STUDIES IN ESSENTIAL OILS

A dissertation submitted to

THE UNIVERSITY OF POONA

for

The Degree of Doctor of Philosophy

by

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INTRODUCTION

India is very rich in essential oils-bearing plants. For the last several years considerable amount of work is being carried out in the National Chemical Laboratory of India, Poona, on the systematic examination of various essential oils of Indian origin. The work incorporated in this thesis forms part of the material collected by the author during the course of these investigations. The National Chemical Laboratory is well provided with the latest type of equipment and chemicals necessary for work or essential oils.

During the course of the present investigation several Indian essential oils have been examined and their constituents characterised and the structures of the new constituents elucidated. In the first paper of the series, isolation and characterisation of a new sesquiterpene hydrocarbon obtained from Malabar lemongrass oil (Cymbo-pogon Flexuosus, Nees ex. Steud Watt) have been described and its structure established. It belongs to the cadinene group and has been named as Y_1-cadinene. Another component isolated from the same oil has been systematically degraded and found to be identical with Elimicin (1, 2, 6 -trimethoxy-4-allylbenzene), which is the main constituent of Manila Elimi oil. In the third paper of the series, the structure of mint-glyoxal, the main constituent of Indian spearmint oil, obtained from the plant grown in our own nursury, has been rigidly established by cyclising it to thymol. Structures of many derivatives of mintglyoxal have also been studied thoroughly. Mintglyoxal is the first glyoxal derivative isolated from essential oils. During these investigations, specially when studying the structure of mintglyoxal, considerable help was obtained from the study of ultra-violet and infra-red spectra of various compounds. Infra-red study was particularly helpful in detecting the cyclopropane ring in mintglyox~~c~~al and its various derivatives. It was also observed, that only limited amount of information is available about the infra-red behaviour of cyclopropane ring-system. Consequently, infra-red spectra of several terpenoid compounds containing isolated or fused cyclopropane ring have been studied in the 3.2-3.4 μ region, which according to recent evidences appears to be more reliable than 9.8 -10 μ region studied by earlier workers. In connection with the infra-red investigation, isolation of the fused-cyclopropane ring containing, tricyclic compound α-santalene became necessary. This has been now isolated in a pure state for the first time along with its isomer-β-santalene by fractionation of santalene fraction of sandalwood oil through a packed column fitted with a batch-strip distillation head. This type of head is likely to be very useful in the separation of the components of essential oils, specially those which are nonpolar in nature. As a continuation of this work, approaches towards the synthesis of the tricyclic-alcohol- α-Santalol have been made and several of its important degradation products synthesised. Ultimate reduction of α-santalic acid to α-santalol with lithium-aluminiumhydride is under investigation.

In the next paper of the thesis, results of our investigation on the tricyclic hydrocarbon longifolene, the main constituent of the higher boiling fraction of Indian turpentine oil, have been described. Two new lactonic derivatives obtained by the ozonisation of longifolene are likely to throw more light on the now accepted structure for this interesting hydrocarbon. Another new bicyclic sesquiterpene hydrocarbon $-\beta$ longifolene isolated from the longifolene fraction has also been investigated.

Finally certain dimeric cyclohexanone derivatives have been examined. This particular investigation is not directly related to the main theme of the thesis, but it was expected that the investigation of these compounds might be helpful in developing suitable approaches for the synthesis of sesqui-,di- and poly-terpenes.

The author has purposely avoided any general introduction on the chemistry of essential oils and terpenes. The subject is too well-known to need any repetition. Most of the salient features required for emphasising a particular point have been incorporated in the body of the thesis, where~~e~~ver necessary.

N.C.L. Poona 8.
India
June 1956

B. B. Ghatge.

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PART I.

CONSTITUENTS OF MALABAR LEMONGRASS OIL.

Structure of the new sesquiterpenic hydrocarbon
y_1- cadinene.

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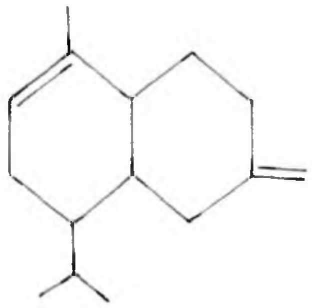
SUMMARY.

Malabar lemongrass oil (Cymbopogon Flexuosus Nees ex. Steud Watt.) has been found to contain a new bicyclic, sesquiterpene hydrocarbon ($C_{15}H_{24}$) containing two double bonds. From systematic examination of this material, its derivatives and degradation products, it has been conclusively established that the hydrocarbon has the following structure:



It belongs to the cadalene group and has been named as y_1-cadinene.

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General Introduction:

Cymbopogon group consists of a wide variety of grasses from which many essential oils of great commercial importance are obtained; e.g. palmarosa oil[1] (motia and sofia), citronella oil and lemongrass oil. Palmarosa oil (motia) obtained from the grass *Cymbopogon martini* Stapf. (Syn. *Andropogon martini* Roxb.) holds a place of prominence among the aromatic grasses in India. Its main constituent is geraniol, which is present to the extent of nearly 90 percent in the Illichpur variety of the oil. However, the most important aromatic grass of India is *Cymbopogon flexuosus* (D.C.) Stapf. from which the commercially important lemongrass oil[2] is obtained. Its main constituent is citral, which is the basic raw material for the synthesis of α- and β-ionones and finally for that of vitamin A. Similarly, citronella oil is also of great commercial importance and is obtained mainly from Java, Ceylon, Formosa[3] and also to some extent from Guatemala, Haiti and Honduras. This oil is a rich source of geraniol and citronellal which are extensively used in perfumary industry.

Apart from the important grasses mentioned above, cymbopogon group also contains many minor members. Botanical identity of some of these is not conclusive and their oils have not been properly examined. In the literature[4] more than 25 specimens of oil obtained from such less well-known grasses have been examined. In many cases the examination did not proceed beyond recording the common physico-chemical constants.

Present investigation:

Recently, we have been getting supply of a similarly less well-known oil from the Department of Agriculture, Government of Madras. The grass was grown under the strict botanical control in the Government Botanical Gardens, Ootacamund, Madras. It is locally known as "Malabar lemongrass oil", though, as will be evident from the subsequent part of the text, it has no~~t~~ similarity to the commercially important lemongrass oil (Cymbopogon flexuosus). The grass was initially identified as Cymbopogon nardus, Rendle, by the systematic botanist, Government of Madras. Later on, it has been examined in Kew Gardens, London, where it has been named as Cymbopogon flexuosus (Nees ex.Steud Watt.). The oil was isolated by hydro-distillation in a copper still and was of excellent quality. It was pale yellow in colour with a sweet persisting odour which should make it an excellent perfume for soap and other cosmetics.

Composition of the oil:

Chakravarti and Bhattacharyya[5,6] have initially examined this oil. The lower boiling fraction was found to contain l-α-thujene, l-α-pinene, l-camphene, l-limonene, l-borneol and l -terpeneol(?). Among the higher boiling components, along with other uncharacterised products, they isolated two sesquiterpene hydrocarbons and two oxygenated components, which have been named by them as "hydrocarbon A, hydrocarbon B, alcohol A and alcohol B", respectively. One of the hydrocarbons, hydrocarbon B was obtained in a comparatively pure state and was also characterised by them to some extent.

Isolation and nomenclature:

In this part this hydrocarbon has been examined in details and its structure established. It has been found to be a new hydrocarbon of ca~~r~~dinenic type and the author would like to name it as 'γ_1-cadinene', and in future it will be referred to only by this name.

In naming th~~is~~ compound, the author has tried to follow the procedure adopted by Haagen-Smit[7] to avoid any unnecessary confusion (this is actually one of the four unknown cadinenic type hydrocarbons referred to as γ-cadinenes by him).

In this investigation γ_1-cadinene was actually isolated from a fresh consignment of the oil obtained from the Government of Madras. For separation of the various constituents of the oil, the most modern fractionation units, fitted with total condensation partial take off type heads were used.

(i) Tower's triple jacketed, electrically heated, fractionating column (....25 plates).

(ii) Emil-Greiner's fractionating column, fitted with automatic fraction collector (.....60 plates).

(iii) Locally fabricated tall column (.....100 plates).

(iv) A small micro-column (....15 plates) was also used whenever necessary.

The lower boiling fractions of the oil were removed by quick distillation in vacuum. The higher boiling fractions were then carefully fractionated through the above mentioned columns. The course of separation was followed by noting the change of boiling point, refractive index and optical rotation of the various fractions. γ_1-cadinene boiled mostly at

125-129^{o}/9 mm. It was once distilled over sodium and then again systematically fractionated through Tower's column using a batch-strip head (Photograph I, in part V), when the material was obtained in a pure state. It was once again distilled over fresh sodium (details will be available in the experimental part).

The general properties of thi~~s~~ present sample of γ_1-cadinene were more or less identical with those described by Chakravarti and Bhattacharyya[5,6], except that the optical rotation and the boiling point were somewhat higher, probably, due to this material being slightly purer. The hydrocarbon was then subjected to systematic examination for the determination of its structure.

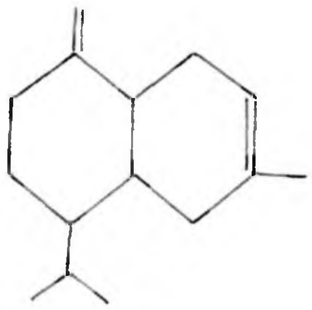
Structure of γ_1-cadinene:

Elemental analysis of y_1-cadinene corresponded to the molecular formula $C_{15}H_{24}$. The determination of unsaturation value with perbenzoic acid distinctly, indicated the presence of two double bonds. It did not show any specific absorption in the ultra violet region, thus indicating that the two double bonds were not in conjugation. To get an idea of the basic ring structure of y_1-cadinene, it was subjected to dehydrogenation with selenium, when copious amount of cadalene was obtained. Cadalene was characterised as its picrate and T.N.B. derivative. The hydrocarbon therefore belonged to the cadinene group of sesquiterpenes.

On hydrochlorination in ethereal solution with anhydrous hydrogenchloride y_1-cadinene formed copious amount of cadinenedihydrochloride,m.p.117-118°. However, unlike cadinene, it failed to give any nitrosochloride. It also failed to give the usual colour reaction of cadinene, though closely related to it.

On ozonisation, γ_1-cadinene formed copious amount of formaldehyde as the only volatile component. This indicated that at least one of the double bonds was of the methylenic type ($=CH_2$). The non-volatile portion ~~of ozonide~~ obtained after decomposition of the ozonide in the usual way, gave various tests for aldehyde and methyl ketone (iodo form test, Legal's test etc.). The second double bond present in γ_1-cadinene, therefore, was of the type $-CH=C<^{CH_3}$.

From these observations one can arrive at the following three structures (I, II and III). All these three structures will explain the formation of cadalene on dehydrogenation, cadinenedihydrochloride on hydrochlorination, formation of formaldehyde, methyl ketone and aldehyde on ozonalysis, and other properties.



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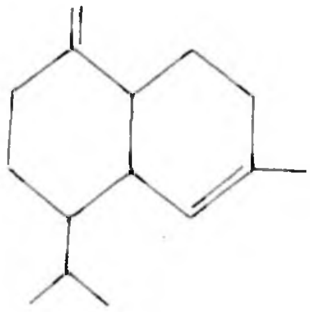

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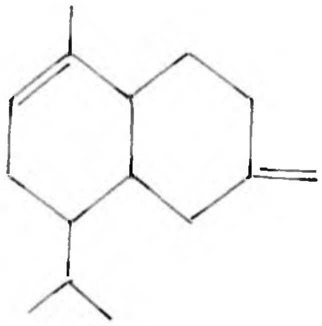

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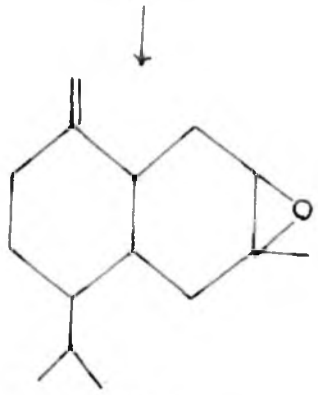

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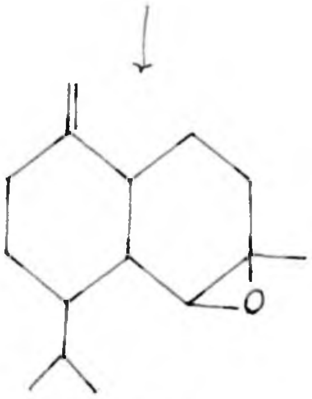

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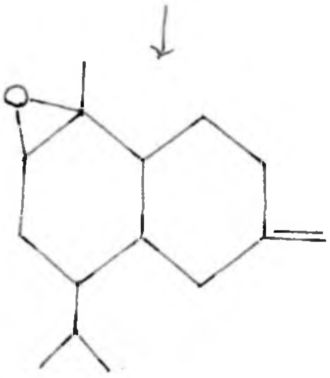

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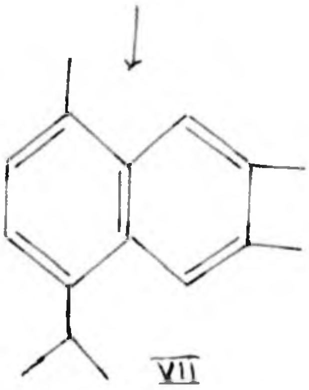

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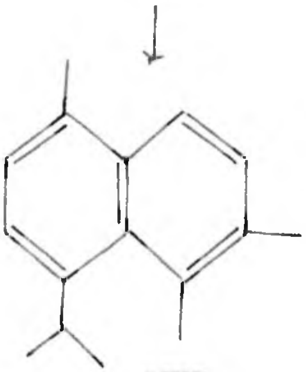

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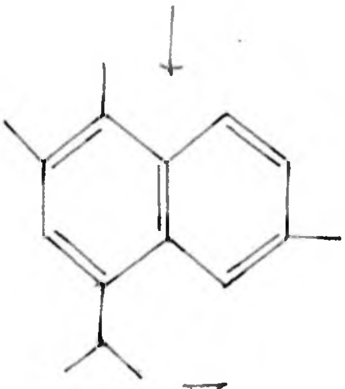

IX

Confirmation of the structure:

To decide among these structures, the author employed the epoxide method as used by Campbell and Soffer[8,9] in establishing the position of double bonds in cadinene itself. In this experiment a sesquiterpene is converted to an epoxide by the reaction with perbenzoic acid. The epoxide ring is then opened by reacting with adequate proportion of magnesiummethyliodide and the resulting tertiary alcohol subsequently dehydrogenated to a substituted cadalene, which can be characterised easily through various derivatives.

At the initial stage in the actual experiment, y_1-cadinene was treated in chloroform solution with a molar proportion of perbenzoic acid. It is now quite well-known that compared to endocyclic double bonds, semicyclic double bonds ($=CH_2$) are slow to react with peracids to form the epoxide. Consequently, in a compound containing two double bonds, one of which is semicyclic, if a molar proportions of peracid is added, it is the endocyclic double bond which reacts preferentially to give a mono-epoxide.

In the present case also when we prepared the mono-epoxide of y_1-cadinene, it was found that the methylene group ($=CH_2$) has remained intact, as the resulting monoepoxide gave copious amount of formaldehyde on ozonolysis.

In the next stage, this monoepoxide was treated with a mole of methylmagnesiumiodide and the tertiary alcohol thus obtained was directly subjected to sulphur dehydrogenation, when, 1,2,6-trimethyl-4-isopropyl-naphthalene (IX) was obtained in very high yield. It was characterised as its picrate and T.N.B. derivative[8] and also by analysis. This result conclusively showed that y_1-cadinene must be represented by the structure (III). Structures (I and II) under similar condition would have given 1,6,7-trimethyl-4-isopropyl-naphthalene (VIII) and 1,5,6-trimethyl-4-isopropylnaphthalene (VIII) respectively. It was very easy to distinguish these compounds from 1,2,6-trimethyl-4-isopropylnaphthalene (IX), as their derivatives differ widely in their melting points[8,11].

Isolation of y_1-cadinene from essential oils has not been reported by any earlier workers. Other similar cadinenic hydrocarbons have been, however, reported in the literature[10].

As γ_1-cadinene is a new terpenic component its infra-red spectrum has been included in this part (Curve I). Strong absorption in the 11.29 and 11.40 μ region indicates the presence of $=CH_2$ double bond. The existance of the other double bond ($-CH{=}C{<}^{CH_3}$) is indicated by strong absorption in 12.29 μ region.

The ultra violet spectrum of γ_1-cadinene, though examined, has not been included in this part for the sake of brevity, as due to the isolated nature of the two double bonds it did not show any sharp specific absorption.

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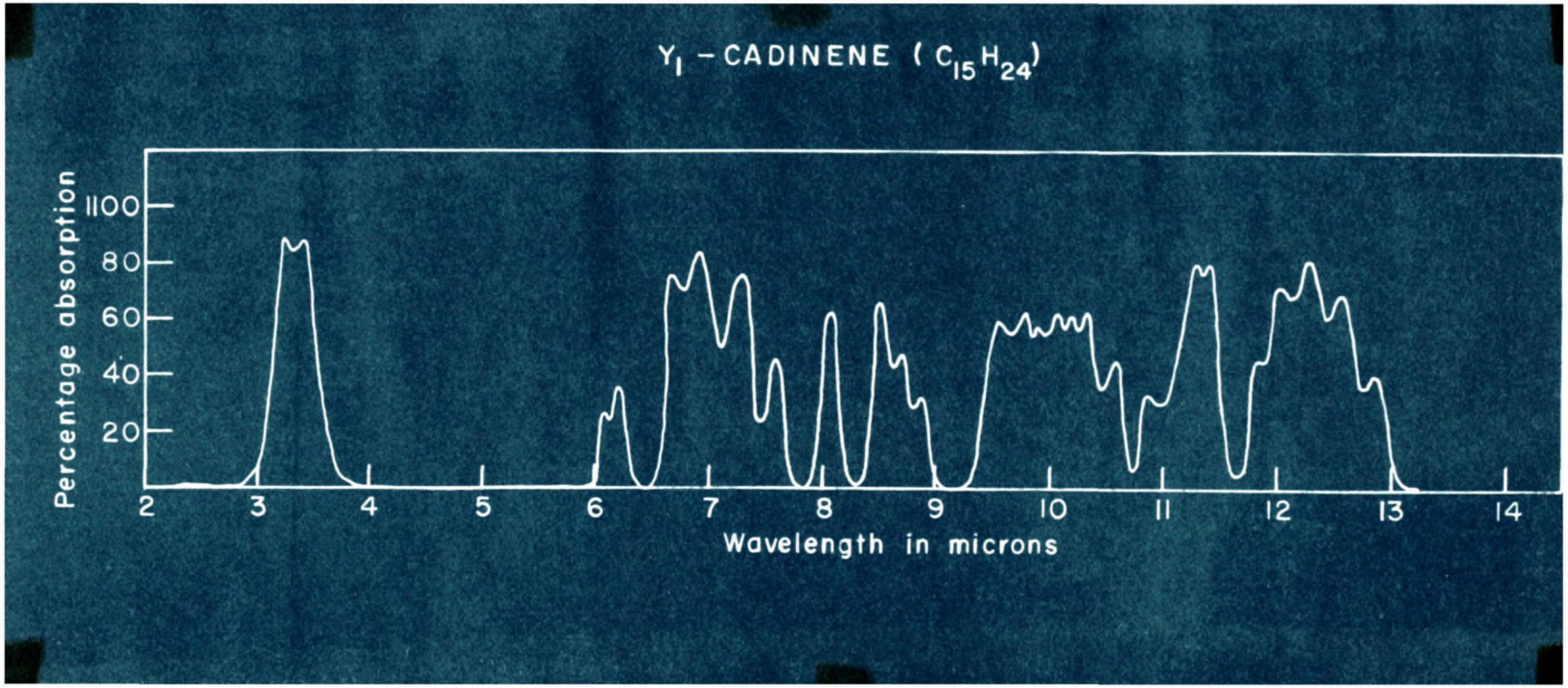

Y$_1$ - CADINENE ($C_{15}H_{24}$)

EXPERIMENTAL.

The oil, as obtained from the Government of Madras, was pale yellow in colour with a sweet persisting odour. It showed the following properties:

n_D^{24}	1.4841;
α_D	-27.6°;
d_4^{30}	0.9351;

acid value 1.1; ester value 8.29.

For the isolation of γ_1-cadinene the following procedure was followed:

The oil was initially distilled in vacuum through Tower's column and divided into three main fractions:

Fraction I	b.p. upto 80°/ 1 mm.
Fraction II	b.p.80-104°/1 mm.
Fraction III	higher boiling residue.

Fraction II was mainly a mixture of γ_1-cadinene along with an another tricyclic hydrocarbon about which the author would not make further discussion in this part. This hydrocarbon fraction was then carefully fractionated in vacuum through Tower's column under high reflux ratio~~s~~ and divided into 14 fractions, about 12 ml. each. On the basis of our previous experience, the course of separation was followed by noting systematically the boiling point and refractive index, and wherever necessary, the optical rotations of various fractions. The details have been recorded in table below:

TABLE I

No. of fraction	b.p./9 mm.	Refractive index at 24°	Optical rotation
1	104-108°	1.4836	
2	110°	1.4852	
3	110-112°	1.4896	
4	112-116°	1.4930	+16°.1
5	116-117°	1.4945	
6	117°	1.4950	
7	117-118°	1.4955	
8	118-120°	1.4974	+ 2°.2
9	120-122°	1.5002	- 0°.7
10	122-125°	1.5040	
11	125-127°	1.5082	
12	127°	1.5090	
13	127-128°	1.5098 (20 ml.)	-22°.6
14 Total distillation	128-129°	1.5126 (70 ml.)	-28°.2

γ_1-cadinene contained in the last seven fractions, but mainly in fractions 13 and 14. These two fractions (90 ml.) were then combined and carefully fractionated through Emil-Greiner's fractionating column fitted with automatic time head, when γ_1-cadinene was obtained in pure state. It was finally purified by distilling two times over sodium. It showed the following properties:-

b.p.128-129/9 mm.

$n_D^{24.5}$ 1.5130

α_D -31°.8

d_4^{30} 0.9262

About 70 g. pure γ_1-cadinene could be isolated from approximately 3 kg. of the oil.

Analysis:

Found: C, 87.82; H, 11.80;

$C_{15}H_{24}$ requires C, 88.16; H, 11.84%.

Unsaturation value:

It was determined by addition with perbenzoic acid solution in chloroform in the usual way. Unsaturation value found (24-48 hours) 2.05 - 2.1.

Dehydrogenation of γ_1-cadinene:

The hydrocarbon (3 g.) was mixed with selenium (12 g.), heated in a adequate flask with a long air condenser at about 290-310° for 36 hours. Dehydrogenation product was distilled in vacuum and then further purified by distilling once over a pinch of zinc dust, b.p.143-145/5 mm. In alcoholic solution with picric acid in the conventional way it gave copious amount of orange-yellow picrate, which after one crystallisation from alcohol gave pure cadalene-picrate,m.p.115.5 - 116°; mixed melting point with an authentic sample remained undepressed.

Ozonisation:

γ_1-cadinene (1 g.) was fully ozonised in carbontetrachloride solution at 0° using a Tower's ozone generator with eight percent ozonised oxygen. The volatile product collected during ozonisation and also after decomposition of the ozonide with water in the conventional way, gave copious amount of formaldehyde, characterised as its dimedone derivative, m.p. and mixed m.p. 189°. The non-volatile portion gave strongly positive test for methyl-ketone (iodoform test,) and aldehyde (Fehling's solution and ammonical silvernitrate solution).

Preparation of the mono-epoxide (VI):

To a cooled solution of the hydrocarbon (20 g.) in chloroform (50 ml.), a chilled (-5°) chloroform solution of perbenzoic acid (317 ml., approximately 0.65 N) was added with shaking and cooling in three instalments during 1½ hours and the mixture left in the frigidaire overnight. The solution was washed free of acidic material with dilute sodiumcarbonate solution followed by water. After drying, (sodiumsulphate), the solvent was removed and the residue carefully fractionated. The main fraction (14 g. b.p.130°/5 mm., $n_D^{25.5}$ 1.4995) was a colourless, mobile liquid. The oxide decolourised bromine in chloroform and did not react with 2:4-dinitrophenylhydrazine indicating the absence of any isomerisation of the oxide to a carbonylic compound. On ozonolysis it furnished copious amount of formaldehyde, characterised as its dimedone derivative m.p.189°; mixed melting point with an authentic sample was undepressed.

Analysis:

Found: C, 80.89; H, 10.76;

$C_{15}H_{24}O$ requires C, 81.76; H, 10.98%.

The analysis showed that probably a trace of the dioxide was also present.

Reaction of mono-epoxide with Grignard reagent:

To a Grignard solution prepared from magnesium (5.5 g.), methyliodide (19.5 ml.) and anhydrous ether (150 ml.) cooled in a freezing mixture, an ethereal solution of the monoxide (14 g.) was added slowly with stirring. The reaction mixture was allowed to reach the room temperature and then finally refluxed for 48 hours. The solution was cooled, decomposed with ice and hydrochloric acid, extracted with ether and the ethereal extract washed successively with a solution of sodiumthiosulphate, sodiumcarbonate and water. The practically colourless solution was dried (sodiumsulphate) and the solvent removed, when 14 g. of a slightly viscous liquid was left behind.

Isolation of 1,2,6-trimethyl-4-isopropylnaphthalene(IX):

The crude carbinol (14 g.) was dehydrogenated with sulphur (6 g.) by heating for 5 hours at 190-210° in the usual manner. On distillation it gave a mobile liquid (10 g.) which was once distilled over zinc dust and then carefully fractionated using a micro-fractionating column (......15 plates) fitted with adequate head. Seven different fractions each about 1·3 g., were collected, the boiling points of which at 5 mm. are recorded: (i) 143°, (ii) 143°, (iii) 144°,

(iv) 146°, (v) 146°, (vi) 146° and (vii) residue. The last three fractions were almost pure 1,2,6-trimethyl-4-isopropylnaphthalene, as treatment with picric acid and trinitrobenzene in alcohol, furnished the corresponding derivatives in pure state after one or two crystallisations. Picrate (alcohol) m.p.142-143°, literature[8], m.p.142-143°; (1,6,7-trimethyl-4-isopropylnaphthalene-picrate[8], m.p. 122-123°; 1,5,6-trimethyl-4-isopropylnaphthalenepicrate[11] m.p.102.5-103.5°).

Analysis:

Found: N, 9.52;

$C_{22}H_{23}N_3O_7$ requires N, 9.56%.

T.N.B. derivative (methanol) m.p.167-168°; literature[8], m.p. 167-168°; (1,5,6-trimethyl-4-isopropylnaphthalene T.N.B. derivative[11] m.p. 160-161°).

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REFERENCES.

1. Guenther, The Essential Oils, IV, p.5-20, (1950).

2. Guenther, The Essential Oils, IV, p.20-37, (1950).

3. Guenther, The Essential Oils, IV, p.65-137, (1950).

4. Guenther, The Essential Oils, IV, p.131-153, (1950).

5. Chakravarti and Bhattacharyya, P.and E.O.R., 1954, , 184-185.

6. Chakravarti and Bhattacharyya, P. and E.O.R., 1955, 46, 365-368.

7. Haagen-Smitt, Fortschritte der Chemie Organischer Naturstoffe, Vol. XII, p.4.

8. Campbell and Soffer, J.Am.Chem.Soc., 1942, 64, 417.

9. Razdan and Bhattacharyya, P. and E.O.R., 1955, 46, 8.

10. Herout and Santavy, Collect.Czech.Chem.Communs, 1954, 19. 118.

11. Sukh Dev and Guha, J.Ind.Chem.Soc., 1948, 25, 69.

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PART II

CONSTITUENTS OF MALABAR LEMONGRASS OIL

Structure of the oxygenated component

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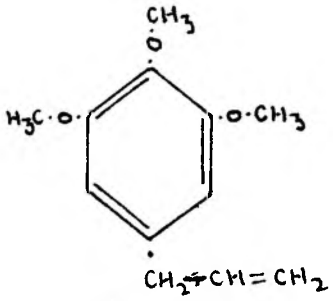
SUMMARY

In this part, the structure of another component of Malabar lemongrass oil has been described. From systematic degradation of this material and its derivatives, it has been found to possess the structure given below:



It is identical with elemicin which is a major component of Manila Elemi oil. The existence of this non-terpenic material in "Malabar lemongrass oil" is very interesting, as most of the other components of the oil are terpenic in nature.

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General introduction:

Isolation and characterisation of γ_1-cadinene from Malabar lemongrass oil has been described in part I of this thesis. Malabar lemongrass oil also contains many other components, one of the fraction b.p.139-40^{o}/9 mm.; n^{24}_{D} 1.5255; α_D +5.16^{o} has been referred to by Chakravarti and Bhattacharyya[1,2]. These authors however could not purify the compound properly and made only preliminary studies about its nature and indicated that it was a methoxylated compound corresponding approximately to a molecular formula $C_{13}H_{18}O_3$. They had named it as 'Alcohol B', as it gave somewhat positive xanthate test. This compound now has been examined in details and its structure established.

Purification:

From a critical examination of this material the author was soon led to believe that it was an optically inactive compound containing small quantities of an alcohol as impurity, which was responsible for the optical rotation of the material and also for the positive response to the xanthate test. This has been proved by intensive fractionation of larger amount of this material through Tower's column using a batch-strip head (photograph I, part V), when an almost optically neutral sample of the material was obtained. This purification of the material could also be achieved by removing the alcoholic impurity as boric ester.

Material thus obtained which was almost analytically pure (as will be indicated later), was used for our investigation

Fraction thus purified showed the following properties:

b.p.128-129/3.5-4 mm.

$n_D^{24.5}$ 1.5221

α_D +1°.1

d_4^{30} 1.0561

Critical examination of the material as detailed below was suggestive of the formula $C_{12}H_{16}O_3$ in preference to $C_{13}H_{18-20}O_3$ suggested earlier[2]. The results of molecular weight determination, 206.26 (Thermister method), and 209.4 (Cryoscopic method), also agreed almost exactly with the formula $C_{12}H_{16}O_3$ (molecular wt. 208.25).

Degradation experiments:

The determination of the methoxyl value of the material gave a value as high as 38.02%. This indicated that the material was most likely a methoxylated benzenoid compound. It was therefore subjected to oxidation with potassium-permanganate when a highly crystalline acid m.p. 169° was obtained in very good yield. This was identified as 3,4,5-trimethoxy-benzoic acid (III) by equivalent weight, analysis, methoxyl estimation,and finally by a mixed melting point with an authentic sample.

On ozonisation, this material furnished copious amount of formaldehyde (IV), which was characterised as its dimedone derivative m.p. and mixed m.p. 189°.

