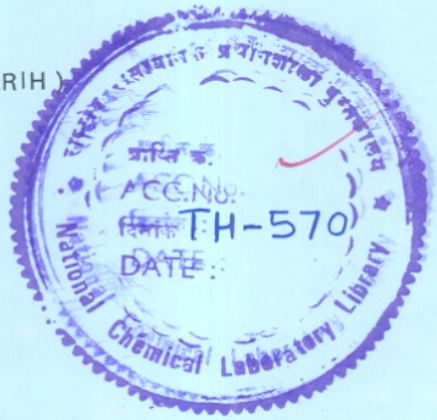
CHEMICAL INVESTIGATION OF SOME INDIAN PLANTS

COMPUTERISED

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
MASTER OF SCIENCE
(PARTLY BY PAPERS PARTLY BY RESEARIH)
IN CHEMISTRY



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1989

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DEDICATED TO MY PARENTS

C E R T I F I C A T E

It is certified that the work incorporated in the thesis 'Chemical investigation of some Indian plants' by Shri S.R. Rojatkar of the National Chemical Laboratory, Poona, 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.

(Dr.B.A. Nagasampagi)
Research Guide

May, 1989

C O N T E N T S

	Page No
General Remarks ..	1-2
CHAPTER I	
Chemical constituents of Azadirachta indica A Juss, A Review from 1986-88	3-18
CHAPTER II	
Chemical Investigation of Azadirachta indica A Juss	19-47
CHAPTER III	
Chemical Investigation of Blainvillea latifolia (D.C.)	48-86
Abstract	87-89
Acknowledgement ..	90

GENERAL REMARKS

GENERAL REMARKS

1. The figure (spectra) numbers, chart numbers, scheme numbers and reference number etc. given in each chapter refer to that particular chapter only. The references and figures are given at the end of each chapter.

2. The temperature are given in centigrade scale.

3. All the solvents were distilled before use. Petroleum-ether refers to the fraction boiling in the range 60-80°.

4. Unless otherwise mentioned all the column chromatographic separations were carried out using the TLC grade silica gel using the dry column technique. The silica gel was activated at 300° for five hours before using for chromatography.

5. The thin layer chromatography (TLC) and preparative TLC plates were prepared by spreading an aqueous suspension of silica gel (200-300 mesh, containing 13% $CaSO_4$ as binder) uniformly over glass plates using an applicator.

6. Layer thickness: TLC plates: 0.2 mm; preparative TLC: 1.1.5 mm. After initial drying at room temperature the plates were activated at 100° for one hour before use.

6. Unless otherwise mentioned, all TLC and preparative TLC were run using mixtures of acetone and pet.ether as solvent. The percentage composition is given in parenthesis (for example, eluent:40:60 means eluent:acetone-pet.ether 40:60).

7. After development, the spot on TLC plates were visualized by exposing them to iodine vapour and/or by spraying with a mixture of H_2SO_4-HNO_3 (1:1) followed by charring in an oven. In case of preparative TLC the band of compounds (after developing) were visualized by spraying a dilute solution of iodine in $CHCl_3$ to the sides (after covering the major central portion with a glass plate).

8. All the melting points reported are uncorrected.

9. Optical rotations were measured in $CHCl^3$ solution using sodium light (5893) as the source on a JASCO DIP-181 digital polarimeter.

10. The UV spectra were recorded in ethanol solution on a Carol-Zeiss 'Specord' UV visible spectrophotometer.

11. The IR spectra were recorded on Perkin-Elmer 599B and Perkin-Elmer "Infracord" 137B model.

12. Mass spectra were recorded on a CEC-2-110B double focussing spectrometer and Finnigan Mat-1020 using direct inlet system at 70 eV.

13. All the ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution (10%) using TMS as internal standard. ^{1}H-NMR chemical shifts are given in δ-scale. Most of the ^{1}H-NMR spectra were recorded at 90 MHz on a Brucker WH-90 (spectrospin) Spectrometer and 80 MHz H-NMR spectra were recorded on a FT 8A (Varian).

14. The ^{13}C-NMR spectra were recorded at 22.63 MHz on a Brucker WH-90 spectrometer. All ^{13}C-NMR spectra were recorded twice as twice as (1) proton noise decoupled or single line spectrum and (2) single frequency offresonance decoupled (SFOD) spectrum.

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

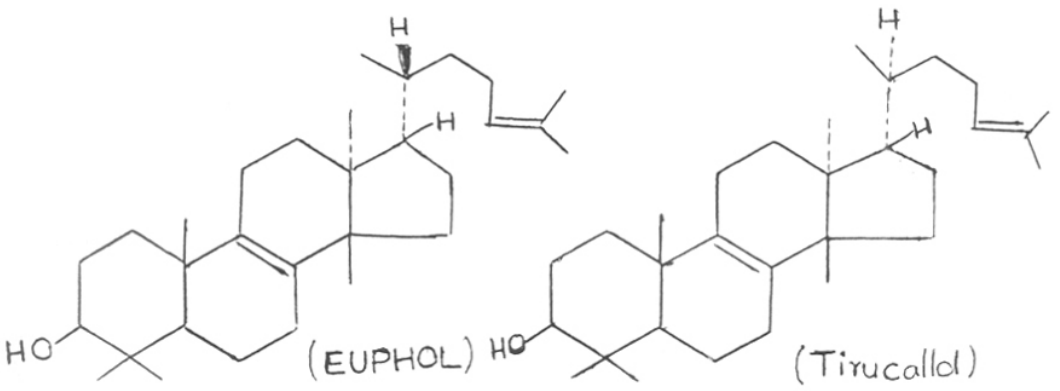
CHAPTER I

Chemical Constituents of *Azadirachta indica* A Juss. A Review from 1986-88

INTRODUCTION

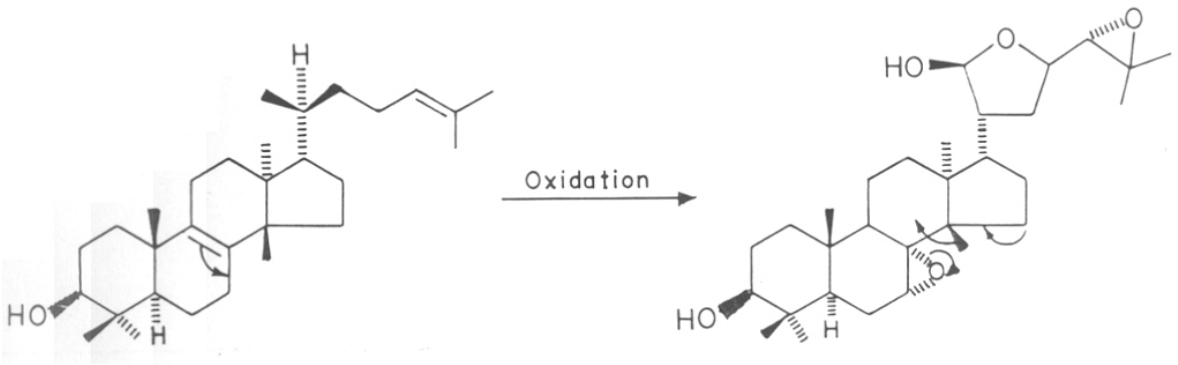
Non edible oil seeds form a minor forest produce of our country and their proper utilization is the urgent need of the hour. These regenarative resources are abundantly available in our country and their under utilization is attributed to various factors. The major non-edible oil seeds are Karanja, Mohua, Neem, Sal and Undi. In most of the cases processes have been developed for the utilization of fats from these for the manufacture of soap only. Recently it has been realised some of these such as Neem, Mohua and Karanja posses excellent insect control activities. In order to exploit these important property a project was initiated in NCL and two products namely Neemrich-I and Neemrich-II have been developed. Both these products exhibit different insect control properties. In addition to this the saturated fat obtained can be utilised for the manufacture of soap. Neemrich-II exhibits the insect antifeedant and growth inhibitory activities and the active principles responsible for this activities have been identified as tetranortriterpenoids.

Tetranortriterpenoids are a class of triterpenes wherein the four carbon atoms of the side-chain are cleaved by enzymatic oxidative degradation. These compounds are the markers in the plant families such as Meliaceae and Rutaceae. They are formed by the cyclization followed by methyl migration and oxidative degradation of squalene. The immediate precursor of these triterpenes appears to be euphol or tirucallol[1], which are the tetracyclic triterpenes.



The biognetic scheme postulated for these triterpene is shown in Chart I. The literature survey of the constituents of Meliaceae and Rutaceae family has revealed the presence of many tetranortriterpenoids with oxidative cleavage of A ring, B ring, C ring and D ring[2]. The constituents in neem however, have in most of the cases C-ring cleaved. There are as many as 45 compounds so far isolated from neem upto 1986[3]. This review covers the remaining tetranortriterpenoids and other compounds isolated from neem from 1986-1988.

In addition to insect control activity many medicinal properties have been attributed from neem such as antifertility, antidiabetic, anticancer and antiviral. Some commercial firms have come out with products for treating Diabetic mellitus[4] and for cosmatic[5]. Many countries such as USA, W.Germany, U.K. and India are actively engaged in confirming the medicinal properties. Table 1 gives the chemical constituents reported from 1986 and Table 2, lists the insect control activity of various constituents. Table 3 summarises the activities of the extracts of the different parts of neem.



TIRUCALLOL

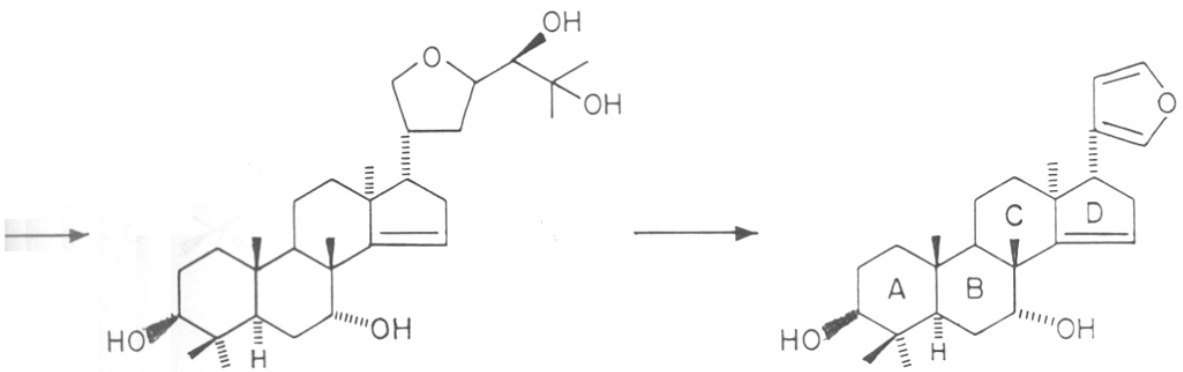
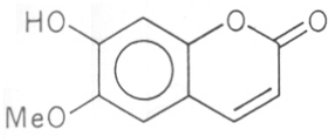


CHART I

CHART II : CHEMICAL CONSTITUENTS FROM NEEM



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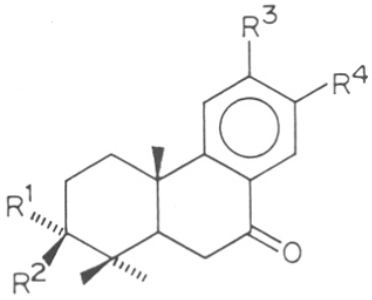


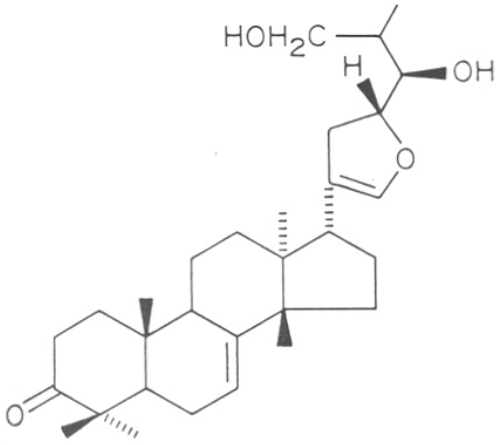
2a. $R^1 = H$, $R^2 = OH$, $R^3 = OH$, $R^4 = OMe$

2b. $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = OMe$

2c. $R^1 = R^2 = O$, $R^3 = Me$, $R^4 = OH$

2d. $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = Me$

2e. $R^1 = H$, $R^2 = H$, $R^3 = OH$, $R^4 = OH$



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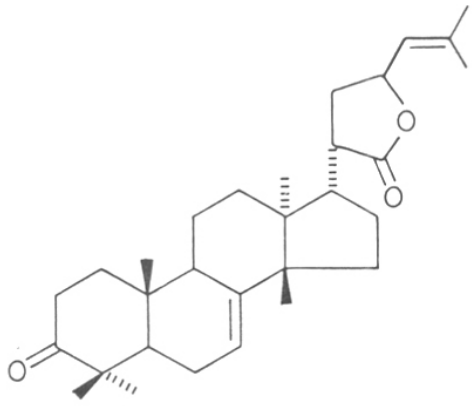

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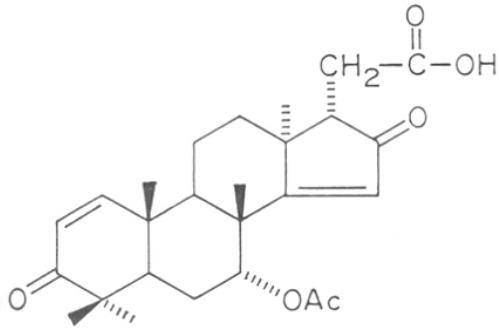

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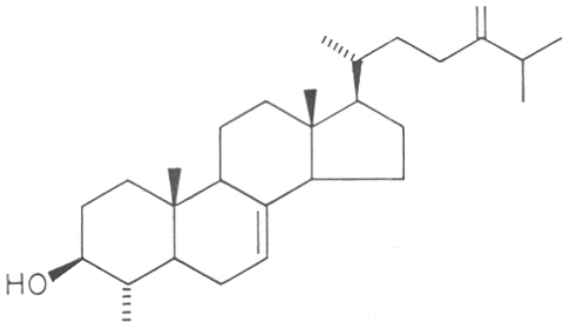
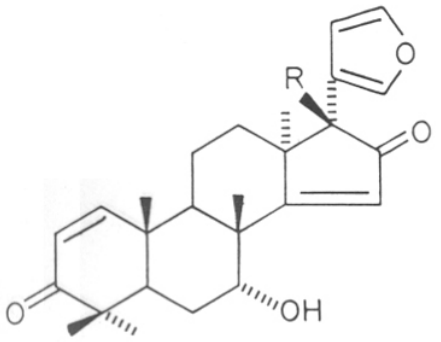
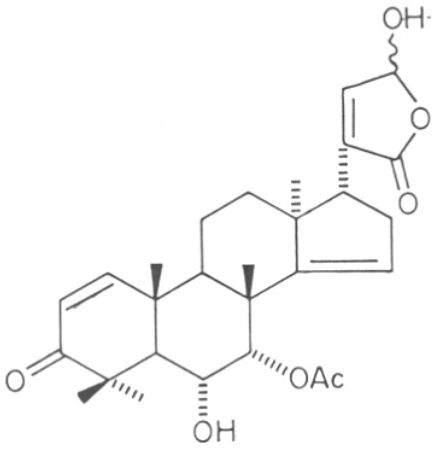


6

CHART-II (cond.)



7 R = H
8 R = OH



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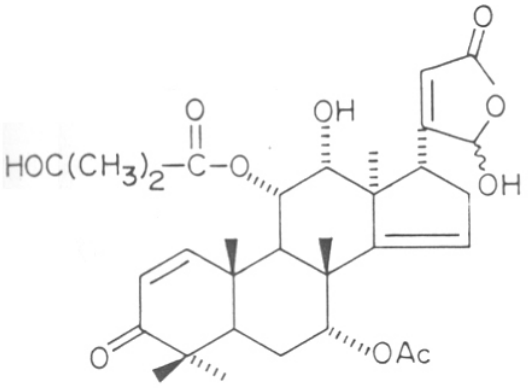

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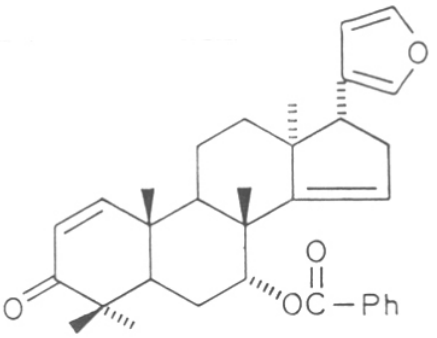

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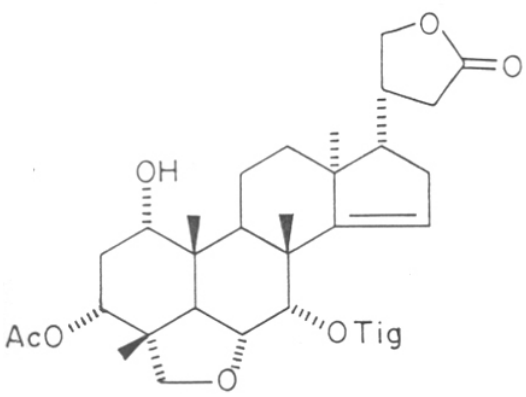

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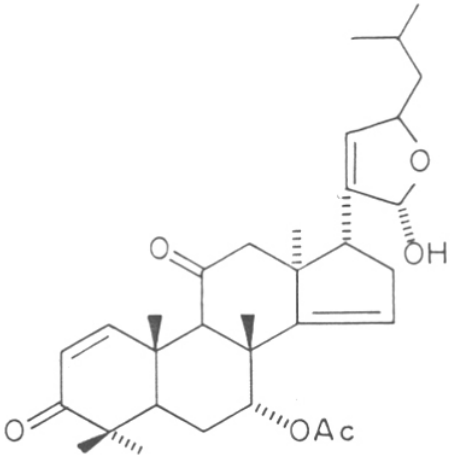

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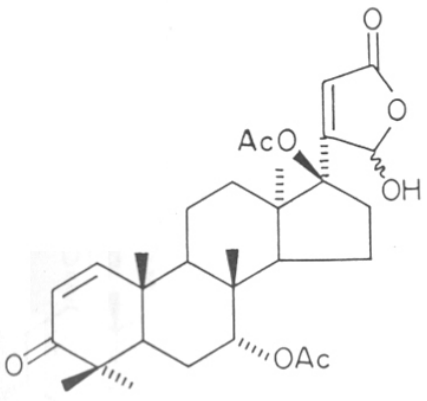

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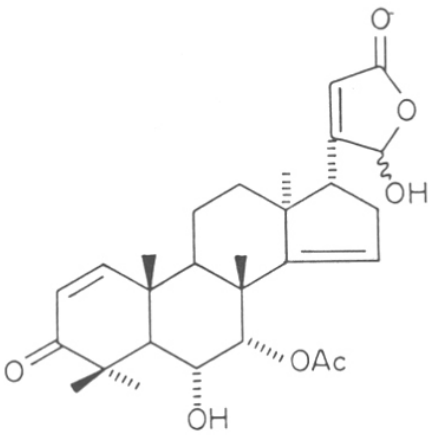

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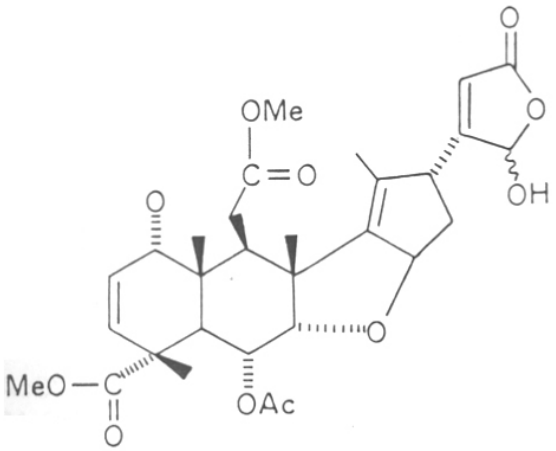

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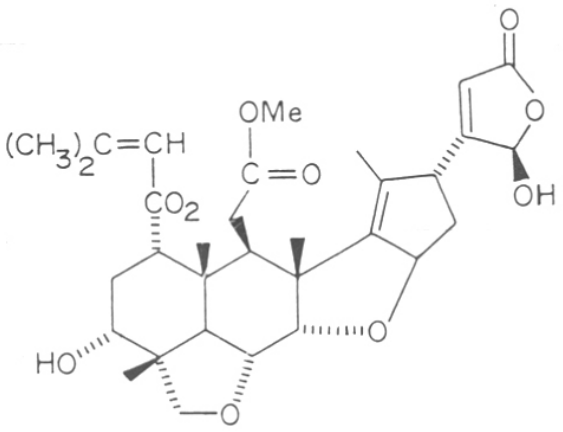

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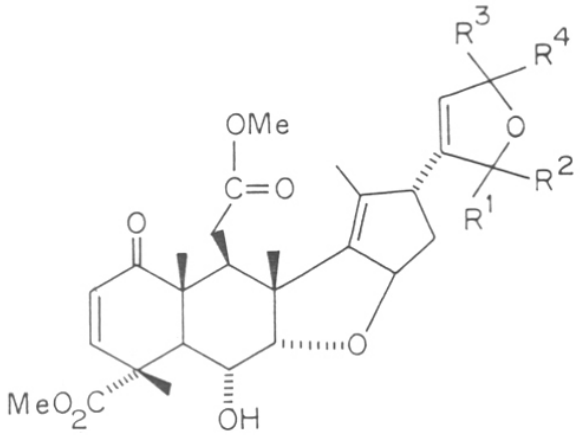
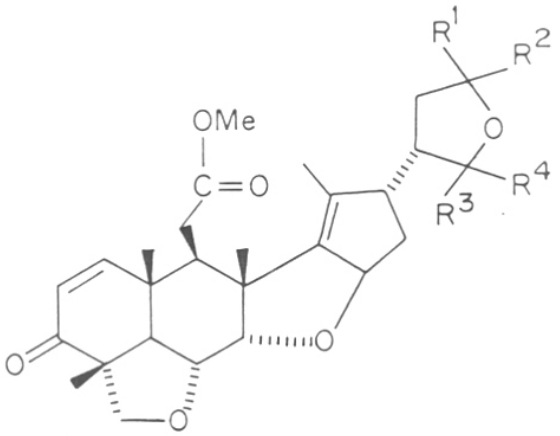


18 $R^1, R^2 = O, R^3 = H, R^4 = OH$

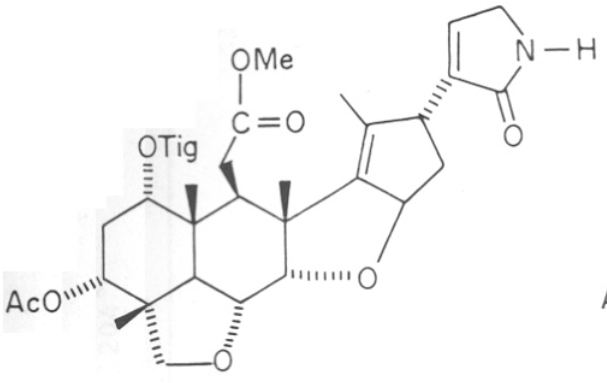
19 $R^1 = H, R^2 = OH, R^3, R^4 = O$



20 $R^1 = H, R^2 = OH, R^3, R^4 = O$

21 $R^1, R^2 = O, R^3 = H, R^4 = OH$

CHART-II (cond.)



