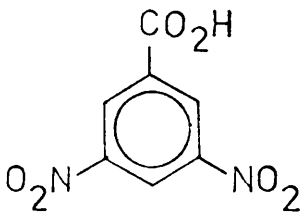
Table 19. Variation of the product distribution[a] from reaction[b] of the trans 3,5-dinitrobenzoate (85) with piperidine.

Time (h)	amines  cis 229	%	trans 43	esters (control/NEt_3)  cis 84	%	trans 85	%	242	esters (reaction)  cis 84	%	trans 85	%	242	alcohols (aminolysis)  cis 98	%	trans 99	%	232
0	-		-	3		97		-	3		97		-	-		-	-	
2	-		-	3		96		1	3		96		1	-		-	-	
5.5	8		92	3		94		3	4		93		3	-		98	2	
9.8	11		89	3		91		6	5		90		5	-		96	4	
23.8	16		84	4		84		12	-		-		-	2		89	9	
31.8	16		84	4		81		15	8		81		11	3		87	10	
48	17		83	5		74		19	8		81		11	3		86	11	
55.8	17		83	5		72		21	9		82		9	3		85	12	
72	17		83	7		68		25	-		-		-	3		85	12	

a. analysis by GLC b. reaction conditions: 123°C, m-xylene

Figure 16. Reaction of trans 6-ester (85) with piperidine: relationship between 4-amine stereochemistry, substrate isomerisation, and distribution of aminolysis products.





243

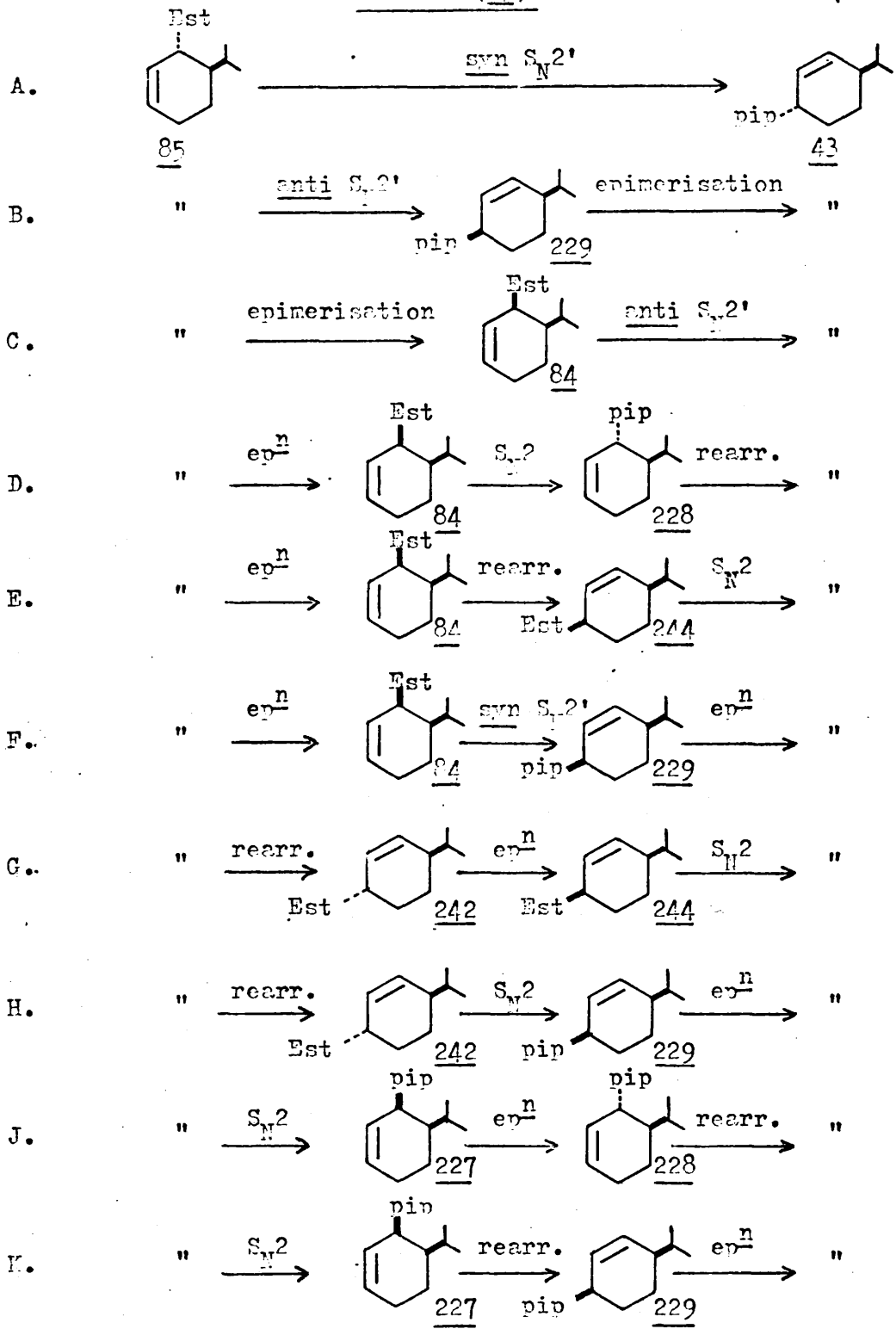
The product distribution was also influenced by the nature of the solvent as shown by the fact that addition of trifluoroethanol,[196] an ionising non-nucleophilic solvent, to the solvent system caused changes in the ester composition and, consequently, in the ratio of cis to trans 4-amines and alcohol distribution (Figures 12, 13, 14, 15) suggesting that the ester isomerisation may proceed, at least partially, by an ionic mechanism.

Control experiments (Figure 15) in which the trans 6-ester (85) was subjected to the reaction conditions in the absence of piperidine also showed variation in the ester composition with time and temperature, but these could not be directly related to values obtained from the reactions in the presence of piperidine, as it appeared that the observed results were a combination of ester isomerisation and ester decomposition reactions, the latter, presumably, being catalysed, in the absence of base, by 3,5-dinitrobenzoic acid (243), liberated by the slight thermal decomposition of the ester. This decomposition reaction was effectively suppressed by performing the control experiment in the presence of an added, relatively non-nucleophilic,base (e.g. triethylamine) whose primary function was to sequester any acid formed by thermal decomposition.

Comparison of the data obtained for 4-amine stereochemistry, alcohol distribution, ester isomerisation during reaction, and ester isomerisation in a control experiment readily showed the inter-relationship of these quantities (Figure 16, Table 19).

This information strongly suggested that the epimeric 4-amines (229, 43) were not being formed from the same source. Rather, the trans 4-amine (43) was formed directly from the trans 6-ester (85), presumably by syn S_N2' reaction (although this had yet to be

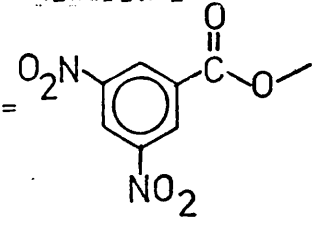
Figure 17. Potential routes to trans 4-amine (43) from trans 6-ester (85).



ep^n = epimerisation

rearr. = allylic rearrangement

pip = piperidyl

Est = 

proved), while the cis 4-amine (229) was formed from the isomerised cis 6- and trans 4-esters (84, 242); it was, therefore, not a product of anti S_N2' reaction.

Having established plausible sources for the 4-amines (229, 43), it then became necessary to determine their modes of formation from these sources (Figures 17, 18).

Potentially, the trans 4-amine (43) may arise from the trans 6-ester (85) by a variety of pathways (Figure 17) but all except syn S_N2' were eliminated:-

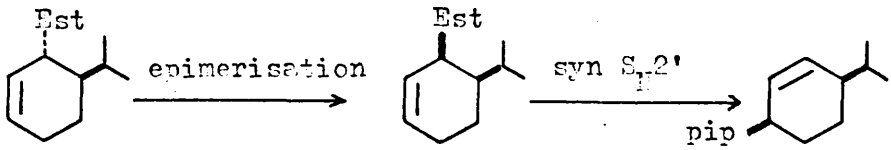
1. Routes involving amine epimerisation or allylic rearrangement (B, D, F, H, J, K) were eliminated by control experiments in which different mixtures of the four isomeric amines (227, 228, 229, 43) were subjected to the reaction conditions in the absence of ester. No isomerisation of the amines occurred, either by epimerisation or allylic rearrangement.

2. Epimerisation of the trans 6-ester (85) to the cis 6-ester (84) was shown to be slight (Table 19), effectively eliminating routes (C,D,E,F) involving this step from being significant pathways to the trans 4-amine (43). Routes D and F have, in fact, already been eliminated in 1. above and later studies with the cis 6-ester (84) will confirm the non-participation of route C, as the second step (anti S_N2' reaction) does not occur.

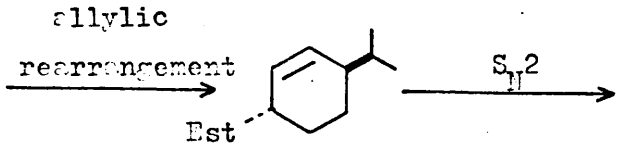
3. Hydrogenation studies demonstrated that only trace amounts (1%) of the cis 4-ester (244) were present in the reaction mixtures and in control experiments performed in the absence of nucleophile; these small quantities could be satisfactorily accounted for* by allylic rearrangement of the cis 6-ester present (84) (Table 19).

* By analogy with later study of the cis 6-ester (84).

Figure 18. Potential routes[a] to cis 4-amine (229) from trans 6-ester (85).

A. 

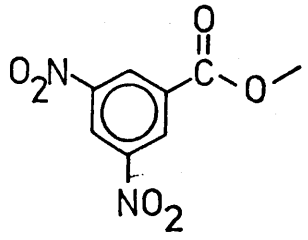
85 84 229

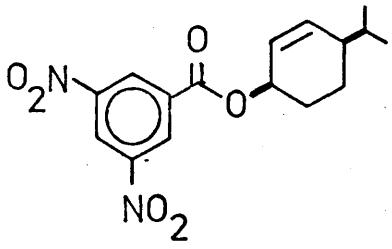
B. " 

"

242

a. Routes involving amine isomerisation are not shown.

pip = piperidyl Est = 



244

rather than by the epimerisation of trans 4-ester (242) to cis 4-ester (244), thereby eliminating route G.

4. Kinetic studies (see later) established that the rate of formation of the trans 4-amine (43) was proportional to the concentrations of the trans 6-ester (85) and piperidine. This further eliminated the complex routes B,C,D,E,F,G,H,J,K since for these routes to exhibit second-order kinetics, all of the steps involved would have to be second-order, which is unlikely for the epimerisations and allylic rearrangements, or the rate of reaction would have to be independent of these isomerisations i.e. they would require to be very fast relative to the S_N2 or S_N2' reactions involved - this has already been shown not to be the case.

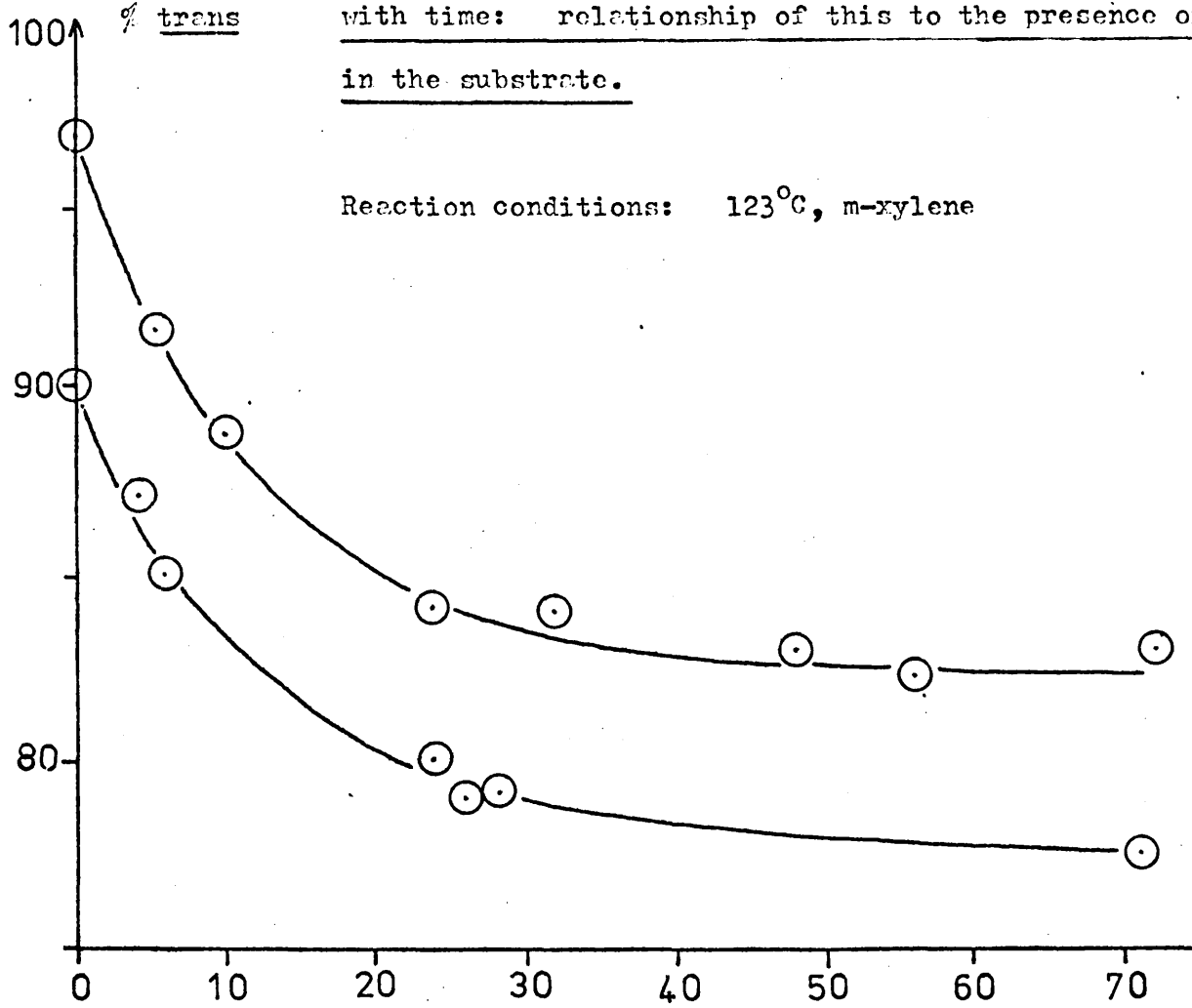
All other plausible pathways having thus been eliminated, the inevitable conclusion from this study must, therefore, be that the trans 4-amine (43) was formed from the trans 6-ester (85) by a syn S_N2' reaction.

Consequently, the cis 4-amine (229) cannot be formed by anti S_N2' reaction from the trans 6-ester (85) since this would require the cis to trans 4-amine ratio to be constant and it must, therefore, be formed by other pathways (Figure 18), most probably involving prior epimerisation or allylic rearrangement of the trans 6-ester (85).

The feasibility of these two possible routes was demonstrated by experiment.

1. The cis 6-ester (84) was shown to react by syn S_N2' reaction, producing cis 4-amine (229) (see later). However, as the epimerisation of trans 6-ester (85) to cis 6-ester (84) was slight, and only 3% of the cis 6-ester (84) was present in the starting material, this route can be only a minor contibutor to the formation

Figure 19. Variation in the ratio of trans 4-amine (43) to total 4-amine (229+43) with time: relationship of this to the presence of trans 4-ester (242) in the substrate.



Reaction conditions: 123°C, m-xylene

substrate composition (%)		
6-ester		4-ester
cis (84)	trans (85)	trans (242)
3	97	0
3	90	7

of the cis 4-amine (229).

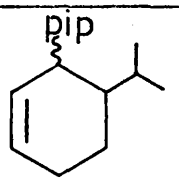
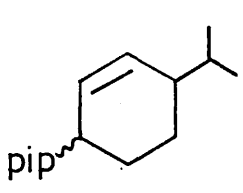
2. The allylic rearrangement product trans 4-ester (242) was shown to react by "normal" S_N2 reaction to produce the cis 4-amine (229) by treatment of a mixture of trans 6- and trans 4-esters (85, 242)* with piperidine. Comparison of the results of this experiment with those from a control experiment, using trans 6-ester (85) alone, demonstrated that the quantity of cis 4-amine (229) formed was directly related to the amount of trans 4-ester (242) available and that the cis 4-amine (229) was therefore being predominantly formed by "normal" S_N2 reaction of the trans 4-ester (242) (Figure 19).

b. Conclusions

It has, thus, been demonstrated that the trans 3,5-dinitrobenzoate (85) and, by analogy, the trans 2,6-dichlorobenzoate (40) will undergo substitution, by piperidine, by a variety of pathways, including the S_N2' reaction. In these systems the stereochemistry of the S_N2' reaction was syn, and no evidence, whatsoever, for anti S_N2' reaction was found. Thus, although the evidence[14] presented by Stork and White is disputed, the present study justifies their conclusion that the S_N2' reaction occurs only in syn fashion in trans cyclohex-2-en-1-yl systems.

* This was available from partial rearrangement of trans 6-ester (85) by heating it in the absence of nucleophile. Use of a mixture (85, 242) circumvented the much more lengthy preparation of pure trans 4-ester (242) by independent synthesis.

Table 20. Comparison of the distribution of amine products from reactions of the cis (84) and trans 6-esters (85) with piperidine.

No	Substrate	Temp. °C	Time h.	 227,228 6-amines %[a]	 229,43 4-amines %[a]
40	trans 2,6-DCB	140	84	16	84
85	trans 3,5-DNB	135	70	10	90
84	cis 3,5-DNB	140	70	30	70
87	cis p-NB	125	85	21	79

a. analysis by GLC

trans 2,6-DCB = trans 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (40)

trans 3,5-DNB = " 3,5-dinitrobenzoate (85)

cis 3,5-DNB = cis 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (84)

cis p-NB = " p-nitrobenzoate (87)

4. Cis Substrates

a. Results

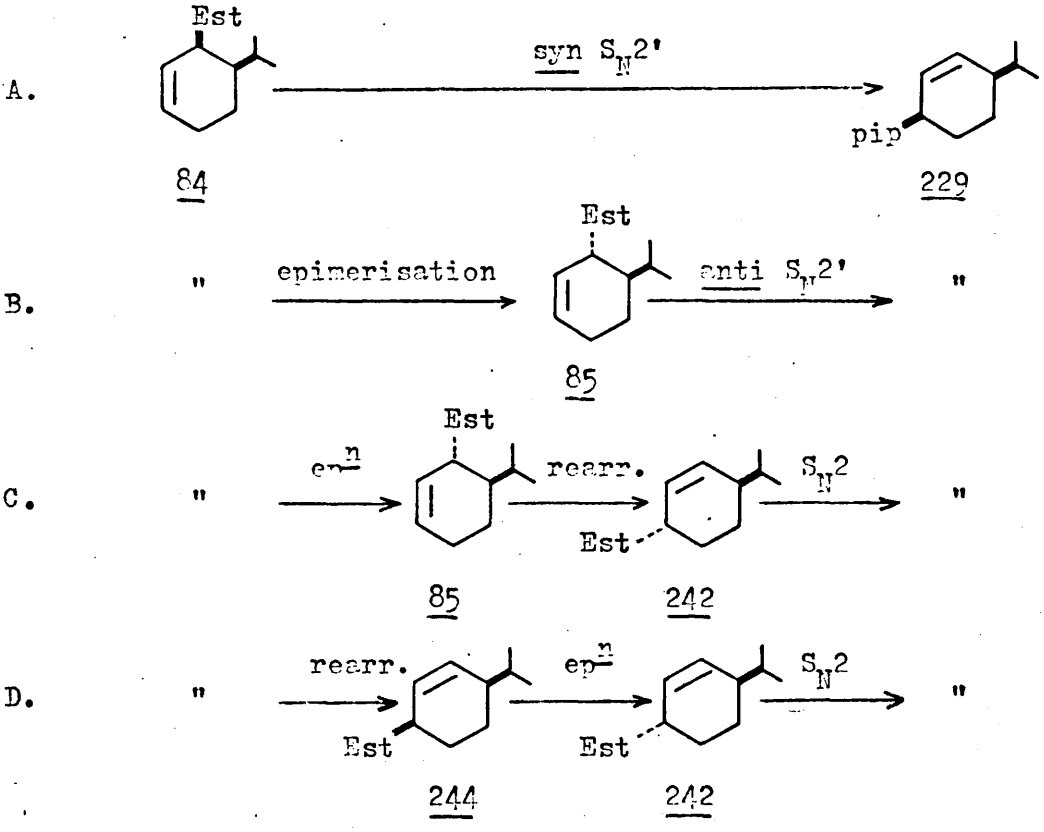
Interpretation of the results obtained from the reactions of the cis p-nitrobenzoate (87)* and cis 3,5-dinitrobenzoate (84) with piperidine, proved to be more complex than had been found in the trans series.

Additional problems in the cis series were caused by

1. Greater amounts of "normal" substitution products (Table 20). These were difficult to analyse because of their poor separation from the aminolysis products (Figure 9).
2. Correlation between the stereochemistry of the 4-amines and the isomerisation of the ester substrates was made more difficult by the different reaction rates of the original and rearranged substrates.
3. Unlike its trans epimer, the cis 3,5-dinitrobenzoate (84) was isomerised significantly by both epimerisation and allylic rearrangement. The trans 6-ester (85), once formed by epimerisation, was, itself, prone to allylic rearrangement. Consequently, during the course of reaction of the cis 6-ester (84) with piperidine, all four of the interconverting esters (84, 85, 244, 242) were present in varying, but significant, amounts.
4. Stereochemically pure cis 3,5-dinitrobenzoate (84), free from its trans epimer (85) was not available and this complicated interpretation of the results.

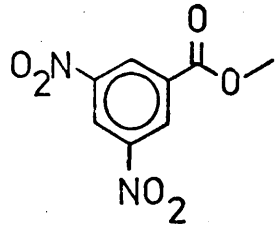
* Only preliminary studies were performed using this substrate (87) since, following extensive study of the trans 3,5-dinitrobenzoate (85), the cis 3,5-dinitrobenzoate was considered a better substrate for comparative study.

Figure 21. Potential routes[a] to cis 4-amine (229) from cis 6-ester (84).



