STUDIES IN CONDENSATION REACTIONS

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SUMMARY

The mechanism of the Thermal Michael reaction, i.e., the condensation of a Mannich base with a compound containing an activated methylene group, has been studied and evidence has been obtained which corroborates the postulated reaction steps. The Mannich bases of both phenyl acetylene and β-naphthol have been prepared and their condensation with cyclohexanone attempted. The former compound fails to react, while a dihydropyran, the hemiketal of (1-[2'-oxocyclohexylmethyl])-(2-hydroxy)-naphthalene is isolated in 85% yield from the reaction of the latter compound.

The structures of the isomeric diMannich bases of acetone, [1,5-bis(dimethylamino)]-pentan-3-one and (1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one, and of the diMannich base of methyl ethyl ketone, [1,5-bis-(dimethylamino)]-(4-methyl)-pentan-3-one, have been corroborated using N.M.R. evidence and the synthesis of bridged bicyclic ketones has been attempted by their condensation with cyclopentanone. This method was only successful in the case of the gem-diMannich base, (1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one. The condensation product,(3-acetyl)-bicyclo[3,2,1]-

octan-8-one, was identified by its physical data and the results of deuteration studies. The two (1,5)-diMannich bases condensed with two molecules of cyclopentanone to give [1,5-bis(2'-oxocyclopentyl)]-pentan-3-ones.

The use of a solvent, ethylene glycol, in the Thermal Michael reaction has also been investigated. Unless there is a particular need for such a condition, it was concluded that the use of excess ketone as solvent is advisable. The mass-spectral fragmentation patterns of a series of ethylene ketals of 2[β-benzyl-ethyl]-cyclopentanones have been examined to determine the positions of substitution in the cyclopentanone rings. This may be applied as a general method to determine the orientation of attack, which this work confirmed to take place invariably at the least substituted position.

C O N T E N T S

INTRODUCTION

The Mannich reaction, or condensation between an amine, formaldehyde and a compound containing an activated hydrogen-atom, was first recognised as a reaction of general type in 1917.[1] Individual reactions had been observed previously,[2,3] but their wide nature was not realised.

An extensive study of the possible variations of reactants was then begun by Mannich. The substituted amines, or Mannich bases, formed as reaction products were found to be unstable and the majority of compounds were, therefore, prepared as their stable crystalline salts. It was shown that ammonia, primary and secondary amines could all be used with success, but attention was focussed mainly on the products formed from the latter. Mannich bases have thus been prepared from aldehydes, ketones, esters, acetylenes and phenols. Presence of two or more activated hydrogen-atoms in such molecules can give rise to multiple condensations. Thus, replacement of both the ortho- and para-hydrogens in suitably substituted phenols leads to the formation of both the mono- and tri-aminocompounds.[4,5]

In a symmetrical ketone such as acetone the possibility of isomeric products does not arise until the mono-amine, 1-amino-butan-3-one (1) has formed. Subsequent attack may then theoretically take place on either side of the carbonyl group, yielding either the symmetrical diamine (2) or the unsymmetrical isomer (3). Two bis-Mannich bases have been described in the literature. As early as 1917, Mannich[6] isolated a diamine, to which he assigned the unsymmetrical structure (3) on degradation evidence. Two groups[7,8] of workers later corroborated this structure by the condensation of the diamine with a known bicyclic compound and further degradative work to give a butanone. Blicke and McCarty[9] succeeded in isolating a different diamine, which they concluded to be the symmetrical isomer (2). This conclusion was substantiated by comparison with an authentic sample of 1,5-dimethylaminopentan-3-one, prepared by Cardwell from 1,5-dichloro-pentan-3-one.

In an unsymmetrical ketone, as in phenols, two or more possible sites at which primary condensation may occur can exist, leading to the possibility of both isomeric mono- and diamines. In methyl ethyl ketone (4), attack may thus theoretically take place at carbon-(a),

leading to the amine (5), or at carbon-(b), leading to the product (6). These may then further react to give diamines of the type (7) to (9).

In practice, only two condensation products have been isolated from methyl ethyl ketone, but work on their identification has been far less complete than in the case of acetone. Mannich and Hof[10] assigned the mono-amine structures (5) and (6) to these products without any rigorous proof. The formation of a di-amine was not considered. Later work by Cardwell,[8] however, showed that the second component was, in fact, a diamine, for which the 1,5-diamino-2-methyl-pentan-3-one structure (8) was favoured.

The structure of the mono-amine was definitely established as the ethyl-substituted isomer (6) by comparison with the degradation product from the un-symmetrical acetone diMannich base (3). The primary Mannich condensation would, therefore, appear to take place on carbon-(b), (4).

Cardwell[8] was able to eliminate completely the possibility that the diamine had the structure (7), as would be produced by a double condensation taking place on carbon-(a). The diamine could be prepared directly

from the primary reaction product, (4-dimethylamino)-(3-methyl)-butan-2-one, by a further Mannich condensation. This limited the structure to the two isomers (8) and (9). Haeussler[11] favoured the gem-disubstituted isomer (9) rather than (8) on the chemical grounds that the compound gave a positive iodoform test. This was, however, contrary to the evidence of Barrett and Chambers,[12] who used the diamine in the synthesis of a known pyrrocoline, the preparation of which could only have been achieved by the application of the 1,3-structure (8).

In an effort to establish the structure of the diamine beyond reasonable doubt, Blicke and McCarty[9] prepared the mono-amine, (1-dimethylaminomethyl)-butan-2-one (5) from 1-chloro-pentan-3-one. Subsequent condensation with formaldehyde and dimethylamine could then only give two possible isomeric diamines, the 1,1-disubstituted butanone (7) or the 1,3-disubstituted isomer (8). Comparison of the diamine prepared by this latter method with that prepared previously showed that the two were identical. The diamine formed in the Mannich condensation from methyl ethyl ketone can, therefore, on purely chemical grounds, be concluded to have the 1,3-disubstituted structure (8).

The products obtained from the Mannich reaction have been widely used in synthetic work, both as the free base and as the quaternary salt. Probably the bulk of these reactions in the case of ketonic Mannich bases have been demonstrated to involve the α,β-unsaturated ketones derived from the decomposition of the base or its salt. This decomposition can be brought about by the action of base or merely by heat, and the unsaturated ketone so released may then be made, for example, to undergo a normal base-catalysed Michael condensation. Such base-catalysed condensations were originally carried out by the direct addition of the vinyl ketone, prepared by external decomposition of the Mannich base, to a basic solution of the other adduct. Yields, however, were found to be much improved by the generation of vinyl ketone in situ.[13] This was effected by the reflux of the free Mannich base with the active methylene compound in the presence of sodium ethoxide. A second modification to the experimental procedure was made by Robinson,[14] who employed the methiodide salt of the Mannich base.

It should be noted that the orientation of attack in the above base-catalysed condensations showed no deviation from the expected course in a normal Michael addition, whether the Mannich base was decomposed in situ or before addition. In any unsymmetrical ketone, such as 2-methyl-cyclohexanone (10), there may exist two activated positions (a) and (b), adjacent to the carbonyl group, at which condensation can occur, resulting in the possibility of isomeric products, (11) and (12). Normal base-catalysed Michael condensations have been found invariably to lead to the gem-disubstituted isomer (12), attack always occurring at the more highly substituted carbon-(a). Rationalisation of this orientation of attack has proved difficult.

It was found,[15] however, that the presence of a base, such as sodium ethoxide was unnecessary for the decomposition, and subsequent condensation, of the Mannich base. Addition of the vinyl ketone entity still occurred if the Mannich base were simply heated in the presence of a reactive ketone. This reaction was at first thought to take place by the normal base-catalysed Michael mechanism, but work[16] involving an unsymmetrical ketone, 2-methyl-cyclopentanone, resulted in the 2,5-

disubstituted isomer (11) and not in the expected gem-disubstituted compound (12). Subsequent studies using a series of Mannich bases with unsymmetrical ketones showed that this last result was not simply an anomaly. It was found that thermal condensation of the Mannich base in the absence of added base, that is a Thermal Michael, gave as the major product the α,α'-disubstituted isomer, whereas presence of base in the same system or Normal Michael, led to the α,α-isomer. Two completely different mechanisms would thus appear to be operating.

The reaction was carried out in these cases by simply heating the Mannich base in excess ketone at 160-180° for a short time, and distilling out the product. High yields of the mono-alkylated product were obtained, the α,α'-substituted isomer always being found in large excess.

The general nature of this reaction becoming apparent, work[17,18] was begun in this department to establish its mechanism. Having eliminated the possibility of an equilibrium existing between the two isomers (11) and (12), a mechanism involving primary thermal decomposition was first tested. Assuming decomposition to the vinyl ketone and amine took place,

three different modes of condensation were considered. The possibility of a simple thermal condensation between the vinyl ketone and the active methylene compound with no base-catalysis was eliminated immediately. No condensation was observed on warming together two such compounds at the normal reaction temperature.

Initial decomposition followed by enamine formation and normal Michael addition was next considered as the reaction sequence. The similarity between the orientation of addition in the Thermal Michael reaction and that observed for a simple enamine alkylation suggested that such a step might be involved. To test this mode of reaction, 2-methyl-cyclohexanone, phenyl vinyl ketone and diethylamine were refluxed together. The reaction was repeated using pyrrolodine, since both of these amines form enamines readily. The yield obtained in both cases was very low and neither reaction showed the selectivity of the Thermal Michael. A large percentage of the product was the α,α-di-substituted isomer (12). Thus, in spite of indications that an enamine intermediate was involved in the reaction sequence, thermal decomposition followed by enamine formation could be discounted as the mode of reaction.

The ready thermal condensation of diethyl malonate with a Mannich base throws further doubt on the postulation of an enamine intermediate.

The third possible mode of condensation to be considered, after primary thermal decomposition, was a base-catalysed Michael addition of the vinyl ketone to the activated methylene compound with abnormal orientation of attack. The condensation of 2-methylcyclohexanone with phenyl vinyl ketone in the presence of triethylamine, an equally volatile nitrogenous base, went in surprisingly low yield and gave the normal Michael product, the α,α-isomer in predominance. This eliminated the abnormal orientation hypothesis.

The Mannich base was, therefore, felt to react in its entirety in the primary reaction step. Nucleophilic attack of the nitrogen lone-pair on the carbonyl group was postulated as the most likely course of reaction, resulting in a Zwitterion (13). A proton-shift involving a six-centred cyclic intermediate could then follow, resulting in a fragmentation to a vinyl ketone and a carbinolamine (14) (Scheme A). The latter were known[19] to exist as intermediates in enamine formation and had been shown[20] to dehydrate smoothly to such at relatively

low temperatures. The carbinolamine formed would thus be expected to lose water immediately and form the enamine (15). The existence of such an enamine intermediate was tested by warming together the dimethylamine enamine of 2-methyl-cyclohexanone and phenyl vinyl ketone. A low yield of products was obtained, containing the same ratio of isomers as in a direct Thermal Michael.

The efficiency of the Thermal Michael reaction was also felt to bear out the above mechanism. As mentioned previously, high yields of products are obtained in relatively short reaction times and the amines used are normally very volatile. If the base were to decompose before enamine formation, the efficiency of the latter reaction would have to be extremely high, as the volatile amine would tend to be lost from the reaction vessel immediately. It thus seemed more likely that the gaseous amine was liberated after the condensation was complete.

Assuming that the above reaction sequence took place, the enamine so formed was then postulated to undergo normal C-alkylation. The exact mechanism of this step is yet in some doubt. In his original work on enamine alkylation, Stork[21] studied the use of both

acrylonitrile and α,β-unsaturated carbonyl compounds. The former could react via a normal Michael addition only and, although he admitted the existence of alternative mechanisms, Stork saw no reason to postulate other than a similar mechanism for the addition of the unsaturated carbonyl compounds to enamines. Any water present would simply hydrolyse the enamine to the 1,5-dicarbonyl compound. (Scheme B, path a).

Another possible mode of reaction considered was the Diels-Alder addition of the vinyl ketone to the enamine, (Scheme B, path b), resulting in the dihydropyran (16), such as have been isolated from the addition of α,β-unsaturated ketones to vinyl ethers. Opitz[23] succeeded in isolating a series of dihydropyrans by the addition of acrolein to enamines at 20°C. These compounds could then be hydrolysed in high yield to the 1,5-diketones.

Subsequent work, published in 1964 by Fleming and Harley-Mason,[24] indicated, however, that a cyclobutane (17) rather than a dihydropyran intermediate was involved in enamine alkylation (Scheme B, route c). Several cyclobutane derivatives[25-27] had been isolated in enamine addition reactions before this time, but no general conclusion could be drawn from their existence, as in

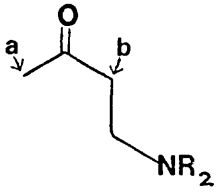
all cases the reaction could not proceed via the alternative mechanisms. The above workers showed, however, that a cyclobutane derivative could be isolated from the addition of both acrylonitrile and methyl vinyl ketone to a series of enamines, Hofmann degradation being used to identify these adducts.

Further work,[28] published in 1967 by the same authors, sought to amend this conclusion. The addition of methyl vinyl ketone to an enamine at a fairly low temperature was shown by spectroscopic data to give the dihydropyran as the first formed adduct. Chemical evidence showed that this adduct could then equilibrate readily to the cyclobutane structure via an immonium enolate (18). Other vinyl ketones gave similar adducts.

Three courses of attack thus seem possible in enamine alkylation (Scheme B). Michael addition (a) may occur resulting in a Zwitterion. This may then equilibrate immediately to either the dihydropyran or cyclobutane, or may give the enamine, which then undergoes hydrolysis. Cyclic Diels-Alder addition (b) is another possible mode of reaction to give the dihydropyran directly. These are known to hydrolyse readily

to 1,5-diketones, as stated previously, whether by direct reaction or by ring-opening to give the Zwitterion is not known. The third possible mode of attack is the direct formation of the cyclobutane derivative by the concerted cycloaddition of the olefin (c).

On consideration of the above results it was felt that several of the mechanistic features postulated for the Thermal Michael reaction required substantiation or clarification, notably the enamine-alkylation step. This was the objective of the present work. Whilst planning this work, considerable attention was paid to the extension of the scope of the Thermal Michael reaction. Previous work had largely involved ketonic Mannich bases, used in a standard experimental procedure. In view of the wide variety of types of Mannich base known, attempts were, therefore, made to employ some of these.