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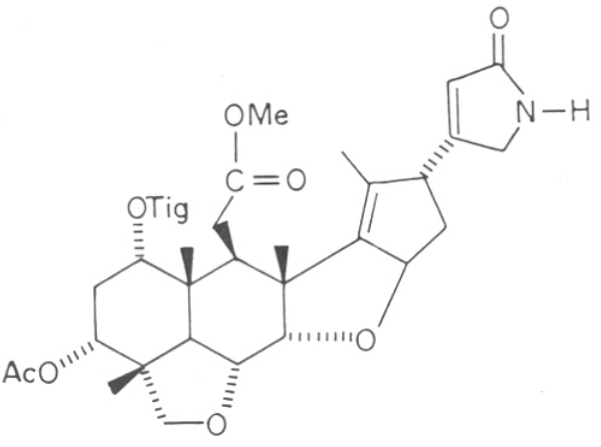

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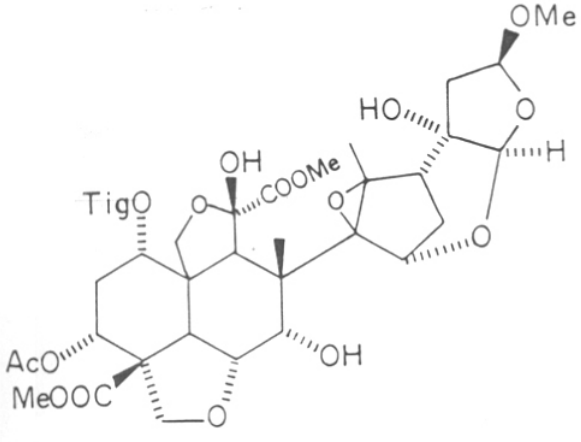

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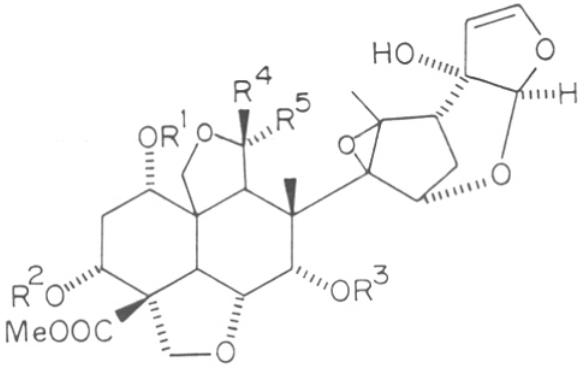

25a	R^1=Tig, R^2=H, R^3=H, R^4=H, R^5=COOMe
25b	R^1=Tig, R^2=Ac, R^3=H, R^4=OCH_3, R^5=COOMe
25c	R^1=Tig, R^2=H, R^3=H, R^4=H, R^5=COOMe
25d	R^1=Cinn, R^2=H, R^3=H, R^4=OH, R^5=COOMe
25e	R^1=H, R^2=Tig, R^3=H, R^4=H, R^5=COOMe

TABLE 1. CHEMICAL CONSTITUENTS FROM NEEM

S.No. (1)	Name of the constituents (2)	Source (3)	Structure No. (4)	Molecular formula (5)	M.P.	$[\ ]_D$ (6)	Reference (7)
A Coumarin							
1	Scopoletin	Fresh, undried winter leaves	1	$C_{10}H_8O_4$	204°		6
B Diterpene							
2	Nimbionol	Root bark	2a	$C_{18}H_{24}O_4$	127-29°	+10.0($CHCl_3$	7
3	Nimbionone	Root bark	2b	$C_{18}H_{22}O_4$	78-79°	+0.03 ($CHCl_3$)	7
4	Nimbione	Stem bark	2c	$C_{18}H_{22}O_3$	102-103°	-	8
5	Nimbinone	Stem bark	2d	$C_{18}H_{22}O_3$	124-125°	-	8
6	Nimbidol	Root bark	2e	$C_{17}H_{22}O_3$	226°	+3.4($CHCl_3$)	9
(C) Tetracyclic Triterpene							
7	Nimbocinone	Undried winter leaves	3	$C_{30}H_{46}O_4$	76-78°	+10($CHCl_3$)	10
8	Nimolinone	Fresh seeds	4	$C_{30}H_{44}O_3$	-	-	11
9	Nimolicinoic acid	Fresh, undried unruptured ripe fruits	5	$C_{26}H_{34}O_6$	92-94°	-14.28 ($CHCl_3$)	12

1	2	3	4	5	6	7	8
10.	24-Methylenelophenol	Heart wood	6	$C_{29}H_{48}O$	164-165°	+4.7	13
11.	7-Deacetyl-17-B-hydroxy azadiradione	Seeds	7	$C_{26}H_{32}O_5$	-	-	14
12.	Nimbocinol	Fresh,undried,ripe fruits	8	$C_{26}H_{32}O_4$	160-160°	-14.28 ($CHCl_3$)	15
13.	Nimocinolide	Fresh leaves	9	$C_{28}H_{36}O_7$	160°	+86.66 ($CHCl_3$)	16
14.	Isonimbocinolide	Fresh leaves	10	$C_{32}H_{42}O_{10}$	80-81°	+25 ($CH\ Cl_3$)	17
15.	Nimocin	Seeds	11	$C_{33}H_{38}O_4$	190-195°	-	16
16.	3-Acetoxy-7-Tigloyl-vilasinnin lactone	Seed oil	12	$C_{33}H_{46}O_8$	242-243°	-22.4 ($CHCl_3$)	22
17.	Azadirachtol	Neem fruits	13	$C_{32}H_{42}O_6$	110-112°	+6.25°	24
18.	Isonimolicinolide	Fresh,undried, unruptured ripe fruits	14	$C_{30}H_{36}O_9$	100-102°	+20 ($CHCl_3$)	12
19	Isonimocinolide	Fresh leaves	15	$C_{28}H_{36}O_7$	165°	+85° ($CHCl_3$)	16

1	2	3	4	5	6	7	8
Tricyclic Triterpene							
20	Isonimbinolide	Stem bark	16	$C_{30}H_{36}O_{11}$	172-173°	-	8
21	Isoazadirolide	Fresh,undried winter leaves	17	$C_{32}H_{42}O_{10}$	130°	+200 ($CHCl_3$)	6
22	Desacetylnimbinolide	Fresh green spring twig	18	$C_{28}H_{34}O_9$	-	-	18
23	Desacetylisonimbinolide	Fresh green spring twig	19	$C_{28}H_{34}O_9$	-	-	18
24	Margosinolide	Green Twig	20	$C_{27}H_{32}O_8$	130°	+50 ($CHCl_3$)	19
25	Isomargosinolide	Green Twig	21	$C_{27}H_{32}O_8$	125°	+14.28 (CH_2Cl_2)	19
26	Salannolactam - (21)	Seed kernels	22	$C_{34}H_{45}NO_9$	213°	+121.8 ($CHCl_3$)	20
27	Salannolactam - (23)	Seed kernels	23	$C_{34}H_{45}NO_9$	Gum	+126.3 (CH_2Cl_2)	20
28	22,23B-Methoxyazadirachtin	Seeds	24	$C_{36}H_{48}O_{17}$	Amorphous	+0.42 (CH_2Cl_2+EtOH -8.1($CHCl_3$)	21
29	3-Deacetyl-11-Deoxy-Aradirachtin	Seeds	25a	$C_{33}H_{42}O_{14}$	149-151°	-40.8° ($CHCl_3$)	22

1	2	3	4	5	6	7	8
30	1-Tigloyl-3-Acetyl-11-methoxy azadirachtin	Neem bark	25b	$C_{36}H_{46}O_{16}$	Amorphous	-1.1 ($CHCl_3$)	21
31	1-Tigloyl-azadirachtinol (Desacetylazadirachtinol)	Seeds	25c	$C_{33}H_{44}O_{15}$	148°	-	23
32	3-Desacetyl-3-Cinnamoyl azadirachtin	Leaves	25d	$C_{42}H_{48}O_{16}$	-	+3.7 ($CHCl_3$)	21
33	3-Tigloylazadirachtol	Seeds	25e	$C_{33}H_{42}O_{14}$	204-206°	-69.4 (CH_2Cl_2)	21

TABLE 2 INSECT CONTROL ACTIVITY OF NEEM CONSTITUENTS

S.No.	CONSTITUENTS TEST	INSECT PEST	ACTIVITY	REFERENCES
1.	Nimbionol	Staphylococcus epidermidis S.aureus, Klebsiella ozaenae	Antibacterial	7
2.	Nimbione	Bacillus subtilis Staphylococcus epidermidis S. aureus, Klebsiella ozaenae	Antibacterial	8
3.	Nimbinone	Bacillus subtilis, Staphylococcus epidermidis, S.aureus, klebsiella ozaenae	Antibacterial	8
4.	Nimbionone	Bacillus subtilis S.Citreus, S.epidermidis, S.aureus, C.hoftmannin, S.pyogenes C.diphtheriae, S.faecalis and S.lactis K.ozaenae, P.vulgaris, A.aerogenes, A.calcoaceticus, S.typhi, S. typhy Para A, S.typhimurium E.coloacae, S.Sonnei, C.freundii, K.pneumoniae, E.Coli and S.marcescens	Antibacterial	7
5.	7-deacetyl-17B-hydroxy azadiradione	Heliothis virescens	Growth Inhibition	14
6.	Isonimbocinolide	mosquitoes (Aedes aegypti)	Growth Regulator	17
7.	Nimocin	Housefly (Musca domestica) Mosquitoes (Aedes aegypti)	Growth Regulator	16
8.	Isonimolicinolide	Pulse bettle (Callasobruschus analis)	Growth Regulator)	12
9.	Salannolactam-21	Mexican bean bettle (E.verivestis)	Antifeedant	20
10.	Salannolactam-23	Mexican bean bettle (E.verivestis)	Antifeedant	20
11.	Desacetylazadirachtinol	Tobacco budworm (Heliothis virescens)	Inhibition	23

TABLE 3 BIOLOGICAL ACTIVITY OF NEEM EXTRACTIVES

S.No.	Extractives	Insect pest	Activity	References
1.	Neem seeds aqeous extract	Lipaphis erysimi (Katl) (Mustard aphid)	Aphidicidal	25
2.	Neem oil + Custard apple oil	Nephotettix virescense (Rice green leaf hopper)	Synergetic	26
3.	Neem oil	Tribolium castaneum Herbst (Red flour bettle)	Synergetic	27
4.	Neem leave powder + Vitex negundo leaves powder	Sitophilus oryzae	Repellent	28
5.	Neem seed powder	Rhizopertha dominica	Repellent	29
6.	Neem oil + Neem seed Kernel oil + Karanja oil	Heliothis armigera	Insecticidal	30
7.	Neem seed extract	Bombax mori (L)	Growth inhibition	31
8.	Neem kernel suspension with various insecticides i) Dichlorvos ii) Cypermethrin iii) Chlorpyriphos iv) Carbaryl v) Quinalphor vi) Fenthion vii) Fenvalerate	Schistocerca gregaria forsk (Desert locust)	Oviposition deterrent	32
9.	Methanol extract of neem	Crocidolomia binotalis Zell	Inhibition	33

S.No.	Extractives	Insect Pest	Activity	References
10.	Neem leaves dry powder+water and alcoholic extract of leaves	Aspergillus niger	Fungicidal	34
11.	Morgosan-O	Culex pipiens fatigans Aedes aegypti	Larvicidal	35

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CHAPTER II

Chemical Investigation of *Azadirachta indica* A. Juss

INTRODUCTION

The famous Indian "Neem-tree" (Azadirachta indica A.Juss, Family Meliaceae) has long had the reputation of possessing a plethora of biological activities. With the recent increasing awareness of the health hazards and pollution of the environment caused by the conventional insecticides the relatively less hazardous natural products are being examined for their possible role in pest management. Neem has been a major focus of attention on account of its manifold activities and relative aboundance.

The first report of the pesticidal properties of neem in India appeared 1927 when Mann and Burns[1] observed that during the locust cycle of 1926-27, adult locusts did not feed on neem leaves. This was followed by Chopra[2] who used the extract of neem leaves as contact poison on grubs of weevils. Since then, a number of publications describing the various activities from different parts of neem tree have appeared[3]. So far seventy four tetranortriterpenoids, eight aromatic diterpenoids, seven flavanoids and one coumarin have been isolated from different parts of neem tree.

It was in 1964 the structure of the first major bitter principle nimbin was elucidated by Narayanan et al.[4] of NCL. Since then the chemistry of the constituents of neem has made a rapid progress and as a result all the above mentioned compounds have been isolated and identified from neem. Of these azadirachtin and desacetylazadirachtol[5] deserve special mention in view of their excellent biological activities. On the other hand, the study of the biological activity of neem was restricted till

1975 to mostly neem oil and the extracts of different parts of the plant. Although Pradhan and co-workers demonstrated in 1962 that water suspension of neem kernel powder exhibited good antifeedant activity against locusts, it was only in 1972 that the active principle was isolated by Butterworth et al.[6] who named it as azadirachtin. Based on the chemical evidence and spectral data, the structure was proposed to azadirachtin in 1975[7] by Nakanishi and co-workers only to be revised in 1986 by three International groups of workers[8-10] including Nakanishi et al. This is due to highly oxygenated and complex nature of the molecule of azadirachtin which makes its chemical synthesis for commercial exploitation rather impossible.

In recent years greater attention is being paid to possibilities of commercialising the neem potential by formal product development. Margosan-O, the first commercial product is being manufactured in USA. Neem-guard and Neemark are the two commercial neem products in India which are based on the concentrate of neem are being manufactured by Akshay Chemicals, Bombay and Western Coast Co.Ltd., Bombay respectively. The neemguard the first Indian commercial product is marketted by Gharda Chemical Ltd., Bombay.

The chemistry of Azadirachtin remains an interesting topic for several reasons. It requires a sound knowledge of its chemistry for total synthesis of azadirachtin and the structure-activity relationship studies on azadirachtin would throw more light on biological activities and the mechanism of action of azadirachtin as an insect antifeedant and growth inhibitor. Recently Steven Ley and co-workers have reported

the synthesis of a fragment of azadirachtin, the polyoxygenated decalin[11] which shows antifeedant properties and considerable structural homology with members of the limonoid series, such as azadirachtin and salannin.

Present work on Azadirachta indica, A.Juss.

Keeping in line with the modern trends in pest management a major project was initiated at NCL in 1979 entitled "Pest Control Agents from plant sources". The objective was to (i) screen a number of plant extracts for various pest control activities (ii) to isolate and identify the active principles (iii) to synthesise the active principles for commercial exploitation if economically feasible (iv) to develop processes for active rich fractions of the more abundantly available plant material especially where synthesis of the active principles may be economically untenable. The concept of using the active-rich fractions originated from NCL under auspecies of the above project. During our initial screening programme, neem was first choice in view of the reported pest control activity which had aroused great interest all over the world and relative abundance in India. While the work on antifeedant activity of azadirachtin and related compounds was in progress in other countries like USA and W.Germany, we concentrated in addition on the activities such as ovicidal and aphidicidal also.

During the developmental work on azadirachtin-rich fraction from neem for commercial exploitation as a biodegradable pesticide, seventeen known and two new tetranortriterpenoids possessing the nimbin skeleton (C-ring broken) have been isolated from the seed extract. During our screening of neem fractions for ovicidal activity, surprisingly we

obtained for the first time oviposition detterent (repellent) activity against potato tuber moth, a serious pest affecting the potato tubers. As the active principles were present in minute quantities, the concept of obtaining an active-rich fraction originated out of necessity and this prompted us to develop the process.

The name **NEEMRICH** was coined in NCL for the active-rich fraction and this particular fraction exhibiting oviposition deterrent activity was termed NEEMRICH-I.

Activity of NEEMRICH-I

1) Oviposition deterrent and antifeedant activity are exhibited against the adults and larvae of potato tuber moth respectively at 2.5% dosage. Residual activity in lab. experiments lasts for 15-20 days.

2) Aphidicidal and miticidal activity are observed at 1% dosage with no residual activity in lab.experiments.

3) Mosquito larvicidal activity is found at 10.0 ppm (lab.level).

The fraction exhibiting Antifeedant and Growth inhibitory activity was termed as NEEMRICH-II.

Activity of NEEMRICH-II

1) Antifeedant activity against Spodoptera litura, is observed to the extent of 75% at 1% dosage.

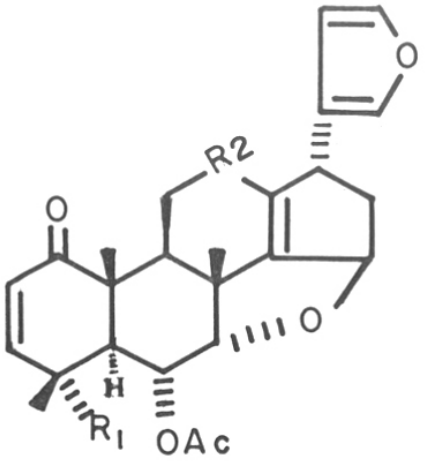
2) Growth inhibitory activity is observed against Spodoptera litura. No survival at 10 ppm.

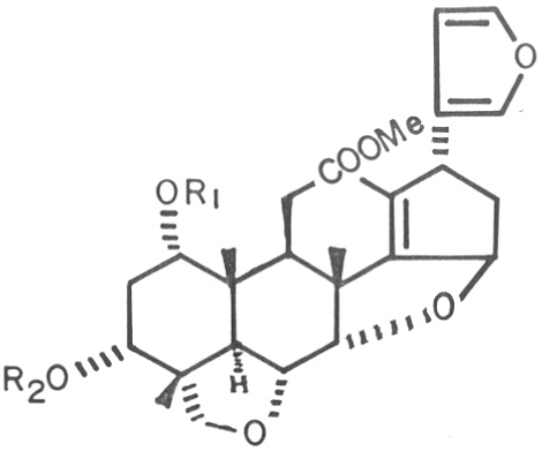
Two new tetranortriterpenoids possessing nimbin skeleton have been isolated from the ethanol extract of neem seeds. One is an aldehyde which we name it as nimbanal while the other is the 3-acetyl derivatives of salannol. So far only three tetranortriterpenoids possessing the

formyl group have been isolated from the related species, Melia azedarch and this is the first report of the occurrance of a triterpene aldehyde from neem.

Compound (1)

The triterpene fraction of the ethanol extract of neem seeds was chromatographed over silica gel (column grade) using acetone:pet.ether solvent mixture for elution gradient. Then repeated preparative TLC in ethyl acetate-benzene (15:85%) gave compound (1), a white crystalline material which had a m.p.195-197° (acetone:pet.ether). It was found to have a molecular formula $C_{29}H_{34}O_8$ from its mass spectrum which exhibited at M^+ peak at 510. The UV spectrum of compound (1) showed λ_{max} 210nm (ϵ 12940) and a band in its IR spectrum (Fig. 1) at 1680 cm^{-1} clearly indicated the presence of an α,β -unsaturated ketone, which was further supported by the AB quartet at δ 5.995 and 6.12 (10.136 Hz) in ^{1}H-NMR and the C-1 carbonyl frequency at 201.141(s) in ^{13}C-NMR spectrum. The presence of formyl group was evident by a signal at δ 9.24 as a singlet in its ^{1}H-NMR spectrum (Table 1). Amongst other signals important ones observed are at δ 1.31 s (H-19), δ 1.27s (H-29) and 1.37s (H-30) due to tertiary methyl groups, a doublet at 1.68 assignable to methyl on the double bond and singlets at δ 1.198 and 3.63 assignable to acetyl and carbomethoxy groups respectively. The characteristic signals at 6.33, 7.24 and 7.33 revealed the presence of a -substituted furan ring. A critical comparison of the spectral data of compound (1) with those of three triterpene aldehydes ochinal[12] (8.88 br dd, H-12), ochinolal[13] (9.74s, H-28) and sendanal[14] (9.5s, H-28) isolated from Melia azedarach





1. R_1 = CHO , R_2 = COOMe
2. R_1 = COOMe, R_2 = CHO
3. R_1 = R_2 = COOMe
4. R_1 = $COCH_2$ $CHMe_2$ R_2 = Ac
5. R_1 = $COCH_2$ $CHMe_2$ R_2 = H
6. R_1 = $COC(Me)=CH-Me$ R_2 = Ac
7. R_1 = R_2 = H

revealed a close resemblance with those of ochinolal. The only difference between nimbanal and achinal appeared to be the presence of an enone moiety in the ring A of nimbanal. One of the possible positions for the enone group in ring A such as -C(1H) = C(2H) - C(3)(=O) - is ruled out as nimbanal is not identical with a transformation (oxidation) product of ochinolal. Hence the ring A in nimbanal should contain the system -C(3H) = C(2H) - C(1)(=O)- as in nimbin[4,15] (3) which is supported by the close similarity of the characteristics (^{1}H-NMR, IR and UV) in both compounds.

The spin decoupling studies gave the maximum information about the structure. Irradiation of th broad triplet at δ 5.58 ppm affected the signals of 2.19 dd and 2.10 dd which all collapsed into sharp singlets and caused slight effect on 3.73. And irradiation at the signal centered at δ 2.15 caused the collapse of the signal at δ 5.58(br.t) into broad singlet and the signal at 3.73d caused the collapse of the same signal into sharp singlet. This means that the signal at δ 5.58 (br.t) is due to the H-15; and 2.10dd, 2.19dd and 3.78d are assignable to H-16a, H-16b and H-17 respectively. The nmr signals at δ 7.33 when irradiated caused the expected effect on 6.33(m) which collapsed into a sharp singlet and after irradiation at 5.20dd the signals at 3.27d and 4.08d collapsed into a sharp singlets. This clearly indicated that the signal 5.20 dd is due to the H-6, and the signals at δ 3.27d and 4.08d are due to H-5 and H-7 respectively.

