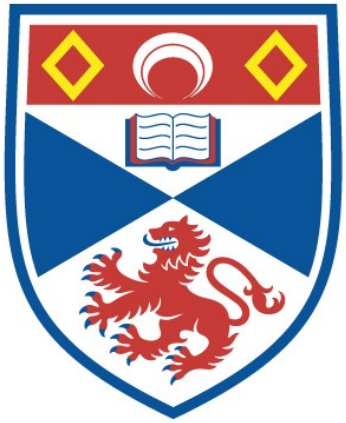
RESEARCHES IN THE TERPENE SERIES

William Wilson Cuthbertson

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1945

"RESEARCHES IN THE TERPENE SERIES"

being a Thesis

presented by

WILLIAM WILSON CUTHBERTSON, B.Sc.,

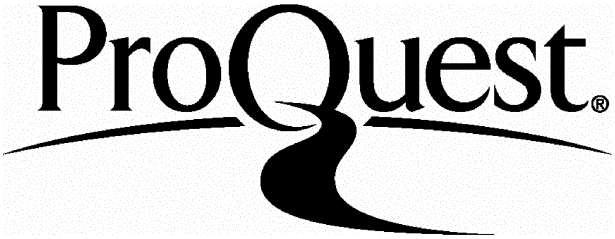
to the

UNIVERSITY OF SAINT ANDREWS

in application for

the

DEGREE OF DOCTOR OF PHILOSOPHY.



Declaration.

I hereby declare the following Thesis to be a record of results of experiments carried out by me, and furthermore that the Thesis is my own composition, and has not been previously presented for a Higher Degree.

The investigation was conducted in the Chemical Research Laboratory of the United College, under the direction of Professor John Read, M.A., Ph.D., Sc.D., F.R.S.

Certificate.

I hereby certify that Mr. W. W. Cuthbertson B.Sc., has spent eight terms at Research Work under my supervision in the Chemical Research Laboratory of the University of St. Andrews, that he has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and that he is qualified to submit the accompanying Thesis in application for the Degree of Doctor of Philosophy.

Director of Research.

University Career and Research Experience.

I entered the United College, University of St. Andrews, in October 1939, and pursued the recognised course for graduation in Science, and graduated B.Sc. in Chemistry and Physiology in June 1942. In June 1943 I was awarded Post-graduate Honours of the Second Class in Chemistry.

I was admitted as a Research Student in October 1943, having obtained a Grant from the Department of Scientific and Industrial Research. This Grant was held by me until the termination of my studies in St. Andrews in September 1945.

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THEORETICAL SECTION.

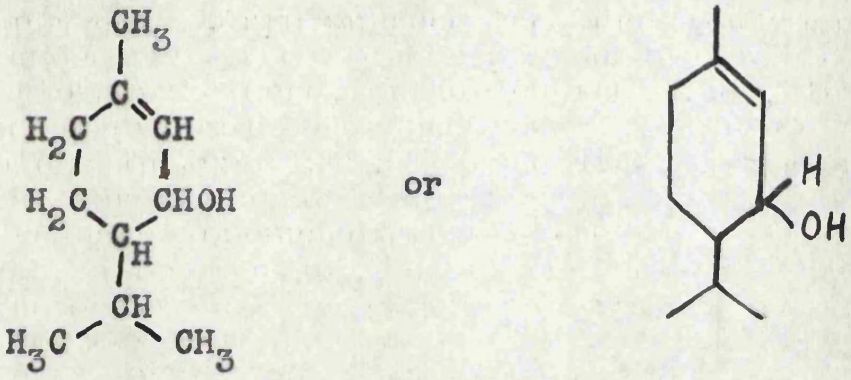
PART I.

Piperitols.

Derivatives of Piperitol

INTRODUCTION.

Piperitol, the $\alpha\beta$-unsaturated alcohol derived from piperitone is Δ'-menthen-3-ol (I).



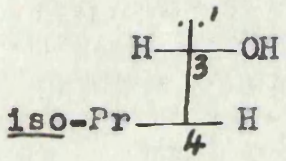
(I)

Unlike its saturated analogue, menthol, which occurs in quantity, together with menthone, in the oil of Mentha piperita, piperitol does not appear to occur widely in nature. The corresponding ketone, piperitone, is a constituent of many Eucalyptus oils, and during their researches on these oils, Baker and Smith isolated l-piperitol from the oil of Eucalyptus radiata ('A Research among the Eucalypts' 2nd. edn. Sydney 1920). The occurrence of piperitol in this oil is capricious however, and it is only found at certain seasons.

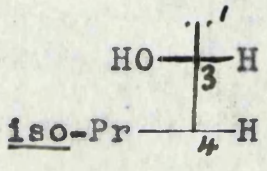
Simonsen, who isolated d-piperitone from the oil of a Himalayan grass, Andropogon Jwarancusa, has also discovered d-piperitol in an unidentified species of the same family (Indian Forest Records, 1924, 10, viii.).

Stereochemistry of piperitol.

Piperitol has two dissimilar asymmetric carbon atoms at positions 3 and 4; there should therefore be four optically active forms, and two externally compensated forms, corresponding to the projection formulae:



(I)



(II)

Varieties corresponding to both formulae are known. By steam-distilling l-piperityl-trimethyl-ammonium iodide with silver oxide, Read and Storey (J., 1930, 2770) obtained two dextro-rotatory piperitols, one of which decomposed spontaneously after a few days with liberation of water. By analogy with the neo-menthols, this unstable piperitol has been designated neo-piperitol, and is regarded as having the hydroxyl and iso-propyl groups in cis-position to one another, as in configuration (II). The piperitols discovered by Baker and Smith, and Simonsen are mirror images, to which configuration (I) has been assigned.

The scarcity of piperitol in essential oils is thereby explained by the spontaneous dehydration of the neo-variety

/neo-variety to give water and α-phellandrene. The presence of piperitol in these oils is therefore dependent on the production of the stable variety.

Attempts to prepare piperitol.

Attempts to reduce piperitone to piperitol by means of sodium and alcohol were unsuccessful, owing to reduction of the double-bond, and the production of a mixture of isomeric menthols (Read and Cook, J., 1925, 2782). Simonsen, however, has prepared a small quantity of dl-piperitol by reduction of piperitone with aluminium iso-propylate and iso-propyl alcohol, according to the method of Ponndorf (J.S.C.I., 1930, 49, 540).

Another possible method was the preparation of piperitylamine, and thence piperitol by treatment with nitrous acid. The preparation of piperitylamine from piperitone oxime was unsuccessful, again owing to reduction of the double- bond, and formation of menthylamines(Read, Cook, and Shannon, J., 1926, 2232).

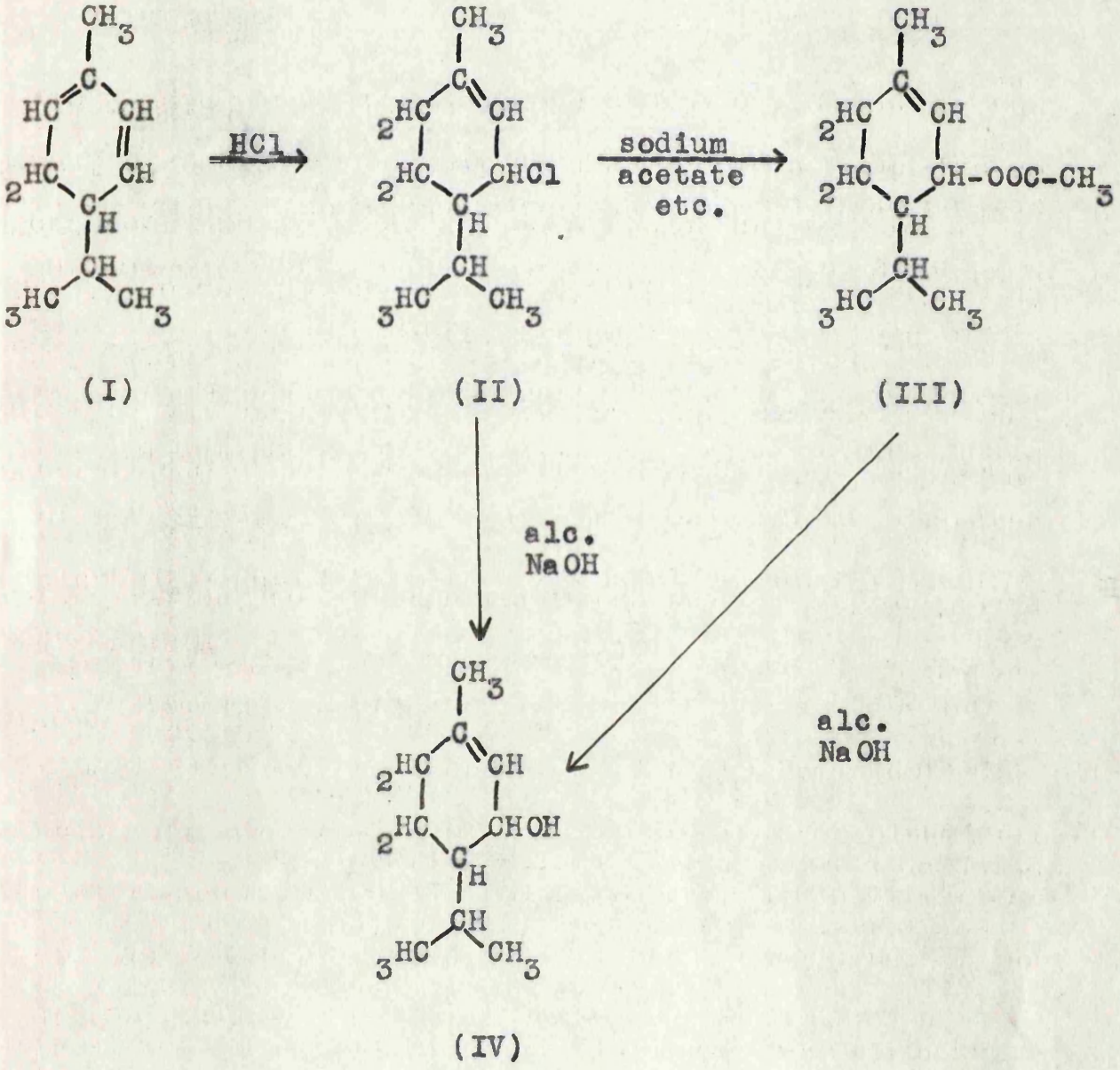
dl-piperitylamine was eventually obtained by Read and Storey(loc. cit.), by reduction of piperitone azine with zinc powder and glacial acetic acid. Methylation, and/

/and treatment of the resulting quaternary ammonium iodide with silver oxide gave dl-piperitol, and dl-neo-piperitol. The active compounds were obtained by resolving the dl-piperitylamine with tartaric acid; the l-base is produced by using d-tartaric acid.

Aims of the present work on piperitol.

Although piperitol has been obtained by Read and Storey, this material was not stereochemically pure, and the yield of material was not very great. A new method for preparing piperitol has been claimed, and stated to give good yields of the substance (E.P., 532614, 1941). Accordingly it was decided to prepare piperitol by this method, and attempt to convert the the material to a crystalline ester, such as the 3:5-dinitrobenzoate, which was obtained by Read and Walker(J., 1934, 308) in a minute yield(13%). With larger quantities of piperitol available, it was hoped to obtain a sufficient amount of an ester, which could be crystallised to stereochemical purity, and hydrolysed to give a stereochemical pure piperitol.

SCHEME FOR PREPARATION OF PIPERITOL FROM l-α-PHELLANDRENE.