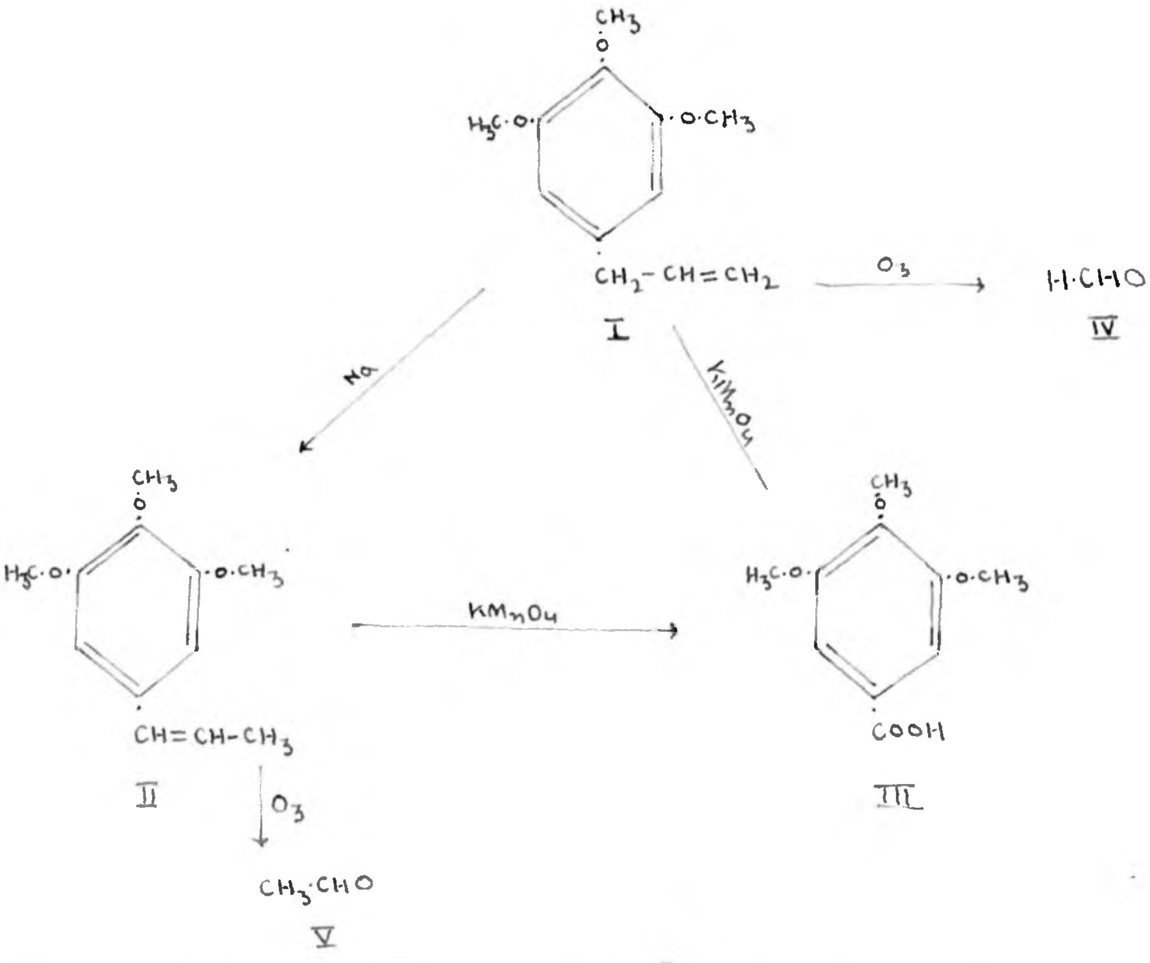
Identification as elemicin:

From these degradation studies and the physical data recorded earlier, the material appeared to be 'elemicin' 1,2,6-trimethoxy-4-allylbenzene (I), whose properties as mentioned in the literature are recorded below for ready reference.

b.p.152-156°/17 mm[3]; 144-147°/10mm.[4]

n_D^{20} 1.52848[4]

d_{20} 1.063[4]



Elemicin has been shown by Semmler[5] to be the major constituent of Manila elemi oil. It has also been found to be present in a few other volatile oils[6,7].

Conversion to isoelemicin:

Identity of the compound under discussion as elemicin was further confirmed by distilling over sodium according to the procedure described by Semmler[5], when it was converted to almost pure optically neutral iso-elemicin(II) having the following properties:

b.p.150-153°/10 mm;
$n_D^{25.5}$ 1.5486;

These properties almost agreed with those described in the literature for iso-elemicin:

b.p.153-156/10 mm.;
n_D^{20} 1.54679.

The identity of the isomerised product as iso-elemicin was established as follows:-

(i) Oxidation with potassiumpermanganate gave 3,4,5-trimethoxybenzoic acid (III), m.p.169°;

(ii) Ozonisation gave copious amount of acetaldehyde(V), characterised as its dimedone derivative, m.p.138-139°, and finally ;

(iii) bromination gave the dibromide, m.p.88-89°, identical with dibromide described in the literature.[8]

The methoxylated fraction isolated from Malabar lemongrass oil was, therefore, clearly identical with elemicin. But as indicated by elemental analysis of the material and also its isomerised product, iso-elemicin, it probably contains a non-alcoholic impurity which was also not completely eleminated during sodium treatment. Most likely, that Malabar lemongrass oil might be containing a dimethoxy benzonoid derivative somewhat similar to elemicin and having a boiling point close to that of elemicin.

EXPERIMENTAL

Isolation of elemicin:

Elemicin was isolated from the higher-boiling residue of Malabar lemongrass oil (vide part I, page ; fraction III, residue). This residual fraction was initially distilled through Tower's column and the material boiling between 104-115°/1 mm. was collected. This fraction (450 g.) was then intensively fractionated under high reflux ratio through the same column and divided into about 14 fractions of 20 ml. each. The course of fractionation was followed by noting the boiling point, refractive and the solubility in 70% alcohol. The results are tabulated below:

No.of fractions	b.p./0.6 mm.	refractive index at 24°	Solubility in 70% alcohol
1	98-100°	1.4978	insoluble
2	100-102°	1.4980	partially soluble
3	102-104°	1.4990	"
4	106°	1.5018	"
5	106-110°	1.5008	"
6	110°	1.5162	soluble
7	111°	1.5178	"
8	111°	1.5178	"
9	111°	1.5180	"
10	111°	1.5190	"
11	111°	1.5190	"
12	111°	1.5190	"
13	111°	1.5200	"
14 Total distillation	113-115°	1.5236	"

Fractions 1 to 5 were partially composed of hydrocarbon as indicated by the insolubility of this material in 70% alcohol. Fractions 6 to 13, which were soluble in 70% alcohol, were composed mostly of an oxygenated material about which the author would not make further reference.

Fraction 14, which was actually the total distillate of the entire residue left after removal of the earlier fractions described above, was mainly composed of elemicin. By careful fractionation through Tower's column, it was divided into many batches using a batch-strip head (photograph in part V), when finally almost pure elemicin was obtained. This fraction did not give any xanthate test but as shown by its analysis, it probably still contained traces of a hydrocarbon or non-alcoholic oxygenated material, as an impurity. It showed the following properties:

b.p.139-40°/9 mm., 114-115°/0.6 mm.

n_D^{28} 1.5248.

d_4^{30} 1.058

α_D +1°.0

<u>Molecular weight</u>:

Molecular weight was determined by Thermister and also by Cryoscopic methods.

<u>Thermister method</u>: Found: 206.26.

<u>Cryoscopic method</u>: Found: 209.45. $C_{12}H_{16}O_3$ requires: 208.25.

<u>Analysis</u>:

Found: C, 70.21; H, 7.80; methoxyl, 38.62; $C_{12}H_{16}O_3$ (trimethoxy) requires: C, 69.21; H, 7.75; methoxyl, 44.7%.

The material described above was mostly used in our experiments.

Elemicin having similar properties could also be isolated by removing the alcoholic impurity as boric ester. For this purpose, elemicin fraction (50 g.), boric anhydride (6.8 g) and anhydrous toluene (350 ml.) were heated with azeotropic distillation arrangement during 36 hours. After removal of the solvent, elemicin was removed by vacuum distillation. Boric ester of the alcoholic contaminents was retained in the flask as residue. The elemicin fraction (40 g.) thus purified was then carefully fractionated through Tower's column, when nearly pure elemicin, having properties comparable to those recorded earlier, was obtained.

Oxidation with potassium permanganate and isolation of 3,4,5-trimethoxy-benzoic acid:

Potassiumpermanganate (12 g.) was added in small quantities at short intervals to a mechanically stirred mixture of elemicin (4 g.), water (300 ml.) and sodiumhydroxide (0.5 g.). After the oxidation was complete (5 hours) the reaction mixture was filtered. The precipitated manganous oxide was washed with a little water and the combined filtrate was acidified with a dilute sulphuric acid. In about 5-10 minutes time the 3,4,5-trimethoxy benzoic acid started separating out. The solution was however left in the frigidaire overnight. The crystals were separated by filtration and washed with a little water when pure 3,4,5-trimethoxy benzoic acid (2.5 g) was obtained, m.p.169°, which did not change on further crystallisations from alcohol. Mixed melting point with an authentic sample remained unchanged.

Analysis: Found: C, 56.91; H, 5.61; methoxyl, 42.64; eq.wt. 210.5

$C_{10}H_{12}O_5$ requires: C, 56.60; H, 5.70; methoxyl, 43.8% eq.wt. 212.0.

Ozonolysis:

Elemicin (1 g.) was ozonised in usual way using a standard ozone generator. The volatile material, which was trapped in ice water, was composed entirely of formaldehyde, characterised as its dimedone derivativel m.p.189° and mixed melting point with an authentic sample 189°.

Conversion to iso-elemicin:

Elemicin fraction (20 g.) was mixed with sodium (5 g.) and was refluxed under reduced pressure (10 mm., bath temperature 150-160°) for about 20 minutes and then distilled under vacuum in the usual way, when isoelemicin was obtained as a mobile, colourless liquid (15 g.) having following properties:

b.p. 150-153°/10 mm.

$n_D^{25.5}$ 1.5486

α_D 0°

d_4^{30} 1.064.

These values are more or less same as described in the literature[1] b.p.153-156°/10 mm.

n_D^{20} 1.54679

d_{20} 1.063.

Ozonolysis of isoelemicin: (isolation of acetaldehyde):

Isoelemicin (1 g.) was ozonised in usual way. The volatile matter was identified as acetaldehyde through its dimedone derivative, m.p.138-39°; mixed m.p. with an authentic sample remained undepressed.

Oxidation of isoelemicin with potassiumpermanganate:

By following the same procedure as in the case of elemicin itself, isoelemicin (4 g.) was oxidised with potassiumpermanganate, when 3,4,5-trimethoxybenzoic acid (2.5 g.), m.p. 169° was obtained. Mixed melting point with an authentic sample remained undepressed.

Preparation of isoelemicin dibromide:

Isoelemicin was finally characterised as its dibromide. The material (2 g.) was dissolved in carbontetrachloride and was brominated by using requisite quantity of bromine with ice cooling. After removal of solvent the dibromide was purified by crystallisation from petrol-ether (40-60°) when it was obtained as stout colourless needles, m.p.89-90° (literature[10], 89-90°).

Analysis:

Found: Br., 43.41;

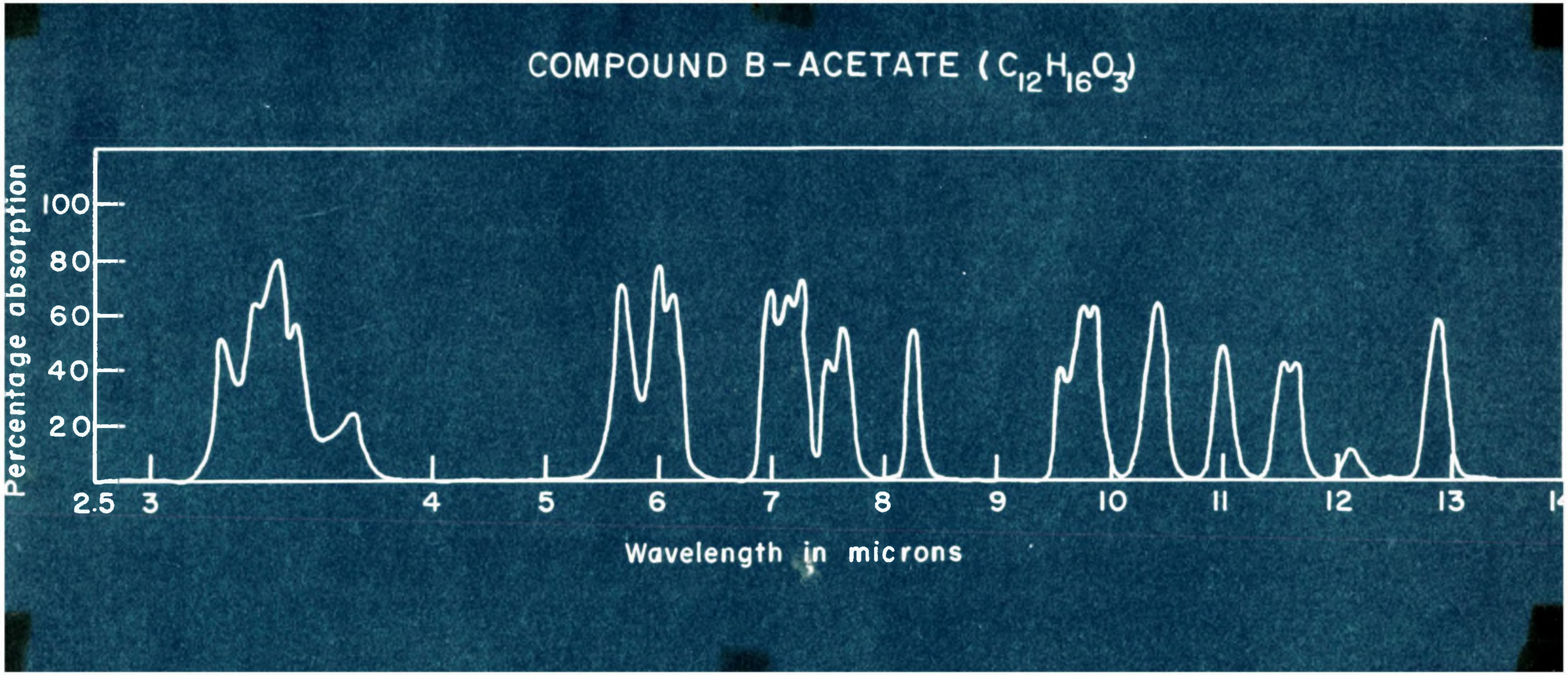
$C_{12}H_{16}O_3Br_2$ requires Br.43.4%.

Structure of compound B (XIV):-

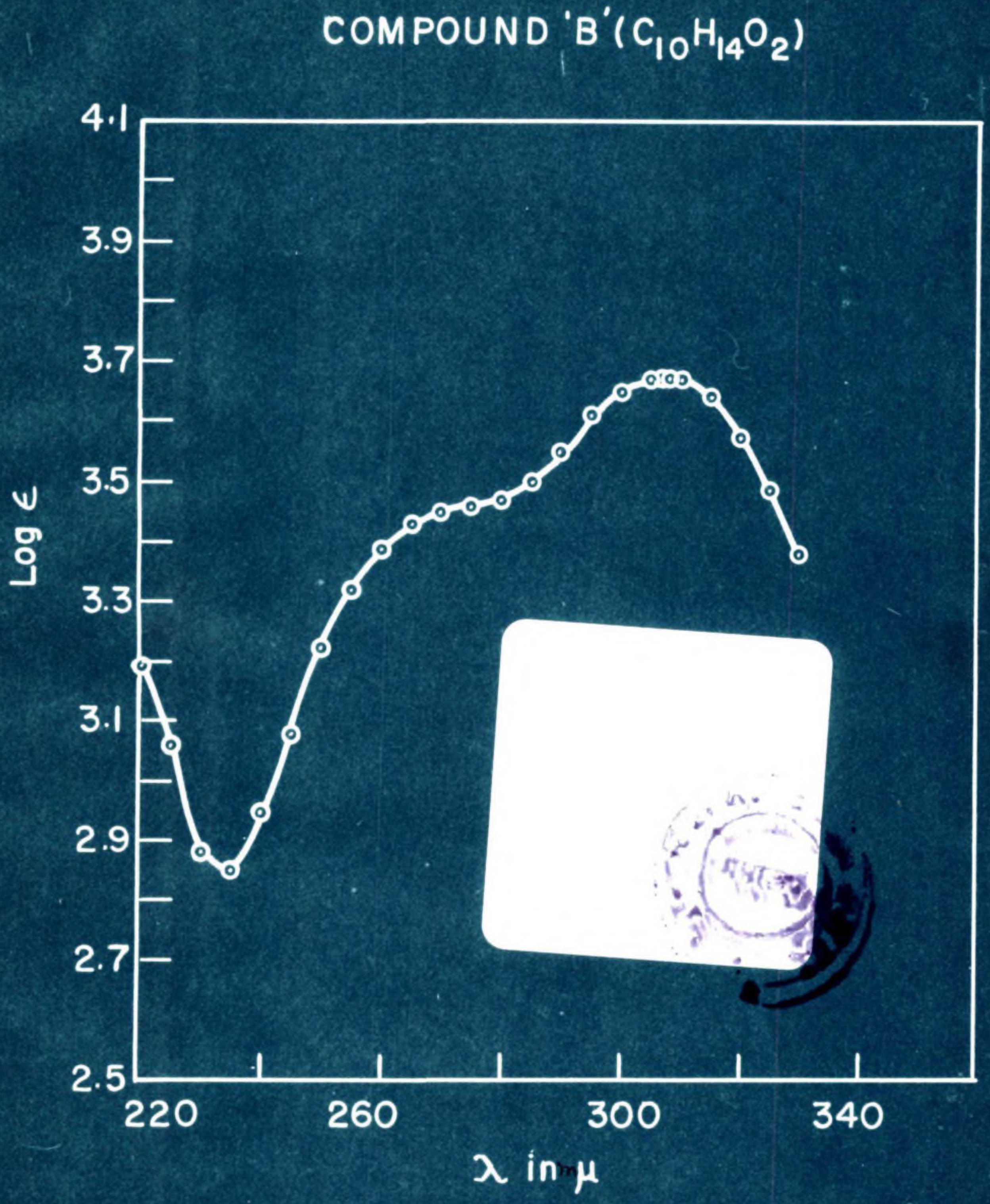
Analysis of the material and its acetate showed that the compound has the same molecular formula as mintglyoxal ($C_{10}H_{14}O_2$) and was evidently formed from the latter only through cyclisation and rearrangement. Infra-red spectrum (Curve III, p. 53) indicated that the cyclopropane ring was ruptured during acetylation (Curve II, p. 51). This compound showed somewhat strong ultraviolet absorption (Curve 3, p. 52); λmax 307 mμ, log ε 3.67). It gave dark bluish green colouration with ferric chloride, somewhat similar to mintglyoxal.

On ozonolysis the compound B formed acetone as the only volatile component. Non-volatile portion gave strong test for aldehyde (Fehling's solution) and methylketone (iodoform). On hydrogenation in presence of Adam's catalyst, the material absorbed two moles of hydrogen. It also reacted with Feigl's sodiumperiodate silvernitrate reagent[17], indicating the location of two oxygen atoms on two adjoining carbon atoms. These results indicated that the compound B may be represented by the structure (XIV). It may also exist in tantomeric form (XIVa) which will explain the ~~formation~~ presence of methylketone in the non-volatile products of ~~the~~ ozonolysis.

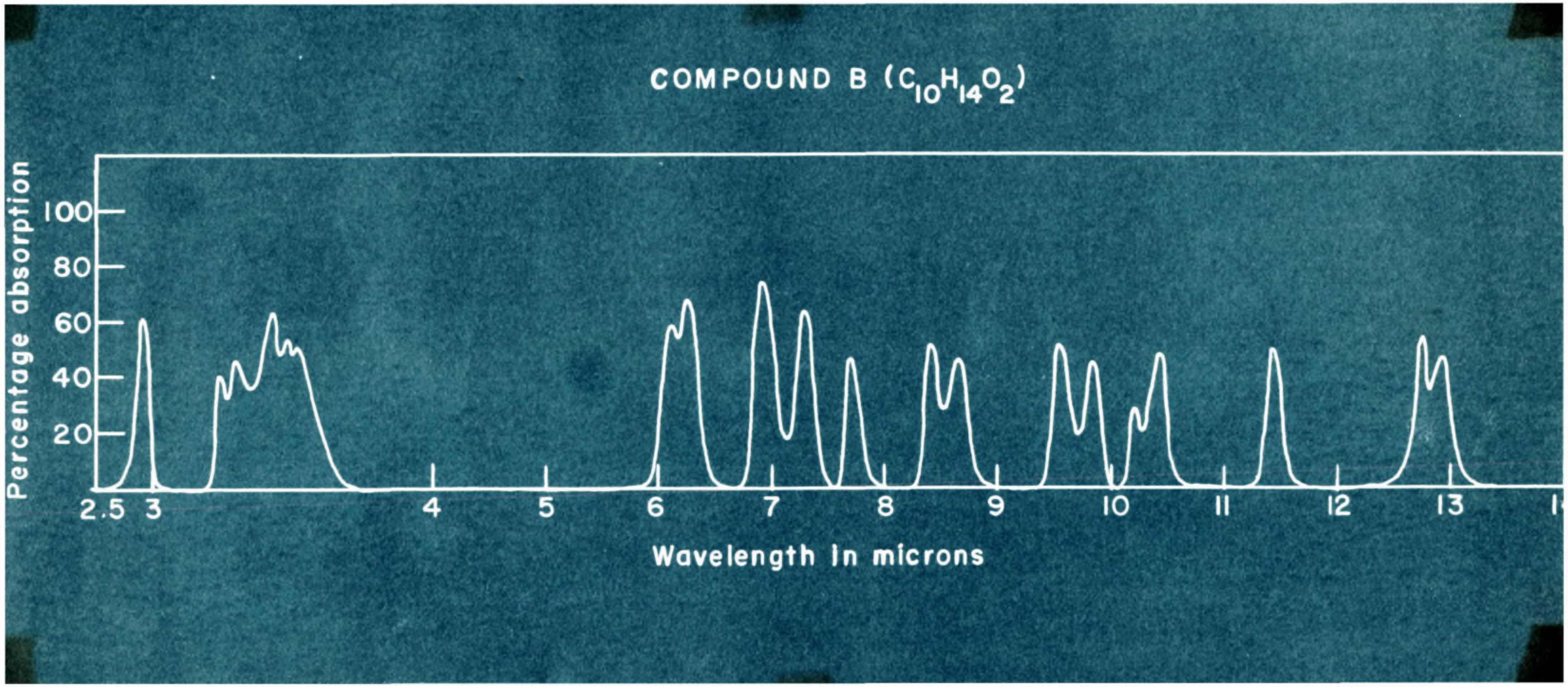
Compound B (XIV) or its acetate (XII) may also possibly play the role of intermediate products in the formation of (IX).



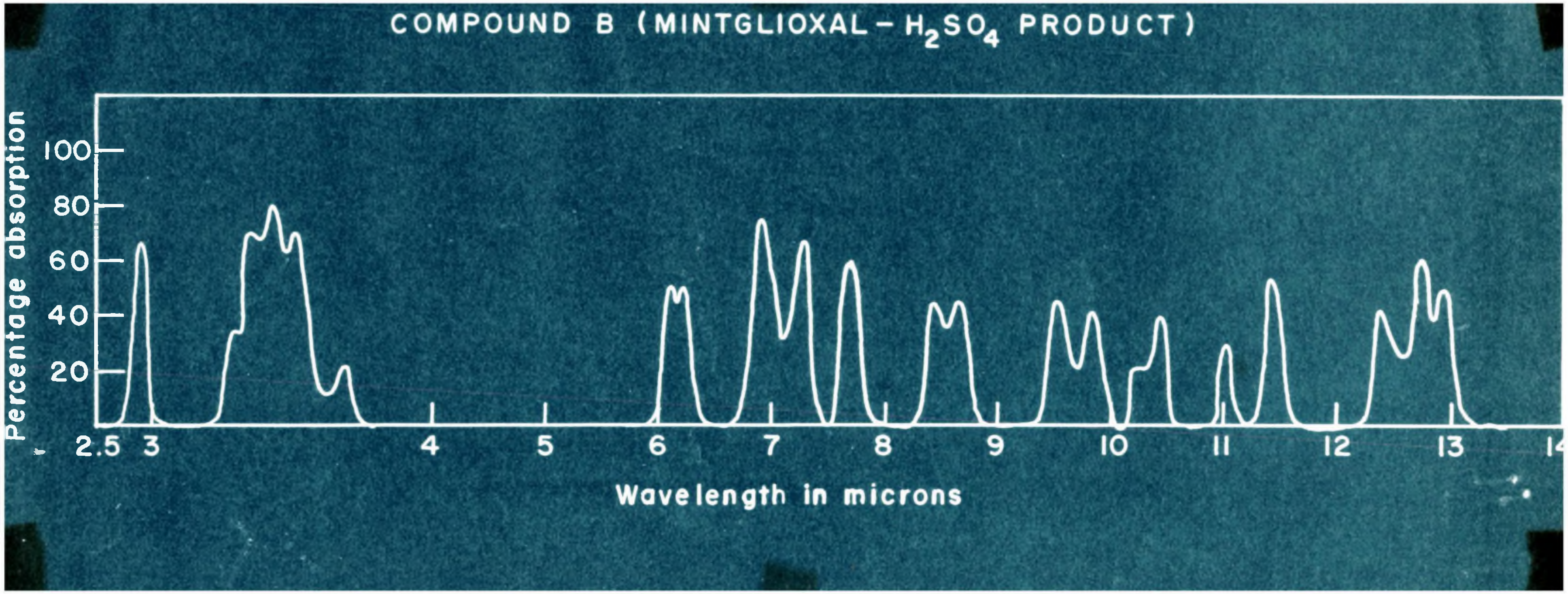
COMPOUND B-ACETATE ($C_{12}H_{16}O_3$)



COMPOUND 'B' ($C_{10}H_{14}O_2$)



COMPOUND B ($C_{10}H_{14}O_2$)



COMPOUND B (MINTGLIOXAL - H_2SO_4 PRODUCT)

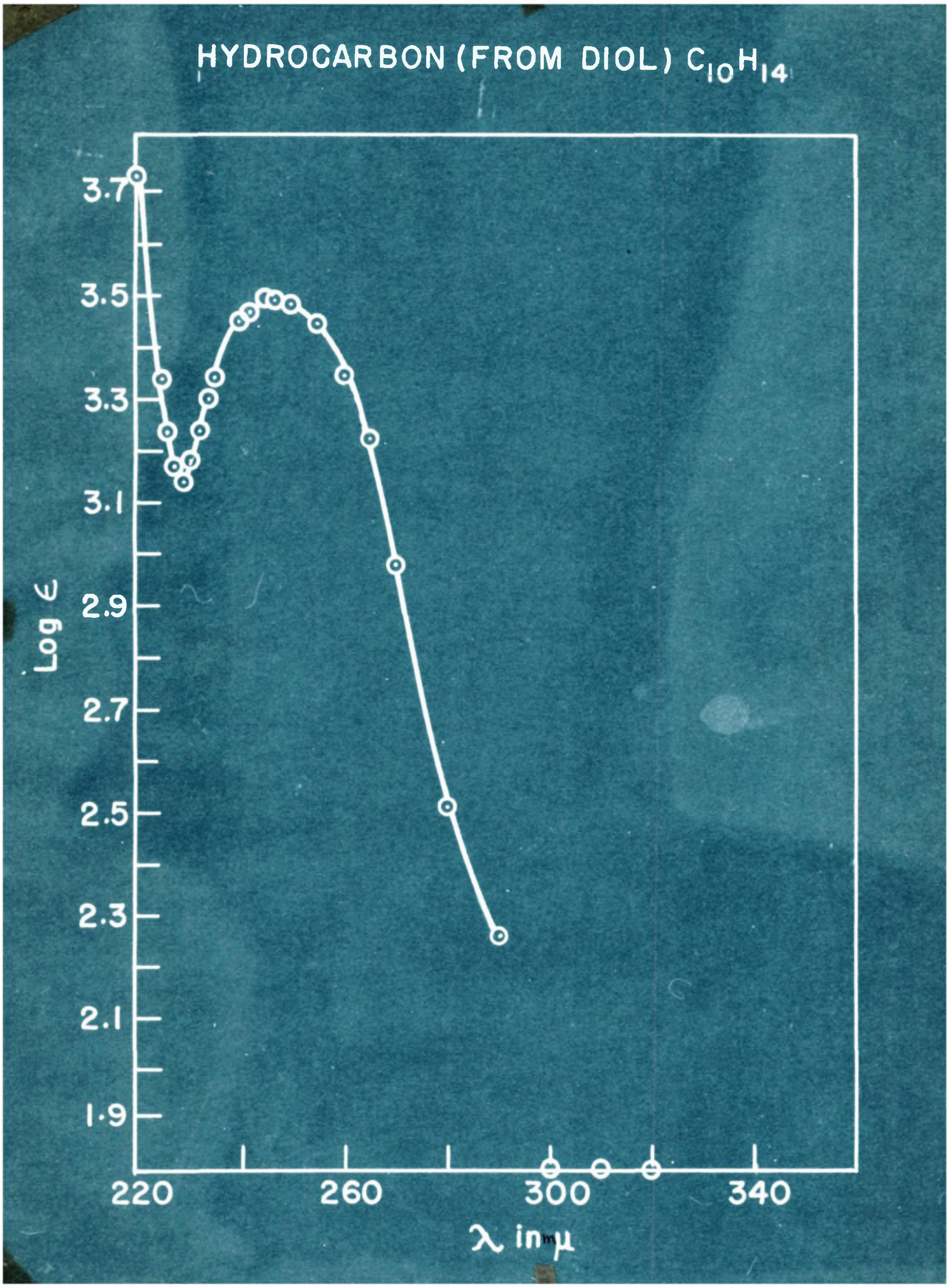
Formation of compound B from mintglyoxal by cyclisation with dilute sulphuric acid:

The formation of the crystalline compound B ($C_{10}H_{14}O_2$ m.p.78.5°; XIV) from mintglyoxal by treatment with acetic anhydride has been described above. The same compound could also be obtained by treating mintglyoxal at room temperature with dilute sulphuric acid (4%). Identity of the compound thus obtained with that of compound B was established by systematic degradative experiments, infra-red (Curve IV , p.54) and ultraviolet spectroscopy and finally by mixed melting point.

Cyclisation of reduction product of mintglyoxal:

On reduction with lithiumaluminiumhydride, mintglyoxal produces two isomeric crystalline diols:
(i) $C_{10}H_{18}O_2$; m.p. 148°; and (ii) $C_{10}H_{18}O_2$, m.p.80°.

These can be easily separated through their differential solubility in organic solvents. Both of these compounds contain cyclopropane ring and are otherwise also identical and are evidently sterio-isomers. They are soluble in water and on warming the aqueous solutions in presence of dilute sulphuric acid (2%), both these diols gave a mixture of hydrocarbons ($C_{10}H_{14}$; XVII to XIX) formed evidently simultaneous cyclisation and dehydration. Components of this mixture were however not separable through distillation. Infra-red spectrum (Curve V : p.58) of this mixture, indicated the presence of a



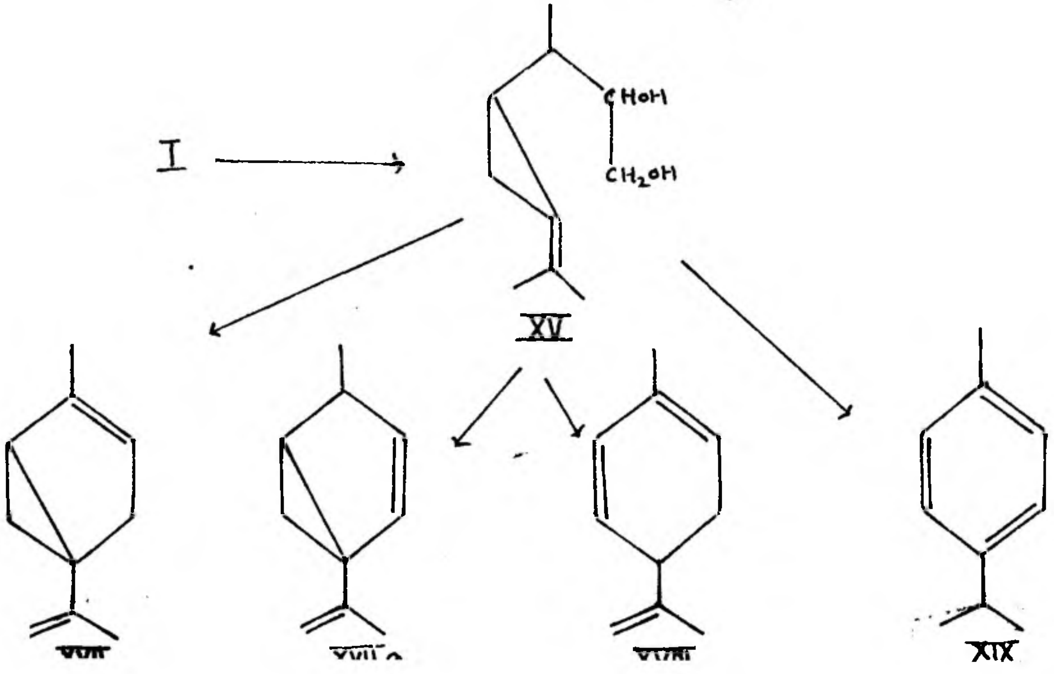
HYDROCARBON (FROM DIOL) $C_{10}H_{14}$

component containing cyclopropane ring. The curve also indicated the presence of aromatised ring system (absorption in 6.61 and 6.64 μ region). This was also supported by the ultraviolet absorption of the mixture (Curve 4, p.56) which confirmed that it was predominently aromatic in nature. Determination of unsaturation value with perbenzoic acid showed the presence of approximately 0.6 double bond. This was further supported by catalytic hydrogenation in presence of Adam's catalyst when hydrogenation became extremely slow after hydrogen proportional to about 0.6 double bond had been absorbed.

