STUDIES IN TERPENOIDS

A THESIS

SUBMITTED TO THE

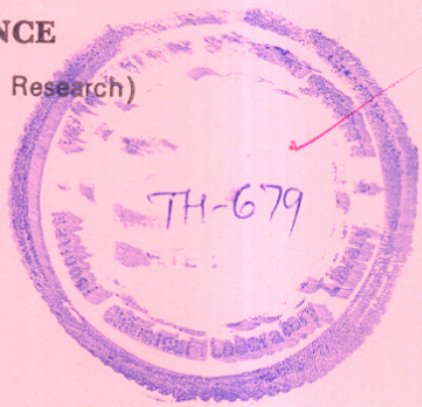
UNIVERSITY OF POONA

FOR THE DEGREE OF

MASTER OF SCIENCE

(Partly by Papers and Partly by Research)

IN CHEMISTRY



BY

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1991

CERTIFICATE

It is certified that the work incorporated in the thesis 'Studies in terpenoids', by Mrs. S.S Sawant of the National Chemical Laboratory, Pune, was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(N.R. Ayyangar)
Research Guide

JUNE, 1991

CONTENTS

General Remarks

1. The figure (spectra) numbers, chart numbers, scheme numbers, reference numbers etc. given in each chapter refer only to that particular chapter. The references and figures are given at the end of each chapter.
2. The temperatures are given in centigrade scale.
3. All solvents were distilled before use. Petroleum ether referes to the fraction boiling in the range of 60-80°.
4. The TLC and preparative TLC plates were prepared by spreading an aqueous suspension of TLC grade silica gel (containing 13% $CaSO_4$ as binder) uniformly over glass plates using an applicator. Layer thickness: TLC plates, 1mm; preparative TLC, 2 mm. After initial drying at room temperature the plates were activated at 100° for 1 hour before use.
5. For TLC and PLC mixtures of acetone: pet ether were used as developing solvent system.
6. After development, the spots of TLC plates were visualised by exposing them to iodine vapour and by spraying with a mixture of H_2SO_4-HNO_3 (1:1) followed by charring in an oven. In the case of preparative TLC plates, the bands of compounds (after developing) were visualised by spraying a dilute solution of iodine in CCl_4 to the sides (after covering the major central portion with a glass plate).
7. All solid compounds (except those mentioned as gum)

were recrystallised to constant m.p. (solvent of crystallisation in parentheses). All m.ps. were recorded on a Koffler block and are uncorrected.

8. The UV spectra were recorded in methanol solutions on a Shimadzu, UV-260.

9. The IR spectra were recorded on Perkin Elmer 683, Infrared spectrometer and Perkin Elmer 1605, FT-IR in $CHCl_3$ solution.

10. Mass spectra were recorded on Furnigan Mat-1020 automated GC/MS.

11. NMR spectra were recorded in $CDCl_3$ solution on WH-90 FT (Bruker) spectrometer and MSL-300FT, using TMS as internal standard. NMR chemical shifts are given in δ-scale.

12. The ^{13}C-NMR spectra were recorded at 300 MHz on a MSL-300 FT spectrometer, using TMS as internal standard in $CDCl_3$ solution. ^{13}C-NMR spectrum was recorded twice as 1) Proton noise decoupled or single line spectrum and 2) single frequency off resonance decoupled (SFOD) spectrum.

13. GLC was carried out on Hewlett Packard 5890 with 3390A integrator, at 70°C on carbowax 20M-5% supported on Chromosorb W (6' x 1/8").

14. The X-ray data was obtained using a CAD-4F-11M diffractometer and the structure was solved by direct method using MULTAN-78.

CHAPTER I

CHAPTER I

SINGLET OXIDATION OF α-SANTONIN

INTRODUCTION:

α-Santonin 1 a eudesmanolide, is a biologically active constituent of Artemisia species, belonging to family compositae. It is a eudesmane type sesquiterpene lactone with a 6,12-olide moiety as typically shown in structure 1. This type of compounds are widely distributed in the genus Artemisia. The first reported isolation of 1 was from the flower heads of Artemisia Cina Berg[1]. It was later isolated from a number of species belonging to genus Artemisia[2,3].

BIOLOGICAL ACTIVITIES:

The availability of modern, refined methods for testing anticarcinogenic agents has encouraged the systematic search for cancerostatic agents amongst natural products. Many of the sesquiterpenes isolated from family compositae, chiefly sesquiterpene lactones such as germacranolides, guaianolides, pseudoguaianolides and elemanolides show antitumor activity[4]. Some sesquiterpene lactones have been shown to possess antibacterial, antifungal or helminthic properties[5]. The sesquiterpene lactones with α-methylene-γ-lactone moiety fused on various skeletons are a rapidly expanding group of natural

products, comprising to date more than 400 compounds. These unsaturated lactones have considerable biological activities, such as allergic agents, cytotoxic and anti-tumor agents, regulator of plant growth, antimitotic activity and antischistosomal agents[6]. Certain sesquiterpenoids (e.g. santonin) and steroids (Prednisolone) containing a normal cyclohexa-dienone unit are well known to exhibit cytotoxic and anti-inflammatory activity, respectively, and from chemicopharmacological point of view endo-exo-cross dienone seem to be much more reactive against biological nucleophiles than the normal ones[7].

α-Santonin, has been widely used as an important vermifuge in folk medicine[2]. It has generated a lot of interesting chemistry in the past few years. Recently 1 has attained significance as a potential parent compound for antitumor and antimicrobial drugs.

Various reactions on 1 have been studied in detail. The reactions include synthetic as well as photochemical and microbial conversion of 1 into different products (Chart 1) e.g. chemical transformation of 1 in $CHCl_3$ gave dichloro derivative 2 and tetrachloro derivative 3[8]. While chlorination of 1 with PCl_5 gave two compounds, trichloro compound 4 in which carbonyl is absent and three chlorine atoms are introduced with rearrangement and formation of double bonds; monochloro compound 5 in which chlorine atom is introduced at carbonyl position and a conjugated system is formed by introduction of double

bonds. Whereas chlorination with $SOCl_2$ gave only a trichloro compound 4 which is also formed by treating 1 with PCl_5[9]. Further, an abnormal chlorination of 3-hydroxy-4,5-α-epoxy-α-santonin 6 with methanesulfonyl chloride gave 3-chloro-4,5-epoxy compound 7[10]. Also unusual bromination of α-tetrahydro santonin 8 gives 2, 14, dibromo compound 9[7].

4,5-dihydro α santonin 10 after many steps like oxidation, phenylselenenylation, ketalization, deketelization etc. gave vulgarin 11, C_4-epivulgarin 12 and arglanine 13[11]. Chemical transformation of 8 gave arglanine 13 and santamarine 14[12]. 1 was reported to get transformed into tuberiferine 15 and artecalin 16[13]. Another reference reports chemical transformation of 1 into two alcohols, arsantin 17 and arsanin 18[14]. Also 8 gets chemically transformed into a α-methylene-γ-lactone yomogin 19[15].

Microbial transfromation of 1 with Pseudomonas Cichorii S. is reported to give a rearranged product lumisantonin 20[16], which has been isolated as a major product of photochemical transformation of 1. Also 20 was formed by microbial transformation of 1 with streptomyces aureofaciens[17]. Microbial transformation of 1 to its dihydro derivative 1,2-dihydro-α-santonin 21, using Cunninghametta blankesleeana and Streptomyces aureofaciens has also been reported in the literature[18].

Photochemical transformation of 1 has also been

studied extensively (scheme-I). First reported photochemical transformation showed conversion of 1 to different transformed products using different solvents like methanol, ethanol and dioxane as shown in the scheme-I[19]. Barton et al reported photochemical transformation of 1 to 20 which was converted by further photochemical transformation to isophotosantonic lactone 22[20]. He has also reported photochemical transformation of 1 in aqueous acetic acid, which gave o-acetylisophotosantonic lactone 23[21].

1 is easily converted by photochemical rearrangement, hydrolysis and dehydration to the known crystalline dienone lactone 24 which is the intermediate for the synthesis of pachydictyol-A 25[22].

Lumisantonin 20 which is a photochemical transformation product of 1 is known to give after further irradiation a rearranged product 2,4-cyclohexadienone 26 which is an intermediate for conversion of 20 to photosantonic acid 27[23].

SINGLET OXYGEN[24]

Sensitized photooxygenation of olefins represent convenient methods for introduction of oxygen at specific sites. When an aerated solution containing a monoolefin, diene or polyene and sensitizer is irradiated with light that can be absorbed by the sensitizer, oxygenated products are formed whose nature depends upon the

structure of the substrate and the lability of the initial photoproducts under the reaction conditions.

Ordinarily, only light absorbed by the sensitizer can promote photooxygenations and because the excited singlet states of most sensitizers are too short lived to interact efficiently with other species, the triplet states are usually required in the transfer of energy to oxygen. Triplet (^{3}sens) sensitizer interacts with ground state oxygen ($^3O_2$) to give singlet oxygen ($^1O_2$) and ground state singlet sensitizer (^{1}sens) with net spin preservation. Molecule accepts singlet oxygen and forms a product.

$$\text{Sens} \xrightarrow{h\nu} {}^1\text{Sens}$$

$$^1\text{Sens} \longrightarrow {}^3\text{Sens}$$

$$^3\text{Sens} + {}^3O_2 \longrightarrow {}^1O_2 + {}^1\text{Sens}$$

Present work:

Although photochemical transformation of 1 has been studied in great detail, no work has been reported on the photooxidation of it. Hence the present work was undertaken to study singlet oxidation of 1. This photooxidation was studied in two solvents, methanol and chloroform.

Photo-oxidation of 1 in methanol: 1 was irradiated at 200W in methanol in presence of catalytic quantity of Sensitizer Rose Bengal for 11 hours at room temperature,

the reaction mixture, obtained after usual workup and repeated preparative thin layer chromatographic separation gave three major compounds **20**, **28** and **29** in the yields 33.6mg, 10 mg and 7 mg respectively. Compound **20** was identified as lumisantonin by comparing its spectral data with those reported for lumisantonin in the literature[25].

Compound **28**: m.p. 159°C, in its mass spectrum exhibited M^+ ion peak at m/e 278 indicating the molecular formulae $C_{16}H_{22}O_4$. In the FT-IR spectrum, presence of a band at 1780.7 cm^{-1} indicated the presence of a lactone ring. One more carbonyl absorption band at 1703 cm^{-1} was thought to be due to α,β-unsaturated ketone in a cyclopentane ring. Further a band at 1670 cm^{-1} confirmed presence of a double bond. The presence of an α,β-unsaturated ketone system was confirmbed by λ_{max} 239 (ϵ =11,120) in the uv spectrum. In the NMR spectrum, a three proton singlet at 0.87 was assigned to a tertiary methyl group. A three proton doublet with coupling constant, 7Hz at δ 1.27 was attributed to a secondary methyl group. A three proton multiplet at δ 1.88 indicated presence of a methyl group on a double bond. Presence of a methoxy group was evident by a three proton singlet at δ 3.22. A one proton doublet at δ 4.8 with coupling constant of 10Hz observed in the NMR was attributed to the lactone proton (H-6). Chemical shift and nature of H-6 (doublet) indicated presence of a double bond at C_{4-5}. Absence of

any signal around δ5.0 in the NMR spectrum revealed that the double bond must be tetrasubstituted.

This spectral data led to the structure 28. It may be mentioned here that a compound named as methylether was isolated as a photochemical transformation product way back in 1957 by D. Arigoni et al[19]. However, no data is available and the compound was not characterised. As per the above data their methylether is the same as compound 28. The structure and stereochemistry of 28 was confirmed by a single x-ray crystallographic studies.

Crystal structure of 28:

$C_{16}H_{22}O_4$, M=278, crystals belong to orthorhombic space group $P2_12_12_1$ with cell dimensions a=9.578(1), b=12.444(1), c=12.449(1) Å, volume V=1483.8 Å^3, Z=4. Crystal of the size 0.11 x 0.15 x 0.3 mm was used for data collection with MoKα radiation (λ=0.7107 Å). The reflections were measured with an index range of h 0 to 10, K 0 to 13, l 0 to 14 using $\omega/2\theta$ scan mode within range of 0 to 23.5° on CAD-4F-11M single crystal X-ray diffractometer. Structure was solved by direct methods using MULTAN 78[26]. A full matrix refinement[27] of scale factor, positional and anisotropic thermal parameters for non-hydrogen atoms is in progress. The current R value is 0.076, for 663 ($|F_o| \geq 3\sigma|F_o|$) reflections. Atomic scattering factors were taken from international tables for X-ray crystallography[28].

