STUDIES IN SESQUITERPENES

(HIMACHALENES)

A Thesis submitted to the Poona University
for the degree of Doctor of Philosophy.

by

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POONA

1965

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of the investigation carried out by me under the supervision of Dr. Sukh Dev, Ph.D., D.Sc. Chapter II (fractionation) and a part of Chapter III (physico-chemical evidences and dehydrogenation studies) was submitted in the form of a thesis entitled "Studies in Sesquiterpenes" to the Indian Institute of Science, Bangalore, for the award of M.Sc. degree.

In keeping with the general practice in the reporting of scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Due acknowledgement has been made for the results of micro-analyses, etc. reported in this thesis.

Supervisor

Candidate

C O N T E N T S

CHAPTER I

INTRODUCTION

RECENT PROGRESS IN SESQUITERPENE CHEMISTRY

Modern physical methods of isolation and structure determination, coupled with a better understanding of biogenetic and organic chemical mechanistic basis that is available today, have almost revolutionised the study of the chemistry of natural products. One of the important fields in which the impact has been rather astounding is the field of sesquiterpenoids. About a decade and a half ago, the structures of barely a few members were known in complete detail and only ten types of different skeletons had been reported. However today no less than fortyfour basic types* (Chart I) have been recorded and even now new systems are being discovered; the number of compounds for which complete structures (including absolute stereochemistry) have been reported run into well over hundred. Even a cursory survey of all the various types of sesquiterpenes known todate, is not possible in a reasonable space, and consequently this introductory chapter will very briefly cover some of the newer types described recently. The choice has been arbitrary but an attempt has been made to cover twentyfive types (the structures indicated by the * in Chart I) which appear to be interesting from biogenetic standpoint.

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*This survey covers literature available in this Laboratory upto February 1964.

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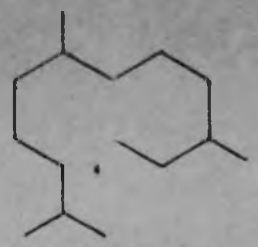
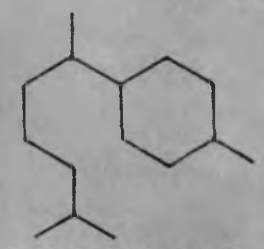


FARNESANE

MONOCYCLIC



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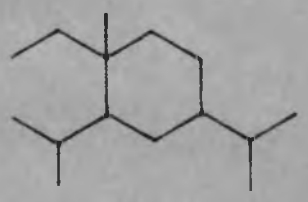

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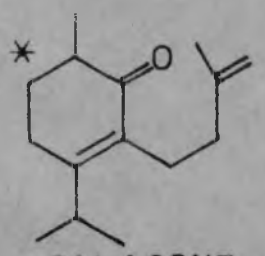

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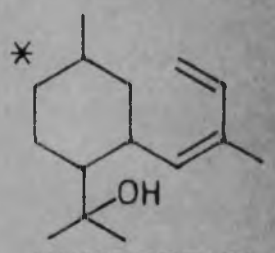

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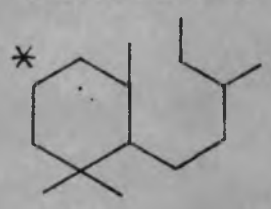

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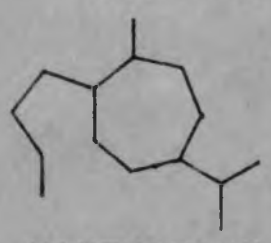

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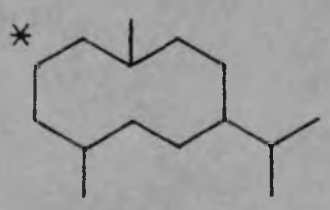

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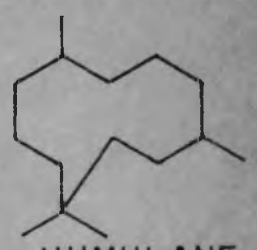

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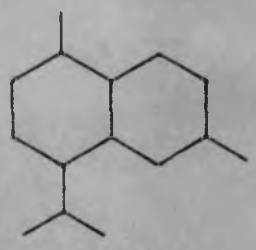

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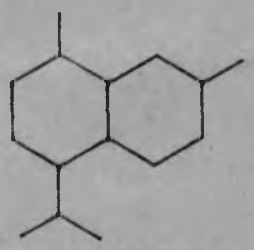

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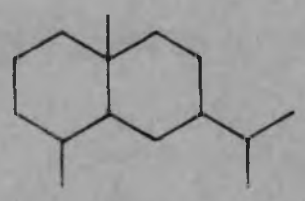

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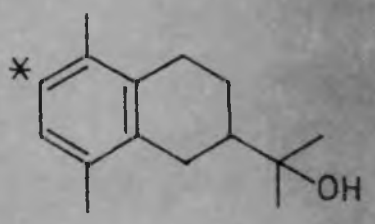

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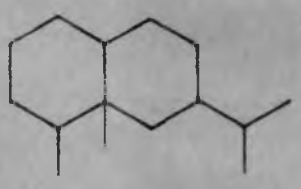

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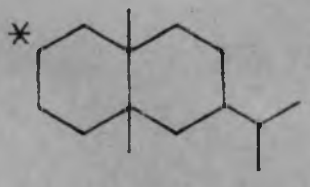
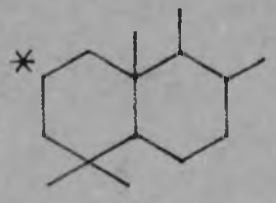


VALERANE



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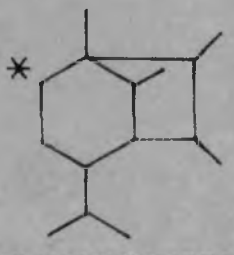

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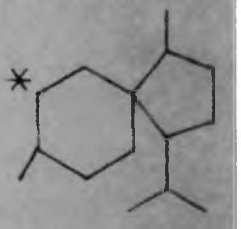
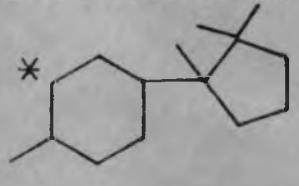


ACORANE



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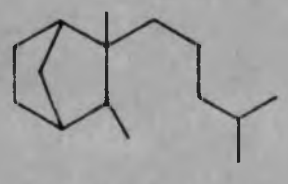
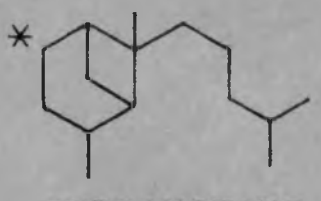


β-SANTALANE



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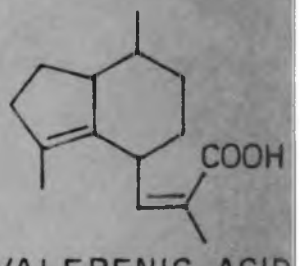
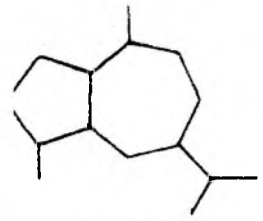


VALERENIC ACID

CHART I. SESQUITERPENE TYPES

(If only one member is known of a type, it is represented as such in this Chart).



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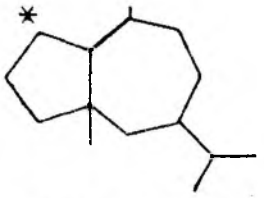

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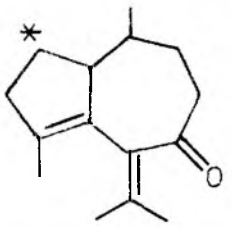

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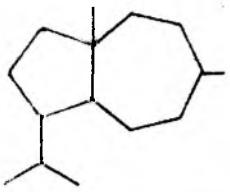
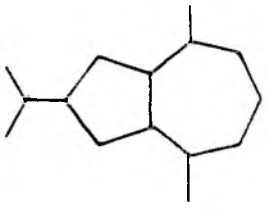


DAUCANE



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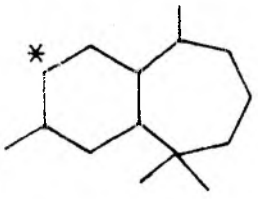
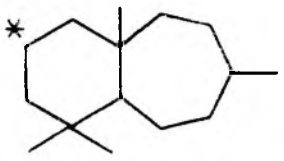
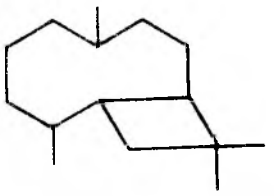


HIMACHALANE

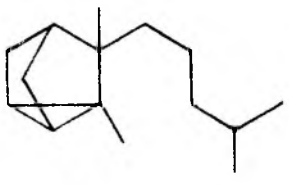


WIDDRANE

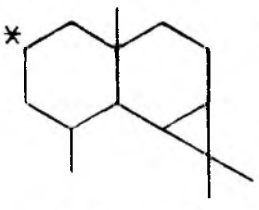


CARYOPHYLLANE

TRICYCLIC



α-SANTALANE



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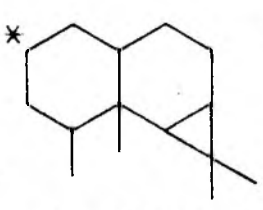

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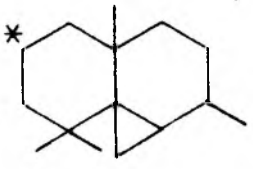

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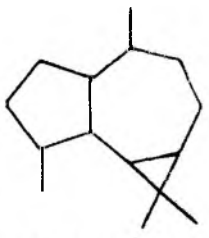

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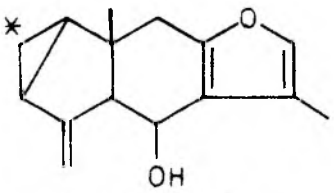
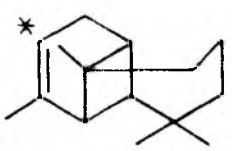
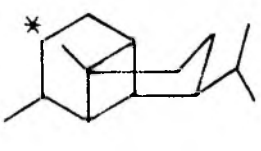


LINDERENE



α-LONGIPINENE



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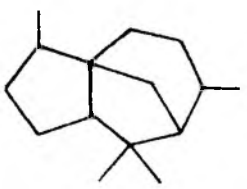

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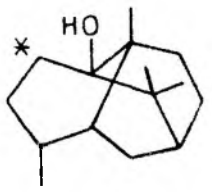
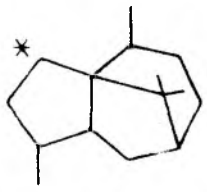


PATCHOULI ALCOHOL



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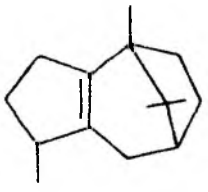

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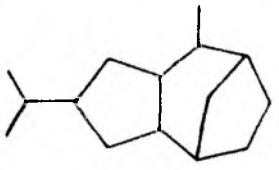

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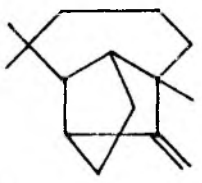
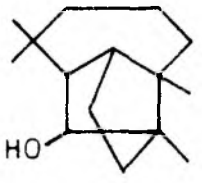


LONGIFOLENE



JUNIPEROL

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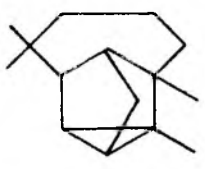


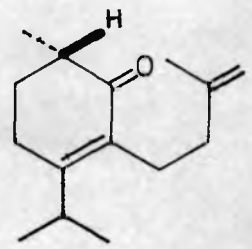
LONGICYCLENE

CHART I. (Continued)

MONOCYCLIC

Calacone:

Calacone (1) is an interesting type recently isolated from sweet flag oil (Acorus calamus L.) by Sorm and co-workers[1]. The basic carbon framework which cannot follow from the coiling of the farnesol chain, was confirmed by synthesis. The biogenesis may be considered



(1)

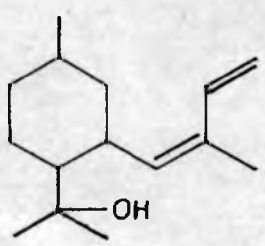
n_D^{20} 1.5170

$[\alpha]_D$ + .9°

as a result of secondary alkylation of a paramethane skeleton with another isoprene unit.

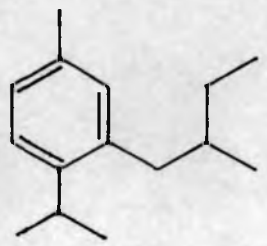
Humbertiol:

Humbertiol[2] (2), isolated from Humbertia madagascariensis, gave cadalene and (3) as dehydrogenation products. Structure (2) is supported by spectral data and degradation results.



(2)

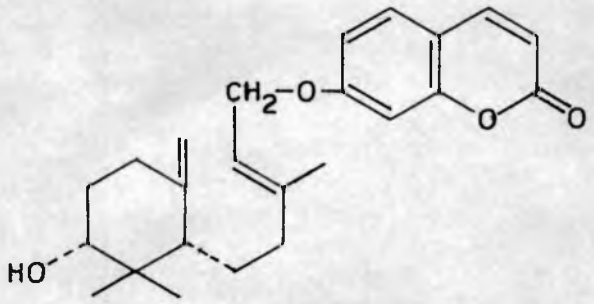
b.p. 80°/.03 mm



(3)

Farnesiferane:

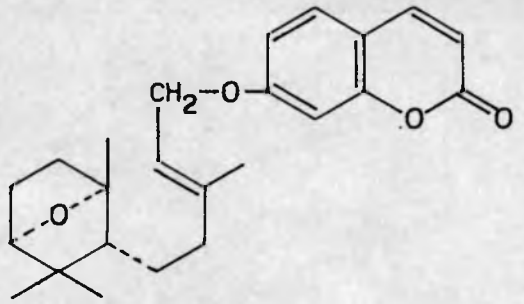
Farnesiferol B (4) and C (5), isolated from Asafoetida, belong to a new type biogenetically closely related to iresane type[3] which are discussed later.



(4)

m.p. 113.5 - 114.5°

$[\alpha]_D$ +10°



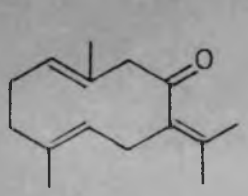
(5)

m.p. 84 - 85°

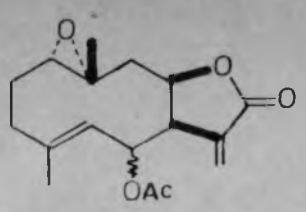
$[\alpha]_D$ -29.6°

Germacrane:

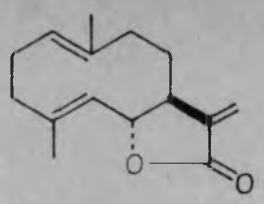
The establishment of nine- and eleven-membered carbocyclic rings in caryophyllene and humulene started an interesting chapter in terpenoids, viz. the occurrence of medium-ring terpenoids in Nature. So when in 1957, Barton and de Mayo[4] presented evidence for the occurrence of a ten-membered cycle in pyrethrosin, a crystalline component of Chrysanthemum cinerariaefolium, the gap had been closed. It was soon found that germacrone, $C_{15}H_{22}O$, isolated from Bulgarian "zdravets" oil (Geranium macrorhizum L.) by Sorm and co-workers[5] in 1957 was the



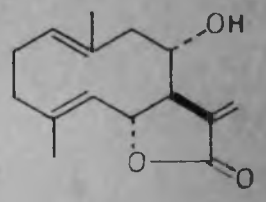
GERMACRONE



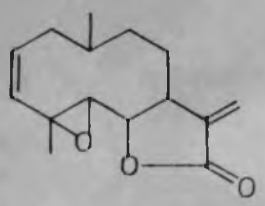
PYRETHROSIN



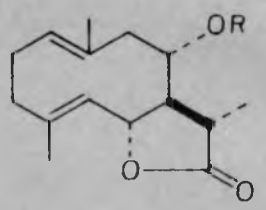
COSTUNOLIDE



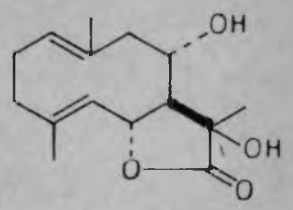
HYDROXYCOSTUNOLIDE



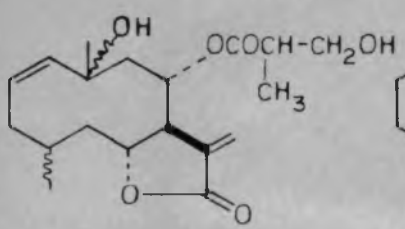
PARTHENOLIDE



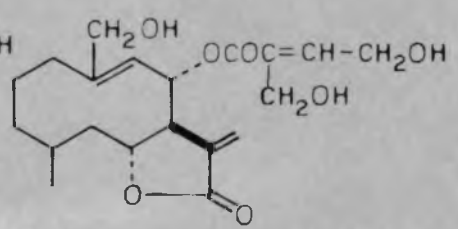
a) R=H, BALCHANOLIDE
b) R=Ac, ACETYL BALCHANOLIDE



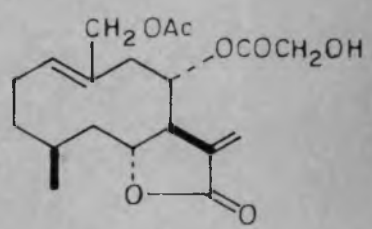
HYDROXYBALCHANOLIDE



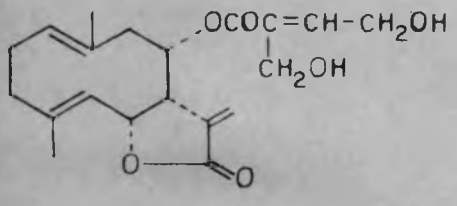
ARCTIOPICRIN



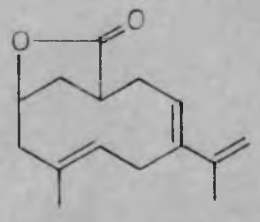
CNICIN



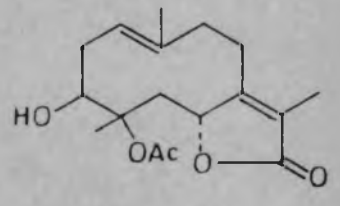
SCABIOLIDE



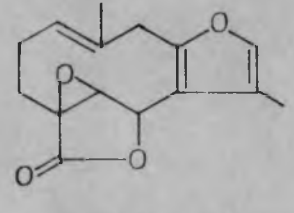
EUPATORIOPICRIN



ARISTOLACTONE



GAFRININ



LINDERANE

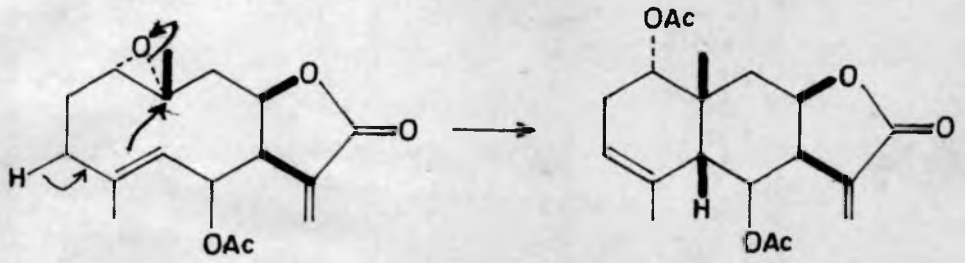
CHART II. TEN-MEMBERED SESQUITERPENES

simplest member of the ten-membered sesquiterpenoids. The establishment of structures of these terpenoids was followed by the isolation and structure determination of a number of other members of this group. Chart II and Table I summarise the present position in this area.

Table I - Ten-membered sesquiterpenes

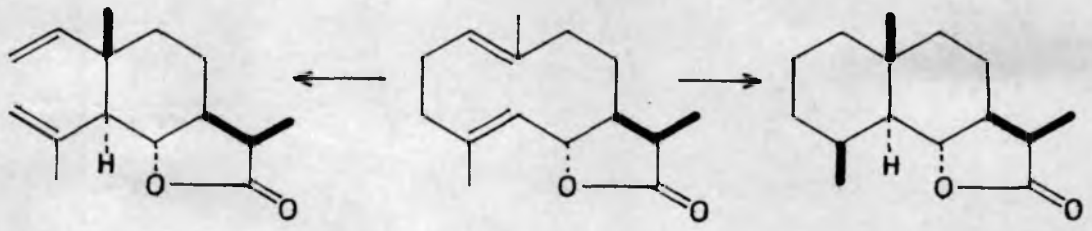
	Compound	m.p.	$[\alpha]_D$	Ref.
1	Germacrone	56-57°	0	5
2	Pyrethrosin	198-200°	-31°	4
3	Costunolide	107°	+128°	6,7
4	Hydroxy costunolide (isolated as acetyl derivative).	98°	-37.4°	8
5	Parthenolide	116.5-117°	-81.4°	9
6	Balchanolide	150°	+183°	10
7	Isobalchanolide	143°	+122°	10
8	Acetylbalchanolide	125-126°	-21.4°	11
9	Hydroxybalchanolide	163°	+99°	10
10	Arctiopicrin	115°	+133°	12
11	Cnicin	143°	+158°	13
12	Scabiolide	120°	+101°	14
13	Eupatoriopicrin	157-161°	+95°	15
14	Aristolactone	110-111°	-156°	16
15	Grafinin	110°	-16.1°	17
16	Linderane	190-191°	+183.3°	18

An important chemical feature of this group of compounds is the facility with which these undergo transannular reactions and sometimes exhibit anomalous spectral characteristics, a characteristic of the medium ring chemistry. Thus pyrethrosin (6) under acidic condition undergoes cyclisation to cyclopyrethrosin acetate[19] (7).



(6) (7)

Dihydrocostunolide (8) on hydrogenation is converted into santonolide[6] C (9) whereas it yields saussurea lactone[20] (10) on pyrolysis.

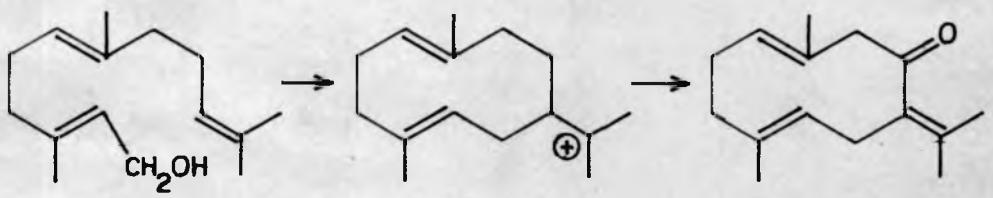


(10) (8) (9)

The high end absorption shown by germacrone and costunolide in the UV region is attributed to the geometry of the ten-membered ring in permitting the electron delocalisation between adjacent but non-conjugated double

bonds[21,22].

The biogenesis of ten-membered sesquiterpenoids has been discussed by Hendrickson[23]. According to him trans-farnesol (11) cyclises to form a ten-membered ring which is the precursor for germacrone (12) and germacrolides. As a matter of fact, Ruzicka[24] in 1953 while



(11) (12)

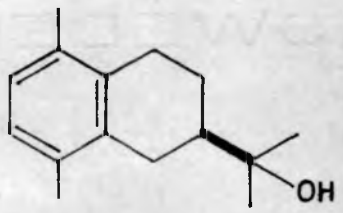
discussing the biogenesis of sesquiterpenoids invoked intermediates of germacrane type. The work of Barton[4] and Sorm[25] supports the hypothesis that systems of selinane- and guaiane-types arise from further cyclisation of the ten-membered intermediates.

BICYCLIC

Occidol:

(+)-Occidol, isolated from Thuja occidentalis L. has been shown to possess a modified eudesmane skeleton (13) by degradative results, which is further supported

by an unambiguous synthesis[26].



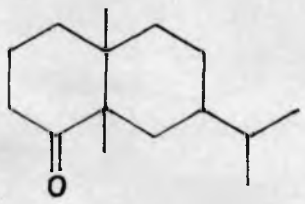
m.p. 69-70°

$[\alpha]_D$ +163.7°

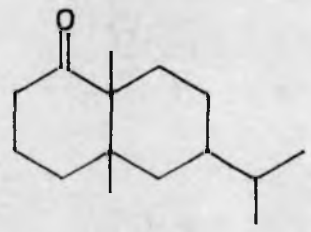
(13)

Valerane:

Valeranone, a saturated bicyclic ketone isolated from Valeriana officinalis, was shown to be identical with jatamansone[27]. Investigation carried out by one set of workers[28] led to the formulation of valeranone as (15), while another group of workers working independently arrived at two possible alternatives (14) and (15), and later succeeded in presenting unequivocal evidence in favour of structure (14)[29].



(14)



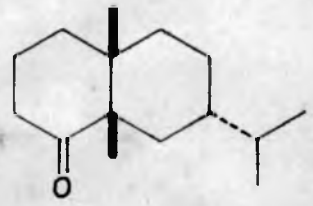
(15)

n_D^{20} 1.4944

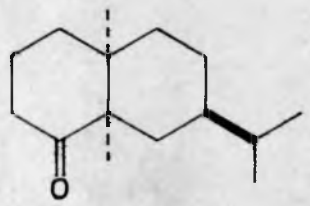
$[\alpha]_D$ -43°

The determination of the absolute stereochemistry of valeranone has reached an interesting situation now.

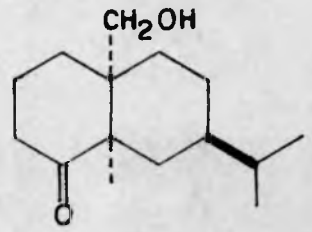
While the Czech workers[30] have adduced evidence, including an X-ray structure determination of a valeranone derivative that valeranone has the absolute structure (16), another set of workers[31] present data in favour of the structure (17) which would appear to be more correct.



(16)



(17)



(18)

m.p. 53-54°

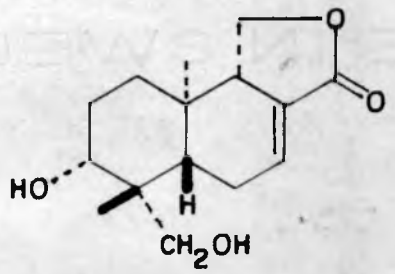
$[\alpha]_D$ -71.0°

Another member of this type, namely hydroxy-valeranone (18), has been isolated along with its acetate independently by two groups of workers[32,33].

Iresane:

It has been suggested at one time that coiling of the polyisoprenoid chain in a manner that is characteristic of di- and tri-terpenoids may, as well be unlikely in the case of farnesol[34,24]. So when in 1954, Djerassi and co-workers[35,39] isolated iresin and adduced evidence in favour of (19), it was stated that the "missing link" has been discovered! Till today fifteen members of this family

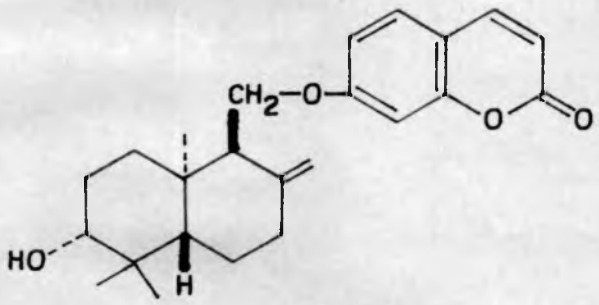
have been discovered and these have been summarised in



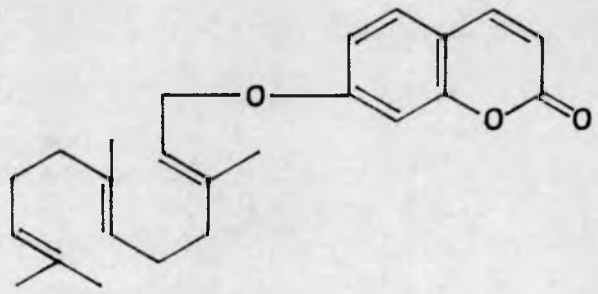
(19)

Chart III and Table II.

The compound farnesiferol[36] A, present in Asafoetida as an ether derived from an alcohol of iresin type and umbelliferone, is shown to be (20). Farnesiferol A (20), B (4) and C (5) can be considered to be formed by oxidative cyclisation of umbelliprenine[37] (21) which has been characterized twenty years back.

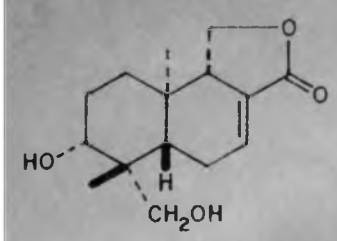


(20)

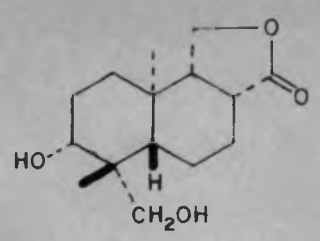


(21)

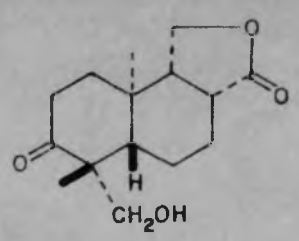
It is interesting to note that whereas iresin, isoiresin and farnesiferol possess the absolute stereochemistry at rings A and B which is opposite to that commonly encountered in the triterpenoids, the remaining members which lack the hydroxyl group at C_3, possess the



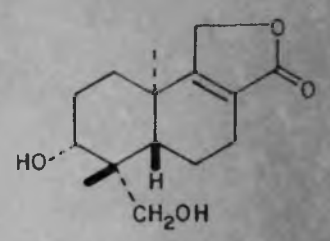
IRESIN



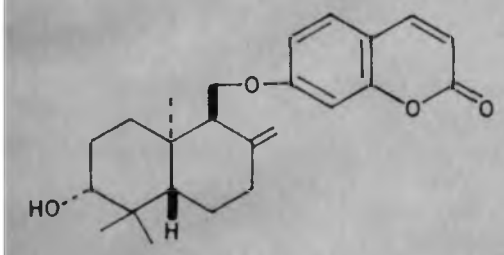
DIHYDROIRESIN



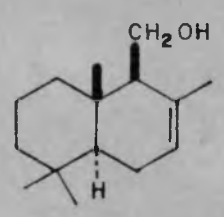
DIHYDROIRESONE



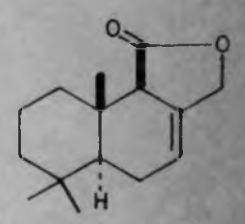
ISOIRESIN



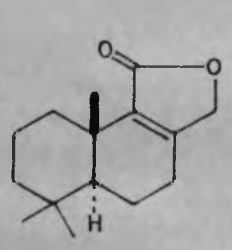
FARNESIFEROL A



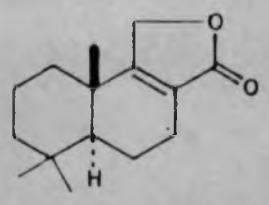
DRIMENOL



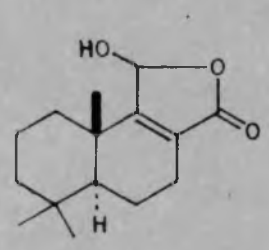
DRIMENIN



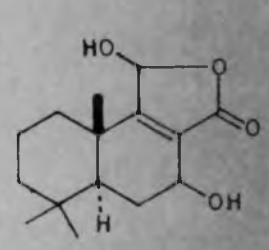
ISODRIMENIN



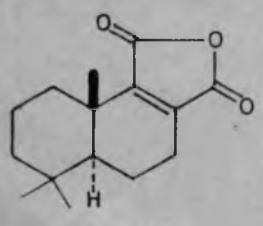
CONFERTIFOLIN



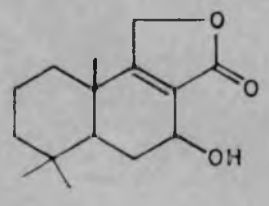
VALDIVIOLIDE



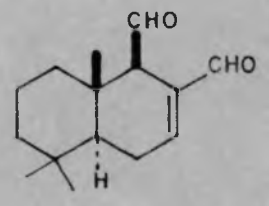
FUEGIN



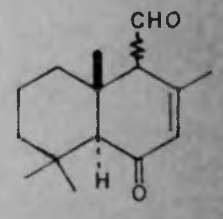
WINTERIN



FUTRONOLIDE



POLYGODIAL



TADEONAL

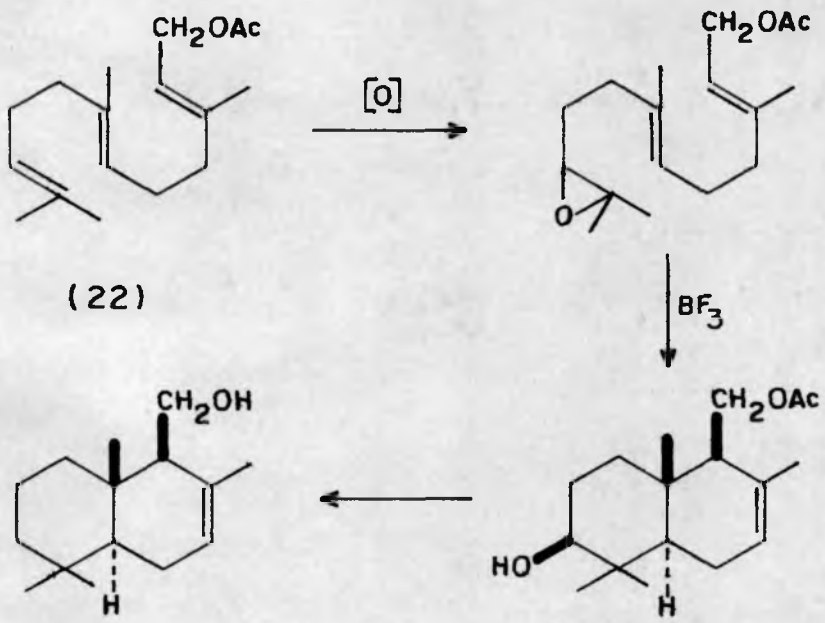
CHART III. IRESANE TYPE SESQUITERPENES

Table II - Iresane type sesquiterpenes

	Compound	m.p.	$[\alpha]_D$	Ref.
1	Iresin	140-142°	+21°	38
2	Dihydroiresin (isolated as acetyl derivative)	212-213°		40
3	Dihydroiresone	215-219°	+62°	40
4	Isoiresin (isolated as di-acetate)	166-168°	-70°	40
5	Farnesiferol A	155-155.5°	-55°	36
6	Drimenol	97-98°	-18°	41
7	Drimenin	133°	-42°	42
8	Isodrimenin	131-132°	+87°	42
9	Confertifolin	152°	+72°	42
10	Valdiviolide	177-178°	+111°	43
11	Fuegin	170-172°	+76°	43
12	Winterin	158°	+109°	43
13	Futronolide	215-217°		43
14	Polygodial	57°	-131°	44
15	Tadeonal	50°	-210°	45

ring fusion typical of triterpenoids.

The biogenesis of sesquiterpenoids of this group, evidently, must follow the scheme of cyclisation so well established for di- and tri-terpenoids. In this connection, it is interesting to note that trans farnesyl-acetate (22) on selective oxidation, followed by acid catalysed cyclisation led to (±)-drimenol (23)[46,47].



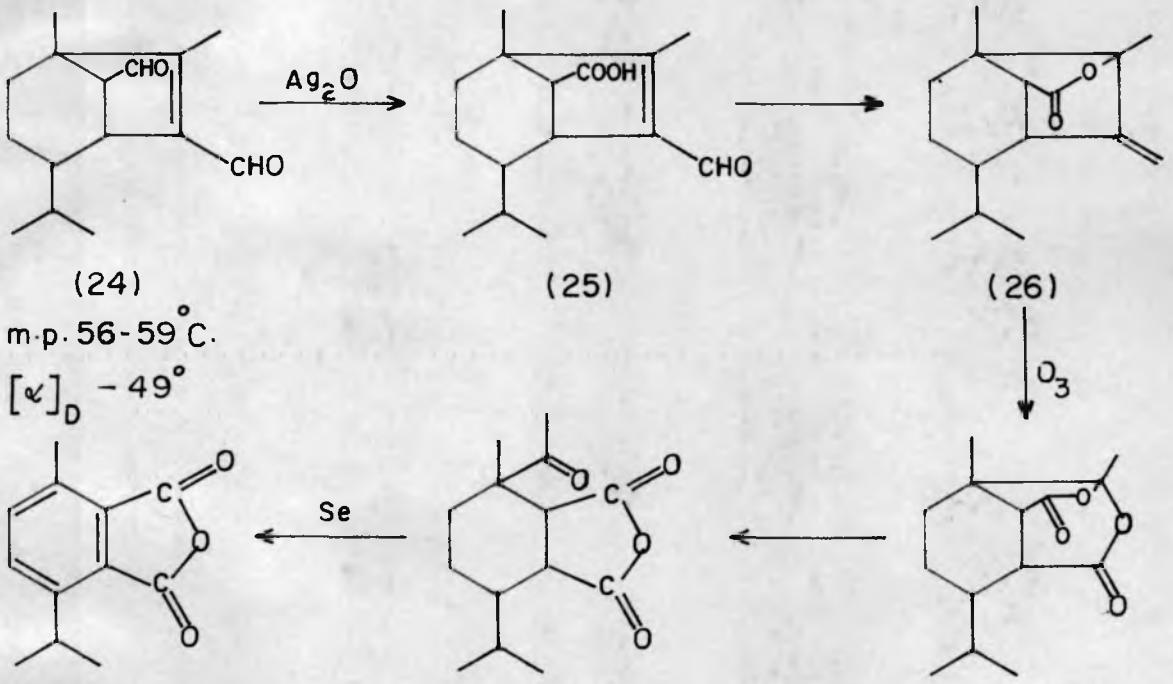
(22)

(23)

Helminthosporane:

Recently P. de Mayo and co-workers[48] reported that the toxin helminthosporal produced by the fungus Helminthosporium sativum is a modified sesquiterpene containing

two aldehyde functions. On silver oxide oxidation, a monocarboxylic acid (25) was obtained which on treatment with sodiumborohydride underwent an allylic rearrangement resulting in (26). The lactone (26) was degraded to phthalic anhydride (27) whose identity was proved by synthesis.



(24)
m.p. 56-59°C.
$[\alpha]_D$ -49°

(25)

(26)

(27)

These results together with the presence of a quaternary methyl (NMR) point to structure (24) for helminthosporal. This has been confirmed by an elegant total synthesis of helminthosporal by Corey and Nozoe[49].

It has been suggested by P. de Mayo[50] that the biogenesis of helminthosporal follows a pathway similar to that proposed for longifolene (cf. Chart VIII) and is depicted below. This has been confirmed by degradation experiments on labelled helminthosporal.

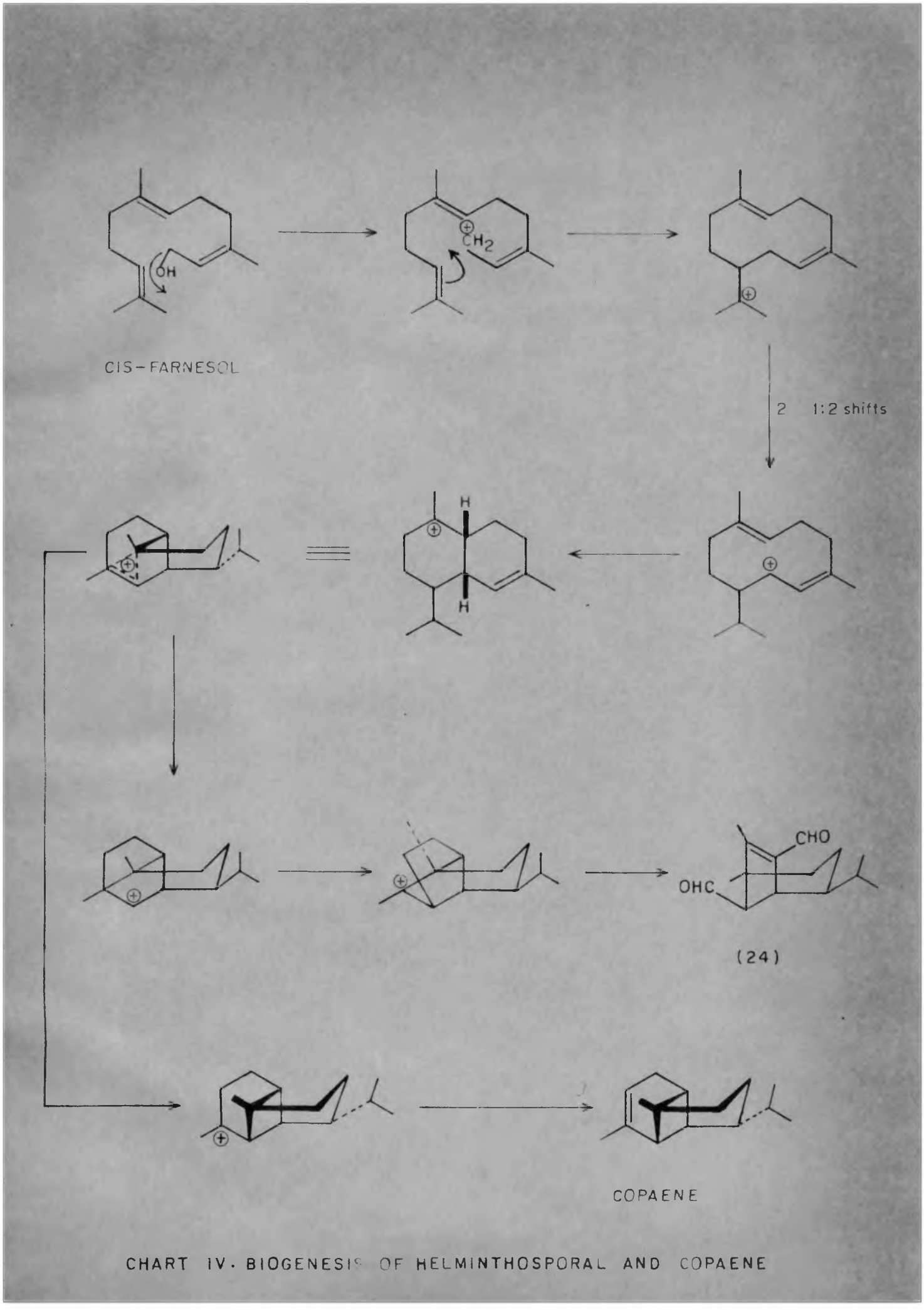
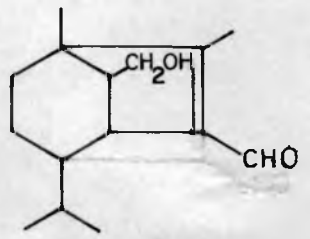


CHART IV. BIOGENESIS OF HELMINTHOSPORAL AND COPAENE

Recently a closely related alcohol (28) has been isolated by Japanese workers[51].



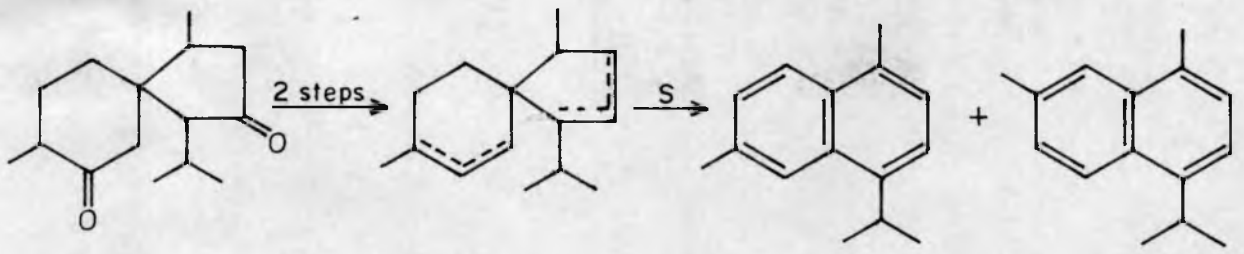
(28)

Helminthosporol

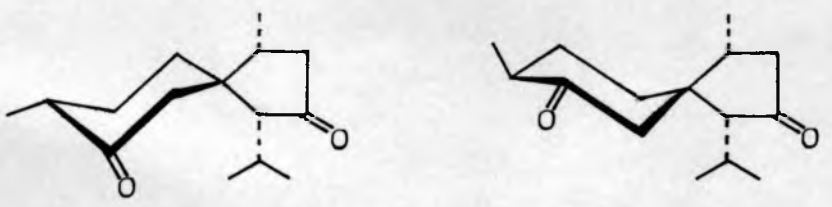
m.p. 98°, $[\alpha]_D$ -28.7°

Acorane:

Acorone (29), a bicyclic diketone obtainable from sweet flag oil (Acorus calamus L.), is the first natural product with a spirane skeleton[52]. As expected, dehydrogenation of acordiene (30) gave both cadalene (31) and the isomeric 1,7-dimethyl-4-isopropylnaphthalene (32). Other



(29) (30) (31) (32)

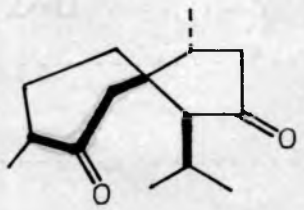


Acorone

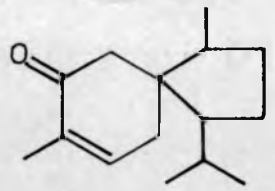
m.p. 101°, $[\alpha]_D$ + 144°

Isoacorone

m.p. 97°, $[\alpha]_D$ -90°



Cryptoacorone
m.p.107-108° $[\alpha]_D$ +97·7°



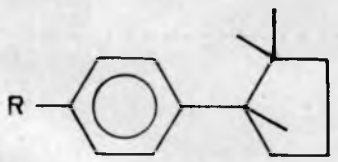
Acorenone
b.p.161°/10 mm
n_D^{20} 1.5039 $[\alpha]_D$ -22·3°

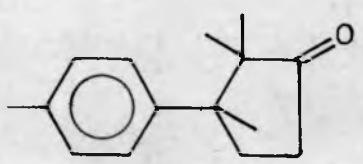
members of this family include isoacorone, cryptoacorone[53], acorenone[54]. Recently evidence has been presented in favour of the absolute stereochemistry depicted above for acorone and its stereoisomers[55].

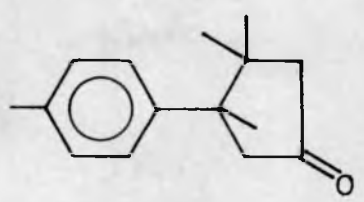
The biogenesis of these spiroterpenes has been discussed later.

Cuparane:

Cuparene (33) and the related acid (34) were first reported by Enzell and Erdtman[56] in 1958. Cuparene has been synthesised recently by Raphael and co-workers[57]. Two more members of this series, namely α- and β-cuparenones[58] (35,36) have been added to this group of sesquiterpenoids.







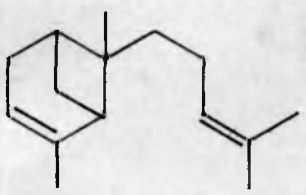
(33) R=CH_3, Cuparene
b.p. 138°/19 mm, $[\alpha]_D$ +65°
(34) R=COOH, Cuparenic acid
m.p. 158-160° $[\alpha]_D$ +63°.

(35) α-Cuparenone
m.p. 52-53°
$[\alpha]_D$ +177.1°

(36) β-Cuparenone
b.p. 114-115°/.8 m
n_D^{30} 1.5292
$[\alpha]_D$ +48°

Bergamotane:

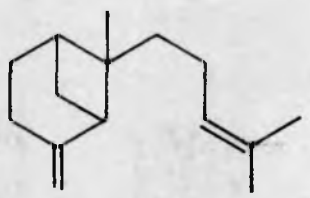
Bergamotene was first isolated by Sorm and co-workers[59,60] from bergamot oil. Though no data pertaining to its structure determination has apparently been published, the following structure (37) has been reported for this compound in the "Collection of IR spectra"[60]. Sometime back, the same compound has been



(37)

n_D^{20} 1.4904

$[\alpha]_D$ -44.1°



(38)

b.p. 120-130°/1 mm

n_D^{27} 1.4949, $[\alpha]_D$ +35.8°

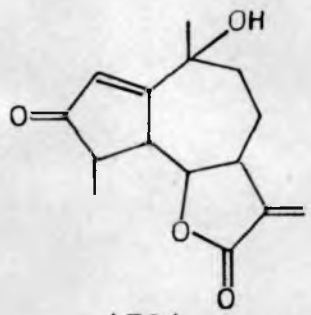
isolated from the essential oil of Lansium anamalayanum Bedd., a study of its NMR spectrum supported the abovementioned structure (37) for bergamotene[61].

An isomer of bergamotene termed β-bergamotene has been recently isolated from the oil of Valeriana wallichi and has been shown to possess the structure (38)[62].

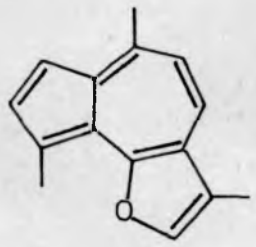
The biogenesis of these compounds which, in a sense is related to that of acorone, will be discussed later.

Parthenane:

This class of compounds is, in practice, a sub-group of the important family of sesquiterpene lactones called guaianolides[63] (for e.g. 39).

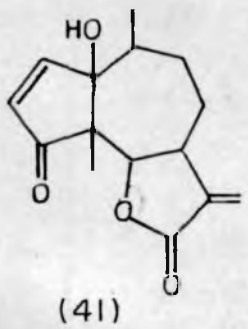


(39)

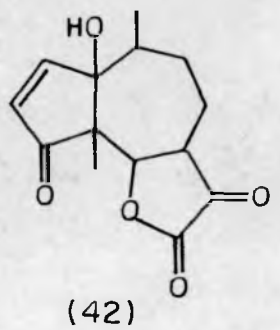


(40)

Parthenin, $C_{15}H_{18}O_4$, isolated from Parthenium hysterophorus L., was first thought to possess the structure (39)[64] based on the usual degradation studies, especially its dehydrogenation to artemazulene (40). However, a critical evaluation of the NMR spectrum of parthenin necessitated a renewal of the above structure to (41). This structure was confirmed[65] by the isolation of S-(+)-α-methylglutaric acid on potassium permanganate oxidation of nor-parthenone (42). The structure is bio-



(41)

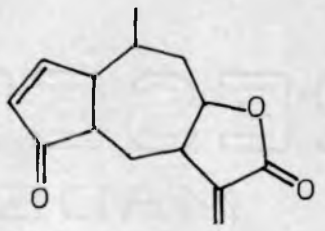


(42)

genetically interesting as it involves an extra step of

isomerization (methyl migration) of normal guaianolide skeleton at the final stage. This work dictated a re-investigation of several of the earlier guaianolide structures and surprisingly it was found that a number of compounds originally assigned the normal guaianolide skeleton, in fact, possessed a rearranged skeleton. These compounds which constitute fifty percent of guaianolides known todate have been shown in Chart V and physical properties collected in Table III.

A nor-compound, Mexicanin E[80] apparently belonging to this series has been isolated from Helenium mexicanum H.B.K. and assigned the structure (43).



(43)

m.p. 100.5 - 101.5°

$[\alpha]_D$ -47°

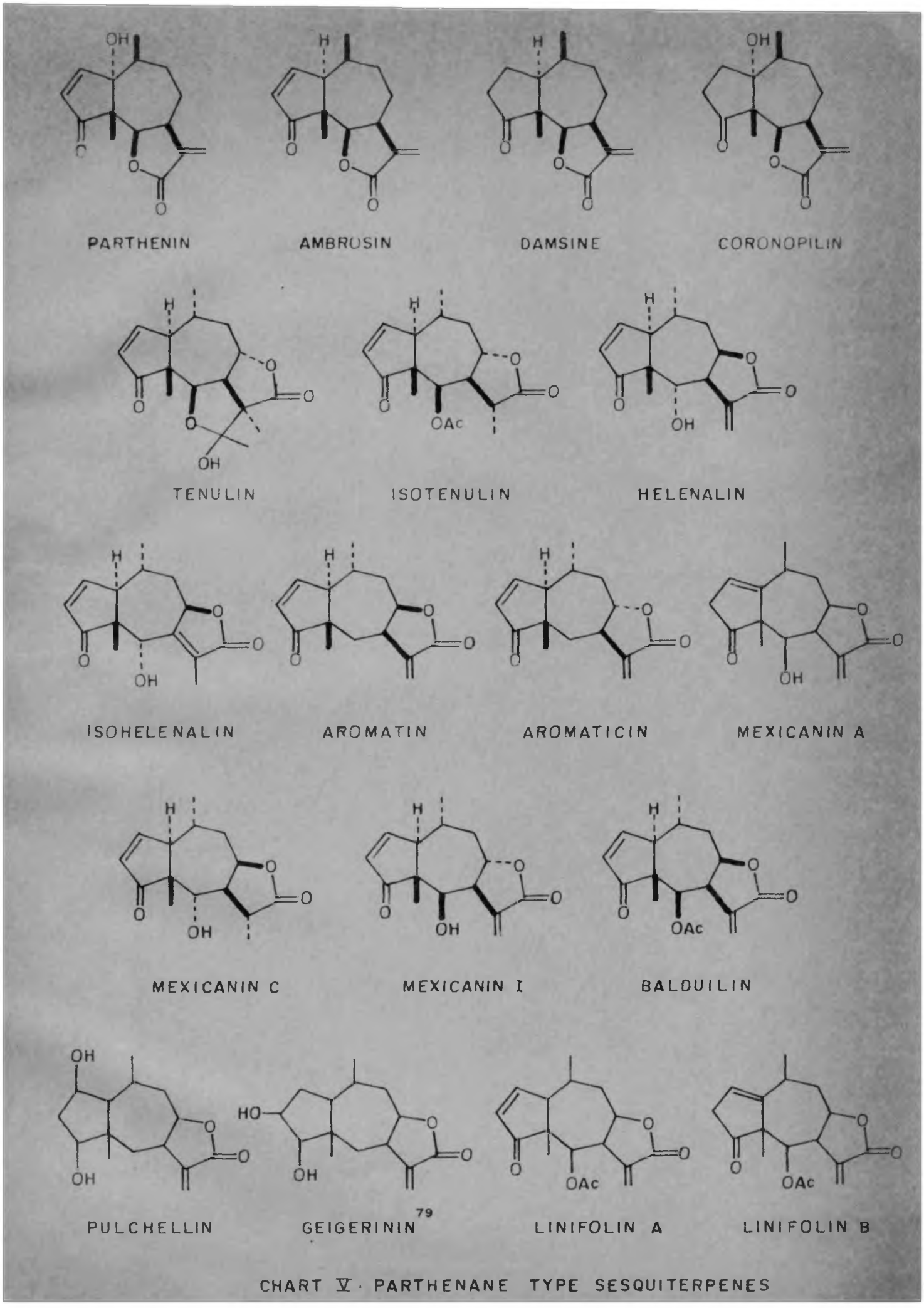


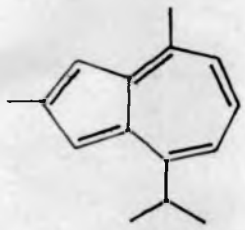
CHART V · PARTHENANE TYPE SESQUITERPENES

Table III - Parthenane type sesquiterpenes.

