I. The Reversibility of the Rearrangement of o-Hydroxy Sulphones.

II. A Synthesis of some Azulene Derivatives.

T H E S I S

presented for the degree of

Doctor of Philosophy

by

ROBERT REID COATS, B.Sc., A.I.C.,

at the

University of Glasgow.

April, 1941.

I N D E X

PART I. THE REVERSIBILITY OF THE REARRANGEMENT OF O-HYDROXY SULPHONES.

PART II. A SYNTHESIS OF SOME VETIVAZULENE DERIVATIVES.

PART I.

THE REVERSIBILITY OF THE REARRANGEMENT OF o-HYDROXY SULPHONES.

PREFACE.

The alkali derivatives of methylene di-β-naphthol, described by Smiles as covalent, seemed to afford a readily accessible class of substances containing an unusual form of water of crystallisation.

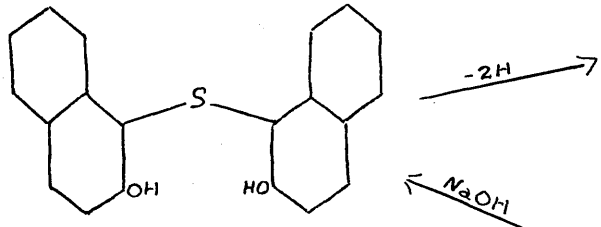
In this connection, the idea of alkali metal covalency, applied by Smiles to include the mechanism of the o-hydroxy diphenyl sulphone rearrangements, was considered. In testing (and incidentally disproving) this, it was observed that many of these rearrangements are reversible, and with the examination of these the first part of this thesis is concerned.

In the meantime, an improved technique for the preparation of the alkali derivatives of methylene dinaphthol had been developed by Dr. D. T. Gibson, and this enabled their covalent character to be tested directly by conductivity. They were, in fact, found to be conducting.

HISTORICAL INTRODUCTION.

The work on the rearrangement of the hydroxy sulphones arose out of an investigation by Warren and Smiles[1] into the constitution of iso-β-naphthol sulphide.

Henriques[2] observed that when 2-naphthol-1-sulphide (I) is oxidised with alkaline ferricyanide, it loses two atoms of hydrogen and yields a dehydro-sulphide. On reducing this substance, he obtained not the original sulphide, but an 'iso'-β-naphthol sulphide which could be converted back into the sulphide (I) under the influence of alkali.



Dehydro-sulphide

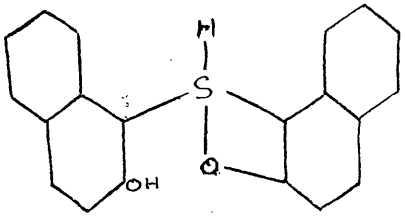
+ 2H

(I)

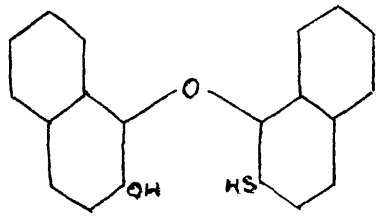
iso-β-naphthol sulphide

Warren and Smiles, rejecting the structure (II) put forward by Lesser and Gad[3] for the iso-sulphide, proposed and confirmed the structure (III), at the

same time showing the rearrangement to be intramolecular.



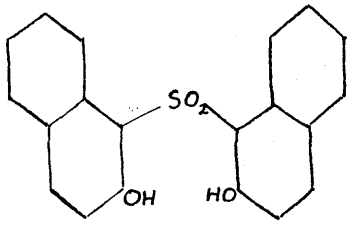
(II)



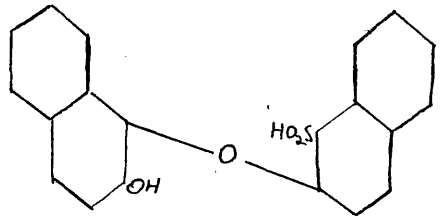
(III)

In a subsequent publication[4], Warren and Smiles showed that the oxidation of the thiol (III) to the corresponding sulphinic acid restrained the rearrangement in alkali, thus proving the negative character of the sulphur to be of fundamental importance.

The rearrangement was regarded by Warren and Smiles[5] as a direct displacement of oxy-naphthol from the positive α-carbon atom by the more negative thiol ion, the positivity of the α-carbon atom being increased in this case by the tautomeric character of the β-hydroxyl, and they decided that, in the case of 2-naphthol-1-sulphone (IV), since this sulphur is now in a more positive state than the β-hydroxyl, the reverse type of change might be expected to occur with the formation of the sulphinic acid (V).

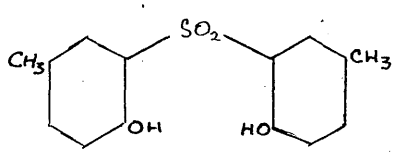


(IV)



(V)

They found that with one molecule of alkali at 150° the rearrangement did, in fact, take place and showed that while 6-bromo-2-naphthol-1-sulphone behaved similarly, p-cresol sulphone (VI), and the mono-methyl ether of (IV) showed no rearrangement.

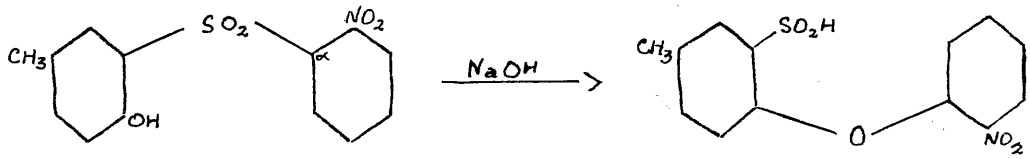


(VI)

The failure of these last two sulphones to rearrange indicated the necessity of the positive character of the α -carbon atom.

This rearrangement was regarded as a direct displacement of sulphonyl from the positive α -carbon atom by the more negative β -hydroxyl, accompanied by the migration of a proton in the reverse direction.

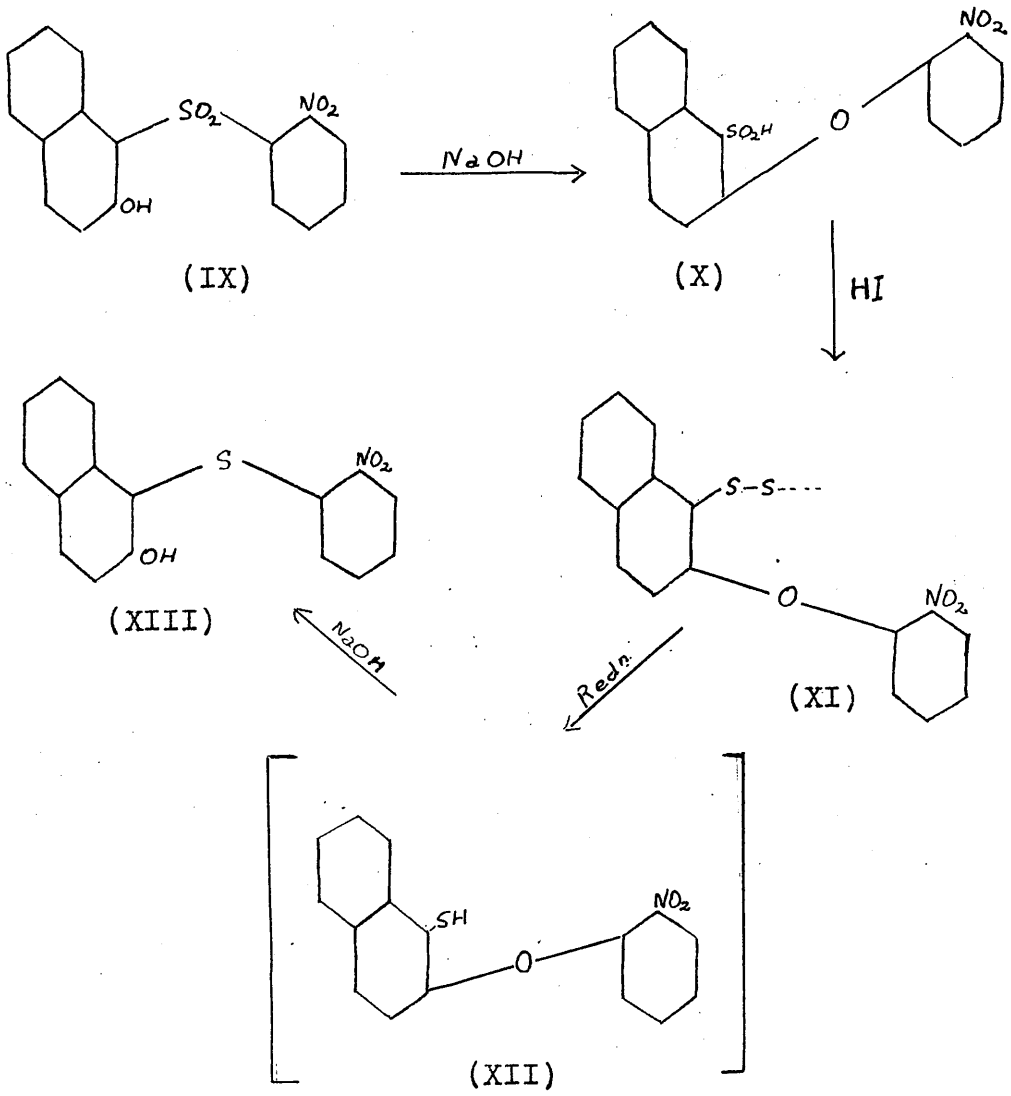
Further experiments were made to justify this view[6] and the rearrangement proved to be of wide occurrence. Thus, in the sulphone (VII), the hydroxyl is ortho to the sulphonyl group and the α-carbon atom is positive on account of the electron attracting nitro group in the ortho position. In accordance with the above view, this sulphone was found to undergo rearrangement, the change to the sulphinic acid (VIII) taking place slowly but smoothly at 15° in presence of one molecule of alkali.



(VII) (VIII)

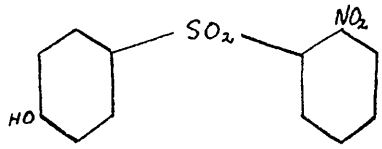
The sulphone (IX) was also investigated and was found to rearrange to the sulphinic acid (X). In both of these cases (VII and IX) it was demonstrated that the shift of o-nitrophenyl from sulphur to oxygen could be reversed on interchanging the relative electronic states of the two atoms by reduction of the sulphinic acid to mercaptan. Thus the disulphide (XI), on reduction in alkaline solution, gave the thiol (XII), which was not isolated but immediately suffered rearrangement, giving

the expected sulphide (XIII). By this means the complete cycle (IX⟶X⟶XIII⟶IX) could be followed.



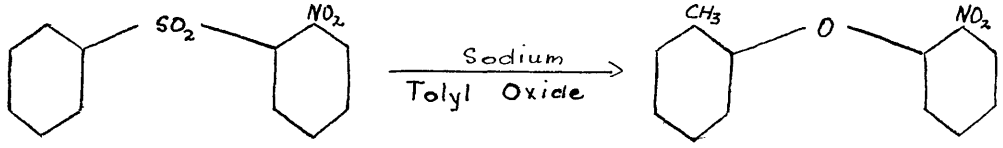
In a subsequent paper[7] Levi and Smiles described several additional points in connection with this rearrangement. They found that the p-hydroxy sulphone (XIV) would

not rearrange, but was hydrolysed to the o-nitro phenol, showing the importance of the spacial position of the hydroxyl group.



(XIV)

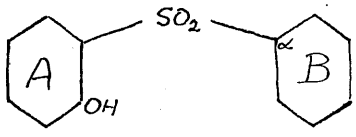
They further deduced that the rearrangement should take place inter-molecularly, and in accordance with this view, it was found that the benzene-sulphonyl group of (XV) could be displaced by sodium tolyl oxide, giving the o-nitrophenyl-o-tolyl ether (XVI).



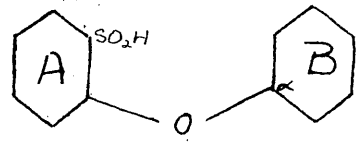
(XV) (XVI)

Up to this stage the work on the rearrangement of the hydroxy sulphones had been purely quantitative, and for a further study of the factors influencing the rearrangement, a more accurate method of measuring the speed of the reaction was required. A suitable colorimetric

method was devised by Kent and Smiles[8]. The various sulphones of the type (XVII) were dissolved in alkali under standard conditions of temperature, molecular dilution, etc., and the time taken for the intensely red solutions to change to the pale yellow of the corresponding sulphinic acids (XVIII) were noted. These times gave a comparative measure of the rate of change.



(XVII)



(XVIII)

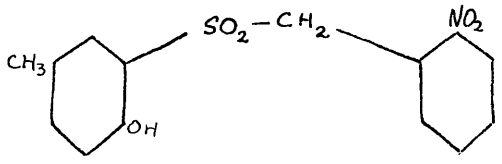
In the following table are given the times (in minutes) for completion of the rearrangement in N/15 solution at 50°. Under A and B are given the substituents in the parent sulphone (XVII).

	A	B	1.25 mols aq. NaOH	1.25 mols NaOEt in EtOH
1)	5-Methyl	2-Nitro	315	240
2)	3:5-Dimethyl	2-Nitro	93	61
3)	5:6-Benzo	2-Nitro	5	$2\frac{1}{2}$
4)	5-Hydroxy	2-Nitro	125	-
5)	5-Methoxy	2-Nitro	360	-
6)	4-Hydroxy	2-Nitro	420	-
7)	5-Methyl	4-Chlor 2-nitro	125	-
8)	5-Methyl	2:4-Dinitro	Very rapid with hydrolysis	
9)	5-Chloro	2-Nitro	Thioxin formation	
10)	5-Methyl	3-Nitro	No rearrangement.	

As a result of these and previous experiments, it was evident that the chief conditions controlling the process were:-

1) The close proximity of the oxygen atom to the α-carbon atom (for p-hydroxy sulphones do not rearrange).
2) The positive character of the α-carbon atom, increased positivity being favourable to the change (dinitro derivatives rearrange much faster than mononitro).
3) The capacity of the oxygen atom to act as a donor of electrons.

4) The character of the medium as expressed by its tendency to remove a proton from the hydroxyl (alcoholic alkali is better than aqueous alkali).



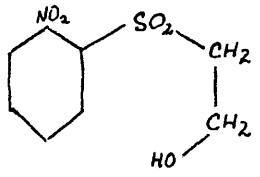
(XIX)

The effect of (2) was also shown by the fact that the 2-nitrobenzyl sulphone (XIX) was inert.

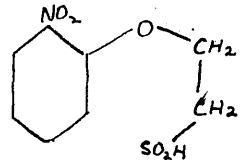
The effect of (3) is seen from an examination of the result of varying the substituents in A, these being interpreted in terms of their influence on the 2-hydroxyl group as a source of electrons.

Following on from this, it became clear that if this interpretation of the part played by the hydroxyl group was correct, a sulphone such as (XX), containing an aliphatic hydroxyl group should be even more active than the naphthol derivative (No.3 in table).

Under the usual conditions, this sulphone yielded the sulphinic acid (XXI) so rapidly that measurement of the speed was not possible.

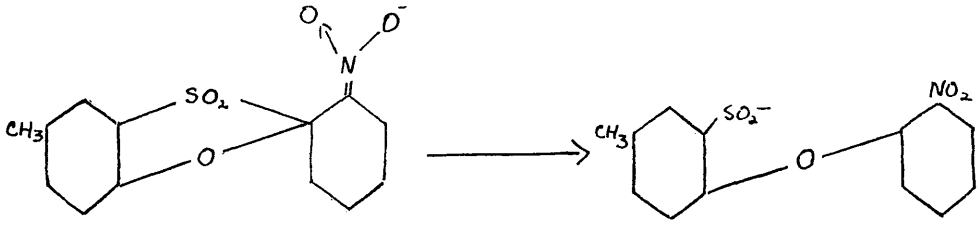


(XX)



(XXI)

A mechanism involving a nitronic ion has been suggested to explain the ready rearrangement of the o-nitrophenyl sulphones. This postulates the intermediate formation of an unstable quinonoid nitronic ion, e.g., (XXII), in which the intramolecular migration of an electronic charge produces the sulphinic acid (XXIII).

