

THE MUSK ODOUR

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The Musk Odour is of great importance in all branches of perfumery. Compounds possessing a Musk Odour are found in the following six structural types :—benzene, tetralin, indane, nitro, steroid and macrocyclic. It is possible to select certain chemicals, each with an odour reminiscent of natural musk but with special odour characteristics of their own, which can be used in perfumes for a variety of purposes. The macrocyclic chemicals are of special interest on account of their structural similarity to Muscone, the active ingredient of Musk from the deer.

INTRODUCTION

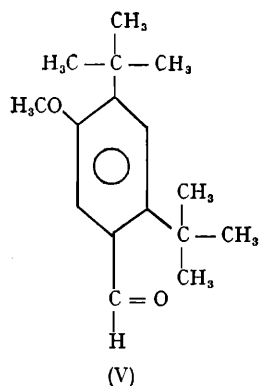
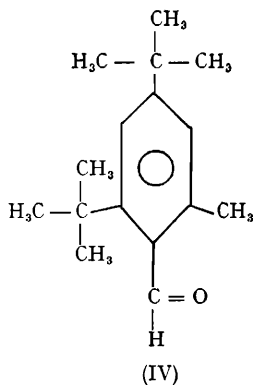
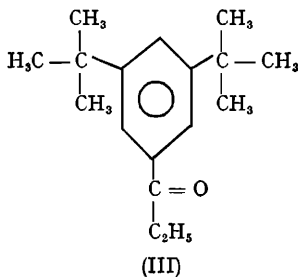
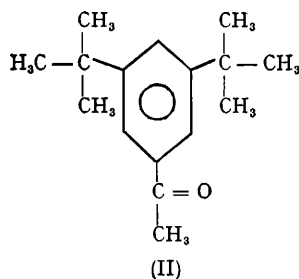
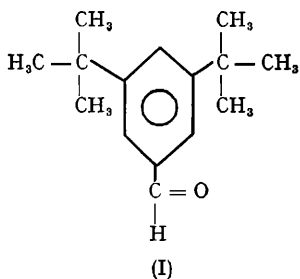
MUSK-LIKE PRODUCTS are employed in every branch of perfumery from the most expensive handkerchief perfumes down to the cheapest of industrial deodorants. Natural musk has been known for centuries and is obtained from the musk deer. This animal, which lives in high altitude wooded districts, possesses a pouch which contains the "musk grain". These grains are extracted with alcohol and allowed to stand for several months. After filtration the musk tincture is obtained and this alcoholic solution is employed to impart character and tenacity to high-class perfumes. Other animal sources of products which possess musk-like odours are : rat, duck, shrew, beetle, ox, alligator, goat, civet-cat, rock-badger and zebra. Certain plants also give off musk-like odours and these include angelica, ambrette seeds and less importantly, mallow, thistle and orchis.

In 1906 the odour principle of the musk-grains was isolated and named Muscone. In 1926, Ruzicka revealed its structure as 3-methyl-1-cyclopentadecanone. In view of this revelation, it is not surprising that much time and money has been spent on the production of macrocyclic compounds in the search for chemicals with musk-like odours. It must be remembered that other musk-like bodies had been synthesised many years before muscone was discovered. The classical example is musk Baur, trinitro-*tertiary*butyltoluene, prepared by Baur in 1888. The value of this product in those days is illustrated by the fact that it was diluted with nine times its weight of acetanilide and sold at half the price of the natural tonquin musk. In 1889, Baur prepared trinitro-*tertiary*butylxylene, which is known

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today as musk xylene and costs only a few shillings a pound in the concentrated form.

At the moment, no less than six different structural classes of compounds possessing the musk odour are known: The benzene, the tetralin, the indane, the nitro, the steroid and the macrocyclic musks. It seems remarkable that such widely divergent structures can produce odours with one distinct characteristic and in all fairness an examination of the hundreds of "musk-like" bodies so far produced, reveals considerable odour differences. Nevertheless, it is generally acknowledged that an odour identifiable with the original muscone is present and justifies the general



classification of "musk". Perhaps Beets' wording of "a somewhat uniform odour type" is descriptive.

