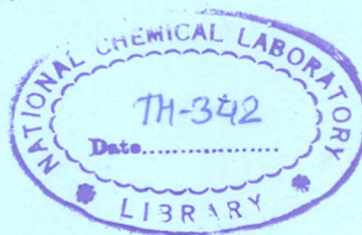


ISOLATION AND SOME INTERESTING TRANSFORMATIONS OF TERPENIC COMPOUNDS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

COMPUTERISED



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1981

Dedicated To

My Father

Shri Gajanan Narayan Bhat

And My Mother

Smt. Nagaveni Gajanan Bhat

ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to Dr. G.H. Kulkarni, Scientist, National Chemical Laboratory, Poona, for his valuable guidance throughout the course of this investigation. I am also thankful to Dr. H.B. Mitra, Deputy Director, National Chemical Laboratory, Poona, for his keen interest and constant encouragement.

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(N.G. Bhat)

National Chemical Laboratory

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August 1981.

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GENERAL INTRODUCTION

GENERAL INTRODUCTION

The study of natural products, derived from the Plant Kingdom, forms an important aspect of organic chemistry. Studies of natural products, not only increase and deepen our scientific knowledge but also provide a basis for highly developed industry.

The importance of the study of natural products in India can hardly be over-emphasised, especially in view of the fact that India possesses a wealth of most abundant and diversified flora. This is but natural as this subcontinent is fortunate in having a variety of climatic and soil conditions, suitable for healthy growth of plants, herbs, grasses etc.

A great progress has been achieved in the chemistry of "Natural Products" as a result of the extensive work carried out by organic chemists in this field. Highly effective separation techniques such as precise fractionation, elaborate column chromatography, high pressure liquid chromatography, gas-liquid and thin-layer chromatography and the availability of modern physical methods for structure elucidation may be attributed to this phenomenal progress achieved during the last few years. The advent of gas-liquid, high pressure liquid and thin-layer

2

chromatography on preparative scale has opened up possibilities for the isolation of new compounds and the reaction products in the purest form. The physical methods viz., ultraviolet, infrared, nuclear magnetic resonance spectroscopy, optical rotatory dispersion, circular dichroism, X-ray crystallography and mass spectrometry have revolutionised the successful elucidation of the structure and absolute configuration of organic compounds. Further during this period, development of many new reagents and reactions have also helped in this work. The better understanding of the biogenetic pathways and organic chemical mechanistic theories also aided to arrive at the correct conclusions during the structure elucidation. A brief summary of the present work is described below.

The research work carried out under the title "Isolation and some interesting transformations of terpenic compounds" deals with four main aspects viz.,

- (A) Conversion of (+) car-3-ene (I) into methyl (+) gla-chrysanthemate (II) and its 3-substituted vinyl analogues possessing 1R or 1S configuration.
- (B) Prins reaction on (+) car-3-ene (I) and oxidation studies on some of the products obtained from Prins reaction.

(C) Transformations of (+) car-3-ene (I) leading to methyl 1R and dl-cis-2,2-dimethyl-3-(2-oxopropyl)-cyclopropane carboxylate (XLIX), important intermediates in the synthesis of insecticides of the "Synthetic Pyrethroids" group.

(D) Isolation of taraxasteryl acetate (LVIII) from the hexane extract of the leaves of the Costus plant, Saussurea Lappa Clarke and Prins reaction on taraxasteryl acetate (LVIII).

Many plants are known to possess insecticidal property. Amongst them, the prominent one is Chrysanthemum Cinerariaefolium¹ (Compositae family). The insecticidal property of the dried flowers of this plant has been known from ancient times. Pyrethrum represents the dried flowers of the plant, Chrysanthemum Cinerariaefolium. Detailed chemical examination of the constituents of pyrethrum extract showed^{2,3,4} that the insecticidal property associated with the flowers of the plant is due to the presence of a mixture of esters viz., pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I and jasmolin II (for structures please see pages 29&30). These compounds are esters of (+) trans chrysanthemic acid and (+) trans pyrethric acid². Later on, many new esters of (+) trans chrysanthemic acid have been prepared and found

to possess insecticidal property. It has also been found⁵ that esters of (+) 1R-trans and (+) 1R-cis-chrysanthemic acids are potent insecticides while the esters of the corresponding optical antipodes are not active, or much less active.

The importance of this class of insecticides is due to its unique property of having low mammalian toxicity and higher insecticidal activity. Because of these properties, "Pest Control Agents" of this class are becoming very popular all over the world, inspite of their high cost.

Though many methods for the preparation of chrysanthemic acid have been reported^{6,7} in literature, most of them lack selectivity and thus resulted in the formation of racemic mixture, the separation of which is a tedious job. Efforts have already been made to synthesise, selectively, the (+) 1R-trans⁸ and (+) 1R-cis^{9,10} chrysanthemic acids from naturally occurring compounds, mainly from (+) car-3-ene (I).

(+) Car-3-ene (I), a monoterpene, is an abundantly occurring cheap indigenous material and is mainly considered as a by-product of Pine oil (Pinus longifolia). Efforts have been already made to utilise this by-product for good uses, for example, by converting it into (+) trans-

chrysanthemic acid¹¹, a component of natural pyrethrins and (-) menthol, a very useful chemical used in perfumery and drugs.

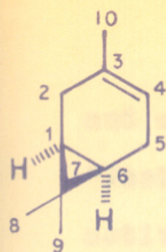
In continuation of the efforts in this direction, (+) car-3-ene (I) has now been utilised for the preparation of methyl (+) cis-chrysanthemate (II), possessing the desired 1R configuration.

CHAPTER 1 describes the work regarding the preparation of methyl 1S(+) cis-2,2-dimethyl-3-(2-phenylprop-1-enyl)-cyclopropane carboxylate (III) from (+) car-3-ene (I). The keto aldehyde (V) obtainable from (+) car-3-ene (I), via trans carane diol (IV) in good yields, on Grignard reaction with methyl magnesium iodide afforded the diol (VI) which, on Jones chromic acid oxidation furnished the hydroxy ketone (VII). Baeyer-Villiger oxidation of the hydroxy ketone (VII) gave the hydroxy acetate (VIII) which, on saponification with methanolic potash afforded the crystalline diol (IX). Jones chromic acid oxidation of the diol (IX) furnished (+) dihydrochrysanthemolactone (X) and hydroxy acid (XI, R = H). The acid (XI, R = H) could also be obtained from the lactone (X) by saponification with alkali. Esterification of the acid (XI, R = H) followed by acid catalysed dehydration¹² of the resulting ester (XI, R = CH₃) gave the methyl 1R(+) cis-chrysanthemate (II).

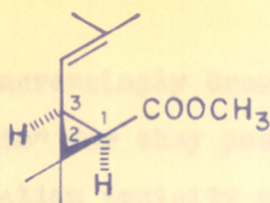
Dehydration of the hydroxy acetate (VIII) with POCl_3/Py afforded a mixture of two isomeric unsaturated acetates (XII) and (XIII) which were separated by chromatography over silicic acid impregnated with 10% silver nitrate. Saponification of the unsaturated acetate (XII) gave the chrysanthemyl alcohol (XIV). Jones chromic acid oxidation of the alcohol (XIV) followed by esterification of the resulting acid afforded methyl 1R(+) cis-chrysanthemate (II).

Treatment of the hydroxy ketone (VII) with p-toluene sulphonic acid¹² (PTS) afforded the unsaturated ketone (XV) which, on Grignard reaction with phenyl magnesium bromide furnished the alcohol (XVI), as a mixture of diastereomers. Potassium permanganate oxidation of the alcohol (XVI) in acetone-acetic acid-water mixture gave the keto diol (XVII) in the neutral portion and the mixture of diastereomeric hydroxy acids (XVIII, R = H) in the acid part. Esterification of the hydroxy acid (XVIII, R = H) gave the mixture of diastereomeric hydroxy methyl esters (XVIII, R = CH_3) which on dehydration¹² with PTS afforded the desired unsaturated ester (III).

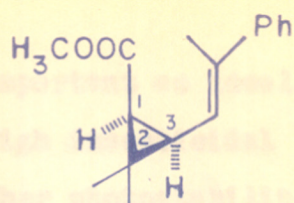
Synthetic pyrethroids (biologically active chrysanthemates and modified cyclopropane carboxylic acid esters of various alcohols), related to natural pyrethrins



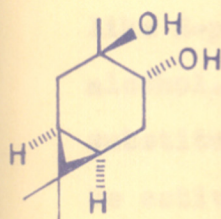
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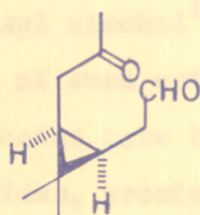
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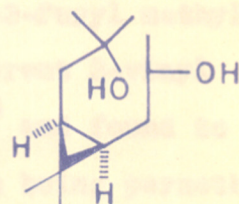
III



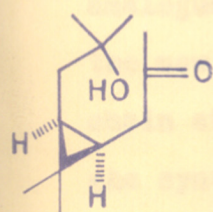
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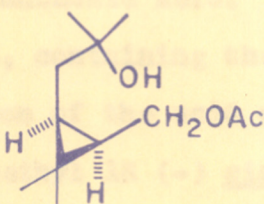
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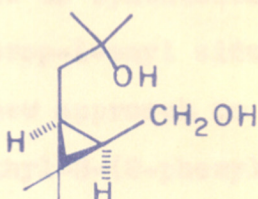
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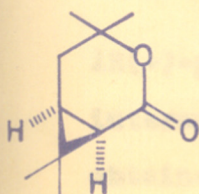
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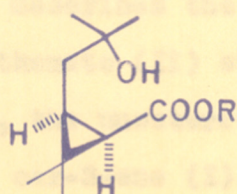
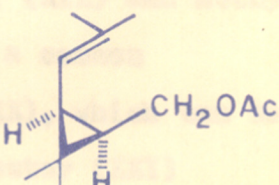
VIII



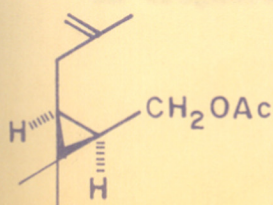
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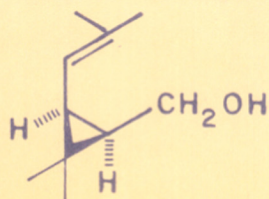
X

XI, R = H; R = CH₃

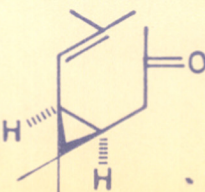
XII



XIII



XIV



XV

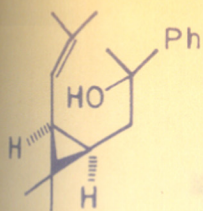
and cinerins are increasingly becoming important as ideal "Pest Control Agents" for they possess high insecticidal activity, low mammalian toxicity and higher photostability¹³. Chemically, they are the esters of 2,2-dimethyl-3-vinyl substituted cyclopropane carboxylic acids with alcohols like 3-phenoxy benzyl alcohol¹⁴ or 5-benzyl-3-furyl methyl alcohol. A number of such esters with different 3-vinyl substituted side chains have been prepared¹⁵ and found to be active insecticides, prominent among them being permethrin and cypermethrin. Recently, in our laboratory, Mane et al.^{16,17} have synthesised the diphenyl vinyl and methyl phenyl vinyl analogues of chrysanthemic acid. With a view to synthesise the new pyrethroid, containing the 2-phenylprop-1-enyl side chain at C₃-position of the acid moiety, a new approach to the synthesis of methyl 1R (-) cis-2,2-dimethyl-3-(2-phenylprop-1-enyl) cyclopropane carboxylate (XIX) was undertaken starting from (+) car-3-ene (I).

CHAPTER II describes the synthesis of (XIX) and methyl 1R(+)-cis-chrysanthemate (II) starting from a common intermediate viz., the unsaturated ketone (XX), which can be obtained from (+) car-3-ene (I). The keto ester (XXI) obtainable from (I) via the trans carane diol (IV), in good yields was converted to the ethylene ketal ester (XXII) which, on Grignard reaction with methyl magnesium iodide furnished

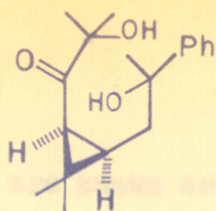
the ketal alcohol (XXIII). Dehydration and deketalisation of (XXIII) with PTS in benzene afforded a mixture of two isomeric unsaturated ketones viz., (XX) and (XXIV), in which the former predominated. These were separated by chromatography. Action of phenyl magnesium bromide on (XX) gave the alcohol (XXV). The unsaturated alcohol (XXV), on potassium permanganate oxidation gave the keto diol (XXVI) and the hydroxy acid (XXVII, R = H). Esterification of the hydroxy acid (XXVII, R = H) followed by dehydration¹² of the resulting ester (XXVII, R = CH₃) with PTS in benzene afforded the unsaturated ester (XIX).

The acid (XXVIII) obtainable from the ester (XIX) was esterified with *m*-phenoxy benzyl alcohol to furnish the active insecticidal ester (XXIX). Treatment of the unsaturated ketone (XX) with methyl magnesium iodide afforded the alcohol (XXX) which, on potassium permanganate oxidation gave the keto diol (XXXI) and the hydroxy acid (XI, R = H). Esterification of the hydroxy acid (XI, R = H) followed by dehydration¹² of the resulting ester (XI, R = CH₃) furnished the methyl 1R(+)-cis chrysanthemate (II).

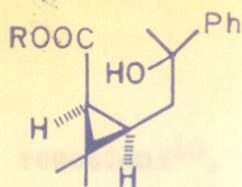
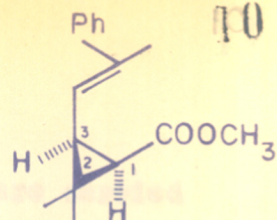
The work presented in CHAPTER III describes the Prins reaction on (+) car-3-ene (I) and oxidation studies on some of the products obtained from Prins reaction. Reactions of olefins with formaldehyde, other aldehydes and



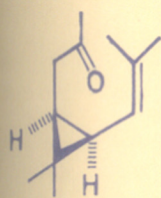
XVI



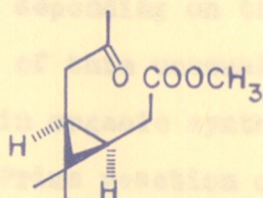
XVII

XVIII, R = H; R = CH₃

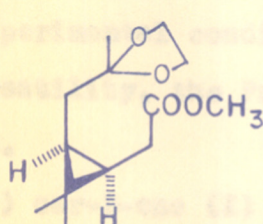
XIX



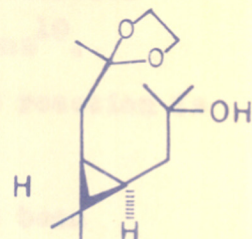
XX



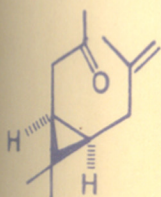
XXI



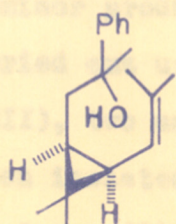
XXII



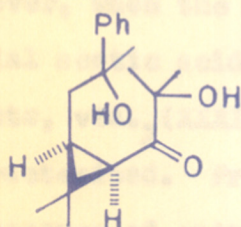
XXIII



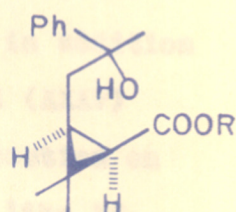
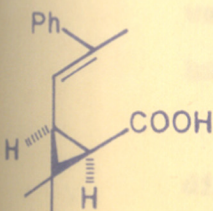
XXIV



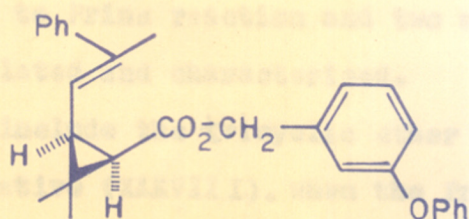
XXV



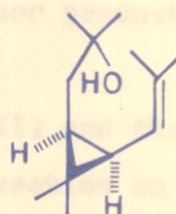
XXVI

XXVII, R = H;
R = CH₃-

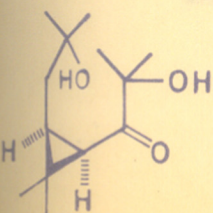
XXVIII



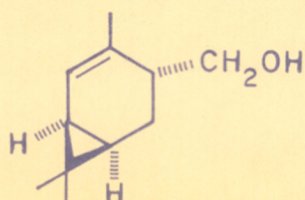
XXIX



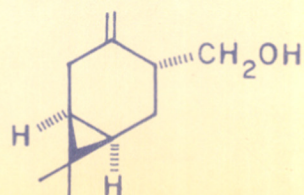
XXX



XXXI



XXXII



XXXIII

ketones are known as Prins reactions¹⁸. They are carried out in the presence of inorganic acids, acetic acid or metal chlorides as catalysts and the major products consist of a 1,3-dioxane, 1,3-glycol or an unsaturated alcohol depending on the experimental conditions¹⁹. Because of this unusual versatility, the Prins reaction is useful in organic syntheses.

Prins reaction on (+) car-3-ene (I) has been reported^{20,21} to give mainly the endo alcohol (XXXII) along with the corresponding exo double bond isomer (XXXIII) as the minor product. However, when the Prins reaction was carried out using glacial acetic acid,^{22,23} in addition to (XXXII), two more products, viz., (XXXIV) and (XXXV) have been isolated and characterised. Prins reaction on (+)-car-3-ene (I) in the presence of catalysts like BF_3 and H_2SO_4 gave the ether (XXXVI)²². In order to investigate the minor products formed, (+) car-3-ene (I) was subjected to Prins reaction and two new minor products have been isolated and characterised.

These include the tricyclic ether (XXXVII) and the dioxane derivative (XXXVII.I). When the Prins reaction on (+) car-3-ene (I) was carried out at slightly higher temperature (160-170^o/bath) and for prolonged period, another acetate could be isolated, identified as 2-

acetoxy methyl-p-menth- $\Delta^{5,8}$ diene (XXXIX).

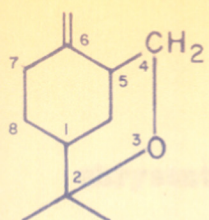
Jones chromic acid oxidation of the endo alcohol (XXXII) furnished a mixture which was separated into acidic and neutral parts. The acid (XL, R = H) was converted into its methyl ester (XL, R = CH₃). The neutral portion after chromatographic purification afforded the ester (XLI) and conjugated ketone (XLII), identified by spectral data. Jones chromic acid oxidation of the tricyclic ether (XXXVII) gave mainly a mixture of two products which was separated into acidic and neutral parts. The neutral part was identified as a solid nor-ketone (XLIII). The acid (XLIV, R = H) was esterified to afford the methyl ester (XLIV, R = CH₃). The nor-ketone (XLIII) was reduced with lithium aluminium hydride to furnish the solid alcohol (XLV, R = H) which, on acetylation (Ac₂O/Py) gave the liquid acetate (XLV, R = Ac).

As already mentioned, (+) car-3-ene (I) is an abundantly occurring bicyclic monoterpene hydrocarbon. This hydrocarbon is known to undergo a variety of reactions, such as Friedel-Crafts²¹ type acylation, Prins reaction²¹, epoxidation²⁴ etc. The stereochemistry of these reactions has been studied extensively. Similarly, the other two

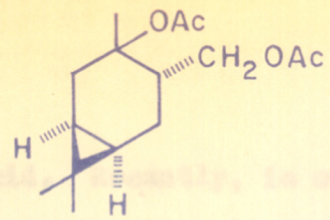
double bond isomers of (+) car-3-ene (I) viz., car-2-ene and car-4-ene have been subjected to a variety of reactions.^{21,25,26} With a view to ascertain the effect of the nature of the substituent at C₄-position on the cleavage of the C₂C₃ epoxide of car-2-ene derivatives, the epoxidation of the methyl ester (XL, R = CH₃) and its rearrangement under mild alkaline and acidic conditions were undertaken. Epoxidation of the methyl ester (XL, R = CH₃) was carried out using perbenzoic acid to give the corresponding α -epoxide (XLVI). This α -epoxide (XLVI) was found to rearrange on alumina to give the rearranged hydroxy esters, identified as (XLVII) and (XLVIII). The ester (XLVII) could also be obtained as one of the products from (XLVI) under acidic conditions. These epoxidation studies have been described in CHAPTER III of the thesis.

CHAPTER IV describes the work regarding the preparation of methyl-1R and dl-cis-2,2-dimethyl-3-(2-oxopropyl) cyclopropane carboxylate (XLIX) and also the δ -lactone of 2,2-dimethyl-3-(2-hydroxypropyl)-cis-cyclopropane-1-carboxylic acid (L).

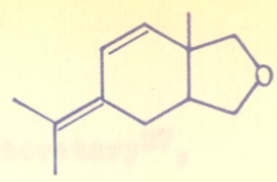
Methyl 1R-cis-2,2-dimethyl-3-(2-oxopropyl)-cyclopropane carboxylate (XLIX) is an important intermediate from which Japanese⁹ workers have synthesized (+) cis-



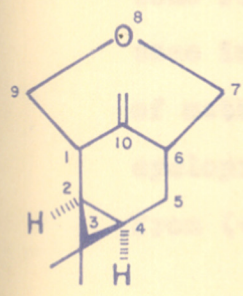
XXXIV



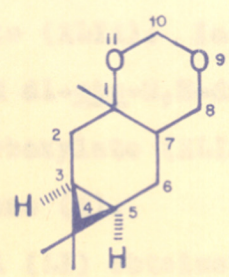
XXXV



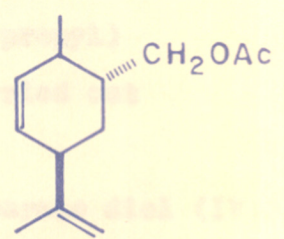
XXXVI



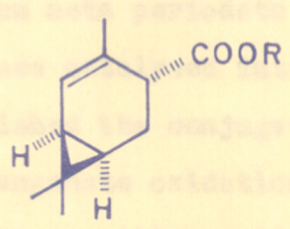
XXXVII



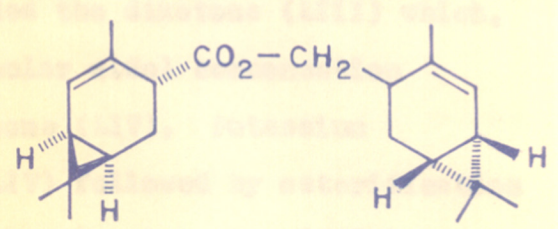
XXXVIII



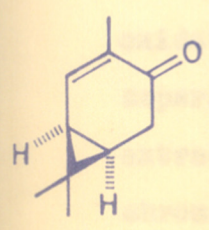
XXXIX



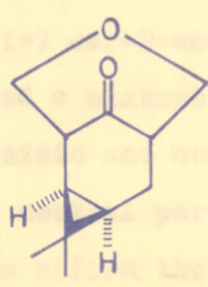
XL, R=H; R=CH₃



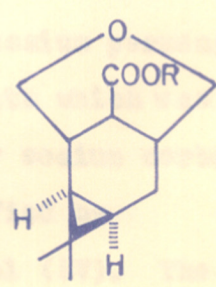
XLI



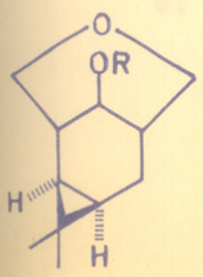
XLII



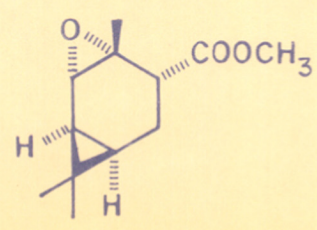
XLIII



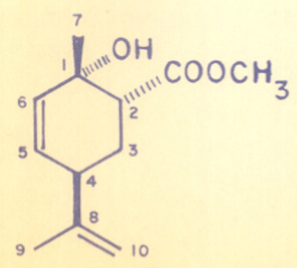
XLIV, R=H; R=CH₃



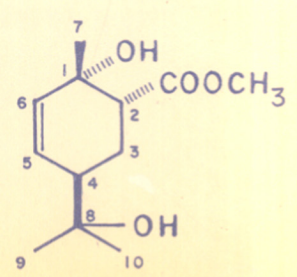
XLV, R=H; R=Ac



XLVI



XLVII



XLVIII

chrysanthemic acid. Recently, in our laboratory²⁷, a new synthetic pyrethroid called "Indothrin" and also some related insecticides have been synthesised from the same intermediate (XLIX). In this connection, the syntheses of methyl 1R and dl-cis-2,2-dimethyl-3-(2-oxopropyl) cyclopropane carboxylate (XLIX) have been carried out from (+) car-3-ene (I).

The ketol (LI) obtainable from trans carane diol (IV), on Grignard reaction with methyl magnesium iodide gave the diol (LII). Oxidative cleavage of the diol (LII) with sodium meta periodate afforded the diketone (LIII) which, on base catalysed intramolecular aldol condensation furnished the conjugated ketone (LIV). Potassium permanganate oxidation of (LIV) followed by esterification of the resulting acid gave the dl-keto ester (XLIX).

The unsaturated ketone (XX), mentioned earlier and obtainable from (+) car-3-ene (I), on potassium permanganate oxidation afforded a mixture of two products which was separated into acidic and neutral parts by sodium carbonate extraction. The neutral portion was purified by chromatography to afford the diketo alcohol (LV). The acidic part, on esterification with an ethereal solution of diazomethane afforded the 1R-keto ester (XLIX).

It has been reported²⁸ that some esters of 1R-cis-2,2-dimethyl-3-(prop-1-enyl) cyclopropane carboxylic acid are found to be more active than the corresponding esters of chrysanthemic acid. In this connection, the synthesis of 6-lactone of 1R-cis-2,2-dimethyl-3-(2-hydroxy propyl)-cyclopropane carboxylic acid (L) was initially undertaken starting from the unsaturated ketone (XX), with a view to convert ultimately the lactone (L) into active insecticides. The unsaturated ketone (XX) on reduction with sodium borohydride gave the alcohol (LVI, R = H) which, on acetylation furnished the unsaturated acetate (LVI, R = Ac). Oxidation of (LVI, R = Ac) with potassium permanganate afforded an acid which was characterised through its methyl ester (LVII). Saponification of (LVII) followed by treatment of the resulting hydroxy acid with p-toluene sulphonic acid in benzene furnished the liquid nor-lactone (L).

CHAPTER V deals with the isolation of taraxasteryl acetate (LVIII) from the leaves and stalks of costus plant, Saussurea Lappa Clarke and also describes the Prins reaction on taraxasteryl acetate (LVIII). The costus plant, Saussurea Lappa Clarke, belonging to the Compositae family, is grown at high altitudes in Kashmir and the hill districts of Punjab²⁹. From the hexane extract of the leaves and stalks of this plant, taraxasteryl acetate (LVIII) was

isolated as per the procedure already described³⁰.

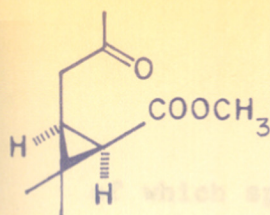
Prins reaction on taraxasteryl acetate (LVIII) was carried out using paraformaldehyde and glacial acetic acid (72 hr. refluxing). Three products have been isolated and characterised. These included 3 β -acetoxy-20-acetoxy-28-acetoxy-methyl taraxastane (LIX), 3 β -acetoxy-21-acetoxy-methyl- ψ -taraxastene (LX) and 3 β -acetoxy-28-acetoxymethyl- ψ -taraxastene (LXI). The double bond isomerised product of taraxasteryl acetate (LVIII) viz., ψ -taraxasteryl acetate (LXII) was also isolated during Prins reaction on (LVIII) and was characterised by comparative spectral data (IR, PMR).

During the course of these investigations, liberal use of modern techniques such as infrared, ultraviolet, nuclear magnetic resonance, mass spectroscopy and thin-layer chromatography has been made. For the isolation of the compounds, column chromatographic technique using adsorbants like alumina, silica gel and silica gel impregnated with silver nitrate is employed. However, due to the non-availability of high pressure liquid chromatography, in this laboratory, we could not make use of this latest technique.

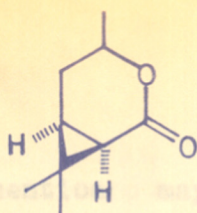
For the sake of brevity, a general introduction to terpenoids has been avoided. The subject has already been covered adequately by a number of well-known publications



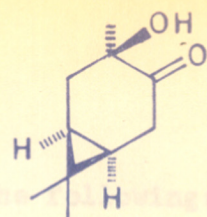
547.596/.599(043)
BHA



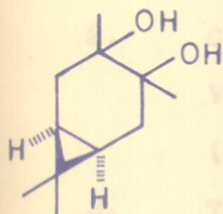
XLIX



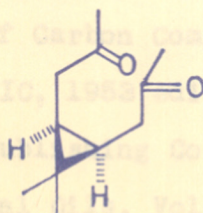
L



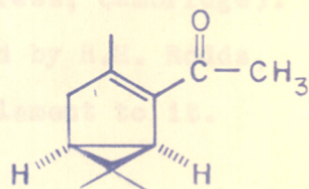
LI



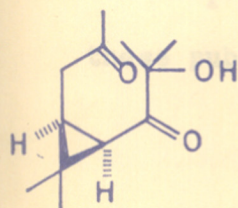
LII



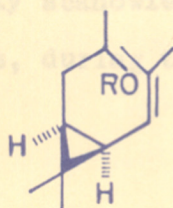
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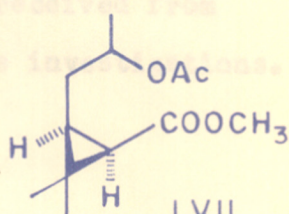
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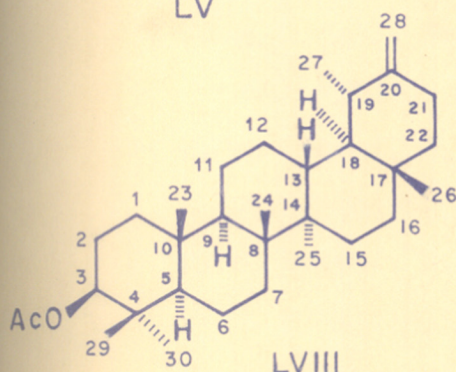
LV



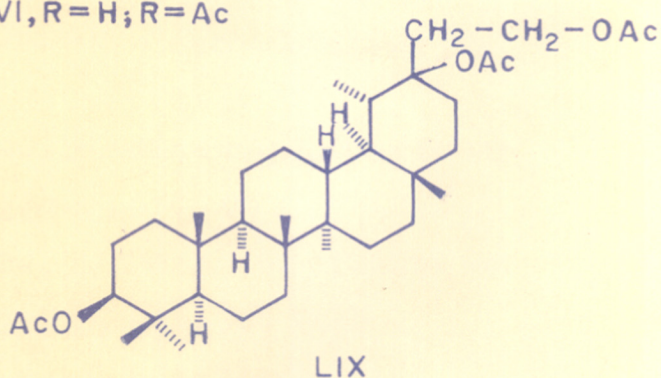
LVI, R=H; R=Ac



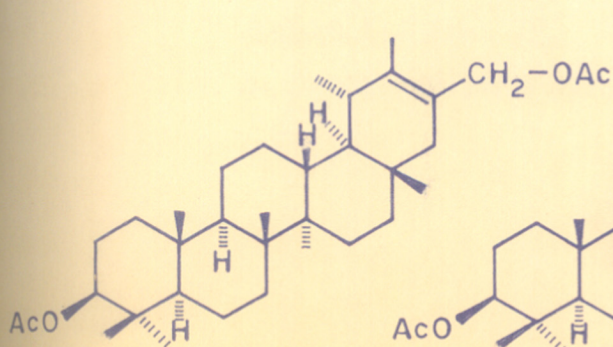
LVII



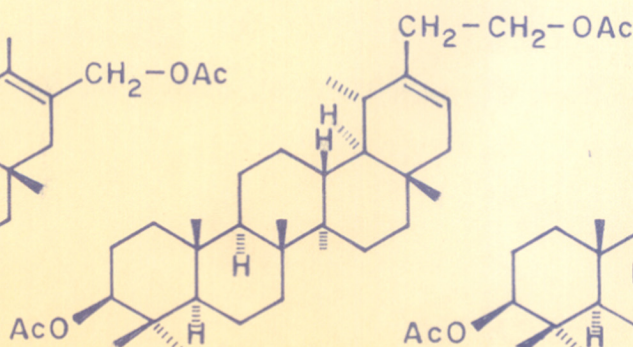
LVIII



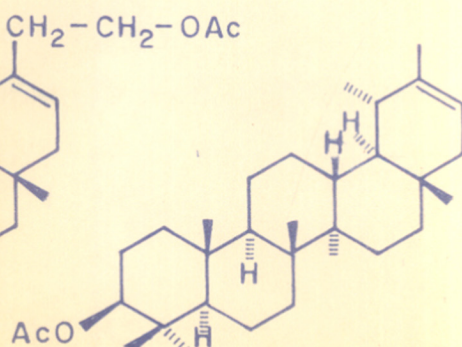
LIX



LX



LXI



LXII

of which special mentioned may be made of the following:

1. Terpenes by J.L. Simonsen and W.C.J. Ross,
Vol. 1-5, 1957 edition (University Press, Cambridge).
2. Chemistry of Carbon Compounds, edited by R.H. Rodds,
Vol. IIB, IIC, 1953 edition and supplement to it.
(Elsevier Publishing Co.).
3. The Essential Oils, Vol. 1-6, by E. Guenther
(D. Van Nostrand Co. Inc. N.Y.).

I gratefully acknowledge the help I received from
these publications, during the course of the investigations.

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GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All temperatures are recorded on the centigrade scale.
3. Unless otherwise stated, all rotations were in chloroform solutions. Concentrations are expressed in g/100 ml of the solution.
4. The ultraviolet spectra were recorded in ethanol solution on a Perkin-Elmer 350 and Carl-Zeiss 445069 ratio recording spectrophotometers.
5. The infrared spectra of liquids were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer infracord spectrophotometer, model 137-B using sodium chloride optics.
6. The PMR spectra were taken in carbontetrachloride solution, unless otherwise mentioned, using tetramethylsilane as the internal reference on a A-60 and T-60 MC Varian instruments and the chemical shifts are measured in τ units.
7. The mass spectra were recorded on a CEC-21-110B mass spectrometer.
8. Acid washed activated alumina standardised as per Brockmann's procedure and silicic acid for chromatographic purposes, after activation, were employed for column chromatography.

9. TLC analyses were carried out on glass plates coated with a mixture of silicic acid and plaster of Paris (85:15; 200 mesh), and activated at 120° for 3 hr. Solvent systems used were pet.ether, benzene, ethyl acetate and acetone or a suitable mixture of two or more of these solvents, depending upon the nature of the compounds. The plates were developed by keeping in an iodine chamber or by spraying with H₂SO₄.
10. Numbers given to charts, figures and structures in each chapter of the thesis refer to that particular chapter only.
11. References pertaining to each chapter are given at the end of that particular chapter.
12. Unless otherwise stated, all solutions were dried over anhydrous sodium sulphate.
13. Unless otherwise stated, all b.ps. refer to the bath temperatures.
14. In the list of IR bands given in the experimental section, the significant bands described in the theory are underlined.
15. A brief summary of each chapter is given at the beginning of that chapter.
16. In the description of PMR signals, the abbreviations br.s, br.d and br.m mean broad singlet, broad doublet and broad multiplet respectively.
17. Infrared bands are expressed in frequency $\nu = \text{cm}^{-1}$.
18. The thick liquid compounds which were found to be unstable above 200°(bath)/1 mm were not purified by distillation.

CHAPTER - I

STEREOSPECIFIC CONVERSION OF (+) CAR-3-ENE INTO
METHYL (+) CIS-CHRYSANTHEMATE AND METHYL IS CIS-
2,2-DIMETHYL-3-(2-PHENYLPROP-1-ENYL)-CYCLOPROPANE
CARBOXYLATE

S U M M A R Y

The trans carane diol (II) obtainable from (+)-car-3-ene (I), on oxidation with sodium meta periodate, gave the keto-aldehyde (III) which, on Grignard reaction with methylmagnesium iodide, afforded the diol (IV). Jones chromic acid oxidation of the diol (IV) furnished the hydroxy ketone (V). Baeyer-Villiger oxidation of the hydroxy ketone (V) using perbenzoic acid gave the hydroxy acetate (VI) which, on saponification with methanolic potash afforded the diol (VII). Jones chromic acid oxidation of the diol (VII) furnished the lactone (VIII) and hydroxy acid (IX, R = H). The acid (IX, R = H) could also be obtained from the lactone (VIII) by saponification with alkali. Esterification of the acid (IX, R = H) followed by acid catalysed dehydration of the resulting ester (IX, R = CH₃) gave the methyl (+) cis-chrysanthemate (X).

Dehydration of the hydroxy acetate (VI), with POCl₃/Py afforded a mixture of the two unsaturated isomeric acetates (XI) and (XII), which were separated by chromatography. The endo-isomer (XI) was saponified with methanolic potash to get the chrysanthemyl alcohol (XIII). Jones chromic acid oxidation of the alcohol (XIII), followed by esterification of the resulting chrysanthemic acid (XIV) gave the methyl (+) cis-chrysanthemate (X) in fair yields.

Dehydration of the hydroxy ketone (V) with p-toluene sulphonic acid (PTS) gave the unsaturated ketone (XV) which, on Grignard reaction with phenyl magnesium bromide afforded a mixture of diastereomeric unsaturated alcohols (XVI). The diastereomeric unsaturated alcohols (XVI), on oxidation with potassium permanganate furnished the keto diol (XIX) in the neutral part and a mixture of diastereomeric hydroxy acids (XVII, R = H) which, on esterification with an ethereal solution of diazomethane gave a mixture of diastereomeric hydroxy methyl esters (XVII, R = CH₃). Dehydration of hydroxy methyl esters (XVII, R = CH₃) with PTS afforded methyl 1S (+)-cis-2,2-dimethyl-3-(2-phenylprop-1-enyl) cyclopropane carboxylate (XVIII).

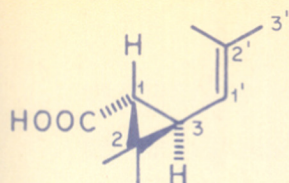
I N T R O D U C T I O N

Pyrethrum represents the dried flowers of Chrysanthemum cinerariaefolium Vis (Pyrethrum cinerariaefolium, Trev), a member of the Compositae family. The powder of flowers has been used as an insecticide from ancient times. The plant appears to have originated from the Middle and North East. At present Kenya is the major producing country. The discovery of pyrethrum as an insecticide, its production and history of its uses are discussed by Gnsdinger¹ and Shepard².

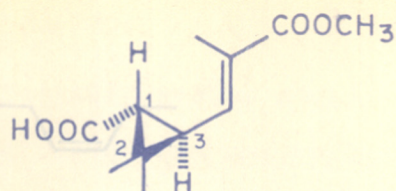
The insecticidal principles in pyrethrum are called "Pyrethrins" and for a long time have been considered harmless to mammals and plants while very toxic to insects. Today they are becoming increasingly important as insect control agents because they possess a unique combination of desirable properties including exceptionally good insecticidal activity, low mammalian toxicity and rapid biodegradation. These features, combined with their broad spectrum of insecticidal activities and an unusually rapid paralytic effect - "knock down" - on flying insects, have made them commercially successful and also environmentally safe. However, their uses are limited mainly by high cost and also by their photo-instability.

These valuable properties of pyrethrum stimulated detailed examination of the chemical constitution of the active principles in the first quarter of 20th century. Staudinger and Ruzicka³, for the first time, isolated two active compounds from the pyrethrum extract and identified them as esters of (+) trans-chrysanthemic acid and (+) trans-pyrethric acid with the ketol, pyrethrolone and named them as pyrethrin I and pyrethrin II respectively. Later on, four more active esters viz., cinerin I, cinerin II⁴, jasmolin I and jasmolin II^{5,6,7} were also isolated from pyrethrum extract. Thus the insecticidal activity of pyrethrum is attributed to the presence of these six constituents. Out of these esters, pyrethrin I, cinerin I and jasmolin I contain (+) trans-chrysanthemic acid as the common acid moiety while pyrethrin II, cinerin II and jasmolin II contain (+) trans-pyrethric acid (a substituted (+) trans-chrysanthemic acid) as the common acid moiety. This class of active insecticidal esters, occurring in pyrethrum was named as "pyrethroids". Now the word "Pyrethroid" is not limited to natural pyrethrins alone but is applied also to biologically active chrysanthemates and modified cyclopropane carboxylic acid esters of various alcohols.

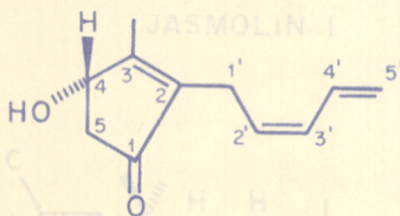
Thus the monoterpene (+) trans-chrysanthemic acid viz., Δ^2 ,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropane-1-



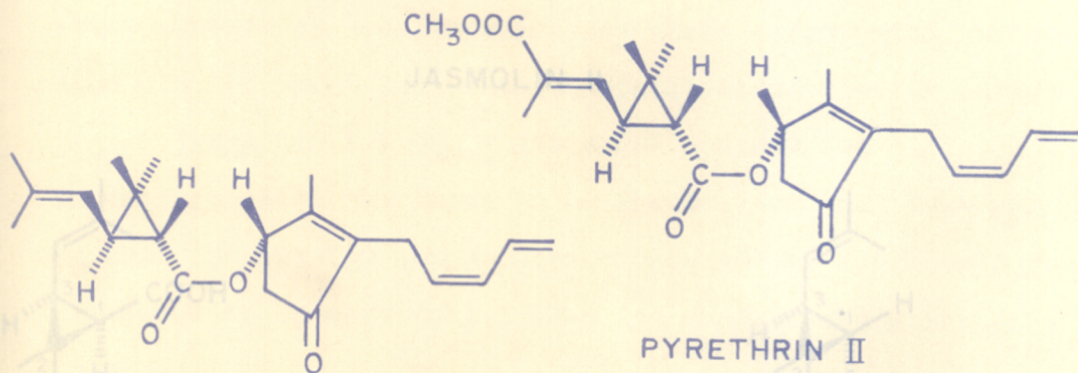
1R (+) TRANS CHRYSANTHEMIC
ACID



1R (+) TRANS PYRETHRIC
ACID

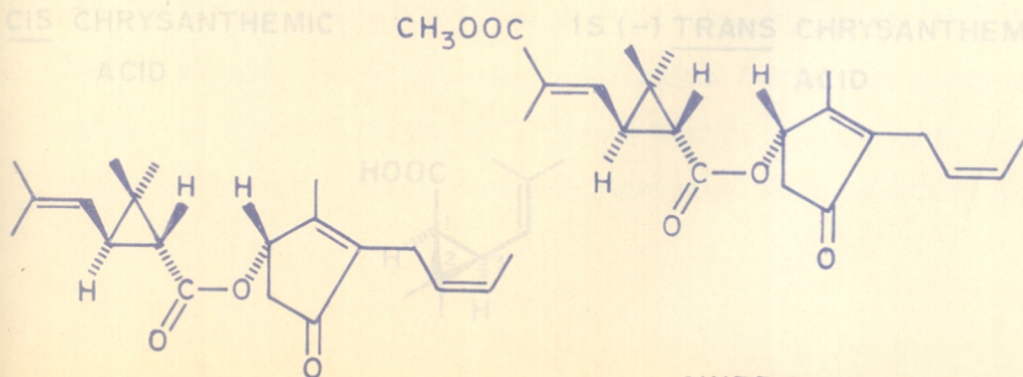


(+) PYRETHROLONE



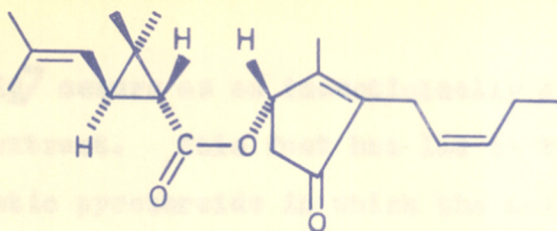
PYRETHRIN I

PYRETHRIN II

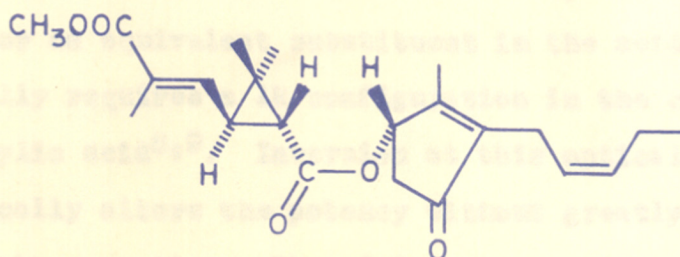


CINERIN I

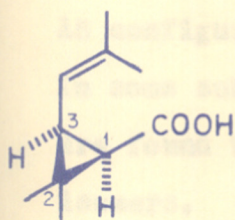
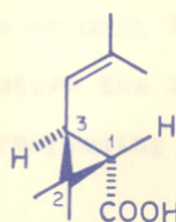
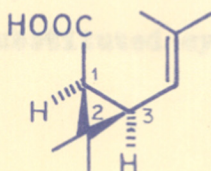
CINERIN II



JASMOLIN I



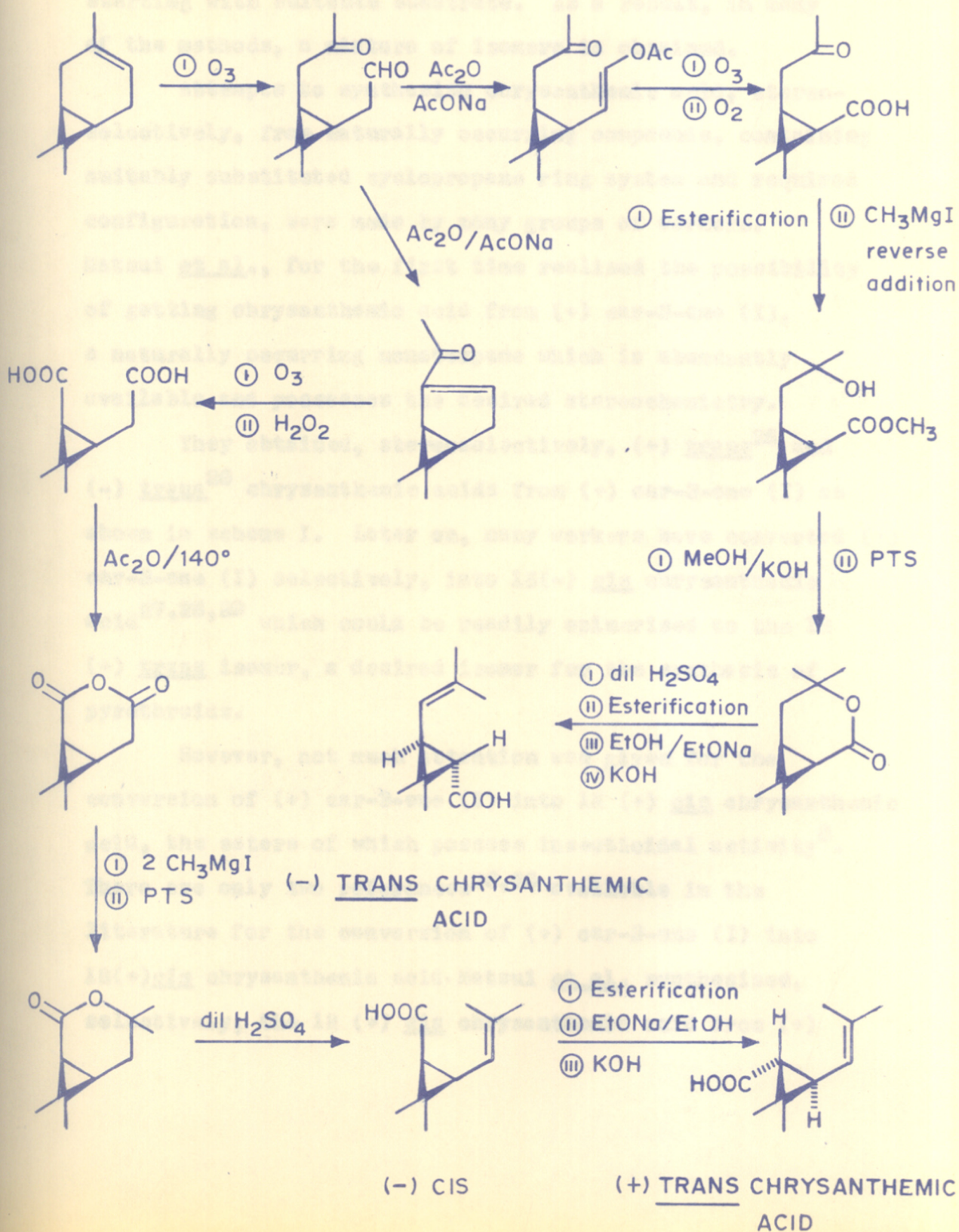
JASMOLIN II

1R (+) CIS CHRYSANTHEMIC
ACID1S (-) TRANS CHRYSANTHEMIC
ACID1S (-) CIS CHRYSANTHEMIC ACID

carboxylic acid⁷ occurs as an insecticidally active ester in pyrethrum extract. This fact has led to the preparation of many synthetic pyrethroids in which the acid moiety is (+) trans-chrysanthemic acid.

To possess high insecticidal activity, pyrethroids must have a precise steric relationship between an unsaturated centre in the alcohol moiety and gem dimethyl group or an equivalent substituent in the acid moiety. This generally requires a 1R configuration in the cyclopropane carboxylic acid^{8,9}. Inversion at this optical centre drastically alters the potency without greatly changing the physical properties. Thus (+) trans and (+) cis-chrysanthemic acids possess 1R configuration and their esters with suitable alcohols are found to be active insecticides whereas esters of (-) trans and (-) cis acids which possess the 1S configuration are found to be inactive or much less active. In some substituted chrysanthemic acid esters the 1R-cis esters are found to be more active than the corresponding 1R-trans¹⁰ isomers.

A number of ingenious syntheses of the racemic chrysanthemic acids¹¹⁻¹³ and also of the (+) trans acid^{14,19} are on record, so also their resolution forms the subject matter of several patents²⁰⁻²³ and papers²⁴. In most of these methods, a substituted cyclopropane ring is built up,



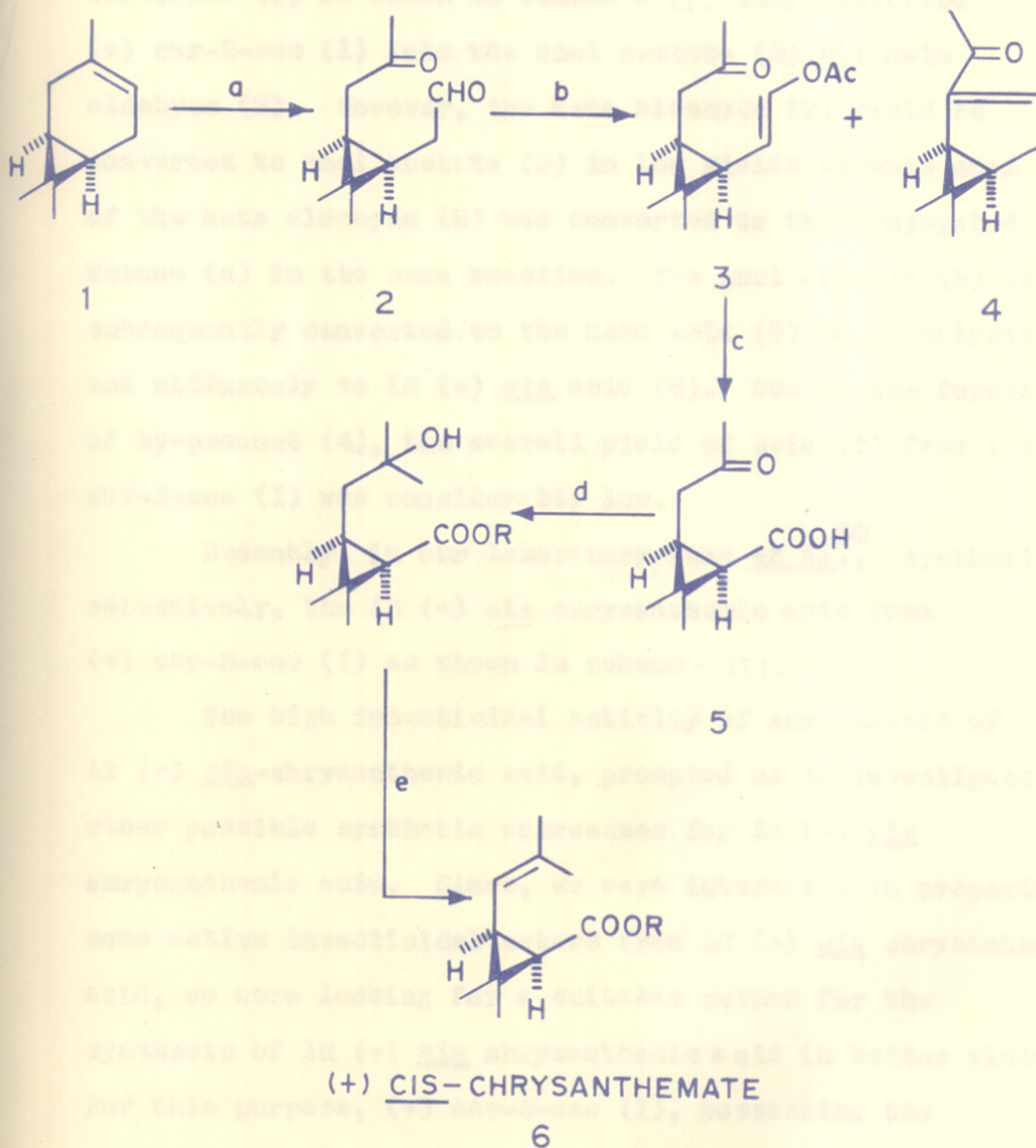
starting with suitable substrate. As a result, in many of the methods, a mixture of isomers is obtained.

Attempts to synthesise chrysanthemic acid, stereoselectively, from naturally occurring compounds, containing suitably substituted cyclopropane ring system and required configuration, were made by many groups of workers. Matsui *et al.*, for the first time realised the possibility of getting chrysanthemic acid from (+) car-3-ene (I), a naturally occurring monoterpene which is abundantly available and possesses the desired stereochemistry.

They obtained, stereoselectively, (+) trans²⁵ and (-) trans²⁶ chrysanthemic acids from (+) car-3-ene (I) as shown in scheme I. Later on, many workers have converted (+) car-3-ene (I) selectively, into 1S(-) cis chrysanthemic acid^{27,28,29} which could be readily epimerised to the 1R (+) trans isomer, a desired isomer for the synthesis of pyrethroids.

However, not much attention was given for the conversion of (+) car-3-ene (I) into 1R (+) cis chrysanthemic acid, the esters of which possess insecticidal activity⁸. There are only two references^{26,30} available in the literature for the conversion of (+) car-3-ene (I) into 1R(+)cis chrysanthemic acid. Matsui *et al.* synthesised, selectively, the 1R (+) cis chrysanthemic acid from (+)

SCHEME II



a ① OZONOLYSIS

b $\text{Ac}_2\text{O} / \text{AcONa}$ c ① OZONOLYSIS
② O_2

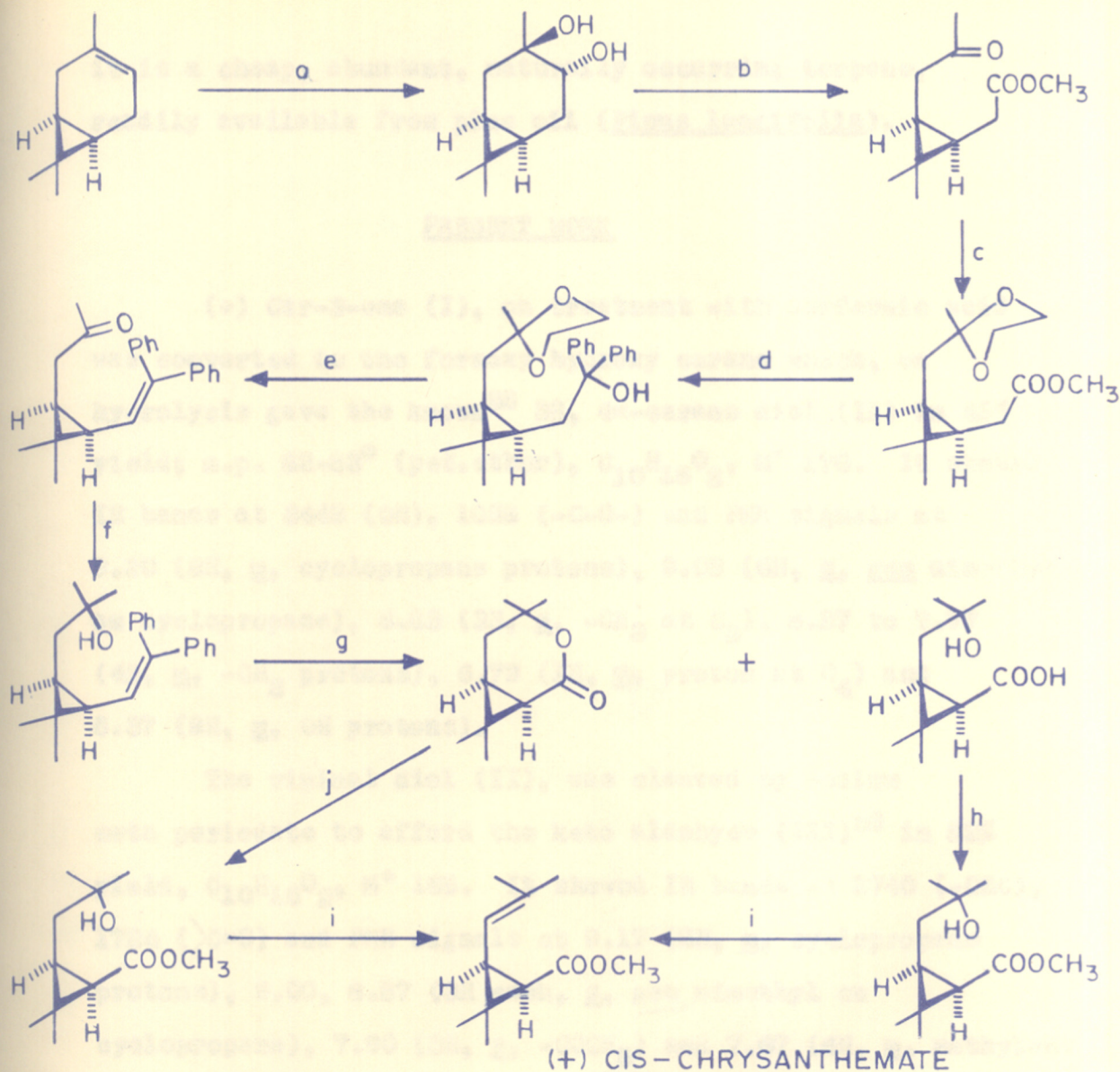
d ① ESTERIFICATION

② REVERSE GRIGNARD WITH
 $\text{CH}_3 \text{MgI}$ e $\text{POCl}_3 / \text{Py}$ or
PTS

car-3-ene (I) as shown in scheme - II. They converted (+) car-3-ene (1) into the enol acetate (3) via keto aldehyde (2). However, the keto aldehyde (2) could be converted to enol acetate (3) in low yields because much of the keto aldehyde (2) was converted to the conjugated ketone (4) in the same reaction. The enol acetate (3) was subsequently converted to the keto acid (5) by ozonolysis and ultimately to LR (+) cis acid (6). Due to the formation of by-product (4), the overall yield of acid (6) from (+) car-3-ene (I) was considerably low.

Recently, in our laboratory, Mane et al.³⁰ synthesised, selectively, the LR (+) cis chrysanthemic acid from (+) car-3-ene (I) as shown in scheme - III.

The high insecticidal activity of some esters of LR (+) cis-chrysanthemic acid, prompted us to investigate other possible synthetic approaches for LR (+) cis chrysanthemic acid. Since, we were interested in preparing some active insecticidal esters from LR (+) cis chrysanthemic acid, we were looking for a suitable method for the synthesis of LR (+) cis chrysanthemic acid in better yields. For this purpose, (+) car-3-ene (I), possessing the configuration of 1S and 6R at the cyclopropane ring juncture, was considered to be an ideal starting material. In addition



a (I) HCOOH

(II) H_2O_2

b (I) Jones reagent

(II) MeOH / H^+

c (I) Ethylene glycol

(II) PTS

d Grignard with PhMgBr

e (I) PTS

(II) H_2O

f Grignard with CH_3MgI , g (I) Ozonolysis

h Esterification with CH_2N_2 (II) Jones reagent

i $\text{POCl}_3 / \text{Py}$ or PTS

j (I) Methanolic potash

(II) Esterification with CH_2N_2

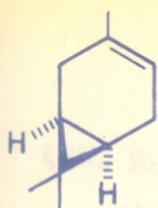
it is a cheap, abundant, naturally occurring terpene, readily available from pine oil (Pinus longifolia).

PRESENT WORK

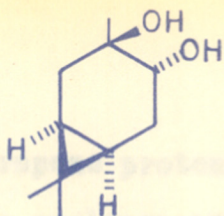
(+) Car-3-ene (I), on treatment with performic acid was converted to the formoxy hydroxy carane which, on hydrolysis gave the known²⁸ 3 β , 4 α -carane diol (II) in 45% yield; m.p. 82-83° (pet.ether), $C_{10}H_{18}O_2$, M^+ 170. It showed IR bands at 3448 (OH), 1058 (-C-O-) and PMR signals at 9.30 (2H, m, cyclopropane protons), 9.03 (6H, s, gem dimethyl on cyclopropane), 8.83 (3H, s, -CH₃ at C₃), 8.27 to 7.77 (4H, m, -CH₂ protons), 6.73 (1H, d, proton at C₄) and 6.37 (2H, m, OH protons).

The vicinal diol (II), was cleaved by sodium meta periodate to afford the keto aldehyde (III)²⁸ in 82% yield, $C_{10}H_{16}O_2$, M^+ 168. It showed IR bands at 2740 (-CHO), 1724 (>C=O) and PMR signals at 9.17 (2H, m, cyclopropane protons), 9.00, 8.87 (3H each, s, gem dimethyl on cyclopropane), 7.90 (3H, s, -COCH₃) and 7.67 (4H, m, methylene protons α to >C=O).

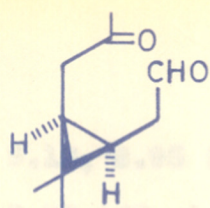
The freshly prepared keto aldehyde (III), on treatment with methyl magnesium iodide (2.5 moles) afforded the liquid diol (IV) in 70% yield, $C_{12}H_{24}O_2$, M^+ 200. It showed IR bands at 3448 (OH), 1057 (-C-O-) and PMR signals at 9.43



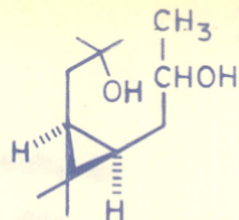
I



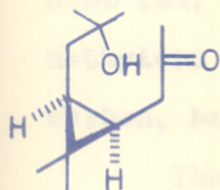
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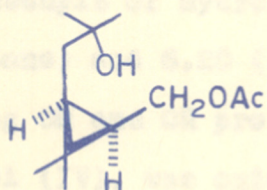
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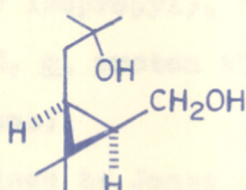
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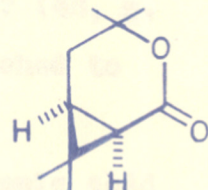
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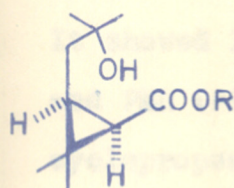
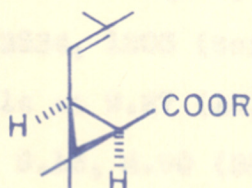
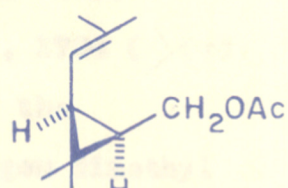
VI



VII

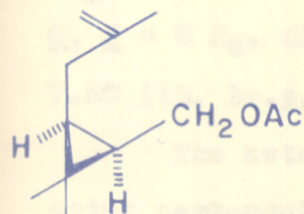


VIII

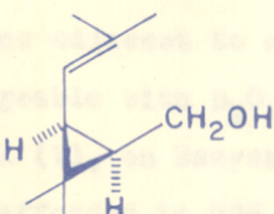
IX, R=H; R=CH₃X, R=CH₃

XI

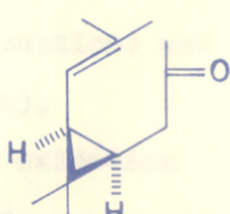
XIV, R=H



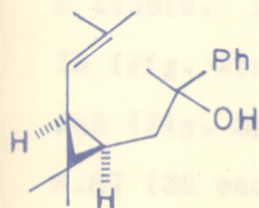
XII



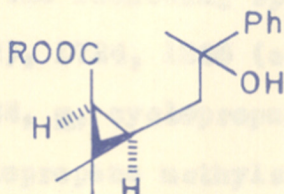
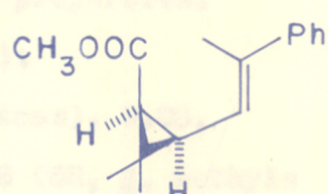
XIII



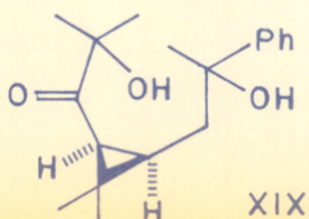
XV



XVI

XVII, R=H; R=CH₃

XVIII



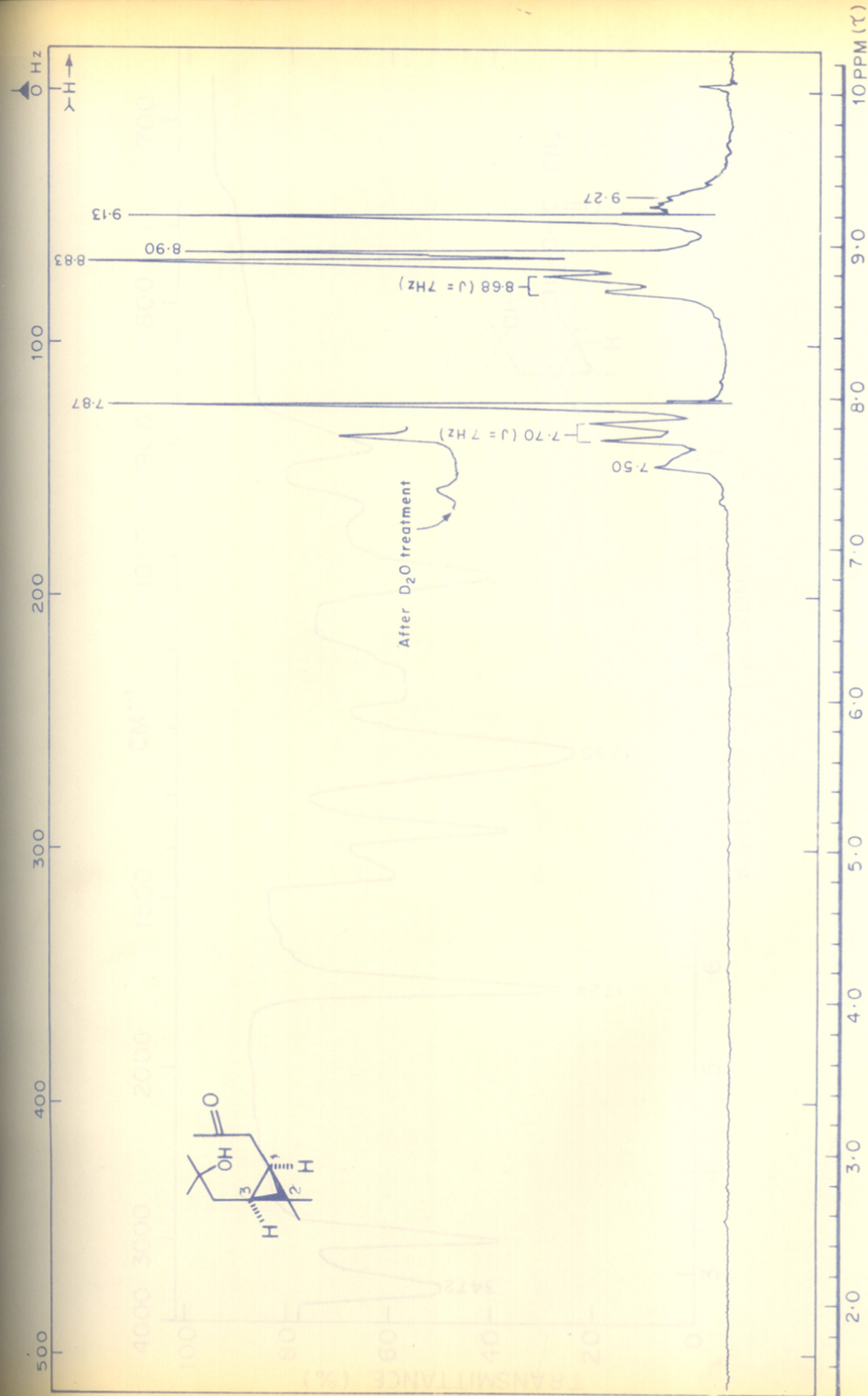
XIX

(2H, m, cyclopropane protons), 9.13, 8.95 (3H each, s, gem dimethyl on cyclopropane), 8.83 (3H, d, J = 6Hz, methyl attached to carbon, bearing secondary hydroxy group 8.80 (6H, s, methyls of hydroxy isopropyl), 8.67 (4H, m, methylene protons) and 6.20 (sH, m, proton attached to carbon, bearing OH and OH protons).

