CHEMICAL INVESTIGATION OF SOME INDIAN TREES AND SYNTHESIS OF SOME RELATED COMPOUNDS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

by

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PUNE - 411 008 (India)

JANUARY 1979

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PART - I

PHENOLIC CONSTITUENTS OF THE BARK AND HEARTWOOD OF CHLOROXYLON SWIETENIA DC.

INTRODUCTION

The family Rutaceae comprises about one hundred and fifty genera with sixteen hundred species. Because of their medicinal properties, these plants are very well known. The order Rutales is formed by the families, Rutaceae, Simaroubaceae, Meliaceae, Bruseraceae, and Cneoraceae, of which only Rutaceae and Meliaceae are known to contain coumarins. Alkaloids with diverse structural types, viz. quinoline, furoquinoline, acridine, quinazoline, protoberberine, 1,2-benzophenanthridine, aporphine, protopine, etc. are reported from this family. Different types of coumarins such as simple coumarins, furano-coumarins, dihydrofuranocoumarins, chromenocoumarins and bis-coumarins have been encountered in these plants. Both the classes of compounds, coumarins and alkaloids, are very characteristic of this family. Lignans are also isolated, but the number is comparatively very small. In the recent years, the rutaceous plants are being examined for their chemical constituents in large number. The work done on these classes of compounds is reviewed from time to time. Seshadri et al.[1] have reviewed coumarins till 1970. But the reviews compiled by Pakrashi et al.[2] and very recently by Waterman et al.[3] on alkaloids and coumarins respectively are restricted only to the Rutaceae family.

The genus Chloroxylon has only one species Swietenia. In "A dictionary of flowering plants and ferns" (J.C.Willis, revised by H.K.Airyshaw, 7th ed., Cambridge University Press, 1966), Chloroxylon D.C. together with Flindersia is classified under Flindersiaceae (Engl.), "somewhat intermediate between Rutaceae and Meliaceae".

Chloroxylon swietenia DC (East Indian satinwood) is a moderate sized tree with a rather short-bole and spreading crown, common in dry deciduous forests throughout the Indian peninsula and in Ceylon, where it attains a large size.[4] The wood is cream coloured to golden yellow, darker in the centre but with no distinct heartwood. Its lusture and silvergrain gives it a special place among Indian ornamental woods. In addition, it is strong, hard and heavy, durable to insect and fungus attack. It is difficult to saw and machine; because of its interlocked and twisted fibers, it turns well and finishes to a beautiful surface, taking a high and lasting polish. It can be used for all classes of furniture, panelling, building timber and a variety of other purposes. The wood can cause skin eruptions, probably because of its alkaloidal constituents.

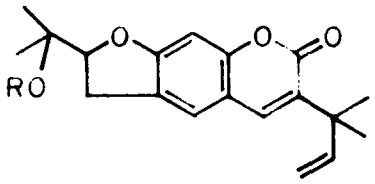
From the bark Mookerjee and Bose[5] isolated skimmianine (XIII), a furoquinoline and one of the most widely distributed alkaloids. Kalyaneraman and Pai[6] found the coumarin, rutamarin (II), but no skimmianine is found in the bark from Madras.

King et al.[7] isolated xanthyletin (III), xanthoxyletin (IV) and 7-demethylsuberosin (IX) from the heartwood. Vrkoc and Sedmera[8] have examined the heartwood from Madhya-Pradesh and reported the isolation of xanthoxyletin, 7-dimethylsuberosin, luvangetin (V), aesculetin dimethyl ether (X), nodakenetin (XI), skimmianine (XIII) and its demethoxy derivative (XIV), r-fagarine.

Das et al.[9] have isolated xyletanin (XV) from the leaves of C.xyletania.

Bose et al.[10] examined the gum of C.xyletania. By the mk autohydrolysis of the gum, they obtained a degraded gum, a sugar mixture consisting of L-arabinose, D-galactose and three other minor sugars. Complete acid hydrolysis of the degraded gum furnished L-arabinose, D-galactose and an uronic acid fraction.

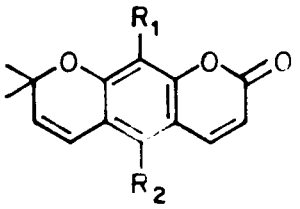
Mujumdar[11,12] from this group had earlier examined bark and heartwood obtained from Kalghatgi (Dharwar). From the heartwood, he isolated 2,4-dihydroxy-5-prenylcinnamic acid (XVI), skimmianine (XIII), an alkaloid, in addition to



CHALEPIN (I); R = H

HELIETTIN (I); R = H

RUTAMARIN (II); R = Ac

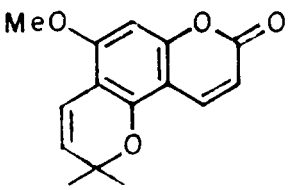


XANTHYLETIN (III); $R_1 = R_2 = H$

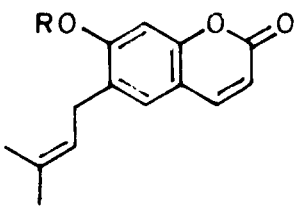
XANTHOXYLETIN (IV); $R_1 = H$, $R_2 = OMe$

LUVANGETIN (V); $R_1 = OMe$, $R_2 = H$

DEMETHYLLUVANGETIN (VI); $R_1 = OH$, $R_2 = H$

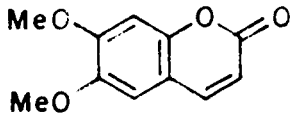


ALLOXANTHOXYLETIN (VII)

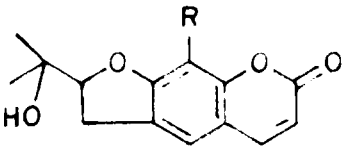


SUBEROSIN (VIII); R = Me

7-DEMETHYL SUBEROSIN (IX); R = H

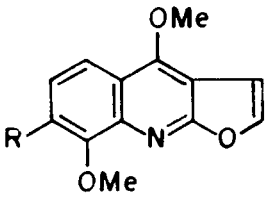


AESCULETIN DIMETHYL-ETHER (X)



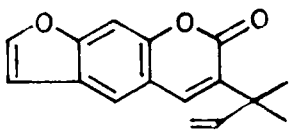
NODAKENETIN (XI); R = H

8-PRENYLNODAKENETIN (XII); R =

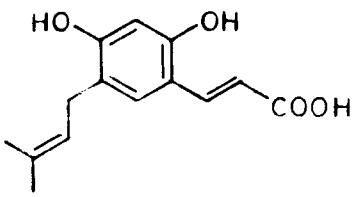


SKIMMIANINE (XIII); R = OMe

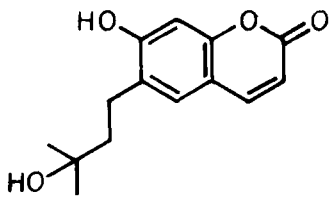
γ-FAGARINE (XIV); R = H



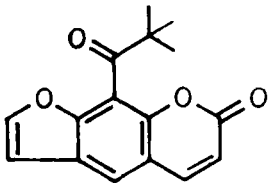
XYLOTENIN (XV)



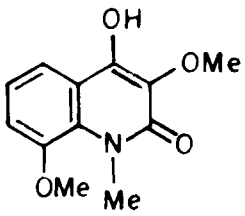
2,4-DIHYDROXY-5-PRENYL CINNAMIC ACID (XVI)



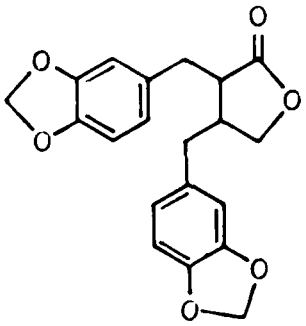
SWIETENOL (XVII)



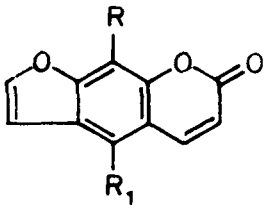
SWIETENONE (XVIII)

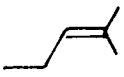
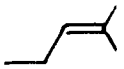
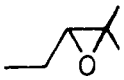
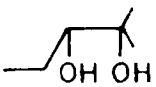
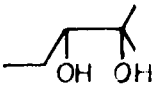
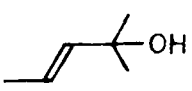
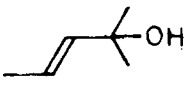


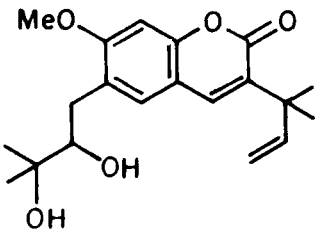
SWIETENIDIN-A (XIX)



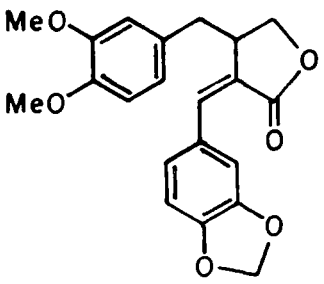
HINOKININ (XX)



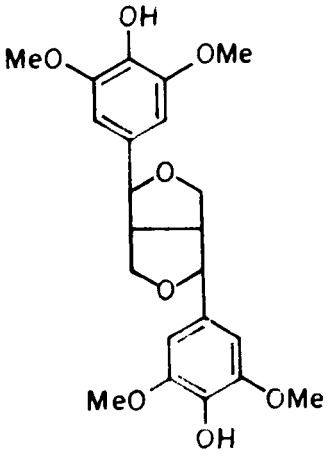
		R	R_1
ISOPIMPINELLIN	(XXI)	OMe	OMe
SWIETENOCOUMARIN-A	(XXII)		H
,,	B (XXIII)		OMe
,,	C (XXIV)		H
,,	D (XXV)		OMe
,,	E (XXVI)		H
,,	F (XXVII)		OMe
,,	G (XXVIII)		OMe
,,	H (XXIX)		H



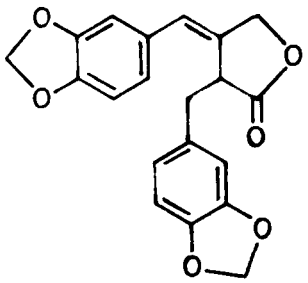
SWIETENOCOUMARIN-I (XXX)



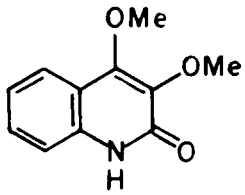
COLLINUSIN (XXXI)



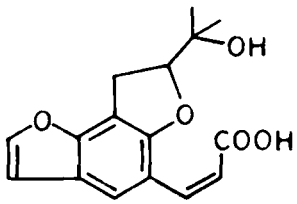
SYRINGARESINOL (XXXII)



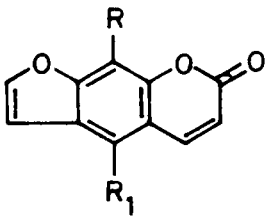
SAVININ (XXXIII)



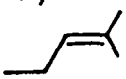
SWIETENIDIN-B (XXXIV)



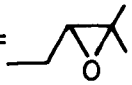
(XXXV)



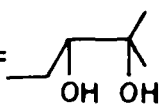
ALLO-IMPERATORIN METHYL-ETHER (XXXVI);
R = OMe, R_1 =

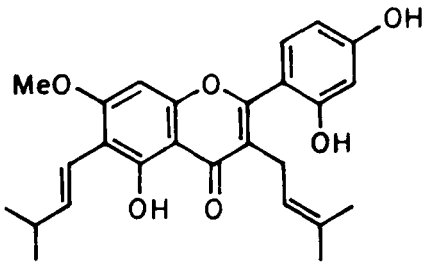


ISOBAKYANGELICOL (XXXVII);
R = OMe, R_1 =

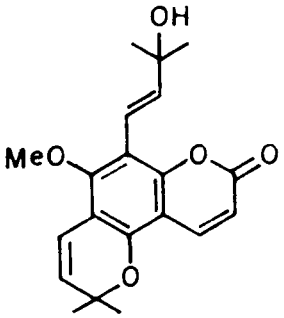


(XXXVIII);
R = OMe, R_1 =

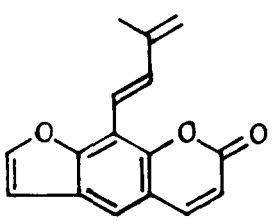




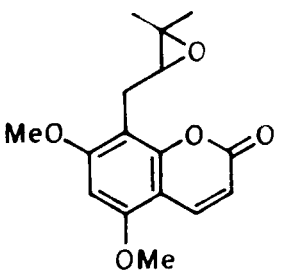
ARTOCARPIN (XXXIX)



AVICENNOL (XL)



(XLI)



SIBIRICIN (XLII)

the coumarins: xanthyletin (III), xanthoxyletin (IV), alloxanthoxyletin (VII), 7-demethylsuberosin and swietenol (XVII). From the bark he has isolated swietenidin A (XIX), an alkaloid; a lignan hinokinin (XX), in addition to the coumarins rutamarin (II), chalepin (I) and swietenone(XVIII).

PRESENT WORK

Because of our interest in wood phenolics of the Rutaceae plants and in continuation of Mujumder's work, we have examined two bark samples of C. swietenia DC obtained from Achalpur (Maharashtra State) and Channapatnam (Karnatak State). The bark from Achalpur contained two known lignans: collinusin (XXXI) and syringaresinol(XXXII) and six known coumarins: suberosine (VIII), rutamarin (II), swietenone (XVIII), xyletanin (XV), aesculetin dimethyl ether (X) and helieltin (I) have been isolated. In addition to these, four new coumarins: demethylluvangetin (VI), a pyranocoumarin and furocoumarins: swietenocoumarins A (XXII) and B (XXIII) have been isolated. It also gave swietenocoumarin G (XXVIII).

The bark from Chennapatnam gave rutamarin as a major constituent together with suberosin (VIII), swietenocoumarin A (XXII) and B (XXIII), chaleṗin (I) and swietenone (XVIII). In addition to these, the following new compounds: swietenocoumarins C (XXIV), D (XXV), E (XXVI), F (XXVII), H (XXIX), I (XXX), 8-prenylnodakenetin (XII),and an alkaloid swietenidin B (XXXIV) have been isolated.

Examination of the heartwood obtained from Madhya Pradesh revealed the presence of the known coumarins: 7-demethylsuberosin (IX), nodakenetin (XI), xanthoxyletin(IV) alloxanthoxyletin (VII) and an alkaloid skimmianine(XIII).

DISCUSSION AND RESULTS

Examination of the bark obtained from Achalpur (Dist.Amaravati, Maharashtra State)

Cold extraction of the powdered bark with acetone yielded a yellowish syrupy extract which was successively extracted with hexane, benzene, ether, chloroform and acetone. The hexane-benzene extracts showed similar behaviour on TLC silica gel. The combined extract was extracted with sodium bicarbonate. The sodium bicarbonate insoluble extract was chromatographed over a column of silica gel using hexane, benzene and acetone as eluent with increasing polarity. Each fraction was monitored on TLC and similar fractions were pooled and worked up together; and eight compounds have been isolated. Swietenocoumarins A (XXII) and B (XXIII) are the two new coumarins, and the following six compounds are known coumarins: suberosine(VIII) rutamarin (II), swietenone (XVIII), xyletenin (XV), aesculetin dimethyl ether (X) and hâliettin (I).

Compound 1 (Swietenocoumarin A) crystallised as colourless needles from hexane, m.p. 113°, $C_{16}H_{14}O_3$ (M^+ 254); $\overline{\nu}_{max}$ 1710 cm^{-1} (α,β-unsaturated lactone), and UV absorptions at $\lambda_{max.}^{EtOH}$ (log ϵ): 244 (4.48), 248 (4.50), 263.2 (4.05), 296 (4.19), 332(4.85). The NMR spectrum in $CDCl_3$(Fig.1)

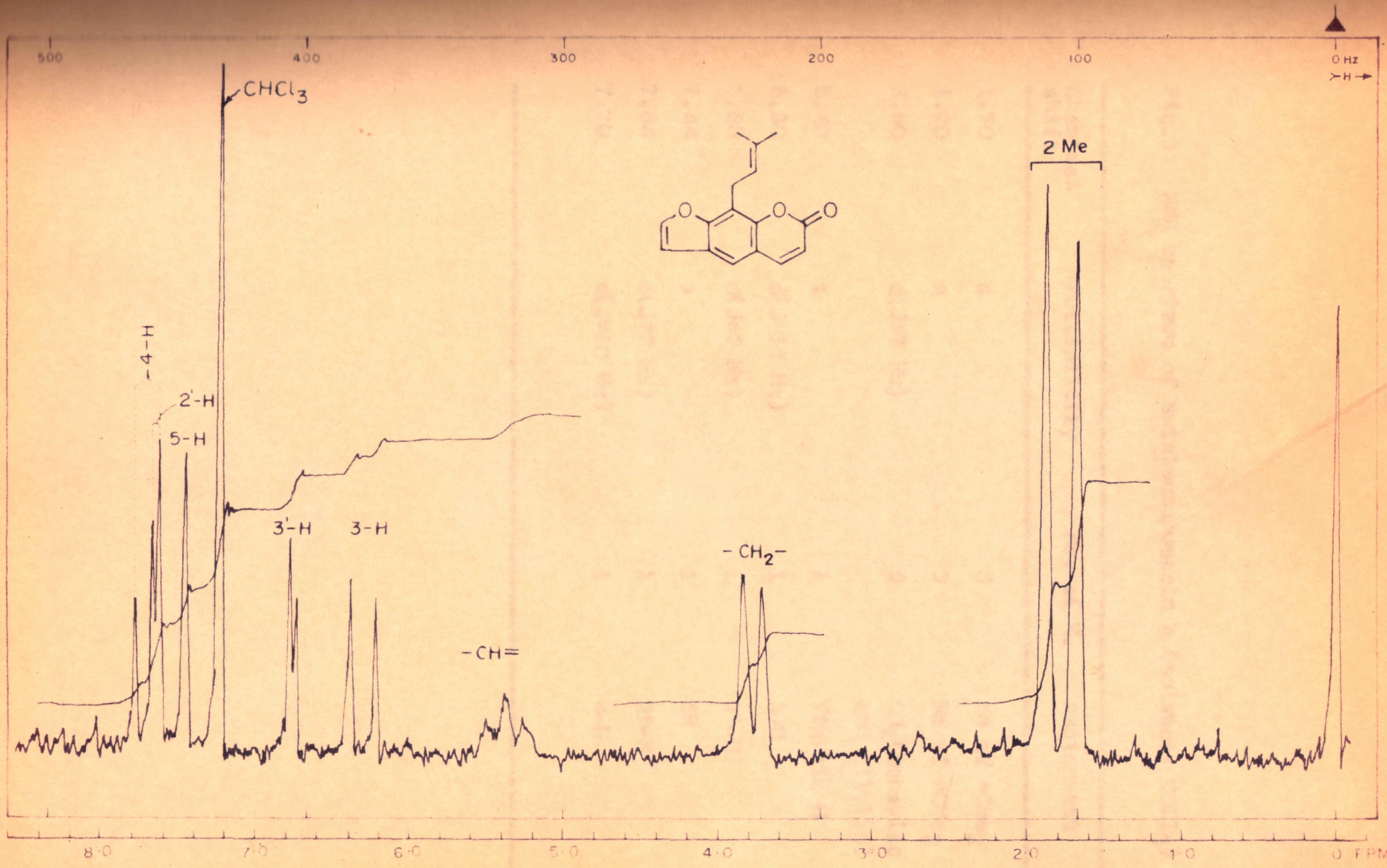


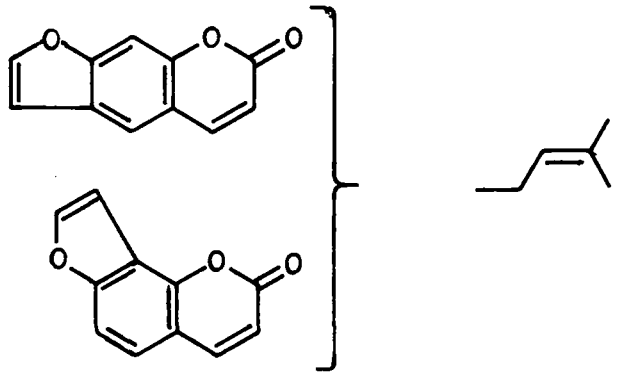
FIG. 1. NMR SPECTRUM OF SWIETENOCOUMARIN-A IN $CDCl_3$

Fig.1: NMR spectrum of swietenocoumarin A (solvent: $CDCl_3$)

Chemical shift	Multiplicity	No. of H.	Assignment
1.70	s	3	Me of $=CMe_2$
1.90	s	3	Me of $=CMe_2$
3.80	d(J=7 Hz)	2	CH_2(benzylic and allylic)
5.40	t	1	Vinylic H
6.30	d(J=10 Hz)	1	3-H
6.80	d(J=2 Hz)	1	3'-H
7.44	s	1	5H
7.64	d(J=2 Hz)	1	2'-H
7.70	d(J=10 Hz)	1	4-H

shows the characteristic pattern of signals for a furanocoumarin: doublets (J=2 Hz) at 7.64 and 6.80, which are assignable to 2'-H and 3'-H of furan. A pair of doublets (J= 10 Hz) at 7.70 and 6.30 corresponds to the 4- and 3-H of the coumarin ring. The methyl siglets at 1.70 and 1.90 together with a broad triplet at 5.40 (vinylic H) and a doublet at 3.80 (benzylic and allylic methylene) represents the 3,3-dimethylallyl group attached to a aromatic ring. The lone aromatic proton which is seen as a singlet at 7.44 can be assigned to a 5-H rather than 8-H of a furanocoumarin ring system.

Based on the above data two structures can be suggested to compound 1.

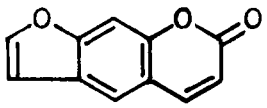
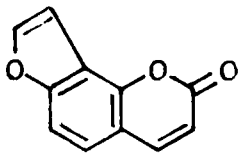
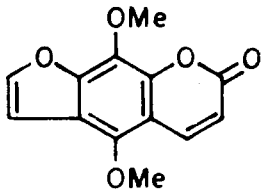
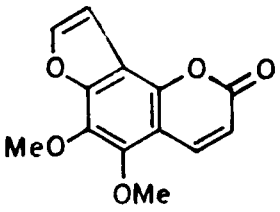
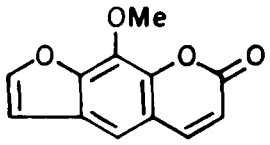
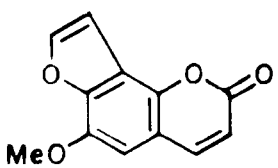


The angular structure is ruled out because of the general observation that the 3'-H of a angular furanocoumarin is seen around 7.10 to 7.20, compared with the chemical shift of the same proton in the linear furanocoumarins. The 3'-H in compound 1 is seen at 6.80 as in the case of other linear

furanocoumarins. Table 1 gives the chemical shifts of some of the furanocoumarins and their UV values. Although some of the earlier workers[13] have distinguished the linear and angular furanocoumarins based on the fact that the former shows a characteristic band between λmax. 242-245 and above 260 nm there is no sharp distinction between the two types as is seen in some of the examples given in Table 1. Its mass spectrum (Fig.2) shows molecular ion as the base peak at m/e 254, and other peaks at m/e 239(M-15), 211(M-15-28), M-199(M-71), 171 (M-71-28) (Chart 1). Hence compound 1, swietenocoumarin-A, can be represented by the structure(XXII).