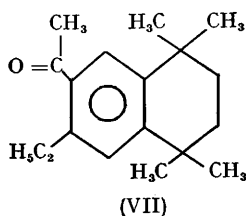
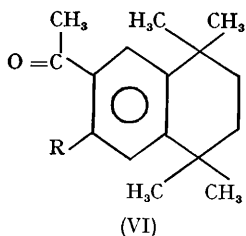
The whole field of musk-chemistry is so vast that this discussion must be limited to a few well-defined types of structures and an attempt will be made to indicate how changes in structure influence odour and where possible, to describe the odours involved.

THE BENZENE MUSKS

From a structural point of view the two simplest molecules possessing a musk-like odour are 3,5-ditertiarybutylbenzaldehyde (I) and 3,5-ditertiarybutylacetophenone (II). The former is too unstable to be of interest in perfumery. The latter has a fine, sweet musk odour reminiscent of musk ketone and ambrette with just a touch of the sandalwood note, and one is tempted to wonder why it is not produced commercially. The corresponding propiophenone (III) is somewhat similar in character but less intense and with more accent on the woodiness. Two other simple musk-like compounds are: 2-methyl 4,6-ditertiarybutylbenzaldehyde (IV) and 2,4-ditertiarybutyl 5-methoxybenzaldehyde (V). It is of course possible to place some of the nitromusks in the benzene section but they form a more logical section of their own.

THE TETRALIN MUSKS

Although many tetralin compounds giving some degree of musk odour have been produced, the main interest centres around the structure:



In the absence of the R radicle the compound is odourless, but if R is a methyl group then the compound possesses a fine musk odour. In the case where R is an ethyl group, the compound 1,1,4,4-tetramethyl-6-ethyl-7-acetyl-1,2,3,4-tetrahydronaphthalene (VII) possesses an odour which is outstanding in the musk field. It has the fine clean quality of musk ketone with some of the intensity of ambrette. In addition it has a subtle shading of the woodiness found in the macrocyclic musks.

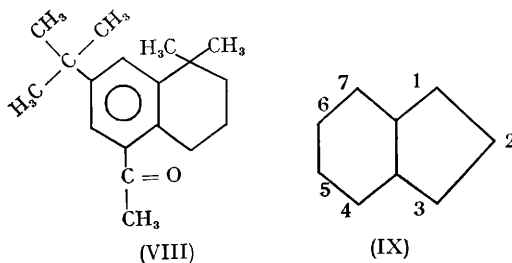
Another tetralin musk which possesses a clean pleasant but rather weak odour is 1.1-dimethyl-7-*tertiary*butyl-5-acetyl-1.2.3.4-tetrahydronaphthalene (VIII) :—

Beets¹ has put forward the following requirements for musk odour in the tetralin and indane classes :—

- (1) More than 14 and less than 20 carbon atoms with an optimum at C16 to C18.
- (2) An indane or a tetralin skeleton.
- (3) An acyl and a secondary or tertiary alkyl group as separate substituents in the aromatic nucleus with an optimum for acetyl and tertiary butyl.
- (4) One of the carbon atoms of the non-aromatic ring bound to the aromatic nucleus is tertiary or quaternary with an optimum when it is quaternary.

THE INDANE MUSKS

It has been suggested by Beets² that in an indane derivative the presence of an acyl group and of two tertiary or quaternary carbon atoms as substituents in the benzene nucleus, are the minimum requirements for musk odour. Such tertiary or quaternary carbon atoms may both be part of the non-aromatic ring or one of them may be introduced as a separate alkyl group. The stronger musks are obtained when an acyl group and two quaternary carbon atoms are present. In the indane structure (IX) the following effects are found :



