# STUDIES IN SESQUITERPENES
## ( Newer Perspectives of Longifolene )



. A THESIS

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CERTIFIED that the work incorporated in the thesis "STUDIES IN SESQUITERPENES" (Newer Perspectives of Longifolene) submitted by Mrs. Shantee P. Vaidya was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

U.R. Nayak

(Dr. U.R. Nayak)
Supervisor

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PREFACE:

"The true worth of an experimentor consists in his pursuing not only what he seeks in his experiment, but also what he did not seek."

- CLAUDE BERNARD

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NEXT to pharmaceuticals (for human health) and agrochemicals (for crop protection), aroma chemicals constitute an important aspect of the organic chemical industry. Fragrances are, nowadays, routinely incorporated in a great number of products of daily use. Atleast two thousand synthetic aroma chemicals are in use throughout the world.

Man's search for substances which can produce new flavours and fragrances, substitute for expensive and/or scarce ones, or augment and enhance existing desirable ones, continues apace. The thrust of fragrance research in the last few years has been towards the synthesis of compounds that can be substituted for existing substances which, in their natural forms, are expensive to procure or are becoming scarce.

Research in aroma chemicals can be divided into three general categories: (a) synthesis of naturally occurring chemicals, for example, phenylethyl alcohol, which occurs in rose oil; (b) chemical modification of abundant naturally occurring materials e.g. acetylated vetiver oil ("vetivert acetate") from vetiver oil, vanillin from lignin, the

products derived from $\alpha$-pinene such as $\alpha$-terpineol and isobornyl acetate and tremendous quantities of $\beta$-pinene are pyrolyzed to $\beta$-myrcene which is then used to make aroma chemicals with valuable floral notes; and (c) synthesis based on industrial organic feedstocks e.g. nitro musks. For a tropical country like, India, the second category for research in aroma chemicals viz. the chemical modification of abundant naturally occurring materials (terpenic hydrocarbons, nonedible oils etc.) is of special significance.

Speciality Isoprenoid Aroma Chemicals

The sesquiterpenes and their derivatives comprise about 2000 naturally occurring representatives, and are the major sub-group of isoprenoid natural products. These compounds are derived from more than 100 different carbon skeletons. Although 500 sesquiterpene derivatives have been found in flavours, only about 20 seem of importance for the formation of flavours, if subjected to severe criteria. The aroma compounds of the sesquiterpene series seem to be associated with certain carbon skeletons. In any event, we still have no indication as to the occurrence in natural flavour complexes, of compounds such as cedranes, santalanes, vetivanes, spirovetivanes and germacranes which, on the other hand, constitute very important chemical classes in the chemistry of fragrances. Compared with the monoterpene derivatives,

the flavour value of sesquiterpene compounds is small, although some of their representatives have been found to be character-impact compounds.

Whereas sesquiterpene hydrocarbons, with few exceptions, have inferior characteristic organoleptic properties, the ethers of this series- so far as they are known- are distinguished by outstanding odour qualities. Once the general value of these compounds as aroma components is recognized, as in the case with monoterpenoid ethers (e.g. rose oxide), the importance of this group of compounds will rapidly grow.

Several essential oils rich in oxygenated sesquiterpenes (e.g. sandalwood oil, santalum album L.) find extensive use in perfumery. Therefore, with longifolene available in commercial quantities, it is not surprising that efforts have been directed to evaluate its derivatives in perfumery compositions. A number of compounds have been found to possess desirable characteristics and their preparation as well as their use in perfumery have been covered by patents. A brand new aroma chemical (Necelone, acetylalloisolongifolene) with an enchanting woody-amber fragrance has been developed recently at the National Chemical Laboratory, from alloisolongifolene- a new remarkably catalyst-specific isomer of longifolene..

According to the National Science Foundation, research and development (R & D) primarily falls into one of three

parameters: (a) basic research, in exploring the unknown; (b) applied research, to satisfy a need and (c) development, to develop tangible processes and products. Viewed in the context of this definition, R & D effort on longifolene at the National Chemical Laboratory during the past decade has been a totally rewarding experience. The work described in the present thesis essentially falls under the basic research parameter of R & D on longifolene- the evergreen sesquiterpene of Pinus longifolia.

# CHAPTER-1

## SESQUITERPENES : A MINISCULE OVERVIEW

# SESQUITERPENES: A MINISCULE OVERVIEW

## TERPENES: GENERAL

THE CHEMISTRY of terpenic compounds has long been an inspiration to the creative endeavours of the organic chemist. The terpenes[1] constitute one of the most widespread groups of naturally occurring compounds characterized by a great diversity of chemical structures. They are generally regarded as derivatives of isoprene, wherein the isoprene units are arranged in a head-to-tail fashion, although there are some exceptions to this arrangement. The terpenes are therefore classified according to the number of isoprene units in their carbon skeletons, with a simple terpene being regarded as two isoprene units. Terpenes are classified as in Table 1.

Table 1. Classification of Terpenes

| Isoprene units | Carbon atoms | Classification |
|---|---|---|
| 1 | 5 | hemiterpene |
| 2 | 10 | monoterpenes |
| 3 | 15 | SESQUITERPENES |
| 4 | 20 | diterpenes |
| 5 | 25 | sesterterpenes |
| 6 | 30 | triterpenes |
| 8 | 40 | tetraterpenes |
| >8 | >40 | polyterpenes |

The terpenes are further classified as acyclic, monocyclic, bicyclic, tricyclic etc. Although the term terpenes might seem to be appropriate only for unsaturated hydrocarbons, it is generally recognised to apply not only to isoprene oligomers, but also to their derivatives e.g. alcohols, ketones, esters etc. The term terpenoid properly designates such derivatives. Terpenes, especially the oxygenated derivatives, are important flavour and perfume materials. In general, their mammalian toxicity is relatively low. Many are listed as GRAS (generally recognised as safe) food additives and flavourings. Numrous monographs on terpenes and their derivatives as fragrance materials and on their biological aspects have been published. In referring to individual compounds terpene chemists use trivial names almost exclusively because the systematic names are frequently unmanageably long and complicated and often obscure the terpenic nature of the compound.

Chemists dealing with volatile terpenic mixtures rely heavily on gas-liquid chromatography (glc) in conjunction with mass spectrometry, nmr, $^{13}C$ nmr, infrared and UV spectroscopy. Fractional distillation is the most commonly used method of separating terpenic mixtures into their components but on a smaller scale, liquid-liquid and liquid-solid chromatography are also employed, especially to separate close-boiling components and less volatile compounds. Use of these modern analytical methods has

relegated boiling points, melting points of derivatives, refractive indices and other conventional physical properties to a position of secondary importance, although they are frequently used in commercial product specifications.

The need to systematize and rationalize the ever-increasing number of naturally occurring terpenes led Ruzicka to propound the Biogenetic Isoprene Rule[2]. It states that each class of terpenoids is formed from an acyclic precursor which is cyclized and further elaborated (rearrangement/dimerization) according to a limited number of well-defined stereoelectronic principles[3]. It is the triumph of this hypothesis that it successfully accommodates in constitutional and configurational detail the great diversity of terpenoid structures found in nature. The conceptual edifice of the Biogenetic Isoprene Rule is matched and complemented by the biochemical work[4] which has elucidated in extraordinary detail the precise mechanism whereby lanosterol is synthesised in living systems.

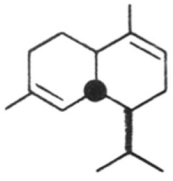
In nature, the two most abundant natural sources of terpenes are (a) turpentine oil and (b) other essential oils; nearly all commercially important terpenes were obtained from these sources until relatively recently. Since about the late 1950's, synthetic methods have been developed for manufacturing most of the industrially important monoterpenes and these synthetics have taken over a large share of the

market. Essential oils[5] are still used in substantial quantities for their flavour and aroma characteristics, which largely depend on their terpenic content.

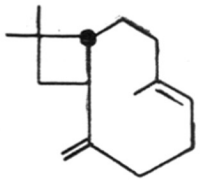
SESQUITERPENES

The chemistry of the sesquiterpenes with their 15 carbon atoms-corresponding to three isoprene units-arranged in an acyclic, monocyclic, bicyclic, tricyclic or tetracyclic skeleton has undergone a period of rapid development during the past three decades following the introduction of chromatographic separation techniques and physical methods of structural analysis. It has been estimated that atleast 2000 sesquiterpenes and their derivatives (corresponding to more than 100 different carbon skeletons) have been discovered in nature; their structures can be simple or complex. Some of the technologically important sesquiterpenes are listed in Table 2 and their structures given (Figure 1)

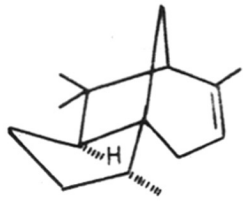
FIGURE - 1.



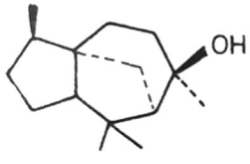
α-CADINENE



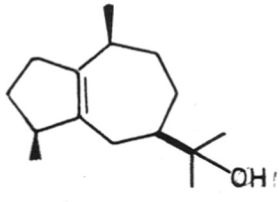
CARYOPHYLLENE



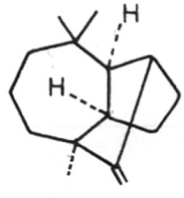

α-CEDRENE



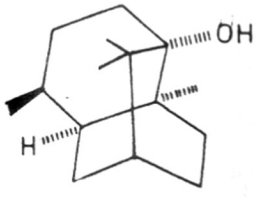

CEDROL



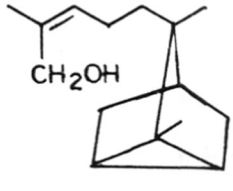

GUAIOL



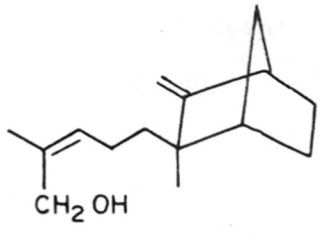

LONGIFOLENE




PATCHOULI ALCOHOL




α-SANTALOL




β-SANTALOL

Table 2. Some Technologically Important Sesquiterpenes from Natural Sources

| No. | Sesquiterpenes | Essential oils |
|---|---|---|
| 1. | $\alpha$ -Cadinene | Cubebs |
| 2. | Caryophyllene | Clove |
| 3. | $\alpha$ -Cedrene | Cedarwood |
| 4. | Cedrol | Cedarwood |
| 5. | Guaiol | Guaiac wood |
| 6. | Longifolene | Indian turpentine |
| 7. | Patchouli alcohol | Patchouli |
| 8. | $\alpha$ -Santalol | Sandalwood |
| 9. | $\beta$ -Santalol | Sandalwood |

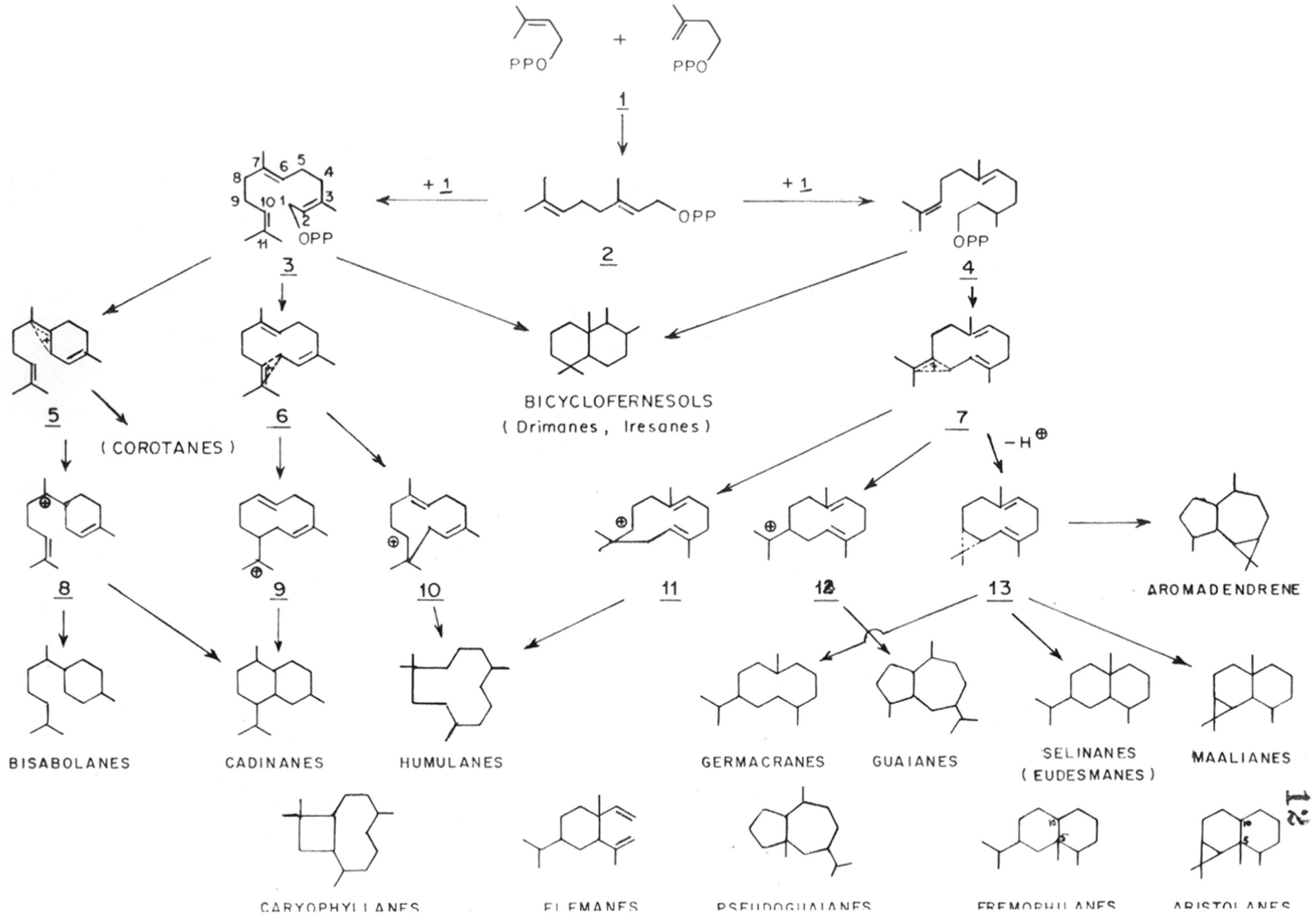
The sesquiterpenes which primarily occur in higher plants- less frequently in lower plants and in the animal kingdom (e.g. in insects)- are often steam-volatile and comprise not only of mostly unsaturated hydrocarbons (including some alkynes) but also alcohols, ketones, aldehydes and carboxylic acids. They may also contain three to seven-membered ether rings and furan rings. Chlorine and bromine-containing sesquiterpenes, as well as nitrogen-containing compounds with 15 carbon atoms (sesquiterpene alkaloids) isolated predominently from Nymphaeaceae also deserve mention. Compounds with only 12 or 14 carbon atoms (norsesquiterpenes) can also be derived from

certain sesquiterpenes.

The sesquiterpene lactones occurring in Compositae and also in other plant families, have attracted particular attention. The first compound of this class, α-santonin, which was isolated in crystalline form in 1830, is still the object of intense study[7]. So far about 700[6] sesquiterpene lactones are known; worthy of special mention[8] are the germacranolides, guaianolides, pseudoguaianolides, selinanolides (≡eudesmanolides) and eremophilanolides. Most of them are saturated or αβ-unsaturated γ-lactones. Apart from a few δ-lactones a couple of β-lactones have also been found. A trilactone, bilabolide, is also known alongisde about 25 dilactones.

In addition to isolation and structure elucidation of numerous new compounds, recent advances in sesquiterpene chemistry have included a better knowledge of stereochemistry of the molecules, their reactivity and rearrangements, and their biogenesis. In this connection the outstanding successes achieved in the synthesis of sesquiterpenes should be emphasised. Several earlier structural assignments have been corrected by syntheses and application of modern physical methods. Thus the "vetivanes", formerly regarded as hydroazules, proved to be spirocyclic agarospiranes or eremophilanes with a decalin skeleton. The detection of sesquiterpenes with toxic and interesting biological properties e.g. cytotoxic activity, also deserves mention.

FIG. 2. BIOGENESIS OF SESQUITERPENES



According to Ruzicka and Hendrickson, 2-*cis*-6-*trans*-farnesyl pyrophosphate 3 or the corresponding 2-*trans*-6-*trans* compound 4 is regarded as the biological precursor of almost all sesquiterpenes; it is formed from acetyl coenzyme A *via* mevalonic acid, isopentenyl pyrophosphate 1 and geranyl pyrophosphate 2 (Figure 2). For steric reasons, a 2-*trans*-6-*cis*-farnesyl-, a 2-*cis*-6-*cis*-farnesyl- or a nerolidyl precursor has to be assumed for a few sesquiterpenes. Removal of the pyrophosphate group from 3 or 4 yields carbocations whose formulation as nonclassical cations 5 and 6 or 7 explains their cyclization to two cyclic cations each [e.g. 9 and 10 from 6; 11 and 12 from 7]. These can afford most of the sesquiterpenes by processes such as 1,2- or 1,3-hydride shifts, electronically or sterically controlled cyclizations with the two remaining double bonds ("Markownikoff" and "anti-Markownikoff" cyclizations), Wagner-Meerwein rearrangements and 1,2-methyl shifts. Considerable singificance attaches to the biogenetic formation of diastereoisomers and enantiomers. It should however be noted that many hypotheses regarding the biosynthesis of sesquiterpenes that are based on structure, stereochemistry and reactivity still require experimental proof *in vivo*[9].

The future of terpene research will still be concerned primarily with the isolation and structure

elucidation of new compounds which could be important as missing biosynthetic links or biologically active substances or as reactants for the study of chemical problems. The sesquiterpenes throw up problems of a largely stereochemical nature. The course of their numerous rearrangements provides information about relationships between stereochemical and electronic factors and the reactivity of the compounds. The chemistry of nonclassical carbocations has also profited from work on sesquiterpenes. The photochemistry of the sesquiterpenes is still in its infancy. Synthesis of sesquiterpenes must nearly always have to be carried out stereoselectively; they can contribute to the solution of problems in preparative chemistry.

Knowledge of reactivity, photochemistry and synthesis stimulate research into sesquiterpene biogenesis, a field that will become increasingly important in the future. The aim is to elucidate the formation of numerous carbon skeletons and to obtain information about the reasons behind the frequently complex setereospecific biosynthetic pathways that could also be of interest for the biogenesis of other natural products. In this connection, importance also attaches the site of formation and of deposition of the sesquiterpenes in plants and to their distribution throughout the plant and animal kingdoms. The biological properties of some sesquiterpenes show that they are not merely

metabolic "waste products". For instance, they are of significance as plant growth substances, growth regulators and sex attractants of fungi. Others function as the juvenile hormones essential for normal development of insects or occur as components of insect secretions. These aspects have opened up an area of sesquiterpene research that is of potential interest e.g. for the solution of practical problems of influencing the growth of cultivated plants and in crop protection.

Sesquiterpenes can provide impetus to drug research also. The starting point of such work is the pharmacological effects determined so far for a relatively small number of compounds. They include cytotoxic, antibiotic, fungistatic, virostatic, anthelmintic, antiphlogistic and sedative properties, thus covering a fairly broad spectrum . Considerable uncertainty still sourrounds the extent to which the sesquiterpenes contribute to the manifold and frequently unspecific action of the essential oils in which they occur. Mention should be made here of the importance of sesquiterpene research for the chemistry of essences and of aromas and flavours.

Reactions. The two most important commercial reactions of sesquiterpenes are esterification and oxidation to obtain aroma products; sesquiterpene acetates are especially valued for this application. Acylation of longifolene/alloiso-

longifolene and hydroxylation of caryophyllene yield products useful in perfumery.

An interesting antiulcer drug geranyl farnesyl acetate (gefarnate) has been developed[10]. A synthesis of this compound involves reaction of farnesyl bromide with diethyl malonate to produce, after hydrolysis, farnesyl malonic acid which is decarboxylated to obtain farnesyl acetic acid. Esterification of the acid with geraniol gives geranyl farnesyl acetate (Figure 3).

Manufacture. With a few exceptions, the limited number of commercially available sesquiterpenes have been isolated from natural sources, primarily essential oils to which they impart characteristic organoleptic properties. Isolation is usually accomplished by extraction, fractionation, crystallisation or a combination thereof. In general, the commercial products are not highly pure compounds, unless they are amenable to crystallisation, e.g. cedrol.

The literature on the synthesis and transformations of sesquiterpenes is voluminous and mostly of academic interest. An excellent, comprehensive review of efforts of the total synthesis[11] of sesquiterpenes has been published. The two most important sesquiterpenes synthesized commercially are nerolidol and farnesol. When geranyl-neryl acetone reacts with acetylene, dehydro-nerolidol forms. Hydrogenation of the latter over a Lindlar=type catalyst produces a mixture (ca. 60:40 trans :cis) of the geometrical isomers of nerolidol[12].

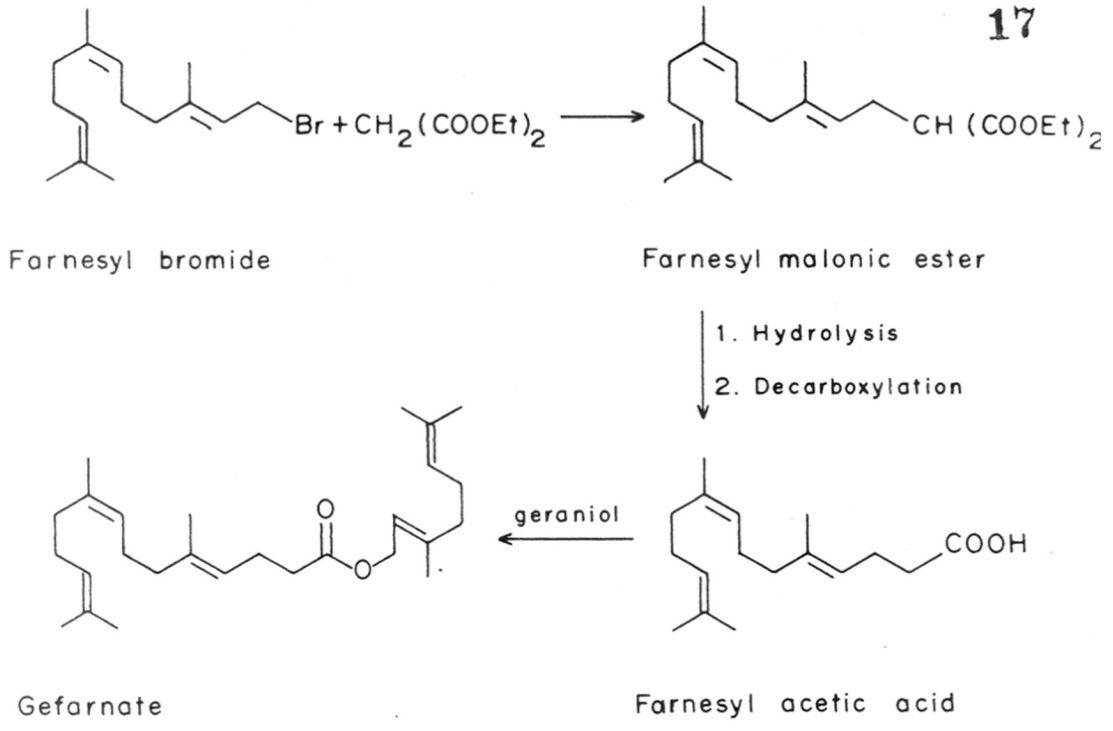



FIGURE 3



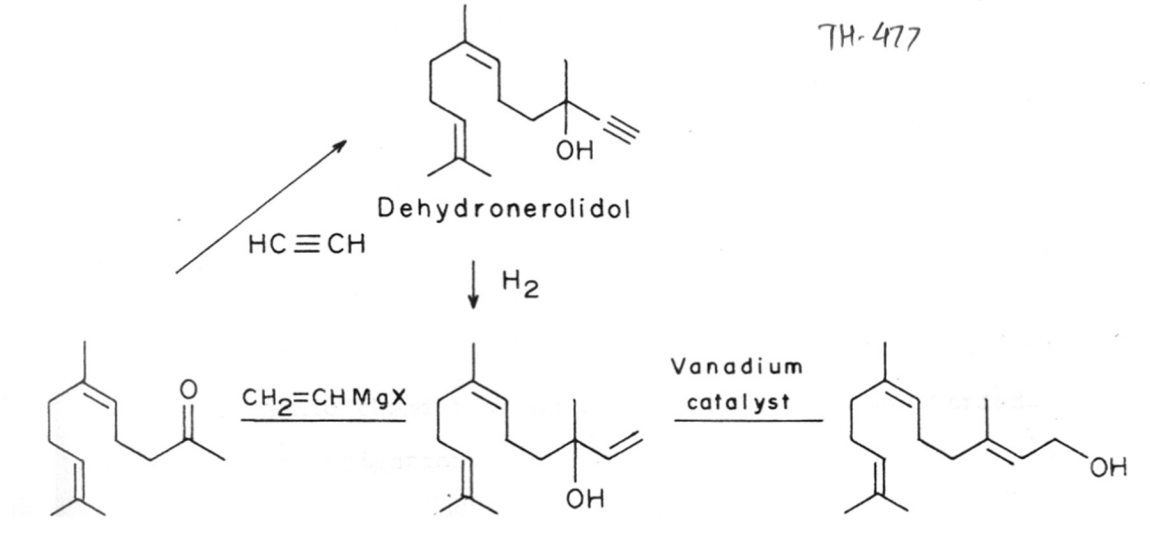





FIGURE 4

Geranyl-neryl acetone also reacts with Grignard reagent producing nerolidol directly[13] (Figure 4). In both cases, the trans:cis ratio of the nerolidol formed depends on the trans:cis ratio of the geranyl acetone. Farnesol can be produced from nerolidol by isomerization over a vanadium catalyst in essentially the same waylinalool can be converted to geraniol-nerol.

Uses. Sesquiterpenes are used almost exclusively in perfumery;[6,14] very small amounts are used in flavours. Interest in sesquiterpenes as pharmaceutical intermediates is increasing.

CONCLUSION

The biosynthesis[15] of sesquiterpenes, as with all biosynthetic work, is at an exciting stage of development. The increasing use of $^{13}C$ NMR indicates that the challenges of deriving sophisticated biosynthetic schemes can be met with adequate effort and intellect. The wide range of biological[16] activity exhibited by this group of compounds merits increasing attention to their biosynthetic derivation.

Within the field of sesquiterpenoid chemistry[17] one finds a wide range of oxygenated function, of ring size and of mechanistic change. In the words of Barton and de Mayo[18] (1957), if no other type of organic compound were known, organic chemistry would still be a rich and varied field of investigation.

# REFERENCES


1 a Newman A A, Chemistry of Terpenes and Terpenoids, Academic Press, London (1972).

b Derfer J M & Derfer M M, Ency Chem Tech, 22 (1983) 709.

2 Ruzicka L, Experientia, 9 (1953); Proc Chem Soc(Lond) (1959) 341.

3 Hendrickson J B, Tetrahedron, 7 (1959) 82.

4 Cornforth J D, Quart Rev Chem Soc, 23 (1969) 125.

5 Rogers J A (Jr), Ency Chem Tech, 16 (1981) 307.

6 Ohloff G, Prog Chem Org Nat Prod, 35 (1978) 471.

7 McMurry T H B & Rane D F, J Chem Soc C (1971), 1389, 3851.

8 a Yoshioka H, Timmerman B N & Mabry T J, Sesquiterpene Lactones, University of Tokyo Press (1973).

b Fischer N H, Olivier E J & Fischer H D, Prog Chem Org Nat Prod, 38 (1979) 47.

9 Parker W, Roberts J S & Ramage R, Quart Rev Chem Soc, 21 (1967) 331.

10 Cardoni C, Covaleri B & Adami E, J Med Chem, 6 (1963) 467.

11 a Heathcock C H, The Total Synthesis of Natural Products Vol. 2 (Ed J ApSimon) Wiley,New York (1973).

b Heathcock C H, Graham S L, Pirrung M C, Plavac F & White C T, The total Synthesis of Natural Products, Vol 5 ( Ed J ApSimon) Wiley, New York (1983).

11 c Vandewalle M & DeClarcq P, Tetrahedron, 41 (1985) 1767.

12 Isler O Ruegg R, C dit Jean, Wagner H & Bernhard K, Helv Chim Acta, 39 (1956) 897.

13 Ofner A, Kimel W, Holmgren A & Forrester F, Helv Chim Acta, 42 (1959) 2577.

14 a Taylor W I, Chant B & Loveren G V, Encyl Chem Tech, 16 (1981) 947.

b Fragrance Chemistry Ed E T Theimer, Academic Press, New York (1982).

c Fragrances and Flavours: Recent Developments Ed. S Torrey, Noyes Data Corporation, New Jersey (1980).

15 a Cordell G A, Chem Rev, 76 (1976) 425.

b P Manitto, Biosynthesis of Natural Products, Ellis Horwood Ltd., Chichester, pp 237-255 (1981).

16 a Rodriguez E, Towers G H N & Mitchell J C, Phytochemistry, 15 (1976) 1573.

b Stoessl A, Stothers J B & Ward E W B, Phytochemistry 15 (1976) 855.

17 Rucker G, Angew Chem Int Ed, 12 (1973) 793.

18 Barton D H R & deMayo P, Quart Rev Chem Soc, 11 (1957) 189.

# CHAPTER-2

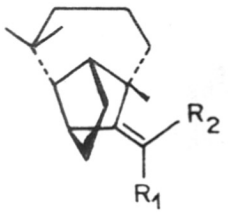
## ANOMALOUS JONES OXIDATION OF 12-IODOLONGIBORNANE-4-ONE / 12-BROMOLONGIBORNANE-4-ONE FORMATION OF NOVEL HALOGEN FREE DIACID / LACTONE ACID

## A B S T R A C T

12-Iodolongibornane-4-ol 7 (prepared by hydrolysis of the trifluoroacetate resulting from ω-iodolongifolene 3 by action of $CF_3COOH/CH_2Cl_2$) has been shown to undergo anomalous Jones oxidation generating iododiketone 13 (26%) and the iodine-free diacid 19 (19%) which has been characterized as its dimethyl ester 20. Under similar conditions the bromo-analogue 6 gives the bromodiketone 12 (42%) and the bromine-free lactone-acid 14 (9%); the latter has been further transformed into the hydroxydiester 17. Formation of the abnormal halodiketones 12/13 has been mechanistically rationalized in terms of neighbouring group participation by the spatially well-disposed halogen in the enolic form of the monohaloketones 21/25, thus activating the C-3 site in these substrates for attack by chromic acid. Anchimeric assistance by carbonyl oxygen of the initially formed halodiketones 12/13 results in the formation of lactone-acid 14 in both cases; in the case of the iodo compound 13, however, the HI liberated in the reaction brings about reduction of the lactone-cleaved iodo-diacid 33 generating the iodine-free diacid 19.

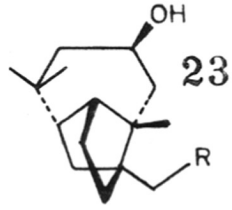
IN LONGIFOLENE 1, the ethylenic linkage is well-shielded[1] and crowding at the more-substituted end of the olefinic bond is so severe that approach of the nucleophile/radical is essentially blocked. Hence it is not surprising that the chemistry of longifolene is replete with examples of sterically-diverted[2] abnormal products during electrophilic addition/oxidation reactions with a variety of reagents. The electrophilic reaction of a strong acid of the type trifluoroacetic acid (TFA) with a double bond bearing a bulky electronegative halogen exemplified by ω-iodolongifolene 3 and the anomalous behaviour of Jones reagent with the resulting hydroxylated iodolongibornane 7, in a comparative study with the bromo-analogue 2, appeared to be of theoretical interest and hence the study was undertaken.

ω-Iodolongifolene 3 was prepared from 1 by the action of pyridine-iodine monochloride complex in AcOH, exposed to TFA in dichloromethane at ambient temperature and the resulting trifluoroacetate hydrolysed with alkali; after chromatographic separation of the faster-moving iodolefins 4 (33%), the polar 12-idolongibornane-4-ol 7 (PMR: CHOH, a multiplet[4] at 4.08δ was obtained in a manner reminiscent[3] of the bromo-analogue 6 from 2 but in a considerably lower yield (30% of 7 as compared to 65% of 6). While preparing the bromodiketone 12 (required for another study) by Jones oxidation of the bromoalcohol 6, we had earlier

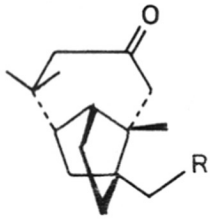



1 $R_1 = R_2 = H$
2 $R_1 = Br$; $R_2 = H$
3 $R_1 = I$; $R_2 = H$

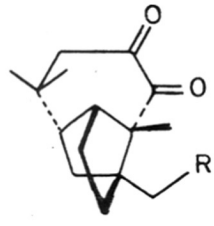

4



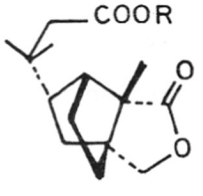

5 R = H
6 R = Br
7 R = I



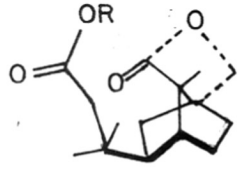

8 R = H
9 R = Br
10 R = I



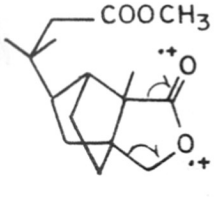

11 R = H
12 R = Br
13 R = I



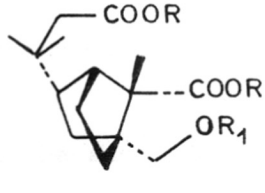


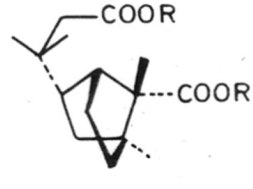

14 R = H
15 R = Me




15a




16 $R = R_1 = H$
17 R = Me; $R_1 = H$
18 R = Me; $R_1 = Ac$

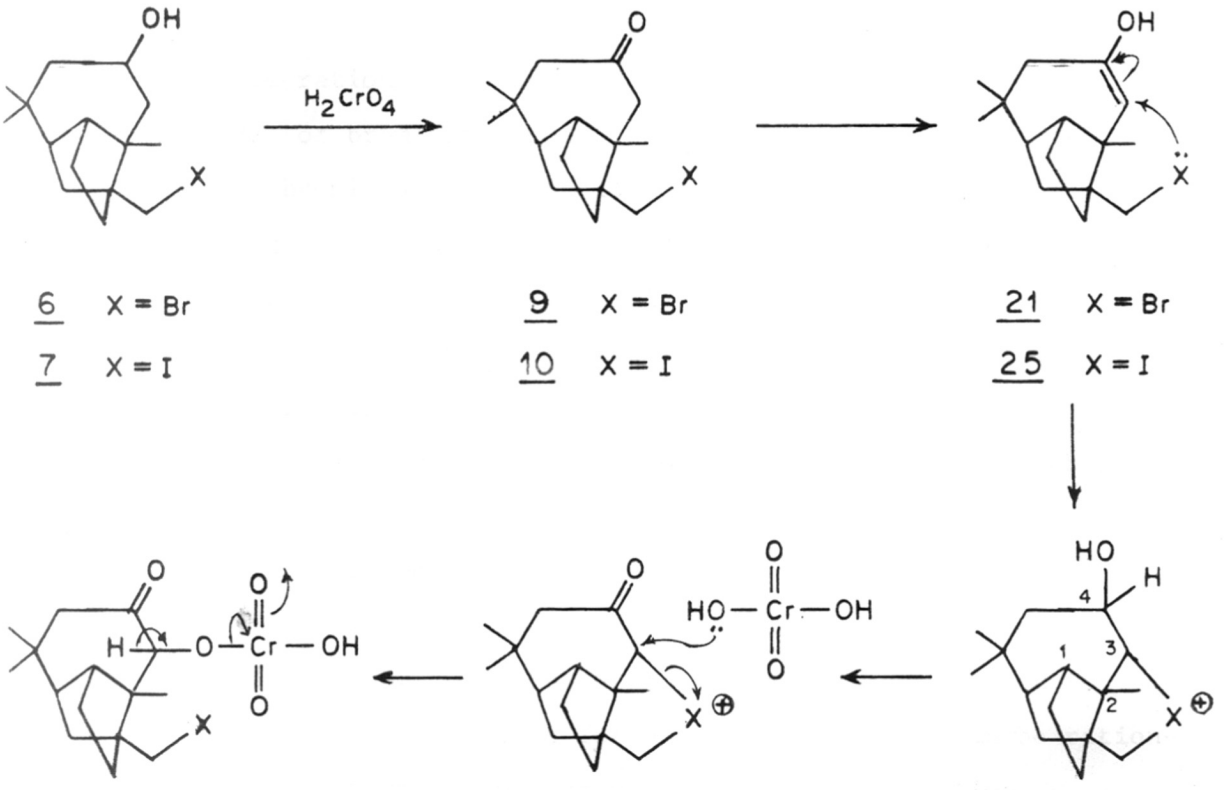



19 R = H
20 R = Me

reported[3b] the formation of a unique lactone-acid (bromine-free, 9%) but not discussed its structure. On the basis of spectral data of its methyl ester ($C_{16}H_{24}O_4$, $M^+$ 280) it is now formulated as 15 (ester; acid 14). From its IR spectrum 15 is clearly a γ-lactone-ester (1780, 1730 $cm^{-1}$) and the base peak at m/z 207 in its mass spectrum can be explained by fragmentation of the lactone moiety in 15 as shown in 15a (i.e., $M^+ - CH_3 - CH_2OCO$). When the non-bromoalcohol[4] 5 was similarly oxidised with excess of Jones reagent, the resulting product was simply the monoketone 8 without evidence of any diketone 11/ lactone-acid 14, thus indicating neighbouring group assistance by the bromine atom sterically located as in 6 for the observed products formation (bromodiketone 12 ⟶ lactone-acid 14) in this case. In a comparative study, the iodoalcohol 7 was also subjected to Jones oxidation under similar conditions. As in the case of the bromoalcohol 6 which generated the unusual bromodiketone 12 (42%), oxidation of 7 with excess of reagent for a prolonged period also gave the abnormal iododiketone 13 (26%) in the neutral part; more interesting, however, was the isolation of an iodine-free diacid 19 (19%) from the alkali soluble part in contrast to the lactone-acid 14 resulting from the bromo-analogue 6 .

Mechanistically, the anchimeric assistance[5] by the halogen atom in the Jones oxidation of the bromoalcohol 6/

SCHEME — 1




6 X = Br
7 X = I

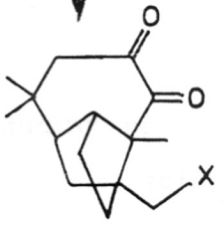
9 X = Br
10 X = I

21 X = Br
25 X = I

22 X = Br
26 X = I

23 X = Br
27 X = I

24 X = Br
28 X = I

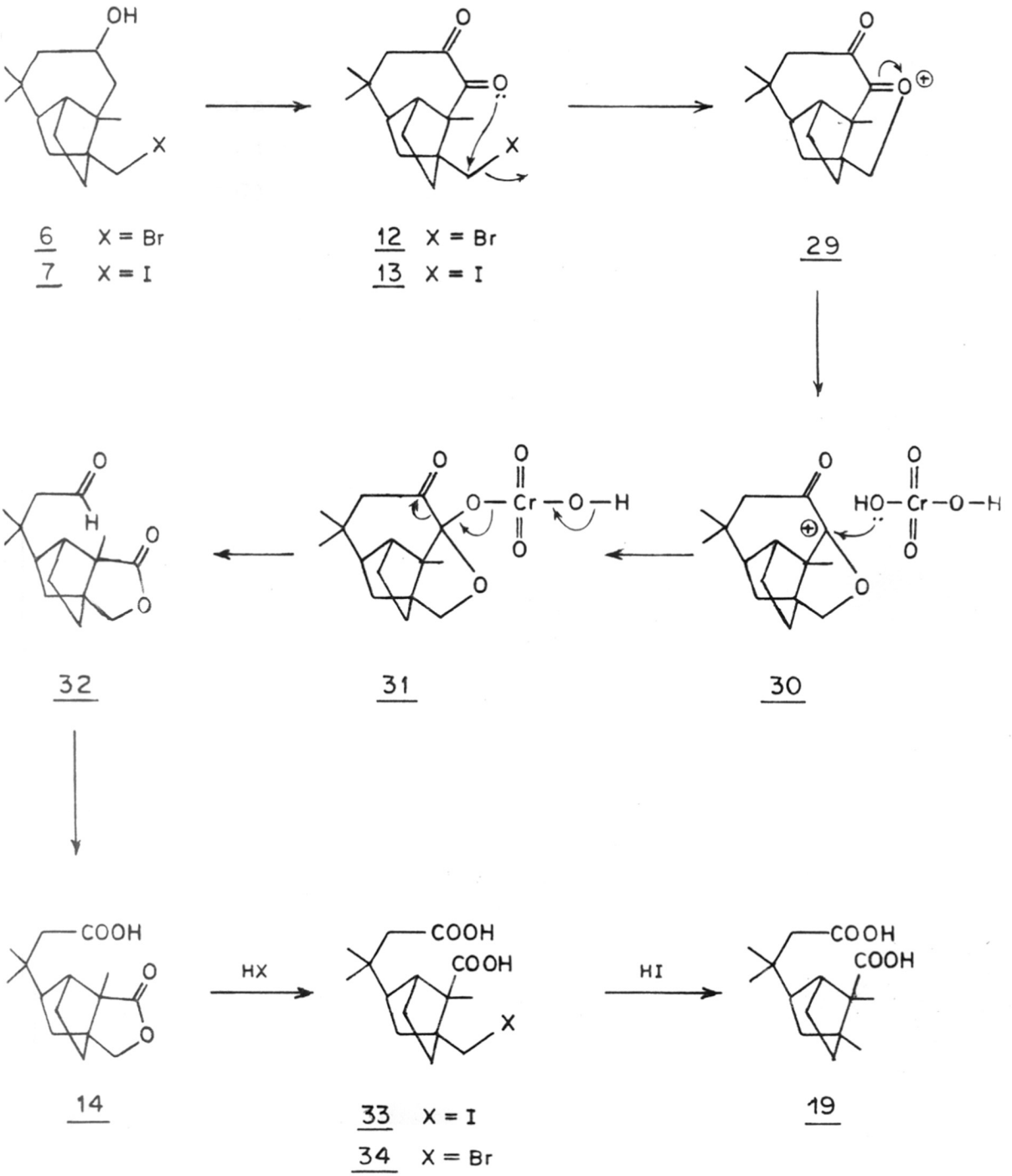


12 X = Br
13 X = I

iodoalcohol 7 to the bromodiketone 12/iododiketone 13 can be rationalized as in Scheme 1. The enolic form 21/25 of bromomonoketone 9/iodomonoketone 10 (resulting from chromic acid[6] oxidation of 6/7) generates the hydroxyhalogenonium ion 22/26 as a consequence of neighbouring group participation by the spatially well-disposed halogen atom, thus activating the C-3 site in 21/25 for attack by chromic acid (cf 23/27) to generate the bromodiketone 12/iododiketone 13 via 24/28. In conformity with Scheme 1, when preformed bromomonoketone 9 was treated with Jones reagent, it afforded the bromodiketone 12 in 62% yield.

Formation of the halogen-free lactone-acid 14/diacid 19 from the bromoalcohol 6/iodoalcohol 7 when exposed to excess of Jones reagent for an extended period can be rationalized in terms of neighbouring group participation by carbonyl oxygen[7] of the initially-formed bromodiketone 12/iododiketone 13 (Scheme 2). While the mechanistic pathway is common for both 12/13 upto lactone-acid 14 as elaborated in Scheme 2, a departure can be invoked at this point. In the case of the iodo compound 13, HI liberated in the reaction displaces iodine in the lactone-cleaved iododiacid 33 by hydrogen, thus generating the iodine-free diacid 19; this reducing property is typical of only HI[8] (not of HBr). Failure to isolate any bromodiacid 34

## SCHEME – 2




6 X = Br
7 X = I

12 X = Br
13 X = I

29

30

31

32

14

33 X = I
34 X = Br

19

indicates that it prefers to relactonise to 14. It must also be mentioned here that when preformed bromodiketone 12 was oxidised with excess of Jones reagent, lactone-acid 14 was formed to the extent of 28% besides unchanged 12 (40%).

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

Light petroleum refers to fraction b.p.60-80°. Solvent extracts were dried over anhydrous $Na_2SO_4$. Melting and boiling points are uncorrected; mp's were taken in capillaries on a Electrothermal melting point apparatus. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded as smears (liquids) or nujol mulls (solid) on a Pyc-Unicam SP-3 IR spectrophotometer. PMR spectra were obtained on a Varian T-60/FT-80A/Bruker WH-90 spectrometers and mass spectra on a CEC spectrometer model 21-110B, using an ionising voltage of 70 eV and a direct inlet system.

ω-Bromolongifolene 2/ω-Iodolongifolene 3. These were prepared[9] by methods reported by Suryawanshi and Nayak.

12-Bromolongibornane-4-ol 6 This was prepared[3b] by the method reported earlier.

12-Iodolongibornane-4-ol 7

To a stirred solution of TFA (48 ml, 69 g, 0.6 mol) cooled to 5°-10° in a bath of ice water was added dropwise a solution of ω-iodolongifolene 3 (48 g, 0.14 mol) in $CH_2Cl_2$ (200 ml) during 1 hr; stirring was continued for 24 hr at room temperature. The mixture was quenched in ice-cold aqueous $Na_2CO_3$ solution, the organic layer separated and aqueous portion extracted with fresh $CH_2Cl_2$ (3 x 100 ml). The combined organic extract was washed with brine, dried and

solvent removed. The crude mixture in ethanol (100 ml) was hydrolysed with 15% aqueous ethanolic KOH (50 g of KOH in 30 ml of water and 400 ml of EtOH) at room temperature overnight. After removing most of the ethanol, the mixture was diluted with water (1 litre), extracted with EtOAc (3 x 150 ml), washed with brine, dried and solvent removed. The crude product (TLC: 2 spots) was resolved on a column of silica gel: Fr. 1, light petroleum, 5 x 200 ml, mixture of iodoolefins 4 (16 g, 33%). Fr. 2, light petroleum-benzene (1:1), 5 x 200 ml, mixture. Fr. 3, ethyl acetate, 4 x 200 ml, iodoalcohol 7 (15 g, 30%), m.p.117° (pet.ether). IR (Nujol): 3370, 1190, 1005, 605. PMR ($CDCl_3$): $\delta$ 4.08 (m, 1H, C<u>H</u>-OH), 3.26 (q, J=14 Hz, C<u>H</u>$_2$-I), 0.94, 0.89, 0.88 (3H each, <u>tert</u>-Me's). MS: m/z 348 ($M^+$), 203 (base peak, M-18-127). (Found: C, 52.2; H, 7.4; I, 35.1. $C_{15}H_{25}OI$ requires C, 51.7; H, 7.2; I, 36.5%).

<u>Anomalous Jones oxidation of bromoalcohol 6: Formation of 12-bromolongibornane-3,4-dione 12 and lactone-acid 14</u>

Bromoalcohol 6 (129 g, 0.43 mol) in acetone (600 ml) was oxidised with excess of Jones reagent while stirring and cooling the flask in ice water; eight 100 ml portions of the reagent were added at intervals of 24 hr. The mixtures was diluted with water, extracted with EtoAc (3 x 500 ml) and separated into acid (9 g; 9% <u>vide infra</u>) and neutral (105 g) by extraction with 10% aqueous $Na_2CO_3$ solution. The neutral material solidified and was recrystallized from light petroleum to give colourless needles of bromodiketone 12, m.p.106-110°

(29 g). The residue from the filtrate was chromatographed on a column of $SiO_2$ gel/IIa (2.1 kg): Fr. 1, light petroleum, 4 x 500 ml, mixture of bromoolefins (19 g). Fr. 2, light petroleum-benzene (1:1), 6 x 500 ml, bromodiketone 12 (19 g, total yield = 29 + 19 = 48 g, 42%). Fr. 3, benzene, 4 x 500 ml, mixture 9 + 12. Fr. 4, benzene-ethylacetate (9:1), 4 x 500 ml, bromomonoketone 9 (6 g, 6%).

The crude acid (obtained by acidification of above aqueous $Na_2CO_3$ extract) was recrystallized from EtoAc to furnish colourless prisms of lactone-acid 14, m.p.149-151°. Its methyl ester 15 (prepared by diazomethane method) was a liquid b.p.180°(bath)/0.2 mm. IR(smear): 1780 ($\gamma$-lactone), 1730 (COOMe), 1235, 975. PMR ($CCl_4$): $\delta$ 3.93 (s, 2H, $-C\underline{H}_2OCO$); 3.46 (s, 3H-$COOC\underline{H}_3$); 2.05 (s, 2H, $-C\underline{H}_2COOCH_3$); 1.20 (s, 3H, $C\underline{H}_3$-C-COO-); 0.90, 0.86 (two singlets, 3H each, tert -Me's). MS: m/z 280 ($M^+$); 207 (base peak). (Found: C, 68.3; H, 8.6. $C_{16}H_{26}O_4$ requires: C, 68.6; H, 8.6%).

Hydrolysis of lactone-acid 14: Formation of hydroxy diacid 16 hydroxy diester 17

A mixture of lactone-acid 14 (3 g) and 10% aqueous KOH solution (100 ml) was heated on a waterbath for 1 hr. The mixture was cooled, acidified with dil HCl, extracted with EtoAc, washed with brine, dried and solvent removed. The crude hydroxy diacid was esterified with ethereal $CH_2N_2$ and the resulting product (TLC: 2 spots) was chromatographed on $SiO_2$ gel; Fr. 1, benzene-EtoAc (9:1), 2 x 100 ml, lactone

ester 15. Fr. 2, benzene-EtoAc (1:1), 5 x 50 ml, hydroxy-dimethyl ester 17; b.p. 170°(bath)/1 mm (0.9 g). IR (smear): 3480, 1740, 1285, 1140, 1035. PMR($CCl_4$): $\delta$ 3.48 (s, 6H, $COOCH_3$ x 2) 3.40 (q, 2H, $CH_2OH$, J = 10 Hz); 2.03 (s, 2H, $CH_2COOCH_3$); 1.1, 0.83 x 2 (three tertiary Me singlets). MS: m/z 312 ($M^+$). (Found: C, 65.4; H, 8.9. $C_{17}H_{28}O_5$ requires: C, 65.4; H, 9.0%).

On treatment with $Ac_2O$-pyridine 17 gave the mono-acetate 18 as a colourless liquid b.p. 190°(bath)/2 mm. IR (smear): 1750, 1735, 1140, 1045. PMR ($CCl_4$): $\delta$ 4.40 (q, 2H, $CH_2OAc$, J=12 Hz); 3.43 (s, 3H, $COOCH_3$); 2.1 (s, 2H, $CH_2COOCH_3$); 2.0 (s, 3H, $OCOCH_3$); 1.20 (s, 3H, $CH_3$-$\overset{|}{\underset{|}{C}}$-COOMe); 2 x 0.85 (two tertiary methyls). (Found: C, 64.7; H, 8.9. $C_{19}H_{30}O_6$ requires: C, 64.4; H, 8.5%).

Jones oxidation of bromomonoketone 9: Formation of bromo-diketone 12

Pure bromomonoketone 9 (2 g) in acetone (20 ml) was treated with Jones reagent (20 ml) and stirred at room temperature for 6 hr. The mixture was worked up as usual. The neutral part gave a solid, which on recrystallisation from light petroleum, afforded the bromodiketone 12 (1.4 g, 67%) identified by m.p., IR/PMR).

Jones oxidation of bromodiketone 12: Formation of lactone-acid 14

Pure bromodiketone (2 g) in acetone (20 ml) was treated with excess of Jones reagent; four 10 ml portions of reagent was added at intervals of 24 hr, while stirring at room temperature. The mixture was diluted with water, extracted with EtOAc and separated into neutral and acid parts by extraction with 10% aqueous $Na_2CO_3$ solution. The acid (0.5 g, 28%) was identified as the lactone-acid 14 (m.p., IR/PMR) while the neutral part identified as unchanged bromodiketone 12 (0.8 g, 40%).

Anomalous Jones oxidation of iodolacohol 7: Formation of 12-iodolongibornane-3,4-dione 13 and diacid 19

Iodoalcohol 7 (7 g) in acetone (150 ml) was treated with excess of Jones reagent while stirring and cooling the mixture in ice water; four 20 ml portions of reagent were added at intervals of 12 hr. The mixture was diluted with water, extracted with EtoAc and separated into acid (1.1 g, 19%) and neutral (2 g, 26%) by extraction with 10% aqueous $Na_2CO_3$ solution. The neutral solid was recrystallized from light petroleum to furnish colourless needles of iododiketone 13, m.p.136-38°. IR (Nujol): 1690, 1190, 980. PMR ($CCl_4$): $\delta$ 3.43 (q, 2H, $CH_2I$, J=10 Hz); 1.16, 1.13, 1.03 (three tertiary methyl singlets). MS: m/z 360 ($M^+$).

(Found: C, 50.0; H, 5.9; I, 33.2. $C_{15}H_{21}O_2I$ requires: C, 50.0; H, 5.8; I, 35.3%).

The solid acid (obtained by acidification of the above $Na_2CO_3$ extract) was recrystallized from acetonitrile to furnish colourless prisms of the diacid 19, m.p.169-171° (1.1 g, 19%). Its dimethyl ester (2 $CH_2N_2$ method) was a liquid b.p.160°(bath)/1 mm. IR(smear): 1730, 1235, 1135. PMR ($CCl_4$): δ 3.58, 3.53 (two s, 3H each, 2 x $COOCH_3$); 2.06 (s, 2H, $CH_2COOCH_3$); 1.18 (s, 3H, $CH_3$-C-COOMe); 1.08, 0.81 x 2 (three tertiary methyl singlets). MS: m/z 296 ($M^+$). (Found: C, 69.7; H, 9.7. $C_{17}H_{28}O_4$ requires: C, 68.9; H, 9.4%).

Normal Jones oxidation of iodoalcohol 7: 12-Iodolongibornane-4-one 10

Iodoalcohol 7 (2.2 g) in acetone (25 ml) was treated with Jones reagent till the reaction mixture was just orange. After only 10 min the mixture was worked up as usual; the neutral part solidified and was recrystallized from light ptroleum to furnish colourless needles of iodomonoketone 10 m.p.122-24° (0.7 g, 30%). IR (Nujol): 1685, 1310, 1190, 600. PMR ($CCl_4$): δ 3.16 (q, 2H, $CH_2I$; J=10 Hz); 1.06, 1.00, 0.91 (three tertiary methyl singlets) (Found: C, 52.3; H, 6.9; I, 34.5. $C_{15}H_{23}OI$ requires: C, 52.0; H, 6.7; I, 36.7%).

Normal Jones oxidation of bromoalcohol 6; 12-Bromo-longibornane-4-one 9

Bromoalcohol 6 (3.45 g) in acetone (35 ml) was treated with Jones reagent till the mixture was just orange. After only 5 min the mixture was diluted with water, extracted with EtoAc (3 x 50 ml), washed with 10% aqueous $Na_2CO_3$, brine, dried and solvent removed. The crude solid was recrystallized from light petroleum to furnish colourless needles of 12-bromolongibornane-4-one 9, m.p.72° (1.4 g, 41%) identified[3b] by IR/PMR.

# REFERENCES


1 a) Sukh Dev, Prog Chem Org Nat Prod 40 (1981) 73.

b) Lamture J B & Nayak U R, Indian J Chem 22B (1983) 993.

2 Yadav J S, Chawla H P S, Sukh Dev, Prakasa Rao A S P & Nayak U R. Tetrahedron 33 (1977) 2441.

3 a) Mehta G & Kapoor S K, J org Chem 39 (1974) 2618.

b) Vaidya S P, Suryawanshi S N, Jadhav P K & Nayak U R, Indian J Chem (communicated).

4 Prahlad J R, Nayak U R & Sukh Dev, Tetrahedron 26 (1970), 663.

5 a) Capon B & McManus S P, Neighbouring Group Participation Vol 1 (Plenum Press, New York) 1976).

b) le Noble W J, Highlights of Organic Chemistry (Marcel Dekker, N Y) 1974, 690.

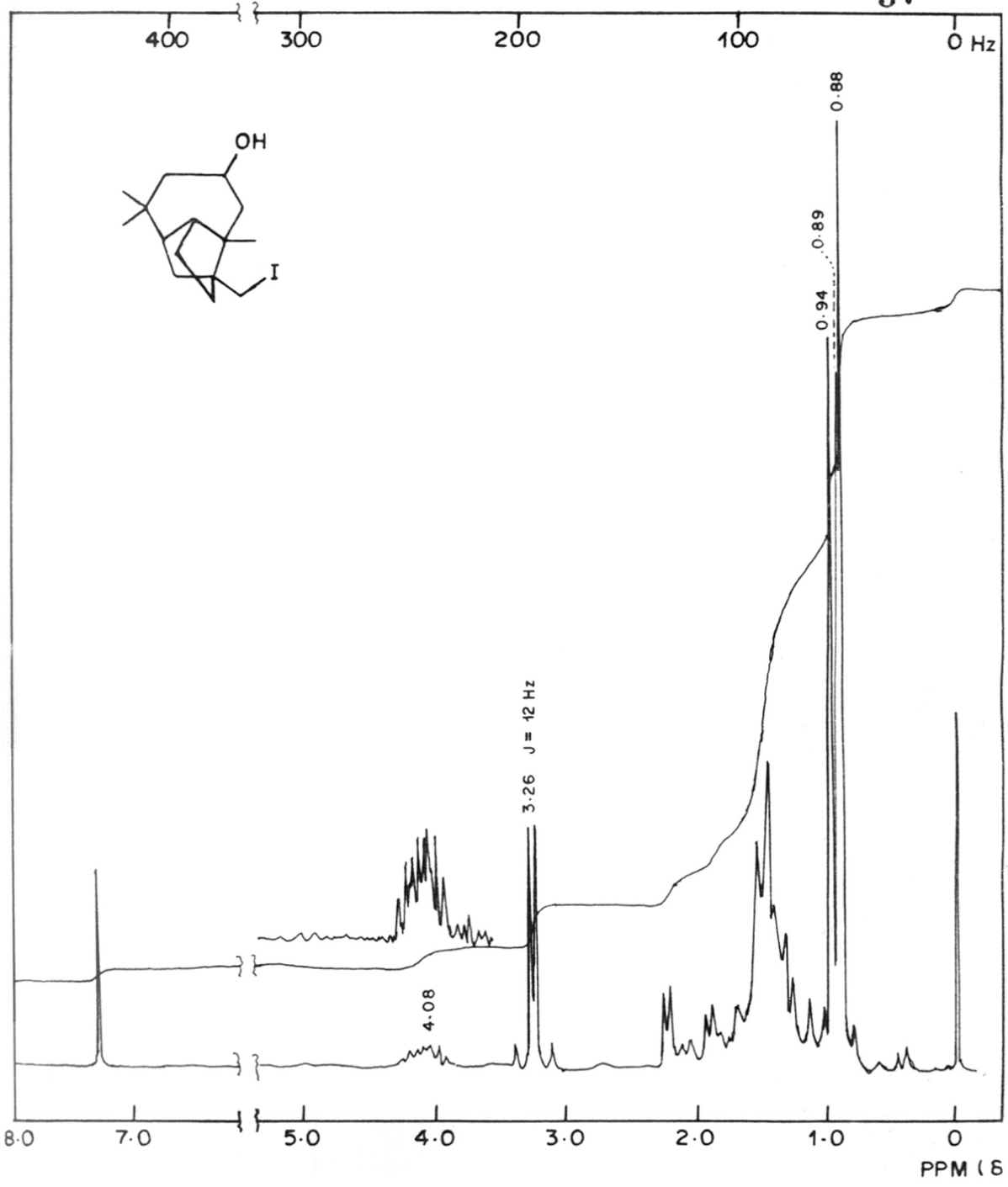
6 House H O, Modern Synthetic Reactions (Benjamin, California) 1972, 261.

