Effects of Structural Modifications on the Odour of Jasmone Analogues

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Jasmone (1) and methyl jasmonate (2) are well known and organoleptically important constituents of the essential oil, concrete and absolute of jasmin *(Jasminium grandiflorum).* Because of the commercial value of the jasmin oils and extracts, a great deal of research has been carried out on these two materials and the chemical literature abounds with their syntheses. Inevitably, synthetic chemists have turned their attention not only to the naturally occurring substances themselves, but also to analogues and in particular those which are easier to prepare or which might be expected to possess some practical advantage over the natural prototypes. Thus such materials as dihydrojasmone (3), 2-heptylcyclopentanone (4) and methyl dihydrojasmonate (5) have become important perfumery chemicals.

In order to direct such research, perfumery chemists have endeavoured to identify any structure/odour correlations which exist in this group of compounds. In the 1930s Werner observed that 5- and 6-membered cyclic ketones bearing an alkyl group in the position alpha to the carbonyl possessed useful jasmin odours but only if they contained between 9 and 15 carbon atoms in total, 11 being the optimum.[1] He also noted that those ketones with a straight chain substituent had a more agreeable bouquet than the branched chain isomers. On considering the structures of a wide range of jasmin chemicals, both cyclic and open chain, Boelens concluded

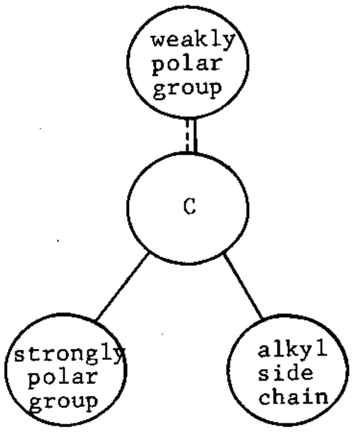
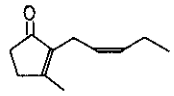


Figure 1. Reproduced from **Cosmetics and Perfumery,** 1974, **89**(9), 77, by permission of Allured Publishing Corp.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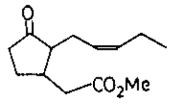
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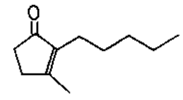
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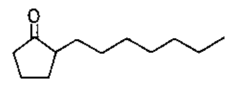
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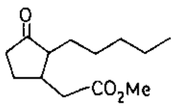
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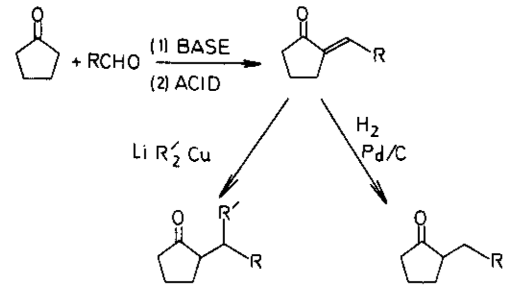