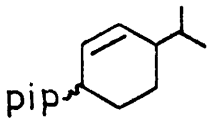
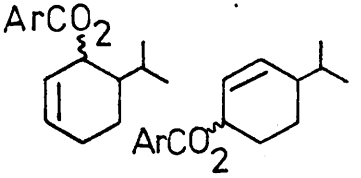
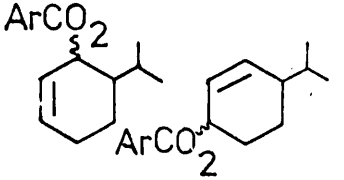
ep^n = epimerisation pip = piperidyl

rearr. = allylic rearrangement

Est = 

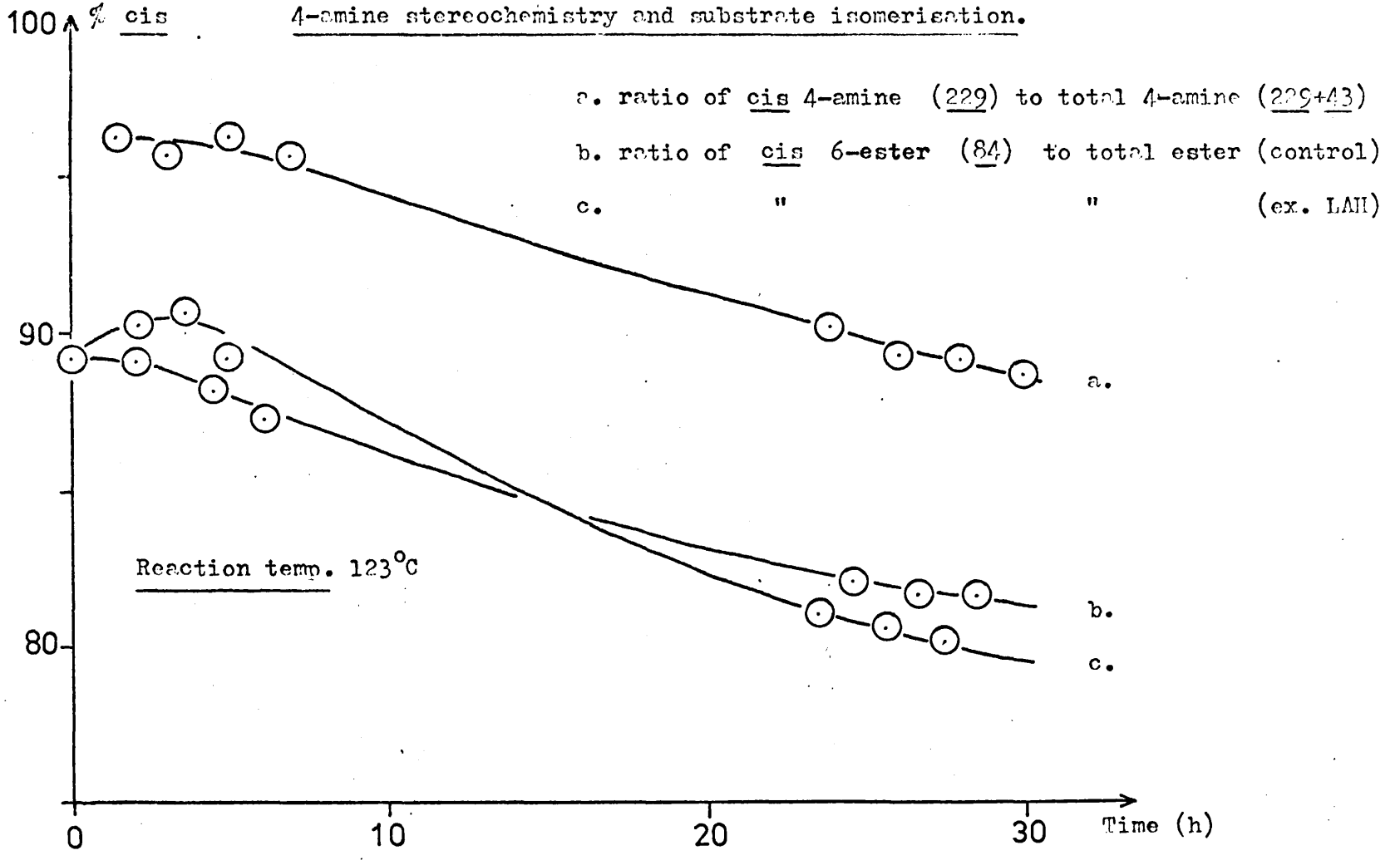
a. routes involving amine isomerisation are not shown

Table 21. Variation of the product distribution[a] from reaction[b] of the cis 3,5-dinitrobenzoate (84) with piperidine.

Time (h)	amines		esters (control/NEt_3)[c]			esters (reaction)[c]		
								
	cis	trans	cis-6	cis-4 / trans-6	trans-4	cis-6	cis-4 / trans-6	trans-4
	229	43	84	244,85	242	84	244,85	242
0	-	-	89	11	0	89	11	0
1.5	96	4	89	10	1	90	10	1
3	96	4	89	10	1	89	10	1
5	96	4	88	11	1	88	11	1
7	95	5	87	12	1	-	-	-
24	90	10	82	16	2	81	17	2
26	89	11	82	16	2	81	17	2
28	8	11	81	17	2	80	18	2
30	88	12	-	-	-	-	-	-

a. analysis by GLC b. 123°C, m-xylene c. analysed as allylic alcohols (ex. LAH reduction)

Figure 20. Reaction of cis 6-ester (84) with piperidine: relationship between 4-amine stereochemistry and substrate isomerisation.



(i) cis 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (84).

The stereochemistry of the 4-amine products (229, 43) from reaction of the cis 3,5-dinitrobenzoate (84) with piperidine, was shown to alter during the course of reaction as was the composition of the ester, either in the reaction mixture, itself, or in a control experiment, employing triethylamine (Figure 20, Table 21). This reaction was studied for only 30 hours, as, after that time, amine decomposition became serious.

The observed change in the ratio of stereoisomeric 4-amines (229, 43) paralleled the change in ester composition although the correspondence was not so close as with the trans 3,5-dinitrobenzoate (85). The discrepancy was probably due to differences in the reaction rates of the cis 6-ester (84) and its isomers, particularly the trans 6-ester (85). Kinetic studies (see later) established that the cis 6-ester (84) reacted 1.13 times as fast as its trans epimer (85) by syn S_N2' reaction, but that the trans epimer (85) reacted almost twice as fast as cis 6-ester (84) by aminolysis. Consequently, the ratio of stereoisomeric 4-amines did not mirror the ester isomerisation exactly but showed an apparent excess of cis-4 amine above that expected, since the trans 6-ester (85) preferentially reacted by aminolysis.

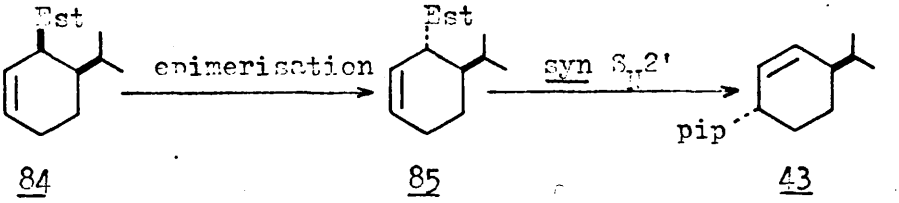
Allowing for this, the change in the ratio of the stereoisomeric 4-amines was seen to be directly related to the ester isomerisation and it was concluded, in analogy with the trans series, that the cis 4-amine (229) was formed directly from the cis 6-ester (84) while the trans 4-amine (43) was formed from the isomerised esters (85, 242).

Various pathways are available for the formation of the cis 4-amine (229) from cis 6-ester (84) (Figure 21).

1. Studies with the trans 6-ester (85) have already shown that

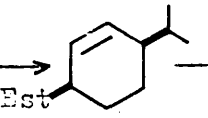
Figure 22. Potential routes[a] to trans 4-amine (43) from cis 6-ester (84).

A.



84 85 43

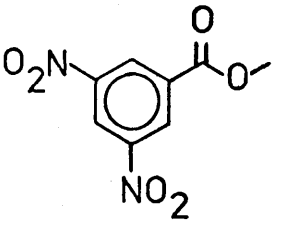
B. " rearr. S_N2 "



244

rearr. = allylic rearrangement

pip = piperidyl

Est = 

a. routes involving amine isomerisation are not shown

anti S_N2' reaction did not occur, thereby eliminating route B.

2. Only trace amounts (< 2%) of trans 4-ester (242) were formed under reaction conditions or in control experiments (Table 21) suggesting that only minor amounts of cis 4-amine (229) could be formed via routes C and D. [Studies in the trans series have already demonstrated that the trans 4-ester (242) will, indeed, react by S_N2 mechanism to produce cis 4-amine (229)].

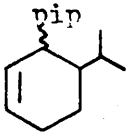
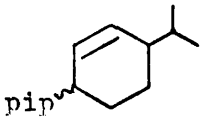
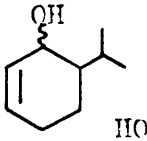
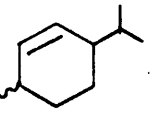
3. Kinetic studies demonstrated that the rate of formation of the cis 4-amine (229) was proportional to both the concentration of cis 6-ester (84) and piperidine. This information confirmed the non-participation of routes C and D since these would not be expected to exhibit second-order kinetics (see p.65).

Thus, the only plausible route to cis 4-amine (229) in agreement with the available data is the syn S_N2' route (Route A).

Consequently the trans 4-amine (43) cannot be formed directly from cis 6-ester (84) by anti S_N2' reaction, and it must be formed indirectly from the isomerised trans 6- and cis 4-esters (85, 244) (Figure 22).

The trans 6-ester (85) has already been shown to produce trans 4-amine (43) by a syn S_N2' process, but attempts to ascertain that the cis 4-ester (244) would produce trans-4-amine (43) by S_N2 reaction were frustrated by competition from the syn S_N2' reaction of the trans 6-ester (85). However, it appeared reasonable to assume that the cis 4-ester (244) would undergo S_N2 reaction with piperidine since its trans epimer (242) had been shown to do so. In any case, the amount of trans 4-amine (43) formed could be accounted for by syn S_N2' reaction of the trans 6-ester (85) without any need for contribution from possible S_N2 reaction of the cis 4-ester (244).

Table 22. Product distribution[a] from reaction of the cis p-nitrobenzoate (87) with piperidine.

						amines				alcohols			
													
						cis	trans	cis	trans	cis	trans	cis	trans
Reaction no.	Temp. °C	Time h.	Ester mg.	Piperidine µl.	m-xylene µl.	227,228 %		229 %	43 %	98 %		99,233 %	232 %
1	125	85	10	9	100	21		53	26	50		47	3
2	185	110	5	4.5	100	18		73	9	55		43	2
2. alcohols produced from LAH reduction of the corresponding esters =										81		19	-

a. analysis by GLC

(ii) cis 6-isopropyl cyclohex-2-en-1-yl p-nitrobenzoate (87).

Preliminary studies indicated that the cis p-nitrobenzoate (87) was reacting similarly to the cis 3,5-dinitrobenzoate (84) and that analogy between them is probably valid. However, further studies would be necessary to demonstrate this rigorously.

The cis p-nitrobenzoate (87) yielded products from "normal" and "abnormal" substitution and aminolysis (Table 22, reaction 1). As with its 3,5-dinitrobenzoate analogue (84), the ratio (67 : 33) of the 4-amine stereoisomers (229 : 43) was not closely paralleled by the ratio (50 : 50) of unrearranged to rearranged alcohols (98 : 99 + 233 + 232) nor, in another experiment was the 4-amine ratio (89 : 11) mirrored by the ratio (81 : 19) of unrearranged to rearranged esters (Table 22, reaction 2). These differences were probably due, as has been inferred for the cis 3,5-dinitrobenzoate (84), to the differing reaction rates of the unrearranged and rearranged ester.

b. Conclusions

The cis 3,5-dinitrobenzoate (84) has been shown to react with piperidine by S_N2' reaction. The stereochemistry of this reaction was shown to be syn and any potentially "anti S_N2'" product was satisfactorily accounted for by alternative pathways. Insufficient evidence was obtained for the cis p-nitrobenzoate (87) but all the available data showed its behaviour to be similar to the cis 3,5-dinitrobenzoate (84).

Table 23. Rates of formation of

a. cis 4-amine (229) from cis 6-ester (84)

b. trans 4-amine (43) from trans 6-ester (85)

a. cis 4-amine (229)					b. trans 4-amine (43)				
Concentration			Initial	k = rate	Concentration			Initial	k = rate
Est mg.	pip µl.	m-xyl µl.	rate $M.l.^{-1}h.^{-1}$	constant $l.M.^{-1}h.^{-1}$	Est mg.	pip µl.	m-xyl µl.	rate $M.l.^{-1}h.^{-1}$	constant $l.M.^{-1}h.^{-1}$
10	9	100	2.33×10^{-3}	7.00×10^{-3}	10	9	100	2.04×10^{-3}	6.13×10^{-3}
5	9	100	1.17×10^{-3}	7.03×10^{-3}	5	9	100	0.96×10^{-3}	5.78×10^{-3}
10	4.5	100	1.12×10^{-3}	6.73×10^{-3}	10	4.5	100	1.03×10^{-3}	6.19×10^{-3}

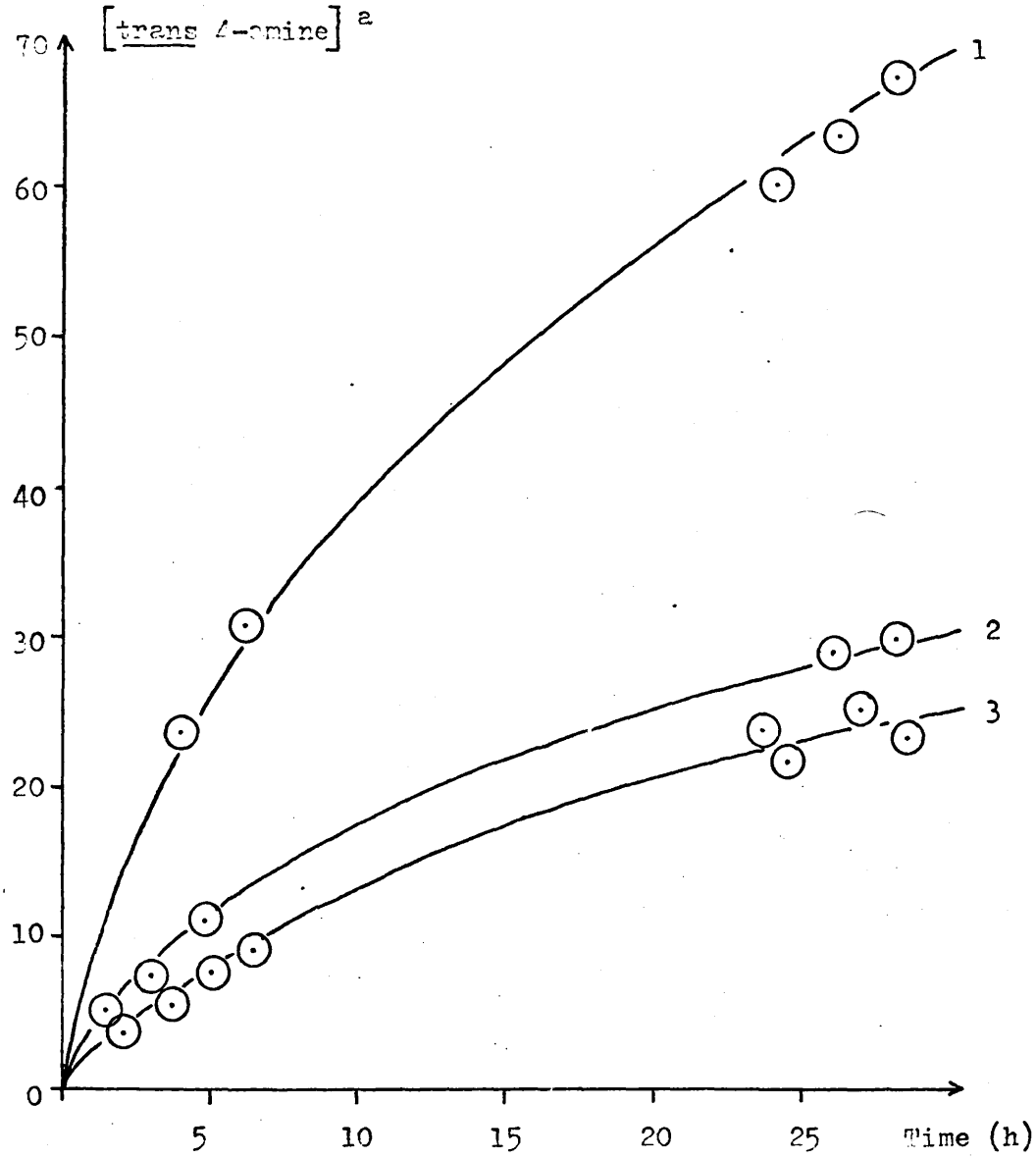
$$\text{Ratio} = k_{cis}/k_{trans} = 1.13$$

Est = 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (84, 85)

pip = piperidine

m-xyl = m-xylene

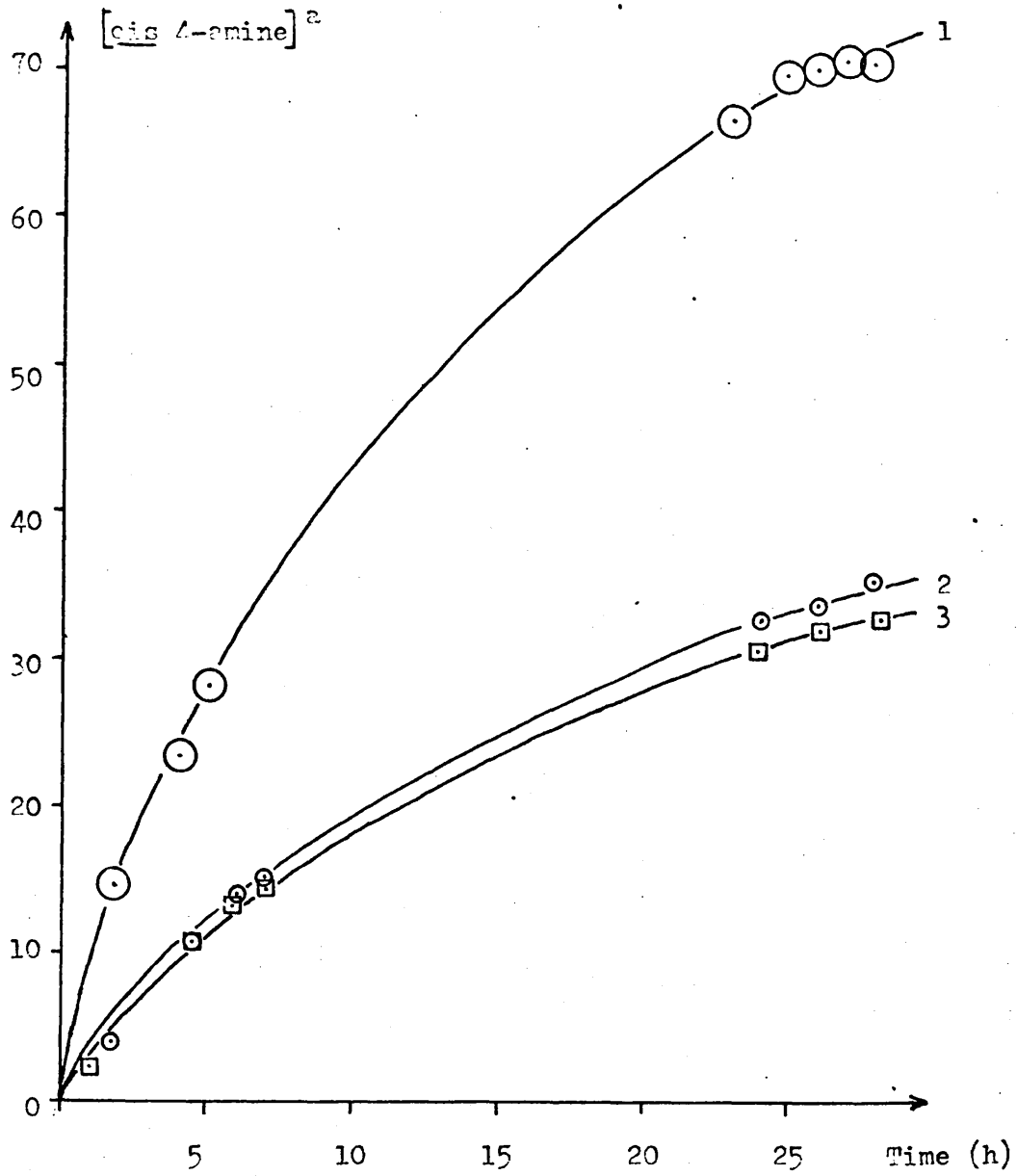
Figure 23b. Kinetic order of the reaction of trans 6-ester (85) with piperidine to produce trans 4-amine (43): variation in the concentration of trans 4-amine (43) with time.



Initial concentrations of reactants (123°C; m-xylene, 100µl.)	[trans 6-ester] mg.	[piperidine] µl.
reaction 1	10	9
reaction 2	10	4.5
reaction 3	5	9

a. expressed as % of the internal standard ($n.C_{20}H_{42}$)

Figure 23a. Kinetic order of the reaction of cis 6-ester (84) with piperidine to produce cis 4-amine (229): variation in the concentration of cis 4-amine (229) with time.



Initial concentrations of reactants (123°C; m-xylene, 100µl.)	[cis 6-ester] mg.	[piperidine] µl.
reaction 1	10	9
reaction 2	5	9
reaction 3	10	4.5

a. expressed as % of the internal standard ($n.C_{20}H_{42}$)

5. Reaction kinetics

The complexity of the reacting system (Figure 8) hampered kinetic analysis of the reactions of the ester substrates (84, 85) with piperidine and all attempts to obtain rate data by following the reaction course in a single experiment failed.

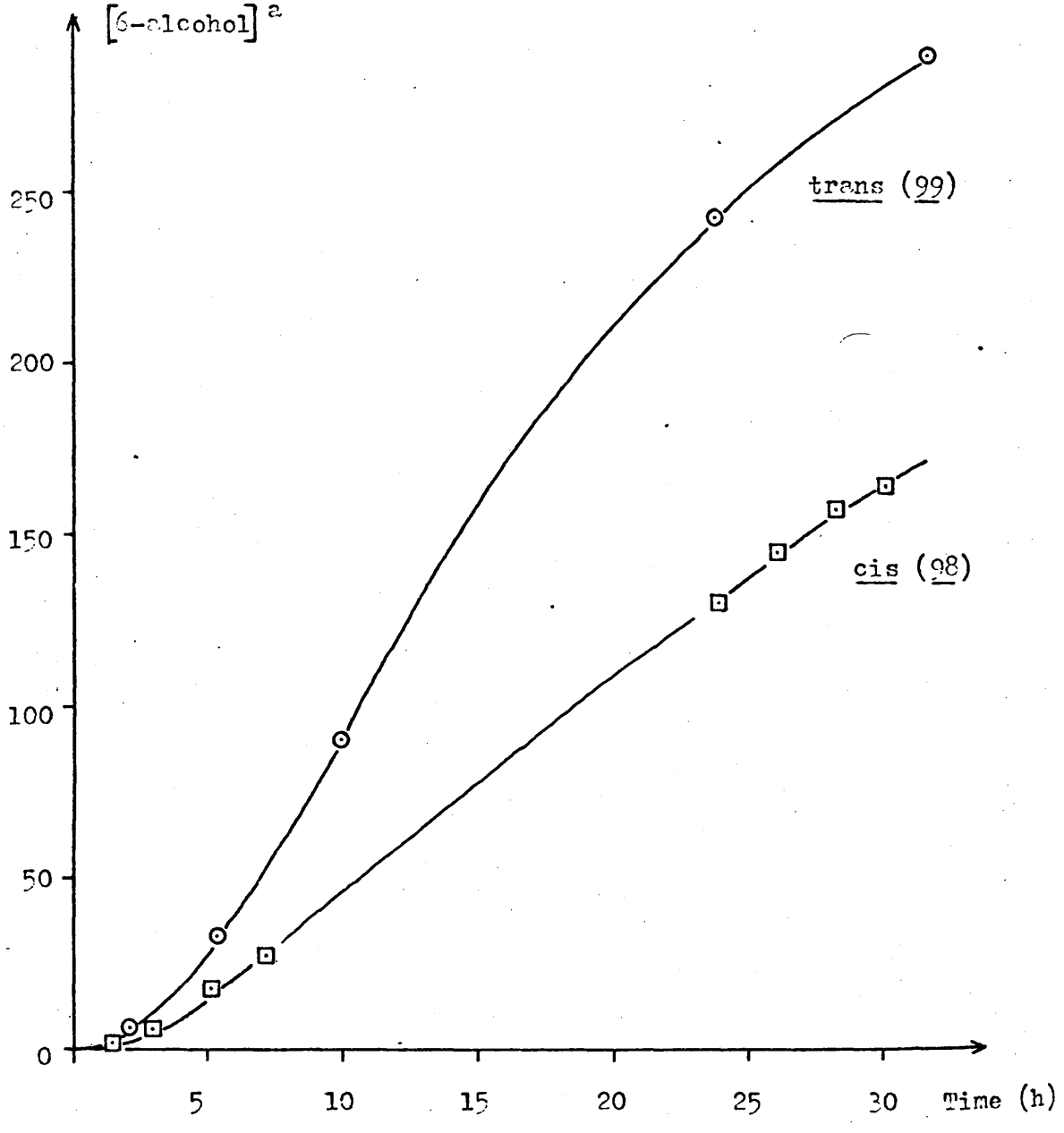
However, by performing reactions with different initial concentrations of substrates (84, 85) and piperidine, kinetic information was obtained for the syn "abnormal" substitution (S_N2') and aminolysis reactions (Figures 23, 24, Table 23).