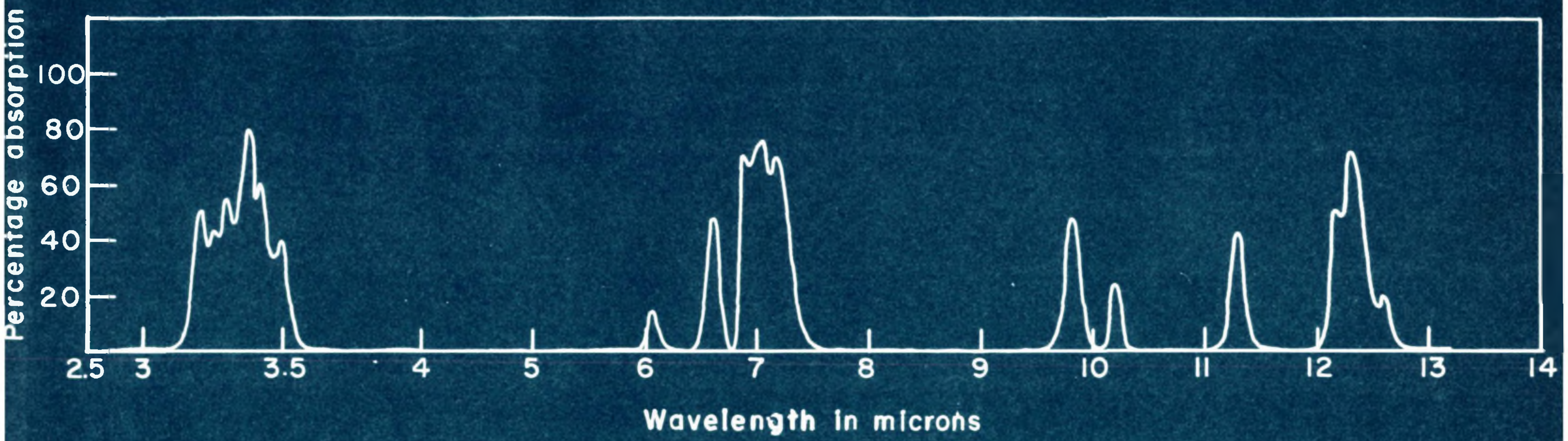
Ozonisation:

On ozonisation the hydrocarbon mixture gave formaldehyde as the only volatile component. It did not contain any acetone. The non-volatile portion gave test for an aldehyde (Fehling's solution) and methylketone (iodoform).

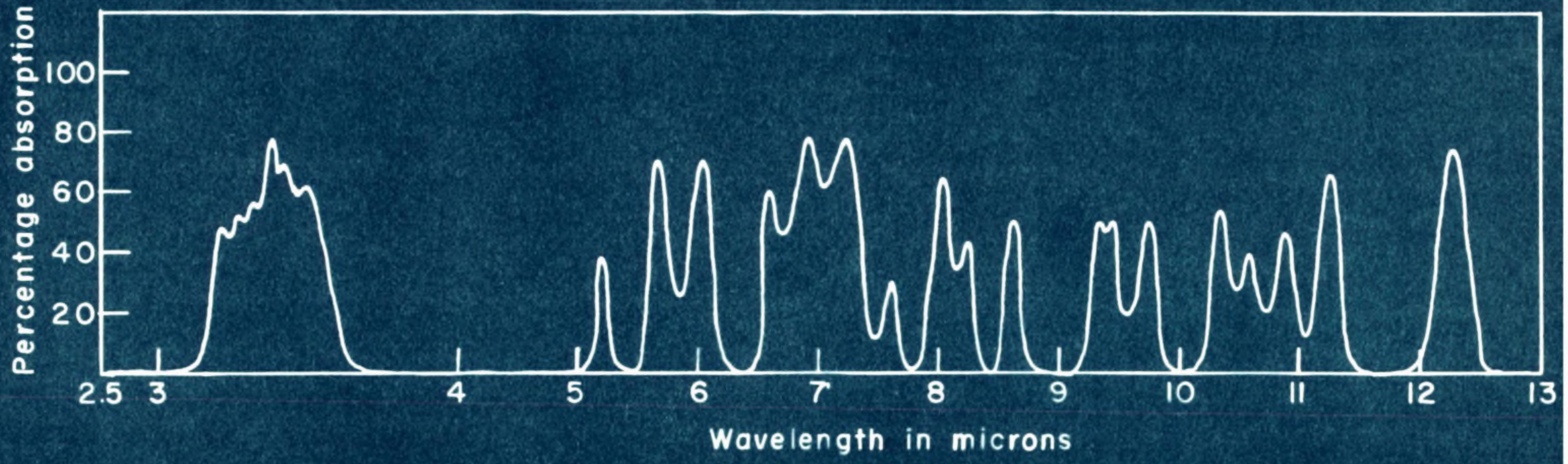
From these results it was concluded that this hydrocarbon fraction was a mixture of (XVII~~a~~ and XVIIa) along with p-cymene (XIX) in which the latter predominated. The mixture may also contain small amount of (XVIII) which probably was responsible for the u.v. peak at 243 mμ.



HYDROCARBON ($C_{10}H_{14}$) FROM DIOL



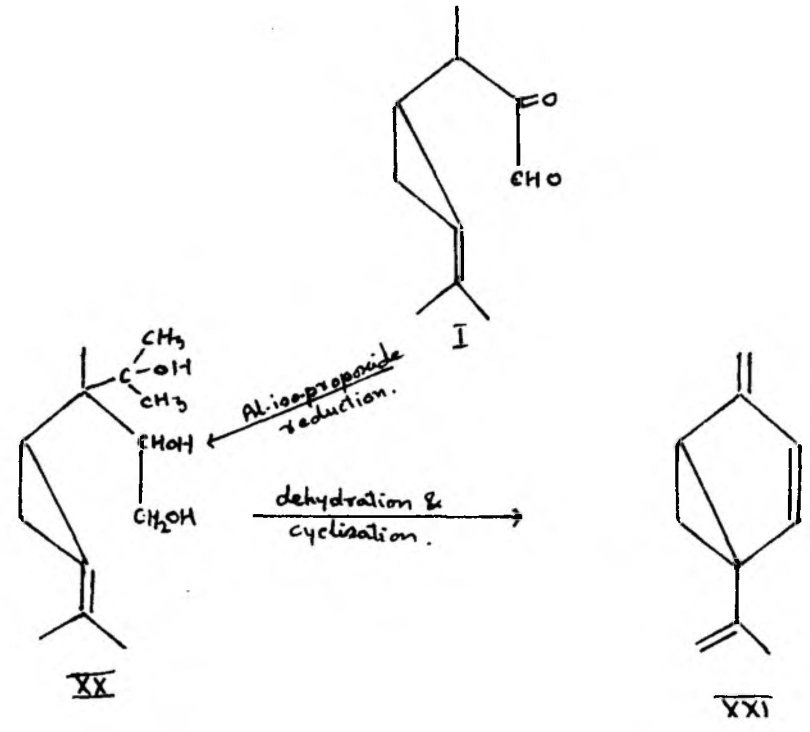
HYDROCARBON (DIOL) AFTER HCl TREATMENT ($C_{10}H_{14}$)

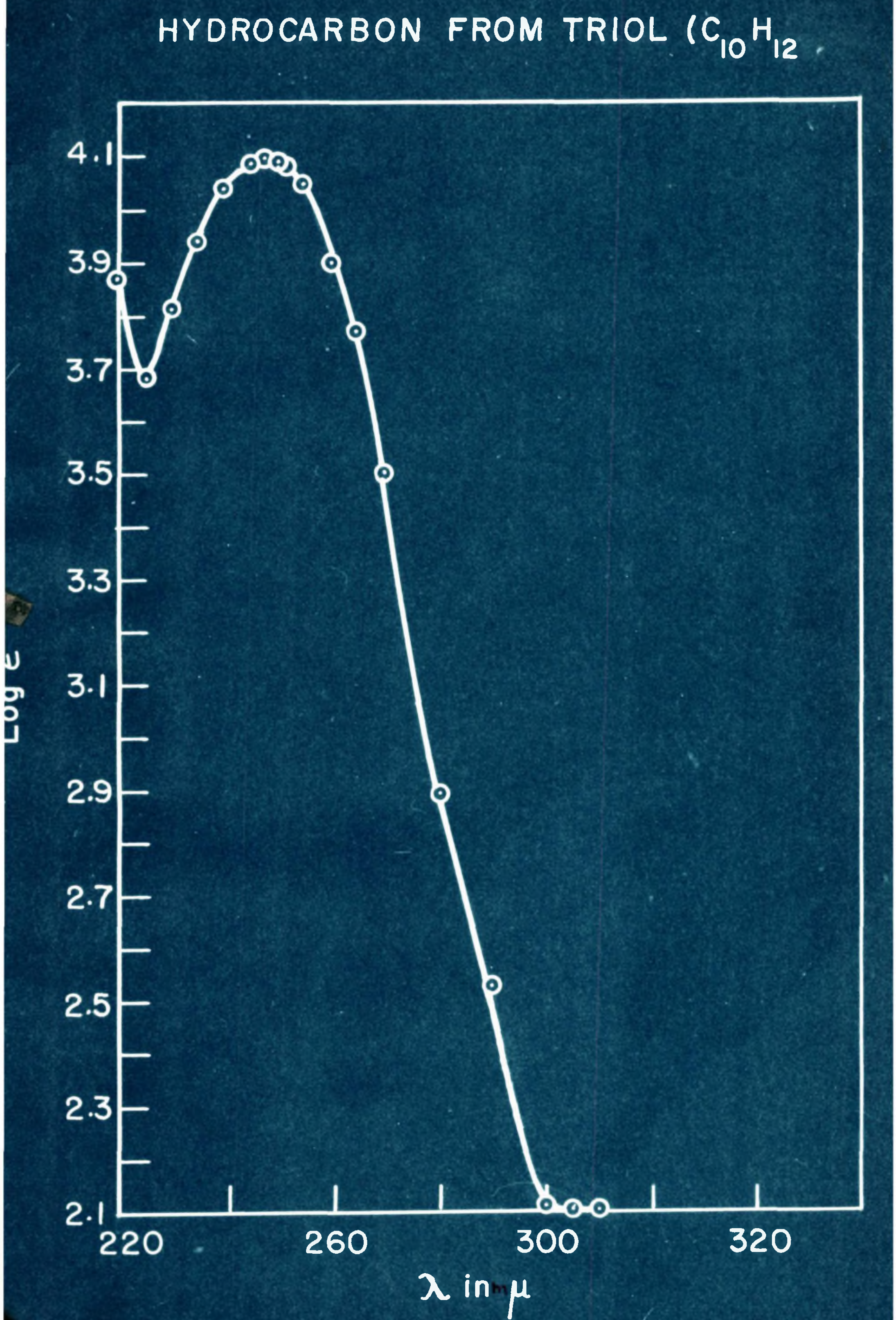


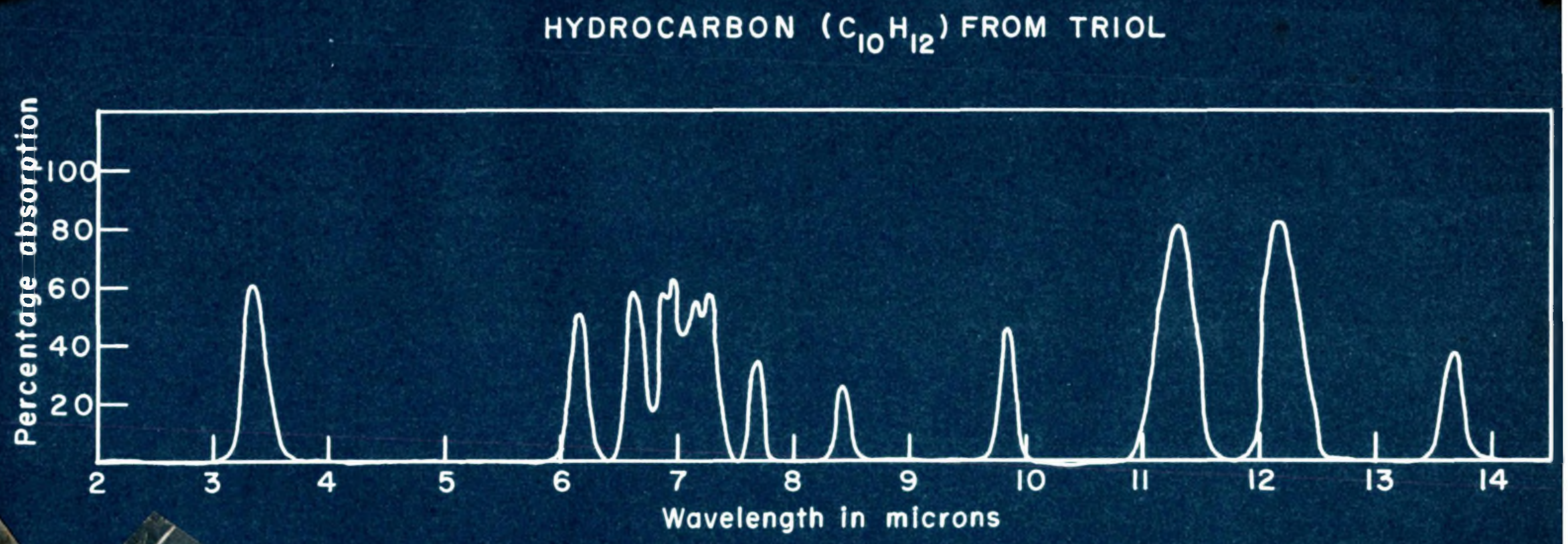
For the complete conversion of the above mixture to p-cymene it was hydrochlorinated in anhydrous ethereal solution, which obviously also resulted in rupturing of the cyclopropane ring. The hydrochlorinated product was then dehydrochlorinated and subsequently treated with sm ll amount of sulphur when nearly pure p.cymene was obtained; the properties of which agreed fairly well with those described in literature[18, 19]. Identity was established in conventional way by oxidising with potassium permanganate to p.hydroxy-isopropylbenzoic acid, m.p.155-156°

Cyclodehydration of Triol:

It has been found that with aluminium-isopropoxide in isopropyl alcohol, mintglyoxal, along with the usual diol, forms a crystalline triol to which Chakravarti and Bhattacharyya have assigned the structure (XX). The product is formed by condensation of mintglyoxal with a molecule of acetone followed by reduction.




HYDROCARBON FROM TRIOL ($C_{10}H_{12}$
Log ε
4.1
3.9
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
220
260
300
320
λ in mμ


HYDROCARBON ($C_{10}H_{12}$) FROM TRIOL

This compound also on treatment with dilute sulphuric acid (2%) eliminates isopropyl alcohol and acetone and simultaneously cyclises with dehydration to produce a hydrocarbon ($C_{10}H_{12}$) having the following properties:

b.p. 182-184°/710 mm.

n_D^{27} 1.5307

α_D - negligible

d_4^{30} 0.9212

Its properties are very different from the hydrocarbon mixture described earlier (page and 72b). It showed strong absorption in ultraviolet region, λmax 248 mμ log E = 4.098, (Curve 5, p 61) characteristic of a conjugated diene system. Its infrared spectrum indicated the existance of cyclopropane ring (Curve VII, p.62). On ozonisation it gave considerable amount of formaldehyde as the only volatile component. Non-volatile portion gave test for aldehyde and methylketone. From these evidences the hydrocarbon has been assigned the structure (XXI).

The result of the experiments described in this part, specially the isolation of thymol (ref. page 47) confirmed the structure(I) for mintglyoxal.

Reaction of the semicarbazone of the mintglyoxal:

Mintglyoxal forms a monosemicarbazone ($C_{11}H_{17}O_2N_3$)(XXII), the properties of which have been to some extent described by Chakravarti and Bhattacharyya.

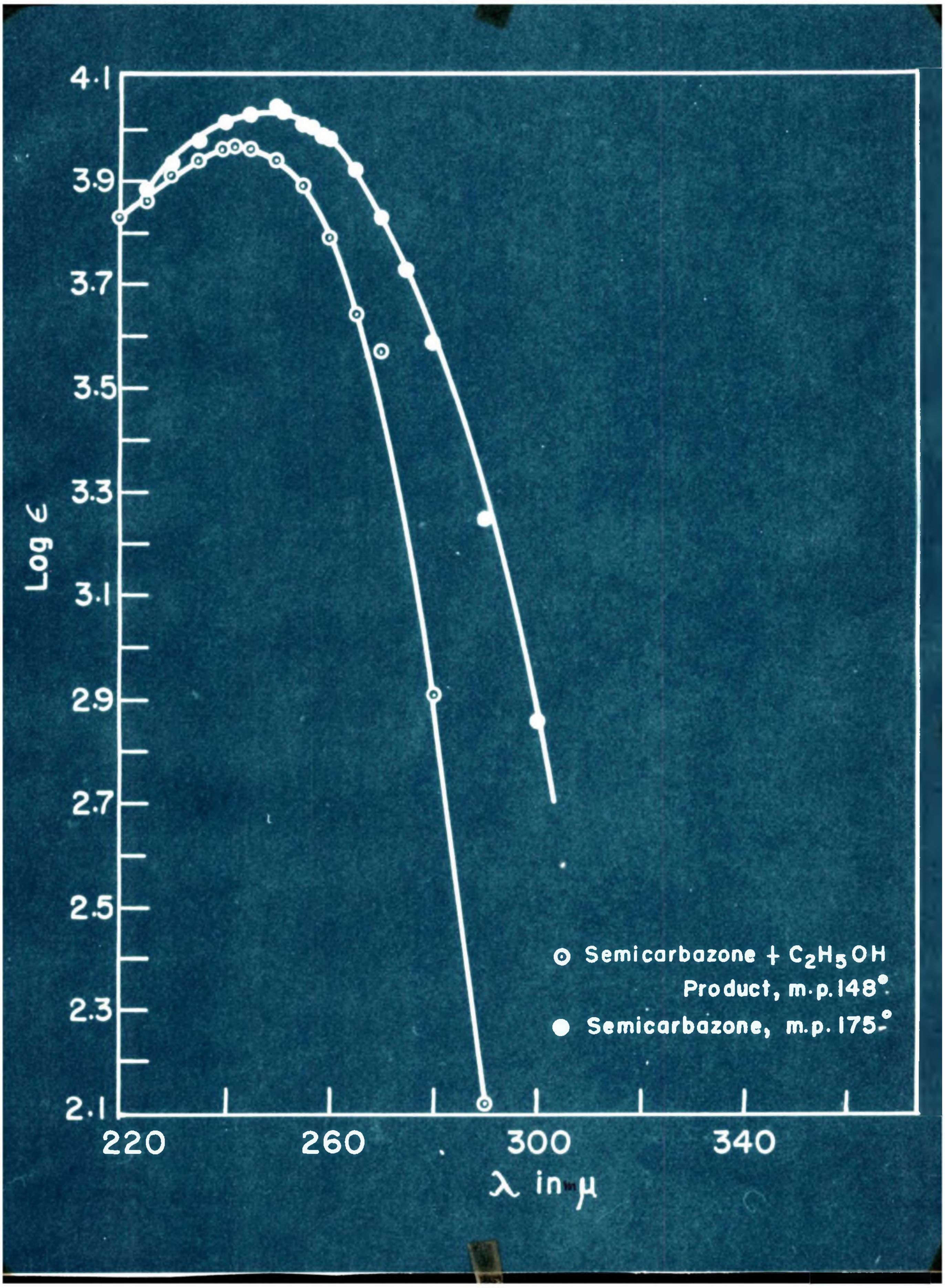
m.p.175°

λmax. 250 mμ log E = 4.04

This material is rather a tricky compound. It is very suseptible to temperature-conditions. As such the material is not very soluble in alcohol and is insoluble in other organic solvents However, if it be heated with boiling ethanol for a few minutes only, it suddenly goes into solution with simultaneous liberation of trace of ammonia, which, however, may be only a side reaction. The compound thus formed (m.p.148°) is different from the original semicarbazone (m.p.175°).

Analysis of the material indicated the molecular formula $C_{13}H_{23}N_3O_3$. Its carbon percentage is considerably lower than that of the original semicarbazone. It was possibly not a simple molecular compound of the original semicarbazone with alcohol, as on long drying at 100° under high vacuum the material remained unaltered. Peculiarly enough, this compound was easily soluble in organic solvents like benzene, carbontetrachloride ethylacetate and was also very soluble in water. A similar but different crystalline compound (m.p.166.5°) was also obtained by treating the semicarbazone with methanol. When the semicarbazone of mintglyoxal was heated with water alone on a steam-bath for about an hour, it also went into solution, but the product thus formed could not be crystallised.

The crystalline compounds formed with alcohols appeared to be somewhat unusual. It has not, as yet, been possible to assign any particular structure to these compounds but certain informations collected are quite interesting. When describing out results we are taking only the ethanol-decomposition product into consideration.


4.1
3.9
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
Log ε
220
260
300
340
λ in mμ
○ Semicarbazone + C_2H_5OH Product, m.p. 148°.
● Semicarbazone, m.p. 175°.

(i) Analysis of the material indicated a lower carbon content (C, 57.9; H, 8.28; N, 16.33; - for the original semicarbazone, C, 59.16; H, 7.7; N, 18.8%). Evidently, during the addition of ethanol no dehydration has taken place. Probably, the product was formed by simple addition of a molecule of ethanol, mechanism of which we are not in a position to explain.

(ii) Ultraviolet spectrum (Curve 6, p.65) of the material λ_{max} 244 mμ log ε = 3.9638 indicated that probably the original chromophoric system ($\overset{O}{\overset{\|}{C}}-C=N-NH-CONH_2$) has not been seriously altered.

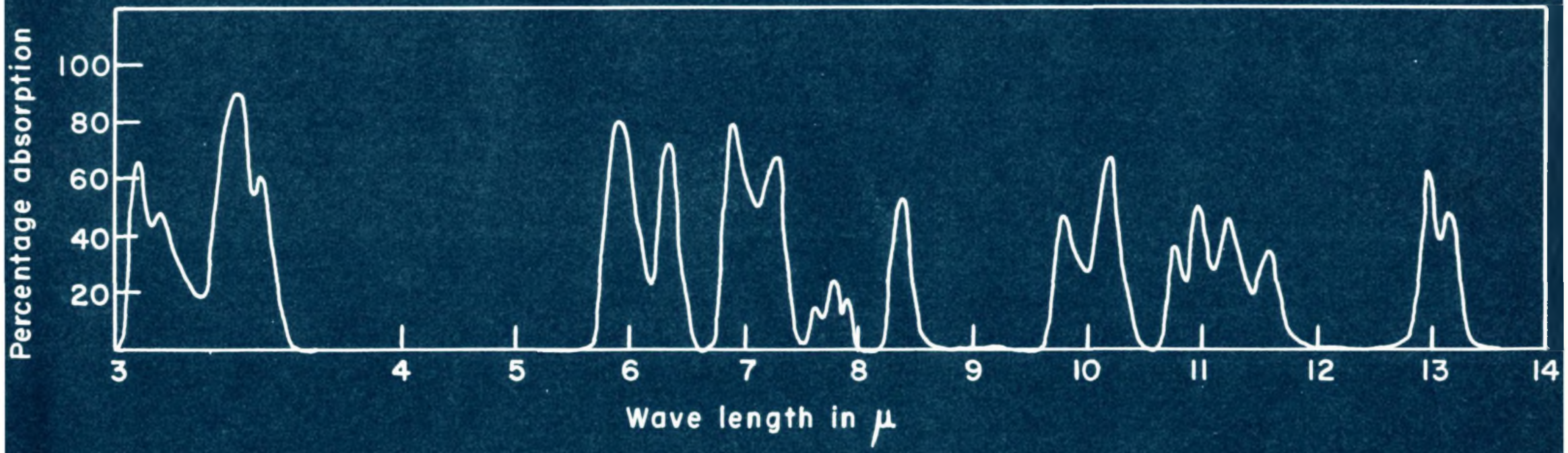
(iii) Infra-red spectrum (Curve VIII, p. 67) of the material showed the presence of hydroxyl group (absorption at 3.07μ). Absorption in 3.15 & 9.78 μ regions indicated the presence of the cyclopropane ring.

(iv) Ozonisation of the material formed copious amount of acetone and also formaldehyde as the volatile components. This indicated that the isopropylidene group ($>C=C<^{CH_3}_{CH_3}$) has remained intact and consequently the product has not been formed through any cyclisation of the compound.

(v) The compound was optically active ($[\alpha]_D$ +61.41 in alcohol). This suggested that the cyclopropane ring was not ruptured during the reaction, which was also the conclusion drawn from infra-red spectroscopy.

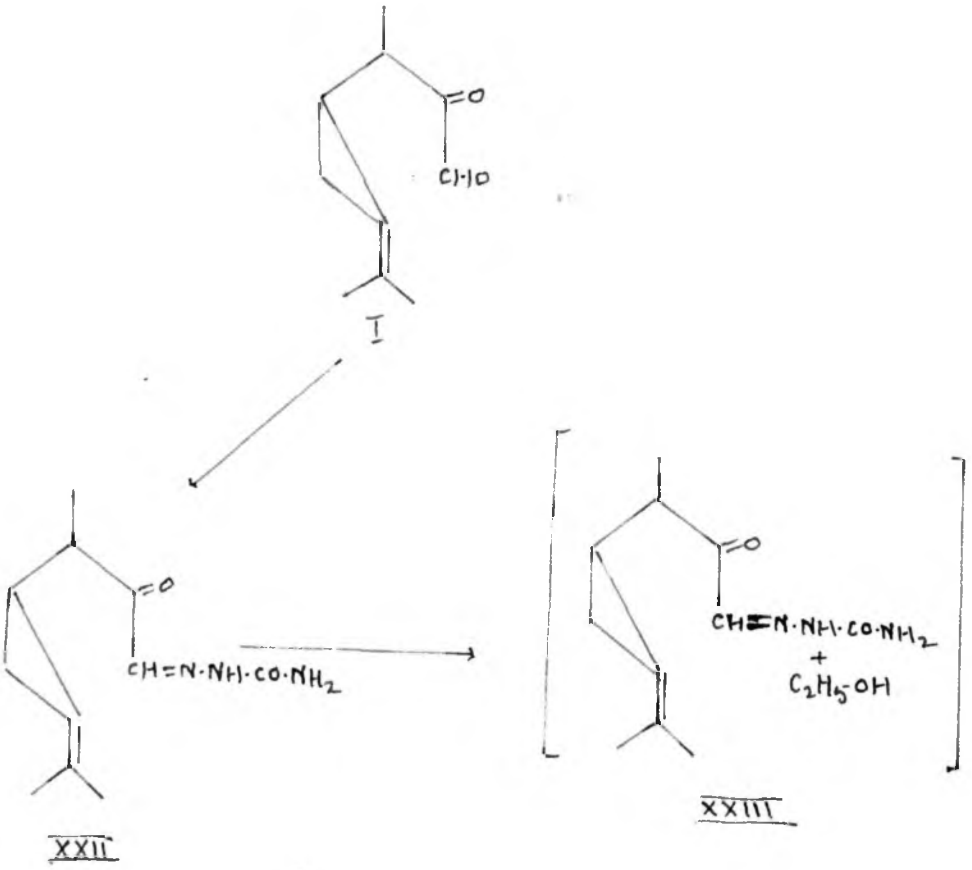
From these evidences, which are also supported by analysis it appeared that the compound has been formed by the addition of a molecule of alcohol to one molecule of semicarbazone without fundamentally changing the chromophoric part present in the semi-carbazone molecule.

SEMICARBAZONE-ETHYL ALCOHOL DERIV.



Curve VIII

With the evidences now described above, the structure of this compound can be best represented as XXIII.



E_X_P_E_R_I_M_E_N_T_A_L

Isolation of mintglyoxal:

Mintglyoxal was isolated by employing basically the same procedure adopted by Chakravarti and Bhattacharyya (loc.cit.). Spearmint oil was initially fractionated using an efficient fractionating column and the fraction, b.p.95-104/3 mm.; n_D^{27}1.5038; which was almost pure mintglyoxal, was collected. From this fraction pure mintglyoxal was isolated by low temperature (-15°) crystallisation from petrolether (40-60°). The material thus isolated had the following properties:

b.p. 100-102/2-3 mm.
n_D^{27} 1.5058
$[\alpha]_D$ +180°.8 (in alcohol)
d_4^{30} 1.047.

Cyclisation of mintglyoxal with acetic anhydride: Isolation of acetate A (VIII) and acetate B(XII):

A mixture of mintglyoxal (100 g.), aceticanhydride (100 g.) and sodiumacetate (4 g.) was refluxed on an isomantle with due protection against moisture for 60 hours. Excess of aceticanhydride and the acetic acid formed during the reaction were removed by initially heating the reaction mixture at bath temperature 150-155° under water pump suction. The residue of the acetylated mixture was then totally distilled under vacuum (1 mm.). The distillate was then carefully fractionated through efficient micro column (~15 plates) and divided into 10 fractions about 10 g. each. The course of fractionation was mainly followed by observing the b.p. and refractive index of various fractions. Fractions having similarity in properties were mixed together and repeatedly refractionated and finally two fractions were obtained.

(i) Acetate A, b.p.114-115°/9 mm., n_D^{26} 1.~~7~~5139
yield: 40 g.

(ii) Acetate B, b.p.135-137°/9 mm., $n_D^{24.5}$ 1.5170
yield: 30 g.

intermediate fractions were rejected.

Properties of acetate A:

Analysis: Found: C, 75.66; H, 7.49

$C_{12}H_{14}O_2$ requires C,75.86; H, 7.42%.

Isolation of compound A (IX):

Compound A (30 g.) was ~~isolated~~ prepared by saponification of the acetate A (38 g.) by refluxing with alcoholic potash (300 ml. 10%) for about 2 hours and isolat~~ed~~ing the resulting product in the usual way, taking due notice of its phenolic nature. The product was initially collected by distillation and then further purified by careful fractionation through micro-column; b.p.98-100°/9-10 mm.; $n_D^{24.5}$ 1.5427; d_4^{30} 1.0054.

Analysis: Found: C, 81.03; H, 8.19

$C_{10}H_{12}O$ requires C, 81.04; H, 8.16%

Infra-red spectrum determined in the usual way, shows benzonoid ring with further conjugation, absorption at 6.40 µ region (Curve I, p.48).

Ultraviolet absorption spectrum was determined in alcoholic solution (Curve 1, p.46). The absorption was characteristic of a phenolic ring system. Somewhat strong absorption at 283 mµ to 284 mµ is indicative of further conjugation.

Ozonolysis of compound A (IX):

Material (1 g.) was ozonised in carbontetrachloride solution and the products characterised in the usual way. Volatile product contained only formaldehyde (dimedone derivative m.p. and mixed m.p.189°). Non-volatile portion gave test for aldehyde (Fehling's solution) and for methyl ketone (iodoform).

Hydrogenation and isolation of thymol(X):

Compound A (2.6 g.) in ethanol (60 ml.) was hydrogenated in presence of Adam's catalyst (0.2 g.) using a magnetic stirrer. Hydrogen equivalent to one double bond (about 490 ml.) was quickly absorbed in less than two hours. The hydrogenated product was isolated by distillation, b.p.90-92/9-10 mm., $n_D^{23.5}$ 1.5140. It was characterised as thymol after crystallisation from petrol-ether (40-60°); m.p.50-51°; remained unchanged when mixed with an authentic sample of thymol. It was further characterised by preparing the following derivatives:

Phenyl urathane, m.p. and mixed m.p.106-107°;
literature[20] -- m.p.106-107°.
Analysis: Found N, 4.98; $C_{17}H_{19}N$ requires N, 5.2%

Naphthylurathane, m.p. and mixed m.p.159-160°;
literature[21] -- m.p.160°.
Analysis: Found: N, 4.40; $C_{21}H_{21}O_2N$ requires N, 4.39%.

The identity of the hydrogenated product as thymol was therefore confirmed.

Properties of acetate B:

Analysis: Found: C, 69.57; H, 7.79.

$C_{12}H_{16}O_3$ requires C,69.21; H, 7.74%.

Infra-red spectrum (Curve II, p.51) indicated that the cyclopropane ring has been ruptured.

Isolation of compound B:

Compound B (20 g.) was isolated by the saponification of acetate B (28.g.) by following the same procedure as in acetate A. The final product, compound B, was first totally distilled and then carefully fractionated through a micro column. The purified material, which solidified immediately, showed the following properties: b.p.120-121°/9 mm., m.p.74-75°(crude). It was twice crystallised from normal hexane, m.p.78.5°.

Analysis: Found: C, 72.52; H, 8.27

$C_{10}H_{14}O_2$ requires : C, 72.26; H, 8.49%.

Infra-red spectrum (Curve III, p.53) was determined in the usual way and showed no specific absorption in 9.8 - 10 and 3.23 - 3.32 µ region showing the absence of cyclopropane ring. The absorption at 6·11µ region was also indicative of ketone grouping.

Ultra-violet absorption spectrum (Curve 3 , p.52) was determined in alcoholic solution. λmax 307 mµ log E 3.67.