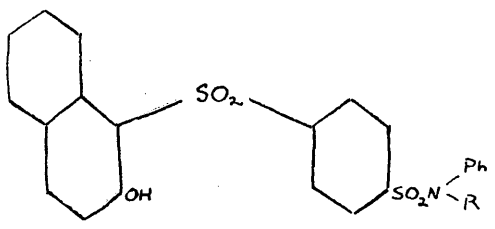


(XXII) (XXIII)

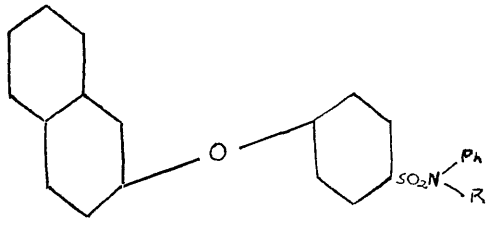
Some evidence for this theory is provided by the colour change during rearrangement. The colourless sulphones give deep red solutions in alkali, and during rearrangement this colour fades to the pale yellow of the sodium sulphinates.

Further evidence of the probability of this

mechanism was obtained by a study of the p-sulphonyl sulphones by Warren and Smiles[9]. It was found that sulphones of the type ((XXIV);, R = H or CH_3) undergo rearrangement at 150° with one molecule of alkali to give the ether (XXV) with loss of sulphur dioxide.

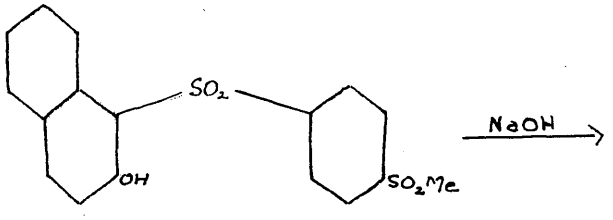


(XXIV)

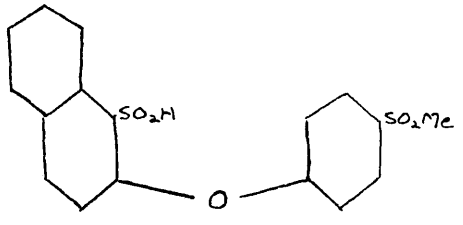


(XXV)

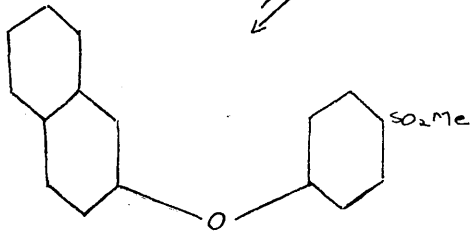
The sulphone (XXVI) behaved similarly, giving the ether (XXVIII), but in presence of excess alkali the sulphinic acid (XXVII) survived.



(XXVI)

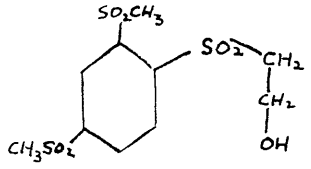


(XXVII)



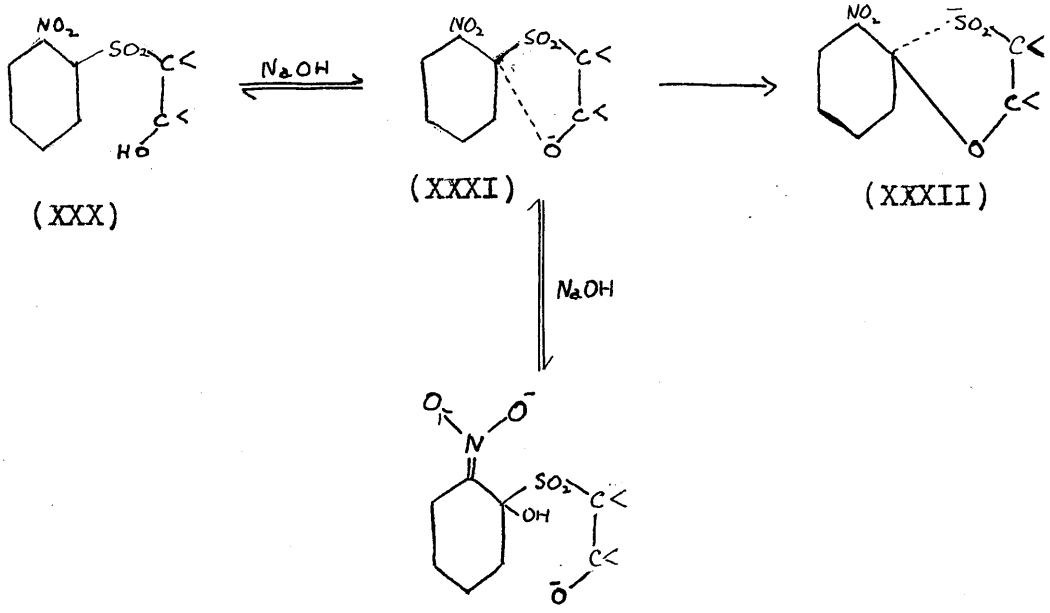
(XXVIII)

In these sulphones, the α-carbon atom is positive on account of the sulphonyl group in the para position, and therefore no mechanism of the type available in the o-nitro sulphones is possible. It was therefore concluded that while a mechanism of the type discussed is not essential to the rearrangement, it may contribute towards the facile rearrangement of the o- and p-nitro sulphones, and the relatively powerful conditions required for sulphones like (IV), (XXIV) and (XXVI) may be due to the impossibility of such a mechanism in these cases.



(XXIX)

On the other hand, more recent experiments with the sulphone (XXIX), which has been shown to have a speed of rearrangement comparable to that of the corresponding dinitro derivative and which exhibited no colour during the rearrangement, have disposed Smiles to the view that the red colour is due to a nitronic ion formed in a side equilibrium, and that this has no direct influence on the speed of the rearrangement. He has accordingly suggested the following mechanism (private communication):



(XXXIII)

The main reaction is (XXX) ⟶ (XXXI) ⟶ (XXXII) in all cases. The intermediate product (XXXI) is an ionised sodium salt which is in equilibrium with the sulphone (XXX), and which, whenever the negative oxygen comes within the influence of the positive ∝-carbon atom, immediately gives the sulphinic acid (XXXII).

The coloured ion (XXXIII), formed by a side reaction, is in equilibrium with the colourless ion (XXXI) and, while not being an essential intermediate

product, may be present in considerable amount during the whole course of the rearrangement.

In the case of the aliphatic sulphones, the alcoholic character of the hydroxyl displaces the equilibrium ((XXX) $\longleftrightarrow$ (XXXI)) to the left. In addition, the much higher electron availability of the oxygen will cause an almost immediate conversion of (XXXI) to (XXXII). Thus the amount of (XXXI) (and consequently of (XXXIII)) present in the solution at any time must be very small, a fact which explains the absence of colour in the solution during the rearrangement of these sulphones.

PREPARATION OF MATERIALS.

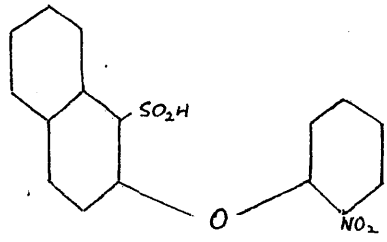
The sulphones were prepared by the following methods described by Smiles and his collaborators[6,8,10]. :-

1) By the condensation of the appropriate phenol with o-nitrophenylchlorothiol and the oxidation of the resulting sulphide with perhydrol in glacial acetic acid.
2) By the condensation of o-nitrophenylthiol with an aliphatic chlorhydrin and the oxidation of the acetylated sulphide, followed by hydrolysis of the acetyl sulphone.
3) By the condensation of an o-hydroxy phenylthiol with dinitrochlorobenzene, followed by oxidation as before.
4) By the condensation of p-benzoquinone with o-nitrobenzene sulphinic acid.

The sulphinic acids were prepared by the rearrangement of the corresponding sulphones in dilute sodium hydroxide solution. The isolation of some of these sulphinic acids in a pure state presented some difficulties owing to their marked tendency to revert to the sulphone in hydroxylic solvents. In such cases, Smiles's procedure of acidifying the alkaline solution, collecting

the precipitated sulphinic acid and recrystallising it from acetone or alcohol was found to be impracticable, and special methods were adopted to suit individual cases.

EXPERIMENTAL.

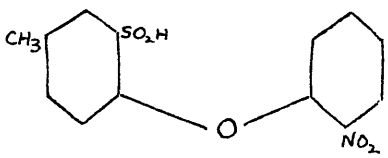


2-Nitrophenyl-1-sulphino-2-naphthyl ether.

2-Nitrophenyl-2-hydroxy-1-naphthyl sulphone was obtained by oxidising the corresponding sulphide (9 g.) suspended in glacial acetic acid (225 cc.) with perhydrol (30 cc.) at 90° till solution was complete. On cooling, the solution deposited yellow prisms which, after recrystallisation from glacial acetic acid, had m.p. 180-181°. This method gave a better yield (60%) than that of Levi, Rains and Smiles[6], using the acetylated sulphide.

A solution of the sulphone (5 g.) in sodium hydroxide solution (200 cc., 0.1N) was heated (60-70°) till the red colour had faded to pale yellow (20 min.). The cooled solution was acidified with hydrochloric acid and the white precipitate collected and dried. It was purified by dissolution in "methylated ether", the

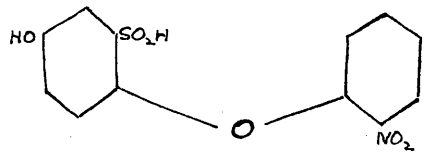
solution dried over sodium sulphate and an equal volume of ligroin (80-100°) added. Most of the ether was allowed to evaporate at room temperature and the product collected and dried. It formed white needles, m.p.116°, almost insoluble in dry ether, and gave an intense purple colour with concentrated sulphuric acid. Levi, Rains and Smiles[6] crystallised the sulphinic acid from aqueous acetone and recorded m.p. 118°. This procedure, no matter how expeditiously carried out, was found to give an almost quantitative yield of the sulphone having m.p. 180° which was not depressed by the admixture of an authentic sample of the sulphone.



2-Nitrophenyl-3-sulphino-p-tolyl ether.

A solution of 2-nitrophenyl-4-hydroxy-m-tolyl sulphone (5 g.), prepared as described by Levi, Rains and Smiles[6], in sodium hydroxide solution (250 cc., 0.1N) was heated (50-60°) for 45 minutes. The cooled solution was acidified and the precipitate collected and recrystallised from aqueous acetone. It formed white

needles, m.p. 134°, and gave an intense blue colour with concentrated sulphuric acid. Levi, Rains and Smiles[6] record m.p. 132-133°.

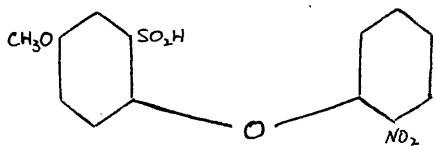


2'-Nitro-4-hydroxy-2-sulphinodiphenyl ether.

A solution of 2'-nitro-2:5-dihydroxydiphenyl sulphone (5 g.), prepared according to Kent and Smiles[8], in sodium hydroxide solution (12 cc., 2N), was maintained at 70-80° for three hours. It was acidified with hydrochloric acid, extracted with ether, and the solution evaporated to dryness. The sulphinic acid was isolated in two distinct forms. On recrystallisation from water it formed hexagonal plates, m.p. 98°. This form was soluble in dry ether, but the solution rapidly deposited felted needles, insoluble in dry ether, m.p. 98° with effervescence but without darkening. Both forms gave an intense blue colour with concentrated sulphuric acid, and each was easily convertible into the other by recrystallisation from the appropriate solvent.

The analysis of both forms indicates that they are the monohydrate of the sulphinic acid. Kent and Smiles[8] record the substance as being anhydrous and give m.p. 64°, but both forms were found to resist dehydration over phosphorus pentoxide for three weeks at 15°/½ mm., and at 45°/½ mm. the hexagonal plates decomposed to a dark green deliquescent powder in a few hours. This softened and melted at 80-90°. Except for a slight depression of melting point, the needle form was unaffected by this treatment.

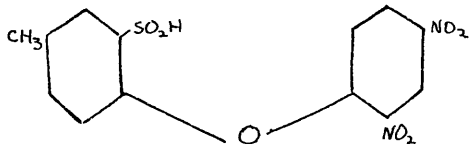
Found:	(plates)	C, 46.2;	H, 3.72;	N, 4.58%
	(needles)	C, 46.0;	H, 3.78;	N, 4.35%
$C_{12}H_9O_6NS.H_2O$ req.		C, 46.0;	H, 3.73;	N, 4.44%



2'-Nitro-4-methoxy-2-sulphinodiphenyl ether.

2'-Nitro-2-hydroxy-5-methoxydiphenyl sulphone (1 g.), prepared as described by Kent and Smiles[8], was dissolved in sodium hydroxide solution (5 cc., 2N) and the solution maintained at 60-70° for 8 hours, after

which it was acidified with hydrochloric acid. It was extracted with ether and the solution allowed to crystallise. The product had m.p. 128° and gave an intense blue colour with concentrated sulphuric acid. Kent and Smiles[8] record the m.p. 122-123°.



2:4-Dinitrophenyl-3-sulphino-p-tolyl ether.

2:4-Dinitrophenyl-4-hydroxy-m-tolyl sulphone was prepared by heating the corresponding sulphide (4 g.) with perhydrol (4.8 cc.) in glacial acetic acid (8 cc.) for 3 hours at 90°. The solution was cooled and the sulphone precipitated by the careful addition of water. On recrystallisation from glacial acetic acid it had m.p. 151.5°. Kent and Smiles[8] record the m.p. 139-140°.

Found: C, 46.16; H, 3.08; N, 8.32%

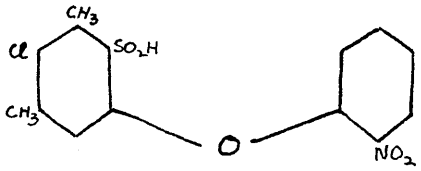
$C_{13}H_{10}O_7N_2S$ req.: C, 46.15; H, 2.96; N, 8.28%.

This sulphone (2.5 g.) was dissolved in sodium hydroxide solution (30 cc., 0.4N), the solution allowed to stand for five minutes, diluted with water and

acidified. The sulphinic acid was extracted with alcohol-free ether and precipitated from the dried solution with ligroin. It formed long white needles which, after recrystallisation from ether/ligroin, had m.p. 140°. The sulphinic acid gave no colour with concentrated sulphuric acid unless a trace of anisole was added, when a strong blue colour was obtained. Kent and Smiles[8] record m.p. 117-118°.

Found: C, 46.41; H, 3.28; N, 8.23%,

$C_{13}H_{10}O_7N_2S$ req.: C, 46.15; H, 2.96; N, 8.28%.



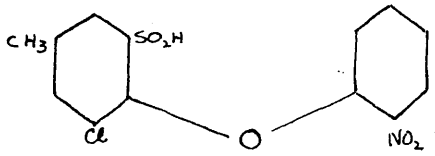
4-Chloro-2'-nitro-6-sulphino-3:5-dimethyldiphenyl ether.

5-Chloro-2'-nitro-2-hydroxy-4:6-dimethyldiphenyl sulphone, prepared as described by McClement and Smiles[10], was dissolved in dilute sodium hydroxide solution (1.5 mols), the orange-red colour fading rapidly to pale yellow. The solution was acidified and extracted with ether. On standing for a short time, the ethereal solution deposited white needles which after recrystallisation from ether had m.p. 131° and gave an intense blue

colour with concentrated sulphuric acid.

Found: N, 4.18%,

$C_{14}H_{12}O_5NClS$ req.: N, 4.10%.

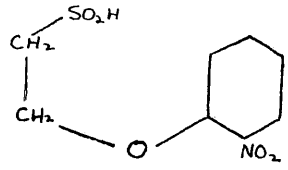


2-Chloro-2'-nitro-6-sulphino-4-methyldiphenyl ether.