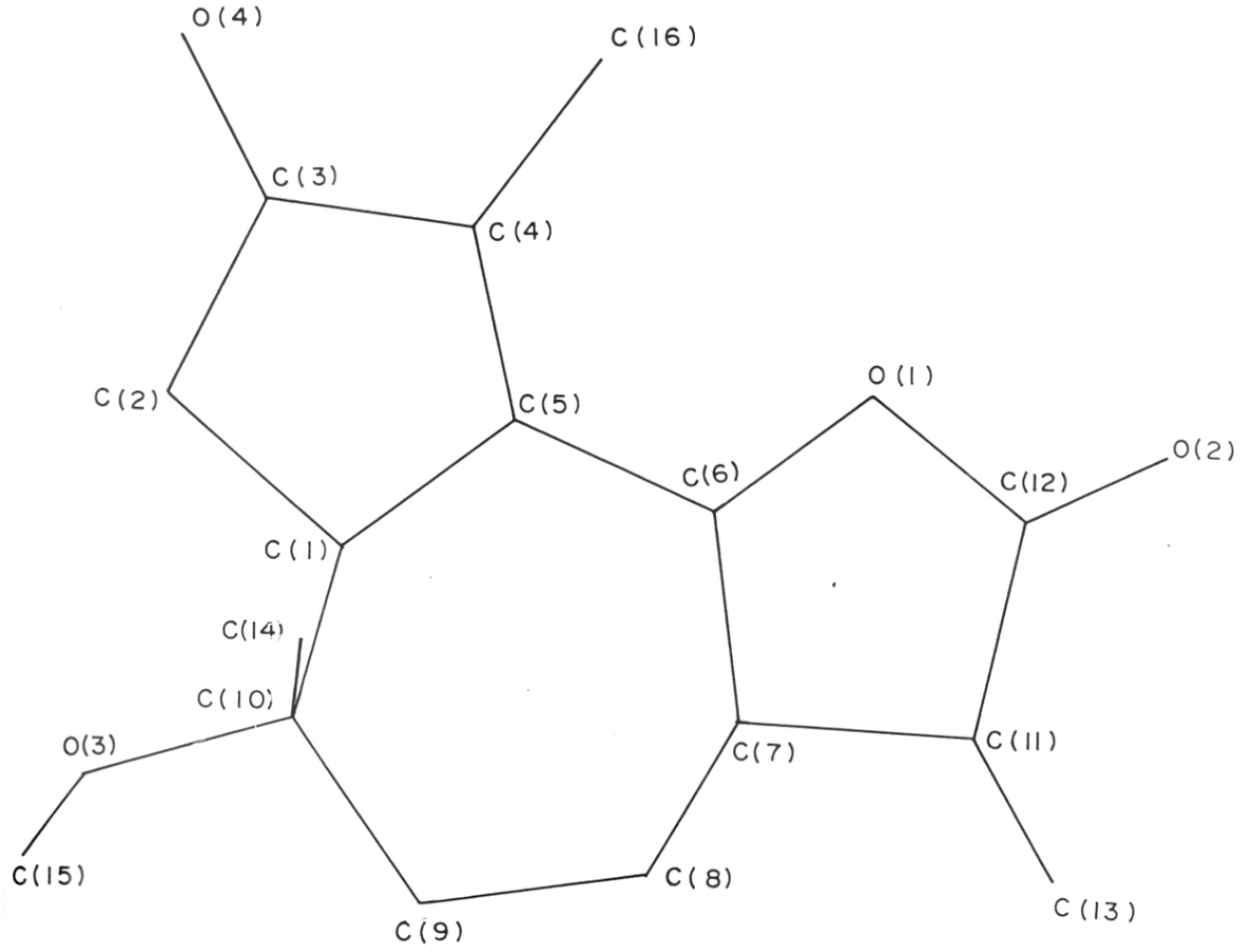


FIG. A

Discussion: The atomic co-ordinates at R=0.076 for non-hydrogen atoms are given in Table 2. A view of the molecule down (001) plane is shown in Fig. A. Bond lengths and bond angles are listed in Table 3.

A γ-lactone ring assumes an envelope conformation with C(7) being at the tip of the flap. While cyclopentanone ring is planer. Seven membered ring has a twist chair conformation. Corresponding torsion angles are listed in Table 4.

Compound **29**: Molecular formula, $C_{16}H_{22}O_5$ was assigned to **29** on the basis of M^+ molecular ion peak at m/e 294 in the mass spectrum $[M-18]^+$. Peak at m/e 276 indicated presence of a hydroxy group. In the FT-IR of **29** presence of a band at 3443.5 cm^{-1} confirmed presence of a hydroxy group. Bands at 1780 cm^{-1} and 1708 cm^{-1} were assigned to the lactone carbonyl and the carbonyl in cyclopentenone system respectively. Band at 1635 cm^{-1} was attributed to the carbon-carbon double bond. That **29** possessed three methyl groups was evident from a singlet at δ 1.04 (tertiary methyl) a doublet with coupling constant 7.0Hz at δ 1.27 (secondary methyl) and a multiplet at δ 1.93 (methyl on the double bond). A doublet at δ 4.8 with coupling constant 10.0Hz indicated the presence of a lactone proton (H-6) with only one proton on adjacent carbon, C-7 (i.e. C-5 is substituted). A three proton singlet at δ 3.33 was attributed to a methoxy group. A

downfield doublet due to H-C-OH at 4.28 with coupling constant of 3Hz suggested the position of hydroxy group at C-1 and next to carbonyl group.

Acetylation of **29** gave its acetate **30** in which one proton doublet at δ 4.28 in **29** shifted downfield to δ 5.44 position in **30** which confirmed the presence of secondary hydroxy group. Stereochemistry of the hydroxy group is assumed to be β as coupling constant of H-1 and H-2 is 3Hz and as H-1 is α-oriented H-2 also has to be α-oriented and hence hydroxy group has to be β.

Thus this compound can be represented as in structure **29**.

Photooxidation of **1** in chloroform: **1** was irradiated at 200W in chloroform in presence of catalytic amount of sensitizer Rose Bengal for 11 hours at room temperature. The reaction mixture obtained after usual workup and repeated preparative thin layer chromatographic seperation gave three major compounds, compound **20**, compound **31** and compound **32**, in the yields of 47.1 mg, 5.2 mg and 4.0 mg respectively. **20** which is a major product was identified as lumisantonin.

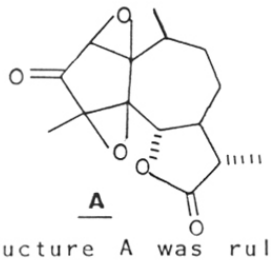
Compound **31**: mp, 238°C in its mass spectrum exhibited M^+ ion peak at m/e 278 indicating the molecular formula $C_{15}H_{18}O_5$. In the IR spectrum, presence of a absorption band at 1780 cm^{-1} indicated presence of lactone ring. One

more band at 1733 cm^{-1} could be due to the presence of a cyclopentanone moiety or a cyclohexanone with neighbouring functional groups responsible for the shift of the carbonyl band to higher wavenumber. Its NMR showed the presence of a secondary methyl group (H-13), a doublet at δ1.22 with coupling constant 6.22Hz. A three proton singlet at δ1.21 and another three proton singlet at δ1.25 were assigned to presence of two tertiary methyl groups (H-14 and H-15). A one proton doublet at δ4.38 with a coupling constant 10.38Hz observed in the NMR was attributed to the lactone proton (H-6). An AB quartet was observed at δ3.23 (J=3.45 Hz) and at δ3.74 (J=3.45Hz). Absence of any signal around δ5.0 indicated absence of olefinic proton. Absence of conjugated ketone was deduced by the absence of UV absorption band around λ220nm. correlated proton spectroscopic data (COSY) of **31** (Fig. 7) clearly confirmed the presence of a secondary methyl (H-13), a doublet due to H-6 and an AB quartet.

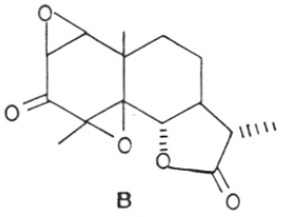
A critical comparison of the spectral data of **31** with those of **1** clearly revealed following points.

1. Addition of two oxygen atoms in **31**.
2. Absence of olefinic bonds and presence of an AB quartet (NMR).
3. Absence of proton at C-5 (NMR).
4. Upfield shift of H-6 in the NMR.
5. Addition of two rings (molecular weight).
6. Shifting of carbonyl absorption band to higher wavenumber from 1675 cm^{-1} in **1** to 1733 cm^{-1} in **31**.

From all this data two possible structures A and B emerge for 31.



A



B

Structure A was ruled out as it cannot explain the presence of an AB quartet. Moreover it possesses two secondary methyl groups which are not shown in NMR of 31. While structure B explains all the requirements. The carbonyl band at 1733 cm^{-1} in IR could be explained due to the presence of two epoxides at $C_{1,2}$ and $C_{4,5}$ positions. In literature such shift of carbonyl band at higher wave number is reported[29]. ^{13}C-NMR of 31 is in agreement with the structure assigned.

Dreiding models of 31 show that both the epoxide rings should be eigher α or β. Since the doublet due to H-6 proton is centred at δ 4.37, the epoxide at $C_{4,5}$ has to be α-oriented in analog with reported signals in maritima 33[30], δ 4.34 and arbusculin 34[31], δ 4.35. Hence $C_{1,2}$ epoxide in 31 also has to be α-oriented. Hence 31 is 1,2-α,4,5-α-diepoxy-α-santonin. This compound has been obtained by chemical transformation of 1 by treating it with meta chloroperbenzoic acid in presence of a radical inhibitor 4,4'-thiobis (6-t-butyl-3-methyl phenol) along with two monoepoxides of 1 i.e. α-epoxide 35 and β-epoxide

36[9]. However no spectral data for the diepoxide corresponding to 31 are reported.

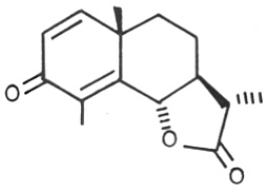
There are reports in the literature about the formation of epoxides at the sight of olefinic bonds during singlet oxidation[32].

Compound 32: 32 in its mass spectrum exhibited M^+ ion peak at m/e. 278, indicating its molecular formula $C_{15}H_{18}O_5$. In the IR spectrum of 32 two carbonyl absorption bands at 1790 cm^{-1} and 1728 cm^{-1} indicated presence of a lactone and cyclohexanone respectively, as in 31. Its NMR showed a three proton doublet at δ 1.25 with coupling constant 7Hz and two, three proton singlets at δ1.2 and 1.23 indicating presence of one secondary and two tertiary methyl groups respectively. H-6 was observed as a doublet at δ3.73 with coupling constant 10Hz. An AB quartet was observed at δ3.24 and δ3.96 with coupling constant 3.25 Hz. These spectral data indicated that 32 is closely related to 31. Major difference between 31 and 32 was in chemical shift of H-6 in the NMR. In 31, H-6 doublet was observed at 4.38, whereas in 32 it was observed at δ3.73. Hence it was deduced that stereochemistry of epoxide at $C_{4,5}$ is β-oriented in 32. Hence $C_{1,2}$-epoxide in 32 has to be β-oriented. Structure assigned to 32 is 1,2-β-4,5-β-diepoxide-α-santonin. Although 4,5-α-epoxy-α-santonin 35[10] and 1,2-β-epoxide of 3β-hydroxy-4,5-dihydro-α-santonin 37[10] have been isolated as products of chemical

transformation of 1, this is the first report of 1,2-β-4,5-β-diepoxide-α-santonin.

CHART - I

TRANSFORMATION PRODUCTS OF ∝ - SANTONIN.



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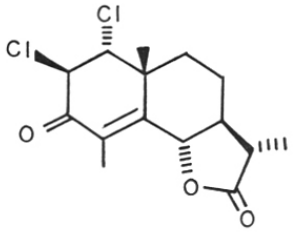

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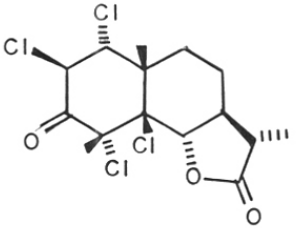

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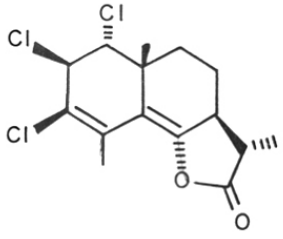

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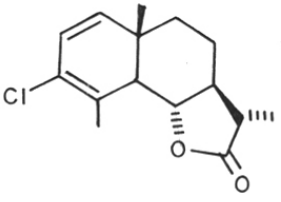

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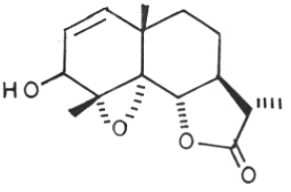

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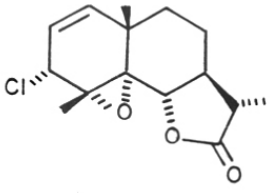

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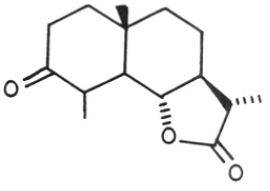

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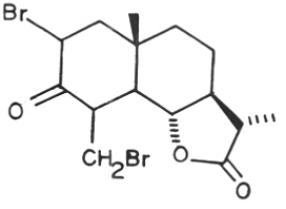

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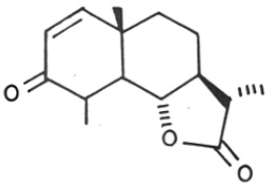

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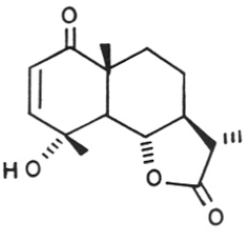

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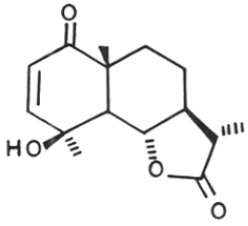

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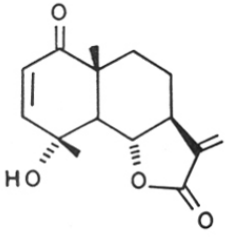

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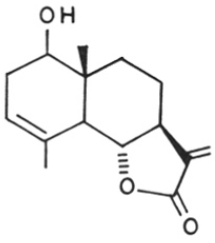

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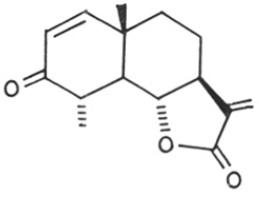

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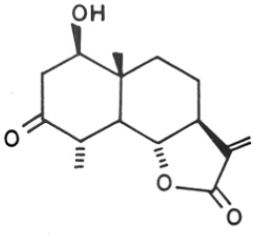

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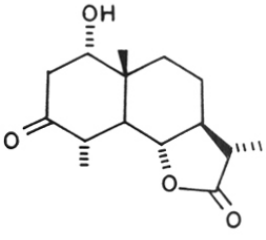