Ozonolysis:

The material (1 g.) in carbontetrachloride solution was ozonised in the conventional way. The volatile portion was composed only of acetone ~~only~~, characterised as ~~its~~ iodoform ~~test~~. Non-volatile portion after decomposing the ozonide as usual gave tests for aldehyde (Fehling's solution test etc.) and methyl ketone (iodoform test).

Isolation of compound B from the reaction of sulphuric acid with mintglyoxal:

Mintglyoxal (10 g.) and dilute sulphuric acid (300 ml. 4%) were stirred in a beaker with a mechanical stirrer for 24 hours at room temperature when only small amount of unreacted oil left. The reaction mixture was kept overnight at room temperature when considerable amount of long crystals separated which were filtered washed free from acid and crystallised from normal-hexane, m.p.78°; ~~exactly~~ identical with the compound B from acetic anhydride reaction.

Reduction of mintglyoxal with lithium aluminium hydride: Isolation of diols (diol A) and (diol B):-

The reduction was basically carried out according to the method of Chakravarti and Bhattacharyya. Mintglyoxal (190 g.) was reduced in ethereal solution with lithium aluminium hydride (85 g.) in the usual way. The reaction product after decomposition with alcohol, water etc. was exhaustively extracted with ether. After removing the ether the residue was crystallised from benzene-petrol-ether mixture, when diol (diol A 34 g.; $[\alpha]_D$ +110°.3 in alcohol) was obtained, m.p.146-147°. It could be crystallised from the same solvent mixture. The mother liquor left after removal of diol(A), on concentration and cooling gave the diol(B) which was repeatedly crystallised from the same solvent mixture; m.p.80-80.5° which remained unchanged even after further crystallisation, yield: 59 g., $[\alpha]_D$+108°.2 (alcohol).

Analysis: Found: C, 70.94; H, 10.40

$C_{10}H_{18}O_2$ requires: C, 70.55; H, 10.66%.

Cyclisation of diols (diol A) and (diol B): Isolation of hydrocarbon mixture:

As both the diols gave the same product on cyclodehydration only one experiment concerning diol(A) is being described.

The diol (34 g.) was dissolved in water (1. 8 l) and dilute sulphuric acid (55 g. in 200 ml. water) added to it. The solution which was initially clear became turbid on warming on a water bath for a few minutes, but instead of further processing on water bath, the material was directly steam-distilled. Most of the hydrocarbon mixture came over during 20-30 minutes. It was extracted with ether, dried, ether removed and residual hydrocarbon distilled at ordinary or 100 mm. pressure. For purification it was twice distilled over sodium.

b.p.180-182/710 mm.
$n_D^{24.5}$ 1.4980.
$\alpha_D + 3^{\circ}.65$
d_4^{30} 0.8638

Analysis: Found: C, 89.33; H, 10.22
$C_{10}H_{14}$ requires: C, 89.49; H, 10.51%.

Ultra-violet spectrum (Curve 4 , p.56) was determined in alcoholic solution; λ max 245 mμ log E = 3.498.

Infra-red spectrum (Curve IV, p.58) determined in the conventional way showed absorption in the following region 3.21 μ and 9.83 μ (cyclopropane); 6.61 μ (benzonoid ring system).

Ozonolysis of the material (1 g.) in ethyl acetate or carbon-tetrachloride solution formed formaldehyde (dimedone derivative) as the only volatile component. Non-volatile portion after decomposition of ozonide gave tests for aldehyde (Fehling's solution etc.) and methyl ketone (iodoform test.).

<u>Conversion to p.cymene (XIX)</u>:

The hydrocarbon mixture described above was a mixture of p.cymene (XIX) and the compounds (XVII, XVIIa and XVIII). For conversion to p.cymene the product (4 g.) was hydrochlorinated (24 hours) in ethereal solution and dehydrochlorinated with alcoholic potash (30 ml., 10%) and the product thus obtained after usual processing was dehydrogenated with small amount of sulphur (5 hours at 190-200°) and the final product was once distilled over zinc dust, b.p.172-174°/700-710 mm.; $n_D^{24.5}$ 1.4940; yield; 2.5 g. These properties were almost identical with those of p.cymene described in literature[18,19]. The identity with p.cymene was further confirmed by oxidation of this material according to Wallach[22] to p.hydroxy-isopropylbenzoic acid, m.p.155-156°.

<u>Cyclodehydration of triol (XX):</u>
<u>Isolation of a hydrocarbon (XXI)</u>:

The triol was obtained by following the same procedure as employed by Chakravarti and Bhattacharyya (loc.cit.) Mintglyoxal (80 g.) on reduction with aluminiumisopropoxide (75 g.) in isopropyl alcohol (1.5 l.) gave along with other products the crystalline triol (XX; 15 g.) which could be crystallised from a mixture of ether-petrol-ether, m.p.121-122°; $[\alpha]_D$ +110°.6 (alcohol).

The triol (14 g.) was cyclodehydrated by following exactly the same procedure as described earlier in the case of diol (XV) and the result~~ed~~ing hydrocarbon also isolated by following the same procedure. It was distilled twice over sodium.

b.p. 182-184°/710 mm.
n_D^{27} 1.5307.

Analysis: Found: C, 90.64; H, 9.24
$C_{10}H_{12}$ requires: C, 90.85; H, 9.15%.

Ultraviolet spectrum (Curve 5 , p.61) determined in alcoholic solution, λmax 248 mμ, log E = 4.098.

Infra-red spectrum (Curve VII, p.62) was determined in the usual way, which indicated the presence of cyclopropane ring (9.84 μ region).

Ozonolysis carried out in carbontetrachloride gave formaldehyde (dimedone derivative) as the only volatile product. Non-volatile portion after decomposition the ozonide gave tests for aldehyde (Fehling's solution etc.) and methylketone (iodoform etc.)

The reaction of the semicarbazone of mintglyoxal with various alcohols:

Mintglyoxal semicarbazone (XXII) was prepared according to the method described by Chakravarti and Bhattacharyya (loc.cit.). On treatment with requisite amount of semicarbazide hydrochloride and sodium acetate in alcoholic solution at room temperature mintglyoxal gave a quantitative yield of semicarbazone. After quick crystallisation from methanol it was obtained in pure state m.p.175°. It was insoluble in most of the organic solvent and was very sparingly soluble in alcohol before decomposition.

For the preparation of the ethyl alcohol derivative a mixture of semicarbazone (20 g.) and ethyl alcohol (100 ml.)

was refluxed on the water bath. After heating for about 5-10 minutes the semicarbazone almost suddenly went into solution. Refluxing, however, was continued for half an hour. Most of the alcohol was removed under suction and the concentrate cooled when the reaction product was obtained in crystalline form in almost quantitative yield and in a pure state. It could be further purified if necessary by recrystallising from alcohol or benzene.

m.p. 148° $[\alpha]_D$ +61°.41 (in alcohol).

Analysis: Found: C, 57.94; H, 8.28; N, 16.33

$C_{11}H_{17}O_2N_3 \cdot C_2H_5OH$ requires C, 57.97; H, 8.61; N, 15.60%.
($C_{13}H_{23}O_3N_3$)

It is easily soluble in usual organic solvents and also in water.

Ultraviolet spectrum was determined in alcoholic solution

λ max 244 mμ, log E = 3.9638 (Curve 6 , p.65)

It was not very fundamentally different from that of the semicarbazone of mintglyoxal itself.

Infra-red spectrum (Curve VIII, p.67) determined in the usual way showed the presence of cyclopropane ring (3.15 & 9.78 μ regions).

Ozonisation of the material gave acetone (iodoform test) and formaldehyde (dimedone derivative) as the volatile products. This indicated the isopropylidene isopropenyl side-chain had remained intact.

***

REFERENCES.

1. Guenther, The Essential Oils, III, 677, (1949).
2. Fluckiger, Ber., 1876, 9, 473.
3. Beyer, Arch.Pharm., 1876, 221, 283.
4. Kremers and Schreiner, Pharm.Rev., 1896, 14, 244.
5. Fritzche Brothers,Inc., New York, Descriptive Catalogue of Essential Oils, 1894., 33.
6. Nelson, U.S.Dept.Agr., Bur.Chem., Circ.No:92.
7. Elze, Chem.Ztg., 1910, 34, 1175.
8. Trimble, Am.J.Pharm., 1885, 57, 484.
9. Haensel, Chem.Zentr., 1907, I, 1332.
10. Schimmel and Co., Ber., 1898, April, 28.
11. Chakravarti and Bhattacharyya, P. and E.O.R., 1954, 45, 217-18.
12. Chakravarti and Bhattacharyya, P. and E.O.R., 1955, 46, 256-268
13. Chakravarti, Dasgupta, and Bhattacharyya, P. and E.O.R., 1955, 46, 330-333.
14. Tiemann and Schmidt, Ber., 1896, 29, 913.
15. Tiemann and Schmidt, Ber., 1897, 30, 27.
16. Semmler, Ber., 1909, 42, 2016.
17. Feigl, Spot-Tests, II, Organic Application, p.100-102.
18. Bert, Bull.Soc.Chem.(4), 1925, 37, 1251.
19. Richter and Wolff, Ber., 1930, 63, 1721.
20. Weehuizen, Rec.trav.chim., 1918, 37, 268.
21. French and Wirtel, J.Am.Chem.Soc., 1926, 48, 1378.
22. Wallach, Liebigs Ann., 1891, 264, 10.

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PART IV

Infra-red spectra of compounds containing cyclopropane ring system.

(3·2 to 3·4 μ region).

***

-SUMMARY.-

While studying the structure of mintglyoxal, considerable help was obtained from "Infra-red spectra" of this compound and its various derivatives for the detection of cyclopropane ring. Cyclopropane ring occurs as an integral part in many essential oil components. Infra-red spectroscopy has not as yet been extensively used for the detection of cyclopropane ring in these compounds. For this reason, several terpene derivatives containing cyclopropane ring, as such, or in fused bicyclic or tricyclic systems, have been studied in the 3.2 - 3.4 μ region, which from the recent observation of cole appears to be more dependable than 9.8 - 10 μ region studied by earlier workers. In this region there is usually no serious interferance from other functional groups. The compounds examined are Δ^3-carene, tricylene, teresantalic acid, tricycloekasantalic acid, α-santalol, α-santalylacetate, α-santalene and mintglyoxal and its derivatives.

***

General introduction

In part III of this thesis, the elucidation of the structure of mintglyoxal by conversion to various derivatives through cyclisation and cyclodehydration has been described. During these experiments considerable help was taken from infra-red spectra of the various compounds, specially for detecting the presence or absence of cyclopropane ring. The usual method of detecting the presence of cyclopropane ring in organic compounds is as follows:-

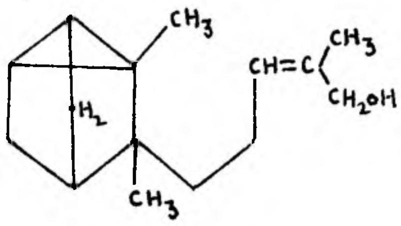
The compound in question is hydrohalogenated with hydrogenchloride, hydrogenbromide etc., and the quantity of halogen present is estimated. Both double bonds and cyclopropane ring react with hydrogen halides under these conditions; the amount of double bond, however, can be estimated by other methods (per acid oxidation etc.), the balance of halogen accounting for the cyclopropane ring. This method of hydrohalogenation, however, is unsuitable for poly functional compounds and specially for those which like mintglyoxal are sensitive to chemical reagents. As an alternative, the method of infra-red spectroscopy is quite convenient. The compounds containing cyclopropane ring shows strong absorption in the region 3.23 - 3.3 μ and 9.8 - 10 μ[1].

Derfer, Pickett and Boord[1] have studied fourteen simple cyclopropane derivatives and found 9.8 - 10 μ region to be very specific for cyclopropane ring. Their results have been further confirmed by Marrison[2], Wiberley and Bunce[3].

Most of the specimen studied by these authors were simple derivatives of cyclopropane.

Present investigation:

Cyclopropane ring forms an integral part ~~in~~ of many important terpenes. It is present in Δ^3 - and Δ^4-carenes, thyjane, α- and β-thujene, sabinene, aromadendrene, α-santalol and allied derivatives like teresantalol, teresantalic acid and sesquiterpene derivatives like gurjunene, copaene, ledol etc. For this reason infra-red spectra of several terpenoids including various derivatives of mintglyoxal and α-santalol in 9.8 - 10 μ region have been previously studied in this laboratory by Chakravarti, ~~and~~ Dasgupta and Bhattacharyya[4]. Though normally this region is quite dependable for the detection of cyclopropane ring, Cole[5] has pointed out that interference is sometimes created by the presence of hydroxyl groups. According to him, absorption study in the region 3.23 - 3.32 μ should be more conclusive. For this reason the infra-red spectra of the following cyclopropane ring containing terpene derivatives have been studi in this region. Compounds examined are (i) α-santalol (I), (ii) α-santalyl-acetate (II), (iii) α-santalene (III), (iv) tricyclo-ekasantalic acid (IV), (v) teresantalic acid (V), (vi) teresantalol (VI), (vii) tricyclene (VII), (viii) Δ^3-carene (VIII), (ix) mintglyoxal (IX) and its derivatives (X and XI).



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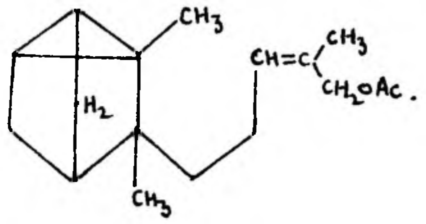

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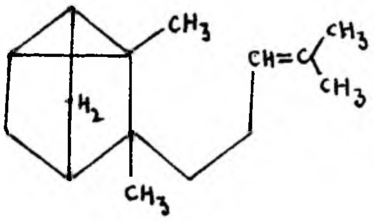

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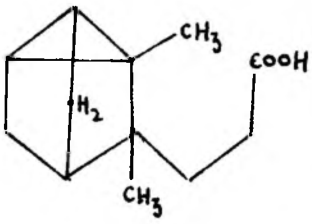

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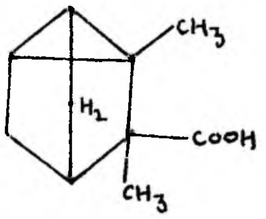

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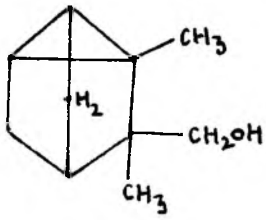

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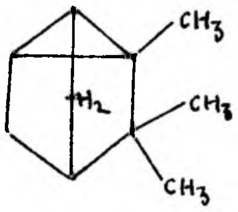

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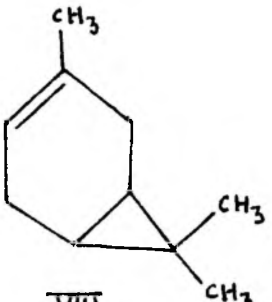

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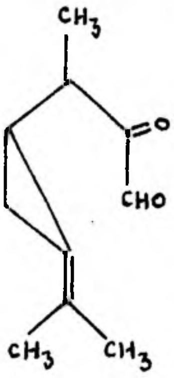

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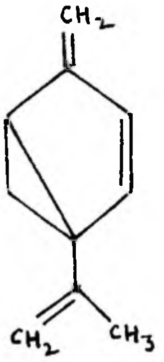
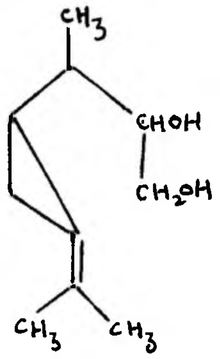


XI



X

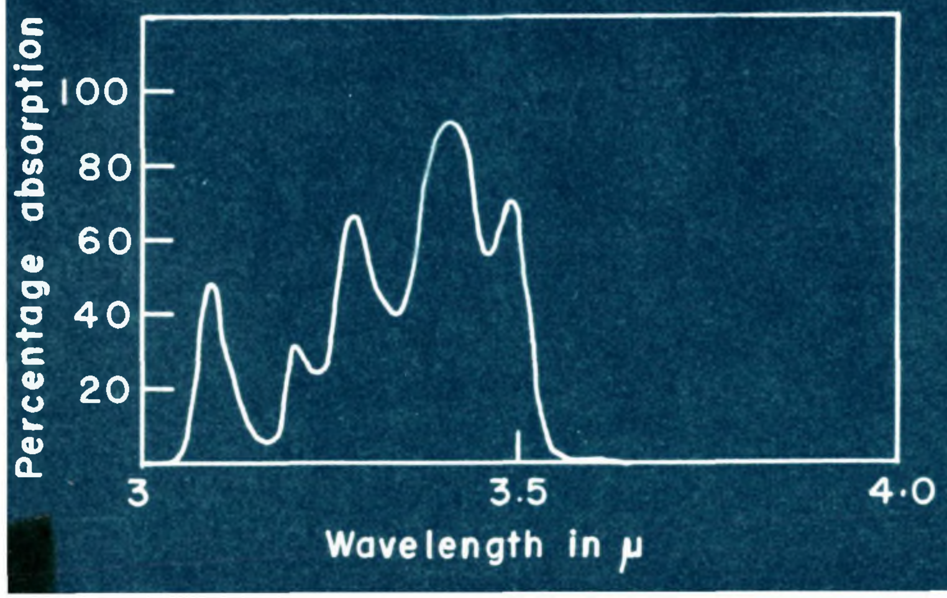
In compounds (I to VI) cyclopropane ring occurs in a highly complicated fused tricyclic system, in Δ^3-carene (VIII) cyclopropane ring contains a gem-dimethyl group and is fused with a cyclohexane ring. This is also partly true for compound (XI). Mintglyoxal (IX) and its derivative (X) contain unattached cyclopropane ring. The spectral characteristics are recorded in table below:

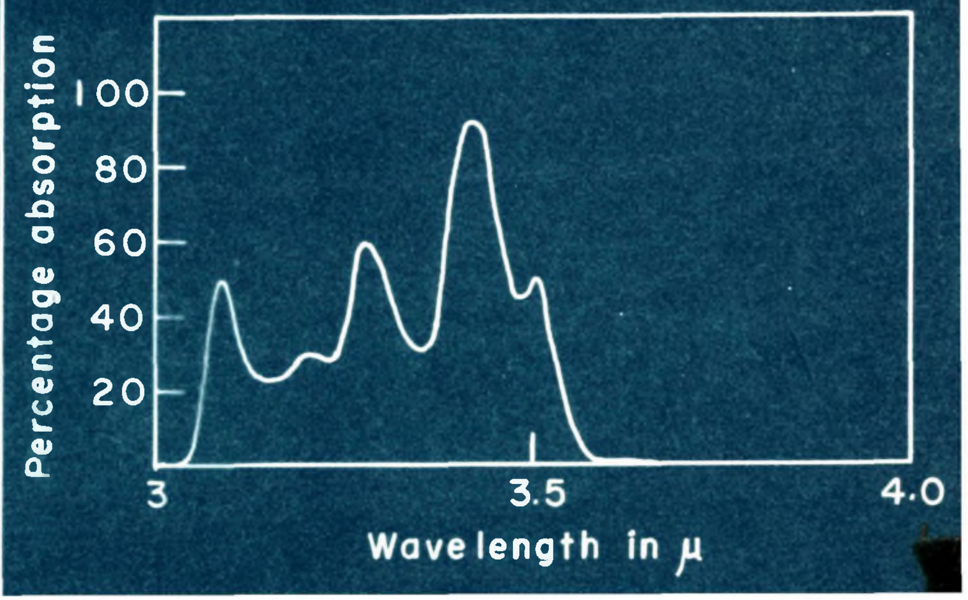
TABLE I

Compound	Characteristic absorption region in μ for cyclopropane ring.	Reference
1. α-santalol(I)	3.28	Curve I, p. 79
2. α-santalylacetate(II)	3.28, 3.29	Curve II p. 80
3. α-santalene(III)	3.28	Curve I(part V) p. 99
4. Tricycloekasantalic acid (IV)	3.29, 3.30	Curve III p. 81
5. Teresantalic acid (V)	3.28, 3.32	Curve IV, p. 82
6. Teresantalol (VI)	3.29	Curve V, p. 83
7. Tricyclene (VII)	3.28	Curve VI p. 84
8. Δ^3-carene (VIII)	3.33	Curve VII, p. 85
9. Mintglyoxal (IX)	3.33	Curve VIII, p. 86
10. Crystalline diol (X) (Li.Al.H4 - m.p.145°)	3.32	Curve IX, p. 87
11. Triol-hydrocarbon (XI)	3.27, 3.31	Curve X, p. 88

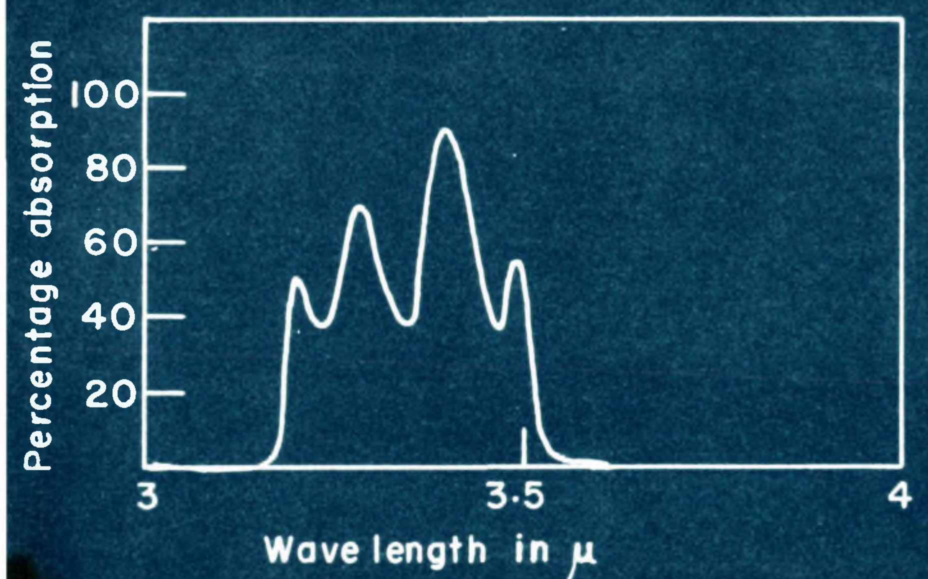
In this investigation pure specimens of the materials were employed. For the determination of infra-red spectra, a "Grubb-Parson" single beam spectrometer with a lithiumfluoride prism was used. All the substances were studied as films using a thin smear between two rock-salt plates in the case of liquids and as solutions in carbondisulphide in the case of both liquids and solids.