(I) (II) (III)

(IV)

Preparation of piperitol. (E.P., 532614, 1941)

In the present research piperitol is being prepared from l-α-phellandrene (I) by addition of gaseous hydrogen chloride, which adds on at either end of the conjugated system, one of the possible products being piperityl chloride (II), from which piperitol may be obtained in either of two ways:

(i) By treatment with alcoholic sodium hydroxide.

(ii) By treatment with sodium acetate and glacial acetic acid to give piperityl acetate (III), and hydrolysis of the latter to piperitol (IV) with alcoholic sodium hydroxide.

The first method was found to give a low yield of piperitol, having also a low rotatory power. In the second method, however, the yield was higher, and the product had a much higher rotatory power, since it was possible to purify the piperityl acetate by vacuum distillation, before hydrolysing it to piperitol. The piperityl chloride could not be purified in this way, as it decomposed with liberation of hydrogen chloride.

The yield of piperitol obtained does not approach the theoretical, but the reason for this is quite apparent, when the addition of the hydrogen chloride is taken into account. The hydrogen chloride may add on to the phellandrene in either of two ways, only one of which will give rise to piperitol, the other possible product being carvotanacetol(Δ′-menthen-6-ol).

The yield may be further diminished by the formation of neo-piperityl acetate, which would give the unstable neo-piperitol on hydrolysis. A small terpene fraction was obtained in the hydrolysis of the piperityl acetate, which may have resulted from some neo-piperitol. It has not been possible, however, to separate any neo-piperityl acetate from the piperityl acetate, and the preponderating product appears to be the latter substance.

The yield of piperitol was 25%, calculated on the phellandrene, and the material had a rotatory power of -34.2°(homog. The yield of piperitol obtained by Read and Storey (loc. cit.) was 10%, calculated on the piperitone.

The values of $[\alpha]_D$ for piperitols obtained by the various workers are appended below.

Baker and Smith (loc. cit.),	l-piperitol	-43.7°
Simonsen (loc. cit.),	d-piperitol	+46.0°
Read and Storey (loc. cit.),	d-piperitol	+43.7°
Read and Walker (loc. cit.),	l-piperitol	-24.5° (alcohol)
Present work,	l-piperitol	-34.2°

Although the piperitol obtained in the present research is purer than any yet obtained by synthetic methods, it is not so pure as the naturally occurring material, isolated by Baker and Smith. Even after keeping for two years, the material showed no tendency to eliminate water, indicating that no neo-piperitol was present.

Attempt to detect presence of carvotanacetol in piperitol.

In order to determine, if possible, whether any carvotanacetol was produced in the piperitol preparation, a quantity of piperitol was oxidised to the corresponding ketone, piperitone, by means of chromic acid mixture. The resulting ketone was then treated with a solution of sodium in alcohol, in order to racemise the piperitone present. The product was then converted to the oxime in the usual manner. The oximes of optically active piperitone are syrupy materials, but that of inactive piperitone is crystalline, hence the reason for racemising the ketone. It was hoped also, that the amount of piperitone oxime produced might give an indication of the amount of piperitol in the original material. Since the oximes of piperitone are soluble in acid, and those of carvotanacetone are not, a possible method of separating any of the latter is therefore suggested, In the experiment carried out, a small amount of crystalline dl-piperitone-α-oxime was isolated, but the major part of the acid soluble oximes remained as a syrup. The material insoluble in acid was also a syrup, and failed to crystallise even after seeding with a crystal of carvotanacetone oxime.

Although no positive proof has been obtained of the presence of carvotanacetol, it is noteworthy that, even after racemisation with sodium ethoxide, the ketone product had a/

/a positive rotation, indicating that some substance other than piperitone was present.

Derivatives of piperitol.

No crystalline derivative of piperitol has yet been obtained in a state of purity, and the preparation of such a derivative, even in an impure state, is attended by considerable difficulty. Indeed the only easy method of characterising piperitol is by oxidation to the corresponding ketone, and conversion of the latter to the oxime.

The menthols are easily characterised by conversion to p-nitrobenzoates etc. by treatment with acid chlorides, but such a procedure has not so far been possible with the piperitols. Acid chlorides exert a strong dehydrating action on piperitol, decomposing it to α-phellandrene. Read and Walker(loc. cit.), however, have obtained what is possibly a pure 3;5-dinitrobenzoate of piperitol, by treatment of the alcohol with 3:5-dinitrobenzoyl chloride in pyridine. The yield of crude material was only 13%, owing to formation of α-phellandrene.

In the present research, various new methods have been applied in an attempt to obtain a derivative in greater yield, and by hydrolysis of the latter to obtain a stereochemically/

/stereochemically pure piperitol.

By a variation of the method used for the preparation of piperityl acetate from the hydrogen chloride addition-compound of phellandrene, it was thought that it might be possible to obtain other esters of piperitol. Two methods have been investigated:

(i) Treatment of the addition-compound with the sodium salt of an acid in presence of a solvent such as glacial acetic acid or alcohol.

(ii) Treatment of the addition-compound with the silver salt of an acid, when silver chloride might be expected to split out, and the acid radicle attach itself to the piperitol residue. The acids used were 3:5-dinitrobenzoic acid, and l-menthoxy-acetic acid, as their sodium and silver salts.

Dinitrobenzoates.

Attempts to prepare 3:5-dinitrobenzoates of piperitol have been made, using both the above methods.

Method (i)

Treatment of the addition-compound with sodium 3:5-dinitrobenzoate in glacial acetic acid at room temperature gave only dinitrobenzoic acid. A similar experiment carried out in the heat gave the same result, the solvent in this case being alcohol.

Method (ii)

On heating the addition-compound with silver 3:5-dinitrobenzoate in alcohol, some silver chloride was produced, but it was found that decomposition of the addition-compound had occurred, and the resulting hydrogen chloride had reacted with the silver salt to give silver chloride, and dinitrobenzoic acid.

l-Menthoxyacetates.

Methods similar to those applied to the dinitrobenzoates have been utilised for the l-menthoxyacetates.

Method (i).

Interaction of the addition-compound with sodium/

/sodium l-menthoxyacetate in glacial acetic acid, gave only menthoxyacetic acid, owing to the decomposition of the sodium salt by the glacial acetic acid. This experiment was repeated, using alcohol as the solvent, with similar results.

Method (ii)

The addition-compound was gently heated with silver l-menthoxyacetate in alcoholic solution, but, as in the case of the dinitrobenzoate, decomposition of the addition-compound led to the production of menthoxyacetic acid.

Owing to the ready decomposition of the addition-compound in the heat, it was decided to utilise a method which might give esters of piperitol in the cold.

Utilisation of a basic solvent for the interaction of the addition-compound with an acid in the cold.

Treatment of the addition-compound in the cold with an acid in presence of a basic solvent, which would remove the hydrogen chloride produced, was thought to be a favourable possibility.

$$C_{10}H_{17}Cl + HOOC.R \longrightarrow C_{10}H_{17}OOC.R + HCl$$

The base used was dimethylaniline, which also acted as a solvent for the reactants, in addition to removing any hydrogen chloride produced in the reaction. The experiments were/

/were carried out in the cold, the acids used being 3:5-dinitrobenzoic acid, and l-menthoxyacetic acid.

In no instance was any ester of piperitol isolated from the reaction mixture.

Interaction of the addition-compound with oxalic acid.

It was thought possible that the acids hitherto used in the attempts to prepare esters of piperitol, may have been too weak to react with the addition-compound, and it was decided to try oxalic acid, which is a much stronger organic acid.

Accordingly, the addition-compound was shaken with a concentrated solution of oxalic acid and sodium oxalate in water, but again no ester was obtained.

Application of the method of Ester Interchange to the preparation of piperityl esters.

In view of the failure to obtain esters of piperitol, using the hydrogen chloride addition-compound of phellandrene as a starting material, it was decided to apply the method of Ester Interchange to the preparation of piperityl esters.

Ester Interchange.

This reaction is also known as "alcoholysis", and many examples of it have been described. The process is simply the esterification of an ester, as illustrated by the following equation:

$$CH_3COOC_2H_5 + HOCH_3 \longrightarrow CH_3COOCH_3 + HOC_2H_5$$

Like esterification, the process is reversible, and will attain equilibrium unless one of the products is removed continuously. This is usually effected by distillation. The reaction can be catalysed by various substances, the most active of which is sodium alcoholate, but hydrogen chloride, or sulphuric acid will also serve.

In the present research, piperitol has been heated with ethyl l-menthoxyacetate, using sodium ethoxide as a catalyst. The temperature of the experiment was 120°, and at this temperature, the piperitol decomposed to phellandrene. This method is therefore not satisfactory, and a lower temperature cannot be used, otherwise the interchange will not take place.

Interaction of piperitol with triphenylchloromethane.

Since piperitol is dehydrated by acid chlorides, it was decided to use a compound with a reactive chlorine atom, without having such a vigorous action as an acid chloride. Such a compound is triphenylchloromethane, which has three phenyl radicles attached to the same carbon atom, thus making the chlorine atom labile, and very reactive.

$$C_{10}H_{17}OH + Cl.C(C_6H_5)_3 \longrightarrow C_{10}H_{17}.O.C(C_6H_5)_3 + HCl$$

By heating piperitol with triphenylchloromethane in dry pyridine, a syrupy product was obtained, which crystallised after some time. Analysis showed the material to be triphenylmethyl-piperityl-ether. Since the substance is an ether, and not an ester, it is not possible to obtain piperitol from it by any process. Although the compound is useful as a crystalline derivative for characterising piperitol, it is of no use as a means of preparing a stereochemically pure piperitol.

THEORETICAL SECTION.

PART II.

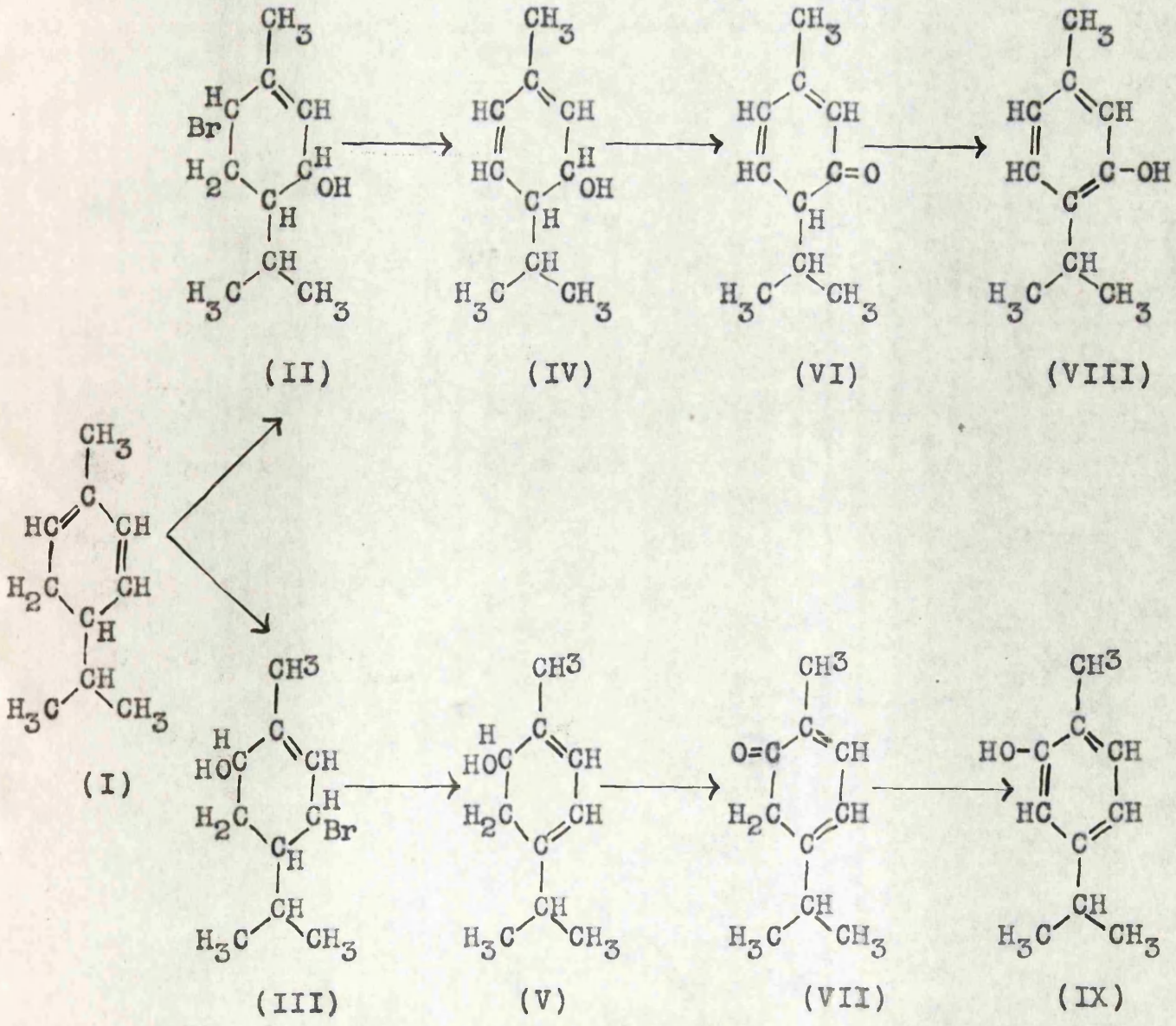
Experiments on conversion of Phellandrene to Thymol.