7 Tanida H, Nishiya T & Irie T, J org Chem 44 (1979) 3337.

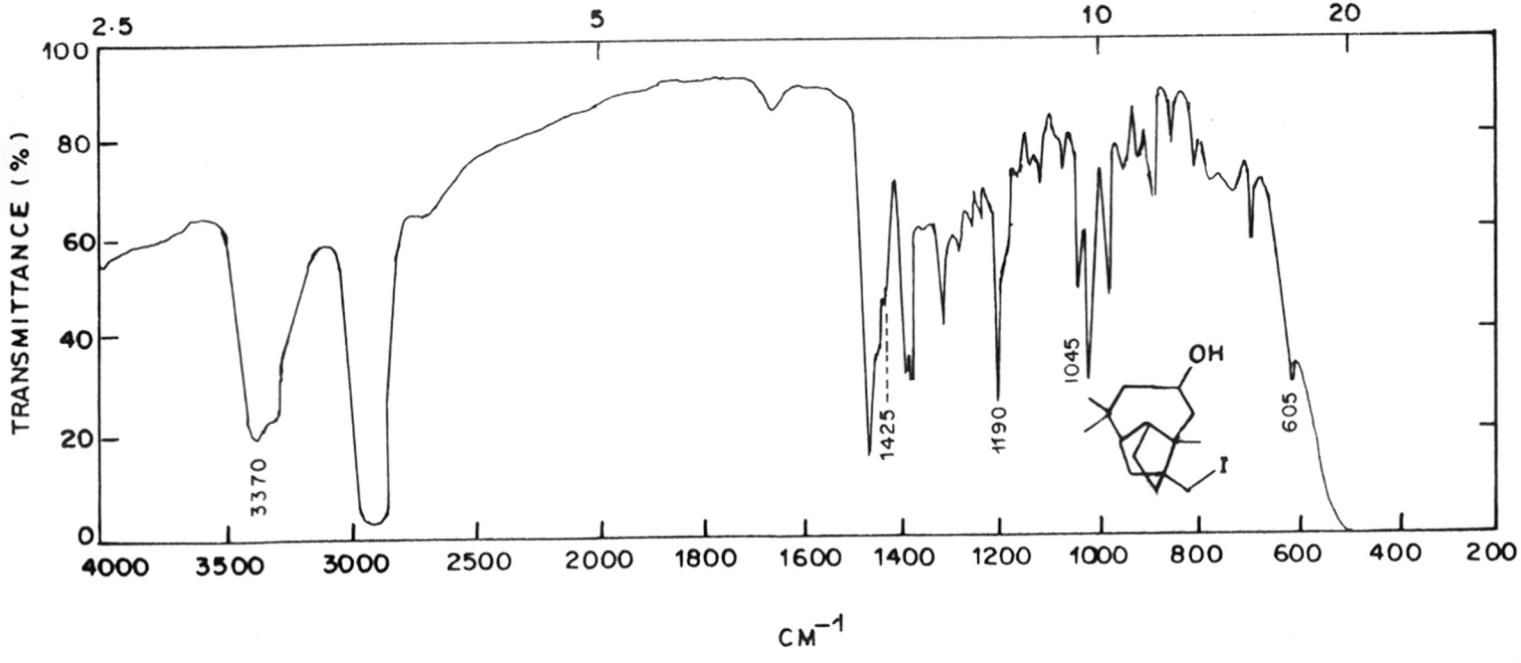
8 Fieser L F & Fieser M, Reagents for Organic Synthesis Vol. 1 (John Wiley, New York) 1967), 449.

9 Suryawanshi S N & Nayak U R, Indian J Chem 17B (1979) 304

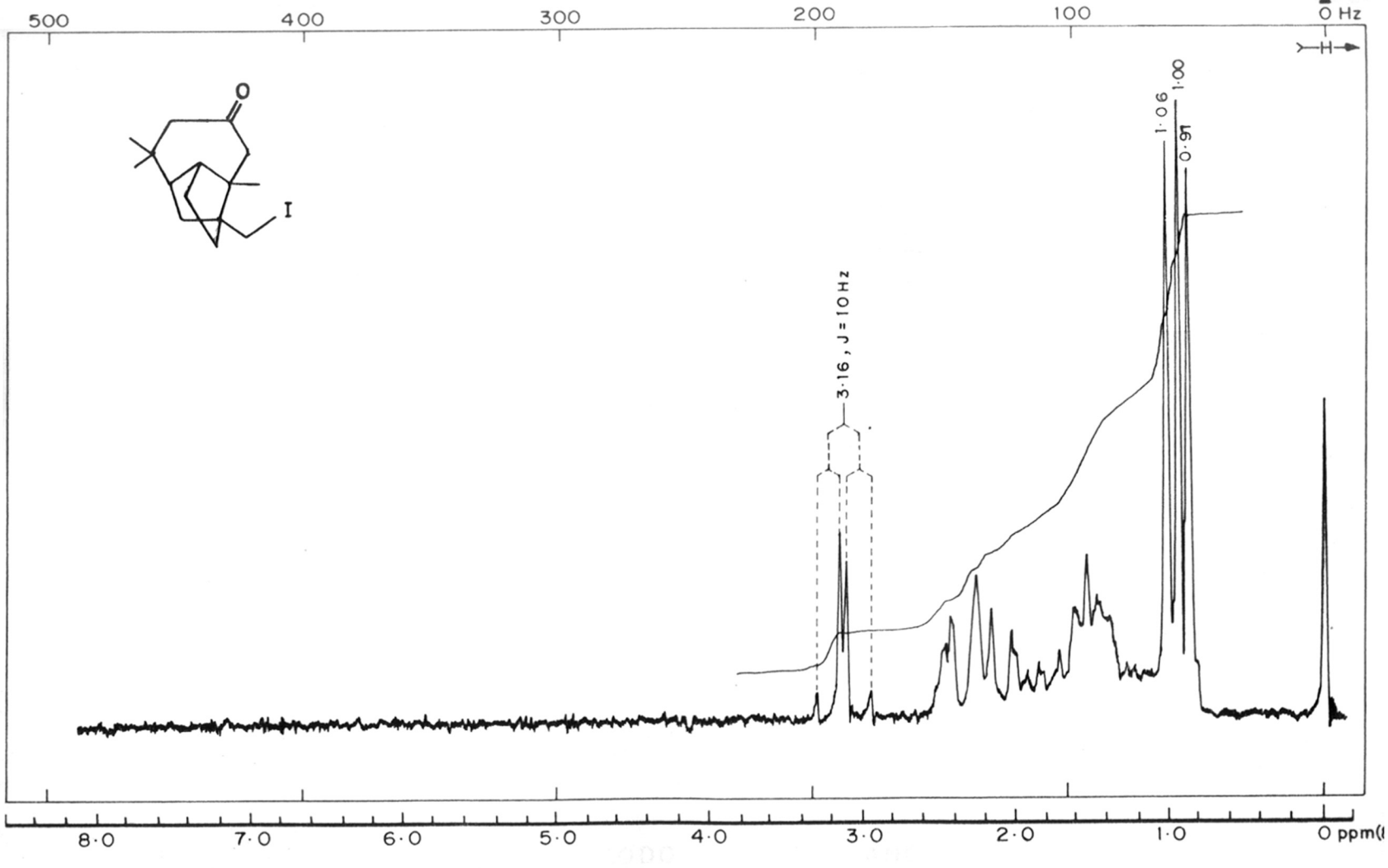
10 Bowden, Heilbron I M, Jones E R H & Weedon B C L, J Chem Soc (1946) 39.



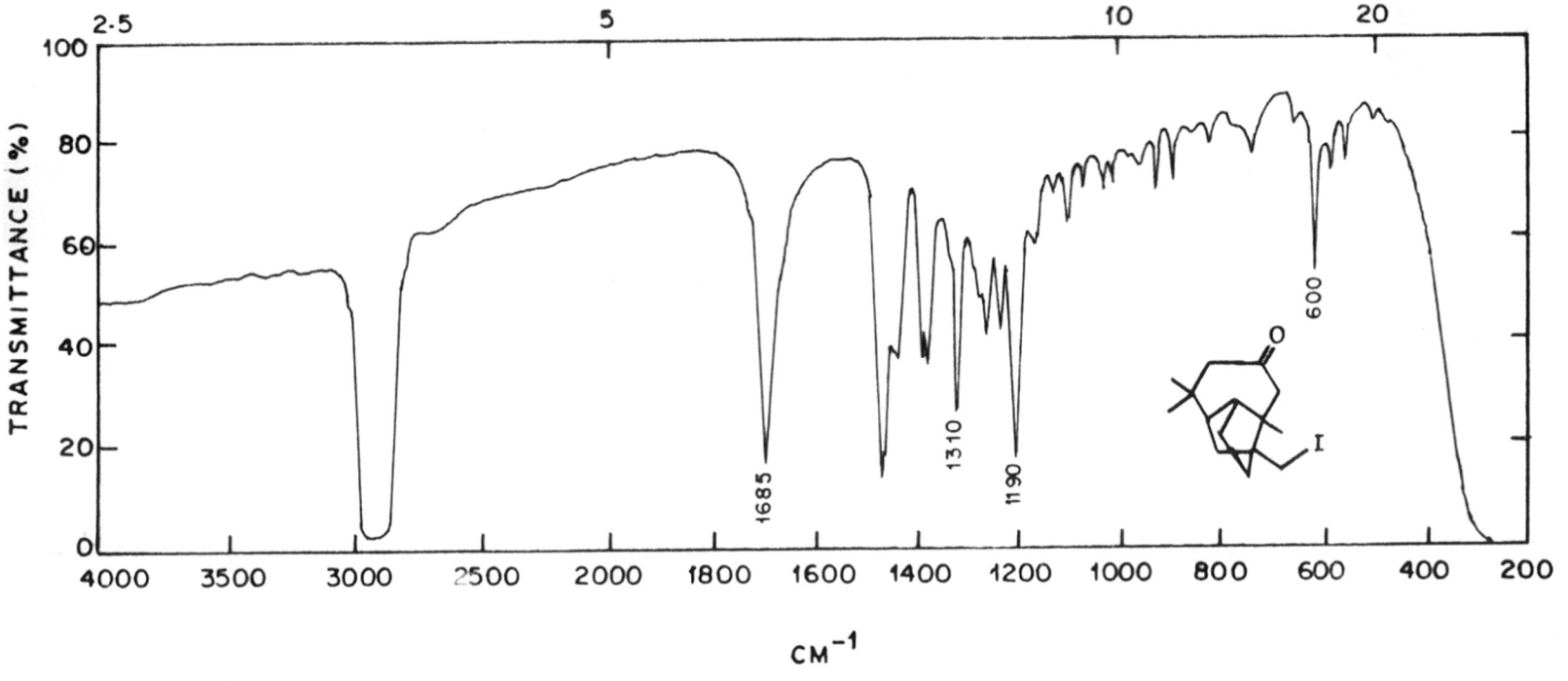

PMR SPECTRUM OF 12-IODOLONGIBORNANE-4-OL 7



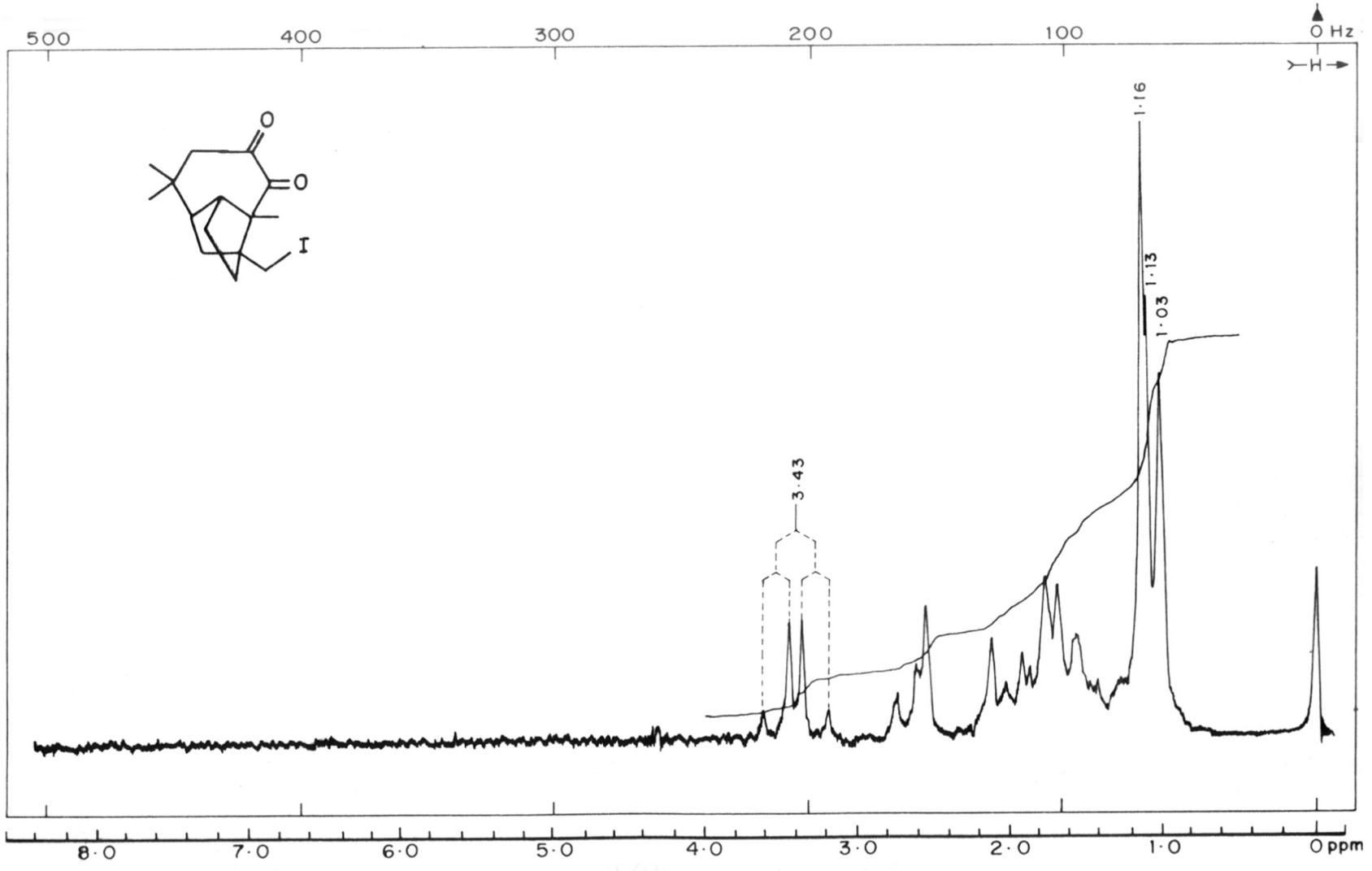

IR SPECTRUM OF 12-IODOLONGIBRNANE-4-OL 7



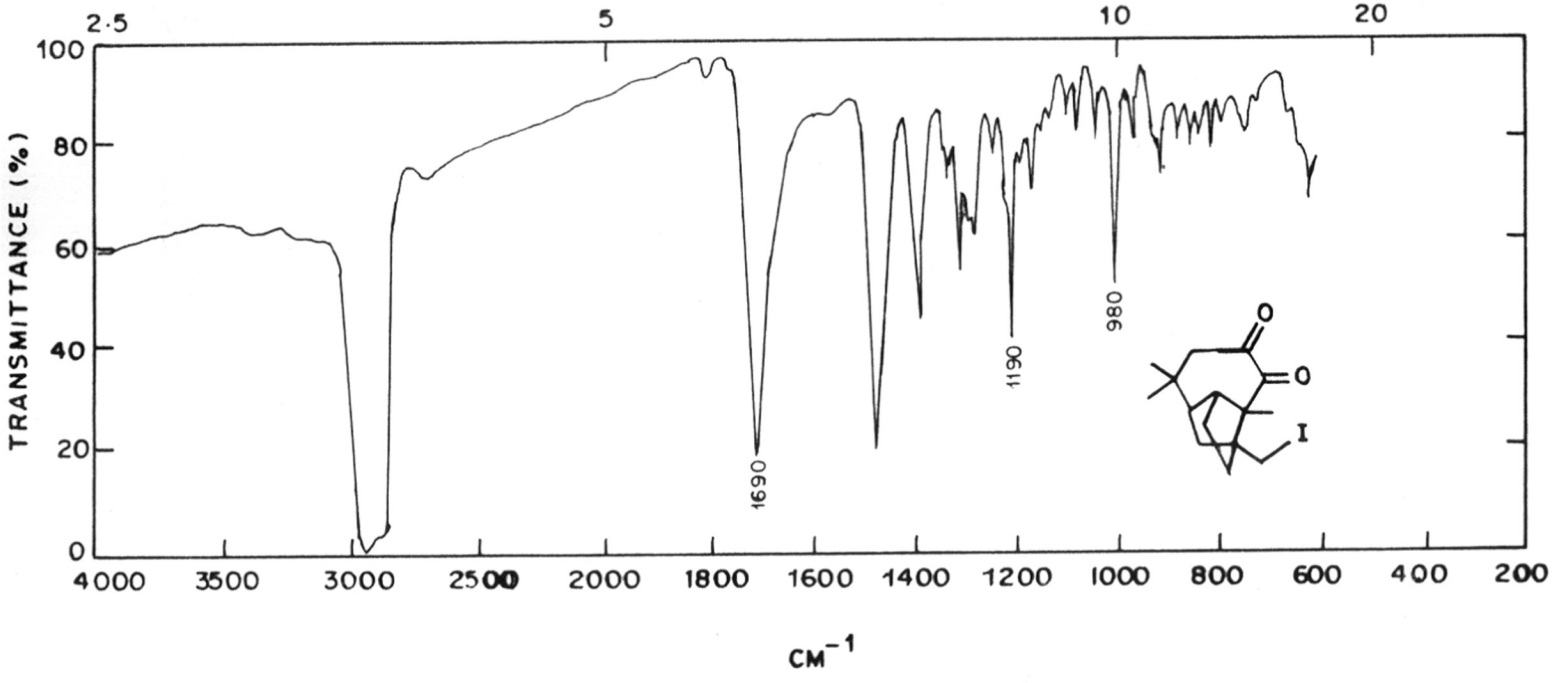

PMR SPECTRUM OF 12-IODOLONGIBRNANE-4-ONE 10



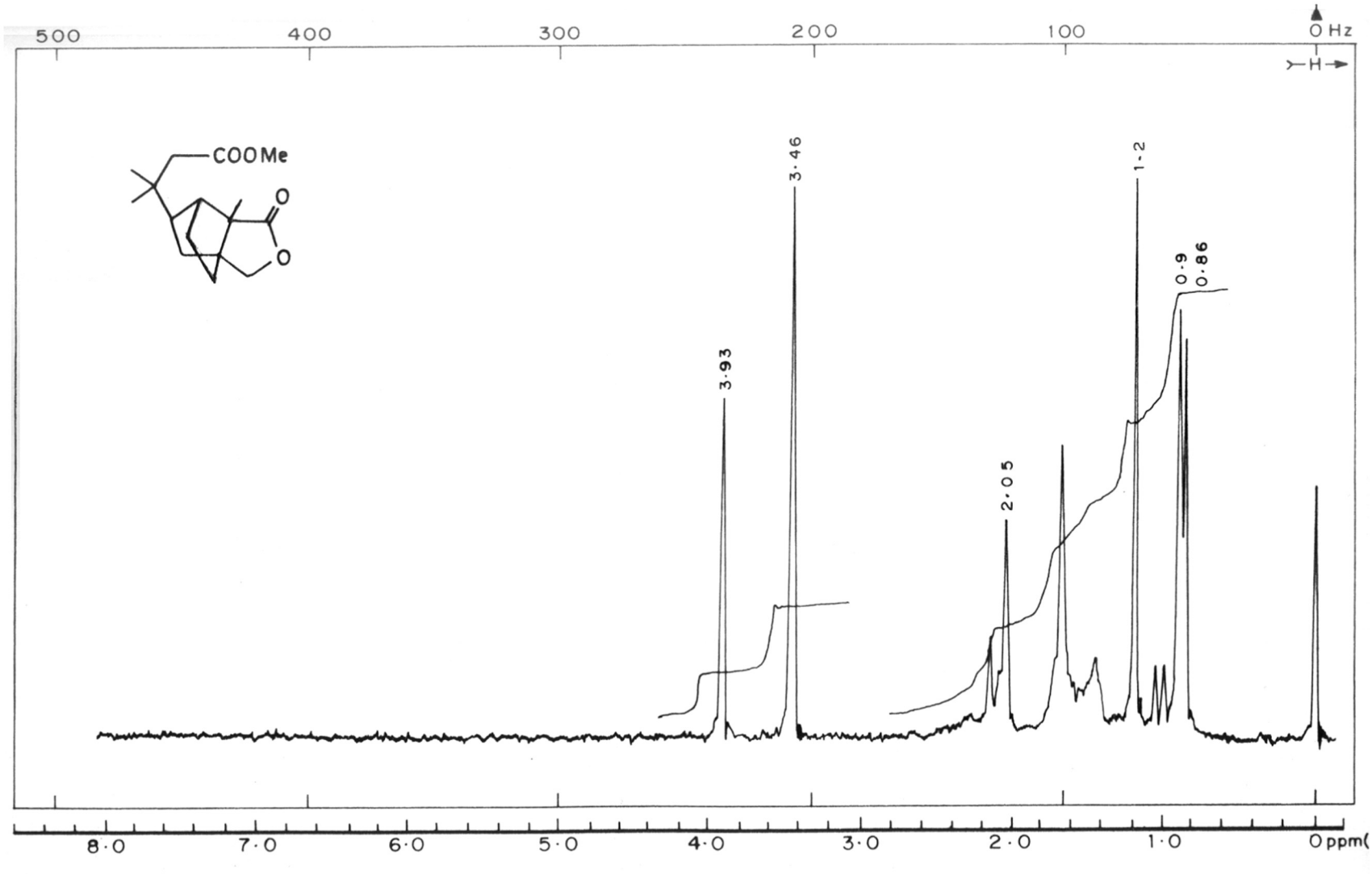

IR SPECTRUM OF 12-IODO LONGIBORNANE-4-ONE 10




PMR SPECTRUM OF 12-IODOLONGIBORNANE-3,4-DIONE 13

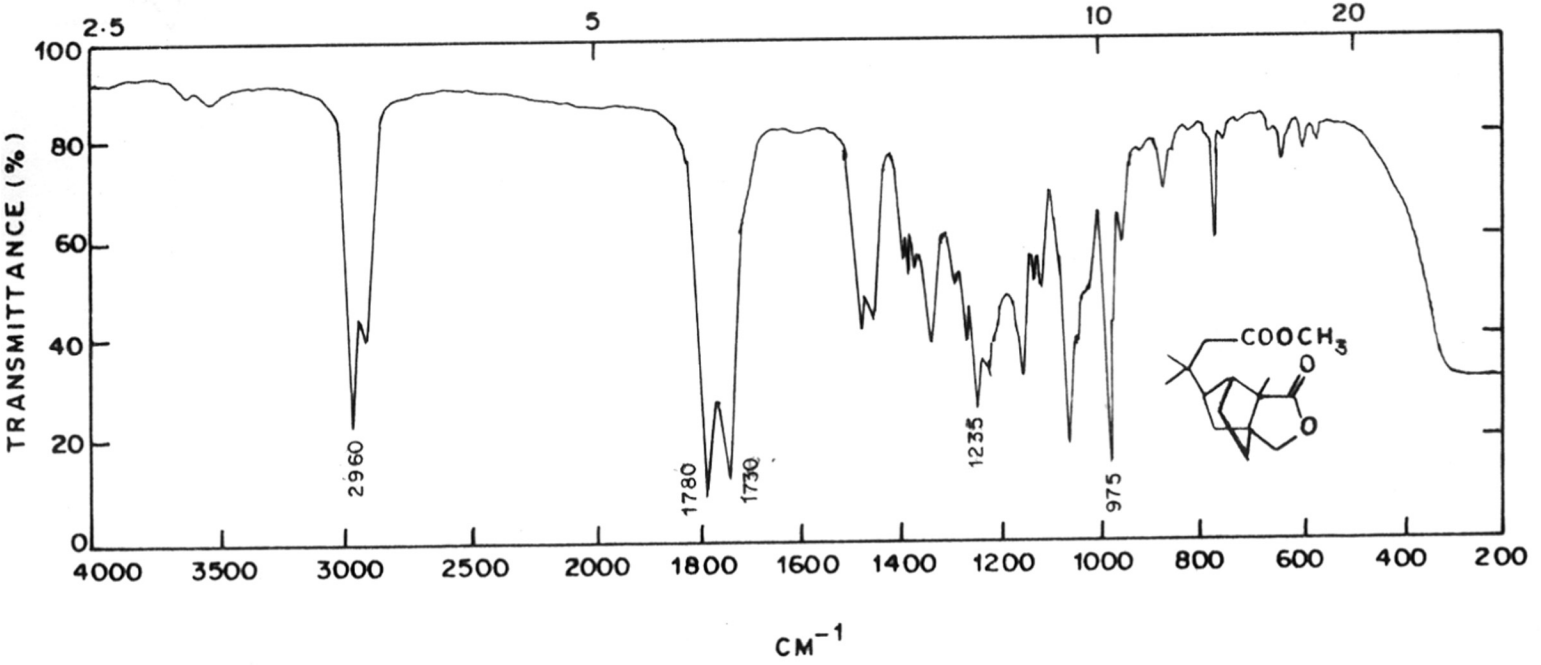



IR SPECTRUM OF 12-IODOLONGIBRNANE-3,4-DIONE 13






PMR SPECTRUM OF LACTONE ESTER 15

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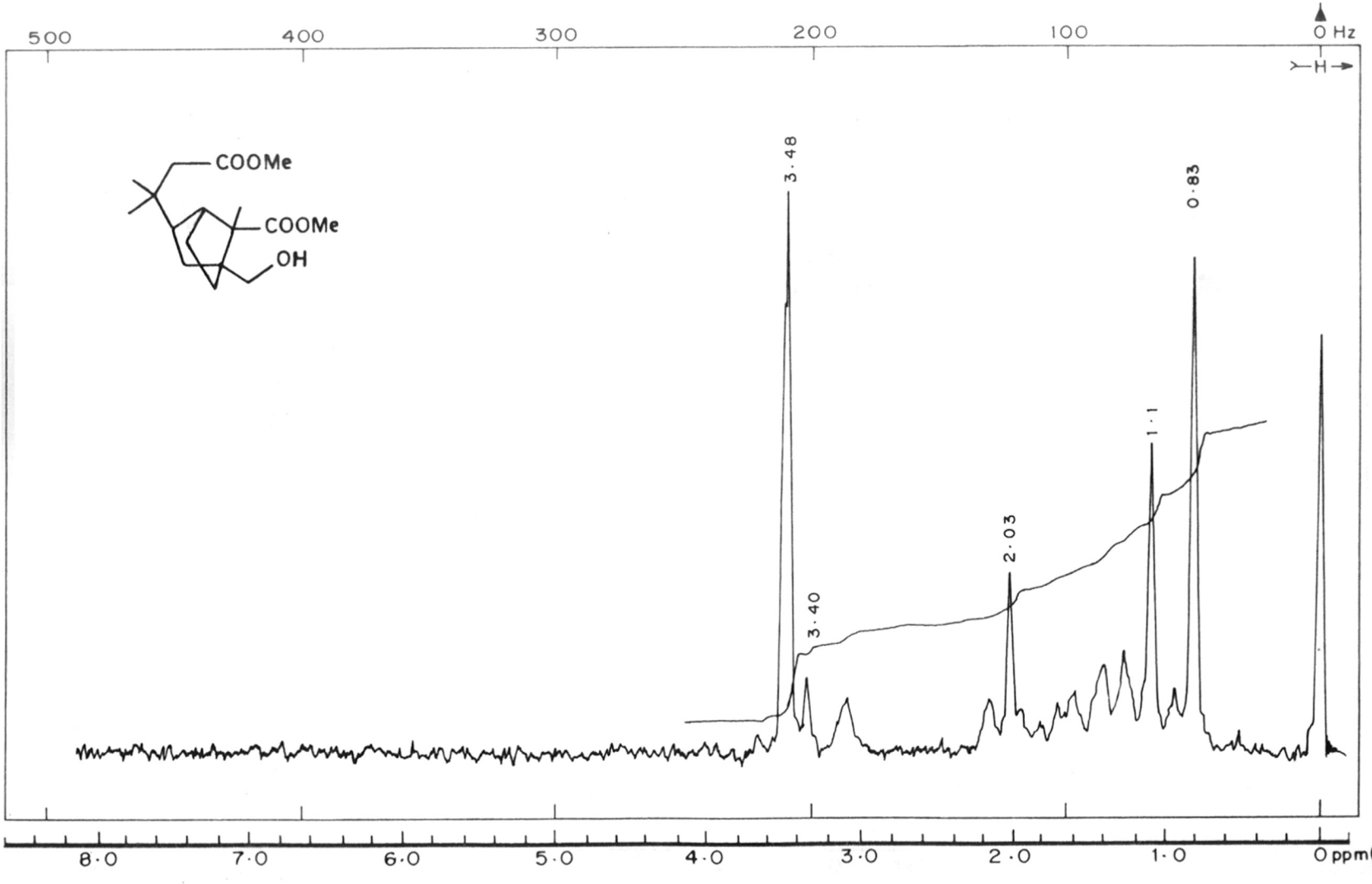
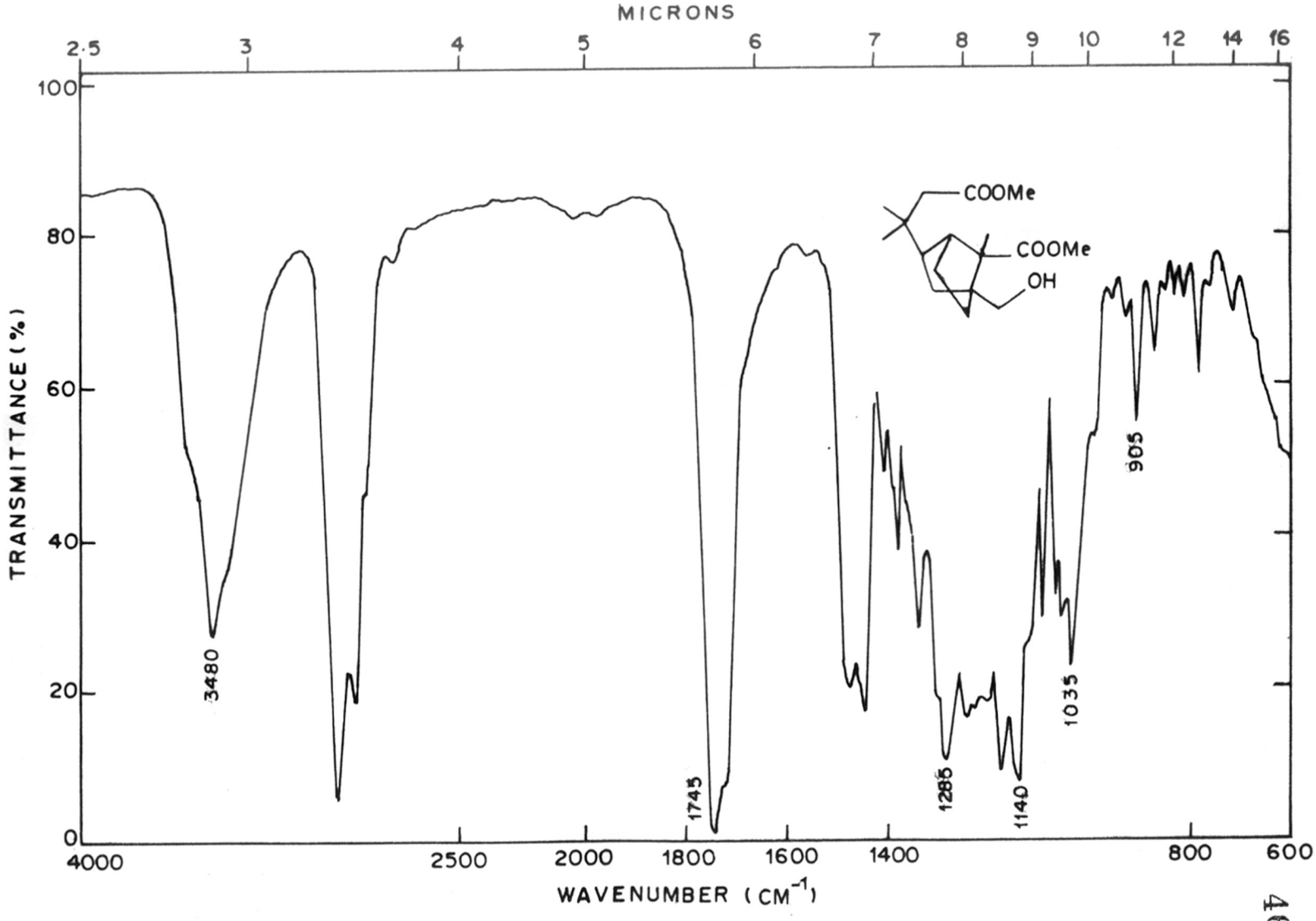



PMR SPECTRUM OF HYDROXY DIESTER 17

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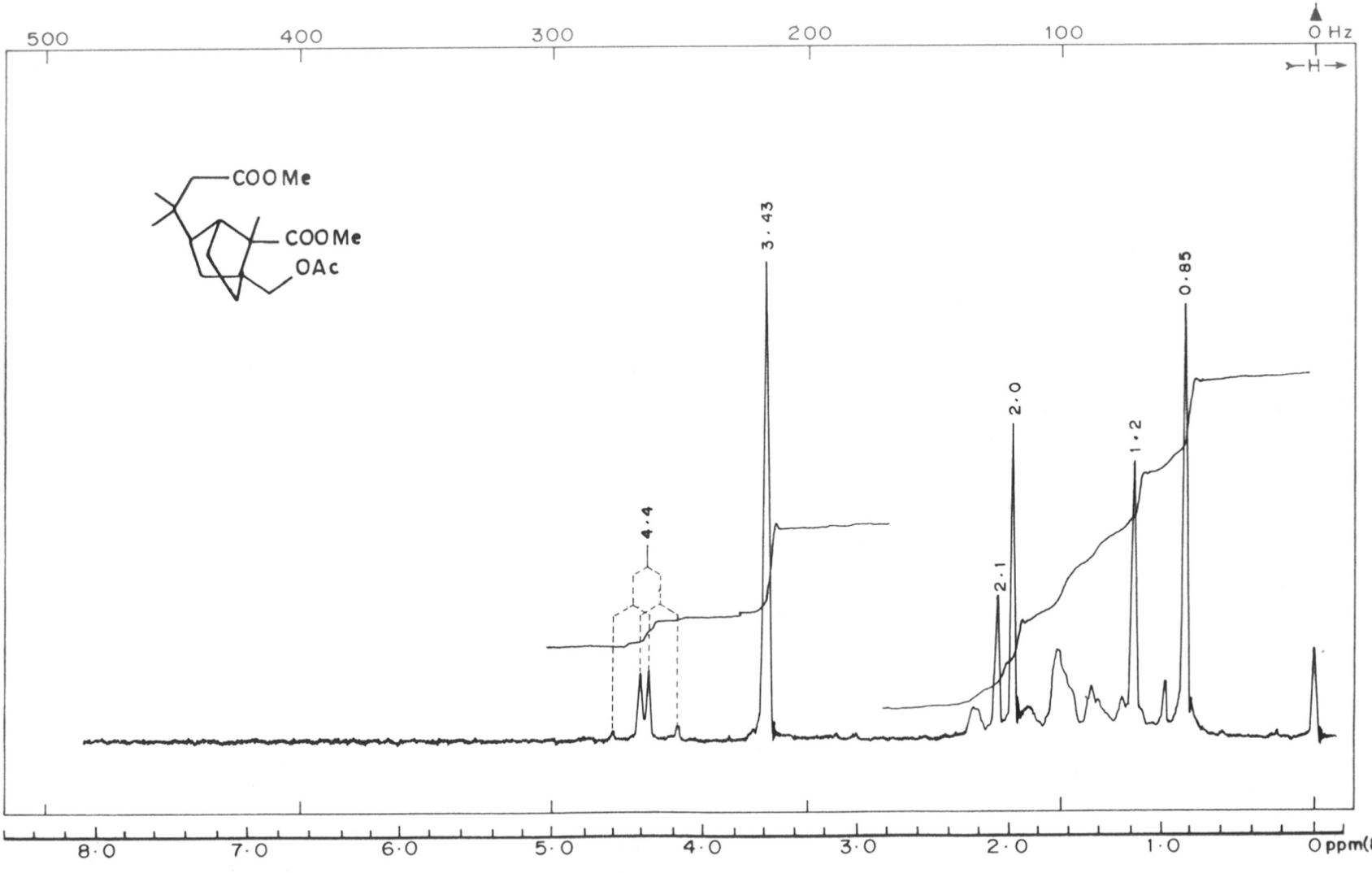
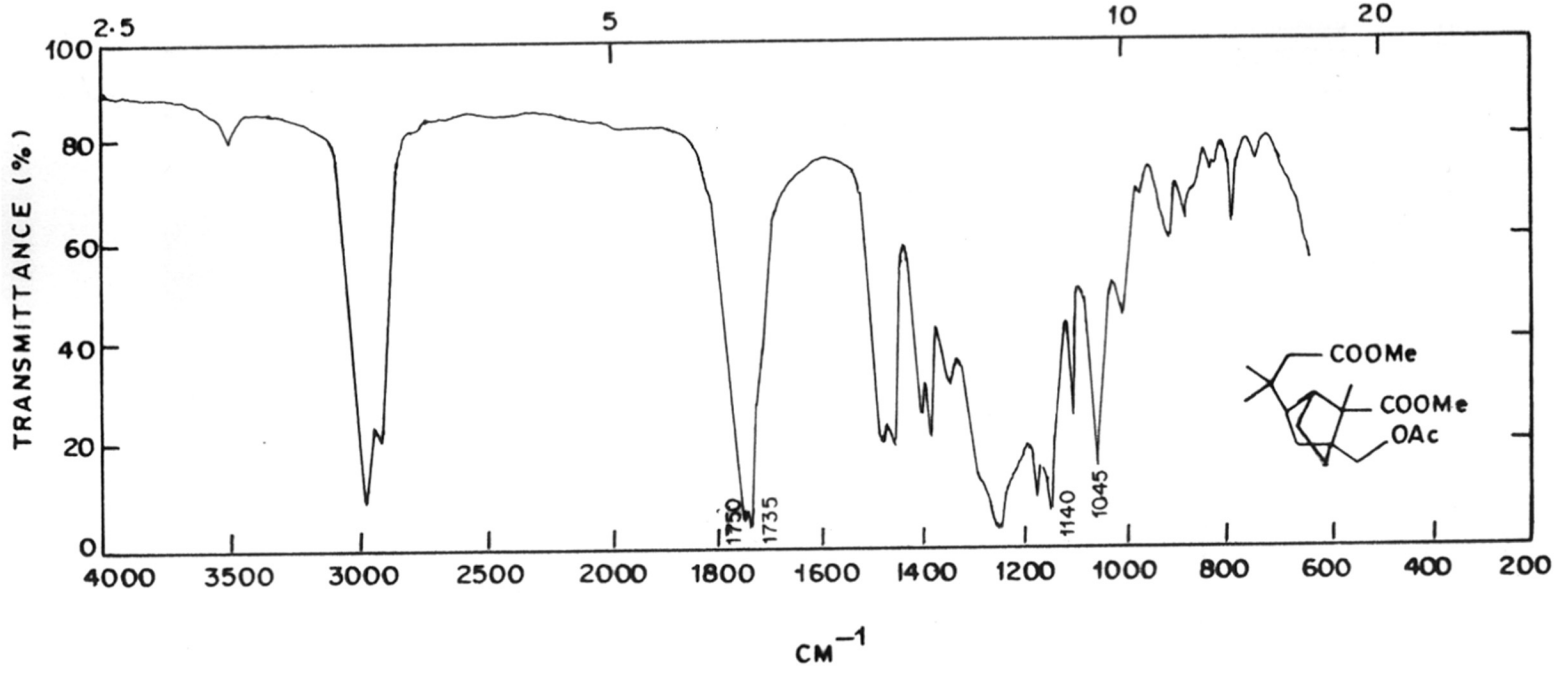



PMR SPECTRUM OF DIESTER ACETATE 18

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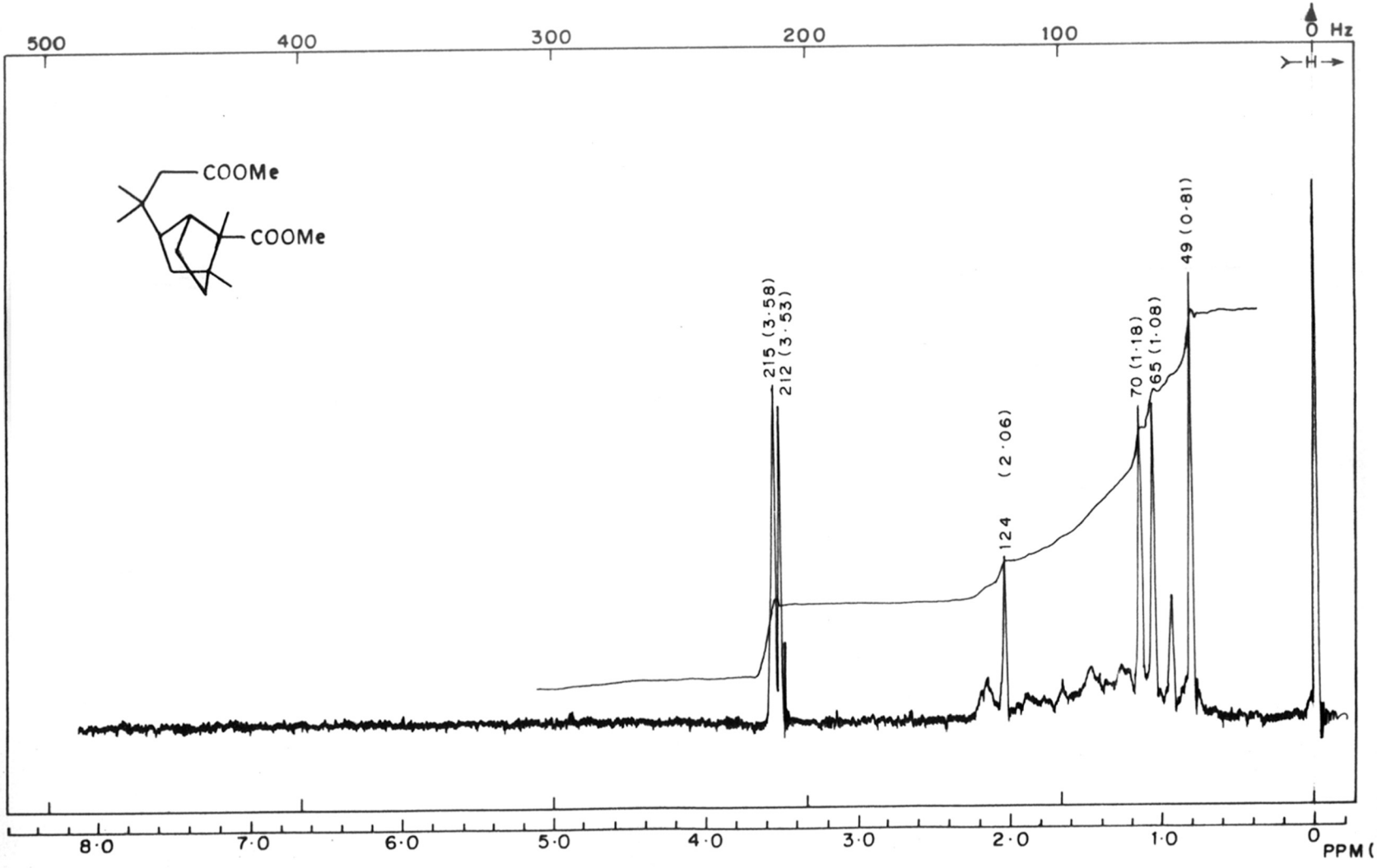
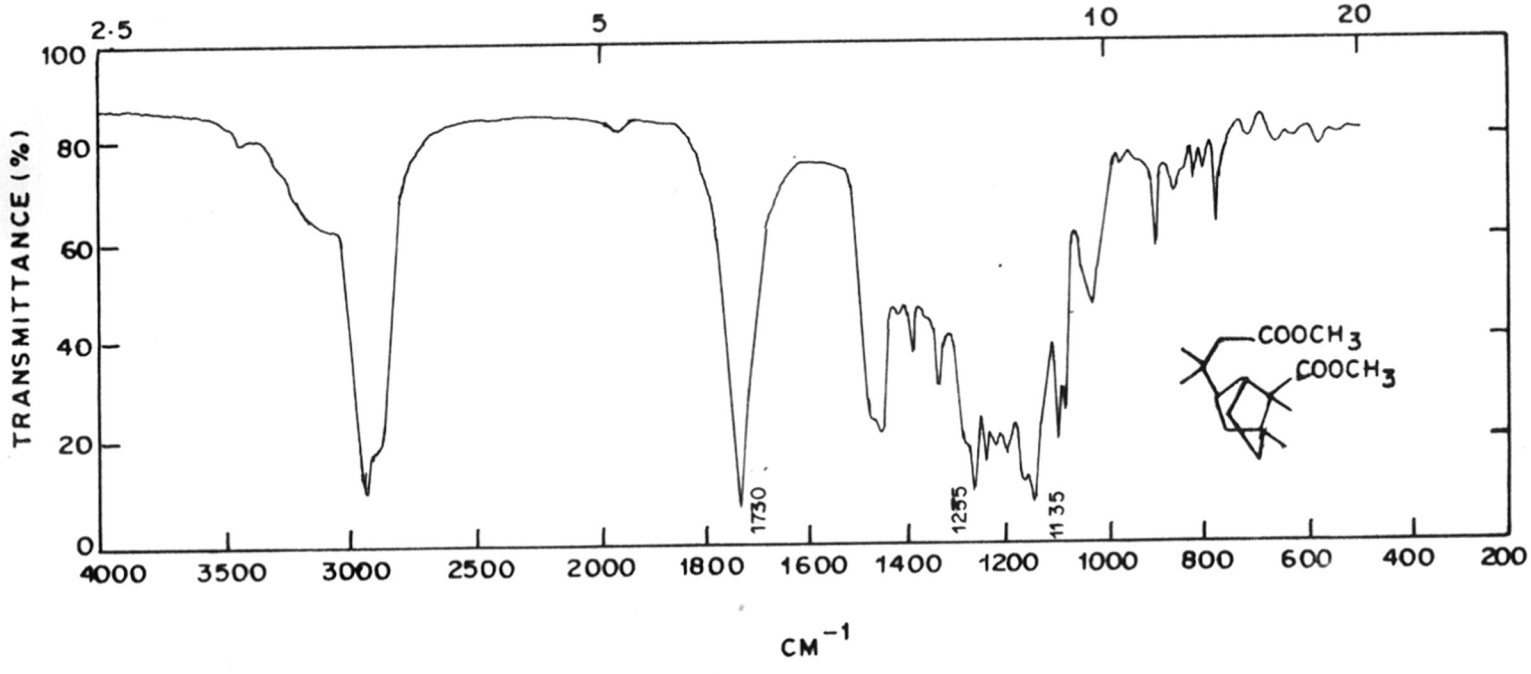



PMR SPECTRUM OF DIESTER 20




IR SPECTRUM OF DIESTER 20

# CHAPTER-3

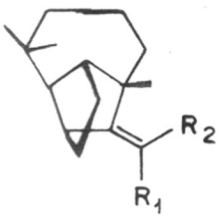
## NEIGHBOURING GROUP PARTICIPATION BY CARBONYL OXYGEN IN THE LONGIBORNANE SYSTEM : UNIQUE REACTIVITY OF 12-BROMOLONGIBORNANE 3,4-DIONE

## A B S T R A C T

The placement of a keto group at C-3 in 12-bromolo-longibornane 18 has been shown to confer a unique reactivity to the molecule readily explainable in terms of neighbouring group participation by carbonyl oxygen. Thus when 12-bromo-longibornane-3,4-dione 6 is treated with acetone in aqueous alkali, a unique solvolysis/anhydroacetonebenzil-type of aldol condensation takes place generating the novel longi-bornane-based cyclopentenone diol 8; the assigned structure has been confirmed by X-ray analysis of its crystalline monoacetate 9. On exposure of bromodiketone 6 in dioxane to aqueous alkali/NaOMe in MeOH, it generates 12-hydroxy-longi-bornane-3,4-dione 20/12-methoxylongibornane-3,4-dione 22. On dehydration of 9 with $BF_3.OEt_2$, 12-acetoxy-longibornene-based cyclopentenone 23 is formed.

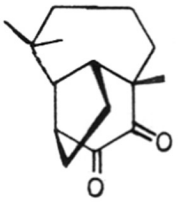
THE CLEAVAGE of cyclic $\alpha$-diketones/$\alpha$-ketols with alkaline hydrogen peroxide generating carboxylic acids is a useful reaction[1] which has been exploited[2] by us recently in the transformation of the bridged tricyclic longifolene 1 to the bicyclic azulene 5 via longidione 3 $\rightarrow$ $\alpha$-longiforic acid 4. In a proposed synthetic venture, when a similar cleavage was attempted on 12-bromolongibornane-3,4-dione 6, the expected bromodiacid 7 was not formed at all. Instead, structure 8 of the isolated neutral crystalline compound has proved to be quite unprecedented and has been finally confirmed by an X-ray analysis.

$\omega$-Bromolongifolene 2 (prepared[3] from 1 by the action of pyridine perbromide) was exposed to trifluoroacetic acid in dichloromethane at room temperature, the resulting trifluoroacetate hydrolysed with alkali and the product oxidized with excess of Jones reagent to furnish[4] the bromodiketone 6. Attempted oxidation of bromodiketone 6 in acetone with alkaline hydrogen peroxide in the usual fashion[5] failed to give any acid but afforded a crystalline, bromine-free sparingly soluble, high-melting neutral compound ($C_{18}H_{26}O_3$) in a good yield. It was thus clear that an unusual reaction in which hydrogen peroxide had not participated but involved only acetone, had taken place. This was proved to be so by omitting hydrogen peroxide and just treating bromodiketone 6 in acetone with aqueous NaOH at ambient temperature when the same crystalline compound




1 $R_1 = R_2 = H$

2 $R_1 = Br$; $R_2 = H$

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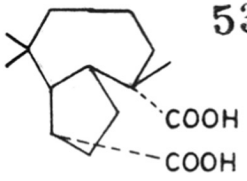


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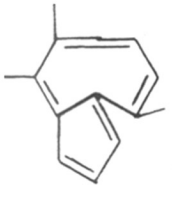

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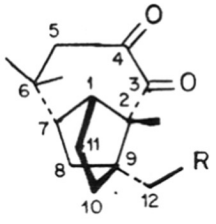


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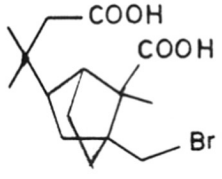
20 R = OH

22 R = OMe

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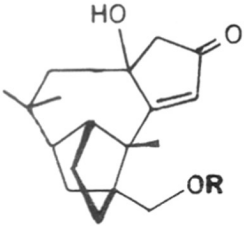


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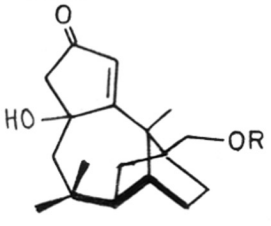
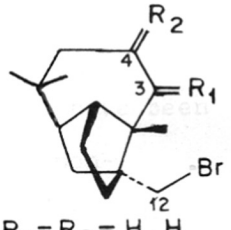



8 R = H

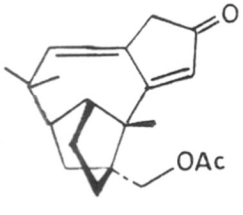
9 R = Ac




18 $R_1 = R_2 = H, H$

19 $R_1 = O$; $R_2 = H, H$

21 $R_1 = H, H$; $R_2 = O$

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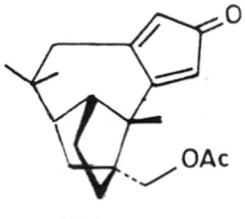


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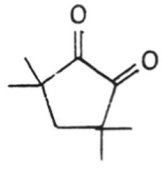


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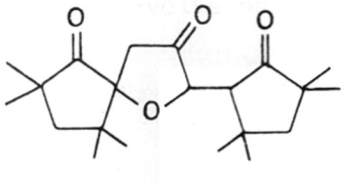


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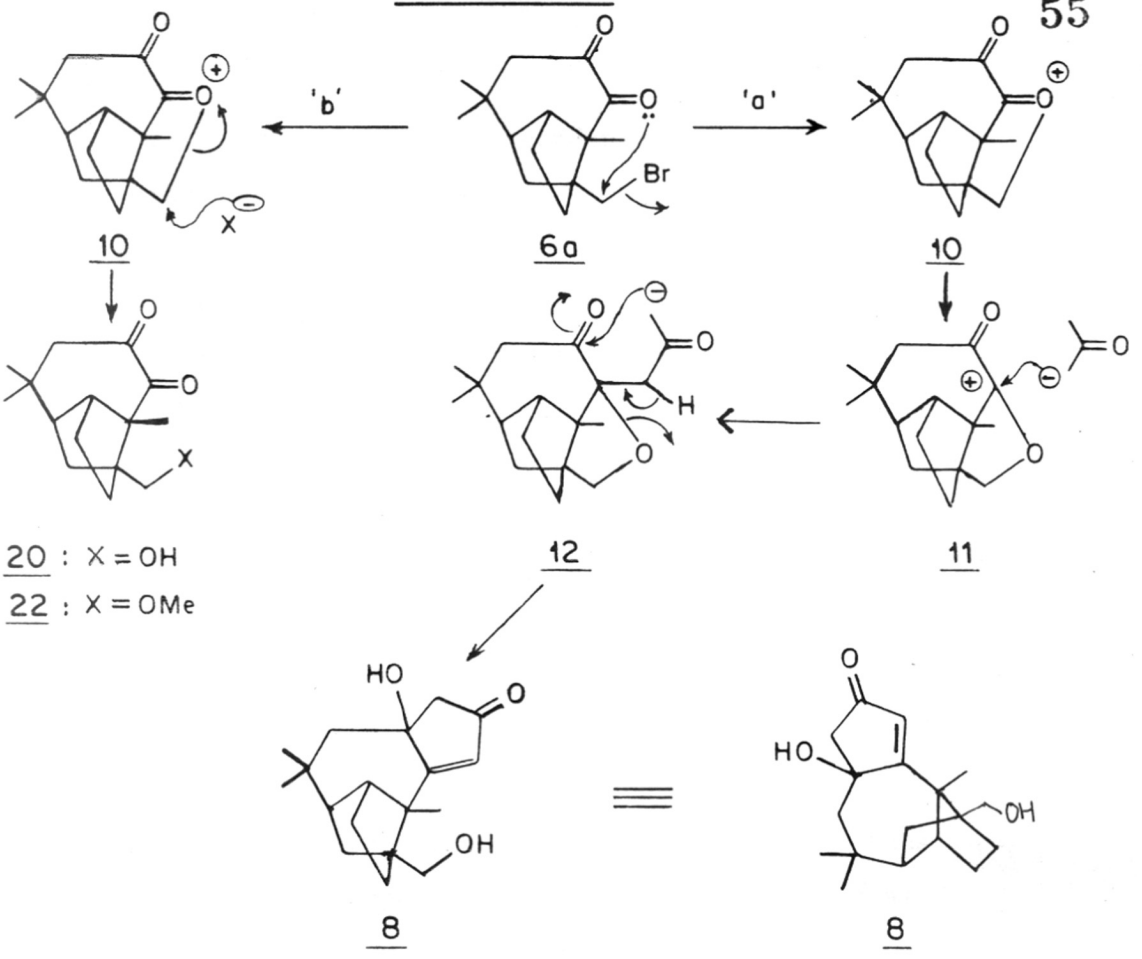
was again formed (54% yield). In its IR spectrum bands at 3490, 1690, 1585 $cm^{-1}$ indicated hydroxyl and conjugated keto groups; on acetylation under mild conditions it gave a crystalline hydroxymono acetate ($C_{20}H_{28}O_4$) suggesting the parent compound to be diol in which one of the hydroxyl groups is tertiary. On mechanistic considerations (vide infra) structure 8 was derived for the compound in question which satisfied all the observed spectral/chemical data. At this stage a direct X-ray diffraction study[6] of the acetylated compound dictated its structure as 9 thus vindicating the proposed mechanistic rationale (Scheme 1'a').

In base-catalysed aldol condensation, enolisable[7] aliphatic and alicyclic 1,2-dicarbonyl compounds have been known to furnish 1:2 adducts with a monoketone; non-enolizable[8] 1,2-dicarbonyl compounds under similar conditions generally afford 1:1 adducts. A 1-oxaspiro [4.4] nonane derivative 14 (formed through a 1:2 aldol-type adduct from reaction of 3,3,5,5-tetramethylcyclopentane-1,2-dione 13 with acetone in alkaline medium) reported recently by Kivekas and Simonen[9] is however quite unusual among aldol-type adducts generated via reactions of enolizable or non-enolizable 1,2-diketones in that two molecules of the diketone are utilized in the formation of 14; earlier reported[7] cases involve only one molecule of the dicarbonyl substrate.

## SCHEME – 1

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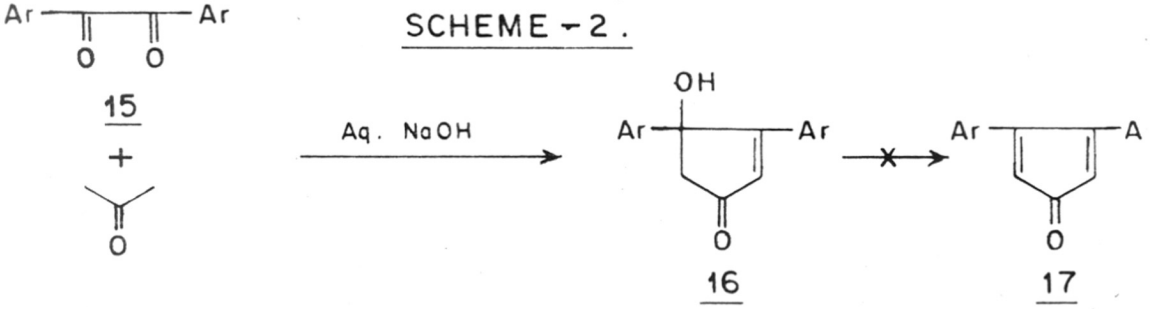


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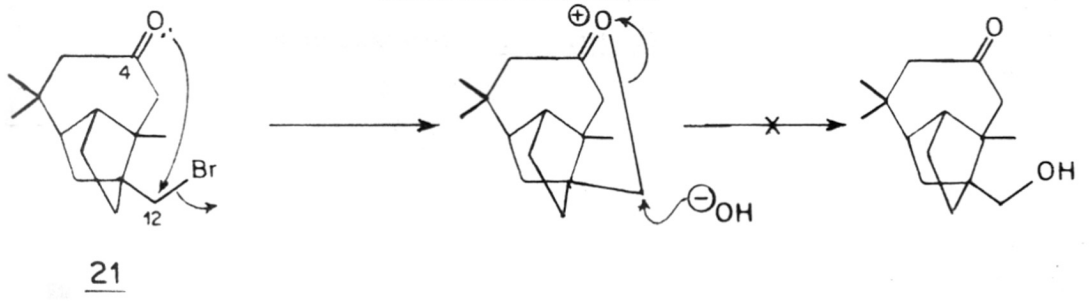
## SCHEME – 3.