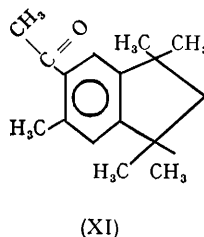
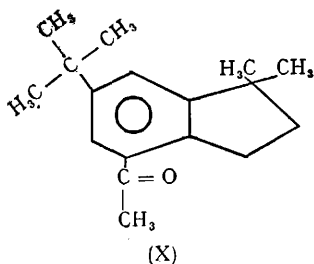
The compound 1.1-dimethyl-6-*tertiary*butylindane is odourless, but the introduction of a carbonyl group in the 4 position produces the musk odour. The aldehyde group (formyl) produces a fairly strong musk with an odour like musk ketone with the ambrette effect also in evidence. The methyl ketone (acetyl) is strongly musk-like, the ethyl ketone (propionyl) compound has a sweet intense musk odour and is very strong and lasting.

The propyl ketone (*isobutyryl*) compound possesses a faint musk odour, but is rather fugitive.

The compound 4-acetyl-6-*tertiary*butylindane is odourless, but the introduction of one methyl group in the 1 position results in a compound with an odour of medium strength and somewhat like musk ketone with some ambrette sweetness. Although the initial odour is quite strong, it is not long lasting. The introduction of a second methyl group in the 1 position produces quite dramatic results, the new compound possessing a strong, clean intense odour similar to musk ketone. The odour remains on the smelling slip for a reasonably long period of time. When the substituents in the 1.1 position are methyl and ethyl, the resulting compound is rather similar in odour to the 1.1-methylmethyl compound but has inferior lasting powers.

The introduction of an *isopropyl* group in the 6 position results in a musk compound of medium strength. When the substituent is *tertiary* butyl the odour is of a strong musk ketone type and long lasting : a *secondary* butyl group produces only a weak odour similar to musk ketone and which is not long lasting. The introduction of a *tertiary* amyl group results in a strong smelling musk rather similar to the corresponding tertiary butyl compound.

Two outstanding indane musks are, 4-acetyl-1.1-dimethyl-6-*tertiary*-butylindane (X) and 6-acetyl-1.1.3.3.5-pentamethylindane (XI) :—

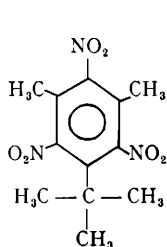


Compound X possesses a fine strong odour somewhat similar to musk ketone but more intense and with a suggestion of jasmin. Compound XI is a strong musk-like body somewhat sharp and fruity. A large range of indane musks has been described³.

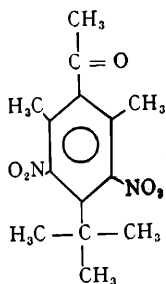
THE NITRO MUSKS

It will be noticed that the important nitromusks all possess a high degree of substitution. The five commercially available nitro musks are :

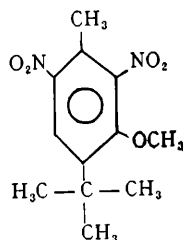
musk xylene (XII), musk ketone (XIII), musk ambrette (XIV), moskene (XV) and tibetine (XVI).



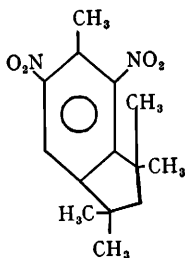
(XII)



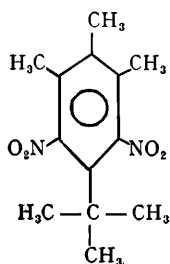
(XIII)



(XIV)



(XV)



(XVI)

(moskene could also be placed in the category of an indane compound.)

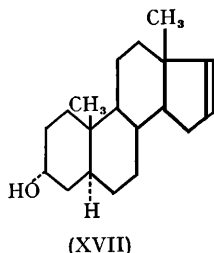
The above five compounds possess the following odour characteristics :

<i>Musk xylene</i>	Full, not intense, "chemically".
<i>Musk ketone</i>	Cleaner and sweeter than xylene.
<i>Musk ambrette</i>	Intense, rather metallic-blackberry, a little of the ester intensity, sharp.
<i>Moskene</i>	Somewhat similar in odour to ambrette but rather weaker and lacking the penetrating intensity.
<i>Tibetine</i>	Has an odour rather similar to musk xylol with a little of the musk ketone effect.