Further evidence in support of this was forthcoming by the disappearance of the AB quartet in 2,3-dihydronimbanal obtained by the selective

PAGE NO. 26 TO 27 MISS

TABLE 1 : ^{1}H NMR data for compound (1) and (4)

Proton	(1)	(4)
H1	-	4.9603, t(3.645, 3.08)
H2	5.9957, d (10.136)	-
H3	6.1231, d(10.136)	4.8475, t(3.085, 2.644)
H5	3.2708, d(12.339)	2.72, d(12.78)
H6	5.2025, dd(12.34, 3.08)	3.971, dd (12.56, 3.305)
H7	4.0812, d (3.085)	4.1549, d (3.085)
H11a	2.8402, dd (18.429,4.848)	-
H11b	3.048, dd (18.509,5.288)	-
H15	5.572, m	5.4841, m
H16a	2.1985, dd(13.22, 6.61)	-
H16b	2.1079, dd(12.476, 8.544)	-
H17	3.7825, d (5.63)	3.692, m
H18	1.6868, d (1.322)	1.6476, d (1.322)
H19	1.3171, s	0.945, s
H21	7.2419, m	7.3398, m
H22	6.3361, m	6.3409, m
H23	7.33, m	7.286, m
H28	9.2495, s	3.608, s
H29	1.273, s	1.209, s
H30	1.3759, s	1.3024, s
COOMe	3.6381, s	3.2806, s
OCOMe	1.9879, s	2.0712, s
H4'	-	1.001, d (6.61)
H5'	-	

90 MHz, δ scale in ppm, TMS as int. standard. Figures in parentheses denote coupling constants.

TABLE 2 : ^{13}C NMR spectral data of compounds (1), (3) and (4) (in $CDCl_3$ at 25.05 MHz, TMS as internal standard, values in δ).

Carbon No.	(1)	(3)	(4)
C-1	201.141(s)	201.794(s)	71.619(d)
C-2	129.200(d)	127.120(d)	30.415(t)
C-3	143.238(d)	143.238(d)	71.034(d)
C-4	47.507(s)	47.312(s)	42.958(s)
C-5	51.667(d)	53.096(d)	41.398(d)
C-6	68.694(d)	68.889(d)	72.918(d)
C-7	84.617(d)	84.942(d)	86.046(d)
C-8	48.092(s)	48.222(s)	49.132(s)
C-9	40.813(d)	38.864(d)	40.098(d)
C-10	51.927(s)	51.732(s)	40.553(s)
C-11	34.249(t)	34.379(t)	28.725(t)
C-12	173.523(s)	174.888(s)	173.133(s)
C-13	135.669(s)	135.244(s)	134.854(s)
C-14	146.032(s)	147.852(s)	146.942(s)
C-15	87.411(d)	87.346(d)	88.191(d)
C-16	41.463(t)	41.788(t)	39.384(t)
C-17	49.717(d)	49.782(d)	49.782(d)
C-18	16.897(q)	16.832(q)	12.998(q)
C-19	14.817(q)	16.832(q)	15.597(q)
C-20	126.925(s)	126.275(s)	127.445(s)
C-21	139.208(d)	139.273(d)	139.208(d)
C-22	110.613(d)	110.743(d)	111.003(d)
C-23	144.927(d)	146.552(d)	143.043(d)
C-28	119.519(s)	173.783(s)	78.053(t)
C-29	20.796(q)	21.056(q)	19.757(q)
C-30	12.868(q)	12.933(q)	17.092(q)
OCOMe	170.339(s)	170.794(s)	170.664(s)
OCOMe	17.092(q)	17.352(q)	21.186(q)
COOMe 31	-	41.788(q)	-
COOMe 32	38.539(q)	38.864(q)	51.537(q)
C-1′	-	-	172.743(s)
C-2′	-	-	43.673(t)
C-3′	-	-	25.216(d)

Table 2 continued :

Carbon No.	(1)	(3)	(4)
C-4′	-	-	22.941(q)
C-5′	-	-	22.811(q)

Signal multiplication in the single frequency off resonance decoupled (SFOD) spectrum.

The signals are assigned tentatively by comparison with those reported for similar compounds.

PAGE NO. 31 TO 35 MISS

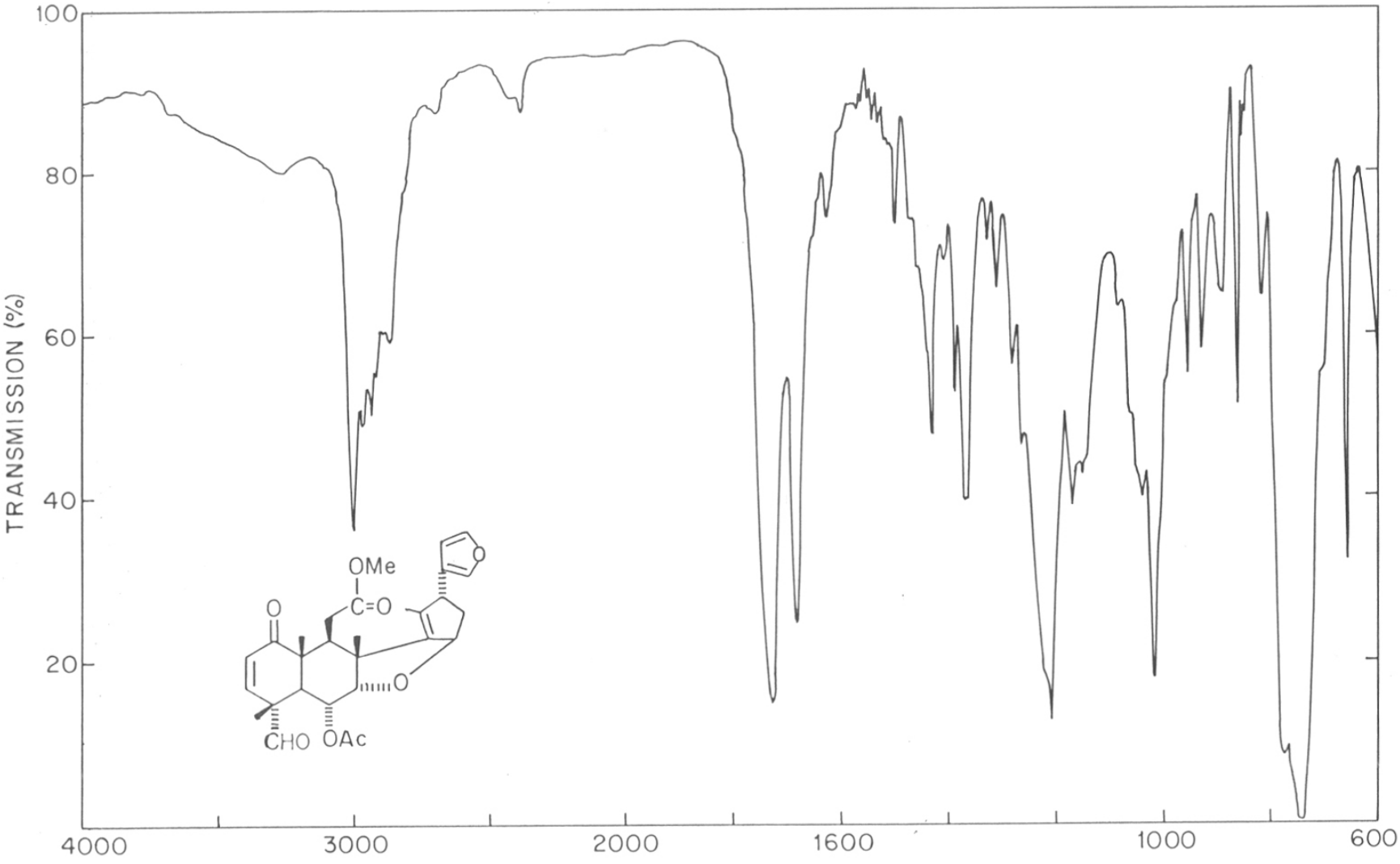


FIG. 1 : IR SPECTRUM OF COMPOUND (1)

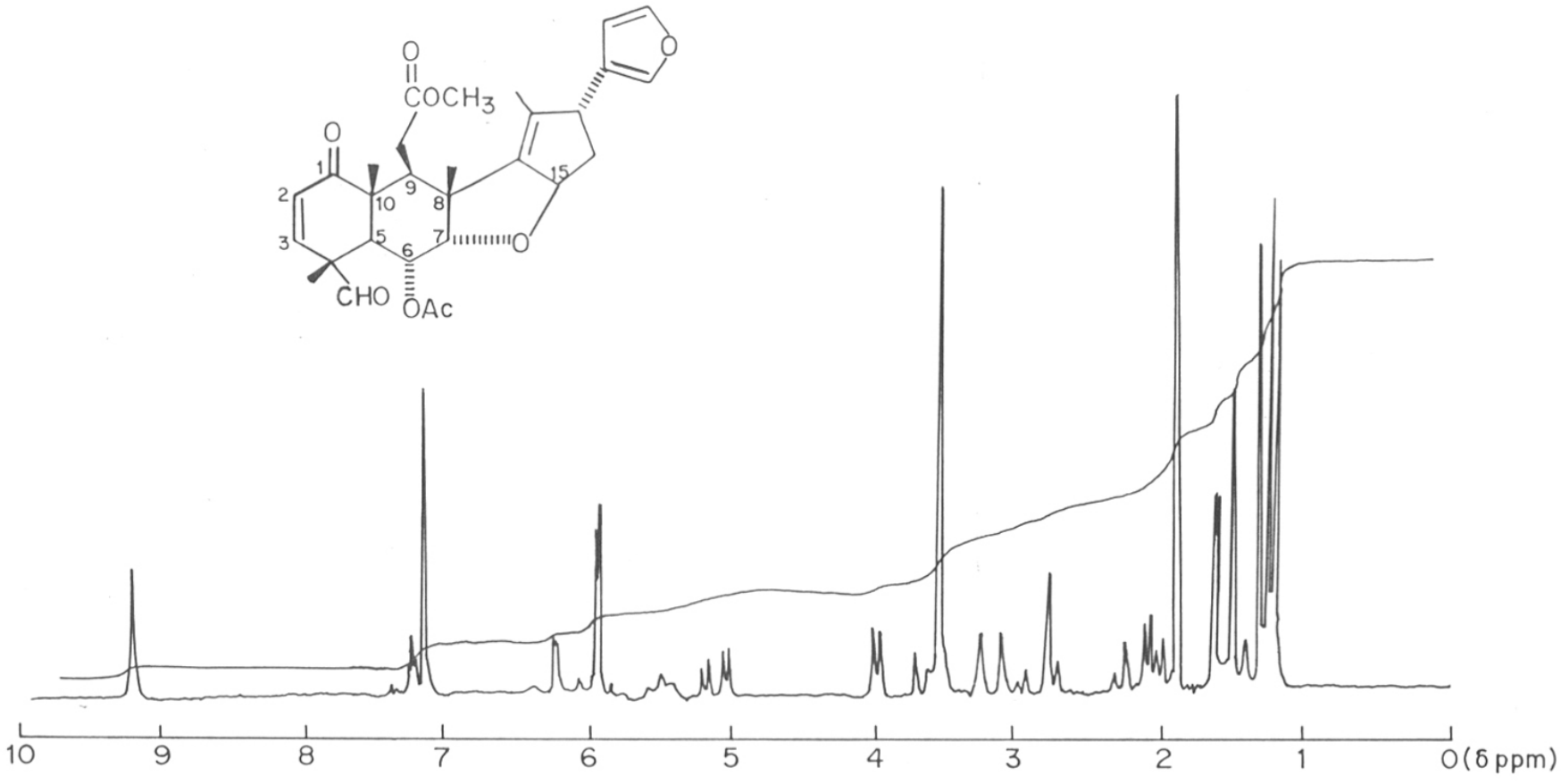


FIG. 2: ^{1}H NMR SPECTRUM OF COMPOUND (1)

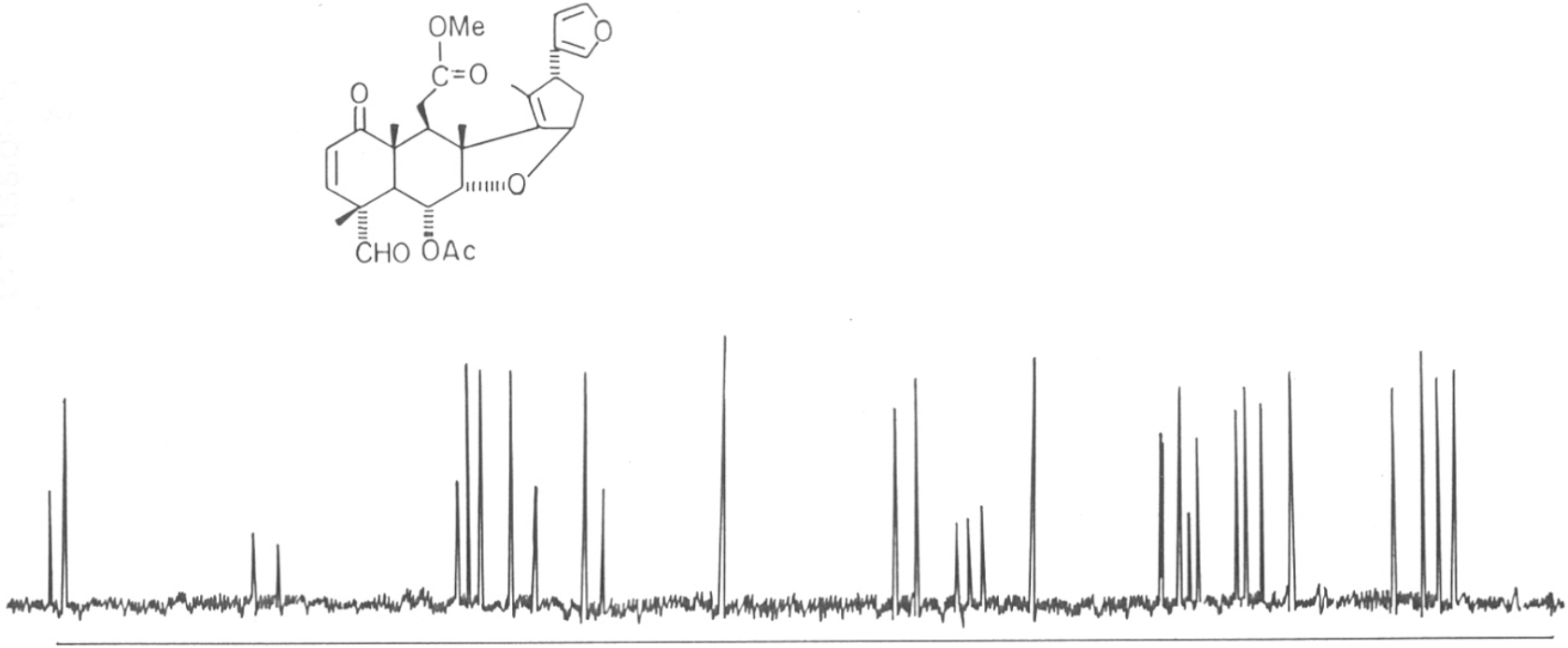


FIG.3: ^{13}C NMR SPECTRUM OF COMPOUND (1)

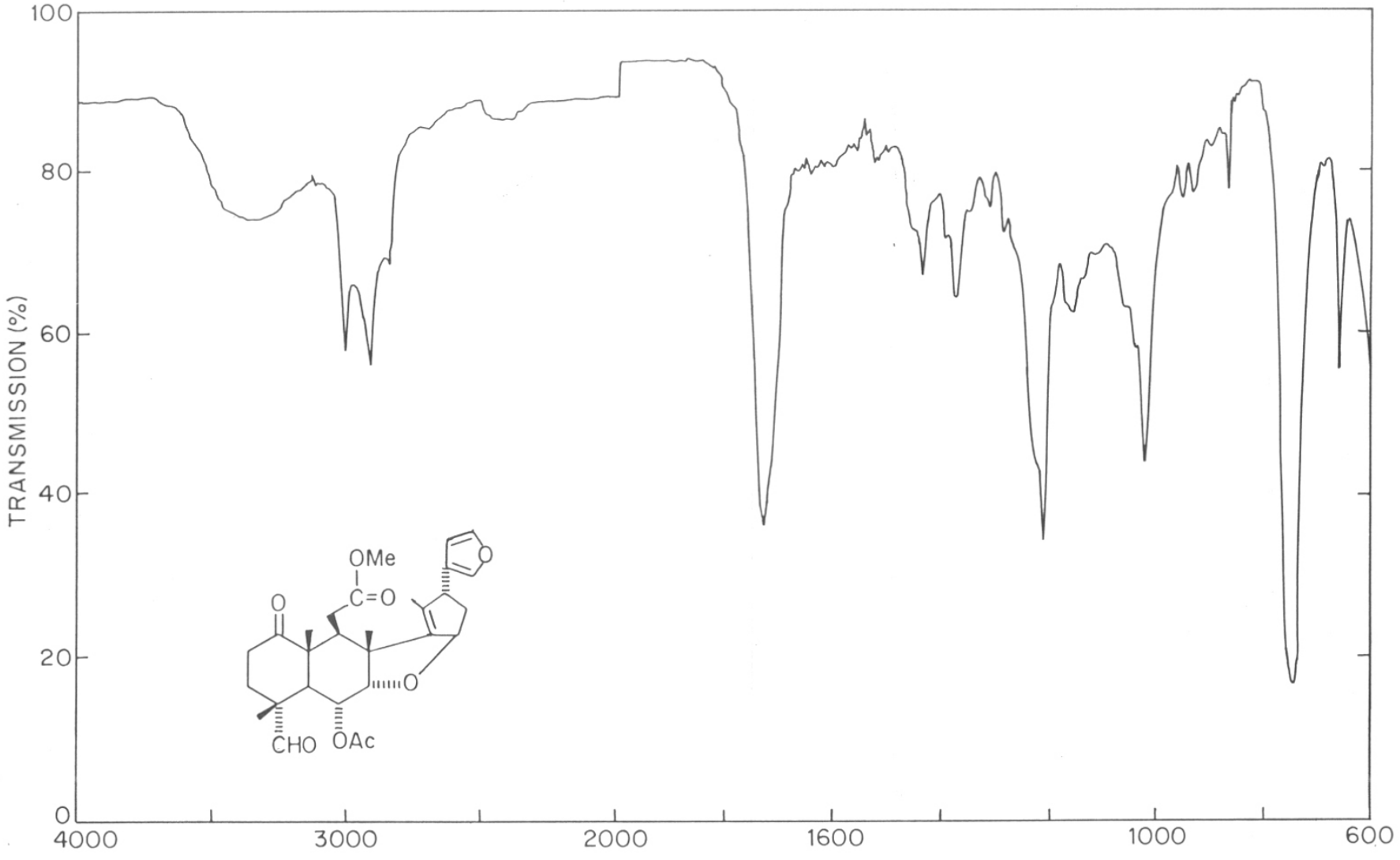


FIG.4: IR SPECTRUM OF DIHYDRO DERIVATIVE OF COMPOUND (1)

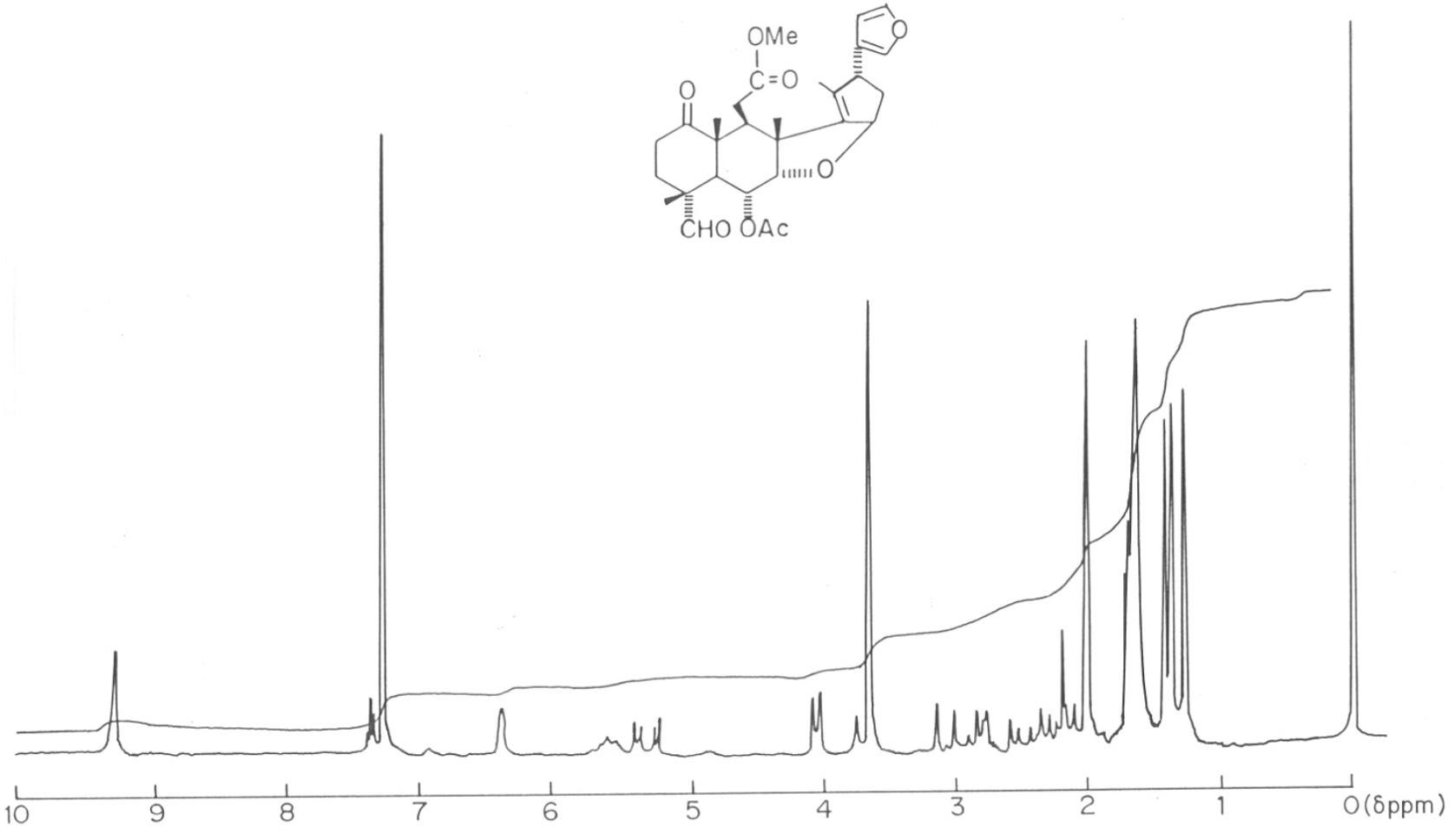


FIG.5: ^{1}H NMR SPECTRUM OF DIHYDRO DERIVATIVE OF COMPOUND (1)