Base-catalyzed aldol[10] condensation of the aromatic 1,2-diketone benzil 15 with acetone is known[11] to yield the interesting cyclopentenone ketol, anhydroacetonebenzil 16, which does not dehydrate to the stable cyclopentadienone[12] 17 (cf Scheme 2). The anhydroacetonebenzil-type of bisaldol reaction now observed in the case of the alicyclic bromo-diketone 6 is however unprecedented in non-aromatic $\alpha$-diketone chemistry; the special reactivity observed in the case of 6 must beattributed to the presence of a sterically well-disposed bromine at C-12 in the compact longibornane framework, functioning as a good leaving group in a highly efficient neighbouring group participation[13] by the carbonyl oxygen[14] (n-electrons) at C-3 as shown in 6a (Scheme 1'a'). The crucial electron-deficient oxygen species 10 thus generated then triggers off a series of reactions as elaborated in Scheme 1'a', eventually leading to the unique product 8. The distinguishing feature in the case of bromodiketone 6, however, is that the base-catalysed reaction with acetone not only involves a mixed ketone condensation of the type anhydroacetonebenzil 16 but also a concomitant solvolysis of bromine in the reaction pathway (cf 12). When 12-bromolongibornane-4-one[4b] 21 (which lacks the 3-keto group) was similarly treated with acetone in alkaline medium, there was no reaction and starting material was recovered unchanged (vide infra). Dehydration of

the tertiary hydroxyl in 9 with $BF_3$-etherate in refluxing benzene gave a dienone-acetate for which the heteroannular structure 23 (and not 24) has been assigned on the basis of its PMR signal at $\delta$ 2.93 - a 2H singlet assignable to a methylene sandwiched between a double bond and a carbonyl group, present in only 23.

From the above account it is clear that in 12-bromo-longibornane 18, the placement of a keto group at C-3 (19) confers special reactivity to the molecule in terms of anchimeric assistance by carbonyl oxygen. Thus, when bromo-diketone 6 was stirred with aqueous NaOH for only three minutes, solvolysis was complete affording 20; a similar reaction with 12-bromolongibornane-4-one 21 (devoid of the 3-keto group) was a failure. This indicates that a neighbouring group participation of the type depicted in Scheme 3 is not operative for steric reasons (unfavourable 6-membered ring as compared to favourable 5-ring in the case of bromo-diketone 6, endowed with a 3-keto group, Scheme 1'b'). Exposure of 6 to sodium methoxide in methanol at ambient temperature resulted in facile transformation to 12-methoxy-longibornane-3,4-dione 22. These two compounds 20/22 constitute straightforward examples of neighbouring group participation by carbonyl oxygen in a solvolytic reaction, observed in longifolene chemistry for the first time (Scheme 1'b'). It must also be mentioned here that displacement

of bromine in 6 by the acetate nucleophile was not possible; action of KOAc in AcOH or in DMF (room temperature/95°) resulted only in recovery of starting material.

Acknowledgement

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# EXPERIMENTAL

Light petroleum refers to fraction b.p.60-80°. Solvent extracts are dried over anhydrous $Na_2SO_4$. Melting and boiling points are uncorrected; m.p's were taken in capillaries on a Electrothermal melting point apparatus. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded as smear (liquid) or nujol mull (solid) on a Pye-Unicam SP-3 IR spectrometer. PMR spectra were obtained on a Varian T-60/FT-80A/Brucker WH-90 spectrometer. CMR spectrum was recorded on the Brucker instrument and mass spectra on a CEC spectrometer model 21-110B, using an ionising voltage of 70 eV and a direct inlet system. The X-ray data for compound 9 were collected on a Enraf-Nonius CAD-11M diffractometer.

Action of alkaline $H_2O_2$ on bromodiketone 6 in acetone: Formation of 8

To a stirred mixture of 6 (5 g), acetone (50 ml) and 2N aqueous NaOH (50 ml) was added dropwise 30% $H_2O_2$ (15 ml) during 10 min. The mixture was further stirred for 4 hr, diluted with water, extracted with ethyl acetate, washed with brine, dried, solvent removed and the solid residue recrystallized from ethyl acetate to furnish colourless prisms of the cyclopentenone diol 8, m.p.225° (3.1 g, 66 %). IR (Nujol): 3490, 3300, 1690, 1585, 1020. PMR (pyridine): $\delta$5.68 (s, 1H, C=CH-C=O); 4.33 (unresolved

q, 2H, $C\underline{H}_2OH$); 3.20 (s, 2H, O=C-$C\underline{H}_2$-C-OH); 1.98 (q, 2H, $C\underline{H}_2$-C-OH, J=16 Hz); 0.73 (s, 9H, three tertiary Me's). MS: m/z 290 $M^+$ (Found: C, 74.9; H, 9.1. $C_{18}H_{26}O_3$ requires: C, 74.9; H, 9.0%).

The aqueous alkaline portion on acidification and extraction gave only a negligible amount of acid.

Action of aqueous NaOH-acetone on 6: Formation of 8

To a stirred solution of 6 (2 g) in acetone (20 ml) was added 2N aqueous NaOH (20 ml) and stirred for 4 hr at room temperature. The mixture was dilued with water, extracted with ethyl acetate, washed with brine, dried, solvent removed and the crude solid recrystallized from ethyl acetate to furnish pure 8 (identified by m.p., m.mp., IR and PMR).

On acetylation of 8 with acetic anhydride-pyridine at 28°, the monoacetate 9 crystallized from methanol in colourless needles, m.p. 187°. X-ray: Data were collected by using the $\omega/2\theta$ scan technique upto $2\theta$ = 48°. Three standard reflections were monitored after every 2000 seconds of exposure time to check for crystal decay, if any. The structure was refined using full matrix least square technique with anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms were fixed based on stereochemical considerations and their positions verified by difference Fourier synthesis. UV: $\lambda_{max}$ 235 nm (MeOH, $\epsilon$ 11590). IR (nujol): 3430, 1730, 1685, 1585, 1250, 1030,. PMR ($CCl_4$): $\delta$ 5.95 (s, 1H, C=C$\underline{H}$-C=O); 4.16 (q, 2H,

$C\underline{H}_2OAc$, , J=10 Hz); 2.93 (C-O$\underline{H}$, does not exchange with $D_2O$; 2.53 (s, 2H, O=C-$C\underline{H}_2$-C-OH); 2.10 (s, 3H, $OCOC\underline{H}_3$); 1.30, 1.26, 0.80 (3H each, tertiary Me singlets). MS: m/z 332 ($M^+$). (Found: C, 72.5; H, 8.5. $C_{20}H_{28}O_4$ requires:C, 72.3; H, 8.5%).

On tosylation of 8 with tosyl chloride in pyridine at 0°, the monotosylate 8 (R=Ts) recrystallized from benzene-light petroleum in colourless microprisms, m.p.163°. IR(nujol):3440, 1685, 1580, 1195, 1170, 850. PMR ($CDCl_3$):$\delta$ 7.90, 7.45 (two d, 2H each, ar-H, J=9 Hz); 5.62 (s, 1H, C=C$\underline{H}$-C=O); 4.11 (s, 2H, $C\underline{H}_2OTs$); 2.48 (s, 3H, ar-$C\underline{H}_3$); 2.47 (brs, 2H, HO-C-$C\underline{H}_2$-C=O); 1.25, 1.16, 0.73 (three tertiary Me singlets). (Found: C, 67.1; H, 7.5. $C_{25}H_{32}O_5S$ requires: C, 67.6; H, 7.3%).

Dehydration of 9 with $BF_3.OEt_2$: Formation of 23

A mixture of 9 (1 g), dry benzene (50 ml) and $BF_3.OEt_2$ purified, 3 drops) was refluxed on a waterbath for 3 hr. It was then washed with 5% aqueous $NaHCO_3$, brine, dried, solvent removed and the crude solid recrystallized from light petroleum to furnish colourless needled of 23, m.p. 102° (0.39 g, 41%). UV:$\lambda_{max}$ 293 nm(MeOH:$\epsilon$ = 18,140). IR(nujol):1730, 1690, 1550, 1245. PMR($CCl_4$):$\delta$ 6.3 (s, 1H, $\underline{H}$C=C-C=C$\underline{H}$-C=O); 5.33 (bs, 1H, C=C$\underline{H}$-C=O); 4.10 (s, 2H, $C\underline{H}_2$-OAc); 2.93 (s, 2H, C=C-$C\underline{H}_2$-C=O); 1.96 (s, 3H, OCO-$C\underline{H}_3$); 1.26, 1.20, 1.00 (three tertiary Me singlets). CMR($CDCl_3$): 204.7(s), 177.2(s), 171.1(s), 136.7(d), 136.2(d), 133.5(s). (Found: C, 76.2; H, 8.5. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

Solvolysis of 6 with aqueous NaOH: Formation of 20

To a stirred solution of 6 (1 g) in dioxane (10 ml) was added 2N aqueous NaOH (10 ml) at room temp. After 3 min the mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried solvent removed and the crude solid recrystallized from light petroleum to afford colourless micro crystals of 20, m.p. 83-84° (0.5 g, 62%). IR (nujol): 3400, 1700, 1020. PMR ($CCl_4$): 3.68 (q, 2H, $C\underline{H}_2$-OH, J=11 Hz); 1.8 (s, 2H, $C\underline{H}_2$-CO); 1.16 x 2, 1.06 (three tertiary Me singlets). MS: m/z 250 ($M^+$). (Found: C, 71.7; H, 9.0. $C_{15}H_{22}O_3$ requires: C, 72.0; H, 8.9%).

Solvolysis of 6 with NaOMe in MeOH: Formation of 22

To a stirred solution of NaOMe (50 mg) in dry MeOH (15 ml) was added bromodiketone 6 (1 g) and stirred at room temp. for 15 min. The mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried, solvent removed and the residue distilled to furnish 22 as a colourless liquid b.p.190° (bath)/1 mm (0.75 g, 89%) which solidified slowly; m.p.86-88° (light petroleum). IR (nujol): 1720, 1080, 1020, 990, PMR ($CCl_4$): 3.66 (s, 2H, $C\underline{H}_2$-$OCH_3$); 3.08 (s, 3H, $OC\underline{H}_3$); 1.10 x 2, 086 (three tertiary Me singlets). MS: m/z 264 ($M^+$). (Found: C, 72.0; H, 9.2. $C_{16}H_{24}O_3$ requires: C, 72.7; H, 9.2%).

# REFERENCES


1 a) E Kyburz, B Riniker, H R Schenk, H Heusser and O Jeger, Helv Chim Acta, 36, 1891 (1953).

b) Y Ogata, Y Sawaki and M Shiroyama, J Org Chem, 42, 4061 (1977).

2 R P Deshpande, P K Jadhav and U R Nayak, Indian J Chem, 17B, 266 (1979).

3 S N Suryawanshi and U R Nayak, Indian J Chem, 17B, 304 (1979).

4 a) G Mehta and S K Kapoor, J Org Chem, 39, 2618 (1974).

b) G Mehta, S K Kapoor, T N Guru Row and K Venkatesan, Tetrahedron Lett, 2653 (1974).

c) S P Vaidya, S N Suryawanshi, P K Jadhav and U R Nayak, Indian J Chem (in press).

5 R P Deshpande, S N Suryawanshi and U R Nayak, Indian J Chem, 17B, 617 (1979).

6 K R Acharya, S S Tavale and T N Guru Row, Proc Indian Acad Sci (Chem Sci) 93, 271 (1984).

7 S Yang-Lan, M Muller-Johnson, J Oelhdrich, D Wichman J M Cook and U J Weiss, J Org Chem 41, 4053 (1976).

8 C F H Allen and J A VanAllan, J Org Chem, 17, 845 (1952).

9 R Kivekas and T Simonen, Acta Chem Scand, B 33, 627 (1979).

10 a) A T Nielsen and W J Houlihan, Organic Reactions, 16, 1 (1968).

b) T Mukaiyama, Organic Reactions 28, 203 (1982).

11 a) F R Japp and C I Burton, J Chem Soc, 51, 431 (1887).

b) F R Japp and T S Murray, J Chem Soc, 71, 144 (1897).

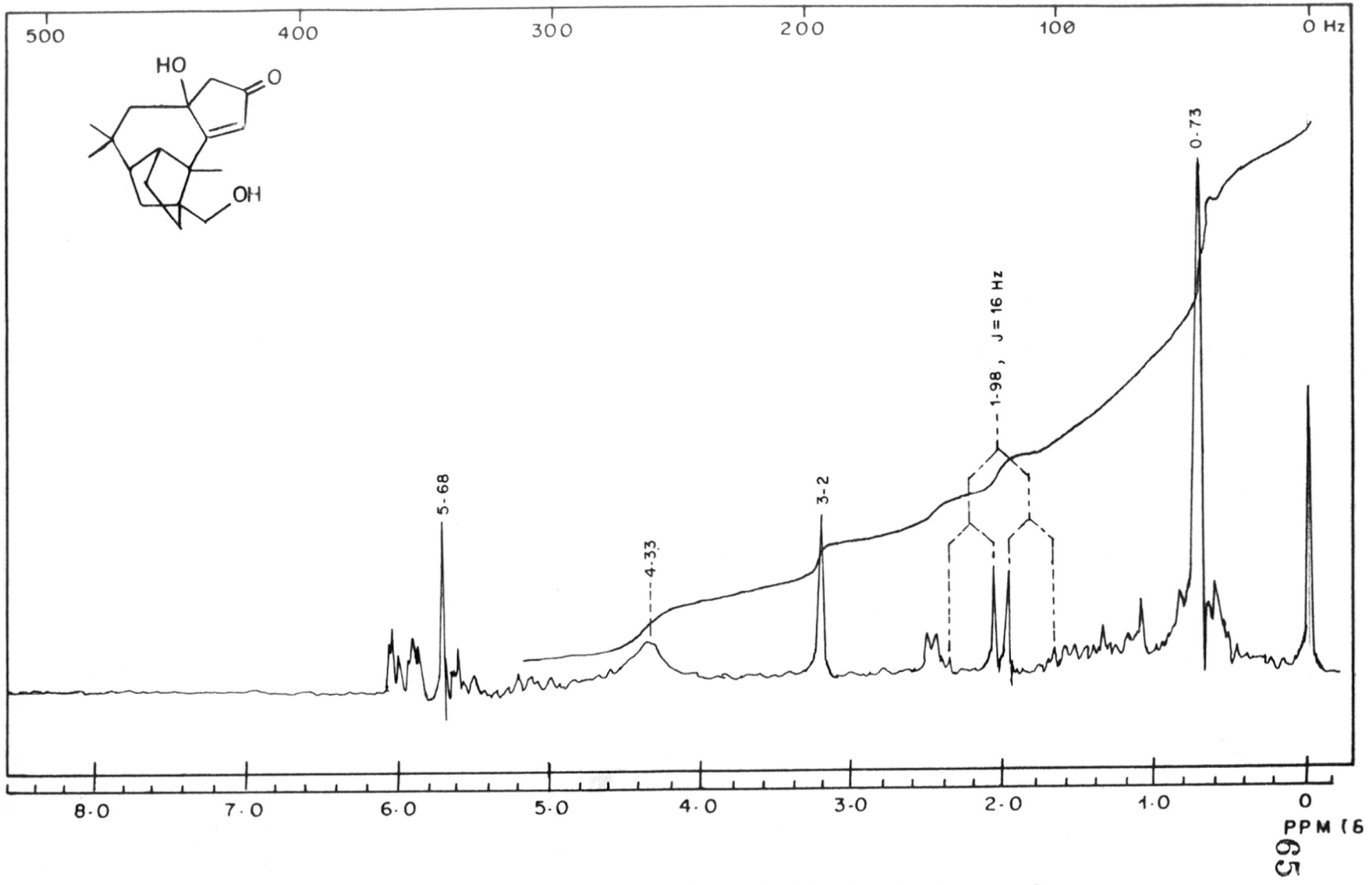
c) C F H Allen and J A VanAllan, J Am Chem Soc, 72, 5165 (1950).

12 M A Ogliaruso, M G Romanelli and E I Becker, Chem Rev, 65, 261 (1965).

13 a) B Capon and S P McManus, "Neighbouring Group Participation" Vol 1, Plenum Press, New York (1976).

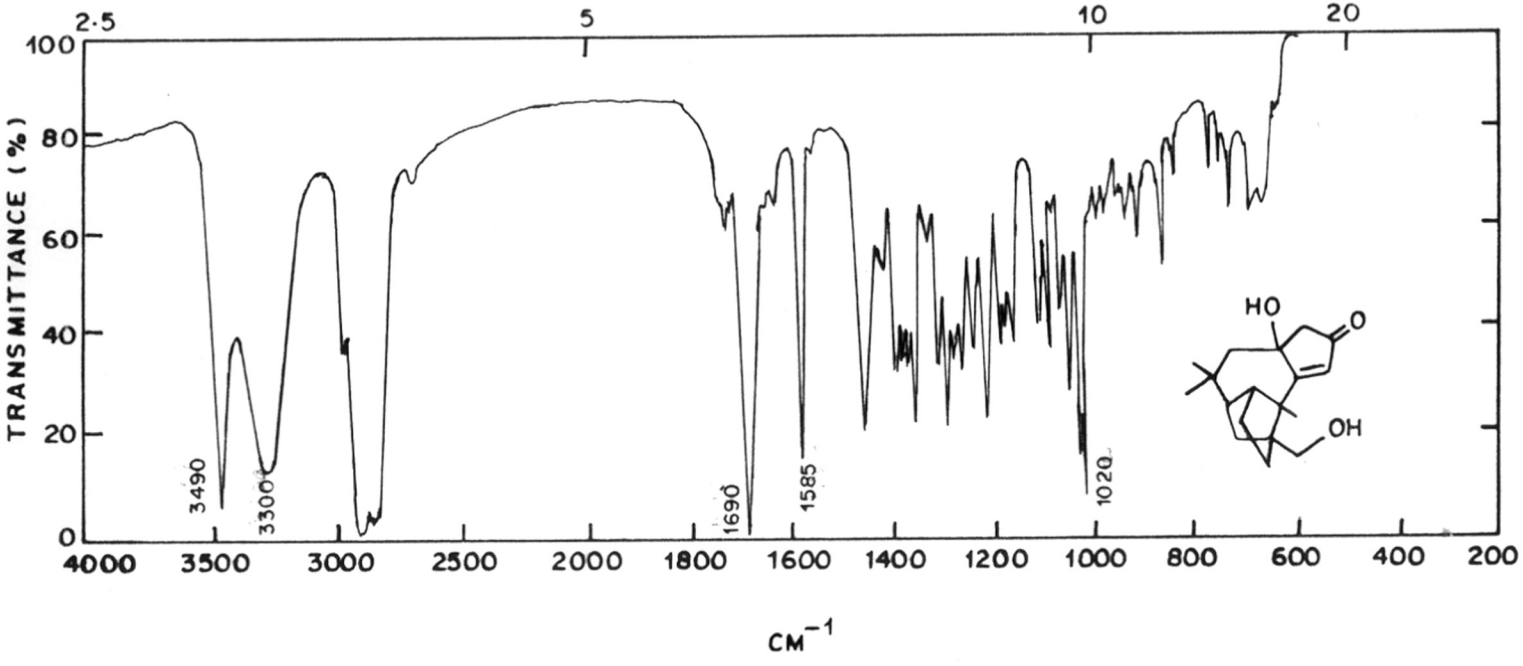
b) W J le Noble, "Highlights of Organic Chemistry", p. 690, Marcel Dekker, New York (1974).

14 H Tanida, T Nishiya and T Irie, J Org Chem, 44, 3337 (1979).

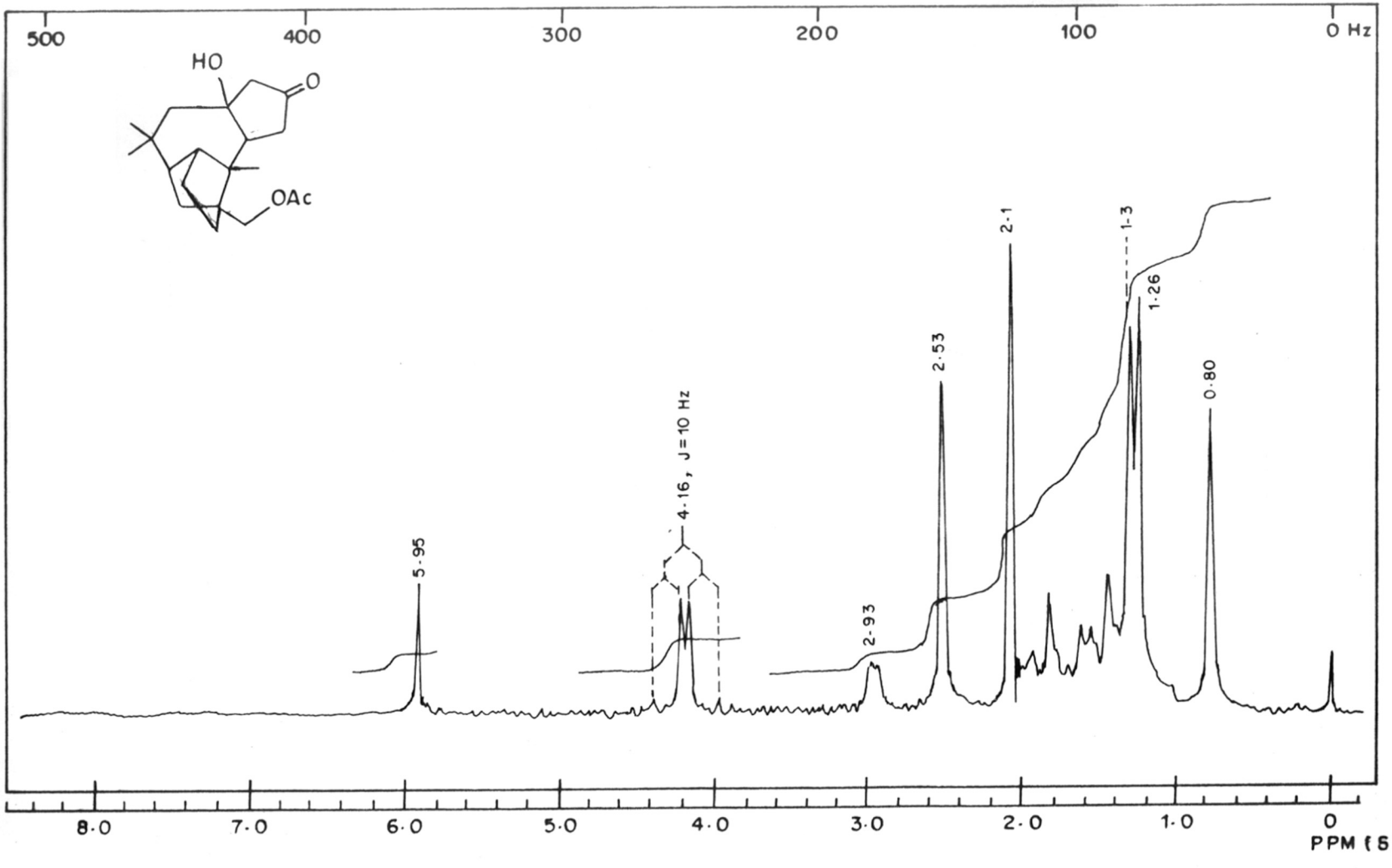





PMR SPECTRUM OF CYCLOPENTENONE DIOL **8**




IR SPECTRUM OF CYCLOPENTENONE DIOL 8

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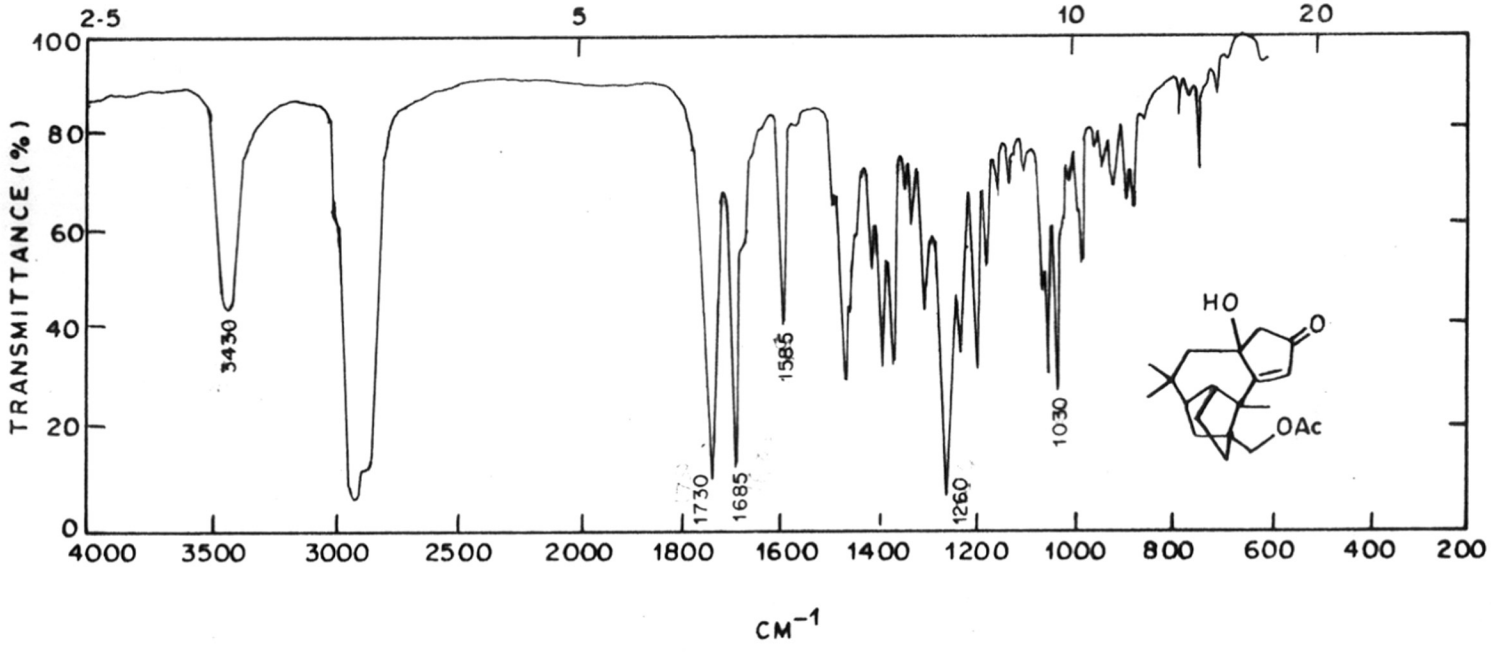


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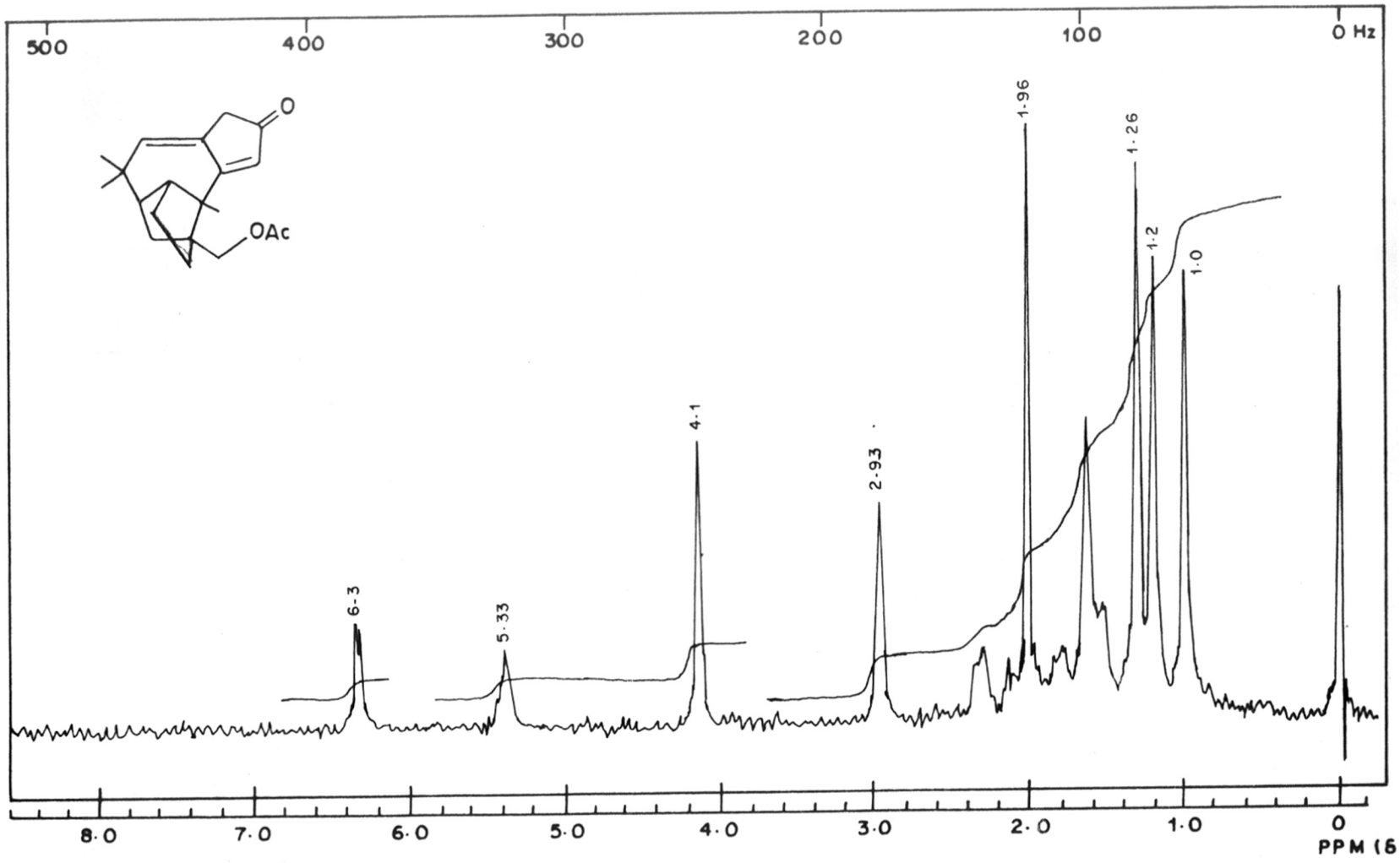


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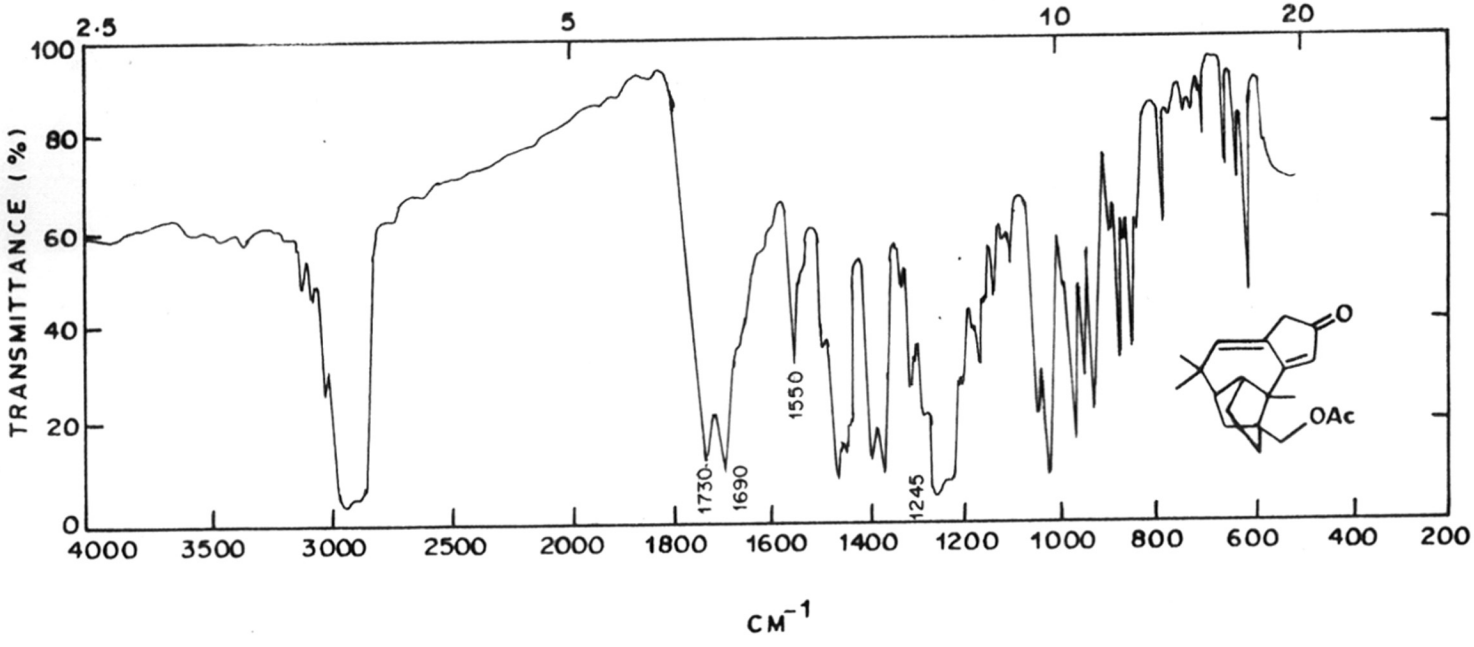


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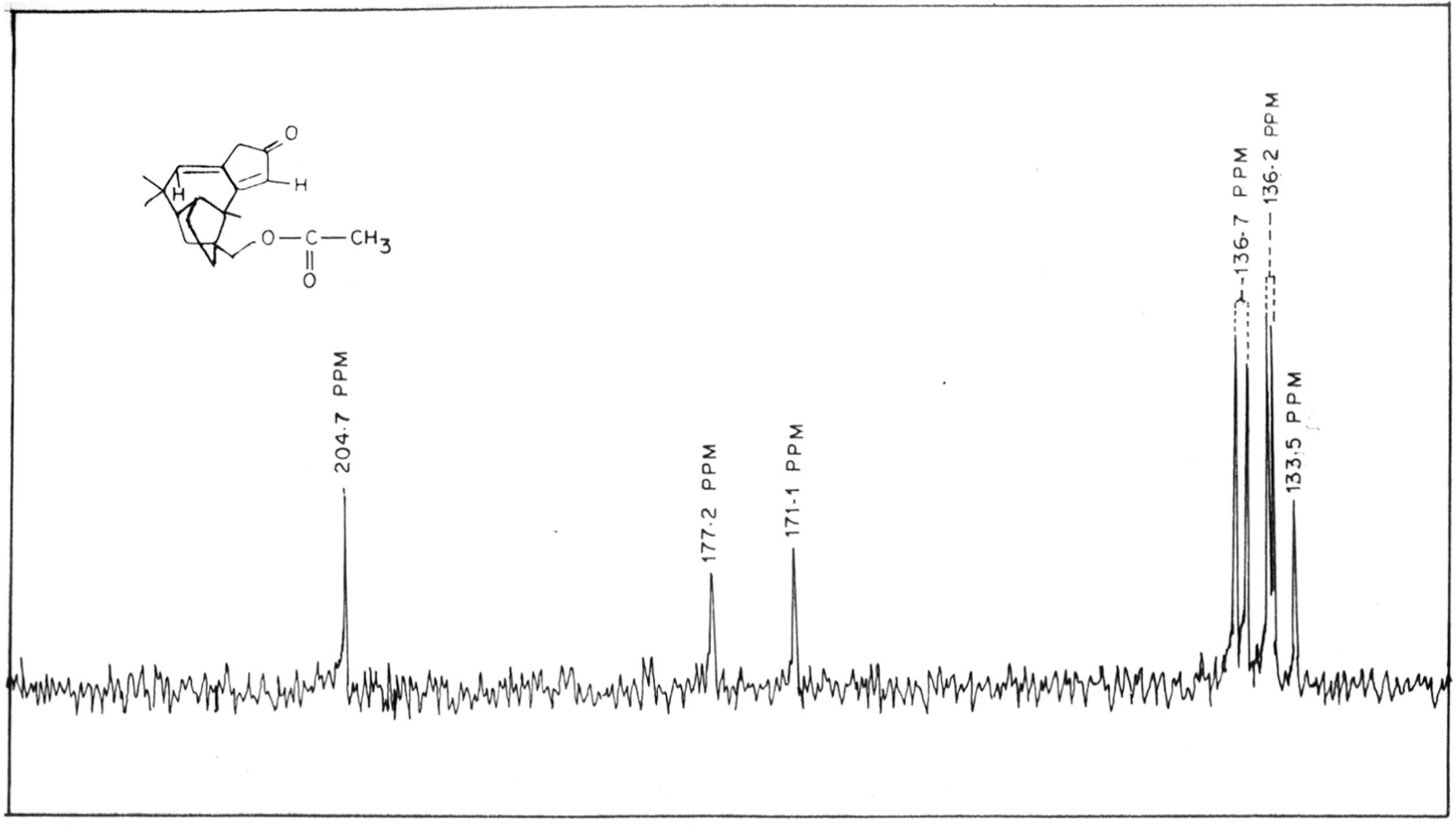
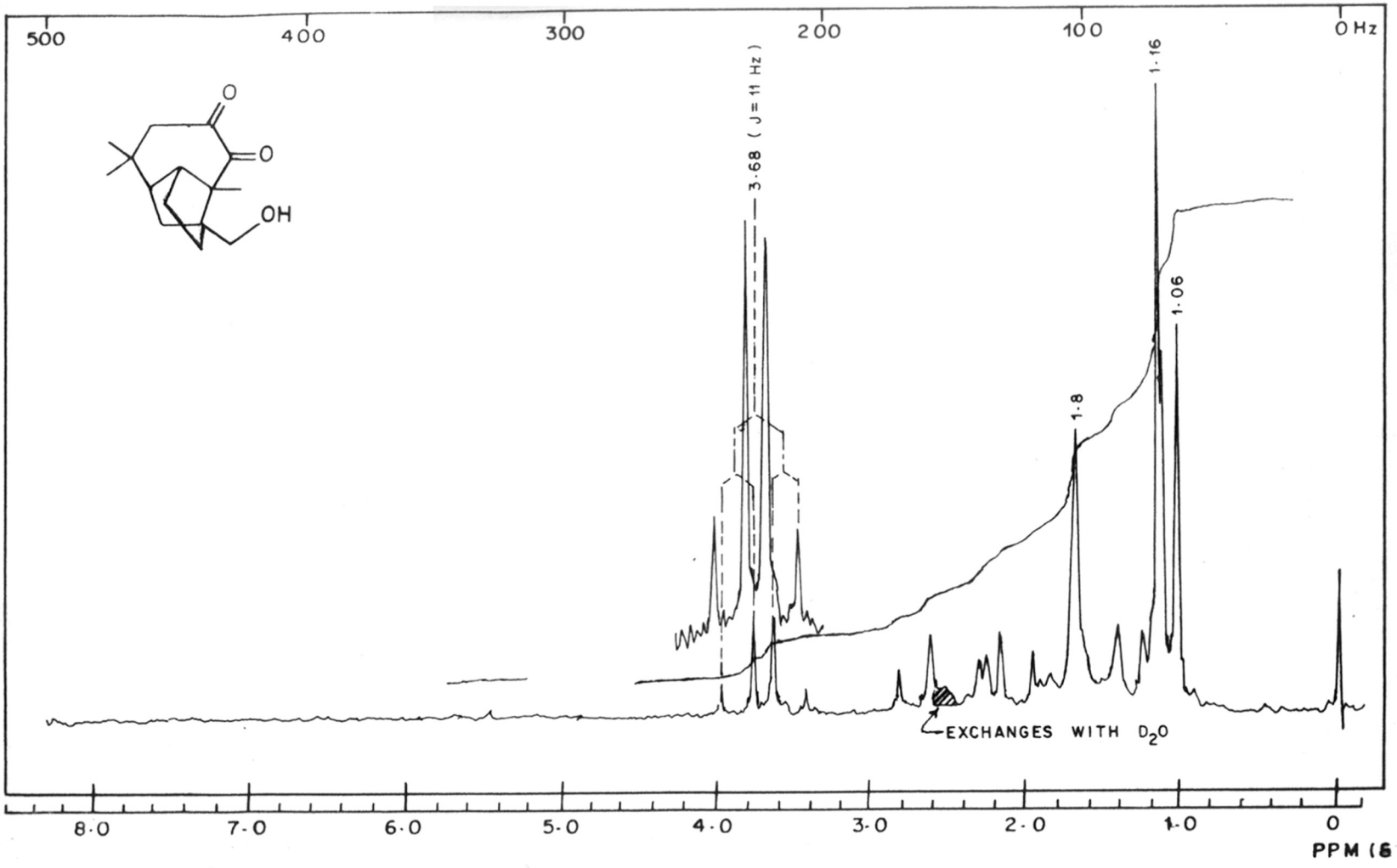
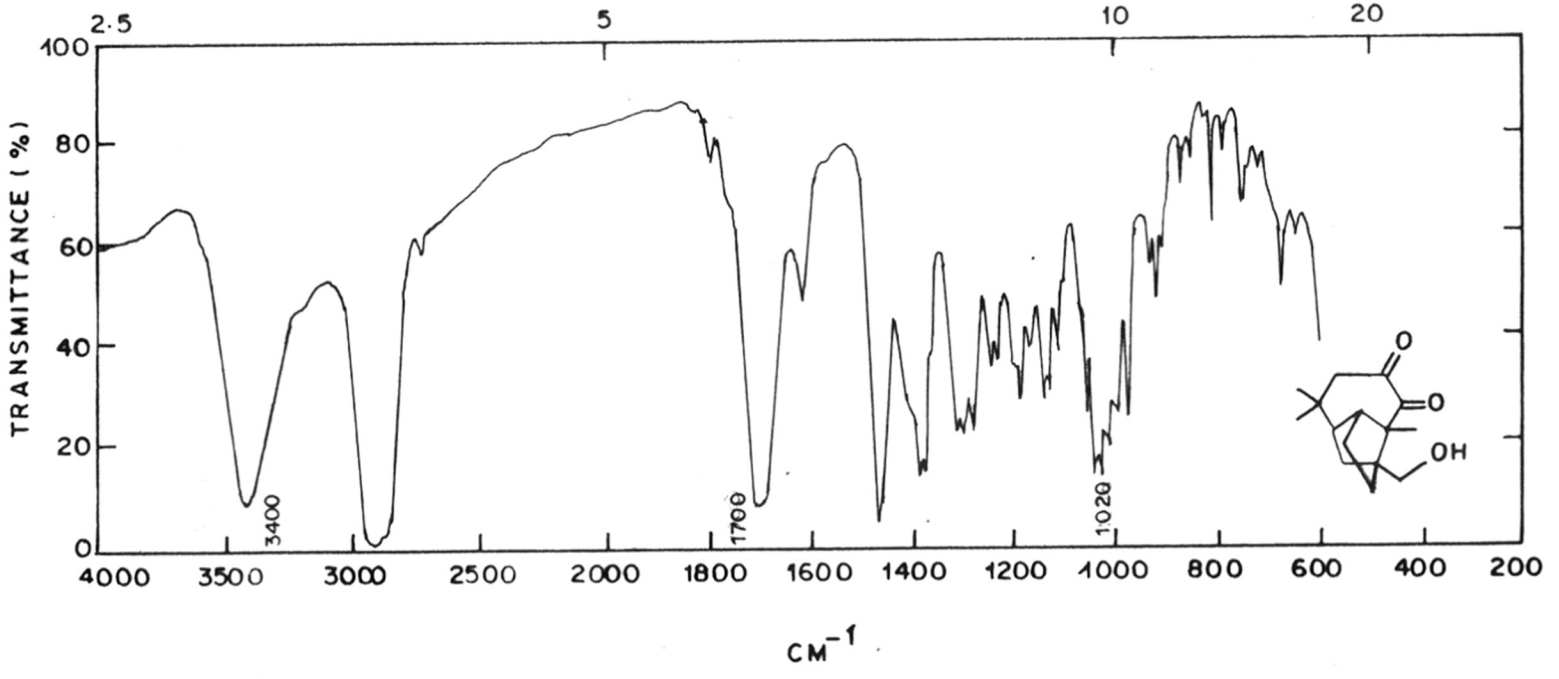



OFF-RESONANCE $^{13}$CMR SPECTRUM OF CYCLOPENTENONE 23




PMR SPECTRUM OF DIKETOALCOHOL 20

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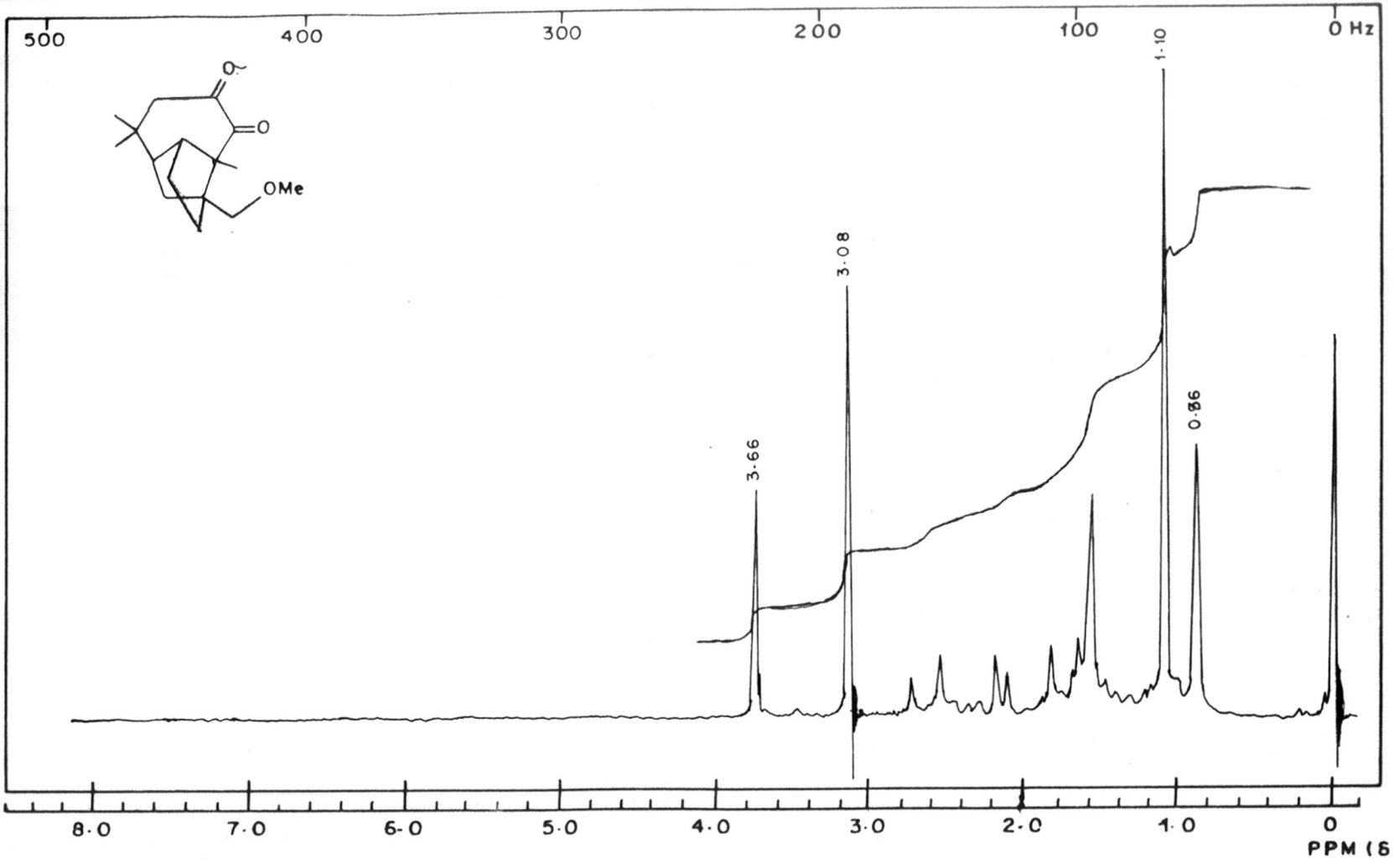
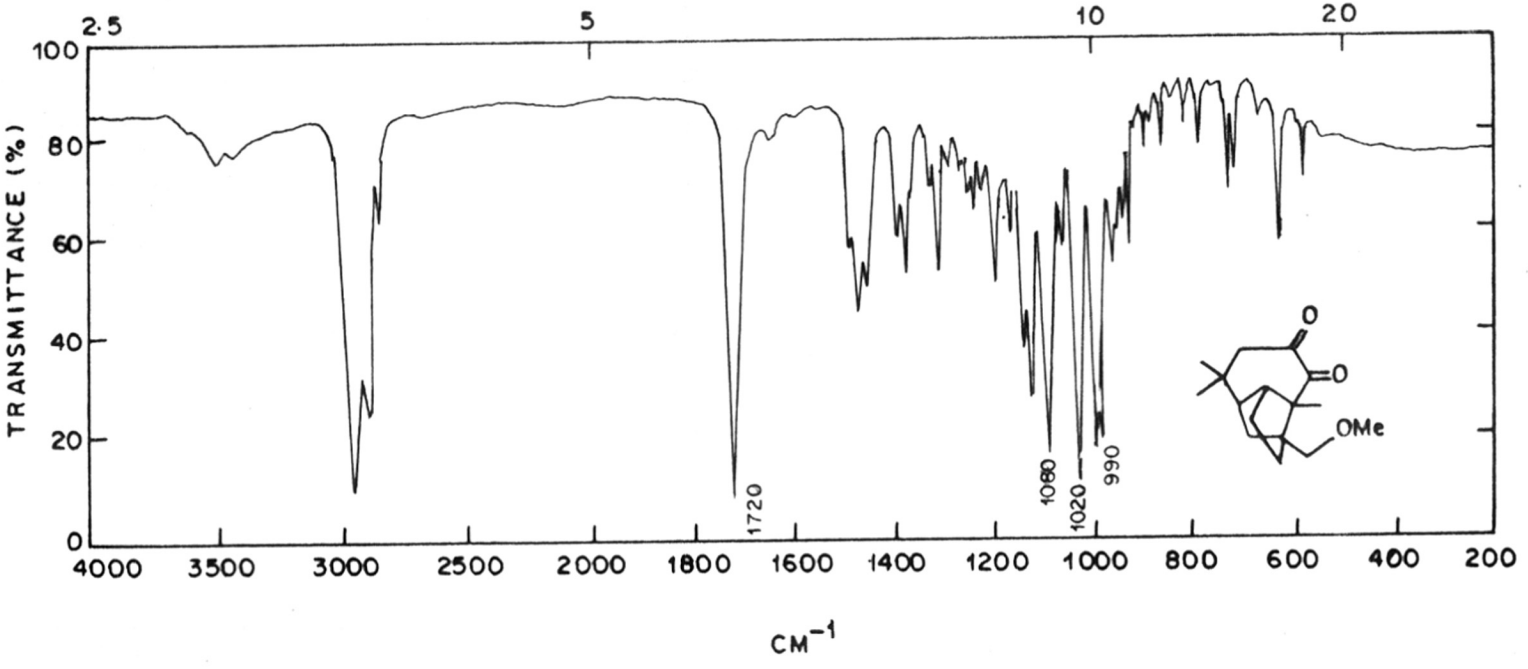



PMR SPECTRUM OF DIKETOMETHYL ETHER 22




IR SPECTRUM OF DIKETO METHYL ETHER 22

# CHAPTER - 4

## 9-METHYLENELONGIBORNANE : LEWIS ACID INDUCED TRANSANNULAR HYDRIDE SHIFT / REARRANGEMENT TO 9-METHYLISOLONGIFOLENE / 1,1,3-TRIMETHYL-7-ISOPROPYL TETRALIN

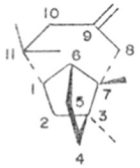
## ABSTRACT

9-Methyllongibornyl-9-cation 5 (R=Me) generated from 9-methylene-longibornane 2, on exposure to $BF_3OEt_2$ in benzene, has been shown to undergo a transannular 1,5-hydride shift in the "reverse" fashion (C-2 to C-9) to give the crucial 9-methyllongibornyl-2-cation 6 (R=Me) which then traverses the familiar Berson mechanistic pathway [entirely analogous to that of longifolene 1 ⟶ isolongifolene 13 (R=H)] ending up finally in 9-methyl-isolongifolene 13 (R=Me). Furthermore, 1,1,3-trimethyl-7-isopropyltetralin 17 (R=Me) has also been isolated from 2 [via 13 (R=Me)] in a second-stage rearrangement under more energetic conditions, reminiscent of the transformation of isolongifolene 13 (R=H) ⟶ 1,1-dimethyl-7-isopropyltetralin 17 (R=H). The tetralin 17 (R=Me) has also been synthesized from cumene in eight steps.

THE SYNTHESIS of 9-methylenelongibornane 2 and some of its reactions have been described[1] recently. Longifolene 1 and 9-methylene-longibornane 2 both incorporate an exocyclic methylene moiety in their structures but they differ in one important respect: longifolene can, of necessity, only undergo transannular reactions[2] and deep-seated rearrangements[2] independent of each other while theoretically 2 can successively suffer both of these. The carbocation 5 derived from 2 is spatially so strategically placed (see 2a) that it can initiate a transannular 1,5-hydride shift in the "reverse" fashion i.e. from C-2 to C-9 (considering the C-9 to C-2 shift, first observed[3] in the hydration of longifolene, to be "forward" hydride transfer). The crucial longibornyl-2-cation 6 (R=Me) thus generated is now well-set for the familiar deep-seated multiple rearrangements following the Berson[4] mechanistic pathway to finally collapse into the isolongifolene skeleton 13 (R=Me) (Scheme 1). Practical realization of this theoretical rationale forms the highlight of this paper.

The Lewis acid, $BF_3.OEt_2$, is a remarkable reagent which has proved to be extremely useful for the transformation[5] of longifolene 1 into a totally new skeleton isolongifolene 13 (R=H) under mild conditions (catalytic amount in benzene at ambient temperature). When these conditions were applied to 9-methylenelongibornane 2, however, the double bond just migrated inside the ring generating[1] the endocyclic olefin 3

1

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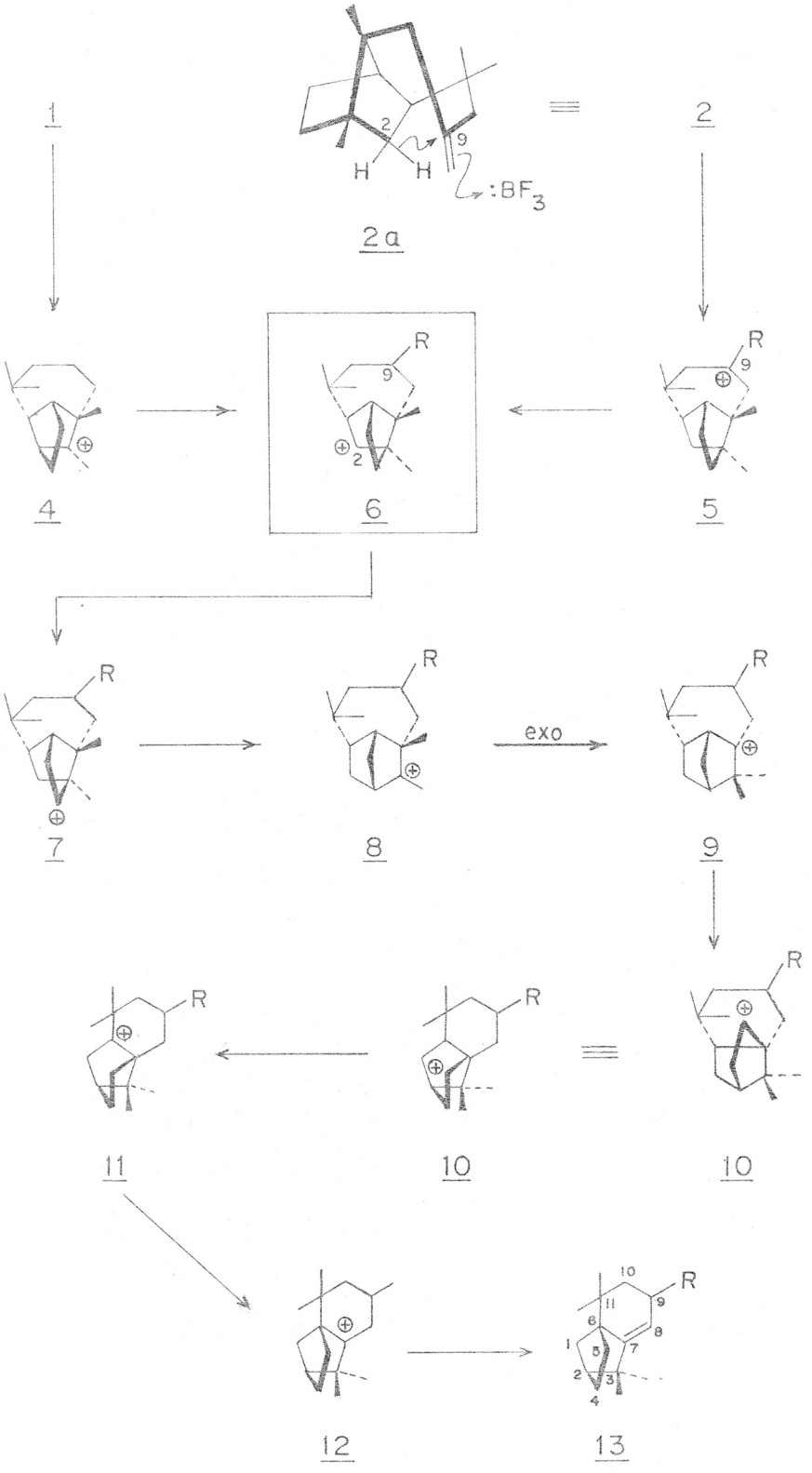
3

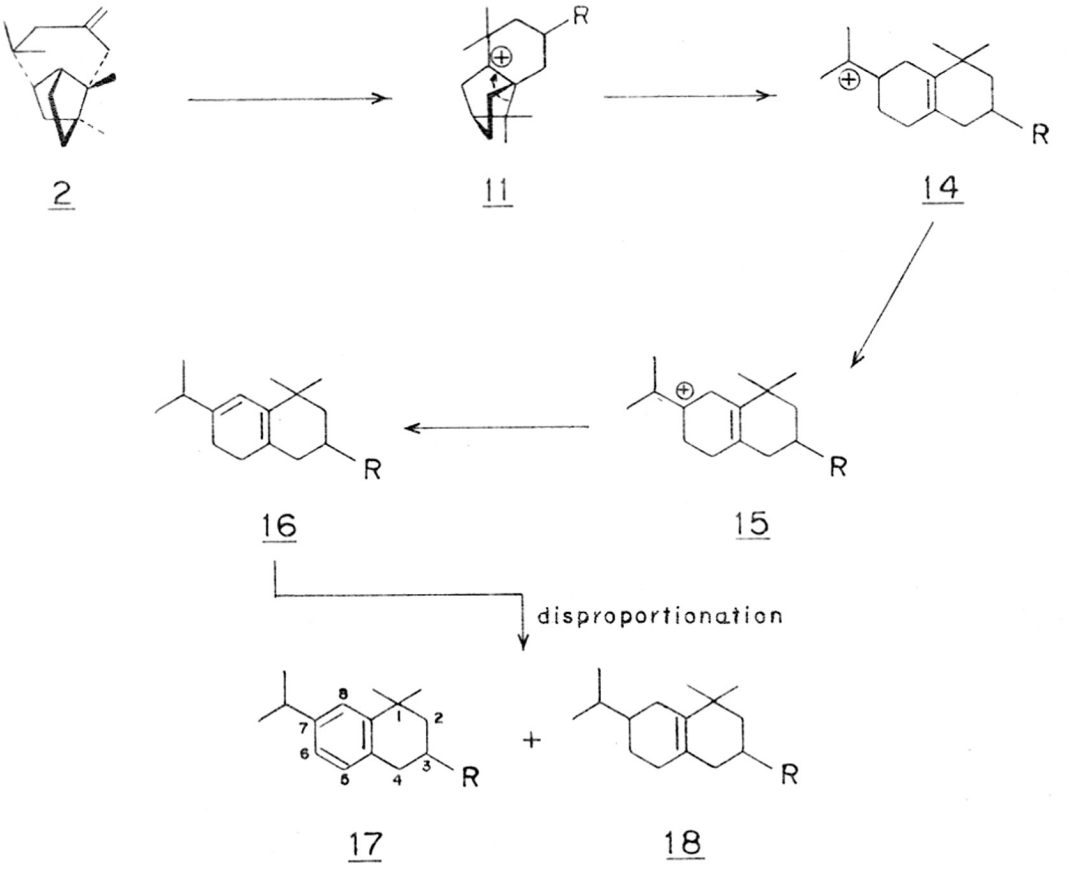



SCHEME 1

and nothing more deep-seated. Refluxing the reaction mixture for a prolonged period failed to bring about any further transformation of 3. Only when the amount of the Lewis acid was increased tenfold (in refluxing benzene) was there an indication of the formation of a new compound ($AgNO_3$-silica gel TLC: 2 spots) which was then separated from the known 3 (13%) by chromatography over this adsorbent. The faster-moving new hydrocarbon $C_{16}H_{26}$ ($M^+$ 218) (16%) was readily characterized as the sought-after (see Scheme 1) 9-methyl-isolongifolene 13 (R=Me) by the multiplicity of the lone olefinic proton in its PMR spectrum, which was quite diagnostic; while in the case of isolongifolene 13 (R=H) it was a triplet, in this case it was a doublet at $\delta$ 4.95 (J=2 Hz) which is in accord with a single neighbouring proton (of the secondary methyl at C-9).