Figure 2

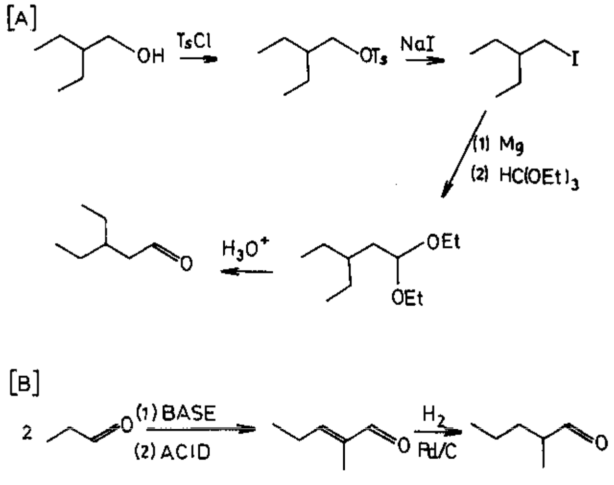
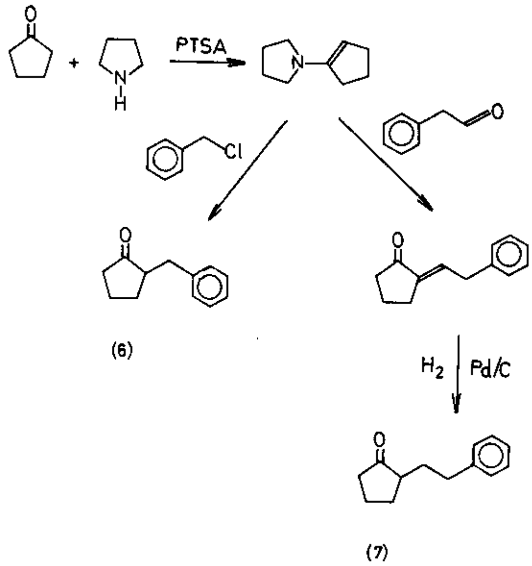


Figure 3



that all jasmine chemicals possess a molecular structure having a strongly polar group, a weakly polar group and a alkyl chain arranged around a central carbon atom as shown in figure 1. He added that the alkyl chain should be unbranched and unsubstituted since branching or substitution causes an increase in the fruity nuances at the expense of the jasmin character of the material.[2]

Examination of the chemical and patent literature reveals that variations to structures of the natural jasmin materials have been made mainly in terms of length of side chain, presence/absence/stereochemistry of the annular and side chain double bonds and the nature of the substituent on the 3-position of the cyclopentane nucleus. Relatively few materials have been made which possess branched or substituted side chains. In view of this, and since Werner and Boelens have both stated that modifications to the side chain can affect the odour, we decided to synthesise a range of jasmin analogues containing branched, substituted or cyclic side chains in order to assess the extent of these structure/odour effects. In order to reduce the number of structural variables, and thus simplify interpretation of results, we considered only saturated 2-alkylcyclopentanones and substituted derivatives thereof.

Synthesis

The materials under discussion in the present work were prepared using well established synthetic methods. The three key reactions employed, aldol condensation, hydrogenation and organocuprate addition, are shown in figure 2. Using these three simple techniques, a wide range of substituted cyclopentanones were prepared using appropriate combinations of aldehydes and organocuprates. Most of the aldehydes used in these preparations are commercially available; some were not and thus had to be synthesised. Two typical examples of such syntheses are shown in figure 3. Some materials were more conveniently prepared by other methods; for example, alkylation of cyclopentanone pyrrolidine enamine led to 2-benzyl- and 2-(2-phenylethyl)cyclopentanone, (6) and (7) respectively.

All of the materials thus produced were isolated in a high degree of purity and their spectral properties were entirely consistent with those expected for the proposed structures. Most of these materials exist as mixtures of diasteriomers. In all cases, the predicted number of isomers were observed, the various pairs separating on GC. Since the odours of the pairs were essentially indistinguishable, each material was assayed as a mixture with no attempt at separation and resolution.

Odour/Structure Correlations

In order to simplify interpretation of the organoleptic assessments, the odour of each material was described in terms of the eight descriptors applied most frequently in the initial 'blind' odour descriptions. Obviously the weightings given are arbitrary and varied from one perfumer to another; however, the "average" values shown in the figures do serve to illustrate the patterns which exist. The eight descriptors chosen as the key facets of the odour characters of the materials in question can be defined as follows:

ethereal—a harsh chemical quality, reminiscent of ether and other low boiling solvents
jasminic—the jasmine character present in such materials as cis jasmone and dihydrojasmone
rosaceous—the herbaceous aspects of rose and geranium
peachy-lactonic—undecalactone/nonalactone type odour
waxy/oily—a bland nondescript odour, reminiscent of vegetable oils and waxes
herbaceous—typical green herbaceous character
fruity—harsh fruity, amyl acetate like
camphoraceous—odour reminiscent of camphor and related materials

Figures 4-12 show the odours of the principal materials prepared for this study, described in terms of these eight descriptors and arranged into groups based on features of molecular structure. However, it should be noted that, since the mechanism of organoleptic perception is still a subject of debate, correlations between molecular structure and odour do not necessarily indicate a relationship of cause and effect.

