Section of Anæsthetics.

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Anæsthetic Ether.

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UNDER the term "ethers" are included those substances obtained from two molecules of an alcohol by the abstraction of one molecule of water. In their chemical relationship they are oxides of alcoholic radicles analogous to the oxides of the alkali metals, potassium, sodium, &c.—e.g., K_2O, Na_2O, R_2O, where $R = (CH_3)$, (C_2H_5), (C_3H_7), &c.

The chief method of preparation consists in acting upon the alcohols with a dehydrating agent, such as strong sulphuric acid. This is heated to a temperature of 140° C. and the alcohol gradually and continuously run into it, while the ether that is formed distils over into a receiver.

The first view of the reaction was that it was a case of simple dehydration, but there is no doubt that this hardly expresses the complete view of the case. The action of the sulphuric acid is to form ethyl hydrogen sulphate, which, acting upon another molecule of alcohol, forms ether and regenerates the sulphuric acid. The reaction is, therefore, continuous, and a small quantity of sulphuric acid should suffice theoretically to convert a large amount of alcohol into ether, but in practice its action is limited by the occurrence of reduction and various side reactions, which gradually tend to bring the main reaction to an end, and necessitate the provision of fresh acid.

When a single alcohol, containing only one alcoholic radicle, such as methyl or ethyl alcohol, is employed as the source of ether, the product necessarily contains only one kind of radicle and is called a simple ether;

but if a mixture of two alcohols is used, not only are the corresponding two ethers formed, but there is formed a third ether, which, since it contains two radicles, is called a mixed ether. For example, while methyl and ethyl alcohol yield respectively only dimethyl and diethyl ether, a mixture of the two yields dimethyl ether, diethyl ether, and in addition the mixed ether, methyl-ethyl ether.

$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!O$	$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!O$	$\begin{matrix}C_2H_5\\CH_3\end{matrix}\!\!>\!O$
Dimethyl ether.	Diethyl ether.	Methyl-ethyl ether.

Dimethyl Ether.—The lowest member of the series, dimethyl ether or dimethyl oxide, is a gas boiling at $-20°$ C. It is obtained from methyl alcohol by the general method outlined above. Some is formed whenever ether is made from mixtures of methyl and ethyl alcohols, and a little is therefore present in ether made from methylated spirit. It is largely used for the production of artificial cold.

Methyl-ethyl Ether.—The next member of the series contains another CH_2 and is the mixed ether, methyl-ethyl ether, mentioned above; this is formed from a mixture of methyl and ethyl alcohol. It is therefore formed, as we shall see later, when ether is made from methylated spirit, and it is found in unfractionated commercial methylated ether. Its boiling point is $+ 11°$ C.

Diethyl Ether.—The third member of the series is the most important as it constitutes the bulk of what we term anæsthetic ether. It is the only product where ethyl alcohol or rectified spirit is employed in the manufacture of ether. When pure it boils at 35° C. and has a specific gravity of 0.720.

It is said to have been discovered in 1542, by Valerius Cordus, but was possibly known before his time. It is not intended to enter into the historical question of who was the first to observe its anæsthetic properties. The theories of its formation from alcohol and sulphuric acid were formerly exceedingly vague. It was long considered to contain sulphur, which, if present, could only have been due to imperfect purification. Even to the present time, this view is reflected in the fact that it is often labelled and called "sulphuric ether" or "ether sulph."

As a class the ethers are volatile, inflammable, mobile liquids of low specific gravity. Although, chemically, they are fully saturated bodies, and are therefore stable and not very reactive, yet the presence of the oxygen atom, which under certain circumstances is capable of assuming

a quadrivalent character, renders them liable to form peroxides analogous to hydrogen peroxide. In fact, a well-defined addition product made from dimethyl ether is known.

Manufacture of Anæsthetic Ether.

Undoubtedly the best available source for the preparation of diethyl ether for all purposes is ethyl alcohol, which can be produced on a large scale in a tolerable state of purity, but the duty of over 20s. per gallon on this article prevents the economical production of ether from it. The only other source is that mixture of methyl and ethyl alcohols known as methylated spirit. The variety used is called industrial spirit. Its composition is 95 per cent. of alcohol and 5 per cent. of *wood* naphtha (methyl alcohol), and it differs from the ordinary methylated spirit sold to the public in containing no *mineral* naphtha. It can be distinguished from the latter variety by forming a clear mixture with water. As it contains the two alcohols mentioned above, it yields the three ethers—dimethyl, diethyl, and methyl-ethyl ether.