Experiments on conversion of Piperityl acetate to

Δ^{6}-Menthenone-3.

Attempt to prepare thymol from l-α-phellandrene.

Phellandrene can be obtained in quantity from many Eucalyptus oils, and a method of converting it to thymol would be of considerable value, if the method could be applied to large scale production. Experiments were carried out according to the following scheme:



Since phellandrene (I) has a conjugated system, the addition of hypobromous acid to it, would be expected to give rise to two products. These bromo-hydroxy-compounds (II) and (III), on treatment with alcoholic potash, should eliminate hydrogen bromide, thus introducing a double bond, and giving two alcohols (IV) and (V) respectively. Oxidation of these alcohols with Beckmann's reagent should yield two ketones (VI) and (VII), which would enolise to thymol (VIII) and carvacrol (IX), in presence of alkali.

Addition of hypobromous acid to phellandrene.

Two possible methods are available for the addition:
(i) A stream of air laden with bromine vapour may be passed into a mixture of phellandrene and water under vigorous stirring. The progress of the reaction may be ascertained in this method by using a tared vessel containing bromine, and discontinuing the addition when the calculated amount of bromine has been absorbed.
(ii) The bromine may be dissolved in aqueous potassium bromide, and the calculated amount dropped into the stirred mixture of phellandrene and water.

The second method was that adopted in the present work, since the amount of bromine added can be controlled more/

/more easily, and a more accurate quantity added.

An attempt to purify the oily product of this reaction by distillation in a high vacuum, resulted in decomposition, with liberation of hydrogen bromide and water. It was therefore decided to treat the material in the crude state with alcoholic potash.

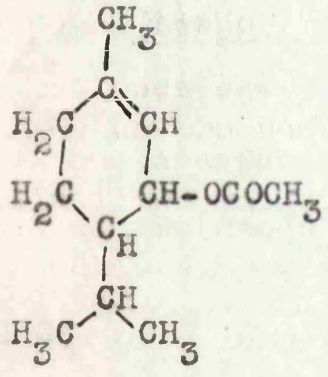
Hydrolysis of Bromo-hydroxy-phellandrene with alcoholic potash.

The product of the hydrolysis was a brown oil, which distilled without decomposition, and was separated into three fractions by this method. Since these fractions ought to be alcoholic in nature, a sample of each was treated with p-nitrobenzoyl chloride in dry pyridine, in an attempt to obtain a crystalline derivative of the alcohol. In no case was a crystalline compound isolated, so it was decided that the hydrolysis might be incomplete. Accordingly, a Lassaigne Test was carried out on the fractions, and the presence of bromine was detected. Hydrolysis was therefore repeated using a very large excess of potash, and heating for a much longer time. Even this drastic treatment, however, failed to eliminate the bromine, which must be very firmly attached to the molecule. Nevertheless, a quantity of the material was oxidised by Beckmann's method, in the hope that there might be some alcoholic material present, which would be converted to a ketone. The reaction product, however, was completely insoluble in alkali,/

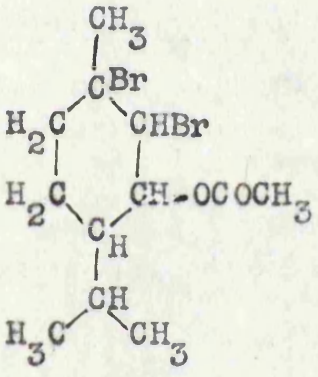
/alkali, indicating that no phenolic material was present. In view of the exceedingly great stability of the bromo-compound it appears impossible to obtain thymol from phellandrene by this method.

Attempt to convert piperityl acetate to Δ^6-menthenone-3.

The ketone, Δ^6-menthenone-3, has not previously been obtained, and it was anticipated that the substance might be somewhat unstable, and be very readily isomerised to the corresponding Δ' compound, piperitone.



(I)



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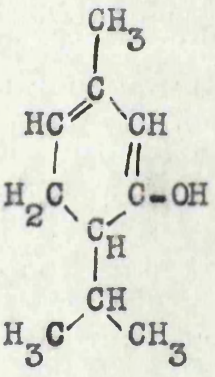

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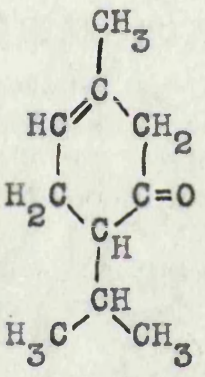


(IV)

Bromination of piperityl acetate (I) will yield a dibromo-compound (II), which, on treatment with alcoholic potash, should eliminate two molecules of hydrogen bromide, thus introducing a double-bond in the Δ^6 position, and also in the Δ^2 position. In addition the alcoholic potash will hydrolyse the acetate group, and the final product will be an alcohol (III) which is the enolic form of the ketone, Δ^6-menthenone-3, (IV). This ketone might be expected to isomerise very readily to piperitone, but by preparation of a semicarbazone from the reaction product, it might be possible to determine whether

/whether the Δ^6 or Δ^1 isomer is produced, since the semicarbazone of the latter is known.

In the experiments carried out on this scheme, a small amount of piperitone semicarbazone has been isolated, but this was the only definite product, since the other products were oils which did not crystallise. The fact that piperitone semicarbazone was produced, however, indicates that some Δ^6-menthenone-3 was produced, but isomerised to piperitone.

THEORETICAL SECTION.

PART III.

Methylation of l-piperitylamine.

Methylation of l-piperitylamine.

In the course of a research on the production of piperitol from piperityl-trimethyl-ammonium iodide, Read and Walker (J., 1934, 308) obtained a highly laevo-rotatory substance ($[\alpha]_D$ -355°), which was then assumed to be N-methyl-l-piperityl-amine. Later, however, the correspohding methylated l- and d-neo-menthylamines were prepared by Read and Hendry (Ber., 1938, 2544) and were found to possess much lower rotatory powers. The close relationship between the menthylamines and piperitylamines indicates that the methylated piperitylamines should have rotatory powers of the same order of magnitude as the methylated menthylamines. It seems possible, therefore, that the substance obtained by Read and Walker was not N-methyl-l-piperitylamine, and it was therefore desirable that the pure N-methyl- and N-dimethyl- derivatives of piperitylamine should be prepared, and their physical constants determined.

Production of piperitylamine.

The piperitylamine for use in the above research was prepared according to the method of Read and Storey (J., 1930, 2770), by reduction of piperitone azine with zinc powder and glacial acetic acid. In this case, however, the yields of dl-piperitylamine were variable, and did not approach those quoted by Read and Storey. A considerable amount of zinc was/

/was left undissolved, even after stirring for longer than the specified time. Experiments carried out using different samples of zinc powder gave similar results, and an attempt to catalyse the reaction with copper sulphate, and platinum chloride was also unsuccessful. Since it was not possible to obtain an active sample of zinc powder, attention was then directed to the use of other metals in the reduction of piperitone azine.

A mixture of zinc and iron powders was tried but this again was unsuccessful.

Magnesium powder was found to react very readily with glacial acetic acid, and a good yield of basic material was obtained. This, however, was menthylamines, produced by reduction of the double-bond.

In all the reductions of piperitone azine with zinc and glacial acetic acid, the preponderating product was piperitone, formed presumably by hydrolysis of the azine.

Despite the low yields, a sufficient quantity of dl-piperitylamine was obtained for use in the research. The inactive base was resolved as described by Read and Storey (loc. cit.), using d-tartaric acid. The less soluble diastereoisomer was l-piperitylamine hydrogen d-tartrate, which was readily obtained pure after recrystallisation from hot water.

Experiments on the Methylation of l-piperitylamine.

Application of the method of Read and Hendry (loc. cit.) to the methylation of l-piperitylamine was unsuccessful, and the methylation was therefore carried out by using carefully controlled amounts of methyl iodide and sodium methoxide, in order that the product should consist mainly of the mono- and di-methyl- bases.

Separation of the two methyl bases was effected by acetylation or benzoylation, which affected only the mono-methyl base. It was then possible to extract the dimethyl-base from the ethereal solution of the acetylation product by means of dilute hydrochloric acid. The mono-methyl base was then obtained by hydrolysis of the acetyl derivative with concentrated hydrochloric acid.

In the present research, N-methyl- and N-dimethyl-l-piperitylamine have been prepared, and have been found to possess rotatory powers analagous to those of the menthylamines.

THEORETICAL SECTION.

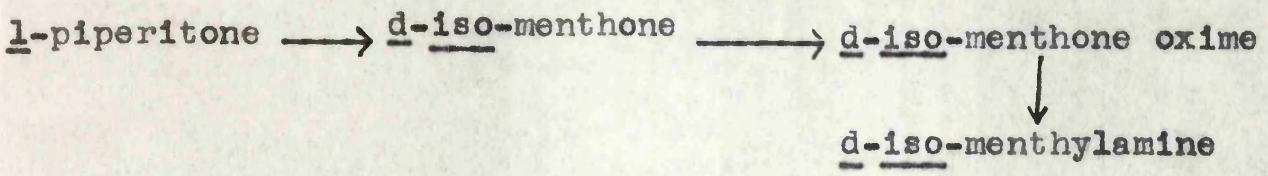
PART IV.

Methylation of d-iso-menthylamine.

Methylation of d-iso-menthylamine.

The N-methyl-, and N-dimethyl- derivatives of l-, and d-neo-menthylamine have already been described by Read and Hendry(loc.cit.), and those of l-piperitylamine have been prepared in the present research. In order to complete the series of methylated bases, the N-methyl-, and N-dimethyl- derivatives of d-iso-, and d-neo-iso-menthylamine have yet to be prepared. Until a method becomes available for the preparation of neo-iso-menthylamine in greater amount, it will not be possible to undertake any experiments with this substance. It is hoped however to isolate some neo-iso-menthylamine from the residues of the d-iso-menthylamine preparation. This will be described in a later section.