THE STEROID MUSKS

Quite frankly, the steroid musks are of academic interest only. It appears that only a very small group of steroids possess an appreciable

odour and that the conformation of the molecule exerts an important influence on the odour. Representative of the class is Δ^{16} androsten 3α -ol, (XVII) :—



The corresponding 3 B compound is practically odourless.

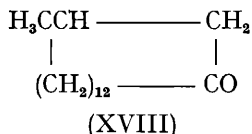
THE MACROCYCLIC MUSKS

This class of musk compound is of obvious interest if only because Muscone (XVIII), the active odour principle of natural musk, falls under this heading. Stoll⁴ has concluded that the basic ring structure must contain at least 14 and less than 19 members, and at least one functional group. The musk odour is strongest when the functional group is a lactone. Next in strength comes the carbonyl group. The anhydrides and carbonates produce weak musk odours while atoms such as oxygen, sulphur and nitrogen create very weak musk effects. The introduction of a second carbonyl group destroys the odour and a second ester group weakens it. When oxygen is introduced in the chain of a macrocyclic lactone, the odour is reduced.

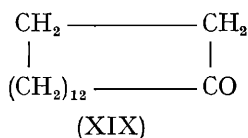
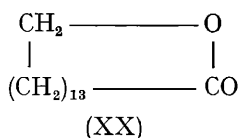
It is rather surprising that a compound such as ethylene brassilate should possess a strong musk odour and it is possible that the two ester groups are sufficiently close to act as a single functional group.

The following six macrocyclic compounds present an interesting odour picture :—

3 methyl 1 cyclopentadecanone (Muscone)

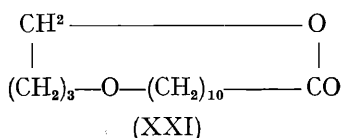
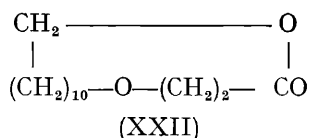


This chemical was not examined in this investigation. The natural musk in which it occurs, possesses a fine clean musk odour which is strongly interblended with a civet and castoreum effect.

Cyclopentadecanone*Pentadecanolide*

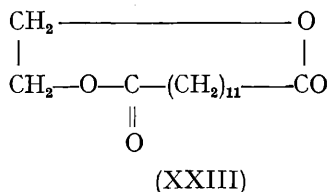
This compound is extremely woody in odour. In addition to the typical clean musk odour there is a strong woodiness. Other macrocyclic chemicals possess woodiness of odour but the effect is usually towards santalol. In this case, the cedrol note is strongly in evidence.

This possesses the musk intensity of ambrette but is strongly santalol-like with a touch of cedrol. Very suggestive of blackberries.

12-oxa-hexadecanolide*4-oxa-pentadecanolide*

This chemical possesses a fine musk odour with a back-note of santalol. It also possesses a slight fruity note.

A medium strength sweet musk with a distinct woodiness.

Ethylene brassilate

A sweet intense musk with a suggestion of ambrette and blackberries. The woodiness is quite absent.

FIXATIVE PROPERTIES OF THE MUSKS

For a long time the nitromusks were regarded as fixatives for other more volatile odours. In recent years it has been said that these chemicals although persistent in odour themselves had no power to inhibit odour loss in other chemicals. However, most writers include the nitromusks in their lists of fixatives. The following experiment gives some indication of the fixative power of musk xylol. Four samples were examined from a smelling slip.

1. Pure benzyl acetate.
2. Benzyl acetate plus 10% musk xylol.
3. Benzyl acetate plus 10% benzyl benzoate.
4. Benzyl acetate plus 5% musk xylol and 5% benzyl benzoate.

