STUDIES RELATED TO THE MICHAEL REACTION

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for the degree of Ph.D.

by

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SUMMARY

Part I

The thermal Michael reaction has been investigated from the point of view of both scope and mechanism. The reaction has been shown to be of considerable synthetic usefulness wherever the active methylene compound used is capable of facile enamine formation.

The mechanism of the reaction has been shown to involve the initial attack of the Mannich base on the active methylene compound, followed by decomposition of the adduct to give a vinyl ketone and a carbinolamine. The reaction is completed by formation of an enamine from the carbinolamine and alkylation of this by the vinyl ketone, the water produced in the dehydration of the carbinolamine serving to hydrolyse the resultant alkylated enamine. Consistent with this mechanism, the general pattern of oreintation parallels that of enamine chemistry, with allowance being made for the elavated temperatures involved in the thermal reaction.

Part II

Synthetic approaches to a proposed intermediate in sesquiterpene biogenesis have been only partially successful. After the facile generation of a suitably substituted seven-membered ring, difficulty has been encountered in the transformation of a 1,1-diester into a 1-keto function in a 2-substituted cycloheptene. The conformational

complexities of such compounds have been investigated in the development of a viable synthetic route for this transformation. Later, problems have been encountered in the alkylation of a 2-substituted cycloheptanone to form a six-carbon side chain.

ACKNOWLEDGEMENTS

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CONTENTS

PART I

THE THERMAL MICHAEL REACTION

INTRODUCTION:

The Michael reaction[1], or 1,4-addition of an active methylene compound across the conjugated system of an αβ-unsaturated ketone, aldehyde or carboxylic acid derivative, has provided in its diverse ramifications since its discovery[2] in 1887, one of the major methods of formation of a new carbon-carbon bond. The extent of its usefulness can, perhaps, best be attributed to the number and accessibility of donors and acceptors which readily undergo condensation under the conditions of the reactions.

The reaction is generally base catalysed, but, as the base used to form the anion of the donor molecule is regenerated in the course of the reaction, only a catalytic amount is theoretically required. As with many other widely used synthetic organic reactions, complications can often arise and, most commonly in the case of the Michael reaction, the products can undergo further transformation under the prevailing basic conditions e.g. aldol cyclisation, diaddition, "abnormal" Michael[1a] This complication necessitates the mildest possible reaction conditions but has in turn provided much of the interest of the reaction.

One of the most general applications of the reaction is that of a vinyl ketone of the type (1) with a compound containing a

methylene group, activated by a neighbouring carbonyl function, to yield a 1,5-dicarbonyl compound. In the case of active methylene compounds which are symmetrically substituted the reaction product is formed alpha to the carbonyl group. However, in the case of unsymmetrically substituted compounds, there are, in general, two possible primary sites of alkylation, although in the majority of cases one or other is predominantly formed under the reaction conditions used.

In the condensation of unsymmetrical ketones with vinyl ketones in the presence of basic catalysts, condensation is found[2] to occur mainly, if not exclusively, at the more highly substituted active centre. Thus, when 2-methylcyclohexanone (2) is condensed[3] with methyl vinyl ketone (1,R=Me) using either Triton B or ethanolic potassium hydroxide as basic medium, the 2,2-substituted cyclohexanone (3) is formed and when methyl-n-butyl ketone (4) is condensed with methyl vinyl ketone using lithamide as catalyst, substitution takes place at the methylene rather than at the methyl position. A similar orientation pattern is observed in the Robinson modification of the Michael reaction; i.e. the condensation[4] of 2-methylcyclohexanone with the methiodide of 4-diethylaminobutan-2-one (5), in the presence of sodamide to

give 10-methyl-$\Delta^{1:9}$-octalone-2(6).

In general, therefore, the more highly substituted product can be obtained by condensation under basic conditions. There would appear to be no immediately obvious rationalisation for the exclusive formation of 2,2-substituted materials in the Michael reactions described above, since it has been demonstrated[5,6] that, although there is a preference for the enolate anion (7) to predominate over the isomer(8) at equilibrium, this is of the order of 60:40. Moreover, it would be expected that (7) being more sterically hindered would react with a vinyl ketone at a lower, or at best comparable, rate to (8). House[2c] has considered two explanations for this phenomenon. The first is that, under the conditions of the Michael reaction, the mono-alkylated products are interconvertible, e.g. (2)→(10)⇌(9). This hypothesis he tested and disproved, showing that little, if any, appreciable retro-reaction is taking place. However, there is a second possibility, namely that the 2,6-isomer is more rapidly converted to polyalkylated products than the 2,2, a fact in accordance with his earlier findings[5] in the methylation of 2-methylcyclohexanone. At present there is no more profound explanation available and the high specificity of the alkylation does not appear to be completely understood.

The specific generation of the less highly substituted mono-alkylated product of unsymmetrical ketones is best effected by the condensation of the vinyl ketone with the enamine[7] of the ketone, formed by the elimination of a mole of water between the ketone and a secondary amine. Competition between N-alkylation and C-alkylation, found in the condensation of enamines with alkyl halides, is not found with vinyl ketones since in this case N-alkylation is reversible. Enamine alkylation has found wide synthetic application since its introduction and even in the case of symmetrically substituted compounds may be the method of choice where centres sensitive to strong base are present in the molecule.

Although it is generally found that enamine alkylations give only the less highly substituted product, some notable exceptions have appeared. It has been shown[8] that, when the pyrrolidine enamine of 2-methylcyclohexanone is condensed with methyl acrylate, a mixture containing approximately equal proportions of the 2,2 & 2,6-substituted products, (9) & (10), are found. There authors claim, therefore, that the selectivity of the enamine alkylation procedure is by no means as great as is generally supposed.

As in the case of alkylation of the enolate anions of unsymmetrical ketones, the specificity found in most cases of enamine alkylation is not immediately explicable on the basis of the structure of the starting enamine. Stork[7a] has stated that the less substituted enamine is formed from unsymmetrical ketones and the same conclusion has been reached by Opitz[9]. Even 2-phenylcyclohexanone has been shown[10] to give the less highly substituted enamine by U.V. spectral data. However, House has since given the ratio of (11) to (12) as 85:15, quoting unpublished results of Berchtold[11] and recently Gurowitz[12] has shown that the position of the double bond is highly dependent both on the nature of the 2-substitutent and on the amine used. Although for 2-methylcyclohexanone the pyrrolidine enamine exists 90% in the less highly substituted form, the diethylamine enamine is only 25% in this form with the morpholine enamine intermediate at 50%. These authors discount the effect of basisity on double bond position and invoke a balance of steric factors and overlap of the nitrogen lone pair with the π-electrons of the double bond as an explanation. The existence of both isomeric forms in the enamines of aliphatic unsymmetrical ketones has been demonstrated by n.m.r. studies by two groups[13,14] and by the subsequent reaction with 4-nitrophenylazide[14]. It would,

therefore, appear that, as is the case with enolate anions, the product distribution is not entirely dependent on the structure of the starting enamine.

The main drawbacks in the use of vinyl ketones as the acceptor moiety in Michael reactions are their inherent instability and tendency to polymerise especially at elevated temperatures and in the presence of the basic catalysts frequently employed. In the mid-thirties, however, attempts were made to find suitable compounds which would have greater stability than vinyl ketones but which would break down under the prevailing reaction conditions to liberate the vinyl ketone in situ. Early attempts by Allen[15] and later Robinson[4] to use β-chloroketones as precursors were largely unsuccessful, but in 1935 Abdullah[16] condensed acetoacetic ester (13) with β-dimethylaminopropiophenone (14) at room temperature in the presence of sodium ethoxide to give (15). Here the base served as a catalyst both for the decomposition of the Mannich base to the vinyl ketone (1,R=Ph) and for the resultant Michael condensation. More recently it has been shown[17] that the quaternary salts of Mannich bases breakdown rapidly to give the vinyl ketone and the kinetics of the process have been investigated.

Mannich[18] in 1937 under similar conditions successfully condensed 2-dimethylaminomethylcyclohexanone (16) with acetoacetic ester and in the same year Robinson published the first of a series of papers[4,19] in which he used the quaternary salts of β-dialkylamino ketones as synthetic intermediates in reactions to form condensed cyclohexenone derivatives. These quaternary salts had the added advantage over the free Mannich base of increased thermal stability, but were still readily decomposed in the presence of basic condensing agents, such as sodamide or sodium ethoxide, and had the property of liberating the reactant at minimal concentration and optimal reactivity. In these reactions e.g. (17)→(18) the intermediate 1,5-diketone undergoes further aldol condensation and dehydration where possible under the reaction conditions to give a substituted cyclohexenone. Although this Robinson modification has been widely used[20], from the yields that are quoted it would appear that except in certain favourable circumstances these are rarely greater than 50%. This has, however, been improved by purification of the quaternary salts employed[21]. In general it would seem that the relative merits of the classical Michael condensation of the active methylene compound and the vinyl ketone and the Robinson modification via the Mannich base or its

methiodide must be assessed in any individual case.

Although the thermal instability of Mannich bases at elevated temperatures was well known, this property was not used systematically for alkylation purposes until 1952.

Snyder had also shown[22] that nitroparaffins and gramine(19) could be condensed in the synthesis of tryptamine derivatives and[23] that Mannich bases could readily undergo amine exchange reactions in the presence of other secondary amines. Lions[24], however, made use of the fact that Mannich bases break down smoothly when heated in the presence of active methylene compounds such as ketones, thiols and nitroparaffins to give in many cases good yields of the desired alkylated product. In some, but by no means all, cases Lions carried out the reaction without any added basic catalyst. Here the amine is again extruded from the reaction mixture, more volatile amines being preferred for this reason, and the reagent is said to be added across the resultant vinyl ketone. Somewhat surprisingly where the product is a 1,5-diketone capable of cyclisation, as in the secondary aldol reaction of the classical and Robinson Michael reactions, such reaction does not take place. The reaction by this thermal method is alleged

to be cleaner than the classical and Robinson procedures, yields are frequently higher, little polymer is formed and competing condensations are said to be minimised.

In none of the cases studied by Lions[24] was there any dubiety as to the site of alkylation and it is only when the reaction is applied to unsymmetrical ketones that its true nature is revealed. Thermal condensation[25] of 2-methylcyclopentanone (20) with either β-dimethylaminopropiophenone (14) or 4-dimethylanimo butan-2-one (21) gives exclusively 2,5-substituted products (22) and (23) and not 2,2-substitution as would have been confidently predicted by analogy with known classical Michael orientation. In addition, House[26] noted that by refluxing a mixture of cyclopentanone (24) and 4-diethylaminobutan-2-one (25), according to the method of Lions, a mixture of diketone (26) and diaddition product, the triketone (27), was obtained. It was noted that the orientation of alkylation in this case was again abnormal. It would appear that the modification of the Michael reaction developed by Lions is, in fact, a separate reaction, despite its being classified[27] as a Robinson-Michael reaction. The name thermal-Michael reaction has therefore been ascribed to it[25].

In the light of these findings it was decided to apply the thermal condensation of Mannich bases to a varied selection of active methylene compounds with a view to examining further the synthetic scope of the reaction. In particular, the orientation of substitution in unsymmetrical ketones required further study to establish the generality of the observed substitutional abnormalities. Thereafter, the mechanistic route of the process which had not yet been elucidated beyond a rationalisation[26,28] was worthy of more detailed investigation.

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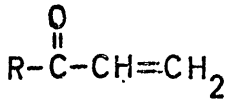

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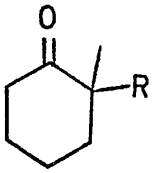
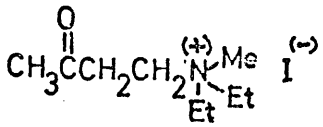


2 R=H

3 R=$CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$



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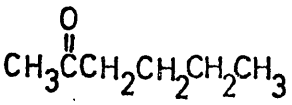

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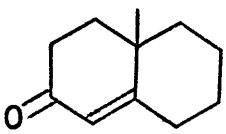

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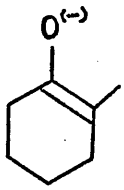

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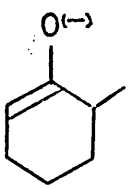

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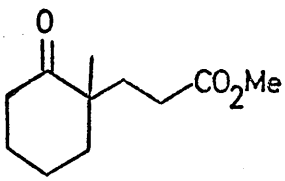

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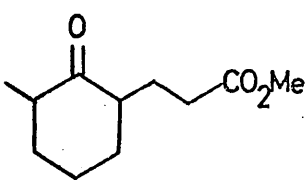

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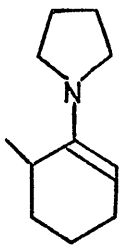

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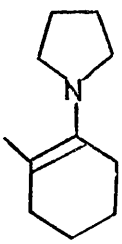

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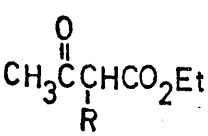
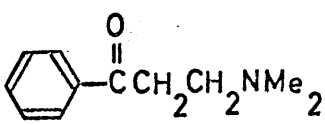


13 R=H

15 R=$CH_2CH_2\overset{O}{\overset{\|}{C}}Ph$



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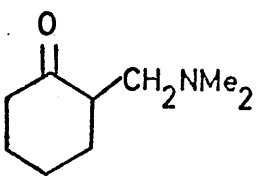

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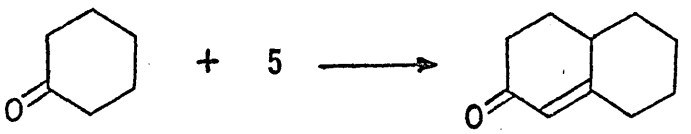

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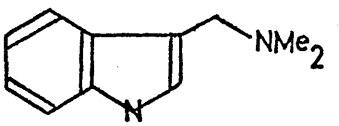

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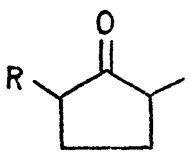

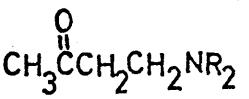

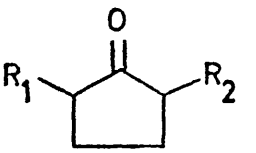

20 R = H

22 $R = CH_2CH_2C(=O)Ph$

23 $R = CH_2CH_2C(=O)CH_3$

21 $R = CH_3$

25 $R = CH_2CH_3$

24 $R_1 = R_2 = H$

26 $R_1 = H$; $R_2 = CH_2CH_2C(=O)CH_3$

27 $R_1 = R_2 = CH_2CH_2C(=O)CH_3$

DISCUSSION:

As an immediate extension of the condensation[1] of β-dimethylaminopropiophenone (1) and 2-methylcyclopentanone (2), this Mannich base was condensed with 2-methylcyclohexanone (3), following the general procedure of Lions[2]. This yielded 76% of a yellow viscous oil which showed three components on g.l.c. analysis in the ratio 17:2:1.

The first of these could be isolated from the crude product by crystallisation as a white solid, $C_{16}H_{20}O_2$. This showed a doublet methyl signal centred at 9.03τ (J=6cps) in the n.m.r. spectrum and had carbonyl absorption at 1712 & 1688cm^{-1} in the infra-red, corresponding to cyclohexanone and aryl ketone respectively. By comparison of this data along with the mass spectrum and g.l.c. retention time of an authentic sample, this was shown to be 2-methyl-2(β-benzoylethyl) cyclohexanone (4). The authentic sample was prepared by the reaction of phenyl vinyl ketone (5) and the pyrrolidine enamine of 2-methylcyclohexanone (6) under standard conditions[3]. The product, obtained in 74% yield, showed no depression in a mixed melting point with the material isolated from the original reaction mixture.

Careful preparative t.l.c. effected the separation of the two minor components. The first of these showed a similar n.m.r. spectrum to (4) with the absence of the methyl signal. This was

shown by complete spectral and g.l.c. comparison with an authentic sample to be 2-(β-benzoylethyl) cyclohexanone (7). This was prepared by the thermal condensation[2] of (1) and cyclohexanone and was obtained in 96% yield as a white solid with carbonyl absorption at 1712 & 1688cm^{-1} in the infra-red spectrum corresponding to cyclohexanone and aryl ketone respectively. The appearance of (7) must have been due to an impurity of cyclohexanone in the 2-methylcyclohexanone used in the reaction.

The third component also had a similar n.m.r. spectrum to (4), but exhibited a singlet methyl signal at 8.95τ and its infra-red spectrum had carbonyl absorption at 1707 & 1689cm^{-1}. By comparison of spectral and g.l.c. data this was shown to be identical to a sample of 2-methyl-2(β-benzoylethyl) cyclohexanone (8), prepared in 64% yield by the condensation[4] of phenyl vinyl ketone and 2-methylcyclohexanone in ethanolic potassium hydroxide.

It, therefore, appeared that the findings[1] concerning the orientation of alkylation in the cyclopentanone case were extendable to cyclohexanone. Since this reaction was obviously different, from the point of view of orientation, from both the classical and Robinson Michael reactions, some more detailed investigation of the mechanistic route was pertinent.

Since, in normal base catalysed Michael reactions with unsymmetrically substituted cycloalkanones, the predominant, if not exclusive, product is the more highly substituted isomer, the possibility existed that the observed product (4) is the kinetically controlled product. The fact that this kinetic control is in evidence would seem reasonable since the reaction times involved in the thermal reaction are short in comparison with the normal Michael reaction and the amine is removed from the reaction sphere by evaporation, so disturbing the hypothetical equilibrium. Accordingly, a sample of the 2,6-substituted product (4) was treated under the "equilibrating" conditions employed in the production of the 2,2-substituted product (8). However, on g.l.c. analysis of the products, no apparent change in the composition was noted and, consequently, the kinetic control hypothesis is invalid. This is in accordance with the findings of House[5] who has shown, by deuteration studies, that no appreciable conversion of (9) & (10) takes place in potassium tert-butoxide.

The effect of varying the temperature and time of the reaction on the product yield and distribution was then examined. When the reaction was run for 1 hour at 130°, the yield dropped to 62%

but no significant variation in the relative proportions of the 2,2 & 2,6-substituted products was observed on g.l.c. analysis. A more dramatic drop in yield was encountered when the reaction was carried out by heating for $2\frac{1}{2}$ hours at 110°, a mere 25% of product being recovered. Once again, the relative proportions of the two isomers were unaffected. It would seem, therefore, that the yield of product is enhanced by the use of elevated temperatures, a sufficiently high temperature being employed to ensure ready decomposition of the Mannich base. Experience has also shown (see later) that the use of prolonged reaction times of greater than around 1 hour add little to the yield.

An interesting side effect of this sequence of reactions the import of which will be discussed more fully below, has been caused by an impurity of cyclohexanone in the 2-methylcyclohexanone usedin the condensations. G.l.c. analysis showed this to be in the region of 5% and all attempts to remove it by fractionation were unsuccessful. The product of alkylation of this,(7), has been isolated, as described above. The proportion of this product relative to the normal alkylation product (4) was, however, found to increase as the temperature of the reaction was decreased in

the above sequence. Since, from the yield of total product and the percentage of (7) present in it, practically all the cyclohexanone impurity is being consumed in each reaction, it seems that, whatever the mechanistic course of the reaction is, it must be compatible with a greatly enhanced reactivity of cyclohexanone over 2-methylcyclohexanone.

Since Mannich bases are known[6] to decompose thermally into the amine and the vinyl ketone at the temperatures involved in the reaction, it could be argued that this is the initial step in the reaction. There are then three possible modes of condensation which should be considered. It is possible that 2-methylcyclohexanone (3) and phenyl vinyl ketone (5) undergo an uncatalysed thermal condensation. However, when a mixture of the two was refluxed for 30mins., only vinyl polymer could be obtained on removal of the excess ketone, and the reaction was not considered further.

The two other mechanisms might seem more plausible. These were that either a base catalysed Michael condensation with abnormal orientation takes place or that, following the formation of the dimethylamine enamine of (3), alkylation occurs by the normal enamine pathway. When β-dimethylaminopropiophenone (1) was condensed with diethyl malonate by refluxing for one hour at 140°, a 42% yield of

product was obtained. This was shown by g.l.c. analysis to consist essentially of a single component and further distillation yielded an analytical sample which exhibited the expected spectral characteristics of β-benzoylethyldiethyl malonate (11). The infra-red spectrum showed aryl ketone absorption at 1693cm^{-1} and the split carbonyl[29] of the substituted malonic ester at 1737cm^{-1} and 1754cm^{-1}. Since diethyl malonate is one of the most frequently used Michael donors and, in general, yields from Michael reactions involving it are comparable, if not greater, than for those with cyclohexanone, the comparatively low yield of product obtained is surprising. Diethyl malonate, of course, cannot form an enamine and so only the base catalyses route is effective here, and it is presumably by this mechanism that alkylation takes place. No indication of the orientation of substitution can be gleaned from this symmetrical case and so the base catalysed route was tested on the 2-methylcyclohexanone case.

A similar product distribution to the original thermal condensation would be envisaged if phenyl vinyl ketone, an amine and 2-methylcyclohexanone, in three-fold molar excess, were refluxed together. Any enamine formation, such as is required for the latter mechanism, would be precluded by the use of a tertiary amine

and, accordingly, 2-methylcyclohexanone, phenyl vinyl ketone and triethylamine were refluxed for 30 mins. The product which was obtained in 50% yield showed on g.l.c. analysis a mixture of (4) & (8) in the proportions 12:88% respectively. On the basis of previous base catalysed condensations, this was as expected and there is thus no compelling evidence for a base catalysed reaction.

The reaction was then repeated using two different secondary amines, diethylamine and pyrrolidine, both of which were capable of undergoing the enamine reaction required for the latter mechanism. This mechanism was originally suggested by House[7] who had obtained, from the thermal condensation of cyclopentanone and 1-diethylamino-butan-3-one (12), a mixture of the diketone (13) and the triketone (14). He stated that (14) presumably arose from formation of the diethylamine enamine of the cyclopentanone in(12) in the reaction vessel and reaction with a further molecule of methyl vinyl ketone. However, on refluxing diethylamine with phenyl vinyl ketone and 2-methylcyclohexanone it has been found that 42% of product is obtained showing a 38:62% composition of (4) & (8) respectively by g.l.c. analysis. The pyrrolidine reaction carried out in the same way yielded 34% of material shown to be (4) & (8) in the proportions 75:25%. Since neither of these reactions

exhibits the degree of selectivity found in the thermal reaction with the Mannich base (1), or that found later with (15) & (16), (see also later), the initial step in the mechanistic sequence cannot involve the breakdown of the Mannich base to amine and vinyl ketone but would seem to involve the Mannich base in its entirety. The product distribution in the above reactions is not, however, as markedly in favour of the 2,2-product as is normally expected in base-catalysed condensations. The 2,6-substituted product presumably arises via the formation of the enamine of 2-methyl-cyclohexanone, followed by condensation with the phenyl vinyl ketone. Thus the amines are acting both as bases and nucleophiles. The higher proportion of 2,6-product found in the pyrrolidine case is a measure of the greater ease of formation of enamines by this secondary amine.

The initial step of the reaction sequence, therefore, involves both the ketone and the Mannich base and the most reasonable combination of these is achieved by attack of the nitrogen lone pair on the carbonyl group of the ketone to give the zwitterionic intermediate (17). If this is indeed the case, then the use of the Mannich base hydrochloride instead of the free Mannich base should inhibit the reaction. In practice, when the hydrochloride of (1)

was refluxed with 2-methylcyclohexanone no alkylated products corresponding to (4) or (8) could be isolated.

It is envisaged that thermal decomposition of the zwitterionic adduct (17) then proceeds via a six membered transition state, (17) → (18) + (5) as shown, the charges being neutralised as a result. Carbinolamines, such as that (18) so formed, are known[8] to be intermediates in enamine formation although the detection[9] of such species by physico-chemical methods has not proved completely satisfactory. However, Triebs[10] has shown the intermediacy of the carbinolamine (19) in the condensation of 2-carbethoxycyclopentanone and benzylamine. This can be dehydrated smoothly by heating in benzene at 70°C to give the enamine (20). It seems reasonable, therefore, to assume that the carbinolamine (18) can dehydrate in a similar fashion to yield the enamine (21). The intermediacy of an enamine could account for the observed preferential alkylation of cyclohexanone over 2-methylcyclohexanone since enamines of the former are more easily prepared.

If an enamine is, in fact, an intermediate in the reaction then it should undergo thermal condensation with phenyl vinyl ketone to give on hydrolysis a similar product distribution to the original condensation. A mixture of phenyl vinyl ketone (5) and the enamine (6) of 2-methylcyclohexanone was refluxed for 15 mins. after dropwise

addition of the vinyl ketone over 15 mins. A molar equivalent of water was added and after further heating for 5 mins., a 33% yield of product was obtained on distillation. This showed the same product distribution as the original condensation by g.l.c. analysis. The low yield is accounted for by polymerisation of the vinyl ketone and decomposition of the enamine, the reagents not being liberated under such advantageous conditions as in the thermal reaction.

It was also found that when a mixture of phenyl vinyl ketone and water was added to the enamine as in the previous reaction, a 40% yield of product was obtained showing the same product composition by g.l.c. analysis. Again the yield is lower due to the poor conditions employed but from the results of these two experiments it would seem reasonable to suggest that after reaction of the enamine with the vinyl ketone, the mole of water liberated from the carbinolamine (18) suffices to produce the diketone (4) on hydrolysis of its preceding enamine.

The need for a lone pair of electrons to act as a nucleophile has already been demonstrated and that on nitrogen in Mannich bases has been shown to be suitable. The possibility of a

similar reaction utilising the lone pair on oxygen as an initial step, however, was not unreasonable, a hemi-ketal type of intermediate being formed, and it was decided to investigate this possibility before claiming the uniqueness of the enamine route. To test this β-acetoxypropiophenone (22) was prepared[11] and reacted under normal thermal conditions with both cyclohexanone and 2-methylcyclohexanone. These reactions gave product yields of 47 & 43% respectively which showed one similar major component on g.l.c. analysis. The material was isolated by preparative t.l.c. as a white solid, $C_{18}H_{16}O_2$. This showed a single carbonyl absorption at 1687cm^{-1} in the infra-red and its n.m.r. spectrum showed ten aromatic protons between 2.1 & 2.8τ, two vinyl protons 4.05τ & 4.32τ and four methylene protons between 6.8 & 7.3τ. From this data, this was assumed to be a dimer of phenyl vinyl ketone formed by decomposition of (22). On the basis of these findings it is proposed that the intermediacy of the enamine is unique and that the mechanistic course of the reaction to this point is as already determined.

Two explanations are possible for the formation of the small amounts of 2,2-substituted product (8) encountered in the thermal condensation with 2-methylcyclohexanone and (1). As has been

mentioned previously, the specificity of enamine alkylation is not[12] as great as at first thought[3] and the 5% of (8) could be explained as arising from the other double bond isomer of the enamine (23), which has been shown[13] to be present to the extent of 40% in the equilibrium. Another possible explanation is that the 2,2-substituted product arises from a small amount of initial thermal breakdown of the Mannich base followed by base catalysed condensation of the ketone and the vinyl ketone, the liberated amine serving as condensing agent.

One point which adds considerable weight to the scheme presently proposed for the reaction course over that proposed by House[7] is the efficiency of the reaction. If the scheme proposed by House, with initial breakdown of the Mannich base into vinyl ketone and dimethylamine were to operate, the efficiency of enamine formation by the extremely volatile amine must be outstanding. Yields of at least 95% of product have been obtained in the reaction of cyclohexanone with (1), the reaction liberating almost all the dimethylamine and being complete in 20 mins. This unusual efficiency would seem best explained by a scheme such as that proposed here which does not liberate the dimethylamine in gaseous form until alkylation is complete.

The remaining step in the reaction, the mechanism of the reaction of the enamine with the vinyl ketone is worthy of some comment. In his comprehensive paper on enamine alkylation[3], Stork represents the enamine alkylation of vinyl ketones as a typical electrophilic olefin type reaction (24) → (25) and, despite conceding that the reaction might be a Diels-Alder four-centre type, states that "in the absence of further data we see no reason to abandon the usual enamine alkylation mechanism". By analogy with the work of Longley[14] on enol ethers, Opitz[15] had proposed a dihydropyran intermediate for the addition of aldehyde enamines to $\alpha\beta$-unsaturated aldehydes e.g. (26) → (27) and a similar mechanism has been invoked[16] for the reaction of enamines with 2-chlorovinyl ketones. Cyclobutanes had also been proposed[17] as intermediates by Fleming and Harley-Mason in the addition of enamines to certain electrophilic olefins; but, in a more recent paper, Fleming[18], by extensive spectroscopic examination of the adducts of enamines and methyl vinyl ketone, states that the first formed product is a dihydropyran. The chemical reactions, however, indicate a ready equilibrium between the dihydropyran (28) with the cyclobutyl compound (29) via an immonium enolate intermediate.

