ISOLATION AND TRANSFORMATION OF NATURALLY OCCURRING TERPENES

A THESIS

SUBMITTED TO

THE UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

BUVAJI MANIKRAO MANE

M. Sc.

DIVISION OF ORGANIC SYNTHESIS

NATIONAL CHEMICAL LABORATORY

POONA - 411 008 (INDIA)

1980

ACKNOWLEDGEMENT

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

I am grateful to Mr. P.P. Pai, Dr. K.G. Gore, Dr. G.D. Joshi, Dr. S.V. Hiremath and Dr. S.P. Pathak for their generous help and cheerful co-operation.

The services of the co-workers from microanalysis and spectroscopy sections are gratefully acknowledged.

I am greatly indebted to the University Grants Commission, New Delhi, for the award of Teacher Fellowship and also to the Principal, Fergusson College, Poona, for granting me leave for carrying out this work.

I am very grateful to the Director, National Chemical Laboratory, Poona, for permitting me to carry out this work in this Laboratory.

(B. M. MANE)

National Chemical Laboratory
Poona 411 008

22nd July 1980

C O N T E N T S

GENERAL INTRODUCTION

GENERAL INTRODUCTION

The study of natural products, derived from the Plant Kingdom, formsan 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 sub-continent 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 modern physical methods for structure determination may be attributed to this phenomenal progress achieved during the last few years. The advent of gas-liquid, high pressure liquid and thin-layer 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 revolutionized 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 determination. A brief summary of the present work is described below.

The research work carried out under the title "Isolation and Transformation of naturally occurring terpenes" deals with three main aspects viz.

1) Conversion of (+)car-3-ene into methyl (+)cis chrysanthemate and its 3-substituted vinyl analogues possessing 1R or 1S configuration.

2) Transformations of terpenes like car-3-ene and saussurealactone, the latter being obtained from the naturally occurring costunolide and

3) Isolation and characterisation of some polar compounds obtained from the hexane extract of the plant Artemisia brevifolia, a plant from the Compositae family, and of North Indian origin.

Many plants are known to possess insecticidal property. Amongst them, the prominent one is Chrysanthemum cinerariaefolium[1] (Compositae family). The insecticidal property of this plant has been known from ancient times. Detailed chemical examination of the constituents of C. cinerariaefolium showed[2,3,4] that the insecticidal property associated with this 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 page 24]. These compounds are the esters of (+)trans chrysanthemic acid and (+)trans pyrethric acid[2]. Later on, many esters of (+)trans chrysanthemic acid have been prepared and found to possess insecticidal property. It has also been found[5] 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

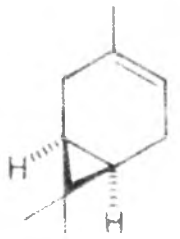
this class of "Pest Control Agents" is becoming very popular all over the world, inspite of its high cost.

Though many methods for the preparation of chrysanthemic acid[6,7] are reported most of them lack the selectivity and 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 *trans*[8] and (+)1R *cis*[9] chrysanthemic acids from naturally occurring compounds, mainly from (+)car-3-ene.

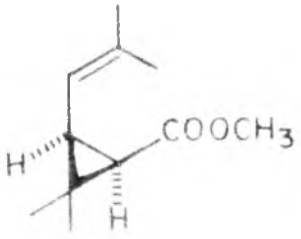
(+)Car-3-ene, a monoterpene, is an abundantly occurring cheap indigenous material and is mainly considered as a by-product of Pine Oil (*Pinus longifolia*). Efforts have been already made to put this by-product to good uses, for example, by converting it into (+)*trans* chrysanthemic acid[10], a component 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.

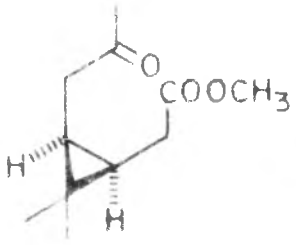
CHAPTER I describes the work regarding the preparation of (II). The keto ester (III) obtainable from (I), in good yields was converted to the ethylene ketal ester (IV)



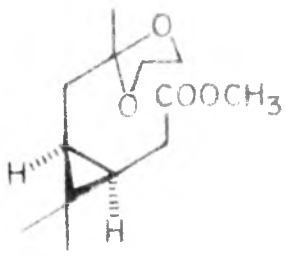
I



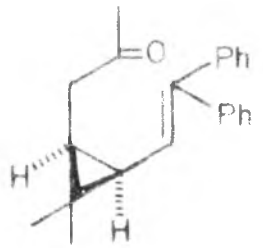
II



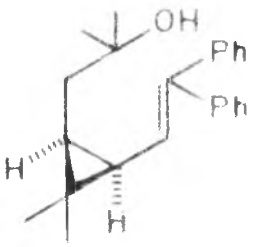
III



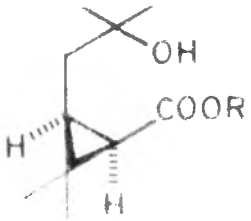
IV



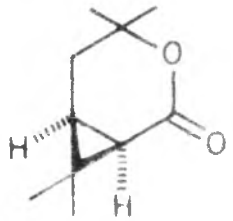
V



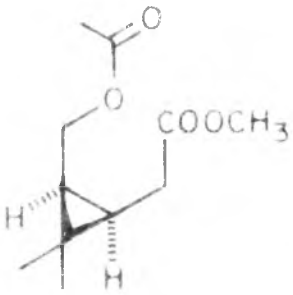
VI



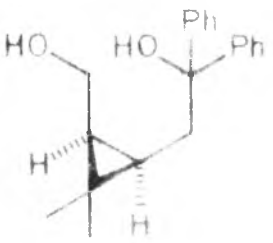
VII



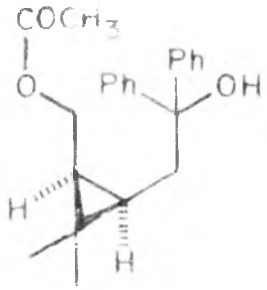
VIII



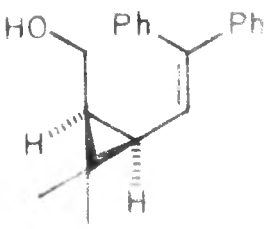
IX



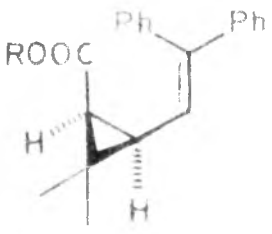
X



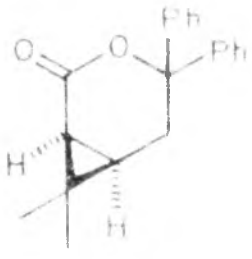
XI



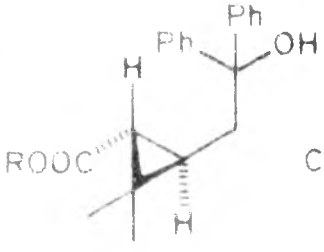
XII



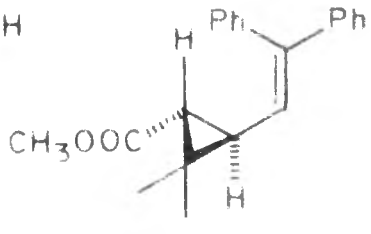
XIII



XIV



XV



XVI

which, on Grignard reaction with phenyl magnesium bromide followed by deketalisation and dehydration afforded the unsaturated ketone (V). Action of methyl magnesium iodide on (V) gave the alcohol (VI). The unsaturated alcohol (VI), on ozonolysis followed by oxidative decomposition of the resulting ozonide gave hydroxy acid (VII, R=H) and (+)dihydro chrysanthemolactone (VIII). The latter could be converted to hydroxy acid (VII, R=H) by saponification. Treatment of ester (VII, R=CH_3) with paratoluene sulphonic acid afforded the desired ester[11] (II).

Synthetic pyrethroids (biologically active chrysanthemates and modified cyclopropane carboxylic acid esters of various alcohols), related to natural pyrethrins and cinerins are increasingly becoming important as ideal "Pest Control Agents" for they possess high insecticidal activity, low mammalian toxicity and higher photostability[12]. Chemically, they are the esters of 2,2-dimethyl-3-vinyl substituted cyclopropane carboxylic acids with alcohols like 3-phenoxy benzyl alcohol[13] or 5-benzyl-3-furyl methyl alcohol. A number of such esters with different 3-vinyl substituted side chains have been prepared[14] and found to be active insecticides, prominent among them being permethrin and cypermethrin. With a view to synthesise some more new pyrethroids, we have synthesised three new acid moieties from (+)car-3-ene. These are (1) methyl 1<u>R</u> <u>cis</u> and methyl

1R trans 2,2-dimethyl-3(2,2-diphenyl vinyl)-cyclopropane carboxylates. (2) Methyl 1R cis 2,2-dimethyl-3(2-phenyl prop-1-enyl)-cyclopropane carboxylate and (3) methyl 1R cis 2,2-dimethyl-3(2-phenyl-2-chloro-vinyl)-cyclopropane carboxylate.

CHAPTERS II-A and II-B describe the work regarding the preparation of these three new acid moieties.

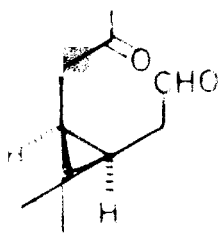
For the preparation of acids containing 2,2-diphenyl vinyl side chain at 3-position of cyclopropane, car-3-ene (I) was converted to the known[10] acetate ester (IX), via. the keto ester (III). Grignard reaction using phenyl magnesium bromide (5 moles) on acetate ester (IX) afforded, mainly, the diol (X) which on acetylation (Ac_2O/Py) gave the hydroxy monoacetate (XI). Dehydration of hydroxy monoacetate (XI), followed by hydrolysis gave the unsaturated alcohol (XII). Jones chromic acid oxidation of the alcohol (XII) afforded the cis acid (XIII, R=H) which was characterised through its methyl ester as the methyl 1R cis 2,2-dimethyl-3(2,2-diphenyl vinyl)cyclopropane carboxylate (XIII, R=CH_3).

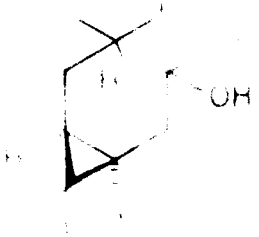
The diol (X), on oxidation with Jones chromic acid, gave exclusively the lactone (XIV) which, on hydrolysis with sodium hydroxide afforded the trans hydroxy acid (XV, R=H), characterised through its methyl ester (XV, R=CH_3). Acid catalysed dehydration of (XV, R=CH_3) gave the methyl

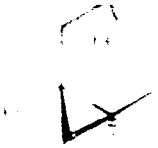
1R trans 2,2-dimethyl-3(2,2-diphenyl vinyl)-cyclopropane carboxylate (XVI). This work is dealt with in Chapter II-A of this thesis.

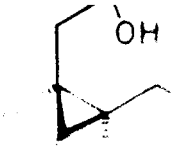
The ketoaldehyde[15] (XVII), obtainable from (+)car-3-ene (I), on treatment with phenyl magnesium bromide gave the diastereomeric mixture of diols of structure (XVIII). This diol (XVIII) was used to prepare two new cyclopropane carboxylic acids. For the preparation of methyl 1R cis 2,2-dimethyl-3(2-phenyl-prop-1-enyl)-cyclopropane carboxylate (XXIII), the diol (XVIII) was oxidised with Jones chromic acid to furnish the keto alcohol (XIX) which, on Baeyer-Villiger oxidation using perbenzoic acid followed by saponification of the resulting benzoate gave the diol (XX). Jones chromic acid oxidation of the diol (XX) afforded both, the lactone (XXI) and hydroxy acid (XXII, R=H). The latter could also be obtained from the lactone (XXI) by saponification. The acid (XXII, R=H) was characterised through its methyl ester (XXII, R=CH_3). Prolonged treatment of the hydroxy ester (XXII, R=CH_3) with PTS afforded the methyl 1R cis 2,2-dimethyl-3(2-phenyl-prop-1-enyl)cyclopropane carboxylate (XXIII) as a single double bond geometric isomer.

For the preparation of Methyl 1R cis-2,2-dimethyl-3(2-phenyl-2-chloro-vinyl) cyclopropane carboxylate (XXVI),

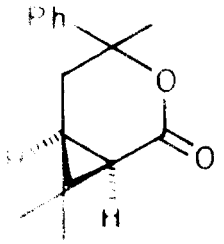


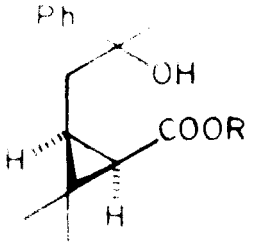


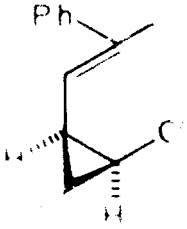


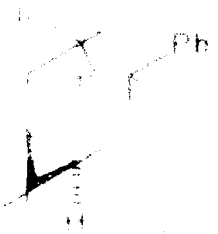


XX

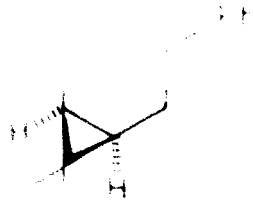


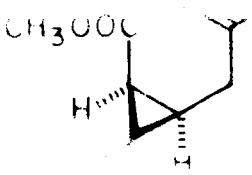






XXII



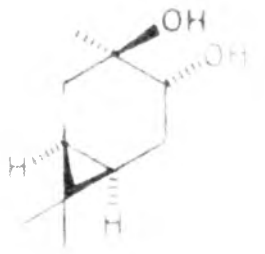


the diol (XXIII) was acetylated to give hydroxy acetate (XXIV). Dehydration of the acetate (XXIV) followed by oxidation of the resulting unsaturated acetate with potassium permanganate afforded the acetate acid, the methyl ester of which could be converted to hydroxy ester (XXV) by treatment with silica gel. Jones chromic acid oxidation of hydroxy ester (XXV) gave the keto ester (XXVI) which, on treatment with PCl_5 afforded the methyl 1S-cis-2,2-dimethyl-3(2-phenyl-2-chloro-vinyl)cyclopropane carboxylate (XXVII).

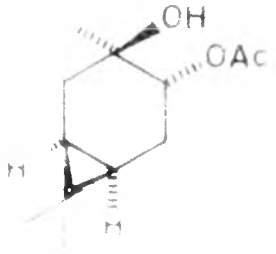
These syntheses are described in Chapter II-B of the thesis.

As already mentioned, (+)car-3-ene is an abundantly occurring bicyclic monoterpene hydrocarbon. This hydrocarbon is known to undergo a variety of reactions, such as Friedel-Crafts[16] type acylation, Prins reaction[16], epoxidation[17] etc. and the stereochemistry of these reactions have been studied extensively. Similarly, the other two double bond isomers of car-3-ene viz. car-2-ene and car-4-ene have been subjected to a variety of reactions[16,18,19]. However, the carene derivatives, possessing an exo double bond, like car-3(10)-ene have not been studied much, though their perfumery properties are known[20].

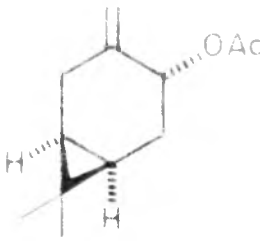
We have now prepared a 4-substituted car-3(10)-ene and tried to establish the stereochemistry of its epoxidation



XXVIII

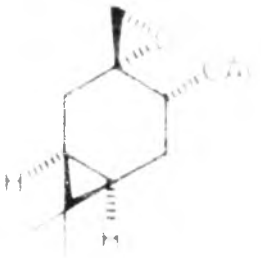


XXIX

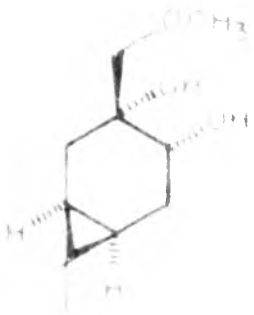


XXX

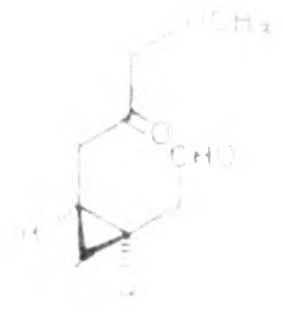
XXXI



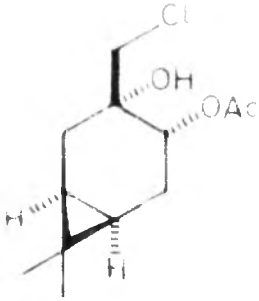
XXXII



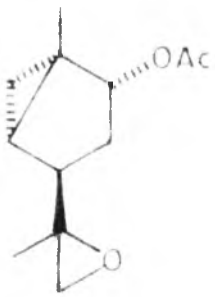
XXXIII



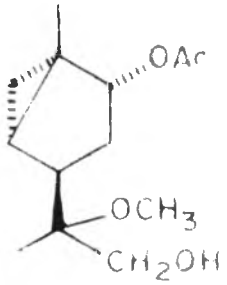
XXXIV



XXXV



XXXVI



XXXVII

reaction and carried out some transformations of the resulting epoxide.

The hydroxy monoacetate (XXIX) obtainable from car-3-ene(I) via the diol (XXVIII) gave, on treatment with $POCl_3$/Py, two unsaturated acetates[21] (XXX) and (XXXI). They have been separated by column chromatography. Epoxidation of the acetate (XXX) gave an epoxide (XXXII) which on LAH reduction gave the known cis carane 3α,4α diol, proving the stereochemistry of the epoxide (XXXII) to be α. Epoxide (XXXII) on treatment with methanolic alkali afforded the triol monomethyl ether (XXXIII) which was cleaved to give keto-aldehyde (XXXIV) by sodium meta-periodate. Treatment of the epoxide (XXXII) with $ZnCl_2$ or methanolic hydrochloric acid afforded chlorohydrin acetate (XXXV) as the main product. The epoxide (XXXVI) of the other acetate (XXXI) gave the normal expected product viz. (XXXVII), when treated with methanolic hydrochloric acid.

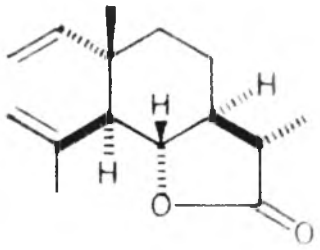
This work is described in Chapter III of the thesis.

Saussurea lactone (XXXVIII) is a monocyclic di-ethenoid sesquiterpene lactone, obtained by the thermal rearrangement of solid dihydrocostunolide[22], the latter being obtained from the naturally occurring costunolide, isolated from the pet. ether extract of the roots of Saussurea lappa, Clarke.

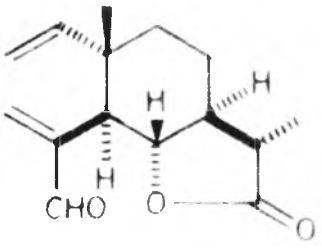
Many interesting reactions of this lactone including epoxidation[23], its conversion to naturally occurring ketone, shyobunone[24] (from Acorus calamus L.) have been already carried out. We have now subjected this lactone (XXXVIII) to oxidation with selenium dioxide. Saussurea lactone (XXXVIII), when oxidised with selenium dioxide, afforded the products, from which, in addition to the normally expected compounds like (XXXIX) and (XL), a crystalline dialdehydo lactone (XLI) is also obtained. This compound (XLI) is probably obtained by the reversible Cope rearrangement of the initially formed lactone (XXXIX), followed by further allylic oxidation. This matter is described in Chapter IV of the thesis.

Artemisia maritima (also known as Artemisia brevifolia)[25] is a plant belonging to the Compositae family. Many species of this plant, grown in different parts of the world, have been examined[25]. This plant is known to contain many sesquiterpenic lactones, santonin being one of the most important constituents[25].

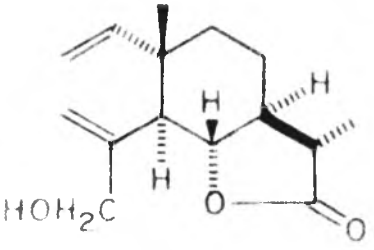
We have now examined the hexane extract of this plant, grown in Kashmir, India, and isolated for the first time, from this species, three known compounds viz. artabsin (XLII), cycloart-23-ene-3β,25 diol (XLIII) and β-sitosterol. The structures assigned to these compounds



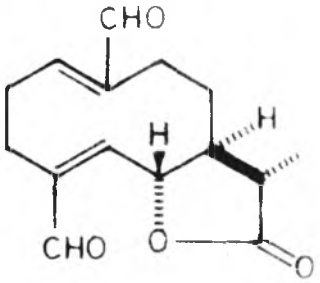
XXXVIII



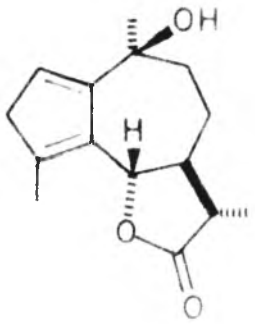
XXXIX



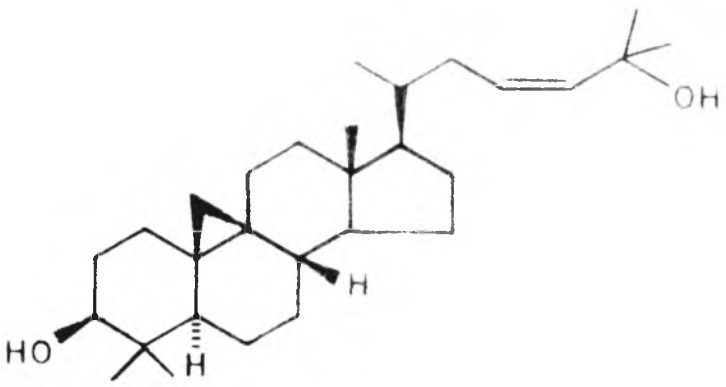
XXXX



XXXXI



XXXXII



XXXXIII

are based on the comparison of their spectral data and physical constants with those reported in literature[28,26,27].

The isolation and characterisation of these compounds are dealt with in Chapter V of the thesis.

During the course of these investigations liberal use of modern techniques such as infrared, ultraviolet, nuclear magnetic resonance and mass spectroscopy and thin layer chromatography has been made. For the isolation of the compounds, column chromatographic techniques using adsorbants like alumina, silica gel and silica gel impregnated with silver nitrate is employed. However, due to the nonavailability 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 of which special mention 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 E.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.

REFERENCES

1 C.B. Gnadinger, "Pyrethrin Flowers", 2nd Ed. McLaughlin Gormley King Co., Minneapolis, Minn. 1936.

2 H. Staudinger and L. Ruzicka, Helv. Chim. Acta 7, 177 (1924).

3 F.B. LaForge and W.F. Barthel, J. Org. Chem. 9, 242 (1944).

4 P.J. Godin, R.J. Sleeman, M. Snarey and E.M. Thain, Chem. and Ind. 371 (1964).

5 M. Elliott, A.W. Farnham, N.F. Jones, P.H. Needham and D.A. Pulman, ACS Symposium Series 2, 80 (1974) and references therein.

6 I.G.M. Campbell and S.H. Harper, J. Chem. Soc. 283 (1945).

7 E.J. Corey and J.M. Jantalat, J. Am. Chem. Soc., 89, 3912 (1967).

8 M. Matsui, H. Yoshioka, H. Sakamoto, Y. Yamada and T. Kitahara, Agr. Biol. Chem. 31, 33 (1967).

9 M. Matsui, H. Yoshioka, Y. Yamada, H. Sakamoto and T. Kitahara, Agr. Biol. Chem. 29, 784 (1965).

10 R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974).

11 W. Cocker, H. St.J. Lauder and P.V.R. Shannon, J. Chem. Soc. Perkin Trans I, 332 (1975).

12 M. Elliott, A.W. Farnham, N.F. Jones, P.H. Needham, D.A. Pulman and J.H. Stevenson, Nature 246, 169 (1973).

13 M. Elliott, Bull. Wld. Hlth. Org. 44, 315 (1971).

14 M. Elliott, A.W. Farnham, N.F. Jones, P.H. Needham and D.A. Pulman, Nature 244, 456 (1973).

15 A.S. Khanra and R.B. Mitra, Indian J. Chem. 14B, 716 (1976).

16 P.J. Kropp, D.C. Heckert and T.J. Flautt, Tetrahedron 24, 1385 (1968).

17 V.S. Joshi, N.P. Damodaran and Sukh Dev, Tetrahedron 27, 475 (1971).

18 G. Ohloff and W. Giersch, Helv. Chim. Acta 51, 1328 (1968).

19 R.K. Razdan and G.W. Hendrick, J. Am. Chem. Soc., 92 6061 (1970).

20 P.J. Kropp, U.S. Patent 3510,510, 5th May 1970; Chem. Abstr. 73, 15039[4].

21 P.J. Kropp, J. Am. Chem. Soc. 88, 4926 (1966).

22 A.S. Rao, A. Paul, Sadgopal and S.C. Bhattacharyya, Tetrahedron 13, 319 (1961).

23 N.S. Bankar and G.H. Kulkarni, Ind. J. Chem. 13, 744 (1975).

24 A.D. Nagh, S.K. Paknikar and S.C. Bhattacharyya, Tetrahedron 20, 2647 (1964).

25 R.G. Kelsey and F. Shafizadeh, Phytochemistry 18, 1591 (1979).

26 K. Vokac, Z. Samek, V. Herout and F. Sorm, Coll. Czech. Chem. Commun. 34, 2288 (1969).

27 J.L. Fourrey, J. Rondest and J. Polonsky, Tetrahedron 26, 3839 (1970).

28 C. Djerassi and R. McCrindle, J. Chem. Soc., 4034 (1962).

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 taken 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 NMR spectra were taken in carbon-tetrachloride 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, ethylacetate 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 H_2SO_4.

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 <u>except</u> in the case of <u>chapter II-A</u>, wherein the references of both chapters, II-A and II-B are given at the end of the chapter II-B.

12 Unless otherwise stated, all solutions were dried over anhydrous sodium sulphate.

13 Unless otherwise stated, all b.ps refer to the vapour 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 NMR signals, the abbreviations br.s, br.d and br.m means broad singlet, broad doublet and broad multiplet respectively.

17 Infrared bands are expressed in frequency $\bar{\nu}$= 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 (+) DIHYDROCHRYSANTHEMOLACTONE AND METHYL (+) CIS CHRYSANTHEMATE

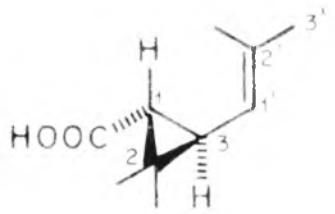
SUMMARY

The trans carane diol (II), obtainable from car-3-ene (I), on oxidation with Jones chromic acid, gave the keto acid which, on esterification ($MeOH/H^+$) afforded the keto ester (IV). Treatment of keto ester (IV) with ethylene glycol and paratoluene sulphonic acid (P.T.S.) gave the ketal ester (V). Grignard reaction on ketal ester (V), using phenyl magnesium bromide gave a solid ketal alcohol (VI) which, on treatment with PTS, furnished the unsaturated ketone (VII). Treatment of methyl magnesium iodide on the ketone (VII) afforded the unsaturated alcohol (VIII). Ozonolysis of the alcohol (VIII), followed by oxidative decomposition of the resulting ozonide by Jones chromic acid, gave a mixture of hydroxy acid (XI) and (+)dihydrochrysanthemolactone (IX). Dehydration of the hydroxy methyl ester (X) with P.T.S. afforded methyl 1R (+) cis chrysanthemate (XII) as the only product, while with $POCl_3/Py$ it ended up with the formation of a mixture of methyl (+) cis chrysanthemate (XII) and double bond isomeric ester (XIII), separated by chromatography.

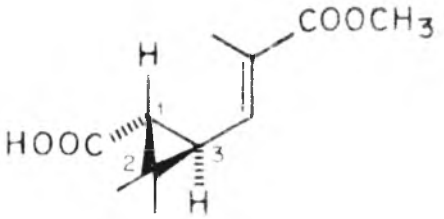
INTRODUCTION

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 Gnadinger[1] and Shepard[2].

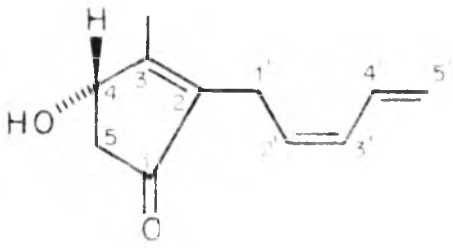
The insecticidal principles in pyrethrum are called "Pyrethrins" and for a long time have been considered harmless to mammals and plants while very toxic to insects. Today they are becoming increasingly important as insect control agents because they possess a unique combination of desirable properties 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 photoinstability.



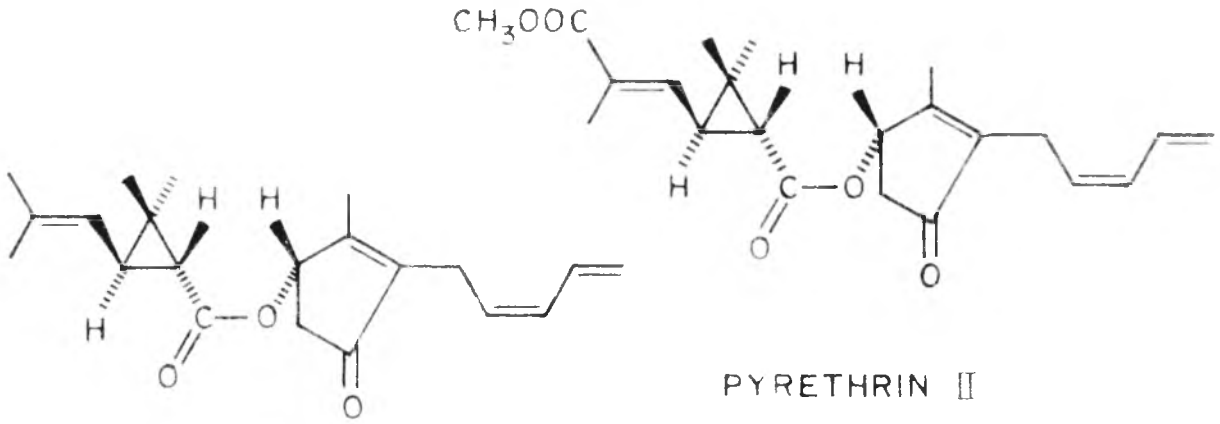
1R (+) TRANS CHRYSANTHEMIC ACID



1R (+) TRANS PYRETHRIC ACID

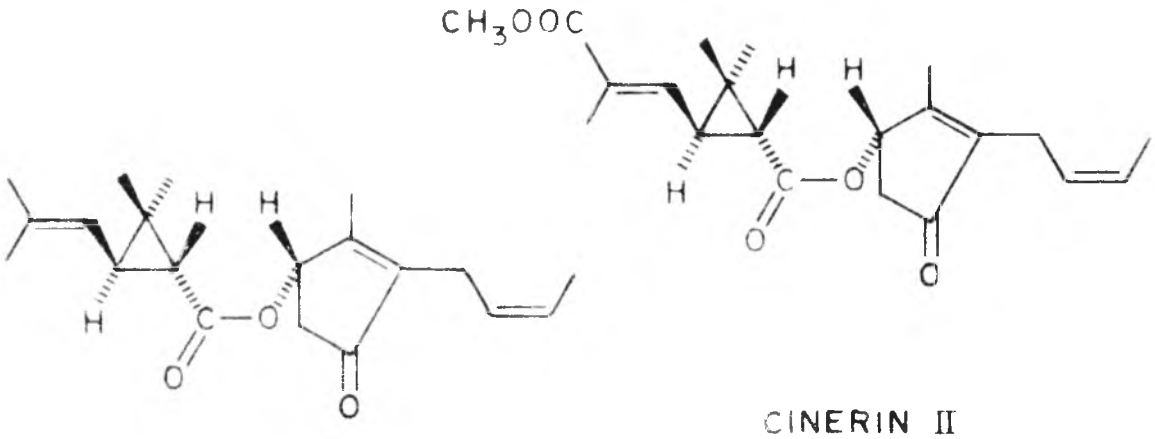


(+) PYRETHROLONE



PYRETHRIN I

PYRETHRIN II

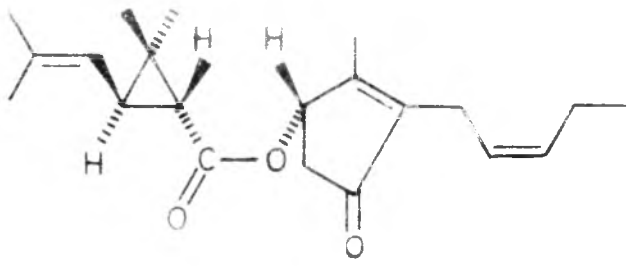


CINERIN I

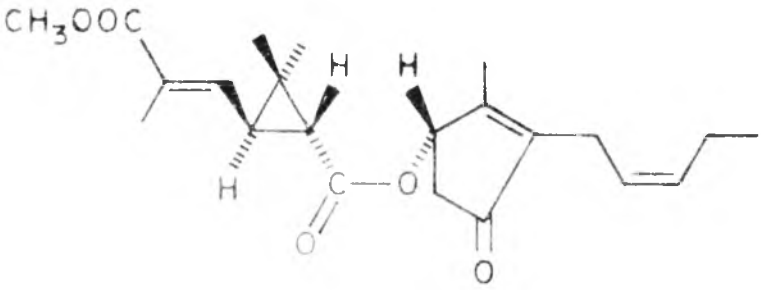
CINERIN II

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 Ruzicka[3], 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 II[4], 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 six 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 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.

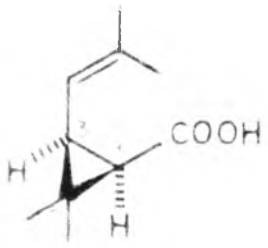
Thus, the monoterpene trans-chrysanthemic acid viz.,



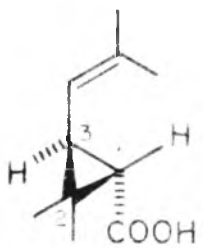
JASMOLIN I



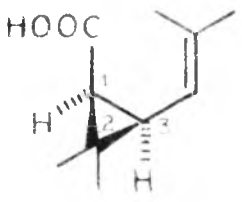
JASMOLIN II



1R (+) CIS CHRYSANTHEMIC ACID



1S (−) TRANS CHRYSANTHEMIC ACID



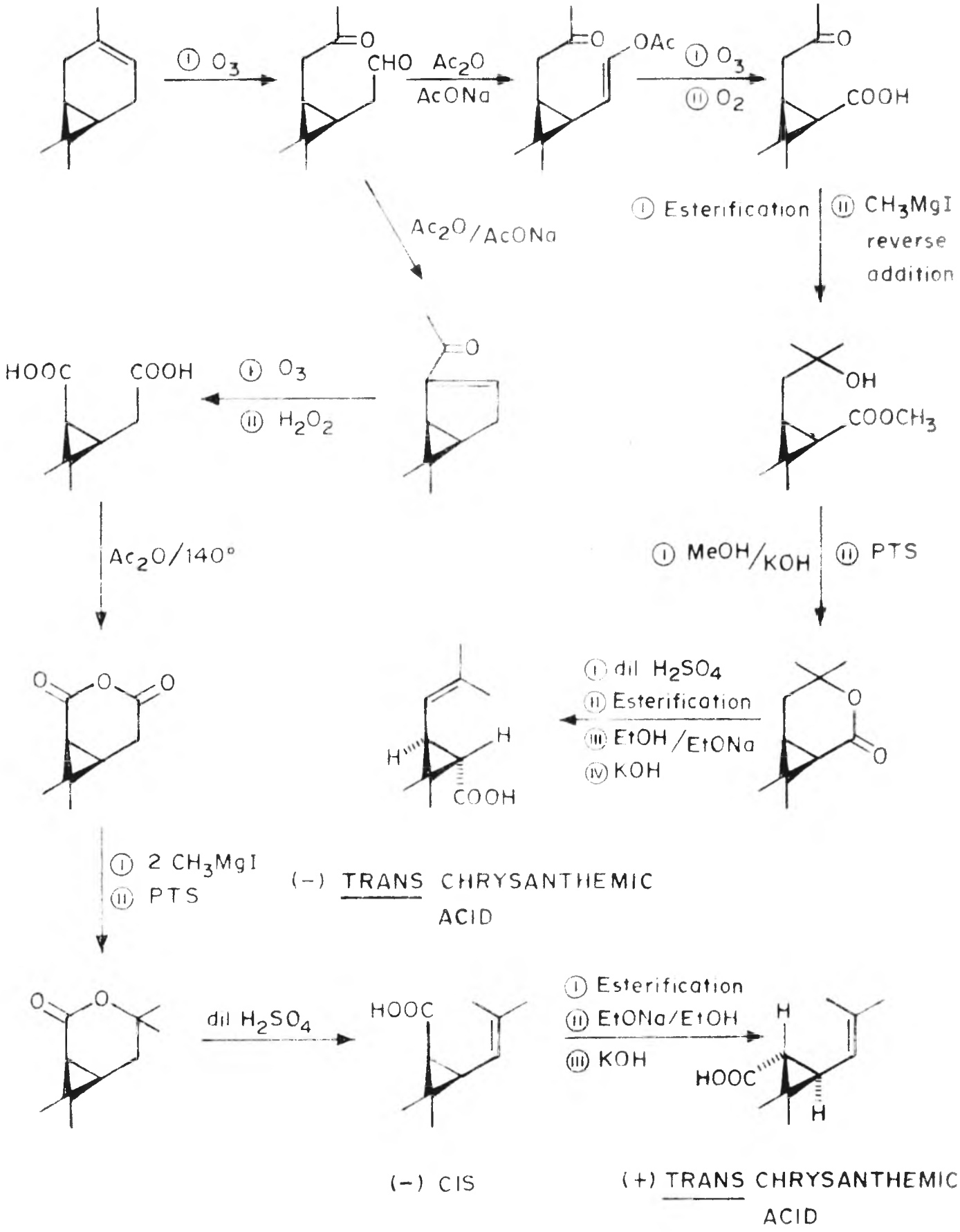
1S (−) CIS CHRYSANTHEMIC ACID

[2,2-dimethyl-3 (2-methyl prop-1-enyl) cyclopropane carboxylic acid] 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 gemdimethyl 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 acids 1R cis esters are found to be more active than the corresponding 1R trans[10] isomers.

A number of ingenious syntheses of the racemic chrysanthemic acids[11-18] and also of the (+)trans acid[14,19] are on record, so also their resolution forms the subject

SCHEME I


① O_3
CHO
Ac_2O
AcONa
OAc
① O_3
② O_2
COOH
Ac_2O/AcONa
① Esterification
② CH_3MgI
reverse
addition
HOOC
COOH
① O_3
② H_2O_2
OH
$COOCH_3$
Ac_2O/140°
① MeOH/KOH
② PTS
① dil H_2SO_4
② Esterification
③ EtOH/EtONa
④ KOH
H
COOH
① 2 CH_3MgI
② PTS
(−) TRANS CHRYSANTHEMIC
ACID
dil H_2SO_4
HOOC
① Esterification
② EtONa/EtOH
③ KOH
HOOC
(−) CIS
(+) TRANS CHRYSANTHEMIC
ACID

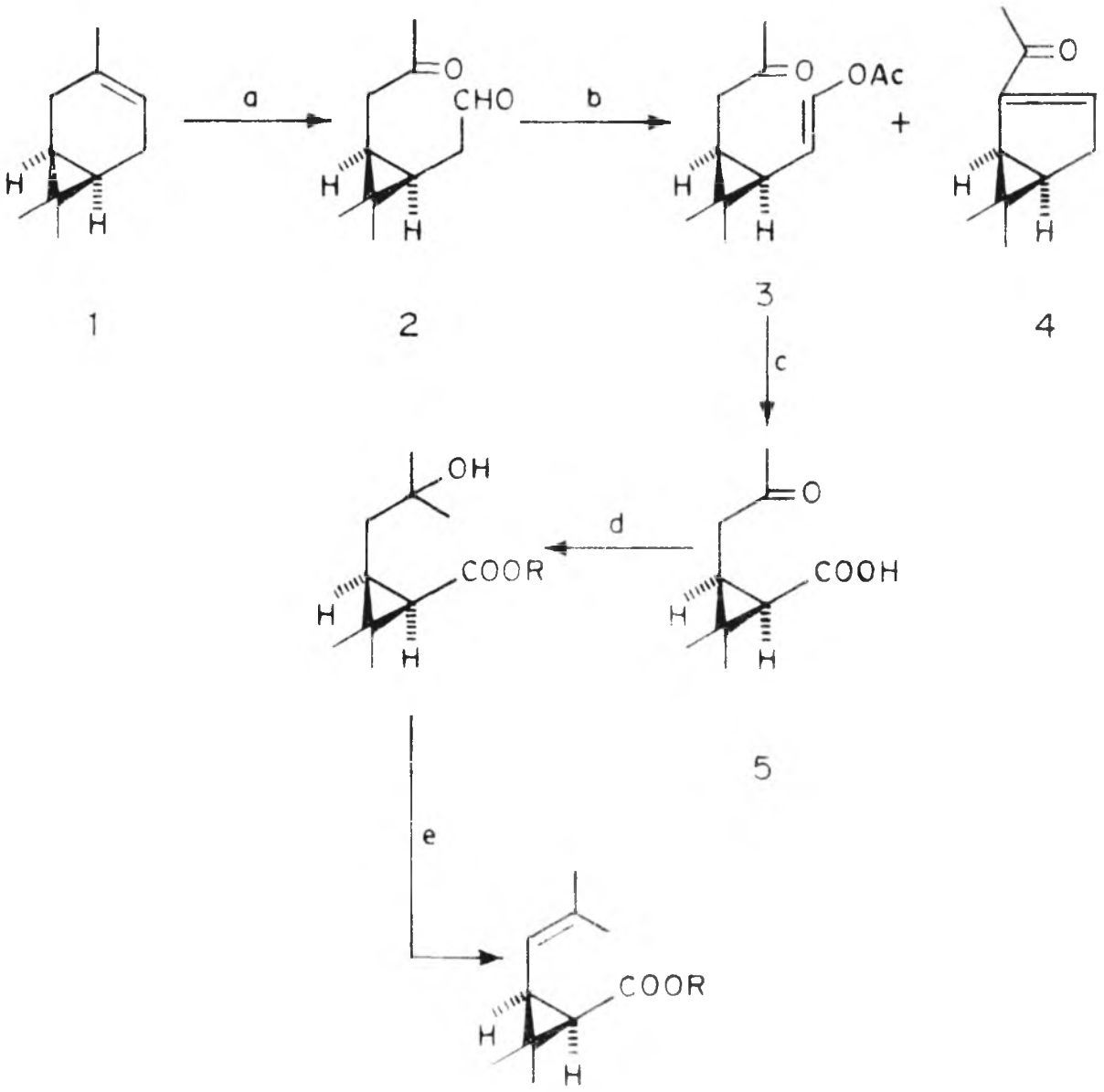
matter of several patents[20-23] and papers[24]. In most of these methods a substituted cyclopropane ring is built up, starting with suitable substrate. As a result, in many of the methods, a mixture of isomers is obtained.

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, a naturally occurring monoterpene which is abundantly available and possesses the desired stereochemistry.

They obtained, stereoselectively, (+)trans[25] and (-)trans[26] chrysanthemic acids from (+)car-3-ene (Scheme I). Later on, many workers have converted (+) car-3-ene, 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 into 1R (+) cis chrysanthemic acid; the esters of which possess insecticidal activity[8].

SCHEME II



(+) CIS-CHRYSANTHEMATE

6

a (i) OZONOLYSIS

b Ac_2O / AcONa

c (i) OZONOLYSIS
(ii) O_2

d (i) ESTERIFICATION
(ii) REVERSE GRIGNARD WITH CH_3MgI

e $POCl_3$ / Py or PTS

The only reference available in the literature is from the Japanese workers[26] who synthesised, selectively, the 1R(+) *cis* chrysanthemic acid from (+) car-3-ene as shown in Scheme II. Matsui *et al.*[26] 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 1R (+) *cis* acid (6). Due to the formation of by-product (4), the overall yield of acid (6) from (+) car-3-ene was considerably low.

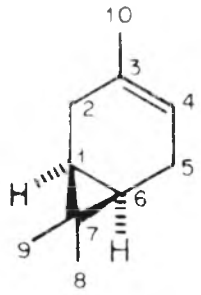
Since, we were interested in preparing some active insecticidal esters from 1R (+) *cis* chrysanthemic acid, we were looking for a suitable method for the synthesis of 1R *cis* chrysanthemic acid in better yields. For this purpose, (+) car-3-ene, possessing the configuration of 1S and 6R at the cyclopropane ring juncture, was considered to be an ideal starting material. In addition, it is a cheap, abundant, naturally occurring terpene, readily available from pine oil (*Pinus longifolia*).

PRESENT WORK

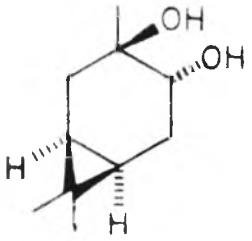
(+) Car-3-ene (I), on treatment with performic acid was converted to the formoxy hydroxy carane which on hydrolysis gave the known[28] 3α,4α-carane diol (II) in 45% yield; m.p. 82-83° (pet. ether), $C_{10}H_{18}O_2$; it showed IR bands at 3448 (OH), 1058 (-C-O-) and NMR signals at 9.3 (2H, m, cyclopropane protons); 9.03 (6H, s, gemdimethyl on cyclopropane); 8.83 (3H s, $-CH_3$ at C_3); 8.27 to 7.77 (4H, m, $-CH_2$ protons); 6.73 (1H, q, proton at C_4) and 6.37 (2H, m, OH protons).

Jones chromic acid oxidation of the diol (II) at 0° gave the keto carboxylic acid (III) in 75% yield. The keto acid (III) was converted into its methyl ester (IV) by methanol and sulphuric acid in almost quantitative yield. The ester (IV), $C_{11}H_{18}O_3$, M^+ 198, b.p. 91-92°/1.5 mm, showed IR bands at 1739, 1150 (ester); 1709 (>C=O) and NMR signals at 9.23, 9.00 (1H each, m, protons at C_1 and C_3 of cyclopropane); 9.1, 8.87 (3H each, s, gemdimethyl on cyclopropane); 7.9 (3H, s, $-COCH_3$); 7.8, 7.67 (2H each, br.s., methylene protons adjacent to carbonyl group of ketone and ester) and 6.4 (3H, s, ester methyl).

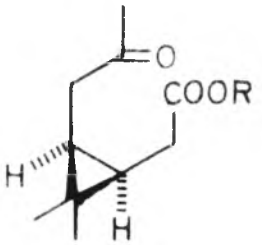
The ester (IV) was converted into its ethylene ketal ester (V) in 95% yield by treating it with ethylene glycol



I

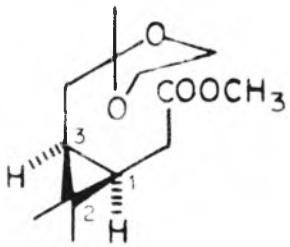


II

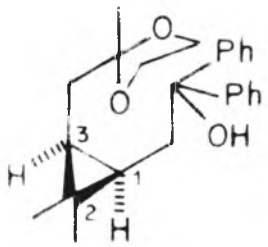


III R = H

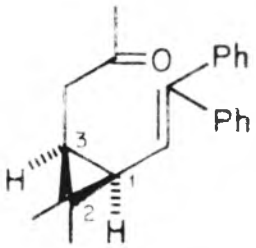
IV R = CH_3



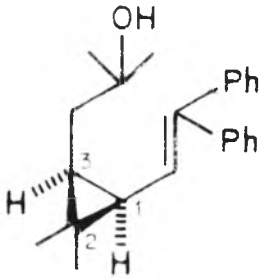
V



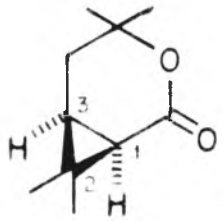
VI



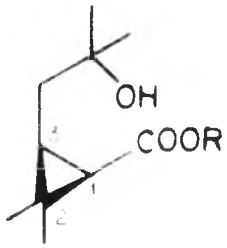
VII



VIII

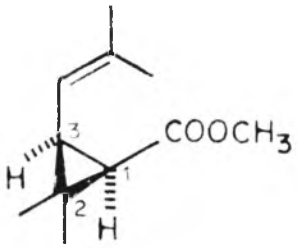


IX

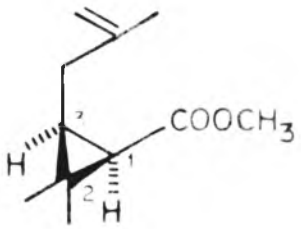


X R = CH_3

XI R = H



XII

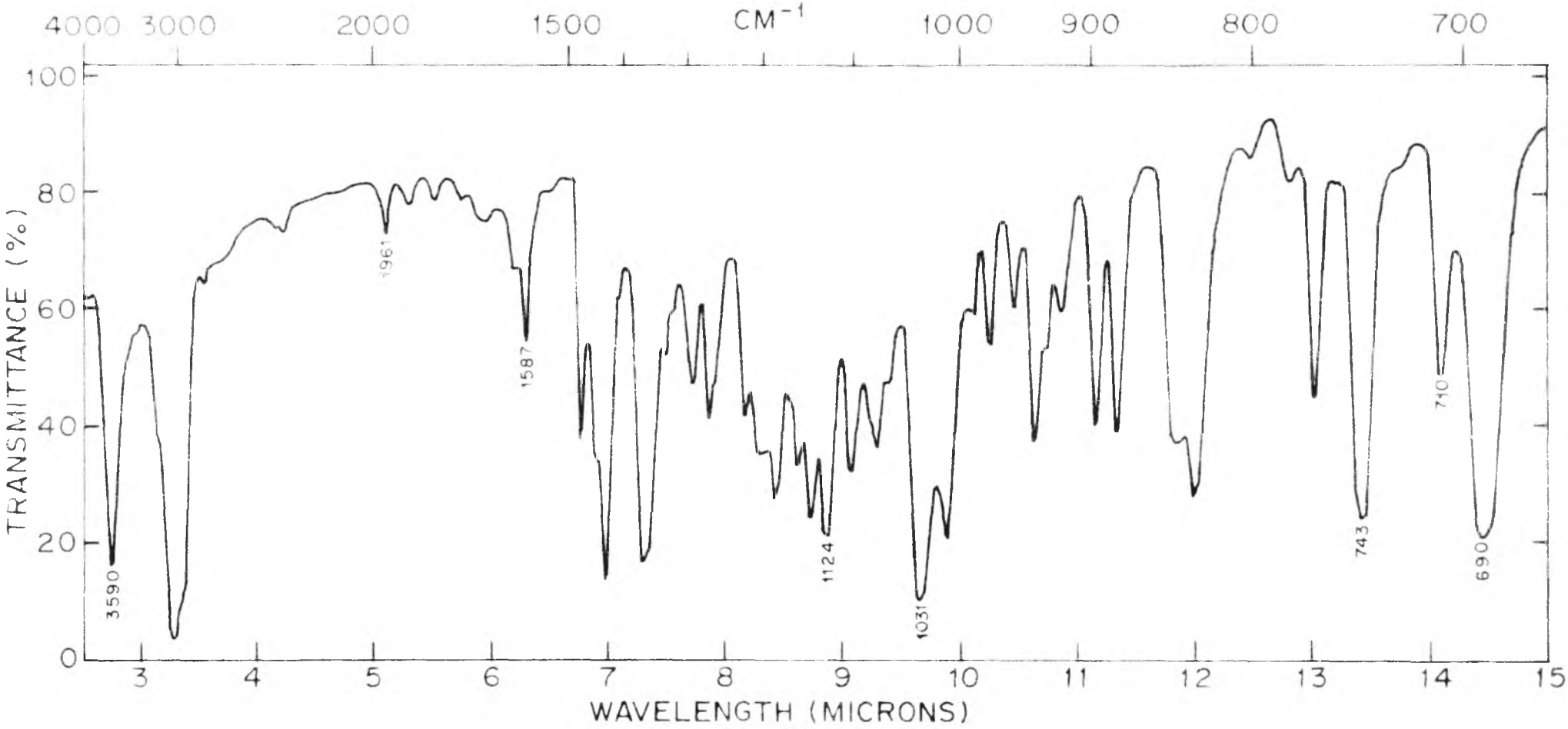


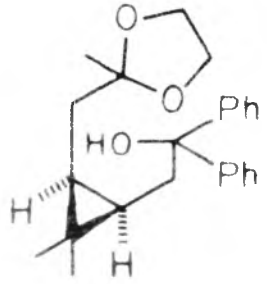
XIII

and catalytic amount of paratoluenesulphonic acid in benzene. The ketal ester (V), $C_{13}H_{22}O_4$, b.p. 104-106°/1 mm, showed IR bands at 1739, 1156 (ester carbonyl) and NMR signals at 9.27 (2H, m, cyclopropane protons at C_1 and C_3); 9.1, 8.9 (3H each, s, gemdimethyl on cyclopropane); 8.75 (3H, s, methyl attached to carbon, bearing the ketal function); 8.52 (2H, d, J = 6 Hz, methylene α to ketal function), 7.83 (2H, d, J = 6 Hz, methylene α to ester), 6.36 (3H, s, ester methyl) and 6.13 (4H, s, ketal methylene protons).

Grignard reaction on ketal ester (V) using excess of phenyl magnesium bromide (3 moles) afforded, in 75% yield, the crystalline solid alcohol (VI), $C_{24}H_{30}O_3$, M^+ 366, m.p. 92° (pet. ether). It showed IR (Fig.1) bands at 3590, 1124 (-OH), 1587, 710, 690 (aromatic) and NMR (Fig.2) signals at 9.47 (2H, m, cyclopropane protons at C_1 and C_3); 9.2, 9.05 (3H each, s, gemdimethyl on cyclopropane); 8.7 (3H, s, methyl attached to carbon bearing ketal function); 8.5 (2H, br.d., methylene protons α to ketal), 7.9 (2H, br.s, methylene protons α to hydroxy function), 6.13 (4H, s, ketal methylenes) and 2.77 (10H, m, aromatic protons).

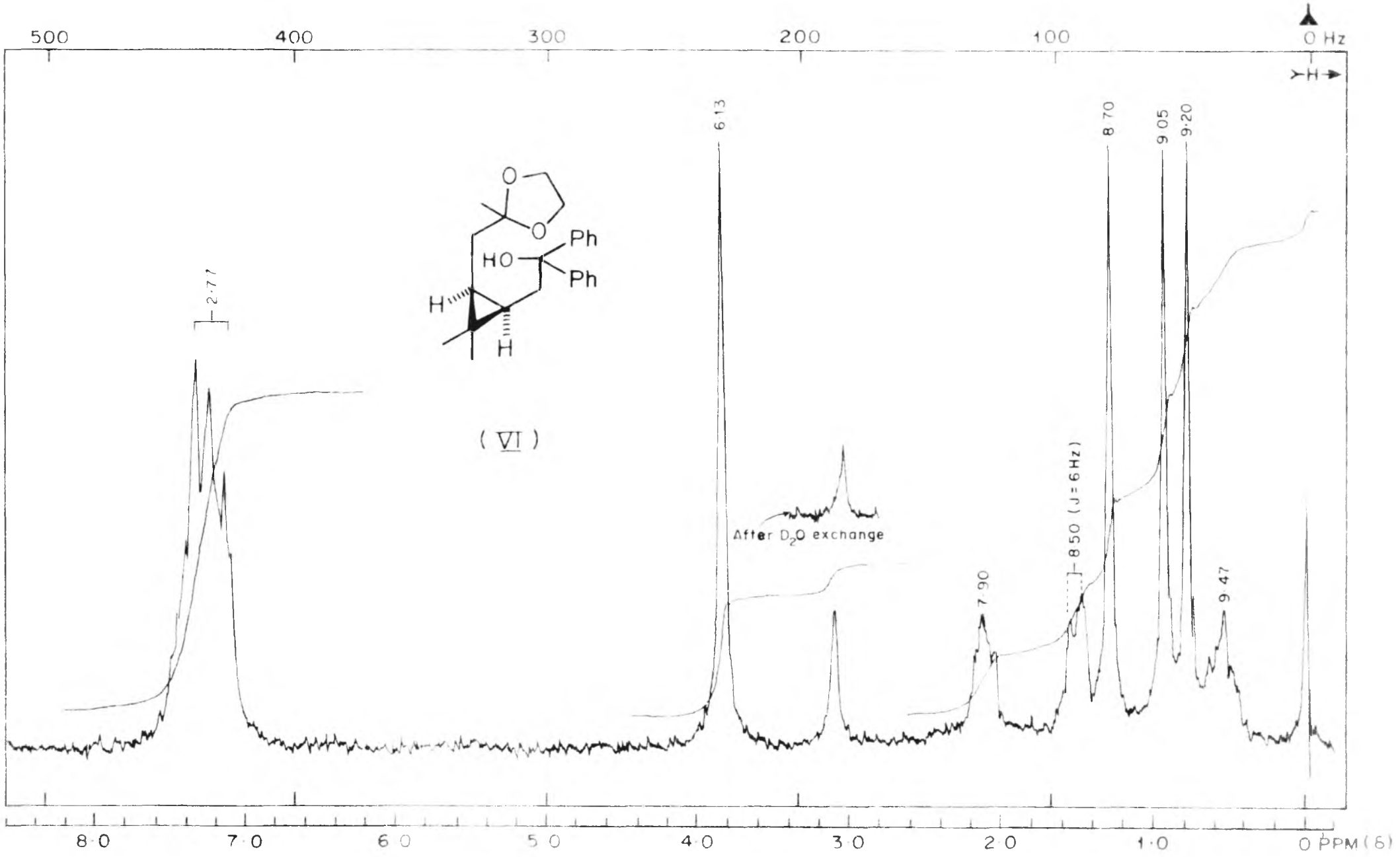
Dehydration and deketalisation of (VI) was achieved


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3590
1961
1587
1124
1031
743
710
690
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


O
O
Ph
HO
Ph
H
H

(VI)

FIG 1.


500
400
300
200
100
0 Hz
δH
6·13
8·70
9·05
9·20
2·71
7·90
8·50 (J=6Hz)
9·47
After D2O exchange
HO
Ph
Ph
H
H
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

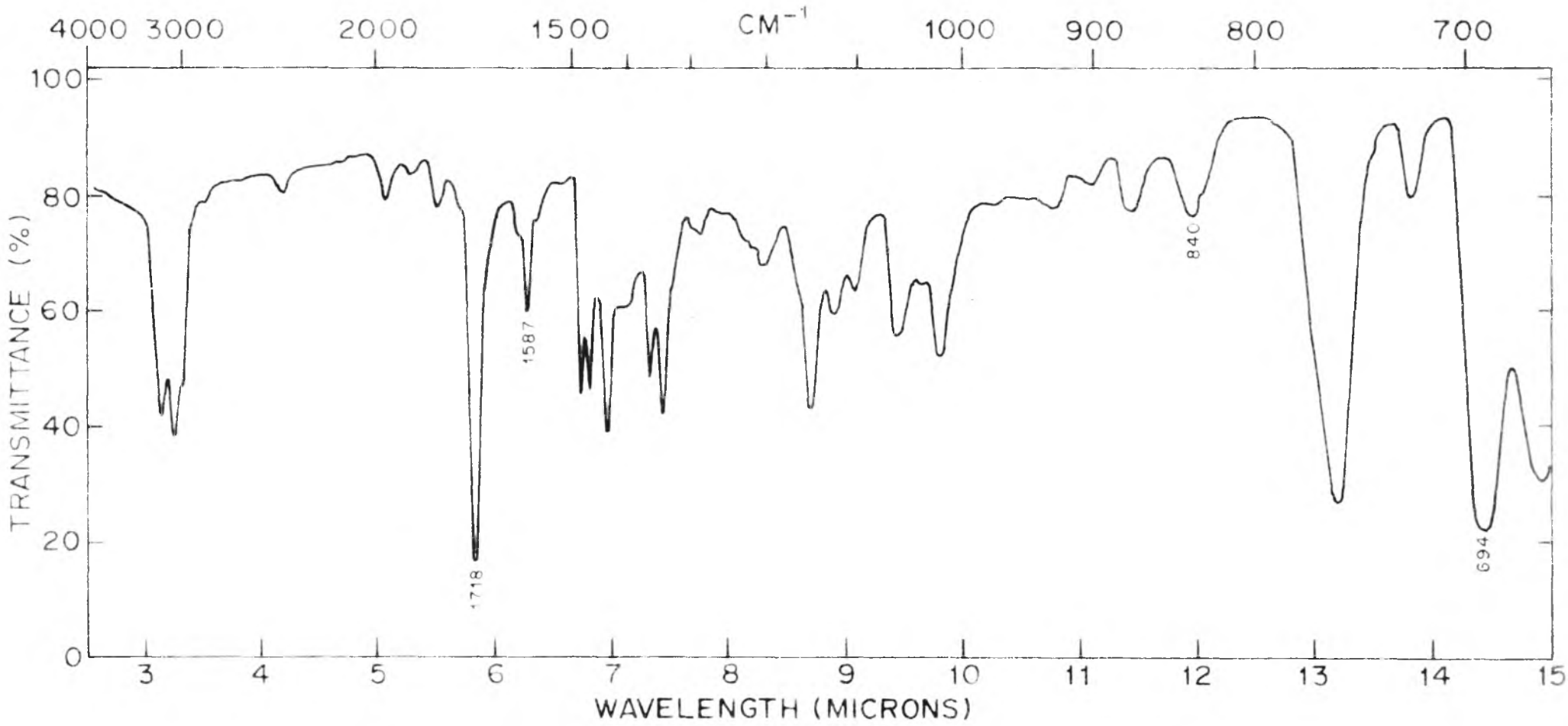
(VI)

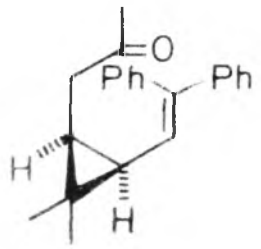
FIG. 2

in one step by treating it with paratoluenesulphonic acid in refluxing benzene to afford the unsaturated ketone (VII), in 95% yield, as a solid, m.p. 62° (pet.ether), $C_{22}H_{24}O$, M^+ 304. It showed IR (Fig.3) bands at 1718 (>C=O), 840 (-CH=C<), 1587, 694 (mono-substituted benzene) and NMR (Fig.4) signals at 9.17 (1H, m, cyclopropane proton at C_3); 8.9 (6H, s, gemdimethyl on cyclopropane); 8.73 (1H, d, J = 4 Hz, proton at C_1); 7.9 (3H, s, $-COCH_3$); 7.55 (2H, d, J = 7 Hz, $-CH_2-$ protons adjacent to >C=O); 4.42 (1H, d, J = 8 Hz, olefinic proton) and at 2.87, 2.77 (5H each, s, aromatic protons).