Owing to its cheaper cost, the ether made from the latter source has practically superseded ether made from rectified spirit. The requirements of a large general hospital, say of 600 beds, for anæsthetic ether amount approximately to one ton per annum, and since the latter variety costs approximately 25 per cent. of the former, we find that no large London general hospital uses ether made from rectified spirit, and figures have been published showing that a large proportion of anæsthetists in private practice also use the methylated variety. Moreover, the recent British Pharmacopœia, always well in the rear of actual practice, has now recognised industrial spirit as a source of ether.

Anæsthetic ethers comprise that made from rectified spirit and two main varieties obtained on a commercial scale from methylated spirit and sold for anæsthetic purposes. These are distinguished by their gravity and are:—

(1) *Ether meth., specific gravity 0.717,* prepared by washing.
(2) *Ether meth., specific gravity 0.720,* prepared by washing and fractionation.

(1) This variety represents the product obtained by the action of sulphuric acid on methylated spirit. Since it has only been washed and not fractionated, it contains all three possible ethers, and on that

account begins to boil at a very low temperature, the actual figures obtained in distilling 100 grm. being given in the following table. It will be seen that the sample possesses no definite boiling point. In distilling a sample, although iced water is running through the condenser, the vapour can be seen pouring out through the end of the condenser before any liquid distils over.

FRACTIONATION OF METHYLATED ETHER.

(1) *Low-boiling variety, specific gravity 0.717.*

	Grammes
First drop at 20° C.	
20·0°—25·0°	3·0
25·0°—29·5°	4·7
29·5°—31·0°	9·8
31·0°—32·0°	9·5
32·0°—32·7°	9·0
32·7°—33·4°	9·1
33·4°—33·9°	10·1
33·9°—34·0°	9·3
34·0°—34·2°	23·6
Residue	8·0
Loss	3·9
Total	100·0

The temperatures recorded in these tables have not been corrected for the influence of changes in the barometric height. They are therefore not comparable among themselves, but serve to show the range within which the particular sample distils.

This ether is the cheapest anæsthetic ether obtainable. It has been and is still used in some of the large London hospitals, and it is preferred by some anæsthetists. Theoretically it is a more volatile product than the next variety, although if the two are allowed to evaporate side by side in similar dishes the rate of evaporation does not vary more than 3 per cent. per hour. Provided it has been well washed it is not necessarily an inferior product, and the presence of the lower homologues is not deleterious from a chemical point of view.

(2) The second variety of methylated ether has not only been washed but it has been subjected to a very careful fractionation, whereby the lower boiling fractions have been eliminated. Provided the fractionation has been efficient, nearly all the dimethyl and methylethyl ethers have been got rid of, and the product corresponds very closely to the variety made from rectified spirit. The figures obtained by the fractionation of one of these and a sample of rectified ether are given in the following tables:—

(2) *Higher boiling variety, specific gravity 0.720.*

		Grammes
First drop at 33° C.		
33·0°—33·6°		2·8
33·6°—33·8°		7·8
33·8°		79·5
	Residue	8·0
	Loss	1·9
	Total	100·0

ETHER FROM RECTIFIED SPIRIT.

		Grammes
First drop at 34·4° C.		
34·4°—34·7°		50·6
34·7°—34·8°		40·8
	Residue	7·0
	Loss	1·6
	Total	100·0

PURE ETHER, FREE FROM ALCOHOL AND WATER.

		Grammes
First drop at 32° C.		
32·0°—34·0°		3·6
34·0°		86·2
	Residue	8·0
	Loss	2·2
	Total	100·0

Freshly made ether from rectified spirit is, as we have seen, practically composed of diethyl oxide with a trace of alcohol and water. Although it may be quite pure when freshly made, yet on standing it is just as likely to oxidise as methylated ether.

It may be pointed out in passing that ether of specific gravity 0.735, containing as it does large amounts of alcohol and water, and, as a rule imperfectly purified, is not intended for, and should not be used for, anæsthetic purposes.

IMPURITIES AND THEIR SIGNIFICANCE.

The impurities that may be present in commercial ethers are either those appertaining to the source from which the ether is derived, or they are those resulting from decomposition of the ether on keeping. Considering the former class we find that rectified spirit contributes alcohol and water, whereas methylated spirit in addition to these yields a small proportion of acetone. The impurities formed on keeping include peroxides, aldehydes, and acids.