By analogy with the work of Fleming[18] on the adduct formed by the pyrrolidine enamine of cyclohexanone and methyl vinyl ketone, the mechanism of enamine alkylation in the thermal condensation may be represented as in Scheme A. Similar initial dihydropyran formation may be envisaged from the dimethylamine enamine of 2-methylcyclohexanone and phenyl vinyl ketone to give the initial adduct. Such species are known to decompose even at room temperature to give the enamine of the alkylated product as shown the intermediacy of the zwitterionic species being a possibility. This on hydrolysis gives rise to the 1,5-diketone isolated from the condensation. Since the thermal reaction is carried out at a much higher temperature than normal enamine alkylations, yet another possible route may be considered, Scheme B. After initial formation of the dihydropyran as in Scheme A, elimination of the secondary amine would yield an unstable pyran species which, under the reaction conditions, would be expected to break down to the diketone (4). Whether, in view of the mobility of the dihydropyran intermediate found by Fleming[18] such amine elimination is likely is, however, a matter of some conjecture.

Because of the vigorous conditions employed in the reaction and the instability of the proposed intermediates both under these conditions and in the presence of the other reactants, it has not proved possible to isolate any of these to support the mechanistic Scheme. In the light of the available evidence and in view of the confirmatory results found in the application of the thermal Michael reaction to a range of active methylene compounds, the mechanistic sequence proposed would seem valid.

The reaction has been applied to a series of Mannich bases of the type (30) to test the effect of the secondary amine employed. The pyrrolidine Mannich base (16), which was unknown, was prepared in 87% yield by the condensation of acetophenone, paraformaldehyde and pyrrolidine hydrochloride, The hydrochloride was obtained as white prisms, mpt 158-9°. The free base was condensed with 2-methylcyclohexanone by refluxing for half an hour at 165° and this yielded on distillation 67% of product. G.l.c. analysis showed this to have a similar product distribution to the dimethylamino case.

The diethylamino Mannich base (15) was prepared by the method of Blicke[19] and was condensed under the above conditions with 2-methylcyclohexanone. Repeated condensations, however, could not hoist the yield of distilled product over 50%. G.l.c. analysis showed the same proportions of 2,2 & 2,6-products (4) & (8) but an enhanced proportion of the extraneous (7).

The morpholino Mannich base (31) was prepared by the method of Lions[20]. The condensation of this with 2-methylcyclohexanone gave, as the best yield, 53% of product, shown by g.l.c. analysis to have a similar composition to that obtained from the diethylamino-Mannich base. A similar product distribution was observed in the condensation of 2-methylcyclohexanone with the piperidino-Mannich base (32) which had been prepared by the method of Mannich[21], the yield of distilled product in this case being only 35%.

Some relevant conclusions as to the synthetic usefulness of the respective Mannich bases can be drawn from the results above. It appears that, of the amines used, dimethylamine and pyrrolidine are the most efficient. Of these, dimethylamine is the more convenient in practice, since it is almost completely

extruded from the reaction vessel in the course of the reaction. This fact has already been noted by Lions[2]. The basicity of the amine is obviously of no relevance since no clear pattern can be drawn between the product yield and basicity; but of more importance would appear to be the rate of enamine formation of the various amines. No overall picture is available since the practical methods used vary but the known sequences of rates pyrrolidine > morpholine > piperidine[22] and dimethylamine > diethylamine[13] are mirrored in the product yields. The rate controlling step in enamine formation is[22] the dehydration of the intermediate carbinolamine and, if this is paralleled in the thermal Michael reaction, the yields from the various Mannich bases would be expected to be as above. The most suitable base, therefore, would seem to be the dimethylamino and this has been the Mannich base of choice in the further examination of the scope of the reaction.

The thermal Michael reaction has been applied to a short series of β-ketoesters and has proved a successful alkylation method, substitution taking place on the more highly substituted alpha position to the ketonic carbonyl group.

The condensation of β-dimethylamino-propiophenone (1) and acetoacetic ester (33) yielded 68% of a clear oil which was shown by g.l.c. analysis to be greater than 90% pure. The product gave a positive ferric chloride test and was shown to have a parent ion at $^{m}/e$ 262 by gas chromatograph/mass spectrometer analysis. Its infra-red spectrum showed carbonyl absorptions at 1692;1720 & 1748cm^{-1} corresponding to aryl ketone, methyl ketone and ester respectively and the n.m.r. spectrum, with a methyl ketone signal at 7.73τ and ester methyl at 8.73τ, was also consistent with the expected product (34). The identity of the product was further confirmed by comparison with a sample prepared by normal base catalysed condensation[4] of phenyl vinyl ketone (5) and acetoacetic ester in ethanolic potassium hydroxide. This was obtained as white needles, mpt 111-2° from benzene and showed identical spectral and g.l.c. properties to the material prepared via the thermal route. This compound had already been prepared by Abdullah[23] by the condensation of (1) and (33) in the presence of sodium ethoxide and a melting point of 120° from ethanol is quoted.

The condensation of β-dimethylaminopropiophenone(1) and 2-carbethoxycyclohexanone (35) proceeded in 70% yield to give a yellow oil shown by g.l.c. analysis to consist of two compounds in the ratio 1:3. Combined gas chromatograph/mass spectrometer analysis showed these to have molecular weights 244 & 302 respectively. The former was shown to be 2(β-benzoylethyl)-cyclohexanone (7) by comparison of the mass spectrum breakdown pattern and g.l.c. retention time with those of an authentic sample. Since the purity of the starting keto ester had been established by g.l.c. analysis, this product can only have occurred by decarbethoxylation of the mono-alkylated product (36) during the course of the reaction. The compound of molecular weight 302, which was isolated in a slightly impure state by preparative t.l.c., gave a negative ferric chloride test and showed no bathochromic shift in its u.v. spectrum on the addition of base. In the light of this and additional spectral data, this was thought to be the mono-alkylated product 2-(β-benzoylethyl)-2- carbethoxycyclohexanone (36). This was confirmed by comparison with an analytically pure sample of (36) prepared in 68% yield by the base catalysed

condensation of phenyl vinyl ketone and 2-carbethoxycyclohexanone. This material showed identical g.l.c. and spectral properties to the material obtained from the thermal reaction with carbonyl absorptions in the infra-red at 1692;1716 & 1739cm^{-1} corresponding to aryl ketone: cyclohexanone and ester respectively and the characteristic ethyl ester signals in the n.m.r. spectrum.

A similar thermal condensation was effected with 2-carbethoxycyclopentanone (37) to yield 65% of a pale yellow oil which showed two products by g.l.c. analysis in the ratio 1:4. Combined gas chromatograph/mass spectrometer analysis of these showed them to have molecular weights 216 & 288, and, by analogy with the previous experiment, these were considered to be 2(β-benzoylethyl) cyclopentanone (38) & 2(β-benzoylethyl)-2-carbethoxycyclopentanone (39) respectively. The former was confirmed by comparison of g.l.c. retention times with an authentic sample[24]. The latter, which had been isolated by preparative t.l.c. was compared by complete spectral and g.l.c. analysis with an analytically pure specimen prepared in

66% yield by base catalysed condensation of phenyl vinyl ketone and 2-carbethoxycyclopentanone. This product gave a negative ferric chloride test and no bathochromic shift in the u.v. spectrum or the addition of base. It showed carbonyl absorptions at 1690;1732 & 1744cm^{-1} in the infra-red spectrum corresponding to aryl ketone, ester and cyclopentanone respectively and had the expected n.m.r. spectrum.

It is noteworthy that in all these cases of alkylation of β-ketoesters, the site of attachment is the more highly substituted carbon atom. This is at variance with the normal orientation observed[3] in alkylation of enamines and with the work of Pelletier[25] who gives the structure (4) for an enamine of this type, which is found to alkylate on the less highly substituted position with methyl vinyl ketone to yield (41). It is possible that the combination of the steric bulk of the pyrrolidine group and the conjugative effect of the benzene ring are of significance in this case. Certainly, the enamines of 2-carbethoxycyclohexanone with the less sterically demanding ammonia[26](42) and cyclohexylamine[27](43) have been shown to be in the fully conjugation position. In addition, the dimethylamine enamine of 2-carbethoxycyclopentanone (44),

which is a proposed intermediate in the condensation in question, has been assigned[28] the fully conjugated structure on the basis of its ultra violet maximum at 309m μ

This enamine (44) was prepared by a slight modification of the original method[28] by bubbling a stream of dry dimethylamine gas through a stirred solution of the β-ketoester with the addition of anhydrous potassium carbonate. The product obtained gave a negative ferric chloride test and was therefore free of β-ketoester. From its ultra violet absorption at 305mμ (ε=10,500) and the absence of a vinyl proton in the n.m.r. spectrum, it would appear that this is, in fact, the fully conjugated, but sterically less favourable structure (44), rather than the alternative (45).

When this enamine was alkylated with phenyl vinyl ketone in the normal way, there was obtained a 59% yield of product which was shown by g.l.c. analysis to contain the two products (38) & (39) obtained in the thermal reaction. Despite the apparent abnormality of the alkylation orientation in the case of β-ketoesters, it would, therefore, seem that this is consistent with the intermediacy of an enamine in the proposed mechanistic scheme.

The condensation of β-dimethylaminopropiophenone (1) with an aliphatic aldehyde of suitable volatility, n-hexaldehyde (46), was successfully carried out in 77% yield by refluxing for 1 hour at 135°. This high yield is once more consistent with the mechanistic requirements proposed earlier. The distilled product showed a single peak on g.l.c. analysis; and aromatic protons (5 x H, multiplet) between 2.0 & 3.0τ and an aldehydic proton at 0.4τ (1 x H, doublet, J= 2.5cps) in the n.m.r. spectrum. Its infra-red spectrum showed two carbonyl peaks at 1692 & 1728cm^{-1} corresponding to aryl ketone and aldehyde respectively. On standing or on attempts to induce crystallisation, the oil solidified to give white feathery needles, mpt 94° (60 - 80 petrol). These analysed for $C_{15}H_{20}O_3$ and had a different retention time under the above g.l.c. conditions. Re-examination of the infra-red spectrum showed that this solid material had no 1728cm^{-1} absorption but had a 1707cm^{-1} peak and a broad hydroxyl band from 3440 to 3600cm^{-1}. The n.m.r. spectrum showed no aldehyde proton but a low field proton at -0.1τ. Since the material was also base soluble, it appears that the crystalline product is 2-(β-benzoylethyl) caproic acid (47) produced by air oxidation of the initially formed 2(β-benzoylethyl) hexaldehyde (48)

The effect of a para-substituent in the benzene ring of the Mannich base has been briefly investigated. β -dimethylamino-p-bromoacetophenone (49) was liberated from its hydrochloride[30] in the normal way and condensed with cyclohexanone by refluxing at 160° for 30 mins. After removal of the excess ketone, this yielded 81% of a solid product, mpt 68-9° (40 - 60 petrol). This was shown by elemental analysis and spectral data to be 2(3'-p-bromophenyl-3'-oxopropyl) cyclohexanone (50). This showed carbonyl absorption at 1690 & 1712cm^{-1} corresponding to aryl ketone and cyclohexanone in the infra-red and a characteristic A_2 B_2 system between 2.0 & 2.5 τ(J = 9cps) in addition to the expected methylene signals in the n.m.r. spectrum. The introduction of the p-bromo substituent, although it has depressed the yield slightly, still constitutes an efficient alkylation method.

The corresponding Mannich base from p-methylacetophenone (51) was prepared[31] and condensed with 2-methylcyclohexanone by refluxing for 30 mins. at 165°. This yielded 71% of product shown by g.l.c. analysis to consist of four components corresponding to 70 : 10 : 5 : & 10% of total product respectively. The first

three components were identified by the separation of samples by preparative t.l.c. and comparison of spectral data and g.l.c. retention times with those of authentic samples. These were shown to be 2-methyl -6(3'-p-tolyl-3'-oxopropyl) cyclohexanone (52); 2(3'-p-tolyl-3'-oxopropyl) cyclohexanone (53) & 2-methyl -2(3'-p-tolyl-3'-oxopropyl) cyclohexanone (54) respectively.

The first of these was prepared by the condensation of the pyrrolidine enamine of 2-methylcyclohexanone (6)[3] with p-tolyl vinyl ketone (55), prepared by steam distillation of the hydrochloride of the Mannich base (51). This yielded 68% of a pale yellow oil which on redistillation solidified to give white crystals, mpt 68-9° (40 - 60 petrol). This showed a single peak by g.l.c. analysis under the above conditions. The infra-red spectrum showed carbonyl absorption at 1688 & 1712cm^{-1} corresponding to aryl ketone and cyclohexanone and the n.m.r. spectrum showed methyl resonances at 7.65 τ (3 x H, singlet) for the aromatic and 9.07 τ (3 x H, doublet, J = 6cps) for the C - 2 methyl.

The second compound (53) was prepared by the thermal condensation of β-dimethylamino-p-methylpropiophenone (51) and cyclohexanone by refluxing for 30 mins. at 165° and was obtained on distillation in

82% yield as a white solid, mpt 78 - 78.5° (40 - 60 petrol/benzene). This material had a similar retention time under the above conditions. The infra-red spectrum showed carbonyl absorptions at 1686 & 1711cm^{-1} for aryl ketone and cyclohexanone and the n.m.r. spectrum was similar to that of (52) with the absence of the methyl doublet.

The third (54) was prepared by the condensation of p-tolyl vinyl ketone (55) and 2-methylcyclohexanone in the presence of ethanolic potassium hydroxide. This was obtained in 52% yield as an oil which showed a single peak by g.l.c. analysis. It showed carbonyl absorptions at 1689 & 1710cm^{-1} in the infra-red corresponding to aryl ketone and cyclohexanone but had a singlet methyl resonance at 8.89τ in the n.m.r. spectrum.

The final product could be obtained as white needles, mpt 89 - 90° by crystallisation from the crude distillation product with ethanol. This had elemental composition $C_{20}H_{20}O_2$, showed a single carbonyl absorption at 1686cm^{-1} in the infra-red spectrum and had a parent ion at $^{m}/_{e}$ 292 in the mass spectrum. The n.m.r. spectrum showed aromatic protons (8 x H) between 2.1 & 2.9τ; aromatic methyls (6 x H, singlet) at 7.62τ; vinyl protons (2 x H) at 4.15 & 4.45τ&

methylene protons (4 x H, multiplet) between 6.8 & 7.3τ. From the available data, this was presumed to be a dimer of p-tolyl vinyl ketone. Double irradiation experiments in the n.m.r. spectrum failed to produce any simplification of the vinyl region indicating that two separate types of vinyl proton were present. This favoured the structure (56) for the dimer and this was confirmed by the production of a methyl resonance at 8.86τ in the n.m.r. spectrum on hydrogenation of the product on 5% palladium/charcoal in ethyl acetate. None of the other possible combinations would have produced this signal.

A proposed mechanistic route to this product is shown in Scheme C. The initial Diels-Alder reaction of αβ-unsaturated carbonyl compounds acting as dienes is well known[32] and the production of the product in this fashion would seem reasonable. The structure of this product is of interest in view of other results on the dimerisation of vinyl ketones produced from Mannich bases. Mannich[33] obtained the symmetrically substituted product (57) from the pyrolysis of the dimethylamino Mannich base of cyclohexanone (58). Roth[34], however, obtained the

dihydropyran derivative (59) from the acetolysis of the piperidino Mannich base of cyclohexanone (60), a product which would yield an alternative structure. In addition, the latter author indicated a similar product from the cycloheptanone Mannich base (61)[35] and from the cyclopentanone analogue (62)[36] obtained the linear dimer (63). The dimerisation of phenyl vinyl ketone has been shown by Alder[37] to give the dihydropyran (64). This is contrary to the expected Diels-Alder product (65) on the basis of bond polarity and would also fail to give a structure consistent with (56).

From the results obtained in the application of the thermal reaction with cyclic ketones to date, it would appear that this may be used with considerable success. However, in the next three examples there is evidence that the potential of the reaction is not as widespread as the earlier findings might lead one to hope.

Following the successful condensation of β-dimethylamino-propiophenone (1) with 2-methylcyclopentanone[1] and 2-methyl-cyclohexanone, the reaction was extended to the homologue, 2-methylcycloheptanone (66); but, despite repeated attempts, no yield greater than 30% of crude product has been obtained

from this condensation. This makes poor comparison with yields of around 75% obtainable with the five & six-membered ring cases. A reflux time of 45 mins. at 170° for (1) & (66) yielded 30% of product. G.l.c. analysis of this showed the presence of four components, accounting for 30 : 15 : 5 & 50% of total product respectively. Attempts to separate analytically pure samples of these by preparative t.l.c. were unsuccessful and recourse was made to gas chromatograph/mass spectrometer analysis. This showed the four components to have molecular weights 340; 258; 258 & 264 respectively.

From examination of the mass spectrum of the first and comparison of this and g.l.c. retention times with an authentic sample, this was found to correspond to 2(β-benzoylethyl) cyclohexanone (7). The original 2-methylcycloheptanone had been prepared by treatment of cyclohexanone with diazoethane and although a g.l.c. analysis of the product of this reaction had shown it to be greater than 95% pure, this must account for the occurrence of (7) in the products. The fact that such a minor impurity can appear as a viable product is a striking example of the relative reactivities of 2-methylcycloheptanone and cyclohexanone under the reaction conditions.

The second and third products have the expected molecular weights for mono-alkylated products and are presumably 2-methyl-7 (β-benzoylethyl) cycloheptanone (67) & 2-methyl-2-(β-benzoylethyl) cycloheptanone (68). Although no definite assignment of which is which can be made, in all other reactions involving unsymmetrical alicyclic ketones, the less highly substituted product has been formed in excess and has had the shorter retention time by g.l.c. analysis on QF 1: APL & SE30 columns. It might, therefore, be reasonable to assume that these are (67) & (68) respectively.

The final product, by a similar investigation of g.l.c. properties and mass spectra to that employed with the first, would appear to be the dimerised phenyl vinyl ketone (75) isolated earler. This product, as will become apparent, is a feature of the reaction products wherever the active methylene compound involved in the condensation is either relatively unreactive or forms an enamine with difficulty.

The thermal condensation is therefore not applicable as a synthetic route from 2-methylcycloheptanone. This might have been anticipated since the enamine of 2-methylcycloheptanone is not reported in the literature and current attempts to form it have proved unsuccessful.

A useful and readily accessible starting material for potential synthetic routes to terpenoid structures, in view of its built-in isopropyl group, would be menthone (69). In line with the general orientation of the thermal condensation this would be expected to alkylate on the unsubstituted carbon atom, α to the carbonyl group. Condensation of menthone and β-dimethylaminopropiophenone (1) by refluxing at 200° for 30 mins. yielded 31% of product boiling at 160-5°/0.5mm. G.l.c. analysis showed the presence of one major component. This was obtained as a crystalline solid mpt. 128° (benzene/petrol) by preparative t.l.c. and was shown by mixed melting point and g.l.c. comparison to be dimerised phenyl vinyl ketone (75). Thus virtually no condensation on menthone has taken place, a fact in agreement with the reluctance[38] of menthone to undergo enamine formation due to the steric inhibition of the neighbouring isopropyl function.

Yet another alicyclic ketone which, on the basis of the observed reactivity effects, might be expected to give a poor yield of product is 2,6-dimethylcyclohexanone (70). Here again the steric effect of the two methyl groups inhibits enamine formation and when this was condensed with β-dimethylamino-propiophenone (1), the best obtainable yield was 40%. G.l.c.

analysis showed this material to consist of two components. Attempts to separate these by preparative t.l.c. were unsuccessful but gas chromatograph/mass spectrometer analysis of the mixture showed them to have molecular weights 258 & 264 respectively. The latter was shown by g.l.c. data and mass spectral breakdown pattern to be identical with the phenyl vinyl ketone dimer (75). The other was presumed to be the expected alkylation product (71) from its molecular weight and general breakdown pattern. However, all further attempts to isolate a pure sample of this for analytical purposes proved unsuccessful. This may have arisen either via the enamine or more likely by base catalysed Michael condensation following the thermal decomposition of the Mannich base.

Although enamines of aliphatic ketones are known[39] to form less readily than those of favourable alicyclic ketones, methyl n—amyl ketone (72) was alkylated with β-dimethylamino-propiophenone (1). These were refluxed for 2 hours at 150° and on distillation a 57% yield was obtained. This showed on g.l.c. analysis one major and two minor components comprising 10 : 85 & 5% of the total product. The last was identified

by g.l.c. retention time with an authentic sample of the phenyl vinyl ketone dimer. The first two, which could not be separated in pure form, both showed a parent ion at $^{m}/e$ 246 by gas chromatograph/mass spectrometer analysis. The former showed the characteristic $^{m}/e$ 71 & 147 peaks expected from the structure (74) from fragmentation[40] on either side of the aliphatic carbonyl group. These peaks were absent in the former compound which showed instead the peak at $^{m}/e$ 203 expected from the isomeric (73) by a similar fragmentation procedure. The yield in this case, although lower than in the alicyclic cases, is tolerable and is in the region expected on the basis of ease of enamine formation.

Since the thermal reaction of Mannich bases with saturated alicyclic ketones had proved, in most cases where enamine formation is favoured, a suitable condensation method, it was decided to extend this to a series of αβ-unsaturated ketones. The formation of dienamines from such species is known[41] and, on the basis of previous findings, a moderate yield of alkylated product might be predicted. An interesting feature of such a reaction is that the αβ-unsaturated ketone is acting, in effect, as a donor in the Michael reaction. Although the participation of αβ-enones as

donors is known[42], there are relatively few examples considering the availability of the requisite enones and the ubiquitous nature of the Michael reaction in synthetic organic chemistry.

The thermal condensation of mesityl oxide (76) and β-dimethylaminopropiophenone yielded 69% of product, which was shown by g.l.c. analysis to consist of one major component. Gas chromatograph/mass spectrometer analysis showed this to have the expected molecular weight for a mono-alkylated product, with parent ion at $^{m}/e$ 230. The base peak was at $^{m}/e$ 83, caused by α-cleavage[40] of the ketone function as shown in (77). Thus alkylation has taken place to give a product substituted on the side of the carbonyl group opposite the double bond. This was confirmed by the n.m.r. spectrum of a solid sample, obtained by preparative t.l.c., which showed a vinyl proton at 3.84τ, in addition to only two singlet methyl signals at 7.86 & 8.15τ. Since αβ-unsaturated ketones are known to alkylate on the α-position of the enone system, both by base catalysis[43] and via an enamine intermediate[41b], this product was unexpected. However, a more recent investigation[44] of the behaviour of the pyrrolidine and morpholine enamines of isophorone (78) on alkylation with Michael acceptors has indicated a more complex pattern.

In an attempt to investigate the generality of this substitution, the condensation was applied to a similarly substituted alicyclic αβ-enone, isophorone (78). Condensation of this with β-dimethylaminopropiophenone was effected by a 1 hour reflux at 200° and gave a 71% yield of product. Trituration of the distillate with ether gave a crystalline material, m.pt. 183°, accounting for 35-40%of the total. This showed carbonyl absorption at 1688 & 1733cm^{-1} in the infra-red spectrum and only acetophenone absorption in the u.v. spectrum. The n.m.r. spectrum showed three singlet methyl reconances at 8.72: 8.91 & 9.01τ and a sharp triplet at 6.17τ (J=8.8cps), integrating for a single proton, but no vinyl signal. In addition, the compound had the composition $C_{18}H_{20}O_3$ by elemental analysis and showed a corresponding parent ion at $^{m}/_{e}$ 284 in its mass spectrum. On the basis of these data, a consistent structure could not be formulated and, in particular, the presence of the extra oxygen atom and the low field triplet in the n.m.r. spectrum could not be explained.

An analagous product, $C_{18}H_{19}O_3Br$, was obtained by the reaction of isophorone with β-dimethylamino-p-bromopropiophenone (49), which gave a 60% yield of distilled product of which the compound isolated comprised 35%. This showed similar spectroscopic

features to the non-brominated material, with carbonyl absorption at 1735 & 1684cm^{-1} in the infra-red spectrum, but with the aromatic protons appearing as an A_2 B_2 quartet in the n.m.r. spectrum.

An X-ray structural analysis of this material has been undertaken by Drs. A.F.Cameron and G.Ferguson (See appendix) and its structure has been shown to be the bicyclic triketone (79). The non-brominated material may then be ascribed the corresponding structure (80). Even with this knowledge, the low-field triplet in the n.m.r. spectrum may not be confidently assigned. However, on treatment of a sample of (80) in dioxan with sodium deuteroxide, the triplet disappeared. The signal is, therefore, due to the enolisable C-2 proton, which is strongly deshielded by a conformationally frozen aroyl group. Since the aromatic protons in (79) appear as a symmetrical A_2 B_2 quartet, the aromatic ring is free to rotate about the Ph - CO bond, but a study of molecular models confirms that non-bonded interactions severely limit rotation about the CO — C-2 bond and the C-2 proton is permanently in the deshielding zones of the carbonyl group and the aromatic ring.

The appearance of the extra carbonyl group must be attributed to peroxide or hydroperoxide present in the isophorone employed, and co-distilling with it, since tests for peroxide on the starting ketone later proved positive. Such base catalysed conversion of hydroperoxides is well authenticated[45] and the production of (80) presumably occurs via the route (81) → (82) → (83) → (80). The exact position of hydroperoxide decomposition in the sequence has not been elucidated.

In addition to this product, two other significant products were observed. The first, which was not isolated, was present in 15-20% in g.l.c. analysis and was shown to correspond to the mono-alkylated product (84) isolated later. The other, present in 35%, was isolated in an impure state by preparative t.l.c. This showed a vinyl proton at 4.18 τ & two methyl signals at 7.88 τ (3 x H, singlet) & 9.01 τ (6 x H, singlet) in the n.m.r. spectrum. This suggested the structure (85) for the product and this was confirmed by comparison with an analytical sample isolated from the condensation of the enamine (86) with phenyl vinyl ketone.

Since the orientation of alkylation was different from that which would be expected by alkylation of dienamines, the morpholine dienamine of isophorone (86) was prepared[41a] and alkylated with phenyl vinyl ketone by the normal method. This gave on distillation a 69% yield of product which showed on g.l.c. analysis four components preparative t.l.c. enabled the separation of three fractions. The first and major, accounting for around 70% of the total, contained two peaks by g.l.c. analysis but from the spectral data and the solid nature of the product, the existence of two distinct compounds is not confirmed. This showed two carbonyl peaks in the infra-red spectrum at 1665 & 1689cm^{-1} and along with the absence of a vinyl proton in the n.m.r. spectrum showed methyl signals at 9.02 τ(6 x H, singlet) and 7.78 τ(3 x H, singlet). This would appear to be the'normal' enamine product (84). The next accounting for 10% of product could not be ascribed a fixed structure on the basis of the available data but in view of its n.m.r. spectrum which showed three distinct methyl signals at 7.65: 8.83 & 9.05τ and a vinyl proton at 4.03τ would appear to be another mono-alkylated product, possibly (87). The final

product, again accounting for around 10% of total, showed two carbonyl peaks at 1669 & 1686cm^{-1} in the infra-red spectrum. Its n.m.r.spectrum had a vinyl proton at 4.07τ and methyl signals at 7.80τ (3 x H, singlet) and 8.98τ (6 x H, singlet). This would appear to be the mono-alkylated product (85).

It would, therefore, appear at first sight that the thermal reaction with αβ-enones cannot proceed through an enamine intermediate, since the predominant site of alkylation differs markedly. However, in the light of the recent findings[44] on the enamines of isophorone where 'abnormal' orientation results were also found, a possible rationalisation appears. If, of the two possible isomeric enamines (88) & (89), the former is the more reactive, then, since the rate of equilibrium between the two forms would be greatly enhanced at the temperatures used in the thermal reaction, preferential reaction of this form might occur. Although some attempts[46] have been made to investigate this equilibrium at higher temperatures, no meaningful conclusions have been drawn from the results.

Although good yields of product had been obtained in the previous reactions, when β-dimethylaminopropiophenone was condensed with cyclopentenone (90) by refluxing for half an hour

at 140°, only a non-distillable tar was obtained from which no observations of product distribution could be made. This is, presumably, due to the extreme instability of the starting enone under most reaction conditions.