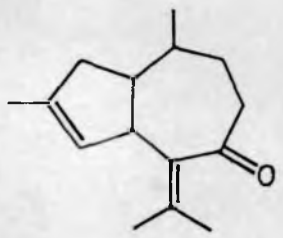
	Compound	m.p.	$[\alpha]_D$	Ref.
1	Parthenin	163-166°	+7.02°	65
2	Ambrosin	146°	-154.5°	66
3	Damsine	111°	-72°	67
4	Coronopilin	177-178°	-30.2°	68
5	Tenulin	indefinite upto 215°	-20 to -24°	69
6	Isotenulin	160-161°	+4 to +8°	70
7	Helenalin	169-172°	-102°	71
8	Isohelenalin	260-262°	-	72
9	Aromatin	159-160°	-6°	73
10	Aromaticin	232-234°	+18°	73
11	Mexicanin A	138-140°	-27°	74
12	Mexicanin B	212-214°	+39°	74
13	Mexicanin C	251-252°	-80°	74
14	Mexicanin I	257-260°	+42.5°	75
15	Balduilin	231-232°	+57°	76
16	Pulchellin	165-168°	-36.2°	77
17	Geigerinin	202-203°	-10.7°	78
18	Linifolin A	195-198°	+33°	70
19	Linifolin B	149-151°	-	70

Zierone:

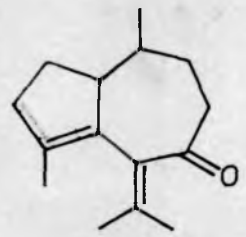
Zierone is a bicyclic unsaturated ketone which on dehydrogenation furnished a new azulene, termed zierazulene, whose structure was confirmed by synthesis as (44). Based on this, structure (45) was proposed for zierone[81]. However,



(44)



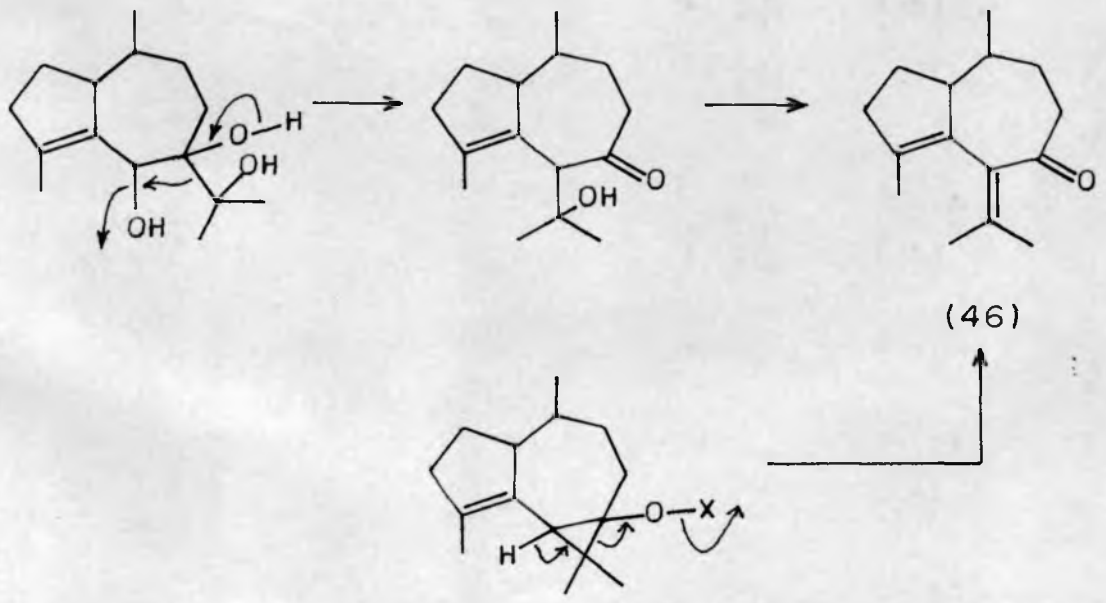
(45)



(46)

b·p·138°/10mm, n_D^{25} 1·5117, $[\alpha]_D$ -150°

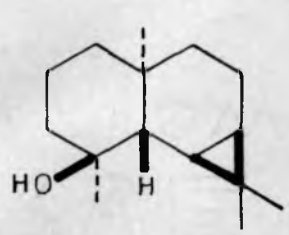
Barton and Gupta[82] found that this structure must be modified as the NMR spectrum of zierone did not display any olefinic proton. Further work by this group led to the revised structure (46)[83]. It has been proposed that zierone, which does not possess the usual cyclized farnesol skeleton, may originate as follows:



TRICYCLIC

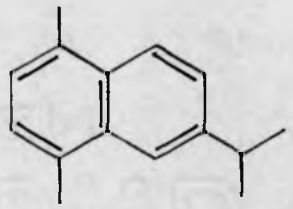
Maaliane:

Maaliol[84], a saturated tricyclic sesquiterpene alcohol, has been isolated from Maali resin (Canarium samonense). Dehydrogenation yielded cudalene mainly, with little of vetivalene (48). The presence of a cyclopropane ring was shown by spectroscopic data and confirmed by chemical evidence. All these led to the establishment of

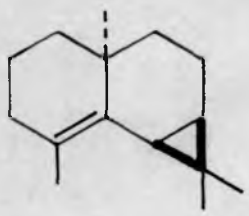


(47)

m.p. 103-104° $[\alpha]_D$ +15·1°



(48)



(49)

$[\alpha]_D$ -135·2°

structure (47) for maaliol which has been confirmed by synthesis[85]. β-Maaliene (49) has also been isolated from Chinese Spikenard oil [Nardostachys jatamansi (Roxb) DC][86].

Calarane:

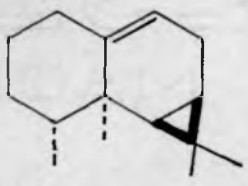
Calarene, $C_{15}H_{24}$, isolated from Chinese Spikenard oil [Nardostachys jatamansi (Roxb) DC] on treatment with formic acid gave a diene (51) which was identified as the product of acid catalysed dehydration of maaliol (47). This result taken in conjunction with spectroscopic data and biogenetic consideration led to the structure (50) or 9,10-double bond

isomer (52) for calarene. The identification of aristolene, prepared from aristolone (53)[87], as structure (52), confirmed the above structure (50) for calarene[86]. Sorm and co-workers[88] and Ourisson and co-workers[89] have isolated the same hydrocarbon (under the name β-gurjunene) independently and arrived at the structure (50). The name calarene has been retained for this hydrocarbon (50) as suggested by Pesnelle and Ourisson[90]. Aristolene (52) has been isolated as a minor product from Nardostachys jatamansi (Roxb)[90].

(50)

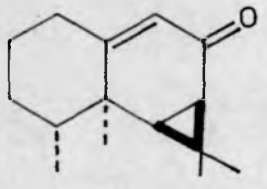
n_D^{20} 1.5051 $[\alpha]_D$ +82°

(51)



(52)

n_D^{20} 1.5047 $[\alpha]_D$ -99°



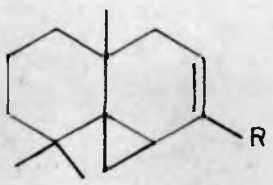
(53)

m.p.100-101°

Thujopsane:

Thujopsene (54) and hinokiic acid (55) were isolated from the oil of Japanese Hiba tree (Thujopsis dolabrata (L.f.) Sieb, et Zucc.,). The presence of a cyclopropane ring in conjugation with double bond was established from molecular

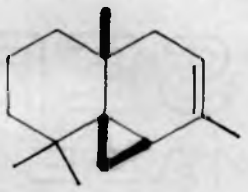
refractivity, catalytic hydrogenation (conjugate addition),



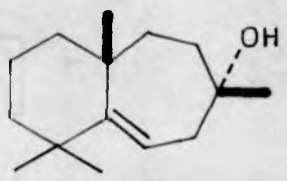
(54) R = CH_3, b.p. 120°C/10 mm
n_D^{25} 1.5031
$[\alpha]_D$ -110°

(55) R = COOH m.p. 169-170°
$[\alpha]_D$ -86°

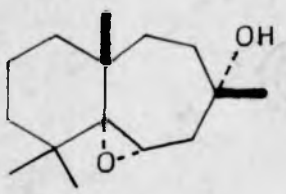
IR and NMR studies[91,92]. Systematic degradation experiments led to the establishment of structure (54) for thujopsene. Recently a total synthesis of thujopsene[93] is reported which establishes the stereochemistry as shown in (56).



(56)



(57)
m.p. 98°, $[\alpha]_D$ + 105°



(58)
m.p. 156-157°, $[\alpha]_D$ -6°

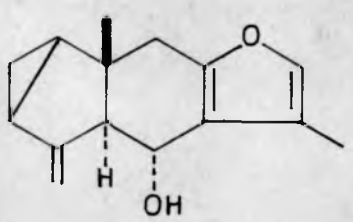
Widdrane:

Thujopsene on treatment with aqueous oxalic acid yielded a sesquiterpene alcohol m.p. 98°C, identified as widdrol[94,93] (57), a constituent of South African Widdringtonia species. The structure of widdrol[95] has been confirmed by a total synthesis[96]. Widdrol epoxide (58)[95] has been isolated from the same oil.

The biogenesis of these compounds, apparently, is related to that of cuparene and this has been discussed later.

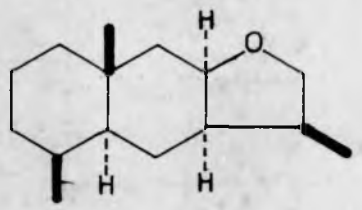
Linderene:

Linderene, the crystalline component of Lindera strychinifolia Vill. has been shown to possess the structure (59)[97]. The structural derivation is based mainly on the spectroscopic data and its conversion to the known hexahydro-atractylone (60).



(59)

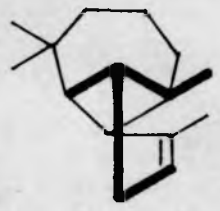
m.p.143-145° $[\alpha]_D$ + 15.14°



(60)

α-Longipinene:

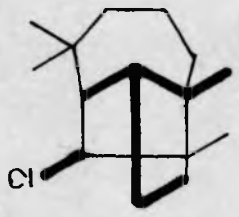
α-Longipinene (61) isolated from Swedish sulphate turpentine was assigned a pinene like structure[98] from its



(61)

b.p.102-106°/10mm. n_D^{22} 1.4924

$[\alpha]_D$ + 36.9°



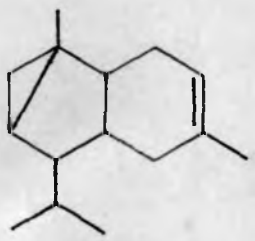
(62)

spectral properties as well as its conversion to longibornyl

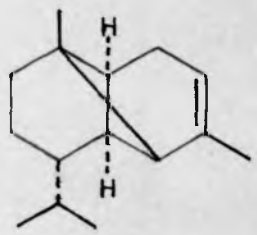
chloride (62) exclusively, on hydrochlorination. It has also been isolated from Indian turpentine oil recently[99].

Copane:

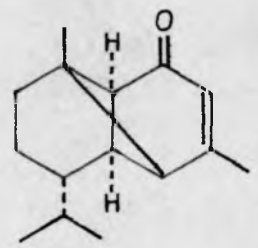
Copaene, the well known tricyclic unsaturated hydrocarbon, which has long been thought to possess the structure (63) has recently been shown by two different groups of workers[100,101] to possess structure (64) instead.



(63)



(64)



(65)

b.p. 114-115°/10 mm
n_D^{30} 1.4864, $[\alpha]_D$ -6.3°

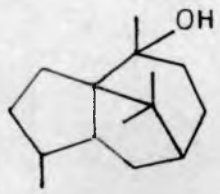
b.p. 128-129°/1 mm
$[\alpha]_D$ +.34°

Mustakone[101], an $\alpha\beta$-unsaturated ketone, isolated from Cyperus rotundus Linn. has been shown to possess the copane skeleton and assigned structure (65).

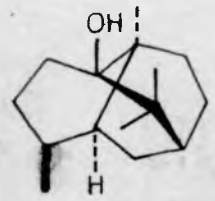
Patchouli alcohol:

Patchouli alcohol isolated from Pogostemon patchouli Pellet, was assigned the structure (66)[102] on the basis of degradation studies carried out on α,β and γ-patchoulenes, hydrocarbon products of dehydration. The above structure was apparently confirmed by an elegant synthesis of α-patchoulene[103]

and its conversion to patchouli alcohol. However, recent X-ray analysis[104] showed that patchouli alcohol is represented

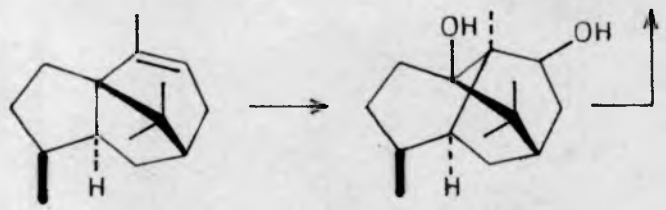


(66)



(67)

m.p. 55-56°, $[\alpha]_D$ -129°

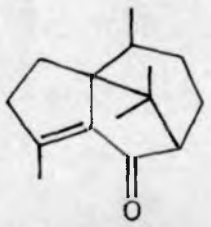


(68) (69)

by a new structure (67). The pyrolysis of patchouli acetate to α- and γ-patchoulenes is accompanied by a rearrangement, which takes place in exactly reverse direction on treatment of α-patchoulene (68) with peracetic acid during the conversion of α-patchoulene to patchouli alcohol.

Isopatchoulene:

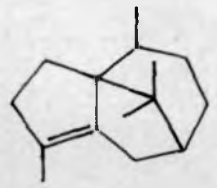
Skeleton originally assigned to patchouli alcohol has been found to constitute an αβ-unsaturated ketone, patchoulenone (70)[105], isolated recently from Cyperus rotundus Linn. A hydrocarbon possessing the structure (71) and identified as cyperene[106] has also been isolated from the same oil.



(70)

m.p. 52·5°

$[\alpha]_D$ -97·1°



(71)

n_D^{20} 1·5058

$[\alpha]_D$ -20°

TETRACYCLIC

Longicyclene:

Longicyclene[107], $C_{15}H_{24}$, the only example of tetracyclic sesquiterpene, has been isolated from Indian turpentine oil (Pinus longifolia). Its structure (72) has been arrived at from a study of its spectral properties taken together with its conversion to longifolene (73).

(72)

b.p. 82°/2 mm

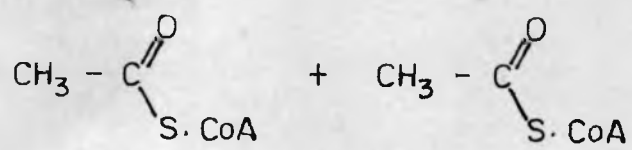
n_D^{30} 1·4888

$[\alpha]_D$ +33·6°

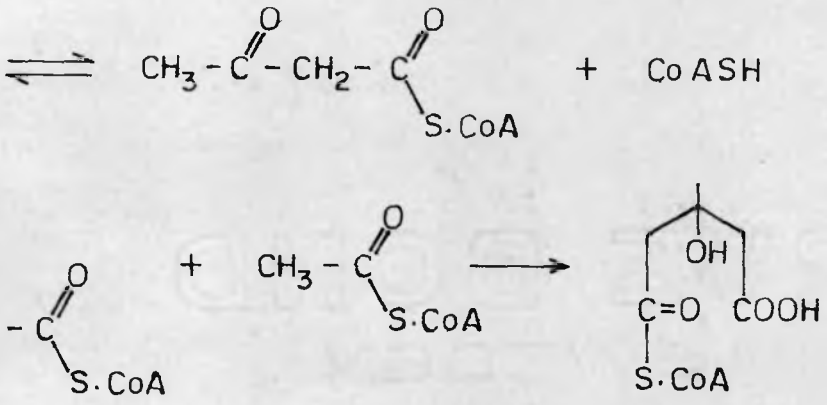
(73)

BIOGENESIS[108,109,110]

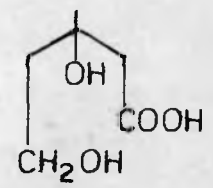
The simplest starting material for all isoprenoids is acetic acid[111] as is shown clearly in the case of cholesterol. Acetic acid in the form of "active acetate" [acetic acid thiol ester of Co-enzyme A (74)] unite to give β-hydroxy-β-methyl glutaryl Co-enzyme A (75) which on enzymatic reduction gives mevalonic acid (76)[112].



(74)



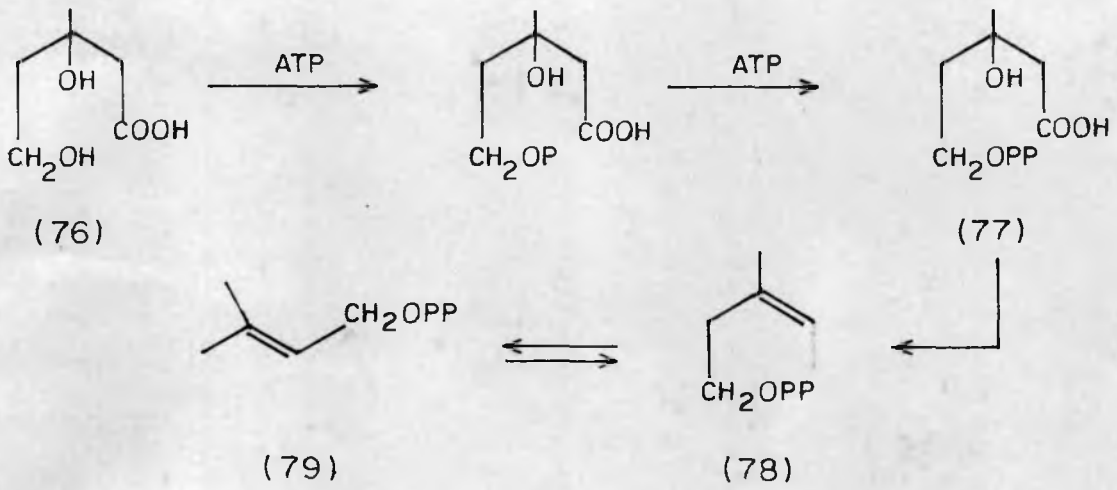
(75)



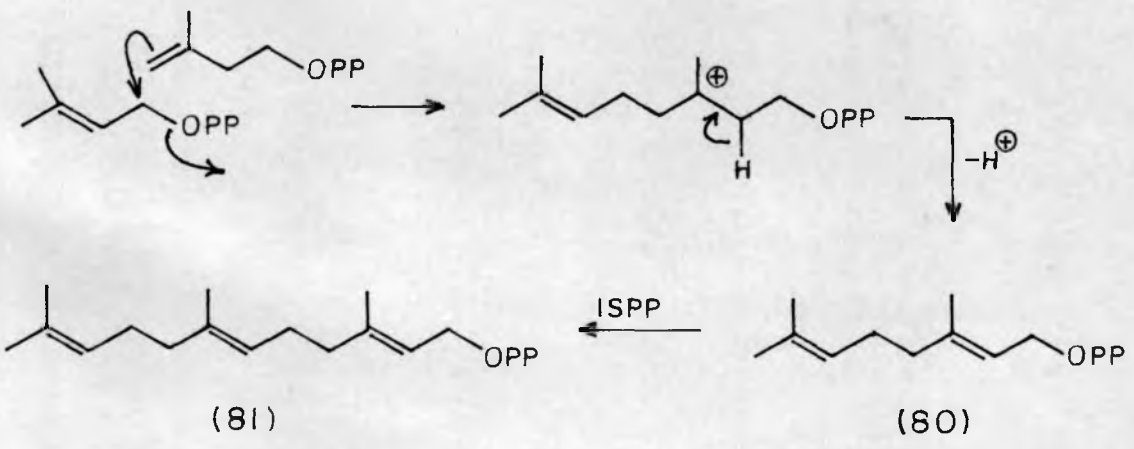
(76)

Mevalonic acid is phosphorylated to mevalonic acid pyrophosphate[113] [MVAPP (77)] with the help of adenosine triphosphate (ATP). MVAPP (77) undergoes decarboxylation and dehydration in the presence of ATP forming isopentenyl pyro-

phosphate[114] [IsPP (78)] which isomerises to dimethylallyl pyrophosphate [DmalPP (79)].



In the presence of the enzyme farnesyl pyrophosphate synthetase, IsPP (78) reacts with DmalPP (79) to give geranyl pyrophosphate [GePP (80)] which then condenses with a second molecule of IsPP (78) to give farnesyl pyrophosphate [FaPP (81)][115]. By secondary transformation namely cyclisation, rearrangement and oxidation, the different monoterpenes are formed from geranyl pyrophosphate, the sesquiterpenes, triterpenes and sterols from farnesyl pyrophosphate and finally diterpenes and carotenoids from geranylgeranyl pyrophosphate.



Initial suggestions about the possible modes of cyclisation of farnesol to yield sesquiterpenoids were made by Ruzicka[24] and has recently been extended by Hendrickson[23]. The farnesol formed from IsPP probably has a trans central double bond and the allylic double bond can assume cis or trans configuration by anionotropic interconversions. No oxidation occurs during cyclisations so that the most common oxidation state of cyclic sesquiterpenes is that of farnesol.

The cyclisation of farnesol chain may be divided into those starting from cis-farnesol (82) and those originating from trans-farnesol (11) and these have been summarised in Chart VI according to Hendrickson.

It is the purpose of the following schematic correlations to bring out how a single cationic species is capable of leading to a variety of structures depending on, what may be termed as, the contour of the enzyme surface.

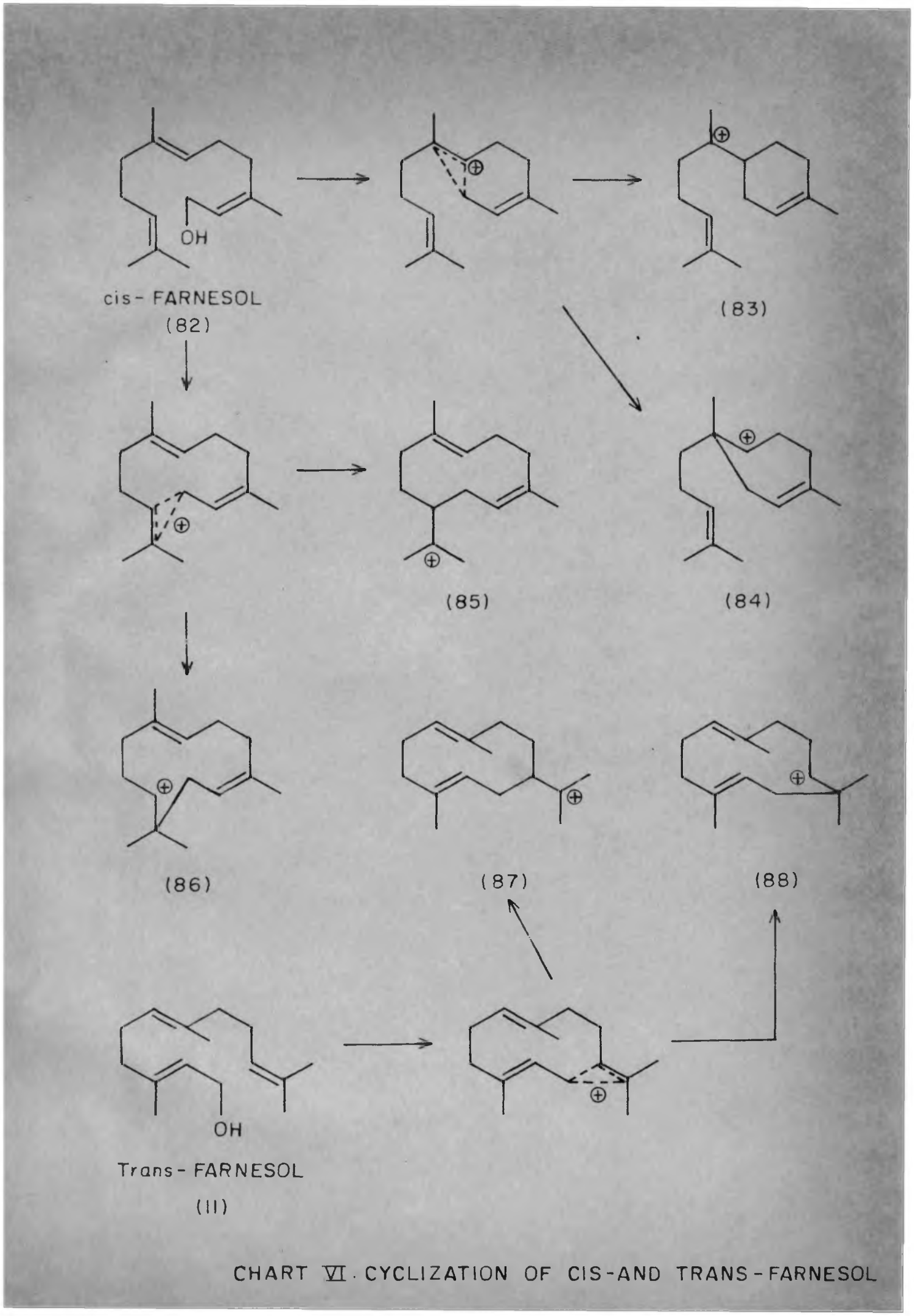


CHART VI. CYCLIZATION OF CIS-AND TRANS-FARNESOL

GROUP A: BISABOLENE, CADINENE, BERGAMOTENE, SANTALENES, ACORONE, CEDRENE, CUPARENE, THUJOPSENE AND WIDDROL[57]

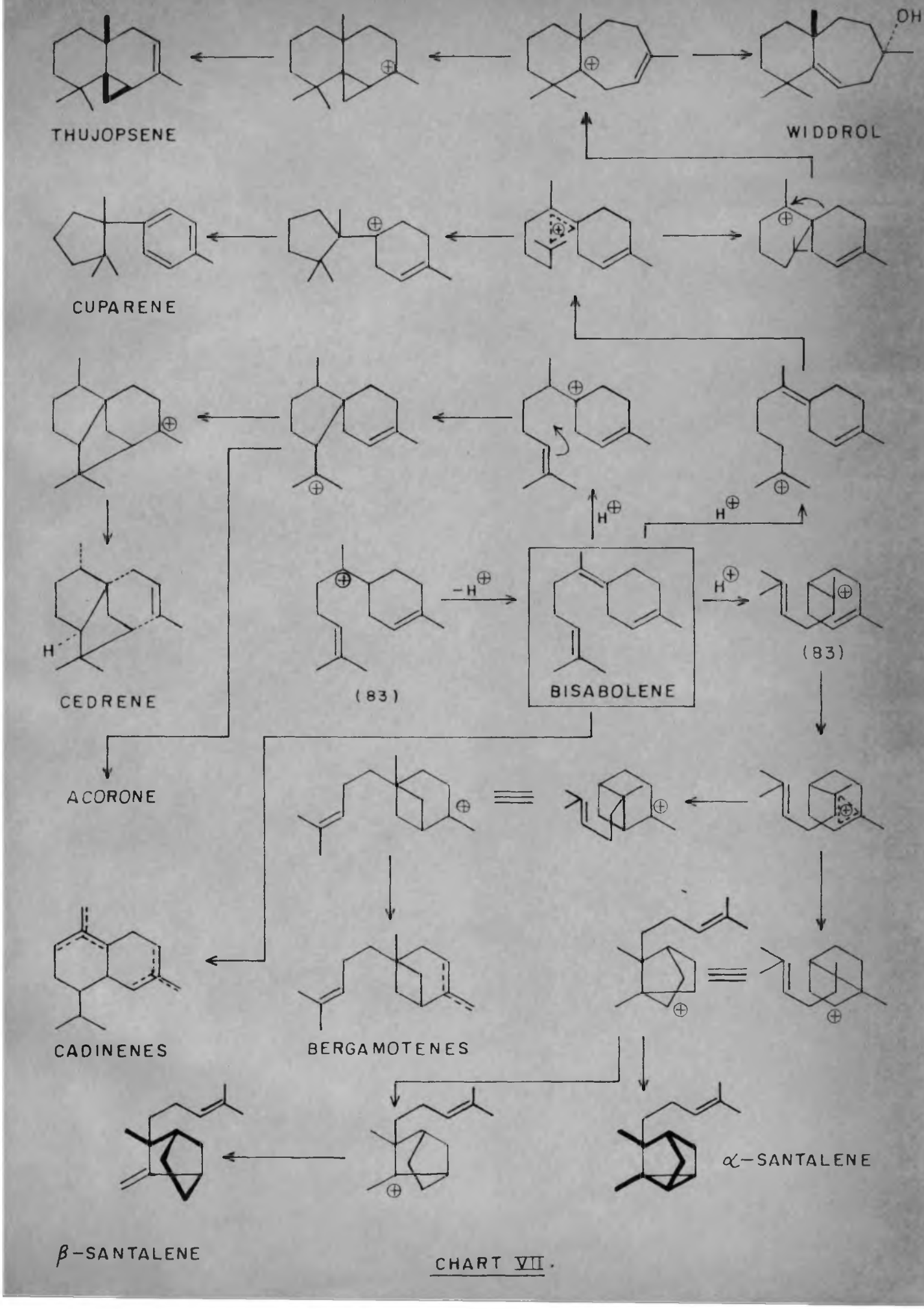


CHART VII.

GROUP B: CARYOPHYLLENE, HIMACHALENE, LONGIFOLENE
LONGICYCLENE AND LONGIPINENE

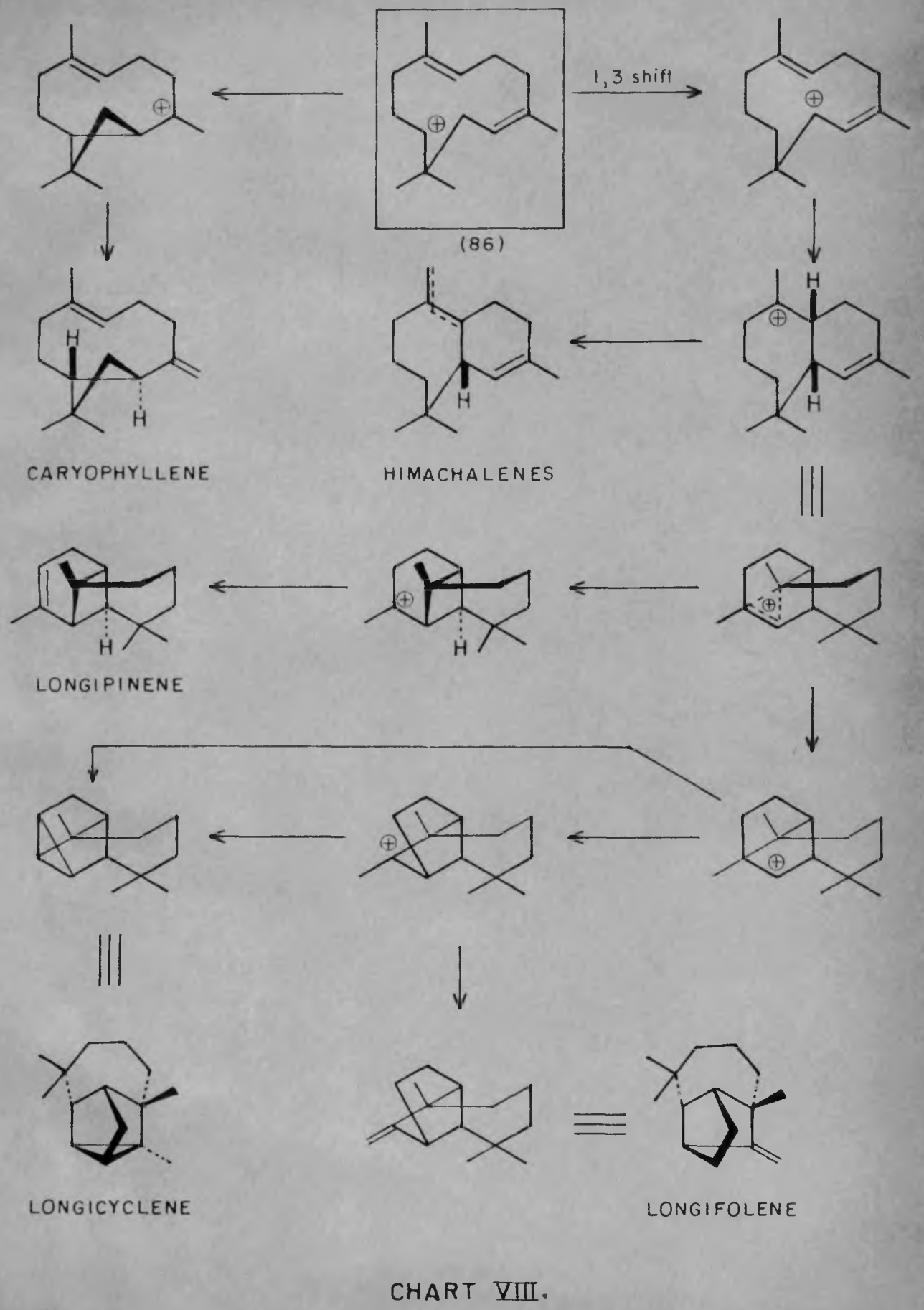
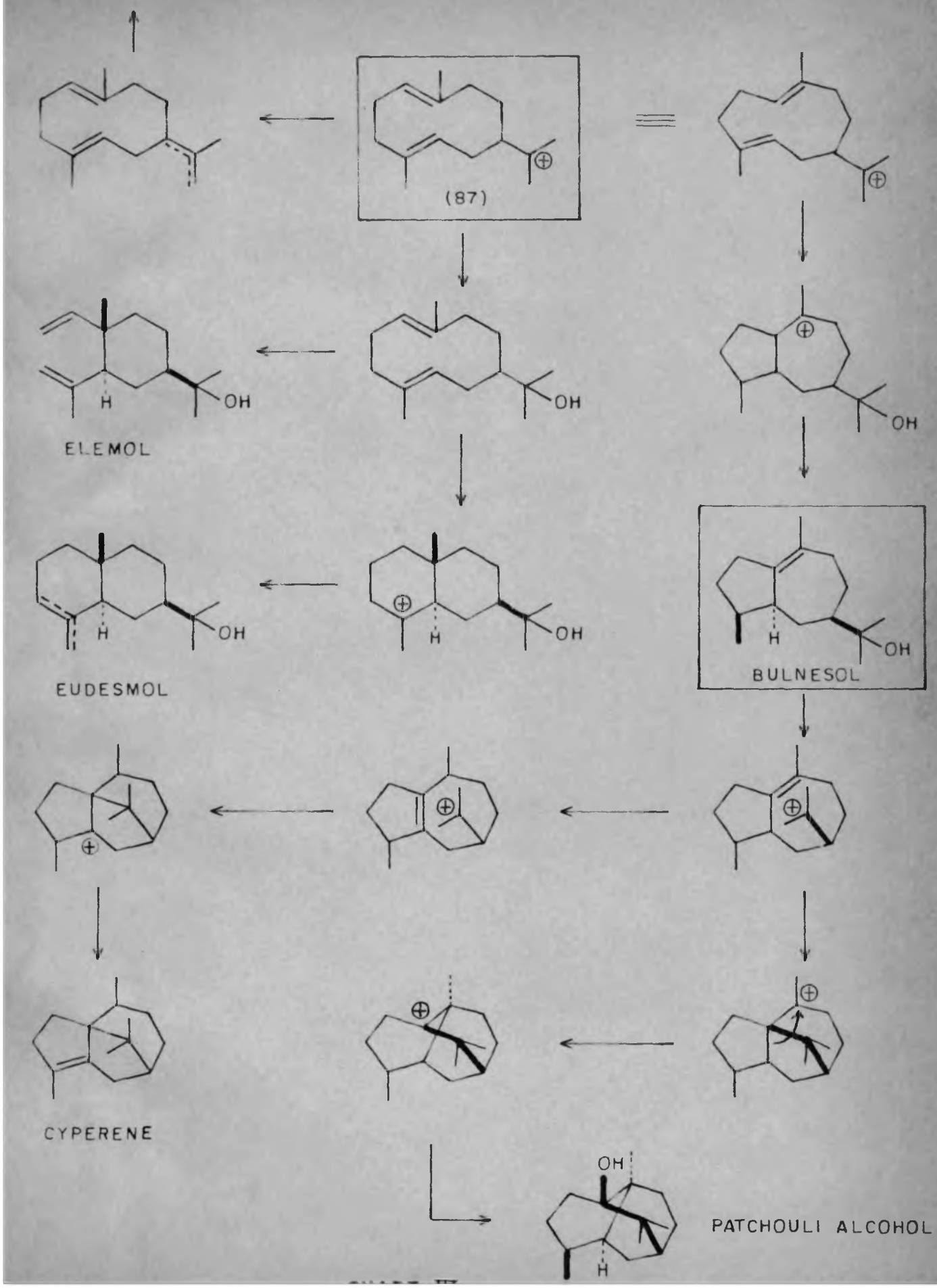
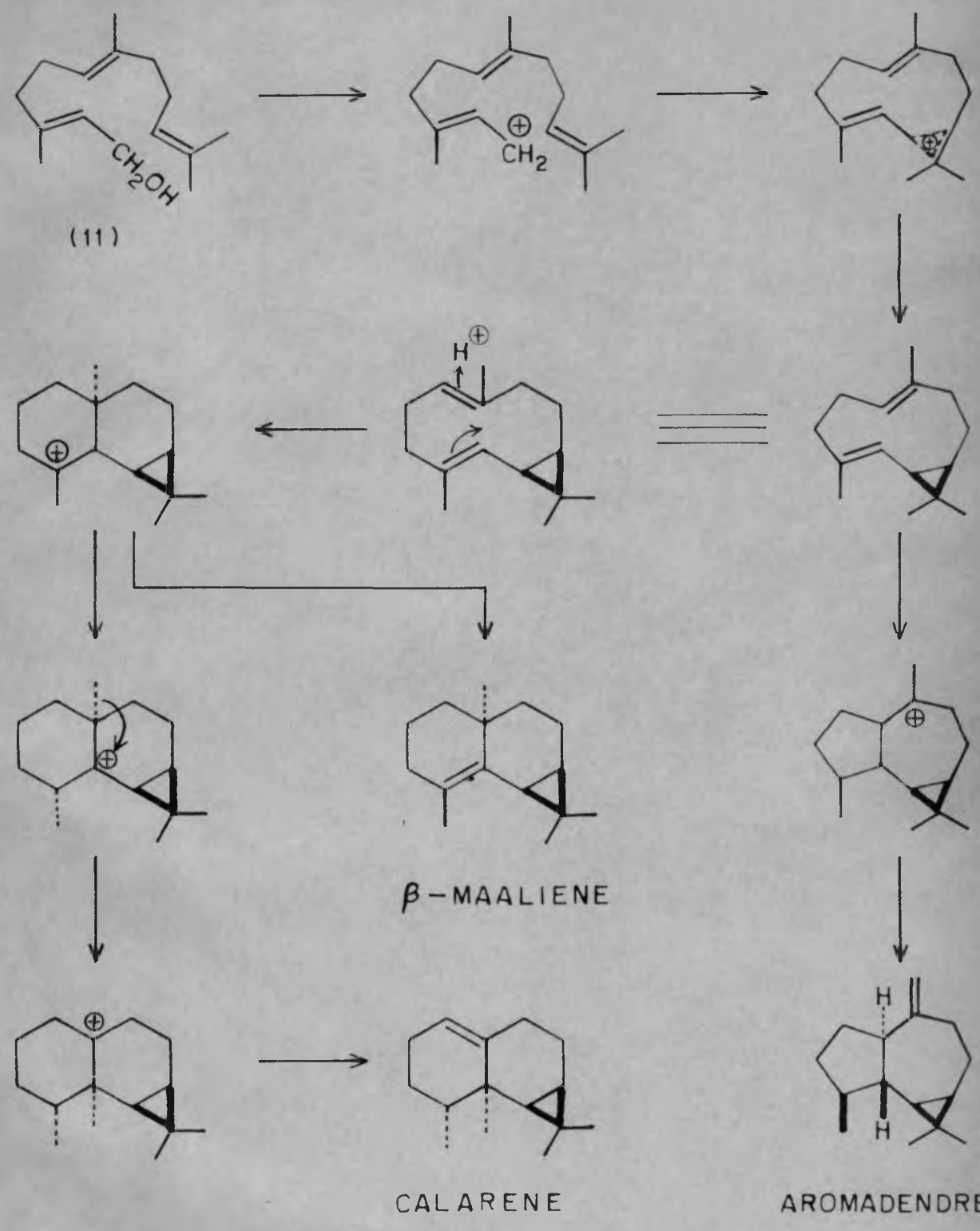


CHART VIII.

GROUP C: GERMACRANE, EUDESMOL, ELEMOL AND GUAIANE TYPES, CYPERENE AND PATCHOULI ALCOHOL[117]



GROUP D: CALARENE, β-MAALIENE AND AROMADENDRENE



(11)

CHART X.

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CHAPTER II

ISOLATION OF HIMACHALENES

The Tree

Cedrus deodara (Roxb) Loud, or Himalayan Cedar is a horizontal branched tree, growing to a height of 200 ft. with a girth of about 30 ft. in the Himalayan regions (4000 - 10,000 ft. high). The bark is brown with a whitish lustre. The leaves are long acicular in shape, grown on the branches in tufts 20 to 60 in numbers. Male catkins are more or less cylindrical and stamens are sub-cylindrical bilocular. Female cones are velvety and pea-green in colour and deliciously fragrant when young and become brown later. Seeds are unequal and somewhat wedge-shaped[1]. The tree is known as Deodara in Sanskrit, Deodar in Hindi and Devataram in Malayalam. The tree yields valuable timber which is extensively used in making railway sleepers and door frames. During the process, a lot of waste wood is produced which in view of its high oil content is usefully employed for obtaining the oil by distillation[2].

THE ESSENTIAL OIL

Past work:

In 1916, Roberts[3] made a preliminary study of the oil. He examined two samples of the oil which had the constants recorded in Table I. On fractionation of the oil, four main fractions were collected, one of which was identified as p-methyl-Δ^3-tetrahydro acetophenone as its semicarbazone. The presence of a phenol was proved but its identity was not established due to its presence in low percentage. The main constituent (50 - 70%) of the oil was shown to be a sesquiterpene

TABLE I

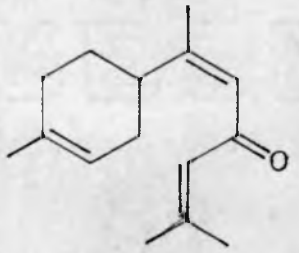
The Essential Oil : Physico-chemical data

Properties	Rao and Sukh Dev[7]	Roberts[3]	I.S.I. Standard*
Colour	Pale yellow	Reddish brown	Light yellow to reddish brown.
Odour	Characteristic odour of the wood.	Balsamic	Heavy balsamic.
Density	$d^{31^\circ}_{31^\circ}$ 0.9277	$d^{15^\circ}_{15^\circ}$ 0.9549, 0.9756	0.9323 to 0.9573
Optical rotation	$[\alpha]_D^{30}$ + 76.66°	$[\alpha]_D^{22}$ + 52.16° + 34.6	+20 to 62°
Refractive index	$n_D^{31^\circ}$ 1.5095	$n_D^{21^\circ}$ 1.5195, 1.5225	n_D^{30} 1.5038 to 1.5120
Acid value	0.065	5.6, 4.5	5
Ester value	3.85	19.3, 4.9	10 to 25
Acetyl value	5.6	30.8, 34.4	25 to 45

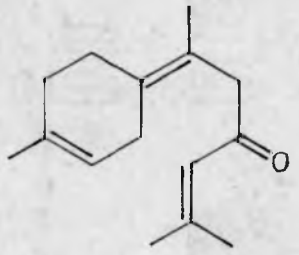
* Specifications for the oil of Himalayan Cedar wood I.S. 1615 - 1960.

fraction, for which he could not prepare a solid derivative. He could, however, isolate from the oil, hexoic, heptoic and stearic acids by hydrolysis.

In 1922, Simonsen and Rau[4] confirmed the main work of Roberts. They did not find any phenol in the oil, but reported the presence of a viscid yellow sesquiterpene alcohol and some esters of fatty acids. In 1934, Pfau and Plattner[5] examined a sample of the essential oil from the wood of the Himalayan Deodar and found that the higher boiling fraction of the oil also contained two isomeric ketones, namely ∝- and β- atlantones (1 and 2 respectively).



(1)



(2)

In 1944, Ruzicka and co-workers[6] isolated a hydrocarbon fraction from the leaf oil of Cedrus atlantica, which formed an optically active crystalline dihydrochloride and monohydrochloride.

Work of Krishna Rao and Sukh Dev:

In 1952, Krishna Rao and Sukh Dev[7] examined the oil more systematically.

They obtained the Deodar wood from Kangra in East Punjab and on steam distillation of the chipped wood, obtained the volatile oil in a yield of 10 - 11%. The oil was coloured yellow

and had the characteristic odour of the wood.

On careful fractionation of the oil through a packed column, five major fractions were collected. The first fraction contained a small percentage of alkali soluble portion (0.022%; benzoate, m.p. 74 - 75°C, copper salt, m.p. 132°C) but its identity was not proved due to lack of sufficient quantity of material. The bulk of fractions I and II was identified as a mixture of p-methyl acetophenone and p-methyl tetrahydro-Δ^3-acetophenone. The presence of p-methyl tetrahydro-Δ^3-acetophenone was confirmed by the oxidative regeneration of acetophenone from its semicarbazone by treatment with sulphuric acid (75%). The major portion of the oil (Fractions III and IV) was shown to consist of sesquiterpenes, named by these authors as α-himachalene (levo-rotatory) and β-himachalene (dextro-rotatory). Both these hydrocarbons yielded the same crystalline dihydrochloride with same melting point as that of Ruzicka's compound[6]. Himachalene dihydrochloride could be readily converted into a monohydrochloride having a melting point same as that reported by Ruzicka. However himachalene derivatives were found to be optically inactive. The last fraction was shown to consist essentially of a tertiary alcohol, termed, himachalol; traces of the atlantones were also identified in this fraction. The relationship of himachalol to the himachalenes was established by the preparation of the same dihydrochloride.

HIMACHALENES

Preliminary investigation by Krishna Rao and Sukh Dev on himachalenes had indicated that these hydrocarbons represent a new type in sesquiterpenes and the present work was undertaken to throw further light on the problem.

The essential oil obtained earlier by Krishna Rao and Sukh Dev was available for further investigation. On careful fractionation under reduced pressure, the oil yielded 15% of α-himachalene, and 45% of β-himachalene. The essential oil was cut into 35 fractions, the optical rotation and boiling point of each fraction being determined and those having identical properties being mixed up. A typical fractionation data is given in Table II (graphically represented in Fig.I).

In order to further purify these hydrocarbons, the respective α- and β- himachalene fractions (vide experimental) were again subjected to precise refractionation at a high reflux ratio, the optical rotation of each fraction being determined to gauge the course of the fractionation. The cuts with almost identical properties were mixed up.

The purity of these hydrocarbons was further checked by gas-liquid chromatography (GLC) and found to give a single peak under a variety of experimental conditions.

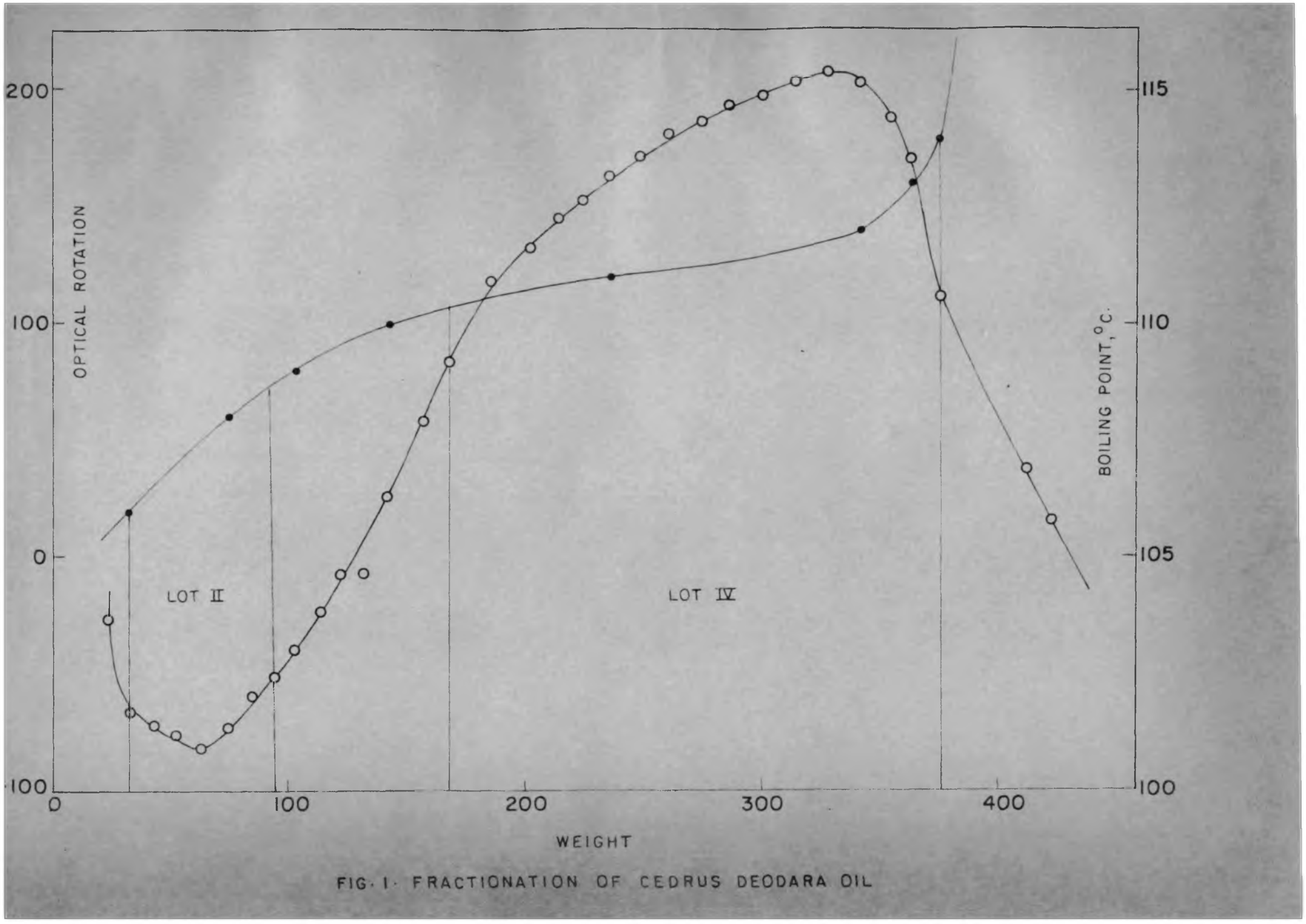


FIG. 1. FRACTIONATION OF CEDRUS DEODARA OIL

EXPERIMENTAL

Fractionation of the essential oil:

Cedrus deodara oil (1760 gms) was fractionated carefully through a glass-helics packed column*, carrying a total-condensation type still-head. A reflux ratio of 1 : 15 was maintained. The course of fractionation was followed by determining the optical rotation of each cut. Cuts having almost same physical properties were mixed up and thus finally five fractions resulted (vide Table II). Given in Table II are the fractionation data for a typical experiment.

TABLE II

Fractionation of Cedrus deodara oil

Fraction No.	Wt. (g)	b.p.**/mm	$[\alpha]_D$	Remarks.
1	22.75	85/5 - 106.5/5	-26.5°	Lot I, lower terpenes.
2	9.37	106/4	-67	

.....contd.

*Supplied by Emil Greiner and Co., New York; the estimated number of theoretical plates under the above working conditions is thirty.

**Here the boiling points are somewhat lower ($\sim 8^{\circ}$) than those actually determined in the conventional apparatus for vacuum distillation, apparently because the location of the manometer in Emil Greiner assembly is such that the pressure recorded is nearer to the correct values.

TABLE II - continued.

Fraction No.	Wt. (g.)	b.p./mm	$[\alpha]_D$	Remarks.
3	10.08	110/5	-71.8	
4	8.65	108 - 109/5	-75.6	lot II mainly ∝-himachalene.
5	10.89	109/4	-81.6	
6	12.35	107 - 108/4	-72.8	
7	10.34	106/3	-59.4	
8	9.01	109/4	-52.1	
9	9.25	105/3	-40.0	
10	10.25	105/3	-24.32	
11	9.47	106/3	-8.46	
12	9.26	106.5/4	-7.16	lot III mixture of ∝- and β-himachalenes.
13	10.22	110/4	+25.5	
14	15.54	112 - 112.5/4	+58.68	
15	9.82	112 - 114/4	+92.74	
16	17.79	112 - 114/4	+118.54	
17	8.81	110/3	-	
18	9.26	113/4	+133.52	
19	10.17	113/4	+144.9	lot IV, mainly β-himachalene.
20	10.8	111 - 112/4	+151.8	
21	11.18	111/4	+162.8	
22	12.29	110/3.5	+170.8	
23	12.52	110/3.5	+179.9	
24	13.93	110/4	+186.8	
25	12.55	110/4	+192.8	

TABLE II - continued.

Fraction No.	Wt. (g.)	b.p./mm	$[\alpha]_D$	Remarks.
26	13.65	113 - 113.5/4	197.1	lot IV mainly β-himachalene.
27	13.62	113/4	+202.7	
28	13.58	111/4	+207.8	
29	13.46	112/4	+202.8	
30	13.1	112 - 113/4	+188.2	
31	9.07	113/4	+170	
32	11.84	112/3.5 - 113/3	+112.7	
33	36.67	113 - 136/3	+37.9	lot V, mainly himachalol.
34	11.45	134 - 141/3	+16.3	

Residue 28 gms.