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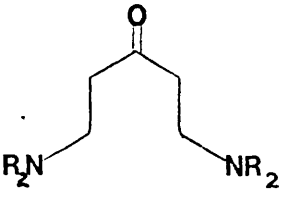

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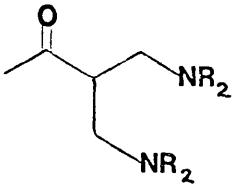

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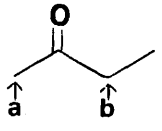

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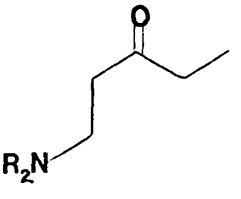

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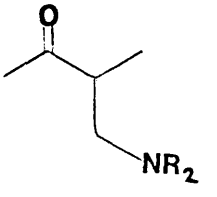

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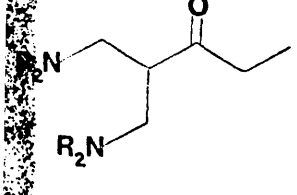

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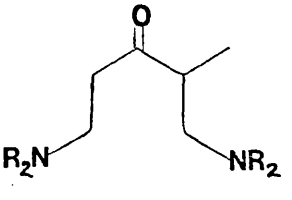

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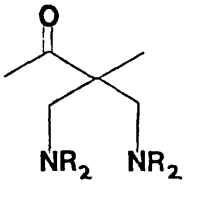

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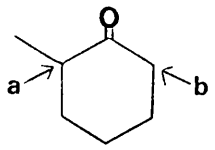

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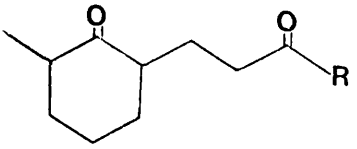

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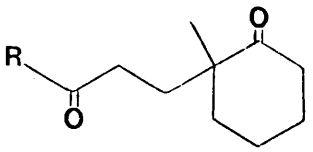

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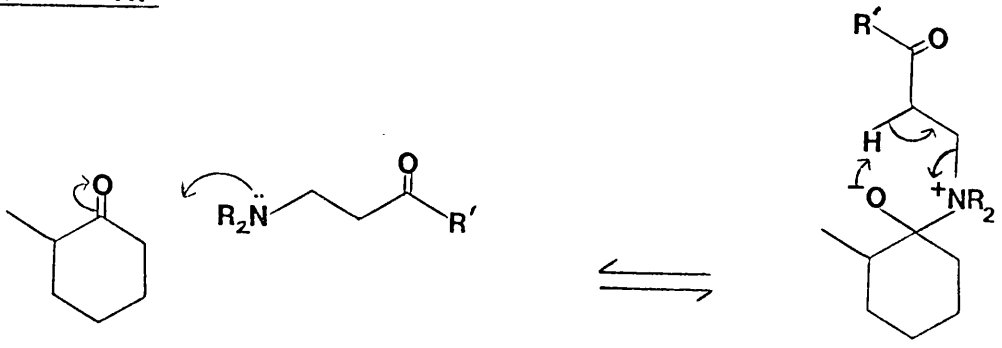

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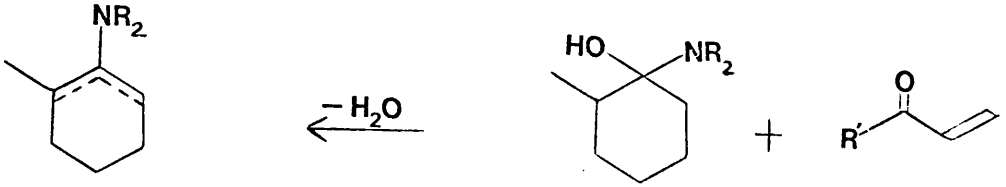

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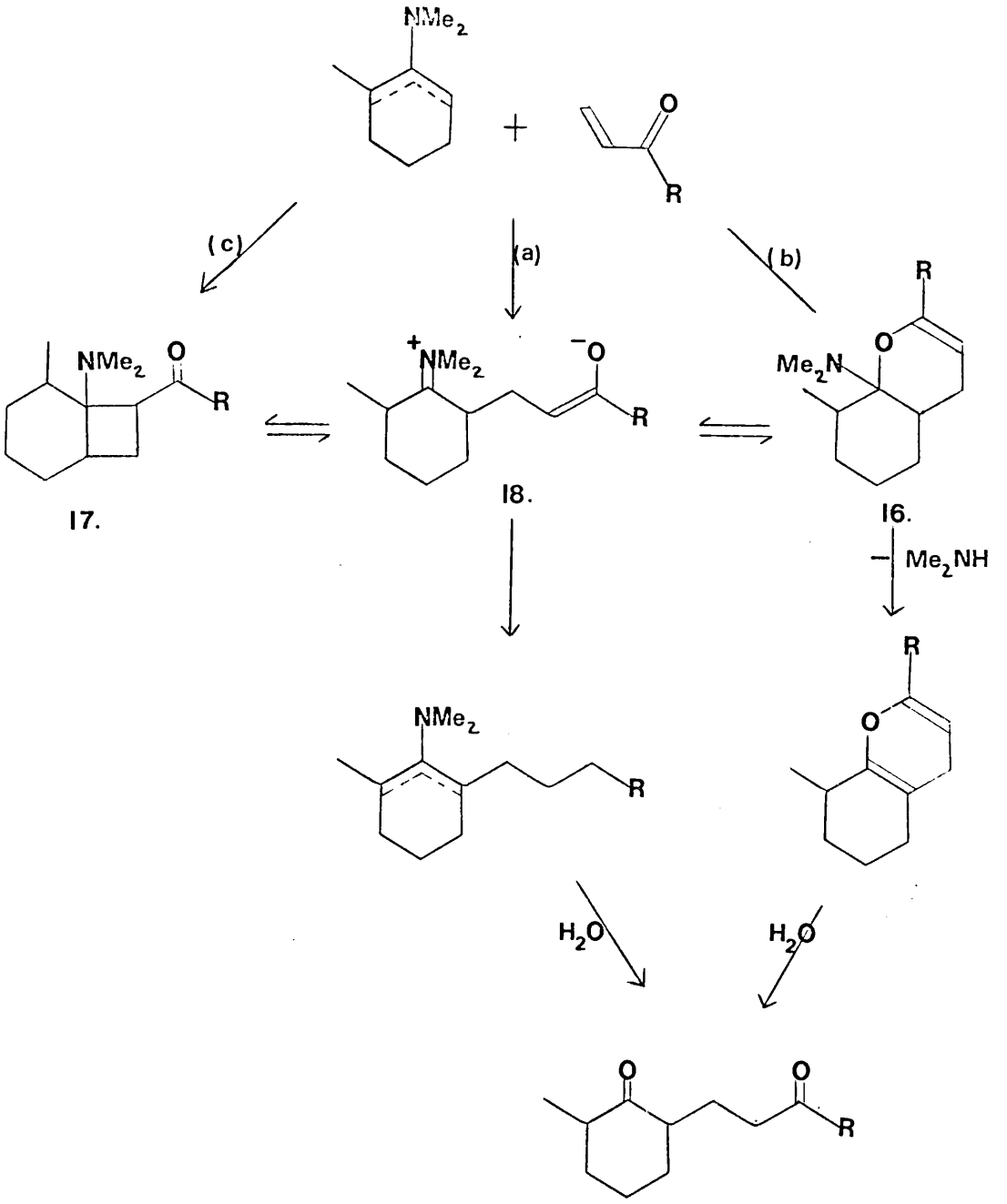
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(a)
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DISCUSSION

In the mechanism of the Thermal Michael reaction postulated (see Introduction), two of the steps require further substantiation. These are (a) the breakdown of the zwitterion (13, Intro.) by a six-centre proton shift and (b) the condensation of the resulting enone and enamine. The simple thermal fragmentation of the Mannich Base had been eliminated as the possible mode of reaction, but no condensation had been attempted in which the breakdown of the zwitterion intermediate was impossible. If the proposed mechanism were correct, no Thermal Michael reaction should be observed under these circumstances.

A β,β-disubstituted Mannich base (1) would seem the most obvious choice of compound to employ in such a test, the proton-shift being effectively blocked by the β-substitution. Such compounds have, however, been shown[1] to react as if they possessed the isomeric structure (2), a thermal retro-Mannich reaction apparently taking place. The immonium intermediate (3) so liberated can react directly with the ketone present to give a Mannich base, which will undergo a Thermal Michael condensation with the usual orientation.

The above rearrangement thus precluding the use of a ketonic Mannich base as the test reactant, the Mannich base of phenyl acetylene, (1-diethylamino)-(3-phenyl)-prop-2-yne (4) was prepared and its thermal condensation with cyclohexanone was investigated. Initial thermal fragmentation having been eliminated as a possible course of reaction, the thermal stability of the Mannich bases under consideration did not influence the choice of reactant.

The amino-propyne and cyclohexanone were reacted together in the usual manner,[2] a 3:1 mixture of ketone and base being refluxed at 160°C for 45 minutes. No diethylamine was liberated during the period of heating and subsequent distillation of the reactants gave only cyclohexanone and a 57% return of the Mannich base. The loss in reagent was due to polymerisation.

It would, therefore, appear that the proposed formation and subsequent breakdown of a zwitterionic species is correct. If the favoured proton-shift is prevented, no Thermal Michael condensation can take place. Although the formation of such an ionic species (5) is possible with (1-diethylamino)-(3-phenyl)-prop-2-yne, the acetylenic bond effectively blocks a six-centred rearrange-

ment. A similar five-centred rearrangement being unfavourable, the zwitterion undergoes the only alternative breakdown, namely a retro-reaction to the original base and ketone.

Having thus substantiated the initial path of attack, it was felt that some more light could be shed on the subsequent enamine alkylation step, whilst simultaneously investigating the scope of the Thermal Michael reaction.

No previous attempts had been made to condense the Mannich base of a phenol with a simple ketone by thermal reaction. Decomposition of the ionic species (6) formed from such phenolic bases would yield the unsaturated ketone (7), an ideal rigidly-held system for a cyclic Diels-Alder addition of the enamine. The Mannich base of β-naphthol, (1-dimethylaminomethyl)(2-hydroxy)-naphthalene (8) was, therefore, prepared by the method of Décombe.[3] Although the presence of the phenolic hydroxyl group in the compound was indicated by the ferric chloride colour test, no absorption due to such a group was apparent in either the infra-red or N.M.R. spectra. This was apparently due to the extremely strong hydrogen-bonding that could take place in this compound (8). Attempts to break this hydrogen-bond by the addition of

deuterated dimethyl sulphoxide to the N.M.R. sample failed, a slight drift away from the base line beneath the aromatic multiplet, in the region of 2·65 τ, being the only indication of the phenolic group in all the N.M.R. spectra obtained. No signal was apparent in the region -10 to 0 τ.

(1-Dimethylaminomethyl)-(2-hydroxy)-naphthalene was then condensed with cyclohexanone, the reaction being somewhat slower than with the dimethylamino-ketonic bases previously employed. A period of reflux of $2\frac{1}{2}$ hours was necessary before dimethylamine ceased to be evolved. A single, crystalline condensation product, $C_{17}H_{18}O_2$, m.pt. 146·5-147°, was obtained from this reaction. Although this molecular formula was that required for the expected condensation product, [1(2'-oxocyclohexylmethyl)]-(2-hydroxy)-naphthalene (9), no carbonyl absorption was present in the infra-red spectrum. The necessary hydroxyl absorption was apparent, but a ferric chloride colour test proved negative, indicating that this was not a phenolic hydroxy group. The N.M.R. spectrum of the product did not shed immediate light on the structure, an aromatic multiplet being present in the region of 2-3 τ together with the typical complex multiplets, 7-9 τ,

characteristic of cyclohexanone condensation products. No signal could be assigned to the hydroxyl group, but the addition of deuterated dimethyl sulphoxide to the N.M.R. sample caused the appearance of a sharp singlet at 3·88 τ. Previous workers[4] have shown that such a signal indicated the presence of a tertiary hydroxyl group in the molecule. From this data it was concluded that the hemiketal of [1(2'-oxocyclohexylmethyl)] (2-hydroxy)-naphthalene (10) had been obtained, and not the expected open chain product. This compound had been isolated previously[5] as the sole condensation product from the reaction of cyclohexanone pyrrolidine enamine with the Mannich base of β-naphthol and a melting point of 143·5-145° had been quoted. The evidence provided by these workers in support of this structure consisted only of the infra-red spectrum and the product's insolubility in aqueous base and negative reaction to ferric chloride solution.

To further substantiate the structure of this hydroxy-compound, attempts were made to open the ketal and isolate a derivative of the straight chain compound. All attempts to isolate the dinitrophenylhydrazone in acidic conditions failed. Although insoluble in aqueous sodium hydroxide solution, the product was found to be

soluble in ethanolic base, formation of the phenolate ion presumably taking place as a necessary feature of dissolution. An attempt was, therefore, made to prevent ring closure by the methylation of the phenolate ion using the action of dimethyl sulphate on the basic solution. The reaction was unsuccessful, a return of starting material being obtained.

Attempts to dehydrate the hydroxy-pyran to give the pyran (11) itself proved more successful. The conditions first employed, concentrated sulphuric acid and p-toluene sulphonic acid, were too severe, but the use of the milder reagents, benzene and p-toluene sulphonic acid, led to the isolation of a white crystalline product, m.pt. $\sim 130^{\circ}$, together with a large return of starting material. The absorption at 3500 $cm.^{-1}$ due to the hydroxyl group had disappeared from the infra-red spectrum of this compound, but a new absorption had appeared at 1714 $cm.^{-1}$ which was difficult to assign. The mass spectral molecular weight of the compound was 236, as required by the pyran (11). Solutions of the dehydration product also discoloured on standing, consistent with the low stability of a pyran.

Isolation of this cyclic reaction product would appear to confirm that the Thermal Michael reaction does proceed via a cyclic Diels-Alder addition (a, scheme A), elimination of dimethylamine occurring to give the extremely reactive pyran, which immediately undergoes hydration. A Michael addition of the enamine to the unsaturated keto-form of the phenol (b, scheme A), giving an enamine, is, however, equally feasible. The third possible mode of reaction, cyclo-addition to give a cyclobutane derivative, may be safely neglected in this case.

A system was next sought in which the cyclic Diels-Alder addition of the enamine to the α,β-unsaturated ketone was impossible. If no condensation were found to occur in such a case, it could be concluded that the Thermal Michael reaction could only proceed via such a concerted cyclic addition. As mentioned in the introduction, several ketonic dimannich bases were known,both of the α,α- and α,α'-disubstituted type. Such bases could presumably undergo a double Thermal Michael reaction, condensing with either two molecules of ketone, or the two α-positions on the same ketone molecule. This latter course of condensation was felt to be most likely to occur

with a gem-disubstituted Mannich base, such as (1-dimethylamino)(2-dimethylaminomethyl)-butan-3-one (12). Examination of molecular models showed that, although the first condensation can occur via a cyclic Diels-Alder addition or via a Michael addition to give 2[(2'-dimethylaminomethyl)(3'-oxo)-butyl]-cyclopentanone (13), the second condensation could only occur by the direct Michael addition of the enamine to the vinyl ketone, a cyclic Diels-Alder addition being sterically impossible in this latter case. The formation of a cyclobutane addition product is also impossible in both steps of the reaction. Thus, if the Thermal Michael reaction proceeds solely through a cyclic addition, the mono-condensation product only should be isolated in the above case. Isolation of a cyclic compound, or bicyclic compound in the case of a cyclopentanone adduct (14) would indicate that a Michael addition had occurred.

Before proceeding with such a condensation it was felt necessary to corroborate the structures of the di-Mannich bases used. As mentioned in the introduction, there had been some controversy over these structures, all evidence presented being of a purely chemical nature. In view of the rearrangements that were known to occur

in some Mannich bases on further reaction, spectral evidence for the structures of these diMannich bases was sought. It was found more convenient to examine the stable crystalline derivatives of these bases, such as the dipicrate or the dihydrochloride, rather than samples of the free base, due to the inherent instability of the latter.