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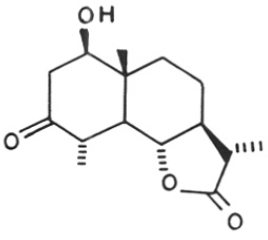

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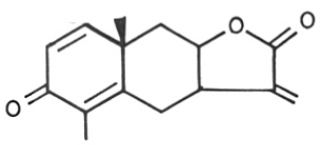

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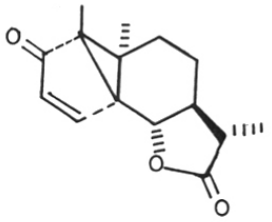

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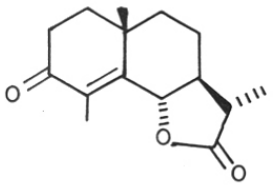

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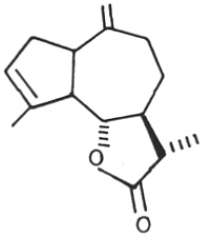

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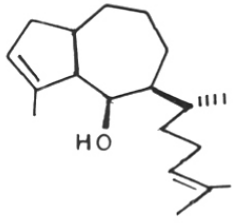

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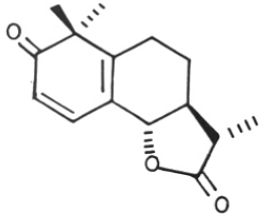

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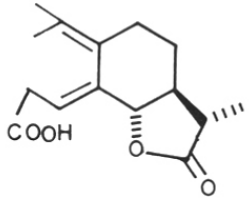

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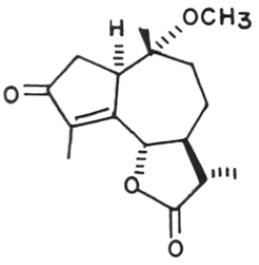

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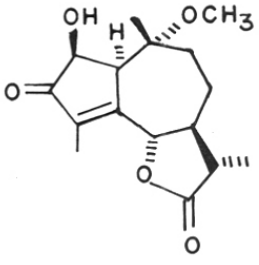

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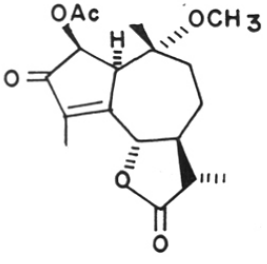

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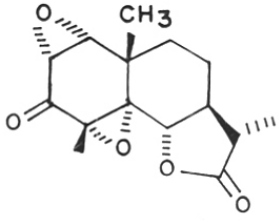

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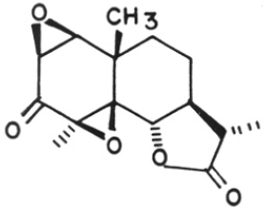

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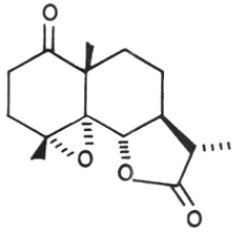

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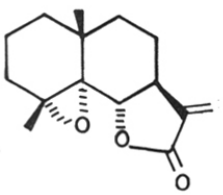

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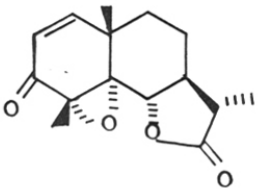

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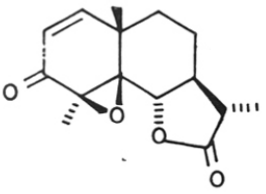

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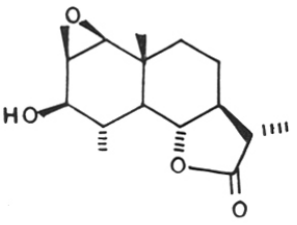

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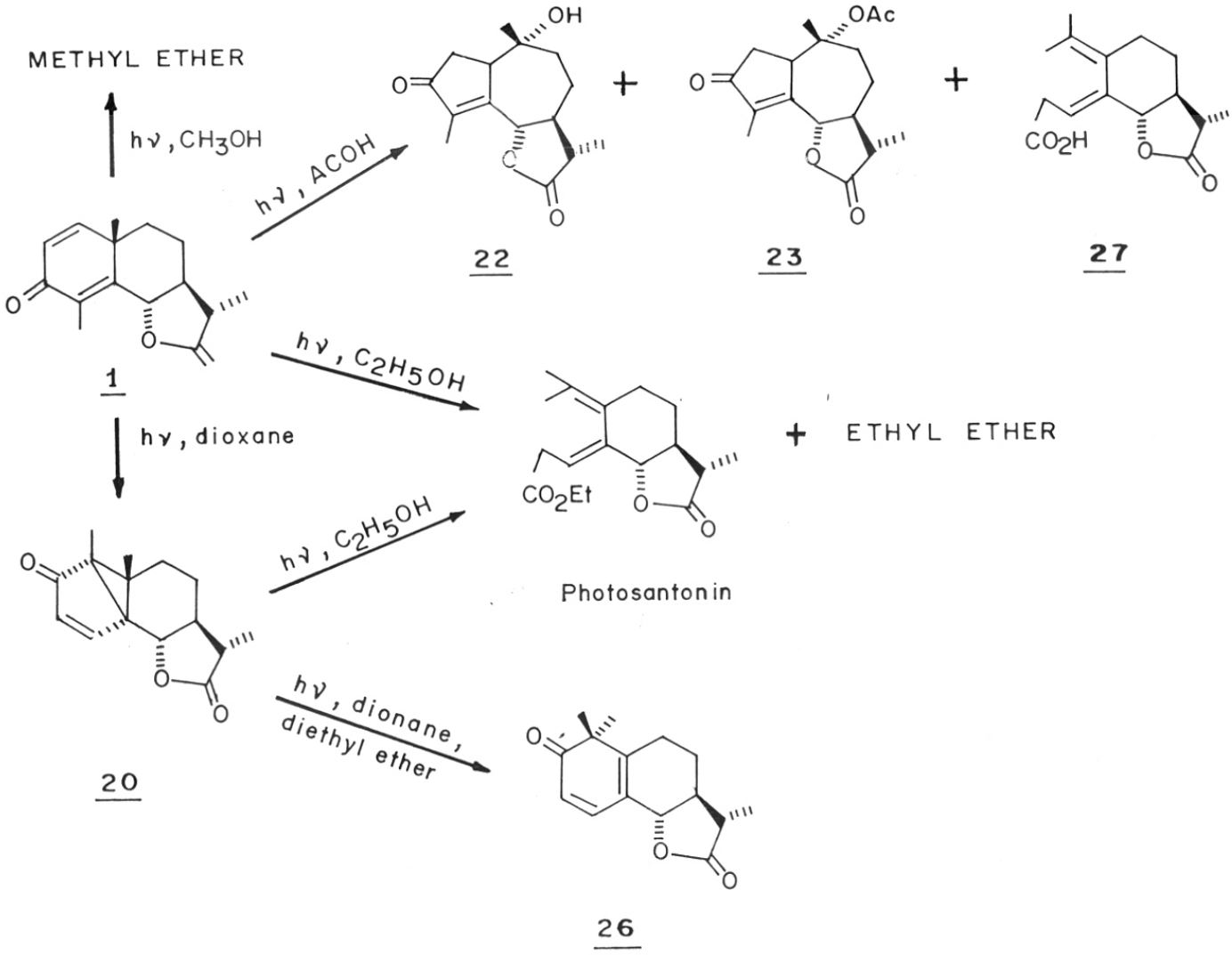
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hν, ACOH
OH
OAc
CO2H
22
23
27
1
hν, C2H5OH
hν, dioxane
CO2Et
+ ETHYL ETHER
Photosantonin
hν, C2H5OH
hν, dionane, diethyl ether
20
26

SCHEME – I

EXPERIMENTAL

Singlet Oxidation in Methanol:

A solution of 200 mg of **1** in 20 ml methanol was taken in a silica tube. To it was added catalytic quantity of Rose Bengal as a sensitizer. This solution was irradiated for 11 hours with a 200W Hanovia medium pressure mercury vapour lamp in a water cooled quartz immersion well apparatus. At the time of this irradiation oxygen was bubbled through the reaction mixture. The reaction was monitored by TLC. Methanol solution was transfered to round bottom flask and the solvent was distilled off on water bath. The residue obtained was seperated into six fractions A (40 mg), B (60.5 mg), C (16.8 mg), D (18.6 mg), E (3.4 mg) and F (9.7 mg) by preparative TLC using acetone:pet-ether (35:65), as developing system.

Fraction A was crystallized in methanol to obtain **20** in the yields of 33.6 mg (16.8%). It was identified as lumisantonin by comparing its physical and spectral data to those reported for lumisantonin in the literature (m.p., IR, NMR and mass).[17,25]

Fractions B and C showed on TLC spot corresponding to α-Santonin **1**, unreacted starting material.

Fraction D and E were combined and further separated by preparative TLC using Acetone:Pet-ether (35:65) mixture as developing system to obtain **28** in the yields of 10 mg (5%) which was further purified by crystallization from methanol.

Compound **28**: m.p. 159°C (methanol); λ_{max} 239 nm (ϵ_{max} 11,120); ν_{max} 3030, 1780.7, 1703, 1670, 1400 cm^{-1}; NMR; Table 1 (Fig.2); MS: m/e (rel. int.%) 278(M^+,24), 246(5), 206(8) 190(7), 91(15), 85(100).

Fraction F was further separated by preparative TLC using above mentioned developing system to obtain **29** in the yields of 7 mg (3.5%).

Compound **29**: gum; λ_{max} 241nm (ϵ_{max} 8,820); ν_{max} 3480, 3030, 1780, 1708, 1650, 1400, 1235 cm^{-1}; NMR, Table 1 (Fig.4); MS: m/e (rel. int.%) 294 (M^+,5), 276(M-18,10), 262(20), 244(8), 189(100), 143(42), 105(40), 91(62), 85(93).

Acetylation of **29**: 4 mg of **29** was acetylated with acetic anhydride and pyridine at room temperature for 16 hrs. After usual workup the product obtained was purified by preparative TLC to get 3 mg of **30**. NMR, Table 1.

Singlet Oxidation in Chloroform:

A solution of 200 mg of **1** in 20 ml chloroform was taken in a silica tube. To it was added catalytic quantity of Rose Bengal as a sensitizer and was irradiated as mentioned earlier. The reaction was monitored by TLC. After 11 hours chloroform was distilled off on water bath and residue obtained was separated into five fractions, A

(55 mg), B (70 mg), C (30 mg), D (8 mg) and E (9 mg) by preparative TLC using Acetone : Pet-ether (30:70) as a developing system.

Fraction A was crystallized in methanol to obtain **28** in the yields of 47.1 mg (23.5%) which was identified as lumisantonin.[17,25]

Fraction B and C contained mostly unreacted -santonin (by TLC) and **28**.

Fraction D was further seperated by preparative TLC using above mentioned developing system to obtain **31** in the yield 5.2 mg (2.6%) which was further purified by crystallization from rectified spirit.

Compound **31**: m.p. 238°C; ν_{max} 3020, 1780, 1733, 1580, 1420, 1235, 1020 cm^{-1}; NMR, Table 1 (Fig.6); MS:m/e(rel. int.%) 278 (M^+,8), 260(M-18,9), 246(19), 235(26), 217(31), 261(35), 149(40), 135(50), 107(59), 91(81), 69(100), 55(92).

Fraction E was further purified by preparative TLC using above mentioned developing system to obtain **32** in the yield 4.0 mg (2%).

Compound **32**: gum, ν_{max} 3015, 2940, 1790, 1728, 1470, 1040 cm^{-1}; NMR, Table 1 (Fig.9); MS:m/e (rel. int.%) 278(M^+,5) 262(M-16,8), 246(15), 235(22), 219(30), 135(31), 122(33), 107(43), 83(92), 69(68).

TABLE 1

NMR SPECTRAL DATA OF COMPOUNDS 28, 29, 31, 32 AND 30

(in $CHCl_3$, TMS as internal standard, figures in parantheses denote coupling constants in Hz, values in δ)

Proton	28*	29*	31**	32*	30*
H-1	2.56(m)	3.06(bd)	3.23(d,3.45)	3.24(d,3.25)	-
H-2	-	4.28(d,3)	3.74(d,3.45)	3.96(d,3.25)	5.44(d,3)
H-6	4.8(d,10)	4.84(d,10)	4.38(d,10.38)	3.73(d,10)	4.86(d,10)
H-7	2.14(m)	2.15(m)	2.31(m)	2.3(m)	2.28(m)
H-13	1.27(d,7)	1.27(d,7)	1.22(d,6.22)	1.25(d,7)	1.29(d,6.5)
H-14	0.87(s)	1.04(s)	1.21(s)	1.2(s)	1.04(s)
H-15	1.88(m)	1.93(m)	1.25(s)	1.23(s)	1.93(m)
$-OCH_3$	3.22(s)	3.33(s)	-	-	3.18(s)
-OAc	-	-	-	-	2.13(s)

s= Singlet; d= Doublet; bd= Broad Doublet; m= Multiplet

*90MHz; **300MHz.