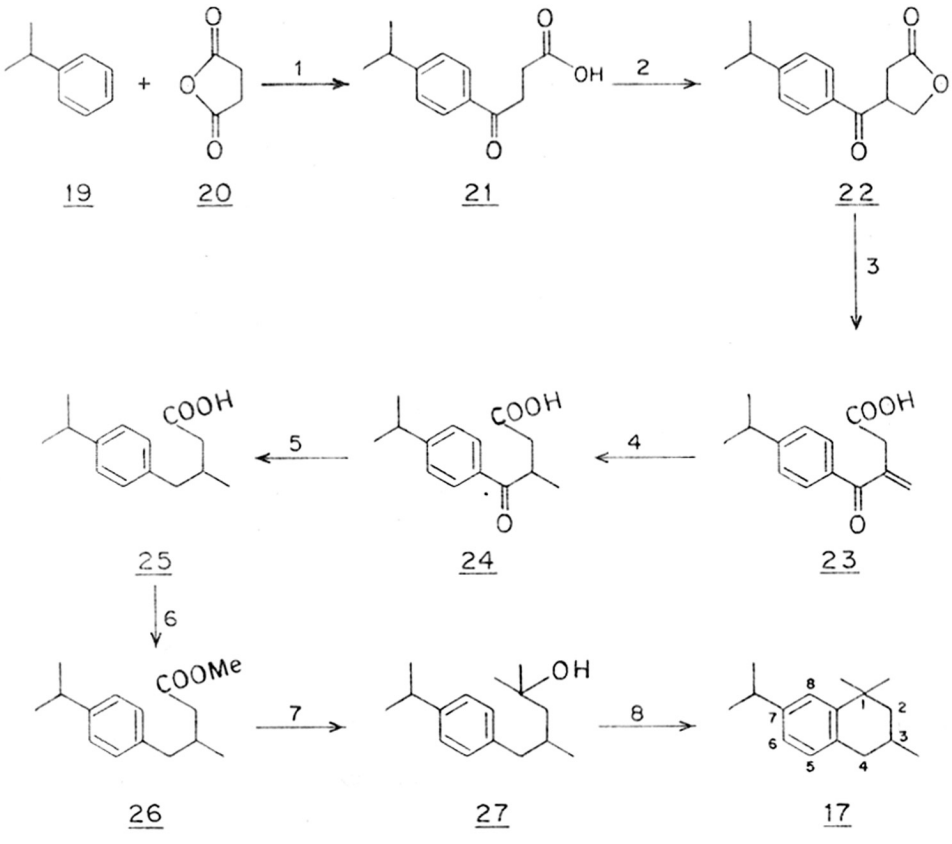
Further rearrangement[6]/disproportionation[6] of 13 (R=Me) (Scheme 2) could also be achieved when 9-methylenelongibornane 2 was exposed to $BF_3.OEt_2$ at a higher temperature (refluxing toluene). On chromatography of the resulting mixture on a column of 15% $AgNO_3$-silica gel, two pure hydrocarbons were separated and characterized as the tetralin 17 (R=Me; 18%) and the octalin 18 (R=Me; 20%) on the basis of their spectral features.

The structure of the substituted tetralin 17 (R=Me), which is new, has also been confirmed by direct comparison with an authentic specimen prepared by synthesis from isopropyl-benzene via the succinic anhydride route[7]. Since methylsuccinic




2 11 14 15 16 17 18

SCHEME 2




Reagents

1. $AlCl_3-PhNO_2$ 2. $CH_2O-NaOH$ 3. NaOMe–MeOH 4. $H_2/PtO_2$–AcOH
5. Amalgamated Zn–HCl–Toluene 6. $CH_2N_2$ 7. MeLi(excess)–$Et_2O$ 8. PPA

SCHEME 3

anhydride would give the wrong positional isomer of 17 (R=Me) i.e. 1,1,2-trimethyl-7-isopropyl tetralin (the reagent is invariably known[8] to react in such a way that the carbonyl group, furthest removed from the methyl, attaches to the aryl nucleus), the route depicted in Scheme 3 was followed for reaching the right tetralin 17 (R=Me). The recently described[9] hydroxymethylation of 3-aroylpropanoic acids ($CH_2O$-NaOH)/easy approach to 3-aroyl-3-butenoic acids (NaOMe-MeOH), after some optimization of the molar ratios of substrate/$CH_2O$/NaOH, afforded 23; catalytic hydrogenation gave 24 with the required extra methyl at the right carbon. A Clemmensen reduction of 24 followed by esterification yielded 26; dimethylation of the ester carbon of 26 by treatment with methyl-lithium generated the tertiary carbinol 27 which, on exposure to polyphosphoric acid cyclized to give the desired 1,1,3-trimethyl-7-isopropyl tetralin 17.

## EXPERIMENTAL

All mp's and bp's are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Freshly purified[10] and distilled borontrifluoride etherate was used. $AgNO_3$-silica gel was prepared by the method of Gupta and Dev[11]. $BF_3.OEt_2$-rearrangement reactions of 2 and chromatographic separations were monitored by $AgNO_3$-silica gel TLC. Solvent extracts were dried over anhydrous $Na_2SO_4$. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded as smears (liquid) or nujol mulls (solid) on Pye Unicam SP-3 IR spectrophotometer. PMR spectra were obtained on Varian T60/FT 80A/Bruker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model H-110B, using an ionizing voltage of 70 eV and a direct inlet system.

9-Methylenelongibornane 2. This was prepared[1] by the Wittig reaction on longibornane-9-one using $Ph_3P{=}CH_2$.

Action of $BF_3.OEt_2$ on 9-methylenelongibornane 2 (refluxing benzene): Formation of olefin 3/9-methylisolongifolene 13(R=Me)

9-Methylenelongibornane 2 (3 g) in dry benzene (50 ml) was treated with $BF_3.OEt_2$ (0.1 ml) and refluxed on a waterbath (17 hr). The mixture was diluted with more benzene, washed with aq.$NaHCO_3$, brine, dried, solvent removed and the residue distilled to give a pure olefin identified as 3 (IR/PMR).

A mixture of 9-methylenelongibornane 2 (1 g), benzene (20 ml) and $BF_3.OEt_2$ (0.3 ml) was refluxed and worked up as before and the product was chromatographed on a column of 15%

$AgNO_3$-silica gel: Fr. 1, light petroleum, 4 x 25 ml, pure 13 R(Me). Colourless liquid, b.p.110°(bath)/0.5 mm (0.155 g, 16%). IR (smear): 1390, 1370, 860, 840. PMR ($CDCl_3$): δ 4.96 (d, 1H, -C=CH-CH-Me, J=2 Hz); 0.90 (d, 3H, sec-Me, J=8 Hz); 1.02, 0.95, 0.91, 0.84 (four tertiary Me singlets). MS: m/z 218 ($M^+$(Found: C, 88.8; H, 11.6. $C_{16}H_{26}$ requires: C, 88.1; H, 11.9%).

Fr. 2, light petroleum, 2 x 25 ml, olefin 3 (13%) (IR/PMR)

Action of $BF_3.OEt_2$ on 9-methylenelongibornane 2 (refluxing toluene): Formation of tetralin 17 (R=Me)/octalin 18 (R=Me)

A mixture of 9-methylenelongibornane 2 ( 1g), dry toluene (20 ml) and $BF_3.OEt_2$ (0.3 ml) was refluxed (17 hr), worked up as usual and the product chromatogaphed on a column of $AgNO_3$-silica gel: Fr. 1, light petroleum, 2 x 25 ml, pure octalin 18 (R=Me). Colourless liquid, b.p.130°(bath)/2 mm (0.2 g, 20%). IR (smear): featureless. PMR ($CCl_4$): δ 0.85 to 1.00 (unresolved signals, 5 x 3H, comprising of two tert.Me + one sec.Me + one isopropyl). MS: m/z 220 ($M^+$). (Found: C, 87.1; H, 12.1. $C_{16}H_{28}$ requires: C, 87.3; H, 12.7%).

Fr. 2, light petroleum, 7 x 25 ml, tetralin 17 (R=Me). Colourless liquid, b.p.130°(bath)/0.6 mm (0.18 g, 18%). IR (smear): 1620, 1505, 840, 820. PMR ($CDCl_3$): δ 7.06 (s, 1H, ar-H); 6.91 (perturbed AB "quartet" with $\delta/J$ very small, 2H, Ar H); 1.25 (d, 6H, isopropyl methyls, J=5 Hz); 1.26, 1.19 (s, 3H each, tertiary Me's); 1.03 (d, 3H, sec-Me, J=5 Hz). MS: m/z 216 ($M^+$). (Found: C, 87.9; H, 11.4. $C_{16}H_{24}$ requires: C, 88.8; H, 11.2%).

Synthesis of 1,1,3-trimethyl-7-isopropyl tetralin 17(R=Me)

3-(p-isopropylbenzoyl)-propanoic acid 21. Prepared[12] by succinoylation of cumene in nitrobenzene with anhydrous $AlCl_3$ as the catalyst: m.p.134°.

Hydroxymethylation of 21: enone acid 23. Formalin (37% soln; 7.3 ml, 99 mmol) was added to a stirred solution of 21 (12.1 g, 55 mmol) in 0.5N NaOH (176 ml, 99 mmol) (molar ratio of 21: HCHO:NaOH = 1:1.8:1.8). After 1 hr at room temp, the mixture was acidified with conc. HCl (12 ml) and stirred overnight. The mixture was poured into water, extracted with ether (3 x 100 ml), washed with aq. $NaHCO_3$, brine, dried and solvent removed to get the crystalline lactone 22 (5.5 g, 46%), m.p.85° (aq.ethanol). IR (Nujol): 1770, 1675, 1605, 1235, 1015, 850. PMR ($CDCl_3$): $\delta$ 7.69 (AB quartet, 4H, ar-H, J=6 Hz); 4.56 (m, 2H, $0=\overset{|}{C}-0-\underline{CH_2}-$); 2.80 (m, 2H, benzylic $\underline{CH}$ and $0=\overset{|}{C}-\underset{\underset{CH_2}{|}}{\underline{CH}}-CH_2$); 1.28 (d, 2 x 3H, isopropyl Me's, J=5 Hz). (Found: C, 72.03; H, 7.13; $C_{14}H_{16}O_3$ requires: C, 72.39; H, 6.94%).

A mixture of 22 (5.5 g, 25 mmol) in 1% methanolic NaOMe (50 ml, 10 mmol) was stirred at room temp for 15 min, acidified with dilute HCl, extracted with ether (2 x 50 ml) and separated the acid with 2% aqueous NaOH. Acidification of the alkaline extract, extraction with ether (3 x 50 ml), washing with brine, drying, removal of solvent and distillation gave the enone acid 23 (3.2 g, 60%), b.p.180°/2 mm. IR (smear): 1710, 1650, 1600, 1000, 855, 800. PMR ($CCl_4$): $\delta$ 7.33 (AB quartet, 4H,

ar-H, J=8 Hz); 5.80, 5.60 (two s, 1H each, $>C=C\underline{H}_2$); 3.4 (s, 2H, $0=\overset{|}{C}-\underset{\|}{C}-C\underline{H}_2COOH$); 2.9 (septet, 1H, benzylic H); 1.22 (d, 2 x 3H, isopropyl Me's, J=8 Hz). (Found: C, 71.0; H, 6.9. $C_{14}H_{16}O_3$ requires: C, 72.4; H, 6.9%).

Methyl-(4-isopropylphenyl)-3-methyl-butanoate 26 from 23. A stirred solution of the enone 23 (2 g) in AcOH (20 ml) was hydrogenated with Adams $PtO_2$ catalyst (55 mg) when the dihydro derivative 24 (1.9 g) was obtained. This was subjected to Clemmensen reduction with amalgamated zinc (10 g), conc.HCl (10 ml), water (5 ml) and toluene (10 ml) at reflux temp for 30 hr; conc. HCl (10 ml) was added at intervals of 6 hr. The crude product was chromatographed on a column of silica gel and the faster-moving pure compound 25 (0.8 g, 45%) separated from the unwanted polar byproduct. Treatment of 25 with ethereal $CH_2N_2$ and distillation afforded the ester 26 as a colourless liquid, b.p.160°(bath)/2 mm. IR(smear): 1745, 1520, 1210, 1160, 810, PMR ($CCl_4$): $\delta$ 3.58 (s, 3H, COOMe); 1.23 (d, 2 x 3H, isopropyl Me's, J=8 Hz); 0.94 (d 3H, sec-Me, J=5 Hz). MS: m/z 234 ($M^+$). (Found: C, 77.2; H, 9.6. $C_{15}H_{22}O_2$ requires: C, 76.9; H, 9.5%).

1,1,3-Trimethyl-7-isopropyl tetralin 17 from ester 26. The ester 26 (0.52 g) in dry ether (20 ml) was treated with excess MeLi (2 ml of 3 molar solution in ether) and stirred under $N_2$ for 17 hr. The mixture was quenched in cold water, the

ether layer separated and the aqueous portion extracted with more ether. The combined organic extract was washed with brine, dried, solvent removed and the residue distilled to yield the carbinol 27 (0.35 g, 70%). IR (smear): 3400, 1150, 820. PMR ($CCl_4$): δ 7.0 (s, 4H, ar-H); 1.21 (d, 2 x 3H, isopropyl Me's, J=6 Hz); 1.13 (s, 2 x 3H, tert.Me's); 0.91 (d, 3H, sec-Me, J=6 Hz). Polyphosphoric acid (from 2.4 ml of $H_3PO_4$ and 4.8 g of $P_2O_5$) was treated with the carbinol 27 (0.32 g) at 100° for 30 min. The mixture was quenched in ice water, extracted with light petroleum and the residue distilled to afford the tetralin 17 (0.2 g, 62%) whose spectral data (IR/PMR) were identical with the tetralin derived from 2 by $BF_3.OEt_2$ rearrangement.

# REFERENCES


1 Goudgaon N M, Shitole H R & Nayak U R, Indian J Chem (in press).

2a) Jadhav P K & Nayak U R, J Sci Ind Res 39 (1980) 36.

b) Sukh Dev, Prog Chim Org Nat Prod 40 (1981) 50.

c) Stehelin L, Lhomme J & Ourisson G, J Am Chem Soc 93 (1971) 1650.

3a) Nayak U R & Sukh Dev, Tetrahedron 8 (1960) 42.

b) Prahlad J R, Nayak U R & Sukh Dev, Tetrahedron 26 (1970) 663.

4a) Berson J A, Hammons J H, McRow A W, Bergman R G, Romanick A & Houston D, J Am Chem Soc 89 (1967) 2590.

b) Yadav J S, Nayak U R & Sukh Dev, Tetrahedron 36 (1980) 309.

c) Yadav J S, Soman R, Sobti R R, Nayak U R & Sukh Dev, Tetrahedron 36 (1980) 2105.

d) Shitole H R & Nayak U R, Indian J Chem 22B (1983) 215.

5a) Ranganathan R, Nayak U R, Santhanakrishnan T S & Sukh Dev Tetrahedron 26 (1970) 621.

b) Beyler R E & Ourisson G, J Org Chem 30 (1965) 2838.

6 Bisarya S C, Nayak U R & Sukh Dev, Tetrahedron Lett (1969) 2323.

7 Berliner E, Organic Reactions 5 (1949) 229.

8a) Rothstein E & Saboor M A, J Chem Soc (1943) 425.

b) Sukh Dev & Guha P C, J Ind Chem Soc 25 (1948) 13.

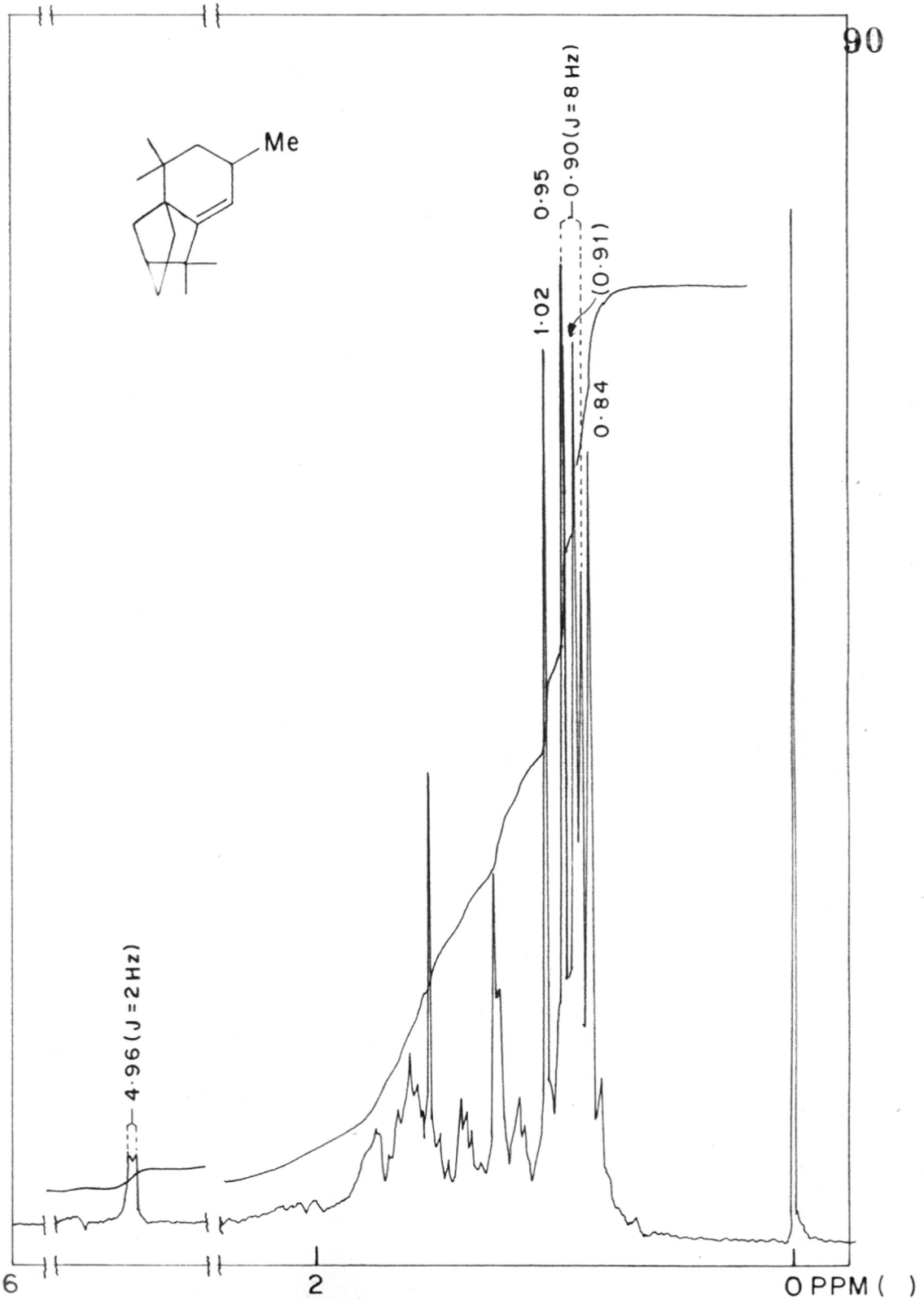
9 Cignarilla G, Grella G & Curzu M M, Synthesis (1980) 825.

10 Fieser L F & Fieser M, Reagents for Organic Synthesis, Vol 1, p 70 (John Wiley NY, 1967).

11 Gupta A S & Sukh Dev, J Chromatog 12 (1963) 189.

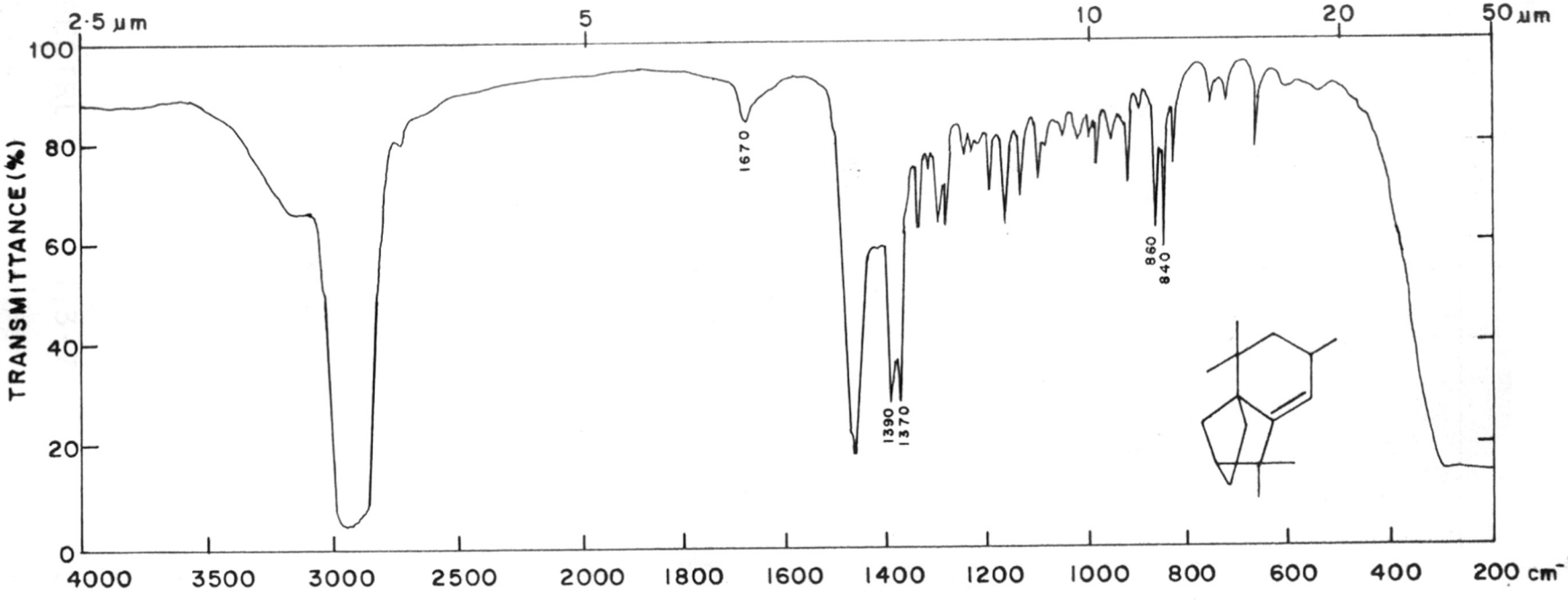
12a) Smith L I & Lo C P, J Am Chem Soc 70 (1948) 2209.

b) Farnum D G, Roger A M & Mehta G, J Am Chem Soc 95 (1973) 8692.

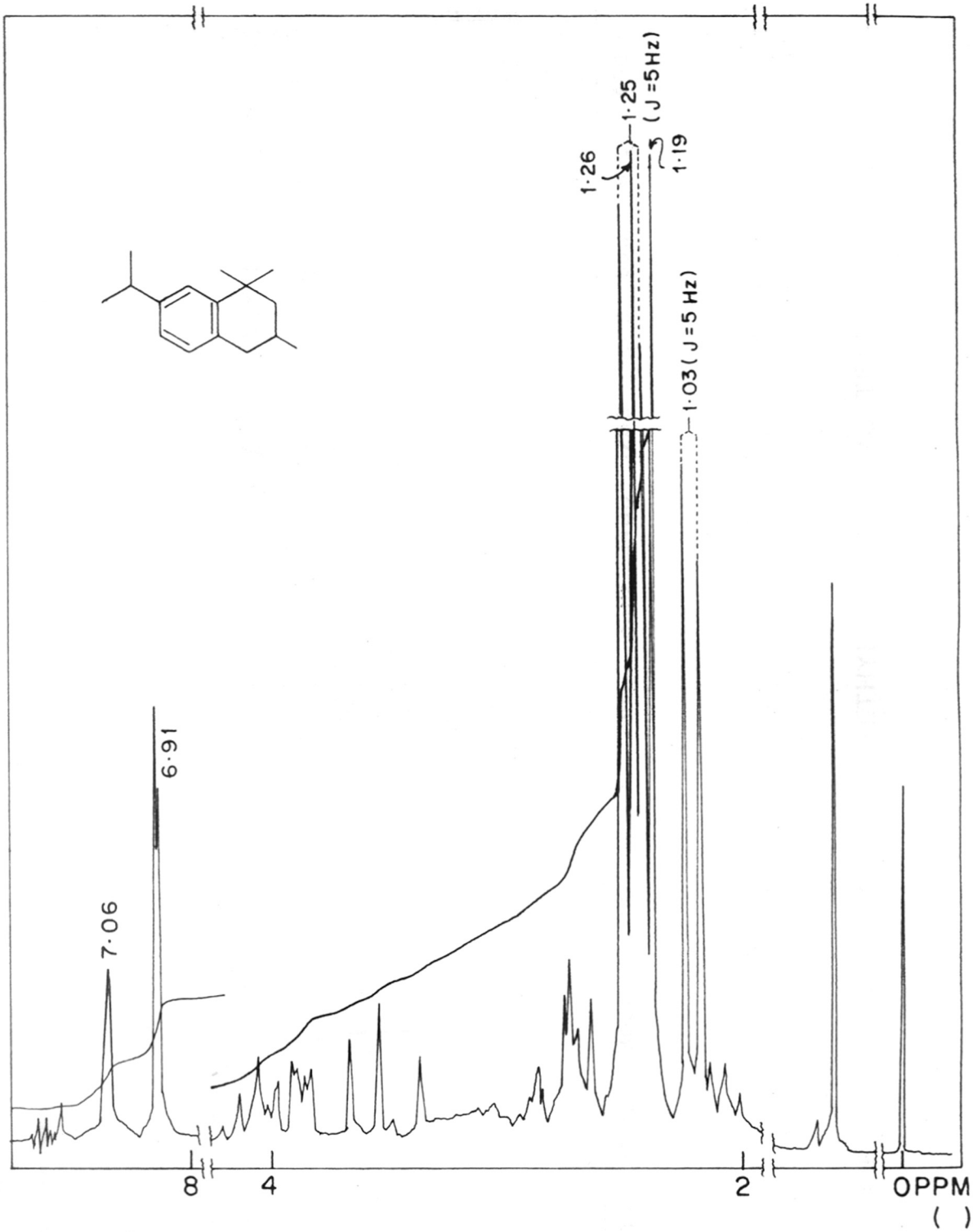



PMR SPECTRUM OF 9-METHYL ISOLONGIFOLENE 13

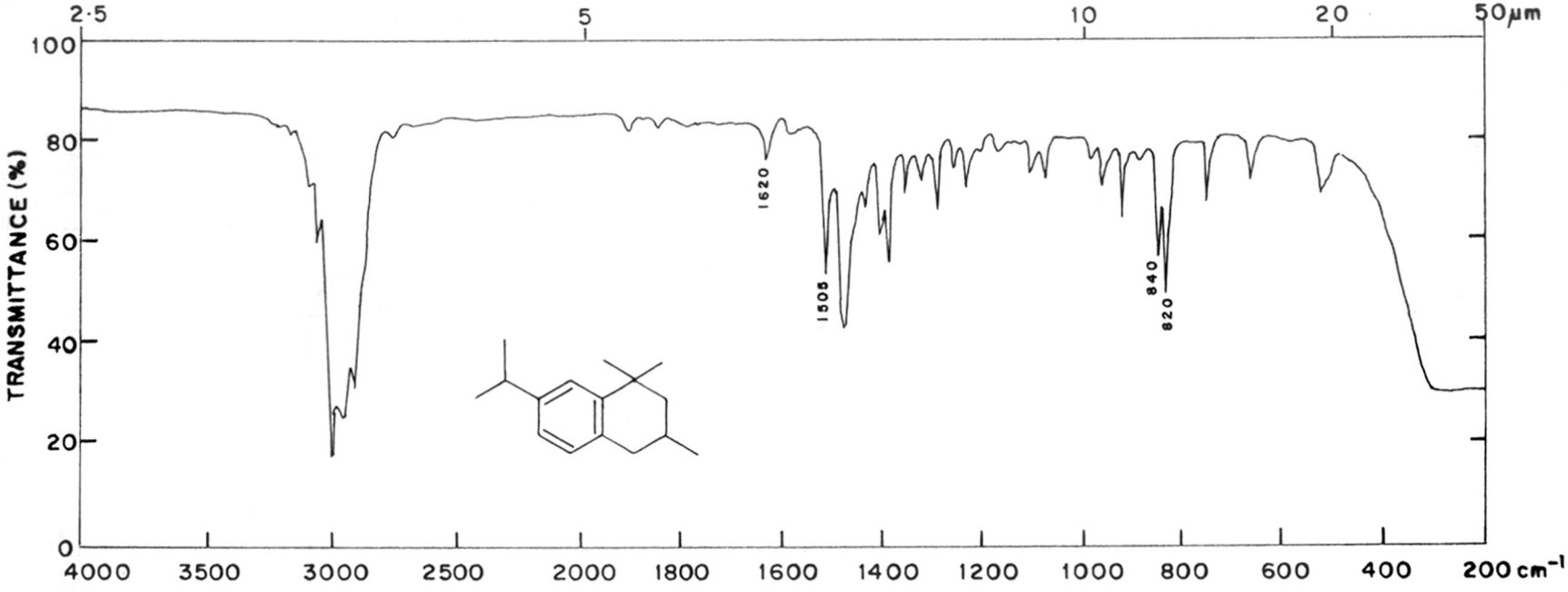
( R = Me )



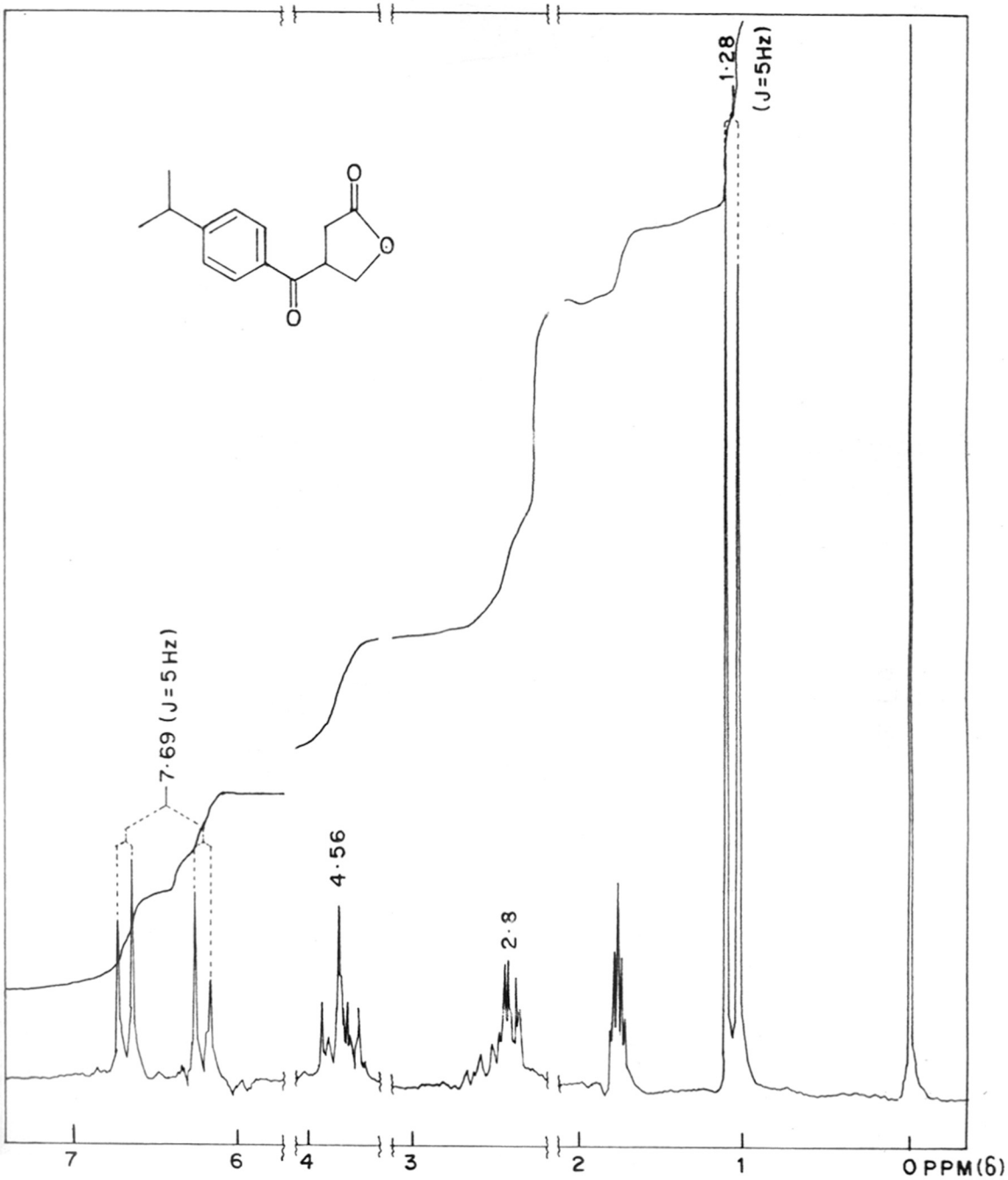

IR SPECTRUM OF 9-METHYL ISOLONGIFOLENE 13 (R = Me)




PMR SPECTRUM OF 1,1,3-7-ISOPROPYL TETRALIN 17 (R=Me)




IR SPECTRUM OF 1,1,3-TRIMETHYL-7-ISOPROPYL TETRALIN 17 (R = Me)

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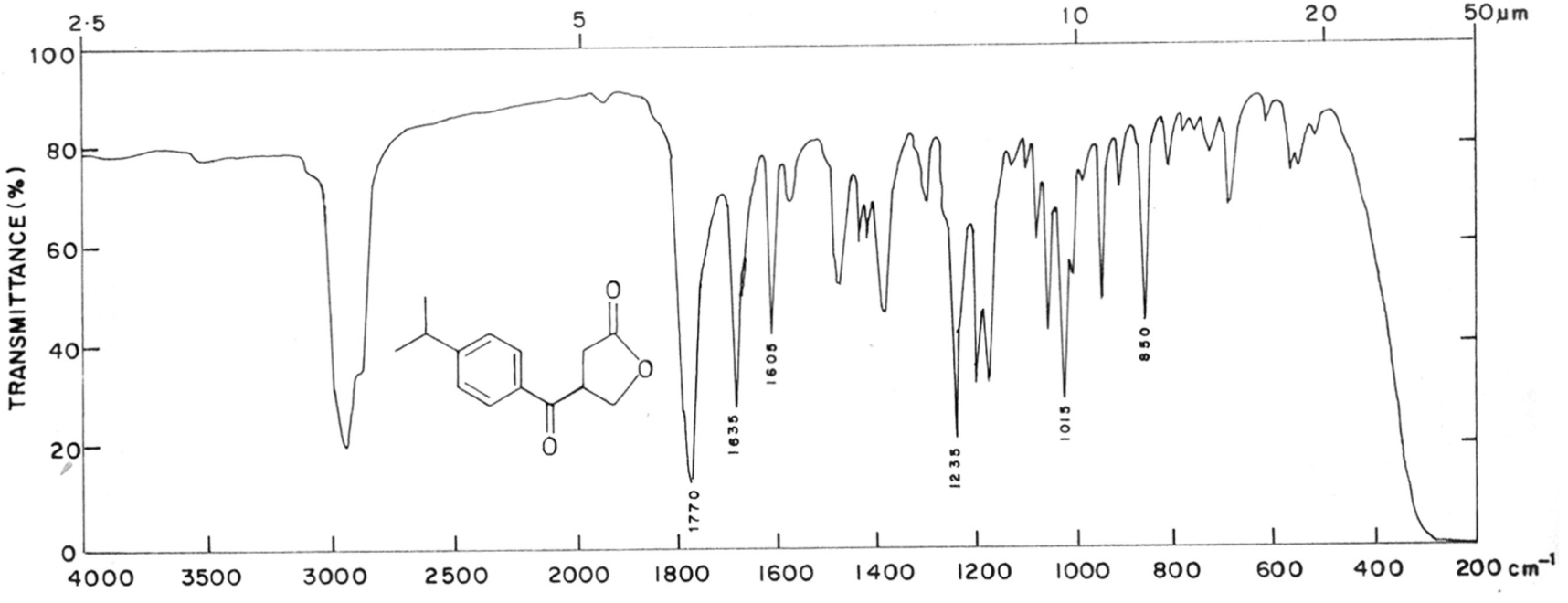


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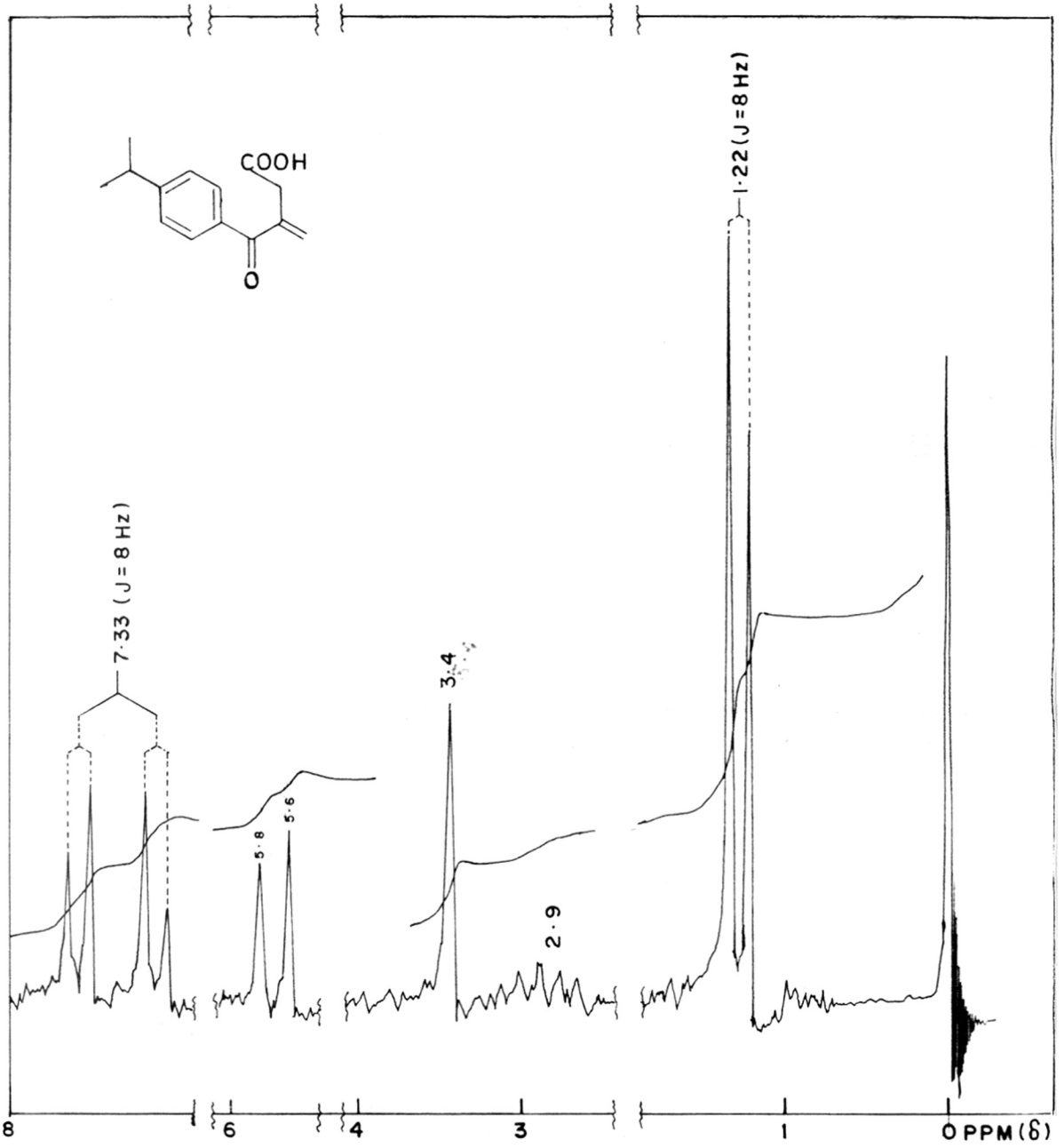
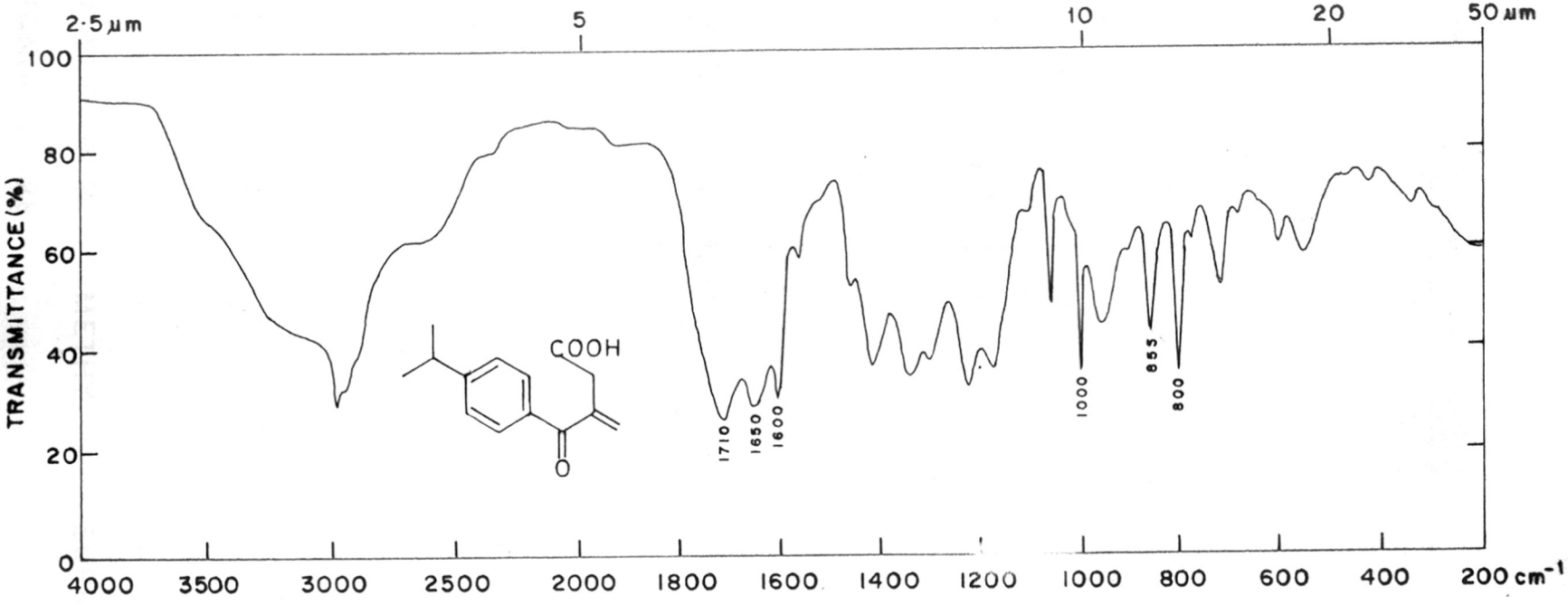



PMR SPECTRUM OF ENONE ACID 23

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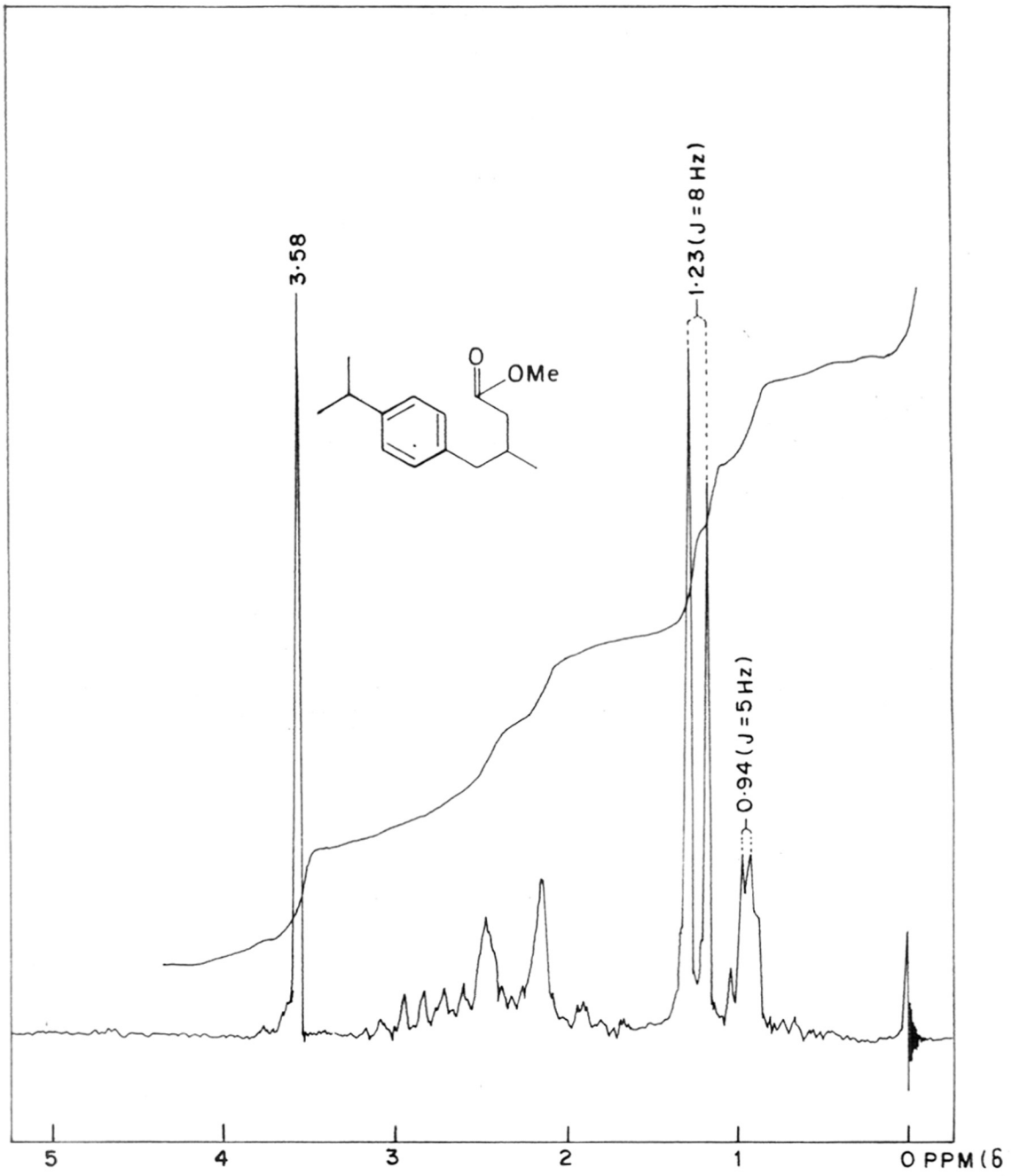
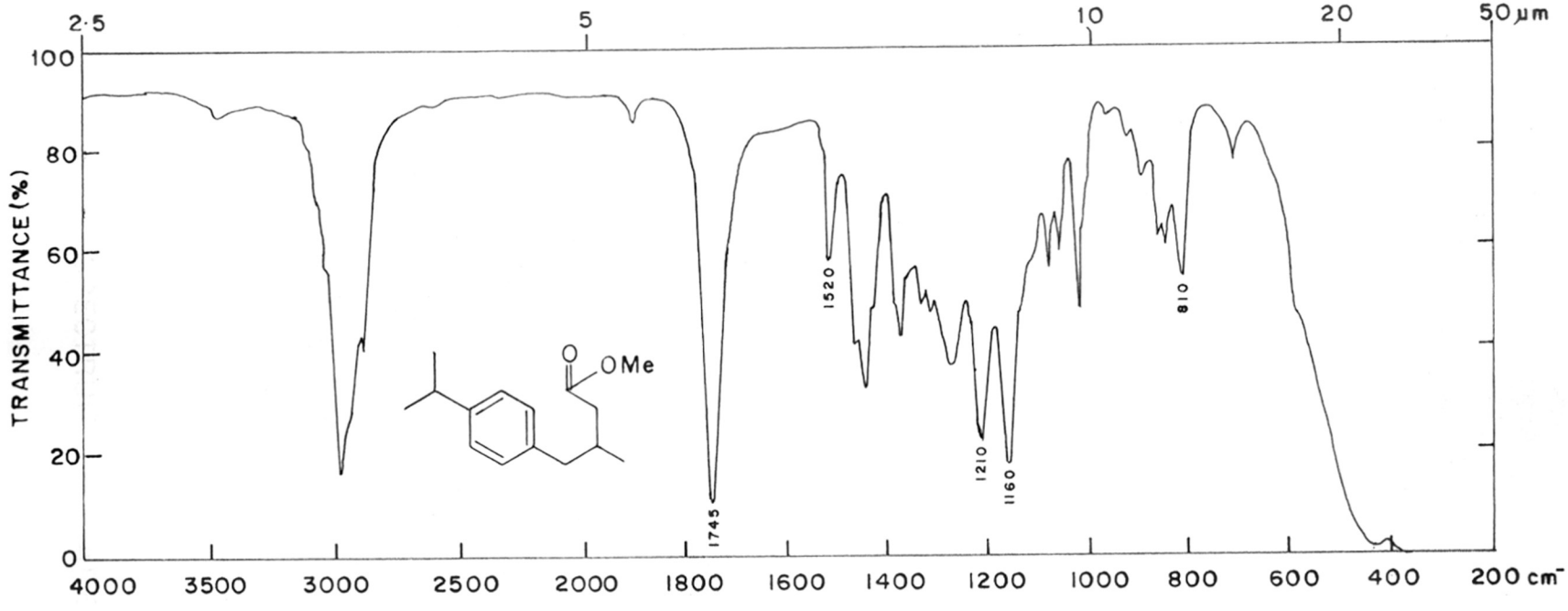
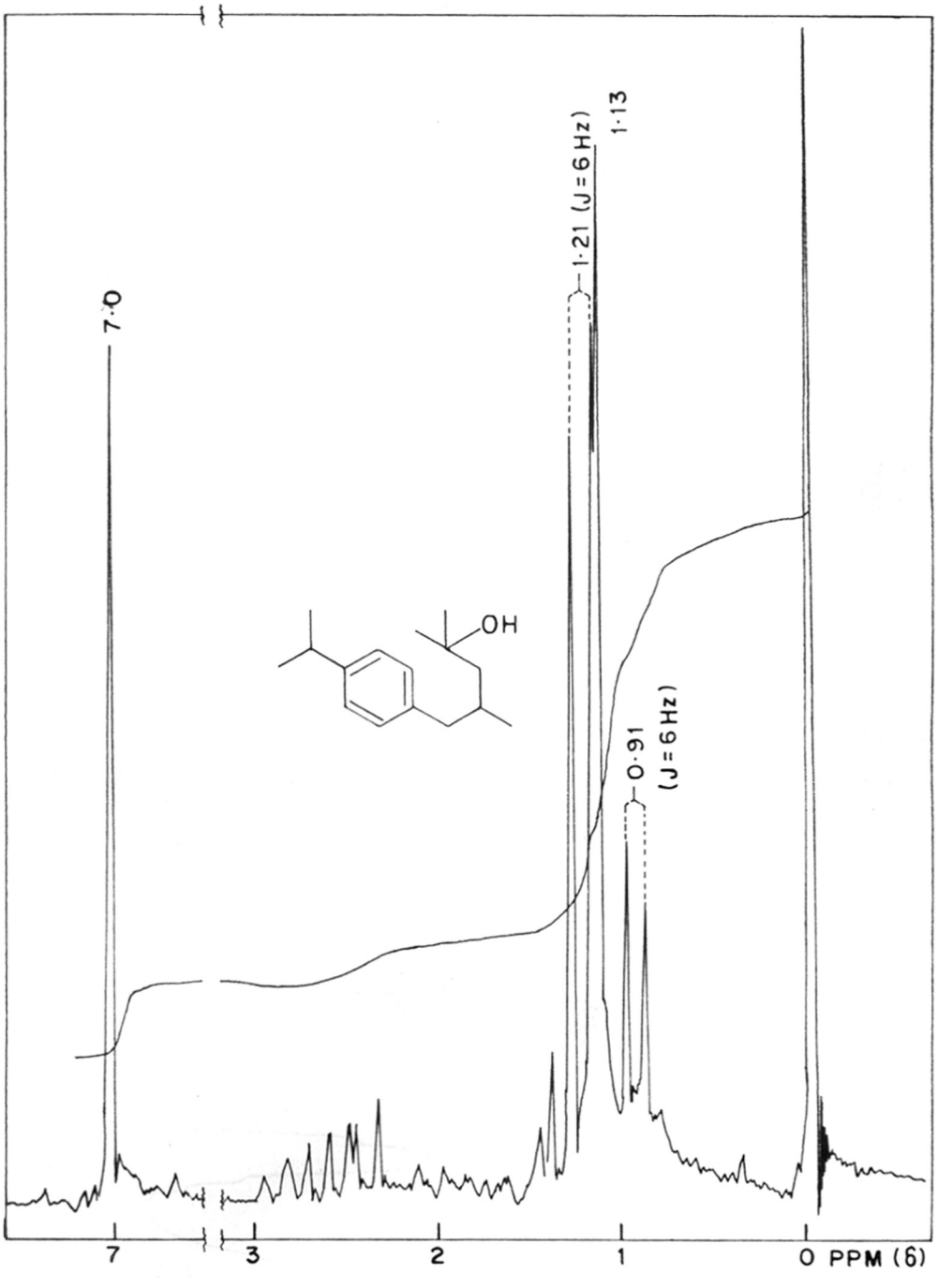


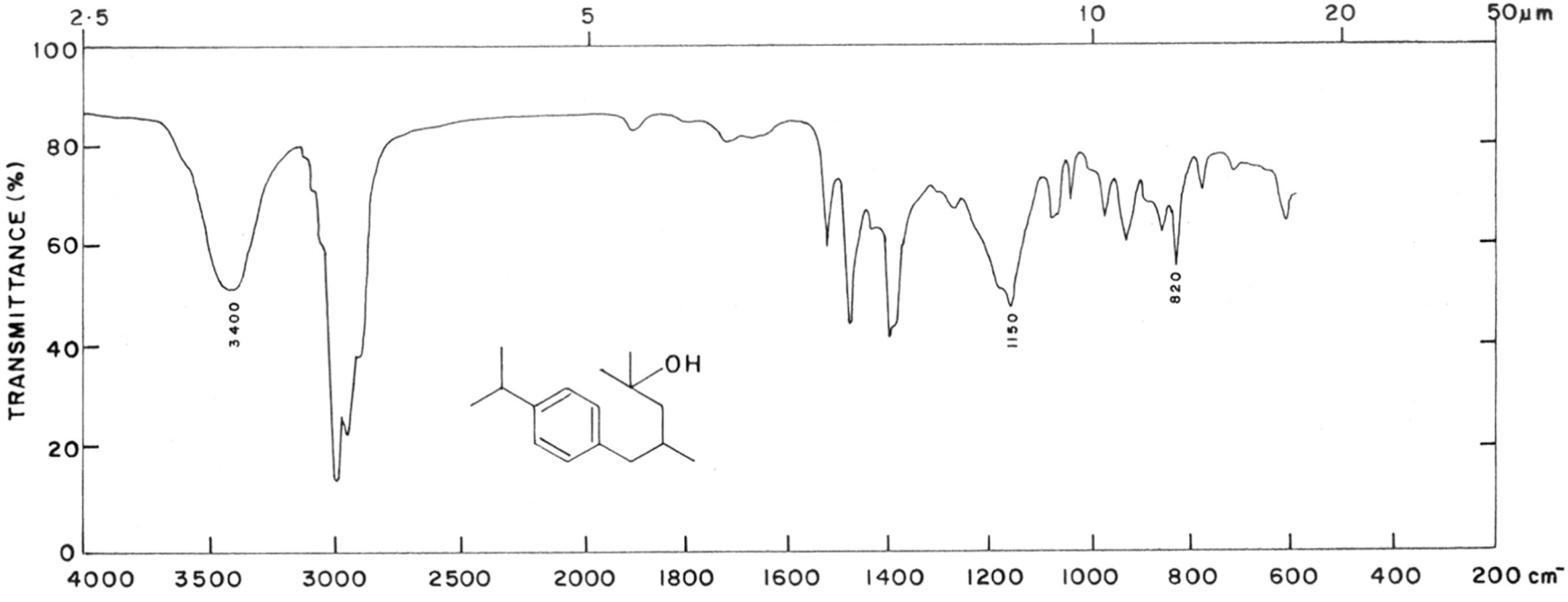

PMR SPECTRUM OF METHYL-(4-ISOPROPYL)-3-METHYL-BUTANOATE 26




IR SPECTRUM OF METHYL-(4-ISOPROPYL)-3-METHYLBUTANOATE 26




PMR SPECTRUM OF CARBINOL 27




IR SPECTRUM OF CARBINOL 27

# CHAPTER-5

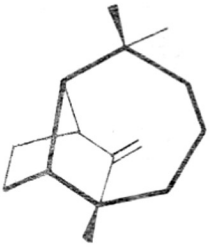
## LONGIHOMOCAMPHENILANE-7,8-DIONE : A STUDY ON THE REACTIVITY OF THE CARBONYL GROUPS VIA MONOFUNCTIONAL DERIVATIVES OF THE DIKETONE

## ABSTRACT

Formation of the C-7 ketone, longiisohomocamphenilone 9, by Raney nickel desulphurization of the monothioketal of longihomocamphenilane-7,8-dione 2, fixes C-8 as the reactive carbonyl (attached to a secondary carbon) of the diketone; longicamphorquinone 4, however, gives longiepicamphor 6 instead of the expected longicamphor 7 by this method. The monoxime derived from 2, on exposure to tosyl chloride/aqueous KOH, undergoes a Beckmann fragmentation to give the cyanoacid 14 which also fixes C-8 carbonyl as the reactive of the two in longidione 2. Kochi oxidative decarboxylation of 14 with Pb(IV)-Cu(II) gives the vinylidene nitrile 17 as the major product.