Cuts (2 to 8) having a maximum negative rotation were mixed and were refractionated for α-himachalene. Similarly lot number IV (fractions 16 - 33) having maximum positive rotation was mixed and refractionated for pure β-himachalene.

α-Himachalene:

The α-himachalene fraction (lot No.II, 256 g.) was refractionated through the same column maintaining a higher reflux ratio (1 : 22).

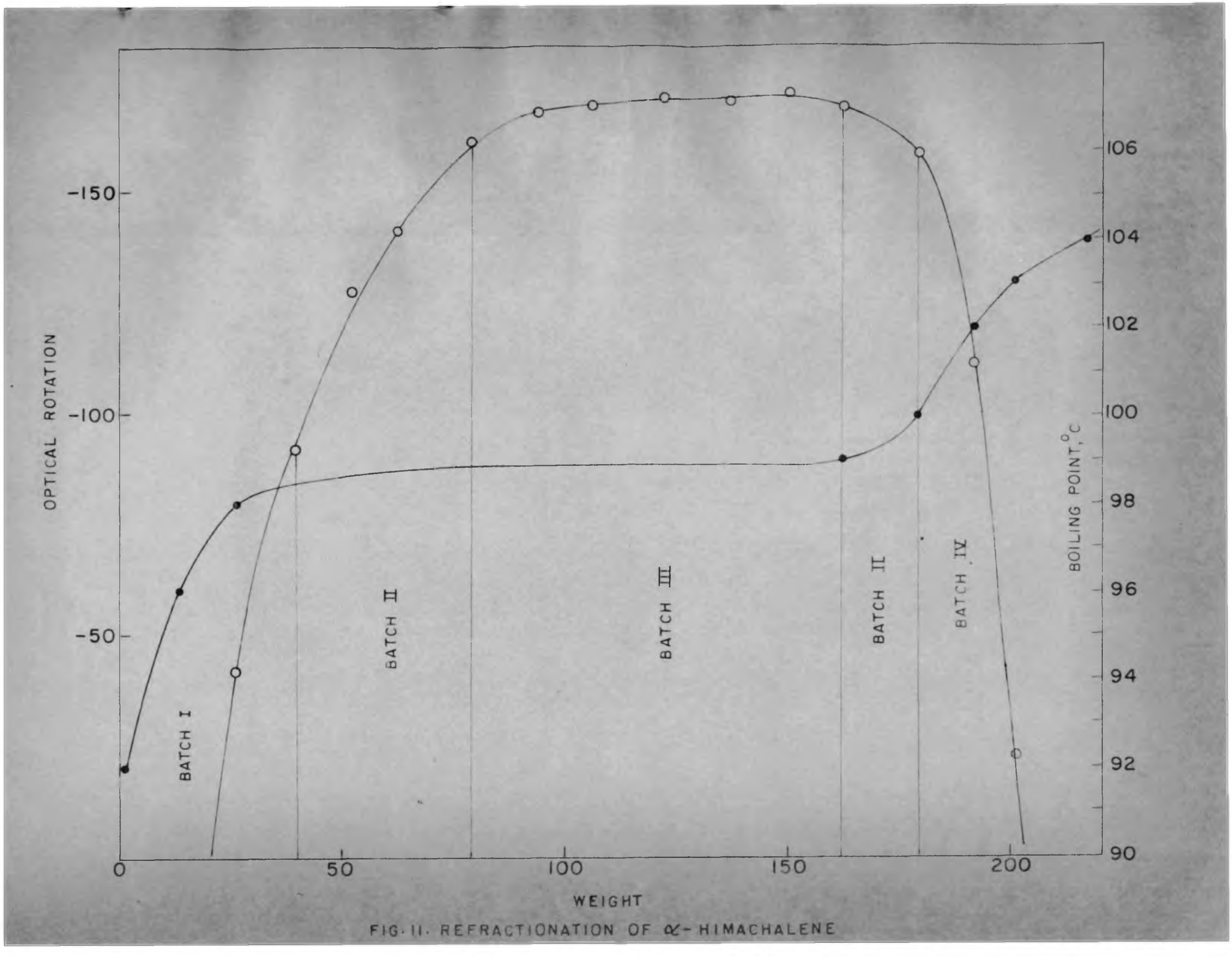


FIG. II. REFRACTIONATION OF α- HIMACHALENE

TABLE III

Refractionation of ∝-himachalene

Fraction No.	Wt.(g.)	b.p./mm	$[\alpha]_D$
1	0.77	92/5	-
2	12.69	93 - 96/5	+30.8
3	12.6	96.5 - 98/5	-42.1
4	13.3	97 - 98/4	-92.1
5	12.05	99/5	-128.1
6	10.75	100/5	-141.3
7	15.25	100/4.5	-161.8
8	3.13	98/4	
9	12.00	98/4	-168.5
10	11.81	99/4.5	-170.0
11	16.40	100/5.5	-171.85
12	1.67	99/5	
13	13.53	99/5	-171.3
14	12.96	99/5	-172.9
15	12.18	98/5	-170
16	16.84	99 - 100/5	-159.8
17	12.42	100 - 102/5	-112.1
18	9.77	102 - 103/5	-23
19	15.42	103 - 104/5	+44.5
20	16.06	104 - 105/5	+123.4
21	13.47	105 - 106/5	+206.5

The fractions having almost identical properties were mixed up to get four batches of ∝-himachalene with different grades of purity (see Fig.II). They were distilled over sodium and stored in dark bottles in a refrigerator. Batch No.III, after distillation over sodium represents the purest ∝-himachalene and its properties are recorded in Table IV. It is a colourless, mobile liquid with a pronounced odour of the wood. [Found: C, 88.22; H, 11.77; $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%].

TABLE IV

Physical properties of himachalenes

Properties	∝-himachalene	β-himachalene
b.p.	93.5°C/2 mm	121 - 122°C/4 mm
Density	d_4^{25} 0.9206	d_4^{25} 0.9330
Refractive index	n_D^{25} 1.50825	n_D^{25} 1.5130
Optical rotation (pure liquid).	$[\alpha]_D^{25}$ -172.7°	$[\alpha]_D^{25}$ +225.8
Optical rotation (in chloroform)	$[\alpha]_D^{27}$ -192.3° (conc. 4.162%)	$[\alpha]_D^{25}$ +224.7 (4.76%)
Molar refractivity	65.85	65.71

β-Himachalene:

The β-himachalene fractions[(lot No.IV) 782 g.] was subjected to precise refractionation exactly as was done for the ∝-isomer.

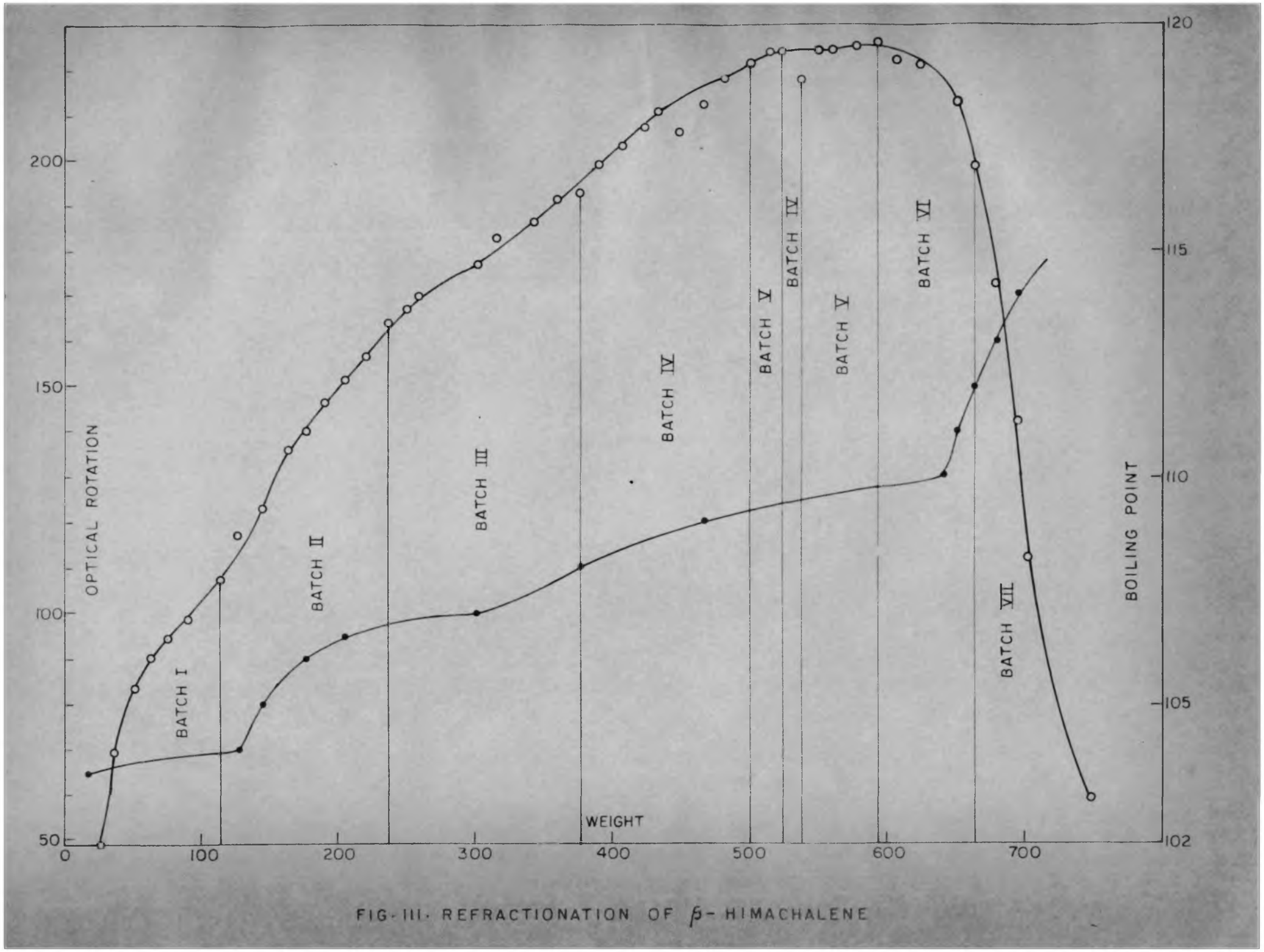


FIG-III. REFRACTIONATION OF β-HIMACHALENE

TABLE V

Refractionation of β-himachalene

Fraction No.	Wt.(g)	b.p./mm	$[\alpha]_D$
1	5.9	100 - 101.5/4	
2	11.66	103.5/4	+25.5
3	8.5	103.5/4	+49
4	12.47	103.5/4 - 104/3.5	+69.5
5	13.33	104/3.5	+83.4
6	10.15	104/3.5	+90
7	12.02	103/3.5	+94.4
8	16.1	103/3.5 - 103.5/3.5	+98.6
9	11.62	103/3.5	+96.7
10	12.15	104/4	+107.2
11	12.44	104/4	+117.1
12	16.57	105/4	+123.2
13	2.65		
14	16.82	104/3.5	+136.4
15	13.92	106/3.5	+140.2
16	14.85	106/3.5	+146.5
17	13.74	106.5/4	+151.4
18	15.55	106.5/4	+156.6
19	15.98	105/3.5	+164.4
20	13.05	105/3	+167.1

.....contd.

Fraction No.	Wt.(g)	b.p./mm	$[\alpha]_D$
21	8.55	105/3	+169.9
22	14.38	107/3.5	+162.5
23	14.15	"	+166
24	16.05	"	+176.7
25	18.36	"	+182.2
26	14.25	"	+181.6
27	13.49	"	+186.4
28	16.53	"	+191.6
29	15.05	108/3.5	+192.7
30	16.00	"	+198.9
31	15.76	"	+203.0
32	16.13	"	+207.3
33	11.2	"	+210.7
34	15	"	+205.7
35	17.45	109/3.5	+211.8
36	17.3	"	+217.86
37	16.7	"	+221.4
38	14.85	"	+224
39	8.27	"	+223.8
40	14.55	"	+217
41	13.55	"	+224
42	10.5	107/3.5	+224.4
43	16.20	"	+225.2

.....contd.

Fraction No.	Wt.(g)	b.p./mm	$[\alpha]_D$
44	14.77	108/4	+225.8
45	14.87	"	+221.8
46	16.65	109/4	+221
47	15.95	"	+218.5
48	9.53	111/4	+212.8
49	14.37	112/4	+199.2
50	15.9	113/4	+173
51	15.05	"	+142.4
52	6.35	114/4	+112.4
53 (Residue)	47	103 - 125/1	+59.4

The fractions having almost identical properties were mixed up to get seven batches of β-himachalene with different grades of purity (see Fig.III). They were distilled over sodium and stored in dark bottles at ~ 5°C. Batch No.V, after distillation over sodium represents the purest β-himachalene and its properties are recorded in Table IV. It is a colourless mobile liquid, with an odour very similar to that of the α-isomer. [Found: C, 88.20; H, 11.79; $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%].

Gas-Liquid Chromatography

Gas-liquid chromatography of the sesquiterpenes was carried out on a Perkin-Elmer Vapour Fractometer Model 154-D using different types of columns namely column K (polyethyleneglycol on diatomaceous earth), column P (succinic polyester of diethyleneglycol on celite) and column SDW (succinic polyester of diethyleneglycol on Chromosorb W). Hydrogen was used as the carrier gas. A typical analysis along with experimental conditions is shown in Figs. IV and V.

SUMMARY

Pure α- and β-himachalenes were isolated by careful fractionation of the essential oil of Himalayan deodar wood.

GAS-LIQUID CHROMATOGRAM

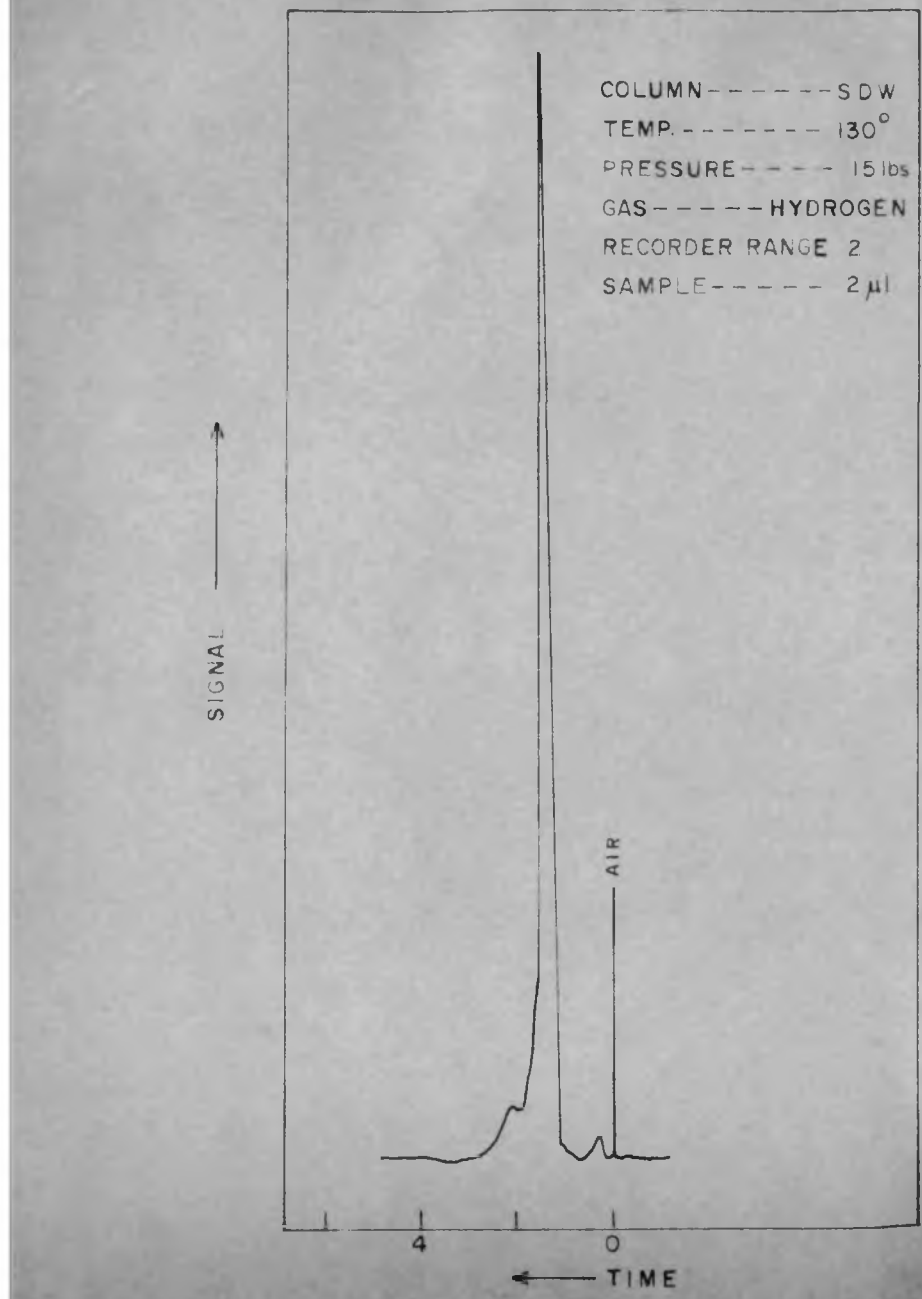


FIG IV α-HIMACHALENE

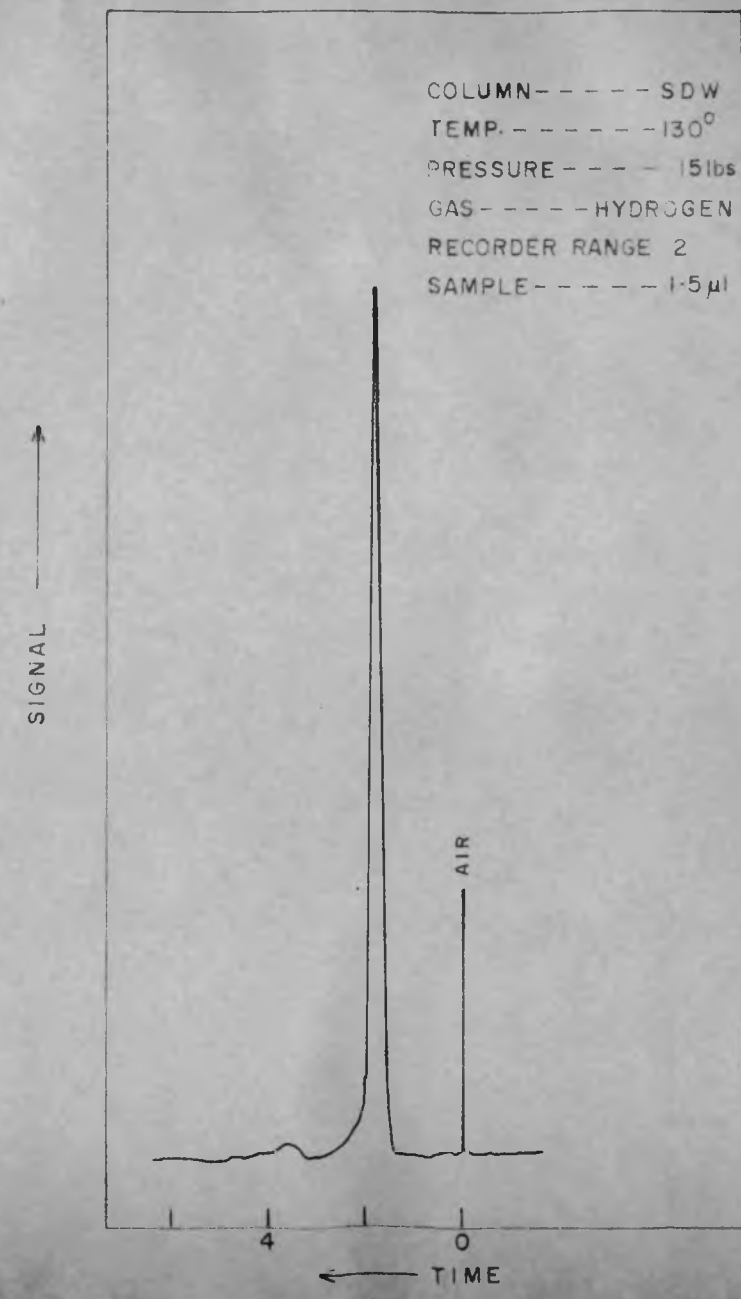


FIG V β-HIMACHALENE

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CHAPTER III

DETERMINATION OF THE STRUCTURE OF HIMACHALENES

The essential oil from Himalayan deodar (Cedrus deodara, Loud) is known[1] to contain two new sesquiterpenoid hydrocarbons, namely α- and β-himachalenes. From preliminary work reported earlier, it was suggested that these closely related hydrocarbons represent a new type in sesquiterpenoids, and the present work which describes the structure elucidation of these compounds,[2] confirms our previous contention.

By the application of gas-liquid chromatography (GLC) it was found that the previously reported hydrocarbons were somewhat contaminated with each other. Table I records the physico-chemical characteristics of thoroughly purified samples.

Table I. Physico-chemical characteristics of α- and β-himachalenes.

	b.p./mm	n_D^{25}	d_4^{25}	M_D	$[\alpha]_D$
α-Himachalene	93-4°/2	1.5082	0.9206	65.85	-192.3°
β-Himachalene	121-2°/4	1.5130	0.9330	65.71	+224.7°

Relationship of α- and β-himachalenes

Both hydrocarbons analysed for $C_{15}H_{24}$ and their molecular refractivity (Table I) suggested these to be bicyclic containing two ethylenic linkages. Though the observed molecular refractivity is lower than the calculated

value (66.13), their bicyclic nature was confirmed by estimating the number of olefinic linkages. Both quantitative catalytic hydrogenation and percamphoric acid epoxidation revealed the presence of two double bonds in each of the hydrocarbons.

Both the hydrocarbons on treatment with gaseous hydrogen chloride in acetic acid yielded the same crystalline dihydrochloride (m.p. 118-119°C), which readily passed into a monohydrochloride (m.p. 51-52°C) on mere recrystallization from methanol. This instability of the dihydrochloride was reflected in the measurements of optical rotation which is clearly dependent on time, and the true value of optical rotation of the hydrochloride could be obtained only by extrapolation to zero time (Fig.I).

The infra-red spectra of tetrahydro-α- and tetrahydro-β-himachalenes(Fig.II), though quite similar, showed significant differences in the intensities of several bands in the fingerprint region. This is readily explainable on the basis of formation of differing amounts of stereo-isomers during hydrogenation. The GLC of the products (Figs.III and IV) disclosed in each case atleast two components; the component with lower retention time being present to the extent of 66% in the case of α-isomer and 15% in the β-isomer. The infrared spectra and physical constants differed from those recorded for several known perhydro bicyclic sesquiterpene systems [3,4] and thus himachalenes belong to a newer type. It is also

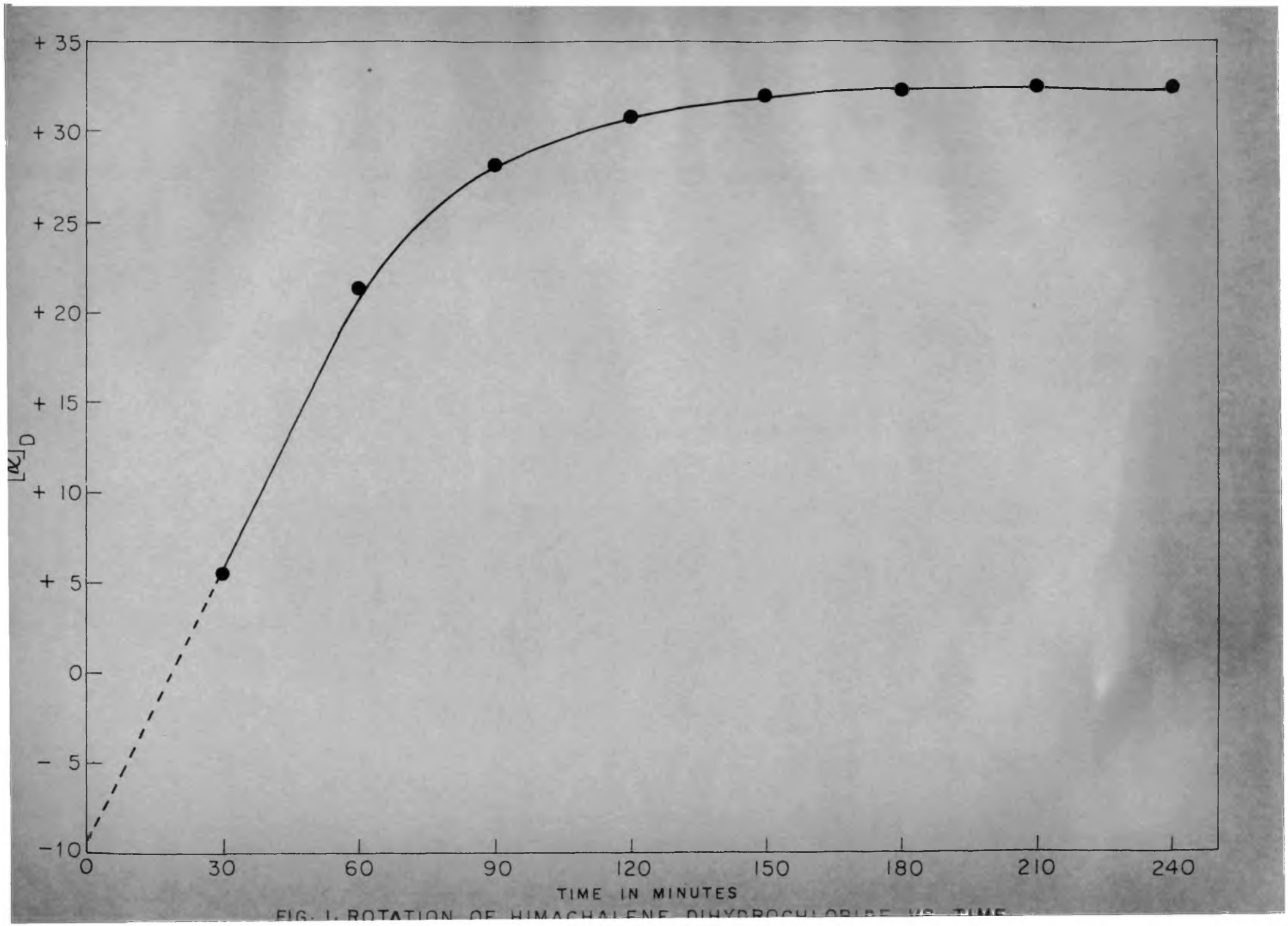

FIG. I. ROTATION OF HIMACHALENE DIHYDROCHLORIDE VS. TIME

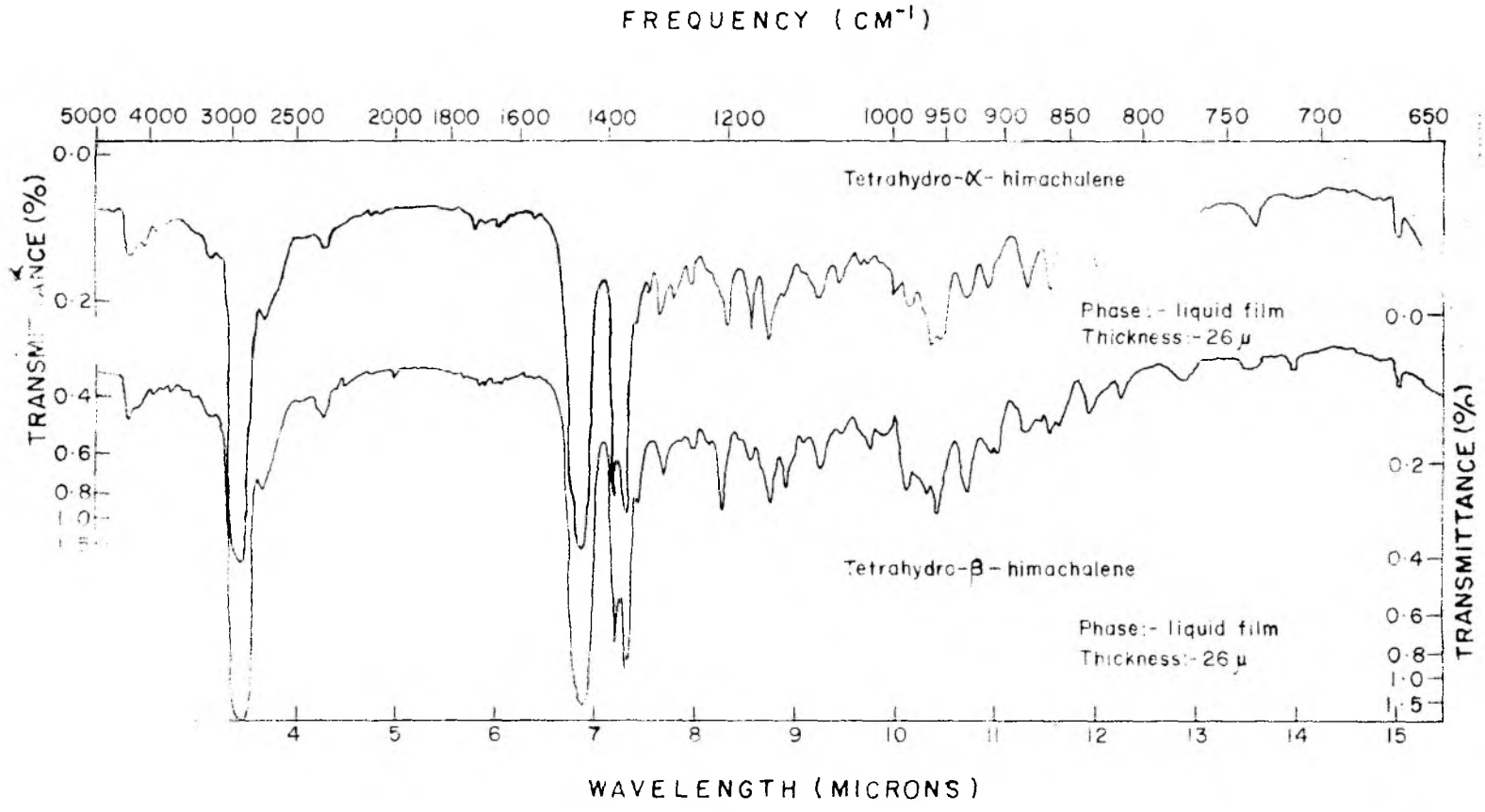

FIG. II. IR SPECTRA OF TETRAHYDROHIMACHALENES

GAS – LIQUID CHROMATOGRAM

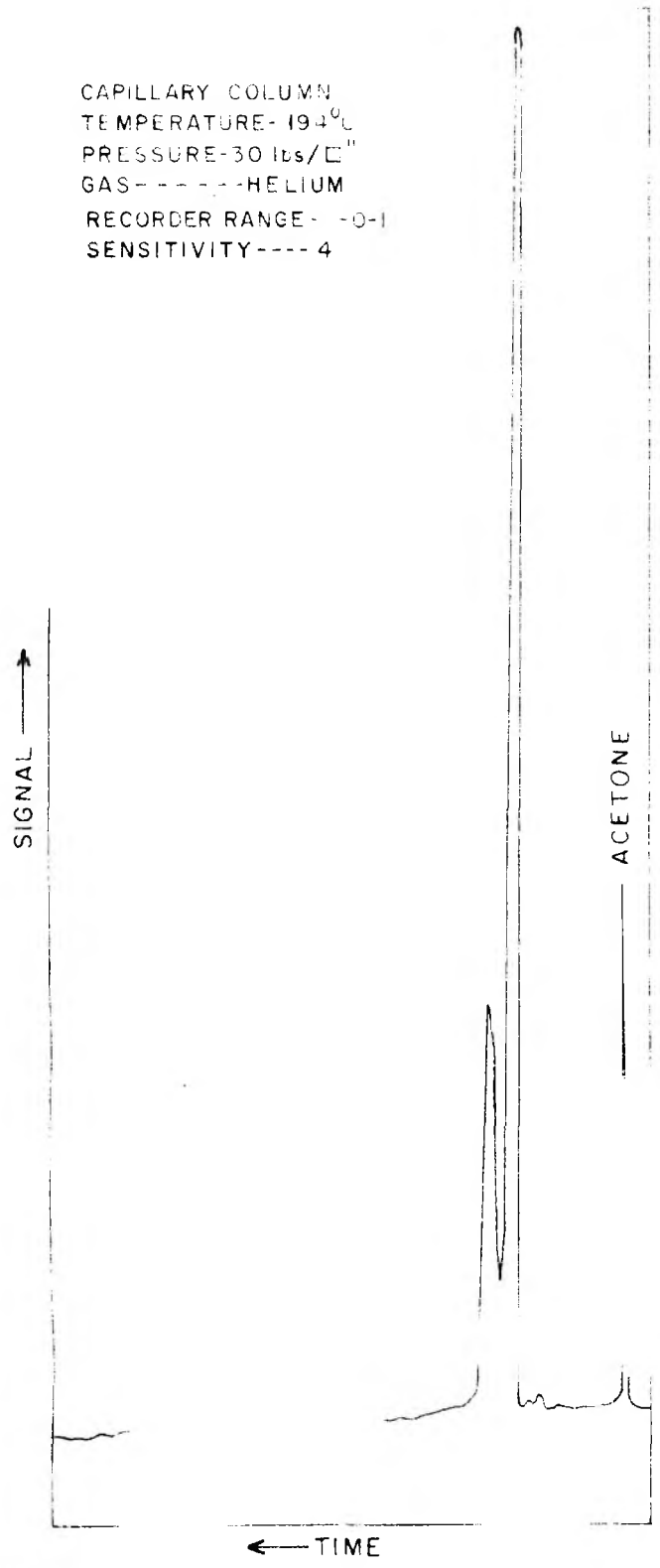

FIG. III. TETRAHYDRO-α- HIMACHALENE

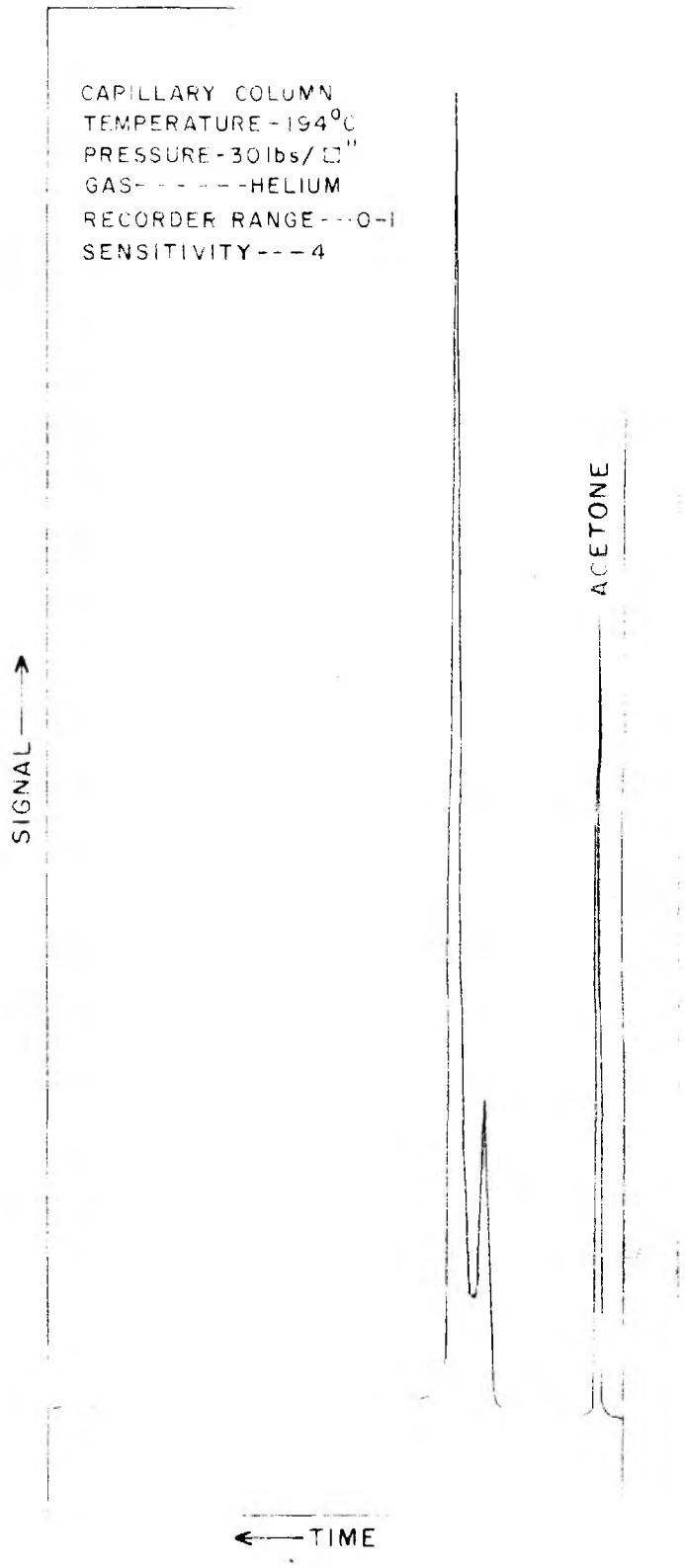

FIG. IV. TETRAHYDRO-β- HIMACHALENE

clear from the above that ∝- and β-himachalenes differ from each other only in the position of an ethylenic linkage(s).

Structural features

In the infrared (Fig.V) ∝-himachalene displayed bands assignable to >C = CH_2 (3060, 1770, 1625, 885 cm^{-1}) and >C = C<$_H$ (1665, 865* cm^{-1}). These assignments were fully

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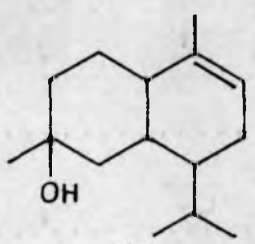
*Though the spectrum of ∝-himachalene shows a band at 820 cm^{-1}, which is well within the range for out-of-plane bending of a trisubstituted ethylenic linkage (800-840 cm^{-1})[5], it has not been assigned to this mode of vibration because in β-himachalene which also contains the same linkage (vide subsequent discussion) this absorption is very much reduced while the absorption at 858 cm^{-1} is quite strong. Moreover dihydro-∝-himachalene in which the asymmetric disubstituted double bond has been reduced but which still contains the trisubstituted double bond,a peak can be observed only at 862 cm^{-1}.

From the present work which unequivocally establishes the structure of himachalenes, it becomes clear that in these compounds the out-of-plane bending vibration of the hydrogen on a trisubstituted double bond lies at abnormally at higher frequencies. Another similar case[6] reported is that of δ-cadinol (i) where the band occurs at 873 cm^{-1}.



(i)

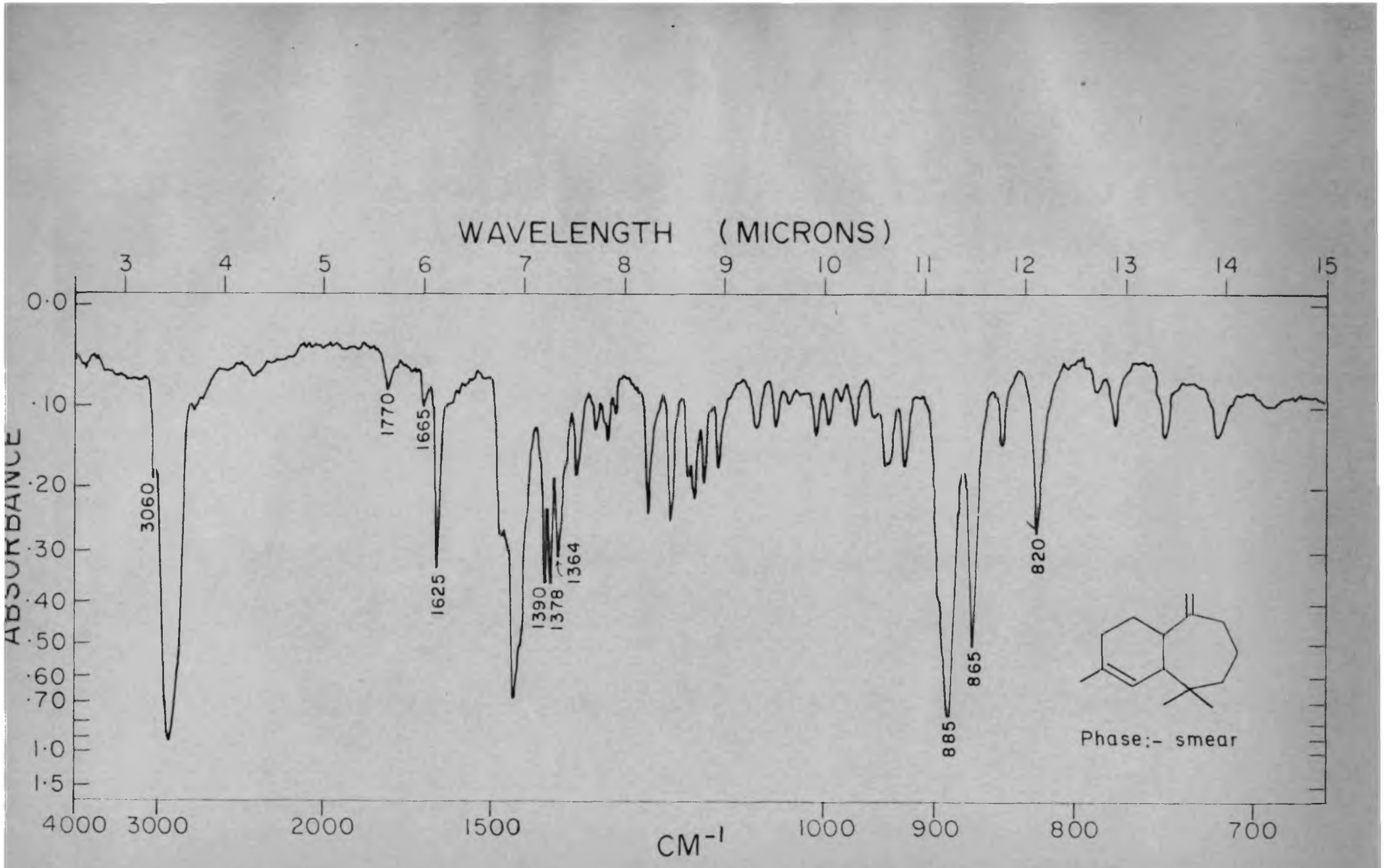


FIG. V. IR SPECTRUM OF α-HIMACHALENE

supported by the NMR spectra of ∝-himachalene (Fig.VI) and dihydro-∝-himachalene (Fig.VII; readily obtainable by hydrogenation in ethanolic solution). On the lower field-strength side, ∝-himachalene showed a peak (2H, almost a singlet) at 283 cps and another at 322 cps (1H, broad singlet) assignable[7] to protons on an asymmetric disubstituted double bond and a trisubstituted ethylenic linkage respectively. In accordance with these assignments dihydro-∝-himachalene showed absorption only for a trisubstituted olefinic linkage [IR (Fig.VIII): 1657, 862 cm^{-1}; NMR (Fig.VII): 1H, broad singlet at 328 cps].

β-Himachalene showed absorption due to one trisubstituted olefinic linkage only [IR (Fig.IX): 1665, 857 cm^{-1}; NMR (Fig.X): 1H, partly split signal at 319 cps]. In view of our previous data then, the other olefinic linkage must be tetrasubstituted. However, in order to rule out the remote possibility of β-himachalene having a cyclopropane ring* rather than another olefinic linkage,

---

*This was thought desirable especially in view of higher discrepancy of molecular refractivity of β-himachalene, and also keeping in mind that the formation of dihydrochloride and tetrahydroderivative could also arise from the rupture of a three-membered ring. Peracid titration has also been found to be abnormal in some cases[8].

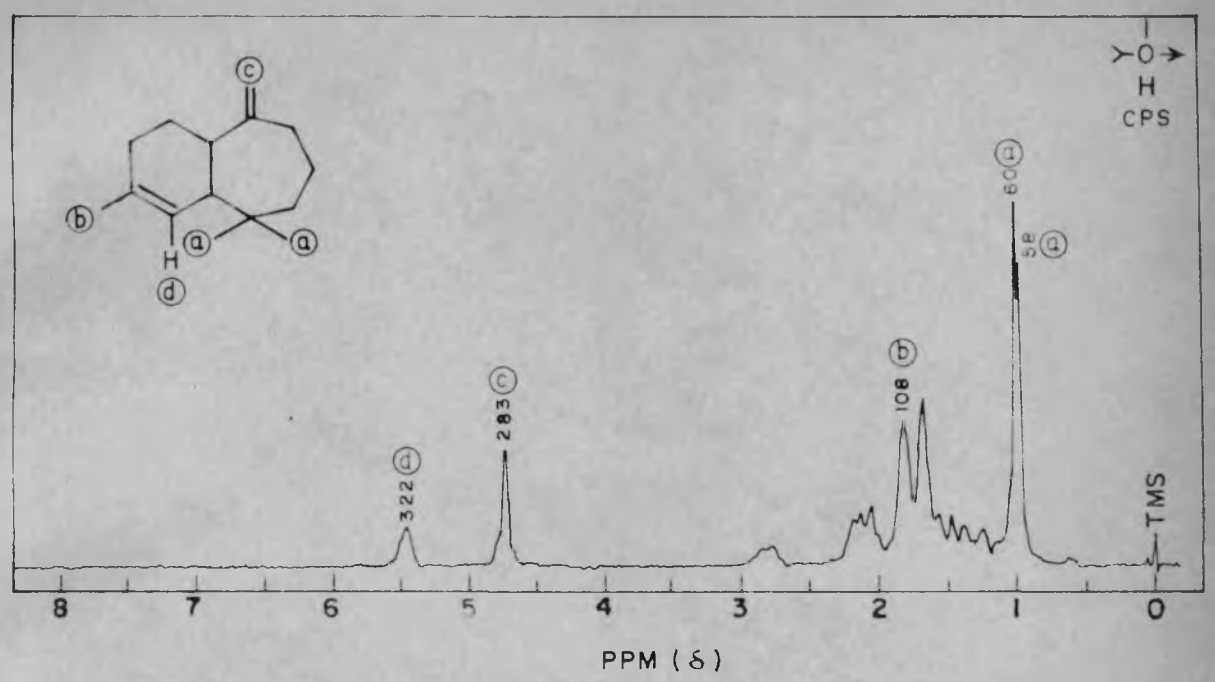


FIG. VI. NMR SPECTRUM OF α-HIMACHALENE

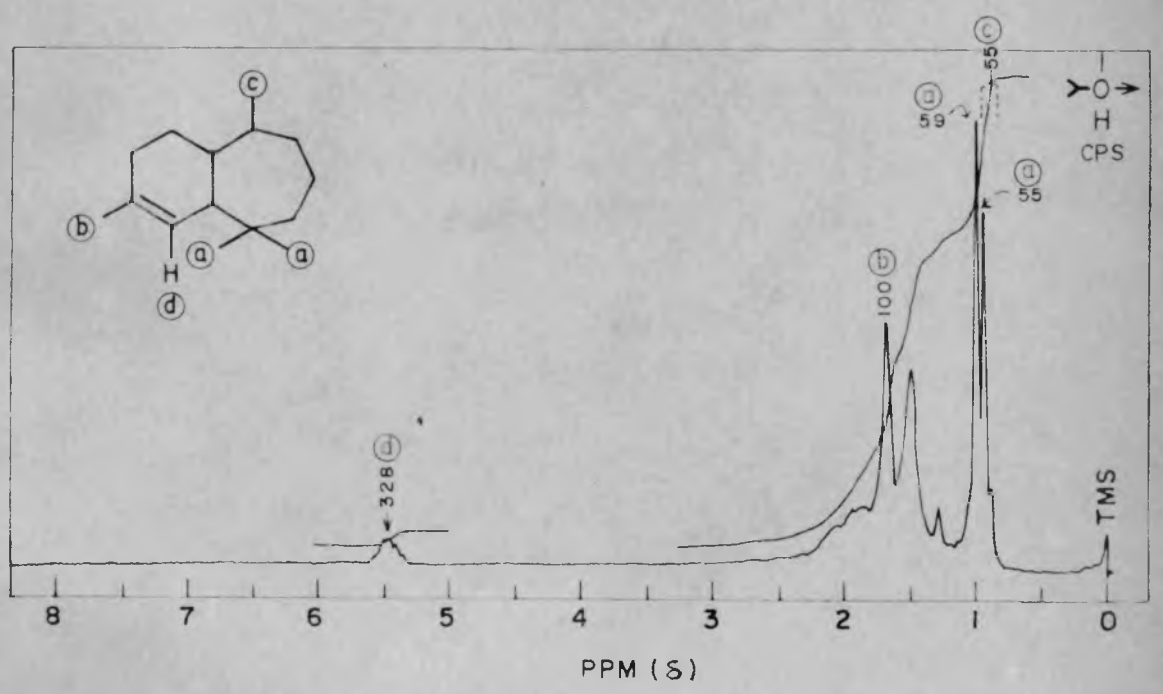
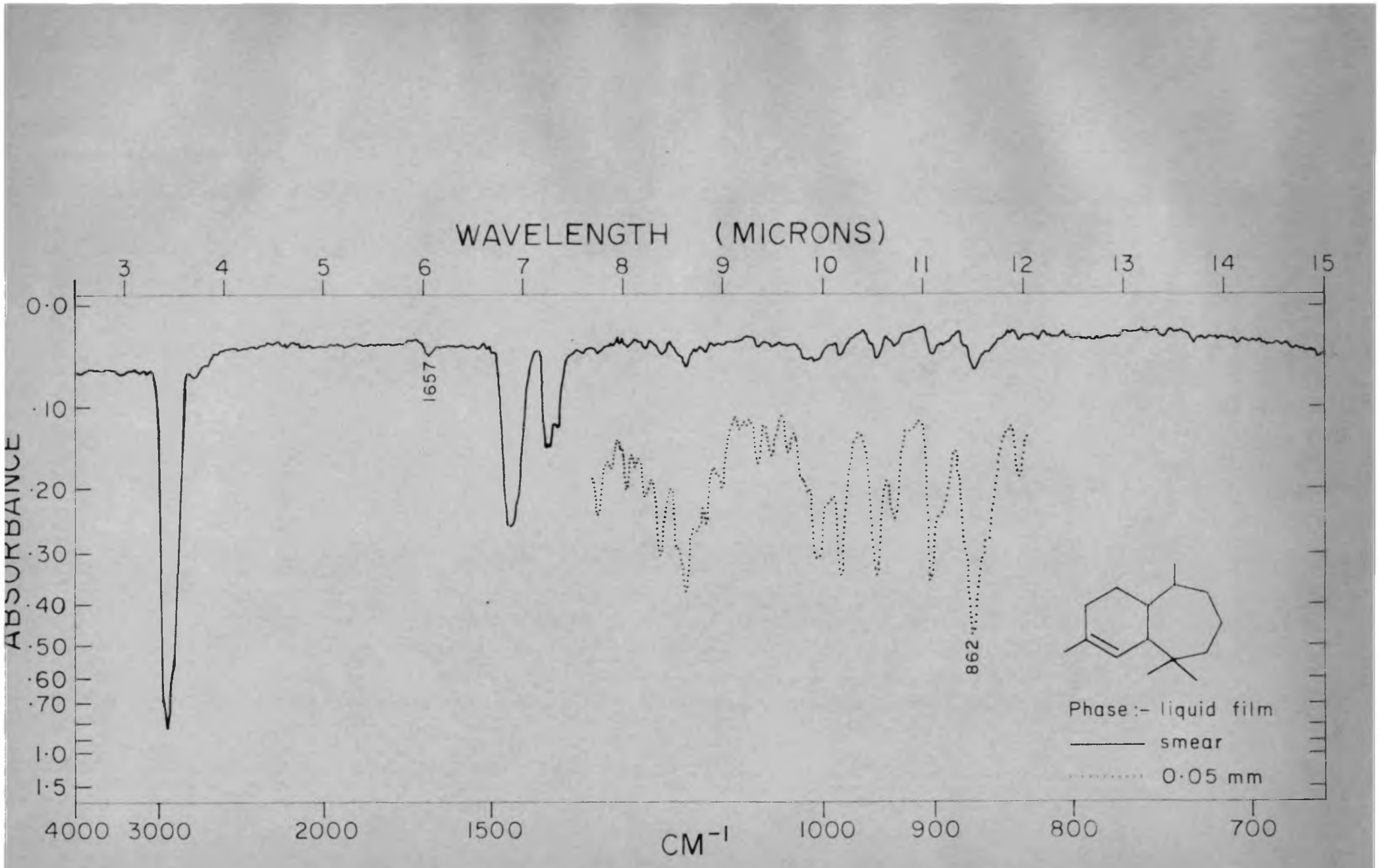


FIG. VII. NMR SPECTRUM OF DIHYDRO-α-HIMACHALENE



FIG· VIII· IR SPECTRUM OF DIHYDRO-α- HIMACHALENE

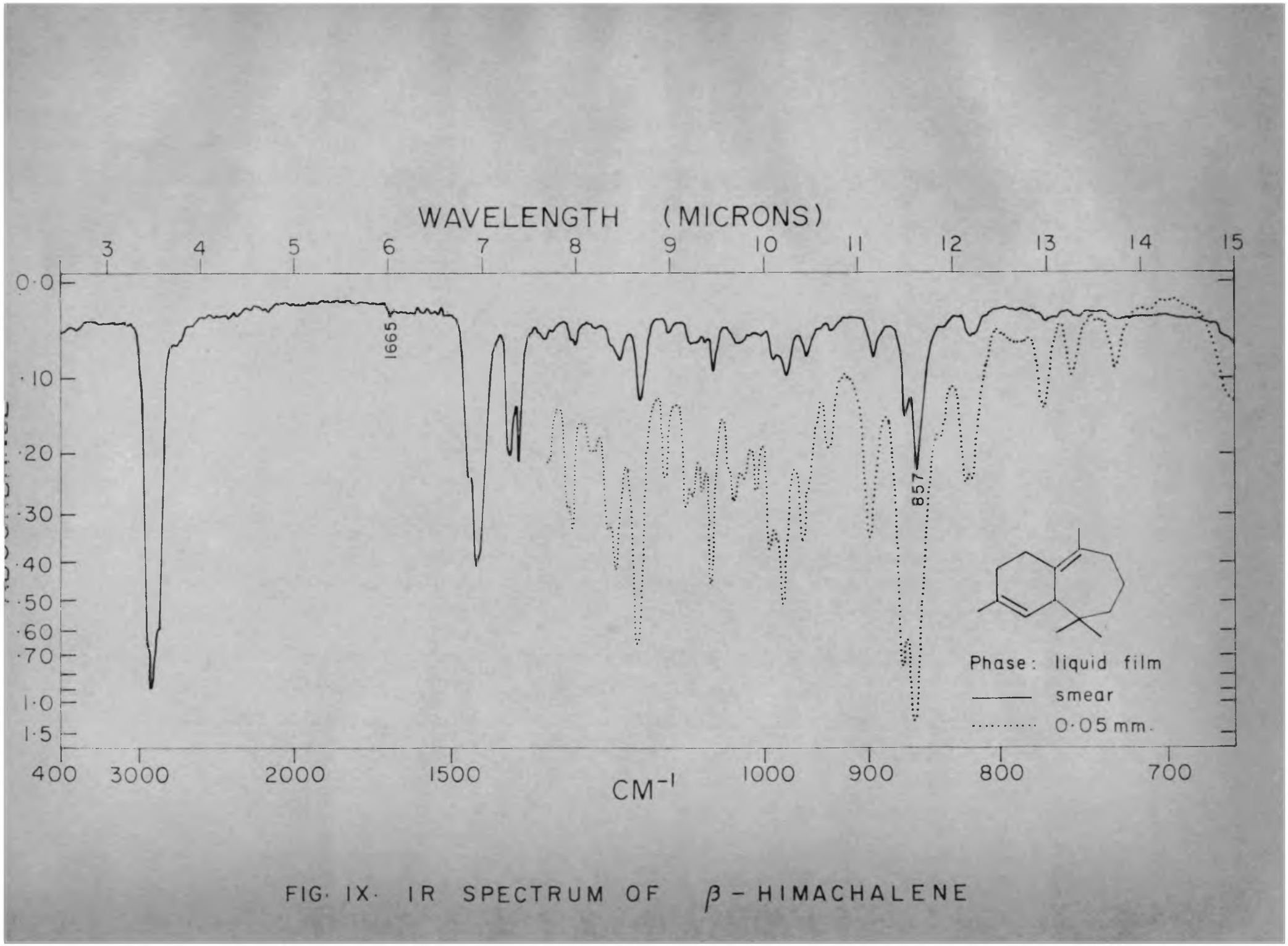


FIG. IX. IR SPECTRUM OF β-HIMACHALENE

the end-absorption[9,10,11] in the ultra-violet of ∝-himachalene, dihydro-∝-himachalene and β-himachalene have been measured and are collected in Table II along with limiting values for trisubstituted and tetrasubstituted ethylenic linkages.