The N.M.R. spectra of the diMannich bases of acetone were first examined. Acetone was reacted with aqueous dimethylamine and formaldehyde solutions in the manner of Mannich and Salzmann.[6] Both a mono-amine and a diamine were isolated from this reaction, the unsymmetrical structure (1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one (12) being assigned to the latter on chemical grounds, as mentioned in the introduction. The crystalline picrate and hydrochloride of this compound were prepared. The isomeric diamine, (1,5-dimethylamino)-pentan-3-one (15) was also prepared as the crystalline hydrochloride, in the non-aqueous medium of glacial acetic acid using Blicke and McCarty's[7] method. The spectra of the free base, the picrate and the hydrochloride were then examined. It had been found by previous workers[8] that the assignment of signals in the

N.M.R. spectrum of a Mannich base was aided considerably if the N.M.R. spectra of the base and its picrate, or hydrochloride, were compared. Protonation causes a downfield shift of 0·75–1 ppm. in the signals of protons adjacent to nitrogen, but has less effect on more distant protons. Consequently, N-Me and Me-CO- proton signals can be distinguished, although these signals occur at much the same frequency in the free base. The unsymmetrical Mannich base of acetone (12) would thus be expected to exhibit two singlets in its N.M.R. spectrum, one due to the methyl ketone (H_a) and another due to the N-methyl protons (H_e), the latter showing a far greater shift than the former. A complex multiplet arising from the five-spin system ($H_{b,c,b',c',d}$) should also be apparent. The symmetric Mannich base (15) on the other hand should exhibit one singlet only, due to the N-methyl protons, together with a symmetrical quartet of the A_2B_2 type. Two such spectra were obtained for the diamines isolated, the data being shown in Table 1. The two singlets occurring in the spectrum of the diamine isolated by Mannich thus corroborated its unsymmetrical structure.

Confirmation of the structure of the dimannich base of methyl ethyl ketone (16) was effected by the same method, this latter compound being prepared as its hydrochloride in acidic conditions.

Its structure having been substantiated, (1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one was then condensed with cyclopentanone to give a mixture of five products, three of which were present in negligible amounts. Distillation failed to effect the separation of this mixture, the molecular weights of the two major components of which were shown to be 166 and 154, using the combined gas-chromatograph-mass spectrometer. The infra-red spectrum of the mixture exhibited absorptions due to both carbonyl and olefinic groups.

Inspection of the dimannich base showed that a possible five isomeric products, m.wt. 166,could arise from its condensation with one molecule of cyclopentanone, structures (17-21.). The possibility of a condensation between one molecule of Mannich base and two molecules of cyclopentanone to give a triketone (22), m.wt. 250,could not be neglected, nor could that of a retro-Mannich reaction to give the mono-Mannich base, which could subsequently condense with cyclopentanone to give the

diketone (23), molecular weight 154. The g.c.m.s. data immediately eliminated the possible existence of the (biscyclopentyl)-compound as a major reaction product.

The two major products were then purified using a combination of chromatographic techniques. It was found impossible to obtain a purity of more than 95%, which reduced the accuracy of analytical data.

The carbon content of the major product, molecular weight 166, yield 19%, analysed for the molecular formula $C_{10}H_{14}O_2$ to within 0·7%. Its infra-red spectrum showed no double bond absorptions, which immediately eliminated the olefinic structures (19-21). Two carbonyl absorptions, 1748 $cm.^{-1}$, 1712 $cm.^{-1}$ were shown. The latter could be assigned to a methyl ketone group which arises in both the remaining possible isomers (17 and 18), whilst the former is slightly higher than that normally observed for an unstrained cyclopentanone system and coincides with the carbonyl absorption shown by (2-morpholino)-bicyclo-[3,2,1]-octan-8-one.[9] The product showed no strong u.v. absorption such as would be shown by a conjugated olefin. The mass spectral fragmentation pattern gave little indication of the structure. The methyl ketone group gave an ion of mass number 43,

$Me-C\equiv O^{+}$. No cleavage of the methyl group alone, to give a fragment (M-15), occurred. Deuteration of the product led to the incorporation of four deuterium atoms only, the molecular ion now appearing at mass number 170 and the ion of m/e 43 shifting to mass number 46. Examination of the isomers (17, 18) shows the presence of six replaceable hydrogen atoms in the spiro-structure (18) and of four in the bridged-ring system (17). The bicyclic structure, [3-acetyl]-bicyclo-[3,2,1]-octan-8-one, which alone satisfies the available evidence, is, therefore, proposed for the product.

The second product found in this reaction, molecular weight 154, analysed for $C_9H_{12}O_2$ to within 0·8% and exhibited absorption due to two carbonyl groups in its infra-red spectru, 1735 $cm.^{-1}$ and 1714 $cm.^{-1}$ Comparison of the G.L.C. retention time of this compound, with that of an authentic sample, established its identity as [2(3'-oxo)butyl]-cyclopentan-1-one (23). The authentic sample was prepared by the condensation of cyclopentanone and (1-diethylamino)butan-3-one as described by Gill.[2] The appearance of this compound results from the slight contamination of the original diMannich base with the mono-amine (1-dimethylamino)butan-3-one. The concentration of the latter may also be increased during the course of the Thermal Michael reaction by a retro-Mannich reaction.

The conclusion can, therefore, be drawn that a cyclic Diels-Alder addition of the vinyl ketone to the enamine is not the sole mechanism of enamine alkylation in the Thermal Michael reaction. The isolation of the bridged bicyclic ketone, (3-acetyl)-bicyclo-[3,2,1]-octan-8-one demonstrates that this alkylation step will proceed via a normal Michael addition (13→14) if alternative reaction paths are impossible. No conclusion can, however, be drawn from this result concerning a general mode of alkylation. The mechanism may vary from reaction to reaction.

As isolation of such a bicyclic product carried considerable mechanistic implication, an attempt was next made to synthesise (3-acetyl)-bicyclo-[3,2,1]-octan-8-one, by means of a Thermal Michael condensation between the Mannich base of cyclopentanone, (2-dimethylaminomethyl)-cyclopentanone, and ethyl acetoacetate. The method proved unsatisfactory, however, a large mixture of products being obtained, from which it proved impossible to isolate the desired compound, (1-cyclopentyl)(3-carbethoxy)-butan-4-one, in sufficient yield.

The alkylation of the pyrrolidine enamine of cyclopentanone (24) with (2-bromomethyl)-acrylic ester (25) was next attempted. The alkylation of enamines of aliphatic ketones with such allyl bromides proceeds in good yield,[10,11] the 4,5-unsaturated carbonyl compounds being obtained as reaction products. The use of the enamine of a cyclic ketone had been shown[12] to result in a double alkylation, involving the two α-positions of the ketone. It was, therefore, hoped to isolate the bicyclic ketonic ester, (3-carbethoxy)-bicyclo-[3,2,1]-octan-8-one (26) in a similarly good yield from the mentioned reaction.

The condensation was first attempted using the conditions employed by Stetter[12] in the alkylation of the enamine of (bis-carbethoxy)-cyclohexanone in a mixed solvent of ethanol and methyl cyanide. No bicyclic product could be detected. To prevent any reduction in the yield due to the hydrolysis of the enamine, benzene was next employed as the solvent. This proved unsatisfactory, however, an insoluble crystalline precipitate forming immediately on the addition of the acrylic ester to the enamine solution. The spontaneity of formation and the infra-red spectrum of this compound indicated

that it was a nitrogen salt. Addition of methyl cyanide, followed by heating to reflux, produced dissolution of the precipitate and the reaction was, therefore, repeated under these conditions.

The reaction mixture was refluxed under nitrogen for three hours and extracted with chloroform, after hydrolysis with 10% sodium chloride solution. A discoloured oil was obtained containing at least six components. Distillation failed to effect the separation of these, rigorous chromatographic purification being needed to obtain pure samples. The main reaction product was a discoloured nitrogenous compound, which could not be hydrolysed to give the desired product. Monoalkylated cyclopentanones formed several of the byproducts. A small quantity of a ketonic ester, $C_{11}H_{10}O_3$, carbonyl absorptions 1750, 1730 $cm.^{-1}$ was isolated. This was identified as the required ester, (3-carbethoxy)-bicyclo-[3,2,1]-octan-8-one (26) (< 10% yield) by its analytical and spectral data. Larger scale preparations of this compound, however, failed completely. A further attempt to improve the yield was made by alteration of the solvent system once more, pure methyl cyanide being employed. No conditions could be found, however, which gave a satisfactory yield of product on a large scale. The attempt to synthesise the bicyclic ketone was, therefore, abandoned.

The condensation of the gem-disubstituted di-mannich base of acetone with cyclopentanone having been studied, the reaction of its isomeric analogue, [1,5-bis(dimethylamino)]-pentan-3-one (15) was investigated. Isolation of a bridged bicyclic decanone system (27) was conceivable in this reaction, but was felt to be unlikely as the normal 3 molar excess of ketone was employed. The isolation of the (bis-cyclopentyl)-triketone (28), resulting from the condensation of one molecule of Mannich base with two molecules of ketone, was more likely.

[1,5-bis(dimethylamino)]-pentan-3-one was refluxed with cyclopentanone until evolution of dimethylamine ceased. A crystalline product separated out of the reactant mixture on neutralisation and dilution with ether. The remaining oil contained one major component, 51% yield, which was isolated as a colourless crystalline solid, m.pt. 50-51·1°, using a silica elution column. This latter product exhibited two carbonyl absorptions at 1737 $cm.^{-1}$ and 1712 $cm.^{-1}$ (2:1 relative intensities) in the infra-red. These values lie within the range predicted for both of the considered structures. The N.M.R. spectrum of the product might also have resulted from

examination of either structure. As both the α- and β-hydrogens in a cyclopentanone system absorb at the same nuclear magentic frequency, no distinction was possible on the basis of the N.M.R. spectrum. Analysis and molecular weight determination, however, gave the molecular formula of this solid as $C_{15}H_{22}O_3$. This identified it as [1,5-bis(2'-oxo-cyclopentyl)]-pentan-3-one (28).

Further examination of the minor reaction product, the floculant, white, crystalline solid, showed it to be a mixture of at least three components. The I.R. and N.M.R. spectra of the mixture were very similar to those of the major product, [1,5-bis(2'-oxocyclopentyl)]-pentan-3-one. No molecular weight determinations were possible due to the involatility of the compounds. This combined evidence would seem to suggest that the solid was a mixture of multicondensation products of a type similar to the (bis-cyclopentyl)-pentanone, the major reaction product.

The condensation of the dimannich base of methyl ethyl ketone, [1,5-bis(dimethylamino)]-2-methyl-pentan-3-one with cyclopentanone was next studied. Reflux of the base in an excess of ketone resulted in one major product, $C_{16}H_{24}O_3$, in 45% yield. The infra-red spectrum of this compound showed carbonyl absorptions at 1740 $cm.^{-1}$ (ε 873) and 1714 $cm.^{-1}$ (ε 316). These extinction coefficients are in agreement with a condensation product from one molecule of base and two molecules of cyclopentanone. The identity of the condensation product was thus established as [1,5-bis(2'-oxocyclopentyl)][2-methyl]-pentan-3-one (30).

The use of dimannich bases in the one-step synthesis of bridged-ring systems would seem from this evidence to be restricted to the gem-disubstituted isomers. In these compounds, the proximity of the second amino-group to the molecule of ketone already added favours the subsequent condensation with the same ketonic molecule. In the 1,3-disubstituted bases, however, the likelihood of the second amino-group and the ketone being close enough to undergo condensation is much reduced and the Mannich base consequently condenses with a second molecule of ketone.

Throughout this work the standard experimental procedure developed by Gill [2] et al had been employed, excess ketone being used as solvent. Substantiation of the presence of an enamine intermediate by the study of the reaction of α-substituted cyclopentanones necessitated the use of somewhat limited quantities of material, however, and a suitable solvent was, therefore, sought. The reaction had been found to proceed in best yield if the temperature were maintained between 160° and 180°. For ease of procedure, therefore, a solvent was needed whose boiling point fell in this range, or, this proving impossible, above it. It was also desirable to maintain a completely homogeneous system throughout the reaction period. The hydroxylic solvent, ethylene glycol, $b.p._{760}$ 199-200°C, was, therefore, employed.

The reaction of cyclopentanone and β-aminopropiophenone (31) was first studied. The use of a three molar excess of ketone as solvent results in a 73% yield[13] of the mono-condensation product, 2-(β-benzoylethyl)-cyclopentanone (32) after a short reaction period of 20 mins. A small amount of a second product, possibly a dicondensation product, can sometimes be detected.

Using ethylene glycol (30 ml. to 0·05 mole base) as solvent, equimolar amounts of cyclopentanone and β-aminopropiophenone were heated together at 150-160° for 45 mins. with stirring. On neutralisation of the reaction mixture and dilution with ether, a crystalline solid precipitated out of solution. This compound, $C_{23}H_{24}O_3$, m.pt. 115-116°, exhibited two carbonyl absorptions, 1687 cm.$^{-1}$ and 1732 cm.$^{-1}$ (2:1). The N.M.R. spectra showed the presence of aromatic and cyclopentanone protons, together with a triplet at 6·87 τ, which could be assigned to protons adjacent to the benzoyl group. The integration indicated the presence of four of this latter type of proton and ten aromatic hydrogens, finally establishing the identity of this product as the dicondensation adduct, either [2,2-bis(β-benzoylethyl)]-cyclopentanone (33) or the 2,5-isomer (34) (6% yield). After removal of this product, the remaining reactant mixture gave a 40% yield of the normal mono-condensation product, 2(β-benzoylethyl)-cyclopentanone (32).

The yield of di-condensation product could be raised to 42% if a mixture of one mole of ketone to two moles of Mannich base were warmed together at 160° in ethylene glycol for a period of 90 mins. The mono-condensation product was also obtained in 19% yield.

The condensation of 2-methylcyclopentanone with β-aminopropiophenone had been attempted by previous workers[14] and had resulted in a 76% yield of (2-methyl)-(5-[β-benzoylethyl])-cyclopentanone. A trace of the 2,2-isomer could be detected by g.l.c. The reaction of 2-ethyl-cyclopentanone with β-aminopropiophenone was, therefore, next investigated, the base being refluxed in a three molar excess of the ketone for 45 mins. Subsequent distillation of the reactant mixture gave a 65% yield of one product, $C_{16}H_{20}O_2$, the infra-red spectrum of which showed two carbonyl absorptions, 1687 cm.$^{-1}$, 1732 cm.$^{-1}$ (1:1). The N.M.R. spectrum contained two complex multiplets due to the presence of aromatic and cyclopentanone protons, together with a triplet at 6·87 τ which could be assigned to protons adjacent to a benzoyl group. The mono-condensation product, (2-ethyl)(5[β-benzoylethyl])-cyclopentanone (35) or its 2,2-isomer (36) had thus been obtained. The yield of this product was increased to 77% when an equimolar mixture of the reactants was warmed to a temperature of 160^{o} for 60 mins.

This increase in yield may be explained by the lower reaction temperature in the second experiment and demonstrates the reaction of the Mannich base as a complete entity in the Thermal Michael reaction. In the first experiment, the reactants had been allowed to reflux together at $>200^{o}C$, leading to an increase in the thermal decomposition of the Mannich base.

Identification of the reaction products using the characteristic mass spectral fragmentation patterns of their ethylene ketals (38) was next attempted. The fragmentation of a ketal group has been shown to follow the normal ether pattern and to overshadow the effect of other functional groups in the molecule. α-Cleavage occurs as the primary decomposition process, followed by a hydride shift to generate the allylic radical. Homolytic fission in this entity then results in the formation of the highly stabilised oxonium ion (scheme B). If the ketal under examination bears α-substituents (R), the initial cleavage will always take place to give the more stable, substituted radical as shown. No peaks of mass (98+R) will be detected.