Meanwhile d-iso-menthylamine has been prepared by catalytic hydrogenation of l-piperitone, according to the following scheme:



Catalytic hydrogenation of l-piperitone in presence of colloidal palladium gives a good yield of d-iso-menthone(60%) (Hughesdon, Smith and Read, J.,1923, 123, 2916), from which d-iso-menthylamine can be obtained by reducing the oxime with sodium and alcohol(Read and Robertson, J., 1926, 2269).

In the work carried out by Read and Robertson, however, the piperitone used was very pure, and had a higher rotation than that available for the present work. Nevertheless it has been found possible to obtain considerable quantities of d-iso-menthylamine, without having to purify the products until the final stage.

The yields are shown below:

85g. l-piperitone α_D -43° (l=1, homog.)

↓

84g. crude d-iso-menthone α_D +47° (l=1, homog.)

↓

100g. crude oxime $[\alpha]_D^{16}$ +27° (c=2.578, EtOH)

↓

100g. crude d-iso-menthylamine hydrochloride
$[\alpha]_D^{15}$ +16.3° (c=1.9535, water)

↓

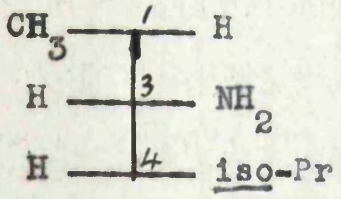
25g. pure d-iso-menthylamine hydrochloride
$[\alpha]_D^{15}$ +23° (c=2.0645, water)

Calculated on the piperitone, this quantity of d-iso-menthylamine hydrochloride represents a yield of 23%.

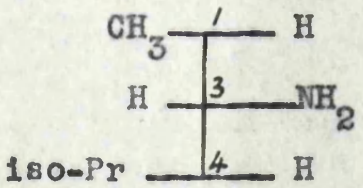
Using purer materials, Read and Robertson obtained a crude d-iso-menthylamine hydrochloride, which had $[\alpha]_D$ +20.63°, and on recrystallisation from acetone/methyl alcohol gave 33% of its weight of pure material.

Preparation of the N-methyl-and N-dimethyl-derivatives of d-iso-menthylamine.

The method utilised for the methylation was the methyl iodide/sodium methoxide method, already applied to d-neo-menthylamine, and l-piperitylamine. In this case,however, the preponderating product was the dimethyl-base, whereas in the methylation of d-neo-menthylamine, roughly equal amounts of the secondary and tertiary bases were produced. The reason for this, however, becomes quite apparent when the relative configurations of the neo-and iso-menthylamines are considered.



(I)



(II)

It will be seen from the appended projection formulae, that d-neo-menthylamine (I) has the $-NH_2$ group in cis-position to the iso-propyl group, whereas in d-iso-menthylamine the two groups are in trans-position to one another. It is to be expected therefore that the $-NH_2$ group in the iso-menthylamine will methylate more easily than that in the neo-menthylamine, since the large iso-propyl group will have a steric effect in the latter case. Indeed this steric effect exerted by the iso-propyl/

/iso-propyl group has already been encountered in work with the corresponding menthols. It has been found that the neo-menthols esterify less readily than the iso-menthols(Read and Grubb, J., 1934, 1779).

Since the methyl iodide method of methylation did not give a sufficient quantity of the secondary base, it was decided to prepare this by the method of Read and Hendry (loc.cit.) via d-iso-menthylglycine. This latter method was found to work well, and gave a good yield of N-methyl-d-iso-menthylamine.

The values of M_D for the series of menthylamines are appended below:

	Menthylamine.		
	l-	d-neo-	d-iso-
$[R.NH_3]Cl$	-70.1°	+41.2°	+45.2°
$[R.NMeH_2]Cl$	-108.4°	+34.3°	+35.5°
$[R.NMe_2H]Cl$	-110.0°	+33.6°	+59.3°
$[R.NMe_3]I$	-127.6°	-63.4°	+ 6.4°

The values for the iso-menthylamines have been obtained from the present research, the remainder are the work of Read and his collaborators.

Table of Rotation Values of the methylated Menthylamines and Piperitylamines.

Base.	Menthylamines.			Piperitylamines.
	l-	d-neo-	d-iso-	l-
$R.NH_2$	-38.2°	+8.7°	+29.4°	-70°
$R.NHCH_3$	-69.2	+26.4	+21.4	-51
$R.N(CH_3)_2$	-59.7	+40.7	+36.5	-59.2
$R.N(CH_3)_3I$	-39.3	~~-20.0~~ -19.5	+ 1.97	- 4.8

The values for the free bases are observed in chloroform solution (c = 2 approx.) in a 2-decimetre tube. The values for the quaternary iodides are observed in aqueous solution, the other factors being the same. The values for the methylated l- and d-neo- menthylamines are the work of Read and Hendry (loc. cit.), the remainder are the result of the present research.

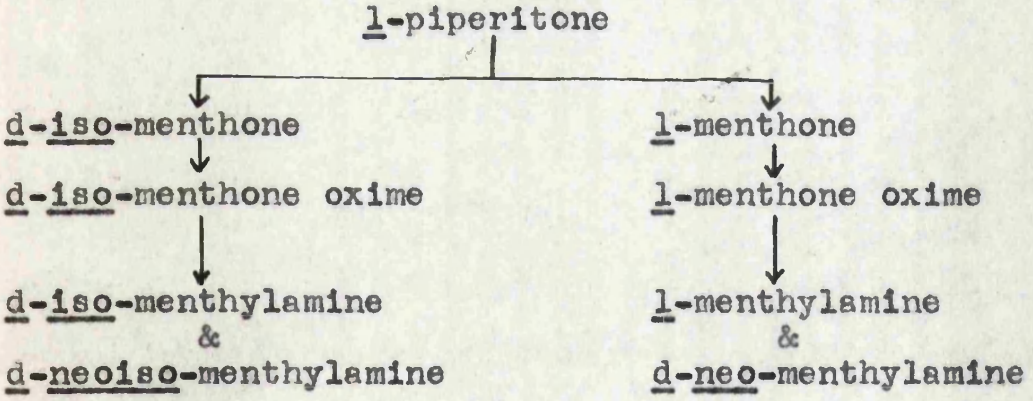
THEORETICAL SECTION.

PART V.

d-Neoiso-menthylamine

Examination of the residual menthylamine after removal of the pure d-iso-menthylamine.

In the preparation of d-iso-menthylamine for work already described (p. 25) a large quantity of impure menthylamine hydrochlorides remained after removal of the pure d-iso-menthylamine hydrochloride. It was thought that this material might be a good source of the comparatively rare d-neoiso-menthylamine, since the mixture ought to contain all four stereoisomeric menthylamines. This may be seen from the appended diagram.



Hydrogenation of l-piperitone gives two menthones, but if the conditions are carefully controlled, the product consists mainly of the d-iso- variety. Reduction of the oxime of d-iso-menthone, however, yields two menthylamines, owing to the introduction of a new asymmetric carbon atom at position 3. The product of the reduction should therefore consist of a mixture of d-iso-menthylamine and d-neoiso-menthylamine. Since the d-iso-menthone was not purified/

/purified before conversion to the oxime, there will also be some l-menthylamine and d-neo-menthylamine present.

d-Neoiso-menthylamine has already been obtained by Read and Robertson (J., 1927, 2168), who prepared it from the mixture of menthylamines produced by treating l-menthone with ammonium formate. The method utilised in the latter research was to convert the menthylamines to the crystalline salicylidene derivatives, and separate the d-neoiso-menthylamine derivative by fractional crystallisation.

In the present research the same method has been used, and a large quantity of crude menthylamines has been converted to the salicylidene derivatives, and the product submitted to fractional crystallisation. In this way salicylidene d-neoiso-menthylamine has been obtained in a pure state in an amount corresponding to 6.5% of the original crude salicylidene compound. The yield obtained by Read and Robertson in the work mentioned above was about 8%. The material obtained in the present work is identical with that prepared by the previous workers both in rotatory power and melting point. A mixed melting point of the two specimens showed no depression.

SUMMARY OF RESULTS.

1. l-Piperitol has been prepared according to the English Patent method, and although the yields are lower then that claimed by the patentees, the product has a much higher rotatory power than any so far obtained by synthetic means. The specimens of l-piperitol showed no tendency to eliminate water spontaneously even after keeping for two years, and therefore no neo-piperitol was present.

2. Various new methods have been utilised in an attempt to obtain a crystalline ester of piperitol, and therefrom a stereochemically pure piperitol by recrystallisation of the ester to optical purity, and hydrolysis to piperitol. No ester has been obtained, but a crystalline ether of piperitol has been prepared, which, however, is useful only as a means of characterising the alcohol.

3. Experiments have been carried out on the possibility of converting piperityl acetate to Δ^6-menthenone-3, which it was hoped to isolate as the oxime. The only product obtained was the oxime of dl-piperitone, which may have been produced by isomerisation of the Δ^6 ketone.

4. Experiments carried out on the conversion of l-α-phellandrene to thymol and carvacrol have been unsuccessful.

5. N-methyl-l-piperitylamine and N-dimethyl-l-piperitylamine have been prepared in a pure state for the first time and characterised. The physical constants of the methylated bases have been found to be analagous to those of the corresponding methylated menthylamines.

6. N-methyl-d-iso-menthylamine and N-dimethyl-d-iso-menthylamine have also been prepared and characterised, thereby completing the series of methylated menthylamines, with the exception of the methyl derivatives of d-neoiso-menthylamine.

7. d-Neoiso-menthylamine has been isolated as the salicylidene derivative from the mixture of menthylamines produced by reduction of the crude oxime of d-iso-menthone, obtained by catalytic hydrogenation of l-piperitone.

EXPERIMENTAL SECTION.

PART I.

Preparation of Piperitol.

Attempts to prepare esters of Piperitol.

Preparation of piperitol.

70g. of l-α-phellandrene, having a specific rotation of -76°, were cooled in ice to about 0°C, and dry hydrogen chloride passed in, until the increase in weight amounted to 18g. This required about two hours. To the reaction mixture, which was dark-red in colour, were added 30g. of sodium hydroxide in alcohol, and the whole allowed to stand for 24 hours at 0°C. Water was then added, and the oil which separated was washed three times with water, and finally dissolved in ether. After drying the ethereal solution over anhydrous sodium sulphate, the ether was removed under diminished pressure, and the residual oil distilled under a pressure of 12 mm., the following fractions being collected:

Fraction (i)

b.p. to 80°, 22.7g., n_D^{16} 1.4820, d^{16} 0.887, $[\alpha]_D^{18}$ -4.35°

Fraction (ii)

b.p. 80-110°, 39.1g., n_D^{16} 1.4750, d^{16} 0.917, $[\alpha]_D^{18}$ -4.92°

Fraction (ii) was redistilled at 12 mm., and yielded a further two fractions:

Fraction (iii)

b.p. 80-95°, 23.1g., n_D^{18} 1.4732, d^{18} 0.900, $[\alpha]_D^{17}$ -5.36°

Fraction (iv)

b.p. 95-105°, 12.5g., n_D^{18} 1.4736, d^{18} 0.930, $[\alpha]_D^{18}$ -11.6°

Fraction (i) seemed to consist of phellandrene, and fraction (iv) of piperitol, although the rotatory powers were very low. The yield of piperitol was about 15%.

Preparation of piperityl acetate.

