STUDIES IN NATURAL PRODUCTS

PART I: A NORDITERPENE HYDROCARBON FROM BUTE INLET WAX

PART II: TERPENOIDS FROM *EUPATORIUM AVAPANA*

by

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April 1970

TO MY WIFE JANET

Supervisor: Dr. Tikam C. Jain

ABSTRACT

Part I

Spectroscopic and gas-liquid chromatographic evidence is presented for the structure of a norditerpene hydrocarbon isolated from Bute Inlet Wax. The synthesis of this hydrocarbon from phytol and its rigorous comparison with 2,6,10,14-tetramethylpentadecane (pristane) is discussed.

Part II

The isolation and structure elucidation of a sesquiterpene hydrocarbon from *Eupatorium ayapana*, complete with its synthesis from β-eudesmol is presented.

Finally, a spectral characterization of a known monoterpenoid constituent of *Eupatorium ayapana* and its derivatives is discussed.

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ACKNOWLEDGMENT

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Part I:

A Norditerpene Hydrocarbon from Bute Inlet Wax

INTRODUCTION

I. Bute Inlet

Bute Inlet, one of the larger fiords of the west coast of British Columbia, discharges into the complicated system of channels lying between the mainland and Vancouver Island at the north end of the Gulf of Georgia[1]. It lies along 125° W. longitude between 50 and 51° N. latitude which places it almost directly north-east of Campbell River. The crooked channel is about forty miles long with an average width of two and one-half miles. The profile of the channel is U-shaped and it varies in depth from 1000-2000 feet along the northern two-fifths of its length and 2000-2200 feet along the southern three-fifths. It is fed by the Homathko and Southgate Rivers which originate in the snow fields of the Coast Range and deposit a layer of fresh water twenty to thirty feet thick at the head of the inlet. The surrounding mountains have been identified as belonging to the Mesozoic (50 to 200 x 10^6 years old) and Cenozoic (0 to 50 x 10^6 years old) periods and are composed mainly of intrusive rocks. Some small deposits of sedimentary and volcanic rocks of the Triassic age (150 to 200 x 10^6 years old) have also been located[2]. The local flora is characterized by a large stand of Lodgepole pine (*Pinus contorta* var. *latifolia*). In fact, out of a total of sixty-seven million board feet of Lodgepole pine for the whole coastal region of British Columbia, thirty million occur contiguous to Bute Inlet.

II. Bute Inlet Wax - An Historical Introduction

Bute Inlet has come under scientific scrutiny during recent years due to the periodic appearance of a semi-consolidated, waxy material which is deposited along the shoreline during particularly cold winters. Records indicate many appearances of the wax over the past several decades; during the winters of 1922, 1935-36, 1950-51, 1955-56. Scientists first

directed attention to this strange material during the winter of 1950 when it was reported that "scow loads" were rolling up on the shore. In another report, we have learned that some of the local inhabitants have collected and stored tons of the wax. During 1951 Carter and Swain of the Pacific Fisheries Experimental Station in Vancouver undertook an investigation into the nature of Bute Inlet Wax. Their findings are reproduced below.[3]

> The Bute Inlet wax consists of esters of fatty acids and fatty alcohols. It solidifies at about 11°C. Its specific gravity 20/20 is 0.8704. Its refractive index at 40° C is 1.4518. It yields 57% unsaponifiable matter (liquid) and 43% fatty acids (solid) and 0.75% glycerol. Chromatographic analyses indicate the unsap was mostly fatty alcohols. It is therefore a liquid wax.
>
> | | |
> |---|---|
> | Iodine values "oil" | 63.0 |
> | Unsap | 78.4 |
> | Fatty acids | 37.8 |
>
> This wax is of vegetable origin and carbon 14 determinations give its age as 0 $\pm$ 300 years.

Swain, continuing his investigation, deduced that, due to the recent age of the wax, it must be derived from the native flora. Sea-weeds and algae were not considered a possibility since they were absent due to the lack of shallow water. He concluded, therefore, that the source must be *Pinus contorta* which was known to deposit huge slicks of pollen on the water during the months of May and June. In order to confirm his conclusions he investigated the chemistry of lodgepole pollen and made the following report.[3]

> Branches bearing staminate cones, amounting to 11.3 lbs. yielded 336.5 g of pollen on shaking them in the laboratory. This is a 6% yield. Some of this pollen was extracted with acetone in a Soxhlet and the extract was extracted with light petroleum to yield a yellow solid amounting to 1.45% of the pollen. Composition and properties of this material are shown in the following table compared with similar data for Bute Inlet Wax.

	Pollen extract	Bute Inlet Wax
m.p., °C	63	11
Iodine value	--	63.0
Unsap - %	47.5	54.3
State at 20°C	solid	liquid
Iodine value	--	78.4
Composition (chromatographic analysis)		
Hydrocarbon	14.5%	5.5%
Fatty alcohols	72 %	94 %
Iodine value	11	--
Fatty acids	52.5%	--
State at 20° C	semi-solid	solid
Iodine value	70.8	37.8

Pollen stored 13 days in a beaker in the laboratory turned mouldy and had a very yeasty smell. The light petroleum extract of the acetone extract amounted to 1.8% of the pollen as sampled (which was 6.9% of the heat dried pollen). It was 49% unsap and 50% fatty acids, all three of these being solid at room temperature.

Pollen stirred in water at room temperature for 13 days first developed a yeasty smell and then changed to a vile odour, and yielded 22% of light petroleum extract (acetone extract). (This percentage is based on the weight of the heat dried pollen- c.f. 6.9% above). This extract was a solid consisting of 17.8% unsap and 73% fatty acids.

These results do not seem to be very promising either in the yield of solvent-soluble material nor in the properties of the solvent soluble material that is there.

III. Origin of Bute Inlet Wax

Swain states that his investigation of lodgepole pollen is not very promising and in summary, it can be said that there are three popular beliefs regarding the origin of Bute Inlet Wax[1]:

1. The wax is an exudate of the pollen of Lodgepole pine (*Pinus contorta*).
2. The wax is a petroleum product or petroleum at an early stage in its formation.
3. The wax is derived from zoo-plankton or from some plant material such as algae.

A recent carbon-14 dating has placed the age of our sample of Bute Inlet Wax at 1025 ± 80 years*. This clearly indicates that the material is not derived from the flora presently growing in the area. Furthermore, this dating raises questions regarding where and how the wax is stored in nature, and the mechanism by which it is released into the surrounding water. However, in the absence of any detailed chemical knowledge about Bute Inlet Wax it is difficult to make any positive deductions concerning its origin[4]. With the objective of obtaining this chemical data, we undertook the systematic investigation of Bute Inlet Wax which is described in Part I of this thesis.

* Radiocarbon age determination done at the University of Saskatchewan.

DISCUSSION

I. Preliminary Examination

Bute Inlet Wax, a tan coloured viscous oil, was first treated with sodium carbonate solution to remove any acidic constituents. However, it was found that the wax consisted entirely of neutral material which displayed intense ester carbonyl absorption at 1740 cm^{-1} in its infrared spectrum. This washed material, Neutral Bute Inlet Wax, which had no significant optical rotation was used for all subsequent experiments. T.L.C. analysis on both silica gel and alumina in different solvent systems indicated that the wax was composed predominantly of one constituent. However, G.L.C. analysis of the saponification products showed the presence of at least forty components. This chromatographic evidence clearly outlined two important properties of Bute Inlet Wax; firstly, the complexity of the mixture and secondly, the difficulty of separating the components by column chromatography. Preliminary fractionation of the high boiling wax, b.p. 220-250°/0.2 mm, by column chromatography combined with a systematic spectral examination of each fraction indicated that Bute Inlet Wax was mainly composed of high boiling lipids. It was found that the conventional approach of saponification followed by separation of acidic and neutral fragments[5,6] was not applicable to this wax, since such a procedure invariably led to highly colored intractable emulsions. Thus, a modified procedure had to be used. Rather than preliminary saponification, it seemed imperative to isolate the individual lipids in a pure form and then follow the conventional technique of hydrolysis. Thus, separation by chromatography on alumina[7] was attempted but it was found that the closely related constituents

of Bute Inlet Wax resisted separation on both alumina and silica gel. However, since the infrared and N.M.R. spectra of Bute Inlet Wax[8] indicated an olefinic system, advantage was taken of the capacity of olefins to complex selectively with silver ions. Thus column chromatography on silica gel impregnated with silver nitrate[9] was successfully employed in this investigation.

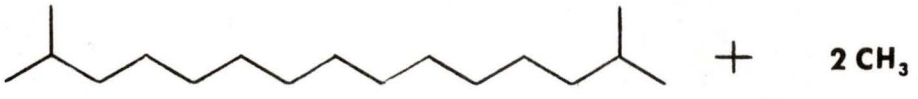
II. Isolation of Bute Hydrocarbon

Neutral Bute Inlet Wax was first chromatographed on a fifteen fold ratio of grade 5 alumina. Six fractions were cut using petroleum ether as eluent; the first two and the last two were set aside and the middle fractions, having identical refractive indices (n_D^{21} 1.4615), were combined. Rechromatography of these two fractions on silica gel impregnated with silver nitrate gave bute hydrocarbon in the petroleum ether fraction. It is pertinent to note that chromatography on either alumina or silica gel failed to yield any bute hydrocarbon due to its co-elution with the lipid constituents. However, complexing with silver ions gave a sharp, clean separation and furnished bute hydrocarbon in 1.5% overall yield.

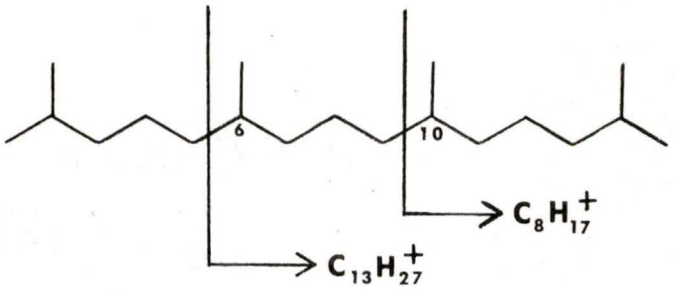
III. Structure Elucidation

Bute hydrocarbon obtained by column chromatography (*vide supra*) was distilled over sodium at 152°/6.0 mm. Its empirical formula was established as $C_{19}H_{40}$ by elementary analysis and by high resolution mass spectrometry (observed mass 268.3125, calculated mass 268.3130). The infrared spectrum (Figure 1, p. 22) of this hydrocarbon displayed a strong doublet at 1385 and 1365 cm^{-1} and a band at 1170 cm^{-1} with a shoulder at 1155 cm^{-1}; both of these signals being attributable to an

isopropyl group. The spectrum was devoid of any olefinic vibration, this being further confirmed by a negative tetranitromethane test. The N.M.R. spectrum (Figure 2, p. 22) was very revealing; it showed an 18 proton doublet at 9.14 τ indicating six equivalent methyl groups. A 22 proton singlet at 8.78 τ accounted for the remaining protons. With this information it was possible to derive a partial structure for bute hydrocarbon; the empirical formula $C_{19}H_{40}$ indicated that the molecule was acyclic and the N.M.R. spectrum indicated the presence of six methyl groups. Thus it could be concluded that there was a straight chain of thirteen carbon atoms. One methyl group could be placed at either end of the chain, but since the infrared spectrum indicated there was a gem-dimethyl group and because the N.M.R. spectrum showed all methyls as equivalent doublets, then the chain must terminate at both ends in



1

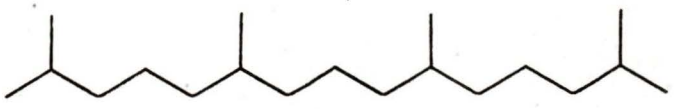


2

a gem-dimethyl group. Thus the partial structure 1 could be deduced leaving two methyl groups to be located on the chain.

The mass spectra of straight chain hydrocarbons have only negligible peaks in the region above m/e 80. On the other hand, branched hydrocarbons display intense peaks in the higher mass region which arise from fragmentation occurring at the sites of branching[10,11]. On the basis of this premise, the mass spectrum of bute hydrocarbon should allow the placement of the remaining two methyl groups. Indeed, intense peaks were found at m/e 113 ($C_8H_{17}^+$) and m/e 183 ($C_{13}H_{27}^+$) which correspond to the fragments indicated in 2. This then established the structure of bute hydrocarbon as 3, a structure which is in accordance with the isoprene rule[12].

Final confirmation of the structure of bute hydrocarbon[13] was provided by a comparative study with an authentic sample of 2,6,10,14-tetramethylpentadecane 3 (pristane). Their physical constants were found to be identical and their infrared, N.M.R. and mass spectra were super-



3

imposable (Figure 1 and 2, p. 22; Appendix 3, p. 64 respectively). Furthermore, a detailed G.L.C. analysis of these hydrocarbons on four stationary phases (Figure 3, p. 23) provided additional evidence for the structure 3.

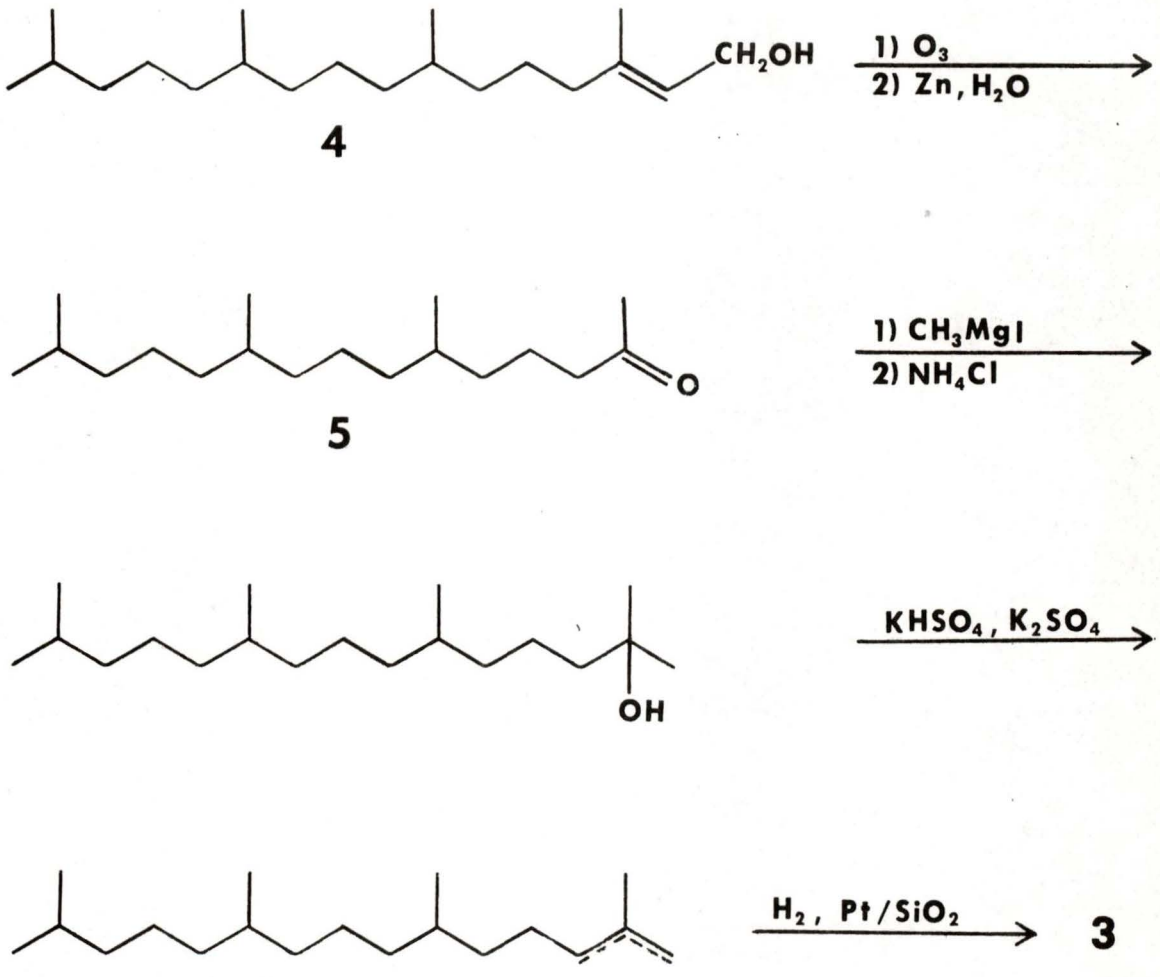
IV. The Expanding Significance of Pristane and Synthetic Studies

Pristane was first isolated in 1917[14] from the liver oil of the basking shark (*Selache maxima*) where it occurs as 14% of the unsaponifiable matter. Later, Toyama made a closer study of the hydrocarbon[15] and found that, although often in small quantitities, it occurs almost invariably in squalene containing shark liver oils and hence gave it the name pristane (Latin: *pristis* = shark). The hydrocarbon usually forms at least 1% of the oil and the amount isolable is 0.5 - 0.7%. Sörensen and Sörensen later identified this hydrocarbon as 2,6,10,14-tetramethylpentadecane 3[16]. On the basis of physical constants and infrared spectrum Pliva and Sörensen demonstrated pristane to be "practically identical" with norphytane 3, synthesized from phytol 4[17], as shown in Scheme 1.

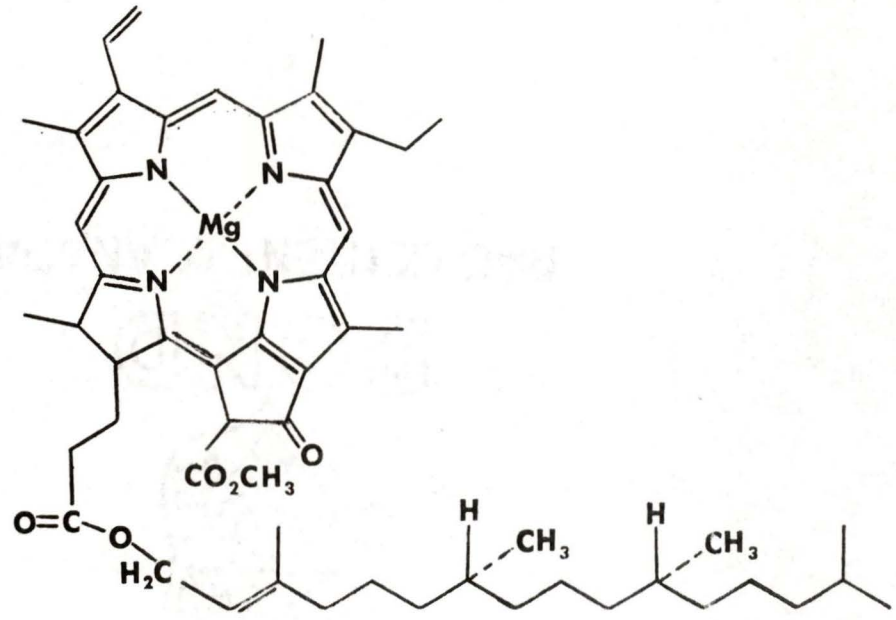
With Sörensen's work terminated little or no attention was paid to pristane until 1962 when Bendoraitis, Brown and Hepner isolated it from crude petroleum[18]. This was the first isolation of an intact terpene from petroleum and was of particular significance in corroborating current theories on the origin of petroleum. Geosynthetic reactions had been postulated for the conversion of carotenoids, steroids and various terpenes into petroleum constituents, but until 1962, no hydrocarbon retaining sufficient structural detail to permit classification as an isoprenoid, had been isolated[19].

Of particular interest here is the postulated geochemical formation of pristane from chlorophyll 6 via the sequence of reactions given in Scheme 2[18].