The odour characters of the 2-n-alkylcyclopentanones support Werner's postulate in that little or no jasmin character is apparent in the lower members of the series, viz, those with propyl and butyl chains. A strong jasmin character appears in 2-pentylcyclopentanone, is at a maximum in 2-hexylcyclopentanone ($C_{11}H_{20}O$) and declines again in 2-heptylcyclopentanone.

We have found that the introduction of a methyl substituent on the first carbon atom of the side chain destroys virtually all jasmin character in the odour of a 2-alkylcyclopentanone as can be seen from figure 5. Thus, from 2-(1-methylbutyl) cyclopentanone up to 2-(1-methylheptyl) cyclopentanone, little or no jasmin note is present in the odours, which are rather nondescript, waxy and oily with some herbaceous character. The effect of increasing the size of the substituent on the first carbon atom on the side chain was investigated by preparing a series of 2-(1-alkylpentyl) cyclopentanones and the results are shown in figure 6. In general the size of the group (from methyl to t-butyl) had little effect on the odour of the material although 2-(1-ethylpentyl) cyclopentanone did possess a much more pronounced herbaceous character with an overall resemblance to sage.

The effect of a substituent on the second position of the side chain is demonstrated by a series of 2-(2-ethylalkyl) cyclopentanones the main side chain varying from butyl to hexyl as illustrated in figure 7. In all cases the jasmin character is replaced by rose, other features such as the increasing importance of lactonic notes on ascending the series being very similar to those of the unsubstituted series. The effect of size of the 2-substituent (from hydrogen to n-propyl) was determined by synthesising a number of 2-(2-alkylpentyl) cyclopentanones (see figure 8). When only hydrogens are present in the 2-position of the side chain the material has a predominantly jasmin character; introduction of a methyl group at this position converts it largely to rose with ethyl or propyl substituents, the odour is strongly rosaceous with no trace of jasmin. 2-(2,2-Dimethylpentyl) cyclopentanone is also strongly rosaceous.

The isomeric series of 2-(x-ethylpentyl) cyclopentanones demonstrates the above effects rather well as evident from figure 9. The unsubstituted parent, 2-pentylcyclopentanone, is strongly jasminic whereas 2-(1-ethylpentyl) cyclopentanone is oily and herbaceous, 2-(2-ethylpentyl) cyclopentanone is rosaceous and in 2-(3-ethylpentyl) cyclopentanone the odour character has returned to jasmin.

This pattern of activity is evident also in the 2-butylcyclopentanones (see figure 10). The parent 2-butylcyclopentanone is not in the correct molecular weight range to possess much jasmin character, but introduction of a 3-methyl group in the side chain causes a stronger jasmin