Under the conditions of this particular test the odour of benzyl acetate itself remains for approximately 600 minutes ; in the presence of 10% of musk xylol, 750 minutes and in the presence of benzyl benzoate 840 minutes. The test, which included both musk xylol and benzyl benzoate, was made to obviate the tendency for the musk xylol to crystallize from the solution. The solution containing both musk xylol and benzyl benzoate retained its odour of benzyl acetate for about 960 minutes. A similar set of experiments were made but in this case a more volatile solvent (namely methyl amyl ketone) was employed. Examined olfactorily from slips, methyl amyl ketone maintained its odour for 17 minutes. The presence of musk xylol increased the odour life to 20 minutes, the benzyl benzoate to 22 minutes and the combination of musk xylol and benzyl benzoate also to 22 minutes. From these tests, it appears that musk xylol does exert some fixative effects although these effects are less positive than those given by benzyl benzoate. The fixative effects of a number of musk-like compounds were examined employing methyl amyl ketone as the solvent. The results are shown below :—

Table 1
ODOUR RETENTION TIME OF METHYL AMYL KETONE

Composition of solution	Retention time in minutes
Methyl amyl ketone pure	17
Methyl amyl ketone + 10% benzyl benzoate	22
Methyl amyl ketone + 10% musk ketone	21
Methyl amyl ketone + 10% 1.1.4.4-tetramethyl-6-ethyl-7-acetyl-1.2.3.4-tetrahydronaphthalene	28
Methyl amyl ketone + 10% 4-acetyl-1.1-dimethyl-6- <i>tertiary</i> -butyl-indane	27
Methyl amyl ketone + 10% 3.5-ditertiary-butyl-acetophenone	26
Methyl amyl ketone + 10% Pentadecanolide	28

It will be seen that musks drawn from the benzene, tetralin, indane and macrocyclic range have the ability to reduce the rate of odour loss of methyl

amylketone to an extent greater than benzyl benzoate or the two nitro musks ketone and xylol.

SUMMARY AND CONCLUSIONS

There is no denying the value of natural musk in high-class perfumery. Unfortunately, natural musks vary from source to source and it is extremely difficult to give an odour description which is characteristic of the named item. While all natural musks from the deer possess the sweet clean musk odour, the degree of "bouquet" varies. In point of fact, one is forced to accept natural musk as a perfume rather than as one characteristic note. Blended with the musk-like odour is the distinct effect of civet with a subtle undertone of castoreum. From this, it can be seen that it is quite impossible to obtain a "natural" musk effect with one particular pure chemical. Nevertheless, the synthetic musks play a very important part in all branches of perfumery. The nitromusks are inexpensive and offer a range of odour effects from the full toning action of the xylene and ketone to the strong almost aggressive effect of ambrette. They are all of great persistence and tend to remain when all other odours have departed. In most cases, they lead to problems of discoloration, particularly in combination with other chemicals.

Of the benzene musks, little is heard but 3,5-ditertiarybutylacetophenone and 3,5-ditertiarybutylpropiofenone offer great possibilities. Of the tetralin musks, 1,1,4,4-tetramethyl-6-ethyl-7-acetyl-1,2,3,4-tetrahydro naphthalene is a first-class product. In the indane field, 4-acetyl-1,1-dimethyl-6-tertiarybutylindane is outstanding. It is of obvious value in high-class perfumery and may be used to replace nitromusks when colour becomes a problem. The macrocyclic musks offer a wide range of products for use in many branches of perfumery. In addition to a sweet musk effect they possess a full woodiness which imparts character to most perfumes. In some ways the macrocyclic musks approach the "bouquet" effect of the natural musk from the deer. The pentadecanolide is perhaps the outstanding example in this class.

ACKNOWLEDGMENT

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INTRODUCTION BY D. E. BUTTERFIELD, B.A.