A solution of 3-chloro-2'-nitro-2-hydroxy-5-methyl diphenyl sulphone (4 g.), prepared as described by McClement and Smiles[10], in sodium hydroxide solution (8 cc., 2N) was heated for 4 hours at 60°. It was acidified with hydrochloric acid and extracted with ether. The sulphinic acid was prepared from the dried solution with ligroin. The sulphinic acid was purified from unchanged sulphone by extracting with sodium acetate solution, acidifying the filtrate and extracting with ether as before. On recrystallisation from ether/ligroin, the product formed white needles m.p. 170°, and gave a strong blue colour with concentrated sulphuric acid.

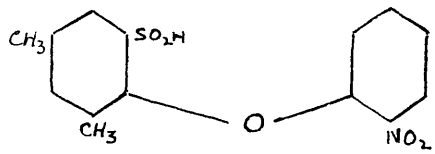
Found: C, 47.90; H, 3.33%,

$C_{13}H_{10}O_5NClS$ req.: C, 47.63; H, 3.05%.



β-o-Nitrophenoxyethane sulphinic acid.

2-Nitrophenyl-β-hydroxyethyl sulphone (3 g.), prepared as described by Kent and Smiles[8], was dissolved in sodium hydroxide solution (130 cc., 0.125N), the solution heated to 50° and acidified with hydrochloric acid. On cooling, the sulphinic acid crystallised out, sometimes in plates, sometimes in needles, m.p. 124°. Kent and Smiles record m.p. 121°.



2'-Nitro-2-sulphino-4:6-dimethyldiphenyl ether.

2'-Nitro-2-hydroxy-3:5-dimethyldiphenyl sulphone (5 g.), prepared as described by Kent and Smiles[8], was heated at 100° with sodium hydroxide solution (40 cc., 0.5N). The solution was acidified and the precipitate

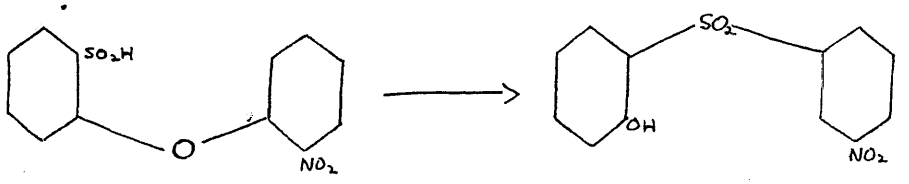
collected and recrystallised from aqueous acetone. It had m.p. 153°. Kent and Smiles record m.p. 129°.

Found: C, 54.68; H, 4.40%,

$C_{14}H_{13}O_5NS$ req.: C, 54.75; H, 4.27%.

THE REARRANGEMENTS.

Under suitable conditions, many of the sulphinic acids (XXXIV) rearrange to the corresponding sulphones (XXXV).



(XXXIV) (XXXV)

The rearrangements were carried out by heating the solutions of the sulphinic acids in aqueous acetone or alcohol, in sodium acetate or formate solution, and in standard buffer solutions.

These buffer solutions were prepared as described by Walpole[11], being chosen for their relatively great buffering action per unit volume, combined with their freedom from organic ingredients which might cause complications. Sufficient buffer solution was used to maintain the pH within 0.2 unit.

The sulphinic acids, (0.1 g) were dissolved in 50 cc. of the buffer solutions, which were then maintained at 50° in stoppered flasks. At suitable intervals the precipitated sulphone was filtered off and weighed in sinter-glass micro funnels.

These funnels were made by drawing out tubing of 8 mm. bore. A wad of glass wool was tightly packed into the top of the stem and fused in place by heating from the outside. The surface of the plug was then ground up with a piece of glass rod, and sintered by gently drawing through it the flame of a micro bunsen till the powdered glass glowed a dull red.

These funnels were found to give quick and efficient filtration of crystalline precipitates such as those of most of the sulphones. Where very fine precipitates were encountered, sinter-glass funnels prepared according to the technique of Briscoe and Lowe[12] were used.

The precipitates were dried in a vacuum desiccator over calcium chloride at room temperature.

The sulphones (except the 'aliphatic' one) gave strong orange-red colours with alkali and no colour with concentrated sulphuric acid, while the sulphinic acids gave an intense blue colour with concentrated sulphuric acid and practically no colour with alkali. Hence the purity of individual crystals could be checked and the progress of conversion in a single crystal seen under the microscope.

From the data obtained in the experiments with

buffer solutions, graphs were drawn showing the relationship between yield and time at various pH values in all cases where reversal was observed, and in one representative case the yield is graphed against the pH after various intervals of time. These graphs will be found on pages 38-40.

EXPERIMENTAL.

2-Nitrophenyl-3-sulphino-p-tolyl ether.

No reversal was observed in sodium acetate solution. In very dilute sodium formate solutions (0.2 - 3.5%), slight crystalline precipitates of the corresponding sulphone were obtained after heating (90°) for 2½ - 5 hours. The precipitate gave no colour with concentrated sulphuric acid, and after crystallisation from aqueous acetone it had m.p. 139-140° alone and 139-141° mixed with an authentic specimen of the sulphone. In more concentrated sodium formate solutions the sulphinic acid decomposed, giving uncrystallisable oils.

A solution of the sulphinic acid in aqueous acetone (30%) was refluxed for 20 hours and allowed to crystallise. The product was almost entirely unchanged sulphinic acid, but on dissolving it in sodium acetate solution, a trace of insoluble material, giving a transient red colour when spotted with sodium hydroxide solution, was isolated. The reversal therefore probably takes place, but only to a very slight extent.

In buffer solutions the reversal was regular but very slow, giving maximum yields of 30% at pH 2.7 after 500 hours and 47% at pH 4 after 800 hours. At pH 5.2

the yield after 850 hours was only 12% but was still steadily increasing.

2'-Nitro-2-sulphino-4:6-dimethyldiphenyl ether.

On heating for 5 hours in various sodium acetate solutions, the sulphinic acid gave appreciable amounts (up to 50%) of the corresponding sulphone, which was identified by melting point and mixed melting point.

After refluxing in aqueous acetone for 5 hours, the sulphinic acid was recovered apparently unchanged, but on flooding the crystals with sodium hydroxide solution under the microscope, bright orange spots developed, indicating minute crystals of sulphone.

The rearrangement was carried out in buffer solutions of pH 2.7 to pH 5.9 at approximately half unit intervals. A maximum yield of 80% was obtained at pH 4.8 after 475 hours. More acid buffers gave lower yields but a more rapid attainment of equilibrium, while in more alkaline buffers the reversal was slower and the yields poorer. (Fig. 3 p.40)

2-Nitrophenyl-1-sulphino-2-naphthyl ether.

The sulphinic acid rearranged to the sulphone very rapidly on dissolution in aqueous acetone or

aqueous alcohol. It was, in fact, found to be quite impossible to crystallise it from these solvents (c.f., Levi, Rains and Smiles, loc. cit.), the product obtained being entirely sulphone, which was identified by melting point, mixed melting point, and transient red colour with sodium hydroxide solution. It gave no trace of blue or purple colour with concentrated sulphuric acid.

When the sulphinic acid was dissolved in cold dilute sodium acetate solution, precipitation of the sulphone began in about 10 minutes and continued for 3 days. After 95-100° a yield of 84% of the sulphone was obtained in 20 minutes.

The sulphone thus obtained gave on recrystallisation from glacial acetic acid two distinct types of crystals - yellow prisms and white needle clusters. The latter appeared to change to the yellow form before melting at 180°. The melting point of a mixture of the two forms was 180°.

In buffer solutions the reversal was rapid, the yield varying from 90% at pH 2.7 in 5 hours to 85% at pH 5.2 in 15 hours.

2'-Nitro-4-hydroxy-2-sulphinodiphenyl ether.

The sulphinic acid (0.25 g.) was dissolved in

sodium formate, sodium acetate, and sodium propionate solutions (3 cc.; 0.16M). After prolonged heating (80°; 10-12 hours) approximately equal precipitates of the sulphone (ca. 25%) were obtained and identified in the usual manner.

No rearrangement was obtained in acetone or buffer solutions but slight decomposition was observed after prolonged heating (300 hours) at pH 4 and pH 2.7.

2'-Nitro-4-methoxy-2-sulphinodiphenyl ether.

No indication of the reversal of this sulphinic acid was obtained in any of the media used.

2:4-Dinitrophenyl-3-sulphino-p-tolyl ether.

On dissolving the sulphinic acid in warm aqueous alcohol, the solution rapidly turned yellow and on cooling, the sulphone crystallised out and was identified in the usual manner.

On heating a solution of the sulphinic acid in dilute sodium acetate solution (80°; 4 hours), a small amount of an unidentified substance, insoluble in dilute sodium hydroxide solution, was obtained, but no indication of reversal was observed.

No rearrangement took place within 300 hours at pH 5.2 or pH 4. At pH 2.7 rearrangement was moderately fast, while at pH 2 it was relatively very fast, a yield of 60% being obtained within one hour, although little more (5%) was obtained on further heating.

4-Chloro-2'-nitro-6-sulphino-3:5-dimethyldiphenyl ether.

On heating the sulphinic acid in sodium acetate solution for 24 hours at 90°, no sulphone was obtained; on heating in sodium formate solution, precipitation started within 5 minutes but soon stopped. It had m.p. 161-165° alone and 163-165.5° when mixed with an authentic specimen of the sulphone.

The sulphinic acid was dissolved in aqueous acetone (30%), and the solution refluxed for 5 hours. On cooling a crystalline precipitate was obtained and identified as the corresponding sulphone in the usual manner. A yield of 88% was obtained.

In buffer solutions the rearrangement was rapid, equilibrium being reached in about 4 hours at pH 2.7-4 with yields of 85-90%. At pH 5.2, however, the maximum yield of 79% was obtained only after heating for 20 hours.

2-Chloro-2'-nitro-6-sulphino-4-methyldiphenyl ether.

The sulphinic acid, on heating in dilute sodium acetate solution at 90° for 2 hours, yielded an appreciable amount of the sulphone, but precipitation was not complete even after several days.

On refluxing a solution of the sulphinic acid in aqueous acetone (40%) for periods up to 40 hours, appreciable amounts of the sulphone were obtained and individual crystals were identified by melting point and colour with dilute sodium hydroxide solution. All crystals gave a weak blue colour with concentrated sulphuric acid, but crystals previously washed with dilute sodium acetate solution gave no such colour.

Note: Some sulphone was refluxed for 3 hours in aqueous acetone, and the product tested for sulphinic acid with concentrated sulphuric acid. No blue colour was obtained.

In buffer solutions at pH 4 - 5.2 the rearrangement was slow but high yields (85%) were obtained after 700 hours. At pH 2.7 a maximum yield of 45% was obtained after 600 hours.

β -o-Nitrophenoxyethanesulphinic acid.

No reversal to the sulphone was observed after

heating the sulphinic acid in various concentrations of sodium acetate solution (0.1 - 1.0%) at 90° for 4½ hours.

After refluxing solutions of the sulphinic acid in water and in aqueous acetone, the sulphinic acid was recovered unchanged.

Heating in buffer solutions of pH 1.8 and 2.3 for 48 hours caused decomposition of the sulphinic acid and the deposition of a red-brown sludge. At pH 5.7 no reversal was observed.

The courses of the various rearrangements are graphed in Figs. 1 and 2 (pp.38, 39). In a typical case 2'-nitro-2-sulphino-4:6-dimethyldiphenyl ether, the yield of sulphone is graphed against the pH of the buffer solution after various intervals of time (Fig.3, p.40). The numbering in Figs. 1 and 2 refers to the table on p. 45.

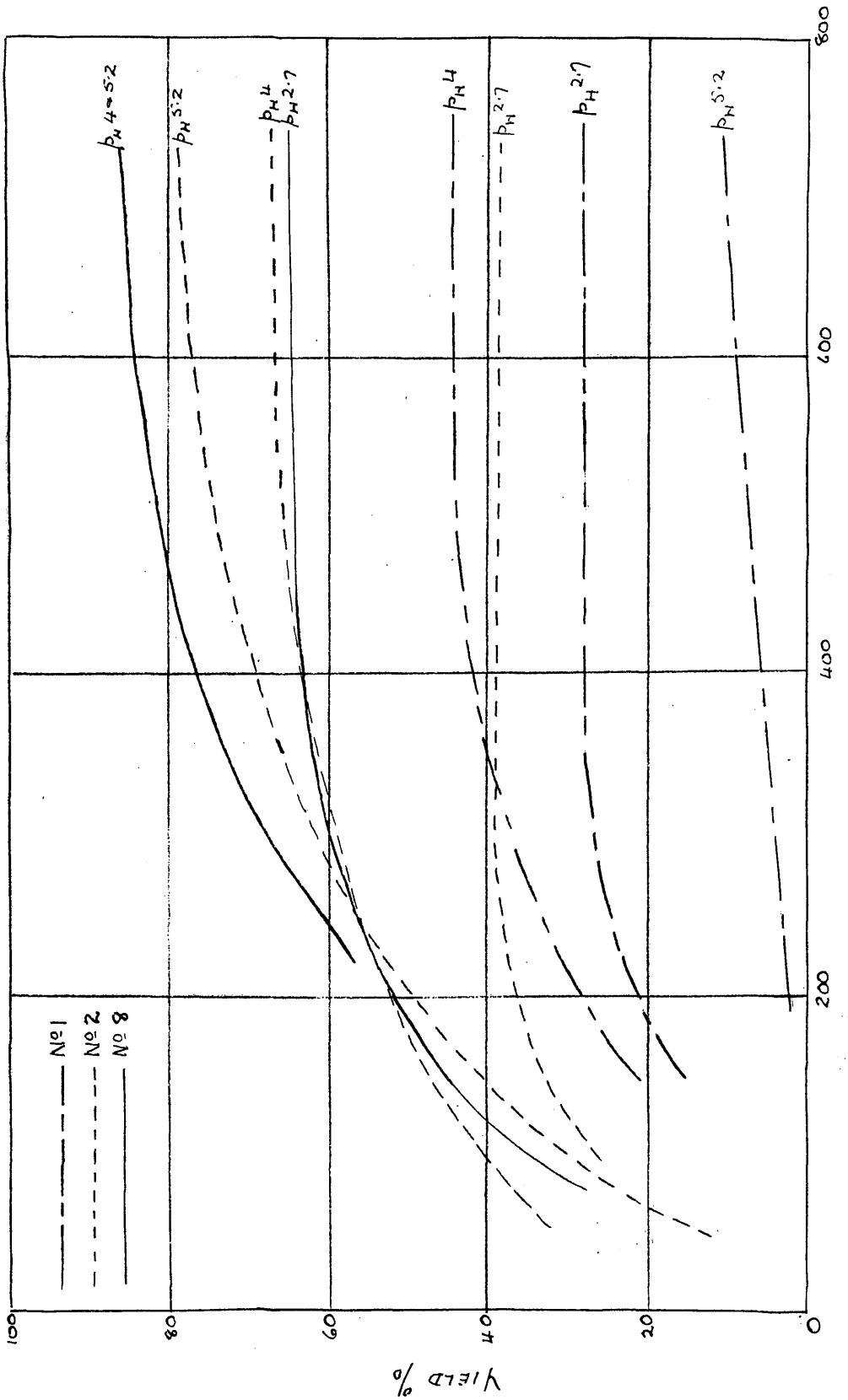
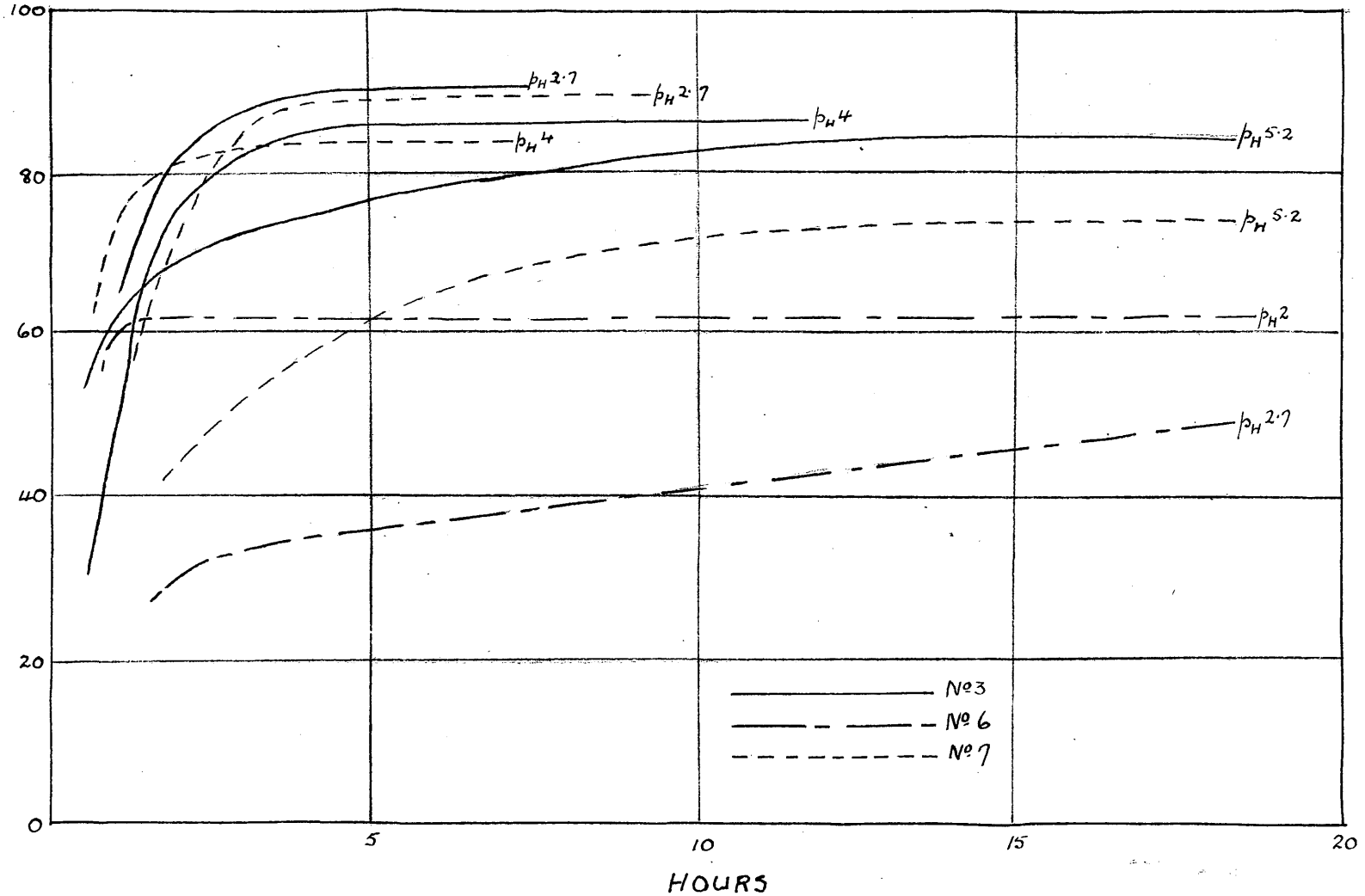