The same Mannich base was condensed with 3-methylcyclohexenone (91) by refluxing for 45 mins. at 200°. This gave, on distillation, 71% of product which showed three components by g.l.c. analysis and attempts to separate these by preparative t.l.c. were unsuccessful. . N.m.r. analysis of the mixture showed the presence of a vinyl proton at 4.15 τ and a triplet centred on 6.30 τ (J=8cps). In addition, two types of methyl signal were present, a singlet at 9.13 τ and a doublet at 8.06 τ (J=2cps). On the basis of the products observed in preceding experiments, along with the n.m.r. findings and integration, it might be suggested that these include the mono-alkylated ketone (92) and the bicyclic ketone (93) as the two major products.

Finally, the condensation was applied to 10-methyl-$\Delta^{1:9}$-octalone-2 (94) and reflux of this for 1 hour at 200° with β-dimethylaminopropiophenone yielded, on distillation, 61% of product. G.l.c. analysis of this showed the presence of one

major and two minor components. Gas chromatograph/mass spectrometer analysis showed the major component to have molecular weight 296, that expected from a mono-alkylated product. A pure sample of this could be isolated by preparative t.l.c. and this showed a singlet methyl signal at 8.80τ and no vinyl proton in the n.m.r. spectrum. This excluded the structure (95) which might have been expected on the basis of the foregoing results and the presence of a single carbonyl peak at 1684cm^{-1} in the infra-red spectrum confirmed the structure as (96). This compound was also obtained as the predominant product in the condensation of the morpholine enamine of the octalone with phenyl vinyl ketone, which proceeded in 61% yield. Thus, in the case of the octalone, alkylation takes place prodominantly on the α-position of the enone system and not on the methylene adjacent to the carbonyl. This fact might be attributed to the relative reactivities of the isomeric enamines (97) & (98) in the alkylation step. Presumably the more highly conjugated isomer (97) which has in addition a more highly substituted double bond

system, has a greater preference to alkylation over the other (98) in the octalone case than in the monocyclic and acyclic cases.

Although the thermal condensation is found to give good yields of alkylated products with αβ-enones, the product complexity in certain cases is greater than might be tolerated for synthetic purposes. However, the more detailed investigations[44] of the alkylations of preformed enamines with Michael adducts shows a similar uncertainty in exact product distribution. With the thermal reaction, most striking is, perhaps, the duality of orientation of substitution found in the cases studied but it is possible that in certain cases, especially where the product may by readily isolated in crystalline form (eg. mesityl oxide), the abnormal orientation found could be of some synthetic value.

EXPERIMENTAL

GENERAL:

Melting points were recorded on a Kofler microscope hot stage and are uncorrected. Routine infra red spectra of liquid films and nujol mulls were recorded on a Unicam SP 200 spectrophotometer. Solution spectra were determined on a Unicam SP 100 double-beam spectrophotometer equipped with an SP 130 sodium chloride prism grating double beam monochromator, operated under vacuum conditions, and a Perkin Elmer 225 spectrophotometer. Ultra violet absorption spectra were determined on a Unicam SP 800 spectrophotometer in ethanolic solution.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on Perkin Elmer R 10 (60 megacycle) and Varian HA 100 (100 megacycle) spectrometers, using approximately 0.3 molar solutions in deuterochloroform with tetramethylsilane as internal standard.

Gas liquid chromatography (g.l.c.) was carried out on Pye Argon and Perkin Elmer F 11 chromatographs. Both analytical and preparative thin layer chromatography (t.l.c.) employed Kieselgel G silica and were developed with iodine vapour unless otherwise stated. Preparative t.l.c. was carried out on plates 0.5mm thick.

Mass spectra were recorded on AEI MS 9 and MS 12 spectrometers and combined gas chromatography/mass spectrometry determinations were made on an LKB 900 spectrometer.

β-dimethylaminopropiophenone hydrochloride

This was prepared in 74% yield as in Organic Syntheses [47] and was obtained as white needles, m.pt. 153-5° (20% ethanol/acetone). The free base (1) was liberated by dissolving the hydrochloride in water, adding 4N sodium hydroxide until the base was completely freed and extracting with ether. The ethereal extracts were washed with brine, dried and evaporated to yield around 90% of the free base (1) which solidified on standing in the refrigerator.

Condensation of β-dimethylaminopropiophenone (1) and 2-methylcyclohexanone (3)

A mixture of 2-methylcyclohexanone (10.0g.; 0.09m.) and β-dimethylaminopropiophenone (5.15g.; 0.03m.) was refluxed under an air condenser for 30 min. at 165°, by which time evolution of dimethylamine from the reaction mixture had subsided. On cooling, the mixture was neutralised with glacial acetic acid, diluted with ether and extracted with brine. The ethereal solution was dried, the ether and excess 2-methylcyclohexanone removed under water pressure and the residue distilled in vacuo to give 5.5g.(76%) of a yellow oil, b.pt. 145-150°/0.05mm., which solidified on standing. G.l.c. analysis on 5% QF 1 at 200° showed the presence of three compounds with retention times of; (a) 5.55 min., (b) 6.00 min., (c) 6.57 min. in the proportions 85;10; and 5% respectively.

Compound (a) could be isolated from the distillate by crystallisation from 40-60 petrol, m.pt. 52°, as white prisms. Found C,78.79; H,7.95. $C_{16}H_{20}O_2$ requires C,78.65; H,8.25%. This showed $\gamma_{C=O}^{CCl_4}$ 1712 cm^{-1} (cyclohexanone) and 1688 cm^{-1} (aryl ketone) in the infra red spectrum, a doublet methyl signal centred at 9.03τ(J = 6cps) in the n.m.r., and a parent ion at m/e 244 in its mass spectrum. This compound was deduced to be 2-(β-benzoylethyl)-6-methylcyclohexanone (4) and confirmed by comparison with an authentic specimen. Samples of compounds (b) and (c) were isolated from the reaction mixture by careful preparative t.l.c. Compound (b) showed a similar n.m.r. spectrum to (a) but no methyl signal was present. Its infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1688 cm^{-1} (aryl ketone) and 1712 cm^{-1} (cyclohexanone). This was concluded to be 2-(β-benzoylethyl)-cyclohexanone (7) and was confirmed by comparison with an authentic sample. Compound (c) also showed a similar n.m.r. spectrum to (a) but had a singlet methyl resonance at 8.95τ. It showed $\gamma_{C=O}^{CCl_4}$ 1689 cm^{-1} (aryl ketone) and 1707 cm^{-1} (cyclohexanone) in the infra red spectrum. By comparison with an authentic sample this was shown to be 2-(β-benzoylethyl)-2-methylcyclohexanone (8).

2-methyl-1-pyrrolidinocyclohex-6-ene (6)

This was prepared by the method of Stork [3] in 72% yield as a clear liquid, b.pt. 70-2°/0.4mm. (Lit. 110-4°/15mm.) and showed $\gamma_{C=C}$ 1640 cm^{-1}.

Phenyl vinyl ketone (5)

β-dimethylaminopropiophenone hydrochloride (15.1g.; 0.07m.) was steam distilled. The distillate was extracted with ether and the ethereal extracts dried. On removal of the solvent, using as little heat as possible, 7.15g.(77%) of material was obtained which showed $\gamma_{C=O}$ 1672 cm^{-1} and $\gamma_{C=C}$ 1610 cm^{-1} in the infra red spectrum. This material was employed without further purification.

2-(β-benzoylethyl)-6-methylcyclohexanone (4)

A mixture of the enamine (6) (5.0g.;0.03m.) and phenyl vinyl ketone (4.0g.; 0,03m.) in dry benzene (30ml.) was refluxed for 24 hrs. in a stream of dry nitrogen. A buffer solution of glacial acetic acid (15ml.), water (15ml.) and sodium acetate (7.5g.) was added and refluxing continued for a further 4 hours. The mixture was allowed to cool, the benzene layer separated and the aqueous layer extracted with benzene. The combined benzene extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate solution and dried. After removal of the solvent under reduced pressure, 5.7g. of material remained, which gave on distillation 5.4g.(74%) of a viscous oil, b.pt. 140-5°/0.04mm., which solidified on standing to give a white solid which was recrystallised from 40-60 petrol, m.pt. 52°. This showed $\gamma_{C=O}^{CCl_4}$ 1712 cm^{-1} (cyclohexanone) and 1683 cm^{-1} (aryl ketone) in the infra red spectrum, a doublet methyl signal centred at 9.04 τ in the n.m.r. and a parent ion at 244 in the mass spectrum. A mixed

melting point showed no deprssion and its g.l.c. retention time on both 5% QF 1 and 1% APL was identical with the sample from the thermal reaction.

2-(β-benzoylethyl)-cyclohexanone (7)

This was prepared in 96% yield by the method of Lions [2] and was obtained as white needles, m.pt. 52° (lit. 53°). The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1688 cm^{-1} (aryl ketone) and 1712 cm^{-1} (cyclohexanone). The g.l.c. retention time on 5% QF 1 at 200° was 6.00 min.

2-(β-benzoylethyl)-2-methylcyclohexanone (8)

Phenyl vinyl ketone (4.3g.; 0.032m.) in dry ether (25ml.) was added over 1 hour to a mixture of 2-methylcyclohexanone (7.25g.; 0.065m.) and ethanolic potassium hydroxide (1g./4ml.) in dry ether (30ml.) at 0°C. The mixture was then stirred at room temperature for 1 hour, poured onto ice, acidified with conc. hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine, dried and the ether and excess 2-methylcyclohexanone removed under reduced pressure. The residue was distilled in vacuo to yield 5.1g.(64%) of a yellow viscous oil, b.pt. 145-150°/0.06mm. G.l.c. analysis on 5% QF 1 at 200° showed the major product to be the expected (8), with trace impurities of the other two. A pure sample was isolated by preparative t.l.c. and this showed $\gamma_{C=O}^{CCl_4}$ 1690 cm^{-1} (aryl ketone) and 1707 cm^{-1} (cyclohexanone) in the infra red spectrum and a singlet methyl signal at 8.94 τ in the n.m.r. Fd. C,78.07; H,8.35. $C_{16}H_{20}O_2$ requires C,78.65; H,8.25%.

Treatment of (4) with potassium hydroxide in ethanol

A sample of the diketone (4) (378mg.) in dry ether (5ml.) was treated with ethanolic potassium hydroxide (1 pellet in 1ml.) and the mixture stirred at room temperature for 1 hour. The mixture was then poured onto ice, neutralised with conc. hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine and dried. On removal of the solvent this yielded 345mg. of material which was shown by g.l.c. analysis to be unchanged starting material.

Condensation of β-dimethylaminopropiophenone and 2-methylcyclohexanone

(a) For 1 hour at 130°

The earlier procedure was repeated using β-dimethylaminopropiophenone (5.4g.;0.03m.) and 2-methylcyclohexanone (9.5g.; 0.09m.) but these were refluxed for 1 hour at 130°. After the above work-up procedure, distillation yielded 4.5g.(62%) of product. G.l.c. analysis of this showed no change in the relative proportions of (4) and (8) but an increased percentage of (7).

(b) For 2½ hours at 110°

The above procedure was repeated using the same quantities of reagents. Following a reflux of 2½ hours at 110° and the same work-up procedure, distillation afforded 1.8g.(25%) of product. G.l.c. analysis again showed the same proportion of (4) and (8) but the amount of (7) present was further enhanced.

Condensation of phenyl vinyl ketone (5) and 2-methylcyclohexanone (3)

(a) In the absence of base

A mixture of 2-methylcyclohexanone (8.4g.; 0.075m.) and phenyl vinyl ketone (3.3g.; 0.025m.) was refluxed for 30 min. at 165°. The mixture was cooled, neutralised with glacial acetic acid, diluted with ether and extracted with brine. The ethereal solution was dried, the ether and excess ketone removed under reduced pressure, but only polymeric material was isolated.

(b) In the presence of triethylamine

A mixture of 2-methylcyclohexanone (8.2g.; 0.073m.), phenyl vinyl ketone (3.2g.; 0.024m.) and triethylamine (2.5g.;0.024m.) was refluxed for 40 min. at 160°. The above work-up procedure gave 3.0g.(50%) of product, b.pt. 150-5°/0.1mm. G.l.c. analysis of this showed the presence of the three isomers, (7) = 18% and the remainder consisting of (4) and (8) in the ratio 12: 88.

(c) In the presence of diethylamine

The above procedure was repeated using 2-methylcyclohexanone (8.7g; 0.078m.), phenyl vinyl ketone (3.4g.; 0.026m.) and diethylamine (1.88g.; 0.026m.). After removal of the solvent and excess ketone, this yielded 2.49g.(42%) of an oil, b.pt. 160-5°/0.2mm. G.l.c. analysis showed the ratio of (4) to (8) to be 38:62 in this case, with (7) being present in the same proportion as (8).

(d) In the presence of pyrrolidine

The above procedure was repeated using 2-methylcyclohexanone (3.36g.; 0.03m.), phenyl vinyl ketone (1.32g.; 0.01 m.) and pyrrolidine (0.71g.; 0.01m.). After removal of solvent and excess ketone, this yielded 820mg.(34%) of an oil, b.pt. 160-5°/0.25mm. G.l.c. analysis showed the presence of (4) and (8) in the ratio 77:23, with (7) amounting to 40% of (4).

Attempted reaction of 2-methylcyclohexanone and β-dimethylaminopropiophenone hydrochloride

A mixture of the hydrochloride (680mg.; 0.003m.) and 2-methylcyclohexanone (1.12g.; 0.01m.) was refluxed for 30 min. at 165°. Following the normal work-up procedure, removal of the ketone yielded no appreciable amounts of alkylated product.

Thermal condensation of phenyl vinyl ketone and the enamine (6)

(a) With water added at end

Phenyl vinyl ketone (1.32g.; 0.01m.) was added dropwise with stirring under nitrogen to the enamine (6) (1.65g.; 0.01m.) at 160-5° over a period of 15 min. and heating continued for a further 15 min. At this point an equivalent amount of water was added and a further 5 min. heating undertaken. On cooling and following the usual work-up procedure, distillation yielded 810mg.(33%) of material which g.l.c. analysis showed to consist of the usual proportions of products from the thermal condensation of 2-methylcyclohexanone and the Mannich base.

(b) With water added at the outset

A mixture of phenyl vinyl ketone (1.32g.; 0.01m.) and water (200mg.; 0.011m.) was added dropwise under nitrogen to the enamine (6) (1.65g.; 0.01m.) with stirring at 160-5°, and heating at this temperature was continued for a further 20 min. By this time, the mixture had become homogeneous. On cooling and work-up, distillation yielded 900mg.(40%) of material, which was shown by g.l.c. to be identical in composition to that isolated from the preceding experiment.

β-acetoxypropiophenone (22)

This was prepared by the method of Roth and Dvorak [11] and was obtained in 19% yield, as white plates m.pt. 53°(petrol) (Lit. 53-4°).

Attempted condensation of β-acetoxypropiophenone and cyclohexanone

A mixture of cyclohexanone (1.12g.; 0.012m.) and β-acetoxypropiophenone (22) (730mg.; 0.004m.) was refluxed for 1¼ hours at 160°. The mixture was diluted with ether, throughly washed with brine and dried. Removal of the solvent and excess cyclohexanone left 407mg.(46.5%) of material, which was shown by g.l.c. analysis to consist largely of a single product, Rt = 10.6 min. on 5% QF 1 at 200° and 45ml./min. The material could be isolated by preparative t.l.c. as a white solid, m.pt. 128° (benzene/petrol). Found, C,81.74; H,5.92. $C_{18}H_{16}O_2$ requires C,81.79; H,6.10%. This showed $\gamma_{C=O}^{CCl_4}$ 1687 cm^{-1} (aryl ketone) in the infra red spectrum and aromatic protons (10xH) between 2.1 and 2.8τ vinyl protons at 4.05and 4.32τ(2xH,singlets), and methylene protons

(4xH) between 6.7 and 7.3τ. This was a dimerised form of phenyl vinyl ketone.

Condensation of β-dimethylaminopropiophenone and diethyl malonate

A mixture of β-dimethylaminopropiophenone (3.5g.; 0.02m.) and diethyl malonate (9.5g.; 0.06m.) was refluxed for 1 hour at 140°. The usual work-up procedure yielded, on distillation, 2.47g.(42%) of a clear oil, b.pt. 150-5°/0.3mm. G.l.c. analysis showed this to consist of essentially a single component, Rt = 24 min. on 5% QF 1 at 175° and 45 ml./min. Found, C,65.03; H,6.71. $C_{16}H_{20}O_5$ requires C,65.74; H,6.90%. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1693 cm^{-1} (aryl ketone) and 1737 and 1754 cm^{-1} (substituted malonic ester). The n.m.r. spectrum showed aromatic protons (5xH, multiplet) between 1.95 and 2.60τ; ethyl ester methylene at 5.81τ(4xH, quartet); ethyl ester methyl at 8.87τ(6xH, triplet). This data corresponds to the mono-alkylated product (11).

β-pyrrolidinopropiophenone hydrochloride

A mixture of acetophenone (4.8g.; 0.04m.), paraformaldehyde (2.0g.; 0.023m.) and pyrrolidine hydrochloride (4.5g.; 0.04m.) in ethanol (12ml.) and two drops of conc. hydrochloric acid was refluxed for 2½ hours. The mixture was filtered hot and allowed to cool. The resultant crystalline mass was recrystallised from ethanol to give 6.8 g.(87%) of product as white prisms, m.pt. 158-9°. Found, C,64.94; H,7.55; N,5.83. $C_{13}H_{18}NOCl$ requires C,65.09; H,7.56; N,5.84%.

Condensation of β-pyrrolidinopropiophenone and 2-methylcyclohexanone

The free base was released from the hydrochloride by basification and ether extraction and was obtained as a clear oil which was not further purified.

A mixture of β-pyrrolidinopropiophenone (16) (1.1g.; 0.006m.) and 2-methylcyclohexanone (1.85g.; 0.017m.) was refluxed for 30 min. at 165°. After the usual work-up procedure, distillation afforded 880mg. (67%) of a pale yellow oil, b.pt. 155-160°/0.3mm. G.l.c. analysis showed this to have the same product distribution as the material obtained from the thermal condensation of the dimethylamino-base (1).

β-diethylaminopropiophenone hydrochloride

This was prepared by the method of Blicke [19] and was obtained in 48% yield, m.pt. 107-8° (ethanol/acetone). (Lit. 108-110°).

Condensation of β-diethylaminopropiophenone (15) and 2-methylcyclohexanone

The free base was obtained from the hydrochloride as in the preceding case and was not further purified.

A mixture of β-diethylaminopropiophenone (15) (2.05g.; 0.01m.) and 2-methylcyclohexanone (3.36g.; 0.03m.) was refluxed for 30 min. at 165°. After cooling and the usual work-up, the product was obtained on distillation as a pale yellow oil, 1.41g.(48%), b.pt. 150-5°/0.2mm. This again showed a similar product distribution to the earlier examples by g.l.c. analysis but with an enhanced proportion of (7).

β-morpholinopropiophenone hydrochloride

This was prepared by the method of Lions [20] and was obtained in 82% yield as white needles, m.pt. 177° (ethanol/acetone). (Lit. 177°).

Condensation of β-morpholinopropiophenone (31) and 2-methylcyclohexanone

The free base was liberated from the hydrochloride as in the previous examples and was used without further purification.

A mixture of β-morpholinopropiophenone (31) (1.54g.; 0.007m.) and 2-methylcyclohexanone (2.24g.; 0.022m.) was refluxed for 30min. at 165°. After the normal work-up, distillation yielded 868mg.(53%) of a pale yellow oil, b.pt. 155-160°/0.25mm. G.l.c. analysis of this material on 5% QF 1 at 200° and 45ml./min. showed a similar product distribution to that found for the diethylamino-Mannich base.

β-piperidinopropiophenone hydrochloride

This was prepared by the method of Mannich [21] and was obtained in 84% yield as white needles, m.pt. 192° (ethanol/acetone). (Lit. 192-3°).

Condensation of β-piperidinopropiophenone (32) and 2-methylcyclohexanone

The free base was liberated from the hydrochloride as in the above examples and used without further purification.

A mixture of β-piperidinopropiophenone (32) (1.53g.; 0.007m.) and 2-methylcyclohexanone (2.24g.; 0.02m.) was refluxed for 30 min. at 165°. After the usual work-up, distillation gave 580mg.(35%) of an oil,

b.pt. 150-5°/0.2mm. G.l.c. analysis again showed a similar product distribution to the diethlyamino-case.

Condensation of β-dimethylaminopropiophenone and acetoacetic ester (33)

A mixture of β-dimethylaminopropiophenone (1) (1.9g.; 0.011m.) and acetoacetic ester (4.2g.; 0.033m.) was refluxed for 45 min. at 180°. The usual work-up procedure yielded, on distillation, 1.92g.(68%) of a clear oil, b.pt. 144-150°/0.05mm. G.l.c. analysis indicated the presence of one major product, greater than 90% of the total, Rt = 3.5 min. on 5% QF 1 at 200° and 45ml./min. and 4.75 min. on 1% SE 30 at 175° and 45ml./min. A sample of enhanced purity was obtained by preparative t.l.c.. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1692 cm^{-1} (aryl ketone), 1720 cm^{-1} (methyl ketone) and 1748 cm^{-1} (ester) and the n.m.r. showed methyl resonances at 7.73τ(3xH,singlet) for the methyl ketone and 8.73τ(3xH,triplet,J=7cps) for the ester methyl. The compound gave a positive ferric chloride test and had a parent ion at m/e 262 in its mass spectrum derived from combined gas chromatograph/mass spectrometer analysis on 1% SE 30. This was presumed to be the mono-alkylated product (34).

Condensation of phenyl vinyl ketone and acetoacetic ester

Phenyl vinyl ketone (5) (1.43g.; 0.011m.) in dry ether was added dropwise at 0°C to a mixture of acetoacetic ester (2.85g.; 0.022m.) and ethanolic potassium hydroxide (from 500mg. KOH and 2.5ml. ethanol)

in ether (10ml.) and the mixture stirred at room temperature for 2 hrs. It was then poured onto ice, acidified with dilute hydrochloric acid and ether extracted. The ethereal extracts were washed with brine and dried. Removal of the solvent and excess acetoacetic ester gave a solid product, 1.95g.(69%), as white needles, m.pt. 111-2° (benzene). (Lit. 120° (ethanol)). Found, C,68.16; H,6.90. $C_{15}H_{18}O_4$ requires C,68.69; H,6.92%. This was shown to be identical to the material (34) prepared in the previous experiment, by comparison of g.l.c. retention times and spectral data.

Condensation of β-dimethylaminopropiophenone and 2-carbethoxycyclohexanone (35)

A mixture of β-dimethylaminopropiophenone (3.4g.; 0.019m.) and 2-carbethoxycyclohexanone (9.8g.; 0.057m.) was refluxed for 30 min. at 160°. The usual work-up yielded, on distillation, 4.1g.(70%) of a pale yellow oil, b.pt. 136-40°/0.01mm. G.l.c. analysis of this showed the presence of two components, Rt = 2.00 and 9.25 min. on 5% QF 1 at 200° and 55ml./min. and 5.5min. and 17.75 min. on 1% SE 30 at 175° and 45ml./min., corresponding to 25% and 75% of the total respectively. Combined gas chromatograph/mass spectrometer analysis showed these to have molecular weights 244 and 302 respectively. The former was shown to be 2-(β-benzoylethyl)-cyclohexanone (7) by comparison of both its mass spectrum and g.l.c. retention times with those of an authentic sample. The latter, which could be isolated in a slightly impure state

by preparative t.l.c., gave a negative ferric chloride test, no bathochromic shift in the u.v. spectrum on the addition of base and showed in the n.m.r. spectrum the ethyl ester methyl resonance at 8.75 τ (3xH,triplet,J=7cps) and aromatic protons between 2.0 and 2.65 τ(5xH, multiplet). This was assumed to be the product, 2-(β-benzoylethyl)-2-carbethoxycyclohexanone (36).

Condensation of phenyl vinyl ketone and 2-carbethoxycyclohexanone (35)

Phenyl vinyl ketone (775mg.; 0.009m.) in dry ether (5ml.) was added dropwise to a mixture of 2-carbethoxycyclohexanone (2.0g.; 0.018m.) and ethanolic potassium hydroxide (from 175mg. potassium hydroxide in 2.0ml. ethanol) in ether (5ml.) at 0°C and the mixture stirred at room temperature for 2 hours. The mixture was then poured onto ice, acidified with dilute hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine and dried. After removal of the solvent and excess ketone under reduced pressure, distillation of the residue yielded 1.2g.(68%) of a colourless oil, b.pt. 155-160°/ 0.2mm., which showed a single peak, Rt = 9.25 min. on 5% QF 1 at 200° and 55ml./min., by g.l.c. analysis, with impurities of less than 5%. Further micro-distillation furnished an analytical sample of (36). Found, C,71.31; H,7.54. $C_{18}H_{22}O_4$ requires C,71.50; H,7.33%. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1692 cm^{-1} (aryl ketone), 1716 cm^{-1} (cyclohexanone) and 1739 cm^{-1} (ester) and the n.m.r. spectrum was identical to that of the material isolated in the previous experiment.

The product gave a negative ferric chloride test and no bathochromic shift in the u.v. spectrum on the addition of base.

Condensation of β-dimethylaminopropiophenone and 2-carbethoxycyclopentanone (37)

A mixture of β-dimethylaminopropiophenone (1.89g.; 0.011m.) and 2-carbethoxycyclopentanone (37) (5.0g.;0.033m.) was refluxed for 30 min. at 160°. After the usual work-up procedure, distillation gave 1.95g.(65%) of a pale yellow oil, b.pt. 150-5°/0.1mm. G.l.c. analysis of this showed it to consist of two products, Rt = 3.6 and 11.75 min. on 1% SE 30 at 175° and 45 ml./min. and 7.00 and 20.75 min. on 5% QF 1 at 200° and 40 ml./min. in the ratio 1:4. Analysis of the mixture by gas chromatography/mass spectrometer showed the respective molecular weights to be 216 and 288. By analogy with the cyclohexanone case, these were assumed to be the expected product (39), of molecular weight 288, and the ester-free material (38), for 216. The latter assignment was confirmed by correlation of g.l.c. retention times with those of an authentic sample [24]. The former was isolated in a slightly impure state by preparative t.l.c. It showed no bathochromic shift in its u.v. spectrum on the addition of base, gave a negative ferric chloride test and had the expected n.m.r. spectrum, with an ethyl ester methyl centred at 8.78τ (3xH,triplet,J=7cps) and aromatic protons between 2.0 and 2.65τ(5xH,multiplet).

Condensation of phenyl vinyl ketone and 2-carbethoxycyclopentanone (37)

Phenyl vinyl ketone (900mg.; 0.007m.) in dry ether (7.5ml.) was added dropwise to a mixture of 2-carbethoxycyclopentanone (2.12g.; 0.014m.) and ethanolic potassium hydroxide (from potassium hydroxide (200mg.) in ethanol (2.5ml.) in dry ether (7.5ml.) at 0°C, and the mixture stirred at room temperature for 2 hours. Work-up as for the condensation with 2-carbethoxycyclohexanone yielded on distillation 1.3g.(66%) of an oil, b.pt. 155-160°/0.2mm. This showed a single peak in g.l.c. analysis, Rt = 20.75 min. on 5% QF 1 at 200° and 40ml./min. Found, C, 70.74; H, 7.28. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1690 cm^{-1} (aryl ketone); 1732 cm^{-1} (ester) and 1744 cm^{-1} (cyclopentanone). The product was, therefore, the mono-alkylated (39).

1-dimethylamino-2-carbethoxycyclopent-1-ene (44)

A steady bubble of dimethylamine gas, dried over potassium hydroxide, was passed for 18 hours through a stirred solution of 2-carbethoxy-cyclopentanone (37) (4.0g.; 0.025m.) in dry benzene (5ml.), with anhydrous potassium carbonate (1.0g.) added. The solution was diluted with ether and filtered. The solvents were removed and the residue distilled to give 3.75g.(80%) of a pale yellow oil, b.pt. 156-60°/30mm. This gave a negative ferric chloride test and showed λmax 305mμ (ε=10,500) (Lit. 309 (ε=11,000)[28]) in the u.v. spectrum. Its n.m.r.

spectrum showed N-methyls at 7.03τ(6xH,singlet); ester methyl at 8.78τ (3xH,triplet,J=7cps) and methylene at 5.89τ(2xH,quarter) and no vinyl proton.

Condensation of the enamine (44) and phenyl vinyl ketone (5)

A mixture of the enamine (44) (750mg.; 0.004m.) and phenyl vinyl ketone (600mg.; 0.004m.) in dry benzene (15ml.) was refluxed for 24 hrs. in a stream of dry nitrogen. Following the addition of 2 ml. of acetate buffer and a further 2 hours reflux, the normal enamine work-up yielded 670mg.(59%) of product. This gave a negative ferric chloride reaction and no bathochromic shift in the u.v. spectrum on the addition of base. G.l.c. analysis on 5% QF 1 at 200° and 40ml./min. showed it to consist of two components, corresponding to those obtained from the thermal reaction, Rt = 7.00 and 20.75 min.