The hydrogen chloride addition compound was prepared as before, using the same amount of phellandrene, and to it were added 63g. of anhydrous sodium acetate, and 500 cc. of glacial acetic acid. After stirring for 24 hours at room temperature, the mixture was diluted with water, and the oil extracted with ether. The ethereal solution was shaken with sodium carbonate solution, water, and dried over anhydrous sodium sulphate. The ether was removed from the dried extract and the residual oil distilled under a pressure of 0.75 mm., the following fractions being obtained:

Fraction (i) — b.p. to 60°, 32.3g.,

Fraction (ii) — b.p. 65-85°, 33g.

Fraction (i) was redistilled at a pressure of 0.5 mm., giving a further two fractions:

Fraction (iii)

b.p. to 45°, 27.5g., n_D^{18} 1.4849, d^{18} 0.865, $[\alpha]_D^{16}$ -20.3°

Fraction (iv)

b.p. 64-70°, 2.4g.

Fractions (ii) and (iv) were combined, and had the following constants: weight 35.4g., n_D^{18} 1.4712, d^{18} 0.975, $[\alpha]_D^{17}$ -26.3°

The combined fractions were regarded as being fairly pure piperityl acetate, and were used for hydrolysis to piperitol. The yield was 35%.

Hydrolysis of piperityl acetate.

35.4g. of piperityl acetate were heated to boiling for one hour with 12g. of sodium hydroxide in 80 cc. of 50% alcohol. The mixture was then diluted with water, extracted with ether, and the extract washed with dilute hydrochloric acid, and finally with water. After drying over sodium sulphate and evaporating away the ether, the residual oil was distilled under diminished pressure, and yielded two fractions.

Fraction (i)

b.p. to 50°/0.75 mm., 3.6g., $[\alpha]_D^{16}$ -5.7°

Fraction (ii)

b.p. 55-65°/0.3 mm., 20g., n_D^{18} 1.4790, d^{18} 0.94, $[\alpha]_D^{15}$ -34.2°

Fraction (ii) consisted of piperitol, the rotation being much higher than that of the specimen obtained in the previous method.

The yield of piperitol calculated on the acetate was 74%, and calculated on the phellandrene 25%.

Oxidation of piperitol.

36g. of piperitol were added to a mixture of 50g. of potassium dichromate, 22 cc. concentrated sulphuric acid, and 250 cc. of water. The piperitol formed a black oil on the surface of the mixture, and on shaking vigorously, the temperature rose rapidly to 60°, and then declined slowly. The cold mixture was extracted with ether, the extract being washed with dilute sodium hydroxide solution, water, and dried over sodium sulphate. Removal of the ether gave a pale yellow oil (28.8g.), which was distilled in vacuo at 10 mm., and passed over at 90-110°. The product was only slightly yellow, and weighed 27g.

n_D^{12} 1.4850 $[\alpha]_D^{16}$ -1.09°

This oil was treated with 0.3g. sodium in 20 cc. of absolute alcohol, and allowed to stand for 24 hours. The mixture was poured into a slight excess of dilute sulphuric acid, and the piperitone extracted with ether. The extract was washed with water, dried over sodium sulphate, and the ether removed by distillation. A brown oil (25.6g.) was obtained, which was distilled at a pressure of 10 mm.

b.p. 100-110°, n_D^{18} 1.4820, $[\alpha]_D$ +2.29° weight: 22.8g.

Preparation of oximes from the oxidation product of piperitol.

22.8g. of the oxidation product prepared above, were treated with 12g. hydroxylamine hydrochloride in 25 cc. water, and just sufficient hot alcohol to render the mixture homogeneous. 27g. of crystalline sodium acetate were then added to depress the acidity, and the whole refluxed for six hours. Most of the alcohol was then removed by distillation under diminished pressure, and the residual oily material dissolved in ether. The ethereal solution was extracted twice with dilute sulphuric acid to remove piperitone oxime. The ether layer was washed with water and dried. Evaporation of the ether gave a brown oil (8.9g.), which did not crystallise.

The acid extract was basified with sodium hydroxide, and the oil which separated was extracted with ether. From this extract, after drying and removing the ether, a brown syrup was obtained, which yielded some crystalline material on stirring with a little methyl alcohol. Recrystallisation from the same solvent, gave stout prisms, having m.p. 118°, and consisting of dl-piperitone -α-oxime.

The yield of recrystallised material was 0.46g., this being the only crystalline product. No oxime of carvotanacetone could be isolated from the oily product of the first ether extract, mentioned above.

Attempts to prepare esters of piperitol.

Piperityl 3:5-dinitrobenzoate.

15g. of the hydrogen chloride addition-compound of phellandrene were stirred for 24 hours at room temperature with 32g. of sodium 3:5-dinitrobenzoate, and 87 cc. of glacial acetic acid. The reaction mixture was poured into water, and shaken thoroughly to dissolve any unchanged sodium salt. The undissolved solid was removed by filtration, and recrystallised from alcohol. It had melting point 205°, and was therefore 3:5-dinitrobenzoic acid. The aqueous filtrate was extracted with ether, and dried over sodium sulphate. Evaporation of the ether yielded an oil, and also some solid material, which was recrystallised from alcohol, and found to be 3:5-dinitrobenzoic acid.

Piperityl 3:5-dinitrobenzoate.

15g. of the addition-compound, 32g. sodium 3:5-dinitrobenzoate, and 50 cc. of absolute alcohol were heated under reflux on a water-bath for six hours. The solid material, consisting of unchanged sodium salt, was removed by filtration, after which the alcohol was distilled away under diminished pressure. A dark coloured solid remained, together with some oil. The solid was recrystallised from alcohol, and had a melting point of 203°, showing it to be 3:5-dinitrobenzoic acid, produced by decomposition of the addition-compound with/

with liberation of hydrogen chloride, which decomposed the sodium 3:5-dinitrobenzoate.

Piperityl 3:5-dinitrobenzoate.

5g. of the addition-compound, and 12g. of silver 3:5-dinitrobenzoate were heated under reflux with 50 cc. alcohol for six hours on a water-bath. Some silver chloride was produced, and the mixture became black. The silver chloride and unchanged dinitrobenzoate were removed by filtration, and washed with hot alcohol. The filtrate was evaporated under diminished pressure, and some solid and oily material were obtained. Recrystallisation of the solid from alcohol, and a melting point determination showed it to be 3:5-dinitrobenzoic acid. As in the previous experiment, decomposition of the addition-compound had occurred during the heating.

Preparation of l-menthoxyacetic acid.

312g. (4 mols.) of l-menthol were placed in a 500 cc. Claisen flask heated in an oil bath at 150°. To the melted menthol were added 11.5g. (1 mol.) of sodium in small pieces, and the mixture kept at 150°, until all the sodium had dissolved. This required about two hours with fresh menthol, and anything from two to twenty hours when a mixture of fresh and recovered menthol was used. Excess menthol was then removed by distillation under diminished pressure, and the solid residue of sodium menthoxide dissolved in 300 cc. of sodium-dry benzene. The solution was transferred to a 1-litre flask, 100 cc. benzene being used to rinse the Claisen flask, and 21.5g. of monochloracetic acid in 300 cc. dry benzene added. A gelatinous precipitate of sodium chloracetate resulted, with an evolution of heat.

The mixture was then heated at 100° for twenty four hours, after which it was extracted twice with water to dissolve out the sodium menthoxyacetate. Any menthol remained in the benzene solution, and was recovered later. The aqueous extract was then acidified with dilute sulphuric acid, and the menthoxyacetic acid was precipitated as a yellow oil, which was extracted with ether. The extract was washed with water and dried over sodium sulphate. On removal of the ether, menthoxyacetic acid was obtained as a dark brown syrup, which was distilled in vacuo at 13 mm., and passed over/

over at 178-180°. $[\alpha]_D^{17}$ -93.5°(alcohol)

Preparation of sodium l-menthoxyacetate.

107g. of l-menthoxyacetic acid were dissolved in 150 cc. absolute alcohol, and to this was added a solution of 11.5g. sodium in 100 cc. alcohol. The sodium l-menthoxyacetate separated out almost at once in a white mass, and soon the contents of the vessel became solid. The material was collected on a filter, and washed with a little alcohol. It was then dried on a water bath, and powdered. The yield of salt was almost theoretical.

$[\alpha]_D^{16}$ -70.01° $[M]_D$ -165.2°(water)

Piperityl l-menthoxyacetate.

25g. of the addition-compound, 50g. sodium l-menthoxy-acetate, and 100 cc. absolute alcohol were stirred together for 24 hours at room temperature. Water was added to dissolve any unchanged sodium salt, and the mixture extracted with ether. Any menthoxyacetic acid was subsequently recovered from the aqueous solution by acidification, and extraction with ether. The former ether extract was dried, and the ether removed by distillation. A brown oil was obtained, which was steam-distilled to remove terpene. The

The residue in the flask was extracted with ether, and dried. Evaporation of the ether yielded a dark brown syrup (1.9g.), which was shown to be menthoxyacetic acid, by its solubility in alkali, and was no doubt produced by hydrogen chloride, from decomposition of the addition-compound, acting on the sodium menthoxyacetate.

Piperityl l-menthoxyacetate.

25g. of the addition-compound, 50g. sodium l-menthoxyacetate, and 140 cc. glacial acetic acid were stirred together for twenty eight hours at room temperature. 500 cc. water were then added, and the mixture extracted twice with ether, using 200 cc. each time. The extract was shaken with dilute sodium carbonate solution to remove menthoxyacetic acid, and finally with water. Evaporation of the ether from the dried extract gave a brown oil. The menthoxyacetic acid was recovered in theoretical amount from the aqueous washings, indicating that no reaction had taken place. The nature of of the brown oil was not investigated, but was possibly unchanged addition-compound.

Preparation of Piperityl l-menthoxyacetate.

17g. of the addition-compound, 32g. silver l-menthoxyacetate, prepared by precipitation from the sodium salt, and 100 cc. alcohol were heated under reflux on a water bath for six hours. The mixture was filtered to remove silver chloride, and unchanged menthoxyacetate, and the filtrate evaporated under diminished pressure. A brown oil remained, which was steam-distilled to remove terpene, and the non-volatile part extracted with ether. Removal of the ether from the dried extract, gave a dark brown syrup, which distilled at 180°/13mm., showing it to be l-menthoxyacetic acid.

Owing to the instability of the addition-compound, it seems impossible to obtain esters of piperitol in this way.

Attempts to prepare piperityl esters by Ester Interchange.

Preparation of Ethyl l-menthoxyacetate.

48g. of l-menthoxyacetyl chloride, and 100 cc. absolute alcohol were heated under reflux on a water bath for three hours. Excess alcohol was distilled away under diminished pressure, and the product, ethyl l-menthoxyacetate, remained. This was redistilled in vacuo, and boiled at 147-8°/12 mm. Yield: 46g. n_D^{12} 1.4585, $[\alpha]_D^{16}$ -87.9°, M_D -212.7°

Analysis:

Found:	C	69.5	H	10.4 %
Calc. for $C_{14}H_{26}O_3$		69.4	H	10.8 %

Piperityl l-menthoxyacetate by Ester Interchange.

24g. ethyl l-menthoxyacetate, and 15g. piperitol were placed in a flask with about 0.2g. sodium. The flask was heated in an oil bath at 120° for four hours, but no ethyl alcohol was evolved, and soon the mixture was seen to contain globules of water, owing to decomposition of the piperitol. The cold reaction mixture was dissolved in ether, and shaken with water to remove alkaline material. Evaporation of the dried extract gave an oil, which was separated into three fractions by distillation under diminished pressure.

Fraction (i) b.p. 64-80°/12 mm.

" (ii) b.p. 90-110°/11 mm.

" (iii) b.p. 145-150°/12 mm.

Fraction (i) had an odour of phellandrene, and was no doubt produced by dehydration of the piperitol at the high temperature.