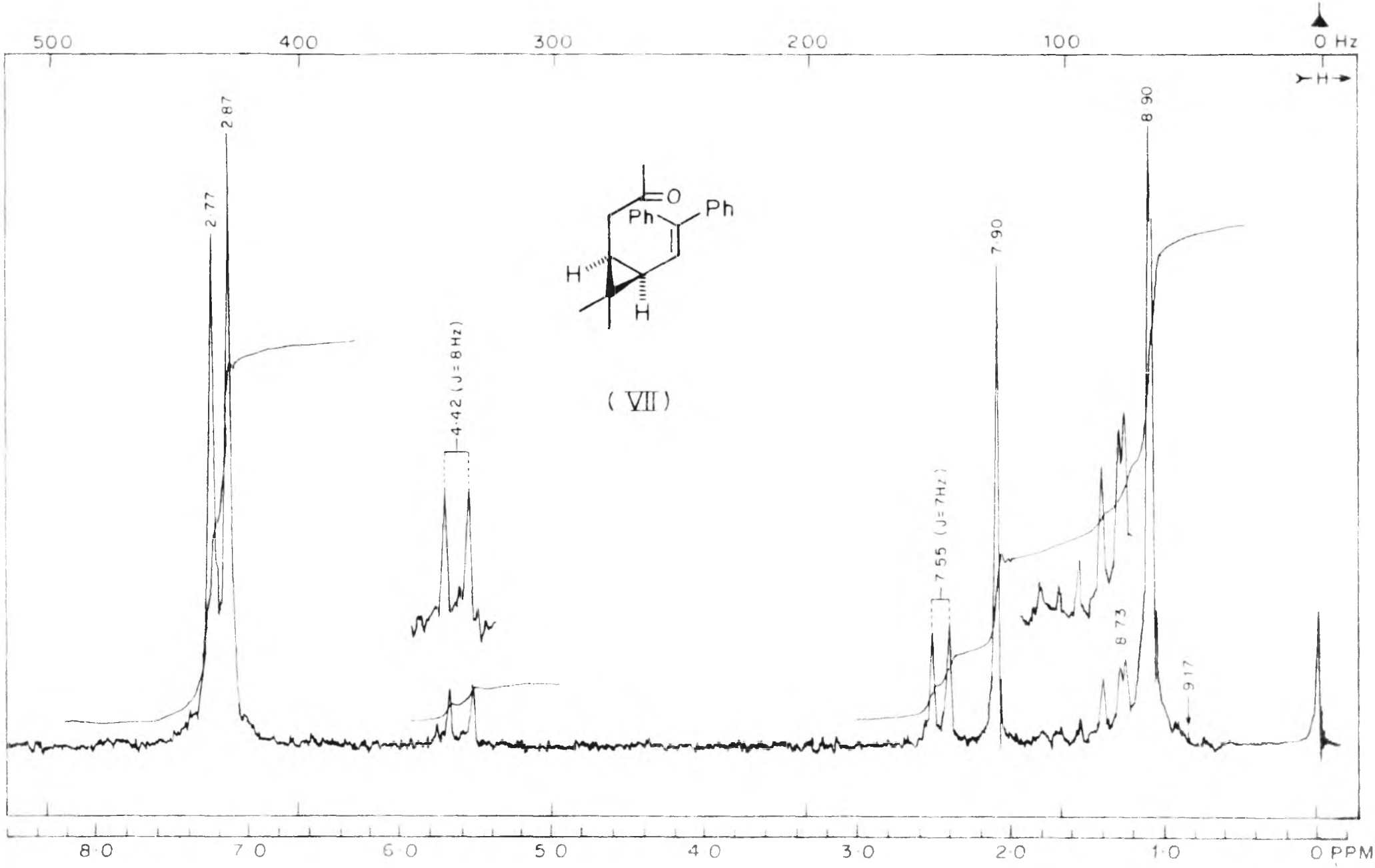
Grignard reaction using methyl magnesium iodide on the ketone (VII) gave the alcohol (VIII) in 90% yield, as a thick viscous liquid, $C_{23}H_{28}O$. It showed IR bands at 3509(OH), 1587, 690 (monosubstituted benzene), and NMR signals at 9.17 (1H, m, proton at C_3); 8.9 (6H, s, gem-dimethyl at C_2); 8.77 (6H, s, methyls attached to carbon bearing -OH); 8.67 (1H, s, proton at C_1); 8.4 (2H, d, J = 6 Hz, methylene protons at C_3); 4.37 (1H, d, J = 8 Hz, olefinic proton) and 2.87, 2.77 (5H each, s, aromatic protons).

The alcohol (VIII) on ozonolysis at 0°, followed by oxidative decomposition of the resulting ozonide using Jones chromic acid reagent at 0°, afforded a mixture of


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1718
1587
840
694
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


O
Ph
Ph
H
H

(VII) FIG. 3.

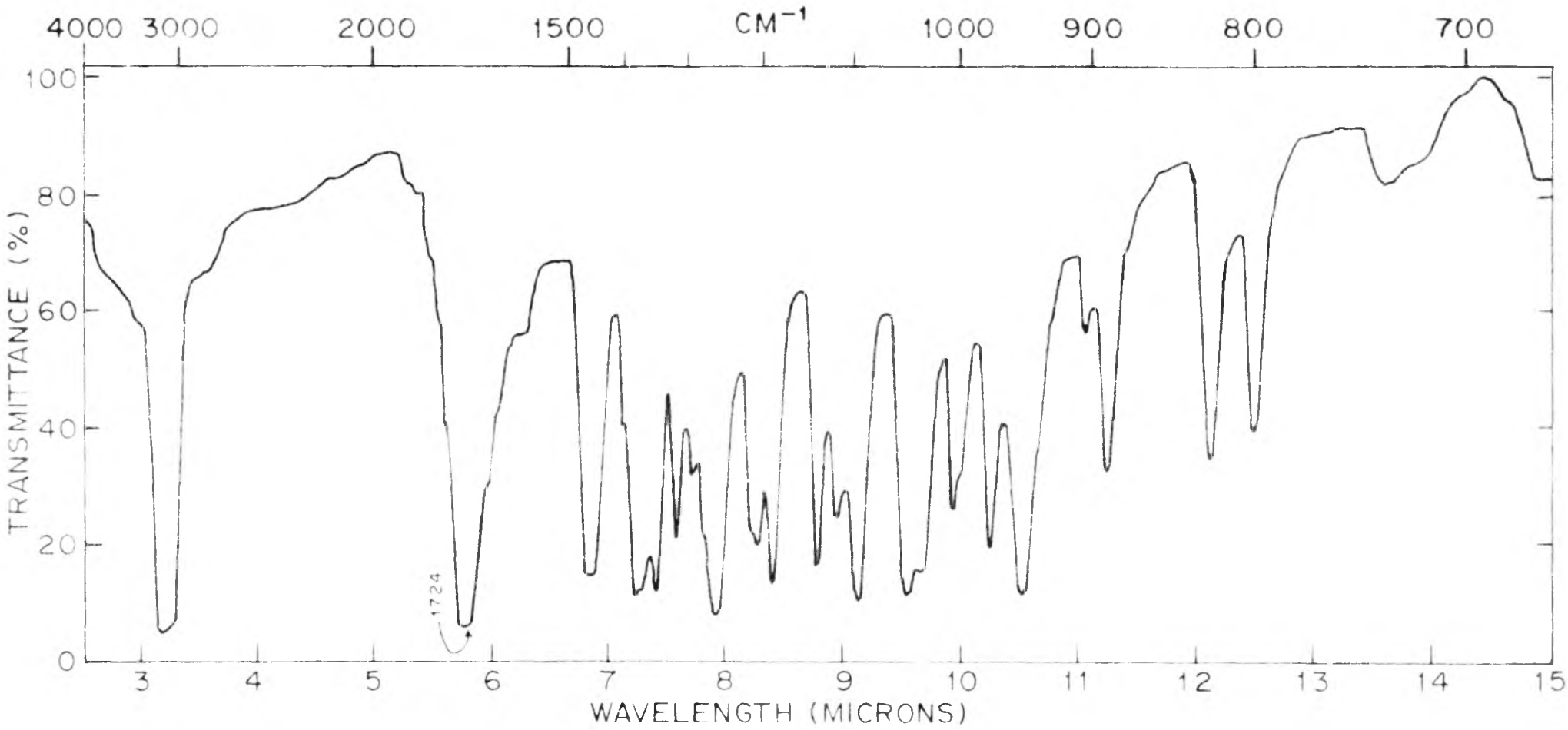

500
400
300
200
100
0 Hz
H
2·87
2·77
4·42 (J = 8 Hz)
7·90
7·55 (J = 7Hz)
8·90
8·73
9·17
O
Ph
Ph
H
H
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

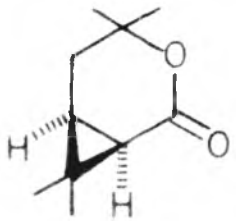
(VII)

FIG. 4.

three products (TLC). These were separated into acidic and neutral parts by sodium carbonate extraction of the crude product. The neutral part, 80% of the product, showed two spots on TLC. They were separated by chromatography over silicic acid (1:20). The earlier fractions, eluted with pet. ether, and 25% benzene in pet. ether gave a solid which was identified as benzophenone by m.p., m.m.p. (48°) and IR spectrum. The later fractions, eluted with benzene and chloroform afforded a solid which was purified by crystallisation from pet. ether to give (+) dihydrochrysanthemolactone (IX), $C_{10}H_{16}O_2$, M^+ 168, m.p. 82-83°, $[\alpha]_D^{28}$ +72° (c, 1.5). It showed IR (Fig.5) bands at 1724 (δ-lactone) and NMR (Fig.6) signals at 8.92, 8.75 (3H each, s, gemdimethyl 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).

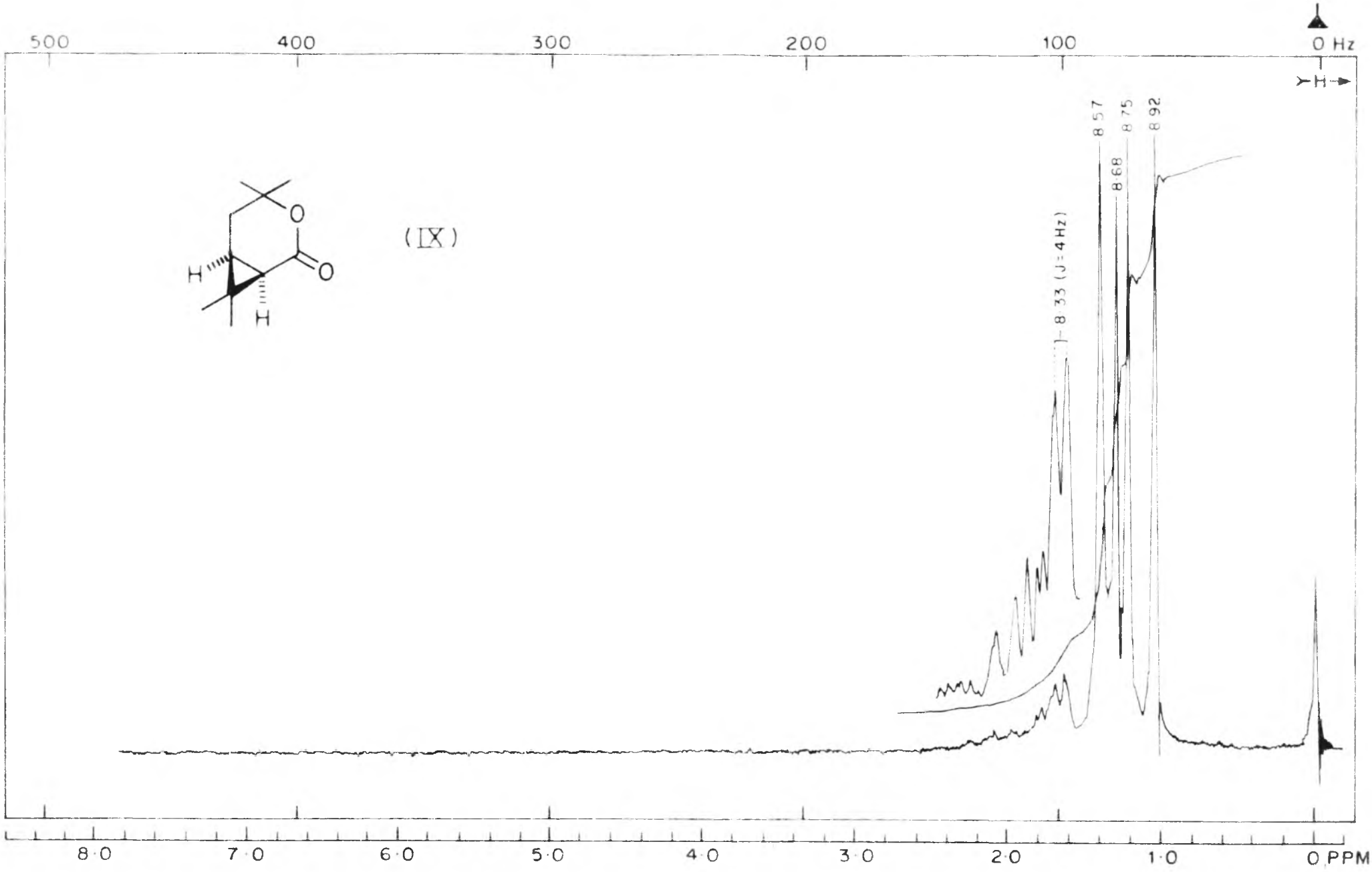
The acidic part (12%) was esterified with an ethereal solution of diazomethane and the resulting ester further purified by distillation to give the TLC pure hydroxy ester (X), $C_{11}H_{20}O_3$, b.p. 110° (bath)/1 mm. It showed IR bands at 3704 (OH), 1724, 1163 (ester) and NMR signals at 8.97 (1H, m, proton at C_3); 8.87 (12H, s,


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1724
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


O
H
O
H

(IX)

FIG. 5.

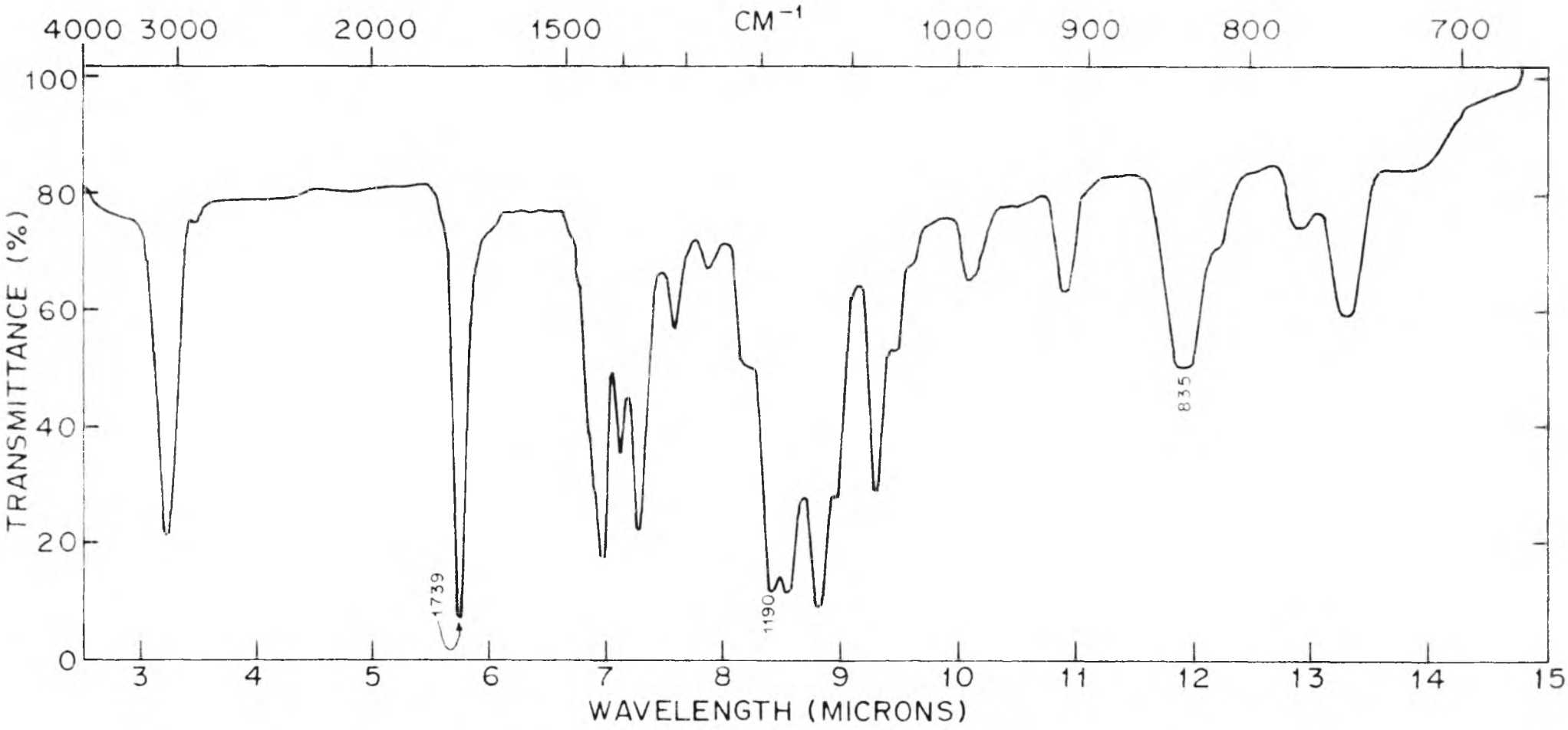

500
400
300
200
100
0 Hz
H
8·57
8·75
8·92
8·68
8·33 (J = 4 Hz)
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ
O
O
H
H

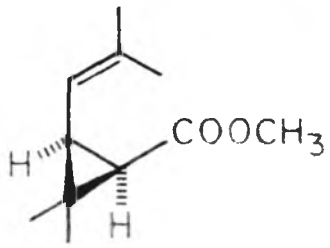
(IX)

FIG. 6

four methyls); 8.62 (1H, s, proton at C_1); 8.28 (2H, d, J = 6 Hz, $-CH_2-$ protons), 6.5 (3H, s, ester methyl) and 7.43 (1H, br.s, exchangeable with D_2O, -OH proton). The hydroxy acid (XI) was also obtained by saponification of the lactone (IX) using methanolic potash. The acid (XI) on esterification with diazomethane gave methyl ester (X).

Dehydration of hydroxy ester (X) with $POCl_3$/ Pyridine at 0^o afforded a mixture of two unsaturated esters (TLC on silver nitrate + silicic acid plate; 6% ethyl acetate in benzene). These two esters were separated by chromatography over silicic acid (1:20), impregnated with 10% silver nitrate. The earlier fractions, eluted with pet. ether and 25% benzene in pet. ether, gave a TLC ($SiO_2/AgNO_3$) pure liquid which was further purified by distillation to afford pure methyl ester of (+)-<u>cis</u> chrysanthemic acid (XII), b.p. 105^o(bath)/10 mm, $C_{11}H_{18}O_2$, $[\alpha]_D^{28}$ $+41^o$ (c, 1.2). It showed IR (Fig.7) bands at 1739, 1190 (ester), 835 (-CH=C<) and NMR ($CDCl_3$, 90 MHz) (Fig.8) signals at 8.81, 8.78 (3H each, s, gemdimethyl on cyclopropane), 8.42 (1H, s, proton at C_1), 8.33, 8.26 (3H each, s, vinyl methyls), 8.13 (1H, s, proton at C_3); 6.4 (3H, s, ester methyl) and 4.67 (1H, d, J = 8 Hz, olefinic proton). The sign and magnitude of the optical


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1739
1190
835
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


COOCH3
H
H

(XII)

FIG. 7.

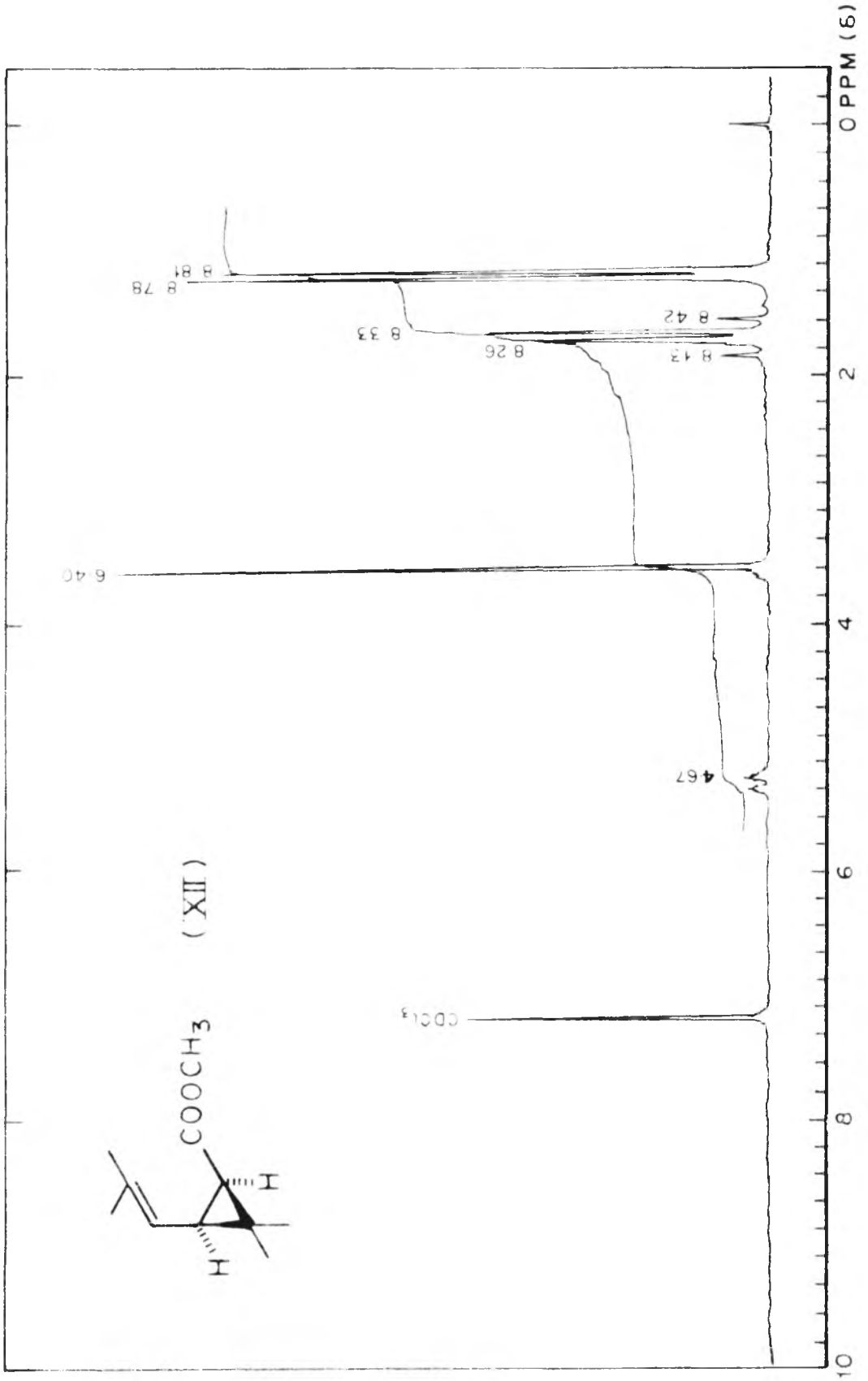
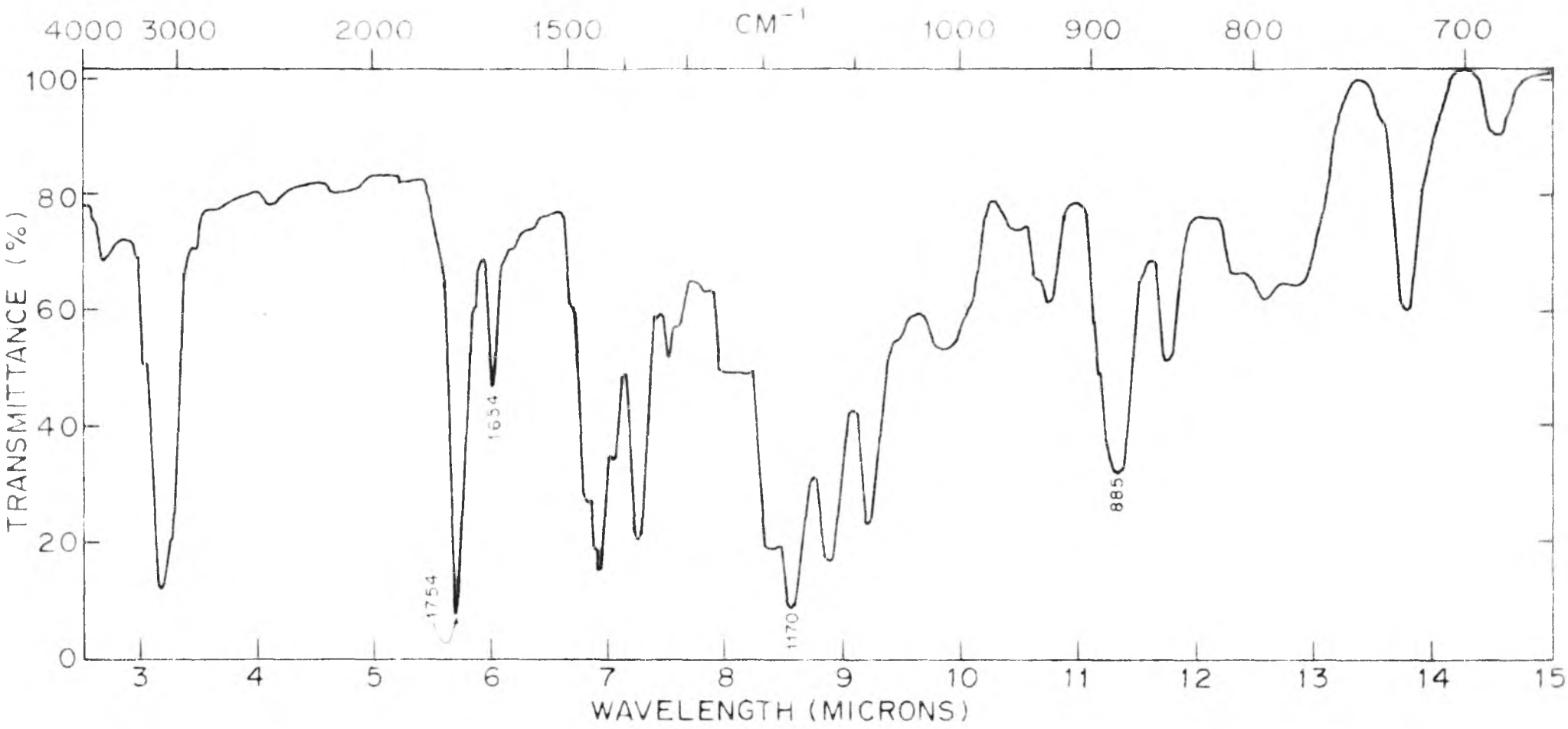

0 PPM (δ)
2
4
6
8
10
8.81
8.78
8.42
8.33
8.26
8.13
6.40
4.67
CDCl3
(XII)
COOCH3
H
H

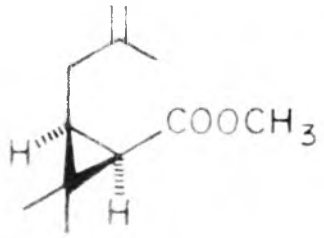
FIG 8

rotation of (XII) and comparison of its spectral data with the one reported in literature[29,30] confirmed that this compound must be methyl (+)cis-chrysanthemate.

The isomeric ester, eluted in the later fractions (TLC single spot) was purified by distillation, b.p.100° (bath)/8 mm and identified as (XIII), $C_{11}H_{18}O_2$, $[\alpha]_D^{28}$ -7.89° (c, 0.76), by spectral data. It showed IR (Fig.9) bands at 1754, 1170(ester), 1654, 885 ($>C=CH_2$) and NMR (Fig.10) signals at 9.17 (1H, m, proton at C_3); 8.8 (6H, s, methyls on cyclopropane); 8.63 (1H, s, proton at C_1); 8.28 (3H, s, vinyl methyl); 7.7 (2H, d, J = 6 Hz, allylic methylene protons at C_3); 6.43 (3H, s, ester methyl) and 5.37 (2H, s, $>C=CH_2$, protons).

When ester (X) was dehydrated by using catalytic quantity of paratoluenesulphonic acid in dry benzene (8 hrs refluxing), a single product was formed which was identified as (XII) by spectral data and physical constants.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1754
1654
1170
885
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


COOCH3
H
H

(XIII)

FIG. 9.

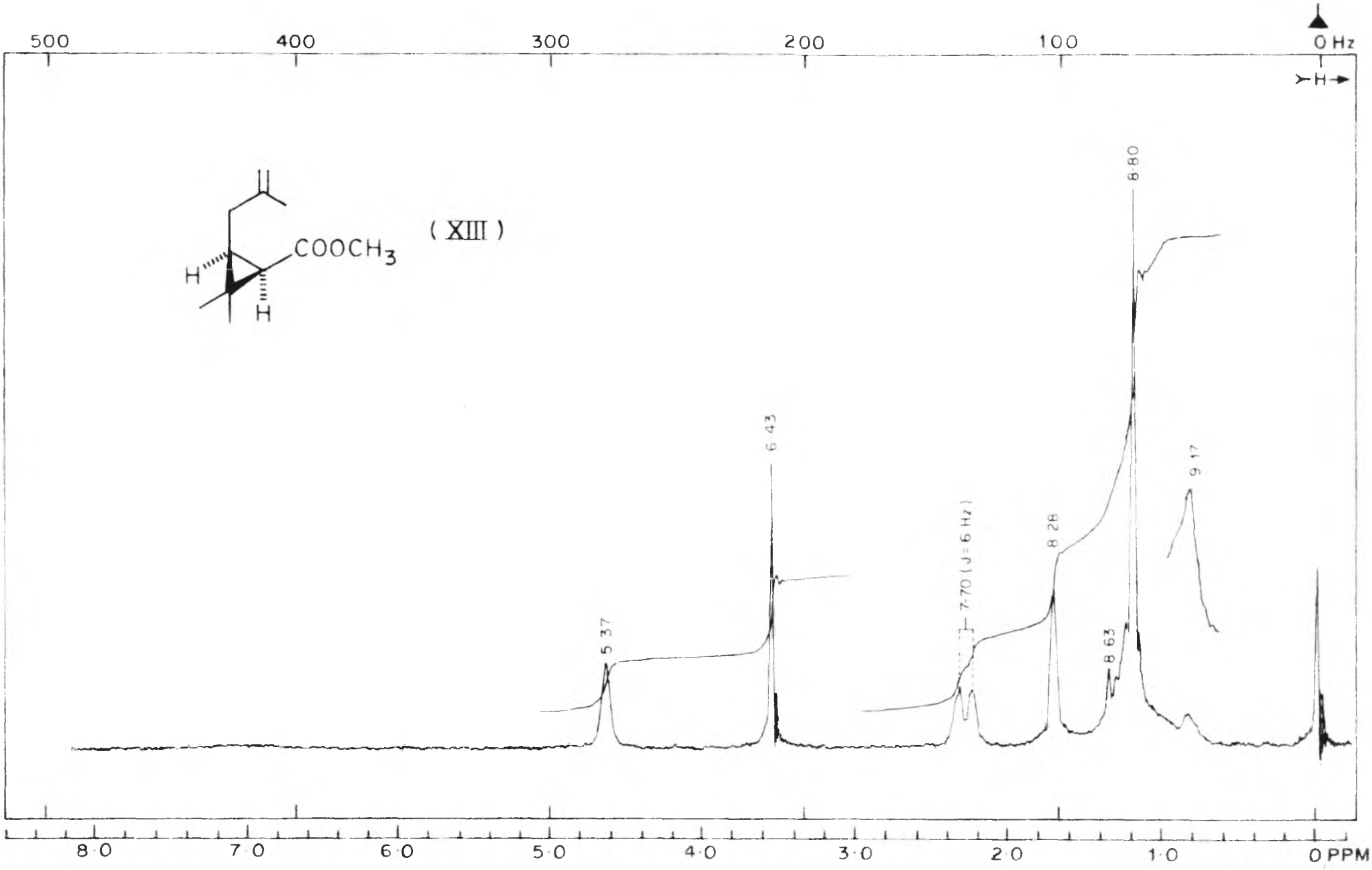

500
400
300
200
100
0 Hz
H
COOCH3
H
H
(XIII)
8·80
6·43
9·17
8·28
7·70 (J = 6 Hz)
5·37
8·63
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIG. 10.

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

Preparation of 3β,4α-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 (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 20-30° (2 hrs). Stirring was continued at that temperature for 6 hrs and allowed to stand overnight. A solution of sodium hydroxide (160 g in 400 ml H_2O) was added slowly to the reaction mixture under stirring and 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 H_2O) was added, slowly, under vigorous stirring, maintaining the temperature at 25°-30°. After stirring for 0.5 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. 87-88°.

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}.

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

A) Preparation of 2,2-dimethyl-3 (2-oxopropyl) cyclopropane-cis-1-acetic acid (III)

To a vigorously stirred solution of 3β,4α-carane diol, (II, 51 g, 0.3 mole) in acetone (300 ml) was added Jones chromic acid reagent (136 ml, 0.36 mole) dropwise, maintaining the temperature below 0° (1.5 hrs). After the addition, it was stirred for 2 hrs 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 neutral material (7.0 g) in the chloroform layer was not investigated. 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, 41.5 g; 75%). This acid was converted to its methyl ester.

B) The keto acid (III, 41.5 g) obtained as above, was refluxed in dry methanol (200 ml) with catalytic amount of conc. sulphuric acid (1 ml) for 5 hrs. Most of the methanol was removed under reduced pressure; diluted with water (200 ml) and extracted with chloroform (150 ml, 75 ml x 2). The chloroform layer was washed with water to free it from acid and dried. Evaporation of chloroform furnished the keto ester (IV) which was further purified by distillation to give a colourless liquid (38 g) b.p. 92° (vapour)/1.5 mm, $[\alpha]_D^{25}$ -26.1° (c, 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 833 cm^{-1}.

Methyl-2,2-dimethyl-3(2,2-ethylenedioxy-propyl) cyclopropane-cis-1-acetate (V).

A mixture of keto-ester (IV, 30 g), distilled ethylene glycol (15 g), paratoluenesulphonic acid (0.3 g) and dry benzene (300 ml) was taken in a 500 ml round bottom flask, fitted with a Dean Stark unit for azeotropic dis-

tillation. The mixture was then heated under reflux till no more water collects (6 hrs). The reaction mixture was then washed with water (150 ml x 2) to remove unreacted ethylene glycol and paratoluenesulphonic acid and dried. Evaporation of benzene afforded the ketal-ester (V) which was purified by distillation; b.p. 104° (vapour)/1.5 mm; yield 34.8 g (95%), $[\alpha]_D^{28}$ +18.9° (c, 3.17).

Analysis: Found: C, 64.95; 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, 1156, 1036, 935, 837 and 775 cm^{-1}.

2,2-dimethyl-3(2,2-ethylenedioxy-propyl)-cis-1(2,2-diphenyl ethan-2-ol) cyclopropane (VI)

A) Preparation of phenylmagnesium bromide 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 (5.04 g, 0.21 mole), dry ether (150 ml) and a crystal of iodine. A solution of bromobenzene (32.93 g, 0.21 mole) in dry ether (100 ml) was slowly added through the dropping funnel. After introducing a few ml of the solution, the reaction mixture was warmed to initiate the reaction

(colour of iodine disappears). The remaining solution was then added dropwise, under stirring. After the addition, the reaction mixture was stirred at room temperature for 1 hr and under reflux for 30 minutes when most of the magnesium dissolves to give a solution of phenyl magnesium bromide in ether.

B) Preparation of (VI)

The above solution of phenyl magnesium bromide in ether, was cooled to 0°. A solution of ketal ester (V, 16.94 g, 0.07 mole) in ether (100 ml) was, then, added dropwise to the Grignard reagent, under vigorous stirring. After the addition, it was stirred for 1 hr at room temperature and 30 minutes under reflux. The excess reagent and magnesium complex were decomposed by adding, dropwise, a saturated solution of ammonium chloride (200 ml) at 0 to 5°. The mixture 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 crude semisolid product (27 g). Crystallization of crude material from pet. ether afforded needle shaped white crystals of ketal alcohol (VI, 19.[illegible] g, 75%), m.p. 92°, $[\alpha]_D^{25}$ +7.89° (c, 1.89).

Analysis: Found: C, 78.58; H, 8.36; $C_{24}H_{30}O_3$ requires: C, 78.65; H, 8.25%.

IR bands at 3520, 3030, 1961, 1887, 1587, 1471, 1429, 1370, 1124, 1031, 1010, 939, 897, 881, 833, 766, 743, 710 and 690 cm^{-1}.

2,2-dimethyl-3 (2-oxopropyl)-cis-1 (2,2-diphenyl vinyl)-cyclopropane (VII)

A solution of ketal alcohol (VI, 17 g) in benzene (200 ml) was refluxed with paratoluenesulphonic acid (0.5 g) for 2 hrs. Water (3 ml) was added and refluxing continued for further 4 hrs. The reaction mixture, was then washed, repeatedly, with water (100 ml x 4) to remove paratoluenesulphonic acid and ethylene glycol. The benzene layer was dried and evaporated to furnish a thick liquid which was chromatographed on alumina (Gr.II, 300 g) and eluted with pet.ether + benzene (1:1), benzene and benzene + chloroform (1:1). The fractions eluted with benzene + pet. ether (1:1) and benzene gave the TLC (14% ethyl acetate in C_6H_6) pure ketone which on cooling at 0° (48 hrs) solidified. Crystallization from pet. ether afforded the white crystals of unsaturated ketone (VII), yield 13.46 g (95%), m.p. 62°, $[\alpha]_D^{32}$ -38.27° (c, 5.48).

Analysis: Found: C, 86.70; H, 8.15; $C_{22}H_{24}O$ requires:

C, 86.80; H, 7.95%.

IR bands at 3175, 3077, 1961, 1718, 1587, 1488, 1471, 1429, 1348, 1149, 1058, 1020, 873, 840, 758 and 694 cm^{-1}.

2,2-dimethyl-3 (2-hydroxy, 2-methylpropyl)-cis-1 (2,2-diphenyl vinyl) cyclopropane (VIII)

A solution of unsaturated ketone (VII, 9.12 g, 0.03 mole) in dry ether (50 ml) was introduced, dropwise, with stirring into the cold solution of methylmagnesium iodide, prepared from magnesium (1.08 g, 0.045 mole) and methyl iodide (6.39 g, 0.045 mole) in dry ether (150 ml). After the addition, it was stirred at room temperature for one hr. and 30 minutes 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 alcohol which was chromatographed on silicic acid (200 g, 1:20) and eluted with benzene to give the pure alcohol (VIII, 8.65 g, 90%) as a thick liquid, $[\alpha]_D^{28}$ +44.44°

(c, 1.98).

Analysis: Found: C, 86.48; H, 8.98; $C_{23}H_{28}O$ requires: C, 86.20; H, 8.81%.

IR bands at 3509, 2985, 2941, 1587, 1439, 1361, 1130, 1058, 1015, 893, 752 and 690 cm^{-1}.

(+)-Dihydrochrysanthemolactone (IX) and methyl-2,2-dimethyl-3 (2-hydroxy, 2-methyl propyl) cyclopropane-1-carboxylate (X) from (VIII).

A stream of ozonised oxygen (approx. 1 g/hr) was passed through an ice cooled solution of alcohol (VIII, 9.15 g) in ethyl acetate (50 ml) till the absorption of ozone was complete (1.5 hr) (tested by starch iodide paper). The solution of ozonide in ethyl acetate was transferred to a 500 ml conical flask; acetone (25 ml) added and cooled to 0°. Jones chromic acid reagent (10 ml) was then added, dropwise, to it with shaking and maintaining the temperature at 0 to 5°. The mixture was kept at the same temperature for one hr. and then 15 minutes at room temperature. It was diluted with water (100 ml) and extracted with ethyl acetate (100 ml, 75 ml). The combined ethyl acetate layer was washed with water, dried and evaporated to give the crude product (8.160 g). It showed, on TLC (14% ethyl acetate in C_6H_6) three spots.

The product was taken up in ether (150 ml) and extracted with 10% aqueous sodium carbonate solution (25 ml x 3). The ether layer was washed with water (75 ml), dried and evaporated to furnish the mixture of two compounds (7.02 g; 85% of the product).

The neutral product (7.02 g) was chromatographed on alumina (Gr.I, 145 g). The earlier fractions eluted with pet. ether and 20% benzene in pet. ether gave benzophenone (m.p., m.m.p. 48° and superimposable IR). The middle fractions eluted with benzene and benzene-chloroform (1:1) gave a solid, which on crystallization from pet. ether afforded the dihydrochrysanthemolactone (IX) as a white crystalline solid; (2.8 g, 34.3% of the product) m.p. 82-83°, $[\alpha]_D^{28}$ +71.83° (c, 1.45).

Analysis: Found: C, 71.45; H, 9.50; $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%.

IR bands at 3077, 1724, 1460, 1379, 1351, 1266, 1190, 1136, 1093, 1047, 976, 948, 880, 826 and 800 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 (1.14 g; 12%). It was esterified by an ethereal solution of diazomethane.

The methyl ester (X) thus obtained, was further purified by distillation to afford a colourless liquid (0.92 g); b.p. 110° (bath)/1.5 mm; $[\alpha]_D^{28}$ -16.3° (c, 1.83).

Analysis: Found: C, 65.58; H, 10.26; $C_{11}H_{20}O_3$ requires: C, 65.97; H, 10.07%.

IR banus at 3704, 3077, 1724, 1439, 1370, 1266, 1212, 1163, 1075, 1042, 995, 952, 901, 881, 847, 816, 784, 755 and 709 cm^{-1}.

Methyl-2,2-dimethyl-3-(2-hydroxy-2-methyl-propyl) cyclopropane-1-carboxylate (X) from lactone (IX)

To a solution of lactone (IX, 0.5 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 hrs. Methanol was removed under suction and residue was then, 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 (0.410 g) by an ethereal solution of diazomethane. Distillation afforded a pure colourless ester (X, 0.364 g), b.p. 110°(bath)/1.5 mm, $[\alpha]_D^{28}$ -17.1° (c, 2.12).

Analysis: Found: C, 66.26; H, 9.88; $C_{11}H_{20}O_3$ requires: C, 65.97; H, 10.07%.

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

Methyl (+)-cis-chrysanthemate [methyl (+)-2,2-dimethyl-3 (2-methyl prop-1-enyl) cyclopropane-cis-1-carboxylate] (XII).

A solution of hydroxy ester (X, 0.554 g) in dry benzene (25 ml) was refluxed with paratoluenesulphonic acid (0.025 g) for 8 hrs. The benzene solution, containing the reaction product was washed with water (25 ml x3), dried and the solvent evaporated to furnish the product (0.435 g). It showed on TLC (6% ethyl acetate in C_6H_6) two spots, the more polar was identical with that of lactone (IX).

The mixture was chromatographed over silicic acid (12 g). Methyl chrysanthemate (XII), the less polar component, was eluted with pet. ether and 1.5% ether in pet. ether. It was further purified by distillation to afford colourless liquid (0.225 g), b.p. 100° (bath)/9 mm, $[\alpha]_D^{26}$ +41.02° (c, 1.24).

Analysis: Found: C, 72.16; H, 10.16; $C_{11}H_{18}O_2$ requires: C, 72.49; H, 9.96%.

IR bands at 3077, 1739, 1429, 1399, 1370, 1316, 1190, 1170, 1136, 1075, 990, 917, 885 and 746 cm^{-1}.

Methyl (-)-2,2-dimethyl-3(2-methyl prop-2-enyl) cyclopropane cis-1-carboxylate (XIII).

To an ice-cooled solution of hydroxy ester (X, 1 g) in dry pyridine (10 ml), was added, dropwise, freshly distilled phosphorous oxychloride (3 g) maintaining the temperature at 0-5°. It was then kept at 10° for 24 hrs and decomposed by pouring it on crushed ice (200 g) with vigorous shaking. The reaction mixture was allowed to attain the room temperature, transferred to a separating funnel and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed, successively, with water, 10% hydrochloric acid, again with water and dried. Evaporation of ether furnished the dehydrated product (0.84 g) which showed on TLC analysis (10% silver nitrate + silicic acid), two spots (8% ethyl-acetate in C_6H_6).

The mixture was separated by chromatography using silicic acid impregnated with 10% silver nitrate (30 g). The less polar component (0.415 g) was eluted with 20% benzene in pet. ether and identified as (XII) by spectral data and optical rotation. $[\alpha]_D^{28}$ +41° (c, 1.2).

The more polar compound (0.36) g) was eluted with benzene + pet. ether (1:1). It was further purified by distillation and characterized as (XIII), b.p. 100°(bath)/8 mm ,

$[\alpha]_D^{28}$ -7.89° (c, 0.76).

Analysis: Found: C, 72.68; H, 9.82; $C_{11}H_{18}O_2$ requires:

C, 72.49; H, 9.96%.

IR bands at 3125, 1754, 1654, 1439, 1379, 1343, 1170, 1130,

1081, 1015, 930, 885, 851, 794 and 725 cm^{-1}.

REFERENCES

1 C.B. Gnadinger, "Pyrethrum Flowers" 2nd Ed. McLaughlin Gormley King Co., Minneapolis, Minn. 1936.

2 H.H. Shepard, "The Chemistry and action of insecticides", McGraw-Hill, New York, p.144 (1951).

3 H. Staudinger and L. Ruzicka, Helv. Chim. Acta, 7, 177 (1924).

4 LaForge, F.B. and W.F. Barthel, J. Org. Chem. 9, 242 (1944).

5 P.J. Godin, M.J. Sleeman, M. Snarey and E.M. Thain, Chem. and Ind. 371 (1964).

6 P.S. Beevor, P.J. Godin and M. Snarey, Chem. and Ind. 1342 (1965).

7 P.J. Godin, M.J. Sleeman, M. Snarey and E.M. Thain, J. Chem. Soc. (C), 332 (1966).

8 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, ACS Symposium Series 2, 80 (1974) and references therein. See also U.K. Patent No.1429166.

9 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic. Sci. 7, 499 (1976).

10 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic. Sci. 6, 537 (1975).

11 H. Staudinger, O. Muntwyler, L. Ruzicka and S. Seibt, Helv. Chim. Acta 7, 390 (1924).

12 I.G.M. Campbell and S.H. Harper, J. Chem. Soc., 283 (1945).

13 S.H. Harper, H.W. Reed and R.A. Thompson, J. Sci. Food Agr., 2, 94 (1951).

14 S.H. Harper and K.C. Sleep, J. Sci. Food Agr. 6, 116 (1955).

15 M. Julia, S. Julia and M. Langlois, Bull. Soc. Chim. Fr. 1007 (1965).

16 M. Julia and A. Guy-Rouault, Bull. Soc. Chim. Fr. 1141 (1967).

17 E.J. Corey and J.M. Jantelat, J. Am. Chem. Soc., 89, 3912 (1967).

18 R.W. Mills, R.D.H. Murray and R.A. Raphael, J.C.S. Perkin I, 133 (1973).

19 M. Matsui and I. Yamamoto, "Naturally occurring insecticides", Editors Jacobson, M and D.G. Crosby, Marcel Dekker, New York, 1971. pp. 67 Ref.113 to 121.

20 B. Goffinet and A. Locatelli, Fr. Patent No.1536458 (1969).

21 British Patent No.1178423 (1970).

22 K. Udea and Y. Suzuki, Ger. offen 2032097 (1971).

23 M. Matsui and K. Moriuchi, Ger. Offen 2043173 (1971).

24 I.G.M. Campbell and S.H. Harper, J. Sci. Food. Agr. 4, 189 (1952).

25 M. Matsui, H. Yoshioka, H. Sakamoto, Y. Yamada and T. Kitahara, Agr. Biol. Chem. 31, 33 (1967).

26 M. Matsui, H. Yoshioka, Y. Yamada, H. Sakamoto and T. Kitahara, Agr. Biol. Chem., 29, 784 (1965).

27 R.K.Sobti and Sukh Dev, Tetrahedron, 30, 2927 (1974).

28 A.S. Khanra and R.B. Mitra, Indian J. Chem. 14B, 716 (1976).

29 W.Cocker, H. Lauder, St.J. and P.V.R. Shannon, J. Chem. Soc. Perkin Trans I, 332 (1975).

30 A.F. Bramwel, L. Cronbie, P. Hemesley and G. Pattenden, Tetrahedron, 25, 1727 (1969).

CHAPTER II-A

STEREOSPECIFIC CONVERSION OF (+) CAR-3-ENE INTO METHYL 1S (+) CIS- AND METHYL 1R (-) TRANS- 2,2-DIMETHYL-3(2,2-DIPHENYL VINYL) CYCLOPROPANE CARBOXYLATES

SUMMARY

The keto ester (IV), obtainable from car-3-ene (I) via carane diol (II), when subjected to Baeyer-Villiger oxidation using perbenzoic acid gave the acetate ester (V). Grignard reaction on acetate ester (V) using phenyl magnesium bromide furnished the diol (VI). Acetylation of the diol (VI) gave hydroxy acetate (IX) which, on dehydration followed by saponification furnished the unsaturated alcohol (VII). Oxidation of (VII) with Jones chromic acid reagent followed by esterification afforded the methyl 1R cis-2,2-dimethyl-3(2,2-diphenyl vinyl) cyclopropane carboxylate (XI).

The diol (VI), on oxidation with Jones chromic acid, gave the lactone (XII) as the only product. Saponification of the lactone (XII) followed by esterification of the resulting hydroxy acid gave the trans hydroxy ester (XIII, R=CH_3). Acid catalysed dehydration of (XIII, R=CH_3) gave the methyl 1R trans 2,2-dimethyl-3(2,2-diphenyl vinyl) cyclopropane carboxylate (XIV).

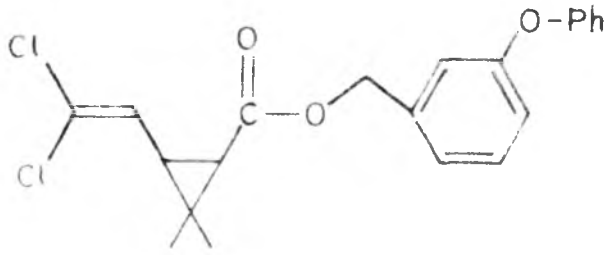
The trans acid (XV) obtainable from the ester (XIV) was esterified with m-phenoxy benzyl alcohol to furnish the ester (XVI).

INTRODUCTION

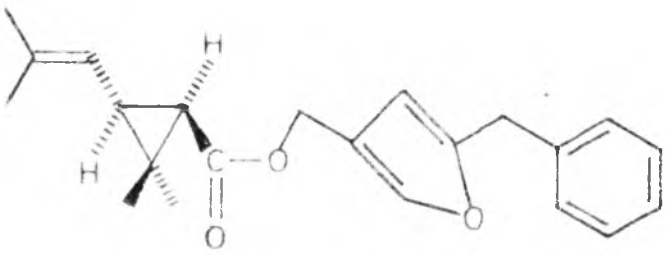
"Synthetic Pyrethroids", bearing a close structural resemblance to natural pyrethrins and cinerins are increasingly becoming important as "Pest Control Agents". These insecticides have an advantage over other insecticides in the fact that they combine high insecticidal activity with low mammalian toxicity[1,2]. They are also superior to natural pyrethrins[3,4] in having higher photostability[5] and are therefore applicable for agricultural use[6]. 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 Permethrin[9] (NRDC 143).

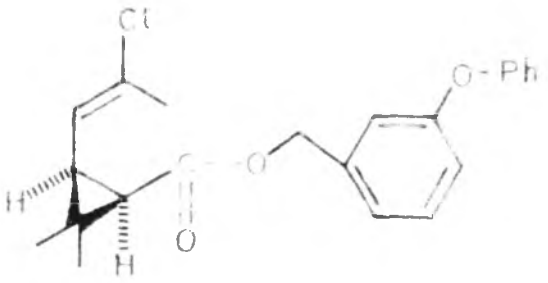
Structurally, most of these synthetic pyrethroids are esters of 2,2-dimethyl-3-vinyl substituted cyclopropane carboxylic acids, with alcohols like 3-phenoxy benzyl alcohol[10,11] as in permethrin or 5-benzyl-3-furyl methyl alcohol as in resmethrin[10]. Variation of the vinyl substituent at the 3-position of the cyclopropane carboxylic acid is possible while maintaining insecticidal activity[8]. The synthesis of the various 3-vinyl substituted analogues was achieved by the reaction of appropriate Wittig reagents



PERMETHRIN



BIORESMETHRIN



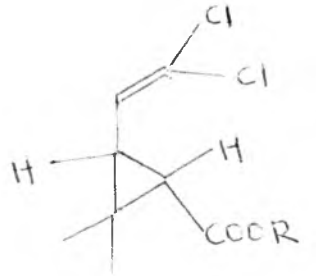
INDOTHRIN

with caronaldehyde ester[13,14]. Permethrin[9] has been synthesised either by a Wittig reaction[14] or from acyclic intermediates involving ring closure of the cyclopropane ring system[15].

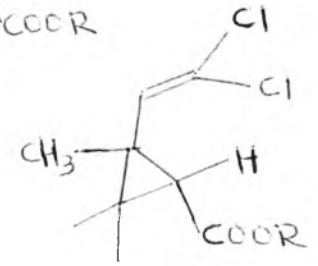
The natural pyrethrins and the synthetic pyrethroid group of insecticides are flexible molecules. Their insecticidal action depends on their ability to adopt a conformation in which all the structural features, essential for potency are appropriately oriented with respect to each other and to a complementary 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 acid with the carboxylic substituent in the 1R configuration, whether the side chain at C-3 is trans or cis to the carboxylic group are active[16-19] whereas esters of the 1S epimer are inactive or much less active. The potency of such esters is also sensitive

to the substitution at or on the side chain at C-3[17,19]. For example,



is more active than



Thus in the acid moiety of the pyrethroids, the side chain attached at C-3 position of the cyclopropane ring system, is a position where structural changes greatly influence insecticidal activity, which again depends on the nature of the substituents in the side chain. However, mammalian toxicity is not appreciably influenced by changes in the structure of the side chain. Thus, a simple modification in the structure of the side chain at C-3 in bioresmethrin[13] where isobutenyl group is replaced by but-1-enyl group produces still greater activity but retain low mammalian toxicity. Similarly esters with simple vinyl substituent was found to be less active than chrysanthemate but monomethyl vinyl ester was more active. Maximum activity[13] was observed in the case of esters with but-1-enyl side chain at C-3.

The high activity is attained in esters with

Z and E butadienyl and pentadienyl substituents[19] at C-3, *trans* and *cis* to the 1R carboxylic centre, provided no methyl groups are at C_3 or C-1 at the cyclopropane ring system. However, Matsui[20] 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[4,13,21] substituted acids were found to be outstandingly potent insecticides, the *cis* esters being usually more active[22]. This observation also leads to the conclusion that presence of methyl group on the vinyl side chain at C-3 (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. The only reference available in literature is from[23,24] M. Jacques *et al.* They have obtained diphenyl vinyl

analogues by synthetic route and showed its ester to possess insecticidal property.

In our laboratory, a new synthetic pyrethroid[25], called "Indothrin" viz. 3-phenoxy benzyl 1R cis-2,2-dimethyl -3(2-chloro-prop-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, a cheap abundant, indigenous by-product from Pine oil (Pinus longifolia).

In continuation of the efforts towards preparing new synthetic pyrethroids, containing different types of 3-substituted vinyl side chains, we have now achieved the synthesis of three new acid moieties, viz.

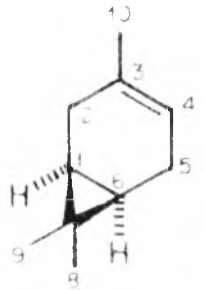
1. Methyl 1R trans 2,2-dimethyl-3 (2,2-diphenyl vinyl) cyclopropane carboxylate (XIV).
2. Methyl 1R cis 2,2-dimethyl-3 (2-phenyl prop-1-enyl) cyclopropane carboxylate (XXV) and
3. Methyl 1S cis 2,2-dimethyl-3 (2-phenyl-2-chloro vinyl) cyclopropane carboxylate (XXXII).

From these acids pyrethroids will be synthesised with alcohols like 3-phenoxy benzyl alcohol and tested for their insecticidal activity.

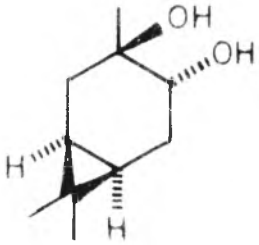
PRESENT WORK

(+)Car-3-ene (I) was converted into trans 3α,4α-carane diol (II), $C_{10}H_{18}O_2$, m.p. 82-83°, by a known[26] method in 45% yield. The diol (II) was oxidised by Jones chromic acid reagent to give the keto carboxylic acid (III) in 75% yield, which was converted to its methyl ester (IV) by methanol/sulphuric acid in almost quantitative yield (see Chapter I of this thesis). The keto ester (IV) was subjected to Baeyer-Villiger oxidation using perbenzoic acid to afford the known[27] acetate ester (V) $C_{11}H_{18}O_4$, in 70% yield, b.p. 110°(bath)/1 mm. It showed IR bands at 1740 (>C=O), 1233 (-O-Ac) and NMR signals at 9.1 (2H, m, cyclopropane protons); 8.97, 8.87 (3H each, s, gem-dimethyl on cyclopropane); 8.02 (3H, s, acetate methyl); 7.72 (2H, d, J = 7 Hz, $-CH_2CO-$); 6.37 (3H, s, $-COOCH_3$) and 5.98 (2H, d, J = 8 Hz, $-CH_2-OAc$).

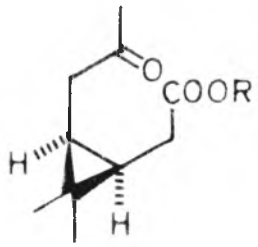
The acetate ester (V) was subjected to Grignard reaction using an excess of phenyl magnesium bromide (5 moles) to furnish the expected diol (VI), $C_{20}H_{24}O_2$, M^+ 296, as the main product along with less polar product. The mixture was separated by chromatography over alumina (1:10) and the diol (VI) was obtained as a thick viscous liquid. It showed IR bands at 3509 (OH), 1020 ($-CH_2-OH$) 1600, 746, 694 (aromatic) and NMR signals at 9.53 (2H, m, cyclopropane protons at C_1 and C_3); 9.1 (6H, s, gemdimethyl



I

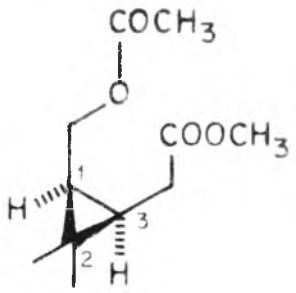


II

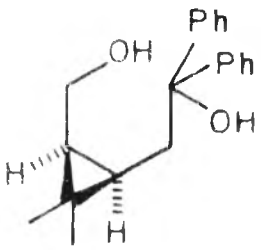


III R = H

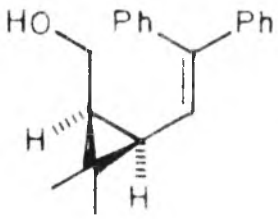
IV R = CH_3



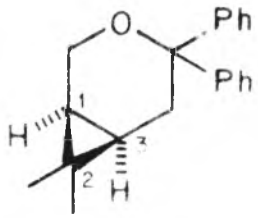
V



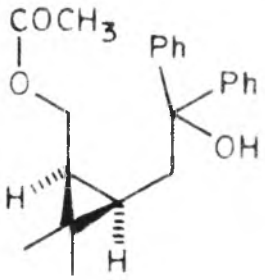
VI



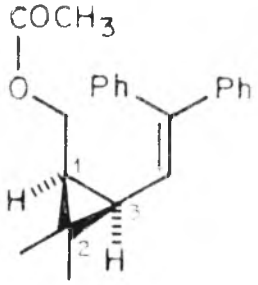
VII



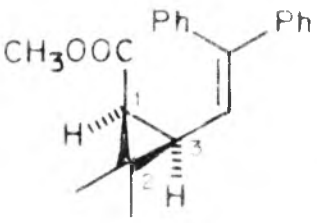
VIII



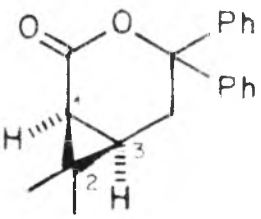
IX



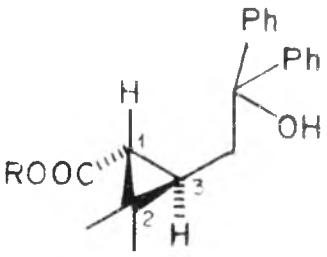
X



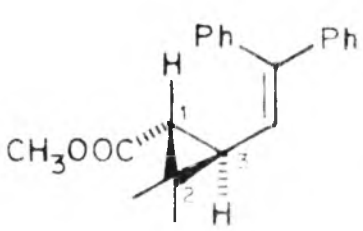
XI



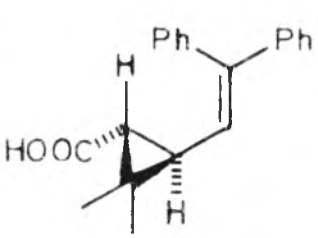
XII



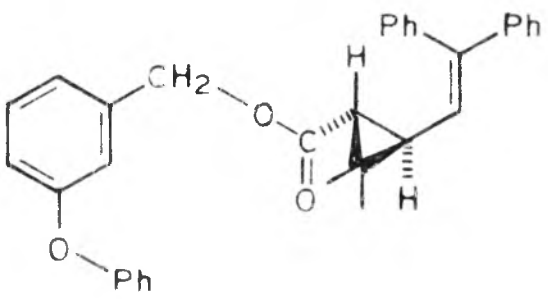
XIII



XIV



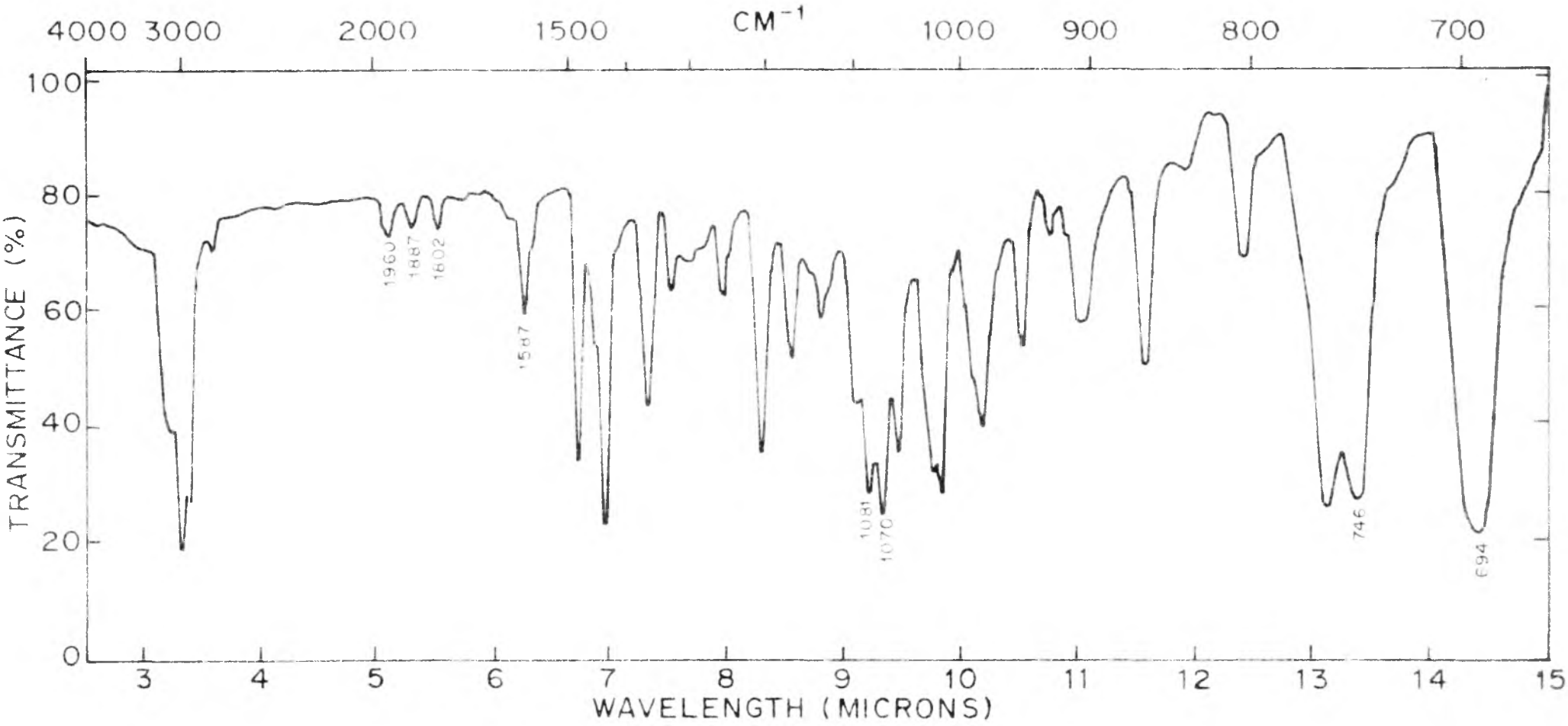
XV

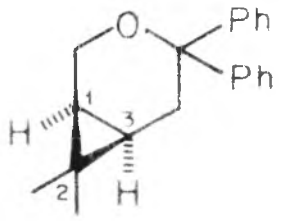


XVI

at C_2); 8.33 - 7.33 (2H, m, $-CH_2$ at C_3); 6.67 (2H, m, $-CH_2O-$ at C_1) and 2.87 (10H, m, aromatic protons).