The diol (IV), was oxidised by Jones chromic acid reagent, under controlled conditions to the hydroxy ketone (V) in 95% yield as a liquid, $C_{12}H_{22}O_2$, M^+ 198. It showed IR bands at 3534, 1205 (tertiary -OH), 1704 ($>C=O$) and PMR (Fig. 1) signals at 9.27 (1H, m, one of the cyclopropane protons), 9.13, 8.90 (3H each, s, gem dimethyl on cyclopropane), 8.83 (7H, s, methyls of hydroxy isopropyl and another cyclopropane proton), 8.68 (2H, d, J = 6 Hz, CH_2 protons at C_3), 7.87 (3H, s, $-COCH_3$), 7.70 (2H, d, J = 6 Hz, CH_2 protons adjacent to carbonyl function) and 7.50 (1H, br.s, exchangeable with D_2O , OH proton).

The keto alcohol (V), on Baeyer-Villiger oxidation using perbenzoic acid afforded in 80% yield, the corresponding hydroxy acetate (VI), $C_{12}H_{22}O_3$, M^+ 214, as a liquid. It showed the following spectral properties. IR (Fig. 2): 3472 (OH), 1724, 1235 (acetate); PMR (Fig. 3): 9.23 (2H, m, cyclopropane protons), 9.00, 8.87 (3H each, s, cyclopropane methyls), 8.78 (6H, s, methyls of hydroxy isopropyl), 8.55 (2H, d, J = 6 Hz, CH_2 protons

FIG. 1. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXYPROPYL)-
-CIS-1-ACETONYLCYCLOPROPANE (V)



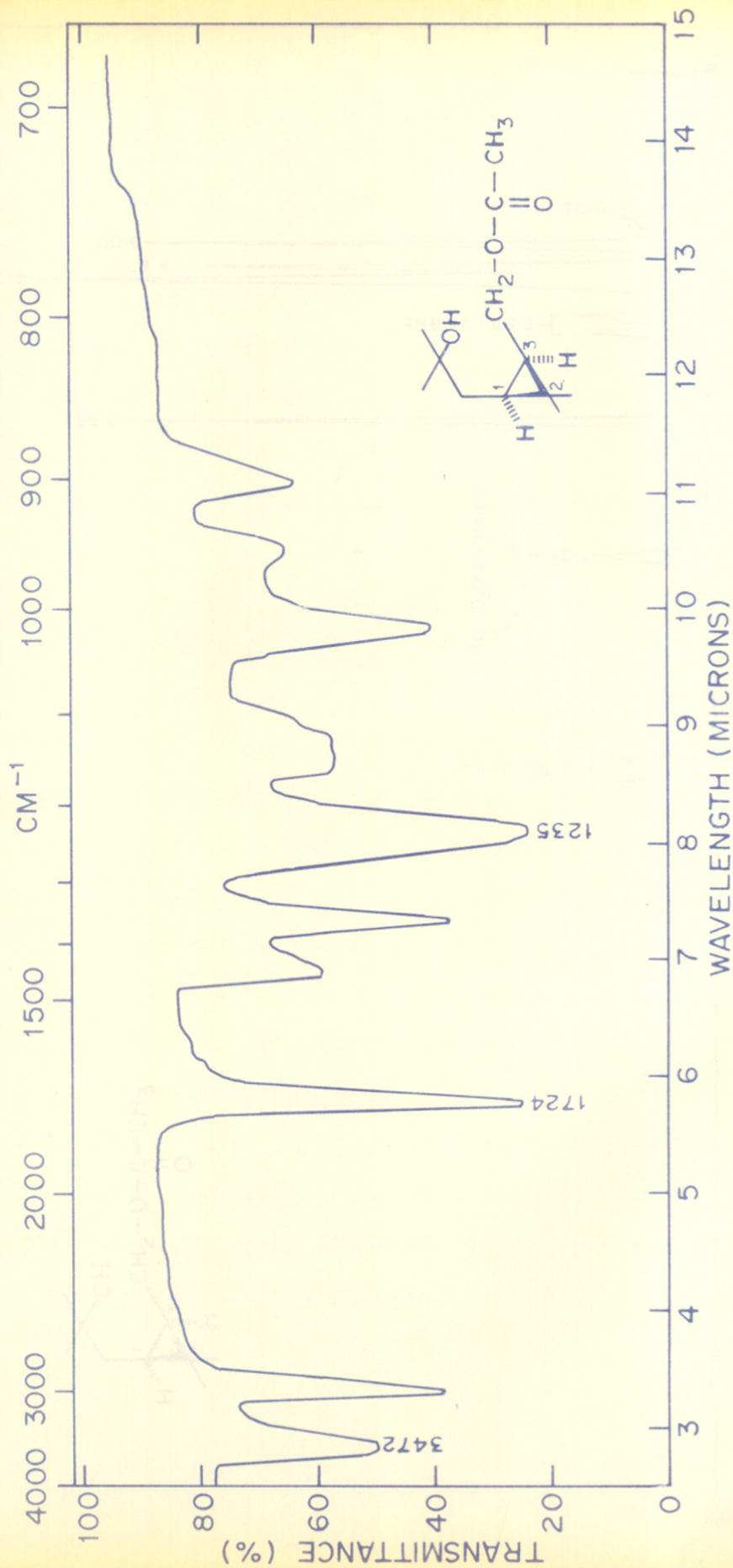


FIG. 2. IR SPECTRUM OF 2,2-DIMETHYL-3-ACETOXYMETHYL CYCLOPROPANE - CIS -
-1-(2'-METHYL)-PROPAN - 2'-OL (VI)

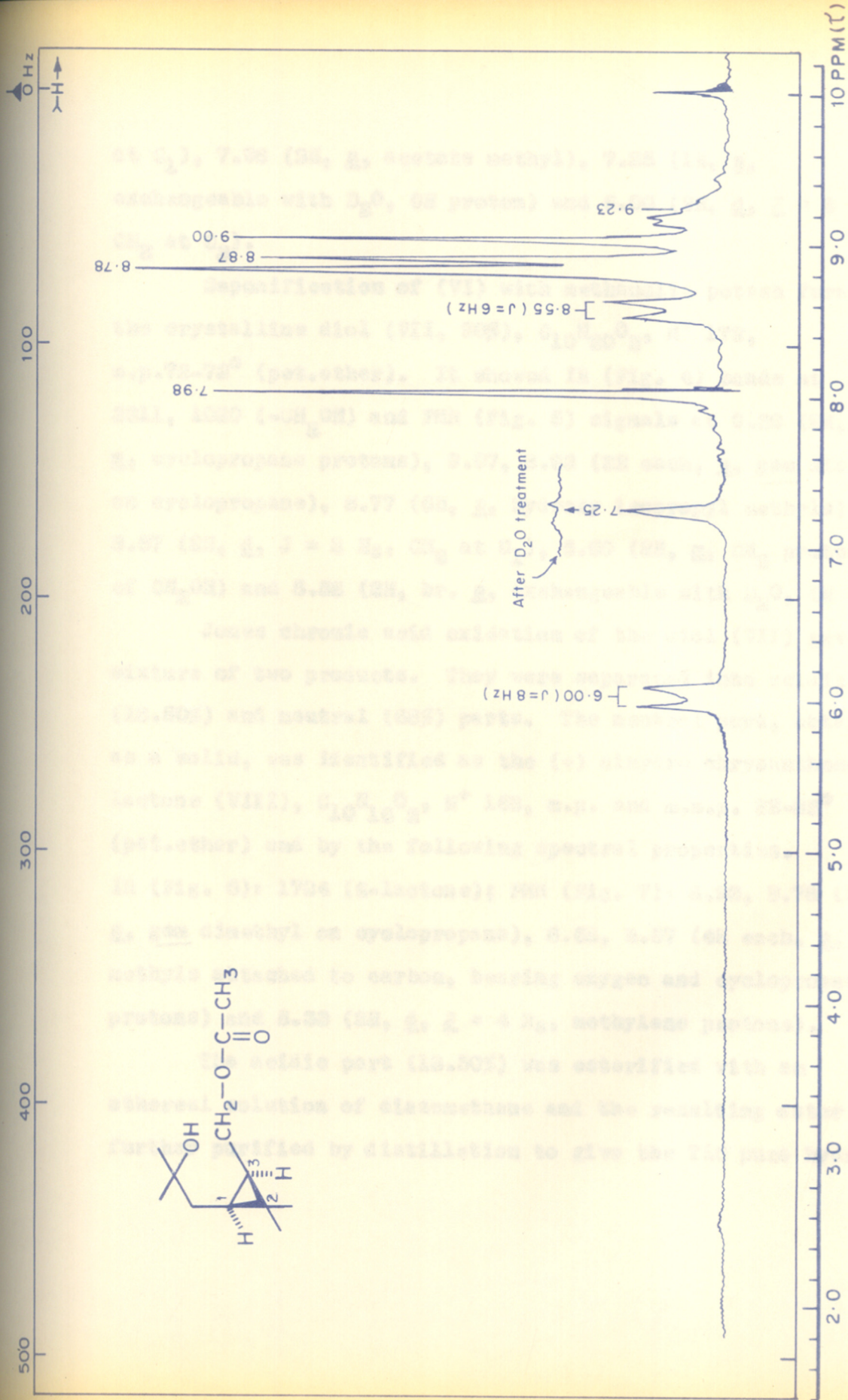


FIG. 3. PMR SPECTRUM OF 2,2-DIMETHYL-3-ACETOXYMETHYL CYCLOPROPANE-

-CIS-1-(2'-METHYL)-PROPAN - 2'-OL (VI)

at C_1), 7.98 (3H, s, acetate methyl), 7.25 (1H, s, exchangeable with D_2O , OH proton) and 6.00 (2H, d, $J = 8$ Hz, CH_2 at C_3).

Saponification of (VI) with methanolic potash furnished the crystalline diol (VII, 90%), $C_{10}H_{20}O_2$, $M^+ 172$, m.p. 72-73° (pet. ether). It showed IR (Fig. 4) bands at 3311, 1020 ($-CH_2OH$) and PMR (Fig. 5) signals at 9.39 (2H, s, cyclopropane protons), 9.07, 8.93 (3H each, s, gem dimethyl on cyclopropane), 8.77 (6H, s, hydroxy isopropyl methyls), 8.57 (2H, d, $J = 8$ Hz, CH_2 at C_1), 6.60 (2H, m, CH_2 protons of CH_2OH) and 5.58 (2H, br. s, exchangeable with D_2O , OH protons).

Jones chromic acid oxidation of the diol (VII) gave a mixture of two products. They were separated into acidic (18.50%) and neutral (68%) parts. The neutral part, obtained as a solid, was identified as the (+) dihydro chrysanthemolactone (VIII), $C_{10}H_{16}O_2$, $M^+ 168$, m.p. and m.m.p. 82-83° (pet. ether) and by the following spectral properties. IR (Fig. 6): 1724 (C-lactone); PMR (Fig. 7): 8.92, 8.75 (3H each, s, gem dimethyl on cyclopropane), 8.68, 8.57 (4H each, s, methyls attached to carbon, bearing oxygen and cyclopropane protons) and 8.33 (2H, d, $J = 4$ Hz, methylene protons).

The acidic part (18.50%) was esterified with an ethereal solution of diazomethane and the resulting ester further purified by distillation to give the TLC pure hydroxy

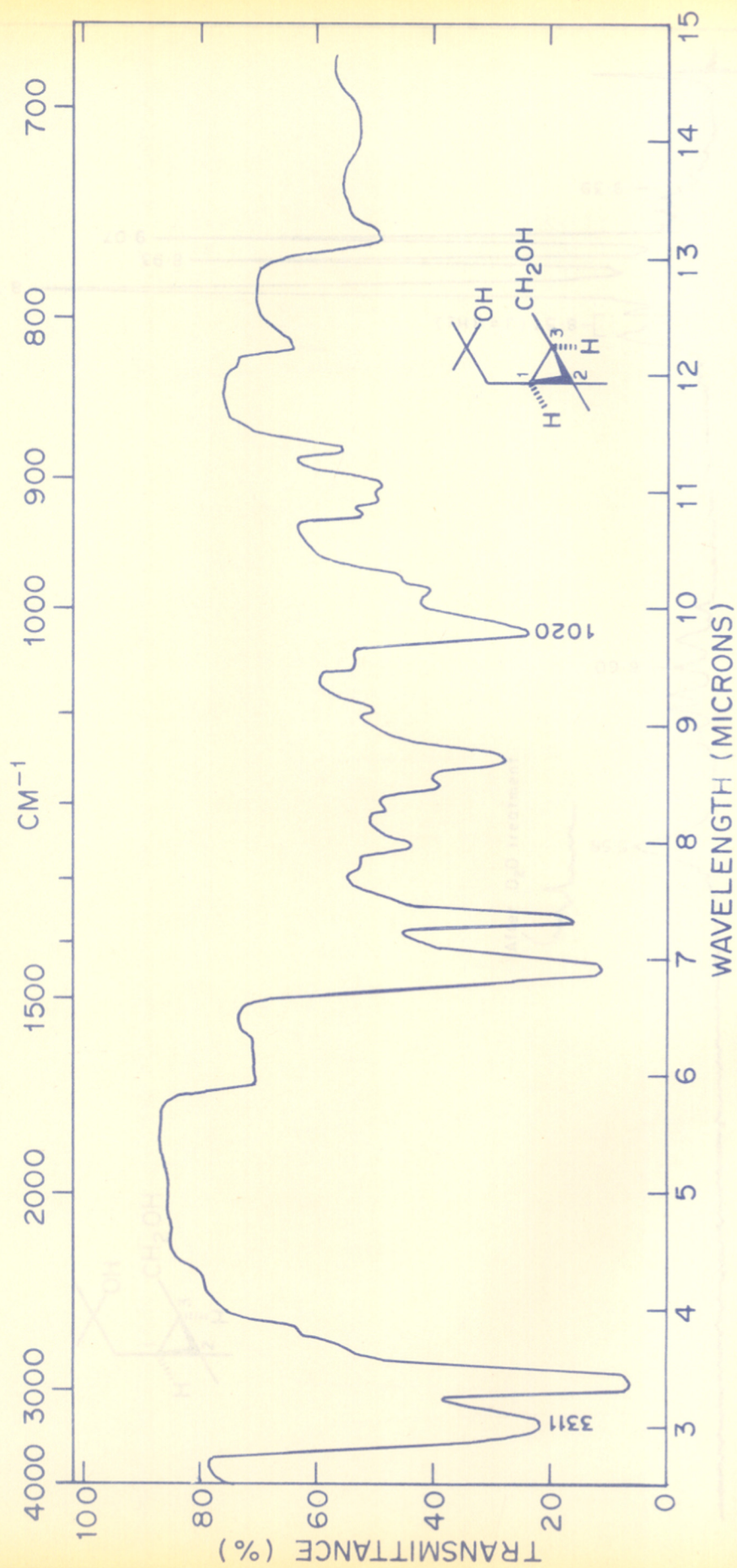


FIG. 4. IR SPECTRUM OF 2,2-DIMETHYL-3-HYDROXYMETHYL CYCLOPROPANE-CIS-1-(2'-METHYL)-PROPAN - 2'-OL (VII)

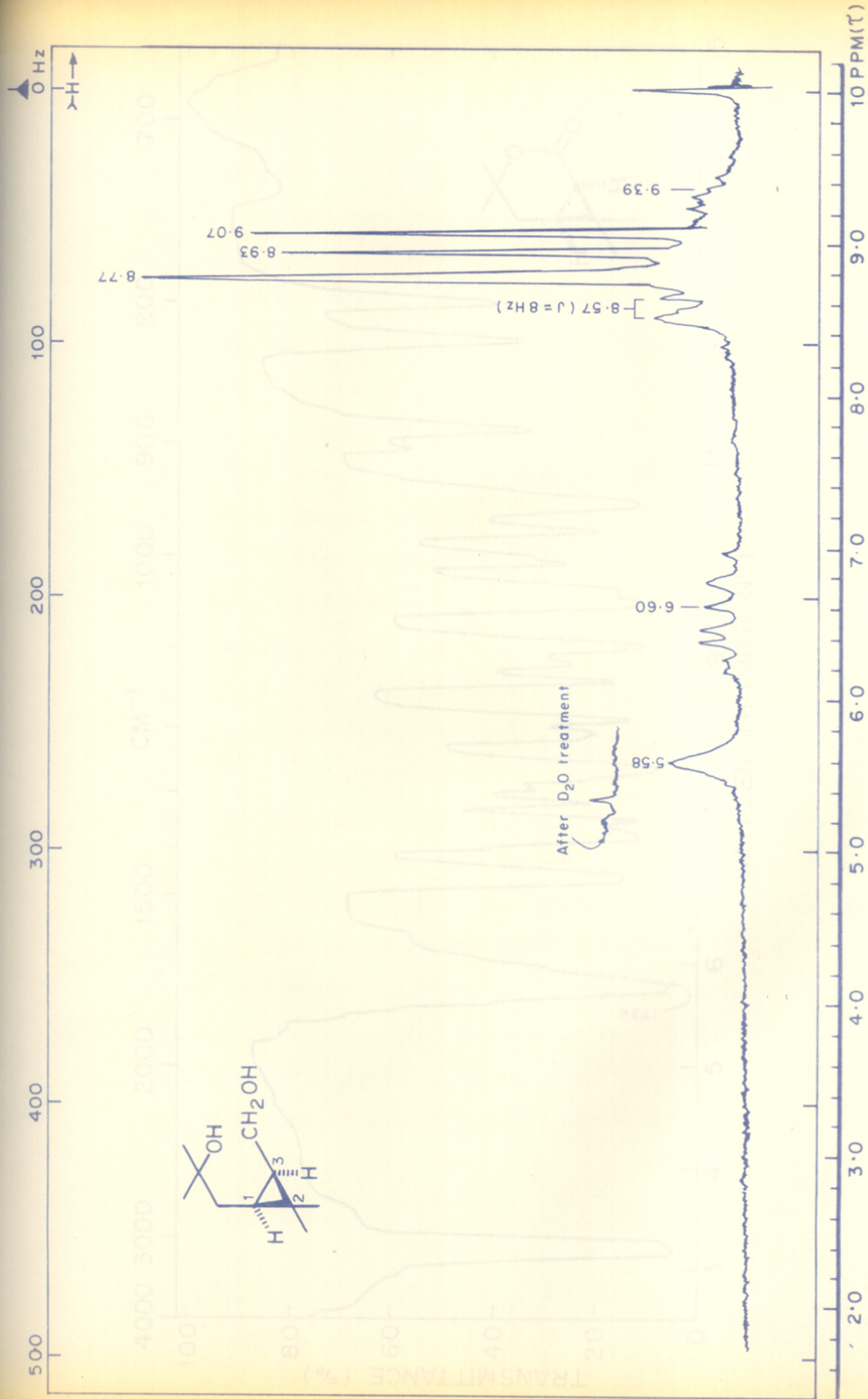


FIG. 5. PMR SPECTRUM OF 2,2-DIMETHYL-3-HYDROXYMETHYL CYCLOPROPANE-
-CIS-1-(2'-METHYL)-PROPAN-2'-OL (VII)

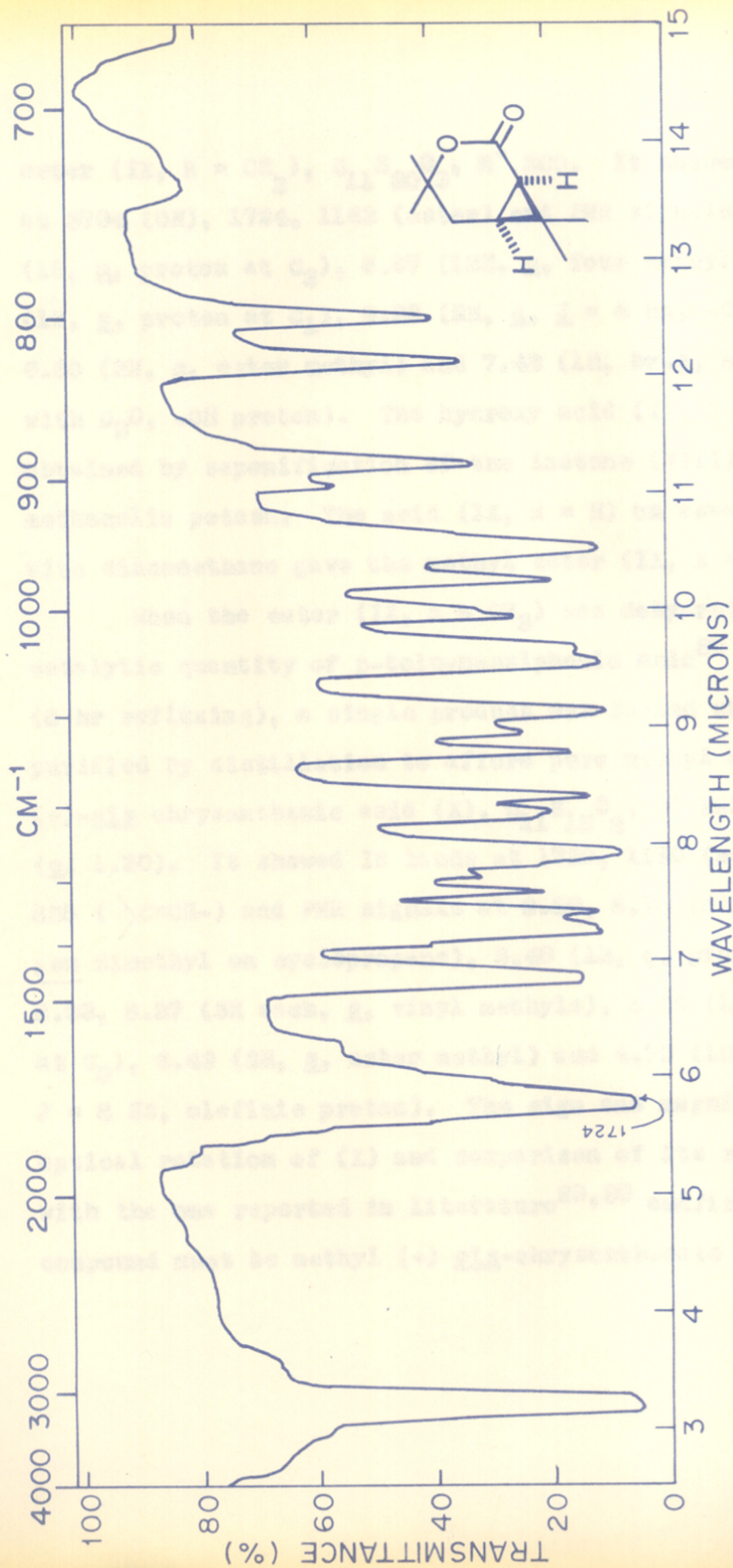
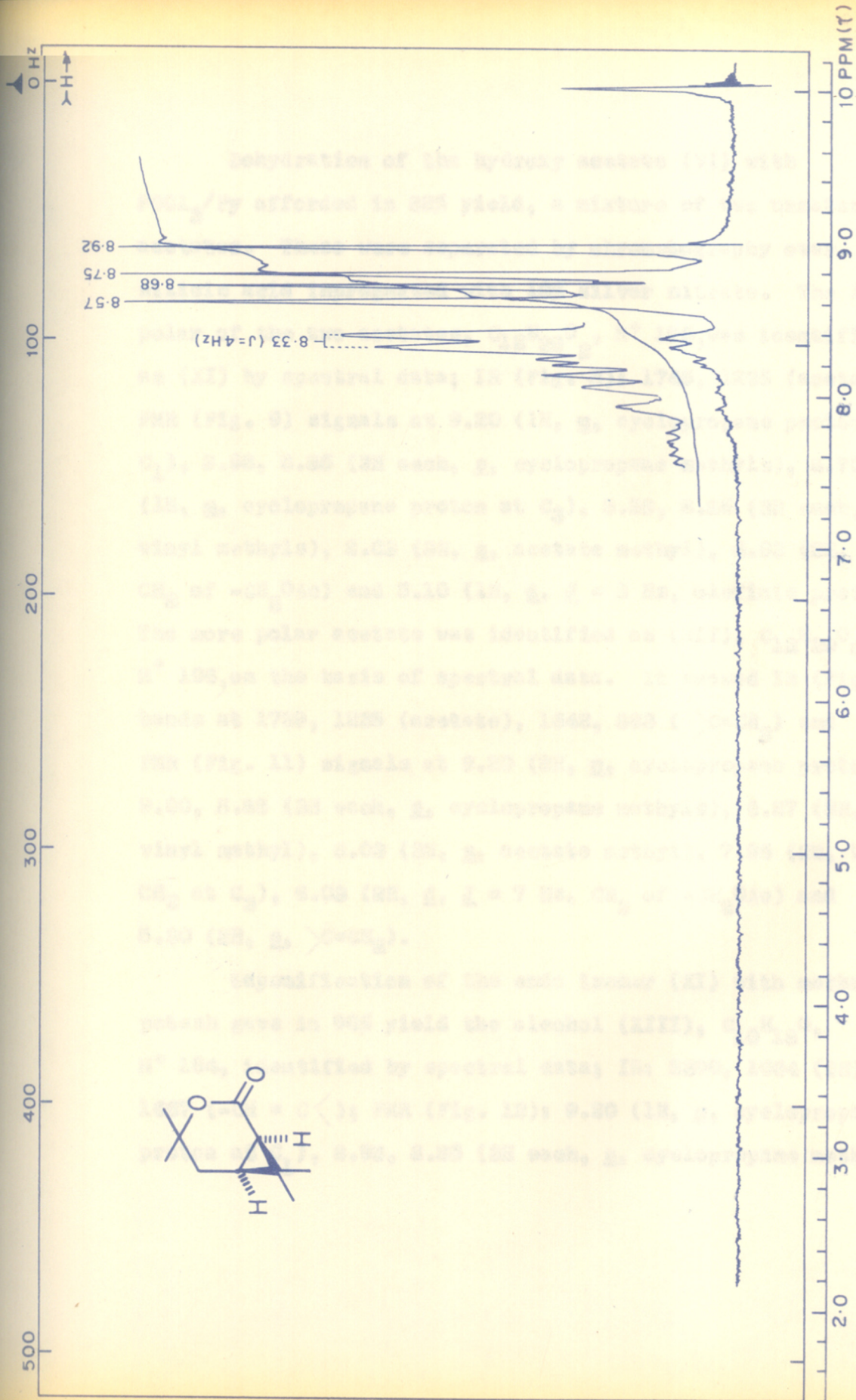


FIG. 6. IR SPECTRUM OF (+) DIHYDRO CHRYSANTHEMO LACTONE (VIII)

ester (IX, R = CH₃), C₁₁H₂₀O₃, M⁺ 200. It showed IR bands at 3704 (OH), 1724, 1163 (ester) and PMR signals at 8.97 (1H, m, proton at C₃), 8.87 (12H, s, four methyls), 8.62 (1H, s, proton at C₁), 8.25 (2H, d, J = 6 Hz, -CH₂ protons), 6.50 (3H, s, ester methyl) and 7.43 (1H, br. s, exchangeable with D₂O, -OH proton). The hydroxy acid (IX, R = H) was also obtained by saponification of the lactone (VIII) using methanolic potash. The acid (IX, R = H) on esterification with diazomethane gave the methyl ester (IX, R = CH₃).

When the ester (IX, R = CH₃) was dehydrated by using catalytic quantity of p-toluenesulphonic acid²⁹ in dry benzene (8 hr refluxing), a single product was formed which was purified by distillation to afford pure methyl ester of (+)-cis chrysanthemic acid (X), C₁₁H₁₈O₂, M⁺ 182, (α)_D²⁸ + 41° (c, 1.20). It showed IR bands at 1739, 1190 (ester), 835 (>C=CH-) and PMR signals at 8.80, 8.75 (3H each, s, gem dimethyl on cyclopropane), 8.40 (1H, s, proton at C₁), 8.33, 8.27 (3H each, s, vinyl methyls), 8.13 (1H, s, proton at C₃), 6.43 (3H, s, ester methyl) and 4.70 (1H, d, J = 8 Hz, olefinic proton). The sign and magnitude of the optical rotation of (X) and comparison of its spectral data with the one reported in literature^{29,30} confirmed that this compound must be methyl (+) cis-chrysanthemate (X).

FIG. 7. PMR SPECTRUM OF (+) DIHYDRO CHRISANTHEMOLACTONE (VIII)



Dehydration of the hydroxy acetate (VI) with POCl_3/Py afforded in 82% yield, a mixture of two unsaturated acetates. These were separated by chromatography over silicic acid impregnated with 10% silver nitrate. The less polar of the two acetates, $\text{C}_{12}\text{H}_{20}\text{O}_2$, M^+ 196, was identified as (XI) by spectral data; IR (Fig. 8): 1745, 1235 (acetate); PMR (Fig. 9) signals at 9.20 (1H, $\underline{m}$, cyclopropane proton at C_1), 8.98, 8.85 (3H each, $\underline{s}$, cyclopropane methyls), 8.70 (1H, $\underline{m}$, cyclopropane proton at C_3), 8.28, 8.25 (3H each, $\underline{s}$, vinyl methyls), 8.02 (3H, $\underline{s}$, acetate methyl), 6.03 (2H, br. $\underline{d}$, CH_2 of $-\text{CH}_2\text{OAc}$) and 5.10 (1H, $\underline{d}$, $J = 8$ Hz, olefinic proton). The more polar acetate was identified as (XII), $\text{C}_{12}\text{H}_{20}\text{O}_2$, M^+ 196, on the basis of spectral data. It showed IR (Fig. 10) bands at 1739, 1235 (acetate), 1642, 883 ($>\text{C}=\text{CH}_2$) and PMR (Fig. 11) signals at 9.20 (2H, $\underline{m}$, cyclopropane protons), 9.00, 8.88 (3H each, $\underline{s}$, cyclopropane methyls), 8.27 (3H, $\underline{s}$, vinyl methyl), 8.03 (3H, $\underline{s}$, acetate methyl), 7.95 (2H, br. $\underline{s}$, CH_2 at C_3), 6.03 (2H, $\underline{d}$, $J = 7$ Hz, CH_2 of $-\text{CH}_2\text{OAc}$) and 5.30 (2H, $\underline{s}$, $>\text{C}=\text{CH}_2$).

Saponification of the endo isomer (XI) with methanolic potash gave in 90% yield the alcohol (XIII), $\text{C}_{10}\text{H}_{18}\text{O}$, M^+ 154, identified by spectral data; IR: 3390, 1064 (OH), 1667 ($-\text{CH}=\text{C}<$); PMR (Fig. 12): 9.20 (1H, $\underline{m}$, cyclopropane proton at C_1), 8.98, 8.85 (3H each, $\underline{s}$, cyclopropane methyls),

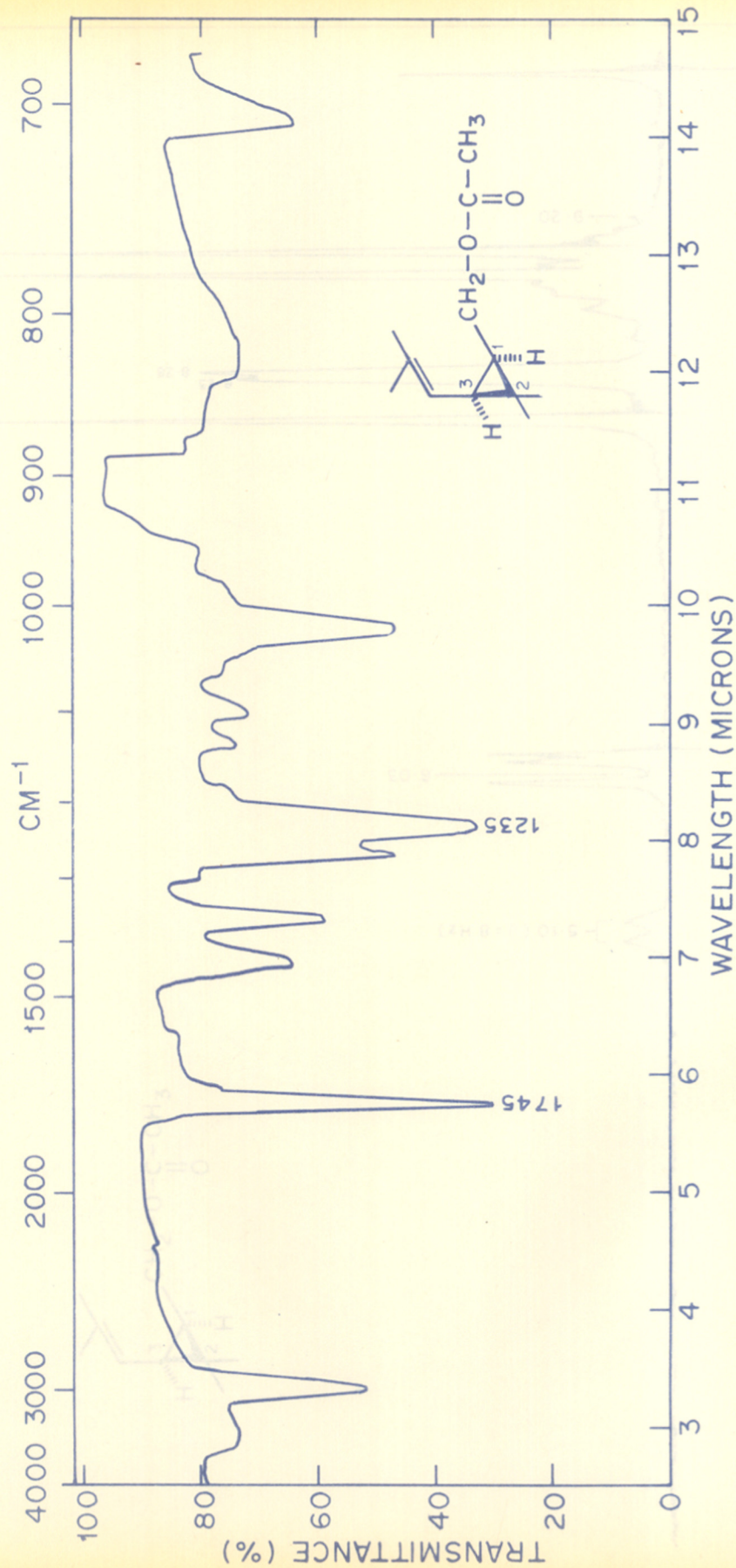


FIG. 8. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-CIS-1-ACETOXY-
-METHYL CYCLOPROPANE (XI)

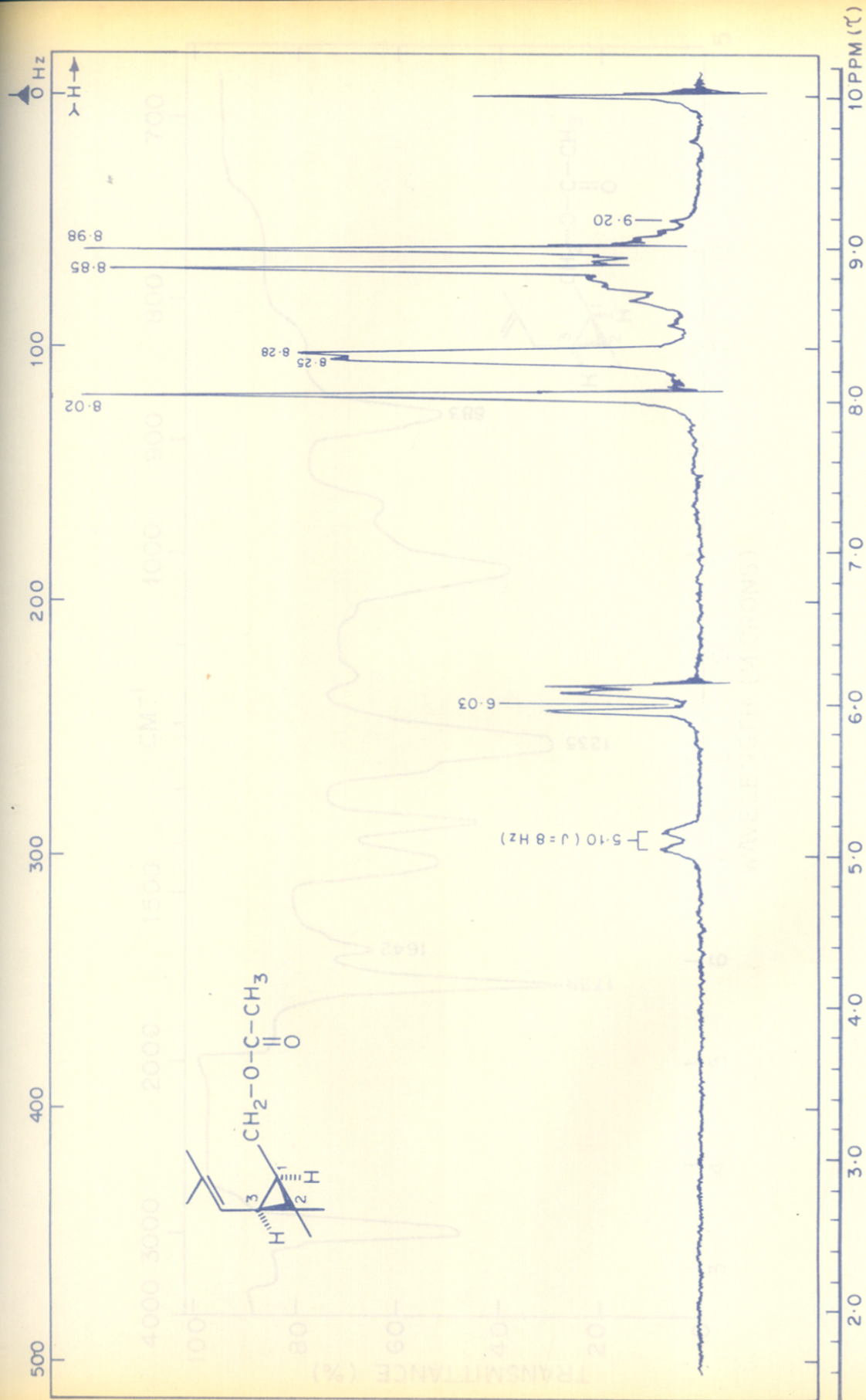


FIG. 9. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-CIS-

-1-ACETOXYMETHYL CYCLOPROPANE (XI)

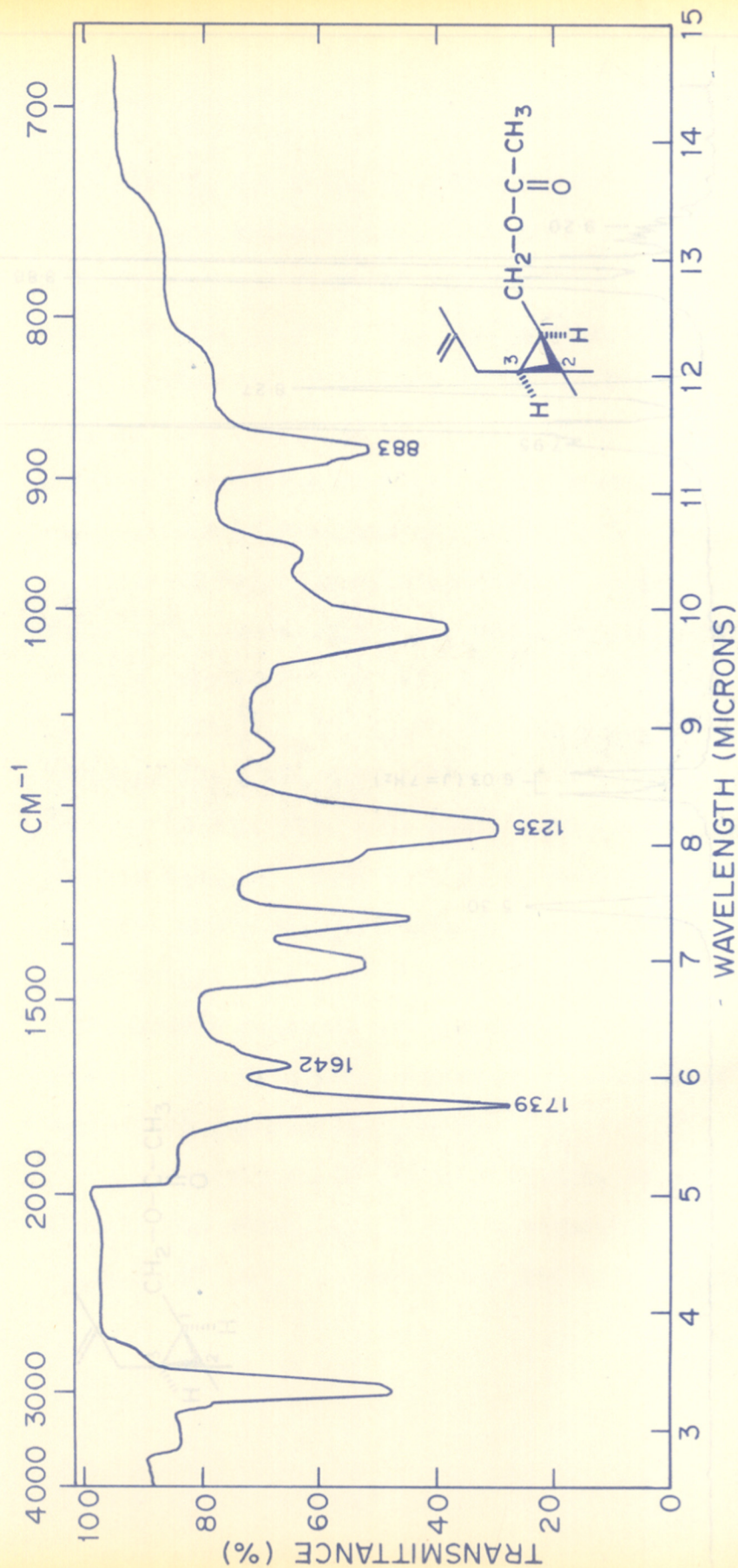


FIG. 10. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-2-ENYL)-CIS-1-ACETOXYMETHYL CYCLOPROPANE (XII)

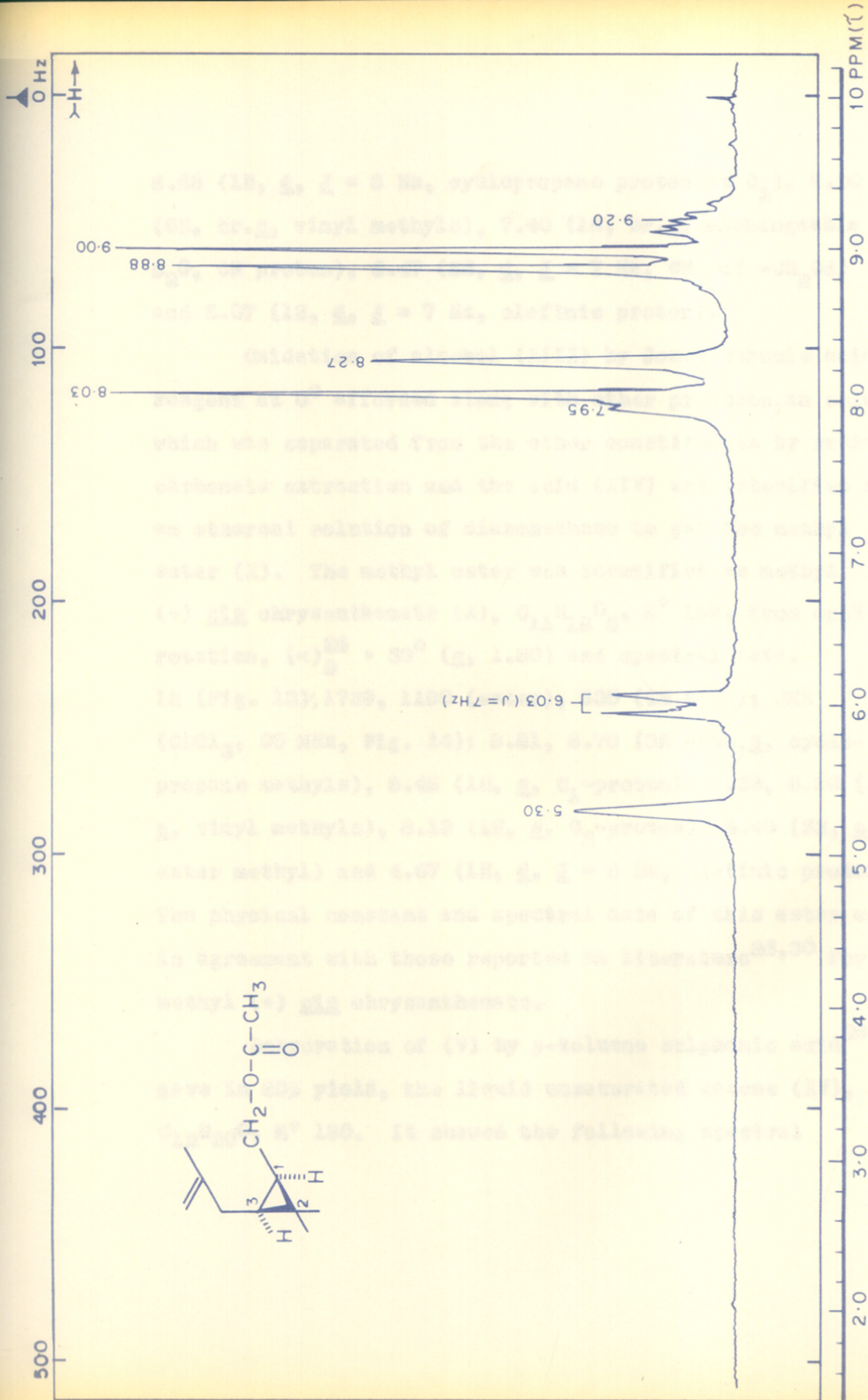


FIG. 11. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-2-ENYL)-CIS-1-ACETOXYMETHYL CYCLOPROPANE (XII)

8.65 (1H, d, $J = 8$ Hz, cyclopropane proton at C_3), 8.30 (6H, br.s, vinyl methyls), 7.40 (1H, br.s, exchangeable with D_2O , OH proton), 6.47 (2H, d, $J = 7$ Hz, CH_2 of $-CH_2OH$) and 5.07 (1H, d, $J = 7$ Hz, olefinic proton).

Oxidation of alcohol (XIII) by Jones chromic acid reagent at 0° afforded along with other products, an acid (XIV), which was separated from the other constituents by sodium carbonate extraction and the acid (XIV) was esterified using an ethereal solution of diazomethane to get the methyl ester (X). The methyl ester was identified as methyl (+) cis chrysanthemate (X), $C_{11}H_{18}O_2$, M^+ 182, from optical rotation, $(\alpha)_D^{28} + 39^\circ$ (g, 1.30) and spectral data. IR (Fig. 13): 1739, 1190 (ester), 835 ($CH = C$); PMR ($CDCl_3$, 90 MHz, Fig. 14): 8.81, 8.78 (3H each, s, cyclopropane methyls), 8.42 (1H, s, C_1 -proton), 8.33, 8.26 (3H each, s, vinyl methyls), 8.13 (1H, s, C_3 -proton), 6.40 (3H, s, ester methyl) and 4.67 (1H, d, $J = 8$ Hz, olefinic proton). The physical constant and spectral data of this ester were in agreement with those reported in literature^{26,30} for methyl (+) cis chrysanthemate.

Dehydration of (V) by p-toluene sulphonic acid²⁹ gave in 80% yield, the liquid unsaturated ketone (XV), $C_{12}H_{20}O$, M^+ 180. It showed the following spectral

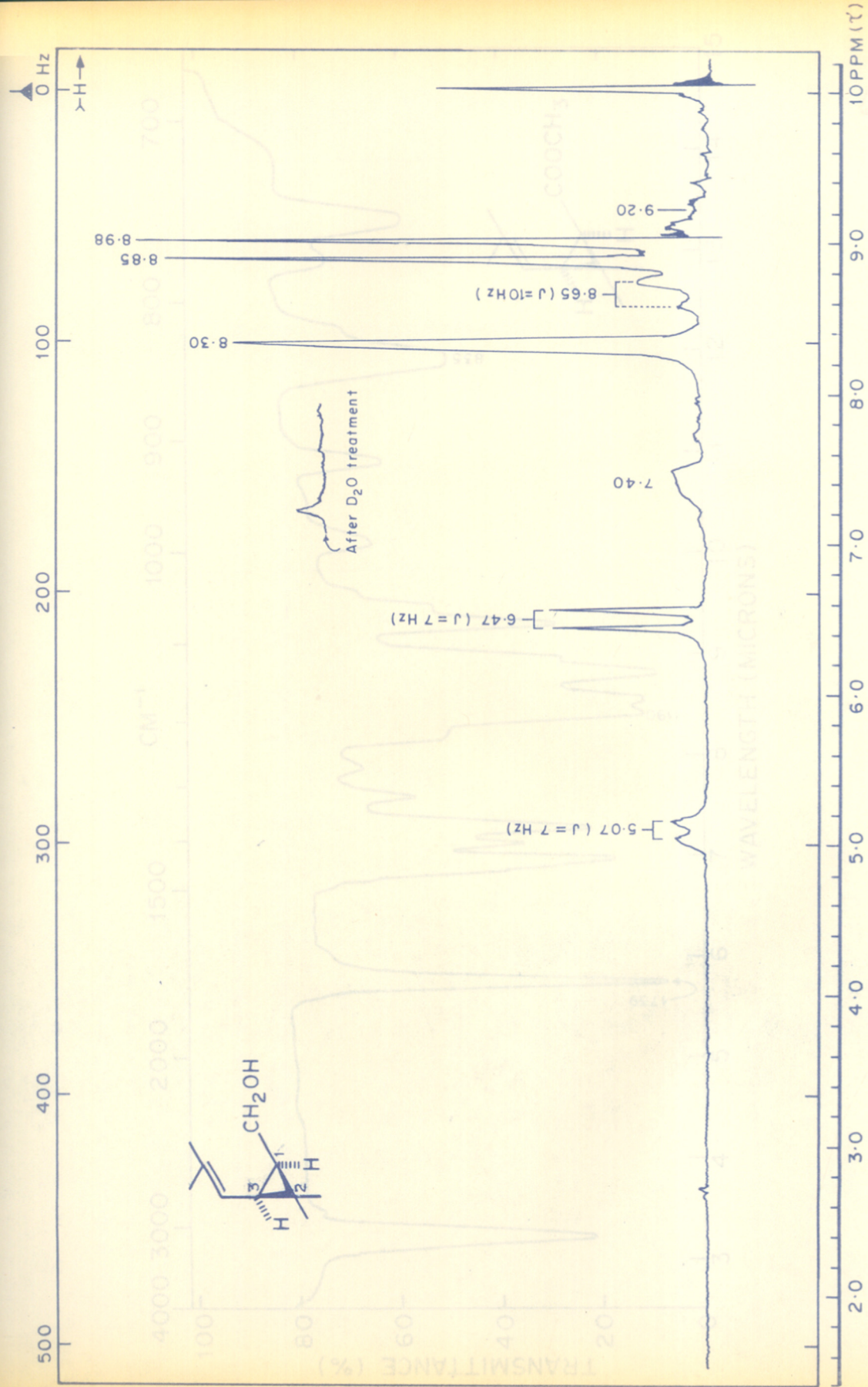


FIG. 12. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-CIS-1-HYDROXYMETHYL-CYCLOPROPANE (XIII)

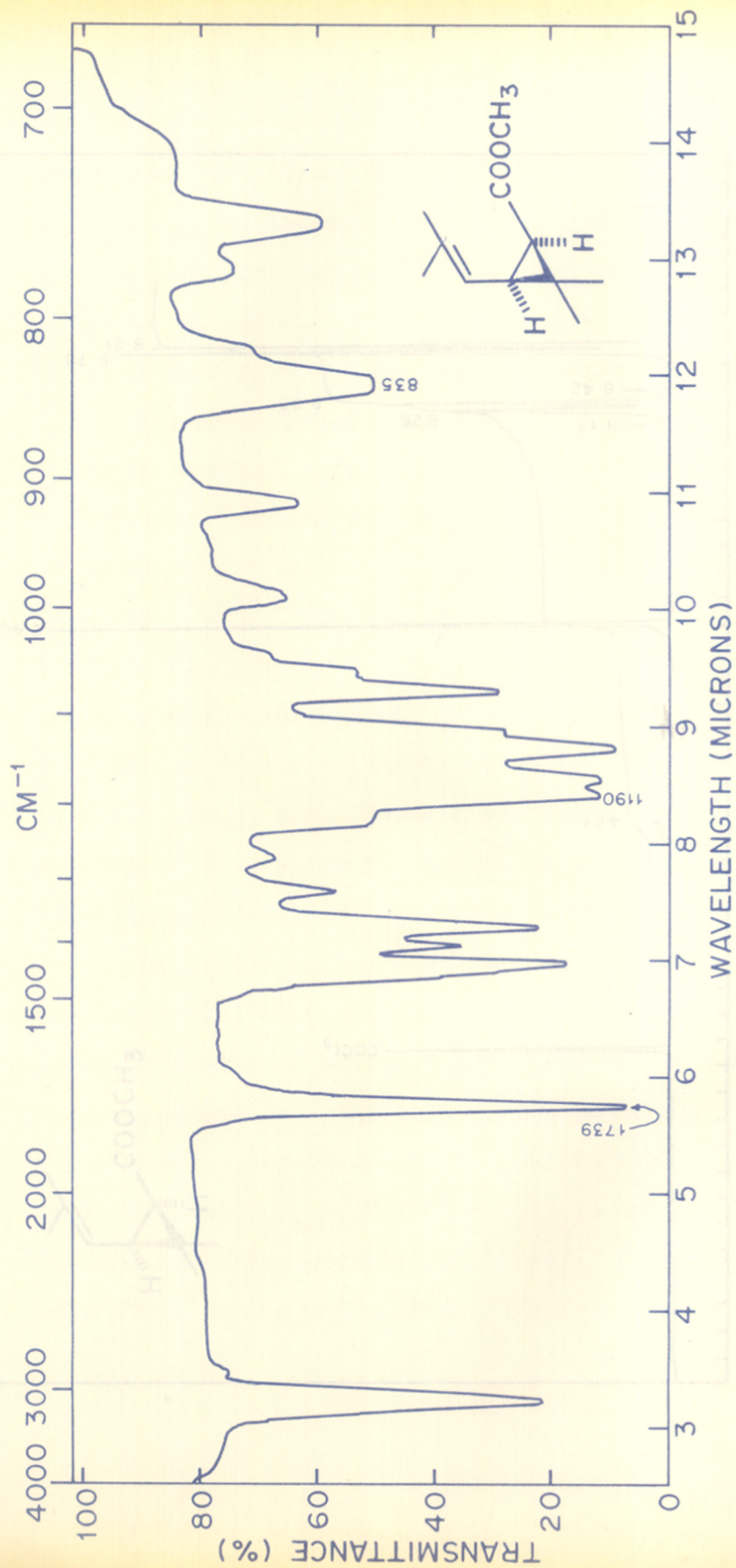


FIG. 13. IR SPECTRUM OF METHYL (+) CIS-CHRYSTHEMATE (X)

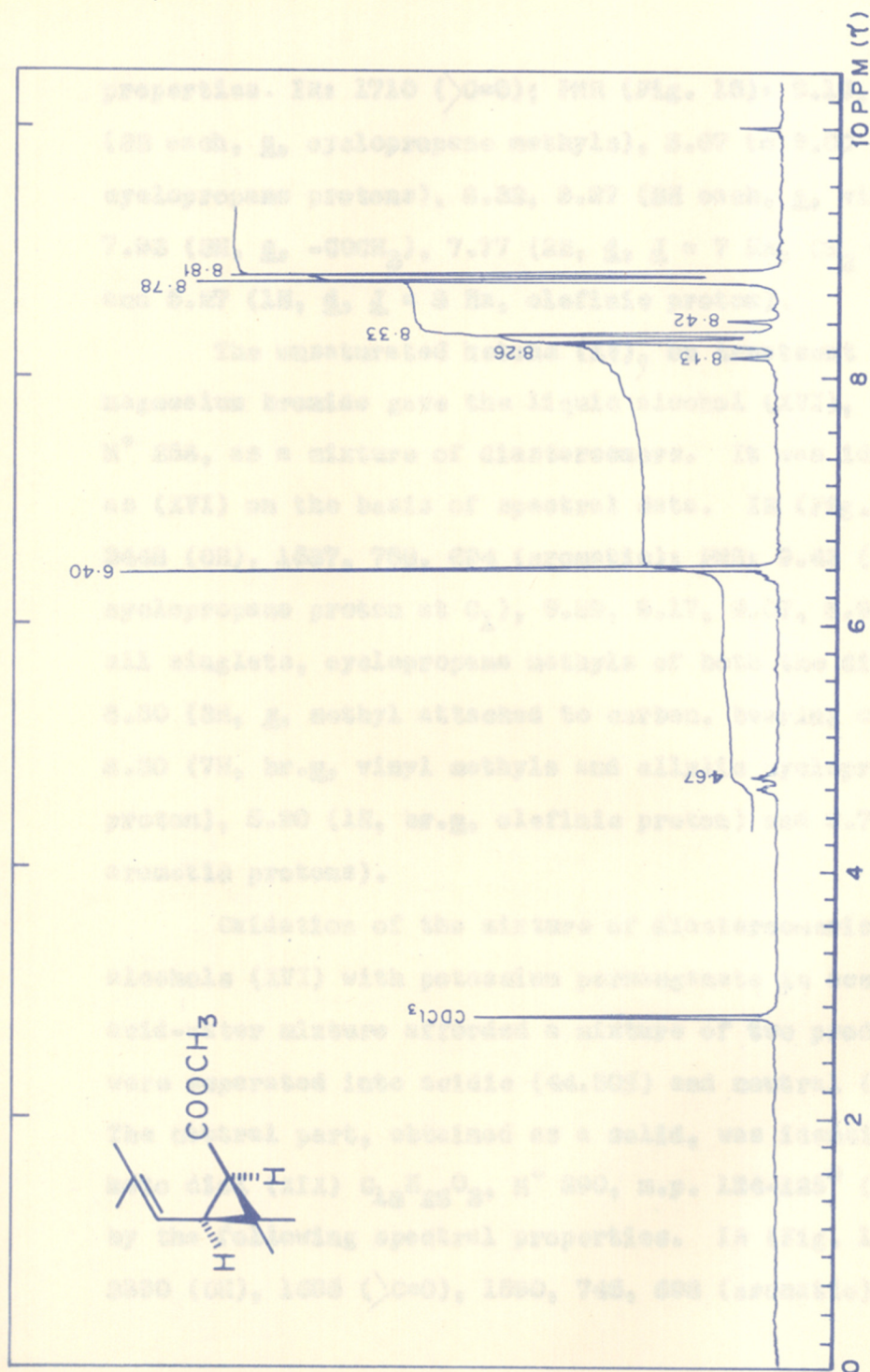


FIG. 14. PMR SPECTRUM OF METHYL (+) CIS-CHRYSTANTHEMATE (X)

properties. IR: 1710 (>C=O); PMR (Fig. 15): 9.10, 8.85 (3H each, s, cyclopropane methyls), 8.67 to 9.00 (2H, m, cyclopropane protons), 8.33, 8.27 (3H each, s, vinyl methyls), 7.93 (3H, s, $-\text{COCH}_3$), 7.77 (2H, d, $J = 7$ Hz, $\text{CH}_2 \alpha$ to >C=O) and 5.27 (1H, d, $J = 8$ Hz, olefinic proton).

The unsaturated ketone (XV), on treatment with phenyl magnesium bromide gave the liquid alcohol (XVI), $\text{C}_{18}\text{H}_{26}\text{O}$, $M^+ 258$, as a mixture of diastereomers. It was identified as (XVI) on the basis of spectral data. IR (Fig. 16): 3448 (OH), 1587, 758, 694 (aromatic); PMR: 9.43 (1H, m, cyclopropane proton at C_1), 9.29, 9.17, 9.07, 8.97 (6H, all singlets, cyclopropane methyls of both the diastereomers), 8.50 (3H, s, methyl attached to carbon, bearing oxygen), 8.30 (7H, br.m, vinyl methyls and allylic cyclopropane proton), 5.20 (1H, br.m, olefinic proton) and 2.73 (5H, m, aromatic protons).

Oxidation of the mixture of diastereomeric unsaturated alcohols (XVI) with potassium permanganate in acetone-acetic acid-water mixture afforded a mixture of two products. They were separated into acidic (44.50%) and neutral (48%) parts. The neutral part, obtained as a solid, was identified as keto diol (XIX) $\text{C}_{18}\text{H}_{26}\text{O}_3$, $M^+ 290$, m.p. 124-125° (pet. ether), by the following spectral properties. IR (Fig. 18): 3509, 3390 (OH), 1695 (>C=O), 1590, 746, 698 (aromatic);

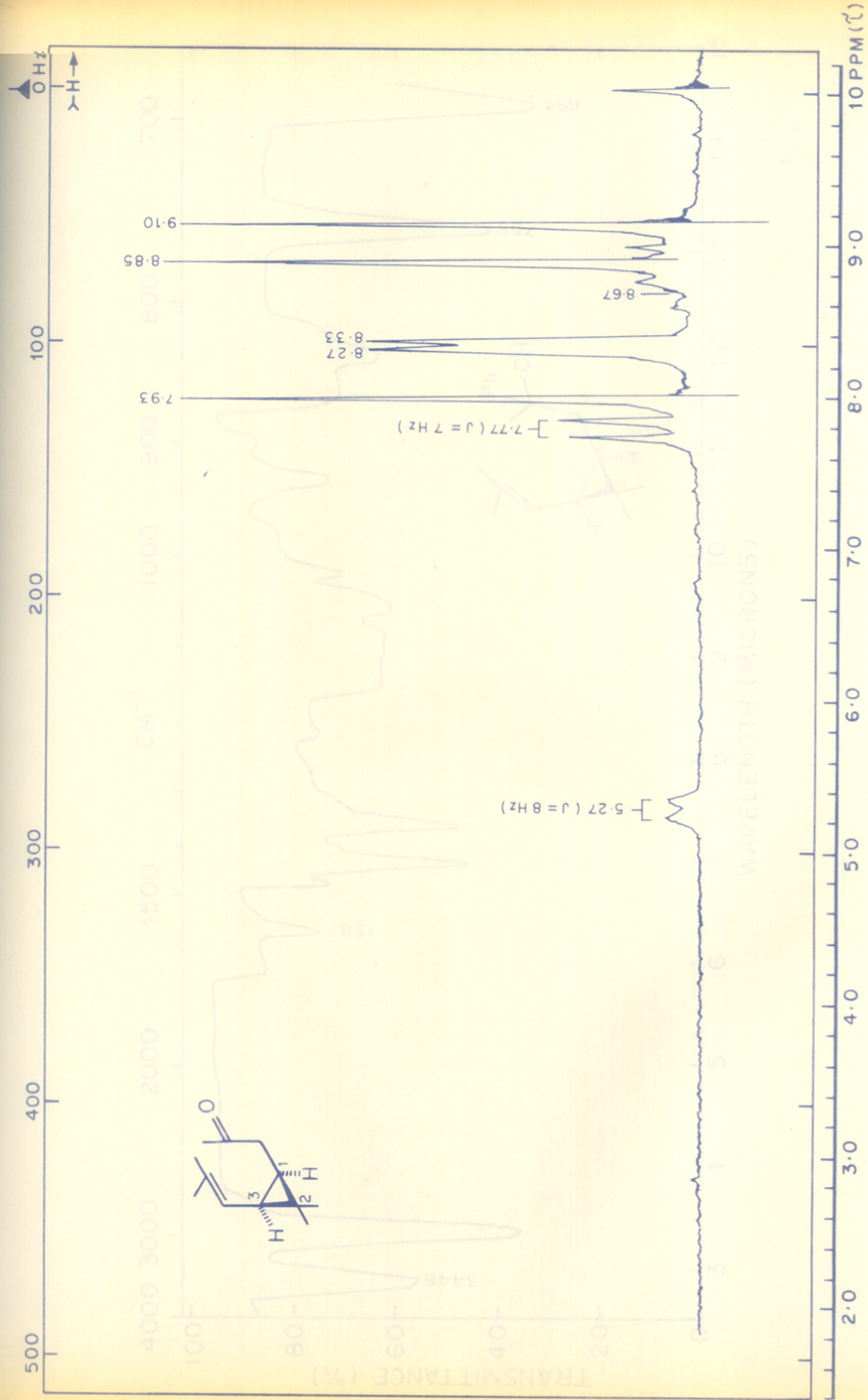


FIG. 15. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-CIS-1-ACETONYL-
-CYCLOPROPANE (XV)

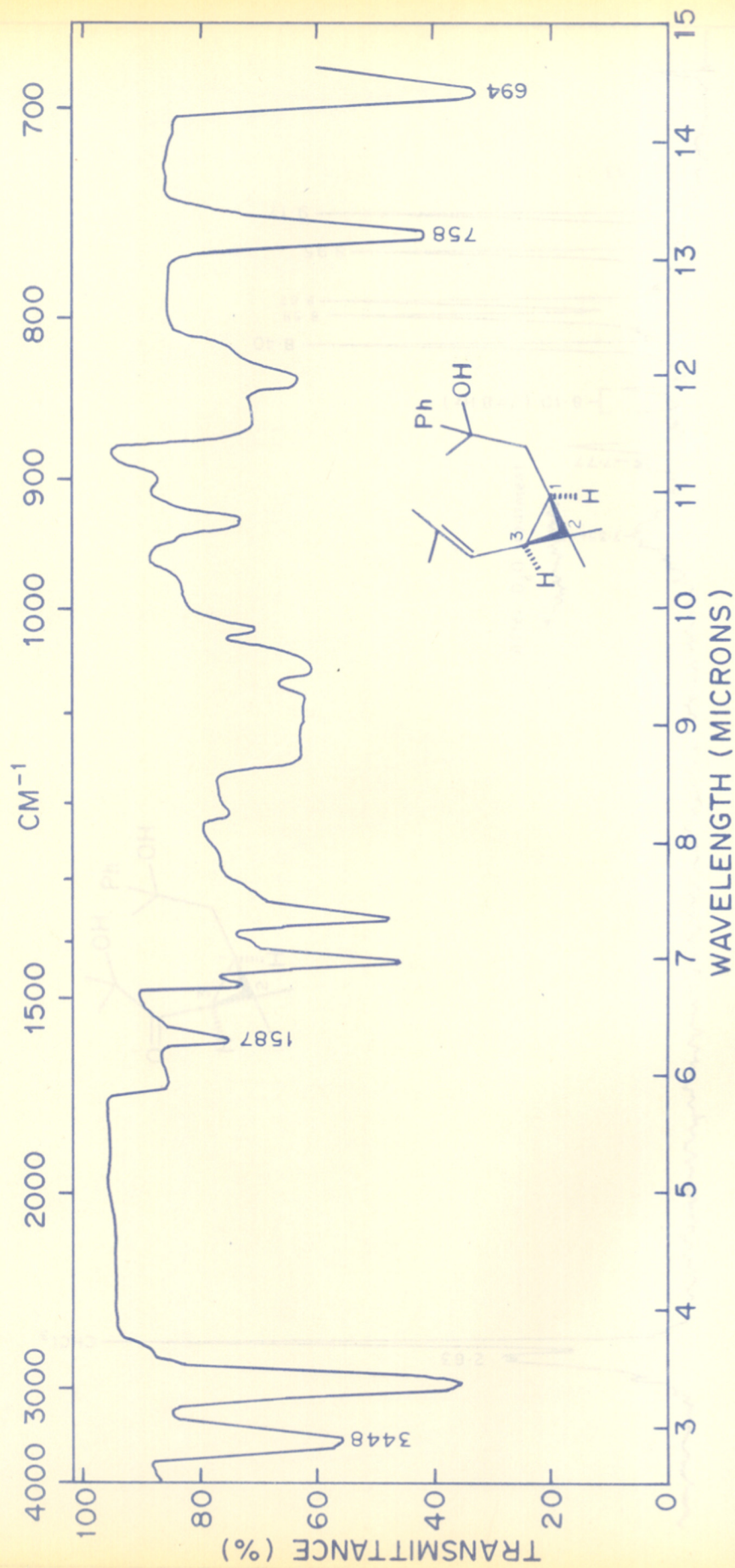


FIG. 16. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-CIS-1-(2-PHENYL-2-HYDROXYPROPYL)-CYCLOPROPANE (XVI)

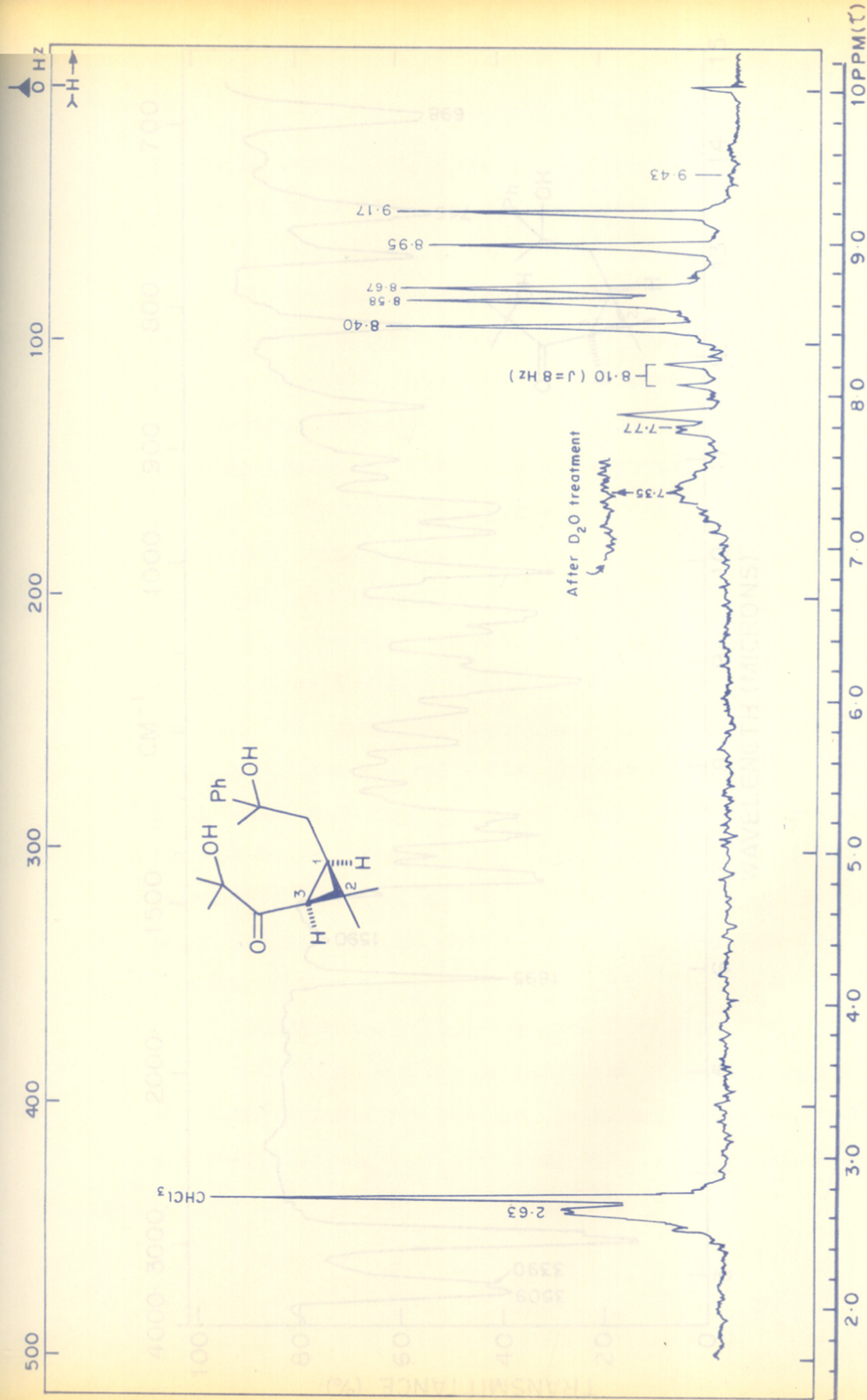


FIG. 17. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXY-1-OXOPROPYL)-

-CIS-1-(2-PHENYL-2-HYDROXYPROPYL)-CYCLOPROPANE (XIX)

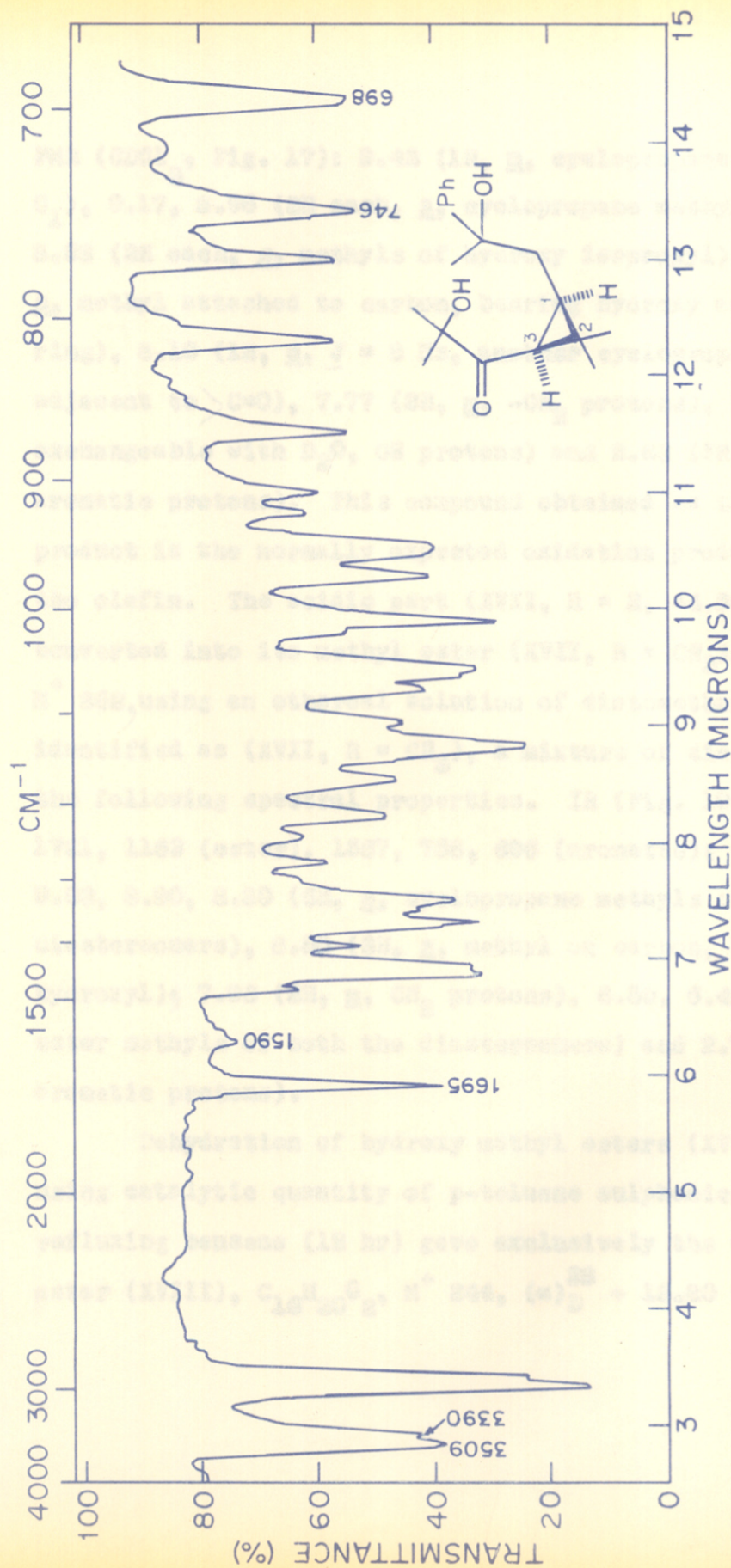


FIG. 18. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXY-1-OXOPROPYL)-CIS-
-1-(2-PHENYL-2-HYDROXYPROPYL)-CYCLOPROPANE (XIX) 62

PMR (CDCl_3 , Fig. 17): 9.43 (1H, $\underline{m}$, cyclopropane proton at C_1), 9.17, 8.95 (3H each, $\underline{s}$, cyclopropane methyls), 8.67, 8.58 (3H each, $\underline{s}$, methyls of hydroxy isopropyl), 8.40 (3H, $\underline{s}$, methyl attached to carbon, bearing hydroxy and phenyl ring), 8.10 (1H, $\underline{d}$, $J = 8$ Hz, another cyclopropane proton, adjacent to $>\text{C}=\text{O}$), 7.77 (2H, $\underline{m}$, $-\text{CH}_2$ protons), 7.35 (2H, br. $\underline{m}$, exchangeable with D_2O , OH protons) and 2.63 (5H, $\underline{m}$, aromatic protons). This compound obtained as the major product is the normally expected oxidation product³¹ from the olefin. The acidic part (XVII, R = H, 44.50%) was converted into its methyl ester (XVII, R = CH_3), $\text{C}_{16}\text{H}_{22}\text{O}_3$, M^+ 262, using an ethereal solution of diazomethane. It was identified as (XVII, R = CH_3), a mixture of diastereomers, by the following spectral properties. IR (Fig. 19): 3559 (OH), 1721, 1163 (ester), 1537, 756, 696 (aromatic); PMR: 9.13, 9.03, 8.90, 8.80 (6H, $\underline{s}$, cyclopropane methyls of both the diastereomers), 8.50 (3H, $\underline{s}$, methyl on carbon, bearing hydroxyl), 7.93 (2H, $\underline{m}$, CH_2 protons), 6.50, 6.43 (3H, $\underline{s}$, ester methyls of both the diastereomers) and 2.77 (5H, $\underline{m}$, aromatic protons).