The rates of formation of cis 4-amine (229) from cis 6-ester (84) and trans 4-amine (43) from trans 6-ester (85) were dependent upon the concentrations of substrate and piperidine and were, therefore, designated as S_N2' (Figure 23, Table 23). The kinetic order of the rates of formation of trans 4-amine (43) from cis 6-ester (84) and cis 4-amine (229) from trans 6-ester (85) could not be determined because they were not formed by a direct process (Figures 18, 22) and because of increased inaccuracy in their estimation relative to the major reaction products.

From the curves shown (Figure 23) initial rates for the syn S_N2' reactions of the cis and trans substrates were calculated (Table 23). Although the accuracy of these measurements must be suspect since it proved impossible to establish the GLC response factors of the amines in relation to the hydrocarbon internal standard employed, their use is justified for comparative purposes, since the cis and trans 4-amines (229, 43) will, very probably, have the same GLC response factors.

Thus, the cis 6-ester (84) was seen to react only slightly faster than its trans 6-epimer (85), the ratio k_{cis}/k_{trans} being 1.13.

Figure 24. Comparative study of the rates of formation of cis and trans 6-alcohols (98, 99) from aminolysis of the cis and trans 6-esters (94, 95), respectively, by piperidine.



Reaction conditions: 123°C; m-xylene, 100µl.
6-ester, 10mg.; piperidine, 9µl.

a. expressed as % of the internal standard ($n.C_{20}H_{42}$)

Although rate constants for the aminolysis reactions of the cis 6- and trans 6-esters (84, 85) could not be determined because of the complex nature of these reactions, estimate of their ratio as "k"$_{cis}$ / "k"$_{trans}$ ~ 1.9 could be made from comparison of the curves for their rates of formation (Figure 24).

6. General conclusions.

This study has shown that the "abnormal" substitution reactions of cyclohex-2-en-1-yl esters with piperidines are, properly, designated syn S_N2', since:-

1. The reaction rates were proportional to the concentrations of substrate and reagent.

2. The "abnormal" syn products did not arise by rearrangement of the substrate or "normal" substitution products.

3. The S_N2' reaction occurred with syn stereochemistry regardless of the configuration of the substrate.

Several implications result from these findings-

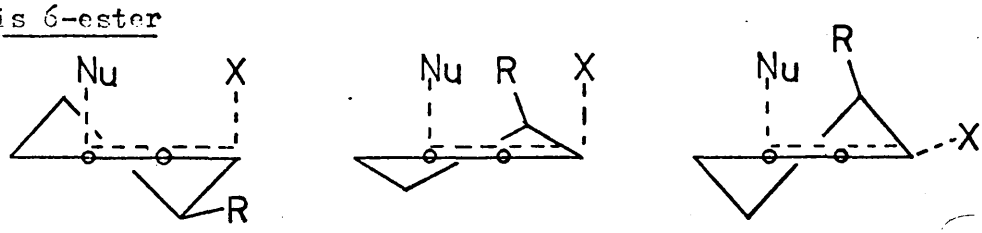
1. The conclusion reached by Stork and White[14] is confirmed although the evidence upon which it was based is disputed.

2. The proposal made in the introduction to this thesis (p.20) that the syn stereochemistry observed by Stork and White[14] may have been due to steric hindrance to anti S_N2' reaction, caused by the trans 6-alkyl groups (39, 40, 41) must be false, since, in the cis 6-isopropyl esters (84, 85) this "steric hindrance" has been largely removed. It appears that the S_N2' reaction does, indeed, have a stereoelectronic preference for syn nucleophile entry, at least in the reactions of cyclohex-2-en-1-yl systems with piperidine.

3. The possibility of hydrogen bonding between incoming piperidine and departing anion has, previously, been used[18,26] to question the validity of the conclusion reached by Stork and White.[14] Similarly, hydrogen bonding may contribute to the observed stereochemistry in the present study but it is improbable that this weak intermolecular force would be of sufficient magnitude[197,198,199] to be solely responsible for this stereoselectivity, particularly since no

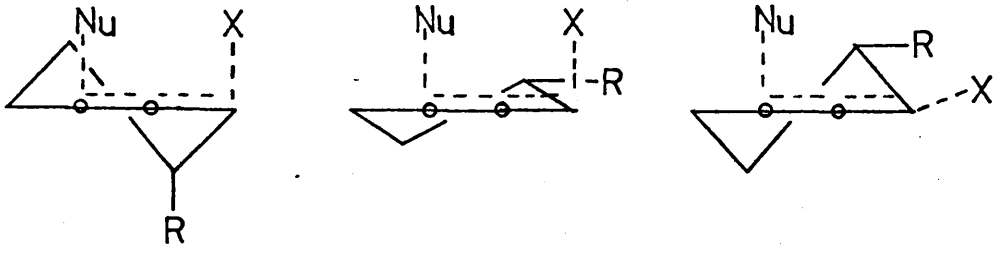
Figure 25. Possible transition states for syn S_N2' reaction.

a. cis 6-ester



A B C

b. trans 6-ester



A B C

R = isopropyl

Nu = piperidine

X = 3,5-dinitrobenzoate

evidence, whatsoever, for anti S_N2' reaction was uncovered. Indeed it has been shown that hydrogen bonding is not necessary for the reaction of amines with allylic chlorides, since

a. no H/D kinetic isotope effect was observed in reaction of α-methyl allyl chloride (11) with Et_2NH and Et_2ND.[200,201]

b. reactions of α-methyl allyl chloride (11) with dimethylamine[202] and trimethylamine[28] were shown to proceed at comparable rates.

4. Only a small difference in reaction rate was observed between the cis and trans substrates (84, 85) (k_{cis}/k_{trans} = 1.13) suggesting that the transition state geometry of the reacting part (Nu-C-C-C X) of the two epimers was similar i.e. that the cis and trans ester groups were both quasi-axial as in A or B (Figure 25) or both quasi-equatorial as in C. If the ester groups in the two epimers were not conformationally similar, the difference in their reaction rates would be much greater since it is known that the rates of displacement of quasi-axial and quasi-equatorial substituents substantially differ.[65,99]

In transition states B and C, steric hindrance to syn S_N2' reaction would be considerably greater for the cis than for the trans esters, the former possessing quasi-axial isopropyl groups which would interfere with the syn approach of nucleophile. Such transition states would, therefore, be expected to cause a rate decrease on going from trans to cis, whereas the opposite is observed. When the C-O bond is quasi-axial, however, as in A, steric hindrance to syn approach of the nucleophile would be similar for cis and trans esters. The observed rate increase in going from trans to cis can then be ascribed to conformational factors, notably to the degree of overlap between the C-O bond and the π-system being more favourable[64,99] in the cis case, where

the isopropyl group is equatorial, than in the trans, where the axial isopropyl group will distort the geometry, causing the C-O bond to be twisted further out of the plane of the π-system than in the cis ester. Thus the syn S_N2' reaction appears to proceed via a transition state (A) in which the C-O bond has attained maximum possible coplanarity with the π-system, in contrast to Stork and White's proposal[14] that C was the favoured transition state for reaction of the 2,6-dichlorobenzoates (39, 40, 41).

5. This study adds further to the flames of controversy regarding the concertedness of the S_N2' reaction. The demonstrated stereoselectivity (stereospecificity?) of the process is indicative of a concerted process in which bond-breaking at C_α is assisted by bond-making at C_δ. Thus, the cyclohex-2-en-1-yl systems studied appeared to react with piperidine by the classical concerted S_N2' mechanism rather than by the ion-pair alternative proposed by Sneen[61] and Bordwell.[48,203,204,205,206]

6. Finally, the syn stereochemistry observed in this study of the S_N2' reaction confirms the predictions made by theoretical studies.[72,78,79,80,85,86,87,91] In particular this study has shown that, for a neutral nucleophile, the stereochemistry of the S_N2' reaction is syn, as suggested by Yates, Epiotis and Bernardi,[91] on the basis of quantitative calculations. Further study using a charged nucleophile would be welcomed as a means of testing their prediction that, in that case, anti stereochemistry is favoured.

EXPERIMENTAL

Part A. Synthesis of allylic esters.

Part B. Synthesis of authentic N-(alkyl cyclohexyl) piperidines.

1. Instrumentation.

M.p. determinations were made using a Kofler hot-stage apparatus. I.r. spectra were recorded on a Pye-Unicam SP1000 or Perkin-Elmer 257 spectrophotometer. Unless otherwise stated, the values reported refer to liquid films. ^{1}H N.m.r. spectra were recorded, for solutions in CCl_4 with Me_4Si as internal standard, with a Varian T60 or HA100 spectrometer. Unless otherwise stated, the values reported refer to the T60 machine. ^{13}C N.m.r. spectra were obtained on a Varian XL100 instrument using $CDCl_3$ solutions. Mass spectra (M.s.) were determined with an A.E.I. MS12 instrument or an LKB 9000 g.l.c. linked mass spectrometer. T.l.c. was performed on Merck silica gel 60 HF_{254} layers (0.25mm. thick for analytical purposes; 1.0mm. thick for p.l.c.). Silver nitrate-impregnated silica layers were prepared by using a slurry of 12.5%, by weight, of $AgNO_3$ in silica gel 60. Analytical g.l.c. was performed on a Perkin-Elmer F11 or Pye-Argon chromatograph and preparative g.l.c. was accomplished using a Pye Series 105 chromatograph. Peaks are identified by their retention time (R.t) in minutes, or by their retention index (R.i.) relative to n.alkane standards. All organic extracts were washed to neutrality by appropriate acidic or basic treatment before being dried over $MgSO_4$, Na_2SO_4, K_2CO_3, or Na_2CO_3. Unless otherwise stated, petrol refers to that fraction of petroleum ether which boils at 60-80°C.

2. Preparation of substrates for Birch reduction.

a. 2-alkyl anisoles.

Dimethyl sulphate was purified by washing with water and dilute Na_2CO_3, and distilled, b.p. 78-79°C/40mm. To a rapidly stirred mixture of the appropriate 2-alkyl phenol, NaOH (1.1 equivalents), and water (4ml. per 1g. of phenol) in a three-necked flask, Me_2SO_4 (1.0 equiv.) was added over 1h. The mixture was then refluxed for 24h., cooled, and extracted with ether. This extract was washed with dilute H_2SO_4, and water, dried over $MgSO_4$, and evaporated to give crude product, purified by distillation and chromatography.

(i) 2-isopropyl anisole (89)

Methylation of 2-isopropyl phenol (102; 50g.) gave 52.0g. (94% yield) of 2-isopropyl anisole (89), b.p. 79-80°C/28mm.

I.r. 1250cm^{-1} (s, ν aryl-O-alkyl)

N.m.r. (100MHz.) δ 7.01 (4H, complex) aromatic H

3.78 (3H, s) OCH_3

3.35 (1H, septet, J=6.5Hz.) $(CH_3)_2CH$

1.23 (6H, d, J=6.5Hz.) $(CH_3)_2CH$

T.l.c. 5% ethyl acetate: petrol, R.f. 0.58

G.l.c. 1.5% QF1; 80°C; nitrogen 15p.s.i., R.t. 3.2 min.

(ii) 2-tert.butyl anisole (90)

Methylation of 2-tert.butyl phenol (103; 150g.) gave, after addition of a further two equivalents of Me_2SO_4 and refluxing for a further 72h., 132g. of product shown to be a mixture of the desired product (90) and starting material (103).

Attempted separation by distillation was unsuccessful, as the products co-distilled. Similarly unsuccessful were attempts to separate the products by ether/NaOH extraction.

Chromatography on a short column of Grade 1 basic alumina with $CHCl_3$ as eluant separated the products, giving 110g. (67% yield) of 2-tert.butyl anisole (90).

I.r. 1240cm^{-1} (s, ν aryl-O-alkyl)

N.m.r. 7.0 (4H, complex) aromatic H

3.8 (3H, s) $OC\underline{H}_3$

1.4 (9H, s) $(C\underline{H}_3)_3C$

M.s. M^+ at m/e 164.

T.l.c. 5% ethyl acetate: petrol, R.f. 0.58

G.l.c. Capillary Carbowax 20M; 160°C; nitrogen 10p.s.i.

R.t. 0.4 min.

b. 2-alkyl anilines.

(i) 2-tert.butyl aniline (91)

Step 1. Preparation of 2,4-dinitro tert.butyl benzene (105)

Nitration[103] of tert.butyl benzene (104; 20g.) gave 25.7g. of a pale yellow oil.

I.r. (cm^{-1}) 1530, 1350 (s, ν aryl-NO_2)

T.l.c. 50% ethyl acetate: chloroform, R.f. 0.80

5% ethyl acetate: petrol, R.f. 0.65, 0.41, 0.24.

G.l.c. 1% SE30; 120°C; nitrogen 15p.s.i. R.i. (%)

1310 (4), 1375 (3), 1415 (70), 1555 (1), 1625 (20), 1700 (2).

Separation by p.l.c. gave three fractions (5% ethyl acetate: petrol).

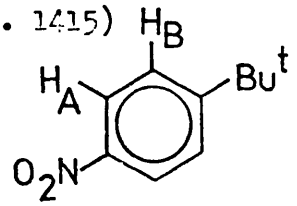
I.r. as above for each fraction.

N.m.r. (100MHz) Fraction 1. (R.f. 0.65, R.i. 1415)

8.13 (2H, d, J=9Hz) $\underline{H}_A$

7.53 (2H, d, J=9Hz) $\underline{H}_B$

1.35 (9H, s) $(C\underline{H}_3)_3C$



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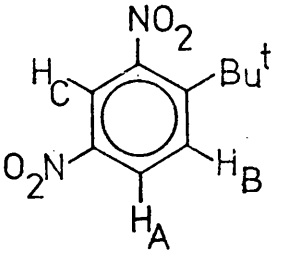
Fraction 2. (R.f. 0.41, R.i. 1625)

8.28 (1H, d of d, J=9Hz., 2Hz.) H_A

8.22 (1H, d, J=2Hz.) H_C

7.82 (1H, d, J=9Hz.) H_B

1.46 (9H, s) $(CH_3)_3C$



105

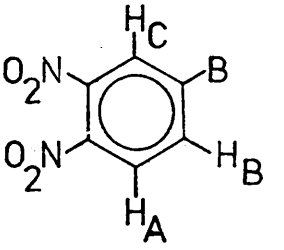
Fraction 3. (R.f. 0.24, R.i. 1700)

7.92 (1H, d, J=9Hz.) H_A

7.88 (1H, d, J=2Hz.) H_C

7.85 (1H, d of d, J=9Hz., 2Hz.) H_B

1.42 (9H, s) $(CH_3)_3C$



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Re-nitration of the remainder of the product mixture at a higher temperature (55°C) over a longer time (2h) was followed by stirring at room temperature for 48h during which time the course of reaction was monitored by g.l.c.

G.l.c. 1% SE30; 120°C; nitrogen 15p.s.i.

	R.i.	1310	1375	1415	1550	1625	1700
original mix.	%	4	3	70	1	20	2
re-nitrated	%	-	1	31	1	60	7
after 24h	%	-	-	12	1	79	8
after 48h	%	-	-	9	1	82	8

Work-up[103] gave, after recrystallisation from methanol, 16.5g. (50% yield) of 2,4-dinitro tert.butyl benzene (105), m.p. 61-62°C (as literature[103]).

Repetition of the reaction using the more forcing conditions, described above, on fresh tert.butyl benzene (104; 50g.) gave 52.8g. (64% yield) of 2,4-dinitro tert.butyl benzene (105), m.p. 61-62°C.

I.r., N.m.r., T.l.c., G.l.c. as for fraction 2, above.

Step 2. Preparation of 2-nitro-4-amino tert.butyl benzene (106).

Reduction[103] of 2,4-dinitro tert.butyl benzene (105; 46g.) gave 28g. (72% yield) of 2-nitro-4-amino tert.butyl benzene (106), m.p. 57.5-58.5°C (literature m.p. 58.5-59.0°C[103]).

I.r. (cm^{-1}) 3510, 3420 (m, ν N-H, primary), 1530, 1370 (s, ν aryl-NO_2)

N.m.r. (100MHz.) δ 7.25 (1H, d, J=9Hz.) $\underline{H}_A$

6.67 (1H, d of d, J=9Hz., 3Hz.) $\underline{H}_B$

6.54 (1H, d, J=3Hz.) $\underline{H}_C$

3.56 (2H, broad s, D_2O exch.) $N\underline{H}_2$

1.34 (9H, s) $(C\underline{H}_3)_3C$

T.l.c. 50% ethyl acetate: petrol, R.f. 0.56.

Step 3. Preparation of 2-nitro tert.butyl benzene (107).

Reductive deamination[103] of 2-nitro-4-amino tert.butyl benzene (106; 21g.) gave 11.8g. (61% yield) of 2-nitro tert.butyl benzene (107), b.p. 33-34°C/0.08mm.

I.r. (cm^{-1}) 1540, 1380 (s, ν aryl-NO_2)

N.m.r. (100MHz.) δ 7.40 (4H, complex) aromatic $\underline{H}$

1.44 (9H, s) $(C\underline{H}_3)_3C$

T.l.c. 5% ethyl acetate: petrol, R.f. 0.59.

G.l.c. 1% SE30; 100°C; nitrogen 15p.s.i., R.t. 6.2 min.

Step 4. Preparation of 2-tert.butyl aniline (91).

Reduction[104] of 2-nitro tert.butyl benzene (107; 12.7g.) gave 7.9g. (75% yield) of 2-tert.butyl aniline (91), b.p. 111-112°C/20mm.

I.r. (cm^{-1}) 3520, 3420 (w, ν N-H, primary), 1310, 1270 (m, ν C-N).

N.m.r. δ 7.0 (4H, complex) aromatic $\underline{H}$

3.8 (2H, broad s, D_2O exch.) $\underline{NH}_2$

1.5 (9H, s) $(C\underline{H}_3)_3C$

T.l.c. 5% ethyl acetate: petrol, R.f. 0.20.

G.l.c. 1% SE30; 75°C; nitrogen 15p.s.i., R.t. 6.6 min.

(ii) N,N-dimethyl 2-tert.butyl aniline (92).

Method 1; formylation / reduction.[105]

Formaldehyde (3ml., 35mmol., 37-40% AnalaR) was added with shaking to a solution of 2-tert.butyl aniline (91; 468mg., 3mmol.) in AnalaR methanol (10ml.). The solution was refluxed for 30 minutes and allowed to cool. Then, $NaBH_4$ (400mg.) was added over 1h at room temperature. The reaction mixture was evaporated to dryness, and the product taken up in CH_2Cl_2, dried over $MgSO_4$ and evaporated to a yellow-red oil which appeared to be a mixture of the intermediate imine (245), mono- (246), and di-N-methylated 2-tert.butyl anilines (92).

I.r. (cm^{-1}) 3520 (w, νN-H, secondary), 1660-1630 (w, νC=N)

N.m.r. δ7.2 (4H, complex) aromatic H

5.2 (2H, s) $N{=}C\underline{H}_2$

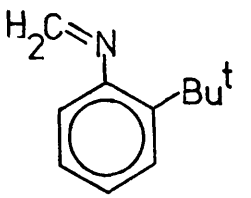
1.5 (9H, s) $(C\underline{H}_3)_3C$

other signals observed at

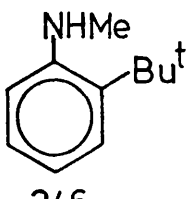
4.8 (broad s) $\underline{NH}$

3.2 (d, J=6Hz.) $C\underline{H}_3$ of $NHCH_3$

and 3.2 (s) $C\underline{H}_3$ of $N(CH_3)_2$



245

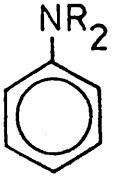


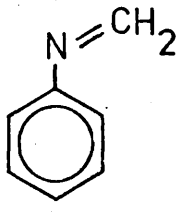
246

M.s. M^+ at m/e 161, 163 corresponding to compounds 245 and 246, respectively.

T.l.c. 5% ethyl acetate: petrol, R.f. 0.13 (w), 0.37 (s), 0.55 (w).

G.l.c. 1% SE30; 70°C; nitrogen 15p.s.i., R.t. (%), 4.6 (80),





247 R = H

249 R = Me

248

7.1 (10), 9.2 (10).

Because of the difficulties encountered above, the reaction sequence was repeated using aniline (247; 280mg., 3mmol.) as a model compound. Purification of the product mixture by p.l.c. (50% ethyl acetate: petrol) gave a yellow-red oil, apparently containing the intermediate imine (248) as major product.

I.r. no νN-H

N.m.r. δ 7.1 (5H, centrosymmetric multiplet) aromatic H

4.9 (2H, s) $N=C\underline{H}_2$

T.l.c. 50% ethyl acetate: petrol, R.f. 0.81

Method 2; direct methylation.[106]

An alternative N,N-dimethylation procedure was then tested on the model compound, aniline (247). On treatment[106] with methyl iodide (2 equivalents), N,N-dimethyl aniline (249) was obtained and shown to be identical to an authentic sample.

Methylation[106] of 2-tert.butyl aniline (91; 6.4g.) by this method gave 5.8g. (76% yield) of N,N-dimethyl 2-tert.butyl aniline (92), b.p. 110-111°C/32mm.

I.r. no νN-H

N.m.r. (100MHz.) δ 7.21 (4H, complex) aromatic H

2.59 (6H, s) $N(C\underline{H}_3)_2$

1.49 (9H, s) $(C\underline{H}_3)_3C$

M.s. M^+ at m/e 177; also, peaks at m/e 162 (M-15) and m/e 147 (M-30), linked by metastable at m/e 134.