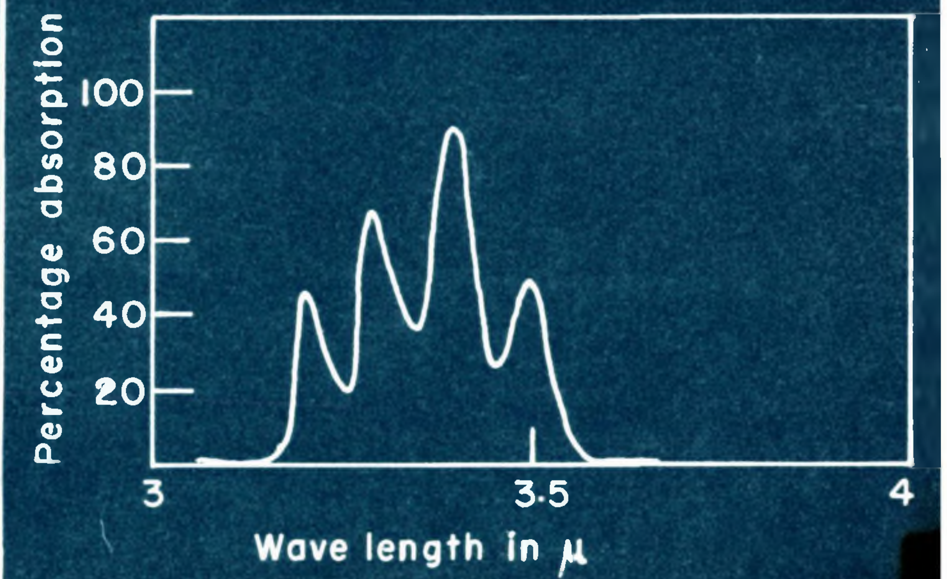
α-SANTALOL


Percentage absorption
100
80
60
40
20
3
3.5
4.0
Wavelength in μ

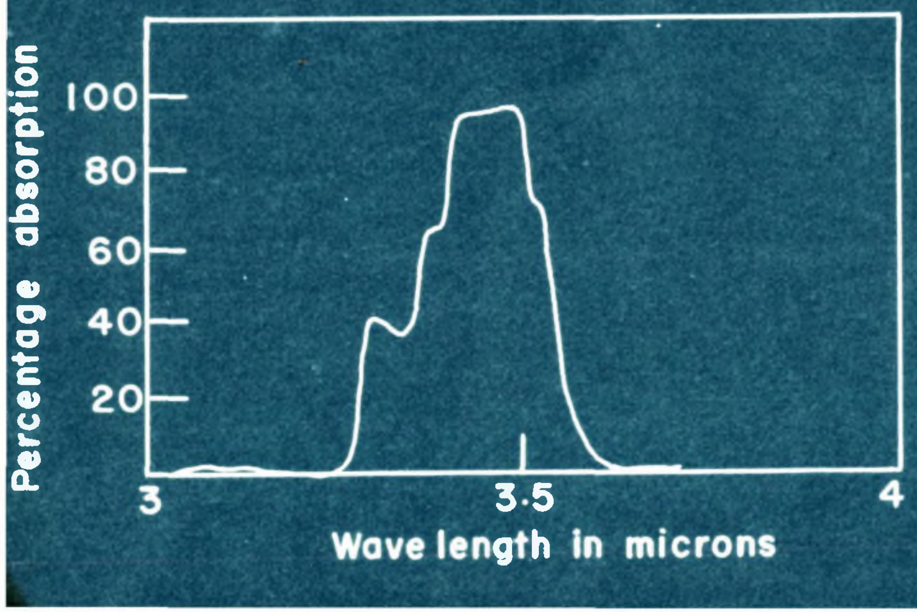

Percentage absorption
100
80
60
40
20
3
3.5
4.0
Wavelength in μ

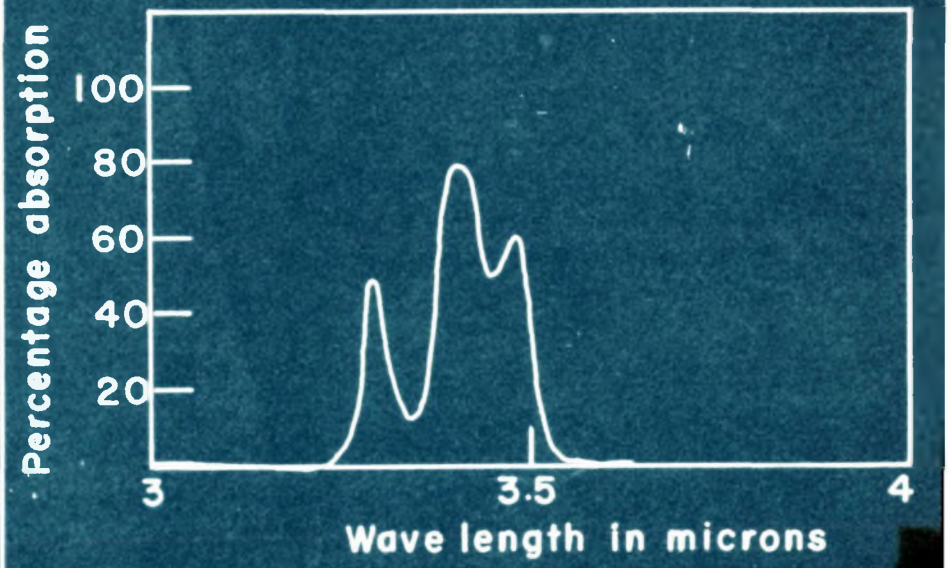
α-SANTALYL-ACETATE



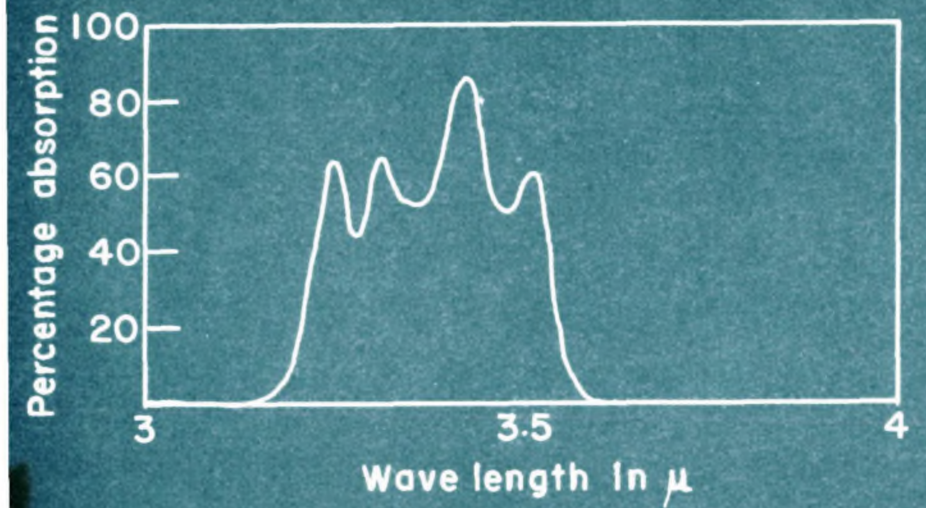


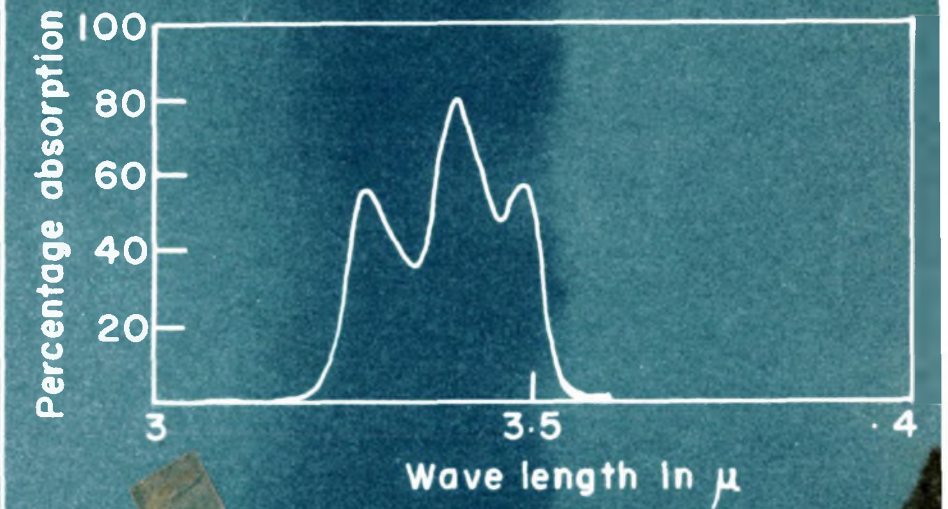
TRICYCLO-EKASANTALIC ACID

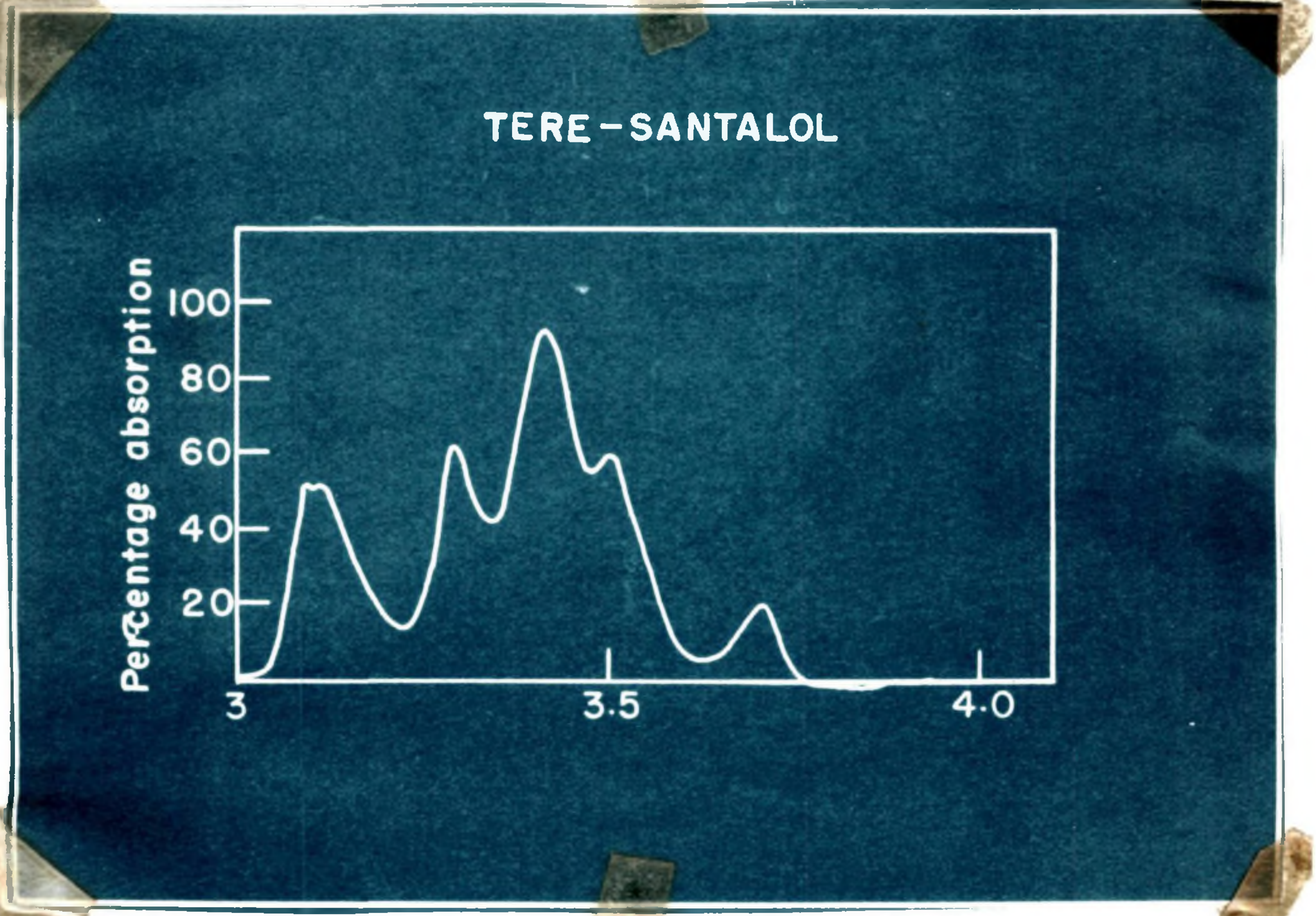




TERESANTALIC ACID

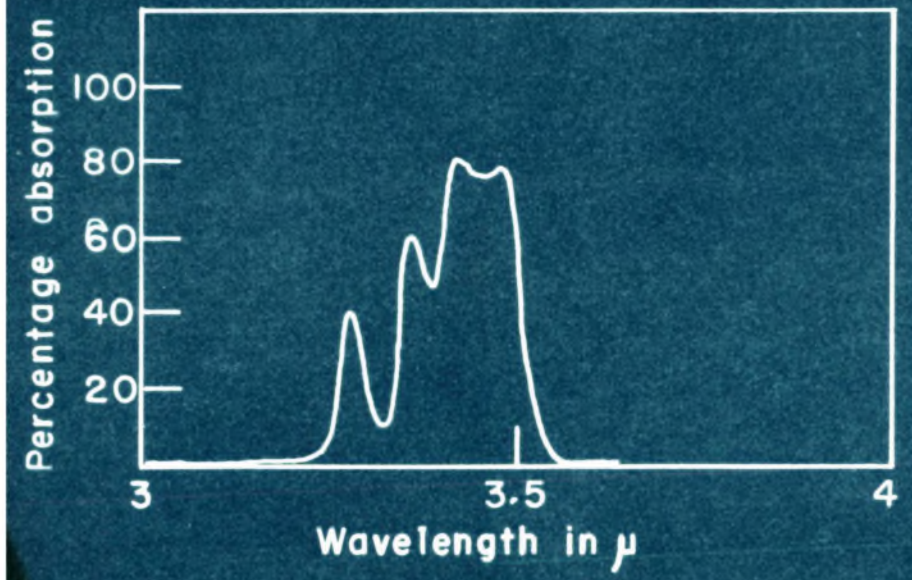


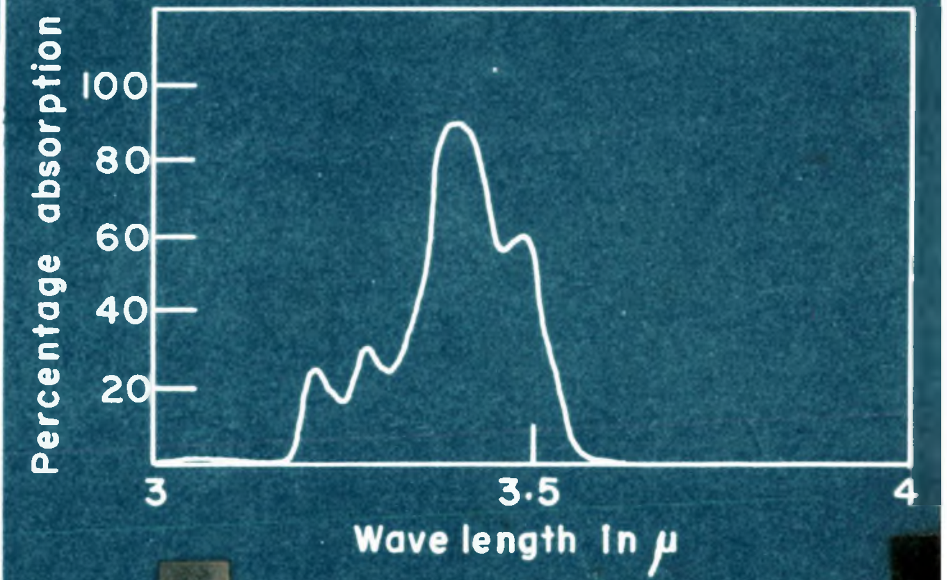




V 6% Soln. in CS_2

TRICYCLENE


Percentage absorption
100
80
60
40
20
3
3.5
4
Wavelength in μ


Percentage absorption
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60
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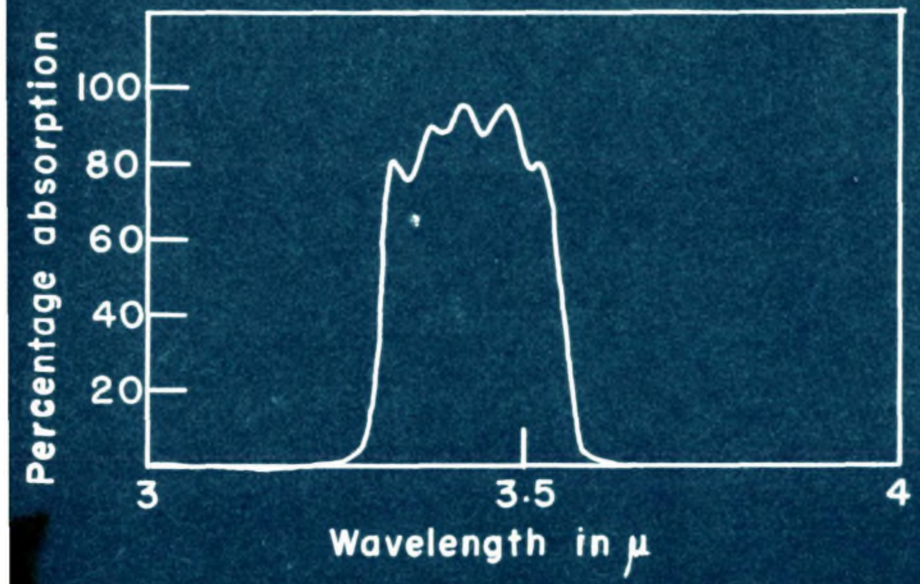
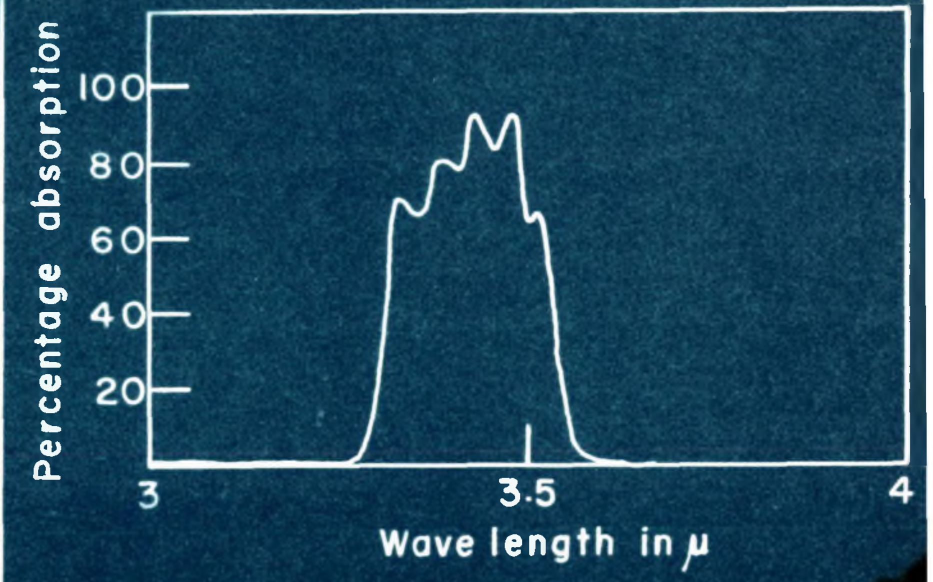
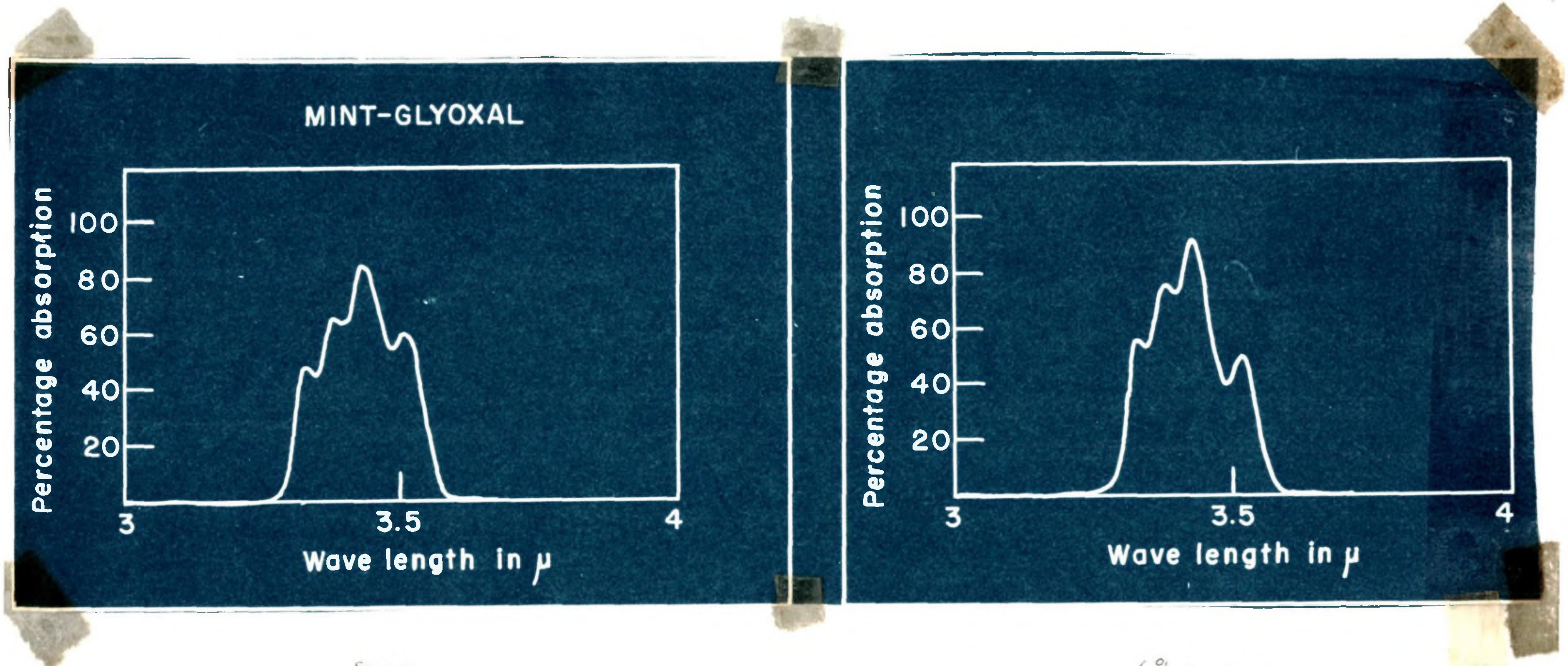
20
3
3.5
4
Wave length In μ

Δ^3CARENE



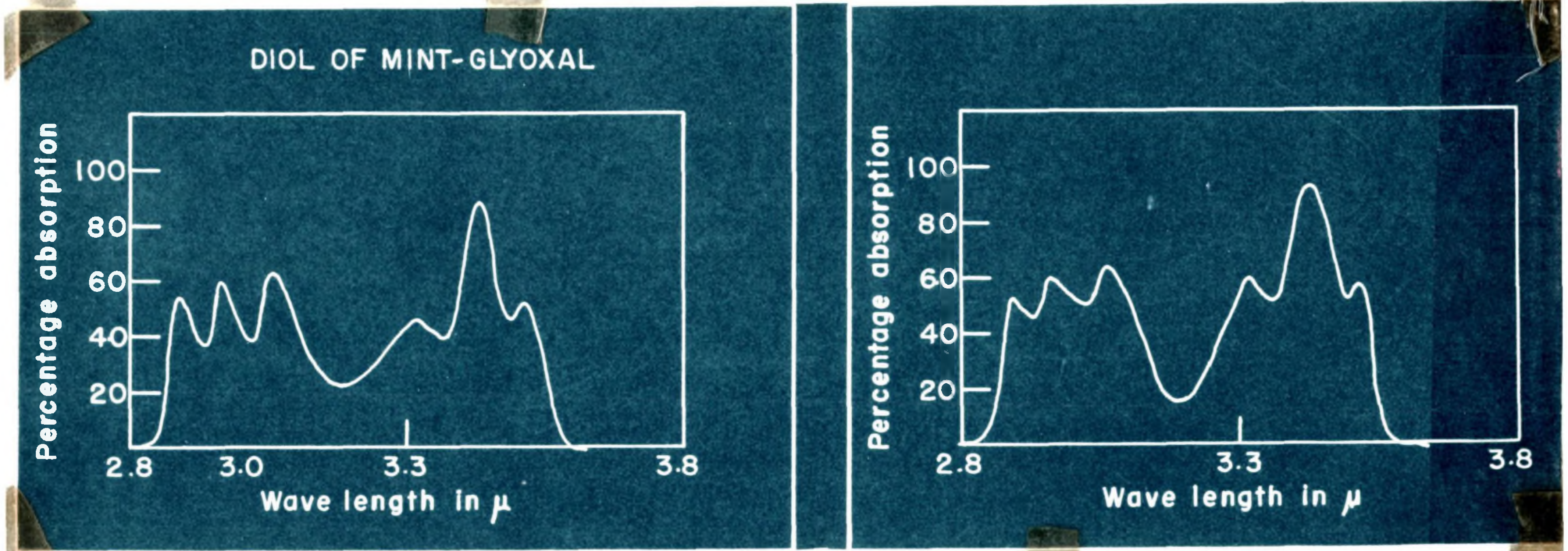




Smear

VIII

6 % soln. in CS_2

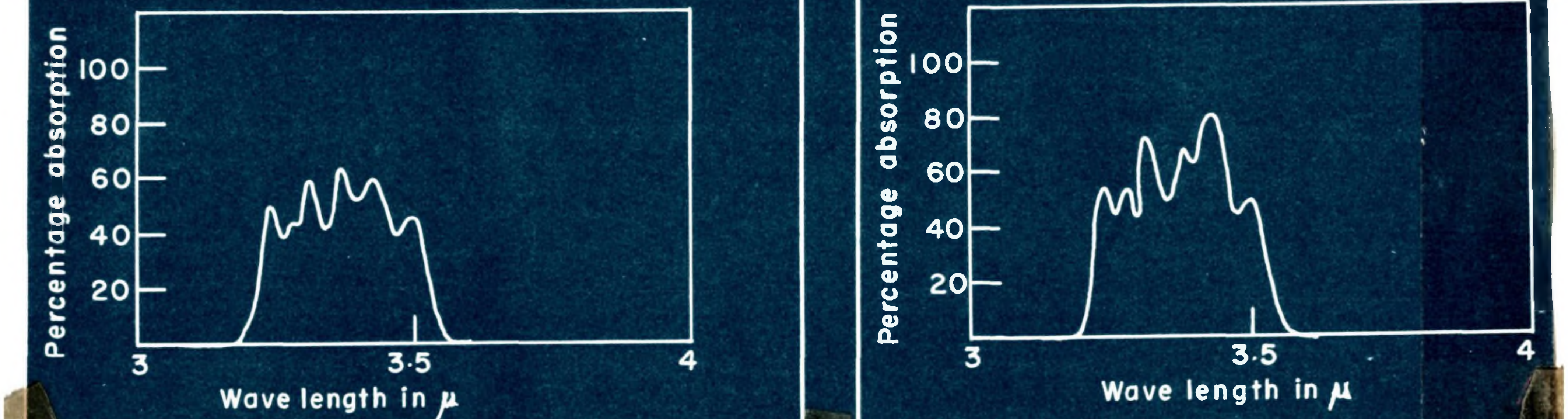


Solid spectra

IX

4 % soln. in CS_2

HYDROCARBON FROM TRIOL



Smear

X

6 % soln. in CS_2

EXPERIMENTAL

The details of infra-red spectra of the various compounds are recorded in table I.

α-santalol(I):

It was isolated by fractionation of the santalol mixture of Indian sandalwood oil, b.p.147-148/5 mm., n_D^{25} 1.5016; α_D +7°.67; unsaturation value 1.02, 1.1 (perbenzoic acid oxidation).

α-Santalyl-acetate(II):

It was prepared by acetylation of α-santalol with excess of acetic-anhydride at room temperature and isolated in the conventional way; b.p.138-139°/5.5 mm.; n_D^{30} 1.4770; α_D +10°.2

α-Santalene(III):

It has been isolated for the first time in pure state by elobarate fractionation of the santalene-mixture of Indian sandalwood oil through an efficient packed column fitted with a batch-strip distillation head, b.p. 116°/6 mm.; $n_D^{24.8}$ 1.4855; α_D+6°.60; d_4^{30} 0.90303; unsaturation value - 1.01, 1.03 (perbenzoic acid).

Tricycloekasantalic acid(IV):

It was obtained by oxidation of α-santalol with potassium-permanganate and crystallised two times from petrol-cum-ether (40-60°) m.p.76°; $[\alpha]_D$ +15°.0.

Teresantalic acid(V):

It was isolated by fractional distillation of the acid-mixture of Indian sandalwood oil and then crystallised from petroleum ether (40-60°)

b.p.126-127°/1 mm.; m.p.157°; $[\alpha]_D$ -75°.9

Teresantalol (VI):

It was prepared by reducing teresantalic acid with lithium aluminiumhydride; crystallised from petroleum ether (40-60°); m.p.113-114°; $[\alpha]_D$ +11°.2.

Tricyclene (VII):

It was prepared according to the method of Kishner[6]; Meerwein and Emster[7] and Chakravarti, Dasgupta and Bhattacharyya[4]; m.p.68°.

Δ^3-carene (VIII):

The hydrocarbon was isolated from Indian turpentine oil by fractionation through Tower's column (......25 plates); b.p.168-170°/710 mm.; n_D^{27} 1.4701; α_D+8°.1.

Isolation of mintglyoxal (IX) and the preparation of its derivatives (X and XI) have been described in part III of this thesis and also in the paper published by Chakravarti and Bhattacharyya[8].

***

R_E_F_E_R_E_N_C_E_S.

1. Derfer, Pickett and Boord, J.Am.Chem.Soc., 1949, 71, 2482.

2. Marrison, J.Chem.Soc., 1951, 1614-1615.

3. Wiberley and Bunce, Analytical Chemistry, 1925, 623.

4. Chakravarti, Dasgupta and Bhattacharyya, P. and E.O.R., 1955, 46, 330-333.

5. Cole, J.Chem.Soc., 1954, 3807-3812.

6. Kishner, C., 1911, (II), 363.

7. Meerwein and Emster, Ber., 1920, 53, 1815.

8. Chakravarti and Bhattacharyya, P. and E.O.R., 1955, 46, 256-268.

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PART V.

INDIAN SANDALWOOD OIL

Isolation of pure α- and β-santalenes.

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Summary.

α- and β-santalenes are the main hydrocarbon components present in Indian sandalwood oil. But as yet, it has not been possible for earlier workers to isolate these components in a pure state. This has now been achieved by using a specially designed "batchstrip head" and the compounds characterised properly. Both the hydrocarbons have been obtained in a completely pure state free from other contaminents. This type of head is extremely useful for the spearation of intricate mixtures of essential oil components, which, otherwise, may be difficult to separate.

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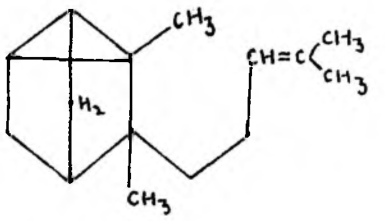
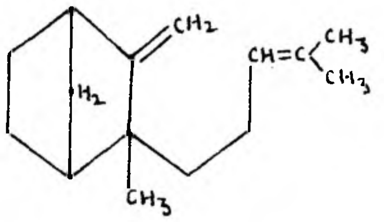
East Indian sandalwood oil obtained from the heartwood of the plant "Santalum-album, L". is one of the most important essential oils produced in India. It is extensively used in the perfumary industry and is highly valued for its fine aroma. It contains about twenty different components[1], hydrocarbons, alcohol, acids, aldehydes, ketones etc. The main hydrocarbon components are (i) α-santalene (I) and (ii) β-santalene(II).



I



II

Many workers[2-7] have worked on these hydrocarbons but it had not been so far possible to separate them in completely pure state. Properties of these hydrocarbons as recorded by different workers are shown below:-

α-Santalene

Schimmel and Co[2] ... b.p.252°/753 mm.; n_D^{15} 1.49205; d_{15}^{15} 0.9132; α_D -3°.34.

Semmler[3] ... b.p.118-120°/9 mm.; n_D 1.491; d_{20} 0.8984; α_D-15°.0

β-Santalene

Guerbet[4] ... b.p.263-264° (corr.) d_0 0.9139
α_D $-28^\circ.55$

Semmler[3] ... b.p.125-127°/9 mm.; n_D 1.4932; d_{20} 0.892;
α_D $-35^\circ.0$

Schimmel and Co[2]... b.p.125-126°/7 mm.; n_D^{20} 1.49460; d_{20} 0.894;
α_D $-41^\circ.3$

Ruzicka and Thomann[5] α_D $-45^\circ.0$.

The purest sample of α- and β-santalenes isolated by Guha and Bhattacharyya[7] had the following properties: -

	b.p./7 mm.	n_D^{20}	d_4^{20}	α_D
α-Santalene	117°	1.4900	0.9102	$2^\circ.4$
β-Santalene	125°	1.4941	0.8940	$-49^\circ.54$

As will be seen from the formulae recorded above α-santalene contains one double bond while β-santalene contains two double bonds. By taking advantage of this fact, Guha and Bhattacharyya (loc.cit.) estimated with per-camphoric acid the amount of unsaturation of the santalenes isolated by them and then by applying the law of mixture determined the percentage purify of these materials and concluded that the purity of α-santalene isolated by them was 93% and that of β-santalene only 88%. From their results it was evident that the samples of α- and β-santalenes isolated by other workers were very much more impure. From mathematical analysis of their results they also predicted the properties of pure α- and β-santalenes as follows:

	Predicted optical rotations
Pure α-santalene	$+6^{\circ}.29$
Pure β-santalene	$-56^{\circ}.36$

However, the actual separations of the two components could not be effected. This has now been done. By employing a comparatively large amount of santalene mixture isolated from sandalwood oil and using an efficient packed column fitted with a special type of batch-strip head (photograph, p. 97), the two hydrocarbons have been separated in a completely pure state. The optical rotations of these samples tally with the values predicted by Guha and Bhattacharyya. The properties of these pure samples are recorded below:

α -santalene

b.p.116°-/6 mm.

$n_D^{24.8}$ 1.4855 ; n_D^{30} 1.48325 (corr.)

d_4^{30} 0.9030

α_D $+6^{\circ}.60$

Molecular refractivity 64.654.

Unsaturation value - 1.01, 1.03.

β- santalene

b.p.123-124°/ 6 mm.

n_D^{25} 1.4937; n_D^{30} 1.49145 (corr.

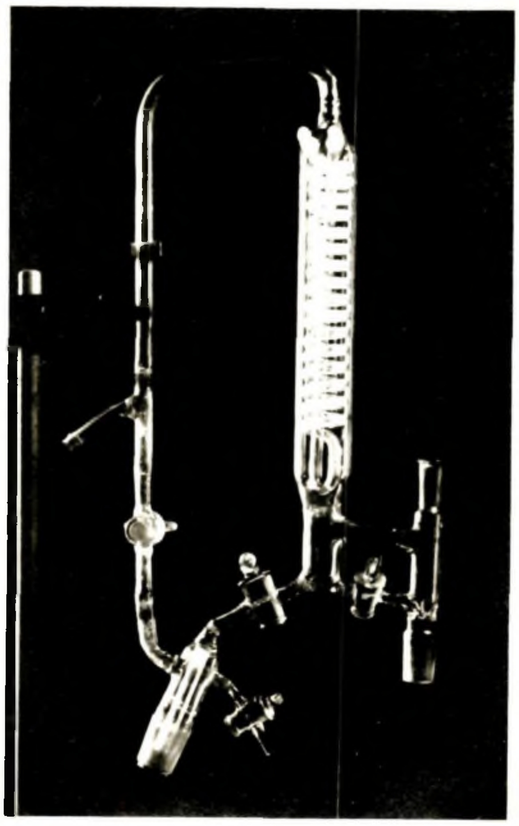
d_4^{30} 0.89066

α_D $-57^{\circ}.06$

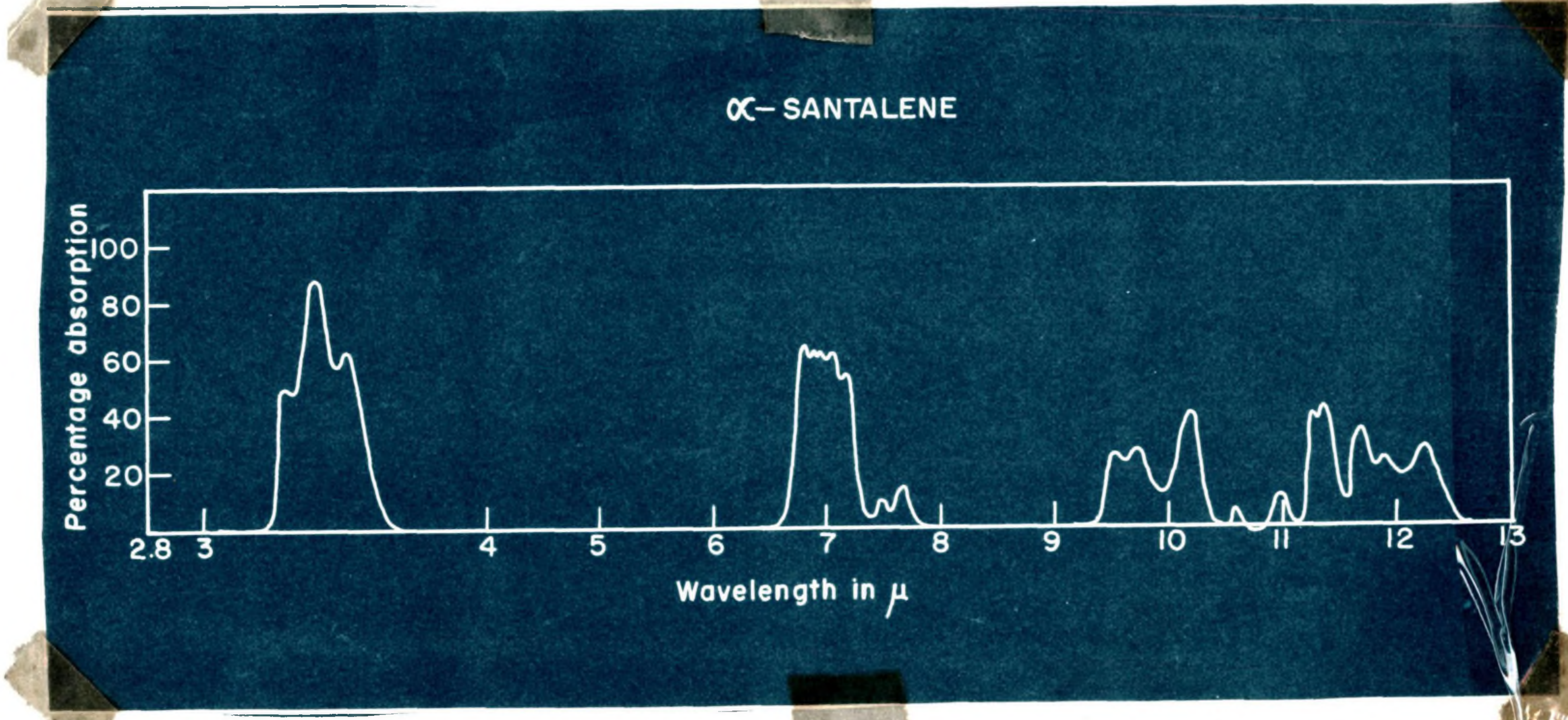
Molecular refractivity 66.202

Unsaturation value 2.01, 2.05

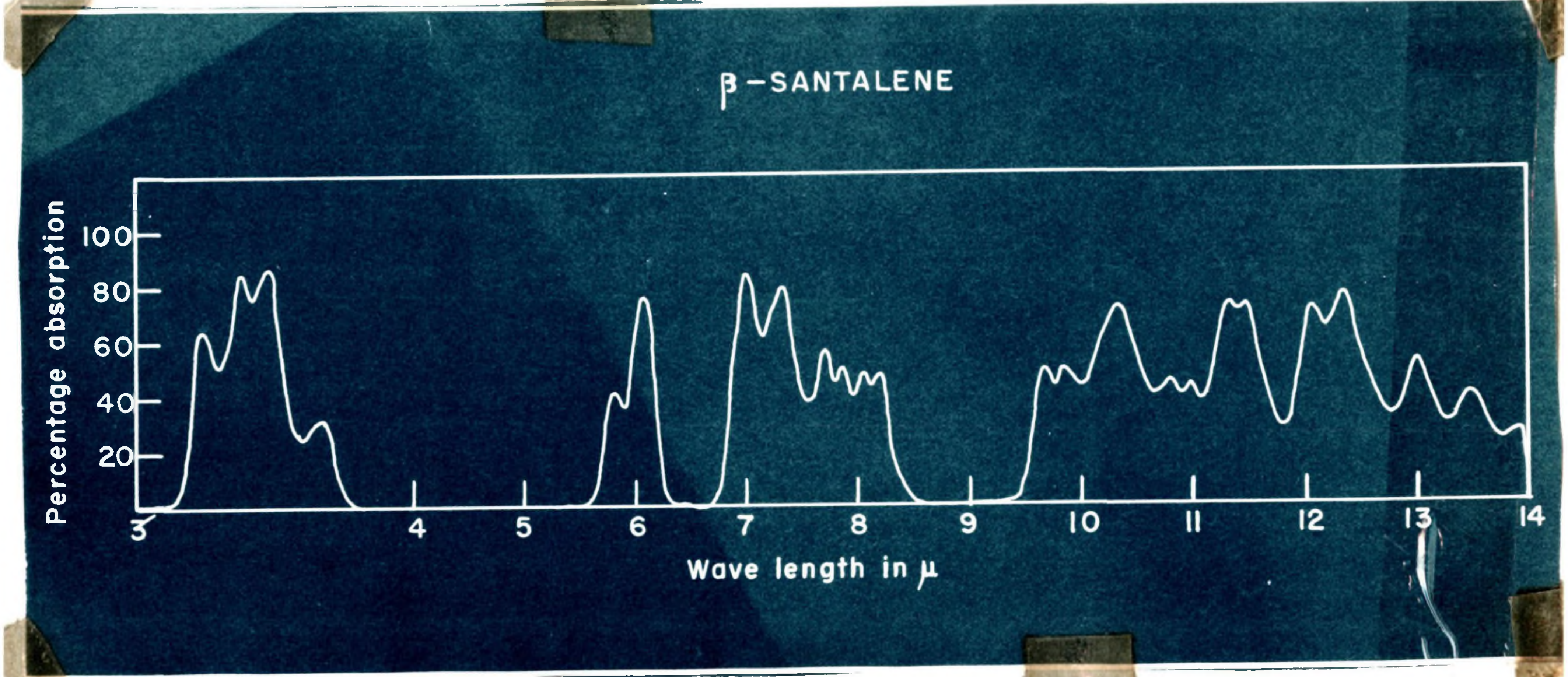
Batch-strip head.