Compound 2 (Swietenocoumarin B): obtained as colourless prisms from hexane, m.p. 145°. $C_{17}H_{16}O_4$ (M$^+$ 284). Its IR spectrum shows characteristic band at 1710 cm^{-1} (<,β-unsaturated lactone) and UV absorption $\lambda_{max.}^{EtOH}$ (log ε): 242(4.17), 248.5 (4.19), 265(4.23), 271(4.24), 312(4.12). The NMR spectrum (Fig.3) is similar to that of the swietenocoumarin A except for the appearance of a three protons signal at 4.33 corresponding to a methoxyl group, and the disappearance of the aromatic proton. However, the signals appearing at 8.30 and 7.30, which are assignable for 4-H and 3'-H, which are shifted downfield by 0.5 to 0.6 ppm as compared to the NMR values of 4-H and 3'-H of swietenocoumarin A. It may be because the two protons are at the peri positions to the methoxyl group showing significant deshielding effect.

TABLE – 1

NAME	STRUCTURE	CHEMICAL SHIFTS				UV ABSORPTIONS
		2'–H	3'–H	3 –H	4–H	
PSORALEN		7·65	6·80	6·33	7·75	211, 240, 245, 298, 325
ANGELICIN		7·67	7·12	6·36	7·78	217, 247, 297
ISOPIMPINELLIN		7·59	6·96	6·25	8·08	224, 254, 269, 312
PIMPINELLIN		7·65	7·08	6·36	8·07	219, 251 304
XANTHOTOXIN		7·66	6·79	6·32	7·73	218, 247, 261 300·5
SPHONDIN		7·70	7·12	6·38	7·75	–

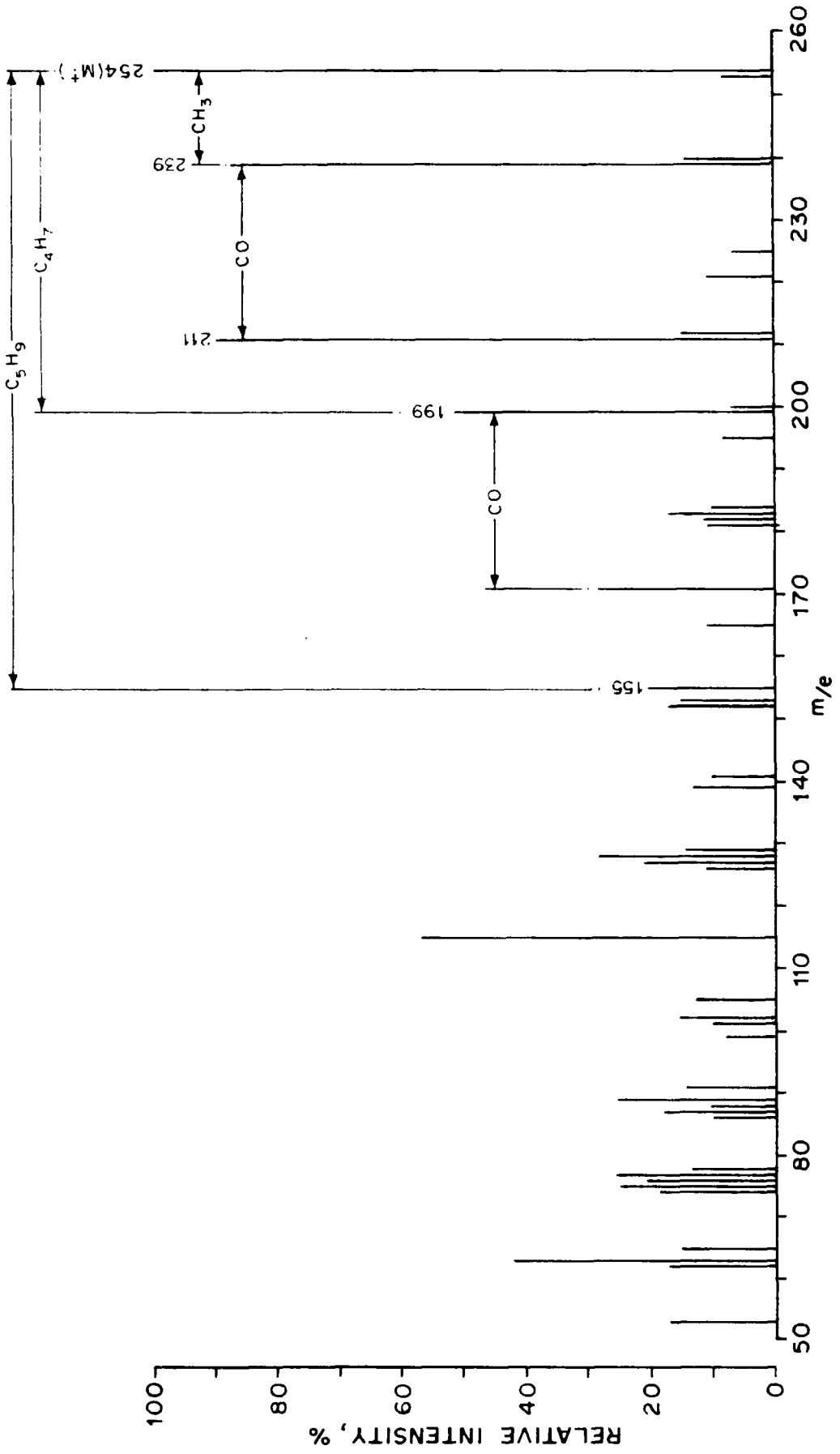
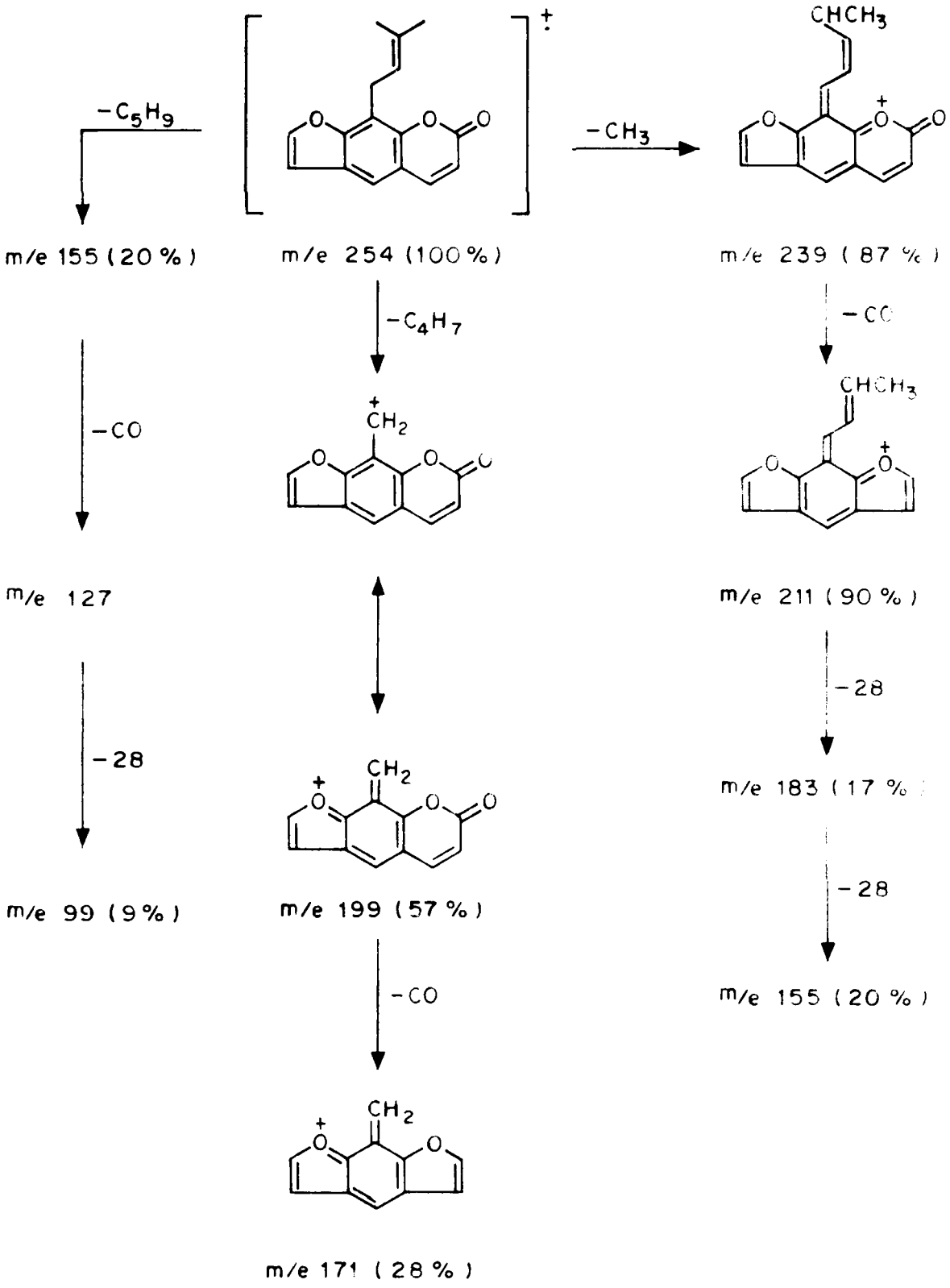

RELATIVE INTENSITY, %
0
20
40
60
80
100
50
80
110
140
170
200
230
260
m/e
254(M+)
239
211
199
155
CH3
CO
CO
C4H7
C5H9

FIG. 2

CHART 1 MASS SPECTRAL FRAGMENTATION OF SWIETENOCOUMARIN-A



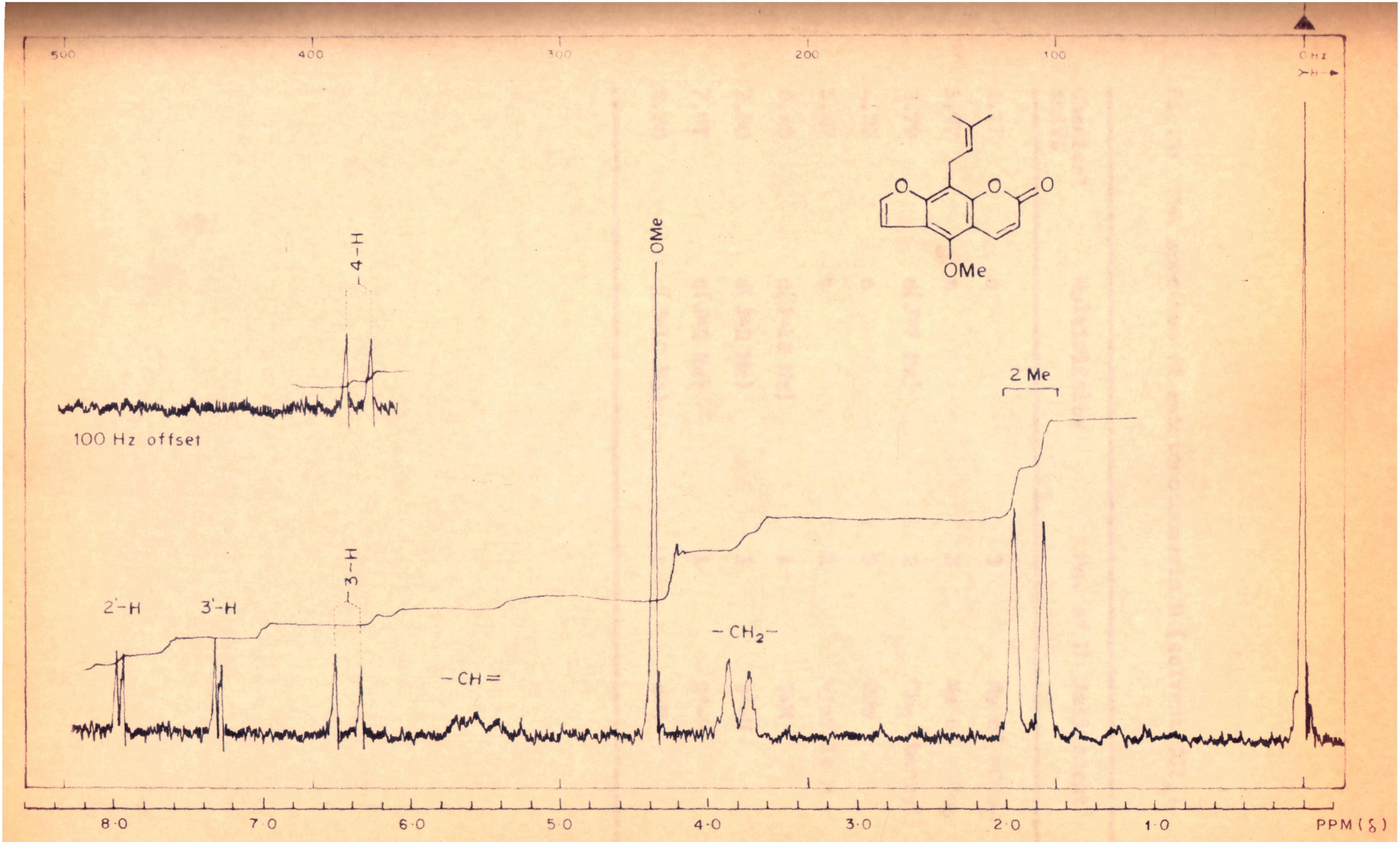


FIG. 3. NMR SPECTRUM OF SWIETENOCOUMARIN-B IN CCl_4

Fig.3: NMR spectrum of swietenocoumarin B (solvent CCl_4)

Chemical shift	Multiplicity	No. of H	Assignment
1.77	s	3	Me of $=CMe_2$
1.97	s	3	Me of $=CMe_2$
3.79	d(J=7 Hz)	2	CH_2 (benzylic)
4.33	s	3	OMe
5.47	t	1	Vinylic H
6.43	d(J=10 Hz)	1	3-H
7.30	d(J=2 Hz)	1	3'-H
7.97	d(J=2 Hz)	1	2'-H
8.30	d(J=10 Hz)	1	4-H

In the mass spectrum it shows m/e 284 as a molecular ion, and other intense peaks at 269 (M-15) 241 (M-43), 229(M-55), 141 (M-143).

All the above data shows that suletenocoumarin B is nothing but 5-methoxy suletenocoumarin A (XXIII).

Further support to show that suletenocoumarin B is 5-methoxy-8-(3,3-dimethylallyl) psoralen, it has been converted to the epoxide (XXV) followed by alkaline hydrolysis to give the acid (XXXV). However, if the dimethyl allyl group is situated at 5-position as in alloimperatorin methyl ether[14] (XXXVI), no such transformation is anticipated.

Compound 3: m.p. 90-91° is identical with UV, IR and NMR data of xyletenin (XV) previously reported from the leaves.[9]

Compound 4, m.p. 88°, $C_{15}H_{16}O_3$ (M^+ 244). ν max. 1720 cm^{-1} (α,β-unsaturated lactone). The NMR spectrum shows the presence of a 3,3-dimethylallyl group (1.67 and 1.75, (3 protons each) together with a doublet (J=7 Hz) centered at 3.25 and a broad triplet at 5.19) attached to an aromatic ring. A three proton signal at 3.90 represents a methoxyl group. A pair of doublet (J=10 Hz) at 6.14 and 7.54, besides two aromatic protons as singlets at 6.70 and 7.10, suggests that the compound is suberosin (VIII), which has been isolated for the first time from this plant. However,

7-demethylsuberosin has been reported by King et al.,[7] Vrkoc and Sedmera,[8] and Mujumdar,[12] from the heartwood. Its further identity is further confirmed by direct comparison with an authentic sample.

Compound 5, m.p.104° is characterised as rutamarin (II) (by direct comparison with the authentic sample and mixed m.p.)

Compound 6, m.p.163-64° is identified as heliettin (I), an isomer of chalepin, which is previously isolated from the leaves.[9]

Compound 7, m.p.143° is characterised as aesculetin dimethyl ether.[8]

Compound 8, m.p.160° is identified as swietenone (XVIII) and confirmed by mixed m.p.[11]

The combined ether-chloroform extract yielded two new coumarins, demethyluvangetin(VI) and swietenocoumarin G(XXVIII) in addition to three known compounds (II, XXXI, XXXII).

Compound 9, m.p. 194-95°, $C_{21}H_{18}O_6$ (M^+ 366). The IR spectrum shows bands at 1750 (lactone C=O), 1650, 1610, (aromatic), 925 cm^{-1} (methylene dioxy group). The NMR spectrum reveals the presence of two proton signal at 2.94 (benzylic methylene) and two methoxyl groups at 3.70 and 3.95. A downfield two proton triplet at 4.70 can be accounted for methylene adjacent to an oxygen. A two proton signal at 6.04 is ascribable to methylene dioxy group. In the low field region of the spectrum five aromatic protons appear as broad signals in the region 6.57-6.80.

Its physical and spectral properties established its identity with that of a lignan collinusin (XXXI) earlier reported from the plant Cleaisanthus collinus[16] (F. Euphorbiaceae).

Compound 10, crystallised as pale yellow needles, m.p. 168°, $C_{22}H_{26}O_8$ (M^+ 418). ν Max. 3500 cm^{-1} (hydroxyl function). Its NMR spectrum shows characteristic signals that are common for tetrahydrofurofuran type lignan having identically substituted phenyl groups. Thus the spectrum shows a singlet of four methoxyl groups at 3.90, two methylene groups attached to oxygen function at 4.27. There are two types of methine protons, a two proton multiplet centered at 3.05 (>CH protons) and other two protons multiplet centered at 4.74 (benzylic and attached to oxygen >CH-) besides a four proton singlet at 6.58 accounting for the four aromatic protons. A phenolic hydroxyl (2H) group is seen at 5.53 (exchangeable with D_2O).

From the above data it is clear that the two phenyl groups have to be of syringic acid type, and the lignan has been identified as syringaresinol (XXXII) not reported from this plant. Syringaresinol has been isolated previously from the bark of Liriodendron tulifera.[17]

Compound 11 (Demethylluvangetin), m.p. 195°, $C_{14}H_{12}O_4$ (M^+ 244). Its IR spectrum shows bands at 3300 (-OH), 1705 cm^{-1} (α,β-unsaturated lactone) and UV absorptions $\lambda_{max.}^{EtOH}$ (log ϵ): 263(4.36), 272(4.37), 337(4.00). It forms under standard conditions crystalline monomethyl ether, m.p. 106-107° and crystalline monoacetate, m.p.120°, which shows the presence of a phenolic hydroxyl group.

The NMR spectrum (Fig.4) indicates two vinylic protons as doublets (J=10 Hz) at 5.70 and 6.40 in conjunction with a singlet at 1.55 for two methyl groups, suggesting the presence of a 2,2-dimethylchromene ring. This is substantiated in the mass spectrum (Fig.5) by a ready loss of a methyl radical from the molecular ion (M^+ 244), giving a base peak at m/e 229, which is in consonance with the expected fragmentation of 2,2-dimethylchromene (Chart 2). A pair of doublets (J= 10 Hz) at 6.20 and 7.60 will account for the 3- and 4-H of coumarin. A singlet at 6.70 can account either for 5- or 8-H of a chromeno-coumarin. The chemical shift of the 4-proton of the chromene ring as well as the coumarin 4-H are not deshielded by any perihydroxyl group, indicating that the hydroxyl is at 8-position and not at 5-position. The NMR spectrum of the acetate (Fig.6) shows an additional signal at 2.45 for acetoxyl group.

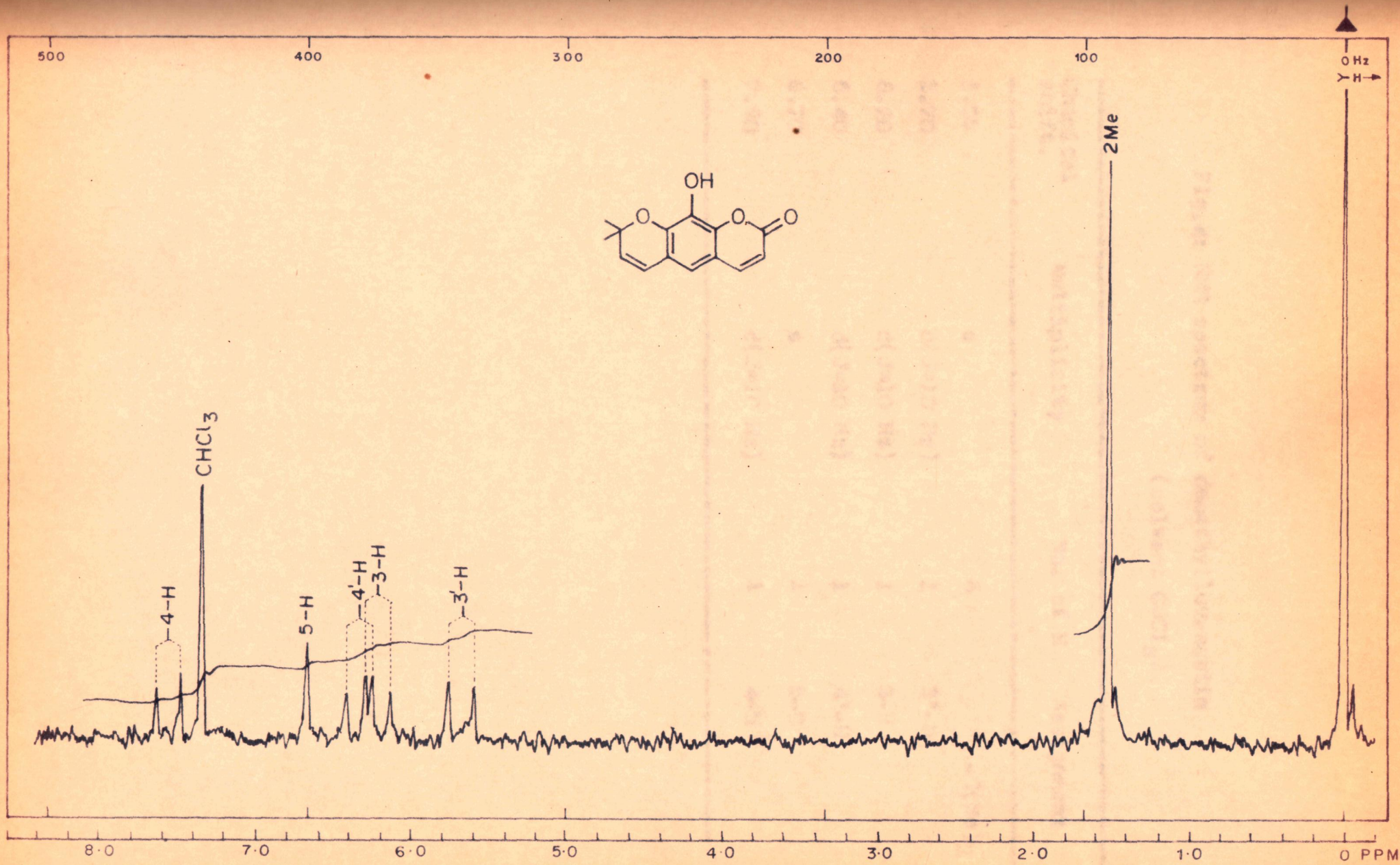


FIG. 4. NMR SPECTRUM OF DEMETHYLLUVANGETIN IN $CDCl_3$

Fig.4: NMR spectrum of dimethylluvangetin (solvent $CDCl_3$)