TABLE 2

Fractional atomic co-ordinates for non-hydrogen atoms of compound 28 at R=0.076

	X	Y	Z
O(1)	0.93816	0.50808	0.37024
O(2)	0.90164	0.66953	0.44093
O(3)	0.65964	0.08671	0.30659
O(4)	1.18286	0.12908	0.36521
C(1)	0.82274	0.22259	0.37789
C(2)	0.92629	0.17590	0.38624
C(3)	1.07065	0.17802	0.36103
C(4)	1.05313	0.28983	0.32999
C(5)	0.91604	0.31591	0.34098
C(6)	0.85322	0.42413	0.31794
C(7)	0.70507	0.44120	0.36418
C(8)	0.59552	0.39342	0.29307
C(9)	0.57283	0.27006	0.31328
C(10)	0.70153	0.19819	0.29328
C(11)	0.69774	0.56645	0.37330
C(12)	0.85491	0.59230	0.39982
C(13)	0.60003	0.61015	0.45701
C(14)	0.75483	0.20211	0.17684
C(15)	0.60369	0.05540	0.41234
C(16)	1.17513	0.35797	0.29398

TABLE 3

Bond lengths (Å) and bond angles (°) for compound 28

Bond length (Å)

O(1)-C(6)	1.476	C(4)-C(5)	1.360
O(1)-C(12)	1.367	C(4)-C(16)	1.512
O(2)-C(12)	1.177	C(5)-C(6)	1.503
O(3)-C(10)	1.454	C(6)-C(7)	1.546
O(3)-C(15)	1.474	C(7)-C(8)	1.496
O(4)-C(3)	1.236	C(7)-C(11)	1.564
C(1)-C(2)	1.563	C(8)-C(9)	1.571
C(1)-C(5)	1.536	C(9)-C(10)	1.543
C(1)-C(10)	1.597	C(10)-C(14)	1.538
C(2)-C(3)	1.559	C(11)-C(12)	1.574
C(3)-C(4)	1.454	C(11)-C(13)	1.503

Bond angle (°)

C(6)-O(1)-C(12)	109.9	C(5)-C(6)-C(7)	114.8
C(10)-O(3)-C(15)	117.0	C(6)-C(7)-C(8)	111.6
C(2)-C(1)-C(5)	103.5	C(6)-C(7)-C(11)	101.8
C(2)-C(1)-C(10)	111.0	C(8)-C(7)-C(11)	114.0
C(5)-C(1)-C(10)	111.7	C(7)-C(8)-C(9)	113.0
C(1)-C(2)-C(3)	103.3	C(8)-C(9)-C(10)	115.5
O(4)-C(3)-C(2)	123.9	O(3)-C(10)-C(1)	107.9
O(4)-C(3)-C(4)	125.7	O(3)-C(10)-C(9)	108.3
C(2)-C(3)-C(4)	110.4	O(3)-C(10)-C(14)	103.3
C(3)-C(4)-C(5)	108.3	C(1)-C(10)-C(9)	111.4
C(3)-C(4)-C(16)	121.8	C(1)-C(10)-C14)	112.1
C(5)-C(4)-C(16)	130.0	C(9)-C(10)-C(14)	113.5
C(1)-C(5)-C(4)	114.3	C(7)-C(11)-C(12)	100.1
C(1)-C(5)-C(6)	120.1	C(7)-C(11)-C(13)	116.0
C(4)-C(5)-C(6)	125.6	C(12)-C(11)-C(13)	112.0
O(1)-C(6)-C(5)	109.2	O(1)-C(12)-C(2)	121.4
O(1)-C(6)-C(7)	104.2	O(1)-C(12)-C(11)	110.2
		O(2)-C(12)-C(11)	128.4

TABLE 4

SOME IMPORTANT TORSION ANGLES

Seven membered ring

C(1)-C(5)-C(6)-C(7)	16.7
C(5)-C(6)-C(7)-C(8)	-82.0
C(6)-C(7)-C(8)-C(9)	83.9
C(7)-C(8)-C(9)-C(10)	-61.0
C(8)-C(9)-C(10)-C(1)	66.3
C(9)-C(10)-C(1)-C(5)	-86.1
C(10)-C(1)-C(5)-C(6)	57.5

Five membered ring

C(1)-C(2)-C(3)-C(4)	-5.5
C(2)-C(3)-C(4)-C(5)	4.7
C(3)-C(4)-C(5)-C(1)	-1.8
C(4)-C(5)-C(1)-C(2)	-1.7
C(5)-C(1)-C(2)-C(3)	4.1

Five membered ring (lactone)

O(1)-C(6)-C(7)-C(11)	36.5
C(6)-C(7)-C(11)-C(12)	-33.1
C(7)-C(11)-C(12)-O(1)	19.7
C(11)-C(12)-O(1)-C(6)	3.2
C(12)-O(1)-C(6)-C(7)	-25.4

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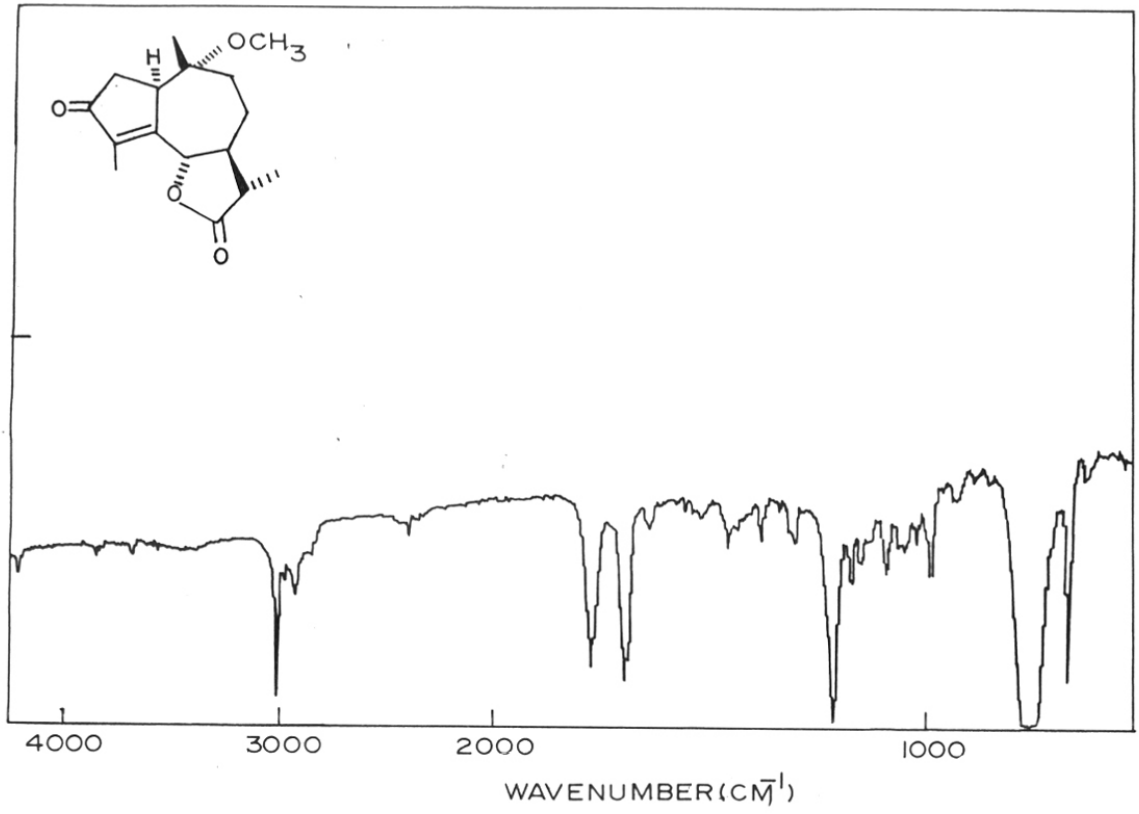