Attempts to prepare the unsaturated alcohol (VII) by preferential dehydration of the tertiary hydroxyl group of (VI) by catalytic quantity of paratoluenesulphonic acid in benzene under refluxing conditions, resulted in the formation of the cyclic ether (VIII), instead of the desired alcohol (VII). The ether (VIII), $C_{20}H_{22}O$, M^+ 278, showed IR (Fig.1) bands at 1960, 1887, 1802, 1587, 746, 694 (aromatic), 1081, 1070 (cyclic ether) and NMR (Fig.2) signals at 9.83 (1H, dd, J_1 = 4 Hz, J_2 = 10 Hz, cyclopropane proton at C_3); 9.13 (1H, d, J = 4 Hz, proton at C_1); 8.97, 8.78 (3H each, s, methyls on cyclopropane); 8.38 (1H, dd, J_1 = 4 Hz, J_2 = 16 Hz, one of the protons of $-CH_2$ at C_3); 7.25 (1H, dd, J_1 = 10 Hz, J_2 = 16 Hz, another proton of $-CH_2$ group at C_3); 6.28 (2H, m, $-CH_2-O-$ at C_1) and 2.9, 2.77 (5H each, br.s, aromatic protons). Considering the 4 line pattern of each proton at C_3 and the two protons of the $-CH_2$ group at C_3, as also the large difference in the chemical shifts of the geminal protons of the $-CH_2$ group at C_3, it appears that they form an AMX system[28]. The ether (VIII) was also obtained by treating the diol (VI) in ethanol with catalytic quantity of sulphuric acid.


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
1960
1887
1602
1567
1081
1070
746
694
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


O
Ph
Ph
1
2
3
H
H

(VIII)

FIG. 1

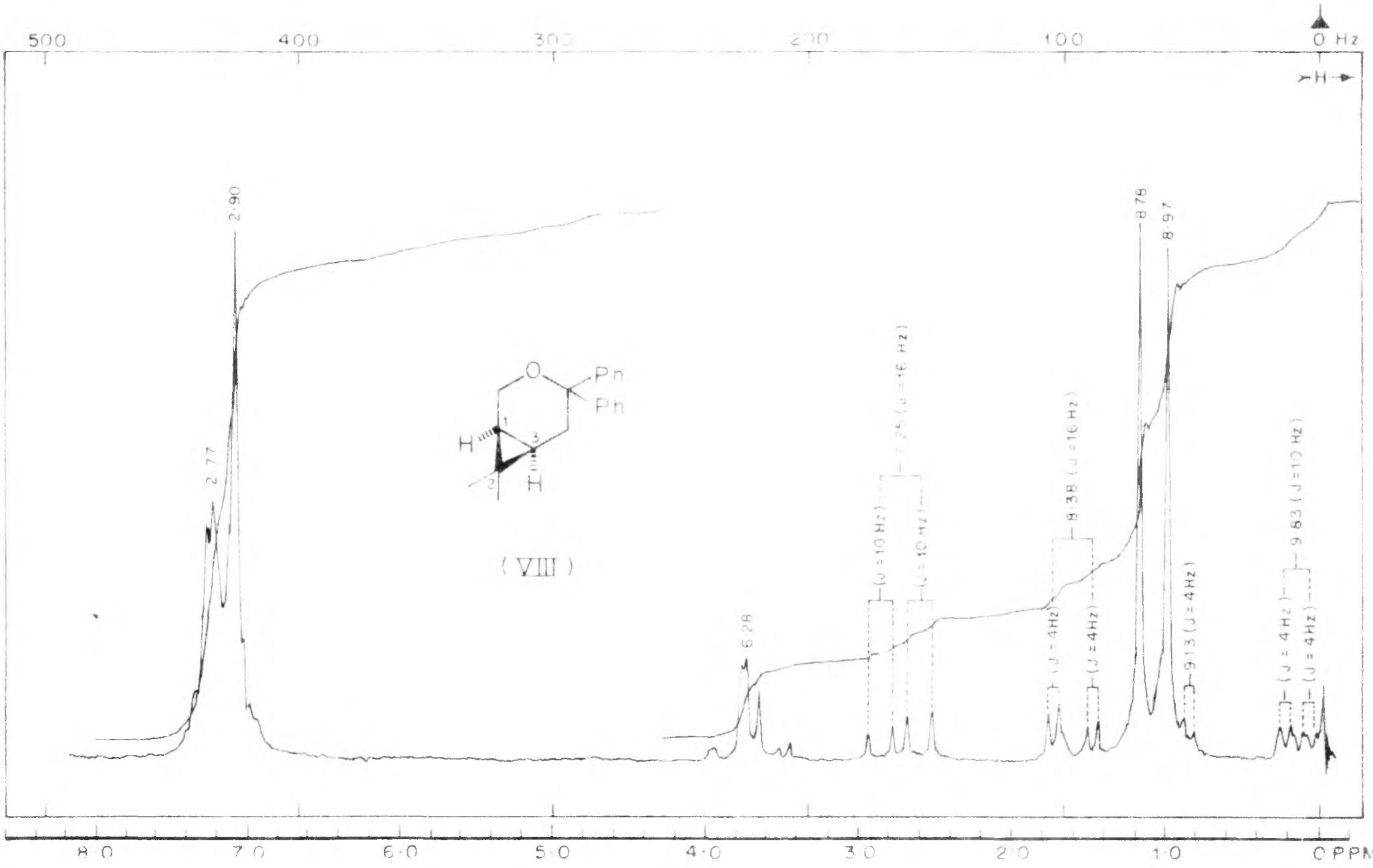
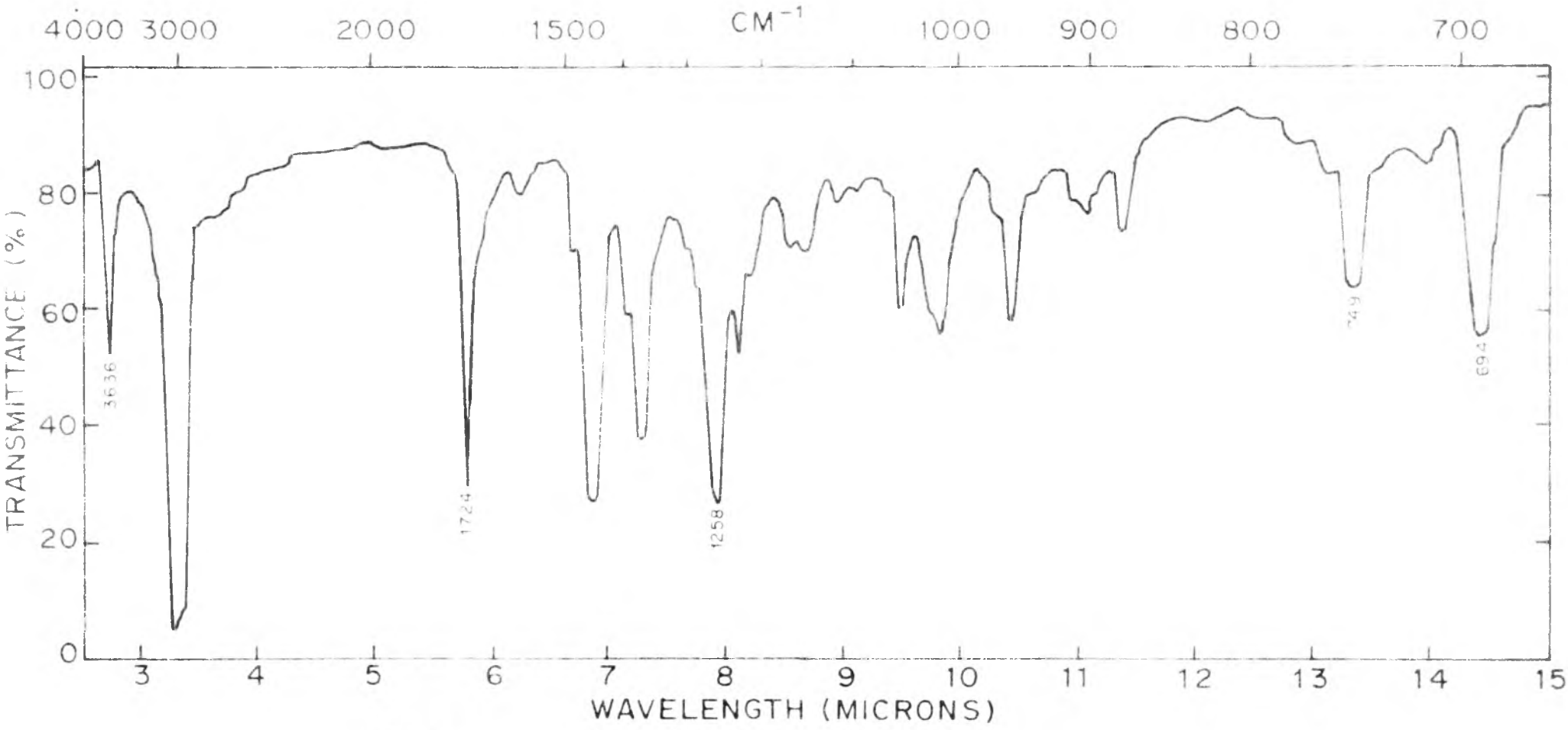

500
400
300
200
100
0 Hz
δH
2·90
2·77
6·28
(J =10 Hz)
7·25 (J =16 Hz)
(J =10 Hz)
8·38 (J =16 Hz)
(J =4Hz)
(J =4Hz)
8·78
8·97
9·13 (J =4Hz)
(J = 4Hz)
9·83 (J =10 Hz)
(J =4Hz)
O
Ph
Ph
H
H
1
2
3
(VIII)
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

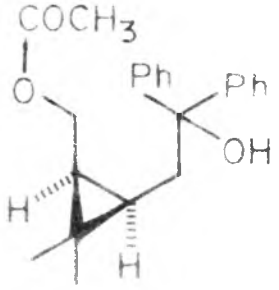
FIG. 2.

In order to overcome this difficulty, the diol (VI) was acetylated (Ac_2O/pyridine) to give quantitatively the crystalline hydroxy monoacetate (IX), $C_{22}H_{26}O_3$, M^+ 338, m.p. 85° (pet. ether). It showed IR (Fig.3) bands at 3636 (OH), 1724, 1258 (acetate), 749, 694 (aromatic) and NMR (Fig.4) signals at 9.37 - 9.13 (2H, m, cyclopropane protons at C_1 and C_3); 9.2, 9.08 (3H each, s, gemdimethyl at C_2); 8.07 (3H, s, acetate methyl); 7.83 (2H, d, J = 6 Hz, $-CH_2-$ at C_3); 7.58 (1H, s, exchangeable with D_2O, -OH proton); 6.12 (2H, d, J = 7.2 Hz, $-CH_2-$ at C_1) and 2.9 (10H, br.s, aromatic protons).

The hydroxy acetate (IX) was dehydrated using catalytic quantity of P.T.S. in refluxing benzene to afford exclusively the unsaturated acetate (X), as a thick liquid, $C_{22}H_{24}O_2$. It showed IR bands at 1739, 1227 (acetate), 1600, 760, 694 (aromatic) and NMR signals at 9.07 (1H, br.s, proton at C_1); 8.93, 8.83 (3H each, s, cyclopropane methyls); 8.65 (1H, d, J = 9 Hz, proton at C_3); 8.07 (3H, s, acetate methyl); 5.92 (2H, d, J = 8 Hz, $-CH_2-$ at C_1); 4.45 (1H, d, J = 9 Hz, olefinic proton) and 3.07, 2.97 (5H each, s, aromatic protons).

Hydrolysis of the unsaturated acetate (X) by methanolic sodium hydroxide (10%) afforded the unsaturated alcohol (VII), as a thick liquid in 95% yield, $C_{20}H_{22}O$. It


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3636
1724
1258
749
694
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


COCH3
O
Ph
Ph
OH
H
H

(IX)

FIG. 3.

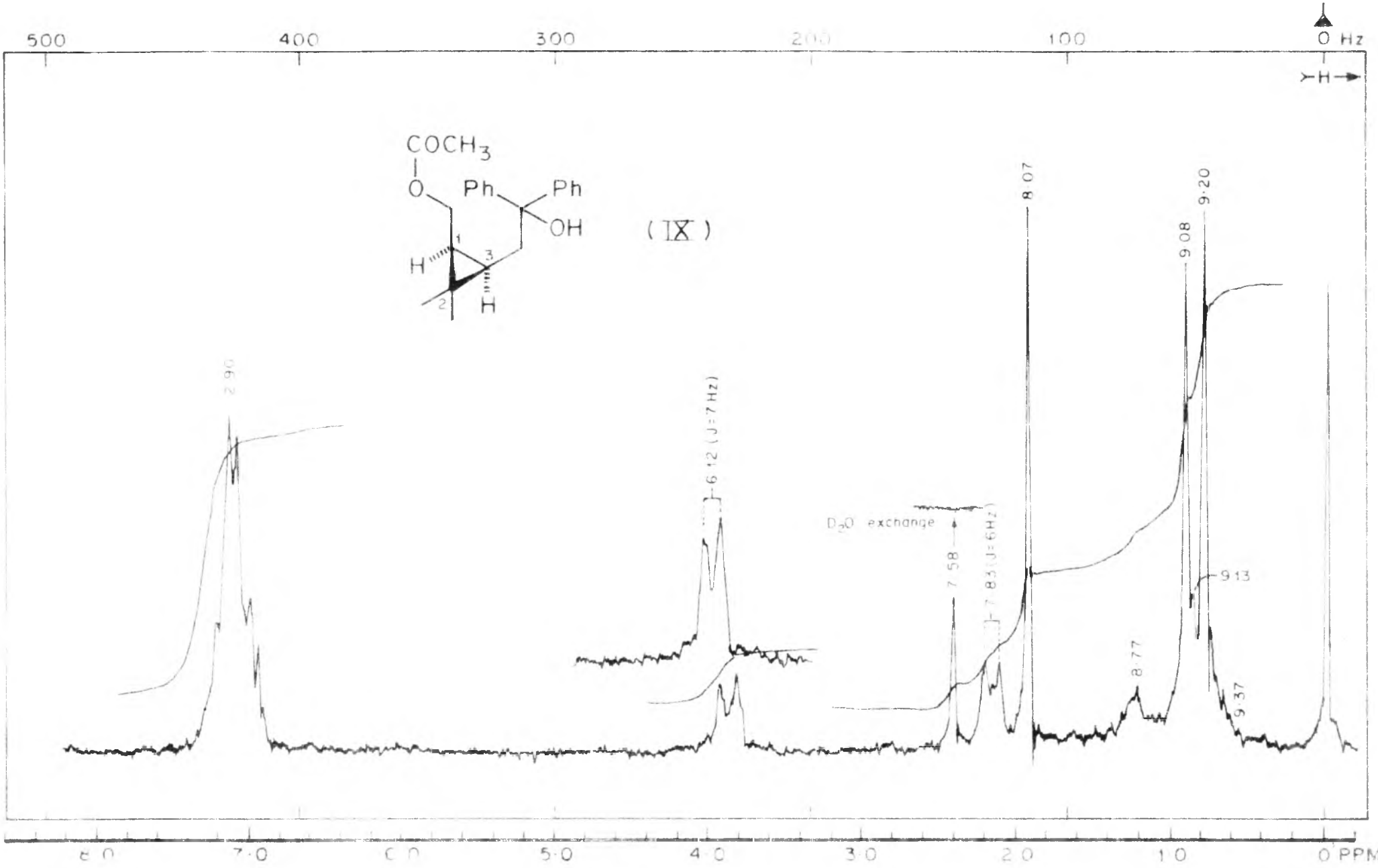

500
400
300
200
100
0 Hz
COCH3
O
Ph
Ph
OH
H
H
1
2
3
(IX)
2.90
6.12 (J=7Hz)
D2O exchange
7.58
7.83 (J=6Hz)
8.07
8.77
9.08
9.20
9.13
9.37
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)

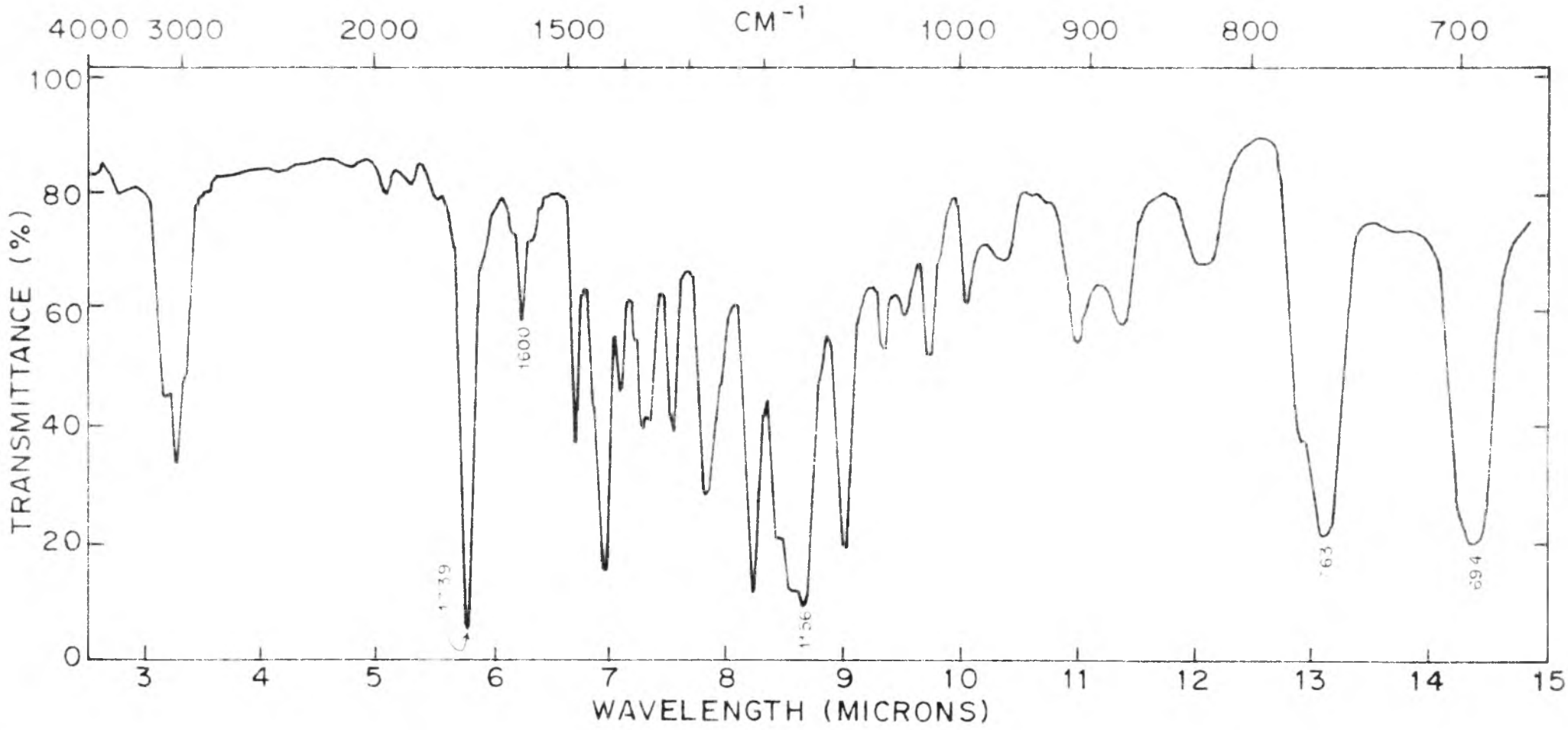
FIG 4

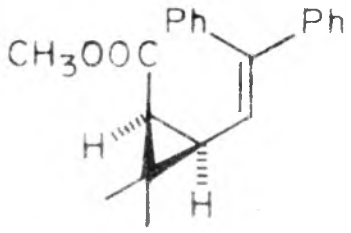
showed IR bands at 3509 (OH), 1005 ($-CH_2-O$), 1600, 758, 694 (aromatic) and NMR signals at 9.1 (1H, br.d, proton at C_1); 8.93, 8.82 (3H each, s, cyclopropane methyls at C_2); 8.67 (1H, d, J = 9 Hz, proton at C_3); 8.32 (1H, s, exchangeable with D_2O, -OH proton); 6.33 (2H, d, J = 8 Hz, $-CH_2-O$ at C_1); 4.37 (1H, d, J = 9 Hz, olefinic proton) and 3.00, 2.9 (5H each, s, aromatic protons).

The alcohol (VII) was oxidised by Jones chromic acid reagent at 0° to afford an acid (70%) which was converted to its methyl ester by an ethereal solution of diazomethane and purified by distillation to afford ester (XI), $C_{21}H_{22}O_2$, b.p. 190° (bath)/1 mm, $[\alpha]_D^{28}$ $+161^\circ$ (c, 1.1). It showed IR (Fig.5) bands at 1739, 1156 (ester), 1600, 763, 694 (aromatic) and NMR (Fig.6) signals at 8.82, 8.75 (3H each, s, cyclopropane methyls); 8.5 (1H, d, J = 5 Hz, proton at C_1); 7.98 (1H, dd, J_1 = 5 Hz, J_2 = 9 Hz, proton at C_3); 6.45 (3H, s, ester methyl); 4.33 (1H, d, J = 9 Hz, olefinic proton) and 2.88, 2.77 (5H each, s,aromatic protons).

During the sequence of these reactions the C_1 centre of (XI) was not disturbed and the <u>cis</u> relationship between C_1 - H and C_3 - H, (as in car-3-ene) was maintained. Hence the ester (XI) must possess <u>cis</u> 1S, 3R configuration.

Jones chromic acid oxidation of the diol (VI) at


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
1600
1739
1156
763
694


Ph
Ph
CH3OOC
H
H

(XI)

FIG. 5.

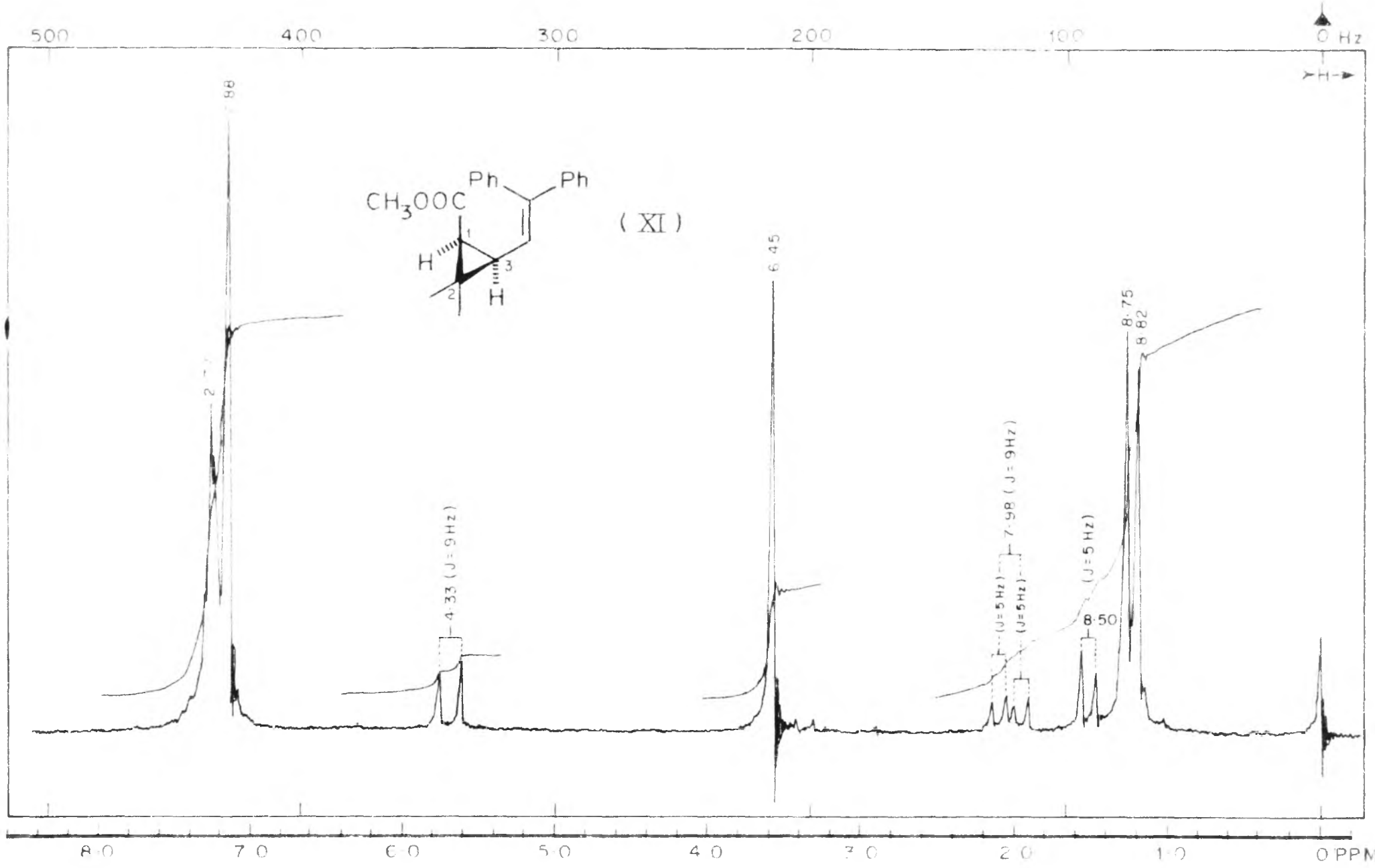
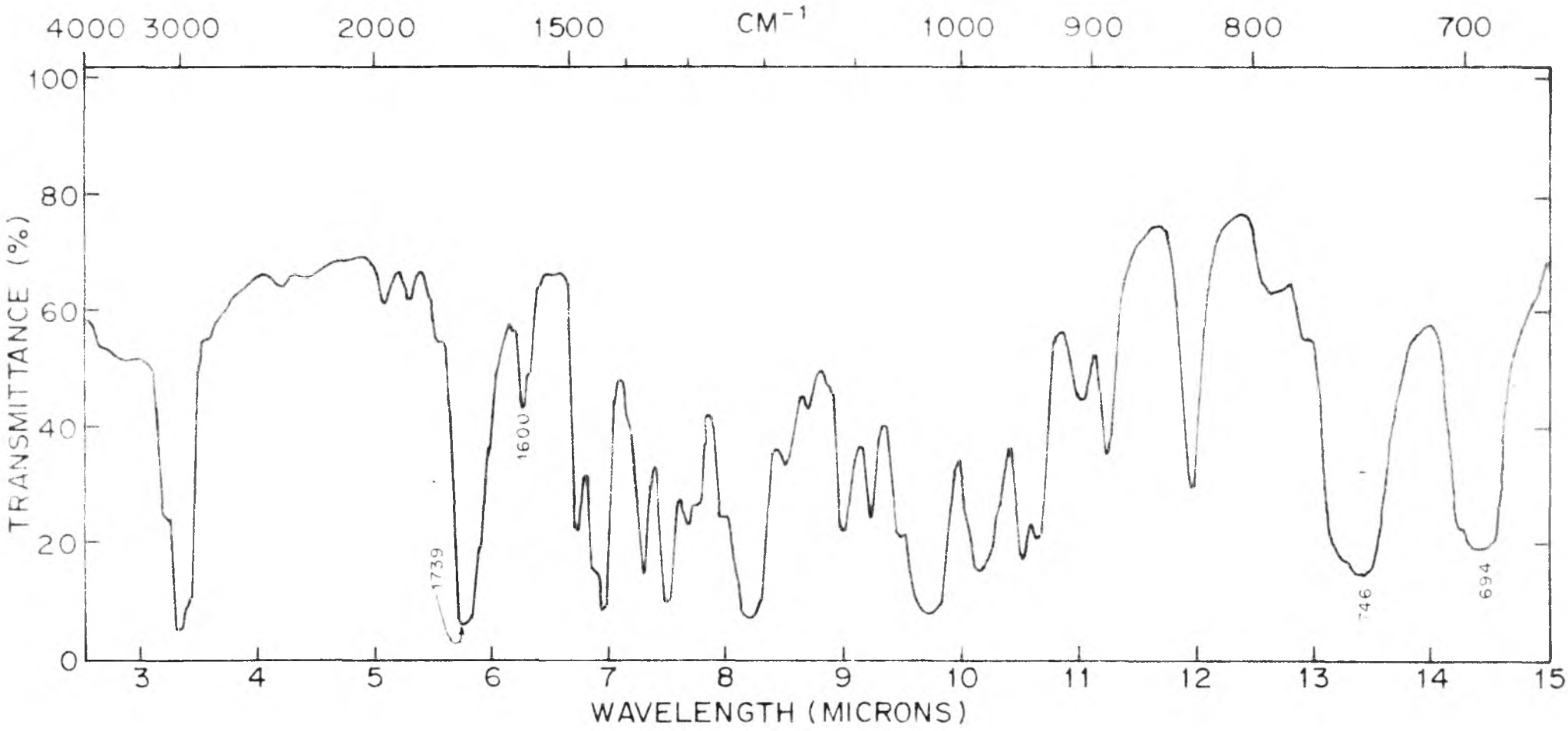

500
400
300
200
100
0 Hz
Ph
Ph
CH3OOC
H
H
1
2
3
(XI)
6·45
8·75
8·82
4·33 (J=9Hz)
7·98 (J=9Hz)
(J=5Hz)
(J=5Hz)
(J=5Hz)
8·50
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

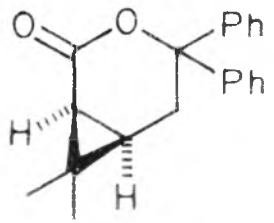
FIG 6

0° gave in 75% yield, the γ-lactone (XII), as a thick liquid, $C_{20}H_{20}O_2$, M^+ 292, $[\alpha]_D^{28}$ +143° (c, 2.8). It showed IR (Fig.7) bands at 1739 (γ-lactone), 1600, 746, 694 (aromatic) and NMR (Fig.8) signals at 9.03 (1H, m, proton at C_3); 8.85, 8.77 (3H each, s, cyclopropane methyls); 8.6 (1H, d, J = 6 Hz, proton at C_1); 7.97 (1H, dd, J_1 = 6 Hz, J_2 = 16 Hz, one of the protons of $-CH_2-$ at C_3); 6.93 (1H, dd, J_1 = 9 Hz, J_2 = 16 Hz, another proton of $-CH_2-$ at C_3) and 2.8 (10H, br.s, aromatic protons).

The lactone (XII) was saponified by excess of methanolic sodium hydroxide under reflux for 4 hrs or at room temperature for 36 hrs to afford exclusively a hydroxy acid (XIII, R=H) which was characterised through its methyl ester (XIII, R=CH_3) $C_{21}H_{24}O_3$, obtained as a glassy thick liquid. It showed IR bands at 3571, 1156 (tertiary -OH), 1709 (ester), 1600, 746, 694 (aromatic) and NMR signals at 9.12, 9.08 (3H each, s, methyls on cyclopropane); 8.78 - 8.97 (2H, m, cyclopropane protons at C_1 and C_3); 7.8 (1H, br.s, exchangeable with D_2O, -OH proton); 7.52 (2H, d, J = 5 Hz, $-CH_2$ at C_3); 6.62 (3H, s, ester methyl) and 3.00 (10H, br.s, aromatic protons).

The hydroxy ester (XIII, R=CH_3) was smoothly and


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
1739
1600
746
694
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


O
O
Ph
Ph
H
H

(XII)

FIG. 7.

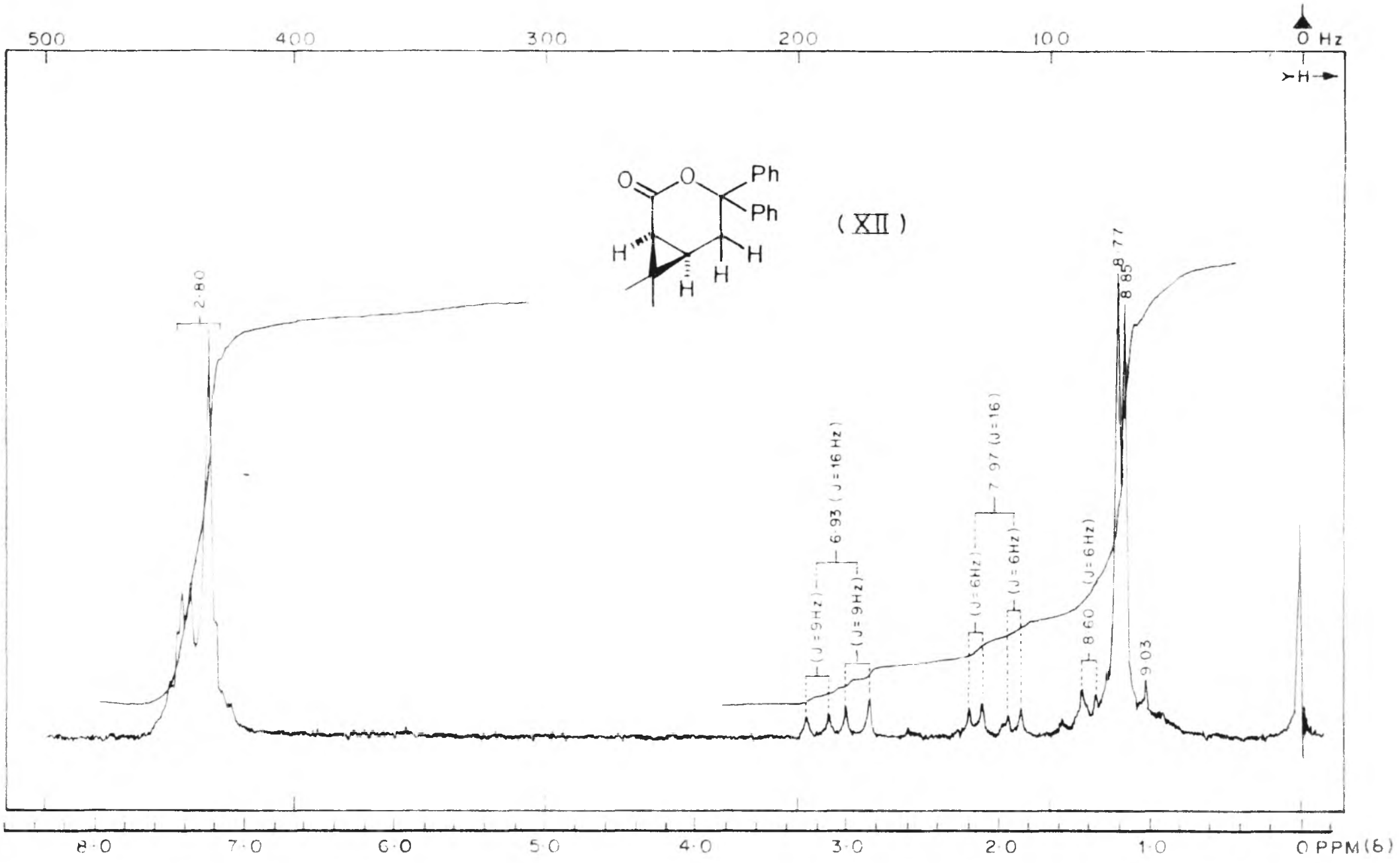

500
400
300
200
100
0 Hz
TMS
Ph
Ph
H
H
H
H
O
O
O
(XII)
2·80
6·93 (J = 16 Hz)
(J = 9Hz)
(J = 9Hz)
7·97 (J = 16)
(J = 6Hz)
(J = 6Hz)
8·60 (J = 6Hz)
8·85
8·77
9·03
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

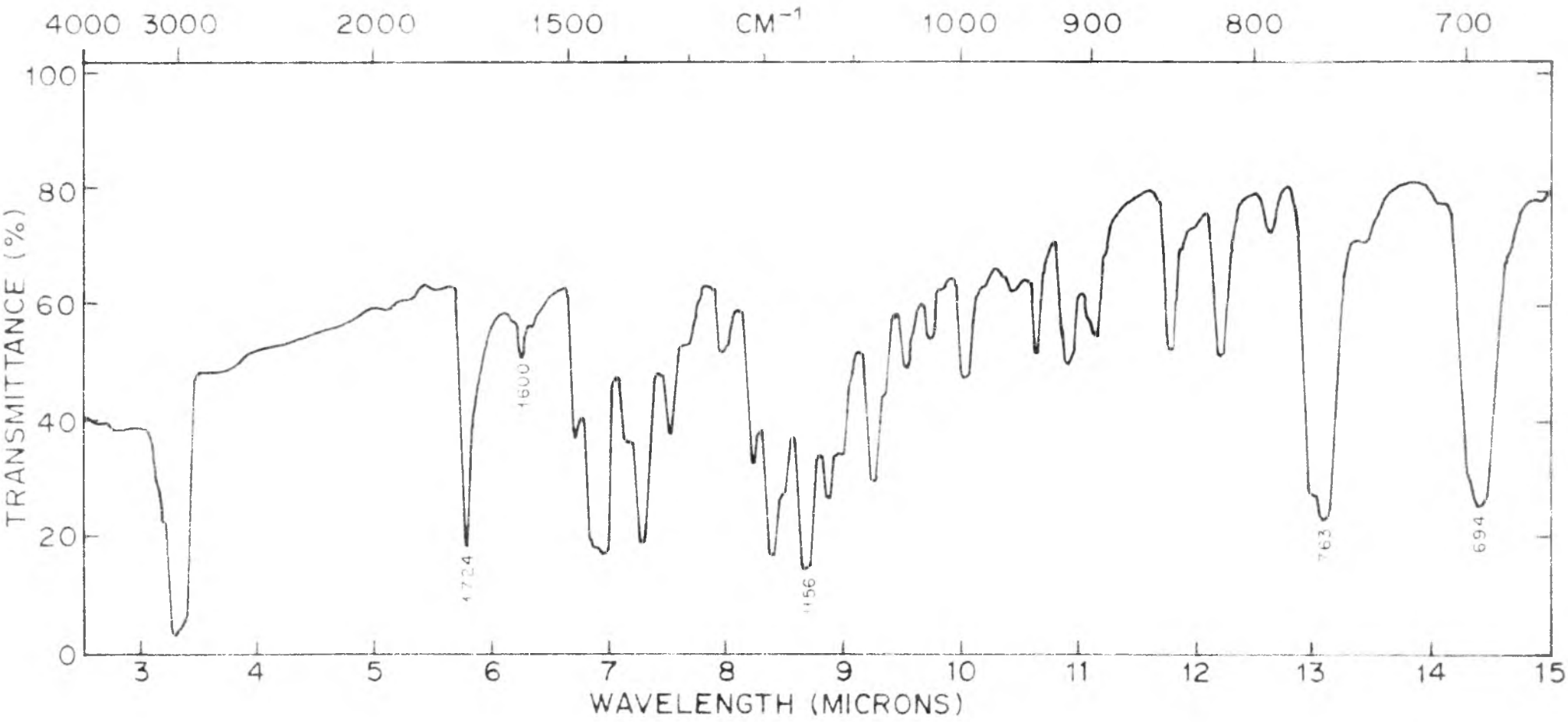
FIG. 8.

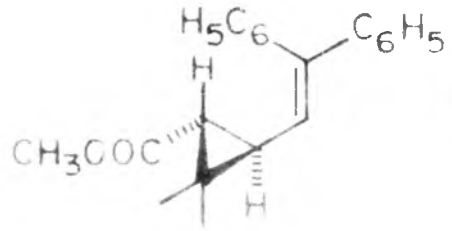
quantitatively dehydrated by PTS in refluxing benzene to afford a solid unsaturated ester (XIV), $C_{21}H_{22}O_2$, M^+ 306, m.p. 89° (pet. ether), $[\alpha]_D^{28}$ -9.0° (c, 1.8). It showed IR (Fig.9) bands at 1724, 1156 (ester), 1600, 763, 694 (aromatic) and NMR (Fig.10) signals at 8.87, 8.63 (3H each, s, cyclopropane methyls); 8.42 (1H, d, J = 9 Hz, proton at C_1); 8.28 (1H, dd, J_1 = 9 Hz, J_2 = 18 Hz, proton at C_3); 6.38 (3H,s, ester methyl); 3.58 (1H, d, J = 9 Hz, olefinic proton) and 2.87, 2.78 (5H each, s, aromatic protons).

The IR and NMR spectra of this compound (XIV) were different from that of <u>cis</u> ester (XI) which, however, was obtained as a liquid. It, therefore, appears that during saponification of lactone (XII), epimerisation at C_1 is also taking place to afford the <u>trans</u> hydroxy acid (XIII, R=H).

The ester (XIV), on hydrolysis with alcoholic alkali, gave the acid (XV) which was converted into its 3-phenoxy benzyl ester (XVI), $C_{33}H_{30}O_3$. The ester (XVI) obtained as semisolid, showed IR (Fig.11) bands at 1709, 1235 (ester), 1575, 758 (aromatic) and NMR (Fig.12) signals at 8.85, 8.63 (3H each, s, methyls on cyclopropane); 8.28 (2H, m, cyclopropane protons at C_1 and C_3); 4.93 (2H, s, benzylic methylene protons); 3.63 (1H, d, J = 8 Hz, olefinic proton) and 2.85 (19H, m, aromatic protons).

This pyrethroid is being tested for its insecticidal property.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
1724
1600
1156
763
694


H5C6
C6H5
H
CH3OOC
H

(XIV)

FIG. 9

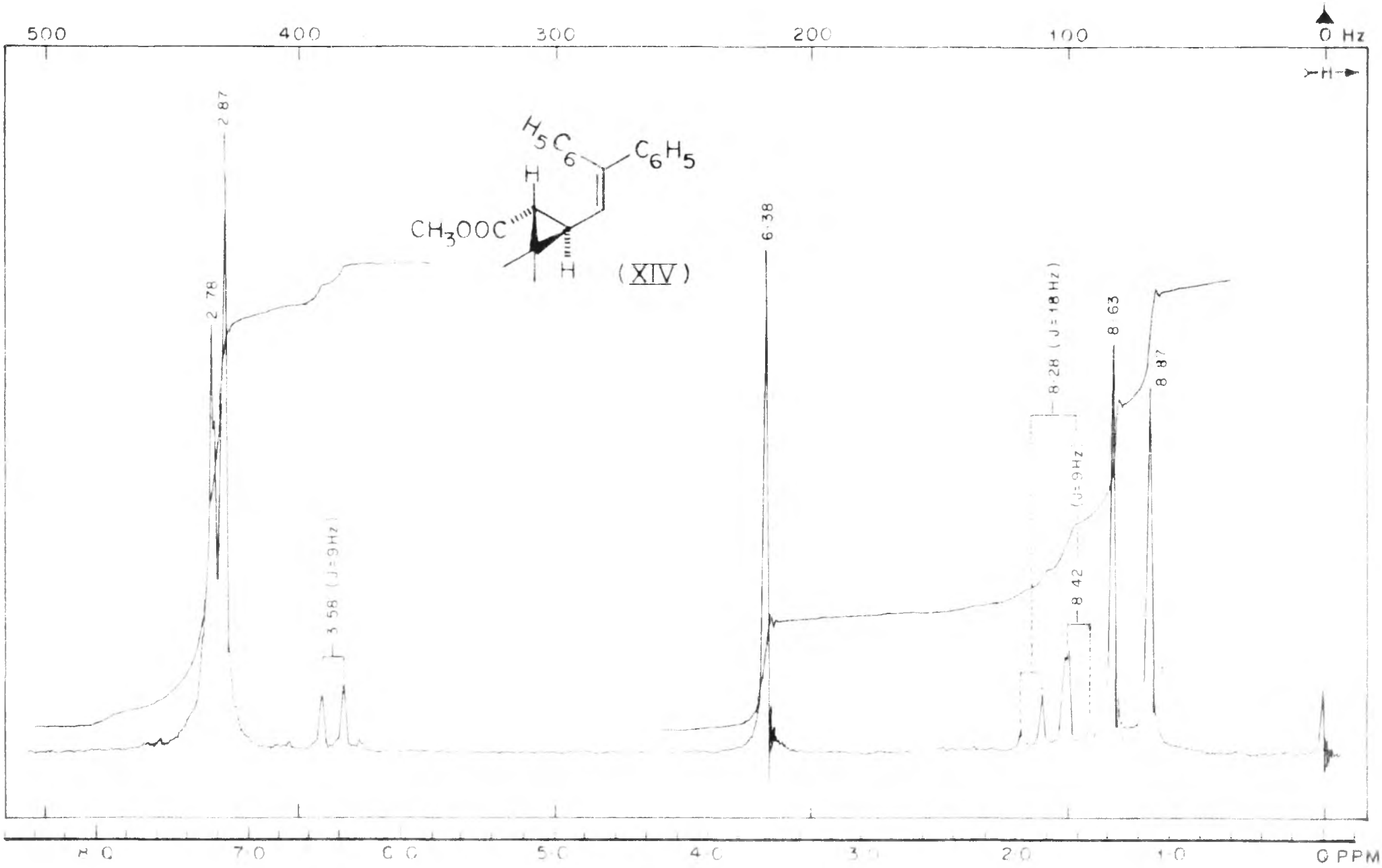
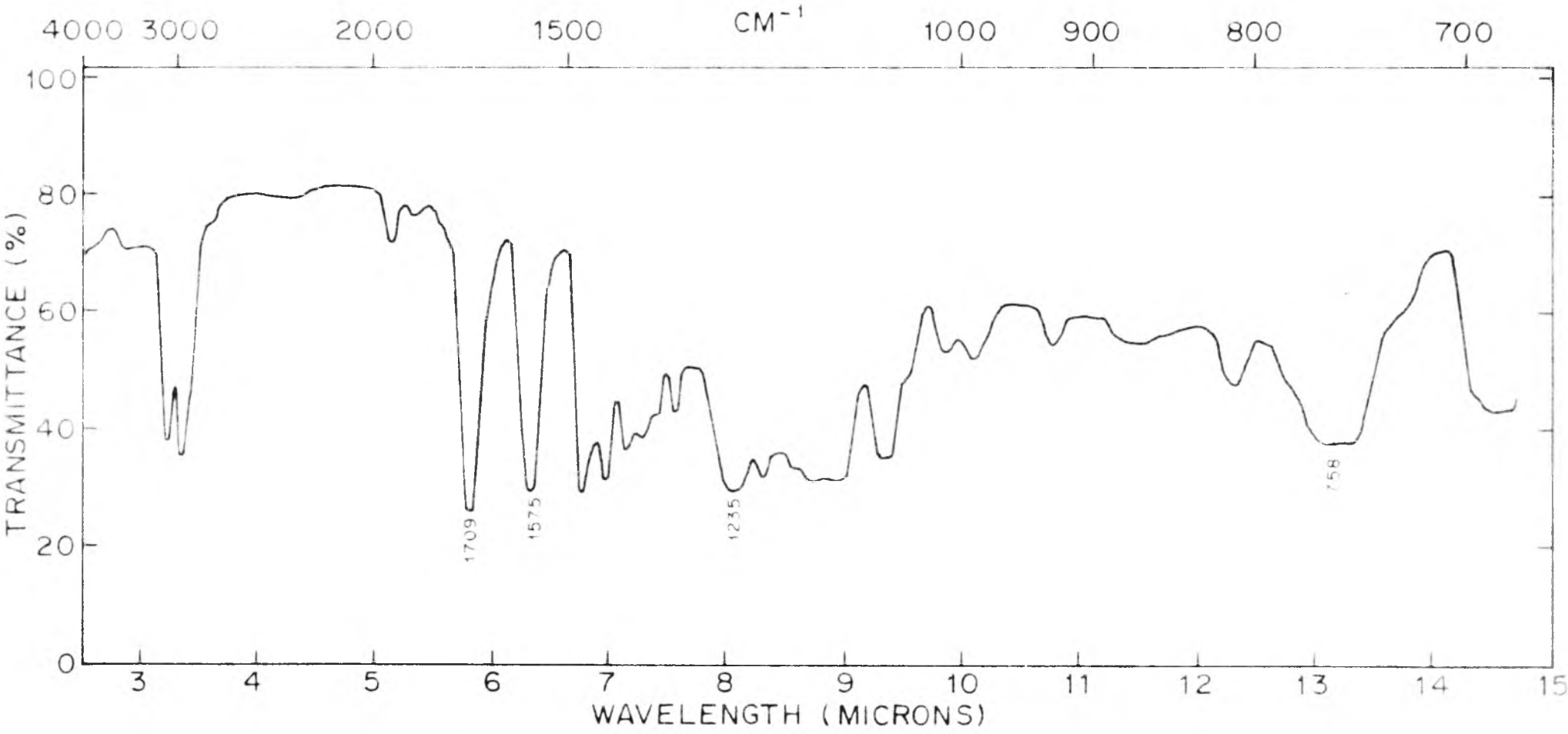
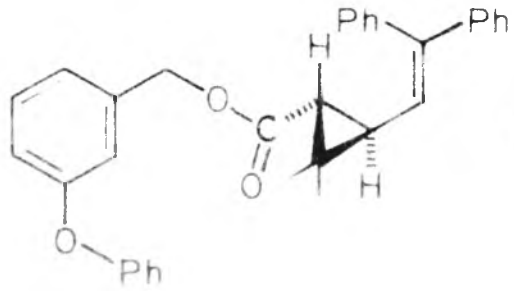
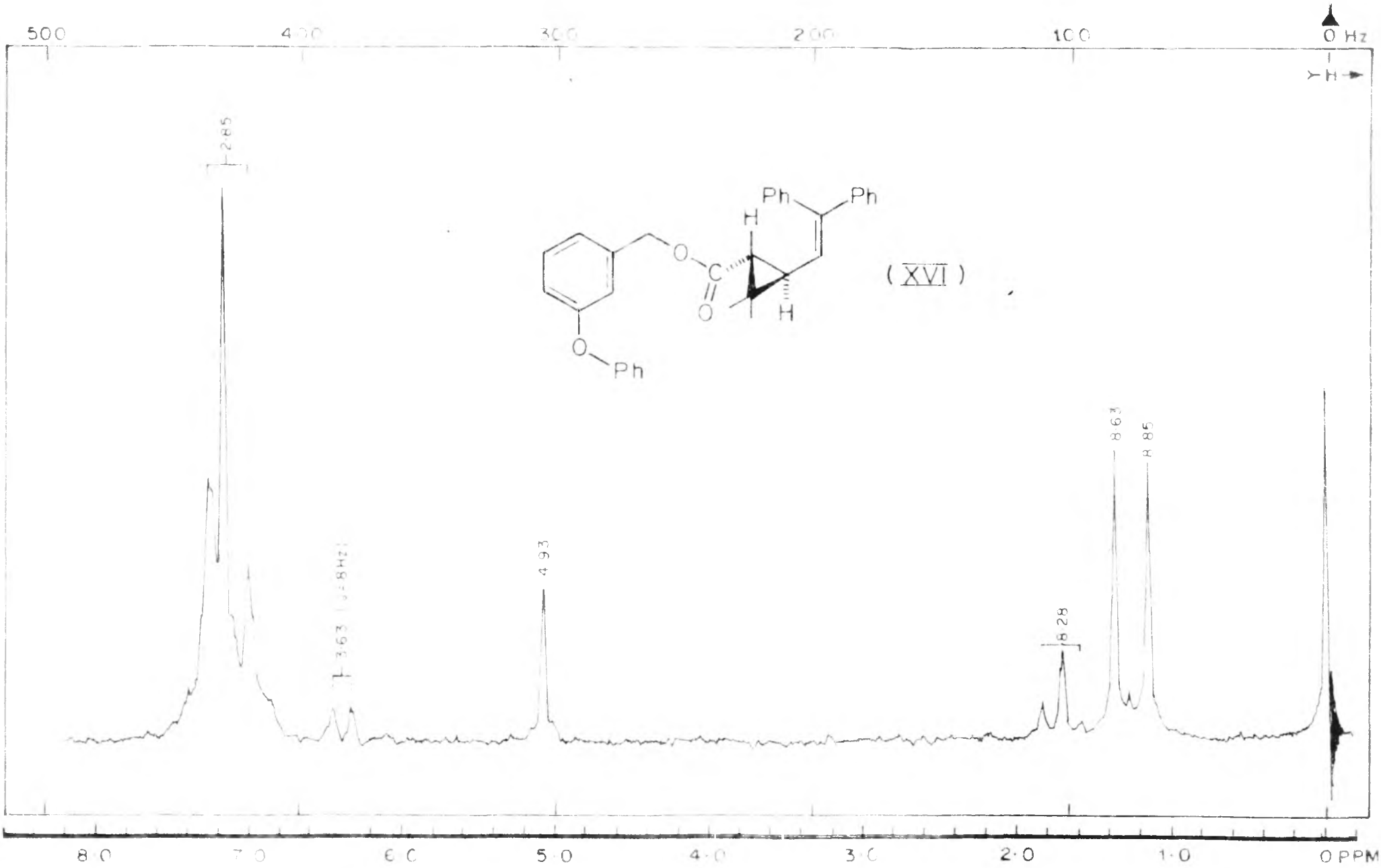

500
400
300
200
100
0 Hz
H
2.87
2.78
3.58 (J=9Hz)
6.38
8.28 (J=18Hz)
8.42
(J=9Hz)
8.63
8.87
H_5C_6
C_6H_5
CH_3OOC
H
H
(XIV)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)

FIG 10


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1709
1575
1235
758
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


Ph
Ph
H
O
C
O
H
O
Ph

(XVI) FIG 11


500
400
300
200
100
0 Hz
2.85
3.63 (J=8Hz)
4.93
8.29
8.63
8.85
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)
Ph
Ph
H
O
C
O
H
O
Ph

(XVI)

FIG 12

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

Methyl 2,2-dimethyl-1-acetoxymethyl-cyclopropane-3-acetate (V)

To a stirred and ice-cooled solution of keto ester (IV, 30 g) [see Chapter I, page 50] in chloroform (100 ml), were added a chloroform solution of perbenzoic acid (200 ml, 1N) and para-toluene sulphonic acid (0.5 g) and the solution stirred for 48 hrs maintaining the temperature of the contents at 10-15°. The solution was then transferred to a separating funnel and washed repeatedly with 10% aqueous sodium carbonate solution to free it from acids. It was then washed with water and dried. Removal of chloroform by distillation gave the product which was further purified by distillation to give the acetate ester (V), 26 g (80%), b.p. 110° (bath)/1 mm, $[\alpha]_D^{28}$ +28.86° (c, 6.8).

Analysis: Found: C, 61.50; H, 8.62; $C_{11}H_{18}O_4$ requires: C, 61.66; H, 8.47%.

Ir bands at 3030, 1740, 1429, 1361, 1233, 1170, 1015, 857 and 823 cm^{-1}.

2,2-Dimethyl-1-hydroxymethyl-cis-3(2,2-diphenyl - ethan-2-ol)-cyclopropane (VI)

To an ice cooled solution of phenyl magnesium bromide, prepared from magnesium (12 g, 0.5 mole) and bromobenzene (78.5 g, 0.5 mole) in dry ether (250 ml) was added, dropwise, a solution of acetate ester[(V), 21.4 g, 0.1 mole] in ether (100 ml), with vigorous stirring. After the addition, the reaction mixture was stirred for 1 hr at room temperature and under reflux for 0.5 hr. The stirred mixture was then cooled to 0° and a saturated solution of ammonium chloride (400 ml) was introduced dropwise. When addition of ammonium chloride was over the mixture was brought to room temperature and stirred for 20 minutes. It was transferred to a separating funnel, ether layer was separated and aqueous portion extracted with ether (100 ml x 2). The combined ether extract was washed with water and dried. Removal of ether by distillation furnished the product (34.4 g). It showed on TLC (20% ethyl acetate in C_6H_6) mainly three spots, differing much in their polarity.

The crude product (34.4 g) was chromatographed on alumina (Gr.II, 350 g) and eluted with pet. ether, pet. ether + benzene (1:1), chloroform, and chloroform + ethyl acetate (4:1).

The earlier fractions, eluted with pet. ether and pet. ether + benzene (1:1) gave the less polar compound, the minor one, which was not investigated further. Fractions eluted with chloroform and chloroform + ethyl acetate (4:1) furnished the diol (VI, 28.38 g) as a thick viscous liquid. Yield 96.0%, $[\alpha]_D^{28}$ +8.9° (c, 2.47).

Analysis: Found: C, 80.78; H, 8.06; $C_{20}H_{24}O_2$ requires: C, 81.04; H, 8.16%.

IR bands at 3509, 3030, 1980, 1818, 1600, 1493, 1449, 1379, 1250, 1163, 1111, 1053, 1020, 905, 870, 838, 746, and 694 cm^{-1}.

Preparation of ether (VIII) from diol (VI)

A solution of diol (VI, 1 g) in dry benzene (100 ml) was refluxed with para-toluene sulphonic acid (0.05 g) for 3 hrs. The benzene solution was washed with water (50 ml x 3) to remove PTS, dried and evaporated to furnish the product (0.850 g) which was chromatographed on silicic acid (20 g) and eluted with pet. ether to furnish (VIII, 0.675 g) as a colourless thick liquid. $[\alpha]_D^{28}$ +278.6° (c, 1.85).

Analysis: Found: C, 86.10; H, 8.22; $C_{20}H_{22}O$ requires: C, 86.28; H, 7.97%.

IR bands at 2985, 1960, 1887, 1802, 1587, 1481, 1439, 1361,

1325, 1250, 1205, 1170, 1136, 1081, 1070, 1053, 1015, 980, 948, 905, 862, 803, 760, 746 and 694 cm^{-1}.

2,2-Dimethyl-1-acetoxymethyl-cis-3(2,2-diphenyl-ethan-2-ol)-cyclopropane (IX)

To a solution of the diol (VI, 10 g) in pyridine (30 ml) was added acetic anhydride (25 ml) and the mixture was kept overnight at room temperature. It was then diluted with water (200 ml) and kept at room temperature for 1 hr. The reaction product was extracted with chloroform (100 ml, 50 ml x 2). The chloroform layer was washed with water (200 ml x 2), 10% hydrochloric acid (100 ml x 2) again with water and dried. Removal of chloroform by distillation afforded solid hydroxy acetate (IX, 11.3 g). Crystallisation from pet. ether afforded fine needles (10.7 g), m.p. 85°, $[\alpha]_D^{28}$ -6.0° (c, 1.95).

Analysis: Found: C, 78.15; H, 7.82; $C_{22}H_{26}O_3$ requires: C, 78.07; H, 7.74%.

IR bands at 3636, 3030, 1724, 1460, 1379, 1258, 1235, 1053, 1020, 957, 877, 749 and 694 cm^{-1}.

2,2-Dimethyl-1-acetoxymethyl-cis-3(2,2-diphenyl vinyl) cyclopropane (X)

A solution of hydroxy acetate (IX, 8 g) in dry

benzene (200 ml) was refluxed with para-toluene sulphonic acid (0.3 g) for 3 hrs. The benzene solution was washed with water (100 ml x 2), dried and evaporated to give dehydrated acetate (X) as a thick liquid; yield 7.3 g (96%) $[\alpha]_D^{28}$ -25.95° (c, 2.0).

Analysis: Found: C, 82.18; H, 7.70; $C_{22}H_{24})_2$ requires: C, 82.46; H, 7.55%.

IR bands at 3030, 1739, 1600, 1493, 1439, 1361, 1227, 1143, 1111, 1064, 1015, 957, 905, 877, 840, 760 and 694 cm^{-1}.

2,2-Dimethyl-1-hydroxymethyl-cis-3(2,2-diphenyl vinyl)cyclopropane (VII)

To a solution of the unsaturated acetate (X, 6.9 g) in methanol (150 ml) was added 30% aqueous solution of sodium hydroxide (50 ml) and the mixture refluxed for 5 hrs. It was then diluted with water (200 ml) and extracted with chloroform (150 ml, 50 ml x 2). The chloroform layer was washed with water (200 ml x 3) and dried. Removal of chloroform gave the unsaturated alcohol (VII, 5.8 g) as a thick liquid.

For analytical purpose further purification of (VII, 1 g) was done by chromatography using silicic acid (20 g) and eluted with chloroform to give TLC pure alcohol (VII), $[\alpha]_D^{28}$ -20.72° (c, 1.93).

Analysis: Found: C, 86.55; H, 7.86; $C_{20}H_{22}$ requires: C, 86.28; H, 7.97%.

IR bands at 3509, 3030, 1600, 1493, 1439, 1370, 1235, 1130, 1064, 1005, 877, 840, 758 and 694 cm^{-1}.

Methyl (+)-cis 2,2-dimethyl-3 (2,2-diphenyl vinyl) cyclopropane-1-carboxylate (XI)

To an ice cooled and stirred solution of the unsaturated alcohol (VII, 4.0 g) in acetone (50 ml) was added Jones chromic acid reagent, dropwise, till brown colour persisted. After the addition it was stirred for half an hour, diluted with water (200 ml) and extracted with chloroform (100 ml, 75 ml x 2). The organic layer was washed with water (200 ml x 3), dried and the solvent distilled off to give the unsaturated acid (80%). This was esterified with an ethereal solution of diazomethane to afford its methyl ester as a liquid (XI, 3.15 g), b.p. 190° (bath)/1 mm, $[\alpha]_D^{28}$ +161.0° (c, 1.1).