T.l.c. 5% ethyl acetate: petrol, R.f. 0.40

G.l.c. 1% SE30; 70°C; nitrogen 15p.s.i., R.t. 4.4 min.

3. Birch reduction;[110] preparation of 6-alkyl cyclohex-2-en-1-ones.

a. General method.

The appropriate anisole or aniline (5g.) was dissolved in a mixture of tetrahydrofuran (THF, 40ml.), tert.butanol (40ml.), and liquid ammonia (200ml., freshly distilled from sodium). The mixture was stirred vigorously in a three-necked flask fitted with an acetone/dry-ice condenser. Lithium (1.4g.) was added over 1h. After a further 1h., ethanol was cautiously added to discharge the blue colour. Petroleum ether and water were then added and the organic layer was rapidly separated, washed with brine, dried over $MgSO_4$, and evaporated to yield the intermediate enol ether or enamine. Analysis of the product mixture was followed by refluxing of the mixture in dilute HCl, until hydrolysis of the intermediate was complete (determined by g.l.c.). The resulting ketonic product was isolated by ether extraction, washing with brine, drying over $MgSO_4$ and evaporation. Purification was effected by a variety of methods.

b. 6-methyl cyclohex-2-en-1-one (93).

Birch reduction of 2-methyl anisole (88; 5g.) gave 3.4g. of a pale yellow oil, after hydrolysis.

I.r. (cm^{-1}) 3060 (w, νC-H alkene), 1720 (m, νC=O), 1690 (s, νC=O, α,βunsaturated), 1650 (w, νC=C).

T.l.c. 5% ethyl acetate: petrol, R.f. 0.09

Separation of this expected[102] mixture was attempted by the method[102] developed by Stork and White.

Thus, treatment of the ketonic mixture with piperidine gave 3.45g. of acid-soluble material.

I.r. (cm^{-1}) 2790, 2710 (w, νC-H, α to N), 1720 (vs, νC=O), 1170, 1130, 1115 (m, νC-N).

Distillation of this product caused partial elimination, giving 3.1g. of distillate containing the desired enone (93).

I.r. as above with addition of 1690cm^{-1} (s, νC=O, α,β unsat.)

N.m.r. δ2.7-1.5 (18H, very complex) C<u>H</u>, C<u>H</u>$_2$

1.12 (30% of 3H, d, J=7Hz.))

1.04 (70% of 3H, d, J=7Hz.)) C<u>H</u>$_3$

plus resonances (21%) for 6-methyl cyclohex-2-en-1-one (93).

T.l.c. 70% ethyl acetate: petrol, R.f. 0.09, 0.21, 0.69.

G.l.c. 1% SE30; temperature programme 40-130°C @ 4C°.min.$^{-1}$ nitrogen 15p.s.i., R.t. (%) 3.2 (20), 28-32 (80).

Separation of this mixture by p.l.c. (70% ethyl acetate: petrol) showed the spot at R.f. 0.69 to be 6-methyl cyclohex-2-en-1-one (93).

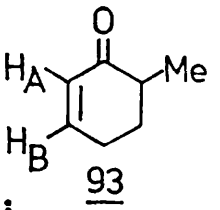
I.r. 1690cm^{-1} (vs, νC=O, α,βunsat.)

N.m.r. (100MHz.) 6.93 (1H, d of t of d, J=10, 4, 1Hz.) H_B

5.95 (1H, d of t, J=10, 2Hz.) H_A

2.5-1.5 (5H, complex) C<u>H</u>, C<u>H</u>$_2$

1.17 (3H, d, J=6Hz.) C<u>H</u>$_3$



93

G.l.c. 1% SE30; temp. prog. 40-130°C @ 4C°.min.$^{-1}$; nitrogen 15 p.s.i., R.t. 3.2 min.

Treatment of the mixture of piperidino-compounds with MeI[102] gave a yellow, crystalline methiodide, m.p. 173-175°C (lit.[102] m.p. 174.5-175.0°C). On base-catalysed elimination, this gave a pale yellow oil shown, by i.r. and t.l.c., to be almost identical to the original ketonic mixture from Birch reduction.

Birch reduction of 2-methyl anisole (88; 15g.) was repeated to give 13.2g. of a colourless oil.

I.r. (cm^{-1}). 3040 (m, ν C-H, alkene), 1220, 1160 (s, ν aryl-O-alkyl).

N.m.r. δ5.6 (2H, broad s) vinyl H

3.5 (3H, s) OCH_3

2.7 (4H, broad s) CH_2

1.6 (3H, s) CH_3

plus other non-assignable, minor resonances.

G.l.c. 2% Carbowax 20M; 70°C; nitrogen 15p.s.i., R.i. (%) 1140 (6), 1200 (7), 1220 (13), 1300 (74).

Acid hydrolysis of the enol ether mixture gave 10.9g. of ketonic mixture.

I.r. (cm^{-1}) 1720 (m, ν C=O), 1690 (vs, ν C=O, α,β unsat.)

N.m.r. signals corresponding to 6-methyl cyclohex-2-en-1-one (93, see above, 80% of mixture)

Attempts to analyse the remaining 20% of impurity signals by double irradiation were non-interpretable.

G.l.c. 1% QF1; 50°C; nitrogen 15p.s.i., R.i. (%) 1170 (2), 1210 (15), 1240 (5), 1290 (78).

2% Carbowax 20M; 70°C; nitrogen 15p.s.i., R.i. (%) 1140 (2), 1290 (5), 1330 (15), 1400 (78).

G.c.-m.s. R.i. (M^+) 1290 (112), 1330, 1400 (both 110).

U.v. $\lambda_{max.}^{EtOH}$ 224nm., (ϵ 7350), 325nm., (ϵ 25)

In an attempt to alter the ratio of what were thought to be conjugated and unconjugated ketones, the ketonic mixture was refluxed for 24h. in dilute NaOH. G.l.c. showed that no change in the ratio was effected.

Preferential epoxidation[111,112] of the β,γ enone (125) was then attempted by stirring the ketonic mixture (536mg., 4.9mmol.), Na_2CO_3 (98mg., 0.9mmol.), m-chloroperbenzoic acid (177mg.,

1.0mmol., calculated as 1.3 equivalents of the amount of β,γenone in the ketonic mixture) in dry CH_2Cl_2 for 22h. The organic layer was removed, washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated to give 402 mg. of a yellow oil.

I.r. 1760, 1740 (m, νC=O, lactone), 1720 (w, νC=O), 1690 (vs, νC=O, α,βunsat.)

N.m.r. signals corresponding to 6-methyl cyclohex-2-en-1-one plus other non-assignable resonances.

T.l.c. 5% ethyl acetate: petrol, R.f. 0.09 (vs), 0.37 (w)

G.l.c. 2% Carbowax 20M; 70°C; nitrogen 15p.s.i., R.i. (%) 1330 (5), 1375 (4), 1400 (91).

Because of the failure of these separation attempts, the chromatographic behaviour of the ketonic mixture was re-examined.

Separation attempts on columns of alumina were unsuccessful. Use of Grade 1 basic, Grade 3 neutral, or $AgNO_3$-impregnated Grade 1 basic alumina gave product mixtures containing no monomeric α,βunsaturated ketone.

Various silica columns were also unsuccessful.

However, t.l.c. on $AgNO_3$-impregnated silica (0.5% acetic acid: chloroform) gave three spots, R.f. 0.25 (m), 0.75 (s), 0.87 (w). Repetition of this on a preparative scale was less successful, however. Thus, 3.3g. of ketonic mixture was applied to five metre-long p.l.c. plates coated with $AgNO_3$-impregnated silica. Double elution gave three poorly defined bands, R.f. 0.3, 0.6, 0.7. From the band at R.f. 0.6, 1.7g. (66% recovery of α,βenone) of apparently pure 6-methyl cyclohex-2-en-1-one (93)*

* This was shown, later, to contain approximately 16% of 2-methyl cyclohex-2-en-1-one (127).

was obtained.

I.r., n.m.r., u.v. as above

M.s. M^+ at m/e 110

G.l.c. 2% Carbowax 20M; 70°C; nitrogen 15p.s.i., R.i. (%) 1290 (3), 1400 (97).

c. 6-isopropyl cyclohex-2-en-1-one (94).

Birch reduction of 2-isopropyl anisole (89; 15g.) gave 13.6g. of a colourless oil.

I.r. (cm^{-1}) 3050 (m, νC-H, alkene), 1720 (m, νC=O), 1690 (w, νC=O, α,βunsat.), 1630 (w, νC=C), 1250 (s, νaryl-O-alkyl), 1150 (vs, νalkyl-O-alkyl).

N.m.r. (100MHz.) δ5.58 (2H, s) vinyl H

3.42 (3H, s) OCH_3

3.10 (1H, septet, J=7Hz.) $(CH_3)_2CH$

2.65 (4H, complex) CH_2

0.92 (6H, d, J=7Hz.) $(CH_3)_2CH$

plus other non-assignable resonances.

T.l.c. 5% ethyl acetate: petrol, R.f. 0.3 (w), 0.7 (s).

G.l.c. Capillary carbowax 20M; 70°C; nitrogen 10p.s.i.

R.i. (%) 1280 (11), 1340 (14), 1395 (61), 1450 (14).

Acid hydrolysis gave 11.7g. of a yellow-red oil (equivalent to 44% yield of desired product from Birch reduction, based on g.l.c. analysis).

I.r. (cm^{-1}) 1720 (m, νC=O), 1690 (vs, νC=O, α,βunsat.)

N.m.r. resonances corresponding to the desired enone (94, 54%), starting material (89, 14%), and other compounds (32%).

T.l.c. chloroform, R.f. 0.4 (w), 0.6 (s), 0.8 (m).

G.l.c. Capillary carbowax 20M; 70°C; nitrogen 10p.s.i.

R.i. (%) 1395 (10), 1425 (2), 1450 (34), 1505 (54).

Separation by p.l.c. (chloroform) was only partially successful. The band at R.f. 0.6 contained 74% of the desired enone (94) and 26% of other ketones, while that at R.f 0.8 was 2-isopropyl anisole (89).

Silica and alumina columns similarly failed to effect a reasonable separation.

The product mixture was separated by preparative g.l.c. (10g. applied to 2% carbowax 20M on Supasorb 60-80mesh; 150°C) to give 2.0g. (38% recovery) of 6-isopropyl cyclohex-2-en-1-one (94, 99.5% pure)

I.r. (cm^{-1}) 3040 (w, νC-H, alkene), 1690 (vs, νC=O), 1630 (w, νC=C).

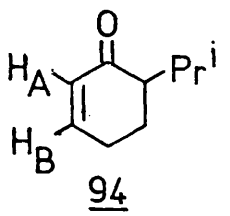
N.m.r. 6.88 (1H, d of t of d, J=10, 4, 1Hz.) $\underline{H}_B$

5.95 (1H, d of t, J=10, 2Hz.) $\underline{H}_A$

2.04 (1H, septet, J=7Hz.) $(CH_3)_2\underline{CH}$

2.5-1.8 (5H, complex) $\underline{CH}$, $\underline{CH}_2$

0.94 (6H, two d, J=7Hz.) $(\underline{CH}_3)_2CH$



94

^{13}C N.m.r. (25.2MHz.) p.p.m. downfield from $(CH_3)_4Si$.

201.214 (s, C-1), 149.241 (d, C-3),

130.030 (d, C-2), 52.801 (d, C-6),

25.827 (d, C-7), 25.330 (t, C-4),

23.263 (t, C-5), 20.565, 18.607 (both q, C-8,9)

M.s. M^+ at m/e 138.

G.l.c. Capillary carbowax 20M; 70°C; nitrogen 10p.s.i.

R.i. 1505.

U.v. $\lambda_{max.}^{EtOH}$ 225nm. (ϵ 9000)

Repetition of the Birch reduction of 2-isopropyl anisole (89; 25g.) over a longer time (2.5h.) gave, after acid hydrolysis, 19.2g. (equivalent to 53% yield of desired product) of a

yellow-red oil.

I.r., n.m.r., t.l.c. as previous Birch reduction.

G.l.c. Capillary carbowax 20M; 100°C; nitrogen 7p.s.i.

R.i. (%) 1425 (14), 1470 (2), 1485 (15), 1535 (69).

Because of the low recovery obtained from previous methods of separation, the use of dry-column chromatography[113] was investigated. Trial experiments indicated that no single solvent could effect a separation but that the mixed system, 30% ethyl acetate: petrol, was suitable, allowing reasonable separation and recovery.

Thus, 7.40g. of ketonic mixture was applied to a 75x5cm. nylon column containing 750g. of pre-equilibrated[113] silica (Woelm Grade 3 silica gel 60 HF_{254} "for dry-column chromatography"). After appropriate slicing of the developed column, 2.51g. (51% recovery) of 6-isopropyl cyclohex-2-en-1-one (94, 95% pure) was obtained. (spectroscopic data as before)

In order to identify the other components of the ketonic mixture, some of the partially separated fractions were examined. These appeared to contain 2-isopropyl cyclohexanone (111), 2-isopropyl cyclohex-2-en-1-one (129), and 2-isopropyl anisole (89).

I.r. (cm^{-1}) Fraction 1. 2-isopropyl anisole (89, see above)

Fraction 2 1720 (vs, νC=0), 1690 (w, νC=0, α,βunsat.)

Fraction 3 1720 (s, νC=0), 1690 (vs, νC=0, α,βunsat.)

G.l.c. Capillary carbowax 20M; 100°C; nitrogen 7p.s.i.

R.i.	1425	1470	1485	1535	
Fr. 1	56	44	-	-	%
Fr. 2	93	2	5	-	%
Fr. 3	30	-	63	7	%
IDENTITY	111	89	129	94	

U.v. Fr. 3 $\lambda_{max.}^{EtOH}$ 233nm. (ϵ 8000)

Other dry-columns produced similar results, and several of the recovered mixtures containing >5% impurity were combined and rechromatogrammed to give further amounts of purified 6-isopropyl cyclohex-2-en-1-one (94).

d. 6-tert.butyl cyclohex-2-en-1-one (95).

Attempted Birch reduction of 2-tert.butyl aniline (91) gave almost complete recovery of starting material.

I.r., n.m.r., t.l.c. as starting material (91).

G.l.c. 1% SE30; 75°C; nitrogen 15p.s.i., R.t. (%) 2.8 (<5), 6.6 (>95).

Attempted Birch reduction of N,N-dimethyl 2-tert.butyl aniline (92) was equally unsuccessful, even after extension of the reaction time to 3h.

I.r., n.m.r., t.l.c. as starting material (92).

Birch reduction of 2-tert.butyl anisole (90; 10g.) gave 9.8g. of a colourless oil.

I.r. (cm^{-1}) 3040 (w, νC-H, alkene), 1660 (m, ν C=C), 1140 (s, ν alkyl-O-alkyl), plus bands corresponding to 2-tert.butyl anisole (90).

N.m.r. non-interpretable

G.l.c. Capillary carbowax 20M; 80°C; nitrogen 10p.s.i. R.i. (%) 1310 (3), 1330 (16), 1380 (17), 1455 (41), 1490 (23).

Acid hydrolysis of this mixture gave 8.9g. (equivalent to 38% yield of desired product, based on g.l.c. analysis) of a yellow oil.

I.r. (cm^{-1}) 1720 (m, νC=O), 1685 (vs, ν C=O, α,βunsat.), plus bands corresponding to 2-tert.butyl anisole (90).

N.m.r. resonances attributable to 2-tert.butyl cyclohexanone (112; 17%), 2-tert.butyl cyclohex-2-en-1-one (130; 18%), 6-tert.butyl cyclohex-2-en-1-one (95; 40%), and 2-tert.butyl anisole (90; 25%).

(data given later - see below).

T.l.c. 5% ethyl acetate: petrol, R.f. 0.4, 0.7

G.l.c. Capillary carbowax 20M; 80°C; nitrogen 10p.s.i.

R.i. (%) 1410 (17), 1465 (18), 1490 (25), 1525 (40)

Separation by p.l.c. (5% ethyl acetate: petrol, double development) gave two bands, R.f. 0.5, 0.8. The broad band centred at 0.5 was divided into three fractions in increasing order of R.f. value.

G.l.c. Capillary carbowax 20M; 80°C; nitrogen 10p.s.i.

R.i.	1410	1465	1490	1525	
Fraction 1	-	2	-	98	% R.f. 0.5-
Fraction 2	12	30	-	58	% R.f. 0.5
Fraction 3	14	78	2	6	% R.f. 0.5+
Fraction 4	2	-	98	-	% R.f. 0.8

This indication of a separation was exploited by the use of column chromatography on Grade 3 silica gel 60. Trials using hexane-benzene and pentane-benzene gradients were monitored by g.l.c. and found to be suitable. Thus, 8.7g. of ketonic mixture was applied to a 2kg. column of silica and eluted with a hexane-benzene gradient. G.l.c. analysis of the fractions collected was followed by appropriate recombination of these fractions to give, in addition to 2-tert.butyl anisole (90), three products:-

(1). 2-tert.butyl cyclohexanone (112; 371mg., 25% recovery; 95% pure)

I.r. 1720cm^{-1} (s, νC=O)

N.m.r. (100MHz.) δ2.4-1.4 (9H, complex) C<u>H</u>, C<u>H</u>$_2$

1.00 (9H, s) (C<u>H</u>$_3$)$_3$C

M.s. M^+ at m/e 154.

(2). 2-<u>tert</u>.butyl cyclohex-2-en-1-one (<u>130</u>; 293mg., 19% recovery; 94% pure).

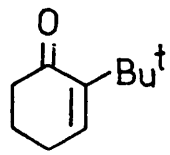
I.r. 1685cm^{-1} (s, νC=O, α,βunsat.)

N.m.r. (100MHz.) δ5.71 (1H, t, J=4Hz.) vinyl <u>H</u>

2.36 (4H, complex) C<u>H</u>$_2$

1.96 (2H, complex) C<u>H</u>$_2$

1.20 (9H, s) (C<u>H</u>$_3$)$_3$C



<u>130</u>

M.s. M^+ at m/e 152.

U.v. $\lambda_{max.}^{EtOH}$ 233nm. (ε 8100).

(3). 6-<u>tert</u>.butyl cyclohex-2-en-1-one (<u>95</u>; 2.29g., 66% recovery; 97% pure).

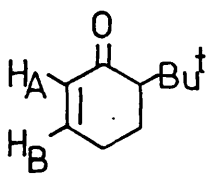
I.r. 1685cm^{-1} (s, νC=O, α,βunsat.)

N.m.r. (100MHz.) δ6.80 (1H, d of t of d, J=10, 4, 1Hz.) <u>H</u>$_B$

5.91 (1H, d of t, J=10, 2Hz.) <u>H</u>$_A$

2.5-1.8 (5H, complex) C<u>H</u>, C<u>H</u>$_2$

1.11 (9H, s) (C<u>H</u>$_3$)$_3$C



<u>95</u>

M.s. M^+ at m/e 152.

U.v. $\lambda_{max.}^{EtOH}$ 225nm. (ε 8000).

Repetition of the Birch reduction of 2-<u>tert</u>.butyl anisole (<u>90</u>; 36g.) using different proportions of the reactants, viz. THF (200ml.), liquid NH_3 (1000ml.), <u>tert</u>.butanol (200ml.), and lithium (7.0g.) gave, after acid hydrolysis, 30.7g. (32% yield of desired product, based on g.l.c. analysis) of product mixture comprising 2-<u>tert</u>.butyl cyclohexanone (<u>112</u>; 18%), 2-<u>tert</u>.butyl cyclohex-2-en-1-one (<u>130</u>; 19%), 6-<u>tert</u>.butyl cyclohex-2-en-1-one (<u>95</u>; 35%), and unreacted 2-<u>tert</u>.butyl anisole (<u>90</u>; 28%).

Column chromatography, as before, gave 7.9g. of 85% pure 6-tert.butyl cyclohex-2-en-1-one. This was further purified by dry-column chromatography (Woelm Grade 3 silica gel 60 HF_{254}; 30% ethyl acetate: petrol) to give 5.6g. of 98% pure enone.

I.r., n.m.r., m.s., t.l.c., g.l.c., u.v. as before.

4. Reduction of 6-alkyl cyclohex-2-en-1-ones; preparation of 6-alkyl cyclohex-2-en-1-ols.

a. General methods.

Reaction conditions (temperature, time, amount of reducing agent) and product distributions have already been detailed in Tables 8, 9, and 10 and will not, therefore, be repeated.

(i) LAH reduction.

A solution of the appropriate 6-alkyl enone in Na-dried ether was added dropwise to a vigorously stirred suspension of LAH, contained in an oven-dried two-necked flask, maintained under an atmosphere of nitrogen. When reaction was complete, water was cautiously added to decompose any excess hydride and hydrolyse the intermediate organo-aluminium complex. The reaction mixture was acidified with dilute HCl and extracted with ether, which was then washed with brine, dried over $MgSO_4$, and evaporated to give product.

(ii) $NaBH_4$ reduction.

Method as above: solvent, THF.

(iii) DBAH reduction.

Method as above: solvents, ether, hexane, THF; reducing agent, 0.9M solution of DBAH in hexane.

(iv) $LiAl(OMe)_3H$ reduction.

A solution of LAH in THF was prepared by stirring 4g. of LAH in 100ml. of THF (dried by distillation from CaH_2) for 4h. Filtration of the suspension through sintered glass, under nitrogen pressure, gave a clear solution, whose concentration was determined[207] to be 0.155M.

A 10% v/v solution of methanol (dried over CaH_2) in THF (dried over LAH) was prepared and stored over molecular sieves (type 3A).

A solution of $LiAl(OMe)_3H$ in THF was then prepared by injection of the required amount of methanol/THF solution (three equivalents of methanol) to a measured amount of the LAH/THF solution.

Reductions were then carried out as detailed above for LAH, itself.

(v) $Li(sec.butyl)_3BH$ and $K(sec.butyl)_3BH$ reductions.

Method as above for LAH: solvent, ether/THF; reducing agents, 1M solution of Li reagent in THF, 0.5M solution of K reagent in THF. In each case, the intermediate organo-boron complex was oxidised by alkaline H_2O_2[208] after addition of water. Inverse addition of reducing agent to substrate was employed in one of the reductions involving the Li reagent.

(vi) Meerwein-Ponndorf-Verley reduction.[175]

A stirred mixture of 6-isopropyl cyclohex-2-en-1-one (94; 20mg., 0.135mmol.) and aluminium isopropoxide (0.5g., 2.45mmol.) in AnalaR isopropanol (10ml.) was refluxed for 20h. The acetone produced during reaction was then slowly distilled over 1h. Aliquots of the reaction mixture were taken at 3, 20, and 21h., acidified with dilute HCl and extracted with ether. The ether

extracts were washed with brine, dried over $MgSO_4$, and evaporated to give products which were examined by g.l.c.

b. 6-methyl cyclohex-2-en-1-ols (96, 97).

LAH reductions of 6-methyl cyclohex-2-en-1-one (93) produced pale yellow oils in 90-99% yields.

I.r. (cm^{-1}) 3400 (s, νO-H), 3040 (w, νC-H, alkene), 1060-990 (vs, νC-O, δO-H).

N.m.r. see separated compounds.