FIG. 1 FT – IR SPECTRUM OF COMPOUND 28

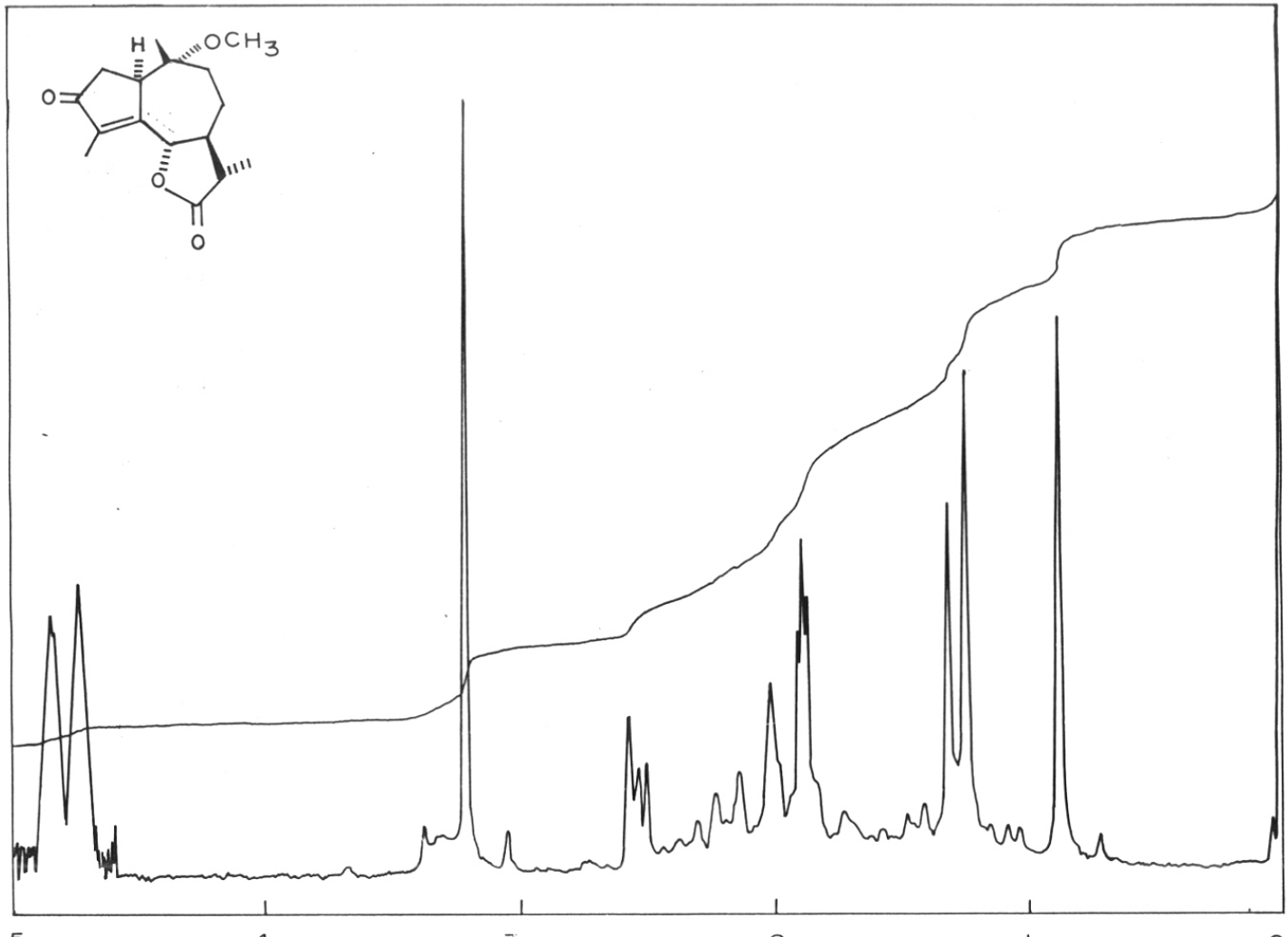


FIG. 2 NMR SPECTRUM OF COMPOUND 28

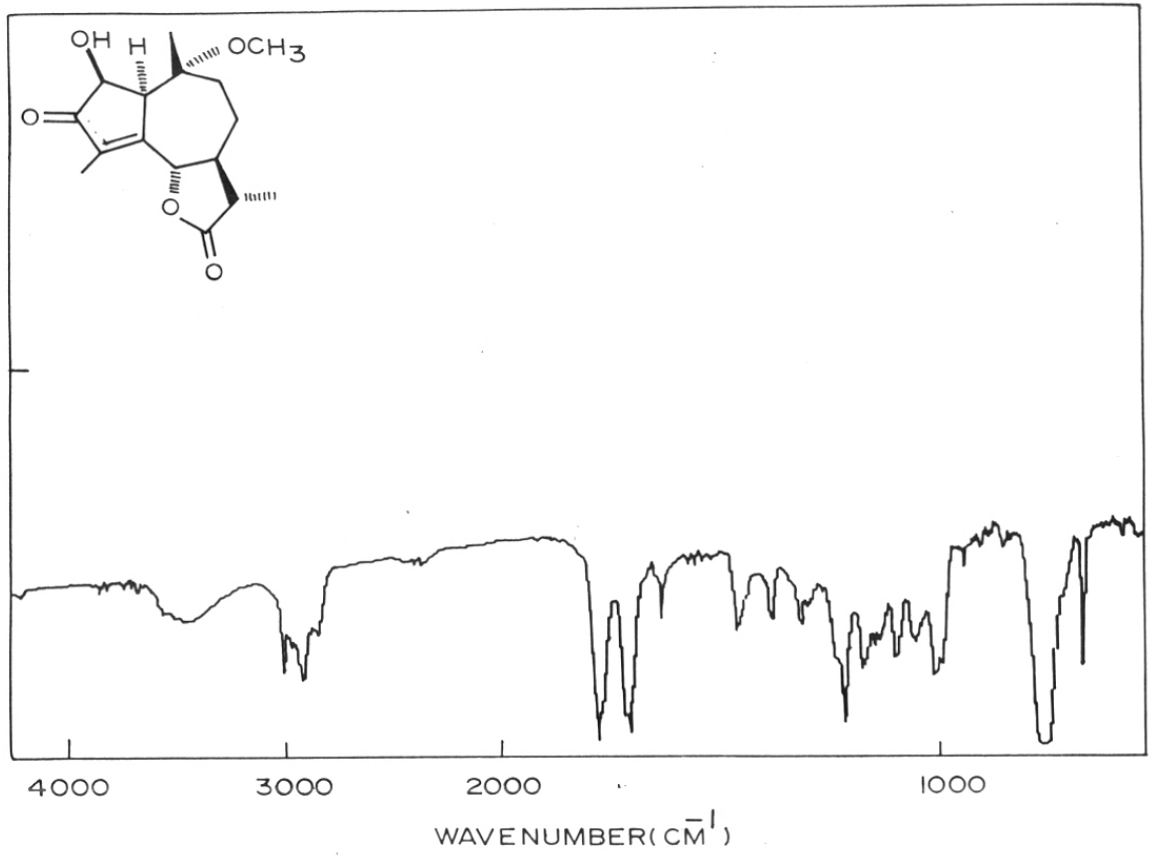


FIG. 3 FT-IR SPECTRUM OF COMPOUND 29

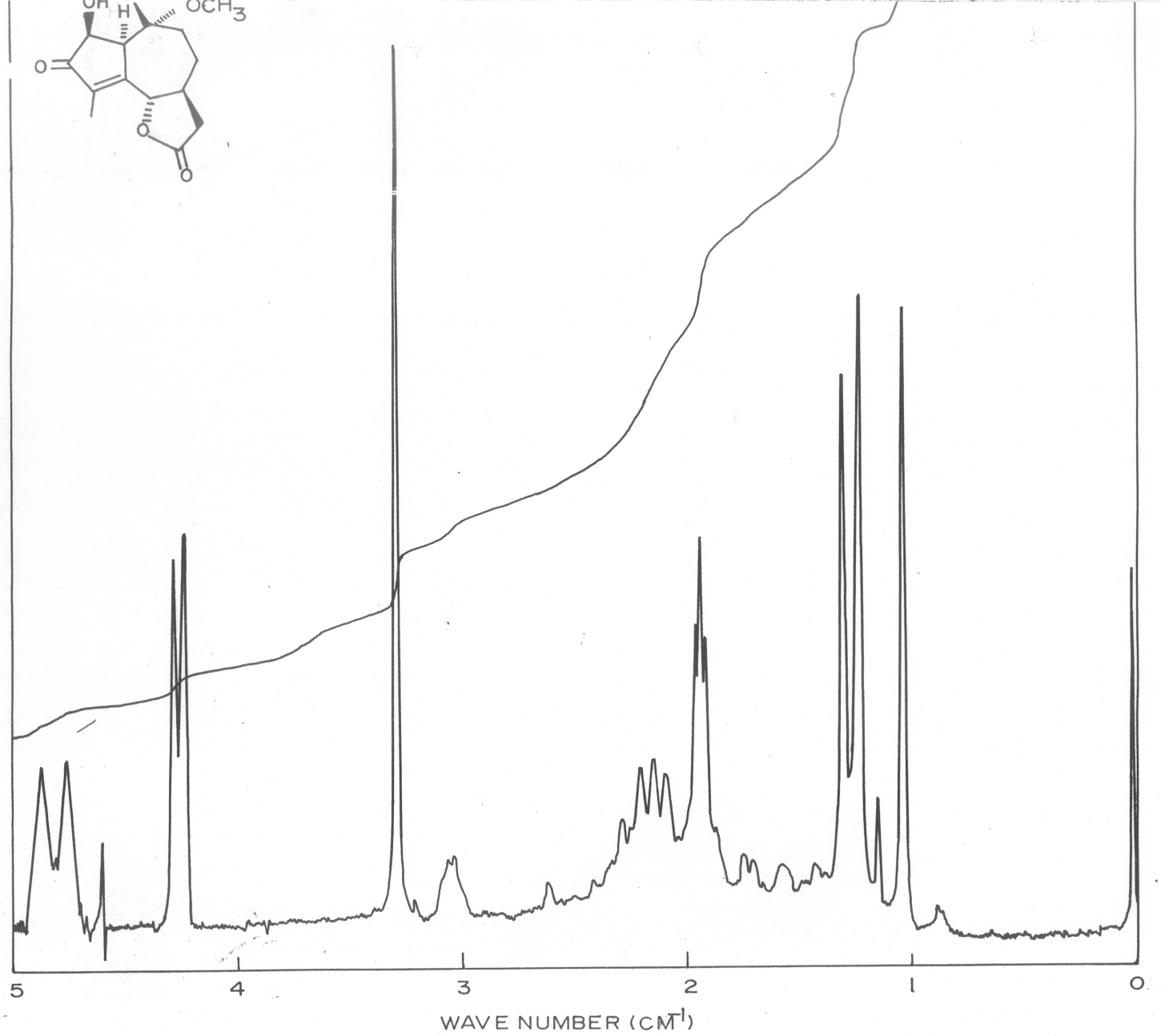


FIG. 4 NMR SPECTRUM OF COMPOUND 29

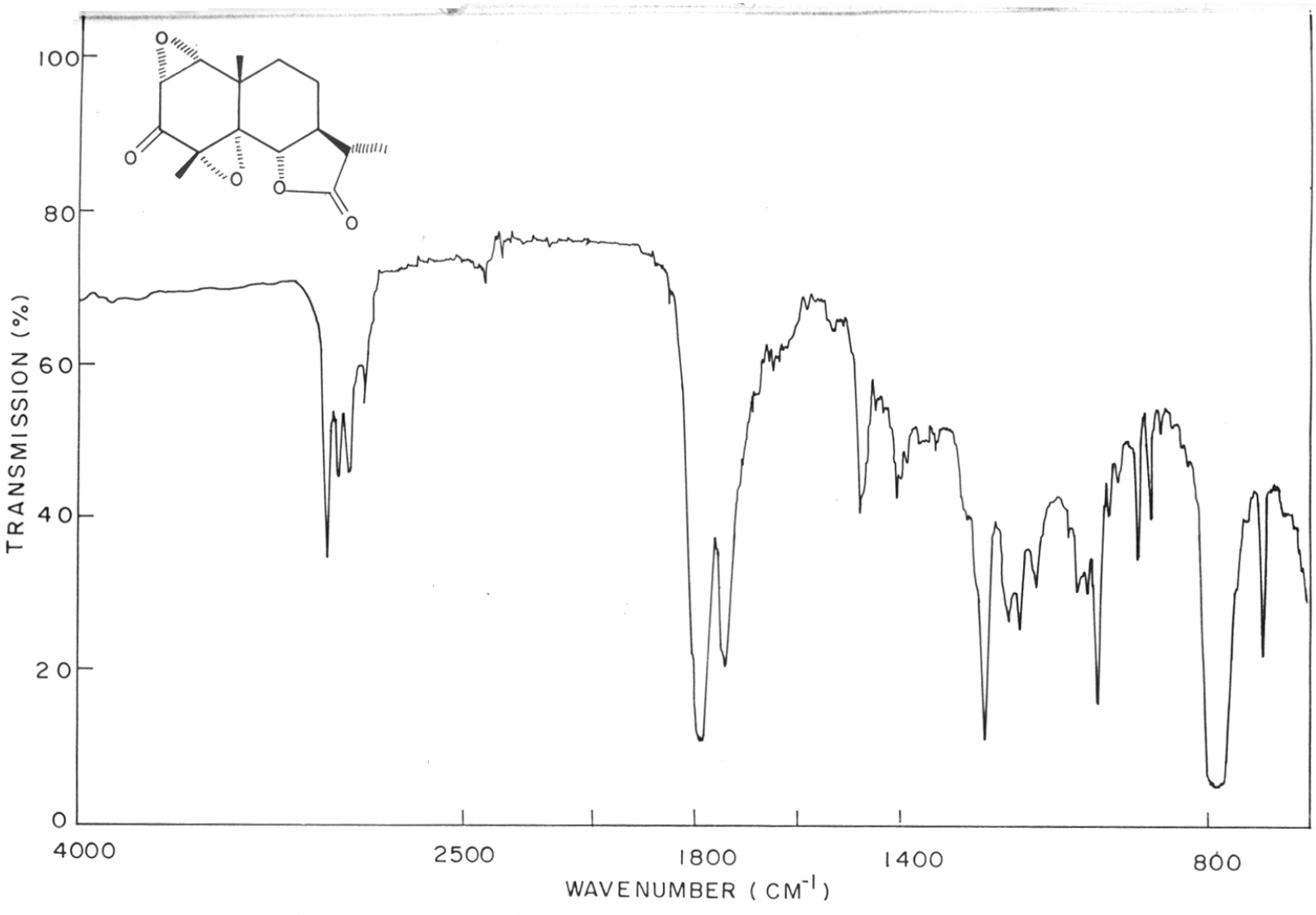


FIG. 5 : IR SPECTRUM OF COMPOUND 31 .

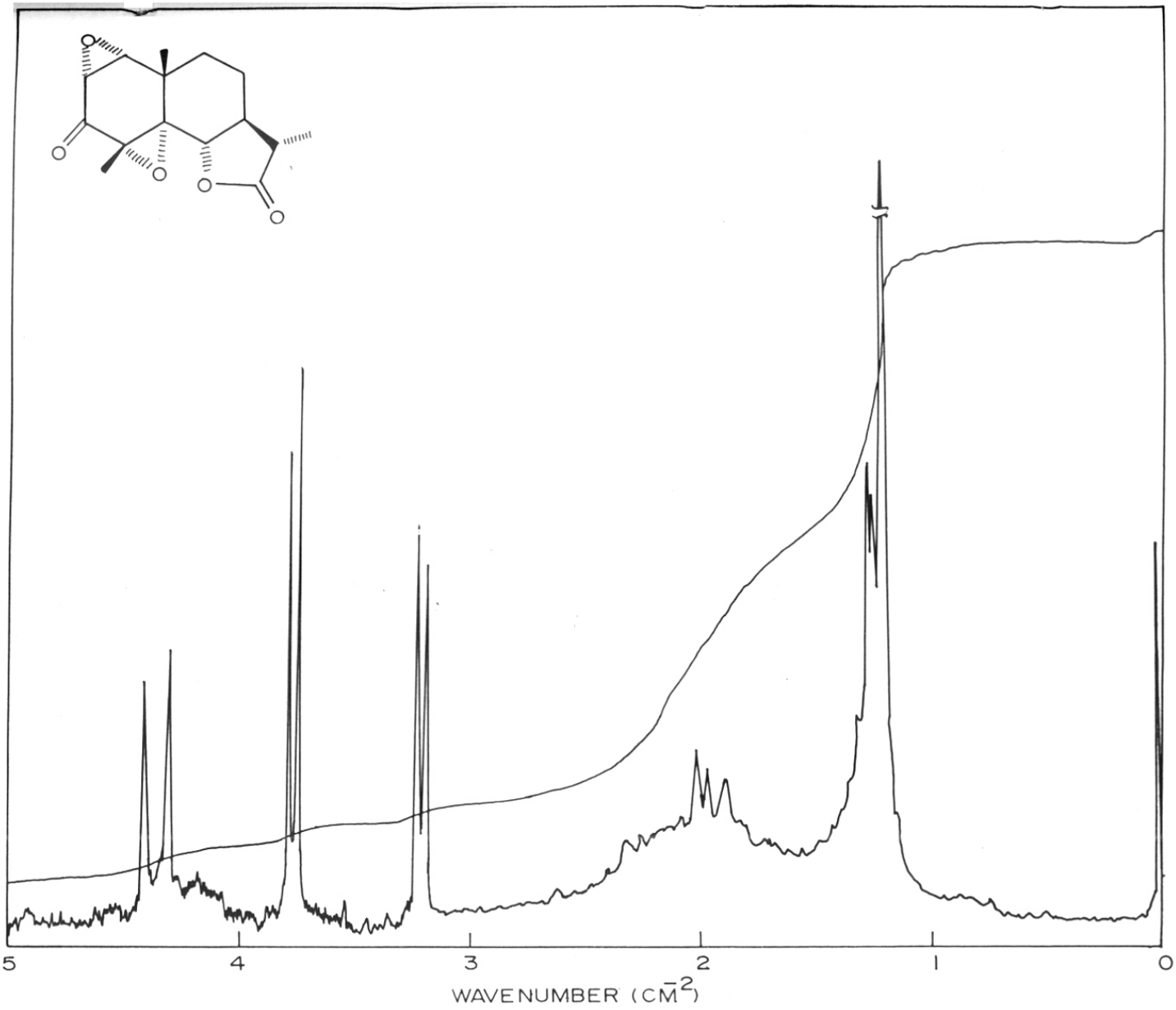
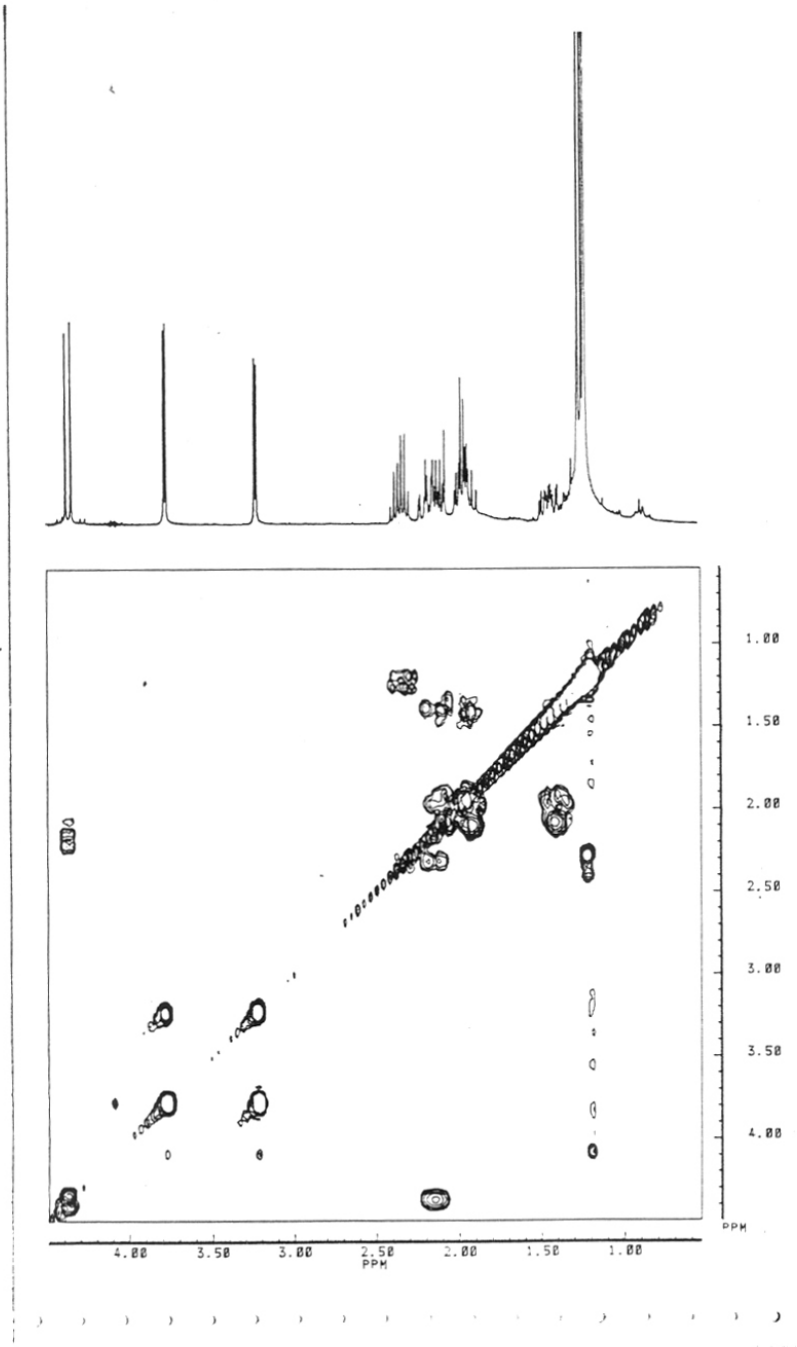


FIG.6 NMR SPECTRUM OF COMPOUND 31



2D-COSY NMR SPECTRUM OF COMPOUND 31.