Fraction (ii) seemed to consist of piperitol, while fraction (iii) was ethyl l-menthoxyacetate.

Piperityl l-menthoxyacetate by Dimethylaniline method.

17g. of the hydrogen chloride addition-compound of phellandrene, 43g. menthoxyacetic acid, and 50 cc. dimethylaniline were mixed in a flask, and allowed to stand at room temperature for two days. The mixture was then dissolved in ether, and shaken several times with dilute sodium hydroxide to remove menthoxyacetic acid, and with hydrochloric acid to remove dimethylaniline. After washing with water, the extract was dried over sodium sulphate, and the ether removed. A dark-brown oil was obtained, which consisted of unchanged addition-compound. No crystalline product was isolated.

Piperityl 3:5-dinitrobenzoate by Dimethylaniline method.

17g. of the addition-compound, 42g. 3:5-dinitrobenzoic acid, and 100 cc. dimethylaniline were stirred together at room temperature for two days. The reaction mixture was then dissolved in ether, and shaken twice with dilute sodium hydroxide to remove dinitrobenzoic acid, and also to decompose any dimethylaniline dinitrobenzoate which might have been formed. Extraction with dilute hydrochloric acid was then carried out to remove dimethylaniline. After washing with water, the extract was dried, and the ether evaporated. The product was a brown oil, and there was no trace of any crystalline material. The oil was unchanged addition-compound, and was completely volatile in steam, indicating its terpene nature.

Interaction of the addition-compound with sodium oxalate.

25g. of the addition-compound were shaken with a solution (500 cc.) of oxalic acid (56g.) and sodium hydroxide (8.8g.) in water. After three days shaking, the mixture was extracted with ether, washed with sodium carbonate, and finally with water. After drying, and removing the ether, a pale yellow oil was obtained. This was steam-distilled, and found to be completely volatile. No solid product was obtained.

Preparation of Triphenylmethyl-piperityl ether.

7.6g. piperitol, 7g. triphenylchloromethane, and 10cc. dry pyridine were heated in a stoppered flask for two hours on a boiling water bath. The mixture was then poured into water, and extracted with chloroform, the extract being washed with dilute hydrochloric acid, water, and dried over sodium sulphate. The chloroform was removed by distillation, and a yellow oil was obtained, from which crystals separated. These crystals were shown to be triphenylcarbinol, by a melting point determination. In order to separate all the triphenylcarbinol, the oil was dissolved in light petroleum in which the carbinol is insoluble, and was precipitated. After removing the petroleum by distillation, the oil was s steam-distilled to remove terpene, and the residue in the flask extracted with chloroform. Evaporation of the dried extract yielded a yellow syrup(3.17g.), which was dissolved in a little alcohol, and placed in a refrigerator. After several weeks, some crystals were obtained. These were recrystallised from alcohol, and melted at 132-133^{0}.
The yield of recrystallised product was 0.25g.

Analysis:

Found:	C	87.9,	H	8.1 %
Calc. for $C_{29}H_{32}O$	C	87.9,	H	8.1 %

EXPERIMENTAL SECTION.

PART II.

Attempts to prepare Thymol from Phellandrene.

Attempts to prepare Δ^6-Menthenone-3 from Piperityl Acetate.

Experiments on the production of thymol from phellandrene.

Preparation of Bromo-hydroxy-l-α-phellandrene.

20g. of l-α-phellandrene, having a specific rotation of -82.2°, were placed in a large flask containing 1 litre of water, and the mixture subjected to vigorous stirring. 24g. bromine in aqueous potassium bromide solution were then added drop by drop, and decolourisation took place almost immediately. A heavy oil separated, which was dissolved in ether, and dried over sodium sulphate. Evaporation of the ether gave a brown oil (30g.) , which was distilled in vacuo. Decomposition took place even in a high vacuum, with liberation of hydrogen bromide and water.

A titrimetric estimation of the amount of hydrogen bromide in the aqueous liquid, after extraction of the oil, indicated an almost complete conversion of the phellandrene to the bromo-hydroxy-compound.

Hydrolysis of Bromo-hydroxy-l-α-phellandrene.

60g. of phellandrene were converted to the bromo-hydroxy-compound, as described above, and the oily product of the reaction separated from the aqueous layer. This material was boiled for two hours with 24g. potassium hydroxide in 200 cc. of 60% alcohol. The reaction mixture was poured into water, and extracted with ether. After drying, and removing the ether, 86g. of a brown oil were/

were obtained. This was distilled under diminished pressure, and yielded the following fractions:

Fraction (i) b.p. 60-65°/10 mm., 42.5g.

" (ii) b.p. 80-98°/10 mm., 12.8g.

" (iii) b.p. 60-80°/ 0.5 mm., 22g.

Fraction (iii) showed signs of decomposition, and was therefore distilled in a high vacuum.

5g. samples of each fraction were treated with p-nitrobenzoyl chloride in pyridine, but no crystalline ester was isolated.

A Lassaigne test was carried out on Fraction (iii), and the presence of bromine was confirmed, indicating that hydrolysis was incomplete. A test sample of the fraction was therefore hydrolysed for four hours with a 50% excess of alcoholic potash, and the product still contained halogen. The bulk of the fraction (12g.) was therefore treated with 5.4g. potassium hydroxide, 100 cc. alcohol, and 15 cc. water, and boiled for eight hours. The product was purified by distillation in a high vacuum, and was found to contain bromine.

Even after this drastic treatment, hydrolysis was still incomplete, but it was decided to oxidise the product, in the hope that some hydrolysed material was present.

Oxidation of the hydrolysis product of Bromo-hydroxy-phellandrene.

The product of hydrolysis described above was oxidised by shaking with Beckmann's chromic acid mixture, until no further rise of temperature occurred. The reaction mixture was poured into water, and extracted with ether. The extract was washed with dilute alkali, water, and dried. Evaporation of the ether yielded a brown oil, which was insoluble in alkali. Acidification of the alkaline washings gave no oily separation, indicating that no phenolic material was present.

The attempted conversion of phellandrene to thymol, therefore, does not appear to be possible by this method.

Experiments on the bromination of piperityl acetate.

20.8g. of piperityl acetate were dissolved in 60 cc. of absolute alcohol, and 5.4 cc. bromine dropped into the solution, the flask being immersed in cold water. Decolourisation took place rapidly, and when all the bromine had been added, the mixture was treated at once with 19g. potassium hydroxide in 130 cc. of alcohol, and heated under reflux for one hour. The reaction mixture was poured into water, and the oil extracted with ether. After drying, and removing the ether, a brown oil remained, which was distilled under diminished pressure, and the following fractions collected:

Fraction (i)

b.p. to 105°/13 mm. 2.2g., n_D^{22} 1.4775

Fraction (ii)

b.p. 106-110°/13 mm. 2.8g., n_D^{22} 1.4765

Fraction (iii)

b.p. 120-127°/13 mm. 7.1g., n_D^{22} 1.4793

1.5g. of each fraction were treated with 2g. of semicarbazide hydrochloride, and 3g. of crystalline sodium acetate in alcohol, and heated under reflux for one hour. The products were obtained by pouring into water, and adding ammonia until alkaline. All three products were oils, but that from fraction (ii) crystallised after some time, and was recrystallised from alcohol. The melting point was 218°, corresponding to the semicarbazone of piperitone. The yield

yield of recrystallised material was 0.034g.

Even after standing for several weeks, the other two products did not crystallise.

EXPERIMENTAL SECTION.

PART III.

Preparation of N-methylated Piperitylamines.

Preparation of Piperitone Azine.

(Read and Storey, J., 1930, 2770)

162g. of finely powdered hydrazine sulphate were added gradually to a cold solution of 100 g. of sodium hydroxide in 100 cc. of water, with cooling and shaking during the addition. 400 cc. methylated spirit were then added, and the mixture heated to boiling on a water-bath. 152g. of piperitone were added, and the heating continued under reflux for eight hours. After standing over-night, the mixture was filtered, and the residue of sodium sulphate washed with methylated spirit. The filtrate was steam-distilled to remove alcohol and unchanged piperitone, and the syrupy residue extracted with ether, and dried over sodium sulphate. Removal of the ether gave a syrup, which on heating in a boiling water bath, lost water, and became darker in colour.

This syrupy product was used for reduction to piperitylamine, as described below.

Reduction of piperitone azine.

70g. of piperitone azine were dissolved in 300 cc. of glacial acetic acid in a 2-litre flask, fitted with a reflux condenser, and a mercury-sealed stirrer. The flask was immersed in cold water, and stirring commenced, after which 75g. of pure zinc powder was added. After stirring for half an hour, a further 25g. of zinc powder, and 50 cc. of/

of glacial acetic acid were added. After two hours, the water bath was gradually heated to boiling, and kept at this temperature for one hour. 500 cc. of hot water were then added, and the mixture filtered immediately, the unchanged zinc being washed with hot water. The filtrate was carefully basified with a concentrated solution of sodium hydroxide, and steam-distilled. The oily layer of the distillate was separated, and acidified with hydrochloric acid to dissolve the piperitylamine, after which it was extracted with light petroleum to remove piperitone. The piperitylamine was obtained from the acid solution by basifying, and extracting with ether. After drying over solid potassium hydroxide, and evaporating the ether, piperitylamine remained as a brown oil. The yield of crude product varied in different preparations, being anything between five and twenty grams.

A considerable quantity of zinc was recovered, and this was not pyrophoric as was found in previous work.

The piperitylamine was redistilled in an atmosphere free from carbon dioxide, and passed over at 96-98°/15 mm. The material was optically inactive.

Reduction of piperitone azine using magnesium.

60g. of piperitone azine were dissolved in 260 cc.of glacial acetic acid, and 100 cc. alcohol, in an apparatus similar to that used in the previous experiment. 35g. of magnesium powder were added in very small amounts, and a vigorous reaction ensued, the reaction vessel requiring to be cooled in ice water. The addition of the magnesium required about two hours, after which the water bath was heated to boiling for one hour. The reaction mixture was treated in the same manner as the previous preparation. The yield of basic material, in this case was much greater being about 30g. On distillation, however, the material passed over at $84^{\circ}/14$ mm., showing it to be menthylamines, produced by reduction of the double bond in the piperitylamine molecule.

Attempts to increase the yield of piperitylamine.

Reduction of the azine by a mixture of zinc and iron powders in glacial acetic acid, gave only a small yield of piperitylamine, comparable with that obtained when zinc alone was used.

Catalysis of the reduction mixture with copper sulphate, and platinum chloride gave similar results, a considerable quantity of zinc being left undissolved.

Resolution of dl-piperitylamine by d-tartaric acid.

130g. of d-tartaric acid were dissolved in a hot mixture of 900 cc. methylated spirit, and 450 cc. water. To this solution was added a hot solution of 134g. of redistilled dl-piperitylamine in 275 cc. of methylated spirit. The flask containing the basic solution was then rinsed out with 183 cc. of methylated spirit, which was added to the mixed solutions. After standing over-night, a mass of colourless crystals was obtained, consisting of l-piperitylamine hydrogen d-tartrate. The yield of the crude material was 70g., the specific rotation being -41.44° (c=1.0015, water).
After two recrystallisations from hot water, the salt was obtained in a pure state, having a specific rotation at 18° of -49.5°(c=1.2025, water). This value is somewhat higher than that quoted by Read and Storey (-43°, loc. cit.).
The yield of the recrystallised material was 50g.

The mother liquors containing the crude d-piperityl-amine were retained, and used later in testing the methylation method of Read and Hendry. (vide Methylation of piperitylamine)

Experiments on the Methylation of piperitylamine.