Yield %
100
80
60
40
20
0
200
400
600
HOURS
No 1
No 2
No 8
$p_H 4 = 5.2$
$p_H^{5.2}$
p_H^4
$p_H^{2.7}$
p_H^4
$p_H^{2.7}$
$p_H^{5.2}$

FIG. 1.

FIG. 2.


100
80
60
40
20
0
5
10
15
20
HOURS
pH 2·7
pH 2·7
pH 4
pH 4
pH 5·2
pH 5·2
pH 2
pH 2·7
No 3
No 6
No 7

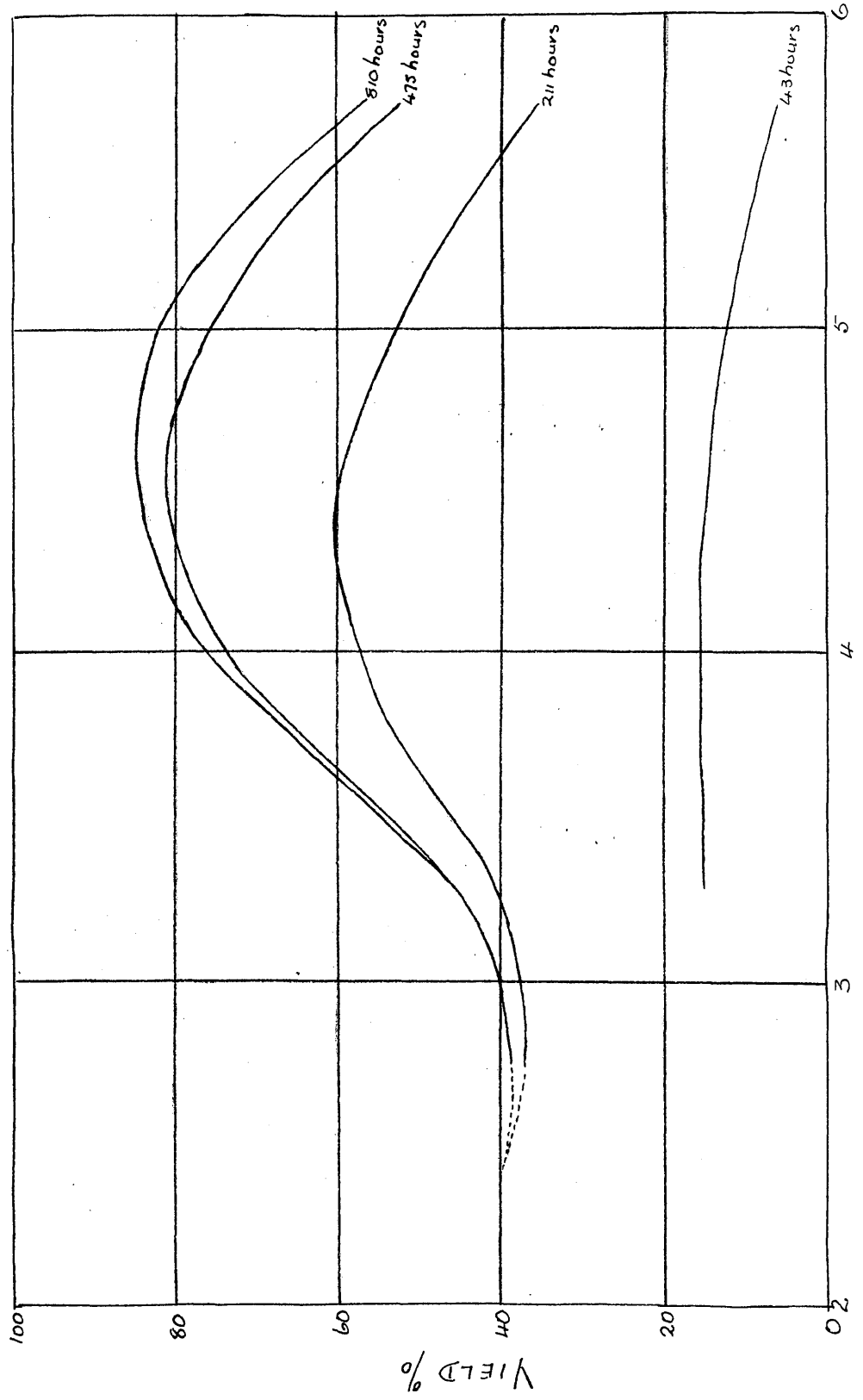
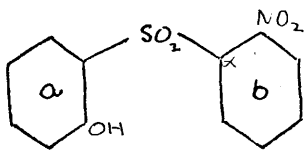

810 hours
473 hours
211 hours
43 hours
YIELD %
100
80
60
40
20
0
2
3
4
5
6
pH

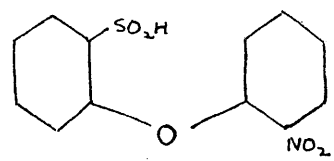
FIG. 3

DISCUSSION.

From a consideration of the results recorded, and more especially of the graphs on pages 38-40, it will be seen that in the rearrangement B ⟶ A, a definite equilibrium is reached between sulphone and sulphinic acid in solution. Sufficient proof of this is afforded by the fact that the reaction may proceed rapidly for a time and then slow down and stop before the sulphinic acid is exhausted.



A



B

In addition, the co-existence of the sulphone and sulphinic acid was established after the completion of the reaction, although the conditions of temperature and pH were materially unchanged.

The rate of attainment of equilibrium varies greatly from case to case, and seems to increase with increasing acidity up to the point at which the insolubility of the sulphinic acid inhibits the reaction. The possibility of following the reaction beyond this point

by using buffers containing sufficient organic solvent to keep the sulphinic acid in solution was considered, but in addition to the possibility of unknown chemical effects of such a solvent and the difficulty of exactly determining the pH, the increased solubility of the sulphone would, as explained below, result in a marked decrease of sulphone precipitated and so introduce an arbitrary factor into the equilibrium.

As might be expected, temperature plays a major part in the reaction, the speed of which increases rapidly with temperature, and in one case (3, p.45) for example, the reaction is complete in 20 minutes at 100°, while at 15° it requires 3 days.

It will be seen from Fig.3 that the extent of the reversal (or the yield of sulphone produced) is also dependent on the pH of the solution, but in this case there is apparently an optimum pH value (which varies from case to case) at which the yield reaches a maximum. It has not, however, been established that this optimum value is real, for, owing to the acetic acid content (and therefore the solvent action) of the buffers increasing with acidity, a new complication is introduced. Equilibrium is established between sulphinic acid and sulphone when they are present in solution in a definite proportion,

and precipitation of the sulphone goes on until this proportion is reached, the solution being saturated with respect to sulphone from the time precipitation starts. If now the solubility of the sulphone is increased by any means, there must be a correspondingly greater amount of sulphinic acid left unchanged when precipitation stops. Thus the slight increase in the solubility of the sulphone, caused by the increasing amount of acetic acid present in the buffers as the acidity is increased must cause a certain drop in the yield of sulphone when the acetic acid content becomes appreciable. This may account for the fact that, although the equilibrium is most rapidly reached in the most acid buffers, the amount of sulphone precipitated may be definitely below the maximum (Fig. 3).

A similar explanation may be given for the failure to detect the rearrangement of 2'-nitro-4-hydroxy-2-sulphinodiphenyl ether in buffer solutions. In this case it seems probable that rearrangement does occur but, owing to the greater solubility of the sulphone, equilibrium is attained before a saturated solution is produced and so no precipitation takes place. This view is supported by the fact that a relatively strong solution of the sulphinic acid in dilute sodium acetate

solution does give a precipitate of the sulphone. It is probable that by using more sulphinic acid in buffer solutions, a precipitate of the sulphone would be obtained, but, since there is a considerable drop in acidity during the reaction, the buffers would no longer be able to maintain the pH within the desired limits.

In order to facilitate the comparison of the speeds of the forward and reverse rearrangements, the results obtained with most of the substances tested, together with those published by Kent and Smiles[8] are given in the following table. Under a and b are given the substituents present in the aromatic nuclei of the parent 2-hydroxy-sulphone A.

The times in the third column (in minutes) are for the completion of the reaction in N/15 solution at 50°; those in the fourth column are the times (in hours) for the attainment of equilibrium at the most favourable pH in ca. N/150 solution at 50°.

No.	a.	b.	A ⟶ B.	B ⟶ A.
1.	5-Methyl	2-Nitro	315	400
2.	3:5-Dimethyl	2-Nitro	93	250
3.	5:6-Benzo	2-Nitro	5	5
4.	5-Hydroxy	2-Nitro	125	Too soluble for comparison
5.	5-Methoxy	2-Nitro	360	No reversal observed
6.	5-Methyl	2:4-Dinitro	Rapid with hydrolysis	2
7.	5-Chloro-4:6-dimethyl	2 Nitro	5	5
8.	3-Chloro-5-methyl	2-Nitro	150	450
9.	β-o-Nitrophenoxyethane sulphinic acid		Practically instantaneous	No reversal observed

As has already been stated, Smiles considered the controlling factors in the rearrangement A ⟶ B to be:

1) The close proximity of the oxygen atom to the α-carbon atom.
2) The positive character of the α-carbon atom, increased positivity being favourable to the change.
3) The capacity of the oxygen atom to act as a donor of electrons.
4) The character of the medium as expressed by its tendency to remove a proton from the hydroxyl.

In the reversal B ⟶ A nothing is known of the importance of the proximity of the sulphur atom, but, provided the reaction is intra-molecular, the condition

would seem to be essential.

Interconversion of A and B is evidently facilitated in both directions

a) By the positive character of the α-carbon atom (for the formation of the sulphone from 2:4-dinitrophenyl-3-sulphino-p-tolyl ether is very much more rapid than in the case of the mono-nitro compound).

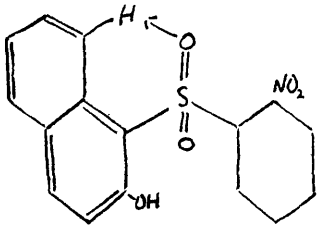
b) By the capacity of the oxygen atom to act as a donor of electrons,(as will be seen from a consideration of the substituents in A and their influence on the 2-hydroxyl as an electron source).

The character of the medium obviously controls the direction of the rearrangement, since it can take place in either direction with all other factors common. It will be seen that, with one significant exception, 9, the corresponding reversals B $\longrightarrow$A, although distinctly slower, follow roughly the same order, and in particular, that 6-methyl or 5:6-benzo substitution, which was present in all the very rapid rearrangements studied by McClement and Smiles[10], also favours rapid reversal (Nos. 3 & 7, Fig.2), whereas those not so substituted reverse very much more slowly (Fig.1).

It would seem that 6-methyl substitution, by causing electron accession at the sulphonated carbon

atom, at least partly overcomes the adverse influence of the sulphonyl group, and so the reaction in both directions is more rapid with compounds so substituted.

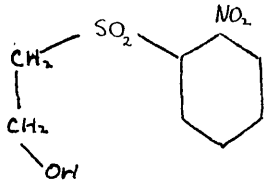
It is, moreover, possible that the effect of 6-methyl substitution may be related to the formation of a ring. Co-ordination of sulphonyl with methyl (or CH) might result in a preferential position for the double bond in the aromatic ring (c.f. Shah[13]) in such a way as to simulate the insolation of the hydroxyl in the aliphatic sulphones.



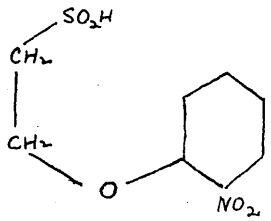
(XXXVI)

This would be more pronounced in alkaline media, and its breakdown in neutral media would be accompanied by regeneration of the sulphone.

Kent and Smiles[8] found that with a sulphone with an aliphatic hydroxyl group C, the change C ⟶ D is very much more rapid than any of the aromatic types A ⟶ B.



C



D

This may be attributed to the fact that with the former, the oxygen is 'insulated' by an aliphatic chain and so its donor capacity is not diminished by the kationoid action of the sulphonyl group.

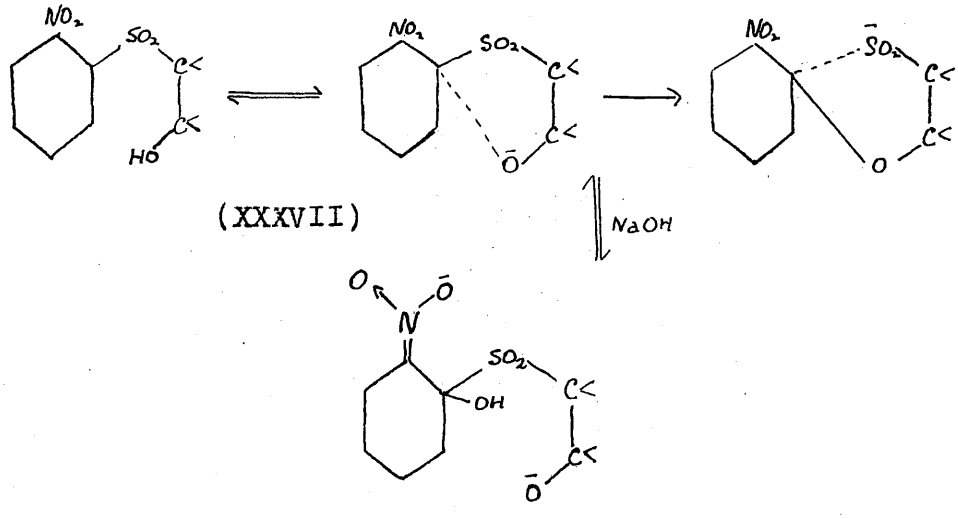
In view of the above it was all the more surprising that the sulphinic acid D showed no evidence of reversibility whatever. The investigation of this particular case was rendered more difficult by the fact that the sulphinic acid is rather unstable in acid solution and, in addition, the much greater solubility of the sulphone, besides complicating its isolation, must have a considerable effect on any equilibrium which might be formed. Consequently, while this exception appears significant, and has been repeatedly verified, it is felt that more evidence, including that from other similar sulphones, should be sought before its theoretical significance can usefully be considered.