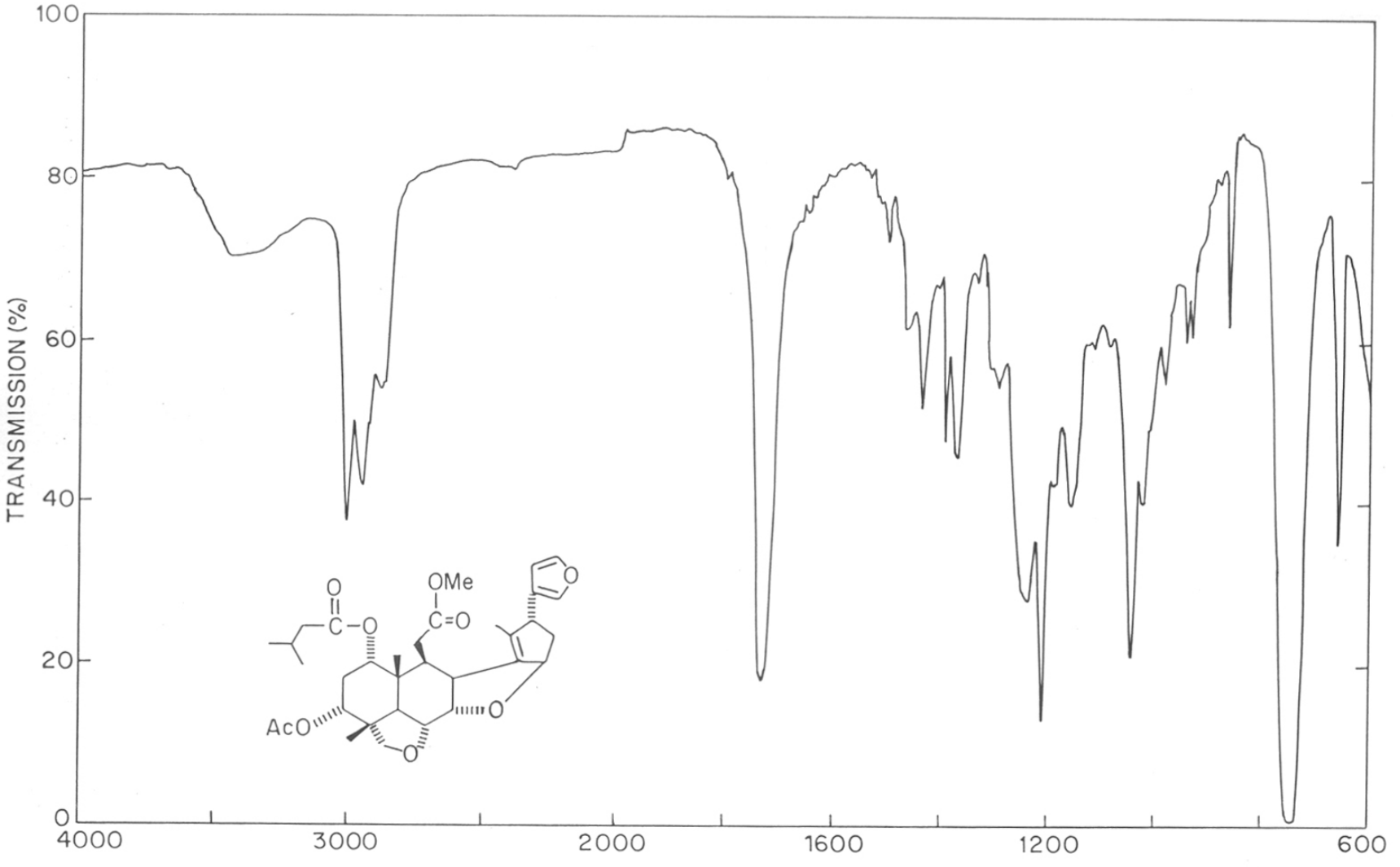


FIG. 6 : IR SPECTRUM OF COMPOUND (4)

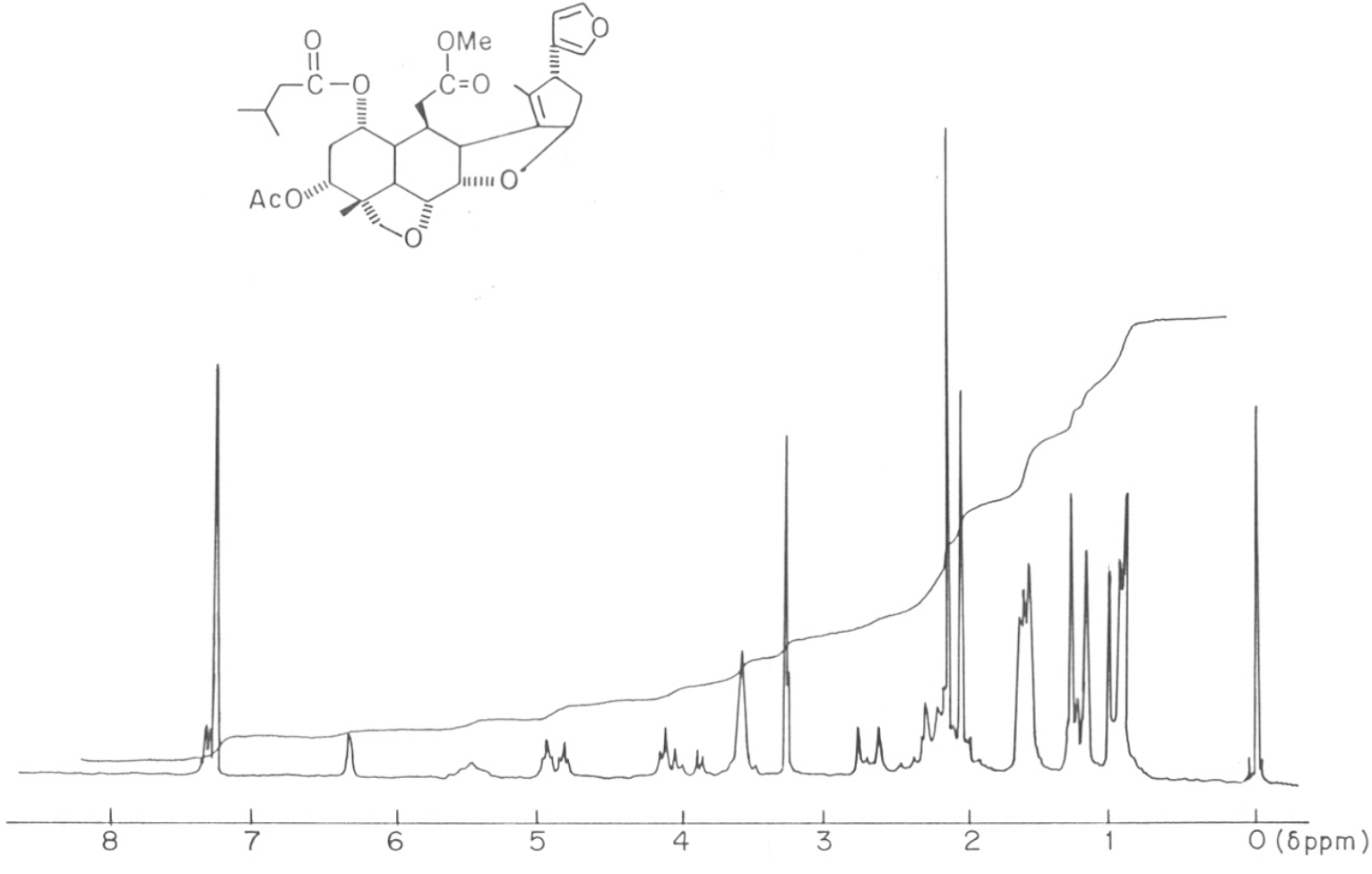


FIG.7: ^{1}H NMR SPECTRUM OF COMPOUND (4)

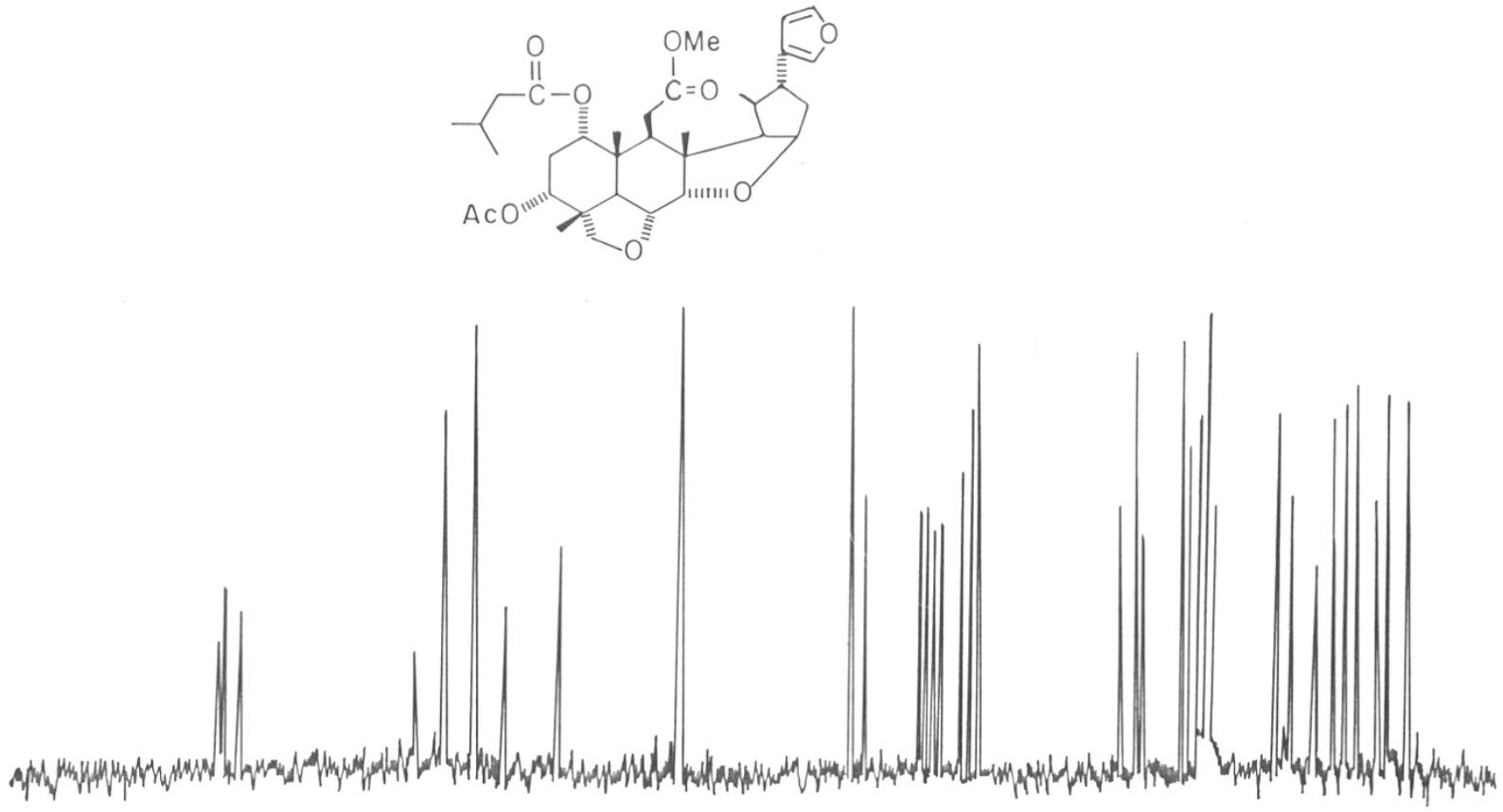


FIG. 8 : ^{13}C NMR SPECTRUM OF COMPOUND (4)

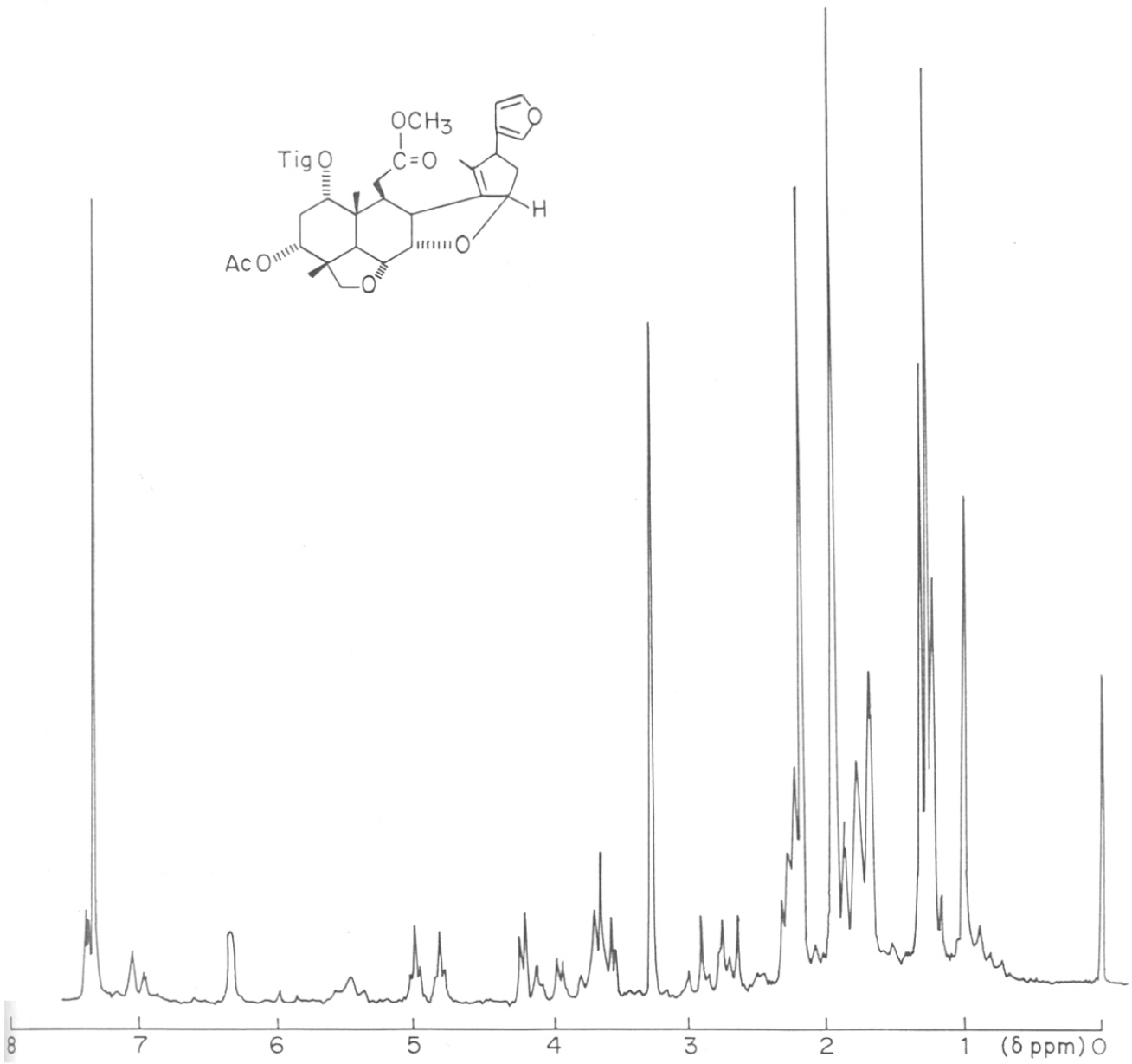


FIG. 9: ^{1}H NMR SPECTRUM OF COMPOUND (6)

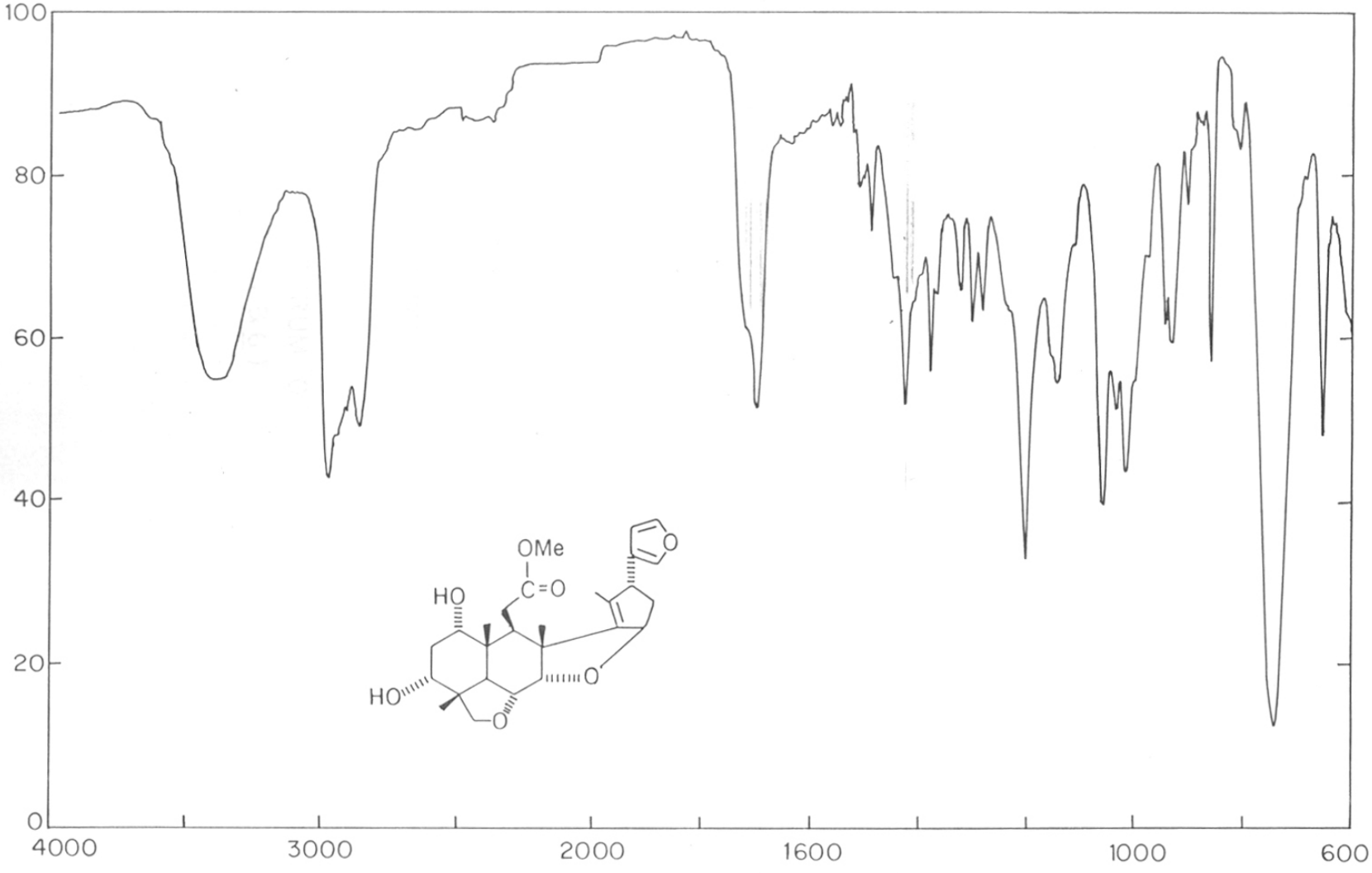


FIG.10: IR SPECTRUM OF COMPOUND (7)

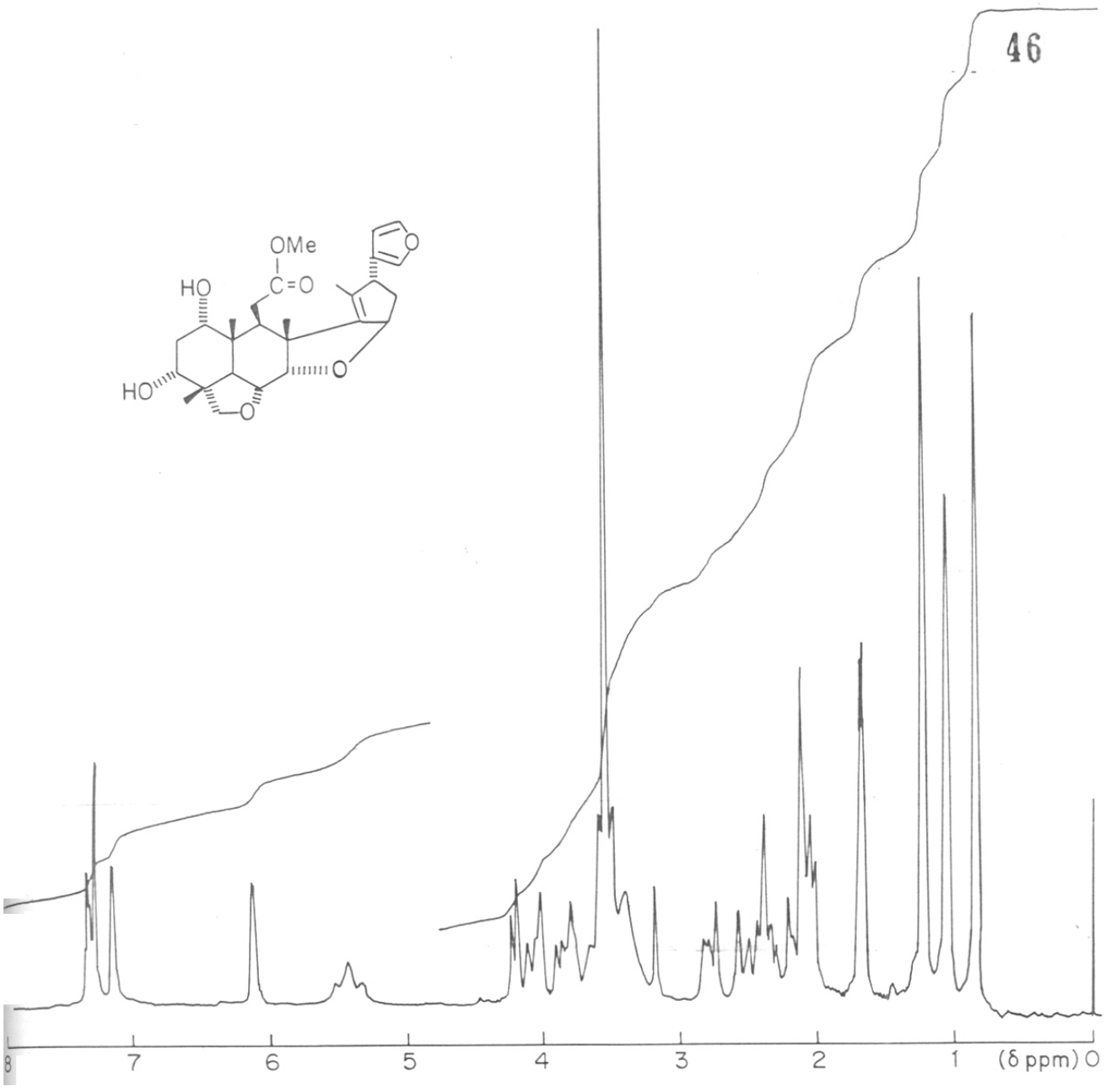


FIG. 11 : H-NMR SPECTRUM OF HYDROLYSED PRODUCT OF COMPOUND (4 & 6)