Analysis: Found: C, 82.18; H, 7.35; $C_{21}H_{22}O_2$ requires: C, 82.32; H, 7.24%.

IR bands at 3077, 1739, 1600, 1493, 1439, 1408, 1379, 1333, 1282, 1220, 1156, 1111, 1070, 1026, 995, 909, 877, 826, 763 and 694 cm^{-1}.

Preparation of lactone (XII) from the diol (VI)

To a stirred solution of the diol (VI, 5 g) in acetone (50 ml), cooled at 0°, was added Jones chromic acid reagent till a brown colour persisted. The mixture was stirred for 0.5 hr at 10°, diluted with water (200 ml) and extracted with chloroform (100 ml, 50 ml x 2). The chloroform layer was washed with water (200 ml x 2), 10% aqueous solution of sodium carbonate (50 ml x 2) again with water and dried. Removal of chloroform furnished the lactone (XII) in 75%, yield (3.73 g) as a colourless thick liquid.

The product (1 g) was further purified by chromatography on silicic acid (20 g) for analytical purposes, $[\alpha]_D^{28}$ +143° (c, 2.8).

Analysis: Found: C, 82.55; H, 6.98; $(C_{20}H_{20})_2$ requires: C, 82.15; H, 6.89%.

IR bands at 3030, 1980, 1739, 1600, 1493, 1439, 1379, 1333, 1307, 1220, 1176, 1117, 1087, 1031, 985, 952, 939, 889, 837, 746 and 694 cm^{-1}.

Methyl (-) trans-2,2-dimethyl-3(2,2-diphenyl-ethan-2-ol) cyclopropane-1-carboxylate (XIII, R=CH_3)

To a solution of lactone (XII, 5.0 g) in methanol (100 ml) was added 30% aqueous solution of sodium hydroxide

(25 ml) and the mixture was kept at room temperature for 36 hrs (or under reflux for 4 hrs). Most of the methanol was removed under reduced pressure. The residue was diluted with water (150 ml) and extracted with ether (100 ml) to remove neutral material (0.165 g, not investigated).

The aqueous portion was acidified with 20% sulphuric acid and extracted with ether (100 ml, 50 ml x 2). The ether layer was washed with water (100 ml x 2), dried and evaporated to furnish the hydroxy acid (XIII, R=H) as a thick liquid. This acid was converted into its methyl ester (XIII, R=CH_3) by an ethereal solution of diazomethane, yield 3.78 g, $[\alpha]_D^{28}$ -28.3°, (c, 1.41).

Analysis: Found: C, 77.65; H, 7.42; $(C_{21}H_{24})_3$ requires: C, 77.75; H, 7.46%.

IR bands at 3571, 3077, 2985, 1961, 1709, 1600, 1481, 1429, 1361, 1156, 1117, 1070, 1042, 943, 870, 844, 746 and 694 cm^{-1}.

Methyl (-)-trans-2,2-dimethyl-3 (2,2-diphenyl-vinyl) cyclopropane-1-carboxylate (XIV)

A solution of hydroxy ester (XIII, R=CH_3, 3 g) in dry benzene (150 ml) was refluxed with para-toluene sulphonic acid (0.075 g) for 3 hrs. The benzene solution was washed with water (100 ml x 2) to remove PTS and dried. Evaporation of

benzene gave gummy ester (XIV, 2.71 g). Crystallisation from pet. ether afforded white crystals, identified as (XIV), m.p. 89°, $[\alpha]_D^{28}$ -9.0° (c, 1.80).

Analysis: Found: C, 82.40; H, 7.12; $C_{21}H_{22}O_2$ requires: C, 82.32; H, 7.24%.

IR bands at 3030, 1724, 1600, 1493, 1429, 1370, 1333, 1258, 1220, 1190, 1156, 1130, 1081, 1047, 995, 936, 917, 847, 820, 763 and 694 cm^{-1}.

Preparation of (XVI) from (XV)

The acid (XV, 0.5 g) was treated with potassium carbonate (0.35g) in water (5 ml) and stirred for 2 hrs 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 collects (4 hrs). To the above mixture was added 3-phenoxybenzyl triethyl ammonium bromide (0.8 g) and the refluxing continued for further 8 hrs. 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 (0.78g) which showed minor polar impurities on TLC (12% ethyl acetate in benzene). The product was separated by chromatography on silicic acid (20 g). The less polar, the main product was eluted with pet. ether + benzene (1:1) and identified as the

ester (XVI; 0.65 g).

Analysis: found: C, 83.15; H, 6.49; $C_{33}H_{30})_3$ requires: C, 83.51; H, 6.37%.

IR bands at 3077, 2985, 1709, 1575, 1471, 1429, 1399, 1316, 1235, 1064, 813 and 758 cm^{-1}.

CHAPTER II-B

SYNTHESIS OF

METHYL 1R CIS (-)2,2-DIMETHYL-3(2-PHENYL-PROP-1-ENYL) CYCLOPROPANE CARBOXYLATE

AND

METHYL 1S CIS, 2,2-DIMETHYL-3(2-PHENYL-2-CHLORO VINYL) CYCLOPROPANE CARBOXYLATE

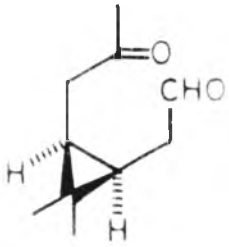
FROM (+) CAR-3-ENE

SUMMARY

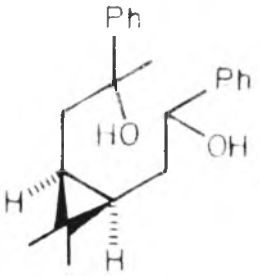
The keto aldehyde (XVII), obtainable from car-3-ene (I) via carane diol (II), on treatment with phenyl magnesium bromide afforded a mixture of diastereomeric diols (XVIII). The diols (XVIII), on controlled oxidation with Jones chromic acid gave the diastereomeric keto alcohols (XIX). Baeyer-Villiger oxidation of the keto alcohols (XIX) gave the benzoate (XX) as the major product. Saponification of the benzoate (XX) followed by oxidation with Jones chromic acid reagent, of the resulting diol (XXII) afforded the lactone (XXIII) and hydroxy acid (XXIV, R=H). The acid (XXIV, R=H) could also be obtained from the lactone (XXIII) by saponification with alkali. Esterification of the acid (XXIV, R=H) followed by acid catalysed dehydration of the resulting ester (XXIV, $R=CH_3$) gave the methyl 1R cis 2,2-dimethyl-3(2-phenyl prop-1-enyl) cyclopropane carboxylate (XXV) as a single double bond isomer.

Acetylation of the diol (XVIII) gave the hydroxy acetate (XXVI) which, on dehydration afforded the unsaturated acetate (XXVII). Potassium permanganate oxidation of (XXVII) followed by esterification of the resulting acetate acid gave an acetate ester which was converted to the hydroxy ester (XXIX, $R=CH_3$). Jones chromic acid oxidation of (XXIX, $R=CH_3$) gave the keto ester (XXXI) which, on treatment

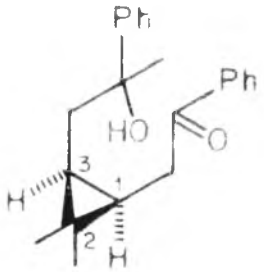
with PCl_5 furnished the methyl 1<u>cis</u> 2,2-dimethyl-3(2-phenyl-2-chloro vinyl) cyclopropane carboxylate (XXXII).



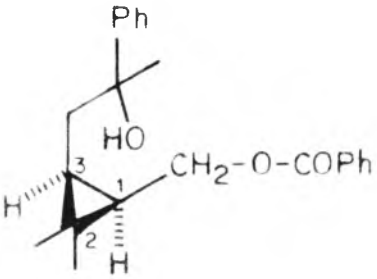
XVII



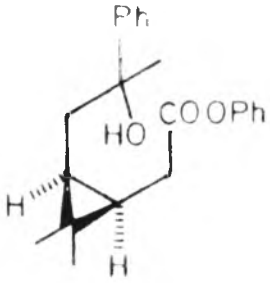
XVIII



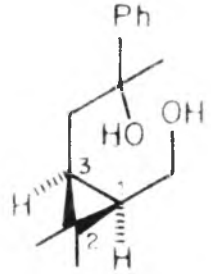
XIX



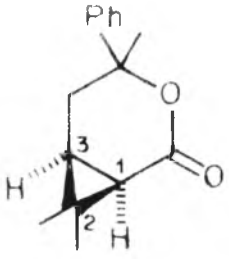
XX



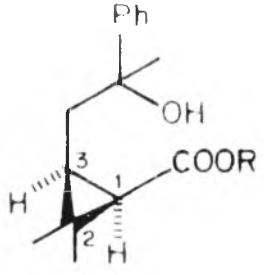
XXI



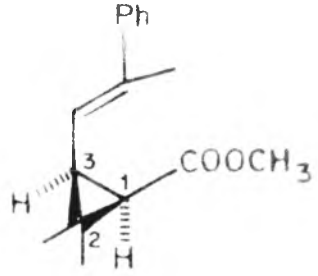
XXII



XXIII



XXIV



XXV

In continuation of our efforts towards utilising car-3-ene for the preparation of different acid moieties of pyrethroids, we have achieved the synthesis of two more analogues of chrysanthemic acid, possessing different side chains at C_3 position.

PRESENT WORK

1. Synthesis of Methyl 1R-cis-2,2-dimethyl-3(2-phenyl prop-1-enyl) cyclopropane carboxylate (XXV)

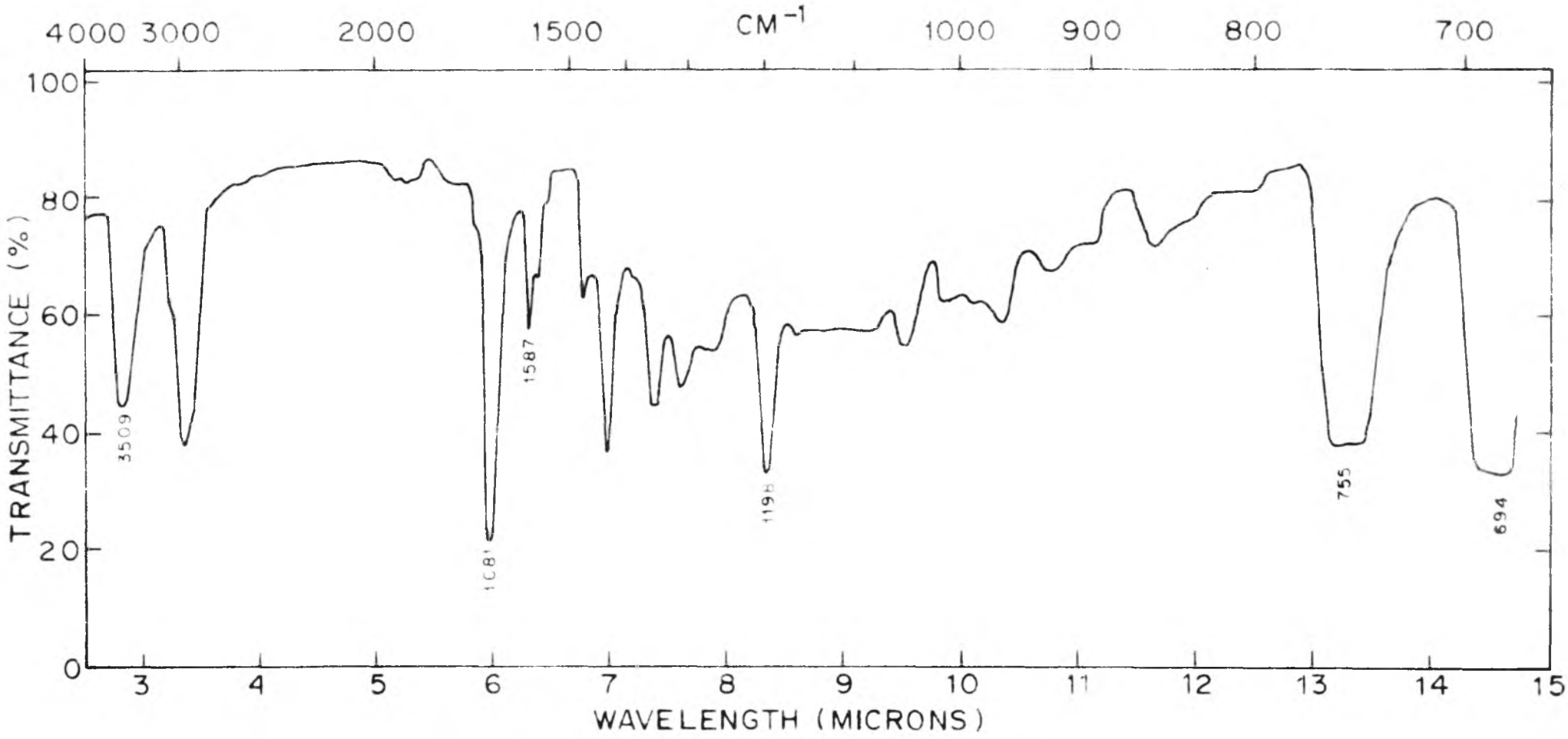
3R,4R-Carane diol (II), obtainable from (+)car-3-ene (I) in 45% yield by a known[26] method, was cleaved by sodium meta periodate to afford the keto aldehyde (XVII) in 82% yield, $C_{10}H_{16}O_2$, b.p. 85-87°/1.5 mm. It showed IR bands at 2740 (-CHO), 1724 (>C=O) and NMR signals at 9.17 (2H, m, cyclopropane protons); 9.0, 8.87 (3H each, s, gemdimethyl on cyclopropane); 7.9 (3H, s, $-COCH_3$) and 7.67 (4H, m, methylene protons).

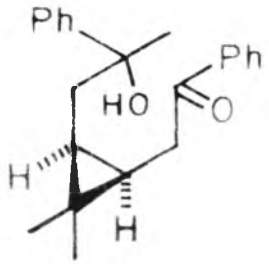
The freshly prepared keto aldehyde (XVII), on treatment with phenyl magnesium bromide (2.5 moles), afforded the liquid diol (XVIII) as a mixture of diastereomers, in 90% yield, $C_{22}H_{28}O_2$. It showed IR bands at 3448 (OH), 1053 (-C-O-), 1600, 755, 694 (aromatic) and NMR signals at 9.7 (2H, m, cyclopropane protons); 9.42, 9.35, 9.28, 9.12 (6H total, s, gemdimethyls of diastereomers); 8.58 (3H, s, $CH_3-\overset{OH}{\underset{|}{C}}-$), 8.47 (4H, br.s, methylene protons); 5.4 (1H, q,

J_1 = 5 Hz, J_2 = 9 Hz, H-C-OH) and 2.82 (10H, s, aromatic protons). Attempts to separate diastereomers were not successful. The diol (XVIII) was used to prepare two different 2,2-dimethyl-3(vinyl substituted) cyclopropane carboxylic acids.

For the preparation of title compound, the diol (XVIII) was oxidised by Jones chromic acid reagent, under controlled conditions, to the hydroxy ketone (XIX) (85%), as a liquid, $C_{22}H_{26}O_2$. It showed IR (Fig.13) bands, at 3509, 1138 (tertiary -OH), 1681 (Ph-C=O), 1587, 755, 694 (aromatic) and NMR (Fig.14) signals at 9.42 (1H, m, proton at C_3); 9.27, 9.2, 9.07, 8.93 (6H total, s, methyls at C_2 of both the diastereomers); 8.52, 8.48 (3H, s, CH_3-C-) of the diastereomers); 8.35 (2H, d, J = 6 Hz, $-CH_2$ at C_3); 7.3 (2H, br.m, $-CH_2$-C=O) and centered at 2.8, 2.27 (10H total, m, aromatic protons). Attempts to separate the diastereomers were fruitless.

The diastereomeric hydroxy ketone (XIX), when subjected to Baeyer-Villiger oxidation with perbenzoic acid for 72 hrs, gave the hydroxy benzoate (XX) in 70% yield, $C_{22}H_{26}O_3$, as a thick liquid. The purified benzoate (XX) showed the following spectral properties. IR: 3509, 1058(OH), 1701, 1258 (benzoate), 1587, 758, 694 (aromatic); NMR: 9.3 (1H, m, proton at C_3); 9.23, 9.08 (3H each, s, methyls at C_2);


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3509
1681
1587
1196
755
694
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


Ph
Ph
HO
O
H
H

(XIX)

FIG. 13.

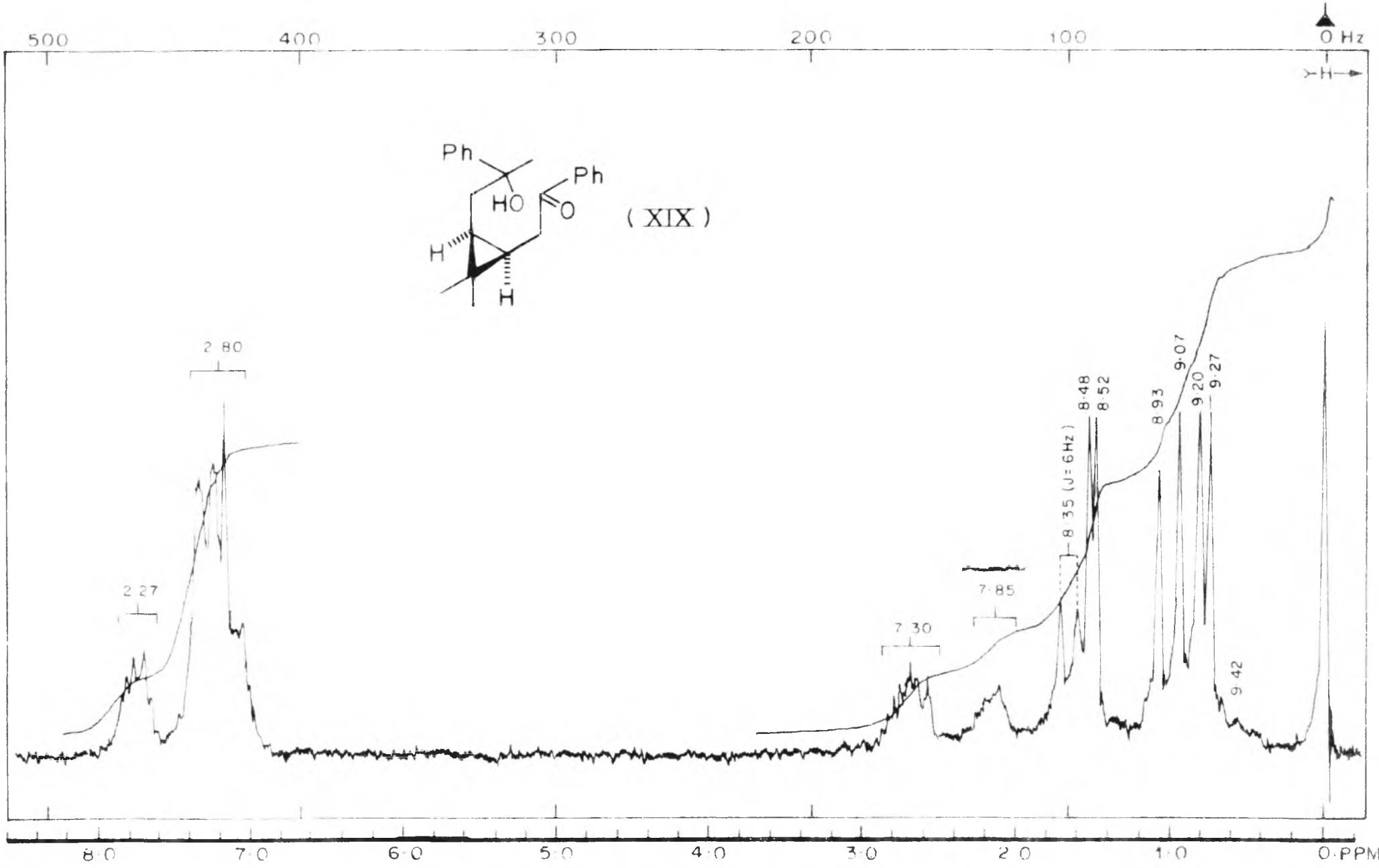

500
400
300
200
100
0 Hz
Ph
HO
Ph
O
H
H
(XIX)
2·80
2·27
7·85
7·30
8·35 (J=6Hz)
8·48
8·52
8·93
9·07
9·20
9·27
9·42
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0·PPM(δ)

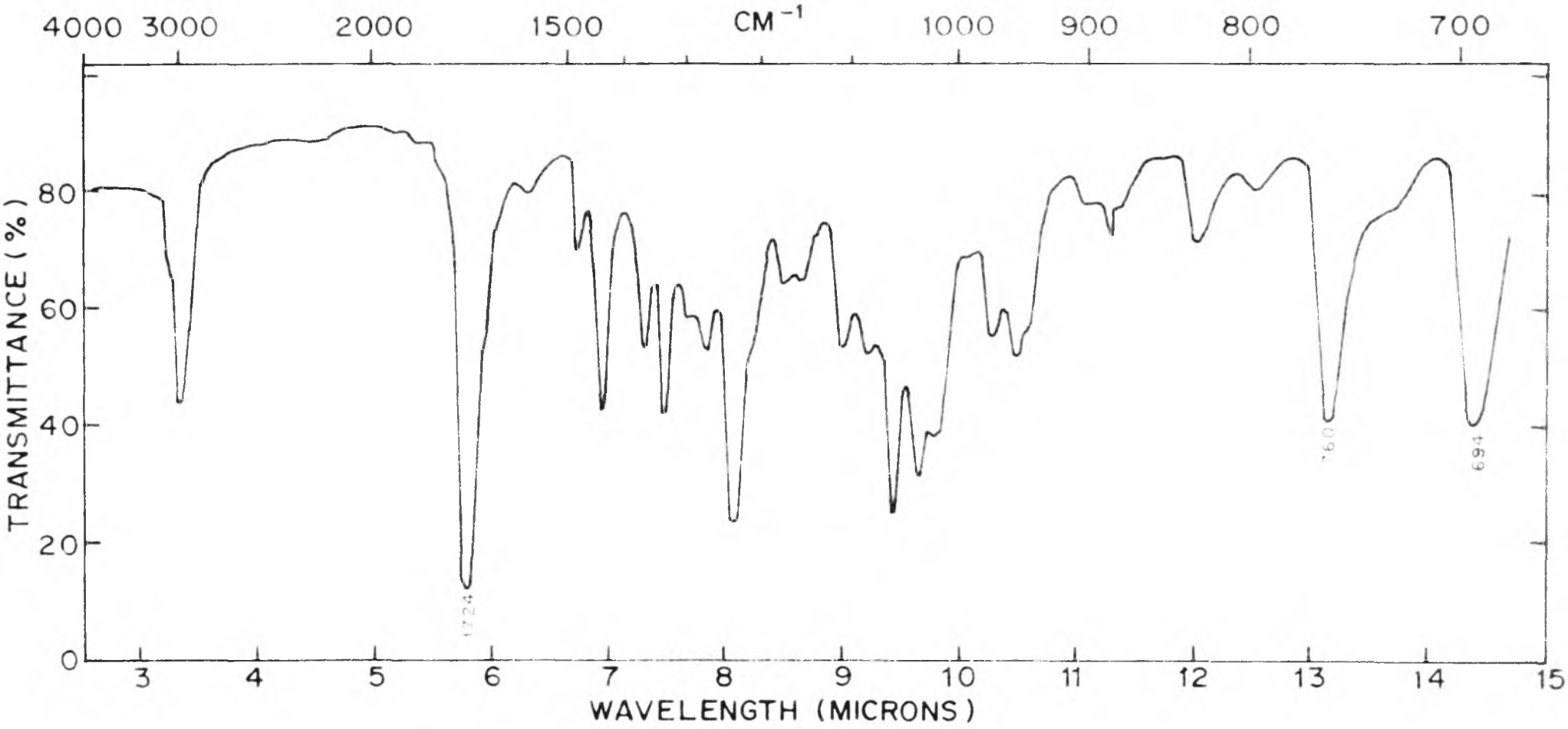
FIG. 14.

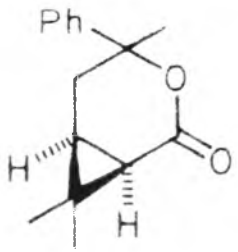
8.95 (1H, s, proton at C_1); 8.5 (3H, s, CH_3-C-OH); 8.18 (2H, d, J = 6 Hz, $-CH_2$ at C_3); 5.9 (2H, t, J = 7 Hz, $-CH_2$ at C_1) and 2.75, 2.13 (10H total, m, aromatic protons).

Baeyer-Villiger oxidation of ketone (XIX), in fact, should furnish two products viz. the benzoate (XX) and the phenyl ester (XXI). According to the observation and prediction[29], the ester (XXI) should have been formed in major quantity. However, under the present experimental conditions, the benzoate (XX) was formed in major quantity and the other product i.e. (XXI) was not isolated and characterised.

The crude, Baeyer-Villiger oxidation product of (XIX) on saponification with methanolic potash, furnished, in neutral portion, the diol (XXII), $C_{15}H_{22}O_2$, M^+ 234, as a viscous liquid and showed the following spectral properties. IR; 3390, 1010 ($-CH_2OH$), 1587, 760, 697 (aromatic); NMR; 9.43 (1H, m, proton at C_3); 9.13 (6H, s, methyls at C_2); 8.95 (1H, s, proton at C_1); 8.48 (3H, s, CH_3-C-OH); 8.15 (2H, m, CH_2 at C_3); 6.63 (2H, m, $-CH_2$ at C_1) and 2.8 (5H, m, aromatic protons).

Jones chromic acid oxidation of the diol (XXII) gave a mixture of two products in 90% yield. They were separated into acidic (30%) and neutral (70%) parts. The neutral part, obtained as a liquid, was identified as the lactone (XXIII),


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
TRANSMITTANCE (%)
0 20 40 60 80
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
1724
760
694


Ph
O
H
O
H

(XXIII)

FIG. 15

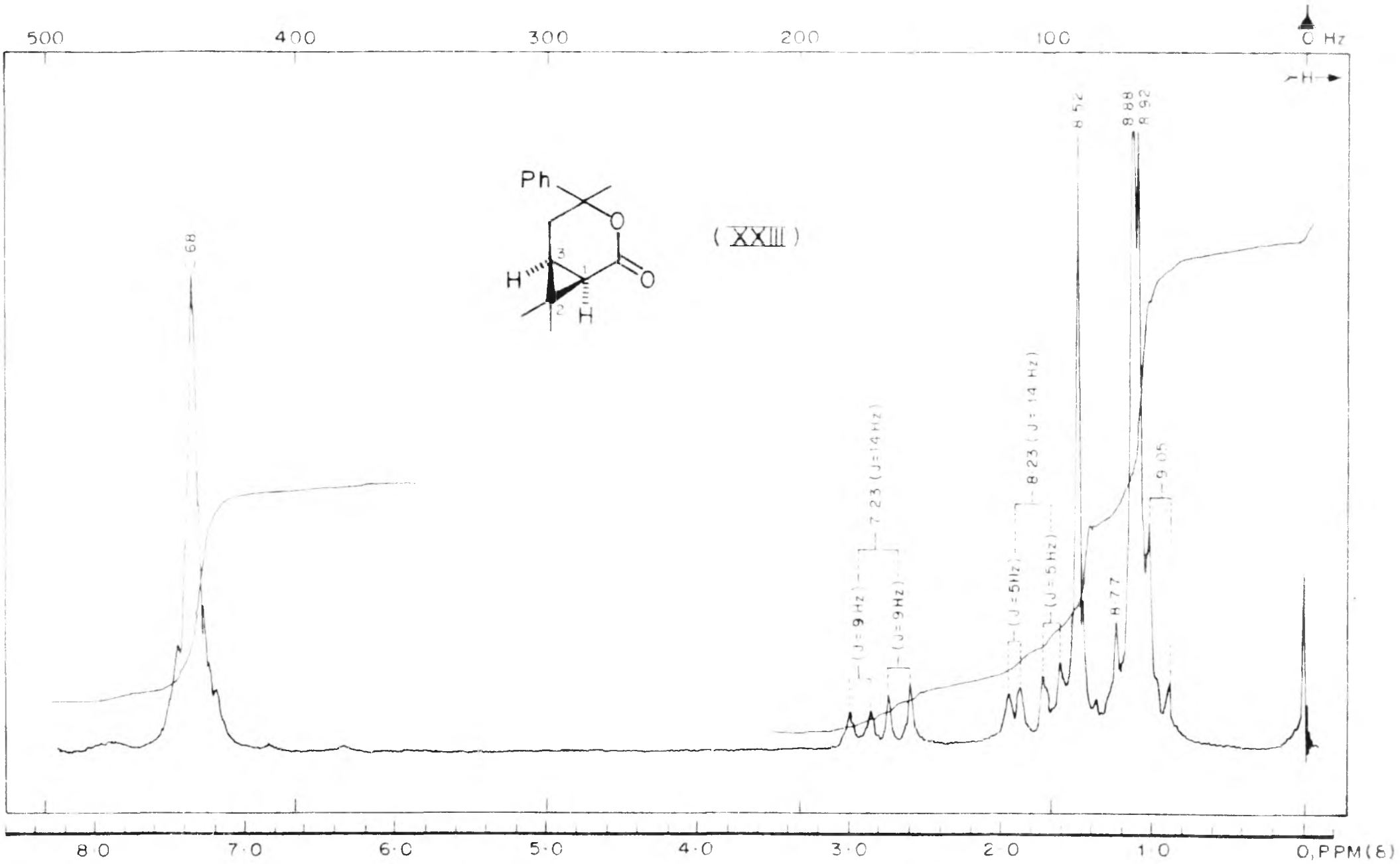

500
400
300
200
100
0 Hz
Ph
O
O
H
H
1
2
3
(XXIII)
6.8
7.23 (J=14 Hz)
(J=9 Hz)
(J=9Hz)
(J=5Hz)
8.23 (J=14 Hz)
8.52
8.88
8.92
8.77
9.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0, PPM(δ)

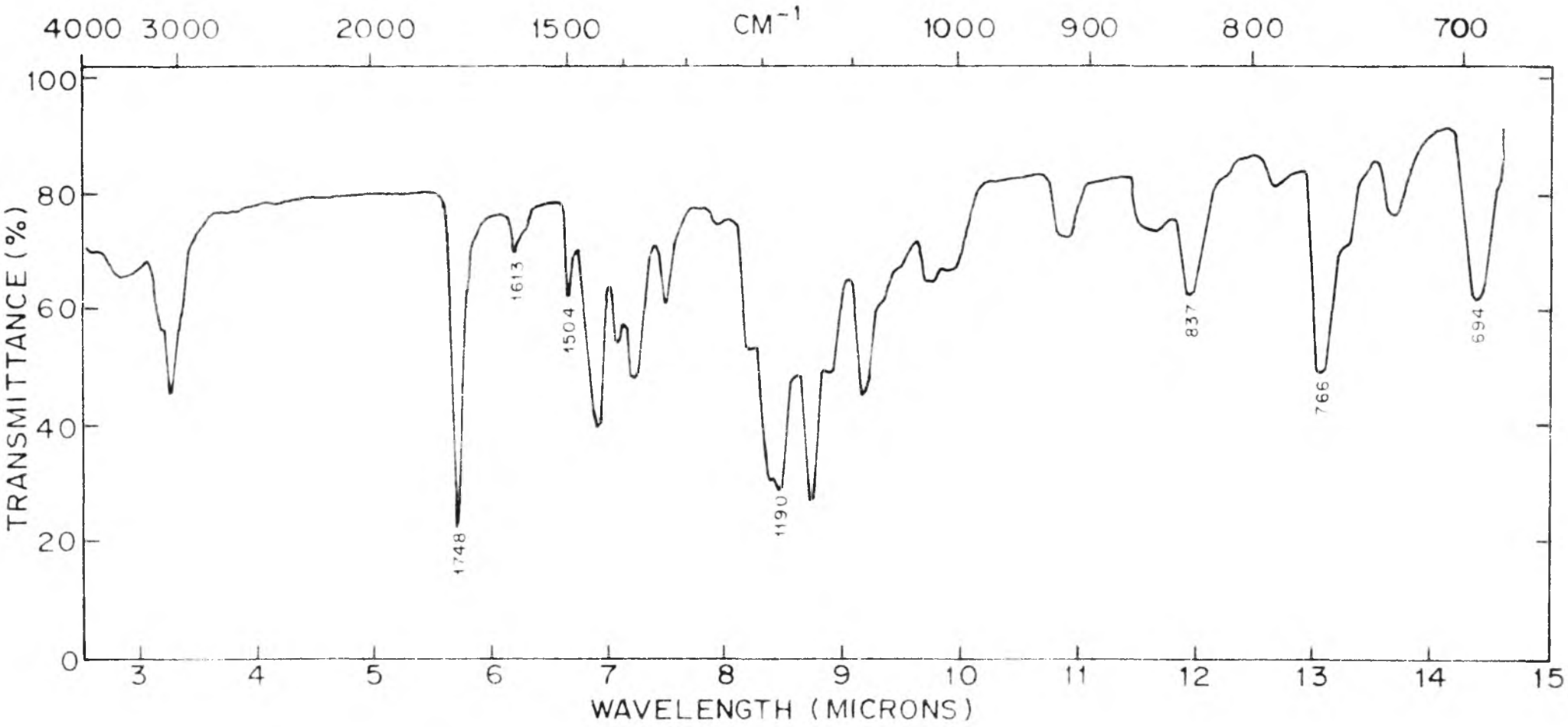
FIG. 16.

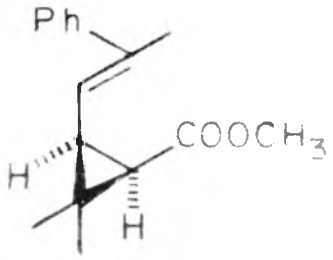
$C_{15}H_{18}O_2$ by following spectral properties. IR (Fig.15); 1724 (δ-lactone), 760, 694 (aromatic); NMR (Fig.16); 9.05 (1H, m, proton at C_3); 8.92, 8.88 (3H each, s, methyls at C_2); 8.77 (1H, s, proton at C_1); 8.52 (3H, s, CH_3-$\overset{|}{C}$-O); 8.23 (1H, dd, J_1 = 5 Hz, J_2 = 14 Hz, one of the protons of CH_2- at C_3); 7.23 (1H, dd, J_1 = 9 Hz, J_2 = 14 Hz, another proton of -CH_2 at C_3) and at 2.68 (5H, br.s aromatic protons).

The acid part (30%) was converted into its methyl ester (XXIV, R=CH_3), $C_{16}H_{22}O_3$, by an ethereal solution of diazomethane. It showed the following spectral properties. IR; 3509 (OH), 1709, 1170 (ester); NMR; 9.13, 9.05 (3H each, s, C_2-methyls); 8.72 (1H, s, C_1 proton); 8.53 (3H, s, CH_3-$\overset{|}{C}$-OH); 7.98 (3H, m, -CH_2 at C_3 and -OH proton, exchangeable with D_2O); 6.53 (3H, s, -COOCH_3) and 2.9 (5H, m, aromatic protons).

The same acid (XXIV, R=H) was also obtained by saponification of the lactone (XXIII) with methanolic sodium hydroxide, identified by spectral data and physical constants of its methyl ester (XXIV, R=CH_3).

Dehydration of hydroxy ester (XXIV, R=CH_3), using catalytic quantity of paratoluene sulphonic acid in refluxing benzene, gave exclusively, the unsaturated ester (XXV), $C_{16}H_{20}O_2$, M^+ 244, $[\alpha]_D^{28}$ -16.9° (c, 2.95), as a solid, m.p. 60° (pet. ether). It showed IR (Fig.17) bands at 1748,


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1748
1613
1504
1190
837
766
694
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


Ph
COOCH3
H
H

(XXV) FIG 17

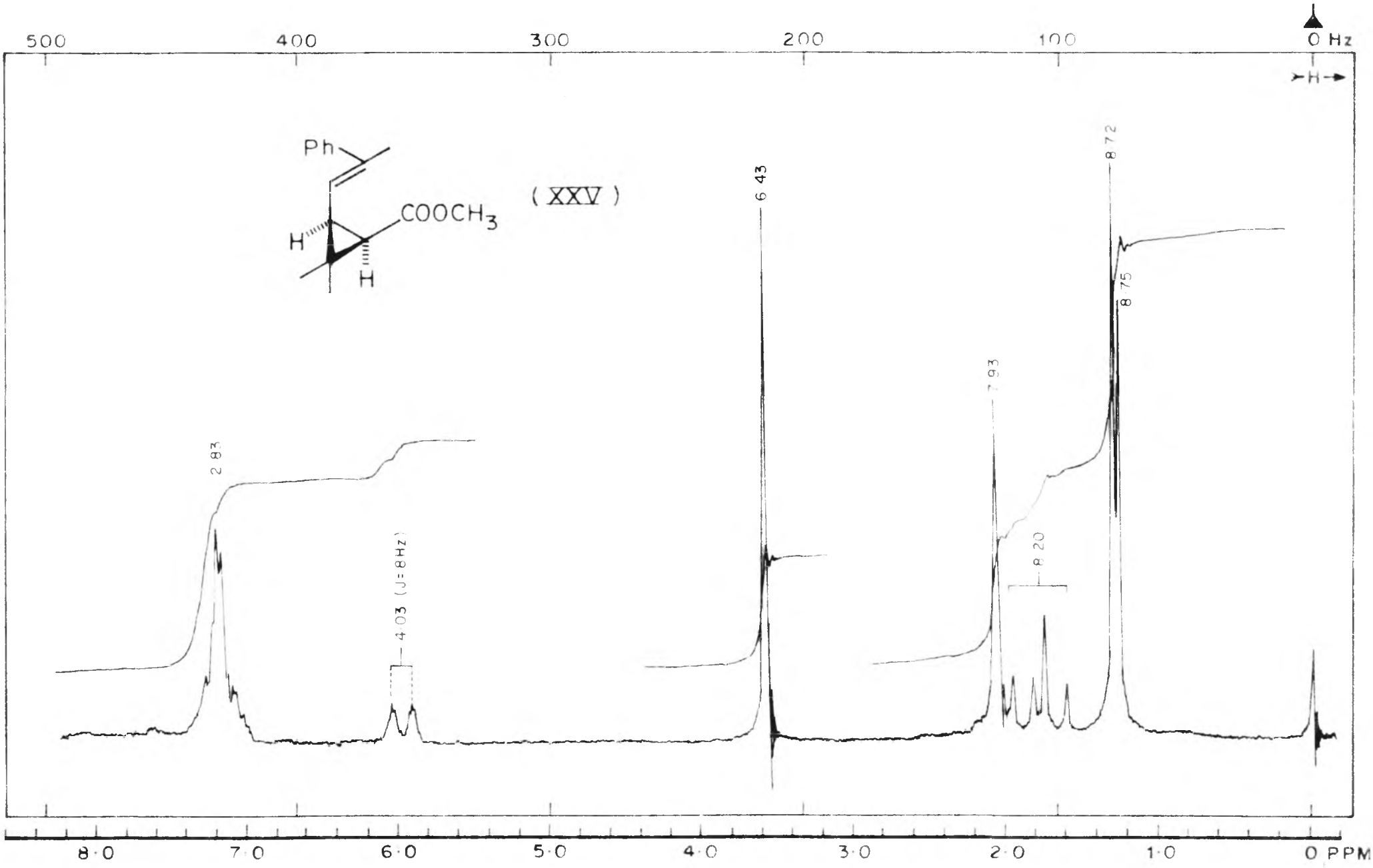

500
400
300
200
100
0 Hz
Ph
COOCH3
H
H
(XXV)
2.83
4.03 (J=8Hz)
6.43
7.93
8.20
8.72
8.75
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

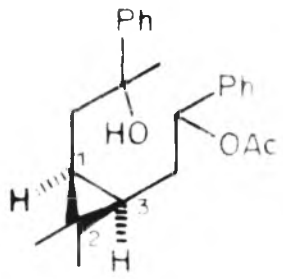
FIG. 18.

1190 (ester), 837 (trisubstituted double bond), 1613, 1504, 766, 694 (aromatic) and NMR (Fig.18) signals at 8.75, 8.72 (3H each, s, methyls on cyclopropane); centered at 8.2 (2H, m, protons at C_1 and C_3); 7.93 (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).

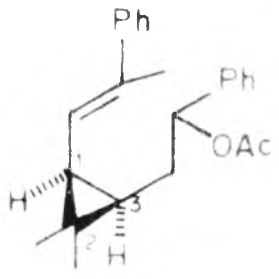
During the dehydration of hydroxy ester (XXIV, R=CH_3) to give (XXV), two double bond geometric isomers are possible. It appears from the NMR spectrum that only one, thermodynamically stable[30] isomer is formed during prolonged treatment of (XXIV, R=CH_3), with P.T.S. and this isomer has been tentatively assigned stereostructure (XXV) in which the bulkier groups are <u>trans</u> to one another.

2. <u>Synthesis of Methyl 1S cis-2,2-dimethyl-3(2-phenyl-2-chloro vinyl) cyclopropane carboxylate (XXXII)</u>

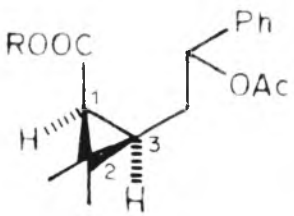
The diol (XVIII) on treatment with Ac_2O/pyridine, gave a mixture of the diastereomeric hydroxy monoacetates (XXVI), as a thick liquid $C_{24}H_{30}O_3$. It showed IR bands at 3509, 1015 (OH), 1724, 1227 (acetate), 1587, 758, 694 (aromatic) and NMR signals at 9.63 (2H, m, cyclopropane protons at C_1 and C_3); 9.38, 9.23, 9.2, 9.08 (6H total, s, methyls at C_2 of both diastereomers); 8.55 (3H, s, CH_3-$\overset{|}{C}$-O); 8.4 (4H, m, methylenes at C_1 and C_3); 8.05 (3H, s, acetate methyl); 4.34 (1H, m, benzylic proton,



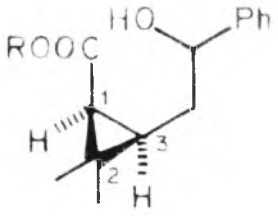
XXVI



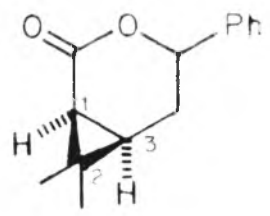
XXVII



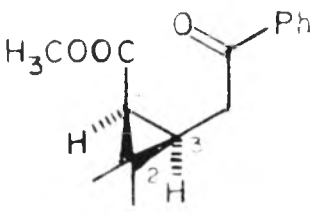
XXVIII R = H or CH_3



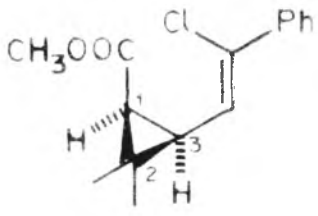
XXIX



XXX



XXXI

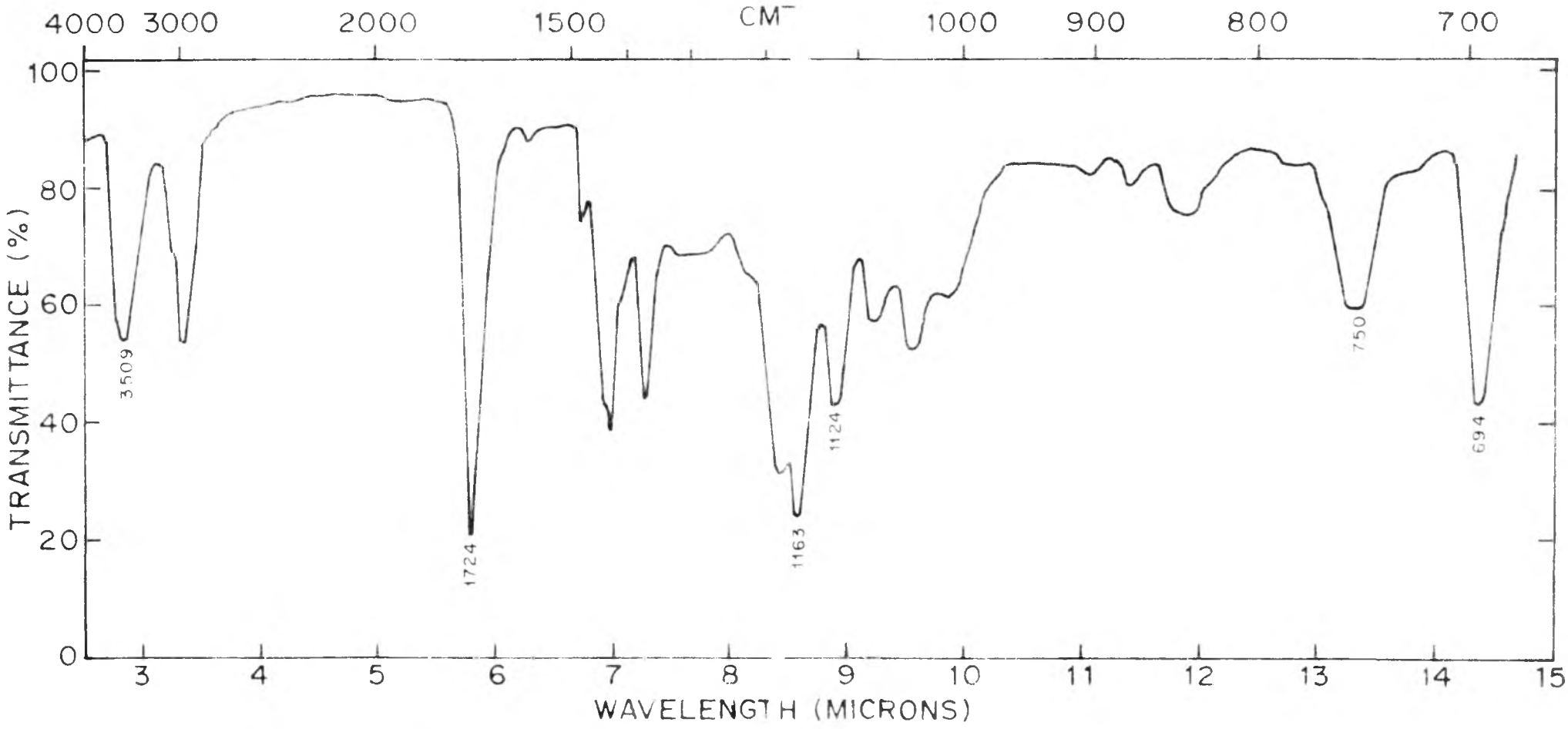


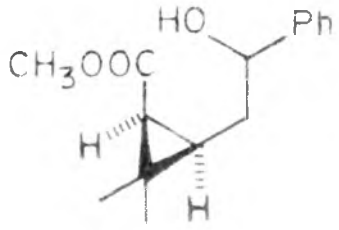
XXXII

i.e. H-C-OAc) and 2.82 (10H, s, aromatic protons). The acetate (XXVI), obtained as a mixture of diastereomers, could not be separated into its isomers.

The acetate (XXVI) was dehydrated by paratoluene sulphonic acid in refluxing benzene to afford the mixture of diastereomeric unsaturated acetates (XXVII) $C_{24}H_{28}O_2$, obtained as a viscous liquid. It showed IR bands at 1739, 1220 (acetate), 1587, 755, 694 (aromatic) and NMR signals at 9.4 (1H, m, proton at C_3); 9.15, 9.0, 8.93, 8.87 (6H total, s, methyls at C_2 of diastereomers); 8.67 (1H, d, J = 9 Hz, allylic proton at C_1); 8.23 (2H, m, methylene protons); 8.00 (3H, s, acetate methyl); 7.93 (3H, s, vinyl methyl); 4.55 (2H, m, benzylic and olefinic protons) and 2.8, 2.77 (10H total, s, aromatic protons).

The acetate (XXVII) was subjected to oxidation by potassium permanganate in acetone in the presence of acetic acid and water to afford the acetate acid (XXVIII, R=H) in 40% yield. This acid was converted into its methyl ester (XXVIII, $R=CH_3$) by an ethereal solution of diazomethane. However, the acetate ester (XXVIII, $R=CH_3$) was found to be sensitive towards silicic acid and was completely converted to hydroxy ester (XXIX, $R=CH_3$) during chromatography over silicic acid. The purified ester (XXIX, $R=CH_3$), $C_{15}H_{20}O_3$, obtained as a thick liquid showed IR bands (Fig.19) at 3509,


4000 3000 2000 1500 CM⁻ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3509
1724
1163
1124
750
694
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


HO
Ph
CH3OOC
H
H

(XXIX)

FIG. 19

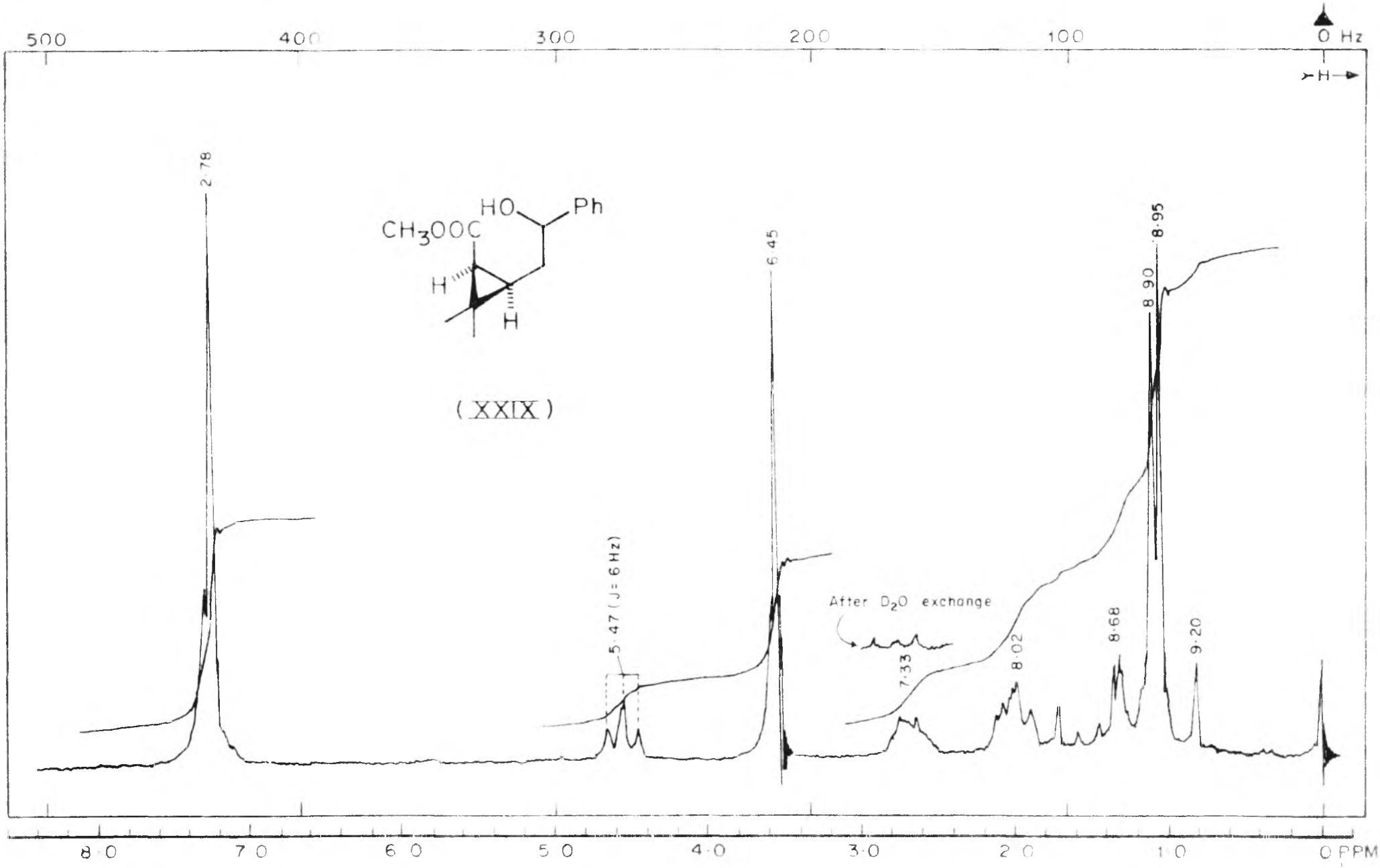
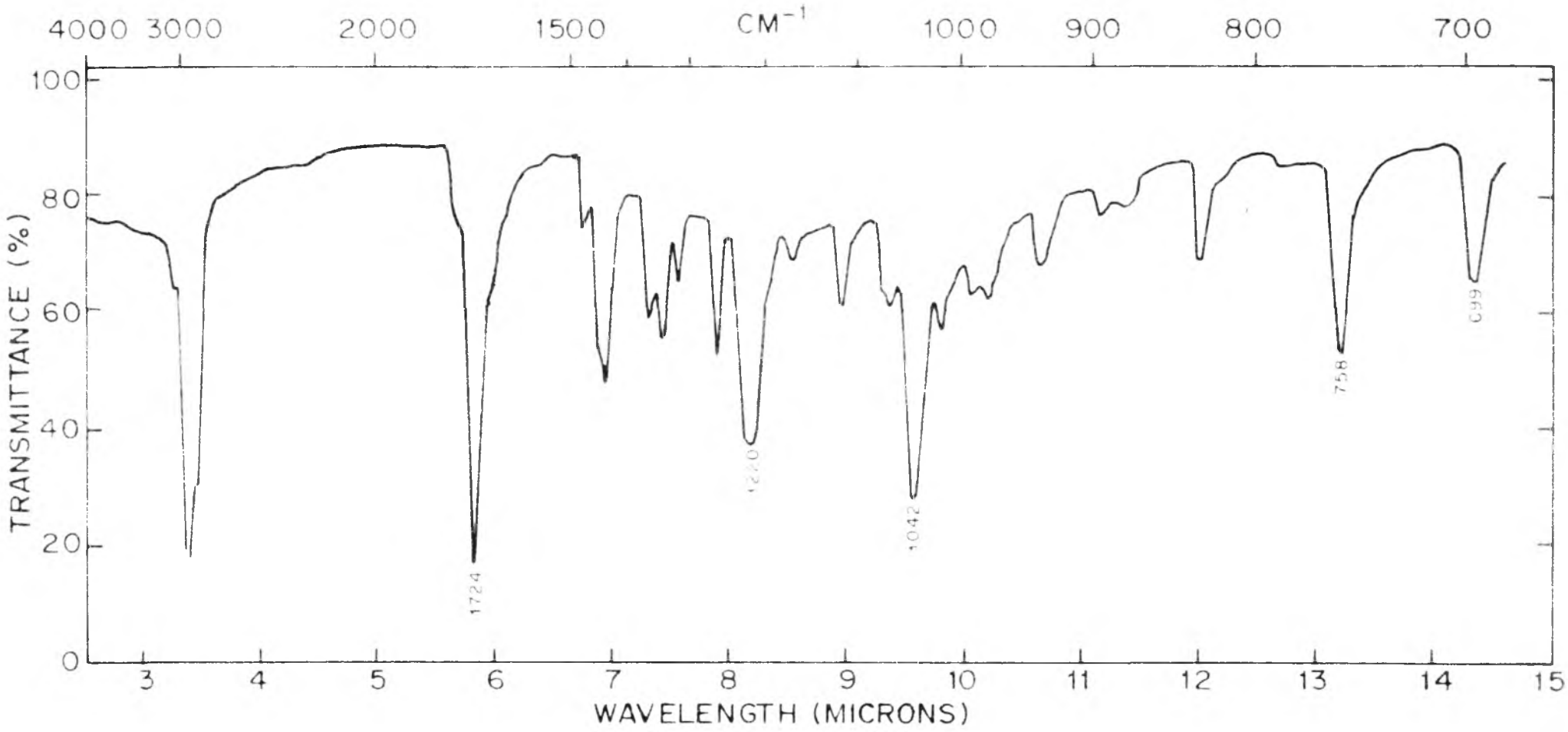

500
400
300
200
100
0 Hz
τ-H→
2·78
HO
Ph
CH3OOC
H
H
(XXIX)
6·45
8·90
8·95
5·47 (J = 6 Hz)
After D2O exchange
7·33
8·02
8·68
9·20
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

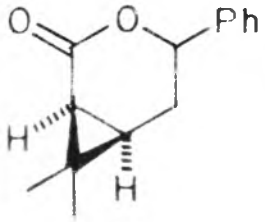
FIG. 20.

1124 (OH), 1724, 1163 (ester), 750, 694 (aromatic) and NMR (Fig.20) signals at 9.2 (1H, s, proton at C_3); 8.95, 8.9 (3H each, s, methyls at C_2); 8.68 (1H, br.d, proton at C_1); 8.02 (2H, br.m, methylene at C_3); 7.33 (1H, br.s, exchangeable with D_2O, -OH proton); 6.45 (3H, s, ester methyl); 5.47 (1H, t, J = 6 Hz, benzylic proton) and 2.78 (5H, s, aromatic protons).

The cis relationship between carboxylic group at C_1 and side chain at C_3 was proved by preparing the solid lactone (XXX) from hydroxy acid (XXIX, R=H) obtainable from hydroxy ester (XXIX, R=CH_3). Thus, the ester (XXIX, R=CH_3) on saponification, afforded the acid which was treated with paratoluene sulphonic acid in dry benzene under reflux to furnish solid lactone (XXX), $C_{14}H_{16}O_2$, M^+ 216, m.p. 136° (benzene + pet. ether), $[\alpha]_D^{28}$ +49° (c, 1.14). It showed IR (Fig.21) bands at 1724, 1220 (α'-lactone), 758, 699 (aromatic) and NMR (Fig.22) ($CDCl_3$) signals at 8.83, 8.77 (3H each, s, gemdimethyl on cyclopropane); 8.4 (3H, m, $-CH_2$ and H at C_3); 7.85 (1H, s, proton at C_1); 4.78 (1H, dd, J_1 = 4 Hz, J_2 = 12 Hz, benzylic proton) and 2.77 (5H, s, aromatic protons).

Jones chromic acid oxidation of (XXIX, R=CH_3), at 0° afforded the keto ester (XXXI) in 85% yield, $C_{15}H_{18}O_3$, M^+ 246, $[\alpha]_D^{28}$ +60.3° (c, 2.3), m.p. 61°. It showed IR (Fig.23)


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1724
1240
1042
758
699
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


O
O
Ph
H
H

(XXX)

FIG 21

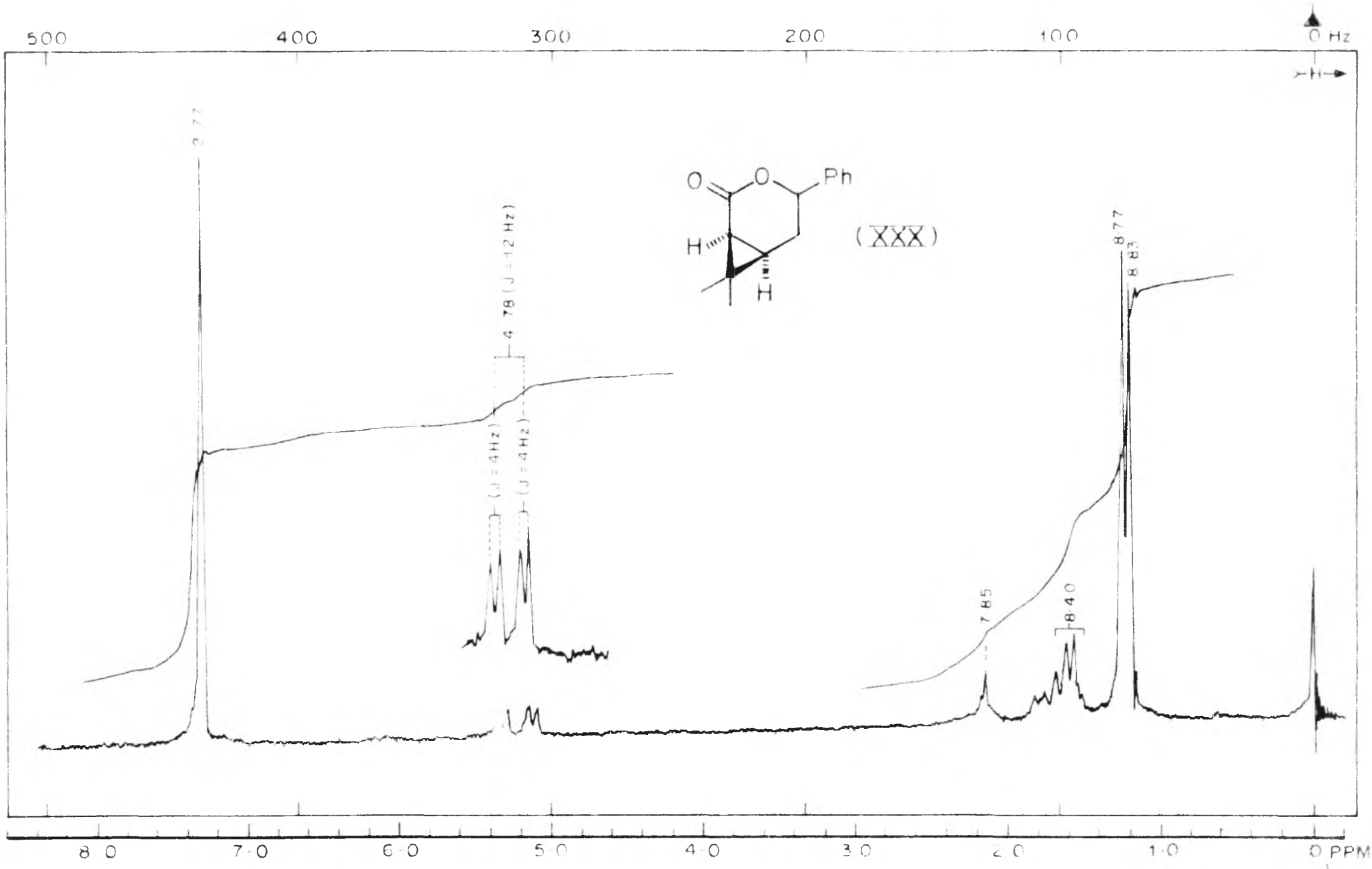
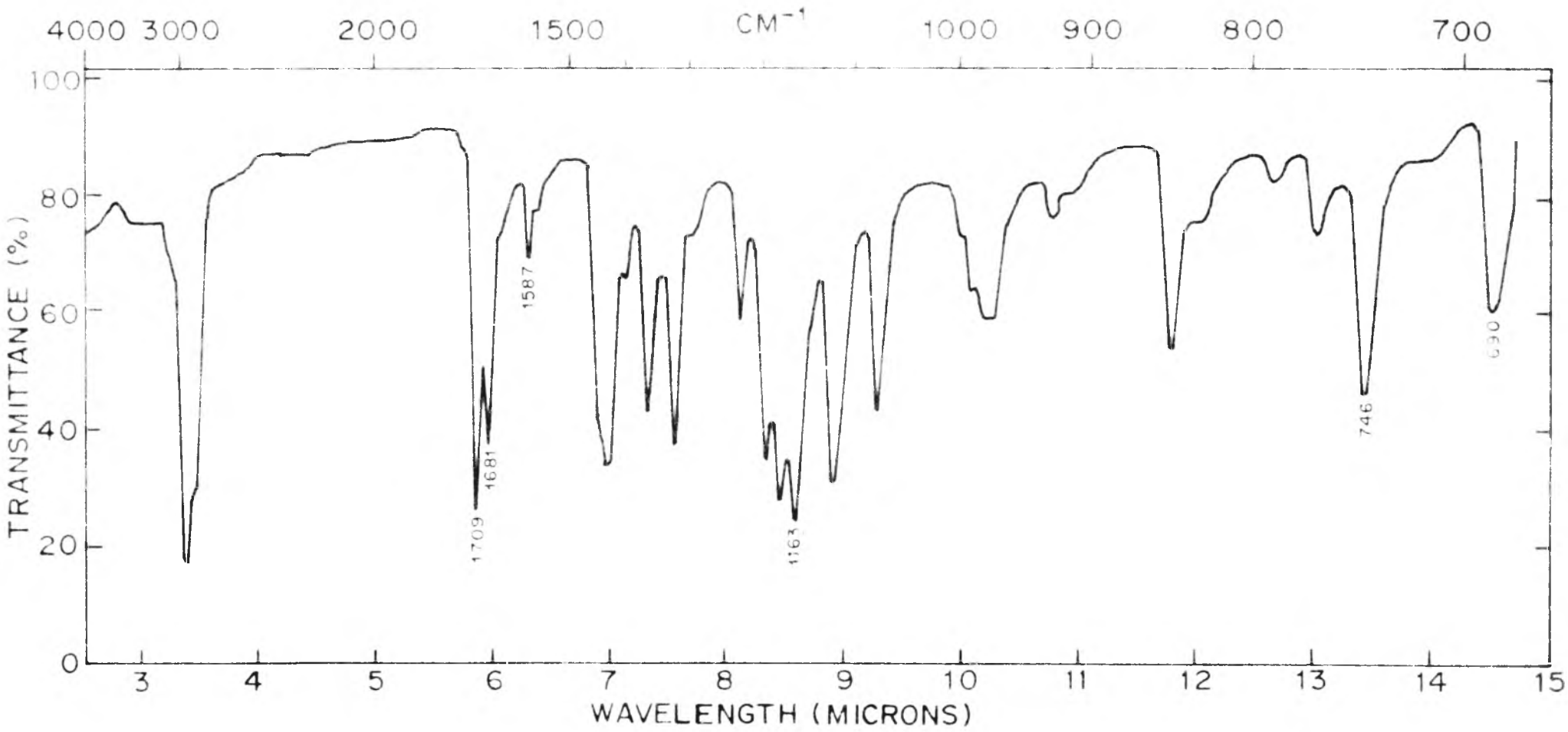
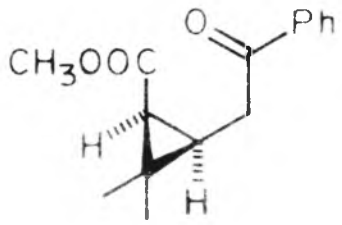

500
400
300
200
100
0 Hz
→H←
2·77
4·78 (J = 12 Hz)
(J = 4Hz)
(J = 4Hz)
O
O
Ph
H
H
(XXX)
8·77
8·83
7·85
8·40
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIG. 22.

bands at 1709, 1163 (ester), 1651 (O=C-Ph), 1587, 746, 690 (aromatic) and NMR (Fig.24) signals at 8.83, 8.72 (3H each, s, methyls at C_2); 8.43 (2H, m, protons at C_1 and C_3); 6.67 (2H, m, methylene at C_3); 6.42 (3H, s, ester methyl) and 2.57, 2.08 (5H total, m, aromatic protons).