2-(β-benzoylethyl)-cyclopentanone (32), the corresponding disubstituted product (33 or 34) and the (β-benzoylethyl)-(2-ethyl)-cyclopentanone (35 or 36) were hydrogenolysed in turn over a palladium catalyst, the benzoyl group being reduced to the benzyl group under such conditions. The ethylene ketals of the resulting 2(β-benzylethyl)-cyclopentanones were then prepared.

2(β-benzylethyl)-cyclopentanone yielded a ketal, $C_{16}H_{22}O_2$, which exhibited the characteristic absorption bands in the infra-red region 1400-1000 $cm.^{-1}$ and a singlet at 6·15 τ in its N.M.R. spectrum. The mass spectrum of this compound (M.S. No.1) was characteristic of a monosubstituted cyclopentanone. Two ions only were detected in more than 20% abundance, the oxonium ion (41) mass 99 (R.A. 100%) and the benzylic ion (42) mass 91 (R.A. 25%). No peak was present at mass 217, corresponding to the (β-benzylethyl)-oxonium ion (43).

The disubstituted product gave a ketal whose mass-spectral fragmentation pattern was somewhat more complex (M.S. No.2). If the 2,2-disubstituted isomer were under examination, the predominant peak in the mass-spectrum of this compound would be that of mass 99. The base peak in the observed spectrum was, however,

found to be at mass 113. Peaks at 217 (R.A.48%) and 99 (R.A. 42%) were also observed. This spectrum could only be rationalised on the basis of the 2,5-bis(β-benzylethyl)-cyclopentanone structure (38b) (Scheme C). It was, therefore, concluded that the expected 2,5-disubstitution product had been obtained.

The mass spectrum of the ketal from the ethyl-cyclopentanone product also corroborated the generalisation that a Thermal Michael condensation will occur at the least substituted α-position in a ketone, indicating the presence of an enamine intermediate. The base peak occurred at mass 127, the ion of mass 113 only being present in 65%. The unsubstituted oxonium ion (41), mass 99, was apparent in the relatively small amount of 57% (M.S. No.3). As in the previous example, this fragmentation pattern can only arise from the examination of (2-ethyl)(5-[β-benzylethyl])-cyclopentanone ethylene ketal (38d) (Scheme D).

The condensation of β-aminopropiophenone with (2-ethyl)(5-carbethoxy)-cyclopentanone (39) was next investigated. The Mannich base was refluxed in a 3 molar excess of ketone for 90 minutes, it being found more satisfactory to use the latter as solvent rather

than employ ethylene glycol. Negligible dimethylamine was liberated during the period of reflux and no condensation product could be detected in the reactant mixture. The two major components of this mixture were shown to be (2-ethyl)-cyclopentanone and (2-ethyl)(5-carbethoxy)-cyclopentanone by G.L.C.

An attempt was then made to prepare the pyrrolidine enamine of (2-ethyl)(5-carbethoxy)-cyclopentanone. The ketone was refluxed overnight with excess pyrrolidine under a water separator. Very little water was removed from the system and no enamine could be isolated from the resultant discoloured reactant mixture. The conditions prevailing in this attempted enamine preparation are very similar to those in a Thermal Michael condensation, pyrrolidine being a more efficient reagent in the formation of enamines under such circumstances than dimethylamine. It may, therefore, be concluded that the probability of formation of an enamine intermediate in the attempted thermal condensation of (2-ethyl)(5-carbethoxy)-cyclopentanone with β-aminopropiophenone is extremely low. The Thermal Michael reaction, therefore, fails to proceed in this case.

The above work thus corroborates the primary reaction steps in the postulated mechanism for the Thermal Michael reaction. The formation of (a) a zwitterion and (b) an enamine intermediate are confirmed. No definite conclusion can be drawn about the exact mode of enamine alkylation. Although a cyclic addition reaction appears to take place in cases such as the β-naphthol example, the reaction can proceed equally well where such a cycloaddition is impossible. This in itself might be taken as an indication that the alkylation proceeds by a normal Michael addition to give an ionic intermediate (Path a, Scheme B, Introduction). If the conditions are favourable, this may then equilibrate to the cyclic form. The relative stabilities and reactivities of the three isomeric forms will influence the position of this equilibrium. As has been shown for both Diels-Alder and 1,2-cycloaddition reactions, the mechanism will vary from case to case. The usefulness of further work into this mechanistic detail is, therefore, questioned.

EXPERIMENTAL - GENERAL

All melting points were determined on a Kofler microscope hot stage and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam S.P. 200 spectrophotometer. Solution spectra were recorded on a Unicam S.P. 100 double-beam spectrophotometer, equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum conditions. Ultra-violet absorption spectra were determined on a Unicam S.P. 800 spectrophotometer in ethanolic solution. Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R. 10 (60 megacycle) spectrometer in deutero-chloroform with tetramethylsilane as an internal reference.

Thin-layer chromatography (t.l.c.) employed Kieselgel G silica. Column chromatography was carried out using B. & H. Silica, referred to as 'fine silica'. Gas-liquid chromatography (g.l.c.) was carried out on Pye Argon chromatographs and preparative g.l.c. on a Pye 105 chromatograph. High resolution mass spectra were recorded on an A.E.I. MS 12 mass spectrometer. Combined gas-chromatographic, mass-spectral work was performed on an LKB 9000A gas chromatograph-mass spectrometer.

(1-diethylamino)(3-phenyl)-prop-2-yne (4).

This was prepared in 61% yield by the method of Mannich and Chang[15] and was obtained as a colourless oil, $b_{0.07}$ 94-96° (lit. b_{18} 137°). The liquid film I.R. spectrum of the product did not exhibit the characteristic acetylene absorption in the region of 2100 $cm.^{-1}$. Study of the N.M.R. spectra, however, confirmed that the correct Mannich base had been obtained:- 8·91 τ (6 x H, triplet, J = 7 cps.) 7·40 τ (4 x H, quartet, J = 7 cps.) 6·40 τ (2 x H, singlet) 2·72 τ (5 x H, multiplet).

Condensation of (1-diethylamino)(3-phenyl)-prop-2-yne (4) and cyclohexanone.

(1-diethylamino)(3-phenyl)-prop-2-yne (6·2 g. ; 0·03 mole) and cyclohexanone (9·3 g. ; 0·09 mole) were refluxed together for 45 min. under a water condenser. The solution deepened in colour during heating, but no diethylamine was evolved during the course of reaction. After dilution with water, the mixture was extracted with ether, there being no need to neutralise the mixture of products with glacial acetic acid in the normal fashion. Distillation of the combined ether extracts

gave 6·26 g. cyclohexanone, b_{18} 50-52° and 3·49 g. (1-diethylamino)(3-phenyl)-prop-2-yne, b_{18} 140-142°. The identity of the two fractions was established as such by correlation of boiling points and examination of I.R. spectrum. Comparative t.l.c. work with an authentic sample of (1-diethylamino)(3-phenyl)-prop-2-yne confirmed the identity of the higher boiling fraction.

(1-dimethylamino)(2-hydroxy)-naphthalene (8)

This was obtained as a white crystalline solid, m.pt. 72-73° (lit. 76-76·5°) in 52% yield using the method of Décombe.[3] Some difficulty was experienced in obtaining a crystalline product. The length of heating was found to be critical, good yields only being obtained if the reactants were warmed for a maximum of 10-15 mins. on a water-bath.

The I.R. spectrum of the product showed no hydroxyl absorption in the region of 3500 $cm.^{-1}$, although a red colouration was obtained with ferric chloride solution. The N.M.R. spectrum showed no absorption which could be assigned to a phenolic proton:- 7·68 τ (6 x H, singlet) 6·04 τ (2 x H, singlet) 2·65 τ (6 x H, multiplet) (CCl_4 solution). No change was produced in this spectrum on

addition of either deuterium oxide or deuterated dimethylsulphoxide. A slight deviation from the base line was apparent under the aromatic multiplet at 2·65 τ.

Condensation of (1-dimethylaminomethyl)-(2-hydroxy)-naphthalene (8) and cyclohexanone.

(1-dimethylamino)(2-hydroxy)naphthalene (10 g. ; 0·047 mole) and excess cyclohexanone (45 g. ; 0·36 mole) were refluxed together for 2½ hrs. under a water condenser, until gaseous dimethylamine ceased to be evolved. The solution was neutralised with glacial acetic acid, diluted and extracted with ether. After removal of the ether and excess cyclohexanone under reduced pressure, a white crystalline product (> 80%) remained, m.pt. 146·5-147° (petroleum ether, 60-80°). Found: C, 79·90; H, 6·92. $C_{17}H_{18}O_2$ requires C, 79·97; H, 6·71%. Molecular weight 254 ($C_{17}H_{18}O_2$ requires 254). The mass spectrum exhibited a strong peak at 236, produced by loss of water from the molecular ion. The I.R. spectrum showed $\nu_{O-H}^{CCl_4}$ 3595 cm.$^{-1}$, but no carbonyl absorptions. Addition of deuterated dimethylsulphoxide to the N.M.R. sample produced a sharp singlet at 3·88 τ. The u.v. spectrum exhibited characteristic naphthalene

absorption, all absorption bands appearing at a slightly higher wavelength than in naphthalene itself, which is consistent with conjugation of the aromatic system to oxygen.

The product was insoluble in sodium hydroxide solution, but dissolved readily in Claisen's alkali. There was no colouration with ethanolic ferric chloride solution. This data is consistent with that expected for the hemiketal of 1(2'-oxocyclohexylmethyl)-(2-hydroxy)-naphthalene (lit. m.pt. 143·5-145°).[5] (10).

Methylation of 1(2'-oxocyclohexylmethyl)-2-hydroxy naphthalene, hemiketal (10).

The naphthol hemiketal was dissolved in Claisen's alkali (25 ml. water, 100 ml. methanol, 35 g. potassium hydroxide) and an equimolar amount of dimethyl sulphate was added with stirring at room temperature. After stirring for a further 24 hrs. the mixture was extracted with ether. The ether extracts yielded a single product, a white solid,which I.R. and m.pt. showed to be starting material.

Dehydration of 1(2'-oxocyclohexylmethyl)-(2-hydroxy)-naphthalene,hemiketal (10).

The naphthol hemiketal (10) was refluxed with benzene and a small amount of p-toluene sulphonic acid for 36 hrs. under a Dean and Stark water separator, until all water had been removed from the system. The benzene was then removed under reduced pressure. T.L.C. showed the presence of two components in the resulting mixture. After separation on a silica column (eluant:- petroleum ether, ethyl acetate mixtures), the smaller of these was identified as starting material. The second, a white crystalline solid, m.pt. $\sim 130^{\circ}$, M.W. 236, was unstable in solution. It exhibited an absorption at 1714 $cm.^{-1}$ (CCl_4 soln.). The hydroxyl absorption at 3595 $cm.^{-1}$ had virtually disappeared. This is consistent with the pyran (11).

(1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one (12).

This compound, b_{18} 84-96°, was isolated as the free base in 13% yield using the method of Mannich and Salzman.[6] A lower boiling fraction, b_{18} 66-68°, identified as the mono-condensation product, 1-dimethyl-amino-butan-3-one was collected in 4% yield.

The low yields in this experiment were caused by the high degree of polymer formation. In an effort to cut down the latter, hydroquinone was added as a radical inhibitor and the entire experiment was conducted in the dark. No appreciable increase in the percentage yield was found. Small scale experiments, in the order of 0·5 mole quantities of dimethylamine and formaldehyde, were found to be more successful than larger scale preparations.

The crystalline dipicrate, m.pt. 134-136° from ethanol (lit. 136·5°)[16] was prepared by addition of an ethanolic solution of picric acid to a similar solution of the amine. The dihydrochloride, m.pt. 148·5-150° from methanol ether (lit. 150-151°)[7] was also prepared, by passage of dry hydrogen chloride through an ethereal solution of the amine.

Condensation of (1-dimethylamino)-(2-dimethylamino-methyl)-butan-3-one (12) and cyclopentanone.

(1-dimethylamino)-(2-dimethylaminomethyl)-butan-3-one (12·4 g. ; 0·072 mole) and cyclopentanone (18·6 g. ; 0·22 mole) were refluxed together for 2½ hrs. under a water condenser, until no further dimethylamine was

evolved. The mixture was cooled, neutralised with glacial acetic acid and extracted with ether. After drying the extracts, the ether and excess cyclopentanone were removed under vacuo, leaving a discoloured oil (9·6 g.). T.L.C. showed the presence of at least six components, one of which was a small amount of cyclopentanone. Separation by distillation was then attempted, the following arbitrary fractions being taken at a pressure of 0·7 mm. Hg:-

(i)	86-96°	0·70 g.
(ii)	98-108°	5·08 g.
(iii)	110-116°	
(iv)	136-140°	
(v)	144-158°	
(vi)	160° +	0·90 g.

The bulk of the product was contained in fractions (ii) - (v), which were recombined on T.L.C. and I.R. evidence, no effective separation of the various components having resulted from distillation.

Fractions (i) and (vi) were discarded, no sign of a carbonyl absorption at a wavenumber greater than 1740 $cm.^{-1}$ being present in their I.R. spectra. Fraction (i) contained the small amount of cyclopentanone remaining in the product mixture after the initial work-up.

G.L.C. analysis (5% QF1, 150°C, 40 ml. min.$^{-1}$) of the recombined fractions showed the present of five components, three of which were present in negligible amounts.

Peak	1.	2.	3.	n-$C_{20}H_{42}$	4.	5.
Retention Index	0·4	0·56	0·81	1·0	1·5	2·1
Amount Present	Neg.	Neg.	✓	-	Neg.	✓

I.R. spectrum of the product mixture is shown in Table 2. Combined gas chromatographic, mass spectral work gave the molecular weight of peak (5) as 166 and that of peak (3) as 154.

Small amounts of virtually pure samples of peaks (3) and (5) were obtained using preparative G.L.C. Large scale separation was attempted simultaneously using a silica column with ethyl acetate, petroleum ether mixtures as eluant. T.L.C. was used to follow the progress of products down the column and the fractions collected were subjected to G.L.C. analysis (see Table 3).

Fraction A consisted mainly of peak (3), fraction B contained 50% peak (5) together with a small amount of (3) and negligible amounts of (1), (2) and (4). Fraction C was 90% peak (5) and fraction D again mainly (5).

Final purification of samples of peaks (3) and (5) was effected using preparative G.L.C., attempts at further purification using plate chromatography having been unsuccessful. It was estimated that a 19% yield (~2·2 g.) of peak (5) and a 3% yield (0·4 g.) of peak (3) had been obtained.

Peak (5) - ~95% purity

Found: C, 71·57; H, 8·56. $C_{10}H_{14}O_2$ requires C, 72·26; H, 8·49%. Molecular weight is 166 ($C_{10}H_{14}O_2$ requires 166). Infra-red solution spectra gave $\nu_{C=O}^{CCl_4}$ 1748 $cm.^{-1}$ 1712 $cm.^{-1}$. No olefinic absorptions were present. N.M.R. shows: 7·6-8·4 τ (multiplet), 7·82 (singlet superimposed on multiplet) ~7·0-7·4 (weak multiplet).