In general, it is to be expected that A $\longrightarrow$ B will be more rapid than the reverse change, for the α-carbon atom in the former is subject to electron withdrawal by both nitro and sulphonyl groups, but only by the nitro group in the latter. This means that factor (3) - the positivity of the α-carbon atom - operates with greater effect in the sulphone than the sulphinic acid.

It only remains to be considered why, if the

present rearrangement is a true reversal of the Smiles rearrangement, the latter is characterised by a strong red colour (the fading of which has actually been used as a measure of the progress of the reaction), whereas the reversal shows no colour at any stage.

Originally Smiles attributed the red colour to a nitronic ion which he considered to be an intermediate product in the reaction, but later experiments replacing the activating nitro group by methyl sulphonyl, in which no red colour developed, convinced him that the colour effects must be due to a side equilibrium, and in a private communication he suggested the following mechanism as being the most consistent with the known facts:-



(XXXVII)

(XXXVIII)

Coloured ion

Now it is evident that in the more acid media of reversal, the equilibrium (XXXVII) $\rightleftharpoons$ (XXXVIII) will be so much less favourable to (XXXVIII) that the colour will be inappreciable.

It is now apparent that an examination of the equilibrium in the same buffers from the sulphone side would be a useful extension of this work.

BIBLIOGRAPHY.

1. Warren and Smiles: J.C.S., 1930, 956.
2. Henriques: Ber., 1894, 27, 2993.
3. Lesser and Gad: Ber., 1923, 56, 907.
4. Warren and Smiles: J.C.S., 1931, 914.
5. Warren and Smiles: J.C.S., 1931, 2207.
6. Levi, Rains and Smiles: J.C.S., 1931, 3264.
7. Levi and Smiles: J.C.S., 1932, 1488.
8. Kent and Smiles: J.C.S., 1934, 422.
9. Warren and Smiles: J.C.S., 1932, 1040.
10. McClement and Smiles: J.C.S., 1937, 1020.
11. Walpole: J.C.S., 1914, 2514.
12. Briscoe and Lowe: J.C.S., 1934, 1379.
13. Shah: J.C.S., 1939, 950.

PART II.

A SYNTHESIS OF SOME AZULENE DERIVATIVES.

HISTORICAL INTRODUCTION.

Since the earliest investigations of the essential oils, frequent mention has been made of blue fractions obtained in the distillation of certain oils, and of the development of the colour in others by the action of heat, acids, dehydrating and oxidising agents. In some cases the oils are coloured blue even before distillation. As early as the 15th century, camomile oil was noted for its striking blue colour. In 1864, Gladstone[1] recorded the investigation of many essential oils and the study in some detail of the blue substance obtained by the distillation of wormwood oil. This included the qualitative examination of the absorption spectrum of a solution of the blue oil in alcohol, and its reaction to various simple chemical reagents. He proposed to name the blue substance "coerulein", but the name "azulene", suggested by Piesse[2], has been generally adopted. Altogether, over 260 ethereal oils which contain azulene or azulene forming substances have been described, corresponding to almost 20% of the oils investigated.

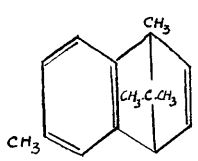
Various conjectures as to the structure of azulene have been made. At one time, the problem was considered settled by the discovery of copper salts in oils distilled

through untinned copper condensers. Gladstone[1], on heating the blue oil with soda-lime, obtained ammonia "or some volatile alkali". Kachler[3] considered it to be a polymer of camphor with the formula $(C_{10}H_{16}O)_3$, and for a long time it was considered to be an oxygenated substance on account of its formation by heating certain sesquiterpene fractions with air or oxygen in an autoclave[4]. Barbier and Bouveault isolated from geranium oil an intensely blue fraction to which they ascribed the formula of an ether $(C_{10}H_{17})_2O$.

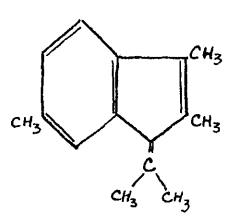
As a result of an examination of their absorption spectra, Tschirch[5] concluded that the blue fractions of the various essential oils were closely related, but it was not until 1915 that the work of Sherndal[6] paved the way for a successful elucidation of the problem. Up to this time, opinion had been divided as to whether the blue oils were relatively homogeneous or whether the colour was due to the presence of small amounts of an intensely blue compound. In either case, isolation of the pure compound proved impossible until Sherndal discovered and made use of the solubility of azulene in strong mineral acids, and its subsequent regeneration on dilution. Since it cannot be extracted from the strong acid solution with organic solvents, this method forms an ideal means of separating the azulene from sesquiterpene

and other impurities. Isolated in this way, and purified by distillation in steam and subsequently in vacuo, Sherndal obtained azulene as a slightly viscid liquid with a weak phenolic odour, intensely blue in thin layers and black in quantity. Analysis and molecular weight determination showed it to have the formula $C_{15}H_{18}$.

Later work by the same author[7] showed that azulene readily yields a picrate composed of one molecule of azulene to one of picric acid, the resulting compound being well suited to its identification and purification. Sherndal, by catalytic reduction of azulene with palladium, obtained an octohydro derivative $C_{15}H_{26}$, which he considered to be fully saturated. For this reason and because of its readiness to form a picrate, Sherndal suggested for azulene a tricyclic structure containing an aromatic nucleus. He interpreted its non-reducibility by sodium and alcohol as evidence of the absence of hydroaromatic conjugated double bonds, and suggested some such structure as (I).



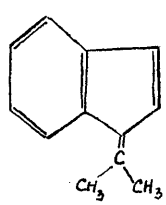
(I)



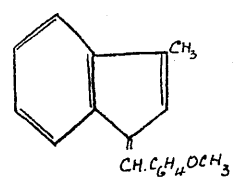
(II)

About the same time, Auspurger[8] isolated from milfoil oil a blue hydrocarbon $C_{15}H_{18}$, which he claimed to have reduced with palladium to $C_{15}H_{28}$. This hydrocarbon was more fully investigated by Kremers[9], who also, though without analysis, assumed the formula $C_{15}H_{28}$ for the reduction product. By the oxidation of azulene, Kremers claimed the formation of acetone, acetic acid, and a methylated phthalic acid, and assigned to azulene the hypothetical formula (II) or analogue.

Ruzicka and Rudolph[10] criticised these formulae on the ground that a structure such as (I) could not possibly be coloured at all, and that it was very unlikely that (II) would be blue, since dimethylbenzfulvene (III) is only bright yellow, and even with relatively strong colour-deepening groups as in methylanisylbenzfulvene (IV), the colour is still only yellow[11].



(III)

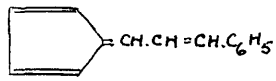


(IV)

Using the azulene from camomile and milfoil oil, Ruzicka and Rudolph were unable to repeat the oxidation

experiments of Kremers, obtaining only a mixture of the lower fatty acids and carbon dioxide, and in particular, they failed to detect any phthalic acid. They therefore concluded that there is no aromatic ring in azulene. Their unsuccessful attempt to isomerise azulene into aromatic substances by heating with formic acid is interesting in view of later work in this direction. Pointing out the discrepancy between the octohydroazulene obtained by Sherndal, and the decahydro derivative which was described by Kremers as having the same physical constants, Ruzicka and Rudolph were emphatic that the compound in question was $C_{15}H_{26}$ and stated that its molecular refraction agrees best with that calculated for a bicyclic hydrocarbon containing one double bond. Summarising the results up to that time, they stated that the blue colour of azulene is limited to a particular, hitherto unknown, grouping of five double bonds in a bicyclic skeleton devoid of aromatic rings. For a system of five double bonds to be capable of producing the blue colour of azulene they showed to be within the bounds of possibility by comparing the blue-red styryl fulvene (V)[12] with the analogous phenyl fulvene which is only red. Since the change from three to four conjugated double

bonds produces a change of colour from red to blue-red, it is conceivable that the introduction of a suitable fifth double bond might result in the formation of a blue fulvene derivative.



(V)

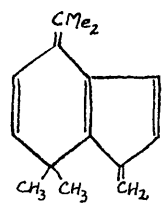
By dehydrogenating eucalyptus oil, guaiol and gurjune balsam oil with sulphur, Ruzicka, Pontalti and Balas[13] obtained azulenes, two of which they isolated in the form of picrates. Since then, dehydrogenation of the sesquiterpene and sesquiterpene alcohol fractions of various essential oils by means of sulphur, selenium, and palladium has become the standard method for the preparation of azulenes.

A large number of supposedly different azulenes has been reported and named from their respective natural oils, but it now appears that the number of distinct compounds is much smaller than was originally thought. Ruzicka and Rudolph showed, by a determination of the mixed melting points of picrates and styphnates, that the azulenes from milfoil and camomile oil were identical, but that they were distinct from S-guaiazulene, obtained from guaiene or guaiol by dehydrogenation with

sulphur. Ruheman and Lewy[14] believed camazulene and the azulene from lignite tar to be identical, since the mixed melting points of their picrates were not depressed by mixture. Herzenberg and Ruheman[15] had previously shown from absorption spectrum measurements that the lignite tar azulene and that obtained from gurjunene were identical. On the other hand, Ruzicka and Haagen-Smit[16] cast doubt on the validity of these conclusions, maintaining that in many cases the mixed melting points of the picrates of similar substances (e.g., the naphthalene hydrocarbons), especially if these be isomers, are not depressed, and they advocated the use of the styphnates, which are free from this abnormality, for the identification and comparison of the azulenes. They also criticised the absorption spectrum methods of Herzenberg and Ruheman as being insufficiently accurate, and quoted the findings of Janssen and Peteri who, using the same methods as Herzenberg and Ruheman, obtained identical spectra for different azulenes. The method of Ornstein[17], however, did distinguish between the different azulenes. By a determination of the mixed melting points of the picrates and styphnates, Ruzicka and Haagen-Smit showed S-guaiazulene, Se-guaiazulene, camazulene, and elemazulene to be distinct from each other, while the kessazulene of Asahina and Nakanishi[18] was

shown to be identical with S-guaiazulene. From the closeness of the physical constants of these azulenes, a similarity of ring structure was deduced. Several years later, Pfau and Plattner[19] isolated a new azulene - vetivazulene - from vetiver oil, and showed that many of the azulenes already reported were identical with S-guaiazulene.

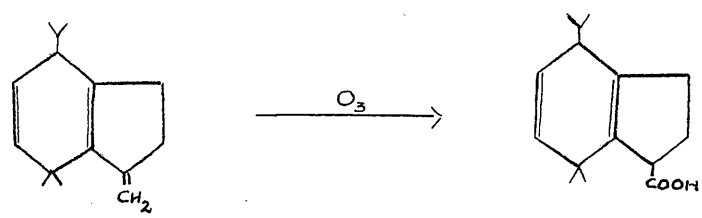
Investigation of the oxidation products of the above azulenes showed, in most cases, the presence of oxalic, acetic and isobutyric acids and acetone. On the basis of this, Ruzicka and Haagen-Smit put forward the tentative formula (VI) for elemazulene, but sought in vain dimethylmalonic acid among the oxidation products.



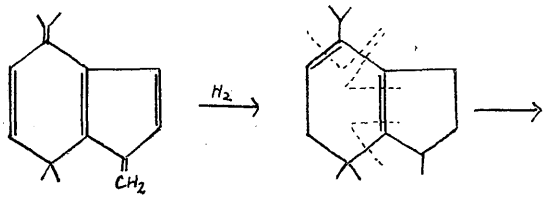
(VI)

Realising the futility of attempting to obtain large fragments in the oxidation of azulene itself, subsequent workers took a greater interest in the oxidation of partly reduced azulenes. Melville[20] traced the hydrogenation curve of S-guaiazulene and showed that the critical point (at which the blue colour disappeared) occurred at 55% hydrogenation, while there was a distinct break when 3 - 5 double bonds had been saturated.

In agreement with Auspurger and Kremers, he showed that a decahydro derivative is obtainable by these methods although in the latter stages reduction was very slow, and he considered the octohydroazulenes described in the literature to be mixtures of deca-, octo- and hexahydroazulene. Melville treated with ozone azulene which had been reduced to the critical point and failed to detect acetone, formic acid or formaldehyde in the oxidation products. He did isolate as their p-phenyl phenacyl esters, isobutyric acid and an acid $C_{14}H_{21}COOH$. To explain this, he assumed the reduced compound to be bicyclic and to have two double bonds which had resisted ozonolysis. Using Ruzicka's formula for elemazulene, he represented the reaction thus:

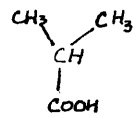


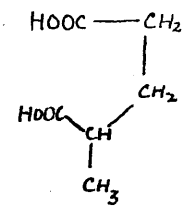
Repeating this oxidation, Birrell[21] detected formic acid, isobutyric acid, a-methylglutaric acid and the acid $C_{14}H_{21}COOH$ already mentioned. This he adduced as supporting Ruzicka's formula, and he interpreted the reaction thus:-



Azulene

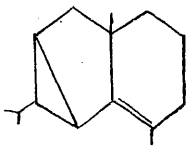
Hexahydro azulene



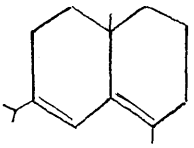


Birrell met the objection to the survival of a gem-dimethyl grouping in a dehydrogenation product by stating that "where one of the gem-dimethyl groups has to be split off on dehydrogenation, it forms an obstacle to the formation of an aromatic ring, (cf. the cyclisation and dehydrogenation of vitamin A to give 1:6-dimethylnaphthalene with loss of the gem-dimethyl groups from the (β-ionone ring)"[22]. It had already been fairly conclusively shown that azulene did not contain an aromatic ring. Pfau and Plattner, however, stated later that on the analogy of known examples[23], sesquiterpenes of this type should give substituted hydrindenes by splitting off one or both gem-dimethyl groups on dehydrogenation with sulphur or selenium.

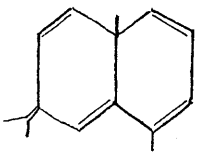
As a result of an investigation into the constitution of a-gurjunene, Treibs[24] assigned to a-gurjunene the structure (VII) and to iso-a-gurjunene the structure (VIII).



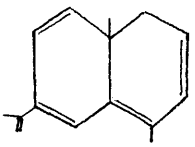
(VII)



(VIII)



(IX)

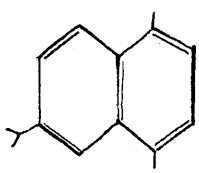


(X)

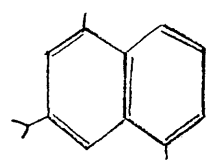
These, he argued, would be expected to give eudalene on dehydrogenation, whereas they, in fact, give gurjunazulene. Since, according to Kompa, the sesquiterpene leden yields both cadalene and azulene on dehydrogenation, Treibs assumed that the two classes of compounds must be closely related, and suggested the structure (IX) or (X) for gurjunazulene, but Pfau and Plattner criticised these structures on the ground that in the dehydrogenation of (VII), and especially (VIII), eudalene should be formed at least to some extent.

Attacking the problem from a different angle, Pfau and Plattner[19] attempted the isomerisation of azulene to naphthalene or hydronaphthalene derivatives (cf. Ruzicka's unsuccessful attempt using formic acid[10]). By passing the vapour of S-guaiazulene over silica gel at 300° under vacuum, naphthalene hydrocarbons were obtained in good yield, but unfortunately these were found to be mixtures, showing the probability of the migration of alkyl groups. More successful was the dehydrogenation of the product

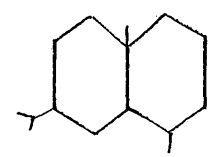
obtained by the treatment of guaiol with hydrogen iodide and red phosphorus. After separation of the azulene, there was isolated a naphthalene hydrocarbon $C_{15}H_{18}$ which was identified as 1:4-dimethyl-6-isopropylnaphthalene (XI). Similarly from vetiver oil, 1:5-dimethyl-7-isopropyl-naphthalene (XII) was isolated, the identity of these substances being established by comparison with synthetic specimens already prepared[26].