Scheme 1


CH2OH
1) O3
2) Zn, H2O
4
O
1) CH3MgI
2) NH4Cl
5
OH
KHSO4, K2SO4
H2, Pt/SiO2
3

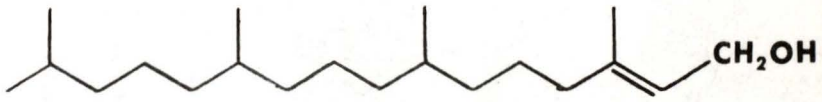
Scheme 2



6

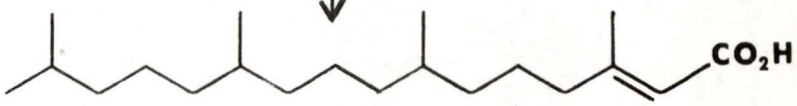
hydrolysis

porphyrin residue +



4

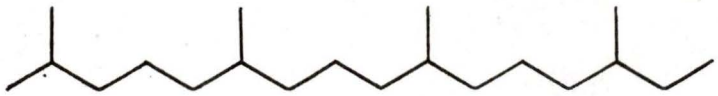
oxidation



decarboxylation

3

Interestingly enough, this same sequence of reactions has been proposed to explain the occurrence of pristane in the liver oil of certain fishes[18]. It is believed that the intestinal flora is responsible for the conversion of chlorophyll from plankton into pristane. It also seems likely that phytane 7 and pristane 3 could be derived from the

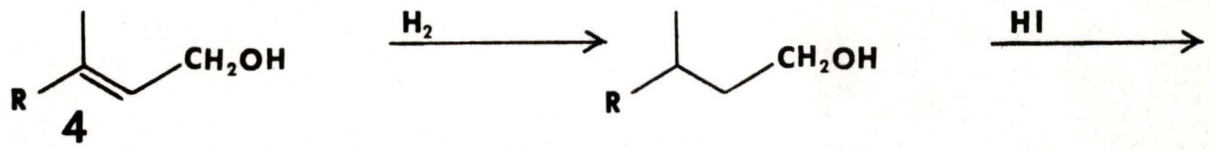


7

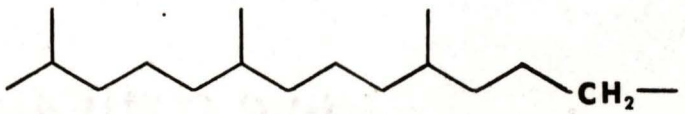
isoprenoid side chains of a phosphate containing lipid, diphytanyl-phosphatidyl glycerophosphate, that is a major constituent of salt water bacteria. Kates, in his work on the lipids of *Halobacterium cutirubrum*, did another synthesis of pristane which is shown in Scheme 3[20].

Certain rocks, as old as three billion years, have been found to contain organic compounds including isoprenoids[21] such as pristane 3 and phytane 7. Many recent geochemical investigations have demonstrated that these compounds are ubiquitously distributed in the geophase and they are therefore being increasingly used as biological markers. It is interesting to note also, that the first lunar samples will be carefully examined for the presence of such biological markers[22] which have already been detected in extraterrestial material[20].

Scheme 3


R
CH2OH
4
H2
CH2OH
HI
CH2I
KOH
KMnO4
CO2H
CH3OH
HCl
CO2CH3
LiAlH4
CH2OH
TsCl
CH2OTs
LiAlH4

3

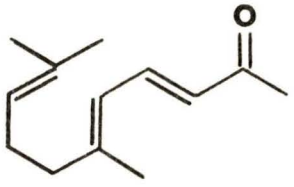
R = 
CH2—

V. Some Aspects of Phytol Chemistry

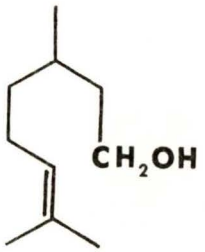
With the importance of pristane and its likely geochemical and biochemical synthesis from phytol established, it is relevant to discuss some of the more important aspects of the chemistry of this diterpene alcohol.

The monounsaturated aliphatic diterpenoid alcohol, phytol ($C_{20}H_{40}O$), was first isolated by Willstatter in 1907 during an investigation into the nature of the chlorophyll molecule[23]. It was not until 1928, however, that its structure was proved by Fischer[24]. The key step in the structure elucidation was chromic acid oxidation of phytol 4 to 6,10,14-trimethyl-2-pentadecanone 5, the structure of which was proved by synthesis from farnesol 8 as shown in Scheme 4.

The following year Fischer completed the synthesis of phytol 4 from pseudo-ionone 9[25], thus providing unequivocal proof of its structure. Fischer's synthesis was not stereospecific but this was no cause for concern since naturally occurring phytol had never been shown to be optically active, even though it had two asymmetric centers. A later stereospecific synthesis from citronellol 10[26] produced (-) -phytol having a rotation, $[\alpha]_D$ - 0.21°. Renewed efforts with natural phytol 4



9



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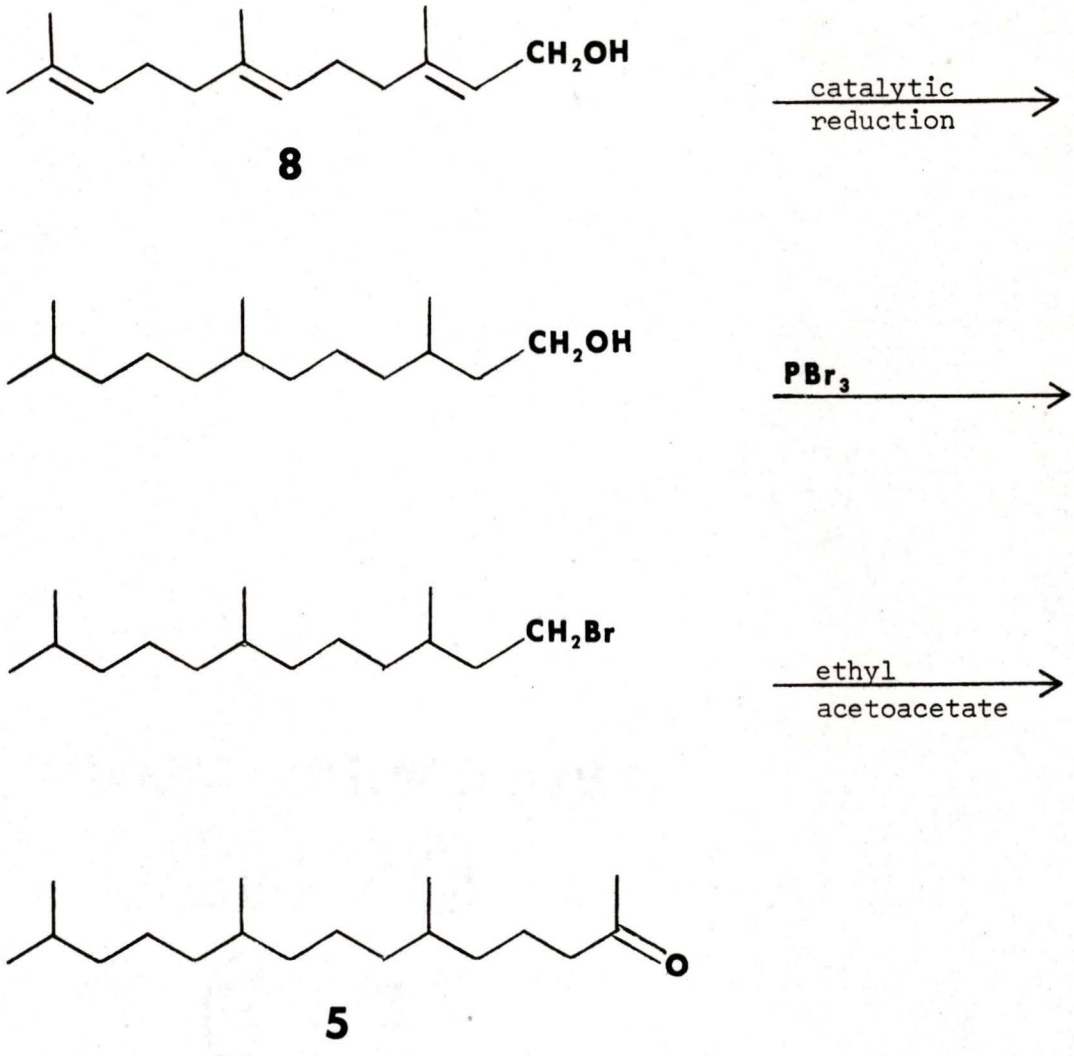
Scheme 4



enabled the same workers to isolate (+)-phytol, having a rotation opposite and equal to that of the synthetic sample. Further investigation into the stereochemistry of phytol 4[27] led to the conclusion that natural phytol was not a racemate but a latent optically active compound, and that synthetic (-)-phytol had steric uniformity at C_{11} but was racemic at C_7 and was not, therefore, the optical antipode of natural (+)-phytol.

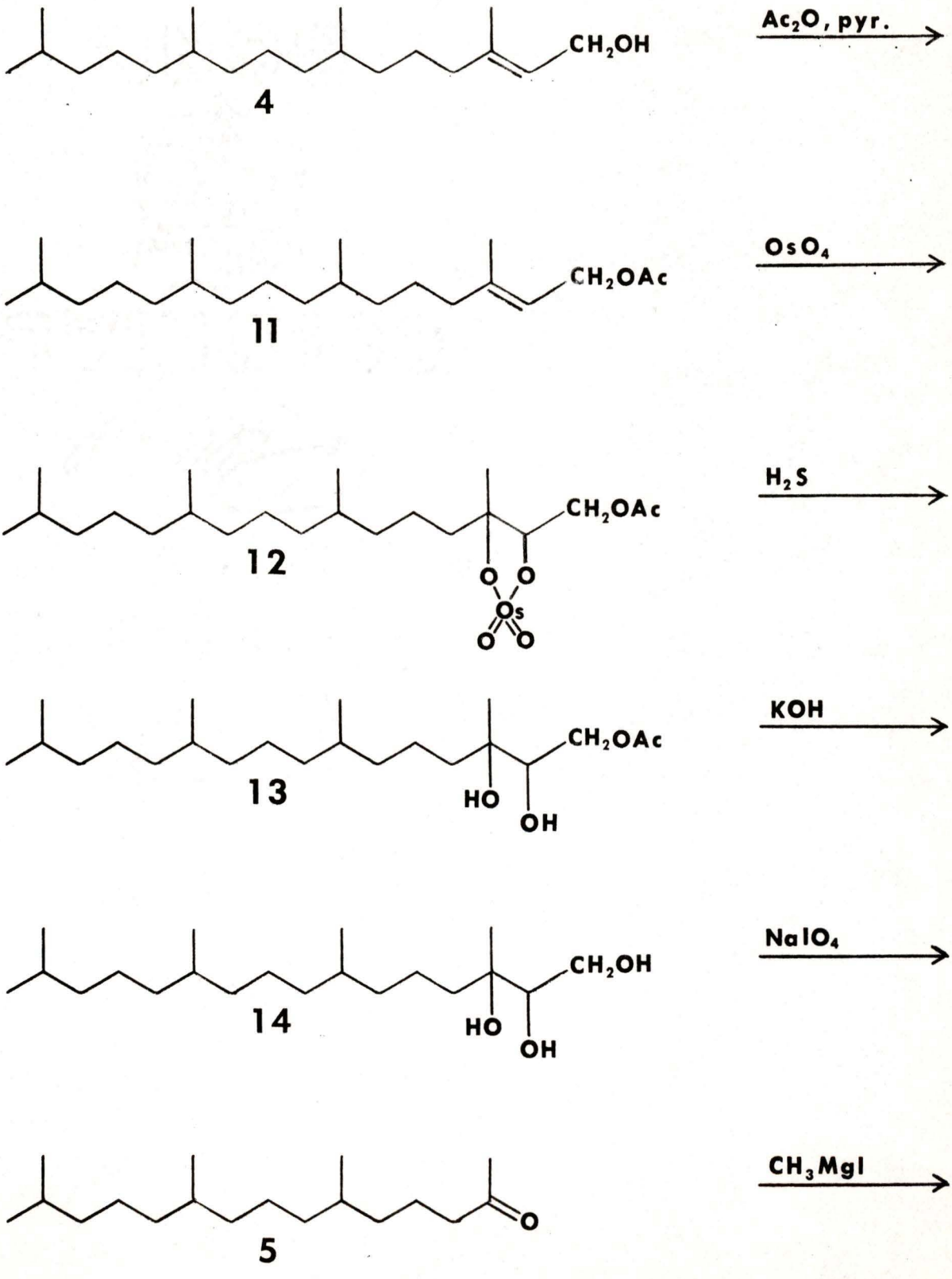
The absolute configuration of phytol was not finally settled until 1959, when the C_7 position was shown to have the R configuration[28], and in 1965 when the C_{11} position was also established as R[29]. Thus the complete configuration of natural (+)- phytol was given as trans- (7R, 11R)[30].

VI. Synthesis of Norphytane[31] - Present Work

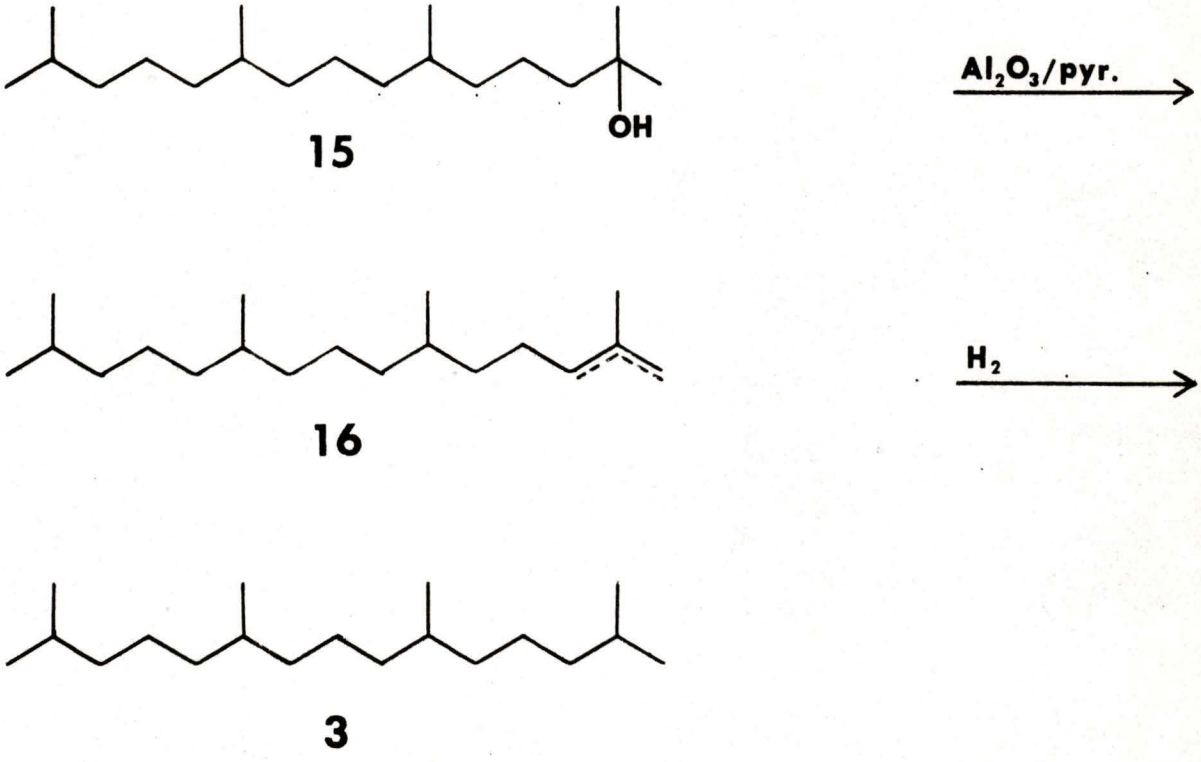
With the structure of bute hydrocarbon established as 2,6,10,14-tetramethylpentadecane 3 (pristane), attention was turned to its identity with norphytane. Sörensen has shown (*vide supra*), on the basis of refractive index, density and infrared spectrum that norphytane and pristane are "practically identical"[17]. However, these physical constants are not diagnostic for closely related hydrocarbons, and hence, any comparison based solely on physical constants should not be regarded as chemically sound. Moreover, in the absence of any characteristic or intense bands in the finger print region, any correlation by infrared spectroscopy calls for further substantiation. Careful examination of Sörensen's experimental work leaves some doubt regarding the purity of his synthetic norphytane. The reasons are two-fold; firstly, his heavy reliance on physical constants, and secondly, his failure to fully characterize the oxygenated intermediates. Because of this, coupled with the growing importance of pristane in both geochemical and biochemical work as discussed above, a rigorous spectral comparison of pristane and norphytane was desirable. With this objective in mind, norphytane was synthesized from phytol 4 as shown in Scheme 5.

The allylic alcohol moiety of phytol 4 could be conveniently used to modify the twenty carbon atom skeleton to the desired nineteen carbon atom chain of norphytane. Furthermore, the allylic alcohol lent itself

Scheme 5


CH2OH
4
Ac2O, pyr.
OsO4
CH2OAc
11
H2S
CH2OAc
12
O
O
Os
O
O
KOH
CH2OAc
13
HO
OH
NaIO4
CH2OH
14
HO
OH
CH3MgI
O
5

Scheme 5 (Continued)

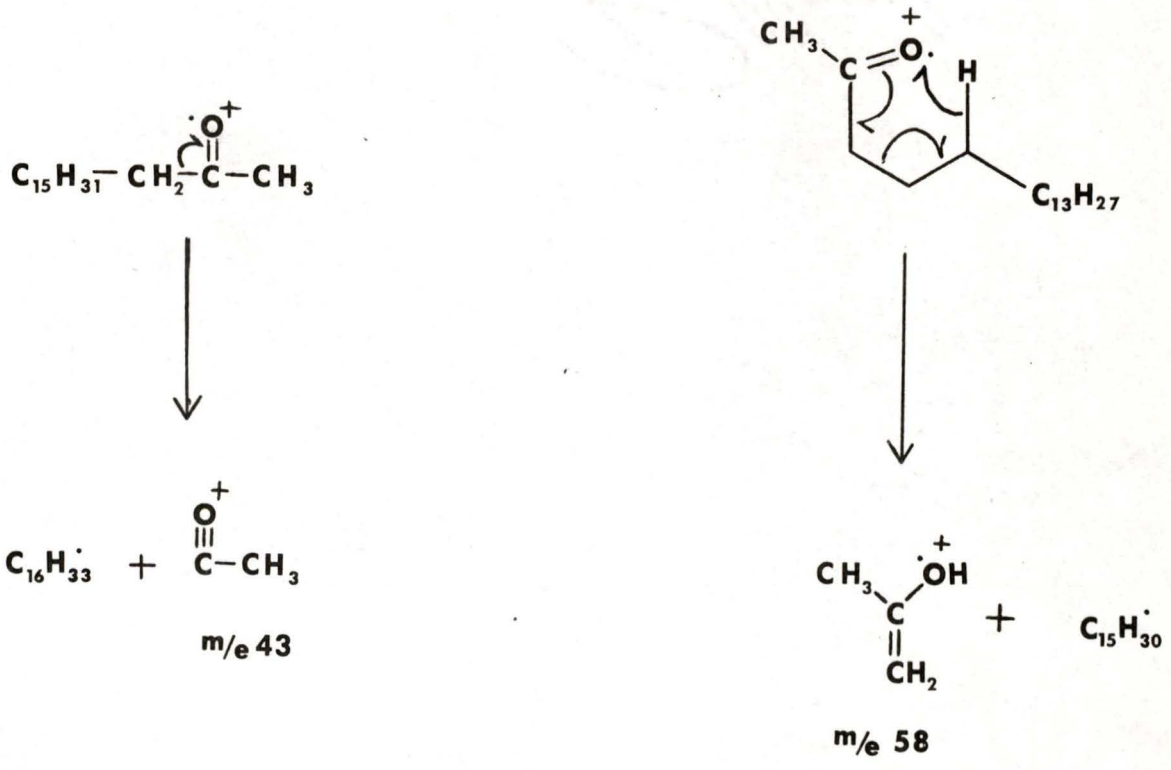


well to the preparation of a crystalline derivative, which, in view of the difficulties encountered by previous workers in the purification of this high boiling diterpene[16], was considered a key step in the synthesis. In this way then, the synthesis could be started from a fully characterized crystalline material, thus leaving no doubt concerning the purity or constitution of subsequent liquid intermediates. (It is relevant to note that, with the exception of the triol 14, all synthetic intermediates (Scheme 5) are high boiling liquids.) The most convenient way to prepare the needed crystalline derivative was to osmylate phytol 4, then hydrolyse the resulting osmic ester to yield the corresponding triol 14, as shown in Scheme 5.