This data is in agreement with that expected for (3-acetyl)-bicyclo-[3,2,1]-octan-8-one (17).

Peak (3) ~95% purity

Found: C, 69·34; H, 8·93. $C_9H_{12}O_2$ requires C, 70·1; H, 9·15%. Molecular weight is 154 ($C_9H_{12}O_2$ requires 154). $\nu_{C=O}^{CCl_4}$ 1735 cm.$^{-1}$, 1714 cm.$^{-1}$, together with slight absorption at 1748 cm.$^{-1}$ due to small amount of peak (5) present. No olefinic absorptions were exhibited. N.M.R. spectrum shows:- 7·5 τ (2 x H, triplet, J = 4 cps.) 7·5-8·4 τ (10 x H, multiplet) 7·91 (singlet).

The above spectral data fits that required for [1(2'-oxo)-cyclopentyl]-butan-3-one (23). The identity of this product was confirmed by comparison with an authentic sample of this compound. Mixed injections and comparison of retention times on two g.l.c. columns (5% QF1, 150°C and 1% OV17, 125°C) showed the two samples to be identical.

Deuteration of (3-acetyl)-bicyclo-[3,2,1]-octan-8-one (17).[17]

Sodium metal (50 mg.) was added to a mixture of dry peroxide-free dioxan (2 ml.) and deuterium oxide (2 ml.). (3-acetyl)-bicyclo-[3,2,1]-octan-8-one (50 mg.) was then added to this reagent and the two were warmed together at 70°C for 15 mins. under nitrogen. The

dioxan and deuterium oxide were removed under reduced pressure and a further 1 ml. deuterium oxide was added before extraction with ether. Removal of solvent from the dried extracts yielded a partially crystalline product, G.L.C. analysis of which showed the present of two components, A and B, present in the ratio 1:1. Pure samples of these compounds were obtained using plate chromatography.

Compound A was isolated as a slightly discoloured oil. Its I.R. spectrum showed $\nu_{C=O}^{CCl_4}$ 1754 cm.$^{-1}$ and 1710 cm.$^{-1}$. G.L.C. analysis gave its retention index as 2·1 relative to n-$C_{20}H_{42}$ (5% QF1, 150°C), which was the same as that of the starting material on a similar column. The mass spectrum of A gave the molecular weight as 170, a fairly large peak being present at 169. There was no sign of an ion at m/e 166. This data was consistent with incorporation of four deuterium atoms into the starting material (17).

Compound B was obtained as a white crystalline solid, m.pt. 123·5-125°C, retention time 1·2 relative to n-$C_{20}H_{42}$ on the above column. Its I.R. spectrum showed $\nu_{C=O}^{CCl_4}$ 1728 cm.$^{-1}$, $\nu_{O-H}^{CCl_4}$ 3605 cm.$^{-1}$. The yield of this product decreased on reduction of the heating period of the reactants. The tricyclic structure, (40), was felt to be a possibility for this hydroxy-ketone.

Synthesis of (3-acetyl)-bicyclo-[3,2,1]-octan-8-one (17)

Diethyl Bis(hydroxymethyl)-malonate.

Diethyl bis(hydroxymethyl) malonate was prepared in 80% yield by the condensation of formaldehyde with diethyl malonate as described in Organic Syntheses.[18] Despite extreme precautions to dry the product, all attempts to crystallise the clear, viscous oil failed.

(2-bromomethyl)-acrylic ester (25).

(3-bromo)-(2-bromomethyl)-propionic acid was obtained in 75% yield by the bromination[19] of diethyl bis(hydroxymethyl) malonate. The yield was found to be much improved if the reactant mixture was allowed to reflux for three hours only. Direct esterification[19] of the crude acid resulted in a 23% yield of (2-bromomethyl)-acrylic ester, $b_{1.0}$ 60-65°, together with a 24% yield of the saturated dibromocompound, ethyl (3-bromo)(2-bromomethyl) propionate, $b_{1.0}$ 75-80°.

Condensation of (2-bromomethyl) acrylic ester (25) and cyclopentanone pyrrolidine enamine (24).

This condensation was first attempted, using the method of Stetter,[12] by the addition of a solution of

(2-bromomethyl) acrylic ester in ethanol to a 2 mole excess of the enamine in a mixture of methyl cyanide and ethanol (1:1). A large mixture of products was obtained after reflux and hydrolysis, distillation failing to effect a separation of these compounds. No carbonyl absorption in the region of 1750 $cm.^{-1}$ was exhibited in the I.R. spectrum of the mixture, indicating an absence of a bridged bicyclic cyclopentanone system.

The reaction was repeated using the solvent systems:- (a) anhydrous benzene, (b) benzene, methyl cyanide, (c) methyl cyanide. A~5% yield of the desired bicyclic ester was obtained using solvent (b) on a small scale.

(2-bromomethyl) acrylic ester (1·0 g. ; 0·005 mole) in benzene (10 ml.) was added with stirring to a solution of enamine (3·0 g. ; 0·02 mole) in benzene (20 ml.) under nitrogen. A white crystalline solid precipitated out of solution immediately on the addition. From its I.R. spectrum and the spontaneity of its formation, it was concluded that this was a quaternary nitrogen salt. Addition of a small amount of methyl cyanide cause dissolution. The mixture was refluxed under nitrogen for three hours and the benzene removed under reduced pressure. The residue, a dark viscous

oil, was taken up in chloroform and hydrolysed by refluxing with 10% aqueous sodium chloride solution. The chloroform extracts were dried and the mixture of at least six products were separated into three main groups using preparative t.l.c. . The I.R. spectrum of the foremost group of compounds exhibited a carbonyl absorption in the region of 1750 $cm.^{-1}$. Further chromatographic purification gave a clear oil (estimated yield ~ 5%), which was shown to be pure by g.l.c. (5% QF1, 150°C, R_t 1·42 relative to n-$C_{20}H_{42}$). Found: C, 67·27; H, 8·07. $C_{11}H_{16}O_3$ requires C, 67·32; H, 8·22%. Molecular weight 196 ($C_{11}H_{16}O_3$, 196). The I.R. spectrum shows $\nu_{C=O}^{CCl_4}$ 1750 $cm.^{-1}$, 1730 $cm.^{-1}$, $\nu_{C-H}^{CCl_4}$ 2880 $cm.^{-1}$, $\nu_{C-O-}^{CCl_4}$ 1175 $cm.^{-1}$, 1192 $cm.^{-1}$. N.M.R. shows:- 8·68 τ (3 x H, triplet, J = 7 cps.) 7-8·3 τ (~11 x H, multiplet), 5·76 τ (2 x H, quartet, J = 7 cps.). From this data it was concluded that the desired product, (3-carbethoxy)-bicyclo-[3,2,1]-octan-8-one (26) had been obtained.

Insufficient product was obtained from this small scale preparation to continue with the remaining synthetic steps. Attempted large scale preparations using the above conditions failed completely. Small scale preparations in the solvent, methyl cyanide gave similarly

small yields. Monoalkylated cyclopentanones appeared to be among the products. A nitrogen containing compound, possibly an N-alkylated product, formed a large proportion of the product mixture. This did not yield the desired product on heating or hydrolysis.

[1,5-bis(dimethylamino)]-pentan-3-one (15).

The method of Blicke and McCarty[7] was used to prepare this compound in 15% yield as its crystalline dihydrochloride, m.pt. 199-200° (lit. 202-203°). Recrystallised from methanol ether.

The dipicrate was prepared by addition of ethanolic picric acid solution to a solution of the hydrochloride in ethanol, m.pt. 146·5-148° (lit. 155-156°).

The free Mannich base was obtained by addition of 6N sodium hydroxide solution to an aqueous solution of the hydrochloride, followed by extraction with ether (x6). T.L.C. showed slight contamination of the resulting amine, but no further purification was done. For N.M.R. data, see Table 1.

Condensation of [1,5-bis(dimethylamino)]-pentan-3-one (15) and cyclopentanone.

[1,5-bis(dimethylamino)]-pentan-3-one (2·6 g. ; 0·015 mole) and cyclopentanone (4·5 g. ; 0·05 mole) were refluxed for 110 mins. under a water condenser until no further dimethylamine was liberated. The mixture was neutralised with glacial acetic acid in the normal fashion and ether was added to the diluted solution. A crystalline product (1·4 g., m.pt.~100°) precipitated out of solution at this stage. This was removed by filtration and the remaining products extracted with ether. After removal of the ether and excess cyclopentanone, a discoloured oil (2·7 g.) remained. This contained one main component.

Purification of the oil, using a silica column with ethyl acetate, petroleum ether mixtures as eluant, yielded a pure sample of this latter compound, a white crystalline solid (1·9 g., 51% overall yield), m.pt. 50-51·5°C from benzene petroleum ether. Found: C, 71·82; H, 8·87. $C_{15}H_{22}O_3$ requires C, 71·97; H, 8·86%. Molecular weight, 250 ($C_{15}H_{22}O_3$ requires 250). The I.R. absorption spectrum exhibits $\nu_{C=O}^{CCl_4}$ 1737 cm.$^{-1}$, 1712 cm.$^{-1}$. N.M.R. exhibits:- 7·47 τ (triplet, J = 7 cps.) 7·6-8·8 τ (multiplet). This data agrees with that expected for [1,5-bis(2'-oxocyclopentyl)]-pentan-3-one (28).

Recrystallisation of the minor reaction product from either ethanol or benzene, ether proved unsatisfactory. Floculant crystals of an indefinate melting point were obtained. The I.R. absorption spectra exhibits $\nu_{C=O}^{CCl_4}$ 1737 cm.$^{-1}$, 1712 cm.$^{-1}$. N.M.R. exhibits:- 7·48 τ (triplet, J = 7 cps.) 7·6-8·6 τ (multiplet). T.L.C. (100% EtOAc) showed that the solid consisted of at least four compounds. The I.R. spectra of the two major components, isolated by preparative t.l.c. exhibited the two carbonyl absorptions quoted previously. Mass-spectral molecular weight determination proved impossible due to the involatile nature of these compounds. This evidence agrees with that required for multicondensation products, of a similar nature to the major reaction product.

[1,5-bis(dimethylamino)]-2-methyl-pentan-3-one (16)

This was obtained in 25% yield, using the method of Mannich and Hof,[20] as the crystalline dihydrochloride, m.pt. 190-191° (lit. 192-193°). Recrystallised from methanol ether.

Difficulty was experienced in obtaining a crystalline dipicrate on addition of an ethanolic solution of picric acid to a similar solution of the hydrochloride. The resulting picrate appeared to be unstable, m.pt. 60-62^{o} (one recrystallisation, ethanol)

The free amine was obtained by basification and extraction with ether. Addition of solid sodium chloride was found necessary to ensure complete removal of the Mannich base from the aqueous layer. Although T.L.C. showed the presence of a small amount of impurity, the amine was used with no further purification.

No definite colouration was given on the addition of ethanolic ferric chloride solution to the base. The iodoform test was inconclusive, a faint cloudiness appearing. The latter test was negative when performed on a solution of hydrochloride.

Condensation of [1,5-bis(dimethylamino)]-(2-methyl)-pentan-3-one (16) and cyclopentanone.

[1,5-bis(dimethylamino)]-(2-methyl)-pentan-3-one (1·6 g. ; 0·009 mole) and cyclopentanone (2·2 g. ; 0·027 mole) were refluxed for 90 mins. under a water condenser, until no further dimethylamine was liberated. The

solution was neutralised with glacial acetic acid and extracted with ether. After removal of the ether and excess cyclopentanone, a discoloured oil (1·62 g.) consisting of one major component remained. Subsequent purification, using a silica column with ethyl acetate, petroleum ether as eluant, gave approximately 1·0 g. (45%) of this product, an oil. Found: C, 72·83; H, 8·92. $C_{16}H_{24}O_3$ requires C, 72·69; H, 9·15%. Molecular weight: 264 (required for $C_{16}H_{24}O_3$, 264). The I.R. spectrum showed $\nu_{C=O}^{CCl_4}$ 1740 cm.$^{-1}$ (ε 873), 1714 cm.$^{-1}$ (ε 316). N.M.R. spectrum:- 7·39 τ (3 x H, multiplet, J = 7 cps.), 7·6-8·7 τ (multiplet), 8·90 τ (3 x H, doublet, J = 7 cps.). This data is in agreement with that required for [1,5-bis-(2'oxocyclopentyl)]-(2-methyl)-pentan-3-one (30).

(2-ethyl-2-carbethoxy)-cyclopentanone.

This was obtained from the Dieckmann cyclisation of diethyl adipate followed by immediate alkylation with ethyl bromide, in the mode described by Nicole and Berlinguet.[21] The product distilled over as a clear liquid, $b_{2.0}$ 82°C, in 62% yield and was found to be G.L.C. pure (7% F60, 1% X, 95°, R_t 7·69 relative to n-$C_{10}H_{22}$).

(2-ethyl-5-carbethoxy)-cyclopentanone (39).

(2-ethyl-2-carbethoxy)-cyclopentanone was rearranged to the (2-ethyl-5-carbethoxy)-cyclopentanone in 72% yield ($b_{2.0}$ 104-106°) using the method of Sisido.[22] (R_t 10·4 relative to n-$C_{10}H_{22}$ on above column.)

(2-ethyl-)cyclopentanone.

Decarbethoxylation of (2-ethyl-2-carbethoxy)-cyclopentanone (39) by the method of Nicole and Berlinguet[21] yielded 57% 2-ethyl-cyclopentanone, b_{40} 76-82° (G.L.C. R_t 0·82 relative to n-$C_{10}H_{22}$).

β-aminopropiophenone (31).

This was prepared as its stable crystalline hydrochloride, m.pt. 155-156° from ethanol, acetone using the method given in Organic Syntheses.[23]

The free amine was liberated from the hydrochloride as required by basification of an aqueous solution of the latter using 6N sodium hydroxide solution followed by extraction with ether.

Condensation of (β-aminopropiophenone) (31) and cyclopentanone.

(A) Ethylene glycol as solvent, ketone: base = 1:1

β-aminopropiophenone (10·5 g., ; 0·06 mole) (31), cyclopentanone (5 g. ; 0·06 mole) and ethylene glycol (30 ml.) were heated under a condenser with stirring for 45 mins. at 150-160°C. The mixture was neutralised with glacial acetic acid and extracted with ether, a crystalline solid separating out of solution on addition of the ether. A 6% yield of this product (m.pt. 115-116° from benzene, petroleum ether) was obtained. Found: C, 79·37; H, 6·99. $C_{23}H_{24}O_3$ requires C, 79·28; H, 6·94%. The I.R. spectrum showed $\nu_{C=O}^{CCl_4}$ 1687 cm.$^{-1}$, 1732 cm.$^{-1}$ (2:1). N.M.R. ($CDCl_3$ solution): 6·89 τ (4 x H, triplet, J = 7 cps.), 7·6-8·7 τ (10 x H, multiplet), 1·9-2·8 τ (10 x H, multiplet). This data is in agreement with that predicted for a di-condensation product, either 2,2-bis(β-benzoylethyl)-cyclopentanone (33) or 2,5-di(β-benzoylethyl)-cyclopentanone (34).

Extraction of the remaining mixture with ether, yielded a discoloured oil. Distillation gave 5·04 g. (40% yield) of the normal mono-substitution product, 2-(β-benzoylethyl)-cyclopentanone (32).

(B) Ethylene glycol, ketone: base = 1:2.