Methylation by the method of Read and Hendry (Ber., 1938, 2544)

Crude d-piperitylamine was obtained from the mother liquors of the optical resolution, redistilled, and used as described below.

40g. of crude d-piperitylamine, were heated with 12g. of ethyl chloracetate for four hours at 130° in a flask fitted with a reflux air-condenser, carrying a soda-lime tube. The reaction mixture was then heated under reflux on a water bath for two hours with 300 cc. of 5% methyl alcoholic potassium hydroxide, in order to saponify any piperityl-glycine ester. The unchanged piperitylamine was then removed by steam-distilling the alcoholic solution, and recovered as the hydrochloride. The alkaline residue in the distillation flask was then concentrated on a water bath to about 80 cc., cooled in ice water, and saturated with carbon dioxide. No piperityl glycine was precipitated, but some oily material was obtained, which showed no tendency to crystallise.

It seemed, therefore, that this method was not suitable for the methylation of piperitylamine, although being quite satisfactory for the menthylamines.

Methylation of d-neo-menthylamine by the Methyl Iodide method.

This experiment was carried out to test the method of methylation, before applying it to l-piperitylamine.

30g.(1 mol.) of d-neo-menthylamine in 90 cc. of dry methyl alcohol were heated gently under reflux for 30 minutes with 12 cc.(1 mol.) of methyl iodide. 4.5g.(1 atom) of sodium in 50 cc. dry methyl alcohol were then added, and heating continued for 30 minutes. A further 6 cc. of methyl iodide were added, and the mixture heated for 30 minutes. Finally 6 cc. methyl iodide, followed by 4.5g. sodium in 50 cc. dry methyl alcohol were added, and heating continued for a further 30 minutes. The reaction mixture was steam-distilled, the distillate made faintly acid with dilute hydrochloric acid, and evaporated to dryness on a water bath. The last traces of water were removed from the solid by stirring with small amounts of alcohol, and evaporating to dryness. The mixed hydrochlorides weighed 36 g., and had $[\alpha]_D$ +16.4° (c=2.045, water). The values of $[\alpha]_D$ for the hydrochlorides of the N-methyl- and N-dimethyl-d-neo-menthylamines are +16.7° and +15.3° respectively, indicating that the product from this reaction is probably mainly the mono-methyl base.

Separation of the two bases was carried out by acetylation, and benzoylation.

Acetylation of the mixture of methylated bases.

15g. of the mixed hydrochlorides were basified, and the free bases extracted with ether, and dried over sodium sulphate. This extract gave, on evaporation, 12g. of basic material, which was acetylated by boiling gently with 10 cc. of acetic anhydride for 30 minutes. The reaction mixture was poured into dilute sodium hydroxide solution to remove free acid, and extracted with ether. The ethereal solution was then extracted three times with dilute hydrochloric acid to remove N-dimethyl-d-neo-menthylamine. Acetyl-N-methyl-d-neo-menthylamine remained in the ether, and was obtained as a mobile syrup (8g.) on evaporating the dried solution. The acetyl compound was redistilled under diminished pressure.

b.p. 142°/7 mm., 7.2g., n_D^8 1.4890, $[\alpha]_D^{15}$ +34.7° (c=2.077, $CHCl_3$)

Analysis:

Found:	C	73.5	H	11.8 %
Calc. for $C_{13}H_{25}ON$	C	74	H	11.8 %

The N-dimethyl-d-neo-menthylamine was obtained from the acid washings by basifying, and extracting with ether. The crude product (6g.) was redistilled under diminished pressure.

b.p. 87°/8 mm., 5g., n_D^{14} 1.4650, $[\alpha]_D^{17}$ +53° (c=3.108, $CHCl_3$)

Benzoylation of the mixture of methylated bases.

20g. of the mixed hydrochlorides were benzoylated in aqueous solution by shaking with 18 cc. benzoyl chloride, and keeping the mixture faintly alkaline throughout. Excess benzoyl chloride was destroyed by addition of more sodium hydroxide, and the mixture extracted with ether. The ethereal solution was then extracted three times with dilute hydrochloric acid to remove N-dimethyl-d-neo-menthylamine. Evaporation of the dried ether solution gave benzoyl-N-methyl-d-neo-menthylamine as a pale yellow syrup (26g.), which crystallised partly on addition of a little methyl alcohol, and immersion in freezing mixture. The crystalline material was collected on a filter, and washed with a little ice-cold methyl alcohol, and had melting point 67°, which agreed with that quoted by Read and Hendry (loc. cit.).

Basification of the acid washings, and extraction with ether gave a further quantity of N-dimethyl-d-neo-menthylamine, which was redistilled as before, giving 7g. of pure material.

$[\alpha]_D^{16}$ +53.8° (c=2.087, $CHCl_3$)

Preparation of d-neo-menthyl-trimethylammonium iodide.

2g. of N-dimethyl-d-neo-menthylamine, 5 cc. methyl iodide, and 5 cc. dry methyl alcohol were gently heated under reflux for one hour. Methyl alcohol and excess methyl iodide were distilled away, and the quaternary ammonium iodide was obtained as a white mass. Recrystallisation from acetone gave the pure material, which melted at 161°.

$[\alpha]_D^{15}$ -20°(c=2.069, water).

These values are also in agreement with those quoted by Read and Hendry (loc. cit.)

Methylation of l-piperitylamine.

25g. of l-piperitylamine, obtained by basifying a solution of the pure hydrogen tartrate, and redistilling the product, were methylated in the following manner.

To a solution of the base in 75 cc. of dry methyl alcohol were added 10.4 cc. of methyl iodide, and the mixture heated to gentle boiling for 30 minutes, after which a solution of 3.85g. of sodium in 60 cc. of dry methyl alcohol was added, and heating continued for a further 30 minutes. A second portion of 5.2 cc. of methyl iodide was then added, and after heating under reflux for 30 minutes, 5.2 cc. of methyl iodide and 3.85g. of sodium in 60 cc. of dry methyl alcohol were added. The reaction mixture was then heated for a further 30 minutes, and steam-distilled. The distillate was acidified with dilute hydrochloric acid, and evaporated to dryness on a water-bath. Even after stirring with alcohol, and evaporating to remove the last traces of water, the product was somewhat sticky, and it was therefore treated with sodium hydroxide, and the liberated base extracted with ether. Removal of the ether from the dried extract gave a dark brown oil (15g.), which was acetylated to separate the mono- and di-methyl bases.

Acetylation of methylated piperitylamine.

15g. of the methylated piperitylamine were boiled gently for 30 minutes with 13 cc. of acetic anhydride. The reaction mixture was shaken with an excess of sodium hydroxide solution, and the oily product extracted with ether. The ethereal solution was then extracted three times with dilute hydrochloric acid to remove N-dimethyl-l-piperitylamine.

Evaporation of the dried ether extract gave a dark brown syrup (11.7g.), which was distilled in vacuo, two fractions being obtained:

Fraction (i)	b.p. 60°/7 mm.	1.9g.
Fraction (ii)	b.p. 152°/7 mm.	8.4g.

Fraction (i) was terpene in nature, and had an odour of phellandrene. Fraction (ii) was a pale yellow syrup, which, on addition of a little methyl alcohol, and immersion in a freezing mixture, yielded some crystalline material. This was removed by filtration, and placed on porous plate in a vacuum desiccator over-night, to remove last traces of syrup. The material was recrystallised from aqueous methyl alcohol, and had melting point 111-112°.

$[\alpha]_D^{17}$ -87.9° (c=2.008, $CHCl_3$)

Analysis showed the material to be acetyl-N-methyl-l-piperityl-amine.

Found:	C 73.8,	H 10.7 %
Calc. for $C_{13}H_{23}ON$,	74.8,	11.0 %

N-dimethyl-l-piperitylamine.

The acid extract, containing the dimethyl-base, was treated with sodium hydroxide solution, and the oil extracted with ether. Evaporation of the dried extract gave a brown oil, which was distilled under diminished pressure.

b.p. 91°/ 7mm., 3.2g., n_D^{15} 1.4763, $[\alpha]_D^{18}$ -59.2°(c=2.069, $CHCl_3$)

The product was a pale yellow oil, with a basic odour, which did not appear to combine readily with atmospheric carbon dioxide, in contrast to the primary base.

Analysis showed the material to be N-dimethyl-l-piperityl-amine.

Found:	C 79.8,	H 12.6 %
Calc. for $C_{12}H_{23}N$,	79.5,	12.7 %

Hydrolysis of Acetyl-N- methyl-l-piperitylamine.

As there was not sufficient crystalline acetyl derivative, the syrupy material was used for the hydrolysis, and had a specific rotation of -79.7°(c=2.6475, $CHCl_3$)

6.2g. of the syrup were boiled with 25 cc. of concentrated hydrochloric acid for 8 hours, but very little hydrolysis took place, as there was still some undissolved syrup remaining after the heating. The mixture was therefore placed in a sealed tube with a further 25 cc. of acid, and heated at 100° for 8 hours. Basification of the reaction/

reaction mixture gave an oil, which was extracted with ether. Removal of the ether from the dried extract yielded a brown oil, which was distilled in vacuo.

b.p. 98°/9 mm., n_D^{19} 1.4729, $[\alpha]_D^{17}$ -51.04° (c=2.057, $CHCl_3$)

The yield of material was 0.5g., and some unchanged acetyl compound remained in the distillation flask. Analysis of the product showed it to be slightly impure N-methyl-l-piperitylamine.

Found:	C 73.2,	H 11.3 %	
Calc. for $C_{11}H_{21}N$	79.0,	12.6 %	

Methylation of N-dimethyl-l-piperitylamine.

1.5g. of the dimethyl base were boiled gently with 5 cc. of methyl alcohol, and 5.cc. of methyl iodide for 15 minutes. Evaporation of the solvent and excess methyl iodide gave a white solid residue of the quaternary ammonium iodide. This was dissolved in cold acetone, and the solvent allowed to evaporate at room temperature. The product, l-piperityl-trimethyl-ammonium iodide was obtained as white crystals, which melted with decomposition at 186°.

$[\alpha]_D^{17}$ -4.8° (c=2.094, water)

Analysis

Found:	C 48.3,	H 8.2 %	
Calc. for $C_{13}H_{26}NI$	48.2,	8.1 %	

EXPERIMENTAL SECTION.

PART IV.

Preparation of N-methylated d-iso-menthylamines.

Hydrogenation of l-piperitone.

Preparation of d-iso-menthone.

0.3g. of palladium chloride were dissolved in 25 cc. of water, to which three drops of dilute hydrochloric acid had been added, and the solution heated to boiling. The cooled solution was transferred to the hydrogenating bottle, and the vessel containing the palladium chloride washed with a further 25 cc. of water, this also being added. 0.5g. of gum arabic were dissolved in 200 cc. of boiling water, and the cooled solution placed in the bottle. Finally, 50g. of l-piperitone(α_D^{16}-42°) were added, and the bottle placed in the machine. The bottle was then evacuated by means of a water-pump, until the liquid began to boil. After the boiling had continued for a few minutes in order to expel dissolved air, shaking was commenced, and hydrogen at a pressure of 100 lbs. per square inch admitted to the bottle. Absorption of hydrogen at this pressure was rapid, and the reaction was complete in less than half an hour.

The contents of the bottle were transferred to a separating funnel, and the bottle rinsed with ether. The aqueous liquid was extracted three times with ether, and the extracts dried over sodium sulphate. No alkali must be allowed contact with the product, owing to its ready racemisation. Removal of the ether from the dried extract gave a yellow oil.

The average yield from a number of preparations was 49g.,

and the average value of α_D +47° (l=1, homog.)