Dehydration of hydroxy methyl esters (XVII, R = CH_3) using catalytic quantity of p-toluene sulphonic acid in refluxing benzene (12 hr) gave exclusively the unsaturated ester (XVIII), $\text{C}_{16}\text{H}_{20}\text{O}_2$, M^+ 244, $(\alpha)_D^{25} + 16.80$ (c, 0.70),

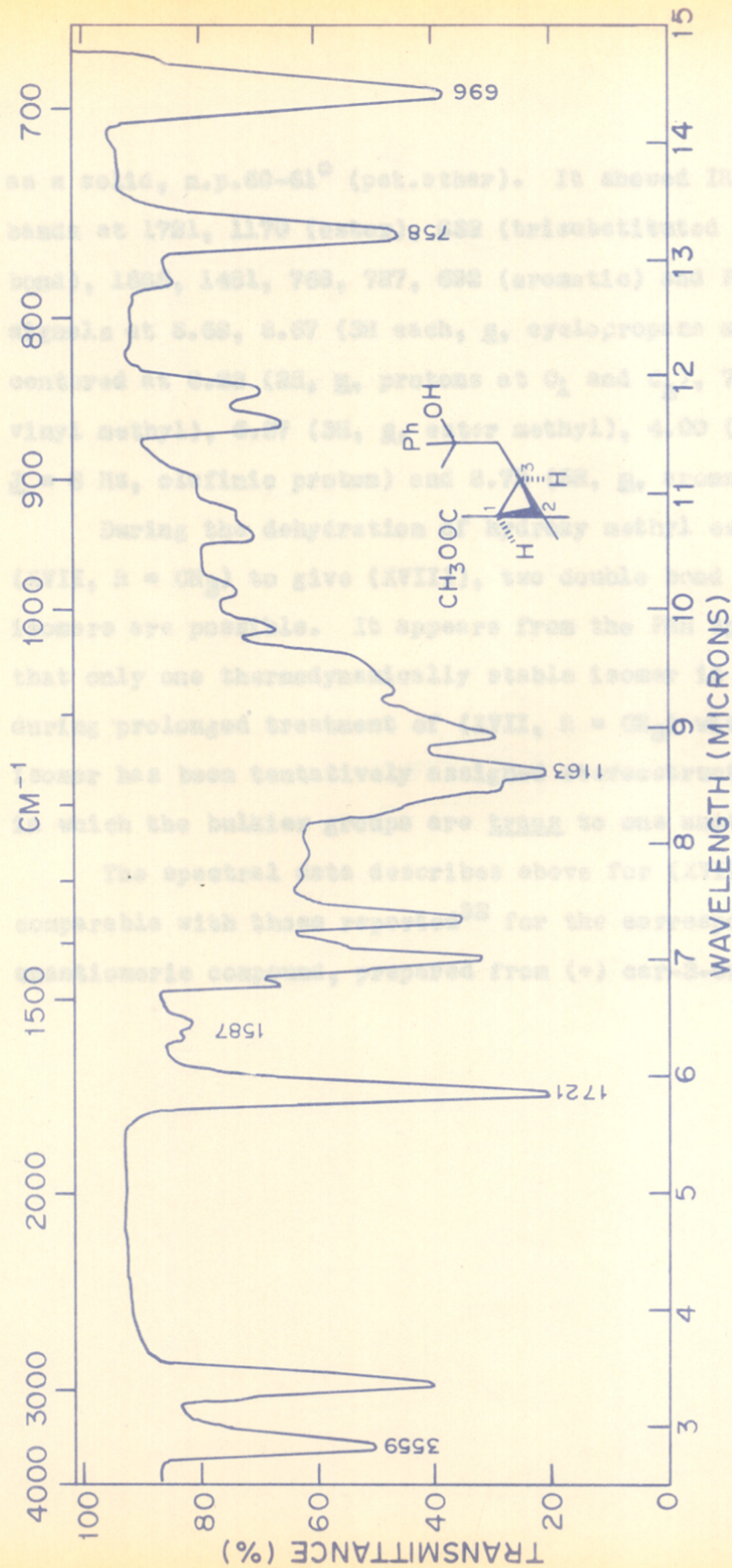


FIG. 19. IR SPECTRUM OF METHYL IS (+)-CIS-2,2-DIMETHYL-3-(2-PHENYL-2-HYDROXY-
-PROPYL) CYCLOPROPANE - CARBOXYLATE (XVII, $R = \text{CH}_3$)

as a solid, m.p. 60-61° (pet. ether). It showed IR (Fig. 20) bands at 1721, 1170 (ester), 832 (trisubstituted double bond), 1585, 1481, 762, 727, 692 (aromatic) and PMR (Fig. 21) signals at 8.68, 8.67 (3H each, s, cyclopropane methyls), centered at 8.23 (2H, m, protons at C₁ and C₃), 7.90 (3H, s, vinyl methyl), 6.37 (3H, s, ester methyl), 4.00 (1H, d, J = 8 Hz, olefinic proton) and 2.75 (5H, m, aromatic protons).

During the dehydration of hydroxy methyl ester (XVII, R = CH₃) to give (XVIII), two double bond geometric isomers are possible. It appears from the PMR spectrum that only one thermodynamically stable isomer is formed during prolonged treatment of (XVII, R = CH₃) with PTS and this isomer has been tentatively assigned stereostructure (XVIII) in which the bulkier groups are trans to one another.

The spectral data describes above for (XVIII) were comparable with those reported³² for the corresponding enantiomeric compound, prepared from (+) car-3-ene (I).

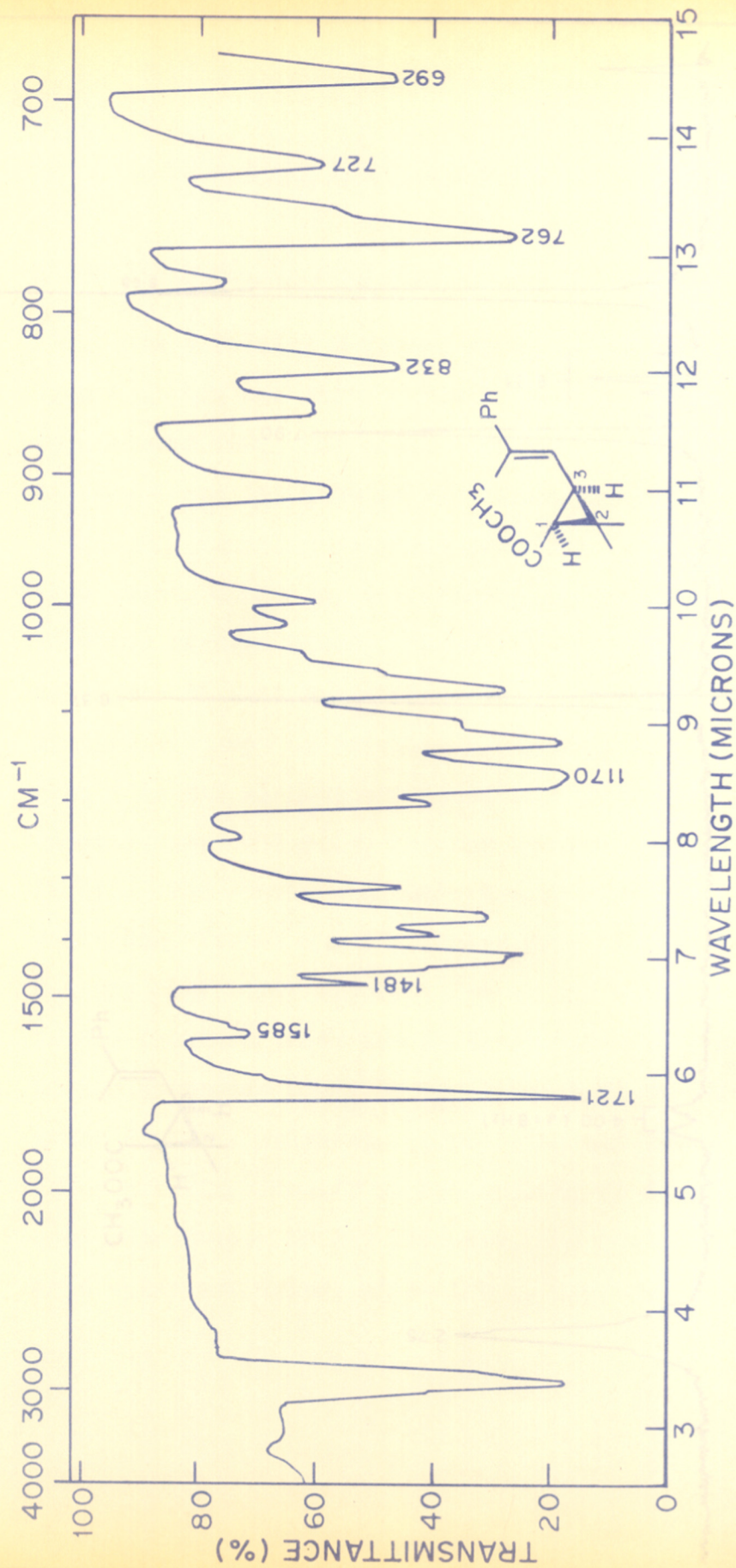


FIG. 20. IR SPECTRUM OF METHYL IS (+)-CIS-2,2-DIMETHYL-3-(2-PHENYL PROP-1-ENYL) CYCLOPROPANE CARBOXYLATE (XVIII)

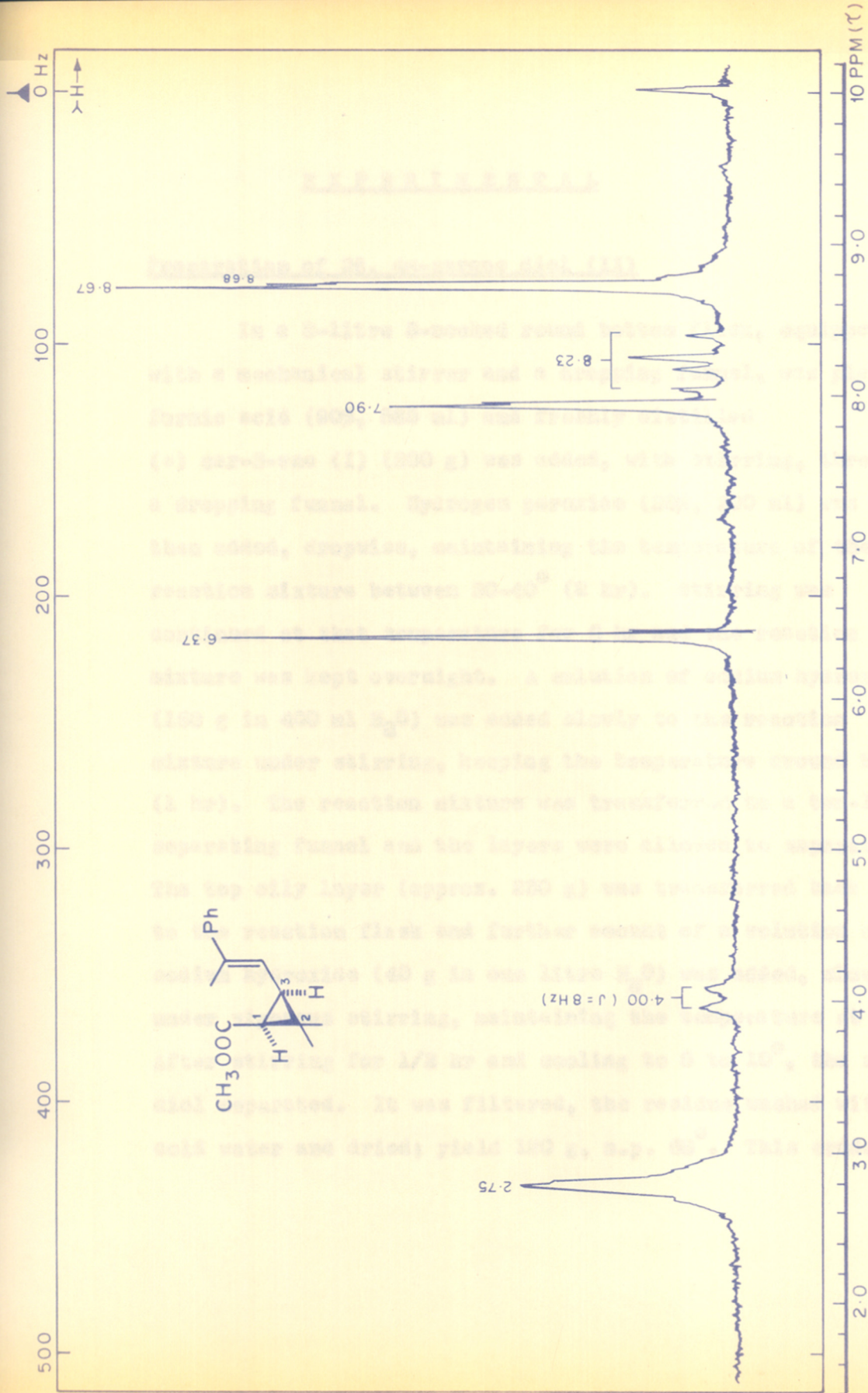


FIG. 21. PMR SPECTRUM OF METHYL IS(+) - CIS-2,2-DIMETHYL-3-(2-PHENYLPROP-1-ENYL)-CYCLOPROPANE CARBOXYLATE (XVIII)

EXPERIMENTAL

Preparation of 38. 4 α -carane diol (II)

In a 2-litre 3-necked round bottom flask, equipped with a mechanical stirrer and a dropping funnel, was placed formic acid (90%, 525 ml) and freshly distilled (+) car-3-ene (I) (200 g) was added, with stirring, through a dropping funnel. Hydrogen peroxide (30%, 300 ml) was then added, dropwise, maintaining the temperature of the reaction mixture between 30-40° (2 hr). Stirring was continued at that temperature for 6 hr and the reaction mixture was kept overnight. A solution of sodium hydroxide (160 g in 400 ml H₂O) was added slowly to the reaction mixture under stirring, keeping the temperature around 25° (1 hr). The reaction mixture was transferred to a two-litre separating funnel and the layers were allowed to separate. The top oily layer (approx. 250 g) was transferred back to the reaction flask and further amount of a solution of sodium hydroxide (40 g in one litre H₂O) was added, slowly, under vigorous stirring, maintaining the temperature at 25-30°. After stirring for 1/2 hr and cooling to 5 to 10°, the solid diol separated. It was filtered, the residue washed with cold water and dried; yield 120 g, m.p. 68°. This crude

diol was crystallised from pet. ether + 5% ethyl acetate to give 110 g of diol (II, 45%) m.p. 57-58°.

Analysis

Found: C, 70.81; H, 10.52;

$C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%.

IR bands at: 3448, 2900, 1460, 1375, 1058, 945 and 815 cm^{-1} .

2,2-Dimethyl-3-(2-oxopropyl)-cyclopropane-1-acetaldehyde (III)

In a 1-litre 3-necked flask equipped with an overhead mechanical stirrer, were taken carane diol (II, 51 g, 0.30 mole), methanol (200 ml) and water (75 ml). The contents were stirred at room temperature for 10 minutes. Finely powdered sodium meta periodate (70.60 g, 0.33 mole) was then added, portionwise to the above solution under stirring. After the addition (1/2 hr) the reaction mixture was stirred for 2 hr, filtered and the residue washed with methanol (50 ml), the combined filtrate was diluted with water (300 ml) and extracted with chloroform (150 ml + 75 ml x 2). The chloroform layer was washed with water (250 ml x 3), dried and evaporated to give the keto aldehyde (III, 41.50 g, 82%), b.p. 85-87° (vapour)/1.50 mm.

Analysis

Found: C, 70.95; H, 9.48;

$C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%.

IR bands at: 2985, 2740, 1724, 1439, 1351, 1163, 1124, 1047 and 962 cm^{-1} .

2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-cis-1-(2-hydroxy-propyl)-cyclohexane (IV)

A solution of keto aldehyde (III, 10 g, 0.072 mole) in dry ether (50 ml) was introduced, dropwise, under stirring into an ice-cooled solution of methyl magnesium iodide, prepared from magnesium turnings (6 g, 0.24 mole) and methyl iodide (34 g, 0.24 mole) in dry ether (150 ml). After the addition, it was stirred at room temperature for 2 hr. under reflux and kept overnight. The reaction mixture was cooled to 0° and a cold saturated solution of ammonium chloride (100 ml) was introduced dropwise into it with vigorous stirring. After stirring for 1/2 hr at room temperature, it was transferred to a separating funnel. The ether layer was separated and aqueous portion extracted with ether (100 ml x 2). The combined ether layer was washed with water, dried and evaporated to furnish the diol (IV, 9.80 g, 70%) as a colourless viscous liquid, b.p. 150° - 155° /0.50 mm.

Analysis

Found: C, 72.01; H, 12.10;

$\text{C}_{12}\text{H}_{24}\text{O}_2$ requires C, 71.95; H, 12.08%.

IR bands at: 3448, 2985, 1449, 1368, 1198, 1124, 1057, 980, 935, 907, 840 and 758 cm^{-1} .

2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-cis-1-(2-oxopropyl) cyclopropane (V)

A solution of the diol (IV, 8 g) in acetone (60 ml) was cooled to $0-5^{\circ}$. Jones reagent (32 ml) was then added dropwise with vigorous stirring. The mass was left at 0° for 1 hr and then diluted with ice cold water (100 ml) and extracted with ether (3 x 100 ml). The ether extract was washed successively with water, 10% aq. NaHCO_3 , again with water and finally with brine and dried. Removal of ether followed by distillation gave the hydroxy ketone (V, 7.60 g, 95%), b.p. $120-125^{\circ}/1.5\text{ mm}$, $(\alpha)_D^{25} + 40.58^{\circ}$ (g, 1.50).

Analysis

Found: C, 72.61; H, 11.12;

$\text{C}_{12}\text{H}_{22}\text{O}_2$ requires C, 72.68; H, 11.18%.

IR bands at: 3534, 3012, 1704, 1449, 1370, 1205, 1143, 982, 903 and 752 cm^{-1} .

2,2-Dimethyl-3-acetoxymethyl-cyclopropane-cis-1-(2'-methyl)propan-2'-ol (VI)

In a 500 ml 3-necked round bottom flask, equipped with an overhead mechanical stirrer, were taken hydroxy ketone (V, 12 g), chloroform (100 ml) and p-toluene sulphonic acid

(0.10 g) and the contents were cooled to 0°. A chloroform solution of perbenzoic acid (61 ml, 1N) was added and the contents were stirred for 6 hr at 0°. Another portion of perbenzoic acid solution (61 ml, 1N) was added and the stirring continued at 10-15° for 72 hr. The reaction mixture was transferred to a 2-litre separating funnel and washed thrice with 10% aqueous sodium carbonate solution (100 ml x 3) to free it from acids. It was then washed with water, dried and evaporated to give 10.40 g (80%) of a liquid material identified as (VI), further purified by distillation, b.p. 115-120°/0.50 mm, $(\alpha)_D^{25}$ - 16.60° (g, 0.84).

Analysis

Found: C, 66.92; H, 10.12;

$C_{12}H_{22}O_3$ requires C, 67.25; H, 10.35%.

IR bands at: 3472, 2985, 1724, 1449, 1361, 1235, 1015 and 902 cm^{-1} .

2,2-Dimethyl-3-hydroxymethyl-cyclopropane-cis-1(2'-methyl)propan-2'-ol (VII)

To a solution of potassium hydroxide (3 g) in water (20 ml) and methanol (150 ml), was added hydroxy acetate (VI, 6 g) and the homogeneous solution was refluxed on water bath for 6 hr. Most of the methanol was removed under suction and the residue diluted with water (200 ml) and extracted thrice with ether (100 ml x 3). The combined ether layer was

washed with water, dried and distilled to furnish crude solid diol (4.40 g, 90%) which was purified by crystallisation to give a crystalline solid (VII), m.p. 72-73° (pet. ether), $(\alpha)_D^{25} -26.5^\circ$ (c, 0.23).

Analysis

Found: C, 69.52; H, 11.48;

$C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%.

IR bands at: 3311, 2941, 1449, 1366, 1149, 1020, 984, 883 and 762 cm^{-1} .

(+) Dihydrochrysanthemo lactone (VIII) from the diol (VII)

To an ice-cooled solution of the diol (VII, 1.50 g) in acetone (20 ml), Jones chromic acid reagent was added dropwise, with shaking till the brown colour persisted. It was kept at 5-10° for an hour, diluted with water (100 ml) and extracted with chloroform (100 ml + 50 ml x 2). The chloroform layer was washed with water and extracted with 10% aqueous sodium carbonate solution (25 ml x 3). The chloroform layer was washed with water and dried. Removal of chloroform furnished a solid (1.00 g, 68%) purified by crystallisation from pet. ether to give a white crystalline solid (VIII), m.p. and m.m.p. 82-83°, $(\alpha)_D^{25} + 78^\circ$ (c, 1.35).

Analysis

Found: C, 71.12; H, 9.23;

$C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%.

IR bands at: 2985, 1724, 1449, 1374, 1264, 1189, 1096, 949 and 889 cm^{-1} .

The aqueous sodium carbonate layer was acidified with 10% sulphuric acid and extracted with ether (100 ml + 75 ml). The ether layer was washed with water (75 ml x 2), dried and evaporated to give the hydroxy acid (IX, R = H, 0.30 g, 18.50%). It was esterified by an ethereal solution of diazomethane. The methyl ester (IX, R = CH_3) thus obtained, was further purified by distillation to afford a colourless liquid (0.20 g), b.p. 110° (vapour)/1.50 mm, (α)_D²⁵ - 16.20° (g, 1.60).

Analysis

Found: C, 65.63; H, 10.26;

$\text{C}_{11}\text{H}_{20}\text{O}_3$ requires C, 65.97; H, 10.07%.

IR bands at: 3704, 3077, 1724, 1439, 1370, 1212, 1163, 1075, 1042, 985, 952, 901, 881, 847, 816, 784, 755 and 709 cm^{-1} .

Methyl 1R cis-2,2-dimethyl-3-(2-hydroxy-2-methylpropyl) cyclopropane carboxylate (IX, R = CH_3) from lactone (VIII)

To a solution of lactone (VIII, 0.50 g) in methanol (25 ml) was added an aqueous solution of potassium hydroxide (2 g in 5 ml of water) and the homogeneous solution refluxed for 4 hr. Methanol was removed under suction and the residue

diluted with water (50 ml) and extracted with ether (75 ml x 2) to remove the neutral material (0.060 g).

The aqueous portion was acidified with 10% sulphuric acid at 5° and extracted with ether (75 ml + 50 ml x 2). The ether layer was washed with water (100 ml x 2), dried and evaporated to furnish the hydroxy acid which was converted into its methyl ester (0.41 g) by an ethereal solution of diazomethane. Distillation afforded a pure colourless ester (IX, R = CH₃, 0.36 g), b.p. 110° (vapour)/1.50 mm, (α)_D²⁵ - 17.10° (c, 2.12).

Analysis

Found: C, 66.26; H, 9.88;

C₁₁H₂₀O₃ requires C, 65.97; H, 10.07%.

IR bands at: 3704, 3077, 1724, 1439, 1373, 1270, 1212, 1165, 1070, 1045, 995, 950, 900, 880, 845, 816, 784, 755 and 710 cm⁻¹.

Methyl (+)-cis-chrysanthemate (methyl 1R-cis (+)-2,2-dimethyl-3(2-methylprop-1-enyl)-cyclopropane carboxylate (X)

A solution of hydroxy ester (IX, R = CH₃, 0.55 g) in dry benzene (25 ml) was refluxed with p-toluene sulphonic acid (0.025 g) for 8 hr. The benzene solution, containing the reaction product was washed with water (25 ml x 3), dried and the solvent evaporated to furnish the product (0.435 g). It showed on TLC (6% ethyl acetate in benzene) two spots, the

more polar was identical with that of lactone (VIII).

The mixture was chromatographed over silicic acid (12 g). Methyl (+) cis chrysanthemate (X), the less polar component, was eluted with pet.ether and pet.ether + ether (2%). It was further purified by distillation to afford colourless liquid (0.225 g), b.p.100°/9 mm, (α)_D²⁵ + 41° (g, 1.20).

Analysis

Found: C, 72.16; H, 10.16;

$C_{11}H_{16}O_2$ requires C, 72.49; H, 9.96%.

IR bands at: 3077, 1732, 1429, 1399, 1370, 1316, 1190, 1170, 1136, 1075, 990, 917, 825 and 746 cm^{-1} .

2,2-Dimethyl-3-(2-methylprop-1-enyl)-cis-1-acetoxymethyl cyclopropane (XI)

To an ice-cooled solution of hydroxy acetate (VI, 20 g) dissolved in pyridine (10 ml), phosphorous oxychloride (1.60 g), was added dropwise with shaking and the reaction mixture was allowed to stand for 24 hr. at room temperature. It was then poured on crushed ice with stirring and the contents allowed to attain room temperature. It was extracted with ether (100 ml + 50 ml x 2), the ether layer was washed with dilute hydrochloric acid, followed by water and dried. Removal of ether furnished a mixture of two

unsaturated acetates $\angle 1.50$ g, 82%, TLC on $\text{SiO}_2 + \text{AgNO}_3$ (10%), 8% ethyl acetate in benzene, two spots⁷. The reaction product was chromatographed on silicic acid 27 g impregnated with 3 g of silver nitrate and eluted with pet.ether, pet.ether + benzene mixtures, benzene and chloroform. The fractions eluted with pet.ether and pet.ether + 10% benzene gave the TLC pure acetate (XI), further purified by distillation, b.p. $100-110^\circ/3$ mm.

Analysis

Found: C, 73.31; H, 10.35;

$\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.43; H, 10.27%.

IR bands at: 2994, 1745, 1443, 1363, 1235 and 1020 cm^{-1} .

The fractions eluted with pet.ether + benzene (1:1) and benzene, gave the pure (TLC) isomeric acetate (XII), purified further by distillation, b.p. $105-110^\circ/3$ mm.

Analysis

Found: C, 73.21; H, 10.39;

$\text{C}_{12}\text{H}_{20}\text{O}_2$ requires C, 73.43; H, 10.27%.

IR bands at: 2992, 1739, 1642, 1439, 1361, 1235, 1018 and 833 cm^{-1} .

2,2-Dimethyl-3-(2-methylprop-1-enyl)-cis-1-hydroxy-
methyl-cyclopropane (XIII)

The acetate (XI, 2.50 g) was added to a solution of potassium hydroxide (2 g) in water (10 ml) and methanol (50 ml) and the homogeneous mixture was refluxed on a water bath for 6 hr. Most of the methanol was removed under suction and the residue diluted with water (100 ml), extracted with ether (100 ml + 75 ml x 2). The combined ether layer was washed with water, dried and evaporated to give a liquid alcohol (1.80 g, 90%), purified by distillation to yield the pure (TLC) alcohol (XIII), b.p. 85-90° (vapour)/1.50 mm, $(\alpha)_D^{25} + 49^\circ$ (g, 1.5).

Analysis

Found: C, 77.61; H, 11.46;

$C_{10}H_{18}O$ requires C, 77.86; H, 11.76%.

IR bands at: 3390, 2976, 1667, 1439, 1366, 1126, 1064
and 840 cm^{-1} .

Methyl (+) cis-chrysanthemeate (X)

To an ice-cooled solution of the alcohol (XIII, 1 g) in acetone (10 ml), Jones chromic acid reagent was added dropwise till the brown colour persisted. After keeping for 1/2 hr, the reaction mixture was diluted with water (50 ml) and extracted with chloroform (100 ml x
+ 50 ml x 2). The combined chloroform layer was washed with water (25 ml x 2)

and extracted with aqueous sodium carbonate solution (10%, 20 ml x 3). The carbonate layer was acidified with HCl, saturated with salt and extracted with chloroform (50 ml x 3). The chloroform layer was dried and the solvent evaporated to give an acid (XIV, 0.40 g). This was esterified with an ethereal solution of diazomethane to give the methyl ester (IX, R = CH₃), purified by chromatography on alumina (Gr. II, 12 g) and eluted with pet.ether, pet.ether + benzene (10%) to give a TLC pure ester (0.20 g), comparable in spectral properties³⁰ with methyl (+)-cis chrysanthemate (X), (α)_D²⁵ + 39° (c, 1.30).

Analysis

Found: C, 72.26; H, 10.16;

C₁₁H₁₈O₂ requires C, 72.49; H, 9.96%.

2,2-Dimethyl-3-(2-methylprop-1-enyl)-cis-1-acetonyl-cyclopropane (XV)

The keto alcohol (V, 8 g) dissolved in dry benzene (300 ml) was refluxed on a water bath with PTS (0.10 g) for 15 hr. The solution was then washed with water repeatedly to remove PTS and dried. Removal of benzene followed by distillation of the residue (6.50 g, 80%) gave the unsaturated ketone (XV) in TLC pure state (SiO₂ + AgNO₃ plate, 6% ethylacetate in benzene),

b.p. 115-120°/2 mm, $(\alpha)_D^{28} + 77^\circ$ (g, 2.40).

Analysis

Found: C, 79.78; H, 11.10;

$C_{12}H_{20}O$ requires C, 79.94; H, 11.18%.

IR bands at: 2967, 1710, 1439, 1366, 1342, 1218, 1149, 1042 and 826 cm^{-1} .

2,2-Dimethyl-3-(2-methylprop-1-enyl)-2-phenyl-2-hydroxypropyl cyclopropane (XVI)

In a 500 ml 3-necked flask, equipped with an overhead mechanical stirrer, a dropping funnel and a reflux condenser, were placed magnesium turnings (0.60 g), a crystal of iodine and dry ether (100 ml). To this, a few mls of a solution of bromo benzene (3.80 g) in dry ether (50 ml) was added initially under stirring and the contents warmed to initiate the reaction. After the reaction was set in, the remaining solution of bromo benzene was added dropwise under stirring and after the addition was complete, it was refluxed for 1/2 hr to dissolve all the magnesium. The solution of phenyl magnesium bromide in ether thus obtained, was cooled to 0° and a solution of the ketone (XV, 4.20 g) in dry ether (50 ml) was added dropwise under stirring. After the addition was complete, the reaction mixture was allowed to attain room temperature, then refluxed for 1 hr and kept over night. The

Grignard complex was then decomposed by addition of saturated ammonium chloride solution at 5-10° and the layers were allowed to separate. The ether layer was removed and the aqueous layer was extracted with ether (100 ml x 2), the combined ether layer washed with water and dried. Removal of ether gave the crude liquid unsaturated alcohol (5 g), which was purified by chromatography over alumina (Gr. II, 75 g) and eluted with pet.ether, pet.ether + benzene mixtures, benzene and ethyl acetate. The fractions eluted with benzene and ethyl acetate which were TLC pure (6% ethyl acetate in benzene), were mixed together (4.60 g) and distilled to get (XVI), b.p. 150-160°/1 mm, (α)_D²⁵ + 28° (c, 1.70).

Analysis

Found: C, 83.87; H, 9.98;

C₁₈H₂₆O requires C, 83.66; H, 10.14%.

IR bands at: 3448, 2941, 1587, 1481, 1449, 1361, 1053, 1020, 758 and 694 cm⁻¹.

Methyl 1S-(+)-cis-2,2-dimethyl-3-(2-phenyl-2-hydroxypropyl), cyclopropane carboxylate (XVII, R = CH₃)

To a solution of the unsaturated alcohol (XVI, 3.70 g) in acetone (25 ml), acetic acid (10 ml) and water (15 ml), powdered potassium permanganate (3.40 g) was added portion-

wise under stirring during 1/2 hr. Stirring was continued for 1/2 hr more and the reaction mixture was treated simultaneously with sodium nitrite (3 g) and sulphuric acid (1:10), when all the manganese dioxide was dissolved. The contents were then transferred to a separating funnel and extracted with ether (100 ml x 3). The ether layer was washed with water and extracted with 10% aqueous sodium carbonate solution (15 ml x 2). The carbonate layer was acidified to 2 pH with hydrochloric acid and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water, dried and evaporated to furnish the hydroxy acid (XVII, R = H, 1.60 g). This was converted to the methyl ester (XVII, R = CH₃) by an ethereal solution of diazomethane and the methyl ester distilled (1.50 g, 39.9%), b.p. 120-130°/2 mm, (α)_D²⁵ + 8.70° (c, 2.6).

Analysis

Found: C, 73.08; H, 8.66;

C₁₆H₂₂O₃ requires C, 73.25; H, 8.45%.

IR bands at: 3559, 2988, 1721, 1587, 1449, 1370, 1163, 844, 758 and 696 cm⁻¹.

The ether layer after extraction with sodium carbonate solution, was repeatedly washed with water (50 ml x 3), dried and evaporated to give the keto diol (XIX) in the neutral part. The neutral part (XIX, 2 g, 48%) was crystallised from

pet.ether to give a solid, m.p.124-125°.

Analysis

Found: C, 74.32; H, 9.08;

$C_{18}H_{26}O_3$ requires C, 74.44; H, 9.03%.

IR bands at: 3502, 3390, 2938, 1625, 1520, 1495, 1462, 1439, 1408, 1370, 1335, 1300, 1220, 1178, 1135, 1110, 1075, 1053, 1010, 973, 952, 909, 870, 812, 770, 746 and 692 cm^{-1} .

Methyl 18(+)-cis-2,2-dimethyl-3-(2-phenylprop-1-enyl)-cyclopropane carboxylate (XVIII)

A solution of hydroxy ester (XVII, R = CH₃, 1.50 g), in dry benzene (75 ml) was refluxed with catalytic quantity of Pts (0.10 g) for 12 hr. The benzene solution was washed with water (100 ml x 2), dried and the benzene evaporated to furnish a solid (1.20 g, 86%) which was crystallised from pet.ether to give ester (XVIII) as white needles, m.p.60-61°, $(\alpha)_D^{28} + 16.80^\circ$ (g, 0.70).

Analysis

Found: C, 78.46; H, 8.07;

$C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%.

IR bands at: 3067, 1721, 1535, 1421, 1439, 1379, 1333, 1170, 1143, 1087, 917, 832, 762 and 692 cm^{-1} .

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CHAPTER - II

A NEW APPROACH TO THE SYNTHESIS OF METHYL IN CIS-2,2-DIMETHYL-3-(2-PHENYLPROP-1-ENYL) CYCLOPROPANE CARBOXYLATE AND METHYL (+) CIS-CERYLANTHEMATE FROM (+) CAR-3-ENE

SUMMARY

The trans carane diol (II) obtainable from (+) car-3-ene (I), on oxidation with Jones chromic acid reagent gave the keto acid (III, R = H) which, on esterification (MeOH/H⁺) afforded the keto ester (III, R = CH₃). Treatment of the keto ester (III, R = CH₃) with ethylene glycol and p-toluene sulphonic acid (PTS) gave the ketal ester (IV). Grignard reaction on ketal ester (IV), using methyl magnesium-iodide gave a liquid ketal alcohol (V), which on deketalisation and dehydration with PTS furnished a mixture of two isomeric unsaturated ketones (VI) and (VII). These were separated by chromatography. Treatment of (VI) with phenyl magnesium-bromide afforded a mixture of diastereomeric alcohols (VIII). Potassium permanganate oxidation of diastereomeric alcohols (VIII) gave the keto diol (IX) as the major product along with a mixture of diastereomeric hydroxy acids (X, R' = H). The latter, on esterification with an ethereal solution of diazomethane afforded a mixture of diastereomeric hydroxy methyl esters (X, R' = CH₃). Acid catalysed dehydration of the methyl ester (X, R' = CH₃) gave the methyl 1R-cis(-)-2,2-dimethyl-3-(2-phenylprop-1-enyl)-cyclopropane carboxylate (XI).

The cis acid (XII) obtainable from the ester (XI) was esterified with m-phenoxy benzyl alcohol to furnish the

active insecticidal ester (XIII).

Treatment of methyl magnesium iodide on the ketone (VI) afforded the unsaturated alcohol (XIV). Potassium permanganate oxidation of the alcohol (XIV) gave the keto diol (XV) in the neutral part and a hydroxy acid (XVI, $R' = H$) which, on esterification with an ethereal solution of diazomethane furnished the hydroxy methyl ester (XVI, $R' = CH_3$). The keto diol (XV) on reduction with lithium aluminium hydride gave the triol (XVII) which, on oxidation with Jones chromic acid reagent gave along with other products a hydroxy acid (XVI, $R' = H$) characterised through its methyl ester and identified as (XVI, $R' = CH_3$). Dehydration of the hydroxy methyl ester (XVI, $R' = CH_3$) with P₂S₅ afforded methyl 1R (+)-cis-chrysanthemate (XVIII) as the major product.

INTRODUCTION

"Synthetic Pyrethroids" which bear a close structural resemblance to natural pyrethrins and cinerins are increasingly becoming important as "Pest Control Agents". These insecticides have an advantage over other insecticides in the fact that they combine high insecticidal activity with low mammalian toxicity^{1,2}. They are also superior to natural pyrethrins^{3,4} in having higher photostability⁵ and are therefore applicable for agricultural use⁶. A number of synthetic pyrethroids^{7,8} have been prepared and used with success during the last few years in UK, USA, Japan and other advanced countries.

An important member of this group in commercial use is Permethrin⁹ (NRDC 143).

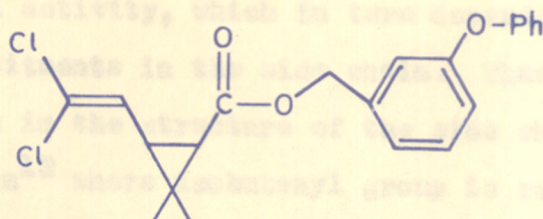
Structurally, most of these synthetic pyrethroids are esters of 2,2-dimethyl-3-vinyl substituted cyclopropane carboxylic acids, with alcohols like 3-phenoxy benzyl alcohol^{10,11} as in permethrin or 5-benzyl-3-furyl methyl alcohol as in resmethrin¹⁰. Variation of the vinyl substituent at the 3-position of the cyclopropane carboxylic acid is possible while maintaining insecticidal activity⁸. The synthesis of the various 3-vinyl substituted analogues was achieved by the reaction of appropriate Wittig reagents on cinnaldehyde

ester^{12,13}. Permethrin⁹ has been synthesised either by a Wittig reaction¹³ or from acyclic intermediates involving ring closure of the cyclopropane ring system¹⁴.

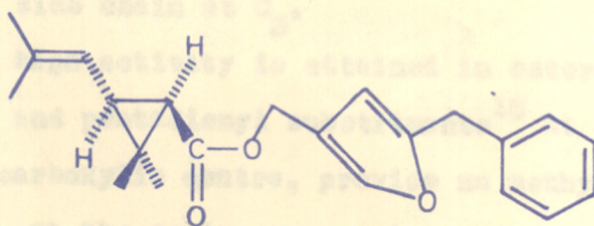
The natural pyrethrins and the synthetic pyrethroid group of insecticides are flexible molecules. Their insecticidal action depends on their ability to adopt a conformation in which all the structural features, essential for potency are appropriately oriented with respect to each other and to a complementary receptor. A characteristic feature of the pyrethroids is the sensitivity of their insecticidal action to changes in the substituents at certain important centres by which either the balance of conformers present, is disturbed or contact of molecule with a receptor is obstructed.

As already mentioned in Chapter I of this thesis, esters of 3-vinyl substituted-2,2-dimethyl cyclopropane carboxylic acids, with the carboxylic substituent in the 1R configuration, whether the side chain at C₃ is trans or cis to the carboxylic group are active¹⁵⁻¹⁸, whereas esters of the epimer are inactive or much less active. The potency of such ester is also sensitive to the substitution at or on the side chain at C₃^{16,18}.

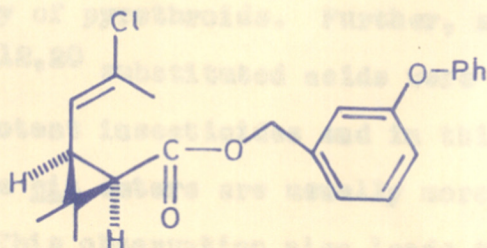
Thus in the acid moiety of the pyrethroids, the side chain attached at C₃ position of the cyclopropane ring system



PERMETHRIN



BIORESMETHRIN



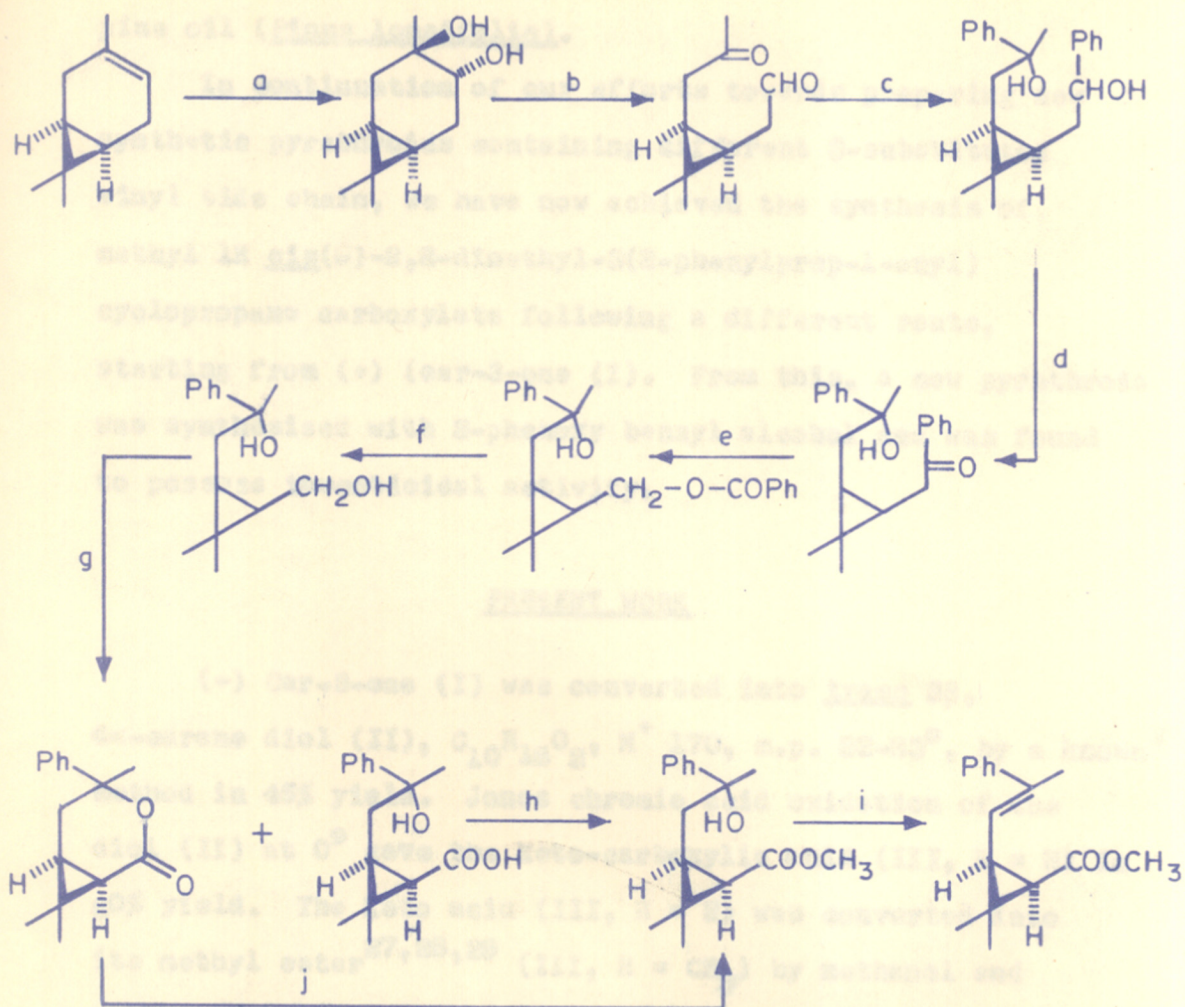
INDOTHRIN

is a position where structural changes greatly influence insecticidal activity, which in turn depends on the nature of the substituents in the side chain. Thus a simple modification in the structure of the side chain at C_3 in bioresmethrin¹² where isobutenyl group is replaced by but-1-enyl group, produces still greater activity but retains low mammalian toxicity. Similarly esters with simple vinyl substituent was found to be less active than chrysanthemates but monomethyl vinyl ester was more active. Maximum activity¹² was observed in the case of esters with but-1-enyl side chain at C_3 .

The high activity is attained in esters with 2 and 3 butadienyl and pentadienyl substituents¹⁸ at C_3 , trans and cis to the 1R carboxylic centre, provide no methyl groups are at C_3 or C_1 at the cyclopropane ring system. However, Matsui¹⁹ observed that increase of the methyl substitution at C_3 contributes to the greater activity e.g. 2,2,3,3-tetramethyl cyclopropane carboxylic acid esters are found to be more active than the corresponding 3-monomethyl derivatives which means presence of an unsaturated side chain is not a must for the activity of pyrethroids. Further, some esters of 3-dihalovinyl^{4,12,20} substituted acids were found to be outstandingly potent insecticides and in this class of insecticides, the cis esters are usually more active²¹ than the trans esters. This observation also leads to the conclusion

that presence of methyl group on the vinyl side chain at C₃ (as in chrysanthemic acids) is not essential for a pyrethroid to possess insecticidal activity as believed earlier.

As already mentioned, many esters of substituted chrysanthemic acids with different alcohols have been prepared and tested for their insecticidal property. However, the diphenyl vinyl and methyl phenyl vinyl analogues of chrysanthemic acid are not much studied. There are very few references available in literature for the synthesis of diphenyl vinyl and methyl phenyl vinyl analogues of chrysanthemic acid. M. Jacques et al.^{22,23} obtained diphenyl vinyl analogues by synthetic route and showed its ester to possess insecticidal property. Recently, in our laboratory, Mane et al.,²⁴ synthesised diphenyl vinyl analogue of chrysanthemic acid from (+) car-3-ene. Mane et al.²⁵ have also synthesised IR cis (-)-2,2-dimethyl-3(2-phenylprop-1-enyl)-cyclopropane carboxylate from (+) car-3-ene, as shown in scheme 1. In our laboratory, a new synthetic pyrethroid²⁶, called "Indothrin" viz., 3-phenoxy benzyl IR cis-2,2-dimethyl-3(2-chloroprop-1-enyl) cyclopropane carboxylate (as a mixture of double bond isomers) has been synthesised and found to possess almost similar type of insecticidal activity as permethrin. This compound has been synthesised starting from (+) car-3-ene (I), a cheap, abundant, indigenous by-product from

a ① HCOOH ② H_2O_2 b NaIO_4

c Grignard reaction with phenyl-magnesium bromide

d Jones reagent

e Baeyer-villiger oxidation with perbenzoic acid

f Methanolic potash

g Jones reagent

h Esterification with CH_2N_2

i PTS

j ① Methanolic potash

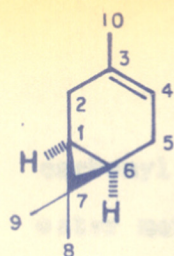
② Esterification with CH_2N_2

pine oil (Pinus longifolia).

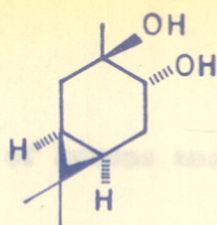
In continuation of our efforts towards preparing new synthetic pyrethroids containing different 3-substituted vinyl side chain, we have now achieved the synthesis of methyl trans-(+)-2,2-dimethyl-3(2-phenylprop-1-enyl) cyclopropane carboxylate following a different route, starting from (+) car-3-ene (I). From this, a new pyrethroid was synthesised with 3-phenoxy benzyl alcohol and was found to possess insecticidal activity.

PRESENT WORK

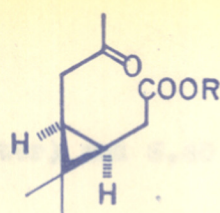
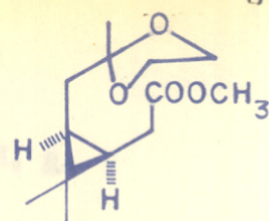
(+) Car-3-ene (I) was converted into trans 3 β , 4 α -carane diol (II), $C_{10}H_{18}O_2$, M^+ 170, m.p. 82-83°, by a known²⁷ method in 45% yield. Jones chromic acid oxidation of the diol (II) at 0° gave the keto-carboxylic acid (III, R = H) in 60% yield. The keto acid (III, R = H) was converted into its methyl ester^{27,28,29} (III, R = CH₃) by methanol and sulphuric acid in almost quantitative yield. The ester (III, R = CH₃), $C_{11}H_{18}O_3$, M^+ 198, showed IR bands at 1739, 1150 (ester), 1709 ($>C=O$) and PMR signals at 9.23, 9.00 (1H each, m, protons at C₁ and C₃ of cyclopropane), 9.10, 8.87 (3H each, s, gem dimethyl on cyclopropane), 7.90 (3H, s, COCH₃), 7.80, 7.67 (2H each, br.s, methylene protons adjacent to



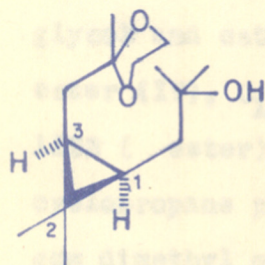
I



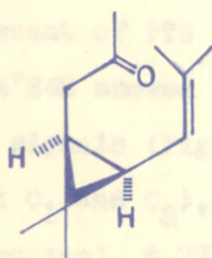
II

III, R=H; R=CH₃

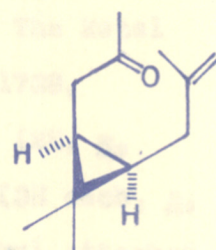
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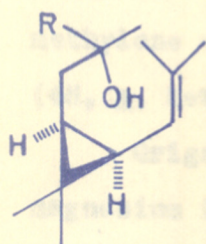
V



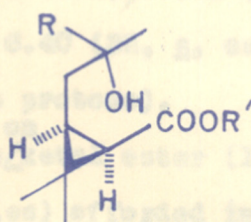
VI



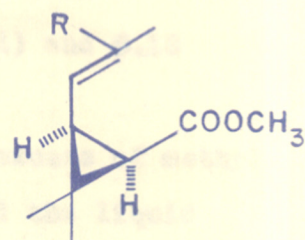
VII



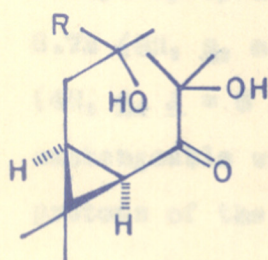
VIII, R=Ph

XIV, R=CH₃X, R=Ph, R'=CH₃

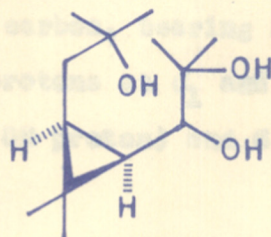
X, R=Ph, R'=H

XVI, R=CH₃, R'=HXVI, R=CH₃, R'=CH₃

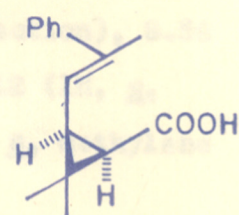
XI, R=Ph

XVIII, R=CH₃

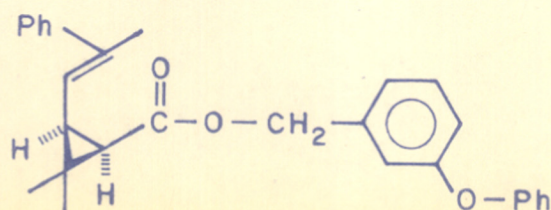
IX, R=Ph

XV, R=CH₃

XVII



XII



XIII

carbonyl group of ketone and ester) and 6.40 (3H, s, ester methyl).

The ester (III, R = CH₃) was converted into its ethylene ketal ester (IV), in 95% yield by treating it with ethylene glycol and catalytic amount of PPS in benzene. The ketal ester (IV), C₁₃H₂₂O₄, M⁺242 showed IR bands at 1739, 1163 (ester) and PMR signals (Fig. 1) at 9.28 (2H, m, cyclopropane protons at C₁ and C₃), 9.13, 8.93 (3H each, s, gem dimethyl on cyclopropane), 8.77 (3H, s, methyl attached to carbon, bearing the ketal function), 8.53 (2H, d, J = 6 Hz, methylene α to ketal function), 7.83 (2H, d, J = 9 Hz methylene α to ester), 6.40 (3H, s, ester methyl) and 6.18 (4H, s, ketal methylene protons).

Grignard reaction ^{on} ketal ester (IV) using excess of methyl magnesium iodide (3 moles) afforded in 90% yield the liquid ketal alcohol (V), C₁₄H₂₆O₃, M⁺ 242. It showed IR bands (Fig.2) at 3571, 1050 (-OH) and PMR signals (Fig.3) at 9.43 (2H, m, cyclopropane protons), 9.12, 8.92 (3H each, s, gem dimethyl on cyclopropane), 8.32 (6H, s, methyls of hydroxy isopropyl), 8.72 (3H, s, methyl on carbon, bearing ketal function), 8.52 (4H, d, J = 6 Hz, CH₂ protons at C₁ and C₃), 8.12 (1H, s, exchangeable with D₂O, OH proton) and 6.12 (4H, s, methylene protons of the ketal).

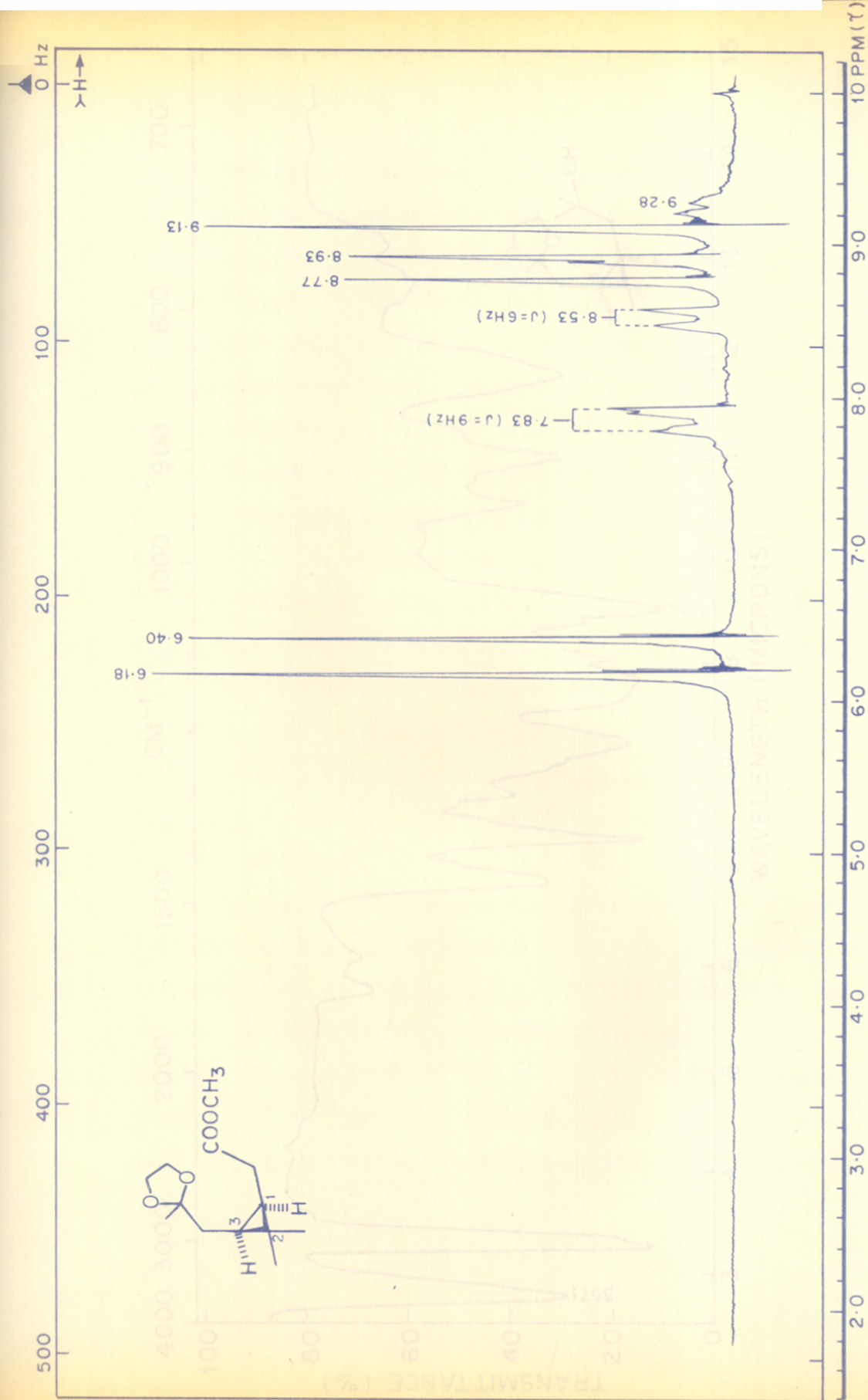


FIG. 1. PMR SPECTRUM OF METHYL-2,2-DIMETHYL-3-(2,2-ETHYLENE DIOXY PROPYL) -
CYCLOPROPANE-CIS-1-ACETATE (IV)

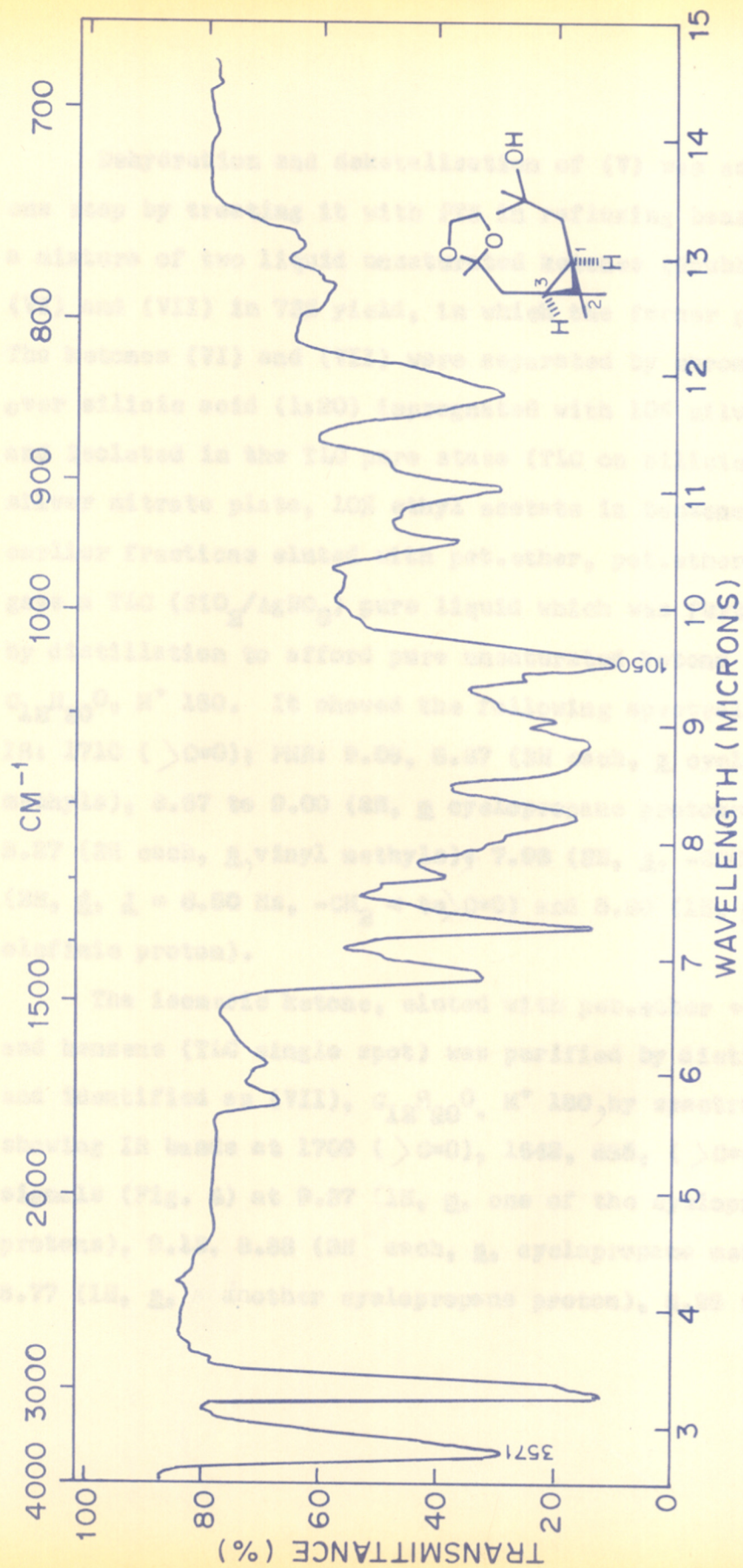


FIG. 2. IR SPECTRUM OF 2,2-DIMETHYL-3-(2,2-ETHYLENE DIOXY PROPYL)-CIS-1-(2-METHYL-2-HYDROXYPROPYL)-CYCLOPROPANE (V)

Dehydration and deketalisation of (V) was achieved in one step by treating it with P₂S₅ in refluxing benzene to afford a mixture of two liquid unsaturated ketones (double bond isomers) (VI) and (VII) in 73% yield, in which the former predominated. The ketones (VI) and (VII) were separated by chromatography over silicic acid (1:20) impregnated with 10% silver nitrate and isolated in the TLC pure state (TLC on silicic acid + silver nitrate plate, 10% ethyl acetate in benzene). The earlier fractions eluted with pet.ether, pet.ether + 10% benzene gave a TLC (SiO₂/AgNO₃) pure liquid which was further purified by distillation to afford pure unsaturated ketone (VI), C₁₂H₂₀O, M⁺ 180. It showed the following spectral properties. IR: 1710 (>C=O); PMR: 9.08, 8.87 (3H each, 2 cyclopropane methyls), 8.67 to 9.00 (2H, 2 cyclopropane protons), 8.32, 8.27 (3H each, 2 vinyl methyls), 7.93 (3H, 2, -COCH₃), 7.72 (2H, 2, 1 = 6.50 Hz, -CH₂ α to >C=O) and 5.20 (1H, 2, 1 = 8 Hz, olefinic proton).