(XI)



(XII)

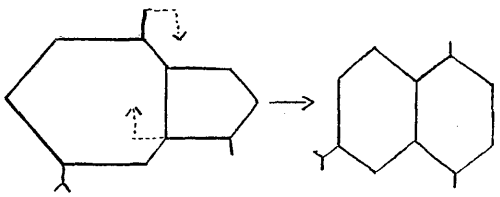


(XIII)

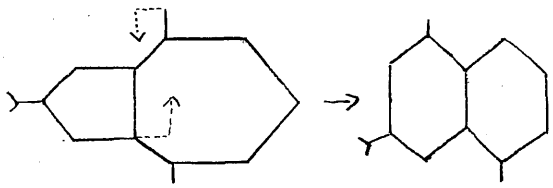
These results might be taken to indicate a eudesmol skeleton (XIII) in azulene, but Pfau and Plattner pointed out that this is incompatible with the fact that fully reduced compounds of the eudesmol type give no azulene on dehydrogenation, while decahydroguaiazulene is again capable of yielding azulene on dehydrogenation. They were therefore forced to the conclusion that the naphthalene hydrocarbon must have been formed by the rearrangement of another ring system.

The sesquiterpene compounds were subjected to graded oxidation which resulted in the opening of one ring

to a dibasic acid. Ring closure of this acid led to the formation of a cyclic ketone with one carbon atom less than the original compound. On catalytic dehydrogenation, this ketone yielded a phenol, thus showing the presence of a seven-membered ring in the sesquiterpene compound. Assuming the skeletons (XIV) and (XV) for the sesquiterpene compounds yielding S-guaiazulene and vetivazulene respectively, the rearrangement to the naphthalene hydrocarbons was explained as follows:-

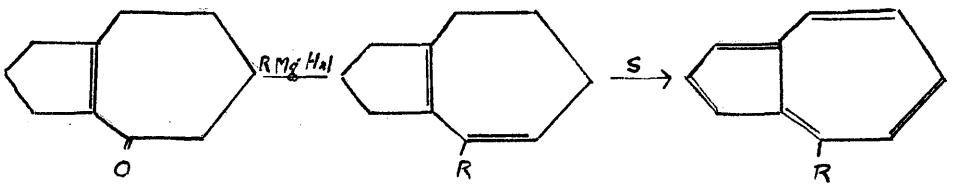


(XIV)



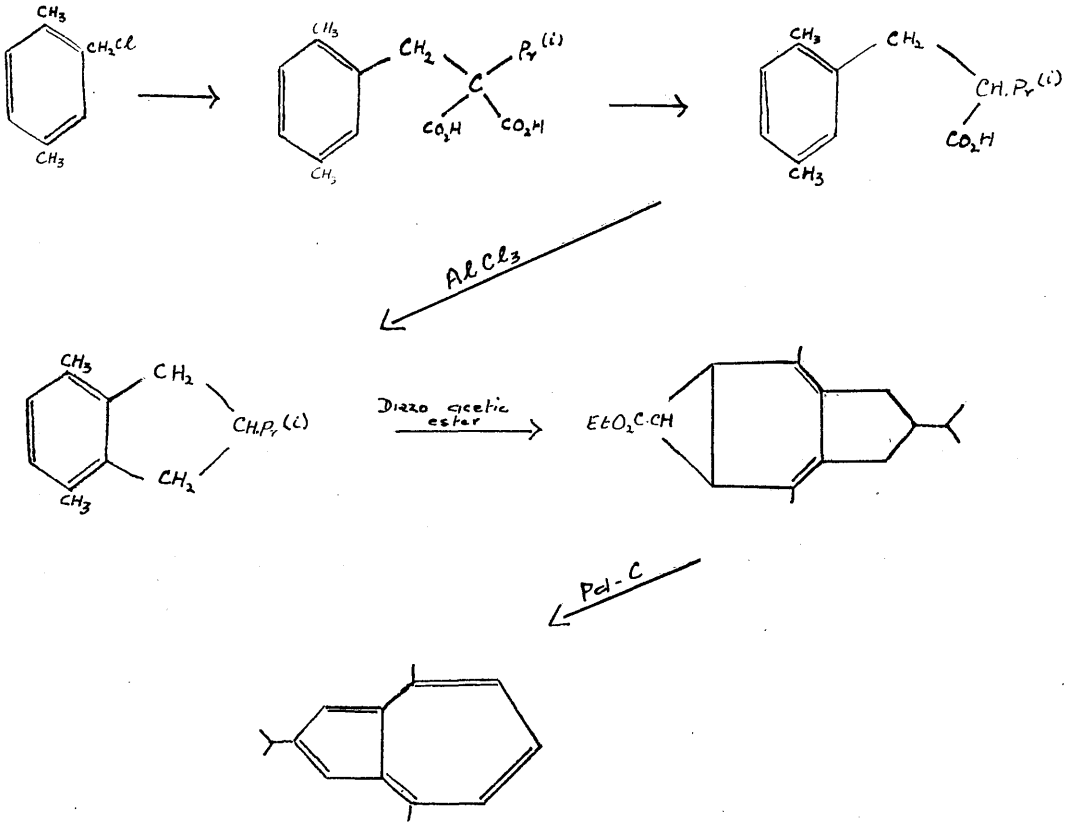
(XV)

In the case of vetivazulene, the skeleton (XV) was confirmed by the synthesis of the above-mentioned phenol. Further proof that the properties of the azulenes were due to a bicyclo-[0,3,5]-decapentaene structure was afforded by the synthesis of the compounds (XV; R=Me, Et and Ph), using the cyclopentenocycloheptanone (XVI), prepared by Huckel and Schnitzpahn[27], as starting material.



(XVI) (XVII)

In a later paper, Pfau and Plattner[26] described the synthesis of the parent azulene body (XVII; R = H) from cyclopentenocycloheptanone (XVI) by hydrogenation, reduction of the carbonyl group, and finally dehydrogenation with palladium-charcoal. Quite recently, 1:4-dimethylazulene was synthesised by Plattner and Wyss[29]. All these synthetic substances have properties similar to those of the natural azulenes, and yield similar derivatives. Pfau and Plattner have also recently synthesised vetivazulene[30] by the method outlined below.



Much work has been done on the absorption spectra of the azulenes. Wolff[31] (1878) recorded the absorption of camomile essence. Hoch[32] (1883), and Tschirch and Hohenadel[33] (1895) showed the similarity of the absorption spectra of the blue fractions of a great number of essential oils. Kremers[9] studied the absorption curves of camazulene, but his results did not agree with those of Ruzicka and Haagen-Smit[16]. Herzenberg and Ruheman[15] investigated the absorption spectrum of gurjunazulene, and Schlapfer and Stadler[34] demonstrated the similarity of the

absorption spectra of the azulenes and that of a blue hydrocarbon from cuprene tar.

Ruzicka and Rudolph[10] compared the absorption spectra of S-guaiazulene and camazulene and found them identical, but Ruzicka and Haagen-Smit, using more accurate methods, were able to distinguish between the two substances. Willstaedt[35], comparing the spectra of S-guaiazulene, camazulene, and lactarazulene, found five identical maxima for the three hydrocarbons. Susz, Pfau and Plattner[36] compared the absorption spectrum of the parent azulene $C_{10}H_8$ with those of S-guaiazulene and vetivazulene. In the ultra-violet, the three spectra are very similar, as are also those of azulene ($C_{10}H_8$) and S-guaiazulene in the visible region. They concluded that these three substances possess the same absorption grouping, namely, bicyclo-[0,3,5]-decapentaene-(1,3,5,7,9).

The question as to whether azulenes exist as such in plants, or whether they are formed during distillation has been discussed by Tschirch and Hohenadel[33], who obtained a blue oil by dry or steam distillation of the resin from sagapens, but observed no blue colour on extraction of the resin with cold petroleum ether. Ruheman and Lewy[14], on steam distillation of powdered camomile blossom, isolated a deep blue oil, but exhaustive extraction of a large

quantity of the blossom yielded only traces of a weakly yellow oil, while the same lot of camomile, after extraction, gave the blue oil again on steam distillation. They therefore concluded that azulene does not exist preformed in plants, and assumed that it must be formed from sesquiterpenes by enzyme action.

Azulenes have been obtained from sources other than the essential oils.

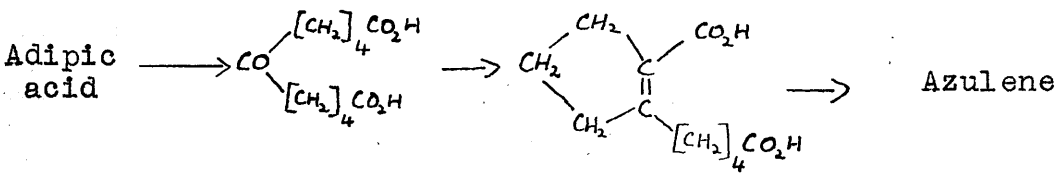
1) An azulene, probably camazulene, has been isolated from the fungus Lactarius deliciosus L.[35,41].

2) A blue oil, precipitated from lignite tar by ferrocyanide[38], was shown on further investigation[14,15] to be camazulene, but this has been questioned by Ruzicka and Rudolph.

3) A blue oil has been obtained by heating with active charcoal at 200-220° the sesquiterpene alcohol from the fusel oils of cane molasses and the sweet potato[37]. A black picrate was isolated and identified as that of S-guaiazulene.

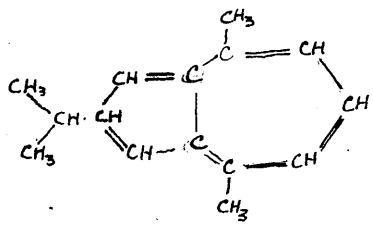
4) Wislicenus and Hentschel[39] recorded that a blue oil was formed during the dry distillation of calcium adipate, and thought it was due to the polymerisation of cyclopentanone. Wallach[40], and much later Ruheman and Lewy[14], investigated the action of dehydrating agents on

cyclopentanone and obtained the mesitylene analogue tris-cyclotrimethylenebenzene. No blue compounds were detected. Pfau and Plattner[28] carried out the dry distillation of calcium adipate in presence of a small amount of nickel catalyst and obtained a blue-green fraction which they showed by absorption spectrum methods to contain azulene. The reaction was assumed to take place as follows:-

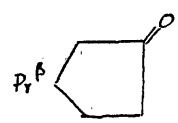


THE SYNTHESIS.

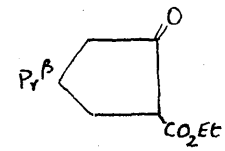
The synthesis of vetivazulene (I) involves the construction of a bicyclo-[0,3,5]-decapentaene structure substituted in the 2, 4 and 8 positions. The method chosen was first to prepare a suitably substituted cyclopentane derivative, on to which might then be built the second half of the molecule. Since, however, the formation of a 7-membered ring directly would be a matter of some difficulty, it was decided to reach this end by enlargement of a 6-membered ring.



(I)



(II)

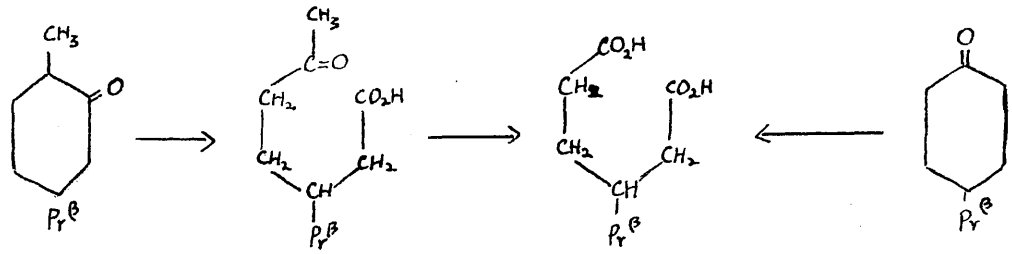


(III)

The first object, then, was the preparation of a reasonably large amount of 3-isopropyl cyclopentanone (II) or ethyl-4-isopropylcyclopentanone-2-carboxylate (III), this being attained by ring closure of β-isopropyladipic acid (VI).

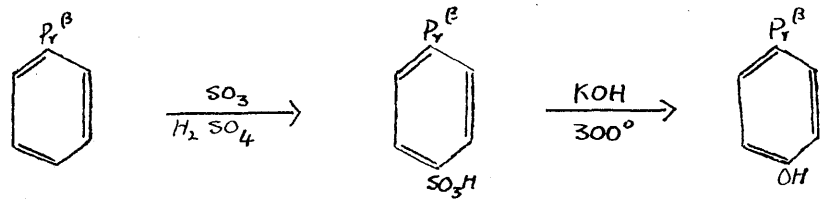
β-Isopropyladipic acid has been prepared by the oxidation of tetrahydrocarvone (IV) in two stages with chromic acid and sodium hypobromite[42], and also by the oxidation of p-isopropylcyclohexanol (VII)[43]. Both these

methods were investigated and the latter chosen as being the most convenient.



(IV) (V) (VI) (VII)

The preparation of p-isopropyl phenol by the condensation of p-isopropyl alcohol and phenol in presence of anhydrous aluminium chloride has been claimed[44]. This reaction was carried out as described and with various modifications, but the main phenolic fraction could not be obtained solid, owing probably to the presence of o- and p-isomers, and the method was abandoned in favour of a more indirect route via cumene sulphonic acid.



The complete synthesis by this route is one involving some thirteen or fourteen stages, so that in the earlier stages very large quantities of material had to be handled. It will be realised, therefore that although a number of the reactions had already been described, methods of working

had to be considerably modified to suit large scale preparations.

Cumene was prepared by the condensation of isopropyl alcohol and benzene, emulsified with 80% sulphuric acid as condensing agent[45]. This method proved to be more convenient, as well as more economical than that of Haworth et al.[46] who condensed isopropyl chloride and benzene by the Friedel-Crafts reaction, but both methods were extensively used.

Cumene is readily sulphonated in the cold by a mixture of concentrated and fuming sulphuric acid[47,48]. The product is most readily purified by recrystallisation of its barium salt, but on a large scale the use of barium carbonate or hydroxide to neutralise the acids proved to be inadvisable, for, owing to the sparing solubility of the barium salt, unreasonably large amounts of water were required to extract it from the barium sulphate. Accordingly, the acid liquors were neutralised with calcium hydroxide and the barium salt precipitated with barium chloride from the filtered solution of the calcium salt. The potassium salt was obtained by titrating a boiling saturated solution of the barium salt with a fairly concentrated solution of potassium carbonate.

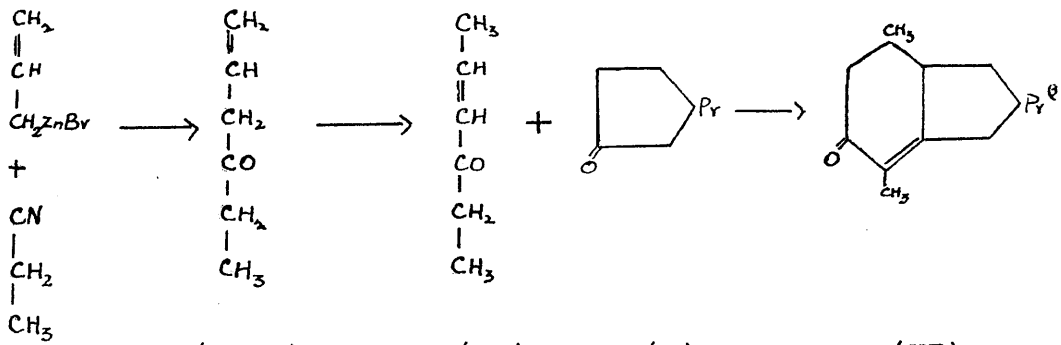
Fusion of the potassium salt in the usual way with potassium hydroxide yielded p-isopropyl phenol[49].

The hydrogenation of p-isopropyl phenol with platinum black has been shown[50] to give a mixture of p-isopropyl cyclohexanol (66%) and p-isopropyl cyclohexame (33%), and this method was tried in a preliminary experiment. Using a Raney nickel catalyst, however, with hydrogen under high pressure, hydrogenation was rapidly effected at 180°C, giving a relatively high yield of p-isopropyl cyclohexanol.