Chemical shift.	Multiplicity	No. of H	Assignment
1.55	s	6	$-C(Me)_2$
5.70	d(J=10 Hz)	1	3'-H
6.20	d(J=10 Hz)	1	3-H
6.40	d(J=10 Hz)	1	4'-H
6.70	s	1	5-H
7.60	d(J=10 Hz)	1	4-H

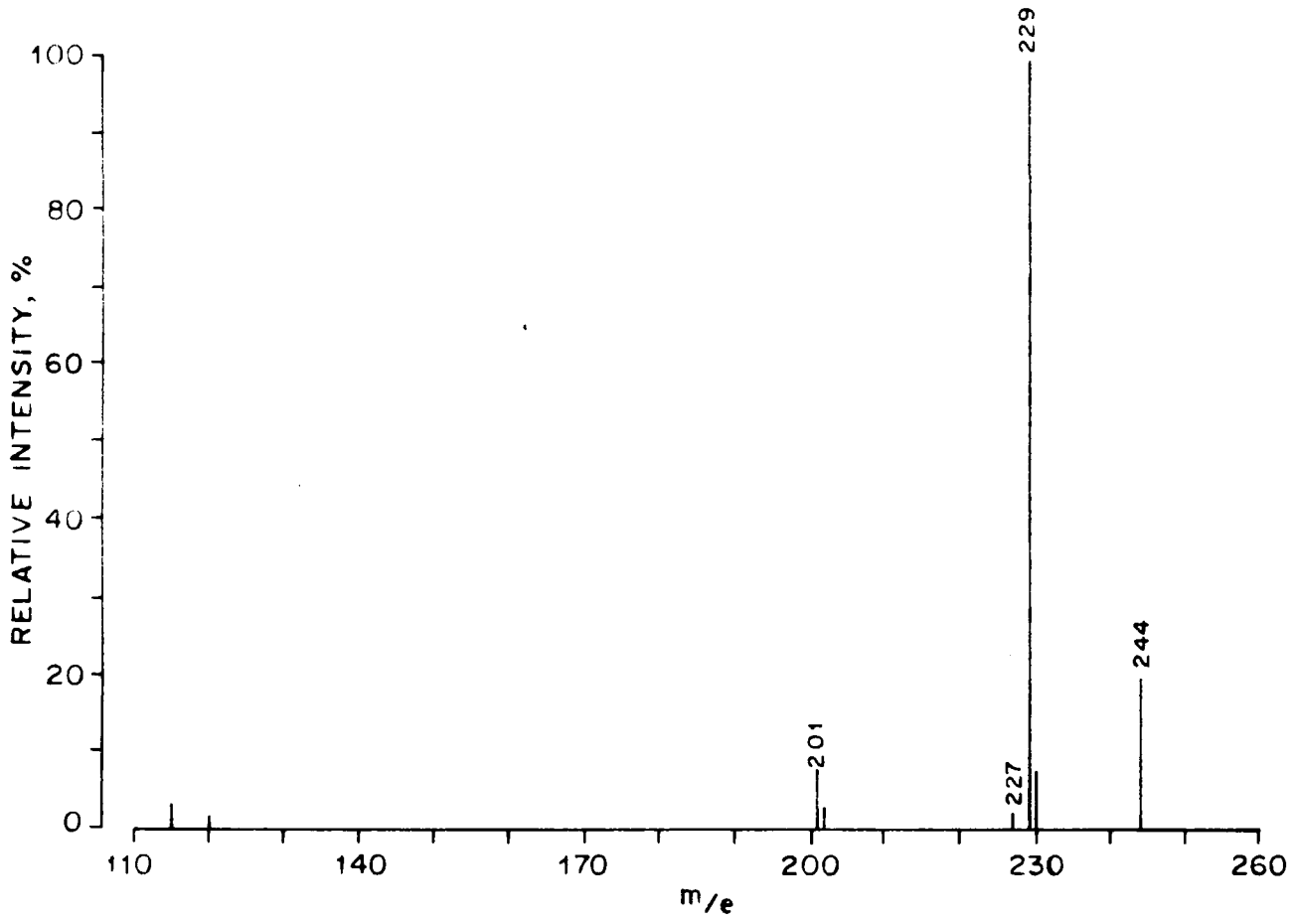
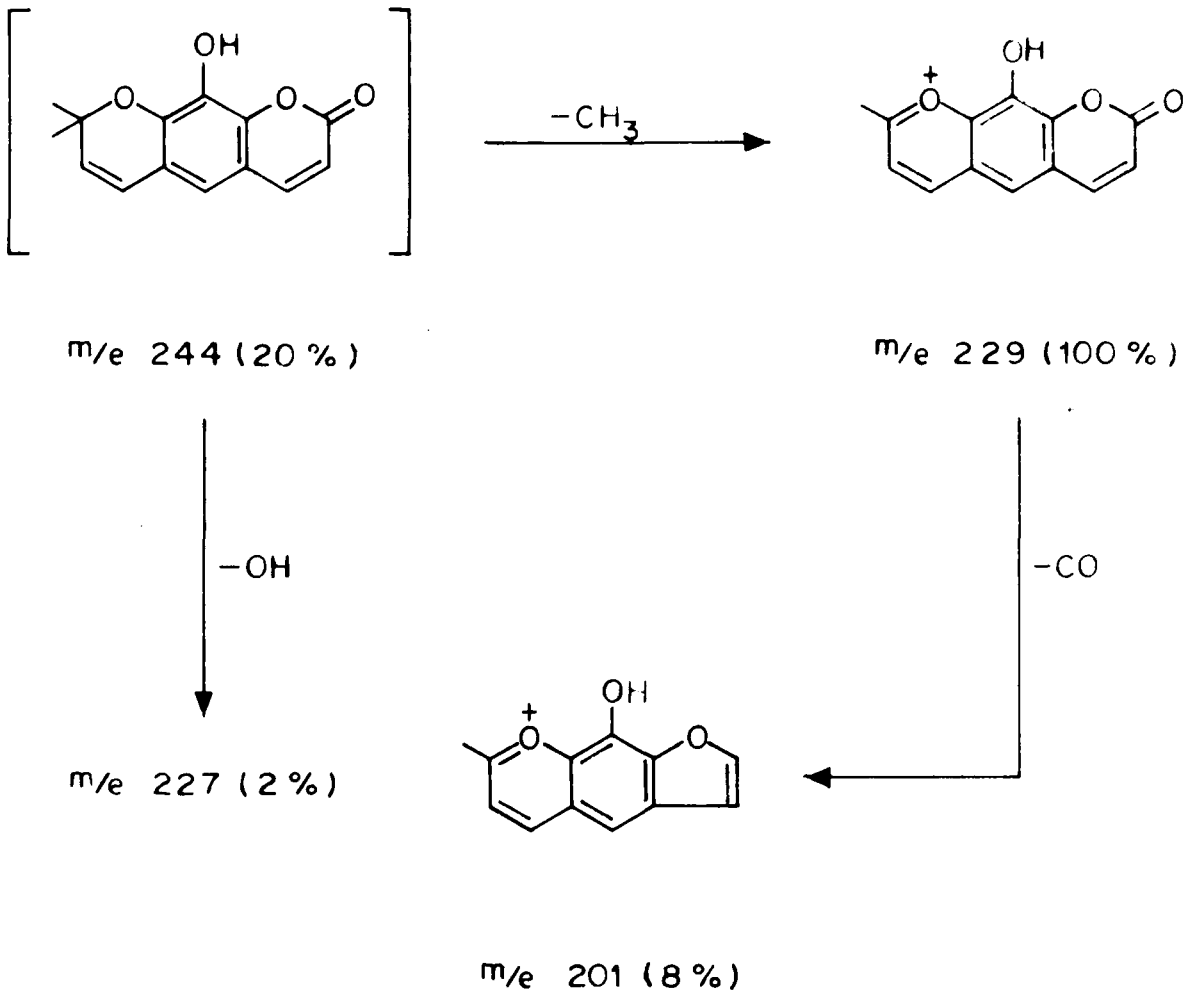

100
80
60
40
20
0
RELATIVE INTENSITY, %
229
244
201
227
110
140
170
200
230
260
m/e

FIG. 5.

CHART 2 MASS SPECTRAL FRAGMENTATION OF DEMETHYLLUVANGETIN



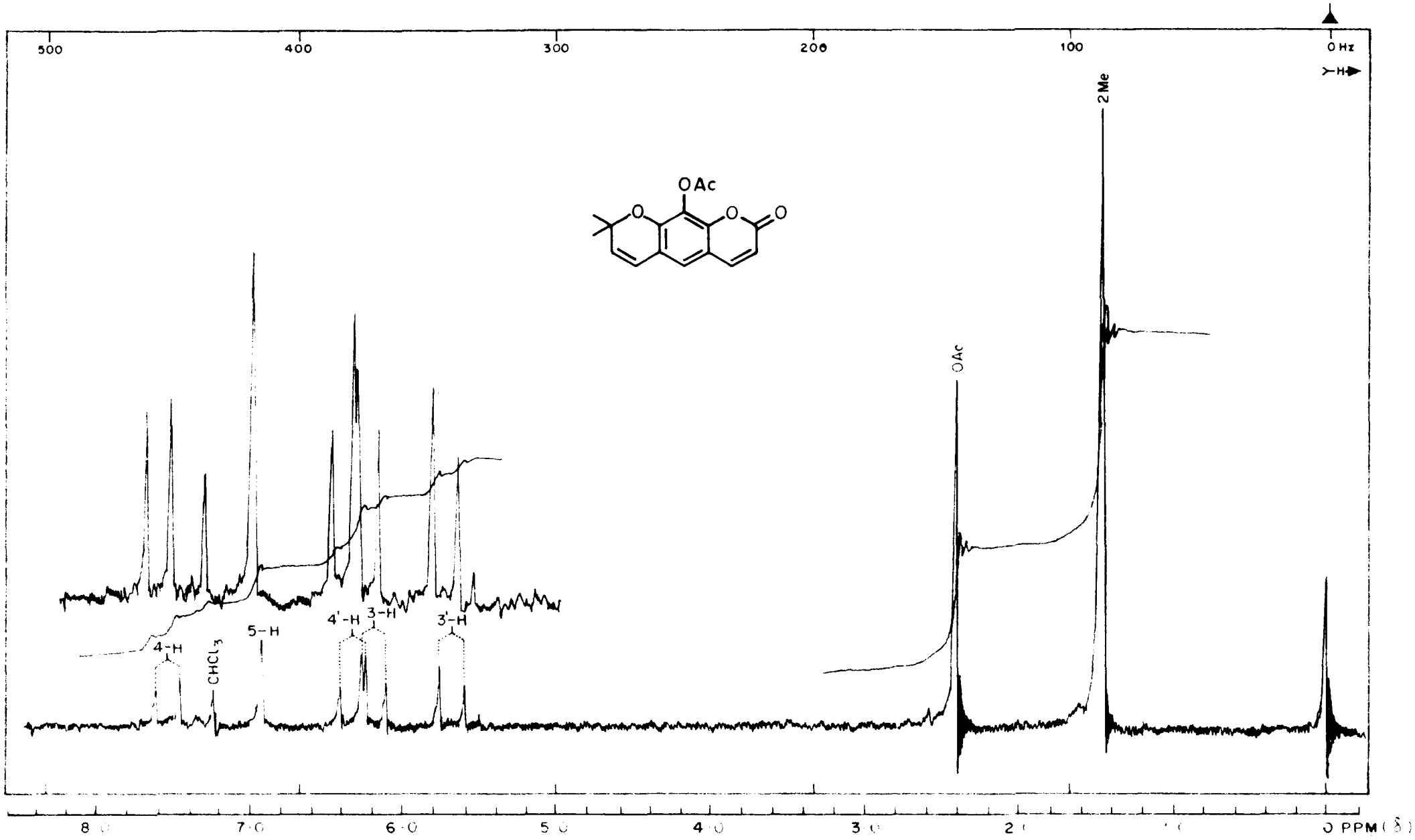

500
400
300
200
100
0 Hz
OAc
2Me
OAc
4-H
CHCl3
5-H
4'-H
3-H
3'-H
8·0
7·0
6·0
5·0
4·0
3·0
2·0
0 PPM (δ)

FIG 6

Fig.6: NMR spectrum of demethylluvangetin acetate

(solvent: $CDCl_3$)

Chemical shift.	Multiplicity	No.of H	Assignment
1.50	s	6	$-CMe_2$
2.45	s	3	$-OCOCH_3$
5.70	d(J=10 Hz)	1	3'-H
6.22	d(J=10 Hz)	1	3-H
6.37	d(J=10 Hz)	1	4'-H
6.94	s	1	5-H
7.57	d(J=10 Hz)	1	4-H

An additional support has been provided by the physical properties of its methyl ether, which are identical with luvangetin (V) (lit.[8] m.p.108°). Hence compound 11 is characterised as demethylluvangetin (VI), a new pyranocoumarin.

Compound 12 (Swietenocoumarin G) obtained as bright yellow needles, m.p. 190°, $C_{17}H_{16}O_5$ (M^+ 300). Its IR spectrum shows bands at 3590 and 1720 cm^{-1} characteristic of alcoholic hydroxyl and carbonyl functions respectively, and UV $\lambda_{max.}^{EtOH}$ ($\log \epsilon$): 235 (4.35), 244 (4.33), 276.5 (4.41); 285(4.43); 3.12 (4.11).

The NMR spectrum (Fig.7) exhibits a typical pattern of signals for furanocoumarin. A pair of doublets (J=10 Hz) at 8.10 and 6.30, corresponds to 4-H and 3-H of the coumarin, and doublets (J=2 Hz) at 7.30 and 7.05 for the 2'-H and 3'-H of the furan ring. A three proton signal at 4.20 for a methoxyl group and a six proton signal at 1.50 suggests the presence of two methyl groups. A two proton singlet appearing at 7.10 remains to be accounted for. The above data suggests it to be a linear furanocoumarin with a methoxyl group at 5-position as the chemical shifts of 4- and 3'-H are shifted downfield significantly, as compared to that in swietenocoumarin- H (XXIX).

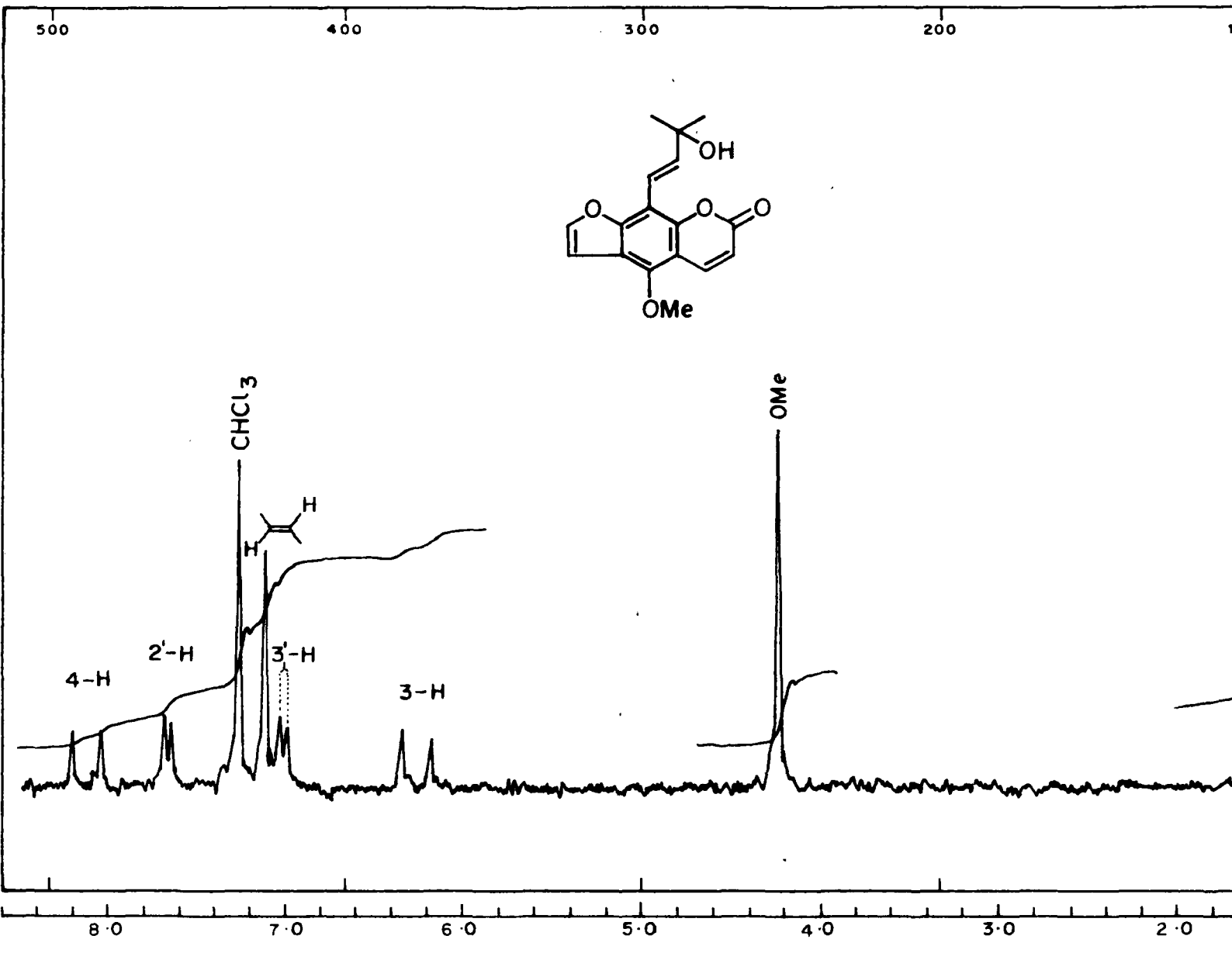


FIG. 7. NMR SPECTRUM OF SWIETENOCOUMARIN-G IN CD

Fig.7: NMR spectrum of swietenocoumarin G (solvent $CDCl_3$)

Chemical shift	Multiplicity	No.of H	Assignment
1.50	s	6	Me_2 of $(Me)_2$-C-OH
4.20	s	3	-OMe
6.30	d(J=10 Hz)	1	3-H
7.08	d(J2 Hz)	1	3'-H
7.10	s	2	Olefinic protons
7.30	d(J=2 Hz)	1	2'-H
8.10	d(J=10 Hz)	1	4-H

Furanocoumarin nucleus with one methoxyl substituent on it accounts for twelve carbon atoms, which implies to show the presence of a C_5 side chain. Out of the five oxygens, three are present in furanocoumarin skeleton and one in the methoxyl group. The remaining oxygen may be present on the side chain as hydroxyl group (IR band: 3590 cm^{-1}).

The above information is quite instructive of the presence of the substituents at both 5- and 8-positions. Since all the protons of the furanocoumarin are accounted for, the remaining downfield signal appearing at 7.10 must be arising from the side chain protons and not from the ring. The olefinic protons attached to an aromatic nucleus are expected to show such a downfield absorption. Thus a side chain of the type Ph-CH=CH-C(Me)$_2$OH can be postulated. The chemical shift of the two olefinic protons is identical resulting in the appearance of the two proton signal as a singlet. Analogously, two such olefinic protons in artocarpin[18] (XXXIX), a flavone, isolated from the heartwood of Artocarpus heterophyllus, appear as a singlet. However, in aviennol(XL), a chromenocoumarin, isolated from Zanthoxylum aviennae[19] (F.Rutaceae) and having an identical C_5 unit as in the present case, the two olefinic protons are seen as doublets (J=16 Hz) at 6.95 and 6.81.