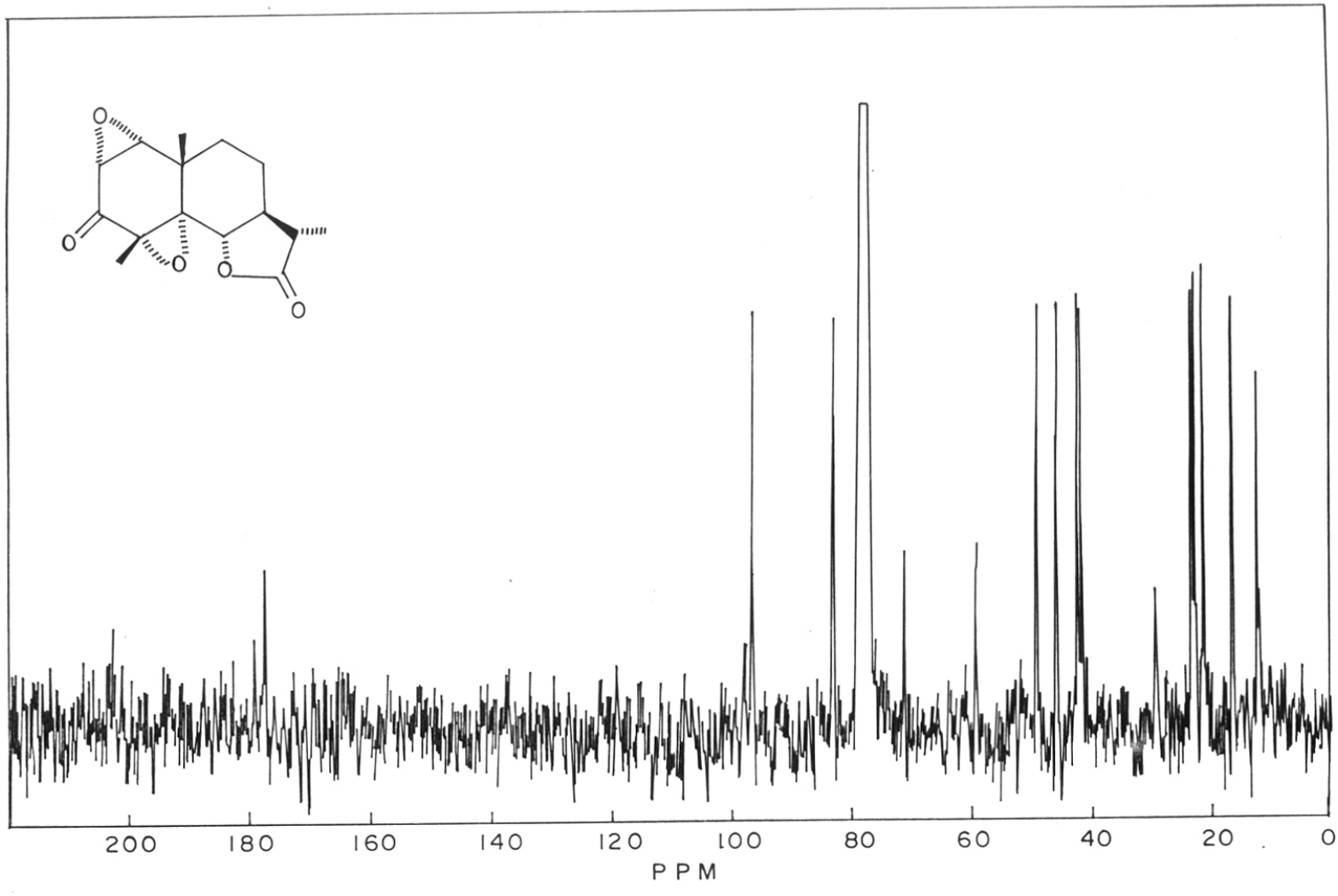


FIG. 7 : ^{13}C-NMR SPECTRUM OF COMPOUND 31

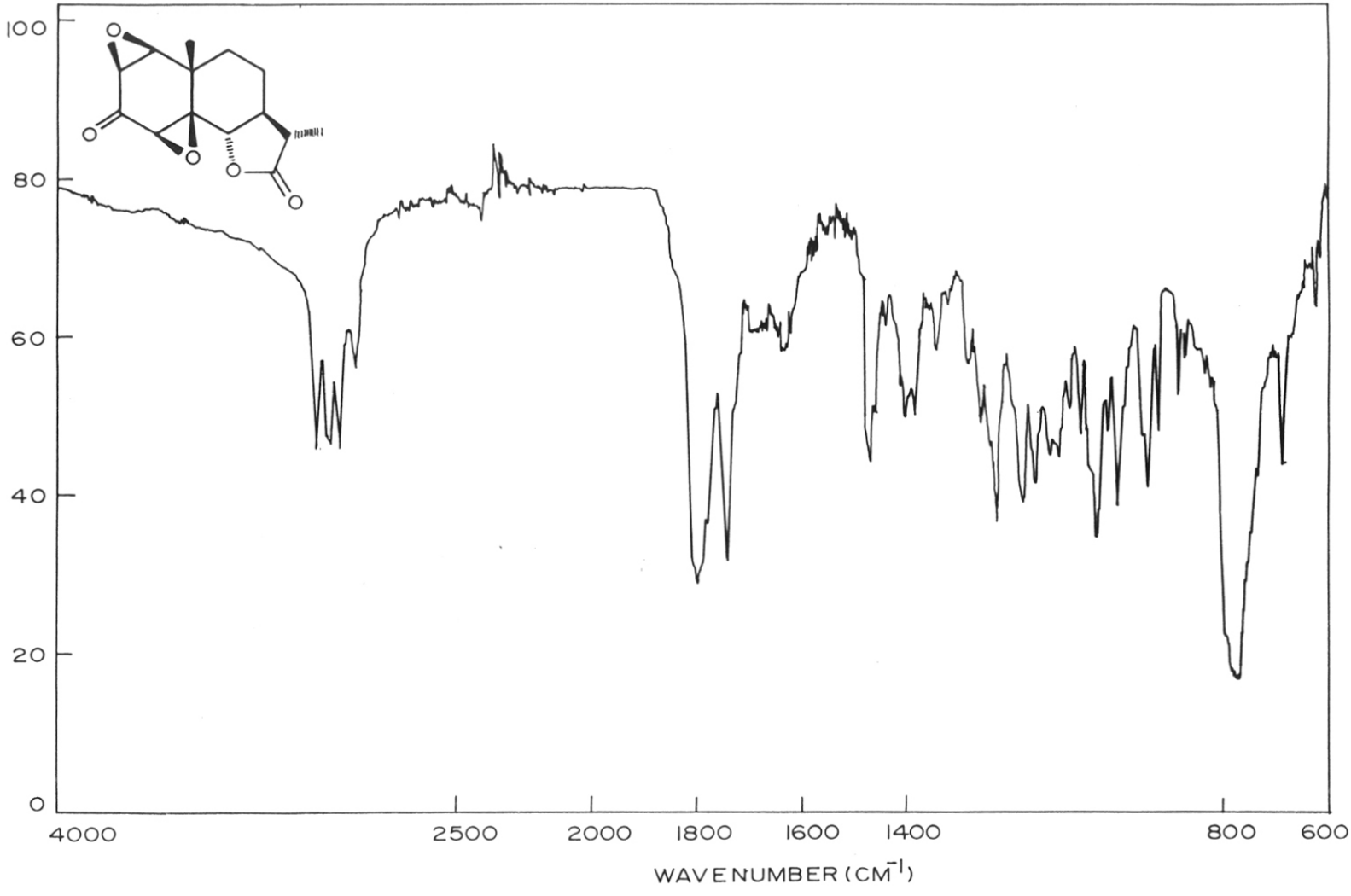


FIG. 8 FT-IR SPECTRUM OF COMPOUND 32

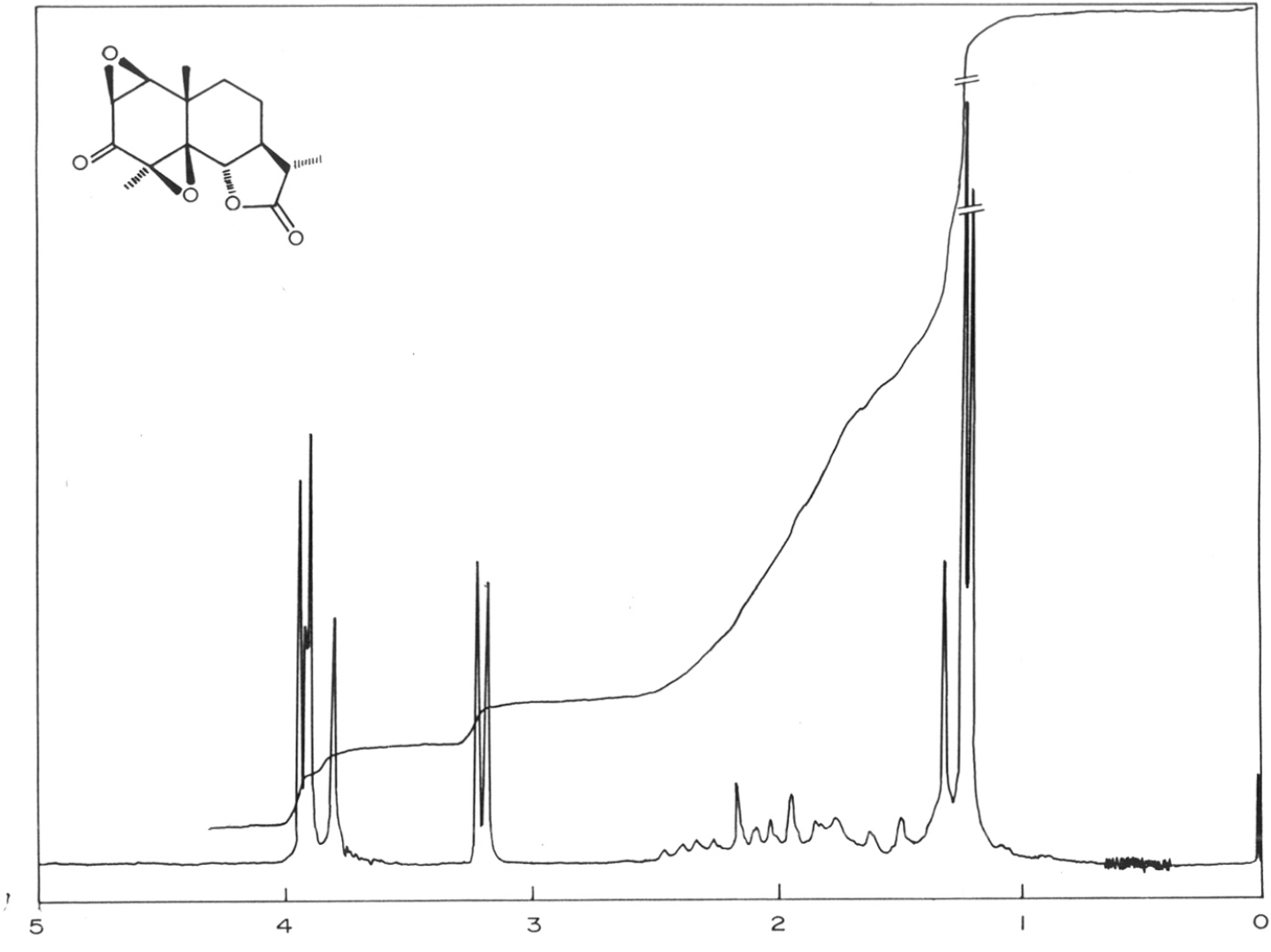


FIG. 9 NMR SPECTRUM OF COMPOUND 32

CHAPTER II

CHAPTER II

CATALYTIC CONVERSION OF Δ^3-CARENE TO p-CYMENE

Introduction:

Terpenes constitute one of the largest groups of pharmaceutically important natural products. Monoterpenes, i.e. terpenes with two isoprene units occur in essential oils obtained from family Coniferae.[1] The oil of turpentine is one of the most important essential oil now obtained from pine tree resins and as a by-product from Kraft paper mills[2]. (+)-3-carene 1 a bicyclic monoterpene was first obtained from turpentine by Simonsen et. al.[3] in 1920, and its structure (1, Chart 1) was later established by electron diffraction.[4,5] Although turpentine is produced on a large scale throughout the world, 1 was not separated in its pure form mainly because there was no market for it, either as a chemical raw material or as an end product in its pure form. Content of 1 in turpentine varies in different parts of the world. World's maximum production of turpentine is in the South Western USA, but this turpentine source contains negligible quantity of 1. West USA and Canada turpentine contains 20-25% of 1, European (from Pinus Sylvestris) 35-40% and that in India and Pakistan (from Pinus longifolia) contains nearly 55-65% of 1.[6-11] In India the total production of turpentine is reported to be 515,100 gallons

(1949-50) and contains about 40% α-pinene 2 β-pinene 3 (Chart 1) and 55-65% of 1 [12,13]. This turpentine is not exploited to its fullest extent due to large amount of 1 present in it, which doesnot have good commercial value as yet mainly because of its property to oxidize to resin when exposed to air[14] making storage of this chemical difficult which decreases its value as a raw material in industry.