Infra-red spectra of the santalenes (Curve 1, p.99 ; Curve II, p.100) have been determined in the usual way. The details of this important separation are recorded in experimental part. The fractional separation through the batchstrip procedure has been known for sometimes but, as yet, it has not found such an extensive use as it deserves. By adopting this procedure it should be possible to effect separation of many terpenoids which otherwise may be considered to be difficult or impracticable.


α– SANTALENE
Percentage absorption
100
80
60
40
20
2.8
3
4
5
6
7
8
9
10
11
12
13
Wavelength in μ

Curve I



β-SANTALENE

Curve II

EXPERIMENTAL.

Pure East Indian sandalwood oil was ~~initially~~ saponified with alcoholic potash. Non-acedic portion after usual processing and drying was initially distilled through a tall column packed with micro m helices (......100 plates) fitted with the usual total condensation partial take-off type head and the fraction boiling upto 130°/5 mm. collected. This fraction was then refluxed and distilled in vacuum over a large excess of sodium to give finally a mixture of hydrocarbons (252 g.). This hydrocarbon mixture was then carefully fractionated under high reflux ratio through the same tall column and divided into large number of batches (about 12 ml. each) The course of separation was followed by noting the boiling point, refractive index and optical rotation of each fraction. The results are recorded below in Table I.

......

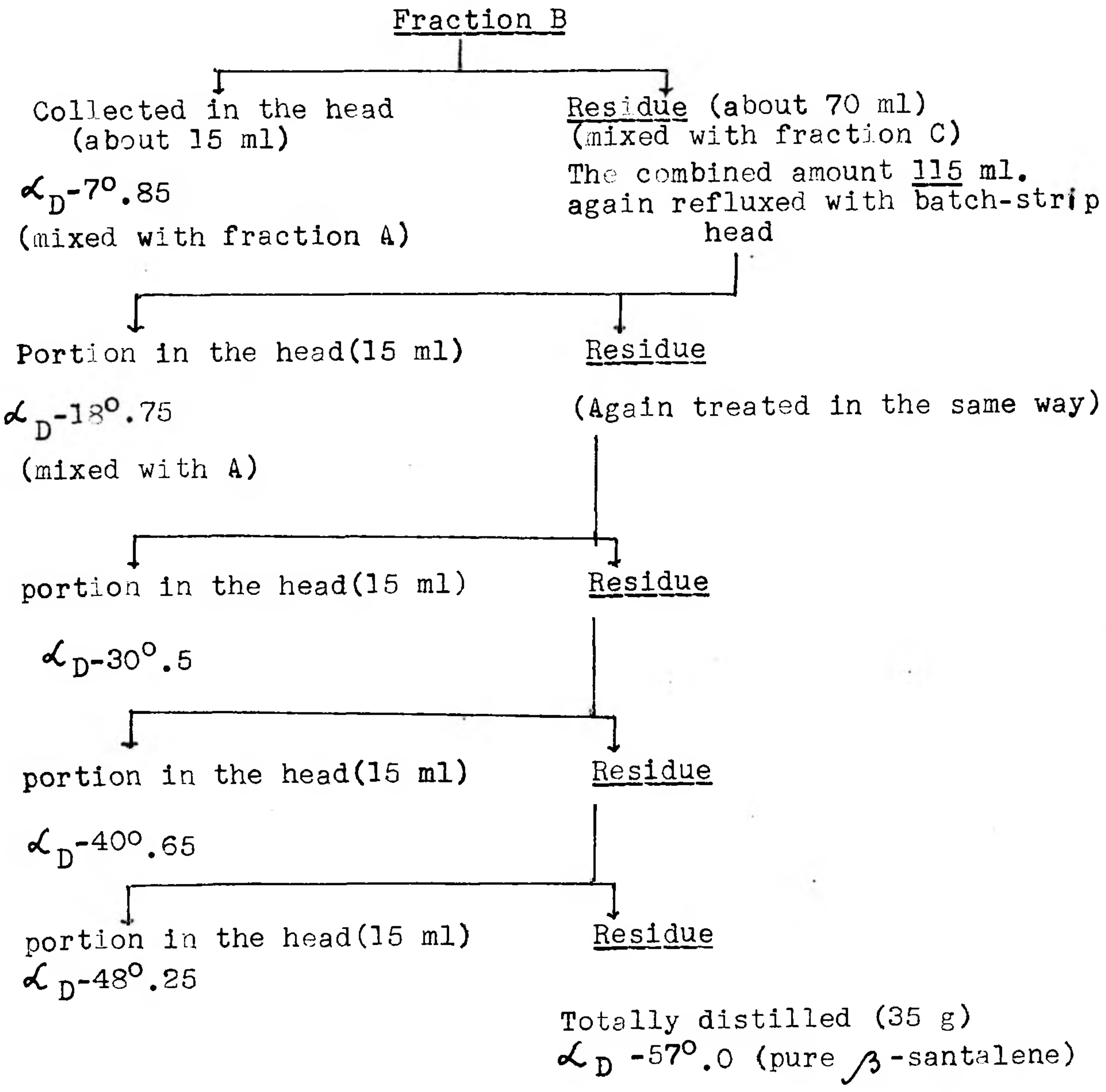
TABLE I

No. of fraction		b.p./6 mm.	n_D^{25}	α_D
1		114-116°	1.4880	-15°.2
2		116°	1.4887	-12°.4
3		116°	1.4885	-12°.25
4		116°	1.4883	-13°.74
5		116-117°	1.4888	-15°.20
6		117-118°	1.4892	-17°.05
7		118°	1.4895	-18°.30
8		118°	1.4895	-20°.000
9		118°	1.4900	-21°.53
10		118°	1.4900	-22°.85
11		118-119°	1.4901	-25°.0
12		119°	1.4905	-27°.05
13		119°	1.4908	-28°.52
14		119°	1.4910	-30°.80
15		119°	1.4912	-34°.15
16		119°	1.4917	-37°.85
17		119°	1.4922	-39°.05
18		119°	1.4924	-41°.75
19		119°	1.4928	-43°.60
20		119-120°	1.4929	-46°.4
21		122°	1.4929	-47°.45
22	Residue	Totally distilled.		

Fractions 1 -11 were combined together	<u>Fraction A</u>
Fractions 12 - 17 were combined together	<u>Fraction B</u>
Fractions 18 - 22 were combined together	<u>Fraction C</u>

Isolation of β-santalene (II):

The fraction B was refluxed under total reflux with a batch-strip head fitted on the Tower's column (,,,,....25 plates) at about 5 mm. pressure. Batches were collected at an interval of one hour each time. The details are shown in a schematic form below:-



β-Santalene thus obtained was once again distilled over sodium.

Properties of β-santalene sample:

b.p.123-124°/6 mm.

n_D^{25} 1.4937

α_D -57°.06

d_4^{30} 0.89066

Molecular refractivity = 66.202.

Unsaturation value as determined by oxidation with perbenzoic acid (24-48 hours) : 2.01, 2.05.

Infra-red spectrum (Curve II) was determined in the usual way. It indicated $=CH_2$ grouping (absorption at 11·35μ region).

Isolation of α-santalene(I):

The fraction A and some of the batches, showing low negative rotation obtained during rectification of fractions B and C, were combined together and the total amount (160 ml.) was subjected to batch-strip distillation at 5 mm. pressure. The batches (about 13 ml. each) were collected at an interval of about 30 minutes. The details are recorded below in table II:

TABLE II

No. of batch	optical rotation
1	-2°.0
2	+2°.01
3	-1°.8
4	-1°.9
5	-4°.3

6 The residue was then totally distilled and was rejected as a mixture. The first five fractions were combined

together and again subjected to batch-strip distillation. In the beginning, a few ml. of the first run were distilled out under high reflux ratio before the batch-strip head was put into operation and then the following batches were collected (Table III).

TABLE III

No.		optical rotation	amount
1	a few ml. of the first run rejected	+ 2°.20	7 ml
2	through a batch-strip head	+6°.64	15 ml
3	""	+ 6°.56	15 ml
4	""	+ 0°.8	13 ml
5	""	-2°.3	13 ml
6	the residue	rejected	

The fractions 2 and 3, which were pure α-santalene, were combined together and then distilled once again over sodium(~~yield~~ yield 23 g.) The properties were as follows:-

b.p.116°/6 mm.

$n_D^{24.8}$ 1.4855

α_D +6°.60

d_4^{30} 0.9030

molecular refractivity = 64.654.

Unsaturation value was determined by oxidation with perbenzoic acid (24-48 hours)

value found: 1.01, 1.03

Infra-red spectrum (Curve I) determined in the usual way showed cyclopropane ring (absorption at 3·28 μ and 10·21 ? μ regions).

REFERENCES.

1. Guenther, The Essential Oils, Vol.V., p.185-187, (1952).

2. Schimmel and Co., Ber., 1910, Oct., 107; 1910, April, 165.

3. Semmler, Ber., 1907, 40, 3321; 1910, 43, 1898.

4. Guerbet, Compt.rend., 1900, 130, 417, 1324. Bull.Soc.Chim. (3), 1900, 23, 217-, 540.

5. Ruzicka and Thomann, Helv.Chim.Acta, 1935, 18, 361.

6. Simonsen, The Terpenes, Vol.2, p.551 (1932).

7. Guha and Bhattacharyya, J.Ind.Chem.Soc., 1944, 21, 270.

PART VI

SYNTHETIC EXPERIMENTS IN THE SANTALOL SERIES

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SUMMARY

α-Santalol and allied compounds are the main constituents of sandal-wood oil. There is considerable scope for improvement in the method of synthesis for these compounds described by earlier workers. New approaches towards the synthesis of these compounds are described in this part. Teresantalic acid is quantitatively reduced with lithium-aluminiumhydride to teresantalol, which is in its turn can be converted via teresantatal to tricycloekasantalic acid through Reformatsky's reaction with bromo-acetic ester. Reduction of tricycloekasantalic acid with lithiumaluminiumhydride gives a quantitative yield of the alcohol-tricycloekasantalol. This alcohol can be oxidised with chromic acid according to Semmler[6] to the aldehyde tricycloekasantalal, which is also obtained by direct ozonisation of α-santalol. The aldehyde-tricycloekasantalal can be converted by Reformatsky's reaction with α-bromopropionic ester according to the procedure of Bhattacharyya[7] to α-santalic acid, reduction of which with lithiumaluminiumhydride is a suitable route for the synthesis of α-santalol.

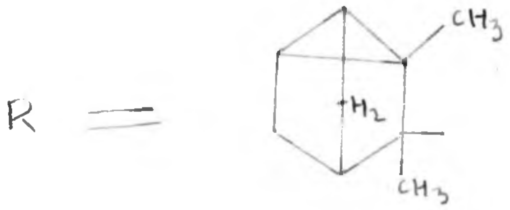
General introduction

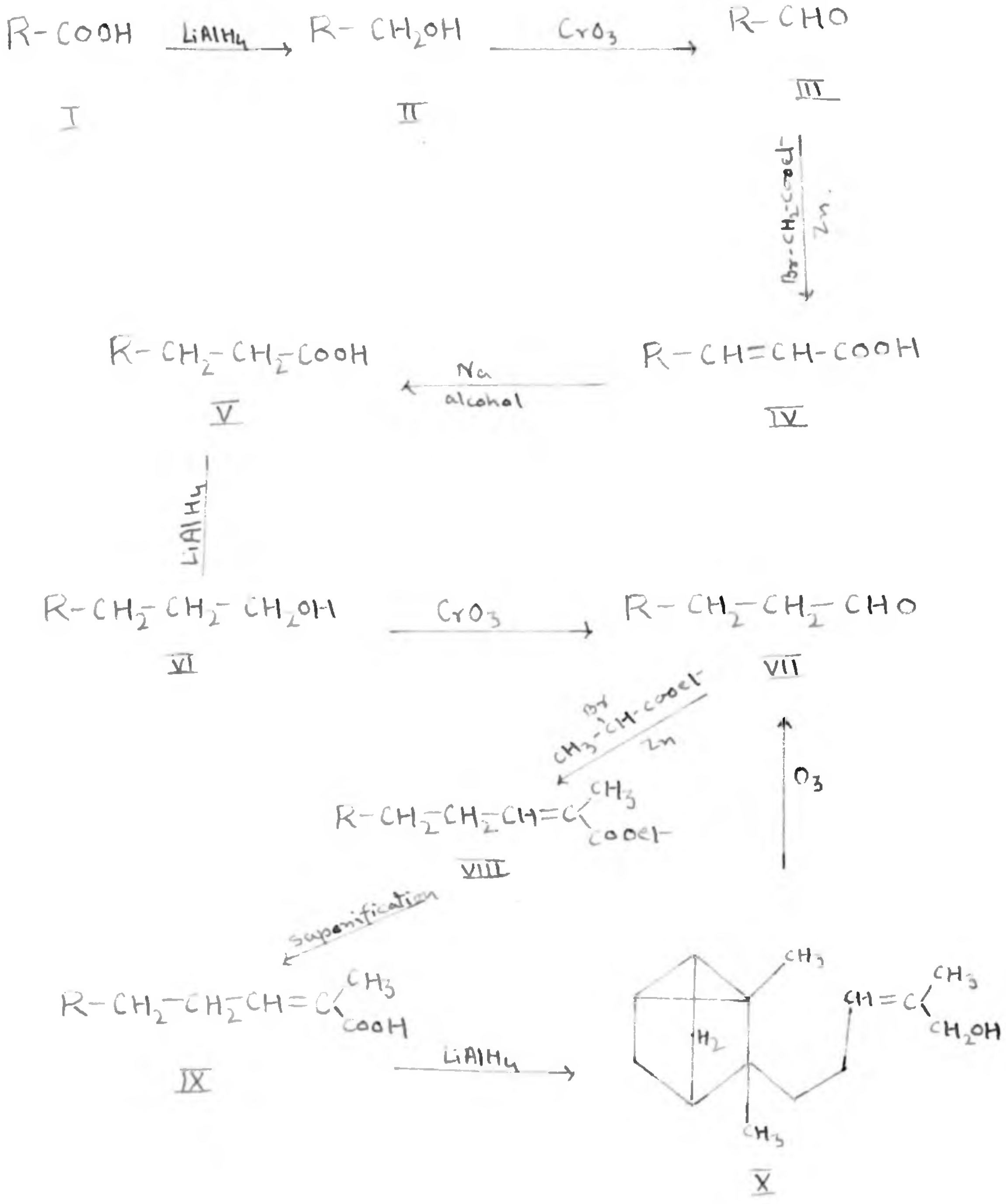
East Indian sandalwood oil obtained from the plant 'Santalum album,L", is one of the most important essential oils of Indian origin. The oil contains more than 15 different components comprising of acids, aldehydes, ketones, esters, alcohols, hydrocarbons etc. Many workers have made significant contribution towards the eludidation of the structures of various constituents of this oil. The number of references are so numerous that it will be difficult to enumerate all of them. For this reason the author is mainly referring to the volumes of 'Terpenes' by Simonsen[1,2], where most of the references have been systematically recorded. Simonsen himself is one of the most distinguished contributors in this field.

Of the various constituents of sandalwood oil, α-santalol (X) is the most important. Guha and Bhattacharyya[3] have made synthetic approaches in this field and have described synthesis of tricycloekasantalic acid (V) in very poor yield. They also continued it further by synthesising α-santalal ~~(XI)~~ and α-santalol (X) from tricyclo-ekasantalal (VII). Yields in these stages were also unsatisfactory due to formation of several by products. Therefore, there is considerable scope for developing a more satisfactory method.

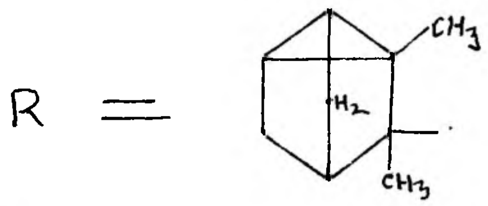
Present work:

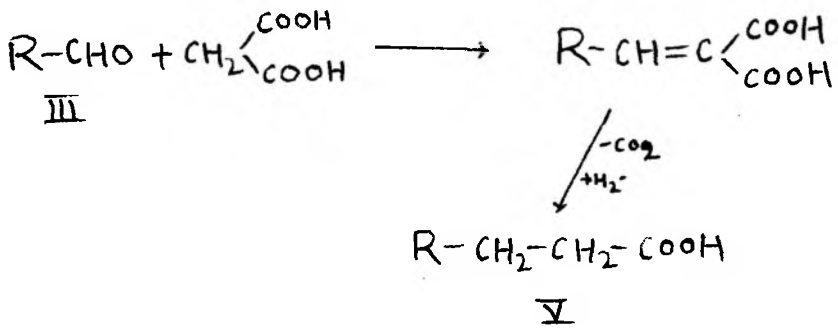
In this paper a new approach toward the synthesis of α-santalol (X) has been described. Starting material for this synthesis was teresantalic acid (I), synthesis of which has been achieved by


R =
CH3
H2
CH3


R-COOH
I
LiAlH4
R-CH2OH
II
CrO3
R-CHO
III
Br-CH2-COOEt
Zn.
R-CH=CH-COOH
IV
Na
alcohol
R-CH2-CH2-COOH
V
LiAlH4
R-CH2-CH2-CH2OH
VI
CrO3
R-CH2-CH2-CHO
VII
Br
CH3-CH-COOEt
Zn
R-CH2-CH2-CH=C(CH3)(COOEt)
VIII
O3
Saponification
R-CH2-CH2-CH=C(CH3)(COOH)
IX
LiAlH4
CH3
H2
CH3
CH=C(CH3)(CH2OH)
X

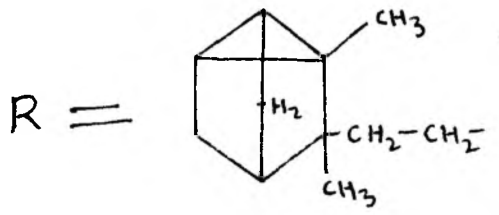
earlier workers[4]. In the present case teresantalic acid (I) was isolated from sandalwood oil itself. It was reduced in ethereal solution with lithiumaluminiumhydride to teresantalol (II) in quantitative yield. Oxidation of teresantalol with chromic acid in acetic acid solution according to the method of Ruzica[5] gave teresantalal (III). This aldehyde was then condensed with bromoacetic ester in presence of zinc to give dehydro-tricyclo-ekasantalic acid, the reduction of which with sodium and alcohol gave tricyclo-ekasantalic acid (V). Yields during the Reformatsky's reaction and subsequent operations were, however, not as satisfactory as desired. Certain quantity of teresantalol (II) and teresantalic acid (I) was obtained as by-products. The formation of these latter compounds is difficult to explain, but these were possibly formed by Cannizzaro's reaction of unreacted teresantalal (III) which escaped condensation with bromoacetic ester. This was also responsible for the comparitively low yield of tricycloekasantalic acid (V). It may be pointed out that aldehyde-teresantalal is a tertiary aldehyde without any available hydrogen at α-carbon-atom and should therefore be suseptible to Cannizzaro's reaction like tertiary butaraldehyde, but due to steric hindrance arising out of its tertiary nature, it will be somewhat sluggish in its reactions, though it is not completely innert as it forms carbonyl derivatives without any serious difficulty. As an alternative route for the preparation of tricycloekasantalic acid, the following sequence of reactions are also being investigated.

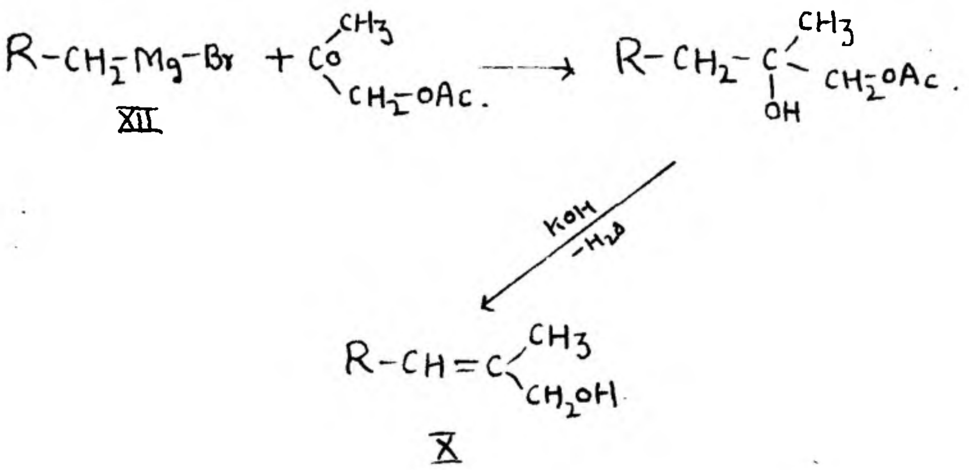




$$\underset{\text{III}}{R{-}CHO} + CH_2\begin{matrix}COOH\\COOH\end{matrix} \longrightarrow R{-}CH{=}C\begin{matrix}COOH\\COOH\end{matrix} \xrightarrow[+H_2]{-CO_2} \underset{\text{V}}{R{-}CH_2{-}CH_2{-}COOH}$$

In further continuation of our approaches towards α-santalol (X) it was possible to reduce tricycloekasantalic acid (V) with lithiumaluminiumhydride to the corresponding alcohol-tricycloekasantalol (VI) in quantitative yield. Tricycloekasantalic acid (V) utilized in this reaction was actually isolated by oxidation of sandalwood oil with potassiumpermanganate, which is the most convenient route for the preparation of this acid. The bromide of tricyclo-ekasantalol has already been converted to α-santalol by Bhattacharyya[7] by reacting its Grignard derivative (XII) with acetoxy-acetone and subsequent dehydration and hydrolysis.





The aldehyde-tricycloekasantalal (VII) obtained by the oxidation of the above alcohol or directly by ozonisation of natural α-santalol has also been converted by the same author[7] to α-santalic acid through Reformatsky's reaction with α-bromopropionic ester and subsequent dehydration. The present author is pursuing the reduction of α-santalic acid to α-santalol with lithiumaluminiumhydride.

E X P E R I M E N T A L

Teresantalic acid (I):

It was isolated from sandalwood oil itself. Sandalwood oil was first saponified with alcoholic alkali. After partial removal of alcohol and dilutation with water the non-acidic portion was extracted with ether. The alkaline-aqueous liquor on acidification furnished the acids, which were extracted out with ether. The ethreal extract, after removal of ether, was then fractionated through a small fractionating column. Teresantalic acid boiled mainly at 126-127°/1 mm. It was purified by vacuum sublimation at 1-2 mm; bath temperature 100°; m.p.157° $[\alpha]_D$ -75.9°.

Teresantalol (II):

Teresantalic acid (6.4 g.) was reduced in ethereal solution with lithiumaluminiumhydride (3 g.) in the usual way. After decomposition of the reaction mixture with ethylacetate, alcohol, water etc. teresantalol was exhaustively extracted with ether and after removal of ether purified by crystallisation from petroleum-ether; yield 4.5 g. A further quantity could also be isolated from the mother liquor, m.p.113-114°, $[\alpha]_D$ +11.2°. Analysis: Found : C, 78.71 ; H, 10.27 ;
$C_{10}H_{16}O$ requires: C, 78.89 ; H, 10.60 %.

Teresantalal (III):

Teresantalal was prepared by the oxidation of teresantalo with chromic acid following the basic method of Ruzica. Teresantalol (4.5 g.) was dissolved in glacial acetic acid (20 ml.) and oxidised by slow addition of chromic acid (2.01 g.) dissolved in glacial acetic acid (10 ml.) under ice cooling.

After the addition was complete the reaction mixture was heated on the water bath for about twenty minutes. After dilution with water, the reaction mixture was extracted with ether, washed successively with water, bicarbonate and water and dried (sodium sulphate). Ether was initially removed on water-bath and finally by using a vacuum pump. Teresantalal which was left as residue was used as such in the next operation without further purification. yield 4 g.

Tricycloekasantalic acid (V):

A mixture of purified zinc wool (1.7 g.) and anhydrous benzene (10 ml.) containing a trace of iodine was taken in a small three necked flask fitted with mechanical stirrer, condenser, dropping funnel, guard tubes etc. The mixture was warmed on water bath and then a mixture of teresantalal (4 g.), bromoacetic ester (4.5 g.) and anhydrous benzene (20 ml.) was slowly added. The reaction mixture was further heated on the water bath for about three hours. After cooling it was decomposed with dilute sulphuric acid in the cold and the benzene layer, after usual purification and washing, was dried (sodium sulphate). The residue left after complete removal of banzene was mixed with acetic-anhydride and heated in an oil-bath at 120° for an hour. Excess of aceticanhydride was decomposed with water and the reaction mixture was extracted with ether. The ethereal solution was washed with water, bicarbonate and again with water and dried (sodium sulphate). After removal of ether the residue was dissolved in absolute alcohol (50 ml.) and reduced by addition of metalic sodium in small pieces (3 g.). After the addition of sodium was complete water (15 ml.) was added and the reaction mixture refluxed on the water-bath for an hour. Excess of alcohol was then removed under reduced pressure, the residue diluted with water and extracted with ether. Aqueous and ethereal extracts were treated separately.

Ether extract: This extract after removal of ether and usual processing furnished the solid material which after sublimation was identified as teresantalol, m.p.114°, mixed m.p. with an authentic sample remained undepressed, yield 0.5 g.

Aqueous solution: This portion after acidification was extracted with ether. The ethereal solution after washing and drying (sodium sulphate) followed by removal of ether gave a mixture of organic acids which was fractionally distilled and divided into two fractions:

(i) b.p. upto 135°/1 mm.	yield 0.4 g.
(ii) b.p.135-160°/1 mm.	yield 1.3 g.

Fraction (i) was solidified on cooling. It was purified by sublimation and identified as teresantalic acid, m.p. and mixed m.p. with an authentic sample 157°. Fraction (ii) also on cooling became semisolid and after processing on a porous plate left a solid material which was further purified by repeated micro-vacuum sublimation, m.p.76°; $[\alpha]_D+15.^{\circ}a$. Its identity with tricycloekasantalic acid was established by mixed melting point with an authentic sample obtained by oxidation of sandalwood oil with permanganate.

Tricycloekasantalol (VI):

It was prepared by reduction of tricycloekasantalic acid with lithiumaluminiumhydride in ethereal solution.

Tricycloekasantalic acid required for this reaction was obtained by oxidation of sandalwood oil with potassium-permanganate. It was purified by crystallising two times from petroleum-ether (40-60°), m.p.76°;$[\alpha]$ D +15°.1. Tricycloekasantalic acid (5 g.) on reduction with lithium-aluminiumhydride (2.5 g.), following the same procedure as in the case of teresantalic acid, furnished pure tricycloekasantalol (3.5 g), b.p.89-90°/1.1 - 1.2 mm.;

$n_D^{29.5}$ 1·4862 ; α_D +10°·6.

Analysis : Found C,79·80 ; H,11·23 ;

$C_{12}H_{20}O$ Requires C,79·94 ; H,11·18 % .

Tricycloekasantalal etc.

Tricycloekasantalal can be obtained by ozonisation of α-santalol or by oxidation of tricycloekasantalol with chromic acid according to the method of Semmler (loc.cit). It can be converted by following the procedure of Bhattacharrya (loc.cit) to α-santalic acid, Reduction of the latter to α-santalol with lithiumaluminiumhydride is being investigated.

* * *

REFERENCES.

1. Simensen, The Terpenes, Vol.II, p.243-271 (1949).

2. Simonsen, The Terpenes, Vol.III, p.98-107, 179-188 (1952).

3. Guha and Bhattacharyya, J.Ind.Chem.Soc., 1944, 21, 280.

4. Ashina and Ishidate, Ber., 1935, 68, 83.

5. Ruzica and Liebl, Helv.Chim.Acta., 1926, 9, 140.

6. Semmler and Bode, Ber., 1907, 40, 1135-1136.

7. Bhattacharyya, Science and Culture, 1947, 13, 209

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PART VII

Longifolene fraction of Indian turpentine oil

Experiments on longifolene and β-longifolene

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SUMMARY

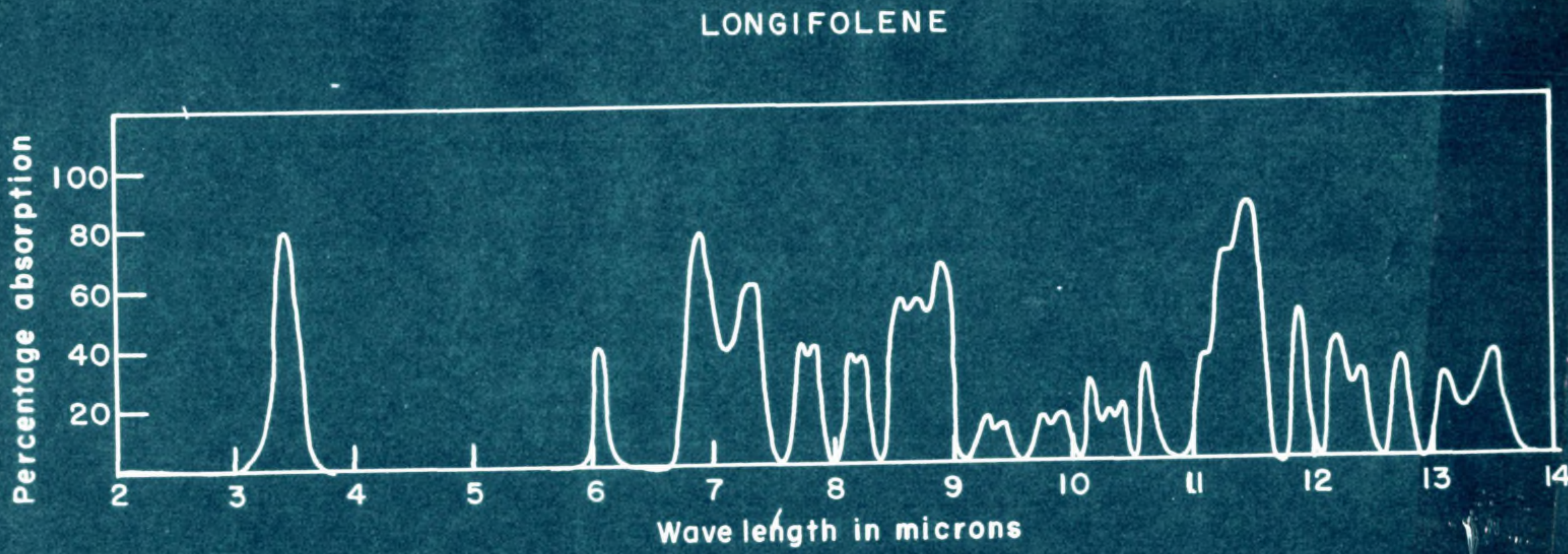
Longifoelene is a tricyclic sesquiterpene hydrocarbon present in the higher boiling fraction of Indian turpentine oil. This compound has been studied intensively and many derivatives and degradation products prepared. Two new lactonic products prepared through ozonisation of pure longifolene should throw new light on the now accepted structure (I) for this compound. A new bicyclic sesquiterpene hydrocarbon - β-longifolene containing two double bonds has also been isolated from the longifo~~e~~lene fraction and informations collected about its structure and also for its conversion to some isomers.

Indian turpentine oil

Indian turpentine oil from pinus longifolia differs considerably from turpentine oil of French or American origin. Instead of a high percentage of α-pinene; it contains a high proportion of a bicyclic monoterpenic hydrocarbon Δ^3-carene. It also contains about 10% of a sesquiterpene hydrocarbon which has been named by Simonsen as 'Longifolene'. Most of the original work on the constitution of longifolene has been carried out by Simonsen and recorded in two exhaustive papers[1]. Simonsen also suggested a tentative structure (I) for this hydrocarbon. Apart from its degradation to certain ultimate products like (i) as dimethyl succinic acid, (ii) dimethyl malonic acid etc., he also prepared (iii) two C_{14}-monocarboxylic acids (longifolic acid and isolongifolic acid), (iv) a C_{15}-diketone (longifdione) and (v) its oxidation product, a dicarboxylic acid, longiforic acid etc.