Treatment of (XXXI) with PCl_5 at 80 to 90° for 5 hrs gave a mixture of two products, the less polar being in minor quantity (10%). The more polar product (85%) was identified as the phenyl chlorovinyl ester (XXXII), $C_{15}H_{17}O_2Cl$. It showed IR (Fig.25) bands at 1724, (>C=O), 758, 690 (aromatic) and NMR (Fig.26) signals at 8.68 (6H, s, methyls at C_2); 8.18 (1H, d, J = 9 Hz proton at C_1); 7.68 (1H, t, J = 9 Hz, proton at C_3); 6.38 (3H, s, ester methyl); 3.48 (1H, d, J = 9 Hz, olefinic proton) and centered at 2.6 (5H, m, aromatic protons).


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
1709
1681
1587
1163
746
690
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


O
Ph
CH3OOC
H
H

(XXXI)

FIG 23

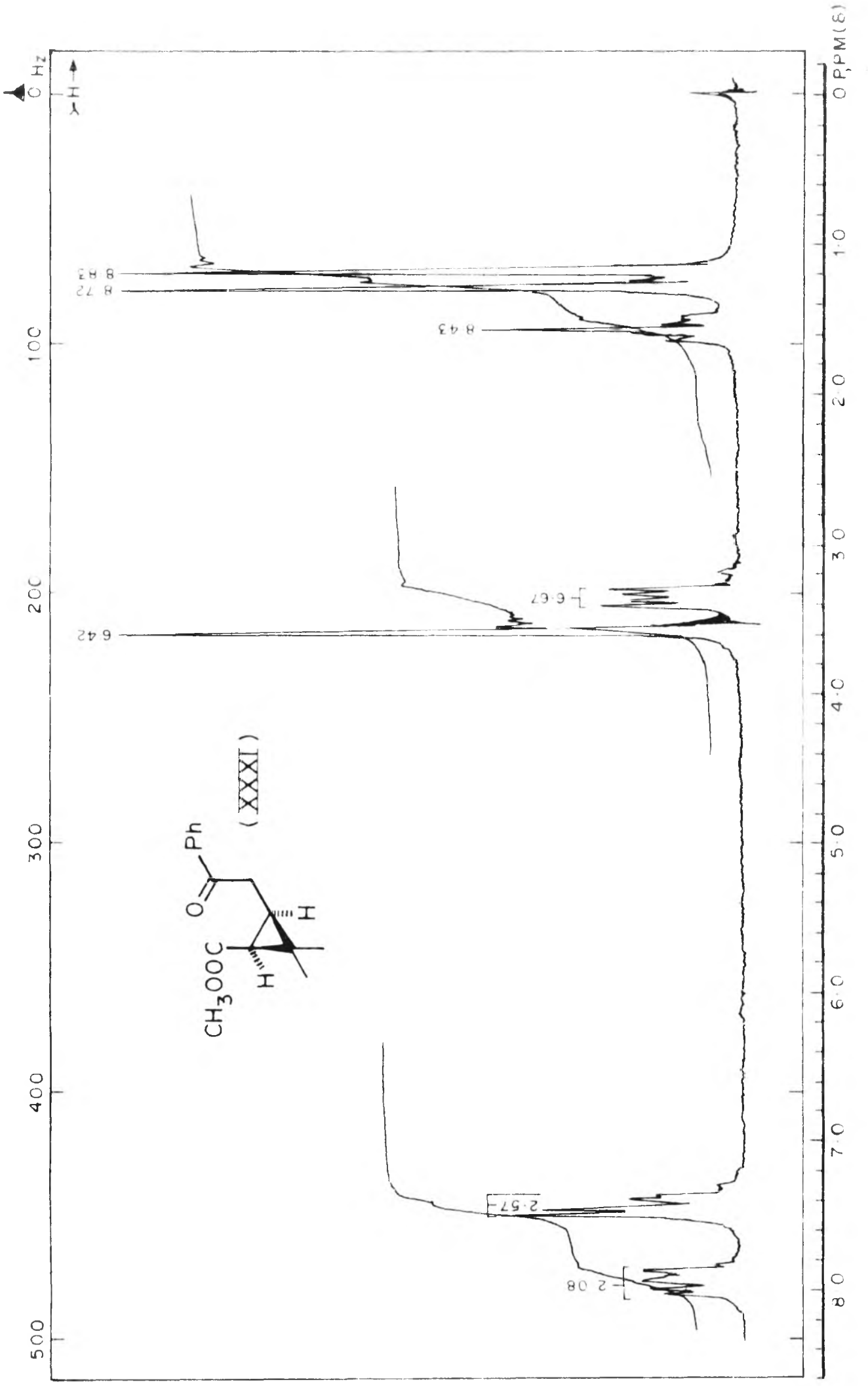
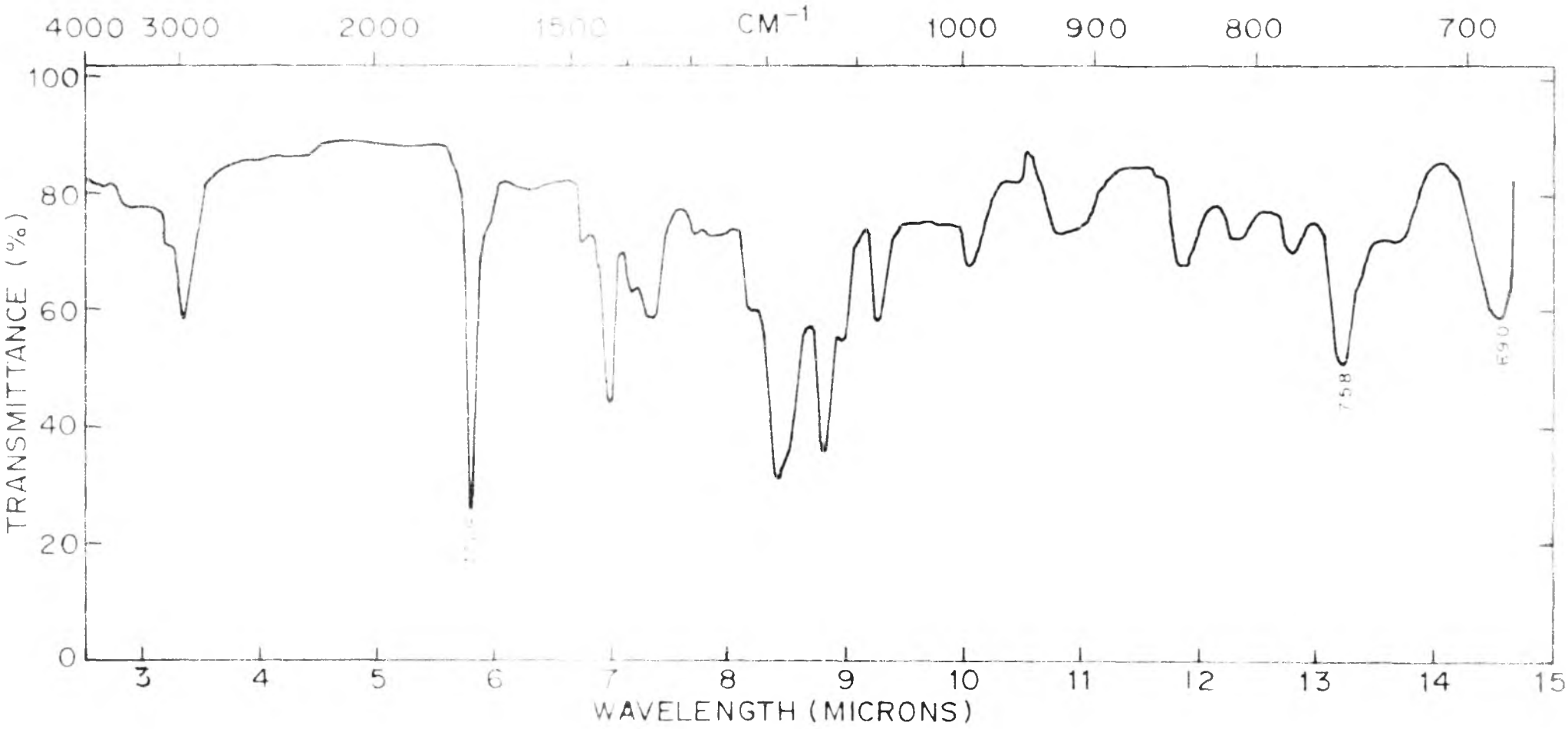
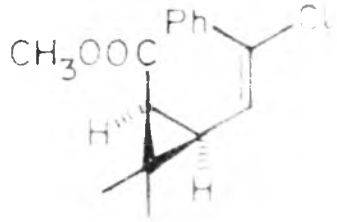

0 Hz
100
200
300
400
500
8.72
8.43
6.42
6.67
2.57
2.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)
Ph
O
H
H
CH3OOC
(XXXI)

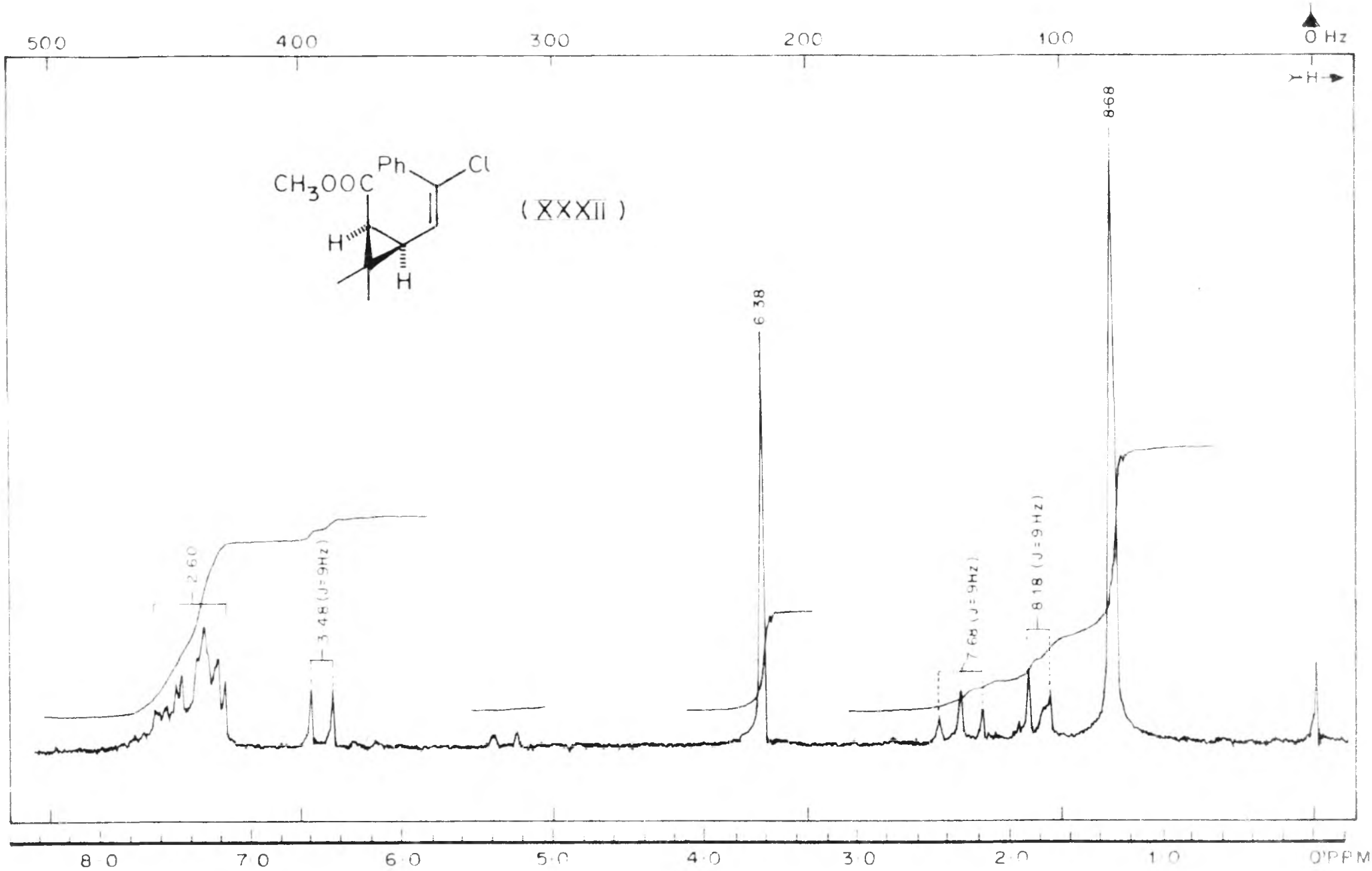
FIG. 24.


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
758
690


Ph
Cl
CH3OOC
H
H

(XXXII)

FIG. 25


500
400
300
200
100
0 Hz
TMS
8·68
6·38
2·60
3·48 (J=9Hz)
7·68 (J=9Hz)
8·18 (J=9Hz)
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

Ph
Cl
CH3OOC
H
H

(XXXII)

FIG. 26

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

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

In a 1-litre 3-necked flask equipped with an overhead mechanical stirrer, were taken carane diol (II, 51 g, 0.3 mole), methanol (200 ml) and water (75 ml). The contents were stirred at room temperature for 10 minutes. Finely powdered sodium metaperiodate (70.6 g, 0.33 mole) was then added, portionwise, to the above solution with stirring. After the addition (30 minutes), the reaction mixture was stirred for 2 hrs, 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 ketoaldehyde (XVII, 41.5 g, 82%); b.p. 85-87°/1.5 mm.

Analysis: Found: C, 70.90; H, 9.48; $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%.

IR bands at 2985, 2742, 1724, 1439, 1351, 1163, 1124, 1047 and 962 cm^{-1}.

2,2-Dimethyl-3(2-phenyl-2-hydroxy-propyl)-1 (2-phenyl ethan-2-ol) cyclopropane (XVIII)

To an ice cooled solution of phenylmagnesium bromide prepared from magnesium (10.56 g, 0.44 mole) and bromobenzene

(69.0 g, 0.44 mole) in dry ether (250 ml), was added dropwise, a solution of keto-aldehyde (XVII, 33.6 g, 0.2 mole) in ether (100 ml), with vigorous stirring. After the addition it was stirred for 1 hr at room temperature and 20 minutes under reflux. The reaction mixture was cooled to 0° and a saturated solution of ammonium chloride (300 ml) was introduced, dropwise, with vigorous stirring. After the addition, it was stirred for 0.5 hr at room temperature and transferred to a separating funnel. The ether layer was separated and the aqueous portion extracted with ether (100 ml, 75 ml). The combined ether extract was washed with water (200 ml) and dried. Ether was distilled off to give the crude product (66 g).

This product showed on TLC (18% ethyl acetate in C_6H_6) one main spot, along with minor quantities of less polar impurities. The less polar impurities were separated from main product viz. the diol (XVIII) by chromatography over alumina (Gr.II, 660 g). The less polar impurities (not investigated) were removed by eluting the column with pet. ether + benzene (1:1) and benzene while the main product was eluted with chloroform to give 62.5 g (96.4%) of diol (XVIII) as a gummy liquid, $[\alpha]_D^{28}$ +3.72° (c, 3.76). Analysis: Found: C, 80.96; H, 8.84; $(C_{22}H_{28})_2$ requires: C, 81.44; H, 8.70%.

IR bands at 3448, 2985, 1600, 1481, 1439, 1361, 1053, 930, 905, 862, 755 and 694 cm^{-1}

2,2-Dimethyl-3-(2-phenyl-2-hydroxy-propyl)-cis-1 (2-oxo-2-phenyl-ethyl) cyclopropane (XIX)

To a stirred solution of diol (XVIII, 22.0 g, 0.065 mole) in acetone (200 ml) cooled at -10°, was added, dropwise, Jones chromic acid reagent (25 ml, 0.06 mole); maintaining the temperature below 0°. After the addition, stirring was continued for 0.5 hr at the same temperature. The mixture was then diluted with cold water (250 ml) and extracted with chloroform (150 ml, 75 ml x 2). The chloroform extract was washed with water (200 ml x 3), 10% aqueous solution of sodium carbonate (100 ml), again with water and dried. Removal of chloroform afforded the keto alcohol (XIX), as a colourless thick liquid (TLC single spot), yield 18.6 g, 85%, $[\alpha]_D^{28}$ +16.82° (c, 3.57).

Analysis: Found: C, 82.16; H, 8.00; $C_{22}H_{26}O_2$ requires: C, 81.95; H, 8.13%.

IR bands at 3509, 2985, 1681, 1587, 1481, 1439, 1361, 1198, 1053, 966, 858, 755 and 694 cm^{-1}.

2,2-Dimethyl-3(2-phenyl-2-hydroxy-propyl)-cis-1 (benzoyloxy methyl)cyclopropane (XX)

To an ice cooled and stirred solution of hydroxy ketone (XIX, 25 g) in chloroform (50 ml), a chloroform solution of

perbenzoic acid (100 ml, 1N) and para-toluene sulphonic acid (0.5 g) were added and the contents stirred at 10-15° for 12 hrs. Another portion of perbenzoic acid (100 ml, 1N) was then added and the stirring continued for 60 hrs. After 72 hrs the chloroform solution was washed with saturated solution of sodium carbonate (100 ml x 2), water (200 ml x 2) and dried. Removal of chloroform by distillation afforded the crude product (24.2 g). It showed on TLC (12% ethyl acetate in C_6H_6) two spots.

However, the polarity of expected benzoate (XX) hardly differs from that of hydroxy ketone (XIX). Hence for analytical purpose a part (1 g) of the product was purified by chromatography on silicic acid (1:20) and eluted with benzene + chloroform (1:1) in small cuts, to give pure hydroxy benzoate (XX, 0.690 g) as a thick viscous liquid, $[\alpha]_D^{28}$ +6.1° (c, 2.3).

Analysis: Found: C, 78.50; H, 7.32; $(C_{22}H_{26})_3$ requires: C, 78.07; H, 7.74%.

IR bands at 3503, 2985, 1701, 1587, 1481, 1439, 1361, 1307, 1258, 1105, 1058, 1015, 930, 758 and 694 cm^{-1}.

2,2-Dimethyl-3 (2-phenyl-2-hydroxy-propyl)-1-hydroxymethyl cyclopropane (XXII)

The crude product (23.5 g), obtained from (XIX) by treatment with PBA, was dissolved in methyl alcohol (300 ml)

and an aqueous solution (30%) of sodium hydroxide (30 ml) was added to it. The mixture was refluxed for 5 hrs, alcohol was removed under suction, the residue diluted with water (200 ml) and extracted with chloroform (150 ml, 75 ml x 2). The chloroform layer was washed with water (200 ml x 3), dried and the solvent evaporated to give the product (15 g). It showed on TLC (20% ethyl acetate in C_6H_6) two spots, the more polar being the major component. They were separated by chromatography on silicic acid (300 g). The less polar, viz. the unreacted keto-alcohol (XIX) was eluted with chloroform + benzene (3:2) while the diol (XXII, 11.7 g) was eluted with chloroform + etayl acetate (1:3); $[\alpha]_D^{28}$ -13.7° (c, 3.07).

Analysis: Found: C, 76.74; H, 9.58; $C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%.

IR bands at 3390, 2985, 1587, 1439, 1361, 1148, 1058, 1010, 930, 862, 750 and 697 cm^{-1}.

Preparation of lactone (XXIII) and Methyl (-) cis, 2,2-dimethyl-3(2-phenyl-2 hydroxy-propyl)cyclopropane-1-carboxylate (XXIV)

To an ice cooled and stirred solution of the diol (XXII, 5 g) in acetone (75 ml) was added Jones chromic acid reagent, dropwise, till brown colour persisted. After the addition, the reaction mixture was stirred for one hr

at 5-10°, diluted with water (150 ml) and extracted with ether (150 ml, 75 ml x 2). The ether layer was washed with water (200 ml x 2), dried and the solvent evaporated to furnish a thick liquid (4.55 g). This product showed, on TLC (12% ethyl acetate in C_6H_6) two spots.

An ethereal solution (150 ml) of the above product was extracted with 10% aqueous solution of sodium carbonate (20 ml x 2) washed with water, dried and evaporated to furnish the lactone (XXIII, 3.16 g, 69%) as a viscous liquid, $[\alpha]_D^{28}$ +23.7° (c, 2.36).

Analysis: Found: C, 78.07; H, 7.98; $C_{15}H_{18}O_2$ requires: C, 78.23; H, 7.88%.

Ir bands at 2985, 1744, 1493, 1459, 1370, 1333, 1242, 1111, 1058, 1036, 952, 885, 820, 760 and 624 cm^{-1}.

The aqueous alkaline portion was cooled, acidified with 10% sulphuric acid and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed with water (75 ml), dried and evaporated to give the hydroxy acid (XXIV, R=H, 1.36 g, 30%) as a liquid. The hydroxy acid (XXIV) was treated with an ethereal solution of diazomethane at 0° and worked up to give the methyl ester (XXIV, R=CH_3), as a thick liquid, $[\alpha]_D^{28}$ -9.56° (c, 1.68).

Analysis: Found: C, 73.42; H, 8.56; $C_{16}H_{22}O_3$ requires: C, 73.25; H, 8.45%.

IR bands at 3509, 2935, 1709, 1429, 1381, 1170, 1124, 943, 840, 758 and 694 cm^{-1}.

Preparation of Hydroxy ester (XXIV, R=CH_3) from lactone (XXIII)

The lactone (XXIII, 5 g) was exposed to 10% methanolic sodium hydroxide (100 ml) for 36 hrs at room temperature (or 4 hrs under reflux). It was then diluted with water (200 ml) extracted with ether (75 ml x 2) to separate the neutral material (not investigated). The aqueous alkaline portion was acidified with 10% sulphuric acid and extracted with ether (100 ml, 50 ml x 2). The ether layer was washed with water, dried and evaporated to give the hydroxy acid (XXIV, R=H) which on treatment with an ethereal solution of diazomethane, gave the methyl ester (XXIV, R=CH_3), as a thick liquid, $[\alpha]_D^{28}$ -9.63° (c, 2.49).

Analysis: Found: C, 73.04; H, 8.26; $C_{16}H_{22}O_3$ requires: C, 73.25; H, 8.45%.

IR bands at 3509, 2935, 1710, 1429, 1381, 1172, 1124, 943, 845, 755 and 694 cm^{-1}.

Methyl 1R (-)cis-2,2-dimethyl-3(2-phenyl-prop-1-enyl) cyclopropane carboxylate (XXV)

A solution of hydroxy ester (XXIV, R=CH_3, 3 g) in dry benzene (150 ml) was refluxed with catalytic quantity of para-toluene sulphonic acid (0.150 g) for 8 hrs. The benzene solution was washed with water (100 ml x 2), dried and the benzene evaporated to furnish a solid (2.8 g) which was crystallised from pet. ether, to give ester (XXV), as white needles, (2.25 g), m.p. 60°, $[\alpha]_D^{28}$ -16.9° (c, 2.95).

Analysis: Found: C, 78.61; H, 8.38; $C_{16}H_{20}O_2$ 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-acetoxy-2-phenyl-ethyl)-cis-1 (2-phenyl prop-2-yl)cyclopropane (XXVI)

To a solution of the diol (XVIII, 3) g) in pyridine (50 ml) was added acetic anhydride (35 ml) and the mixture was kept at room temperature for 20 hrs. It was then diluted with water (250 ml) and kept at room temperature for 2 hrs when the excess amount of acetic anhydride was hydrolysed. The mixture was extracted with ether (150 ml, 100 ml x 2), the ether layer washed successively with water, 10% hydrochloric acid, saturated solution of sodium carbonate and finally with water. The ether layer was dried and evaporated

to furnish the pure monoacetylated product (XXVI) as a thick liquid in almost quantitative yield (32.95 g), $[\alpha]_D^{25}$ -5.3° (c, 2.65).

Analysis: Found: C, 78.24; H, 8.42; $C_{24}H_{30}O_3$ requires: C, 78.65; H, 8.25%.

IR bands at 3509, 2985, 1724, 1587, 1481, 1439, 1361, 1227, 1053, 1015, 930, 758 and 694 cm^{-1}.

2,2-Dimethyl-3 (2-acetoxy-2-phenyl-ethyl)-cis-1 (2-phenyl prop-1-enyl)cyclopropane (XXVII)

A solution of hydroxy acetate (XXVI, 28 g) in dry benzene (250 ml) was refluxed with catalytic amount of paratoluene sulphonic acid (0.150 g) for 8 hrs. The reaction mixture was washed with water (100 ml x 2) to remove p.t.s. and the benzene layer dried. Evaporation of benzene afforded the dehydrated product (26 g) which was purified by chromatography on silicic acid (400 g). Fractions eluted with pet. ether + benzene (1:1) and benzene, afforded TLC (12% ethyl acetate in C_6H_6) pure dehydrated acetate (XXVII), yield 25 g (94%), $[\alpha]_D^{28}$ +8.6° (c, 2.8).

Analysis: Found C, 82.58; H, 8.34; $C_{24}H_{28}O_2$ requires: C, 82.72; H, 8.10%.

IR bands at 2985, 1739, 1587, 1481, 1439, 1361, 1220, 1015, 755 and 694 cm^{-1}.

Methyl 2,2-dimethyl-3 (2-hydroxy-2-phenyl-ethyl)-cyclopropane-cis-1-carboxylate (XXIX, R=CH_3).

In a 1-litre, 3-necked round bottom flask equipped with overhead stirrer, was placed the unsaturated acetate (XXVII, 16 g), acetone (200 ml), water (25 ml) and acetic acid (15 ml). To the stirred solution was added powdered potassium permanganate (10 g, 1.2 mole), during 0.5 hr, maintaining the temperature at 40 to 50°. After the addition, the stirring was continued for 1.5 hrs at the same temperature. It was then treated with sulphur dioxide gas till a colourless solution was obtained. The colourless solution was diluted with water (300 ml) and extracted with ether (150 ml, 100 ml x 2). The ethereal solution was concentrated to 150 ml and extracted with 10% aqueous sodium hydroxide solution (100 ml, 50 ml). The neutral part was not investigated. The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid and extracted with ether (100 ml, 75 ml x 2). The ether layer was washed with water (100 ml x 2), dried and evaporated to furnish the crude acid (XXVIII, R=H) which was converted into its methyl ester (XXVIII, R=CH_3) by an ethereal solution of diazomethane.

The acetate ester (XXVIII, R=CH_3, 5.0 g) in pet.ether (100 ml) was adsorbed on a silicic acid (100 g) column for

3 hrs and eluted with pet. ether + benzene (1:1), benzene and chloroform. The fractions eluted with chloroform furnished a pure hydroxy ester (XXIX, R=CH_3, 4.2 g) as a thick liquid, $[\alpha]_D^{28}$ -2.25° (c, 2.67).

Analysis: Found: C, 72.84; H, 7.95; $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%.

IR bands at 3509, 2985, 1724, 1481, 1429, 1370, 1183, 1163, 1124, 1042, 840, 750 and 694 cm^{-1}.

Preparation of lactone (XXX)

To a solution of hydroxy ester (XXIX, R=CH_3, 1.5 g), in methanol (25 ml), was added 50% aq. solution of sodium hydroxide (5 ml) and refluxed for 3 hrs. The reaction mixture was cooled, diluted with water (50 ml) and extracted with ether (50 ml x 2) to remove neutral part. The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed with water (75 ml x 3), dried and evaporated to furnish the hydroxy acid (XXIX, R=H, 0.98 g) as a thick liquid. The acid (XXIX, R=H) was taken in dry benzene (25 ml) and the solution refluxed with P.T.S. (0.050 g) for 4 hrs. The solution was washed with water (20 ml x 2), dried and the solvent evaporated to furnish the solid (0.67 g). It was crystallised from 15% pet. ether in benzene to furnish crystalline lactone (XXX), m.p. 136°, $[\alpha]_D^{28}$ +49° (c, 1.14).

Analysis: Found: C, 77.68; H, 7.52; $C_{14}H_{16}O_2$ requires: C, 77.75; H, 7.46%.

IR bands at 2941, 1724, 1481, 1439, 1370, 1342, 1266, 1220, 1111, 1042, 1015, 935, 830, 758 and 699 cm^{-1}.

Methyl 2,2-dimethyl-3 (2-oxo-2-phenyl-ethyl)cyclopropane-cis-1-carboxylate (XXXI)

To a solution of hydroxy ester (XXIX, R=CH_3, 5 g) in acetone (50 ml), cooled at -10°, was added Jones chromic acid reagent till brown colour persisted. The mixture was allowed to remain at 0 to 5° for 0.5 hr. It was then diluted with water (100 ml) and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed with water (100 ml x 3), dried and evaporated to furnish a semisolid which was crystallised from pet. ether to afford white crystalline keto ester (XXXI, 3.3 g), m.p. 61°, $[\alpha]_D^{25}$ +60.3° (c, 2.32).

Analysis: Found: C, 73.34; H, 7.26; $C_{15}H_{18}O_3$ requires: C, 73.14; H, 7.37%.

IR bands at 2941, 1709, 1681, 1587, 1429, 1361, 1325, 1227, 1198, 1183, 1162, 1124, 1075, 976, 847, 766, 746 and 690 cm^{-1}.

1R Methyl 2,2-dimethyl-3 (2-chloro-2-phenyl-vinyl) cyclopropane-cis-1-carboxylate (XXXII)

To a solution of keto ester (XXXI, 1.5 g) in dry

dichloromethane (20 ml), was added phosphorus pentachloride (1 g) and the mixture was refluxed for 8 hrs. The reaction mixture was then poured on crushed ice (20 g) with stirring, allowed to attain room temperature and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed with water (50 ml x 2), dried and evaporated to give a mixture of two products (TLC). They were separated by chromatography over silicic acid (30 g). The less polar, the minor one (10%) was eluted with pet. ether (not investigated) while the more polar, the major product (85%) of the reaction was eluted with pet. ether + benzene (1:1) and pet. ether + benzene (1:2), to furnish the pure chloroester (XXXII), as a thick liquid (0.875 g).

Analysis: Found: C, 68.34; H, 6.22; Cl, 12.78;

$(C_{15}H_{17})_2Cl$ requires: C, 68.19; H, 6.44; Cl, 13.26%.

IR bands at 2985, 1724, 1481, 1429, 1361, 1190, 1136, 1081, 995, 917, 844, 758 and 690 cm^{-1}.

REFERENCES

1 R.D. Verschoyle and J.M. Barnes, Pestic Biochem. and Physiol. 2, 208 (1972).

2 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and B.C. Pearson, Nature, 213, 493 (1967).

3 R.M. Sawicki and M. Elliott, J. Sci. Food Agric. 16, 85 (1965).

4 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Nature, 248, 710 (1974).

5 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman and J.H. Stevenson, Nature, 246, 169 (1973).

6 Ian J. Graham - Bryce, Chem. and Ind. 545 (1976).

7 F. Barlow, A.B. Hadaway, L.S. Flower, J.E.H. Grose and C.E. Turner, Pestic. Sci. 8, 172 and 291 (1977).

8 M. Elliott, "Synthetic Pyrethroids" A.C.S. Symposium series No.42 (1977) p.1 and references cited therein.

9 N. Itaya, T. Matsuo, N. Ohno, T. Mizutani, F. Fujita and H. Yoshioka, "Synthetic Pyrethroids" A.C.S. Symposium Series No.42 (1977) p.45.

10 M. Elliott, Bull. Wld. Hlth Org. 44, 315 (1971).

11 K. Fujimoto, N. Itaya, Y. Okuno, T. Kadota and T. Yamaguchi, Agri. Biol. Chem. 37, 2681 (1973).

12

13 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Nature, 244, 456 (1973).

14 M. Elliott, N.F. Janes and Pulman, D.A., J. Chem. Soc. Perkin Trans I 2470 (1974).

15 M.S. Glenn and W.G. Scharpf, ACS Symposium series No.42 (1977), p.116.

16 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, ACS Symposium series No.2, 80 (1974).

17 M. Elliott and N.F. Janes, ACS Symposium series No.42, 29 (1977).

18 D. Owen John, J. Chem. Soc. Perkin Trans I, 1331 (1976).

19 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic Sci 7, 499 (1976).

20 M. Matsui and T. Kitahara, Agri. Biol. Chem. 31, 1143 (1976).

21 P.E. Burt, M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic Sci 5, 791 (1974).

22 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic Sci 6, 537 (1975).

23 Leon Velluz, Nomine, Gerard, Martel, Jacques C.R. Acad. Sci. Paris. Ser.C. 268(25), 2199 (1969).

24 Chem. Abstr. 70, 68572 p.
Martel Jacques, Huynh Chanh, Fr.1,505413 (01.C07c)
15 Dec. 1967.

25 R.B. Mitra and others, Indian Patent Application No.761/Del/78.

26 A.S. Khanra and R.B. Mitra, Indian J. Chem. 14B, 716(1976).

27 R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974).

28 N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry" Illustration from Steroid Field", Prentice-Hall, San Francisco, p.47 (1964).

29 H.O. House, Modern Synthetic Reactions, pp.123-129 W.A. Benjamin Inc., New York, 1965.

30 W. Cocker, H. Lauder, St.J. and P.V.R. Shannon, J. Chem. Soc. Perkin Trans I, 332 (1975).

CHAPTER III

EPOXIDATION
OF DEHYDRATION PRODUCTS
OF CARANE-3β-HYDROXY-4α-ACETATE

SUMMARY

Acetylation of 3β,4α-carane diol (VIII) gave the hydroxy monoacetate (VII). Dehydration of acetate (VII) with $POCl_3$/Py furnished a mixture of two acetates (IX) and (X) which were separated by column chromatography using silicic acid impregnated with 10% silver nitrate. The acetate (IX), on treatment with m-chloro perbenzoic acid gave the epoxide (XI) and the triol monoacetate (XIII). Reduction of epoxide (XI) with LAH afforded the known 3α,4α carane diol (XII) thus proving the stereochemistry of epoxide (XI) as α. Metaperiodate oxidation of triol mono acetate (XIII) gave the keto acetate (XIV). Treatment of epoxide (XI) with CH_3OH/KOH afforded the triol monomethyl ether (XV) which, on acetylation gave the hydroxy methoxy acetate (XVI). The compound (XV), on treatment with metaperiodate afforded the keto aldehyde (XVII) thus proving the presence of vicinal diol grouping. Epoxide (XI), on treatment with CH_3OH/HCl afforded the chlorohydrin acetate (XX) and chloro diol (XXI), the latter could be converted to chloroketo aldehyde (XXII) by cleavage with sodium metaperiodate.

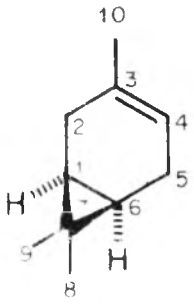
Epoxidation of the acetate (X) gave the epoxide (XXIII) which, on treatment with MeOH/HCl gave the normal product (XXIV) which could be converted to the diacetate (XXV).

INTRODUCTION

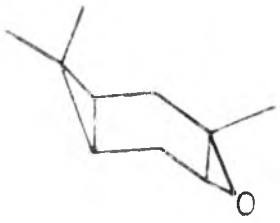
(+)car-3-ene (I), the naturally occurring bicyclic monoterpene hydrocarbon is known to react with organic peracids to form an epoxide[1]. This epoxide has been assigned the stereostructure (II) and confirmed[2,3]. In this structure the cyclopropane ring containing gemdimethyl group and the epoxide ring are trans to each other. The epoxide (II) is called α-epoxide. The other possible isomer (III) in which the epoxy ring is cis to the cyclopropane ring has also been prepared[4,5] and named as β-epoxide (III).

A number of transformations[6-10] of these two stereoisomeric epoxides of car-3-ene have been carried out with many reagents to furnish a variety of products; some of them being used as intermediates in important synthesis[3,11]. Similarly the other two double bond isomers of car-3-ene viz. car-2-ene[12-16] (IV) and car-4-ene[12,17] (V) have been epoxidised and their chemistry studied extensively. However, the carene-derivatives, possessing an exo double bond, like car-3(10)-ene (VI) were not given much attention though their perfumery properties are known[18].

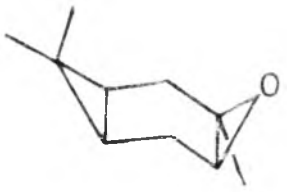
Substituted car-3(10)-enes have been obtained[11,19-22]



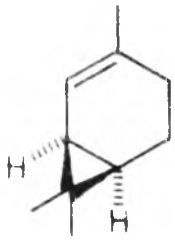
I



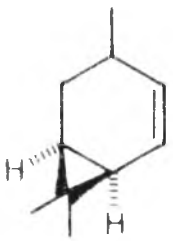
II



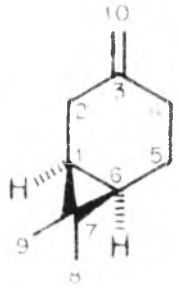
III



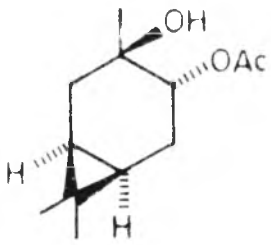
IV



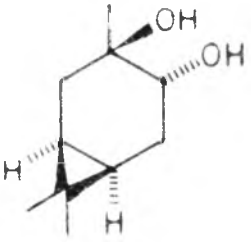
V



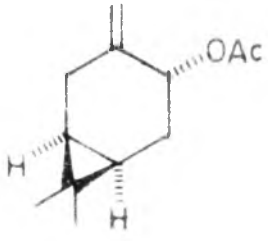
VI



VII



VIII



IX

and characterised mostly as minor products, during some transformations of car-3-ene. However, the first simple preparative method for getting 4-substituted car-3(10)-ene was reported by P.J. Kropp[3]. He prepared the monoacetate (VII) of 3α,4α-caranediol (VIII) and dehydrated it with POCl$_3$/pyridine to afford a mixture of (IX) and (X) in 65 to 70% yield. Formation of (X) has been recorded as the first example of cyclopropyl participation in the carane series and of the rearrangement of a carane derivative to other bicyclic system. The two esters, (IX) and (X) were separated by preparative GLC and characterised by spectral data and chemical reactions. Of these, compound (IX) is the normal product of dehydration of (VII), while the compound (X) is formed by a rearrangement involving cyclopropyl participation.

Although the stereochemistry of reactions like Friedel-Crafts[13] type acylation, Prins reaction[13], epoxidation[8] etc. of (+)car-3-ene, has been extensively studied and found to give mainly the α-oriented addition and substitution products, not much is known about the stereochemistry of such reactions on the car-3(10)-ene derivatives. The mixture of unsaturated acetates (IX) and (X) possesses a pleasant, sweet odour and is likely

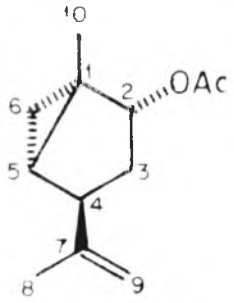
to find use in perfumery.[18]

The two acetates (IX) and (X) have now been separated by us, by employing column chromatography over silicic acid impregnated with silver nitrate. With a view to explore the possible perfumery properties of some of the derivatives of these two acetates and also to ascertain, whether transannular cyclopropyl participation is involved in some of the rearrangements of these compounds, the epoxidation of the acetate, (IX) and (X), and the rearrangements of the corresponding epoxides under acidic and alkaline conditions have been carried out.

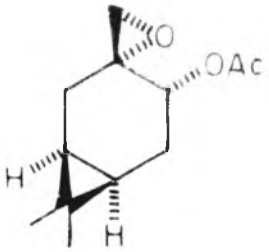
PRESENT WORK

(+)Car-3-ene (I) was converted to the 3β,4α-carane diol (VIII) by treating it with performic acid, as described in Chapter I of the thesis. The diol (VIII), on treatment with Ac_2O/pyridine, furnished 3β-hydroxy carane 4α-acetate (VII) as a solid, m.p. 71° (pet. ether). It showed IR bands at 3636 (OH), 1739 and 1266 (acetate) and NMR signals at 9.26 (2H, m, C_1 and C_6 protons); 9.0, 8.97 (3H each, s, gemdimethyl at C_7); 8.83 (3H, s, C_3 methyl), 8.0 (3H, s, -O-CO-CH_3) and 5.53 (1H, q, C_4 proton).

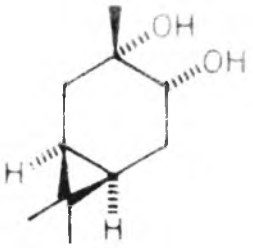
The hydroxy monoacetate (VII) was dehydrated with $POCl_3$/pyridine at 0° to furnish the dehydrated product (70%) which showed two spots on TLC (10% silver nitrate



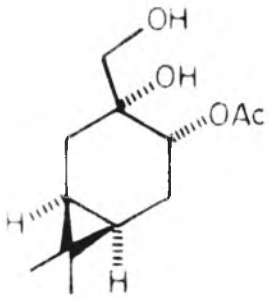
X



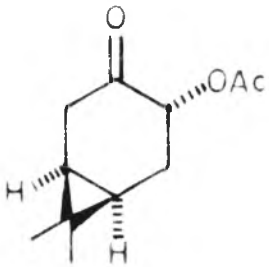
XI



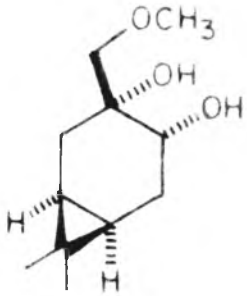
XII



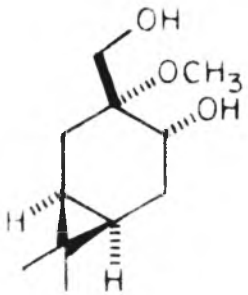
XIII



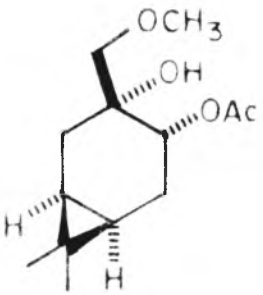
XIV



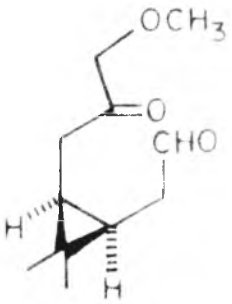
XV



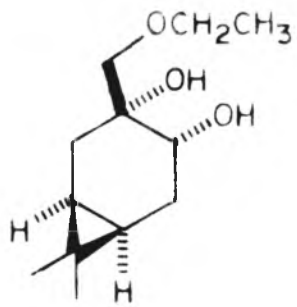
XV a



XVI



XVII

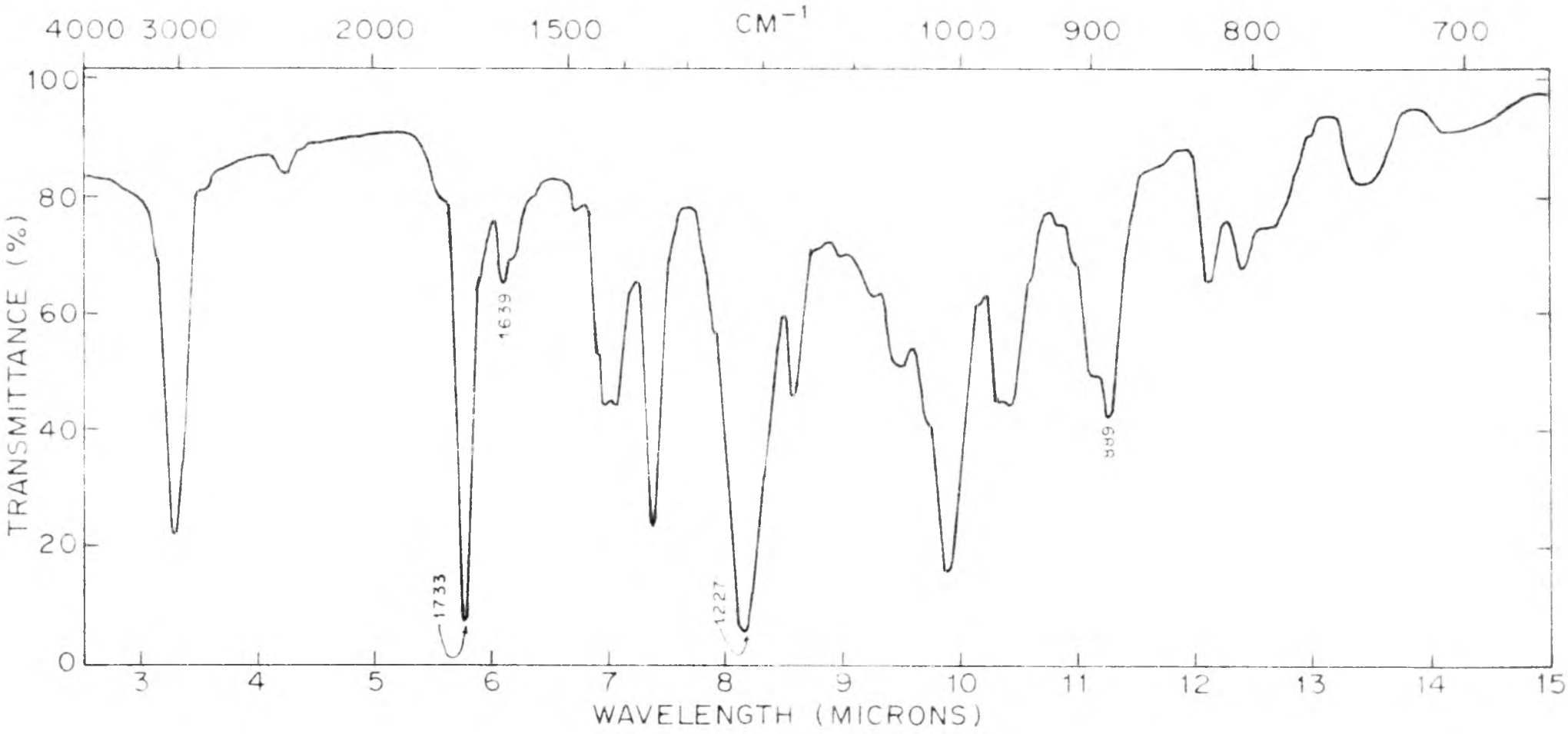


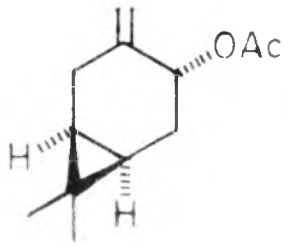
XVIII

on silicic acid). The two unsaturated acetates, the dehydrated products, were separated by column chromatography using silicic acid impregnated with 10% silver nitrate.

The less polar (35%) of the unsaturated acetates was eluted in the earlier fractions of chromatography, purified by distillation and identified as (IX), $C_{12}H_{18}O_2$, M^+ 194, b.p. 110-115° (bath)/6 mm. It showed IR (Fig.1) bands at 1738, 1227 (acetate), 1639, 889 ($>C=CH_2$) and NMR (Fig.2) signals at 9.3 (2H, m, cyclopropane protons at C_1 and C_6); 9.1, 9.0 (3H each, s, gemdimethyl on cyclopropane); 8.33 (2H, m, C_5 protons); 8.02 (3H, s, acetate methyl); 7.65 (2H, m, allylic methylene protons); 5.2 (2H, m, olefinic protons at C_{10}) and 4.93 (1H, t, J= 4 Hz, C_4 proton).

The more polar unsaturated acetate (33%), the other dehydrated product of (VII), was eluted in the tail fractions of chromatography, purified by distillation and was identified by spectral data as (X), $C_{12}H_{18}O_2$, M^+ 194, b.p. 100-110°(bath)/5 mm. It showed (Fig.3) bands at 1739, 1242 (acetate), 1653, 885 ($>C=CH_2$) and NMR (Fig.4) signals at 9.63 (2H, m, C_6 methylene protons of cyclopropane); 9.0 (1H, m, C_5-proton of cyclopropane); 8.87 (3H, s, methyl at C_1); 8.53 (2H, m, C_3 methylene protons);


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
1733
1639
1227
909
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


OAc
H
H

(IX)

FIG. 1

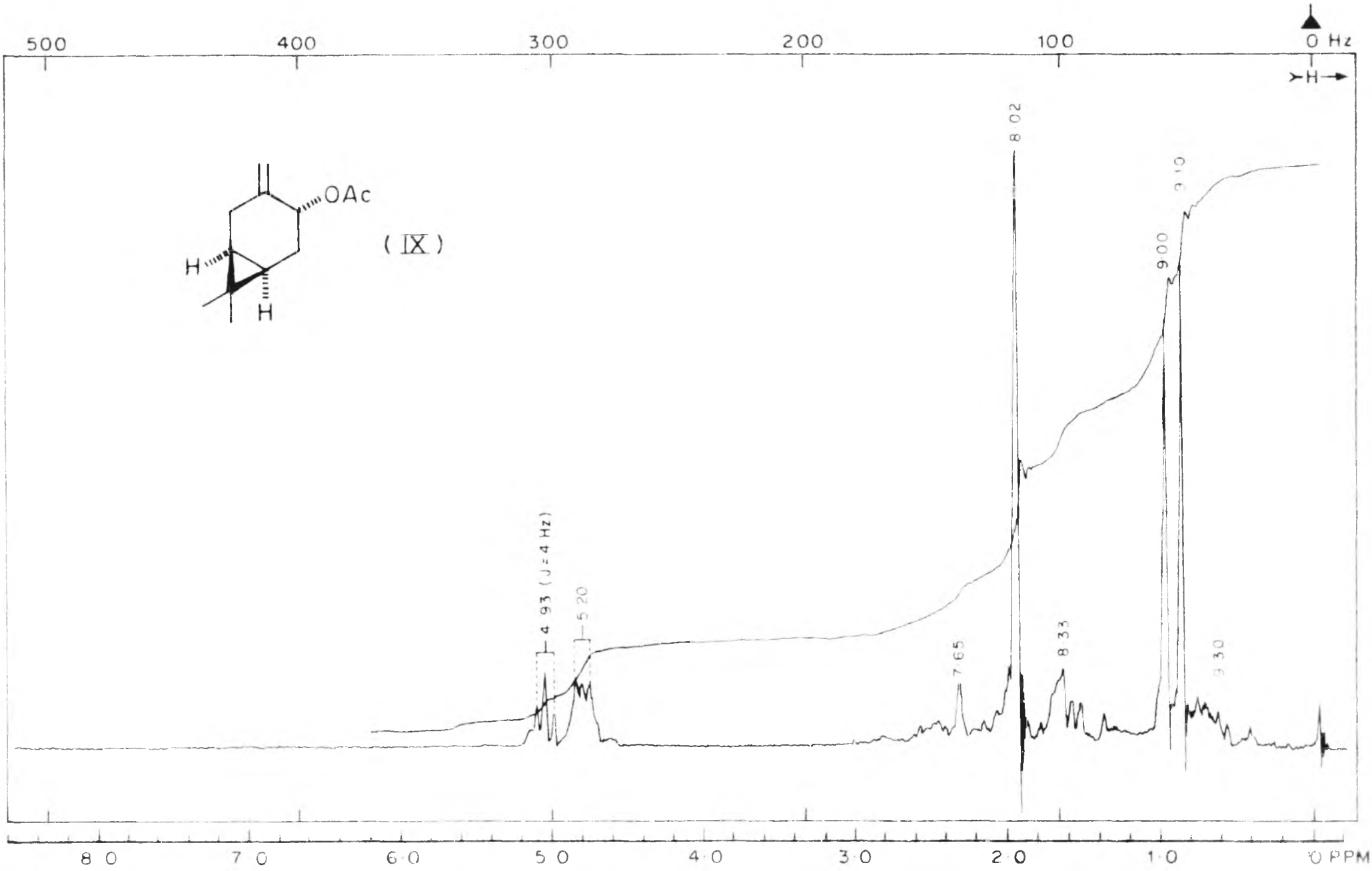
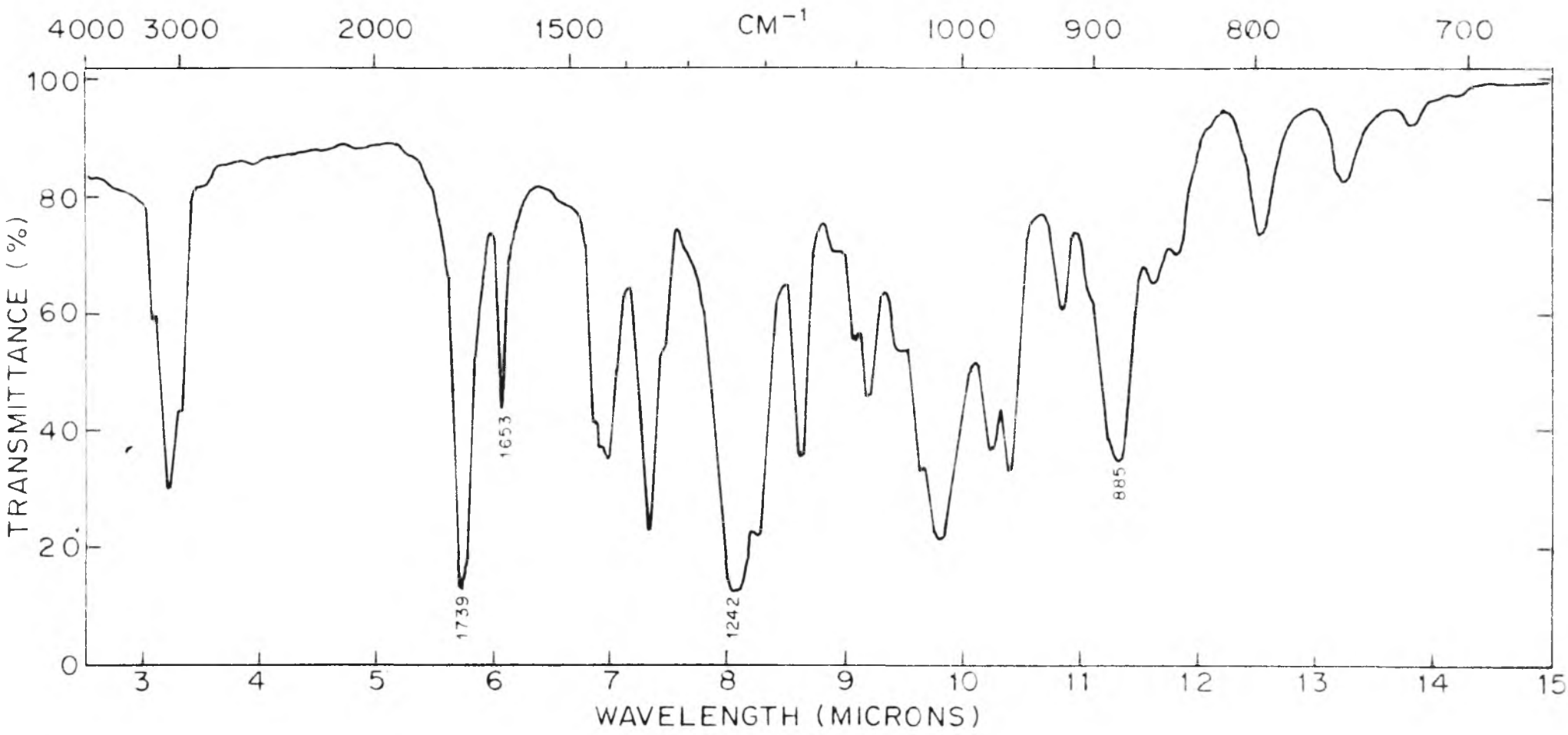
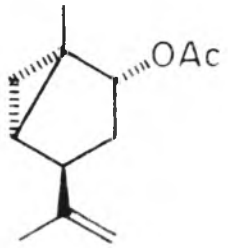

500
400
300
200
100
0 Hz
→H←
OAc
H
H
(IX)
8 02
9 10
9 00
4 93 (J=4 Hz)
5 20
7 65
8 33
9 30
8 0
7 0
6 0
5 0
4 0
3 0
2 0
1 0
0 PPM (δ

FIG 2


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1739
1653
1242
885
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OAc

(X)

FIG 3

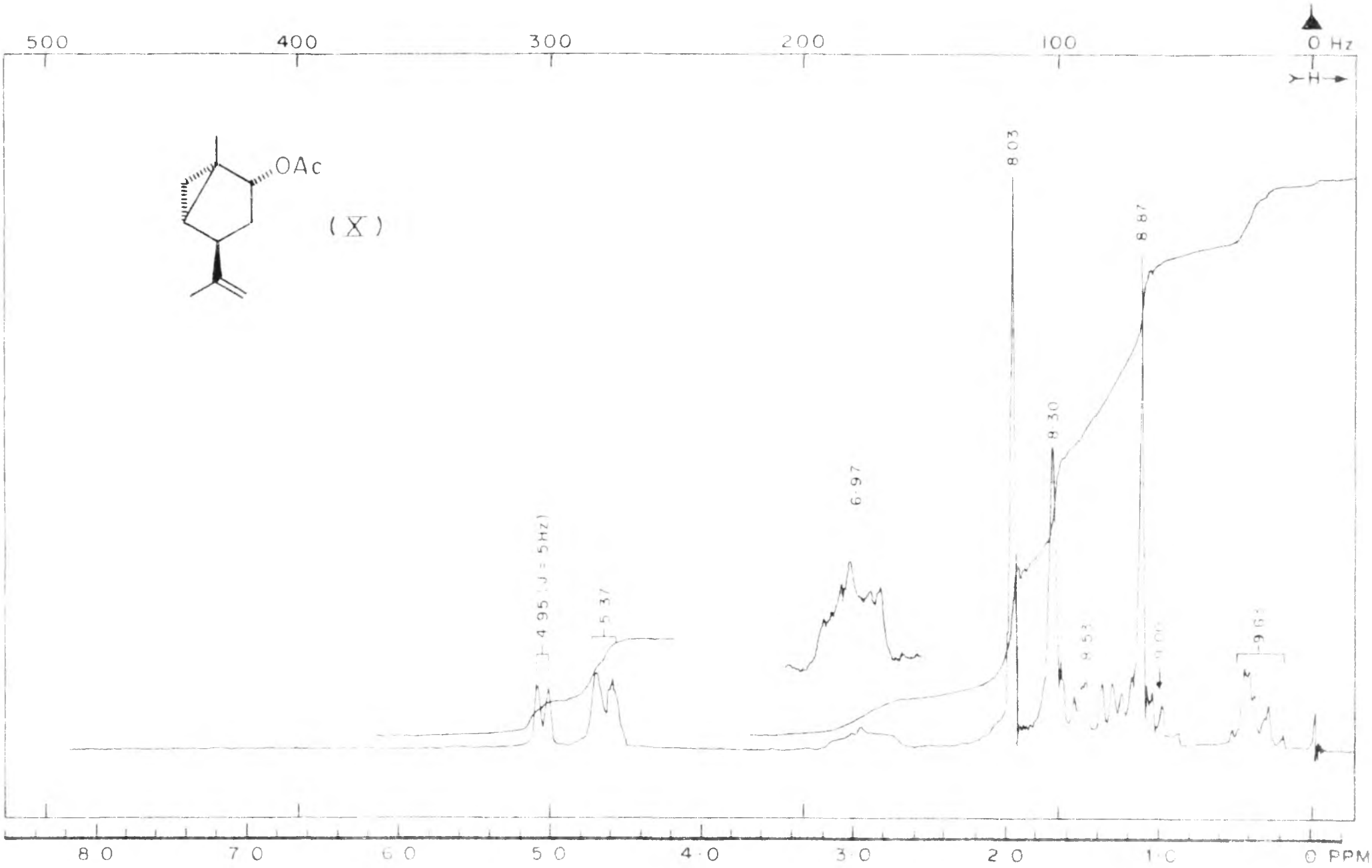

500
400
300
200
100
0 Hz
OAc
(X)
8.03
8.87
8.30
6.97
4.95 (J = 5Hz)
5.37
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)

FIG 4

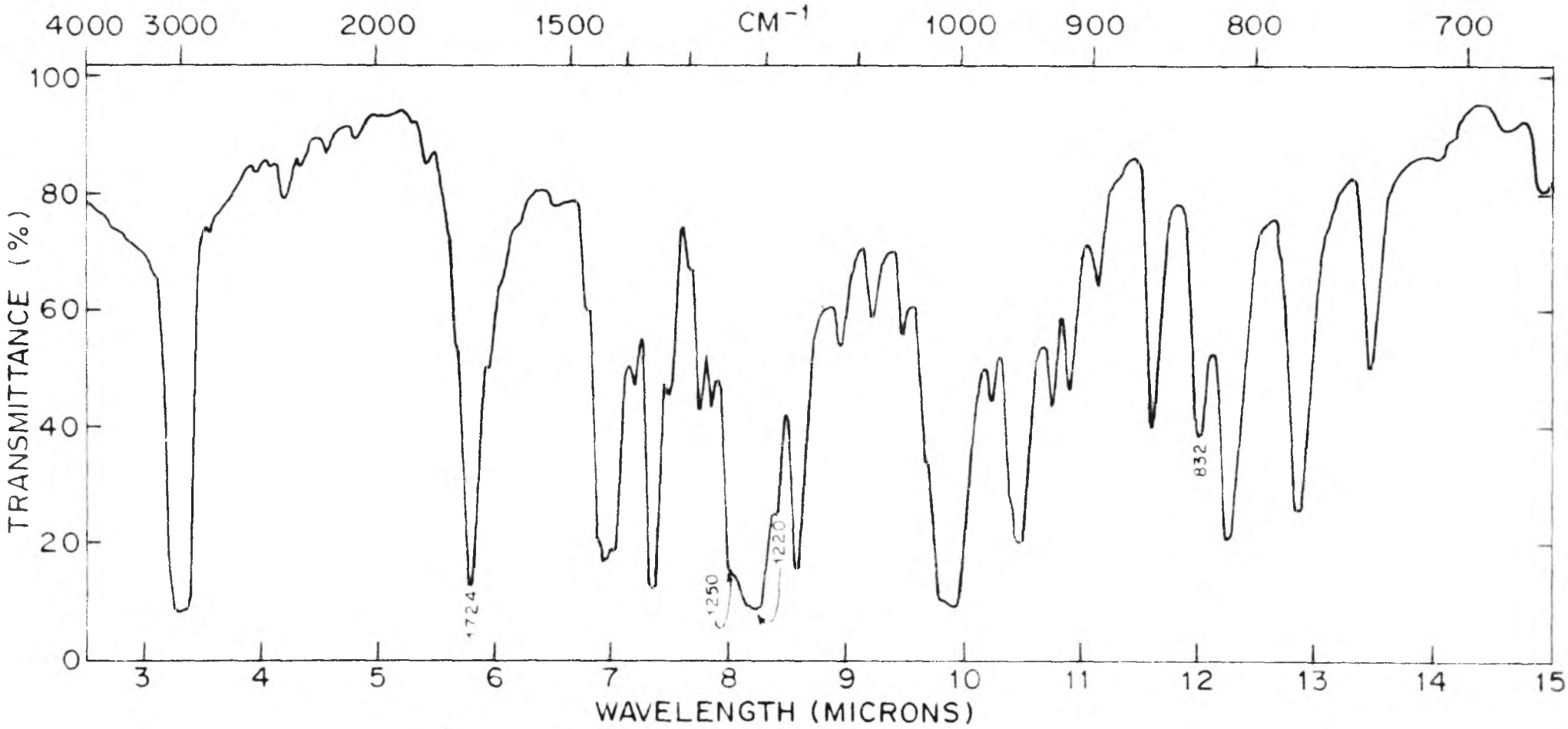
151

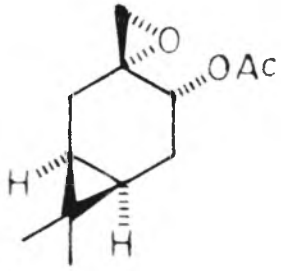
8.3 (3H, s, vinyl methyl at C_7); 8.03 (3H, s, acetate methyl); 5.97 (1H, m, C_4-proton); 5.37 (2H, m, olefinic protons of $>C=CH_2$ at C_7) and 4.95 (1H, d, J = 5 Hz, C_2-proton). The above spectral properties of (IX) and (X) were comparable with those reported[3] in literature.