T.l.c. 10% ethyl acetate: petrol, R.f. 0.20

30% ethyl acetate: petrol, R.f. 0.56

chloroform, R.f. 0.53

G.l.c. 2% Carbowax 20M; 70°C; nitrogen 15p.s.i.,

R.i.	1290	1390	1400	1445	1470	1490
IDENTITY	110	140,137	93	96	97	128

Capillary Carbowax 20M; 70°C; nitrogen 10p.s.i.,

R.i.	1285	1370	1380	1425	1455	1475
IDENTITY	110	140,137	93	96	97	128

G.c.-m.s. 5% Carbowax 20M; 110°C.,

R.t.	42.0	44.4	48.4	58.5	69.2	79.8	mins.
M^+ (m/e)	114	114	110	112	112	112	
IDENTITY	140	137	93	96	97	128	

The identity of the saturated ketone (110), saturated alcohols (140, 137) and 6-methyl enone (93) was established by g.l.c. co-injection of these samples with authentic materials.

Separation attempts by t.l.c., multiple development t.l.c., and column chromatography were unsuccessful.

P.l.c. on $AgNO_3$-impregnated silica separated the 6-methyl cyclohex-2-en-1-ols (96, 97) from the other products. (As detected by g.l.c. and i.r.)

Attempts to separate the alcohols (96, 97) as their 2,6-dichlorobenzoate derivatives were unsuccessful (see later).

Preparative g.l.c. (5% Carbowax 20M on Supasorb 60-80 mesh) of the alcohol mixture gave four fractions.

(1) 2-methyl cyclohexanol (140, 137; 5mg., 8% recovery; 93% pure)

I.r. (cm^{-1}) 3400 (vs, νO-H), 1065, 1050, 1040 (vs, trans νC-O, δO-H), 980 (s, cis νC-O, δO-H).

M.s. M^+ at m/e 114.

(2) cis 6-methyl cyclohex-2-en-1-ol (96; 66mg., 21% recovery; 86% pure)

I.r. (cm^{-1}) 3400 (vs, νO-H), 3030 (m, νC-H, alkene), 1660 (w, νC=C), 985 (vs, νC-O, δO-H).

N.m.r. (100MHz.)

δ5.83 (2H, complex)	vinyl H
3.97 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.)	cis CHOH
2.2-1.2 (6H, complex, 1H D_2O ex.)	CH, CH_2, OH
1.05 (3H, d, J=6Hz.)	CH_3

M.s. M^+ at m/e 112.

Analysis. Found: C, 75.02; H, 10.97%. $C_7H_{12}O$ requires C, 74.95; H, 10.78%.

(3) trans 6-methyl cyclohex-2-en-1-ol (97; 172mg., 27% recovery; 93% pure).

I.r. (cm^{-1}) 3400 (vs, νO-H), 3030 (m, νC-H, alkene), 1660 (w, νC=C), 1060, 1035, 1015 (vs, trans νC-O, δO-H)

N.m.r. (100MHz.)

δ5.67 (2H, complex)	vinyl H
3.77 (1H, broad s, $w_{\frac{1}{2}}$=14Hz.)	trans CHOH
2.2-1.2 (6H, complex, 1H D_2O ex.)	CH, CH_2, OH
1.07 (3H, d, J=6Hz.)	CH_3

M.s. M^+ at m/e 112.

(4) 2-methyl cyclohex-2-en-1-ol (128; 53mg., 24% recovery; 88% pure).

I.r. (cm^{-1}) 3400 (vs, ν O-H), 3040 (w, ν C-H, alkene), 1640 (vw, ν C=C), 1065, 1040, 985, 950 (s, ν C-O, δ O-H).

N.m.r. (100MHz.) 5.51 (1H, broad s) vinyl H

3.96 (1H, broad s, $w_{\frac{1}{2}}$=11Hz.) CHOH

2.2-1.4 (6H, complex, 1H D_2O ex.) CH, CH_2, OH

1.79 (3H, s) CH_3

M.s. M^+ at m/e 112.

Reductions by $NaBH_4$ gave yellow oils (93-95% yields) containing more of the saturated ketone (110) and saturated alcohols (140, 137) than observed with LAH (Table 8). These were analysed and separated as above.

c. 6-isopropyl cyclohex-2-en-1-ols (98, 99).

LAH reductions of 6-isopropyl cyclohex-2-en-1-one (94) produced pale yellow oils in 90-99% yields.

I.r. (cm^{-1}) 3400 (s, νO-H), 3040 (w, νC-H, alkene), 1050-910 (vs, νC-O, δ O-H).

N.m.r. see separated compounds.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.43, 0.47.

chloroform, R.f. 0.40.

ether, R.f. 0.68.

G.l.c. Capillary Carbowax 20M; 90°C; nitrogen 7p.s.i.

R.i.	1425	1510	1535	1555	1620
IDENTITY	111	141	94	138,98	99

The mixtures were separated by preparative g.l.c. since t.l.c. and column chromatography failed to effect a separation.

Preparative g.l.c. (2% Carbowax 20M; 115°C) gave

(1) cis 6-isopropyl cyclohex-2-en-1-ol (98; 91mg., 16% recovery;

98% pure).

I.r. (cm^{-1}, CCl_4 solution) 3620 (m, νO-H), 3020 (m, νC-H, alkene), 1650 (vw, νC=C), 1050, 910 (s, νC-O, δO-H).

N.m.r. (100MHz.) δ5.88 (2H, complex) vinyl H

4.16 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis CHOH

2.3-1.2 (7H, complex, 1H D_2O ex.) CH, CH_2, OH

1.04 (6H, two d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 140.

Analysis. Found: C 77.10; H, 11.62%. $C_9H_{16}O$ requires C, 77.09; H, 11.50%.

(2) trans 6-isopropyl cyclohex-2-en-1-ol (99; 700mg., 60% recovery; 99% pure).

I.r. (cm^{-1}, CCl_4 solution) 3620 (m, νO-H), 3020 (m, νC-H, alkene), 1650 (vw, νC=C), 1040 (s, νC-O, δO-H).

N.m.r. (100MHz.) δ5.71 (2H, complex) vinyl H

4.07 (1H, broad s, $w_{\frac{1}{2}}$=14Hz.) trans CHOH

2.2-1.2 (7H, complex, 1H D_2O ex.) CH, CH_2, OH

0.93 (6H, two d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 140.

The other components of the mixture separated by preparative g.l.c. were shown, by comparison of their i.r. and n.m.r. spectra with those of authentic material, to be cis and trans 2-isopropyl cyclohexanol (141, 138; see pp.128,131) and 2-isopropyl cyclohexanone (111; see p.126). Further confirmation was afforded by g.l.c. co-injection of these authentic materials with the mixture.

Reductions were investigated using different reducing agents and conditions in order to achieve high stereoselectivity. The results from these are given in Table[9].

When these efforts failed the separation of the alcohols by dry-column chromatography[113] was investigated. After small-scale trials, 400mg. of mixture (g.l.c. analysis below) was applied to a 50x2.5cm. nylon column containing 200g. of Woelm Grade 3 silica gel 60 HF_{254} which had been pre-equilibrated[113] with the solvent system, 30% ethyl acetate: petrol. The resultant band, R.f. 0.5-0.7, was divided, and analysed by g.l.c.

G.l.c. Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.

R.i.	1425	1535	1555	1620	weight
mixture	2	3	66	29 %	
fr. 1	95	2	2	1 %	6mg.
fr. 2	88	4	5	3 %	5mg.
fr. 3	1	2	96	1 %	24mg.
fr. 4	-	-	94	6 %	66mg.
fr. 5	-	-	73	27 %	119mg.
fr. 6	-	-	39	61 %	85mg.
fr. 7	-	-	6	94 %	36mg.

Thus, only 34% recovery of 90+% pure cis alcohol (98), and only 31% recovery of 90+% pure trans alcohol (99) were obtained.

Attempted separation of the alcohols as their 2,6-dichloro benzoate esters failed (see later, pp 112, 113)

The best separation method for the alcohols was via fractional crystallisation of their 3,5-dinitrobenzoates (see pp. 119-120).

d. 6-tert.butyl cyclohex-2-en-1-ols (100, 101).

LAH reductions of 6-tert.butyl cyclohex-2-en-1-one (95) produced pale yellow oils in 92-98% yields.

I.r. (cm^{-1}) 3400 (vs, νO-H), 3040 (w, νC-H, alkene), 1100-900 (s, νC-C, δO-H).

N.m.r. see separated compounds.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.65, 0.59.

chloroform, R.f. 0.54.

ether, R.f. 0.75.

G.l.c. Capillary Carbowax 20M; 90°C; nitrogen 10p.s.i.

R.i.	1410	1545	1570	1625
IDENTITY	112	142	139,100	101

The cis and trans 2-tert.butyl cyclohexanols (142, 139) and 2-tert.butyl cyclohexanone (112) were identified by g.l.c. co-injection with authentic materials and by comparison of their i.r. and n.m.r. spectra, after separation, with those of the authentic compounds. (see pp. 127, 128)

Separation of the mixture by column chromatography (silica gel, benzene) was partially successful on a small scale but, on a larger scale, was disappointing - from 1.70g. of alcohol mixture, containing 71% cis (100) and 24% trans (101) alcohols, only 266mg. (21% recovery) of cis 6-tert.butyl cyclohex-2-en-1-ol (100; 96% pure) was obtained. G.l.c. analysis of the separated fractions also showed the appearance of components which were not present in the original mixture. I.r. analysis indicated that these were neither ketonic nor alcoholic but were possibly polyethers.

I.r. (cm^{-1}) 1270 (m), 1120-1020 (vs), 810 (vs).

P.l.c. separation of the alcohol mixture was more successful. Thus, 750mg. of alcohol mixture (as above) yielded 318mg. of cis 6-tert.butyl cyclohex-2-en-1-ol (100) when carefully chromatogrammed. Rerunning of partially separated fractions increased this figure to 397mg. (76% recovery) while a total of only 43mg. of 50+% pure trans alcohol (101) was recoverable.

Preparative g.l.c. separation of the alcohol mixture was

effective. Thus, preparative g.l.c. (2% Carbowax 20M; 140°C) gave

(1) cis 6-tert.butyl cyclohex-2-en-1-ol (100; 262mg., 29% recovery; 98% pure).

I.r. (cm^{-1}, CCl_4 solution) 3625 (m, νO-H), 3020 (m, νC-H, alkene), 1650 (w, νC=C), 985, 940 (m, νC-O, δO-H).

N.m.r. (100MHz.) δ5.82 (2H, complex) vinyl H
4.24 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis CHOH
2.2-1.2 (6H, complex, 1H D_2O ex.) CH, CH_2, OH
1.04 (9H, s) $(CH_3)_3C$

M.s. M^+ at m/e 154.

(2) trans 6-tert.butyl cyclohex-2-en-1-ol (101; 59mg., 29% recovery; 88% pure).

I.r. (cm^{-1}, CCl_4 solution) 3600 (m, νO-H), 3020 (m, νC-H, alkene), 1650 (w, νC=C), 1040-1020 (m, νC-O, δO-H).

N.m.r. (100MHz.) δ5.63 (2H, complex) vinyl H
4.16 (1H, broad s, $w_{\frac{1}{2}}$=16Hz.) trans CHOH
2.2-1.2 (6H, complex, 1H D_2O ex.) CH, CH_2, OH
1.04 (9H, s) $(CH_3)_3C$

M.s. M^+ at m/e 154.

5. Preparation of model compound for esterification reactions; 3,5,5-trimethyl cyclohex-2-en-1-ol (172).

Reduction of freshly distilled 3,5,5-trimethyl cyclohex-2-en-1-one (173; 8g., 58mmol.) by LAH (1.27g., 33mmol.) in ether at 0°C, using the method previously described gave 6.9g. (86%

yield) of 3,5,5-trimethyl cyclohex-2-en-1-ol (172), b.p. 52-54°C/ 0.05mm.

I.r. (cm^{-1}) 3350 (s, νO-H), 3040 (w, νC-H, alkene), 1040, 1020, 990 (s, νC-O, δO-H).

N.m.r. (100MHz.) δ5.42 (1H, complex, $w_{\frac{1}{2}}$=6Hz.) vinyl H
4.24 (1H, broad s, $w_{\frac{1}{2}}$=19Hz.) CHOH
2.0-1.3 (4H, complex) CH_2
1.71 (3H, t, J=1Hz.) vinyl CH_3
1.03 (3H, s) CH_3
0.94 (3H, s) CH_3

M.s. M^+ at m/e 140.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.35

G.l.c. Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i., R.i. 1580.

On storage, the pure allylic alcohol (172) apparently polymerised, as detected by i.r., t.l.c., and g.l.c. after 4 days. Consequently, the alcohol was freshly prepared by LAH reduction each time it was required.

6. Esterification.

a. 2,6-dichlorobenzoates.

2,6-dichlorobenzoyl chloride (171) was prepared by refluxing a mixture of 2,6-dichlorobenzoic acid (184; 4.5g.) and freshly distilled thionyl chloride (8ml.) for 24h. Distillation at atmospheric pressure removed excess thionyl chloride, and the residue was then distilled at reduced pressure to give 4.5g. (92% yield) of 2,6-dichlorobenzoyl chloride (171), b.p. 129-130°C/20mm.

I.r. 1810cm^{-1} (s, νC=O).

N.m.r. only one resonance at δ7.4 (s).

M.s. M^+ at m/e 208, with ^{37}Cl isotope peaks at 208, 210, 212, 214 (relative intensities 100: 100: 33: 3).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.60.

Further quantities of 2,6-dichlorobenzoyl chloride (171) were prepared by a simpler, more efficient method. Two drops of dimethyl formamide was added to a vigorously stirred mixture of 2,6-dichlorobenzoic acid (184; 10g., 5.2mmol.) and oxalyl chloride (13.2g., 10.4mmol.) in benzene (100ml.). Stirring was continued for 18h. and the resulting solution concentrated on a rotary evaporator. Distillation of the residue gave 10.4g. (95% yield) of 2,6-dichlorobenzoyl chloride (171).

(i) 3,5,5-trimethyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (175).

Method 1. (pyridine/2,6-dichlorobenzoyl chloride[14])

Attempted esterification[14] of 3,5,5-trimethyl cyclohex-2-en-1-ol (172; 1.40g., 10mmol.) gave 602mg. of crude product containing less than 5% of the desired ester (175).

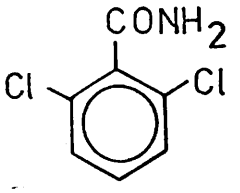
I.r. 1740 (w, νC=O, ester), 1670, 1640 (vs, ?), 1270, 1140 (w, νC-O, ester).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.65 (w, ester), 0.56 (s, ?), 0.47 (m, ?), 0.45 (w, ?).

Repetition over shorter reaction time (90mins.) gave 1.55g. of crude product. Separation by dry-column chromatography (35x2.5cm. column of Woelm Grade 3 silica gel 60 HF_{254}; 30% ethyl acetate: petrol) gave 232mg. (8% yield) of ester.

I.r. (cm^{-1}) 1740 (vs, νC=O), 1270, 1140 (s, νC-O), 800, 785 (m, νC-Cl).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.65.



250

Repetition of the reaction, on 1/10th scale, in a sealed tube at 60°C for 24h. gave higher yield. The excess acid chloride (171) was not converted to the amide (250) prior to work-up, as had been done above.[14] The crude product (266mg., 85% yield) was unsuccessfully chromatographed on Grade 1 neutral alumina (43% recovery, poor separation).

Alcohol (172; 560mg., 4mmol.), acid chloride (171; 1.056g., 5.05mmol.) and pyridine (2ml.) were stirred at 45°C for 18h. The reaction mixture was poured into 5% ice-cold HCl (45ml.) and extracted with ether. The extracts were washed with 5% $NaHCO_3$, water, dried over Na_2CO_3, and evaporated to give 1.334g. of crude product. Hexane (25ml.) was added and the flask was allowed to stand at 25°C for 3h. Filtration through Celite and evaporation of the filtrate gave 1.153g. of product which was purified by dry-column chromatography (10x1.5cm. column of Grade 3 neutral alumina; 450ml. of hexane) to give 825mg. (66% yield) of ester, recrystallised from hexane to give 671mg. (53% yield) of pure ester (175) as needles, m.p. 75.4-76.0°C.

I.r. (cm^{-1}, CCl_4 solution) 3020 (w, νC-H, alkene), 1740 (vs, νC=O), 1270, 1140 (s, νC-O).

N.m.r.

7.3 (3H, s)	aromatic H
5.5 (2H, multiplet plus broad s)	vinyl H, CHOCOAr
1.9-1.5 (4H, complex)	CH_2
1.7 (3H, s)	vinyl CH_3
1.1 (6H, s)	CH_3

M.s. M^+ at m/e 312 (^{37}Cl isotope peaks at 314, 316).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.65.

Analysis Found: C, 61.38; H, 5.82%. $C_{16}H_{18}O_2Cl_2$ requires C, 61.35; H, 5.79%.

Method 2. (n.butyl Li/2,6-dichlorobenzoyl chloride).

To a stirred solution of alcohol (172; 378mg., 2.7mmol.) in LAH-dried THF (2ml.), maintained at 0°C, under an atmosphere of nitrogen, 1.5ml. of a 20% w/v solution of n.butyl Li in hexane was added. After stirring for 20 min., a solution of 2,6-dichlorobenzoyl chloride (171; 1.0g., 4.8mmol.) in THF (3ml.) was added. The resulting solution was stirred at 0°C for 2h., then left to stand at 25°C overnight. Ether (5ml.) was added, followed by water (5ml.). The reaction mixture was neutralised by addition of dilute HCl, then extracted with ether which was then washed with brine and evaporated to give crude product which, apparently, was a mixture of starting materials (171, 172), desired product (175; estimated yield less than 10%), and 3,5,5-trimethyl cyclohex-2-en-1-yl chloride (176).

Dry-column chromatography (silica; benzene) failed to separate the mixture, but p.l.c. (30% ethyl acetate: petrol) did effect separation of the major component, the allylic chloride (176; 230mg., 54% yield)

I.r. (cm^{-1}) 3020 (w, νC-H, alkene), 1390, 1370 (m, ν C-C, gem dimethyl), 750, 735 (m, νC-Cl).

N.m.r.

5.6 (1H, complex)	vinyl H
5.2 (1H, broad s, $w_{\frac{1}{2}}$=13Hz.)	CHCl
2.2-1.2 (4H, complex)	CH, CH_2
1.6 (3H, s)	vinyl CH_3

M.s. no M^+ at m/e 158. Base peak at m/e 123 (presumably loss of chlorine from M^+).

Repetition of the reaction using 1 equivalent of n.butyl Li gave similar results, as did repetition using 1.1 equiv. of n.butyl Li and acid chloride (171).

Method 3. (NaH/2,6-dichlorobenzoyl chloride[182])

A stirred mixture of alcohol (172; 160mg., 1.14mmol.) and NaH (60% suspension; 112mg., 3mmol.) in Na-dried ether (5ml.) was refluxed under a nitrogen atmosphere for 18h. Addition of 2,6-dichlorobenzoyl chloride (171; 300mg., 1.35mmol.) and refluxing for a further 4h. gave a mixture containing none of the desired ester, as determined by t.l.c.

Repetition, using the higher boiling ethers, THF or dimethoxyethane, gave similar results.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.67 (m), 0.62 (m), 0.58 (m), 0.48 (s).

Method 4. (ion-exchange resin/2,6-dichlorobenzoic acid[183])

General process: A mixture of alcohol (172), 2,6-dichlorobenzoic acid (184), and ion-exchange resin was stirred in a suitable solvent. Reaction progress was monitored by t.l.c. and, at an appropriate stage, was terminated by filtration of the reaction mixture through Celite. The filtrate was washed with 5% $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated to give crude product. Purification was effected by treatment with hexane and filtration through Celite to remove acid, followed by dry-column chromatography (Grade 5 neutral alumina; hexane) and crystallisation.

Estimates of reaction yields were obtained for those cases where products were not analysed by use of the formula below.

$w_E = (w_T.M_E)/(M_E + r.M_A)$ where w_E= weight of ester (mg.)

w_T= total weight of product (mg.)

M_E and M_A= molecular weights of ester (175) and acid (184)

r = ratio of acid (184) to ester (175).

The ratio, r, was determined from the n.m.r. spectrum of the

crude product mixture.

The results from these experiments are summarised below.

Reaction no.	1	2	3	4	5	6	7	8	9	10	11
alcohol mg.	140	140	140	140	140	1400	140	140	140	140	140
alcohol mmol.	1.0	1.0	1.0	1.0	1.0	10.0	1.0	1.0	1.0	1.0	1.0
acid mg.	260	260	210	200	210	2050	290	191	191	210	210
acid mmol.	1.36	1.36	1.1	1.04	1.1	10.7	1.5	1.0	1.0	1.1	1.1
I.E.R. mg.	80	50	45	45	45	560	45	40	40	45	45
solvent	B	B	B	B	B	B	B	THF	THF	E	E/H
solvent ml.	10	5	4	4	4	40	4	4	4	4	4
temperature °C	25	45	reflux	25	25	25	25	25	55	25	25
time h.	48	72	21	114	114	114	21	18	18	21	21
crude prod. mg.	197	157	-	161*	177*	1438*	162*	-	-	-	-
% yield	63	50	-	52*	56*	46*	52*	-	-	-	-
pure prod. mg.	-	79	-	-	-	1121	-	-	-	-	-
% yield	-	25	-	-	-	36	-	-	-	-	-
m.p.	74.9-76.0°C				75.0-76.0°C						

T.l.c. (50% ethyl acetate: petrol) of crude products.

	R.f.	1	2	3	4	5	6	7	8	9	10	11
?	0.74	∘	∘	∘	∘	•	·	·	O	O	O	O
ester	0.65	O	O	∘	O	O	O	O	∘	∘	∘	∘
alcohol	0.47	∘	∘	∘	∘	∘	∘	∘	O	O	O	O
?	0.41								∘	∘		
acid	0.10	O	O	O	O	O	O	O	O	O	O	O

NOTES: (1) I.E.R. = Dowex 50W X-8, 20-50 U.S. mesh.

(2) solvents: B = benzene, E = ether, E/H = 3% ether/hexane

(3) * indicates value calculated from n.m.r. spectrum.

Because of the low yields obtained in these attempts, control experiments were performed using ion-exchange methods. These were monitored by t.l.c. and showed that esterification was in competition with acid-catalysed hydrolysis of the ester and with 'polymerisation' of the alcohol. The experiments comprised mixtures of the reactants and product in which one had been omitted, as below.

Reaction no.	1	2	3	4
alcohol mg.	140	140	-	-
acid mg.	205	-	205	-
ester mg.	-	-	144	144
I.E.R. mg.	56	56	56	56

solvent: benzene, solvent vol. 4ml, temperature 25°C, time 100h.

Experiment 1 was a normal esterification, giving similar results to those obtained before.

Experiment 2 showed the appearance of a spot at R.f. 0.74 (previously observed in esterification attempts) and indicated that it was arising from the instability of the alcohol (172) under the reaction conditions. Presumably, this was due to acid-catalysed polymerisation of the alcohol.

Experiments 3 and 4 indicated that the ester was liable to hydrolyse under the reaction conditions, as evidenced by the appearance of spots at R.f. 0.47 and 0.10, corresponding to the alcohol (172) and acid (184), respectively.