LONGIHOMOCAMPHENILANE-7,8-DIONE 2 (longidione) is a ring-enlarged bridged, tricyclic ∝-diketone derived[1] from longifolene 1 by reaction with a variety of oxidants but generally formed in poor yields. It has been characterized[2] by the preparation of several monoderivatives- monosemicarbazone, monophenylhydrazone, mono-p-bromophenylhydrazone and monoxime. Apart from the quinoxaline derivative 3 (formed by reaction with O-phenylenediamine), no derivative in which the second carbonyl group has reacted[2] has been prepared. It has also been proved[3] that longidione possesses ∝-to the dicarbonyl group only a single unenolizable hydrogen atom and was assumed to be consequently at the bridgehead as in 2. Since longidione 2 is known to yield only homogeneous monoderivatives, the carbonyl at C-7 was presumed[2] to be the more hindered since it was attached to a tertiary carbon as compared to C-8 attached to a secondry carbon. Since we have experimental proof (vide infra) that this statement is not generally true, it became necessary to provide chemical evidence which unambiguously fixes the C-8 carbonyl as the reactive moiety of the diketone 2 which gives only monoderivatives.

Longicamphorquinone[4] 4 (a 1,2-diketone structurally closely related to 2), on treatment with ethanedithiol/boron-trifluoride etherate, afforded only a monothioketal; on Raney nickel desulphurization this gave an isomer of longicamphor[5] 7



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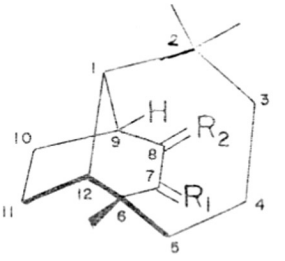
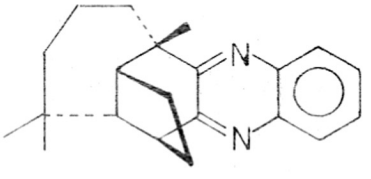



2 : $R_1 = R_2 = O$

8 : $R_1 = O$, $R_2 = \begin{matrix} S \\ S \end{matrix}$]

9 : $R_1 = O$, $R_2 = H, H$

13 : $R_1 = O$, $R_2 = NOH$

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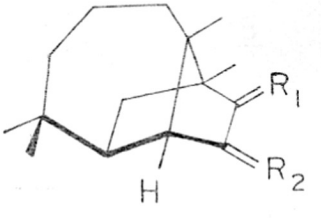
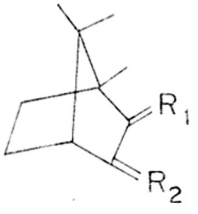



4 : $R_1 = R_2 = O$

5 : $R_1 = \begin{matrix} S \\ S \end{matrix}$] ; $R_2 = O$

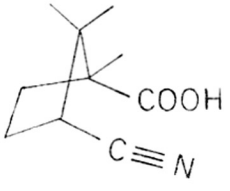
6 : $R_1 = H, H$ ; $R_2 = O$

7 : $R_1 = O$ ; $R_2 = H, H$




10: $R_1 = R_2 = O$

11: $R_1 = O$; $R_2 = NOH$

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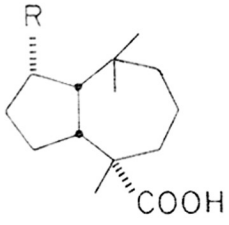
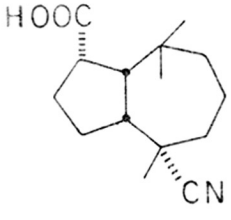



14: R = CN

16: R = COOH

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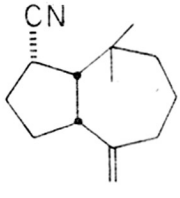


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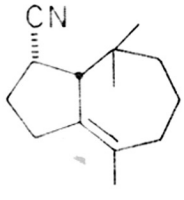


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i.e. longiepicamphor 6 (necessarily arising from thioketal 5) instead of the expected ketone 7, which should have formed if ethane-dithiol had attacked the carbonyl attached to the secondary carbon in 4. When the monothioketal of longidione 2 was similarly prepared and desulphurized, the resulting monoketone was identified with the known C-7 ketone, longi-isohomocamphenilone[6] 9; on this basis its precursor thioketal should be formulated as 8. In the latter case the derivative formation has therefore taken place at the carbonyl attached to the secondary carbon while in the former example 4 the carbonyl linked to the tertiary carbon was involved in thioketal formation.

In an earlier paper[7] we have described the tosylchloride/pyridine-induced Beckmann fragmentation[8] of the ketoximes derived from the pair camphor/longicamphor. In the present work, the monoxime 11 of camphor-quinone 10 was also treated with tosyl chloride but in aqueous alkali at ambient temperature. The crystalline product, isolated from the alkaline reaction mixture by acidification, was readily characterized as the cyano acid 12, arising from a Beckmann fission. Under similar reaction conditions, the monoxime of longidione 2 also gave a cyano acid (m.p.129°; 53%) for which structure 14 (and not 15) could be assigned on the basis of its PMR data: the downfield 3H-singlet at 1.37 $\delta$ is characterestic[10] of the tertiary methyl on a carbon

bearing a carboxyl group, is present in 14 only; this fixes the oxime structure as 13. The cyano group in 14 was however quite resistant to hydrolysis; even after refluxing the compound in ethylene glycolic KOH for several hours, it failed to give $\Delta$-longiforic acid[9] 16 (IR spectrum exhibited cyano and amide absorption bands). In conformity with the assigned structure 14, the cyano acid gave the vinylidene nitrile 17 (plus minor amount of 18) on Kochi[11] oxidative decarboxylation with Pb(IV)-Cu (II); this chemical evidence also confirms the structure 13 for its progenitor oxime.

## EXPERIMENTAL

All m.p's and b.p's are uncorrected. Light petroleum refers to the fraction b.p.60-80°. Solvent extracts were dried over anhydrous $Na_2SO_4$. Tosyl chloride used was freshly purified[12] and recrystallized. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded as smear (liquid) or nujol mull (solid) on a Pye Unicam SP-3 IR spectrophotometer. PMR spectra were taken on a Varian T 60/FT 80A/Bruker WH-90 FT spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system.

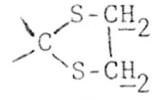
Longidione 2. This was prepared from ω-bromolongifolene via the simplified sequence of reactions described[9] by Deshpande, Suryawanshi and Nayak.

Longidione quinoxaline 3.

A mixture of longidione 2 (2.34 g), AcOH (25 ml) and o-phenylenediamine (2.34 g) was refluxed for 4 hr. The mixture was quenched in ice water, the separated solid was filtered off and recrystallized from MeOH to give colourless crystals of the quinoxaline derivative 3, m.p.134°(2 g, 66%). IR (Nujol): 1550, 772. PMR ($CCl_4$): δ 7.40 to 8.00 (m, 4H, aromatic); 3.43 (m, 1H, HC-C=N as in 3); 1.37, 1.10, 0.93 (three tertiary Me singlets). MS: m/z 306 ($M^+$, base peak). (Found: C, 82.6; H, 8.6; N, 8.8. $C_{21}H_{26}N_2$ requires: C, 82.3; H, 8.6; N, 9.1%).

Longicamphorquinone 4. This was prepared by the action of $SeO_2$-AcOH on longicamphor.

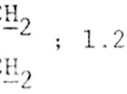
Longicamphorquinone monothioketal 5

A mixture of longicamphorquinone 4 (1.2 g), AcOH (1 ml), ethanedithiol (0.6 ml) and $BF_3.OEt_2$ (0.6 ml) was kept at room temp. overnight. The separated solid was filtered off and recrystallised from MeOH when the monothioketal 5 was obtained in colourless needles m.p.142-44° (0.85 g, 52%). IR(Nujol): 1740, 1180, 1100, 865 $cm^{-1}$. PMR ($CCl_4$): $\delta$ 2.93 to 3.57 (m, 4H,  ; 1.12, 1.02 x 2, 0.82 (four tertiary Me singlets). (Found: C, 65.1; H, 8.6; S, 20.0. $C_{17}H_{26}OS_2$ requires: C, 65.8; H, 8.4; S, 20.6%).

Desulphurization of monothioketal 5: Formation of longiepicamphor 6

A mixture of monothioketal 5 (0.5 g), ethanol (50 ml) and Raney nickel (W-2, 5 g) was refluxed on a waterbath (17 hr). The mixture was filtered, the precipitate thoroughly washed with more EtOH and the filtrate taken to dryness. Distillation of the residue gave longiepicamphor 6 as a colourless liquid b.p.125°(bath)/0.5 mm which solidified m.p.55° (0.25 g; 69%). IR (Nujol): 1740, 1420, 1200, 1170, 1060. PMR ($CCl_4$): $\delta$1.05 x 2, 0.90, 0.83 (four tertiary Me singlets). (Found: C, 81.8; H, 11.4. $C_{15}H_{24}O$ requires: C, 81.8; H, 11.0%).

Longidione monothioketal 8

A mixture of longidione 2 (11.7 g), AcOH (10 ml), ethanedithiol (5 ml) and $BF_3.OEt_2$ (5 ml) was kept at room temp (48 hr). The mixture was poured into water (50 ml), extracted with benzene (3 x 100 ml), washed with aqueous $NaHCO_3$, brine, dried, solvent removed and the residue recrystallized from MeOH when the monothioketal 8 was obtained in colourless micro prisms m.p.99°-101° (4.2 g, 27%). IR (Nujol): 1695, 1080, 990, 930. PMR ($CCl_4$): δ 2.67 to 3.57 (m, 4H,  ; 1.20, 1.13, 1.02 (three tertiary Me singlets). MS: m/z 310 ($M^+$, base peak). (Found: C, 65.9; H, 8.6; S, 19.7. $C_{17}H_{26}OS_2$ requires: C, 65.8; H, 8.4; S, 20.6%).

Desulphurization of monothioketal 8. Formation of longi-isohomocamphenilone 9

A mixture of monothioketal 8 (1 g), ethanol (100 ml) and Raney nickel (W-2, 12 g) was refluxed (17 hr) and the isolated product m.p.68-69° (0.63 g, 69%) was identified as the C-7 ketone 9 (m.mp. IR/PMR).

Camphorquinone monoxime 11

A mixture of camphorquinone 10 (5.0 g), ethanol (50 ml), hydroxylamine hydrochloride (2.3 g) and pyridine (2.3 ml) was refluxed for 1 hr. The mixture was diluted with water (200 ml), saturated with sodium chloride, extracted with benzene (100 ml x 3), washed with brine, dried, solvent

removed and the residue recrystallized from benzene-light petroleum to give colourless prisms of the monoxime 11, m.p.112-14° (2.1 g, 38%). IR (Nujol): 3200, 1740, 1640, 1010, 940, 890. PMR (pyridine): $\delta$ 3.43 (d, 1H, -CH-C=N as in 11, J=4 Hz), 1.03, 0.87 x 2 (three tertiary methyl singlets). MS: m/z 181 ($M^+$). (Found: C, 65.6; H, 8.5; N, 8.8. $C_{11}H_{15}O_2N$ requires: C, 66.1; H, 8.3; N, 7.9%).

Action of tosyl chloride/aq. KOH on monoxime 11: Formation of cyano acid 12

A solution of the monoxime 11 (1.8 g) in aqueous KOH (3 g in 30 ml of water) was treated with tosyl chloride (1.9 g) and stirred for 3 hr. The mixture was diluted with water (50 ml), filtered and the filtrate acidified with HCl and cooled. The separated solid was filtered off and recrystallized from benzene to afford the cyano acid 12, m.p.151-52° (0.95 g, 52%). IR (Nujol): 2200, 1690, 1290, 1170, 1130, 955. PMR ($CDCl_3$): $\delta$ 11.09 (br s, 1H, -COOH); 1.27, 1.25, 1.17 (three tertiary Me singlets). (Found: C, 66.6; H, 8.4; N, 7.3. $C_{10}H_{15}O_2N$ requires: C, 66.3; H, 8.3; N, 7.7%).

Longidione monoxime 13

A mixture of longidione 2 (14 g), ethanol (100 ml), hydroxylamine hydrochloride (5 g) and pyridine (5 ml) was refluxed on a waterbath (16 hr). The mixture was poured into water (200 ml), cooled and the separated solid filtered off. Recrystallization from light petroleum gave colorless crystals of the monoxime 13, m.p.224-25° (11.3 g, 77%). IR (Nujol):

3000, 1700, 1600, 1060, 970, 940. PMR($CDCl_3$): $\delta$ 9.97 (b, 1H, NH, exchanges with $D_2O$); 3.90 (m, 1H, HC-$\dot{C}$=N as in 13); 1.13, 1.10, 1.02 (three tertiary Me singlets). Mass: m/z 249 ($M^+$). (Found: C, 70.9; H, 9.6; N, 5.9. $C_{15}H_{23}O_2N$ requires: C, 72.3; H, 9.3; N, 5.6%).

Action of tosylchloride/aq KOH on monoxime 13: Formation of cyano acid 14

A solution of monoxime 13 (20 g) in aqueous KOH (24 g in 240 ml of water) was stirred and treated with tosyl chloride (16 g) in small portions (during 0.5 hr). After stirring for 1 hr more, the mixture was diluted with water (100 ml), filtered and the filtrate cooled and acidified with HCl. The separated solid was filtered off and recrystallized from benzene-light petroleum to furnish colourless crystals of the cyano acid 14, m.p.127-29° (10.5 g, 53%). IR (Nujol): 2500-2700 (br), 2200, 1690, 1260, 1190, 950. PMR ($CCl_4$): $\delta$ 11.40 (br s, 1H, COOH); 2.90 (m, 1H, -$H_2C$-$\dot{C}$H-CN as in 14); 1.37, 1.18 x 2 (three tertiary Me singlets). (Found: C, 72.3; H, 9.5; N, 5.6. $C_{15}H_{23}O_2N$ requires: C, 72.3; H, 9.3; N, 6.6%).

Methyl ester of cyano acid 14 ($CH_2N_2$ method): colourless liquid, b.p.200°(bath)/2 mm. IR (smear): 2200, 1725, 1240, 990. PMR ($CCl_4$): $\delta$ 3.60 (s, 3H, COOMe); 1.23, 1.10, 1.05 (three tertiary Me singlets). MS: m/z 263 ($M^+$). (Found: C, 73.5; H, 9.7; N, 5.3. $C_{16}H_{25}O_2N$ requires: C, 73.0; H, 9.6; N, 5.3%).

Pb(IV)-Cu(II) oxidative decarboxylation of cyano acid 14: Formation of cyano olefins 17/18

A mixture of cyano acid 14 (15.1 g), dry benzene (600 ml), lead tetraacetate (61 g), pyridine (1 ml) and cupric acetate (1 g) was stirred under reflux for 2 hr. Excess LTA was then decomposed by addition of ethanediol (17 ml) and stirring for 10 min more. The mixture was cooled, benzene layer decanted off and the residue thoroughly extracted with more benzene (3 x 100 ml). The combined organic extract was successively washed with 5% aqueous KOH, water, brine, dried, solvent removed and the residue distilled to yield a mixture of olefinic nitriles b.p.130-35°/1 mm (9.4 g). This was chromatographed on a column of 15% $AgNO_3$-silica gel (250 g; 10 cm x 2.6 cm): Fr. 1, light petroleum-benzene (1:1), 6 x 200 ml, pure. Fr. 2, benzene, 9 x 200 ml, pure.

Fr.1 was distilled to give the endocyclic olefin 18 as a colourless liquid, b.p.160°(bath)/0.7 mm (1.35 g, 11%). IR(smear): 2180, PMR ($CCl_4$): $\delta$ 1.77 (br s, 3H, vinylic Me); 1.23, 1.17 (two tertiary Me singlets). CMR ($CDCl_3$; off-resonance) 134.26 (s, C=N); 130.11 and 123.81 (two s, >C=C<). MS: m/z 203. (Found: C, 82.8; H, 10.1; N, 6.8. $C_{14}H_{21}N$ requires: C, 82.7; H, 10.4; N, 6.9%).

Fr. 2 was distilled to furnish the vinylidene nitrile 17 as a colourless liquid b.p.170°(bath)/1 mm (5.1 g, 41%) which became a waxy solid on keeping; m.p.47-48°. IR (smear): 2900, 2180, 1625, 900. PMR ($CCl_4$): $\delta$4.73 (s, 2H, $\rangle C=CH_2$), 1.13, 1.07 (two tertiary Me singlets). Mass: m/z 203 ($M^+$). (Found: C, 82.1; H, 10.3; N, 7.5. $C_{14}H_{21}N$ requires: C, 82.7; H, 10.4; N, 6.9%).

## REFERENCES


1 For e.g. See a) Lhomme J & Ourisson G, Recherches 15 (1966) 16.

b) Jadhav P K & Nayak U R, J Sci Ind Res 39 (1980) 36.

c) Sukh Dev, Prog Chem Org Nat Prod 40 (1981) 50.

2 Simonsen J L & Barton D H R, The Terpenes Vol III, p.96 Cambridge University Press (1951).

3 Naffa P & Ourisson G, Bull Soc Chim (1954) 1115.

4 Shitole H R & Nayak U R, Indian J Chem 23B (1984) 415.

5 Suryawanshi S N & Nayak U R, Tetrahedron Lett (1977) 2619; Indian J Chem 19B (1980) 1.

6 Mehra M M, Ghatge B B & Bhattacharyya S C, Tetrahedron 21 (1965) 637.

7 Satyanarayana N, Shitole H R & Nayak U R, Indian J Chem (in press).

8a) Donaruma L G & Heldt W Z, Organic Reactions 11 (1960) 1.

b) Smith P A S in Molecular Rearrangements Vol 1 ed P de Mayo (Interscience NY) 1963) p. 483.

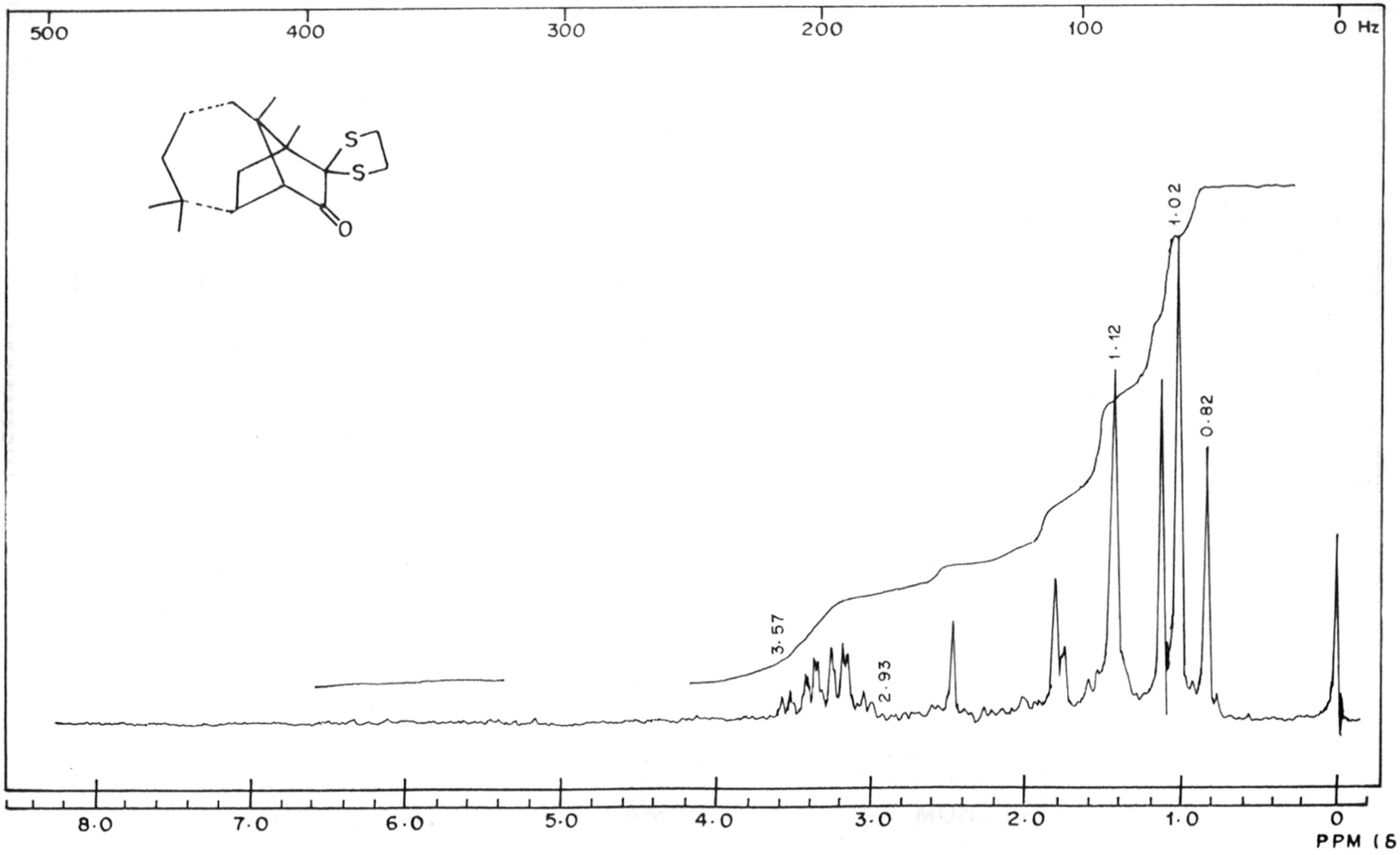
c) Conley R T & Ghosh S in Mechanisms of Molecular Migrations Vol 4 ed. Thyagarajan B S (Wiley, N Y) 1971, p.197.

9 Deshpande R P, Suryawanshi S N & Nayak U R, Indian J Chem 17B (1979) 617.

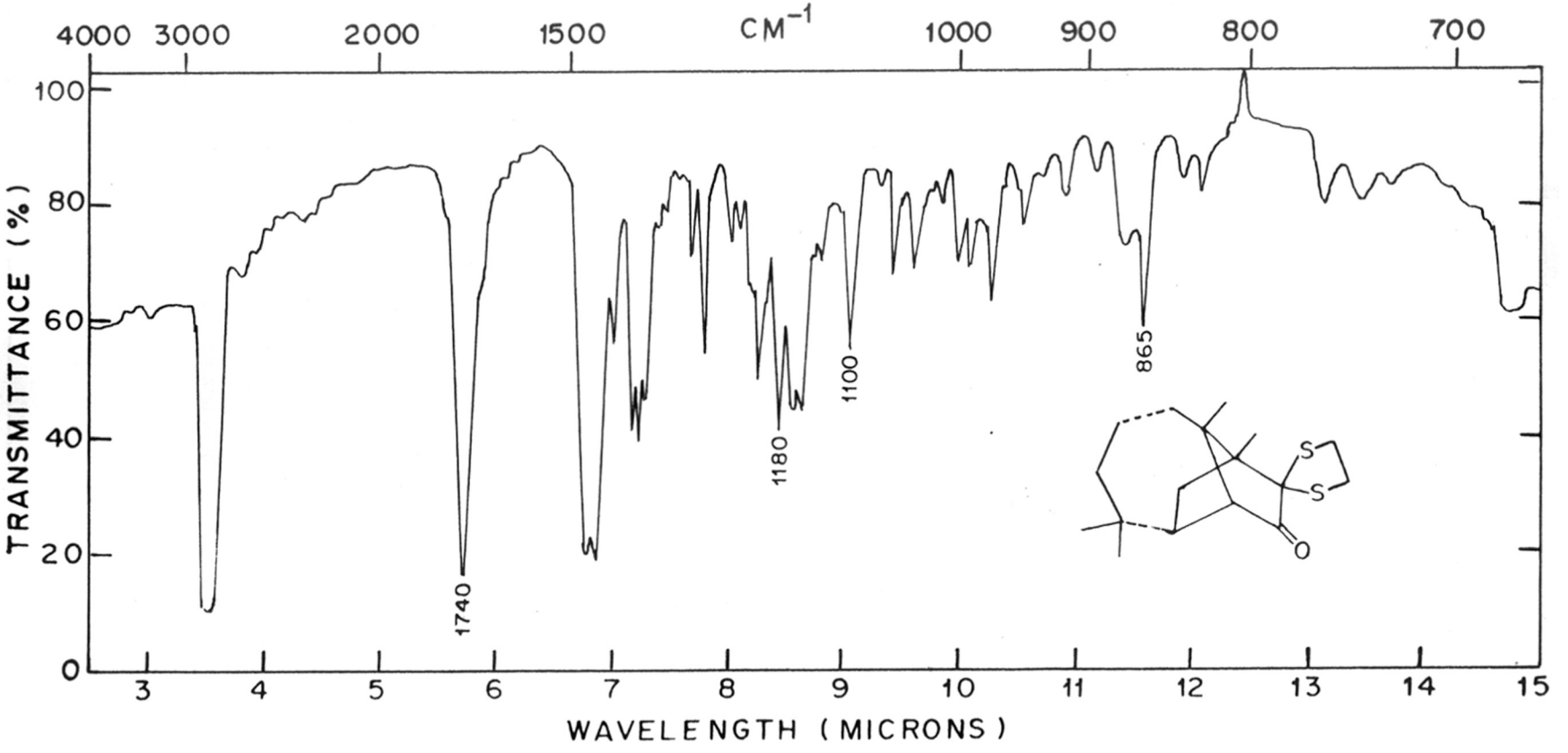
10 Gokhale P D, Joshi A P, Sahni R, Naik V G, Damodaran N P, Nayak U R & Sukh Dev, Tetrahedron 32 (1976) 1391.

11 Sheldon R A & Kochi J K, Organic Reactions 19 (1972) 279.

12 Fieser L F & Fieser M, Reagents for Organic Synthesis Vol 1 John Wiley, New York (1967) p.1179.




PMR SPECTRUM OF LONGICAMPHOR-QUINONE MONOTHIOKETAL 5

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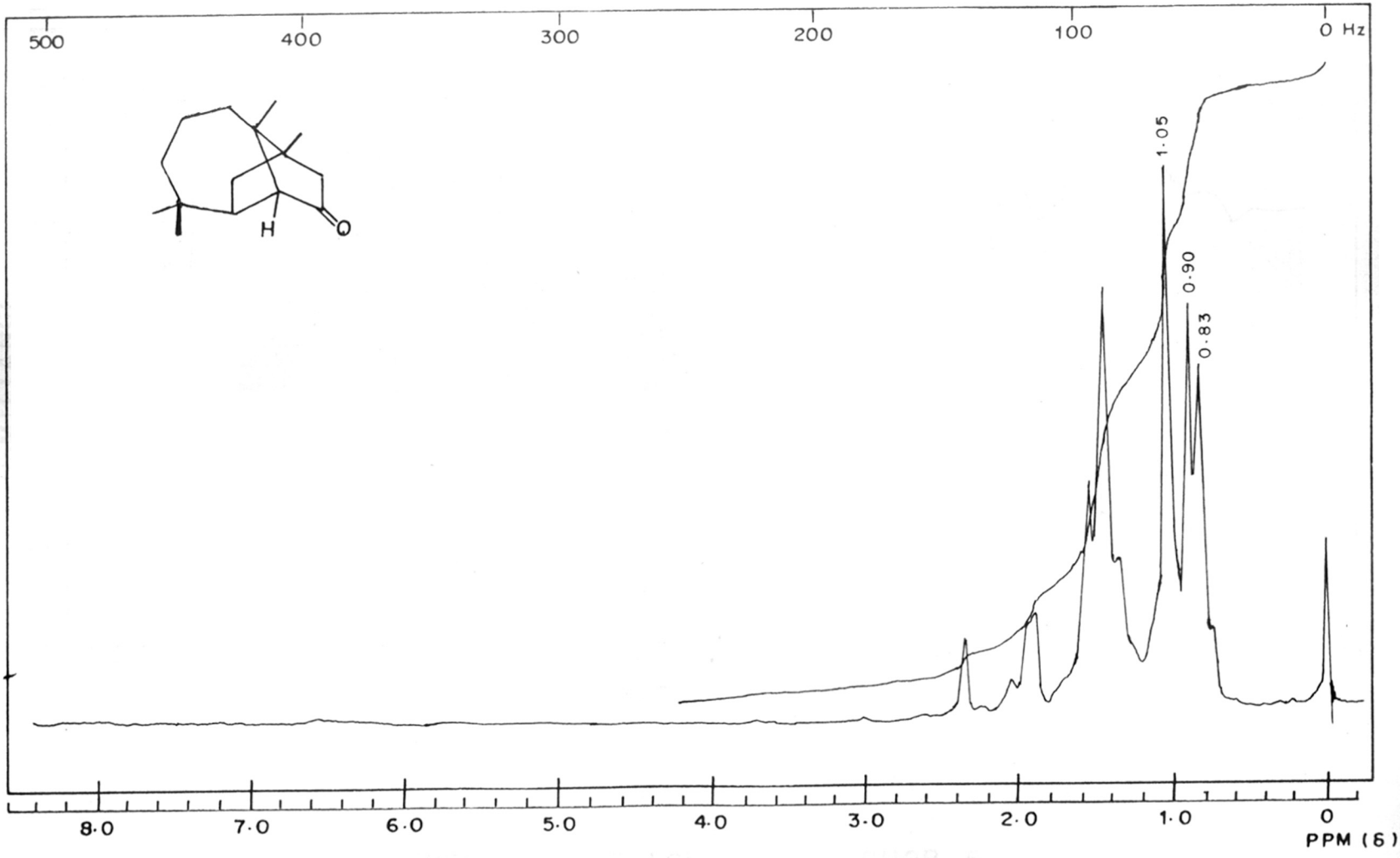


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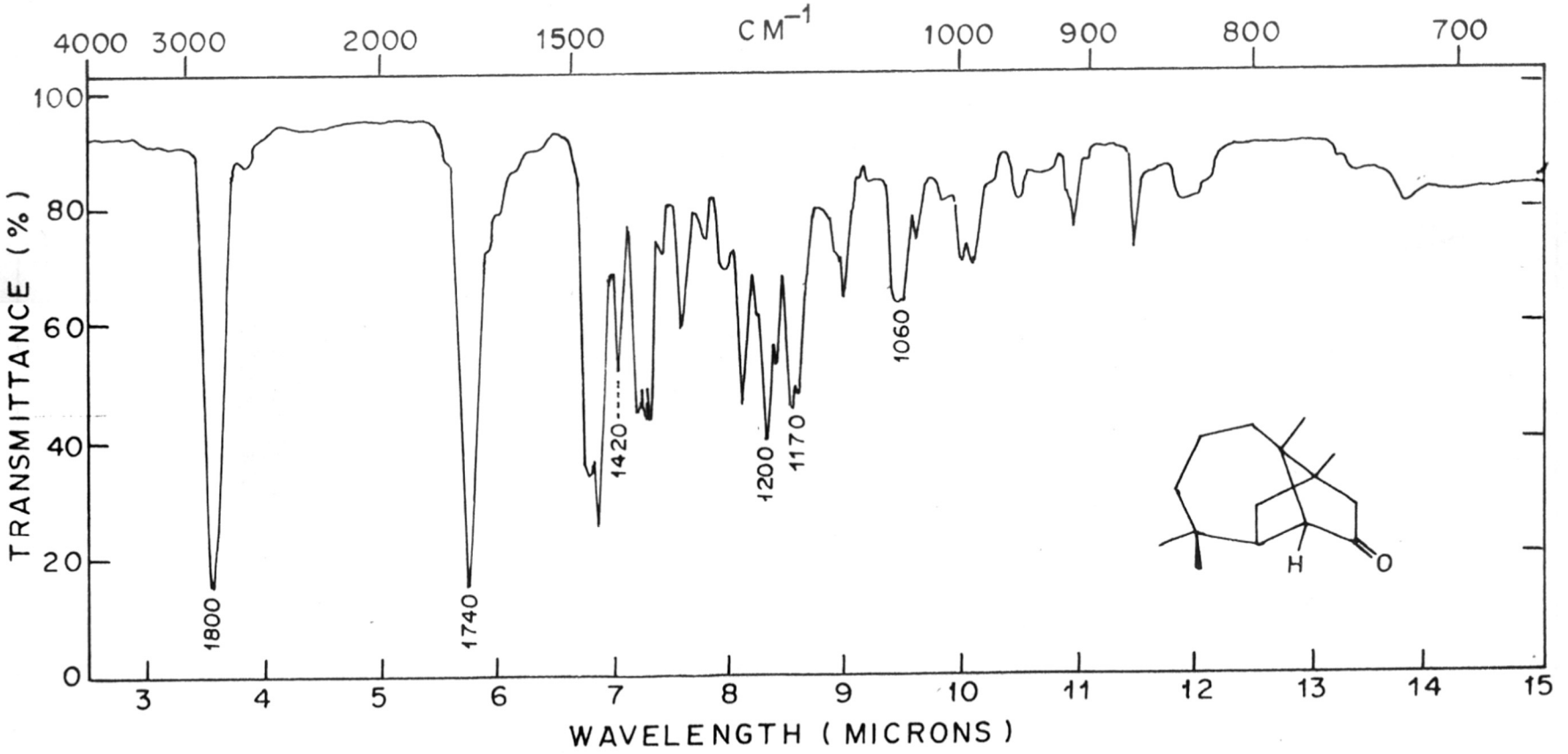


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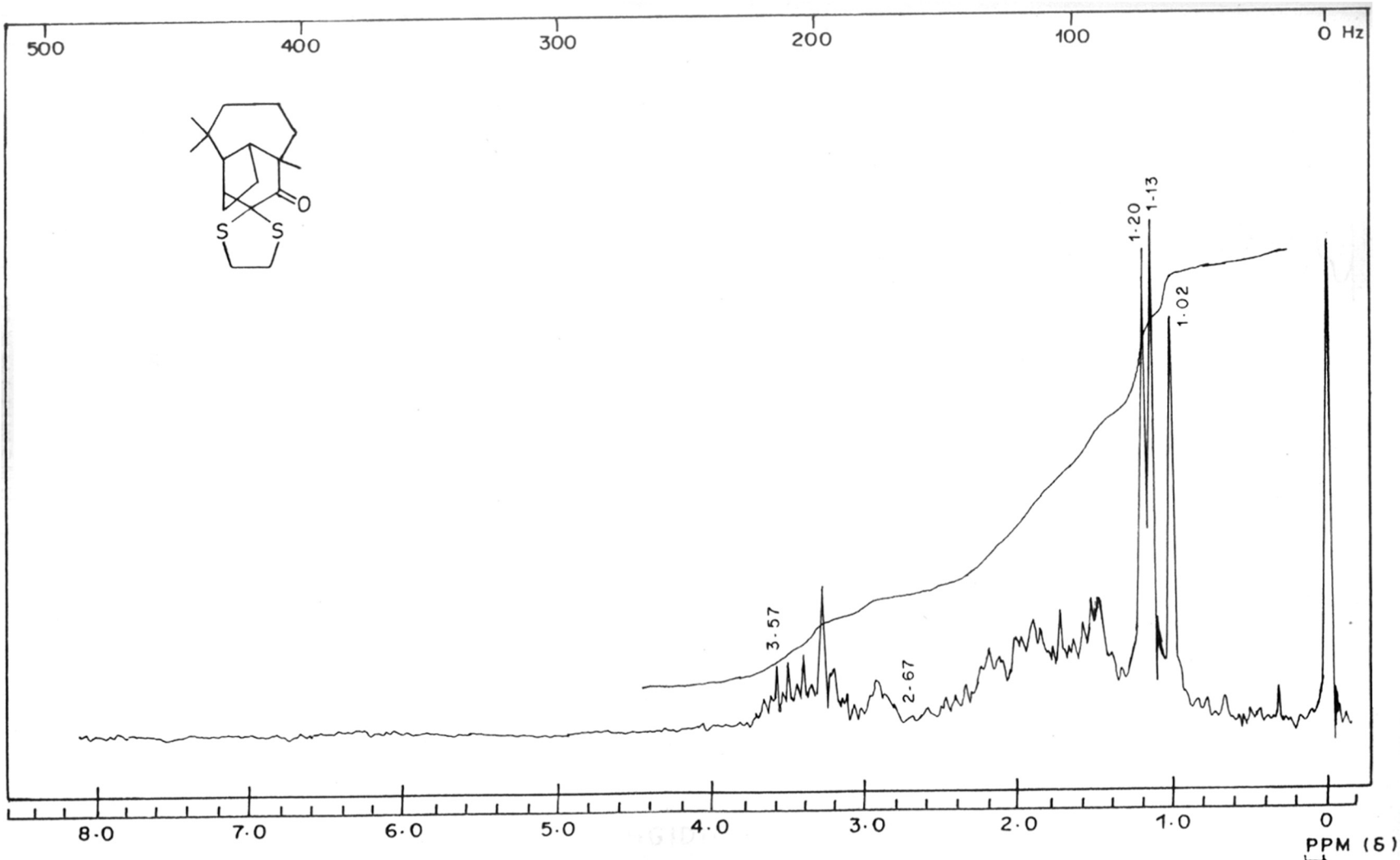


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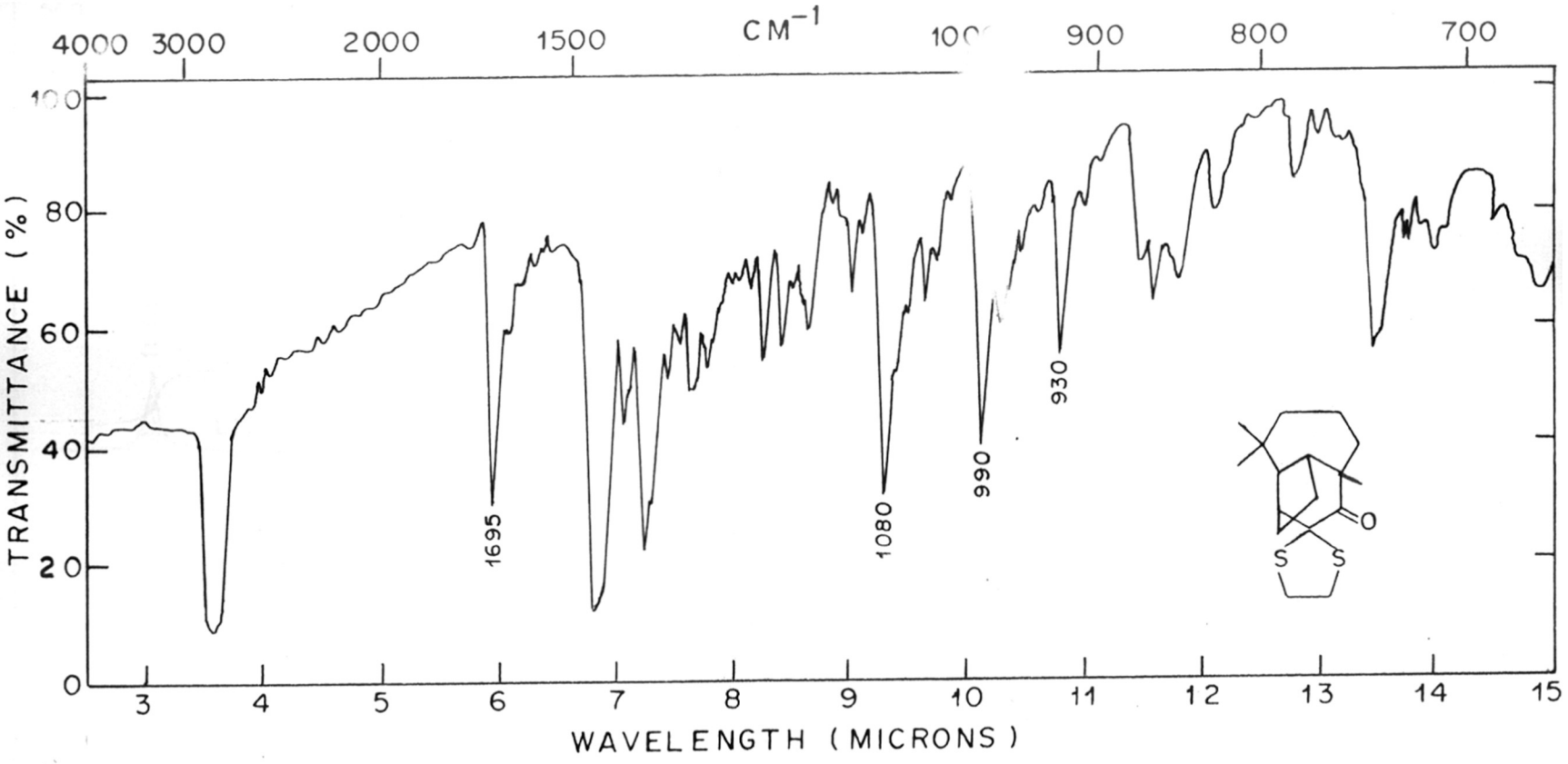


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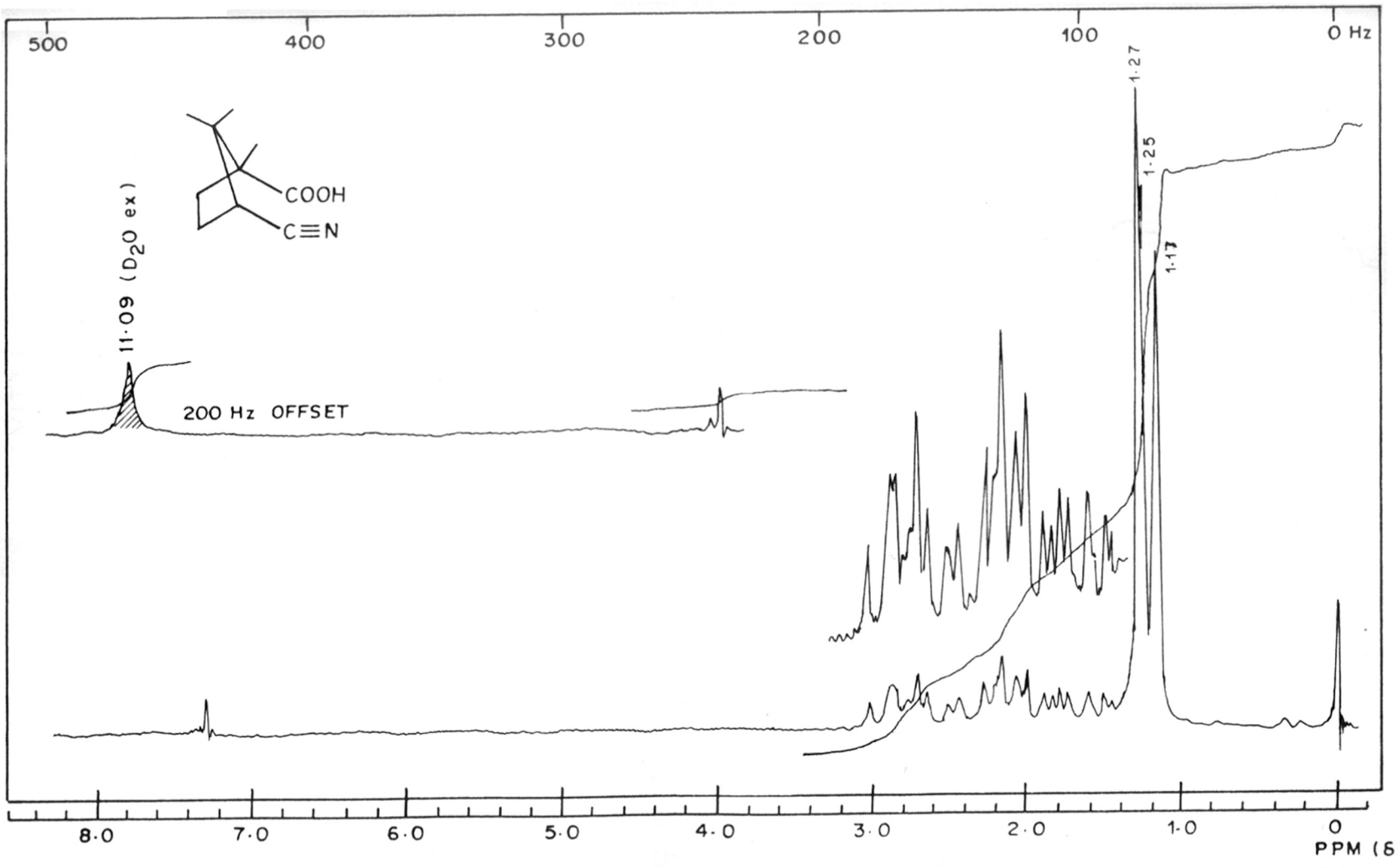


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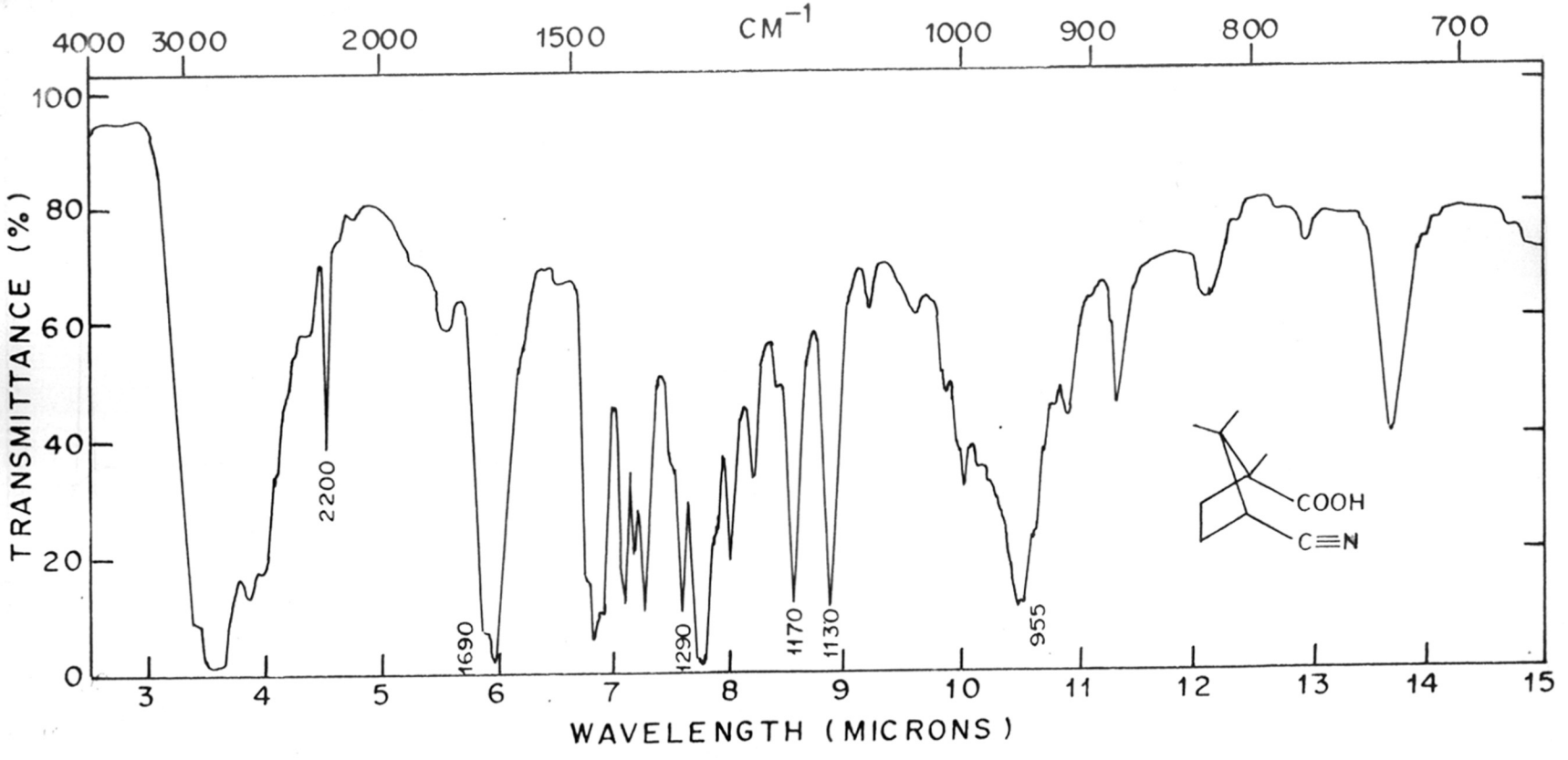


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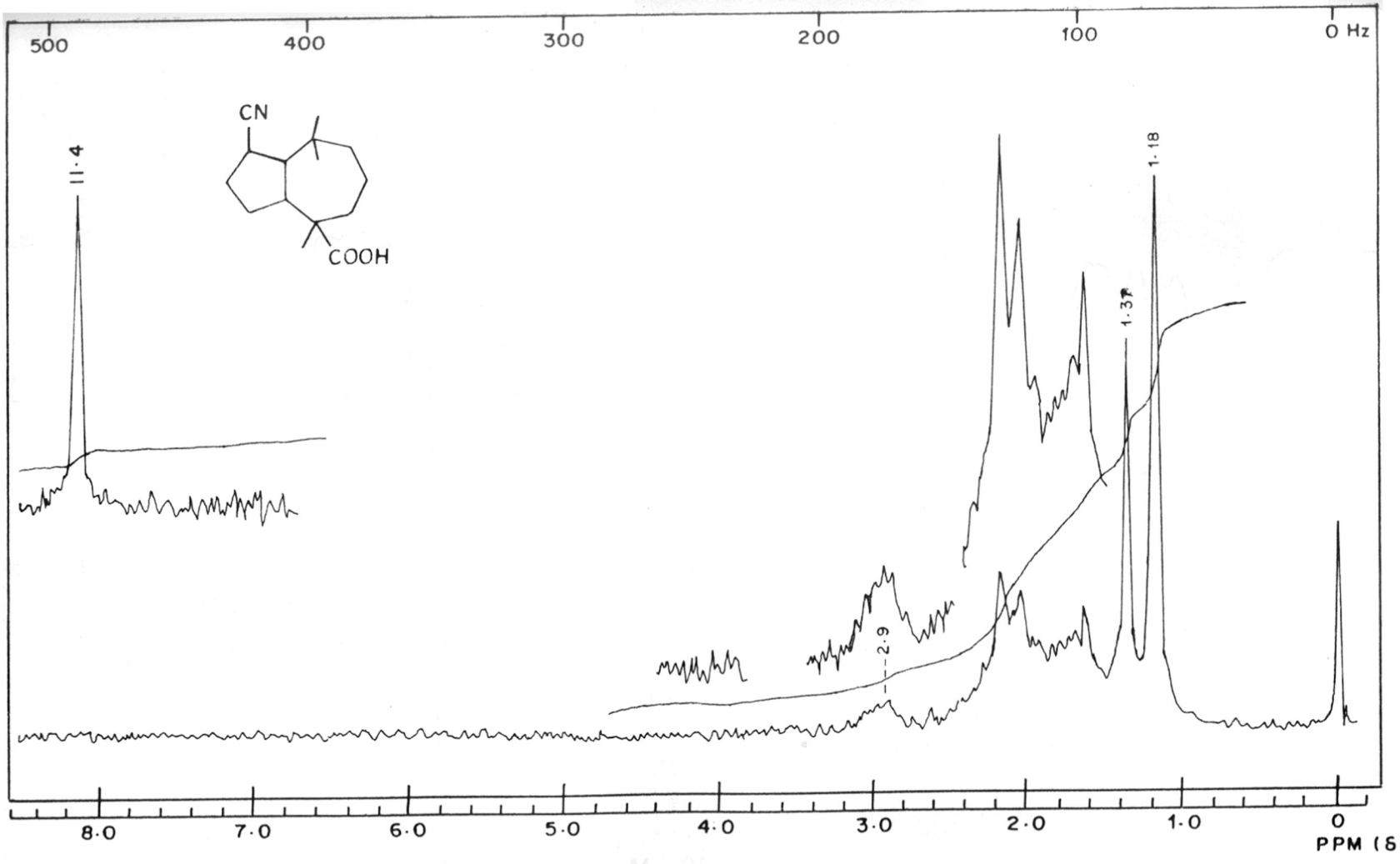


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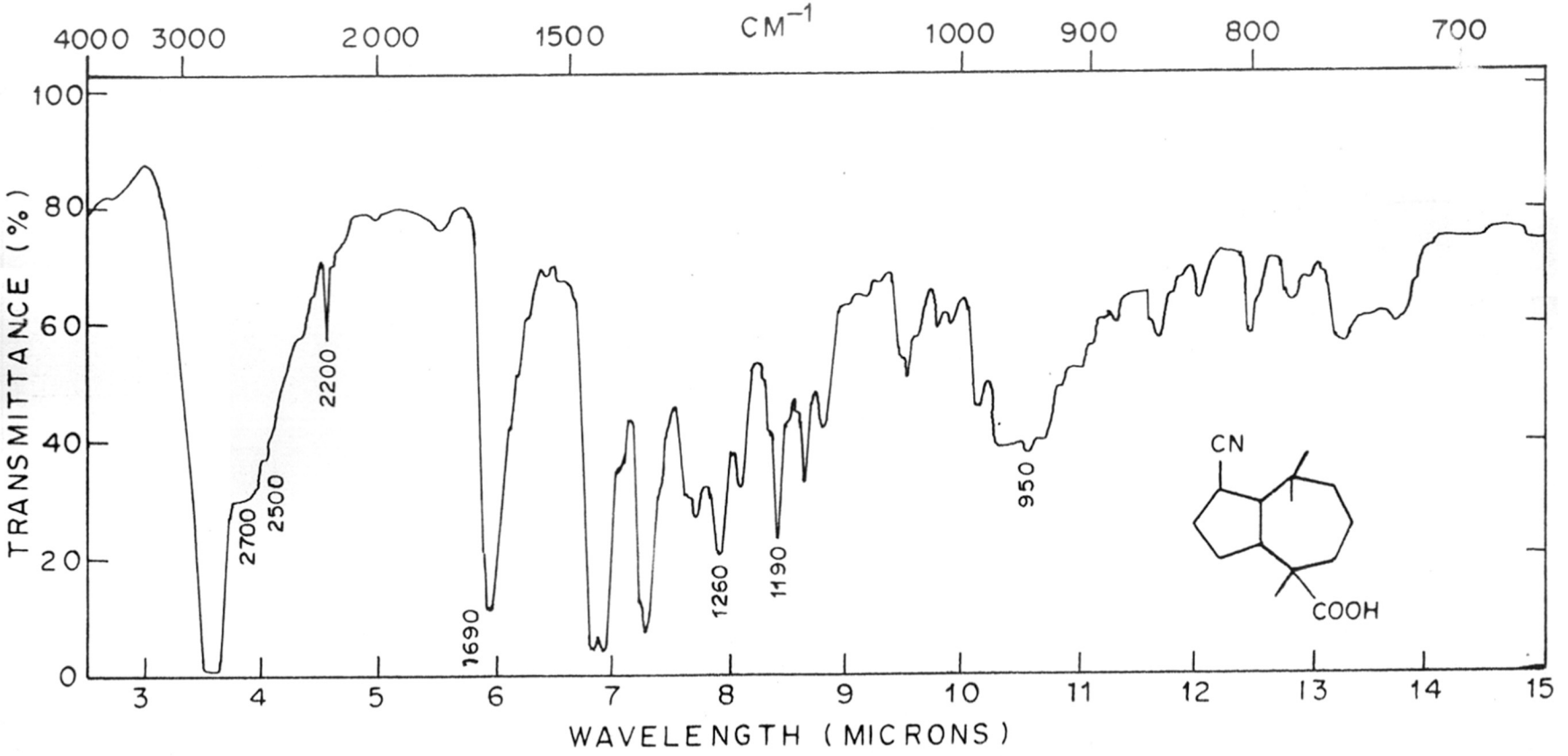
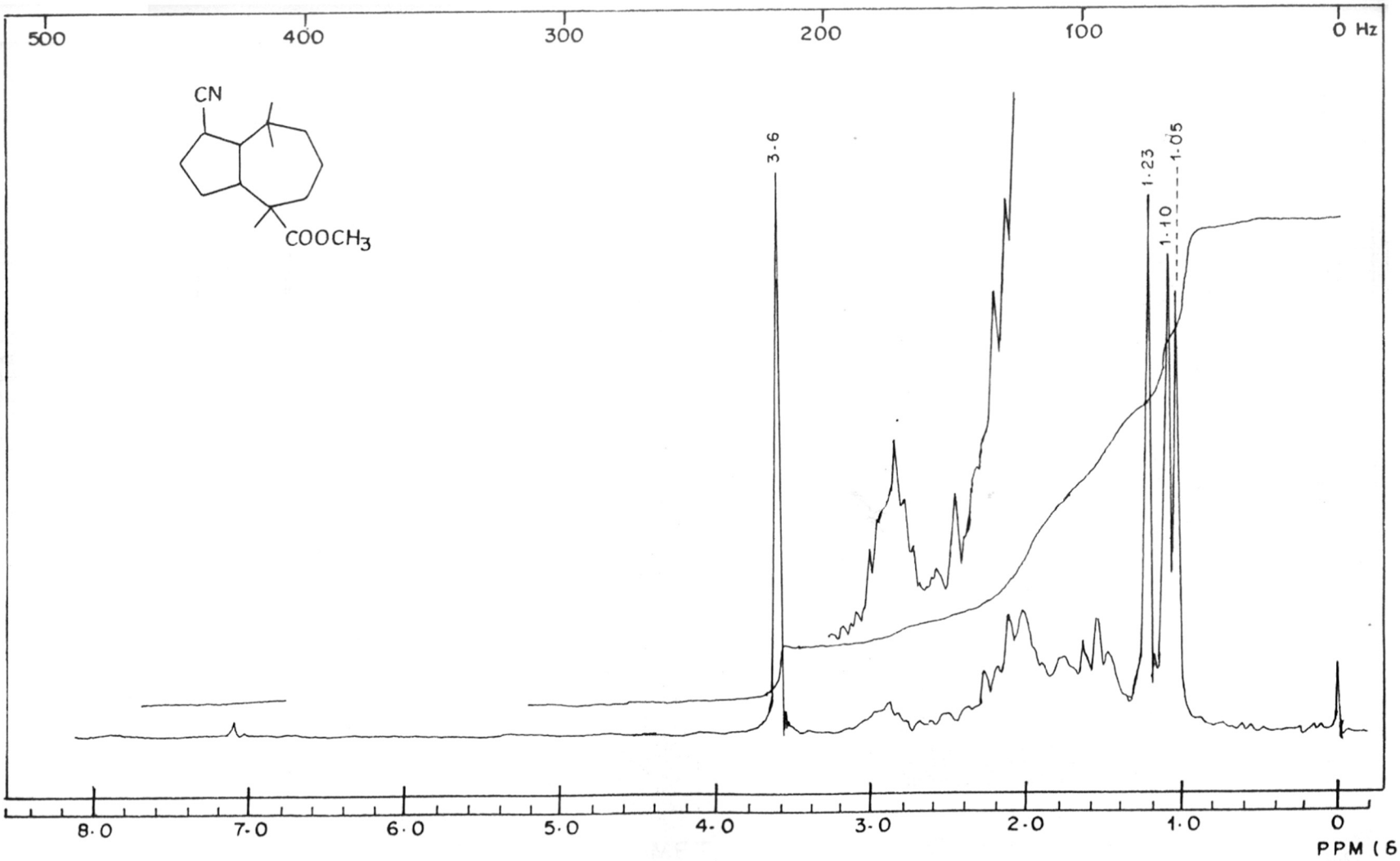
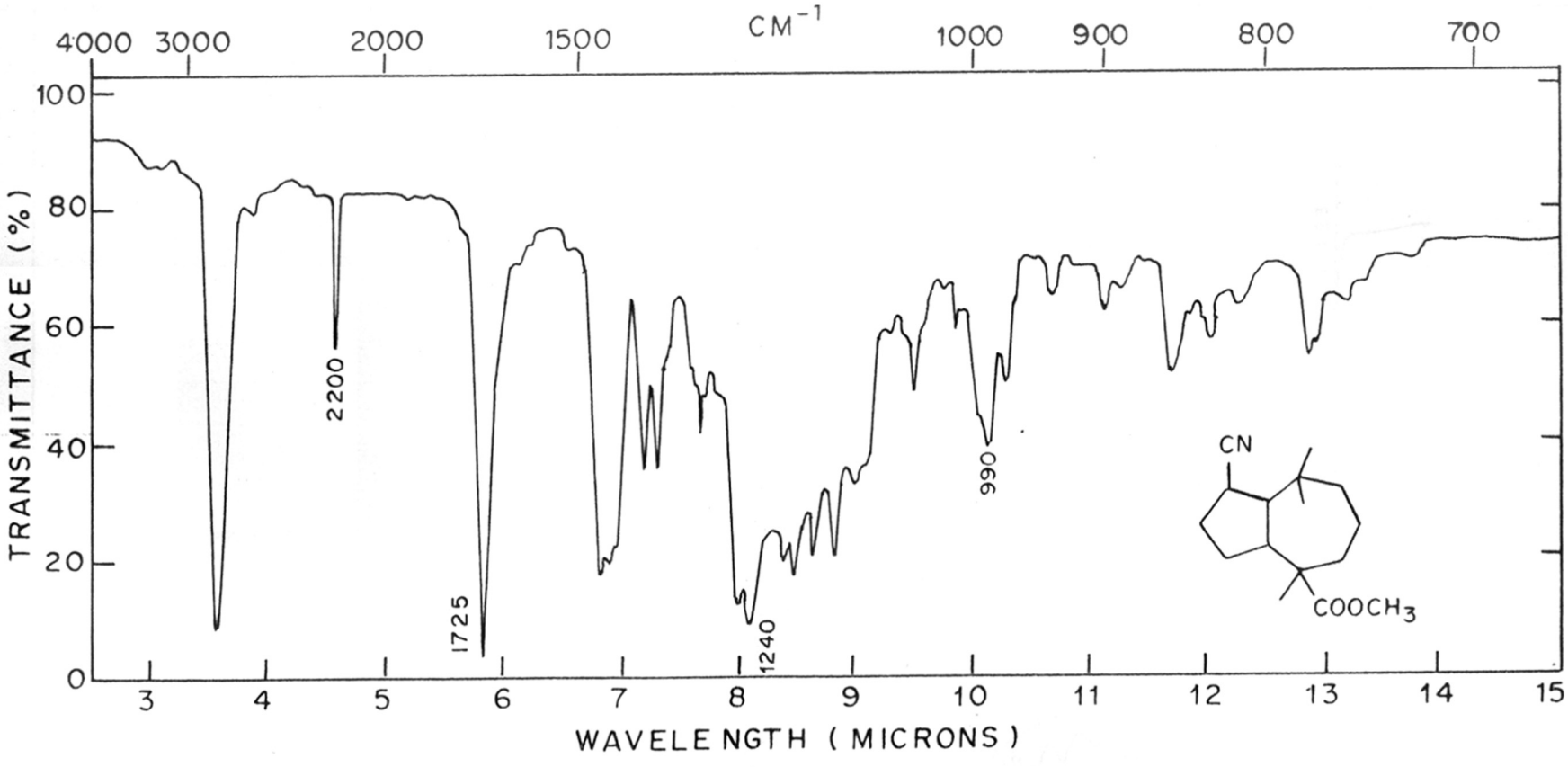