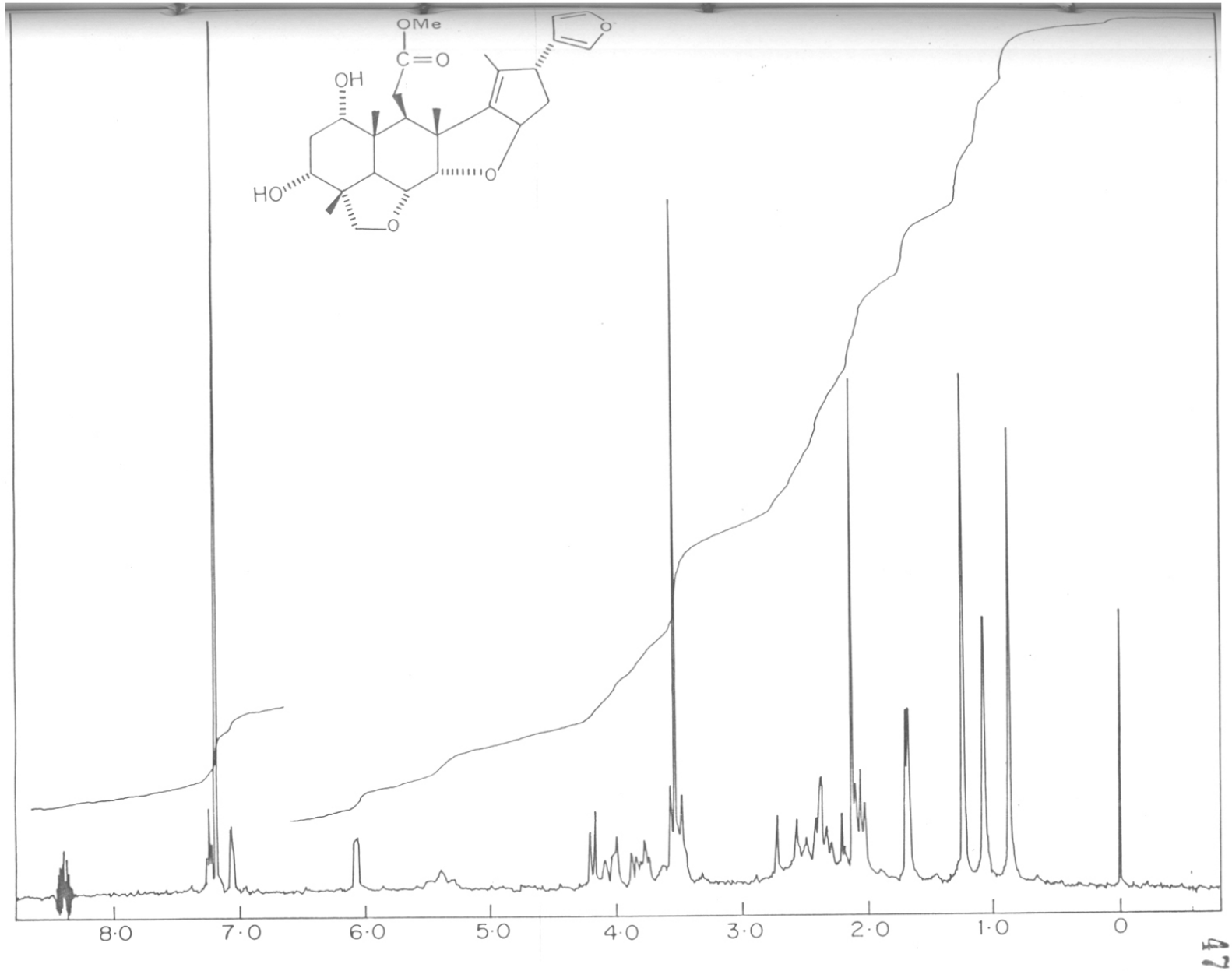


FIG. 12: ^{1}H-NMR OF HYDROLYSED PRODUCT OF COMPOUND (4)

CHAPTER III

Chemical Investigation of *Blainvillea latifolia* (D.C.)

INTRODUCTION

Naturally occurring sesquiterpene lactones are compounds with 15 carbon atoms formed via head to tail condensation of three isoprene units followed by cyclization and oxidative transformations to produce a cis or trans fused lactone ring. They are widely distributed in most genera of Compositae with the exception of the evolutionary advanced tribe, the Tagatae[1] and sporadically in the genera of Umbelliferae, Magnoliaceae, Lauraceae, Winteraceae, Illiciaceae, Aristolochiaceae, Menispermaceae, Cortiariaceae and Acanthaceae[2].

The isolation and structure elucidation of sesquiterpene lactones have increased dramatically in the last two decades. The increasing interest in this group of natural products can be attributed to two reasons; firstly sesquiterpene lactones have been successfully used as markers in the biochemical systematic (chemotaxonomy) studies mainly in compositae[3-8]; secondly, more recently a number of sesquiterpene lactones have received considerable attention due to their various biological activities, which has resulted in an additional increase in the biological activity related publications[9-14].

In addition to above two reasons, the recent advances in the field of separation techniques such as adsorption chromatography, thin layer chromatography (TLC), gas liquid chromatography (GLC) and high performance liquid chromatography (HPLC) have simplified the isolation and purification of these compounds to a great extent. The development of modern physical methods of structural analysis such as IR, UV, PMR, ^{13}C-NMR and mass spectrometry, circular dichroism (CD) and X-ray crystallography has made

made possible to elucidate the correct structures of all natural products including sesquiterpene lactones.

Classification

Sesquiterpene lactones are mostly colourless solid or gum in nature, bitter, relatively stable, lipophyllic constituents which are biogentically derived from trans-trans farnasyl pyrophosphate followed by an initial cyclization and subsequent oxidative modification. The major type of lactones are classified on the basis of their carbocyclic skeleton as germacranolides, eudesmanolides, guainolides, pseudoguainolides, eremophilanolides and xanthanolides which are resulting from enzyme mediated cyclization. The less common classes of sesquiterpene lactones are secoeudesmanolides, chrymoranolides, bakkanolides, secoambrosanolides and secohelenanolides. Germacranolides are the biognetic precursors of all other classes of sesquiterpenes[15].

The germacranolides are having a cyclodecadiene ring structure with double bonds[16] in C-1, 10 and C-4,5 positions. The germacranolides are further classified into four sub-groups[17,18], namely (i) germacrolide (ii) melampolides (iii) heliangolides and (iv) cis-cis germacranolides [Chart I, Scheme I] depending upon the configuration of the double bonds of the above four subgroups; the germacrolides represent the largest subgroup, then an increasing number of melampolides[19] and heliangolides[20] and the last subgroup cis-cis germacranolides represent the smallest ones which have been isolated recently[21-23].

Biogenesis

The acetyl Co-enzyme A is the biogenetic origin of pyrophosphate esters of trans-trans farnesol, cis-trans farnesol or nerolidol[24]. The biogenetic theory assumes that the biosynthesis of sesquiterpenoids including sesquiterpene lactones takes place by modifications and/or cyclization of the above pyrophosphate ester [Chart I (Scheme I)]. The first step in the biogenesis is the cyclization of pyrophosphate esters of trans-trans farnesol, cis-trans farnesol or nerolidol into a 1,10; 4,5-germacradiene cation which later undergoes various oxidative modifications and recyclizations to give various types of sesquiterpene lactones.

The γ-lactone formation, typical of Compositae involves [Chart II Scheme II] oxidation of side-chain and introduction of lactonic oxygen at C-6 or C-8 and eventual ring closure to form either a costunolide or inunolide respectively. It represents the most elementary cyclic sesquiterpeneb lactone, since it retains two of three double bonds of the farnesyl pyrophosphate in the trans-trans configuration. The details about the formation of the γ-lactone are not known but two possible routes have been suggested. The first of these may well be responsible for the occasional occurence of the lactone of type A [Chart II (Scheme II)] in those plant groups which normally elaborate furano-sesquiterpenoids (Lauraceae, Senecioceae) although its relevance to the formation of type lactones so prevalent in compositae is less clear [Chart II Scheme II]. An alternative proposal[25] [Chart II Scheme III] involves oxidation of isopropenyl side-chain of sesquiterpenes followed by introduction of oxygen at C-6 or C-8 presumably after cyclization of germacrodiene and

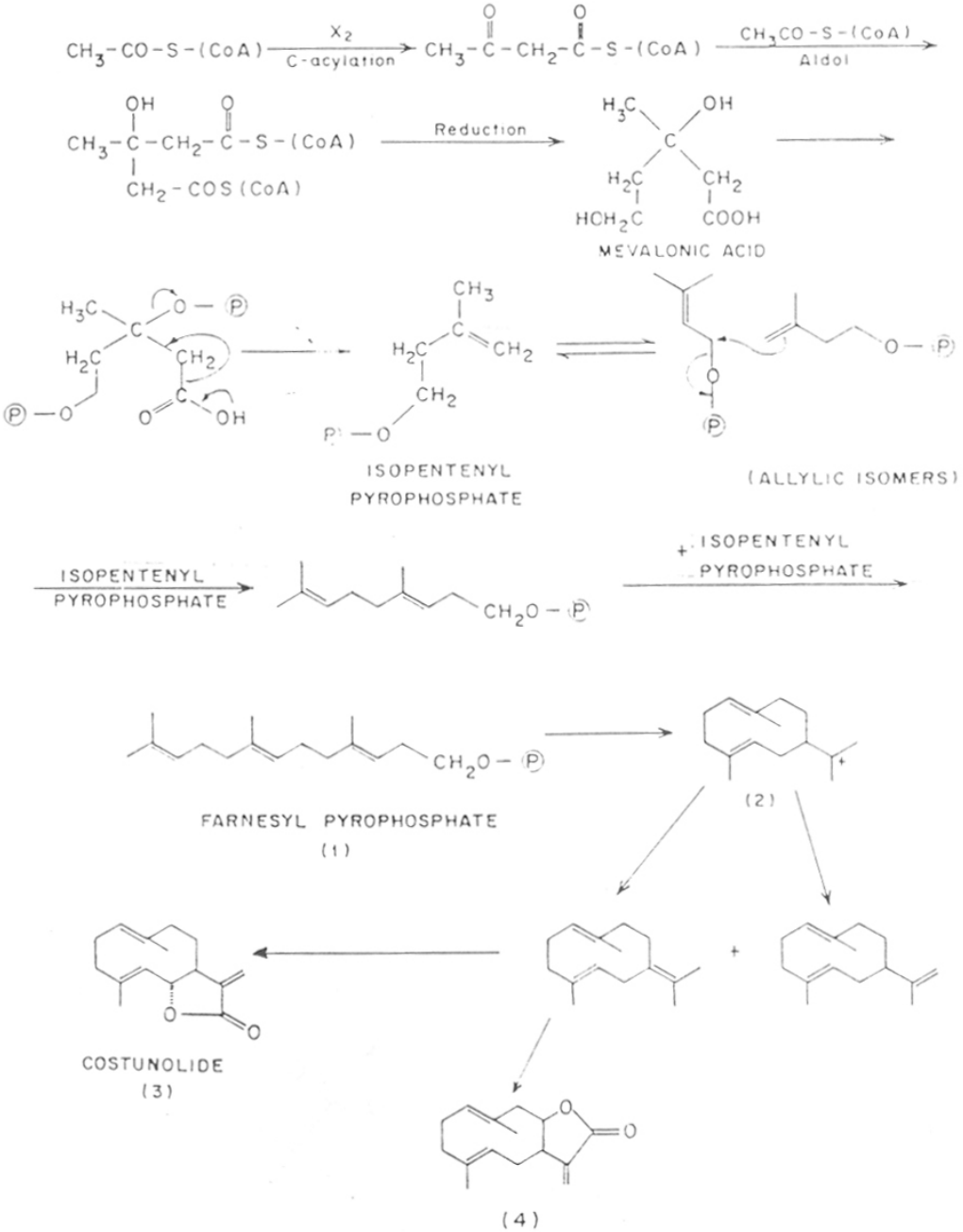
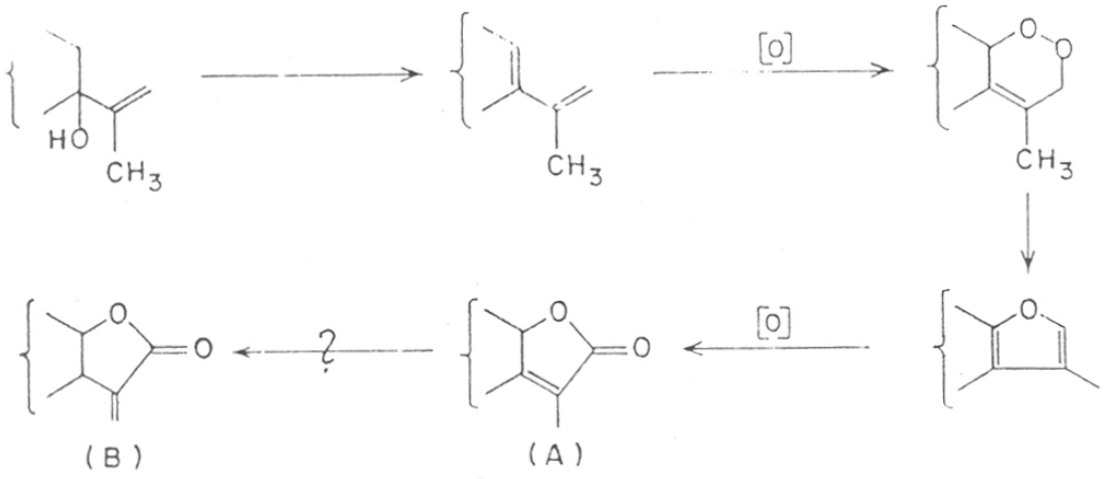
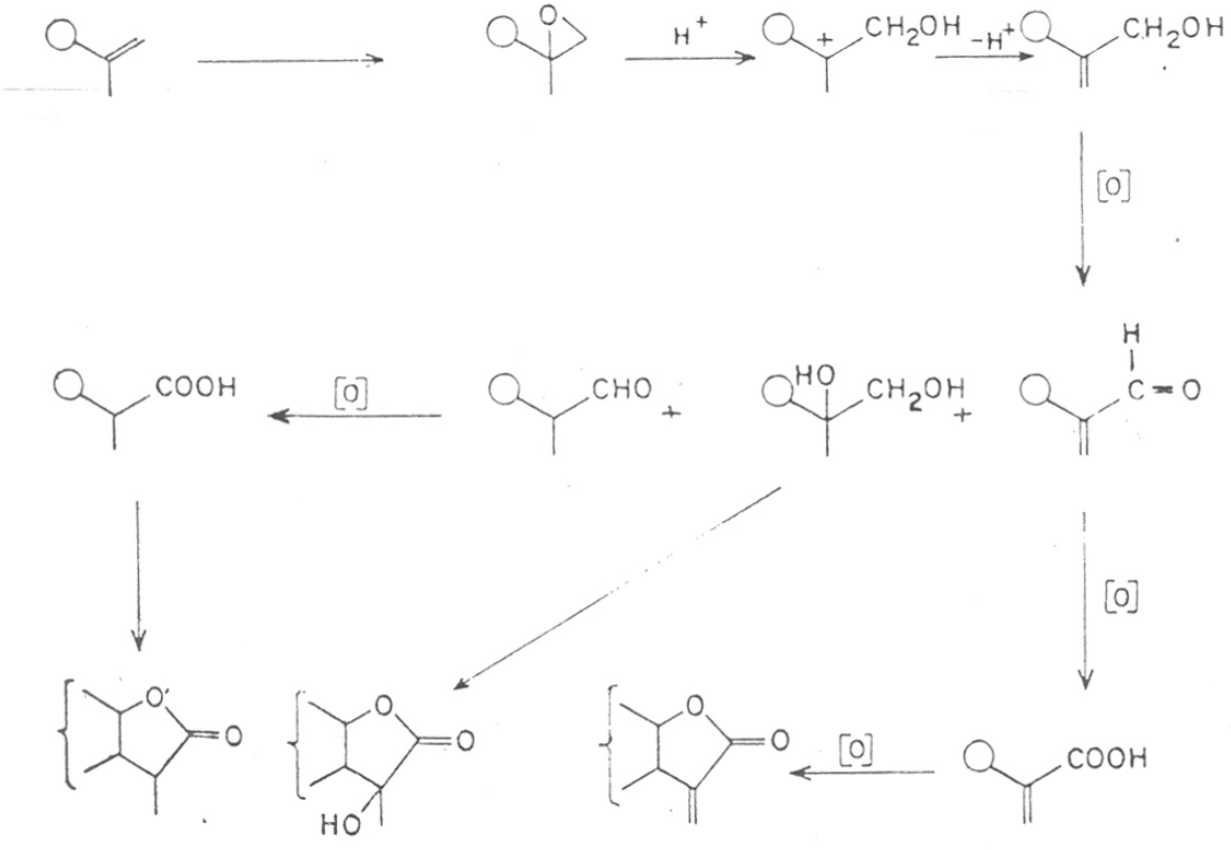


CHART I (SCHEME I)

CHART - II



SCHEME II



SCHEME III

lactone ring closure. As a general route this mechanism appears more attrative to sesquiterpene lactones since the epoxide, alcohols, aldehyde and acids listed in the Scheme-III sometimes already oxidised at requisite ring position are widely distributed in nature, since the postulated intermediates occasionally accompany the lactone end-products.

Previous work on Blainvillea species

The genus Blainvillea (Family Compositae, tribe Heliantheae, subtribe Ecliptinae), contains as many as ten species[26]. Blainvillea dichotoma was the first species which had been investigated chemically by F. Bohlmann et al.[27] afforded, in addition to known compounds, seven new sesquiterpene lactones. Four sesquiterpene lactones were related to elephantin, two melampolides and a further one was a cis-cis germacranolide. Then after four years a second publication came in print by P. Singh et al.[28] who investigated the aerial parts of B.acmella to report in addition to widespread triterpenoids, desacetylovatifolin, desacylgrazielic acid tiglate, 8β-(Methylbutyryloxy)-9β-hydroxy-14-oxo acanthospermolide, four new germacranolides and seven acanthospermolides. The roots gave ovatifolin, two widespread thiophenacetylenes and two daucane derivatives. The isolation of acanthospermolides was of taxonomic interest as this type of sesquiterpene lactones had not been observed previously in any genus of the subtribe Ecliptinae.

Present work on Blainvillea latifolia (D.C.)

As regards the species Blainvillea latifolia (Family Compositae, Tribe Heliantheae, subtribe Ecliptinae), so far there is no report on the chemical examination. As a part of our screening programme of plant extracts for insect control activity this plant extract was screened for the biological activity. However, it did not show any activity.

An acetone extract of the aerial parts of B.latifolia when chromatographed over silica gel, gave a major sesquiterpene lactone fraction. After repeated column chromatography and preparative impregnated silver nitrate TLC with acetone-pet.ether gave a major sesquiterpene lactone (1). Another related but minor sesquiterpene lactone was present in traceas. (4).

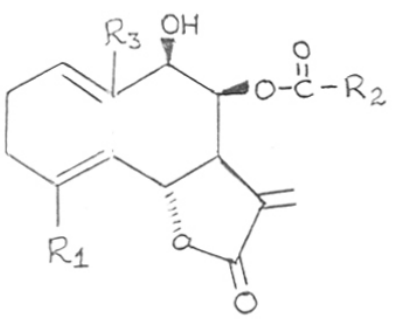
Compound (1)

This compound was found to be a polyoxygenated sesquiterpene lactone from its chemical and spectral properties. However, its structure could be elucidated from the spectral characteristics of the compound and its transformation products and was confirmed by single crystal X-ray crystallography as 8β-isobutyryloxy-9β-hydroxy-10-acetoxymethyl germacrene-6,7-olide. The stucture of the other compound (4) recently isolated from a related species B.acmella[28] follows from the comparison of the spectral data of (1) and its derivatives (2) and (3) will be discussed in this Chapter.

Compound (1), had a m.p.159-160° (acetone-pet.ether) and was found to have a molecular formula $C_{21}H_{28}O_7$ from its elemental analysis and also from its mass spectrum which exhibited a M^+ peak at m/e 392; showed

in its IR spectrum (Fig. 1) the presence of a hydroxy group (3580 cm^{-1}), an α,β -unsaturated-γ-lactone (1760 cm^{-1}) and an acetate (1740 cm^{-1} and 1240 cm^{-1}). Its ^{1}H-NMR spectrum (Table 1) while supporting the presence of the α,β -unsaturated-γ-lactone by the characteristic signals at 5.86 and 6.35 due to the exomethylene group, also exhibited the presence of a vinylic methyl group at 1.80, an acetyl group at 2.05, an isopropyl group at δ 1.15 and 1.17, two olefinic hydrogens at δ 4.76 and 5.33 and an AB quarter (2H) at δ 4.45 and 4.64 assignable to CH_2OR group. The ^{13}C-NMR of compound (1) Table 2, while supporting the presence of a CH_2OR group revealed the presence of three carbonyl groups, three olefinic bonds and three methyl groups. The molecular formula and the above spectral data clearly suggested that the compound under discussion is a sesquiterpene lactone.

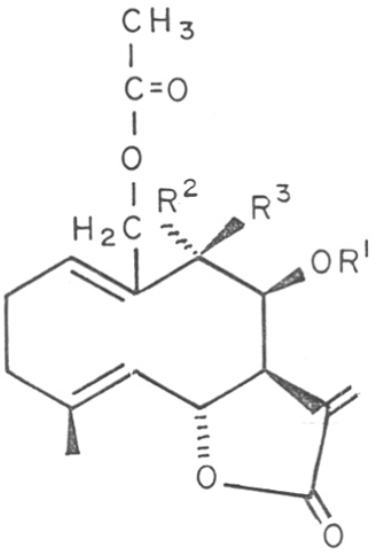
The nature of the hydroxyl group in compound (1) was determined as secondary by its acetylation to give compound (2) and by oxidation to give a ketone (3). This led to the assignment of the signal at δ 4.43 in the ^{1}H-NMR of compound (1) to CHOH as it moved downfield to δ 5.38 in compound (2) and was absent in compound (3). This observation further revealed that CH_2OR group must be present as CH_2OAc or $CH_2\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH(CH_3)_2$. The multiplicity of the signals due to exomethylene group of the α,β-unsaturated-γ-lactone indicated that compound (1) had an oxygen substituent at C-8 position[29]. The above data leads to the following partial structure.