Condensation of β-dimethylaminopropiophenone and n-hexaldehyde (46)

A mixture of n-hexaldehyde (6.0g.; 0.05m.) and β-dimethylamino-propiophenone (3.0g. 0.017m.) was heated under reflux for 1 hour at 135°. Following the usual work-up, distillation yielded 3.03g.(77%) of a clear oil, b.pt. 128-130°/0.1mm., which showed $\gamma_{C=O}^{CCl_4}$ 1692 cm^{-1} (aryl ketone) and 1728 cm^{-1} (aldehyde) in the infra red spectrum. The n.m.r. spectrum had an aldehyde proton signal at 0.40τ(1xH, doublet,J=2.5cps) and aromatic protons between 2.0 and 2.6τ(5xH, multiplet) and g.l.c. analysis on 5% QF 1 at 200° and 45ml./min.

showed this to consist of a single product, Rt = 5.0min. This was ascribed the structure (48). On standing for a few hours, the material solidified and was recrystallised from 60-80 petrol as white, feathery needles, m.pt. 94°. Found, C,72.46; H,8.09. $C_{15}H_{20}O_3$ requires C,72.55; H,8.12%. This product showed $\gamma_{C=O}^{CCl_4}$ 1692 cm^{-1} and 1707 cm^{-1} and a broad O-H band between 3440 and 3600 cm^{-1}. The n.m.r. spectrum showed an acid proton at -0.1τ, the remainder of the spectrum being unaltered, except for the disappearance of the aldehyde proton. The material was also base soluble and was assumed on this basis to be the corresponding acid (47), with Rt = 12.6 min. under the above g.l.c. conditions.

β-dimethylamino-p-bromopropiophenone hydrochloride

This was prepared by the method of Knott [30] and was obtained in 57% yield, m.pt. 195-6° (ethanol/acetone) (Lit. 196°).

Condensation of β-dimethylamino-p-bromopropiophenone (49) and cyclohexanone

The free Mannich base (49) was obtained from the hydrochloride in the normal manner and was isolated as a solid, m.pt. 66-7°(decomp.) (40-60 petrol).

A mixture of cyclohexanone (1.47g.; 0.013m.) and β-dimethylamino-p-bromopropiophenone (1.2g.; 0.005m.) was refluxed for 30 min. at 160°. After the usual work-up procedure, removal of the excess ketone

yielded a solid, 1.26g.(81%), m.pt. 68-9° (40-60 petrol). Found, C,57.72; H,5.24. $C_{15}H_{17}O_2Br$ requires C,58.24; H,5.54%. This showed $\gamma_{C=O}^{CCl_4}$ 1690 cm^{-1} (aryl ketone) and 1712 cm^{-1} (cyclohexanone) in the infra red spectrum and the expected n.m.r. spectrum with an aromatic A_2B_2 system between 2.05 and 2.50τ(4xH) and other protons between 6.9 and 7.2τ(α to carbonyl) and 7.7 to 8.4τ(normal). This was the mono-alkylated product (50).

β-dimethylamino-p-methylpropiophenone hydrochloride

This was prepared by the method of Adamson [31] and was obtained in 68% yield, m.pt. 164-5°(ethanol/acetone) (Lit. 168°).

Condensation of β-dimethylamino-p-methylpropiophenone (51) and 2-methylcyclohexanone

A mixture of β-dimethylamino-p-methylpropiophenone (51) (5.0g.; 0.026m.) and 2-methylcyclohexanone (9.1g.; 0.078m.) was refluxed for 30 min. at 165°. After the normal work-up procedure, distillation yielded 4.78g.(71%) of a pale yellow oil, b.pt. 150-5°/0.3mm. G.l.c. analysis of the product on 5% QF 1 at 200° and 45 ml./min. indicated the presence of four components of retention times 11.8;12.9;14.8 and 23.4 min. respectively comprising 70; 10; 5 and 10% of the total.

The last of these could be obtained as white needles, m.pt. 89-90°, by fractional crystallisation of the crude oil from ethanol. Found, C,82.00; H,7.20. $C_{20}H_{20}O_2$ requires C,82.16; H,6.89%. This

compound showed $\gamma_{C=O}^{CCl_4}$ 1686 cm^{-1} in the infra red spectrum and had a parent ion at m/e 292 in the mass spectrum. The n.m.r spectrum showed aromatic protons bewween 2.1 and 2.9τ(8xH), aromatic methyls at 7.62 τ (6xH, singlet), vinyl protons at 4.15 and 4.45τ(2xH, two peaks) and methylene protons between 6.8 and 7.3τ(4xH, multiplet). Double irradiation of the vinyl protons failed to produce any simplification, indicating the presence of two distinct types of vinyl proton. Hydrogenation of this product on 5% palladium/charcoal in ethyl acetate yielded a product which showed a methyl signal at 8.86τ in the n.m.r. spectrum. On this basis, the structure (56) is proposed for the product.

Separation of the three remaining components of the mixture was effected by preparative t.l.c. These were shown by comparison of spectral data and g.l.c. retention times with those of authentic samples to be (52), (53) and (54) respectiveky.

Condensation of p-tolyl vinyl ketone (55) and the enamine (6)

The vinyl ketone was obtained from the corresponding Mannich base (51) by steam distillation and ether extraction. The enamine was prepared as described earlier.

A mixture of the enamine (6) (2.5g.; 0.015m.) and the vinyl ketone (55) (1.65g.; 0.015m.) in dry benzene (15ml.) was refluxed for 24 hrs. in a stream of dry nitrogen. A buffer solution of glacial acetic acid (7.5ml.), water (7.5ml.) and sodium acetate (3.85g.) was added and

refluxing continued for a further 4 hours. On cooling, the benzene layer was separated and the aqueous layer extracted with benzene. The benzene extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and dried. Removal of the solvent and distillation of the residue yielded 2.7g.(68%) of a pale yellow oil, b.pt. 150-3°/0.3mm., which solidified on standing to give a solid, m.pt. 68-9°(petrol). Found, C,78.77; H,8.77. $C_{17}H_{22}O_2$ requires C,79.03; H,8.58%. This showed $\gamma_{C=O}^{CCl_4}$ 1688 cm^{-1} (aryl ketone) and 1712 cm^{-1} (cyclohexanone) in the infra red spectrum and methyl signals at 7.65 τ(3xH,singlet) for the aromatic methyl and 9.07τ(3xH,doublet, J=6cps) for the secondary methyl in the n.m.r. spectrum. G.l.c. analysis on 5% QF 1 at 200° and 45ml./min. showed a single peak of Rt = 11.8 min. This was the 2,6-substituted product (52).

2(3'-p-methylphenyl-3'-oxopropyl)cyclohexanone (53)

A mixture of β-dimethylamino-p-methylpropiophenone (51) (2.4g.; 0.013m.) and cyclohexanone (4.5g.; 0.04m.) was refluxed for 30 min. at 160°. Following the usual work-up procedure, there was obtained, on distillation, 2.5g.(82%) of product, b.pt. 150-5°/0.3mm., which solidified on standing to give a white solid, m.pt. 78-78.5° (benzene/petrol). Found, C,78.66; H,8.20. $C_{16}H_{20}O_2$ requires C,78.65; H,8.25%. This showed $\gamma_{C=O}^{CCl_4}$ 1686 cm^{-1} (aryl ketone) and 1711 cm^{-1}(cyclohexanone) in the infra red spectrum. G.l.c. analysis on 5% QF 1 at 200° and 45ml./min. showed a single peak, Rt = 12.9 min.

Condensation of 2-methylcyclohexanone and p-tolyl vinyl ketone (55)

A mixture of 2-methylcyclohexanone (2.4g.; 0.02m.) and p-tolyl vinyl ketone (1.55g.; 0.01m.) was condensed in the normal manner in the presence of ethanolic potassium hydroxide, from potassium hydroxide (0.33g.) in ethanol(1.3ml.). The usual work-up gave 1.42g. (52%) of product, b.pt. 150-5°/0.3mm. This showed a single peak by g.l.c. analysis, Rt = 14.8 min. on 5% QF 1 at 200° and 45ml./min. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1689 cm^{-1} (aryl ketone) and 1710 cm^{-1} (cyclohexanone) and the n.m.r. spectrum gave a singlet methyl resonance at 8.89τ.

2-methylcycloheptanone (66)

This was prepared by the method of McKillop [48] and was obtained in 56% yield, as a colourless oil, b.pt. 73-8°/20mm.

Condensation of β-dimethylaminopropiophenone and 2-methylcycloheptanone

A mixture of β-dimethylaminopropiophenone (2.8g.;0.016m.) and 2-methylcycloheptanone (66) (6.0g.; 0.05m.) was refluxed for 45 min. at 170°. The normal work-up procedure yielded, on distillation, 1.2g. (30%) of product, b.pt. 150-5°/0.25mm. G.l.c. analysis showed this to consist of four components of retention times 4.5; 7.4; 8.4; and 11.3 min. on 1% SE 30 at 175° and 55ml./min., amounting to 30; 15; 5; and 50% of the total respectively. Attempts to separate these by preparative t.l.c. were not completely successful and identification of the products was effected by gas chromatograph/mass spectrometer

analysis on 1% SE 30. This showed the peaks to have molecular weights of (a) 230; (b) 258; (c) 258 and (d) 264. (a) was found to have identical mass spectrum and g.l.c. retention data to the mono-alkylated cyclohexanone (7), arising from an impurity of cyclohexanone in the starting ketone. (d) compared in both mass spectral cracking pattern and g.l.c. retention times to the dimeric form of phenyl vinyl ketone (75) isolated previously. (b) and (c), on the basis of their molecular weights, are presumably the two isomeric mono-alkylated methylcycloheptanones (67) and (68).

Condensation of β-dimethylaminopropiophenone and menthone (69)

A mixture of menthone (9.24g.; 0.06m.) and β-dimethylaminopropiophenone (3.54g.; 0.02m.) was refluxed for 30 min. at 200°. Following the usual work-up, 2.34g. (31%) of a yellow oil, b.pt. 160-5°/0.5mm. was obtained on distillation. G.l.c analysis on 5% QF 1 at 200° and 45ml./min. showed this to consist largely of a single product, Rt = 10.6 min. Purification of this material by preparative t.l.c. yielded a solid, m.pt. 128° (benzene/petrol). This was shown to be the dimerised phenyl vinyl ketone (75), by comparison with an authentic sample from another source, by mixed melting point and corresponding g.l.c. data.

Condensation of β-dimethylaminopropiophenone and 2,6-dimethylcyclohexanone (70)

A mixture of β-dimethylaminopropiophenone (2.1g.; 0.012m.) and

2,6-dimethylcyclohexanone (4.5g.; 0.036m.) was refluxed for 45 min. 160°. After the normal work-up, distillation afforded 1.2g.(40%) of product, b.pt. 157-163°/0.3mm. G.l.c. analysis of this on 5% QF 1 at 200° and 55ml./min. showed the presence of two components, Rt = 7.8 and 9.6 min., in the ratio 1:2. Attempts to separate these by chromatographic methods were unsuccessful, but gas chromatograph/mass spectrometer analysis on 1% SE 30 gave their molecular weights as 258 and 264 respectively. The first corresponds to the mono-alkylated product (71) and the other to the phenyl vinyl ketone dimer (75).

Condensation of β-dimethylaminopropiophenone and methyl n-amyl ketone(72)

A mixture of β-dimethylaminopropiophenone (3.5g.; 0.02m.) and methyl n-amyl ketone (72) (7.0g.; 0.06m.) was refluxed for 2 hours at 150°. Following the usual work-up procedure, distillation gave 2.8g.(57%) of a pale red oil, b.pt. 165-70°/0.3mm. G.l.c. analysis showed this to consist of one major and two minor components, Rt = 4.3; 6.0 and 13.5 min. on 1% SE 30 at 175° and 45ml./min., comprising 10; 85 and 5% of the total product respectively. The last was identified by g.l.c. retention time as the dimer (75). The other two were shown by gas chromatograph/mass spectrometer analysis both to have the expected molecular weight 246 for mono-alkylation. The former, however, showed the characteristic peaks at m/e 71 and 147, expected from the structure (74). These were absent in the other which showed a peak at m/e 203, corresponding to the isomeric (73).

Condensation of β-dimethylaminopropiophenone and mesityl oxide (76)

A mixture of mesityl oxide (76) (7.1g.; 0.073m.) and β-dimethylaminopropiophenone (4.0g.; 0.024m.) was refluxed for 2 hours at 130°. The normal work-up procedure yielded on distillation 3.65g.(69%) of a pale yellow oil, b.pt. 190-5°/0.9mm. Found, C,78.05; H,7.98. $C_{15}H_{18}O_2$ requires C,78.23; H,7.88%. G.l.c. analysis of this showed it to consist of one major product, Rt = 9.0 min. on 1% SE 30 at 150° and 45ml./min. and 18.2 min. on 5% QF 1 at 175° and 45ml./min. Gas chromatograph/mass spectrometer analysis showed this to have molecular weight 230 and had as base peak m/e 83. Preparative t.l.c. furnished a solid sample, m.pt. 94° (methanol), which showed in the n.m.r. spectrum aromatic protons between 2.0 and 2.7τ(5xH,multiplet), a vinyl proton at 3.84τ(1xH,broad) and methyl signals at 7.86 and 8.15τ(3xH, finely subsplit singlets). The infra red spectrum had a single carbonyl peak, $\gamma_{C=O}^{CCl_4}$ 1685 cm^{-1} (broadened).

Condensation of β-dimethylaminopropiophenone and isophorone (78)

A mixture of isophorone (78) (7.0g.; 0.051m.) and β-dimethylaminopropiophenone (3.0g.; 0.017m.) was refluxed for 1 hour at 200°. Following the usual work-up, distillation of the residue yielded 3.24g.(71%) of a red oil, b.pt. 200-220°/0.25mm. G.l.c. analysis on 5% QF 1 at 200° and 45ml./min. showed the presence of two major and three minor components, Rt = 9.8, 12.1, 16.8, 20.8, and 26.5 min.

accounting for 15, 5, 35, 35 and 5% of the total respectively. Trituration of the crude distillate with ether yielded a white, crystalline product, m.pt. 183° (methanol), corresponding to the fourth product on g.l.c. analysis. Found, C,75.71; H,6.74. $C_{18}H_{20}O_3$ requires C,76.03, H,7.09%. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1688 and 1733 cm^{-1} and only aryl ketone absorption was visible in the ultra violet spectrum. The mass spectrum confirmed the molecular weight as 284 and the n.m.r. spectrum had three singlet methyl signals at 8.72, 8.91 and 9.01 τ and a sharp 1xH triplet at 6.17 τ(J=8.8cps), but no vinylic signal. Separation of the other major product was effected by preparative t.l.c., although a sample of analytical purity could not be obtained. This showed a vinyl proton at 4.18τ and two methyl signals at 7.88τ(3xH,singlet) and 9.01τ(6xH,singlet) in the n.m.r. spectrum. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1668 and 1685 cm^{-1} and, on the basis of these data and comparison with an analytical sample isolated from another source, this was ascribed the structure (85).

Condensation of isophorone and β-dimethylamino-p-bromopropiophenone (49)

A mixture of isophorone (10.3g.; 0.075m.) and β-dimethylamino-p-bromopropiophenone (5.6g.; 0.025m.) was refluxed for 30 min. at 200°. Following the normal work - up, there was obtained 4.97g.(60%) of product as a dark red oil. Trituration of this with ether yielded a

white solid, around 35% of the total by weight, m.pt. 173-4° (methanol). Found, C,59.09; H,5.39. $C_{18}H_{19}O_3Br$ requires C,59.50; H,5.27%. This showed $\gamma_{C=O}^{CCl_4}$ 1684 and 1735 cm^{-1} in the infra red spectrum and a similar n.m.r. spectrum to the corresponding procuct isolated in the previous experiment, with three methyl resonances at 8.70, 8.89, and 9.00τ, aromatic protons as an A_2B_2 system between 2.2 and 2.6τ, and a 1xH, triplet at 6.17τ(J= 8 cps).

Treatment of (80) with sodium in deuterium oxide

A sample of (80) (35mg.) in dry dioxan (2ml.) was stirred in a stream of dry nitrogen for 1½ hours with a solution of sodium (25mg.) in deuterium oxide (1ml.) at 50-60°. The mixture was cooled, the dioxan removed under reduced pressure and the aqueous solution extracted with chloroform. The chloroform extracts were washed with deuterium oxide, dried and the chloroform removed. The n.m.r. spectrum of the resultant solid showed the loss of the triplet at 6.17τ.

Preparation of the enamine (86)

This was prepared in 53% yield by a method similar to that used by Opitz [41a]. The product was obtained as a pale yellow oil, b.pt. 100-5°/0.2mm. and showed λmax = 275mμ (ε= 12,000) (Lit. λmax = 277mμ (ε= 12,800). The picrate was obtained as yellow needles, m.pt. 134-5° (ethanol). Found, C,50.89; H,5.73. $C_{18}H_{34}N_4O_8$ requires C,50.94; H,5.70%.

Condensation of the enamine (86) with phenyl vinyl ketone

A mixture of phenyl vinyl ketone (1.5g.; 0.011m.) and the enamine (86) (2.5g.; 0.011m.) in dry benzene (30ml.) was refluxed for 24 hours in a stream of dry nitrogen. A buffer solution of glacial acetic acid (7.5ml.), water (7.5ml.) and sodium acetate (3.75g.) was added and refluxing continued for a further 4 hours. The mixture was cooled and the benzene and aqueous layers separated. The aqueous layer was extracted with benzene and the combined benzene extracts washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, water and dried. Removal of the solvent yielded, on distillation, 2.10g. (69%) of a pale yellow oil, b.pt. 155-160°/0.01mm. G.l.c. analysis on 5% QF 1 at 200° and 45 ml./min. showed the presence of one major and three minor products, Rt = 9.8, 12.1, 16.8 and 25.0 min., accounting for 55, 20, 10 and 10% of the total respectively. Separation of these was effected by preparative t.l.c. into three fractions. The first, consisting of the first two peaks, showed $\gamma_{C=O}^{CCl_4}$ 1665 and 1689 cm^{-1} in the infra red spectrum and a parent ion at m/e 270 on gas chromatograph/mass spectrometer analysis. In addition the n.m.r. spectrum had methyl signals at 9.02τ(6xH, singlet) and 7.78τ(3xH, singlet) and no vinyl proton. Found, C,79.88; H,8.23. $C_{18}H_{22}O_2$ requires C,79.96; H,8.20%. This has been given the structure (84). The last component by g.l.c. could not be isolated in a sufficiently pure state to ascribe a fixed structure, but the n.m.r. spectrum showed three

distinct methyl signals at 7.65, 8.83 and 9.05τ. This also showed a parent ion at m/e 270 and is tentatively ascribed the structure (87). The third g.l.c. product showed $\gamma_{C=O}^{CCl_4}$ 1669 and 1686 cm^{-1} in the infra red spectrum and its n.m.r. spectrum showed a vinyl proton at 4.07τ and methyl signals at 7.80τ(3xH, singlet) and 8.98τ(6xH, singlet). Found, C,79.88; H,8.15. $C_{18}H_{22}O_2$ requires C,79.96; H,8.20%. This was the mono-alkylated product (85).

Condensation of β-dimethylaminopropiophenone and 3-methylcyclohexenone

A mixture of 3-methylcyclohexenone (91) (6.6g.; 0.06m.) and β-dimethylaminopropiophenone (3.54g.; 0.02m.) was refluxed for 45 min. at 200°. Following the normal work-up procedure, there was obtained, on distillation, 3.52g.(71%) of an oil, b.pt. 154-8°/0.2mm. Found, C,79.25; H,7.46. $C_{16}H_{18}O_2$ requires C,79.31; H,7.49%. G.l.c. analysis on 5% QF 1 showed the presence of one major and two minor components, Rt = 11.5,14.1 and 18.8 min. at 200° and 45ml./min. comprising 10, 60 and 25% of the total respectively. Attempts to separate these by preparative t.l.c. were unsuccessful. An n.m.r. spectrum of the crude mixture showed a vinyl proton at 4.15τ, a triplet centred on 6.30τ (J=8cps) and two methyl signals, at 9.13τ(singlet) and 8.06τ(doublet, J=2cps).

10-methyl-$\Delta^{1:9}$-octalone-2 (94)

This was prepared in 55% yield by the method of Ross [4]. It was obtained as a clear oil, b.pt. 74-8°/0.25mm., Rt = 15.9 min. on 10%

APL at 150° and 55ml./min. The n.m.r. spectrum showed a methyl signal at 8.77τ(3xH,singlet) and a vinyl proton at 4.28τ(1xH,broad singlet).

Condensation of β-dimethylaminopropiophenone and the octalone (94)

A mixture of 10-methyl-$\Delta^{1:9}$-octalone-2 (94) (5.0g.; 0.033m.) and β-dimethylaminopropiophenone (1.77g.; 0.01m.) was refluxed for 1 hour at 200°. On work-up, there was obtained 2.1g.(61%) of product, b.pt. 177-180°/0.25mm., as a clear viscous oil. G.l.c. analysis on 1% QF 1 at 200° and 50ml./min. showed it to consist of one major and two minor products, Rt = 4.0, 9.8 and 16.3 min., accounting for 10, 75 and 15% of total respectively. The major product, which could be isolated by preparative t.l.c., showed a single carbonyl absorption in the infra red spectrum, $\gamma_{C=O}^{CCl_4}$ 1684 cm^{-1}. Found, C,80.85; H,8.15. $C_{20}H_{24}O_2$ requires C,81.04; H,8.16%. The n.m.r. spectrum had aromatic protons between 2.0 and 3.0τ(5xH,multiplet), a methyl signal at 8.79τ(3xH, singlet) and no vinyl proton. This corresponds to the mono-alkylated product (96). Attempts to isolate either of the minor components was unsuccessful.

Preparation of the enamine (97)

A mixture of 10-methyl-$\Delta^{1:9}$-octalone-2 (94) (2.8g.; 0.017m.) and morpholine (4.5g.; 0.051m.) in toluene (30ml.) was refluxed under azeotropic distillation for 36 hours. Removal of the solvent and excess morpholine and distillation of the residue yielded 2.5g.(62%)

of a pale yellow oil, b.pt. 110-5°/0.25mm., which was transparent in the infra red carbonyl region. The u.v. spectrum showed λmax = 263mμ (ε= 12,000) and a picrate was obtained, m.pt.139-140° (ethanol). G.l.c. analysis showed the presence of two isomers, Rt = 6.3 and 8.8 min. on 5% APL at 150° and 55ml./min. in the ratio 6:1.

Condensation of the enamine (97) and phenyl vinyl ketone

A mixture of the enamine (97) (1.15g.; 0.005m.) and phenyl vinyl ketone (700mg.; 0.005m.) in dry benzene (20ml.) was refluxed for 24 hours in a stream of dry nitrogen. 4ml. of the usual acetate buffer solution were added and refluxing continued for a further 2 hours. The mixture was cooled and, following the usual enamine work-up, distillation gave 1.02g.(61%) of a clear viscous oil, b.pt. 182-7°/ 0.35mm. G.l.c. analysis showed the predominant product to correspond to that isolated from the thermal reaction. The n.m.r. of a sample, isolated by preparative t.l.c., again showed no vinyl proton, a methyl signal at 8.83τ(3xH,singlet) and aromatic protons between 2.0 and 2.7τ(5xH,multiplet).

APPENDIX

X-ray analysis of 2-p-bromobenzoyl-1,5,5-trimethylbicyclo(2.2.2)octa-6,8-dione (79)

This work was undertaken by Drs. A.F.Cameron and G.Ferguson [49].

The unit cell dimensions were determined from oscillation and Weissenberg photographs taken with Cu-Kα radiation (λ=1.5418Å) and from precession photographs taken with Mo-Kα radiation (λ=0.7107Å). The space group was uniquely determined from the systematic absences observed in the 0k0 and h0l spectra.

Intensity data were obtained from equatorial and equi-inclination Weissenberg photographs, taken from a small crystal rotating about the c-axis, using the multiple film technique. Some 2000 data were estimated visually by comparison with a calibrated wedge and were corrected for Lorentz and polarisation factors. No allowance was made for absorption and unobserved reflexions were not considered.

The position of the bromine atom was found by Patterson methods and the other non-hydrogen atoms were found from the first electron-density distribution, calculated with the observed amplitudes and the signs appropriate to the bromine atom. The atomic parameters have been refined by further electron density calculations and by (full matrix) least-squares methods. The value of R is 0.099.

The structure and conformation of the molecule are shown in Fig I and a list of crystal data is given below.