Its mass spectrum (Fig.8) shows molecular ion at m/e 300, and other intense peaks at m/e 285 (M-15), 282(M-18),

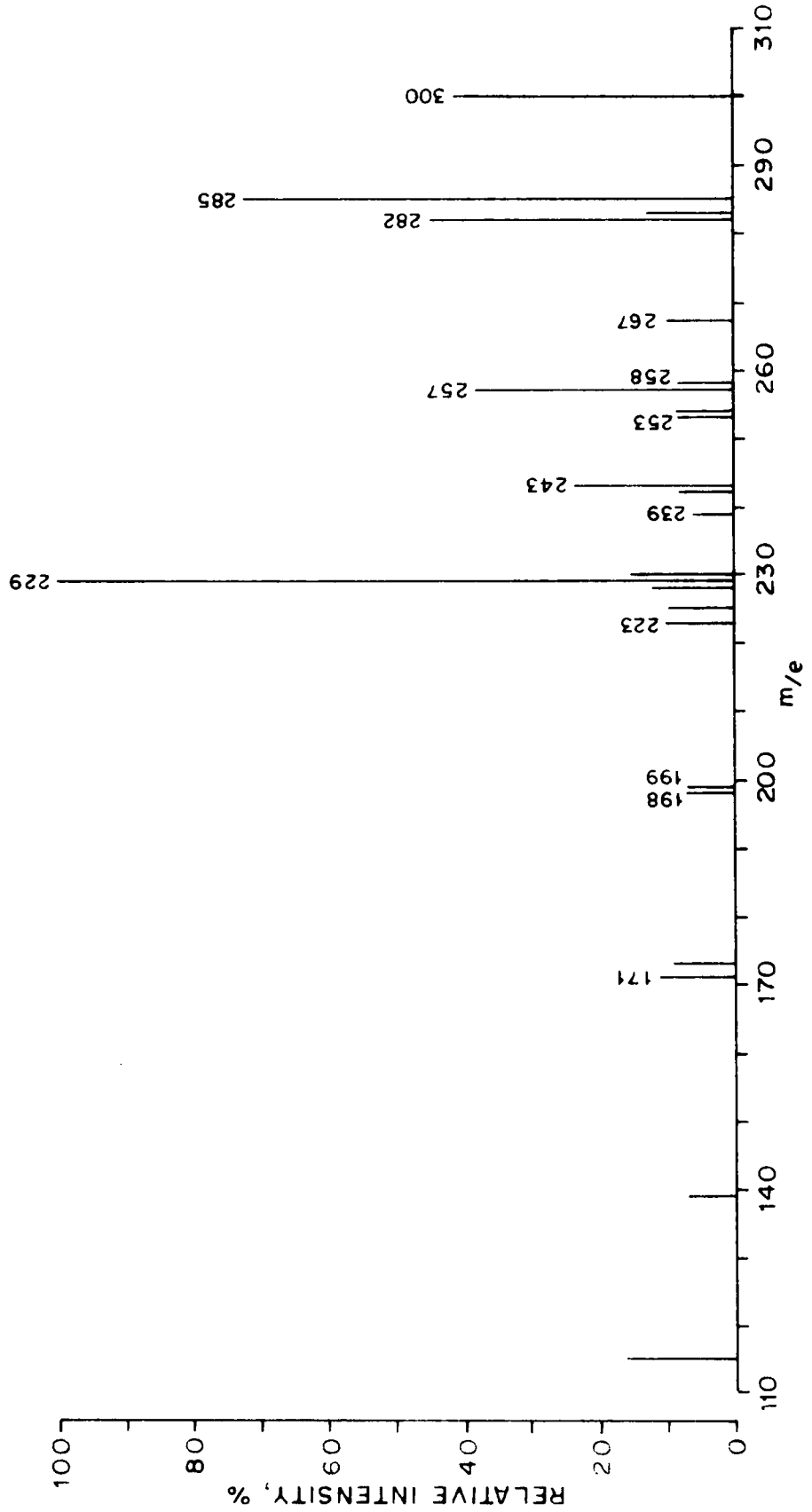
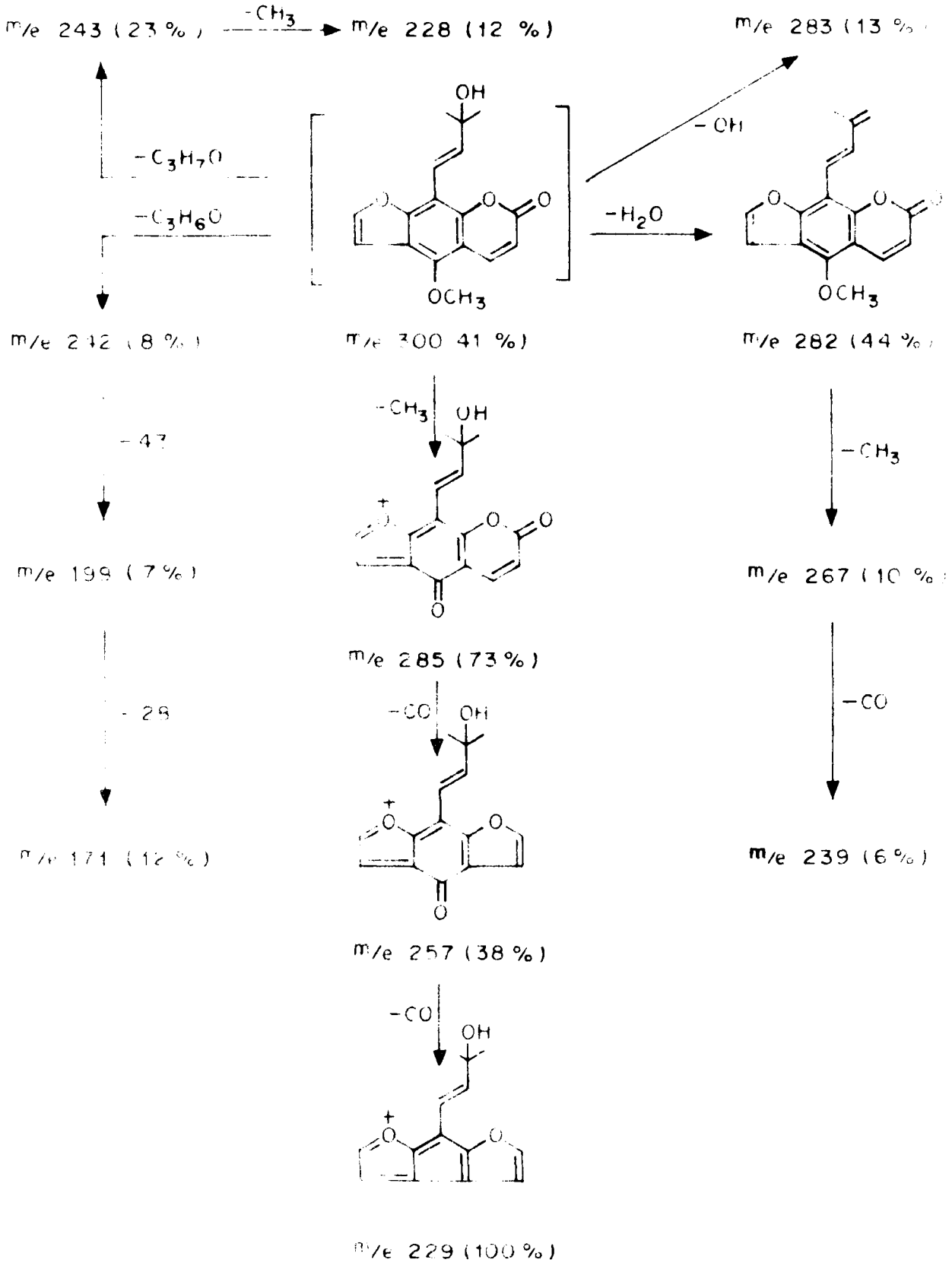

RELATIVE INTENSITY, %
100
80
60
40
20
0
110
140
170
200
230
260
290
310
m/e
300
285
282
267
258
257
253
243
239
229
223
199
198
171

FIG. 8.

CHART 3 MASS SPECTRAL FRAGMENTATION OF SWIETENOCOUMARIN-G



257(M-43), 243(M-57), 229(M-71) (base peak), 173 (M-171), 171(M-173) (chart 3).

In view of the data outlined above, the compound is represented by structure (XXVIII) and named swietenocoumarin G. Another compound swietenocoumarin H having remarkable similarity with that of swietenocoumarin G has been isolated (for more discussion, see compound 19).

The bicarbonate soluble hexane-benzene extract on purification over a column of silica gel gave an alkaloid, swietenidin A (XIX).

Compound 13, m.p. 158-59°, $C_{12}H_{13}NO_4$ (M^+ 235). It gave an orange colour with Dragendorff's reagent indicating a positive test for alkaloids. This is characterised as swietenidin A (XIX) by its physical properties and direct comparison with the authentic sample (lit.[20] m.p. 159°).

Examination of the bark from Channapatnam (Karnatak State)

The cold acetone extract of the bark was adsorbed on the extracted bark powder and successively extracted in a soxhlet with hexane, benzene, ether, chloroform and acetone.

Examination of hexane and benzene extract

The hexane and benzene extracts showed similar behaviour on TLC silica gel (1:9 acetone:benzene) and the combined extract on chromatographic separation over a column of silica gel yielded seven compounds (compounds 14-20).

Compounds 14 to 17 were identical with the known coumarins: rutamarin (II), suberosin (VIII), swietenocoumarins A (XXII) and B (XXIII) respectively, isolated from the earlier source. One of the other three compounds (18-20) has been characterised as isopimpinellin (XXI), a known coumarin and other two compounds now named as swietenocoumarin H (XXIX) and I (XXX) are the new furanocoumarins not encountered earlier.

Compound 18, m.p. 150° is characterised as isopimpinellin (XXI) identical in all respects with the authentic sample (lit.[21] m.p. 149-150°).

Compound 19 (swietenocoumarin H), m.p. 157-58°, $C_{16}H_{14}O_4$ (M^+ 270). Its IR shows bands at 3350, 1725 cm^{-1} for hydroxyl and lactone carbonyl groups respectively.

The NMR spectrum (Fig.9) displays characteristic furanocoumarin doublets (J=10 Hz) at 6.30 (3-H) 7.68(4-H) and (J=2 Hz) 6.76 (3'-H), 7.68(2'-H) and an aromatic proton at 7.46(5-H)A six proton singlet at 1.50 and a two proton singlet at 7.18 indicates that the C_5 unit, may be of the identical nature as in swietenocoumarin G (XXVIII), is at C-8.

On treatment with acetic anhydride and pyridine swietenocoumarin H (XXIX) gave a yellow crystalline compound devoid of an acetoxyl group as shown by its IR and NMR spectra.

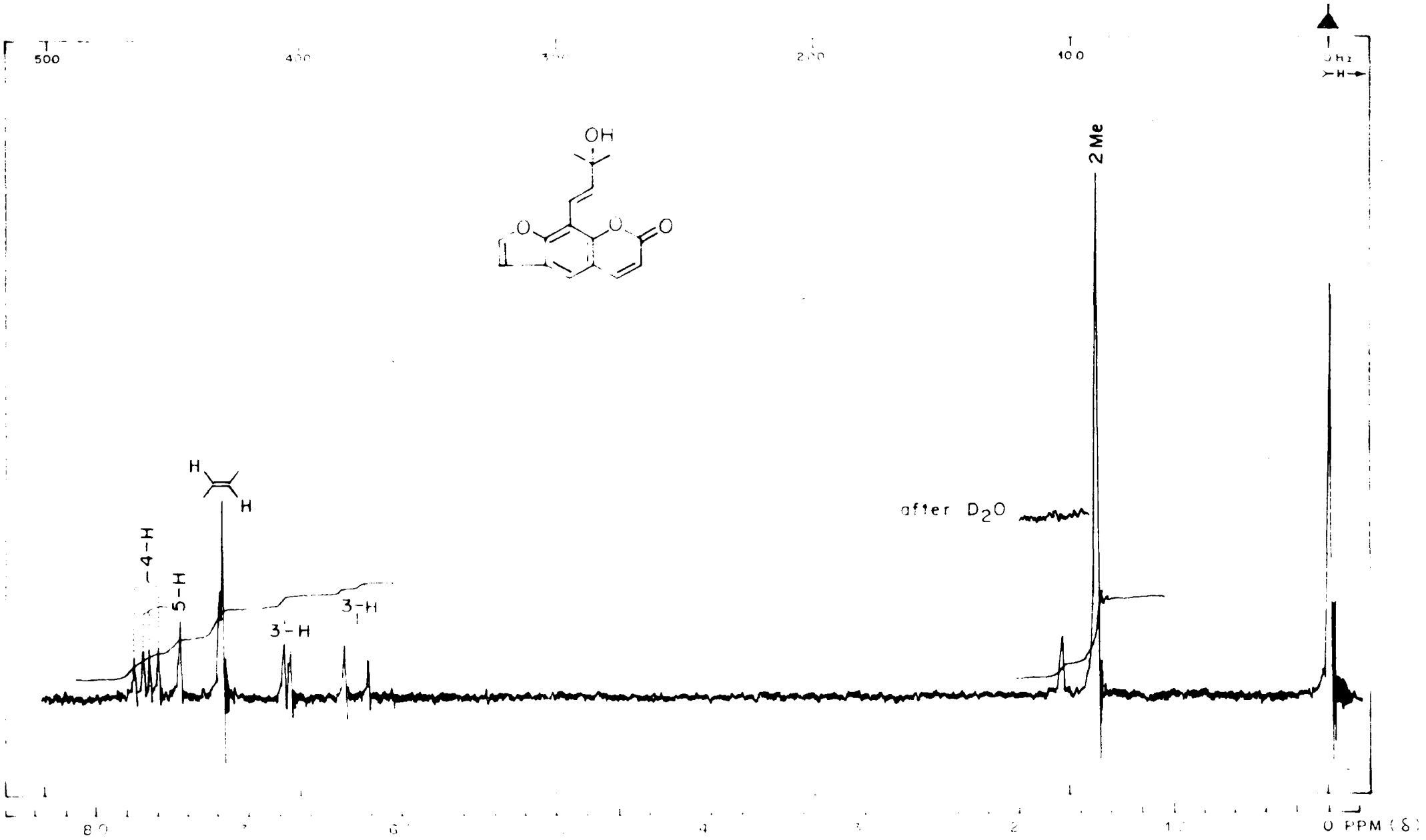


FIG. 9 NMR SPECTRUM OF SWIETENOCOUMARIN-H IN CCl_4

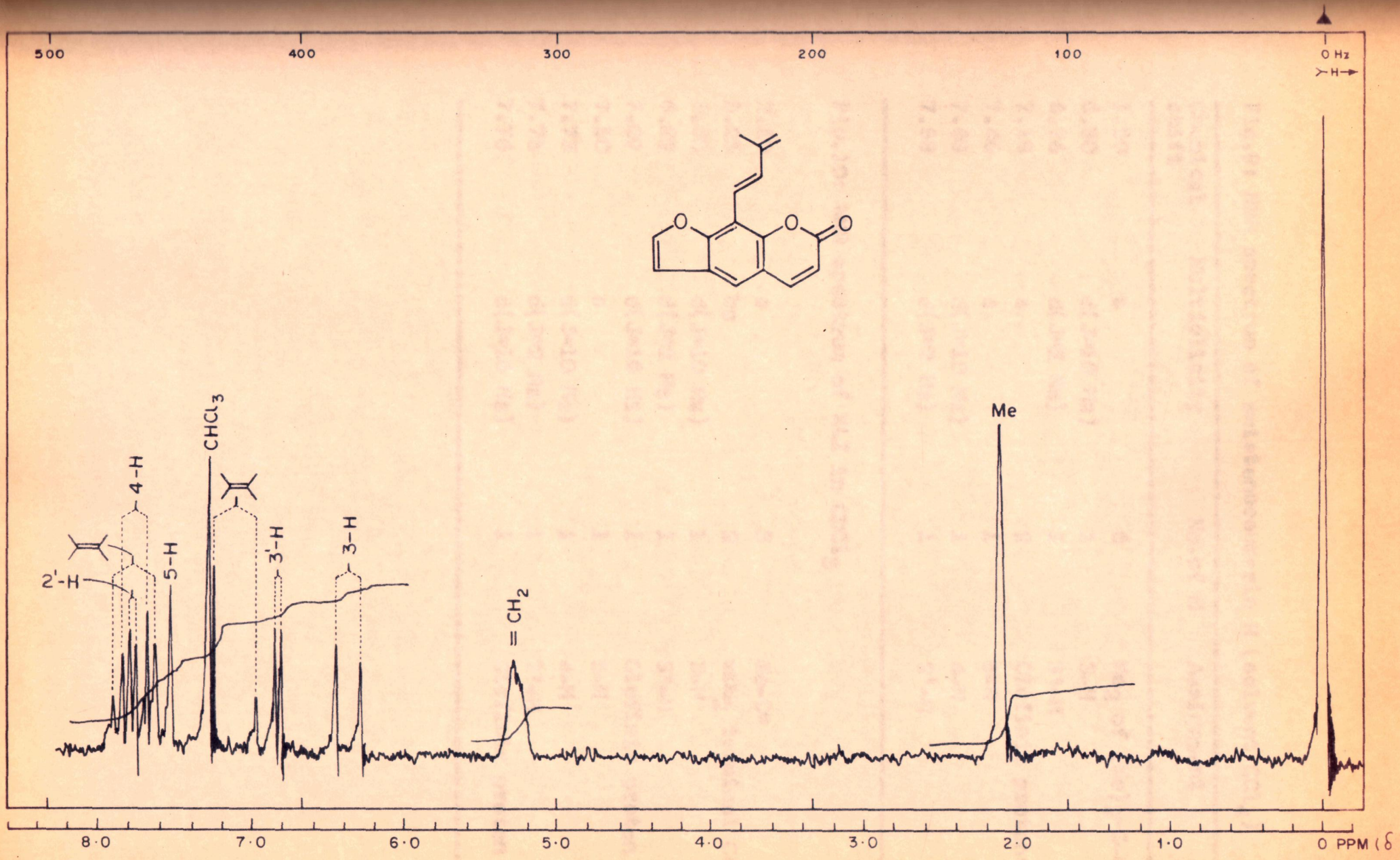


FIG. 10. NMR SPECTRUM OF (XLI) IN $CDCl_3$

Fig.9: NMR spectrum of suletenocoumarin H (solvent CCl_4)

Chemical shift	Multiplicity	No.of H	Assignment
1.50	s	6	Me_2 of $(Me)_2$-C-OH
6.30	d(J=10 Hz)	1	3-H
6.76	d(J=2 Hz)	1	3'-H
7.18	s	2	Olefinic protons
7.46	s	1	5-H
7.68	d(J=10 Hz)	1	4-H
7.68	d(J=2 Hz)	1	2'-H

Fig.10: NMR spectrum of XLI in $CDCl_3$

2.10	s	3	Me-C=
5.25	bs	2	=CH_2 terminal CH_2
6.35	d(J=10 Hz)	1	3-H
6.82	d(J=2 Hz)	1	3'-H
7.09	d(J=16 Hz)	1	Olefinic proton
7.50	s	1	5-H
7.73	d(J=10 Hz)	1	4-H
7.75	d(J=2 Hz)	1	2'-H
7.76	d(J=16 Hz)	1	Olefinic proton

The product has resulted in the loss of water (or ACOH) during acetylation, as shown in its NMR spectrum (Fig.10) by the presence of only one methyl group (2.10) and a terminal methylene group (5.25). The two ethylenic protons are seen as separate doublets (J=16 Hz) at 7.09 and 7.76 and is in agreement with the structure (XLI).

Its mass spectrum shows m/e 270 as a molecular ion and other fragment ions peaks at m/e 255 (M-15), 227 (M-43), 213 (M-57), 199 (M-71).

Compound 20 (swietenocoumarin I)obtained as a gum, $C_{20}H_{26}O_5$ (M^+ 346). Its IR spectrum shows absorption bands at 3400 (-OH), 1700 cm^{-1} (α,β-unsaturated lactone). The NMR spectrum (Fig.11) shows a six protons signal at 1.44, two broad doublets at 4.92 and 5.17 and a quartet centered at 6.13 indicating the presence of a 1,1-dimethylallyl group. A singlet at 3.85 can be ascribed to a methoxyl group. Three single proton singlets appearing at 6.64, 7.17 and 7.37 can be attributed to the 5-H, 8-H and 4-H of the coumarin ring. The appearance of a six proton signal at 1.20, a broad signal at 3.20-3.70 integrating for one proton and a two proton multiplet at 2.27-3.07 suggests the presence of another C_5 side chain.

Of the total oxygens two appear in coumarin ring and the third as a methoxyl group. The remaining oxygens

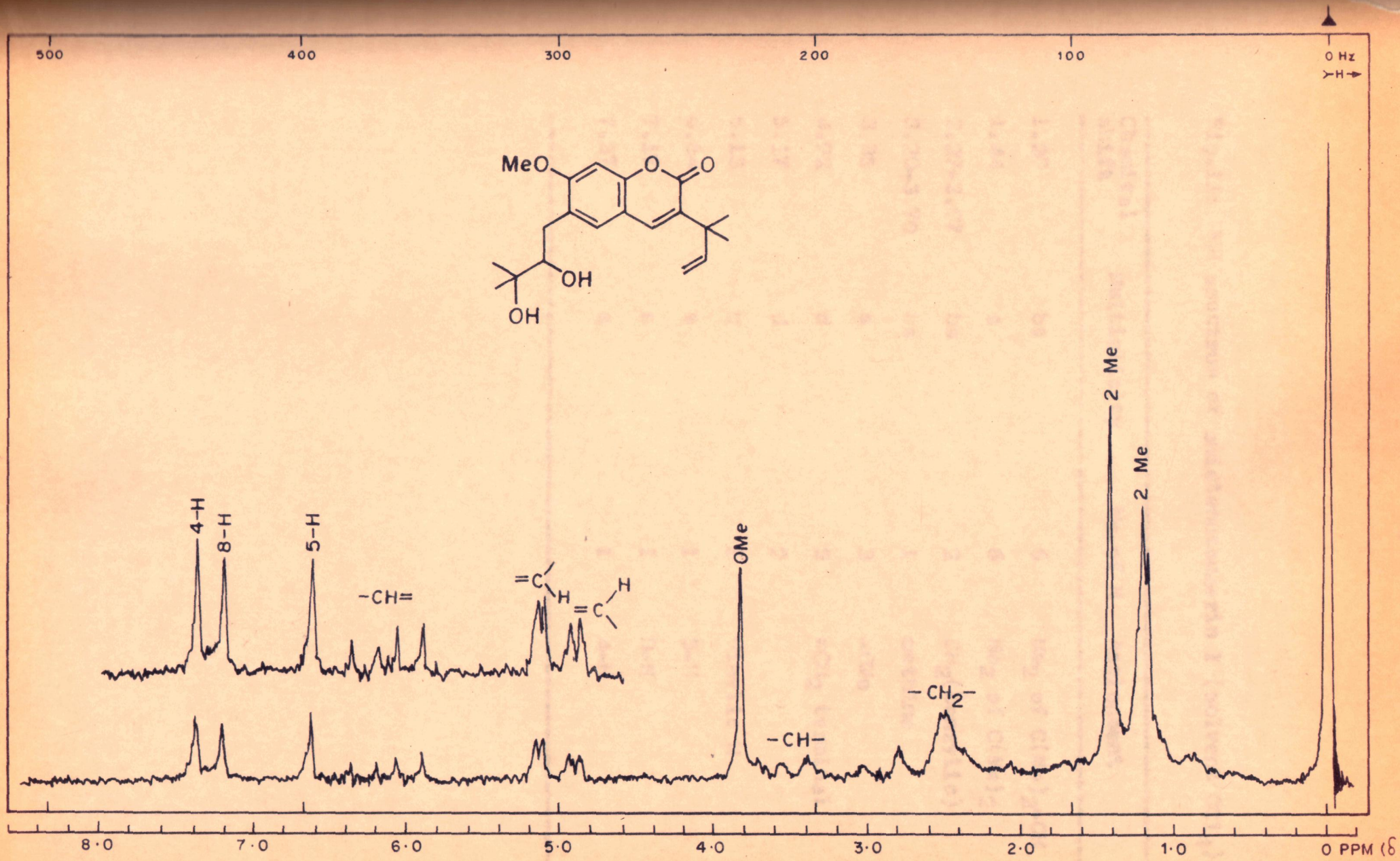
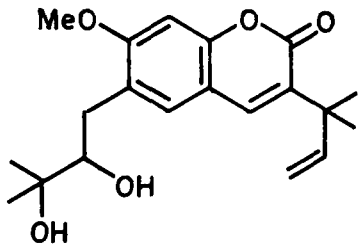


FIG. 11. NMR SPECTRUM OF SWIETENOCOUMARIN-I IN CCl_4

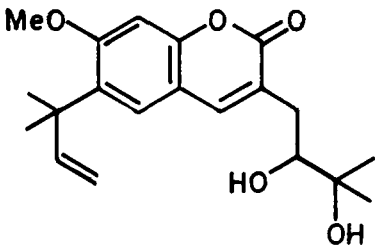
Fig.11: NMR spectrum of swietenocoumarin I (solvent CCl_4)

Chemical shift	Multiplicity	No.of H	Assignment
1.20	bs	6	Me_2 of $C(Me)_2$-OH
1.44	s	6	Me_2 of $C(Me)_2$
2.27-3.07	bs	2	CH_2(benzylic)
3.20-3.70	bs	1	methine
3.85	s	3	-OMe
4.92	d	2	$=CH_2$ terminal
5.17	d	2	"
6.13	q	1	Vinylic H
6.64	s	1	5-H
7.17	s	1	8-H
7.37	s	1	4-H

appear to be present as hydroxyls (as shown by its IR: 3400 cm^{-1}), forming a part of the C_5 side chain. The characteristic coumarin doublets are absent and the signal at 7.37 indicates that one of the side chains is at C-3 position of a coumarin nucleus. The presence of a methoxyl group at 7-position rather than at 6 is favourable biogenetically. The absence of any ortho or meta coupled signals enables to show that the substitution is at 6- and 7-positions only. Thus a 2,3-dihydroxy-3,3-dimethylallyl side chain may be present at C-6 of a coumarin. The above data suggests structure (XXX) and (XXXa) to this coumarin.



XXX



XXX a

The former structure is preferred on the basis that 3-substituted 1,1-dimethylallyl coumarins (e.g. xylotenin, rutamarin) have been encountered in Chloroxylon swietenia and other Rutaceous plants.

The compound forms a diacetate (M^+ 430) as indicated by its NMR spectrum, which shows additional signals at 1.77 and 1.90 due to acetoxyl group.