R_1 or R_3 may be CH_3
or CH_2OAc or $-CO-CH(CH_3)_2$
R_2 = OAc or $-CO-CH(CH_3)_2$

As it is easy to locate H-7 in the ^{1}H-NMR spectrum of a sesquiterpene lactone which is centered around δ 3.0 as a multiplet, irradiation of the multiplet at δ 2.91 in the spectrum of compound (1) effected a change in the characteristic signals due to H-13a and H-13b as expected. In addition, it also caused the collapse of a double doublet at 4.9 assignable to H-6 which in turn on irradiation effected a change in the signal due to the H-7 and in the doublet at δ 4.74. This doublet signal was identified as due to H-5 from the fact that when irradiated it caused the collapse of the olefinic methyl doublet at δ 1.81 thus revealing the presence of an olefinic methyl group at C-4. Logically CH_2OR must be at C-10. The broad doublet at 6.0 was assigned to H-8, as it coupled with H-7, H-13a and H-13b and also with the doublet at δ 4.43 already assigned to the secondary hydroxy group. This enabled us to place the secondary hydroxyl group at C-9 which is supported by the change in the pattern and chemical shift of CH_2OR at C-10 in the ^{1}H-NMR spectra of compound (2) and (3) respectively. There was a pronounced chemical shift in the ^{1}H-NMR of compound (3) as the AB quartet originally centered at δ 4.45 and 4.64 in compound (1) had shifted to δ 4.12 and 5.11. Similarly the signals due to H-8 and H-7 recorded a downfield shift of 0.2 and 1.0 ppm respectively, whereas H-6 moved upfield by 0.18 ppm probably due to the cone effect of the carbonyl at C-9. The septet at 2.50 was readily identified as isopropyl methine as it coupled with both the secondary methyl groups. As derived earlier one of the olefinic bond is at C_{4-5} and hence the another is placaed at C_{1-10} on biogenetic grounds.

As regards the stereochemistry the coupling constant between H-6 and H-7 (J=10 Hz) indicated them to be trans to each other, revealing



1] R^1= Isobutyryloxy, R^2 = H, R^3 = OH

2] R^1= ,, , R^2 = H, R^3 = OAc

3] R^1= ,, , R^2, R^3 = O

4] R^1= 2-methylbutyryloxy, R^2 = H, R^3 = OH

5] R^1= ,, , R^2 = H, R^3 = OAc

6] R^1= ,, , R^2, R^3 = O

TABLE 1 ^{1}H-NMR Spectral data of compounds (1-6)

	(1) (400 MHz)	(2) (90 MHz)	(3) (80 MHz)	(4) (90 MHz)	(5) (90 MHz)	(6) (80 MHz)
H-1	5.33 dd (br)	5.53	5.48 overlapped with H-5	5.36 dd (br)	5.46 m	5.48 overlapped with H-5
H-2		Four protons multiplet near 2.33 ppm.	-	Four protons multiplet near 2.33 ppm.	Four protons multiplet near 2.35 ppm.	-
H-3						
H-5	4.76 d (br) (J=10Hz)	4.73 d (br) (J=10Hz)	5.48 overlapped with H-1	4.74 d (br) (J=10Hz)	4.74 d (br) (J=10Hz)	5.48 overlapped with H-1
H-6	4.92 dd (J=10.5,10Hz)	4.92 dd (J=10.5,10Hz)	4.74 dd (J=10.5,10Hz)	4.94 dd (J=10.5,10Hz)	5.0 dd (J=10.5,10Hz)	4.74 dd (J=10.5,10Hz)
H-7	2.91 dddd (J=10,4,3.5,3Hz)	3.02 dddd (J=10,4,3.5,3Hz)	4.04 overlapped with part of CH_2-OAC	2.97 dddd (J=10,4,3.5,3Hz)	3.04 dddd (J=10,4,3.5,3Hz)	4.06 overlapped with part of CH_2-OAC
H-8	6.0 d (br) (J=1.5Hz)	5.95 d (br) (J=1.5Hz)	6.2 d (J=1.5Hz)	6.02 d (br) (J=1.5Hz)	6.06 d (br) (J=1.5Hz)	6.20 d J=1.5Hz)
H-9	4.43 d (J=1.5Hz)	5.38 overlapped with H-1	--	4.42 d (J=1.5Hz)	5.41 overlapped with H-1	--
H-13	6.37 d (J=3.5Hz)	6.30 d (J=3.5Hz)	6.48 d (J=3.5Hz)	6.40 d (J=3.5Hz)	6.34 d (J=3.5Hz)	6.48 d (J=3.5Hz)
H-13^1	5.86 d (J=3Hz)	5.70 d (J=3Hz)	5.60 overlapped with H-1, H-5	5.90 d (J=3Hz)	5.75 d (J=3Hz)	5.60 overlapped with H-1, H-5
H-14	4.45 d (J=13Hz)	4.44 d (J=13Hz)	4.12 d (J=13Hz)	4.48 d (J=13Hz)	4.38 d (J=13Hz)	4.13 d (J=13Hz)
H-14^1	4.64 d (J=13Hz)	4.62 d (J=13Hz)	5.11 d (J=13Hz)	4.68 d (J=13Hz)	4.62 d (J=13Hz)	5.06 d (J=13Hz)

Table 1 (contd.)

	(1)	(2)	(3)	(4)	(5)	(6)
H-15	1.81 d (J=1.5Hz)	1.75 d (J=1.5Hz)	1.92 d (J=1.5Hz)	1.82 d (J=1.5Hz)	1.75 d (J=1.5Hz)	1.94 d (J=1.5Hz)
OAC	2.04 S -	2.03 S 2.05 S	2.20 S -	2.04 S -	2.03 S 2.05 S	2.20 S -
OCOR	1.17 d (J=7Hz)	1.16 d (J=7Hz)	1.22 d (J=7Hz)	2.30 tq (J=7Hz)	2.33 tq (J=7Hz)	2.44 tq (J=7Hz)
	1.15 d (J=7Hz)	1.14 d (J=7Hz)	1.16 d (J=7Hz)	1.62 ddq (J=7Hz)	1.68 ddq (J=7Hz)	1.63 ddq (J=7Hz)
	2.56 Septet	2.57 overlapped with H-2, H-3	2.58m (J=7Hz)	1.44 ddq (J=7Hz)	1.48 ddq (J=7Hz)	1.44 ddq (J=7Hz)
				0.91 t (J=7Hz)	0.91 t (J=7Hz)	0.93 t (J=7Hz)
				1.13 d (J=7Hz)	1.13 d (J=7Hz)	1.14 d (J=7Hz)

TABLE 2 ^{13}C-NMR Spectrum of Compound (1)[d].

Carbon atom	δC/p.p.m.	Multiplicity
C-1	138.623[a]	d
C-2	39.40	t
C-3	25.736	t
C-4	135.829	s
C-5	127.38[a]	d
C-6	80.652	d
C-7	50.950	d
C-8	75.128	d
C-9	74.93	d
C-10	135.699	s
C-11	141.938	s
C-12	169.429[b]	s
C-13	122.896	t
C-14	59.85	t
C-15	17.287[c]	q
C-1'	176.188[b]	s
C-2'	34.379	d
C-3'	19.917[c]	q
C-4'	18.917[c]	q
OAC	171.963[b]	s
	21.121[c]	q

a-c Assignments with the same sign may be interchanged.

d The ^{13}C-NMR spectrum was obtained for a $CDCl_3$ solution with a Bruker WH-90 spectrometer. Chemical shifts are expressed in p.p.m. relative to internal Me_4Si.

the trans nature of the lactone ring. J_{7-8} and J_{8-9} are less than 4 Hz and hence must be cis to each other and therefore the H-8 and H-9 must be α-oriented. However, the stereochemistry of the olefinic bonds and the position of the acetate and the isopropyl groups could not be fixed due to th paucity of the material. Hence a single crystal X-ray chromatography was done to confirm the structure and relative stereochemistry of compound (1). The ^{13}C-NMR of compound (1) (Table 2) was in full accord with the structure assigned.

Crystal structure determination of compound (1)

Crystal data for (1), $C_{21}H_{28}O_7$, M=392.4, orthorhmbic, space group $P2_12_12_1$ (D_2^4: No.19), 9=8.648 (1), b=13.567(2), c=17.464(2) A, U=2049. A^3, Dc=1.272 g cm^{-3}, Z=4, F(000)=840;; monochromatic Mo-Kα radiation (α= 0.7107A), =1.021 mm^{-1}.

STRUCTURE DETERMINATION

A unique data set was obtained (2θ limit 48°) using a CAD4F-11M diffractometer with an ω-2θ scan. The structure (Figure A) was solved by direct methods using **MULTAN 78**[30] and was refined to a final R value of 0.069 for 1304 ($|Fo| \geq 3\sigma|Fo|$) reflections by full matrix least squares. The estimated standard deviations in bond length and bond angles are 0.01 A and 0.8° respectively.

A Cruickshank[31] type of weighting scheme was employed with a = 6.0, b = 1.0, c = 0.025. Tables of structure factor, amplitude, thermal parameters and hydrogen parameters are deposited. The atomic scattering factors were taken from the International Tables for X-ray crystallography[32].

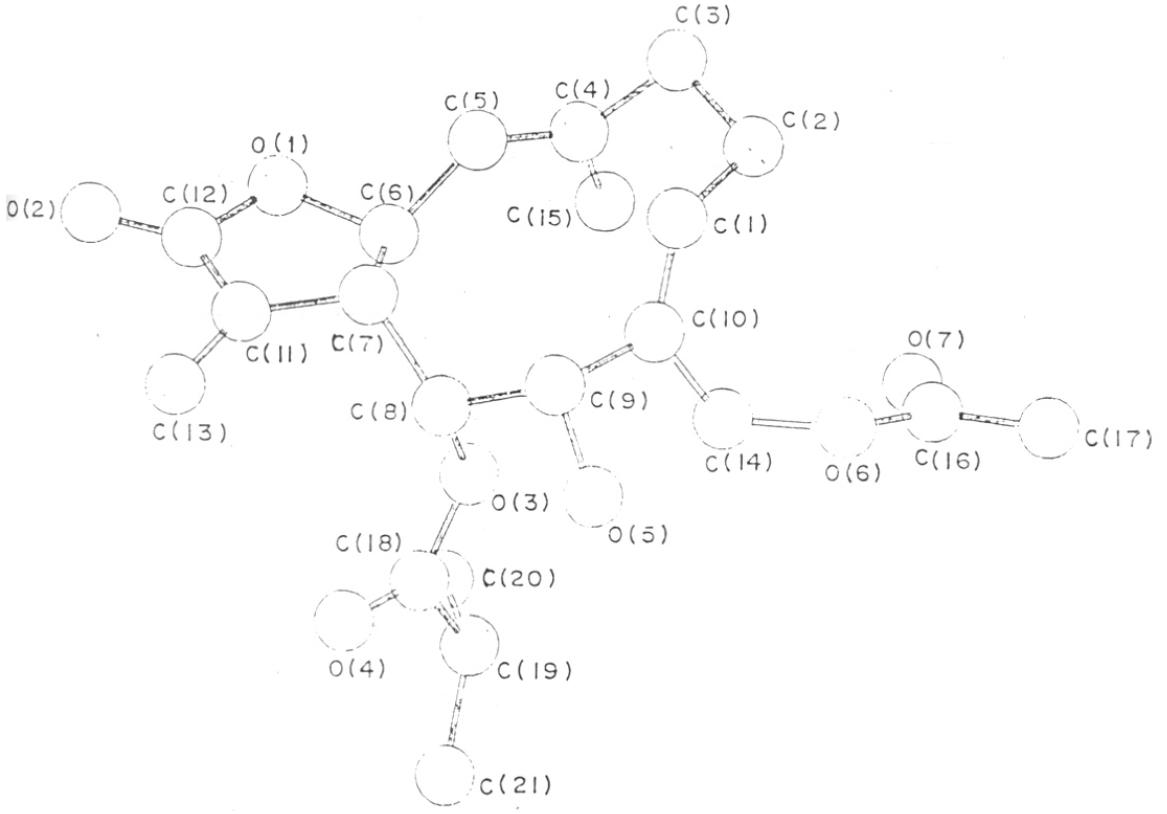

C(3)
C(5)
C(4)
C(2)
O(1)
O(2)
C(12)
C(6)
C(15)
C(1)
C(10)
O(7)
C(11)
C(7)
C(8)
C(9)
C(13)
C(14)
O(6)
C(16)
C(17)
O(3)
O(5)
C(18)
C(20)
O(4)
C(19)
C(21)

Fig. A

Table 3

Fractional atomic coordinates ($\times 10^4$) with their standard deviations in parantheses and equivalent values of the isotropic temperature factor coefficients.

$$Beq = \frac{4}{3}(B_{11}a^2+B_{22}b^2+B_{33}c^2)$$

	X	Y	Z	Beq(A^{o2})
C(1)	5566(9)	10356(5)	4579(4)	3.02
C(2)	4256(9)	9920(7)	5006(4)	2.69
C(3)	4457(10)	8783(6)	5083(5)	2.91
C(4)	4860(10)	8389(6)	4315(5)	2.96
C(5)	6353(10)	8330(6)	4114(5)	3.15
C(6)	7029(9)	8340(5)	3348(5)	3.51
C(7)	8182(7)	9200(5)	3225(4)	2.90
C(8)	7582(7)	10189(5)	2909(4)	2.98
C(9)	7079(8)	10956(5)	3482(4)	3.05
C(10)	5584(8)	10752(5)	3894(4)	3.55
C(11)	9403(10)	8713(6)	2761(5)	3.41
C(12)	9252(11)	7674(6)	2826(5)	3.54
C(13)	10534(11)	9133(9)	2328(7)	3.21
C(14)	4110(8)	10971(7)	3454(5)	3.91
C(15)	3553(12)	8213(8)	3772(6)	6.23
C(16)	1700(11)	11580(8)	3979(7)	4.77
C(17)	1036(14)	12465(9)	4346(7)	4.81
C(18)	6486(12)	10175(8)	1650(5)	3.53
C(19)	4967(11)	10080(8)	1215(5)	4.19
C(20)	4401(16)	9087(13)	1255(9)	3.80
C(21)	5068(13)	10584(10)	C463(7)	3.62
O(1)	7914(6)	7440(4)	3205(3)	3.70
O(2)	10074(8)	6999(4)	(2613(4)	4.11
O(3)	6286(5)	10004(4)	2391(3)	4.35
O(4)	7708(7)	10385(7)	1357(3)	4.10
O(5)	6991(6)	11885(4)	3114(4)	4.00
O(6)	3241(6)	11747(4)	3833(3)	3.86
O(7)	1095(7)	10826(5)	3859(4)	7.54

Table 4

Intramolecular bond lengths (Å) and angles (°) with their standard deviations in parentheses.

C(1)-C(2)	1.48(1)Å	C(1)-C(10)	1.31(1)Å
C(2)-C(3)	1.56(1)	C(3)-C(4)	1.48(1)
C(4)-C(5)	1.34(1)	C(4)-C(15)	1.50(1)
C(5)-C(6)	1.46(1)	C(6)-C(7)	1.55(1)
C(6)-O(1)	1.462(9)	C(7)-C(8)	1.54(1)
C(7)-C(11)	1.49(1)	C(8)-C(9)	1.51(1)
C(8)-O(3)	1.463(8)	C(9)-C(10)	1.51(1)
C(9)-O(5)	1.418(9)	C(10)-C(14)	1.52(1)
C(11)-C(12)	1.42(1)	C(11)-C(13)	1.36(1)
C(12)-O(1)	1.37(1)	C(12)-O(2)	1.22(1)
C(14)-O(6)	1.45(1)	C(16)-O(6)	1.38(1)
C(16)-O(7)	1.17(1)	C(16)-C(17)	1.48(2)
C(18)-O(3)	1.33(1)	C(18)-O(4)	1.21(1)
C(18)-C(19)	1.52(1)	C(19)-C(20)	1.43(2)
C(19)-C(21)	1.48(2)		

C(2)-C(1)-C(10)	129.3(7)°	C(1)-C(2)-C(3)	110.7(7)°
C(2)-C(3)-C(4)	107.7(7)	C(3)-C(4)-C(5)	119.0(8)
C(3)-C(4)-C(15)	117.0(8)	C(5)-C(4)-C(15)	123.5(8)
C(4)-C(15)-C(6)	128.7(8)	C(5)-C(6)-C(7)	113.0(6)
C(5)-C(6)-O(1)	111.0(6)	C(7)-C(6)-O(1)	105.6(6)
C(6)-C(7)-C(8)	119.2(6)	C(8)-C(7)-C(11)	115.5(6)
C(6)-C(7)-C(11)	101.4(6)	C(7)-C(8)-C(9)	117.4(6)
C(7)-C(8)-O(3)	109.3(5)	C(9)-C(8)-O(3)	108.0(5)
C(8)-C(9)-C(10)	116.0(6)	C(8)-C(9)-O(5)	109.1(6)
C(10)-C(9)-O(5)	109.6(6)	C(1)-C(10)-C(9)	121.4(6)
C(1)-C(10)-C(14)	122.1(7)	C(9)-C(10)-C(14)	116.3(6)
C(7)-C(11)-C(12)	109.4(7)	C(7)-C(11)-C(13)	128.8(8)
C(12)-C(11)-C(13)	121.8(9)	C(11)-C(12)-O(1)	110.3(7)

..2/-

Table 4 (contd.)

C(11)-C(12)-O(2)	131.9(8)	O(1)-C(12)-O(2)	117.7(8)
C(10)-C(14)-O(6)	110.3(6)	C(17)-C(16)-O(6)	108.9(9)
C(17)-C(16)-O(7)	128.0(10)	O(6)-C(16)-O(7)	123.0(10)
C(19)-C(18)-O(3)	111.0(8)	C(19)-C(18)-O(4)	124.3(9)
O(3)-C(18)-O(4)	124.7(9)	C(18)-C(19)-C(20)	110.5(10)
C(18)-C(19)-C(21)	110.6(9)	C(20)-C(19)-C(21)	119.7(10)
C(6)-O(1)-C(12)	109.3(6)	C(8)-O(3)-C(18)	118.2(6)
C(14)-O(6)-C(16)	117.8(7)		

Table 5

Some important torsion angles.

Ten membered ring

C(1)-C(2)-C(3)-C(4)	-47.7(9)
C(2)-C(3)-C(4)-C(5)	89.8(9)
C(3)-C(4)-C(5)-C(6)	-154.3(8)
C(4)-C(5)-C(6)-C(7)	120.7(9)
C(5)-C(6)-C(7)-C(8)	-90.8(8)
C(6)-C(7)-C(8)-C(9)	91.3(8)
C(7)-C(8)-C(9)-C(10)	-72.2(8)
C(8)-C(9)-C(10)-C(1)	97.4(8)
C(9)-C(10)-C(1)-C(2)	-166.4(7)
C(10)-C(1)-C(2)-C(3)	110.9(9)

Five membered ring

C(6)-O(1)-C(12)-C(11)	5.4(9)
O(1)-C(12)-C(11)-C(7)	8.3(10)
C(12)-C(11)-C(7)-C(6)	-17.2(8)
C(11)-C(7)-C(6)-O(1)	19.7(7)
C(7)-C(6)-O(1)-C(12)	-16.2(8)

Table 6

Some important Torsional Angles (in degrees)

C(1) - C(2) - C(3) - C(4)	56
C(2) - C(3) - C(4) - C(5)	-89
C(3) - C(4) - C(5) - C(6)	153
C(4) - C(5) - C(6) - C(7)	-75
C(5) - C(6) - C(7) - C(8)	-63
C(6) - C(7) - C(8) - C(9)	132
C(7) - C(8) - C(9) - C(10)	-51
C(8) - C(9) - C(10)- C(1)	-53
C(9) - C(10)- C(1) - C(2)	151
C(10)- C(1) - C(2) - C(3)	-118
C(9) - C(10)- O(1) - C(1)	112
C(14)- C(10)- O(1) - C(1)	-111
C(10)- O(1) - C(1) - C(2)	119
C(15)- C(4) - O(2) - C(5)	-117
C (4)- O(2) - C(5) - C(6)	116
C(3) - C(4) - C(5) - O(2)	-103

D I S C U S S I O N

The atomic co-ordinates for non-hydrogen atoms are given in Table 3. A view of the molecule is shown in Fig.A. Bond lengths and angles are listed in Table 4. The conformation of the ten membered ring in chair-chair (Table 5) and is similar to that found in the structure of Tamaulipin[33]. Thus the compound is a trans-trans germacranolide. The trans annular separation C(1).....C(5) is 2.95 A. However, there is no trans annular interaction as the two double bonds are trans with respect to each other. The five membered ring has an envelope conformation. The molecules are held togethr by an intramolecular hydrogen bond between O(2) (X,Y,Z) and O(5) (1-X, ½ + Y, ½ + Z) [2.48Å].

Compound (4)

Compound (4), colourless gum, molecular formula, $C_{22}H_{30}O_7$ (M^+, 406), showed in its IR spectrum (Fig. 8) the presence of a hydroxy group (3560 cm^{-1}), an α,β-unsaturated-γ-lactone (1760 cm^{-1}) and an acetate (1740 cm^{-1} and 1240 cm^{-1}). Its ^{1}H-NMR spectrum (Table 1) while supporting the α,β-unsaturated-γ-lactone by the characteristic signals at δ 5.90 and 6.40 due to the exomethylene group, also exhibited the presence of a vinylic methyl group at 1.82, an acetyl group at 2.04, an 2-methyl-butyryloxy methyl groups at 0.91(t) and 1.13d, two olefinic hydrogens 4.68 at 4.48 and 4.68 assignable to CH_2OR group.

The nature of the hydroxyl group in compound (4) was determined as secondary by its acetylation to give (5) and by oxidation to give a ketone (6). This led to the assignment of the signal at 4.42 in the

^{1}H-NMR of compound (4) to CHOH as it moved downfield to 5.41 in (5) and was absent in compound (6). This observation further revealed that CH_2OR group must be present as CH_2OAc or $-CH_2-O-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{CH}}-CH_2CH_3$. The multiplicity of the signals due to exomethylene group of the α,β -unsaturated -γ-lactone indicated that in compound (4) had an oxygen function at C-8.

A critical comparison of the physical constants and the spectral data revealed its identity with one of the compound possessing the same structure (4) isolated from the related species, B.acmella[28]. The spectral data (^{1}H-NMR, Table 1) of its derivatives (5) and (6) were in agreement with the structure proposed for compound (4).