Table II. End-absorption.

	ϵ_{210}	ϵ_{215}	ϵ_{220}	ϵ_{225}
∝-Himachalene	8704	3636	948.4	627.5
β-Himachalene	7836	6952	4327	2869
Dihydro-∝-himachalene	2318	1271	695	373.6
Trisubstituted double bond[9]	1400-4700	600-3500	240-1800	
Tetrasubstituted double bond[9]	4400-10000	3900-9200	3400-6700	

The NMR spectrum of ∝-himachalene (Fig.VI) clearly revealed the presence of two quaternary methyls (sharp, partly overlapping 3H signals at 58, 60 cps) and one methyl on an olefinic linkage (3H signal at 108 cps). These assignments are borne out from the NMR spectrum of dihydro-∝-himachalene [(Fig.VII), 3H signals at 55 and 59 cps; 3H doublet centered at 55 cps - mostly submerged under the quaternary methyl signal - J = 6 cps, assignable to - CH-$\underline{CH_3}$; $\underline{CH_3}$-C = C signal at 100 cps]. β-Himachalene (Fig.X) displayed signals for two quaternary methyls (44 and 58 cps) and two methyls on a

double bond (6H absorption at 104 cps).

The total number of methyl groups in himachalene were also estimated by infrared measurements[12,13,14] and the results are in accord with three methyls in α-himachalene and four in β-himachalene.

Determination of the carbon skeleton

To gain insight in the carbon frame-work of himachalenes, the dehydrogenation of these hydrocarbons was investigated. Pure α-himachalene or pure β-himachalene on selenium dehydrogenation yielded an identical reaction product (GLC). In view of this, large scale experiments were carried out on a mixture of these hydrocarbons (~1:1) which was more easily available.

Himachalenes on Se-dehydrogenation (305-310°C/48 hrs) yielded three main products in the ratio of 39(A), 28(B) and 30(C) per cent. However on sulphur dehydrogenation (210-215°/2 hrs) the product consisted essentially of A (Fig.XI, 56%) and B (33%), only traces of C (<5%) being formed. Fractional distillation of selenium dehydrogenation product yielded A and C more or less in a pure state. The first component A, was readily identified as 2-methyl-6-(ᵖ-tolyl)-heptane (1) by comparison (physical constants, UV and IR) with an authentic sample; likewise component C was easily recognised as cadalene (2). For the characterization of compound B sulphur dehydrogenation product was

GAS-LIQUID CHROMATOGRAM

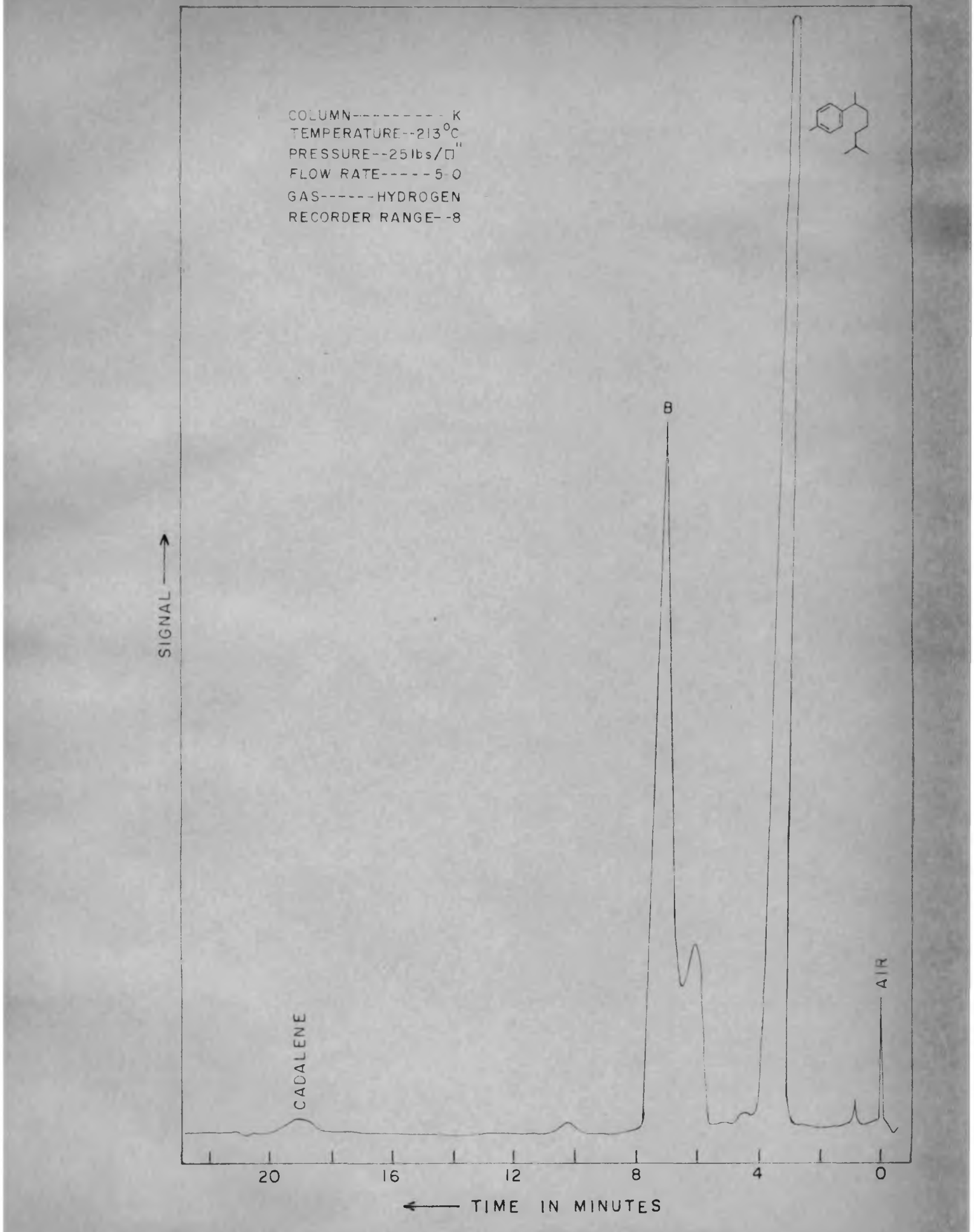
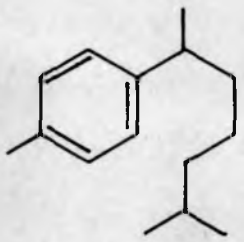
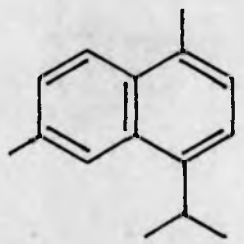


FIG. XI. PRODUCTS OF SULPHUR DEHYDROGENATION OF HIMACHALENES

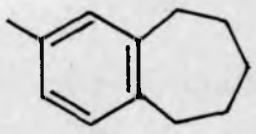


(1)



(2)

fractionated when an approximately 1:1 mixture of A and B was obtained. This on oxidation with nitric acid yielded terephthalic acid and trimellitic acid in approximately equal amounts, hence it was suspected that compound B must be a 1,2,4-trisubstituted benzene. This was clearly borne out from its infrared absorption in the 1650-1950 cm^{-1} region.[5] A comparison of this pattern (Fig.XII) with those for (1) and 2-methyl benzosuberane (3) (Fig.XII) clearly revealed that the first absorption pattern is a summation of absorption patterns due to (1) and 2-methyl benzosuberane.



(3)

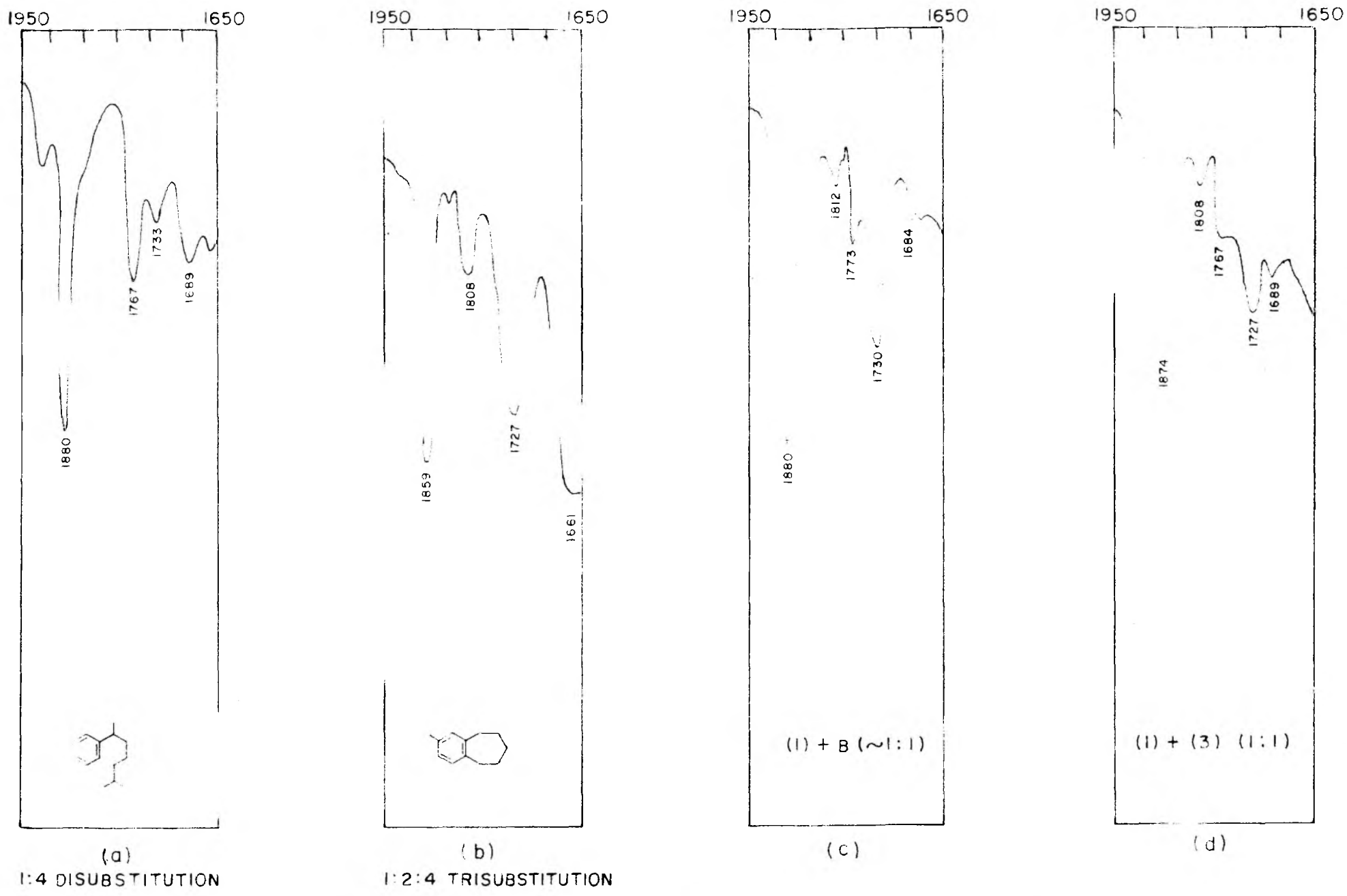


FIG. XII. AROMATIC SUBSTITUTION PATTERNS 1950-1650 CM^{-1}

From the above data it was argued that himachalenes have a carbon skeleton capable of scission* to an intermediate

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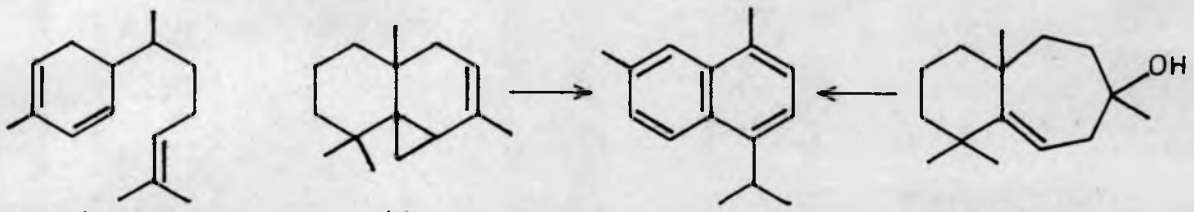
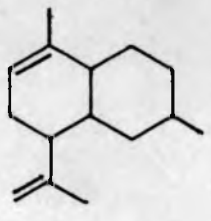
*Though cyclization of a monocyclic sesquiterpene of the type corresponding to (1), namely zingiberene (ii), to cadalene during dehydrogenation is known, the reverse case i.e. the formation of (1) from a bicyclic sesquiterpene of cadalene type, has not been reported so far[15,16,17] and appears unlikely.



(ii) (iii) (iv) (v)

In connection with the above remarks it may be noted that thujopsene[18] (iii) and widdrol[19] (v) on selenium dehydrogenation give 1,7-dimethyl-4-isopropyl naphthalene (iv).

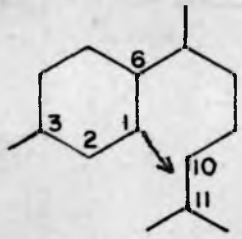
It may also be pointed out that the formation of cadalene should not be taken as an infallible proof for the carbon skeleton of a bicyclic sesquiterpenoid. It is conceivable that some sesquiterpenes might have been assigned a cadalenic structure though, in fact, they may belong to some other type. Attention is drawn in this connection to hydrocarbon (vi) which from published data[20] would appear to be a suspect.



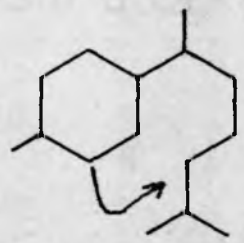
(vi)

that can, later, give rise to both 2-methyl-(6-p-tolyl)-heptane (1) and cadalene (2) and component B, may as well represent the original carbon frame-work of himachalenes.

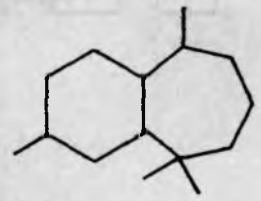
Taking into consideration the above experimental results it becomes apparent that himachalenes have a carbon-skeleton (4) with carbon 1 attached to a position on the other part of the molecule. Noting the fact that β-himachalene has a tetrasubstituted ethylenic linkage and, further, bearing in mind the nature of the methyl groups, the linkage in (4) must be between C_1 and C_{11}; structure (5) stands ruled out as it would have one terminus of the tetra-



(4)



(5)



(6)

substituted ethylenic linkage at the bridge-head and this is sterically prohibited[21]. Thus the carbon frame-work of himachalenes may be provisionally represented as (6).

In order to gain clear experimental support for the presence of a geminal dimethyl group in himachalenes, and thus adduce evidence in favour of C_1 - C_{11} linkage, nitric acid oxidation of himachalenes was investigated. The acids produced in oxidation were converted into methyl

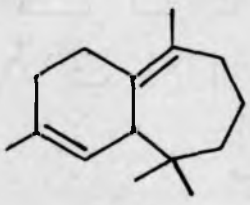
esters and their composition established by GLC (Fig.XIII). The various components were isolated by a combination of fractionation and partition chromatography and characterised by comparison with authentic samples. In this way, the products of nitric acid oxidation were established as -

dimethyl malonic acid	(4%)
α,α-dimethyl succinic acid	(20%)
α,α-dimethyl glutaric acid	(38%)
α,α-dimethyl adipic acid	(13%)
succinic acid	(25%)

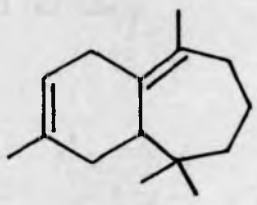
These results clearly establish the carbon frame-work of himachalenes as (6).

Structure of β-himachalene

Based on the above considerations, β-himachalene may be represented by (7) or (8). Of these structures (7) is



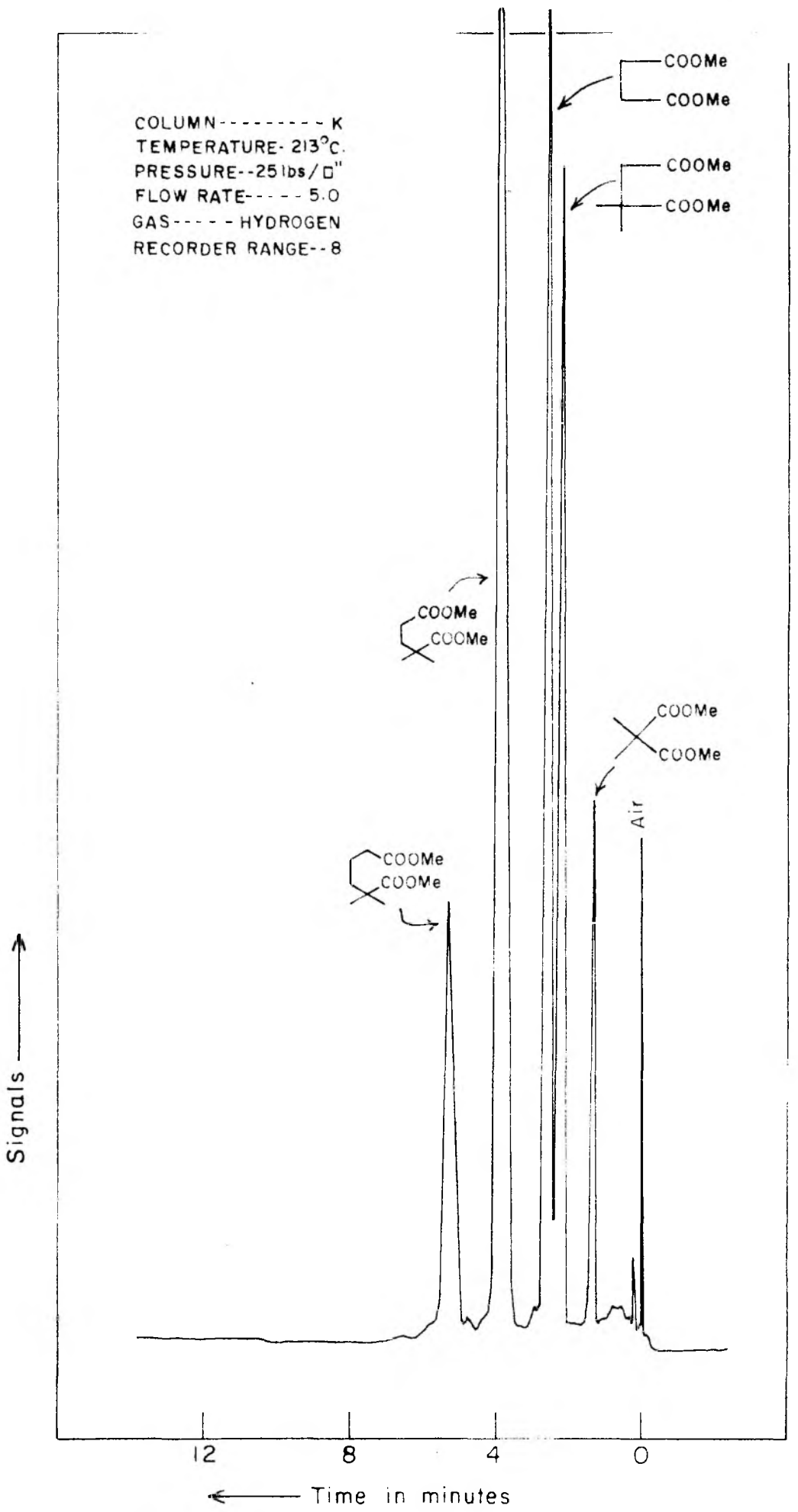
(7)



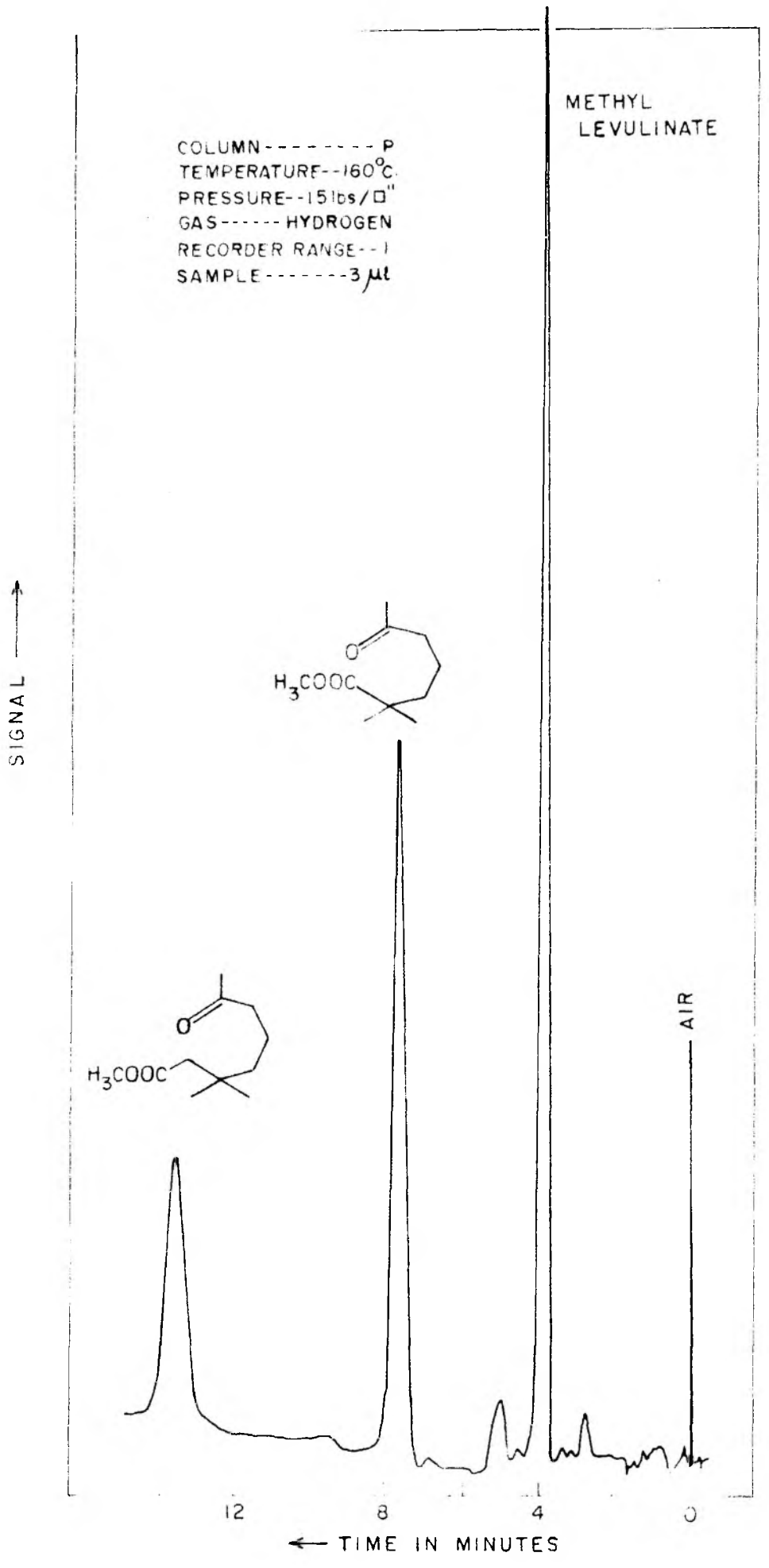
(8)

preferred because of the isolation of significant amount of succinic acid during nitric acid oxidation. Unequivocal evidence supporting the structure (7) for β-himachalene came from the results of oxidative ozonolysis. The acidic portion was esterified and its GLC (Fig.XIV) showed the presence of atleast three components in the ratio of 36, 43 and 20%. These were

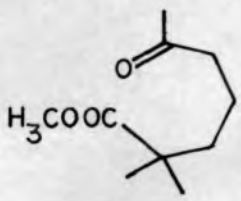
GAS-LIQUID CHROMATOGRAM



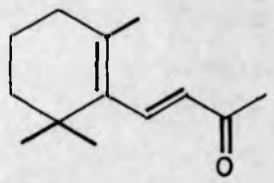
GAS-LIQUID CHROMATOGRAM



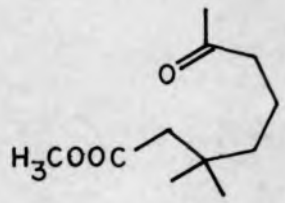
separated by fractionation and preparative GLC. The lowest boiling component (36%) was readily identified as methyl levulinate. The next component (43%) was also a keto-ester and was identified as methyl geronate (9) by comparison of its semicarbazone with that from an authentic sample [prepared from β-ionone[22](10)]. The highest boiling



(9)



(10)



(11)

component (20%) was also a methyl ketone (positive iodoform test; $\nu^{C=O}$ 1720). On mechanistic considerations (Fig.XV), this component was thought to be methyl homogeronate (11) (methyl-ε-acetyl-β,β-dimethyl caproate), a conclusion which was confirmed by comparison with authentic sample synthesised*

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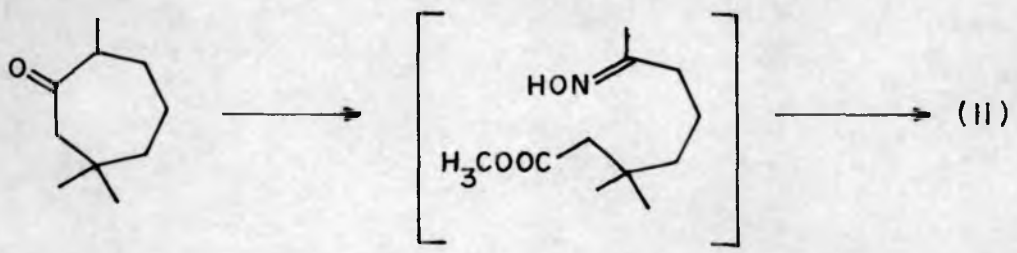
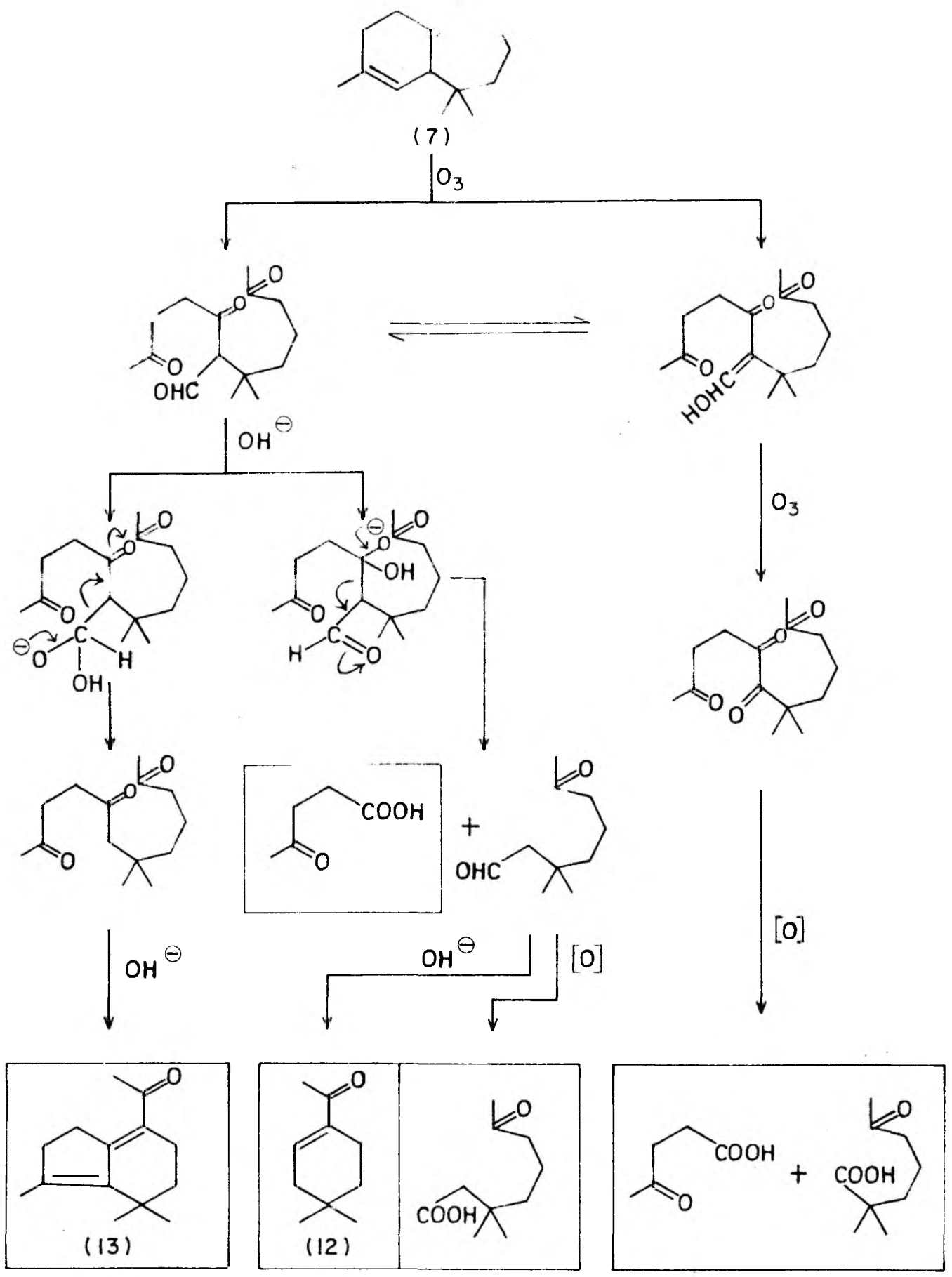
*The preparation of ε-acetyl-β,β-dimethyl caproic acid from tetrahydroeucarvone by potassium permanganate oxidation has been described by Baeyer and Villiger[23]. The following procedure proved to be far superior. Tetrahydroeucarvone (vii) was subjected to base catalysed ethylnitrite-ketone fission[24] and the intermediate oxaminoester (viii) was directly converted into methyl homogeronate (11) with formalin and hydrochloric acid.



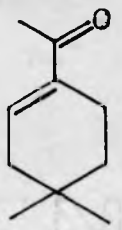
(vii) (viii)



FIG·XV OZONOLYSIS OF β-HIMACHALENE

from tetrahydroeucarvone (vii).

Since the neutral portion was bound to contain polyketones and cyclized products, it was further treated with base to isolate identifiable products. Thus after alkali treatment two pure products could be isolated. The lower boiling ketone was isolated as its semicarbazone, m.p. 215-217°, λ_{max} 257 mμ (ε 26240) and was expected on mechanistic grounds to be 1-acetyl-4,4-dimethyl cyclohexene (12). This was confirmed by comparison with an authentic sample* +.



(12)

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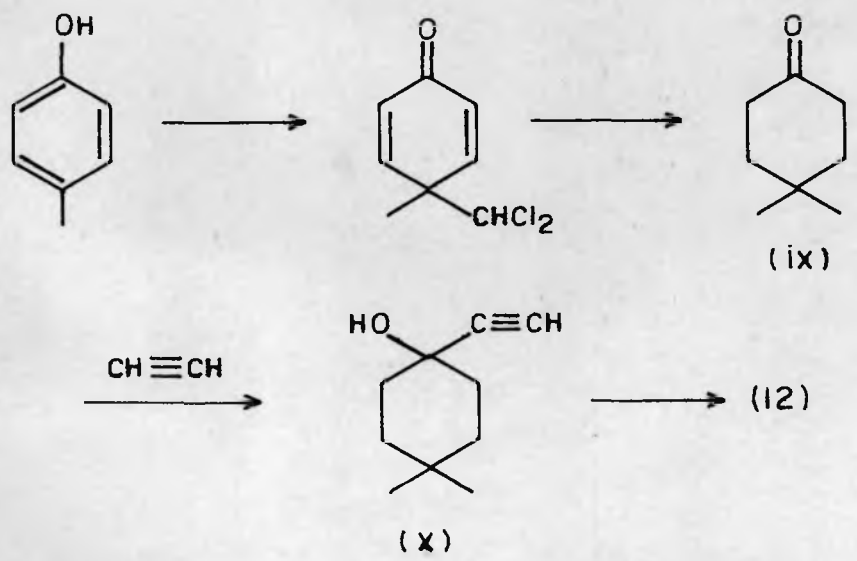
*The formation of 1-acetyl-4,4-dimethyl cyclohexene (12) was reported by Henbest[25] as a by-product of the acid catalysed cyclization of citral anil. He synthesized it starting from p-cresol via 4,4-dimethyl cyclohexanone (ix) as shown below:



The second unsaturated ketone was also isolated through its semicarbazone and this analysed for $C_{14}H_{20}O$. The UV spectrum (Fig.XVI) showed a peak at 317 mμ (ε 18,200) indicating it to be an α:β, γ: δ doubly unsaturated ketone. In the infrared (Fig. XVII), it showed bands at 1647 (C=O) and 1531 cm^{-1} (C=C)*. The NMR spectrum of this compound (Fig. XVIII) showed the presence of two quaternary methyls (6H, sharp singlet at 52 cps), one olefinic methyl and one $\underline{CH_3}$-CO (6H, singlet at 126 cps). There was no signal in the

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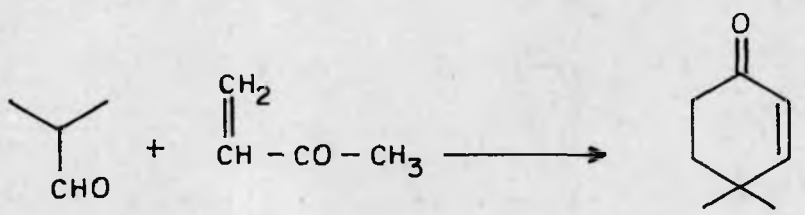
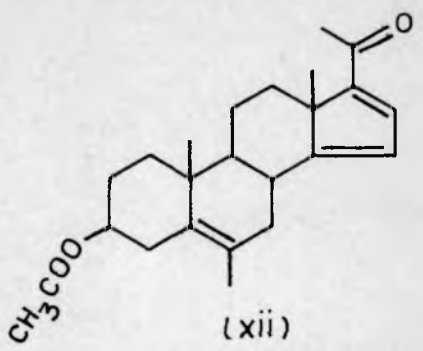
An authentic sample of (12) could be prepared according to Henbest's scheme, but in poor yields. A better procedure was as follows: Base catalysed addition of methyl vinyl ketone to isobutyraldehyde gave 4,4-dimethyl cyclohexene-2-one[26] (xi) which was quantitatively hydrogenated to (ix). Ethynylation in the presence of potassium tertiary amyloxide yielded (x) which rearranged to (12) in excellent yield by heating in aqueous acetic acid with mercury treated resin.



(xi)

+This was kindly prepared by Mr.K.C. Srivastava.

*Though this value is rather low for C=C stretching vibration, it is not considered unlikely since similar values are reported by Kirk and co-workers[27] for (xii) [$\nu^{C=C}$ 1534 cm^{-1}].



(xii)

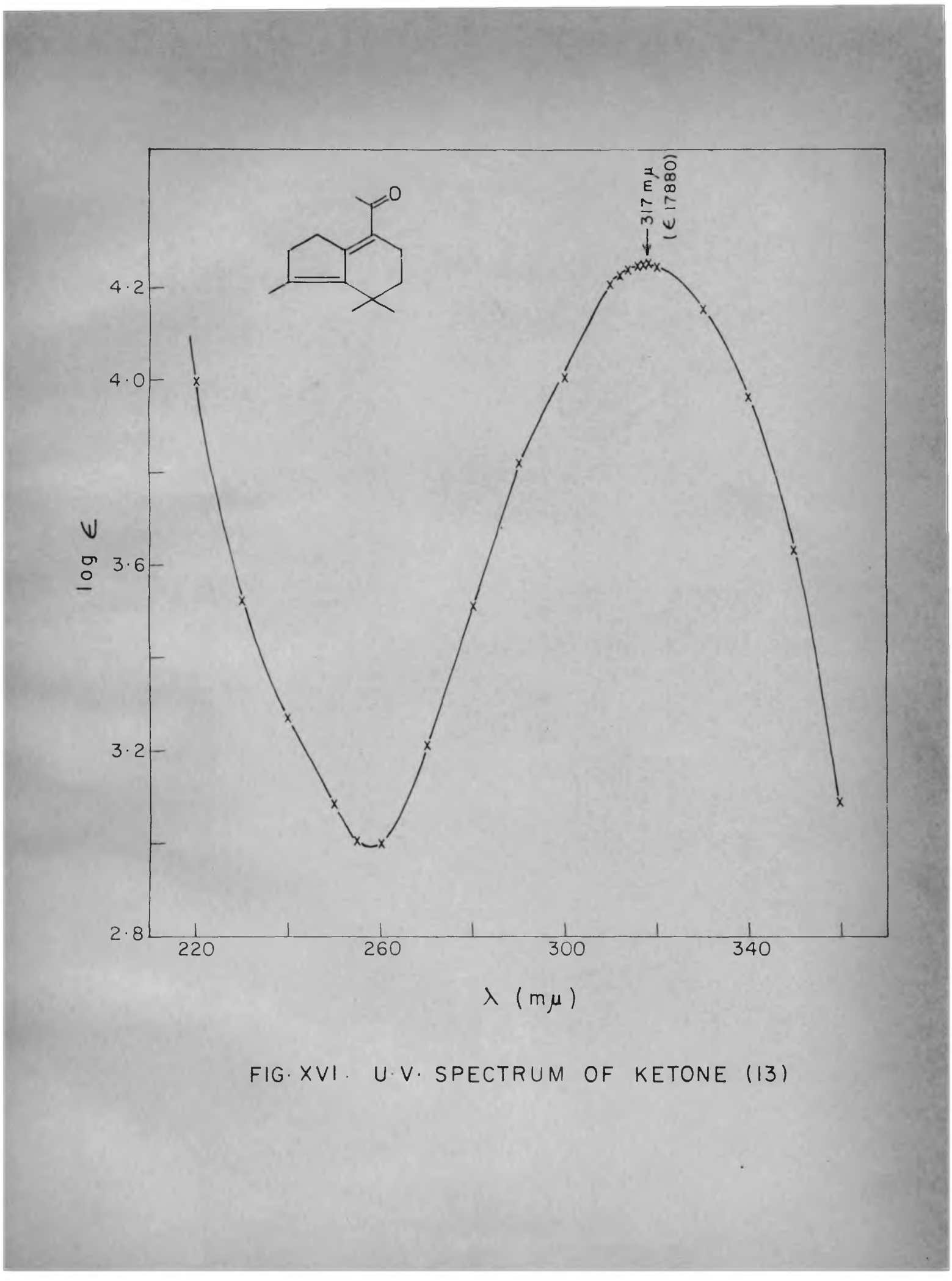


FIG. XVI. U.V. SPECTRUM OF KETONE (13)

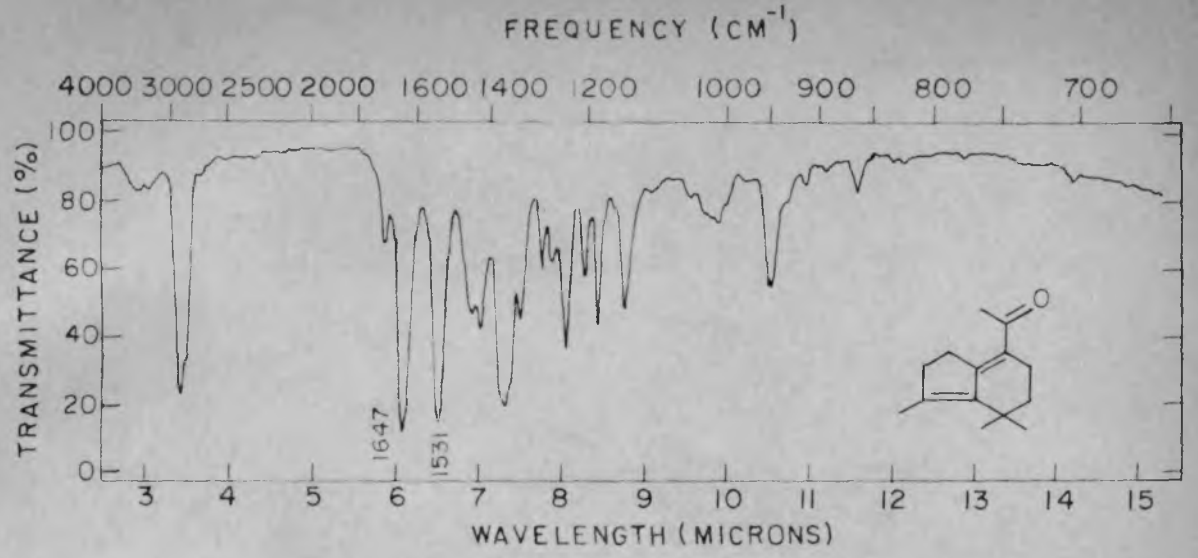


FIG. XVII IR SPECTRUM OF KETONE (13)

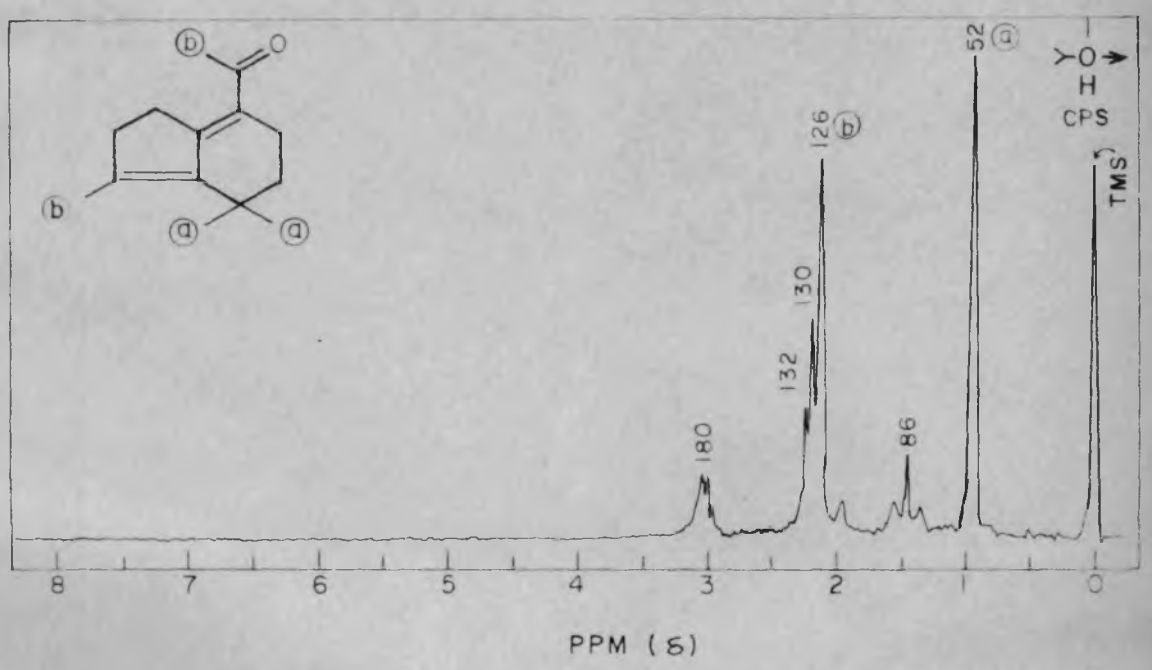
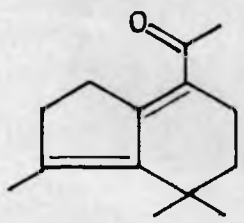


FIG. XVIII NMR SPECTRUM OF KETONE (13)

vinyl proton region. This data is in full accord with the structure (13) expected on mechanistic considerations.

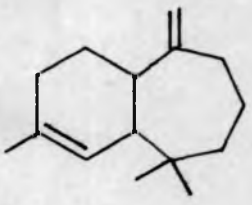


(13)

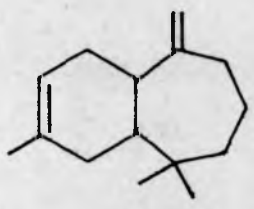
The isolation and complete characterization of the above products, the genesis of which is readily rationalized on the basis of structure (7) for β-himachalene (Fig. XV) fully confirms the structure of β-himachalene which must be represented as (7).

Structure of α-himachalene

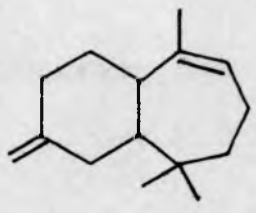
On the basis of the carbon skeleton deduced for himachalenes, α-himachalene could have the following three gross structures (14), (15) and (16). Of these structure (14)



(14)



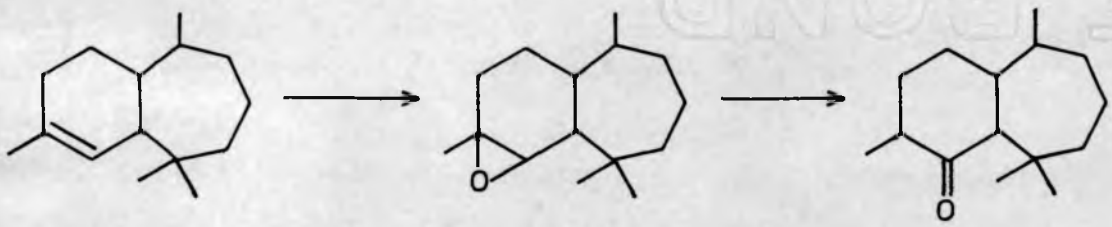
(15)



(16)

is to be preferred on biogenetic consideration discussed later (Chapter VI). Support for this formula for α-himachalene was gathered as follows. Dihydro α-himachalene (17) on epoxidation yielded the oxide (18) which as expected showed in the NMR

spectrum (Fig. XIX) signals for -CH-$\underline{CH_3}$ (3H, doublet J = 5 cps centered at 57 cps) and two quaternary methyls (6H, singlet at 65 cps), methyl on carbon attached to oxygen (3H, singlet at 76 cps) and a proton on a 1,2-epoxide ring (1H signal at 165 cps, essentially a singlet). The oxide on brief treatment with borontrifluoride etherate at -10° smoothly passed into a ketone ($\nu^{c=o}$ 1697 cm^{-1}) which in the infrared (Fig.XX) did not show any absorption around 1410 cm^{-1} (scissoring frequency of a methylene group adjacent to a carbonyl group)[5]. The formation of such a ketone (19) is possible only on the basis of structure (14).