(ii) 6-methyl cyclohex-2-en-1-yl 2,6-dichlorobenzoates (39, 81).

Method 1. (pyridine/2,6-dichlorobenzoyl chloride[14])

Esterification[14] of a mixture of methyl cyclohex-2-en-1-ols (96, 59%; 97, 27%; 128, 14%; 115mg., 1.05mmol.) with 2,6-dichloro-

benzoyl chloride (280.mg.,1.30mmol.) gave 42mg. (14% yield) of ester mixture.

I.r. (cm^{-1}) 1755 (vs, νC=O), 1285, 1160 (s, νC-O), 810, 790 (m, νC-Cl).

T.l.c. petrol, R.f. 0.05 (w), 0.1 (vs), 0.2 (w).

10% ethyl acetate: petrol, R.f. 0.2 (w), 0.4 (vs), 0.6 (w).

chloroform (on $AgNO_3$-impregnated silica), R.f. 0.6 (w), 0.75 (vs), 0.8 (w).

G.l.c. attempts to chromatograph the esters on various columns failed (columns used:- 2% Carbowax 20M, 1.5% QF1, 1% SE30).

Purification of the ester mixture was attempted by p.l.c. (10% ethyl acetate: petrol) but this failed to separate the mixture into its ester components, although it did serve to remove impurities from the mixture.

Various attempts were made to separate the ester mixture obtained by p.l.c. but all were unsuccessful; methods used:-

(1) p.l.c. on $AgNO_3$-impregnated silica; chloroform,

(2) multiple development p.l.c.; x5; 10% ethyl acetate: petrol,

(3) crystallisation from various solvents or "from the melt",

(4) column chromatography on acetyl cellulose; petrol.

Repetition of the esterification reaction gave a similar mixture of esters, after p.l.c. purification.

I.r. as above.

N.m.r. (100MHz.) δ7.30 (3H, s) aromatic H

5.92 (2H, complex) vinyl H

5.5-5.3 (1H, 3 broad s) CHOCOAr of three esters

2.2-1.5 (5H, complex) CH, CH_2

1.2-1.1 (3H, 3 overlapping d, J=6Hz.) CH_3

(iii) trans 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (40)

Trans 6-isopropyl cyclohex-2-en-1-ol (99; 700mg., 5.0mmol.) was esterified[14] with 2,6-dichlorobenzoyl chloride (171; 1.2g., 5.7mmol.) in dry pyridine (2.5ml.) to give crude product, purified by dry-column chromatography (Grade 3 neutral alumina; hexane) and p.l.c. (10% ethyl acetate: petrol) to give 288mg. of ester. Recrystallisation (x3) from 40-60° petroleum ether gave 232mg. (15% yield) of trans ester (40) m.p. 67.0-67.6°C (literature[14] m.p. 66.5-67.2°C).

I.r. (cm^{-1}, CCl_4) 3030 (w, νC-H, alkene), 1740 (vs, νC=O), 1280, 1150 (vs, νC-O).

N.m.r. (100MHz.) δ7.26 (3H, s) aromatic H

5.83 (2H, complex) vinyl H

5.61 (1H, broad, $w_{\frac{1}{2}}$=15Hz.) CHOCOAr

2.2-1.2 (6H, complex) CH, CH_2

0.99 (6H, two d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 312. ^{37}Cl isotope peaks at m/e 314, 316.

T.l.c. 10% ethyl acetate: petrol, R.f. 0.50.

Reduction of the ester with LAH, in ether, gave 99% pure trans 6-isopropyl cyclohex-2-en-1-ol (99), as detected by g.l.c. (Capillary Carbowax 20M; 90°C; nitrogen 7p.s.i., R.i. 1620)

(iv) cis 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (82).

Because of the difficulty involved in obtaining stereochemically pure cis 6-isopropyl cyclohex-2-en-1-ol (98), some of the esterification attempts used cis/trans alcohol mixtures (98, 99).

Method 1. (pyridine/2,6-dichlorobenzoyl chloride)

Attempted esterification[14] by adding acid chloride (171; 96mg., 0.42mmol.) to a mixture of alcohols (98, cis, 77%: 99,

trans, 23%) in dry pyridine (0.2ml.) was only partially successful.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.69 (m, ester), 0.57 (m, cis alcohol), 0.53 (w, trans alcohol).

Further heating for 24h. and further addition of acid chloride made little significant difference.

Repetitions of the reaction at 25°C for 48h., at 60°C for 6h. and 100°C for 4h. were similarly unsuccessful.

Repetition of the reaction in a sealed tube at 60°C for 10h. failed, even after addition of a further equivalent of acid chloride (171) and heating for a further 100h.

Attempts to separate the ester mixtures obtained (in less than 15% yields) by crystallisation, or t.l.c., or column chromatography also failed, although the esters were separable from the alcohols by p.l.c.

Further esterification attempts, therefore, used pure cis alcohol (98) rather than cis/trans mixtures.

Thus, cis alcohol (98; 20mg., 0.14mmol.), acid chloride (171; 30mg., 0.145mmol.) and pyridine (56μl.) were heated to 50°C for 2h. A further 15mg. (0.077mmol) of acid chloride was added and heating was resumed for 2h. Na-dried benzene (200μl.) was added and the mixture stirred at 25°C for 18h. The mixture was acidified with 5% HCl then extracted with ether. The ether extract was washed with brine, 5% $NaHCO_3$, dried over $MgSO_4$, and evaporated to give 40mg. of crude product, containing ester (82), alcohol (98), acid (184) and an unidentified compound. Further washing with 5% $NaHCO_3$, followed by dry-column chromatography (Grade 1 basic alumina; hexane), gave 11mg. of crude ester. Purification by p.l.c. (50% ethyl acetate: petrol) gave 6mg. (13% yield) of almost

pure ester. Repeated attempts to crystallise this failed.

I.r. (cm^{-1}, CCl_4 solution) 1740 (vs, νC=O), 1270, 1140 (vs, νC-O), plus impurity bands (see below).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.69 (vs), 0.60 (vw), 0.57 (vw).

Repetition of this on a larger scale (200mg. alcohol) gave 314mg. of crude product, to which 5ml. of alumina-dried pentane was added. The filtrate obtained from passage of this through Celite was shown to contain ester, plus impurities. P.l.c. of 170mg. of this fraction (30% ethyl acetate: petrol, double development) gave 93mg. of alcohol-containing mixture and 70mg. of crude ester. Purification by dry-column chromatography (Grade 1 basic alumina; ether) gave 58mg. of ester which could not be crystallised. Repetition of the p.l.c. step still failed to give pure ester.

I.r. (cm^{-1}, CCl_4 solution) 1740 (s, νC=O, ester). As had been previously found, the intensity of this band was less than that of hydrocarbon bands. Also present was a strong, unidentified band at 1150-950.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.69 (vs), 0.60 (w), 0.57 (w).

The alcohol-containing fraction isolated from p.l.c. above was retreated with acid chloride and pyridine and stirred at room temperature for 12 days. Work-up and purification, as before, gave 22mg. of ester-containing product but, once again, it proved impossible to purify the ester completely.

Method 2. (NaH/2,6-dichlorobenzoyl chloride[182]).

A mixture of cis alcohol (98; 29mg., 0.21mmol.) and NaH (60% suspension in benzene; 9mg., 0.22mmol.) in Na-dried ether (4ml.) was refluxed, with stirring, under a nitrogen atmosphere,

for 30min. A solution of 2,6-dichlorobenzoyl chloride (171; 52mg., 0.22mmol.) in ether was added, and the resulting mixture refluxed for 1h., then stirred at 25°C for 48h. T.l.c. examination of the reaction at each stage showed only starting material.

Reactions using 3 equivalents of NaH or 1.33 equivalents of 100% NaH were similarly unsuccessful, as were attempts using THF or dimethoxyethane as solvents.

Method 3. (ion-exchange resin/2,6-dichlorobenzoic acid[183])

Alcohol mixture (98, cis, 53%; 99, trans, 47%; 75mg., 0.54mmol.), 2,6-dichlorobenzoic acid (184; 113mg., 0.59mmol.) and 20mg. of Dowex 50W X-8 ion-exchange resin were stirred in 2ml. of Na-dried benzene at 25°C. The reaction was monitored by t.l.c. No reaction occurred until the mixture was refluxed (after 48h.). Earlier additions of 25mg. of acid (184; after 20h.) and 20mg. of ion-exchange resin (after 28h.) had failed to cause esterification. After 100h. (=52h. at reflux), the mixture was filtered through Celite and the filtrate evaporated. Hexane was added to the residue, which was then allowed to stand for 2h. before being filtered through Celite to give 105mg. of crude product. Dry-column chromatography (Grade 5 neutral alumina; hexane) gave 74mg. (44% yield) of product, comprising ester (65%) and unidentified impurity (35%). Attempts to crystallise this from various solvents or "from the melt" were unsuccessful, as were separation attempts by p.l.c.

I.r. (cm^{-1}) 3040 (w, νC-H, alkene), 1740 (vs, νC=O), 1270, 1145 (s, νC-O), 800, 775 (s, νC-Cl).

N.m.r. (a) ester=65%

δ 7.3 (3H, s) aromatic H

5.9-5.4 (3H, complex) vinyl H, + CHOCOAr

2.2-1.2 (6H, complex) $\underline{CH}$, $\underline{CH}_2$

0.9 (6H, d, J=6Hz.) $(\underline{CH}_3)_2CH$

(b) impurity=35%: two resonances at 7.1-6.1 and 2.2-1.2 (relative intensities 1:5, both very complex)

M.s. M^+ at m/e 312. ^{37}Cl isotope peaks at 314, 316.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.69

Repetition of the reaction, using 70mg. alcohol mixture, 106mg. of acid, and 25mg. of ion-exchange resin in 3ml. benzene, under reflux for 144h., gave 109mg. of crude product. Dry-column chromatography gave 58mg. (37% yield) of ester-containing mixture. As above, this proved to be inseparable.

Attempts to perform the esterification reaction in other solvents met with no success. Hexamethylphosphortriamide, THF and ether all gave only starting materials, as did attempts to use other ion-exchange resins (Amberlite 120, Amberlite C-50).

Method 4. (trifluoroacetic anhydride/2,6-dichlorobenzoic acid)

Cis alcohol (98; 20mg., 0.14mmol.), acid (184; 27mg.,0.14mmol.) and trifluoroacetic anhydride (185; 0.2ml.,1.8mmol.) were stirred at 25°C for 1h. The solution was added to cold, dilute NaOH and extracted with benzene. Washing with water, drying over $MgSO_4$, and evaporation gave 7mg. of product, apparently the allylic trifluoroacetate (186) and traces of ester (82).

I.r. (cm^{-1}) 1780 (s, νC=O, trifluoroacetate), 1740 (m, νC=O, ester)

T.l.c. 50% ethyl acetate: petrol, R.f. 0.73 (s), 0.69 (m).

The reaction was repeated, this time forming the mixed anhydride before addition of the alcohol. The acid (184; 27mg., 0.14mmol.) was stirred in 77µl. (0.56mmol.) trifluoroacetic anhydride (185) for 20h. Excess $(CF_3CO)_2O$ was blown off by

nitrogen, and cis alcohol (98; 20mg., 0.14mmol.) in benzene (0.5ml.) was added. The mixture was stirred for 2h., basified with distilled water containing a few drops of 5% $NaHCO_3$, and extracted with ether. Washing with water, drying over $MgSO_4$, and evaporation gave 35mg. of crude product shown to be a mixture of trifluoroacetate and the desired ester, the latter in too small a quantity to be useful.

I.r. (cm^{-1}) 3040 (w, νC-H, alkene), 1780 (s, νC=O, trifluoroacetate), 1740 (m, νC=O, ester), 1270 (m, νC-O, ester), 1210, 1150 (vs, νC-O, trifluoroacetate).

T.l.c. 50% ethyl acetate: petrol, R.f. 0.73 (vs), 0.69 (m).

Method 5. (dicyclohexyl carbodi-imide/2,6-dichlorobenzoic acid)

Cis alcohol (98; 20mg., 0.14mmol.), 2,6-dichlorobenzoic acid (184; 27mg., 0.14mmol.) and dicyclohexyl carbodi-imide (185; 25mg., 0.14mmol.) were stirred, at 25°C, under a nitrogen atmosphere, in 1ml. of CH_2Cl_2 (pre-dried by passage through a Grade 1 basic alumina column). The reaction was monitored by t.l.c. and shown to give only traces of ester, even after 12 days.

(v) 6-tert.butyl cyclohex-2-en-1-yl 2,6-dichlorobenzoates (41, 83).

Method 1. (pyridine/2,6-dichlorobenzoyl chloride)

Esterification[14] of cis 6-tert.butyl cyclohex-2-en-1-ol (100; 50mg.) gave 11mg. of mixture shown to be predominantly unreacted starting material with only traces of ester.

Repetition, on a larger scale, at 100°C for 3h., gave similar results. P.l.c. separation (10% ethyl acetate: petrol) of this mixture gave 13mg. of ester-containing fraction which resisted attempts to purify it by further p.l.c. (benzene) and by crystallisation.

I.r. (cm^{-1}) 1740 (m, νC=O), 1280 (m, νC-O), plus impurity bands.

Repetition of the reaction, in a sealed tube, at 60°C, for 4h., was equally unsuccessful.

When the reaction was performed at 85°C for 72h., only intractable tars, shown by t.l.c. and i.r. to contain neither starting material nor desired product, could be obtained, even after repeated ether extraction of the acidified reaction mixture. The mixture, itself, was chromatographed on a Grade 3 neutral alumina column and eluted with pentane but, again, neither ester nor alcohol was obtained.

Attempts to esterify an alcohol mixture containing 58% of trans 6-tert.butyl cyclohex-2-en-1-ol (101) by use of the sealed tube method failed to produce any ester (as detected by i.r. and t.l.c.) after reaction for 18h. at room temperature, followed by 4h. at 60°C.

Method 2. (n.butyl Li/2,6-dichlorobenzoyl chloride)

Using procedures developed in the study of the esterification of the model compound, 3,5,5-trimethyl cyclohex-2-en-1-ol (172; p.107) a 10% w/v solution of cis 6-tert.butyl cyclohex-2-en-1-ol (100) in LAH-dried THF was treated with n.butyl Li and 2,6-dichlorobenzoyl chloride (171). No esterification occurred, only starting material being detectable by t.l.c.

b. Other esters.

(i) cis 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (84)

Esterification of a mixture of cis and trans 6-isopropyl cyclohex-2-en-1-ol (98, cis, 77%; 99, trans, 23%; 1.85g.) with 3,5-dinitrobenzoyl chloride/pyridine gave 3.55g. (82% yield) of ester mixture. Fractional recrystallisation from hexane gave, after 4 recrystallisations, 1.44g. (54% recovery) of cis ester (84).

The mother liquors from the crystallisations were concentrated and crystallised. Combination of these with the "top crop" gave a total of 1.82g. (68% recovery) of cis 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (84; 97.5% cis) m.p. 102.6-103.2°C.

I.r. (cm^{-1}, CCl_4 solution) 3105 (w, νC-H, aromatic); 3040 (w, νC-H, alkene), 1730 (s, νC=O), 1630 (w, νC=C), 1550, 1340 (vs, ν aryl-NO_2), 1270, 1165 (s, νC-O).

N.m.r. (100MHz.)

δ9.15 (3H, complex)	aromatic H
6.04 (2H, complex)	vinyl H
5.58 (1H, broad complex, $w_{\frac{1}{2}}$=8Hz.)	CHOCOAr
2.2-1.2 (6H, complex)	CH, CH_2
1.06 (3H, d, J=6Hz.)	CH_3
0.97 (3H, d, J=6Hz.)	CH_3

M.s. M^+ at m/e 334.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.70

G.l.c. Analysed as 6-isopropyl cyclohex-2-en-1-ol (98, 99) - product from LAH reduction.

Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i., R.i. (%), 1555 (97.5), 1620 (2.5).

Analysis. Found: C, 57.45; H, 5.4; N, 8.5%. $C_{16}H_{18}N_2O_6$ requires C, 57.5; H, 5.45; N, 8.4%.

^{13}C N.m.r. (25.2MHz.) p.p.m. downfield from $(CH_3)_4Si$

162.163 (s, C-10), 148.786 (s, C-13,15) 135.226 (d, C-2, J_r=60Hz.), 184.642 (s, C-11), 129.384 (d, C-12,16, J_r=90Hz.), 123.845 (d, C-3, J_r=60Hz.), 122.255 (d, C-14, J_r=90Hz.), 71.001 (d, C-1, J_r=55Hz.), 44.947 (d, C-6), 28.919 (d, C-7), 26.531 (t, C-4), 21.290, 20.916, 20.676 (C-5,8,9).

(ii) trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (85).

Esterification of 6-isopropyl cyclohex-2-en-1-ol (98, cis, 41%; 99, trans, 59%; 3.02g.) with 3,5-dinitrobenzoyl chloride/pyridine gave 6.775g. (94% yield) of crude product. Fractional crystallisation from hexane gave, after 3 recrystallisations, 2.25g. (60% recovery) of trans ester (85), m.p. 79.1-79.8°C (lit.[102] m.p. 79.7-80.7°C).

I.r. (cm^{-1}, CCl_4 solution) 3100 (m, νC-H, aryl), 3040 (w, νC-H, alkene), 1735 (s, νC=O), 1630 (m, νC=C), 1550, 1340 (vs, ν aryl-NO_2), 1270, 1165 (s, νC-O).

N.m.r. (100MHz.)

δ9.15 (3H, complex)	aromatic H
5.98 (1H, complex)	vinyl H
5.65 (2H, complex)	vinyl H, CHOCOAr
2.2-1.2 (6H, complex)	CH, CH_2
1.05 (3H, d, J=6Hz.)	CH_3
0.97 (3H, d, J=6Hz.)	CH_3

M.s. M^+ at m/e 334.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.70

G.l.c. Analysed as 6-isopropyl cyclohex-2-en-1-ol (98, 99) - product from LAH reduction.

Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.

R.i. (%), 1555 (2), 1620 (98).

^{13}C N.m.r. (25.2MHz.) p.p.m. downfield from $(CH_3)_4Si$

162.572 (s, C-10), 148.756 (s, C-13,15), 134.531 (s, C-11), 133.060 (d, C-2, J_r=56Hz.), 129.483 (d, C-12,16, J_r=85Hz.), 125.401 (d, C-3, J_r=56Hz.), 122.309 (d, C-14, J_r=85Hz.), 74.575 (d, C-1, J_r=50Hz.), 44.130 (d, C-6), 27.226 (d, C-7), 24.738 (t, C-4), 21.107 (t, C-5), 20.767, 17.955 (q, C-8,9).

(iii) cis 6-isopropyl cyclohex-2-en-1-yl 2,4-dichlorobenzoate (86)

2,4-Dichlorobenzoic acid was recrystallised from ethanol. Treatment with oxalyl chloride (see p.105) gave 2,4-dichlorobenzoyl chloride (188), b.p. 139-41°C/21mm.

I.r. (CCl_4 solution) 1795cm^{-1} (s, νC=O).

T.l.c. 30% ethyl acetate: petrol, R.f. 0.55.

Method 1. (pyridine/2,4-dichlorobenzoyl chloride)

A mixture of cis 6-isopropyl cyclohex-2-en-1-ol (98; 20mg., 0.14mmol.), 2,4-dichlorobenzoyl chloride (188; 29mg., 0.14mmol.), and pyridine (56μl.) was stirred in a sealed tube, at 25°C, for 3h. Excess pyridine was blown off with nitrogen and the residual solid taken up in ether (5ml.) and washed with water, containing 10 drops of 5% HCl, water, containing 10 drops of 5% $NaHCO_3$, and water. The ether extracts were dried over $MgSO_4$ and evaporated by a stream of nitrogen to give 27mg. of crude product. Dry-column chromatography (Grade 1 basic alumina; ether) gave 18mg. of colourless oil.

I.r. (cm^{-1}, CCl_4 solution) 1735 (s, νC=O), 1710 (s, ?), 1280, 1120 (m, νC-O).

N.m.r. showed resonances expected for ester (86)

δ7.7	(1H, d of d, J=8, 1Hz.)	$\underline{H}_A$
7.3	(1H, d of d, J=2, 1Hz.)	$\underline{H}_C$
7.1	(1H, d of d, J=8, 2Hz.)	$\underline{H}_B$
5.9	(2H, complex)	vinyl $\underline{H}$
5.4	(1H, complex)	$C\underline{H}OCOAr$
2.2-1.2	(6H, complex)	$C\underline{H}$, $C\underline{H}_2$
0.9	(6H, d, J=6Hz.)	$(C\underline{H}_3)_2CH$

also showed impurity bands (25%) - aromatic resonances as above (3H) plus aliphatic resonances (2.2-1.2, 6H).

M.s. M^+ at m/e 312.

T.l.c. 30% ethyl acetate: petrol, R.f. 0.60

alumina; 50% ethyl acetate: petrol, R.f. 0.7.

Repetition of this reaction gave the same results. Attempts to separate the unidentified impurity from the desired ester by crystallisation from various solvents were unsuccessful as were attempts to achieve a chromatographic separation by dry-column or t.l.c. techniques.

Method 2. (NaH/2,4-dichlorobenzoyl chloride)

A mixture of cis 6-isopropyl cyclohex-2-en-1-ol (98; 20mg., 0.14mmol.) and NaH (100%; 7mg., 0.28mmol.) in 1ml. of Na-dried ether was stirred for 24h., at 25°C, under a nitrogen atmosphere. A solution of 2,4-dichlorobenzoyl chloride (188; 30mg., 0.142mmol.) in 1ml. of ether was added over 1h. and stirring was continued for 4 days. A further 2ml. of ether was added and the mixture was washed with 2ml. water, dried over $MgSO_4$, and chromatogrammed on Grade 1 basic alumina to give 20mg. of product, which was further separated by p.l.c. (30% ethyl acetate: petrol) to give 6mg. of ester-containing fraction. Once again, however, the ester was contaminated with an inseparable impurity.

I.r., n.m.r., t.l.c. as above

Method 3. (trifluoroacetic anhydride/2,4-dichlorobenzoic acid)

A solution of 2,4-dichlorobenzoic acid (190; 29mg., 0.144mmol.) in $(CF_3CO)_2O$ (185; 80 l, 0.58mmol.) was stirred in a sealed tube at 25°C for 3 days. The excess anhydride was then blown off with a stream of nitrogen, and 6-isopropyl cyclohex-2-en-1-ol (98; 20mg., 0.14mmol.) was added and stirring was continued for 5h. The mixture was taken up in ether and washed with water, containing 15 drops of 5% $NaHCO_3$. Filtration through a 2x0.5cm. column of

Grade 1 basic alumina gave 16mg. of product, predominantly the trifluoroacetate (186).

I.r. (cm^{-1}, CCl_4 solution) 3040 (w, νC-H, alkene), 1785 (vs, νC=O), 1220, 1160 (vs, νC-O).

T.l.c. 30% ethyl acetate: petrol, R.f. 0.62.

(iv) cis 6-isopropyl cyclohex-2-en-1-yl p-nitrobenzoate (87).