PAGE NO. 70 TO 71 MISS

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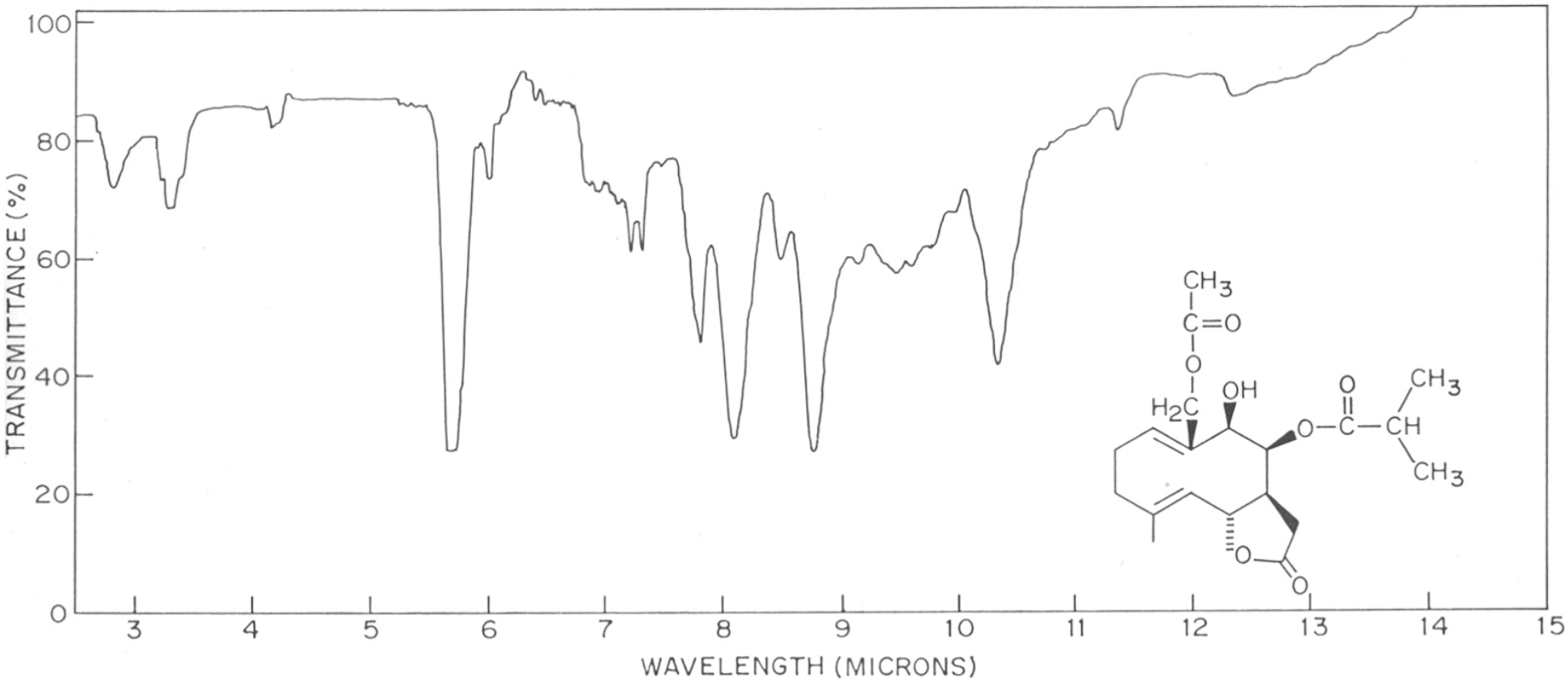


FIG. 1 IR SPECTRUM OF COMPOUND (1)

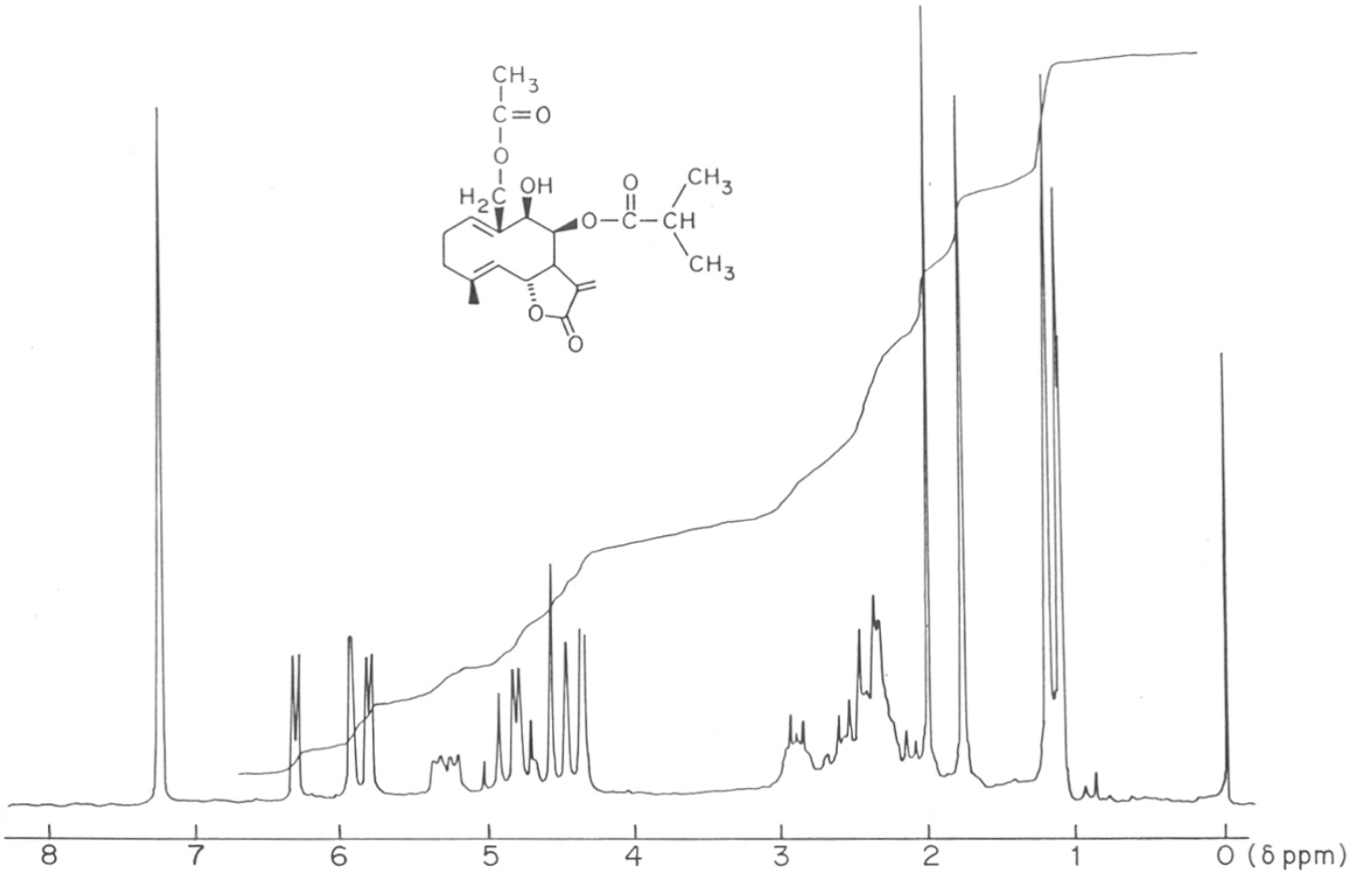


FIG. 2. ^{1}H NMR SPECTRUM OF COMPOUND (1)

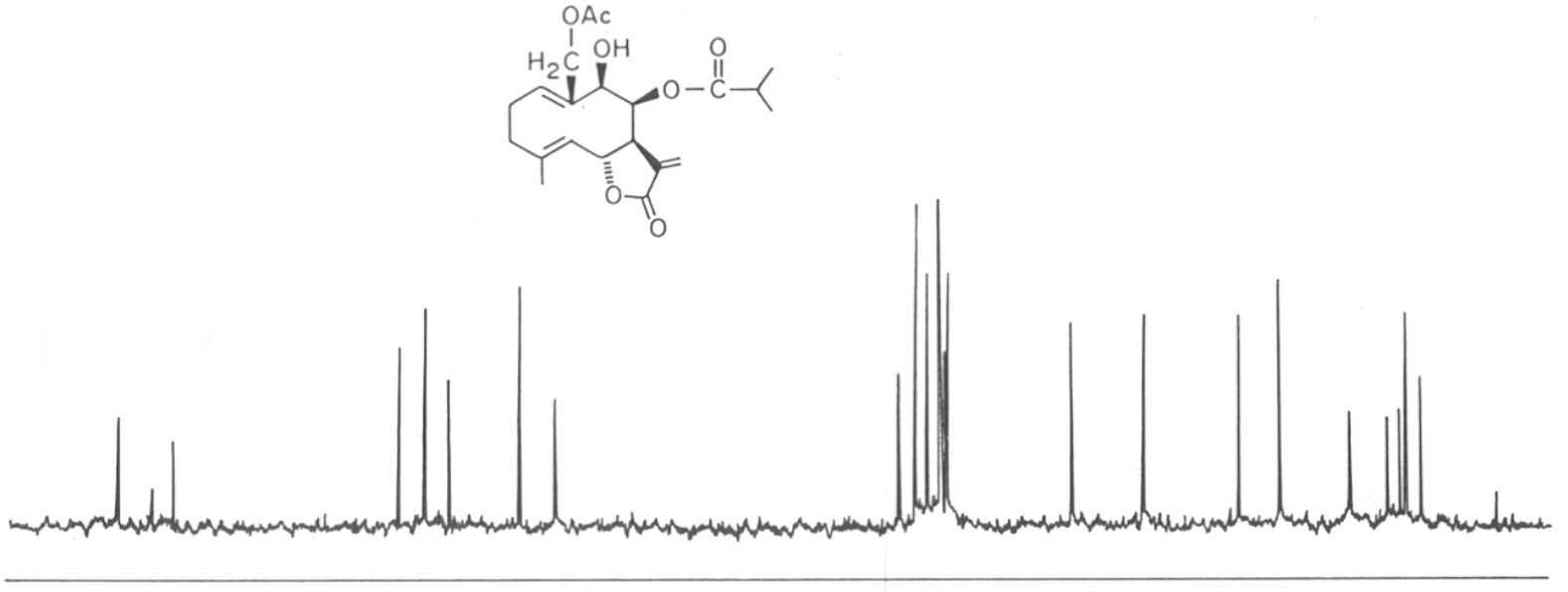


FIG. 3. ^{13}C NMR SPECTRUM OF COMPOUND (1)

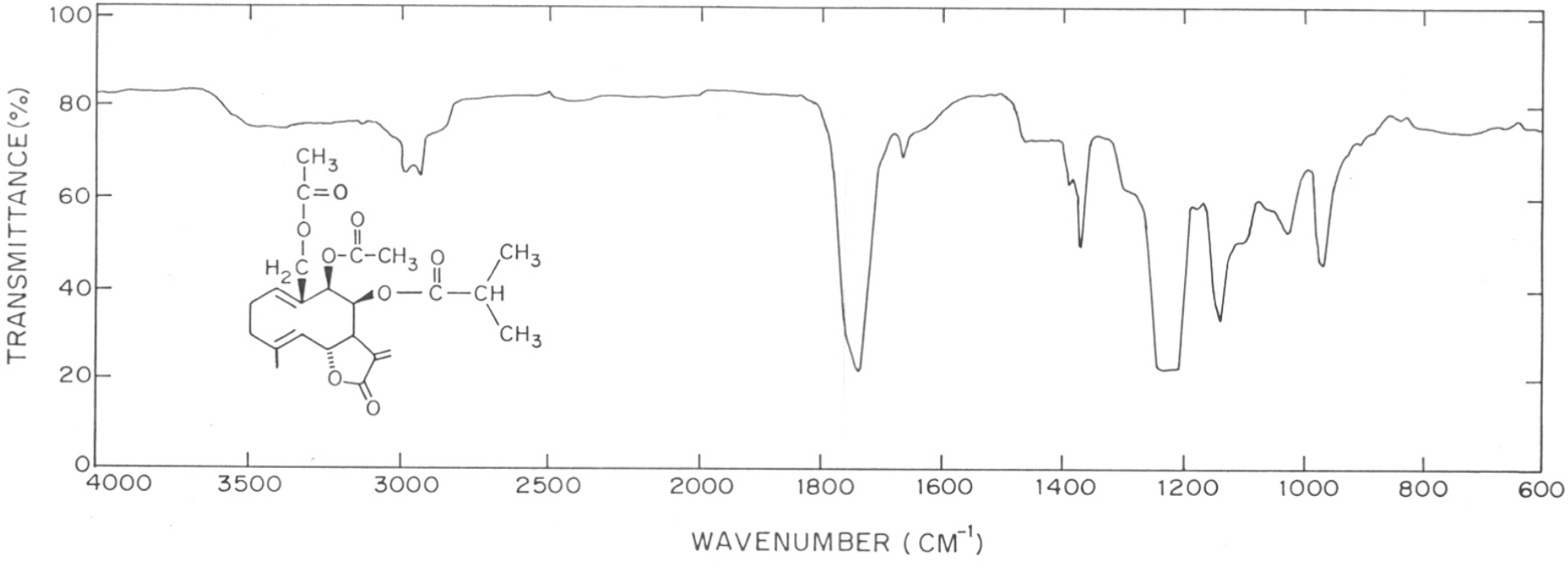


FIG. 4 IR SPECTRUM OF COMPOUND (2)

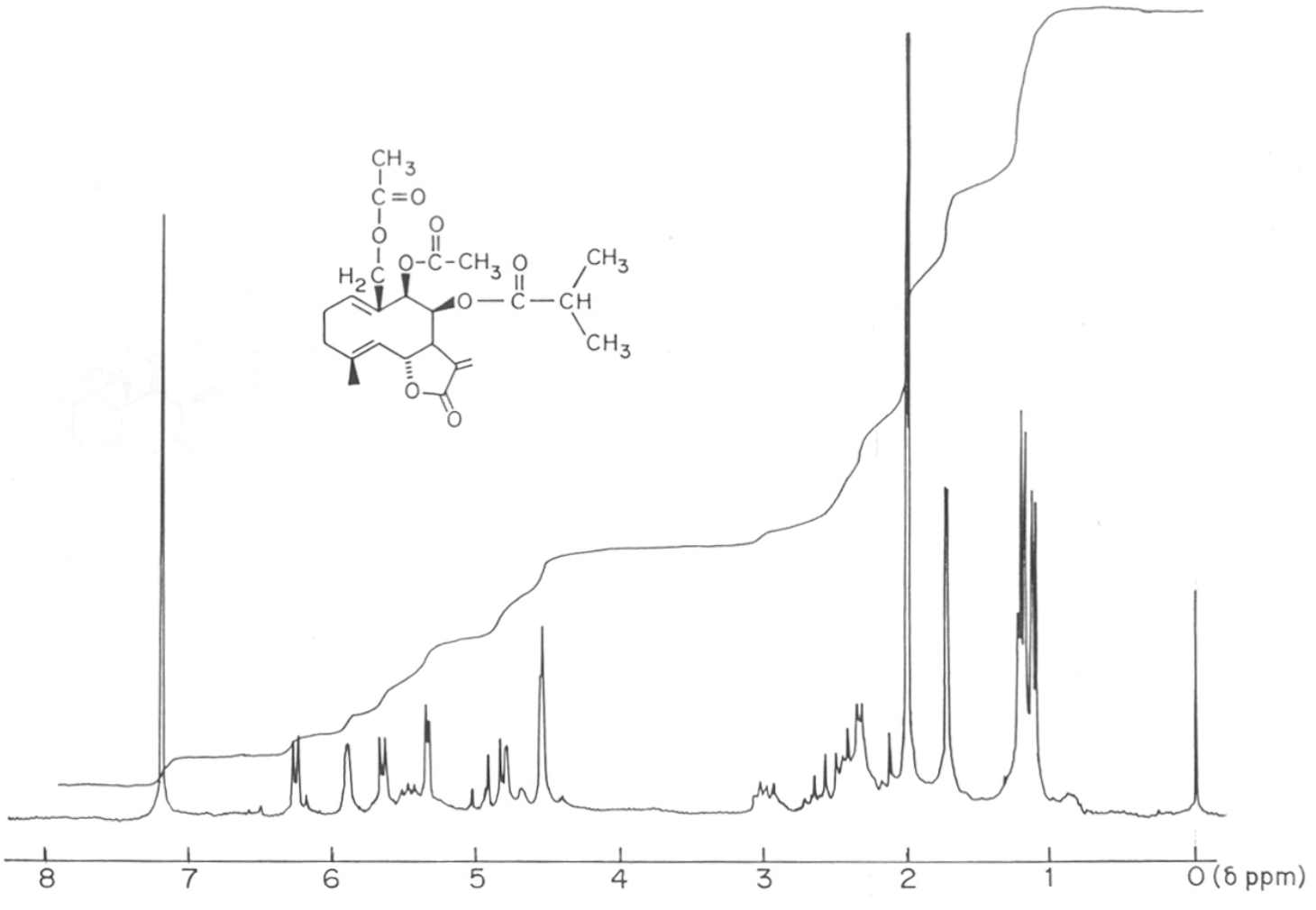


FIG. 5. ^{1}H NMR SPECTRUM OF COMPOUND(2)

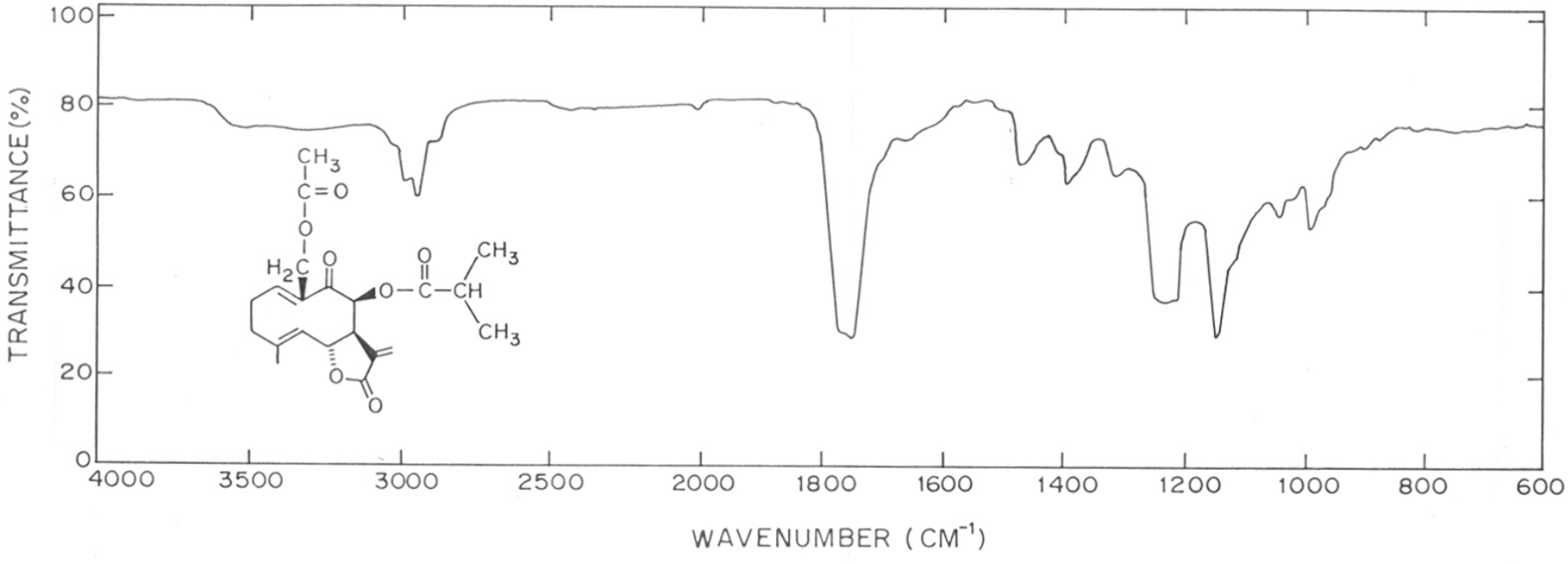


FIG. 6 IR SPECTRUM OF COMPOUND (3)

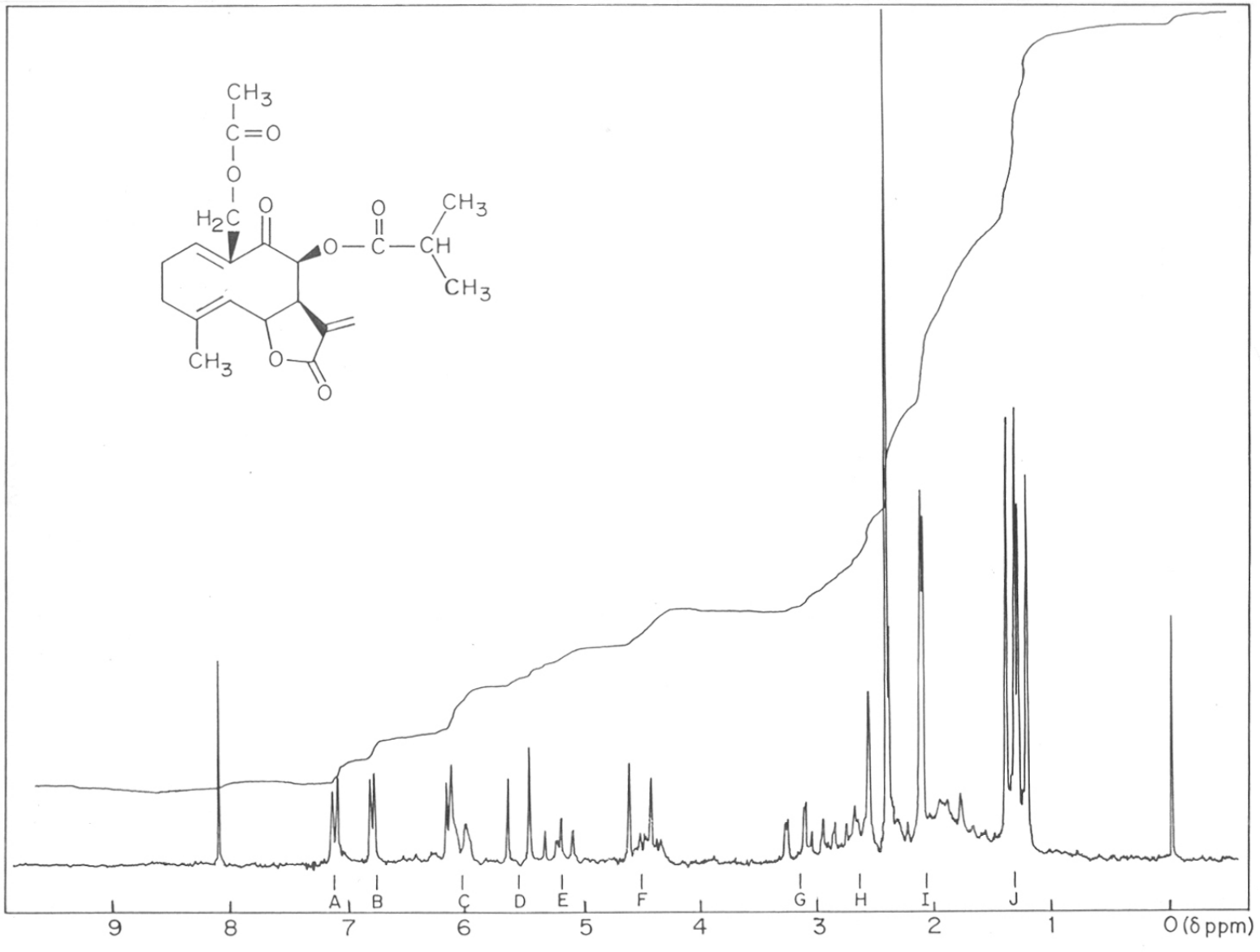


FIG. 7 ^{1}H NMR SPECTRUM OF COUMPOUND (3)