The isomeric ketone, eluted with pet.ether + benzene (1:1) and benzene (TLC single spot) was purified by distillation and identified as (VII), C₁₂H₂₀O, M⁺ 180, by spectral data showing IR bands at 1709 (>C=O), 1642, 885, (>C=CH₂) and PMR signals (Fig. 4) at 9.37 (1H, 2, one of the cyclopropane protons), 9.13, 8.88 (3H each, 2, cyclopropane methyls), 8.77 (1H, 2, another cyclopropane proton), 8.28 (3H, 2, vinyl

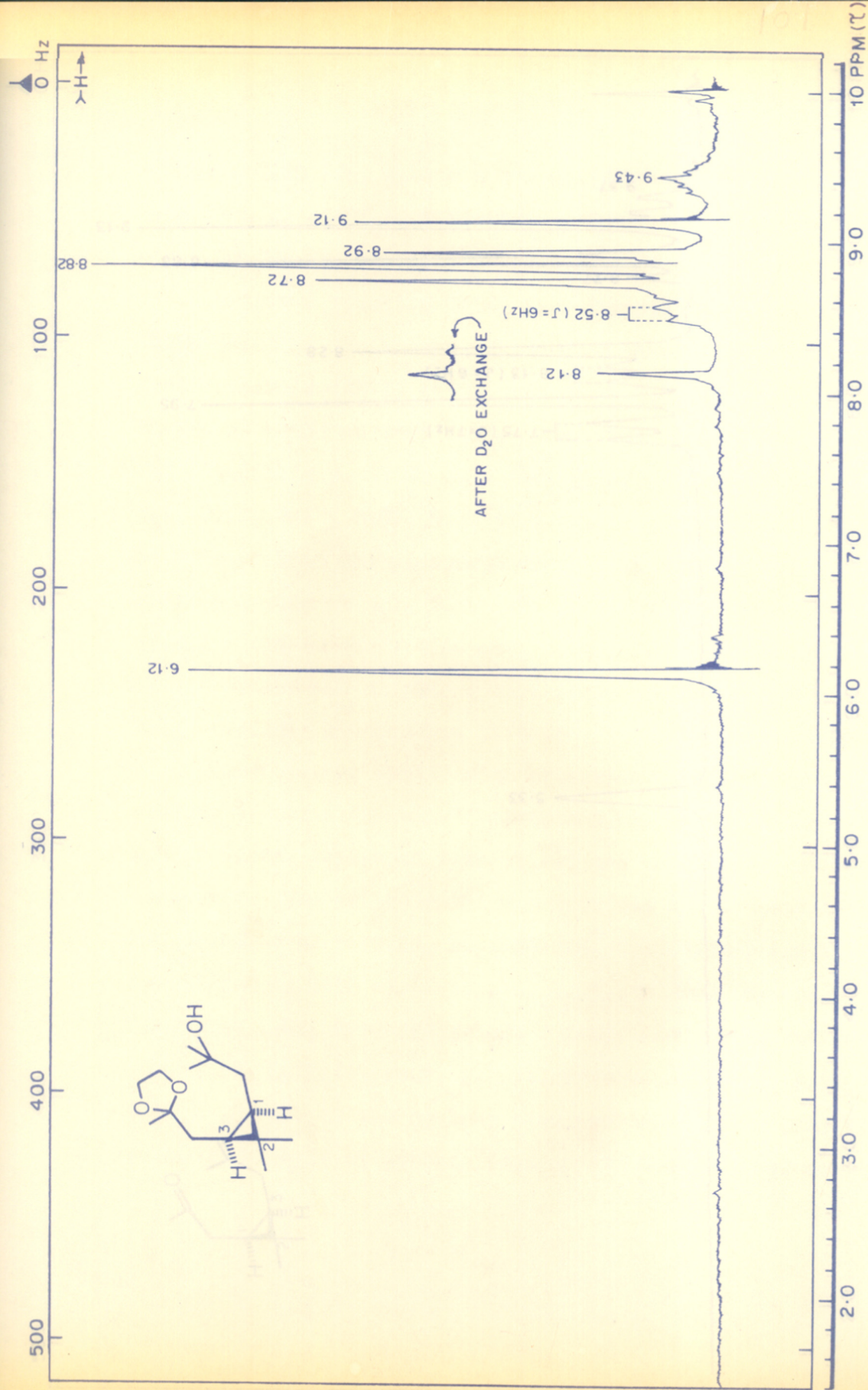


FIG. 3. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2,2-ETHYLENEDIOXYPROPYL)-CIS-1-(2-METHYL-2-HYDROXYPROPYL)-CYCLOPROPANE (V)

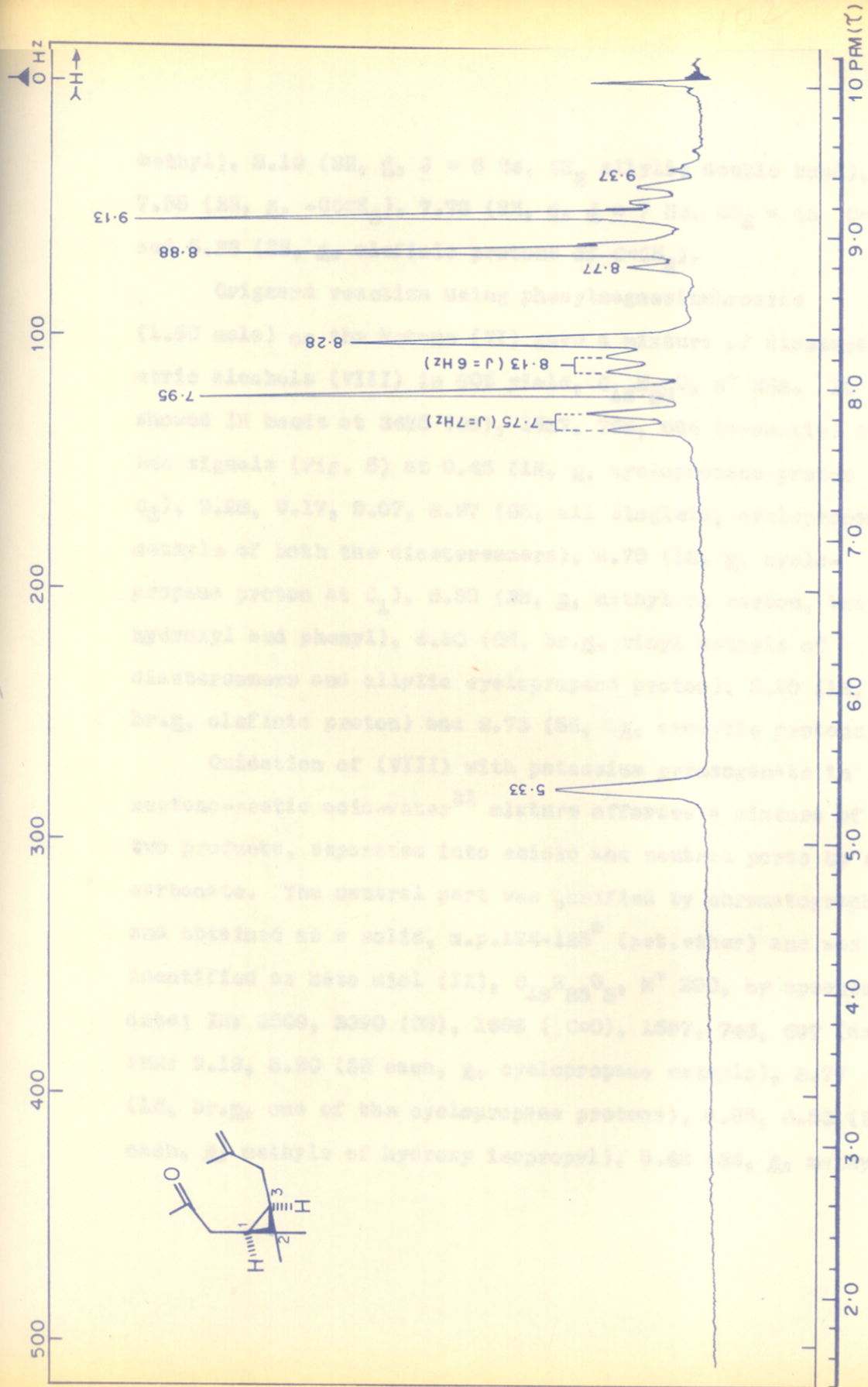


FIG. 4. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYLPROP-2-ENYL)-CIS-1-(2-OXOPROPYL)-

-CYCLOPROPANE (VII)

methyl), 8.13 (2H, d, $J = 6$ Hz, CH_2 allylic double bond), 7.95 (3H, s, $-\text{COCH}_3$), 7.75 (2H, d, $J = 7$ Hz, CH_2 α to $\text{C}=\text{O}$) and 5.33 (2H, s, olefinic protons of $\text{C}=\text{CH}_2$).

Grignard reaction using phenylmagnesiumbromide (1.50 mole) on the ketone (VI) gave a mixture of diastereomeric alcohols (VIII) in 80% yield, $\text{C}_{18}\text{H}_{26}\text{O}$, M^+ 258. It showed IR bands at 3425 (OH), 1587, 758, 694 (aromatic) and PMR signals (Fig. 5) at 9.45 (1H, m, cyclopropane proton at C_3), 9.28, 9.17, 9.07, 8.97 (6H, all singlets, cyclopropane methyls of both the diastereomers), 8.70 (1H, m, cyclopropane proton at C_1), 8.50 (3H, s, methyl on carbon, bearing hydroxyl and phenyl), 8.30 (6H, br.m, vinyl methyls of diastereomers and allylic cyclopropane proton), 5.20 (1H, br.m, olefinic proton) and 2.73 (5H, m, aromatic protons).

Oxidation of (VIII) with potassium permanganate in acetone-acetic acid-water³¹ mixture afforded a mixture of two products, separated into acidic and neutral parts by sodium carbonate. The neutral part was purified by chromatography and obtained as a solid, m.p. 124-125° (pet. ether) and was identified as keto diol (IX), $\text{C}_{18}\text{H}_{26}\text{O}_3$, M^+ 290, by spectral data; IR: 3509, 3390 (OH), 1698 ($\text{C}=\text{O}$), 1597, 746, 697 (aromatic); PMR: 9.13, 8.90 (3H each, s, cyclopropane methyls), 8.77 (1H, br.m, one of the cyclopropane protons), 8.65, 8.53 (3H each, s, methyls of hydroxy isopropyl), 8.42 (3H, s, methyl

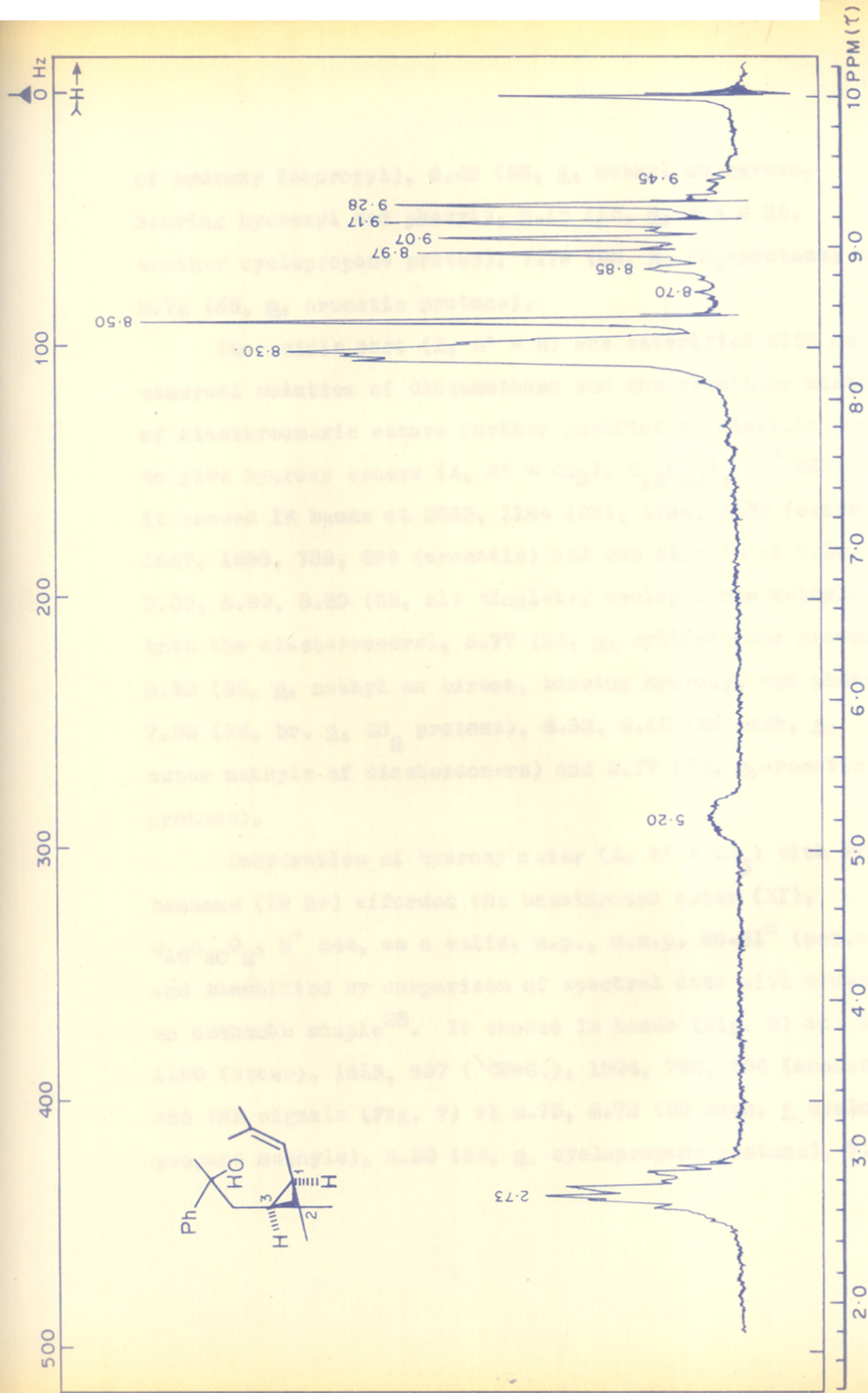


FIG. 5. PMR SPECTRUM OF 2,2-DIMETHYL-1-(2-METHYL PROP-1-ENYL)-CIS-3-(2-PHENYL)-2-HYDROXYPROPYL)-CYCLOPROPANE (VIII)

of hydroxy isopropyl), 8.42 (3H, s, methyl on carbon, bearing hydroxyl and phenyl), 8.15 (1H, d, $J = 8$ Hz, another cyclopropane proton), 7.79 (2H, m, CH_2 -protons) and 2.75 (5H, m, aromatic protons).

The acidic part ($X, R' = H$) was esterified with an ethereal solution of diazomethane and the resulting mixture of diastereomeric esters further purified by distillation to give hydroxy esters ($X, R' = \text{CH}_3$), $\text{C}_{16}\text{H}_{22}\text{O}_3$, $M^+ 262$. It showed IR bands at 3509, 1124 (OH), 1724, 1163 (ester), 1587, 1550, 758, 694 (aromatic) and PMR signals at 9.12, 9.03, 8.90, 8.80 (6H, all singlets, cyclopropane methyls of both the diastereomers), 8.77 (2H, m, cyclopropane protons), 8.50 (3H, s, methyl on carbon, bearing hydroxyl and phenyl), 7.93 (2H, br. d, CH_2 protons), 6.53, 6.43 (3H each, s, ester methyls of diastereomers) and 2.77 (5H, m, aromatic protons).

Dehydration of hydroxy ester ($X, R' = \text{CH}_3$) with PTS in benzene (12 hr) afforded the unsaturated ester (XI), $\text{C}_{16}\text{H}_{20}\text{O}_2$, $M^+ 244$, as a solid, m.p., m.m.p. 60-61° (pet. ether) and identified by comparison of spectral data with those of an authentic sample²⁵. It showed IR bands (Fig. 6) at 1748, 1190 (ester), 1613, 837 ($\text{CH}=\text{C}$), 1504, 766, 694 (aromatic) and PMR signals (Fig. 7) at 8.75, 8.72 (3H each, s cyclopropane methyls), 8.20 (2H, m, cyclopropane protons), 7.93

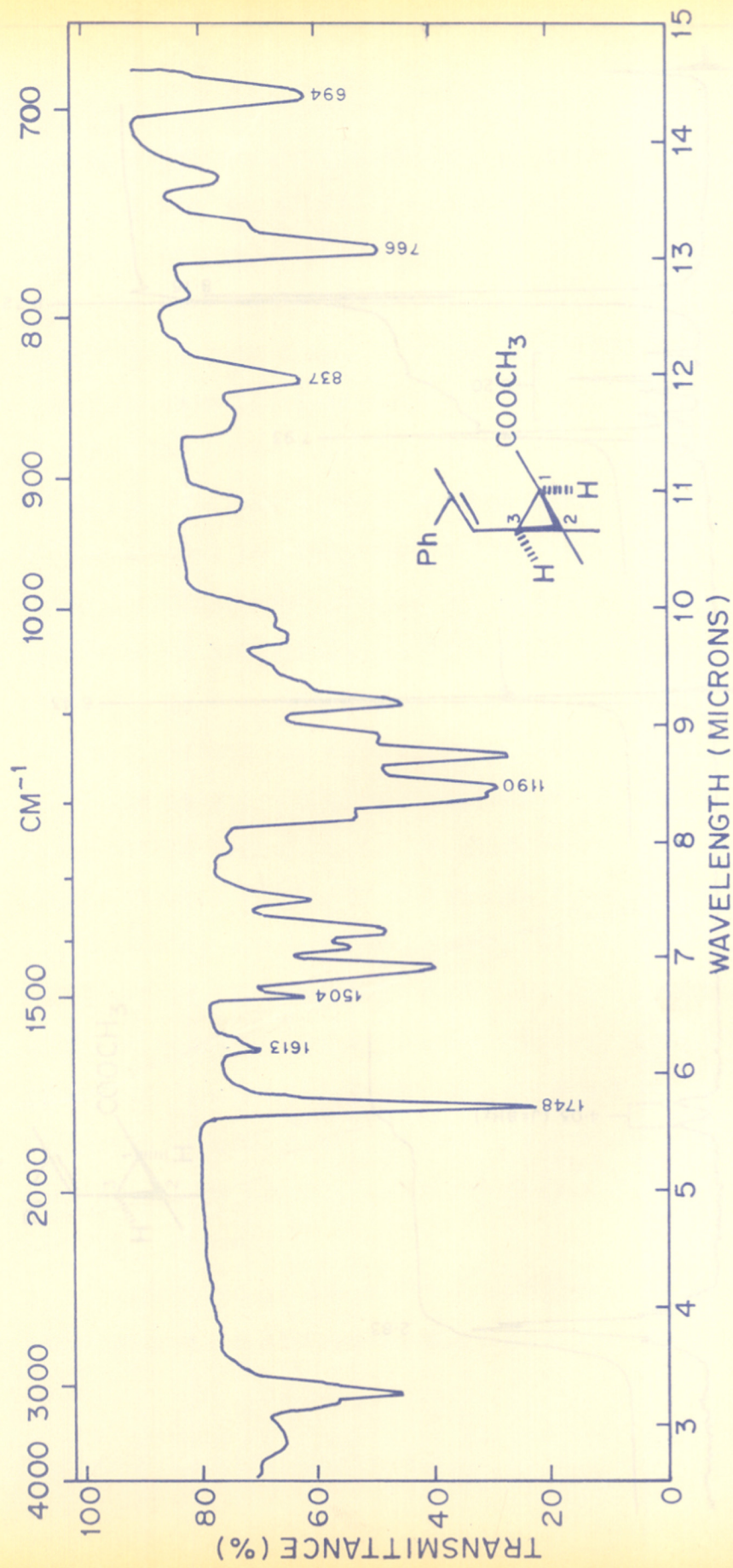


FIG. 6. IR SPECTRUM OF METHYL-1R-CIS-2,2-DIMETHYL-3-(2-PHENYL PROP-1-ENYL)-CYCLOPROPANE CARBOXYLATE (XI)

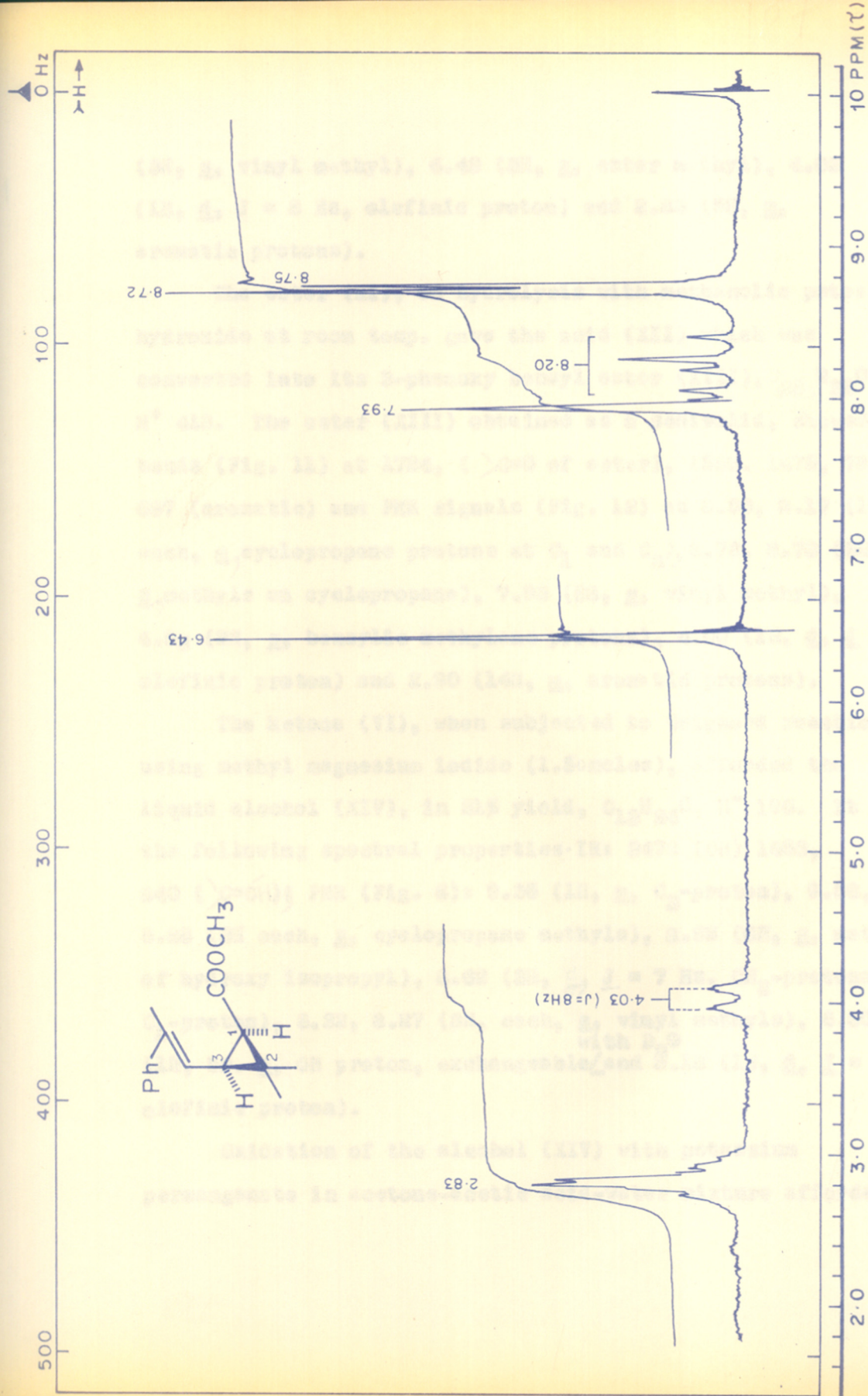


FIG. 7. PMR SPECTRUM OF METHYL-IR-CIS-2,2-DIMETHYL-3-(2-PHENYLPROP-1-ENYL)-

-CYCLOPROPANE CARBOXYLATE (XI)

(3H, s, vinyl methyl), 6.43 (3H, s, ester methyl), 4.03 (1H, d, $J = 8$ Hz, olefinic proton) and 2.83 (5H, m, aromatic protons).

The ester (XI), on hydrolysis with methanolic potassium hydroxide at room temp. gave the acid (XII) which was converted into its 3-phenoxy benzyl ester (XIII), $C_{28}H_{28}O_3$, $M^+ 412$. The ester (XIII) obtained as a semisolid, showed IR bands (Fig. 11) at 1724, ($>C=O$ of ester), 1582, 1475, 752, 687 (aromatic) and PMR signals (Fig. 12) at 8.90, 8.17 (1H each, m, cyclopropane protons at C_1 and C_3), 8.73, 8.70 (3H each, s, methyls on cyclopropane), 7.93 (3H, s, vinyl methyl), 4.93 (2H, s, benzylic methylene protons), 4.00 (1H, d, $J = 8$ Hz, olefinic proton) and 2.90 (14H, m, aromatic protons).

The ketone (VI), when subjected to Grignard reaction using methyl magnesium iodide (1.5 moles), afforded the liquid alcohol (XIV), in 81% yield, $C_{13}H_{24}O$, $M^+ 196$. It showed the following spectral properties: IR: 3472 (OH) 1653, 840 ($>C=CH$); PMR (Fig. 8): 9.35 (1H, m, C_3 -proton), 9.08, 8.88 (3H each, s, cyclopropane methyls), 8.82 (6H, s, methyls of hydroxy isopropyl), 8.62 (3H, d, $J = 7$ Hz, CH_2 -protons and C_1 -proton), 8.32, 8.27 (3H, each, s, vinyl methyls), 6.80 (1H, br. s, OH proton, exchangeable with D_2O) and 5.18 (1H, d, $J = 9$ Hz, olefinic proton).

Oxidation of the alcohol (XIV) with potassium permanganate in acetone-acetic acid-water mixture afforded

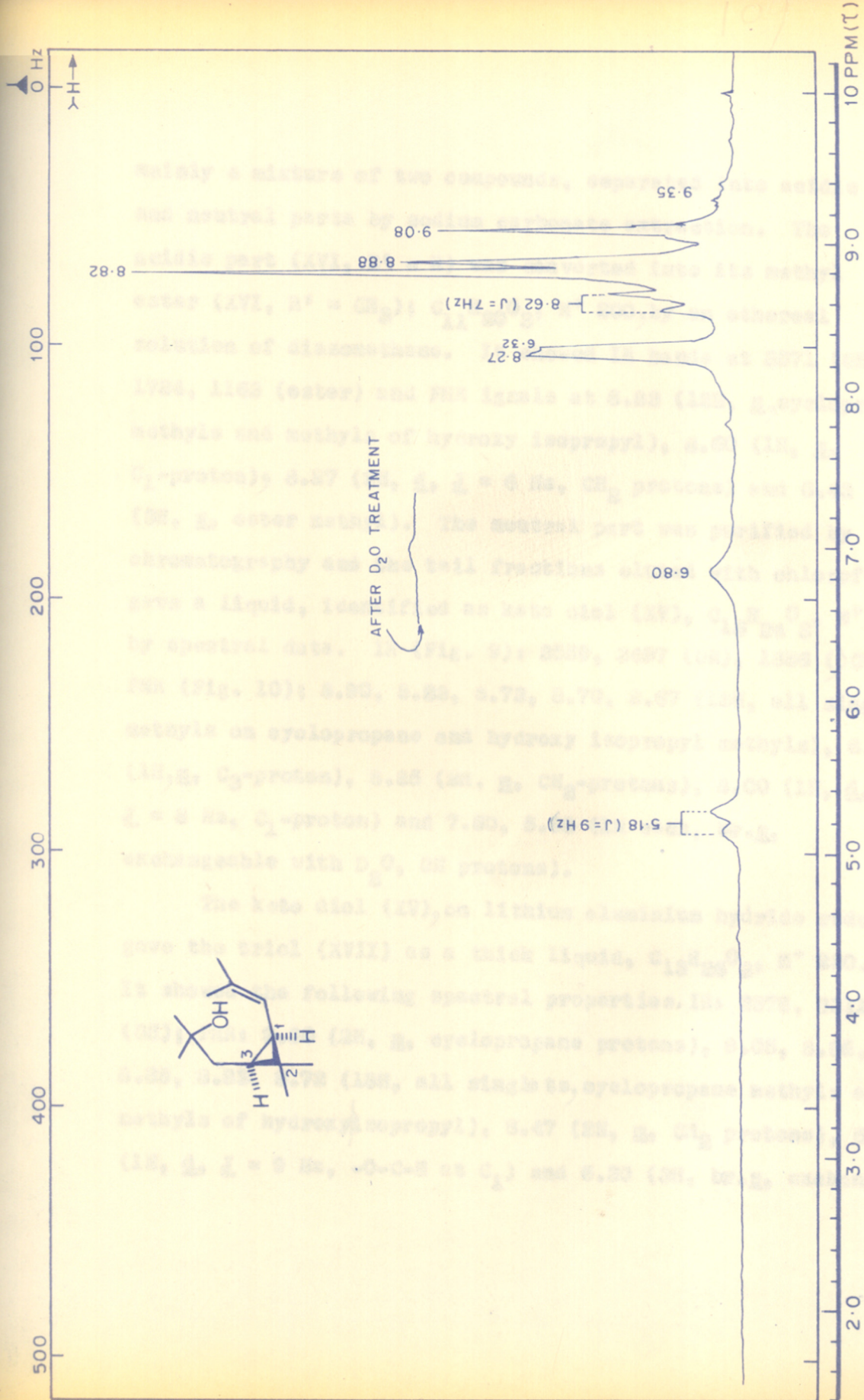


FIG. 8. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXYPROPYL)-CIS-1-(2-METHYLPROP-1-ENYL)-CYCLOPROPANE (XIV)

mainly a mixture of two compounds, separated into acidic and neutral parts by sodium carbonate extraction. The acidic part (XVI, $R' = H$) was converted into its methyl ester (XVI, $R' = CH_3$); $C_{11}H_{20}O_3$, $M^+ 200$, by an ethereal solution of diazomethane. It showed IR bands at 3571 (OH), 1724, 1163 (ester) and PMR signals at 8.83 (12H, s, cyclopropane methyls and methyls of hydroxy isopropyl), 8.60 (1H, s, C_1 -proton), 8.27 (2H, d, $J = 6$ Hz, CH_2 protons) and 6.43 (3H, s, ester methyl). The neutral part was purified by chromatography and the tail fractions eluted with chloroform, gave a liquid, identified as keto diol (XV), $C_{13}H_{24}O_3$, $M^+ 228$, by spectral data. IR (Fig. 9): 3559, 3497 (OH), 1686 ($>C=O$); PMR (Fig. 10): 8.90, 8.83, 8.73, 8.70, 8.67 (18H, all singlets, methyls on cyclopropane and hydroxy isopropyl methyls), 8.42 (1H, m, C_3 -proton), 8.25 (2H, m, CH_2 -protons), 8.00 (1H, d, $J = 8$ Hz, C_1 -proton) and 7.60, 5.98 (1H each, br. s, exchangeable with D_2O , OH protons).

The keto diol (XV), on lithium aluminium hydride reduction gave the triol (XVII) as a thick liquid, $C_{13}H_{26}O_3$, $M^+ 230$. It showed the following spectral properties. IR: 3378, 3311, 1026 (OH); PMR: 9.30 (2H, m, cyclopropane protons), 9.05, 8.95, 8.88, 8.83, 8.72 (18H, all singlets, cyclopropane methyls and methyls of hydroxy isopropyl), 8.47 (2H, m, CH_2 protons), 6.87 (1H, d, $J = 9$ Hz, -O-C-H at C_1) and 6.30 (3H, br. s, exchangeable

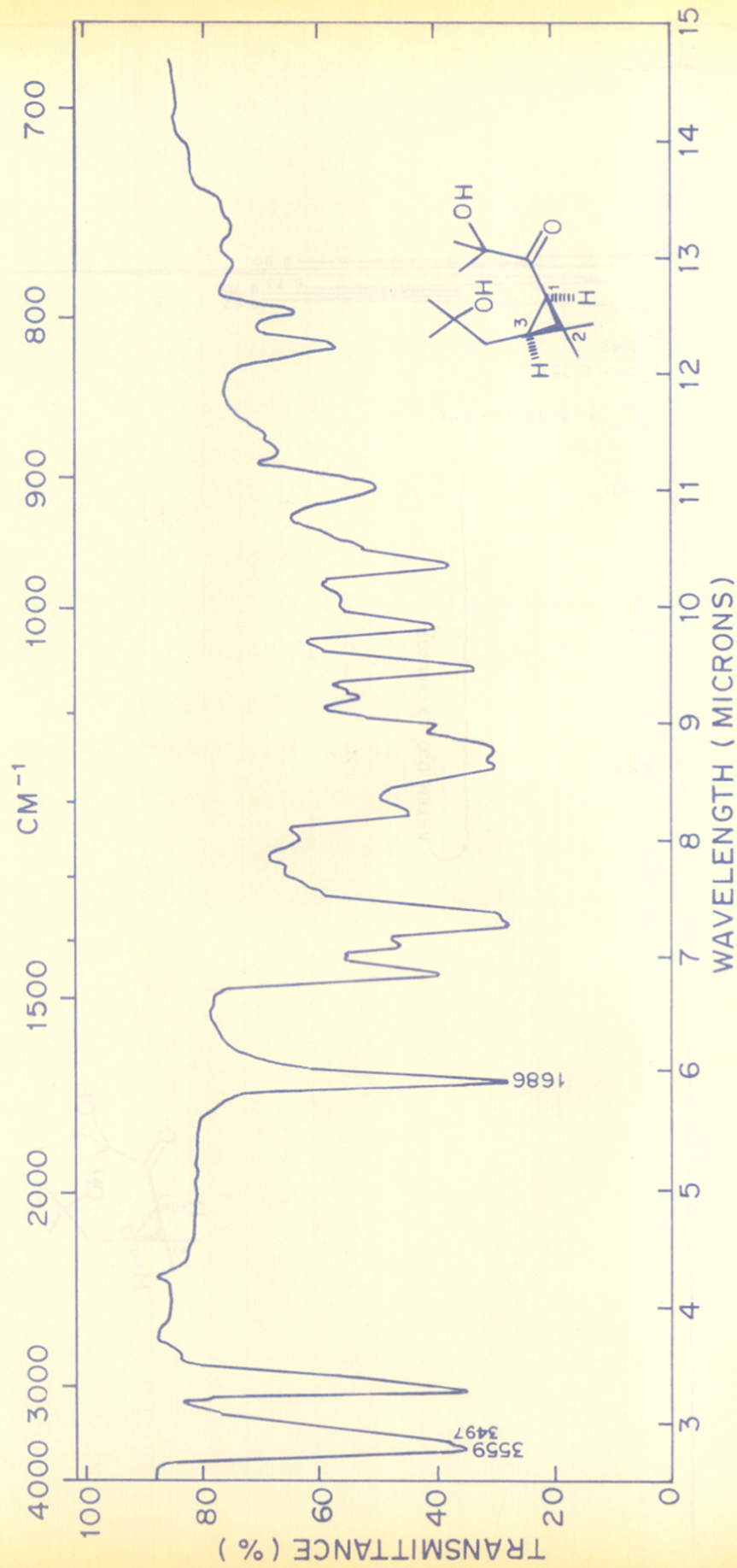


FIG. 9. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXYPROPYL)-CIS-1-(2-METHYL-2-HYDROXY-1-OXOPROPYL)-CYCLOPROPANE (XV)

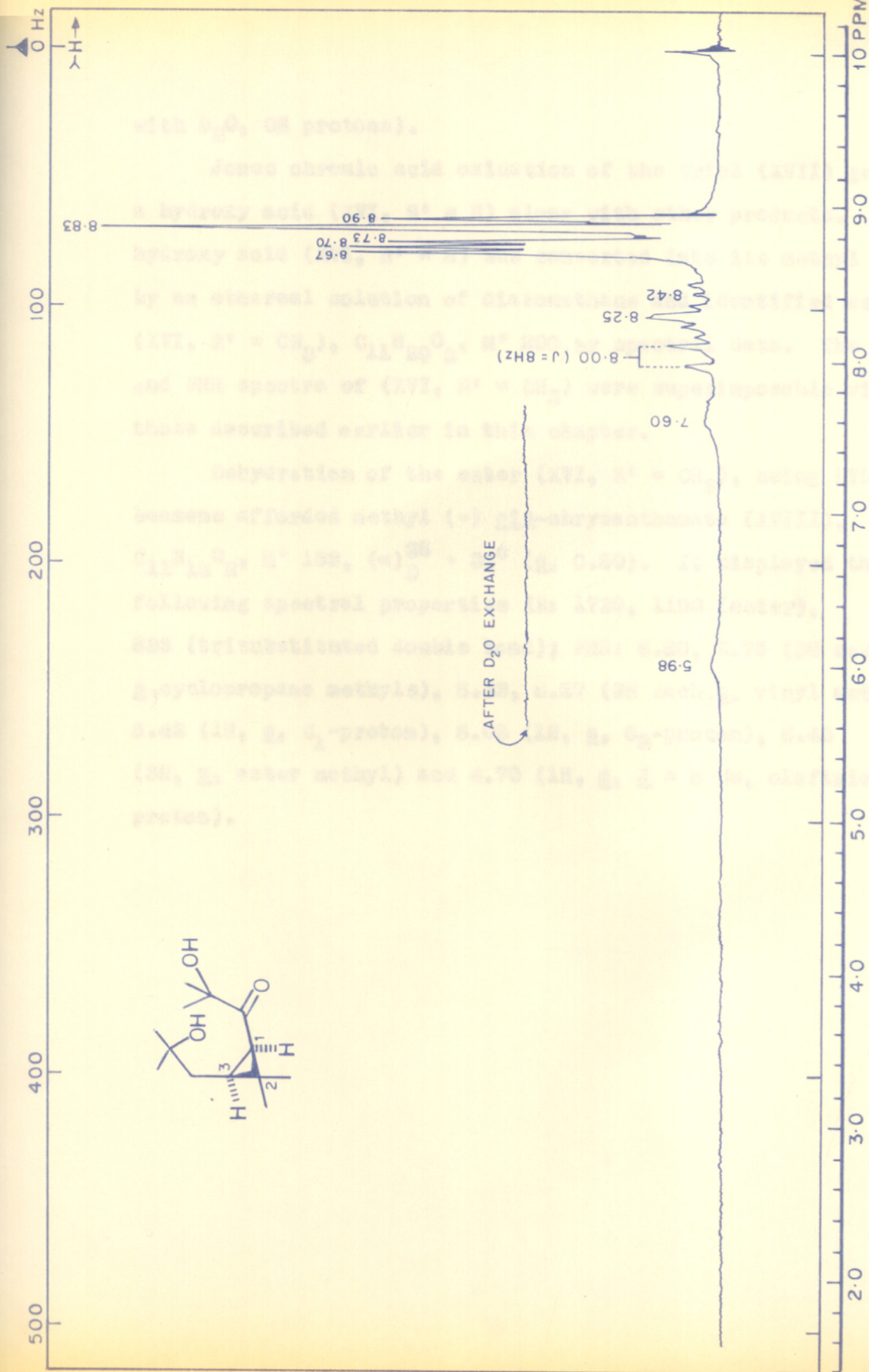


FIG. 10. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-METHYL-2-HYDROXYPROPYL)-CIS-1-(2-METHYL-2-HYDROXY-1-OXOPROPYL)-CYCLOPROPANE (XV)

with D_2O , OH protons).

Jones chromic acid oxidation of the triol (XVII) gave a hydroxy acid (XVI, $R' = H$) along with other products. The hydroxy acid (XVI, $R' = H$) was converted into its methyl ester by an ethereal solution of diazomethane and identified as (XVI, $R' = CH_3$), $C_{11}H_{20}O_3$, $M^+ 200$, by spectral data. The IR and PMR spectra of (XVI, $R' = CH_3$) were superimposable with those described earlier in this chapter.

Dehydration of the ester (XVI, $R' = CH_3$), using PTS in benzene afforded methyl (+) cis-chrysanthemate (XVIII), $C_{11}H_{18}O_2$, $M^+ 182$, $(\alpha)_D^{25} + 38^\circ$ (d, 0.80). It displayed the following spectral properties IR: 1739, 1190 (ester), 835 (trisubstituted double bond); PMR: 8.30, 8.75 (3H each, d, cyclopropane methyls), 8.33, 8.27 (3H each, d, vinyl methyls), 8.43 (1H, d, C_1 -proton), 8.08 (1H, d, C_3 -proton), 6.43 (3H, d, ester methyl) and 4.70 (1H, d, $J = 8$ Hz, olefinic proton).

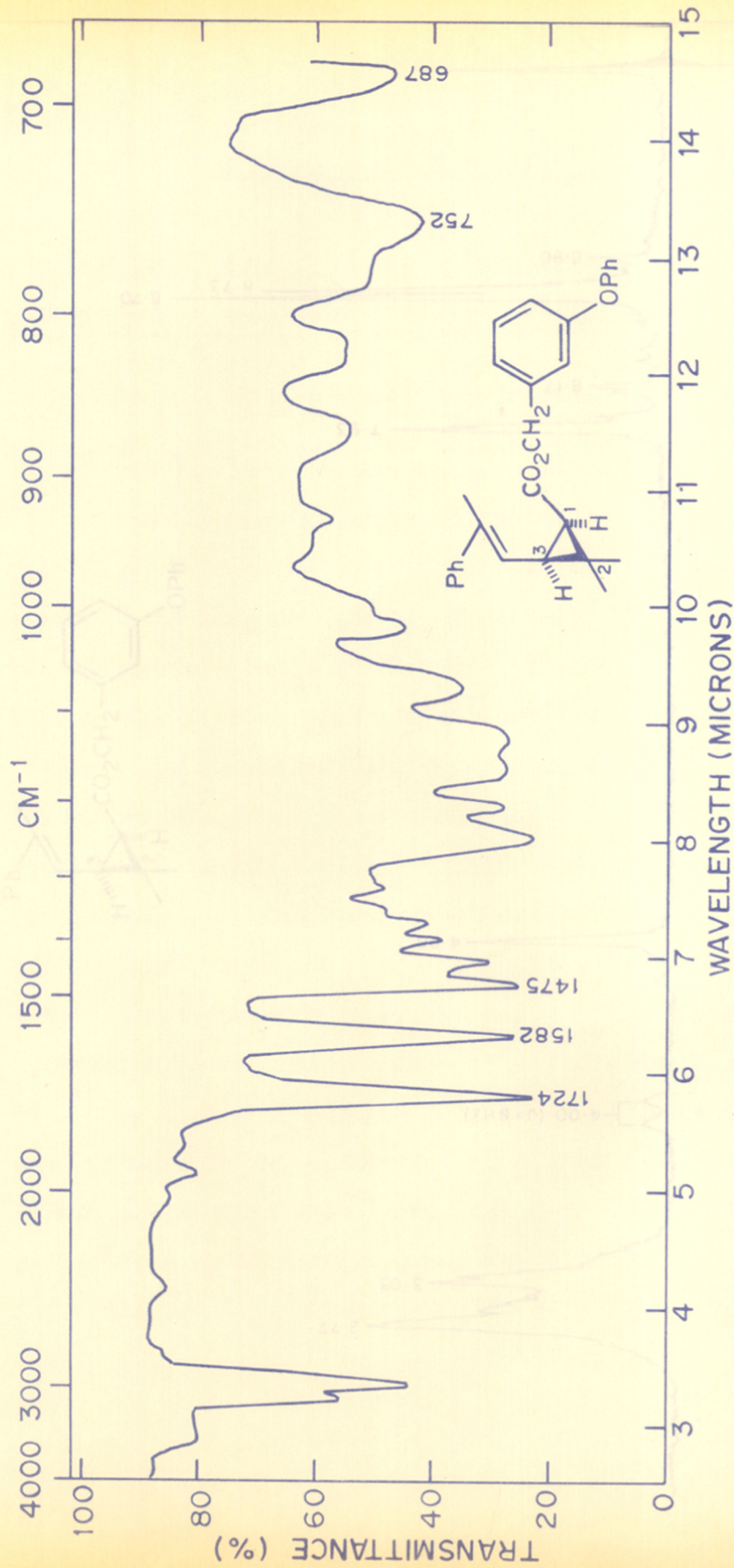


FIG. 11. IR SPECTRUM OF 3-PHENOXY BENZYL-1R-CIS-2,2-DIMETHYL-3-(2-PHENYLPROP-1-ENYL)-CYCLOPROPANE-CARBOXYLATE (XIII)

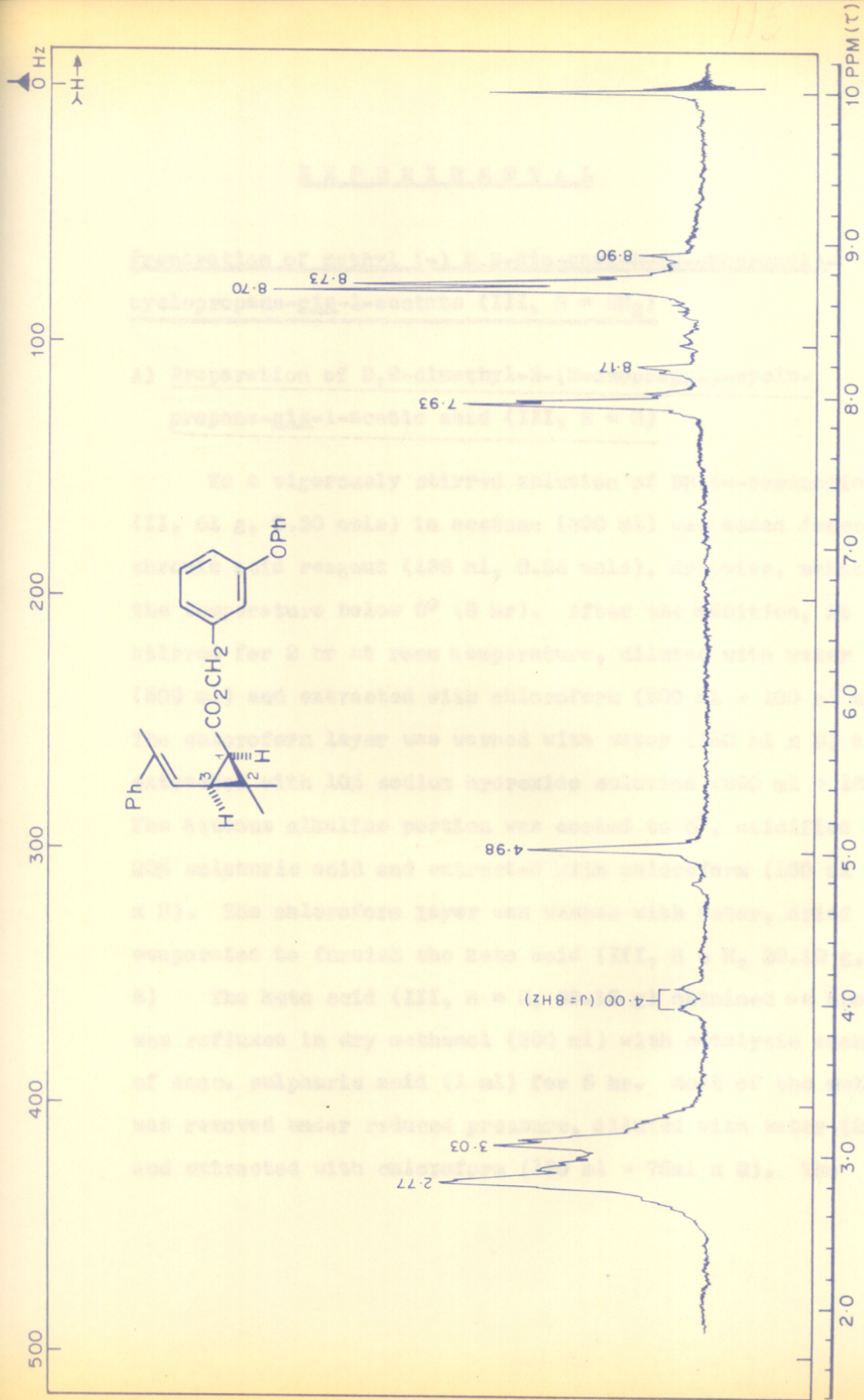


FIG. 12. PMR SPECTRUM OF 3-PHENOXY BENZYL-1R-CIS-2,2-DIMETHYL-3-(2-PHENYL PROP-1-ENYL)-CYCLOPROPANE-CARBOXYLATE (XIII)

EXPERIMENTALPreparation of methyl (-) 2,2-dimethyl-3-(2-oxopropyl)-cyclopropane-cis-1-acetate (III, R = CH₃)A) Preparation of 2,2-dimethyl-3-(2-oxopropyl)-cyclopropane-cis-1-acetic acid (III, R = H)

To a vigorously stirred solution of 3 β ,4 α -caranediol (II, 51 g, 0.30 mole) in acetone (300 ml) was added Jones chromic acid reagent (136 ml, 0.36 mole), dropwise, maintaining the temperature below 0° (2 hr). After the addition, it was stirred for 2 hr at room temperature, diluted with water (500 ml) and extracted with chloroform (200 ml + 100 ml x 2). The chloroform layer was washed with water (150 ml x 2) and extracted with 10% sodium hydroxide solution (200 ml + 150 ml). The aqueous alkaline portion was cooled to 5°, acidified with 20% sulphuric acid and extracted with chloroform (150 ml + 75 ml x 2). The chloroform layer was washed with water, dried and evaporated to furnish the keto acid (III, R = H, 33.10 g, 60%).

B) The keto acid (III, R = H, 33.10 g) obtained as above was refluxed in dry methanol (200 ml) with catalytic amount of conc. sulphuric acid (1 ml) for 5 hr. Most of the methanol was removed under reduced pressure, diluted with water (200 ml) and extracted with chloroform (150 ml + 75ml x 2). The

chloroform layer was washed with water to free it from acid and dried. Evaporation of chloroform furnished the keto ester (III, $R = CH_3$) which was further purified by distillation to give a colourless liquid (32.50 g), b.p. 92° (vapour)/1.50 mm, $(\alpha)_D^{25} - 26.1^\circ$ (g, 5.22).

Analysis

Found: C, 66.48; H, 9.32;

$C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%.

IR bands at: 3077, 2985, 1739, 1709, 1600, 1429, 1346, 1150, 1010 and 838 cm^{-1} . The neutral material (7.00 g) in the chloroform layer was not investigated further.

Methyl-2,2-dimethyl-3-(2,2-ethylenedioxypropyl)cyclopropane-cis-1-acetate (IV)

A mixture of keto ester (III, $R = CH_3$, 30 g), freshly distilled ethylene glycol (15 g), PTS (0.30 g) and dry benzene (300 ml) was taken in a 500 ml round bottom flask fitted with a Dean-Stark unit for azeotropic distillation. The mixture was then heated under reflux till no more water collected (6 hr). The reaction mixture was then washed with water (150 ml x 2) to remove unreacted ethylene glycol and PTS and dried. Evaporation of benzene afforded the ketal ester (IV) which was purified by distillation, b.p. 104° (vapour)/1.50 mm; yield 34.80 g (95%), $(\alpha)_D^{25} + 18.9^\circ$ (g, 3.17).

Analysis

Found: C, 64.65; H, 9.42;

$C_{13}H_{22}O_4$ requires C, 64.44; H, 9.15%.

IR bands at: 3030, 2985, 1739, 1418, 1361, 1299, 1163,
1036, 935, 837 and 775 cm^{-1} .

2,2-Dimethyl-3-(2,2-ethylenedioxypropyl)-cis-1-(2-methyl-
2-hydroxypropyl)-cyclopropane (V)

A) Preparation of methylmagnesium iodide reagent

In a one-litre three necked flask fitted with an overhead mechanical stirrer, a reflux condenser and a dropping funnel, were taken magnesium turnings (4 g), dry ether (150 ml) and a crystal of iodine. A few drops of methyl iodide in ether were slowly introduced in the reaction mixture when the colour of iodine disappeared. The remaining solution of methyl-iodide (24 g) in ether (100 ml) was then added, dropwise, under stirring. After the addition, the reaction mixture was stirred at room temperature for 1 hr when most of the magnesium dissolved to give a solution of methyl magnesium iodide in ether.

B) Preparation of (V)

A solution of ketal ester (IV, 20 g) in ether (100 ml) was, then added dropwise to the above Grignard reagent at 0° under vigorous stirring. Stirring was continued for 1 hr at room temperature and 1 hr under reflux. Excess of the reagent

and magnesium complex were decomposed by adding dropwise, a saturated solution of ammonium chloride (200 ml) at 0 to 5° and was stirred for 30 minutes at room temperature. The ether layer was separated and the aqueous portion extracted with ether (100 ml x 2). The combined ether layer was washed with water, dried and evaporated to furnish the ketal alcohol (V, 20 g, 90%), b.p. 120-130°/1 mm, $(\alpha)_D^{25} - 5.30^\circ$ (g, 3.70).

Analysis

Found: C, 69.12; H, 10.76;

$C_{14}H_{26}O_3$ requires C, 69.33; H, 10.81%.

IR bands at: 3571, 3030, 1460, 1376, 1299, 1218, 1135, 1107, 1050, 944, 907 and 844 cm^{-1} .

2,2-Dimethyl-3-(2-methylprop-1-enyl)-cis-1-(2-oxopropyl)-cyclopropane (VI)

A mixture of ketal alcohol (V, 11 g), PTS (0.10 g) in dry benzene (300 ml) was heated under reflux for 12 hr, with an arrangement for removing the water formed, azeotropically. Water (5 ml) was then added and the mixture refluxed for additional 4 hr. It was then washed repeatedly with water to remove PTS and ethylene glycol, dried and evaporated to give a mixture of two unsaturated ketones (VI and VII) (6 g, 73.3%), b.p. 115-120°/2 mm. (TLC on $SiO_2 + AgNO_3$ plate, 10% ethyl

acetate in benzene, two spots). The above mixture of ketones was chromatographed on silicic acid (108 g) impregnated with silver nitrate (12 g) and eluted with pet.ether, pet.ether + benzene mixtures and benzene. The fractions eluted with pet.ether and pet.ether + 10% benzene gave a TLC pure liquid (VI, 4.50 g, 75% of the mixture, $(\alpha)_D^{28} - 76.8^\circ$ (g, 1.20).

Analysis

Found: C, 79.85; H, 11.20;

$C_{12}H_{20}O$ requires C, 79.74; H, 11.18%.

IR bands at: 2967, 1710, 1439, 1368, 1342, 1215, 1149 and 826 cm^{-1} .

The fractions eluted with pet.ether + benzene (1:1) and benzene gave the TLC pure ketone (VII) which was further purified by distillation, b.p. 115-120°/2 mm.

Analysis

Found: C, 79.60; H, 11.02;

$C_{12}H_{20}O$ requires C, 79.74; H, 11.18%.

IR bands at: 2985, 1702, 1642, 1445, 1370, 1351, 1220, 1160, 1047 and 885 cm^{-1} .

2,2-Dimethyl-1-(2-methylprop-1-enyl)-cis-3-(2-phenyl-2-hydroxypropyl)-cyclopropane (VIII)

To an ice-cooled solution of phenyl magnesium bromide in dry ether, prepared from magnesium (0.60 g) and bromobenzene (4 g), a solution of the ketone (VI, 4.50 g) in dry

ether (50 ml) was added dropwise under stirring. After the complete addition, the reaction mixture was refluxed for 1 hr and kept overnight. The Grignard complex was then decomposed by addition of aqueous ammonium chloride solution at $5-10^{\circ}$. The ether layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was washed with water (100 ml x 2), dried and distilled to give the crude liquid mixture ^{of} diastereomeric unsaturated alcohols (VIII, 5.20 g, 80.60%), purified by chromatography (Al_2O_3 ; 1:20) to eliminate less polar impurities. The fractions eluted with benzene and chloroform gave a liquid, (VIII, 4.50 g), b.p. $150-60^{\circ}/1$ mm, $(\alpha)_D^{25} -27.5^{\circ}$ (c, 1.70).

Analysis

Found: C, 83.52; H, 10.07;

$\text{C}_{15}\text{H}_{26}\text{O}$ requires C, 83.66; H, 10.14%.

IR bands at: 3425, 2950, 1587, 1481, 1431, 1361, 1053, 1020, 930, 837, 758 and 694 cm^{-1} .

Methyl 1R-6S, 2,2-dimethyl-3-(2-phenyl-2-hydroxypropyl)-cyclopropane carboxylate (X, R' = CH_3)

To a solution of the unsaturated alcohol (VIII, 3.70 g) in acetone (25 ml), acetic acid (10 ml) and water (15 ml), powdered potassium permanganate (3.40 g) was added, portionwise, under stirring during 1/2 hr. Stirring was

continued for 1/2 hr more and the reaction mixture was treated simultaneously with sodium nitrite (3 g) and sulphuric acid (1:10), till all the manganese dioxide dissolved and a clear yellow solution obtained. It was then diluted with water (100 ml) and extracted with ether (100 ml x 3). The ether layer was washed with water (100 ml x 2) and extracted with 10% aqueous sodium carbonate solution (50 ml x 2). The carbonate layer was acidified with hydrochloric acid to 2 pH and extracted with chloroform (50ml x 3). The chloroform layer was washed with water (50 ml x 2), dried and distilled to give the hydroxy acid (X, R' = H; 1.60 g) which was esterified with an ethereal solution of diazomethane to give the diastereomeric hydroxy esters (X, R' = CH₃, 1.30 g, 34.60%), b.p. 120-30°/2 mm, $(\alpha)_D^{25} - 8.65^\circ$ (g, 2.60).

Analysis

Found: C, 73.10; H, 8.62;

C₁₆H₂₂O₃ requires C, 73.25; H, 8.45%.

IR bands at 3509, 2976, 1724, 1587, 1550, 1481, 1429, 1361, 1163, 1124, 1075, 943, 869, 844, 758 and 694 cm⁻¹.

The ether layer after extraction with sodium carbonate solution was repeatedly washed with water (50 ml x 3), dried and evaporated to give the keto diol (IX) in the neutral part. The neutral part (IX, 2 g, 48%) was crystallised from pet.ether

to give a solid, m.p. 124-25°.

Analysis

Found: C, 74.21; H, 9.12;

$C_{18}H_{26}O_3$ requires C, 74.44; H, 9.03%.

IR bands at: 3502, 3390, 2985, 1698, 1597, 1493, 1460, 1439, 1408, 1370, 1333, 1299, 1220, 1175, 1136, 1111, 1075, 1053, 1010, 973, 952, 909, 870, 813, 769, 746 and 697 cm^{-1} .

Methyl 1R-cis-2,2-dimethyl-3-(2-phenylprop-1-enyl)-cyclopropane carboxylate (XI)

A solution of hydroxy ester (X, $R' = CH_3$, 1.30 g) in dry benzene (75 ml) was refluxed on a water bath with PTS (0.10 g) for 12 hr. It was then washed with water (100 ml x 2), dried and distilled to furnish the crude unsaturated ester (XI).

It was chromatographed on Gr. II alumina (1:20) and the fractions eluted with pet.ether and pet.ether + 10% benzene gave a TLC pure solid (XI, 1 g, 82.60%) crystallised from pet.ether, m.p. and m.m.p. 60-61°, $(\alpha)_D^{28} - 16.50^\circ$ (g, 1.50).

Analysis

Found: C, 78.50; H, 8.31;

$C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%.

IR bands at: 3067, 1748, 1613, 1504, 1439, 1379, 1333, 1190, 1143, 1087, 917, 837, 766 and 694 cm^{-1} .

2,2-Dimethyl-3-(2-hydroxy-2-methylpropyl)-cis-1-(2-methylprop-1-enyl) cyclopropane (XIV)

A solution of unsaturated ketone (VI, 9 g) in dry ether (50 ml) was introduced, dropwise with stirring into the cold solution of methyl magnesium iodide, prepared from magnesium (1.30 g) and methyl iodide (8 g) in dry ether. After the complete addition it was stirred for two hr. under reflux and kept overnight. The reaction mixture was cooled to 0° and a cold saturated solution of ammonium chloride (150 ml) was introduced, dropwise into it with vigorous stirring. After stirring for 30 minutes at room temperature, it was transferred to a separatory funnel. The ether layer was separated and aqueous portion extracted with ether. The combined ether layer was washed with water, dried and evaporated to furnish the crude alcohol which was chromatographed on silicic acid (180 g, 1:20) and eluted with benzene to give the pure alcohol (XIV, 8 g, 81.60%, b.p. 125-130°/1.5 mm, $(\alpha)_D^{25} - 29.50^\circ$ (c, 1.50).

Analysis

Found: C, 79.25; H, 12.12;

$C_{13}H_{24}O$ requires C, 79.53; H, 12.32%.

IR bands at: 3472, 3012, 1653, 1449, 1370, 1215, 1147, 1058, 1010, 906, 885 and 840 cm^{-1} .

Methyl 1R-cis-2,2-dimethyl-3-(2-methyl-2-hydroxypropyl)-
cyclopropane carboxylate (XVI, R' = CH₃)

To a solution of the unsaturated alcohol (XIV, 5 g) in acetone (25 ml), acetic acid 10 ml and water (25 ml), powdered potassium permanganate (8 g) was added, portionwise, under stirring during 1/2 hr. Stirring was continued for 1/2 hr more, and the reaction mixture was treated simultaneously with sodium nitrite (4 g) and sulphuric acid (1:10), when all the manganese dioxide dissolved and a clear solution was obtained. It was then diluted with water (100 ml) and extracted with ether (100 ml x 3). The ether layer was washed with water and extracted with 10% aqueous sodium carbonate solution (25 ml x 2). The carbonate layer was acidified with hydrochloric acid to 2 pH and extracted with chloroform (75 ml x 3). The chloroform layer was washed with water, dried and distilled to give the hydroxy acid (XVI, R' = H, 1.60 g) which was esterified with an ethereal solution of diazomethane and the resulting ester further purified by distillation to give the TLC pure hydroxy ester (XVI, R' = CH₃, 1.20 g, 23.50%), b.p. 105-110°/1 mm (α_D^{25} - 16.00° (g, 1.20).

Analysis

Found: C, 65.78; H, 9.93;

C₁₁H₂₀O₃ requires C, 65.97; H, 10.07%.

3077

IR bands at 3571, 1724, 1489, 1370, 1266, 1212, 1163, 1075, 1042, 995, 952, 901, 881, 847, 816, 784, 755 and 709 cm^{-1} .

The ether layer after removal of hydroxy acid (XVI, $\text{R}'=\text{H}$), was repeatedly washed with water (100 ml x 2), dried and evaporated to afford the keto diol (XV) in the neutral part. It was purified by chromatography (Al_2O_3 , 1:20) and the tail fractions eluted with chloroform gave the keto diol (XV, 3.20 g, 55%) as a thick liquid.

Analysis

Found: C, 68.13; H, 10.31;

$\text{C}_{15}\text{H}_{24}\text{O}_3$ requires C, 68.28; H, 10.59%.

IR bands at: 3552, 3427, 3030, 1696, 1460, 1408, 1374, 1212, 1161, 1056, 1015, 964, 909, 819 and 800 cm^{-1} .

2,2-Dimethyl-3-(2-methyl-2-hydroxypropyl)-cis-1-(2-methyl-1,2-dihydroxy propyl)-cyclopropane (XVII)

To an ice-cooled solution of lithium aluminium-hydride (0.50 g) in ether (100 ml), a solution of the keto diol (XVI, 2.80 g) in ether (50 ml) was added dropwise during 1/2 hr, with stirring. Stirring was continued for 2 hr at 0° and the reaction mixture was kept overnight. Excess of lithium aluminium hydride was decomposed by careful addition of ethanol followed by water. It was then extracted with ether (100 ml x 3), the ether layer washed with water, dried

and evaporated to give a thick liquid (XVII, 0.89 g, 28.30%).

Analysis

Found: C, 67.56; H, 11.12;

$C_{13}H_{26}O_3$ requires C, 67.78; H, 11.38%.

IR bands at: 3378, 3311, 2976, 1449, 1366, 1250, 1212, 1026, and 899 cm^{-1} .

Methyl 1R-gis-2,2-dimethyl-3-(2-methyl-2-hydroxypropyl)-cyclopropane carboxylate (XVI, R' = CH₃) from (XVII)

To an ice-cooled solution of (XVII, 0.80 g) in acetone (10 ml), Jones chromic acid reagent was added dropwise till a brown colour persisted. The reaction mixture was kept at 0° for 3 hr, diluted with water and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water and extracted with aqueous sodium carbonate solution (10%, 20 ml x 2). The carbonate layer was acidified with hydrochloric acid to 2 pH and extracted with ether (50 ml x 2). The ether layer was washed with water, dried and distilled to give a liquid acid (0.20 g) which was esterified with an ethereal solution of diazomethane to give the hydroxy methyl ester (XVI, R' = CH₃, 0.15 g, 21.50%), (α)_D²⁵ - 15.80° (g, 0.70).

Analysis

Found: C, 65.81; H, 9.82;

$C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%.

IR bands at: 3704, 3077, 1724, 1439, 1373, 1270, 1212, 1165, 1070, 1045, 995, 950, 900, 880, 816, 784, 755 and 710 cm^{-1} .

Methyl (+) cis-chrysanthemeate (XVIII)

A solution of hydroxy ester (XVI, $R' = CH_3$, 0.50 g) in benzene (75 ml) was refluxed with PPS (0.03 g) for 12 hr, using a Dean-Stark unit for azeotropic removal of water. It was then washed with water (50 ml x 2), dried and distilled to give a liquid product (0.30 g). This was chromatographed on silicic acid impregnated with 10% silver nitrate (4.50 g) and eluted with pet.ether and pet.ether + benzene (10%) to give a TLC pure liquid (0.195 g, 42%), (α)_D²⁵ + 38° (c, 0.80%).

Analysis

Found: C, 72.23; H, 10.17;

$C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%.

IR bands at: 3077, 1732, 1429, 1399, 1370, 1316, 1190, 1170, 1136, 1075, 990, 917, 835 and 746 cm^{-1} .

Preparation of (XIII) from (XII)

The acid (XII, 0.50 g) was treated with potassium carbonate (0.40 g) in water (5 ml) and stirred for 2 hr. at room temperature. To this, was added methyl isobutyl ketone

(50 ml) and refluxed in a 100 ml round bottom flask fitted with a Dean-Stark unit for azeotropic distillation, till no more water collected (4 hr). To the above mixture was added 3-phenoxybenzyl triethyl ammonium chloride (0.90 g) and the refluxing continued for further 8 hr. Methyl isobutyl ketone was removed by distillation under reduced pressure and the residue was taken up in ether (100 ml). The ether solution was washed with water, dried and evaporated to give the product (0.70 g) which showed minor polar impurities on TLC (12% ethyl acetate in benzene). The product was separated by chromatography on silicic acid (1.40 g). The main product (less polar) was eluted with pet.ether+benzene (1:1) and identified as the ester (XIII, 0.69 g).

Analysis

Found: C, 81.43; H, 6.97;

$C_{22}H_{22}O_3$ requires C, 81.52; H, 6.84%.

IR bands at: 3106, 2985, 1724, 1582, 1475, 1433, 1242, 1205, 1075, 1015, 870, 820, 752 and 687 cm^{-1} .

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CHAPTER - III

EXAMINATION OF THE SOME MINOR PRODUCTS OF PRINS
REACTION ON (+) CAR-3-ENE AND OXIDATION STUDIES ON
THE PRODUCTS OF THE PRINS REACTION

S U M M A R Y

Prins reaction on (+) car-3-ene (I) afforded, in addition to the major products like car-2-ene-4 α -methanol (II, R = H) and its acetate (II, R = Ac), some minor products which have been isolated by chromatography and characterised by spectral data. These included a tricyclic ether identified as 3,3-dimethyl-8-oxa-tricyclo-(4.3.1.0^{2,4})-dec-10-ene (III) and the dioxane derivative (IV). When the Prins reaction was carried out for a prolonged period at 160^o, in addition to the above products, an acetate was obtained which was assigned structure (V, R = Ac), on the basis of spectral data.

Jones chromic acid oxidation of the alcohol (II, R = H) gave a mixture of four products, from which the acid (VI, R = H), the ester (VII) and the ketone (VIII) have been isolated and characterised by spectral data and chemical reactions. The acid (VI, R = H) was converted into its methyl ester (VI, R = CH₃) with MeOH/H⁺ and characterised by spectral data. Saponification of the ester (VII) gave in the acid part, the acid (VI, R = H) identified through its methyl ester (VI, R = CH₃) and the alcohol (II, R = H) in the neutral part. LAH reduction of the ester (VII), afforded exclusively the alcohol (II, R = H).

Jones chromic acid oxidation of the tricyclic ether (III), afforded a mixture of two products, separated into acidic and neutral parts by sodium carbonate extraction. The acid part gave on crystallisation a solid acid, identified as (IX, R = H), which was converted into its methyl ester (IX, R = CH₃). The neutral part gave the nor ketone (X), identified by spectral data and chemical reactions. Lithium aluminium hydride reduction of the nor ketone (X) furnished a solid alcohol (XI, R = H) which on acetylation (Ac₂O/Py) gave the acetate (XI, R = Ac).