(17) (18) (19)

Further support for this was obtained by the sodium dichromate-acetic acid oxidation of dihydro-∝-himachalene when an ∝:β-unsaturated ketone (20) [λ_{max}^{EtOH} 244 mμ, ε, 15880; IR (Fig.XXI): $\nu^{c=o}$ 1680; NMR: one vinyl H at 339 cps] was obtained which on reduction yielded the corresponding saturated ketone (21) [IR (Fig.XXII): $\nu^{c=o}$ 1720 cm^{-1}] and this, as expected, showed a clear absorption peak at 1406 cm^{-1} in

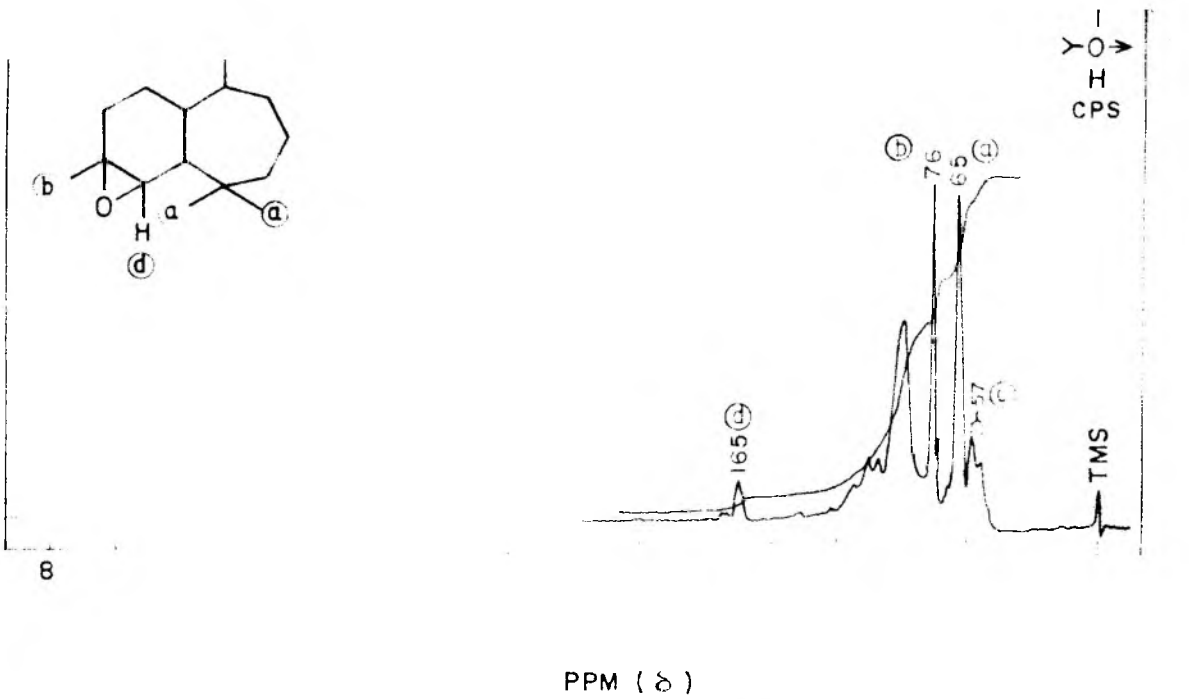
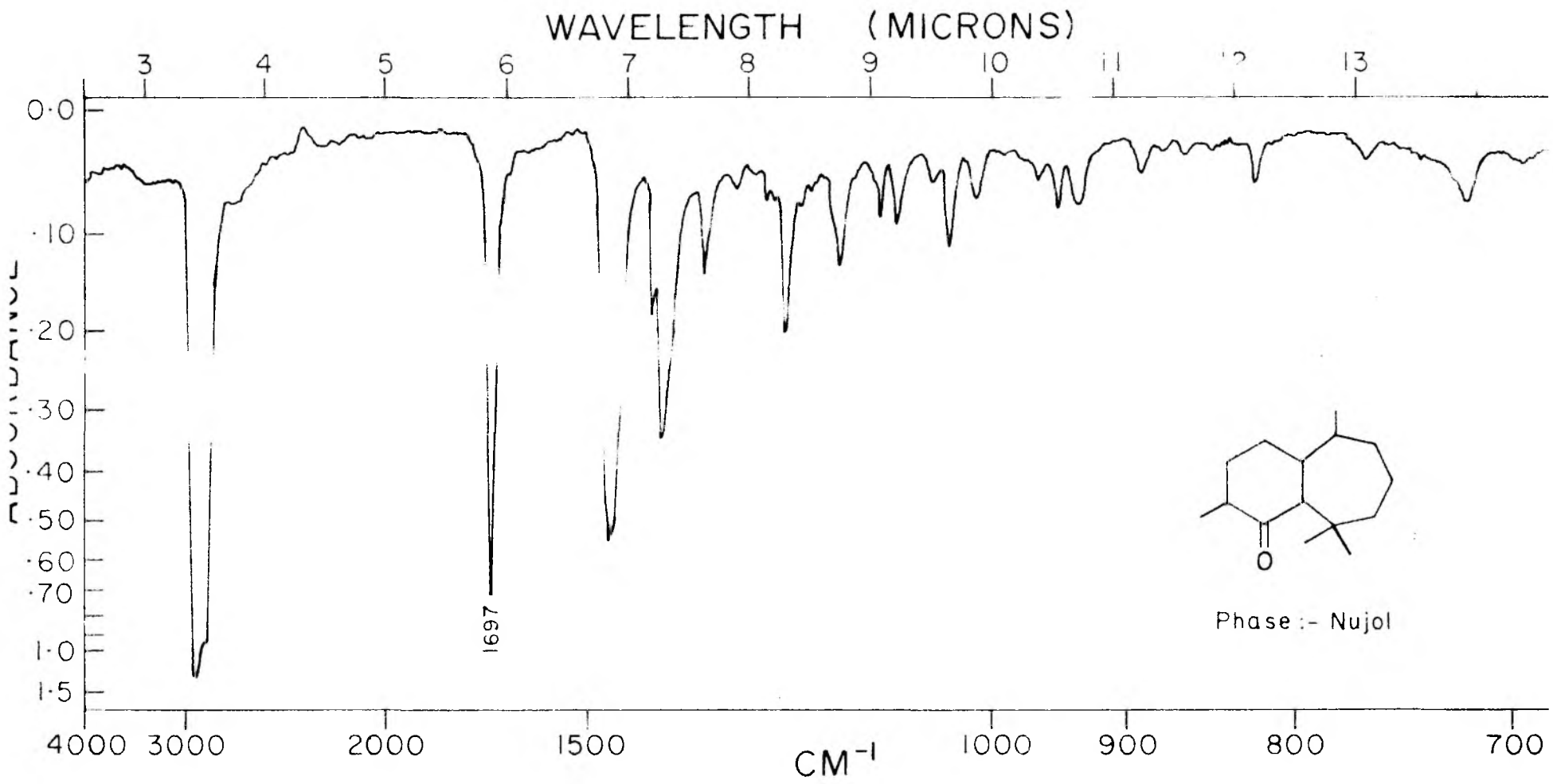
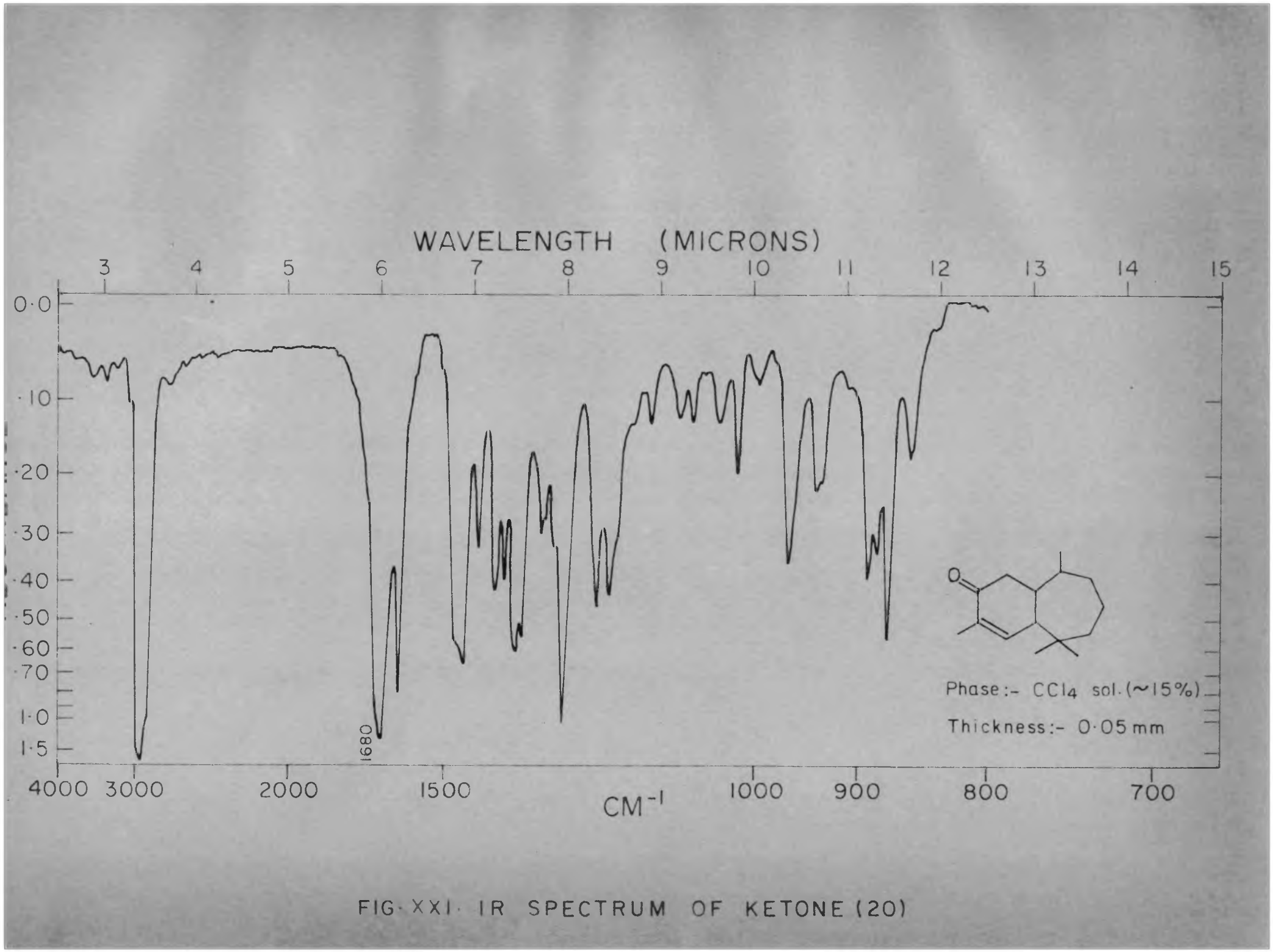


FIG. XIX. NMR SPECTRUM OF DIHYDRO-α-HIMACHALENE EPOXIDE

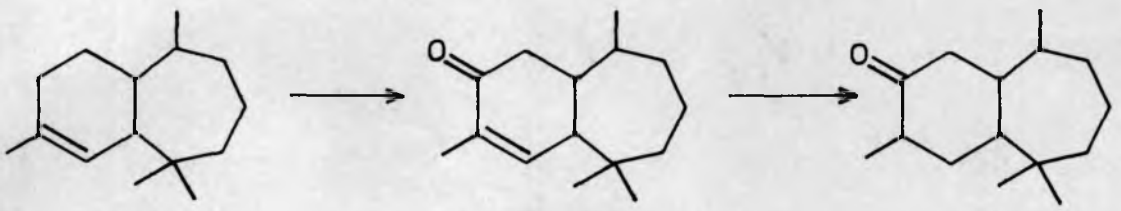


FIG· XX· IR SPECTRUM OF KETONE·



FIG·XXI· IR SPECTRUM OF KETONE (20)

the IR (presence of a methylene group next to a carbonyl).



(17) (20) (21)

The above results clearly define the structure of α-himachalene as (14).

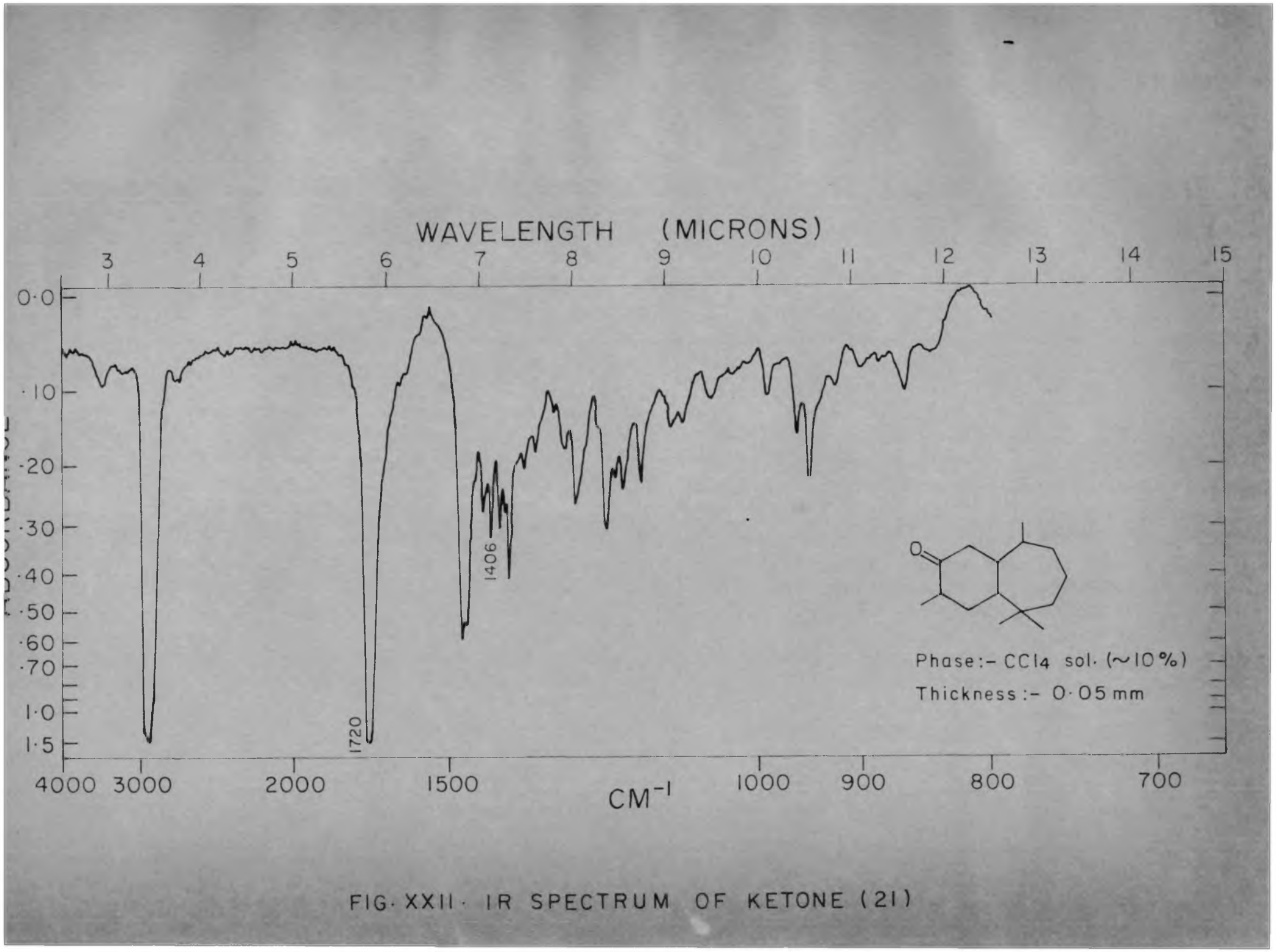


FIG. XXII. IR SPECTRUM OF KETONE (21)

EXPERIMENTAL

All m.ps. and b.ps. are uncorrected. Pet. ether refers to the fraction b.p. 40-60°. All solvent extracts were finally washed with brine, before drying (Na_2SO_4). Rotations were taken in chloroform. For tetranitromethane (TNM) tests, equal amounts of undiluted compound and 10% solution of the reagent in $CHCl_3$ were mixed.

UV spectra were measured on a Beckman DU Spectrophotometer or Beckman DK-2 recording Spectrophotometer. IR spectra were taken on a Perkin-Elmer Infracord, model 137E, as smears; maxima are reported in cm^{-1}. All NMR spectra were taken in ~ 20% solution in CCl_4 with tetramethylsilane as the internal standard on a Varian A-60 Spectrometer; peaks are reported in cps from tetramethylsilane peak.

Hydrochlorides

Himachalene dihydrochloride[1]: An ice-cooled solution of the hydrocarbon (4 g, mixture of α- and β-himachalenes) in glacial acetic acid (8 ml) was saturated with dry HCl gas (3 hr) and the product left overnight. The dihydrochloride (crude yield 1.5 g, 27%) after one crystallization from benzene-pet. ether mixture (1:4) came out in fine long white needles (1.2 g), m.p. 118-119° with decomposition. The specific rotation of the dihydrochloride (c, 10%) was dependent on the age of the solution (Fig. I):

Time (hr)	$[\alpha]_D^{30}$
1/2	+5.6°
1	+21.3°
1-1/2	28.2°
2	30.8°
2-1/2	32.1°
3	32.5°
4	32.0°
6	32.0°
8	31.8°

Himachalene monohydrochloride: A solution of the dihydrochloride (0.7 g) in dry methanol (4 ml), on keeping in refrigerator for two days deposited white needles (0.4 g) which after two recrystallization from methanol gave white shining needles (0.2 g), m.p. 51-52°. The specific rotation of the monohydrochloride (c, 2.1%) was not dependent on time, as shown below:

Time (hr)	$[\alpha]_D^{32}$
1/2	+123.0
1-1/2	123.8
3-1/2	123.0
5-3/4	123.0
8	128.6
24	129.1
80	136.1

Peracid oxidation

To a known quantity of α-himachalene (0.4577 g, 0.002244 mole), or β-himachalene (0.4595 g, 0.00225 mole), an excess of percamphoric acid solution in $CHCl_3$ (0.2581N, 75 ml, i.e. 0.00968 mole) was added and well shaken. At definite intervals, 2 ml of the reaction mixture was withdrawn and excess of peracid determined by iodometric titration. Table III gives the progress of the oxidation against time. In about two hours the oxidation was complete and the number of double bonds was found to be two in both cases.

TABLE III

Peracid consumption of himachalenes

No	Time	Double bond equivalent of acid consumed by α-himachalene.	Double bond equivalent of acid consumed by β-himachalene.
1	Start	1.184	1.301
2	10 min	1.352	1.544
3	30 "	1.640	1.755
4	1 hr	1.823	1.967
5	2 "	1.914	2.028
6	4 "	2.004	1.982
7	24 "	1.959	1.931
8	52 "	1.959	1.931

The resulting solution was filtered and the filtrate worked up by washing with 5% $NaHCO_3$ solution (15 ml x 4) and

drying. The solvent was removed under water-pump suction at room temperature. α-Himachalene diepoxide was obtained as white flakes (75 mg) which was crystallized from pet.ether m.p. 125-126°, $[\alpha]_D^{30}$ -144° (c, 0.25%). (Found: C, 76.40; H, 10.40. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%). β-Himachalene yielded a liquid epoxide (0.34 g): b.p. 126-130°/2 mm n_D^{26} 1.4939, $[\alpha]_D^{26}$ +87° (c, 2%). (Found: C, 75.91; H, 10.12. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%).

Tetrahydrohimachalenes

i) From α-himachalene: α-Himachalene (0.4808 g) in acetic acid (50 ml) over prereduced Adam's Pt catalyst (50 mg) absorbed 140 ml (2.148 mole) H_2 during 2 hr at 24°/693 mm, when absorption of H_2 stopped. The experiment was repeated after adding fresh α-himachalene (0.701 g) when it consumed 194 ml (2.03 mole) of H_2 in 3 hr. The product was filtered, diluted to 250 ml (water) and extracted with pet. ether (50 ml x 4). The extract was washed neutral, dried and solvent removed. The product on distillation gave a colourless liquid (0.95 g): b.p. 132°/14 mm, n_D^{24} 1.4862, d_4^{24} 0.8986, M_D 66.48 (calc: 67.07), $[\alpha]_D^{24}$ -8.252° (c, 8.48%); TNM test, negative. (Found: C, 86.57; H, 13.39. $C_{15}H_{28}$ requires: C, 86.46; H, 13.54%).

ii) From β-himachalene: β-Himachalene (0.585 g) in acetic acid (40 ml) over prereduced Adam's Pt catalyst (85 mg) absorbed 167 ml (2.15 mole) H_2 during 8 hr at 27°/708 mm.

The hydrogenation was quite sluggish and in a number of experiments the time taken for the completion of hydrogenation was 7-8 hr. On working up, a saturated hydrocarbon (0.44 g) was obtained: b.p. 110-111°/3 mm, $n_D^{26.5}$ 1.4876, $d_4^{26.5}$ 0.8997, M_D 66.65 (calc: 67.07), $[\alpha]_D^{24}$ -21.05° (c, 4.285%); TNM test negative. (Found: C, 86.58; H, 13.39. $C_{15}H_{28}$ requires: C, 86.46; H, 13.54%).

Dihydro-α-himachalene (17)

α-Himachalene (0.3838 g) in ethanol (50 ml; distilled over Raney nickel) over prereduced Adam's Pt catalyst (50 mg) absorbed 50 ml (1 mole) H_2 during 1 hr at 22°/693 mm when absorption of H_2 came to a close. The usual work up gave a product (0.33 g): b.p. 98-100°/1 mm, n_D^{24} 1.4972, d_4^{24} 0.9105, M_D 66.24 (calc: 66.63), $[\alpha]_D^{24}$ +59.17° (c, 3.4%); TNM test, yellow colour. (Found: C, 87.40; H, 12.58. $C_{15}H_{26}$ requires: C, 87.30; H, 12.70%).

Dehydrogenations

Selenium-dehydrogenation of pure α-himachalene and pure β-himachalene: α-Himachalene (1 g) and selenium (1.5 g) were mixed and heated at 275° (15 hr) and finally at 325° (36 hr). The product (0.5 g) was isolated by distillation and redistilled over sodium, b.p. 100-108°/2 mm, n_D^{24} 1.5279; GLC (Fig.XXIII) showed the product to consist of A, B and C in the ratio 38.6 : 28.5 : 29.6. The experiment was repeated under identical conditions for β-himachalene (1 g) and the product (0.55 g): b.p. 98-107°/2 mm, n_D^{22} 1.5340, consisted of A, B and C in the ratio

GAS - LIQUID CHROMATOGRAM

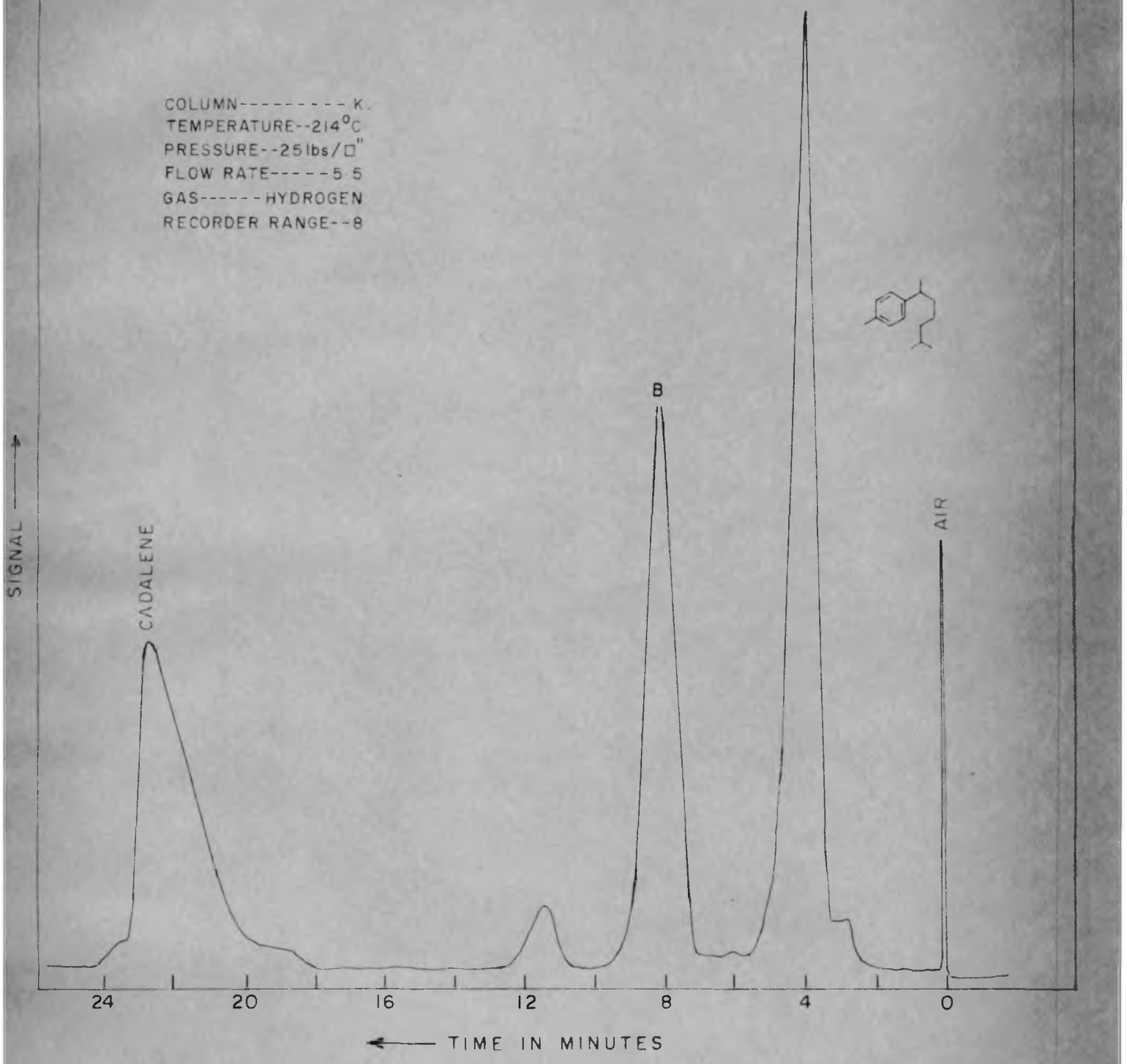


FIG. XXIII. PRODUCTS OF SELENIUM DEHYDROGENATION OF α - HIMACHALENE.

41.8 : 30.7 : 24.2 (GLC).

Selenium-dehydrogenation of himachalene mixture: On preparative scale, the hydrocarbon (9 g, ~ 1:1 mixture of α- and β-himachalenes) and selenium (14 g) were mixed and heated at 305-310° for 48 hr. The product from two experiments (11.4 g) was fractionated (6" Vigreux column):

Fraction No.	Wt.(g)	b.p./mm	n_D^{24}
i	3.16	126-130°/10	1.4911
ii	1.42	133-140°/10	1.5038
iii	1.30	143-153°/10	1.5353
iv	1.88	128°/2	1.5720

2-Methyl-6-(p-tolyl)-heptane (1, fraction i, compound A): Fraction i on passing through a column of basic alumina (grade I, 80 g, 19 x 2.5 cm) readily gave pure 2-methyl-6-(p-tolyl)-heptane (2.57 g) using pet. ether as eluent (25 ml x 4): b.p. 125-126°/11 mm, n_D^{26} 1.4887, d_4^{26} 0.8678, M_D 67.87 (calc: 67.87), $[\alpha]_D^{28}$ +2.54° (c, 7.9%); $\lambda_{max}^{heptane}$ 260 (ε 226.8), 265 (ε 297.2), 273 mμ (ε 278.1); IR spectrum was superimposable on that of an authentic sample (see below). (Found: C, 88.21; H, 11.77. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%).

Fraction i (97 mg) was mixed with aq. nitric acid (1.2 ml of conc. HNO_3 in 2.5 ml of water) and heated in a Carius tube at 195 ± 5°/16 hr. The product was evaporated to dryness and made free from HNO_3 by repeated evaporation with water. The residue (56 mg, m.p. >340°) was collected

and washed with water. The methyl ester was obtained by the action of diazomethane in ether solution: m.p. 138-140°; mixed m.p. with dimethylterephthalate (m.p. 140°) was 138-139°.

Bisabolene was isolated from Chigadmari oil by fractionation and purified via its trihydrochloride[28]. The trihydrochloride (8 g) on refluxing with anhydrous sodium acetate and glacial acetic acid[29], followed by the usual work up yielded pure bisabolene (3.6 g): b.p. 134-138°/12 mm, n_D^{28} 1.4928. Bisabolene (3.6 g) was heated with selenium at 260-280°/30 hr and distilled. The product (2.3 g) on redistillation over sodium gave a fraction (1.8 g), b.p. 128-129°/15 mm, which was shaken with H_2SO_4 (95%, 5 ml), in pet. ether (30 ml). The pet. ether layer was separated, washed neutral (aq.$NaHCO_3$) and worked up to give pure 2-methyl-6-(p-tolyl)-heptane (1.4 g), b.p. 133-136°/16 mm, n_D^{32} 1.4868; $\lambda_{max}^{heptane}$ 260 (ε 401.8), 265 (ε 504.8), 273 mμ (ε 545.6). (Found: C, 88.30; H, 12.00. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%).

Cadalene (2, fraction iv, compound C): Fraction iv (1.88 g) was warmed with trinitrobenzene (1 g) in alcohol (15 ml) and allowed to crystallize. The crude derivative (1.5 g) m.p. 108-109° after recrystallization from alcohol yielded yellow needles m.p. 108-109°; mixed m.p. with an authentic sample (m.p. 112-113°) of trinitrobenzene complex of cadalene was 108-109°. The trinitrobenzene derivative (1 g) was passed through a column of basic alumina (grade I, 30 g, 21 x 1 cm) and eluted with pet. ether when pure cadalene (0.49 g) was

obtained, b.p. 117°/1.3 mm; $\lambda_{max}^{heptane}$ 232 (log ε 4.772), 290 (log ε 3.8), 325 mμ (log ε 2.8445).

The percentage of cadalene in the Se-dehydrogenation product of α- and β-himachalenes was checked by observing the ε max at 325 mμ. Ignoring the absorption of (1) at 325 mμ, the percentage of cadalene was calculated.

TABLE IV

Estimation of cadalene by UV spectra

	ε max at 325 mμ	Percentage of cadalene
Cadalene	699	
2-Methyl-6-(p-tolyl)-heptane	23.55	
α-Himachalene dehydrogenation product.	226.4	32.3
β-Himachalene dehydrogenation product.	218.4	31.2
S-Dehydrogenation product	20.62	2.94

These values are in accord with the GLC data.

Sulphur-dehydrogenation of himachalenes (compound B): The hydrocarbon (15 g, ~ 1:1 mixture of α- and β-himachalenes) and sulphur (7.5 g) were heated together at 210-215°/250 mm for 2 hr and distilled. The yellow distillate (7.5 g) was redistilled over sodium. Since the product was found to be contaminated with starting hydrocarbon (Br solution decolourised),

it was diluted with pet. ether (30 ml) and shaken with H_2SO_4 (95%, 10 ml) for 1 hr. The pet. ether layer separated and shaken again with fresh H_2SO_4 (10 ml) for another hour. The organic layer separated and worked up to yield a product (3.55 g), b.p. 113-119°/6 mm, n_D^{21} 1.5044; Br solution not decolourised. Its GLC is shown in Fig. XI.

The 5-dehydrogenation product (0.195 g) was oxidised as above in a Carius tube and the product (0.179 g) was extracted with water. The residue (49 mg) left was identified as terephthalic acid as above. The aq. extract on evaporation to dryness gave a solid (0.110 g) m.p. 180-190°, which after crystallization from benzene-acetone (2:1, 3 ml) gave a crystalline product, m.p. 202-208°; mixed m.p. with an authentic sample of trimellitic acid (m.p. 208-213.5°, prepared by HNO_3 oxidation of 2-methyl-p-cymene) was 203-212°.

The acid on heating at 250-260° for 1 hr followed by its sublimation at reduced pressure (0.6 mm) yielded the anhydride (25 mg, m.p. 153-157°) which was purified by resublimation, m.p. 160-162°; mixed m.p. with an authentic sample of trimellitic anhydride (m.p. 160-164°) was 160-162.5°. (Found: C, 55.6; H, 2.6. $C_9H_4O_5$ requires: C, 55.26; H, 2.1%).

Nitric acid oxidation:

A mixture of HNO_3 (400 ml, d, 1.31) and vanadium pentoxide (0.4 g) was heated to 100° with stirring and the hydrocarbon (13 g, ~ 1:1 mixture of α- and β-himachalenes)

was added slowly (20 min).When the evolution of the oxides of nitrogen was over (1.5 hr), the product was refluxed (145-150°) with stirring for 3 hr and then evaporated to dryness on a water bath. To this residue conc. HNO_3 (30 ml) was added and again evaporated to dryness. The product was diluted with water and evaporated and the process repeated till the product was free from HNO_3. It was esterified by refluxing (water bath) with absolute methanol (15 ml), benzene (30 ml) and conc. H_2SO_4 (3 ml) for 13 hr. The benzene layer separated and the aq. layer extracted with ether (30 ml x 3) after diluting it to 150 ml with water. The combined organic layers were washed free of acid (aq. $NaHCO_3$) and dried. Removal of the solvent, followed by distillation, gave a low boiling fraction (2.2 g), b.p. 87-102°/25 mm.

The experiment was repeated several times to collect a total of 16.2 g of the above material which was carefully fractionated using a spinning band column*. The following fractions (Table V) were obtained.

---

*PIROS-GLOVER spinning band micro still assembly supplied by H.S.Martin and Co.

TABLE V

Fractionation of HNO_3 oxidation product

Fraction No.	Wt.(g)	b.p./10 mm	n_D^{28}	Result of GLC analysis
1	0.3654	68°	1.4121	Pure a*
2	1.2847	74°	1.4160	a:b :: 41:59
3	2.4114	78°	1.4190	b:c :: 48:47
4	3.305	87-89°	1.4210	b:c :: 42:58
5	3.883	96-101°	1.4241	b:c:d :: 12:24:64
6	3.2388	107-109°	1.4260	d:e:: 82:18
7	0.9596	113-116°	1.4280	d:e :: 27:73

*The letters a,b,c,d and e stand for dimethyl esters of dimethyl malonic acid, succinic acid, ∝,∝-dimethyl succinic acid, ∝,∝-dimethyl glutaric acid and ∝,∝-dimethyl adipic acid respectively.

Dimethylmalonic acid: Fraction No.1 (83 mg) was heated on a water bath for 15 hr with conc. HCl (1 ml), gl. AcOH (0.6 ml) and water (0.4 ml) and the product evaporated to dryness. It was diluted with water several times and evaporated to dryness till it was free from acetic acid; yield 58 mg, m.p. 130-150°. This was once crystallized from water, followed by recrystallization from benzene-methanol mixture(2:1, 3 ml) to give colourless cubes, m.p. 186-187° (Lit. m.p. 192-193°) mixed m.p. with an authentic sample of dimethyl malonic acid (m.p. 191-193°) was 186-187°. [Found: C, 45.20; H, 6.10. $C_5H_8O_4$ requires: C,45.45;

H, 6.10%; neutralisation equivalent 67.7 (calc. 66.06)].

Succinic and α,α-dimethyl succinic acids: Fraction No.4 (0.5 g) was hydrolysed and the crude acid (0.330 g, m.p. 116-145°) was once crystallized from acetone-benzene (1:1, 6 ml); the product (0.103 g, m.p. 172-175°) was recrystallized from water (1 ml) to get pure succinic acid (40 mg), m.p. 184.5 - 185.5°, mixed m.p. with an authentic sample (m.p. 185.5 - 186.5°) was undepressed.

The mother liquor from the above crystallization was evaporated to dryness to yield a product (0.155 g, m.p. 95 - 104°) which was subjected to partition chromatography* on a column (20.5 x 2.2 cm) prepared from silica gel (35 g), chloroform (80 ml) and water (21 ml). It was eluted with $CHCl_3$ containing increasing amounts of n-butanol and the following fractions were collected.

CHROMATOGRAM I

Fraction No.	% of $CHCl_3$	% of BuOH	Vol.(ml) of eluent.	Wt.(mgs) of elute
1	100	0	50	0
2	95	5	50	0
3	90	10	50	5
4	80	20	50 x 4	109
5	60	40	50 x 4	12
6	60	40	50 x 2	0

*In all partition chromatography experiments, silica gel (BDH silica gel for chromatography) was heated to 150-160°/20 hr before use. Chloroform refers to $CHCl_3$ saturated with water. The compound was dissolved in $CHCl_3$-n-BuOH (1 ml, ~ 1:1) and placed on the column which was then eluted with solvent mixtures.

The major fraction (0.103 g, m.p. 75-85°), on repeated crystallization from benzene yielded pure α,α-dimethyl succinic acid m.p. 139-140° (Lit. m.p. 141°); mixed m.p. with an authentic sample (m.p. 140-141°) was undepressed.

α,α-Dimethyl glutaric acid: Fraction No.6 (0.5 g) was hydrolysed to obtain the crude acid (0.410 g, m.p. 42-62°). A portion of it (98 mg) was subjected to partition chromatography on a silica gel column (35 g, 20 x 2.2 cm) as detailed above and the following fractions were collected.

CHROMATOGRAM II

Fraction No.	% of $CHCl_3$	% of BuOH	Vol.(ml) of eluent.	Wt.(mgs) of elute
1	100	-	16 x 3	26.4
2	80	20	16 x 4	62.4
3	80	20	16	5.5
4	80	20	16	0

The major fraction (62 mg, m.p. 60-66°) was crystallized from pet. ether-ether mixture (2:1, 1.5 ml); yield 19 mg, m.p. 81-82°. Mixed m.p. with an authentic sample of α,α-dimethyl glutaric acid* (m.p. 81-82°, Lit. m.p. 85°[30]) was 80.5 - 81.5°. The acid was converted into its anhydride

*The authentic samples of α,α-dimethyl glutaric acid, α,α-dimethyl adipic acid and α,α-dimethyl cyclopentanone were kindly prepared by Mr.J.R.Prahlad following the procedure of Wilcox and Mesirov.[30]

by refluxing with acetic anhydride (0.5 ml) for 3 hr which as expected showed peaks at 1802, 1761 cm^{-1} in the IR spectrum for glutaric anhydride.

<u>α,α-Dimethyl adipic acid</u>: Fraction No.7 (0.592 g) was hydrolysed to yield crude acid (0.516 g, m.p. 60-67°). A part of it (0.210 g) was subjected to partition chromatography on silica gel column (50 g, 20 x 2.6 cm) when a major fraction (88 mg, m.p. 73-76°) was eluted by $CHCl_3$ (100%, 100 ml) which was crystallized from pet. ether-ether mixture (3:1, 4 ml); yield 37 mg, m.p. 87.5-89°. Mixed m.p. (88-89°) with an authentic sample of α,α-dimethyl adipic acid (m.p. 88-89°, Lit. m.p. 89-90°[30]) was undepressed. (Found: C, 54.70; H, 7.67. $C_8H_{14}O_4$ requires: C, 55.16; H, 8.10%).

The crude acid (0.100 g) from fraction No.7 was thoroughly mixed with iron powder (0.100 g) and barium hydroxide (20 mg) and dry distilled. The residue left was steam distilled and the total distillate was extracted with ether (15 ml x 3) and dried. After solvent removal, the product ($\nu_{C=O}$ 1728 cm^{-1}) was converted into 2,4-dinitrophenylhydrazone (HCl method). A recrystallized sample (EtOH), orange glistening needles, m.p. 137-8°, had a mixed m.p. of 138-140° with 2,4-dinitrophenylhydrazone of α,α-dimethyl cyclopentanone (m.p. 141-142°, Lit. m.p. 144°[30]).

<u>Ozonolysis of β-himachalene</u>

A solution of β-himachalene (2.26 g) in chloroform

(60 ml) was ozonised at -10° by bubbling ozonised oxygen (~ 160 mg/hr) till it was no longer absorbed (~ 5.5 hr, KI solution test). The solvent was removed under water-pump suction (~ 50 mm) at room temp. and the ozonide was decomposed by warming gently with hydrogen peroxide (30%, 5 ml), water (20 ml) and sodium carbonate (1 g), first at 60° (1 hr) and finally at ~ 100° (2 hr). The product was cooled and extracted with ether (20 ml x 4) and the ether extracts washed with aq. Na_2CO_3 (~ 10%, 15 ml x 3), then with brine and dried. On solvent removal, a viscous product (1.16 g, neutral) was obtained.

The aq. alkaline layer was acidified (H_3PO_4) and continuously (60 hr) extracted with ether after saturating with ammonium sulphate. The ether extract was washed with brine, dried and ether removed. The crude acidic product (1 g) was esterified (diazomethane) to yield a mixture of methyl esters (GLC, Fig. XIV).

Acidic products

The ester mixture (~ 3.5 g), collected from three experiments was carefully fractionated to give the following fractions:

Fraction	Wt.(g)	b.p./mm	n_D^{27}
i	0.497	86-88°/15	1.4261
ii	0.391	120-123°/15	1.4410
iii	1.051	112/0.2	1.4675

Methyl levulinate (Fraction i): Fraction i (0.25 g) was treated with semicarbazide hydrochloride (0.2 g) in water (0.3 ml) containing pyridine (0.2 ml), followed by methanol to make the solution homogeneous. After several hours, the separated product (0.276 g, m.p. 125-127°) was collected which after repeated recrystallization from methanol, was obtained as fine white needles, m.p. 142-143°; mixed m.p. (142-143°) with semicarbazone of methyl levulinate (m.p. 142-143°) was undepressed.

Fraction i (60 mg) was mixed with 2,4-dinitrophenyl hydrazine (0.100 g) in methanol (4 ml) containing conc. HCl (0.05 ml) and warmed on a water bath. The derivative which was collected after several hours, was recrystallized from methanol to give a yellow solid m.p. 140-140.5°; mixed m.p. with an authentic sample of 2,4-dinitrophenylhydrazone of methyl levulinate (m.p. 140.5 - 141°) was 140-141°.

Methyl geronate (Fraction ii): Fraction ii (0.391 g) was treated with semicarbazide hydrochloride (0.4 g) in water (2 ml) containing pyridine (0.4 ml), followed by methanol to make the solution homogeneous. The product was collected and recrystallized repeatedly to give white microprisms m.p. 156-157°; mixed m.p. with an authentic sample of the semicarbazone of methyl geronate (m.p. 158-159°, see p. 89) was not depressed. (Found: C, 55.10; H, 8.82; N, 17.93. $C_{11}H_{21}O_3N_3$ requires: C, 54.30; H, 8.70; N, 17.27%*).

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*A better analytical result could not be obtained, even with an authentic sample.

Methyl homogeronate: The third ester was best isolated by preparative GLC. A total of 0.375 g of the total ester mixture was injected on column P (succinic polyester of diethyleneglycol on Chromosorb W, 1/2 inch x 2 meters) in four equal lots, at 160° using H_2 (15 lbs/sq.in.) as carrier gas. Three fractions corresponding to each peak (Fig.XIV) were collected in separate receivers kept at -10°. Fraction i (74.4 mg) and fraction ii (69.4 mg) were identified as methyl levulinate and methyl geronate respectively by the preparation of their semicarbazone.

A portion of fraction iii (total 49.8 mg) was converted into semicarbazone (pyridine method) which after recrystallization from methanol yielded white shining flakes, m.p. 114-116°; mixed m.p. with an authentic sample of semicarbazone of methyl homogeronate (m.p. 115-116°, see p. 89) was undepressed. (Found: C, 55.60; H, 8.60. $C_{12}H_{23}O_3N_3$ requires: C, 56.01; H, 9.01%).

The remaining portion of fraction iii was converted into its 2,4-dinitrophenylhydrazone (H_2SO_4 method) which after recrystallization (MeOH) gave light yellow needles, m.p. 94-95°, mixed m.p. with an authentic sample of 2,4-dinitrophenylhydrazone of methyl homogeronate (m.p. 92-93°) was 92-93°. (Found: C, 53.90; H, 6.30. $C_{17}H_{24}O_6N_4$ requires: C, 53.67; H, 6.36%).

Neutral products

The neutral portion (crude, 4 g) obtained from ozonolysis

of β-himachalene (three experiments) was refluxed with aq. KOH (5%, 400 ml) and ethanol (53 ml) for 3 hr (N_2). The product was extracted with ether (30 ml x 4) after saturating with ammonium sulphate, washed with brine and dried. The solvent was flashed off and the product fractionated to give the following fractions:

Fraction	Wt.(g)	b.p./mm	n_D^{29}		
A	0.281	87-94°/4	1.4909	ϵ_{232}^{EtOH}	5962
B	0.946	130-136°/2	1.5292	ϵ_{317}^{EtOH}	6889

1-Acetyl-4,4-dimethyl cyclohexene (12, Fraction A): Fraction A (0.281 g) was converted into semicarbazone (pyridine method) m.p. 205-7°, which after crystallization from ethanol yielded white shining flakes, m.p. 216-217°, λ_{max}^{EtOH} 257 mμ (ε 26,240); mixed m.p. with an authentic sample of the semicarbazone of 1-acetyl-4,4-dimethyl cyclohexene (see p. 93)(m.p. 214-216°) was 214-215°.[Found: C, 62.70; H, 9.10; N, 19.90. $C_{11}H_{19}ON_3$ requires: C, 63.12; H, 9.15; N, 20.08%; M.Wt. 221 (calc.209.29)].

The above semicarbazone (30 mg) was heated with 2,4-dinitrophenylhydrazine reagent (30 mg mixed with ~ 0.05 ml of conc. H_2SO_4 and 5 ml of ethanol) and after several hours, the crystalline derivative (44 mg) m.p. 181-183° was collected. It was recrystallized (ethanol) to yield red glistening needles m.p. 183-184°, $\lambda_{max}^{CHCl_3}$ 254 (ε 16,740), 385 mμ (ε 27,550); mixed m.p. with an authentic sample of 2,4-dinitrophenylhydrazone of 1-acetyl-4,4-dimethyl-cyclohexene (m.p. 182-183°) was 182-182.5°.

(Found: C, 58.30; H, 6.10. $C_{16}H_{20}O_4N_4$ requires: C, 57.82; H, 6.07%).

Ketone (13, Fraction B): Fraction B (0.946 g) was converted into its semicarbazone (pyridine method) and repeatedly recrystallized from ethanol and ethanol-benzene (1:9) mixture to give a pale yellow solid, m.p. 209-210°. (Found: C, 68.90; H, 8.50; N, 15.70. $C_{15}H_{23}ON_3$ requires: C, 68.93; H, 8.87; N, 16.08%).

Pure semicarbazone (0.150 g), oxalic acid (0.310 g) in water (2.5 ml) and n-heptane (10 ml) were mixed and refluxed under stirring till a clear solution was obtained (0.5 hr). The organic layer was separated and the aq. layer extracted with pet. ether (25 ml x 2) and the combined organic layers washed neutral (aq. $NaHCO_3$) and dried. After solvent removal, the product was distilled to give pure ketone as a yellow viscous liquid (76 mg), b.p. 136°/2 mm (bath temp.), n_D^{30} 1.5310; (Found: C, 82.90; H, 10.30. $C_{14}H_{20}O$ requires: C, 82.30; H, 9.87%).

The semicarbazone was converted into the 2,4-dinitrophenylhydrazone as above which after recrystallization (ethanol) gave dark red micro-crystals m.p. 188-189°. (Found: C, 62.26; H, 6.60. $C_{20}H_{24}O_4N_4$ requires: C, 62.48; H, 6.29%).

Dihydro-∝-himachalene epoxide (18).

Dihydro-∝-himachalene (6.9 g, 0.0335 mole) was mixed slowly with excess of a chloroform solution of perbenzoic acid (0.6304 N, 120 ml i.e. 0.0378 mole) at ~ 0°. After 72 hrs, the

product was washed free of acid (10% aq. Na_2CO_3) and dried. The solvent was removed and the product (6.879 g, 93%) distilled, b.p. 110-115°/2 mm, n_D^{30} 1.4881. An analytical sample was prepared by passing the epoxide (1.08 g) through a column of neutral alumina (grade II, 33 g, 16 x 1.6 cm) when major portion (0.65 g) was eluted by pet. ether (50 ml x 8), b.p. 115-117°/2.5 mm, n_D^{30} 1.4873, $[\alpha]_D^{30}$ +20.61°(c, 7.51%); IR spectrum: C—O—C 880, 875, 810 cm^{-1}. (Found: C, 81.51; H, 11.92. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

Isomerization of epoxide (18) to ketone (19)

A solution of the epoxide (6.88 g) in toluene (170 ml) was concentrated (130°) to ~ 150 ml to remove traces of moisture[31]. This solution was cooled to -10° and mixed with freshly distilled BF_3 etherate (4.5 ml). After two hours at -10°, pyridine (10 ml) was added and the product was washed with dil. HCl (~ 3N, 20 ml), brine and dried. After solvent removal, the product was distilled; yield 4.86 g b.p. 108-112°/2.5 mm, n_D^{30} 1.4920. GLC showed the product to be essentially a mixture of desired ketone and the unchanged epoxide.

In an attempt to purify the product, it (4.86 g) was subjected to column chromatography using neutral alumina (grade II, 23 x 3.1 cm, 130 g) and the different fractions collected were shown to be mixtures by GLC. Consequently these fractions were mixed* and finally separated by preparative GLC. The product (6 x 0.5 ml, i.e. 3.22 g) was injected on column P (succinic polyester of diethylene glycol on Chromosorb W, 2.5 cm x 3 meters)

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*GLC showed that the product now consisted of the epoxide

at 200° using N_2 (15 lbs/sq.in) as carrier gas. Three fractions corresponding to three peaks in GLC were collected separately in receivers cooled at -10°. Fraction i (0.532 g) was identified as starting epoxide; fraction ii (0.352 g) as ketone-II. Fraction iii (0.958 g) was a solid and crystallised from pet.ether to give colourless cubes, m.p. 42-43°, $[\alpha]_D^{27}$ -93.56°(c, 3.42%); IR spectrum: Fig.XX. (Found: C, 80.80; H, 11.90. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

No semicarbazone or 2,4-dinitrophenylhydrazone could be prepared from this ketone.

Oxidation of dihydro-α-himachalene to unsaturated ketone (20):

Dihydro-α-himachalene (0.95 g) was heated (66-72°) with sodium dichromate (3 g) in gl. AcOH (45 ml) under stirring for 8 hr. Ethanol (2 ml) was added to the product, followed by water (30 ml) and extracted with benzene (20 ml x 5), washed neutral (aq.Na_2CO_3) and dried. The solvent was removed and the product distilled; b.p. 118-121°/0.8 mm; yield 0.75 g, n_D^{32} 1.5036.

The product was converted into semicarbazone (pyridine method) which after recrystallisation (Ethanol) gave shining white micro needles, m.p. 208-209°, λ_{max}^{EtOH} 271 mμ (ε 34,570). (Found: N, 15.00. $C_{16}H_{27}N_3O$ requires: N, 15.15%).

Pure semicarbazone (1.05 g) on refluxing with aq.oxalic acid regenerated pure unsaturated ketone (0.8 g) which on

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(26%), ketone-I (48%) and a new ketone (ketone-II, 18%) and their retention time are 0.6, 2.8 and 1.9 minutes respectively using column P at 200° and H_2/25 lbs. per sq.in. as carrier gas. The formation of ketone-II is not altogether unexpected taking into consideration the known behaviour of ketone-I to undergo epimerization on alumina column (see Chapter IV).

crystallization from pet. ether gave colourless cubes, m.p. 50-51°, $[\alpha]_D^{30}$ +93.04 (c, 4.17%), λ_{max}^{EtOH} 244 mμ (ε 15,880); NMR: 64,71 cps (3H each, singlets, quaternary methyls), a doublet centered at 63 cps (3H, J = 6 cps, $-CH-\underline{CH_3}$), 94 cps, broad peak (3H doublet assignable to $_H>C=C<^{C}_{CH_3}$ superimposed on other signals) and 339 cps (1H, singlet, vinyl proton on an ethylenic linkage conjugated with a carbonyl group). (Found: C, 81.75; H, 10.90. $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%).

The semicarbazone (0.20 g) was converted into 2,4-dinitrophenylhydrazone (H_2SO_4 method) which after three recrystallizations (Ethanol) gave red shining needles m.p. 155-156°, λ_{max}^{EtOH} 257 (ε 20,120), 386 mμ (ε 32,880). (Found: N, 14.00. $C_{21}H_{28}N_4O_4$ requires: N, 13.99%).

<u>Hydrogenation of the unsaturated ketone (20) to saturated ketone (21)</u>:

The unsaturated ketone (0.486 g) in ethanol (30 ml) over pre-reduced Pd on calcium carbonate (1.25%, 0.75 g) absorbed 80.8 ml (1.36 mole) H_2 at 23°/685 mm during 6 hr. The product was worked up in the usual manner and distilled to give a colourless liquid (0.48 g), b.p. 116°/1.2 mm. An analytical sample of the saturated ketone was prepared via its semicarbazone (see below) by oxalic acid treatment, b.p. 114°/1 mm, n_D^{26} 1.4970, d_4^{24} 0.9828, M_D 66.13 (calc. 67.09), $[\alpha]_D$ +52.2° (c, 1.533%); $\lambda_{max}^{n\text{-heptane}}$ 289 mμ (ε 23.92); IR spectrum: Fig. XXII. (Found: C, 81.12, H, 11.73. $C_{15}H_{26}O$

requires: C, 81.02; H, 11.79%).

The hydrogenation product (0.48 g) was converted into its semicarbazone (pyridine method) which after recrystallization (EtOH) gave white powder m.p. 185-186°. (Found: N, 15.17; $C_{16}H_{29}N_3O$ requires: N, 15.04%).

A part of the saturated ketone (80 mg) was converted into 2,4-dinitrophenylhydrazone which was crystallized (EtOH) thrice to give yellow micro needles, m.p. 130-132°, λ_{max}^{EtOH} 362 mμ (ε 23,130). (Found: N, 14.13. $C_{21}H_{30}O_4N_4$ requires: N, 13.92%).

Methyl geronate from β-ionone[22]

Oxidative ozonolysis of β-ionone (4.69 g) in chloroform (60 ml, containing 1% pyridine) was carried out as described earlier for β-himachalene and the acidic portion (~1 g) obtained was esterified (diazomethane). The product was fractionated and the fraction of b.p. 110-120°/10 mm (0.482 g), n_D^{30} 1.4490 was collected separately. This was converted into the semicarbazone (pyridine method). Repeated recrystallization (methanol) gave an authentic sample of the semicarbazone of methyl geronate, m.p. 158-159°. (Found: C, 54.94; H, 9.10; N, 17.97. $C_{11}H_{21}O_3$ requires: C, 54.30; H, 8.70; N, 17.27%).

Methyl homogeronate from tetrahydroeucarvone

To a cooled solution (-10°) of sodium methoxide in methanol (from 0.3 g of sodium in 30 ml of MeOH), tetrahydroeucarvone* (1.855 g) was added, followed by ethylnitrite[32] (2 ml)

*Kindly supplied by Mr.R.C. Pandey.

and stirred for 1 hr. The product was kept at 0-2° for 24 hr. Through the yellow solution CO_2 was bubbled till no more precipitate of Na_2CO_3 appeared (3 hr) when it was filtered. The filtrate was concentrated and treated with formaldehyde (40%, 2 ml) and aq. HCl (2N, 0.6 ml) and warmed on a water bath with swirling. It was cooled, diluted with water (50 ml) and extracted with ether (25 ml x 4); the ether extract was washed neutral with aq. $NaHCO_3$ and dried. Solvent was removed and the residue distilled: the higher boiling fraction (1.397 g, 62% yield), b.p. 116-118°/3.5 mm, n_D^{30} 1.4370 was the required methyl homogeronate and was shown to be 97% pure by GLC. (Found: C, 65.60; H, 10.32. $C_{11}H_{20}O_3$ requires: C, 65.97; H, 10.07%).

A part of this (0.37 g) was converted into semicarbazone (pyridine method), m.p. 108-111°, which after two recrystallizations from methanol yielded semicarbazone of methyl homogeronate, m.p. 115-116°.

Another portion (0.20 g) of the above keto ester was converted into 2,4-dinitrophenylhydrazone (H_2SO_4 method), m.p. 78-80°, which was twice recrystallized from methanol to yield an authentic sample of 2,4-dinitrophenylhydrazone of methyl-homogeronate, m.p. 92-93°. (Found: C, 54.08; H, 6.50. $C_{17}H_{24}O_6N_4$ requires: C, 53.67; H, 6.36%).

Synthesis of 1-acetyl-4,4-dimethyl cyclohexene* (12)

4,4-Dimethyl cyclohexene-2-one (xi)[26]: To a mixture of methyl vinyl ketone (17.5 g, 0.4 mole) and isobutyraldehyde (18 g, 0.4 mole) in methanol (75 ml), sodium methoxide (1N, 75 ml) was added slowly with occasional swirling and the temp. rose to $\sim 60^{\circ}$. After 1 hr, the product was neutralized (50% AcOH), diluted with water (100 ml) and extracted with ether (75 ml x 3). The organic layer was dried and ether removed. On fractionation, fraction (10.6 g) boiling between 72 - 80°/15 mm, n_D^{30} 1.4628 was separated and further purified via semicarbazone (m.p. 138°, 9.95 g) to get pure 4,4-dimethyl cyclohexene-2-one (4.5 g), b.p. 72 - 73°/15 mm.

A portion (0.20 g) was converted into 2,4-dinitrophenyl hydrazone in the usual manner, which after recrystallization (EtOH) gave a crystalline product, m.p. 137 - 138° (Lit. m.p. 142°[26]).

4,4-dimethylcyclohexanone (ix): The unsaturated ketone (xi, 2 g) in ethanol (20 ml) over prereduced Pd on calcium carbonate (2%, 2 g) absorbed 485 ml of H_2 (1.09 mole) during 3 hr. The usual work up gave the saturated ketone (1.843 g), m.p. 38 - 40° (Lit. m.p. 38 - 40°[33]); IR spectrum: C=O 1712, $>C<^{CH_3}_{CH_3}$ 1362, 1383 cm^{-1}.

A portion (0.20 g) was converted into semicarbazone

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*This preparation was kindly carried out by Mr. K. C. Srivastava.

which after recrystallization gave white prisms m.p. 196 - 198° (Lit. m.p. 202°[33]).

4,4-Dimethyl-1-ethynyl cyclohexanol (x): A solution of the ketone (ix, 2 g) in dry ether (30 ml) and a solution of potassium (2 g) dissolved in tertiary amyl alcohol (30 ml) were added to a saturated solution of acetylene[34] in ether (150 ml) at -15° over a period of 2 hr. Acetylene was continued to bubble for 1 hr and finally at a reduced rate for 5 more hr. The reaction mixture was decomposed with ammonium chloride solution and ether layer separated. The ether was flashed off and the crude product was directly used for the next step.

1-acetyl-4,4-dimethyl cyclohexene (12): The resin[(11 g), Amberlite IR-120, supplied by L.Light and Co.] was suspended in dil. H_2SO_4 (400 ml), followed by washing it many times with water. It was added to a solution (100 ml) containing mercuric oxide (0.1 g) in dil. H_2SO_4[35]. It was washed with water many times, dried in air and finally in a vacuum desiccator.

A stirred mixture of (x), acetic acid (12 ml), water (1 ml) and the Hg-resin (2 g) was heated under reflux for 1 hr. The catalyst was filtered on cooling, the filtrate diluted with water (50 ml) and made slightly alkaline by 40% NaOH solution. The organic product was extracted with ether (50 ml x 3), dried and ether was removed. On distillation, 1-acetyl-4,4-dimethyl cyclohexene (1.8 g, 79%) was obtained as a colourless liquid: b.p. 80 - 83°/8 mm; λ_{max}^{EtOH} 232 (ε 11,400),

303 mμ (ε 46.5); IR spectrum: C=O 1656, 1692 (shoulder), C=C 1631 cm^{-1}; NMR: 58 (6H, singlet, two $>\underset{|}{C} - \underline{CH_3}$), 134 (3H, singlet, $-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$), 409 cps (1H, quintuplet, $>C=C<_{\underline{H}}$).