A mixture of cis 6-isopropyl cyclohex-2-en-1-ol (98; 100mg., 0.7mmol.) and p-nitrobenzoyl chloride (140mg., 0.75mmol.) in pyridine (500 l) was stirred, at room temperature, for 1h. The mixture was extracted with ether, which was washed with dilute HCl, water, dried over $MgSO_4$, and evaporated to give crude product. Recrystallisation from hexane gave 80mg. of pure ester (87), m.p. 83.7-84.5°C.

I.r. (cm^{-1}, CCl_4 solution) 3040 (w, νC-H, alkene), 1725 (vs, νC=O), 1345 (s, νaryl-NO_2).

N.m.r. (100MHz.) δ8.32 (4H, d of q, J=9, 1Hz.) aromatic H
6.18 (2H, complex) vinyl H
5.56 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) CHOCOAr
2.3-1.2 (6H, complex) CH, CH_2
0.96 (6H, two d, J=7Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 289.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.68

G.l.c. Analysed as 6-isopropyl cyclohex-2-en-1-ol (98, 99) - product from LAH reduction.
Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.
R.i. (%), 1555 (98.5), 1620 (1.5)

Analysis: Found C, 66.1; H, 6.6; N, 5.0%. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.85%.

Part B. Synthesis of authentic N-(alkyl cyclohexyl) piperidines

1. Hydrogenation of alkyl phenols.

The appropriate alkyl phenol (20g.) was hydrogenated over PtO_2 (1g.) in acetic acid (200ml.), at pressures from 15-50 atmospheres, at room temperature. When hydrogen uptake had ceased, the catalyst was removed by filtration through Celite, the filtrate was basified with 6N NaOH, and extracted with ether. The ether extracts were washed with brine, dried over K_2CO_3, and evaporated to give crude product, which was used directly or purified by distillation.

(a)* Thus, hydrogenation of 2-isopropyl phenol (102) gave, after distillation, 11.0g. (53% yield) of a mixture (b.p. 66-68°C/30mm.) of 2-isopropyl cyclohexanone (111; 23%), cis 2-isopropyl cyclohexanol (141; 64%), and trans 2-isopropyl cyclohexanol (138; 13%), as analysed by g.l.c.

(b)* Hydrogenation of 4-isopropyl phenol (199) gave 10.4g. (50% yield) of a mixture (b.p. 105-106°C/30mm.) of 4-isopropyl cyclohexanone (205; 5%), cis 4-isopropyl cyclohexanol (201; 45%), trans 4-isopropyl cyclohexanol (203; 46%), and an unidentified compound (4%), as analysed by g.l.c.

Also obtained from hydrogenation of 4-isopropyl phenol (199) was 4.1g. (22% yield) of isopropyl cyclohexane (221),

* The spectroscopic and chromatographic data for these mixtures are not reported. Appropriate information may be obtained from the data given for the separate compounds (see later).

b.p. 48-49°C/30mm.

I.r. 1380, 1365cm^{-1} (m, νC-C, isopropyl doublet)

N.m.r. 1.8-1.0 (12H, complex) C$\underline{H}$, C$\underline{H}_2$

0.9 (6H, d, J=6Hz.) (C$\underline{H}_3$)$_2$CH

(c)* Hydrogenation of 2-tert.butyl phenol (103) gave 17.8g. (86% yield) of undistilled mixture containing 2-tert.butyl cyclohexane (222; 17%), 2-tert.butyl cyclohexanone (112; 37%), cis 2-tert.butyl cyclohexanol (142; 37%), trans 2-tert.butyl cyclohexanol (139; 6%), and an unidentified compound (3%).

2. Preparation of alkyl cyclohexanones.

The appropriate alkyl cyclohexanol or alcohol/ketone mixture (from hydrogenation of the corresponding alkyl phenol) was dissolved in approximately 15 volumes of acetone, and titrated with 8N Jones reagent, at 0-5°C. When oxidation was complete, water (100ml.) was added and the solution was extracted with ethyl acetate. The combined organic extracts were washed with water and 5% w/v $NaHCO_3$, dried over K_2CO_3, and evaporated to give crude product, which was purified by distillation.

(a) Oxidation of 4-methyl cyclohexanol (200, 202; 20g., 51% cis, 49% trans) gave 9.2g. (47% yield) of 4-methyl cyclohexanone (204), b.p. 55-56°C/24mm.

I.r. 1715cm^{-1} (vs, νC=O)

N.m.r. δ2.5-2.2 (4H, complex) C$\underline{H}_2$, α to C=O

2.0-1.3 (5H, complex) C$\underline{H}$, C$\underline{H}_2$

1.1 (3H, d, J=7Hz.) C$\underline{H}_3$

* See later for analysis of individual compounds.

M.s. M^+ at m/e 112.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.58.

G.l.c. Capillary Carbowax 20M; 70°C; nitrogen 10p.s.i.
R.i. 1305.

(b) Oxidation of a mixture of 2-isopropyl cyclohexanol and 2-isopropyl cyclohexanone (7g., 77% alcohol, 23% ketone) gave 4.1g. (59% yield) of 2-isopropyl cyclohexanone (111), b.p. 81-82°C/20mm.

I.r. 1710cm^{-1} (vs, νC=O)

N.m.r. δ2.5-1.5 (10H, complex) C<u>H</u>, C<u>H</u>$_2$
0.9 (6H, d, J=6Hz.) (C<u>H</u>$_3$)$_2$CH

M.s. M^+ at m/e 140.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.75

G.l.c. Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.
R.i. 1425

(c) Oxidation of a mixture of 4-isopropyl cyclohexanol and 4-isopropyl cyclohexanone (8g., 91% alcohol, 5% ketone) gave 5.8g. (73% yield) of 4-isopropyl cyclohexanone (205), b.p. 90-91°C/20mm.

I.r. 1715cm^{-1} (vs, νC=O)

N.m.r. δ2.2 (4H, complex) C<u>H</u>$_2$, α to C=O
2.1-1.5 (6H, complex) C<u>H</u>, C<u>H</u>$_2$
0.9 (6H, d, J=6Hz.) (C<u>H</u>$_3$)$_2$CH

M.s. M^+ at m/e 140.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.6

G.l.c. Capillary Carbowax 20M; 100°C; nitrogen 7p.s.i.
R.i. (%), 1545 (96), 1575 (4).

(d) Oxidation of a mixture of 2-tert.butyl cyclohexanol and 2-tert.butyl cyclohexanone (17g., 43% alcohol, 37% ketone) gave 11.6g. (69% yield) of 2-tert.butyl cyclohexanone (112),

b.p. 93-94°C/28mm.

I.r. 1710cm^{-1} (vs, νC=O)

N.m.r. δ2.3-1.2 (9H, complex) C<u>H</u>, C<u>H</u>$_2$

1.0 (9H, s) (C<u>H</u>$_3$)$_3$C

M.s. M^+ at m/e 154.

G.l.c. Capillary Carbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. (%) 1410 (97), 1525 (3).

3. <u>LAH reduction of alkyl cyclohexanones.</u>

<u>General method</u> - see p. 95

(a) LAH reduction of 2-methyl cyclohexanone (<u>110</u>; 6g.) gave 5.2g. (86% yield) of 2-methyl cyclohexanol (<u>140</u>, <u>cis</u>, 30%; <u>137</u>, <u>trans</u>, 70%), b.p. 166-167°C.

I.r. (cm^{-1}, CCl_4 solution) 3630 (s, νO-H), 1065, 1050, 1040 (s, <u>trans</u>, νC-O, δO-H), 980 (m, <u>cis</u>, νC-O, δO-H).

N.m.r. δ3.7 (0.3H, broad s, $w_{\frac{1}{2}}$=8Hz.) <u>cis</u> C<u>H</u>OH

3.3 (1H, s, D_2O ex.) O<u>H</u>

3.0 (0.7H, broad s, $w_{\frac{1}{2}}$=21Hz.) <u>trans</u> C<u>H</u>OH

2.0-1.3 (9H, complex) C<u>H</u>, C<u>H</u>$_2$

1.0 (3H, d, J=6Hz.) C<u>H</u>$_3$

M.s. M^+ at m/e 114.

G.l.c. Capillary Carbowax 20M; 70°C; nitrogen 10p.s.i.

R.i. 1370

10% PEGA; 55°C; argon 40ml.min^{-1} (on Pye Argon chromatograph), R.t. 5.6 min.

(b) LAH reduction of 2-<u>iso</u>propyl cyclohexanone (<u>111</u>; 1.5g.) gave 1.45g. (97% yield) of 2-<u>iso</u>propyl cyclohexanol (<u>141</u>, <u>cis</u>, 40%; <u>138</u>, <u>trans</u>, 60%).

I.r. (cm^{-1}) 3350 (s, νO-H), 1050 (s, trans, νC-O,δO-H), 960 (s, cis, νC-O,δO-H).

N.m.r. 4.0 (0.4H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis CHOH

3.3 (0.6H, broad s, $w_{\frac{1}{2}}$=22Hz.) trans CHOH

2.0-1.0 (10H, complex) CH, CH_2

1.7 (1H, s, D_2O ex.) OH

0.9 (6H, two d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 142.

G.l.c. Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.

R.i. (%), 1510 (40), 1540 (60).

(c) LAH reduction of 4-isopropyl cyclohexanone (205; 2.8g.) gave 2.8g. (98% yield) of 4-isopropyl cyclohexanol (201, cis, 16%; 203, trans, 84%).

I.r. (cm^{-1}) 3350 (vs, νO-H), 1050 (vs, trans, νC-O,δO-H), 960 (w, cis, νC-O,δO-H).

N.m.r. δ3.9 (1H, s, D_2O ex.) OH

3.9 (0.16H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis CHOH

3.4 (0.84H, broad s, $w_{\frac{1}{2}}$=22Hz.) trans CHOH

2.0-1.0 (10H, complex) CH, CH_2

0.9 (6H, d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 142.

G.l.c. Capillary Carbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. (%), 1595 (16), 1625 (84).

(d) LAH reduction of 2-tert.butyl cyclohexanone (112; 5g.) gave 4.9g. (96% yield) of 2-tert.butyl cyclohexanol (142, cis, 47%; 139, trans, 53%).

I.r. (cm^{-1}, CCl_4 solution) 3620 (w, νO-H), 1050 (m, trans, νC-O,δO-H), 960 (m, cis, νC-O,δO-H).

N.m.r. δ4.1 (0.46H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis CHOH

	3.3 (0.54H, broad s, $w_{\frac{1}{2}}$=22Hz.)	trans CHOH
	2.0-1.1 (9H, complex)	CH, CH_2
	0.97 (4.9H, s)	trans $(CH_3)_3C$
	0.94 (4.1H, s)	cis $(CH_3)_3C$

M.s. M^+ at m/e 156.

G.l.c. Capillary Carbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. (%), 1545 (47), 1570 (53).

Recrystallisation of a sample from 60-80° petroleum ether gave trans 2-tert.butyl cyclohexanol (139; 99+% pure by g.l.c.), m.p. 84.5-85.1°C (lit.[102] m.p. 84.5-85.0°C).

(e) LAH reduction of 4-tert.butyl cyclohexanone (206; 10g.) gave 9.8g. (97% yield) of 4-tert.butyl cyclohexanol (207, cis, 12%; 208, trans, 88%). Recrystallisation from 40-60° petroleum ether gave trans 4-tert.butyl cyclohexanol (208; 98+% pure by g.l.c.), m.p. 81.1-82.0°C (lit.[209] m.p. 80.5°C).

I.r. (cm^{-1}, CCl_4 solution) 3615 (m, ν O-H), 1060 (s, ν C-O, δ O-H)

N.m.r.	3.4 (1H, broad s, $w_{\frac{1}{2}}$=22Hz.)	trans CHOH
	1.9 (4H, complex)	H, α to OH
	1.5 (1H, s, D_2O ex.)	OH
	1.1 (5H, complex)	CH, CH_2
	0.9 (9H, s)	$(CH_3)_3C$

M.s. M^+ at m/e 156.

G.l.c. Capillary CArbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. (%), 1640 (1.5), 1670 (98.5).

4. Selectride reduction of alkyl cyclohexanones

Selectride = lithium tri-sec.butyl borchydride

A 10% w/v solution of the appropriate alkyl cyclohexanone in

Na-dried ether was added, dropwise, to a stirred solution of Li(sec.butyl)$_3$BH in ether/THF. Stirring was continued for 30min. after all the ketone had been added, then the excess Selectride was hydrolysed by cautious addition of water, the solution was basified by addition of 6N NaOH, and the intermediate organoborane oxidised by titration with 27.5% H_2O_2. When oxidation was complete, any excess peroxide was destroyed by addition of sodium metabisulphite and the solution was then extracted with ether. The ether extracts were washed with $NaHCO_3$, water, and HCl, before being dried over $MgSO_4$, and evaporated. The crude product was purified, and separated from sec.butanol, by distillation.

(a) Selectride reduction of 2-methyl cyclohexanone (110; 5.6g.), at 0°C, gave 2.1g. (35% yield) of cis 2-methyl cyclohexanol (140), b.p. 61-62°C/40mm.

I.r.	(cm^{-1}) 3400 (vs, νO-H), 980 (s, cis, νC-O, δO-H).	
N.m.r.	3.7 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.)	cis C<u>H</u>OH
	3.3 (1H, s, D_2O ex.)	O<u>H</u>
	1.7-1.2 (9H, complex)	C<u>H</u>, C<u>H</u>$_2$
	1.0 (3H, d, J=6Hz.)	C<u>H</u>$_3$
M.s.	M^+ at m/e 114.	
G.l.c.	Capillary Carbowax 20M; 70°C; nitrogen 10p.s.i.	
	R.i. 1370	

(b) Selectride reduction of 4-methyl cyclohexanone (204; 7.2g.), at -78°C, gave 4.6g. (64% yield) of 4-methyl cyclohexanol (200, cis, 91%; 202, trans, 9%), b.p. 76-77°C/50mm.

I.r.	(cm^{-1}) 3450 (vs, νO-H), 965 (s, cis, νC-O, δO-H).	
N.m.r.	δ3.9 (0.9H, broad s, $w_{\frac{1}{2}}$=8Hz.)	cis C<u>H</u>OH
	3.6 (1H, s, D_2O ex.)	O<u>H</u>
	3.4 (0.1H, broad s, $w_{\frac{1}{2}}$=22Hz.)	trans C<u>H</u>OH

1.9-1.3 (9H, complex) — CH, CH_2

1.0 (3H, s) — CH_3

M.s. M^+ at m/e 114.

G.l.c. Capillary Carbowax 20M; 90°C; nitrogen 7p.s.i.

R.i. (%), 1400 (91), 1415 (9).

(c) Selectride reduction of 2-isopropyl cyclohexanone (111; 2.3g.), at -78°C, gave 1.4g. (60% yield) of cis 2-isopropyl cyclohexanol (141), b.p. 73-74°C/20mm., m.p. 51.0-51.6°C (lit.[210] m.p.50-50.5°C)

I.r. (cm^{-1}) 3350 (s, νO-H), 960 (s, νC-O, δO-H)

N.m.r. δ4.0 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOH

2.0-1.2 (11H, complex, 1H D_2O ex.) — CH, CH_2, OH

0.9 (6H, d of d, J=7Hz.) — $(CH_3)_2CH$

M.s. M^+ at m/e 142.

G.l.c. Capillary Carbowax 20M; 110°C; nitrogen 7p.s.i.

R.i. 1510

(d) Selectride reduction of 4-isopropyl cyclohexanone (205; 2.6g.), at -78°C, gave 1.2g. (46% yield) of cis 4-isopropyl cyclohexanol (201), b.p. 84-85°C/20mm.

I.r. (cm^{-1}) 3350 (vs, νO-H), 960 (s, νC-O, δO-H)

N.m.r. δ3.9 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOH

3.6 (1H, s, D_2O ex.) — OH

2.0-1.3 (10H, complex) — CH, CH_2

0.9 (6H, d, J=6Hz.) — $(CH_3)_2CH$

M.s. M^+ at m/e 142.

G.l.c. Capillary Carbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. 1595.

(e) Selectride reduction of 2-tert.butyl cyclohexanone (112; 6.6g.), at 0°C, gave 6.4g. (96% yield) of cis 2-tert.butyl cyclohexanol (142), m.p. 53.5-54.2°C (lit.[189] m.p. 54-55°C.)

I.r. (cm^{-1}, CCl_4 solution) 3630 (m, ν O-H), 960 (s, νC-O, δO-H)

N.m.r. δ4.1 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis C<u>H</u>OH

2.3 (1H, s, D_2O ex.) O<u>H</u>

1.9-1.0 (9H, complex) C<u>H</u>, C<u>H</u>$_2$

0.9 (9H, s) (C<u>H</u>$_3$)$_3$C

M.s. M^+ at m/e 156.

G.l.c. Capillary Carbowax 20M; 120°C; nitrogen 7p.s.i.

R.i. 1545

(f) Selectride reduction of 4-<u>tert</u>.butyl cyclohexanone (<u>206</u>; 10g.), at -78°C, gave 9.8g. (98% yield) of <u>cis</u> 4-<u>tert</u>.butyl cyclohexanol (<u>207</u>), m.p. 82.0-82.8°C (lit.[211] m.p. 83.5°C).

I.r. (cm^{-1}, CCl_4 solution) 3615 (m, ν O-H), 955 (s, νC-O, δO-H)

N.m.r. δ3.9 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) cis C<u>H</u>OH

2.3 (1H, s, D_2O ex.) O<u>H</u>

1.9-1.2 (9H, complex) C<u>H</u>, C<u>H</u>$_2$

0.9 (9H, s) (C<u>H</u>$_3$)$_3$C

M.s. M^+ at m/e 156.

G.l.c. Capillary Carbowax 20M; 100°C; nitrogen 7p.s.i.

R.i. 1640

5. Preparation of alkyl cyclohexyl toluene-p-sulphonates.

The appropriate alkyl cyclohexanol was treated, at 0°C, with toluene-p-sulphonyl chloride (1.2 equivalents) in dry pyridine. When reaction was complete (t.l.c.), the reaction mixture was poured into ice-cold 10% HCl and the acidic solution was then extracted with ether. The ether extracts were washed with $NaHCO_3$, and water, dried over K_2CO_3, and evaporated to give crude products, which were purified by crystallisation, or used directly.

(a) Tosylation of 2-methyl cyclohexanol (140, cis, 30%; 137, trans, 70%; 4.7g.) gave 9.15g. (84% yield) of 2-methyl cyclohexyl toluene-p-sulphonate (209, cis, 30%; 210, trans, 70%).

Tosylation of cis 2-methyl cyclohexanol (140; 2g.) gave 4.4g. (92% yield) of cis 2-methyl cyclohexyl toluene-p-sulphonate (209), m.p. 55.6-56.5°C (lit.[212] m.p.55.6°C)

I.r. (cm^{-1}) 1370, 1350 (s, $\nu_{as}SO_2$), 1185, 1170 (s, $\nu_{s}SO_2$)

N.m.r. δ 7.7 (2H), 7.3 (2H) A_2B_2 system — aromatic H

4.6 (0.3H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOTs

4.0 (0.7H, broad s, $w_{\frac{1}{2}}$=20Hz.) — trans CHOTs

2.4 (3H, s) — CH_3 (aromatic)

2.1-1.0 (9H, complex) — CH, CH_2

0.8 (3H, two d, J=6Hz.) — CH_3

M.s. M^+ at m/e 268.

T.l.c. $CHCl_3$, R.f. 0.8

(b) Tosylation of 4-methyl cyclohexanol (200, cis, 50%; 202, trans, 50%; 20g.) gave 42.2g. (90% yield) of 4-methyl cyclohexyl toluene-p-sulphonate (211, cis, 50%; 212, trans, 50%).

Tosylation of cis 4-methyl cyclohexanol (200; 4.3g., 91% cis, 9% trans) gave 9.9g. (95% yield) of cis 4-methyl cyclohexyl toluene-p-sulphonate (211; 91% cis, 9% trans).

I.r. (cm^{-1}) 1365, 1355 (s, $\nu_{as}SO_2$), 1180, 1170 (s, $\nu_{s}SO_2$)

N.m.r. δ 7.7 (2H), 7.3 (2H) A_2B_2 system — aromatic H

4.7 (0.5H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOTs

4.0 (0.5H, broad s, $w_{\frac{1}{2}}$=20Hz.) — trans CHOTs

2.5 (3H, s) — CH_3 (aromatic)

2.1-1.1 (9H, complex) — CH, CH_2

1.0 (3H, d, J=6Hz.) — CH_3

M.s. M^+ at m/e 268, and elimination peak at m/e 96.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.67

(c) Tosylation of 2-isopropyl cyclohexanol (141, cis, 40%; 138, trans, 60%; 1.4g.) gave a 70:30 mixture of the desired product, 2-isopropyl cyclohexyl toluene-p-sulphonate (213, cis, 14%; 214, trans, 86%), and one of the starting materials, cis 2-isopropyl cyclohexanol (141). Attempts to increase the extent of reaction of the cis alcohol were unsuccessful.

Tosylation of cis 2-isopropyl cyclohexanol (141; 0.8g.) gave a mixture of the desired product, cis 2-isopropyl cyclohexyl toluene-p-sulphonate, together with starting material and toluene-p-sulphonic acid. Attempts to increase the yield of product were unsuccessful, as were attempts to separate it from the other compounds by washing with NaOH or $NaHCO_3$, or by chromatography on silica or alumina. In each case, toluene-p-sulphonic acid was formed in the separation procedure, presumably by elimination from the toluene-p-sulphonate, once formed.

I.r. (cm^{-1}, CCl_4 solution) 3620 (vw, νO-H), 1370, 1185, 1175 (s, νSO_2), 955 (m, νC-O, δO-H).

N.m.r. δ7.8 (2H), 7.3 (2H) A_2B_2 system — aromatic H

4.9 (0.1H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOTs

4.4 (0.9H, broad s, $w_{\frac{1}{2}}$=22Hz.) — trans CHOTs

2.4 (3H, s) — CH_3 (aromatic)

2.1-1.1 (10H, complex) — CH, CH_2

0.9 (3H, d, J=7Hz.) — $(CH_3)_2CH$

plus resonances corresponding to cis alcohol (141; p.121)

M.s. No M^+ for toluene-p-sulphonate (213, 214) - elimination peak at m/e 124.

T.l.c. 50% ethyl acetate: petrol, R.f. 0.9, 0.8.

(d) Tosylation of 4-isopropyl cyclohexanol (201, cis, 16%; 203,

trans, 84%; 2.5g.) gave 5g. (96% yield) of 4-isopropyl cyclohexyl toluene-p-sulphonate (215, cis, 17%; 216, trans, 83%).

Tosylation of cis 4-isopropyl cyclohexanol (201; 1.1g.) gave 2.1g. (92% yield) of cis 4-isopropyl cyclohexyl toluene-p-sulphonate (215), m.p. 54.3-55.0°C (lit.[14] m.p. 54-54°C)

I.r. (cm^{-1}, CCl_4 solution) 1350, 1185, 1170 (vs, νSO_2)

N.m.r. δ7.7 (2H), 7.3 (2H) A_2B_2 system — aromatic H

4.7 (0.17H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOTs

4.3 (0.83H, broad s, $w_{\frac{1}{2}}$=22Hz.) — trans CHOTs

2.5 (3H, s) — CH_3 (aromatic)

2.0-1.1 (10H, complex) — CH, CH_2

0.9 (6H, d, J=6Hz.) — $(CH_3)_2CH$

M.s. M^+ at m/e 296.