It is necessary to state that, generally speaking, anæsthetic ether is a very well purified substance, and that the standards set each other by

the different manufacturers are high. The amount of these impurities present is exceedingly minute, although it will be understood that where large quantities are administered over a prolonged period, the effect of a very small percentage of irritating aldehydes, for example, may be appreciable.

Alcohol.

Although, strictly speaking, this can be considered an impurity, yet it is a beneficial one, for in some work on this subject by the late Dr. Wade and the writer we found that the more perfectly we freed ether from the alcohol which is always present in the commercial article the more prone to oxidation the ether became. This is quite analogous to what was already recognized with regard to chloroform; in both cases the alcohol acts as a retarding agent to the oxidising changes that the pure substance spontaneously undergoes. Fortunately, it is extremely difficult on a commercial scale to eliminate the last traces of alcohol, and it is undesirable that this should be done. In fact, the recognition of say 2 per cent. of alcohol in ether, as is official in the case of chloroform, would be a decided advantage.

Water.

Excess of water was formerly considered to be a disadvantage, and the last British Pharmacopœia defined a specific test for its presence by directing that no turbidity should be produced on admixture with carbon disulphide. I have had some ether containing water under observation for about ten months, and it seems distinctly to have acted as a preservative. The sample has been kept without any precautions as to light, &c., and the amount of peroxide present is quite negligible. This may either be due to the water as such, or it may have produced a little alcohol by hydrolysis, which, as we have just seen, acts as a preservative.

Acetone.

Acetone is a normal constituent of methylated spirit, and unless specially taken out is found in ether derived therefrom. On the other hand, acetone has never been found in ether made from rectified spirit. The amount is extremely small, being of the order of about 1 in 5,000. Its chief interest is a commercial one and lies in the fact that its presence is indicative of the source of the ether, being very strong

presumptive evidence of its manufacture from methylated spirit, although its absence is no evidence to the contrary, as some firms know how to remove it, and systematically take out the acetone from their methylated ether.

The writer has examined samples of ether sold to hospitals, stated to be made from rectified spirit, which were carefully fractionated methylated ethers, the character of which was suspected from the fact that they contained acetone, and the derivation of which from methylated spirit was confirmed by other methods.

Acetone may be tested for by adding about 1 c.c. of a freshly made 5 per cent. solution of sodium nitroprusside, and then 3 or 4 c.c. of a strong solution of ammonia, followed by solid ammonium chloride. An intense magenta colour quickly develops.

About half the methylated ethers on the market are free from acetone, and, as a rule, these are cleaner in other respects. Apparently the processes used to take out the acetone have also assisted in getting rid of the other impurities.

Peroxides.

These seem to be the first products of the decomposition of ether, and probably consist of hydrogen and ethyl peroxides. They are formed by the action of air and sunlight, hence the necessity of keeping ether as much as possible in the dark.

The test which was official in the last Pharmacopœia was capable of detecting $\frac{1}{4}$ mgr. of hydrogen peroxide in 20 c.c. of ether. This test was not stringent enough, not because this amount is dangerous, but an ether containing even such a small amount of hydrogen peroxide would also contain aldehydes in sufficient quantity to render it very irritating.

The new British Pharmacopœia employs a much more searching test in stating that no yellow colour should be developed within three hours when ether is kept in a completely filled white glass-stoppered bottle in the dark and frequently shaken, and although a freshly distilled ether may comply with it, yet the same ether kept for a month will most probably be found deficient. This test is of high degree of stringency and is comparable with one employed for some time, which consists in mixing the ether with a solution of vanadic acid; the green solution is changed in the presence of peroxides to varying shades of brown and red.

Aldehydes.

The chief of these is acetaldehyde, which is a liquid of a suffocating odour. Aldehydes are invariably present in ether that has begun to decompose, and their presence and amount are important factors in arriving at a decision as to the fitness or otherwise of a sample for anæsthetic purposes.

The new Pharmacopœial test for aldehydes consists in keeping the ether in contact with freshly broken potassium hydroxide in a bottle for an hour. This is not unduly stringent, as the samples that we have been accustomed to choose for anæsthetic purposes will remain uncoloured for at least six hours—the time specified in the German Pharmocopœia—and sometimes more.

It should not be forgotten that in a hospital where the ether is probably never kept for more than a month, it is possible to insist on a higher standard than would be feasible for inclusion in the British Pharmacopœia, where the tests have to be applied to samples which have been kept for a longer period, and have been carried to all parts of the world.

Acids.

These are formed by the further oxidation of acetaldehyde and other aldehydes. Acetic acid is the chief of these. They may be readily tested for, by noting the reaction of the residue left after spontaneous evaporation in a glass dish, or by shaking the ether with water and testing the solution with litmus.