The combined products from a number of preparations were redistilled in vacuo, and passed over at 88°/15 mm. The redistilled material had α_D +48°. Since redistillation resulted in so little purification, it was decided to convert the crude material directly to the oxime.

Preparation of d-iso-menthone oxime.

The following is a typical example of the preparation of the oxime:

To 170g. of crude d-iso-menthone (α_D +48°), and 85g. of hydroxylamine hydrochloride in 170 cc. water, were added 200g. of crystalline sodium acetate in 120 cc. water in order to depress the acidity. Methylated spirit was then added until the mixture was homogeneous, about 900 cc. being required. The mixture was allowed to stand in a stoppered flask for three days at room temperature, and then most of the alcohol was removed by distillation under diminished pressure. The oily oxime was extracted from the residue with ether, and dried over sodium sulphate. Evaporation of the ether gave a viscid syrup. The yield was 202g. n_D^{12} 1.4742, $[\alpha]_D^{17}$ +26.75° (c = 2.578, EtOH)

Reduction of d-iso-menthone oxime to d-iso-menthylamine.

100g. of the crude oxime were dissolved in 800 cc. of absolute alcohol, contained in a 2-litre round-bottomed flask, fitted with an addition-tube, and reflux condenser. The flask was heated on a sand-bath until the alcohol began to boil, and then 150g. of sodium in small pieces was added. The addition of the sodium required about eight hours, and it was found necessary to add additional alcohol occasionally to prevent separation of solid sodium ethoxide. About 600 cc. of alcohol were required for this. When all the sodium had dissolved, the mixture was allowed to cool, some water added, and steam-distilled until no more oily droplets came over. The distillate was faintly acidified with hydrochloric acid, and evaporated to dryness on a water-bath. In this way 100g. of crude d-iso-menthylamine hydrochloride were obtained, having $[\alpha]_D^{15}$ +16.3° (c = 1.9535, water).

The crude material was recrystallised from a hot mixture of 700 cc. acetone, and 70 cc. methyl alcohol. The first fraction to separate consisted of pure d-iso-menthylamine hydrochloride having $[\alpha]_D^{25}$ +23° (c = 2.0645, water). Further fractions had much lower rotation values. The yield of pure material was 24g., representing about 25% of the crude hydrochloride. In all further preparations, it was found possible to obtain the pure hydrochloride in 25% yield by one recrystallisation from acetone-methyl alcohol.

Methylation of d-iso-menthylamine.

30g. of d-iso-menthylamine, liberated from 37g. of the pure hydrochloride, were dissolved in 90 cc. of dry methyl alcohol, and 12 cc. methyl iodide added. The mixture was refluxed gently for 30 minutes, and 4.5g. of sodium in 60 cc. methyl alcohol added, and heating continued for a further 30 minutes. The mixture was again heated for 30 minutes with 6 cc. of methyl iodide, and then 6 cc. methyl iodide, and 4.5g. sodium in 60 cc. methyl alcohol were added. After heating for 30 minutes, the reaction mixture was steam-distilled, the distillate made faintly acid with hydrochloric acid, and evaporated to dryness on a water-bath. The mixture of hydrochlorides so obtained weighed 36.3g., and had $[\alpha]_D^{18}$ +25.9° (c = 2.044, water).

Acetylation of methylated d-iso-menthylamine.

36g. of the hydrochloride obtained above were decomposed with alkali, and the free base extracted with ether. Evaporation of the dried extract gave 30g. of oil with a characteristic basic odour. This was boiled gently under reflux for 1 hour with 25 cc. of acetic anhydride. The reaction mixture was poured into dilute sodium hydroxide, and the oil extracted with ether. The ethereal solution was then extracted/

/extracted three times with dilute hydrochloric acid to remove N-dimethyl-d-iso-menthylamine, the acetyl-N-methyl-d-iso-menthylamine remaining in the ether. Basification of the acid extract, and extraction with ether gave the dimethyl-base. The yield of crude material was 25.12g., which was redistilled under diminished pressure.

b.p. 97°/13mm., n_D^{16} 1.4608, $[\alpha]_D^{15}$ +36.5° (c = 2.1465, $CHCl_3$), 22g.

Analysis.

Found:	C	78.8,	H 13.8 %
Calc. for $C_{12}H_{25}N$,		78.5,	13.7 %

The acetyl-N-methyl-d-iso-menthylamine was obtained as a syrup, which would not crystallise, but was distilled under diminished pressure. The crude material weighed 7.7g.

b.p. 110°/0.6mm., n_D^{14} 1.4827, $[\alpha]_D^{17}$ +33.17° (c = 1.613, $CHCl_3$), 5g.

Analysis.

Found:	C	72.6,	H 11.5 %
Calc. for $C_{13}H_{25}ON$		74.0,	11.8 %

Preparation of d-iso-menthylglycine.

40g.(2.5 Mol.) of d-iso-menthylamine, liberated from 50g. of the pure hydrochloride, were heated in an oil bath at 130°for 4 hours with 12.6g.(11 cc., 1 Mol.) of ethyl chloro-acetate. The reaction mixture was then boiled for 2 hours with 310 cc. of 5% methyl alcoholic potash, in order to saponify the menthylglycine ester. Excess d-iso-menthylamine was then removed by steam-distillation, and the residue concentrated on a water-bath to a volume of about 100 cc. On cooling in freezing mixture, and saturating with carbon dioxide, a precipitate of d-iso-menthylglycine was obtained. This was removed by filtration, and the filtrate again treated with carbon dioxide, when a further small amount of the glycine was obtained. The total yield of material was 13g. Recrystallisation from hot water gave a fibrous mass with no crystalline form. The purified product melted at 183°.

Analysis.

Found:	C	66.5,	H	10.6 %
Calc. for $C_{12}H_{23}O_2N$		67.6,		10.8 %

Preparation of N-methyl-d-iso-menthylamine.

11g. of d-iso-menthylglycine were heated in an oil-bath at 200° for 1 hour, the flask being fitted with a reflux air-condenser, and a soda-lime tube. The glycine melted, and carbon dioxide and water were produced in the reaction. The reaction mixture was cooled, dissolved in ether, and dried over sodium sulphate. Evaporation of the ether, gave a brown oil, which was distilled in vacuo.

b.p. 92°/13 mm., n_D^{16} 1.4612, $[\alpha]_D^{16}$ +21.35° (c=2.108, $CHCl_3$), 6g.

This consisted of N-methyl-d-iso-menthylamine, and was a colourless oil, possessing a pronounced basic odour.

Analysis.

Found:	C	77.2,	H	13.0 %
Calc. for $C_{11}H_{23}N$		78.3,		13.6 %

Benzoyl-N-methyl-d-iso-menthylamine.

2.5g. of N-methyl-d-iso-menthylamine were benzoylated by treatment with 6 cc. of benzoyl chloride, the reaction mixture being kept slightly alkaline throughout. Excess benzoyl chloride was destroyed by adding sodium hydroxide, and the oily product extracted with ether. Evaporation of the ether from the dried extract gave a colourless syrup(4.7g.) which was distilled in a high vacuum.

b.p. 170°/1.3 mm.

The distillate crystallised after keeping for several weeks in a refrigerator, and had m.p. 64°. The material was very soluble in all organic solvents, and could not be recrystallised. It had $[\alpha]_D^{18}$ -10.8° (c = 1.9895, $CHCl_3$)
Analysis showed the substance to be benzoyl-N-methyl-d-iso-menthylamine.

Analysis.

Found:	C	79.7,	H	9.9 %
Calc. for $C_{18}H_{27}ON$,		79.1,		9.9 %

Preparation of d-iso-menthyl-trimethylammonium iodide.

10g. of N-dimethyl-d-iso-menthylamine, 30 cc.methyl iodide, and 30 cc. dry methyl alcohol were heated gently under reflux for 1 hour. Methyl alcohol and excess methyl iodide were removed by distillation, and the solid residue of quaternary iodide recrystallised from acetone. The substance formed colourless plates, which melted at 184°.

$[\alpha]_D^{18}$ +1.97° (c = 1.5225, water), $[M]_D$ +6.4°

Analysis.

Found:	C	48.1,	H	8.6 %
Calc. for $C_{13}H_{28}NI$		47.9,		8.6 %

EXPERIMENTAL SECTION.

PART V.

d-Neoiso-menthylamine.

Preparation of Salicylidene d-neoiso-menthylamine

The crude hydrochloride which remained after all the pure d-iso-menthylamine hydrochloride had separated out was converted to the free base by addition of sodium hydroxide solution, and extraction with ether. Removal of the ether from the dried extract gave 217g. of crude menthylamines. This was treated with 146 cc. of salicylaldehyde, and the resulting salicylidene compound dissolved in chloroform and dried over sodium sulphate. Evaporation of the chloroform gave 382g. of crude salicylidene menthylamines. On recrystallisation from light petroleum, the following fractions were obtained.

(1) m.p. 110-112°, $[\alpha]_D^{17}$ +67°(c = 2.032, $CHCl_3$), 100g.

(2) 75-80°, $[\alpha]_D^{17}$ -1.2°(c = 2.095, $CHCl_3$), 50g.

(3) 80-85°, $[\alpha]_D^{17}$ +10.2°(c = 2.054, $CHCl_3$), 26g.

The first fraction consisted mainly of salicylidene d-iso-menthylamine, but the second fraction which had a slight negative rotation seemed as if it might contain some salicylidene d-neoiso-menthylamine. The second fraction was therefore recrystallised twice from light petroleum, and yielded 24g. of pure salicylidene d-neoiso-menthylamine, having $[\alpha]_D^{17}$ -18.1°(c = 2.1485, $CHCl_3$), and m.p. 99-100°. A mixed melting point taken with an authentic sample of salicylidene d-neoiso-menthylamine showed no depression.

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Report on the Thesis submitted by Mr.W.W.Cuthbertson, B.Sc. for the Degree of Ph.D.

The thesis submitted by Mr.W.W.Cuthbertson,B.Sc. for the degree of Ph.D. is a valuable contribution to two fields of terpene chemistry in the study of which the St.Andrews school under Professor Read have made notable additions.

The main part of the thesis is concerned with the chemistry of the alcohol,piperitol, and related products. Although piperitol occurs in nature it is only found in limited quantity and the methods so far evolved for its preparation in the laboratory have been so laborious that detailed study of its properties has not been possible. Mr.Cuthbertson has now worked out details for its preparation in quantity which invlove only a two stage reaction from the readily available hydrocarbon,l-α-phellandrene. The alcohol was not stereochemically pure but it was, after many failures,characterised by the preparation

of a crystalline ether which is an important advance. It is unfortunate that the work described in the thesis was completed prior to the recent American publication on the use of hydrogen nitrophthalates for the identification of terpene alcohols. If this derivative of piperitol could be prepared it might, through suitable alkaloidal salts, result in the preparation of the stereochemically pure piperitols.

It is disappointing that the ingenious experiments for the conversion of l-α-phellandrene to thymol were unsuccessful since they might have led to results of considerable technical importance.

The third and fourth sections of the thesis deal with the preparation and properties of the methyl and dimethyl derivatives of piperitylamine and the menthylamines. This work, which involved very considerable experimental difficulties, would appear to have been carried out in an extremely able manner. It completes the series of the methyl and dimethyl menthylamines with the exception of the derivatives of d-neoisomenthylamine.

The thesis is extremely well presented and gives

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in a concise manner an account of work of much experimental difficulty which required considerable originality for its successful conclusion. It would suggest that the candidate possesses considerable technical ability and he should in the future contribute to the advancement of science.

I recommend that the candidate be awarded the degree of Ph.D. and in view of the merit of his thesis I do not consider that any further examination, either written or oral, is necessary.

(J.L.Simonsen)

8th February 1946