Various attempts have been made to convert 1 into material of industrial importance using different catalysts. Considerable research work has been carried out on this molecule during the last 70-75 years. 1 an optically active compound has been transformed into various chemicals like Δ^2-carene 4,(-)-menthol 5, m-methadiene 6, p-methadiene 7 and (+)-transchrysanthemic acid 8 (Chart 2). Conversion of 1 to 8 is important as it is part molecule of pyrethroids, synthetic and naturally occuring insecticides. However, the routes are long and arduous, therefore, the final process has not been established yet. The other uses of 1 are as solvent in paints and varnishes[15]. However, none of the above mentioned products have large scale industrial applications[6].

Cymenes also known as cymol have many industrial applications (particularly p-cymene). 9 occurs in several essential oils and is obtained by dehydrogenation of monocyclic terpenes. 9 and o-cymene 10 oxidises to isophthalic and terephthalic acid respectively[16], which

themselves are very important additives in plastics as heat resistant component and in synthetic polyester fibre, respectively. Hydration to camphor and via hydroperoxidation to cresol are some of the important reactions of **9**.[17] The cymenes are used as solvent, in synthetic resin manufacture, in metal polishes and in organic chemical manufacture. Important applications of p-cymene have been reviewed by Verghese in 1965[18]. **9** has been used in the preparation of p-cresol and carvacrol. Cresols in turn are very important, since they are used as herbicide intermediates, insecticides of pyrethroid type and also as fragrances. The other uses for **9** are as heat transfer medium, imitation lemon and beragmot flavour and fragrances and manufacture of organic chemicals.

p-Cymene was until recently imported in India from abroad. Considering its importance, Camphor and Allied Products (Bareilly) have started manufacturing **9** in the country[19]. Apart from this processes for commercial production of **9** there were many attempts to make this chemical from different starting materials, and **1** is one of the compound which has been used for this purpose. V. Krishnasamy has published a few papers around 1980's in which he has reported the physico-chemical studies on chromia and chromia/alumina catalysts[20], the performance of chromia and chromia/Alumina catalysts[21] and chromium (III)-alumina-potassium oxide catalysts[22] in connection with vapour phase dehydrogenation of **1**.

A patent by Goodyear Tyre and Rubber Co., USA describes preparation of cymenes by contacting terpenes or turpentine with an alkali metal carbonate catalyst on support at 300-475°C. The patent claims 100% conversion and 72% selectivity on passing turpentine vapours with nitrogen into S.S. reactor containing 10% K_2CO_3 over alumina, heated to 400°C for the turpentine to cymenes process.

Trichloroacetic acid has been used as a catalyst in order to convert **1** into **9**. This was done in a sealed tube at 175° for 10 hr to give only 12% **9**[23].

Krishnasamy and Balasubramanian claim to have obtained nearly 82% of cymenes using 6% chromia over alumina catalyst in which alumina was obtained from potassium aluminate[24]. Although chromia or chromia/alumina have been used widely as aromatization catalyst in these studies, they show maximum efficiency at around 500°C. Such high temperatures may cause loss of activity of the catalyst because of sintering[25,26,27].

A new process for the production of **9** from **1** was reported in 1980 by Misra et. al.[28]. The reaction involved chlorination or bromination of **1** and then dehydrohalogenation resulted in **9** to the extent of 60-70% (chart 3a).

From turpentine **9** (30%) and **10** (11%) has been reported by using 10% KOH over alumina as a catalyst at 450°C.

All these reports show that various catalysts and reaction conditions have been used to obtain 9 from 1, but so far in none of them zeolites have been used, although these catalysts are holding great promise for the chemical transformations, particularly in the petrochemicals field, for the past many years.

Industrially, 9 is obtained from methods described below:

1. Alkylation of toluene with propene[29,30] (Chart 3b)
2. p-Cymene from natural terpenes[31].
3. By using d-limonene as raw material[32,33].

In view of the importance of 9 and its non-availiability in the country, we concentrated on studying formation of 9 from 1 by using zeolite catalysts. This would give industrial outlet for 1 and at the same time import substitution will be available for 9.

Present work:

We were, attracted by the ease with which cyclic monoterpenes can be converted to aromatic ring systems. Many attempts have been made to convert 1 into cymenes[23,28] and this is the very reaction that we have chosen. It was thought that a new approach is necessary to obtain 9 in good yield from 1 and in our investigation, we have tried a catalyst that is presently holding a lot of potential in various chemical processes, viz. zeolite.

So far zeolites have not been used for the transformation of 1 into 9.

Δ^3-Carene 1 used in this study was obtained from turpentine. As the product was impure due to storage, purification was carried out by fractional distillation using a spinning band column. Purity of the product was found to be 96% by GC analysis. The catalysts used were two types of zeolites. The experiments were carried out in liquid phase and vapour phase.

Liquid phase: Zeolite being highly hygroscopic was activated under reduced pressure at about 400°C for 3 hr in the long necked round bottom flask (Fig.1). The flask was cooled to about 45°C and the required quantity of 1 was added to the flask by slowly releasing the pressure. This was heated while stirring at different temperatures and different time periods. Reactions were monitored by GC. After the reaction was completed amount of p-cymene, 9 cumene 11, toluene 12, Δ^2-carene 4 and unreacted 1 were analysed by GC (Table 1). Presence of 9 was confirmed by comparing its Rf value with that of authentic p-cymene on $AgNO_3$ impregnated TLC. Same reaction when carried out at room temperature or with addition of solvents like benzene, pet-ether showed no change in the starting material. When the reaction was carried out at room temperature no change was observed and the starting material was recovered.

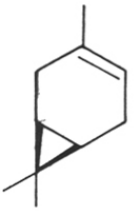
Vapour phase: A zeolite catalyst (ZSM-5 pentacyl) was taken in a quartz glass tube and activated in a

furnace at 500°C for 1 hour. 1 was introduced with a syringe to the vaporiser (Fig.2). Experiments were carried out at different vaporiser temperatures and different temperatures of catalyst bed. Nitrogen was used as a carrier gas at the time of the reaction. Target product 9 was estimated by GC (Table-2) as in case of liquid phase reactions.

In liquid phase reaction along with target compound 9 other products like toluene, Δ^2-carene and cumene were also formed in some experiments in sizable amounts. Unreacted 1 was obtained in small quantity. In an ideal experiment No.11 (Table 1) 9 was obtained in 84.69% while 4 was obtained in 3.75% and 1 was not detected in GC. From Table-1 it can be seen that it is possible to get optimum yield of 1 by selecting proper zeolite catalyst and reaction conditions. In vapour phase reaction only one product i.e. 9 along with one unidentified compound was obtained in sizable amount (22-35%) while starting material 1 was not obtained (Table 2).

In this exploratory study conditions were set up to get a target compound 9 at laboratory level. Further optimization and scaling up is underway, and it is expected to give economically viable method to obtain 9 from a cheap and indigenously abundantly available raw material, Δ^3-carene.

CHART – 1



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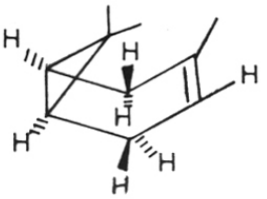

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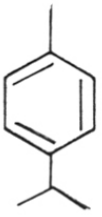

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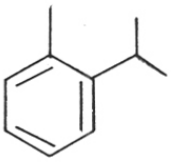

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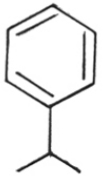

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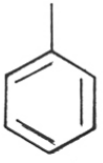

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CHART - 2

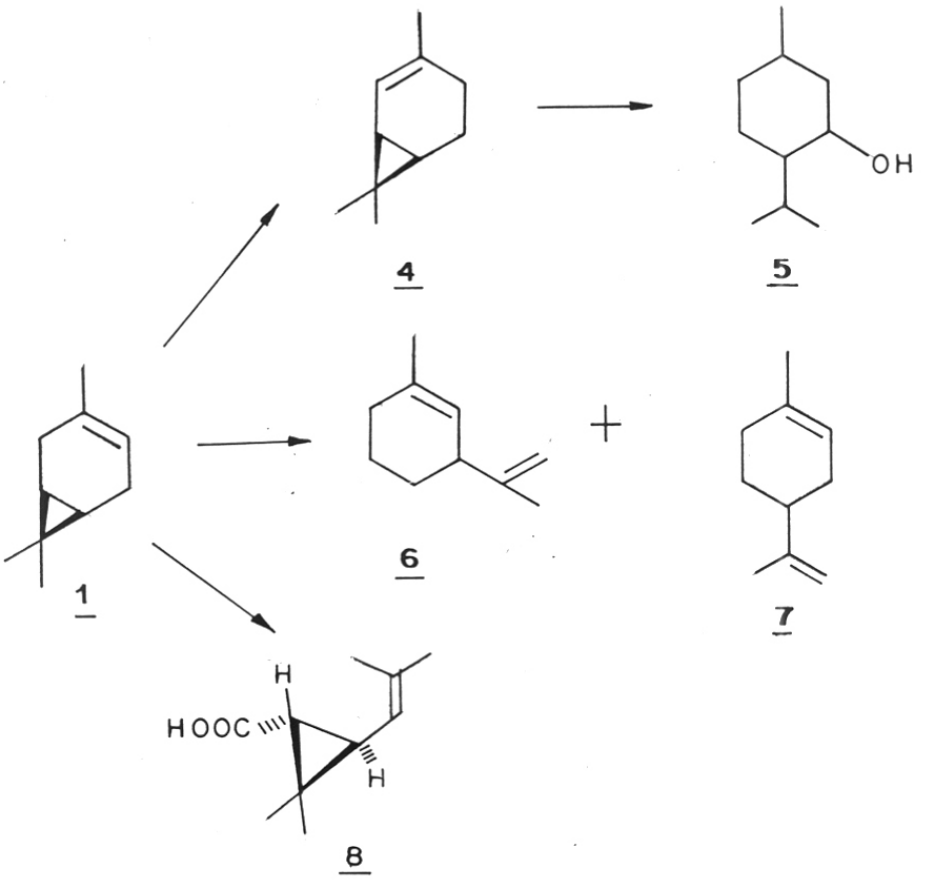
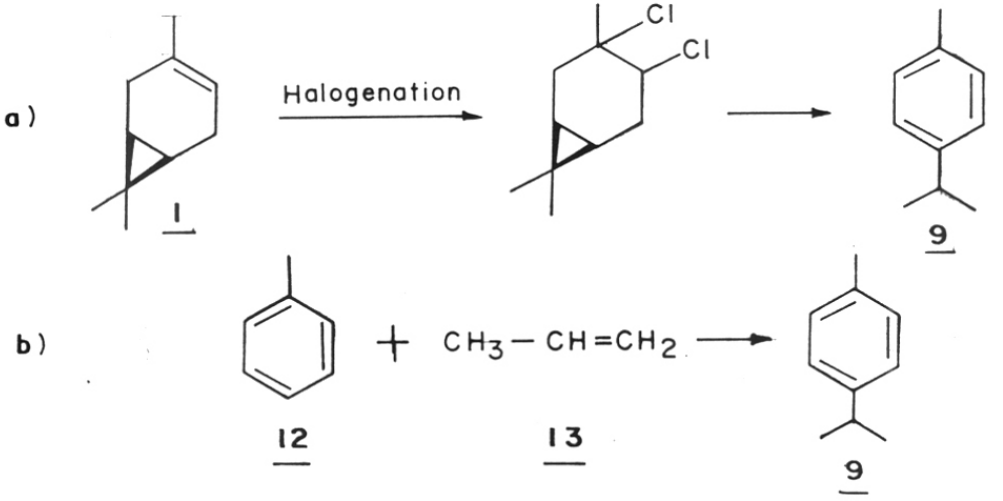


CHART - 3



EXPERIMENTAL

Crude Δ^3-carene 1 was kept overnight on $CaCl_2$. It was then purified by fractional distillation on spinning band column (Distillation system, B/R Model 24T) at reduced pressure of 10mm (distillation temperature 55°C, reflux to distillation ratio 13:1). Distilled 1 was found to be 96.77% pure by GC.

Liquid phase: The zeolite catalyst was taken in a long necked 50 ml round bottom flask. This was connected through a teflon stop cock to the vaccum pump (10 nm). The flask (Fig.1) was heated in a furnace for three hours at 400°C. It was removed from the furnace and allowed to cool down ($\sim$ 45°C), stopcock was closed and vacuum-pump connection was disconnected. Required quantity of 1 (Table 1) was added by slowly releasing the pressure inside the flask. Care was taken that activated catalyst bed doesnot get exposed to atmospheric moisture. The reaction mixture was heated on oil bath with magnetic stirring. The reaction was monitored by GC.