β-aminopropiophenone (10·5 g. ; 0·06 mole) cyclopentanone (2·5 g.; 0·03 mole) and ethylene glycol (30 ml.) were heated together at 160° for 90 mins. 4·5 g. (42% yield) of the crystalline disubstituted product, and 2·5 g. (19%) of the mono-substituted product, 2-(β-benzoylethyl)-cyclopentanone (32) were obtained.

Condensation of (β-aminopropiophenone) (31) and (2-ethyl)-cyclopentanone.

(A) No solvent, ketone: base = 3:1.

β-aminopropiophenone (2·95 g. ; 0·0166 mole) and (2-ethyl)-cyclopentanone (5·6 g. ; 0·05 mole) were refluxed together under a water condenser for 45 mins. Neutralisation with glacial acetic acid and extraction with ether yielded an oil, which on distillation gave two fractions. 1·3 g. of (2-ethyl)-cyclopentanone was collected as the lower boiling fraction, together with 2·62 g. (65% yield) of condensation product, $b_{0.25}$ 150-154°. This was further purified by column chromatography to give a G.L.C. pure sample (retention time 16·25 mins., 5% QF1, 200°C). Found: C, 78·72; H, 8·31. $C_{16}H_{20}O_2$ requires

C, 78·65; H, 8·25%. I.R. spectrum exhibited $\nu_{C=O}^{CCl_4}$ 1687 cm.$^{-1}$, 1732 cm.$^{-1}$ (1:1). N.M.R.: 1·8-2·7 τ (5 x H, multiplet), 6·87 τ (2 x H, triplet, J = 7 cps.), 7·7-8·8 τ (10 x H, multiplet), 9·02 τ (3 x H, doublet, J = 7 cps.). The mono-condensation product, (2-ethyl)-(2-[β-benzoylethyl])-cyclopentanone (36) or the 2,5-isomer (35), would fit the above physical data.

(B) Ethylene glycol as solvent, ketone: base = 1:1.

β-aminopropiophenone (8·9 g.; 0·05 mole), 2-ethyl-cyclopentanone (5·60 g.; 0·05 mole) and ethylene glycol (30 ml.) were refluxed for 60 mins. at 160°C 9·35 g. (77% yield) of the mono-condensation product were obtained.

Condensation of β-aminopropiophenone (31) with (2-ethyl)-(5-carbethoxy)-cyclopentanone (39).

No solvent, ketone: base = 3:1

β-aminopropiophenone (2·0 g.; 0·01 mole) and (2-ethyl)(5-carbethoxy)-cyclopentanone (6·1 g. ; 0·03 mole) were refluxed for 90 mins. Negligible dimethylamine was liberated during the period of reflux. T.L.C. showed the presence of a large proportion of the

starting material after the reaction period. The reactant mixture was, therefore, neutralised with glacial acetic acid taken up into ether and washed with acid to remove any unchanged Mannich base. The remaining products in ethereal solution were then washed consecutively with sodium bicarbonate solution, brine and water and finally dried over anhydrous magnesium sulphate. The solvent volume was reduced and the resultant oil subjected to G.L.C. analysis (7% F60, 1%Z, 95°C).

The latter showed the presence of two compounds with retention indices of 0·80 and 10·4 relative to n-$C_{10}H_{22}$, in the relative amounts 3:2. The first of these products, that present to the slightly larger extent, was identified as 2-ethyl-cyclopentanone and the second as the starting material (2-ethyl)(5-carbethoxy)-cyclopentanone (39). Comparison of retention times and mixed injections with samples of the authentic compounds were used for their identification.

(β-benzylethyl)-cyclopentanones (37).

These were prepared as colourless oils by the hydrogenolysis of the corresponding (β-benzoylethyl)-cyclopentanone over a 5% palladium, charcoal catalyst.[24] The latter was activated by the addition of a few drops of concentrated hydrochloric acid to the ethanolic solution, 100 mg. of catalyst being used for every 500 mg. of benzoyl compound in ethanol (15 ml.). The hydrogenolyses were allowed to proceed for 24 hrs. at room temperature and atmospheric pressure to ensure complete reaction. After filtration and reduction of the ethanol volume, the products were taken up in ether and washed successively with sodium bicarbonate and chloride solutions. The (β-benzoylethyl)-cyclopentanones (37) so obtained were 95% pure and could be used without further purification.

(β-benzylethyl)-cyclopentanones, cyclic ketals (38).

The most satisfactory mode of preparation of these compounds was found to be that used by Marquet et al[25] employing triethyl orthoformate with para-toluene sulphonic acid as a catalyst. The ketone (300 mg.), ethylene glycol (1 ml.), triethyl orthoformate (2 ml.) and

p-toluene sulphonic acid (60 mg.) were refluxed for 60 mins. In all cases, addition of sodium bicarbonate solution and extraction with ether yielded a mixture of products, the major one of which was the cyclic ethylene ketal. A pure sample of this was obtained using plate chromatography.

2(β-benzylethyl)-cyclopentanone, ketal (38a).

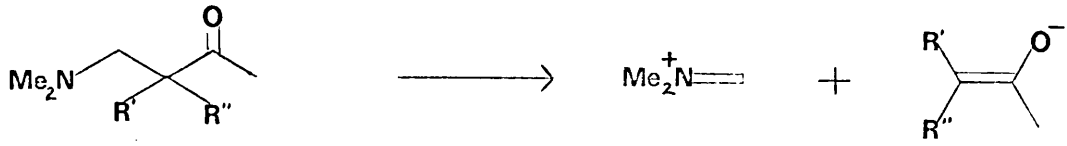
Found: C, 78·21; H, 9·15. $C_{16}H_{22}O_2$ requires C, 78·01; H, 9·00%. Molecular weight found:- 246 (M.S. No. 1). N.M.R. exhibited:- 6·15 τ (4 x H, singlet), 2·8 τ (5 x H, singlet), 7·3-8·8 τ (13 x H, multiplet). I.R. showed absorptions:- 1199, 1106, 1028, 945 $cm.^{-1}$ (CCl_4 solution).

2,5-di(β-benzylethyl)-cyclopentanone, ketal (38b).

Molecular weight, 364 (M.S. No. 2). The I.R. spectrum showed absorptions:- 1027, 1032, 950 $cm.^{-1}$ (CCl_4 solution).

(2-ethyl)(5-[β-benzylethyl])-cyclopentanone, ketal (38c)

Found: C, 78·64; H, 9·51. $C_{18}H_{20}O_2$ requires C, 78·79; H, 9·55%. Molecular weight found:- 274 (M.S. No. 3).



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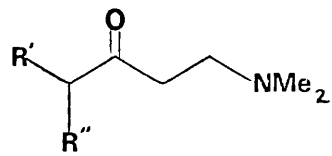

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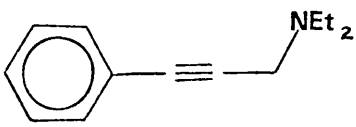

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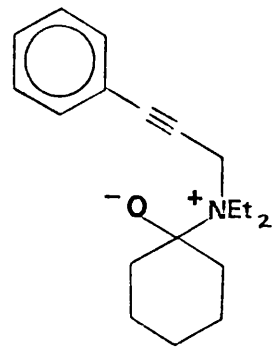

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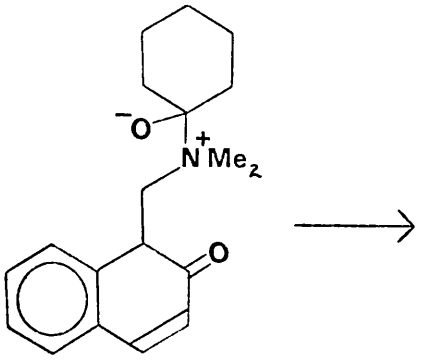

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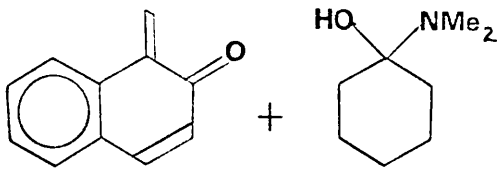

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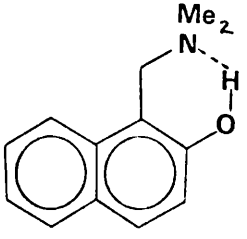

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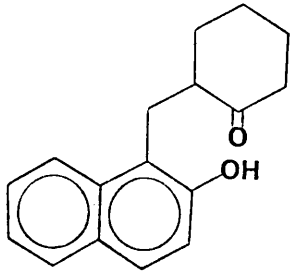

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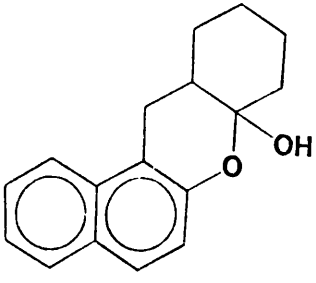

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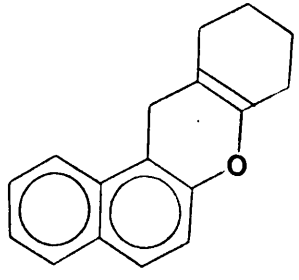

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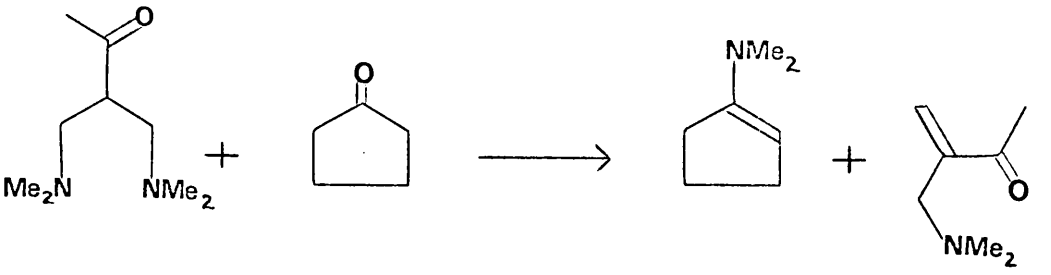

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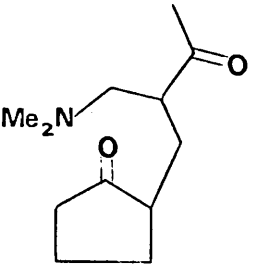

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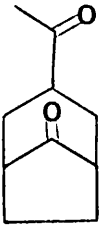

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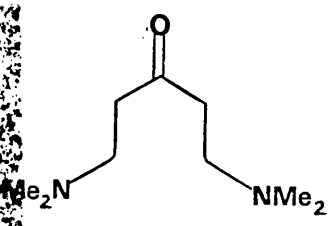

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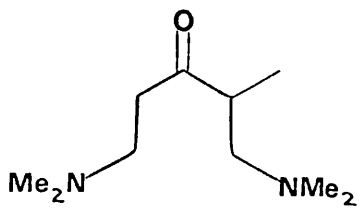

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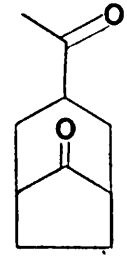

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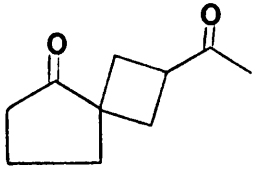

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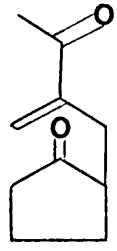

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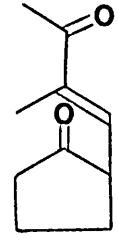

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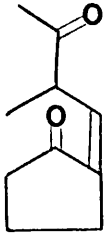

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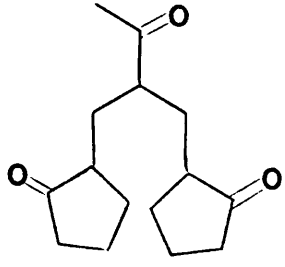

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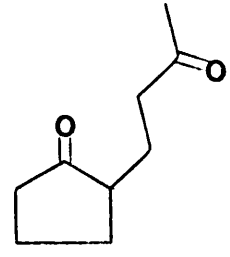

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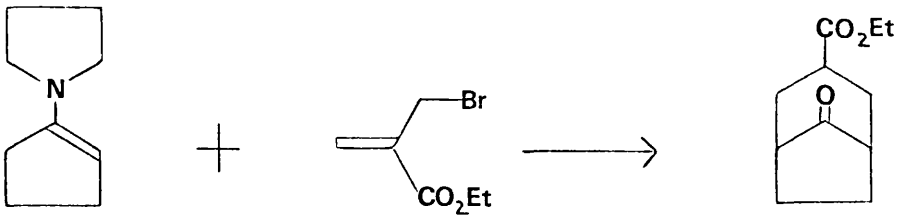

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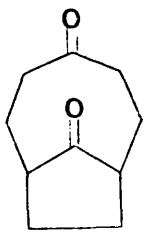

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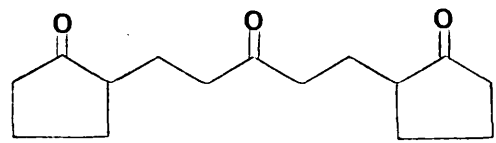

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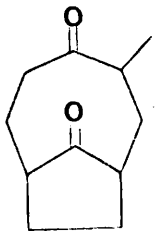

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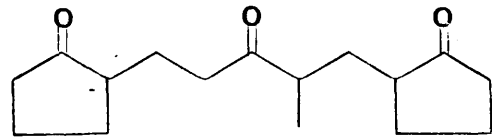

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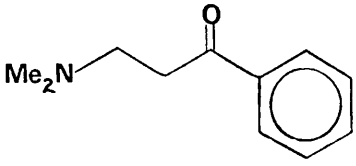

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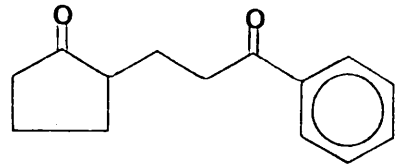

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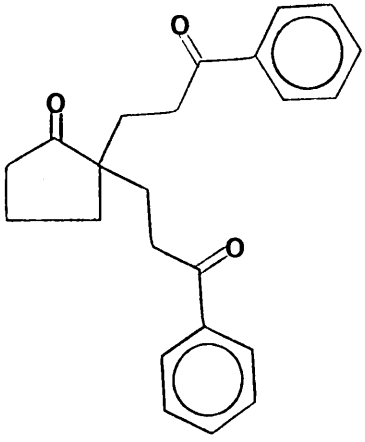

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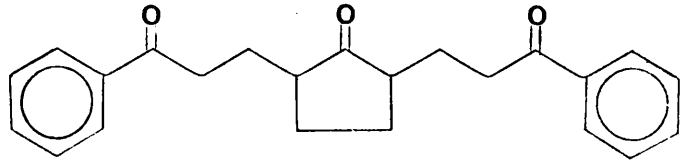

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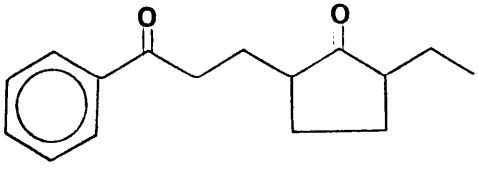

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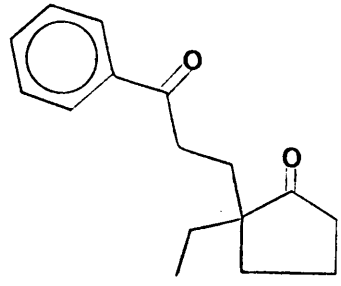

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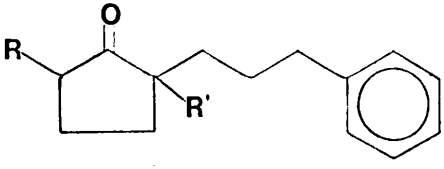

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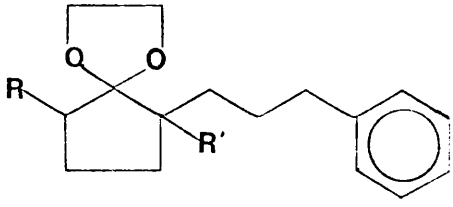
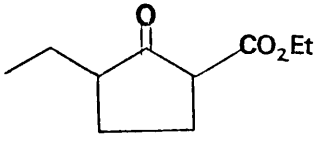


38.