Epoxide of (IX) and its stereochemistry

The acetate (IX), on treatment with m-chloro perbenzoic acid in chloroform solution, gave a mixture of two compounds (TLC; 2 spots; 8% ethyl acetate in C_6H_6). It was separated into its constituents by column chromatography on silicic acid (1:20). The less polar compound, the major product (85%), eluted with benzene was obtained as a solid which was identified as the epoxide (XI), $C_{12}H_{18}O_3$, M^+ 210, m.p. 67° (pet. ether). It showed IR (Fig.5) bands at 1724, 1250 (acetate), 1220, 832 (1,2-epoxide) and NMR (Fig.6) signals at 9.53, 9.37, 9.18 (2H, br.d, each C_1 and C_6 protons); 9.03, 8.93 (3H each, s, gemdimethyl at C_7); 8.73, 8.5, 8.3 (total 4H, br.s each, methylene protons at C_2 and C_5); 7.95 (3H, s, acetate methyl), 7.62, 7.40 (1H each, d, J = 6 Hz, C_{10} protons) and at 5.77 (1H, t, J = 4 Hz, C_4 proton).

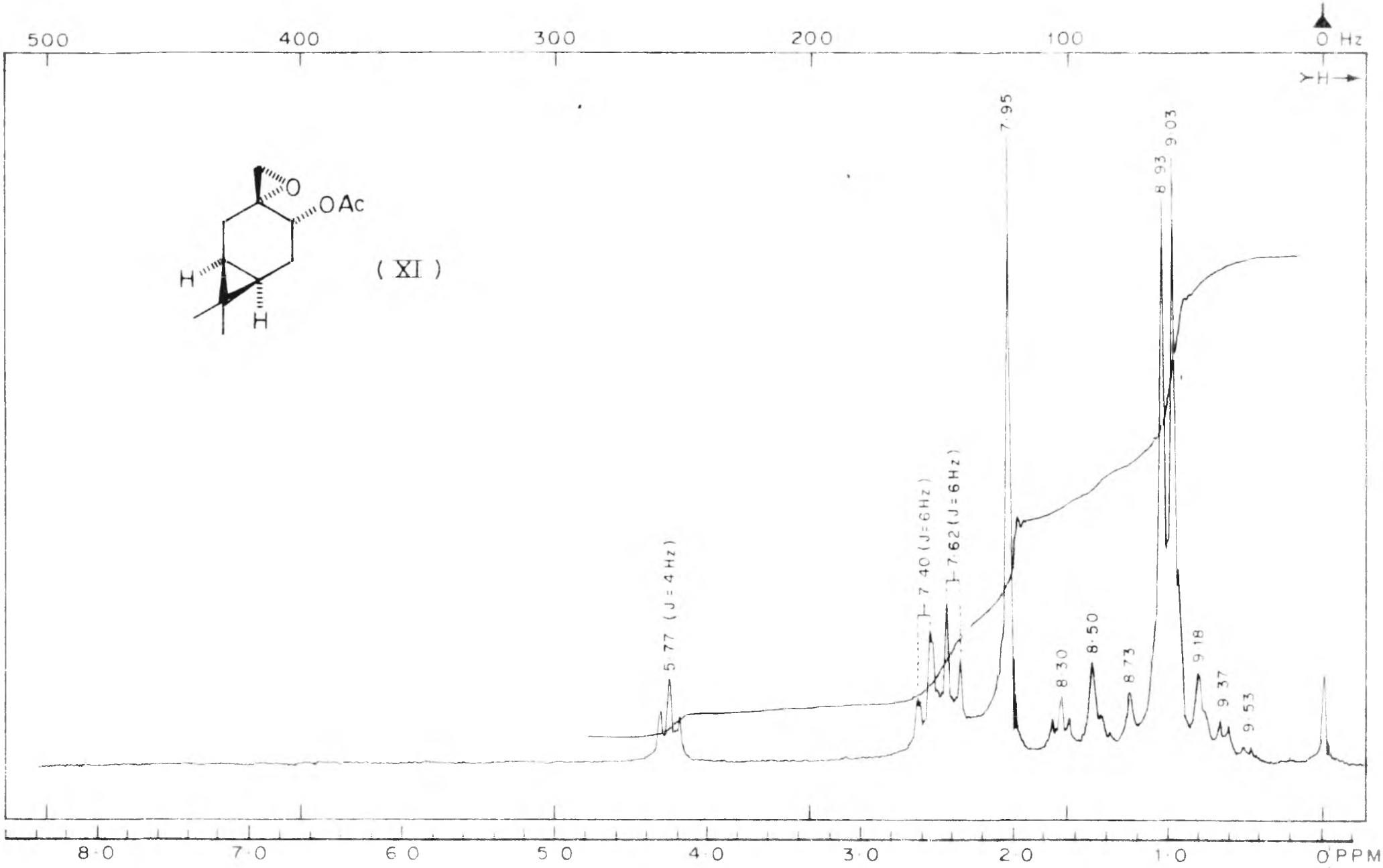
Reduction of the epoxide (XI) with lithium aluminium hydride afforded a crystalline solid, $C_{10}H_{18}O_2$, M^+ 170, m.p. 68° (pet. ether) which was identified as the cis-


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1724
1250
1220
832
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


O
OAc
H
H

(XI)

FIG. 5.


500
400
300
200
100
0 Hz
δH
7·95
8·93
9·03
5·77 (J=4Hz)
7·40 (J=6Hz)
7·62 (J=6Hz)
8·30
8·50
8·73
9·18
9·37
9·53
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

O
OAc
H
H

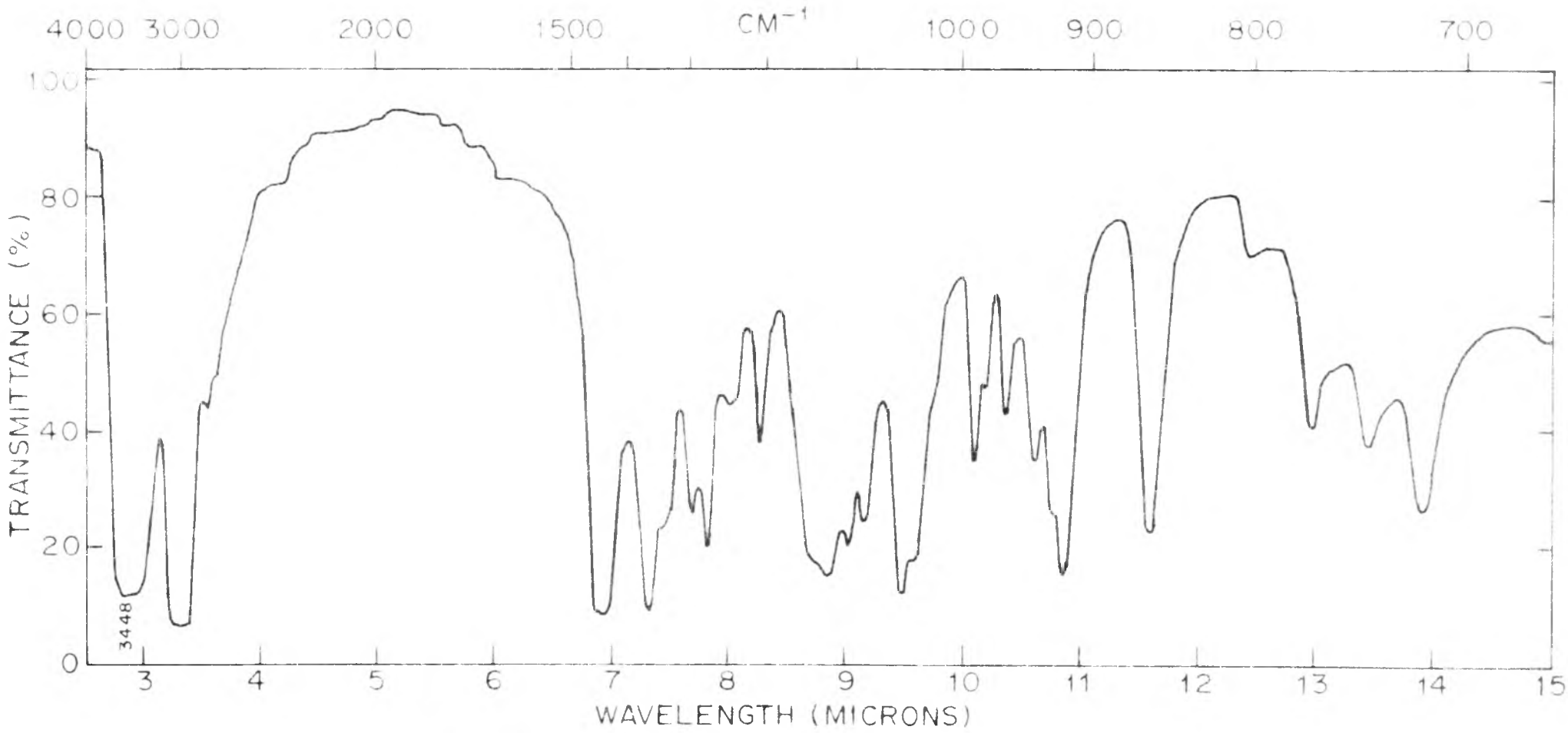
(XI)

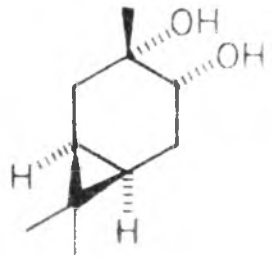
FIG 6

3α,4α-carane diol (XII), according to the spectral data, mentioned below and by comparison with those reported in literature[3]. It showed IR (Fig.7) bands at 3448 (OH) and NMR (Fig.8) signals at 9.34 (2H, m, C_1 and C_6 protons); 9.12, 9.02 (3H each, s, gemdimethyl at C_7); 8.87 (3H, s, methyl at C_3); 8.17 (4H, m, methylene protons at C_2 and C_5); 7.03 (1H, q, C_4 proton) and 7.4 (2H, br.s, exchangeable with D_2O, OH protons).

Formation of <u>cis</u> diol (XII) from the epoxide (XI) establishes the stereochemistry of the epoxide at C_3-C_{10} as α, as given in the stereostructure (XI). It is thus clear that in car-3-(10)-ene derivatives also the approach of the reagent is from the less hindered α side. Approach from β-side is restricted because of the β-oriented cyclopropane ring with gemdimethyl group.

The more polar product formed during epoxidation was eluted in the tail fractions of chromatography to furnish a solid (12%) which was purified by crystallisation. It was identified by spectral and chemical evidences, as the triol monoacetate (XIII), $C_{12}H_{20}O_4$, M^+ 228, m.p. 99° (pet. ether). It showed IR bands at 3571 (OH), 1742, 1227 (acetate) and NMR ($CHCl_3$) signals at 9.34 (2H, m, C_1 and C_6 protons); 9.12, 9.0 (3H, each, s, gemdimethyl at


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3448
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OH
OH
H
H

(XII)

FIG 7

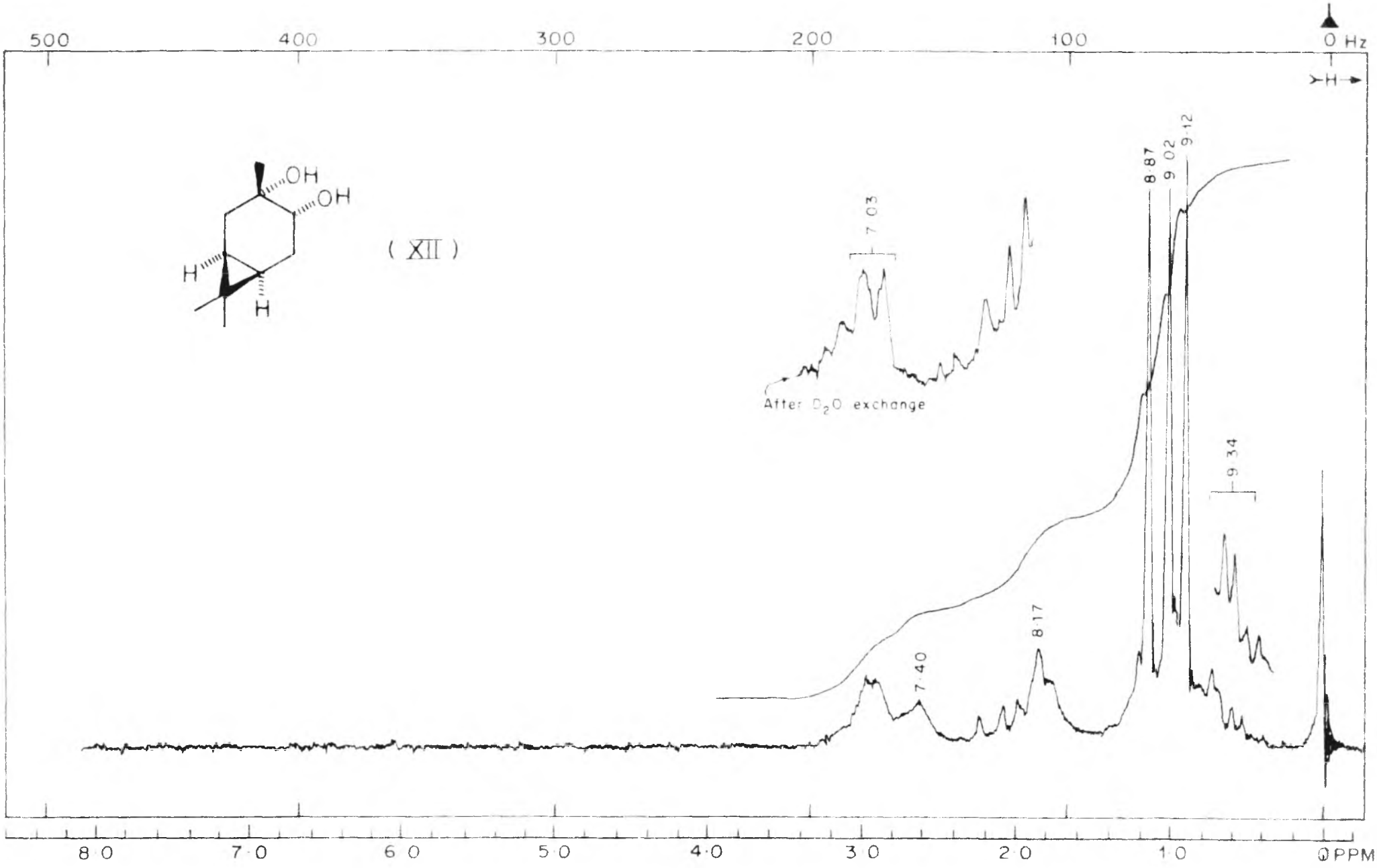

500
400
300
200
100
0 Hz
H
OH
OH
H
H
(XII)
7·03
After D_2O exchange
8·87
9·02
9·12
9·34
7·40
8·17
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIG. 8.

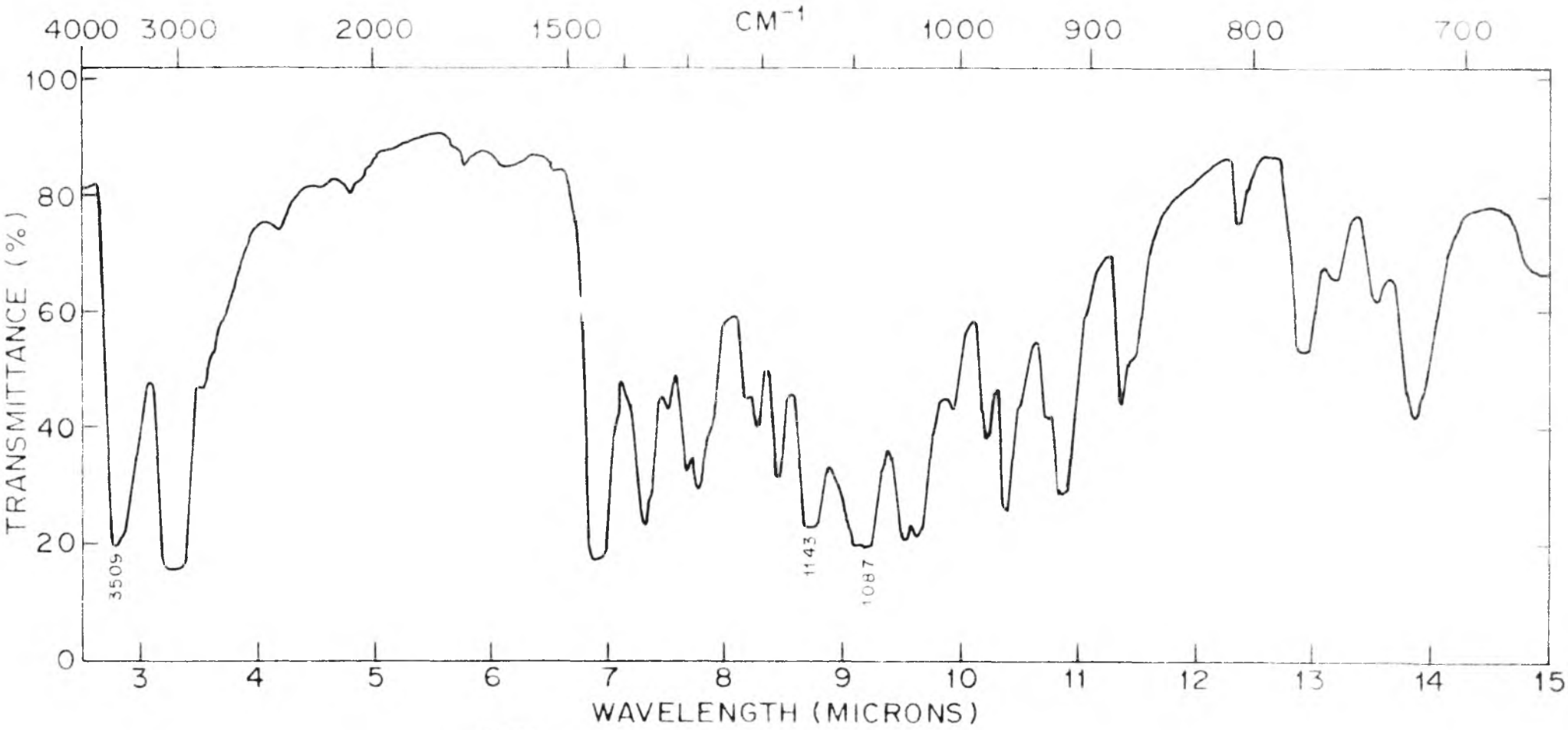
C_7), 7.9 (3H, s, acetate methyl); 6.67 (1H, t, J = 9 Hz, C_4 proton) and 6.17, 5.72 (2H, d each, J = -12 Hz[23,24], C_{10}-CH_2 protons).

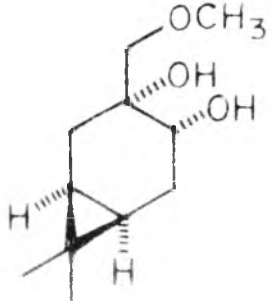
The structure of triol monoacetate (XIII) was further confirmed by the following reaction. Oxidation of (XIII) with sodium metaperiodate gave the liquid nor-keto acetate (XIV) $C_{11}H_{16}O_3$. The freshly prepared keto acetate (XIV) showed IR bands at 1754, 1227 (acetate), 1710 (>C = O) and NMR signals at 9.58 (2H, m, C_1 and C_6 protons); 9.12, 8.87 (3H each, s, gemdimethyl); 7.9 (3H, s, acetate methyl); 7.7 (2H, m, methylene adjacent to >C=O) and 5.47 (1H, br.s, C_4-proton). However, further characterisation of nor-keto acetate (XIV) by preparation of solid derivative like 2:4 DNP was not successful.

The formation of keto acetate (XIV) from triol monoacetate (XIII), thus proves the presence of vicinal diol grouping in (XIII) and confirmed the assignment of the structure (XIV). The triol monoacetate is formed by the acid catalysed hydration of the epoxide (XI), probably due to the traces of water present in the reaction mixture.

Action of alkali on epoxide (XI)

The epoxide (XI) was not affected by silicic acid


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3509
1143
1087
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OCH3
OH
OH
H
H

(XV)

FIG 9

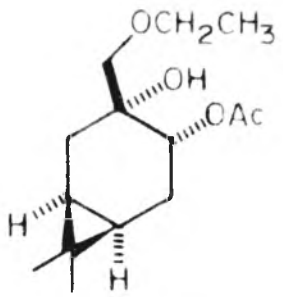
or alumina and hence can be purified by chromatography over both alumina and silica gel without any appreciable rearrangement.

On treatment with a strong alkali like potassium hydroxide in methanol (under reflux for 1 hr), it exclusively gave a solid diol, $C_{11}H_{20}O_3$, M^+ , m.p. 85° (pet. ether) which has been assigned the structure (XV) on the basis of spectral and chemical evidences given below.

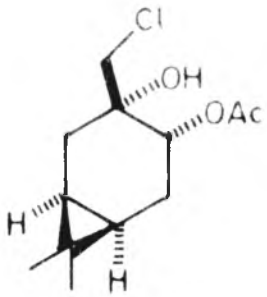
It showed λ (Fig.9) bands at 3504, 1087(sh), 1143 (ether) and NMR signals at 9.27 (2H, m, C_1 and C_6 protons); 9.1, 9.0 (3H each, s, gemdimethyl at C_7); 8.17 (4H, m, methylene protons at C_2 and C_5); 7.28 (2H, br.s exchangeable with D_2O, -OH protons); 6.75 (2H, br.s, methylene protons at C_{10}) and 6.63 (4H, br.s, $-OCH_3$ at C_{10} and C_4 proton).

During the treatment with methanolic potassium hydroxide, in addition to the opening of the oxirane ring of (XI), the acetyl group at C_4 is also hydrolysed to -OH group. Here two alternative structures viz. (XV) and (XVa) are possible for the compound. The structure (XV) is favoured for the following reasons:

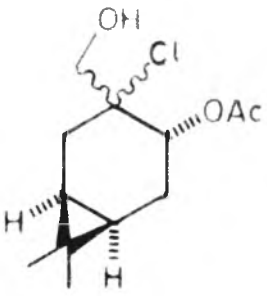
1) On acetylation (Ac_2O/Py), the compound (XV) gave



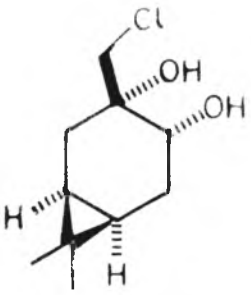
XIX



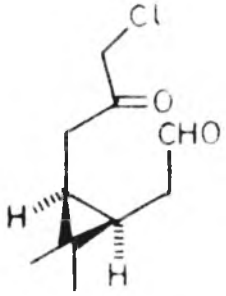
XX



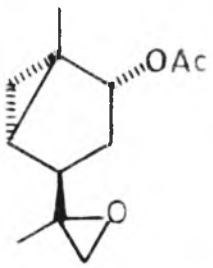
XX a



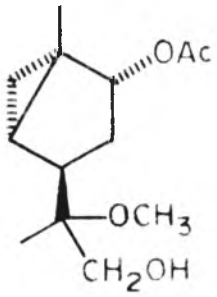
XXI



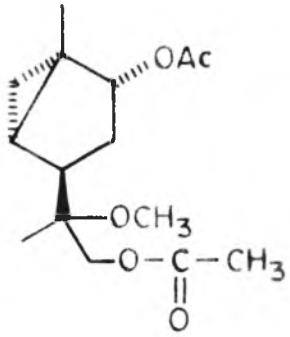
XXII



XXIII



XXIV

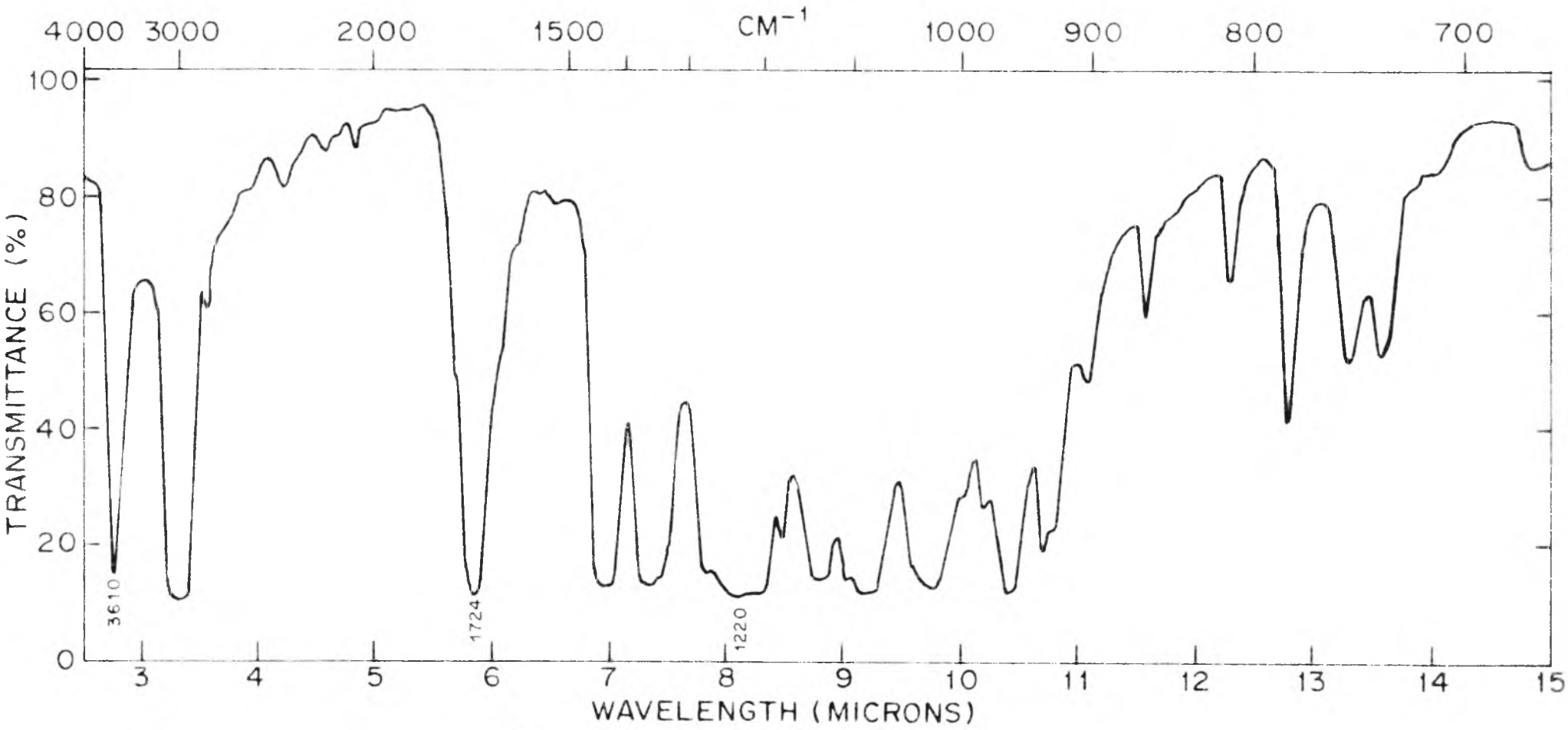


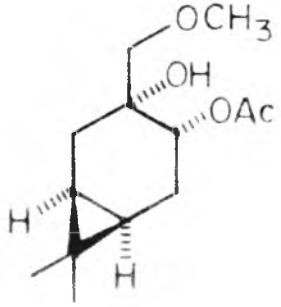
XXV

only a hydroxy monoacetate (XVI), $C_{13}H_{22}O_4$, M^+ 242, m.p. 84° (pet. ether). It showed IR (Fig.10) bands at 3510 (OH), 1724, 1220 (acetate) and NMR (Fig.11) signals at 9.4, 9.23 (2H, br.d each, C_1 and C_6 protons); 9.02, 8.97 (3H each, s, gemdimethyl at C_7); 8.0 (3H, s, acetate methyl); 7.8 (1H, s, exchangeable with D_2O, OH proton); 6.9 (2H, s, methylene protons of C_{10}); 6.73 (3H, s, $-OCH_3$ at C_{10}) and 5.5 (1H, t, J = 9 Hz, proton at C_4).

2) When treated with sodium metaperiodate in acetone, the diol (XV) was cleaved, giving initially the keto/aldehyde (XVII) which, however, being unstable underwent intramolecular aldol condensation, giving a mixture of products. But the IR and NMR spectra of freshly prepared sample clearly indicated the presence of (XVII) as the major product. It showed IR bands at 2801 (CHO), 1724 (>C=O) and NMR signals at 9.3 (2H, m, cyclopropane protons at C_1 and C_6); 9.12, 8.87 (3H each, s, gemdimethyl at C_7); 7.68 (4H, m, $-CH_2-C(=O)-$); 6.65 (3H, s, $-OCH_3$); 6.17 (2H, s, CH_2-O of C_{10}) and 0.3 (1H, s, -CHO proton).

Formation of monoacetate indicated the presence of only one primary or secondary hydroxyl group while formation of keto/aldehyde proved the presence of vicinal diol grouping. These results are in agreement with structure (XV) only.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3610
1724
1220
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OCH3
OH
OAc
H
H

(XVI)

FIG. 10.

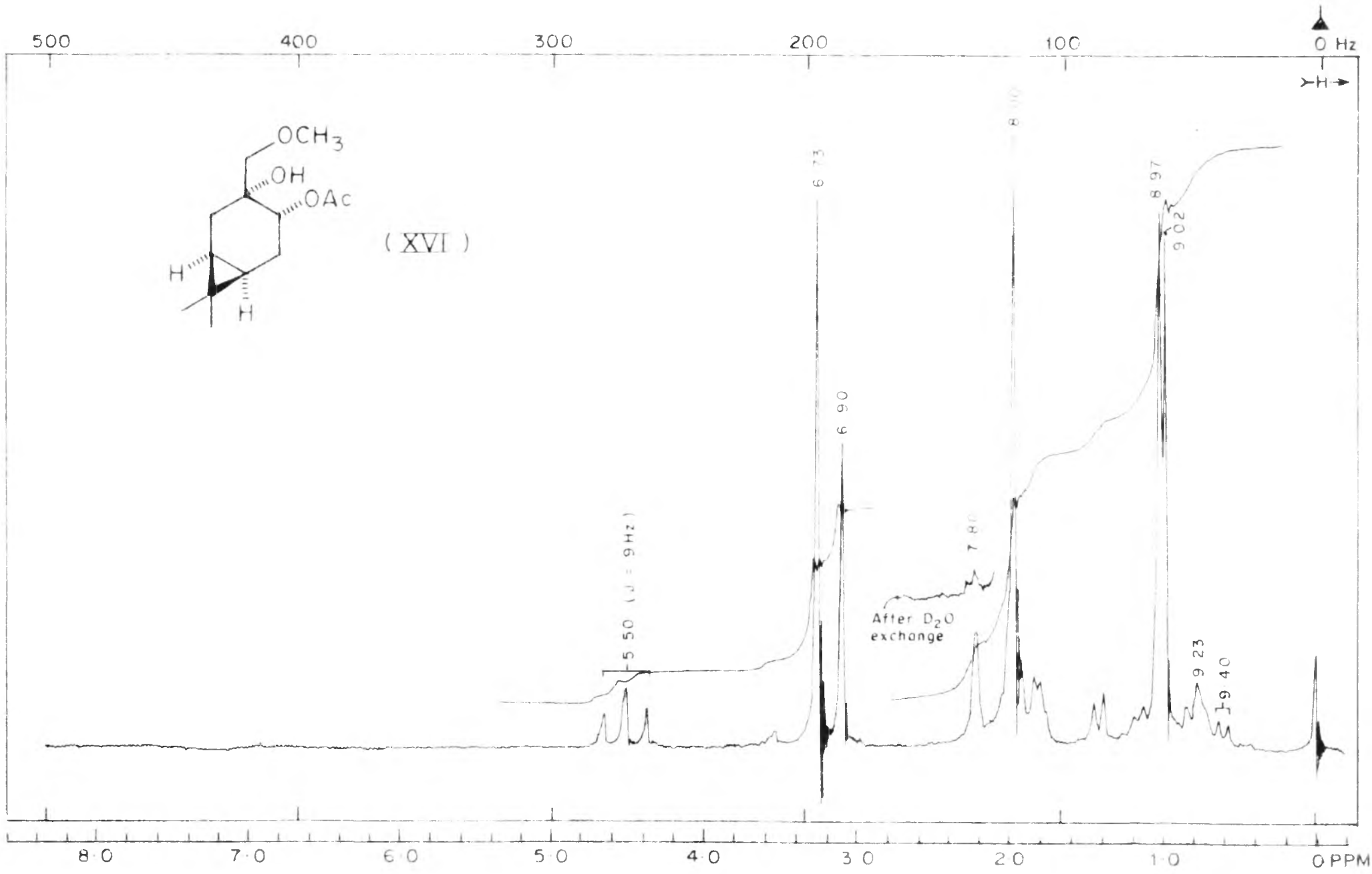

500
400
300
200
100
0 Hz
OCH3
OH
OAc
H
H
(XVI)
6 73
6 90
8 10
8 97
9 02
5 50 (J = 9Hz)
7 80
After D2O exchange
9 23
9 40
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIG 11

The epoxide (XI), when allowed to react with ethanolic potassium hydroxide, gave the corresponding C_{10} ethyl ether diol (XVIII) as the only product, $C_{12}H_{22}O_3$, M^+ 214, m.p. 79° (pet. ether). It showed IR bands at 3571 (OH), 1111 (ether) and NMR signals at 9.23 (2H, m, protons at C_1 and C_6); 9.13, 9.0 (3H each, s, gemdimethyl at C_7); 8.8 (3H, t, J = 7 Hz, CH_3 of $O-CH_2-\underline{C}H_3$); 8.2 (4H, m, methylene protons of C_2 and C_5); 6.73 (2H, s, $C_{10}-CH_2$) and 6.53 (2H, q, methylene of $O-\underline{C}H_2-CH_3$).

The ethyl ether diol (XVIII), on acetylation with Ac_2O/Py, afforded a thick liquid hydroxy monoacetate (XIX), $C_{14}H_{24}O_4$. It showed IR bands at 3704 (OH), 1739, 1235 (acetate), 1099 (ether) and NMR signals at 9.23 (2H, m, protons at C_1 and C_6); 9.02, 8.98 (3H each, s, gemdimethyl at C_7); 8.85 (3H, t, J = 7 Hz, $-CH_3$ of $-OCH_2-CH_3$); 8.03 (3H, s, acetate methyl); 6.88 (2H, s, $C_{10}-CH_2$); 6.63 (2H, q, methylene protons of $O-CH_2-CH_3$) and 5.5 (1H, t, J = 9 Hz, C_4-proton).

Action of acid on epoxide (XI)

As mentioned earlier, the epoxide (XI) was not much affected by silicic acid but when treated with hydrochloric acid (1N) in methanol at 10° for 24 hrs, it afforded a mixture of two products. They were separated

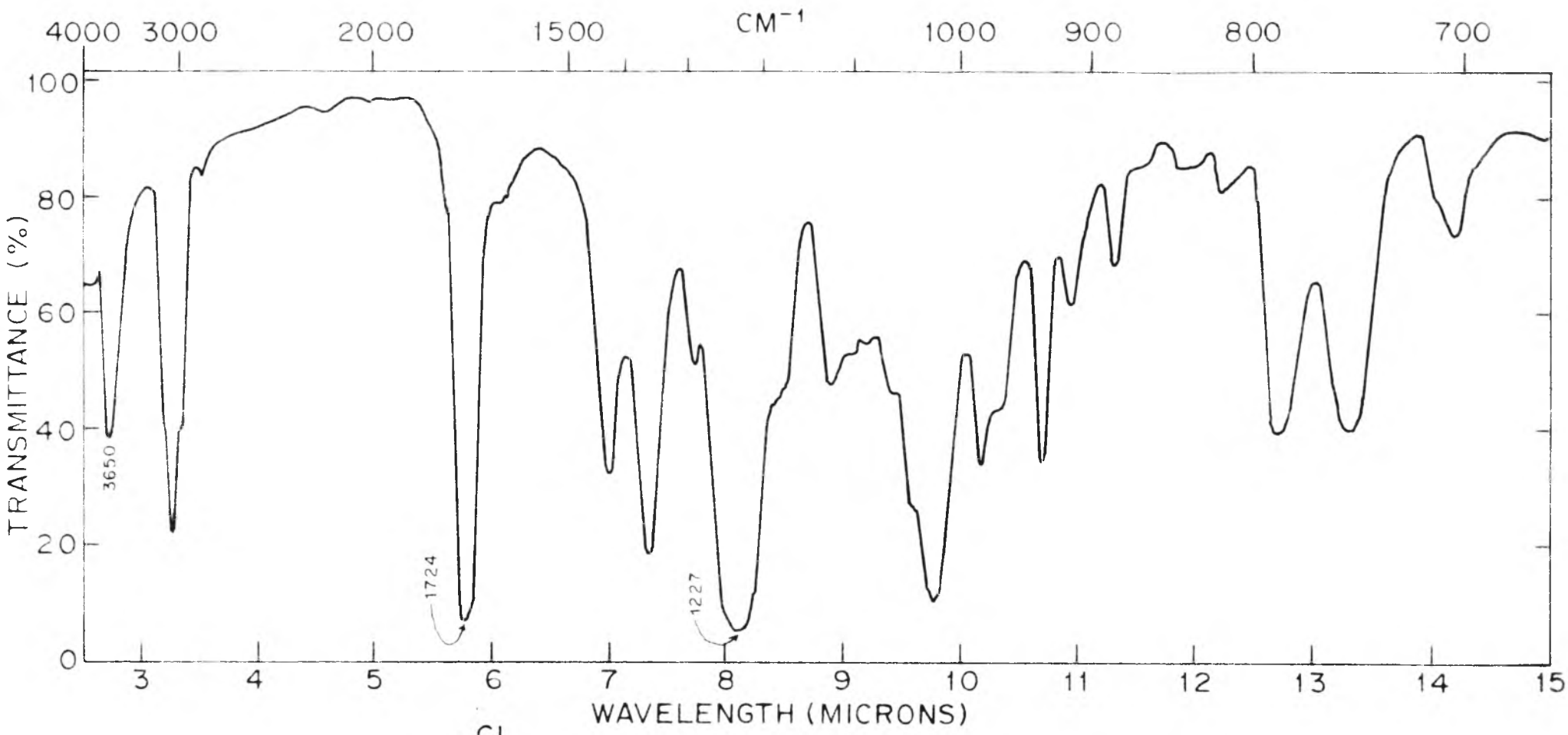
by chromatography over silicic acid. The less polar compound was found to be the major product and was obtained as a thick liquid. Elemental analysis and mass spectrum (M^+ 246, and a peak of 248 due to Cl^{37}) indicated the presence of chlorine and the molecular formula was found to be $C_{12}H_{19}O_3Cl$. The IR spectrum showed the presence of hydroxyl and acetate groups. These data indicated that the compound is a chlorohydrin and two structures viz. (XX) and (XXa) are possible.

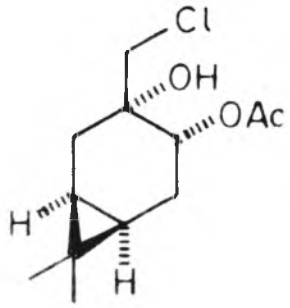
The structure (XX) for the compound was favoured on the basis of spectral and chemical evidences given below.

1) It showed IR (Fig.12) bands at 3650 (OH), 1724, 1227 (acetate) and NMR (Fig.13) signals at 9.2 (2H, m, C_1 and C_6 protons); 8.98 (6H, s, gemdimethyl at C_7); 7.98 (3H, s, acetate methyl); 7.63 (1H, s, exchangeable with D_2O, -OH proton); 6.63 (2H, s, $-CH_2Cl$) and 5.4 (1H, t, J = 7.8 Hz, C_4-proton).

2) Further acetylation (Ac_2O/Py) of (XX) under normal conditions was not successful, indicating the tertiary nature of the hydroxyl group.

3) On hydrolysis with hydrochloric acid (4N) in methanol at room temperature, the compound (XX)


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3650
1724
1227
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


Cl
OH
OAc
H
H

(XX)

FIG. 12.

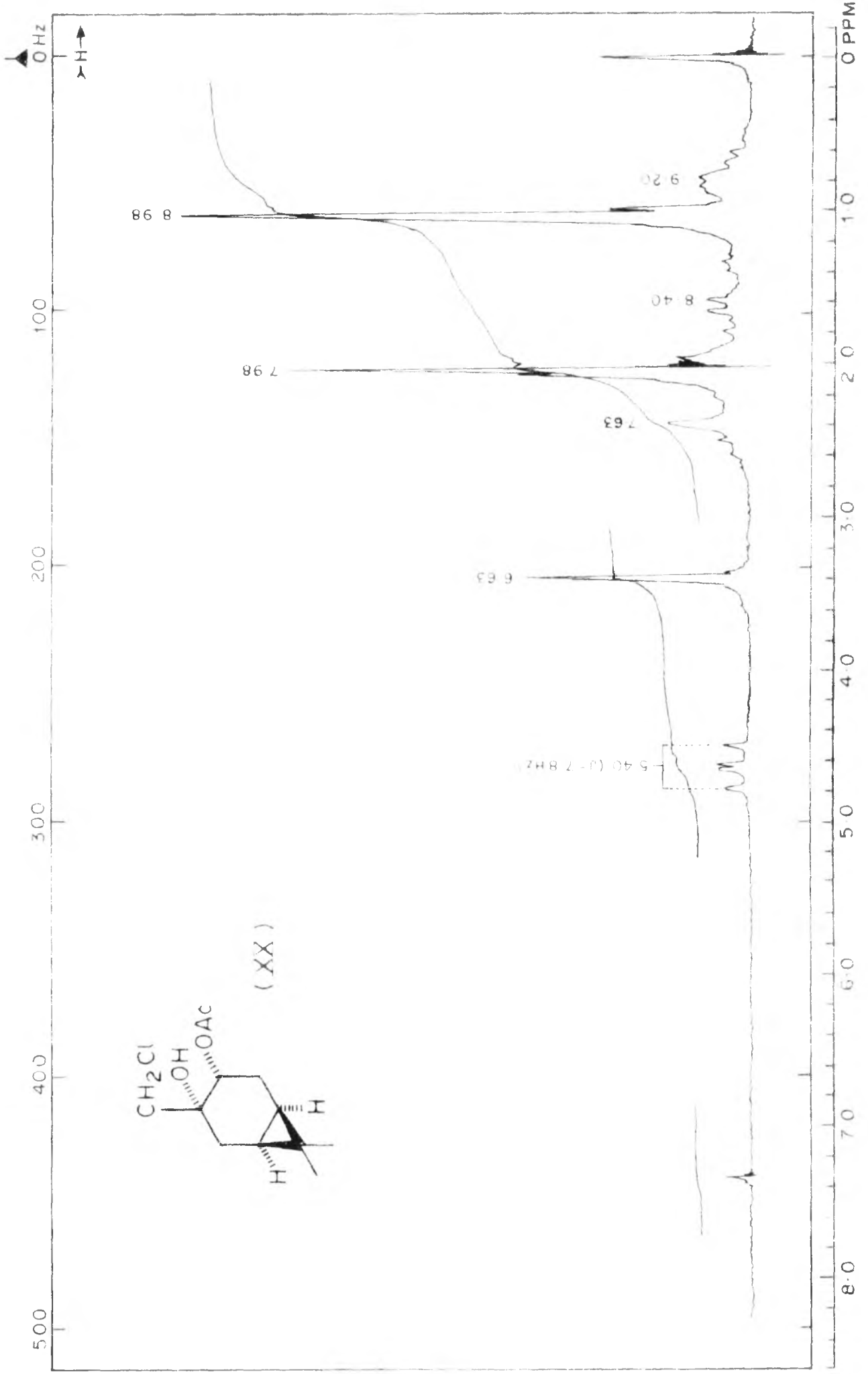

0 Hz
100
200
300
400
500
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM
9.20
8.98
8.40
7.98
7.63
6.63
5.40 (J = 7.8HZ)
(XX)
CH2Cl
OH
OAc
H
H

FIG. 13

afforded a solid diol (XXI), $C_{10}H_{17}O_2Cl$, M^+ 204 (206 due to Cl^{37}) m.p. 138° (20% pet. ether in ether). The diol (XXI) showed IR bands at 3510, 1047 (OH) and [illegible] 1_3) signals at 9.23 (2H, m, C_1 and C_6 protons); 9.07, 8.97 (3H each, s, gemdimethyl at C_7); 7.97 (4H, m, C_2 and C_5 methylene protons) and 6.4 (3H, br.s, $-CH_2Cl$ at C_3 and C_4-proton).

The signals at 6.4 in the NMR spectrum of (XXI) and (XX) indicated the presence of either $-CH_2-Cl$ or $-CH_2OH$ grouping at C_3. To find out the location of -1 in (XXI), the compound (XXI) was treated with sodium metaperiodate to undergo cleavage [indicated by comparative TLC with (XXI)]. It afforded an unstable ketoaldehyde (XXII) which was characterised by IR and NMR data as follows. It showed IR bands at 3825 (-CHO), 1724 (>C=O of ketone and aldehyde) and NMR signals at 9.1, 8.88 (8H total, br.s, gemdimethyl and two cyclopropane protons); 7.7 (4H, br.m, both the $-CH_2-C(=O)$ protons); 6.07 (2H, s, $CO-CH_2Cl$) and 0.33 (1H, s, CHO proton). However, the keto aldehyde could not be fully characterised due to its instability. Formation of keto aldehyde (XXII) from (XXI) indicated that vicinal diol grouping is present in (XXI). This is possible only when Cl is at C_{10} position as given in structure (XXI).

The more polar product $C_{13}H_{22}O_4$, m.p. 84° formed during treatment with hydrochloric acid in methanol (14), was identified as (XVI) which was also obtained from (XV) by acetylation. The identity was confirmed by superimposable IR and NMR spectra, m.p. and m.m.p. (84°) and its conversion to the methoxy diol (XV), m.p. 85°.

Action of conc. hydrochloric acid (4N) in methanol

The epoxide (I), when treated with hydrochloric acid (4N) in methanol at room temperature for 24 hrs afforded a solid which showed two spots on TLC (10% ethyl acetate in C_6H_6). They were separated by column chromatography over silicic acid. The less polar, the minor product, was identified as the chlorohydrin acetate (XX), according to superimposable IR and NMR spectra. The more polar, the major product, was characterised as (XXI) on the basis of its m.p., m.m.p. (138°) and superimposable IR and NMR spectra.

Action of zinc chloride on (XI)

With a view to find out the possibility of transannular cyclopropyl participation as was observed during dehydration of hydroxy monoacetate (VII), the epoxide (XI) was treated with anhydrous zinc chloride in benzene under reflux. However, instead of rearrangement involving cyclopropyl participation or ring contraction[3], it afforded

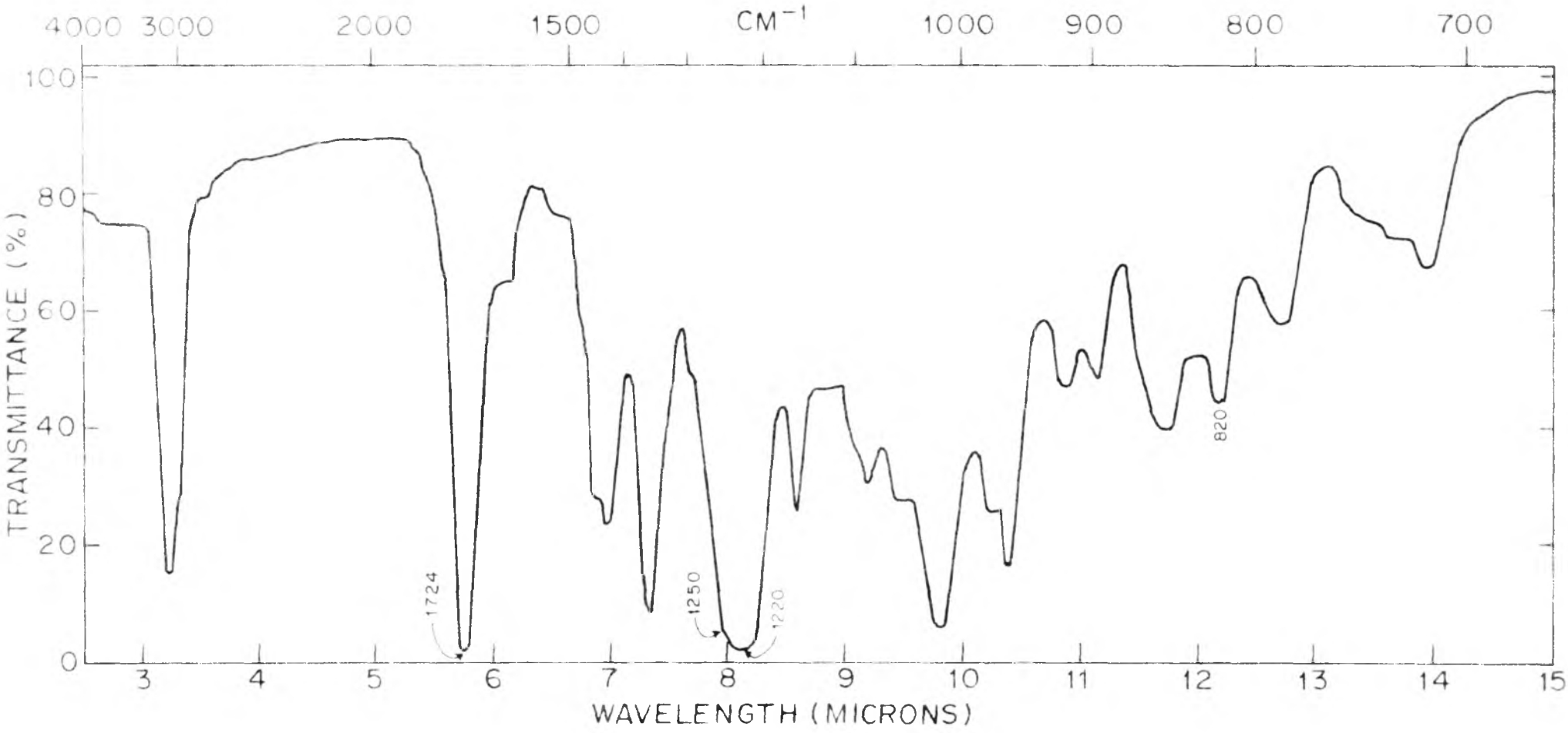
the chlorohydrin acetate (XX) as the major product which was identified by comparative TLC, superimposable IR and NMR spectra and its hydrolysis by MeOH-HCl to (XXI) m.p. and m.m.p. 138°.

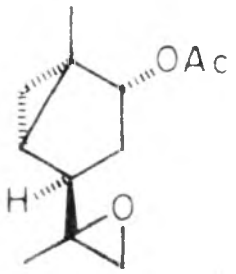
Epoxidation of (X) and action of acid on its epoxide (XXIII)

The other dehydrated product of diol monoacetate (VII) viz. compound (X), on treatment with m-chloroperbenzoic acid, gave the liquid epoxide (XXIII), $C_{12}H_{18}O_3$, M^+ 210. It showed IR (Fig.14) bands at 1724, 1250 (acetate), 1220, 820 (1,2 epoxide) and NMR (Fig.15) signals at 9.67, 9.4, 9.0 (3H total, ms, cyclopropane protons at C_5 and C_6); 8.88 (3H, s, methyl at C_1); 8.68 (3H, s, methyl at C_7); 8.00 (3H, s, acetate methyl); 7.62, 7.33 (1H each, d, J = 6 Hz, C_8 methylene protons of the epoxide); 7.5 (1H, m, C_4-proton) and 4.94 (1H, br.d, C_2 proton).

Epoxide (XXIII), on treatment with hydrochloric acid (1%) in methanol at 10° for 24 hrs, afforded a methoxy acetate alcohol as the major product which was purified by chromatography over silicic acid and assigned the structure (XXIV), $C_{13}H_{22}O_4$, M^+ 242, on the basis of the following spectral and chemical evidences.

1) The compound (XXIV) showed IR bands at 3636 (OH), 1724, 1242 (acetate) and NMR signals at 9.68, 9.30 (3H, ms, C_5 and C_6 protons); 8.87 (6H, s, methyls


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1724
1250
1220
820
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OAc
H
O

(XXIII)

FIG. 14.

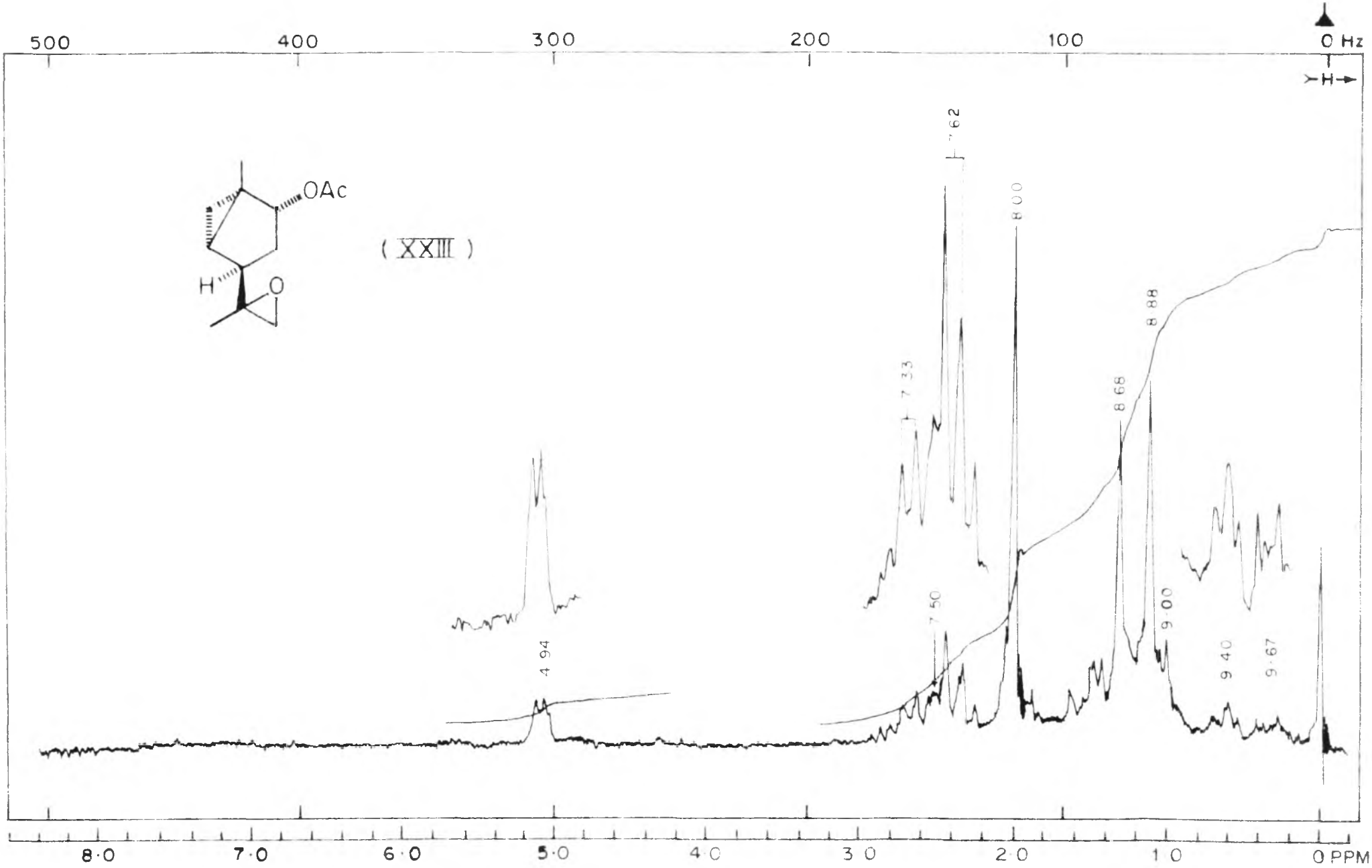

500
400
300
200
100
0 Hz
H
OAc
H
O
(XXIII)
7.62
8.00
7.33
8.68
8.88
7.50
9.00
4.94
9.40
9.67
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIG. 15

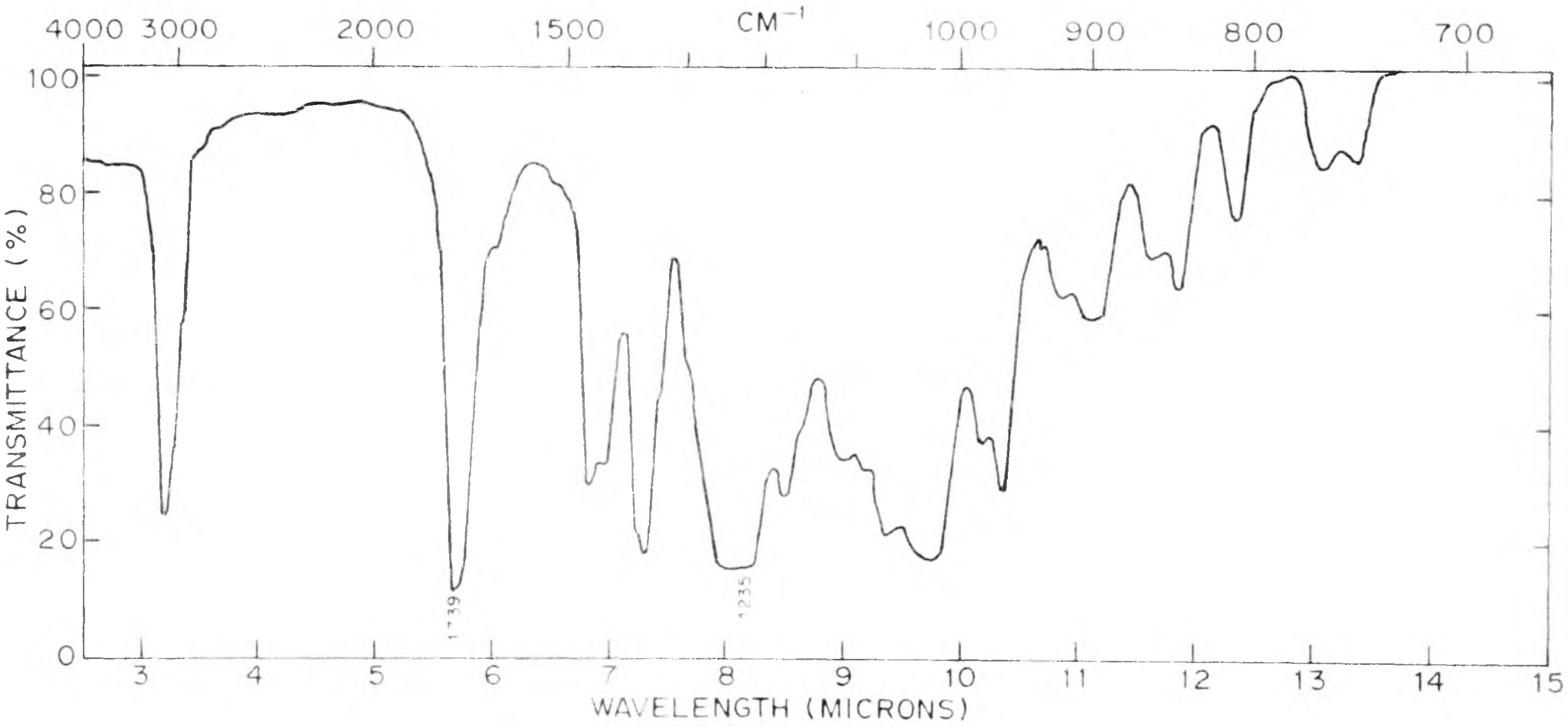
at C_1 and C_7); 8.52 (2H, br.d, methylene protons at C_3); 7.98 (3H, s, acetate methyl); 7.45 (2H, br.m, exchangeable with D_2O, OH proton and C_4-proton); 6.78 (3H, s, $-OCH_3$ at C_7); 6.58 (2H, s, methylene protons of $-CH_2-OH$ at C_7) and 4.9 (1H, br.s, C_2 proton).