The 2,4-dinitrophenyl hydrazone, m.p. 182 - 183° (Lit. m.p. 185.5 - 186°[25]) and semicarbazone, m.p. 214 - 216° (Lit. m.p. 216 - 218°[25]) were prepared as described earlier.

The estimation of the number of methyl groups by IR:

A solution of known concentration of tetrahydro-β-himachalene in CCl_4 was prepared and the infrared spectrum of this solution was taken in the region 1410 to 1360 cm^{-1} in a sodium chloride cell of thickness 0.02 mm using calcium fluoride prism, in a Grubb Parsons double pass, double beam spectrophotometer at a temperature of 29°C. A slit constant of 0.5 mm and a gain of 9 were employed.

The integrated molecular absorption was then calculated in arbitrary units by counting the number of squares under the peaks.

The same procedure was repeated with α-himachalene and β-himachalene under identical conditions and the number of methyl groups in himachalenes was calculated by assuming the number of methyl groups in tetrahydro-β-himachalene to be four.

The spectrophotometer used plots percentage absorption against wave-length: Since Beer's law is not applicable to percentage absorption, the percentage transmission was

calculated by substracting the area under the peaks from the total integrated area enclosed between the wave numbers 1410 and 1360 cm^{-1}. The spectra are shown in Fig.XXIV and calculations are given below:

Concentration of tetrahydro-β-himachalene in CCl_4 = 0.1848 g.mols/litre

Total integrated area = 762.8

Area under the peak = 130.5

$\frac{I}{Io}$ = Fraction of light transmitted $\propto \frac{632.3}{762.8}$

O.D. = $\log \frac{I}{Io} \propto \log \frac{632.3}{762.8}$ = 0.0816

O.D. for one g. mol/litre $\propto \frac{0.0816}{0.1848}$ = 0.4416

Specific absorption coefficient per methyl group $\propto \frac{0.4416}{4} = \underline{0.1104}$

Concentration of ∝-himachalene in CCl_4 = 0.307 g.mol/litre

Total integrated area = 819.8

Area under the curve = 169

Absorption ∝ area under the curve ∝ 169

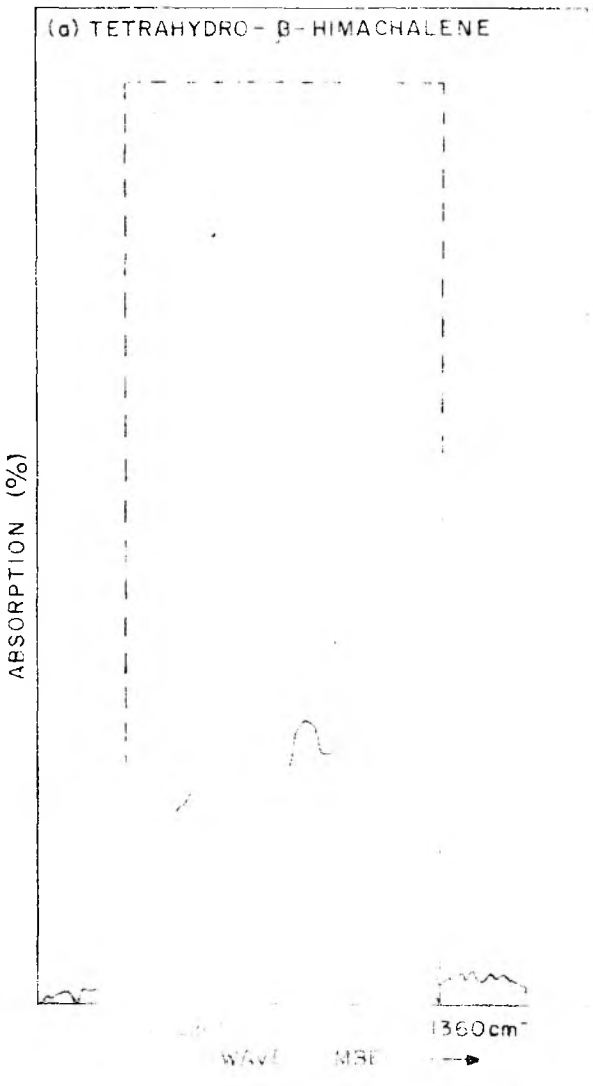
Transmission ∝ (total area - area under the curve) 650.8

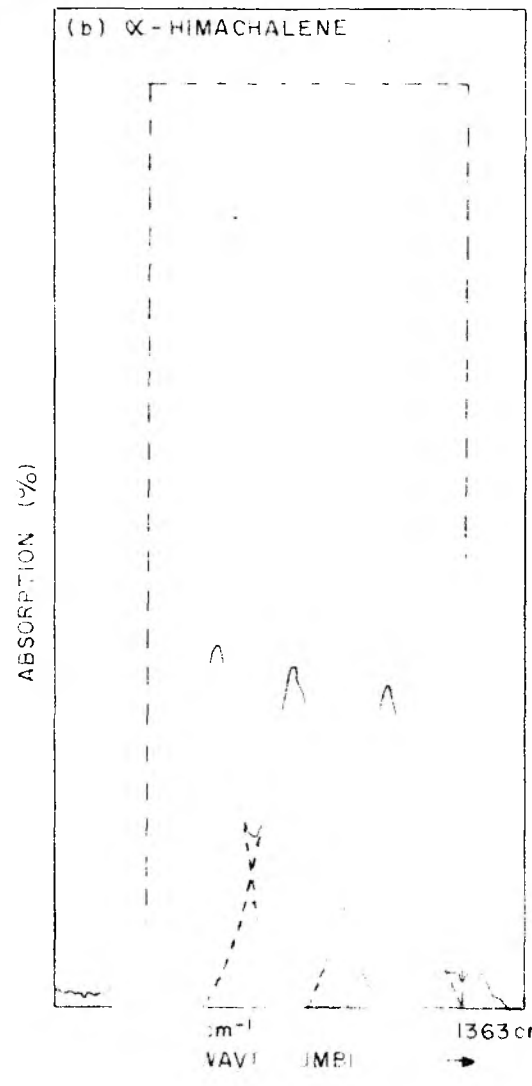
Fraction of light transmitted = $\frac{I}{Io} \propto \frac{650.8}{819.8}$

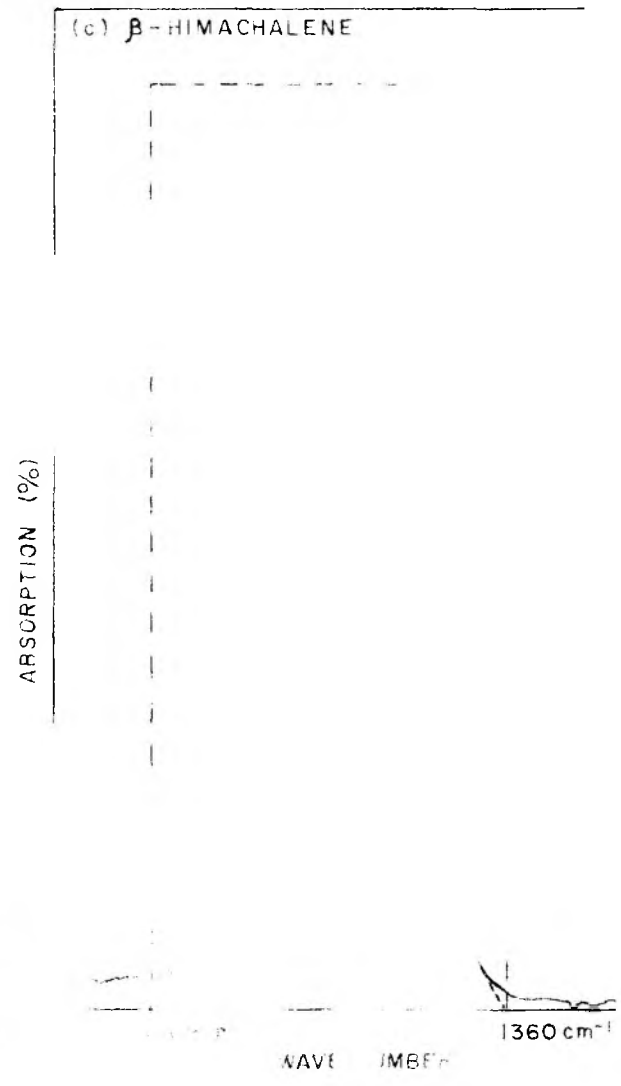
Optical density = $\log \frac{Io}{I} \propto \log \frac{819.8}{650.8}$ = 0.1003

Optical density for one g. mol. $\propto \frac{0.1003}{0.307}$ = 0.3257

Number of methyl groups = $\frac{0.3257}{0.1104} = \underline{2.959}$


(a) TETRAHYDRO - β - HIMACHALENE
ABSORPTION (%)
1360cm⁻¹
WAVE NUMBER


(b) α - HIMACHALENE
ABSORPTION (%)
1363 cm⁻¹
WAVE NUMBER


(c) β - HIMACHALENE
ABSORPTION (%)
1360 cm⁻¹
WAVE NUMBER

Concentration of β-himachalene in CCl_4 = 0.2207 g. mol/litre

Total integrated area = 817.7

Area under the curve = 148.25

$O.D. = \log \frac{Io}{I} \propto \frac{817.7}{669.45}$ = 0.0869

O.D. for one g. mol/litre $\propto \frac{0.0869}{0.2207}$ = 0.3938

Number of methyl groups = $\frac{0.3938}{0.1104}$ = 3.567

Gas-liquid Chromatography:

Analytical GLC was carried out either on Perkin-Elmer Vapour Fractometer model 154C or model 154D. For preparative GLC, the latter was used. GLC of tetrahydro-α- and tetrahydro-β-himachalenes* were determined using a capillary column [polyethylene glycol monostearate (25%) on silicone treated Chromosorb W (60/80 mesh)]. Various experimental conditions of the analysis have been included in the respective figures.

SUMMARY

From a study of spectral data and dehydrogenation results, structures (14) and (7) have been arrived at for α- and β-himachalenes respectively. Ozonolysis results of β-himachalene confirmed the above structure (7) whereas oxidation studies proved α-himachalene structure as (14) beyond doubt.

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*We are thankful to Van Ameringen - Haebler Inc., Union Beach, N.J. for the GLC.

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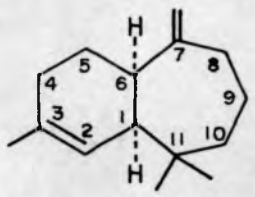
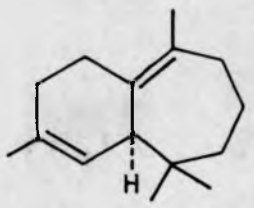
CHAPTER IV

ABSOLUTE STEREOCHEMISTRY OF HIMACHALENES

In the previous Chapter we have described the evidence which led to the establishment of the structures of himachalenes. The work, described in this Chapter, enables us to assign the absolute stereo-structures (1) and (2) to ∝- and β-himachalene respectively.



(1)



(2)

∝-HIMACHALENE

Nature of ring-fusion: A worthwhile approach to the solution of this problem appeared to be the preparation of 7- or 2-oxohimachalane and a study of its equilibration. This, of course, is based on the assumption that the relative stabilities of the himachalenes with cis- and trans-ring-junction are deducible, as discussed below, from the principles of conformational analysis.

It has been experimentally established that in both ∝β-tetramethylene cycloheptanone (3)[1] and ∝β-pentamethylenecyclohexanone (4)[2], the trans-isomers are favoured by a large factor* at equilibration. Unlike decalins, cis-

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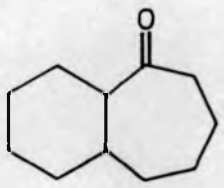
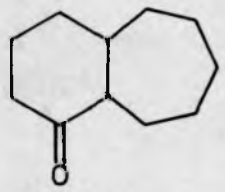
*(3): 100% trans after equilibration using NaOMe for 0.5 hr.
(4): 87 ± 2.5% trans after equilibration using NaOMe for 20 hr.

and trans- perhydrobenzosubarane can assume a large number[+]

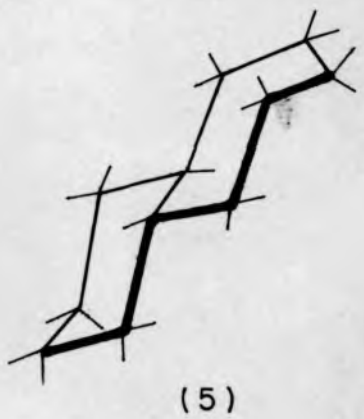


(3)



(4)

of conformations. A study of models (Dreiding) and an estimation of the interaction energy difference between the various conformers according to the method of Turner[3+] showed that a reasonable estimate of energy barrier between the energetically most favourable conformer (5) of trans-perhydrobenzosuberane and the corresponding conformer (6) of the cis- isomer would be of the order of 2-3 Kcal/mole, a value which would guarantee almost complete epimerization of the cis- to the trans-ketone at equilibration as has actually been observed experimentally. A similar analysis



(5)

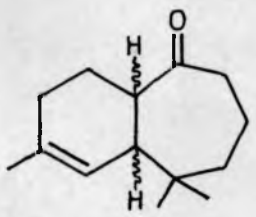
(6)

of the himachalanes (cis- and trans- ring junction) reveals

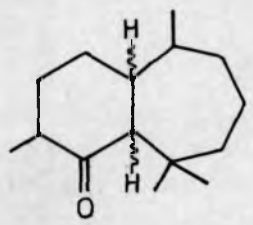
[+]For details, see Appendix to this Chapter.

that the presence of the gem-dimethyl grouping at C_{11} (himachalane numbering) accentuates the energy difference (estimated to be ~ 4 Kcal/mole*) between the cis- and trans-isomers, such that the trans-ketones (2- or 7-oxohimachalanes) would be favoured at equilibrium.

Ozonolysis of α-himachalene under carefully controlled conditions (ethyl acetate containing 1% pyridine and 1 mole of ozone at -70°) was investigated with the hope that the vinylidene linkage would be attacked preferentially to furnish the required ketone (7) suitable for equilibration studies. However, surprisingly, it was found that it is the trisubstituted ethylenic linkage which was preferentially attacked. Though this result could not have been predicted *a priori* for a cis-ring-fusion of the rings in α-himachalene, a study of the models indicates that only if the ring junction is cis, a preferential attack on the trisubstituted double bond could possibly be rationalized.



(7)



(8)

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*See Appendix to this Chapter.

The only alternative* available was to study the equilibration of ketone (8) described in the previous Chapter, though the ketone (8) is not ideally suitable for equilibration studies as results could be complicated because of an additional site for epimerization (C_3). However, clearcut evidence in favour of cis-junction in ∝-himachalene could be obtained from this study.

The ketone (8, henceforth referred to as ketone-I) obtained by borontrifluoride-induced isomerization of dihydro-∝-himachalene epoxide was found to be quite labile. By mere adsorption from its pet. ether solution of ketone-I on a column of alumina (grade II/neutral), ketone-I underwent epimerization to an isomer (ketone-II) to the extent of 8%. When pure ketone-I or ketone-II or their mixtures were treated with potassium tertiary butoxide in tertiary butanol, the product consisted of four ketones (Fig.I) in which the major component (55%) was a new ketone (ketone-IV), while ketone-II and ketone-I were formed to the extent of 30% and 5% respectively. It has been possible to separate these components with the exception of the other minor ketone-III. Table I summarises the properties of these isomeric ketones; their IR spectra are shown in Figs. XX (Chapter III), II and III.

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*In connection with the structure of himachalene monohydrochloride, the trans-ketone corresponding to (7) has been prepared and found to be stable to epimerizing conditions (vide Chapter V).

GAS-LIQUID CHROMATOGRAM

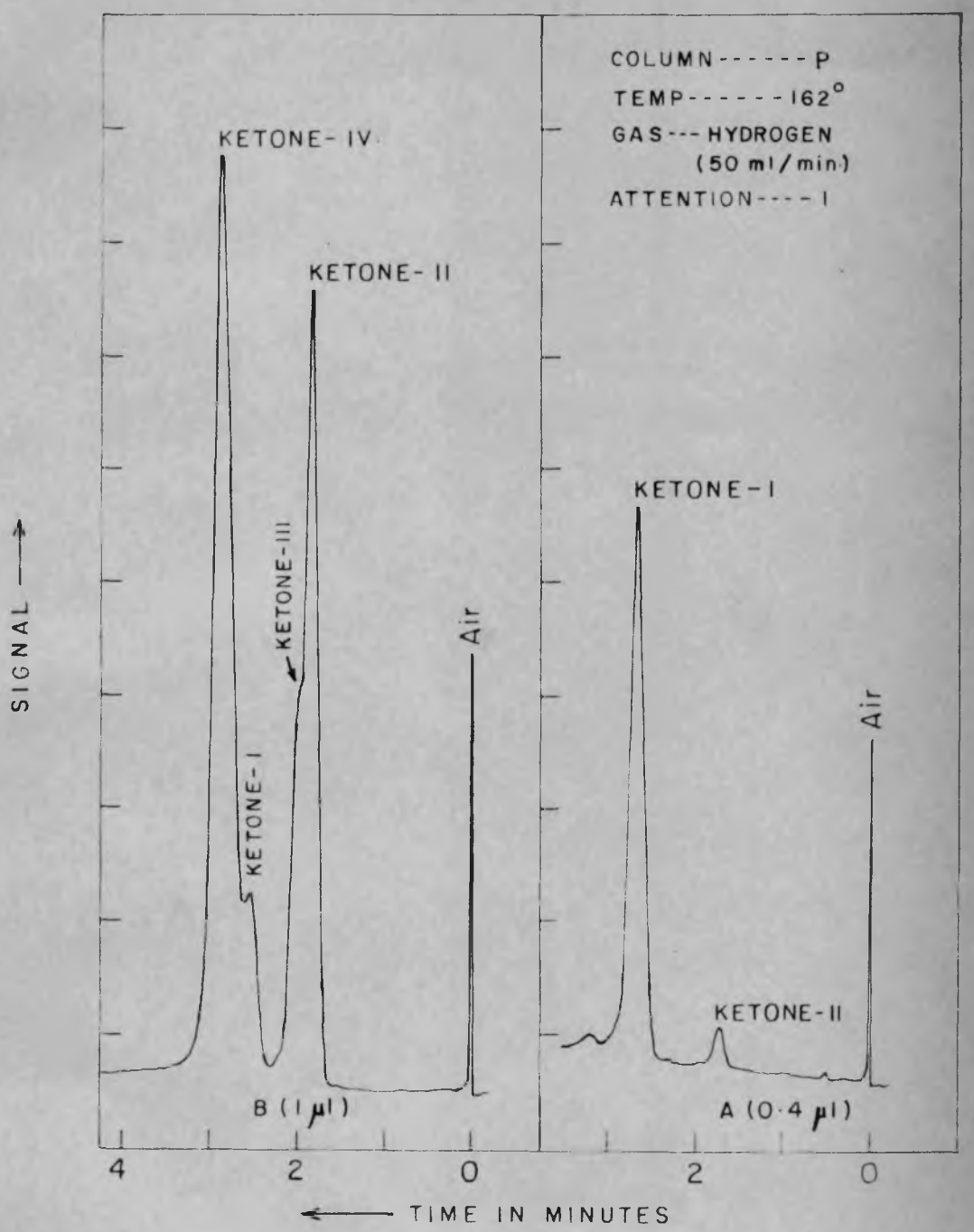


FIG. 1. EQUILIBRATION PRODUCTS OF KETONE-I

A) ALUMINA

B) POTASSIUM TERTIARY BUTOXIDE

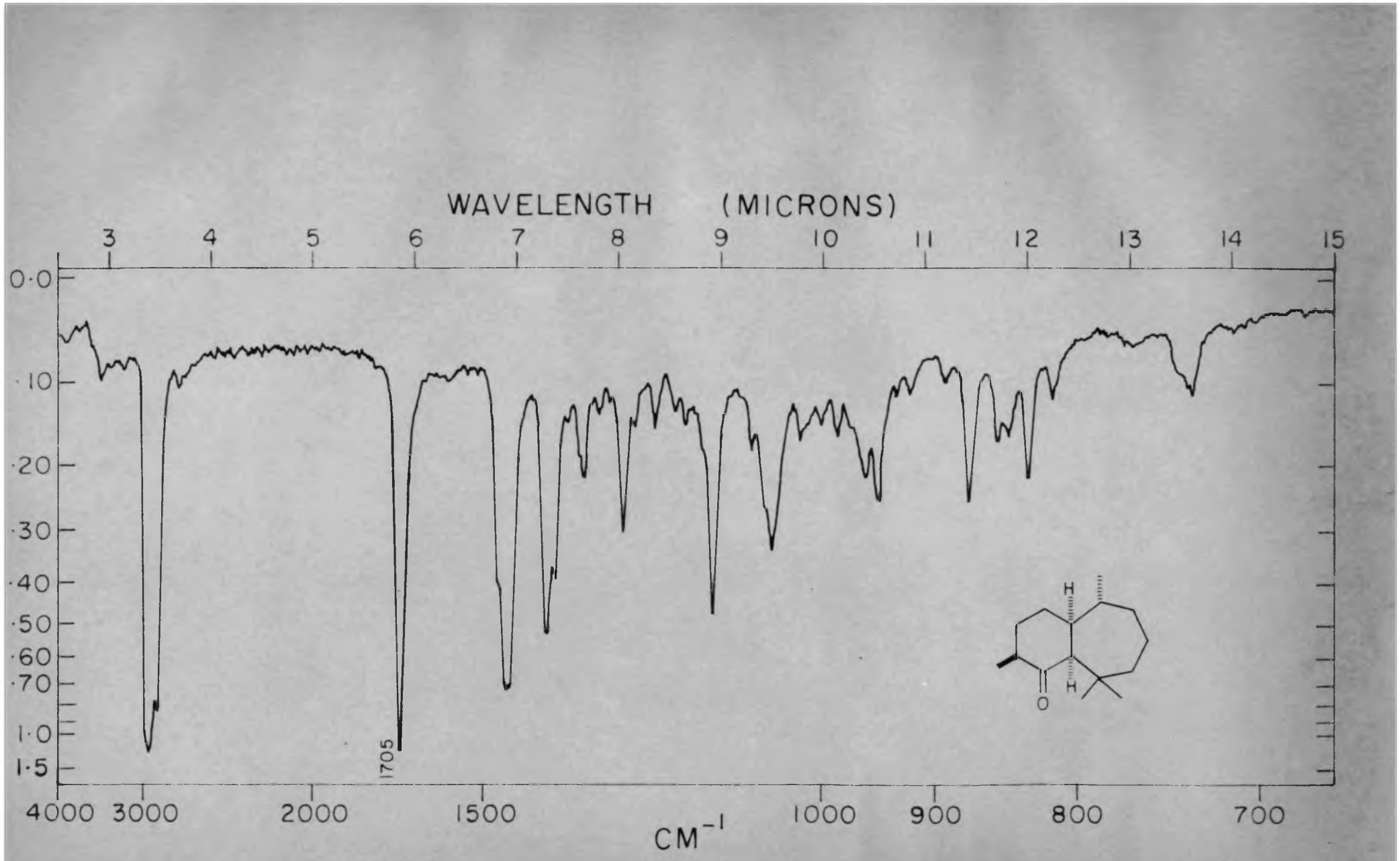


FIG. II. IR SPECTRUM OF KETONE-II

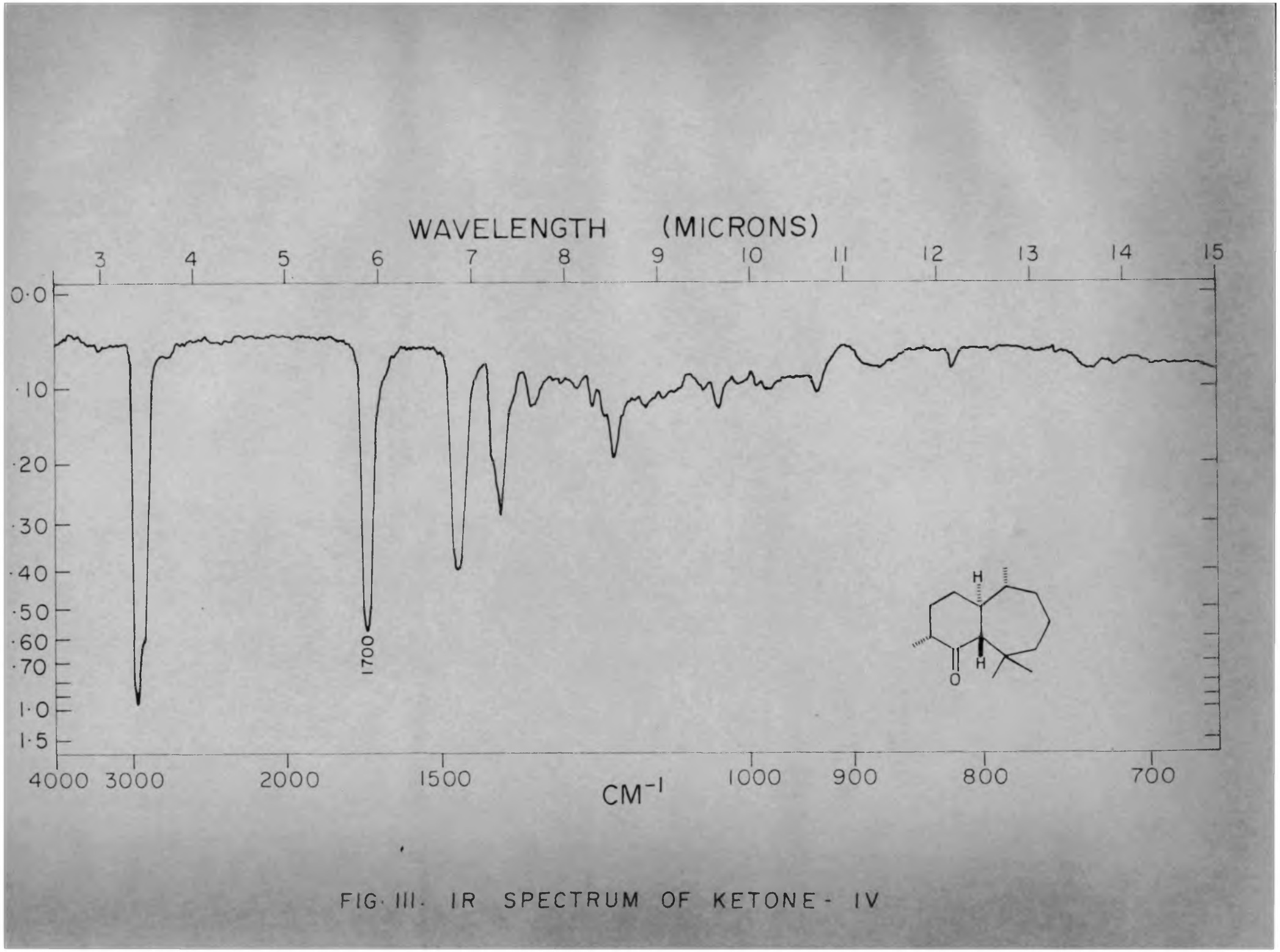


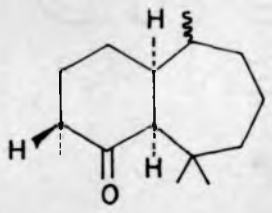
FIG. III. IR SPECTRUM OF KETONE - IV

TABLE I

Properties of isomeric ketones

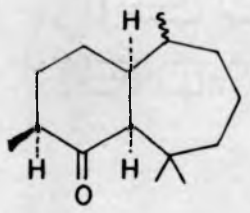
	Ketone-I	Ketone-II	Ketone-IV*
m.p.	42 - 43°	-	-
b.p.	-	128°(bath)/ 1.5 mm	128-130°(bath)/ 2 mm
n_D^{30}	-	1.4885	1.4888
$[\alpha]_D$	-93.56°	-10.6°	+79.6°
γ c=o	1697 cm^{-1}	1705 cm^{-1}	1700 cm^{-1}

*Only 83% pure by GLC, the contaminent being ketone-I (8%) and ketone-II (6%).



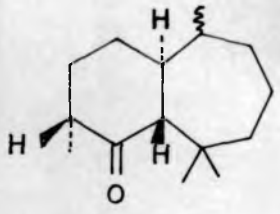
trans–cis

(9)



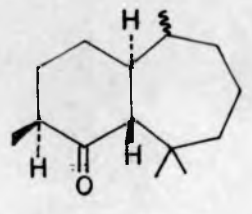
cis –cis

(10)



cis–trans

(11)

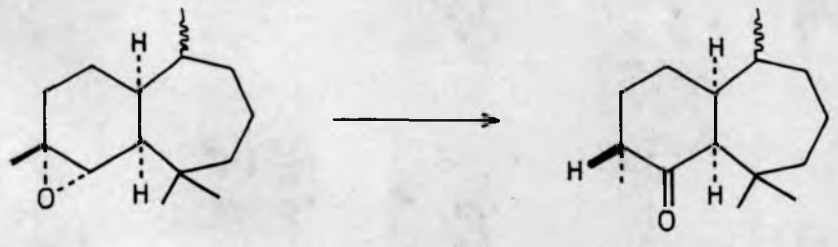


trans – trans

(12)

Four stereo-structures (9-12) are possible for the ketone (8)*. Since ketone-I is present only to a very small extent at equilibrium, this must represent the thermodynamically least stable isomer while ketone-IV which is greatly favoured at equilibration, should conform to the thermodynamically most stable structure. In view of the known behaviour of ketone (4) and a consideration of interaction energies discussed earlier, it follows that ketone-I be represented by (9) while stereo-structure (11) should be assignable to ketone-IV. It follows from this that in ∝-himachalene the rings must be cis-fused. On the basis of this formulation for ∝-himachalene, a closer look at the result of equilibration of the ketones can be made.

The epoxidation of dihydro-∝-himachalene should quite reasonably occur from the less hindered ∝-face of the molecule when dihydro-∝-himachalene epoxide** can be written as (13). The BF_3-induced isomerization of the epoxide is visualised as a one-step concerted process[4] leading to the stereostructure(9)

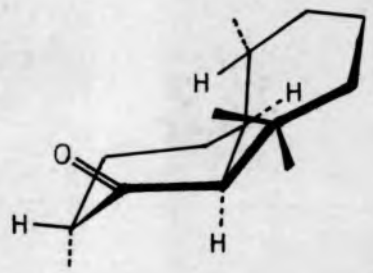


(13) (9)

*The stereochemistry at C_6 and C_7 will remain unchanged during epimerization.

**An examination of models (Dreiding) shows that in the

for the ketone-I. Of the several[+] conformers possible for (9), the conformation (14) appears to be most likely from a study of its NMR spectrum (Fig.IV). Ketone-I displayed its quaternary methyls at 45 and 73 cps while the remaining methyls occurred as doublets centered at 58 and 59 cps. It is clearly seen that one of the quaternary methyls has suffered considerable paramagnetic shift which



(14)

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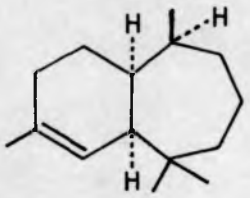
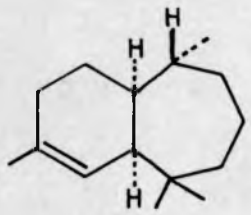
hydrogenation of ∝-himachalene, the attack on the semicyclic olefinic linkage could occur as to give (i) or (ii) depending on the conformation of the seven-membered ring in ∝-himachalene. However, in



(i)



(ii)

dihydro ∝-himachalene it is only the ∝-face which is less hindered for attack on the trisubstituted ethylenic linkage (in the six-membered ring) by the per acid.

[+]Eight well-defined conformations (see cis- perhydrobenzosuberane system in the Appendix).

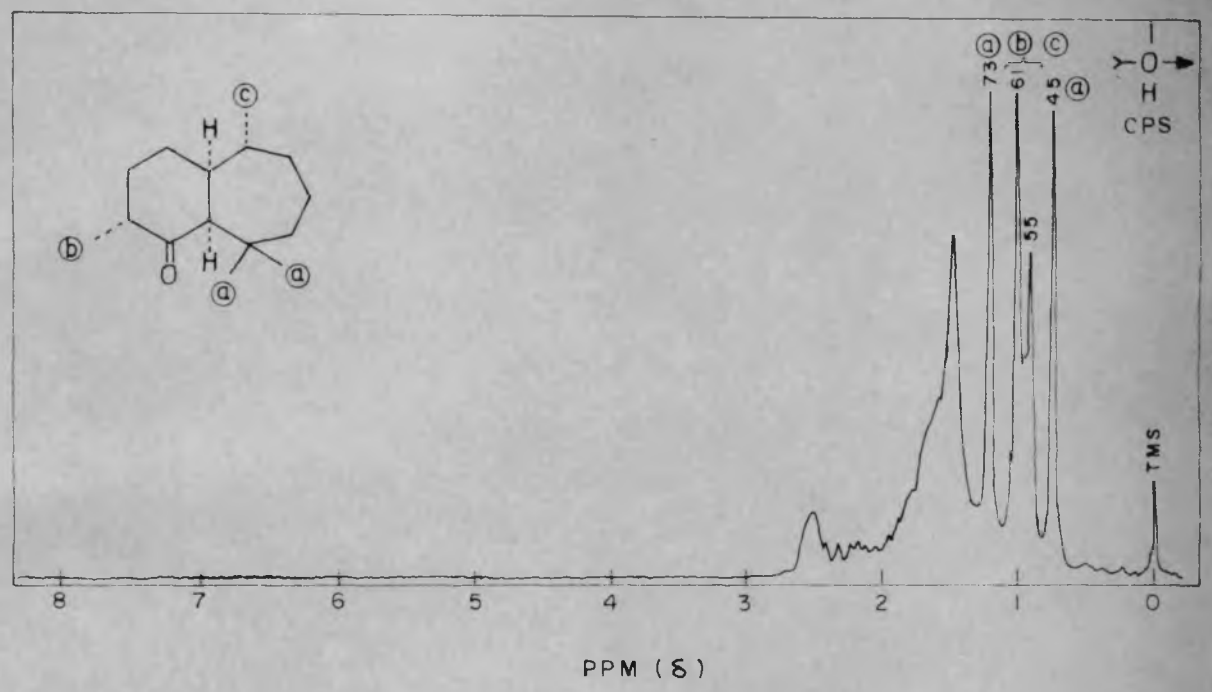


FIG. IV. NMR SPECTRUM OF KETONE-I.

could be explained only due to the anisotropy of C=O linkage, and for this to be effective only conformation (14) is tenable as is clear from Fig.V. Similar cases of deshielding

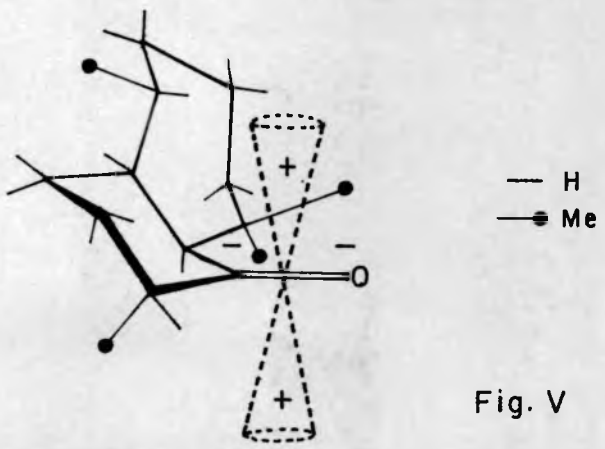
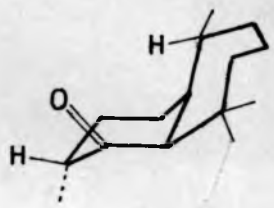


Fig. V

have been recorded in literature[5]. It must be pointed out that one consequence of this preferred conformation* for ketone-I

---

*From a consideration of interaction energy it is hard to see why this conformation should be preferred over (iii). However the "flip over" conformation in which the C_3-methyl and C_6-C_7 bond would become equatorial, would appear to be less likely as in these the C_1-C_{11} becomes axial and this carries a gemdimethyl group, thus greatly increasing the interaction energy.



(iii)

would be that the configuration of the methyl at C_7 should be as shown in (14), as, in the alternative conformation, the interaction between the C_7-methyl and β-methyl at C_{11} would be prohibitive.

The above conclusions about the stereochemistry of ketone-I are supported by circular dichroism (CD) measurements (Fig.VI). An application of the octant rule[6] (Fig.VII) would predict a negative Cotton effect for the conformation (14) of ketone-I and as can be seen from Fig.VI, it is experimentally borne out.

The preferred conformation of ketone-IV would appear to be (15) and this is in accord with the NMR spectrum (Fig.VIII): quaternary methyl signals at 55 and 58 cps. Octant rule (Fig.VII) would predict a positive sign for the Cotton effect for this conformation, as has been experimentally observed (Fig.VI).

Two alternative stereostructures (10,12) could be assigned to ketone-II. However a decision in favour of (10) can be arrived at on the basis of the fact that epimerization at C_1 in ketone-I (14) would necessarily take place through the "flip over" conformation as the trans-locking of the rings is possible only through the diequatorial bonds. This would mean that epimerization at C_1 would directly result in the most stable structure (ketone-IV). However, since this is not observed experimentally as partial epimerization of ketone-I over alumina did not produce

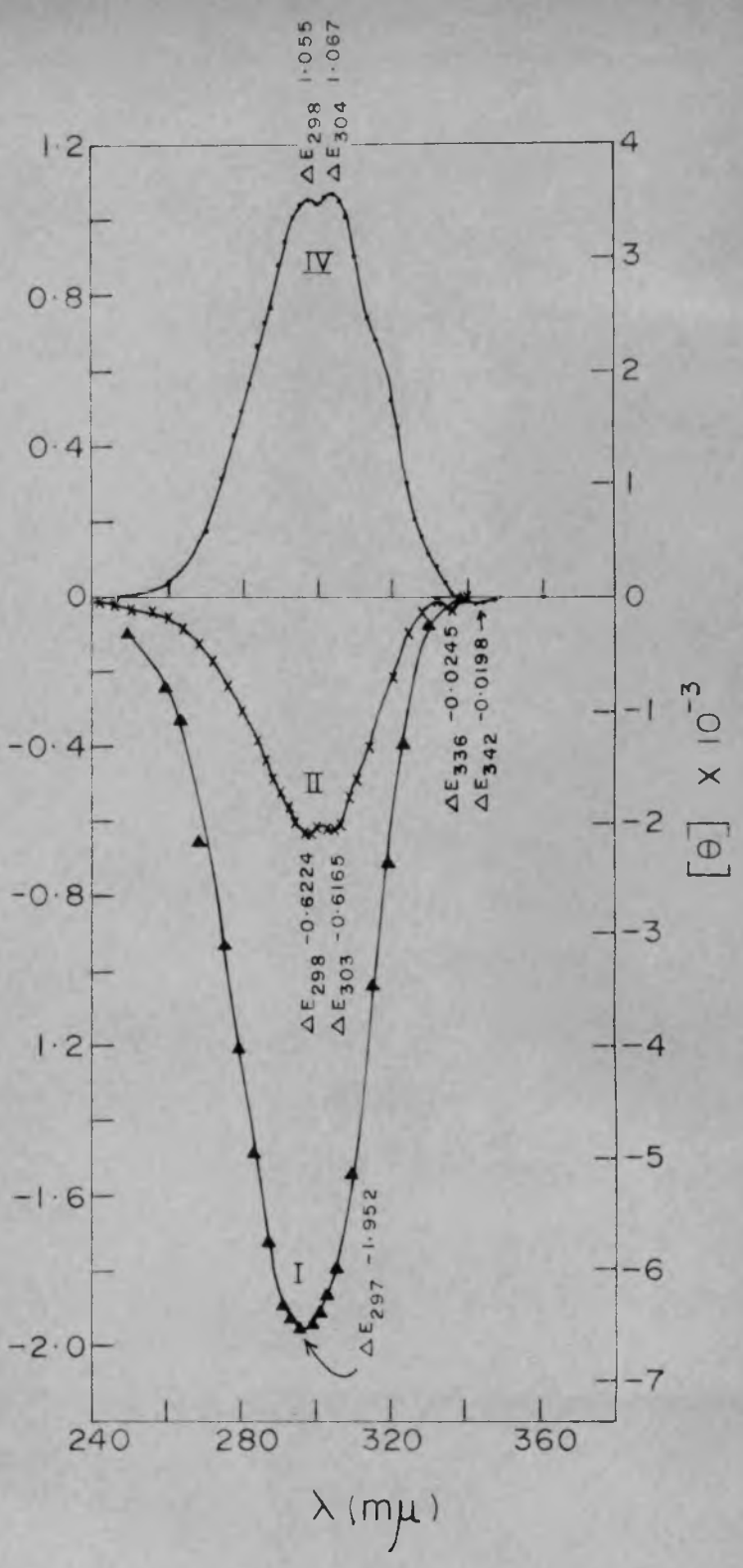
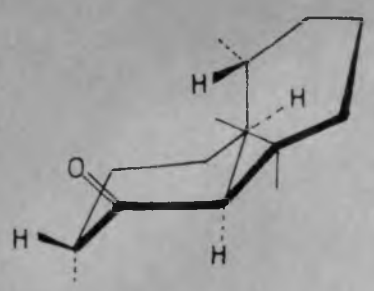
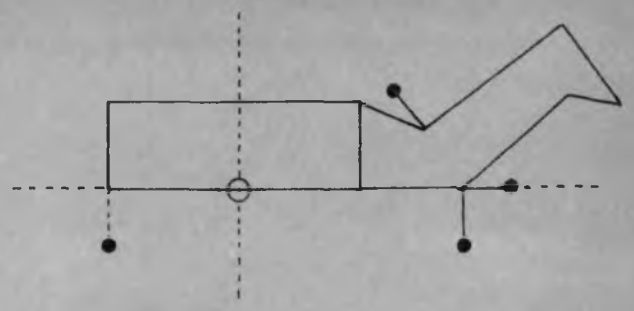


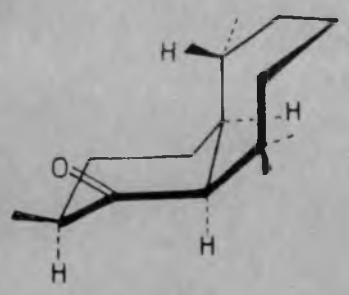
FIG. VI CD CURVES OF KETONES - I , - II AND - IV



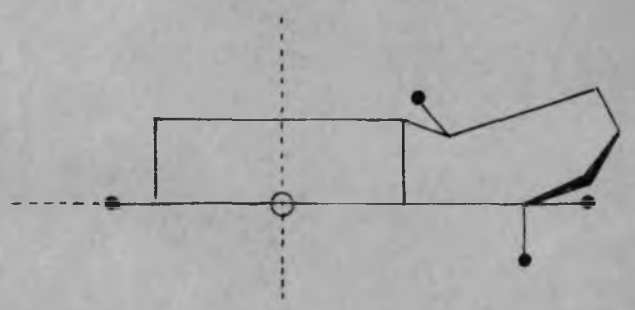
(14)



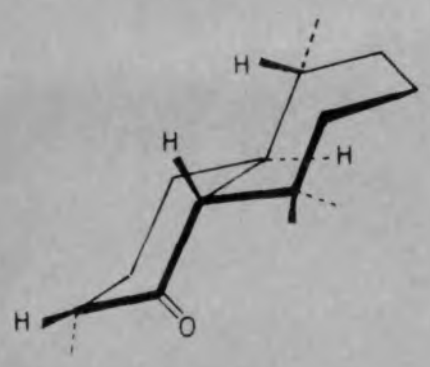
PREDICTION: NEGATIVE



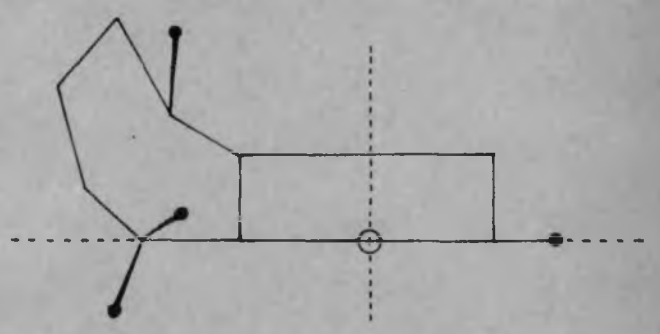
(16)



PREDICTION: WEAK NEGATIVE



(15)



PREDICTION: POSITIVE

FIG. VII. OCTANT DIAGRAMS OF KETONES - I (14), - II (16) AND - IV (15).

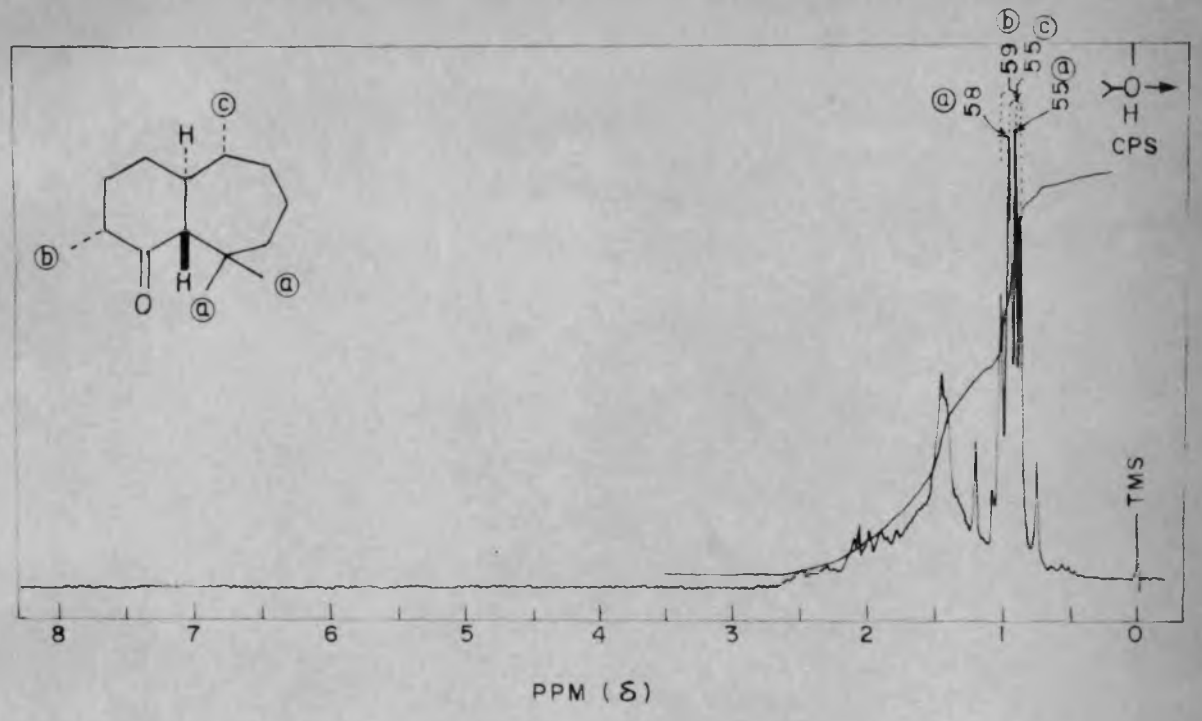


FIG. VIII NMR SPECTRUM OF KETONE - IV

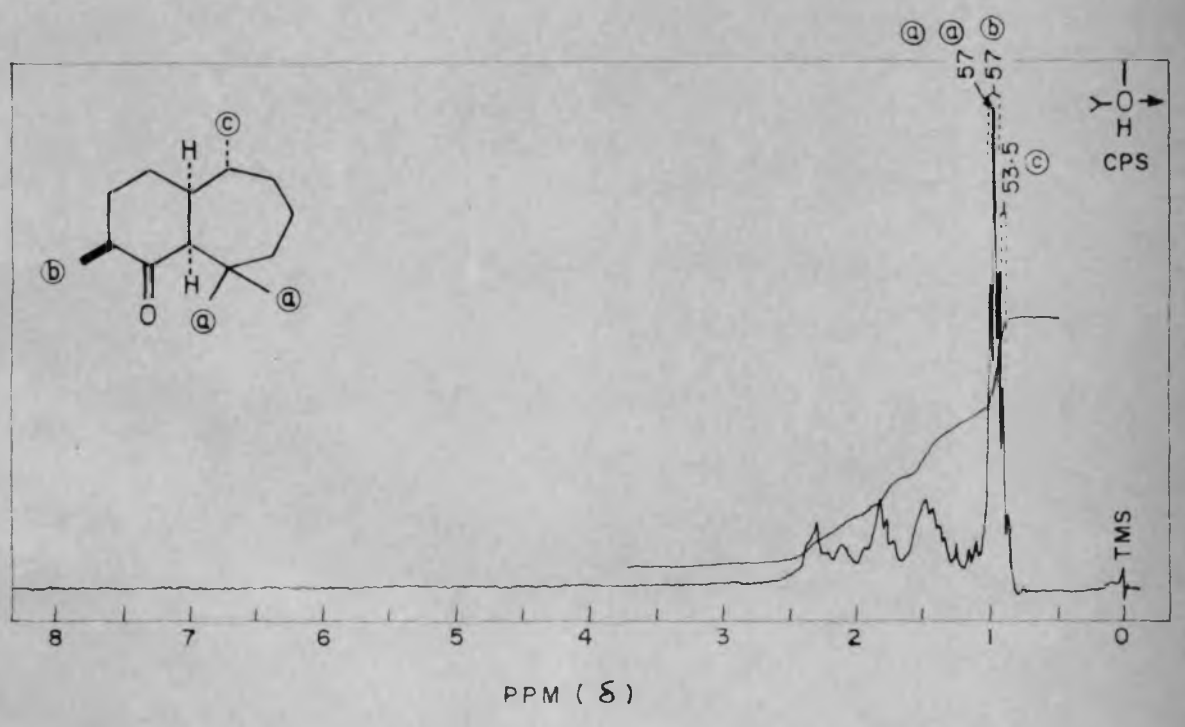
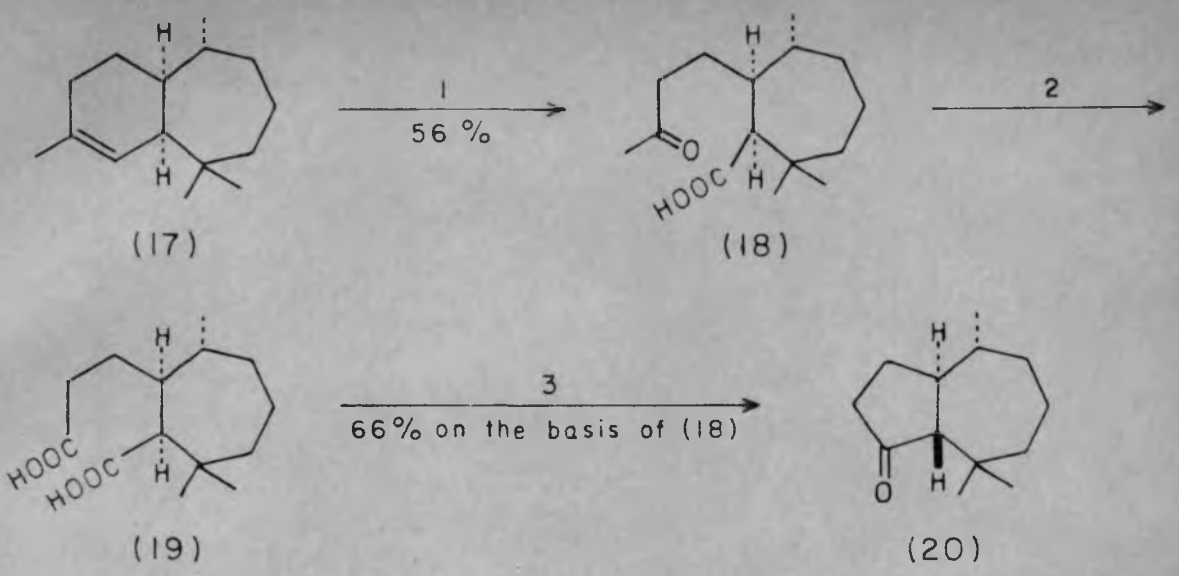


FIG. IX. NMR SPECTRUM OF KETONE- II

ketone-IV, but mostly ketone-II, it would mean that in this reaction only epimerization at C_3 has taken place and consequently ketone-II may be represented by (10). The preferred conformation for this would appear to be (16) which is consistent with its NMR (Fig.IX) and CD measurements (Figs.VI,VII).

Absolute stereochemistry: The consistency in the observed sign of the Cotton effect and that predictable on the basis of octant rule for the ketones I, II and IV, as discussed above, would require that these also represent the absolute stereochemistry of the molecules. This has been further checked by a direct chemical correlation of ∝-himachalene with a compound of known absolute stereochemistry.

Dihydro-∝-himachalene (17) was converted to ketone (20) by following the procedure outlined in Fig.X. It was anticipated that the product of the pyrolysis of the dicarboxylic acid (19) would be thermodynamically equilibrated[7]. The product was purified through its semicarbazone and the IR spectrum of the compound is shown in Fig.XI. This spectrum is almost superimposable on that of the crude product obtained after pyrolysis directly, which would mean that essentially a single ketone is produced in the Blanc reaction. The ketone was expected to have the trans-ring fusion in view of the known behaviour

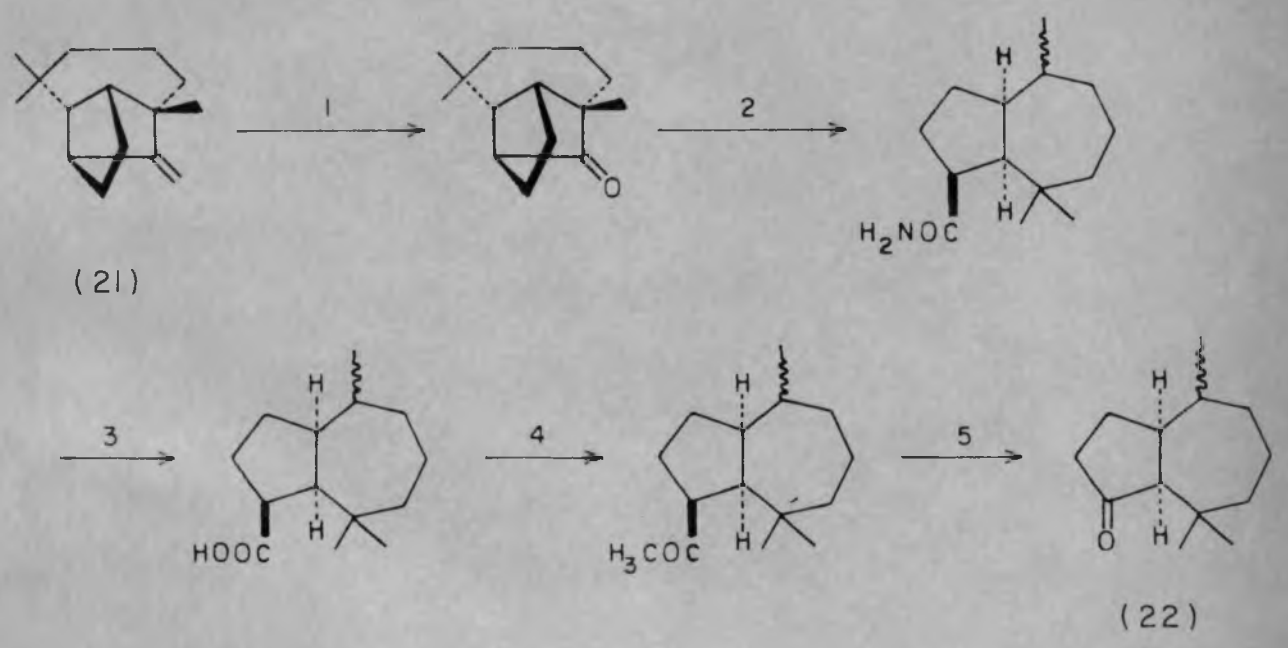


REAGENTS: 1, O_3 / $CHCl_3$ AT -10° ; H_2O_2 OXIDATION

2, NaOBr

3, PYROLYSIS OF Ba SALT

FIG. X.