Key

Figure 4

Figure 5

Figure 6

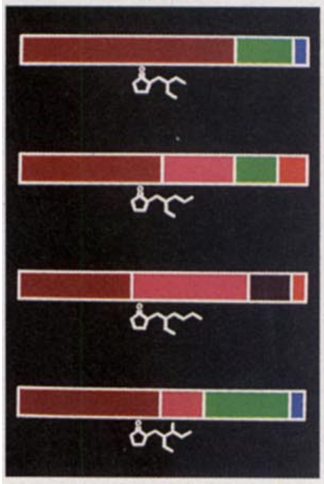


Figure 7

Figure 8

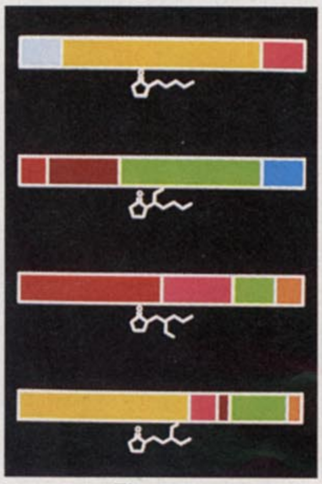


Figure 9

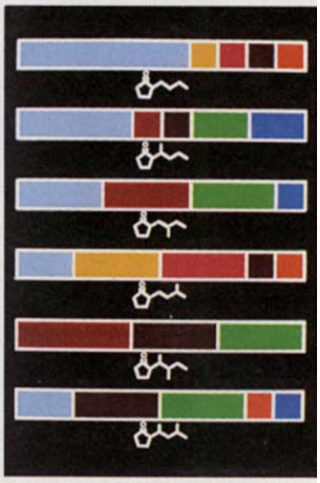


Figure 10

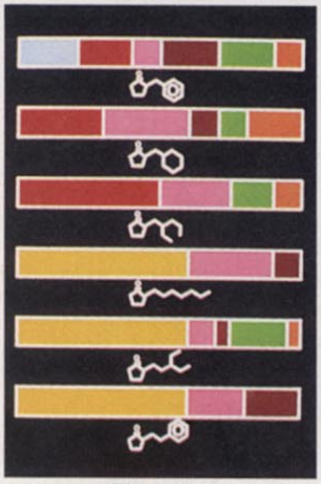


Figure 11

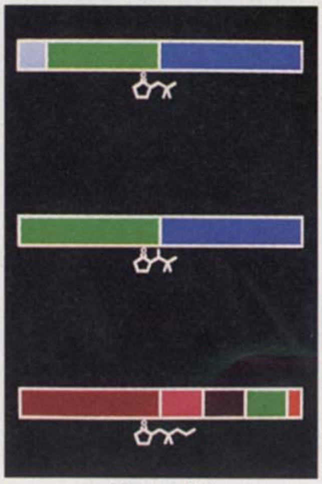
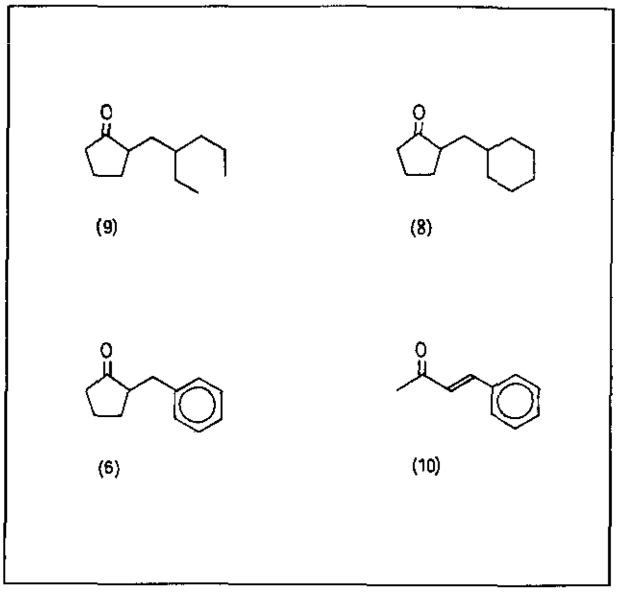


Figure 12

note to appear in the odour. 2-(1-Methylbutyl) cyclopentanone has an oily/herbaceous character while 2-(2-methylbutyl) cyclopentanone is rosaceous. 2-(1,2-Dimethylbutyl) cyclopentanone possesses both oily and rosaceous notes whereas 2-(1, 3-dimethylbutyl) cyclopentanone is predominantly oily/herbaceous with no jasmin character. This suggests that the effect of the methyl group on the first side chain carbon atom is more disruptive to the jasmin character than to that of the rose.