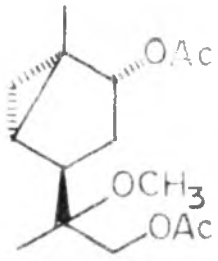
2) On acetylation (Ac_2O/Py) the compound (XXIV) gave the liquid diacetate (XXV) $C_{15}H_{24}O_5$, M^+ 284. It showed IR (Fig.16) bands at 1739, 1235 (acetate) and NMR (Fig.17) signals at 9.67, 9.37 (3H, ms, C_5 and C_6 protons); 8.9 (6H, s, methyls at C_1 and C_7); 8.5 (2H, d, J =) Hz, C_3-methylene protons); 8.0, 7.97 (6H total, s, acetate methyls); 7.43 (1H, m, C_4-proton); 6.83 (3H, s, $-OCH_3$ at C_7); 6.03 (2H, br.d, methylene protons at C_8) and 5.0 (1H, br.s, C_2-proton).

No ring opened products were formed in this rearrangement reaction and the other minor products of the transformation of epoxide (XXIII), with acid, were not investigated.

DISCUSSION

The formation of (XV) and (XVIII) from (XI) by alkali in methanol and ethanol respectively and (XX) by hydrochloric acid in methanol and zinc chloride, appears to proceed by SN_2 mechanism as shown in Scheme I. The


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
1739
1235
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


OAc
OCH3
OAc

(XXV)

FIG. 16.

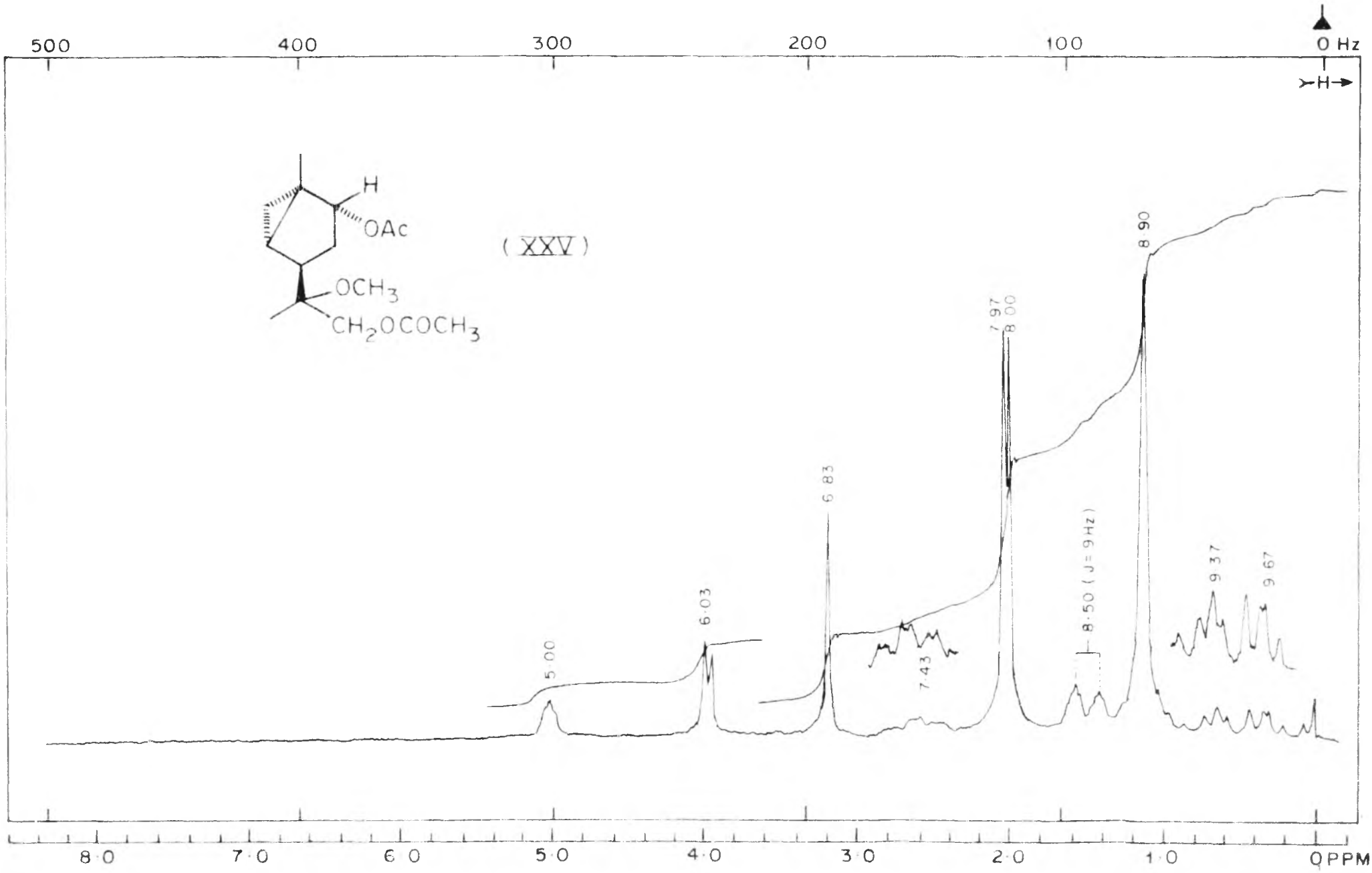
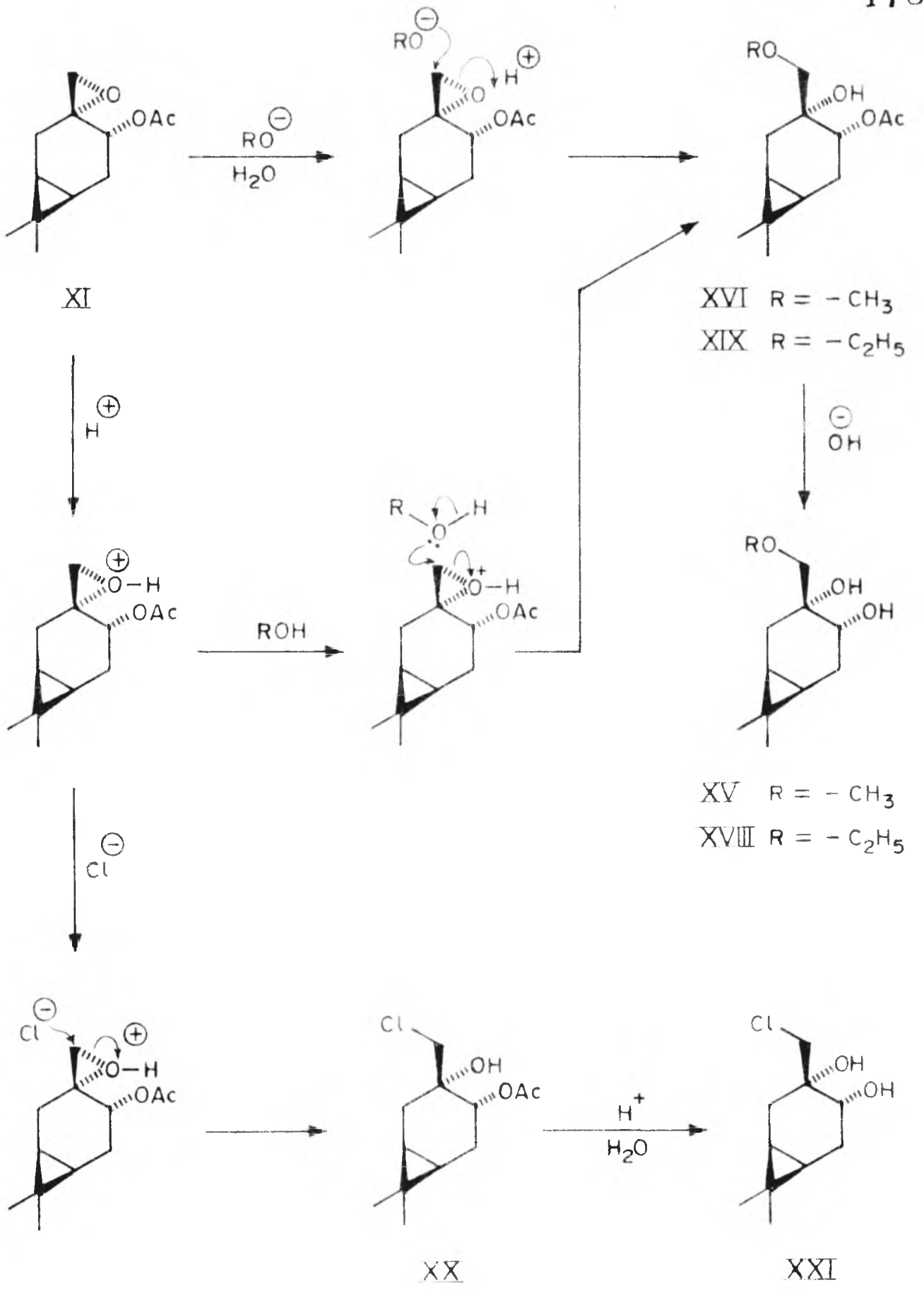

500
400
300
200
100
0 Hz
H
H
OAc
OCH3
CH2OCOCH3
(XXV)
5·00
6·03
6·83
7·43
7·97
8·00
8·50 (J = 9Hz)
8·90
9·37
9·67
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIG. 17

preferential attack by a nucleophile at C_{10} position of the epoxide (XI) can be explained on the basis of steric factors. The β-oriented methyl substituted cyclopropane system inhibits the attack of nucleophiles at C_3 as reported in literature[10], in the case of carane 3α,4α epoxide.

The acid catalysed opening of epoxide (XI) also appeared to proceed by S_N2 mechanism and not by S_N1 path as was expected. Here, most probably, the epoxide ring is protonated but not opened to form carbonium ion. The protonated epoxide ring, as shown in Scheme I, is further attacked by a nuclophile at C_{10} position which is more open for the approach.


RO
H2O
H
ROH
Cl
OH
H+
H2O
OAc
OH
O–H
XI
XVI R = –CH3
XIX R = –C2H5
XV R = –CH3
XVIII R = –C2H5
XX
XXI

SCHEME I

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

Bicyclo[4.1.0]heptan-4α-acetoxy-3β-ol-3,7,7 trimethyl (VII)

To a solution of 3β-4α caranediol (VIII, 85 g, 0.5 mole) in dry pyridine (100 ml) was added acetic anhydride (75 g, 0.75 mole). The reaction mixture was kept overnight at room temperature and then heated on a steam bath for 0.5 hr. It was cooled to room temperature and poured on ice-cooled water (500 ml) with stirring and allowed to stand at room temperature for 1 hr. It was then heated on steam bath for 0.5 hr and cooled. The diluted solution was extracted with chloroform (300 ml, 100 ml x 2) and the chloroform layer washed with water (250 ml x 3), 20% aqueous hydrochloric acid (100 ml x 2), again with water (250 ml) and finally with saturated solution of sodium carbonate and water. The organic layer was dried and evaporated to give solid monoacetate (VII), which was crystallised from pet. ether to give white crystals (77 g), m.p. 71°, $[\alpha]_D^{25}$ -13.5° (c, 1.9).

Analysis: Found: C, 67.78; H, 9.35; $C_{12}H_{20}O_3$ requires: C, 67.89; H, 9.50%.

IR bands at 3636, 2941, 1739, 1439, 1361, 1266, 1130, 1000, 971, 952 and 913 cm^{-1}.

Bicyclo[4.1.0]heptane-4α-acetoxy-7,7 dimethyl-3 methylene (IX) and bicyclo[4.1.0]hexane-2α-acetoxy-4β-isopropenyl-1-methyl (X)

In a one-litre 3-necked round bottom flask, equipped with an overhead stirrer, was placed hydroxy monoacetate (VII, 65 g) and dry pyridine (250 ml). The solution was cooled to 0° and distilled phosphorus oxychloride (60 g) was introduced, dropwise, with stirring and maintaining the temperature between 0° to 5°. After the addition, it was stirred for 2 hrs at the same temperature and kept overnight at 15°. It was then added slowly to crushed ice (300 g) with shaking and further diluted with water (250 ml). The diluted mixture was extracted with ether (500 ml, 100 ml x 4), the ether layer washed with water (300 ml x 3), 20% aqueous hydrochloric acid (200 ml x 2) followed by water and dried. Removal of ether afforded the product (51 g) which showed on TLC (10% $AgNO_3$ + SiO_2) three spots (6% ethyl acetate in C_6H_6) the two less polar compounds being in major proportion.

The mixture was separated by chromatography on silicic acid impregnated with 10% silver nitrate (1000 g) and eluted as indicated below.

Fraction	Solvent	Vol. (ml)	Quantity (g)
1	Pet. ether	2000	Nil
2	Pet.ether + benzene (3:1)	500	
3	Pet. ether "	500	7.345
4	" " "	500	
5	" " "	500	
6	Pet.ether + benzene (1:1)	500	
7	" "	500	11.815
8	"	500	
9	" "	500	
10	Benzene	250	3.217
11	Benzene	500	
12	"	500	17.337
13	"	500	1.318
14	Ethyl acetate	1500	8.523

Fractions 2 to 8 showed a single spot on TLC analysis (silicic acid with 10% silver nitrate; 6% ethyl acetate in C_6H_6) which corresponded to the least polar of the spots in the original mixture. They were mixed together and distilled to give the pure acetate (IX, 18.2 g). b.p. 110-115° (bath)/6 mm, $[\alpha]_D^{28}$ -15.3° (c, 1.48).

Analysis: Found: C, 74.56; H, 9.12; $C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%.

IR bands at 3080, 1738, 1639, 1429, 1361, 1227, 1170, 1053, 1010, 962, 882, 826, 806 and 746 cm^{-1}.

Fractions 9 and 10 showed two spots on TLC analysis. Fractions 11 and 12 showed a single spot, corresponding to the middle spot in the TLC analysis of the starting mixture. It (17.337 g) was further purified by distillation and identified as (A), b.p. 95-105° (bath)/6 mm, $[\alpha]_D^{28}$ +47.3° (c, 2.2).

Analysis: Found: C, 73.88; H, 9.12; $C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%.

IR bands at 3077, 1739, 1653, 1429, 1361, 1242, 1163, 1087, 1020, 976, 962, 885, 800 and 758 cm^{-1}.

Fractions 13 and 14 showed a complex pattern on TLC. These fractions were not investigated further.

Bicyclo[4.1.0]heptane-4α-acetoxy-7,7 dimethyl-3(10)-α-oxirane (AI) and

Bicyclo[4.1.0]heptane-4α-acetoxy-3,10-diol-7,7 dimethyl (AII)

To an ice-cooled solution of 4α acetate car-3(10)-ene (A, 15 g, 0.077 mole) in chloroform (100 ml) was added slowly a solution of 85% pure m-chloroperbenzoic acid (15.7 g, 0.091 mole) in chloroform (150 ml), with stirring and

maintaining the temperature below 5°. After the addition, the mixture was stirred for 1 hr and kept at 20°C for 24 hrs. The chloroform solution was then washed with 10% aqueous solution of sodium carbonate (150 ml, 75 ml), water (200 ml x 2) and dried. Evaporation of chloroform afforded a thick material (16.14 g) which showed on TLC (8% ethyl acetate in C_6H_6) two spots, differing much in their polarity. They were separated by chromatography on silicic acid (250 g). The less polar compound the major one, was eluted with benzene and benzene + chloroform (2:1) to give a solid (13.5 g) which was crystallised from pet. ether and characterised as the epoxide (XI), m.p. 67°, $[\alpha]_D^{28}$ -30.36° (c, 2.28).

Analysis: Found: C, 68.44; H, 8.63; $C_{12}H_{18}O_3$ requires: C, 68.54; H, 8.63%.

IR bands at 2985, 1724, 1439, 1381, 1290, 1250, 1220, 1163, 1117, 1005, 952, 930, 917, 862, 832, 816, 778 and 741 cm^{-1}.

The more polar compound which was eluted with chloroform + ethyl acetate (1:1), was obtained as a solid (1.7 g). It was crystallised from pet.ether and identified as the triol monoacetate (XIII), m.p. 99°, $[\alpha]_D^{28}$ +20.61°, (c, 1.65).

Analysis: Found: C, 63.27; H, 8.78; $C_{12}H_{20}O_4$ requires: C, 63.13; H, 8.83%.

IR bands at 3571, 3030, 1742, 1449, 1370, 1227, 1117, 1042, 966, 939, 926, 881, and 775 cm^{-1}.

Bicyclo [4.1.0]heptane-3α,4α-diol-3,7,7 trimethyl (XII)

A solution of epoxide (XI, 0.5 g) in dry ether (50 ml) was added, dropwise, to an ice-cooled and stirred solution of lithium aluminium hydride (0.8 g) in dry ether (100 ml). After the addition it was stirred for 2 hrs at 0° and kept for 48 hrs at 25°. The excess lithium aluminium hydride was decomposed by adding distilled ethanol at 0° and then with water. The ether solution of the product was washed with water (100 ml x 2) and dried. Evaporation of ether afforded a solid which was crystallised from pet. ether to afford white needles of (XII, 0.31 g), m.p. 68°, $[\alpha]_D^{28}$ +14.7° (c, 1.2).

Analysis: Found: C, 70.28; H, 10.74; $C_{10}H_{18}O_2$ requires: C, 70.54; H, 10.66%.

IR bands at 3448, 2985, 1439, 1381, 1299, 1274, 1205, 1130, 1111, 1064, 990, 962, 922, 862, 769 and 719 cm^{-1}.

Bicyclo[4.1.0]heptane-4α-acetoxy-7,7 dimethyl-3-oxo (XIV)

To a solution of triol monoacetate (XIII, 1 g) in

acetone (50 ml) and water (10 ml) was added finely powdered sodium meta periodate (1.1 g). The mixture was stirred for 1.5 hr at room temperature, filtered and the residue washed with acetone (10 ml). The combined acetone solution was diluted with water (100 ml) and extracted with ether (100 ml, 75 ml). The ether layer was washed with water (100 ml x 2) dried and evaporated to give keto acetate (XIV, 0.7 g) as a thick liquid.

Analysis: Found: C, 67.73; H, 8.52; $C_{11}H_{16}O_3$ requires: C, 67.32; H, 8.22%.

IR bands at 3030, 1710, 1754, 1724, 1600, 1439, 1362, 1227, 1031 and 714 cm^{-1}.

Bicyclo [4.1.0] heptane-3x,4x-diol-7,7 dimethyl-10 methoxy (XV)

To a solution of epoxide (XI, 2 g) in methanol (50 ml) was added 50% aqueous solution of potassium hydroxide (10 ml). The mixture was refluxed for 2 hrs, cooled, diluted with water (100 ml) and extracted with ether (100 ml , 50 ml). The ether layer was washed with water (100 ml x 2), dried and evaporated to furnish a solid (1.7 g) which was crystallised from pet. ether to give white needles of (XV), m.p. 85°, $[\alpha]_D^{28}$ +28.13° (c, 0.64).

Analysis: Found: C, 65.81; H, 10.20; $C_{11}H_{20}O_3$ requires: C, 65.97; H, 10.07%.

IR bands at 3509, 2985, 1439, 1361, 1282, 1205, 1183, 1143, 1087, 1047, 962, 917, 881, 775 and 722 cm^{-1}.

Bicyclo [4.1.0]heptane-4α-acetoxy-7,7 dimethyl-1β-methoxy-3α-ol (XVI)

A solution of diol (XV, 0.5 g) in pyridine (2 ml) was treated with acetic anhydride (2 ml) for 20 hrs at room temperature. The mixture was diluted with water (25 ml); kept at room temperature for 0.5 hr and on steam bath for 20 minutes. It was then cooled and extracted with ether (25 ml x 2). The ether layer was washed successively with water (25 ml x 2), 10% hydrochloric acid (20 ml) followed by water (25 ml x 2) and dried. Ether was flashed off to furnish a solid (0.51 g) which was crystallised from pet. ether to give white needles of (XVI), m.p. 84°.

Analysis: Found: C, 64.33; H, 9.28; $C_{13}H_{22}O_4$ requires: C, 64.44; H, 9.15%.

IR bands at 3610, 3030, 1724, 1439, 1361, 1220, 1136, 1075, 1020, 957, 935, 866, 813, 781, 752 and 738 cm^{-1}.

2,2 dimethyl-3(2-oxo-3 methoxypropyl) cyclopropane-1-acetaldehyde (XVII)

A solution of diol (XV, 0.5 g) in acetone (15 ml) and water (5 ml) was stirred with sodium metaperiodate (0.65 g) for 1.5 hr. The mixture was filtered, residue washed with acetone (5 ml) and the filtrate diluted with water (100 ml). It was then extracted with ether (50 ml, 25 ml x 2), the ether layer washed with water (100 ml x 2) and dried. Evaporation of ether furnished ketoaldehyde (XVII, 0.35 g). However, this product was found to be unstable even at room temperature. Hence spectra were recorded with the freshly prepared sample.

IR bands at 3030, 2801, 1724, 1613, 1439, 1361, 1266, 1130, 1087, 962, 917, 863 and 772 cm^{-1}.

Bicyclo[4.1.0] heptane-7,7 dimethyl-3α,4α-diol-1β-ethoxy (XVIII).

A solution of epoxide (XI, 1 g) in ethanol (35 ml) was treated with 50% aqueous sodium hydroxide (5 ml) under reflux for 1.5 hrs. It was then cooled, diluted with water (50 ml) and extracted with ether (50 ml x 2). The ether layer was washed with water (50 ml x 2), dried and evaporated to give a solid which was crystallised from pet. ether to obtain white needles of (XVIII, 0.75 g).

m.p. 79°, $[\alpha]_D^{28}$ +12.5° (c, 1.34).

Analysis: Found: C, 67.38; H, 10.16; $C_{12}H_{22}O_3$ requires: C, 67.25; H, 10.35%.

IR bands at 3571, 3030, 1439, 1361, 1282, 1227, 1205, 1111, 1036, 962, 917, 885, 870, 769 and 722 cm^{-1}.

Bicyclo[4.1.0] heptane-4α-acetoxy-7,7 dimethyl-10-ethoxy-3α-ol (XIX)

A solution of ethoxy diol (XVIII, 0.4 g) in pyridine (3 ml) was treated with acetic anhydride (2 ml) for 20 hrs at room temperature. Working up as usual afforded the acetate alcohol (XIX, 0.35 g) as thick liquid.

Analysis: Found: C, 65.91; H, 9.22; $C_{14}H_{24}O_4$ requires: C, 65.59; H, 9.44%.

IR bands at 3704, 3077, 1739, 1439, 1361, 1235, 1099, 1020, 980, 930, 905, 862 and 784 cm^{-1}.

Action of hydrochloric acid (1%) on epoxide(XI); Bicyclo[4.1.0]heptane-4α-acetoxy-10-chloro-7,7 dimethyl-3α-ol (XX) and Bicyclo[4.1.0]heptane-4α-acetoxy-7,7 dimethyl-10-methoxy 3α-ol (XVI)

To a solution of epoxide (XI, 1 g) in methanol (25 ml) was added 1% hydrochloric acid (3 ml). The

mixture was kept at 10° for 24 hrs, diluted with water (50 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water (100 ml x 2), dried and evaporated to give a mixture of two products (TLC, 6% ethyl acetate in C_6H_6). They were separated by chromatography on silicic acid (20 g). Fractions eluted with benzene and benzene + chloroform (1:1) afforded a single spot (TLC) compound (0.53 g) as a viscous liquid which was identified as the chlorohydrin acetate (XV), $[\alpha]_D^{28}$ -14.40° (c, 1.24).

Analysis: Found: C, 58.82; H, 7.3; Cl, 14.1; $C_{17}H_{19}O_3Cl$ requires: C, 58.42; H, 7.71; Cl, 14.4%.

IR bands at 3550, 3030, 1724, 1439, 1361, 1227, 1124, 1020, 980, 935, 885, 787 and 749 cm^{-1}.

The fractions eluted with chloroform afforded a solid (0.38 g) which was crystallised from pet. ether and identified as (XVI), m.p. 84°.

Analysis: Found: C, 64.32; H, 9.20; $C_{13}H_{22}O_4$ requires: C, 64.44; H, 9.15%.

IR bands at 3636, 3030, 1724, 1439, 1361, 1235, 1143, 1093, 1026, 957, 935, 905, 866, 784 and 752 cm^{-1}.

Action of hydrochloric acid (4N) on the epoxide (XI); Bicyclo[4.1.0]heptane-1β-chloro-7,7 dimethyl-3α,4α diol (XXI)

A solution of epoxide (XI, 1 g) in methanol (25 ml) was treated with 4N hydrochloric acid (3 ml) for 20 hrs at room temperature. It was then diluted with water (50 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water (100 ml x 2), dried and evaporated to give a solid (0.8 g) which showed two spots on TLC (10% ethyl acetate in C_6H_6). The product was crystallised from ether + 20% pet. ether to afford TLC pure needle shaped crystals, identified as (XXI), m.p. 138°, $[\alpha]_D^{28}$ -8.93° (c, 1.12).

Analysis: Found: C, 58.25; H, 8.50; Cl, 16.05; $C_{10}H_{17}O_2Cl$ requires: C, 58.68; H, 8.31; Cl, 17.36%.

IR bands at 3610, 3030, 1449, 1370, 1299, 1258, 1183, 1075, 1047, 962, 893, 772 and 746 cm^{-1}.

The mother liquor of (XXI) was chromatographed over silicic acid (5 g) and eluted with benzene + chloroform (1:1) to afford a thick liquid (0.178 g) which was identified as chlorohydrin acetate (XX).

The compound (XXI) could also be obtained from (XX) by treatment with 4N hydrochloric acid under the

above experimental conditions, m.p. and m.m.p. 138° (superimposable IR).

2,2 Dimethyl-3(2-oxo-3-chloropropyl) cyclopropane-1-acetaldehyde (XXII)

To a solution of chlorohyarin (XXI, 1 g) in acetone (50 ml) and water (5 ml) was added sodium metaperiodate (1.1 g). The mixture was stirred for 1.5 hrs, filtered and the residue washed with acetone (5 ml). The combined filtrate was diluted with water (100 ml) and extracted with ether (75 ml x 2). The ether layer was washed with water (100 ml x 2), dried and evaporated to give chloro-keto aldehyde (XXII, 0.7 g). Due to its sensitive nature towards heat and air, it was not purified further and spectra were recorded with the freshly prepared material. IR bands at 3077, 2825, 1724, 1600, 1449, 1370, 1274, 1205, 917 and 752 cm^{-1}.

Action of anhydrous zinc chloride on epoxide (XI)

A solution of epoxide (XI, 1 g) in dry benzene (50 ml) was refluxed with fused zinc chloride (1 g) for 1½ hrs. The benzene solution was washed with water (50 ml x 3), dried and evaporated to give a mixture of three products (TLC three spots; 8% ethyl acetate in C_6H_6). The mixture was separated by chromatography on silicic acid (20 g). The least polar, the unreacted epoxide

(XI, 0.22 g) was eluted with benzene. Elution with benzene chloroform (1:1) gave a thick liquid (0.45 g) which was identified as the chlorohydrin acetate (...) $[\alpha]_D^{28}$ -14.6° (c, 1.43).

Analysis: Found: C, 58.15; H, 7.92; Cl, 14.60; $C_{12}H_{19}O_3Cl$ requires: C, 58.42; H, 7.71; Cl, 14.4%.

IR bands at 3704, 3077, 1724, 1429, 1361, 1227, 1134, 1020, 980, 935, 885, 791 and 752 cm^{-1}.

The more polar material (complex pattern on TLC; 12% ethyl acetate in C_6H_6) eluted with chloroform and ethyl acetate was not investigated further.

Bicyclo [3.1.0]hexane-2α-acetoxy-4β(1,2 epoxy isopropyl) -1-methyl (...III)

To a solution of the unsaturated acetate (... g) in chloroform (50 ml) was added a solution of 85% pure m-chloroperbenzoic acid (3.5 g) in chloroform (50 ml) at 0°. The mixture was stirred for 1 hr and kept for 20 hrs at room temperature. The chloroform solution was washed with 10% aqueous solution of sodium carbonate (25 ml x 2), water (50 ml x 2) and dried. Evaporation of chloroform gave a liquid material (single spot) which was identified as epoxide (...III, 3.1 g) $[\alpha]_D^{28}$ +20.24° (c, 1.38).

Analysis: Found: C, 68.35; H, ...; $C_{12}H_{18}O_3$ requires: C, 68.54; H, 8.63%.

IR bands at 3080, 1724, 1429, 1361, 1250, 1220,
1163, 1081, 1015, 957, 917, 851 and 820 cm^{-1}.

Action of hydrochloric acid (1%) on the epoxide (XXIII); Bicyclo[3.1.0]hexane-2α-acetoxy-4β (1-hydroxy-2-methoxy-isopropyl)-1-methyl (XXIV)

A solution of epoxy acetate (XXIII, 2.5 g) in methanol (50 ml) was exposed to 1% hydrochloric acid (6 ml) at 10° for 24 hrs. It was then diluted with water (150 ml) and extracted with ether (75 ml, 50 ml x 2). The ether layer was washed with water (100 ml x 3), dried and evaporated to give a mixture of two products. They were separated by chromatography on silicic acid (60 g). The fractions eluted with benzene + chloroform (1:1) gave the major product (1.8 g) as a thick liquid which was identified as (XXIV).

Analysis: Found: C, 64.23; H, 9.38; $C_{13}H_{22}O_4$ requires: C, 64.44; H, 9.15%.

IR bands at 3626, 3077, 1724, 1460, 1361, 1242, 1170,
1087, 1015, 962, 922, 844 and 749 cm^{-1}.

Bicyclo[3.1.0]hexane-2α-acetoxy-4β(1-acetoxy-2-methoxy-isopropyl)-1-methyl (XXV)

A solution [illegible] alcohol (XXIV, 0.5 g)

pyridine (3 ml) was treated with acetic anhydride (2 ml) for 20 hrs at room temperature. The mixture was, then, diluted with water (25 ml), kept 1 hr at room temperature, and extracted with ether (20 ml). The ether layer was washed with water (25 ml), 10% hydrochloric acid (25 ml) followed by water and dried. Evaporation of ether afforded the diacetate (XXV, 0.48 g) as a thick liquid.

Analysis: Found: C, 62.95; H, 8.74; $C_{15}H_{24}O_5$ requires: C, 63.36; H, 8.51%.

IR bands at 3077, 1739, 1460, 1381, 1235, 1170, 1111, 1064, 1020, 962, 901, 844, 810 and 766 cm^{-1}.

REFERENCES

1 M. Kuczynski and Z. Chabudzinski, Roczniki Chem. 29, 437 (1955).

2 A. Suzuki, M. Miki and M. Itoh, Tetrahedron 23, 3631 (1967).

3 P.J. Kropp, J. Am. Chem. Soc., 88, 4926 (1966).

4 M. Kuczynski and Z. Chabudzinski, Roczniki Chem. 34, 177 (1960).

5 W. Cocker and D.H. Grayson, Tetrahedron Lett. 4451 (1969).

6 Z. Chabudzinski and M. Kuczynski, Roczniki Chem. 33, 871 (1959).

7 M. Kuczynski and A. Labza, Bull. Acad. Polon. Sci. Ser. Sci. Chim. 9, 551 (1961).

8 V.S. Joshi, N.P. Damodaran and Sukh Dev, Tetrahedron 27, 475 (1971).

9 R.L. Bettine and C. McDaniel, J. Org. Chem. 32, 2910 (1967).

10 W. Cocker and D.H. Grayson, J. Chem. Soc. Perkin Trans I, 1217 (1975).

11 K. Gollnick and G. Schade, Tetrahedron 22, 133 (1966).

12 G. Ohloff and W. Giersch, Helv. Chim. Acta 51, 1328 (1968).

13 P.J. Kropp, D.C. Neckert and T.J. Flautt, Tetrahedron 24, 1385 (1968).

14 P.P. Pai, S.S. Joshi, K.S. Gore and S.H. Kulkarni, Indian J. Chem. 18B, 549 (1979).

15 R.K. Razdan and G.R. Kendrick, J. Am. Chem. Soc., 92, 6061 (1970).

16 R.S. Prasad and Sukh Dev, Tetrahedron 32, 1437 (1976).

17 Z. Chabudzinski and D. Sedzik, Roczniki Chem. 40, 1889 (1966).

18 P.J. Kropp, U.S. Patent 3510,510, 5th May 1970. See: Chem. Abstr. 73, 15039a

19 Z.G. Isaeva, G. Sh. Bikbulatova and B.A. Arbuzov, Dokl. Akad. Nauk. SSSR, 171, 107 (1966). See: Chem.Abstr. 66, 38063 (1967).

20 B.A. Arbuzov, Z.G. Isaeva and G.Sh. Bikbulatova, Izv. Akad. Nauk. SSSR. Ser. Khim. 8, 1825 (1968); See: Chem. Abstr. 70, 29079' (1969).

21 V.V. Ratner, Z.G. Isaeva and B.A. Arbuzov, Izv. Akad. Nauk. SSSR. Ser. Khim. 12, 2766 (1969); Chem. Abstr. 72, 121711c (1970).

22 H. Kuczynski and M. Krystyna, Roczniki Chem. 43, 943 (1969).

23 N.S. Bacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry" pp.30 (1966).

24 T. Takahashi, Tetrahedron Lett. 656 (1964).

CHAPTER IV

SELENIUM DIOXIDE OXIDATION OF SAUSSUREALACTONE

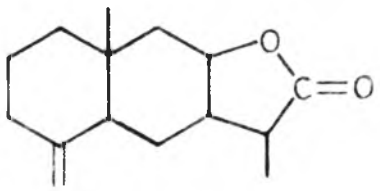
SUMMARY

Saussurea lactone (VI), on oxidation with selenium dioxide afforded a mixture of five products from which three compounds viz. (XIX), (XX) and (XXI) have been isolated and characterised. The monoaldehydo-lactone (XIX), on reduction with $NaBH_4$ afforded the hydroxy lactone (XXI) which on acetylation gave the acetate lactone (XXII). Oxidation of (XIX) with selenium dioxide gave the dialdehydo lactone (XX), thus proving that (XIX) is an intermediate in the formation of (XX) from (VI). Spectral properties of (XX) are described in detail.

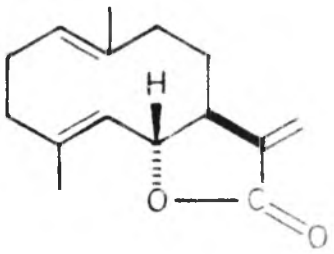
INTRODUCTION

The alcohol extract of the Costus roots (Saussurea lappa, Clarke), on vacuum distillation, has been reported[1] to give, from a fraction boiling at 180-210°/11 mm, a crystalline lactone, m.p. 147-48° (pet. ether or methanol), $C_{15}H_{22}O_2$, which was named as Saussurealactone. Rao and Varma[2] subsequently assigned the monoethenoid bicyclic structure (I) to the lactone, on the basis of its dehydrogenation data. Later A.S. Rao et al.[3] revised the earlier structure (I) and established that the lactone possesses not one but two double bonds and hence is monocyclic in nature. The IR spectrum of the lactone showed the presence of two types of double bonds viz. $R-CH=CH_2$ (909 cm^{-1}) and $R_1R_2C=CH_2$ (892 cm^{-1}). In view of this and the conversion of saussurealactone into 1-methyl-7-ethyl naphthalene, they suggested that it may have the elemane type of carbon skeleton.

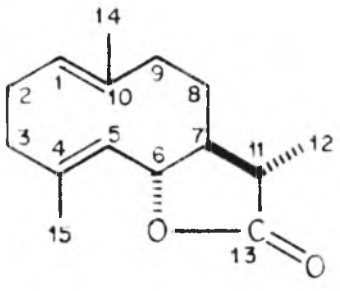
Rao and Varma obtained this lactone from costus root extract, distilled at high temperature while in connection with the work on the composition of the costus root oil[4], obtained under mild conditions, it was not possible to isolate Saussurealactone, although such oil contains substantial amount of costunolide (II) and some



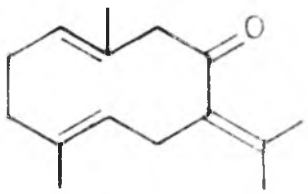
I



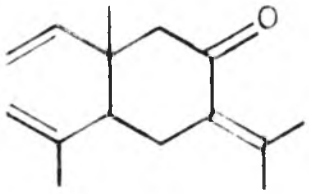
II



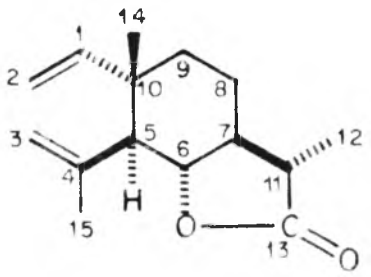
III



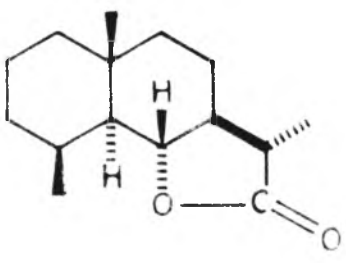
IV



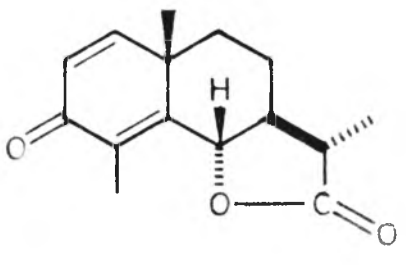
V



VI



VII



VIII

dihydrocostunolide (III). Since, on pyrolysis, germacrone (IV) is known[5,6] to give pyrogermacrone (V), possessing an elemane skeleton, it was thought that Saussurealactone also may be a similar type of thermal rearrangement product, obtained from dihydrocostunolide. This was further proved[3] by subjecting dihydrocostunolide (III) to thermal rearrangement, when saussurealactone could be obtained from the pyrolysis product. On this basis the gross structure (VI) was assigned to saussurealactone, which explained quite satisfactorily the spectral properties.

Formation of saussurealactone (VI) from dihydrocostunolide (III) whose absolute configuration at C_6, C_7 and C_{11} is known, established the stereochemistry of the lactone (VI) at these centres. The stereochemistry at C_{10} and C_5 of (VI) was determined[7] by cyclising the lactone (VI) to a bicyclic product which on catalytic hydrogenation gave Santanolide 'C' [8,9] (VII) whose stereostructure is known. Subsequently the structure and stereochemistry of saussurealactone have been unambiguously confirmed by synthesising it[10] and also its tetrahydro derivative[11] from santonin (VIII).

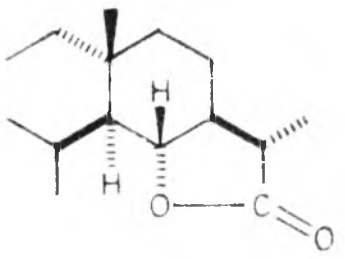
<u>Some transformations of saussurealactone and related compounds</u>.

Saussurealactone (VI) has been converted to

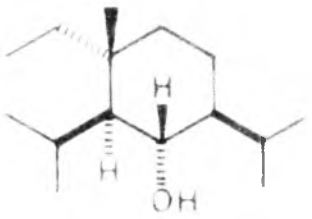
its tetrahydro derivative (IX) which on controlled LAH reduction[12] followed by Huang-Minlon reduction, afforded the alcohol (X). The alcohol (X) was also obtained by the catalytic hydrogenation of the unsaturated alcohol (XI). The alcohol (XI), prepared from costunolide[13] by a sequence of reactions, gave a ketone (XIa) viz. shyobunone which has been isolated by Japanese workers[14] from natural source Acorus calamus L. (Shyobu). Tetrahydro-saussurealactone (IX) has also been synthesised from elemol[15].

Taking advantage of the difference in the reactivity of the two double bonds in saussurealactone towards oxidation[16] reactions, its epoxidation studies have been carried out. Saussurealactone (VI), on treatment with one mole of perbenzoic acid is known to give mainly a mixture of two monoepoxides[17] (XII) and (XIII), along with minor quantity of the diepoxide. The rearrangements of these two epoxides using BF_3 and methanolic hydrochloric acid have been studied[17].

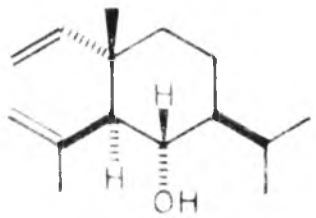
Saussurealactone, obtainable from dihydrocostunolide by thermal (Cope's) rearrangement is known to give dihydrocostunolide (III) by reversible reaction[18], demonstrating the reversibility of the Cope's reaction in the case of



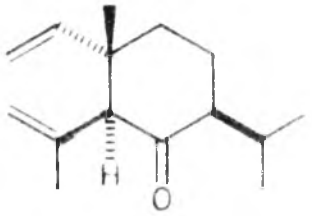
IX



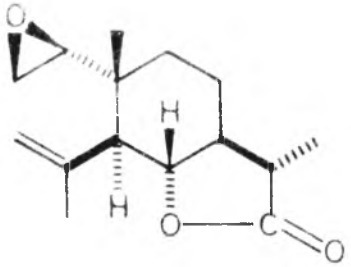
X



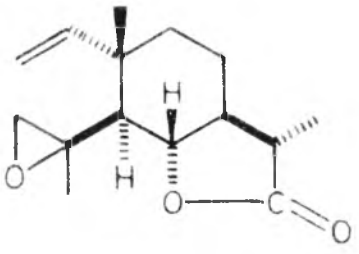
XI



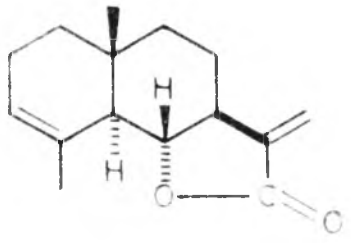
XI A



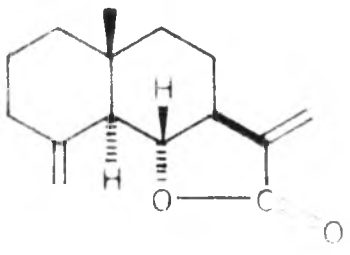
XII



XIII



XIV

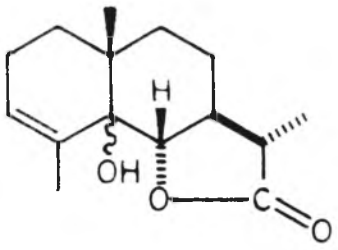


XIV A

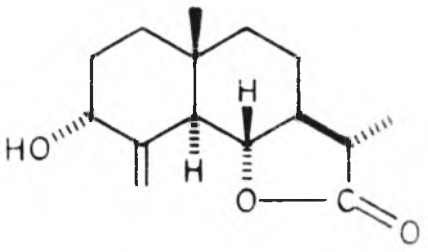
germacrenolides.

Saussurealactone (VI) possesses two double bonds of which, only the one at C_3 - C_4 has methyl and methine groups in the allylic position. The other double bond, however, does not have any such oxidisable groups in the allylic position.

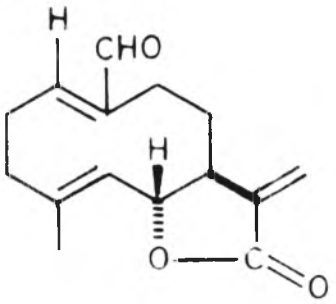
In the case of α-cyclodihydrocostunolide (XIV), selenium dioxide oxidation is reported[19] to give, as the major product, the tertiary hydroxy lactone (XV) even when a methyl and methylene are available for oxidation at the allylic positions. This behaviour is somewhat abnormal though such examples are reported[20] in the case of $\Delta^{8(14)}$ steroids, while in the case of α-cyclodihydrocostunolide[21] (XIVa) the oxidation by the same reagent is normal and affords the normal expected product (XVa). Costunolide and dihydrocostunolide are known[22,23] to undergo oxidation at the allylic positions, when subjected to selenium dioxide oxidation, to give the aldehydelactone[22] (XVI) and the hydroxylactone[22,23] (XVII) respectively, along with some isomerised products. However, santenolide[24] (XVIII) did not undergo any allylic oxidation with selenium dioxide though it possesses allylic methylene and methine groups.



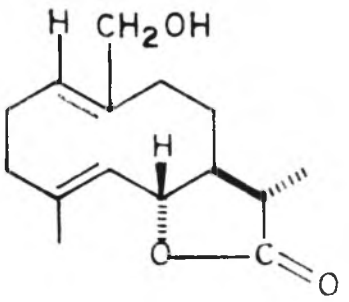
XV



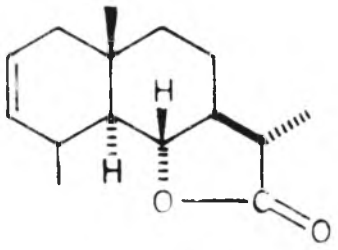
XV A



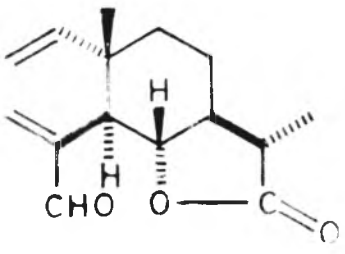
XVI



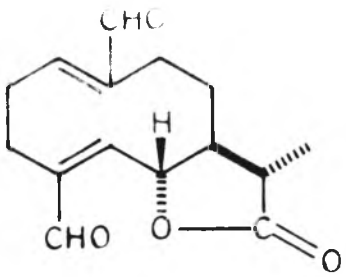
XVII



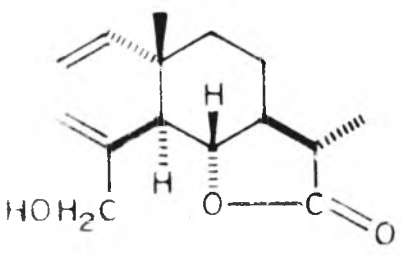
XVIII



XIX



XX



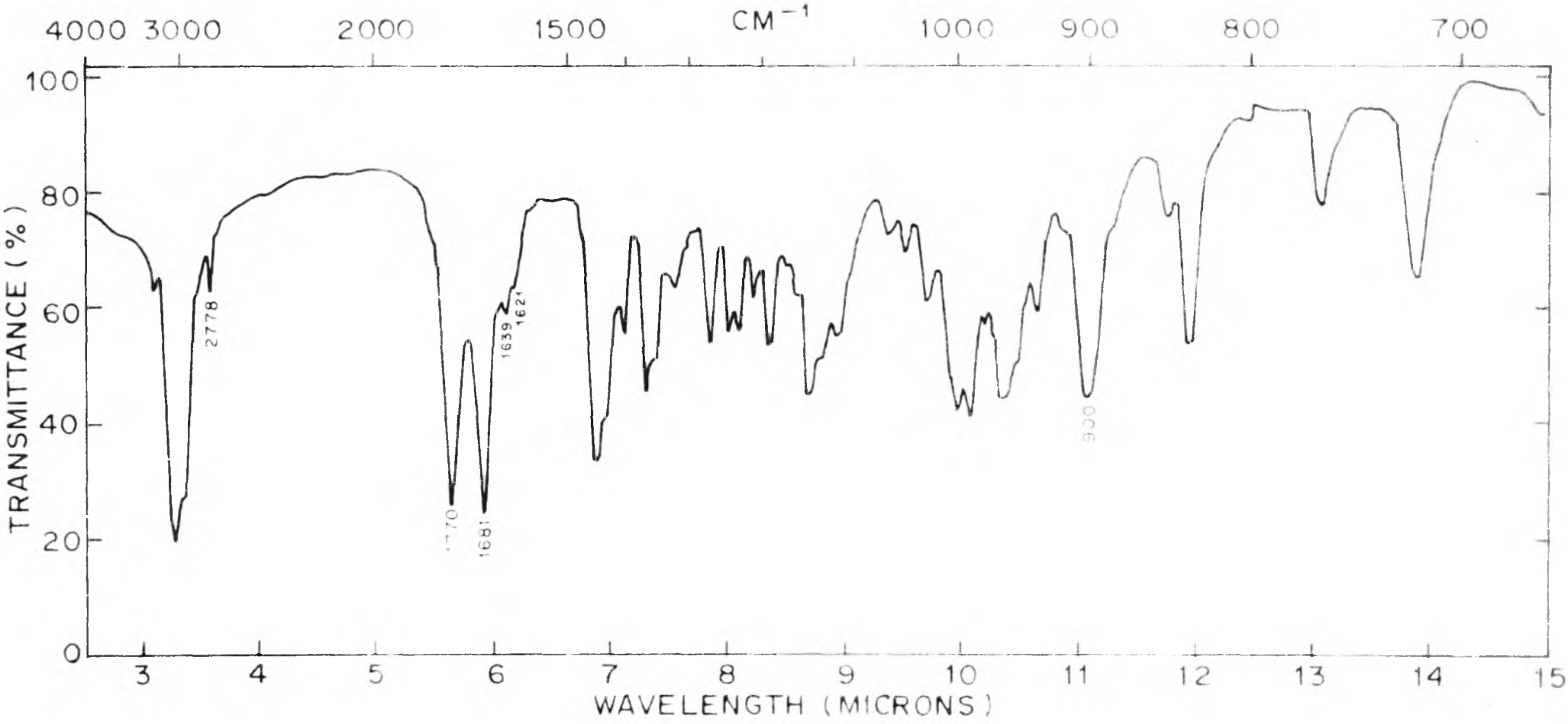
XXI

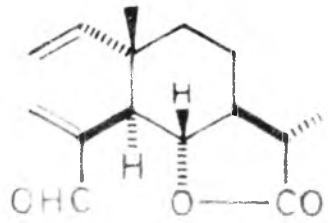
In continuation of the studies in this direction, the saussurealactone (VI) is now subjected to selenium dioxide oxidation, with a view to identify and characterise the different products formed during the reaction.

PRESENT WORK

Saussurealactone (VI), obtainable from dihydrocostunolide (III), was subjected to selenium dioxide oxidation (refluxing benzene, 20 hrs) to afford a mixture, consisting of five compounds (TLC, 30% acetone in benzene). Out of these, three compounds were isolated in pure state from the reaction mixture, by chromatography followed by crystallization.

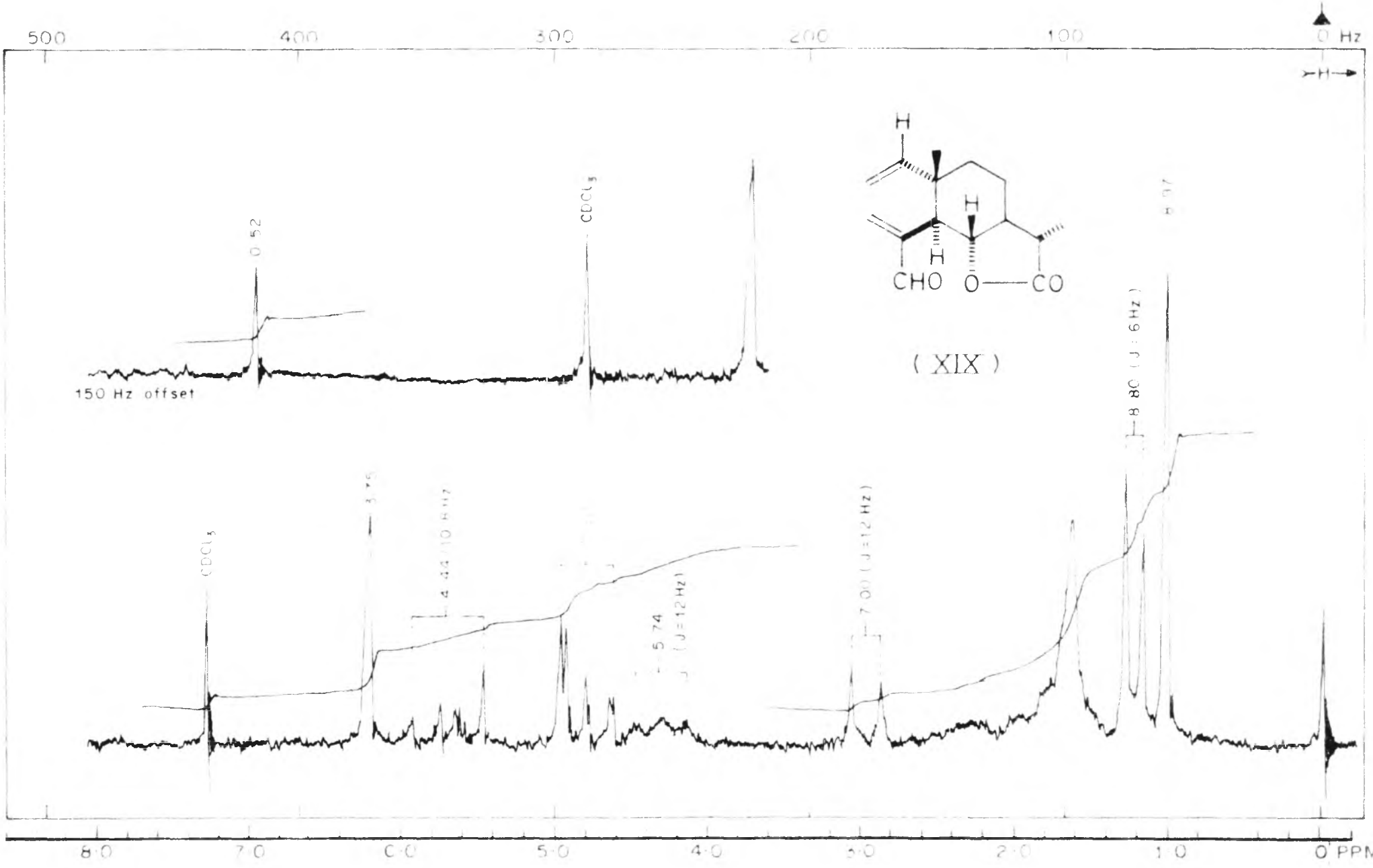
The least polar of these, the major product of the reaction (30%) was identified as the conjugated aldehydolactone (XIX), $C_{15}H_{20}O_3$, M^+ 248, m.p. 150-52° (10% pet.ether in benzene). It showed IR (Fig.1) bands at 1770 (γ-lactone), 1681, 2778 (-CHO), 1639, 1621, 900 (conjugated and non-conjugated $>C=CH_2$) and NMR ($CDCl_3$) [Fig.2] signals at 8.97 (3H, s, C_{10}-methyl); 8.8 (3H, d, J = 6 Hz, C_{11}-methyl); 7.00 (1H, d, J = 12 Hz, C_5 allylic proton); 5.74 (1H, t, J = 12 Hz, C_6 proton); 5.2 (2H, m, C_2 olefinic protons); 4.44 (1H, m, C_1 olefinic proton); 3.75 (2H, s, conjugated C_3 - olefinic protons) and 0.52 (1H, s, aldehydo proton). UV λ_{max} 218 mμ, ϵ_{max} 8000. It gave a 2:4 dinitrophenyl


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
2778
1770
1681
1639
1621
900
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


H
H
OHC
O
CO

(XIX)

FIG. 1


500
400
300
200
100
0 Hz
H
0·52
CDCl3
150 Hz offset
CDCl3
3·75
4·44 (10 H)
5·74 (J=12 Hz)
7·00 (J=12 Hz)
8·80 (J=6 Hz)
8·07
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

H
H
H
CHO
O
CO

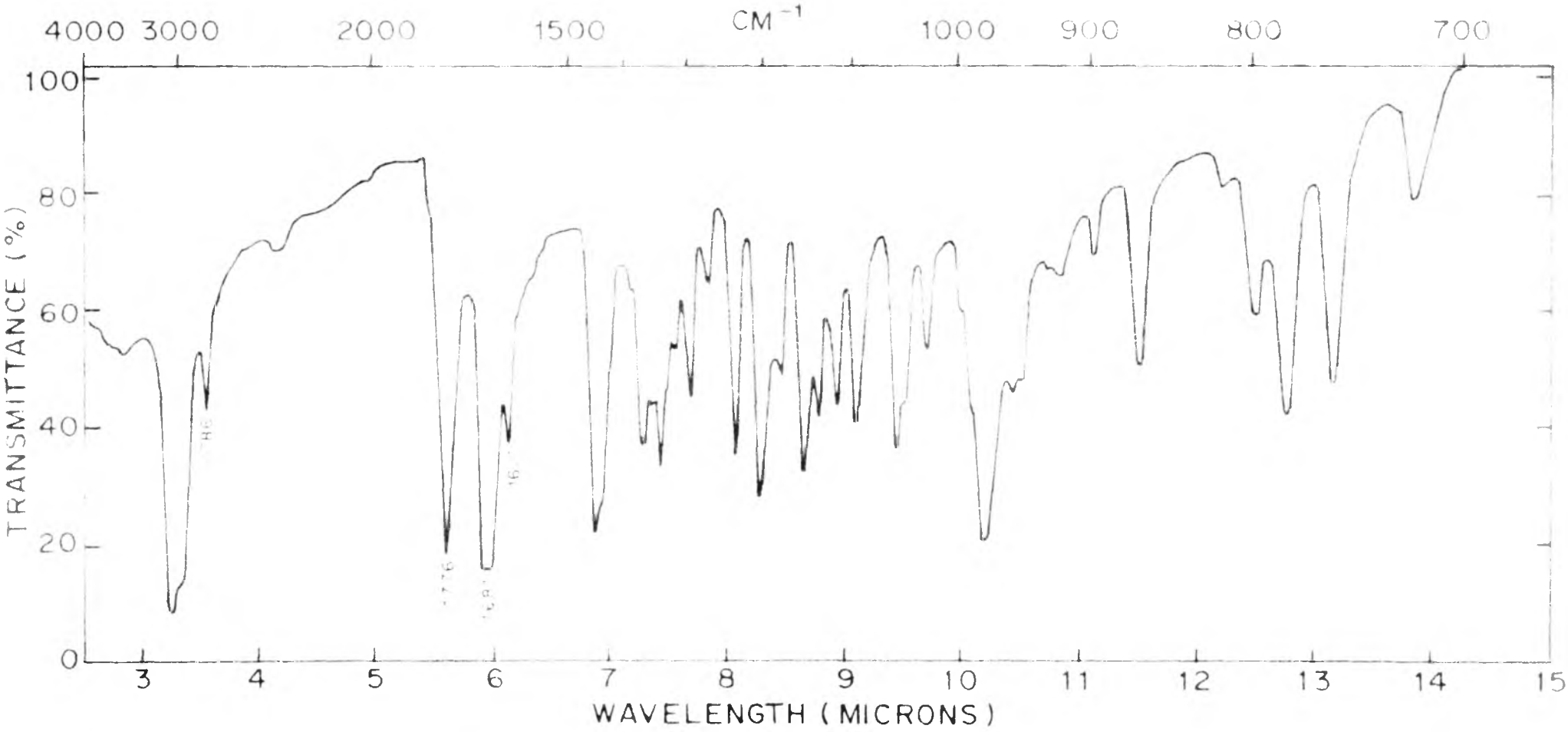
(XIX)

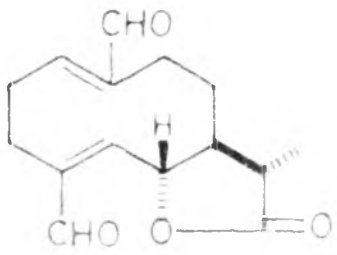
FIG 2

hydrazone $C_{21}H_{24}O_6N_4$, m.p. 190-2°C.

From the middle fractions of chromatography a crystalline solid was isolated in low yield (< 1%) and identified as the dialdehydolactone (XX), $C_{15}H_{18}O_4$, M^+ 262 m.p. 200-202° (30% pet. ether in benzene). It showed the following spectral data. IR (Fig.3) bands at 1776 (γ-lactone), 1681, 2786 (-CHO), 1621 (conjugated >C=C<); NMR ($CDCl_3$) (Fig.4) signals at 8.81 (3H, d, J = 7.2 Hz, C_{11}-methyl); 4.73 (1H, t, J = 11 Hz, C_6 proton); 3.47 (1H, t, J = 8 Hz, C_1-olefinic proton); 3.87 (1H, d, J = 10 Hz, C_5-olefinic proton) and at 0.53, -0.17 (1H each, s, aldehydoprotons). UV λ_{max} 225 mμ, ϵ_{max} 20000. The compound (XX) gave a 2:4-dinitrophenyl hydrazone derivative $C_{27}H_{26}O_{10}N_8$ m.p.207°.

From the tail fractions of chromatography of the reaction product, a low melting solid was isolated in pure state (TLC). It was identified as the hydroxylactone (XXI), $C_{15}H_{22}O_3$, m.p. 36-37°, $[\alpha]_D^{25}$ +42° (c, 1.2). It showed IR (Fig.5) bands at 3650 (OH), 1776 (γ-lactone), 1639, 892 (> $C=CH_2$) and NMR signals at 8.92 (3H, s, C_{10}-methyl); 7.4 (1H, s, exchangeable with D_2O, OH proton); 6.67 (1H, d, J = 10 Hz, C_5 allylic proton); 6.14 (2H, s, $-CH_2-O$ at C_4); 5.93 (1H, t, J = 10 Hz, C_6-proton); 5.14 (4H, m, olefinic protons at C_2 and C_3) and 4.27 (1H, m, C_1-olefinic proton).