CRYSTAL DATA:

Molecular formula - $C_{18}H_{19}O_3Br$

Molecular weight - 363

monoclinic

a - $17.71 \pm 0.05\text{Å}$

b - $9.25 \pm 0.02\text{Å}$

c - $10.63 \pm 0.03\text{Å}$

β - $106.5^\circ \pm 0.2^\circ$

Unic cell volume - 1669 Å^3

No. of molecules/unit cell - 4

Space group - $P2_1/c$

No. of intensities estimated - 1828

Density - 1.44g.cm^{-3} (by flotation in KI/H_2O solution)

Density (calc.) - 1.44g.cm^{-3}

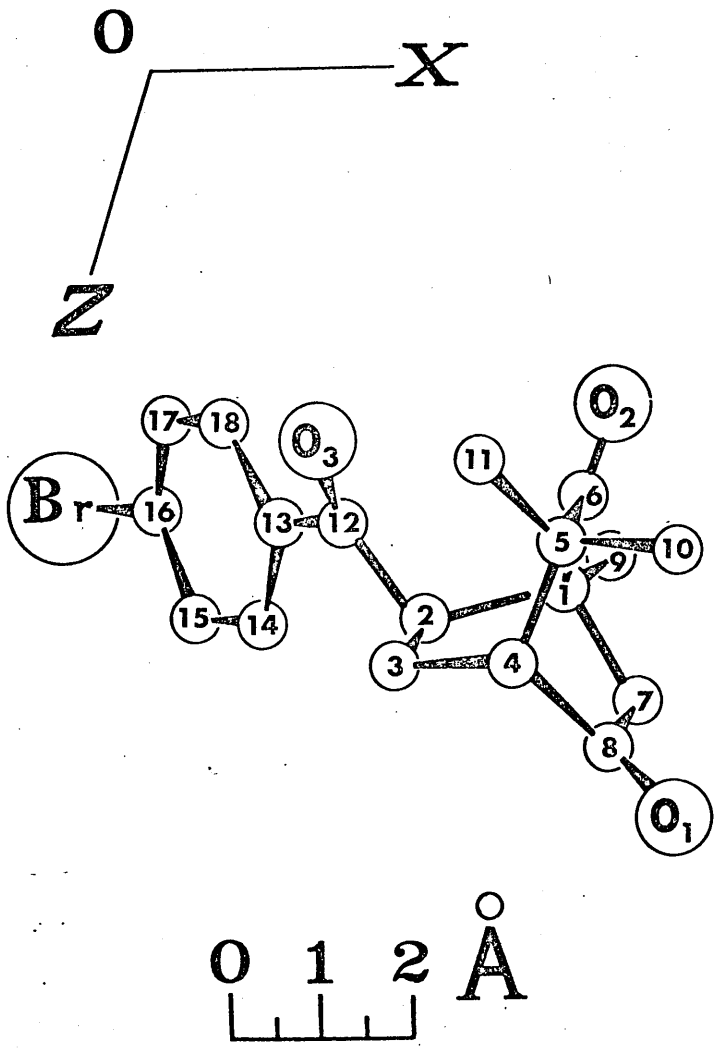

Fig I

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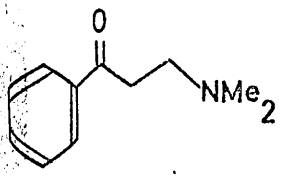

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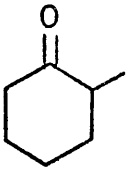

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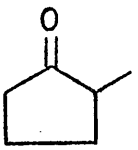

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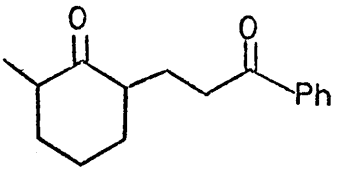

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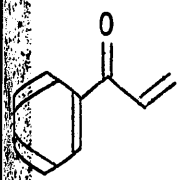

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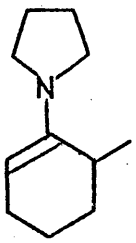

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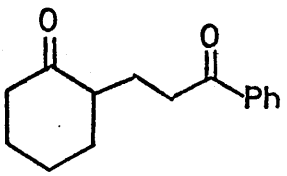

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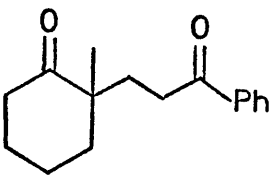

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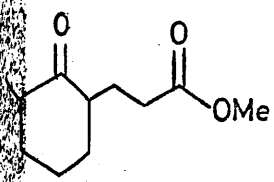

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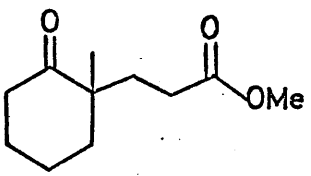

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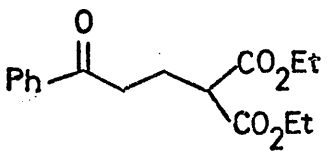

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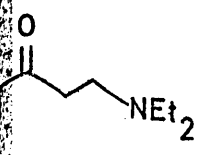

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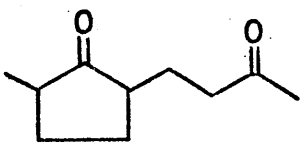

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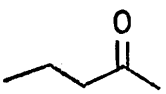

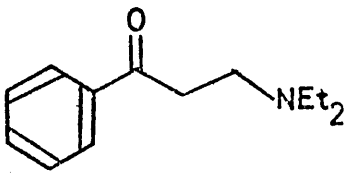

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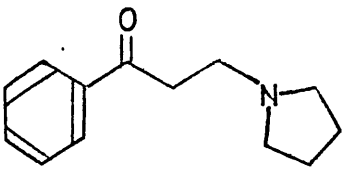

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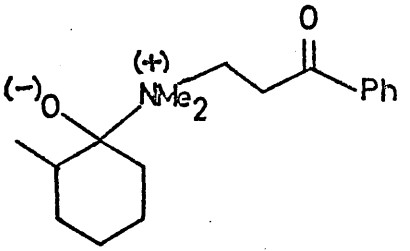

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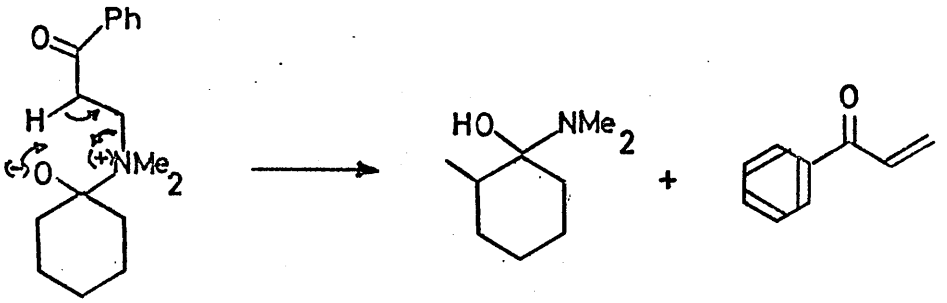

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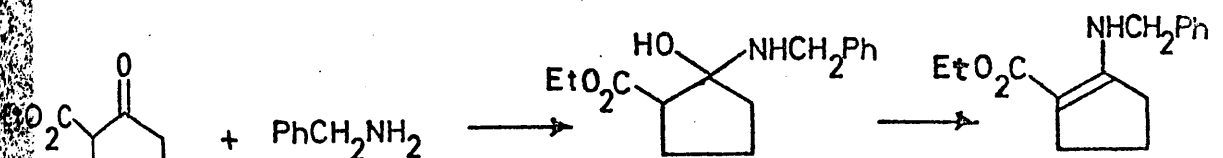

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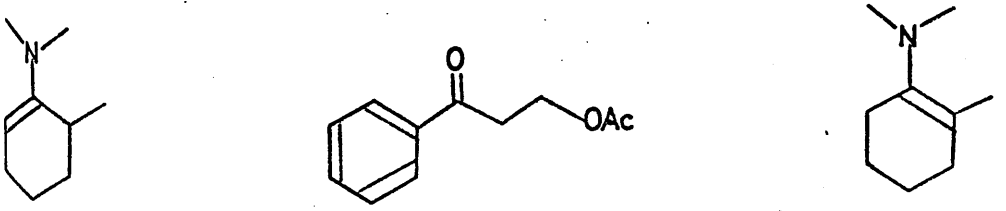

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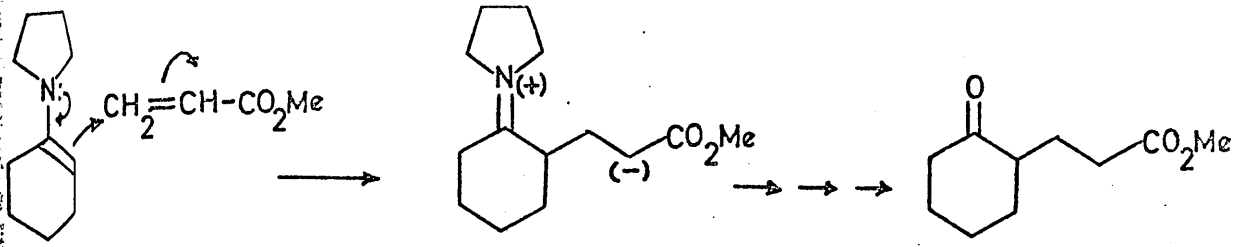

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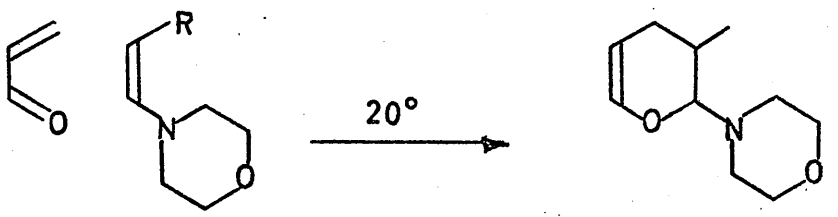

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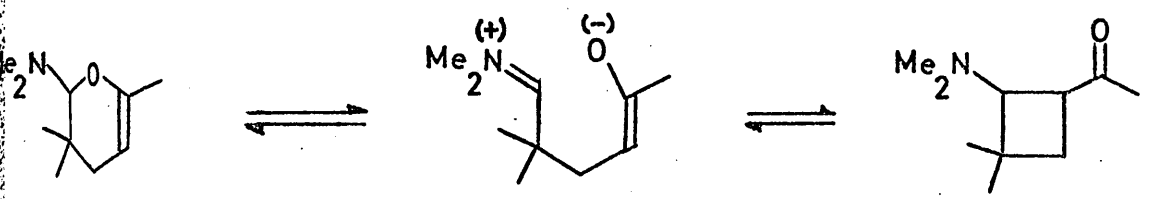

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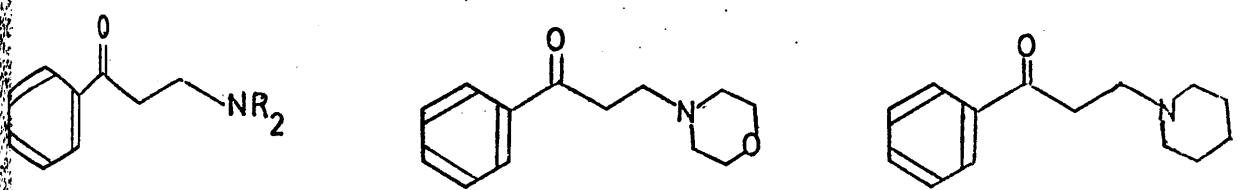

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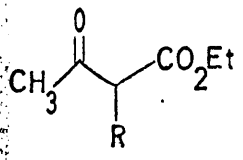
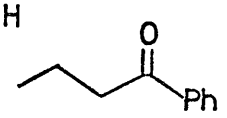
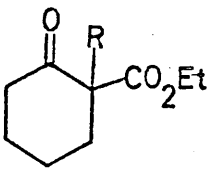
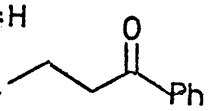


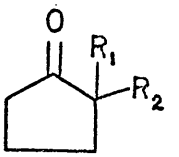
33 R=H

34 R= 

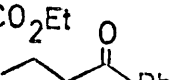


35 R=H

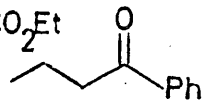
36 R= 

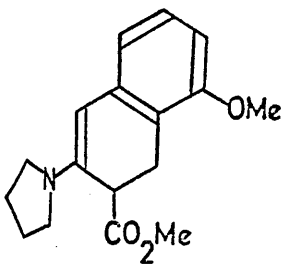


37 R_1=H ; R_2=CO_2Et

38 R_1=H ; R_2= 

39 R_1=CO_2Et

R_2= 



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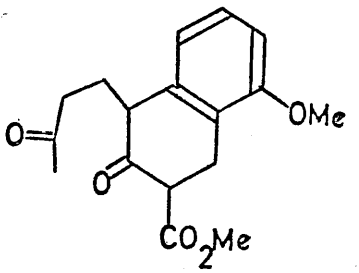

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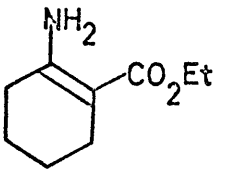

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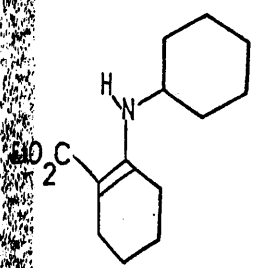

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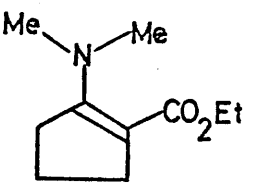

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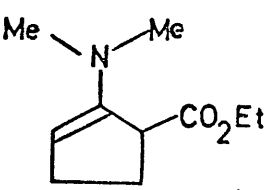

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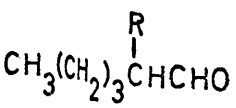
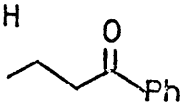
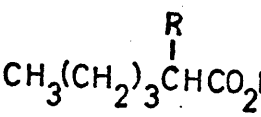
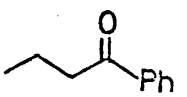
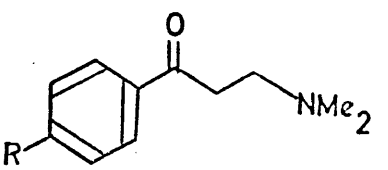


46 R=H

48 R= 

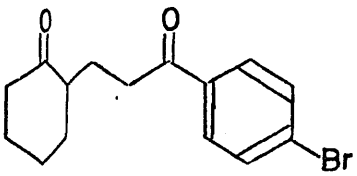


47 R= 



49 R=Br

51 R=Me



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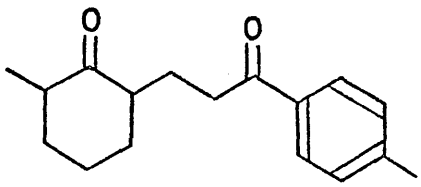

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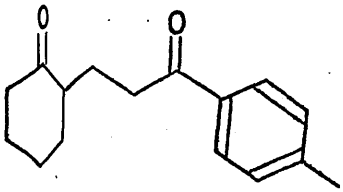

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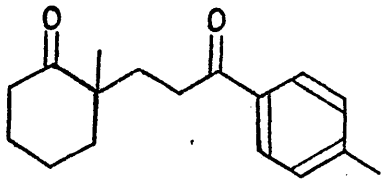

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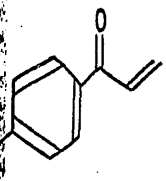

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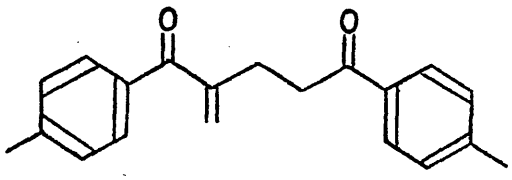

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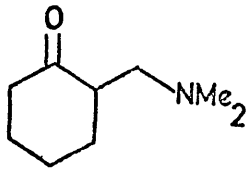

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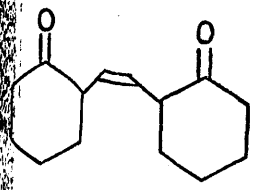

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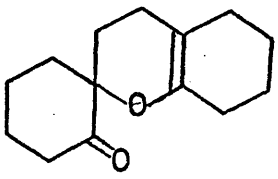

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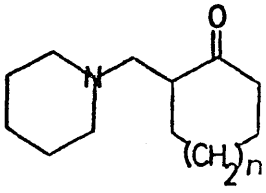
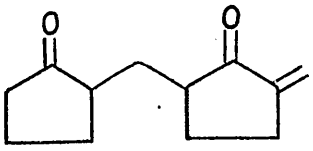


60 n = 1

61 n = 2

62 n = 0



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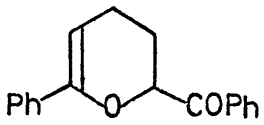

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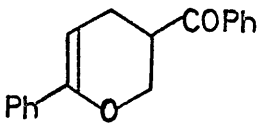

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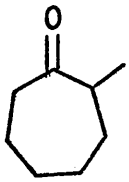

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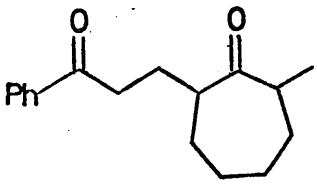

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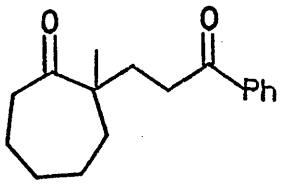

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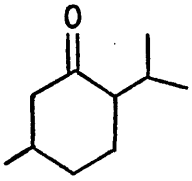

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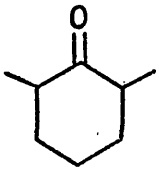

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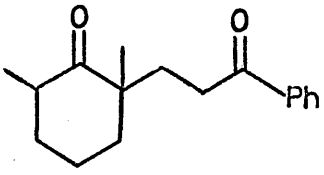

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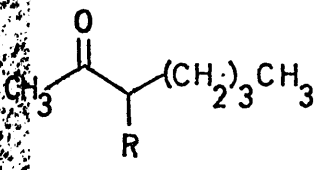
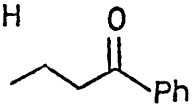
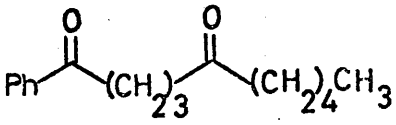


72 R = H

73 R = 



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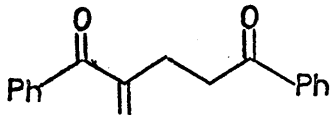

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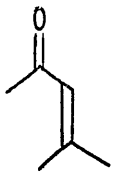

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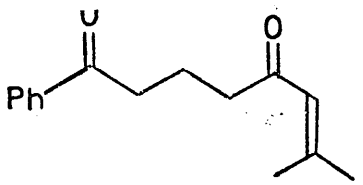

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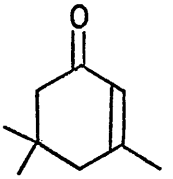

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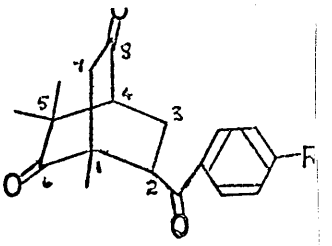
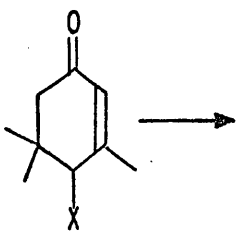


79 R = Br

80 R = H



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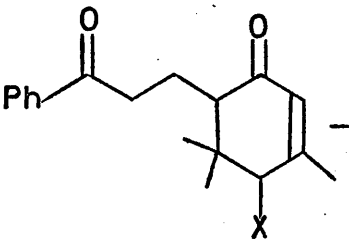

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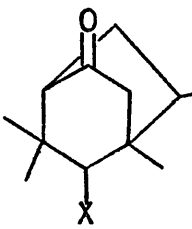

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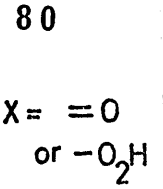
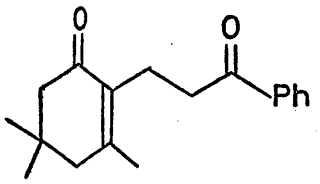


80

X = =O

or $-O_2H$



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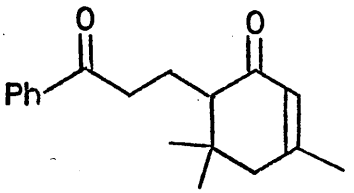

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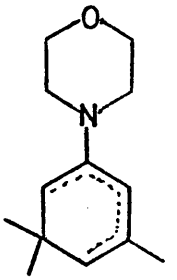

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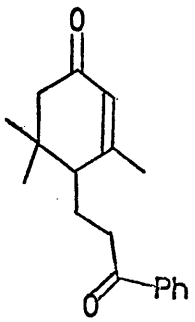

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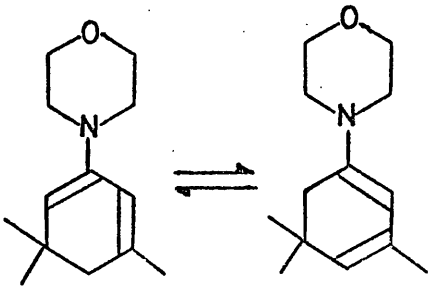

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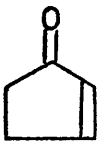

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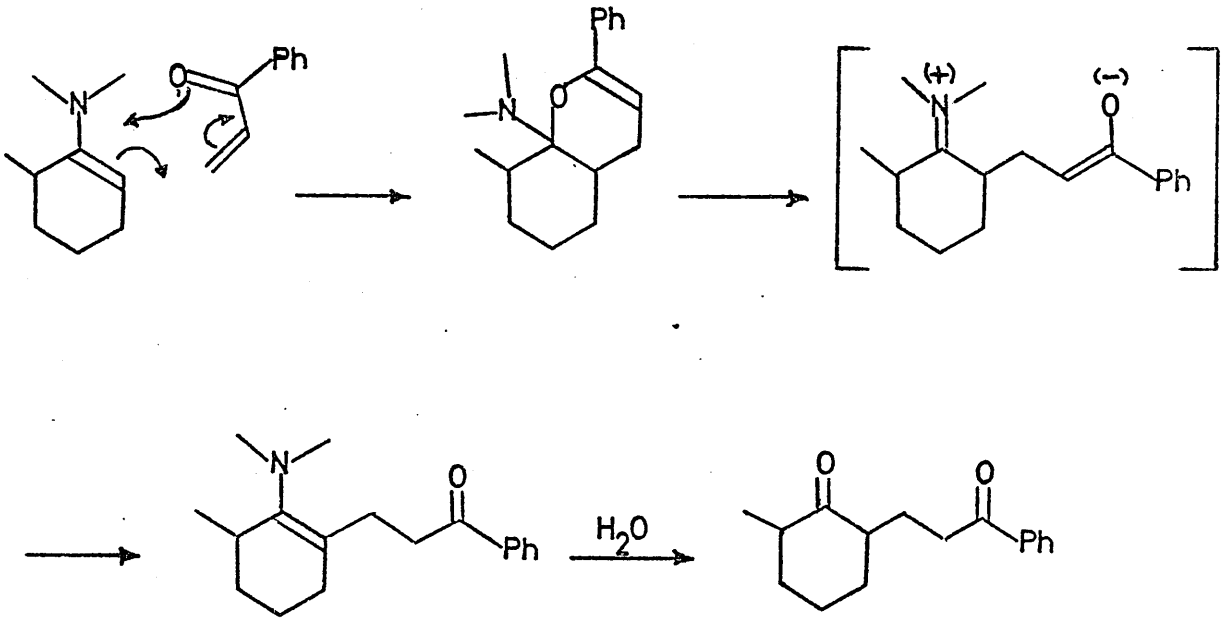
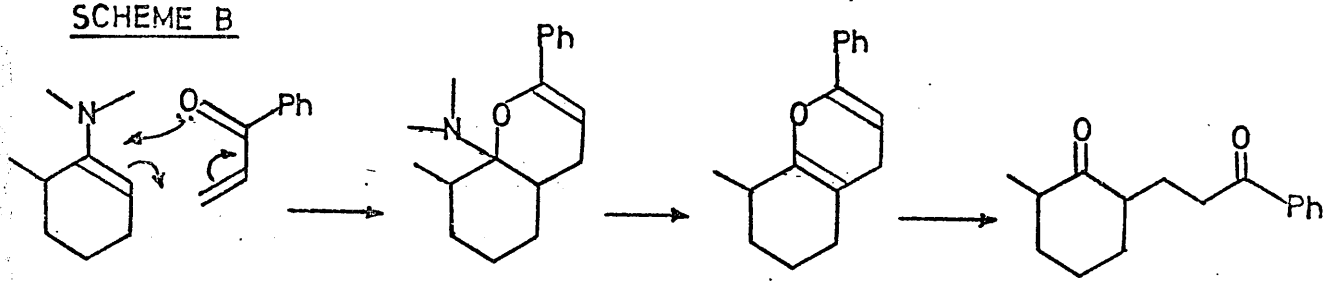
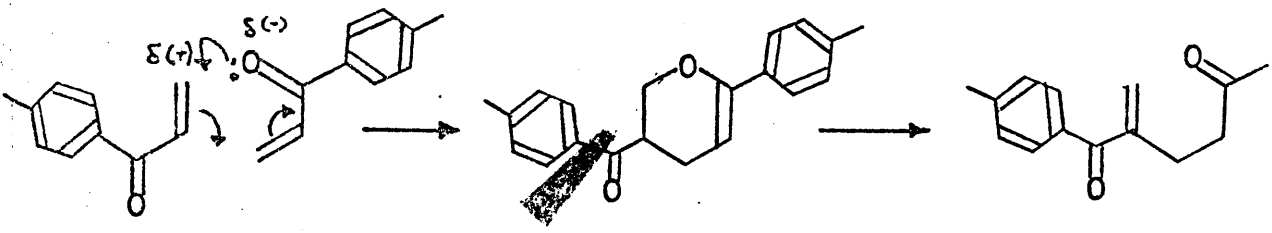


SCHEME B



SCHEME C



PART II

SYNTHETIC APPROACHES TO AN INTERMEDIATE IN SESQUITERPENE BIOGENESIS

INTRODUCTION:

In recent years the sesquiterpenes, with their widely divergent structural forms, have provided a major field for organic research. This group of substances, constructed from only fifteen carbon atoms, shows a greater diversity of structures than any other class of terpenoids and raises a fascinating range of problems. Both structural elucidation and synthesis have been complicated by rearrangements and work on the subject has provided the basis for a number of reviews(1).

A major group of sesquiterpenes possesses the bicyclo (5.3.0) or guaiane skeleton (1), which is found to exist in a variety of structural modifications. In addition to this large group, there exists another group of sesquiterpenes, based on the bicyclo (5.3.0) skeleton, which would appear at first sight to be a sub-group of the guaiane class. This is the daucane class (2), which differs markedly from the guaianes in the position of the methyl and isopropyl functions, and is, in fact, a distinct sesquiterpene class in its own right. Only three naturally occurring compounds in this class have been isolated: carotol (3); daucol (4) and laserpitine (5). All three are derived from the Umbelliferae family, and their structures are now virtually established.

Carotol was first isolated from the essential oil of Daucus carota in 1925 by Asahina and Tsukamoto[2]. Dehydrogenation experiments by Sorm[3] yielded as the major product 1,7-dimethyl-4-isopropylnaphthalene (6), suggesting a structural type not observed in the previously isolated sesquiterpenes and anomalous with regard to the isoprene rule[4]. The same suthor suggested[5] the structure (7) for carotol on the basis of this and further chemical and degradative evidence; but, later[6], when, from milder sulphur dehydrogenation, he obtained no naphthalenes but a mixture of azulenes, the structure (3) was proposed.

Degradative work showed the existence of a seven membered ring by two independent proofs and gave the positions of the functional groups from the triol (8). Although the alternative formulation (9) had also been put forward[7], the validity of (3) was confirmed by an n.m.r. study[8] and the steriochemistry of this has now been established by Levisalles and Rudler[9]. It is now possible to write the absolute configuration of carotol as (10). The ring junction here is stereoisomeric with that in naturally occurring widdrol (11)[10] and thujopsene (12)[11]. Prompted by this, the French authors have attempted a correlation between (+)-carotol and a substance of known configuration. From (-)-dehydro-carvone

they have [12] synthesised (13) and thereby reaffirmed their earlier stereochemical findings by n.m.r. and circular dichroism measurements. In addition, concordant results have been obtained[13] from the correlation of (13) with the compounds (14) & (15) obtained by degradation of carotol acetate (16).

The work on the structural elucidation of daucol (4)[14] closely parallels that on carotol, a fact which may be attributed to their co-existence in Daucus carota. Its structure was proposed by Sorm[6] along with that of carotol and it was used by Schoolery[8] as the basis of his n.m.r. studies. The stereochemistry of daucol was determined by Levisalles and Rudler[8] and is given by (17).

It is perhaps relevant to mention here the isolation of a hydrocarbon, daucene, $C_{15}H_{24}$, from column chromatography of the sequiterpene fraction of Daucus carota by Pigulevski[15], The same author[16] prepared daucene by dehydration of carotol with a trace of sulphuric acid and showed it to have an infra-red spectrum similar to natural daucene. No structure is postulated for this substance, although it is said to have the azulenic skeleton with two double bonds, since it yields daucane (2) on hydrogenation. Whether this is a true naturally occurring compound or is produced by dehydration of carotol on chromatography is a matter of some conjecture.

The last, naturally occurring, known member of this series, laserpitine (5), was isolated as early as 1865 by Feldmann[17] as the crystalline bitter principle from the roots of Laserpitium latifolium L. Following the reassessments of the carotol structure[6,8] Sorm[18] considered the proposed structure (18)[19] of laserpitine questionable. N.m.r. spectra of laserol (19) and dihydrolaserol (20) gave results not in agreement with the suggested structure (18). After extensive chemical and degradative work, the structure (21) was proposed and unambiguously verified by an X-ray analysis of p-bromobenzoyllaserol (22).

The remaining point of debate in the structural assignments of the daucane sesquiterpenes is the nature of the ring junction. The X-ray work[18] indicates a trans-fusion in laserpitine, whereas the French authors[9,12,13] have considerable chemical and spectral evidence in favour of a cis-fusion for carotol. It would, indeed, be surprising if these compounds had a dissimilar stereochemistry at this point, but no doubt further work by the two groups will clarify the situation.

Apart from the few remaining structural uncertainties, there is some speculation as to the biogenetic pathway by which the daucane carbon skeleton is attained. With the increasing

sophistication of tracer studies, further impetus is being added to an aspect of sesquiterpene chemistry, which was only rationalised in the '50s' by Ruzicka and his colleagues[4,20] in terms of the isoprene rule. This work was developed by Hendrickson[21], who proposed a theoretical scheme for the production of the diverse structural types of sesquiterpenes from farnesol. In addition, the subsequent developments on the biogenesis of sesquiterpenes are the subject of a recent review[22].

On the basis of the findings to date, the daucane skeleton may be arrived at speculatively from cis-farnesol (23) in two ways. After ionisation of the allylic hydroxyl, we can envisage formation of the ten-membered ring cation (25) by the intermediacy of the non-classical carbonium ion (24) as proposed by Hendrickson[21]. Cyclisation of (25) and subsequent shift of the methyl group from C-7 to C-8 would then give the required carbon skeleton (26) (Scheme A) The weak point of this Scheme, according to Souchek[23], is the complexity of the mechanism, whereby a series of energetically unfavourable enzymatic reactions must be assumed. Other possible routes are by direct cyclisation of farnesyl pyrophosphate (Scheme B) or by the intermediacy of the seven-membered ring carbonium ion proposed by Hendrickson[21] (Scheme C). Both these schemes are energetically more plausible

and some elegant tracer work by Souchek[23] has shown the incorporation of (1- ^{14}C)- acetate to be consistent with either Scheme B or Scheme C, as shown by the asterisks, but not with Scheme A. However, as stated earlier, the assignment of a trans-ring fusion by Souchek is in doubt. This would require deprotonation of (27) to (28) and a stereospecific hydration of the diene.