The effect of benzene and cyclohexane rings



(9) (8) (6) (10)

as isosteric units for open chains is very interesting (see figure 11). 2-(Cyclohexylmethyl) cyclopentanone (8) and 2-benzylcyclopentanone (6) are approximately isosteric with one configuration of 2-(2-ethylpentyl) cyclopentanone (9). The odours of the two materials with cyclic side chains are similar to that of the open chain analogue although the aromatic ring seems to have more effect on the odour than does cyclohexyl. In fact the odour of 2-benzyclopentanone is very similar to that of benzylideneacetone (10)—a not too surprising observation since these two molecules also have similar molecular shapes. The odours of 2-(2-phenylethyl) cyclopentanone, 2-(3-ethylpentyl) cyclopentanone and straight chain materials such as 2-heptyclopentanone are quite similar, suggesting that, if the first two carbon atoms in the side chain are unsubstituted, the actual composition of the remainder of the carbon chain is relatively unimportant as far as the basic odour character of the material is concerned; although Werner's restrictions on empirical formula (i.e. C9—C15) would obviously still apply.

That the shape of the chain can be much more important than the number of carbon atoms it contains is further demonstrated by the fact that short, highly substituted side chains give rise to distinctly camphoraceous odours as shown in figure 12. For example, the odour of 2-(1,2,2-trimethylpropyl) cyclopentanone is strongly reminiscent of that of borneol whereas, by way of comparison, 2-(2,2-dimethylpentyl) cyclopentanone which is almost isomeric with it, possesses strong rosaceous notes with no camphoraceous character.

Discussion

The structure/odour effects described above can be summarised as follows:

- Unsubstituted 2-alkylcyclopentanones exhibit predominantly jasmin odours if the chain contains 5,6 or 7 carbon atoms.
- A substituent on the first carbon atom of the side chain of 2-alkylcyclopentanones considerably reduces the odour value of the material, removes all or most of the jasmin character and replaces it with oily and herbaceous notes.
- A substituent on the second carbon atom of the side chain of 2-alkylcyclopentanones has the effect of replacing the jasmin character by rose.
- A substituent on the third carbon atom of the side chain of 2-alkylcyclopentanones has relatively little effect on the odour character.
- 2-Alkylcyclopentanones having short, highly substituted side chains, possess camphoraceous odours.

In attempting to rationalise these observations it was considered that the effect of the substituent on the conformation of the side chain could be a means by which a non-functional group might cause a large enough change in a molecule to be responsible for such variations in odour. Figure 13 shows Newman projections of the three possible staggered conformations around the ring-chain bond of a 2-n-alkylcyclopentanone. Inspection of space filling models shows that conformation I is more favourable than the other two since in conformation II the hydrogens attached to the second carbon atom in the chain buttress against the carbonyl oxygen and in III the same methylene group interacts severely with the cis-hydrogen on C-3 of the cyclopentanone nucleus. Thus it is reasonable to concluded that an all staggered chain joined to the ring as shown in conformation I is the most stable configuration of a 2-n-alkylcyclopentanone.

Figure 14 shows two Courtauld models of 2-pentylcyclopentanone in this conformation,