(a) R=H, R′=H
(b) R=$(CH_2)_3$Ph, R′=H
(c) R=H, R′=$(CH_2)_3$Ph
(d) R=Et, R′=H
(e) R=H, R′=Et



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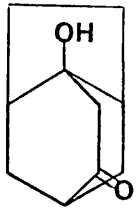

40.

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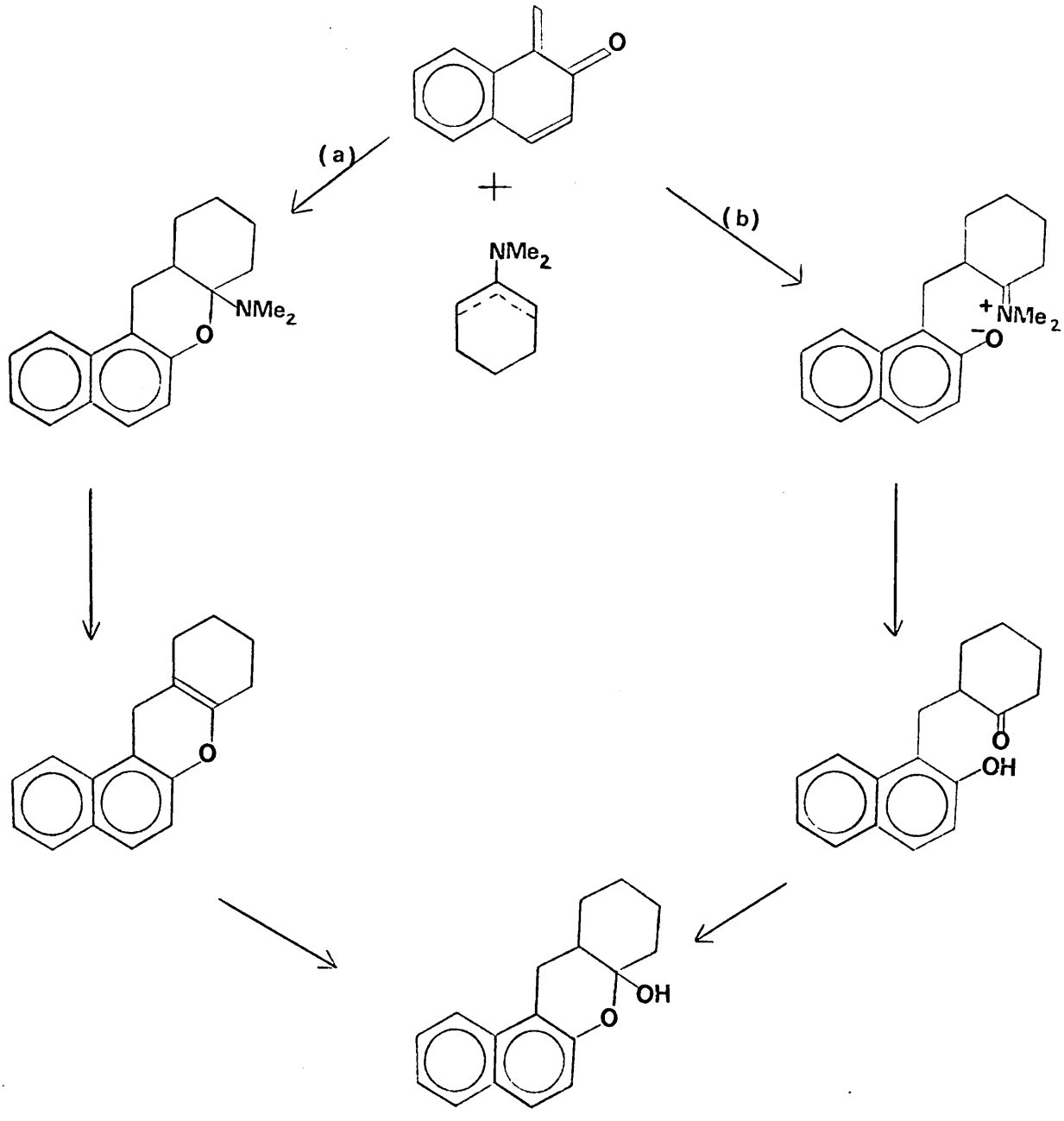
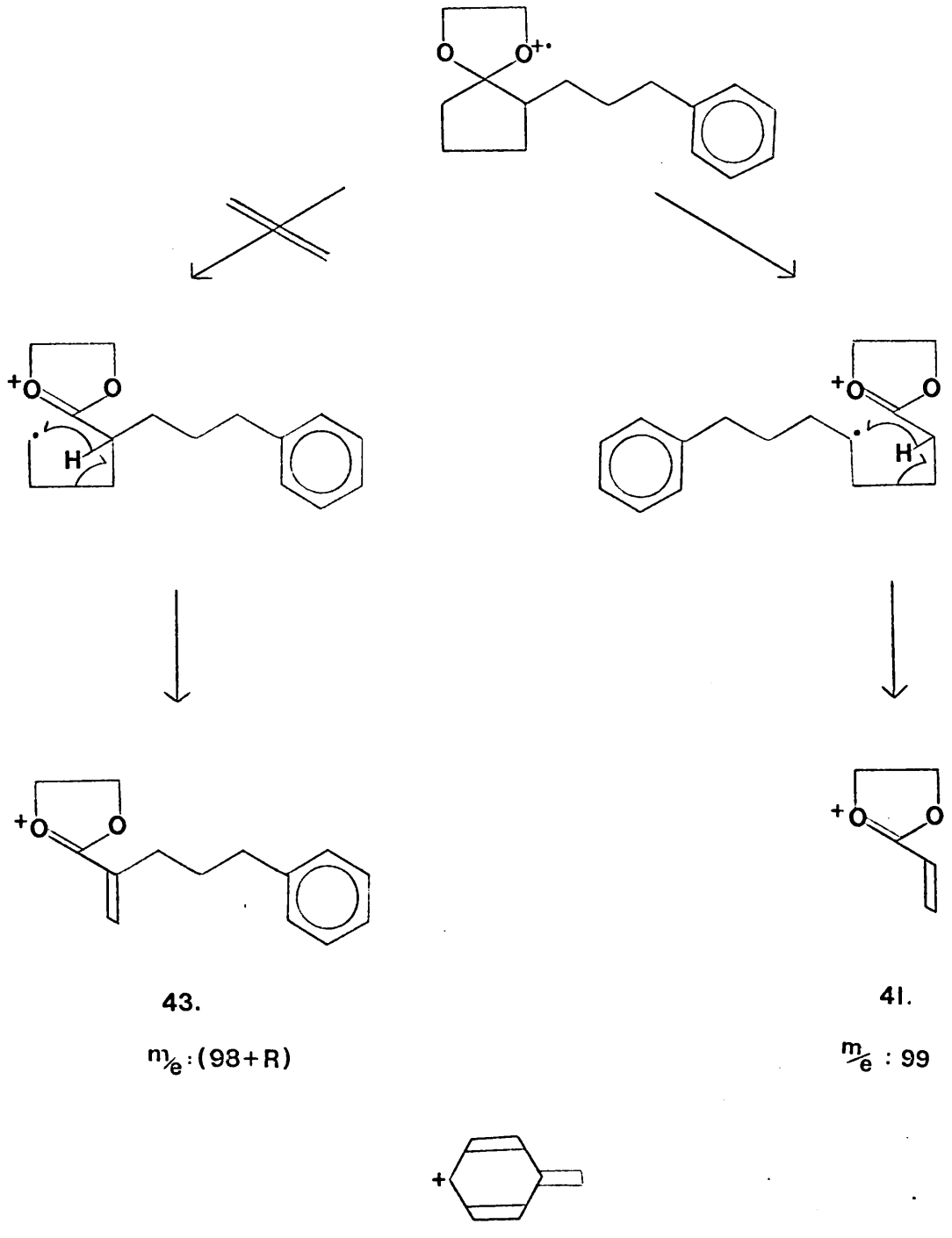


SCHEME B :-



43.

m/e : (98+R)

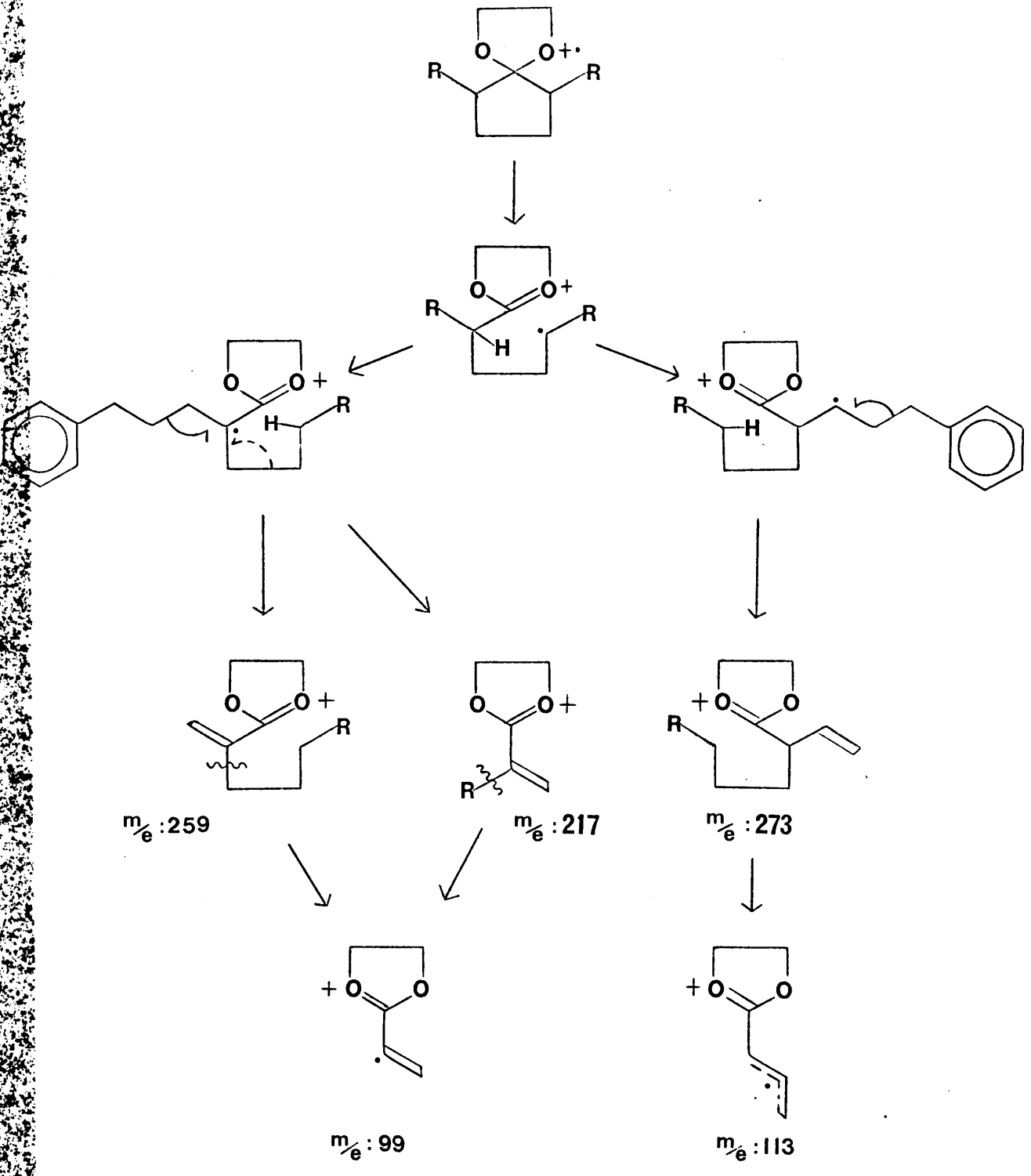
41.

m/e : 99

42.