The use of *in vitro* reactions to simulate the biogenetic pathways for the production of natural products is now being encountered with increasing regularity in the literature, and in the sesquiterpene field in particular. The earlier work in this direction has largely been summarised by Eschenmoser[24] in his paper on the acid catalysed cyclisations of terpenoid polyenes. Stork[25] has examined the stereochemistry of polyene cyclisation, with special reference to the cyclisation of farnesyl acids and derivatives and this approach has been developed most notably by van Tamelen in his biogenetic-type syntheses[26] of (±) farnesiferol A (29) and C (30).

Having a suitable route[27] to substituted seven membered rings readily available and with the current vogue of *in vitro* reactions in mind, it was decided to test the viability of the intermediate carbonium ion (31), proposed by Hendrickson[21]. A synthesis

of the tosylate (32), corresponding to (31), would lead on solvolysis to (31) which under the reaction conditions would be expected to undergo further transformations. A subsequent analysis of the products by modern techniques might indicate the presence of some relevent sesquiterpenoids and so add weight to the proposed intermediacy of (31).

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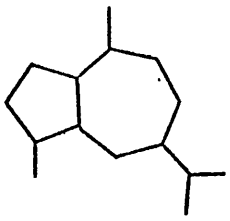

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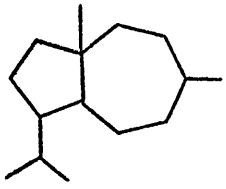

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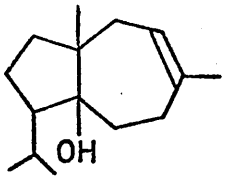

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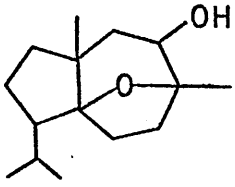

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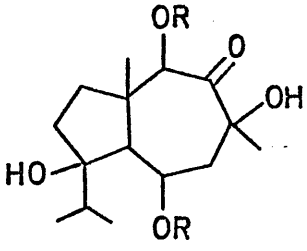

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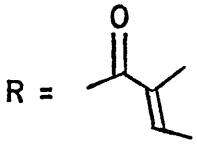

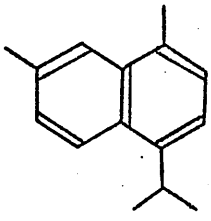

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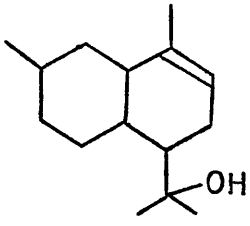

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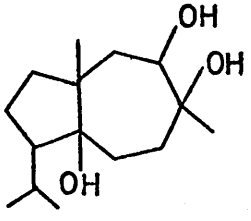

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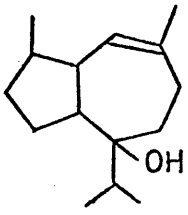

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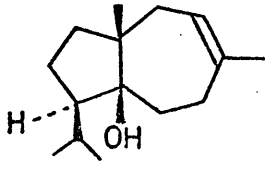

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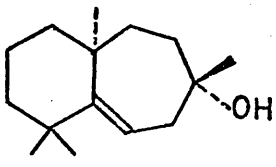

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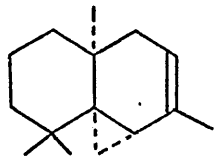

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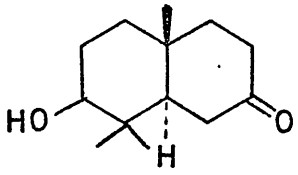

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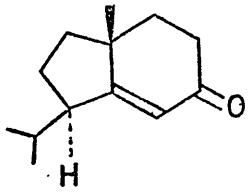

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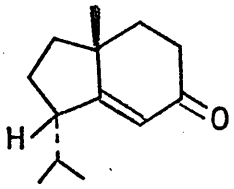

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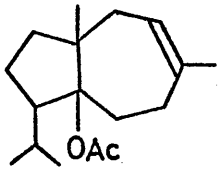

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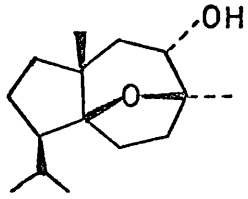

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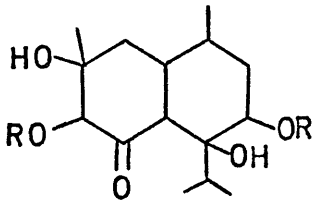

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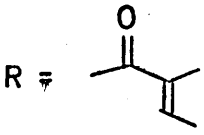

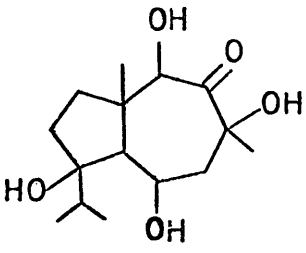

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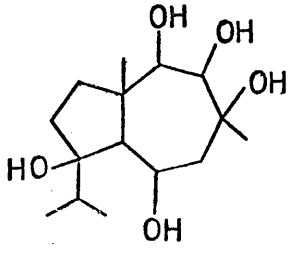

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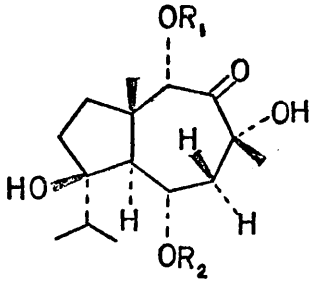

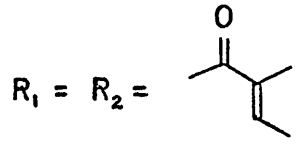

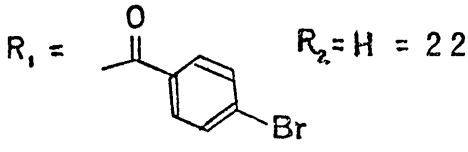

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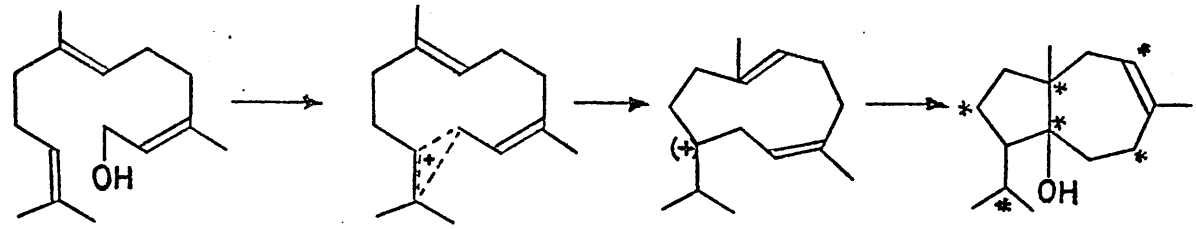

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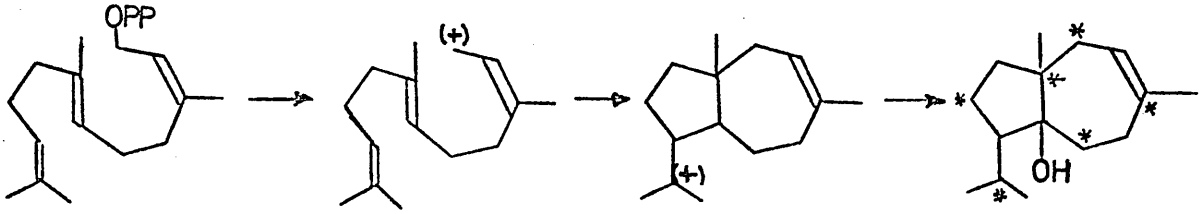

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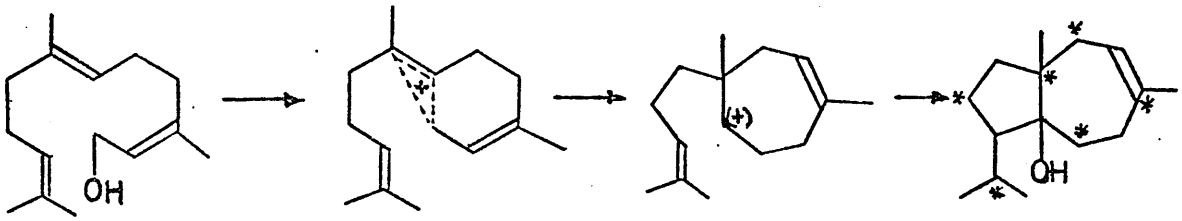

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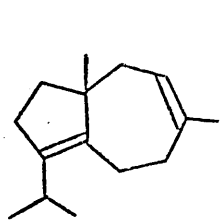

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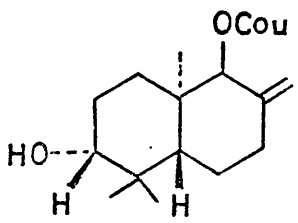

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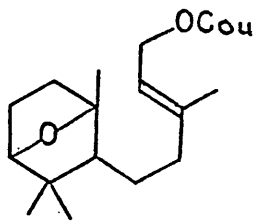

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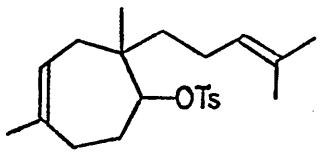

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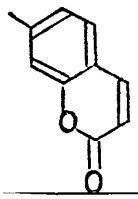

DISCUSSION:

It was envisaged that the most profitable synthetic approach to the synthesis of the required tosylate (1) would involve the initial formation of a suitably substituted dimethylcycloheptene derivative and subsequent elaboration of the six-carbon side chain. The most suitable intermediate to this end would appear to be the dimethylcycloheptenone (2) which on alkylation with 1-bromo-4-methylpent-3-ene (3), reduction of the product to the alcohol and subsequent tosylation would yield the tosylate (1) as indicated in Scheme A.

The general proposed route to the ketone (2) is outlined in Scheme B. Condensation of 2-carbethoxy-5-methylcyclopentanone (4) with crotonaldehyde would yield the bicyclic alcohol (5). Treatment of this with p-toluenesylphonyl chloride and fragmentation of the resultant tosylate mixture (6) with sodium ethoxide[1] should lead to the cycloheptene dicarboxylic ester (7). Hydrolysis and decarboxylation of this would give the mono-acid (8) which on oxidative decarboxylation with lead tetraacetate[2] would form the acetate (9). reduction of this product with lithium aluminium hydride and oxidation of the resultant alcohol (10) would furnish the desired ketone (2).

Dieckmann condensation of diethyl adipate and subsequent methylation by the method of Nicole[3] yielded 2-carbethoxy-2-methylcyclopentanone (11) in 79% yield. G.l.c. analysis of this showed it to consist of a single component. In addition, it gave a negative ferric chloride test; showed a singlet methyl signal at 8.76τ in the n.m.r. spectrum for the C-2 methyl group and had carbonyl absorption as a double peak 1733 and 1753cm^{-1}.

The 2,2-substituted product (11) was smoothly converted in 75% yield into the isomeric 2-carbethoxy-5-methylcyclopentanone (4) by treatment[4] with sodium ethoxide. This showed under the g.l.c. conditions used for (11) above a single peak with longer retention time. It gave a positive ferric chloride test, showed a doublet methyl resonance centred at 8.92τ (J=6cps) in the n.m.r. and carbonyl absorption in the infra-red spectrum at 1731 and 1755cm^{-1}.

The condensation of (4) with crotonaldehyde was initially attempted by refluxing with triethylamine in benzene[5] but this gave on work-up almost complete return of starting material. However, condensation was effected by reaction of the two components with a catalytic amount of sodium ethoxide in ethanol at -70°C. This yielded on distillation 77% of product which g.l.c. analysis showed to consist of three components with retention times of 15.9; 32.5 & 35.3 mins. on 5%APL

at 150° amounting to 5,65 & 30% of the total respectively. From previous work[6] these were presumably the epimeric alcohols (5) and the aldehyde-ester (12). Integration of the aldehyde proton signal at 0.28τ in the n.m.r. spectrum against the ester methylene signal indicated that the aldehyde-ester was present in no more than 5%. This was thought to be the first of the g.l.c. products in view of the percentage occurrence and the epimeric nature of the alcohols which would give closer retention times. This was confirmed by removal of this impurity by preparative t.l.c. and n.m.r. analysis of the product (5). This showed C-5 methyl at 8.9τ (3XH, singlet), C-2 methyl at 9.09 τ (3XH, doublet, J=7cps) and ester methyl at 8.74 τ (3XH, triplet, J=7cps). The infra-red spectrum showed carbonyl absorption at 1735 & 1761cm^{-1} corresponding to the ester and C-8 carbonyls respectively and hydroxyl absorption, free at 3631cm^{-1} and bonded as a broad band between 3400 & 3560cm^{-1}. No attempts were made to separate the axial and equatorial alcohols but it might be suggested from the equilibrating conditions used in the condensation and from the relative proportions of products obtained on tosylation that the equatorial is the epimer in preponderance. It has also been found here that if prolonged heating is applied during distillation, considerable retro-aldol reaction can occur to give increasing proportions of the aldehyde ester. This can largely be overcome by small batch flash distillation.

The mixture of epimeric alcohols (5) was converted to a mixture of epimeric tosylates (6) by treatment with p-toluenesulphonyl chloride in pyridine. The resulting crude product was separated by fractional crystallisation into two isomers of m.pt.162-30 & 81-2°. The former (12%) showed carbonyl absorption at 1734 & 1766cm^{-1} corresponding to the ester and C-8 carbonyls respectively and tosylate bands at 1178 & 1371cm^{-1} in the infra-red. The n.m.r. spectrum showed the characteristic[5] C-4 proton at 5.3τ with half-band width of around 10cps, the aromatic methyl at 7.52τ (3XH, singlet) and aromatic protons as an A_2B_2 system between 2.1 & 2.7τ in addition to the features shown in (5). The latter (88%) corresponded to the other epimer by t.l.c. & showed a half-band width of 4cps for the C-4 proton at 5.6τ in the n.m.r. in addition to the expected peaks as found in the other epimer. The infra-red spectrum showed carbonyl absorption at 1736 & 1766cm^{-1} for the ester and C-8 carbonyl groups and tosylate bands at 1179 & 1379cm^{-1}. From the half-band width of the C-4 proton signal in the n.m.r. it may be deduced that the first isolated epimer is the axial and the second the equatorial tosylate. Although these half-band widths are not as great as already recorded[5] the trend is similar and the assignment of the two epimers made is confirmed by the subsequent series of experiments.

In an attempt to prepare the cycloheptene ester (7) via the bridge scission process[1], the mixture of epimeric tosylates was treated with sodium ethoxide in ethanol. Following work-up the product was separated from the unreacted axial tosylate by distillation[7]. Unexpectedly, g.l.c. of the resultant clear oil showed two products in the ratio 2:3. Combined gas chromatograph/ mass spectrometer analysis confirmed the isomeric nature of the products which had both molecular weight 268, that of the expected diester (7) and similar fragmentation patterns. The mechanism of this ring scission has been discussed[5] and on this basis a single product (7) would be expected. This would be produced from the equatorial tosylate via a β-elimination process (6a → 7), the axial tosylate being returned unchanged.

The possibility that the second product might be an elimination product of the axial tosylate under the reaction conditions could not be overlooked and, accordingly, the reaction was repeated on a sample of axial tosylate. However, following the same work-up procedure, only unchanged axial tosylate could be isolated, as expected.

Treatment of the equatorial tosylate under the reaction conditions above but with careful neutralisation to pH 7 under ice cooling yielded around 80% of a clear liquid which g.l.c. analysis showed

to be a single pure compound corresponding to the isomer of longer retention time produced from the epimeric tosylate mixture. Redistillation furnished an analytically pure sample which showed carbonyl absorption at 1735cm^{-1} for the ester. The n.m.r. spectrum showed an ester methyl at 8.78τ (6 X H, triplet, J = 7cps); The C-2 methyl at 9.11τ (3 X H, doublet, J = 7cps); the C-5 methyl at 8.32τ (3 X H, broad singlet) and a vinyl proton at 4.65τ(1 X H, multiplet).

These conflicting results could be interpreted in two ways. Either the single product isolated in this last experiment represents the initial product which is capable of equilibration to yield the mixture; or it represents a final product derived from the initially formed mixture under the conditions of isolation. In order to clarify the situation attempts were made to convert the isomeric mixture under a series of conditions into the single compound. A sample of the mixture, having been subjected to a given set of conditions, was analysed by g.l.c. Refluxing a sample for 72 hours in the presence of p-toluenesulphonic acid in chloroform; sodium ethoxide solution as used in the original reaction; or hydrochloric acid in ethanol produced no significant change in the product conposition. Since the elimination product of the equatorial tosylate was obtained as a single compound and the isomeric mixture could not be converted into it by subjection to prolonged reaction

conditions, it would seem justified in the light of earlier findings[1,5] to assign to this product the structure (7) of the expected cycloheptene-diester.

Since some isomerisation process was occurring during the reaction, steps were taken to decide which factor or factors in the work-up or purification process were responsible. The possibility of thermal isomerisation was considered first and a sample of diester (7) was subjected for 15 mins. to a series of temperatures between 65 & 180°C. The product was then analysed by g.l.c. but in all cases the pure diester remained unchanged. The effect of chemical reagents was then tested, a sample of the pure diester being refluxed for 15 mins. in ethanol with an additional reagent and, following a suitable isolation procedure, the product was analysed by g.l.c. It was found, as a result that dilute hydrochloric acid; dilute sulphuric acid and p-toluenesulphonic acid produced isomerisation whereas no change could be detected with acetic acid; sodium acetate; axial tosylate or sodium ethoxide.

From these results which show the diester (7) to be isomerised in acid, the other product is ascribed the structure (13). Cycloheptene has been shown[8] to exist in a chair conformation and an examination (see figures 7a & 13a) of a model of (7) shows severe

non-bonded interactions between the axial hydrogens at C_3 & C_6 and one of the carbethoxyl groups. Isomerisation to (13) removes the carbethoxyl interaction with the C_6 hydrogen and although that at C_3 remains, this transformation must provide sufficient relief of non-bonded interactions to account for the facile isomerisation of the initially formed product of the reaction.i.e.(6)→(7)⇌(13).

The root cause of the isomerisation as seen from the results above would appear to be the use of excess hydrochloric acid in the neutralisation of the sodium ethoxide or p-toluenesulphonic acid produced during the distillation by thermal decomposition of the unreacted axial tosylate. In practice, it has now been found that if the axial tosylate is removed by fractional crystallisation from the original epimeric tosylate mixture, the minimum acid is used for neutralisation of the ethoxide during the work-up under ice cooling and the ethereal extracts are thoroughly washed with brine to remove traces of unreacted acid, a single isomer (7) is obtained on distillation.

In an attempt to hydrolyse the diester (7), it was refluxed overnight with potassium hydroxide in methanol. This yielded 82% of a clear viscous oil which analysed for $C_{13}H_{20}O_4$. On methylation with diazomethane, a sample of this showed a single peak on g.l.c. analysis. The infra-red spectrum of the hydrolysis product showed peaks at 1708 & 1738cm^{-1} in the carbonyl region attributable to carboxylic acid and ester absorption respectively. The n.m.r. spectrum showed

an ethyl ester with methyl at 8.73τ (3xH, triplet, J=7cps) and methylene at 5.74τ (2xH, quartet) and an acid proton at -0.17τ as a broadened singlet. Since the n.m.r. spectrum showed in addition the C-2 & C-5 methyl signals and vinyl proton as in the diester, the product was obviously not the dicarboxylic acid (14) or mono-carboxylic acid (8) which might have been envisaged but the half-ester (15).

A similar reaction in aqueous methanol and potassium hydroxide gave an 80% yield of the same product. Hydrolysis with potassium hydroxide in aqueous dioxan gave, after overnight reflux, a 75% yield of product which was shown by t.l.c. to be predominantly the half-ester (15), with a minor component which was thought to be one of the acids, (8) or (14), purely on the basis of its greater polarity.

Treatment of the equatorial tosylate with potassium hydroxide in aqueous dioxan under reflux for 30 mins. gave on work-up a good yield of a half-ester. This is in accordance with the proposed mechanism[1] for the ring-scission process whereby the hydroxyl ion replaces the ethoxide ion normally used as the nucleophilic species in this case. It was hoped that this on hydrolysis would yield the dicarboxylic acid (14); however, attempts to produce this were totally unsuccessful. Methylation of a sample of this half-ester with diazomethane and subsequent g.l.c. analysis showed that this was identical to the methyl ester of the half-ester (15) produced by hydrolysis of the diester (7). This fact was further confirmed by comparison of spectral data.

If we assume the bicyclic equatorial tosylate has

the configuration (6a) then this gives rise to the half-ester (15a). It is suggested that hydrolysis of this axial ester grouping is inhibited both by the C-2 methyl group on one side and the steric crowding produced by the transition state. Since this half-ester is identical to that isolated by the half-hydrolysis of the diester (7), preferential hydrolysis of the equatorial ester grouping in this must occur. Since both axial and equatorial esters are affected by the C-2 methyl interactions, the difficulty in completely hydrolysing (7) can be attributed to the steric environment of the axial grouping.

The resistance of both carbethoxyl groups to hydrolysis must be attributed to steric crowding produced by the methyl group at C-2 since the hydrolysis of the corresponding cycloheptene derivative without the methyl functions has been successfully effected[5].

Since base-catalysed hydrolysis of the diester was proving impractical and the use of acid-catalysed hydrolysis was precluded because of the sensitivity of the system towards isomerisation, it was decided to synthesise the mono-carboxylic acid by an alternative though less direct route. This is shown in Scheme C and involves initial formation of the half-ester (15) followed by decarboxylation to the mono-ester (16) and subsequent hydrolysis.

The half-ester (15) was smoothly decarboxylated by refluxing in pyridine for 4 hours. This gave the pure mono-ester (16) in 76%

yield which showed a single peak on g.l.c. analysis. The infra-red spectrum showed a single carbonyl absorption at 1732cm^{-1} and was transparent in the hydroxyl region. The n.m.r. spectrum showed a single ethyl ester with methyl signal at 8.76 τ(3xH, triplet, J = 7cps) and a vinyl proton at 4.53τ in addition to the C_2 & C_6 methyl signals as before.

The mono-ester was hydrolysed with potassium hydroxide in methanol by overnight reflux and gave 83% of the mono-acid (8). This was shown to be a single compound by g.l.c. analysis of the methyl ester prepared by treatment of the acid with diazomethane. The acid showed carbonyl absorption at 1707cm^{-1} only and a peak at 3531cm^{-1} for free hydroxyl and a broad band from 2500cm^{-1} to 3400cm^{-1} for bonded hydroxyl in the infra-red. The n.m.r. spectrum showed an acid proton at 0.8τ and a vinyl proton at 4.60τ. Cycloheptene acids are known[9] to undergo facile lactonisation but no evidence of this was found in this case.

Although this alternative route to the mono-acid was more tedious than the hydrolysis-decarboxylation one-stage process originally attempted, which might have been expected to succeed, the overall yield of product from the three stages is reasonable.

At this point a new potential route[10] to the mono-ester (16) directly from the diester (7) became available from which yields of

60-80% had been generally obtained in other cases. Accordingly the diester was treated with sodium cyanide in dimethyl sulphoxide but even on protracted reaction times very little conversion took place. This, therefore, gave no advantage over the already proven route which had the added advantage of facile product separation.

The mono-acid (8) was then treated with lead tetraacetate and potassium acetate in pyridine after the general method of Cope[2] The lead tetraacetate, prepared from red lead and acetic acid[11] and freshly recrystallised from acetic acid, was used dampened with acetic acid as it was found that this prevented decomposition of the lead tetraacetate and produced a cleaner reaction. This yielded 56% of product which was shown both by t.l.c. and g.l.c. analysis to consist of a mixture of products. Attempts to isolate these by preparative t.l.c. were largely unsuccessful. The only isolable product showed no vinyl proton in the n.m.r. but an acetate methyl resonance at 7.98τ as a singlet. In view of this evidence and a shoulder at 1765cm^{-1} in the liquid film infra-red spectrum, the acetoxy -lactone structure (17) may be tentatively ascribed to this product.

It was clear that this transformation, facile in theory, was not a practical feasibility. This situation was aggravated by the fact that with the presence of the double bond in the seven membered ring the normal carboxyl to hydroxyl conversion route via the Baeyer-Villiger[12] reaction could not be employed because of epoxidation of the double bond. Although in a symmetrical case this might have been successfully

regenerated, the specificity of the double bond position required in this case, and the duality of possible product were against this route.

In view of the successful application[2] of the lead tetraacetate method on a cycloheptenone acid by Cope, it was decided to reapply this to the half-ester (15) with a view to obtaining the acetoxy-ester (18). This on reduction with lithium aluminum hydride would be expected to lead to the diol (19) which on periodate cleavage would lead directly to the required ketone (2).

The reaction of lead tetraacetate with the half-ester (15) gave a 66% yield of product. However, g.l.c. analysis indicated the presence of several products. Attempts to separate these were fruitless and in view of the results from the mono-acid (8) and the multiplicity of products formed it was decided to abandon this route.

Bearing in mind the diverse applications[13] of the lead tetra-acetate oxidation method for the conversion of an acid to the corresponding lower acetate, and especially the successful application of the method to cyclohept-4-ene carboxylic acid (20) by Cope[2], the failure of the method was at first surprising. Such acetoxy-lactone formation had been noted[14,15] but in both these cases this was found as a minor by-product. However, a subsequent paper[16] has shown that acetoxy-lactone is the major product in the attempted lead tetra-

acetate oxidative decarboxylation of a number of bicyclic unsaturated acids (eg.21 & 22). From the work of these authors, it would appear that the application of this reaction is of doubtful potential in the case of unsaturated acids.

At this point it was decided to explore other potential routes to the ketone (2) from the diester (7). Since the hydrolysis of the diester to the diacid (14) was not practicable, the obvious starting materials were the diester itself or the half-ester (15).

One route to the carbonyl compounds from malonic esters is that developed by Curtius[17,18]. This involves formation of the bis-hydrazide, conversion to the bis-azide and subsequent rearrangement to the ketone via the bisurethan. This is outlined in Scheme D and provides an attractive route which has the added advantage in view of the acid-labile double bond of being conducted at a suitable pH. However, repeated attempts under varying conditions to form the bis-hydrazide were unsuccessful. This may again be attributed to the steric environment of the diester (7) and is in line with the findings of Smith[19], who states that the formation of hydrazides from the esters of disubstituted malonic esters becomes increasingly difficult with the increasing size of substituents.

The next proposed route involved the intermediacy of the amino-alcohol (23). Such compounds are known[20] to undergo periodate cleavage in a manner similar to glycols to yield carbonyl compounds. This cleavage of the amino-alcohol (23) might be envisaged as producing the ketone (2).

The route is outlined in Scheme E. Starting from the readily accessible diester, the half-ester (15) was obtained by hydrolysis in the normal way. The original method[21] of converting this to the amino-acid (24) via treatment of the potassium salt of the half-ester with hydrazine hydrate to give the hydrazide and subsequent classical Curtius rearrangement[22] may be ruled out on the basis of inhibited hydrazide formation discussed above. However, treatment of the acid chloride of the half-ester with sodium azide and subsequent Curtius rearrangement might prove practical.

From the half-ester (15), the acid-chloride(25) was best prepared by refluxing with thionyl chloride in benzene. This gave an 88% yield of material showing the expected high absorption at around 1800cm^{-1} in the infra-red spectrum corresponding to the acid chloride carbonyl. In addition, the infra-red spectrum was transparent in the hydroxyl region showing complete conversion of the acid to acid chloride. This material was used in the next stage without further purification.

The acid chloride (25) was smoothly converted into the corresponding azide (26) by treatment with a 25% aqueous solution of sodium azide in acetone at 0°C. The azide was identified by the appearance of a sharp, intense bond in the infra-red spectrum at 2130cm^{-1}, due to N ≡ N stretching, and the disappearance of the acid chloride carbonyl band at 1800cm^{-1}.

A solution of the azide (26) in dry benzene was refluxed to effect the Curtius rearrangement to the isocyanate (27). The progress of this reaction could be measured by the removal of aliquots from the solution and estimation of the two compounds by infra-red analysis. The formation of the isocyanate was followed by the appearance of a sharp, intense peak at 2270cm^{-1}. After 1½ hours reflux, the reaction was complete with no 2130cm^{-1} absorption visible. On removal of solvent a 73% overall yield of product was obtained for the conversion of acid chloride to isocyanate.