Since phytol 4 undergoes aerial oxidation it was converted to its

relatively more stable acetoxy derivative 11 which was oxidized with osmium tetroxide yielding the osmic ester 12. Treatment of 12 with H_2S followed by basic hydrolysis led to the crystalline triol 14, m.p. 56-57°. The triol 14 displayed hydroxyl absorption in the infrared (Appendix 1, p. 55) at 3445, 1210 and 1086 cm^{-1}. Its N.M.R. spectrum (Appendix 2, p. 60) showed a 12 proton doublet at 9.13 τ, a sharp singlet at 8.85 τ due to methyl on a carbon bearing hydroxyl and a broad 6 proton band resonating at 5.8-6.7 τ. This was reduced to a 3 proton multiplet on exchange with D_2O. The shortening of the twenty carbon atom skeleton of phytane-1,2,3-triol 14 was accomplished smoothly through oxidation with

Scheme 6



sodium meta-periodate to yield the ketone 5, $C_{18}H_{36}O$. This intermediate was characterized by an infrared band at 1717 cm^{-1} and by intense peaks in its mass spectrum at m/e 43, rationalized by α-cleavage, and m/e 58, rationalized by McLafferty rearrangement[11] (Scheme 6). Its N.M.R. spectrum (Appendix 2, p. 60) showed a 12 proton doublet at 9.13 τ, a 3 proton singlet at 7.89 τ due to methyl adjacent to carbonyl and a 2 proton triplet at 7.61 τ due to the *alpha*-methylene protons. The ketone 5 was further characterized through its semicarbazone, m.p. 65-67° (lit.[24] 66-67°). The synthesis of the norphytane skeleton was completed by reaction of the ketone 5 with methyl Grignard reagent to produce the tertiary alcohol 15 which was not characterized but dehydrated directly to a mixture of olefins 16. Careful integration of either the vinyl proton signal or the vinylic methyl signal in the N.M.R. spectrum indicated a ratio of 3:7, norphytene-1 to norphytene-2. Finally, the olefinic mixture 16 was hydrogenated quantitatively to yield norphytane 3 in 85% yield based on the weight of the triol 14.

VII. Comparison of Pristane, Norphytane and Bute Hydrocarbon

Having synthesized G.L.C. pure norphytane, the next objective was to make a thorough comparison of bute hydrocarbon and pristane with the synthetic material. Physical constants suggested their identity; this was further confirmed by their infrared and N.M.R. spectral features which are shown in Figures 1 and 2. The mass spectral fragmentation pattern (Appendix 3, p. 64) was essentially identical for the three hydrocarbons. Finally, G.L.C. behaviour (Figure 3) of the three compounds on four stationary phases confirmed their structural identity.

Figure 1.

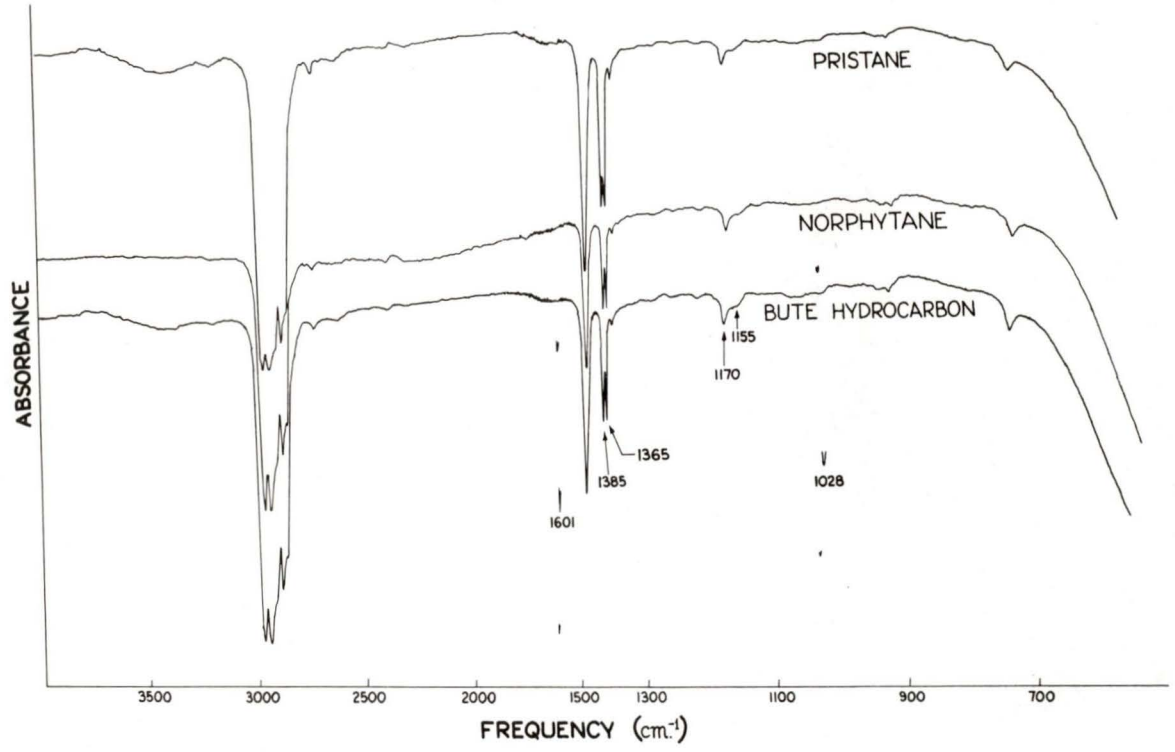


Figure 2.

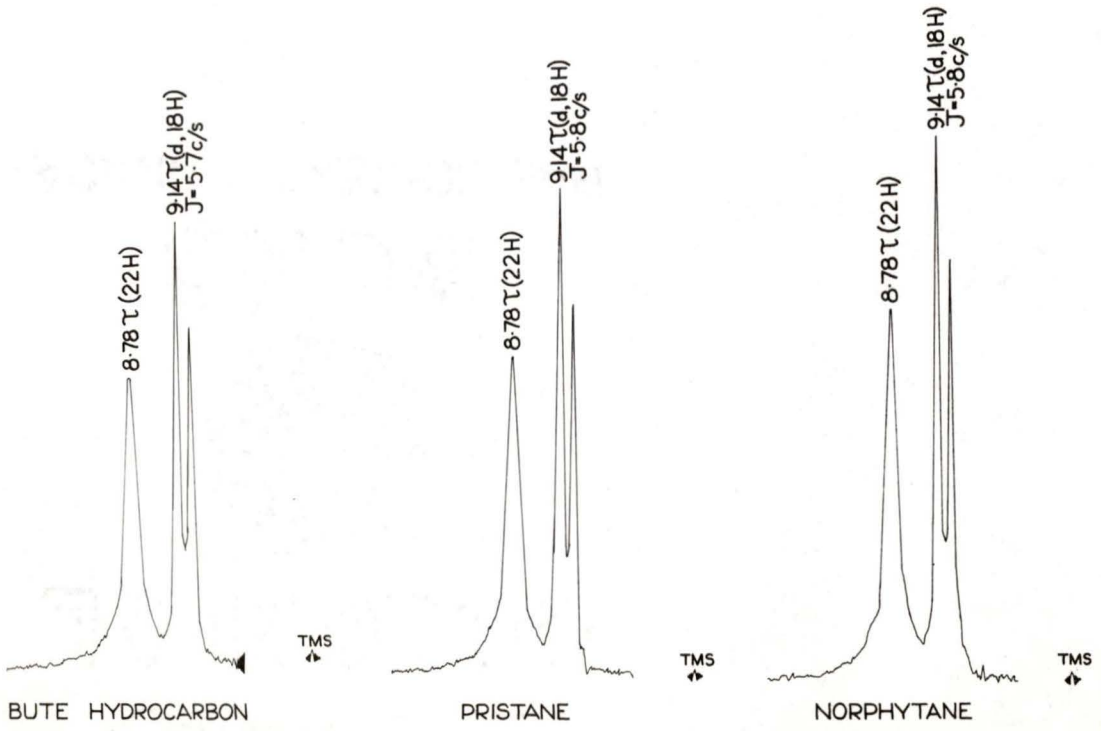


Figure 3.

RELATIVE RETENTION TIMES

OF $C_{19}H_{40}$

SAMPLE	STATIONARY PHASE* DEGS	MPS OIL	APL	MPS GUM
NONADECANE	1.00	1.00	1.00	1.00
PRISTANE	0.52	0.42	0.43	0.58
NORPHYTANE	0.52	0.42	0.44	0.58
BUTE HYDROCARBON	0.52	0.42	0.44	0.58

*DEGS = DIETHYLENE GLYCOL SUCCINATE

MPS = METHYL PHENYL SILICONE

APL = APIEZON L

EXPERIMENTAL

All melting points and boiling points are uncorrected; melting points were determined on a Kofler hot stage. Infrared spectra were recorded with a Perkin-Elmer infracord Model 337, calibrated with polystyrene film; a Model 700 was used for routine work. Nuclear magnetic resonance spectra were obtained by Mrs. C. Greenwood using a Varian Associates Model HA-60 spectrometer. The mass spectra were measured by Mr. G. L. Owen with a Hitachi-Perkin-Elmer RMU-6E single focus mass spectrometer. Gas-liquid chromatographic analyses were carried out on a Perkin-Elmer Gas Chromatograph Model 810 (with flame ionization detector) equipped with 6 ft x 0.25 in columns with helium as a carrier gas. Petroleum ether refers to the fraction boiling 37-49°. T.L.C. plates were prepared, 25 μ thick, from Camag silica gel and alumina. Evaporations *in vacuo* were carried out on a Büchi flash evaporator. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York.

Characteristics of Bute Inlet Wax

Crude Bute Inlet Wax (305 g) was dissolved in $CHCl_3$ (1 l) and washed with saturated Na_2CO_3 solution. The organic layer was washed to neutrality with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield 326 g. The excess weight was due to difficulty in removing water; thus the wax was reprocessed and redried to yield Neutral Bute Inlet Wax as a tan colored oil; n_D^{21} 1.4621, α_D ± 0.0.

I.R. Spectrum (film)-Appendix 1, p. 54:

1740, 1655, 1175, 718 cm^{-1}.

U.V. Spectrum (cyclohexane): λ_{max} 197.5 mμ.

A sample of Neutral Bute Inlet Wax was filtered through a ten-fold ratio of silica gel; elution with 1:1 petroleum ether-benzene gave a colorless mobile liquid having n_D^{25} 1.4595 and infrared spectrum identical to that of Neutral Bute Inlet Wax. Fractionation gave a material with b.p. 240-250°/0.5 mm and n_D^{25} 1.4589.

Anal. Found: C, 80.26; H, 13.12.

Found: C, 80.30; H, 12.83.

Preliminary Chromatography

Neutral Bute Inlet Wax (9.89 g) was chromatographed on neutral grade 5 alumina (300 g). Elution with petroleum ether gave a fraction (7.172 g) having n_D^{21} 1.4601 which was rechromatographed on a sixty-fold ratio of grade 5 alumina. Elution with petroleum ether in 200 ml fractions gave as the third cut 5.574 g of colorless oil having n_D^{21} 1.4608 and showing a single spot on T.L.C. Fractionation of this material gave bute ester which was characterized as follows:

b.p. 220-230°/0.2 mm

n_D^{21} 1.4597

Optical Rotation (30°): α_D -0.002

α_{578} +0.004

α_{546} +0.002

α_{436} +0.003

α_{365} +0.004

I.R. Spectrum (film): 1740, 1655 (weak), 1174, 718 cm^{-1}.

N.M.R. Spectrum (CCl_4) τ-Appendix II p. 59:

9.12 (br t), 6.04 (br t), 4.75 (t).

Mass Spectrum: The highest measureable peak had mass 506.5064

(calc. for $C_{34}H_{66}O_2$ 506.5063). However very small peaks were visible up to ca. m/e 600.

Anal. Found: C, 80.51; H, 13.21.

Attempted Hydrolysis Experiments

A. Hydrolysis was attempted by refluxing Neutral Bute Inlet Wax with excess alcoholic KOH. However, an intractable highly colored emulsion resulted and this experiment had to be modified (*vide infra*). It was possible, however, to obtain some acidic material as its ammonium salt. Regeneration of the acid with dilute HCl gave 1.35 g of acid, which after recrystallization from petroleum ether had m.p. 42-46°.

Anal. Found: O, 6.48.

B. Neutral Bute Inlet Wax was chromatographed first on alumina and then on silica gel impregnated with silver nitrate as described below. A fraction (28 g), eluted with 1:1 petroleum ether-benzene and having n_D^{21} 1.4614 was dissolved in C_6H_6 (100 ml), EtOH (250 ml) and H_2O (50 ml) to which was added KOH (50 g) and refluxed overnight. The solvent was removed *in vacuo*, the residue dissolved in water and extracted with petroleum ether (3 x 700 ml). The organic layer was washed to neutrality with brine, dried over Na_2SO_4 and evaporated *in vacuo* to yield 12 g of neutral material. Acetylation of this material followed by a detailed G.L.C. analysis indicated the presence of about 40 components. The neutral material failed to yield any pure benzoate derivative, thus further indicating inhomogeneity.

Hydrogenation of Bute Ester

Bute ester (1.996 g) obtained from preliminary chromatography

(*vide supra*) was hydrogenated in EtOAc with Adam's catalyst (96 mg). Filtration, evaporation and recrystallization gave hydrogenated Bute ester (1.267 g); m.p. 55-58°.

I.R. Spectrum: no >C=C< vibration.

U.V. Spectrum: no characteristic absorption.

Mass Spectrum: The mass spectrum displayed peaks up to m/e 676. The highest, accurately measureable peak at m/e 620 had an exact mass of 620.6459 (calc. for $C_{42}H_{84}O_2$ 620.6471).

Anal. Found: C, 81.35; H, 13.75.

Bute Hydrocarbon 3

Neutral Bute Inlet Wax (100 g) was chromatographed on grade 5 alumina (1500 g) as shown below.

No.	Solvent	Volume	Weight	n_D^{21}
1	petroleum ether	500 ml	0.017	
2	petroleum ether	500 ml	0.568	
3	petroleum ether	500 ml	55.8	1.4615
4	petroleum ether	500 ml	26.1	1.4617
5	petroleum ether	500 ml	0.351	
6	petroleum ether	500 ml	0.050	
7	EtOAc	2100 ml	5.436	
8	4:1 EtOAc:HOAc	3500 ml	1.134	

Fractions 3 and 4 above, having similar refractive indices were

combined and rechromatographed on a 30 fold ratio of silica gel impregnated with silver nitrate.* Elution with petroleum ether (2 l) brought out a waxy forerun and the following 750 ml of petroleum ether contained almost pure bute hydrocarbon 3 (2.022 g). Distillation over sodium gave G.L.C. pure material in 1.5% yield; b.p. 152°/6.0 mm, n_D^{21} 1.4393.

Optical Rotation (neat): α_D -0.003

α_{578} ±0.0

α_{546} ±0.0

α_{436} ±0.0

α_{365} -0.004

I.R. Spectrum (film)-Figure 1, p. 22:

1385, 1365 (doublet), 1170 broad band with a shoulder at 1155 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ - Figure 2, p. 22:

9.14 (18H, d, J=5.7 Hz), 8.78 (22H, s).

Mass Spectrum-Appendix 3, p. 64:

M^+ 268, % Σ_{27} 1.10.

High resolution mass measurement:

Calcd. for $C_{19}H_{40}$: 268.3130.

Found: 268.3125.

Anal. Calcd. for $C_{19}H_{40}$: C, 84.99; H, 15.01.

Found: C, 84.74; H, 15.18.

---

*Preparation of this adsorbent is described in reference 9. In this work the silica gel-silver nitrate was prepared using exactly one-half the prescribed amount of silver nitrate with no noticeable effect on the activity of the adsorbent.

Pristane 3 (2,6,10,14-tetramethylpentadecane)

Commercially available pristane (K & K Laboratories) was distilled over sodium at 150°/6.0 mm giving G.L.C. pure pristane 3. All spectra were superimposable on those of bute hydrocarbon (see Figures 1 and 2, p. 22; Appendix 3, p. 64).

Phytol 4

Commercially available phytol (K & K Laboratories), 75% pure by G.L.C. was purified by column chromatography on silica gel followed by fractional distillation. The fraction boiling at 170-85° (bath)/0.25 mm was G.L.C. pure (> 99%) phytol 4 obtained as a colorless liquid.

I.R. Spectrum (film)-Appendix 1, p. 54:

3340, 1670, 1375, 1365, 1000 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 59:

9.14 (12H, d, J=5.6 Hz), 8.35 (3H, s), 8.07 (2H, br m), 7.59 (1H, s), 5.91 (2H, d, J=7.0 Hz), 4.62 (1H, br m).

Mass Spectrum-Appendix 3, p. 66:

M^+ 296, % Σ_{29} 1.09; M-H_2O 278, % Σ_{29} 0.47.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.00; H, 13.60.

Found: C, 80.49; H, 13.61.

Phytyl Acetate 11

Freshly distilled phytol 4 turns light yellow on standing due to aerial oxidation. It was converted to its relatively more stable acetate (acetic anhydride-pyridine method). Phytyl acetate 11 was distilled* at

*Attempted purification by column chromatography on alumina invariably led to its hydrolysis.

145-146°/0.25 mm as a clear liquid.

I.R. Spectrum (film)-Appendix 1, p. 54:

1740 (acetoxy carbonyl), 1670 (>C=C<), 1375 and 1360 (gem-dimethyl)

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 59:

9.14 (12 H, d, J=5.5 Hz), 8.79 (br s), 8.33 (3H, br s), 8.03 (3H, s), 5.45 (2H, br d, J=7.2 Hz), 4.5-4.8 (1H, br m).

Anal.** Calcd. for $C_{22}H_{42}O_2$: C, 78.04; H, 12.50.

Found: C, 79.44; H, 12.95.

Phytane-1,2,3-triol 14

A solution of OsO_4 (1 g) in petroleum ether-ether (1:1, 60 ml) was slowly added in 2 portions to a stirred solution of phytyl acetate 11 (1.3 g) dissolved in petroleum ether-ether (1:1, 40 ml) containing anhydrous pyridine (3 ml), and the reaction mixture was stirred at room temperature for 4 days in the dark[32,33]. The bulk of the solution was concentrated to ca. 25 ml and the solid osmic ester collected, dissolved in benzene-methanol (1:1, 120 ml) and saturated with H_2S with cooling. The brownish-black precipitate was filtered off and washed with benzene (10 ml). The solvent was removed *in vacuo* and the residual gum [1.25 g; ν_{max} (film): 3450 (hydroxyl), 1745 (acetate) cm^{-1}] was hydrolysed by refluxing with aqueous methanolic KOH. The reaction mixture was worked up by extraction into ether yielding phytane-1,2,3-triol 14, crystallized

** A better analysis of this G.L.C. pure specimen could not be obtained presumably due to its tendency towards partial hydrolysis on standing. However its mass spectrum displayed a weak molecular ion peak at m/e 338 with an intense peak at m/e 278 due to the M- CH_3CO_2H fragment (see Appendix 3, p. 67).

from acetone-acetonitrile to give white crystals, m.p. 56-57°.