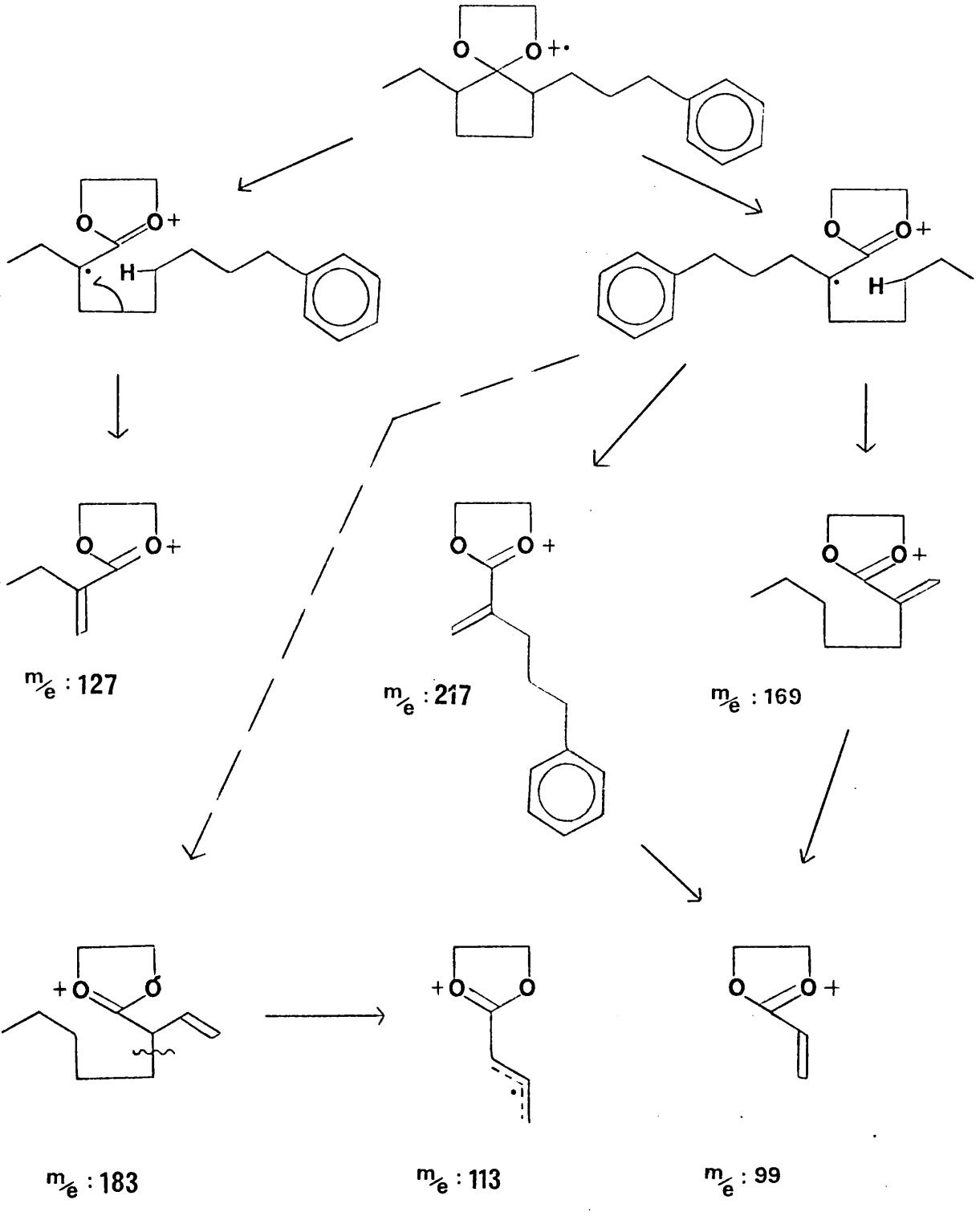
m/e : 91

SCHEME C :-

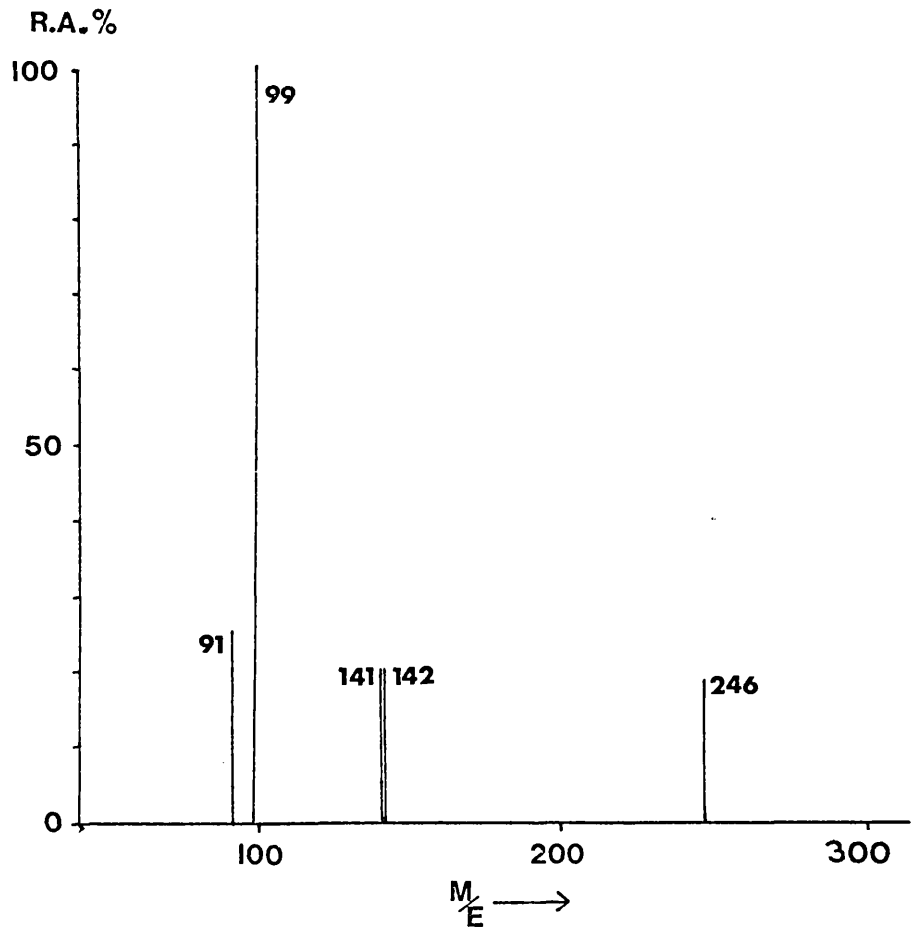


R = $(CH_2)_3Ph$

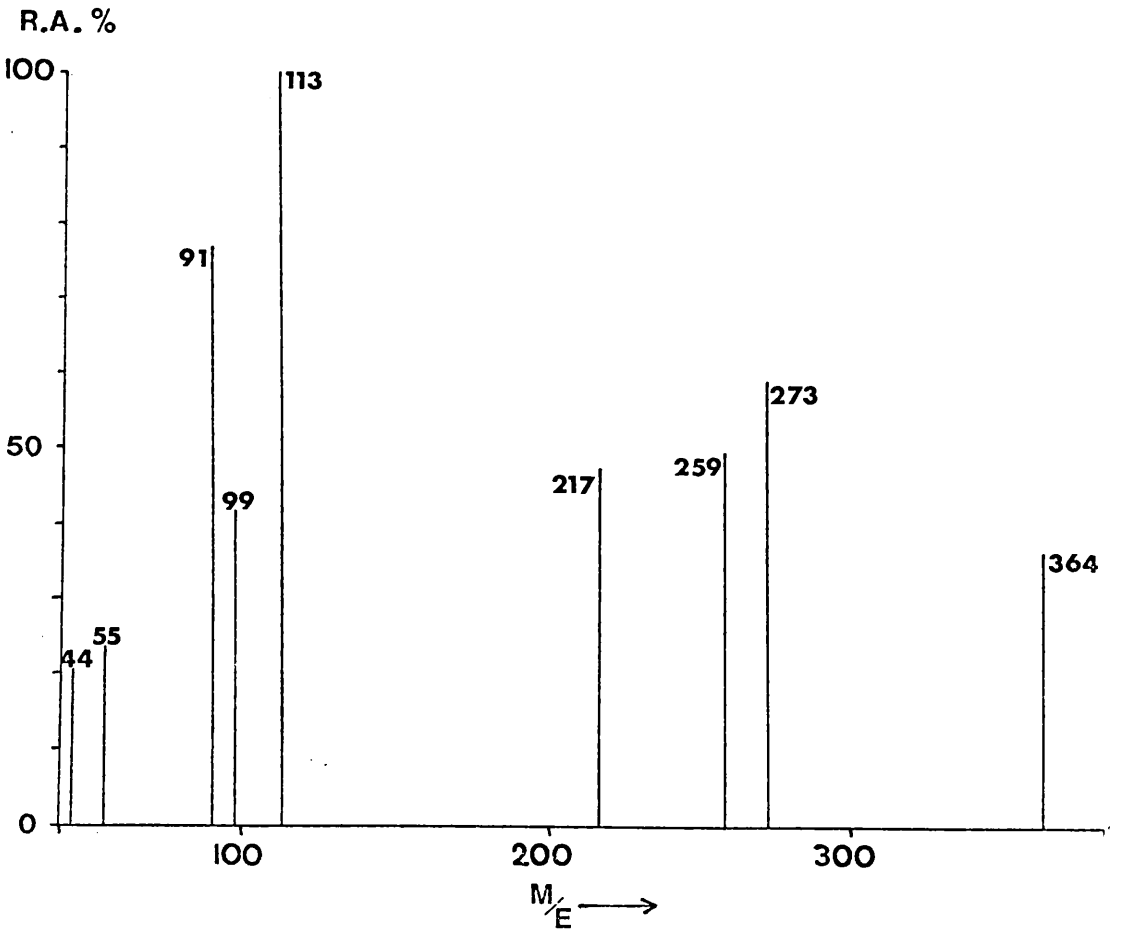
SCHEME D :-



M.S. No.1; 2-(β-benzylethyl)-cyclopentanone, ketal.



M.S. No.2 ; 2,5-bis(β-benzylethyl)-cyclopentanone , ketal.



M.S. No.3 ; (2-ethyl)(5-[β-benzylethyl]) -cyclopentanone , ketal.

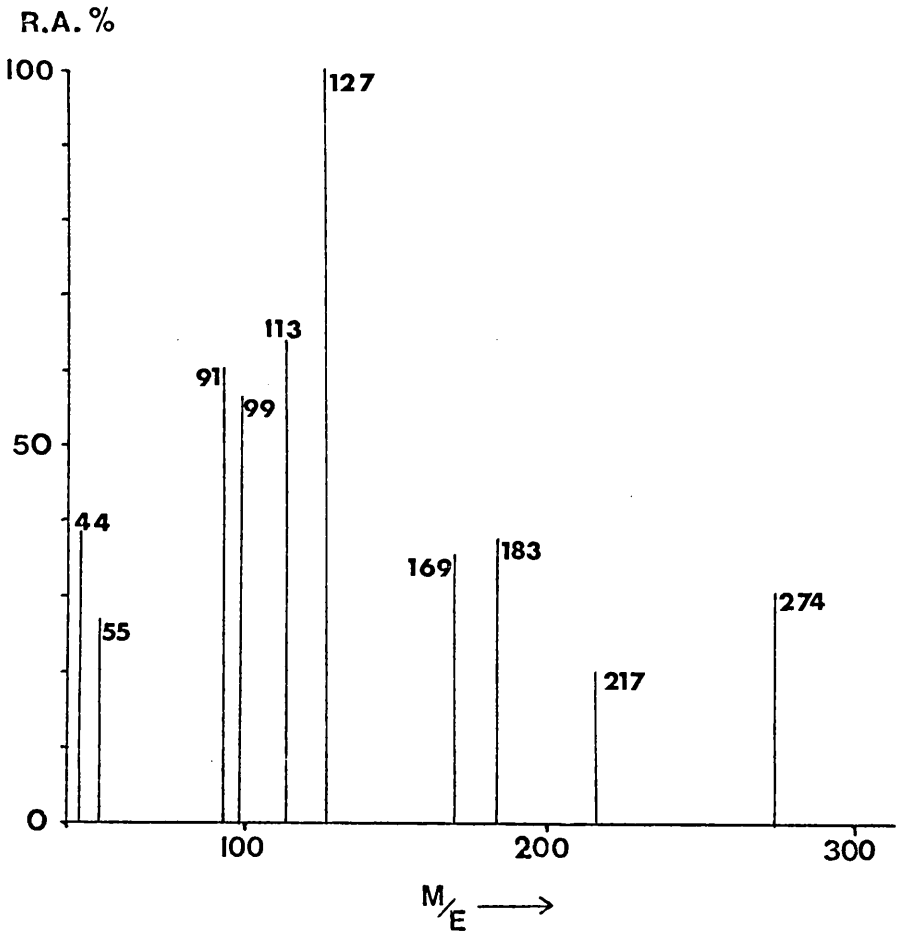
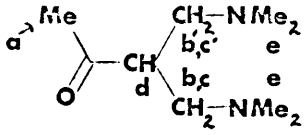
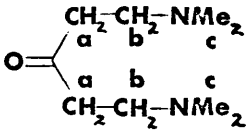


Table 1.



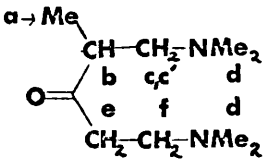
12.

Compound	Solvent	H_a	H_e	$H_{b,c,d,b',c'}$
Free base	$CDCl_3$	7·89 τ (singlet, 3 x H)	7·83 τ (singlet, 12 x H)	Assignment impossible. No integral.
Dihydrate	Pyridine	7·71 τ (singlet)	7·40 τ (singlet)	Low solubility prevented resolution of spectra.
Hydro-chloride	D_2O	7·56 τ (singlet)	7·01 τ (singlet)	Complex multiplet 6·0-7·3 τ. No apparent symmetry



15.

Compound	Solvent	H_c	$H_{a,b}$
Dihydrate	Pyridine	7·2 τ ?	Sample appears to decompose in soln.
Hydro-chloride	D_2O	7·11 τ (singlet, 12 x H)	Symmetric multiplet, 6·72 τ. Four lines apparent, 6·60, 6·66, 6·78, 6·86 τ (8 x H)



16.

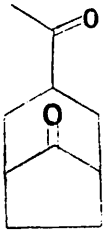
Compound	Solvent	H_a	H_d	$H_{b,c,c',e,f}$
Free base	$CDCl_3$	8·95 τ (singlet, J=6cps 3xH)	7·8 τ (singlet, 12 x H)	Multiplet 7·2-7·5 τ. (7 x H)
Dihydrate	Pyridine	8·77 τ (Doublet, J = 6cps)	7·01 τ	Integral and expansion impossible
Hydro-chloride	D_2O	8·72 τ (Doublet, J = 6cps)	7·11 τ (singlet)	Multiplet 6·4-7·0 τ

Table 2

Solution I.R. of Product Mixture

(Condensation of (1-dimethylamino)(2-dimethylaminomethyl)-butan-3-one with cyclopentanone).

Assignment of Absorp.		Expt. Values	Theoretical Values ($cm.^{-1}$)		
			17	19	20 & 21
ν_{C-H}	$CR_1R_2=CHR_3$	840	-	-	840-790
"	$CR_1R_2=CH_2$	885	-	895-885	-
"	$CR_1R_2=CH_2$	1415	-	1420-1410	-
$\nu_{C=C}$	$CR_1R_2=CH_2$	1645	-	~1655	-
"	$CR_1R_2=CHR_3$	1670	-	-	~1670
"	$CR_1R_2=CH_2$	1684	-	-	-
$\nu_{C=O}$	$CH_3.CO.R.$	1723	~1725	~1725	~1725
"		1745	-	1740	1740
"	Bicyclic	1756	~1750	-	-



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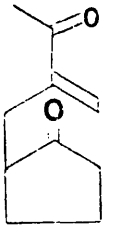
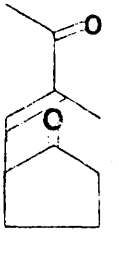


19.



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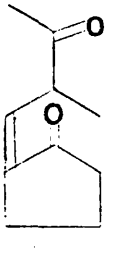
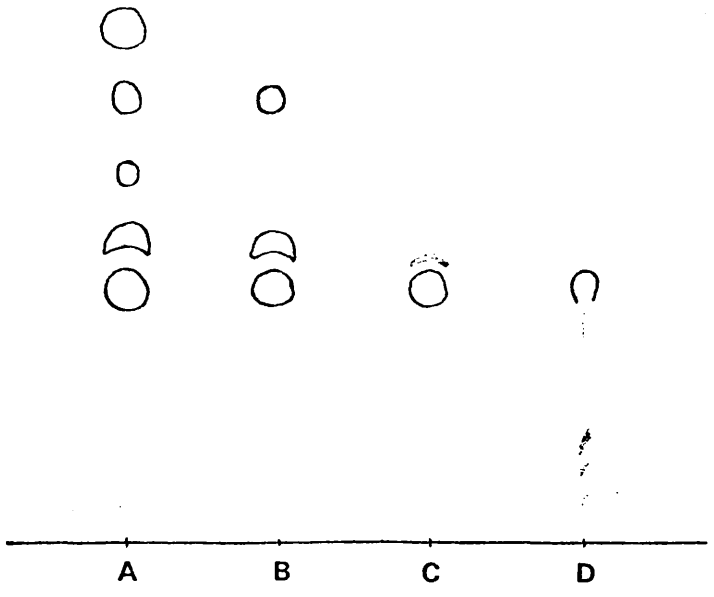


21.

Table 3.

(40% EtOAc, 60% petroleum ether).



Condensation products of cyclopentanone and (1-dimethylamino)(2-dimethylaminomethyl)-butan-3-one.

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