The field covered by musks is now a very wide one indeed with the discovery in the last few years of further types of compounds possessing a musk odour. However, there is no denying the fact that natural musk is still of great value in high-class perfumery. Unfortunately, the natural musk does vary from source to source and it is difficult to give an odour description to characterise this material. While the sweet clean musk odour is always present, the degree of "bouquet" varies. Consequently, one is forced to accept natural musk as a perfume rather than as one characteristic note. We find, in fact, that blended with its musk-like odour are distinct effects of civet, together with a subtle undertone of castoreum. In this connection, it is interesting to note the occurrence of civetone—which is a macrocyclic musk compound—in natural Civet itself. In view of the complexity of the natural musk odour, it is quite impossible to obtain a natural "musk effect" with one pure chemical. Nevertheless, the synthetic musks do play a very important part in all branches of perfumery. Of the synthetics, the nitro musks were the first to be discovered and are also the least expensive. They offer a range of odour effects from the full toning action of musk xylene and ketone to the strong and almost aggressive effect of Ambrette. They are all of great persistence and tend to remain when most other odours have departed. However, in many cases, they lead to problems of discoloration, particularly in combination with other chemicals.

Today, besides the nitro musks, we now know of five other groups of compounds with a musk-like odour. They are: the benzene, indane, tetralin, macrocyclic and steroid musks.

Of the benzene musks, little has been heard but it is interesting to note that one of these, namely 3 : 5 ditertiary butyl benzaldehyde (I) is apparently the simplest compound known to possess a musk odour. Unfortunately, it is unstable on account of the aldehyde group but two other closely related compounds, 3 : 5 ditertiary butyl acetophenone (II) and the corresponding propiophenone (III), offer great possibilities. A considerable amount of work has been carried out on the Tetralin musks and of these, 1.1.4.4-tetra methyl 6-ethyl 7-acetyl 1.2.3.4-tetrahydronaphthalene (VII), is a first class product. A wide range of Indane compounds has also been worked upon and several possess the Musk odour. In this field, 4-acetyl 1.1-dimethyl 6-tertiary butyl Indane (X) is outstanding. It is of obvious value in high class perfumery and like the Tetralin musks, may be used to replace the nitro musks when discoloration is a problem. There is a wide range of macrocyclic musks, which are of importance to the perfumer. In addition to a sweet musk effect, they also possess a full woodiness which imparts character to most perfumes. In some ways, the best

of the macrocyclics approach the "bouquet" effect of the natural musk. In this class Pentadecanolide (XX) is perhaps the most outstanding example.

Although Steroids have been discovered which possess a musk odour, they are of no commercial importance.

It can be confidently predicted that further types of compound with a musk odour will be discovered. As the literature indicates, work has already been carried out in the field of tricyclic compounds with some degree of success. In fact, it is possible that the next 10 years will see almost as great a change in the types of synthetic musks in general use as has occurred during the last decade!

The author also describes a series of simple experiments carried out to illustrate the fixative effect of several musk compounds. Two common perfumery materials were used as the basis for these experiments. These were, benzyl acetate and methyl amyl ketone and the effect on their rate of evaporation of adding 10 per cent of various musk compounds was determined. The experiments showed that while the simple nitro musks and a high-boiling solvent (benzyl benzoate) undoubtedly had some fixative effect, a much increased effect is obtained by the use of certain musks drawn from the benzene, indane, tetralin and macrocyclic series.

As a footnote to the paper, it is interesting to reflect upon the wide range of chemical structures which have now been shown to possess the "musk odour". It almost seems as if the more we learn the less specific become the structural requirements for the "musk odour". In fact, Dr. Beets has suggested that the minimum requirements are basically a molecular weight of 2-300, a closely-packed molecular structure that is of bulky profile and an easily accessible functional group.

DISCUSSION

DR. H. W. HIBBOTT: How far do these fixatives, being what they may be, affect vapour liquid chromatography, because if they do, then it may be that we have a better notion of what a fixative should be.

MR. D. E. BUTTERFIELD: I presume you are meaning, how would they affect the performance of a material on a chromatographic column? I have certainly no direct evidence myself or any knowledge of experiments to that end, although I know that the author has considered gas chromatography as a possible tool for investigating fixation. These simple experiments, as I am sure Mr. Pickthall would agree, really need carrying further to see whether this difference between say, nitro musks or benzyl benzoate and the macrocyclics can be confirmed by other techniques. Also, the extent to which other types of compounds possess these properties.