I.R. Spectrum ($CHCl_3$)-Appendix 1, p. 55:

3445, 1210, 1086 cm^{-1} (hydroxyl).

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 60:

9.13 (12 H, d, J=5.6 Hz), 8.85 (s), 5.8-6.7 (broad 6 proton band reduced to a 3 proton multiplet after exchange with D_2O).

Mass Spectrum-Appendix 3, p. 68:

M-CH_3 315, % Σ_{27} 0.21.

Anal. Calcd. for $C_{20}H_{42}O_3$: C, 72.67; H, 12.81.

Found: C, 72.70; H, 12.68.

$NaIO_4$ Oxidation of Phytane-1,2,3-triol 14

A solution of $NaIO_4$ (360 mg dissolved in 1 ml H_2O and diluted with 9 ml MeOH) was slowly added to the triol 14 (233 mg) dissolved in MeOH (9 ml) and the reaction mixture was set aside for 24 h at room temperature in the dark. The solvent was removed *in vacuo* and the residue diluted with water (30 ml) and extracted with ether (3 x 20 ml). The combined extract was washed with brine (2 x 15 ml), dried over Na_2SO_4 and the solvent removed under suction, to yield a yellow oil (208 mg). Filtration through silica gel (4.2 g) with petroleum ether (50 ml) afforded the ketone 5 as a clear mobile liquid (188 mg); b.p. 194-197° (bath)/8.5 mm.

I.R. Spectrum (film)-Appendix 1, p. 55:

1717 cm^{-1} (acyclic ketone).

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 60:

9.13 (12 H, d, J=5.7 Hz), 7.89 (3H, s), 7.61 (2H, br t).

Mass Spectrum-Appendix 3, p. 69:

M^+ 268, $\%\Sigma_{27}$ 1.16.

Anal. Calcd. for $C_{18}H_{36}O$: C, 80.52; H, 13.52.

Found: C, 79.65; H, 13.05.

The ketone 5 was further characterized by its semicarbozane, m.p. 65-67° (lit.[24] 66-67°).

Grignard Addition to the Ketone 5

A solution of ketone 5 (219 mg) in dry ether (15 ml) was added under a nitrogen atmosphere to 5 equivalents of MeMgI (prepared from 125 mg Mg and 740 mg MeI) and the mixture was stirred at room temperature for 1 h. Ether was removed with a swift current of nitrogen and replaced with anhydrous benzene (40 ml) and the reaction mixture was refluxed for 24 h. The mixture was then cooled and rapidly acidified with saturated NH_4Cl solution. The product was extracted with ether (3 x 30 ml) and the combined ether extract was washed with brine (15 ml), dried and evaporated to yield the alcohol 15 (245 mg); ν_{max} (film) 3390 cm^{-1} (hydroxyl). There was apparently some dehydration during the work-up, evidenced by a band at 910 cm^{-1} in its infrared spectrum. Consequently, the product was used as such for the subsequent reaction, without any further purification.

Dehydration of the Alcohol 15

The crude alcohol 15 (245 mg) was mixed with pyridine impregnated (2%) alumina (500 mg) and heated in an atmosphere of nitrogen at 150-170° for 1 h[34]. The reaction mixture was slurried with ether, filtered and dried over Na_2SO_4. Removal of solvent *in vacuo* furnished a mobile liquid

(200 mg) which was filtered through silica gel and then distilled at 175° (bath)/7.0 mm to give a mixture of olefins 16 (158 mg).

I.R. Spectrum (film): 1652, 1380, 1365, 1173, 1154 and 886 cm^{-1}.

Anal. Calcd. for $C_{19}H_{38}$: C, 85.63; H, 14.37.
Found: C, 85.51; H, 14.42.

Norphytane 3

A solution of olefins 16 (80 mg) in absolute ethanol (20 ml) containing 10% Pd-C (20 mg) was stirred at room temperature under hydrogen until absorption ceased. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give norphytane 3 in quantitative yield. It was distilled over sodium as a clear mobile liquid; b.p. 165-170° (bath)/7.0 mm, no coloration with tetranitromethane. The overall yield was 85% based on the weight of the triol 14.

I.R. Spectrum (film)-Figure 1, p. 22:
1385, 1365, 1170 and 1155 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Figure 2, p. 22:
9.14 (18H, d, J=5.8 Hz), 8.78 (22H, s).

Mass Spectrum-Appendix 3, p. 64:
M^+ 268, $\%\Sigma_{27}$ 1.19.

Anal. Calcd. for $C_{19}H_{40}$: C, 84.98; H, 15.02.
Found: C, 85.09; H, 14.70.

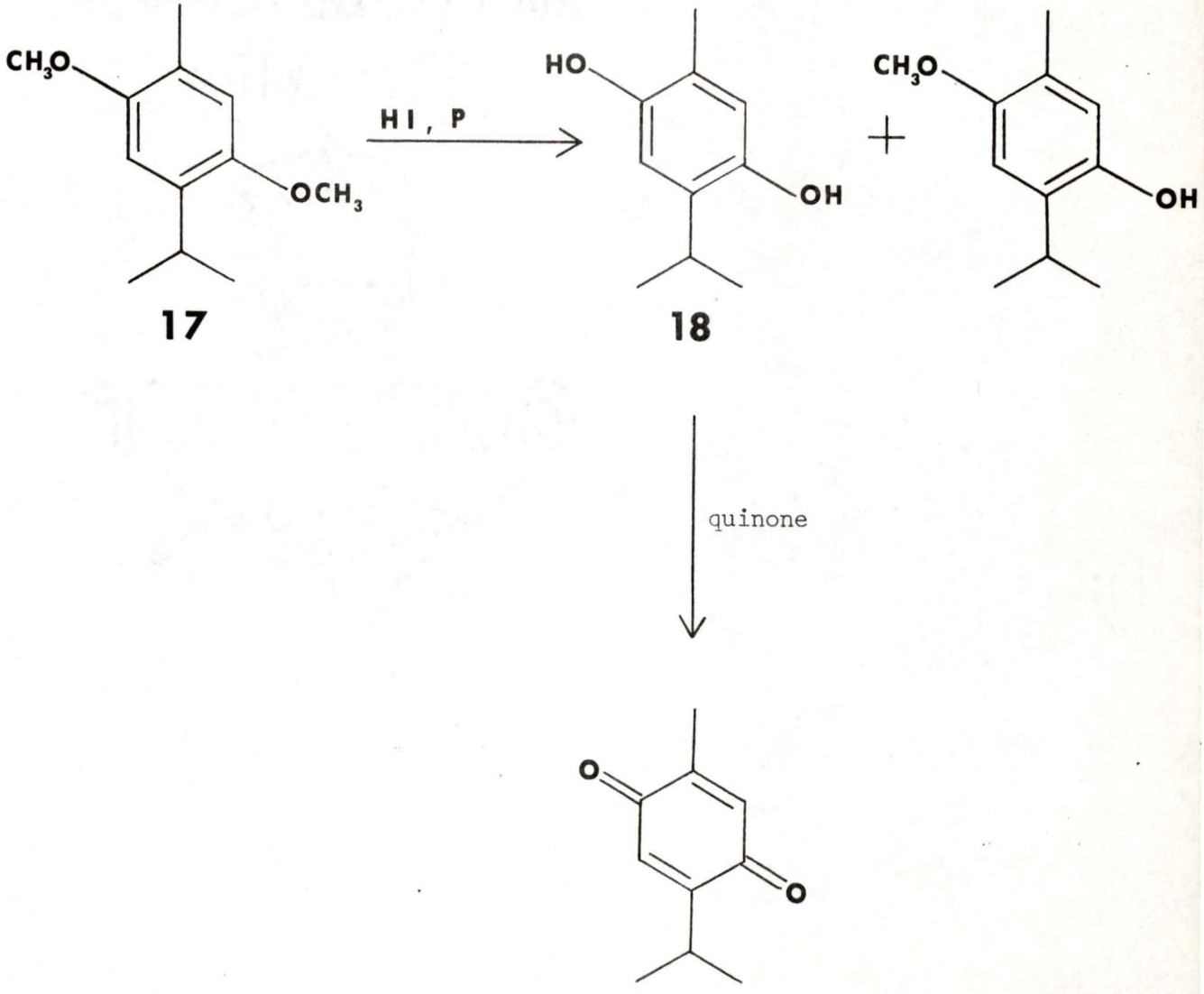
Part II:

Terpenoids From *Eupatorium Ayapana*

INTRODUCTION

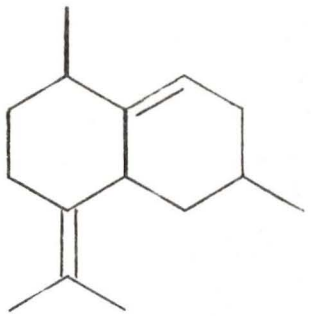
Semmler, in 1908, reported the isolation of a sesquiterpene hydrocarbon along with a monoterpenoid 17 from *Eupatorium ayapana*[35]. The structure elucidation of 17 was carried out by the sequence of reactions shown in Scheme 7. However, no structure was proposed for the sesquiterpene hydrocarbon. With the objective of establishing the structure of Semmler's hydrocarbon we investigated the essential oil of *E. ayapana* which yielded both the sesquiterpene and the monoterpenoid 17. Our

Scheme 7



investigation has confirmed, through rigorous spectral and chemical identification, the structure 17, deduced by Semmler purely on chemical grounds. Furthermore, we have elucidated the structure of Semmler's hydrocarbon and made a thorough spectral comparison with an authentic sample.

It is interesting to note that in 1956 Dhingra investigated *E. odoratum*[36] and found a hydrocarbon having structure 19 which he named eupatene. The physical constants of eupatene 19 and Semmler's hydrocarbon isolated during the present investigation are notably similar. Regrettably however, a sample of eupatene was not available for comparison and therefore no conclusions can be drawn. Therefore, to avoid any con-



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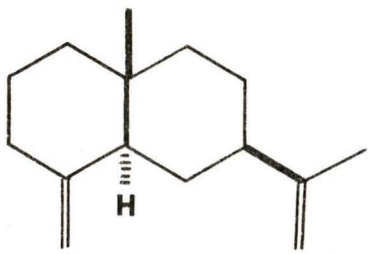
fusion the name Semmler's hydrocarbon has been retained for the sesquiterpene isolated from *E. ayapana*.

DISCUSSION

I. Structure Elucidation of Semmler's Hydrocarbon 20

The molecular formula of Semmler's hydrocarbon 20 was shown by analysis and mass spectrometry to be $C_{15}H_{24}$. It gave a positive tetranitromethane test and showed terminal methylene in its infrared spectrum (Appendix 1, p. 55). Catalytic hydrogenation of Semmler's hydrocarbon proceeded smoothly with the uptake of 2 moles of hydrogen to yield a



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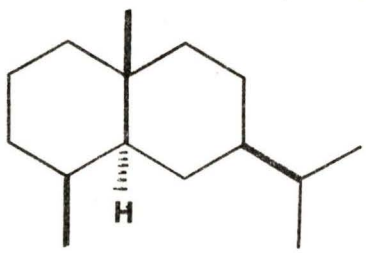

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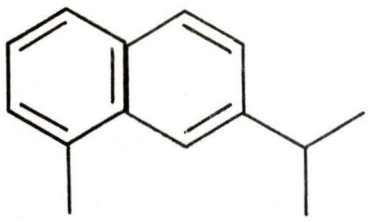
fully saturated hydrocarbon 21, $C_{15}H_{28}$. Thus Semmler's hydrocarbon must have two double bonds and be bicyclic.

The N.M.R. spectrum of Semmler's hydrocarbon 20 (Appendix 2, p. 60) showed the presence of one angular methyl group at 9.28 τ and one vinylic methyl group resonating as a triplet (J=1Hz) at 8.25 τ. The small coupling constant of this triplet is typical of allylic coupling[37,38] between a methyl and a terminal methylene group.

The gross carbon skeleton of Semmler's hydrocarbon 20 was established by dehydrogenation[39,40] which led to the formation of eudalene 22 in 40%

yield, identified by comparison with an authentic sample. This



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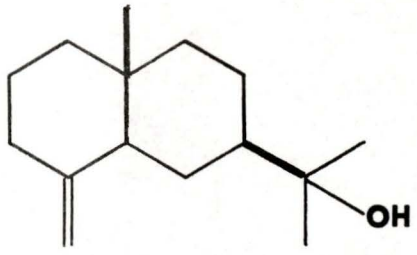


23

reaction accounts for 14 carbon atoms. The remaining carbon atom, presuming that the hydrocarbon is an isoprenoid[12], must be located at C_{10}; this position is also consistent with the N.M.R. data presented above.

Saturation of an ethereal solution of Semmler's hydrocarbon 20 with dry hydrogen chloride yielded the dihydrochloride derivative, identified as selinene dihydrochloride. These data then, led to the structure 20 for Semmler's hydrocarbon.

Finally, β-selinene 20 was prepared by dehydration of β-eudesmol 23[41], whose structure and stereochemistry are well established[42]. A mass

spectral comparison (Appendix 3, p. 70) and a G.L.C. comparison (Figure 4) showed β-selinene and Semmler's hydrocarbon 20 to be identical, thus establishing the structure and absolute configuration which is implicit in structure 20.

Figure 4

SAMPLE	STATIONARY PHASE* CARBOWAX 4000	SE-30	APL
Semmler's Hydrocarbon	12.55	5.74	18.40
β-selinene	12.57	5.76	18.42

* SE-30 = silicone oil

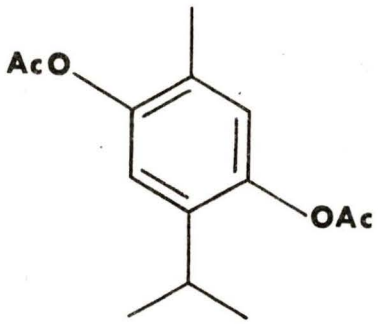
APL = apiezon L

II. Characterization of 2,5-dimethoxy-p-cymene 17

The molecular formula, $C_{12}H_{18}O_2$, of the dimethoxy terpene was established by analysis and mass spectrometry. Its N.M.R. spectrum (Appendix 2, p. 61) displayed an aromatic methyl singlet at 7.81 τ and two methoxy methyl singlets at 6.26 and 6.24 τ. The isopropyl group resonated as a 6 proton methyl doublet at 8.80 τ and a 1 proton quartet at 6.75 τ. The two aromatic protons were evidenced by two singlets at 3.35 and 3.29 τ. This spectrum can be accounted for only by a 1,2,4,5 substitution pattern as in 17.

Grignard hydrolysis[43] of 17 gave, in 79% yield, the dihydroxy

derivative 18, m.p. 144°. Spectroscopic characterization of this compound (cf. experimental) confirmed its structure. 2,5-Dihydroxy-p-cymene 18 was quantitatively converted to the diacetate 24 by the acetic anhydride-



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pyridine method. The diacetoxy derivative melted at 78-79.5° and displayed the expected spectroscopic features as described in the experimental part.

EXPERIMENTAL

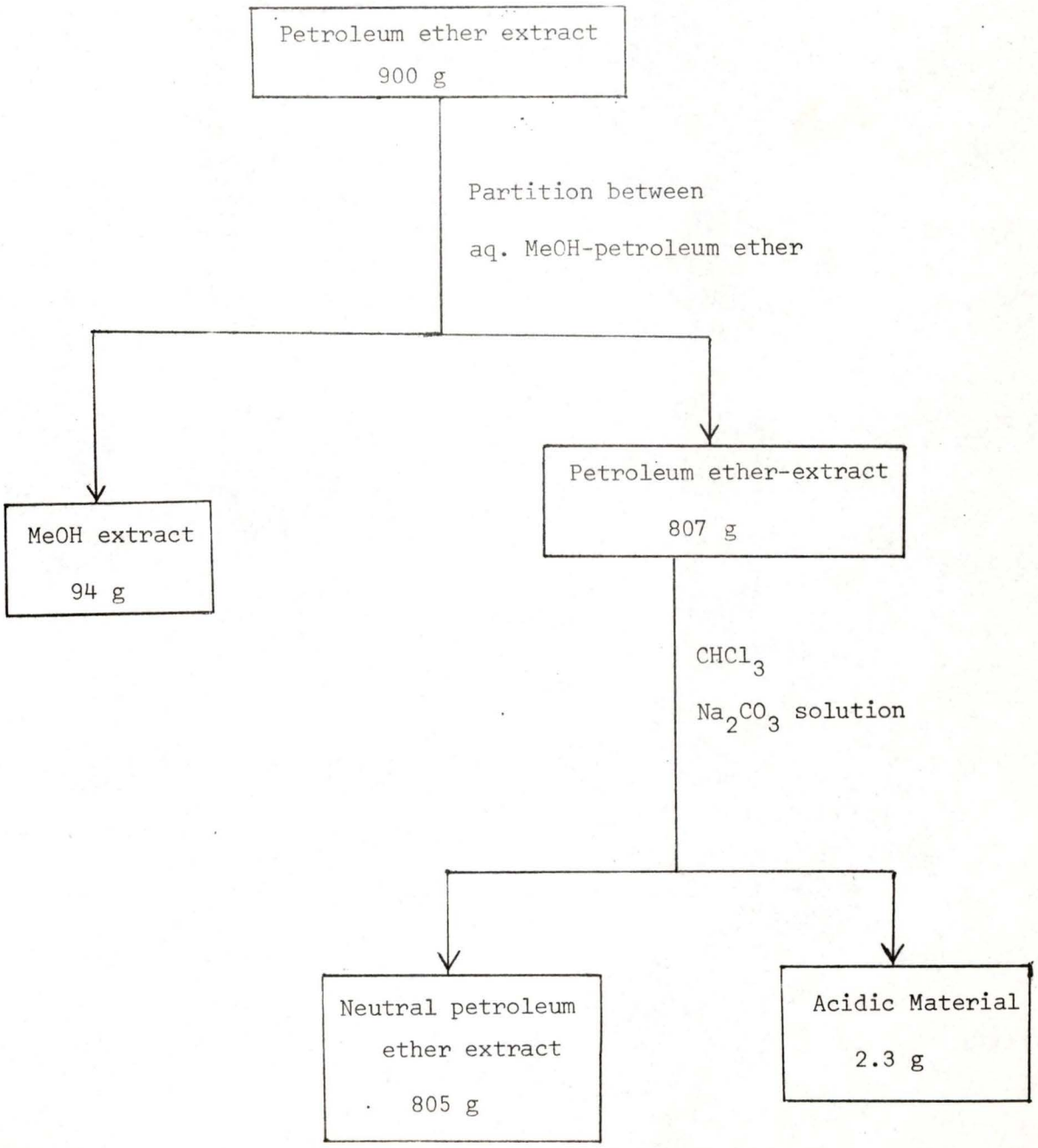
All melting points and boiling points are uncorrected; melting points were determined on a Kofler Hot Stage. Rotations were determined in chloroform with a Perkin-Elmer 141 polarimeter. Infrared spectra were recorded with a Perkin-Elmer Infracord Model 337, calibrated with polystyrene film; a model 700 was used for routine work. Nuclear magnetic resonance spectra were obtained by Mrs. C. Greenwood using a Varian Associates Model HA-60 spectrometer. Ultraviolet spectra were determined on a Unicam SP. 700 spectrophotometer. The mass spectra were measured by Mr. G. L. Owen with a Hitachi-Perkin Elmer RMU-6E single focus spectrometer using an ionizing energy of 70 eV. Gas-liquid chromatographic analyses were carried out for all liquid samples on a Microtek Model 220 gas chromatograph equipped with flame ionization detector and using helium as a carrier gas. Petroleum ether refers to the fraction boiling 37-49°. T.L.C. plates were prepared, 25 μ thick, from Camag silica gel and alumina. Evaporations *in vacuo* were carried out on a Büchi flash evaporator. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York and by Scandanavian Microanalytical Laboratory, Denmark.