The methyl ester (VI, R = CH₃) was treated with perbenzoic acid to give the α -epoxide (XII) which on rearrangement over alumina gave hydroxy esters (XIII) and (XIV), identified by spectral data.

INTRODUCTION

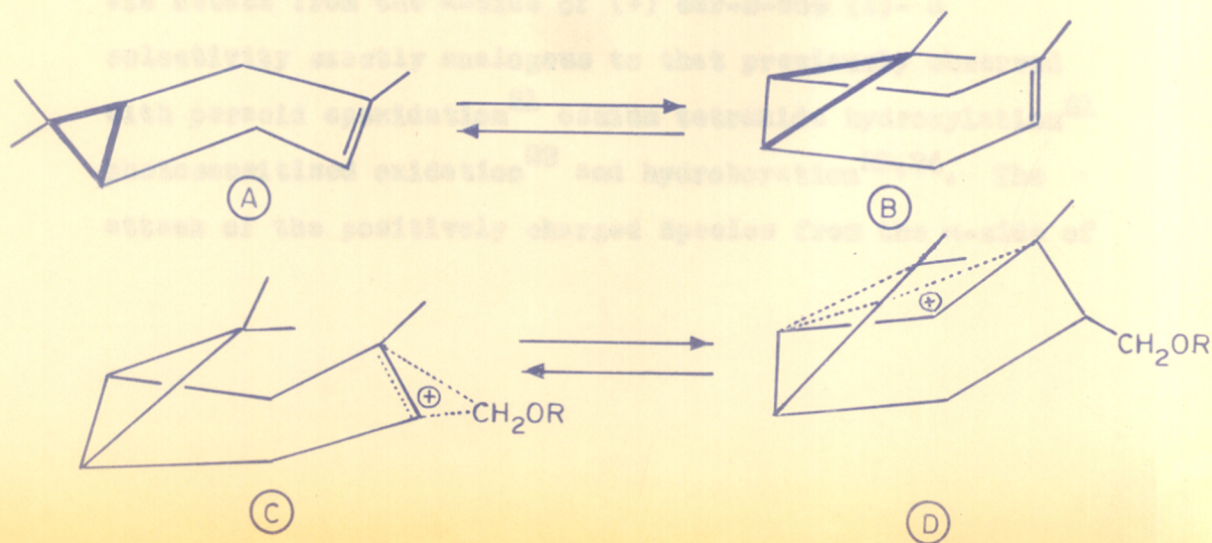
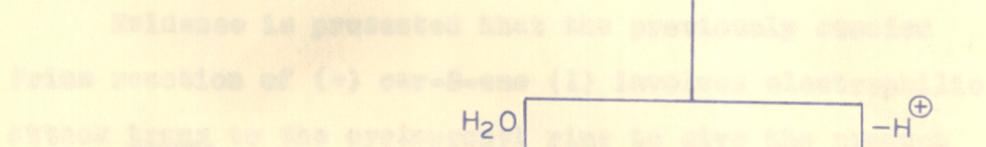
Reactions of olefins with formaldehyde, other aldehydes and ketones are known as Prins reactions¹. They are carried out in the presence of inorganic acids, acetic acid or metal chlorides as catalysts. Three main products are possible and of these, which one predominates, depends on the nature of the olefin and the reaction conditions as shown in scheme - I. When the product is the 1,3-diol or the dioxane, the reaction involves addition to the $C = C$ as well as to the $>C = O$ and the resulting carbonium ion attacks the $C = C$ as shown by scheme - I. Ethylene itself reacts only under drastic conditions. Olefins of the types $R_2C = CH_2$ and $RCH = CH_2$ give mainly 1,3 dioxanes, olefins of the types $RCH = CH-R'$ afford 1,3-glycols, but usually in low yield. Blomquist² (1957) found that addition of cyclohexene to a slurry of paraformaldehyde in acetic acid-sulfuric acid at 50-70° afforded as the major products, trans-2-hydroxy-methyl-1-cyclohexanol diacetate (26%) and the trans-1,3-dioxane (10%); two other minor products also formed in the same reaction were characterised. The Prins reaction proceeds generally with ease and when it is catalysed, often at sub-zero temperatures. However, with bicyclic terpenes, they lead to transformations of the carbon skeleton. Despite intensive investigations the

mechanism of the Prins reaction is still obscure²⁻⁹. The most convincing and so far generally accepted is the mechanism suggested by Arnold et al.^{3,10,11} according to which the first stage of the Prins reaction involves a nucleophilic attack of the olefin on the carbon atom of the polarized carbonyl group followed by the formation of an intermediate complex, stabilizing itself by a double bond and proton shift.

The Prins reaction has been carried out on a number of terpenic compounds, viz., (+) car-3-ene¹², camphene¹³, d-limonene¹⁴, α -pinene¹⁵, 2-norbornene¹⁶ and longifolene¹⁷.

G. Ohloff et al.¹² have first carried out the Prins reaction on (+) car-3-ene (I) in presence of glacial acetic acid. They were able to get car-2-ene 4 α -methanol (II, R = H) and its acetate (II, R = Ac) as the major products of the Prins reaction on (+) car-3-ene (I). Later on, P.J.Kropp et al.¹⁸ repeated the Prins reaction on (+) car-3-ene (I). In addition to the above mentioned products, one more minor product was identified as (XV). They got a mixture consisting of four minor components but were unable to identify them.

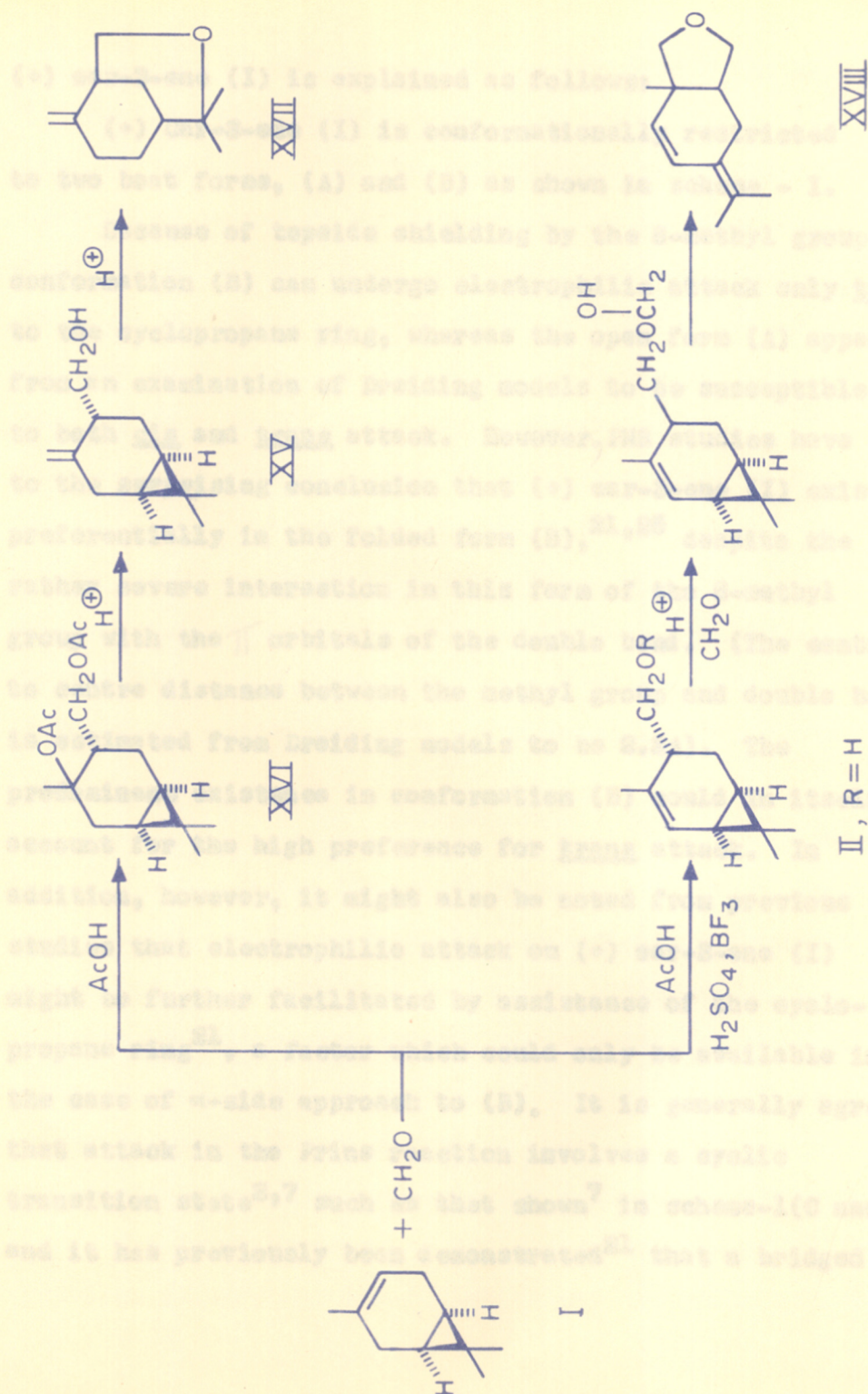
So in order to investigate the compounds formed during the Prins reaction on (+) car-3-ene (I), Chlebicki et al.^{19,20} repeated this reaction. In presence of glacial acetic acid,



treatment of (+) car-3-ene (I) with paraformaldehyde afforded car-2-ene 4-methanol (II, H) as the main product, together with small amount of 4-hydroxymethyl-3/10/-carene (XV). Studying the reaction of (+) car-3-ene (I) with paraformaldehyde in anhydrous acetic acid, they found that two additional products were also formed. These included the diacetate of 4-hydroxy methyl caranol-3 (XVI) and the bicyclic ether 2,2-dimethyl-6-methylene-3-oxa-bicyclo-(3.3.1)-nonane (XVII). However, when the reaction was carried out in presence of H_2SO_4 or BF_3 , the ether (XVIII) was formed as shown in scheme - II. The mechanism of formation of (XVIII) was similar to the mechanism depicted for the Prins reaction on cyclohexene².

Evidence is presented that the previously studied Prins reaction of (+) car-3-ene (I) involves electrophilic attack trans to the cyclopropyl ring to give the product having the newly introduced C_4 substituents in an α -orientation. Prins reaction which presumably involves attack by a positively charged species, proceeds selectively via attack from the α -side of (+) car-3-ene (I)- a selectivity exactly analogous to that previously observed with peracid epoxidation²¹ osmium tetroxide hydroxylation²¹ photosensitized oxidation²² and hydroboration^{23,24}. The attack of the positively charged species from the α -side of

SCHEME - II



(+) car-3-ene (I) is explained as follows:

(+) Car-3-ene (I) is conformationally restricted to two boat forms, (A) and (B) as shown in scheme - I.

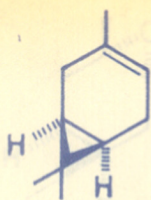
Because of topside shielding by the 8-methyl group, conformation (B) can undergo electrophilic attack only trans to the cyclopropane ring, whereas the open form (A) appears, from an examination of Dreiding models to be susceptible to both cis and trans attack. However, PMR studies have led to the surprising conclusion that (+) car-3-ene (I) exists preferentially in the folded form (B),^{21,25} despite the rather severe interaction in this form of the 8-methyl group with the π orbitals of the double bond. (The centre to centre distance between the methyl group and double bond is estimated from Dreiding models to be 2.2Å). The predominant existence in conformation (B) could in itself account for the high preference for trans attack. In addition, however, it might also be noted from previous studies that electrophilic attack on (+) car-3-ene (I) might be further facilitated by assistance of the cyclopropane ring²¹, a factor which could only be available in the case of π -side approach to (B). It is generally agreed that attack in the Prins reaction involves a cyclic transition state^{2,7} such as that shown⁷ in scheme-1(C and D) and it has previously been demonstrated²¹ that a bridged

intermediate of this type in which the 6-membered ring is constrained to a boat form, is favourably disposed towards involvement by the cyclopropane ring. There are only a few papers in the literature dealing with the reaction of (+) car-3-ene (I) with formaldehyde^{12,18,19,20,26}. Although the Prins reaction on (+) car-3-ene (I) is known¹² to give as the major product, the endo alcohol (II, R = H) and its acetate (II, R = Ac), different workers^{12,18,19,20} have reported the isolation of different minor products of the Prins reaction. So in order to investigate the minor products formed in the reaction, the Prins reaction on (+) car-3-ene (I) was repeated and two new products have been isolated and characterised. These included a 1,3-dioxane derivative (IV) and a novel tricyclic ether (III).

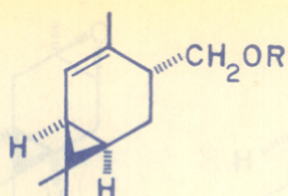
PRESENT WORK

(+) Car-3-ene (I), on treatment with paraformaldehyde and glacial acetic acid (48 hr, refluxing), afforded a mixture which was saponified with methanolic potash so as to facilitate better separation. The mixture consisted of four compounds (TLC, 10% ethyl acetate in benzene). Out of these, three compounds were isolated in pure state from the reaction mixture by chromatography followed by distillation.

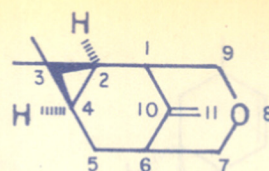
The least polar of these, the minor product of the reaction (8.40%) was identified as the tricyclic ether (III)



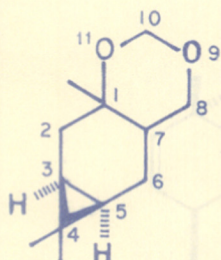
I



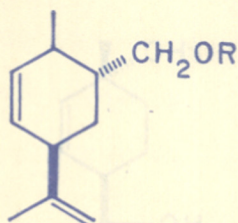
II, R=H; R=-Ac



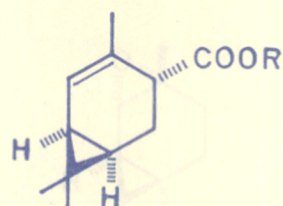
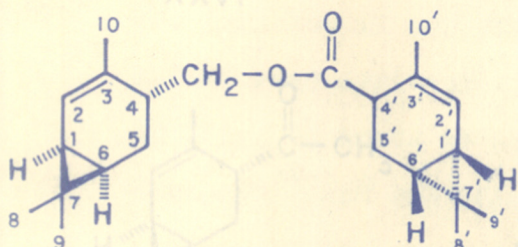
III



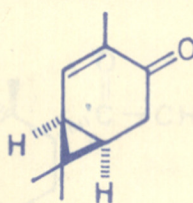
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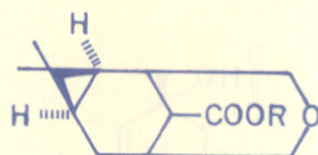
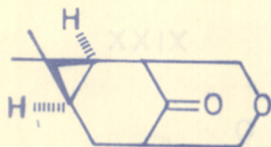
V, R=H; R=Ac

VI, R=H; R=CH₃

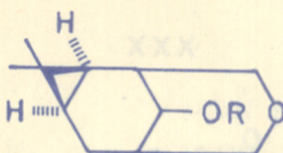
VII



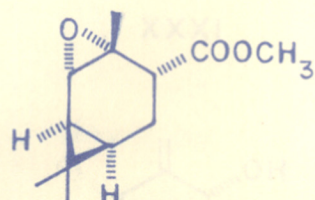
VIII

IX, R=H; R=CH₃

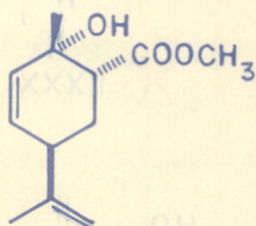
X



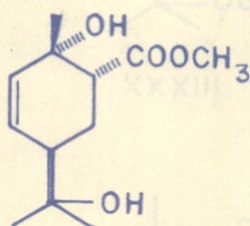
XI, R=H; R=Ac



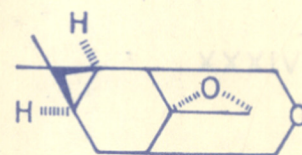
XII



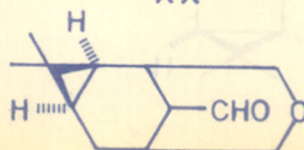
XIII



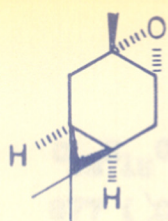
XIV



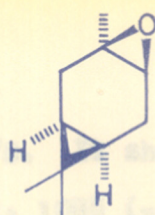
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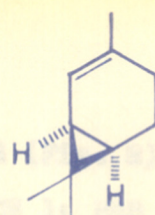
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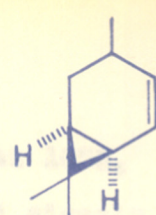
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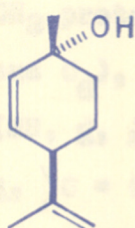
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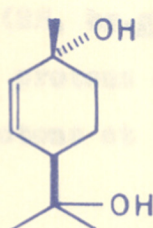
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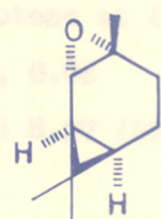
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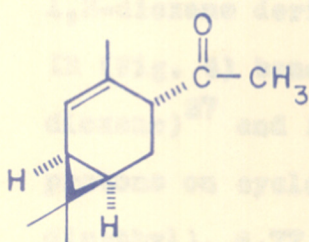
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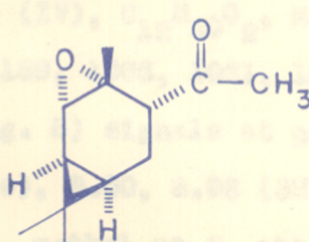
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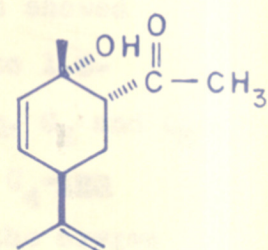
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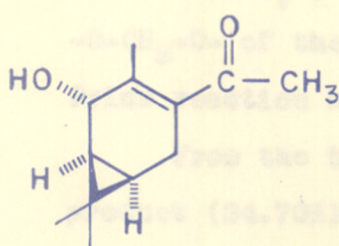
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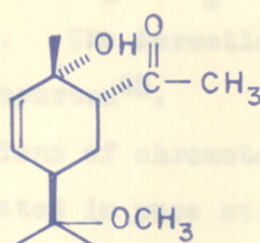
XXX



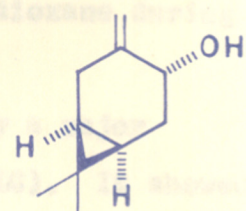
XXXI



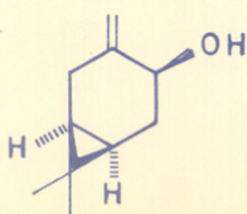
XXXII



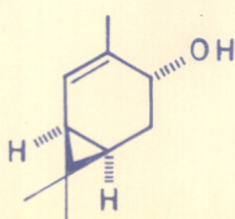
XXXIII



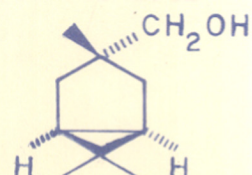
XXXIV a



XXXIV b



XXXV



XXXVI

$C_{12}H_{18}O$, M^+ 178. It showed IR (Fig. 2) bands at 1653, 877 ($>C = CH_2$), 1085 ($-CH_2-O-CH_2-$); PMR (Fig. 3) signals at 9.23 (2H, m, C_2 and C_4 -protons on cyclopropane), 9.03, 8.97 (3H each, s, gem dimethyl at C_3), 8.02 (2H, br. s, CH_2 protons at C_5), 7.50 (2H, br. s, methine protons at C_1 and C_6), 6.58 (2H, m, CH_2 protons at C_7 or C_9), 6.08 (2H, d, $J = 10$ Hz, CH_2 protons at C_9 or C_7) and 5.37 (2H, s, $>C = CH_2$).

From the middle fractions of chromatography, a liquid was isolated in low yield (2.00%) and identified as the 1,3-dioxane derivative (IV), $C_{12}H_{20}O_2$, M^+ 196. It showed IR (Fig. 4) bands at 1159, 1066, 1031, 1010 (due to 1,3-dioxane)²⁷ and PMR (Fig. 5) signals at 9.48 (2H, m, C_3 and C_5 protons on cyclopropane), 9.00, 8.93 (3H each, s, C_4 -gem dimethyl), 8.77 (3H, s, methyl at C_1 attached to the oxygen of the dioxane), 8.37 (2H, m, CH_2 at C_6), 7.80 (1H, m, methine at C_7), 6.63 (2H, m, CH_2 at C_8) and 5.28 (2H, m, $-O-CH_2-O-$ of the dioxane). The formation of dioxane during Prins reaction has been reported²⁸.

From the tail fractions of chromatography a major product (34.70%) was isolated in pure state (TLC). It showed a strong hydroxyl band in its IR spectrum. It was acetylated (Ac_2O/Py) to give a known¹⁸ acetate and identified as (II; $R = Ac$), $C_{13}H_{20}O_2$, M^+ 208. It showed IR bands at 1748

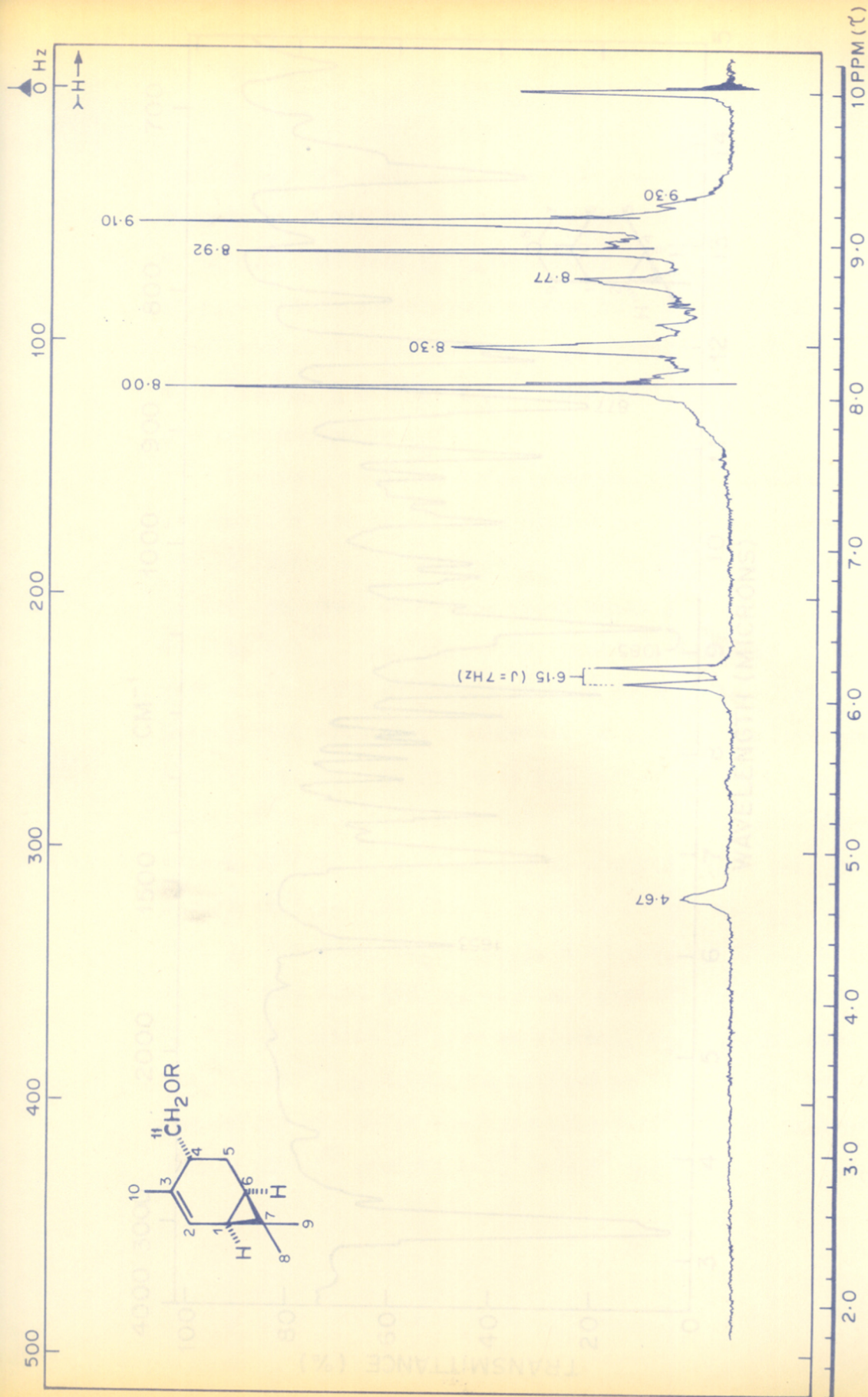


FIG. 1. PMR SPECTRUM OF 3,7,7-TRIMETHYL-4 α -ACETOXYMETHYL-BICYCLO-(4.1.0)-HEPT-2-ENE-(11, R=Ac)

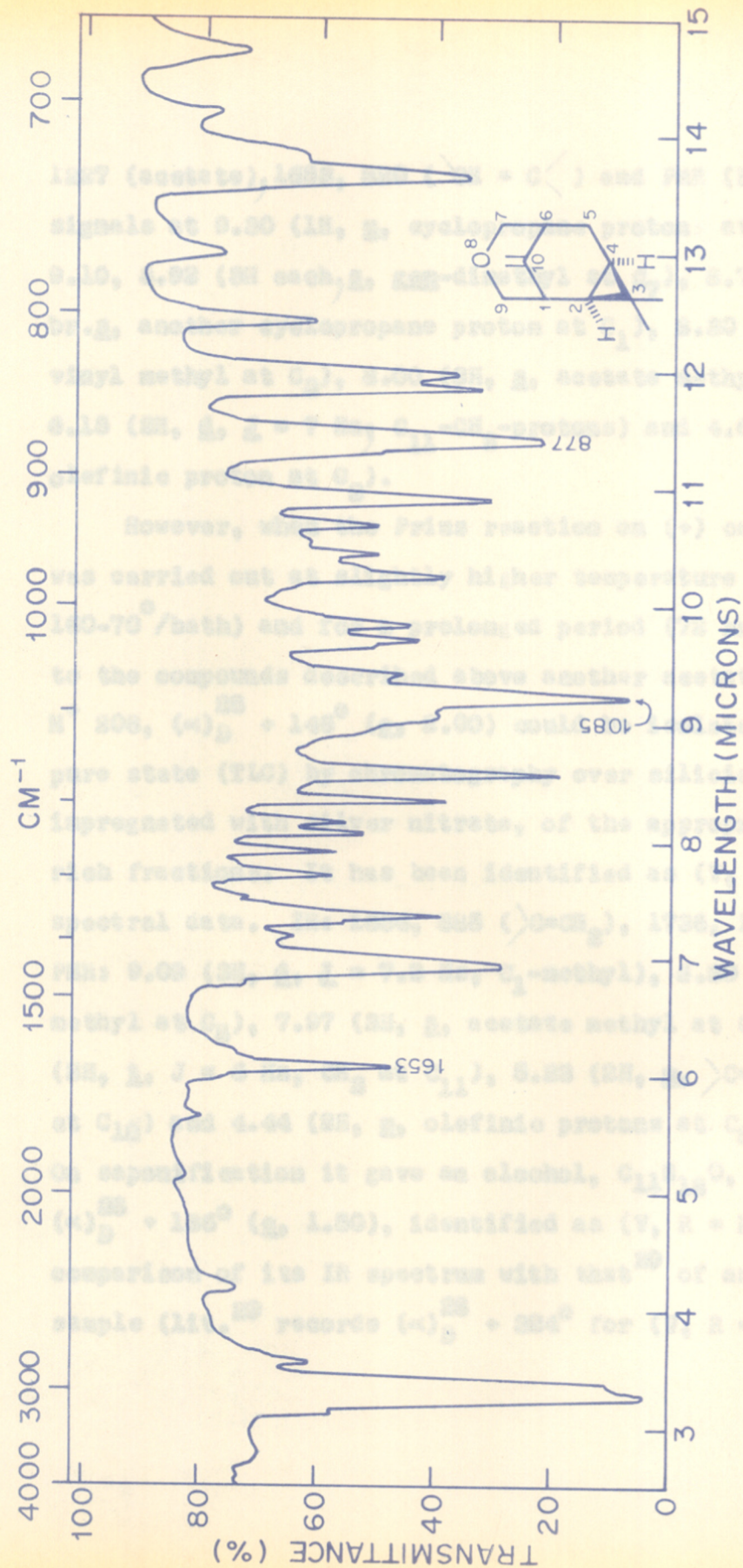


FIG. 2. IR SPECTRUM OF 3,3-DIMETHYL-8-OXA-TRICYCLO-(4.3.1.0^{2,4})-DEC-10-ENE (III)

1227 (acetate), 1653, 820 ($\text{CH} = \text{C} \angle$) and PMR (Fig. 1) signals at 9.30 (1H, m, cyclopropane proton at C_8), 9.10, 8.92 (3H each, s, gem-dimethyl at C_7), 8.77 (1H, br. s, another cyclopropane proton at C_1), 8.30 (3H, s, vinyl methyl at C_3), 8.00 (3H, s, acetate methyl at C_{11}), 6.15 (2H, d, $J = 7$ Hz, $\text{C}_{11}\text{-CH}_2$ -protons) and 4.67 (1H, br. s, olefinic proton at C_2).

However, when the Prins reaction on (+) car-3-ene (I) was carried out at slightly higher temperature (around $160\text{-}70^\circ/\text{bath}$) and for a prolonged period (72 hr), in addition to the compounds described above another acetate, $\text{C}_{13}\text{H}_{20}\text{O}_2$, $\text{M}^+ 208$, $(\alpha)_{\text{D}}^{28} + 146^\circ$ (d, 2.00) could be isolated in the nearly pure state (TLC) by chromatography over silicic acid impregnated with silver nitrate, of the appropriate acetate rich fractions. It has been identified as (V, R = Ac) by spectral data. IR: 1634, 885 ($\text{C}=\text{CH}_2$), 1736, 1220 (acetate); PMR: 9.09 (3H, d, $J = 7.2$ Hz, C_1 -methyl), 8.20 (3H, s, vinyl methyl at C_3), 7.97 (3H, s, acetate methyl at C_{11}), 6.00 (2H, t, $J = 6$ Hz, CH_2 at C_{11}), 5.23 (2H, m, $\text{C}=\text{CH}_2$ protons at C_{10}) and 4.44 (2H, m, olefinic protons at C_5 and C_6). On saponification it gave an alcohol, $\text{C}_{11}\text{H}_{18}\text{O}$, $\text{M}^+ 166$, $(\alpha)_{\text{D}}^{28} + 186^\circ$ (d, 1.50), identified as (V, R = H), by comparison of its IR spectrum with that²⁹ of an authentic sample (lit.²⁹ records $(\alpha)_{\text{D}}^{28} + 324^\circ$ for (V, R = H); however,

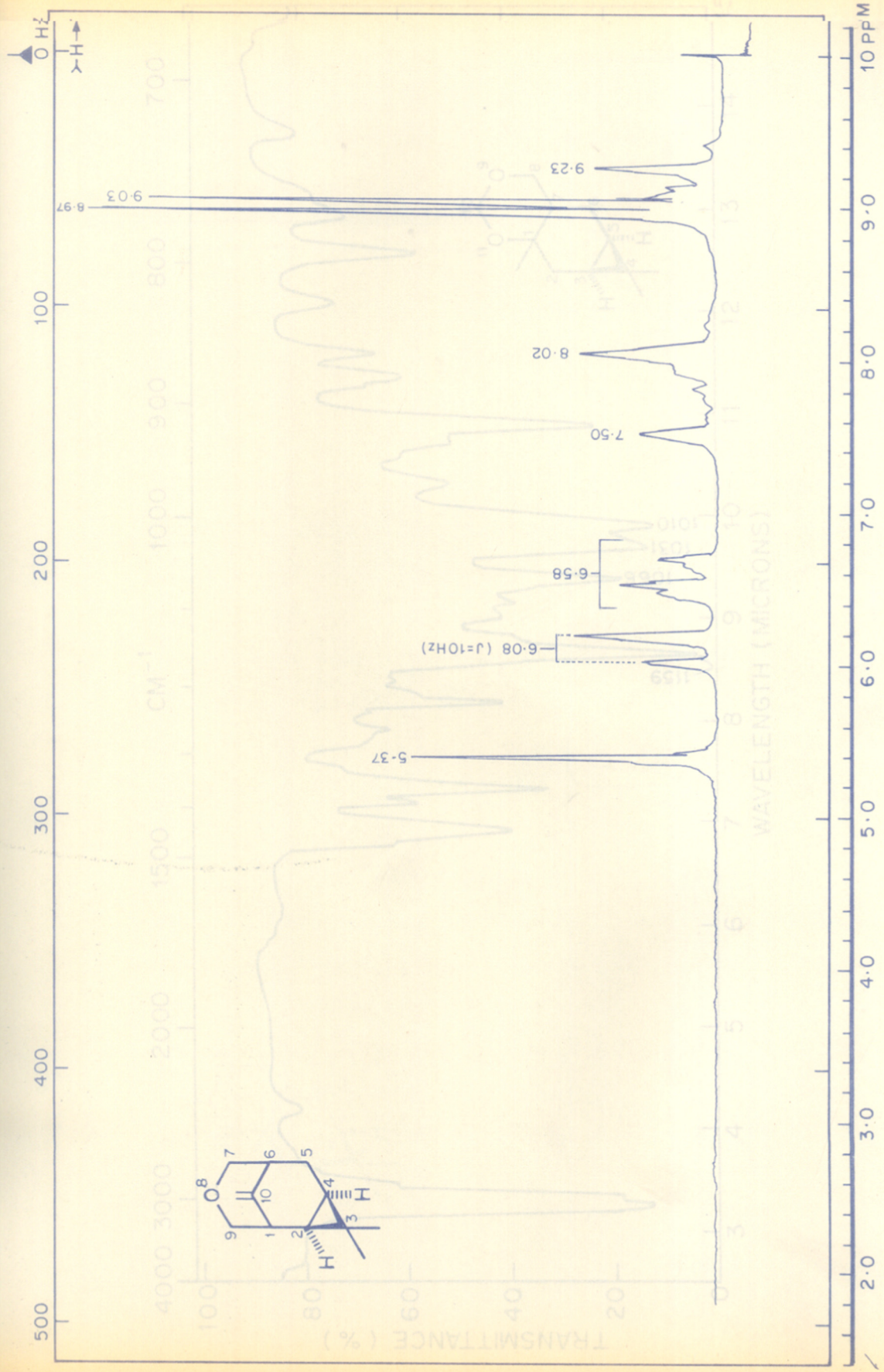


FIG. 3. PMR SPECTRUM OF 3,3-DIMETHYL-8-OXA-TRICYCLO-(4.3.1.0^{2,4})-DEC-10-ENE (III)

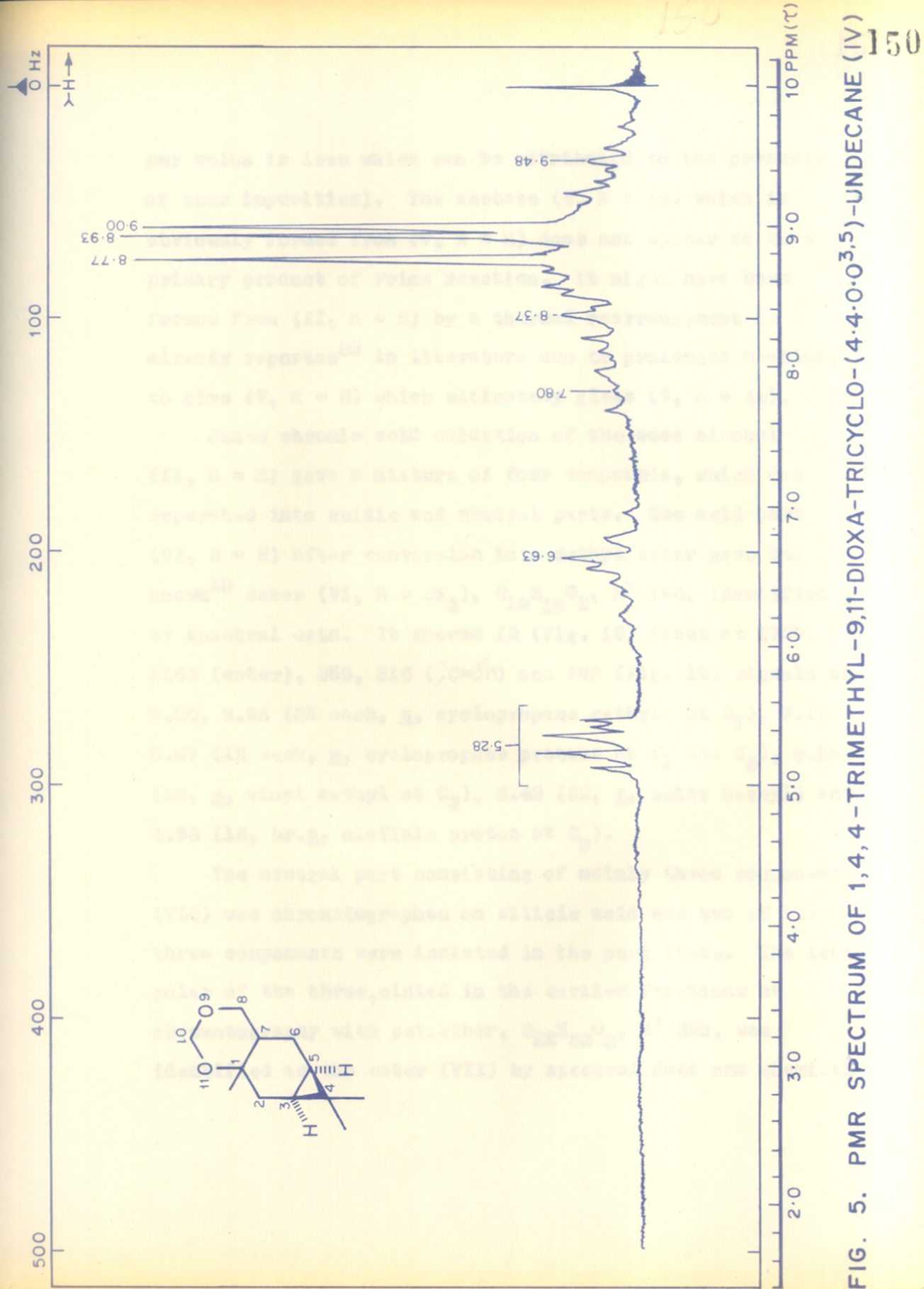


FIG. 5. PMR SPECTRUM OF 1,4,4-TRIMETHYL-9,11-DIOXA-TRICYCLO-(4.4.0.0^{3,5})-UNDECANE (IV)

our value is less which can be attributed to the presence of some impurities). The acetate (V, R = Ac) which is obviously formed from (V, R = H) does not appear to be a primary product of Prins reaction. It might have been formed from (II, R = H) by a thermal rearrangement as already reported²⁹ in literature due to prolonged heating, to give (V, R = H) which ultimately gives (V, R = Ac).

Jones chromic acid oxidation of the endo alcohol (II, R = H) gave a mixture of four compounds, which was separated into acidic and neutral parts. The acid part (VI, R = H) after conversion into methyl ester gave the known¹⁸ ester (VI, R = CH₃), C₁₂H₁₈O₂, M⁺ 194, identified by spectral data. It showed IR (Fig. 15) bands at 1739, 1163 (ester), 855, 816 (>C=CH) and PMR (Fig. 16) signals at 9.20, 8.98 (3H each, s, cyclopropane methyls at C₇), 9.10, 8.67 (1H each, m, cyclopropane protons at C₁ and C₆), 8.28 (3H, s, vinyl methyl at C₃), 6.42 (3H, s, ester methyl) and 4.53 (1H, br.s, olefinic proton at C₂).

The neutral part consisting of mainly three components (TLC) was chromatographed on silicic acid and two of the three components were isolated in the pure state. The least polar of the three, eluted in the earlier fractions of chromatography with pet. ether, C₂₂H₃₂O₂, M⁺ 328, was identified as the ester (VII) by spectral data and chemical

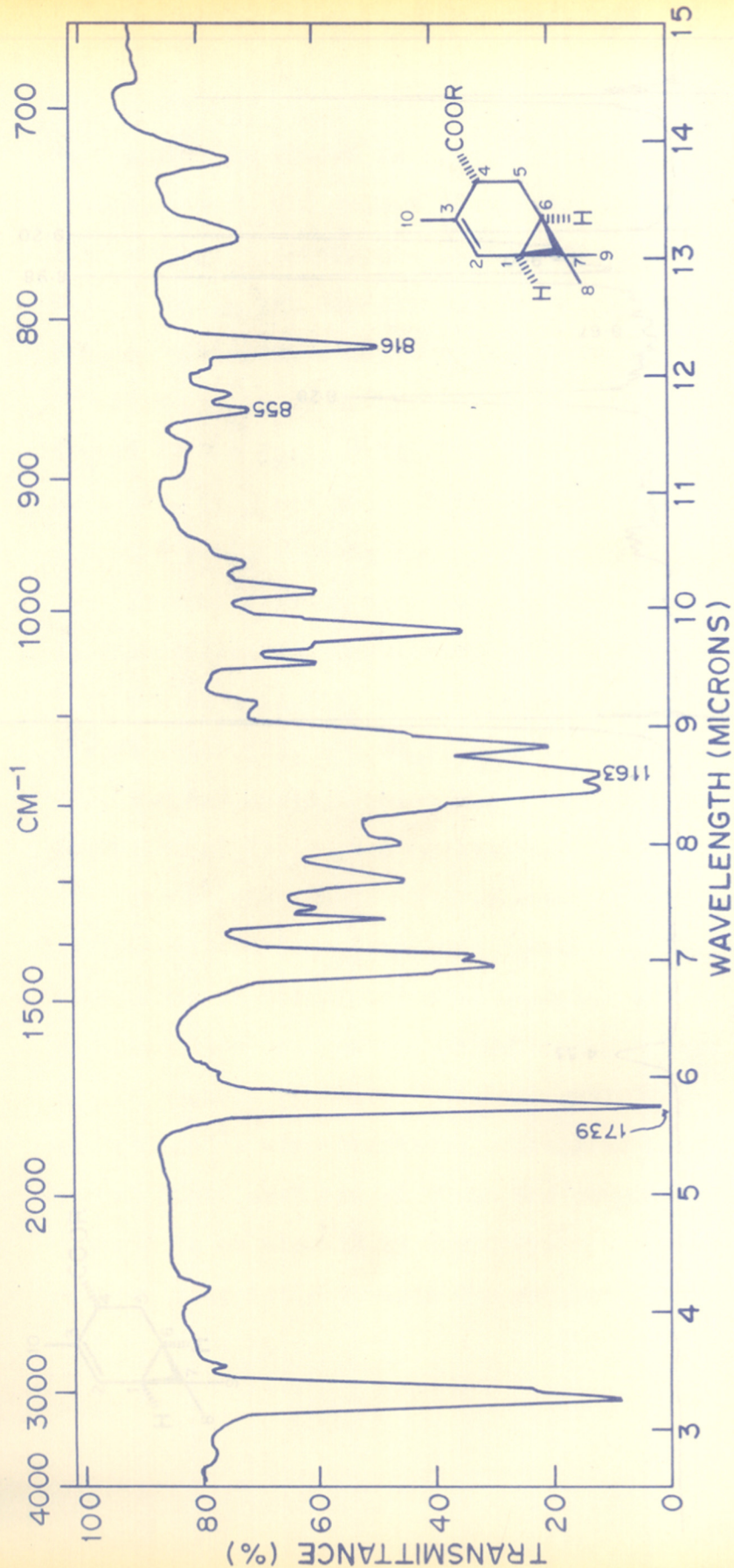


FIG. 15. IR SPECTRUM OF 3,7,7-TRIMETHYL-4 α -CARBOMETHOXY-BICYCLO-(4.1.0)-HEPT-2-ENE (VI, R=CH₃)

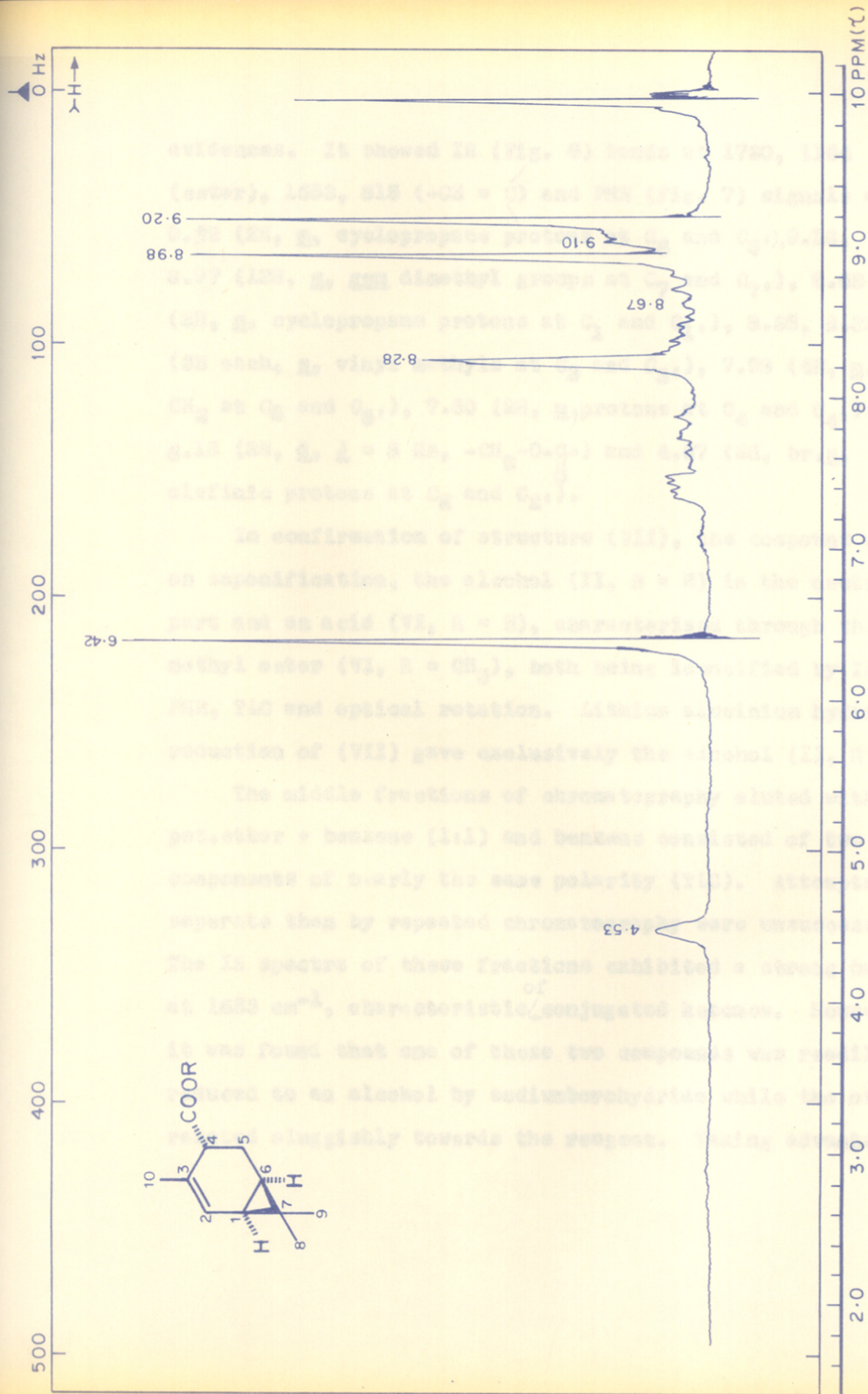


FIG. 16. PMR SPECTRUM OF 3,7,7-TRIMETHYL-4 α -CARBOMETHOXY-BICYCLO-(4.1.0)-HEPT-2-ENE (VI, R=CH₃)

evidences. It showed IR (Fig. 6) bands at 1730, 1164 (ester), 1653, 815 ($-\text{CH}=\text{C}$) and PMR (Fig. 7) signals at 9.32 (2H, m, cyclopropane protons at C_6 and C_6'), 9.18, 8.97 (12H, s, gem dimethyl groups at C_7 and C_7'), 8.63 (2H, m, cyclopropane protons at C_1 and C_1'), 8.35, 8.32 (3H each, s, vinyl methyls at C_3 and C_3'), 7.98 (4H, m, CH_2 at C_8 and C_8'), 7.50 (2H, m, protons at C_4 and C_4'), 6.15 (2H, d, $J = 8 \text{ Hz}$, $-\text{CH}_2-\text{O}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$) and 4.67 (2H, br. s, olefinic protons at C_2 and C_2').

In confirmation of structure (VII), the compound gave on saponification, the alcohol (II, $\text{R} = \text{H}$) in the neutral part and an acid (VI, $\text{R} = \text{H}$), characterised through the methyl ester (VI, $\text{R} = \text{CH}_3$), both being identified by IR, PMR, TLC and optical rotation. Lithium aluminium hydride reduction of (VII) gave exclusively the alcohol (II, $\text{R} = \text{H}$).

The middle fractions of chromatography eluted with pet. ether + benzene (1:1) and benzene consisted of two components of nearly the same polarity (TLC). Attempts to separate them by repeated chromatography were unsuccessful. The IR spectra of these fractions exhibited a strong band at 1653 cm^{-1} , characteristic ^{of} conjugated ketones. However, it was found that one of these two compounds was readily reduced to an alcohol by sodiumborohydride while the other reacted sluggishly towards the reagent. Taking advantage

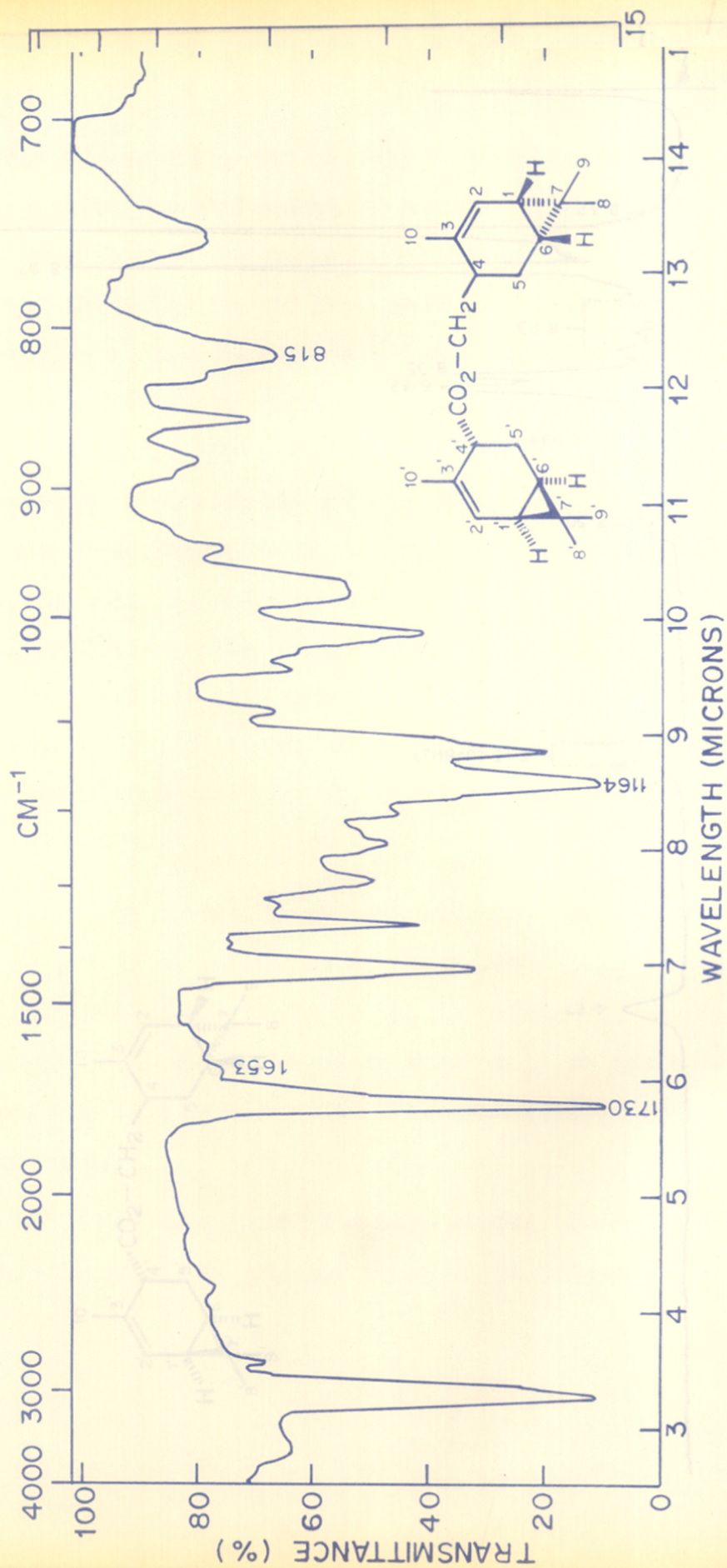


FIG. 6. IR SPECTRUM OF (3,7,7-TRIMETHYL-BICYCLO-(4.1.0)-HEPT-2-ENE-4-YL)-METH-
-3',7',7'-TRIMETHYL-BICYCLO-(4.1.0)-HEPT-2'-ENE-4'-CARBOXYLATE (VII)

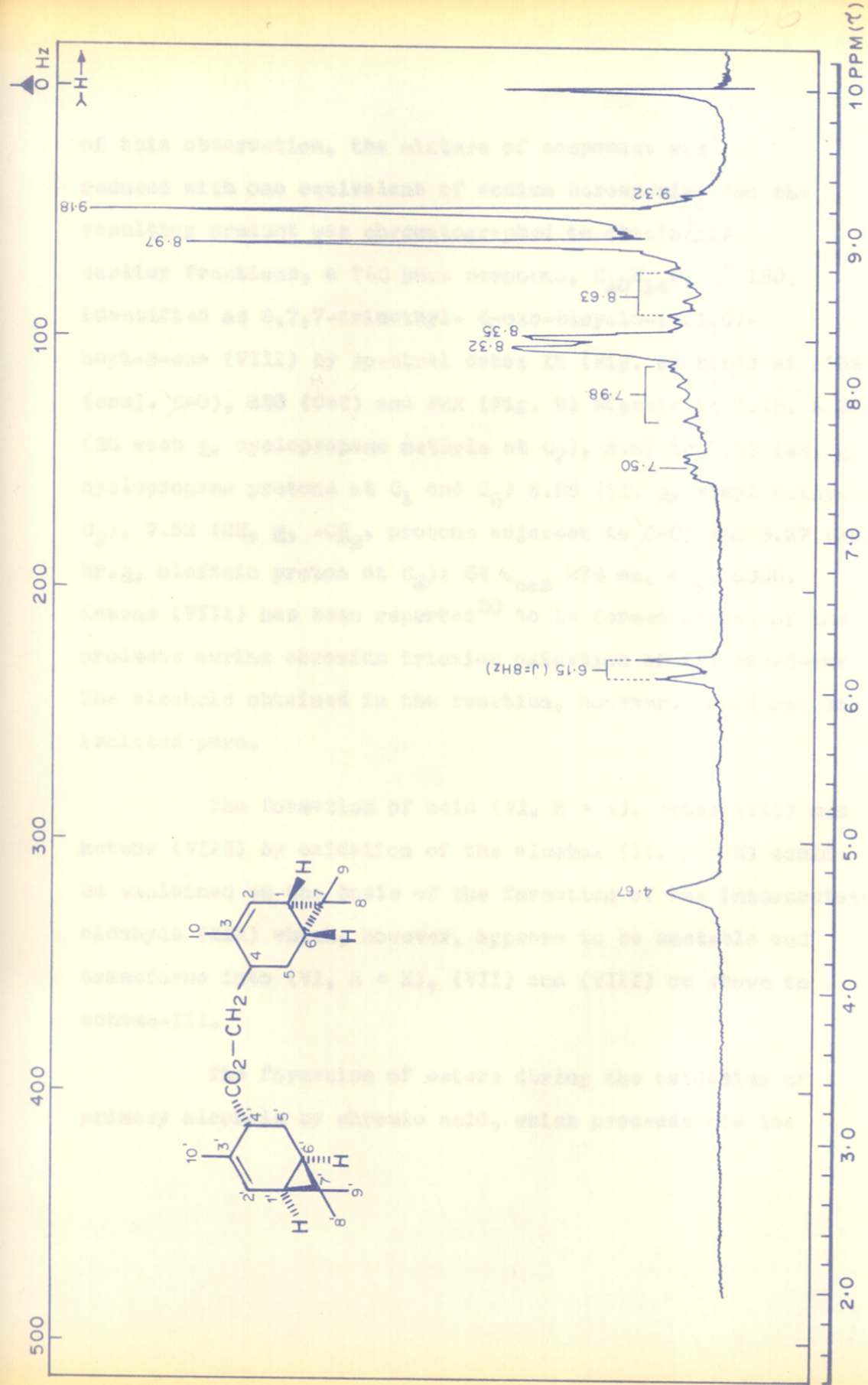


FIG. 7. PMR SPECTRUM OF (3,7,7'-TRIMETHYL-BICYCLO-(4.1.0)-HEPT-2-ENE-4-YL)-METHYL-
-3',7',7'-TRIMETHYL-BICYCLO-(4.1.0)-HEPT-2'-ENE-4'-CARBOXYLATE (VII) 156

of this observation, the mixture of compounds was reduced with one equivalent of sodium borohydride and the resulting product was chromatographed to obtain ⁱⁿthe earlier fractions, a TLC pure compound, $C_{10}H_{14}O$, M^+ 150, identified as 3,7,7-trimethyl- 4-oxo-bicyclo-(4.1.0)-hept-2-ene (VIII) by spectral data; IR (Fig. 8) bands at 1653 (conj. $C=O$), 830 ($C=C$) and PMR (Fig. 9) signals at 9.15, 8.78, (3H each s, cyclopropane methyls at C_7), 8.67 to 9.03 (2H, m, cyclopropane protons at C_1 and C_6) 8.25 (3H, s, vinyl methyl at C_3), 7.52 (2H, m, $-CH_2-$ protons adjacent to $C=O$) and 3.27 (1H, br.s, olefinic proton at C_2); UV λ_{max} 274 nm, ϵ_{max} 6000. Ketone (VIII) has been reported³⁰ to be formed as one of the products during chromium trioxide oxidation of (+) car-3-ene (I). The alcohols obtained in the reaction, however, could not be isolated pure.

The formation of acid (VI, R = H), ester (VII) and ketone (VIII) by oxidation of the alcohol (II, R = H) could be explained on the basis of the formation of the intermediate aldehyde (XIX) which, however, appears to be unstable and transforms into (VI, R = H), (VII) and (VIII) as shown in scheme-III.

The formation of esters during the oxidation of primary alcohols by chromic acid, which proceeds via the

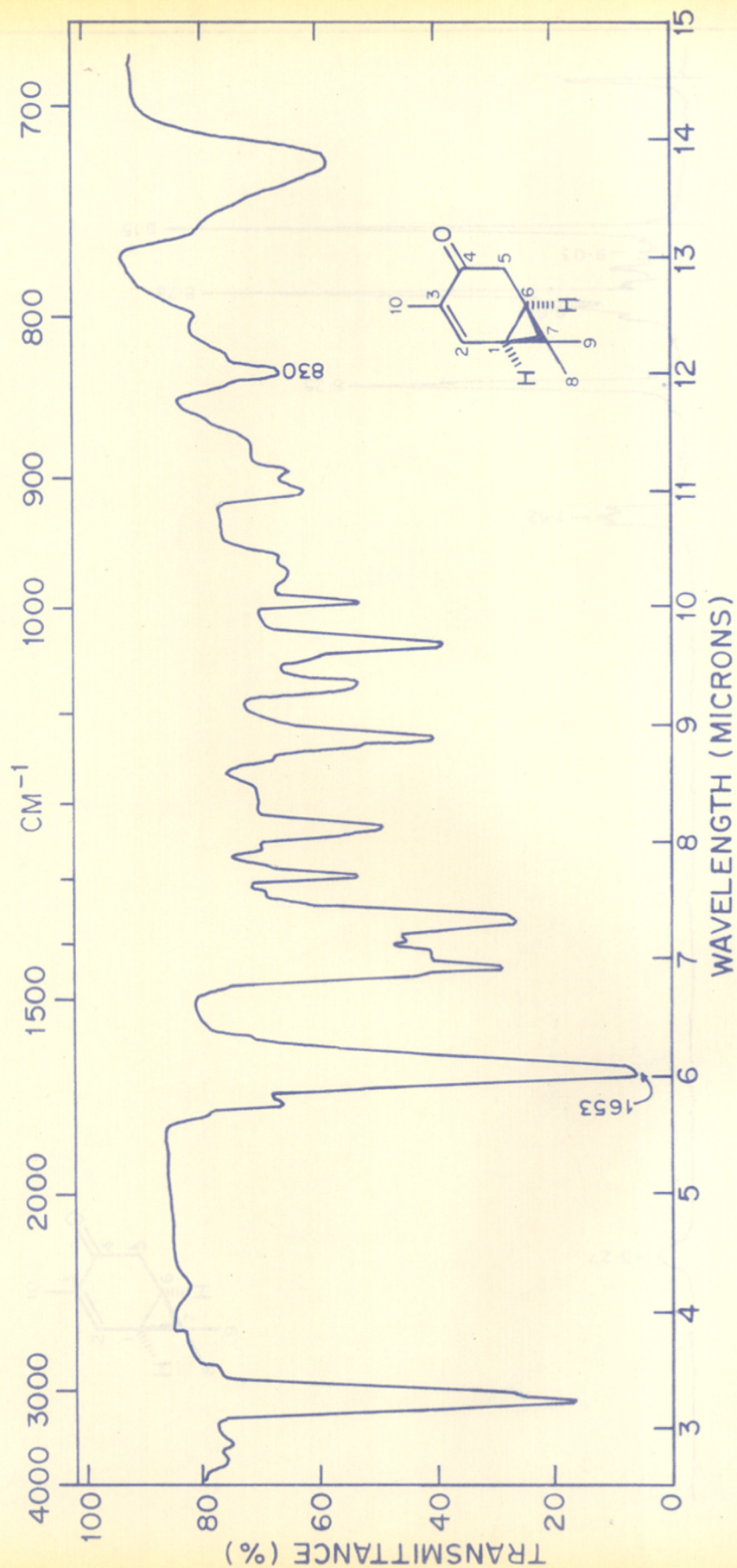
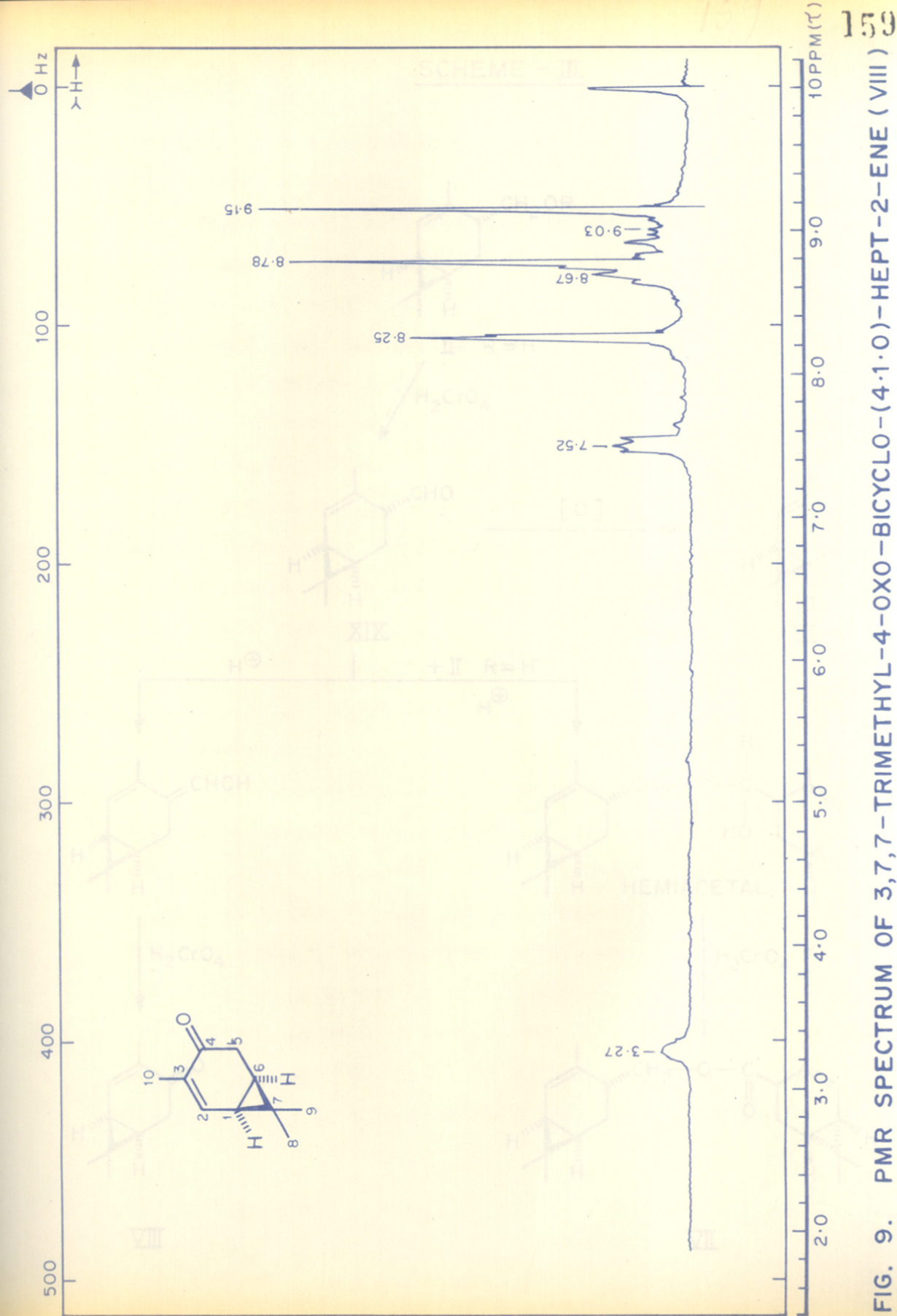
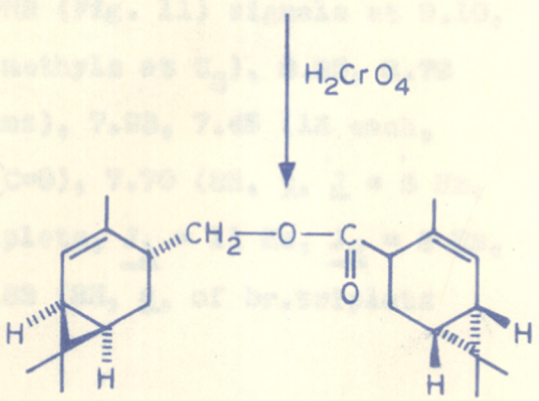
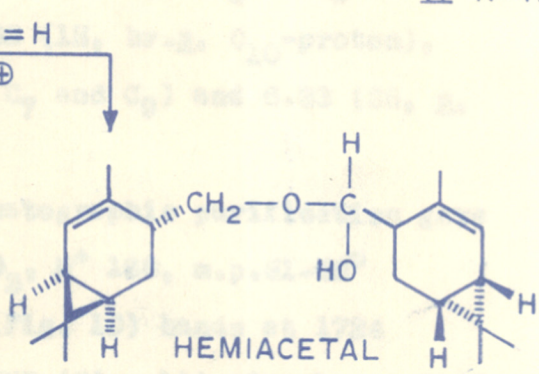
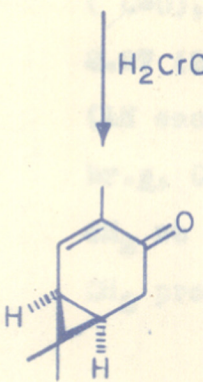
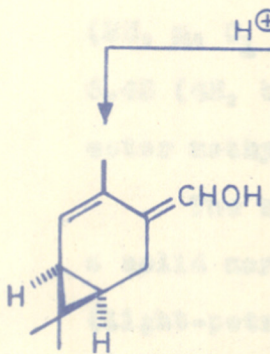
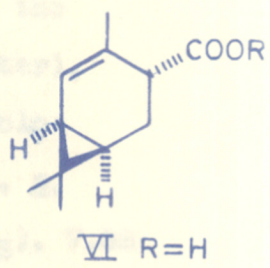
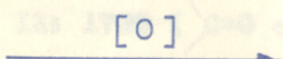
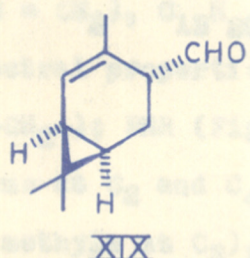
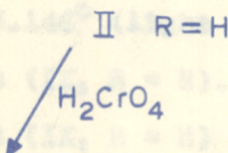
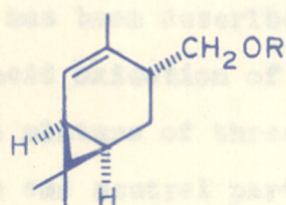


FIG. 8. IR SPECTRUM OF 3,7,7-TRIMETHYL-4-OXO-BICYCLO-(4.1.0)-HEPT-2-ENE (VIII)





formation of the hemi-acetal of the aldehyde formed with the starting alcohol has been described in literature³¹.