The oxidation of p-isopropyl cyclohexanol with alkaline permanganate[43] and with concentrated nitric acid was investigated, but a better yield was obtained using 50% nitric acid at a moderate temperature in presence of a trace of ammonium vandate as catalyst; (cf. oxidation of cyclohexanol to adipic acid[51]).

p-Isopropyl adipic acid was esterified, and ring closure effected by the Dieckman reaction in toluene. The product, ethyl-4-isopropylcyclopentanone-2-carboxylate (III), yielded on hydrolysis and decarboxylation 3-isopropylcyclopentanone (X).

By condensing this ketone with ethyl propenyl ketone (IX), the formation of 2-isopropyl-4:7-dimethyl-$\triangle^{4(9)}$-5-ketotetrahydrohydrindene (XI) was expected.



(VIII) (IX) (X) (XI)

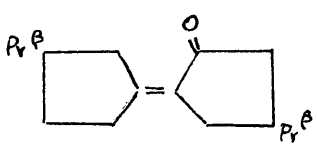
Ethyl propenyl ketone has been prepared by Blaise[52] by condensing allyl zinc iodide with propionitrile. An attempt to improve this method using magnesium turnings and modern Grignard technique proving a failure, the method of Blaise with modifications was successfully used on a small scale. Since the reagents are somewhat expensive, however, a cheaper method by the oxidation of ethyl propenyl carbinol was sought.

Ethyl propenyl carbinol was prepared from ethyl bromide and crotonaldehyde by a Grignard reaction. Oxidation to the ketone by a reverse Pondorf reaction[53] proved unsuccessful, but oxidation with chromic acid after protection of the double bond by bromination appeared to take place normally. All attempts at debromination with sodium iodide[54] and with zinc dust failed however. Courtot and Pierron[55] treated ethyl propenyl carbinol with dry hydrogen chloride and oxidised the product 4-chloro-Δ^2-hexene with dichromate and sulphuric acid, but on repeating

this, yields were found to be poor both in quality and quantity.

Since that of Blaise is the only really satisfactory method among those described, this method was adopted on a larger scale than previously, the starting materials, allyl bromide and propionitrile, being prepared from cheap sources by standard methods[56,57].

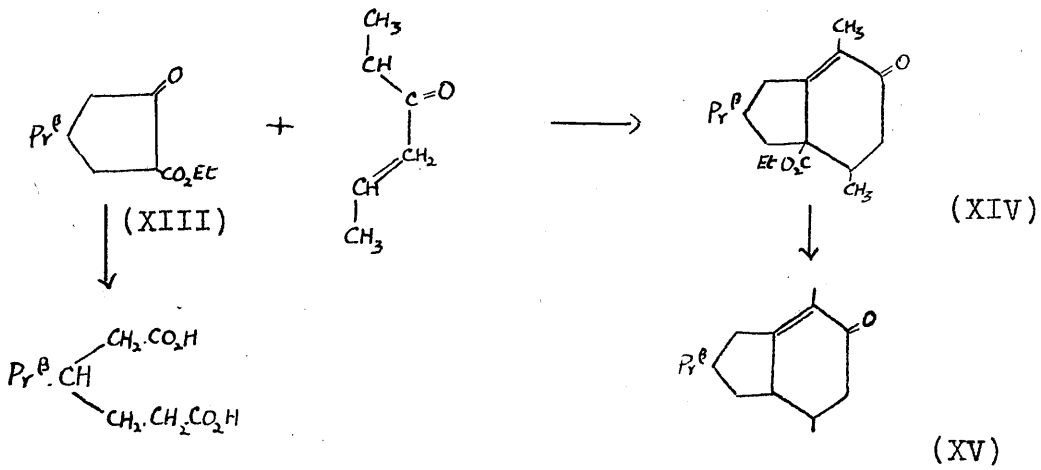
Several attempts were made to condense the sodio compound of 3-isopropyl cyclopentanone with ethyl propenyl ketone, but this method had to be abandoned owing to the readiness with which 3-isopropyl cyclopentanone condenses with itself to give a di-isopropyl-cyclopentylidenecyclopentanone, probably (XII). This condensation takes place readily even at -20° on adding 3-isopropyl-cyclopentanone to a stirred suspension of sodamide in dry ether. The ketone itself did not form any of the usual derivatives, but was catalytically reduced and the saturated ketone characterised by its oxime and semicarbazone.



(XII)

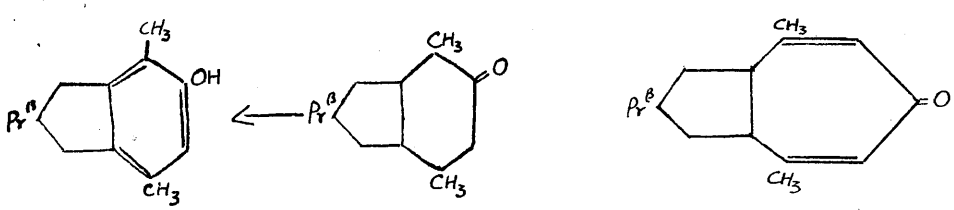
The sodio compound of ethyl-4-isopropylcyclopentanone-2-carboxylate (XIII) did not react to any appreciable extent with ethyl propenyl ketone in boiling

benzene, but condensation took place readily in absolute alcohol. As might be expected, the main reaction was accompanied by a certain amount of ring fission of the starting material to β-isopropyl adipic acid. Attempts to reduce this wastage by using alcohol carefully dried by distillation over aluminium isopropylate met with little success, and this side reaction necessarily absorbed a considerable amount of material.



On treatment of the ketoester (XIV) with 20% alcoholic potassium hydroxide, hydrolysis was accompanied by decarboxylation - a result which was rather surprising considering that the carbethoxyl group in question is quaternary and that a certain amount of steric hindrance by the 4-methyl group is to be expected. Steps were therefore taken to confirm the structure (XV).

In the course of a study of the ketonic constituents of vetiver oil, Pfau and Plattner[58] isolated a ketone $C_{15}H_{22}O$, to which they assigned the name β-vetivone. Catalytic reduction of this with platinum yielded tetrahydro-β-vetivol, which, on oxidation with chromic acid, gave a dicarboxylic acid $C_{15}H_{26}O_4$. Ring closure of this acid resulted in the ketone (XVII) which was catalytically dehydrogenated to the phenol (XVI), the structure of which was proved by synthesis. This showed the presence of a 7-membered ketonic ring in β-vetivone, and the structure (XVIII) was suggested and later[59] confirmed.



(XVI) (XVII) (XVIII)

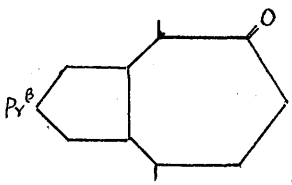
Dehydrogenation of (XV) in boiling p-cymene was carried out and the phenol (XVI) isolated from the dehydrogenation products. As a further proof of its structure, the same compound (XV) was catalytically reduced to 2-isopropyl-4:7-dimethyl-5-ketohydrindane (XVII), the derivatives of which were shown to have the correct analyses and the semicarbazone to have a melting point in reasonable agreement with that described by Pfau and Plattner. It is, of course,

possible that the ketone (XVII) prepared by reduction of (XV) and that described in the literature are steriosomers, and this may be the explanation of the small discrepancy (6^{o}) in the melting points of their semicarbazones.

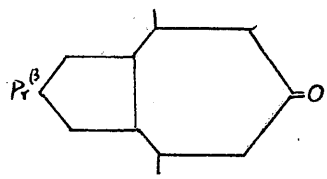
The hydrogenation was effected by shaking with palladium black in absolute alcohol. Since the absorption always ceased before the calculated amount of hydrogen had been absorbed, and since the yields of oxime and semicarbazone were considerably smaller than was expected it must be assumed that the liquid is a mixture. The pure ketone was obtained by hydrolysis of its recrystallised semicarbazone, and the fraction which did not form a semicarbazone submitted to further hydrogenation without result.

Ring enlargement of saturated cyclic ketones by means of diazomethane has already been studied by various workers[60, 61, 62]. Adamson and Kenner[63] treated 2-methyl cyclohexanone in alcoholic solution with nitrosomethylurethane in presence of anhydrous potassium carbonate, and obtained a number of products including both 2- and 3-methylcycloheptanone which were separated by shaking with a saturated bisulphite solution, 3-methylcycloheptanone alone forming a bisulphite compound. Using similar methods, 2-isopropyl-4:7-dimethyl-5-ketohydrindane (XVII) yielded a mixture from which no bisulphite compound could

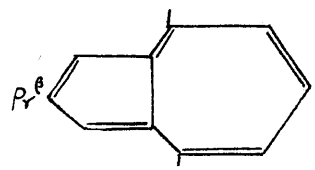
be isolated. Treatment with semicarbazide, however, yielded a fairly homogeneous semicarbazone, this being taken to indicate the preferential formation of either (XIX) or (XX). Subsequent analysis of the semicarbazone,



(XIX)



(XX)



(XXI)

however, did not agree with the empirical formula $C_{16}H_{29}ON_3$ for (XIX) or (XX), but did agree with the empirical formula $C_{15}H_{27}ON_3$. If the analysis results are accepted, the product would seem to be a stereoisomer of the starting material, since its physical properties definitely exclude the possibility of the two compounds being identical.

Should further investigation prove the compound in question to be, after all, $C_{16}H_{29}ON_3$, it would be justifiable to assume it to be either (XIX) or (XX).

There are, of course, a number of possible stereoisomers of these compounds, but it is possible for the ketone prepared from 2-isopropyl-4:7-dimethyl-5-ketohydrindane to be identical with the tetrahydro-β-vetivone described by Pfau and Plattner.

On the other hand, since (XX) would be expected to form a bisulphite compound more readily than (XIX), the latter structure for the synthetic ketone seems to be the more likely one. Both, of course, should be capable of yielding, on dehydration and dehydrogenation, the same vetivazulene (XXI), which was the ultimate end of this part of the research.

Unfortunately the work had to be interrupted at this point in order to take up a war appointment with Imperial Chemical Industries Ltd. This is the more regrettable since the synthesis had just reached its most interesting stage.

EXPERIMENTAL.

p-Isopropyl phenol.

Anhydrous aluminium chloride (20 g.) was added in four lots to a mixture of phenol (7 g.), dry isopropyl alcohol (4.5 g.), and petroleum ether (40 cc., b.p. $>120^{\circ}$). When the vigorous reaction had subsided, the mixture was maintained at 120 - 130° for 6 hours, after which it was decomposed with ice water, the solution extracted with ether and the phenols isolated from the ethereal solution by shaking with sodium hydroxide solution. The alkaline solution was acidified and the phenols extracted with ether and purified by vacuum distillation. The above quantities were varied and the solvent changed to tetrachlorethane, but all experiments yielded only liquid fractions with boiling points approximately $95\text{-}105^{\circ}/10$ mm.

Isopropyl chloride.

A mixture of anhydrous zinc chloride (310 g.), concentrated hydrochloric acid (164 cc. d. 1.16) and isopropyl alcohol (60 g.) was strongly heated. The reaction was very vigorous and the isopropyl chloride allowed to distil off through a cooled column and collected in a series of cooled receivers. Yield 74%. B.p. of

purified product 34.5 - 35.5°. The zinc chloride was recovered and used repeatedly.

Cumene.

A mixture of isopropyl chloride (128 g.) and benzene (380 g.) was added during 3 hours to a suspension of anhydrous aluminium chloride (25 g.) in boiling benzene (880 g.) and the mixture boiled 1 hour longer. The cooled solution was shaken with ice-water, dried and distilled. The product was redistilled through an efficient column and a yield of 72%, b.p. 150 - 152.5° obtained.

Cumene.

A mixture of benzene (250 g.) and isopropyl alcohol (100 g.) was run slowly (10 min.) into vigorously stirred 80% sulphuric acid (2000 cc.) at 65°. The emulsion was stirred at that temperature for 3 hours, allowed to separate and the top layer siphoned off. It was washed with potassium carbonate solution and water, dried and distilled. On redistillation, a yield of 136 g. (68%) was obtained, b.p. 150 - 152.5°.

The acid layer was brought up to strength by drawing off 110 cc. and replacing it with concentrated sulphuric acid, the slight excess being to allow for sulphonation. It was then used for the next run.

p-Cumene potassium sulphonate.

A mixture of fuming sulphuric acid (600 g.; 12% SO_3) and concentrated sulphuric acid (400 g.) was slowly added with shaking to cumene (500 g.), the temperature being kept below 40°. The mixture was shaken occasionally until it became homogeneous (1 hour), allowed to stand 3 hours and poured into water (4000 cc.). Sufficient calcium hydroxide (760 g.) to neutralise the acid was added in a smooth paste and the mixture filtered. The residue was extracted with hot water (3000 cc.), filtered and the combined filtrates evaporated to 2 litres and filtered from a small amount of calcium salts. A slight excess of barium chloride solution was then added and the precipitated barium salt collected and dried. The barium salt (500 g.) was dissolved in boiling water (6000 cc.) and potassium carbonate solution added till the solution was just alkaline to phenolphthalein. The barium carbonate was removed by filtration and the solution evaporated to dryness.

Note. If the acid liquors are neutralised by barium carbonate or hydroxide, very large quantities of hot water are necessary completely to extract the barium salt, and in addition, if the carbonate be used, frothing causes the actual neutralisation to be a lengthy and tedious operation.

p-Isopropyl phenol.

p-Cumene potassium sulphonate (150 g.) was stirred into fused potassium hydroxide (300 g.) at 280° over a period of 30 minutes. The temperature of the mixture was slowly raised to 300° (10 min.), by which time two layers had separated. When cold, the solid was dissolved in water, and the solution cooled and acidified. The phenol layer was separated off and washed with sodium carbonate and water, a little carbon tetrachloride being added to increase the density and prevent crystallisation. The fraction b.p. 220 - 240° solidified immediately on cooling. A yield of 50 - 55% was obtained. On redistillation the main fraction had b.p. 217 - 222°. A sample recrystallised from petroleum ether had m.p. 62 - 63°.

p-Isopropyl cyclohexanol.

The Raney nickel catalyst used in this reduction was prepared by adding 50% Al-Ni alloy (16 g.; 100 mesh) to a stirred solution of potassium hydroxide (16 g.) in water (300 cc.). When the reaction had subsided, the temperature was raised slowly in the water bath to 100° and maintained until the reaction had practically ceased (2 hours). The alkaline solution was decanted off and the catalyst washed six times with hot water by decantation, and once with alcohol.

p-Isopropyl phenol (200 g.) and Raney nickel (8 g.) were placed in a high pressure autoclave (monel liner) and hydrogen to a pressure of 100 atmospheres at 180° added. Stirring was effected with a stainless steel chain stirrer, the gland being lubricated with glycerol. The pressure dropped rapidly to 30 atmos., whereupon it was raised by the addition of more hydrogen. Absorption stopped when the theoretical amount had been absorbed (3 hours). The product was filtered and distilled without further purification, a yield of 160 g. (80%) boiling at 102 - 110°/15 mm. being obtained.

β-Isopropyl adipic acid.

(1) The method of Braun and Werner[43] was used with slight modifications. p-Isopropyl cyclohexanol (25 g.) was added to a solution of potassium permanganate (75 g.) in water (1000 cc.) and, with vigorous stirring, a solution of potassium hydroxide (12.5 g.) in water (50 cc.) was added (30 min.), the temperature being kept below 5°. The mixture was stirred vigorously for 9 hours and allowed to stand overnight. Excess permanganate was destroyed with hydrogen peroxide and the manganese dioxide filtered off. The product was extracted with ether in a soxhlet and esterified as described below, 20 g. of the ester being obtained.

(2) Ammonium vanadate (0.2 g.) was dissolved in a mixture of concentrated nitric acid (250 cc.) and water (125 cc.). The solution was heated to 50 - 60° on a water-bath and p-isopropyl cyclohexanol (100 g.) run in with vigorous stirring at such a rate as to maintain the temperature at 50 - 55° without further external heating (4 - 5 hours). After heating at 100° for 30 min., the water and excess nitric acid were removed by vacuum distillation on the water-bath: (stronger heating at this stage may cause a violent reaction). The acid was not further purified.