T.l.c. chloroform, R.f. 0.6

(e) Attempted tosylation of 2-tert.butyl cyclohexanol (142, cis, 47%; 139, trans, 53%) and of cis 2-tert.butyl cyclohexanol (142) was unsuccessful, only starting materials and decomposition products being recovered.

(f) Tosylation of trans 4-tert.butyl cyclohexanol (208, 6g.) gave 11.5g. (97% yield) of trans 4-tert.butyl cyclohexyl toluene-p-sulphonate (220), m.p. 89.1-90.0°C (lit.[14] m.p. 87.5-88.3°C).

Tosylation of cis 4-tert.butyl cyclohexanol (207; 9.5g.) gave 18.0g. (95% yield) of cis 4-tert.butyl cyclohexyl toluene-p-sulphonate (219), m.p. 79.0-79.8°C (lit.[14] m.p. 77.5-78.5°C).

I.r. (cm^{-1}, CCl_4 solution) 1370, 1185, 1170 (s, νSO_2)

N.m.r. δ7.7 (2H), 7.3 (2H) A_2B_2 system J_{AB}=8Hz. aromatic H

4.7 (1H, broad s, $w_{\frac{1}{2}}$=8Hz.) — cis CHOTs

OR

4.3 (1H, broad s, $w_{\frac{1}{2}}$=20Hz.) — trans CHOTs

2.4 (3H, s) — CH_3 (aromatic)

	2.0-1.1 (9H, complex)	$C\underline{H}$, $C\underline{H}_2$
	0.9 (9H, s)	$(C\underline{H}_3)_3C$
M.s.	M^+ at m/e 310.	

6. Solvolysis of toluene-p-sulphonates: preparation of alkyl cyclohexyl piperidines.

NOTE: The g.l.c. properties of the amine products, on three separate g.l.c. columns, have already been recorded in Table 15

The appropriate alkyl cyclohexyl toluene-p-sulphonate was refluxed in redistilled piperidine (2.5ml. per 1g. of substrate) for 24h. The reaction mixture was acidified with dilute HCl, and extracted with ether. The ether extracts were then discarded and the acid solution was basified with dilute NaOH, and extracted with ether. The ether fraction was washed with brine, dried over K_2CO_3, and evaporated to give crude product, which was purified by distillation.

(a) Solvolysis of 2-methyl cyclohexyl toluene-p-sulphonate (209, cis, 30%; 210, trans, 70%; 8g.) gave 0.85g. (16% yield) of N-(2-methyl cyclohexyl) piperidine (191, cis, 49%; 192, trans, 51%), b.p. 160-161°C/44mm.

I.r.	(cm^{-1}, CCl_4 solution)	1153, 1145, 1108, 1100 (m, νC-N)
N.m.r.	δ2.8 (2H, complex)	)
	2.4 (2H, complex)	) $C\underline{H}$, $C\underline{H}_2$ α to N
	2.1 (1H, complex)	)
	1.8-1.2 (15H, complex)	$C\underline{H}$, $C\underline{H}_2$
	0.9 (3H, d, J=6Hz.)	$C\underline{H}_3$
M.s.	M^+ at m/e 181.	

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.91 (trans), 0.65 (cis).

(b) Solvolysis of cis 2-methyl cyclohexyl toluene-p-sulphonate (209; 4.0g.) gave 1.7g. (63% yield) of N-(trans 2-methyl cyclohexyl) piperidine (192).

I.r., n.m.r., m.s. as in (a) above.

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.91.

(c) Solvolysis of 4-methyl cyclohexyl toluene-p-sulphonate (211, cis, 50%; 212, trans, 50%; 8g.) gave 1.8g. (33% yield) of N-(4-methyl cyclohexyl) piperidine (193, cis, 56%; 194, trans, 44%) b.p. 170-171°C/44mm.

I.r. (cm^{-1}, CCl_4 solution) 1151, 1145, 1113, 1097 (m, νC-N)

N.m.r. δ2.7 (1H, complex))
2.3 (3H, complex)) CH, CH_2 α to N
2.0 (1H, complex))
1.8-1.2 (15H, complex) CH, CH_2
0.9 (3H, d, J=6Hz.) CH_3

M.s. M^+ at m/e 181.

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.71 (cis), 0.60 (trans)

(d) Solvolysis of cis 4-methyl cyclohexyl toluene-p-sulphonate (211, cis, 91%; 8g.) gave 1.7g. (32% yield) of N-(4-methyl cyclohexyl) piperidine (193, cis 14%; 194, trans, 86%), b.p. 120-121°C/18mm.

I.r., n.m.r., m.s. as in (c) above.

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.71 (w, cis), 0.60 (s, trans).

(e) Solvolysis of a 70:30 mixture of 2-isopropyl cyclohexyl toluene-p-sulphonate (213, cis, 14%; 214, trans, 86%) and

cis 2-isopropyl cyclohexanol (141) gave no tertiary amine product, the only detectable products being olefin and toluene-p-sulphonic acid. Normal work-up gave two fractions:- i. an acid extract shown by t.l.c. and i.r. to contain only piperidine, and ii. an ether extract, containing olefin, cis alcohol (141), and toluene-p-sulphonic acid.

I.r. i. 3300cm^{-1} (vs, νN-H)

ii. (cm^{-1}) 3400 (vs, νO-H), 3020 (m, νC-H, alkene), 1650 (w, νC=C), 1160, 1050 (s, νSO_2), 960 (s, νC-O, δO-H).

T.l.c. chloroform, R.f. 0.7, 0.6, 0.3-0.0 (streak).

(f) Solvolysis of 4-isopropyl cyclohexyl toluene-p-sulphonate (215, cis, 17%; 216, trans, 83%; 5g.) gave 2.1g. (59% yield) of N-(4-isopropyl cyclohexyl) piperidine (195, cis, 75%; 196, trans, 25%), b.p. 69-71°C/20mm.

I.r. 1150, 1115, 1100 (m, νC-N).

N.m.r. δ2.4 (4H, complex) } CH, CH_2 α to N
2.0 (1H, complex) }
1.7-1.2 (16H, complex) CH, CH_2
0.9 (6H, d, J=6Hz.) $(CH_3)_2CH$

M.s. M^+ at m/e 209.

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.70 (s, cis), 0.65 (w, trans).

(g) Solvolysis of cis 4-isopropyl cyclohexyl toluene-p-sulphonate (215; 2g.) gave 0.78g. (55% yield) of N-(trans 4-isopropyl cyclohexyl) piperidine (196, 91% trans). Purification of this amine by dry-column chromatography (Grade 3 basic alumina; 50% ethyl acetate: petrol) gave 0.68g. (87% recovery) of colourless needles, m.p. 100.1-100.7°C, which were shown (by g.l.c.), somewhat

surprisingly in view of the sharp m.p. observed, to have the same epimer distribution as the "crude" material.

I.r., n.m.r., m.s. as in (f) above.

T.l.c. on alumina; 50% ethyl acetate: petrol, R.f. 0.70 (w, cis), 0.65 (s, trans).

(h) Solvolysis of trans 4-tert.butyl cyclohexyl toluene-p-sulphonate (220; 9.2g.) gave 2.3g. (35% yield) of N-(cis 4-tert.butyl cyclohexyl) piperidine (197), b.p. 140-141°C/25mm.

I.r.	(cm^{-1}, CCl_4 solution)	1145, 1120, 1105 (m, νC-N)
N.m.r.	δ2.4 (4H, complex)	CH, CH_2 α to N, CH_{ax} on C_3,C_5.
	2.1 (3H, complex)	
	1.8-1.0 (13H, complex)	CH, CH_2
	0.9 (9H, s)	$(CH_3)_3C$
M.s.	M^+ at m/e 223.	
T.l.c.	on alumina; 50% ethyl acetate: petrol, R.f. 0.91	

(k) Solvolysis of cis 4-tert.butyl cyclohexyl toluene-p-sulphonate (219; 10g.) gave 2.8g. (39% yield) of N-(trans 4-tert.butyl cyclohexyl) piperidine (198), b.p. 136-137°C/30mm. Recrystallisation of the distilled material from hexane gave m.p. 56.5-57.9°C.

I.r.	(cm^{-1}, CCl_4 solution)	1155, 1105 (m, νC-N)
N.m.r.	δ2.4 (4H, complex)	CH, $CH_2\alpha$ to N
	2.1 (1H, complex)	
	1.7 (4H, complex)	CH_{ax} β to N
	1.4-1.0 (11H, complex)	CH, CH_2
	0.9 (9H, s)	$(CH_3)_3C$
M.s.	M^+ at m/e 223.	
T.l.c.	on alumina; 50% ethyl acetate: petrol, R.f. 0.63.	

Part C Reactions of 6-isopropyl cyclohex-2-en-1-yl esters (40, 84, 85, 87) with piperidine.

1. General methods.

(a) Reactions in the absence of solvent.

A solution of the ester (50mg.) in freshly distilled piperidine (80μl.), contained in a teflon-capped sealed tube was heated at 130°C for 24h.[14] After cooling, the reaction mixture was taken up in n.pentane (5ml.) and filtered through Celite. Distilled water (1ml.) was added and the mixture was shaken, then centrifuged, and the water was drawn off. The pentane extract was dried by passage through Na_2CO_3 and evaporated by a stream of nitrogen to give a mixture of products and unreacted esters.

Hydrogenation (PtO_2/methanol/1 atmosphere H_2/25°C) afforded the corresponding products and esters.

NOTES. (1) The work-up procedure described had, already, been shown, by trial experiments involving the solvolysis of 3,5,5-trimethyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (175) in piperidine, to be superior to that employed by Stork and White.[14]

(2) The efficiency of the work-up procedure was checked, at each stage, by g.l.c. (see later).

(b) Reactions in m-xylene solution.

A solution of the ester (10mg.) and piperidine (9μl.) in m-xylene (100μl.), incorporating 1% w/v of $C_{20}H_{42}$ as an internal standard, was sealed in a teflon-capped tube and heated at temperatures from 100°C to 145°C, for varying times. In initial experiments, the work-up procedure, above, was used, while later studies employed direct injection of the reaction mixture into the

g.l.c. column.

During the first few hours of reaction, however, excessive "tailing" by piperidine interfered with the analysis. Washing the analytical sample (in 200μl. of ether) with 50μl. of distilled water separated the piperidine from the tertiary amine products, allowing direct injection of the ethereal solution.

As above, the products and starting materials were analysed before and after hydrogenation.

2. Analysis of products and substrates.

(a) Products.

(i) G.l.c.

The reaction products were analysed by g.l.c. on three separate columns and, after hydrogenation, were coinjected on these three columns with authentic samples of N-(4-isopropyl cyclohexyl) piperidines (195, 196), 2-isopropyl cyclohexanols (141, 138) and 4-isopropyl cyclohexanols (201, 203).

Typical g.l.c. traces from reaction of the cis and trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoates (84, 85; Figure 9) and their trans 2,6-dichlorobenzoate analogue (40; Figure 10) have already been shown. The separation of all the products on the most effective g.l.c. column is shown below.

G.l.c. 5% Carbowax 20M + 1% KOH; 150°C; nitrogen 20p.s.i.

R.i.	1780	1805	1845	1895	1930	1980	2005	2015
amines	-	227,228	-	-	229	43	?	?
alcohols	98	-	99,232	233	-	-	-	-

The other columns were less effective, failing to separate the 6-amines (227, 228) from cis 6-alcohol (98), although they

did cleanly separate the 4-amines (229, 43) from one another and from the other products.

The separation of the amine products, both before and after hydrogenation, is shown more clearly by the analysis of the reaction products and hydrogenation products from 6-isopropyl cyclohex-2-en-1-yl 2,6-dichlorobenzoate (40), since no alcohols were formed, using this substrate.

G.l.c. 5% Carbowax 20M + 1% KOH; 145°C; nitrogen 20p.s.i.

	R.i.	1730	1805	1890*	1930	1980	2010**
reaction products	%	-	13	-	22	65	-
hydrogn products	%	6	8	23	-	-	63

5% Carbowax 20M + 1% polyethyleneimine (PEI); 100°C; nitrogen 20p.s.i.

	R.i.	1475	1495	1520*	1570	1610**
reaction products	%	6	7	-	22	65
hydrogn products	%	6	8	23	-	65

10% Carbowax 20M + 2% PEI; 130°C; nitrogen 20p.s.i.

	R.i.	1600	1650	1695*	1740	1775	1800**
reaction products	%	-	13	-	22	65	-
hydrogn products	%	6	8	23	-	-	63

None of the columns employed effected a separation of the trans 6- and cis 4-isopropyl cyclohex-2-en-1-ols (99, 232). However, hydrogenation of these to their separable, saturated analogues allowed their estimation. (as 138, 201)

* shown to be N-(cis 4-isopropyl cyclohexyl) piperidine (229)

** shown to be N-(trans 4-isopropyl cyclohexyl) piperidine (43)

G.l.c. 5% Carbowax 20M + 1% KOH; 130°C; nitrogen 20p.s.i.

R.i.	1765	1780	1790	1815	1845	1895
unsat. alcohols	-	98	-	-	99,232	233
sat. alcohols	141	-	138	201	203	-

(ii) G.c.-m.s.

The reaction products and hydrogenation products were analysed by g.c.-m.s. (using a 5% Carbowax 20M + 1% KOH column)

R.i.	1780	1805	1845	1895	1930	1980	2005	2015
M^+ (m/e)	140	207	140	140	207	207	127	113
amines	-	227,228	-	-	229	43	?	?
alcohols	98	-	99,232	233	-	-	-	-

Fragmentation schemes:-

N-(4-isopropyl cyclohex-2-en-1-yl) piperidines (229, 43); m/e (%) 207 (14), 192 (7), 179 (27), 165 (15), 164 (100), 137 (98), 122 (33), 86 (22), 84 (30), 79 (29). See Figure 11.

N-(6-isopropyl cyclohex-2-en-1-yl) piperidines (227, 228); m/e (%) 207 (6), 179 (2), 164 (5), 138 (12), 137 (100), 136 (8), 123 (7), 122 (63), 95 (8), 84 (9), 81 (8), 80 (10), 79 (13). See Figure 11.

4- and 6-isopropyl cyclohex-2-en-1-ols (98, 99, 232, 233); m/e (%) 140 (4), 122 (14), 98 (24), 97 (48), 91 (14), 81 (16), 80 (29), 79 (39), 70 (100).

unidentified compounds; R.i. 2005; m/e (%) 127 (74), 126 (13), 113 (8), 112 (19), 85 (20), 84 (87), 70 (37), base peak at 43 (100).

R.i. 2015; m/e (%) 113 (100), 112 (34), 98 (34), 85 (15), 84 (45).

(b) Substrates.

The ester substrates (40, 84, 85, 87) were unsuitable for direct g.l.c. analysis and were, therefore, examined as the allylic alcohols (98, 99, 232, 233) resulting from their reduction by LAH, in ether, at 25°C. The g.l.c. analysis of these alcohols has

already been shown (p. 141). In practice, the measured areas of the g.l.c. peaks corresponding to these LAH reduction products was a composite of alcohols arising from two different sources, viz. from LAH reduction of residual ester in the reaction mixture, and from aminolysis of ester by piperidine. Thus, in order to determine the composition of the available ester "pool" at any stage of reaction, it was necessary to subtract the amounts of the various alcohols formed by aminolysis (obtained from g.l.c. of the reaction mixture before LAH reduction) from the amounts of alcohols detected after LAH reduction of the reaction mixture.

This analysis showed that the original esters (40, 84, 85, 87) were not stable under the reaction conditions, undergoing epimerisation and allylic rearrangement.

3. Results.

(a) Product distribution and ester composition during reaction.

The relevant data have already been reported (Figures 12-16, Tables 15-17) and will not, therefore, be repeated.

(b) Isomerisation of substrates.

(i) In presence of piperidine.

The esters were shown to isomerise during the course of reaction by analysing the residual ester at various stages of the reaction. (see 2(b) above). The results obtained have already been used (Figures 14, 16, 20; Tables 16b, 18, 19, 21) and will not be repeated.

(ii) In absence of piperidine.

By performing reactions, as before, but without piperidine, it was shown that the esters isomerised (see Figure 15, 20; Tables

19, 21).

Addition of 5 drops of 2,2,2-trifluoroethanol to the reaction mixture was shown to increase the rate of isomerisation to a small extent (Figure 15).

Both of these studies were accompanied by ester decomposition reactions. G.c.-m.s. studies showed the major product to be polymers of the diene (180). m/e (%) 122 (100%), 121 (22%), 107 (79%), 93 (54%), 91 (52%), 79 (50%), 77 (56%).

Addition of triethylamine (9µl.) to the reaction mixture in place of piperidine suppressed the ester decomposition. (Figures 16, 20; Tables 19, 21).

(c) Isomerisation of products.

Mixtures containing only the amine reaction products were obtained by taking up the reaction mixture in ether and extraction with dilute HCl. Basification of the acid extract, followed by ether extraction, washing with brine, Na_2CO_3 drying, and evaporation by a stream of nitrogen gave amine mixtures free of alcohols and esters.

G.l.c. 5% Carbowax 20M + 1% KOH; 145°C; nitrogen 20p.s.i.

R.i.	1805	1930	1980
mixture 1 %	17	24	59
mixture 2 %	31	50	19
IDENTITY	227, 228	229	43

These mixtures were sealed in tubes, together with appropriate quantities of piperidine and m-xylene (containing 1% $nC_{20}H_{42}$ as an internal standard), and heated, at 123°C, for 43h. C.l.c analysis showed that no change in the composition of the amine mixtures had occurred and that the amines were, therefore, stable to isomerisation under the reaction conditions.

(d) Reaction of trans 4-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (242) with piperidine.

A solution of trans 6-isopropyl cyclohex-2-en-1-yl 3,5-dinitrobenzoate (85; 97% trans, 3% cis; 20mg.) in m-xylene (200µl; 1% w/v n.$C_{20}H_{42}$) was sealed in a tube and heated, at 123°C, for 16h., when g.l.c. showed the ester to be a mixture of trans 6-ester (85; 90%), cis 6-ester (84; 3%), and trans 4-ester (242; 7%). Reaction of this mixture with piperidine (16µl.), at 123°C, was monitored by g.l.c. and shown to give approximately 7% more cis 4-amine (229) than equivalent experiments performed with 97% pure trans 6-ester (85) as substrate (see Figure 19).

4. Kinetic studies.

(a) General method.

A mixture of ester (84 or 85; 5 or 10mg.) and piperidine (4.5 or 9µl.) in m-xylene (100µl.) containing 1% w/v n.$C_{20}H_{42}$ as internal standard was sealed in a teflon-capped tube and maintained at 123 ± 1°C in a thermostatted oil-bath. Samples were removed periodically and the 4-amine (229, 43) concentrations, relative to the internal standard, were determined by g.l.c. (5% Carbowax 20M + 1% KOH; 145°C; nitrogen 20p.s.i.), utilising (i) direct injection and (ii) injection of a sample pre-washed with water (see p. 141) G.l.c. response factors for the various compounds (229, 43, 98, 99, 232, 233) were not obtainable because the relevant compounds could not be separately examined, but it was assumed that the response factors of the most important compounds, the epimeric 4-amines (229, 43), would be the same.

(b) Results

(i) Production of N-(4-isopropyl cyclohex-2-en-1-yl) piperidines (229, 43).

It was found that, in any single experiment, the variation of amine concentrations and functions thereof (e.g. [amine], ln. [amine], 1/[amine]) with time exhibited complex behaviour from which kinetic parameters could not be obtained. Similarly, calculation of the specific first- and second-order rate constants from the formulae below failed to show consistency and, therefore, yielded no meaningful kinetic information. Although disappointing, such findings were not surprising in view of the complexity of the reacting system (Figure 8).

$k_1 = 1/t \cdot \ln. a/(a-x)$ $\quad$ $k_2 = 1/t(b-a) \cdot \ln. a(b-x)/b(a-x)$

where k_1 = specific first-order rate constant

k_2 = specific second-order rate constant

t = time (h.)

a = initial concentration of ester (mole.litre^{-1})

b = initial concentration of piperidine (mole.litre^{-1})

x = concentration of amine at time t (mole.litre^{-1})

Similarly unsuccessful were plots of functions of the ester concentration ([ester], ln. [ester], 1/[ester]) versus time, as determined after LAH reduction (see p. 143)

However, by performing reactions with different initial concentrations of ester and piperidine, the reaction rates and order could be determined by graphical methods. The results from these experiments have already been utilised (Figures 23, 24; Table 23) and will not, therefore, be repeated.

NOTE (i) Because of the small scale of these experiments (viz. 5 or 10mg. ester; 4.5 or 9µl. piperidine) accurate measurement of

the initial concentration of ester and piperidine was important. To allow comparison of results from different experiments, the initial ester concentration, relative to internal standard, was determined, as above, by g.l.c. This figure was then "normalised" to 500% of the internal standard by application of a suitable multiplier. Identical multiplication of the measured amine concentrations during the ensuing reaction gave corrected results which could be compared with those from other experiments, involving different initial concentrations.

NOTE (ii) Because of the inherent lack of precision in the kinetic studies reported, it is intended that the kinetic parameters obtained be taken, essentially, as being for comparative purposes within this study rather than as absolute values.

NOTE (iii) Because of the complexity of the reacting system, only initial rates and rate constants could be calculated. These were obtained from the graphs of amine concentration versus time shown in Figure 23, by measuring the tangent to the curve at time t=0. The slope of this is equal to the initial rate of the reaction, and, based on the assumption that the response factors for the amines (229, 43) are equal to that of the internal standard, the rate and rate constant can be determined. (This assumption is valid for comparison of the rates of the reactions of the cis (229) and trans amines (43) but may no be so for comparison of these with other compounds).

A typical calculation is set out below.

From Figure 23, using 10mg. ester and 9μl. piperidine,

Slope of tangent at t=0 is [trans 4-amine]/t

= 5.75% of internal standard /h.

internal standard = 100mg./10ml. = 3.55×10^{-2} mole.litre^{-1}

therefore, 5.75% of internal st. = 2.04×10^{-3} mole.litre^{-1}

Rate of reaction = 2.04×10^{-3} mole.litre^{-1}.h^{-1}.

Rate constant = k = Rate/$[E]_o \cdot [pip]_o$

where $[E]_o$ = initial concentration of ester (mole.litre^{-1})

and $[pip]_o$ = initial concentration of piperidine (mole.litre^{-1})

$[E]_o$ = 10mg./100µl. = 0.3mole.litre^{-1}

$[pip]_o$ = 9µl./100µl. = 1.1 mole.litre^{-1}

therefore, k =(2.04/0.3x1.1) x 10^{-3} litre.mole^{-1}.h.$^{-1}$

i.e. k = 5.7 x 10^{-3} litre.mole^{-1}.h.$^{-1}$

(ii) Production of 6-isopropyl cyclohex-2-en-1-ols (98, 99).

Comparative rates of formation of cis (98) and trans (99) alcohols from aminolysis of cis 6-ester (84) and trans 6-ester (85), respectively, were obtained by plotting the concentration of these alcohols versus time , after normalisation of the initial concentrations of esters. However, initial rate constants and rates could not be determined because of the complex kinetic behaviour of the reactions producing these compounds.

The relevant results have already been shown in graphical form and will not, therefore, be repeated.

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