Vapour phase: The reactor tube made of quartz glass was filled with catalyst to a length of 4cm (2g) and placed at the centre of furnace B (Fig.2). Catalyst was activated at 500°C for 1 hour in presence of nitrogen as carrier gas. 1 (0.7 ml) was introduced into the vaporizer (vaporiser temp. 180°C) through a syringe. The reaction product was condensed in the receiver and analysed by GC.

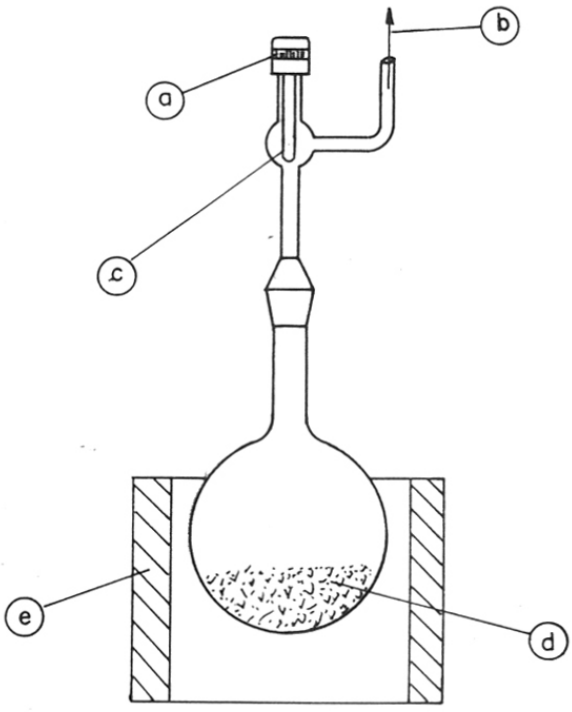


FIG -1

a) Teflon Screw
b) Suction
c) Teflon rod
d) Zeolite
e) furnace

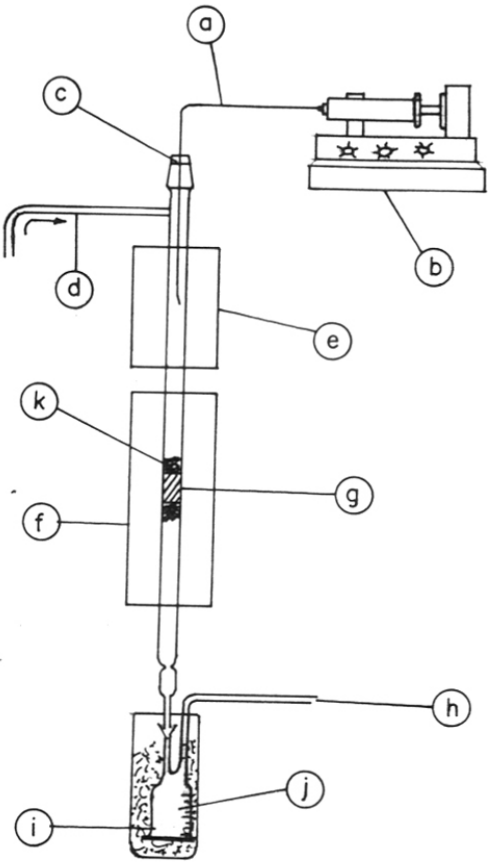


FIG. 2

a) Syringe needle
b) Syringe pump
c) Septum
d) Nitrogen gas
e) Furnace A
f) Furnace B
g) Catalyst bed
h) To aspirator
i) Ice + Salt
j) Glass wool
k) Receiver

(Table 2).

GC analysis: Product obtained was dissolved in acetone and 0.1 l of this solution was injected on carbowax column at oven temperature 70°C, injector temperature 240°C and detector temperature 300°C. Authentic samples of Δ^2-carene, p-cymene, cumene and toluene were also injected on GC column under same conditions and retention time of authentic samples and that of peaks in experiment samples were compared. Co-injection of authentic samples with experiment samples were carried out.

$AgNO_3$-impregnated TLC: 10g $AgNO_3$ was dissolved in distilled water and to it 88.3g silica gel (200 mesh) and 11.7g anhydrous $CaSO_4$ was added to form slurry. TLC plates were prepared with applicators. They were allowed to dry and then activated at 100°C for 1 hour. experimental samples were spotted on this TLC plate along with authentic Δ^3-carene and p-cymene. Plates were developed in benzene: pet-ether (10:90). Plates were sprayed with sulfuric acid:nitric acid (1:1) mixture and heated in oven at 120°C. Charring pattern and Rf value of the compounds were confirmed.

TABLE I

GC ANALYSIS OF LIQUID PHASE REACTION OF 1

Expt. No.	Catalyst[a] (g)	1 (ml)	Oil bath Temp.(°C)	time (min)	Percentage Toluene (1.4-1.5)[d]	Δ^2-Carene (2.25)[d]	Δ^3-Carene (2.45)[d]	Cumene (2.88)[d]	p-Cymene (4.7)[d]	Unidentified (5.17)[d]	(6.9)[d]	(1.57)[d]
1.	0.5[b]	4	168	160	0.7	-	3.7	24.90	27.51	19	13	2.17
2.	2.01[b]	4	213	60	2	5.88	-	-	78.67	-	-	9.3
3.	2.01[b]	3	206	60	3.37	11.0	-	-	62.0	-	-	18.38
4.	2.07[b]	4	200	60	12.39	5.5	-	-	69.0	-	-	-
5.	2.02[b]	4	222	60	5.9	10.0	-	-	59.67	-	-	17.69
6.	2.01[b]	4	212	60	6.0	5.08	-	29.99	26.4	14.6	11.38	-
7.	2.1[b]	4	208	60	5.5	3.47	-	25.34	23.90	17.9	12.08	-
8.	2.04[c]	3	180	90	1.4	5.2	-	10.16	59.71	-	-	13.18
9.	1.88[c]	3	183	30	25.67	13.72	-	6.34	55.94	-	-	-
10.	2.06[c]	3	191	45	25.72	14.77	-	-	59.5	-	-	-
11.	0.998[c]	2	215	15	-	3.75	-	-	84.69	-	-	11.03

(a): Catalyst was activated at 400°C for 3 hours under reduced pressure of 10mm

(b): "EB", ZMS-5, Pentacyl catalyst. (c): Isomerization catalyst. (d): Retention time

TABLE 2

GC ANALYSIS OF VAPOUR PHASE REACTION OF 1

Experiment No.	Temperature °C		Product %	
	Catalyst*	Vaporiser	p-Cymene	Unidentified
1	200	200	65	35
2	200	180	75	25
3	180	180	65	34
4	200	180	78	22
5	180	180	77	23

*Catalyst used was "EB", ZSM-5, Pentacyl

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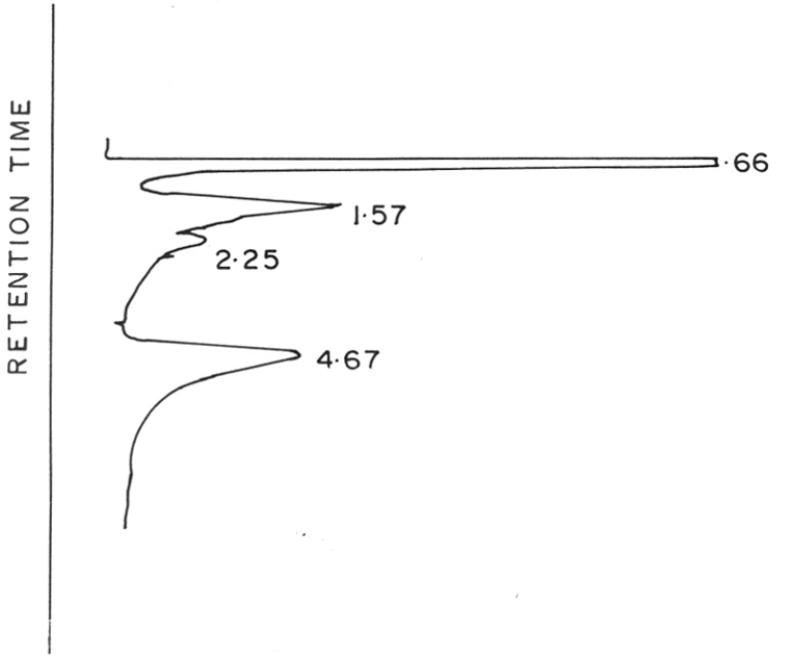
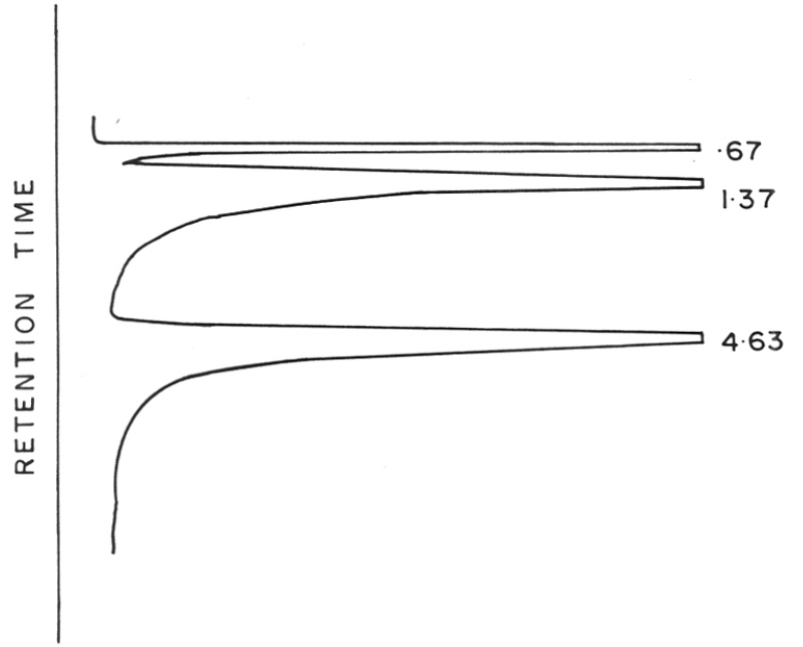


GC OF SAMPLE FROM LIQUID PHASE EXPERIMENT 11



GC OF SAMPLE FROM VAPOUR PHASE EXPERIMENT 4.

ABSTRACT

The thesis entitled "Studies in Terpenoids" deals with the chemical transformation of terpenoids namely, α-Santonin a sesquiterpene lactone and Δ^3-Carene a monoterpenoid, and isolation and structure elucidation of transformed products by physical and spectroscopic methods The thesis comprises of two chapters.

Chapter I:

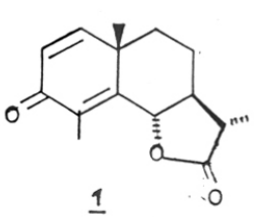
SINGLET OXIDATION OF α-SANTONIN:

α-Santonin 1 was irradiated at 200w in methanol by bubbling oxygen through the solution by using Rose Bengal as sensitizer in two different solvents, methanol and chloroform.

From the reaction product using methanol three compounds 2, 3 and 4 were obtained. Compound 2 was identified as lumisantonin by comparing its physical and spectral data with those reported for lumisantonin in the literature. Structure of compound 3 was elucidated by its spectroscopic data which was further confirmed by X-ray crystallography. Compound 4 was found to be mono hydroxy derivative of compound 3. Its structure and stereochemistry was confirmed by spectroscopic methods.

From the reaction product obtained using chloroform three compounds lumisantonin 2, 5 and 6 were obtained. Compound 5 was identified as 1,2-α, 4,5-α-diepoxy-α-santonin by spectroscopic methods including correlated

spectroscopy (300MHz, 2D). Compound 6 was identified as 1,2-β,4,5-β-diepoxy-α-santonin by spectroscopic methods.



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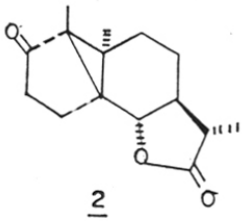

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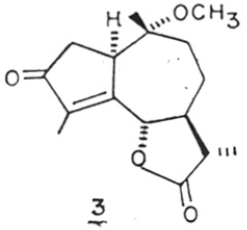

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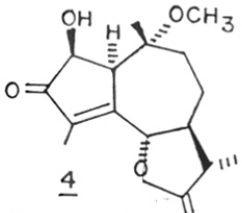

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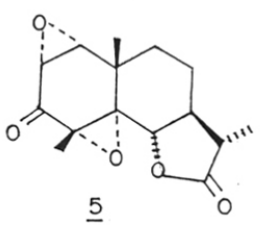

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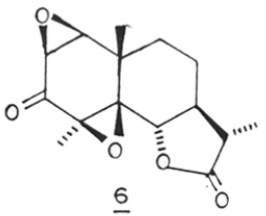

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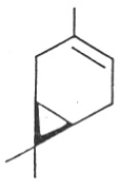
Chapter II:

CATALYTIC CONVERSION OF Δ^3-CARENE TO p-CYMENE:

Δ^3-Carene 7, obtained from terpentine was purified by distillation and subjected to dehydrogenation using different zeolite catalysts. The reaction proceeds with the formation of a number of compounds. Parameters such as temperature of reaction, catalyst properties and substrate: catalyst concentration were studied in order to get the maximum yield of p-cymene 8, the target molecule of this reaction. Estimation of p-cymene and unreacted Δ^3-carene was carried out by Gas Liquid Chromatography. In the study two approaches were followed 1. liquid phase reactions and 2. vapour phase reactions.

The liquid phase catalytic reactions were optimised to get nearly 84% yield, while the vapour phase yielded

maximum 78% p-cymeme. Without optimization the two methods were compared.



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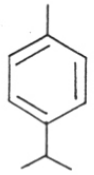

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S.S. Sawant.

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