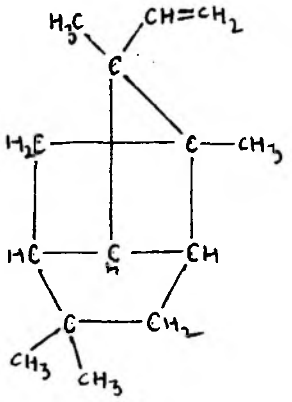
Structure of longifolene

Recently a series of papers[2-9] mainly by French workers have appeared on the structure of longifolene. From X-ray crystallographic study of the crystalline monohydrochloride and monohydrobromide of longifolene and certain chemical evidences collected along with, longifolene has been assigned the structure (II) and its hydrochloride or hydrobromide the structure (III). Structures II and III could also be written in a different way (IIa) and (IIIa). Thus, the longifolene is somewhat similar in structure to the bicyclic sesquiterpene hydrocarbon β-santalene[10] (IV) which is one of the constituents

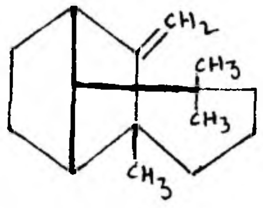

LONGIFOLENE
Percentage absorption
100
80
60
40
20
2
3
4
5
6
7
8
9
10
11
12
13
14
Wave length in microns

Curve I

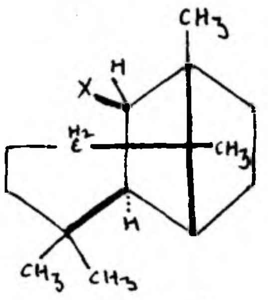
of East Indian sandalwood oil. On ozonisation longifolene produces (i) longifolic acid (V), which has now been shown to be a C_{15}-acid and not a C_{14}-acid as originally postulated by Simonsen (loc.cit.), (ii) a C_{14}-ketone (VI). Oxidation with chromic acid produces the same two compounds and a C_{15}-diketone, longif-dione which is very similar to camphor-quinone in appearance and like it can be easily oxidised to a corresponding dicarboxylic acid - longiforic acid. The hydrochloride (III or IIIa) is formed by Wagner rearrangement during hydrochlorination and is similar to bornyl-chloride obtained from camphene. Like bornyl-chloride it also forms a Grignard's reagent, from which, a borneol like C_{15}-secondary alcohol (VII) can be prepared. This alcohol can be oxidised with chromic acid to a liquid C_{15}-ketone (VIII).



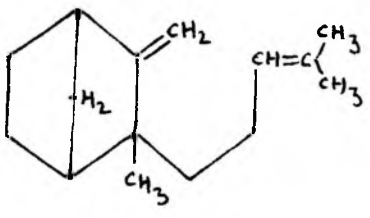
I



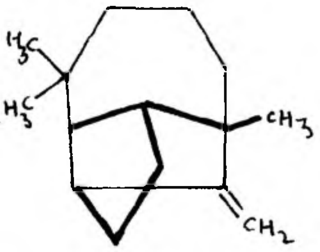
II



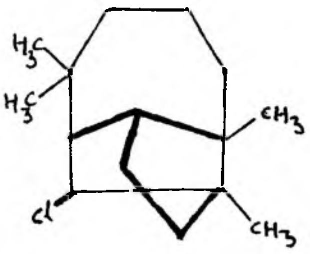
III



IV



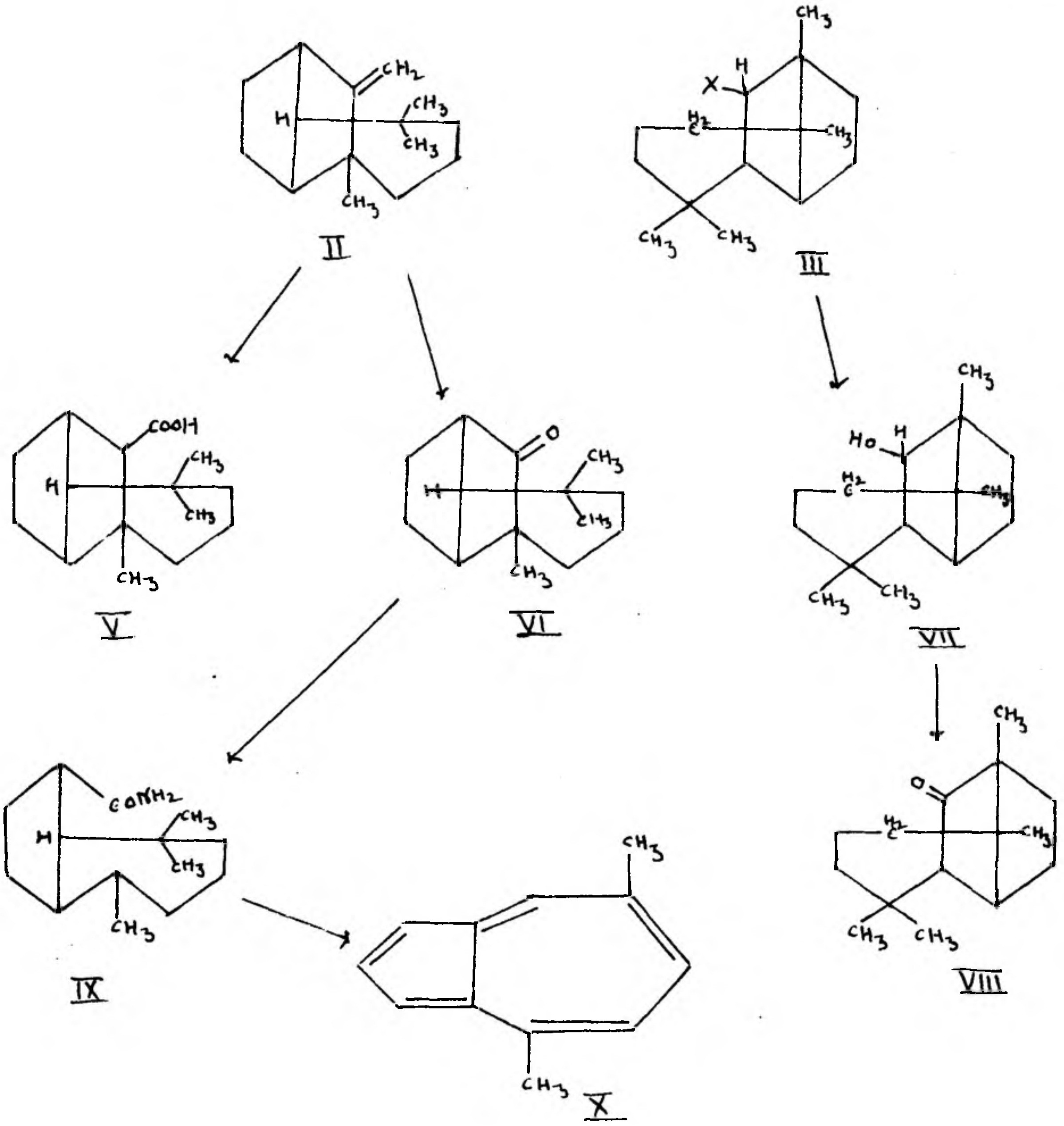
IIa



IIIa

Possibility of isolating azulene derivative

Longifolene (II and IIa) is a fused structure of two five membered and one seven membered rings. In the amide (IX) prepared by Naffa and Ourisson from (VI) one of the five membered rings has been opened leaving a fused five and seven membered ring system. Such a system on dehydrogenation should produce an azulene (X). This does not appear to have been done so far. According to the accepted convention of terpene chemistry such a chemical evidence is highly desirable.



Present work

We have been interested in the chemistry of longifolene for quite sometime, but because of the publication of the results of the French workers, our investigation lost some of its original significance. But certain results collected by us are still quite important and have been recorded in this thesis. We were fortunate in having at our disposal a large amount of longifolene, a five gallons - sample of which was supplied to us by the Government Turpentine Factory, ~~of~~ Bereilly (India). This was subjected to intensive fractiohation, using a 80-100 plates packed column fitted with total condensation partial take-off type head and divided it into about 100 fractions; the course of separation being followed by noting (i) boiling point, (ii) refractive index and (iii) optical rotation. Those fractions which, according to existing information, should be rich in longifolene were converted to the hydrochloride by treatment with anhydrous hydrogen-chloride.

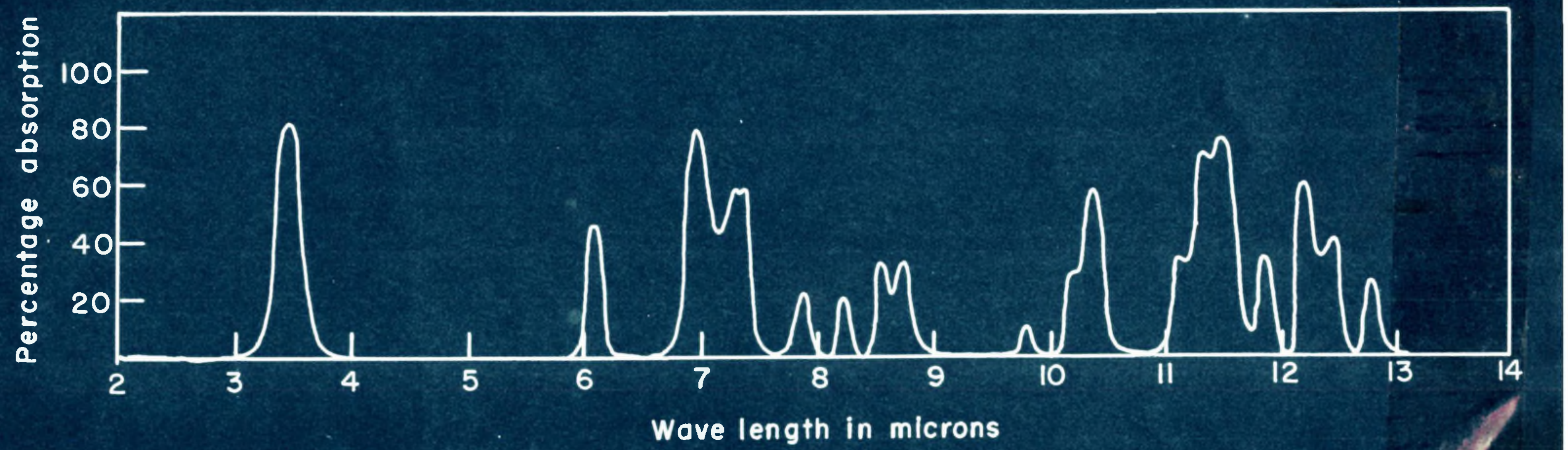
Detection and isolation of a new hydrocarbon: β-longifolene:

During hydrochlorination it was noted that even after repeated hydrochlorination, about 20% of the hydrochlorinated product remained in the liquid state and did not crystallise even on intensive cooling at pretty low temperature. When pure longifolene, prepared by dehydrohalogenation of the pure crystalline hydrochloride, according to Naffa and Ourisson (loc.cit.) was again subjected to hydrochlorination, almost a quantitative yield of the hydrochloride was obtained. It was therefore concluded that the longifolene fraction contains another hydrocarbon which does not give a crystalline hydrochloride. This conclusion was further supported by a second series of observations. When pure longifolene regenerated from the hydrochloride was subjected to ozonisation, it formed an ozonide which was soluble in carbontetrachloride. However, if under identical conditions, an equal amount of natural longifolene, isolated by fractionation of the oil was subjected to similar treatment, it formed an ozonide which was not completely soluble in carbon tetrachloride. This was an indication that natural longifolene contains small amount of another hydrocarbon more unsaturated than longifolene, the ozonide of which is less soluble in carbon tetrachloride than that of longifolene itself. Seventy grams (70 g.) of this hydrocarbon have now been actually isolated by us from the tail fractions of the longifolene distillates. We want to name this hydrocarbon as 'β-longifolene'. It has the following properties:

b.p.126/9 mm.
n_D^{25} 1.5025
α_D + 28.9°;
d_4^{30} 0.9153.

Structure of β-longifolene

Infra-red spectrum of β-longifolene (Curve II) is different from that of longifolene (regenerated from the hydrochloride) (Curve I). It contains two double bonds as determined from comparative quantitative oxidation with perbenzoic acid. On ozonisation copious amount of formaldehyde indicated the presence of a $=CH_2$ group in β-longifolene, and in this respect, it was similar to longifolene itself, the

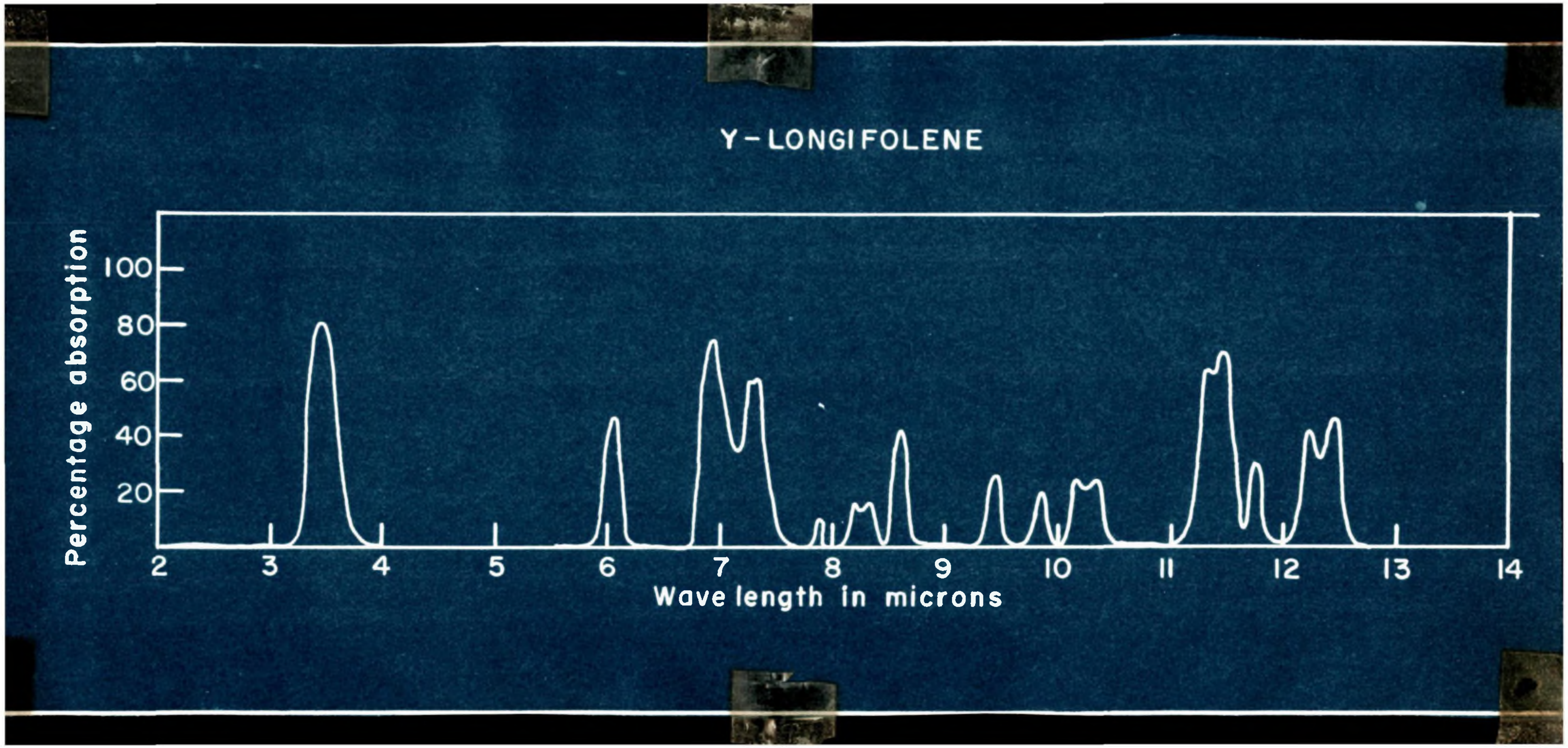


β—LONGIFOLENE

only double bond of which was in the form of $=CH_2$ group. The non-volatile portion of the ozonide of β-longifolene was aldehydic in nature, as it reduced Fehling's solution and ammonical silver nitrate solution very easily. The other double bond present in its molecule therefore should be of the type $-CH=\overset{|}{C}-$. Infra-red spectrum of β-longifolene (Curve II, p127) supports this contention. Apart from its absorption in 11.3 - 11.4 μ region which is characteristic for $=CH_2$ group it also shows absorption in 10.36 μ region which is suggestive of a $-CH=CH-$grouping. The U.V. spectrum of β-longifolene does not show any strong absorption indicating that two double bonds are not in conjugation. On dehydrogenation with sulphur or selenium β-longifolene gives a product which does not form any picrate or T.N.B. derivative. β-longifolene, therefore, does not contain a ring-system of cadalene or eudalene type. The systematic degradation of β-longifolene is being actively pursued. Since β-longifolene contains two double bonds with a molecular formula $C_{15}H_{24}$, according to isprene theory it must be bicyclic in structure. At present we are not in a position to suggest more about its structural relationship to longifolene itself.

γ-longifolene:

β-longifolene which is dextrorotatory, on hydrochlorination, forms a liquid dihydrochloride which on dehydro-halogenation with alkaline ethylene glycol produced a hydrocarbon having the following properties:


Y-LONGIFOLENE
Percentage absorption
100
80
60
40
20
2
3
4
5
6
7
8
9
10
11
12
13
14
Wave length in microns

b.p.116-18/9 mm.
$n_D^{25.5}$ 1.5020
α_D-2.44°.

We wish to name it as ' γ-longifolene'. γ-Longifolene also contains $=CH_2$ group, as it gives formaldehyde on ozonolysis. The non-volatile product gives strong positive test for aldehyde and negative test for methyl ketone. It is therefore very much similar to the parent hydrocarbon β-longifolene, though differing from it in certain points, specially its low boiling point. A large amount of this hydrocarbon has now been isolated by another method. In connection with the preparation of pure longifolene, we subjected a large amount of natural longifolene to hydrochlorination. The residual viscous liquid which was a mixture of longifolene hydrochloride and β-longifolene hydrochloride was converted to the hydrocarbon state by dehydrohalogenation with alkaline ethylene glycol. The hydrocarbon mixture thus obtained was then subjected to intensive fractionation when substantial quantity (about 300 g.) of γ-longifolene having properties comparable with γ-longifolene prepared directly from β-longifolene was obtained:

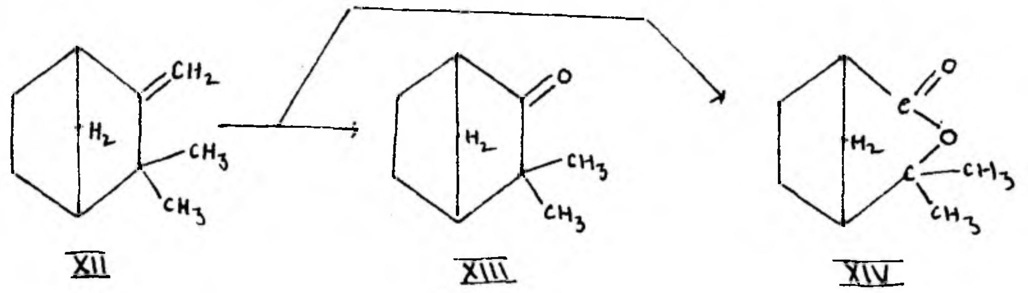
b.p.116-17/9 mm;
$n_D^{25.5}$ 1.5007;
α_D-3.68°.

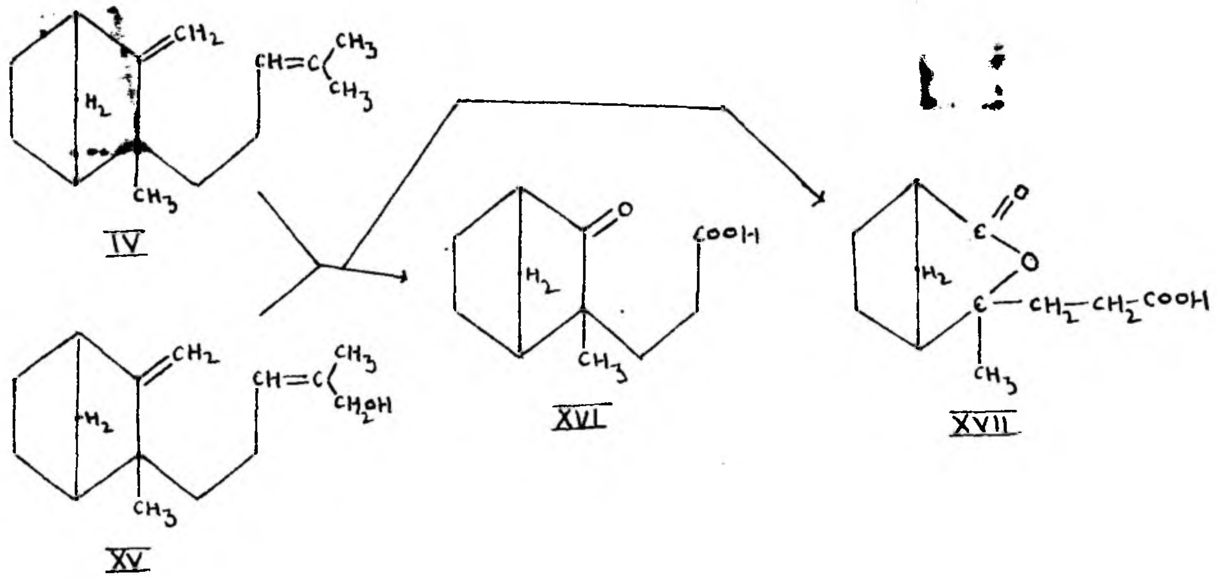
Ozonisation has indicated that like longifolene and β-longifolene, γ-longifolene also contains $=CH_2$ groups as it forms plenty of formaldehyde. It is possible, therefore, that γ-longifolene is formed from β-longifolene through some rearrangement of the $-CH=CH$-double bond present in the latter.

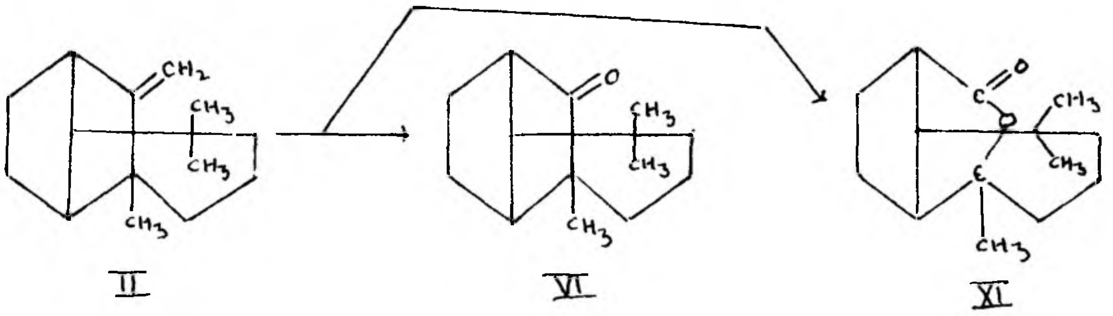
New information on the structure of longifolene:

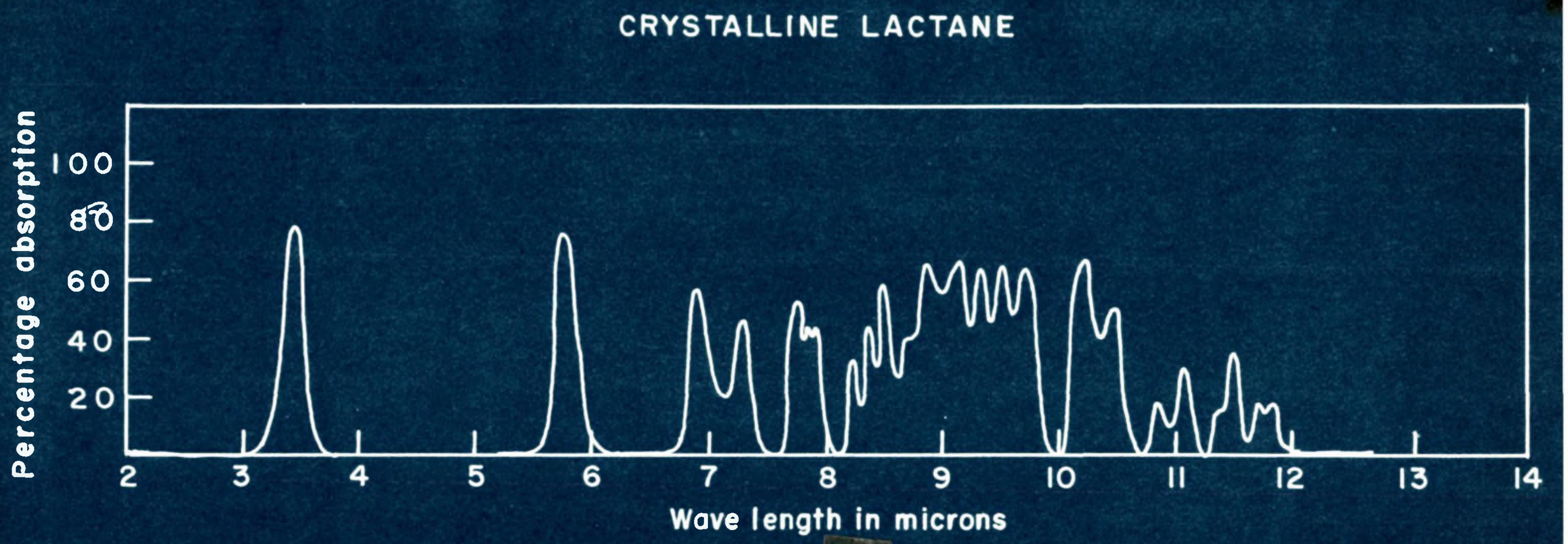
In our investigation on the structure of longifolene itself, we concentrated most of our efforts on getting an azulene derivative out of it. As a prelude to this, we subjected the C_{14} ketone (VI) to various chemical operations; (i) treatment with persulphuric acid, (ii) Grignard's reaction with magnesium methyliodide, (iii) intensive ozonolysis, (iv) peracetic acid (acetic acid, hydrogenperoxide), (v) alkaline hydrogenperoxide and (vi) alkali fusion etc. But in all the cases we met with failure. Our idea was to convert C_{14}-ketone (VI) through oxidative clevage to a lactone (XI) and then subject the same to dehydrogenation with a view to obtain the azulene (X). In these experiments we were guided by the information known from ozonisation of β-santalene (IV) and camphene (XII).

It has been found that when camphene (XII) is subjected to ozonisation it forms the ketone, camphenelone (XIII) and the lactone, campholoide (XIV). Similarly when β-santalene (IV) and β-santalol (XV) are subjected to ozonisation one of the main products is the lactonic acid (XVII) formed presumably through the intermediate ketone (XVI). Having failed in our attack to open the C_{14}-ketone (VI) through the reactions indicated above, we subjected a large amount of longifolene prepared by regeneration from the hydrochloride to intensive ozonisation. The ozonide was decomposed in the usual way. All the acidic products formed during ozonisation (mainly longifolic acid) were removed by exhaustive extraction with alkali. The non-acidic portion was then fractionated carefully through an efficient packed column. Initially small amount of unreacted longifolene distilled out, followed by a fraction which was composed entirely of the C_{14}-ketone (VI)



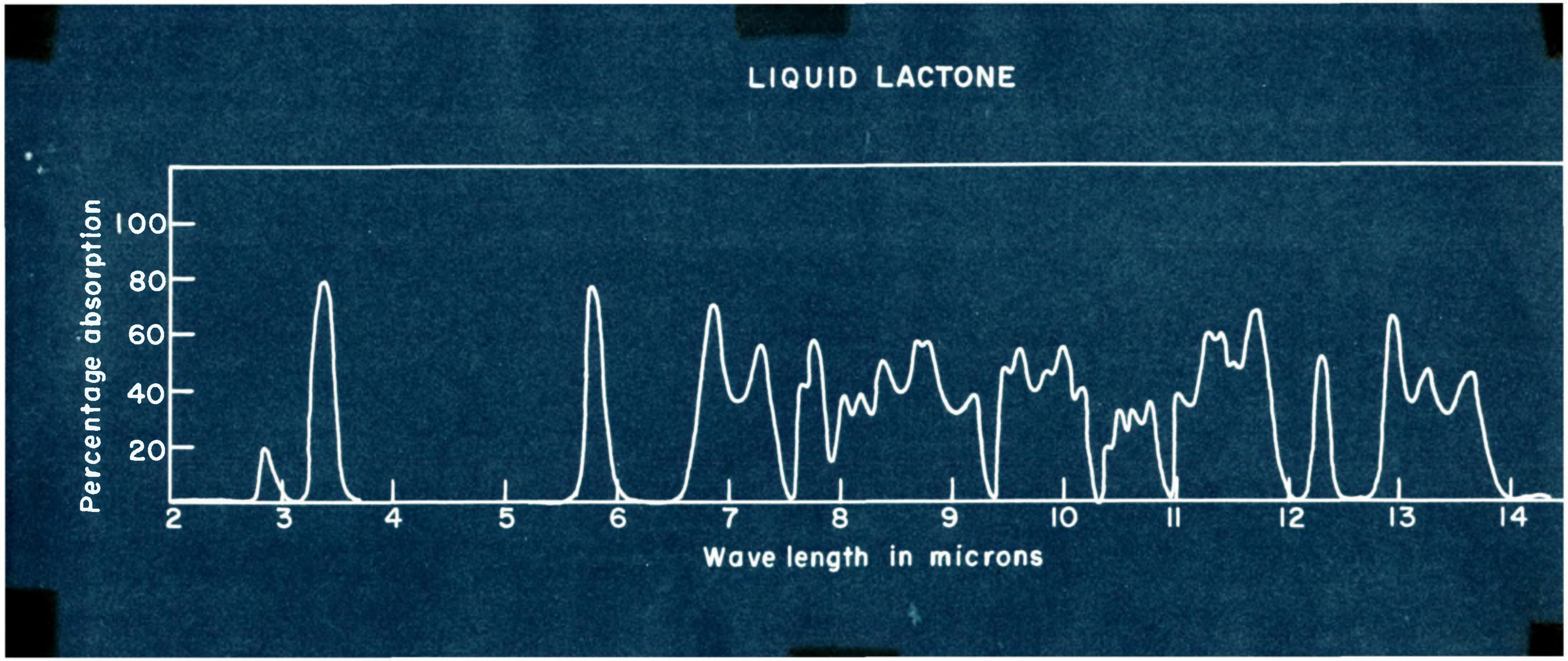





CRYSTALLINE LACTANE
Percentage absorption
100
80
60
40
20
2
3
4
5
6
7
8
9
10
11
12
13
14
Wave length in microns

Isolation of new lactones

The residue in the flask (about 15 g. from 100 g. of longifolene) of the above experiment was then saponified by refluxing for 48 hours with alcoholic potash. After removal of solvent, followed by addition of water, the alkali soluble portion (A) and the alkali-insoluble portion (B) were separated in the usual way. The alkali-soluble portion (A) on acidification furnished a small amount of a solid (0.4 g. from 100 g. longifolene) which on crystallisation showed a sharp m.p.135.5°. Its analysis indicated the molecular formula $C_{14}H_{22}O_2$. It was a neutral compound. From its mode of isolation it was clear that it was a lactone. This was confirmed by infra-red spectrum of the compound (Curve IV. p.133) when a very strong absorption at 5.76 μ region characteristic of lactone, was observed (Curve IV, p.133). The lactone ring in this compound must be highly hindered as it was found to be very difficult to rupture the lactone ring with treatment with alkali. The alkali-insoluble portion (B) was also lactonic in nature. It was a liquid and was further purified by careful fractionation through a packed micro-fractionating column. The main fraction (3-4 g. from 100 g. of longifolene) analysed correctly for $C_{14}H_{22}O_2$. Like the solid lactone it also showed strong absorption in the 5.76 μ region (Curve V, p 135) characteristic of lactone group. On repetition of our experiments, we sometimes failed to isolate the solid lactone but the liquid lactone could be obtained in every experiment. In conformity with the structure of lactones (XIV) and (XVII) obtained from camphene (XII) and β-santalene (IV), these two lactones should



LIQUID LACTONE

be basically represented by (XI). These may be sterioisomers, but, as yet, we have not paid any serious attention to their structural relationship. We wish to name the solid lactone as nor-longilactone and the liquid one as nor-isolongilactone.

Failure to get azulene

In the next stage of our experiments, we subjected both the lactones before and after reduction with lithium-aluminiumhydride, to dehydrogenation with sulphur and selenium but from the dehydrogenation product we failed to get any azulene. In view of the structure (II) assigned to longifolene, a lactone of this type which is, presumably, formed by opening one of the five membered rings, should give an azulene. The failure to get the same is difficult to explain. But, in view of the extremely strong crystallographic evidence of the hydrochloride and hydrobromide and vis-a-vis that of longifolene, we do not want to make any further comments on these results. However, it was felt necessary to record these for future reference.