Any acid reaction should immediately condemn an ether for anæsthetic purposes, because its presence is a sign that decomposition has taken place. Very few samples indeed give an acid reaction. One I remember was a sample sent to me from a special hospital where operations were infrequent. This had been bought and was labelled as ether made from rectified spirit. The anæsthetist noticed the peculiar odour and that it seemed "weak." The presence of acetone and its behaviour on fractionation showed that it had been made from methylated spirit; moreover, the fact that it was exceedingly acid showed that it had seriously decomposed, and this was borne out by the presence of much peroxide and aldehyde.

The Testing of Ether.

For a large institution the testing of ether resolves itself into a comparison of the results obtained by applying the foregoing tests to a series of 1-lb. samples obtained from all the leading manufacturers, and it is quite easy to arrange them in order of merit. The absolute amount of any impurity is not so important as its relative amount. There are generally some which give negative tests for the presence of all the known impurities.

Fractionation.

In order to be certain which variety of methylated ether is being supplied, and to distinguish between methylated and rectified ethers, it is necessary to submit the samples and bulk to fractionation. The evidence shows which of the three varieties is under consideration. A very efficient still-head must be employed.

Specific Gravity.

This alone gives very little information, because, taking an extreme case, an ether of specific gravity 0.717 can be increased to 0.720 by the addition of rectified spirit. It is necessary to point out the limits of this test because the specific gravity has been quoted as evidence of purity in a case of a patient dying under the influence of ether as an anæsthetic.

For anæsthetists who desire to obtain a rough idea of the ether they employ, the test with potassium iodide solution will be useful. Probably a more comprehensive test is one that I have employed for some years. It was first intended that it should be used as a test for vinyl alcohol, which is said to be present in commercial ethers. It was found to be unsuitable for this purpose, nevertheless it will quickly indicate freedom from decomposition products such as aldehyde and peroxides. It consists in adding to the ether a dilute solution of potassium permanganate containing 1 in 10,000, with 1 in 1,000 of sodium carbonate. Pure ether has no immediate action on this, very little change being observed in five minutes, but ether containing aldehyde or peroxides will quickly decolorise it, the rate of reduction being a very good index of the quality of the ether.

DISCUSSION.

Dr. DUDLEY BUXTON said that the members of the Section would welcome so useful a communication as the one Mr. Finnemore had presented. That gentleman's name was already well known to anæsthetists in connexion with valuable work done by him, in collaboration with the late Dr. Wade, on chloroform and ethyl chloride and published in the *Proceedings of the Chemical Society*. Mr. Finnemore had referred to the assumption of tetravalency by the oxygen molecule in the lower ethers, and on this point the speaker desired to ask whether that fact could explain the evolution of heat occurring when ether and chloroform were shaken together, as during the preparation of the A.C.E. and kindred mixtures. It was commonly stated that mere mixing, in contrast to chemical union, did not cause the molecular phenomena which gave rise to the evolution of heat. Was there any evidence that in these mixtures the union was more intimate than mere solution? The speaker believed that the evaporation of the ingredients was not that represented by their proportional values in their solutions.

The PRESIDENT (Dr. Harold Low) said he quite agreed that the best thanks of the Section should be given to the reader of the paper, for the subject was one of great interest to them as anæsthetists. It was extremely important that the purest of drugs should be used in their work. He (the President) thought that impure ether containing the deleterious compound acetaldehyde was not infrequently sold for anæsthetic purposes. He would like to ask whether it was possible to detect its presence by the smell. One point to which he might perhaps draw attention was the liability of ether to form peroxides in the presence of air and sunlight. He would therefore warn anæsthetists not to keep their ether in large half-filled bottles of clear glass.

Mr. C. J. LOOSELY pointed out that when chloroform and ether were mixed an effervescence took place as well as an evolution of heat, and that also in spite of this and the increased temperature there was a contraction of volume which could be demonstrated by inverting a drop-bottle immediately after shaking the mixture; bubbles would then be found to enter.

Mr. FINNEMORE, in replying to the discussion, stated that evolution of heat and contraction in volume were observed when other substances—e.g., alcohol and water—were mixed, and, as far as he knew, no claim had yet been made that chemical action occurred. In the case of chloroform and ether no evidence was yet available which showed definitely that chemical combination took place, although the evaporation of a mixture of the two was not uninfluenced by the presence of the other ingredient. In reply to the President's remarks, it was possible for a trained nose to detect the presence of aldehyde in ether.