DR. H. W. HIBBOTT : By analogy is there not some connection between retention time on a chromatographic column and the retention times you mention ?

MR. D. E. BUTTERFIELD : Possibly, though the separation of the constituents of a mixture on a column depends on the column itself and not on the other constituents which are present.

DR. B. L. RAO : What is the effect of reducing the carbonyl group to the alcohol in these compounds and does it lead to any loss of odour ?

MR. D. E. BUTTERFIELD : From the evidence, for example in the Indane series, it is pretty certain that you need an acyl group present for pronounced musk odour. That is, you need the carbonyl group itself. Although I do not recall any particular compounds of this type containing the alcohol group, I think that reduction would certainly remove the musk odour. Whether you get a different odour or just attenuation of the musk character, I do not know. Something comparable, I think, is known about the constituents of Civet. The alcohol Civetol, which occurs in natural civet has, I believe, a definite but weak musk odour, but can be oxidised to the odorous civetone. I think there is another comparable case among the amber compounds.

DR. A. W. MIDDLETON : The author gives values for odour retention for methyl amyl ketone of 17 minutes which is increased to 27-28 minutes after replacement of 10 per cent methyl amyl ketone by macromolecules. The 10 per cent is a bulk concentration whereas the relevant concentration is that in the evaporating surface. A surface concentration of about 40 per cent macromolecule (moles per cent) would explain the odour retention times. Has the author any data regarding the surface concentration ?

MR. D. E. BUTTERFIELD : This is an interesting possibility and could explain the different retention times found, other than on the basis of physical interaction in the bulk of the liquid. Unfortunately, we have no data on surface concentration.

DR. A. W. MIDDLETON : You would expect that the surface concentration would differ with the different types of chemicals you put in.

MR. D. E. BUTTERFIELD : Yes that is true. It would certainly be interesting to extend this work to further types of compounds, particularly as the compounds yielding high retention times differ significantly in structure from those having little "fixative" effect. Comparison of the macrocyclic ester, ethylene brassylate with benzyl benzoate could be of interest.

MR. F. ATKINS : I would like to draw attention to the last line in *Table 1*.

This surely throws some light on the old controversies "Is natural musk a true fixative"? I have always believed it to be a superb blender but not a true fixative capable of evening out the varying rates of evaporation of the more and the less volatile components of a perfume blend. The opposite view has been defended by references to the Van der Waals effect of the macrocyclic bodies present in natural musk. If 10 per cent of pentadecanolide prolongs the evaporation time of methyl amyl ketone by about 50 per cent, how much natural musk would be needed to produce even this modest increase in "lasting power" in a perfume?

MR. D. E. BUTTERFIELD : Naturally, one must agree that natural musk in the concentrations normally used can have very little fixative effect. The author's results do show however that the newer musks have this unusual effect of decreasing the rate of evaporation of methyl amyl ketone compared with more orthodox materials. The figures quoted in *Table 1* certainly don't prove that any musks exert an important fixative effect in practice, but do suggest that there is anomalous behaviour which is worthy of further investigation.

SOCIETY OF COSMETIC CHEMISTS OF GREAT BRITAIN

1960 Summer Conference

THE 1960-61 Summer Conference of the Society was held on the 24th and 25th of August at the Royal Society of Arts.

The Conference opened with a Cocktail Party on the evening of the 24th, when all participants and their guests were received by the President and Mrs. Hibbott.

The Scientific Sessions took place on the 25th of August, and the Society's President, Dr. H. W. Hibbott, took the chair for the morning session. In opening the Conference, the President welcomed those attending and extended a special welcome to the members of the American Society, which included their President, Mr. H. J. Amsterdam, and to other overseas visitors. For the afternoon session, Dr. R. H. Marriott, Immediate Past-President, was in the chair.

The eight papers having been circularized in full to all participants prior to the Conference, the authors in the main restricted themselves to introductory remarks which allowed for a full discussion after each paper. Four of the papers are reprinted in this issue of the *Journal*, and the remainder will appear in subsequent issues.