The isocyanate was then treated with potassium hydroxide in aqueous methanol for ½ hour under reflux in an attempt to form the amine (28). From the work-up, there was obtained an overall yield of 80%, consisting of 53% neutrals and 27% of acidic material. The acidic fraction was shown by t.l.c to consist of a major and a minor component. Separation of these was effected by preparative

t.l.c. in a dioxan/benzene/acetic acid solvent system. The minor component was shown by spectral correlation to be the half-ester (15), which had presumably arisen from hydrolysis of the starting acid-chloride (25) before reaction with sodium azide had taken place. The major component showed an acid proton at -1.45τ and a vinyl proton at 4.33τ in addition to the two normal methyl signals at C-2 & C-5 in the n.m.r. spectrum. The infra-red spectrum showed carbonyl absorption at 1703cm^{-1} and a broad hydroxyl band from 2400 - 3500cm^{-1}. From this data and the indicated presence of nitrogen from an elements test, this would appear to be the amino-acid (29) which is formed by hydrolysis of both the ester and isocyanate function. This is neither unexpected nor undesirable, since after the next reductive step both the amino-acid and the amino-ester would give rise to the required amino-alcohol (23).

The neutral fraction showed two main components in the ratio 1:2 by g.l.c. analysis. These were subjected to gas chromatograph mass spectrometer analysis and were shown to have molecular weights of 211 & 222 respectively. The former had the expected molecular weight for the amino-ester (28) and showed peaks at $^{m}/_{e}$ 138 for loss of carbethoxyl: 194 for loss of ammonia and 121 for loss of ammonia from the 138 base peak. That this was the amino-ester

was confirmed by the isolation of this material from the mixture by preparative t.l.c. This showed ester methyl at 8.74 τ : C-5 methyl at 8.31τ : C-2 methyl at 9.21τ and a vinyl proton at 4.5 τ in the n.m.r. spectrum and had carbonyl absorption at 1734cm^{-1} for the ester grouping in the infra-red. In addition N-H stretching absorptions were observed at 3440 & 3400cm^{-1}.

The product of molecular weight 222 could not be isolated in completely pure form but was shown not to contain nitrogen, a fact which might have been inferred from the even molecular weight. The infra-red spectrum showed twin carbonyl peaks at 1729 & 1760cm^{-1} and from this data the structure (30) is suggested for the product. The formation of such bicyclic compounds from medium rings has already been noted [23] e.g. the cyclononene diester (31) gave on chromatography the 4:3:1 bicyclic structure (32). Here a transannular reaction is proposed with elimination of ethoxide. In addition a purely thermal rearrangement of (33) to (34) has been observed[24]. No evidence of such transannular reactions have been found in the diester (7), however. It is suggested in this case that (30) is formed from the azide (26) by ring closure and loss of azide. Presumably in the cycloheptene case, the more favourable leaving group, azide, is required for steric or thermodynamic reasons to induce this transformation, whereas in the cyclononene case ethoxide is a sufficiently good leaving group, since strong basic and acidic

and thermal conditions have produced no cyclisation of the diester (7) but no real confirmation of structure (30) was obtained.

At this juncture the remaining steps were performed on the amino-acid (29). This was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to give a 75% yield of product. Column chromatography on alumina gave the major product. This non-acidic material showed a vinyl proton at 4.56τ : C-5 methyl at 8.30τ : C-2 methyl at 9.04 and 9.25τ in the n.m.r. spectrum. Deuterium oxide exchange showed the loss of a peak at 7.89τ, attributable to the hydroxyl proton. In addition the infra-red spectrum was transparent in the carbonyl region and showed a hydroxyl absorption at 3634cm^{-1}. On the basis of this evidence the product was assigned the structure of the required amino-alcohol (23).

The amino-alcohol (23) was then treated with aqueous sodium metaperiodate in methanol for 24 hours at room temperature. This yielded a clear volatile liquid which showed one predominant product on t.l.c. analysis which in addition gave an orange colouration with 2,4-dinitrophenylhydrazine spray. This was isolated by preparative t.l.c. and exhibited a single peak by g.l.c. analysis. The compound showed carbonyl absorption at 1710cm^{-1} and gave an orange 2,4-dinitrophenylhydrazone which

analysed for the derivative of the ketone (2). Final confirmation of the production of the required ketone was given by the n.m.r. spectrum which showed the C-2 methyl at 8.93τ as a sharp doublet, J=6cps; the C-5 methyl as a finely split triplet, J=1.5cps at 8.23τ and the vinyl proton at 4.45τ as a subsplit triplet.

This was undoubtedly the required ketone (2) and, although the overall yields from the half-ester (15) are reduced due to unforeseen by-products which introduce separation difficulties, this is a feasible route. However, before attempting to improve this sequence or take steps to eliminate the trouble spots it was decided to approach the second half of the problem, the attachment of the side chain, and so test the overall viability of the proposed route.

In view of the small quantity of the ketone (2) available at this point it was decided to explore the subsequent steps to the tosylate (1) using the more readily accessible 2-methyl-cycloheptanone (35) as a model. Since this differs from the ketone (2) only by a methyl group at C-5 and the double bond, neither of which would be expected to participate in any of the proposed steps to the tosylate, it seemed justifiable that any reactions successfully performed on this might reasonably be expected to work on the cycloheptenone.

The first route attempted was the most direct, involving alkylation of 2-methylcycloheptanone with 1-bromo-4-methyl pent-3-ene (3). 2-methylcycloheptanone was obtained by ring expansion of cyclohexanone on treatment with diazoethane[25] and the monobromide (3) by the method of Gamboni[26] starting from butyrolactone

Condensation of these was initially attempted via the lithium enolate of 2-methylcycloheptanone by treatment[27] of the ketone with n-butyl lithium in tetrahydrofuran followed by addition of the bromide to the resultant solution. This gave a poorish yield of product which showed a singlet methyl signal at 9.11τ and a doublet methyl at 9.07τ in the n.m.r. in addition to a peak which disappeared on deuterium oxide exchange. This last peak might be assigned to a hydroxyl group and this was confirmed by the infra-red spectrum which showed hydroxyl absorption at 3625cm^{-1}.

This product would appear to be the aldol self-condensation product of 2-methylcycloheptanone shown in (36). This must arise from incomplete formation of the enolate followed by reaction of the enolate formed with excess ketone in preference to the less acceptable bromide.

A further attempt to effect the alkylation using sodamide in tetrahydrofuran was again unsuccessful although this method had been usefully employed by Corey[28] to alkylate a bicyclic α-substituted ketone with a similar long chain alkyl halide.

In view of the obvious difficulty with which the alkylation was proceeding, and the relative inaccessibility of the bromide (3), it was decided to attempt various alternative alkylation methods using the available n-hexyl bromide. This was of similar steric bulk to the bromide (3) and the effect of the double bond on the alkylation step was not expected to be crucial.

Attempted alkylation with potassium tert-butoxide in tert-butanol even with increased reaction times gave at best 20% of isolable material and this was shown to be mainly the self-condensed 2-methylcycloheptanone aldol product already encountered.

The use of triphenylpotassium in diglyme [30] on 1,2-dimethoxyethane[31] also gave no isolable alkylation products and at this point it was decided that the alkylation of the ketone using a bromide of this nature did not constitute a practicable synthetic route.

The difficulty encountered in alkylating 2-substituted cyclo-heptanones and their resistance to a variety of chemical reactions e.g. enamine formation, is a striking example of the dangers of extending the scope of a synthetic reaction to another ring system. The alkylation of a bicyclo (2.2.1) ketone (37) with a compound similar to (3) was effected smoothly by Corey[28] but this is

totally inapplicable to the corresponding cycloheptanone. This reluctance to alkylation must stem from the difficulty in effecting complete enolate formation from the substituted cycloheptanone. That enolate which is formed then appears to prefer condensation with the unreacted ketone to substitution on the bromide.

With the failure of the bromide (3) as an alkylating agent, it was decided to build on the side-chain in stepwise fashion. Michael addition of acrolein to 2-methylcycloheptanone would give the aldehyde (38). A selective Wittig reaction with one mole of the isopropylidene ylid (39) should lead to predominant if not total reaction at the more reactive[32] aldehydic function to give the ketone (40). This on reduction and tosylation would give (1) as shown in Scheme F.

However, treatment of 2-methylcycloheptanone with acrolein in ethanol with a catalytic amount of sodium hydroxide at -70°C gave predominantly returned starting material.

It was therefore decided to amend the starting material and determine whether the above sequence could be applied to 2-carbethoxycycloheptanone (41), which would be expected to participate more favourably in the Michael condensation.

On obtaining the alkylated β-keto-ester (42), it was proposed, as in Scheme G, first to reduce this with lithium aluminum hydride to the diol (43). Selective primary tosylation using a single mole of p-toluenesulphonyl chloride should yield the mono-tosylate (44) which on treatment with lithium aluminum hydride[33] would give the alcohol (45). This on tosylation would produce the compound desired by the previous route.

2-carbethoxycycloheptanone (41) was prepared from the reaction of diethyl carbonate and cycloheptanone in the presence of sodium hydride by an adaptation of the method of Ayerst[34]. This gave an improved 60% yield of product which g.l.c. analysis on 7%F60/1%Z at 125° showed to be a single compound. The condensation of this with acrolein proceeded smoothly in the presence of a catalytic amount of sodium ethoxide in ethanol at -70°C to yield on distillation two fractions.

The first of boiling point 117-22°/0.2mm. showed a single peak by g.l.c. analysis. This gave a negative ferric chloride test and from the presence of an aldehydic proton at 0.23τ in the n.m.r. and the lack of hydroxyl absorption in the infra-red in addition to the expected[35] spectral features was shown to be the required addition product (46).

The second fraction of boiling point 165-75 °/0.2mm. showed similar features to the first in the n.m.r. spectrum but had no aldehydic resonance. Its infra-red spectrum showed the presence of a hydroxyl function and on the basis of these facts this was presumed to be the aldol-product, the bicyclic alcohol(47).

For the Wittig reaction on this Michael adduct, the required phosphonium salt, isopropyltriphenylphosphonium iodide was prepared in 88% yield from a melt of triphenylphosphine and isopropyl iodide following the method of Wittig[36]. The ylid was produced by treatment[37] of the phosphonium salt in tetrahydrofuran with n-butyl lithium and the aldehyde added in tetrahydrofuran. This procedure produced on work-up no appreciable product but an excellent return of starting material.

The modified procedure of Corey[38] using sodium hydride in dry dimethyl sulphoxide was then attempted. This produced a viscous oil which on column chromatography and subsequent spectral and g.l.c. investigation was shown to be a mixture of starting material and the alcohol (47), the latter being the predominant product.

In the light of these investigations, it appears that although the dimethylcycloheptenone (2) is available, with difficulty, its subsequent elaboration to the biogentic precursor via (1) presents problems which have yet to be solved.

EXPERIMENTAL:

2-carbethoxy-2-methylcyclopentanone (11)

This was prepared by the method of Nicole[3] and was obtained in 79% yield as a clear liquid, b.pt. 110-2°/20mm. This showed a single peak with Rt = 17.5 min. on 7% F60/1% Z at 100° and 40 ml./min. by g.l.c. analysis. It showed a singlet methyl resonance at 8.76τ in the n.m.r. spectrum; $\gamma_{C=O}^{CCl_4}$ 1733 and 1753 cm^{-1} in the infra red and gave a negative ferric chloride test.

2-carbethoxy-5-methylcyclopentanone (4)

This was prepared by treatment of (11) with sodium ethoxide following the procedure of Sisido[4] and was obtained in 75% yield as a clear liquid, b.pt. 113-6°/20mm. G.l.c. analysis indicated the presence of a single component, Rt = 22.0 min. on 7% F60/1% Z at 100° and 40 ml./min. This gave a positive ferric chloride test; showed a doublet methyl resonance centred at 8.92τ (J = 6cps) in the n.m.r. and had $\gamma_{C=O}^{CCl_4}$ 1731 and 1755 cm^{-1} in the infra red spectrum.

1-carbethoxy-4-hydroxy-2,5-dimethylbicyclo(3.2.1.)octan-8-one (5)

A mixture of 2-carbethoxy-5-methylcyclopentanone (4) (25 g.; 0.147 m.) and freshly distilled crotonaldehyde (11.35 g.; 0.162 m.) cooled in ice, was added to a solution of sodium (200 mg.) in anhydrous ethanol (200 ml.), with a few crystals of hydroquinone added, at -70°C over 1 hour with stirring and the mixture left to

stir a further two hours at room temperature. Glacial acetic acid was added to pH 7 and the ethanol removed under reduced pressure. The residue was dissolved in ether, washed with brine, saturated sodium bicarbonate, water and then dried. On removal of the ether, distillation of the residue yielded 27.2 g.(77%) of a clear viscous oil, b.pt. 170-5°/0.2 mm. G.l.c. analysis on 5% APL at 150° and 50 ml./min. showed the presence of the two epimeric alcohols (5) with Rt = 32.5 and 35.3 min. and the aldehyde-ester (12) with Rt = 15.9 min., comprising 65;30; and 5% of total product respectively. Integration of the aldehyde proton at 0.28τ against the ester methylene signal showed the aldehyde-ester impurity to be less than 5% by n.m.r. The n.m.r. spectrum of a pure sample of alcohol (5), obtained by preparative t.l.c., showed in its n.m.r. spectrum C-5 methyl at 8.97τ (3xH,singlet); C-2 methyl at 9.09τ (3xH,doublet, J=7cps); ester methyl at 8.74τ (3xH,triplet,J = 7cps). The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1735 cm^{-1} (ester) and 1761 cm^{-1} (bicyclic ketone) and $\gamma_{O-H}^{CCl_4}$ 3631 cm^{-1} (free hydroxyl) and 3400-3560 cm^{-1} (bonded hydroxyl). Found C,64.15; H,8.46. $C_{13}H_{20}O_4$ requires C,64.98; H,8.39%.

1-carbethoxy-2,5-dimethyl-4-tosyloxybicyclo(3.2.1)octan-8-one (6)

A solution of p-toluenesulphonyl chloride (18.5 g.; 0.097 m.) in dry pyridine (75 ml.) was added dropwise with stirring to a mixture of the epimeric bicyclic alcohols (5) (15.5 g.; 0.065 m.) at 0°C and the mixture allowed to stir at room temperature for four days.

The reaction mixture was then poured onto ice (75 g.) and left to stand for 24 hours. The product was extracted with ethyl acetate and the organic layers washed thoroughly with dilute hydrochloric acid to remove excess pyridine; with sodium bicarbonate solution; water and then dried. On removal of the solvent there was obtained a viscous light red oil, which partly solidified on standing to give 19.9 g. (79.5%) of product. The whole was dissolved in hot ethanol and, on cooling, 2.4 g. of a white crystalline solid, m.pt. 162-3°, were obtained. (Found C,60.88; H,6.51. $C_{20}H_{26}O_5S$ requires C,60.90; H,6.64%). This was shown by n.m.r. to be the axial epimer of (6) by the C-4 proton signal at 5.3τ, with half band width of 10 cps. The n.m.r. spectrum also showed C-5 methyl at 9.13τ(3xH, singlet); C-2 methyl at 9.09τ(3xH, doublet, J = 7 cps); ester methyl at 8.70τ(3xH, triplet, J = 7 cps); aromatic methyl at 7.52τ(3xH, singlet) and an A_2B_2 aromatic proton system between 2.1 and 2.7τ. The infra red spectrum showed $\gamma^{CCl_4}_{C=O}$ 1734 cm^{-1} (ester) and 1766 cm^{-1} (bicyclic ketone) and $\gamma^{CCl_4}_{SO_2}$ 1178 and 1371 cm^{-1}. The residue could be crystallised from ethanol to yield white needles, m.pt. 81-2°. (Found C,61.06; H,6.44. $C_{20}H_{26}O_5S$ requires C,60.90; H,6.64%). This was shown to be the more polar equatorial epimer from the half band width of the C-4 proton of 4 cps at 5.6τ. The n.m.r. spectrum also showed C-5 methyl at 9.10τ(3xH, singlet); C-2 methyl at 9.05τ(3xH, doublet, J = 7 cps);

ester methyl at 8.72τ(3xH,triplet,J = 7 cps); aromatic methyl at 7.51τ(3xH,singlet) and aromatic protons (4xH) as an A_2B_2 system between 2.1 and 2.7τ. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1736 cm^{-1} (ester) and 1766 cm^{-1} (bicyclic ketone) and $\gamma_{SO_2}^{CCl_4}$ 1179 and 1379 cm^{-1}.

Treatment of the epimeric tosylates (6) with sodium ethoxide

A solution of the epimeric tosylates (6) (12 g.; 0.031 m.) in hot anhydrous ethanol (60 ml.) was added to a solution of sodium ethoxide in ethanol (from 0.915 g. sodium and 120 ml. ethanol) at 60°C. An almost immediate precipitation occurred and the mixture was refluxed with stirring for a further 15 min. It was then cooled, poured onto ice, acidified with 6N hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine, dried and the ether removed to yield a mixture which gave on distillation 6.23 g. of a clear oil, b.pt. 105-8°/0.2 mm. G.l.c. analysis of the product showed it to consist of two components in the ratio 2:3 with retention times 34.1 and 41.8 min. on 10% APL at 150° and 45 ml./min. and 54.0 and 66.0 min. on 1% SE30 at 100° and 60 ml./min. respectively. Combined gas chromatograph/mass spectrometer analysis on 1% SE30 confirmed the isomeric nature of the products which both had molecular weight 268, that of the anticipated product, 1,1-dicarbethoxy-2,5-dimethylcyclohept-4-ene (7).

Attempted conversion of the isomeric mixture

A 25 mg. sample of the isomeric mixture obtained above was

subjected to the following treatments and the products analysed by g.l.c.

(a) A sample of the isomeric mixture was refluxed for 72 hours in 5 ml. of chloroform with 10 mg. of p-toluenesulphonic acid added. The mixture was cooled, 5 ml. of water added and the solution neutralised with 4N sodium hydroxide. The organic layer was separated and the aqueous layer extracted with chloroform. The combined organic layers were washed with brine, dried, the chloroform removed and the mixture analysed by g.l.c. No apparent change in the proportion of the two isomers was observed.

(b) A sample was refluxed for 72 hours in 5 ml. of the sodium ethoxide solution used in the original reaction. The mixture was subjected to the work-up procedure for the original reaction and the product showed no composition change on g.l.c. analysis.

(c) A sample was refluxed for 72 hours in a mixture of 5 ml. of ethanol and 1 ml. of conc. hydrochloric acid. The mixture was then poured onto ice, neutralised with 4N sodium hydroxide, extracted with ether and isolated as in (a). G.l.c. analysis of the product showed no change.

Treatment of the axial tosylate (6) with sodium ethoxide

The axial tosylate (6) (100 mg.) was treated with sodium ethoxide in ethanol, as for the epimeric mixture. Following the same work-up procedure, there was obtained 92 mg. of product, which was shown

by t.l.c. and its infra red spectrum to be identical with the starting axial tosylate.

Treatment of the equatorial tosylate (6) with sodium ethoxide

A solution of pure equatorial tosylate (6) (13 g.; 0.034 m.) in hot anhydrous ethanol (65 ml.) was added to a solution of sodium ethoxide (from 1 g. sodium and 125 ml. ethanol) at 60° and the mixture refluxed for 15 min. The mixture was cooled, poured onto ice, carefully neutralised to pH 7 with 6N hydrochloric acid and extracted with ether. The ethereal extracts were washed thoroughly with brine, dried and the ether removed to give, on distillation of the residual oil, 7.0 g. (78%) of a clear liquid, b.pt. 103-6°/0.2 mm. G.l.c. analysis showed this to be a single compound Rt = 41.7 min. on 10% APL at 150° and 45 ml./min. (Found C,66.88; H,8.83. $C_{15}H_{24}O_4$ requires C,67.14; H,9.01%) This was the expected diester (7) and showed $\gamma_{C=O}^{CCl_4}$ 1735 cm^{-1} (ester) and $\gamma_{C-H}^{CCl_4}$ 3033 cm^{-1} (double bond) in the infra red spectrum. The n.m.r. spectrum showed ester methyl (6xH, triplet, J = 7 cps) at 8.78τ; C-2 methyl (3xH, doublet, J= 7 cps) at 9.11τ; C-5 methyl (3xH, broad singlet) at 8.32τ and a vinyl proton (1xH, multiplet) at 4.65τ.

Attempted equilibration of the pure diester (7)

(a) Thermal treatment

A sample of pure diester (7) was heated and aliquots removed for g.l.c. analysis on 10% APL at 150°. Heating times of 15 min. over a

range of temperatures between 65° and 180° showed no equilibration on g.l.c. analysis.

(b) Effect of reagents

A sample of pure diester (7) (25mg.) was refluxed for 15 min. in 5ml. ethanol in the presence of an additional reagent. The mixture was cooled, flooded with water, neutralised if necessary and ether extracted. The ether extracts were brine washed, dried and , on the removal of solvent, the residue analysed by g.l.c. on 10% APL at 150°. The results obtained are shown in the table.

Reagent	Quantity	Result
hydrochloric acid	2 drops	isomerisation
sulphuric acid	2 drops	isomerisation
acetic acid	5 drops	no change
sodium acetate	10mg.	no change
p-toluenesulphonic acid	10mg.	isomerisation
axial tosylate	10mg.	no change
sodium ethoxide	from 10mg. Na	no change

Attempted hydrolysis of the diester (7)

(a) Potassium hydroxide - methanol

A solution of the diester (7) (6.0g.; 0.022m.) and potassium hydroxide (1.5g.) in methanol (50ml.) was refluxed for 16 hours. On cooling the excess methanol was removed under reduced pressure,

the residue dissolved in water and extracted with ether. The ethereal extracts were discarded. The aqueous layer was carefully neutralised with dilute hydrochloric acid, extracted with ether and the ethereal extracts washed thoroughly with brine and dried. Removal of the solvent and distillation gave 4.48g.(82%) of a clear, viscous oil, b.pt. 133-6°/0.25mm. Found, C,65.01; H,8.14. $C_{13}H_{20}O_4$ requires C,64.98; H,8.39%. The product, on methylation with diazomethane, showed a single peak, Rt = 21.5min. on 10% APL at 150° and 60ml/min. The n.m.r spectrum showed an acid proton at -0.1τ(1xH,broad singlet); ethyl ester methyl at 8.73τ(3xH,triplet,J=7cps) and methylene at 5.74 τ (2xH,quartet) and a vinyl proton at 4.6τ(1xH,broadened singlet), in addition to the C-2 and C-5 methyl signals as noted in the diester(7) The infra red spectrum showed $\gamma^{CCl_4}_{C=O}$ 1708 cm^{-1} (acid) and 1738 cm^{-1} (ester) and $\gamma^{CCl_4}_{O-H}$ 3628 cm^{-1} (free hydroxyl) and 2400-3500 cm^{-1} (bonded hydroxyl). This was, therfore, not the expected diacid (14) or the monoacid (8) but the half-ester (15).

(b) Potassium hydroxide - methanol - water

A solution of the diester (7) (2.0g.; 0.007m.) and potassium hydroxide (0.5g.) in a mixture of methanol (20ml.) and water (5ml.) was refluxed for 16 hours. Following the work-up procedure employed in (a), there was obtained 1.5g.(80%) of product which showed identical t.l.c. and spectral properties to the half-ester (15).

(c) Potassium hydroxide - aqueous dioxan

A solution of the diester (7) (1.5g.; 0.006m.) and potassium hydroxide (0.4g.) in a mixture of water (3ml.) and dioxan (20ml.) was refluxed for 16 hours. The mixture was cooled and extracted with ether. The aqueous layer was carefully neutralised with 6N hydrochloric acid, extracted with ether and the ethereal layers washed with brine, sodium bicarbonate solution, water and dried. Removal of the solvent yielded 1.0g.(75%) of product, which was shown to be mainly the half-ester by t.l.c. analysis. A small more polar impurity might have been the dicarboxylic acid.

Treatment of the equatorial tosylate (6) with KOH in aq. dioxan

A solution of the equatorial tosylate (6) (200mg.) in dioxan (5ml.) was added to a stirred solution of potassium hydroxide (50mg.) in water (1ml.) and the mixture refluxed for 30min. It was then cooled diluted with water and carefully neutralised with 6N hydrochloric acid. The mixture was ether extracted and the extracts washed with brine and dried. Removal of the solvent yielded 110mg. of an oil which had similar infra red and n.m.r. spectra to the half-ester (15). Methylation of a sample and subsequent g.l.c. analysis on 10% APL at 150° and 60ml./min. showed a single peak, Rt = 21.5min., corresponding to that of the half-ester (15).

1-carbethoxy-2,5-dimethylcyclohept-4-ene (16)

A solution of the half-ester (15) (4.0g.;0.017m.) in dry pyridine (25ml.),with a few boiling stones added, was refluxed for 4 hours. The pyridine was removed under reduced pressure and the residue dissolved in ether and washed with 4N sodium hydroxide to remove any unchanged acid. The ethereal layer was washed with brine, dried and distilled to yield 2.47g.(76%) of the mono-ester (16) as a clear liquid, b.pt. 85-90°/0.25mm. Redistillation yielded an analytical sample. (Found, C,72.83; H,10.16. $C_{12}H_{20}O_2$ requires C,73.43; H,10.27%. This showed $\gamma^{CCl_4}_{C=O}$ 1732 cm^{-1} (ester) and $\gamma^{CCl_4}_{C-H}$ 3035 cm^{-1} (double bond) in the infra red spectrum and had Rt = 18min. on 10% APL at 125° and 55ml./min. by g.l.c. analysis. The n.m.r. spectrum showed ester methyl at 8.76τ(3xH,triplet,J=7cps); C-5 methyl at 8.31τ(broadened singlet); C-2 methyl at 9.10τ(3xH,doublet,J=5cps); and vinyl proton at 4.53τ(1xH,broad).

1-carboxy-2,5-dimethylcyclohept-4-ene (8)

A solution of the mono-ester (16) (2.2g.;0.011m.) and potassium hydroxide (0.75g.) in methanol (25ml.) was refluxed for 16 hours. The mixture was cooled and the methanol removed under reduced pressure. The residue was dissolved in water, extracted with ether and the ethereal extracts discarded. The aqueous solution was cooled in ice and the acid liberated by careful addition of 6N hydrochloric acid. The mixture was extracted with ether and the ethereal extracts

washed with brine, dried and evaporated to yield on distillation 1.53g.(83%) of a clear, viscous oil, b.pt. 120-4°/0.35mm. Found, C,71.42; H,9.48. $C_{10}H_{16}O_2$ requires C,71.39; H,9.59%. This showed $\gamma_{C=O}^{CCl_4}$ 1707 cm^{-1} (acid) and $\gamma_{O-H}^{CCl_4}$ 3531 cm^{-1} (free hydroxyl) and 2500-3400 cm^{-1} (bonded hydroxyl) in the infra red spectrum. The n.m.r. spectrum showed a vinyl proton at 4.60τ(1xH,broad); acid proton at 0.8τ(1xH,broad) in addition to the C-2 and C-5 methyls as before. G.l.c. analysis of the corresponding methyl ester, prepared by methylation with diazomethane, showed a single peak with Rt = 12.7min. on 10% APL at 125° and 45ml./min.

Treatment of the mono-acid (8) with lead tetraacetate

A solution of the mono-acid (8) (1.0g.; 0.06m.) and anhydrous potassium acetate (5.8g.) in glacial acetic acid (20ml.) was heated to 70°C and freshly recrystallised lead tetraacetate (4.0g.) added in portions with stirring over ½ hour. Evolution of carbon dioxide occurred and the mixture was stirred for a further ½ hour at 70± 5°C until evolution had ceased. The mixture was cooled, diluted with water and extracted with pentane. The combined pentane extracts were washed with 10% sodium bicarbonate solution, dried and evaporated to yield 610mg.(56%) of product. Both t.l.c. and g.l.c. analysis on 10% APL at 125° showed the presence of a number of products. Attempts to purify this by preparative t.l.c. were unsuccessful, the only reasonably pure product isolable showing an acetate methyl at 7.98τ

in the n.m.r. spectrum, but no vinyl proton and no vinyl methyl signal. This was possibly the acetoxy-lactone (17) in view of a shoulder at around 1765 cm^{-1} (liquid film) in the infra red carbonyl region.

Preparation of the acid chloride (25)

Thionyl chloride (3.6g.; 0.03m.) was added dropwise to a solution of the half-ester (15) (5.0g.; 0.021m.) in dry benzene (25ml.) and the mixture refluxed for 2 hours. Removal of the benzene and excess thionyl chloride under reduced pressure yielded 4.80g. (88%) of a liquid which showed $\gamma_{C=O}$ 1735 cm^{-1} (ester) and 1800 cm^{-1} (acid chloride) and was transparent in the hydroxyl region in a liquid film infra red spectrum. This was used in the next stage without further purification.