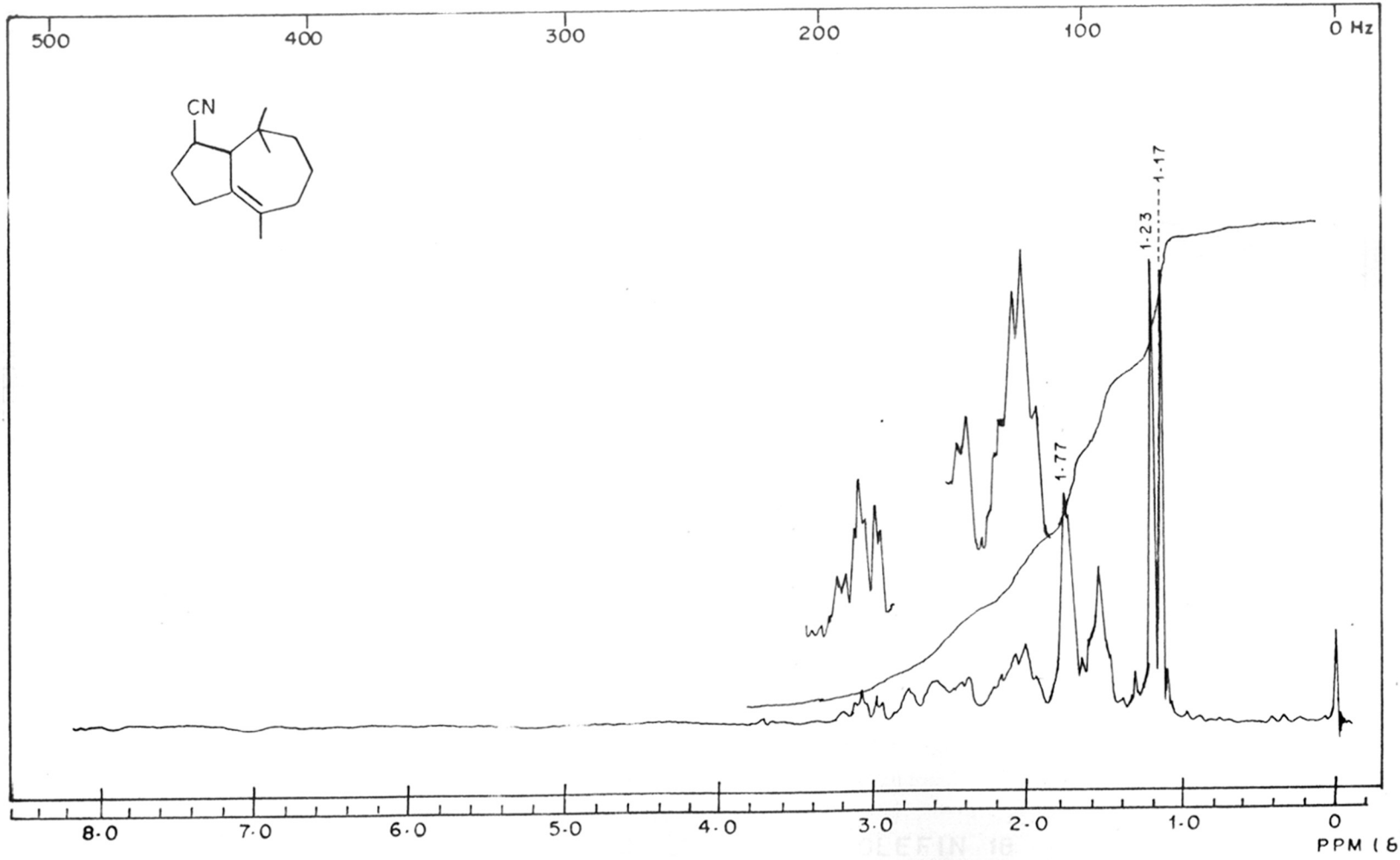

IR SPECTRUM OF CYANOACID 14



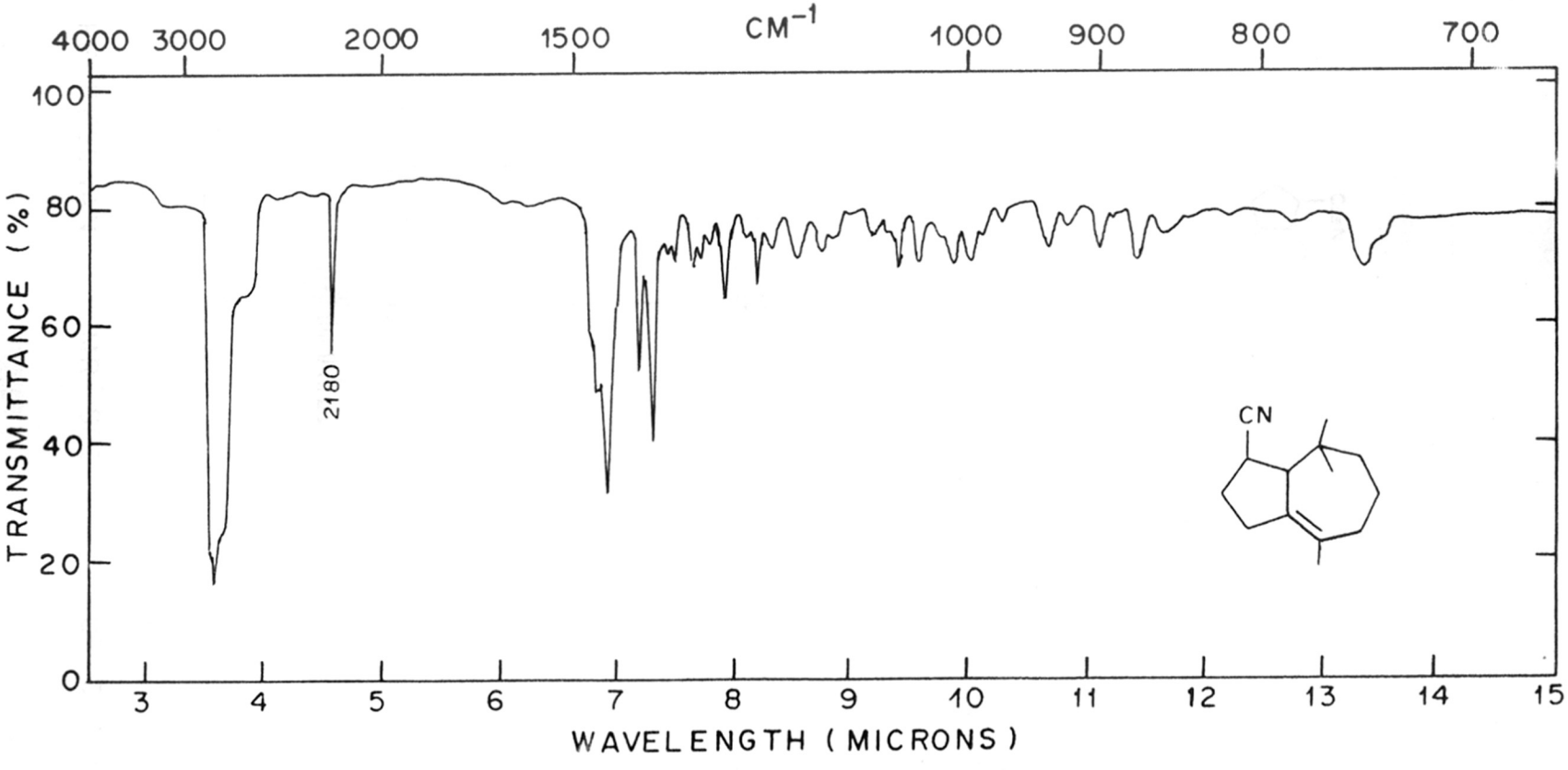

PMR SPECTRUM OF METHYL ESTER OF 14 ; 15



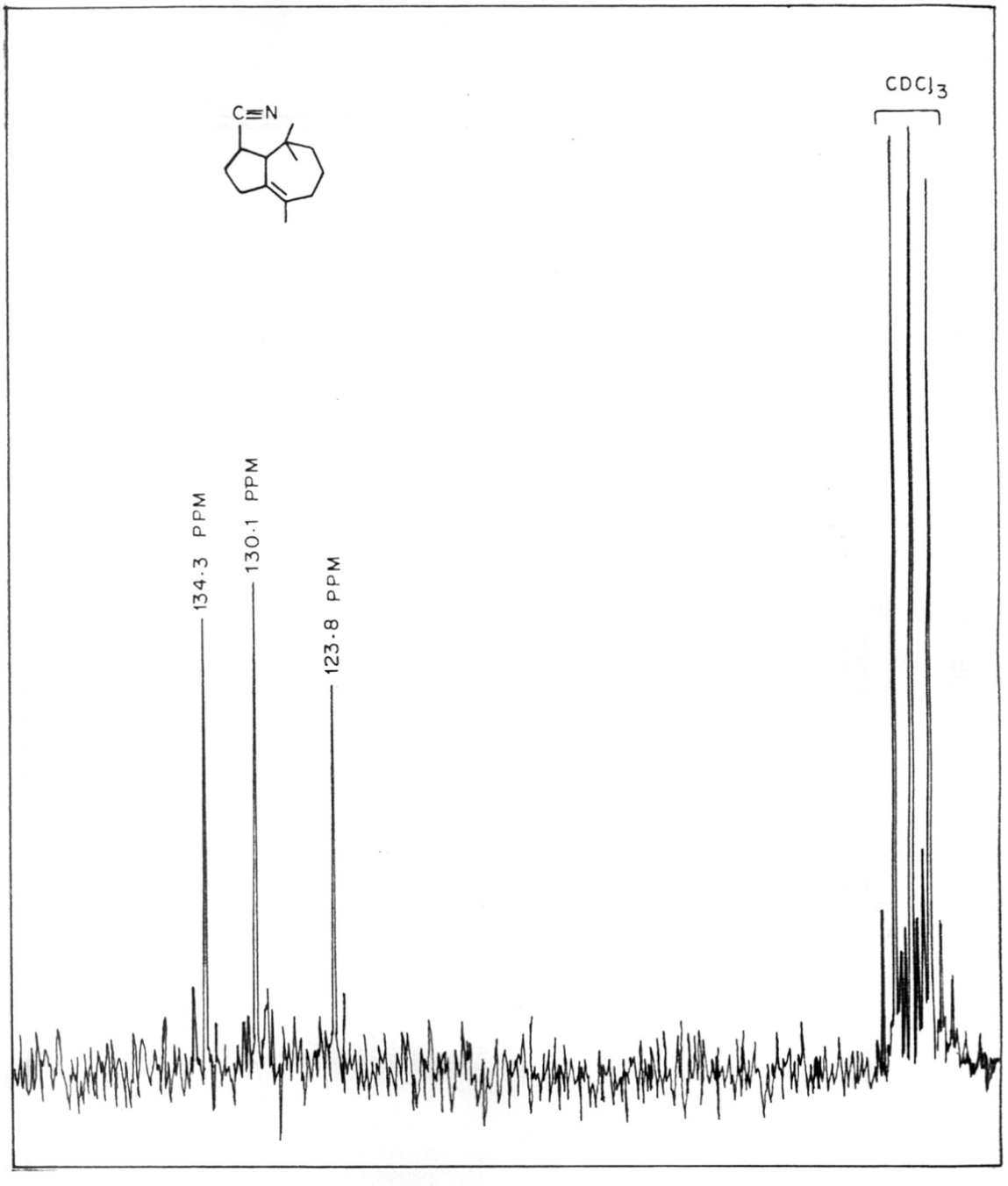

IR SPECTRUM OF METHYLESTER OF 14 : 15



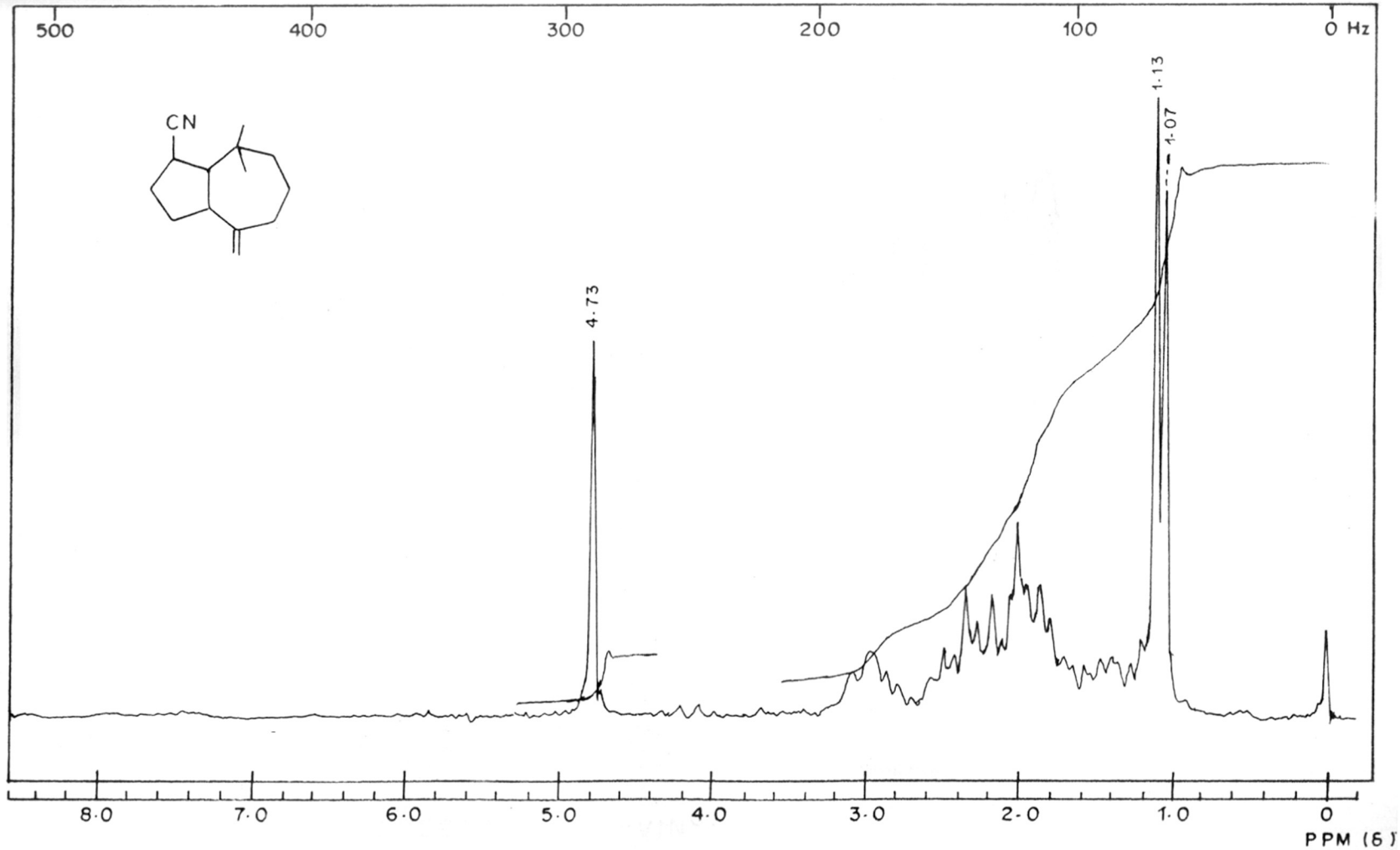

PMR SPECTRUM OF CYANO OLEFIN 18



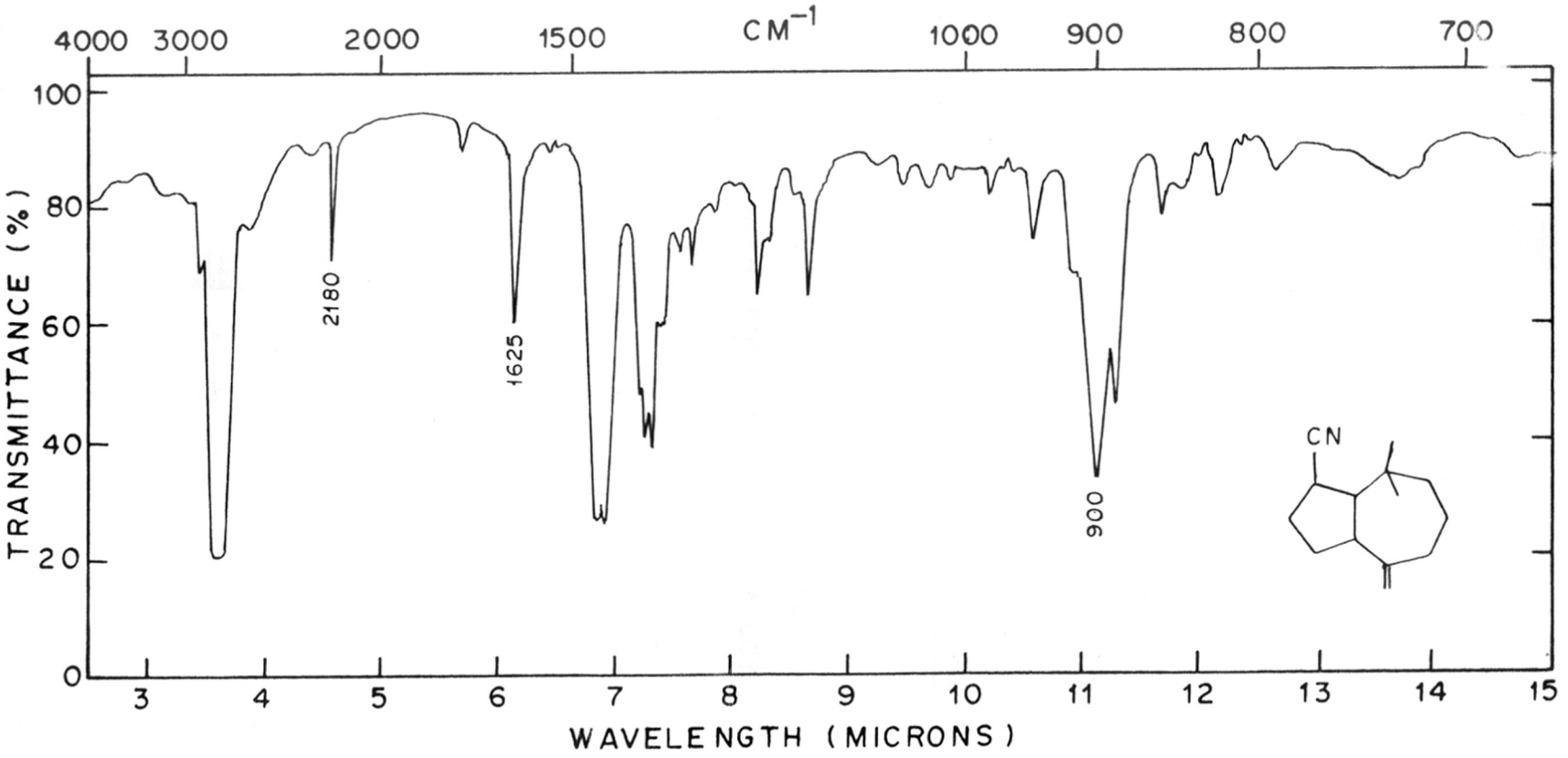

IR SPECTRUM OF CYANO OLEFIN 18




OFF-RESONANCE CMR SPECTRUM OF CYANO OLEFIN 18




PMR SPECTRUM OF VINYLIDENE NITRILE 17




IR SPECTRUM OF VINYLIDENE NITRILE 17

# CHAPTER-6

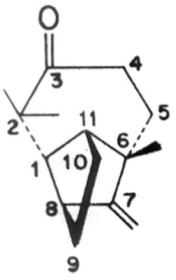
## REACTION OF SOME LONGIBORNANE-BASED $\delta$-BROMOKETONES WITH SODIUM-POTASSIUM ALLOY

ABSTRACT

While 5-ketolongifolene 2/11-ketolongicyclene 3 undergo Wagner-Meerwein rearrangement to give the expected 3-keto-8-bromolongibornane 5/11-keto-8-bromolongibornane 6 on exposure to HBr-AcOH, 3-ketolongifolene 1, however, fails to give 5-keto-8-bromolongibornane 4 but generates, instead, the trans-annular tetracyclic dibromide 7. The acetate 9 (derived from 3β-alcohol 8 obtained by LAH reduction of 1) on treatment with HBr-AcOH, followed by hydrolysis and oxidation however affords 4. When these three γ-bromoketones were exposed to sodium-potassium alloy in ether, only 5 suffers the expected fragmentation to give the bicyclic keto-olefin 18 (plus 19); only reductive debromination takes place in the case of the other two: 4 → 15 and 6 → 17 The bromodiketone 13, on reaction with the alloy gives a complex mixture from which only one pure compound could be isolated and characterized as the fragmented vinylidene dione 21 (15%).

Our interest in the synthesis of β-santalene[1] and other bicyclic sesquiterpenes from bridged tricyclic longifolene derivatives prompted us to prepare some longibornane-based γ-bromoketones and study the action of sodium potassium alloy on these substrates for achieving olefin forming ring fragmentation[2].

The ready accessibility of 3-ketolongifolene[3] 1/5-ketolongifolene[3] 2 and 11-ketolongicyclene[4] 3 suggested the addition of hydrogen bromide to these substrates for delivering the γ-bromoketones 4/5 and 6 respectively via a Wagner-Meerwin rearrangement. While the reaction was realized in practice in the case of 2/3, a transannular cyclization (Scheme 1) between the proximal C-3 and C-7 interfered when 1 was exposed to HBr-AcOH; the crystalline compound thus formed was characterized as the novel adamantoid[5] dibromide 7. 5-Keto-8-bromolongibornane 4 was however generated in an indirect manner as follows: 3β-acetoxy-longifolene 9 (from 8 via LAH reduction of 3-ketolongifolene 1) on exposure to HBr-AcOH gave the expected bromoacetate 10 (R=Ac) which on hydrolysis/oxidation afforded 5-keto-8-bromolongibornane 4 without any difficulty. The fourth substrate selected for the study was a bromo-1,2-diketone of the type 13 in which the bromine is on the γ-carbon with respect to one of the keto groups. It has been report ed[6] that this bromodiketone is formed in an abnormal



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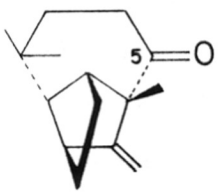

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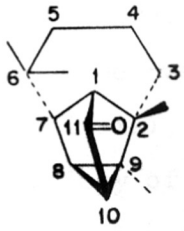

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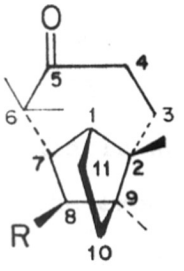
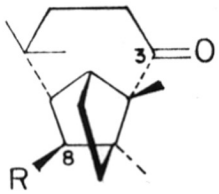


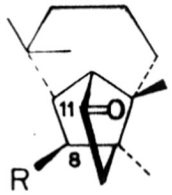
4 : R = Br

15 : R = H



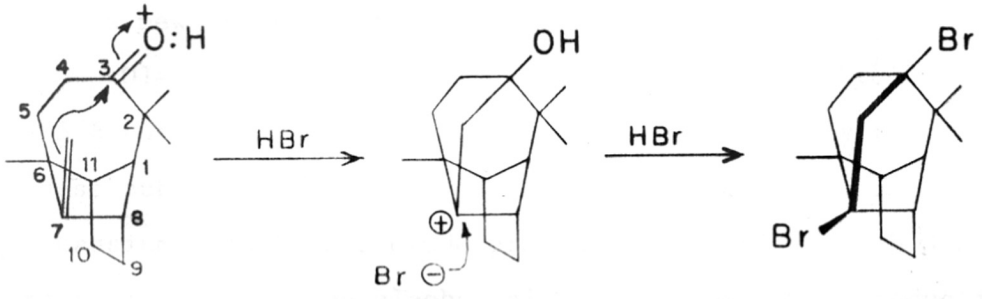
5 : R = Br

19 : R = H



6 : R = Br

17 : R = H



1

7

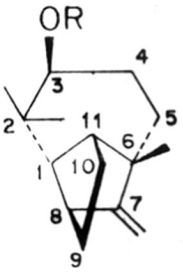
SCHEME 1

Jones oxidation of the bromoalcohol 11. In order to work out an efficient and cheap method for generating 11 from ω-bromolongifolene[7] by hydration (involving Wagner-Meerwein rearrangement/transannular hydride transfer/hydrolysis), considerable experimentation was done using a variety of acidic reagents (acetic acid - 50% sulphuric acid, dioxane - 50% sulphuric acid, monochloracetic acid-acetic acid, chloracetic acid/trichloracetic acid in dichloromethane under a variety of reaction conditions) but with disappointing results. Finally the targeted alcohol was obtained in a decent yield (65%) after several optimization experiments with trifluoroacetic acid (TFA) which resulted in reducing the amount of the expensive TFA to only one-fourth of reported[6a] use; in our large-scale work this improvement was highly significant. Oxidation of 11 with a large excess of Jones reagent for a prolonged period gave the major bromodiketone 13 (42%; plus the minor bromomonoketone 12, 6%) in the neutral part, along with a new lactone acid*.

Olefin-forming ring fragmentation of the γ-bromoketones 4/5/6 and the bromodiketone 13 was then studied by reacting these substrates in anhydrous ether with liquid sodium-potassium alloy[8]; the crude product was oxidised with Jones reagent (so that any alcohol also formed by ketone reduction

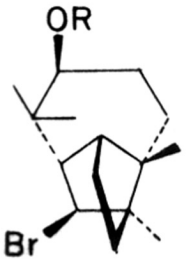
*Assignment of structure and mechanism of its formation will be discussed elsewhere.


7




8 : R = H

9 : R = Ac

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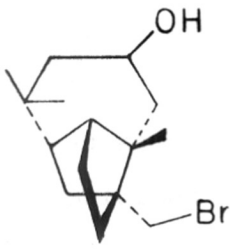


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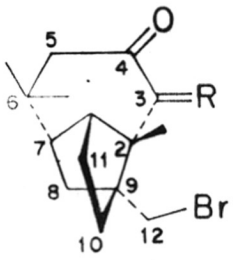
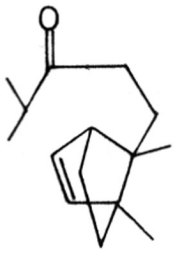



12 : R = H, H

13 : R = O

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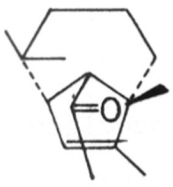


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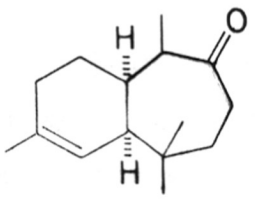


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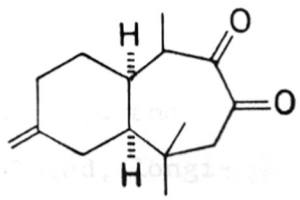


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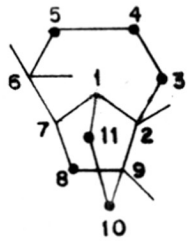



20

in the alloy reaction was reconverted to the carbonyl compound) before distillation. In the case of the bromo-ketones 4/6, the alloy reaction failed to give the expected fragmented products 14/16 but afforded the reductively debrominated compounds 15/17 as the only products. On the other hand, the product-outcome in the case of 5 was a binary mixture consisting of the ring-fragmented bicyclic keto-olefin 18 (35%) and the bromine-free ketone 19 (34%) which were separated on a column of 15% $AgNO_3$-silica gel. The himachalane-based keto-olefin 18 is a useful synthon which has been transformed[9] into $\gamma$-himachalene- a naturally occurring sesquiterpene of Cedrus atlantica. It must however be mentioned here that the sodium-potassium alloy reaction on the bromo-ketone 4/5/6 has effectively given 5-ketolongibornane 15/3-ketolongibornane 19/11-ketolongibornane 17 thus providing the three missing ketolongibornanes out of the possible six, (see 20: the other known three being 4-keto-, 8-keto- and 10-keto-longibornanes). From the diagnostic point of view the spectral data (IR/PMR) of the six, closely related, longi-bornane-based ketones assume importance and hence they have been gathered in Table 1.

Table 1. Diagnostic spectral data (IR/PMR) of all six possible ketolongibornanes

| No. | Longibornane 20 | IR ($\nu$, $cm^{-1}$) C=O | IR ($\nu$, $cm^{-1}$) $-CH_2-CO-$ | PMR ($\delta$; tertiary Me singlets only) |
|---|---|---|---|---|
| 1. | 3-Keto | 1695 | 1435 | 1.08, 1.02, 0.90, 0.77 |
| 2. | 4-Keto[10] | 1700 | 1420 | 1.03, 0.88, 0.88, 0.85 |
| 3. | 5-Keto | 1690 / 1730 [+] | 1435 | 1.06, 0.90, 0.86, 0.83 |
| 4. | 8-Keto[11] | 1740 | - | 1.14, 1.00, 0.91, 0.91 |
| 5. | 10-Keto[12] | 1740 | 1420 | 1.08, 1.00, 0.92, 0.88 |
| 6. | 11-Keto[13] | 1740 | 1420 | 1.05, 1.05, 0.90, 0.83 |

[+] Split carbonyl (Fermi resonance)

When a longibornane-based $\gamma$-bromoketone with an additional keto group as in 13 was exposed to sodium-potassium alloy in ether as described earlier, a complex mixture was formed unlike in the previous three cases. On chromatography over silica gel only one pure compound, $C_{15}H_{22}O_2$ ($M^+$ 234), could be isolated and was characterized as the expected himachalane-based olefinic diketone 21 (15% yield). It may also be mentioned here that when the bromodiketone 13 was refluxed with zinc in dioxane (or DMF) for several hours, there was no evidence of any fragmented vinylidene diketone in the resulting complex reaction mixture.

## EXPERIMENTAL

Light petroleum refers to fraction b.p.60-80°. Solvent extracts were dried over anhydrous $Na_2SO_4$. Melting and boiling points are uncorrected: m.p's were taken in capillaries on a Electrothermal melting point apparatus; b.p's refer to bath temp. in those cases where short path bulb-to-bulb distillations were carried out. $AgNO_3$-silica gel was prepared by the method[14] of Gupta and Sukh Dev. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded smears (liquid) or nujol mulls (solid) on a Pye Unicam SP-3 IR spectrophotometer. PMR spectra were obtained on a Varian T60/FT 80A/Bruker WH-90 spectrometers and mass spectra on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system.

3-Ketolongifolene 1/5-ketolongifolene 2. These were prepared via the LTA reaction sesquence on longifolol as described by Jadhav and Nayak[3].

11-Ketolongicyclene 3. This was prepared by hydration/oxidation of dehydrolongifolene as reported[4].

HBr addition to 5-ketolongifolene 2: Formation of 3-keto-8-bromolongibornane 5

A mixture of 5-ketolongifolene 2 (2.0 g) and 32% HBr-AcOH (20 ml) was kept at room temp. (18 hr). The mixture

was poured into water (100 ml), extracted with ether, washed with 5% aqueous $Na_2CO_3$, brine, dried, solvent removed and the residue recrystallized from methanol to furnish colourless crystals of 3-keto-8-bromolongibornane 5, m.p.122-23° (1.95 g). IR (nujol): 1700, 915, 890, 785, 730. PMR ($CCl_4$): $\delta$ 3.97 (dd, 1H, -CHBr); 1.30, 1.27, 1.13, 0.83 (four tertiary Me singlets). Mass: m/z 298, 300 ($M^+$). (Found: C, 60.7; H, 7.9; Br, 26.7. $C_{15}H_{25}OBr$ requires: C, 60.2; H, 7.7. Br, 26.3%):

Action of HBr on 3-ketolongifolene 1: Formation of adamantoid dibromide 7

A mixture of 3-ketolongifolene 1 (0.8 g) and 32% HBr-AcOH (10 ml) was kept at room temp. (18 hr). The mixture was poured into water, extracted with ether, washed with 5% aq. $Na_2CO_3$, brine, dried, solvent removed and the residue chromatographed on silica gel/IIa (30 g; 40 cm x 1.5 cm): Fr. 1, light petroleum-benzene (1:1), 4 x 50 ml, pure. Fr. 2, benzene, 2 x 50 ml, mixture (0.25 g).

Fr. 1, which solidified was recrystallized from methanol to yield colourless needles of the tetracyclic dibromide 7, m.p.139-40° (0.55 g). IR (Nujol): 955, 890, 860. PMR ($CCl_4$): $\delta$ 2.97 (s, 2H, Br-C-$CH_2$-C-Br); 1.32, 1.17, 1.08 (three tertiary Me singlets). Mass: m/z 281, 283 ($M^+$-Br).

(Found: C, 50.2; H, 6.3; Br, 43.6. $C_{15}H_{22}Br_2$ requires: C, 49.7; H, 6.1; Br, 44.2%).

5-Keto-8-bromolongibornane 4

3-Ketolongifolene 1 (2.18 g) in dry ether (25 ml) was added dropwise to a stirred slurry of LAH (0.4 g) in ether (50 ml). At the end of reaction (3.5 hr; TLC:benzene) the mixture was successively treated with water (0.4 ml), 15% aqueous NaOH (0.4 ml) and water (1.2 ml). After stirring for another 15 minutes the grannular precipitate was filtered off, washed thoroughly with more ether, dried and solvent removed. The residue was refluxed with $CHCl_3$ containing 1 drop of 12N HCl (15 min.). The mixture was washed with water, dried, solvent removed and the residue chromatographed on silica gel/ IIa (60 g; 46 cm x 2 cm): Fr. 1, light petroleum-benzene, 4 x 100 ml, transannular oxide (liquid, 0.61 g). Fr. 2, benzene, 6 x 100 ml, pure.

Fr. 2 which solidified was recrystallized from light petroleum to furnish the 3β-alcohol 8, m.p.108-109° (1.3 g). On acetylation with $Ac_2O$ (10 ml) in pyridine (10 ml) at room temp. (16 hr) it gave the acetate 9 as a colourless liquid b.p.120°(bath)/0.9 mm (1.39 g); m.p.71-72°. IR (Nujol): 1740, 1660, 1260, 895. PMR ($CCl_4$): $\delta$ 4.93 (m, 1H, -C<u>H</u>OAc); 4.87 and 4.63 (two s, 1H each, >C=C<u>H</u>$_2$); 2.67 (m, 1H, allylic H); 1.90 (s, 3H, OCOC<u>H</u>$_3$); 1.00, 0.97, 0.90 (three tertiary

Me singlets). Mass: m/z 262 ($M^+$, base peak). (Found: C, 78.1; H, 10.1. $C_{17}H_{26}O_2$ requires: C, 77.8; H, 10.0%).

A mixture of the acetate 9 (1.1 g) in 32% HBr-AcOH was kept at 30° for 18 hr and the isolated product hydrolysed with 10% methanolic KOH (10 ml) at room temp. overnight. The crude product was purified by chromatography over silica gel/IIb; Fr. 1, light petroleum-benzene, 2 x 50 ml, mixture. Fr. 2, benzene, 4 x 50 ml, pure bromoalcohol 10 (R=H), was recrystallized from light petroleum, m.p.110-12° (0.55 g). IR (Nujol): 3200, 1040, 780. PMR ($CCl_4$): δ 3.93 (dd, 1H, HC-CHBr); 3.30 (m, 1H, -CHOH); 1.13, 0.93, 0.83 x 2) (four tertiary Me singlets). (Found: C, 60.4; H, 8.6; Br, 26.1. $C_{15}H_{25}OBr$ requires: C, 59.8; H, 8.3; Br, 26.5%).

Oxidation of bromoalcohol 10 (R=H) (0.2 g) with Jones reagent gave 5-keto-8-bromolongibornane 4 as a colourless liquid (0.16 g). PMR ($CCl_4$):δ3.63 (dd, 1H,-CHBr); 1.17, 1.13, 1.07, 0.90 (four tertiary Me singlets).

HBr addition to 11-ketolongicyclene 3: Formation of 11-keto-8-bromolongibornane 6

A mixture of 11-ketolongicyclene (8.0 g) and 32% HBr-AcOH (50 ml) was kept at room temp. (24 hr). The mixture was poured into water (250 ml), extracted with ether, washed with 5% aqueous $Na_2CO_3$, brine, dried and solvent removed. The crude solid was fractionally crystallized from EtOH to get

the frist crop of pure 6 as colourless needles, m.p.178-79° (4 g, 36%). IR (Nujol): 1750, 1420, 860, 780, 740. PMR ($CCl_4$): $\delta$4.20 (dd, 1H, -$\underset{1}{C}$H-$\underset{1}{C}$HBr, $J_1$=6 Hz, $J_2$=2 Hz); 1.10, 1.03, 1.00 x 2 (four tertiary Me singlets). Mass: m/z 298. 300 ($M^+$). (Found: C, 59.9; H, 7.8; Br, 26.6. $C_{15}H_{23}OBr$ requires: C, 60.2; H, 7.7; Br, 26.8%). A second crop of crystals, m.p.120-30° (2.0 g) (obtained by addition of 5 ml of water to the filtrate) was found to be a mixture of 6 + 4-bromo-11-keto-longibornane. Further dilution of the filtrate with water (5 ml) gave the third crop of pure 4-bromo-11-keto-longibornane. IR (smear): 1750, 1420, 725. PMR ($CCl_4$): $\delta$ 3.90-4.83 (m, 1H, -$\underset{1}{C}$HBr-$CH_2$-); 1.10, 1.05, 1.00, 0.90 (four tertiary Me singlets). Mass: m/z 298, 300 ($M^+$). (Found: C, 60.0; H, 8.0; Br, 26.4. $C_{15}H_{23}OBr$ requires: C, 60.2; H, 7.7; Br, 26.8%).

12-Bromolongibornane-3,4-dione 13

To a stirred solution of TFA (207 g, 138 ml; 1.5 mol) cooled to 5-10° in a bath of ice-water, was added dropwise a solution of $\omega$-bromolongifolene (139 g; 0.5 mol) in $CH_2Cl_2$ (400 ml) during 1.5 hr; stirring was continued for 24 hr more at room temp. The mixture was quenched in ice-cold aqueous $Na_2CO_3$ solution, the organic layer separated and the aqueous portion extracted with fresh $CH_2Cl_2$ (3 x 200 ml). The combined organic extract was washed with brine, dried and solvent removed. The crude mixture (173 g) in EtOH

(300 ml) was hydrolyzed with 15% aqueous ethanolic KOH (140 g of KOH in 100 ml of water and 700 ml of EtOH) at room temp. overnight. After removing most of the ethanol on a waterbath, the mixture was diluted with water (3 litres), extracted with EtOAc (3 x 500 ml), washed with brine, dried and solvent removed. The residue was carefully distilled at 1 mm, using a short vigreux column and a controlled oil bath held at 150° so that most of the unwanted bromololefins mixture (12 g) was removed. The pot-residue (129 g) consisting mostly of the bromoalcohol 11 was dissolved in acetone (600 ml) and oxidised with excess of Jones reagent while stirring and cooling the flask in ice-cold water; eight 100 ml portions of the reagent were added at intervals of 24 hr. The mixture was diluted with water, extracted with EtOAc (3 x 500 ml) and separated into acid (9 g, 9%) and neutral (105 g) by extraction with 10% aqueous $Na_2CO_3$ solution. The neutral material solidified and was recrystallized from light petroleum to give colourless needles of bromodiketone 13 m.p. 106-110° (29 g). The residue from filtrate was then chromatographed on a column of silica gel/IIa (2.1 kg): Fr. 1, light petroleum, 4 x 500 ml, mixture of bromoolefins (19 g). Fr. 2, light petroleum-benzene (1:3), 6 x 500 ml, bromodiketone 13 (19 g, total yield 29 + 19 = 48 g, 42%). Fr. 3, benzene, 4 x 500 ml, mixture of 12 + 13. Fr. 4, benzene-EtOAc (9:1), 4 x 500 ml, pure 12-bromolongi-bornane-4-one (6 g, 6%).

12-Bromolongibornane-3,4-dione 13: m.p.109-111° (light petroleum). IR (Nujol): 1700, 1690, 995. PMR ($CCl_4$): $\delta$ 3.63 (AB q, 2H, $-C\underline{H}_2Br$, J=10 Hz); 1.13, 1.11, 1.01 (three tertiary Me singlets). Mass: m/z 312, 314 ($M^+$). (Found: C, 58.1; H, 6.9; Br, 26.2. $C_{15}H_{21}O_2Br$ requires: C, 57.5; H, 6.7; Br, 25.5%).

12-Bromolongibornane-4-one 12: m.p.72° (light petroleum). (IR (Nujol): 1700, 930. PMR ($CCl_4$): $\delta$3.29 (q, 2H, $-C\underline{H}_2Br$, J=12 Hz); 1.08, 1.00, 0.93 (three tertiary Me singlets). Mass: m/z 298, 300 ($M^+$). (Found: C, 60.8; H, 7.7; Br, 26.8. $C_{15}H_{23}OBr$ requires: C, 60.2; H, 7.8; Br, 26.7%).

Na-K alloy reaction with 3-keto-8-bromolongibornane 5: Formation of bicyclic keto-olefin 18 and 3-ketolongibornane 19

Na-K alloy (liquid, 1:5) was prepared by heating sodium (3 g) and potassium (15 g) under xylene until melted and carefully mixing the molten metals with a stirring rod and keeping the alloy in one large globule. On cooling the alloy remained liquid and 11.5 ml was pipetted out and transferred to a 3-necked flask equipped with a dropping funnel, condenser and a $N_2$-gas inlet tube. To the stirred suspension of the alloy in dry ether (100 ml) was added dropwise a solution of 3-keto-8-bromolongibornane 5 (11.5 g) in ether (200 ml). The mixture became dark blue during addition (1 hr). After 3 hr, 20% EtOH in light petroleum

(250 ml) was added, poured into water, extracted with ether (3 x 100 ml), washed with brine, dried and solvent removed. The residue was dissolved in acetone (250 ml), treated with Jones reagent (12 ml) and the isolated crude product (7 g) was chromatographed on 15% $AgNO_3$-silica gel (160 g; 54 cm x 3 cm): Fr. 1, light petroleum, 4 x 250 ml, 3-keto-longibornane 19: colourless liquid b.p.100° (bath)/0.5 mm (2.95 g, 35%). IR (smear): 1695, 1435, 1160, 1060. PMR ($CCl_4$): 1.08, 1.02, 0.90, 0.77 (four tertiary Me singlets). Mass: m/z 220 ($M^+$. base peak). (Found: C, 82.0; H, 11%. $C_{15}H_{24}O$ requires: C, 81.8; H, 11.0%).

Fr. 2, light petroleum-benzene (1:3), 5 x 200 ml, bicyclic keto-olefin 18: colourless liquid b.p.130°(bath)/0.5 mm (2.85 g, 34%). IR (smear): 1700, 1410, 800. PMR ($CCl_4$): 5.22 (bs, 1H olefinic ); 1.65 (bs, vinylic Me); 0.98 (d, 3H, CHMe J=5 Hz); 1.03, 0.93 (two tertiary Me singlets). Mass: m/z 220 ($M^+$). (Found: C, 81.7; H, 11.1. $C_{15}H_{24}O$ requires: C, 81.8; H, 11.0%.

Na-K alloy reaction on 5-keto-8-bromolongibornane 4: 5-keto-longibornane 15

5-Keto-8-bromolongibornane 4 (0.68 g) in dry ether (50 ml) was reacted with Na-K alloy (0.7 ml) as described for 5; in this case no blue colour was formed during the reaction. The isolated product was distilled to give a colourless liquid b.p.130°(bath)/0.6 mm (0.5 g, 95%) which was characterized as

pure 5-ketolongibornane 15. IR (smear): 1730, 1690, 1435. PMR ($CCl_4$):δ0.83, 0.86, 0.90, 1.06 (four tertiary Me singlets). (Found: C, 80.8; H, 10.4. $C_{15}H_{24}O$ requires: C, 81.8; H, 11.0%).

Na-K alloy reaction on 11-keto-8-bromolongibornane 6: 11-ketolongibornane 17

11-Keto-8-bromolongibornane 6 (0.5 g) in dry ether (50 ml) was reacted with Na-K alloy (0.5 ml) in the usual manner. On distillation a colourless liquid b.p.125°(bath)/0.5 mm (0.31 g, 85%), m.p.55° characterized as pure 11-keto-longibornane 17 was obtained. IR (Nujol): 1740, 1420, 1200, 1170, 1060. PMR ($CCl_4$):δ 1.05 x 2, 0.90, 0.83 (four tertiary Me singlets). (Found: C, 81.8; H, 11.4. $C_{15}H_{24}O$ requires: C, 81.8; H, 11.0%).

Na-K alloy reaction on 12-bromolongibornane-3,4-dione 13: Formation of bicyclic vinylidene dione 21

12-Bromolongibornane-3,4-dione 13 (3.16 g) in dry ether (100 ml) was reacted with Na-K alloy (4 ml) in the usual fashion. The complex mixture (TLC; 1.98 g) isolated in this case was chromatographed on silica gel (60 g; 48 cm x 1 cm): Fr. 1, benzene, 4 x 100 ml, pure. Fr. 2, benzene-EtOAc (98:2), 3 x 100 ml, mixture. Fr. 3, benzene-EtOAc (90:10), 4 x 100 ml, mixture.

Fr. 2 was distilled to furnish the vinylidene dione 21 as a pale yellow liquid b.p.160°(bath)/0.5 mm (0.28 g, 15%).

IR (smear): 3060, 1700, 1645, 1410, 885. PMR ($CCl_4$): $\delta$ 4.77, 4.68 (two singlets, 1H each, $>C=C\underline{H}_2$); 1.18 (<u>d</u>, 3H, <u>sec</u>-<u>Me</u>, J=5 Hz); 1.10, 1.07 (two tertiary Me singlets). Mass: m/z 234. (Found: C, 78.8; H, 10.5. $C_{15}H_{22}O_2$ requires: C, 76.8; H, 9.5%).

# REFERENCES


1 Jadhav P K & Nayak U R, Indian J Chem 16B (1978) 1051.

2 Hamon D P G, Taylor G F & Young R N, Synthesis (1975) 428.

3 Jadhav P K & Nayak U R, Tetrahedron Lett (1976), 4855; Indian J Chem 16B (1978) 952.

4 a) Suryawanshi S N & Nayak U R, Indian J Chem 18B (1979) 190.

b) Lamture J B, Suryawanshi S N & Nayak U R, Indian J Chem 21B (1982) 819.

5 Stehelin L, Lhomme J & Ourisson G, J Am Chem Soc 93 (1971) 1650.

6 a) Mehta G & Kapoor S K, J Org Chem 39 (1974) 2618.

b) Mehta G, Kapoor S K, Guru Row T N & Venkatesan K, Tetrahedron Lett (1974) 2653.

7 Suryawanshi S N & Nayak U R, Indian J Chem 17B (1979) 304.

8. Fieser L F & Fieser M, Reagents for Organic Synthesis, John Wiley, New York, 1967, Vol. 1, p.1102.

9. Jadhav P. K, Suryawanshi S N & Nayak U R, Indian J Chem 19B (1980) 144.

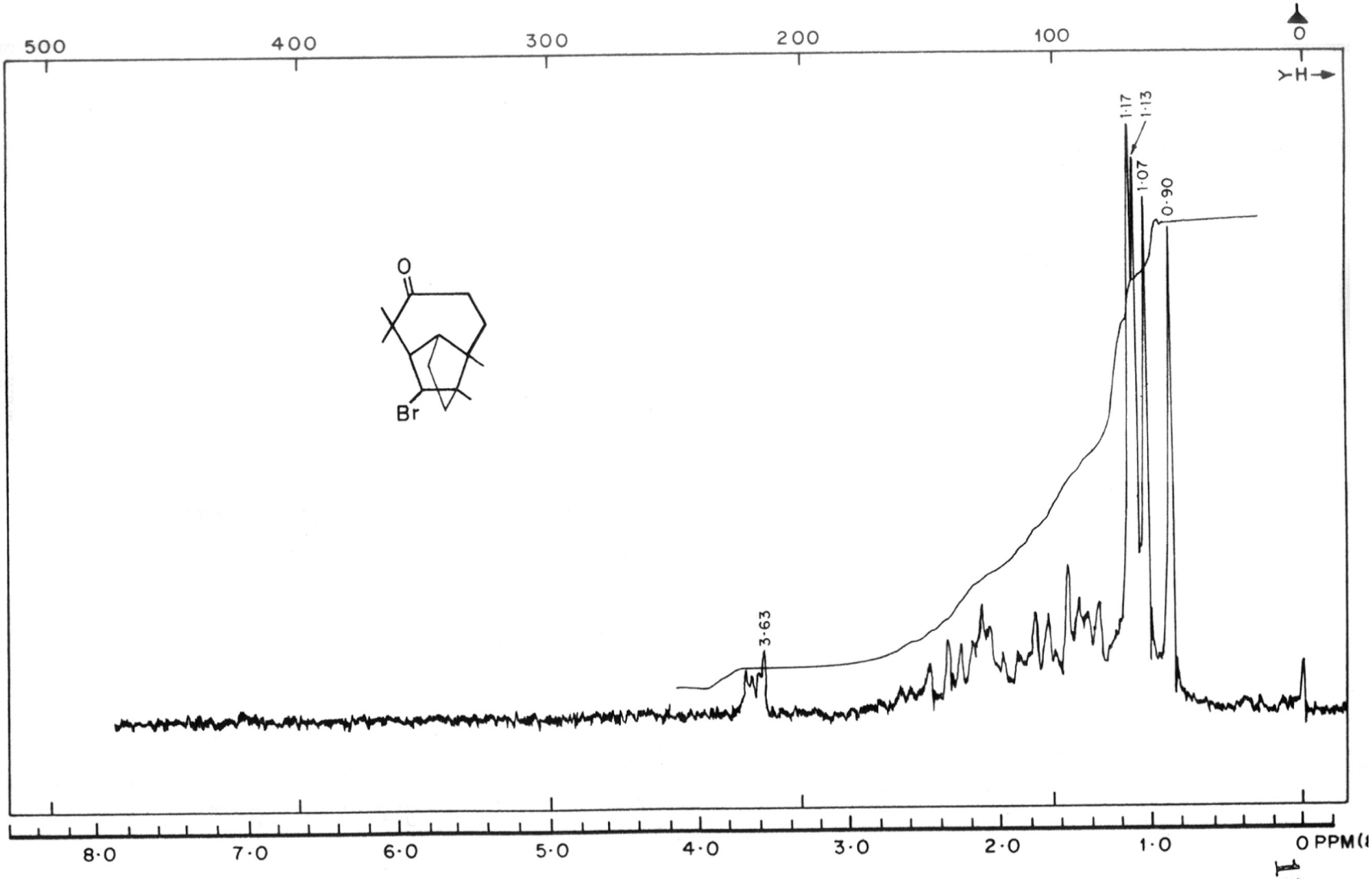
10 Nayak U R & Sukh Dev, Tetrahedron 8 (1960) 42.