REAGENTS: 1, O_3 ; 2, $NaNH_2$; 3, HYDROLYSIS ; 4, MeLi ;

5, CF_3COOOH, HYDROLYSIS, $Na_2Cr_2O_7$ / AcOH

FIG. XV.

of the bicyclo-(5,3,0)-decane[8] *. The NMR spectrum is shown in Fig.XIV. It should be noted that one of the quaternary methyl signals has considerably shifted downfield (70 cps) due to the anisotropy of C=O function.

Ourisson and co-workers** have carried out the degradation of longifolene (21), a compound of known absolute stereochemistry[10], to ketone (22) by the route outlined in Fig.XV. A direct comparison of the IR spectrum of this ketone (Fig.XII) with that of our material (Fig.XI) described above showed the two to be clearly different. However when these authors passed the ketone (22) through a column of basic alumina, equilibration took place to produce a material having its IR spectrum (Fig.XIII) almost

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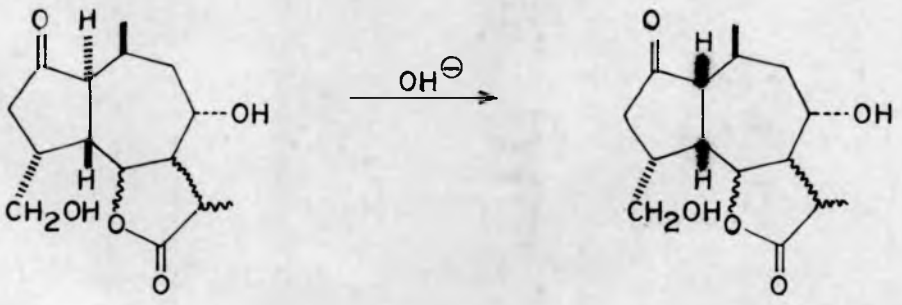
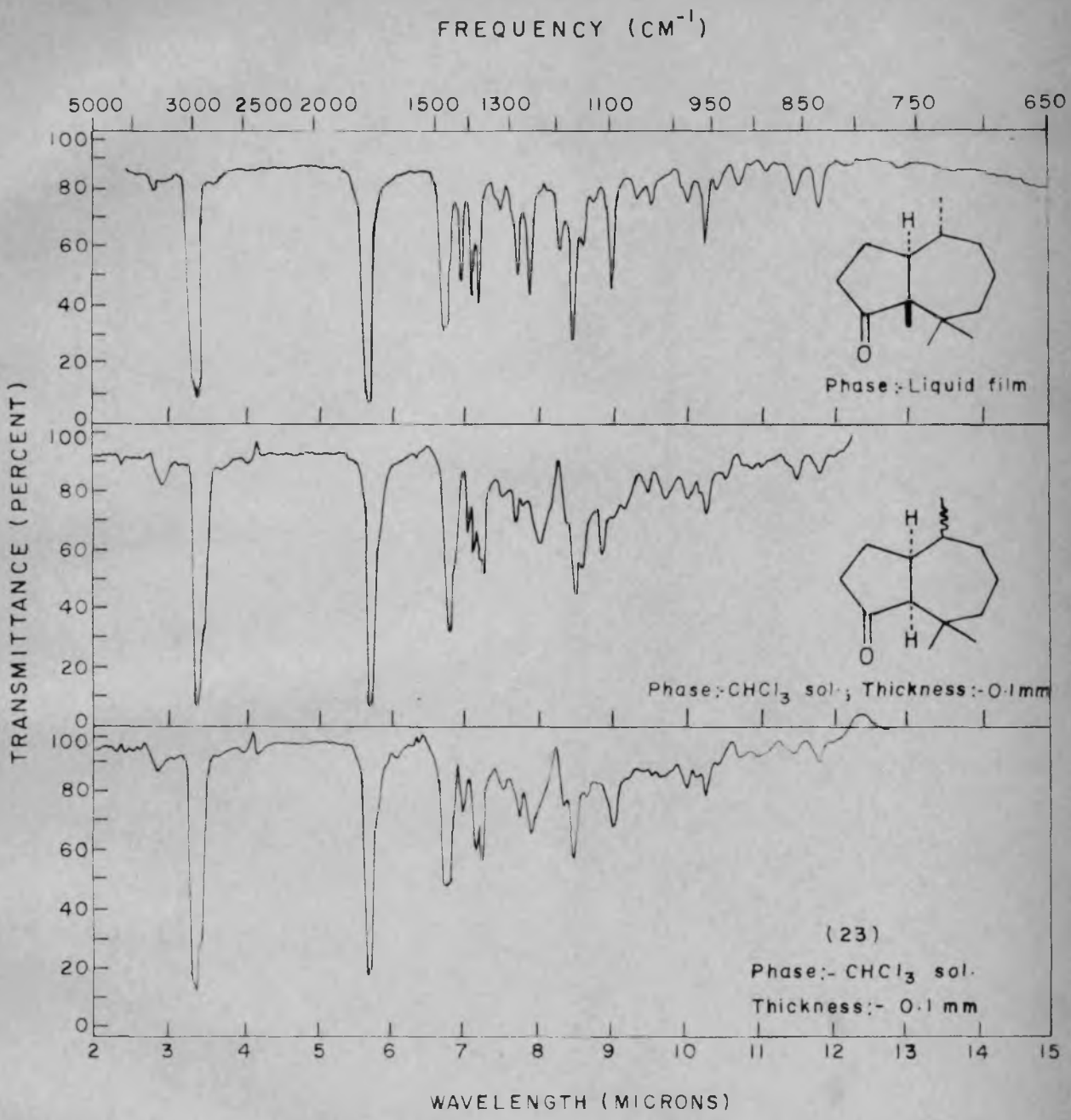
*However compare the base catalysed equilibration of hexahydrolactucin (iv) into iso-hexahydrolactucin (v)[9].



(iv) (v)

**We are grateful to Prof.G. Ourisson for this information prior to its publication.



FIGS. XI–XIII. IR SPECTRA OF KETONES (20),(22) AND (23)

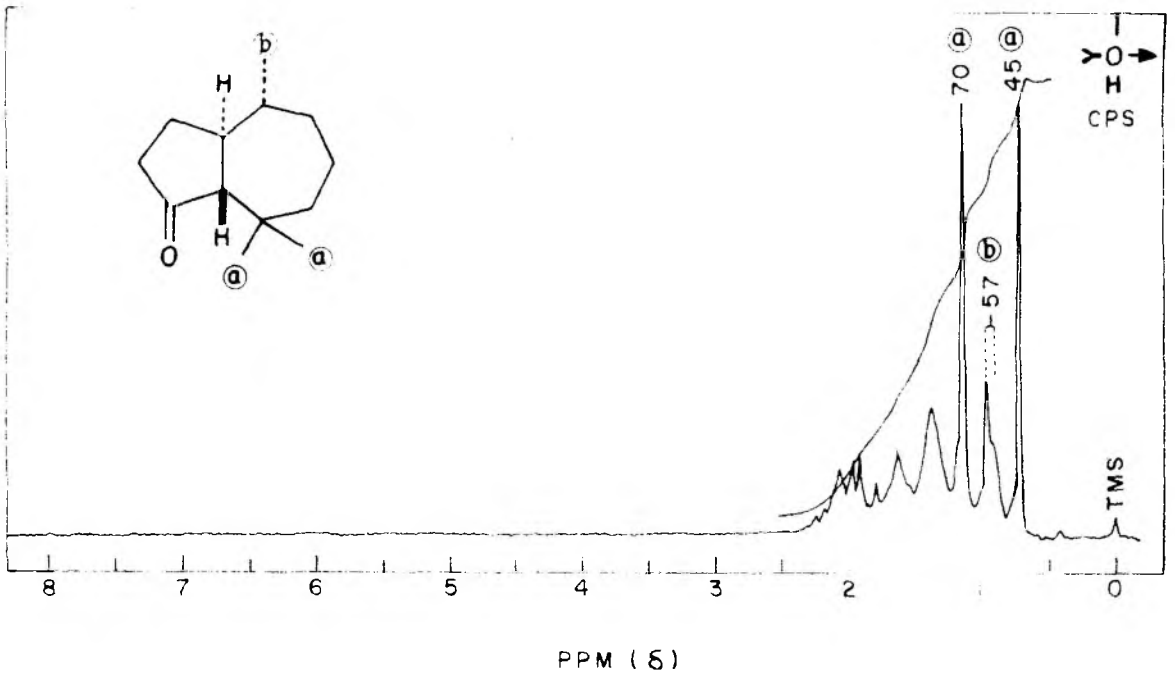
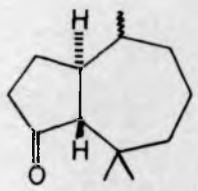


FIG XIV. NMR SPECTRUM OF KETONE (20)

identical with that of our ketone. Since in this treatment epimerization only at C_1 is possible, the equilibrated compound must be represented by (23).

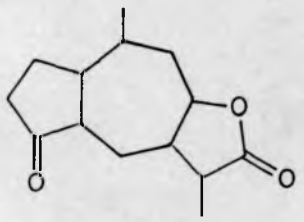


(23)

Fig.XVI depicts the CD curves for these three ketones. It is at once apparent that ketones (20, 23) have the same sign and position of the CD maxima* and consequently must have identical absolute stereochemistry. Thus ∝-himachalene must have the same absolute stereochemistry as longifolene and the absolute stereostructure (1) for ∝-himachalene follows.

---

*The difference in the intensity of absorption could either be assigned to lesser purity of their material or ketones (20,23) might differ in the configuration at C_6. Similar behaviour is shown by epimeric (at C_1) tetrahydromexicanin E[11] (vi).



(vi)

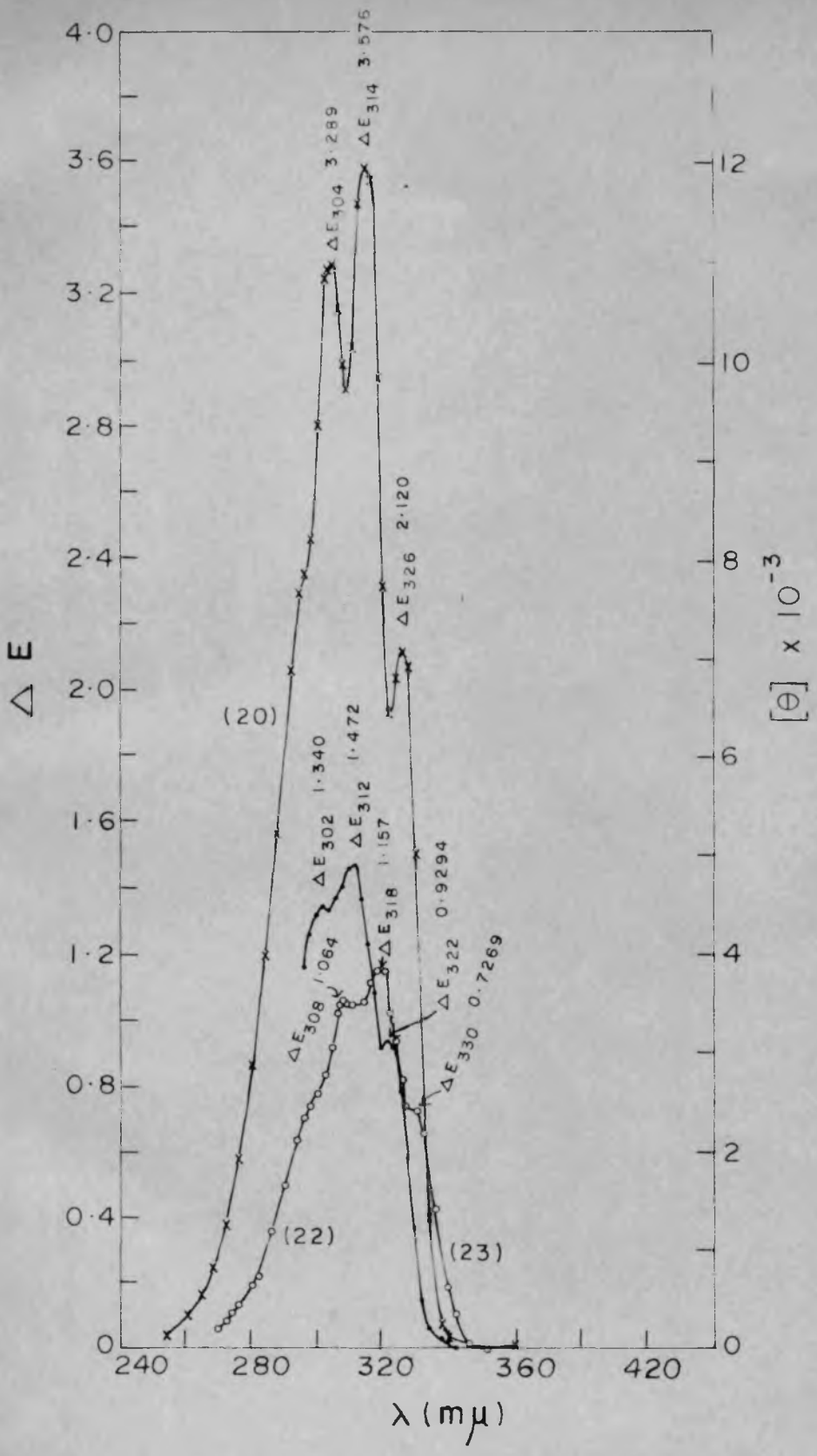


FIG. XVI. CD CURVES OF KETONES (20), (22), AND (23)

Several conformations for ∝-himachalene are possible assuming that both the rings are occurring in quasichair conformation. The conformation (24)* would appear to account best for the observed NMR spectrum wherein both the quaternary methyl groups have similar chemical shift (58, 60 cps) and the vinylic proton on the trisubstituted double bond must make a dihedral angle of $\sim 90^{\circ}$ with the adjacent proton at the ring junction to account for its non-coupling.

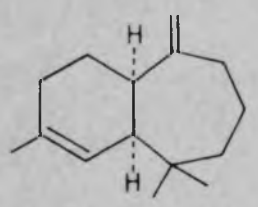
β-Himachalene

Since ∝- and β-himachalenesare related through the crystalline dihydrochloride during the formation of which, the asymmetric centre at C_1 remains unaffected, ∝- and β-himachalene must have the same absolute stereochemistry at C_1 and consequently, β must be represented as (2). Conformation (25) would appear to fit best for β-himachalene which will account for the observed shielding of one of the quaternary methyls and in this conformation, the mutual orientation of the olefinic linkage (C_6-C_7) and one of the methyls at C_{11} is such as to meet this requirement. The

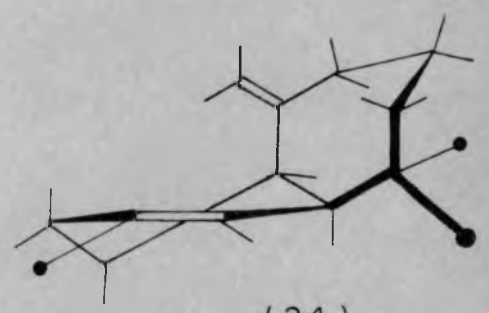
---

*This conformation should lead to dihydro-∝-himachalene wherein the methyl at C_7 would be trans to the bridgehead proton; this is opposite to what has been deduced earlier in connection with the conformation of ketone-I. This could be rationalized on the reasonable assumption that the conformation in which the molecule gets adsorbed on the catalyst surface is different from this.

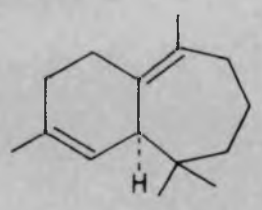
dihedral angle between the olefinic proton and the tertiary hydrogen at the ring junction is also in accord with the type of signal observed for the vinylic proton.



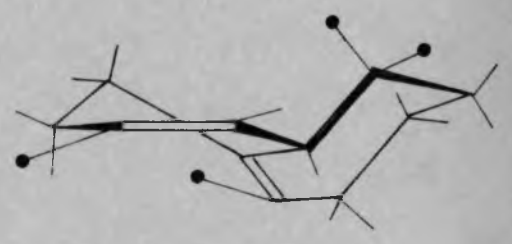
(1)



(24)



(2)



(25)

EXPERIMENTAL

For general remarks, please turn over to p.67. GLC reported herein were carried out on Aerograph, model A-350-B. The CD curves were taken in dioxane solution (2-3%) at the University of Strasbourg, through the kind courtesy of Prof. G. Ourisson.

Ozonolysis of α-himachalene

A solution of α-himachalene (1.117 g) in ethyl acetate (30 ml) containing pyridine (1%) was ozonised at -70° by bubbling ozonised oxygen (160 mg/hr, for 100 minutes, i.e. 1 mole). The solvent was removed under water pump suction (~50 mm) at room temp. and the ozonide was reduced by stirring with lithium aluminium hydride[12] (0.4 g) in ether (60 ml) for 2 hr under cooling and left overnight. A saturated solution of sodium potassium tartarate (10 ml) was added to this solution under cooling and the product extracted with ether (25 ml x 4), washed and dried. After solvent removal, a gummy product (1.2 g) was obtained which was purified by passing through a column of neutral alumina (gr.II, 18 x 1.6 cm, 38 g).

CHROMATOGRAM I

Fraction No.	Eluent	Volume (ml)	Wt.(mgs) of eluate
1	Pet.ether	4 x 50	203
2	Benzene	7 x 50	55
3	1% Methanol + 99% benzene	8 x 50	580
4	"	5 x 50	80
5	5% Methanol	4 x 50	86

The 3rd fraction after sublimation gave a yellow gum (0.55 g), b.p. 157° (bath)/1.6 mm, IR spectrum: OH 3333 cm^{-1}, >C = CH_2 893 cm^{-1}. (Found: C, 75.68, H, 12.10. $C_{15}H_{24}O_2$ requires: C, 74.95; H, 11.74%). Attempts to prepare 3,5-dinitrobenzoate or phenyl urethane failed to give a solid derivative.

Epimerization of ketone-I

The preparation of ketone-I (m.p. 42-43°) from dihydro-∝-himachalene has been described in the previous Chapter.

a) Epimerization over alumina: Pure ketone-I (0.103 g) in pet. ether solution (0.5 ml) was dropped on a column of neutral alumina (grade II, 27 x 0.7 cm, 5 g) and left for 40 hr. On elution after this interval, with pet.ether

(50 ml x 2), a liquid product (95 mg), b.p. 125-8°(bath)/ 1 mm, $[\alpha]_D$ - 87.2° (c, 3.33%) [cald. for a mixture of ketone-I and -II in the ratio 92:8 is -86.62°], was isolated. GLC of the product is shown in Fig.I.

b) Equilibration using potassium tertiary butoxide: Pure ketone-I (0.102 g) was refluxed with potassium tertiary butoxide (0.20 g of potassium dissolved in 5 ml of tertiary butanol) for 9 hr under nitrogen. The product was acidified with dil. HCl (0.6 ml of conc. HCl diluted to 10 ml) and extracted with ether (15 ml x 4) after saturating with ammonium sulphate. The ether extract was washed, dried and distilled after solvent removal; yield 75 mg, b.p. 140-145°(bath)/3 mm, n_D^{30} 1.4905, $[\alpha]_D$ +19.9° (c, 2.54%). GLC of this product is shown in Fig.I.

Ketone-II (42 mg, 83% pure) on similar equilibration yielded a mixture (24 mg), $[\alpha]_D$ +21.8° (c, 1.12%), consisting of ketones-II and -IV in the ratio 26:59 (GLC).

Isolation of ketone-II and ketone-IV: On preparative scale, a mixture of ketones-I and-II (75:15, 0.712 g) was refluxed (3 hr) with potassium tertiary butoxide (1.5 g of potassium dissolved in 37.5 ml of tertiary butanol) under nitrogen and worked up as detailed above; yield 0.624 g, b.p. 117-118°/ 2 mm. The equilibrated product (0.460 g) was chromatographed on a column of neutral alumina (grade II, 24 x 1.7 cm, 46 g) and the following fractions were collected.

CHROMATOGRAM II

Fraction No.	Eluent	Volume (ml)	Wt.(mgs) of eluate	Remarks.
1	Pet.ether	5 x 20	42	
2	"	3 x 20	72	Ketone-II (100% pure)
3	"	8 x 20	86	Mixture
4	" 10% benzene 100% benzene	12 x 40 4 x 40 2 x 30	185	Ketone-IV (75% pure)
5	Benzene	8 x 30	5	-

Fraction 2 was distilled; yield 47 mg, b.p. 128°(bath)/1.5 mm, n_D^{30} 1.4880, $[\alpha]_D$ -10.6° (c, 2.92%). (Found: C, 81.37; H, 11.72. $C_{15}H_{26}O$ requires: C, 81.01; H, 11.79%).

Fraction 4 (0.160 g) rich in ketone-IV was rechromatographed on neutral alumina column (grade II, 1 x 27.5 cm, 20 g). The major portion was eluted with pet. ether (10 x 40 ml) and distilled; yield 70 mg, b.p. 128-130°(bath)/3 mm, n_D^{30} 1.4888, $[\alpha]_D$ +79.1° (c, 2.07%). GLC showed it to be 83% rich in ketone-IV. (Found: C, 81.08; H, 12.12. $C_{15}H_{26}O$ requires: C, 81.01; H, 11.79%).

Ozonolysis of dihydro-α-himachalene

A solution of dihydro-α-himachalene (5.3 g) in $CHCl_3$ (60 ml) containing pyridine (1%) was ozonised at -10° by bubling ozonised oxygen (~ 180 mg/hr) till it was no longer

absorbed (6hr, KI solution test). The solvent was removed under water pump suction (~ 50 mm) at room temp. and the ozonide was decomposed by warming gently with hydrogen peroxide (30%, 15 ml), water (25 ml) and sodium carbonate (2.5 g), first at 60° (1 hr) and finally at 100° (2 hr). The product was cooled and extracted with ether (20 ml x 3) to yield a gum (1.5 g) which was not examined further. The aqueous alkaline layer was acidified (8 ml of H_3PO_4) and extracted with ether (25 ml x 4) after saturating with ammonium sulphate. The extract was washed, dried and ether removed to yield crude acid (3.7 g).

A portion of the acid (0.310 g) was esterified (diazomethane); yield 0.310 g, b.p. 105-107°/2 mm; n_D^{30} 1.4765. It readily formed a semicarbazone (pyridine method) which after crystallisation was obtained in white crystals m.p. 193-195°C.

The above acid (2.77 g) was treated with semicarbazide hydrochloride (1.6 g) dissolved in water (2 ml) and pyridine (1.6 ml), followed by ethanol (10 ml) to make the solution homogeneous. After 48 hr, the separated product (3 g, m.p. 182-183°) was collected and crystallized from ethanol twice to yield white shining flakes; m.p. 195-196°. (Found: N, 13.6. $C_{16}H_{29}O_3N_3$ requires: N, 13.49%).

The semicarbazone (1.2 g), oxalic acid (2.4 g) in water (17 ml) and toluene (20 ml) were mixed and refluxed

under stirring till a clear solution was obtained (2 hr). The organic layer separated and the aqueous layer extracted with ether (15 ml x 3), and the combined organic layers washed with brine and dried. After solvent removal, the product (0.850 g) was used for the hypobromite oxidation. An analytical sample was obtained by distilling a small portion of the purified keto-acid; b.p. 165°(bath)/1.3. (Found: C, 71.27; H, 10.69. $C_{15}H_{26}O_3$ requires: C, 70.83; H, 10.30%).

Sodium hypobromite oxidation

The purified keto-acid (1.25 g) in dioxane (21 ml) was treated with sodium hypobromite [1.2 ml of bromine dissolved in a solution of NaOH (2.7 g in 21 ml of water)] in the course of 55 minutes at 0° and with stirring. The product was stirred for 3 more hr and left overnight. To the above solution, sodium bisulphite (1.5 g) was added to destroy the excess of hypobromite and acidified with conc. HCl (25 ml). It was extracted with ether (20 ml x 5) after saturating with ammonium sulphate, washed, dried and solvent removed; yield 1.273 g.

Ketone (20): The above oxidation product (1.273 g) was mixed with iron powder (1.2 g) and barium hydroxide (0.3 g) and dry distilled at 250 mm. The residue left was steam-distilled (1.5 ml) and the total distillate extracted with ether (3 ml x 4) and dried. After solvent removal, the product was distilled; yield 0.612 g, b.p. 92-94°/1.5 mm,

n_D^{30} 1.4847. An analytical sample of the saturated ketone was prepared via its semicarbazone (see below) by oxalic acid treatment; b.p. 89.5-90°/1.5 mm, n_D^{30} 1.4820, $[\alpha]_D$ +189.1° (c, 2.6%), (Found: C, 80.54, H, 11.60. $C_{13}H_{22}O$ requires: C, 80.35; H, 11.41%).

The pyrolysis product was converted into its semicarbazone (pyridine method) as described earlier and after repeated recrystallization (benzene-MeOH) gave an analytical sample m.p. 202-202.5° (Found: C, 67.3, H, 10.14. $C_{14}H_{25}ON_3$ requires: C, 66.89, H, 10.03%).

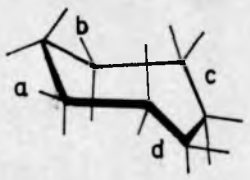
The semicarbazone was converted into 2,4-dinitrophenyl hydrazone as described earlier, which after repeated crystallizations from ethanol gave shining yellow flakes, m.p. 174-175°C.

Equilibration: Pure ketone (20, 97 mg) was refluxed with potassium tertiary butoxide (0.2 g potassium dissolved in 5 ml of tertiary butanol) for 3 hr under nitrogen and worked up as described earlier; yield 72 mg b.p. 89-90°/1.5 mm, n_D^{34} 1.4793, $[\alpha]_D$ +173.8° (c, 2.75%). The IR spectrum of the equilibrated product was superimposable on that of starting ketone.

APPENDIX

It is generally agreed that the stable conformation of cycloheptane is a deformed chair[13,14,9]. Cyclohexane chair can be fused on to a cycloheptane chair on anyone of the four bonds marked a, b, c and d without deforming the original conformations. Thus we have a total of four conformations possible for trans-fusion (Fig.XVII) and eight for cis-fusion (Fig.XVIII) ignoring of course the mirror images and considering only the chair-chair conformers. The interaction energy of these structures (see Tables III - VI) calculated by examining the models (Dreiding) for extra butane interaction, resulting on fusion of the two chairs and evaluating their energy content from the potential energy for n-butane (Table II) and the dihedral angles (accuracy of measurements $\pm$ 5°) of the interaction.

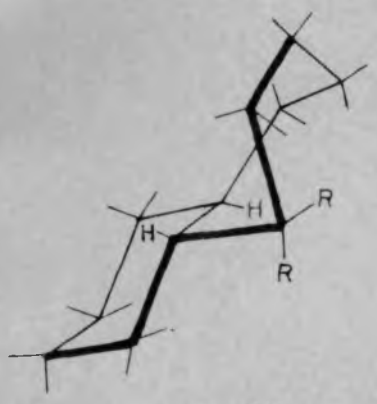
It may also be pointed out that structures resulting from the fusion of cyclohexane chair at a or b are readily interconvertible by a slight manipulation of the carbon 9 (in viii); other two structures are rigid, their entropy factor like the interaction energy (see below) would favour structures with fusion at a or b*.



(vii)

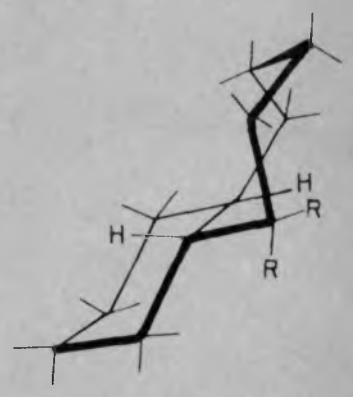
*See also Ref.13a.

TRANS-BICYCLO-[5,4,0]-UNDECANE, CHAIR-CHAIR CONFORMATIONS



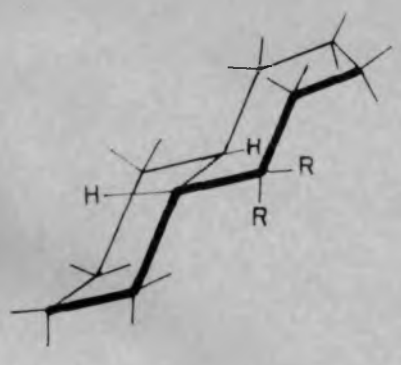
viii

FLEXIBLE (ΔE , 2·1 kcal/mol)



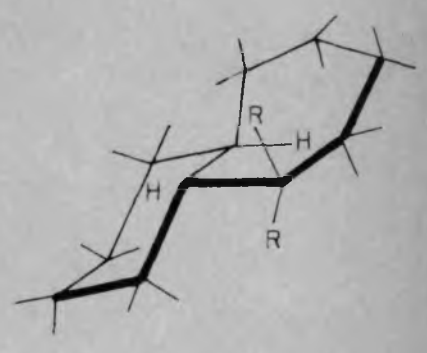
x

RIGID (ΔE , 4·7 kcal/mol)



ix

FLEXIBLE (ΔE , 2·1 kcal/mol)

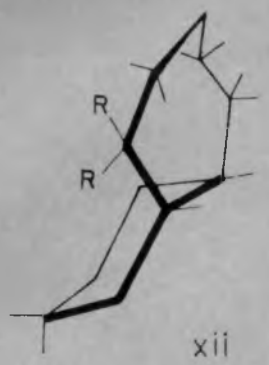


xi

RIGID (ΔE , 4·3 kcal/mol)

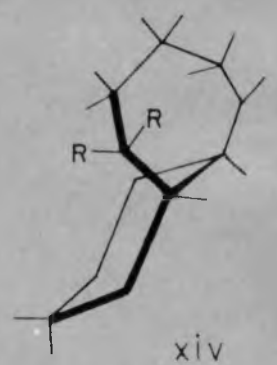
FIG · XVII

CIS-BICYCLO-[5,4,0]-UNDECANE, CHAIR-CHAIR CONFORMATIONS



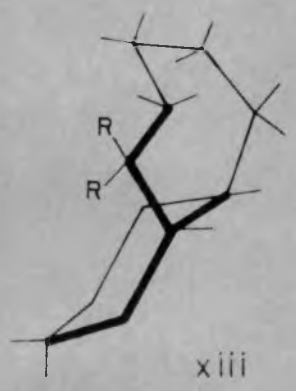
xii

FLEXIBLE (ΔE, 5·9 kcal)



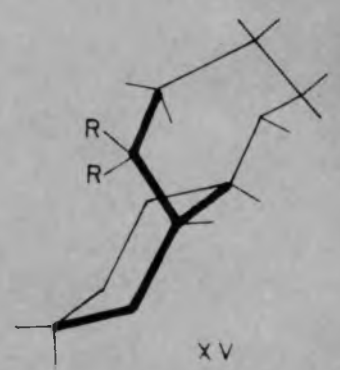
xiv

RIGID (ΔE, 7·5 kcal)



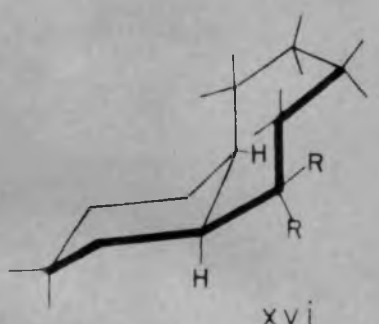
xiii

FLEXIBLE (ΔE, 5·6 kcal)



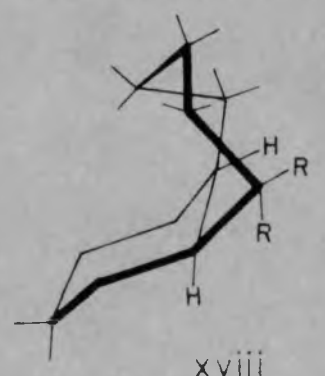
xv

RIGID (ΔE, 6·4 kcal)



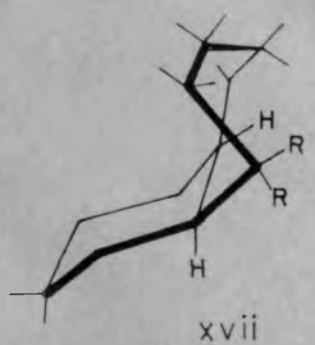
xvi

FLEXIBLE (ΔE, 5·7 kcal)



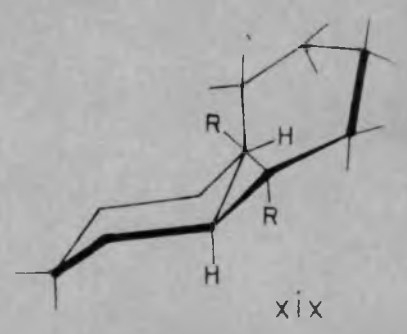
xviii

RIGID (ΔE, 7·3 kcal)



xvii

FLEXIBLE (ΔE, 5·9 kcal)



xix

RIGID (ΔE, 6·2 kcal)

TABLE II

Values for dihedral angles derived from the potential function for the rotation of n-butane about its central bond*

Dihedral angles	Kcal.	Dihedral angle	Kcal
15°	4.5	85	1.5
20	4.4	90	1.7
25	3.9	95	2.0
30	3.6	100	2.6
40	2.8	110	2.9
45	1.6	120	3.5
50	1.05	130	3.0
55	0.9	140	2.6
60	0.9	150	1.65
70	1.05	160	0.75
75	1.05	170	0.30
80	1.20		

*Values are derived from the curve given on p.126 of Ref.3b.

TABLE III

Interaction energy of different conformations of trans-bicyclo-(5,4,0)-undecane.

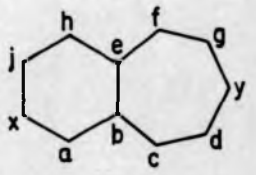
Conformation R=H	Interaction*	Dihedral angle.	E (Kcal/mole)	Total E (Kcal/mole)
viii	ab,cd	145°	2.1	
	ab,ef	180°	0	
	cb,ax	"	"	
	cb,eh	"	"	
	he,fg	""	"	
	fe,hj	"	"	2.1
ix	ab, cd	180°	0	
	ab, ef	"	"	
	cb, ax	"	"	
	cb, eh	"	"	
	he, fg	145	2.10	
	fe, hj	180	0	2.10
x	ab, cd	130	3.0	
	ab, ef	180	0	
	cb, ax	"	"	
	cb, eh	"	"	
	he, fg	90	1.7	
	fe, hj	180	0	4.7

...contd.

TABLE III (Contd.)

Conformation R=H	Interaction*	Dihedral angle.	E (Kcal/mole)	Total E (Kcal/mole)
xi	ab, cd	105	2.7	
	ab, ef	180	0	
	cb, ax	"	"	
	cb, eh	"	"	
	he, fg	150	1.65	
	fe, hj	180	0	4.35

*After cancelling out the interactions common for all chair conformations (for e.g. cdyg in viii) there remains six interactions which are to be taken into account and these are:



1) ab, cd
2) ab, ef
3) cb, ax
4) cb, eh
5) he, fg
6) fe, hj

TABLE IV

Interaction energy of different conformations of 11,11-dimethyl trans-bicyclo-[5,4,0]-undecane.

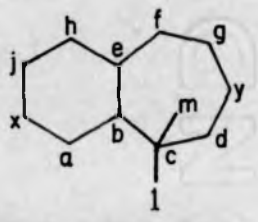
Conformation R=CH_3	Interaction*	Dihedral angle.	E (Kcal/mole)	E for confn. R=H	Total
viii	1c, ba	20°	4.4	2.1	16.5
	1c, be	140	2.6		
	1c, dy	180	0		
	mc, ba	95	2.0		
	mc, be	20	4.4		
	mc, dy	50	1.0		
ix	1c, ba	70	1.0	2.1	9.65
	1c, be	180	0		
	1c, dy	160	0.75		
	mc, ba	70	1.0		
	mc, be	70	1.0		
	mc, dy	35	3.2		
x	1c, ba	15	4.5	4.7	18.9
	1c, be	140	2.6		
	1c, dy	180	0.0		
	mc, ba	20	4.4		
	mc, be	90	1.7		
	mc, dy	50	1.0		

.....contd.

TABLE IV (Contd.)

Conformation R=CH_3	Interaction*	Dihedral angle.	E (Kcal/mole)	E for confn. R=H	Total.
xi	lc, ba	20	4.4	4.35	21.05
	lc, be	140	2.6		
	lc, dy	150	1.65		
	mc, ba	150	1.65		
	mc, be	95	2.0		
	mc, dy	20	4.4		

*With the introduction of a gem dimethyl group at C_{11} six additional interactions, lcba mcba lcbe mcbe lcdy mcdy



are introduced.

Similarly, the interaction energy of the different cis- conformations of bicyclo-[5,4,0]-undecane and its 11,11-dimethyl derivative has been calculated and summarised in Table V.

TABLE V

Interaction energy of different conformation of cis- bicyclo-[5,4,0]-undecane and its 11,11-dimethyl derivative

Conformation	E (kcal/mole)	
	R = H	R = CH_3
xii	5.9	
xiii	5.6	
xiv	7.5	
xv	6.45	
xvi	5.7	12.95
xvii	5.9	16.75
xviii	7.3	17.85
xix	6.25	20.15

SUMMARY

∝-Himachalene has been shown to possess the absolute stereochemistry represented in (24), on the basis of equilibration studies and CD measurements, carried out on ketone (9). This is further supported by the correlation of ∝-himachalene

with longifolene, through a common derivative (20). The absolute stereochemistry (25) of β-himachalene has been deduced.

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(b) see: p.252 in Ref.3b.
(c) R. Paunez and D.Ginsburg, Tetrahedron 9, 40 (1960).

CHAPTER V

STRUCTURE OF HIMACHALENE MONO-HYDROCHLORIDE AND THE PREPARATION OF TRANS-HIMACHALENES

It has been mentioned in Chapter III that himachalene dihydrochloride on mere recrystallisation from methanol yields a monohydrochloride for which several structures can be written. Moreover, since both α- and β-himachalene yield the same dihydrochloride, the stereochemistry at the ring junction may or may not be same as in α-himachalene and in view of the reaction conditions employed in the preparation of the dihydrochloride, it is quite conceivable that the dihydrochloride may, in fact, be a product of thermodynamic control. It was to settle these points that the work described in this Chapter was undertaken.

STRUCTURE OF HIMACHALENE MONOHYDROCHLORIDE

In the IR (Fig.I), the monohydrochloride clearly showed the presence of a vinylidene linkage (3040, 1635 and 887 cm^{-1}). Its PMR spectrum (Fig.II) showed the presence of two quaternary methyls at 48 and 54 cps, a quaternary methyl attached to a carbon carrying chlorine at 97 cps and a two proton signal (very slightly split) at 281 cps assignable to the two protons of the vinylidene linkage. These data help to restrict the number of structures possible for himachalene monohydrochloride to (1) and (2). The monohydrochloride on ozonolysis, followed by dehydrohalogenation yielded a mixture of two ketones (46:52, Fig.III) which were separated by preparative GLC; their properties

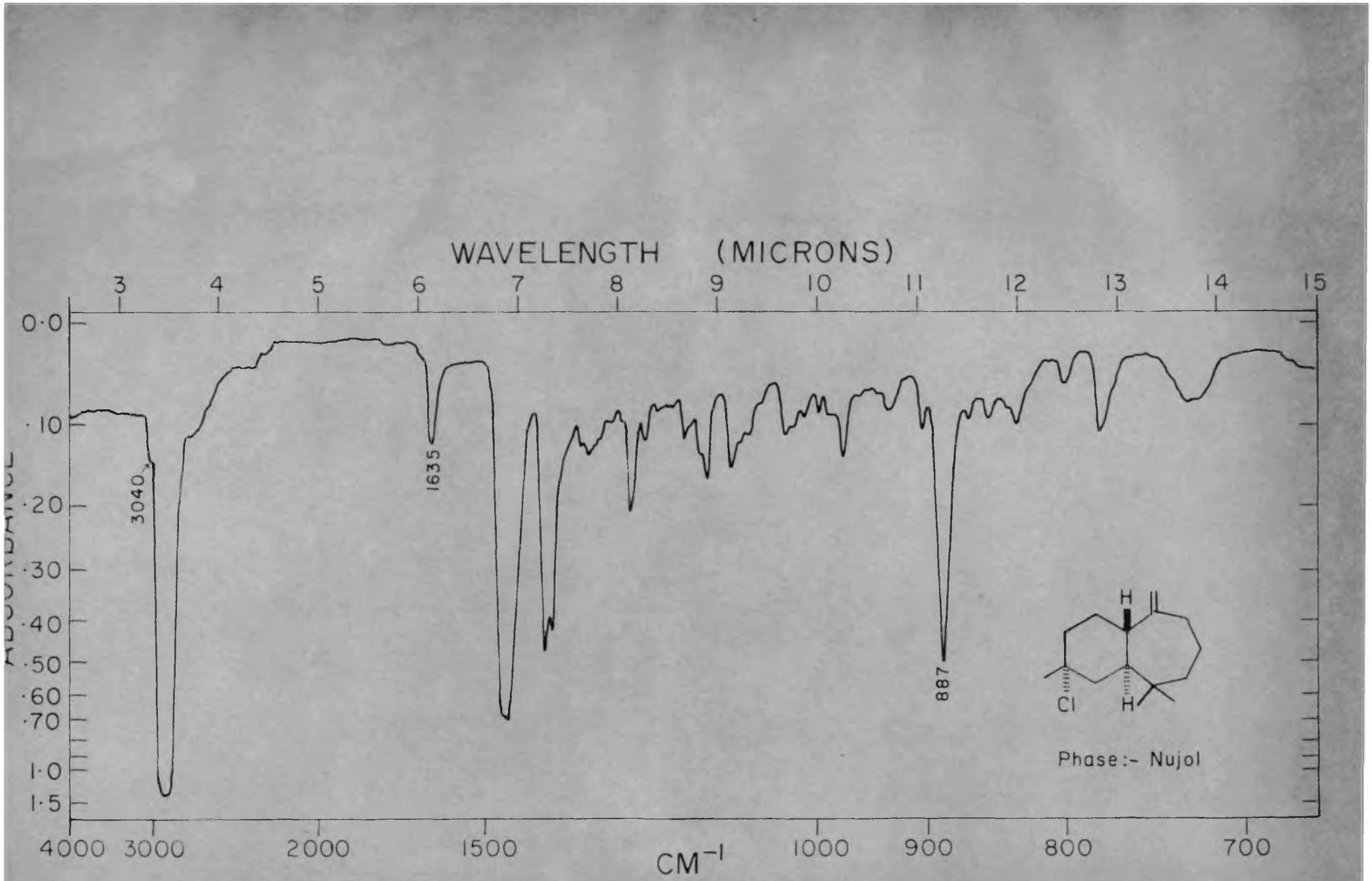


FIG. 1. IR SPECTRUM OF HIMACHALENE MONOHYDROCHLORIDE

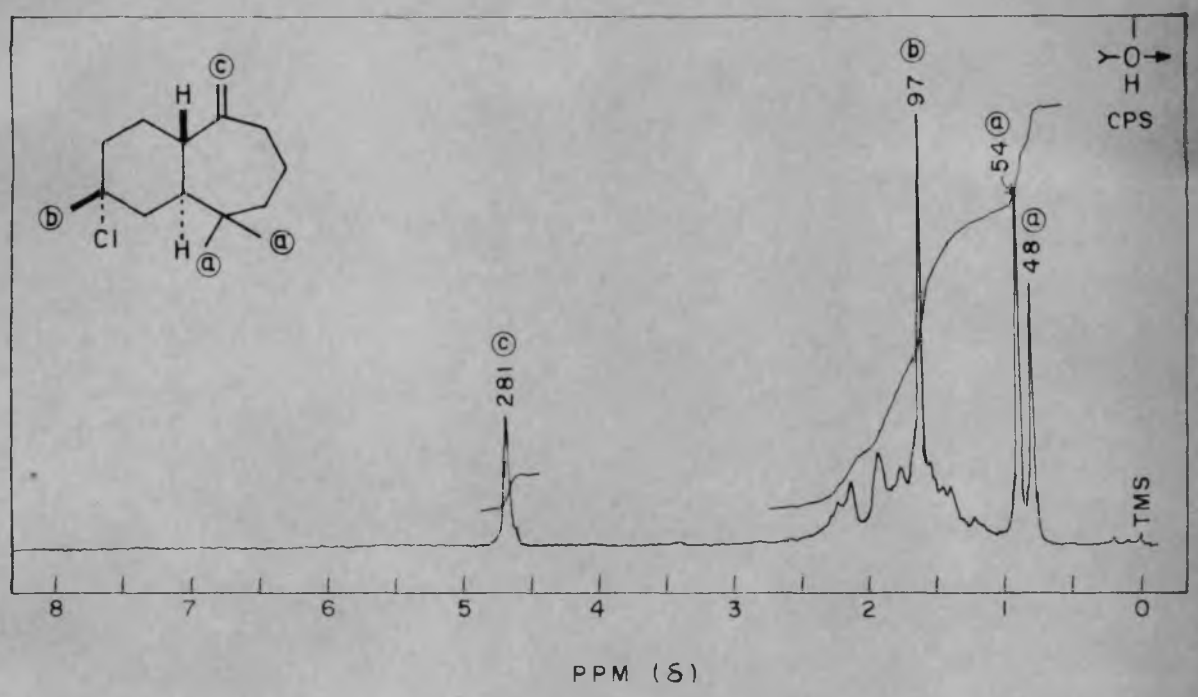


FIG. II. NMR SPECTRUM OF HIMACHALENE MONOHYDROCHLORIDE

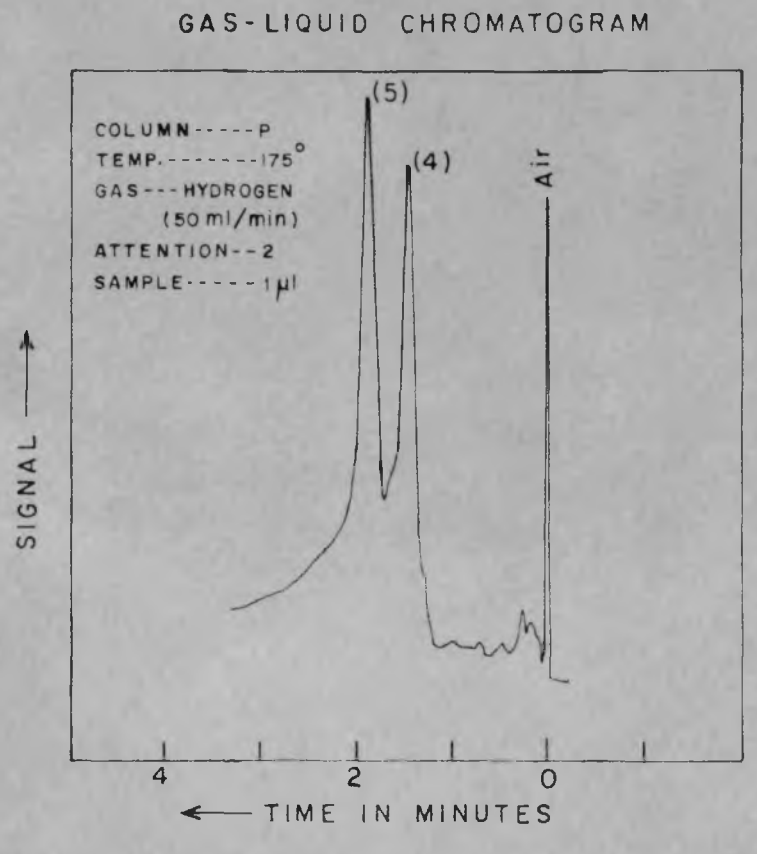
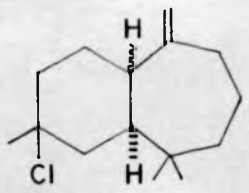
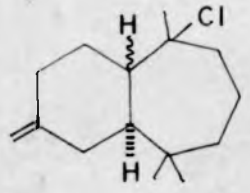


FIG. III. OZONOLYSIS PRODUCT FROM HIMACHALENE MONOHYDROCHLORIDE



(1)



(2)

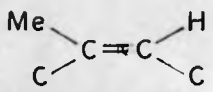
are summarised in Table I and their IR spectra are shown in Fig.IV and V. That both the ketones contain the grouping

TABLE I

Physical properties of ketones (4) and (5)

	Ketone-I(4)	Ketone-II (5)
Purity (GLC)	97%*	93%*
b.p.	130°(bath)/1.5 mm	125-128°(bath)/1 mm
$[\alpha]_D$	-69.9°	+199.4°
γ c=o	1705 cm^{-1}	1710 cm^{-1}
Characteristic IR peaks.	1190, 1145, 890 cm^{-1}	1320, 1285, 1207, 787 cm^{-1}
m.p. of the semi-carbazone.	210-211°	190-191°

*The impurity consists of other ketone in each case.



is clearly borne out from their NMR spectra (Figs.VI and VII, proton signal at 314 and 317 cps respectively); this is possible only if the himachalene monohydrochloride has

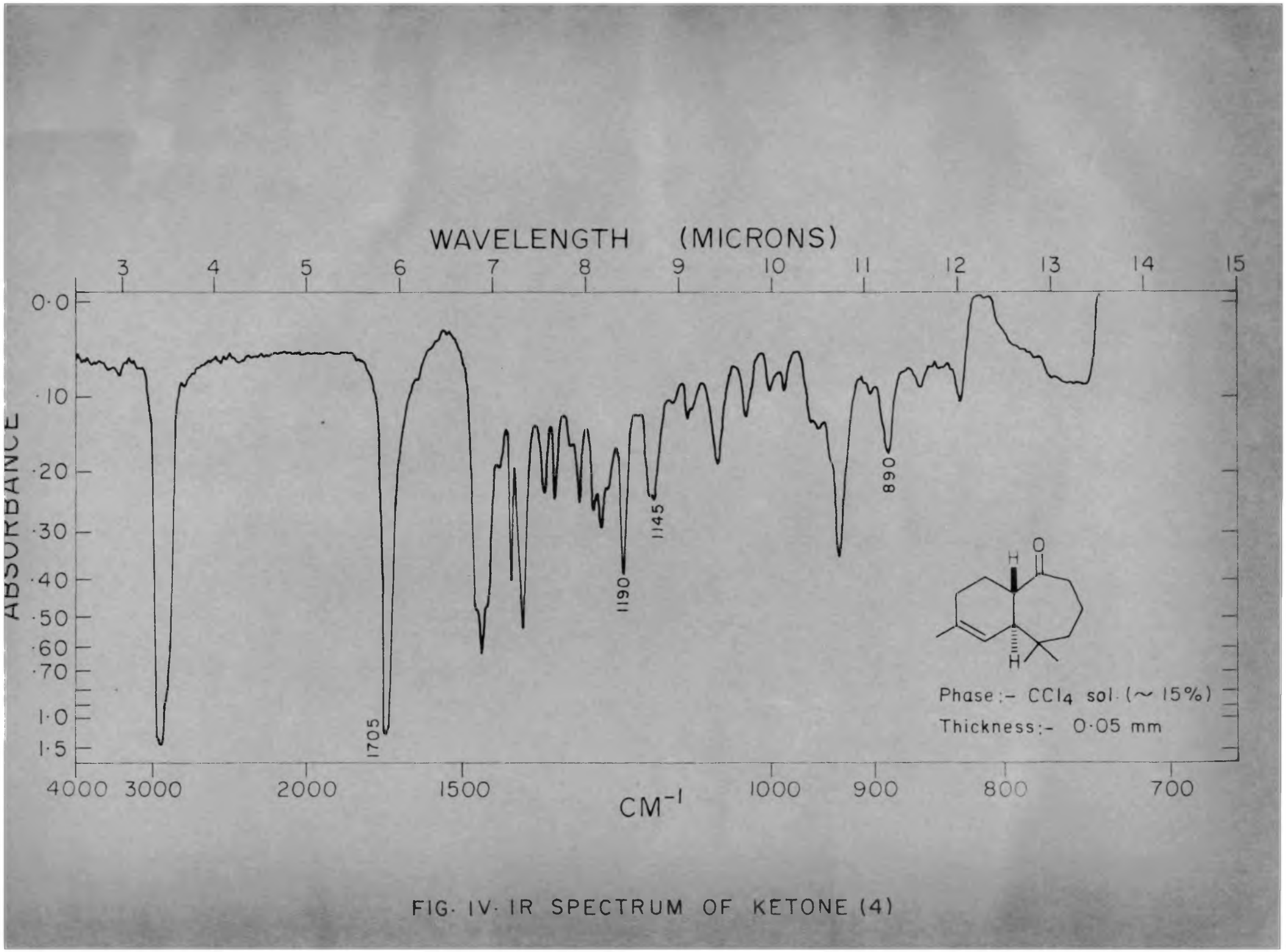


FIG. IV. IR SPECTRUM OF KETONE (4)