Isolation of the Essential Oil

The dried aerial part of *E. Ayapana* (20 Kg) was ground in a Wiley Mill. The powder, in 2 Kg charges, was extracted with petroleum ether for two days in a Soxhlet. The extract was then concentrated *in vacuo* and the residue treated as shown in Scheme 8 to yield 805 g of neutral

petroleum ether extract. Filtration of this material (210 g) through a 10-fold ratio of silica gel using benzene as eluent afforded 73 g of essential oil.

Scheme 8



Semmler's Hydrocarbon 20

The essential oil (73 g) was chromatographed on a 30 fold ratio of silica gel; elution with petroleum ether gave a fraction weighing 10.6 g and further elution with 1:1 petroleum ether-benzene gave a fraction weighing 22.1 g. The petroleum ether fraction (10.6 g) was chromatographed twice on silica gel impregnated with silver nitrate[9] (30 fold and 45 fold ratios) and similar hydrocarbon fractions, as evidenced by G.L.C. analysis, were combined to yield 4.2 g of crude Semmler's hydrocarbon. Distillation of this material over sodium afforded G.L.C. pure Semmler's hydrocarbon 20 (3.1 g) as a clear mobile liquid; b.p. 84-86°/0.4 mm, d_4^{26} 0.9089, n_D^{19} 1.5038, yellow coloration with tetranitromethane.

Optical Rotation (neat) 24°: $[\alpha]_D$ +43.65

$[\alpha]_{578}$ +45.41

$[\alpha]_{546}$ +51.39

$[\alpha]_{436}$ +85.50

$[\alpha]_{365}$ +130.14

U.V. Spectrum (EtOH) mμ: λ_{max} 203, ε 7704.

I.R. Spectrum (film)-Appendix 1, p. 55:

3090, 1645, 884 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 60:

9.28 (3H, s), 8.25 (3H, t, J=1 Hz), 5.56 (1H, br s), 5.30 (3H, d, J=1 Hz).

Mass Spectrum-Appendix 3, p. 70:

M^+ 204, $\%\Sigma_{27}$ 7.44.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84.

Found: C, 87.99; H, 11.68.

Hydrogenation of Semmler's Hydrocarbon 20

Semmler's hydrocarbon 20 (97 mg) was hydrogenated in acetic acid (5 ml) with Adam's platinum catalyst (17 mg). When absorption of hydrogen had ceased the catalyst was filtered off and the solvent removed *in vacuo*. Filtration of the product through silica gel (1 g) afforded the tetrahydro derivative 21 as a clear mobile liquid. Distillation over sodium at 135° (bath)/5.5 mm yielded 70 mg of G.L.C. pure hydrocarbon which showed no coloration with tetranitromethane.

Optical Rotation (c 0.51) 25°: $[\alpha]_D$ +12.94

$[\alpha]_{578}$ +14.11

$[\alpha]_{546}$ +15.68

$[\alpha]_{436}$ +24.70

$[\alpha]_{365}$ +37.45

I.R. Spectrum (film)-Appendix 1, p. 56:

1380, 1365, 1170 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 61:

9.14 (d, J=6.5 Hz), 9.13 (s), 9.13 (d, J=5.5 Hz)

Mass Spectrum-Appendix 3, p. 72:

M^+ 208, % Σ_{27} 4.50

Anal. Calcd. for $C_{15}H_{28}$: C, 86.46; H, 13.54.

Found: C, 86.19; H, 13.37.

Selinene Dihydrochloride

Semmler's hydrocarbon 20 (200 mg) was dissolved in dry ether

(2 ml) at 0° through which dry hydrogen chloride was bubbled. The reaction was stopped when saturation had occurred as evidenced by a slight pink color. The ether was removed at room temperature with a stream of nitrogen and the dihydrochloride recrystallized from ethanol to yield white needles; m.p. 48-52°, $[\alpha]_D^{25}$ -78.70.

I.R. Spectrum (KBr)-Appendix 1, p. 56:

1390, 1370, 1112, 1049, 786, 677, 640 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ: 9.09 (s, 3H), 8.48 (s, 3H), 8.41 (s, 6H).

Mass Spectrum: M^+ 276, % Σ_{27} 0.34 ($C_{15}H_{26}{}^{35}Cl_2$).

Anal. Calcd. for $C_{15}H_{26}Cl_2$: Cl, 25.57.

Found: Cl, 25.58.

The dihydrochloride was found to decompose to a dark coloured gum within a few days of its preparation. It could, however, be stored up to several months at -20°.

Dehydrogenation of Semmler's Hydrocarbon 20

Semmler's hydrocarbon 20 (96 mg) and selenium powder (92 mg) were heated together at 300-320° for 4 h under an atmosphere of nitrogen[39,40]. The reaction mixture was then dissolved in petroleum ether, filtered and evaporated to yield 84 mg of oil which was shown by G.L.C. comparison with an authentic sample to be 40% eudalene 22. (Authentic eudalene was regenerated from its picrate, m.p. 93-95°, by filtration through a column of basic alumina). The eudalene was isolated and purified through its picrate derivative, prepared by heating crude eudalene and excess picric acid in ethanol for 1/2 h. The picrate was crystallized from

ethanol as yellow needles; m.p. 94-95° (mixed melting point showed no depression), infrared spectrum superimposable with that of an authentic sample (c.f. Appendix 1, p. 56).

Anal. Calcd. for $C_{20}H_{19}O_7N_3$: N, 10.17.

Found: N, 10.68.

β-Selinene 20 from β-Eudesmol 23

β-Eudesmol 23 [m.p. 75-78°, $[\alpha]_D^{27}$ + 49.12 (c 1.02); 492 mg] was heated together with alumina impregnated with 2% pyridine (1 g) at 190° for 2 h[34]. The product was dissolved in petroleum ether and filtered through alumina to give 388 mg of a mixture which was shown by G.L.C. to be 90% β-selinene 20. Chromatography on silica gel impregnated with silver nitrate followed by distillation over sodium gave G.L.C. pure β-selinene 20[44] (138 mg); b.p. 155° (bath)/9.5 mm, n_D^{21} 1.5030.

Optical Rotation (c 0.69) 24°: $[\alpha]_D$ +55.21

$[\alpha]_{578}$ +57.53

$[\alpha]_{546}$ +64.92

$[\alpha]_{436}$ +108.26

$[\alpha]_{365}$ +165.65

The I.R., N.M.R. and Mass Spectra (Appendix 1, p. 55, Appendix 2, p. 61, Appendix 3, p. 70) of β-selinene were superimposable on those of Semmler's hydrocarbon.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84.

Found: C, 88.97; H, 11.67.

2,5-Dimethoxy-p-cymene 17

The petroleum ether-benzene fraction of the essential oil (p. 43, 22.1 g) was chromatographed on a 30 fold ratio of grade 1 alumina. A small forerun was eluted with petroleum ether and a larger fraction (7.4 g) containing large amounts of 2,5-dimethoxy-p-cymene was eluted with 1:1 petroleum ether-benzene. This fraction was distilled *in vacuo* and finally re-distilled over sodium at 120°/10.0 mm to furnish G.L.C. pure 2,5-dimethoxy-p-cymene 17 (4.3 g); n_D^{25} 1.5093, d_4^{24} 0.9878, $[\alpha]_D^{25}$ ± 0.0.

U.V. Spectrum (EtOH) mμ: λ_{max} 290 (ε 1968), 222 (ε 3550), 202 (ε 14030).

I.R. Spectrum (film)-Appendix 1, p. 57:
1505, 1210, 1048, 858, 808 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 61:
8.80 (6H, d, J=6.5 Hz), 7.81 (3H, s),
6.75 (1H, q, J=7 Hz), 6.26 and
6.24 (6H, singlets), 3.35 and
3.39 (2H, singlets).

Mass Spectrum-Appendix 3, p. 73:
M^+ 194, $\%\Sigma_{15}$ 9.71.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.
Found: C, 74.26; H, 9.27.

2,5-Dihydroxy-p-cymene 18

2,5-dimethoxy-p-cymene 17 (510 mg) in a small amount of ether was added to MeMgI prepared in the usual way from Mg (150 mg) and excess MeI (this represents 2.5 molar equivalents of Grignard reagent[43]). The

mixture was heated slowly under a stream of nitrogen and after ether had boiled off the temperature was held at 200° for 2 h. The product was then cooled, decomposed with dilute hydrochloric acid and extracted into ether. The organic layer was extracted with dilute NaOH which was then acidified and extracted with ether. The ether layer was washed to neutrality with brine, dried over Na_2SO_4 and evaporated *in vacuo* to yield 346 mg of 2,5-dihydroxy-p-cymene 18 (79%). Recrystallization from benzene followed by sublimation gave pure 18, m.p. 144°.

U.V. Spectrum (EtOH) mμ: λ_{max} 294 (ε 4121), 215 (ε 12810), 203 (ε 34530).

I.R. Spectrum (KBr)-Appendix 1, p. 57:
3330, 1530, 1180, 869, 815 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 62:
8.79 (6H, d, J=7 Hz), 8.43 (1H, s), 7.84 (3H, s), 5.67 (1H, s), 3.48 and 3.99 (2H, singlets).
The quartet at ca. 7 τ was not visible due to insolubility of the material; the two singlets at 8.43 and 5.67 τ disappeared after exchange with D_2O.

Mass Spectrum-Appendix 3, p. 74:
M^+ 166, $\%\Sigma_{27}$ 12.93.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49.
Found: C, 72.39; H, 8.44.

2,5-Diacetoxy-p-cymene 24

Acetylation of 2,5-Dihydroxy-p-cymene 18 with acetic anhydride in pyridine gave a quatitative yield of the diacetoxy derivative 24, crystallized from ethanol, m.p. 78-79.5°.

U.V. Spectrum (EtOH) mμ: λ_{max} 275 (ε 1140), 267 (ε 1140), 202 (ε 31410).

I.R. Spectrum (KBr)-Appendix 1, p. 57:

1755, 1214, 1154, 1145, 1014, 925, 586 cm^{-1}.

N.M.R. Spectrum ($CDCl_3$) τ-Appendix 2, p. 62:

8.82 (6H, d, J=7Hz), 7.87 (3H, s), 7.71 (6H, s), 7.09 (1H, q, J=7 Hz), 3.14 and 3.08 (2H, singlets).

Mass Spectrum-Appendix 3, p. 75:

M^+ 250, $\%\Sigma_{27}$ 3.06.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25.

Found: C, 66.97; H, 7.97.

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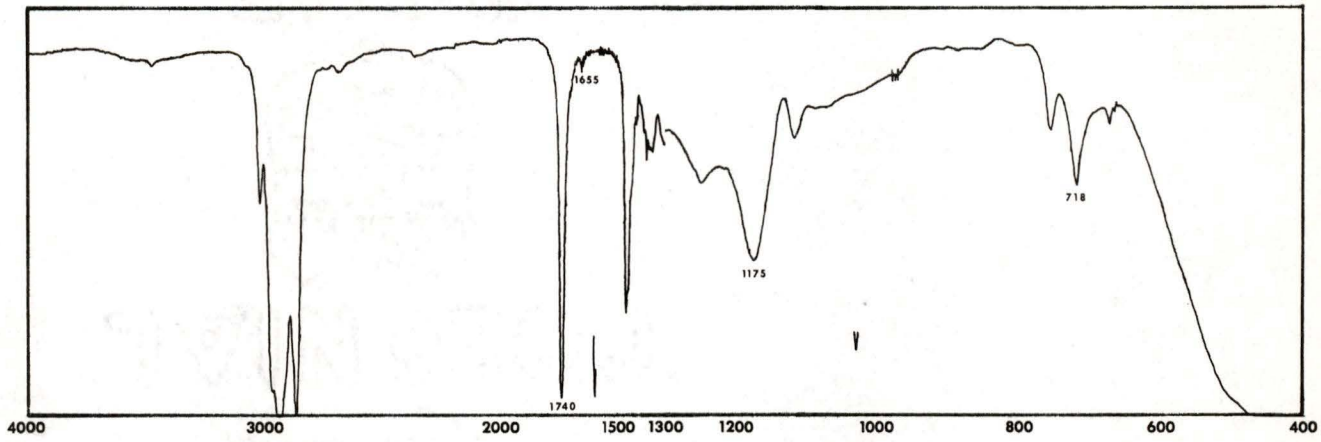
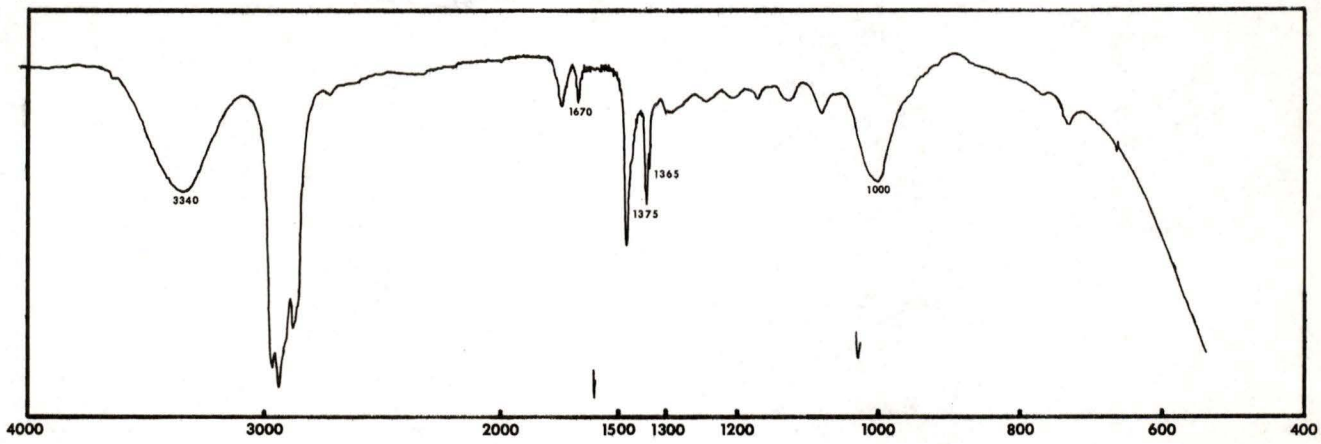
APPENDIX I.

INFRA RED SPECTRA



Neutral Bute Inlet Wax



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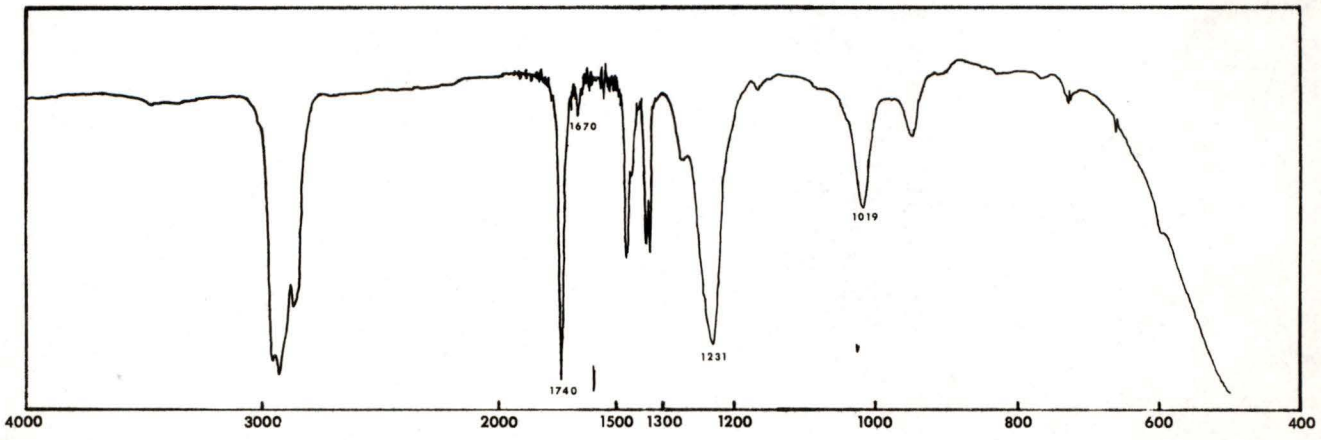
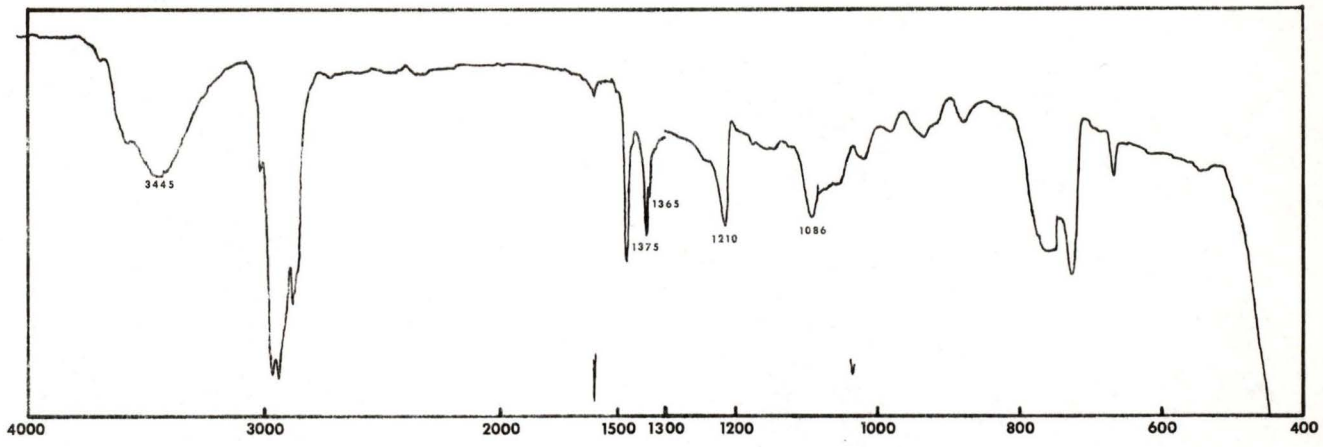
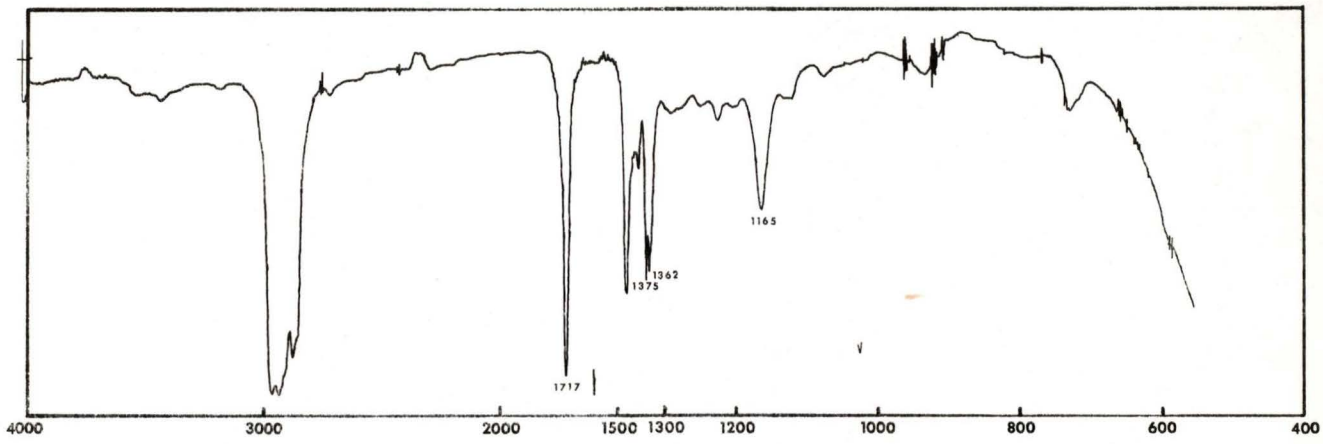