Examination of the ether extract

The ether soluble fraction was extracted with 5% aqueous sodium hydroxide. The alkali extract was then neutralised with hydrochloric acid (10%) and extracted with ether. Solvent was removed to get a gummy product which was a mixture of compounds as shown by TLC(silica gel , 2:8 acetone-benzene) and kept aside.

The alkali insoluble ether extract on chromatographic separation over a column of silica gel, using benzene-acetone with increasing polarity, yielded three compounds of which two are new furanocoumarins.

Compound 21, m.p.146°, $C_{20}H_{16}O_6$ (M^+ 352). IR shows absorptions at 1740 (-C=O); 1640, 1600 cm^{-1} (aromatic). Its NMR spectrum exhibits five aromatic protons in the region 7.20-6.75 and a single proton signal appearing at 7.45 can be attributed to the Ar-CH=. The two proton singlets at 6.05 and 5.95 can be assigned to two methylene dioxy groups. A two proton doublet at 4.30 may be due to the methylene attached to an oxygen. A multiplet centered at 3.70, integrating for a single proton, can account for methine of $Ar-CH_2-CH$. Signals appearing in the region

3.17-2.57 may be arising due to the benzylic methylene forming a part of an ABX system.

The above data are in complete agreement with sevinin (XXXIII) (lit.[22] m.p.146°) previously reported by Lin et al.[22] from the heartwood of Taiwania cryptomerioides (F. Taxodiaceae).

Compound 22 (swietenocoumarin C), m.p. 155°, $C_{16}H_{14}O_4$ (M^+ 270). ν max. 1720 cm^{-1} (α,β-unsaturated lactone) and UV spectrum $\lambda_{max.}^{EtOH}$ (log ϵ): 243 (4.13), 249(4.15), 263(4.10), 269.2(4.11), 310(4.00).

The NMR spectrum (Fig.12) displays characteristic signals which can be attributed to the protons of the furanocoumarin nucleus. The doublets (J=10 Hz) at 7.74 and 6.30 are assigned to 4-H and 3-H, and doublets (J=2 Hz) at 7.70 and 6.80 represent 2'-H and 3'-H respectively. A lone aromatic proton is seen as a singlet at 7.60. The appearance of two methyl singlets at 1.60 and 1.40, and a methylene and a methine protons as a multiplet centered at 3.30 indicates the presence of a C_5 unit.

Furanocoumarin skeleton accounts for three oxygens, hence the fourth oxygen has to be present on the side chain either as a hydroxyl group or an epoxide. However, its

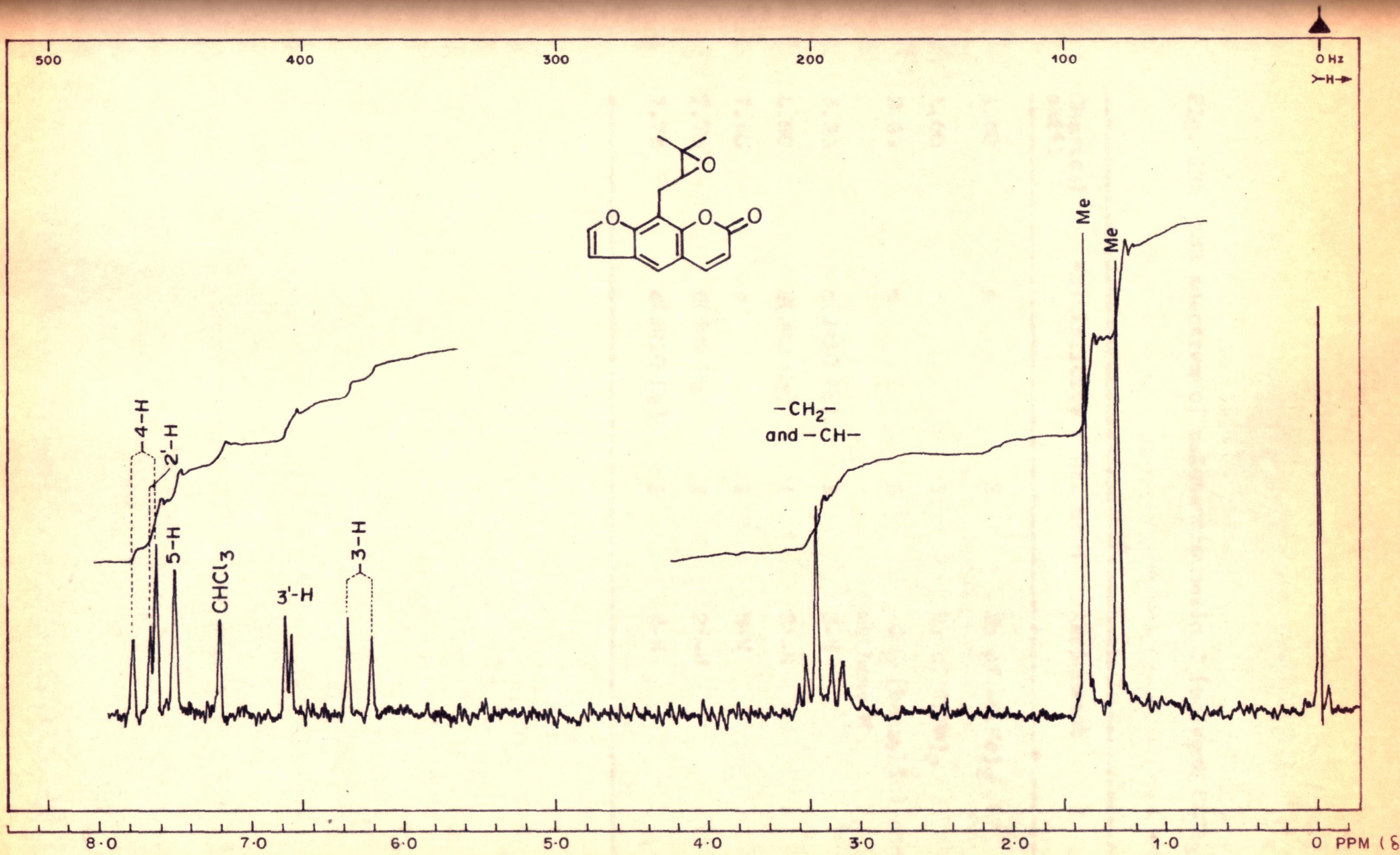


FIG. 12. NMR SPECTRUM OF SWIETENOCOUMARIN-C IN $CDCl_3$

Fig. 12: NMR spectrum of swietenocoumarin C (solvent $CDCl_3$)

Chemical shift	Multiplicity	No. of H	Assignment
1.40	s	3	Me of $-C(Me)_2$
1.60	s	3	Me of $C(Me)_2$
3.30	m	3	$-CH_2$ (benzylic) and methine H
6.30	d(J=10 Hz)	1	3-H
6.80	d(J=2 Hz)	1	3'-H
7.60	s	1	5-H
7.70	d(J=2 Hz)	1	2'-H
7.74	d(J=10 Hz)	1	4-H

IR spectrum lacks hydroxyl absorption. This suggests that there might be a side chain with an epoxide ring on it, which is substantiated by the loss of C_4H_7O ion in the mass spectrum (Fig.13). The chemical shifts of the methylene and methine protons are appearing in the region as that of similar protons of sibiricin[23] (XLII) and isobakygelicol[24] (XXXVII) which have identical C_5 unit. Its mass spectrum (Fig.13) shows base peak at m/e 270 and other peaks at m/e 212, 199, 184, 171, 115 (chart 4). On the basis of the above data, structure (XXIV) is proposed for swietenocoumarin C.

Swietenocoumarin A (XXII) on treatment with perbenzoic acid gave (XXIV) identical (TLC and mixed m.p.) with swietenocoumarin C.

Compound 23 (8-prenylnodakenetin), m.p. 111°, $C_{19}H_{22}O_4$ (M^+ 314). ν max. 3300 (-OH), 1700 cm^{-1} (α,β-unsaturated lactone), and UV absorptions at $\lambda_{max.}^{EtOH}$ (log ϵ): 249.2 (4.23), 262(sh) (3.66), 332(4.16). The NMR spectrum (Fig.14) shows: doublets (J=10 Hz) appearing at 7.4(4-H) and 6.08 (3-H) for coumarin. A broad triplet for vinylic proton at 5.20 in conjunction with a doublet at 3.17 for methylene (benzylic and allylic) and two methyl singlets at 1.80 and 1.66 suggest the presence of a 3,3-dimethylallyl group. A singlet appearing at 6.95, integrating for one proton, can be assigned to an aromatic proton.The presence

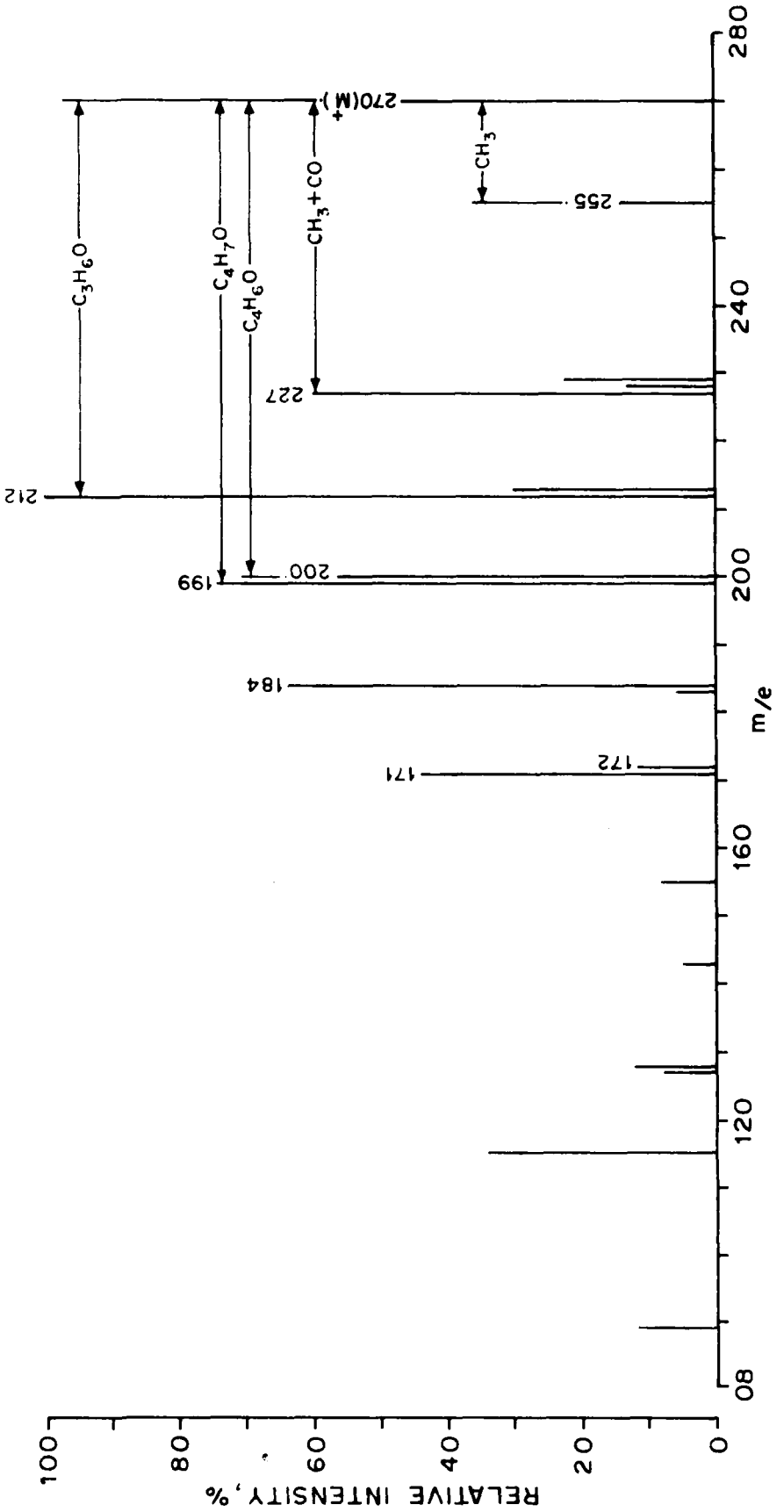
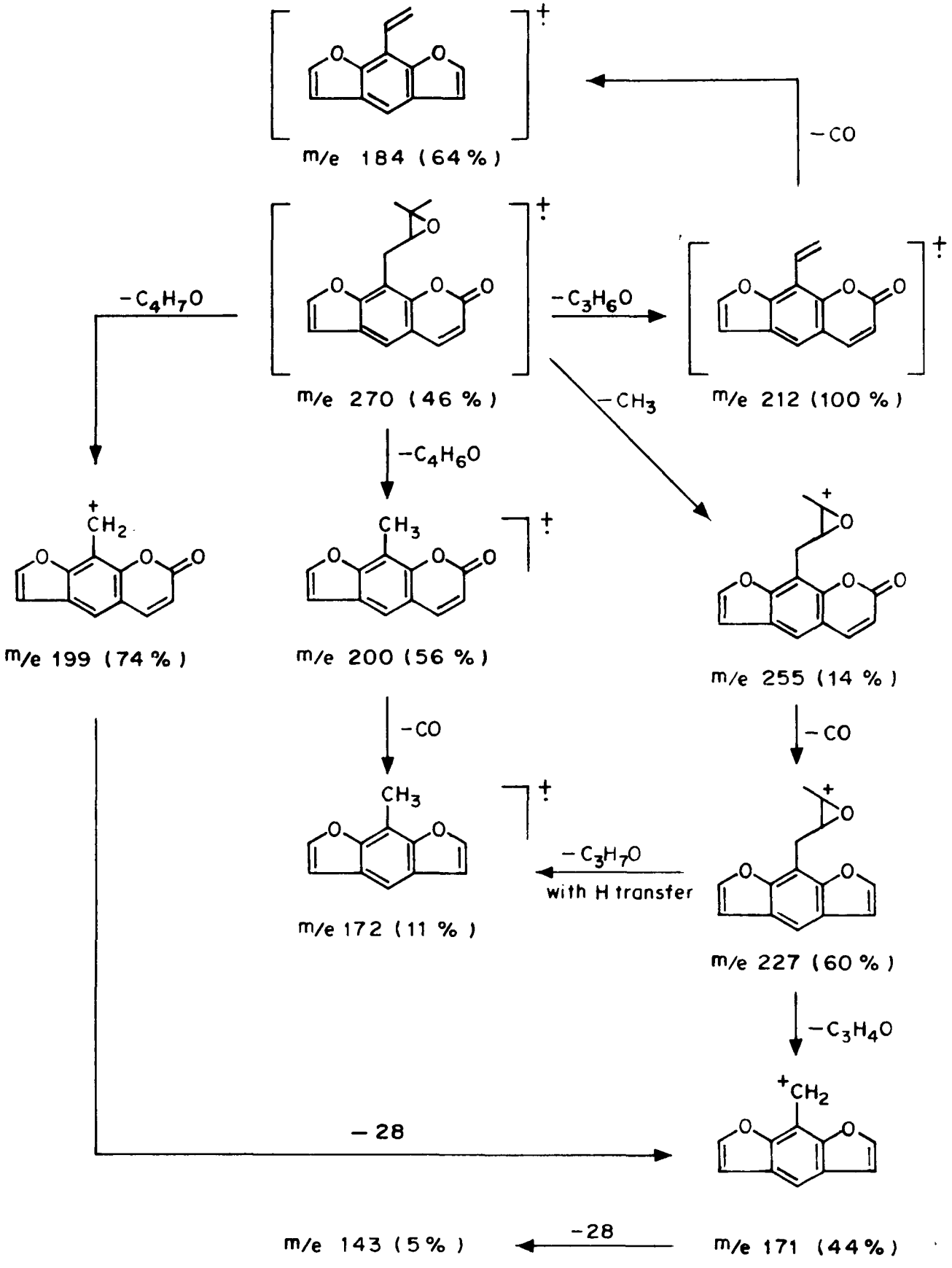

RELATIVE INTENSITY, %
100
80
60
40
20
0
m/e
80
120
160
200
240
280
270(M+)
255
227
212
200
199
184
172
171
CH3
CH3+CO
C4H6O
C4H7O
C3H6O

FIG. 13

CHART 4 MASS SPECTRAL FRAGMENTATION OF SWIETENOCOUMARIN-C



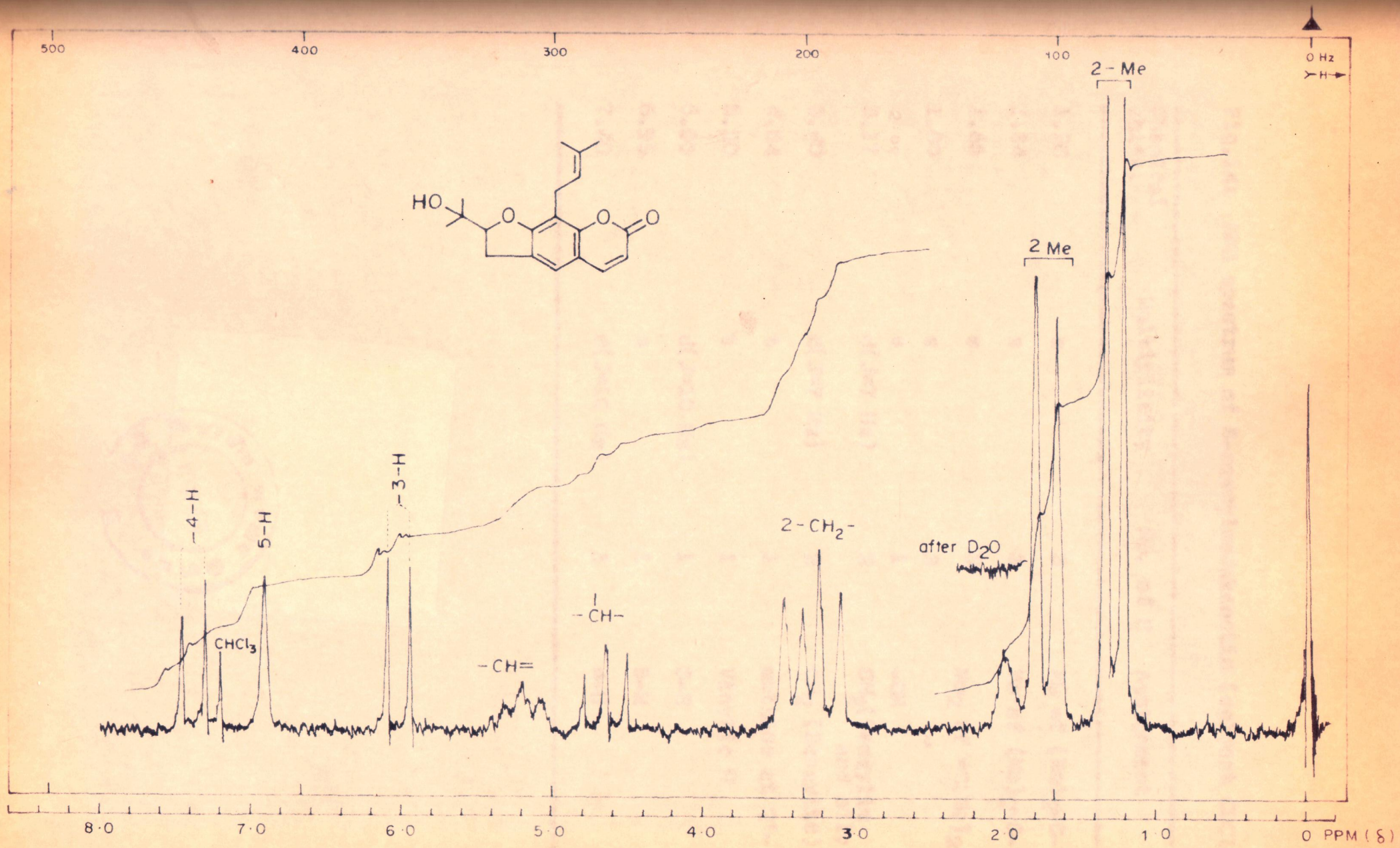


FIG. 14. NMR SPECTRUM OF 8-PRENYLNODAKENETIN IN $CDCl_3$

Fig.14: NMR spectrum of 8-prenylnodakenetin (solvent $CDCl_3$)

Chemical shift.	Multiplicity	No. of H	Assignment
1.20	s	3	Me of $(Me)_2$-C-OH
1.34	s	3	Me of $(Me)_2$-C-OH
1.66	s	3	Me_2 of $=C(Me)_2$
1.80	s	3	"
2.00	s	1	-OH
3.17	d(J=7 Hz)	2	CH_2(Benzylic and allylic)
3.40	d(J=7 Hz)	2	CH_2 (Benzylic)
4.64	t	1	methine at 2'-
5.20	t	1	Vinylic H
6.05	d(J=10 Hz)	1	3-H
6.95	s	1	5-H
7.40	d(J=10 Hz)	1	4-H

of two oxygens in coumarin ring, and the third as a hydroxyl is borne out from its IR absorption at 3300 cm^{-1}. The signals appearing at 1.20 and 1.34 (s, 3H each); 3.40 (d, 2H, J=7 Hz); 4.64 (t, 1H) enable us to account the fourth oxygen as a part of the hydroxyisopropyl dihydrobenzofuran system.

The mass spectrum (Fig.15) shows the molecular ion (m/e 314) as the base peak and other fragment ion peaks at m/e 299 (M-15), 281 (M-15-18), 256(M-58), 255(M-59) (chart 5).

The prenyl side chain can obviously be at 8-position and hence the compound has been identified as 8-prenylnoda-kenetin (XII).