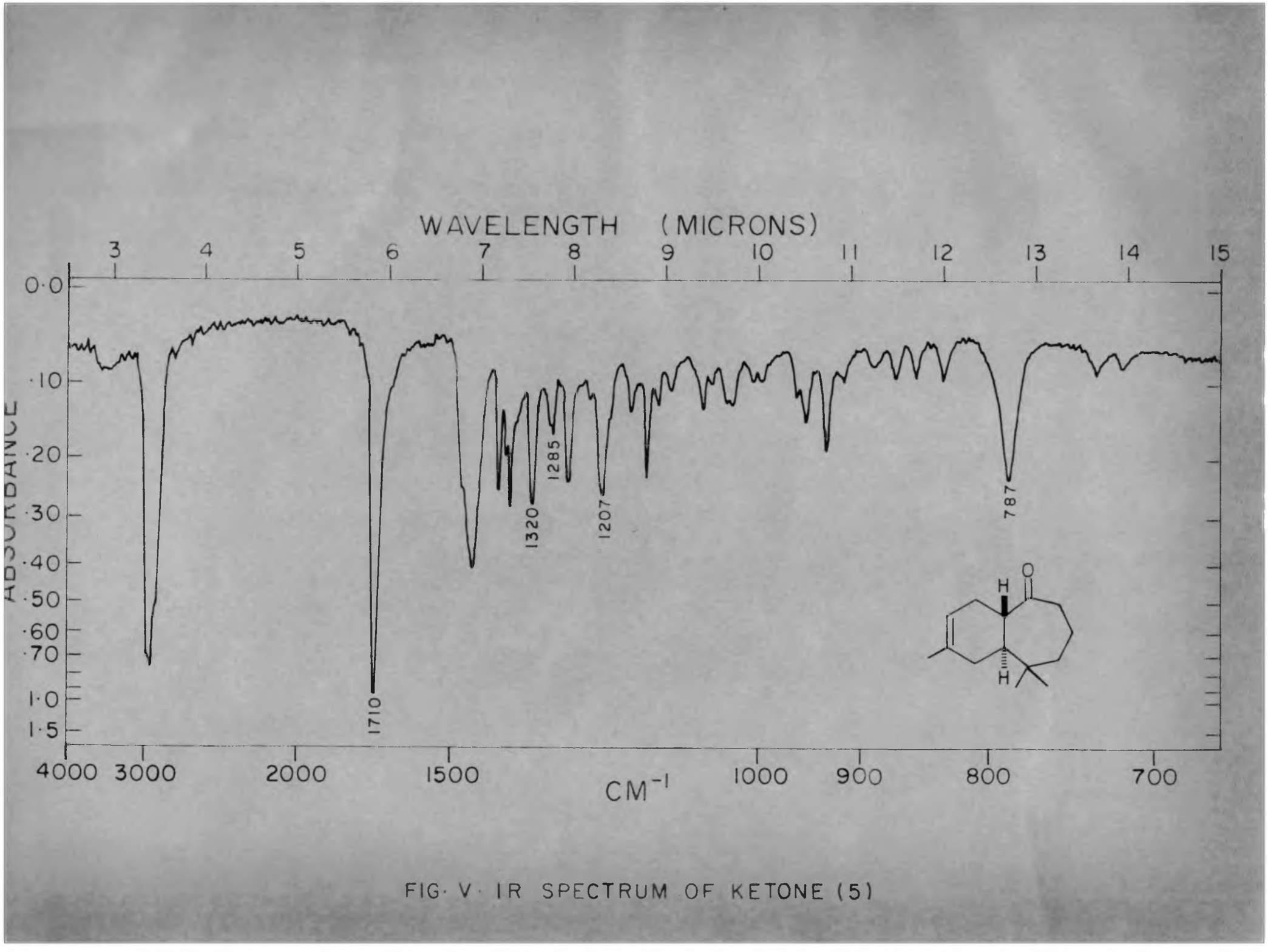


FIG. V. IR SPECTRUM OF KETONE (5)

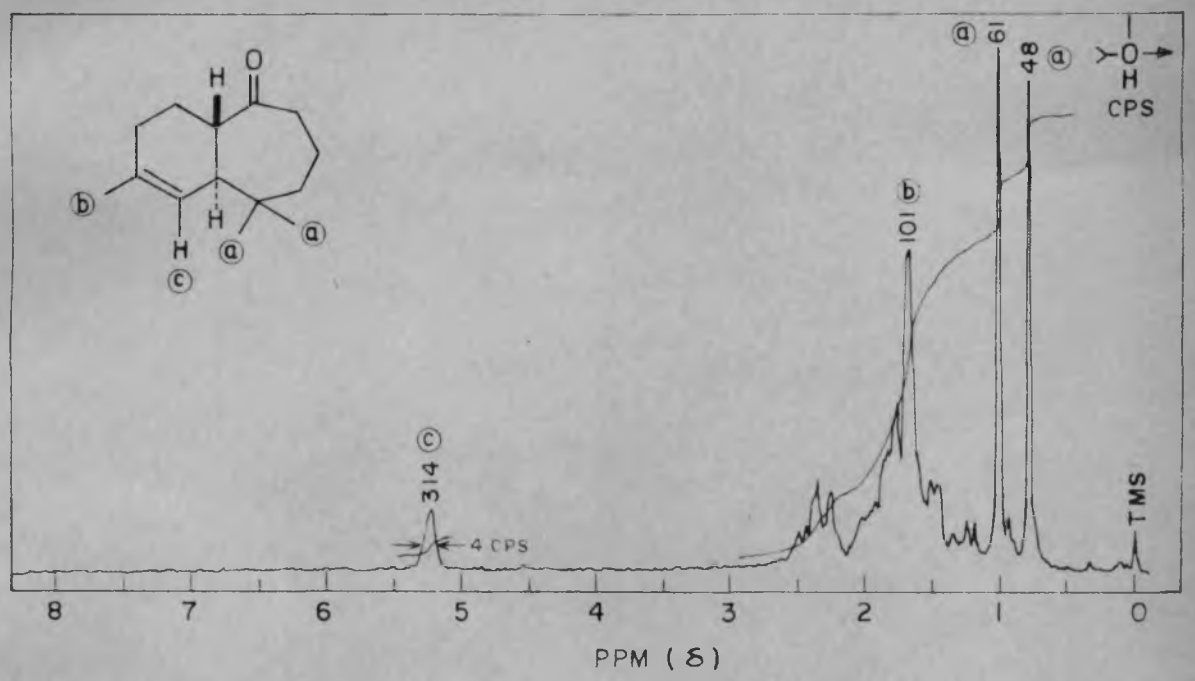


FIG. VI NMR SPECTRUM OF KETONE (4)

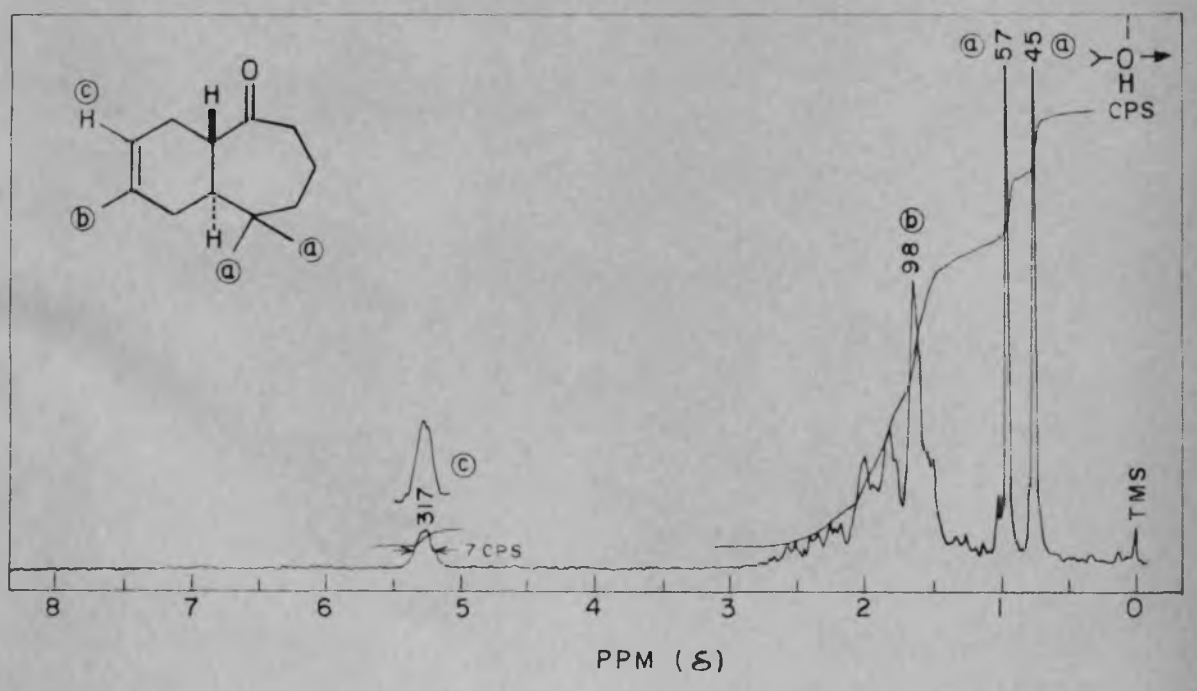
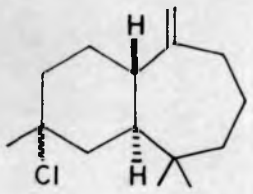
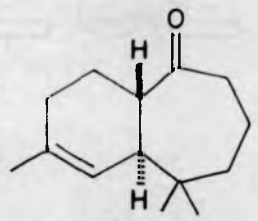


FIG. VII. NMR SPECTRUM OF KETONE (5)

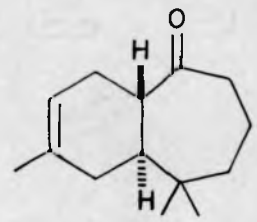
structure (1). Both the ketones were recovered unchanged after treatment (3 hr) with potassium tertiary butoxide in tertiary butanol and hence must possess the thermodynamically more stable ring fusion, which, as has been discussed in the previous Chapter, must be trans. Thus during the preparation of himachalene dihydrochloride from α-himachalene either, an invertion at C_6 takes place (via hydride shift) or else, prior isomerization to β-himachalene must have occurred. Structure (3) can now be written for himachalene monohydrochloride+ while each of ketone-I and -II must be represented by either of the two structures (4) or (5).



(3)



(4)



(5)

+In an effort to fix configuration at C3, the IR spectra of himachalene mono- and di-hydrochlorides, and (-)-cadinene dihydrochloride (of known absolute stereochemistry[1]) have been studied. Though it has been reported that axial and equatorial C-Cl bonds can be distinguished by IR spectroscopy[2], the method could not be applied in the present instance, as even in the case of (-)-cadinene dihydrochloride in which C-Cl bonds are known to be axial, there was no significant absorption in the expected region.

It is known that (-)-cadinene dihydrochloride on dehydrohalogenation gives essentially δ-cadinene[3] (i). This is understandable as the halogen atoms are axially oriented. Since in the dehydrohalogenation of the chloroketone, only ketone-I and -II, both containing a trisubstituted double bond,

A study of the NMR spectra of ketones-I and -II helps in the assignment of their structures. Examination of models* reveals that in structure (4), the dihedral angle between the vinylic and the bridgehead protons is close to 90°, whence from Karplus equation[4] one would expect little coupling between them. On the other hand, for structure (5), the vinyl proton is flanked by a methylene group and hence, at least some broadening of the olefinic signal must take place. Actually the half band width** for

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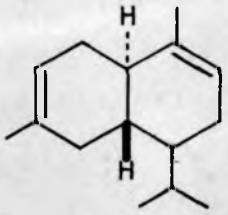
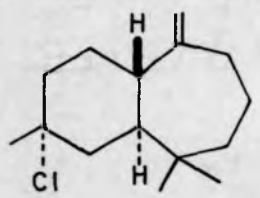
were formed one could possibly infer axial configuration for the halogen in himachalene monohydrochloride (ii).



(i)



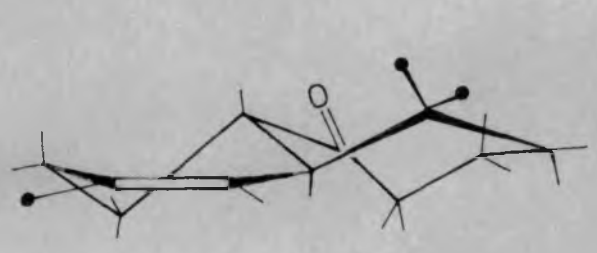
(ii)

It is not possible to deduce in a clear cut fashion the configuration of chlorine at C_7 in the dihydrochloride on the basis of the existing data.

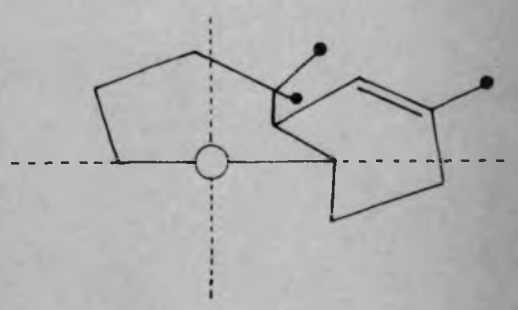
*Quasi-chair - twist chair conformations for the six-and seven-membered rings respectively.

**When coupling is not clear cut to give a distinct pattern, half band width of the signal has been used to check the extent of coupling[5].

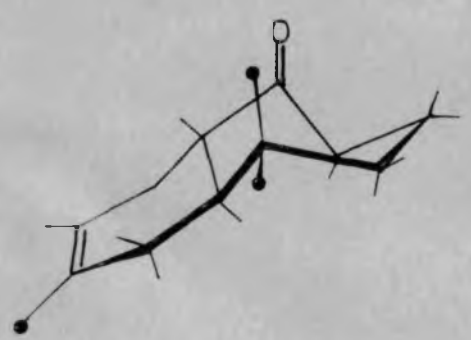
the olefinic protons of ketone-I and -II are 4 and 7 cps respectively and from these, one can assign structure (4) to ketone-I and consequently (5) to ketone-II. The octant rule (Fig.VIII) predicts a positive Cotton effect for the most likely conformations (6) and (7), for the two ketones (4) and (5) respectively and this is in accordance with the CD curves shown in Fig.IX.



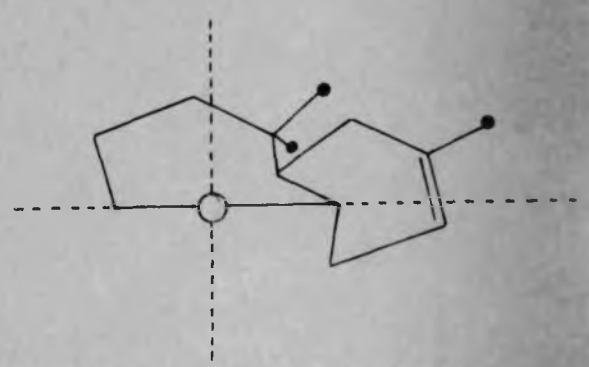
(6)



PREDICTION: POSITIVE



(7)



PREDICTION: STRONG POSITIVE

FIG. VIII. OCTANT DIAGRAMS OF KETONES (6) AND (7)

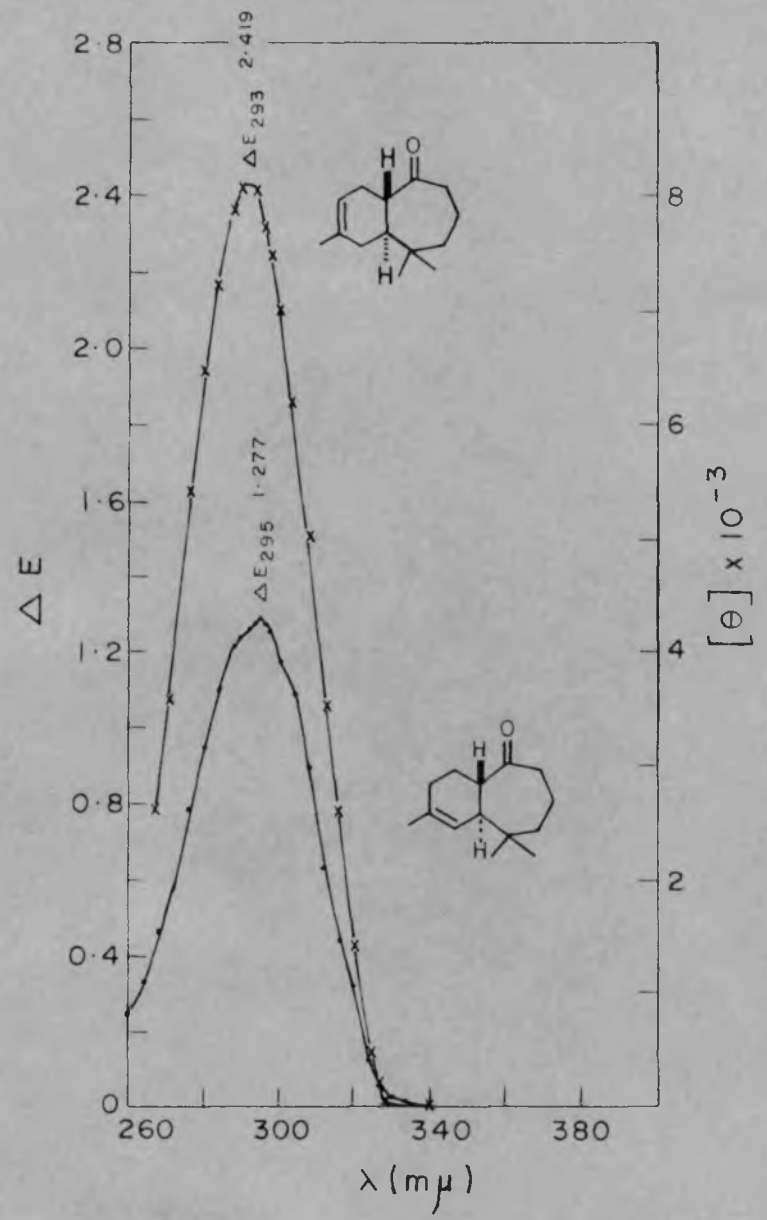
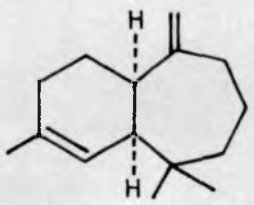


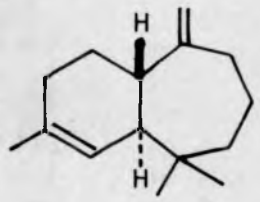
FIG. IX. CD CURVES OF KETONES (4) AND (5)

TRANS-HIMACHALENES

The results described in the previous Chapter provide sufficient basis for the cis- fusion of the rings in ∝-himachalene (8). This is further supported by the demonstration that ketone-I (4) and -II (5) are stable to epimerizing conditions as was anticipated for a trans-ring junction in the bicyclo-system. The derivation of the structure of himachalene monohydrochloride as (ii), provides a unique opportunity for the preparation of trans-∝-himachalene (9) which should be clearly different from the naturally occurring ∝-himachalene (8). This has been experimentally verified.



(8)



(9)

Dehydrohalogenation of himachalene monohydrochloride under mild conditions resulted in a mixture (Fig.X) from which three more or less pure compounds could be obtained. Their properties are given in Table II.

FIG. X. THIN-LAYER CHROMATOGRAM.

SOLVENT SYSTEM: BENZENE-PET ETHER (1:9)

1 & 8, AZOBENZENE.
2, PRODUCT OF DEHYDROHALOGENATION OF HIMACHALENE MONOHYDRO-
-CHLORIDE.
3, TRANS-HIMACHALENE, COMPOUND-A.
4, TRANS-HIMACHALENE, COMPOUND-B.
5, TRANS-HIMACHALENE, COMPOUND-C.
6, α-HIMACHALENE
7, β-HIMACHALENE.

TABLE II

Properties of himachalenes

	Trans-himachalenes			∝-himachalene
	A	B	C	
Structure	(10)	(9)	(11)	(8)
Purity	100%	91%	100%	100%
b.p.	120-124° (bath)/3.5	124-127° (bath)/3.5	115-118° (bath)/3	93-94°/2
n_D^{30}	1.5060	1.5038	1.5055	n_D^{25} 1.5082
$[\alpha]_D$	146.1°	-39.55°	-201.48°	-192.3°
Position of the gem dimethyl in NMR spectrum (cps)	51, 53	43, 58	48, 59	58, 60

Compound-A analysed for $C_{15}H_{24}$ and showed in the infrared (Fig.XI) the presence of a vinylidenic (1642, 885 cm^{-1}) and a trisubstituted (849 cm^{-1}) double bonds. The NMR spectrum (Fig.XIV) supported the above assignments: $>=CH_2$ (2H singlet at 278 cps), $>C=C<_H$ (1H signal centered at 317 cps, half band width 7.5 cps), two quaternary methyls (sharp 3H signals at 51, 53 cps) and a methyl on a double bond (3H signal at 98 cps).

Compound-B [$[\alpha]_D$ -39.55°] could be isolated in 91% purity only. This hydrocarbon ($C_{15}H_{24}$) again showed an exocyclic double bond [IR (Fig.XIII): 3070, 1650,890 cm^{-1};

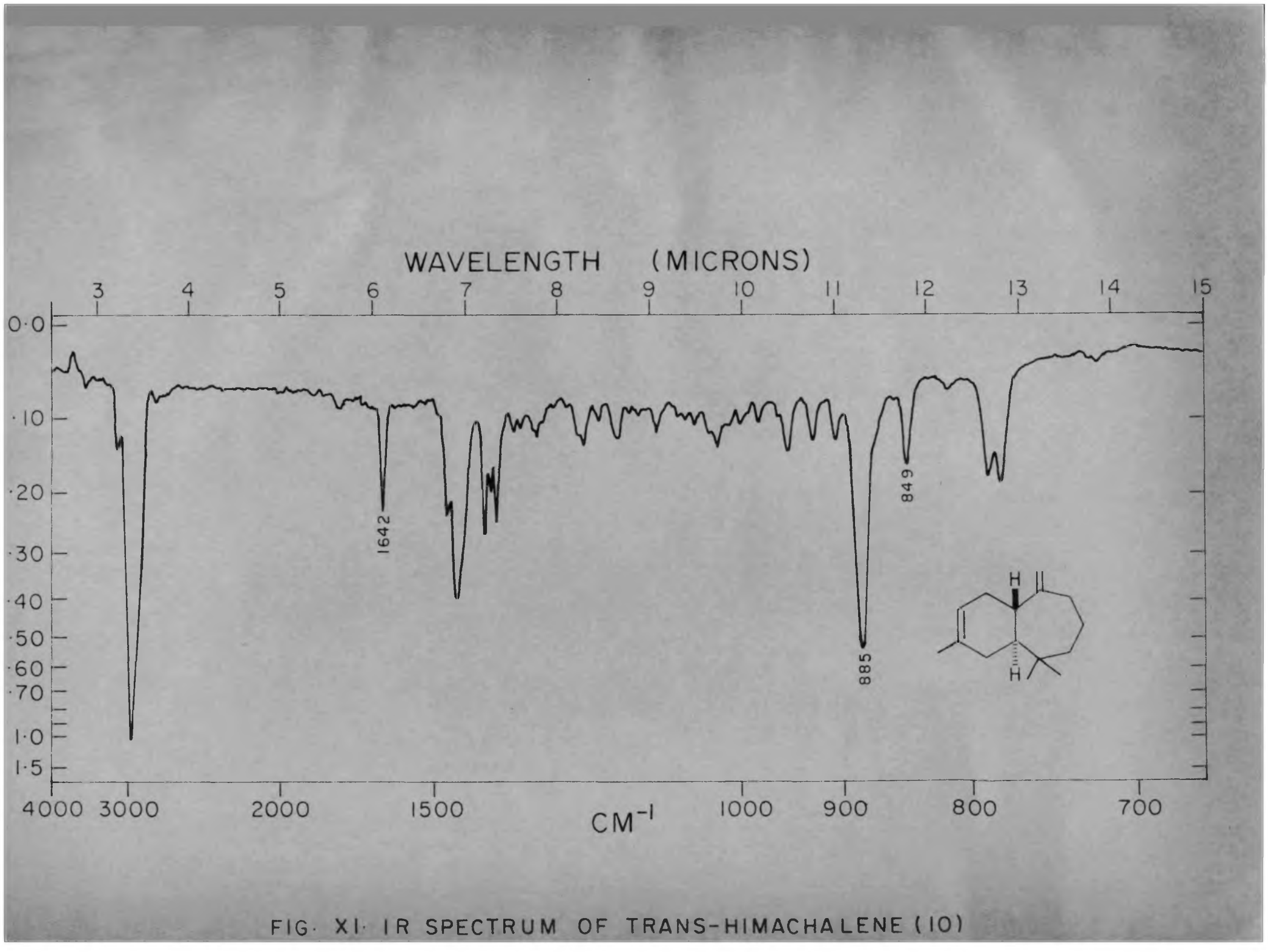
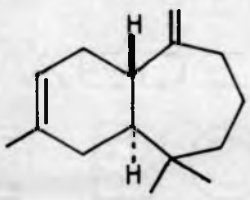


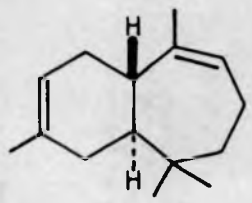
FIG. XI. IR SPECTRUM OF TRANS-HIMACHALENE (10)

NMR (Fig.XII): 2H signal, a doublet centered at 283 cps, J = 4 cps], a trisubstituted double bond (IR: 820 cm^{-1}, NMR: 1H doublet centered at 316 cps, half-band width 5 cps) two quaternary methyls (3H singlets at 43 and 58 cps) and a methyl on a double bond (3H signal at 100 cps).

The above hydrocarbons can clearly be formulated as (10) and (9) which have properties, distinct from those of ∝-himachalene and this provides an unequivocal proof for



(10)



(11)

the cis-fusion in ∝-himachalene. Of the two structures, compound-A can be represented by (10), while structure (9) could be assigned to the other hydrocarbon on the basis of half-band width of the trisubstituted olefinic proton signal. It should be further noted that the NMR spectra of these compounds have much similarity with the NMR spectra of the corresponding ketones discussed earlier. Furthermore, support for the assignment of these structures is forthcoming from a consideration of molecular rotational differences between the pair of ketones ($\triangle M_{(5)-(4)}$ +549.4°) and the pair of hydrocarbons ($\triangle M_{(10)-(9)}$ +378.7°).

The third hydrocarbon (compound-C) has clearly two trisubstituted ethylenic linkages with methyl groups (Fig.XV, 6H signal at 101 cps and 2H signal centered at 324 cps) and can only be formulated as (11).

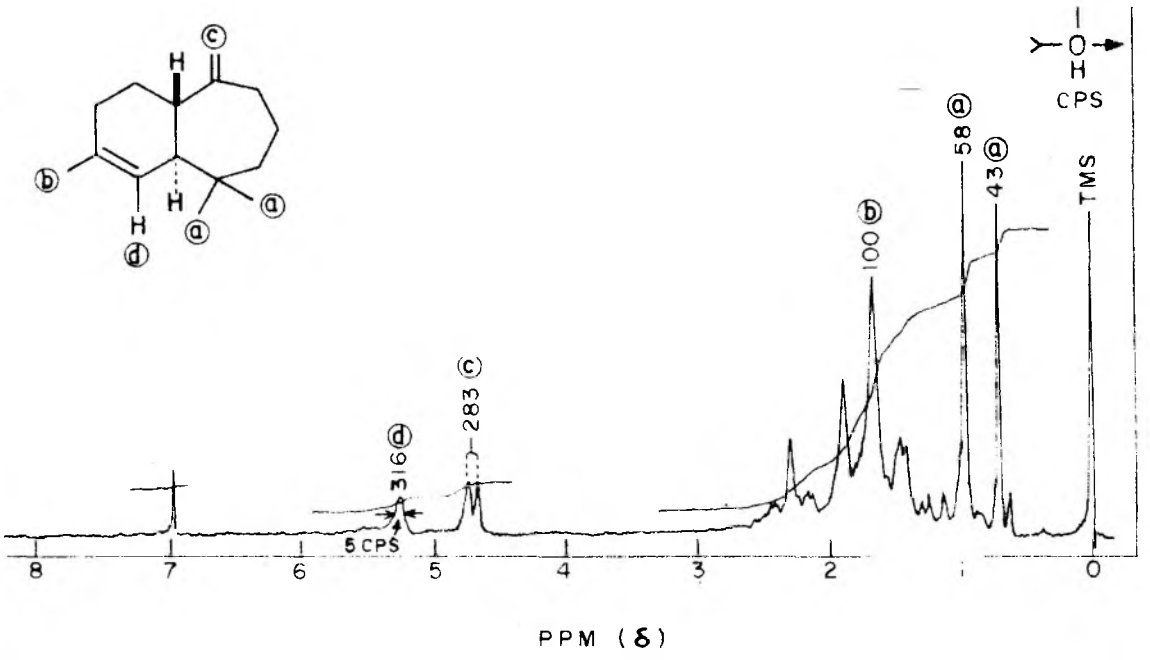


FIG. XII. NMR SPECTRUM OF TRANS-α-HIMACHALENE (9)

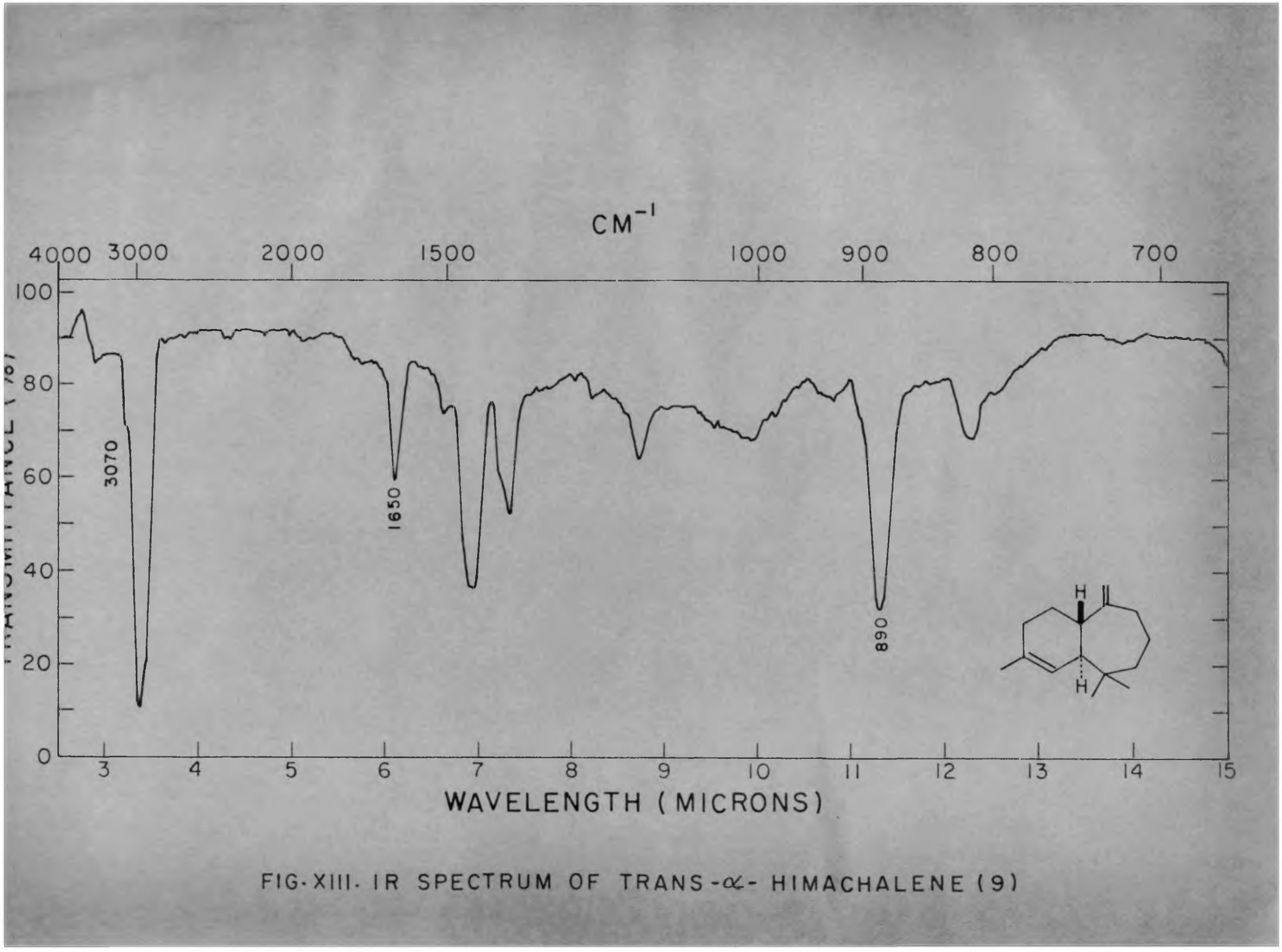


FIG. XIII. IR SPECTRUM OF TRANS-α- HIMACHALENE (9)

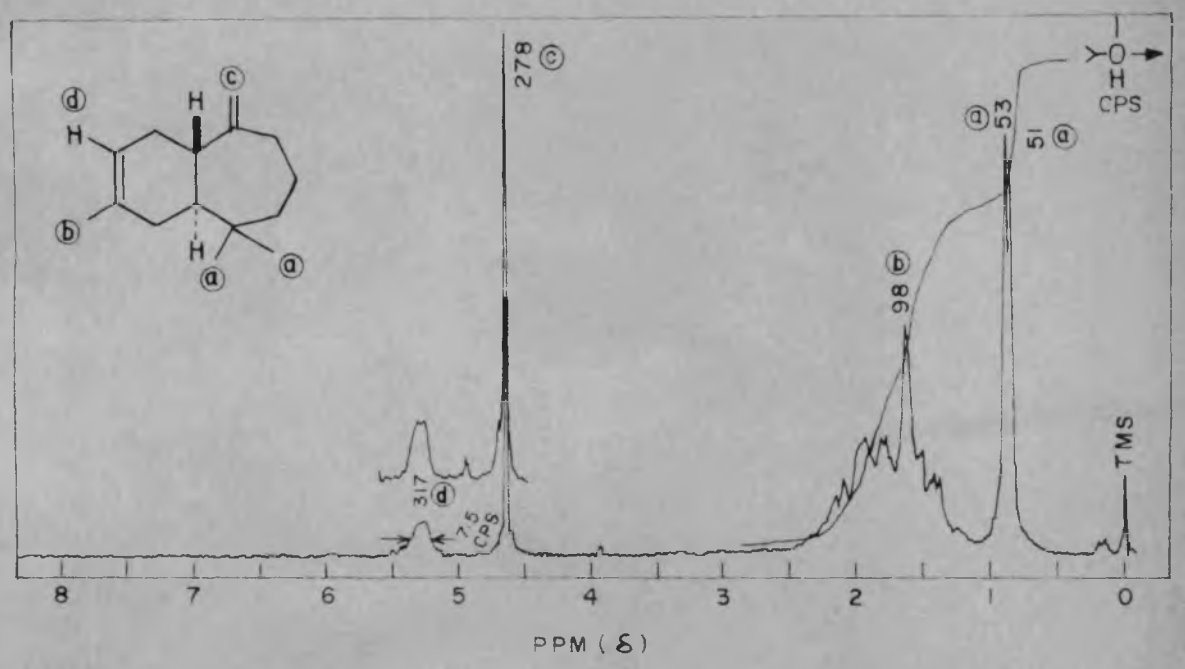


FIG. XIV. NMR SPECTRUM OF (10)

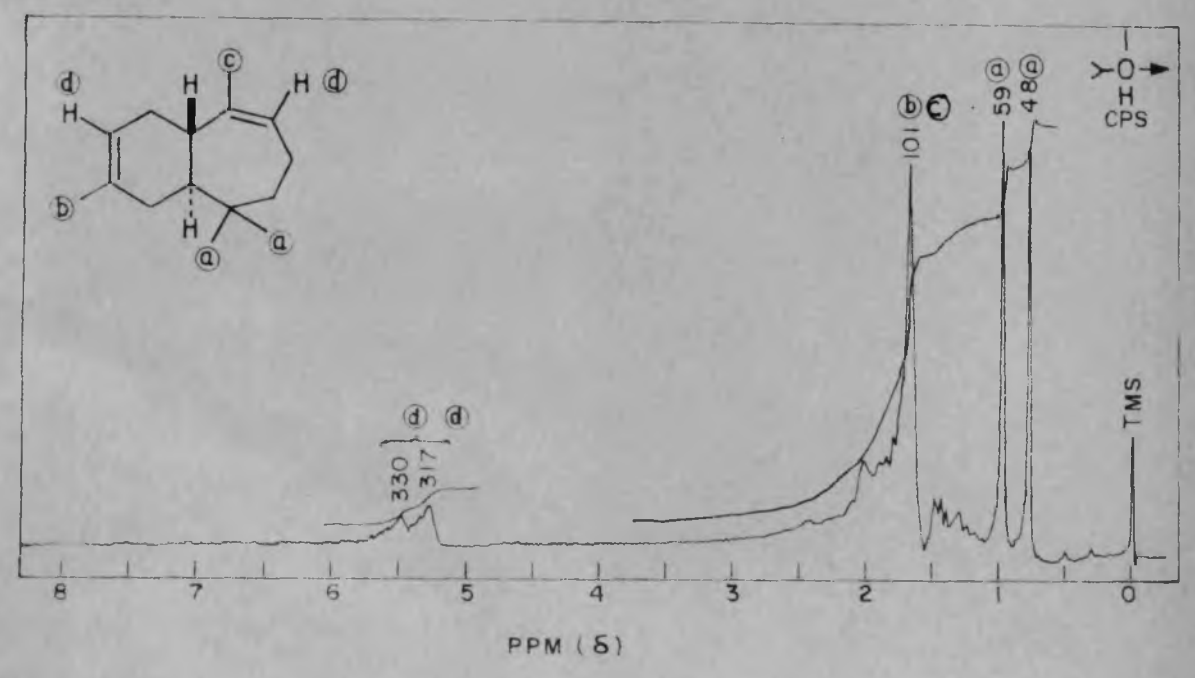


FIG. XV. NMR SPECTRUM OF (11)

EXPERIMENTAL

For general remarks, please see p. 67 . Thin-layer chromatography analyses were carried out using silica gel-silver nitrate mixture, following the procedure of Gupta and Sukh Dev[6].

Ozonolysis of himachalene monohydrochloride

A solution of himachalene monohydrochloride (6.8 g) in $CHCl_3$ (62 ml) was ozonised at -10° by bubbling ozonised oxygen (~ 160 mg/hr) till it no longer absorbed (17 hr, KI solution test). The solvent was removed under water pump suction (~ 50 mm) at room temp. and the ozonide was decomposed by warming gently with water (60 ml), first at 60° (1 hr) and finally at ~ 100° (2 hr). The product was cooled and extracted with pet. ether (65 ml x 4) after saturating with ammonium sulphate and the extract was washed with $NaHCO_3$ solution (20 ml x 2), then with brine, dried and the solvent distilled off; yield 6.7 g.

Dehydrohalogenation[7]: A solution of the above product (6.7 g) in glacial acetic acid (23 ml) was heated on a water bath and treated with fused sodium acetate (7 g). After 4 hr heating, the product was diluted to 100 ml with water and extracted with ether (30 ml x 4). The ether extracts were mixed, washed with $NaHCO_3$ solution (25 ml x 4), then with brine, dried and distilled after solvent removal;

yield 4.36 g, b.p. 112-116°/2 mm.

The product (3.8 g) was separated by preparative GLC by injecting (8 x 0.5 ml) on column P (succinic polyester of diethylene glycol on Chromosorb W, 2.5 cm x 3 meters) at 200° using N_2 (15 lbs/sq. in) as carrier gas. Two fractions corresponding to two peaks, were collected at the 17th and 23rd minute after injection, in receivers cooled at -10°.

Ketone-I (4): Fraction 1 (1.016 g), b.p. 130°/1.5 mm (bath), n_D^{30} 1.5020 was converted into its semicarbazone (pyridine method) which after crystallization from ethanol gave white shining flakes, m.p. 210-211°.(Found: C, 68.29; H, 9.19. $C_{15}H_{25}ON_3$ requires: C, 68.40; H, 9.57%).

The above semicarbazone (0.8 g) on refluxing with aqueous solution of oxalic acid, as described earlier, regenerated ketone-I (0.550 g), b.p. 95-97°/0.9 mm, n_D^{30} 1.5032, $[\alpha]_D$ -69.93° (c, 0.83%). (Found: C, 81.7; H, 11.06. $C_{14}H_{22}O$ requires: C, 82.06; H, 11.28%). GLC showed the product to be 97% pure.

Equilibration: Ketone-I (50 mg) on equilibration using potassium tertiary butoxide (0.2 g of potassium dissolved in 5 ml of tertiary butanol) and after usual work up yielded a product (21 mg), $[\alpha]_D$ -70.1° (c, 0.97%). IR spectrum and GLC were almost identical with those of the starting ketone.

Ketone-II (5): Fraction 2 (0.95 g, 85%) was converted into its semicarbazone (pyridine method) and recrystallised from

ethanol; m.p. 190-191°C.(Found: C, 68.29; H, 9.56. $C_{15}H_{25}ON_3$ requires: C, 68.40; H, 9.57%).

The semicarbazone (0.278 g) on refluxing with oxalic acid, regenerated ketone-II (0.110 g), b.p. 125-130°(bath)/1.1 mm, n_D^{30} 1.5041, $[\alpha]_D$ +199.4° (c, 6.8%). (Found: C, 81.62; H, 11.00. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%). GLC showed the product to be 93% pure.

Equilibration: Ketone-II (75 mg) on equilibration using potassium tertiary butoxide as above, resulted in the recovery of the starting ketone (IR, GLC); yield 34 mg, $[\alpha]_D$ +172.63° (c, 1.91%).

Isomerisation: Ketone-I (90 mg) was refluxed with a solution of oxalic acid (0.5 g) in water (1 ml) and dioxane (4 ml) for 10 hr under N_2. The product was diluted to 30 ml and extracted with pet. ether (15 ml x 3). The pet. ether extract was washed with brine, dried and distilled after solvent removal; yield 56 mg, b.p. 120-122° (bath)/1 mm, n_D^{30} 1.5037, $[\alpha]_D$-37.14° (c, 0.49%). GLC showed the product to consist of ketones-I and -II in the ratio 85:15.

Dehydrohalogenation of himachalene monohydrochloride

a) Alumina method: Himachalene monohydrochloride (1 g) was absorbed on a column of basic alumina (grade I, 2 x 15 cm, 45 g) and eluted after 20 hr, with pet. ether; yield 0.913 g, b.p. 100-102°/2.5 mm, n_D^{30} 1.5054. TLC analysis of the product is shown in Fig.X.

Chromatography: Silica gel impregnated with silver nitrate was prepared as follows: A solution of silver nitrate (15 g)

in aq. ethanol (15 ml of water and 250 ml of ethanol) was mixed with silica gel (-250 mesh, 100 g) and shaken for 1 hr. The solvent was removed under water pump suction and dried at 160-165°C for 6 hr.

A column of silica gel/$AgNO_3$ (28 x 2.6 cm, 53 g) was prepared and the hydrocarbon mixture (1.2 g) was placed on the top of the column and eluted as follows:

CHROMATOGRAM I

Fr.No.	Solvent	Volume (ml)	Weight (mgs)	Remarks.
1	Pet. ether	3 x 50	98	Mixture
2	"	8 x 30	243	"
3	5% Benzene	3 x 30	40	"
4	"	50	185	Compound-A (95% pure)
5	"	4 x 35	163	Pure compound-A
6	10% Benzene	4 x 50	110	Mixture
7	25% "	25	31	"
8	"	2 x 25	80	Compound-B (91% pure)
9	"	2 x 35	25	Mixture
10	50% Benzene	3 x 25	73	Pure compound-C
11	Benzene	6 x 50	37	Mixture

Compound-A: Fraction 5 was distilled; yield 0.151 g, b.p. 120-124°(bath)/3.5 mm, n_D^{30} 1.5060, $[\alpha]_D$ +146.1° (c, 2.234%). (Found: C, 88.45; H, 11.88. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%).

Compound-B: Fraction 8 was distilled; yield 55.6 mg, b.p. 124-127°(bath)/3.5 mm, n_D^{30} 1.5038, $[\alpha]_D$ -39.55° (c, 0.88%).

Compound-C: Fraction 10 was distilled; yield 61 mg, b.p. 115-118°(bath)/3 mm, n_D^{30} 1.5055, $[\alpha]_D$ -201.48° (c, 1.626%), IR spectrum: 1665, 830 cm^{-1} (>C=C<$_H$). (Found: C, 88.41; H, 11.92. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%).

b) Sodium acetate method: To a solution of the monohydrochloride (3 g) in glacial acetic acid (9 ml) at ~ 100°, fused sodium acetate (3 g) was added in two lots at an interval of 10 minutes. The product was heated on a water bath (3.5 hr), cooled and diluted to 80 ml with water. It was extracted with pet. ether (50 ml x 3) and the extract washed with $NaHCO_3$ solution (10 ml x 2), followed by brine and dried. After solvent removal, it was distilled; yield 1.93 g, b.p. 100-102°/2.5 mm, n_D^{30} 1.5050. TLC of the product was very similar to the one obtained by the alumina method (Fig.X).

SUMMARY

The structure of himachalene monohydrochloride has been shown to be (3). The isolation of three trans-himachalenes, from the dehydrohalogenation product of himachalene monohydrochloride is reported. One of them is identified as trans-α-himachalene (9).

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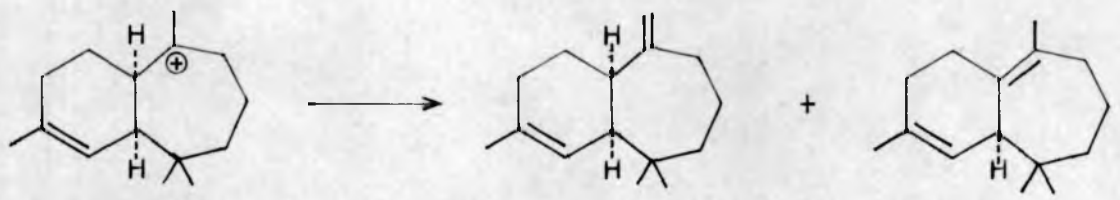
CHAPTER VI

BIOGENETIC CONSIDERATIONS

The biogenesis of sesquiterpenes has been very briefly dealt with in Chapter I wherein it has been indicated that ion (3) which has been considered by Hendrickson[1] as the precursor for longibornyl cation, can stabilize itself to yield himachalenes (Fig.I). The species (3) should give



(3) (4) (5)

rise to α-himachalene (4) with cis- junction and this has actually been shown to be the case as discussed in Chapter IV. Thus the biogenesis of himachalenes and related compounds and that of longifolene and its congeners(longipinene and longicyclene) is intimately linked (Fig.I). The botanical relationship between Pinus longifolia and Cedrus deodara is indicated in Fig.II and it is gratifying to note that the major sesquiterpene components of the two plants arise from a common species (3). The fact that in Cedrus deodara

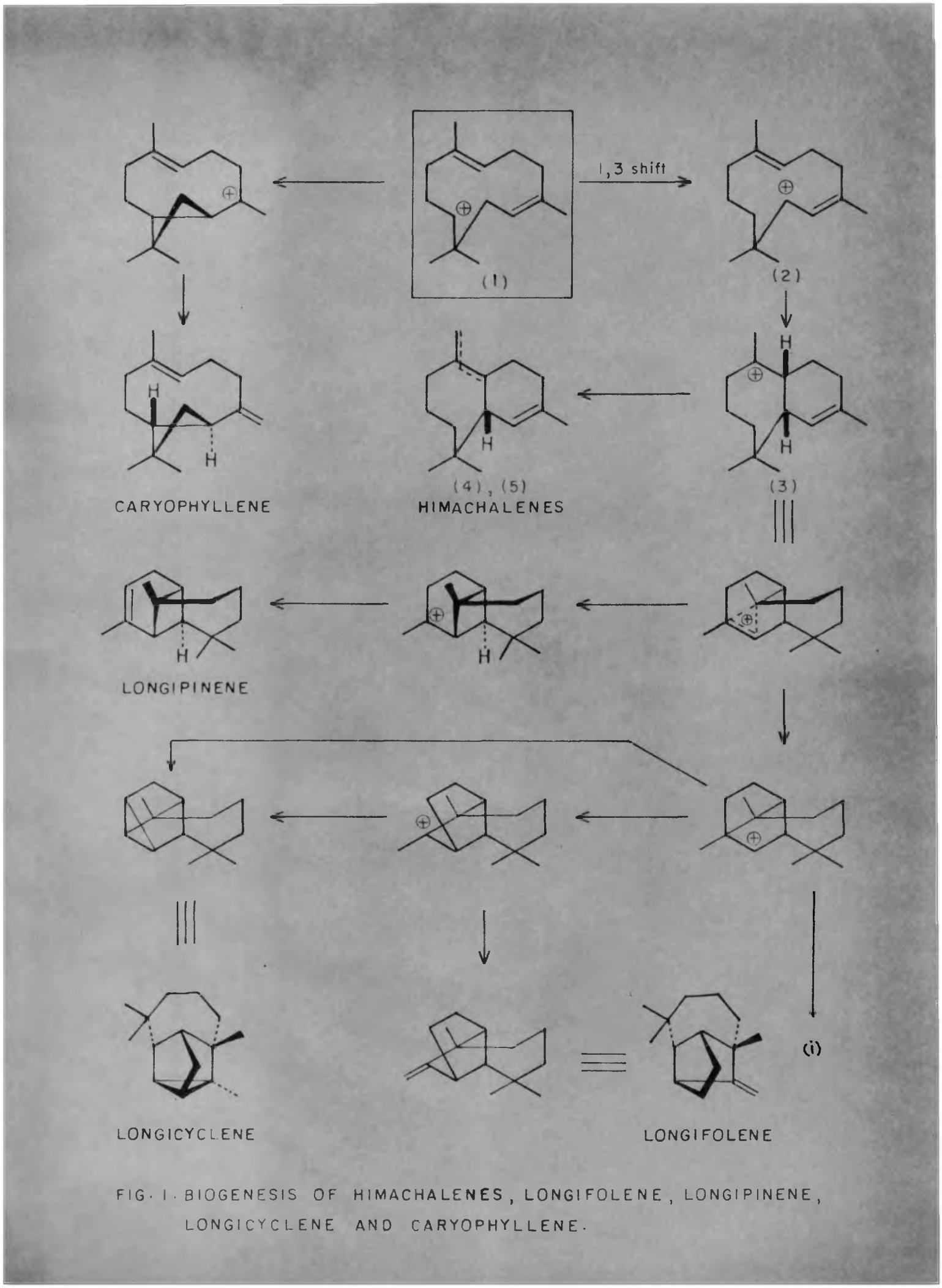


FIG. 1. BIOGENESIS OF HIMACHALENES, LONGIFOLENE, LONGIPINENE, LONGICYCLENE AND CARYOPHYLLENE.

DIVISION: GYMNOSPERMAE[2,3]
CLASS: CONIFERAE (~640 SPECIES)
ORDER: PINALES (~210 SPECIES)
FAMILY: PINACEAE

GENUS: ABIES | KETELEERIA | PSEUDOTSUGA | TSUGA | PICEA | PSEUDOLARIX | LARIX | CEDRUS (4 species) | PINUS (90 spec

SUBGENUS: HAPLOXYLON | DIPLOXYLON

SPECIES: C. DEODARA ROXB (LOUD)
LOCATION: WESTERN HIMALAYAS & MEDITERRANEAN

CONSTITUENTS OF THE ESSENTIAL OIL[4]:

- p-METHYL ACETOPHENONE + p-METHYL Δ^3-TETRAHYDROACETOPHENONE ---~5.0 %
- α-HIMACHALENE ---------- 9.6 %
- β-HIMACHALENE ---------- 38.0 %
- ALLOHIMACHALONE + ar-DIHYDROTURMERONE ---------- 1.4 %
- LONGIBORNEOL ---------- 3.4 %
- HIMACHALOL ---------- 13.0 %
- ALLOHIMACHALOL ---------- 7.5 %
- α- & β-ATLANTONE ---------- 14.6 %
- (UNIDENTIFIED FRACTION) ---------- 6.5 %

P. LONGIFOLIA
HIMALAYAN REGION

CONSTITUENTS OF THE ESSENTIAL OIL[4]:

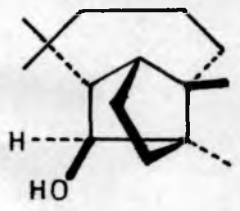
- α-PINENE ---------- 7 %
- β-PINENE ---------- 18 %
- Δ^3-CARENE ---------- 52 %
- CARENE (other isomers) ---- 8 %
- LONGIFOLENE ---------- 10 %
- LONGIPINENE, LONGICYCLENE, LONGIBORNYL ACETATE, LONGIBORNEOL, CARYOPHYLLENE OXIDE, HUMULENE OXIDE, CARYOPHYLLENE, HUMULENE, BISABOLENE ---- ~1 %
- UNIDENTIFIED FRACTION ---~4 % (~14 COMPOUNDS)

FIG. II. BOTANICAL RELATIONSHIP BETWEEN PINUS LONGIFOLIA AND CEDRUS DEODARA

the biogenetic sequence essentially* terminates at the ion (3) would mean that the enzymatic facility for the folding over of the cation (3) to a conformation suitable for transformation to longibornyl cation, is not available in Cedrus deodara and the products arise from the stabilization of the species (3). It is worth noting that some of the usual pathways open for the stabilization of carbonium ion have indeed been followed in Cedrus deodara. Thus recent work[4] in this Laboratory has shown the presence of himachalol (6), a product of stabilization by anion collapse and allohimachalol (7), a product of rearrangement -

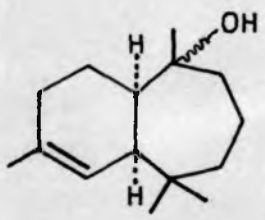
---

*In order to see if minor amounts of longifolene or longiborneol occur in Cedrus deodara and similarly if minor amounts of himachalenes could be detected in Pinus longifolia, work in this direction has been carried out in this Laboratory by S.C.Bisarya. These investigations reveal that the essential oil of Cedrus deodara contains small amount (~ 5%) of longiborneol (i), but himachalenes are absent in Pinus longifolia.

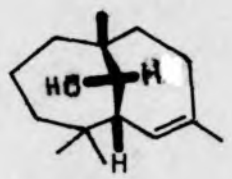


(i)

substitution, in the essential oil of Cedrus deodara besides himachalenes.



(6)



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T. C. Joseph.