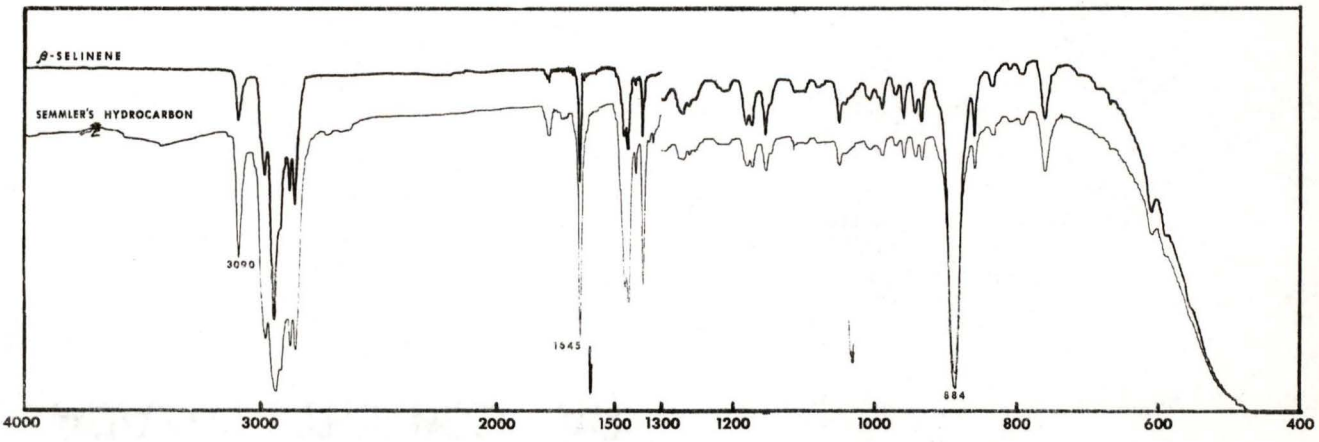
Phytyl Acetate 11



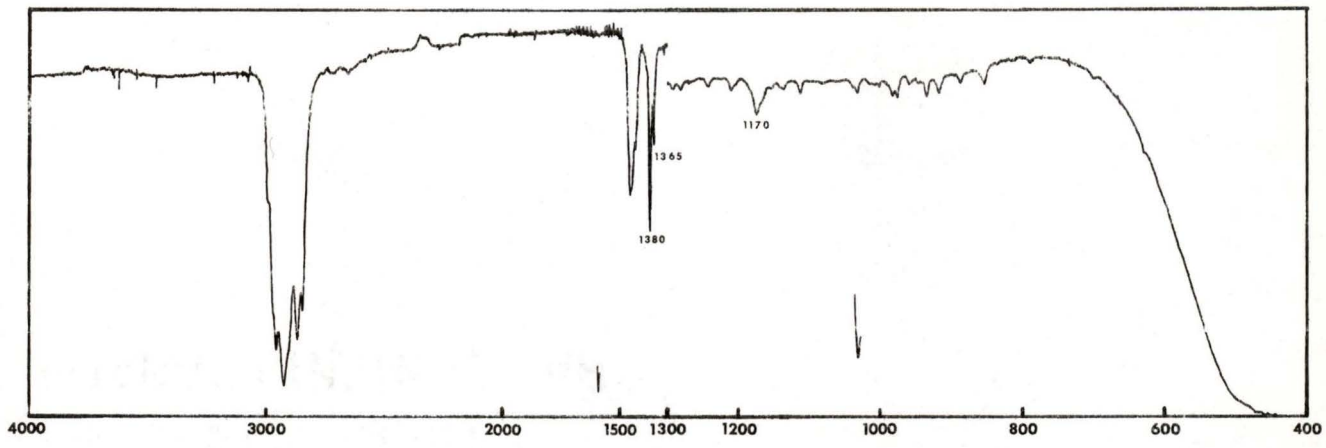
Phytane-1,2,3-triol 14



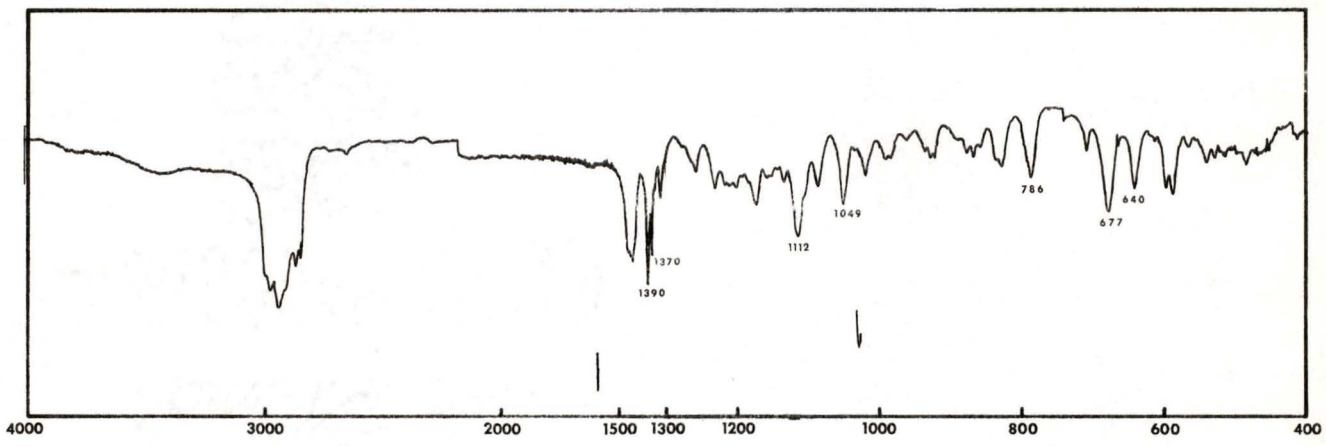
Ketone 5



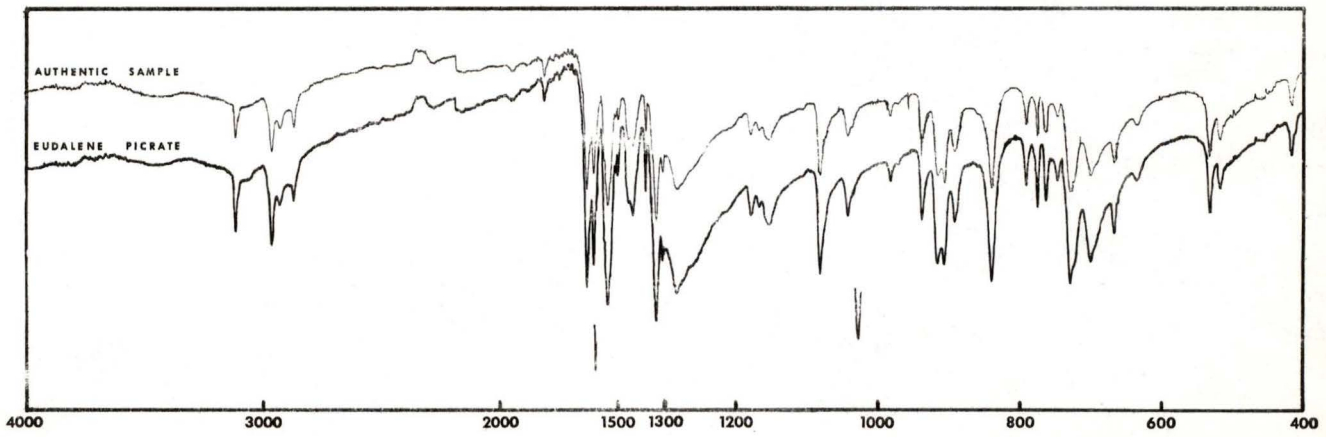
Semmler's Hydrocarbon 20 and β-selinene



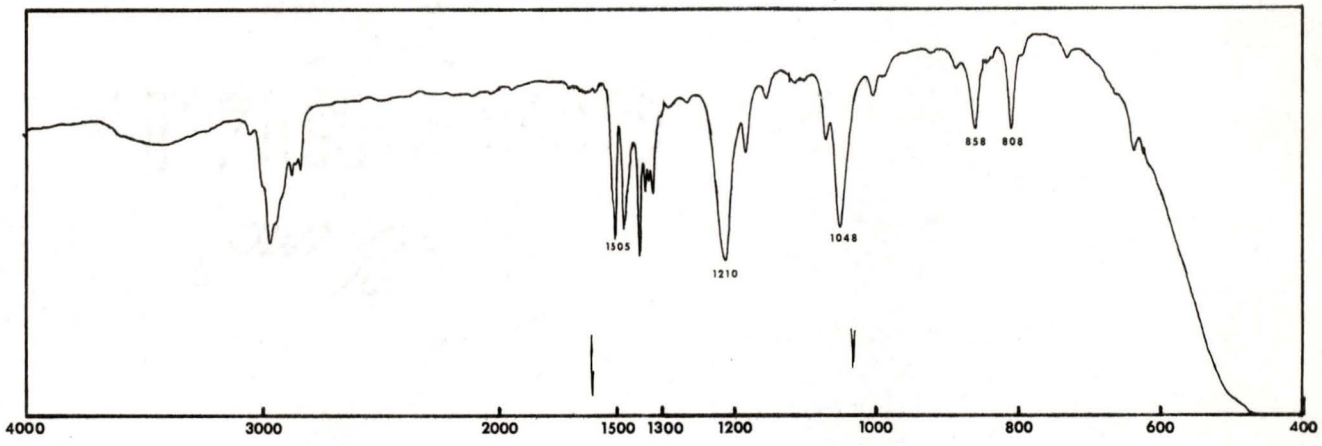
Tetrahydro Derivative 21



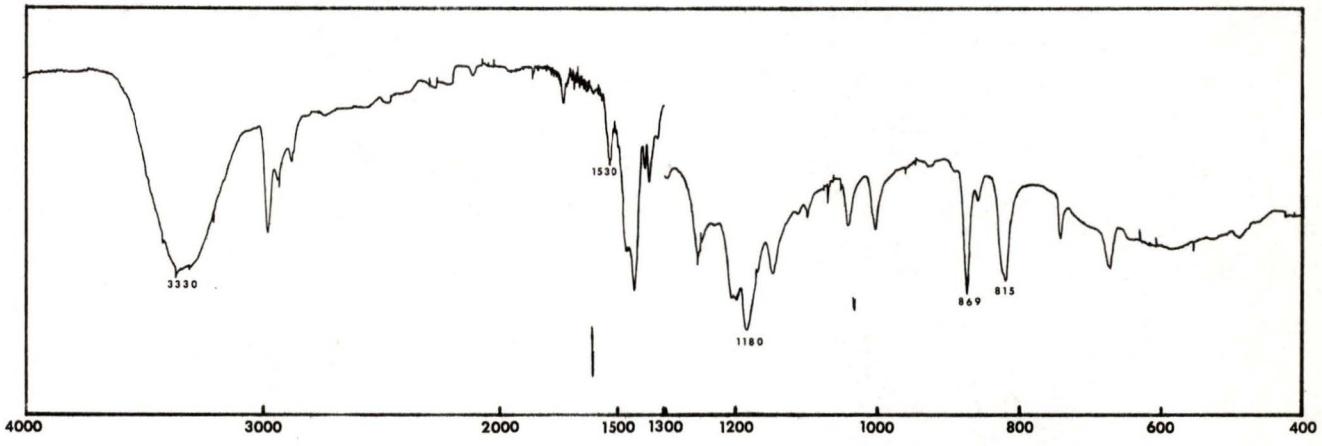
Selinene Dihydrochloride



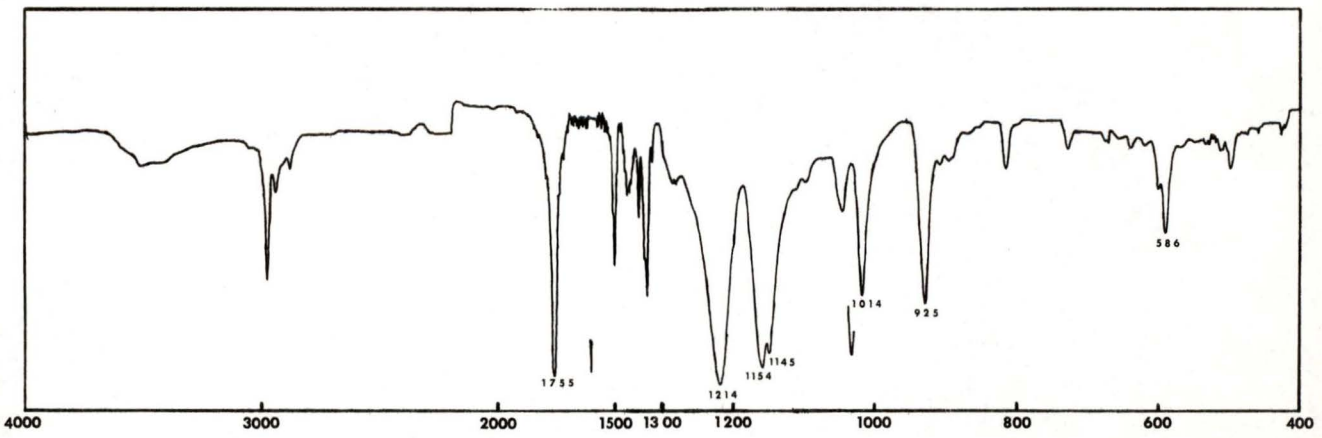
Eudalene Pricrate from Semmler's Hydrocarbon and an Authentic Sample



2,5-dimethoxy-p-cymene



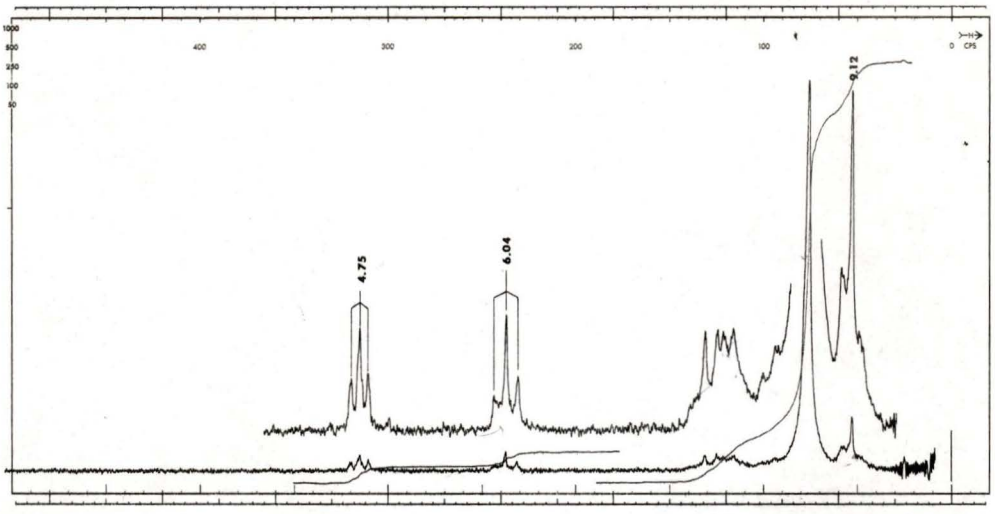
2,5-dihydroxy-p-cymene



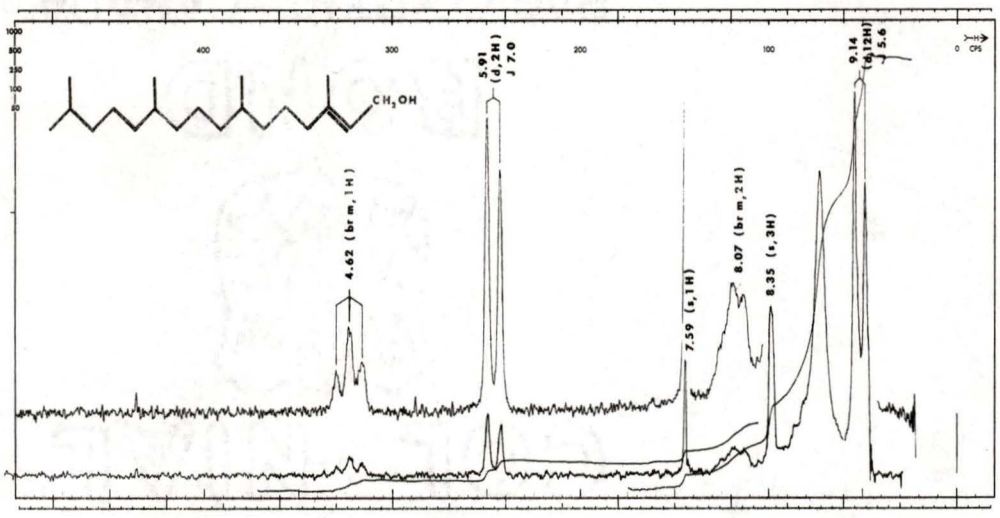
2,5-diacetoxy-p-cymene

APPENDIX II.