11 Naffa P & Ourisson G, Bull Soc Chim (1954) 1410.

12 Suryawanshi S N & Nayak U R, Tetrahedron Lett (1977) 2619; Indian J Chem 19B (1980) 1.

13 Vaidya S P, Shitole H R & Nayak U R, Indian J Chem (communicated).

14 Gupta A S & Sukh Dev, J Chromat 12 (1963) 189.

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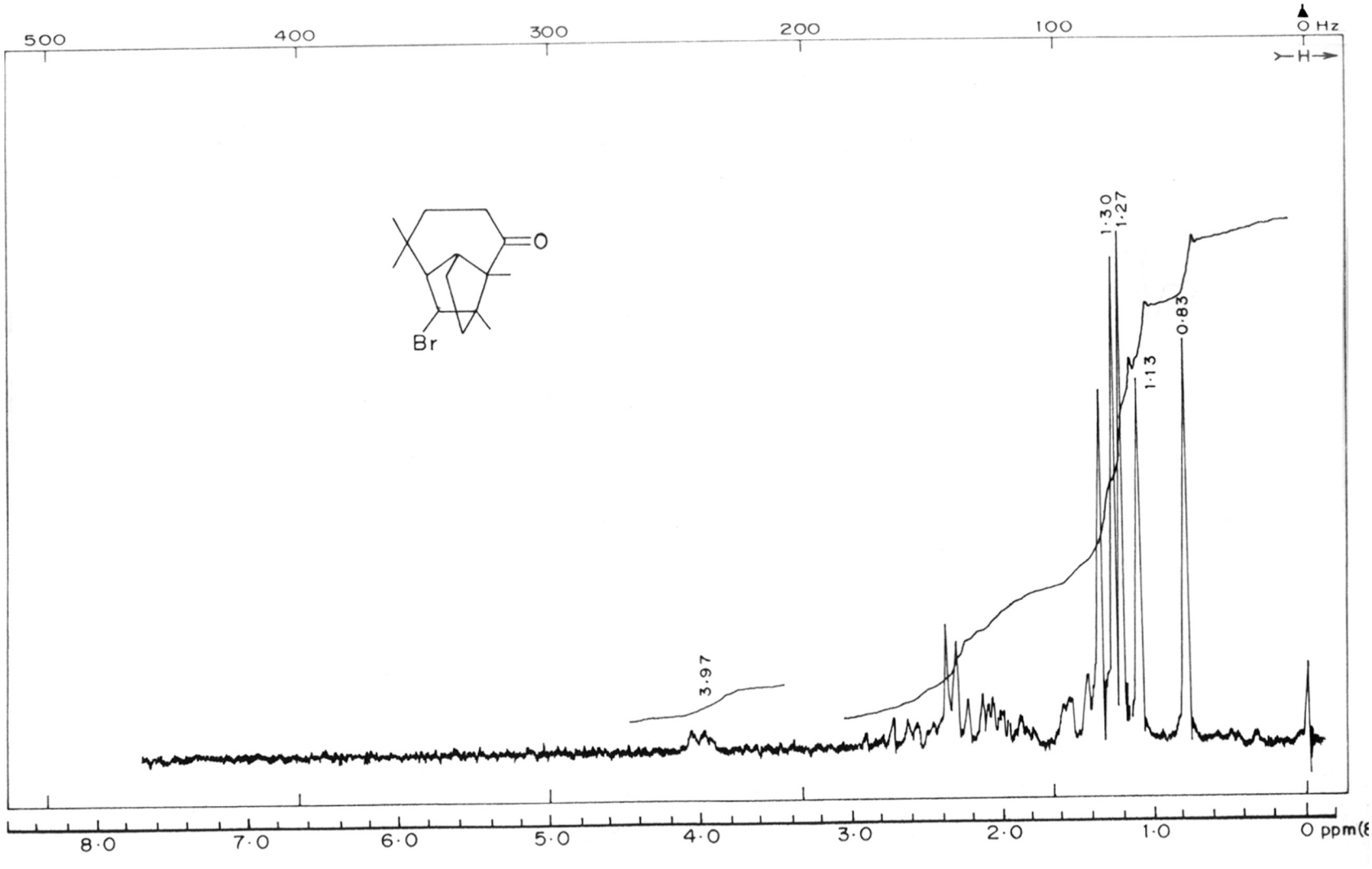


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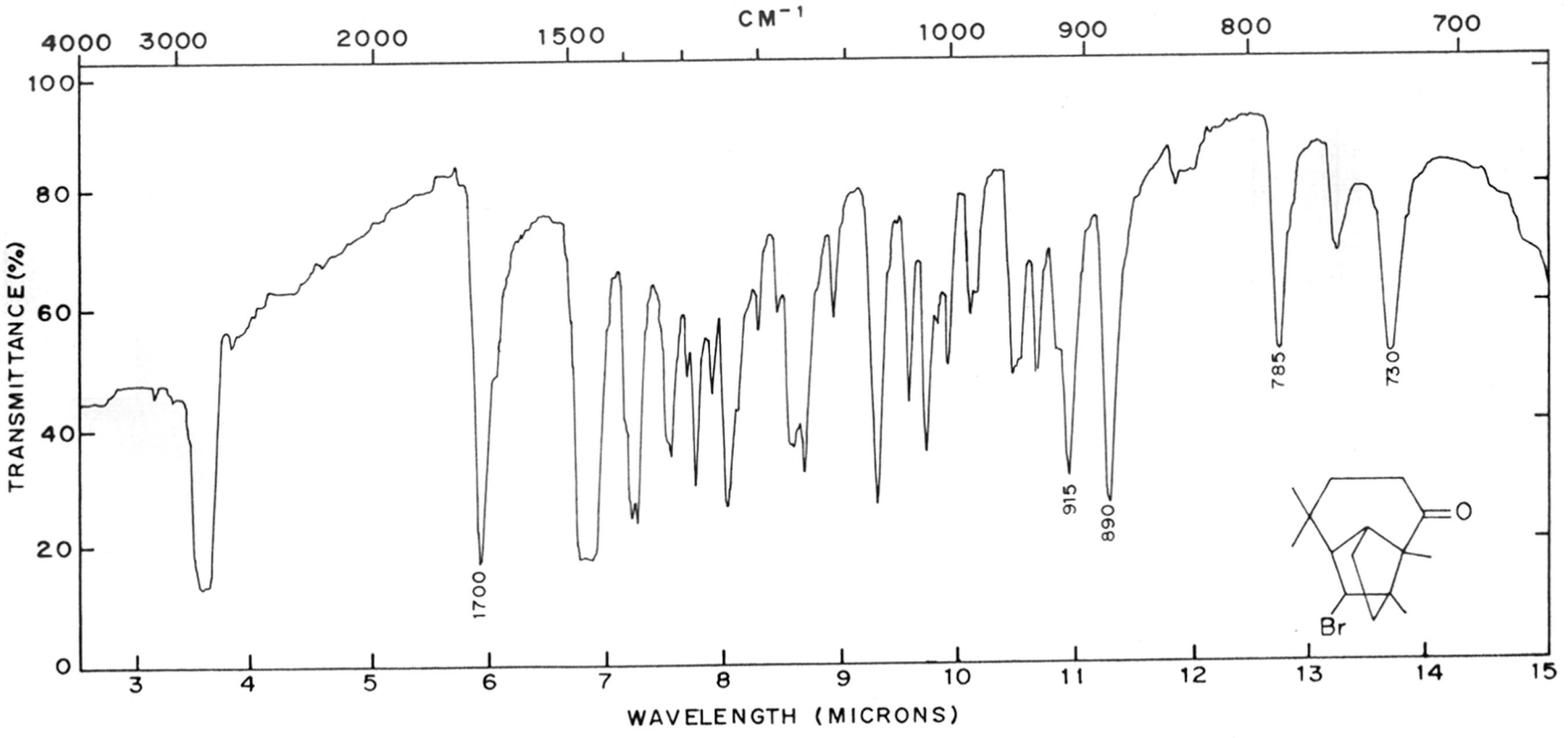


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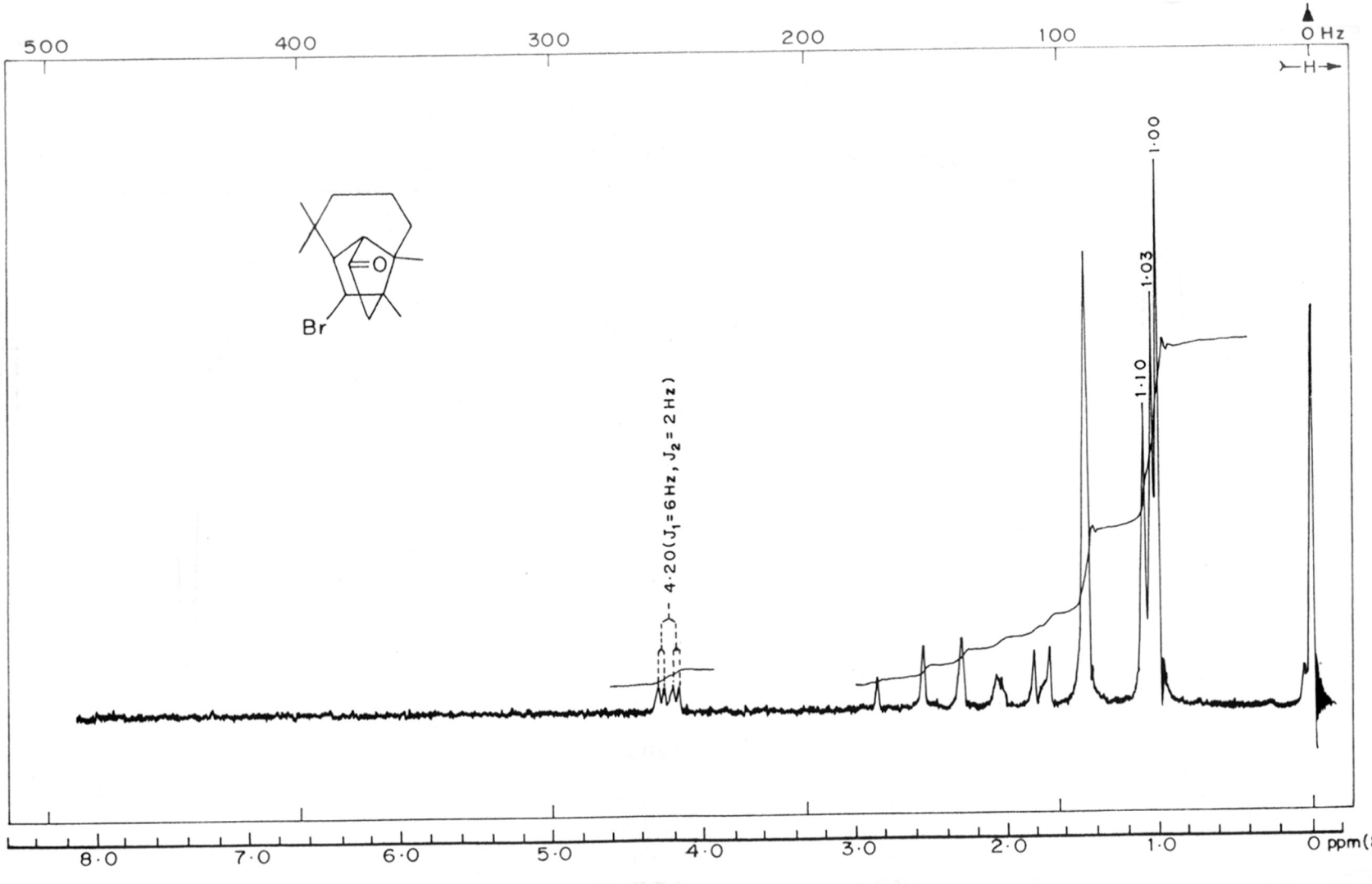


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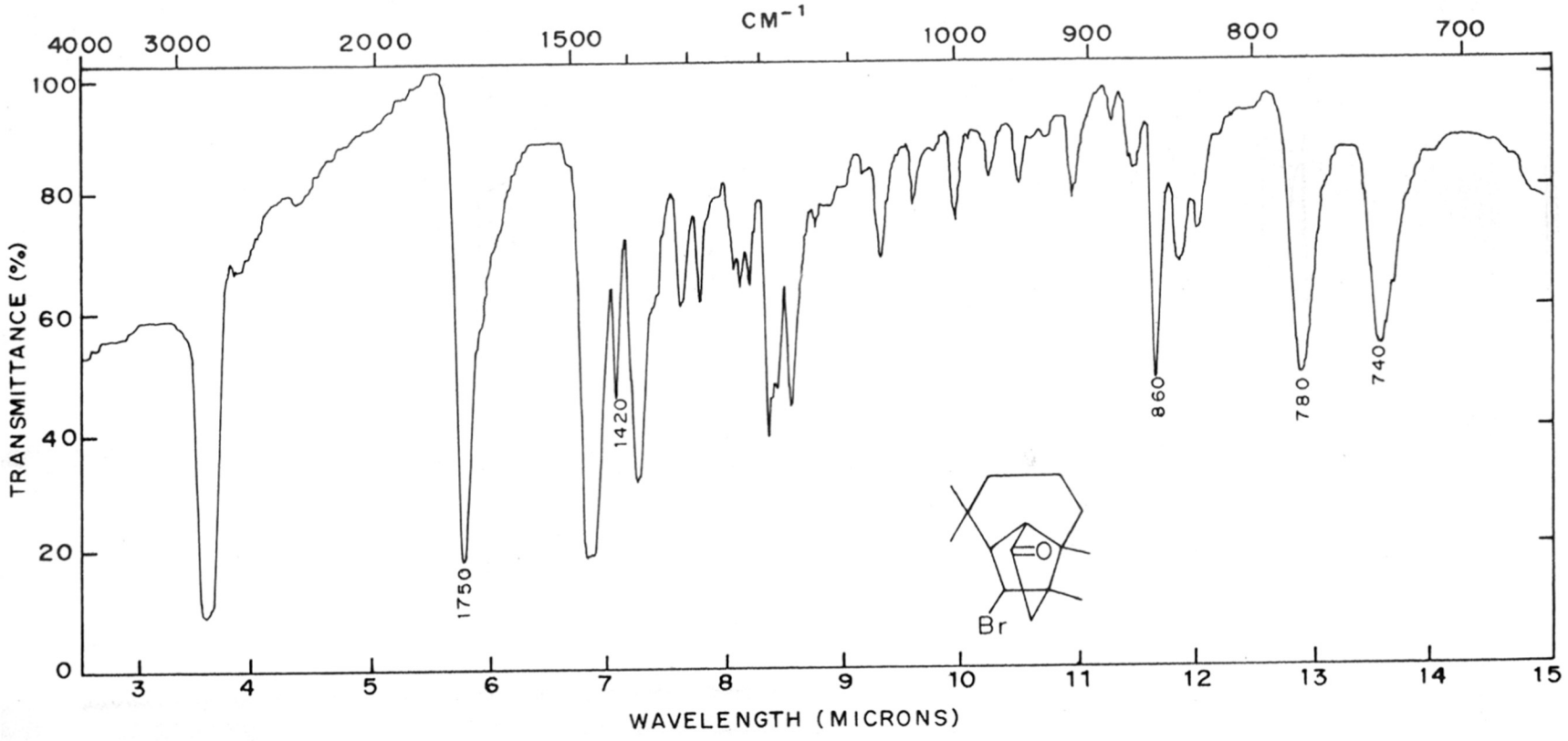


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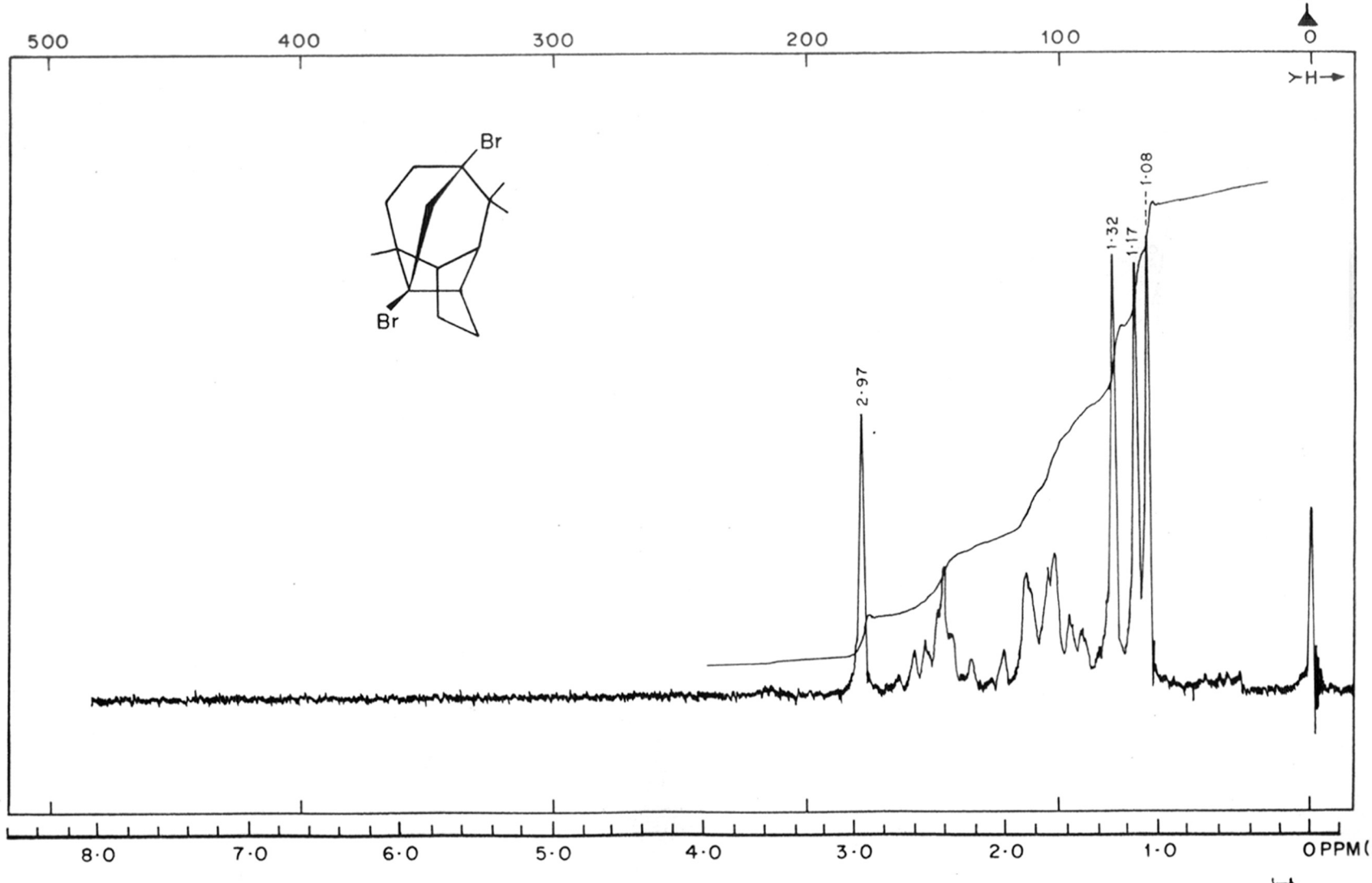


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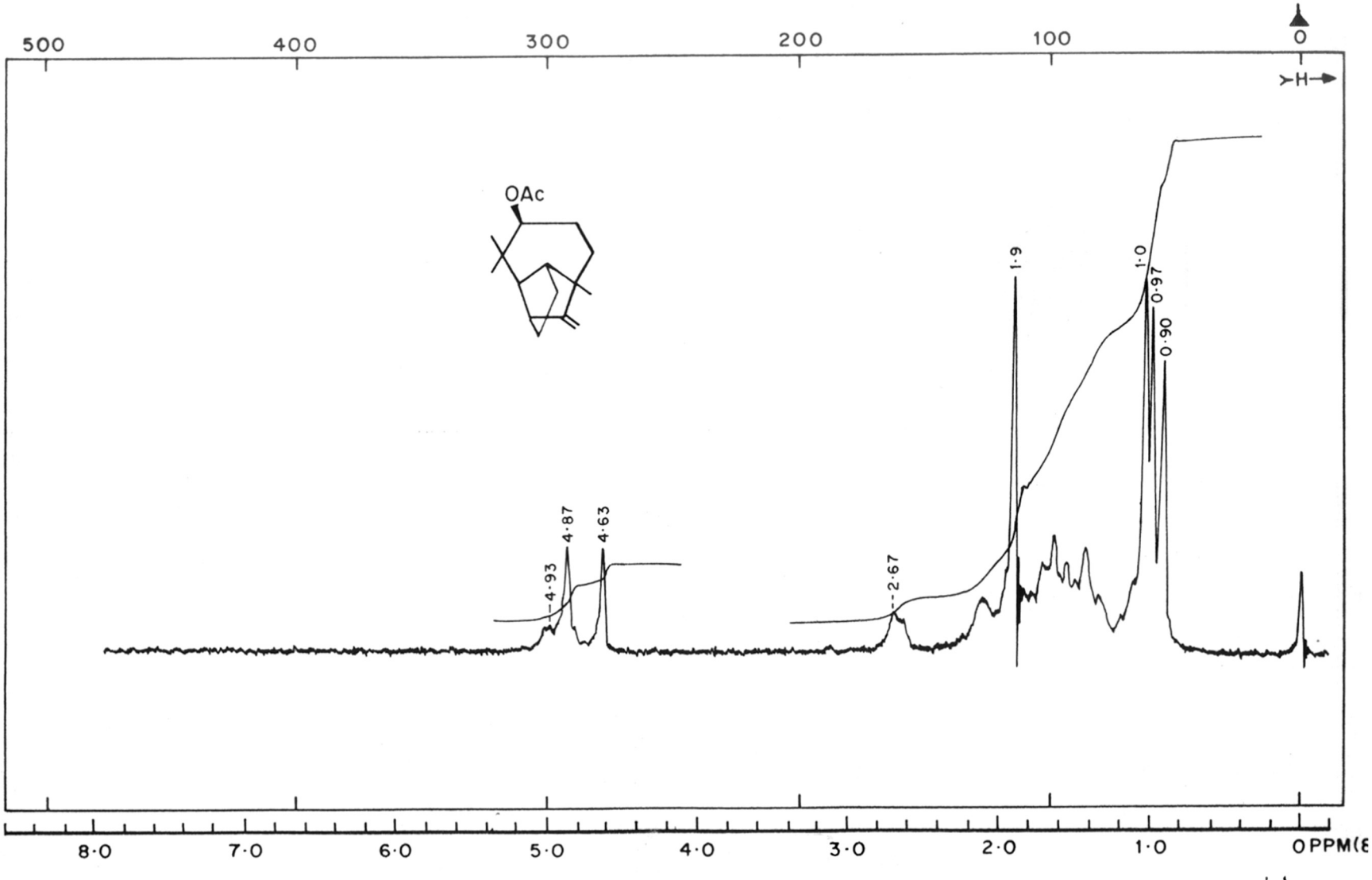


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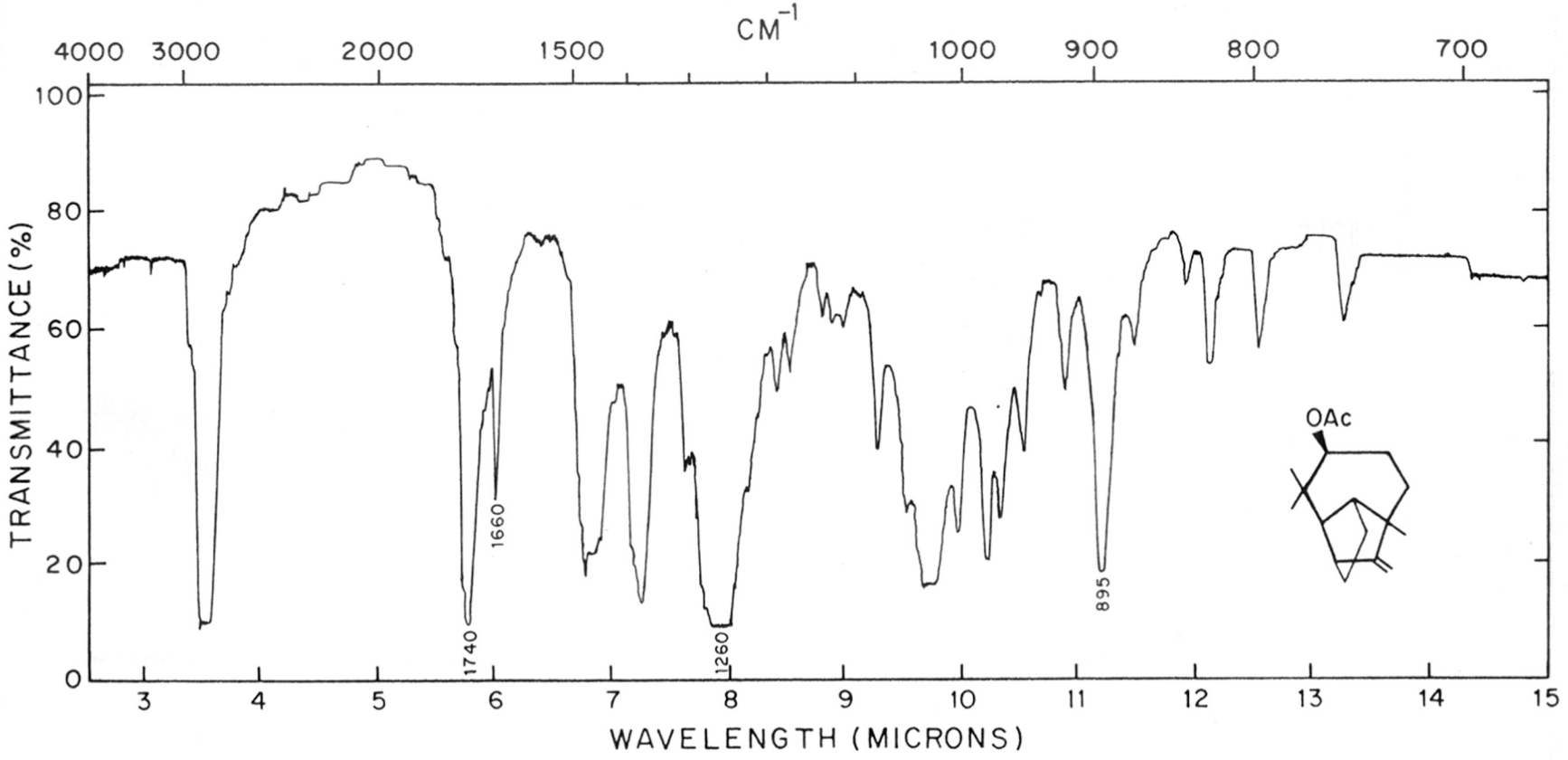


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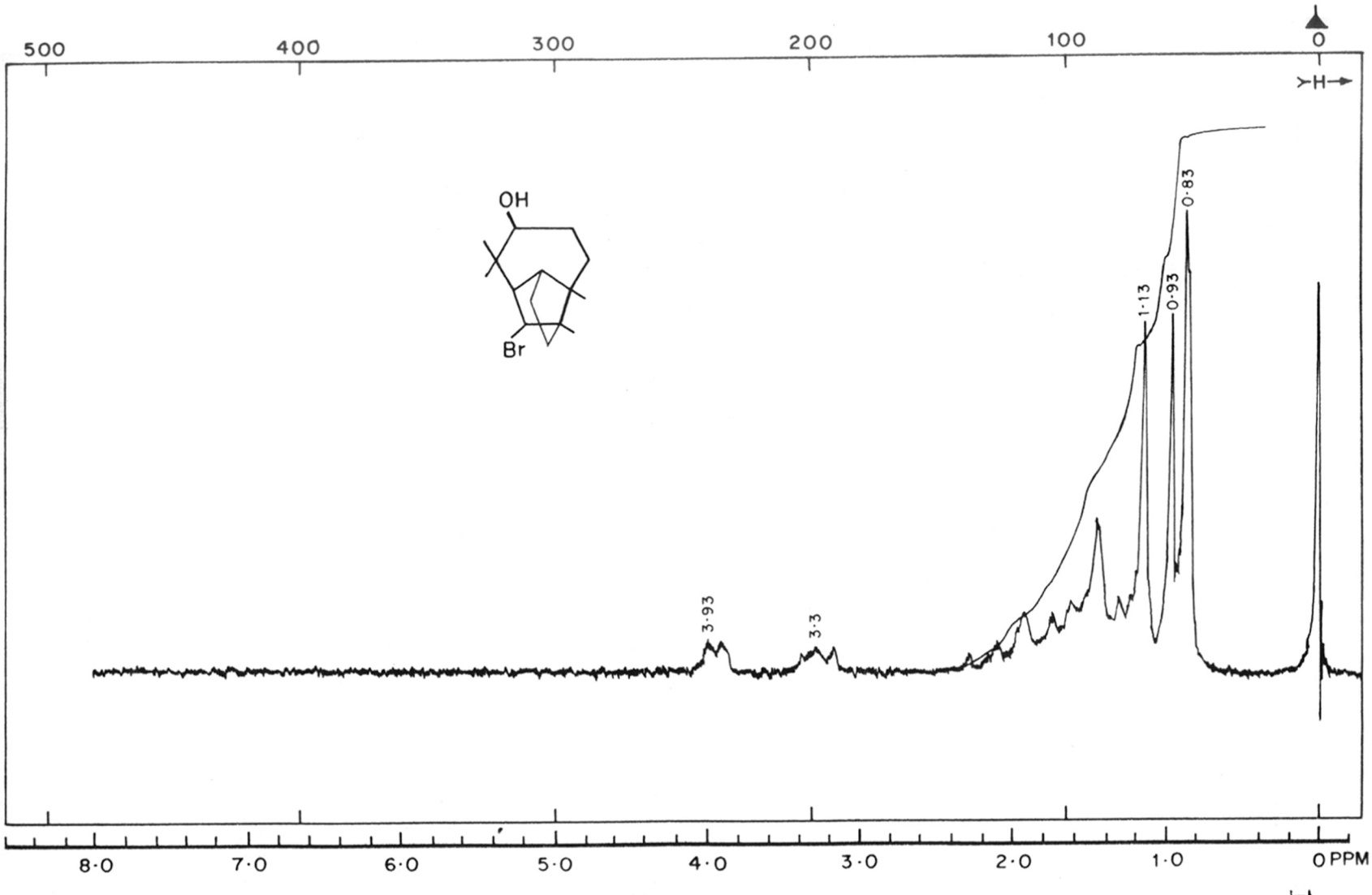


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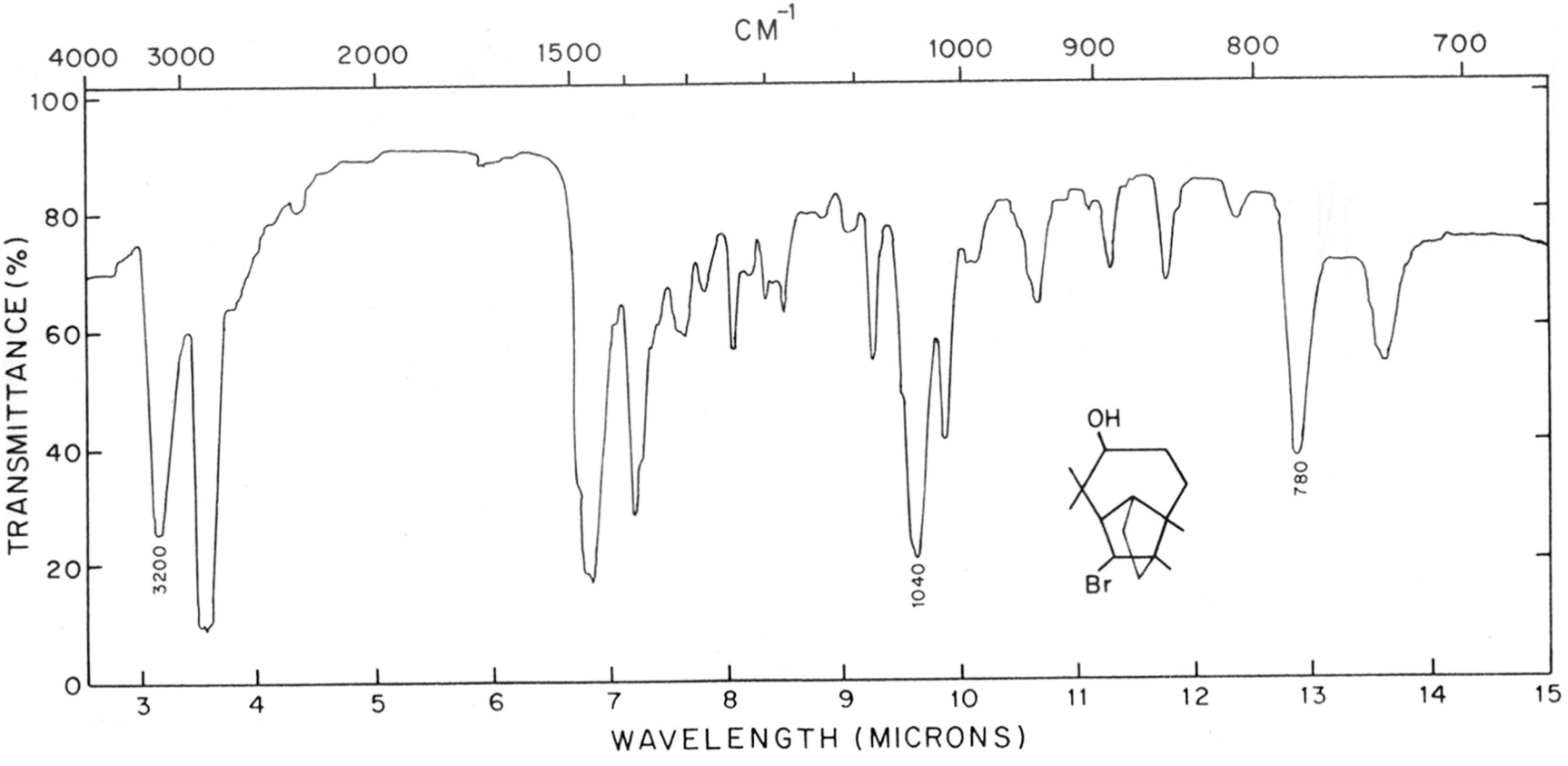


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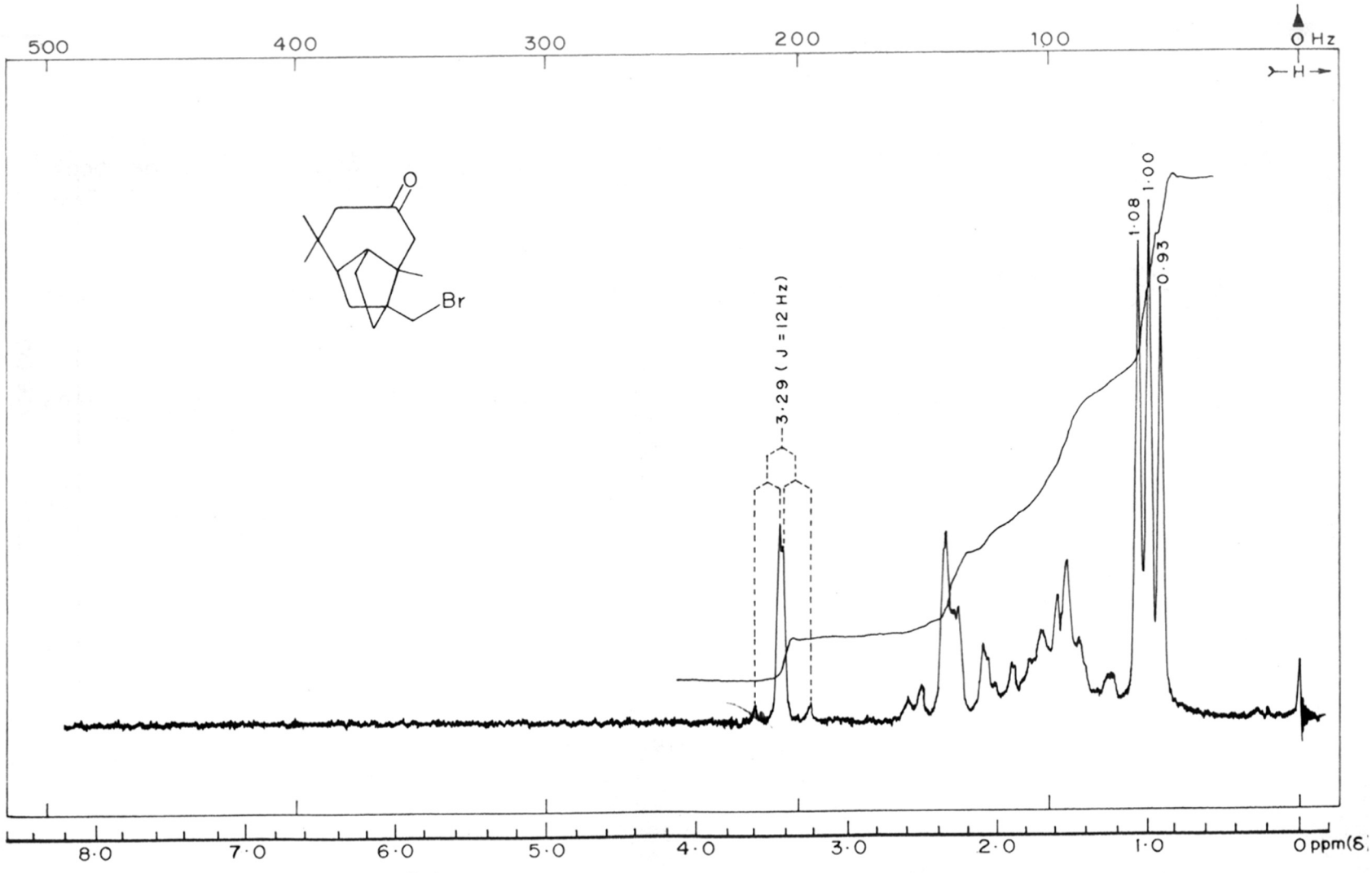


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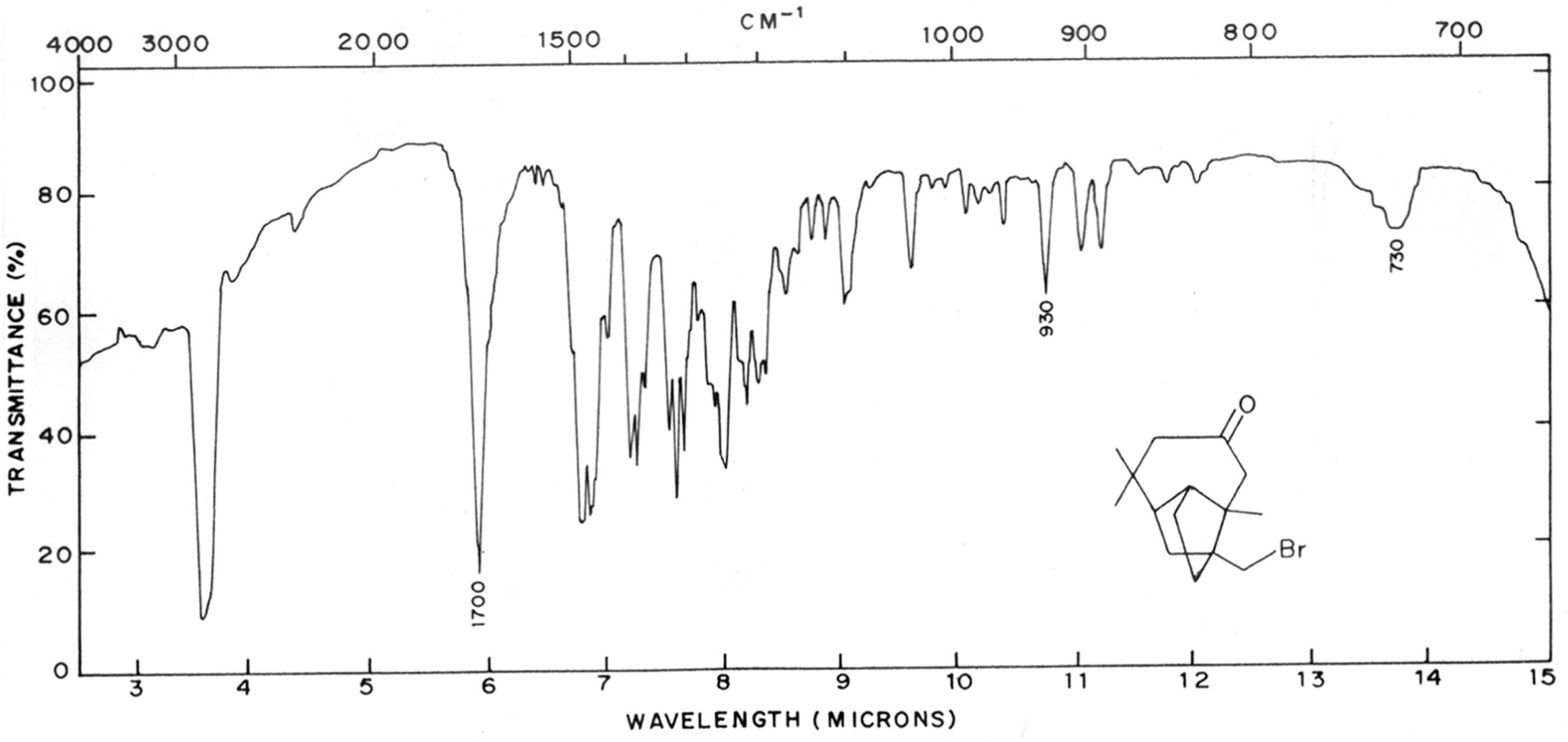


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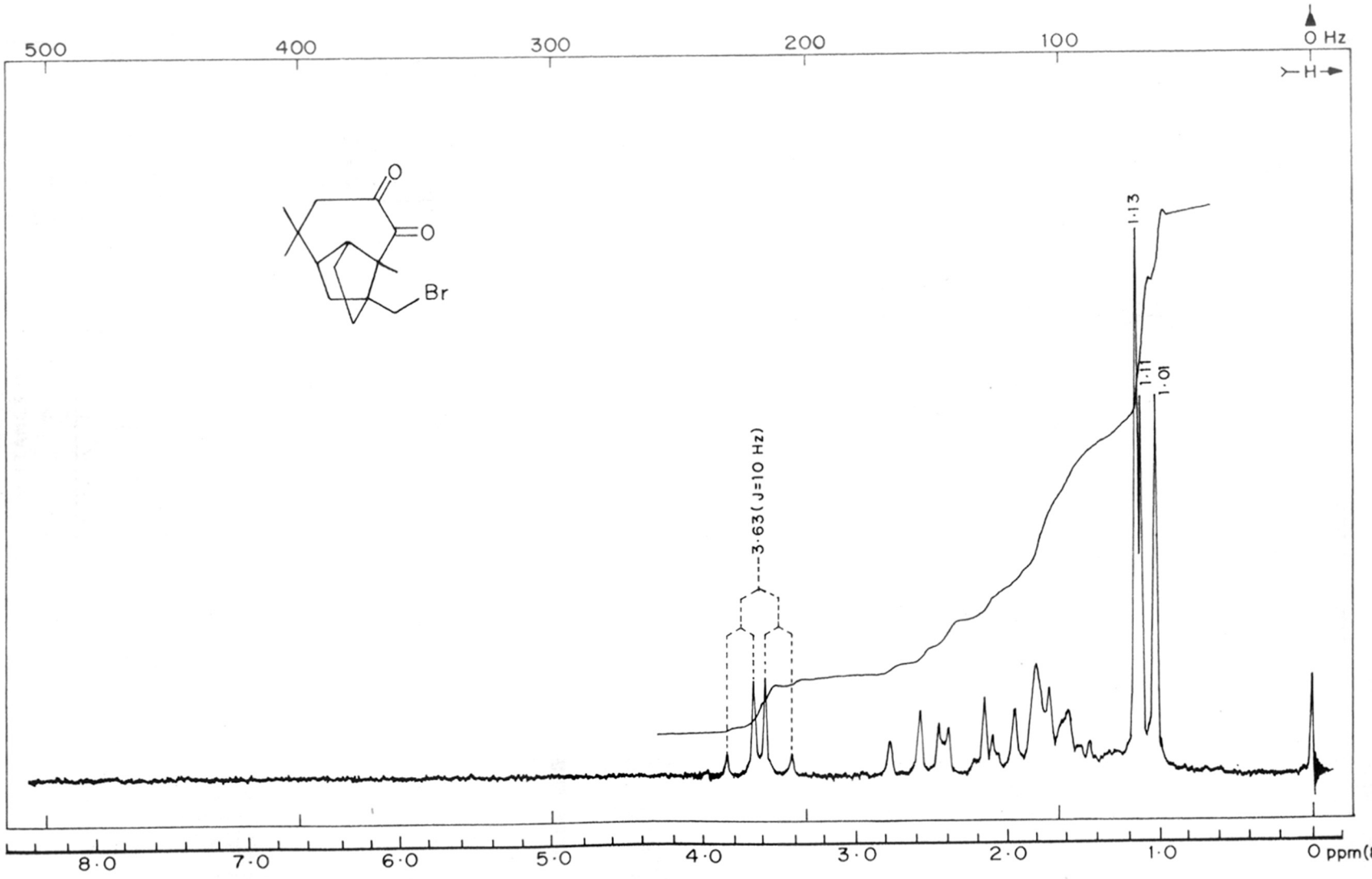


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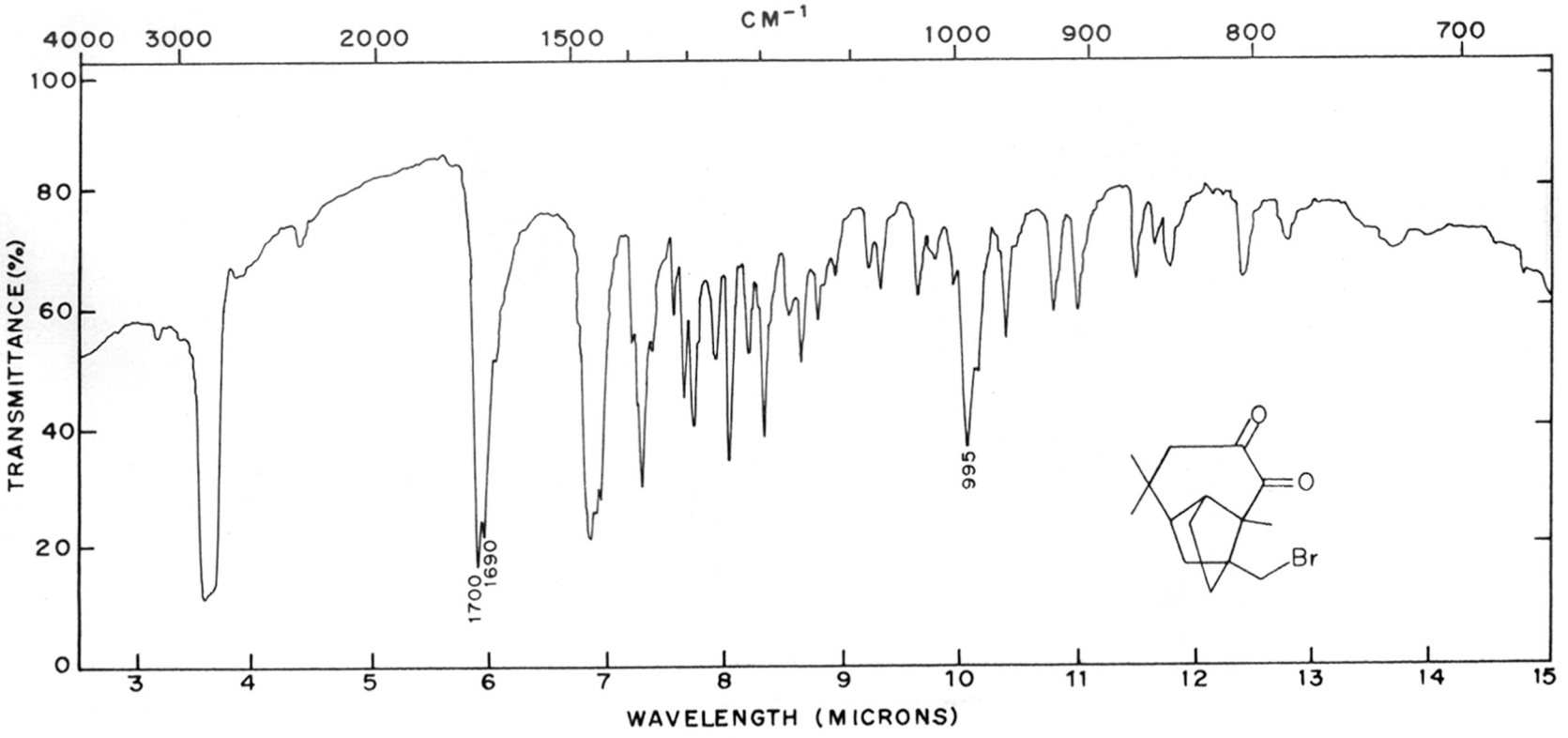


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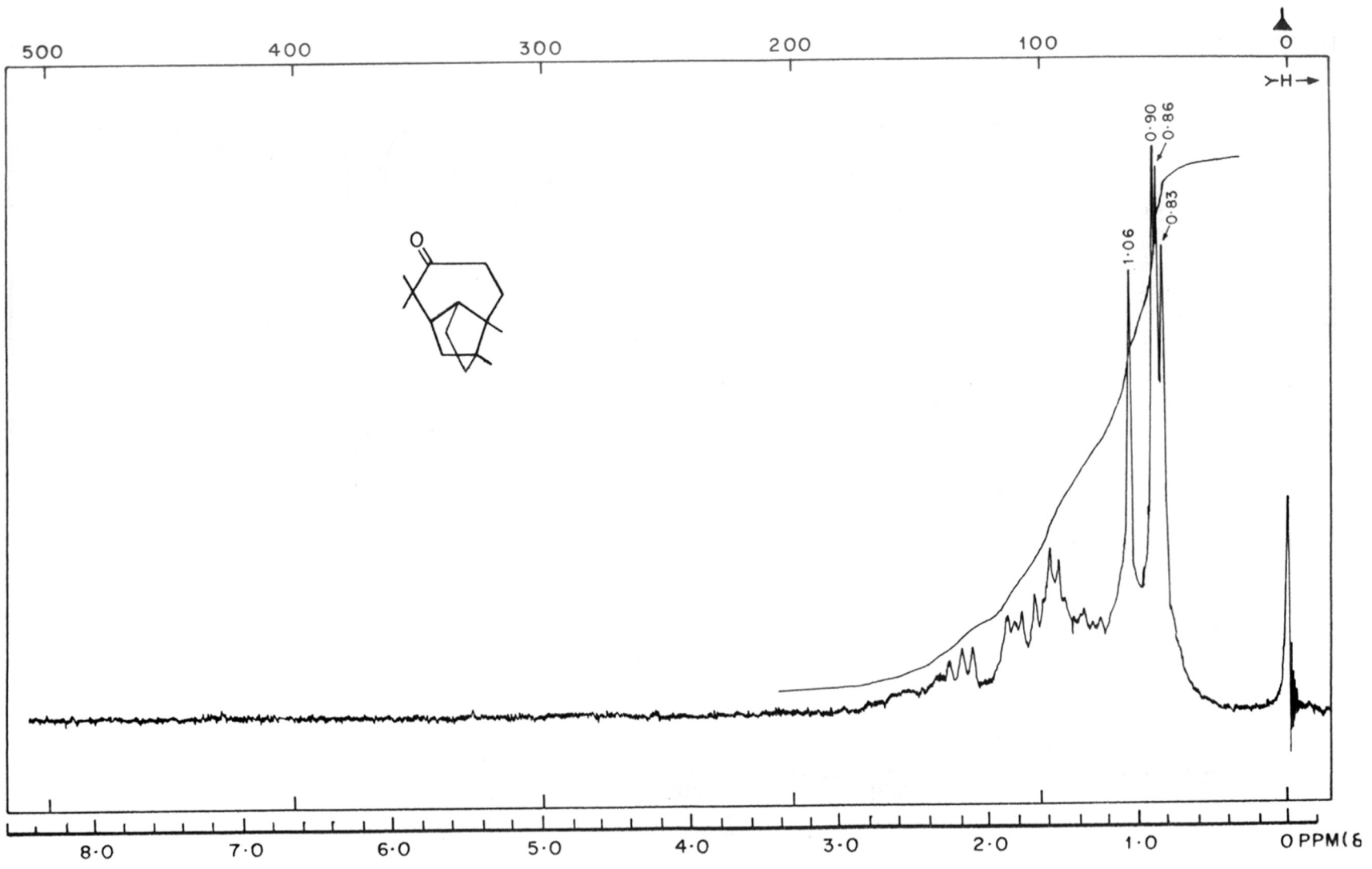


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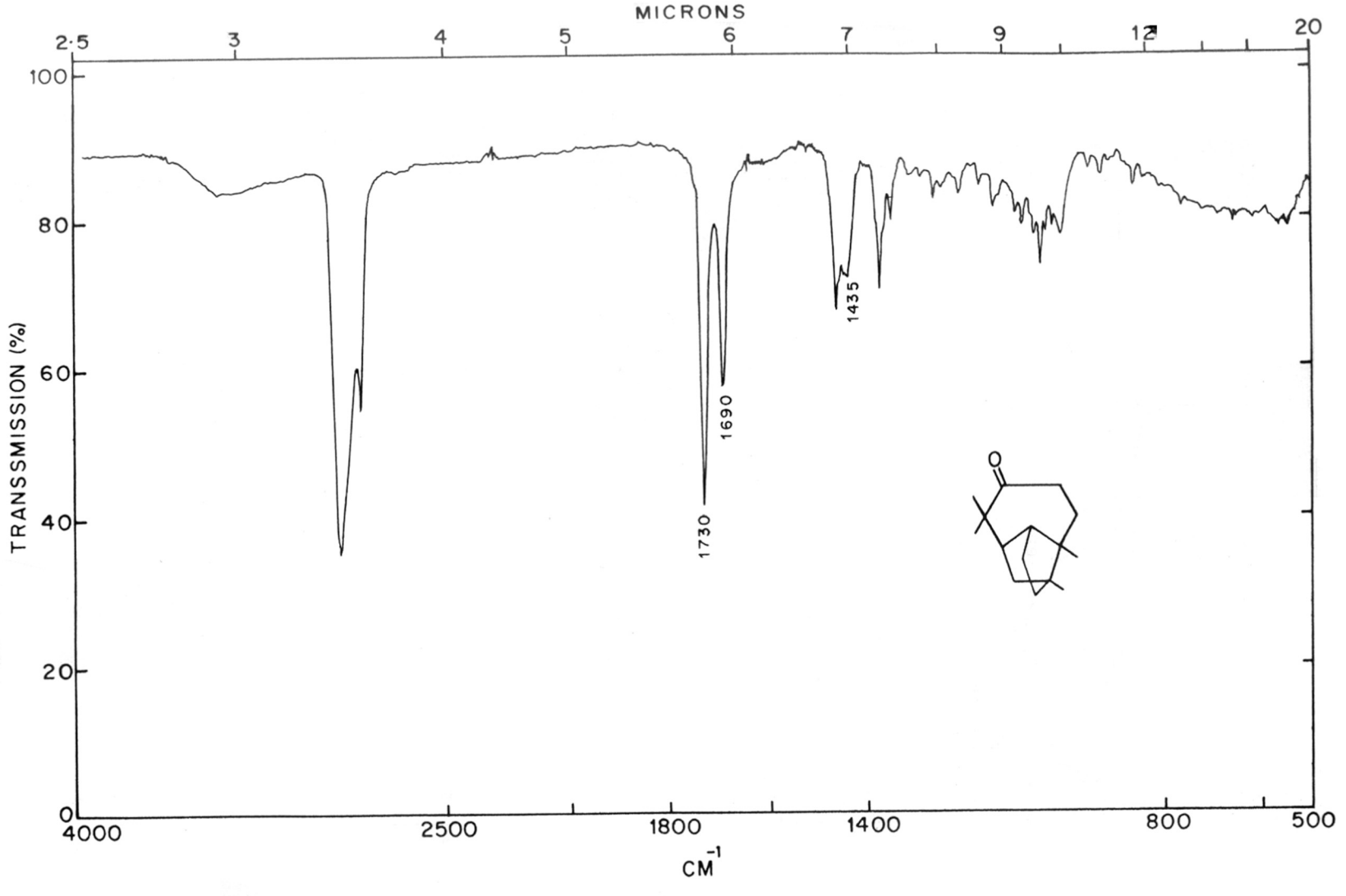


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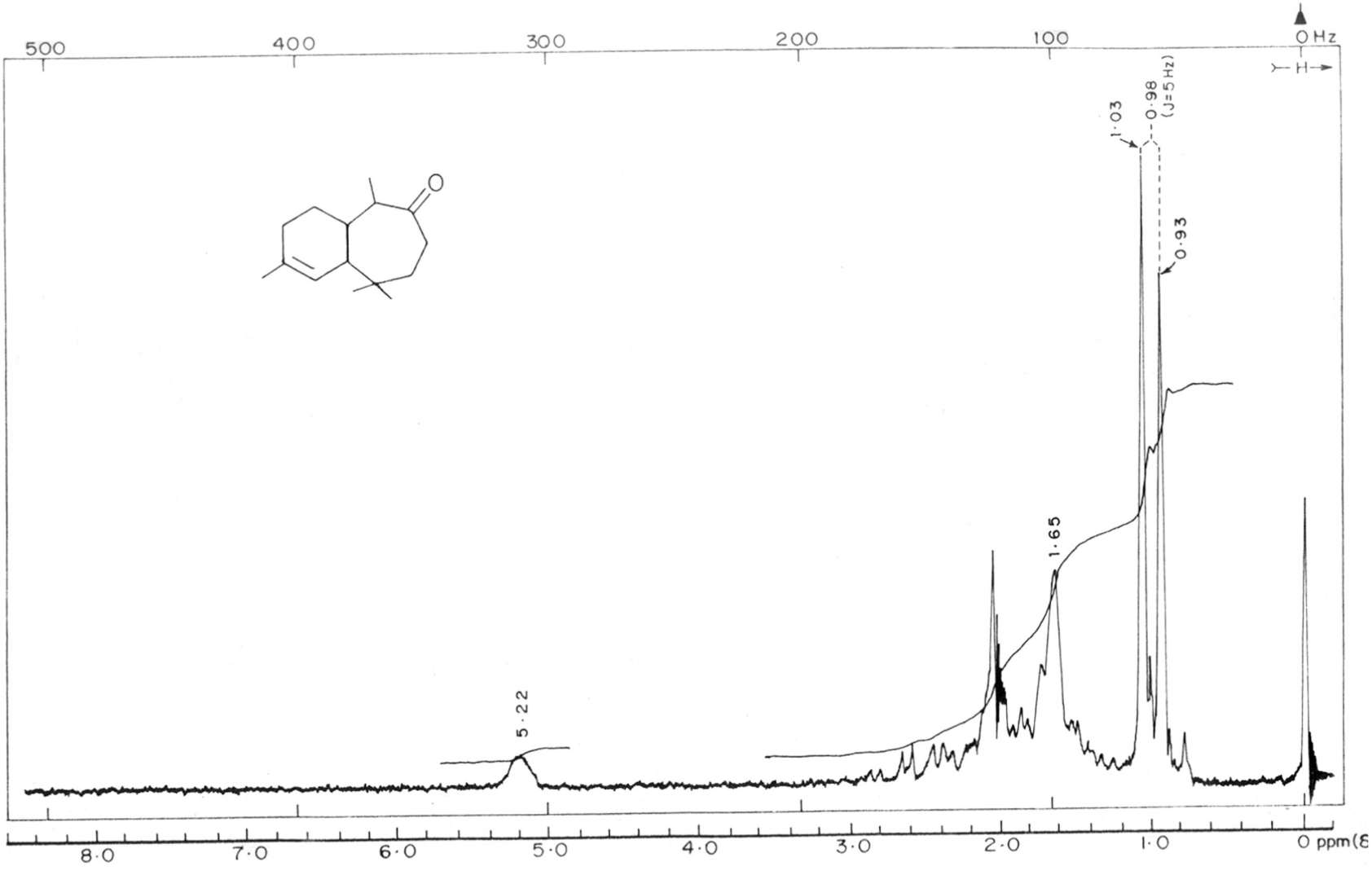


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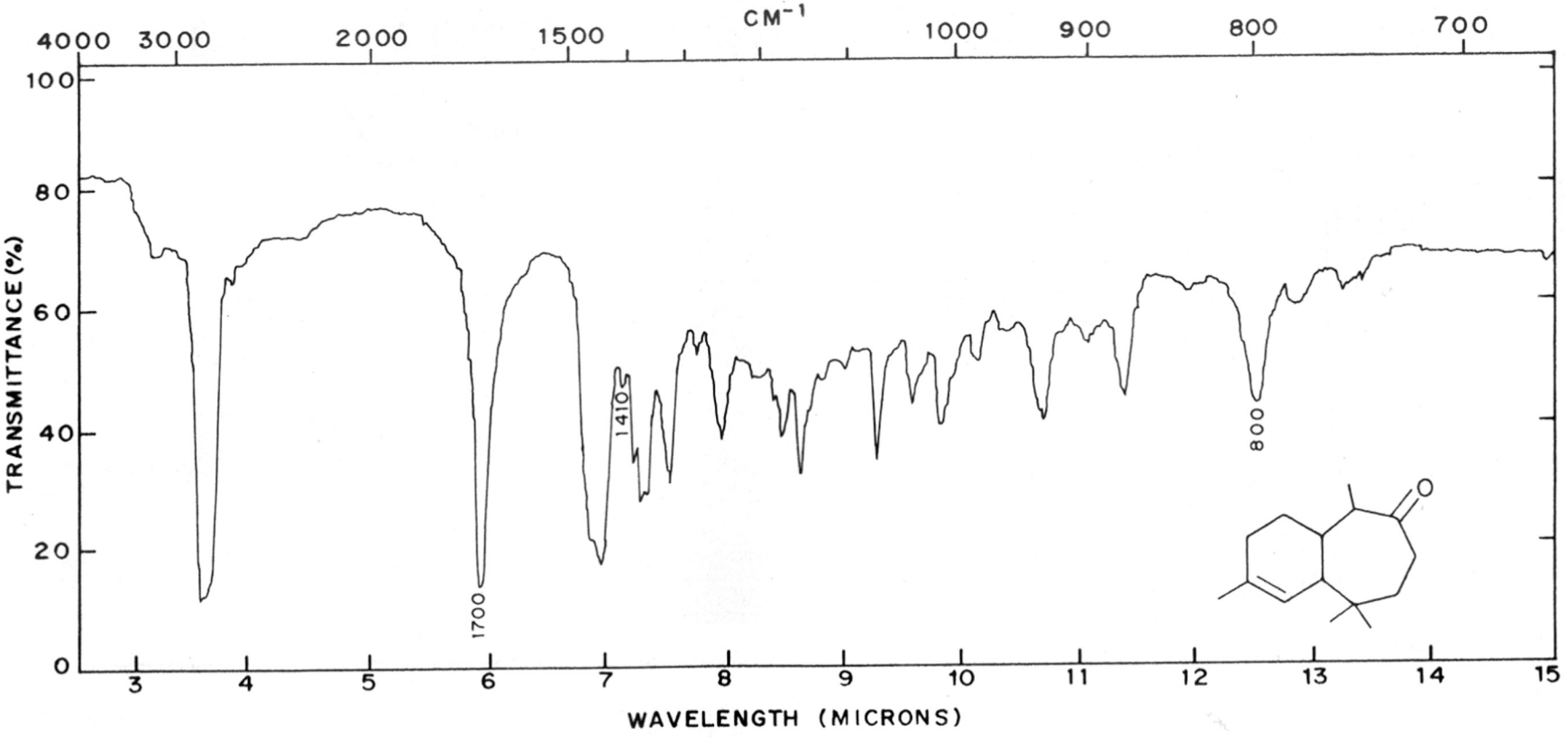


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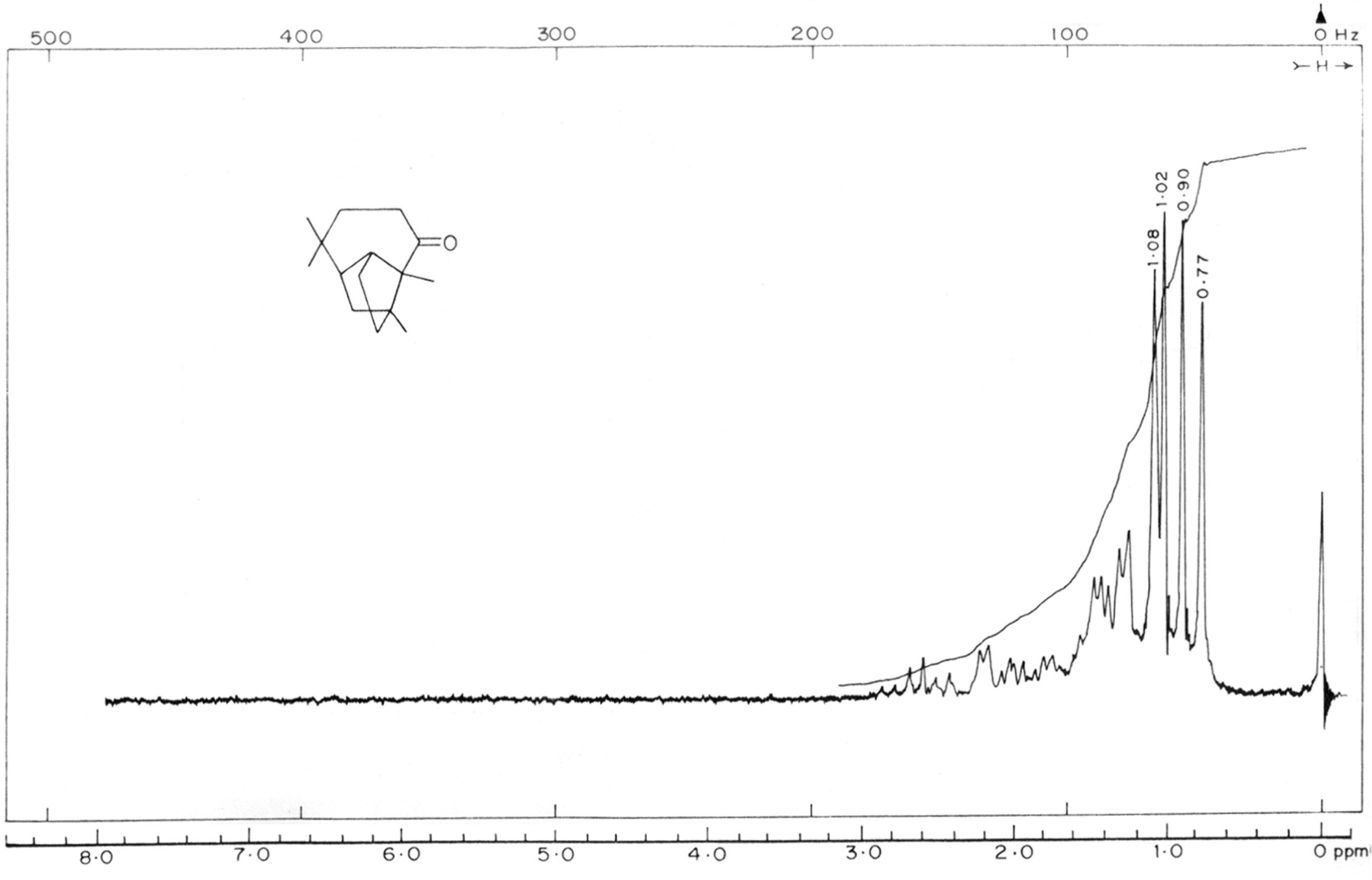