Preparation of the azide (26)

A 25% solution of sodium azide (1.3g.) in water was added dropwise to a solution of the acid chloride (25) (4.80g.; 0.018m.) in dry acetone (25ml.) at 0°C and the mixture allowed to warm up to room temperature and then stirred for 2 hours. The mixture was then flooded with water and extracted with benzene. The combined benzene extracts were washed with brine, dried and the greater part of the solvent removed under reduced pressure. Infra red analysis of the resultant liquid showed a sharp intense peak at 2130 cm^{-1} (liquid film) due to N≡N stretching and the loss of the acid chloride carbonyl peak at 1800cm^{-1}.

Rearrangement of the azide (26) to the isocyanate (27)

A solution of the azide (26) in dry benzene (25ml.) was heated under reflux. The conversion of the azide to isocyanate (27) was monitored by infra red analysis of aliquots removed from the reaction. After $1\frac{1}{2}$ hours, the azide peak at 2130 cm^{-1} had disappeared and had been replaced by an isocyanate peak at 2270 cm^{-1}. At this point the benzene was removed under reduced pressure to yield 2.95g.(73% overall from the acid chloride) of isocyanate (27) which was used without further purification.

Hydrolysis of the isocyanate (27)

A solution of the isocyanate (27) (2.95g.; 0.012m.) and potassium hydroxide (2.0g.) in a mixture of water (6.0ml.) and methanol (80ml.) was refluxed for 30 min. The mixture was poured onto ice and ether extracted. The ethereal extracts were washed with brine, dried and distilled to yield 1.40g.(53%) of neutral material, b.pt. 100-120°/ 0.25mm. The aqueous solution was carefully acidified with 6N hydrochloric acid and extracted with ether. The ethereal extracts were washed with brine, dried and evaporated to yield 630mg.(27%) of acidic material (overall yield = 80%). T.l.c. analysis of the acidic fraction showed it to consist of two components. The minor one corresponded to the half-ester (15) and the major, which was isolated by preparative t.l.c., showed an acid proton at -1.45 τ; C-5 methyl at

8.23τ; C-2 methyl at 9.03τ and a vinyl proton at 4.33τ. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1703 cm^{-1} (acid) and a broad hydroxyl band from 2400 cm^{-1} to 3500 cm^{-1}. This was the amino-acid (29). G.l.c. analysis of the neutral fraction indicated two major components with Rt = 14.2 and 23.0 min. on 1% SE 30 at 100° and 55ml./min. in the ratio 1:2. Gas chromatograph/mass spectrometer analysis on 1% SE 30 showed these to have molecular weights of 211 and 222 respectively. The first had the molecular weight expected of the amino-ester (28) and showed a base peak at m/e 138 corresponding to the loss of the carbethoxyl group and peaks at m/e 194 for loss of ammonia and 121 for loss of ammonia from the base peak ion. N.m.r. analysis of a crude sample of this, isolated by preparative t.l.c., showed ester methyl at 8.74τ(3xH,triplet,J=7cps); C-5 methyl at 8.31τ (3xH,broadened singlet); C-2 methyl at 9.21τ(3xH,doublet,J=6cps) and a vinyl proton at 4.5τ(1xH,broad). The infra red spectrum had $\gamma_{C=O}^{CCl_4}$ 1734 cm^{-1} (ester) and $\gamma_{C=O}^{CCl_4}$ 3400 and 3440 cm^{-1}. The second had molecular weight 222 and showed loss of carbethoxyl at m/e 149. An impure sample of this was isolated by preparative t.l.c. and showed $\gamma_{C=O}^{CCl_4}$ 1729 cm^{-1} (ester) and 1760 cm^{-1}. On the basis of this data and the absence of nitrogen, the structure (30) is suggested.

Reduction of the amino-acid (29)

A solution of the crude amino-acid (29) (0.7g.) in dry tetrahydrofuran (20ml.) was added to a stirred suspension of lithium

aluminium hydride (0.4g.) in dry tetrahydrofuran (20ml.) and the mixture refluxed overnight. The mixture was cooled and the excess hydride destroyed by careful addition of a saturated solution of anhydrous sodium sulphate. The resultant mixture was filtered, washed thoroughly with ether, dried and the ether removed to give 460mg.(75%) of product. Column chromatography on Grade 0 alumina effected the separation of the major product which showed a vinyl proton at 4.56τ(1xH,subsplit triplet); C-5 methyl at 8.30τ(3xH, triplet,J=2cps) and C-2 methyl as two pairs of doublets(3xH) at 9.04 τ and 9.25 τ in the n.m.r. spectrum. Deuterium oxide exchange caused the loss of a peak at 7.89τ, corresponding to the hydroxyl proton. The infra red spectrum showed $\gamma^{CCl_4}_{O-H}$ 3634 cm^{-1} (hydroxyl) and was transparent in the carbonyl region.

Treatment of the amino-alcohol (23) with sodium periodate

A solution of sodium metaperiodate (200mg.) in water (4ml.) was added to a solution of the amino-alcohol (23) (150mg.) in methanol (10ml.) and the mixture stirred at room temperature for 24 hours. The mixture was then flooded with water and ether extracted. The ethereal extracts were washed with brine, dried and evaporated to give 90mg.(76%) of a volatile liquid, which showed one major product by t.l.c. analysis. Preparative t.l.c. enabled the separation of a single compound with Rt = 29.4 min. on 7% F 60/1% Z at 75° and 50ml./min. This showed $\gamma^{CCl_4}_{C=O}$ 1710 cm^{-1} (cycloheptanone) in the infra

red spectrum and gave an orange 2,4-dinitrophenylhydrazone, m.pt. 116-7°(ethanol). Found C,56.6; H,5.86; N,17.71. $C_{15}H_{18}N_4O_4$ requires C,56.6; H,5.70; N,17.60%. The n.m.r. spectrum of the ketone showed C-2 methyl at 8.93τ(3xH,doublet,J=6cps); C-5 methyl at 8.23τ(3xH, triplet,J=1.5cps) and a vinyl proton at 4.45τ(1xH,subsplit triplet).

2-methylcycloheptanone (35)

This was prepared by a ring expansion of cyclohexanone on treatment with diazoethane[25] and was obtained as a clear liquid, b.pt. 175-80° in 53% yield. G.l.c. analysis on 7% F 60/1% Z at 75° and 50ml./min. indicated the presence of a single component, Rt = 15.7 min.

1-bromo-4-methylpent-3-ene (3)

This was prepared from butyrolactone by the method of Gamboni[26] and was obtained as a volatile liquid, b.pt. 160-5°.

Attempted condensation of (35) and (3)

A solution of 2-methylcycloheptanone (35) (1.26g.; 0.01m.) in dry tetrahydrofuran (5ml.) was added dropwise to a solution of n-butyl lithium (4ml. of 22% in hexane) in dry tetrahydrofuran (5ml.) and the mixture stirred under nitrogen for 4 hours at -20 to -30°C. The bromide (3) (1.63g.; 0.01m.) in dry tetrahydrofuran (5ml.) was added dropwise and the mixture stirred for 1 hour at 0°C and at room temperature overnight. The mixture was then poured onto ice and extracted with ether. The ethereal extracts were washed with water,

brine and dried to yield, on removal of the solvent and distillation, 430mg. of material, b.pt. 122-5°/12mm. N.m.r. analysis of this showed a hydroxyl proton signal as a sharp singlet at 7.81τ, which disappeared on deuterium oxide exchange, and methyl signals at 9.11 τ (3xH, singlet) and 9.07τ(3xH, doublet, J=6cps). The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1713 cm^{-1} and $\gamma_{O-H}^{CCl_4}$ 3625 cm^{-1}

2-carbethoxycycloheptanone (41)[34]

A mixture of cycloheptanone (50g.; 0.45m.) and ethanol (2ml.) was added dropwise with stirring to a mixture of sodium hydride (43g. of a 50% dispersion in oil), dry ether (200ml.) and diethyl carbonate (108g.; 0.9m.). After the addition of the first few drops of cycloheptanone, a vigorous reaction began and cooling was necessary. The addition of cycloheptanone was completed, with cooling, in 1½ hours and the mixture was stirred a further 3 hours at room temperature. The unchanged sodium hydride was carefully destroyed with glacial acetic acid and the whole dissolved in ice water. The mixture was extracted with ether and the ethereal extracts washed with brine, dried and evaporated. Distillation of the residue gave 48.0g.(60%) of product, b.pt. 130-5°/20mm., which gave a positive ferric chloride test and was shown by g.l.c. analysis on 7% F 60/ 1% Z at 125° and 40ml./min. to be a single compound, Rt = 33.5 min., free from starting cycloheptanone. The infra red spectrum showed $\gamma_{C=O}^{CCl_4}$ 1711 cm^{-1} (cycloheptanone) and 1745 cm^{-1} (ester) and the n.m.r.

spectrum showed the presence of the carbethoxyl function, with methyl at 8.74τ(3xH,triplet,J=7cps) and methylene at 5.81τ(2xH,quartet).

Condensation of 2-carbethoxycycloheptanone (41) and acrolein

To a solution of sodium (100mg) and two crystals of hydroquinone in dry ethanol (50ml.),cooled to -70°C, was added dropwise a cooled mixture of 2-carbethoxycycloheptanone (41) (17.1g.; 0.093m.) and freshly distilled acrolein (6.0g.; 0.118m.) and two crystals of hydroquinone over the period of one hour. The cooling bath was removed and the mixture stirred a further 3 hours at room temperature. Glacial acetic acid was added to pH 7 and the ethanol removed under reduced pressure. The residue was dissolved in ether, washed with water, sodium bicarbonate solution,water and dried. On removal of the solvent and distillation, there were obtained two fractions, (a) of b.pt. 117-122°/0.2mm., 13.2g.(59%) and (b) of b.pt. 165-175°/0.2mm., 3.9g.(17%). The first showed a single peak, Rt = 18.2 min. on 5% APL at 150° and 50ml./min., which gave a negative ferric chloride test. The n.m.r. spectrum showed an aldehyde proton at 0.23τ(1xH, finely split singlet); ester methyl at 8.74τ(3xH,triplet,J=7cps) and methylene at 5.80τ(2xH,quartet). The infra red spectrum had $\gamma_{C=O}^{CCl_4}$ 1716 cm^{-1} (ketone) , 1733 cm^{-1} (ester) and 1709 cm^{-1} (shoulder) (aldehyde) and $\gamma_{C-H}^{CCl_4}$ 2731 cm^{-1} (aldehyde) and was transparent in the hydroxyl region. The second also gave a negative ferric chloride test The n.m.r. spectrum of this had similar features to that of (a) but

had no aldehyde proton resonance. The infra red spectrum showed a hydroxyl absorption at 3617 cm^{-1} (CCl_4).

Isopropyltriphenylphosphonium iodide (48)

This was prepared from a melt of triphenylphosphine (26.2g.) and isopropyl iodide (19.0g.) after the method of Wittig[36] and was obtained in 88% yield, m.pt. 197-8°(ethanol) (Lit. 195-6°(ethanol/ether).

Wittig reaction of the aldehyde-ester (46) and (48)

(a) via n-butyl lithium

To a suspension of isopropyltriphenylphosphonium iodide (48) (9.0g.; 0.022m.) in anhydrous tetrahydrofuran (50ml.) was added n-butyl lithium (1ml. of 23% in hexane) and the mixture stirred under nitrogen for 2 hours. The aldehyde-ester (46) (5.0g.; 0.02m.) in dry tetrahydrofuran (25ml.) was added dropwise, with stirring, and the mixture allowed to stir overnight. It was then washed with saturated ammonium chloride solution, dried and the solvent removed to yield as the major product, by t.l.c. and g.l.c. analysis, starting aldehyde-ester.

(b) via dimsyl sodium

Sodium hydride (25mg. of a 50% suspension in oil) was washed with dry ether under nitrogen, the flask evacuated and the operation repeated. Dimethyl sulphoxide (2ml.), freshly distilled from calcium hydride, was added and the mixture heated with stirring at 75-80°C

until hydrogen evolution was complete (around 45min.). The flask was cooled in an ice bath and the iodide (48) (1.8g.; 4.2mm.) in dry dimethyl sulphoxiee (2ml.) added and the mixture stirred for 10 min. A solution of the aldehyde-ester (46) (1.0g.; 4.0mm.) in dry dimethyl sulphoxide (2ml.) was added dropwise and the mixture heated at 50° for 1 hour. The mixture was then stirred overnight at room temperature, poured into water and extracted with ether. The ethereal extracts were washed w ith brine, dried and evaporated to give 1.03g. of material. Column chromatography on silica gel enabled the separation of two components. The first, and minor, showed identical g.l.c. retention time on 5% APL at 150° to the starting (46). The second was identical to the bicyclic alcohol (47) in spectral and g.l.c. data.

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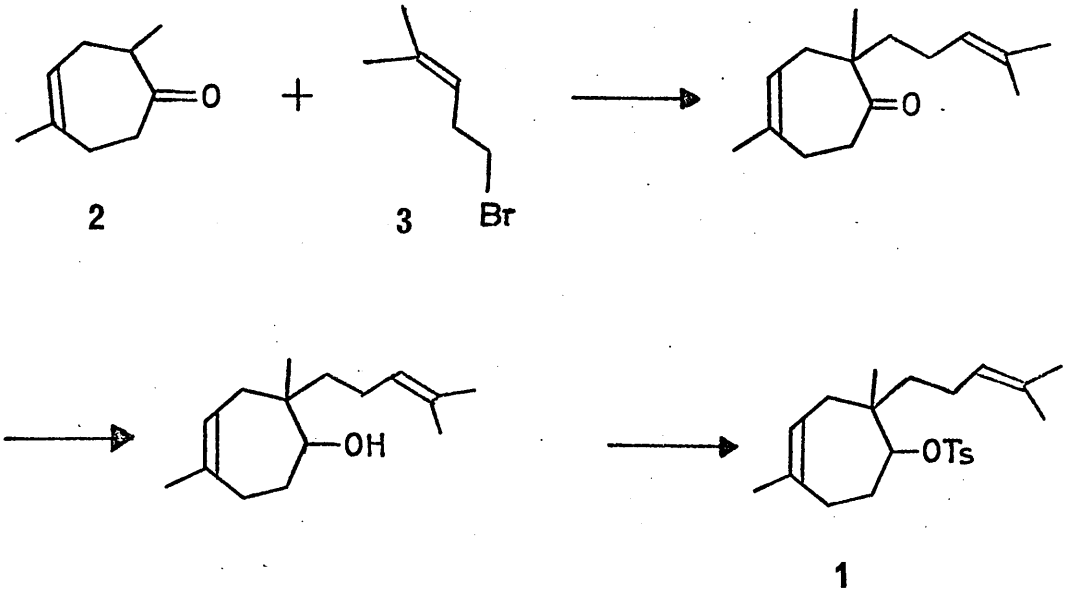

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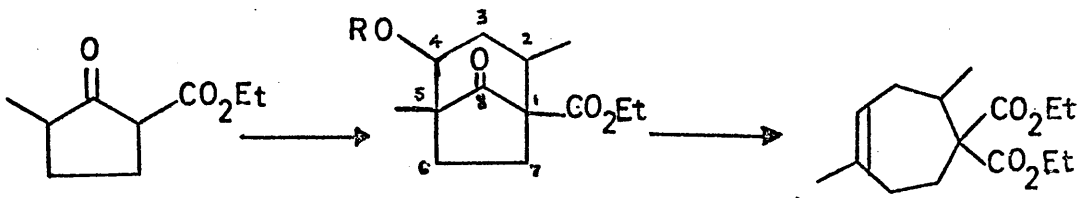

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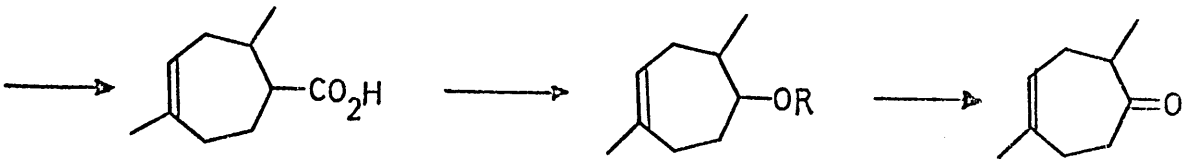

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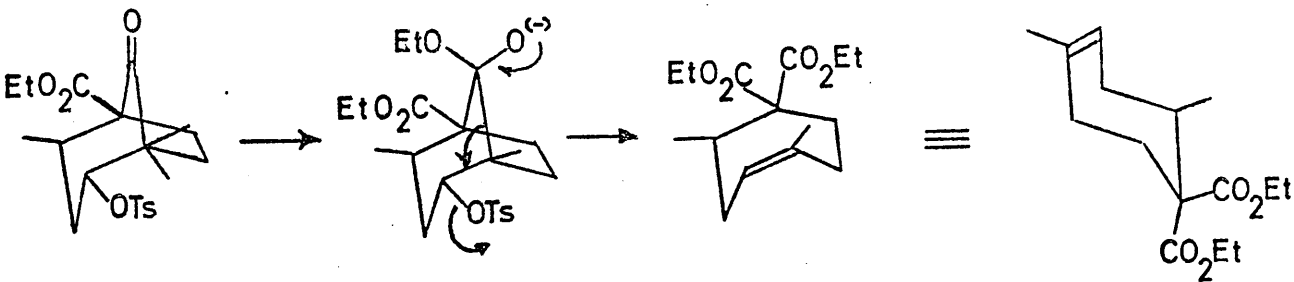

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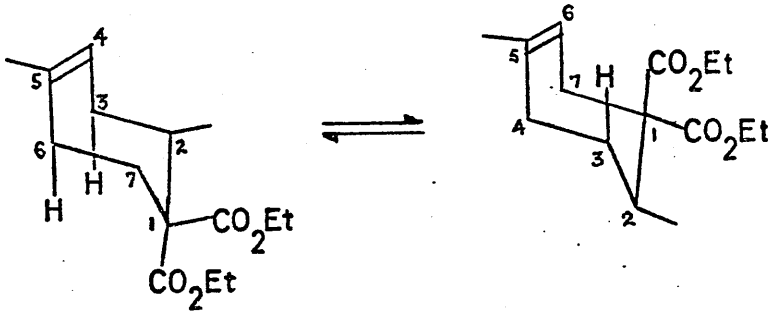

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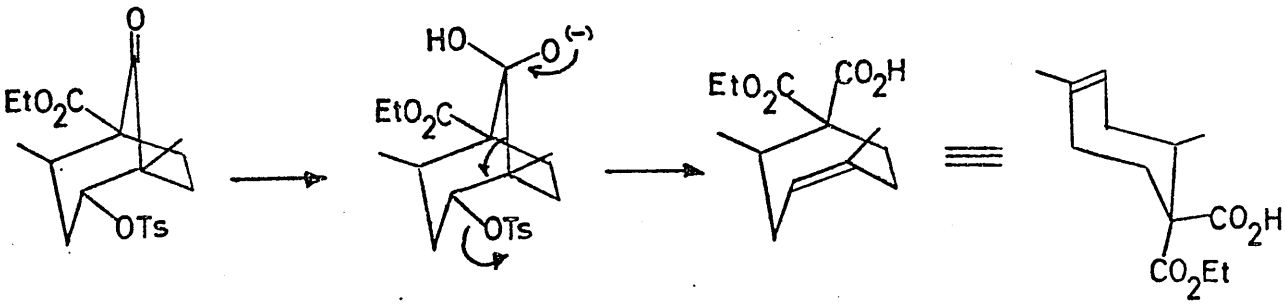

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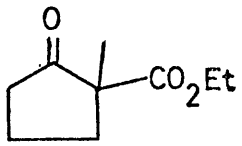

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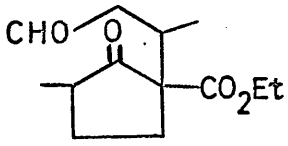

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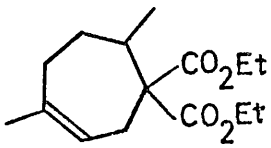

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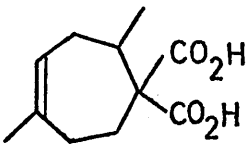

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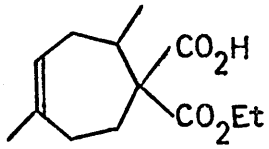

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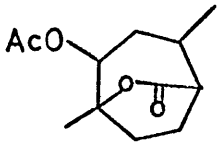

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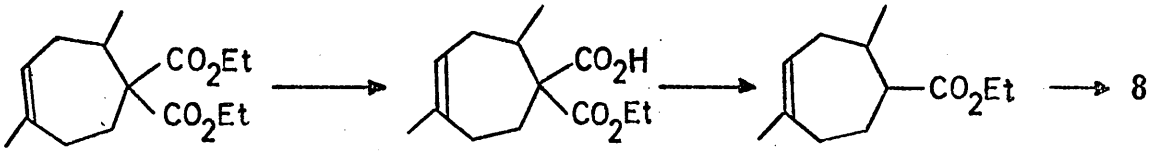

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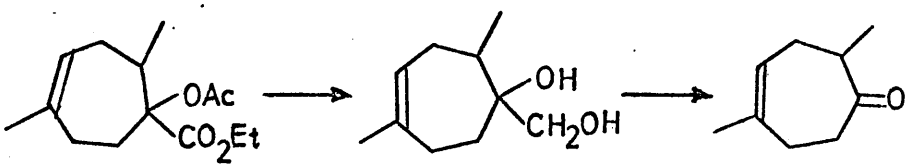

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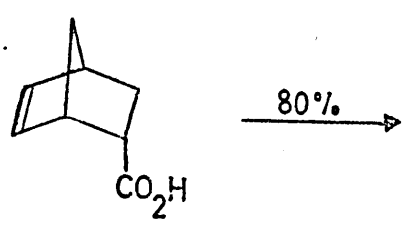

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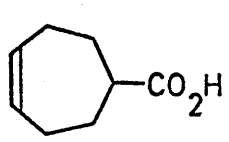

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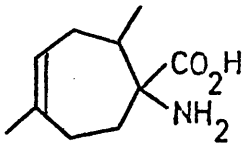

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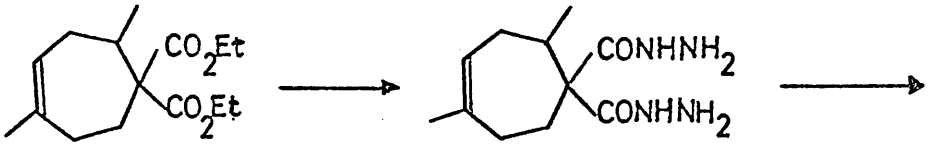

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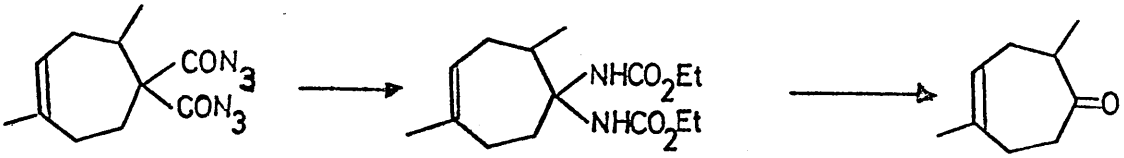

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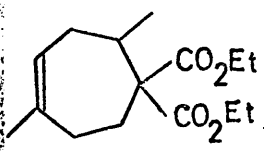

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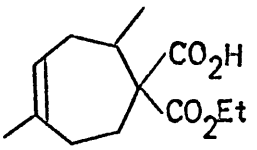

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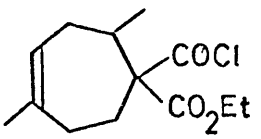

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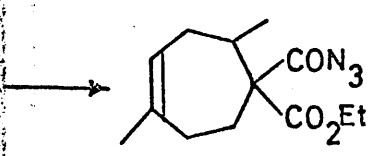

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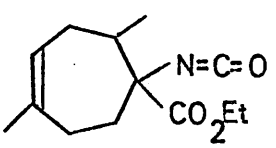

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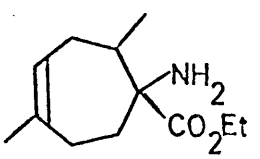

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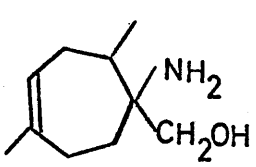

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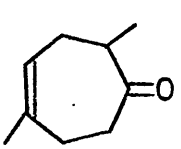

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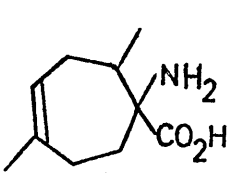

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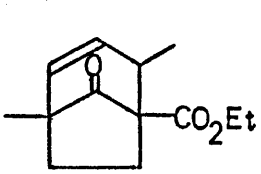

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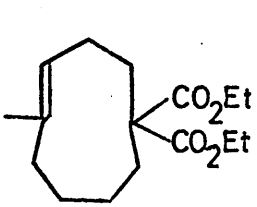

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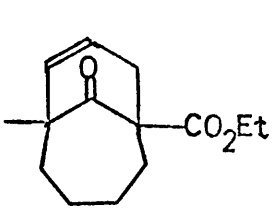

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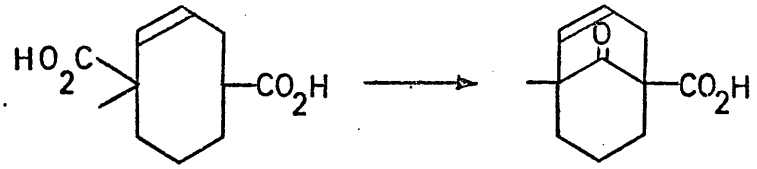

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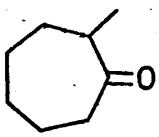

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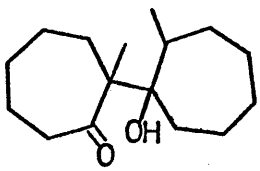

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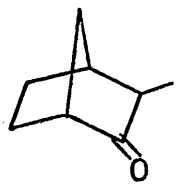

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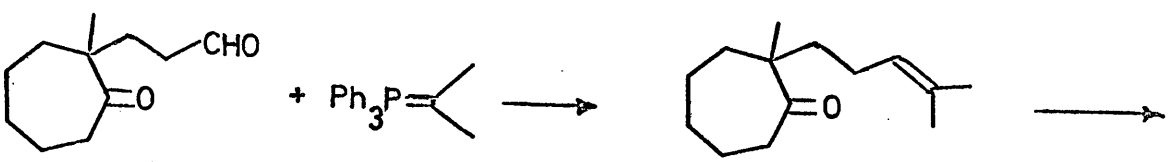

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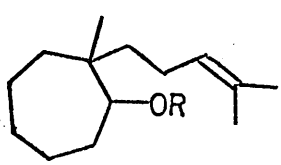

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= (b), Ts = 1

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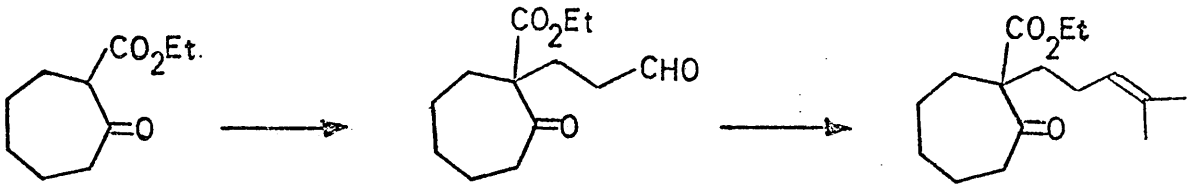

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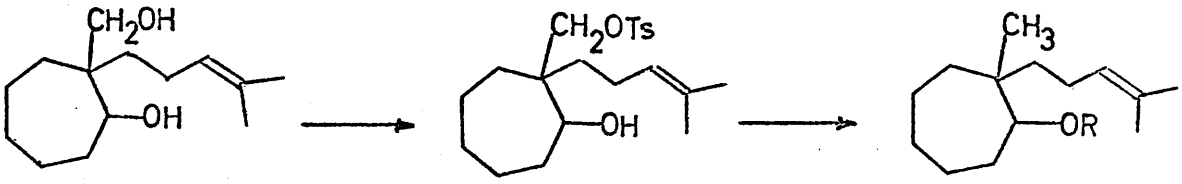

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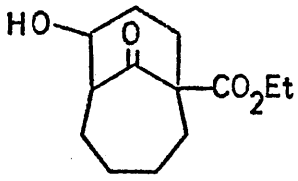
1 : R = Ts



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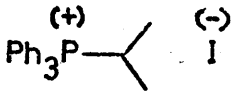

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