NUCLEAR MAGNETIC RESONANCE SPECTRA



Bute Ester



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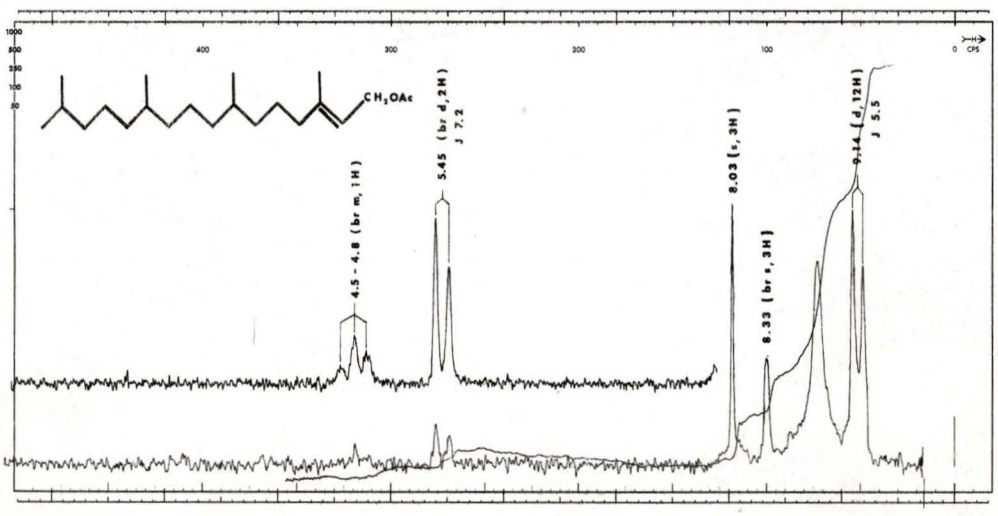
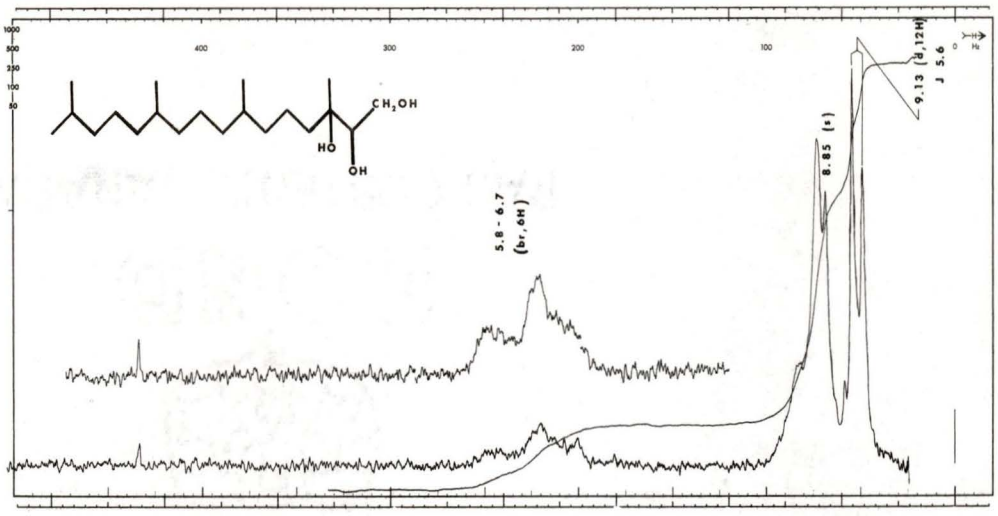
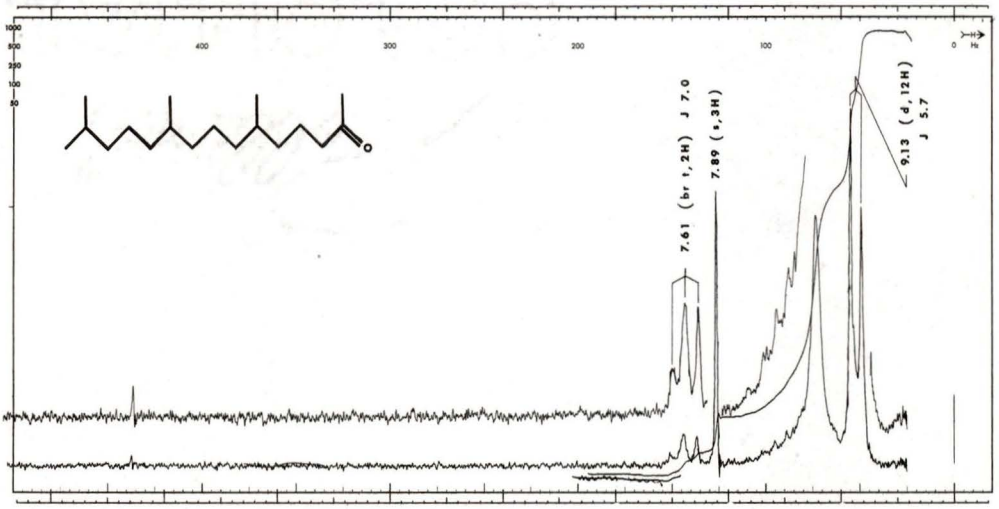


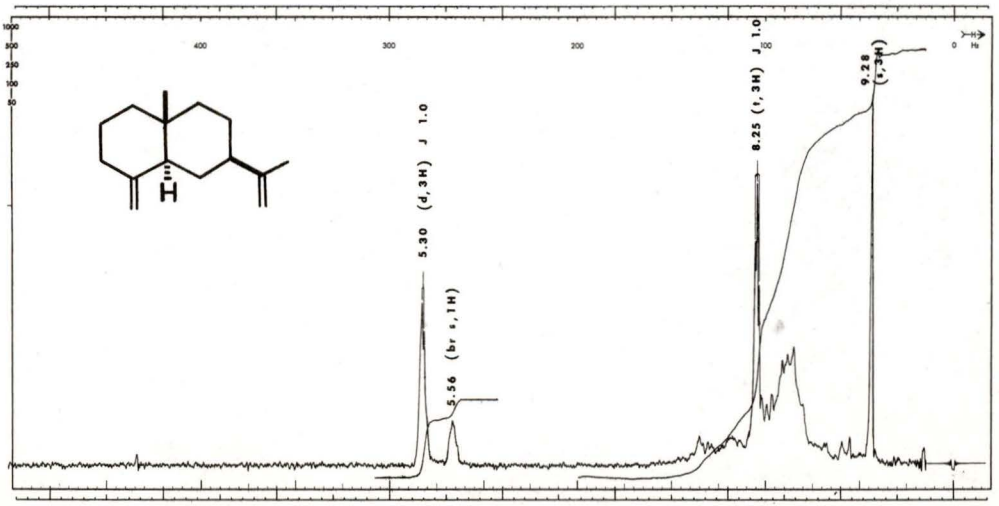
Phytyl Acetate 11



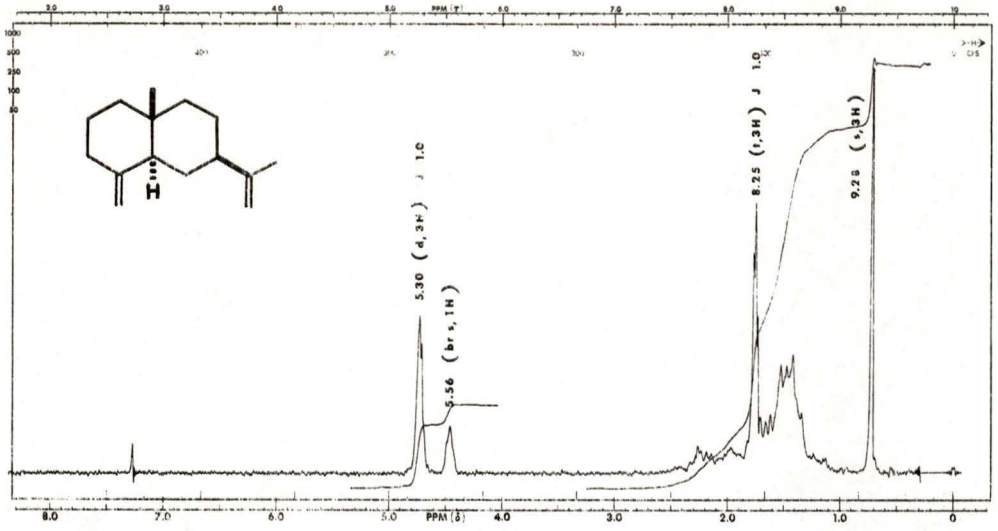
Phytane-1,2,3-triol 14



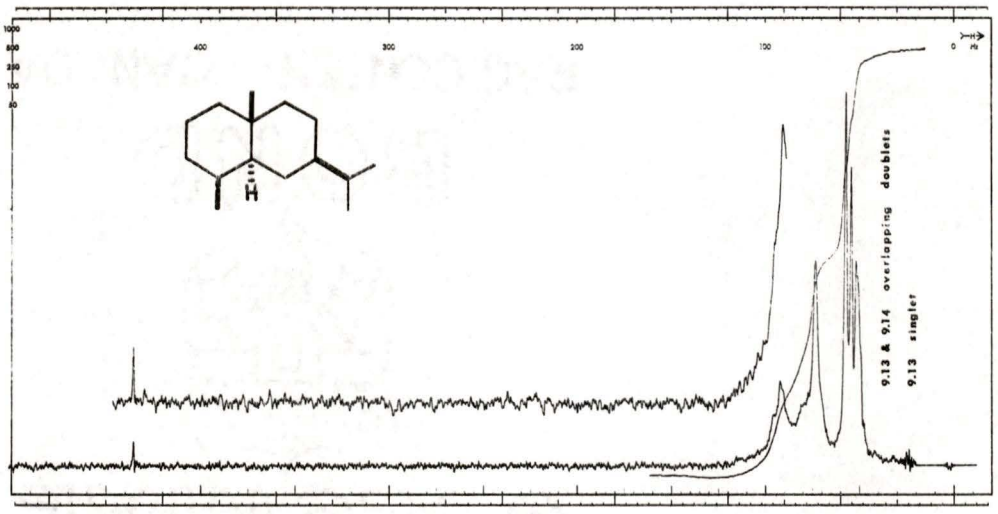
Ketone 5



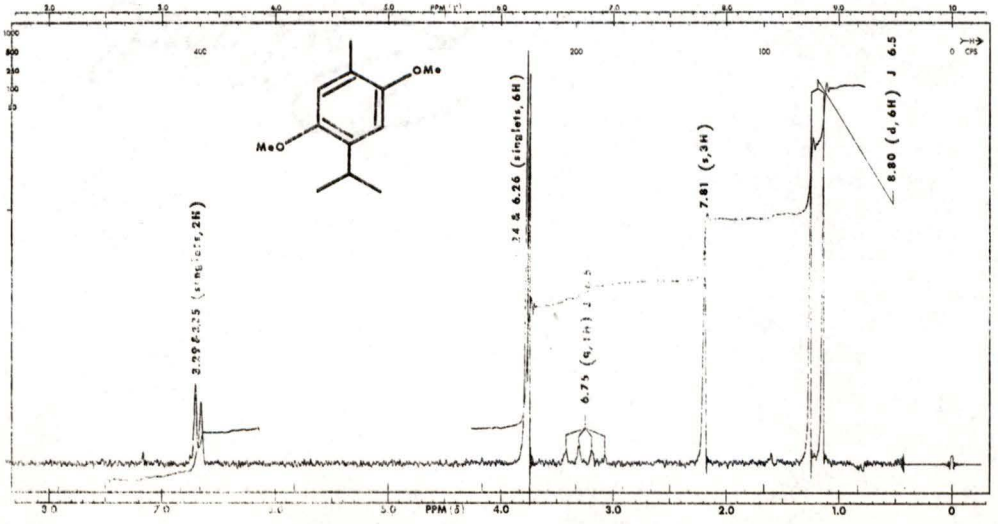
Semmler's Hydrocarbon 20



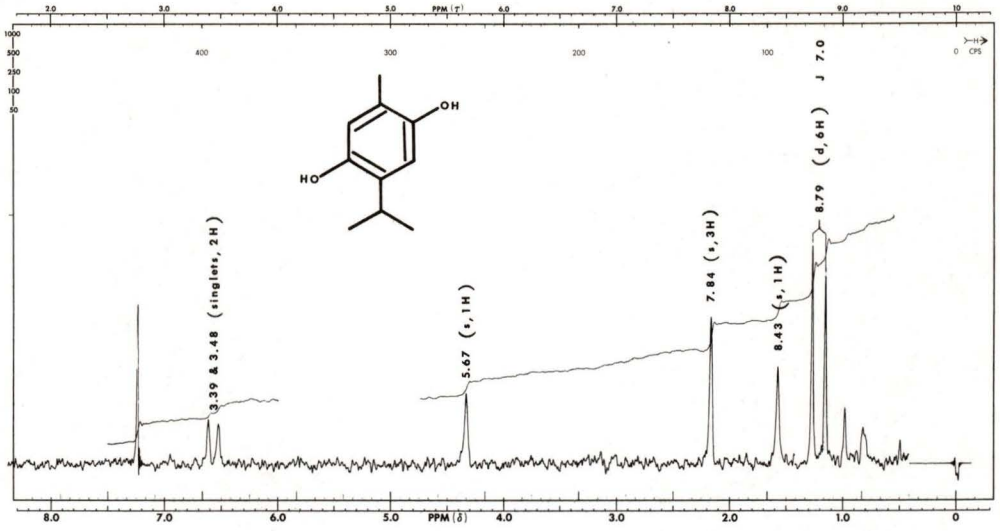
β-selinene 20



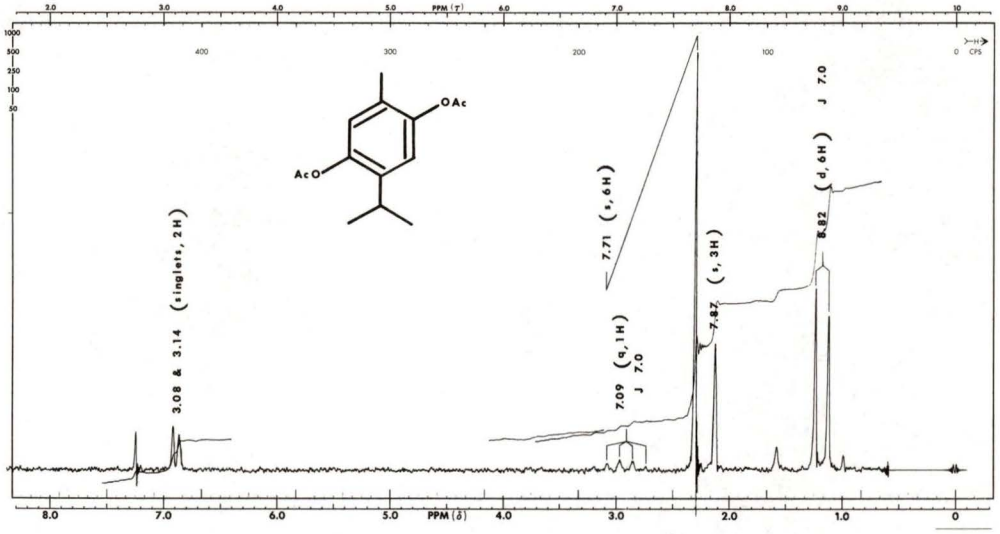
Tetrahydro Derivative 21



2,5-dimethoxy-p-cymene 17



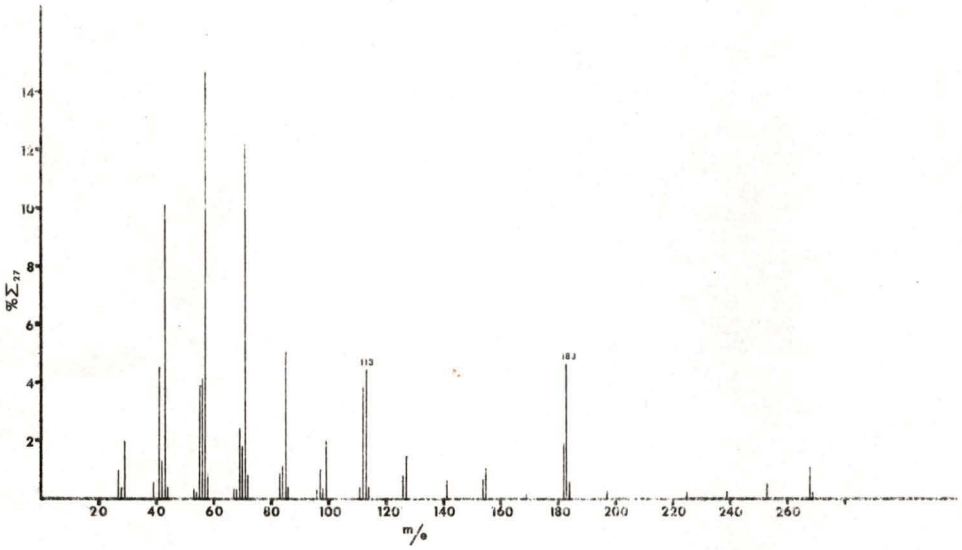
2,5-dihydroxy-p-cymene 18



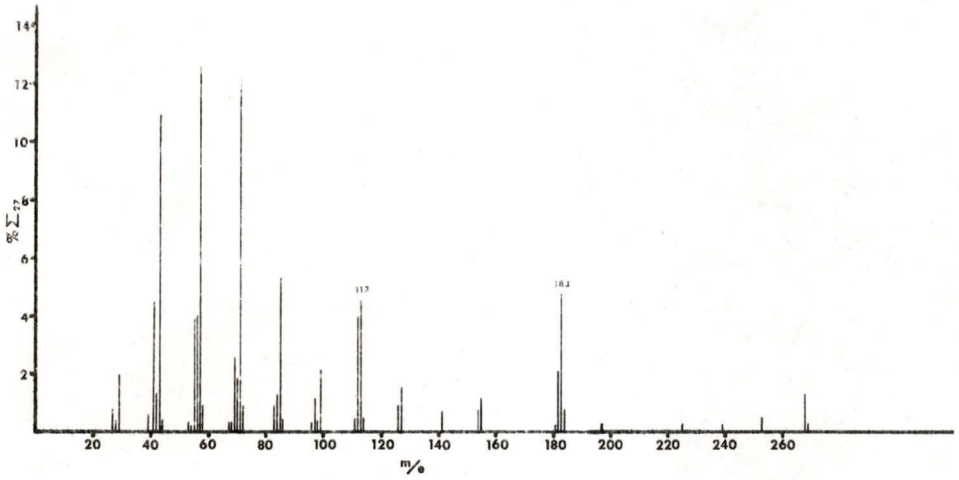
2,5-diacetoxy-p-cymene 24

APPENDIX III.

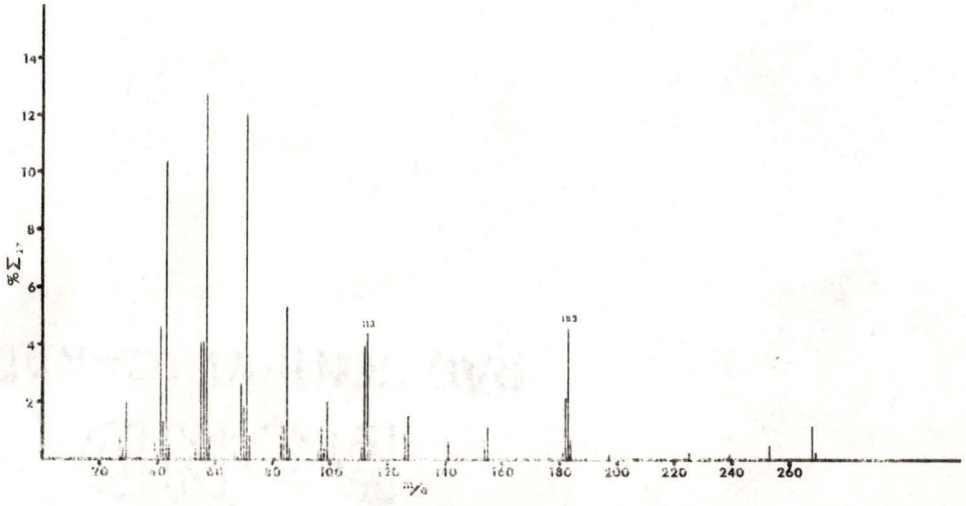
MASS SPECTRA



Bate Hydrocarbon 3



Pristane 3



Norphytane 3

m/e	$\%\Sigma_{27}$			m/e	$\%\Sigma_{27}$		
	Bute Hydrocarbon	Pristane	Norphytane		Bute Hydrocarbon	Pristane	Norphytane
27	0.78	0.80	0.81	126	0.79	0.89	0.86
28	0.40	0.30	0.41	127	1.45	1.54	1.48
29	1.96	1.97	2.03	128	0.17	0.18	0.16
30	0.08	0.07	0.08	140	0.13	0.14	0.13
32	0.13	0.08	0.14	141	0.66	0.71	0.66
39	0.57	0.58	0.61	142	0.10	0.10	0.10
40	0.19	0.19	0.20	154	0.66	0.74	0.68
41	4.53	4.48	4.65	155	1.04	1.16	1.11
42	1.25	1.30	1.33	156	0.16	0.16	0.15
43	10.12	10.19	10.39	169	0.20	0.22	0.21
44	0.41	0.43	0.43	182	1.91	2.07	1.93
45	0.15	0.16	0.15	183	4.65	4.79	4.58
53	0.33	0.32	0.33	184	0.68	0.77	0.69
54	0.22	0.22	0.22	196	0.12	0.14	0.13
55	3.89	3.92	4.07	197	0.25	0.28	0.25
56	4.11	4.04	4.13	211	0.10	0.10	0.10
57	14.70	12.55	12.78	224	0.12	0.12	0.12
58	0.85	0.90	0.88	225	0.25	0.27	0.26
65	0.08	0.08	0.06	238	0.13	0.14	0.13
67	0.36	0.37	0.37	239	0.24	0.26	0.25
68	0.34	0.35	0.34	252	0.09	0.09	0.10
69	2.40	2.55	2.62	253	0.48	0.50	0.48
70	1.79	1.86	1.91	254	0.12	0.12	0.12
71	12.33	12.12	12.14	268	1.09	1.27	1.19
72	0.81	0.86	0.81	269	0.25	0.29	0.27
77	0.07	0.07	0.07				
79	0.08	0.08	0.09				
81	0.18	0.19	0.19				
82	0.13	0.14	0.13				
83	0.83	0.89	0.90				
84	1.14	1.23	1.21				
85	5.14	5.28	5.29				
86	0.39	0.41	0.40				
95	0.12	0.12	0.12				
96	0.29	0.31	0.30				
97	1.04	1.14	1.10				
98	0.36	0.39	0.38				
99	1.96	2.11	2.03				
100	0.19	0.19	0.18				
109	0.07	0.07	0.07				
110	0.08	0.07	0.08				
111	0.40	0.43	0.43				
112	3.87	3.98	3.96				
113	4.46	4.54	4.45				
114	0.42	0.45	0.42				
125	0.16	0.16	0.17				