Examination of the chloroform extract

Fractionation of the chloroform extract on a column of silica gel afforded four new compounds:

Compound 24 (swietenocoumarin D), m.p.150°, $C_{17}H_{16}O_5$ (M^+ 300). Its IR spectrum displays characteristic band at 1725 cm^{-1} (α,β-unsaturated lactone) and UV spectrum $\lambda_{max.}^{EtOH}$ (log ε): 242 (3.83, 249.5(3.86), 263.2(3.87), 270(3.89), 310.5(3.80). The NMR spectrum (Fig.16) shows a three proton singlet at 4.20 (-OMe) and the remaining signals are in complete consonance with the spectrum of swietenocoumarin C (XXIV) except that the lone aromatic proton is absent. The only variation is that the signals

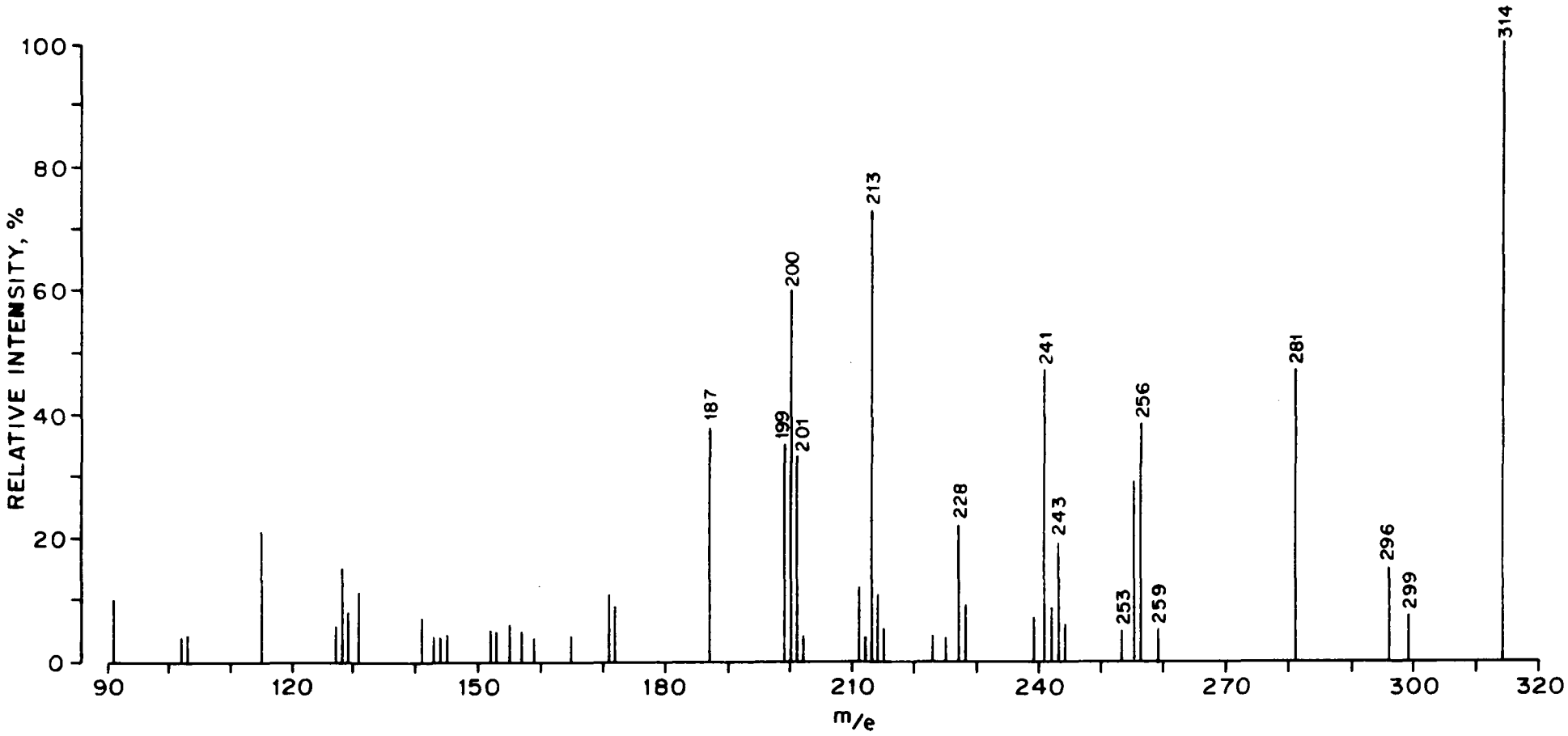
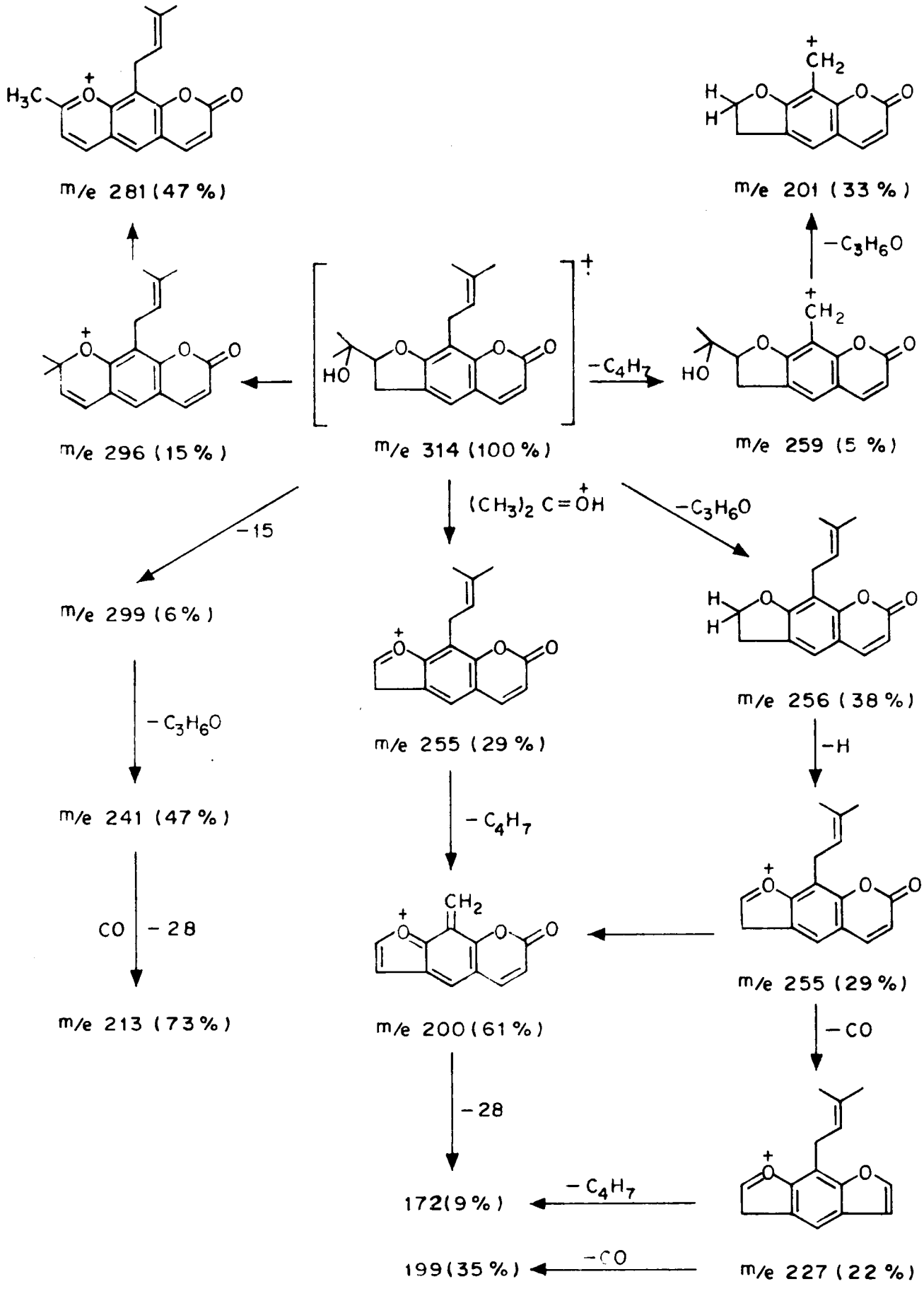

RELATIVE INTENSITY, %
100
80
60
40
20
0
90
120
150
180
210
240
270
300
320
m/e
314
213
200
187
199
201
241
281
256
228
243
296
253
259
299

FIG. 15

CHART 5 MASS SPECTRAL FRAGMENTATION OF 8-PRENYLNODAKENETIN



appearing at 8.12 and 7.07 for 4-H and 3'-H are shifted downfield by 0.38 and 0.27 ppm, confirming that the -OMe is at 5-position.

The mass spectrum shows M^{+} 300 and other intense peaks at m/e 285 (M-15), 258(M-43), 229(M-71, C_4H_7O), and 187. Hence the compound is characterised as swietenocoumarin D (XXV). The validity of these assignments is further augumented by the chemical conversion of swietenocoumarin B (XXIII) to D (XXV) by treating the former with perbenzoic acid.

Swietenocoumarin D (XXV) on refluxing with 10% aqueous sodium hydroxide gave an acid (XXXV), m.p. 160°. Its NMR spectrum (Fig.17) in acetone-pyridine shows signals at: 1.27 and 1.47 (s, 3H each, C-methyls), 3.44(s, 2H, benzylic methylene), 3.97 (s, 3H, -OMe), 4.80 (broad triplet, 1H, methine), 5.97 (d, J=12 Hz, α-H), 6.90 (d, J=2 Hz, 1H, 3'-H), 6.97 (d, J=12 Hz, β-H), 7.47 (d, J=2 Hz, 2'-H).

The isomeric compound (XXXVII) having methoxyl group at 8-position and the epoxy C_5 side chain at 5-position has been reported from Thamnosa montana.[24]

Compound 28, m.p.118°, characterised as chalepin(I) (lit.[25] m.p. 118°), an isomer of helietin, isolated earlier from Ruta chalepensis.

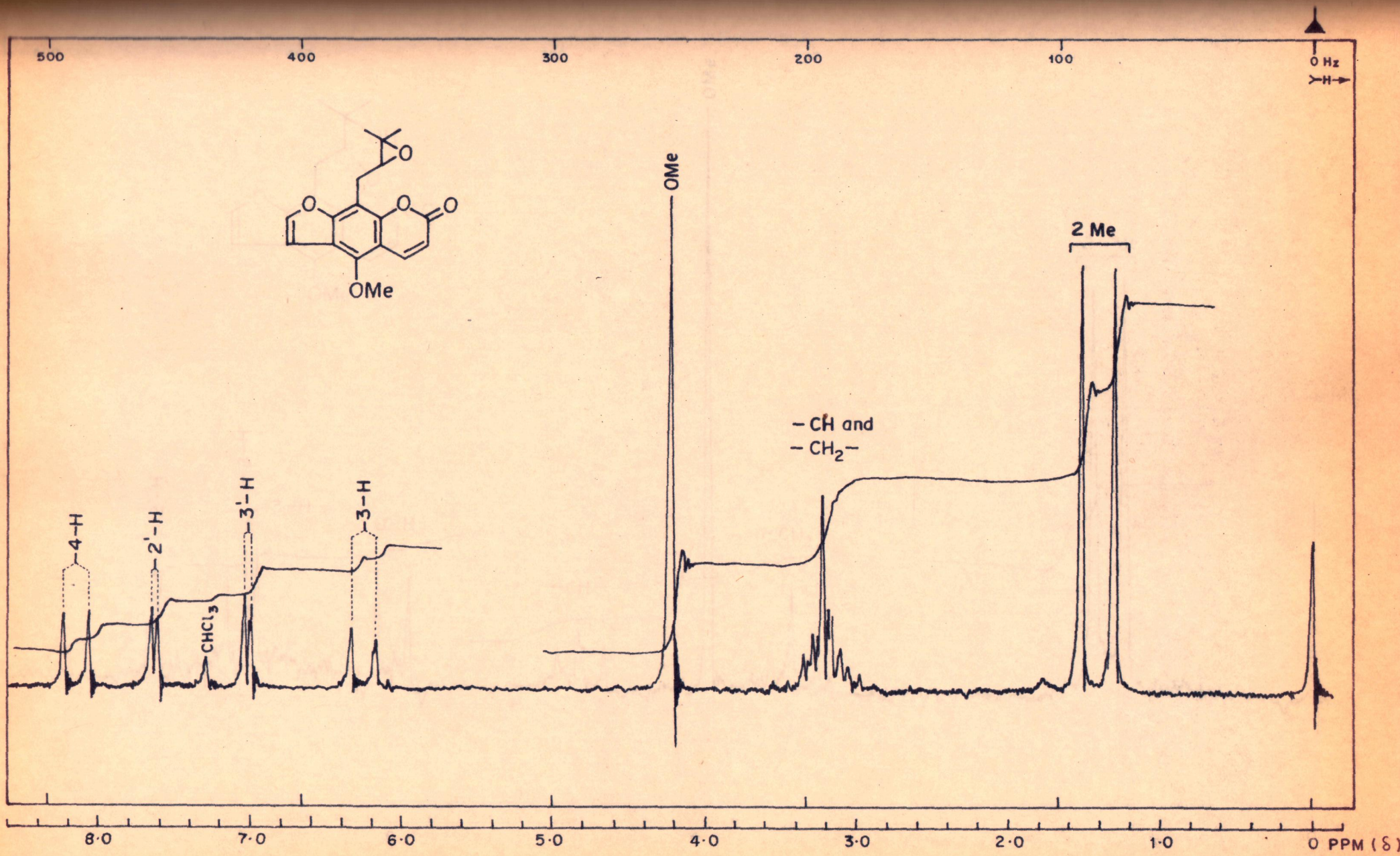


FIG. 16. NMR SPECTRUM OF SWIETENOCOUMARIN-D IN $CDCl_3$

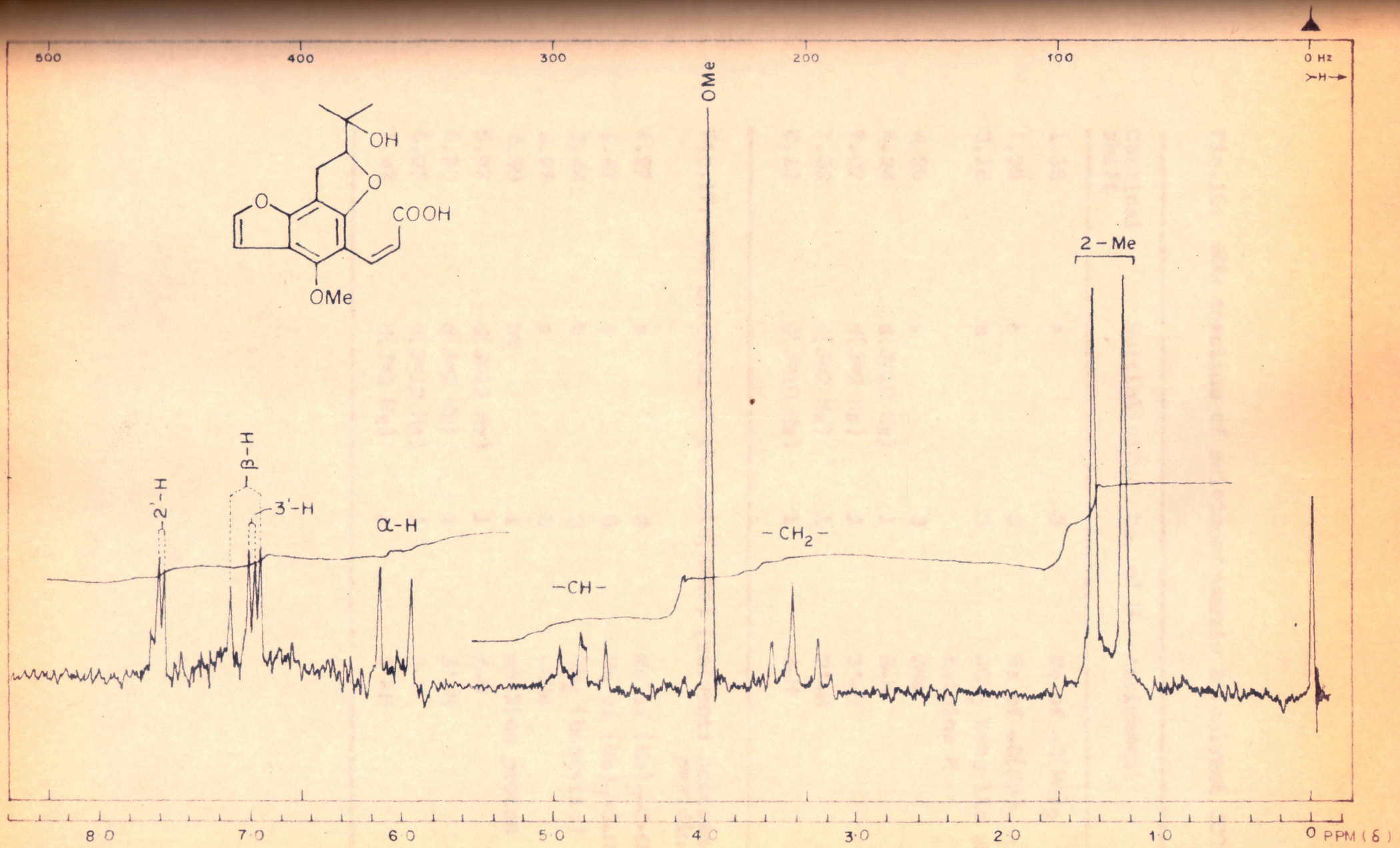


FIG. 17. NMR SPECTRUM OF SWIETENOCOUMARIC ACID IN ACETONE AND PYRIDINE

Fig.16: NMR spectrum of swietenocoumarin D (solvent $CDCl_3$)

Chemical shift	Multiplicity	No. of H	Assignment
1.33	s	3	Me of $-C(Me)_2$
1.55	s	3	Me of $-C(Me)_2$
3.16	m	3	$-CH_2$ benzylic and methine H
4.20	s	3	OMe
6.24	d(J=10 Hz)	1	3-H
7.07	d(J=2 Hz)	1	3'-H
7.62	d(J=2 Hz)	1	2'-H
8.12	d(J=10 Hz)	1	4-H

Fig.17: NMR spectrum of the acid(XXXV) (solvent: Acetone-pyridine

1.27	s	3	Me of $(Me)_2$-C-OH
1.47	s	3	Me of $(Me)_2$-C-OH
3.44	t	2	CH_2 (benzylic)
3.97	s	3	-OMe
4.80	bt	1	methine proton
5.97	d(J=12 Hz)	1	<-H
6.90	d(J=2 Hz)	1	3'-H
6.97	d(J=12 Hz)	1	>-H
7.47	d(J=2 Hz)	1	2'-H

Compound 26 (suletenocoumarin E), m.p.164-66°, $C_{16}H_{16}O_5$ (M^+ 288). Its IR shows absorptions at 3300 (-OH), 1720 cm^{-1} (α,β-unsaturated lactone, and $\lambda_{max.}^{EtOH}$ (log ε): 244.5 (4.16), 248(4.18), 262.5(sh) (3.76), 300(3.87). The NMR spectrum (Fig.18) exhibits two pairs of doublets(J=10 Hz) at 8.09 (4-H), 6.34 (3-H) and (J=2 Hz) at 8.02 (2'-H) and 7.07 (3'-H) suggesting it to be a furanocoumarin skeleton. A singlet at 7.80 accounts for the aromatic proton. The signals at 4.40 (m, 1H, methine), 3.57 (d, J=7 Hz, benzylic methylene) and 1.70 (s, 6H, two methyls) indicate the presence of a C_5 side chain.

Of the total count for oxygens, three account for the furanocoumarin, and the presence of the remaining oxygens as hydroxyls is borne out by its IR spectrum which exhibits O-H streching band at 3300 cm^{-1}. Further it formed a crystalline diacetate (m.p.106°, M^+ 372) indicating the presence of two hydroxyl groups. The NMR spectrum of the acetate (Fig.19) has all the features of the parent compound and shows two additional signals at 2.04 and 1.76 due to acetoxyl groups. The downfield shift of the methine proton by 1.04 ppm indicates the presence of an acetoxyl group on the carbon bearing methine proton.

Its mass spectrum (Fig.20) shows base peak at m/e 187 together with other peaks at m/e 288, 273, 271, 260,

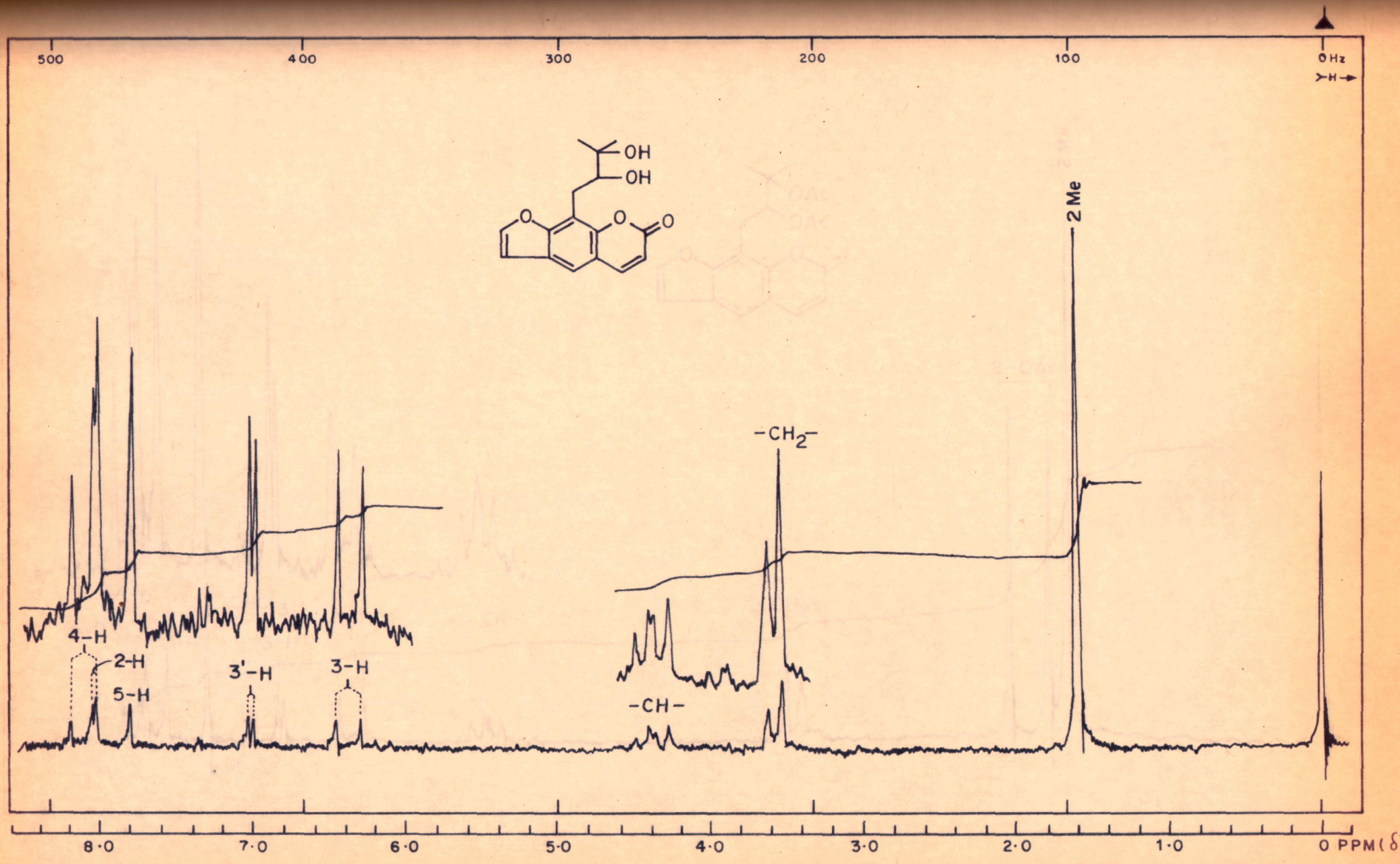


FIG. 18. NMR SPECTRUM OF SWIETENOCOUMARIN-E IN DMSO AND PYRIDINE

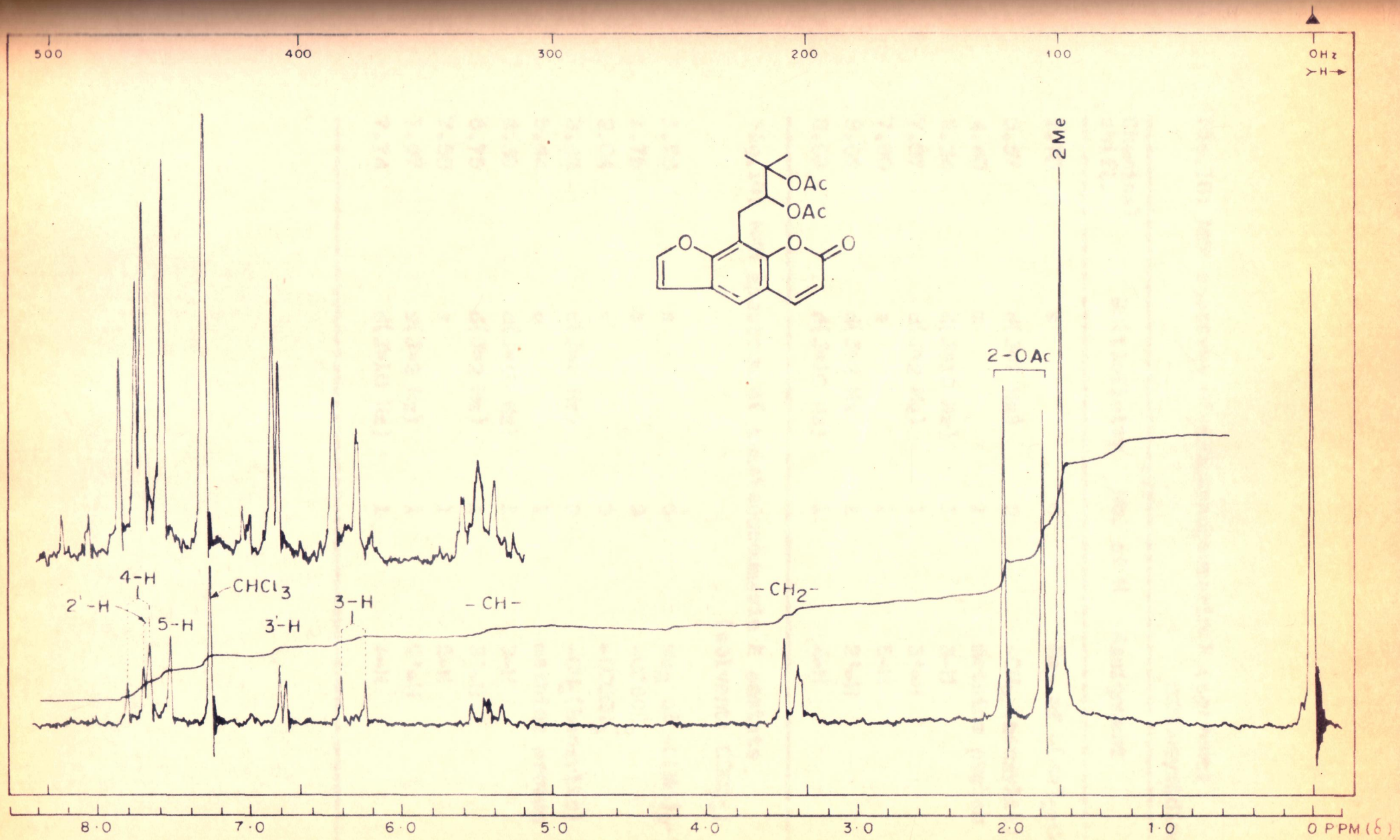


FIG. 19. NMR SPECTRUM OF SWIETENOCOUMARIN-E ACETATE IN $CDCl_3$

Fig.18: NMR spectrum of swietenocoumarin E (solvent: DMSO+pyridine)