Diethyl β-isopropyl adipate.

The crude β-isopropyl adipic acid was dissolved in absolute alcohol (200 cc.) and the solution saturated with dry hydrogen chloride. After standing overnight it was refluxed (1½ hours), the two layers separated and the water and alcohol removed from the top layer under reduced pressure. Yield 135 g., b.p. 145 - 165°/15 mm.

Ethyl-4-isopropylcyclopentanone-2-carboxylate.

Sodium (15 g.) was atomised in dry toluene (200 cc.) and diethyl β-isopropyl adipate (120 g.) added in small quantities, care being taken to keep the reaction under control. When the vigour of the reaction had somewhat

abated, the flask was heated on an oil-bath at 120 - 130° with occasional shaking for 80 minutes. The mixture was then cooled to 0° and ice-cold 10% hydrochloric acid (1000 cc.) added and the mixture shaken until no solid remained. The toluene layer was separated off and the acid layer extracted with toluene. The combined toluene solutions were washed with sodium carbonate solution and water, and dried. On fractionation, a yield of 64 g. (65%), b.p. 134 - 141°/15 mm. was obtained. B.p. on redistillation was 128 - 135°/15 mm.

3-Isopropyl cyclopentanone.

Ethyl-4-isopropylcyclopentanone-2-carboxylate (14 g.) was refluxed with dilute hydrochloric acid (140 cc. 3N) for 4½ hours. The product was steam distilled off, the aqueous layer of the distillate being extracted with ether. A yield of 8.5 g., b.p. 75 - 80°/15 mm. was obtained. The semicarbazone formed readily and had m.p. 192°. The phenyl hydrazone crystallised in plates m.p. 75 - 76.5°. It decomposed rapidly on exposure to the atmosphere.

Ethyl propenyl ketone.

The method of Blaise, using allyl bromide in place of allyl iodide, was the only practicable method

among those attempted. Allyl bromide (57.5 g.) was added slowly to a stirred mixture of fine zinc turnings (35 g.), dry benzene (80 g.), and propionitrile (30 g.). A crystal of iodine was added to start the reaction, but as a rule, a considerable quantity of the allyl bromide had been added before the reaction set in. When it did start, the reaction was vigorous and the flask was cooled in ice. After stirring for 2½ hours, the mixture was allowed to stand 18 hours and then decomposed with ice and 20% sulphuric acid. The benzene layer was separated off, the benzene removed by distillation, and the residue refluxed with twice its volume of 20% sulphuric acid (1 hour). The oil was separated and the acid layer extracted with ether. The combined extracts were washed with sodium carbonate solution and water and dried. On distillation a yield of 13 g., b.p. 133 - 145° was obtained. It readily formed a semicarbazone m.p. 157° from aqueous alcohol.

The following other methods were attempted:-

(1). Allyl magnesium bromide was prepared from allyl bromide (60 g.), dry ether (485 cc.) and magnesium turnings (36 g.). The solution was decanted, cooled in ice, and propionitrile (22 g.) added with stirring (1 hour). The mixture was allowed to stand overnight and decomposed with

ice and sulphuric acid. None of the expected product was obtained.

(2). Ethyl propenyl carbinol was prepared by a Grignard reaction from ethyl bromide (164 g.), ether (350 cc.), magnesium turnings (36 g.), and crotonaldehyde (105 g.) in ether (200 cc.). A yield of 100 g. was obtained. The oxidation of this alcohol to ethyl propenyl ketone was attempted by the following methods:-

(a). The carbinol (10 g.), acetone (66 cc.), benzene (133 cc.) and aluminium isopropoxide (10 g.) were refluxed (24 hours), the mixture acidified with dilute sulphuric acid, washed with water and the solvents removed through a fractionating column. The fraction b.p. 130 - 150° (7 g.) did not form a semicarbazone or a 2:4-dinitrophenylhydrazone, and its smell indicated that it consisted largely of the starting material.

(b). The double bond was protected by bromination, bromine being added to the carbinol (10 g.) in glacial acetic acid (10 cc.) until a faint permanent colour was produced. Chromic anhydride (7.5 g.) in acetic acid (15 cc. 80%) was added slowly with stirring and cooling. After standing overnight, the solution was heated to 60° for 1 hour, diluted with water and extracted with ether. A yield of 10.3 g. b.p. 94 - 104°/10 mm. and 5.3 g. b.p.

104 - 114°/10 mm. was obtained. Debromination with sodium iodide in alcohol failed. Approximately the theoretical amount of iodine was liberated, but none of the required product could be isolated. Debromination with zinc dust yielded only black tars.

(c). Oxidation via 4-chloro-Δ^2-hexene as described by Courtot and Pierron[55] was attempted but the yields were small (2.8 g. ketone from 13 g. alcohol) and poor in quality.

Condensation of isopropyl cyclopentanone and ethyl propenyl ketone.

Isopropyl cyclopentanone (18 g.), dry ether (60 cc.) and powdered sodamide (3.2 g.) were stirred in a slow current of nitrogen for 4 hours. Ethyl propenyl ketone (8 g.) in a little ether was slowly added and stirring continued 4 hours. The mixture was refluxed for 6 hours, allowed to cool and decomposed with dilute hydrochloric acid. The product was extracted with ether, the ether evaporated, and starting material removed in steam. The residue yielded the following fractions:-

(1) 150 - 170°/10 mm. .. 7 g.,
(2) 170 - 190°/10 mm. .. 5.1 g.,
(3) 190 - 220°/10 mm. .. 4 g.

From fraction (2) a solid crystallised out. It formed white plates from aqueous alcohol, m.p. 75.5°.

Di-isopropyl cyclopentylidenecyclopentanone. (XII)

A suspension of sodamide (3.9 g.) in a solution of isopropyl cyclopentanone (14 g.) in dry ether (50 cc.) was stirred in a slow stream of hydrogen. At first there was a brisk evolution of ammonia but after 4½ hours this had practically ceased. Stirring was continued for 2 hours and the mixture left overnight. Ice was added and the ether layer separated and washed with dilute acid and water. The ether was removed and a very little starting material recovered by steam distillation. The residue was extracted with ether and, on working up, yielded a liquid (8.1 g.) b.p. 165 - 175°/10 mm., which partly solidified on freezing. On recrystallisation from alcohol it had m.p. 75 - 76°, and this was not depressed by admixture of the solid obtained in the condensation of 3-isopropyl cyclopentanone and ethyl propenyl ketone.

The experiment was repeated adding the ketone slowly to a suspension of sodamide in ether at -20°C. A fairly rapid current of dry hydrogen was passed into the suspension and at the end of an hour the evolution of ammonia had almost stopped. Water was added and the product worked up as before when 7 g. of the starting material and 5 g. of the same condensation product were obtained.

The product did not readily form the usual derivatives but was characterised by reduction (Pd black in acetone) to the saturated ketone. This formed a semicarbazone m.p. 161.5° from acetone.

Found: C, 69.81; H, 10.85%,
$C_{19}H_{31}ON_3$ req. C, 69.56; H, 10.66%.

It formed an oxime, m.p. 142 - 143.5° from alcohol on refluxing with hydroxylamine hydrochloride in pyridine.

Found: C, 76.28; H, 11.71%,
$C_{18}H_{29}ON$ req. C, 76.50; H, 11.65%.

2-Isopropyl-4:7-dimethyl-5-keto- $\Delta^{4(9)}$ -tetrahydrohydrindene. (XV)

Ethyl-4-isopropylcyclopentanone-2-carboxylate (19 g.) was slowly added with shaking to dry benzene (250 cc.) containing sodium wire (2.1 g.). The sodio compound separated as a white gelatinous mass. This did not condense with ethyl propenyl ketone to any great extent on refluxing for 6 hours.

Sodium (7.17 g.) was dissolved in absolute alcohol (300 cc.) which had been distilled over lime. Ethyl-4-isopropylcyclopentanone-2-carboxylate (60 g.) was added dropwise with shaking. The sodio compound separated, forming a thick paste, and to this ethyl propenyl ketone (22 g.) in absolute alcohol (100 cc.) was added with shaking and cooling. The mixture was left in the cold

for 40 hours and then refluxed for 6 hours. Most of the alcohol was distilled off and ice and ether added to the cooled solution. The ether layer was washed with dilute acid and water and the product worked up in the usual way. A yield of 26.8 g. b.p. 170 - 190°/10 mm. was obtained. This was dissolved in absolute alcohol (140 cc.) containing potassium hydroxide (19 g.) which had been dissolved in the minimum amount of water. The solution was refluxed for 6 hours, filtered from potassium carbonate, and most of the alcohol distilled off. Water was added and the product extracted with ether. A yield of 12.5 g. b.p. 145 - 165°/10 mm. was obtained. A considerable amount of acidic material and some starting material was recovered from the condensation.

2-Isopropyl-4:7-dimethyl-5-hydroxyhydrindene. (XVI).

2-Isopropyl-4:7-dimethyl-5-keto-$\Delta^{4(9)}$-tetrahydrohydrindene (1.5 g.) was refluxed for 14 hours with palladium black (0.1 g.) in p-cymene (15 cc.) in an atmosphere of carbon dioxide. The filtered solution was shaken with sodium hydroxide solution and the extract acidified. The crude phenol (0.1 g.) was sublimed (100°/0.5 mm.) and after 4 recrystallisations from hexane was obtained as small colourless needles, m.p. 131-132°. (Pfau and Plattner record m.p. 129 - 130°).

2-Isopropyl-4:7-dimethyl-5-ketohydrindane. (XVII).

2-Isopropyl-4:7-dimethyl-5-keto- $\Delta^{4(9)}$-tetrahydrohydrindene (12 g.) in absolute alcohol (150 cc.) was shaken with palladium black (0.3 g.) in an atmosphere of hydrogen. Absorption stopped when about 75% of the theoretical amount had been absorbed (24 hours). The alcohol was removed and the ketone converted to the semicarbazone which, after recrystallisation from alcohol, had m.p. 201°.

Found: C, 68.38; H, 10.19; N, 15.70:,
$C_{15}H_{27}ON_3$ req. C, 67.96; H, 10.26; N, 15.85%.

The oxime, prepared by refluxing with hydroxylamine hydrochloride in pyridine and recrystallised from alcohol, was obtained as fine white needles, m.p. 154.5°.

Found: C, 75.14; H, 10.90%,
$C_{14}H_{25}ON$ req. C, 75.26; H, 11.29%.

The semicarbazone was steam distilled with 20% sulphuric acid and the pure ketone isolated.

Reaction of diazomethane on 2-isopropyl-4:7-dimethyl-5-ketohydrindane.

2-Isopropyl-4:7-dimethyl-5-ketohydrindane (2 g.) was dissolved in absolute alcohol (2 cc.) and anhydrous potassium carbonate (0.1 g.) added. Nitrosomethylurethane

(1.4 g.) was added over a period of 3 days, the mixture being kept at 0°. After standing 2 days longer, the solution was filtered and the alcohol removed. The residual oil was shaken for 7 hours with saturated sodium bisulphite solution, but no bisulphite compound was formed. (The starting material does not form a bisulphite compound.) The product was treated with semicarbazide hydrochloride and sodium acetate in cold aqueous alcohol and the semicarbazone, which was slowly formed, filtered off. On crystallisation from alcohol it formed white needles, m.p. 162 - 164°. After several recrystallisations it had m.p. 168°.

Found:	C, 67.93, 68.06;	H, 10.12, 10.16;	N, 15.59%,
$C_{16}H_{29}ON_3$ req.	C, 68.8;	H, 10.47;	N, 15.04%,
$C_{15}H_{24}ON_3$ req.	C, 68.0;	H, 10.26;	N, 15.85%.

BIBLIOGRAPHY.

1) Gladstone, J.C.S., 1864, 1.

2) Piesse C.r., 57, 1016.

3) Kachler Ber., 1871, 4, 36.

4) Semmler and Jakabowicz Ber., 1914, 47, 2252.

5) Tschirch Arch. pharm., 1895, 223, 278.

6) Scherndal J.A.C.S., 1915, 37, 167.

7) Scherndal Ibid., 1537

8) Auspurger Science, 1915, 42, 100.

9) Kremers J.A.C.S., 1923, 45, 717.

10) Ruzicka and Rudolph Helv., 1926, 9, 118.

11) Thiele and Buhner Ann., 1906, 347, 249.

12) Thiele and Bulhorn Ann., 1906, 348, 9.

13) Ruzicka, Pontalti and Balas Helv., 1923, 6, 855.

14) Ruheman and Lewy Ber., 1927, 60, 2464.

15) Herzenberg and Ruheman Ber., 1925, 58, 2249.

16) Ruzicka and Haagen-Smit Helv., 1931, 14, 1104.

17) Ornstein Phys. Zeit., 1927, 28, 688.

18) Asahina and Nakanishi C., 1932, I, 246.

19) Pfau and Plattner Helv., 1936, 19, 858.

20) Melville J.A.C.S., 1933, 55, 3288.

21) Birrell J.A.C.S., 1935, 57, 893.

22) Heilbron, Morton and Webster Biochem. J., 1932, 26, 1194.

23) Ruzicka and Rudolph Helv., 1927, 10, 916.

24) Treibs	Ber., 1935, 68, 1751.
25) Kompa	C., 1933, II, 3121.
26) Ruzicka, Pieth, Reichstein and Eheman	Helv., 1933, 16, 268.
27) Huckel and Schnitzpahn	Ann., 1933, 505, 274.
28) Pfau and Plattner	Helv., 1937, 20, 224.
29) Plattner and Wyss	Helv., 1940, 23, 907.
30) Pfau and Plattner	Helv., 1939, 22, 202.
31) Wolff	Pharm. Zeit., 1878, 82.
32) Hock	Arch. Pharm., 1883, 221, 17.
33) Tschirch and Hohenadel	Arch. Pharm., 1895, 233, 259.
34) Schlapfer and Stadtler	Helv., 1926, 9, 185.
35) Wilstaedt	Ber., 1935, 68, 333.
36) Susz, Pfau and Plattner	Helv., 1937, 20, 469.
37) Tomotsuni and Taira	J.Agr.C.S.Jap., 11, 594.
38) Ruheman and Benthin	Braunkohle, 1925, 23, 765.
39) Wislicenus and Hentschel	Ann., 1893, 275, 312.
40) Wallach	Ber., 1896, 29, 2963; 1897, 30, 1094.
41) Willstaedt	Ber., 1936, 69, 997.
42) Wallach	Ann., 1905, 339, 113.
43) Braun and Werner	Ber., 1929, 62, 1050.
44) Tsukervanik and Nazarova	J.Gen.Chem., 1937, 7, 623.
45) Meyer and Bernhauer	Sitzungsber. (Vienna), 138, IIb, abt.II, 721.
46) Haworth et al.	J.C.S., 1939, 1302.
47) Gerhardt and Cahours	Ann., 1841, 38, 92.

48) Spica — Gaz., 1879, 9, 433.

49) Paterno and Spica — Gaz., 1876, 6, 535.

50) Vavon and Callier — Bul., 1927, (4), 41, 677.

51) Foster — Org.Syn., XIII, 110.

52) Blaise — Bul., 1905, (3), 33, 39.

53) c.f. Reichstein — Helv., 1939, 23, 136.

54) c.f. Schoenheimer — J.Biol.Chem., 1935, 110, 461.

55) Courtot and Pierron — Bul., 1929, (4), 45, 290.

56) Kamm and Marvel — Org.Syn., I, 3.

57) Walden — Ber., 1907, 40, 3216.

58) Pfau and Plattner — Helv., 1939, 22, 640.

59) Pfau and Plattner — Helv., 1940, 23, 791.

60) Barbier — Helv., 1940, 23, 519.

61) Stoll and Scherner — Helv., 1940, 23, 941.

62) Mosettig and Burger — J.A.C.S., 1930, 52, 3456.

63) Adamson and Kenner — J.C.S., 1939, 181.

ACKNOWLEDGMENTS.

In conclusion, I should like to express my appreciation and gratitude to my supervisors, Professor J. W. Cook and Dr. D. T. Gibson for their invaluable guidance, encouragement and interest in the work; to Professor Cumming for the use of the high pressure autoclave at the Royal Technical College, Glasgow; to Mr. James Cameron for micro-analyses; and to the Carnegie Trustees for the award of a Research Scholarship during the years 1939 - 41.