Information on the regeneration of longifolene

We also made certain interesting observations on the regeneration of longifolene from the hydrochloride. It was found that treatment of longifolene hydrochloride with boiling, alkaline-ethyleneglycol did not always regenerate the hydrocarbon with similar optical rotation. In fact the rotation might vary from $+38.7^{\circ}$ to $+7.2^{\circ}$. In all our experiments we regenerated the hydrocarbon from the hydrochloride and ~~the~~ subjected it to intensive fractionation and used only those fractions having an optical rotation of +35° to +38°.

<u>Longifdione and longiforic acid</u>

We have also collected some interesting informations on longifdione. Simonsen usually obtained about 2 g. of this diketone by oxidising 100 g. of longifolene. We, however, found that by carrying out the oxidiation with mechanical stirring and then isolating the final product, longifdione, by fractionating through a small column, it was possible to get nearly 8 g. of this diketone from 100 g. of longifolene. It was also observed that the oxidation of this ketone to longiforic acid could be carried out with better advantage with alkaline hydrogen peroxide. The reaction was almost instantaneous and yield quantitative. This mode of oxidation was definitely of more advantageous than the original oxidation with nitric acid suggested by Simonsen.

E X P E R I M E N T A L.

Isolation of longifolene:

Experimental details about the isolation of longifolene as carried out by us are so extensive that for the sake of brevity we are giving only a very brief outline of the same. The longifolene fraction (15.5 kg.) was initially distilled through a tall (7 ft.) packed column. The lower boiling fraction was rejected. The main fraction boiling at 120-270/ 15 mm. (14 kg.) was then intensively fractionated and divided into about 100 fractions. Course of fractionation, as previously indicated, was followed by noticing optical rotation, refractive index and boiling point, more emphasis being put on the former two properties. Those fractions having $\alpha_D + 35.5^\circ$ to $+ 36.3^\circ$ and $n_D^{27.2}$ 1.5008 - 1.5014 were combined together and fractionated repeatedly. Finally a fraction composed predominantly of 'longifolene' was obtained having following properties:

b.p. 115-16/9 mm.
$n_D^{27.5}$ 1.5013;
$\alpha_D + 36.31^\circ$.

It was finally distilled over sodium when the properties remained more or less same.

Pure longifolene:

Longifolene fraction was converted to the hydrochloride following mainly the procedure of Simonson(loc.cit.) with some modifications necessary for the isolation of γ-longifolene. Longifolene fraction (300 g.) in ether (450 ml.) was saturated with anhydrous hydrogen chloride. After leaving it at room temperature for 48 hours the solvent was removed and the residual material mixed with methyl alcohol (50 ml.) and then cooled to -15° for 2 hours. The precipitated hydrochloride was filtered through a large sintered funnel and pressed thoroughly and washed three times with cooled methanol. The viscous mother liquor was kept aside for isolation of γ-longifolene. In this way about 10 kg. of longifolene fraction was subjected to hydrochlorination. The solid hydrochloride on two crystallisations from petrol-ether furnished pure specimen of the same m.p.60 - 60.5°.

For regeneration of longifolene, the crystalline hydrochloride was refluxed under vigorous stirring with four times its weight of ethylene-glycol containing about 10% caustic potash. The regenerated hydrocarbon was collected initially by vacuum distillation and purified by repeated fractionation through an efficient column and finally refluxed and distilled over sodium.

b.p. 113/9 mm.
n_D^{25} 1.5002;
$\alpha_D +37.8^{\circ}$;
d_4^{30} 0.9328.

Isolation of β-longifolene:

The tail fractions obtained during the preliminary fractionation of longifolene fraction of the oil which showed boiling point about 116/9 mm; n_D^{25} 1.5014; $\alpha_D +30^{\circ}.0$ were combined together and fractionated and divided into many fractions; those having similarity were refractionated and the operations repeated many more times until substantially homogeneous β-longifolene was obtained. It was finally distilled over sodium.

b.p. 126-29/9 mm;
n_D^{25} 1.5025;
α_D +28.9°;
d_4^{30} 0.9153.

Found: C, 87.93; H, 11.71;
$C_{15}H_{24}$ requires : C, 88.39; H, 11.61%

Unsaturation value: 2.0 - 2.2 (perbenzoic acid in chloroform, 24-48 hours);

No. u.v. absorption;

I.R. spectra curve (II, p.127) strong absorption at 11.30 μ (=CH_2); 10.35 μ (-CH=CH-) etc.

Dehydrogenation in conventional way failed to give any picrate forming product.

Ozonisation

It was carried out in carbon tetrachloride solution using standard ozone generator (Tower's). The ozonide was insoluble in carbon tetrachloride and in this respect differed from longifolene, ozonide of which was soluble. After working up the ozonide in usual way the volatile portion was found to be composed entirely of formaldehyde, characterised as its dimedone derivative, m.p. and mixed m.p.190°. Non-volatile portion easily reduced Fehling's solution, ammonical silver nitrate solution and failed to give test for methyl ketone.

Isomerisation of β-longifolene to γ-longifolene

β-longifolene (10 g.) was hydrochlorinated in ether (25 ml.) under ice cooling. After leaving at room temperature for 48 hours, the liquid hydrochloride obtained after removal of ether was decomposed with alkaline ethylene-glycol as in the case of longifolene hydrochloride. The regenerated hydrocarbon was collected by distillation and purified by fractionating over sodium using a 12" micro-column fitted with adequate head.

b.p. 116-17/9 mm.,
$n_D^{25.5}$ 1.5020;
α_D -2.44°
d_4^{30} 0.9337.

Unsaturation value 1.98-2.0 (perbenzoic acid, 24 hours);

No. U.V. Absorption:

I.R. spectra Curve (III, p.129) is similar to β-longifolene with one difference that the (10.35 μ) band has nearly disappeared.

γ-longifolene (from the hydrochlorination ~~of~~ mother liquor of longifolene).

The viscous mother liquor mentioned earlier which was obtained after preliminary separation of longifolene-hydrochloride was a mixture of longifolene hydrochloride and β-longifolene hydrochloride. It was decomposed with alkaline ethylene-glycol as usual. Generated hydrocarbon which was a mixture of longifolene and γ-longifolene was separated by intensive fractionation and refractionation into its constituents. Nearly fifty fractions were collected and examined during this isolation. Finally γ-longifolene obtained was collected by distilling over sodium.

b.p.116-17/9 mm.
n_D^{25} 1.5007;
α_D-3.68°;
d_4^{30} 0.9247;

unsaturation value 1.9-1.98(24 hours).

No U.V. absorption

Found: C, 87.95; H, 11.42%.
$C_{15}H_{24}$ requires: C, 88.39; H, 11.61%.

It was almost identical with γ-longifolene obtained directly from β-longifolene. However, it may possibly contain small amount of longifolene as impurity.

Ozonisation of γ-longifolene

Ozonisation of γ-longifolene was carried out in carbon tetrachloride in the usual way. The volatile component was identified as formaldehyde and the non-volatile product contained aldehyde group and no methyl ketone.

Oxidation of +longifolene with chromic acid

Only regenerated pure longifolene was used for this reaction which was carried out according to the original procedure of Simonsen with the modification that mechanical stirring was employed during the course of reaction. During isolation of the diketone a fractionating column was used. The modified procedure improved the yield of the diketone considerably. The longifolene (100 g.) gave along with longifolic acid(V) and the C_{14}-ketone (VI) about (8 g.) of yellow diketone which could be crystallised from petrol-ether, m.p.94-94.5°, (60-80°), m.p.135-135.5°. It was a neutral material and was evidently a lactone.

Found: C, 75.46; H, 9.82;

$C_{14}H_{22}O_2$ requires:C,75.63; H, 9.97%.

I.R.Absorption: Strong specific absorption at 5.76 μ characteristic of a lactone.

However, the lactonic ring once formed was pretty stable and could not be opened easily through hydrolysis.

Alkali insoluble portion after working up in usual way was carefully fractionated through a packed micro-fractionating column (12", packed with Tower's glass helices) and separated into about 12 fractions 1 cc. each. The fractions were individually examined through a I.R. spectroscope and those showing predominately lactonic characteristic were combined and refractionated when pure lactone (3 g.) was obtained b.p.140-45/ 8 mm.; n_D^{27}1.5118.

Found: C, 75.3; H, 9.89;

$C_{14}H_{22}O_2$ requires:C, 75.63; H, 9.97%.

It showed very strong I.R. absorption at 5.76 μ characteristic of lactone group. In certain experiments, we failed to isolate the solid lactone, but the liquid lactone could be isolated from every experiment.

Dehydrogenation:

Both the lactones solid and liquid were, as such, or after reduction with lithium aluminium hydride, dehydrogenated with selenium in the usual way but no azulenic derivative could be obtained.

R_E_F_E_R_E_N_C_E_S.

1. Simonsen, J.Chem.Soc., 1923, 123, 2642; 1934, 138.

2. Moffett and Rogers, Chem. & Ind., 1953, 916.

3. Naffa and Ourisson, Chem. & Ind., 1953, 917.

4. Ourisson, Chem. & Ind., 1953, 918.

5. Zeiss and Arakawa, J.Am.Chem.Soc., 1954, 76, 1653.

6. Nayak and Sukh Dev, Chem. & Ind., 1954, 899.

7. Naffa and Ourisson, Bull.Soc.Chim., 1954, 1115, 141

8. Ourisson and Ourisson, Bull.Soc.Chim., 1954, 1415.

9. Ourisson, Bull.Soc.Chim., 1955, 895.

10. Guenther, The Essential Oils, Vol.II, p.115 (1949).

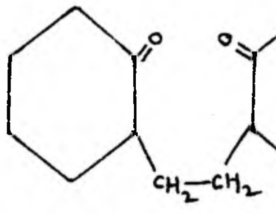
PART VIII

CERTAIN CYCLOHEXANONE DERIVATIVES.

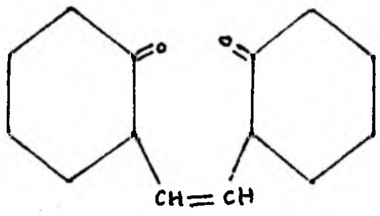
***

Summary

With an ultimate object of preparing 2,2'-diketo-1,2-dicyclohexylethane (I) which should be an useful intermediate in synthetic approaches towards sesqui and poly-terpenes, the ~~and~~ decomposition of Mannich base obtained from cyclohexanone and diethyl amine hydrochloride has been studied. This compound $C_{14}H_{20}O_2$ does not possess the expected diketonic structure of the type (II)

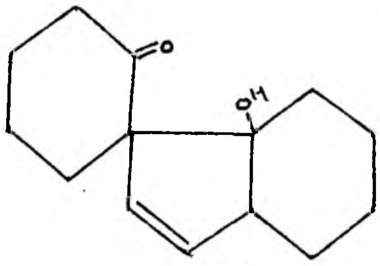


I



II

It is actually a keto alcohol containing one carbonyl and one alcoholic group. Many of the reactions of this compound can be explained on the basis of the following spiro structure(III).

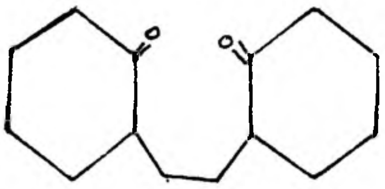


III

Its various derivatives have also been studied critically.

General introduction

In connection with our work on synthetic approaches towards sesquiterpenes and polyterpenes, it was felt that a compound of the type (I) might prove to be useful as a starting material for such an approach. A compound of the type (I) possessing two keto groups could be made to undergo a varieties of reactions to produce miscellenious phenanthrenoid derivatives. The diketone(I) has been previously prepared by Bhattacharyya[1] by two different routes and has been used by him for the synthesis of the hydrophenanthrenoid compound (II). Such a system forms part of the triterpene nucleus like β-amyrin, oleanolic acid (III) etc.



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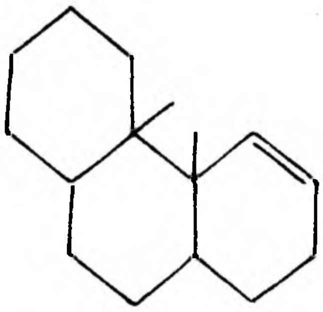
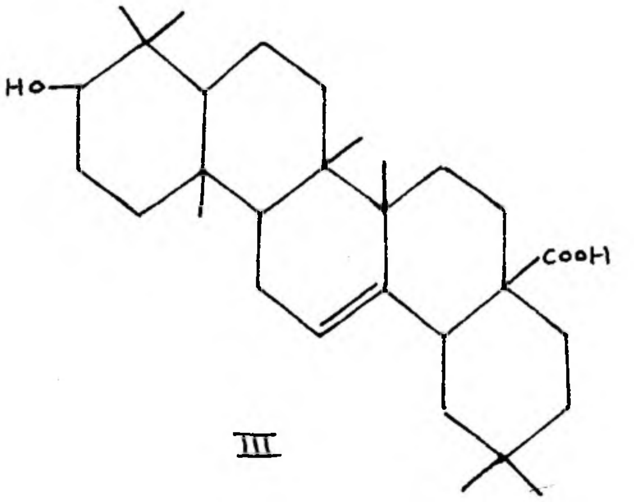


II



III

The routes developed by Bhattacharyya (loc.cit.), though quite unambiguous, were not very short, and could be used for preparative purposes only with some difficulty. The routes involved nearly seven stages. It was, therefore, considered desirable to develop a shorter and more easily approachable route for the preparation of the diketone(I).

As early

As early as 1927, in connection with other work, Mannich and Honig[2] have incidentaly mentioned that when the methoiodide of the Mannich base (IV) from cyclohexanone is heated, it gives a product having a molecular formula $C_{14}H_{20}O_2$ (V). From logical analogy, without experimental evidence, Mannich and Honig had initially imagined this compound to be a diketone, formed presumably by a dimerisation of the Mannich base (IV) with simultaneous elimination of dialkylamine.

After we had somewhat finalised our work on this dimeric compound, we noticed that in a later publication (1941) which we had previously missed due to oversight, Mannich[3] had studied the reactions of this dimeric compound in some details and assigned to it the structure (VI). For the sake of brevity we are giving only the more important points of his findings:

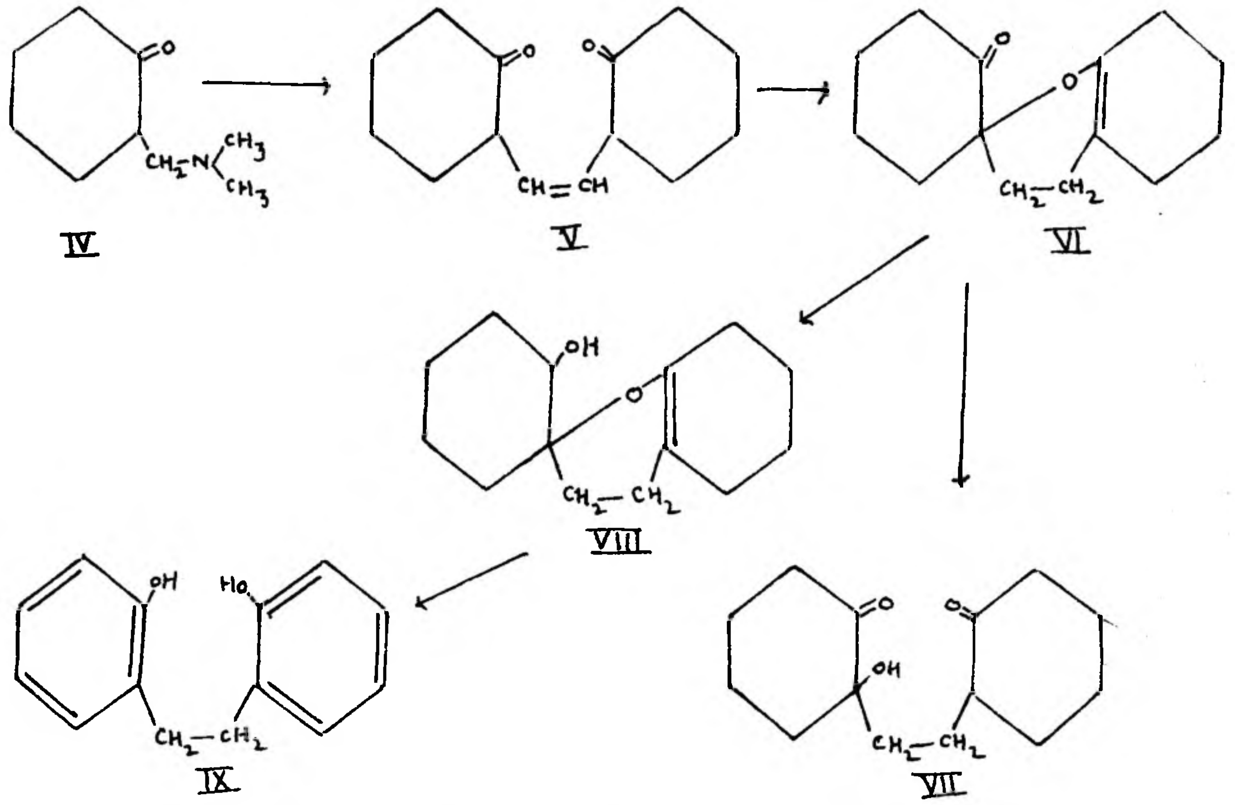
(i) The material analysed correctly for $C_{14}H_{20}O_2$

(ii) It formed only monocarbonyl derivatives, semicarbazo ($C_{15}H_{23}N_3O_2$), m.p.206°; oxime ($C_{14}H_{21}NO_2$), m.p.123°.

(iii) It did not react with methylmagnesiumiodide and therefore the second oxygen function was not in the form of hydroxyl group but in the form of an ether linkage.

(iv) On treatment with mineral acid it gave a solid product $C_{14}H_{22}O_3$, m.p. 154-155° to which he assigned the structure (VII). This solid gave bis-carbonyl derivatives.

(v) Dehydrogenation of (VI) gave o-o'-dihydroxy-1:2-diphenylethane (IX).



Most of the reactions described by Mannich and as recorded above, are easily explainable by the structure (VI) suggested by him.

We hewever, during our investigation collected certain other evidences, some of which are difficult to explain on the basis of the above structure (VI). Our findings and deductions are as follows:

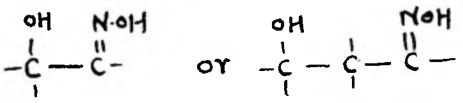
(i) Analytical results suggested the formula $C_{14}H_{20}O_2$.

(ii) A colour reaction with tetranitromethane indicated the presence of double bond.

(iii) On~~e~~ catalytic hydrogenation, hydrogen equivalent to one double bond was absorbed.

(iv) A quantitative reaction with lithiumaluminiumhydride indicated the presence of hydroxyl group. This was further supported by strong infrared absorption shown at 3.18 μ region (Curve I , p.154). These findings about the hydroxyl group were contradictory to the findings of Mannich. Strong absorption at 10.32 μ region also suggested the presence of -CH=CH-linkage which is not explainable from the structure (VI) as shown by Mannich.

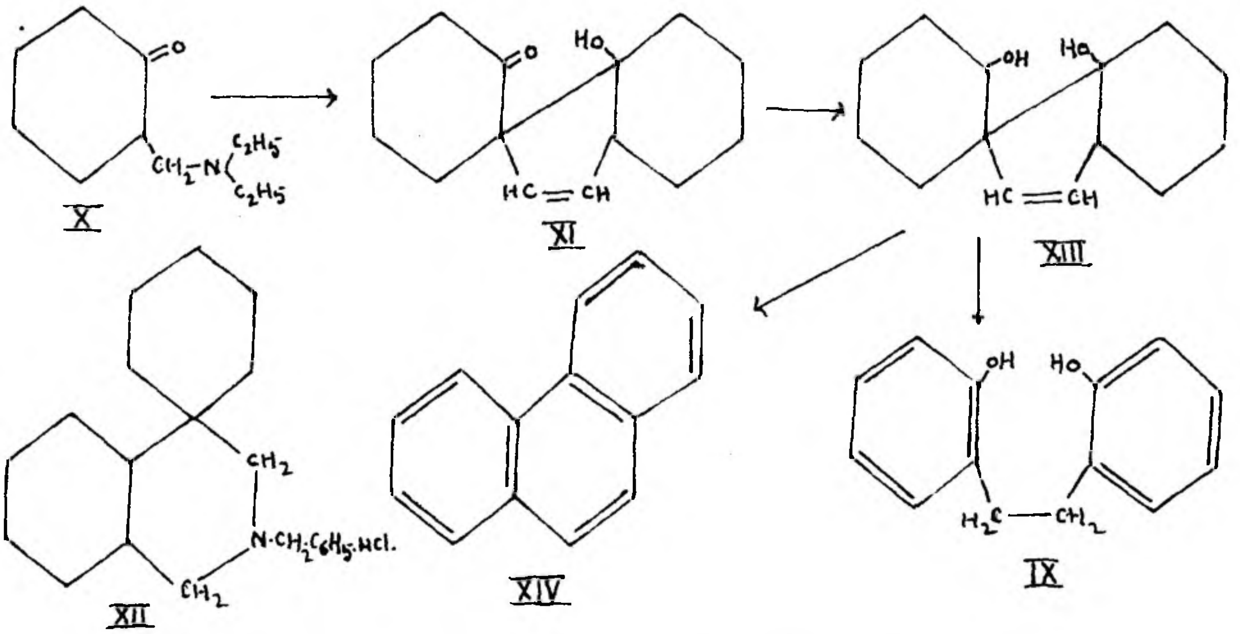
(v) It forms only monosemicarbazone ($C_{15}H_{23}N_3O_2$), m.p.206° and monoxime ($C_{14}H_{21}N\ \ O_2$), m.p.123°. Interestingly enough, it was observed that this monoxime gave a characteristic green chelate with copper salt. This reaction is considered to be specific for acyloinoximes having the general formulae



$-\underset{|}{\overset{\overset{OH}{|}}{C}}-\overset{\overset{N\cdot OH}{\|}}{C}-$ or $-\overset{\overset{OH}{|}}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{\overset{NOH}{\|}}{C}-$ in which the hydroxyl and the oxime groups are in 1:2 or 1:3 positions[4,5].

(vi) On ozonolysis no volatile components like formaldehyde or acetone were obtained. The non-volatile portion, however, gave strong test for aldehyde (Fehling's solution, ammonical silvernitrate solution etc.). This reaction is more suggestive of the presence of -CH=CH-grouping. Formation of aldehyde is not easily explainable on the basis of structure (VI).

The evidences collected by us and as recorded above are suggestive of a structure (XI). This is more in conformity with the structure (XII) suggested for a somewhat similar compound obtained from the Mannich base of cyclohexanone and dibenzylamine[6].



In our studies we also reduced the ketone (XI) with lithiumaluminiumhydride and obtained the diol (XIII). It absorbed one mole of perbenzoic acid indicating the presence of one double bond in the molecule and consequently in the parent compound. This diol on dehydrogenation with selenium gave the same diphenolic compound (IX) originally obtained by Mannich from (VIII); simultaneously a byproduct showing green fluorescence in ultra violet light similar to that of phenanthrene (XIV) was also detected. The formation of this dehydrogenation product (IX) is more easily explainable from the structure (VI).

While decomposing the semicarbazone of (XI), m.p. 206°, we obtained a solid $C_{14}H_{22}O_3$, m.p.148° which normally could be presumed to be identical with the solid ($C_{14}H_{22}O_3$, m.p. 154-155°) obtained by Mannich by treating the ketone (VI) with mineral acids, Whereas the product isolated by him formed bisoxime and bisphenylhydrazone derivatives, our product formed a semicarbazone whose analytical values, though not exact, were nearer to that of a monosemicarbazone than that of disemicarbazone. Even then, this material may be structurally identical with the compound (VII) isolated by Mannich, the difference in melting point may be attributed possibly due to different proposition of the stereoisomers (due to the newly created hydroxyl group).

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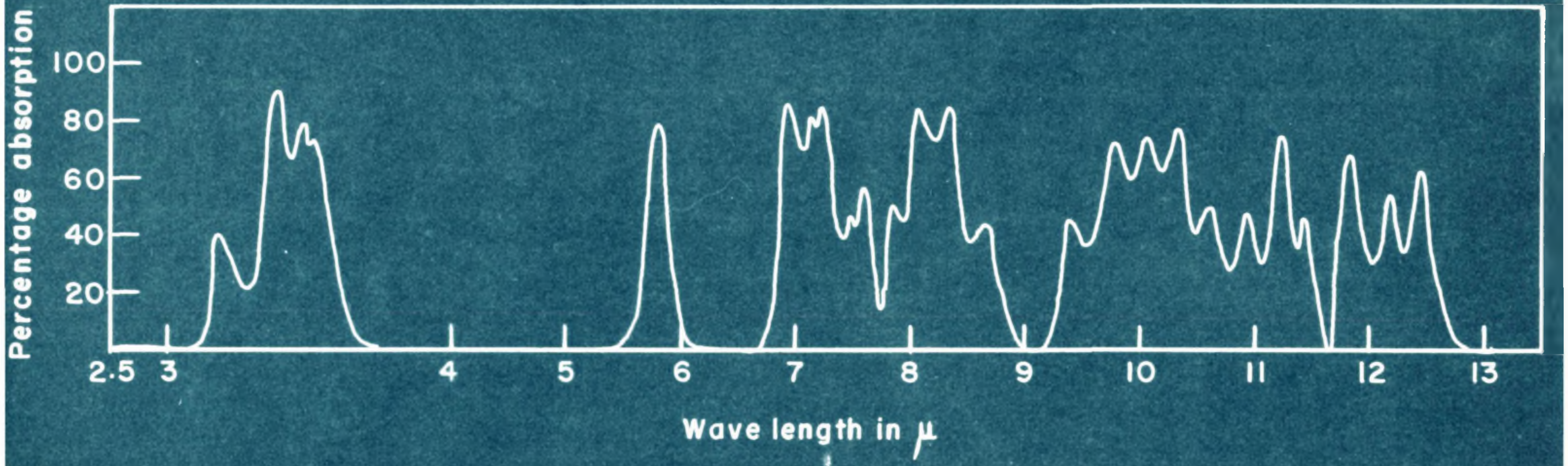
MANNICH BASE DIMER ($C_{14}H_{20}O_2$)



EXPERIMENTAL.

Preparation of the Mannich base - diethylamino-methyl-cyclohexanone (X):

A mixture of diethylaminehydrochloride (38 g.) formalin (28 g.) and cyclohexanone (160 g.) was taken in a flask fitted with reflux condenser and heated in a boiling water bath for about an hour with occasional shaking. The mixture became homogeneous, It was cooled under the tap, then diluted with water (300 ml.) and the insoluble oily portion extracted with ether. The aqueous solution which contained the Mannich base was then made alkaline with caustic soda solution and again thoroughly extracted with ether. The ethereal solution washed with water, dried (sodium sulphate); the Mannich base was obtained after distilling off the ether and finally removing the solvent with the help of a water pump. It was a yellowish coloured material, yield 57 g.

Decomposition of the Mannich base, preparation of (XI)

The above Mannich base (600 g.) was taken in a distillation flask fitted with a condenser etc. and heated in an oil bath. The temperature of the bath was slowly raised to 130° and kept at that temperature for about an hour, during which time the Mannich base decomposed giving almost a quantitative yield of diethylamine (225 g.) as a distillate. For a short time the temperature of the bath was raised upto 150°. The ketonic residue left in the flask (375 g.) was once totally distilled under vacuum and then fractionated through Tower's column, when a first run of about 20 g. of a mixture methylene-cyclohexanone and methylcyclohexenone was obtained. The desired condensation product then distilled out at a steady temperature 130-132°/3.5 mm.; yield of pure product 250 g.; n_D^{27} 1.5080.

positive colour reaction with tetranitromethane.

Analysis: Found: C, 76.23; H, 9.17; active hydrogen 0.34 $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15; active hydrogen 0.45 %.

U.V. absorption was determined in alcoholic solution. There was no strong characteristic absorption.

I.R. absorption: It was determined in the conventional way (Curve I; p.154); strong absorption at 3.18 μ (-OH group), 10.32 μ (-CH=CH-group) and 5.81 μ (keto group).

Ozonisation

The product was ozonised in carbontetrachloride or ethylacetate solution and the ozonide worked up in the usual way. The volatile product did not show any test for formaldehyde or acetone. The non-volatile portion gave usual tests for aldehyde; did not give any colour reaction with ferric chloride and did not respond to iodoform test.

Preparation of the monosemicarbazone

Following the conventional procedure the above ktone (25 g.), semicarbazide-hydrochloride (30 g.), sodiumacetate (45 g.), gave nearly a quantitative yield of monosemicarbazone at room temperature or on mild warming on water bath. It was crystallised two times from large volume of alcohol, yield 33 g.; m.p.206°.

Analysis:Found: C, 65.14; H, 8.14; N, 15.42

$C_{15}H_{23}O_2N_3$ requires : C, 64.99; H, 8.30; N, 15.1%.

Preparation of the monoxime

The ketone (2.2 g.), hydroxylamine hydrochloride (2.2 g.) and sodium acetate (3.5 g.) were dissolved in dilute alcohol and refluxed on a water bath for about an hour. On cooling the oxime separated out. It was crystallised from petroleum ether; m.p. 123-123.5°.

Analysis: Found: C, 71.01; H, 8.6; N, 6.1

$C_{14}H_{21}O_2N$ requires: : C, 71.48; H, 8.9; N, 5.9%.

In aqueous alcoholic solution buffered with ammonium or sodium-acetate, the oxime gave a green precipitate with copper/acetate or copper/sulphate, indicating the presence of 1:2 or 1:3 acyloinoxime grouping.

Decomposition of the semicarbazone and isolation of (VII)

A mixture of semicarbazone (20 g.) and dilute sulphuric acid (200 ml. of 10%) was heated on a boiling water bath for about half an hour when, the decomposition of semicarbazone was complete. The decomposed product was extracted with ether and the ethereal solution was washed, dried (sodium-sulphate) and the ether removed in the usual way. The solid keto-compound, which was left as a residue, was crystallised from petroleum ether, yield 9 g; m.p.148°. It did not give a colour reaction with tetranitromethane, indicating the absence of double bond.

Analysis: Found: C, 70.45; H, 9.14.

$C_{14}H_{22}O_3$ requires : C, 70.55; H, 9.31%.

Semicarbazone of the above solid keto compound

Semicarbazone was prepared in the conventional way and crystallised two times from alcohol, m.p.221°. It however gave somewhat anomalous analytical results.

Analysis: Found: C, 65.13; H, 8.28; N, 15.56
$C_{15}H_{25}O_3N_3$ (mono) requires:C,60.99; H, 8.53; N, 14.25%.
$C_{16}H_{28}O_3$ N_6(di-) requires: C,54.52; H, 8.01; N, 23.85%.

Reduction of liquid ketone (XI) with lithiumaluminiumhydride; isolation of the diol (XIII)

The ketone (5 g.) was reduced in ethereal solution with an excess of lithium aluminiumhydride (1 g.) following the standard procedure. The diol thus produced was isolated by vacuum distillation; b.p.138-140°/0.7 mm.

Analysis: Found: C, 75.80; H, 9.76.
$C_{14}H_{22}O_2$ requires: C, 75.63; H, 9.97%.

Unsaturation value of the diol was determined with perbenzoic acid oxidation; value found 0.97 (22 hours) indicating the presence of one double bond in the diol and consequently also in the parent ketone.

Dehydrogenation of the above diol (XI)

A mixture of above diol (4 g.) and selenium 26 g.) was heated in a metal bath at 290-310° for about 36 hours. The dehydrogenation product was isolated by distillation in vacuum.

From its solubility behaviour towards caustic alkali it appeared predominently phenolic in nature. The phenolic and non-phenolic portions were separated through alkali treatment and other usual operations. The alkali soluble portion was crystallised from benzene-petroleum-ether mixture, m.p.113-114°.

Found: C, 78.17; H, 6.48.
$C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59%.

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REFERENCES.

1. Bhattacharyya, S.C., unpublished paper (communicated to Journal of Indian Chemical Society.).

2. Mannich and Honig, Arch.Pharm., 1927, 265, 598-610.

3. Mannich, Ber., 1941, 74B, 557-564.
Chem.Abs., 1941, 35, 5863.

4. Feigl, Sicher and Singer, Ber., 1925, 58B, 2294.

5. Feigl, Spot-tests (Organic Applications), p.309.

6. Mannich and Hieronimus, Ber., 1942, 75B, 49-64.

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