Chemical shift.	Multiplicity	No. of H	Assignment
1.70	s	6	Me_2 of $-(Me)_2-C-OH$
3.57	d(J=7 Hz)	2	$-CH_2$ (benzylic)
4.40	m	1	methine proton
6.34	d(J=10 Hz)	1	3-H
7.07	d(J=2 Hz)	1	3'-H
7.80	s	1	5-H
8.02	d(J=2 Hz	1	2'-H
8.09	d(J=10 Hz)	1	4-H

Fig.19: NMR spectrum of swietenocoumarin E acetate (solvent: $CDCl_3$)

1.70	s	6	Me_2 of $-C(Me)_2-OAc$
1.76	s	3	$-OCOCH_3$
2.04	s	3	$-OCOCH_3$
3.42	d(J=7 Hz)	2	$-CH_2$(benzylic)
5.44	q	1	methine proton
6.39	d(J=10 Hz)	1	3-H
6.75	d(J=2 Hz)	1	3'-H
7.50	s	1	5-H
7.67	d(J=2 Hz)	1	2'-H
7.74	d(J=10 Hz)	1	4-H

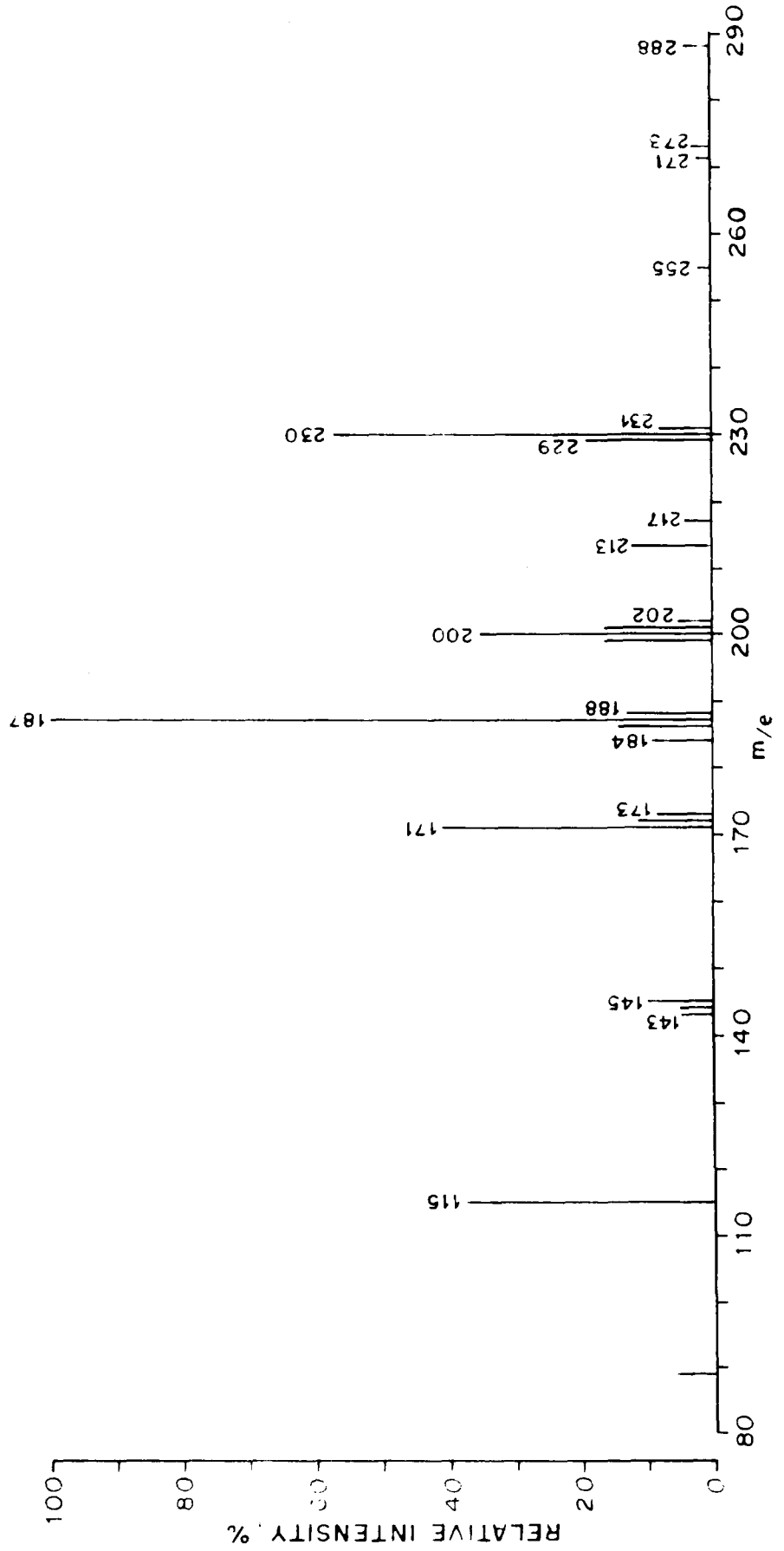
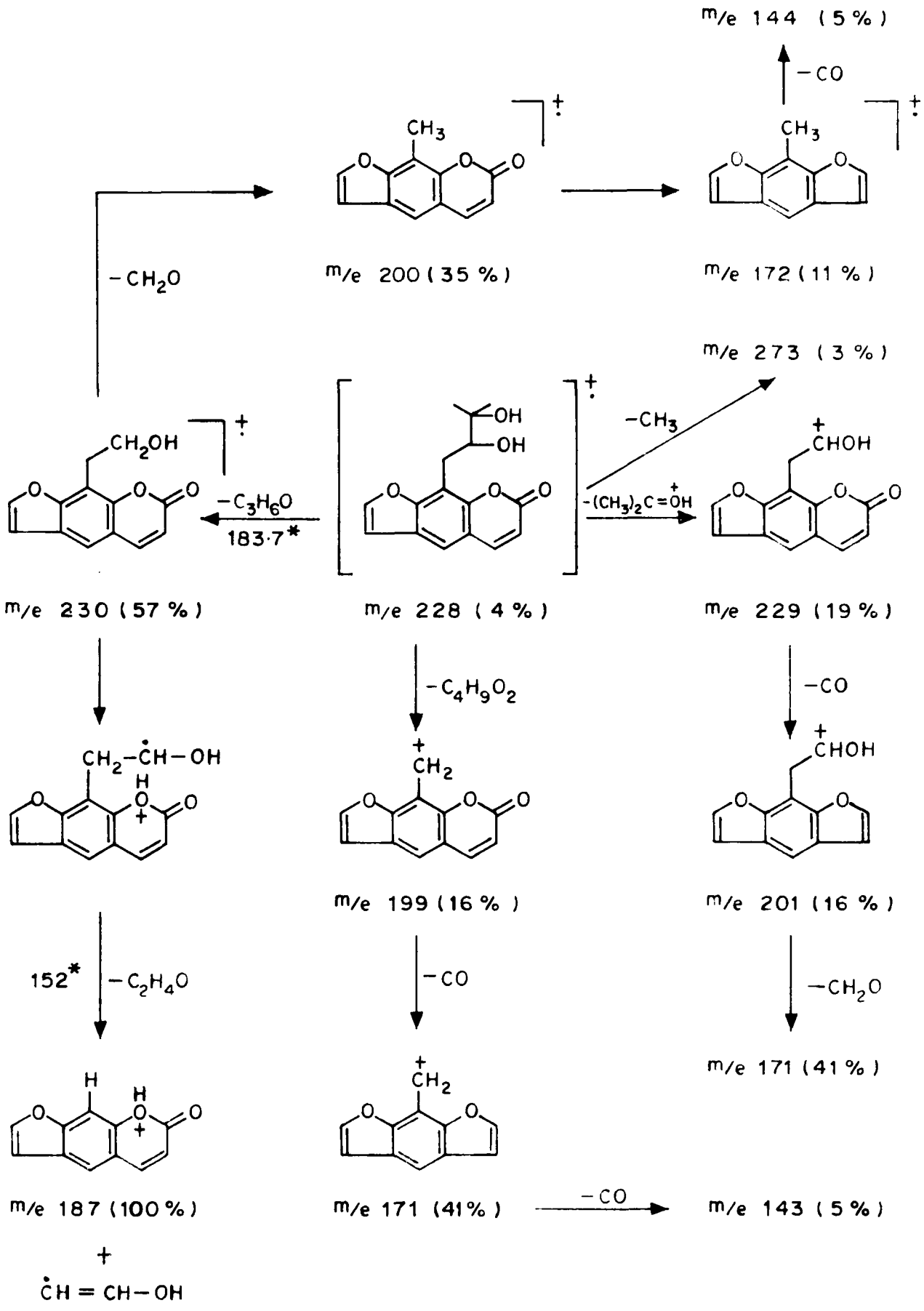

RELATIVE INTENSITY, %
100
80
60
40
20
0
80
110
140
170
200
230
260
290
m/e
288
273
271
255
234
230
229
217
213
202
200
188
187
184
173
171
145
143
115

FIG 20

CHART 6. MASS SPECTRAL FRAGMENTATION OF SWIETENOCOUMARIN-E



255, 230, 229, 200, 199, 186, 171 and 115 (chart 6). Thus the compound (swietenocoumarin F) has been assigned structure (XXVI).

Further evidence in support of structure (XXVI) is obtained by the chemical conversion swietenocoumarin C (XXIV) to E (XXVI) by the treatment of the former with 1% oxalic acid solution.

Compound 27 (swietenocoumarin F) m.p.178-79°, $C_{17}H_{18}O_6$ (M^+ 318). IR shows bands at 3300 (-OH), 1720 cm^{-1} (α,β-unsaturated lactone) and $\lambda_{max.}^{EtOH}$ (log ϵ): 242.8 (3.87), 249.2 (3.88), 245 (3.90), 272(3.91), 311(3.83). The NMR spectrum (Fig.21) is alike that of swietenocoumarin E (XXVI), except an additional signal at 4.20 (OMe) and the absence of an aromatic proton.

Thus structure (XXVII) has been assigned to swietenocoumarin F. The mass spectrum is also in support of structure (XXVII). Further, it formed a crystalline diacetate under standard conditions. The NMR spectrum of the diacetate revealed the presence of two additional singlets appearing at 2.00 and 1.77 ascribable to the acetoxyl group.

Dreyer[25] had reported the isolation of an isomeric furanocoumarin (XXXVIII) in which the methoxyl group is at

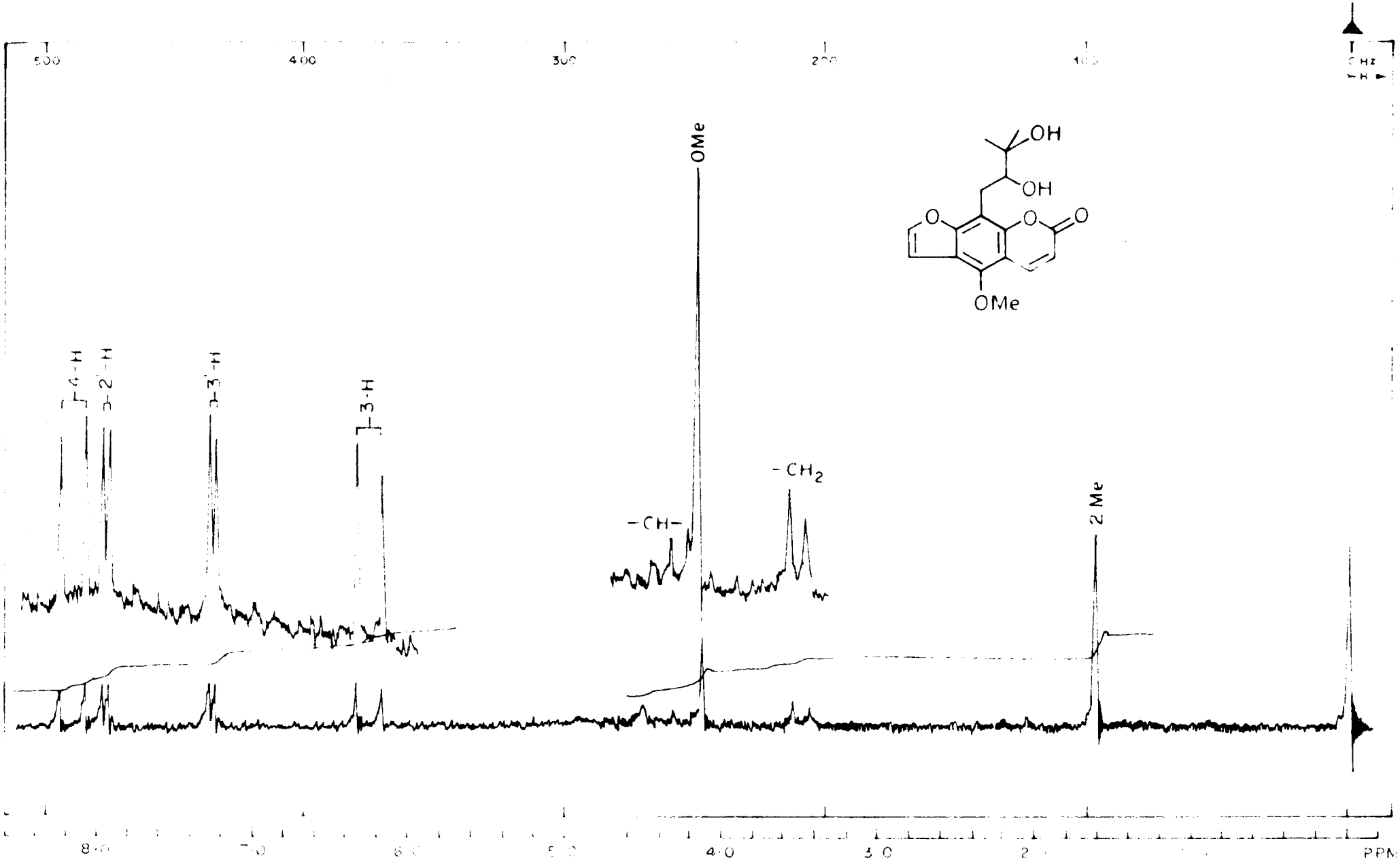


FIG. 21. NMR SPECTRUM OF SWIFTENOCOUMARIN-F IN DMSO AND PYRIDINE

Fig.21: NMR spectrum of swietenocoumarin F

(Solvent: DMSO-pyridine)

Chemical shift	Multiplicity	No. of H	Assignment
1.60	s	6	Me_2 of $-C(Me)_2-OH$
3.53	d(J=7 Hz)	2	$-CH_2$ (benzylic)
4.20	s	3	-OMe
4.32-4.60	m	1	methine proton
6.24	d(J=10 Hz)	1	3-H
7.30	d(J=2 Hz)	1	3'-H
7.95	d(J=2 Hz)	1	2'-H
8x2			
8.17	d(J=10 Hz)	1	4-H

8-position and a 2,3-dihydroxy-3,3-dimethylallyl side chain is at 5-position. The m.p. is close to that of the above furanocoumarin (XXVII), but the conversion of swietenocoumarin D (XX V) to F (XXVII) by the treatment with 1% oxalic acid confirms structure (XXVII) assigned to swietenocoumarin F.

Compound 28 (swietenidin B) obtained as colourless needles, m.p.182°, $C_{11}H_{11}NO_3$ (M^+ 205) responds all tests for alkaloids. Its IR spectrum shows a number of bands at 3395, 1660, 1640, 1610, 1570, 1490, 1420 cm^{-1}, which are characteristic of 2- and 4-quinolones as well as of 2- and/or 4-methoxylated quinolines.[2] Further the carbonyl absorption is in the region 1640-1660 cm^{-1} observed for quinolones with free NH group. The NMR spectrum in DMSO (Fig.22) shows a single proton quartet (J=2 and 9 Hz) at 7.65, a three proton multiplet at 7.37-7.00 which can be assigned to the aromatic protons and two three protons singlets at 4.00 and 3.70 (two methoxyl groups).

Considering the spectral information, structure (XXXIV) can be assigned to swietenidin B. Oxygenation in the 4-position is common among the furoquinolines and 3-alkenyl-2-quinolones of the Rutaceae, but swietenidin A (XIX) and B (XXX IV) are the first quinolone alkaloids with a methoxyl group at 3-position. However, Ziegler

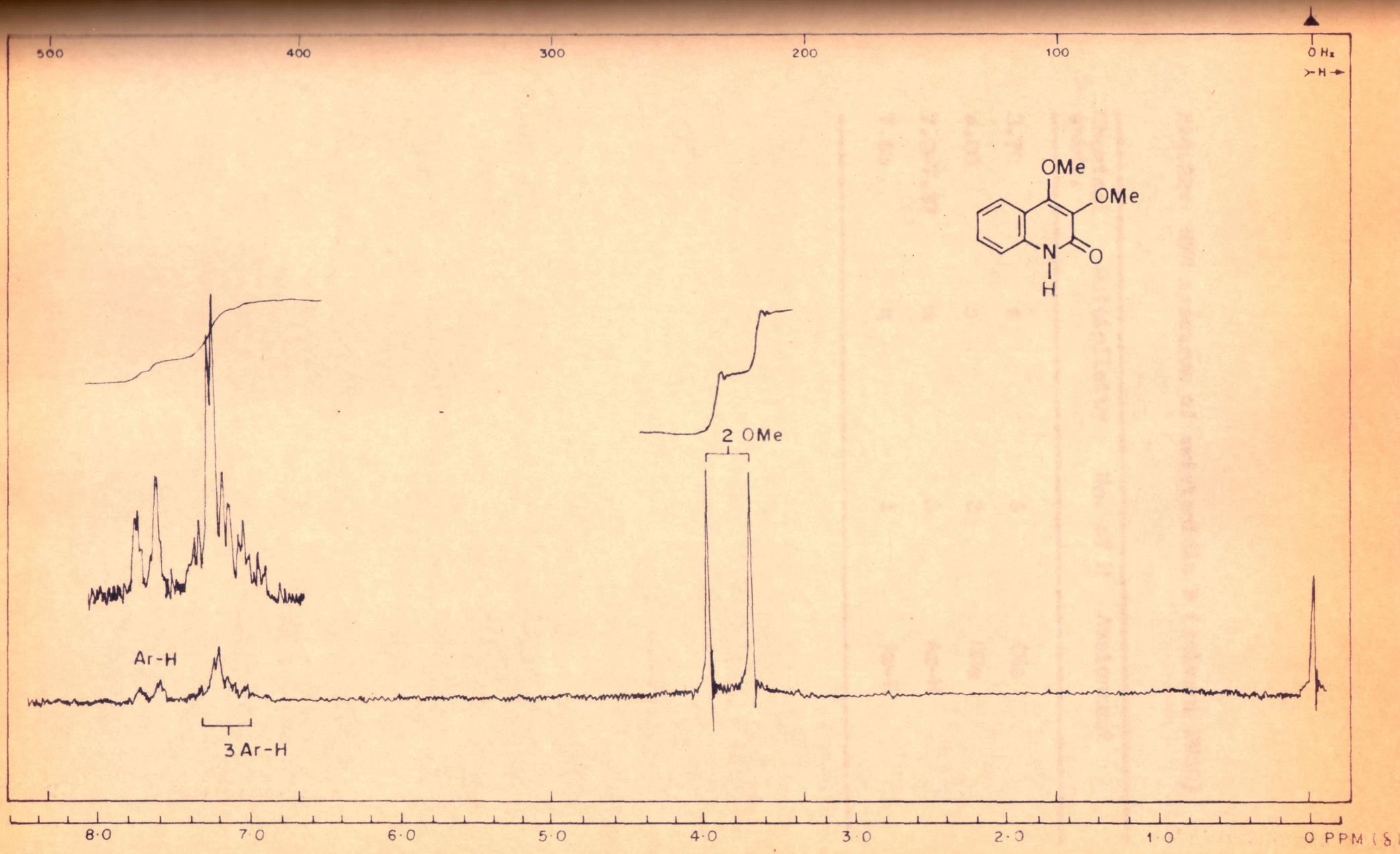


FIG. 22. NMR SPECTRUM OF SWIETENIDIN-B IN DMSO

Fig.22: NMR spectrum of swietenidin B (solvent DMSO)

Chemical shift.	Multiplicity	No. of H	Assignment
3.70	s	3	OMe
4.00	s	3	OMe
7.0-7.37	m	3	Ar-H
7.65	q	1	Ar-H

and Kappe[26] have reported the synthesis of swietenidin B.