Jones chromic acid oxidation of the tricyclic ether (III) (96 hr at 15°) gave a mixture of three compounds (TLC), separated into acidic and neutral parts. The acid part gave a solid, m.p. 145-146° (light petrol), $C_{12}H_{18}O_3$, M^+ 210, identified as (IX, R = H). Esterification (MeOH/ H^+) of the acid (IX, R = H) furnished a liquid methyl ester, (IX, R = CH_3), $C_{13}H_{20}O_3$, M^+ 224. It showed the following spectral properties IR: 1739 (C=O of ester), 1053 ($-\text{CH}_2-\text{O}-\text{CH}_2-$); PMR (Fig. 12): 9.28 (2H, m, cyclopropane protons at C_2 and C_4), 8.93, 8.83 (3H each, s, cyclopropane methyls at C_3), 8.17 (2H, m, CH_2 at C_5), 7.88 (2H, m, C_1 and C_6 -protons), 7.62 (1H, br.s, C_{10} -proton), 6.43 (4H, br.m, CH_2 protons at C_7 and C_9) and 6.33 (3H, s, ester methyl).

The neutral part on chromatographic purification gave a solid nor ketone (X), $C_{11}H_{16}O_2$, M^+ 180, m.p. 61-62° (light-petrol). It showed IR (Fig. 10) bands at 1724 (C=O), 1056 ($-\text{CH}_2-\text{O}-\text{CH}_2-$) and PMR (Fig. 11) signals at 9.10, 8.97 (3H each, s, cyclopropane methyls at C_3), 8.85, 8.72 (1H each, br.s, C_2 and C_4 -protons), 7.93, 7.45 (1H each, br.s, C_1 and C_6 protons α - to C=O), 7.70 (2H, t, $J_1 = 5$ Hz, CH_2 at C_5), 6.35 (2H, d, of triplets, $J_1 = 11$ Hz, $J_2 = 2$ Hz, CH_2 protons at C_9 or C_7) and 5.82 (2H, d, of br. triplets

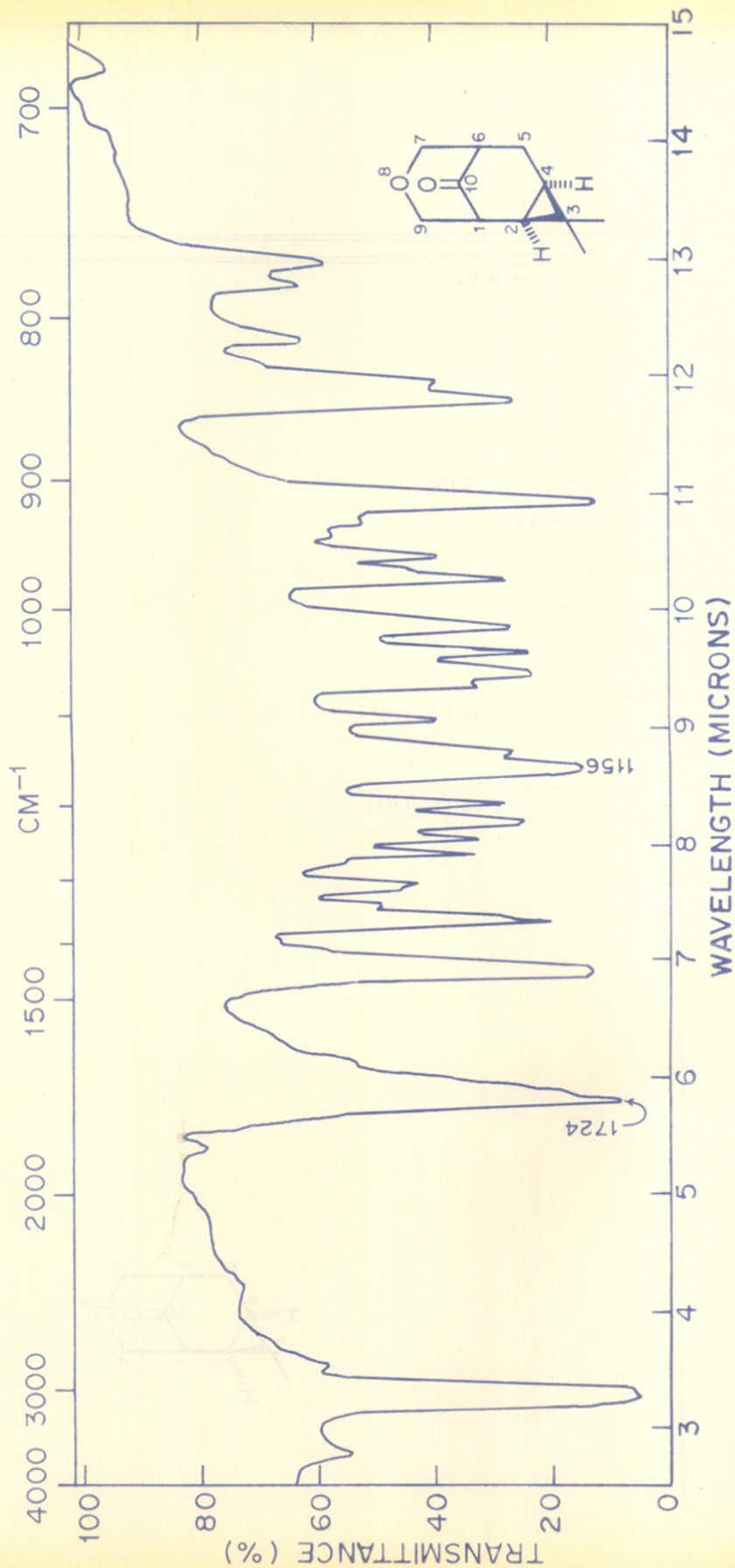


FIG. 10. IR SPECTRUM OF 3,3-DIMETHYL-8-OXA-10-OXO-TRICYCLO-(4.3.1.0^{2,4})-DECANE(X).

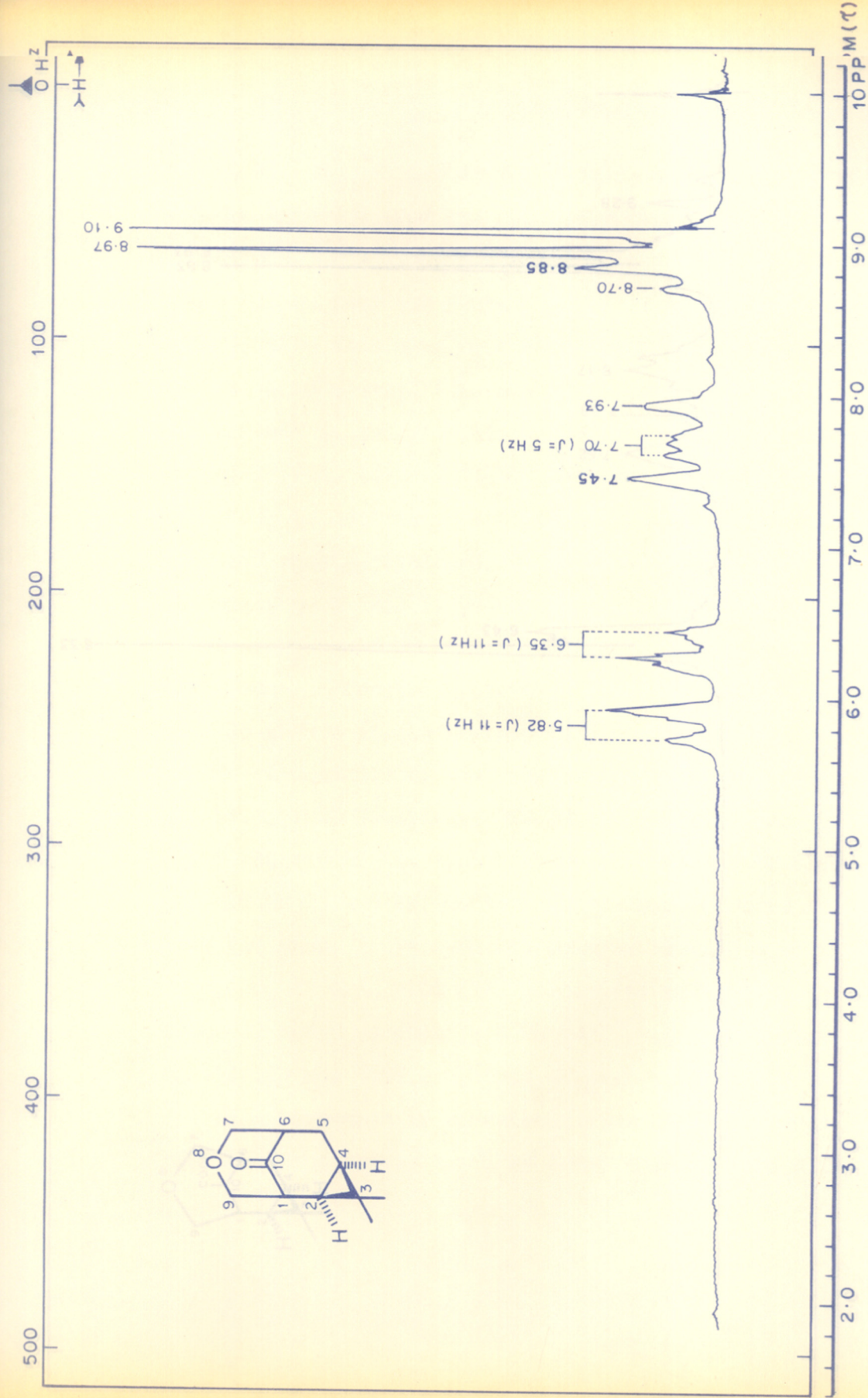


FIG. 11. PMR SPECTRUM OF 3,3-DIMETHYL-8-OXA-10-OKO-TRICYCLO-(4.3.1.0^{2,4})-
- DECANE (X)

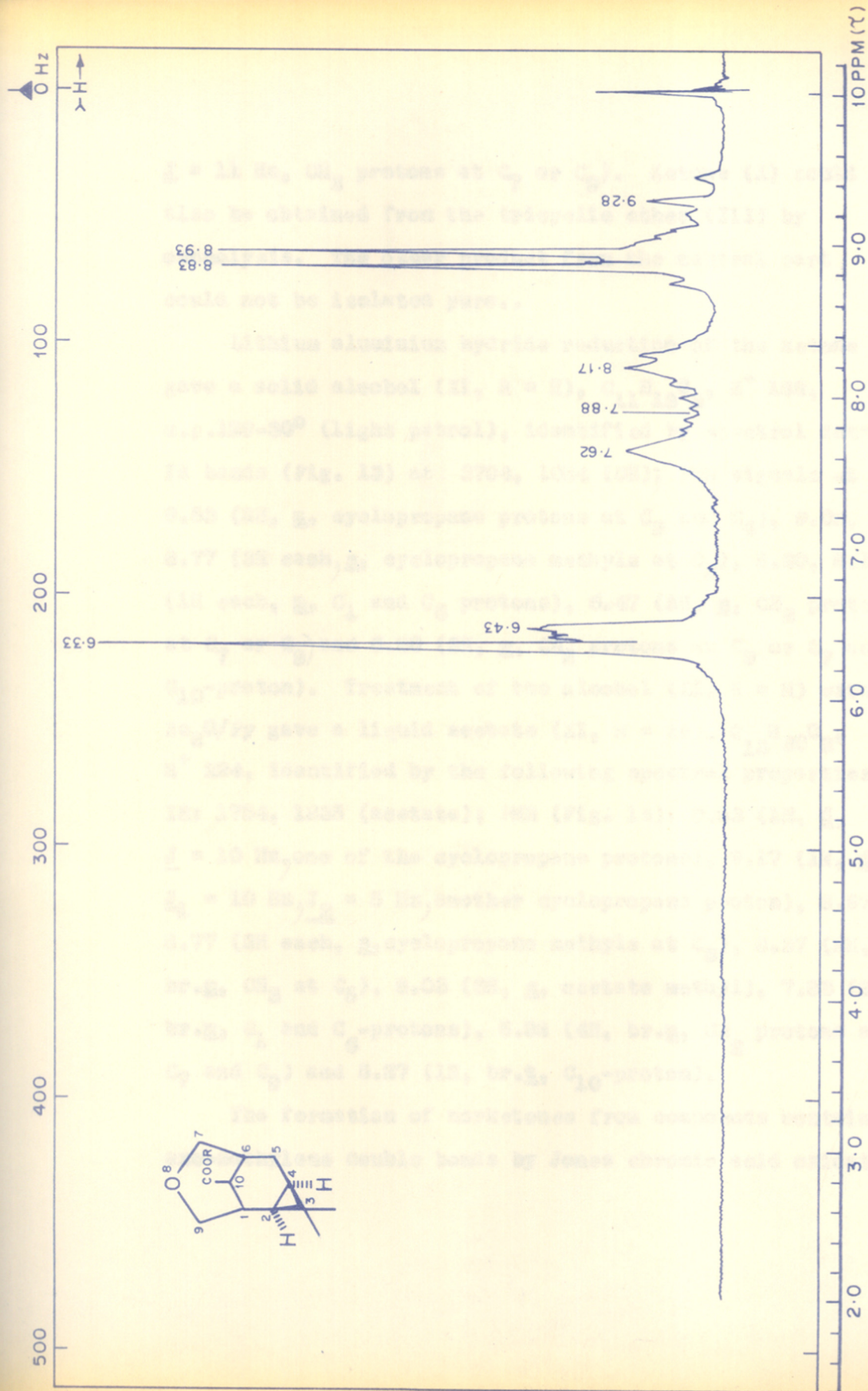


FIG. 12. PMR SPECTRUM OF 3,3-DIMETHYL-8-OXA-10-CARBOMETHOXY-TRICYCLO-

-(4.3.1.0^{2,4})-DECANE (IX, R=CH₃)

$J = 11$ Hz, CH_2 protons at C_7 or C_9). Ketone (X) could also be obtained from the tricyclic ether (III) by ozonolysis. The other product from the neutral part could not be isolated pure..

Lithium aluminium hydride reduction of the ketone (X) gave a solid alcohol (XI, $\text{R} = \text{H}$), $\text{C}_{11}\text{H}_{18}\text{O}_2$, $\text{M}^+ 182$, m.p. $129-30^\circ$ (light petrol), identified by spectral data; IR bands (Fig. 13) at: 3704, 1064 (OH); PMR signals at 9.53 (2H, m, cyclopropane protons at C_2 and C_4), 9.03, 8.77 (3H each, s, cyclopropane methyls at C_3), 8.30, 8.13 (1H each, m, C_1 and C_6 protons), 6.47 (2H, m, CH_2 protons at C_7 or C_9) and 6.20 (3H, m, CH_2 protons at C_9 or C_7 and C_{10} -proton). Treatment of the alcohol (XI, $\text{R} = \text{H}$) with $\text{Ac}_2\text{O}/\text{Py}$ gave a liquid acetate (XI, $\text{R} = \text{Ac}$), $\text{C}_{13}\text{H}_{20}\text{O}_3$, $\text{M}^+ 224$, identified by the following spectral properties. IR: 1754, 1235 (acetate); PMR (Fig. 14): 9.53 (1H, d, $J = 10$ Hz, one of the cyclopropane protons), 9.17 (1H, dd, $J_1 = 10$ Hz, $J_2 = 5$ Hz, another cyclopropane proton), 8.97, 8.77 (3H each, s, cyclopropane methyls at C_3), 8.37 (2H, br.m, CH_2 at C_5), 8.03 (3H, s, acetate methyl), 7.83 (2H, br.m, C_1 and C_6 -protons), 6.28 (4H, br.m, CH_2 protons at C_7 and C_9) and 5.27 (1H, br.t, C_{10} -proton).

The formation of norketones from compounds containing exo-methylene double bonds by Jones chromic acid oxidation

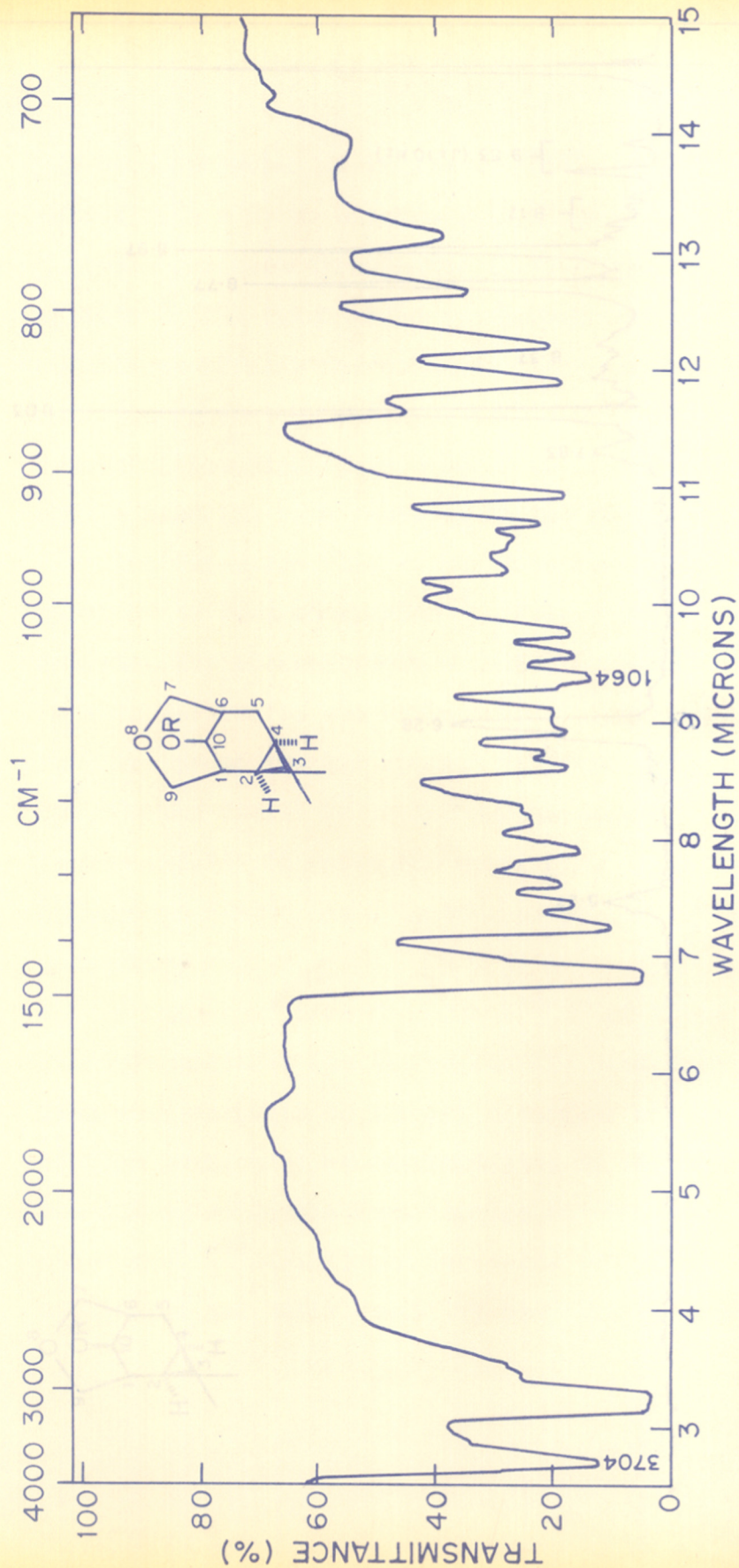
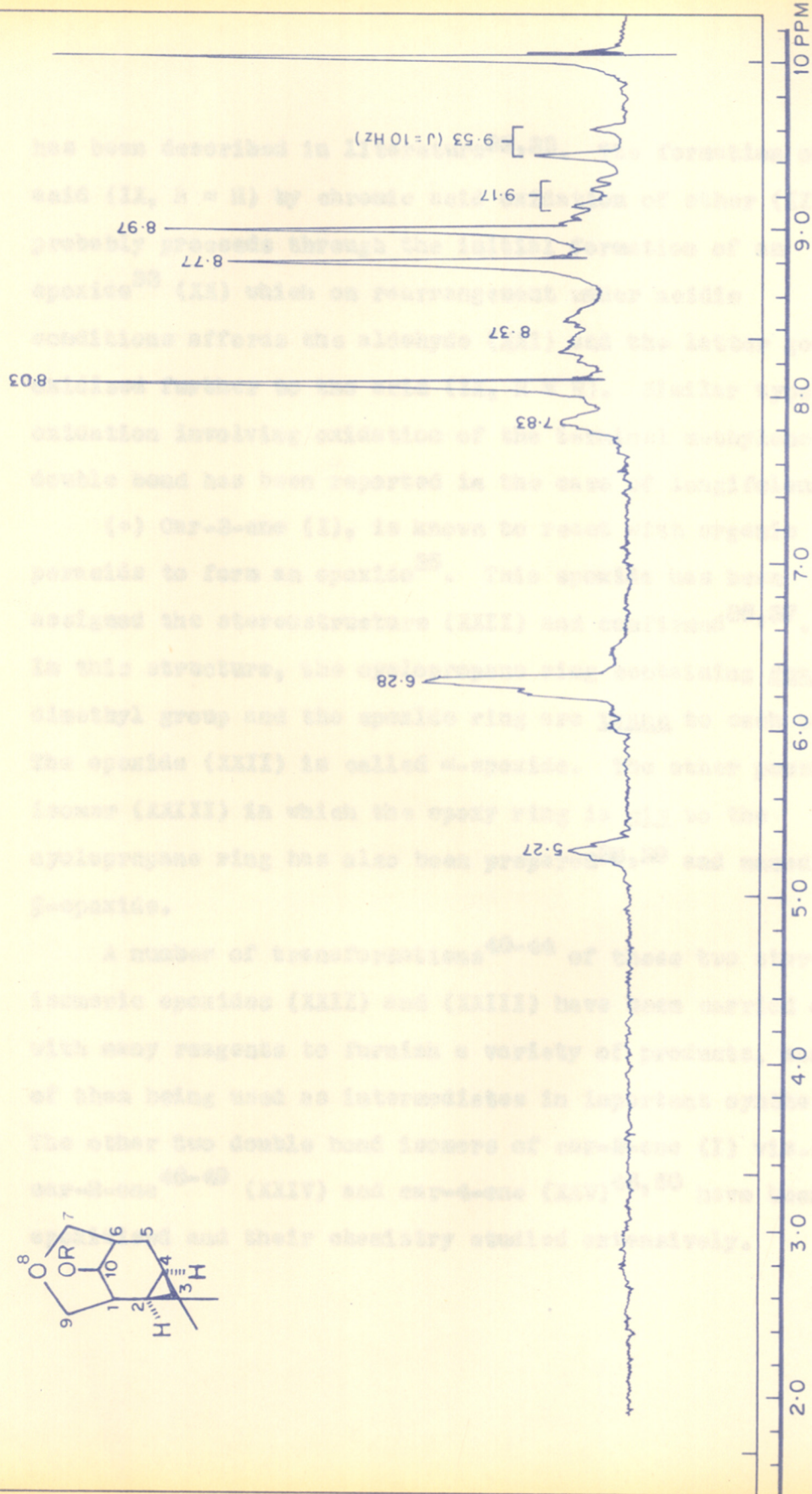


FIG. 13. IR SPECTRUM OF 3,3-DIMETHYL-8-OXA-10-HYDROXY-TRICYCLO-(4.3.1.0^{2,4})-
-DECANE (XI, R=H)

FIG. 14. PMR SPECTRUM OF 3,3-DIMETHYL-8-OXA-10-ACETOXY-TRICYCLO-(4.3.1.0^{2,4})-
-DECANE (XI, R=Ac)



has been described in literature^{32,33}. The formation of acid (IX, R = H) by chromic acid oxidation of ether (III), probably proceeds through the initial formation of an epoxide³³ (XX) which on rearrangement under acidic conditions affords the aldehyde (XXI) and the latter gets oxidised further to the acid (IX, R = H). Similar type of oxidation involving oxidation of the terminal methylene double bond has been reported in the case of longifolene³⁴.

(+) Car-3-ene (I), is known to react with organic peracids to form an epoxide³⁵. This epoxide has been assigned the stereostructure (XXII) and confirmed^{36,37}. In this structure, the cyclopropane ring containing gem dimethyl group and the epoxide ring are trans to each other. The epoxide (XXII) is called α -epoxide. The other possible isomer (XXIII) in which the epoxy ring is cis to the cyclopropane ring has also been prepared^{38,39} and named as β -epoxide.

A number of transformations⁴⁰⁻⁴⁴ of these two stereoisomeric epoxides (XXII) and (XXIII) have been carried out with many reagents to furnish a variety of products, some of them being used as intermediates in important syntheses^{37,45}. The other two double bond isomers of car-3-ene (I) viz., car-2-ene⁴⁶⁻⁴⁹ (XXIV) and car-4-ene (XXV)^{46,50} have been epoxidised and their chemistry studied extensively.

Car-2-ene when treated with peracetic acid and sodiumacetate in methylene dichloride is reported⁴⁶ to give a mixture of compounds (XXVI) and (XXVII) which are formed as a result of the rearrangement of the initially formed epoxide (XXVIII) under acidic conditions. Recently, from our laboratory, Pai et al.⁴⁷, have reported the oxidation studies of 4 α -acetyl-car-2-ene (XXIX) with perbenzoic acid. They isolated in addition to the epoxide (XXX), the rearranged alcohol (XXXI). Under mild alkaline conditions, the epoxide (XXX) underwent rearrangement to the conjugated keto alcohol (XXXII). However, in the presence of acids, in methanol the p-menthane derivatives (XXXI) and (XXXIII) were formed as the major products of the reaction. The rearrangement of oxiranes on alumina solid matrix to allylic alcohols and other rearranged products has been extensively studied. For example, when carane 3,4 α -epoxide (XXII) is rearranged on alumina solid matrix, a mixture of allylic alcohols (XXXIV) and (XXXV) results⁵¹ in addition to the rearranged alcohol (XXXVI), while the corresponding β -epoxide (XXIII) under similar conditions has been reported to give a mixture of three compounds in which the allylic alcohol (XXXIV) is also present.

With a view to ascertain the effect of the nature of the substituent at C₄-position on the cleavage of the C₂-C₃ epoxide of car-2-ene derivatives, the epoxidation of the methyl ester (VI, R = CH₃) and its rearrangement under mild alkaline and acidic conditions were undertaken.

The methyl ester (VI, R = CH₃), on treatment with perbenzoic acid in chloroform solution, gave a mixture of two compounds (TLC, 2 spots, 8% ethylacetate in benzene). It was separated into its constituents by column chromatography on alumina (Gr. II, 1:20). The less polar compound, the major product, eluted with pet.ether + benzene (3:1) was obtained as a solid which was identified as the epoxide (XII), C₁₂H₁₈O₃, M⁺ 210, m.p. 49-50° (pet.ether). It showed IR (Fig. 17) bands at 1742, 1163 (ester), 1026 (epoxide) and PMR (Fig. 18) signals at: 9.10 (2H, m, cyclopropane protons at C₁ and C₆), 9.00, 8.90 (3H each, s, methyls on cyclopropane at C₇), 8.67 (3H, s, methyl at C₃-bearing oxygen), 7.37 (1H, br. d, C₄-proton), 7.28 (1H, s, C₂-proton of epoxide) and 6.37 (3H, s, ester methyl).

The more polar compound, the minor product of the reaction eluted with benzene and benzene + chloroform (1:1) was obtained as a liquid which was identified as the hydroxy ester (XIII), C₁₂H₁₈O₃, M⁺ 210. It showed the following spectral properties. IR (Fig. 19): 3704 (OH),

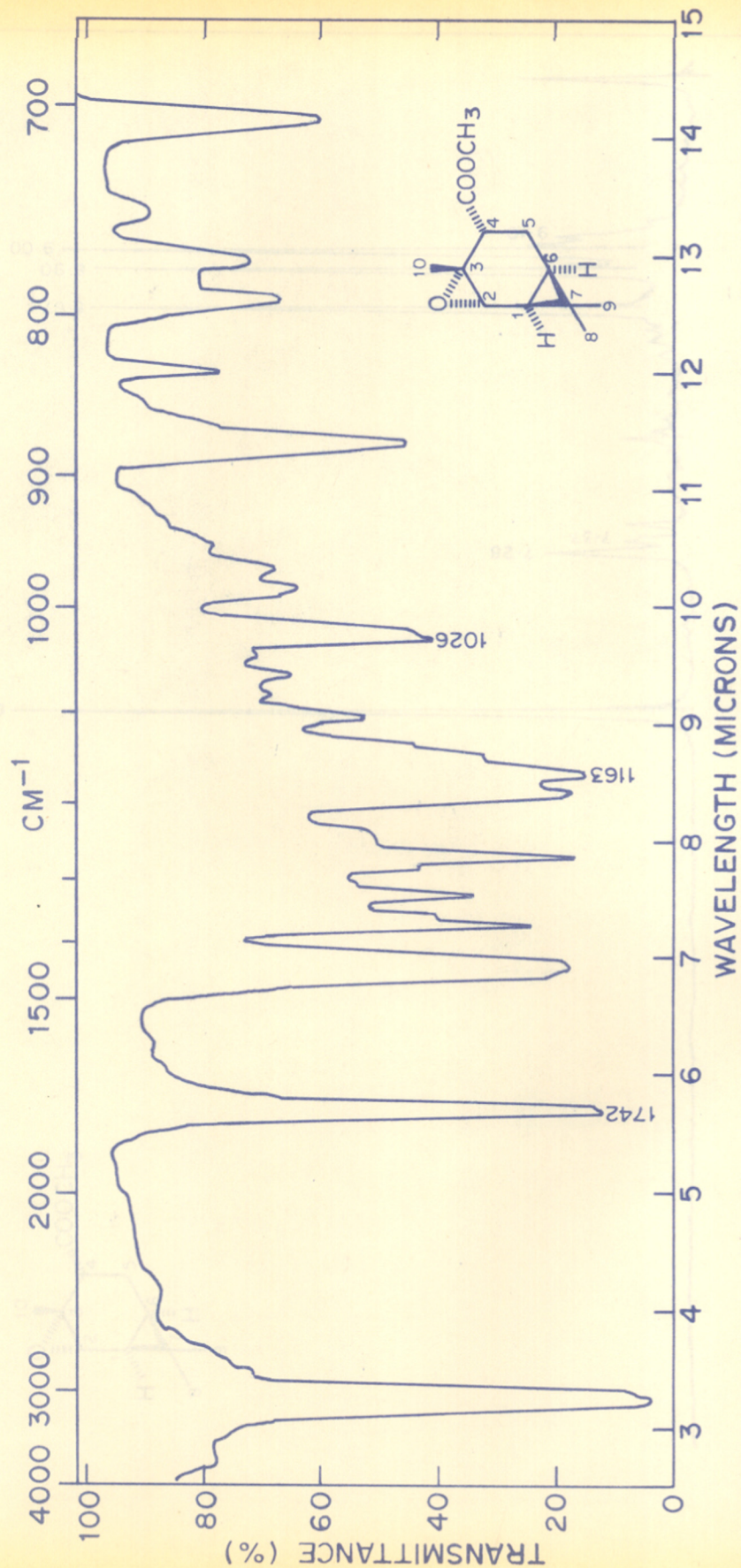


FIG. 17. IR SPECTRUM OF 3,7,7-TRIMETHYL-2 α ,3 α -EPOXY-4 α -CARBOMETHOXY-
-BICYCLO-(4.1.0)-HEPTANE (XII)

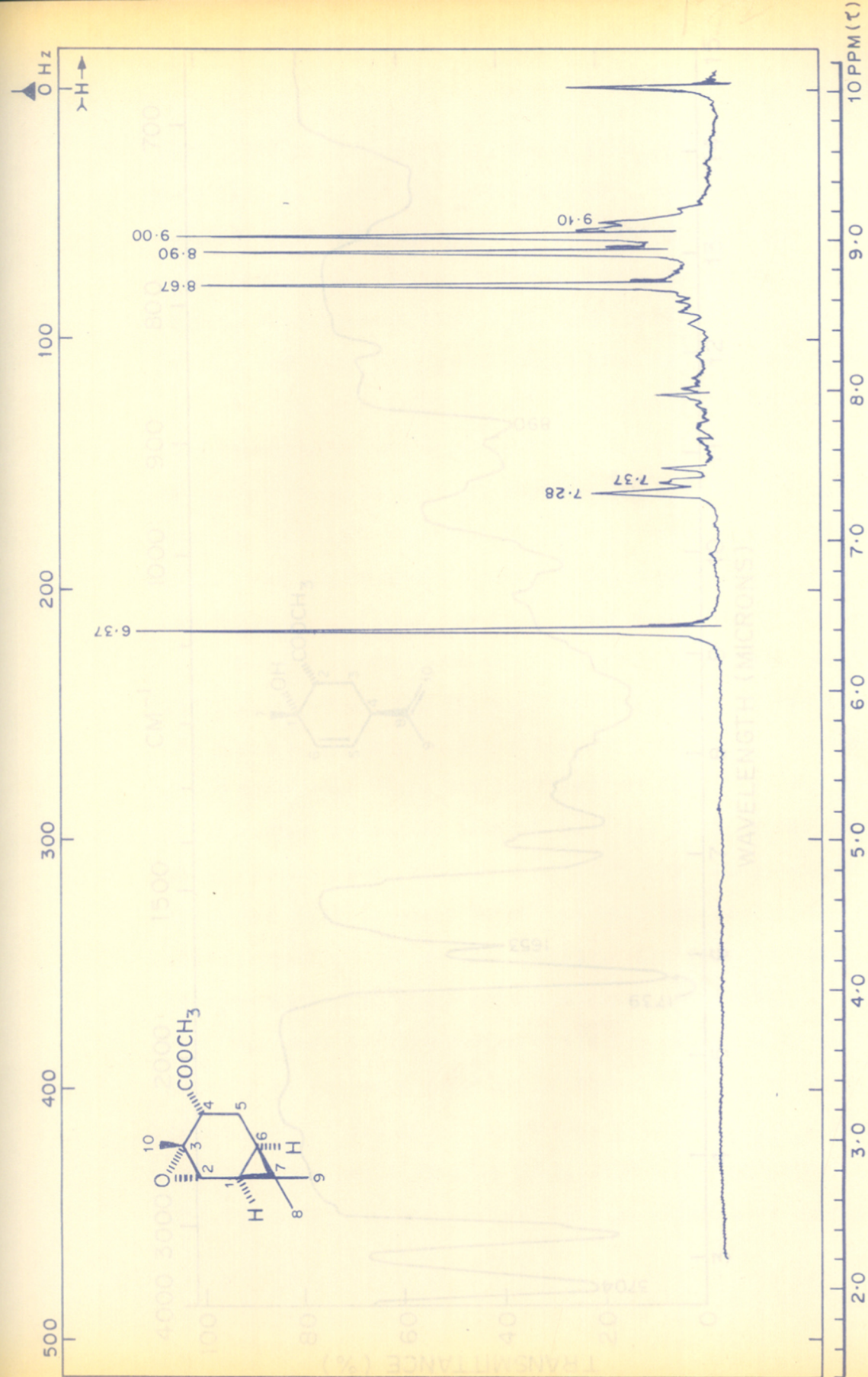


FIG. 18. PMR SPECTRUM OF 3,7,7-TRIMETHYL-2 α ,3 α -EPOXY-4 α -CARBOMETHOXY-1,2-BICYCLO-(4.1.0)-HEPTANE (XII)

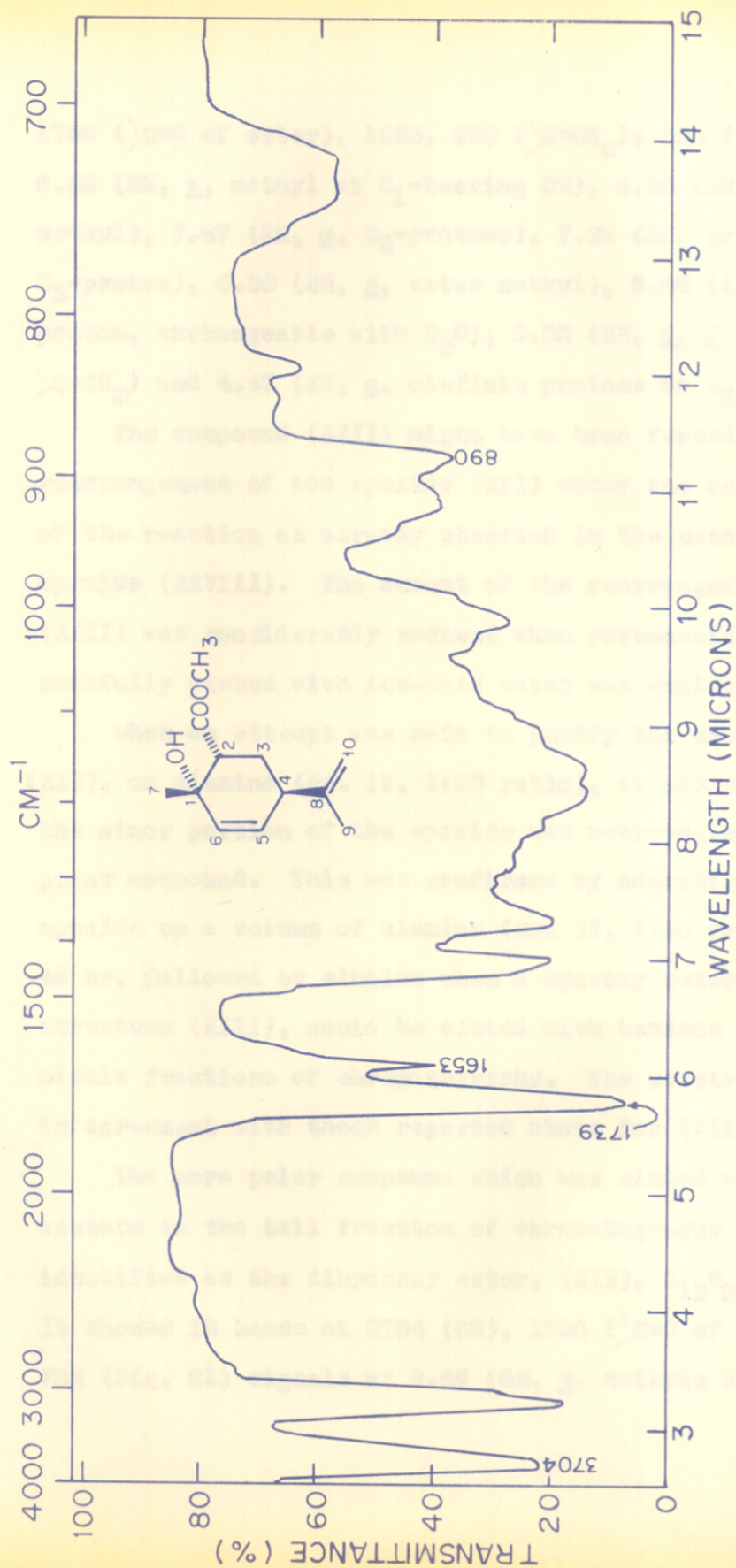


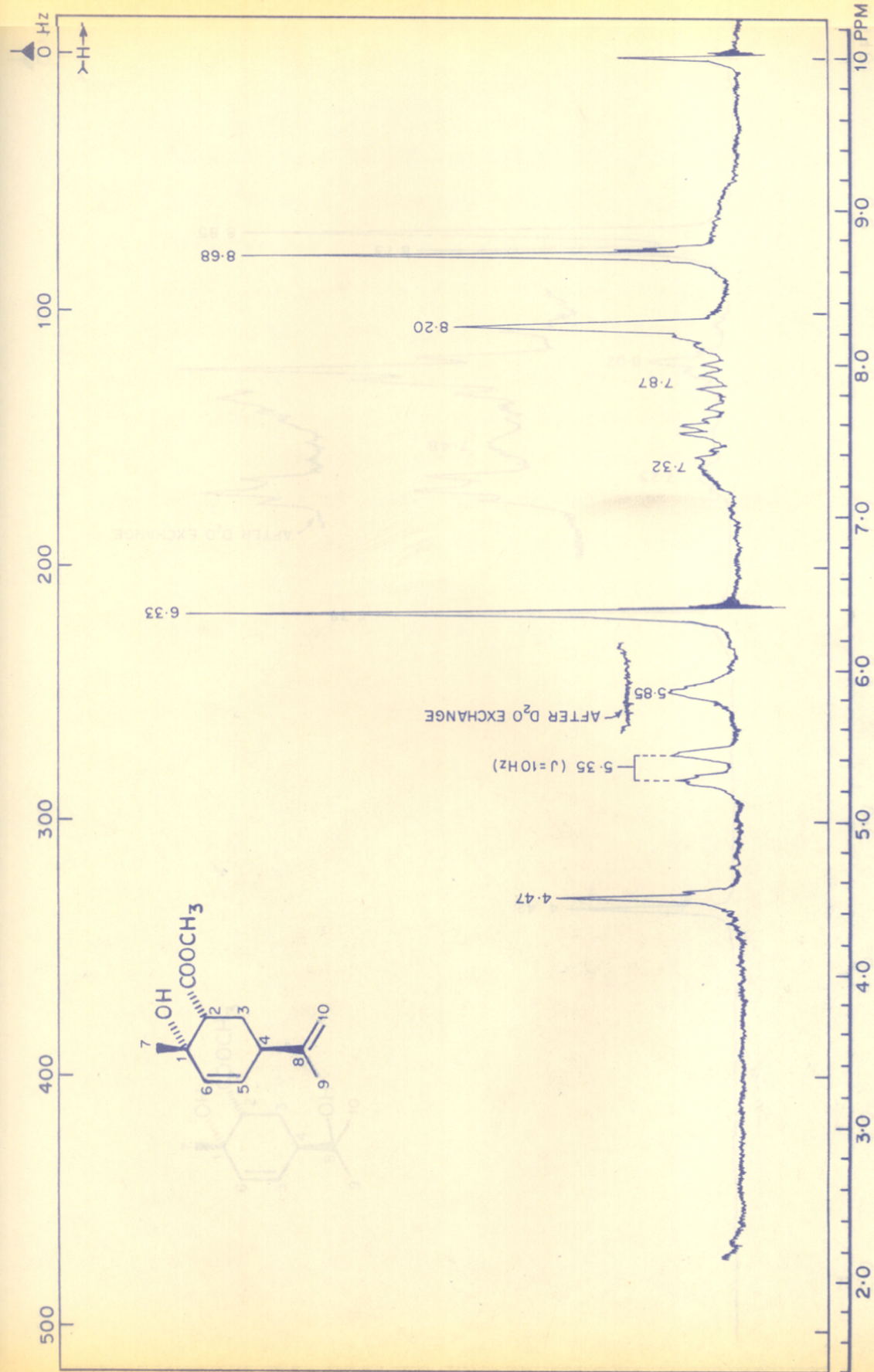
FIG. 19. IR SPECTRUM OF 1 α -HYDROXY-2 α -CARBOMETHOXY-p-MENTH- $\Delta^{5,8}$ -DIENE (XIII)

1739 (C=O of ester), 1653, 890 (C=CH_2); PMR (Fig. 20): 8.68 (3H, s, methyl at C_1 -bearing OH), 8.20 (3H, s, vinyl methyl), 7.87 (2H, m, C_3 -protons), 7.32 (1H, br.m, C_2 -proton), 6.33 (3H, s, ester methyl), 5.85 (1H, s, OH proton, exchangeable with D_2O), 5.35 (2H, d, $J = 10$ Hz, C=CH_2) and 4.47 (2H, s, olefinic protons at C_5 and C_6).

The compound (XIII) might have been formed by the rearrangement of the epoxide (XII) under the acidic conditions of the reaction as already observed in the case of car-2-ene epoxide (XXVIII). The amount of the rearranged compound (XIII) was considerably reduced when perbenzoic acid carefully washed with ice-cold water was employed for epoxidation.

When an attempt was made to purify the crude epoxide (XII), on alumina (Gr. II, 1:20 ratio), it was observed that the minor portion of the epoxide was rearranging to more polar compound. This was confirmed by adsorbing the pure epoxide on a column of alumina (Gr. II, 1:20 ratio) for 48 hr. followed by elution when a hydroxy ester assigned structure (XIII), could be eluted with benzene in the middle fractions of chromatography. The spectral data were in agreement with those reported above for (XIII).

The more polar compound which was eluted with ethyl acetate in the tail fraction of chromatography was identified as the dihydroxy ester, (XIV), $\text{C}_{12}\text{H}_{20}\text{O}_4$, $M^+ 228$. It showed IR bands at 3704 (OH), 1730 (C=O of ester) and PMR (Fig. 21) signals at 8.85 (6H, s, methyls of hydroxy



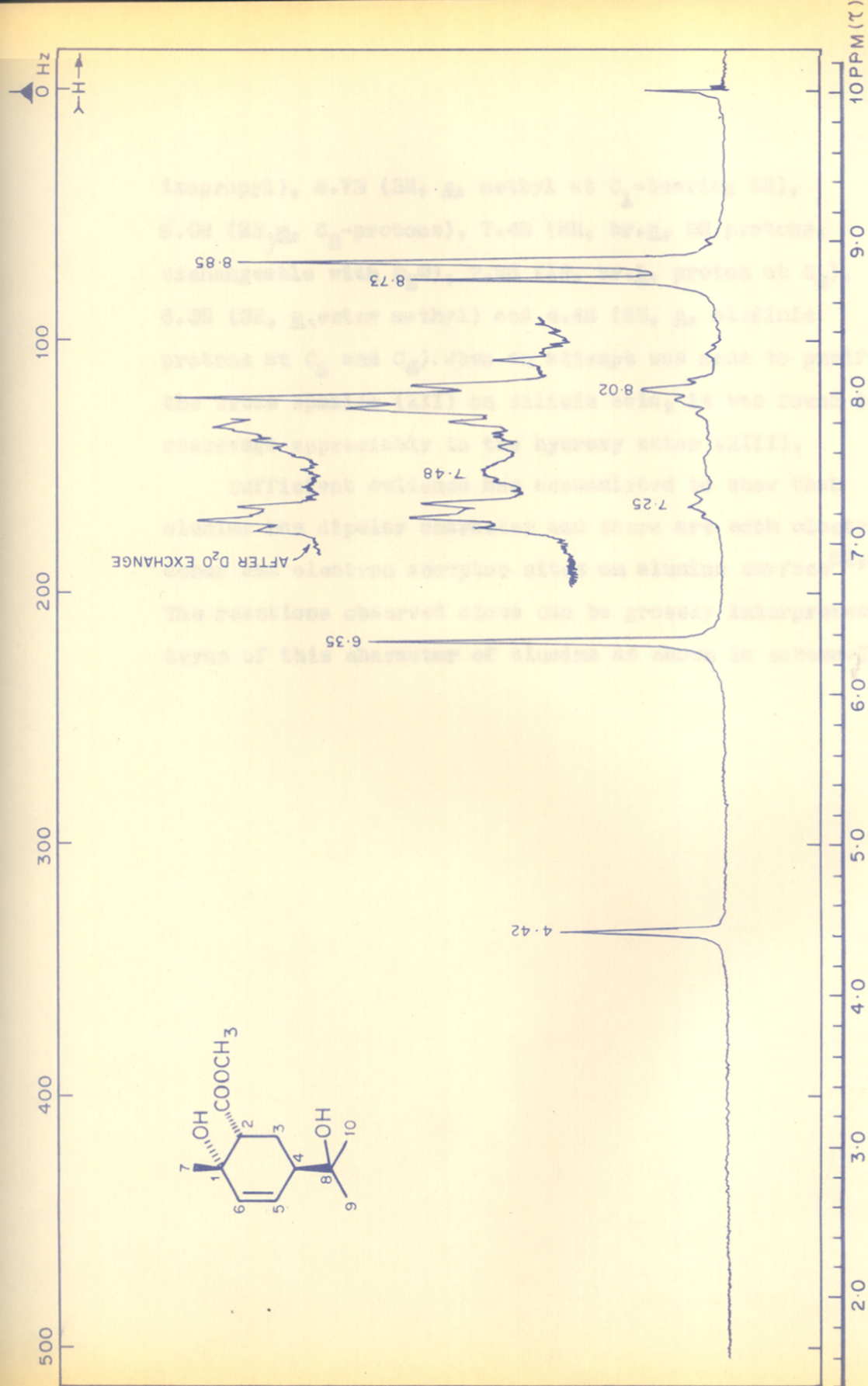
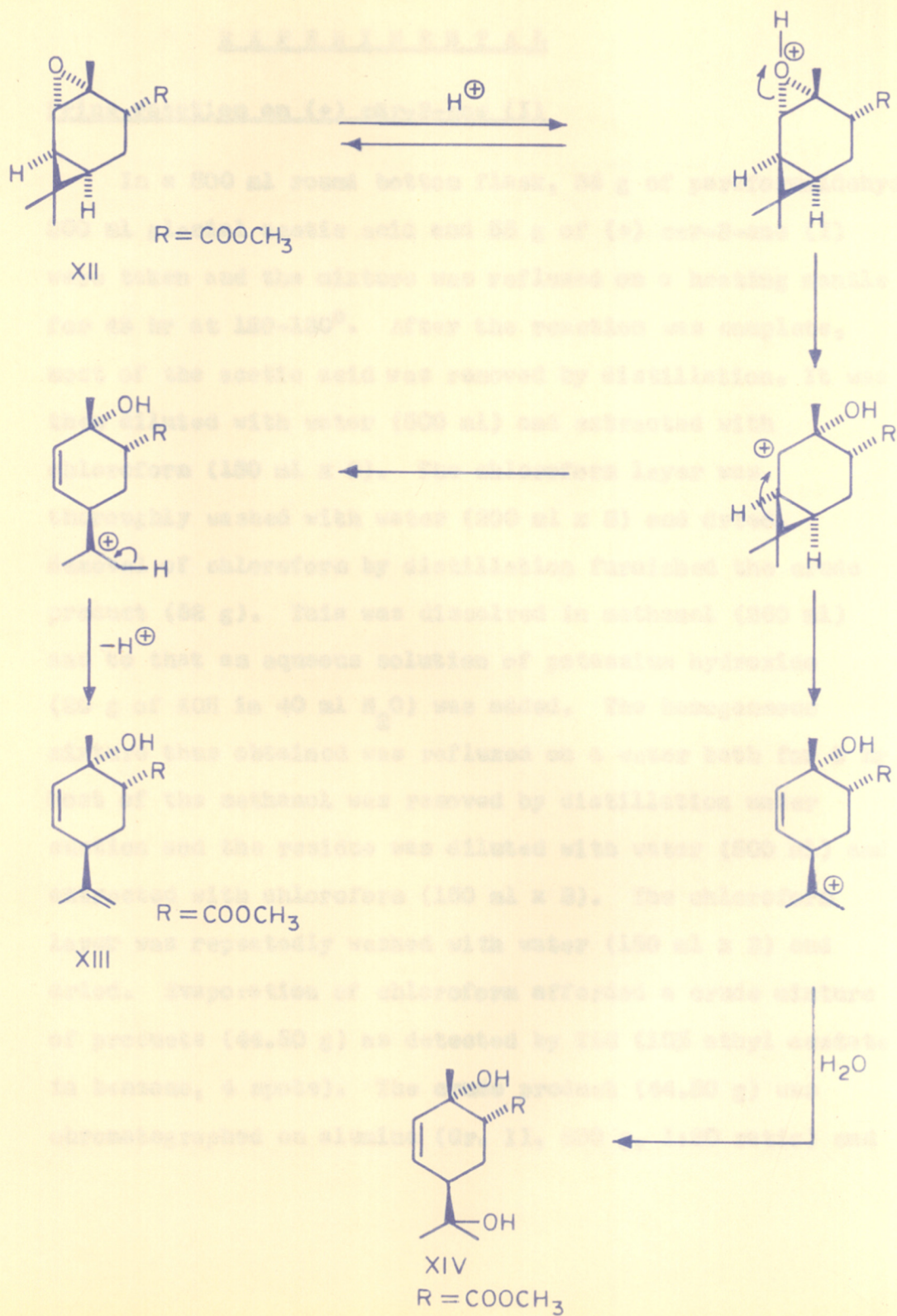


FIG. 21. PMR SPECTRUM OF 1,8-DIHYDROXY-2 α -CARBOMETHOXY-p-MENTH- Δ^5 -ENE (XIV)

isopropyl), 8.73 (3H, s, methyl at C₁-bearing OH), 8.02 (2H, m, C₃-protons), 7.48 (2H, br.s, OH protons, exchangeable with D₂O), 7.25 (1H, br.t, proton at C₂), 6.35 (3H, s, ester methyl) and 4.42 (2H, s, olefinic protons at C₅ and C₆). When an attempt was made to purify the crude epoxide (XII) on silicic acid, it was found to rearrange appreciably to the hydroxy ester (XIII).

Sufficient evidence has accumulated to show that alumina has dipolar character and there are both electron donor and electron acceptor sites on alumina surface^{52,53}. The reactions observed above can be grossly interpreted in terms of this character of alumina as shown in scheme-IV.



EXPERIMENTAL

Prins reaction on (+) car-3-ene (I)

In a 500 ml round bottom flask, 36 g of paraformaldehyde, 300 ml glacial acetic acid and 55 g of (+) car-3-ene (I) were taken and the mixture was refluxed on a heating mantle for 48 hr at 120-130°. After the reaction was complete, most of the acetic acid was removed by distillation. It was then diluted with water (500 ml) and extracted with chloroform (150 ml x 3). The chloroform layer was thoroughly washed with water (200 ml x 3) and dried. Removal of chloroform by distillation furnished the crude product (52 g). This was dissolved in methanol (260 ml) and to that an aqueous solution of potassium hydroxide (20 g of KOH in 40 ml H₂O) was added. The homogeneous mixture thus obtained was refluxed on a water bath for 8 hr. Most of the methanol was removed by distillation under suction and the residue was diluted with water (500 ml) and extracted with chloroform (150 ml x 3). The chloroform layer was repeatedly washed with water (150 ml x 3) and dried. Evaporation of chloroform afforded a crude mixture of products (44.50 g) as detected by TLC (10% ethyl acetate in benzene, 4 spots). The crude product (44.50 g) was chromatographed on alumina (Gr. II, 390 g, 1:20 ratio) and

eluted as follows:

CHROMATOGRAM 1

Fraction	Solvent	Vol. in ml	Material in g
1	Pet.ether	500	2.356
2	"	500	1.673
3	"	500	1.632
4	"	250	1.537
5	"	250	1.432
6	"	250	1.423
7	"	250	1.354
8	"	250	0.235
9	"	250	0.121
10	Pet.ether + benzene(3:1)	500	1.423
11	" "	500	1.234
12	Pet.ether + benzene(2:1)	500	1.182
13	Pet.ether + benzene(1:1)	500	1.148
14	"	500	0.935
15	Benzene	250	0.832
16	"	250	0.822
17	"	250	1.815
18	"	250	1.756
19	"	250	1.658
20	"	250	1.644
21	"	250	1.546
22	"	250	1.523
23	"	250	1.584
24	"	250	1.526
25	Chloroform	500	2.834
26	Acetone	1000	5.680

Fraction 1 of chromatogram 1 showed the presence of starting compound viz., (+) car-3-ene (I) identified by comparative TLC and IR spectrum.

Fractions 12 to 25 showed identical TLC pattern and were found to be pure (TLC, 10% ethyl acetate in benzene). Hence these fractions were mixed together and the solvent evaporated to give the pure alcohol (II, R = H, 21.40 g).

Analysis

Found: C, 79.31; H, 10.85;

$C_{11}H_{18}O$ requires C, 79.46; H, 10.92%.

IR bands at: 3502, 3030, 1652, 1439, 1366, 1198, 1117, 1070, 1031, 1009, 855, 833 and 810 cm^{-1} .

Fraction 26 showed a complex pattern on TLC and was not investigated further.

Fractions 2 to 11 showed three spots in TLC analysis (silicic acid with 10% silver nitrate, 6% ethyl acetate in benzene). Hence these fractions were mixed together and the solvent evaporated to furnish 12.06 g of a mixture. This mixture was rechromatographed on silicic acid (217 g) impregnated with silver nitrate (24 g) and eluted as follows:

CHROMATOGRAM 2

No.	Solvent	Vol.in ml	Material in g
1.	Pet.ether	250	1.213
2.	"	250	1.123
3.	"	250	1.089
4.	Pet.ether + benzene (10:1)	250	0.839
5.	"))	250	0.7340
6.	Pet.ether + benzene (2:1)	250	0.697
7.	"))	250	0.534
8.	Pet.ether + benzene (1:1)	250	0.435
9.	"))	250	0.355
10.	Benzene	250	0.356
11.	Benzene	250	2.0830
12.	Chloroform	250	1.565

Fractions 1 to 5 of chromatogram 2 showed a single spot in TLC analysis (silicic acid with 10% silver nitrate, 6% ethylacetate in benzene) which corresponded to the least polar of the spots in the original mixture. They were mixed together and distilled to give the pure tricyclic ether (III, 4.998 g) b.p. 110-115°/2 mm (α)_D²⁸ $\pm$ 0° (g, 4.50).

Analysis

Found: C, 80.68; H, 10.02;

$C_{12}H_{18}O$ requires C, 80.85; H, 10.18%.

IR bands at: 3030, 1653, 1443, 1361, 1302, 1244, 1205, 1170, 1085, 1031, 1018, 976, 960, 937, 917, 877, 846, 837, 806, and 735 cm^{-1} .

Fraction 6 of chromatogram 2 showed two spots in TLC analysis (silicic acid with 10% silver nitrate, 6% ethyl acetate in benzene) and was not investigated further.

Fractions 7 to 9 of chromatogram 2 showed a single spot in TLC analysis which corresponded to the middle spot of the starting mixture. These fractions were mixed together and the solvent evaporated to give 1.324 g of a pure compound which was identified as dioxane derivative (IV), b.p. 130-135°/1.50 mm, (α)_D²⁸ - 14° (g, 4.00).

Analysis

Found: C, 73.54; H, 10.18;

$C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%.

IR bands at: 3077, 1449, 1397, 1370, 1266, 1227, 1159, 1066, 1031, 1010, 918, 881, 865, 826, 796 and 775 cm^{-1} .

Fractions 11 and 12 showed a single spot in TLC analysis, corresponding to the more polar of the spots in the original mixture and was identified as the alcohol (II, R = H) by comparative TLC and IR spectrum. The other fractions which were mixtures were not examined further.

Acetylation of 3,7,7-trimethyl-4 α -hydroxymethyl-bicyclo-(4.1.0)-hept-2-ene (II, R = H)

To a solution of the alcohol (II, R = H, 5 g) in dry pyridine (15 ml) was added acetic anhydride (10 ml). The reaction mixture was kept overnight at room temperature and then heated on a steam bath for 1 hr. It was cooled to room temperature and poured on ice-cooled water (200 ml) with stirring and allowed to stand at room temperature for 1 hr. The diluted solution was extracted with chloroform (100 ml + 50 ml x 2) and the chloroform layer washed with water (100 ml x 3), 20% aqueous hydrochloric acid (100 ml x 2), again with water (200 ml x 2). The chloroform layer was dried and evaporated to give a liquid acetate (II, R = AC, 4.50 g) which was purified by distillation b.p. 110-120°/1 mm.

Analysis

Found: C, 74.78; H, 9.82;

$C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%.

IR bands at: 3077, 1748, 1653, 1439, 1370, 1227, 1026, 966, 855 and 820 cm^{-1} .

Prins reaction on (+) car-3-ene (I) at higher temperature

In a 500 ml round bottom flask, 55 g of (+) car-3-ene (I), 300 ml of glacial acetic acid and 36 g of para formaldehyde were taken and the mixture was refluxed for 72 hr. in an oil bath at 160-170°. Most of the acetic acid was removed by distillation. It was then diluted with water (500 ml) and extracted with chloroform (150 ml x 3). The chloroform layer was repeatedly washed with water (100 ml x 3) and dried. Evaporation of chloroform afforded a mixture (52 g) which was dissolved in 150 ml of dry pyridine. To this, 100 ml of acetic anhydride was added and the reaction mixture was kept at room temperature for 48 hr. It was then heated on a water bath for 2 hr and poured on ice-cold water (500 ml) with stirring and allowed to stand at room temperature for half an hour. The diluted solution was extracted with chloroform (200 ml x 3) and the chloroform layer washed with water (150 ml x 3), 20% aqueous

hydrochloric acid (100 ml x 3), again with water (150 ml x 2). The chloroform layer was dried and evaporated to furnish a crude mixture (51 g, TLC, 4 spots, 8% ethyl acetate in benzene). This crude mixture was chromatographed on alumina (Gr. II, 1020 g, 1:20 ratio) and eluted as follows :

CHROMATOGRAM 3

No.	Solvent	Vol. in ml	Material in g
1.	Pet.ether	500	2.892
2.	"	500	2.793
3.	"	500	1.234
4.	"	500	1.122
5.	Pet.ether + benzene (1:1)	500	6.894
6.	" "	500	6.735
7.	" "	500	5.690
8.	" "	500	5.234
9.	Pet.ether + benzene (1:2)	500	5.120
10.	" "	500	4.115
11.	" "	500	4.112
12.	Benzene	500	2.123

Fractions 1 to 4 of chromatogram 3 showed three spots in TLC analysis (TLC, 8% ethyl acetate in benzene) and were found to contain according to comparative TLC, the compounds (III), (IV) and (II, R = Ac) respectively.

Fractions 5 to 8 to chromatogram 3 showed a single spot (TLC, silicic acid + 10% AgNO₃, benzene + 6% ethyl acetate). Hence these fractions were mixed together and the solvent evaporated to afford a pure acetate, identified as (II, R = Ac) by comparison of its spectral data¹⁸ with those of an authentic sample.

Fractions 9 to 11 of chromatogram 3 showed two spots in TLC analysis (silicic acid + 10% AgNO₃). These fractions were mixed together and the solvent evaporated to get a mixture of acetates (13.347 g). This was rechromatographed on silicic acid (239 g) impregnated with silver nitrate (27 g) and eluted as follows:

CHROMATOGRAM 4

No.	Solvent	Vol. in ml	Material in g
1.	Pet.ether	250	3.143
2.	"	250	2.079
3.	"	250	1.845
4.	Pet.ether + benzene (3:1)	250	1.449
5.	Pet.ether + benzene (3:1)	250	1.349
6.	Pet.ether + benzene (1:1)	250	1.124
7.	Pet.ether + benzene (1:1)	250	0.354
8.	Benzene	250	0.639

Fractions 1 to 3 of chromatogram 4 showed a single spot in TLC analysis (silicic acid + 10% silver nitrate, 6% ethyl acetate in benzene). These fractions were mixed together to furnish 7.067 g of a pure compound, identified as the acetate (II, R = Ac) on the basis of superimposable IR and PMR spectra and elemental analysis.

Fractions 7 and 8 of chromatogram 4 were found to be pure (TLC, single spot, silicic acid + 10% silver nitrate, 6% ethyl acetate in benzene). These were mixed together to afford an acetate, identified ^{as} (V, R = Ac, 0.993 g), b.p. 110-115°/1.50 mm, $(\alpha)_D^{25} + 146^\circ$ (g, 2.00).

Analysis

Found: C, 75.08; H, 9.56%.

$C_{13}H_{20}O_2$ requires C, 74.96; H, 9.69%.

IR bands at: 3067, 1736, 1634, 1439, 1351, 1220, 1020, 885 and 722 cm^{-1} .

Saponification of 2-acetoxy methyl-p-menth- $\triangle^{5,8}$ -diene (V, R = Ac)

To a solution of the acetate (V, R = Ac, 0.50 g) in methanol (25 ml) was added an aqueous solution of potassium hydroxide (1 g of KOH in 5 ml H_2O). The homogeneous mixture was then refluxed on a water bath for 8 hr. Most of the methanol was removed under suction and the residue diluted with water (200 ml) and extracted with ether (50 ml x 3).

The ether layer was washed with water, dried and distilled to afford a liquid alcohol (V, R = H) which was further purified by distillation, b.p. 105-110°/1 mm, $(\alpha)_D^{28} + 186^\circ$ (g, 1.5).

Analysis

Found: C, 79.31; H, 11.03;

$C_{11}H_{18}O$ requires C, 79.46; H, 10.92%.

IR bands at: 3509, 3030, 1637, 1435, 1361, 1010, 885 and 719 cm^{-1} .

Jones oxidation of 3,7,7-trimethyl-4 α -hydroxymethyl bicyclo-(4.1.0)-hept-2-ene (II, R = H)

To an ice-cooled solution of the alcohol (II, R = H, 5 g) in acetone (50 ml) was added Jones chromic acid reagent until the brown colour persisted. The reaction mixture was kept at 10-15° for 3 hr. It was then diluted with water (150 ml) and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water (100 ml x 2). The organic layer was then extracted with a 10% aq. solution of sodium carbonate (50 ml + 25 ml x 2). The carbonate layer was acidified with dilute hydrochloric acid to 2 pH and then extracted with ether (50 ml x 3). The ether layer was washed with water (100 ml x 3) and dried. Evaporation of ether furnished an acid (VI, R = H, 1.80 g) which was esterified using an ethereal

solution of diazomethane to afford the methyl ester (VI, R = CH₃, 1.70 g), b.p.120-125°/3 mm.

Analysis

Found: C, 74.28; H, 9.27;

C₁₂H₁₈O₂ requires C, 74.19; H, 9.34%.

IR bands at: 3067, 1739, 1439, 1361, 1299, 1250, 1163, 1136, 1020, 982, 855, 816 and 758 cm⁻¹.

The chloroform layer after extraction with sodium carbonate was washed with water (100 ml x 3) and dried. Removal of chloroform gave a liquid mixture (2.50 g) as detected by TLC. (TLC, three spots, 4% ethyl acetate in benzene). This mixture was chromatographed on silicic acid (52 g, 1:20 ratio) and eluted as follows:

CHROMATOGRAM 5

No.	Solvent	Vol. in ml	Material in g
1.	Pet.ether	100	0.221
2.	"	100	0.215
3.	"	100	0.209
4.	Pet.ether + benzene (1:1)	100	0.103
5.	" "	100	0.121
6.	" "	100	0.114
7.	" "	100	0.108
8.	Benzene	100	0.445
9.	Benzene	100	0.335
10.	Chloroform	100	0.331

Fractions 1 to 3 of chromatogram 5 showed a single spot on TLC (4% ethyl acetate in benzene). These were mixed together to give 0.645 g of pure compound which was identified as the ester (VII), b.p. 110-115°/1.20 mm, $(\alpha)_D^{28} + 206^\circ$ (g, 1.50).

Analysis

Found: C, 80.31; H, 9.98;

$C_{22}H_{32}O_2$ requires C, 80.44; H, 9.83%.

IR bands at: 3080, 1730, 1437, 1361, 1299, 1250, 1164, 1130, 1010, 976, 855 and 816 cm^{-1} .

Fractions 4 to 10 of chromatogram 5 showed two spots of nearly the same polarity (TLC, silicic acid + 10% $AgNO_3$, 6% ethyl acetate in benzene). These fractions were mixed together to give a liquid mixture (1.55 g). This was dissolved in 50 ml of methanol and treated with sodium borohydride (0.50 g) during 1/2 hr in small lots and the mixture stirred at room temperature for 48 hr. Most of the methanol was removed by distillation and the residue diluted with water (100 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water (100 ml x 3) and dried. Removal of ether by distillation afforded a liquid mixture (1.40 g) which consisted of three components (TLC, silicic acid + 10% $AgNO_3$, 6% ethyl acetate in benzene). This mixture was rechromatographed on silicic acid (25 g)

impregnated with silver nitrate (3 g) and eluted as follows:

CHROMATOGRAM 6

No.	Solvent	Vol. in ml	Material in g
1.	Pet.ether	100	0.115
2.	"	100	0.080
3.	Pet.ether + benzene (3:1)	100	0.065
4.	Pet.ether + benzene (1:1)	100	0.639
5.	" "	100	0.431
6.	Benzene	100	0.112
7.	Chloroform	100	0.080

Fractions 1 to 3 of chromatogram 6 showed a single spot on TLC (silicic acid + 10% AgNO₃, 6% ethyl acetate in benzene) and were mixed together to furnish 0.195 g of a pure compound, identified as the ketone (VIII),
b.p.110-115°/2 mm.

Analysis

Found: C, 79.81; H, 9.53;

C₁₀H₁₄O requires C, 79.95; H, 9.39%.

IR bands at: 3077, 1653, 1439, 1370, 1299, 1227, 1124, 1064, 1031, 995, 909, 830 and 725 cm⁻¹.

Fractions 3 to 7 of chromatogram 6 showing two spots of close polarity in TLC were not investigated further.

Lithium aluminium hydride reduction of the ester (VII)

To an ice-cooled and stirred solution of LAH (0.50 g) in dry ether (100 ml), a solution of the ester (VII, 0.30 g) in dry ether (50 ml) was added dropwise, during 1/2 hr. Stirring was continued at 0° for 4 hr and the reaction mixture kept at room temperature overnight. Excess of LAH was decomposed by ethanol followed by ^{water}at 0°. The reaction mixture was then transferred to a separating funnel and the layers were allowed to separate. The ether layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was washed with water (100 ml x 2) and dried. Removal of ether gave the alcohol (II, R = H, 0.15 g) which was identified by comparative TLC and superimposable IR and PMR spectra.

Saponification of the ester (VII)

To a solution of the ester (VII, 0.40 g) in methanol (50 ml), was added an aqueous solution of potassium hydroxide (1 g in 5 ml H₂O) and the homogeneous mixture refluxed on a water bath for 6 hr. Most of the methanol was removed by distillation and the residue diluted with water and extracted with ether (100 ml + 50 ml x 2) to separate the neutral part.

The ether layer was washed with water, dried and evaporated to give (0.13 g) of material, identified as (II, R = H) by IR and PMR spectra, $(\alpha)_D^{28} + 139^\circ$ (g, 1.75).

The aqueous layer was acidified to 2pH with dilute hydrochloric acid and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water (50 ml x 2) and dried. Evaporation of chloroform afforded an acid (VI, R = H, 0.15 g) which was esterified using an ethereal solution of diazomethane to afford the ester (VI, R = CH₃, 0.14 g), identified by IR and PMR spectral data, $(\alpha)_D^{28} + 312^\circ$ (g, 1.50).