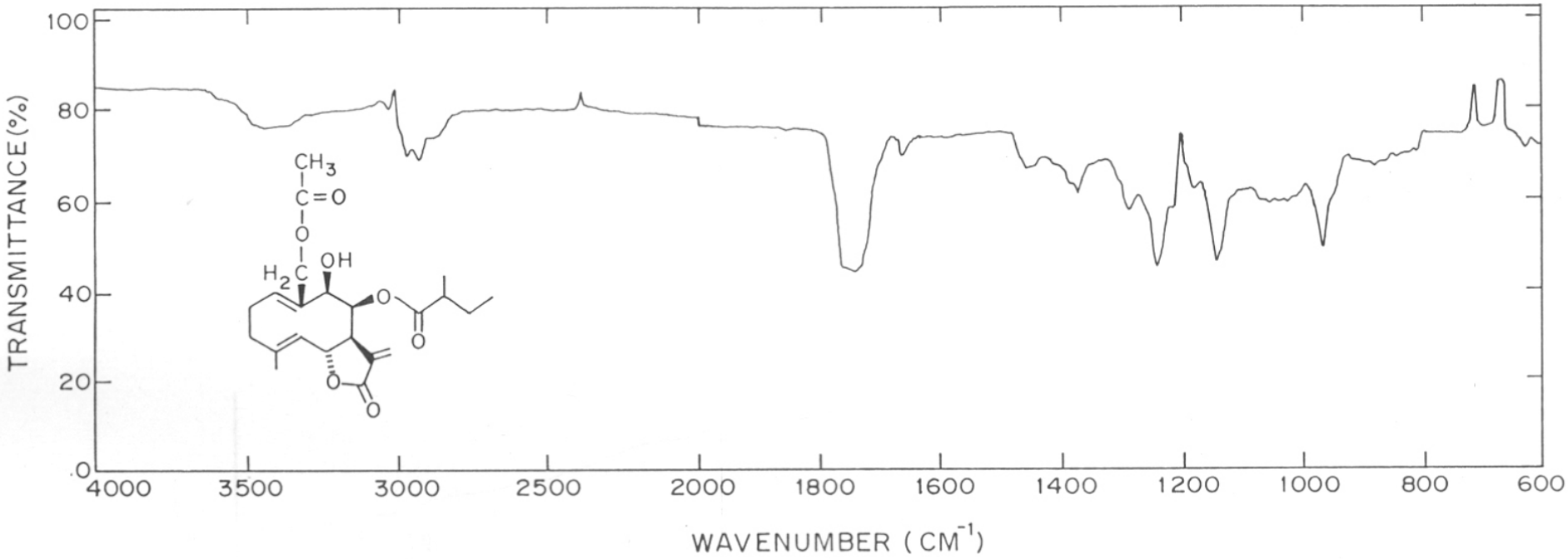


FIG. 8 IR SPECTRUM OF COMPOUND (4)

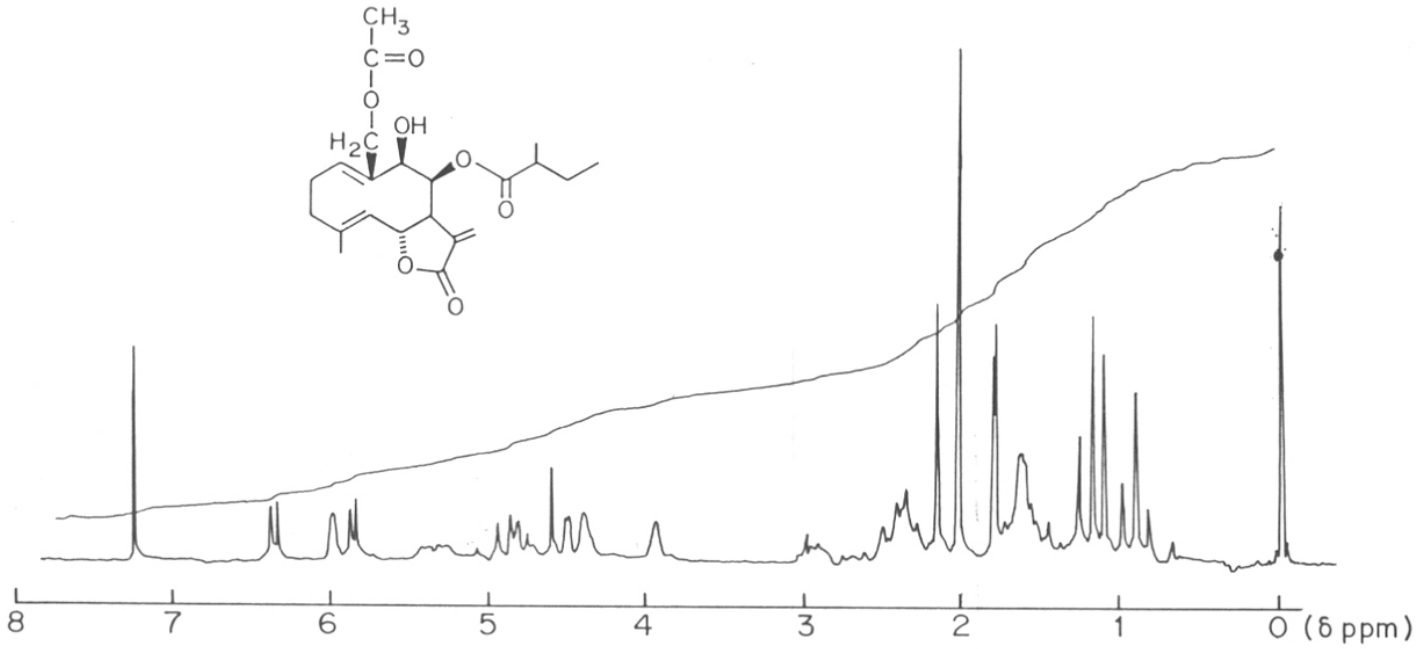


FIG. 9 ^{1}H NMR SPECTRUM OF COMPOUND (4)

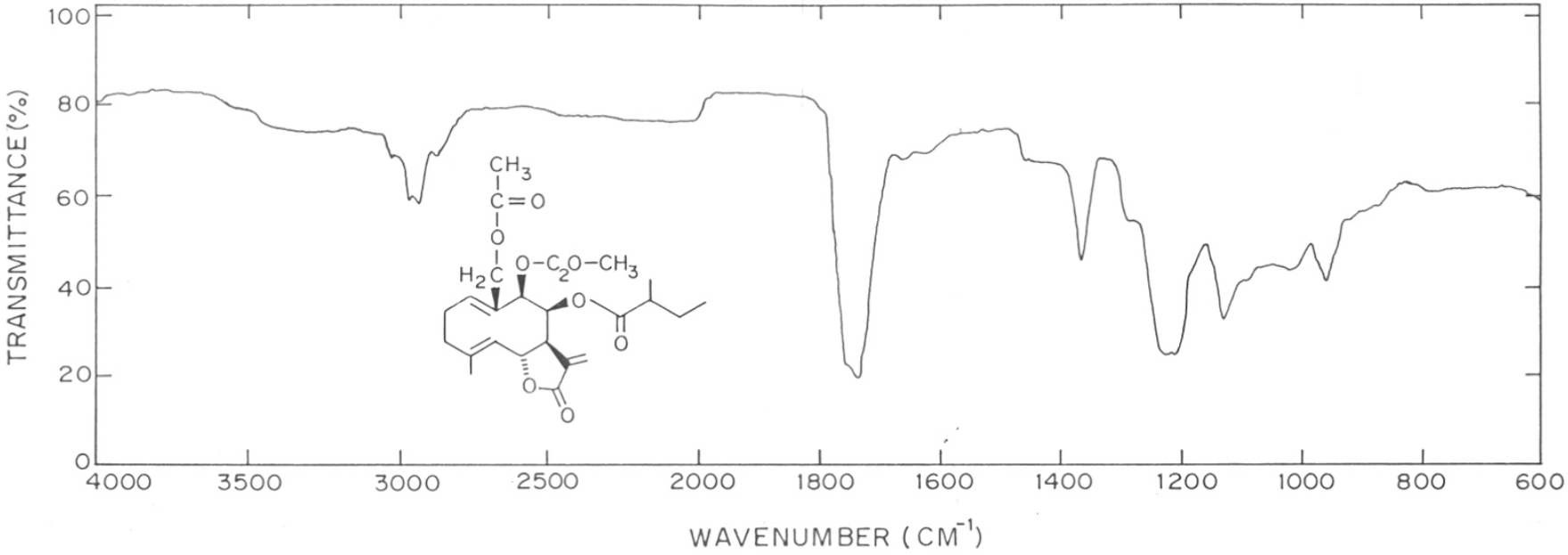


FIG. 10 IR SPECTRUM OF COMPOUND (5)

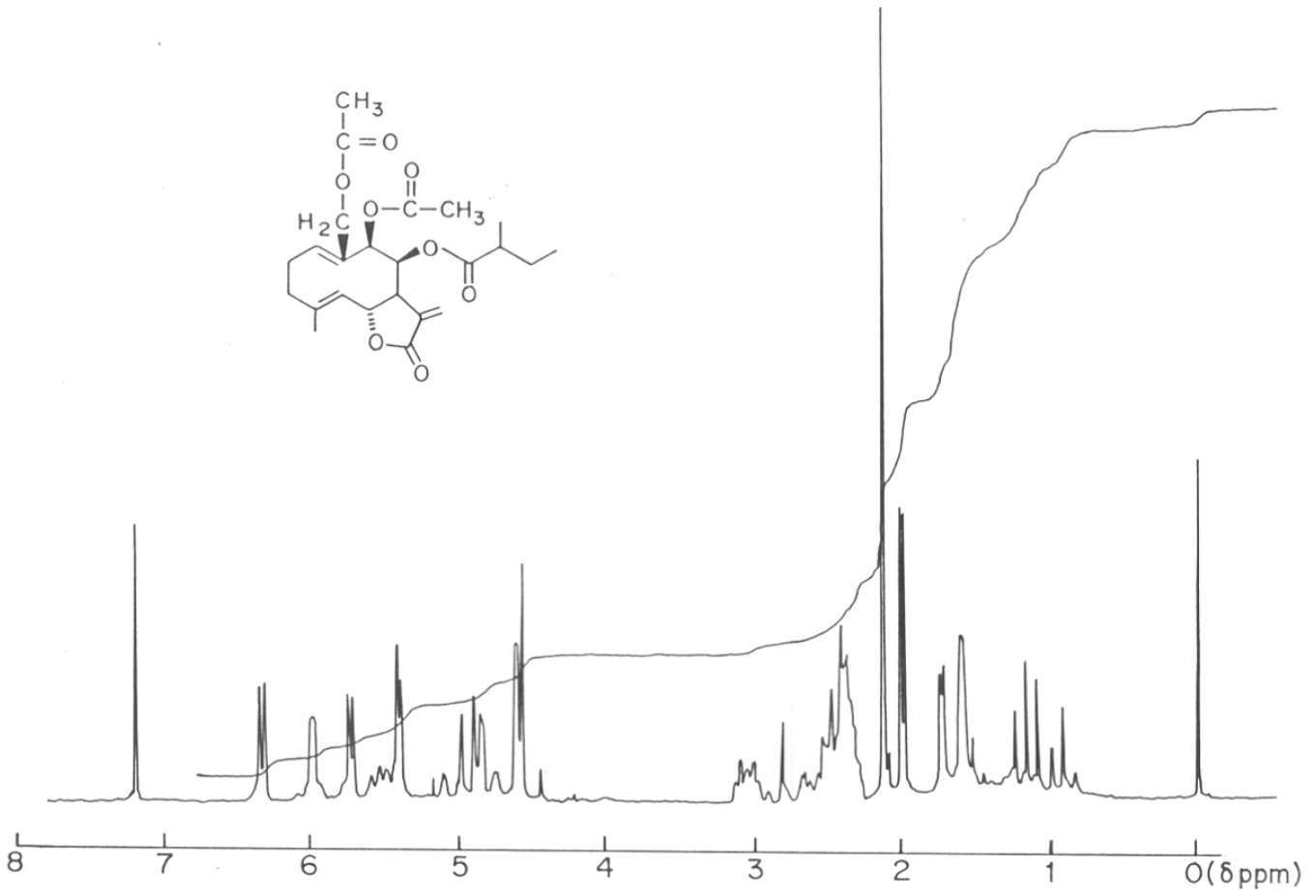


FIG. 11 ^{1}H NMR SPECTRUM OF COMPOUND (5)

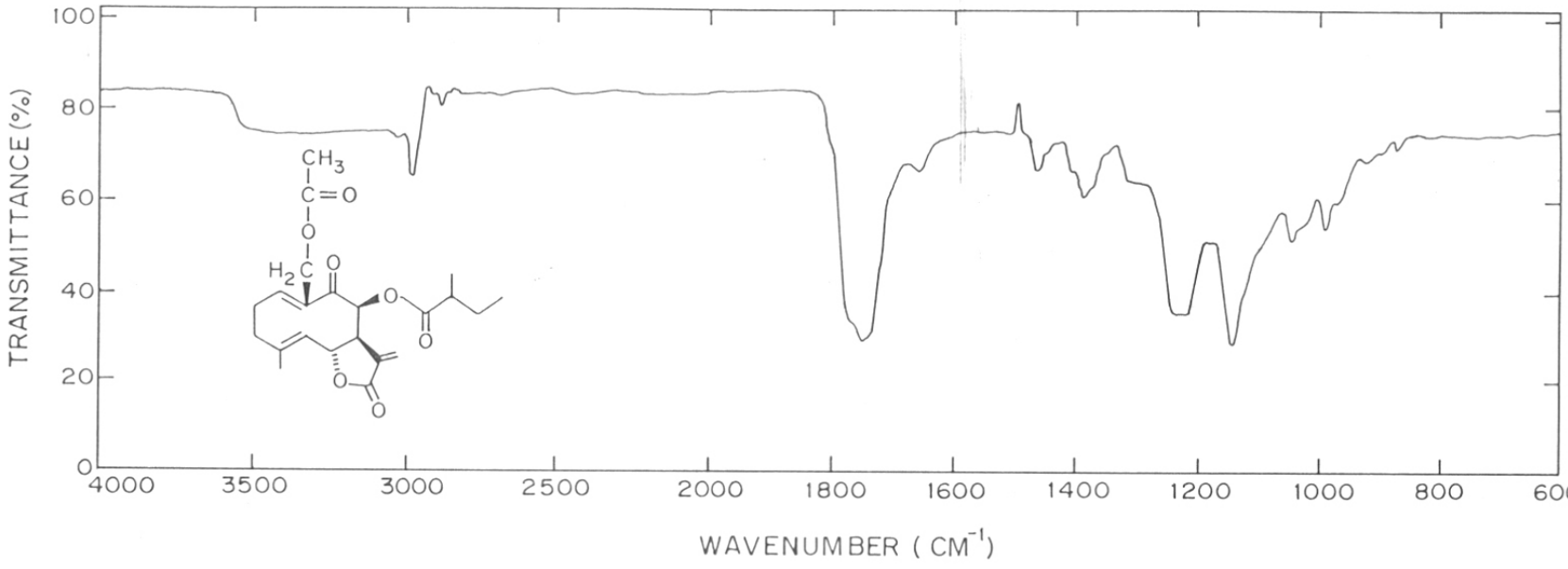


FIG. 12 IR SPECTRUM OF COMPOUND (6)

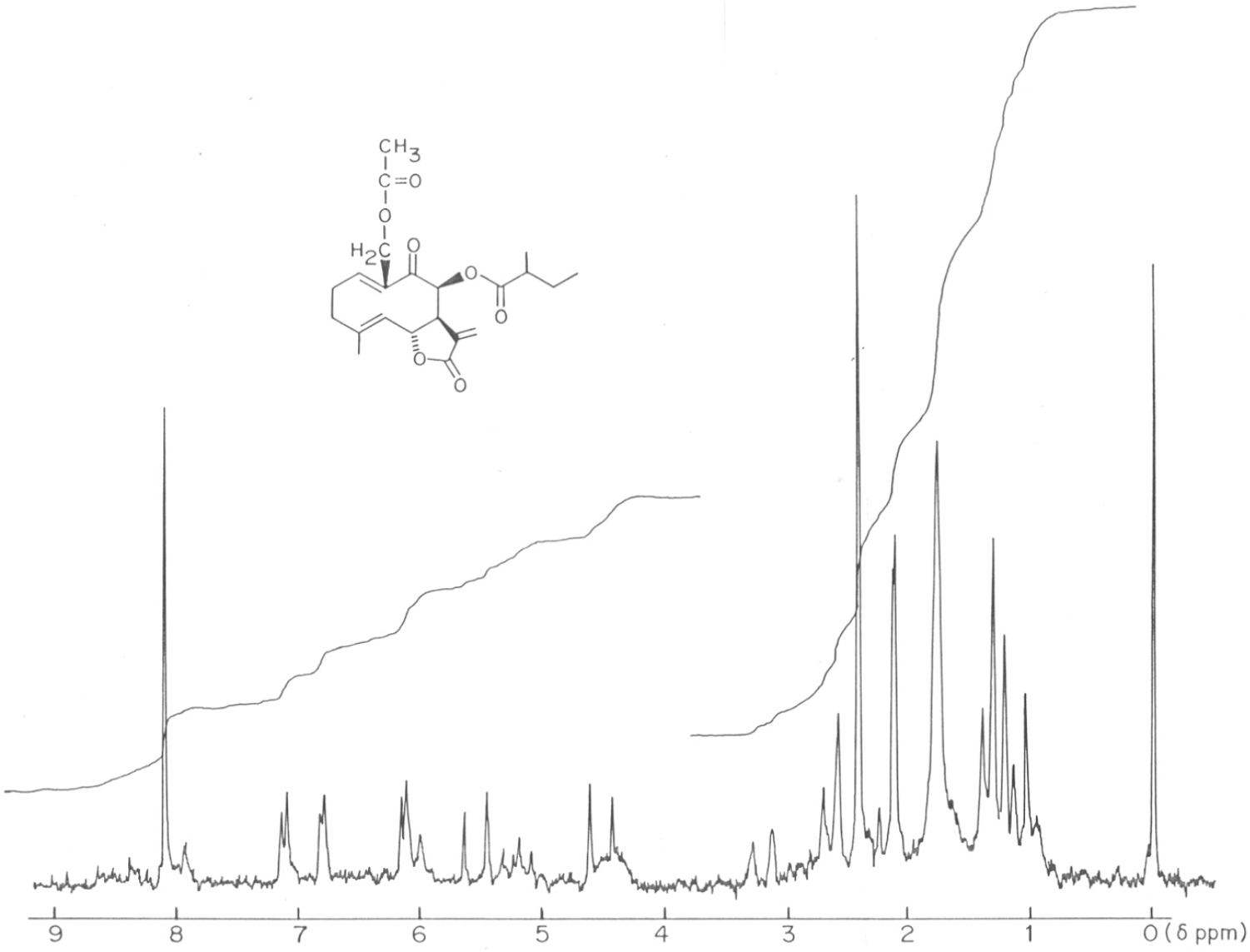


FIG. 13. ^{1}H NMR SPECTRUM OF COMPOUND(6)

ABSTRACT

A B S T R A C T

The thesis deals with the isolation, structure elucidation and chemical tansformations of terpenoids mainly sesquiterpene lactones and tetranortriterpenoids. The thesis comprises of three chapters.

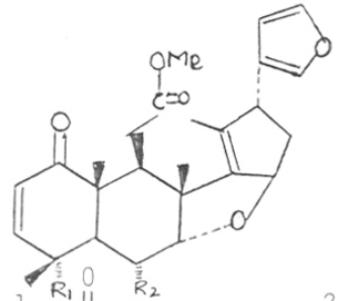
CHAPTER I: CHEMICAL CONSTITUENTS OF AZADIRACHTA INDICA A JUSS, A REVIEW FROM 1986-1988

Review articles describing the constituents and biological activities of neem have already appeared in literature covering the period upto 1986[1,2]. In this chapter the literature data pertaining to the above have been upgraded upto 1988.

CHAPTER II: CHEMICAL INVESTGATION OF AZADIRACHTA INDICA A JUSS

Two new tetranortriterpenoids, an aldehyde named nimbanal (1) and the other salannol-3-acetate (2) have been isolated from the ethanol extract of neem seeds. The structure of (1) has been established by spectral data while that of (2) has been proved by its correlation with salannol[2](3) and salannin (4). Evidence leading to the assignment of structures to these compounds are discussed in this chapter.

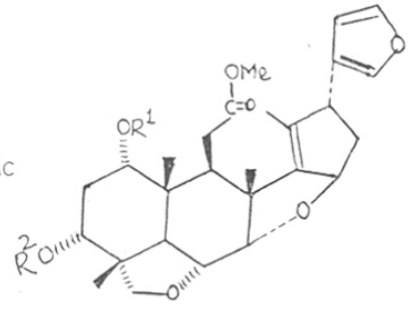
(1)



(2) R^1 = $-\overset{O}{\overset{\|}{C}}-CH_2-CH(CH_3)_2$, R^2=Ac

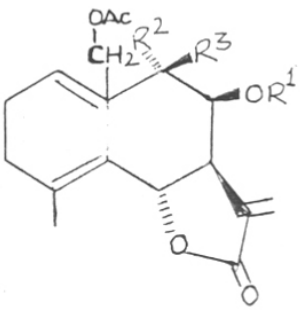
(3) R^1 = $-\overset{O}{\overset{\|}{C}}-CH_2-CH(CH_3)_2$, R^2

(4) R^1 = $-\overset{O}{\overset{\|}{C}}-C(H)=C(CH_3)_2$, R^2=Ac



CHAPTER III: CHEMICAL INVESTIGATION OF BLAINVILLEA LATIFOLIA (D.C.)

Two germacranolides possessing the same carbon skeleton but differing in the side chain (**5** and **6**) have been isolated from the acetone extract of Blainvillea latifolia (D.C.)



(**5**) R^1 = isobutyryloxy, R^2 = H, R^3 = OH

(**6**) R^1 = 2-Methylbutyryloxy R^2 = H, R^3 = OH

(**7**) R^1 = isobutyryloxy R^2 = H, R^3 = OAc

(**8**) R^2 = R^3 = O

The structure and stereochemistry of compound (**5**) identified as 8 -isobutyryloxy-9 -hydroxy-10-acetoxy methyl germacrene-6,7-olide have been established by the combination of chemical, spectroscopic and X-ray crystallographic studies. The structure of the other compound (**6**) recently isolated from a related species B.acmella[3] follows from the comparision of the spectral data of (**5**) and its derivatives (**7**) and (**8**). These aspects are discussed in detail.

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My special thanks are due to Mr. George Samuel for recording 90 MHz PMR and ^{13}C-NMR spectra and for spin decoupling studies of many of the compounds reported here. The assistance received from the staff of the spectroscopic, microanalytical and entomology sections of this laboratory is gratefully acknowledged.

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(S.R. Rojatkar)

May, 1989
NCL, Poona-8.