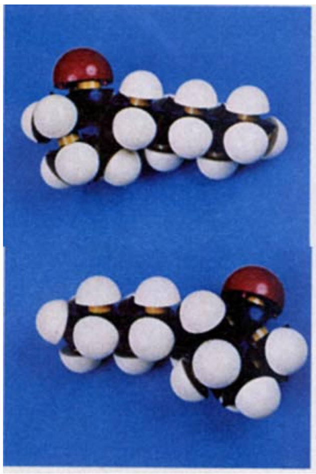


Figure 14

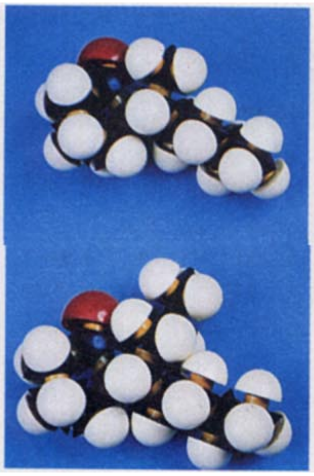


Figure 15

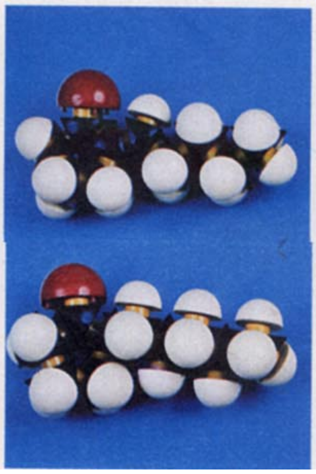


Figure 16

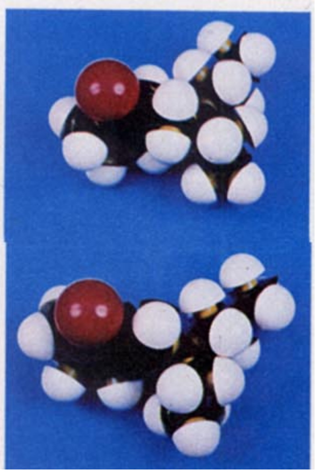
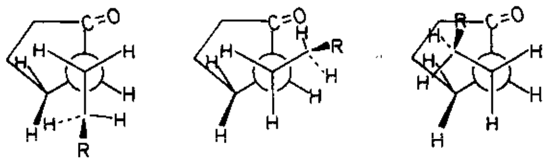


Figure 17



I II III

Figure 13

one being viewed from each side of the cyclopentanone ring. A substituent on the first carbon atom of the side chain does not interfere with this conformation but does obstruct one side of the carbonyl group. This could account for the loss of impact and distinctive odour character by, presumably, reducing the accessibility of the carbonyl as far as any receptor is concerned. This effect is demonstrated in figure 15 which shows Courtauld models of 2-(1-methylpentyl) cyclopentanone and 2-(1-propylpentyl) cyclopentanone. It is evident from this photograph that one face of the carbonyl group is covered to a similar degree by either a methyl or propyl group—in keeping with the similarity in odour of the two materials (see figure 6). It can be seen from figure 14 that any substituent on the second carbon atom of the side chain would interact severely with the hydrogen atoms attached to C-2 and C-3 of the ring and thus distort the stereochemistry of the ring/chain junction.

In these cases, no single configuration stands out as being preferred. All of the most likely configurations give rise to a molecule with a different overall shape from those with straight chains in that they contain a plane of carbon atoms which is almost perpendicular to that of the cyclopentanone ring and separated from it by one methylene group. The upper half of figure 17 demonstrates this effect clearly using 2-(2-ethylbutyl) cyclopentanone as an example. In contrast, those alkyl cyclopentanones with no substituent on the second carbon of the side chain will have a "time average" conformation in which the plane of the side chain lies essentially in the plane of the cyclopentanone ring. Models of 2-benzylcyclopentanone and 2-(cyclohexylmethyl) cyclopentanone exhibit a similar crowding of the ring-ring hydrogens as is observed for ring-chain hydrogens in the case of 2-ethylalkyl chains, thus explaining the similarity of their odours.

Branching and benzene ring substitution further down the chain has no effect on the configuration of the ring/chain junction and thus models of 2-hexylcyclopentanone, 2-(3-ethylpentyl) cyclopentanone and 2-(2-phenylethyl) cyclopentanone suggest that all three would have a similar time average molecular shape—in accord with their general similarity in odours.