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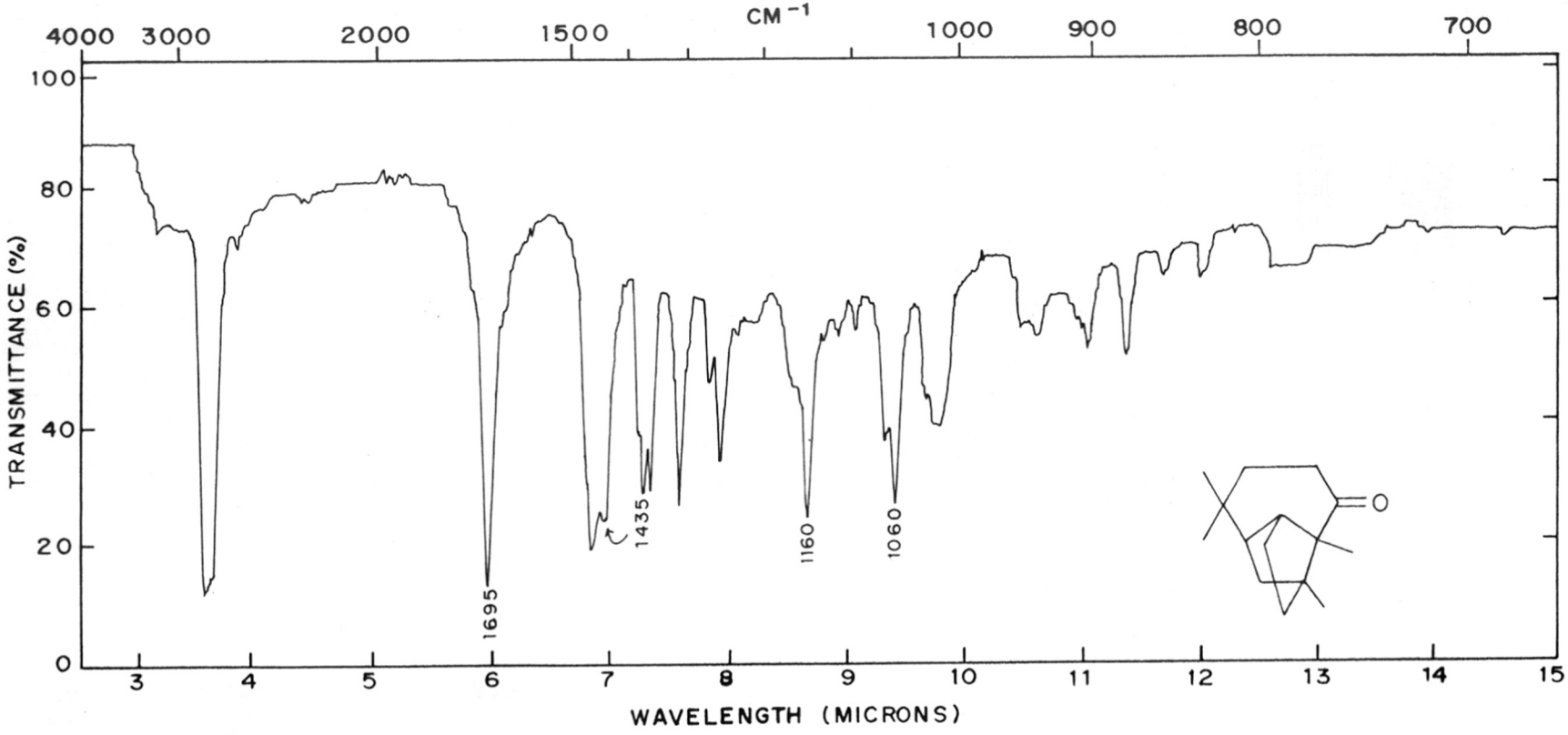


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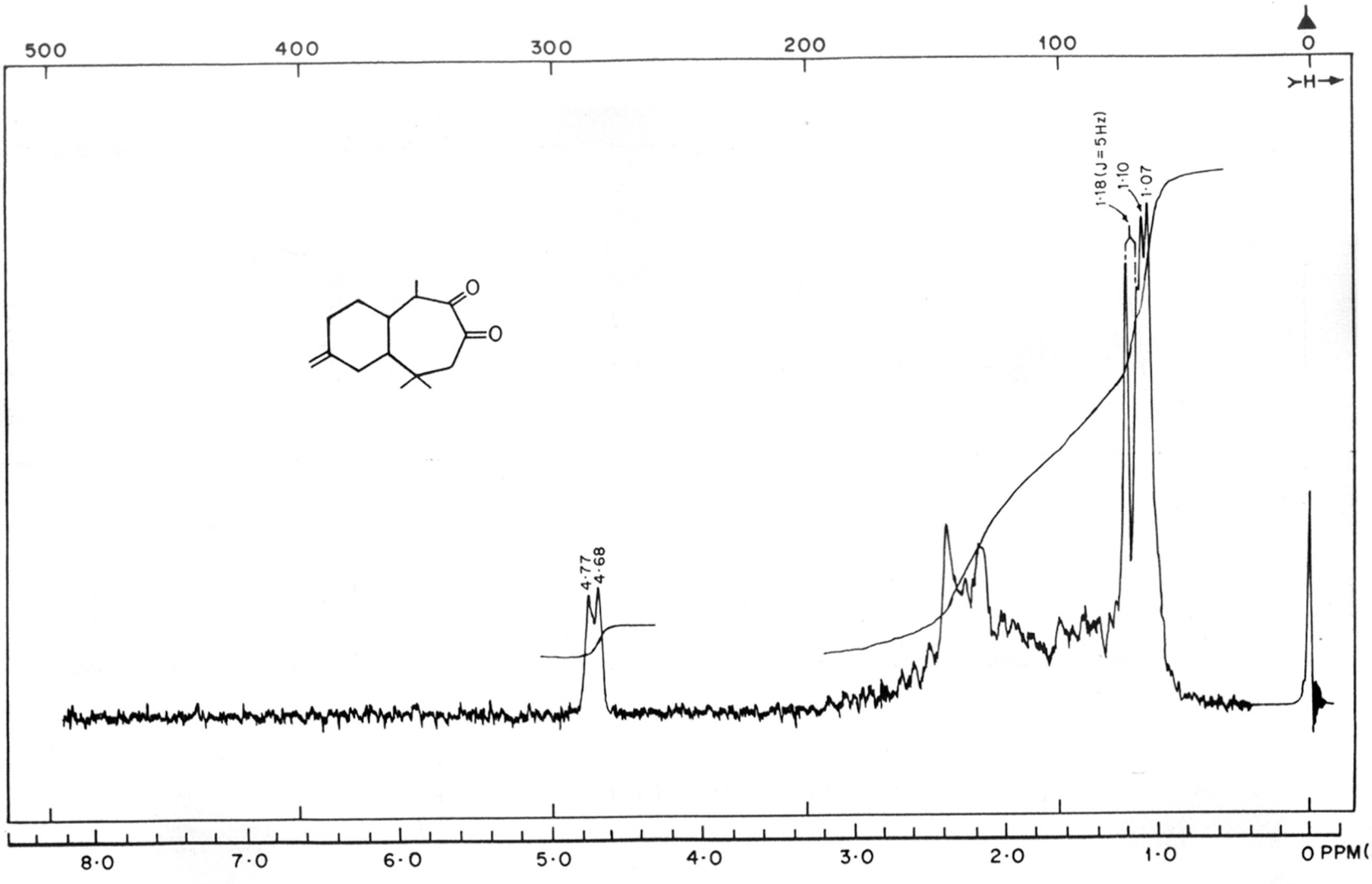


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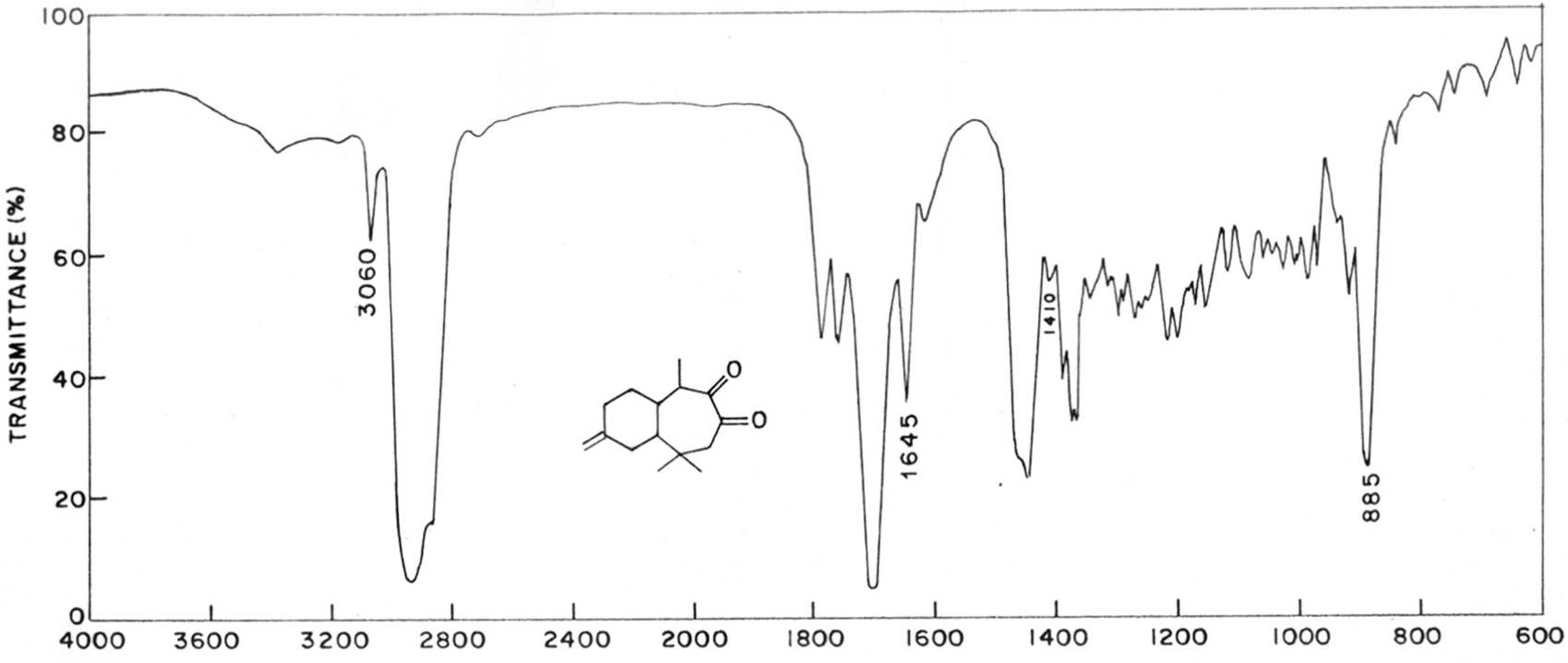



IR SPECTRUM OF VINYLIDENE DIONE 21

# CHAPTER-7

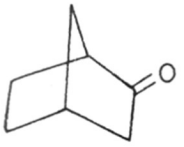
## NITROGEN INSERTION IN THE ISOLONGIFOLANE / LONGIBORNANE SYSTEMS VIA BECKMANN / SCHMIDT REARRANGEMENTS : A COMPARATIVE STUDY

## A B S T R A C T

Novel nitrogen inserted compounds are formed when the 7H-epimeric 8-oxoisolongifolanes 5/6 and longibornane-4-one 7 are subjected to Beckmann/Schmidt rearrangements. While treatment of oxime 8 of 7$\alpha$ H-ketone 5 with tosyyl chloride in pyridine gives the usual lactam 11 (50%) by migration of methine, oxime 9 of 7$\beta$ H-ketone 6 under similar conditions generates the unusual lactam 12 by methylene migration. Refluxing 5 with hydroxylamine-O-sulphonic acid in acetic acid also results in 11 (13%) in a Beckmann-like rearrangement while 6 fails to react under these conditions. When exposed to sodium azide + conc. sulphuric acid in chloroform (Schmidt reaction), 7$\alpha$ H-ketone 5 is transformed into 11 (32%) while 7$\beta$ H-ketone 6 is recovered unchanged. The Beckmann rearrangement (tosyl chloride in pyridine) of oxime 10 derived from longibornane-4-one 7 affords a single lactam (30%) either 14 or 15 while refluxing 7 with hydroxylamine-O-sulphonic acid in acetic acid gives a mixture of the two (16%). The tetrazole 16/17 (42%) is formed when 7 is subjected to Schmidt reaction with excess of hydrazoic acid.

AS PART of our study dealing with electron-deficient skelatal rearrangements in longifolene chemistry[1], we have earlier described synthetically useful carbon insertions[2] via diazomethane[2a]/Arndt-Eistert[2b] reactions. In this paper the results obtained during nitrogen insertion studies in the isolongifolane/longibornane systems via Beckmann[3]/Schmidt[4] rearrangements will be elaborated.

In the case of alicyclic ketoximes/ketones, the Beckmann/Schmidt rearrangements generally afford ring-enlarged lactams, the nitrogen insertion taking place on the more substituted[5] side of the ring. A fragmentation reaction generating olefinic nitriles has been occassionally observed in an abnormal[6] Beckmann while in the case of Schmidt rearrangement, tetrazoles[4b]/ureas[7] (which are otherwise inaccessible and some of which exhibit high biological activity) are formed when an excess of hydrazoic acid is used in the reaction. Although both these reactions have been quite extensively studied, not many examples of bridged bicyclic/tricyclic substrates have been described in the literature. One interesting example which has been subjected to both Beckmann/Schmidt reactions is that of norcamphor[8] 1. In a Beckmann reaction, its oxime 2 afforded the usual lactam 3 while Schmidt reaction on 1 yielded the unusual lactam 4 arising from methylene migration instead of the expected bridgedhead methine migration.

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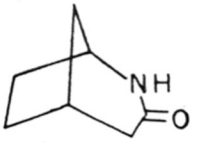
2 : R = NOH

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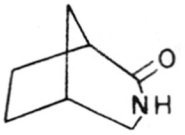


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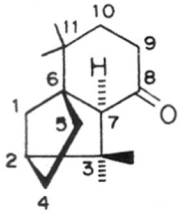


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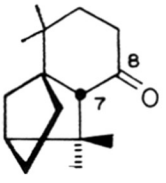


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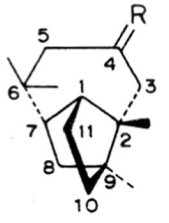
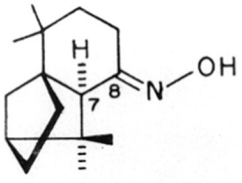



7 : R = O

10 : R = NOH

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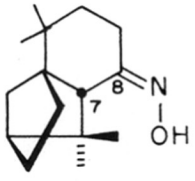


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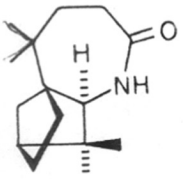
In view of the above account, we selected three readily accessible bridged tricyclic ketones from longifolene chemistry for nitrogen insertion studies via the Beckmann/Schmidt rearrangements: the 7H-epimeric pair[9] of 8-oxoisolongifolanes 5/6 and longibornane-4-one[10] 7. The oximes were prepared by refluxing an ethanolic solution of the ketone with hydroxylamine hydrochloride and pyridine. While the ketoximes 8/9 based on isolongifolane skeleton were single isomers, the ketoxime 10 of longibornane-4-one 7 was a syn/anti mixture (PMR). The tosylate esters of oximes are known to undergo Beckmann rearrangement[11] in neutral/aqueous alkaline medium under mild conditions. Thus when the 7$\alpha$H-ketoxime 8 was treated with tosyl chloride in pyridine at ambient temperature, it afforded a crystalline compound (m.p.124°; $C_{15}H_{25}ON$; yield 50%), which on the basis of its spectral data, was assigned the usual lactam structure 11 arising from methine migration. Under similar conditions, its epimer 9 also generated an isomeric lactam 12 (m.p.197°; 48% yield) but by unusual migration of the methylene group. This was borne out by the diagnostic $\alpha$-proton resonances in the PMR spectra of the two lactams: a 1H doublet at $\delta$3.34 assignable to HC-NH in 11 and two 1H multiplets at $\delta$3.10 and 3.70 due to $CH_2$-$CH_2$-NH in 12. If one invokes the anti-migration rule[12] which generally operates in the Beckmann rearrange-

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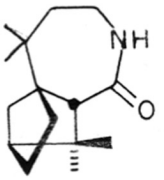


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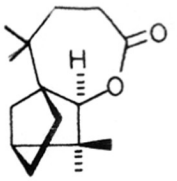


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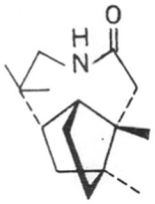


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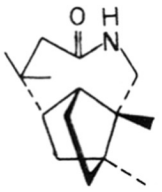


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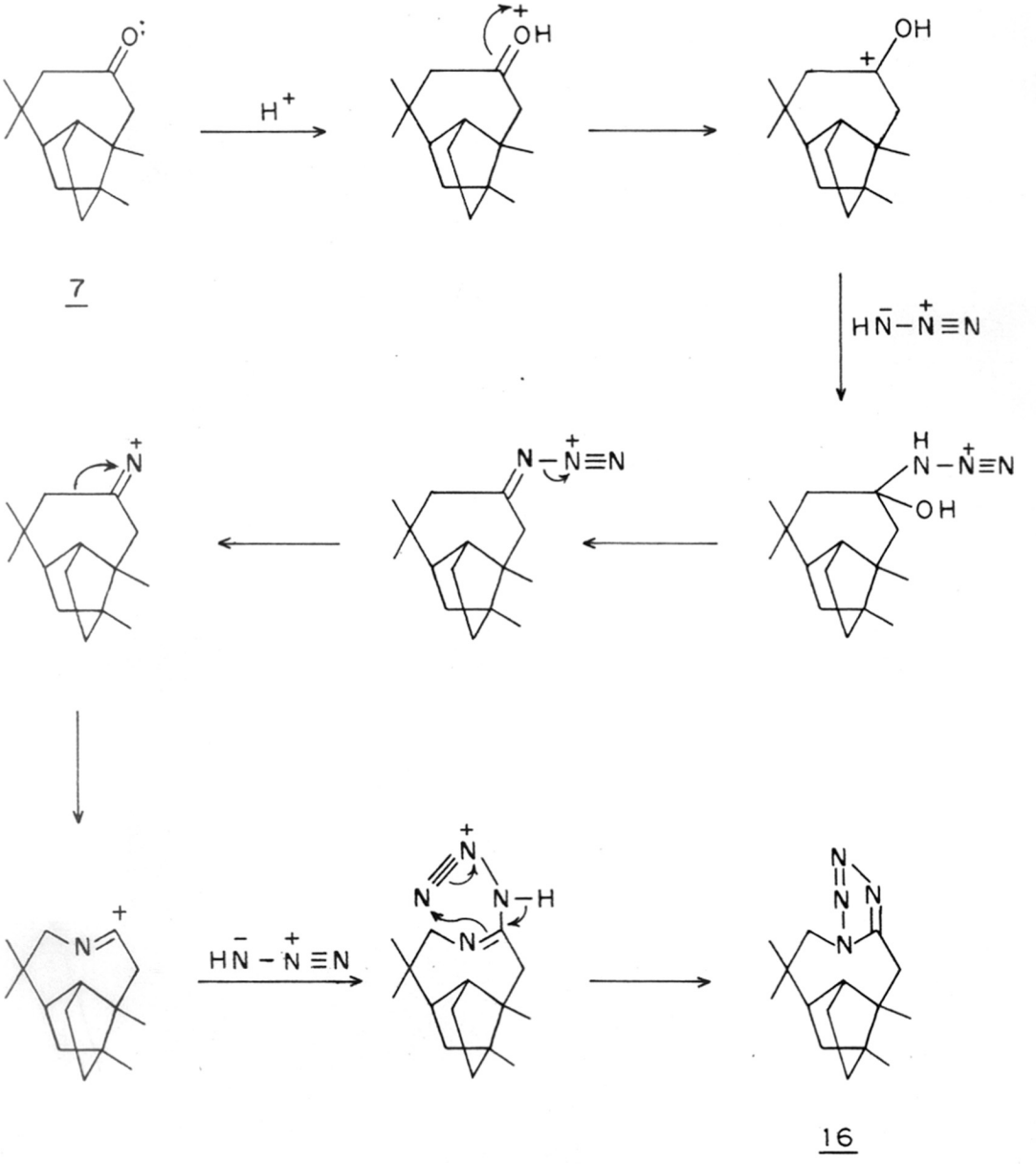
17

ment, it means that the isolongifolane based C-8 oximes 8/9 have opposite configurations-dictated by the C-7H stereochemistry in the parent ketones 5/6.

In a comparative study, when the Schmidt reaction was carried out by exposing the 7$\alpha$H-ketone 5 in chloroform to hydrazoic acid generated in situ (sodium azide + conc. sulphuric acid) at room temperature, a crystalline compound was obtained which could be readily identified as the Beckmann lactam 11 (32% yield); under similar reaction conditions epimer 6 failed to undergo any reaction and was recovered unchanged. This marked difference in behaviour of the two epimeric ketones 5/6 was also reflected in a Beckmann-like rearrangement performed by refluxing the substrate with hydroxylamine-O-sulphonic acid[13] in acetic acid: while 5 generated the lactam 11 (13%), 6 remained essentially unchanged. This steric constraint for attack by nucleophile in the case of 6 was also borne out by its total inertness to m-chloroperbenzoic acid ($CHCl_3$ solution/ room temperature) while its epimer 5 underwent facile oxygen insertion generating lactone[14] 13 under similar conditions.

Despite the fact that synthesis of tetrazoles by Schmidt reaction has found wide applications, systematic studies have not been made in this field. It is not clear




SCHEME 1

how the structure of the ketone affects its capacity for conversion into a tetrazole, although such a relation undoubtedly exists. Longibornane-4-one 7 constitutes a fine example which highlights product divergence during nitrogen insertion in ketones via Beckmann/Schmidt rearrangements. Thus when oxime 10 of ketone 7 was exposed to tosyl chloride in pyridine at room temperature, a single crystalline compound (m.p.177°; $C_{15}H_{25}ON$; yield 30%) was formed which could only be assigned an either/or lactam structure 14/15 since its spectral data failed to distinguish between the two; in the Beckmann-like rearrangement carried out as before, however, the ketone 7 gave a mixture of 14 + 15 (PMR). On the other hand, while reaction of longibornane-4-one 7 in chloroform with an equimolar amount of sodium azide in conc.sulphuric acid resulted in recovery of only starting material, treatment with excess of azide (2 moles) readily furnished a crystalline tetrazole 16/17 (m.p.157°; $C_{15}H_{24}N_4$;42% yield) which can be mechanistically rationalized as shown in Scheme 1 (giving 16).

## EXPERIMENTAL

Melting and boiling points are uncorrected. Light petroleum refers to the fraction b.p.60-80°. Freshly purified[15] and recrystallised tosyl chloride was used. Solvent extracts were dried over anhydrous $Na_2SO_4$. Melting points were taken in capillaries on an Electrothermal melting point apparatus. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded smears (liquids) or as nujol mulls (solids) on a Pye-Unicam SP-3 IR spectrometer. PMR spectra were obtained on Varian T-60/FT-80A/Brucker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

7$\alpha$H-8-oxoisolongifolane 5. This was prepared by the method[16] reported by Nayak.

7$\beta$H-8-Oxoisolongifolane 6. Ketone 5 was epimerized[9b] by refluxing in MeOH with NaOMe to give 6.

4-Oxolongibornane 7. This was prepared by 'hydration' of longifolene as reported[10] earlier.

Oximation of 5, 6 and 7: Formation of oximes 8, 9 and 10

A mixture of the ketone (4.4 g), $NH_2OH.HCl$ (1.68 g), (EtOH (40 ml) and pyridine (1 ml) was refluxed on a waterbath for 5 hr. The mixture was poured into ice water, extracted with ethyl acetate (3 x 50 ml), washed with brine, dried, solvent removed and the crude solid was

recrystallized from MeOH.

7$\alpha$H-8-Oximino-isolongifolane 8. Colourless crystals, m.p.150° (1.1 g, 24%). IR (nujol): 3340, 1660, 930. PMR ($CCl_4$): $\delta$ 1.15, 1.06 x 2, 0.95 (four tertiary Me singlets). (Found: C, 75.6; H, 10.8; N, 6.7. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

7$\beta$H-8-Oximino-isolongifolane 9. Colourless crystals, m.p.188° (1.1 g, 24%). IR (nujol): 3260, 1660 (weak), 940. PMR ($CDCl_3$): $\delta$ 1.26, 0.96, 0.86, 0.83 (four tertiary Me singlets). (Found: C, 76.3; H, 10.7; N, 5.4. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

4-Oximino-longibornane 9 . Colourless crystals m.p, 155-58° (3.8 g. 77%). IR (nujol): 3280, 1590. PMR ($CCl_4$): Methyl region between $\delta$ 0.83-1.00 complex and poorly resolved indicating mixture of syn/anti isomers). (Found: C, 77.2; H, 10.7; N, 6.2. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

Action of tosyl chloride-pyridine on 8, 9 and 10: Formation of lactams 11, 12 and 14/15

A mixture of the oxime (1 g), dry pyridine (10 ml) and tosyl chloride (1.5 g) was kept at room temperature overnight. It was acidified with 1:1 HCl (100 ml), extracted with ethyl acetate, washed with aqueous $Na_2CO_3$, brine, dried, solvent removed and the crude solid recrystallised from MeOH.

7α H-Lactam 11. Colourless crystals, m.p.124° (0.5 g, 50%). IR (nujol): 3340, 1665, 755. PMR ($CCl_4$): δ5.44 (b s, 1H, 0=C-NH); 3.40 (d, 1H, CH-NH, J=5 Hz); 2.4 (m, 2H, $CH_2$-CONH); 1.12 x 2, 1.00 x 2 (four tertiary Me singlets). MS: m/z 235 ($M^+$). (Found: C, 75.8; H, 10.6; N, 5.8. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

7β H-Lactam 12. Colourless crystals, m.p. 197° (0.48 g, 48%). IR (nujol): 3300, 3200, 3060, 1645, 1175, 845. PMR($CDCl_3$): δ 5.95 (b s, 1H, 0=C-NH); 3.70 (m, 1H, one H of $CH_2$-NH-C=0); 3.10 (m, 1H, other H of $CH_2$-NH-C=0); 1.25, 1.11 x 2, 0.97 (four tertiary Me singlets). MS: m/z 235 ($M^+$). (Found: C, 76.6; H, 10.7; N, 5.6. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

Lactam 14/15. Colourless crytals, m.p.177-80° (0.2 g, 30%) IR (nujol): 3240, 3100, 1660. PMR ($CDCl_3$): δ 6.48 (b s CONH), 3.34 (d d 2H, $CH_2$-NHCO, $J_1 = J_2 = 8$ Hz); 2.48 (m, 2H, $CH_2$-CONH); 1.08, 1.02, 0.90, 0.72 (four tertiary Me singlets). (Found: C, 77.5; H, 10.9; N, 5.8. $C_{15}H_{25}ON$ requires: C, 76.5; H, 10.7; N, 6.0%).

Action of $NH_2OSO_3H$ on 5 and 7: Formation of lactams 11 and 14 + 15

A mixture of the ketone (1 g) in gl AcOH (25 ml) and $NH_2OSO_3H$ (1 g) was refluxed for 7 hr. The mixture was diluted with water, extracted with $CHCl_3$ (3 x 50 ml), washed with 10% aqueous $NaHCO_3$, brine, dried and solvent removed.

The crude product in the case of 5 (TLC: 2 spots) was separated by chromatography on a column of silica gel (TLC monitoring): Fr. 1, light petroleum-benzene (1:1), 2 x 50 ml, unchanged 5 (0.06 g). Fr. 2, 10% EtOAc in benzene, 4 x 50 ml, pure solid; this was recrystallized from light petroleum to give the lactam 11 (0.15 g, 13%), identified by m.p., IR/PMR.

In the case of 7, the crude product was solid which was directly recrystallized from light petroleum to furnish colourless crytals m.p. 127-32°. IR (nujol): 3220, 1660. PMR ($CDCl_3$): atleast 8 signals in the methyl region between $\delta$ 0.74 to 1.10. Possibly a mixture of isomeric lactams 14 + 15.

Schmidt reaction on 7$\alpha$H-8-oxoisolongifolane 5: Formation of lactam 11

A stirred mixture of ketone 5 (2.2 g, 10 mmol) in $CHCl_3$ (20 ml) and conc. $H_2SO_4$ (8 ml) was cooled in an ice-bath and treated with $NaN_3$ (1.62 g, 25 mmol) in portions during 30 min. After stirring for 15 min more, the mixture was diluted with ice water; basified with dilute KOH solution, extracted with ether, washed with brine, dried, solvent removed and the mixture chromatographed on silica gel/IIa column (with TLC monitoring): Fr. 1, benzene, 5 x 25 ml, ketone 5 (0.1 g). Fr. 2, 5% EtOAc in benzene, 4 x 25 ml, mixture (0.41 g). Fr. 3, EtOAc, 6 x 25 ml, pure lactam 11 (0.8 g, 32%; identified by m.p., IR/PMR).

Schmidt reaction on longibornane-4-one 7: Formation of tetrazole 16/17

A stirred mixture of ketone 7 (2.2 g) in $CHCl_3$ (20 ml) and conc. $H_2SO_4$ (8 ml) was subjected to Schmidt reaction with $NaN_3$ (1.62 g, 25 mmol) as described for ketone 5. In this case the crude product was a solid which was recrystallised from light petroleum to afford the tetrazole 16 or 17 as colourless needles, m.p. 155-57° (1.1 g; 42%). IR(nujol): 1535, 1100, 1080, 1000, 790. PMR ($CCl_4$): $\delta$ 4.01 (d, 2H, $H_2C$-N, J=5 Hz); 2.65 (s, 2H, $H_2C$-C=N-); 1.05 x 2, 0.96 x 2 (four tertiary Me singlets). MS: m/z 260 ($M^+$, base peak). (Found: C, 69.2; H, 9.2; N, 20.7. $C_{15}H_{24}N_4$ requires: C, 69.2; H, 9.2; N, 21.5%).

Action of m-chloroperbenzoic acid on epimeric ketones 5 and 6

The ketone 5/6 (0.22 g) in $CHCl_3$ (5 ml) and m-chloroperbenzoic acid (0.21 g) were mixed and stirred at room temperature overnight. The mixture was diluted with $CHCl_3$ (20 ml), washed with 2% aqueous KOH, brine, dried and solvent removed. In the case of 5 the crude semi-solid was recrystallised from light petroleum to furnish the lactone 13 (25 mg) identified by m.p., IR/PMR.

In the case of 6 there was no reaction at all and the entire material was recovered unchanged (identified by IR/PMR).

# REFERENCES


1 a) Jadhav P K & Nayak U R, J Sci Ind Res, 39 (1980) 36.

b) Sukh Dev, Prog Chem Org Nat Prod, 40 (1981) 49.

2 a) Shitole H R & Nayak U R, Indian J Chem, 23B (1984) 415.

b) Deshpande R P & Nayak U R, Indian J Chem 18B (1979) 99.

c) Shitole H R & Nayak U R, Indian J Chem, 23B (1984) 707.

d) Satyanarayana N & Nayak U R, Indian J Chem (in press).

3 a) Donaruma L G & Heldt W Z, Organic Reactions 11 (1960) 1.

b) Smith P A S in Molecular Rearrangements Vol 1, Ed. P.de Mayo, Interscience, New York 1963, p. 483.

c) McCarty in The Chemistry of Carbon-Nitrogen Double bond Ed. Patai S, 1970, p. 408.

d) Vinnick M I & Zarakhani N G, Russian Chem Rev, 36 (1967) 51.

4 a) Wolff H, Organic Reactions, 3 (1946).

b) Koldobskii G I, Tereshchenko G F, Gerasimova E S & Bagal L I, Russian Chem Rev, 40 (1971) 835.

5 a) Shechter H & Kirk J C, J Am Chem Soc, 73 (1951) 3087.

5 b) Fusco R & Rossi S, Gazetta, 81 (1951) 511.

c) Conley R T, Chem & Ind (1958) 438.

6 a) Conley R T & Ghosh S in Mechanisms of Molecular Migrations Vol 4, Ed Thyagarajan B S, Wiley, New York, 1971, p. 197.

b) Satyanarayana N, Shitole H R & Nayak U R, Indian J Chem (in press).

7 ApSimon J W & Hunter N R, Tetrahedron Lett (1972) 187.

8 Elderfield R C & Losin E T, J Org Chem, 26 (1961) 1703.

9 a) Ranganathan R, Nayak U R, Santhanakrishnan T S & Sukh Dev, Tetrahedron, 26 (1970) 621; McMillan J A, Paul I C, Nayak U R & Sukh Dev, Tetrahedron Lett (1974) 419.

b) Goudgaon N M, Reddy R T & Nayak U R, Indian J Chem, 24B (1985) 240.

10 Nayak U R & Sukh Dev, Tetrahedron, 8 (1960) 42.

11 a) Heldt W Z, J Org Chem, 26 (1961) 1695.

b) Fleming I & Woodward R B, J Chem Soc Perkin I (1973) 1653.

c) Costa A, Mestres R & Riego J M, Syn Commun, 12 (1982) 1003.

12 Maio G Di & Permutti V, Tetrahedron, 22 (1966) 2059.

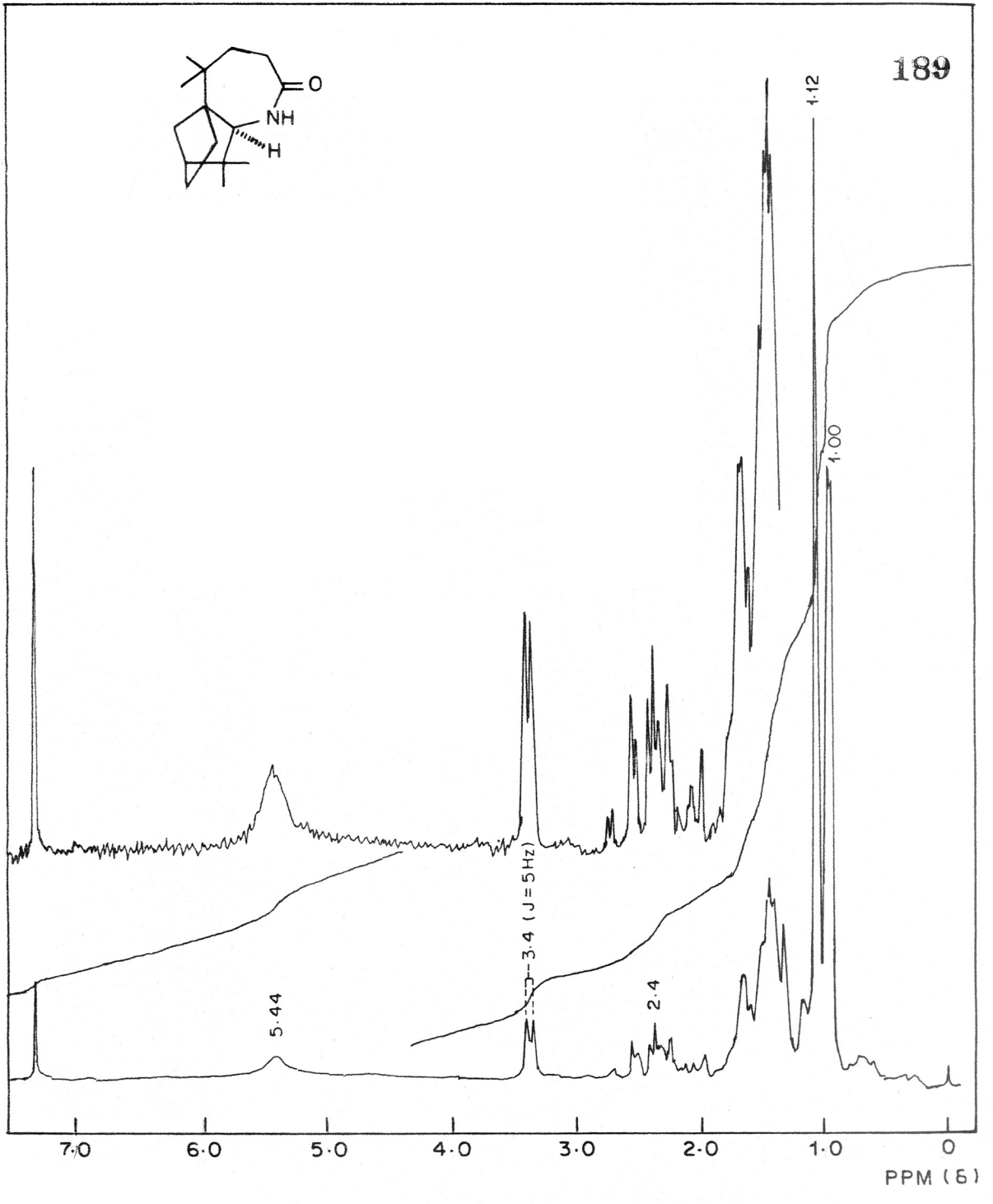
13 a) Olah G A & Fung A P, Synthesis (1979) 537.

b) Krow G R & Szczepanski S, Tetrahedron Lett, 21 (1980) 4593.

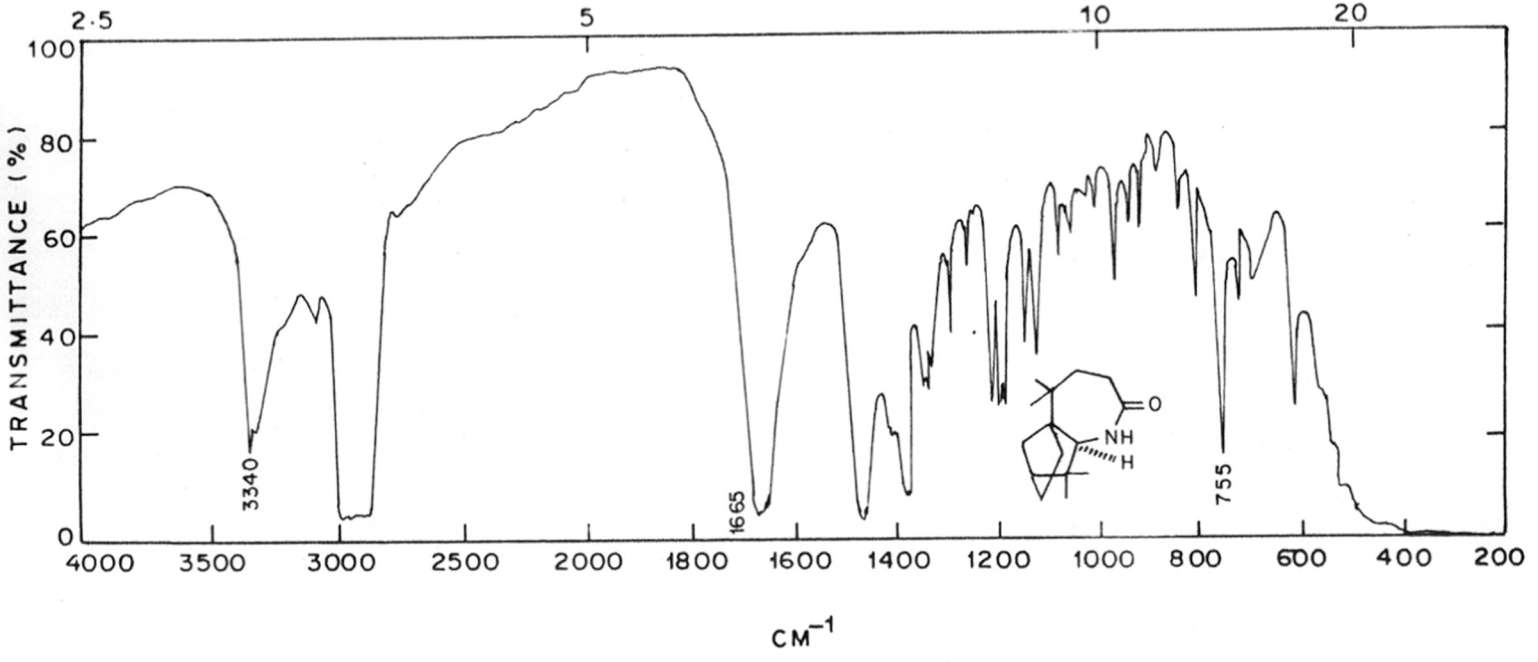
14 Santhanakrishnan T S, Nayak U R & Sukh Dev, Tetrahedron 26 (1970) 641.

15 Fiesar L F & Fiesar M, Reagents for Organic Synthesis, Vol 1, Johny Wiley, New York (1967) p. 1179.

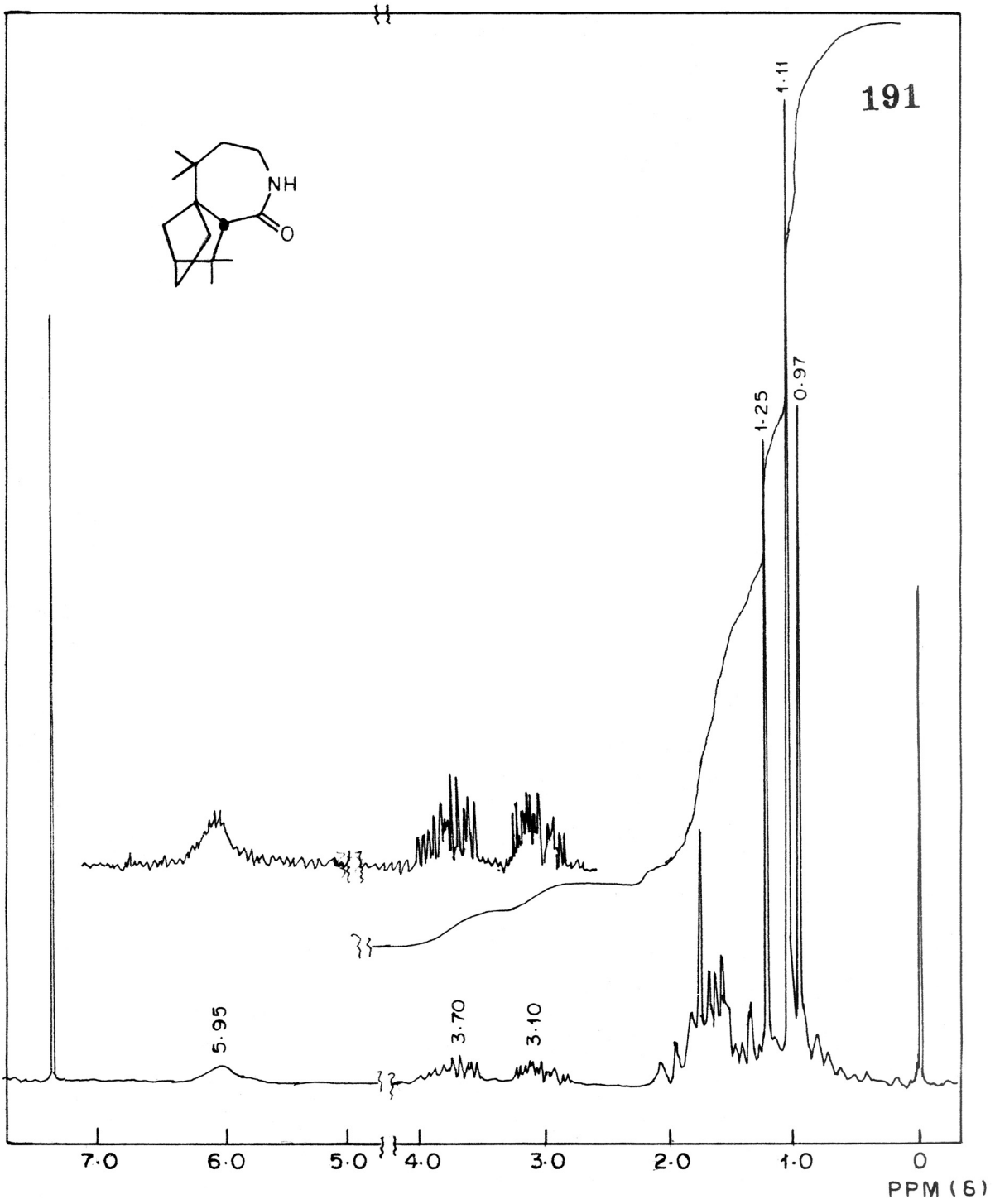
16 Nayak U R, Indian J Chem, 9 (1971) 606.




PMR SPECTRUM OF LACTAM 11




IR SPECTRUM OF LACTAM 11

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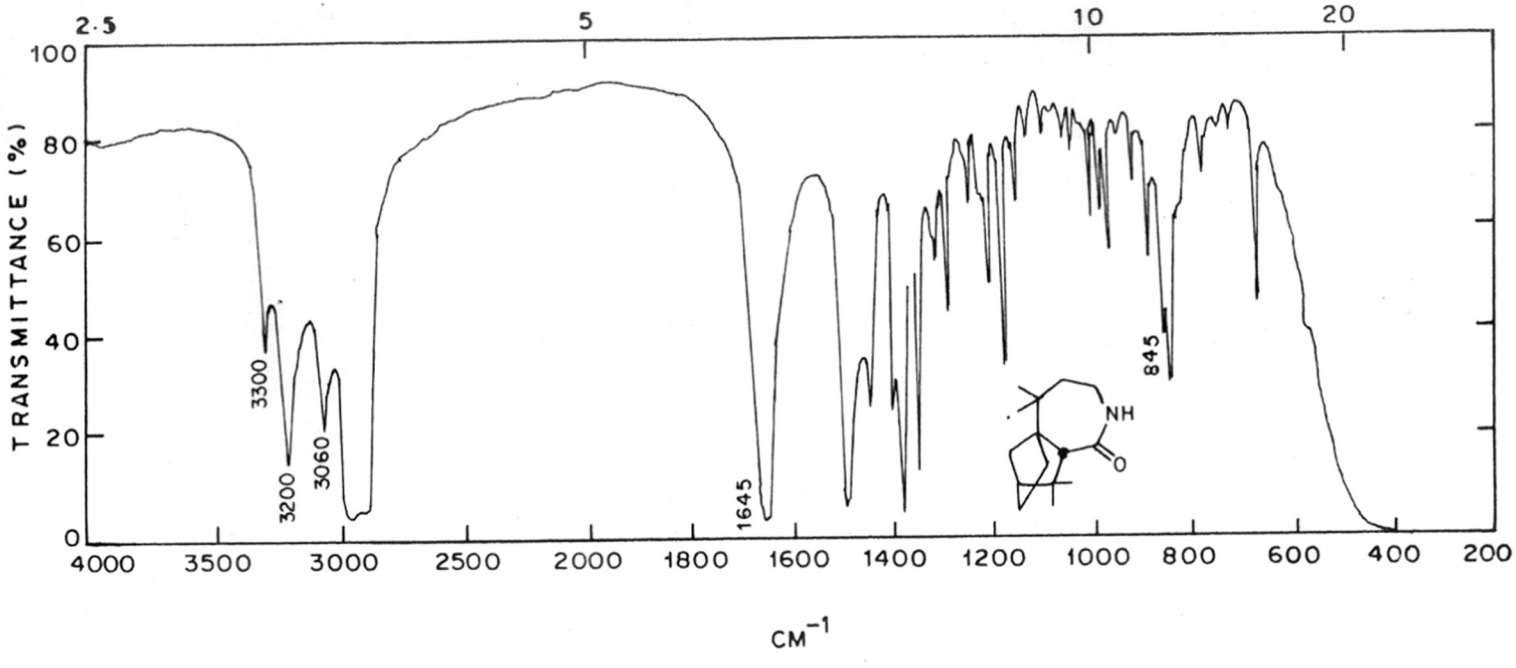


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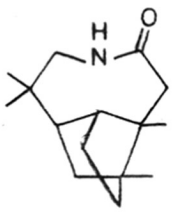

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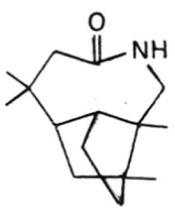
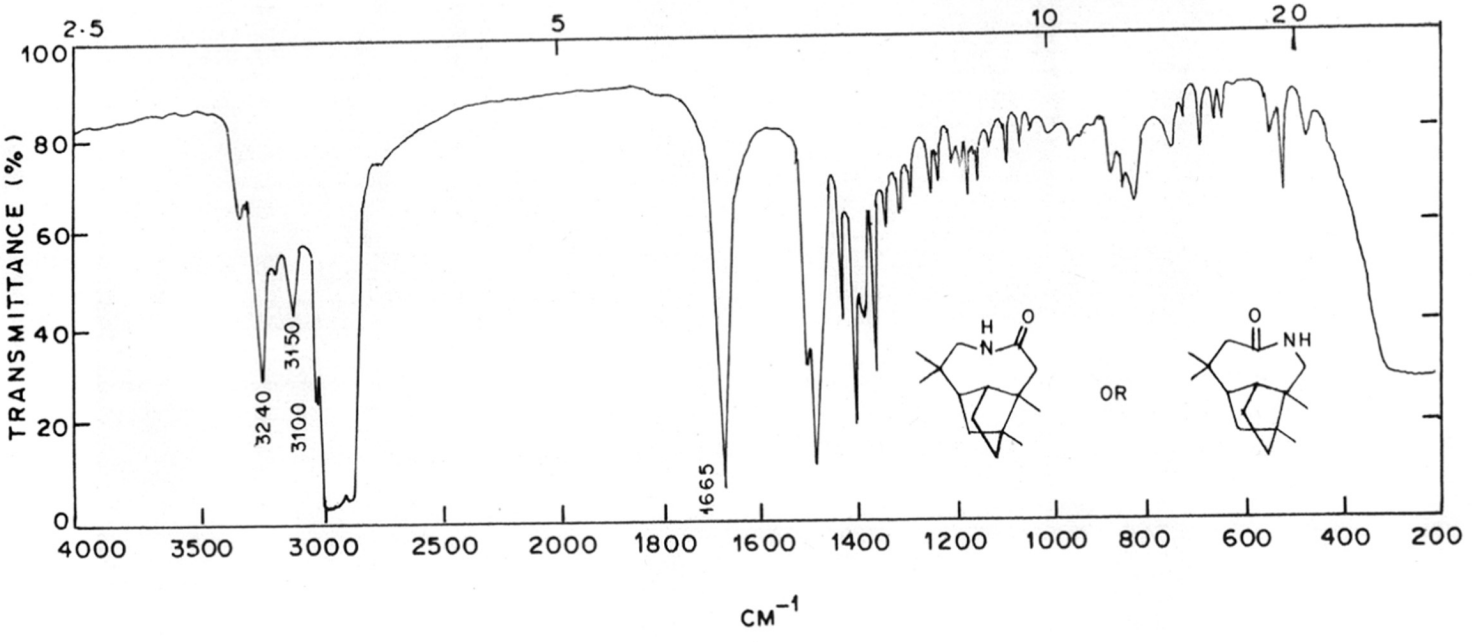





PMR SPECTRUM OF LACTAM 14 / 15

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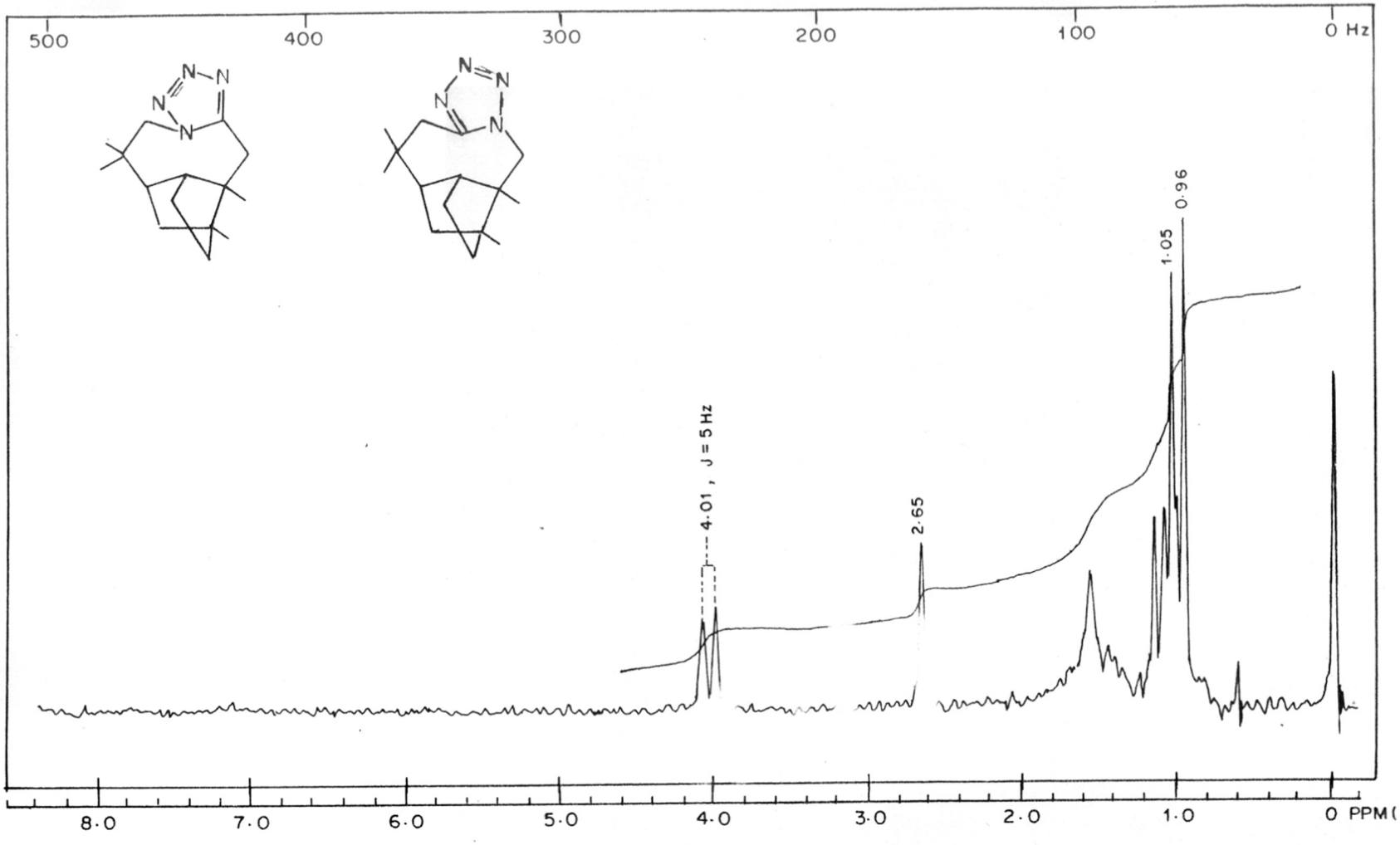
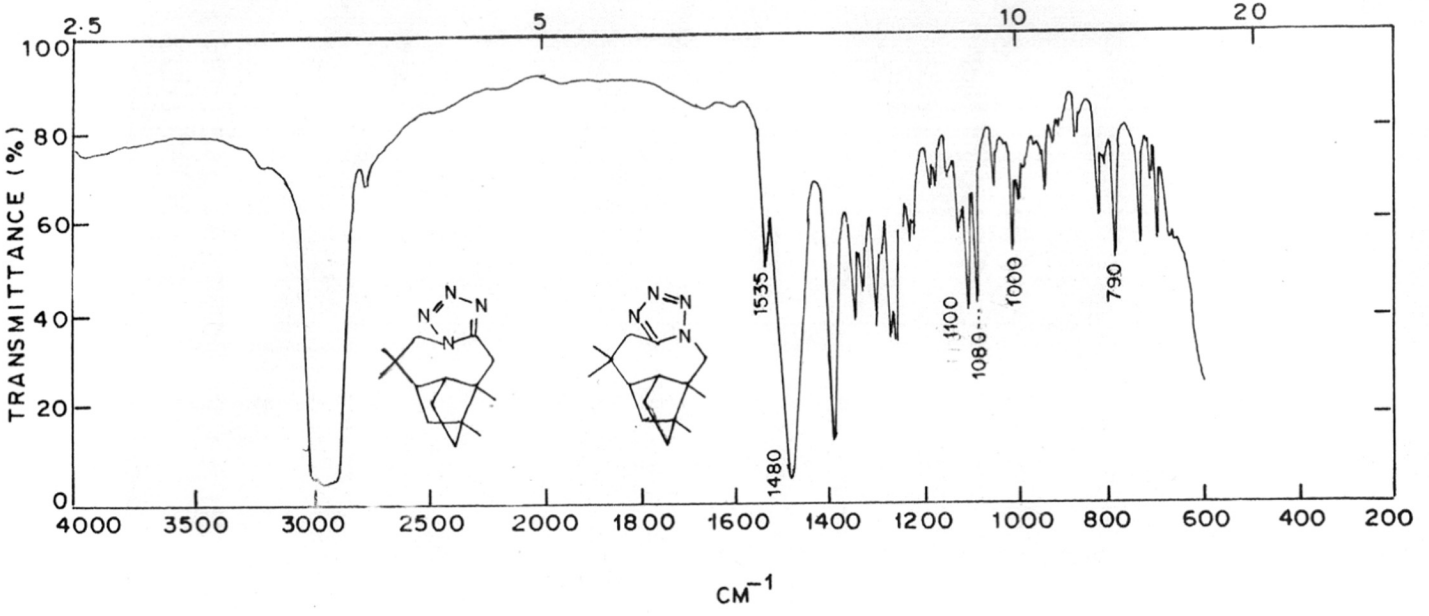



PMR SPECTRUM OF TETRAZOLE 16 / 17




IR SPECTRUM OF TETRAZOLE 16/17

## LIST OF PUBLICATIONS

1. 9-Methylenelongibornane: Lewis and induced transannular hydride shift/rearrangement to 9-methyl isolongifolene/ 1,1,3-trimethyl-7-isopropyl tetralin, vaidya S.P. & Nayak U.R., Indian J. Chem. (in press).
2. Longihomocamphenilane-7,8-dione: A study on the reactivity of the carbonyl groups via monofunctional derivatives of the diketone, Vaidya S.P., Shitole H.R. and Nayak H.R., Indian J.Chem. (in press).
3. Reaction of some longibornane based $\gamma$-bromoketones with sodium-potassium alloy, Vaidya S.P., Suryawanshi S.N., Jadhav P.K. and Nayak U.R., Indian J. Chem. (in press)
4. Neighbouring group participation by carbonyl oxygen in the longibornane system: Unique reactivity of 12-bromo-longibornane-3,4-dione, Vaidya S.P. and Nayak U.R., Tetrahedron (communicated).
5. Nitrogen insertion in the isolongifolane/longibornane systems via Beckmann/Schmidt rearrangements: A comparitive study, Vaidya S.P. and Nayak U.R., Indian J.Chem. (communicated).

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