Jones oxidation of tricyclic ether (III)

To an ice-cooled and stirred solution of the tricyclic ether (III, 5 g) in acetone (50 ml) was added Jones chromic acid reagent (30 ml), dropwise. After the addition, it was kept for four days at 10-15°. It was then diluted with water (100 ml) and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water (100 ml x 2) and then extracted with an aqueous solution (10%) of sodium carbonate (50 ml + 25 ml x 2). The carbonate layer was acidified with dilute hydrochloric acid to 2pH and extracted with ether (50 ml x 3). The ether layer was washed with water (100 ml x 2) and dried. Evaporation of the solvent furnished the acid (IX, R = H, 1 g) which was crystallised

from pet. ether, m.p. 145-146°.

Analysis

Found: C, 68.38; H, 8.75;

$C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%.

IR bands at: 3125, 1732, 1471, 1379, 1307, 1205, 1176, 1042, 1020, 935, 913, 862 and 725 cm^{-1} .

The acid (IX, R = H, 0.30 g) was dissolved in methanol (50 ml) and catalytic amount (3 drops) of sulphuric acid was added to it. The mixture was refluxed on a water bath for 8 hr. Most of the methanol was removed under suction and the residue diluted with water (100 ml) and extracted with ether (25 ml x 3). The ether layer was washed with an aqueous solution (5%) of sodium carbonate (50 ml x 2) to remove unreacted acid, followed by water (50 ml x 3). The ether layer was dried and evaporated to give the methyl ester (IX, R = CH_3 , 0.25 g) which was purified by distillation, b.p. 120-125°/3 mm.

Analysis

Found: C, 69.48; H, 8.73;

$C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%.

IR bands at: 3077, 1732, 1439, 1242, 1190, 1053, 1020, 917, 862 and 758 cm^{-1} .

The chloroform layer after removal of acid portion was washed with water (100 ml x 3) and dried. Evaporation of the

solvent gave the nor ketone (X, 3.40 g), purified by chromatography followed by crystallisation, m.p. 60-61° (pet. ether), $(\alpha)_D^{25} + 58^\circ$ (g, 1.50).

Analysis

Found: C, 73.17; H, 9.08;

$C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%.

IR bands at: 3030, 1724, 1449, 1370, 1307, 1266, 1250, 1225, 1202, 1156, 1105, 1056, 1036, 1015, 976, 957, 917, 847 and 813 cm^{-1} .

Ozonolysis of tricyclic ether (III)

A stream of ozonised oxygen (approx 1 g/hr) was passed through an ice-cooled solution of the ether (III, 1 g) in ethyl acetate (50 ml) till the absorption of ozone was complete (1 hr) (tested by starch iodide paper). The solution of ozonide was treated with water (15 ml) and the ethyl acetate was removed under suction at 50-60°. It was then extracted with chloroform (50 ml x 2). The organic layer was washed with water (50 ml x 3) and dried. Evaporation of chloroform afforded a solid nor ketone (X) which was further purified by crystallisation from pet. ether, m.p. 60-61°, $(\alpha)_D^{25} + 57.60^\circ$ (g, 1.30). The analytical and spectral data were in agreement with those reported for the nor ketone (X) earlier in this chapter.

Lithium aluminium hydride reduction of the nor ketone (X)

To an ice-cooled and stirred solution of lithium aluminium hydride (0.80 g) in dry ether (50 ml) was added a solution of the nor ketone (X, 0.50 g) in dry ether (50 ml), dropwise, during 1/2 hr. After the addition, it was stirred for 2 hr at 0° and kept for 48 hr at 25°. Excess of LAH was decomposed by addition of ethanol at 0° followed by water. The combined ether layer was separated and the aqueous layer was extracted with ether (100 ml x 2), washed with water (100 ml x 2) and dried. Evaporation of ether afforded a solid, which was crystallised from pet. ether to give white needles of (XI, R = H, 0.30 g), m.p. 129-130°, $(\alpha)_D^{25} - 62^\circ$ (g, 1.50).

Analysis

Found: C, 72.56; H, 10.12;

$C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%.

IR bands at: 3704, 3077, 1460, 1379, 1351, 1316, 1266, 1163, 1124, 1054, 1046, 1026, 935, 917, 843, 820, 791 and 763 cm^{-1} .

Acetylation of the alcohol (XI, R = H)

To a solution of the alcohol (XI, R = H, 0.30 g) in pyridine (6 ml) was added, acetic anhydride (15 ml) and kept at room temperature for 24 hr. The mixture was diluted with water (50 ml), kept at room temperature for half an hour and

on water bath for 1 hr. It was then cooled and extracted with ether (50 ml x 3). The ether layer was washed successively with water (25 ml x 3), 10% hydrochloric acid (25 ml x 2) followed by water (25 ml x 3) and dried. Ether was removed to furnish a liquid acetate (XI, R = Ac, 0.25 g) which was purified by distillation, b.p. 110-115°/2.5 mm.

Analysis

Found: C, 69.48; H, 9.12;

$C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%.

IR bands at: 3077, 1754, 1449, 1361, 1235, 1170, 1117, 1075, 948, 917, 847 and 816 cm^{-1} .

Epoxidation of the methyl ester (VI, R = CH₃)

To a cooled solution of the ester (VI, R = CH₃, 2.00 g) in 10 ml chloroform, a chloroform solution of perbenzoic acid (40 ml, 1N) was added and the homogeneous solution was allowed to stand at 0° for 48 hr. After dilution with chloroform (50 ml), it was extracted with aqueous sodium bicarbonate solution (5%) to remove benzoic acid, washed with water and dried. Distillation of chloroform gave the crude epoxide (1.60 g), which consisted of two products according to TLC analysis (8% ethyl acetate in benzene). It was chromatographed on alumina (Gr. II, 32 g, 1:20 ratio)

and eluted as follows:

CHROMATOGRAM 7

Fr.No.	Solvent	Vol. in ml	Material in g
1	Pet.ether	100	0.259
2.	"	100	0.273
3.	Pet.ether + benzene(3:1)	100	0.215
4.	" ¹⁾	100	0.280
5.	Pet.ether + benzene(1:1)	100	0.070
6.	Benzene	100	0.135
7.	Chloroform	100	0.178

Fractions 1 to 4 of chromatogram 7 showed a single spot in TLC analysis (8% ethyl acetate in benzene). Hence these fractions were mixed together to afford a solid epoxide (XII, 1.057 g) purified by crystallisation, m.p.49-50° (pet.ether).

Analysis

Found: C, 68.72; H, 8.82;

$C_{12}H_{18}O_2$ requires C, 68.54; H, 8.63%.

IR bands at: 3077, 1742, 1439, 1370, 1325, 1271, 1162, 1105, 1026, 980, 877, 833, 794, 772 and 707 cm^{-1} .

Rearrangement of the epoxide (XII) over alumina to the hydroxy ester (XIII) and dihydroxy ester (XIV)

A solution of the epoxide (XII) in pet.ether (1.40 g in 15 ml) was adsorbed on a column of alumina (Gr. II, 28 g) developed with pet.ether. The adsorbed material was allowed to stand in contact with alumina for 48 hr. It was then eluted as follows:

CHROMATOGRAM 8

Fr.No.	Solvent	Vol. in ml	Material in g
1.	Pet.ether	100	0.171
2.	"	100	0.135
3.	Pet.ether + benzene (1:1)	100	0.053
4.	Benzene	100	0.221
5.	Benzene	100	0.134
6.	Benzene + chloroform(1:1)	100	0.154
7.	Chloroform	100	0.111
8.	Ethylacetate	100	0.201

Fractions 1 and 2 showed a single spot in TLC analysis (6% ethyl acetate in benzene) and was found to be the epoxide (XII).

Fraction 3 being in small quantity was not examined further.

Fractions 4 to 6 showed a single spot in TLC analysis (10% ethyl acetate in benzene). These fractions were mixed together to furnish the hydroxy ester (XIII, 0.509 g), identified by spectral data, b.p. 125-130°/2.50 mm.

Analysis

Found: C, 68.41; H, 8.78;

$C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%.

IR bands at: 3704, 3125, 1732, 1653, 1429, 1370, 1010, 890 and 833 cm^{-1} .

Fraction 7 showed a mixture of two components in TLC analysis (15% ethyl acetate in benzene) and was not examined further.

Fraction 8 (TLC, a single spot, 15% ethyl acetate in benzene) gave the pure dihydroxy ester (XIV, 0.201 g), b.p. 120-125°/1 mm.

Analysis

Found: C, 63.36; H, 8.93;

$C_{12}H_{20}O_4$ requires C, 63.13; H, 8.83%.

IR bands at: 3704, 3125, 1730, 1439, 1370, 1190, 1124, 1031, 855, 826 and 752 cm^{-1} .

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CHAPTER - IV

CONVERSION OF (+) CAR-3-MNE INTO GRAPOL INTERMEDIATES
FOR SYNTHESIS OF INSECTICIDES OF THE SYNTHETIC
PYRETHROID GROUP

S U M M A R Y

The trans carane diol (II), obtainable from (+)car-3-ene (I), on Jones chromic acid oxidation gave mainly the ketol (III) in the neutral portion and an acid (IV, R = H) which was converted into its methyl ester (IV, R = CH₃). Treatment of ketol (III) with methyl magnesium iodide furnished the diol (V) which, on sodium meta-periodate oxidation afforded the diketone (VI). The base catalysed intramolecular cyclisation of (VI) gave the conjugated ketone (VII). Potassium permanganate oxidation of the conjugated ketone (VII) afforded the dl-keto acid (VIII, R = H) which was esterified to give the dl-keto ester (VIII, R = CH₃).

The unsaturated ketone (IX), on potassium permanganate oxidation under similar conditions gave a mixture of two products which was separated into acidic and neutral parts. The neutral part was identified as the diketo alcohol (X). The acid (VIII, R = H) was converted into its methyl ester (VIII, R = CH₃) possessing the 1R configuration.

Sodium borohydride reduction of the unsaturated ketone (IX) furnished the unsaturated alcohol (XI, R = H) which was acetylated (Ac₂O/Py) to give an unsaturated acetate (XI, R = Ac). Potassium permanganate oxidation of the unsaturated acetate (XI, R = Ac) gave a mixture consisting

of two components. It was separated into acidic and neutral parts. The neutral part was characterised as the keto alcohol acetate (XII). The acid part gave an acetate acid (XIII, $R = H$) which, on esterification gave the acetate ester (XIII, $R = CH_3$). Saponification of the acetate ester (XIII, $R = CH_3$) gave the hydroxy acid (XIV) which, on treatment with p-toluene sulphonic acid in benzene afforded the nor-lactone (XV).

INTRODUCTION

As already mentioned in Chapter I of the thesis, the synthesis of (+) cis-chrysanthemic acid (XVI) has been carried out by the Japanese workers,¹ starting from (+) car-3-ene (I) via the intermediate keto-ester (VIII, R = CH₃). They prepared the keto-ester (VIII, R = CH₃) via the enol-acetate (XVII). But due to the formation of by-product (XVIII) during the enol-acetate preparation, the yield of the latter was quite low. This intermediate keto-ester (VIII, R = CH₃) has been recently employed for the synthesis of some new pyrethroids² in our laboratory. So, it was of interest to explore different methods of synthesis of the keto-ester (VIII, R = CH₃), starting from cheap and abundantly occurring raw material like (+) car-3-ene (I). In our laboratory, some new methods^{3,4} have already been attempted. One of these methods³ involved the ozonolysis of the conjugated bicyclic aldehyde (XIX) followed by oxidative decomposition of the ozonide to give the keto-acid (VIII, R = H) in about 60% yield. The other method employed is potassium permanganate oxidation of the conjugated aldehyde (XIX) under certain conditions. But here, the yield was only 28-35%. Direct potassium permanganate oxidation of (+) car-3-ene (I) has also been reported⁴ to give

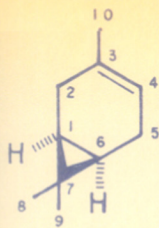
the keto-acid (VIII, $R = H$) along with other acids. The corresponding enantiomeric keto ester (VIII, $R = CH_3$) has been prepared⁵ from (+)-4 α -acetoxymethyl-car-2-ene (XX).

During the Jones chromic acid oxidation of the diol (II), we found that in addition to the keto acid (IV, $R = H$), which is the major product (60%), a substantial amount of neutral material was obtained. In this neutral portion, one of the major compounds was found to be the keto-alcohol (III).

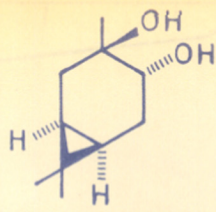
PRESENT WORK

1. Synthesis of methyl dl-gis-2,2-dimethyl-3-(2-oxopropyl) cyclopropane carboxylate (VIII, $R = CH_3$)

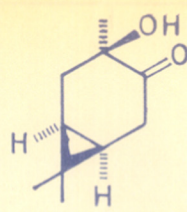
3 β , 4 α -Carane diol (II), obtainable from (+) car-3-ene (I) in 45% yield by a known⁶ method, was oxidised by Jones chromic acid reagent to give the keto carboxylic acid (IV, $R = H$) in 60% yield along with the neutral portion (32%) containing the ketol (III). The latter was purified by chromatography. The keto carboxylic acid (IV, $R = H$) was converted to its methyl ester (IV, $R = CH_3$) by methanol/sulphuric acid in almost quantitative yield (see Chapter II of this thesis). The ketol (III), $C_{10}H_{16}O_2$, M^+ 168, showed the following spectral properties, IR (Fig. 1) bands at: 3636 (OH), 1709 (C=O) and



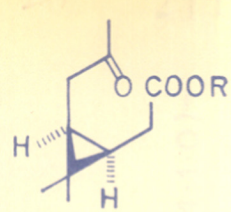
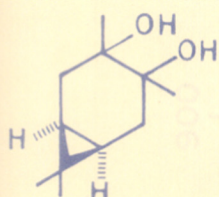
I



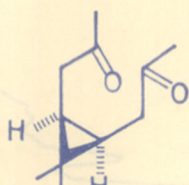
II



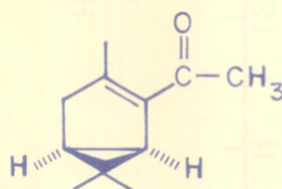
III

IV, R = H;
R = CH₃

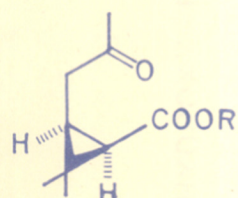
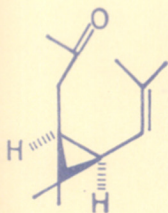
V



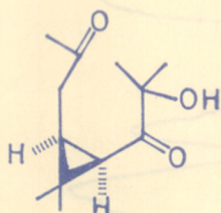
VI



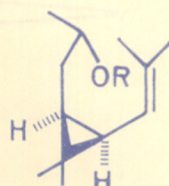
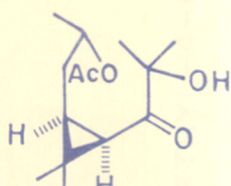
VII

VIII, R = H
R = CH₃

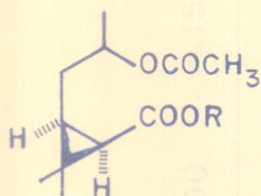
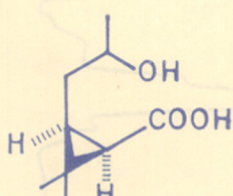
IX



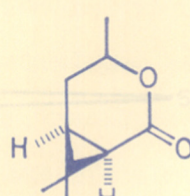
X

XI, R = H
R = -Ac

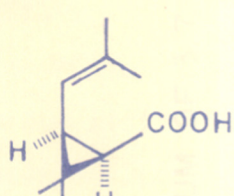
XII

XIII, R = H
R = CH₃

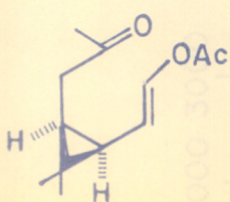
XIV



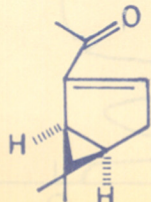
XV



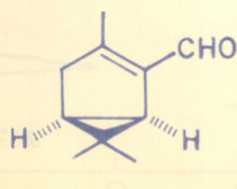
XVI



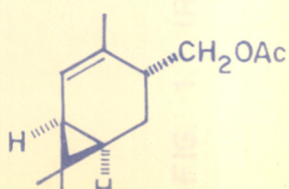
XVII



XVIII



XIX



XX

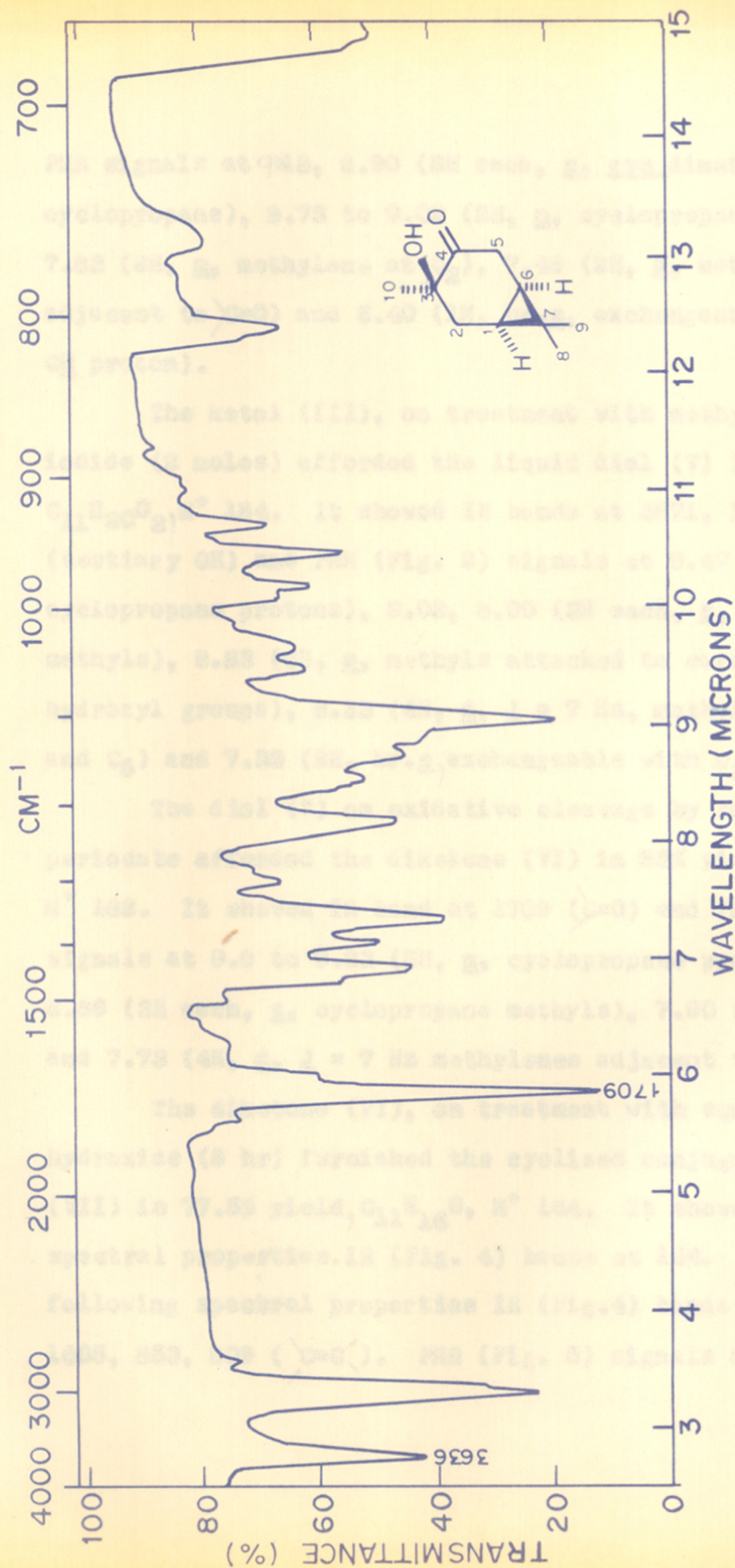


FIG. 1. IR SPECTRUM OF 3,7,7-TRIMETHYL-4-OXO-3 β -HYDROXY-BICYCLO-(4.1.0)-

-HEPTANE (III)

PMR signals at 9.43, 8.90 (3H each, s, gem-dimethyl on cyclopropane), 8.73 to 9.02 (2H, m, cyclopropane protons), 7.83 (2H, m, methylene at C₂), 7.48 (2H, m, methylene adjacent to >C=O) and 6.40 (1H, br. s, exchangeable with D₂O, OH proton).

The ketol (III), on treatment with methyl magnesium iodide (2 moles) afforded the liquid diol (V) in 47.5% yield, C₁₁H₂₀O₂, M⁺ 184. It showed IR bands at 3571, 1094 (tertiary OH) and PMR (Fig. 2) signals at 9.47 (2H, m, cyclopropane protons), 9.03, 8.90 (3H each, s, cyclopropane methyls), 8.83 (6H, s, methyls attached to carbon, bearing hydroxyl groups), 8.33 (4H, d, J = 7 Hz, methylenes at C₂ and C₅) and 7.33 (2H, br. s, exchangeable with D₂O, OH protons).

The diol (V) on oxidative cleavage by sodium metaperiodate afforded the diketone (VI) in 83% yield, C₁₁H₁₈O₂, M⁺ 182. It showed IR band at 1709 (C=O) and PMR (Fig. 3) signals at 9.0 to 9.23 (2H, m, cyclopropane protons), 9.10, 8.85 (3H each, s, cyclopropane methyls), 7.90 (6H, s -COCH₃) and 7.73 (4H, d, J = 7 Hz methylenes adjacent to >C=O).

The diketone (VI), on treatment with aqueous sodium hydroxide (8 hr) furnished the cyclised conjugated ketone (VII) in 77.5% yield, C₁₁H₁₆O, M⁺ 164. It showed the following spectral properties. IR (Fig. 4) bands at 164. It showed the following spectral properties IR (Fig. 4) bands at: 1664 (conj. C=O), 1605, 853, 809 (C=C). PMR (Fig. 5) signals at: 9.20, 8.90

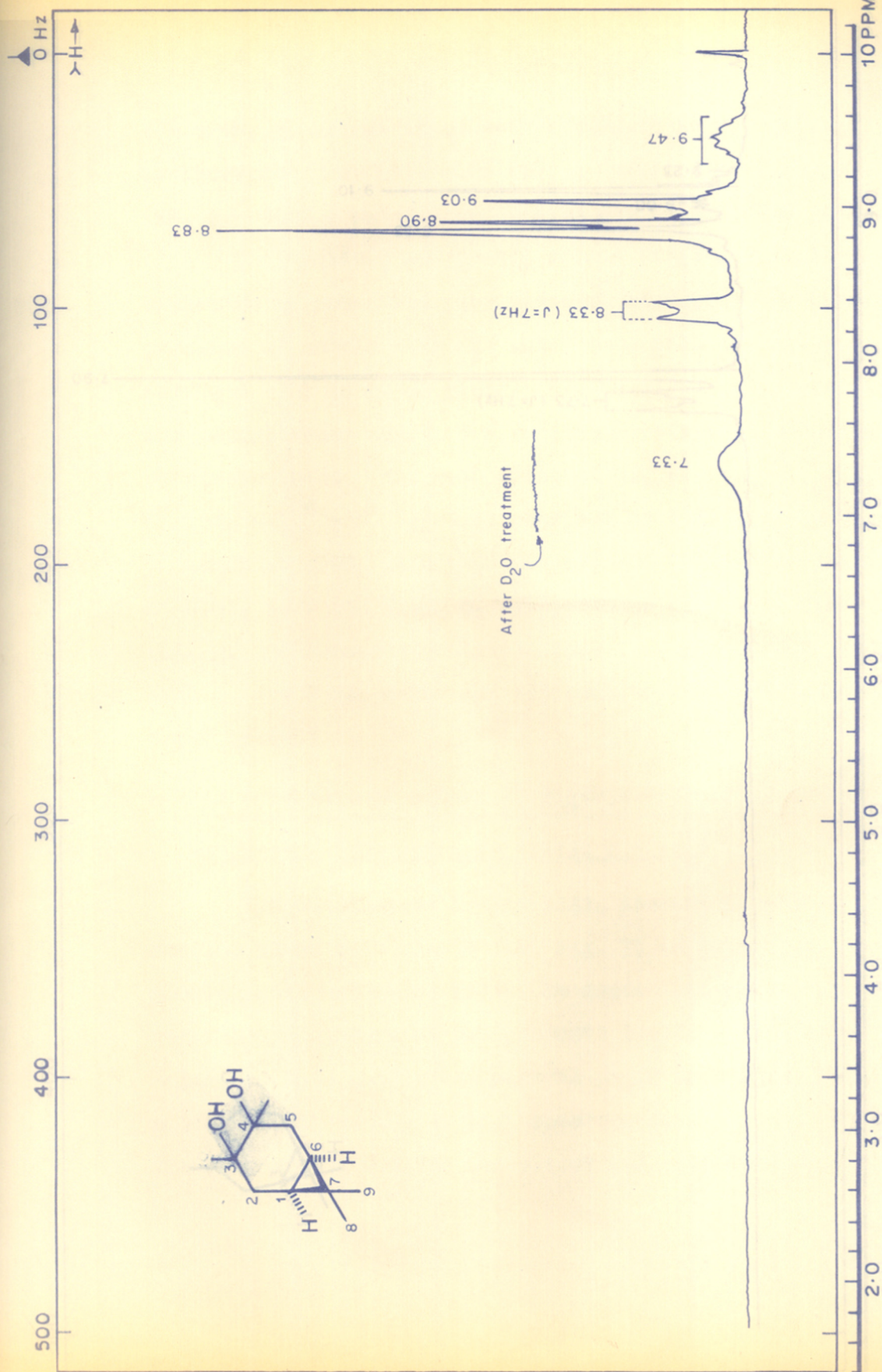
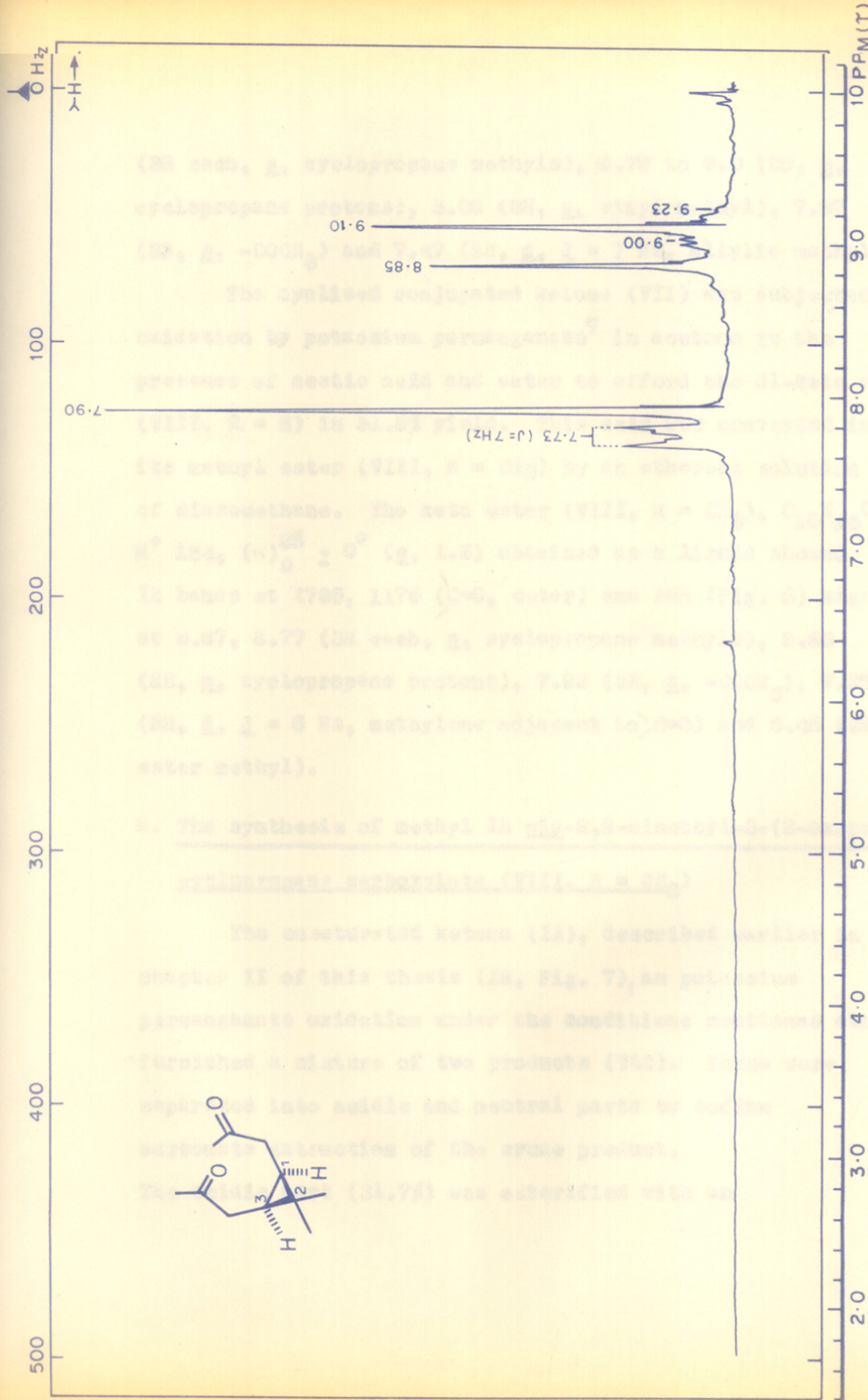


FIG. 2. PMR SPECTRUM OF 3,4,7,7-TETRAMETHYL-3,4-DIHYDROXY-BICYCLO-(4.1.0)-HEPTANE (V)

FIG. 3. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-OXOPROPYL)-CIS-1-(2-OXOPROPYL)-CYCLOPROPANE (VI)



(3H each, g, cyclopropane methyls), 8.70 to 9.0 (2H, h, cyclopropane protons), 8.05 (3H, g, vinyl methyl), 7.87 (3H, g, -COCH₃) and 7.47 (2H, d, J = 7 Hz, allylic methylene).

The cyclised conjugated ketone (VII) was subjected to oxidation by potassium permanganate⁷ in acetone in the presence of acetic acid and water to afford the di-keto acid (VIII, R = H) in 31.5% yield. This acid was converted into its methyl ester (VIII, R = CH₃) by an ethereal solution of diazomethane. The keto ester (VIII, R = CH₃), C₁₀H₁₆O₃, M⁺ 184, (α)_D²⁵ $\pm$ 0° (g, 1.5) obtained as a liquid showed IR bands at 1736, 1176 (C=O, ester) and PMR (Fig. 6) signals at 8.87, 8.77 (3H each, g, cyclopropane methyls), 8.53 (2H, h, cyclopropane protons), 7.92 (3H, g, -COCH₃), 7.25 (2H, d, J = 6 Hz, methylene adjacent to >C=O) and 6.45 (3H, g, ester methyl).

2. The synthesis of methyl 1R cis-2,2-dimethyl-3-(2-oxopropyl)-cyclopropane carboxylate (VIII, R = CH₃)

The unsaturated ketone (IX), described earlier in chapter II of this thesis (IR, Fig. 7), on potassium permanganate oxidation under the conditions mentioned above furnished a mixture of two products (TLC). These were separated into acidic and neutral parts by sodium carbonate extraction of the crude product. The acidic part (31.7%) was esterified with an

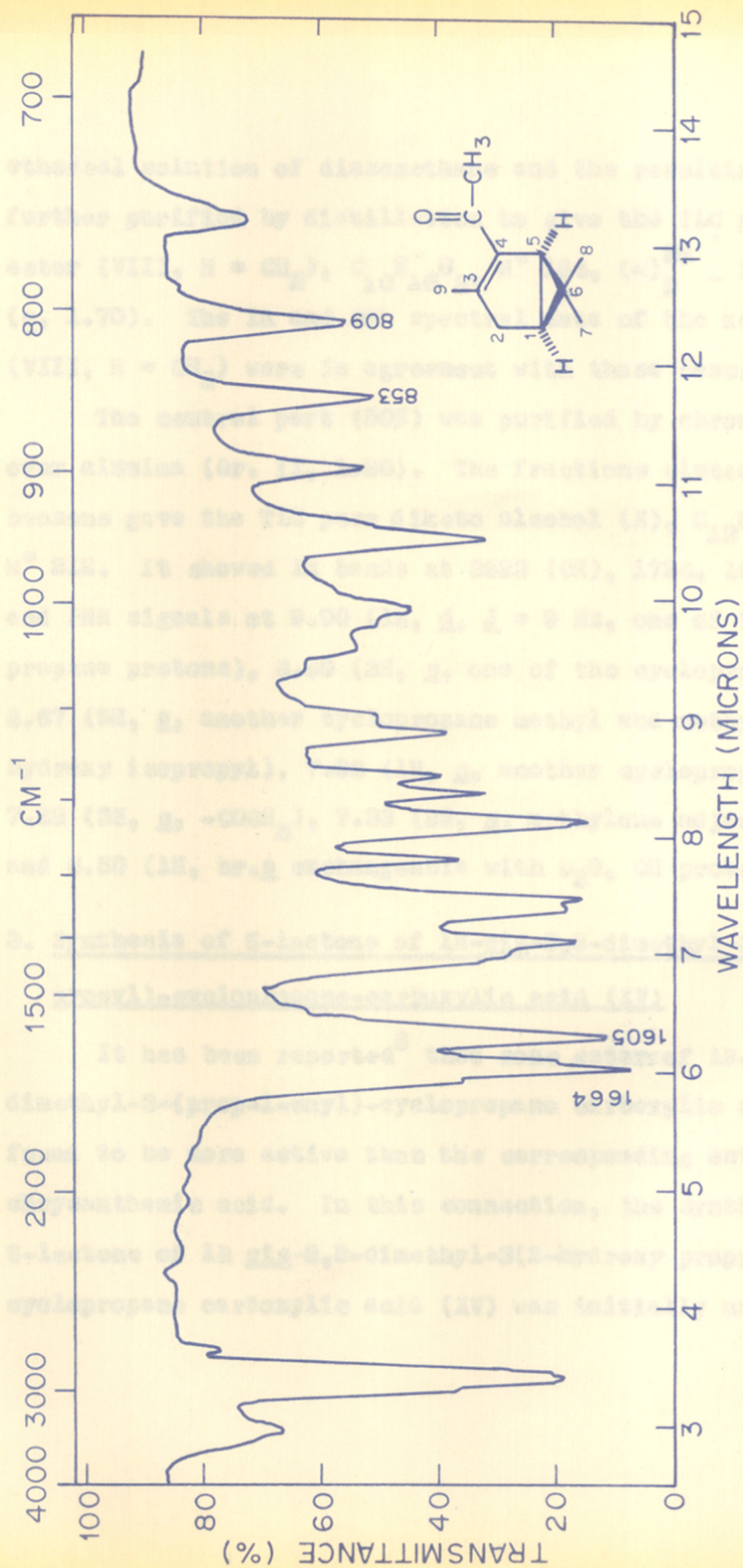


FIG. 4. IR SPECTRUM OF 3,6,6-TRIMETHYL-4-ACETYL-BICYCLO-(3.1.0)-HEX-3-ENE (VII)

etheral solution of diazomethane and the resulting ester further purified by distillation to give the TLC pure keto-ester (VIII, R = CH₃), C₁₀H₁₆O₃, M⁺ 184, (α)_D²⁸ - 38.7° (c, 1.70). The IR and PMR spectral data of the keto-ester (VIII, R = CH₃) were in agreement with those described above.

The neutral part (50%) was purified by chromatography over alumina (Gr. II, 1:20). The fractions eluted with benzene gave the TLC pure diketo alcohol (X), C₁₂H₂₀O₃, M⁺ 212. It showed IR bands at 3623 (OH), 1724, 1692 (>C=O) and PMR signals at 9.00 (1H, d, J = 9 Hz, one of the cyclopropane protons), 8.80 (3H, s, one of the cyclopropane methyls), 8.67 (9H, s, another cyclopropane methyl and methyls of hydroxy isopropyl), 7.93 (1H, s, another cyclopropane proton), 7.82 (3H, s, -COCH₃), 7.33 (2H, s, methylene adjacent to >C=O) and 6.50 (1H, br. s exchangeable with D₂O, OH proton).

3. Synthesis of 6-lactone of 1R-gig-2,2-dimethyl-3-(2-hydroxy-propyl)-cyclopropane-carboxylic acid (XV)

It has been reported⁸ that some esters of 1R-gig-2,2-dimethyl-3-(prop-1-enyl)-cyclopropane carboxylic acid are found to be more active than the corresponding esters of chrysanthemic acid. In this connection, the synthesis of 6-lactone of 1R-gig-2,2-dimethyl-3(2-hydroxy propyl) cyclopropane carboxylic acid (XV) was initially undertaken

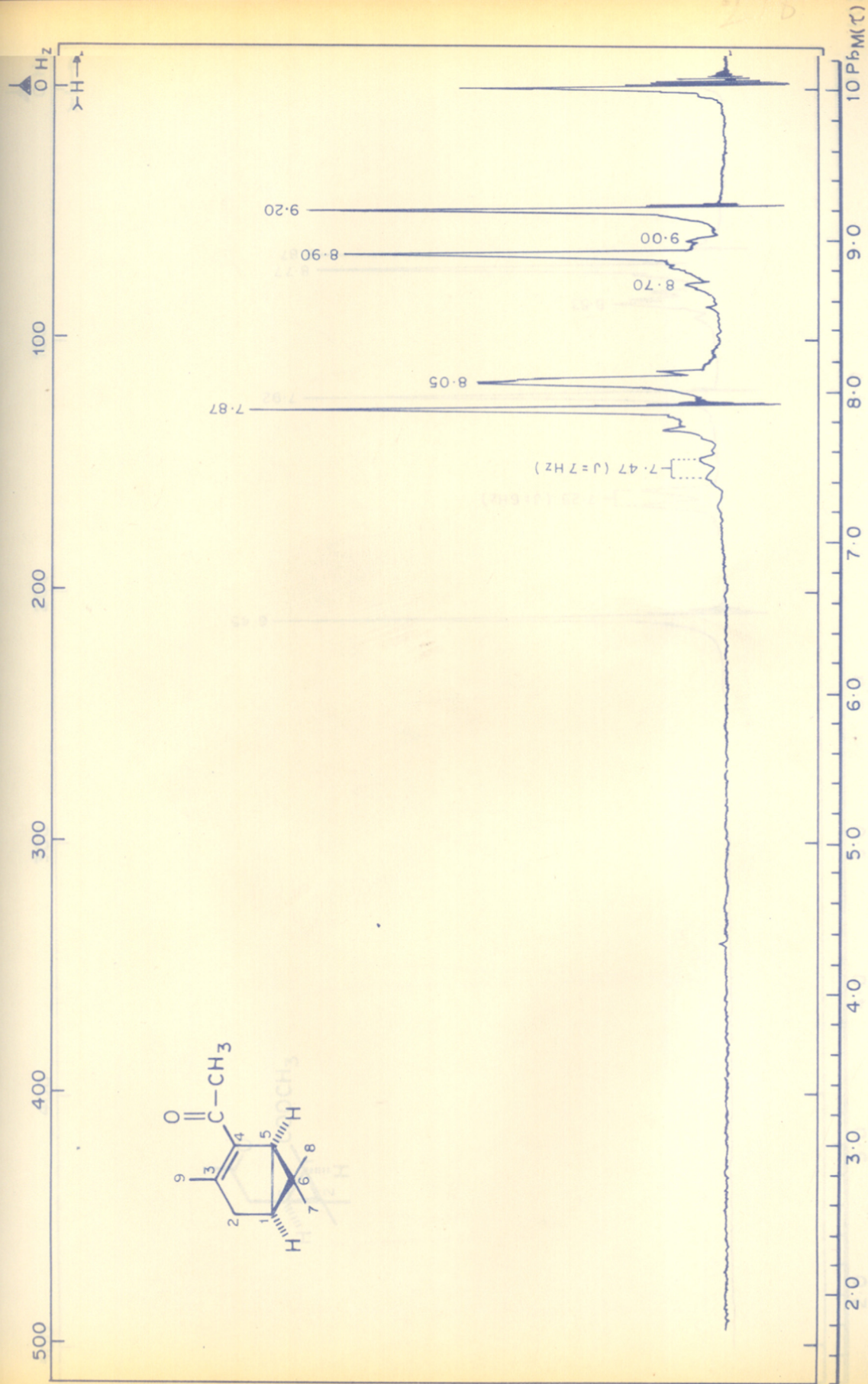


FIG. 5. PMR SPECTRUM OF 3,6,6-TRIMETHYL-4-ACETYL-BICYCLO-(3.1.0)-HEX-3-ENE (VII)

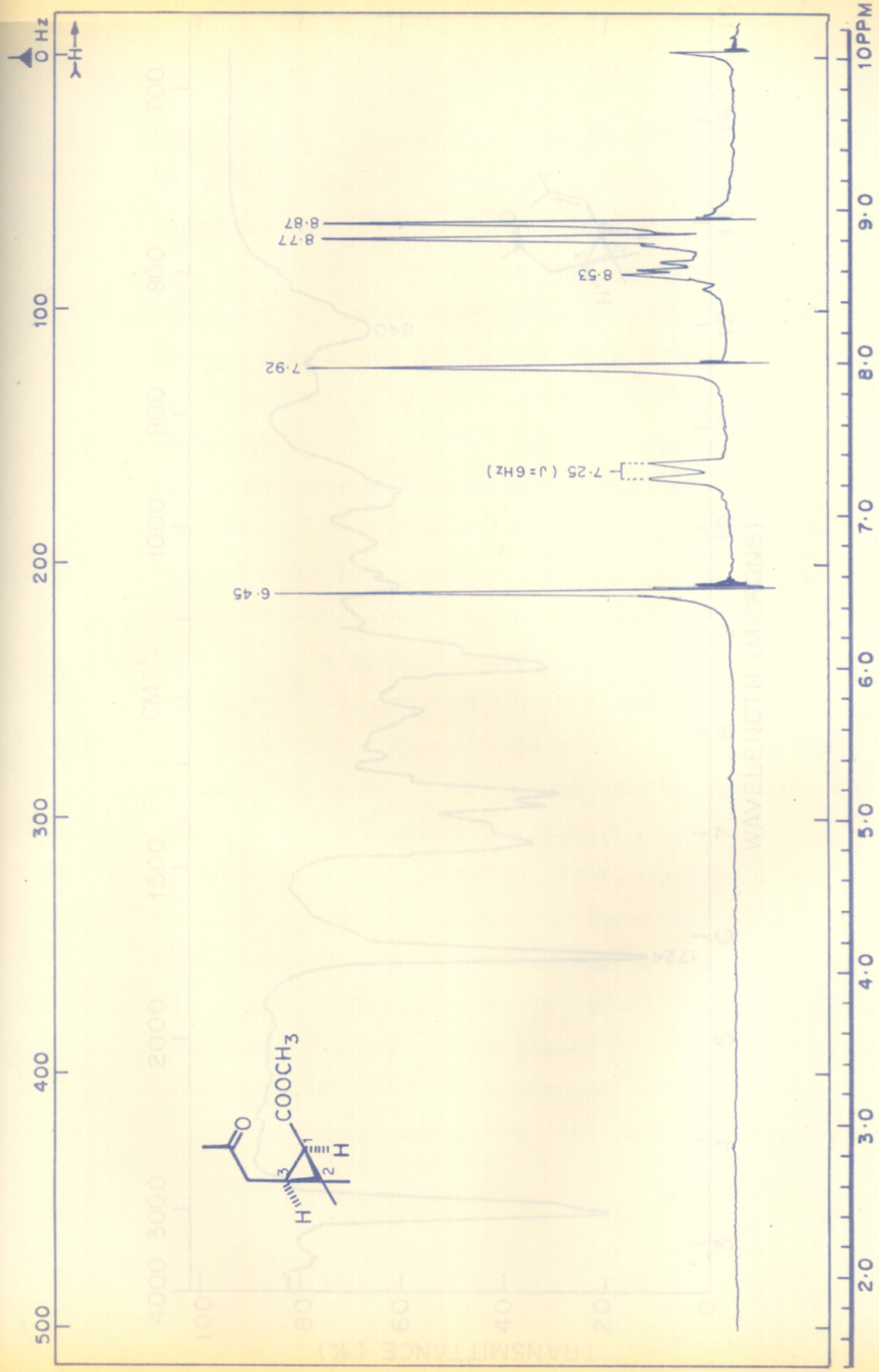


FIG. 6. PMR SPECTRUM OF METHYL-IR-CIS-2,2-DIMETHYL-3-(2-OXOPROPYL)-CYCLO-PROPANE CARBOXYLATE (VIII, R=CH₃)

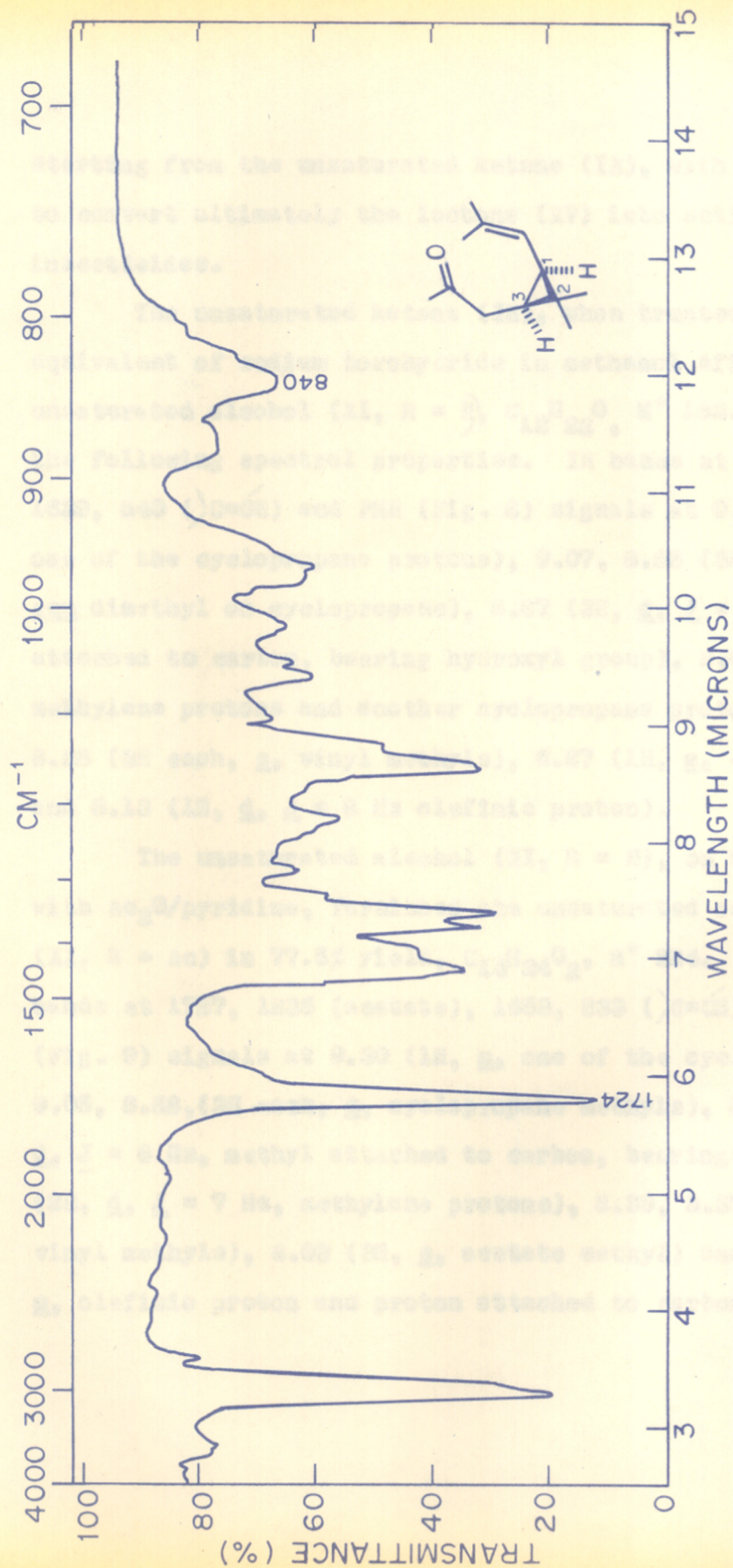


FIG. 7. IR SPECTRUM OF 2,2-DIMETHYL-3-(2-OXOPROPYL)-CIS-1-(2-METHYL PROP-1-1-20
-ENYL)-CYCLOPROPANE (IX)

starting from the unsaturated ketone (IX), with a view to convert ultimately the lactone (XV) into active insecticides.

The unsaturated ketone (IX), when treated with one equivalent of sodium borohydride in methanol afforded the unsaturated alcohol (XI, R = H), $C_{12}H_{22}O$, M^+ 182. It showed the following spectral properties. IR bands at 3448 (OH), 1639, 840 ($>C=CH$) and PMR (Fig. 8) signals at 9.30 (1H, m, one of the cyclopropane protons), 9.07, 8.88 (3H each, s, gem dimethyl on cyclopropane), 8.87 (3H, d, $J = 6$ Hz, methyl attached to carbon, bearing hydroxyl group), 8.63 (3H, m, methylene protons and another cyclopropane proton), 8.30, 8.28 (3H each, s, vinyl methyls), 6.27 (1H, m, $-CH=CH$) and 5.13 (1H, d, $J = 8$ Hz olefinic proton).

The unsaturated alcohol (XI, R = H), on treatment with Ac_2O /pyridine, furnished the unsaturated acetate (XI, R = Ac) in 77.5% yield, $C_{14}H_{24}O_2$, M^+ 224. It showed IR bands at 1727, 1235 (acetate), 1653, 833 ($>C=CH$) and PMR (Fig. 9) signals at 9.30 (1H, m, one of the cyclopropane protons), 9.05, 8.88, (3H each, s, cyclopropane methyls), 8.80 (3H, d, $J = 6$ Hz, methyl attached to carbon, bearing $-OAc$), 8.60 (2H, d, $J = 7$ Hz, methylene protons), 8.30, 8.27 (3H each, s, vinyl methyls), 8.03 (3H, s, acetate methyl) and 6.20 (2H, m, olefinic proton and proton attached to carbon, bearing $-OAc$).

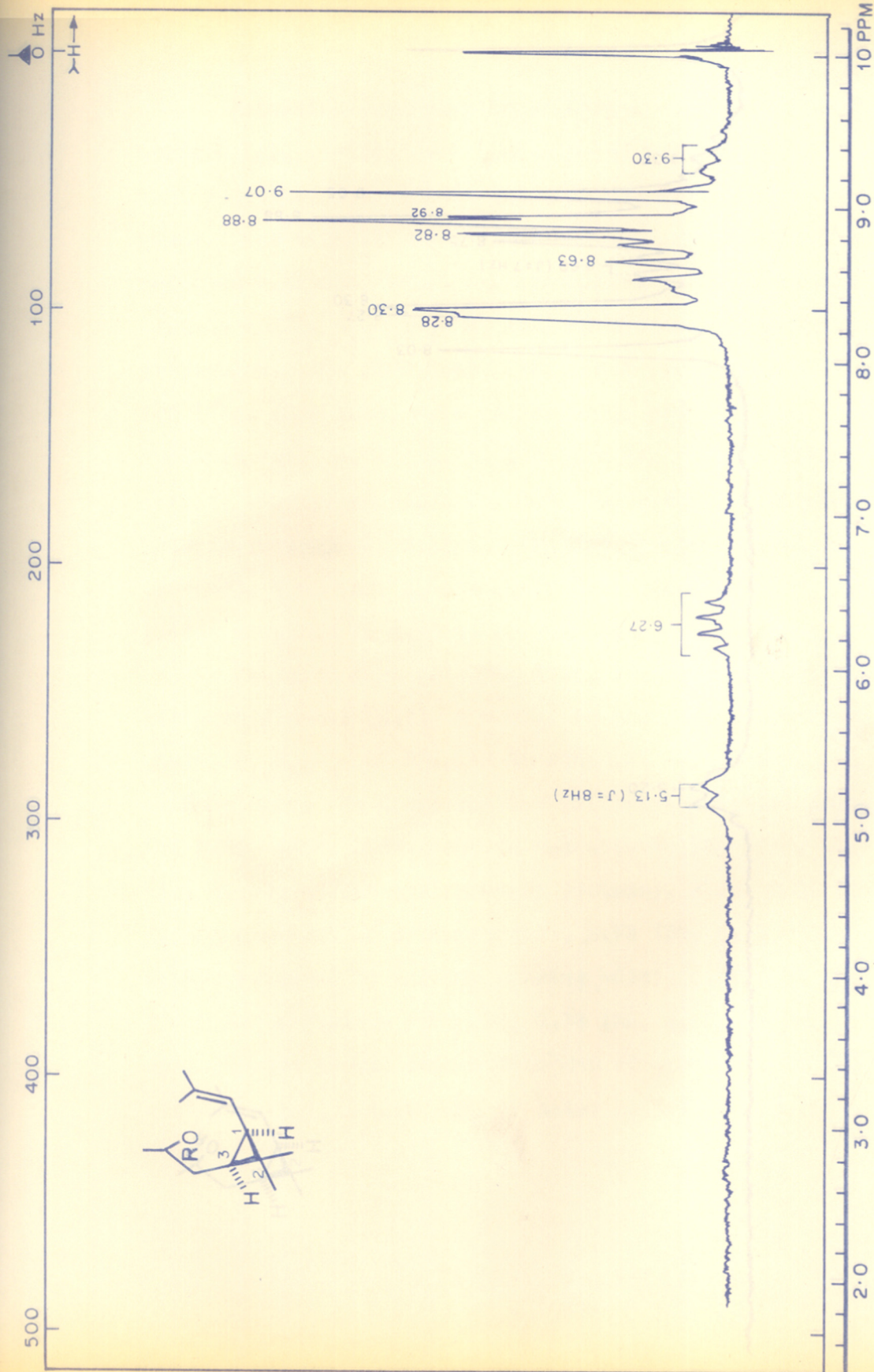


FIG. 8. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-HYDROXY PROPYL) - CIS-1-(2-METHYL-
PROP-1-ENYL) - CYCLOPROPANE (XI, R=H)

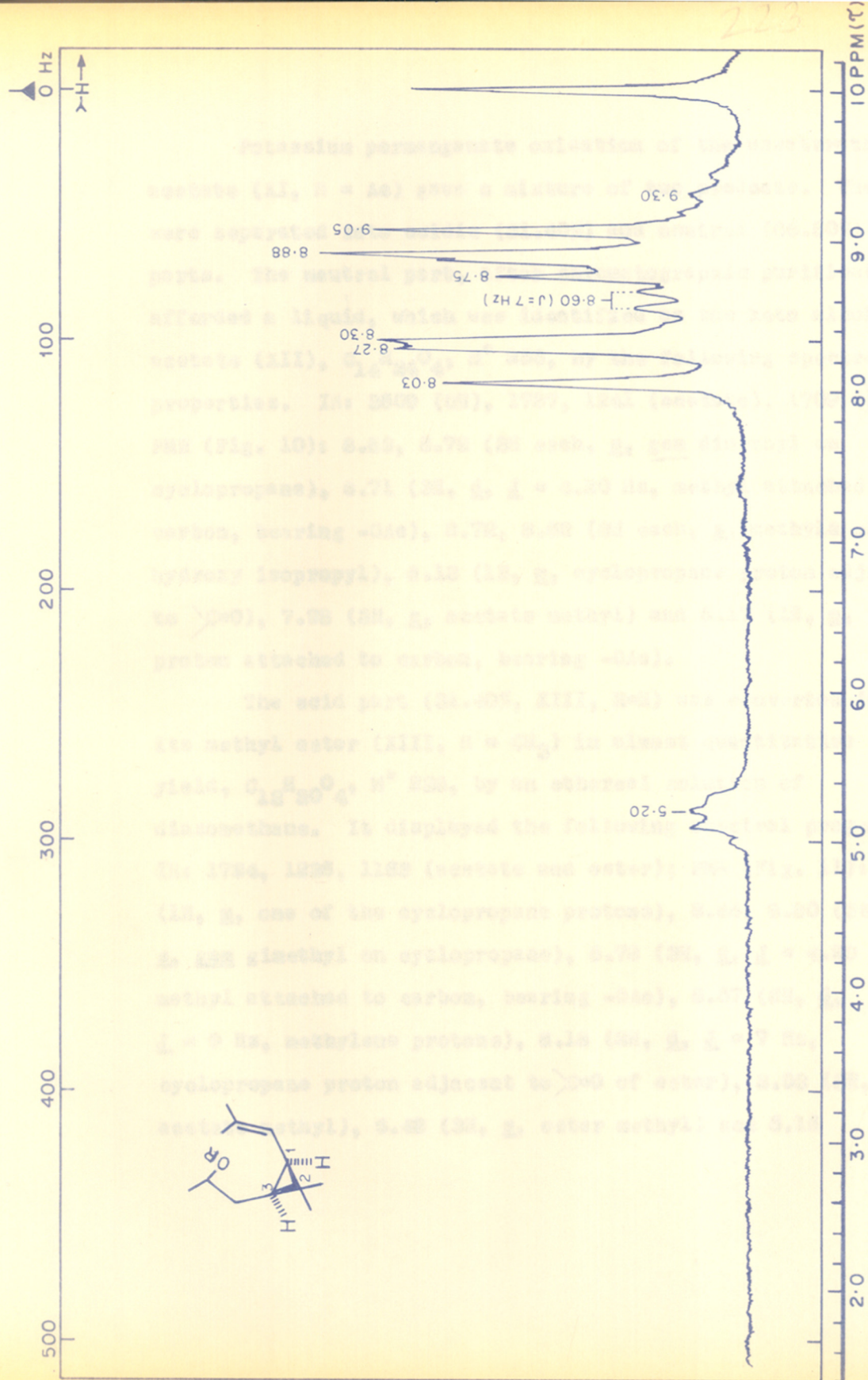


FIG. 9. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-ACETOXYPROPYL) - CIS-1 - (2-METHYLPROP-1-ENYL) - CYCLOPROPANE (XI, R=Ac)

Potassium permanganate oxidation of the unsaturated acetate (XI, R = Ac) gave a mixture of two products. They were separated into acidic (31.40%) and neutral (66.50%) parts. The neutral part, after chromatographic purification afforded a liquid, which was identified as the keto alcohol acetate (XII), $C_{14}H_{24}O_4$, M^+ 256, by the following spectral properties. IR: 3509 (OH), 1727, 1241 (acetate), 1709 ($C=O$); PMR (Fig. 10): 8.83, 8.72 (3H each, s, gem dimethyl on cyclopropane), 8.71 (3H, d, J = 4.20 Hz, methyl attached to carbon, bearing -OAc), 8.72, 8.62 (3H each, s, methyls of hydroxy isopropyl), 8.13 (1H, m, cyclopropane proton adjacent to $C=O$), 7.98 (3H, s, acetate methyl) and 5.17 (1H, m, proton attached to carbon, bearing -OAc).

The acid part (31.40%, XIII, R=H) was converted into its methyl ester (XIII, R = CH_3) in almost quantitative yield, $C_{12}H_{20}O_4$, M^+ 228, by an ethereal solution of diazomethane. It displayed the following spectral properties. IR: 1724, 1235, 1163 (acetate and ester); PMR (Fig. 11): 9.10 (1H, m, one of the cyclopropane protons), 8.85, 8.80 (3H each, s, gem dimethyl on cyclopropane), 8.78 (3H, d, J = 4.20 Hz, methyl attached to carbon, bearing -OAc), 8.57 (2H, d, J = 9 Hz, methylene protons), 8.18 (2H, d, J = 7 Hz, cyclopropane proton adjacent to $C=O$ of ester), 8.03 (3H, s, acetate methyl), 6.42 (3H, s, ester methyl) and 5.15

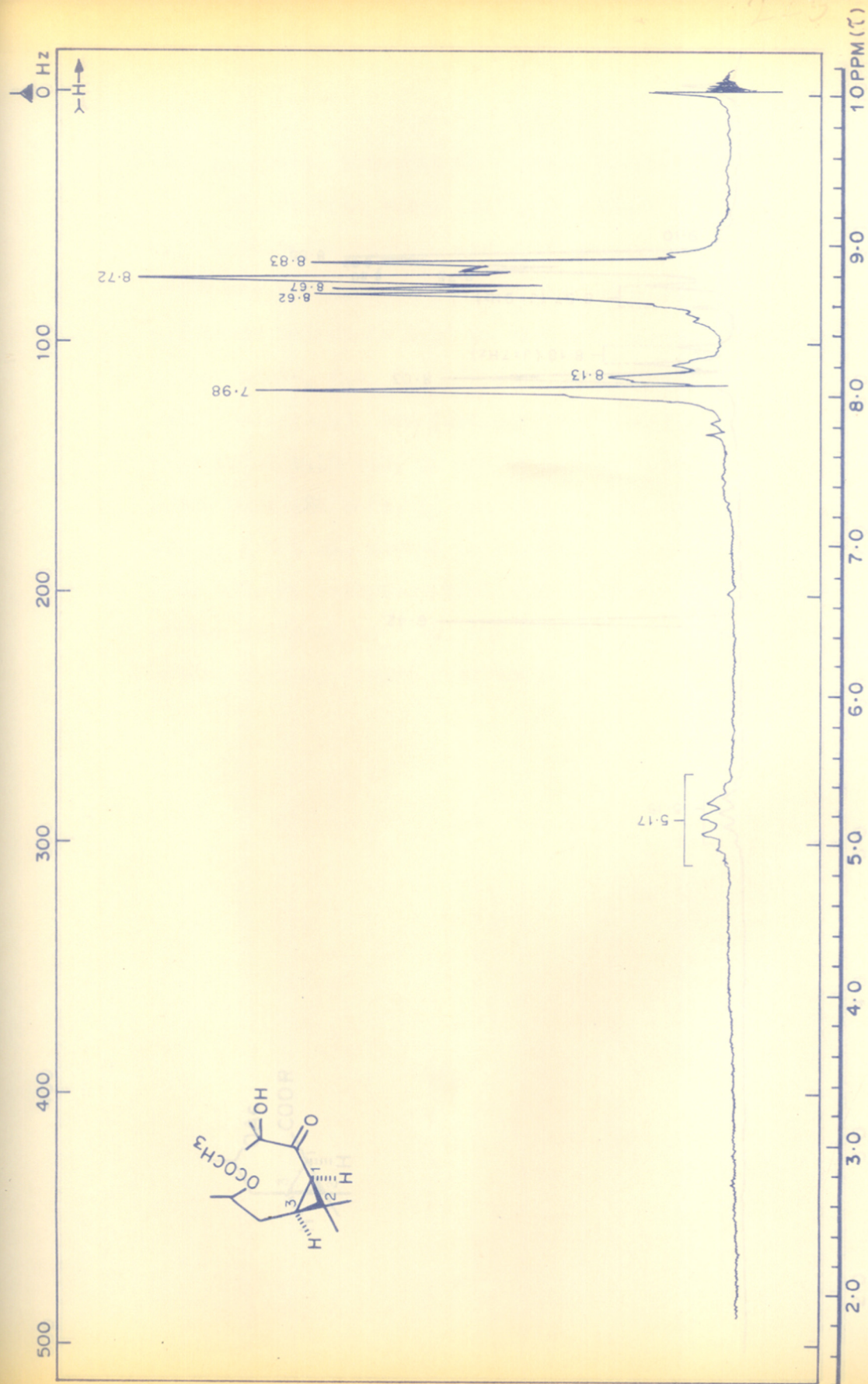


FIG. 10. PMR SPECTRUM OF 2,2-DIMETHYL-3-(2-ACETOXYPROPYL)-CIS-1-(2-METHYL-2-HYDROXY-1-OXOPROPYL)-CYCLOPROPANE (XII)

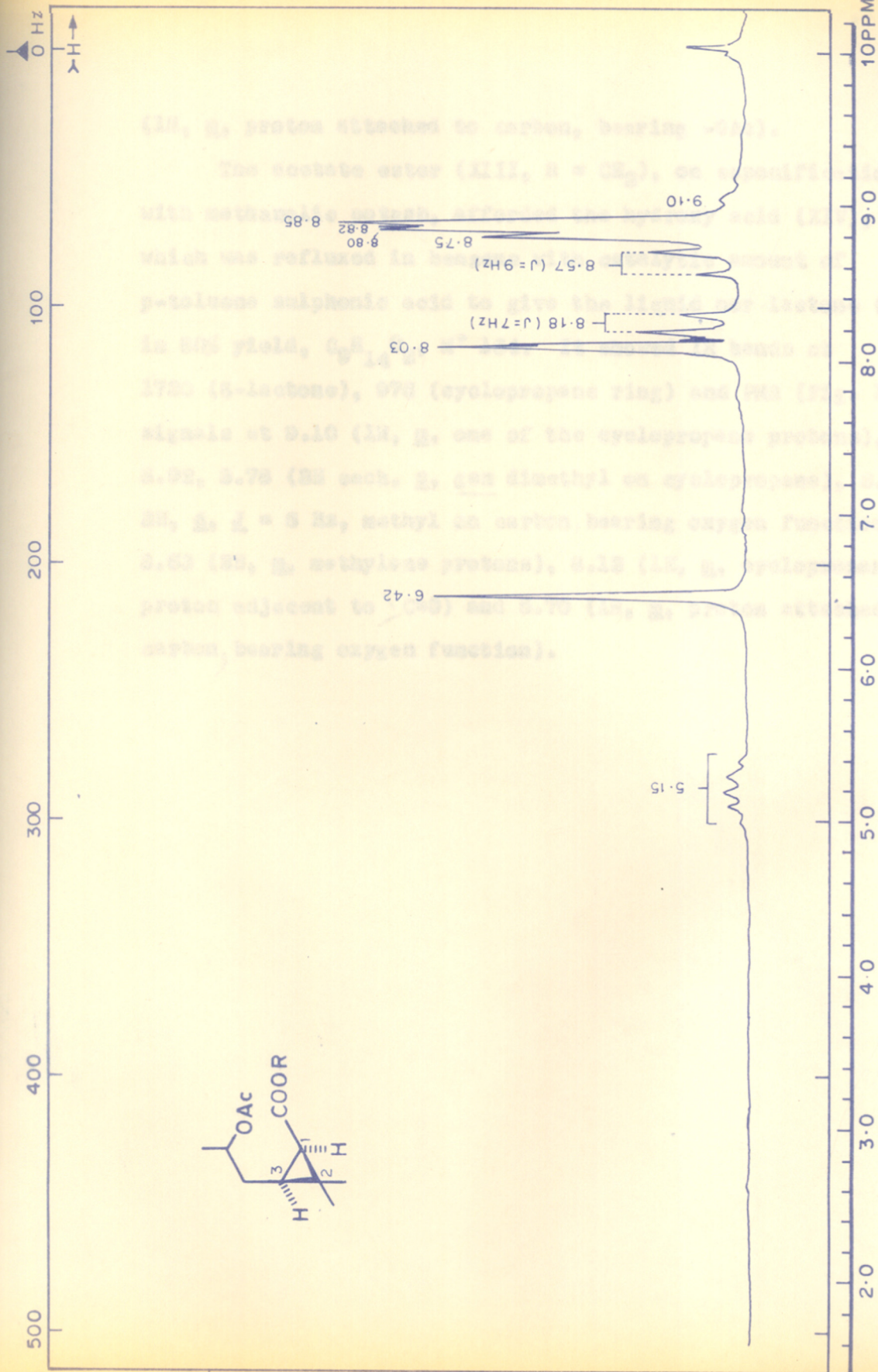


FIG. 11. PMR SPECTRUM OF METHYL-CIS-2,2-DIMETHYL-3-(2-ACETOXYPROPYL)-CYCLO-
-PROPANE-1-CARBOXYLATE (XIII, R = CH₃)

(1H, m, proton attached to carbon, bearing -OAc).

The acetate ester (XIII, R = CH₃), on saponification with methanolic potash, afforded the hydroxy acid (XIV), which was refluxed in benzene with catalytic amount of p-toluene sulphonic acid to give the liquid nor lactone (XV) in 80% yield, C₉H₁₄O₂, M⁺ 154. It showed IR bands at 1730 (δ-lactone), 976 (cyclopropane ring) and PMR (Fig. 12) signals at 9.10 (1H, m, one of the cyclopropane protons), 8.92, 8.78 (3H each, s, gem dimethyl on cyclopropane), 8.83 (3H, d, J = 6 Hz, methyl on carbon bearing oxygen function), 8.63 (2H, m, methylene protons), 8.13 (1H, m, cyclopropane proton adjacent to >C=O) and 5.70 (1H, m, proton attached to carbon, bearing oxygen function).