The series of side chain methylated butylcyclopentanones further demonstrates the above effects. 2-Butylcyclopentanone displays only a slight jasminic character since it is on the limit of Werner's criteria. Addition of a methyl group to the first side chain carbon introduces oily and herbaceous notes; on the second carbon such a substituent produces a rosaceous character and the presence of one on the third carbon corre-

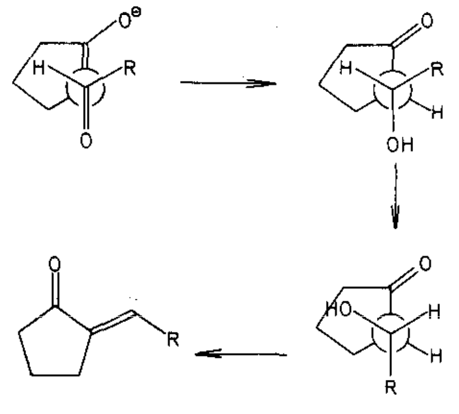


Figure 18

sponds with an overall jasminic/peachy character. It is interesting to note that 2-(1,2-dimethylbutyl) cyclopentanone possesses a distinctly roseaceous character whereas no trace of jasmine is present in the odour of 2-(1,3-dimethylbutyl) cyclopentanone. The latter observation is consistent with the carbonyl blocking effect described above while the former suggests either that the conformational changes brought about by the 2-methyl substituent result in an at least partial unblocking of the carbonyl group of 2-(1,2-dimethylbutyl) cyclopentanone by movement of the 1-methyl group away from it, or that accessibility to that side of the carbonyl group is not a requirement for the presence of a rose character.

It is not surprising that short, highly substituted chains impart a camphoraceous note since these molecules have dimensions close to those of camphor and would thus, on the basis of Amoore's theory,[3] be expected to have such odours.

As stated above, most of the 2-alkylcyclopentanones were prepared by hydrogenation of the corresponding 2-alkylidenecyclopentanones. It was observed that the odours of each pair of corresponding olefinic and saturated materials were very similar. Initially this fact cast considerable doubt upon the above conformational hypotheses since the stereochemistry of the ring/chain junction is quite different in each case. However, on further consideration, the observation was found to lend further weight to the argument. In our experience, the product mixture from aldol condensation of cyclopentanone with an aliphatic aldehyde contains the four possible isomeric olefins produced from dehydration of the intermediate aldol (E- and Z-2-alkylidenecyclopentanone and E- and Z-2-(1-alkenyl) cyclopentanone) but three of these are present only in small amounts. The reaction would thus appear to be highly stereoselective and a rationale for this is shown in figure 18.

The initial addition of cyclopentanone enolate (or indeed enamine) to the aldehyde will go through a trans-anti-planar arrangement as shown with the bulkier alkyl group lying away from the ring (models show a clear preference for this over the alternative in which the alkyl group lies across the ring). This leads to the aldol product shown which must rotate through 120° to place the hydroxyl group opposite to the acidic methine hydrogen atom. Trans-anti-planar elimination of water would then produce the E-isomer as shown. This isomer has a very similar molecular shape to that of the preferred conformer of the saturated analogue—clearly demonstrated in figure 16 which shows Courtauld models of 2-pentylidenecyclopentanone and 2-pentylcyclopentanone. A substituent on the 2-position of the side chain of 2-alkylidenecyclopentanones interacts severely with the hydrogen atoms on C-3 of the ring. This results in a very similar distortion of the side chain to that observed for the saturated analogue as can be seen from figure 17 which shows models of 2-(2-ethylbutyl) cyclopentanone and 2-(2-ethylbutylidene) cyclopentanone.

Conclusion

The odour of 2-alkylcyclopentanones can be radically affected by substituents on the first or second carbon atoms of the side chain, substituents further along the chain having a much lesser effect on the odour character. It is postulated that these effects could be rationalised in terms of obstruction of the carbonyl group by a substituent on the first carbon of the side chain or disruption of the side chain conformation by one on the second position.

Acknowledgement

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