Phytol 4

m/e	$\%\Sigma_{29}$	m/e	$\%\Sigma_{29}$	m/e	$\%\Sigma_{29}$
29	2.05	83	2.78	135	0.12
31	0.26	84	1.27	136	0.10
39	0.67	85	1.79	137	0.53
40	0.20	86	1.01	138	0.49
41	4.39	87	0.26	139	0.26
42	0.87	91	0.18	140	0.50
43	6.47	93	0.27	141	0.35
44	0.33	94	0.26	149	0.77
45	0.26	95	1.11	150	0.12
53	0.68	96	1.22	151	0.26
54	0.27	97	2.21	152	0.20
55	4.96	98	0.52	153	0.14
56	3.01	99	0.68	154	0.10
57	5.43	100	0.17	165	0.18
58	1.07	105	0.12	166	0.12
59	0.51	107	0.18	179	0.17
65	0.16	108	0.11	181	0.10
66	0.14	109	1.17	182	0.24
67	1.25	110	0.63	183	0.10
68	3.08	111	1.46	193	0.15
69	4.54	112	0.67	196	0.71
70	2.36	113	0.43	197	0.17
71	9.97	121	0.16	208	0.12
72	1.04	122	0.34	210	0.29
73	0.14	123	4.18	211	0.12
77	0.23	124	1.33	250	0.24
79	0.39	125	0.89	252	0.15
80	0.52	126	1.72	263	0.17
81	3.24	127	0.46	278	0.47
82	2.21	133	0.10	279	0.13
				296	1.09
				297	0.26

Phytyl Acetate 11

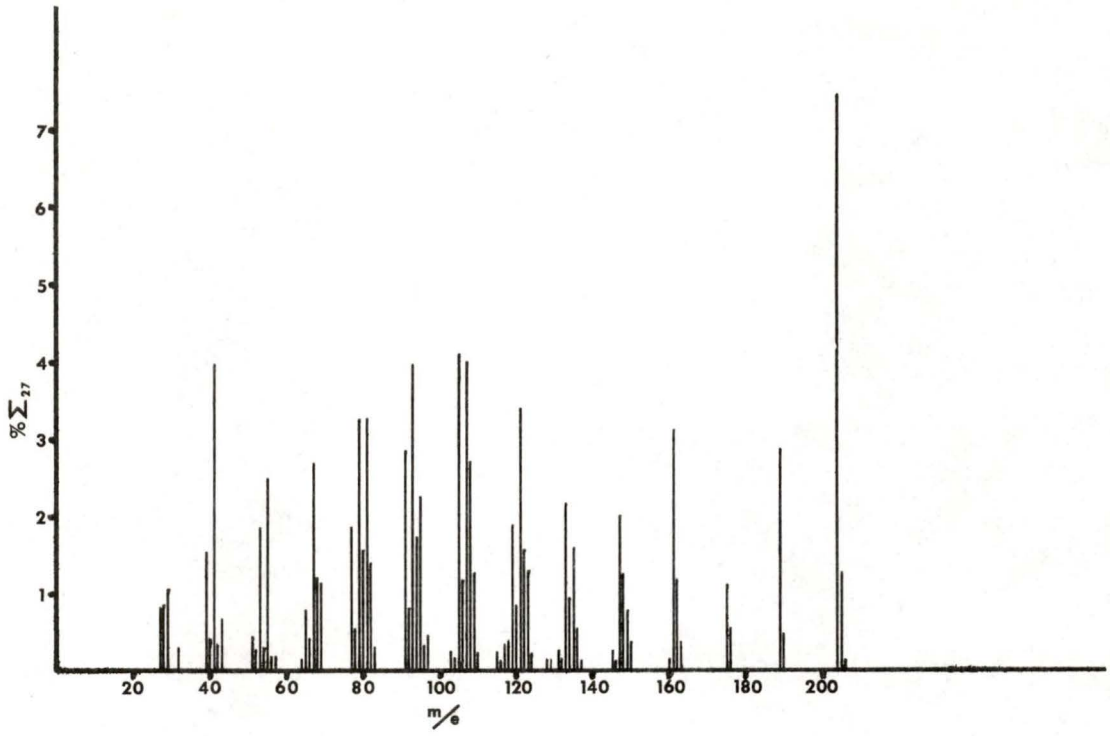
m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	0.87	91	0.24
28	5.28	93	0.37
29	2.10	94	0.59
31	0.17	95	4.13
32	1.53	96	1.76
39	0.84	97	1.80
40	0.30	98	0.28
41	4.96	99	0.21
42	1.21	107	0.21
43	9.07	108	0.12
44	0.42	109	1.19
45	3.12	110	0.72
51	0.13	111	1.11
52	0.11	112	0.27
53	1.13	113	0.19
54	0.31	121	0.13
55	4.64	122	0.14
56	2.01	123	2.42
57	5.22	124	1.23
58	0.55	125	0.53
59	0.20	126	0.49
60	2.04	127	0.18
61	0.10	137	0.52
65	0.28	138	0.32
66	0.28	139	0.16
67	2.13	140	0.14
68	5.09	141	0.15
69	3.78	149	0.11
70	1.30	151	0.17
71	2.77	152	0.17
72	0.18	153	0.10
73	0.13	165	0.10
77	0.42	179	0.21
78	0.11	193	0.13
79	1.14	195	0.08
80	0.40	208	0.15
81	4.14	263	0.12
82	5.31	266	0.12
83	2.58	278	0.85
84	0.53	279	0.20
85	1.06		

Phytane-1,2,3-triol 14

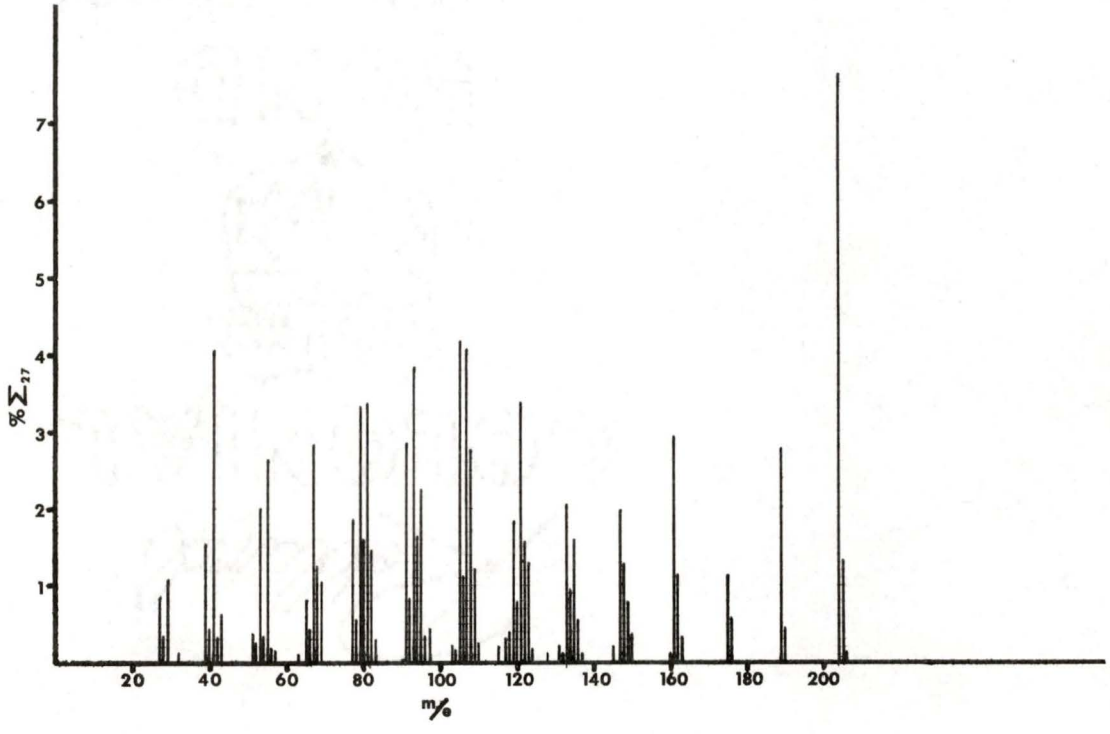
m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	0.55	107	0.21
28	0.29	109	0.89
29	1.57	110	0.42
31	0.43	111	2.97
39	0.41	112	0.35
40	0.12	113	0.61
41	3.81	121	0.15
42	0.82	123	0.56
43	9.82	124	0.24
44	2.35	125	1.89
45	0.91	126	0.29
53	0.30	127	0.37
54	0.14	135	0.11
55	5.04	137	0.29
56	1.28	138	0.13
57	6.27	139	0.83
58	2.10	140	0.18
59	1.22	141	0.23
60	0.12	145	0.19
61	1.10	149	0.15
62	0.25	151	0.13
67	0.61	153	0.39
68	0.58	155	0.14
69	5.23	165	0.11
70	0.87	167	0.18
71	5.56	169	0.23
72	0.50	181	0.13
73	0.18	195	0.15
74	0.20	250	0.61
75	0.17	251	0.15
79	0.15	263	0.11
81	1.21	266	0.11
82	0.47	268	0.45
83	4.26	269	4.33
84	0.62	270	0.89
85	1.99	271	0.10
86	0.21	276	0.10
87	0.75	281	0.34
88	0.32	282	0.11
93	0.22	299	0.10
95	1.21	312	0.24
96	0.34	315	0.21
97	3.75		
98	0.41		
99	0.74		
101	0.25		
104	0.18		
105	9.17		
106	0.51		

Ketone 5

m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	1.07	98	0.27
28	0.75	99	0.42
29	2.41	108	0.12
32	0.17	109	1.99
39	0.88	110	1.78
40	0.26	111	0.89
41	5.33	112	0.33
42	1.52	113	1.07
43	7.80	114	0.15
44	0.54	123	1.06
45	0.27	124	1.28
53	0.56	125	0.69
54	0.29	126	0.67
55	5.58	127	0.30
56	2.51	137	0.52
57	5.43	138	0.49
58	7.69	139	0.19
59	5.54	140	0.44
60	0.26	141	0.20
65	0.11	149	0.18
67	0.84	151	0.17
68	0.98	152	0.14
69	3.61	154	0.10
70	1.79	155	0.11
71	5.63	165	0.50
72	0.54	166	0.11
77	0.11	179	0.34
79	0.19	180	0.17
80	0.12	194	0.27
81	1.37	208	0.19
82	1.16	210	0.99
83	1.96	211	0.21
84	0.72	225	0.19
85	3.46	234	0.16
86	0.38	235	0.13
93	0.16	250	2.46
94	0.16	251	0.53
95	1.99	253	0.32
96	1.01	268	1.16
97	1.24	269	0.26



Semmler's Hydrocarbon



β-selinene

m/e	$\%\Sigma_{27}$		m/e	$\%\Sigma_{27}$	
	Semmler's Hydrocarbon	β-selinene		Semmler's Hydrocarbon	β-selinene
27	0.82	0.85	104	0.16	0.15
28	0.85	0.32	105	4.10	4.17
29	1.06	1.09	106	1.15	1.13
32	0.30	0.11	107	4.00	4.06
39	1.53	1.54	108	2.70	2.77
40	0.41	0.43	109	1.25	1.21
41	3.96	4.06	110	0.22	0.23
42	0.33	0.32	115	0.22	0.21
43	0.66	0.62	116	0.11	0.09
51	0.33	0.36	117	0.33	0.32
52	0.25	0.26	118	0.36	0.40
53	1.84	2.00	119	1.88	1.81
54	0.30	0.32	120	0.84	0.79
55	2.49	2.62	121	3.39	3.38
56	0.19	0.19	122	1.54	1.56
57	0.19	0.15	123	1.29	1.30
63	0.13	0.11	124	0.20	0.19
64	0.09	0.09	128	0.13	0.11
65	0.79	0.81	129	0.13	0.09
66	0.41	0.41	131	0.25	0.21
67	2.68	2.83	132	0.13	0.11
68	1.20	1.26	133	2.14	2.05
69	1.12	1.05	134	0.91	0.92
70	0.09	0.09	135	1.59	1.60
71	0.08	0.06	136	0.54	0.55
75	0.08	0.08	137	0.13	0.11
77	1.84	1.86	145	0.24	0.21
78	0.52	0.55	146	0.11	0.09
79	3.25	3.33	147	1.99	1.98
80	1.54	1.60	148	1.23	1.28
81	3.25	3.38	149	0.76	0.79
82	1.39	1.45	150	0.36	0.38
83	0.30	0.30	159	0.08	0.06
87	0.08	0.09	160	0.13	0.11
89	0.08	0.08	161	3.11	2.94
91	2.83	2.86	162	1.17	1.13
92	0.80	0.83	163	0.35	0.34
93	3.96	3.83	175	1.10	1.13
94	1.72	1.64	176	0.54	0.57
95	2.24	2.24	177	0.08	0.09
96	0.33	0.34	189	2.83	2.79
97	0.44	0.43	190	0.47	0.45
103	0.22	0.21	204	7.44	7.61
			205	1.26	1.32
			206	0.13	0.13

Tetrahydro Derivative 21

m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	0.46	105	0.17
28	0.61	106	0.09
29	0.82	107	0.46
32	0.22	108	0.54
36	0.35	109	8.00
38	0.15	110	1.82
39	0.54	111	1.00
40	0.17	112	0.20
41	3.05	121	0.27
42	0.28	122	0.30
43	1.71	123	2.94
44	0.11	124	1.39
51	0.11	125	1.05
53	0.67	126	0.16
54	0.23	135	0.20
55	4.25	136	0.13
56	0.51	137	1.90
57	1.09	138	1.69
65	0.27	139	0.26
66	0.23	149	0.26
67	3.44	150	0.12
68	1.01	151	0.54
69	4.00	152	0.45
70	0.46	153	0.11
71	0.40	163	0.17
77	0.48	164	0.32
78	0.13	165	5.88
79	0.91	166	1.11
80	0.33	167	0.13
81	5.17	191	0.15
82	1.80	192	0.17
83	4.50	193	2.83
84	2.37	194	0.49
85	0.59	195	0.10
91	0.48	206	0.15
92	0.16	207	0.39
93	0.73	208	4.50
94	0.49	209	0.82
95	6.44	210	0.11
96	5.24		
97	3.22		
98	0.37		
99	0.10		

2,5-dimethoxy-p-cymene

m/e	$\%\Sigma_{15}$	m/e	$\%\Sigma_{15}$
15	1.47	104	0.59
18	0.38	105	1.50
27	0.94	106	0.38
28	1.13	107	0.50
29	0.44	108	0.36
32	0.22	109	0.25
38	0.23	115	0.98
39	2.11	116	0.44
40	0.58	117	0.89
41	1.61	118	0.28
42	0.17	119	1.69
43	0.81	120	0.47
45	0.20	121	1.36
50	0.41	122	0.44
51	1.31	123	0.42
52	0.70	124	0.39
53	1.66	128	0.20
54	0.19	129	0.19
55	0.63	131	0.50
57	0.19	132	0.31
59	0.16	133	0.55
62	0.25	134	0.63
63	0.80	135	0.95
64	0.34	136	1.23
65	1.56	137	0.67
66	0.56	138	0.23
67	0.86	139	0.67
68	0.31	145	0.17
69	0.28	146	0.23
74	0.22	147	0.89
75	0.31	148	0.59
76	0.25	149	2.82
77	3.09	150	0.64
78	1.19	151	1.27
79	1.42	152	0.28
80	0.23	161	0.20
81	0.30	162	0.23
82	0.38	163	1.22
83	0.17	164	4.44
89	0.47	165	1.09
90	0.34	177	0.17
91	3.95	178	0.55
92	0.70	179	16.27
93	1.22	180	2.64
94	0.27	181	0.30
95	0.25	193	0.31
97	0.30	194	9.71
102	0.28	195	1.69
103	1.19	196	0.19

2,5-dihydroxy-p-cymene

m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	0.95	93	0.59
28	0.50	94	0.41
29	0.45	95	2.00
38	0.32	96	0.32
39	1.91	102	0.27
40	0.59	103	0.91
41	1.45	104	0.41
42	0.27	105	1.18
43	1.18	106	0.32
50	0.41	107	1.27
51	1.18	108	0.64
52	0.55	109	0.50
53	1.55	110	0.27
54	0.36	115	0.55
55	1.14	117	0.27
63	0.59	118	0.41
64	0.32	119	0.32
65	1.05	121	0.95
66	0.59	122	0.73
67	1.05	123	2.41
68	0.45	124	0.91
69	0.86	125	0.32
74	0.32	131	0.55
75	0.41	132	0.45
76	0.32	133	1.86
77	2.59	134	0.36
78	0.77	135	0.32
79	1.95	136	0.50
80	0.36	137	1.36
81	0.59	147	0.32
82	0.27	148	0.27
83	0.41	149	0.91
89	0.32	150	1.18
90	0.27	151	27.08
91	1.50	152	3.36
92	0.32	153	0.45
		164	0.36
		165	0.95
		166	12.93
		167	1.73
		168	0.27

2,5-diacetoxy-p-cymene

m/e	$\%\Sigma_{27}$	m/e	$\%\Sigma_{27}$
27	0.84	103	0.58
28	1.84	104	0.30
29	0.48	105	0.64
31	0.58	107	1.02
39	1.54	108	0.34
40	0.80	109	0.40
41	1.64	115	0.34
42	0.68	117	0.22
43	12.97	119	0.32
44	0.48	121	1.04
45	0.32	122	1.04
50	0.20	123	0.76
51	0.64	124	0.36
52	0.42	125	0.22
53	1.38	131	0.28
54	0.20	132	0.38
55	0.80	133	0.58
57	0.22	134	0.20
63	0.32	135	0.26
65	0.80	136	0.28
66	0.38	137	1.52
67	1.04	147	0.30
68	0.48	148	0.22
69	0.56	149	0.96
77	1.96	150	1.74
78	0.56	151	9.86
79	1.40	152	1.30
80	0.24	164	0.48
81	0.42	165	2.04
91	1.56	166	21.44
92	0.28	167	3.48
93	0.72	168	0.38
94	0.28	193	0.26
95	0.62	207	0.54
96	0.20	208	3.89
		209	0.58
		250	3.06
		251	0.52

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1968-1969	National Research Council Postgraduate Scholarship
1967-1968	Government of British Columbia - First Class Scholarship
1966-1967	Government of British Columbia - Second Class Scholarship
1963-1964	Government of British Columbia - First Class Scholarship

Publications:

T. C. Jain and R. J. Striha, "Studies Related to Bute Inlet Wax: The Identity of Norphytane, Pristane and Bute Hydrocarbon", *Can. J. Chem.* 47, 4359 (1969).

T. C. Jain, G. L. Owen and R. J. Striha, "Pristane: A Norditerpene Hydrocarbon from Bute Inlet Wax", *Phytochemistry* 8, 785 (1969).

T. C. Jain, R. J. Striha and E. Stewart, "Structure of α-Dicarvelone", *Experientia* 24, 105 (1968).

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