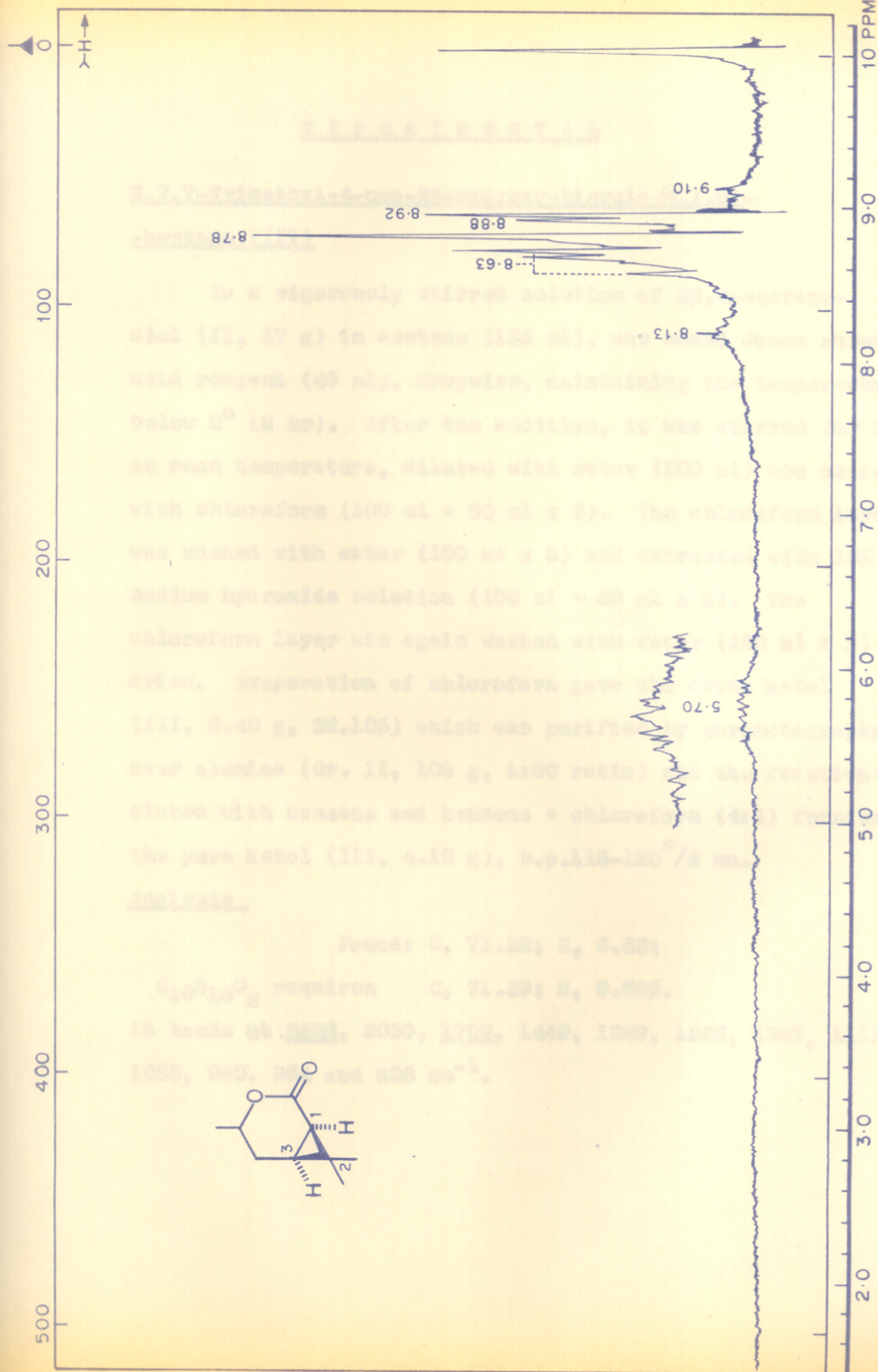


FIG. 12. PMR SPECTRUM OF -

- δ -LACTONE OF IR-CIS-2,2-DIMETHYL-3-(2-HYDROXYPROPYL)-CYCLOPROPANE

CARBOXYLIC ACID (XV)

EXPERIMENTAL3,7,7-Trimethyl-4-oxo-3 β -hydroxy-bicyclo-(4.1.0)-
-heptane (III)

To a vigorously stirred solution of 3 β ,4 α -carane-diol (II, 17 g) in acetone (125 ml), was added Jones chromic acid reagent (45 ml), dropwise, maintaining the temperature below 0° (2 hr). After the addition, it was stirred for 2 hr at room temperature, diluted with water (300 ml) and extracted with chloroform (100 ml + 50 ml x 2). The chloroform layer was washed with water (100 ml x 2) and extracted with 10% sodium hydroxide solution (100 ml + 50 ml x 2). The chloroform layer was again washed with water (150 ml x 2) and dried. Evaporation of chloroform gave the crude ketol (III, 5.40 g, 32.10%) which was purified by chromatography over alumina (Gr. II, 108 g, 1:20 ratio) and the fractions eluted with benzene and benzene + chloroform (4:1) furnished the pure ketol (III, 4.10 g), b.p. 115-120°/2 mm.

Analysis

Found: C, 71.22; H, 9.63;

C₁₀H₁₆O₂ requires C, 71.39; H, 9.59%.

IR bands at: 3636, 3030, 1709, 1449, 1389, 1366, 1227, 1111, 1055, 930, 954 and 806 cm⁻¹.

The aqueous alkaline portion was cooled to 5°, acidified with 20% sulphuric acid and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water, dried and evaporated to furnish the keto acid (IV, R = H, 10.50 g, 57%) which was converted into its methyl ester by an ethereal solution of diazomethane in almost quantitative yield. It was identified as the keto ester (IV, R = CH₃) by comparative TLC, spectral and analytical data.

3.4.7.7-Tetramethyl-3,4-dihydroxy-bicyclo-(4.1.0)-heptane (V)

A solution of the ketol (III, 10 g) in dry ether (50 ml) was introduced, dropwise, with stirring into an ice-cooled solution of methyl magnesium iodide prepared from magnesium turnings (2.8 g) and methyl iodide (16.8 g) in dry ether (150 ml). After the addition, it was stirred at room temperature for one hr and 4 hr under reflux. The reaction mixture was cooled to 0° and a cold saturated solution of ammonium chloride (100 ml) was introduced, dropwise, into it with vigorous stirring. After stirring for 30 minutes at room temperature, it was transferred to a separatory funnel. The ether layer was separated and aqueous portion extracted with ether (100 ml x 2). The combined ether layer was washed with water, dried and evaporated to furnish the crude diol which was chromatographed

on alumina (Gr. II, 1:20) and eluted with benzene and chloroform to give the pure diol (V, 5.2 g, 47.5%) as a thick liquid.

Analysis

Found: C, 71.81; H, 10.78;

$C_{11}H_{20}O_2$ requires C, 71.69; H, 10.94%.

IR bands at: 3571, 3021, 1449, 1374, 1294, 1242, 1094, 985, 926, 880, 858 and 755 cm^{-1} .

2,2-Dimethyl-cis-1,3-di(2-oxopropyl)-cyclopropane (VI)

In a 500 ml 3-necked flask equipped with an overhead mechanical stirrer, were taken the diol (V, 5 g), methanol (50 ml) and water (25 ml). The contents were stirred at room temperature for 10 minutes. Finely powdered sodium meta periodate (6.4 g) was then added, portionwise, to the above solution with stirring. After the addition (30 minutes), the reaction mixture was stirred for 2 hr, filtered and the residue washed with methanol (50 ml); the combined filtrate was diluted with water (250 ml) and extracted with chloroform (100 ml + 50 ml x 2). The chloroform layer was washed with water (100 ml x 2), dried and evaporated to give the diketone (VI, 4.10 g, 83%), which was purified by distillation, b.p. 115-120°/4 mm.

Analysis

Found: C, 72.33; H, 10.12;

$C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%.

IR bands at: 2985, 1702, 1408, 1351, 1227, 1160, 1015 and 957 cm^{-1} .

The compound (VI) gave a 2,4 DNP derivative, m.p. 206-207°.

Analysis

Found: C, 50.79; H, 5.91; N, 20.51;

$C_{23}H_{26}O_3N_2$ requires C, 50.93; H, 4.79; N, 20.66%.

IR bands at: 2985, 1623, 1515, 1449, 1408, 1361, 1325, 1304, 1266, 1215, 1129, 1073, 915, 840, 826, 742 and 722 cm^{-1} .

3,6,6-Trimethyl-4-acetyl-bicyclo-(3.1.0)-hex-3-ene (VII)

In a 250 ml conical flask, 3 g of diketone (VI) and 5% aqueous sodium hydroxide (100 ml) were taken and the reaction mixture was stirred for 8 hr at room temperature. It was then diluted with water (100 ml) and extracted with chloroform (50 ml, 25 ml x 2). The chloroform layer was washed with water (100 ml x 2), dried

and evaporated to furnish the cyclised ketone (VII), which was purified by distillation (2.1 g, 77.5%) b.p. 105-110°/3 mm.

Analysis

Found: C, 80.71; H, 9.73;

$C_{11}H_{16}O$ requires C, 80.84; H, 9.83%.

IR bands at: 2941, 1664, 1605, 1408, 1342, 1282, 1232, 1198, 1176, 1129, 1010, 961, 898, 861, 809 and 755 cm^{-1} . The cyclised ketone (VII) gave a 2,4 DNP derivative, m.p. 134-135°.

Analysis

Found: C, 59.38; H, 5.75; N, 16.12;

$C_{17}H_{20}O_4N_4$ requires C, 59.29; H, 5.85; N, 16.27%.

IR bands at: 2985, 1623, 1587, 1497, 1460, 1370, 1333, 1304, 1274, 1134, 1053, 913 and 740 cm^{-1} .

Methyl-di-cis-2,2-dimethyl-3-(2-oxocyclopropyl)-cyclopropane carboxylate (VIII, R = CH₃)

To a solution of the conjugated ketone (VII, 2 g) in acetone (50 ml), water (15 ml) and acetic acid (10ml), contained in a 3-necked flask equipped with a mechanical stirrer, powdered potassium permanganate (2.9 g) was added in small lots with vigorous stirring; during 30 minutes. After the addition was complete, the heterogeneous reaction mixture was stirred for 30 minutes more. During addition and stirring, the temperature of the contents was maintained below 40°. Sodium nitrite (2 g) and

dilute sulphuric acid (10 ml dilute 40 ml) were then added to the reaction mixture under stirring to dissolve the manganese dioxide precipitate. The clear yellow solution was then transferred to a separating funnel, diluted with water (100 ml) and extracted with chloroform (50 ml, 25 ml x 2). The chloroform layer was then extracted with 10% aqueous sodium carbonate solution (3 x 25 ml) to extract the acid formed in the reaction. The carbonate layer was cooled to 0° and acidified with sulphuric acid to 2 pH. The acid liberated was extracted with chloroform (25 ml x 3). The combined chloroform layer was washed with water (100 ml) and dried. Evaporation of chloroform gave the keto-acid (VIII, R = H, 0.65 g, 31.5%). The keto-acid (VIII, R = H, 0.5 g) was esterified with an ethereal solution of diazomethane to afford the methyl ester (VIII, R = CH₃, 0.45 g, 83%) which was purified by distillation, b.p. 105-110°/5 mm, (α)_D²⁵ ± 0° (g, 1.5).

Analysis

Found: C, 65.27; H, 8.92;

C₁₀H₁₆O₃ requires C, 65.19; H, 8.75%.

IR bands at: 3030, 1736, 1439, 1379, 1355, 1325, 1176, 1136, 1057, 1029, 962, 926 and 855 cm⁻¹.

The neutral part was not examined further.

Methyl-1R-gis-2,2-dimethyl-3-(2-oxopropyl)-cyclopropane
carboxylate (VIII, R = CH₃)

To a solution of the unsaturated ketone (IX, 8.09) in acetone (150 ml), water (25 ml) and acetic acid (15 ml), contained in a 3-necked flask equipped with a mechanical stirrer, powdered potassium permanganate (10.5 g) was added portionwise, with vigorous stirring during half an hour. After the addition was completed, the heterogeneous reaction mixture was stirred for 30 minutes more. During addition and stirring, the temperature of the contents was maintained below 40°. Sodium nitrite (5 g) and dilute sulphuric acid (20 ml diluted to 60 ml) were then added to the reaction mixture under stirring to dissolve the manganese dioxide precipitate. The clear yellow solution was then transferred to a separating funnel, diluted with water (150 ml) and extracted with ether (100 ml x 3). The ether layer was washed with water (100 ml x 2) and then extracted with 10% aqueous sodium carbonate solution (3 x 50 ml). The carbonate layer was cooled to 0° and acidified with sulphuric acid to 2 pH. The acid liberated was extracted with chloroform (25 ml x 3). The chloroform layer was washed with water (50 ml x 2) and dried. Removal of chloroform gave the keto-acid (VIII, R = H, 2.40 g, 31.7%) which was esterified with an ethereal solution of diazomethane to

afford the methyl ester (VIII, R = CH₃, 2.20g), purified by distillation b.p. 105-110°/5 mm, (α)_D²⁸ - 33.7° (g, 2.70).

Analysis

Found: C, 65.32; H, 8.81;

C₁₀H₁₆O₃ requires C, 65.19; H, 8.75%.

IR bands at: 3030, ~~1735~~, 1438, 1382, 1356, 1328, 1180, 1138, 1086, 1029, 960, 925 and 852 cm⁻¹.

The ether layer after removal of acid portion, was repeatedly washed with water (100 ml x 2) and dried. Evaporation of ether afforded the crude diketo-alcohol (X, 4.70 g, 50%), which was purified by chromatography over alumina (Gr. II, 1:20 ratio), and the fractions eluted with benzene furnished the pure diketo-alcohol (X).

Analysis

Found: C, 67.71; H, 9.67;

C₁₂H₂₀O₃ requires C, 67.89; H, 9.50%.

IR bands at ~~3623~~, 3077, ~~1724~~, ~~1692~~, 1471, 1370, 1263, 1163, 1058, 971 and 800 cm⁻¹.

2,2-Dimethyl-3-(2-hydroxypropyl)-cis-1-(2-methylprop-1-enyl)-cyclopropane (XI, R = H)

To an ice-cooled solution of the unsaturated ketone (IX, 4 g) in methanol (75 ml), sodiumborohydride (0.70 g) was added slowly in portions. The reaction product was

stirred at room temperature for 10 hr and then kept at room temperature for 48 hr. It was diluted with cold water (150 ml) and acidified by dil. HCl. It was then extracted with chloroform (50 ml x 3), washed with water (100 ml x 2) and dried. Removal of chloroform gave the crude product (3.5 g, TLC two spots). It was chromatographed over alumina (Gr. II, 70 g, 1:20 ratio) and the fractions eluted with benzene furnished the pure alcohol (XI, R = H, 2.6 g) which is further purified by distillation, 115-120°/2 mm.

Analysis

Found: C, 78.84; H, 12.26;

$C_{12}H_{22}O$ requires C, 79.06; H, 12.16%.

IR bands at: ~~3448~~, 2985, ~~1639~~, 1449, 1370, 1299, 1111, 980, 935 and ~~840~~ cm^{-1} .

2,2-Dimethyl-3-(2-acetoxypropyl)-cis-1-(2-methylprop-1-enyl)-cyclopropane (XI, R = Ac)

To a solution of the alcohol (XI, R = H, 2.1 g) in pyridine (10 ml), acetic anhydride (7 ml) was added. The reaction mixture was kept at room temperature for 48 hr and then heated on a water-bath for 2 hr. It was diluted with water (100 ml) and extracted with chloroform (25 ml x 3). The chloroform extract was washed with dil. hydrochloric acid (5%), followed by water and dried. Removal of chloroform gave an acetate (XI, R = Ac, 2 g, 77.5%) which

was purified by distillation, b.p. 105-110°/3 mm.

Analysis

Found: C, 74.83; H, 10.91;

$C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78%.

IR bands at 2985, 1727, 1653, 1445, 1361, 1235, 1124, 1009, 947 and 833 cm^{-1} .

Methyl-1R-cis-2,2-dimethyl-3-(2-acetoxypentyl)-cyclopropane
carboxylate (XIII, R = CH₃)

In a 500 ml, 3-necked round bottom flask equipped with an overhead stirrer, was placed the unsaturated acetate (XI, R = Ac, 5 g), acetone (125 ml), water (15 ml) and acetic acid (10 ml). To the stirred solution was added powdered potassium permanganate (5.30 g), during half an hour, maintaining the temperature at 40 to 50°. After the addition, the stirring was continued for an hour at the same temperature. It was then treated with sodium nitrite (4 g) and dilute sulphuric acid (20 ml, diluted to 60 ml) under stirring to dissolve the manganese dioxide precipitate. The colourless solution thus obtained was diluted with water (200 ml) and extracted with ether (100 ml + 50 ml x 2). The ether layer was extracted with 10% aqueous sodium hydroxide solution (50 ml + 25 ml x 2). The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid to 2 pH and extracted with

chloroform (50 ml + 25 ml x 2). The chloroform layer was washed with water (60 ml x 2), dried and evaporated to furnish the acid (XIII, R = H, 1.5 g, 31.5%) which was converted into its methyl ester (XIII, R = CH₃, 1.4 g, 87.6%) by an ethereal solution of diazomethane. The acetate ester (XIII, R = CH₃) was further purified by distillation, b.p.125-130°/2 mm.

Analysis

Found: C, 63.27; H, 8.94;

C₁₂H₂₀O₄ requires C, 63.13; H, 8.83%.

IR bands at: 2985, 1724, 1429, 1366, 1235, 1163, 948, 847 and 820 cm⁻¹.

The ether layer after extraction with sodium hydroxide, was thoroughly washed with water (100 ml x 3) and dried. Removal of ether furnished the crude acetate keto-alcohol (XII, 3.8 g, 66.5%) which was purified by chromatography over alumina (Gr. II, 1:20 ratio) and the fractions eluted with benzene and chloroform afforded the pure acetate keto-alcohol (XII), b.p.130-135°/2.5 mm.

Analysis

Found: C, 65.72; H, 9.53;

C₁₄H₂₄O₄ requires C, 65.59; H, 9.44%.

IR bands at: 3502, 3012, 1727, 1702, 1449, 1366, 1241, 1163, 1053, 1014, 952 and 823 cm⁻¹.

6-Lactone of 1R cis-2,2-dimethyl-3-(2-hydroxy propyl)-cyclohexane carboxylic acid (XV)

To a solution of the acetate ester (XIII, R = CH₃, 1.5 g) in methanol (50 ml) was added an aqueous solution of potassium hydroxide (1.5 g in 10 ml) and refluxed for 6 hr. Most of the methanol was removed under suction. The residue was cooled, diluted with water (100 ml) and extracted with ether (50 ml x 2) to remove the neutral part. The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid and extracted with ether (50 ml + 25 ml x 2). The ether layer was washed with water (50 ml x 2), dried and evaporated to furnish the hydroxy acid (XIV, 0.9 g, 79.5%) as a thick liquid. The acid (XIV, 0.9 g) was taken in dry benzene (50 ml) and the solution refluxed with PTA (0.050 g) for 6 hr. The solution was washed with water (25 ml x 2), dried and the solvent evaporated to furnish the crude liquid lactone (XV, 0.65 g, 80%) which was further purified by chromatography over alumina (Gr. II, 1:20 ratio). The fractions eluted with pet. ether and pet. ether + 10% benzene gave a TLC pure liquid lactone (XV).

Analysis

Found: C, 70.21; H, 9.24;

C₉H₁₄O₂ requires C, 70.10; H, 9.15%.

IR bands at: 3030, 1730, 1449, 1370, 1333, 1282, 1176, 1124, 1053, 976 and 901 cm⁻¹.

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CHAPTER - V

ISOLATION OF TARAXASTERYL ACETATE FROM THE LEAVES AND
STALKS OF HAUSSUREA LAFFA CLARKE AND STUDY OF PRINC
REACTION ON TARAXASTERYL ACETATE

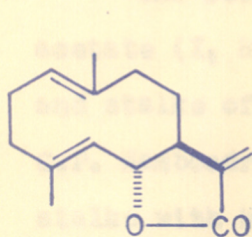
S U M M A R Y

The costus plant, Saussurea Lappa Clarke, belonging to the Compositae family is grown at high altitudes in Kashmir and the hill districts of Punjab. From the hexane extract of the leaves and stalks of this plant, taraxasteryl acetate (I, R = Ac) was isolated as per the procedure already described. Prins reaction on taraxasteryl acetate (I, R = Ac) was carried out using paraformaldehyde and glacial acetic acid. Three products have been isolated and characterised on the basis of IR, PMR and analytical data. These included, 3 β , 20-diacetoxy-28-acetoxymethyl-taraxastane (II), 3 β -acetoxy-21-acetoxymethyl- ψ -taraxastene (IV, R = Ac) and 3 β -acetoxy-28-acetoxymethyl- ψ -taraxastene (V, R = Ac). In addition, the double bond isomerised product viz., ψ -taraxasteryl acetate (VI) could also be isolated from the reaction product. The corresponding diols (IV, R = H) and (V, R = H) were obtained from the acetates (IV, R = Ac) and (V, R = Ac) by saponification and characterised by spectral data.

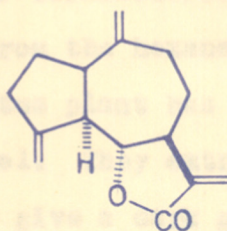
INTRODUCTION

The costus plant, Saussurea Lappa Clarke, belongs to the Compositae family and is mainly grown in India in Kashmir and the hill districts of Punjab at high altitudes¹. The roots of the plant are known to possess medicinal properties and have been prescribed in the indigenous system of medicine^{2,3,4}. The roots also contain a fragrant principle which can be isolated either by steam distillation or solvent extraction. The essential oil obtained from the roots is used in high grade perfumery preparations. In our laboratory, a low temperature solvent extraction procedure for extracting costus root oil using 40-60° pet. ether, has been developed. The oil obtained by this method is free from polymerisation and denaturing.

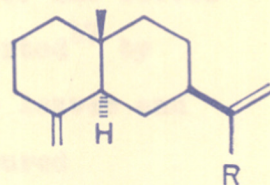
The systematic examination of the solvent extracted costus root oil resulted in the isolation of several compounds, some of which are mentioned below. Costunolide (VII), dehydrocostuslactone (VIII), costol (IX), costic acid (X) and apitoxene (XI) etc.⁵⁻¹⁴. Recently, in our laboratory, ¹⁵Fai et al., have isolated three esters viz., α -amyrin stearate (XII), β -amyrin palmitate (XIII) and lupeol palmitate (XIV) from the hexane extract of the leaves and stalks of the costus plant. The isolation of an alkaloid "Saussurin" has also been reported¹⁶ from the costus plant.



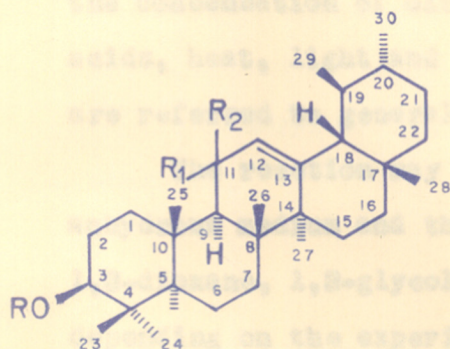
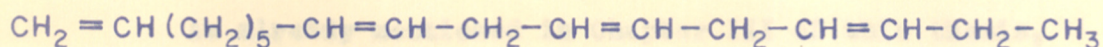
VII



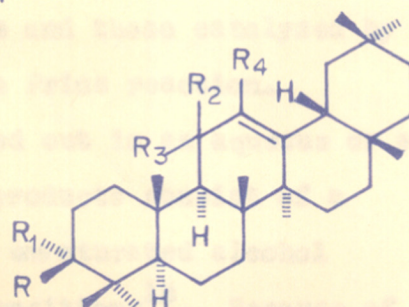
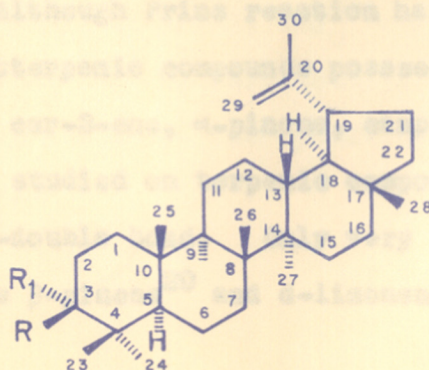
VIII

IX, R = -CH₂OH

X, R = -COOH

XII, R = -CO(CH₂)₁₆CH₃;R₁ = R₂ = H

XI

XIII, R = -OCO(CH₂)₁₄CH₃;R₁ = R₂ = R₃ = R₄ = HR = -OCO(CH₂)₁₄CH₃; R₁ = H

The isolation of taraxasterol (I, R = H) and its acetate (I, R = Ac) from the hexane extract of the leaves and stalks of the costus plant has been reported¹⁷ by C.P. Nambodripad et al. They extracted the leaves and stalks with hexane to give a dark green coloured concentrate in 3.40% yield which, on chromatography over alumina has been reported to yield taraxasteryl acetate (I, R = Ac) and also taraxasterol (I, R = H).

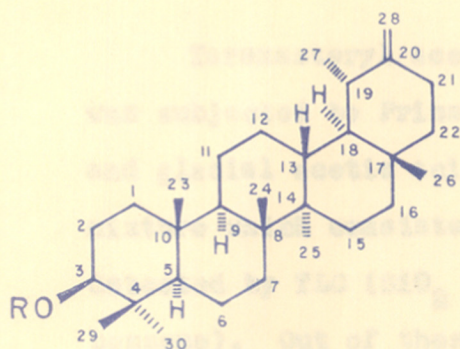
As already mentioned in Chapter III of this thesis, the condensation of olefins with aldehydes is catalysed by acids, heat, light and peroxides and those catalysed by acids are referred to generally as the Prins reaction.

The reaction may be carried out in an aqueous or an anhydrous medium and the major products consist of a 1,3-dioxane, 1,3-glycols, or an unsaturated alcohol depending on the experimental conditions¹⁸. Because of this unusual versatility, the Prins reaction is useful in organic synthesis. It offers a new route to the manufacture of many organic compounds utilising readily available petroleum products¹⁹. Although Prins reaction has been studied on a number of monoterpenic compounds possessing an endo-double bond like (+) car-3-ene, α -pinene, camphene etc., it has not been much studied on terpenic compounds containing an exo-methylene-double bond. Only very few terpenic compounds like β -pinene²⁰ and d-limonene²¹ possessing the

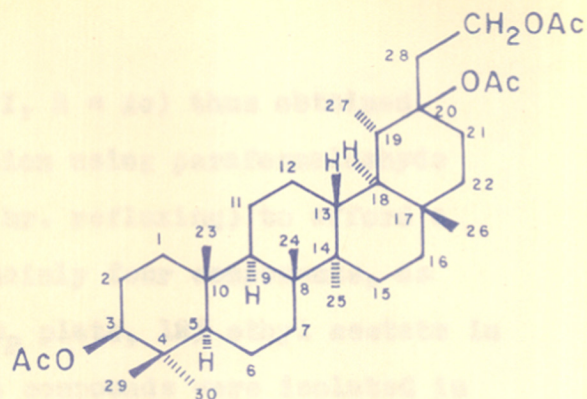
exo-methylene-double bond have been subjected to Prins reaction to yield interesting products. However, this reaction has not been carried out on higher terpenes like di and triterpenes. So far there appears to be no mention of this reaction on taraxasteryl acetate (I, R = Ac). It is known that taraxasteryl acetate and its derivatives undergo double bond isomerisation under acidic conditions²² to yield ψ -taraxasteryl derivatives. So it was felt desirable to isolate the products obtained from Prins reaction on taraxasteryl acetate (I, R = Ac) with a view to ascertain whether, products derived from ψ -taraxasteryl acetate (VI) are also formed during the reaction.

PRESENT WORK

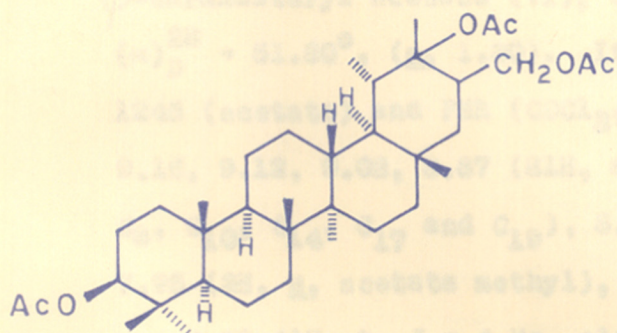
The leaves and stalks of the costus plant were extracted with pet.ether to get a dark green coloured concentrate in 3% yield which on chromatography over silicic acid (1:10 ratio) furnished a crystalline solid, m.p.249-250° (pet.ether + ethyl acetate), $(\alpha)_D^{25} + 99.00$ (g, 1.30). It has been identified¹⁷ as taraxasteryl acetate (I, R = Ac) by physical constants (m.p. and specific rotation) and spectral data (IR, PMR).



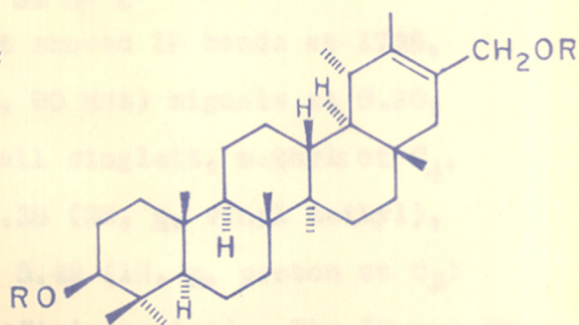
I, R = Ac; R = H



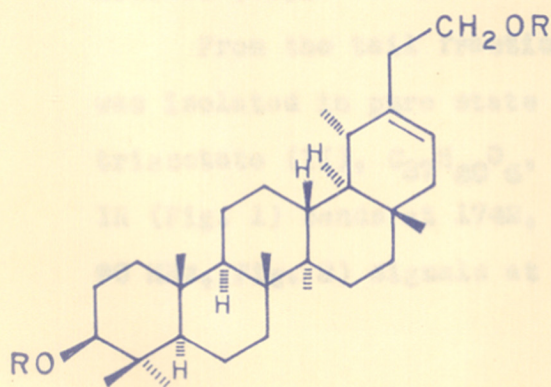
II



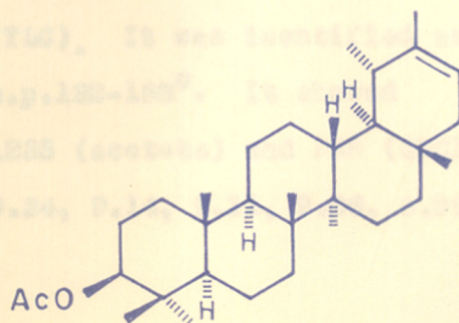
III



IV, R = Ac; R = H



V, R = Ac; R = H



VI

Taraxasteryl acetate (I, R = Ac) thus obtained was subjected to Prins reaction using paraformaldehyde and glacial acetic acid (72 hr. refluxing) to afford a mixture which consisted of mainly four components, as detected by TLC ($\text{SiO}_2 + \text{AgNO}_3$ plate, 12% ethyl acetate in benzene). Out of these, two compounds were isolated in pure state from the reaction mixture, by chromatography over silicic acid.

The least polar of these, was identified as the ψ -taraxasteryl acetate (VI), $\text{C}_{32}\text{H}_{52}\text{O}_2$, m.p. 223-224° ($[\alpha]_D^{25} + 51.50^\circ$, (g, 1.30). It showed IR bands at 1735, 1245 (acetate) and PMR (CDCl_3 , 90 MHz) signals at 9.20, 9.16, 9.12, 9.02, 8.87 (21H, all singlets, methyls at C_4 , C_8 , C_{10} , C_{14} , C_{17} and C_{19}), 8.33 (3H, s, vinyl methyl), 7.95 (3H, s, acetate methyl), 5.49 (1H, m, proton at C_3) and 4.82 (1H, t, J = 4 Hz, olefinic proton). The IR and PMR spectra and specific rotation of (VI) were comparable with those reported²³ in literature for ψ -taraxasteryl acetate (VI).

From the tail fractions of chromatography, a solid was isolated in pure state (TLC). It was identified as the triacetate (II), $\text{C}_{37}\text{H}_{60}\text{O}_6$, m.p. 132-133°. It showed IR (Fig. 1) bands at 1742, 1235 (acetate) and PMR (CDCl_3 , 90 MHz, Fig. 2) signals at 9.34, 9.14, 9.11, 9.06, 8.96

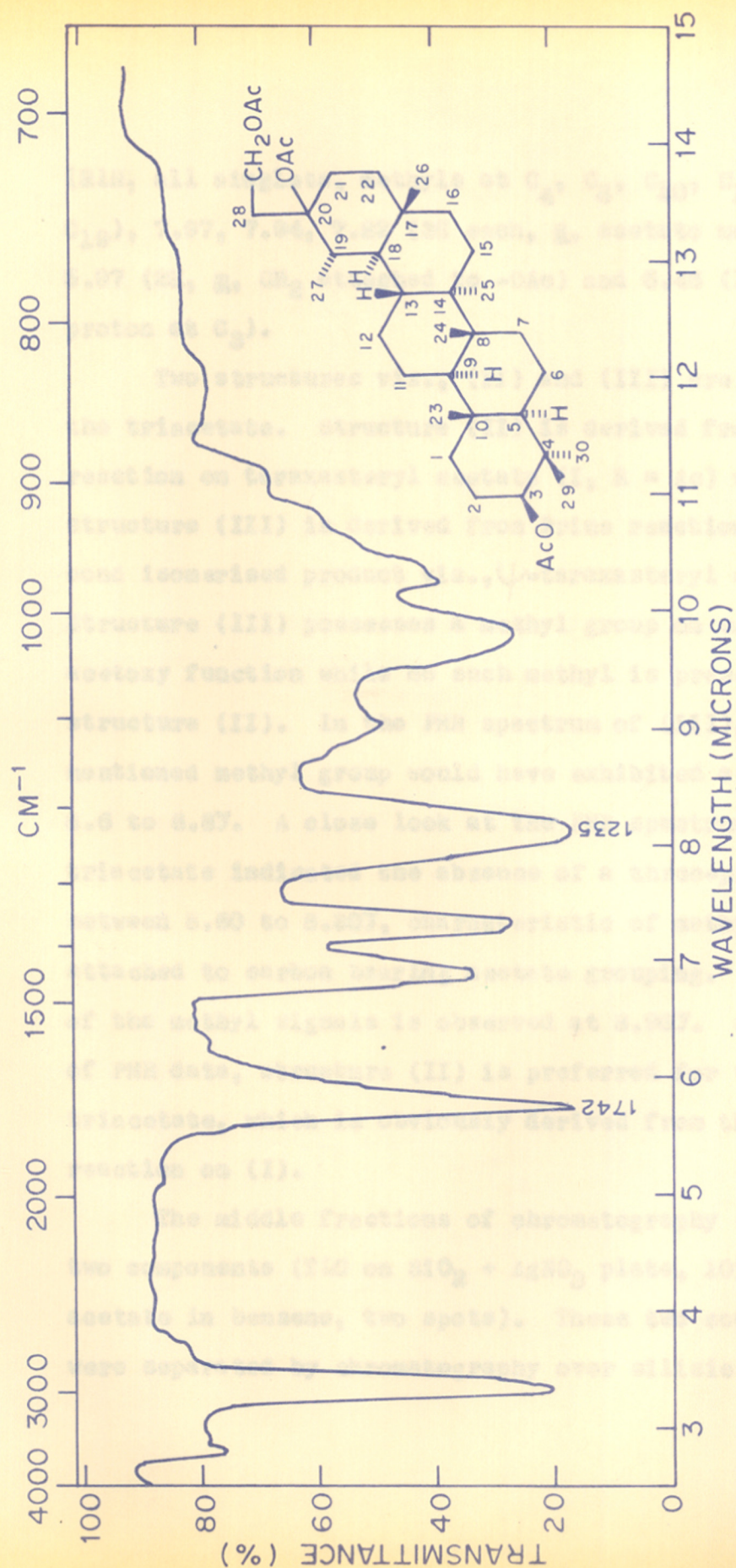


FIG. 1. IR SPECTRUM OF 3β-ACETOXY-20-ACETOXY-28-ACETOXYMETHYL-TARAXASTANE (II)

(21H, all singlets, methyls at C₄, C₈, C₁₀, C₁₄, C₁₇ and C₁₉), 7.97, 7.94, 7.82 (3H each, 2, acetate methyls), 5.97 (2H, 2, CH₂ attached to -OAc) and 5.46 (1H, 2, proton at C₃).

Two structures viz., (II) and (III) are possible for the triacetate. Structure (II) is derived from Prins reaction on taraxasteryl acetate (I, R = Ac) whereas structure (III) is derived from Prins reaction on double bond isomerised product viz., ψ -taraxasteryl acetate (VI). Structure (III) possesses a methyl group on carbon bearing acetoxy function while no such methyl is present in structure (II). In the PMR spectrum of (III), the above mentioned methyl group would have exhibited a signal at 8.6 to 8.8 τ . A close look at the PMR spectrum of the triacetate indicated the absence of a three-proton signal between 8.60 to 8.80 τ , characteristic of methyl group attached to carbon bearing acetate grouping. The lowest of the methyl signals is observed at 8.96 τ . On the basis of PMR data, structure (II) is preferred for the triacetate, which is obviously derived from the Prins reaction on (I).

The middle fractions of chromatography consisted of two components (TLC on SiO₂ + AgNO₃ plate, 10% ethyl acetate in benzene, two spots). These two components were separated by chromatography over silicic acid

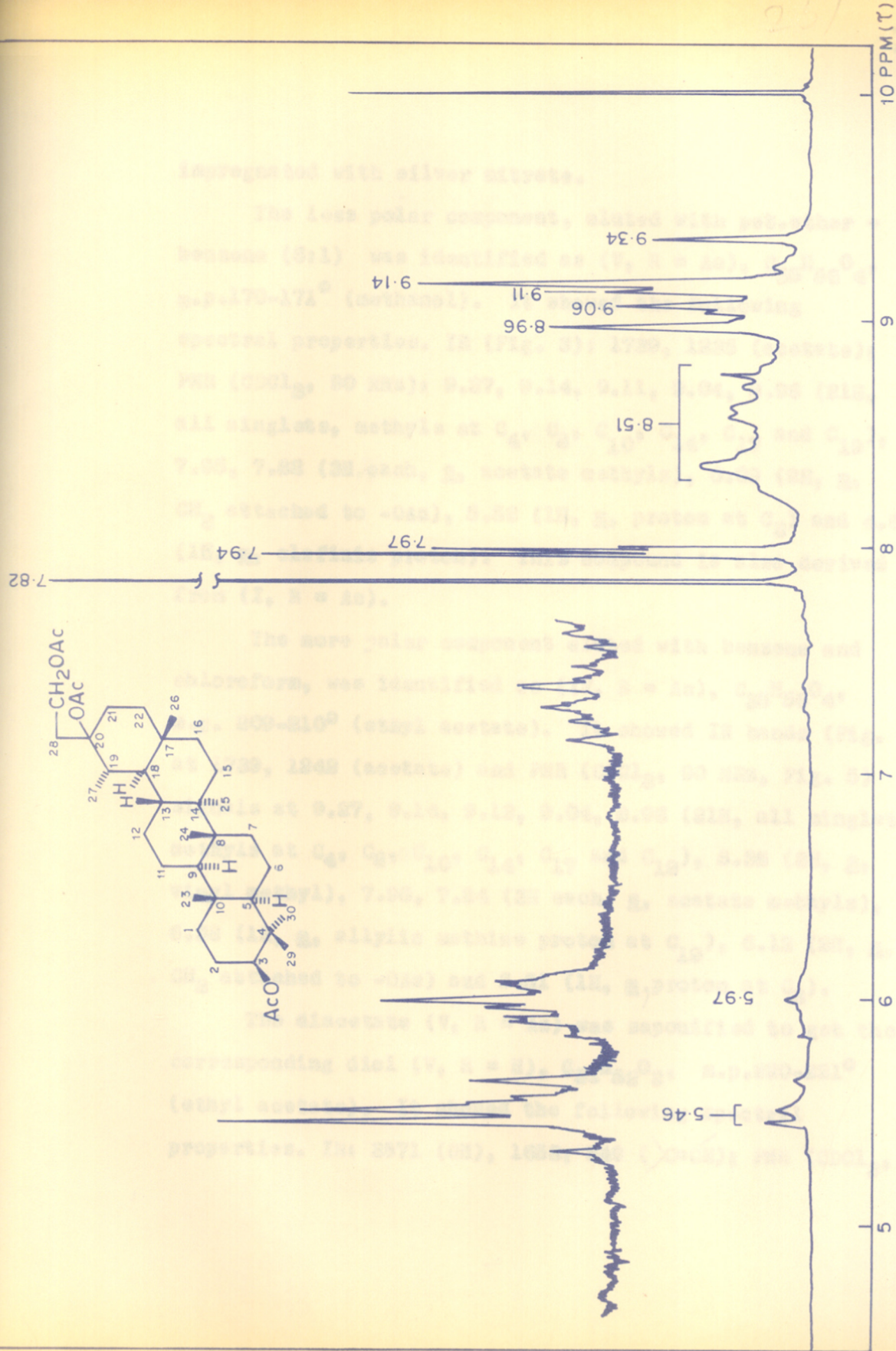


FIG. 2. PMR SPECTRUM OF -3β-ACETOXY-20-ACETOXY-28-ACETOXYMETHYL-TARAXASTANE (II)

impregnated with silver nitrate.

The less polar component, eluted with pet.ether + benzene (5:1) was identified as (V, R = Ac), $C_{35}H_{56}O_4$, m.p. 170-171° (methanol). It showed the following spectral properties. IR (Fig. 3): 1739, 1235 (acetate); PMR ($CDCl_3$, 90 MHz): 9.27, 9.14, 9.11, 9.04, 8.96 (21H, all singlets, methyls at C_4 , C_8 , C_{10} , C_{14} , C_{17} and C_{19}), 7.95, 7.82 (3H each, $\underline{s}$, acetate methyls), 6.09 (2H, $\underline{m}$, CH_2 attached to -OAc), 5.52 (1H, $\underline{m}$, proton at C_3) and 4.62 (1H, $\underline{m}$, olefinic proton). This compound is also derived from (I, R = Ac).

The more polar component eluted with benzene and chloroform, was identified as (IV, R = Ac), $C_{35}H_{56}O_4$, m.p. 209-210° (ethyl acetate). It showed IR bands (Fig. 4) at 1739, 1242 (acetate) and PMR ($CDCl_3$, 90 MHz, Fig. 5) signals at 9.27, 9.14, 9.12, 9.04, 8.96 (21H, all singlets, methyls at C_4 , C_8 , C_{10} , C_{14} , C_{17} and C_{19}), 8.38 (3H, $\underline{s}$, vinyl methyl), 7.96, 7.84 (3H each, $\underline{s}$, acetate methyls), 6.38 (1H, $\underline{m}$, allylic methine proton at C_{19}), 6.12 (2H, $\underline{m}$, CH_2 attached to -OAc) and 5.51 (1H, $\underline{m}$, proton at C_3).

The diacetate (V, R = Ac) was saponified to get the corresponding diol (V, R = H), $C_{31}H_{52}O_2$, m.p. 220-221° (ethyl acetate). It showed the following spectral properties. IR: 3571 (OH), 1653, 849 ($\diagdown C=CH$); PMR ($CDCl_3$,

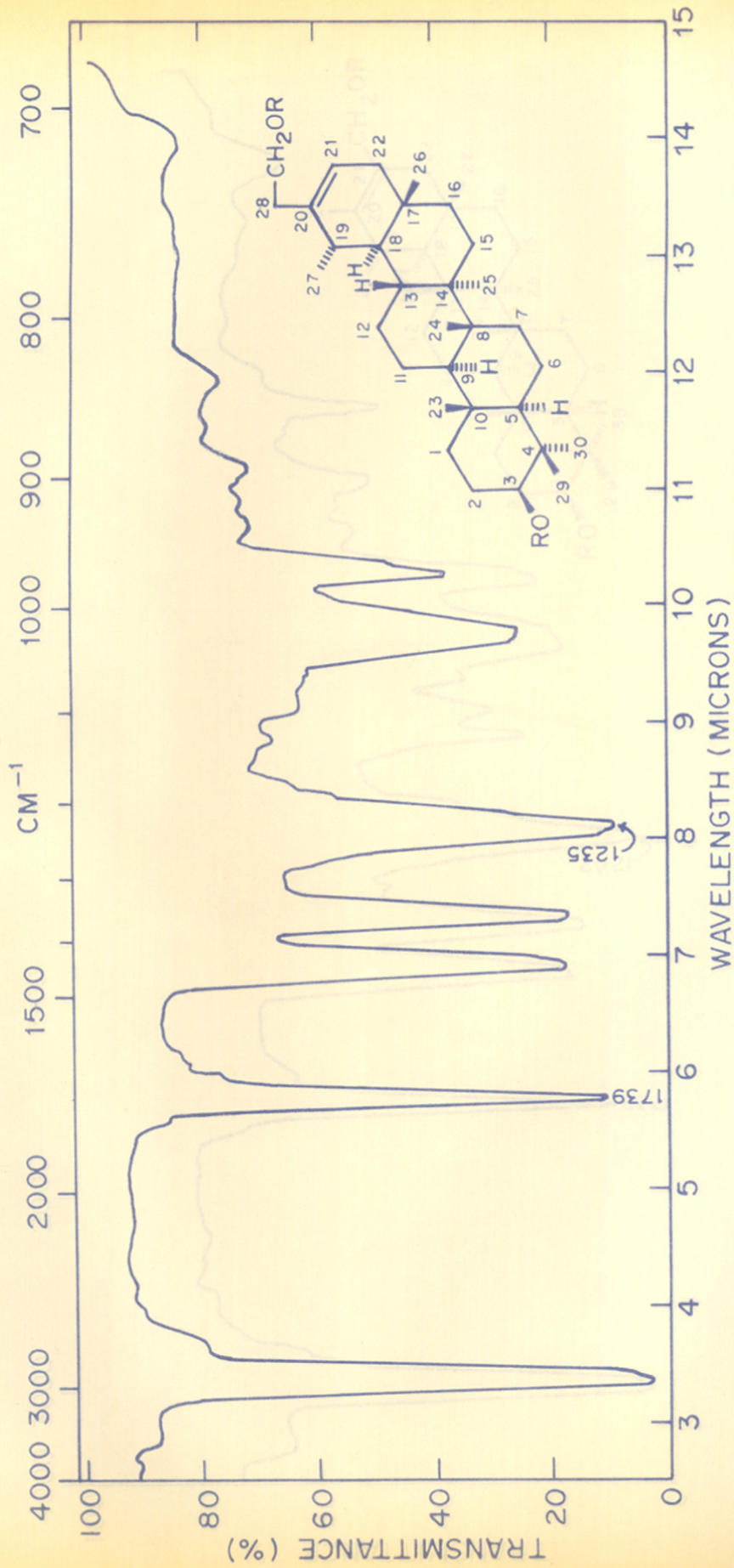


FIG. 3. IR SPECTRUM OF 3β-ACETOXY-28-ACETOXYMETHYL-ψ-TARAXASTENE (V, R=Ac)

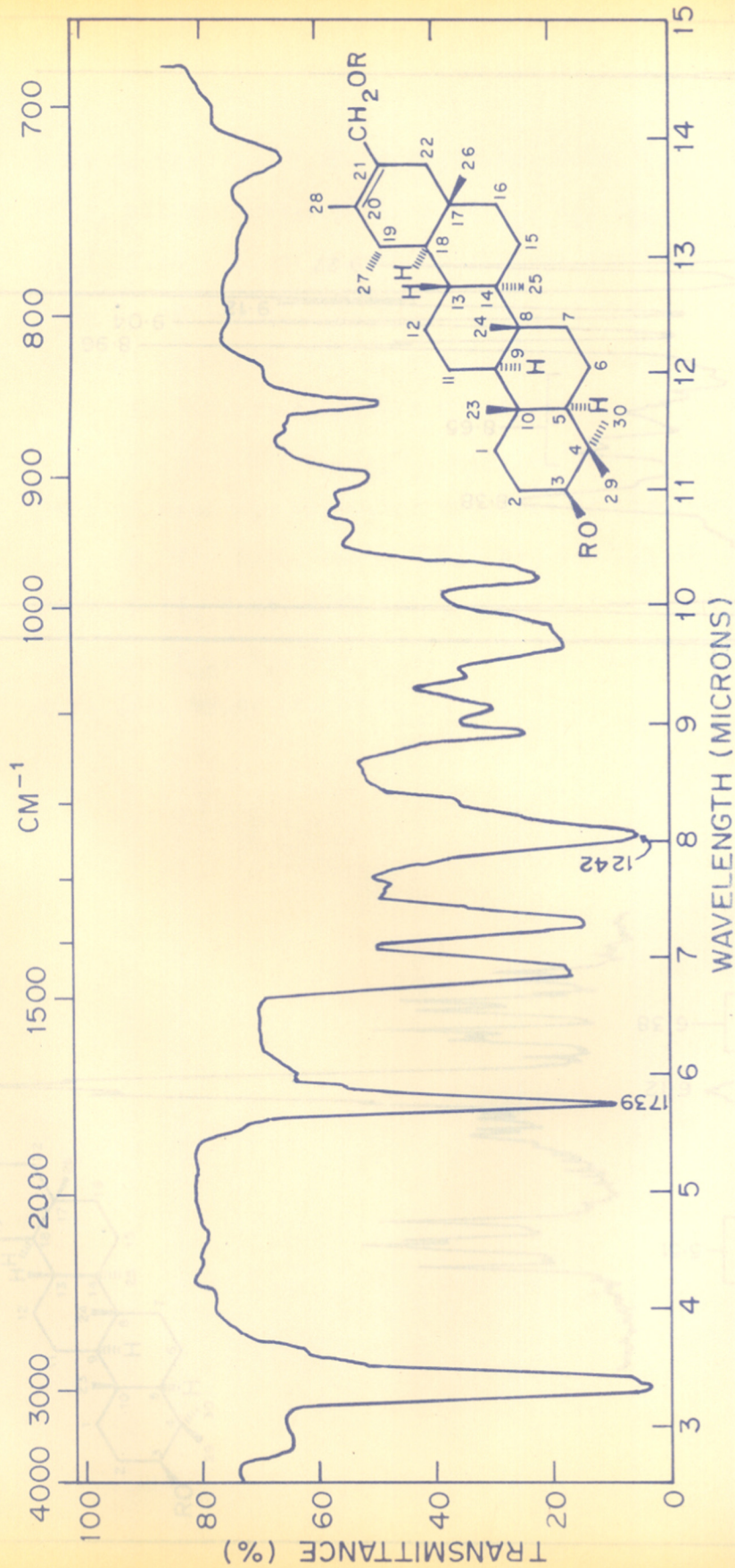


FIG. 4. IR SPECTRUM OF 3β-ACETOXY-21-ACETOXYMETHYL-ψ-TARAXASTENE (IV, R=Ac)

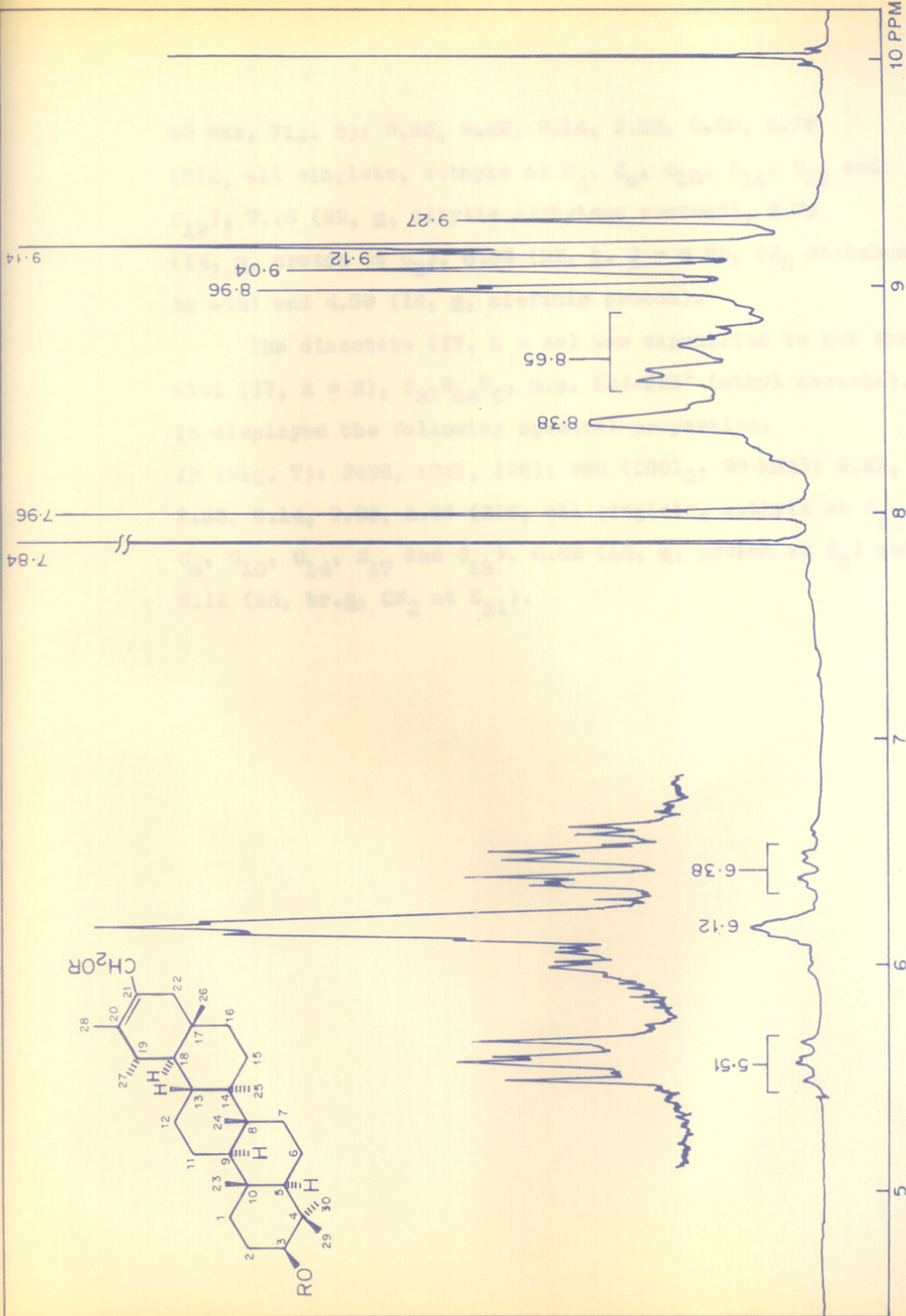


FIG. 5. PMR SPECTRUM OF -

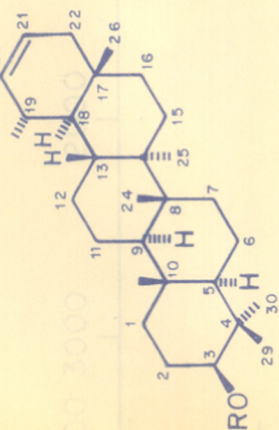
-3 β -ACETOXY-21-ACETOXYMETHYL- ψ -TARAXASTANE (IV, R=Ac)

90 MHz, Fig. 6): 9.26, 9.23, 9.14, 9.03, 9.02, 8.96 (21H, all singlets, methyls at C₄, C₈, C₁₀, C₁₄, C₁₇ and C₁₉), 7.75 (2H, m, allylic methylene protons), 6.78 (1H, m, proton at C₃), 6.33 (2H, t, J = 6 Hz, CH₂ attached to -OH) and 4.59 (1H, m, olefinic proton).

The diacetate (IV, R = Ac) was saponified to get the diol (IV, R = H), C₃₁H₅₂O₂, m.p. 224-225° (ethyl acetate). It displayed the following spectral properties.

IR (Fig. 7): 3436, 1031, (OH); PMR (CDCl₃, 90 MHz): 9.27, 9.26, 9.14, 9.03, 8.95 (21H, all singlets, methyls at C₄, C₈, C₁₀, C₁₄, C₁₇ and C₁₉), 6.82 (1H, m, proton at C₃) and 6.11 (2H, br.s, CH₂ at C₂₁).

CH₂OR



8.96

9.02
9.03

9.23
9.26

9.14

8.47

4.59

6.33 (J=6Hz)

6.78

7.75

5

6

7

8

9

10

PPM (τ)

FIG. 6. PMR SPECTRUM OF -

-3β-HYDROXY-28-HYDROXYMETHYL-ψ-TARAXASTENE (V, R=H)

FIG. 7 IR SPECTRUM OF -3β-HYDROXY-28-HYDROXYMETHYL-ψ-TARAXASTENE (IV, R=H)

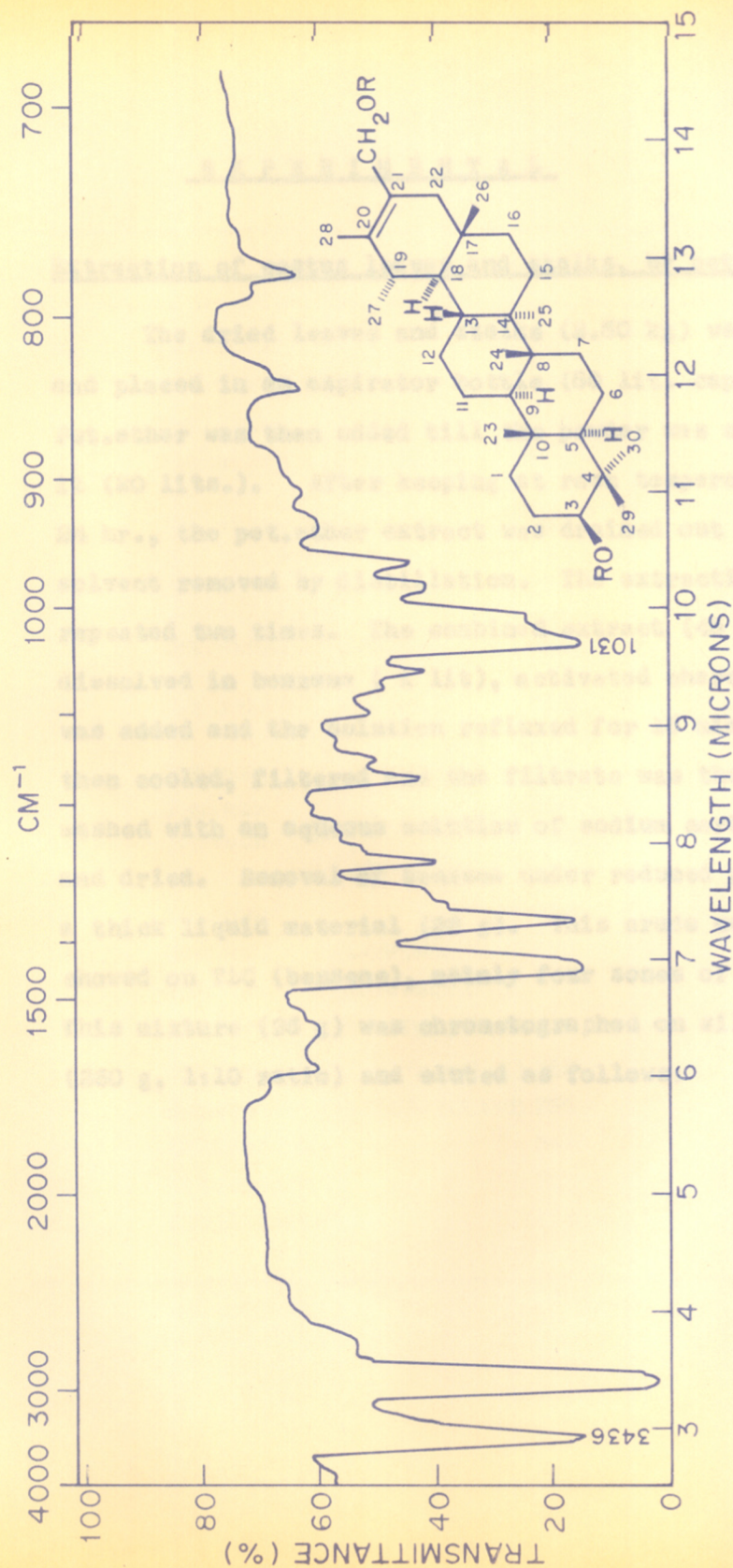


FIG. 7. IR SPECTRUM OF 3β-HYDROXY-21-HYDROXYMETHYL-ψ-TARAXASTENE (IV, R=H)

EXPERIMENTALExtraction of costus leaves and stalks, by pet.ether

The dried leaves and stalks (2.50 kg) were powdered and placed in an aspirator bottle (50 lit. capacity). Pet.ether was then added till the powder was covered with it (20 lits.). After keeping at room temperature for 24 hr., the pet.ether extract was drained out and the solvent removed by distillation. The extraction was repeated two times. The combined extract (45 g) was dissolved in benzene (1 lit), activated charcoal (10 g) was added and the solution refluxed for 15 minutes. It was then cooled, filtered and the filtrate was thoroughly washed with an aqueous solution of sodium carbonate, water and dried. Removal of benzene under reduced pressure gave a thick liquid material (36 g). This crude material showed on TLC (benzene), mainly four zones of mixtures. This mixture (36 g) was chromatographed on silicic acid (360 g, 1:10 ratio) and eluted as follows:

CHROMATOGRAM 1

Fraction	Solvent	Vol.in ml	Material in g
1.	Pet.ether	500	0.758
2.	Pet.ether	500	0.158
3.	Pet.ether	500	0.678
4.	Pet.ether + benzene (3:1)	500	0.415
5.	Pet.ether + benzene (3:1)	500	0.311
6.	Pet.ether + benzene (1:1)	500	0.090
7.	Pet.ether + benzene (1:1)	500	8.750
8.	Pet.ether + benzene (1:1)	500	1.263
9.	Benzene	500	0.545
10.	Benzene	500	3.855
11.	Benzene	250	1.505
12.	Benzene	250	1.364
13.	Benzene	256	0.310
14.	Benzene + chloroform (3:1)	250	0.368
15.	Benzene + chloroform(3:1)	250	0.120
16.	Benzene + chloroform(1:1)	250	0.181
17.	Benzene + chloroform(1:1)	250	0.116
18.	Benzene + chloroform(1:1)	250	0.105
19.	Chloroform	500	0.265
20.	Chloroform	500	1.093
21.	Ethyl acetate	1000	8.543

Fraction 1 showed a single spot in TLC analysis [pet.ether + benzene (1:1)]. Analytical and spectral data showed that it is a straight chain hydrocarbon, m.p. 63-64°. From the m.p., it appears to be C₂₉-hydrocarbon viz., nonacosane (C₂₉H₆₀).

Fractions 2 to 5 showed a mixture and were not examined further.

Fraction 6 showed a single spot in TLC analysis (benzene). It melted at 58-59°. Being in small quantity, it was not examined further. The IR spectrum showed it to be an ester.

Fractions 7 to 9 were found to be a mixture of three compounds [TLC, SiO₂ + 10% AgNO₃, pet.ether + benzene (1:1), 3 spots] and were found to be mixtures of esters of higher fatty acids. By comparative TLC, they were identified as α-amyrin stearate (XII), β-amyrin palmitate (XIII) and lupeol palmitate (XIV), which have been already isolated from the same source. Fractions 10 to 18 (TLC similar, single spot) were mixed together and the solvent evaporated to get a solid which, on repeated crystallisation from pet.ether + ethyl acetate gave a crystalline solid, m.p. 249-250°, (α)_D²⁵ + 99° (g, 1.30). This was identified as taraxasteryl acetate (I, R = Ac) by m.p. and superimposable IR and PMR spectra. [Lit.²⁴ records for taraxasteryl acetate (I, R = Ac) m.p. 256-257° and (α)_D²⁸ + 100°].

Analysis

Found: C, 81.73; H, 11.02;

$C_{32}H_{52}O_2$ requires C, 81.99; H, 11.18%.

IR bands at: 2778, 1724, 1639, 1449, 1370, 1241, 1010, 976 and 883 cm^{-1} .

Prins reaction on taraxasteryl acetate (I, R = Ac)

In a 100 ml round bottom flask, paraformaldehyde (3 g), glacial acetic acid (50 ml) and taraxasteryl acetate (I, R = Ac, 1.50 g) were taken and the reaction mixture was refluxed at 120-130° for 72 hr. After the reaction was complete, most of the acetic acid was removed by distillation. The residue was then diluted with water (200 ml) and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water (50 ml x 2) and dried. Evaporation of chloroform afforded a crude liquid mixture of products (1.60 g), as detected by TLC (10% ethyl acetate in benzene, mainly 4 spots). The crude product (1.60 g) was chromatographed on silicic acid (24 g, 1:15 ratio) and eluted as follows:

CHROMATOGRAM - 2

Fraction	Solvent	Vol. in ml	Material in g
1.	Pet.ether	100	0.121
2.	Pet.ether + benzene(10:1)	100	0.090
3.	Pet.ether + benzene (4:1)	100	0.356
4.	Pet.ether + benzene (4:1)	100	0.223
5.	Pet.ether + benzene (4:1)	100	0.193
6.	Benzene	100	0.154
7.	Benzene + chloroform (1:1)	100	0.178
8.	Chloroform	100	0.153

Fractions 1 and 2 of chromatogram 2 showed a single spot in TLC analysis (8% ethyl acetate in benzene) which corresponded to the least polar of the spots in the original mixture. They were mixed together and the solvent distilled to give a solid (0.221 g) which was further purified by crystallisation with ethyl acetate to afford the ψ -taraxasteryl acetate (VI), m.p.223-224°.

Analysis

Found: C, 81.82; H, 11.12;

$C_{32}H_{52}O_2$ requires C, 81.99; H, 11.18%.

IR bands at: 1735, 1460, 1380, 1245, 1150, 1135, 1100, 1020, 1000, 990, 970, 950, 900, 810 and 775 cm^{-1} .

Fractions 7 and 8 of chromatogram 2 showed a single spot on TLC (12% ethyl acetate in benzene) which corresponded to the more polar of the spots in the original mixture. Hence, these fractions were mixed together and the solvent evaporated to get the solid (0.331 g) which was further purified by crystallisation with methanol to furnish the triacetate (II), m.p.132-133°.

Analysis

Found: C, 73.77; H, 9.96;

$C_{37}H_{60}O_6$ requires C, 73.96; H, 10.07%.

IR bands at: 3012, 1742, 1449, 1370, 1235, 1111, 1020, and 976 cm^{-1} .

Fractions 3 to 6 of chromatogram 2 showed a mixture of two components in TLC analysis (TLC on $SiO_2 + AgNO_3$ plate, 12% ethyl acetate in benzene). These fractions were mixed together and the solvent evaporated to get a mixture of two products (0.90 g). This mixture (0.90 g) was chromatographed on silica gel impregnated with silver nitrate (18 g, 1:20 ratio) and eluted as follows:

CHROMATOGRAM 3

Fraction	Solvent	Vol. in ml	Material in g
1.	Pet.ether + benzene (5:1)	100	0.181
2.	Pet.ether + benzene (5:1)	100	0.113
3.	Pet.ether + benzene (4:1)	100	0.121
4.	Pet.ether + benzene (4:1)	100	0.052
5.	Pet.ether + benzene (1:1)	100	0.153
6.	Benzene	100	0.136
7.	Chloroform	100	0.090

Fractions 1 to 3 of chromatogram 3 showed a single spot in TLC analysis (TLC on $\text{SiO}_2 + \text{AgNO}_3$ plate, 10% ethyl acetate in benzene). These fractions were mixed together and the solvent evaporated to get a solid diacetate (0.42 g) which was further purified by crystallisation with methanol to afford pure diacetate (V, R = Ac), m.p. 170-171°.

Analysis

Found: C, 77.62; H, 10.27;

$\text{C}_{35}\text{H}_{56}\text{O}_4$ requires C, 77.73; H, 10.44%.

IR bands at: 2985, 1732, 1449, 1370, 1235, 1026, 976 and 893 cm^{-1} .

Fractions 4 and 5 of chromatogram 3 showed a mixture of two components and were not separated further.

Fractions 6 and 7 of chromatogram 3 showed a single spot in TLC analysis. (TLC on $\text{SiO}_2 + 10\% \text{AgNO}_3$ plate, 10% ethyl acetate in benzene). These fractions were mixed together to get a solid diacetate (0.22 g) which was further purified by crystallisation with ethyl acetate to furnish pure diacetate (IV, R = Ac), m.p. 209-210°.

Analysis

Found: C, 77.59; H, 10.32;

$\text{C}_{25}\text{H}_{56}\text{O}_4$ requires C, 77.73; H, 10.44%.

IR bands at: 3012, 1732, 1449, 1370, 1242, 1124, 1099, 1064, 1031, 976, 901, 851 and 725 cm^{-1} .

Saponification of the diacetate (IV, R = Ac)

To a solution of the diacetate (IV, R = Ac, 0.20 g) in benzene (15 ml), potassium hydroxide (1 g dissolved in 30 ml of methanol) was added. The reaction mixture was refluxed on a water bath for 8 hr. After distillation of the benzene and alcohol, the reaction mixture was diluted with water and extracted thrice with chloroform (25 ml x 3). The chloroform layer was washed with water and dried. Removal of chloroform gave a solid (0.16 g) which was purified by crystallisation with ethyl acetate to give the TLC pure diol (IV, R = H), m.p. 224-225°.

Analysis

Found: C, 81.37; H, 11.38;

$C_{31}H_{52}O_2$ requires C, 81.52; H, 11.48%.

IR bands at: 3436, 2941, 1447, 1366, 1282, 1174, 1149, 1099, 1058, 1031, 980, 962, 842 and 778 cm^{-1} .

Saponification of the diacetate (V, R = Ac)

To a solution of the diacetate (V, R = Ac, 0.30 g) in benzene (25 ml), potassium hydroxide (1.20 g dissolved in 50 ml of methanol) was added. The homogeneous solution thus obtained was refluxed on a water bath for 8 hr. Most of the methanol and benzene were removed by distillation. The reaction mixture was then diluted with water (100 ml) and extracted with chloroform (50 ml + 25 ml x 2). The chloroform layer was thoroughly washed with water and dried. Removal of chloroform furnished a solid (0.24 g) which was purified by crystallisation with ethyl acetate to afford TLC pure diol (V, R = H), m.p. 220-221°.

Analysis

Found: C, 81.29; H, 11.27;

$C_{31}H_{52}O_2$ requires C, 81.52; H, 11.48%.

IR bands at: 3571, 2985, 1653, 1453, 1379, 1282, 1174, 1087, 1036, 966 and 849 cm^{-1} .

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