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


CHO
H
CHO
O
O

(XX)

FIG 3

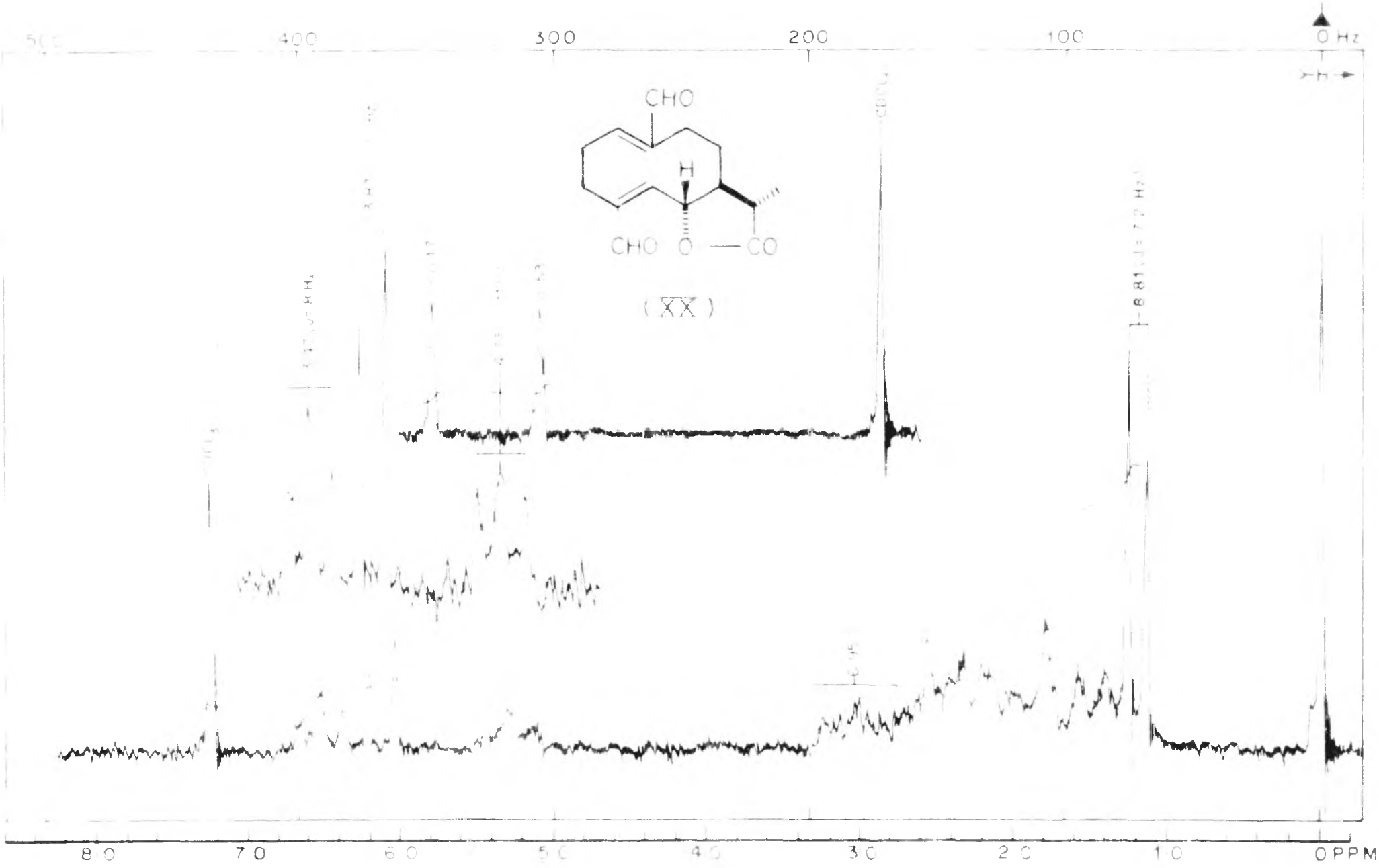

500
400
300
200
100
0 Hz
CHO
H
CHO O — CO
(XX)
8.81, J = 7.2 Hz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)

FIG 4

4000 3000 2000 1500 1000 900 800 700
CM⁻¹
WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
TRANSMITTANCE (%)
HOH2C
O
H
H

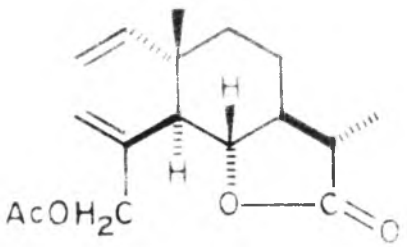
On acetylation, the lactone (XXI) afforded a liquid acetate lactone (XXII), $C_{17}H_{24}O_4$, which showed the following spectral data. IR:1770 (γ-lactone), 1739, 1235 (acetate), 1639, 895 (>C=CH_2); NMR signals at 8.92, 8.78 (3H each, s, C_{10} and C_{11} methyls); 7.97 (3H, s, acetate methyl at C_4); 6.44 (1H, d, J = 15 Hz, C_5-allylic proton); 6.00 (1H, t, J = 12 Hz, C_6 proton); 5.58 (2H, s, $-CH_2OAc$ at C_4); 5.00 (4H, m, C_2 and C_3 olefinic protons) and 4.24 (1H, m, C_1 olefinic proton).

Sodiumborohydride reduction of monoaldehydolactone (XIX) afforded the hydroxylactone (XXI) which was identified by IR, NMR, TLC and physical constants; $[\alpha]_D$ +44° (c, 2.2); $n_D^{31.5}$ 1.5034. The identity was further confirmed by converting it into acetate (XXII) and comparing the spectral properties.

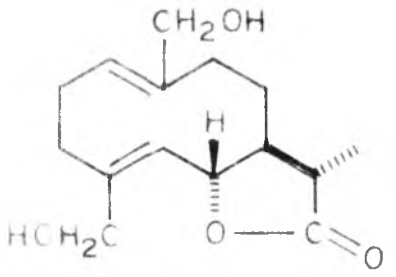
Monoaldehydolactone (XIX) when subjected to selenium dioxide oxidation in refluxing dioxan, afforded the dialdehydolactone (XX) as the major product (50%), identified by comparing its spectral and physical properties. However, when reaction was carried out in refluxing benzene, the yield of (XX) was very low.

DISCUSSION

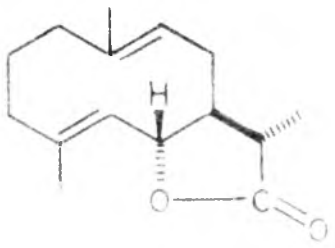
Out of the three oxidation products, the two viz. hydroxylactone (XXI) and monoaldehydolactone (XIX) are the



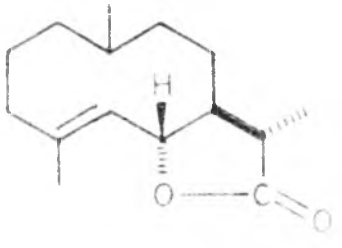
XXII



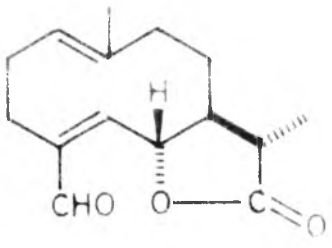
XXIII



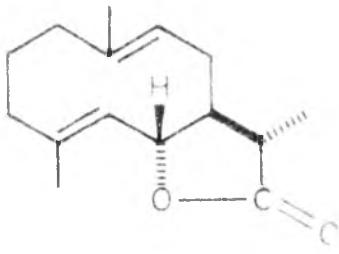
XXIV



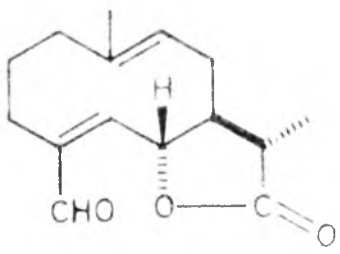
XXV



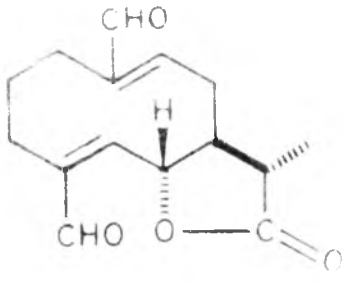
XXVI



XXVII



XXVIII



XXIX

normal expected allylic oxidation products. However, the third product, viz. the dialdehydolactone (XX) appears to be somewhat unusual and hence deserves comments.

The spectral data of (XX) indicated that it contains two aldehyde groups, probably both of which are conjugated. Dihydroxylactone (XXIII), obtained by sodiumborohydride reduction of (XX), showed in its UV spectrum only the end absorption for isolated trisubstituted double bonds (ε_{205}, 3000). This fact eliminated the possibility of any conjugation between the two double bonds.

The NMR spectrum of (XX) indicated the presence of only one secondary methyl viz. one at C_{11}. It, therefore, appears that the two methyl groups at C_4 and C_{10} of saussurea-lactone (VI) are involved in allylic oxidation and must have been converted into the aldehyde groups. This, however, is not possible for a compound like (VI) as such, without undergoing rearrangement. The appearance of the triplet for the C_6-proton in the NMR spectrum of (XX), clearly suggested that there must be one proton on each side of C_6 which is available for coupling, viz. at C_5 and C_7. The C_6 proton, in the spectra of compounds like (VI), (XIX) and (XXI) appeared as triplets at 5.9, 5.74 and 5.93 respectively and even in compounds such as (XXIV) and (XXV)[18] where the C_6 proton is allylic to the double bond at C_4-C_5,

it is observed at 5.55 and 5.52 respectively. The significant downfield shift of the C_6 proton from the normal value of 5.8 - 6.0 to 4.73, suggests that it is in a different environment and such a downfield shift is possible only when it is allylic to a conjugated double bond.

The lactones (VI) and (XIX) possess five olefinic protons, viz. at C_1, C_2 and C_3, and exhibit in their NMR spectra, quite a complex pattern in the olefinic region, whereas the dialdehydolactone (XX) possesses only two olefinic protons, one showing a triplet, and the other a well-defined doublet. The downfield chemical shift of these two olefinic protons clearly suggested that the two double bonds (isolated) must be in conjugation with aldehyde groups. This is also supported by its UV spectrum.

From these considerations it appeared that the lactone possessed the germacrane skeleton and is best represented by the structure (XX) which also satisfactorily explains the splitting pattern of C_1 and C_5 olefinic protons.

As already stated, saussurealactone (VI) is known[16] to give dihydrocostunolide (III), indicating that the conversion of (VI) to (III) is a reversible reaction. In a similar way, the lactone (XIX), formed initially in the

reaction is capable of undergoing, the reversible Cope's rearrangement to give the germacranolide (XXVI), which on further allylic oxidation gives (XX). It appears from the very low yield of (XX), that such a conversion may be proceeding at a slow rate in refluxing benzene. Formation of (XX) from (XIX) by selenium dioxide oxidation in refluxing dioxan (50% yield) proved that (XIX) is an intermediate in the formation of (XX) from (VI).

It has been reported[23] that germacrenolide such as (III), when treated with selenium dioxide in benzene at room temperature, undergo double bond migration, the C_1-C_{10} double bond shifting to C_9-C_{10} position to give the rearranged lactone (XXVII). In the light of this observation the possibility of the intermediate lactone (XXVI) undergoing such a migration to (XXVIII) cannot be ruled out. In such a case the dialdehydolactone would be (XXIX).

The spectral data reported for (XX) can also be satisfactorily explained by the alternative structure (XXIX). The possibility of structure (XXIX) for dialdehydolactone, therefore, cannot be ruled out completely.

However, it appears from the recent work[22], that the isomerization of (III) to (XXVII) is not due to the migration of the double bond at C_1-C_{10} to C_9-C_{10} as reported, but is due to the change in the geometry of the double bond at C_1-C_{10}

from <u>trans</u> to <u>cis</u>. Taking into consideration these facts the dialdehydolactone probably possesses the structure (XX) rather than the other alternative structure (XXIA).

EXPERIMENTAL

Oxidation of saussurealactone by selenium dioxide

To a solution of saussurealactone[(VI , 2.0 g] in dry benzene (50 ml) was added selenium dioxide (2.0 g) and the mixture refluxed on waterbath for 20 hrs, when most of the lactone(VI)reacted, as detected by TLC (30% acetone in benzene). Activated animal charcoal (2.0 g) was added to the reaction mixture and refluxed for additional 20 minutues. It was then filtered, the residue washed with benzene and the solvent removed from the combined filtrate to furnish the crude oxidation product (2.87 g) (TLC, 30% acetone in benzene), 5 spots). The crude product was chromatographed on silicic acid (55 g, 1:20 ratio) and eluted as follows:

CHROMATOGRAM 1

Fraction	Solvent	Vol. in ml	Material in g.
1	Benzene	200	Nil
2	15% $CHCl_3$ in benzene	300	0.04
3	30% " " "	300	0.025
4	40% " " "	200	0.270
5	50% " " "	200	0.473
6	60% " " "	300	0.337
7	$CHCl_3$	150	0.628
8	Acetone	150	

Fractions 2 and 3 of Chromatogram 1 showed the presence of starting compound, viz. saussurealactone (VI).

Fraction 4 afforded a solid in the nearly pure state (TLC), which on crystallization gave a solid in pure state (0.195 g), m.p. 151-52° (10% pet. ether in benzene), M^+ 248, $[\alpha]_D^{25}$ +40° (c, 0.5). It was identified as the aldehydolactone (XIX) from spectral data and chemical reactions. UV: λ_{max} 218 mμ, ϵ_{max} 8000.

Analysis: Found: C, 72.32; H, 8.18; $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%.

IR bands at 3030, 2778, 1770, 1681, 1639, 1621, 1449, 1361, 1266, 1242, 1190, 1149, 990, 962, 900, 837, 786 and 719 cm^{-1}.

It gave a 2:4 DNP derivative $C_{21}H_{24}O_6N_4$, m.p. 190-2°.

Analysis: Found: C, 58.72; H, 5.71; N, 12.82; $C_{21}H_{24}O_6N_4$ requires: C, 58.87; H, 5.65; N, 13.08%.

Fraction 5 also afforded the solid which was crystallised from 10% pet. ether in benzene to give 0.110 g of pure material (TLC), m.p. 151-52°, identified as the aldehydolactone (XIX).

The mother liquors of fractions 4 and 5 of Chromatogram 1 showed identical TLC pattern and showed the presence of (XIX) as a minor compound. Hence the mother liquors

were mixed together and the solvent evaporated to furnish 0.430 g of a mixture. This mixture was re-chromatographed on silicic acid (14 g) and eluted as follows:

CHROMATOGRAM 2

Fraction	Solvent	Vol. in ml	Material in g.
1	C_6H_6	100	Nil
2	3% acetone in C_6H_6	50	0.085
3	3% acetone in C_6H_6	50	0.016
4	5% " "	50	0.060
5	5% " " "	100	0.078
6	50% acetone in C_6H_6	150	0.180

Fraction 2 of Chromatogram 2, on evaporation, afforded the solid which, on crystallization, gave TLC pure solid (0.055 g) m.p. 152°, identified as the aldehydolactone(XIX).

Fractions 4 and 5 were identical according to TLC and showed the presence of two compounds, the less polar of the two being in minor quantity. The combined fractions 4 and 5 of Chromatogram 2 gave a solid which was crystallized from 30% pet. ether in benzene to afford needle shaped crystals (0.065 g), m.p. 200-2°, M^+ 262. It was identified as dialdehydolactone (XX) by spectral

properties; UV: λ_{max} 225 mμ, ϵ_{max} 20,000.

Analysis: Found: C, 68.93; H, 6.85; $C_{15}H_{18}O_4$ requires: C, 68.68; H, 6.92%.

IR bands at 3030, 2786, 1776, 1681, 1621, 1449, 1351, 1342, 1299, 1235, 1205, 1156, 1099, 1058, 976, 870, 800, 781 and 760 cm^{-1}.

It gave a 2:4 DNP derivative, $C_{27}H_{26}O_{10}N_8$, m.p. 207°.

Analysis: Found: C, 51.86; H, 4.25; N, 17.94; $C_{27}H_{26}O_{10}N_8$ requires: C, 52.08; H, 4.18; N, 18.01%.

Isolation of hydroxylactone (XXI)

Fraction 6 of Chromatogram 1 (0.337 g) showed the presence of two compounds on TLC (30% acetone in benzene). They were separated by chromatography on silicic acid (11 g). The less polar of the two compounds, present in small amount, was eluted with 40% $CHCl_3$ in C_6H_6, while the more polar, the major one, was eluted with 60% $CHCl_3$ in C_6H_6 to afford 0.260 g of the pure (TLC, single spot) compound which was identified and characterized as the hydroxy lactone (XXI) m.p. 36-37°, $[\alpha]_D^{25}$ +42° (c, 1.2), $n_D^{31.5}$, 1.5034.

Analysis: Found: C, 72.28; H, 8.65; $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%.

IR bands at 3650, 3077, 1776, 1639, 1481, 1449, 1370, 1250, 1183, 1111, 995, 892, 844 and 719 cm^{-1}.

The compound (XXI) on acetylation (Ac_2O/Py) at room temperature for 20 hrs, gave the liquid acetate-lactone (XXII).

Analysis: Found: C, 70.12; H, 8.15; $C_{17}H_{24}O_4$ requires: C, 69.83; H, 8.27%.

IR bands at 3030, 1770, 1739, 1639, 1439, 1361, 1235, 1105, 995, 895, 837 and 775 cm^{-1}.

The other more polar products of Chromatogram 1 viz. fractions 7 and 8 were not investigated.

Preparation of hydroxylactone (XXI) from aldehydo-lactone (XIX)

To a solution of aldehydolactone (XIX, 0.150 g) in methanol (15 ml) was added sodiumborohydride (0.040 g) and the reaction mixture was kept overnight. It was, then, diluted with water (50 ml) and extracted with chloroform (20 ml x 3). The chloroform extract was washed with water (30 ml x 2), dried and evaporated to furnish a mixture of two products (0.145 g). It was separated by chromatography on silicic acid (5 g). Fractions eluted with 60% chloroform in benzene afforded the TLC pure hydroxylactone (XXI, 0.112 g), m.p. 36-37°, $[\alpha]_D^{25}$ +44° (c, 2.2), $n_D^{31.5}$, 1.5037.

Analysis: Found: C, 71.70; H, 8.98; $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%.

IR bands at 3650, 3030, 1773, 1639, 1449, 1370, 1250, 1190, 1111, 990, 820, 844 and 719 cm^{-1}.

This compound, on acetylation (Ac_2O/Py) gave acetatelactone which was found to be identical with (XXII) according to its IR and NMR spectra.

Preparation of dialdehydolactone (XX) from monoaldehydolactone (XIX)

To a solution of monoaldehydolactone (XIX, 0.048 g) in dioxan (10 ml) was added selenium dioxide (0.1 g) and the mixture refluxed for 8 hrs, when most of (XIX) reacted as detected by TLC. Most of the dioxan was removed under suction, the reaction product diluted with water (30 ml) and extracted with ether (25 ml x 3). The ether layer was washed with water (50 ml x 3), dried and evaporated to furnish a mixture of dialdehydolactone (XX) and more polar product (TLC). The mixture was chromatographed using silicic acid (1.5 g). The fraction eluted with 5% acetone in benzene afforded the solid which, on crystallization from 30% pet. ether in benzene, gave pure dialdehydolactone (XX) (0.018 g), identified by its m.p., m.m.p. 200-2° (superimposable IR and NMR spectra).

REFERENCES

1 P.S. Rao and B.S. Verma, J. sci. and industr. Res., 10B, 166 (1951).

2 P.S. Rao, B.S. Verma, N.K. Ghosh and P.C. Dutta, J. sci. and industr. Res. 17B, 228 (1958).

3 A.S. Rao, A. Paul, Sadgopal and S.C. Bhattacharyya, Tetrahedron 12, 319 (1961).

4 A. Paul, A.V. Bawdekar, R.S. Joshi, J.H. Kulkarni, A.S. Rao, G.R. Kelkar and S.C. Bhattacharyya, Perfum. and Ess. Oil Record 51, 115 (1960); see also: Ibid. 52, 20 (1961); Ibid. 52, 773 (1961); Ibid. 54, 303 (1963).

5 I. Ognjanov, V. Herout, A. Horak and F. Sorm, Coll. Czech. Chem. Comm. 24, 2371 (1959).

6 G. Ohloff, W. Farnow, W. Phillip and G.L. Schade, Ann. 625, 206 (1959).

7 M. Wicki, J. Kalvoda and O. Jegar, Croatica Chem. Acta, 29, 263 (1957); Chem. Abstr. 53, 16197e (1959).

8 A.S. Rao, G.R. Kelkar and S. C. Bhattacharyya, Tetrahedron 9, 275 (1960); Chem. and Ind. 1359 (1958); Chem. and Ind. 1069 (1959).

9 V. Herout and F. Sorm, Chem. and Ind. 1067 (1959).

10 V.K. Honwad, E. Biscovic and A.S. Rao, Tetrahedron, 23, 1273 (1967).

11 D.M. Simonovic, A.S. Rao and S.C. Bhattacharyya, Tetrahedron 19, 1061 (1963).

12 S.M. Shaligram, A.S. Rao and S.C. Bhattacharyya, Tetrahedron 18, 969 (1963) and references cited therein.

13 J.H. Kulkarni, G.R. Kelkar and S.C. Bhattacharyya, Tetrahedron 20, 1301 (1964).

14 M. Iguchi, A. Nishiyama, I. Koyama, S. Yamamura and Y. Hitara, Tetrahedron Lett. 5315 (1968).

15 A.D. Wagh, S.K. Paknikar and S.C. Bhattacharyya, Tetrahedron 20, 2647 (1964).

16 (Miss) R.M. Sathe, G.H. Kulkarni and G.R. Kelkar, Ind. J. Chem. 9, 101 (1971).

17 M.S. Bankar and G.H. Kulkarni, Ind. J. Chem. 13, 744 (1975).

18 T.C. Jain, C.M. Banks and J.B. McCloskey, Tetrahedron Lett. 841 (1970).

19 S.P. Pathak and G.H. Kulkarni, Chem. and Ind. 913 (1968).

20 L.F. Fieser and J. Ourisson, J. Am.Chem. Soc. 75, 4404 (1953).

21 S.P. Pathak and G.H. Kulkarni, Chem. and Ind. 1566 (1968).

22 S. Krishnan, S.K. Paknikar, S.C.Bhattacharyya, A.L.Hall and W. Herz, J. Indian Chem. Soc. 55, 1142 (1978).

23 B.V. Bapat and G.H. Kulkarni, Ind. J. Chem. 9, 808 (1971).

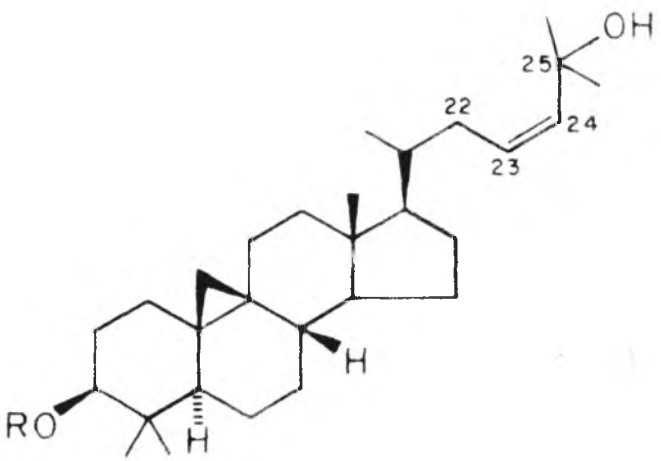
24 G.H. Kulkarni, Chem. and Ind. 1498 (1970).

CHAPTER V

ISOLATION AND CHARACTERISATION OF SOME CONSTITUENTS OF *ARTEMISIA BREVIFOLIA*, WALL

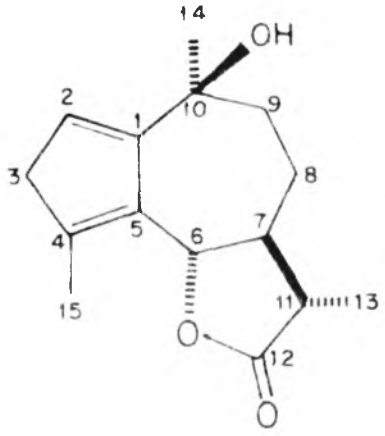
SUMMARY

Artemisia maritima L. (also known as *Artemisia brevifolia*, Wall.) is a member of Compositae family. This species of Kashmir origin (India) was extracted with pet. ether and the polar fractions of the extract examined for its constituents. Separation of the constituents was achieved by column chromatography using alumina/silicic acid. Three compounds in pure form were isolated and identified as artabsin (III), cycloart-23-ene 3β-25 diol (I) and β-sitosterol.



I R = H

II R = Ac



ARTABSIN

III

INTRODUCTION

The spectacular advances in the field of the chemistry of natural products (due to the recent introduction of new and powerful chemical, physical and analytical methods), marked by isolation from plants, of a number of natural products and their structure elucidation, has inspired organic chemist to study the interesting relationships between plants constituents and plants classification i.e. Chemotaxonomy.

Plant chemotaxonomy[1], also known as chemosystematic comparative phytochemistry, is the hybrid discipline between organic chemistry and plant systematics and constitutes one of the most rapidly developing fields in phytochemistry. Chemotaxonomy is basically concerned with the chemical survey of restricted groups of plants, mainly, for secondary constituents (alkaloids, terpenoids, steroids etc.) and the application of the data, so obtained, to plant classification.

A systematic chemical examination of the constituents of the different genera of the family and also of related families, may establish a relationship between the botanical plant classification and plant constituents. Botanical classification is normally based on morphology whereas the plant constituents are dependent on physiology with which

biosynthesis is concerned.

In chemotaxonomy[2], patterns of compounds preferably covering a range of biosynthetic origins, are much more useful than solitary compounds.

There are many organic compounds which are involved in the fundamental metabolic process and hence occur in almost all plants, for example, sugars, fatty acids, amino acids etc. They do not have any taxonomical value. Taxonomically most valuable substances are those which do not play a primary role in the metabolic process. Such substances, the relatively stable by-products, are produced due to their biological environment. They are often referred to as "secondary constituents" and may be found in any part of the plant.

Thus taxonomically related plants should often contain identical or atleast closely related compounds. But it cannot be, by any means, become a general rule because the presence or absence of a particular compound in a certain species depends on the effect of soil and climatic conditions. However, while comparing the constituents of different genera of a given family, some compounds may be missing but the ones which are present, may help in providing a link between them.

The large and taxonomically difficult genus Artemisia (Compositae, tribe Anthemideae) consists of nearly 300 species[3] and found, predominantly in the northern temperate region of the world[4].

The first rational and natural arrangement of the genus was given by Besser[5] who divided the species into four sections viz. Abrotanum, Absinthium, Dracunculus and Seriphidium, on the basis of floral morphology.

Chemical investigations of Artemisia were motivated in the early years, primarily due to the use of Artemisia absinthium as a bitter tonic and also the presence of the medicinally important compound, santonin, in a number of species. In recent years, the investigations are due to the interest in a large group of sesquiterpenoid compounds, most of them lactones that are widely distributed in the Compositae and are found only in this plant family, with one or two exceptions[6,7].

Although many species of Artemisia have been examined with respect to their sesquiterpenoid lactone constituents, about half of these were studied, primarily as sources of santonin.

One of the most interesting and potentially fruitful aspect of the chemistry of this genus is due to the indication, that there may exist relationship between

chemical constitution and sub-genus classification, which is, however, based on the scanty information available. Santonin is found only in a limited number of the members of the section Seriphidium and not in all species of this section. The section, Dracunculus has been found to contain coumarins. Although naphthalenoid sesquiterpenes are typical of the section Seriphidium, several examples of this structural type are found in members of the section Abrotanum. Guaianolides are found in both Seriphidium and Abrotanum species as well as in the Absinthium subgenus.

The question, naturally, arises in view of the few but striking regularities of this kind, whether chemical criteria, based upon the nature of the sesquiterpenoid constituents, might be of taxonomic value and useful in disclosing phytogenetic relationship.

As a part of the study of the terpenoid constituents of plants belonging to the Compositae family, an examination of Artemisia brevifolia, Wall; sub-genus Absinthium was undertaken. Artemisia brevifolia is widely distributed in Himalayas. The specimen used for this study was obtained from Kashmir* (India).

---

* M/s P.J. Jamwal and Sons, Merchants and Govt. Contractors, Kacchi Chowni, Jammu 180 001 (J and K State), India.

PREVIOUS WORK

It appears from the literature that the earlier workers have focussed their attention in studying the species with a view to isolate santonin. Thus, Greenish, for the first time isolated santonin from Indian variety of Artemisia brevifolia[8]. Later on many workers have isolated santonin from this species[9-14]. Smith[15] isolated l-isomer of camphor from it. A group of Japanese workers[16] obtained lumisantonin from Japanese variety of A. maritima. Bal and Prasad[17] have reported that A. maritima is useful as a drug also. Aichner[18] extracted a bitter principle, which is useful as an appetite stimulating compound, from this species. Recently[19], Banthorpe et al. have isolated monoterpenes from A. maritima of England origin.

However, the first systematic study on the constitution of A. maritima was done by Borsutzki[20]. He isolated and identified, apart from santonin, the fatty acids like steric, palmitic, cerotic; lactones like β-santonin, pseudosantonin, α-hydroxy santonin and desmotroposantonin and quercetin.

PRESENT WORK

Except the above compounds in A. maritima (brevifolia), no other lactones or steroidal compounds have been reported This Chapter describes our efforts towards the isolation and identification of the polar constituents from the hexane

extract of *A. maritima*.

The dried leaves, flowers and small stems were ground to a powder and extracted with pet. ether at room temperature. The pet. ether extract showed on TLC analysis, a complex mixture of compounds, with wide range of polarity. It was therefore separated broadly into seven cuts of which only the polar fractions were investigated for isolation of constituents.

1) Pet. ether cut

This cut was found to contain a mixture of long chain hydrocarbons and was not investigated further.

2) Pet. ether + benzene (3:1), (3) Pet. ether + benzene (1:1), (4) benzene and (5) benzene + chloroform (3:2) cuts were found to contain a complex mixture of various esters and alcohols, and were not studied further.

6) Chloroform cut:

This cut afforded a solid which was separated and purified by crystallisation from acetone to give a solid (TLC pure), m.p. 73°, M^+ 364. It showed IR band at 3509 (OH) and NMR signal at 8.75 (s, methylene protons). Acetylation (Ac_2O/Py) afforded a monoacetate, m.p. 52° (pet. ether), M^+ 406, IR: 1754, 1227 (acetate). This data suggested that the compound is long chain alcohol. Jones chromic acid oxidation of the alcohol gave an acid, m.p. 68-70° (pet.ether).

However, this alcohol was not fully characterised.

7) Ethyl acetate cut:

This cut showed, on TLC analysis (30% ethyl acetate in benzene)mainly four compounds. It was systematically chromatographed on silicic acid (1:25) and then pooled into seven fractions out of which the following fractions were studied in detail.

Fraction 4: This fraction which was eluted with 5% ethyl acetate in benzene, afforded a solid from its pet. ether solution. It was separated and purified by repeated crystallisation from pet. ether. The purified compound was identified as ε-sitosterol, $C_{29}H_{50}O$, m.p. 144°, $[\alpha]_D^{28}$ -41° (c, 1.24), M^+ 414 (lit. $[\alpha]_D$ -38.7°, m.p. 143-4°). It showed IR band at 3571 (OH), 830, 794 (-CH=C<) and major NMR signals at 9.3, 9.22, 9.08, 8.98, 8.82 all singlets (methyls) and multiplet centered at 4.87 for olefinic protons.

This assignment was further confirmed by the preparation of its acetate. The acetate, $C_{31}H_{52}O_2$, m.p. 125-127°, $[\alpha]_D^{28}$ -46° (c, 1.10), M^+ 456 (lit. $[\alpha]_D$ -44.7°, m.p. 127-8°) showed IR bands at 1739, 1250 (acetate), 830, 797 (-CH=C<) and NMR signals at 9.3, 9.22, 9.08, 8.98 (s, methyls); 8.05 (3H, s, acetate methyl); 5.52 (1H, m, -C<u>H</u>-OAc) and 4.8 (m, olefinic protons).

The properties of this compound were found to be comparable with the one reported in literature for ε-sitosterol. 21-2

Fraction 5:

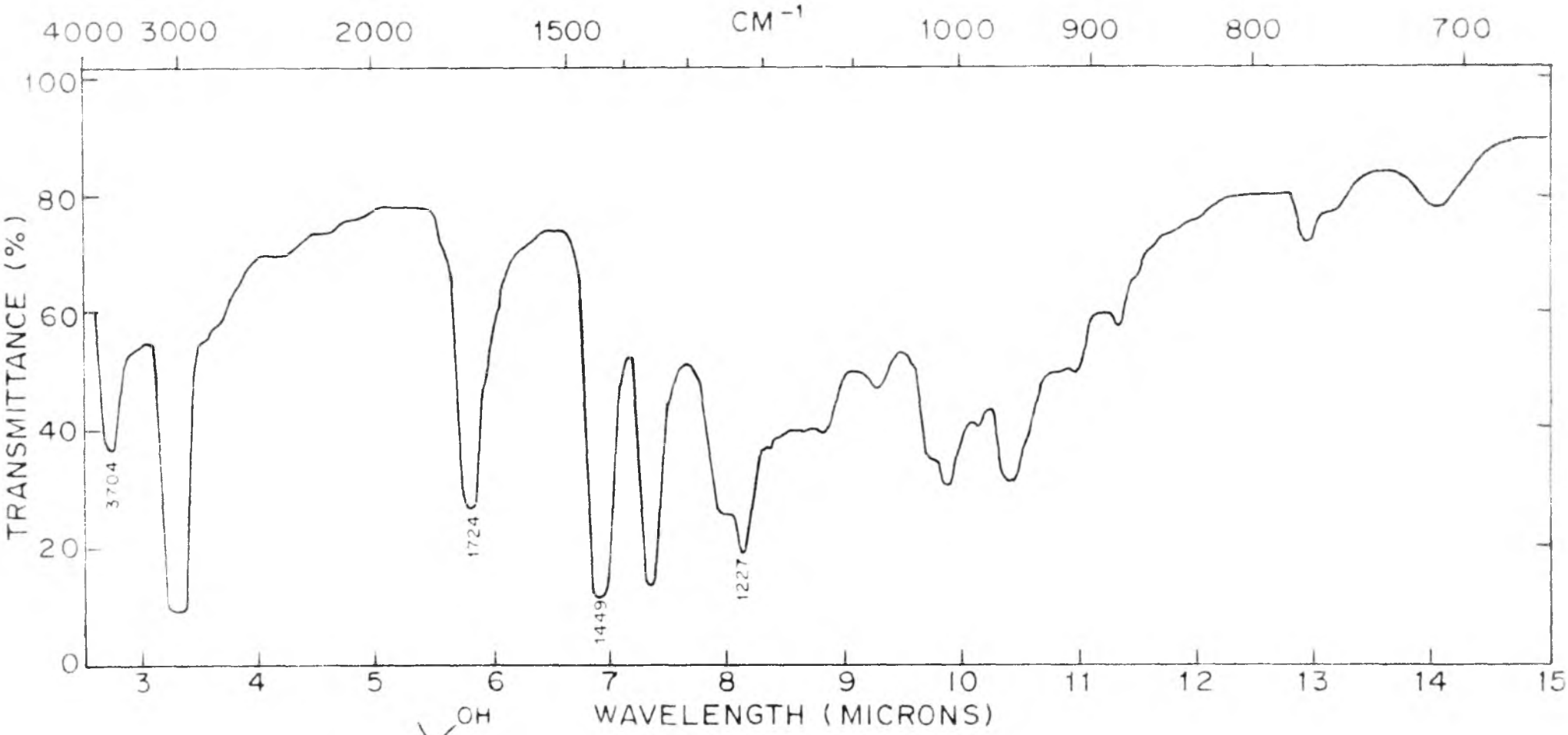
This fraction, eluted with 15% ethyl acetate in benzene, gave a solid from ethanol solution. It was separated, purified by crystallisation from ethanol and identified as cycloart-23-ene-3β,25-diol (I), $C_{30}H_{50}O_2$, m.p. 198°, M^+ 442, $[\alpha]_D^{28}$ +40°, (c, 0.56) (lit. $[\alpha]_D$ +38°, m.p. 198-203°). It showed IR band at 3509 (OH) and NMR signals at 9.68, 9.43 (1H each, m, cyclopropane protons); 8.67 (6H, s, methyls at C_{25}); 6.77 (1H, br.s, exchangeable with D_2O, OH proton) and 4.2 (2H, m, olefinic protons).

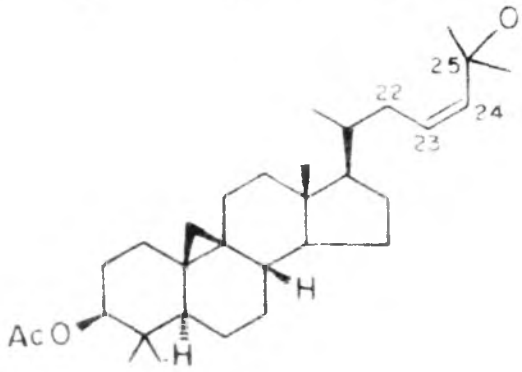
Cycloartene diol (I), on treatment with acetic anhydride/pyridine gave a hydroxy mono acetate (II), indicating that one of the hydroxyl groups is tertiary. The acetate (II), $C_{32}H_{52}O_3$, M^+ 484, m.p. 145°, $[\alpha]_D^{28}$ +46° (c, 0.71) (lit. $[\alpha]_D$ +48°, m.p. 152°) showed IR (Fig.1) bands at 3704 (OH), 1724, 1227 (acetate) and NMR (Fig.2) signals at 9.67, 9.44 (1H each, m, cyclopropane protons); 8.78 (6H, s, methyls at C_{25}); 5.6 (1H, m, C_3 proton) and 4.6 (2H, m, olefinic protons).

These physical and spectral properties of the compound (I) and its acetate (II) were found to be comparable with the one reported in literature[25-28].

Fraction 6:

This fraction was eluted with ethyl acetate and was


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3704
1724
1449
1227
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)


OH
25
22
24
23
H
AcO
H

(II)

FIG. 1

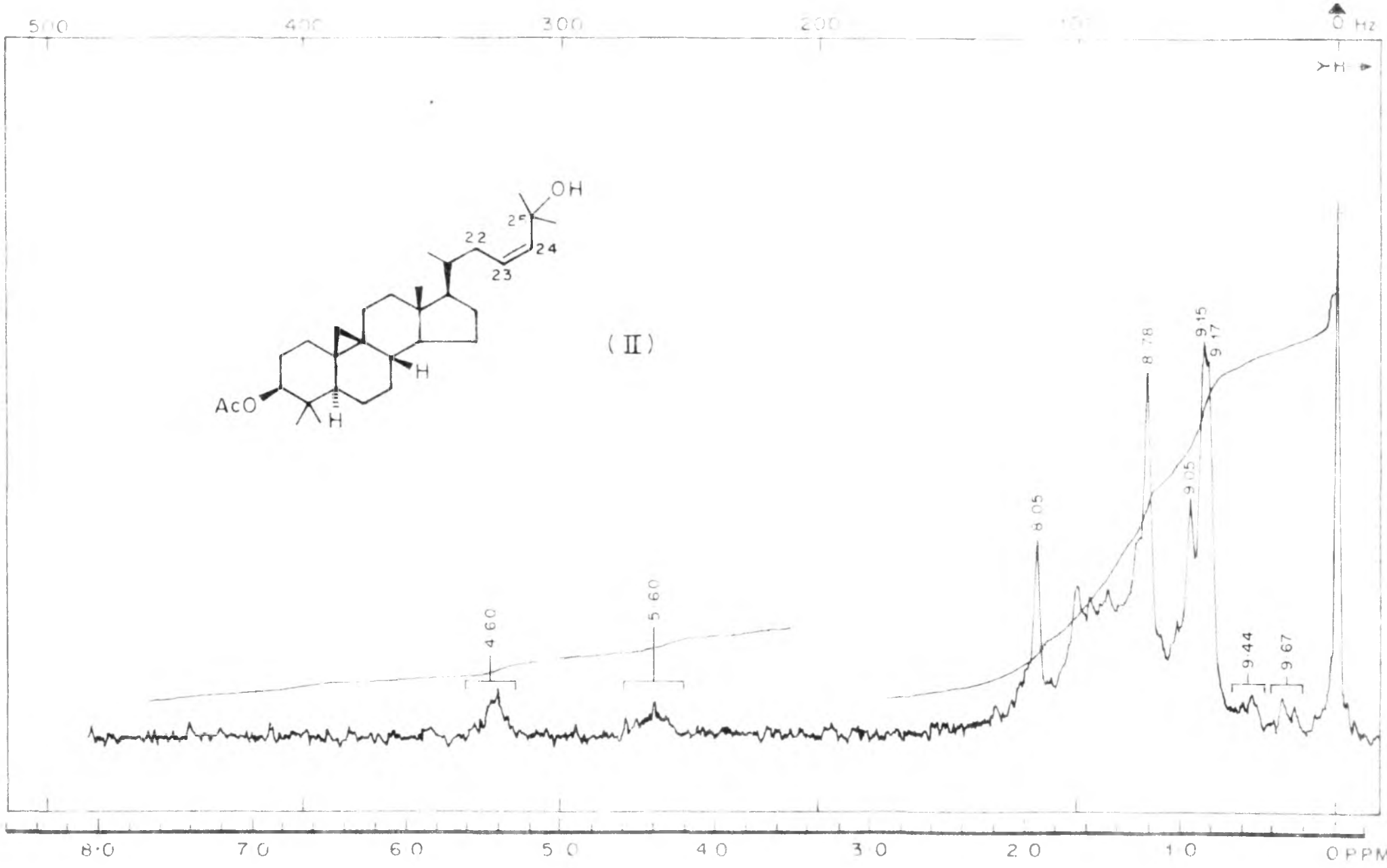
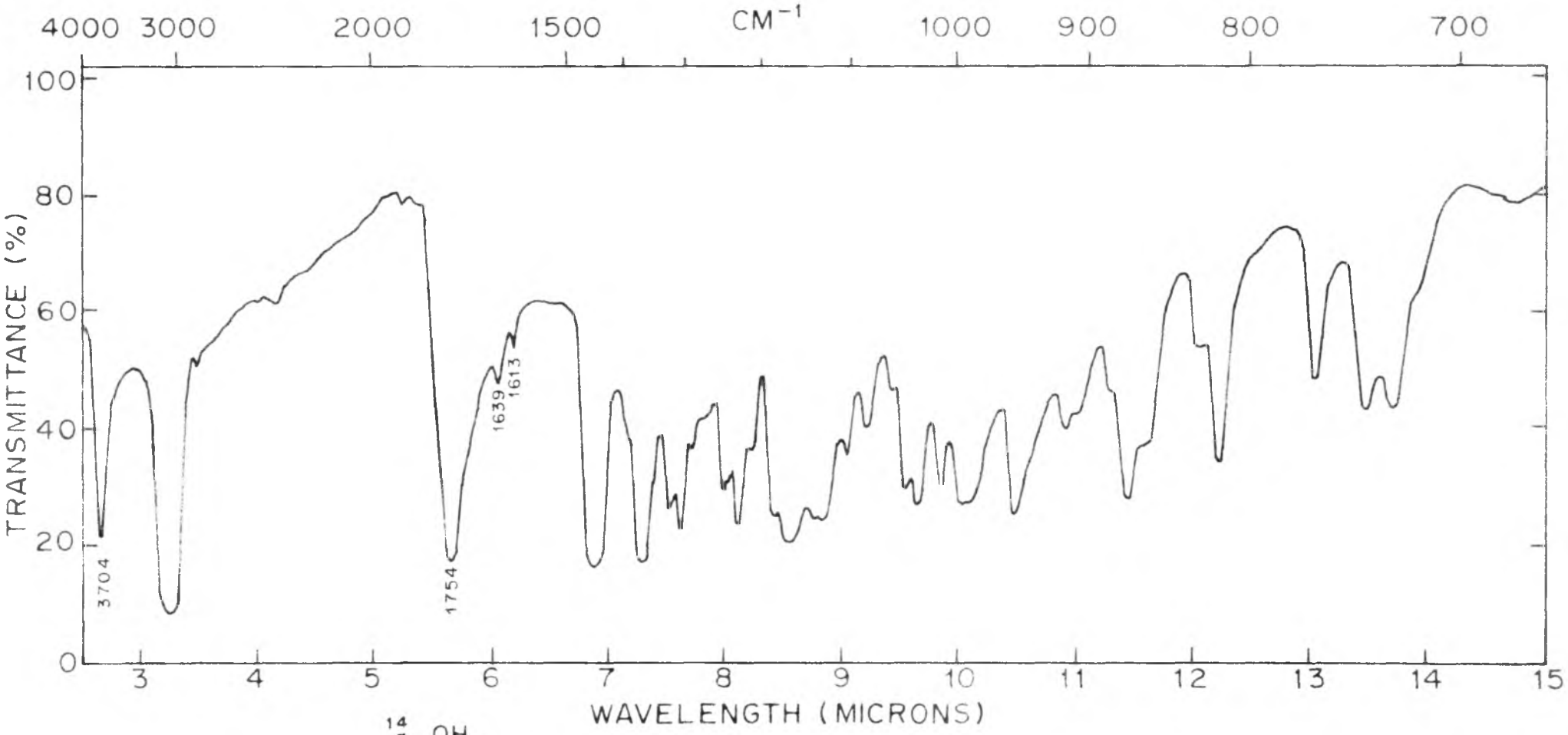
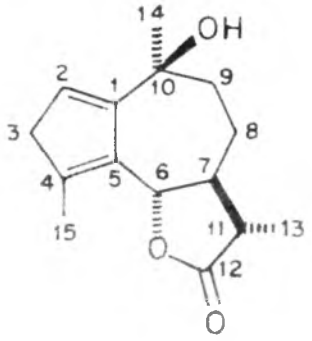

500
400
300
200
0 Hz
δH
OH
25
22
24
23
H
AcO
H
(II)
8.78
9.15
9.17
9.05
8.05
5.60
4.60
9.44
9.67
8·0
7 0
6 0
5 0
4 0
3 0
2 0
1 0
0 PPM (δ)

FIG 2

found to be a mixture of three compounds of close polarity. This fraction was rechromatographed on silicic acid (1:25 ratio) and eluted with(a) benzene (b) 5% ethyl acetate in benzene (c) 15% ethyl acetate in benzene (d) ethyl acetate + benzene (1:1) and(e) ethyl acetate. The fraction eluted with 15% ethyl acetate in benzene, gave a solid, m.p. 198°, which was identified as cycloart-23-ene-3β,25-diol (I) by its m.p., m.m.p. (198°) and superimposable IR and NMR spectra.

The latter fractions eluted with the same solvent afforded a thick viscous material in almost pure state along with minor less polar impurities. This fraction was rechromatographed on silicic acid (1:20 ratio). The less polar impurities were eluted with pet. ether + ether (3:1). The fraction eluted with ether afforded a yellow solid which was purified by crystallisation from 20% pet. ether in ether and identified as artabsin (III), $C_{15}H_{20}O_3$, m.p. 130°, $[\alpha]_D^{28}$ -44.4° (c, 1.76), M^+ 248 (lit. $[\alpha]_D$ -49°, m.p. 133°). It showed IR (Fig.3) bands at 3704(OH), 1754 (γ-lactone), 1639, 1613 (conj -CH=C<) and NMR (Fig.4) signals at 8.78 (3H, d, J = 7 Hz, methyl at C_{11}); 8.43 (3H, s, methyl at C_{10}); 8.17 (5H, br.m, C_8, C_9 and C_7 protons); 7.85 (3H, s, methyl at C_4); 7.67 (1H, br.s, C_{11} proton); 7.2 (2H, br.s, C_3 proton); 4.67 (1H, d, J = 9 Hz, C_6 proton) and 4.1 (1H, s,


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3704
1754
1639
1613
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


14
OH
2
1
10
9
3
8
4
5
6
7
15
11
13
O
12
O

(III)

FIG. 3.

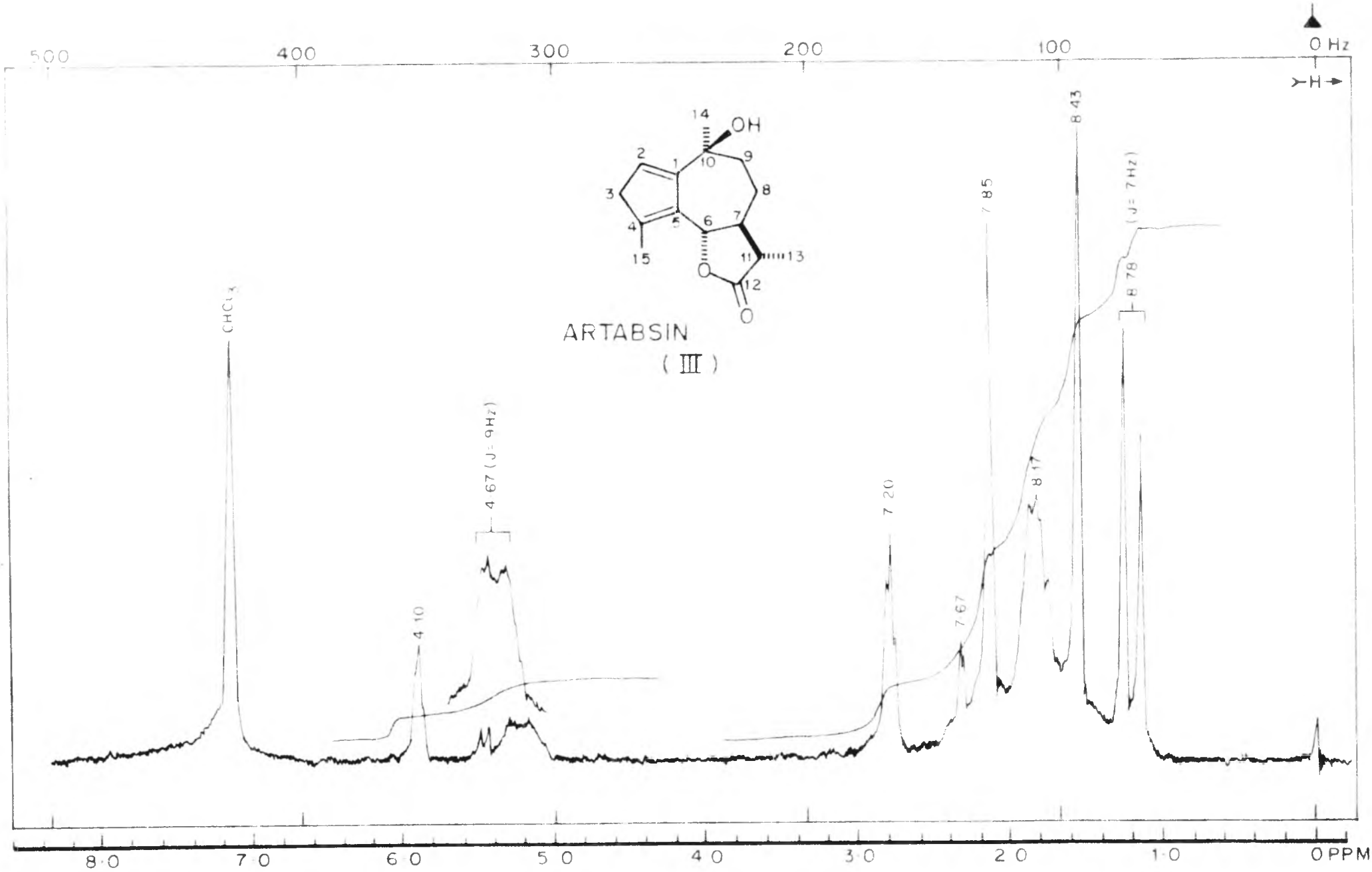

500
400
300
200
100
0 Hz
→H←
OH
14
1
2
3
4
5
6
7
8
9
10
11
12
13
15
O
O
ARTABSIN
(Ⅲ)
CHCl3
4.67 (J= 9Hz)
4.10
7.20
7.67
7.85
8.17
8.43
8.78
(J= 7Hz)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ

FIG. 4.

C_2 proton. The structure was further supported by its UV spectrum, λ_{max} 248 mμ, ϵ_{max} 2733.

The properties of this compound were found to be comparable with the one reported in literature for artabsin[29-31].

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

Extraction of the plant material, Artemisia brevifolia

The dried leaves, flowers and small stems (7 Kg) were powdered and placed in an aspirator bottle (50 lit. capacity). Pet. ether was then added till the powder was covered with it (30 lits). After keeping at room temperature for 24 hrs, the pet. ether extract was drained out and the solvent removed by distillation. The extraction was repeated two times. The combined extract (156 g) was dissolved in benzene (1 lit.), activated charcoal (30 g) was added and the solution refluxed for 15 minutes. It was then cooled, filtered and the benzene removed under reduced pressure to give a waxy material (144 g).

To the above extract was added ethanol (1.0 lit.) and heated on steam bath to dissolve the material. The alcoholic solution was cooled at 15° for 20 hrs and filtered to give a solid material (56 g). This solid showed, on TLC (pet. ether : benzene 1:1) a complex mixture of compounds mostly containing fatty compounds and was not investigated further.

The alcoholic solution, on evaporation afforded an oil (86 g) which showed on TLC (benzene), mainly four zones of mixtures. This mixture was separated on alumina (gr.II,

2.15 kg) and eluted as follows:

CHROMATOGRAM 1

Alumina (gr.II) 2.15 Kg; Oil 86 g

Fraction	Solvent	Volume (in litre)	Material (in g.)
1	Pet. ether	4.0	7.00
2	Pet.ether + benzene (3 : 1)	3.0	1.70
3	Pet.ether + benzene (1 : 1)	3.0	12.55
4	Benzene	3.0	5.36
5	Benzene + Chloroform (3 : 2)	3.0	5.3
6	Chloroform	2.5	10.5
7	Ethyl acetate	2.5	33.47

An acetone solution of fraction 6, on keeping for 24 hrs gave a solid which was further purified by crystallisation from acetone. The purified compound (2.5 g), m.p. 73°, was predicted to be an alcohol.

Isolation of

1) β-Sitosterol and

2) Cycloart-23-ene-3β,25-diol (1)

Fraction 7 contained major portion of the material (33.47 g) and showed mainly 4 spots on TLC (30% ethyl acetate

in C_6H_6). This fraction was rechromatographed on silicic acid (840 g) and eluted as follows:

CHROMATOGRAM 2

Silicic acid: 840 g, material: 33.4 g

Fraction	Solvent	Volume (in litre)	Material (in g.)
1	Benzene	1.5	5.1
2	Benzene	1.5	
3	5% ethyl acetate in C_6H_6	0.750	2.5
4	" "	1.0	5.3
5	15% ethyl acetate in C_6H_6	1.0	6.0
6	Ethyl acetate	0.5	10.0
7	Acetone	1.0	2.3

Fraction 4 in pet. ether, on keeping for 24 hrs at room temperature, afforded a solid (2.3 g). This solid was purified by repeated crystallisation, initially from pet.ether followed by ethanol and identified as β-sitosterol. m.p. 144° $[\alpha]_D^{28}$ -41.0° (c, 1.24), M^+ 414.

Analysis: Found: C,83.76; H, 12.25; $C_{29}H_{50}O$ requires: C, 83.99; H, 12.15%.

IR bands at 3571, 3030, 1639, 1449, 1370, 1124, 1047, 1010, 962, 948, 830 and 704 cm^{-1}.

The compound (β-sitosterol), on treatment with Ac_2O/Py at room temperature for 48 hrs gave, after work up, a solid which was crystallised from ethanol to give pure monoacetate, m.p. 125-27°, $[\alpha]_D^{28}$ -46° (c, 1.10), M^+ 456.

Analysis: Found: C, 81.26; H, 11.32; $C_{31}H_{52}O_2$ requires: C, 81.52; H, 11.48%.

IR bands at 3030, 1732, 1449, 1370, 1250, 1235, 1124, 1026, 962, 952, 897, 830 and 797 cm^{-1}.

Fraction 5 in ethanol solution, on keeping at room temperature for 48 hrs, gave a solid which was filtered, purified by crystallisation from ethanol and identified as cycloart-23-ene-3β-25-diol (I), m.p. 198°, $[\alpha]_D^{28}$ +40.0° (c, 0.56), M^+ 442.

Analysis: Found: C, 81.15; H, 11.17; $C_{30}H_{50}O_2$ requires: C, 81.39; H, 11.38%.

IR bands at 3509, 3030, 1449, 1361, 1274, 1205, 1143, 1036, 962, 909, 881 and 775 cm^{-1}.

The compound (I) was treated with Ac_2O/Py at room temperature for 18 hrs. It was, then, diluted with water and after working up as usual, gave a solid which was crystallised from ethanol and identified as the hydroxy monoacetate (II), m.p. 145°, $[\alpha]_D^{28}$ +46° (c, 0.71), M^+ 484.

Analysis: Found: C, 79.45; H, 10.65; $C_{32}H_{52}O_3$ requires: C, 79.28; H, 10.81%.

IR bands at 3704, 3030, 1724, 1449, 1361, 1227, 1010, 957 and 717 cm^{-1}.

Fraction 6 showed three main spots on TLC (30% ethyl acetate in benzene), with minor less polar impurities. This fraction was rechromatographed on silicic acid as follows:

CHROMATOGRAM 3

Silicic acid (200 g), material 10 g.

Fraction	Solvent	Volume	Material (in g.)
1	Benzene	1 lit.	0.76
2	5% ethyl acetate in benzene	800 ml	1.80
3	15% ethyl acetate in benzene	500 ml	2.82
4	""	400 ml	2.2
5	50% ethyl acetate in benzene	400 ml	0.92
6	Acetone	500 ml	0.55

From an alcoholic solution of fraction 3 a solid was separated, which was filtered and purified by crystallisation from ethanol. The purified material was identified as cycloart-23-ene-3β,25-diol (I) by its m.p., m.m.p. (198°) and

superimposable IR and NMR spectra.

Fraction 4 afforded a thick viscous oil which showed, on TLC (30% ethyl acetate in benzene) one main spot along with minor less polar impurities. This fraction was rechromatographed on silicic acid (45 g) and eluted with pet.ether + ether (3:1) and ether. Fractions eluted with ether gave a yellow solid which was crystallised from 20% pet. ether in ether to afford yellow needles (1.2 g). It was identified as artabsin, m.p. 130°, $[\alpha]_D^{28}$ -44.4° (c, 1.76), M^+ 248; UV: λ_{max} 248; ϵ_{max} 2735.

Analysis: Found: C, 72.16; H, 8.14; $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%.

IR bands at 3704, 3030, 1754, 1639, 1613, 1439, 1361, 1307, 1227, 1170, 1081, 952, 873, 816, 766, 741, and 727 cm^{-1}.

REFERENCES

1 J.B. Harborne, Progress in Phytochemistry [Ed. Reinhold L. and Y. Liwschitz] Interscience Publisher, London, Vol.1, pp.545-588 (1968).

2 H. Erdtman in "Chemotaxonomy and Serotaxonomy" [Ed. J.G. Hawkes] Academic Press, London, New York, p.235 (1968).

3 R.G. Kelsey and F. Shafizadeh, Phytochemistry 18, 1591 (1979).

4 R. Good "The Geography of the Flowering Plants" 4th Edn. (1974) Longman, London.

5 J.J. Besser, Bull. Soc. Imp. Natl. Mosc. 1, 219 (1829).

6 T.R. Govindachari, B.S. Joshi and V.N. Kamat, Tetrahedron Letters 3927 (1964).

7 M. Holub, D.P. Popa, V. Herout and F. Sorm, Coll. Czech. Chem. Commun. 29, 938 (1964).

8 H.G. Greenish and C.E. Pearson, Pharm. J. 106, 2 (1921).

9 H.G. Greenish and C.W. Maplethorpe, Pharm. J. 111, 94 (1923).

10 R.N. Chopra and N.N. Ghosh, Indian J. Med. Res. 13, 533 (1926).

11 N.A. Quzilbash, Indian J. Pharm. 12, 175 (1950).

12 J.L. Simonsen, Pharm. J. 111, 632 (1923).

13 James Coutts, Pharm. J. 123, 603 (1929).

14 M.A. Wahid and Samiullah, Pakistan J. Sci. Ind. Res. 3, 228 (1960).

15 T. Smith and H. Smith Pharm. J. 119, 688, 701 (1927).

16 Satoda et al. Chem. Abstr. 54, 23213^{b} (1960).

17 S.N. Bal and S. Prasad, Indian J. Pharm. 5, 30 (1943).

18 F. Aichner and F. Meister, Chem. Abstr. 63, 1667[e] (1965).

19 D.V. Banthorpe, D. Baxerndale, C. Catford and S.R. Williams, Planta. Med. 20, 147 (1971).

20 L.H. Borsutzki, Arch. Pharm. 288, 336 (1955); Chem. Abstr. 51, 6941 (1957).

21 K.C. Joshi, M.K. Tholia and T. Sharma, Planta. Med. 27, 281 (1975).

22 K.E. Schulte, J. Reisch and G. Rucker, Arch. Pharm. 296, 273 (1963).

23 D.S. Bhakuni, S.N. Srivastava, V.N. Sharma and K.N. Kaul Indian J. Appl. Chem. 24, 197 (1961).

24 C. Krishna, L.P. Joshi and Pahup Singh, J. Ind. Chem. Soc. 50, 561 (1973).

25 A.N. Starratt, Phytochemistry 5, 1311 (1966).

26 L.J. Altman and S.N. Zito, Phytochemistry 15, 829 (1976).

27 J.L. Fourrey, J. Rondest and J. Polonsky, Tetrahedron 26, 3839 (1970).

28 C. Djerassi and R. McCrindle, J. Chem. Soc. 4034 (1962).

29 K. Vokac, Z. Samek, V. Herout and F. Sorm, Coll. Czech. Chem. Commun. 34, 2288 (1969).

30 V.Herout, L. Dolejs and F. Sorm, Chem. and Ind. 1236 (1956).

31 K. Vokac, Z. Samek, V. Herout and F. Sorm, Coll. Czech. Chem. Commun. 37, 1346 (1972).

LIST OF PUBLICATIONS

1 Epoxidation of dehydration products of carane-3α-hydroxy-4α-acetate
B.M. Mane, K.G. Gore and G.H. Kulkarni
Indian J. Chem. 18B, 395 (1979).

2 Selenium dioxide oxidation of saussurealactone
B.M. Mane, S.V. Hiremath and G.H. Kulkarni
Curr. Sci. 47, 677 (1978).

3 Allylic oxidation of (+) car-3-ene
P.P. Pai, B.M. Mane, R.S. Joshi and G.H. Kulkarni
Curr. Sci. 48, 155 (1979).

4 Stereospecific conversion of (+) car-3-ene into (+) dihydrochrysanthemolactone and methyl (+) cis chrysanthemate
B.M. Mane, K.G. Gore and G.H. Kulkarni
Indian J. Chem. (in press).

5 Stereospecific conversion of (+) car-3-ene into methyl 1S (+) cis and methyl 1R (-) trans 2,2-dimethyl-3(2,2-diphenyl vinyl) cyclopropane carboxylates.
B.M. Mane, K.G. Gore and G.H. Kulkarni
Indian J. Chem. (in press).

6 Synthesis of methyl 1R cis (-) 2,2-dimethyl-3(2-phenyl-prop-1-enyl) cyclopropane carboxylate from (+) car-3-ene.
B.M. Mane, P.P. Pai, G.H. Kulkarni and R.B. Mitra
Indian J. Chem. (in press).

7 Synthesis of methyl 1R (+) cis-chrysanthemate and methyl 1S cis 2,2-dimethyl-3(2-phenyl-prop-1-enyl) cyclopropane carboxylate from (+) car-3-ene.
M.G. Bhat, B.M. Mane, G.H. Kulkarni and R.B. Mitra
Indian J. Chem. (Communicated).