Examination of the heartwood obtained from Madhya Pradesh

Cold extraction of the powdered heartwood with acetone yielded a reddish syrupy extract, which was successively extracted with hexane, benzene and chloroform. The hexane extract yielded an alkali soluble 7-demethyl-suberosin (IX), and its insoluble neutral part contained xanthoxyletin (IV) as a major compound.

Extraction of the benzene extract with aqueous sodium hydroxide gave additional quantities of 7-demethyl-suberosin and a gummy complex mixture which was not examined. Hydrochloric acid (2%) soluble part of the benzene extract led to the isolation of skimmianine (XIII). Column chromatography of the neutral benzene extract gave xanthoxyletin (IV) and allexanthoxyletin (VII), previously reported from the bark of Xanthoxylum americanum[27] and later on as the component of Chloroxylon swietenia heartwood.[8] In addition to these, a compound obtained as colourless needles, m.p.191°, is characterised as nodakenetin (XI) (lit.[7] m.p. 191-192°).

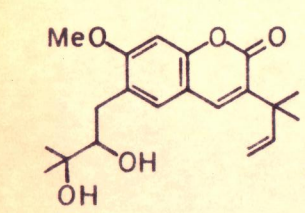
Biogenetic considerations

The biogenesis of coumarins is well established.[28] It has been shown that the biosynthesis of umbelliferon involves the ortho hydroxylation of the trans-p-hydroxy

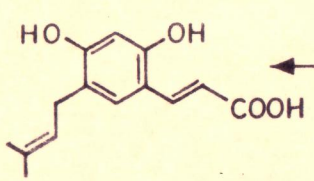
cinnamic acid, its glucosylation and subsequent isomerisation to the *cis*-acid. Prenylation can occur before or after cyclization of the acid. 2,4-Dihydroxy-5-prenyl cinnamic acid has been isolated from the heartwood of *Chlorexylon swietenia*[12] and is not an artefact from 7-demethylsuberosin (IX). The formation of the furan ring from an isoprenoid unit has been well established by various earlier workers.

A number of natural products with C-isoprenoid units modified as epoxide and diol have been reported from time to time. However, the co-occurrence of all these compounds in the same plant assumes considerable biogenetic significance.

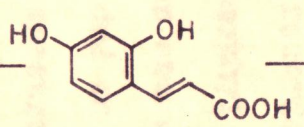
BIOGENESIS OF CHLOROXYLON COUMARINS

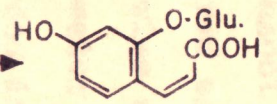


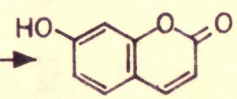
SWIETENOCOUMARIN-I

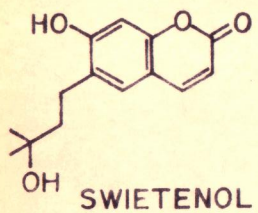


2,4-DIHYDROXY-5-
PRENYL CINNAMIC ACID

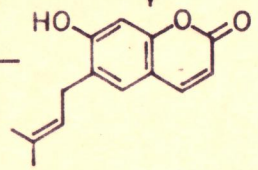




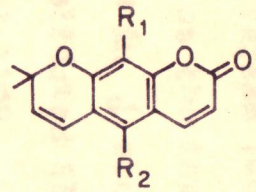




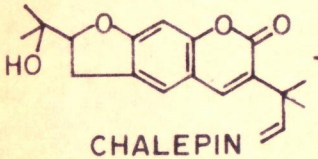
SWIETENOL



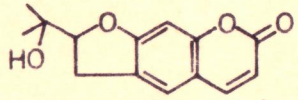
7-DEMETHYLSUBEROSIN



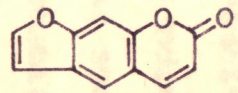
XANTHYLETIN $R_1 = R_2 = H$
XANTHOXYLETIN $R_1 = H$, $R_2 = OMe$
LUVANGETIN $R_1 = OMe$, $R_2 = H$
DEMETHYLLUVANGETIN $R_1 = OH$, $R_2 = H$



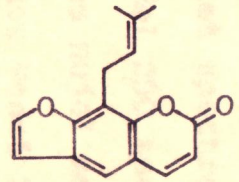
CHALEPIN



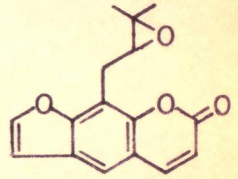
NODAKENETIN



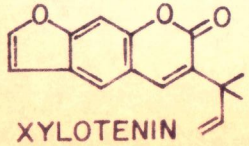
PSORALENE



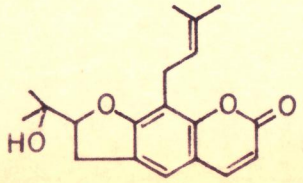
SWIETENOCOUMARIN-A



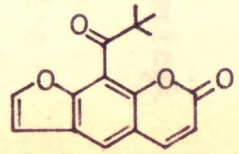
SWIETENOCOUMARIN-C



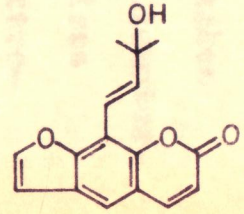
XYLOTENIN



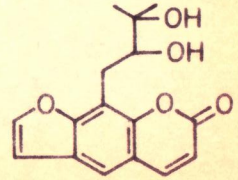
8-PRENYLNODAKENETIN



SWIETENONE



SWIETENOCOUMARIN-H



SWIETENOCOUMARIN-E

GENERAL REMARKS

Melting points are uncorrected and have been taken in capillaries. Ultraviolet spectra were taken in ethanol on a Perkin-Elmer Model 350 spectrophotometer. Infrared spectra were recorded as nujol mulls unless otherwise stated on a Perkin-Elmer Model 221 spectrophotometer or Perkin-Elmer Infracord. The maxima are recorded in cm^{-1}. Proton magnetic resonance spectra were recorded on a Varian T-60 spectrometers, using tetramethyl silane as the internal standard. The chemical shifts are reported in δ scale. Mass spectra were recorded on a Consolidated Electrodynamic Corporation mass spectrometer 21-110B.

EXPERIMENTAL

Extraction of the bark obtained from Achalour

The powdered bark of C. swietenia (2 kg) was extracted with cold acetone. The extract was concentrated to a small volume, mixed with exhausted bark powder and reextracted successively with hexane, benzene, ether, chloroform and acetone to yield 15, 5, 12, 8 and 9 g. of extracts respectively.

Isolation of swietenidin A (XIX)

The hexane and benzene extracts showed similar behaviour on TLC silica gel (1:9 acetone-benzene) and hence were mixed together. The product (20 g) was dissolved in ether (500 ml) and extracted with saturated sodium bicarbonate solution. The aqueous layer was neutralised with 2N hydrochloric acid and extracted with ether. The ether layer was dried over sodium sulphate and the solvent removed. The residue (700 mg) was dissolved in benzene and kept at room temperature, when pink cubes separated, m.p. 158-59°. It gave an orange colour to Dragendorff's reagent, and identified by its m.p. and mixed m.p. as swietenidin A (XIX). (Lit.[20] m.p.158-59°) (Found: C, 61.10; H, 5.40; N, 5.30. $C_{12}H_{13}O_4N$ required C, 61.20; H, 5.20; N, 5.90%).

After removal of bicarbonate extract, the ether layer was washed with water and the organic layer dried over sodium sulphate. Removal of the solvent gave a gummy extract (19 g). This was then chromatographed on a column of silica gel (400 g), and fractions of 250 ml each were collected, and similar fractions were pooled together.

Fractions 1-6 (5 g) contained mostly waxes and have not been examined.

Fractions 7-10 (1.3 g) crystallised as colourless plates from hexane (0.8 g), m.p. 90-91°.

IR: 1705 cm^{-1} (lactone -C=O). NMR (CCl_4): 1.50 (s, 6H, $-C(Me)_2$; 4.90 and 5.14 (two doublets, 1H each, $=CH_2$), 6.20 (q, 2H, vinylic H), 6.70 (d, J=2 Hz, 1H, 3'-H), 7.54 (s, 1H, 8-H); 7.40-7.57 (bm, 2H, 4-H and 5-H); 7.60 (d, J=2 Hz, 1H, 2'-H). This was characterised as xylotenin (IV) (lit.[9] m.p.91°) (Found: C, 74.70; H, 5.60. $C_{16}H_{14}O_3$ requires C, 75.60; H, 5.51%). Fractions 11-19(0.4 g) were mixtures and not examined further.

Fractions 20-22 (0.4 g) crystallized from hexane as colourless needles (0.2 g), m.p.113°. This was identified as swietenocoumarin A (XXII) (Found: C, 75.70; H, 5.43. $C_{16}H_{14}O_3$ requires C, 75.60; H, 5.51%).

Fractions 23-30 (0.5 g) crystallised as colourless prisms from hexane (0.4 g), m.p.145° and identified as swietenocoumarin B (XXIII) (Found: C, 71.70; H, 5.70.

$C_{17}H_{16}O_4$ requires C, 71.80; H, 5.60%).

Fractions 31-36 (0.8 g) were a mixture of swietenocoumarin B and suberosin.

Fractions 37-45 (0.9 g) crystallised from benzene as pale yellow prisms, m.p. 88°, and was characterised as suberosin (VIII) (lit.[15] m.p. 88-89°) (Found: C, 73.40; H, 6.40. $C_{15}H_{16}O_3$ requires C, 78.46; H, 6.35%).

Fractions 46-50 (0.55 g) were a mixture of suberosin rutamarin which were not purified further.

Fractions 51-75 (6.5 g) crystallised as colourless needles (5.9 g), m.p.104-105°.

NMR ($CDCl_3$): 1.40 and 1.80 (s, 6H and 3H each, Me_2 and AC of CMe_2OAc); 3.05 (m, -CH and CH_2 of dihydrofuran ring); 1.42 and 1.48 (s, 3H each, CMe_2), 5.10-4.70 (m, $=CH_2$); 6.10 (q, J=10 and 16 Hz for vinylic H); 7.37 (s, 1H, 4-H), 7.10 (s, 1H 5-H), 6.60 (s, 1H, 8-H). The compound is characterised as rutamarin (II) (lit.[6] m.p. 104-105°) (Found: C, 70.79; H, 5.50. $C_{21}H_{24}O_5$ requires C, 70.79; H, 5.60%).

Fractions 76-79 (0.4 g) were not worked up.

Fractions 80-88 (0.3 g) were mixtures and repeated crystallisations from benzene yielded colourless needles (0.18 g), m.p. 143-44°, M^+ 206. ν max. 1710 cm^{-1} (α,β-unsaturated lactone). NMR ($CDCl_3$): 3.97, 4.00 (s, 3H each, two OMe); 6.30 (d, J=10 Hz, 1H, 3-H), 6.90 (s, 2H, 5-H and 8-H), 7.64 (d, J=10 Hz, 4-H). It was characterised as

aesculetin dimethyl ether (X) (lit.[8] m.p.144°) (Found: C, 64.01; H, 4.79. $C_{11}H_{11}O_4$ requires C, 64.10; H, 4.85%).

Fractions 89-93 (0.35 g) obtained as colourless needles (0.2 g), m.p. 163-64°, M^+ 314. ν max. 3400 cm^{-1}(-OH), 1710 cm^{-1} (α,β-unsaturated lactone). NMR ($CDCl_3$): 1.27, 1.40 (s, 3H each, Me of $-C(Me)_2OH$); 1.51 (s, 6H, Me of $-C(Me)_2$-$CH{=}CH_2$); 1.84 (bs, 1H, exchangeable with D_2O, -OH); 3.30 (d, J=7 Hz, 2H, benzylic methylene); 4.84 (q, 1H, methine of $Ar.CH_2$-CH); 5.24 (bs, 2H, terminal $=CH_2$); 6.24 (d, 1H, vinylic H); 6.87 (s, 1H, 8-H), 7.34 (s, 1H, 5-H); 7.50 (s, 1H, 4-H). This was identified as heliettin (I) (lit.[9] m.p. 166°) (Found: C, 72.60; H, 7.00. $C_{19}H_{22}O_4$ requires C, 72.60; H, 7.20%).

Fractions 94-98 (0.3 g) were not worked up.

Fractions 100-102 (0.26 g) obtained as colourless prisms, m.p. 160°. ν max. 1720, 1700 cm^{-1} (α,β-unsaturated lactone). NMR ($CDCl_3$): 1.50 (s, 9H, $-CMe_3$), 6.43 (d, J=10 Hz, 1H, 3-H); 6.69 (d, J=2 Hz, 1H, 3'-H); 7.50 (s, 1H, 5-H); 7.60 (d, J=2 Hz, 1H, 2'-H); 7.60 (d, J=10 Hz, 1H, 4-H). This was characterised as suletenone (XVIII) (m.p. and mixed m.p.) (lit.[11] m.p. 160-61°) (Found: C, 70.90; H, 5.3. $C_{16}H_{14}O_4$ requires C, 71.10; H, 5.20%).

Examination of ether and chloroform extracts

The ether and chloroform extracts showed similar behaviour on TLC silica gel (1.5:8.5 acetone-benzene) and were mixed. The combined extract (20 g) was fractionated over a column of silica gel (280 mg), using benzene with increasing percentage of acetone as an eluent. Fractions of 100 ml. each were collected.

Fractions 1-38 (7 g) contained rutamarin, colourless needles, m.p. 105°, as a major compound.

Fractions 39-62 (1 g) were mixtures of three to four compounds. Attempts to get pure compounds by chromatography on silica gel and alumina column were unsuccessful.

Fractions 63-67 (0.12 g) obtained as colourless prisms from methanol, m.p. 194-95°. This was characterised as collinusin (XXXI) (lit.[16] m.p.195°) (Found: C, 70.01; H, 4.83. $C_{21}H_{18}O_6$ requires C, 69.90; H, 4.90%).

Fractions 68-81 (0.2 g) were mixtures of two compounds as showed by TLC silica gel (5:95 acetone-benzene). The mixture was purified by passing it through a short column of silica gel (eluent benzene). The faster moving fractions yielded more of collinusin, and the slower moving fractions gave colourless needles from benzene, m.p.141°, characterised as aesculetin dimethyl ether.

Fractions 82-100 (0.1 g) afforded more of aesculetin dimethyl ether (X).

Fractions 101-115 (0.9 g) crystallised from benzene-acetone mixture as colourless prisms, m.p.195°. The compound gave no colour with alcoholic ferric chloride, and was identified as demethylluvangetin (VI) (Found: C, 69.30; H, 5.10. $C_{14}H_{12}O_4$ requires C, 68.90; H, 4.90%).

Fractions 116-119 (0.09 g) were mixtures. Rechromatography over a column of silica gel gave bright yellow needles (0.04 g), m.p.190°, and characterised as swietenocoumarin G (XXVIII) (Found: C, 68.06; H, 5.47. $C_{17}H_{16}O_5$ requires C, 68.00; H, 5.30%).

Further fractions showed no separation and the column was eluted with acetone. Removal of acetone gave a gummy product (5 g). This was then taken up in ether and washed with aqueous sodium hydroxide (5%). Aqueous layer was then neutralized with aq. HCl (10%) and extracted with ether. Ether was removed and the extract (0.7 g) on passing over a column of silica gel gave pale yellow needles (0.11 g), m.p. 168°. It was identified as syringaresinol (XXXIII) (lit.[7] m.p. 170°) (Found: C, 63.30; H, 6.44. $C_{22}H_{26}O_8$ requires C, 63.20; H, 6.20%).

The alkali insoluble extract (3.5 g) was not examined further.

Acetone extract contains mostly tannins and was not examined.

Methylation of demethylluvangetin

A Mixture of demethyluvangetin (0.05 g), dimethyl-sulphate (0.2 ml) and anhydrous potassium carbonate (2 g) in acetone (25 ml) was refluxed for 12 hr. on a water bath. Acetone was then removed and water (25 ml) poured into it, extracted with ether and washed with water. Ether layer dried (Na_2SO_4) and concentrated. The gummy product crystallised from benzene in colourless needles, m.p. 108°. The physical properties were identical with known coumarin luvangetin (V) (lit.[8] m.p. 108°) (Found: C, 69.62; H, 5.10. $C_{15}H_{14}O_4$ requires C, 69.77; H, 5.43%).

Acetate of demethylluvangetin (VI)

Demethylluvangetin (0.025 g), acetic anhydride(1 ml) and a drop of pyridine were heated on a water bath for 2 hr. It gave colourless needles from benzene, m.p. 120°.

Acetone extract containing mostly tannins and was not examined.

Extraction of the bark obtained from Channapatnam (Karnatak St.)

The powdered bark of C. pubistania (8 kg) was extracted with cold acetone. The extract was concentrated under reduced pressure, and then adsorbed on the exhausted powder (300 g). The bark powder was successively re-extracted with hexane, benzene, ether, chloroform and acetone to yield 90, 30, 80, 50 and 30 g. of extracts respectively.

The hexane-benzene extracts showed similar behaviour on TLC silica gel (0.5:9.5 acetone-benzene) and were mixed together. The combined extract was dissolved in methanol (700 ml) and kept overnight at room temperature. The insoluble material mostly waxes and terpenes (72 g) was seperated by filteration. The methanolic filtrate of the hexane-benzene extract contained 48 g. of residue, of which 10 g. was fractionated, on a column of silica gel (300 g). The column was eluted initially with benzene and then with increasing percentage of acetone. Fractions of 200 ml. each were collected and similar fractions pooled together.

Fractions 1-7 (2.2 g) contained an oily material, which was not examined.

Fractions 8-18 (3.7 g) were a mixture of three compounds, and they were further seperated by rechromatography over a short column of silica gel, which yielded rutamarin and swietenocoumarin A.

Fractions 19-22 (0.15 g) obtained as yellow needles (0.09 g), m.p. 150°. IR: 1720 cm^{-1} (-C=O), NMR: (CDCl$_3$). NMR ($CDCl_3$): 4.37 (s, 6H, two OMe); 6.30 (d, J=10 Hz, 1H, 3-H); 7.04 (d, J=2 Hz, 1H, 3'-H); 7.67 (d, J=2 Hz, 1H, 2'-H); 8.17 (d, J=10 Hz, 1H, 4-H). The compound was characterised as isopimpinellin (XXI) (lit.[21] m.p. 150°) (Found: C, 63.20; H, 4.01. $C_{13}H_{10}O_5$ requires C, 64.40; H, 4.10%).

Fractions 23-28 (0.34 g) were a mixture of isopimpinellin and swietenocoumarin H (XXIX).

Fractions 29-31 (0.1 g) crystallised from benzene as pale yellow prisms, m.p. 157-58°, M^+ 270, and identified as swietenocoumarin H (XXIX) (Found: C, 71.31; H, 5.29. $C_{16}H_{14}O_4$ requires C, 71.10; H, 5.20%).

Fractions 32-40 (1.2 g) were subjected to silica gel column chromatography, which gave more of swietenocoumarin H (XXIX)(0.2 g) and a gummy mixture, which showed a mixture of compounds on TLC silica gel (1:9 acetone-benzene) and not examined further.

Fractions 41-44 (0.62 g) were gummy, and purified by repeated column chromatography over silica gel and PLC, using benzene and acetone as eluent. The purified compound (0.1 g) was homogeneous on TLC, but resisted crystallisation. This was identified as swietenocoumarin I (XXX) (Found: C, 69.31; H, 7.49. $C_{20}H_{26}O_5$ requires C, 69.36; H, 7.51%).

Fractions 45-50 (0.4 g) were complex mixtures. Further fractions did not show separation on TLC (silica gel), hence were not examined.

Acetylation of swietenocoumarin H (XXIX).

A mixture of swietenocoumarin H (0.06 g), acetic anhydride (1.5 ml) and pyridine (2 drops) was heated on a water bath for 5 hr. Usual work up gave yellow needles,

m.p. 218° (decomp). This compound was characterized as the dehydrated product (XLI) (Found: C, 75.90; H, 4.53. $C_{16}H_{12}O_3$ requires C, 76.19; H, 4.76%).

Diacetate of swietenocoumarin I (XXX).

A mixture of swietenocoumarin I (0.05 g), acetic anhydride (1.5 ml) and pyridine (2 drops) was heated on a water bath for 4 hr. On its usual work up it gave a low melting solid (0.035 g) (M^+ 430) (Found: C, 66.91; H, 6.97. $C_{24}H_{30}O_7$ requires C, 66.97; H, 6.98%).

Examination of the ether extract

The ether extract (80 g) was taken in ether (350 ml) and extracted with cold aqueous sodium hydroxide (5%). The alkali soluble part was neutralized with hydrochloric acid (5%), and extracted with ether. Removal of the solvent gave 24 g. of gummy extract, and was not examined further.

The neutral extract on removal of solvent gave 55 g. of the gummy residue of which 30 g. was chromatographed over a column of silica gel (800 g). Benzene and benzene-acetone mixtures with increasing polarity were used as eluents. Fractions of 500 ml. each were collected, and each fraction monitored on TLC.

Fractions 1-4 (10 g) were oily in nature and not examined.

Fractions 5–8 (4 g) obtained as yellowish solid crystallised from benzene in yellow prisms (3 g), m.p. 145°, and the compound was characterised as savinin (XXXIII) (lit.[22] m.p. 146°) (Found: C, 68.75; H, 4.70. $C_{20}H_{16}O_6$ requires C, 68.80; H, 4.57%).

Fractions 9–14 (0.8 g) contained swietenocoumarin B (XXIII) as a major compound.

Fractions 15–18 (0.9 g) crystallised from benzene as colourless needles (0.5 g), m.p. 155°, and the compound was identified as swietenocoumarin C (XXIV) (Found: C, 71.02; H, 5.16. $C_{16}H_{14}O_4$ requires C, 71.10; H, 5.20%).

Fractions 19–24 (0.4 g) were mixtures of heliettin and two other minor compounds which were not examined further.

Fractions 25–34 (0.1 g) were purified by passing through a column of silica gel using acetone–benzene (2:8) mixture as eluent. The compound crystallised from methanol (0.06 g), m.p. 194–95°, $(\alpha)_D^{EtOH}$ + 130° and was found identical with collinusin (XXXI) (Lit.[16] m.p. 195°) (Found: C, 69.70; H, 4.76. $C_{21}H_{18}O_6$ requires C, 69.90; H, 4.90%).

Fractions 35–37 (1.5 g) were complex mixtures of four to five compounds, as shown by TLC silica gel (1:9 acetone benzene). Attempts to purify them were unsuccessful. Fractions 38–42 (2.1 g) were mixtures with very close Rf

values as shown by TLC silica gel impregnated with 3% oxalic acid (1.5:8.5 acetone-benzene). These were purified by subjecting it to a silica gel column chromatography. The faster moving fluorescent compound obtained as colourless needles (4 mg) melted at 179-80° and was not characterised due to insufficient quantity. The slower moving compound crystallised as colourless needles from hexane-benzene mixture, m.p. 111°. This was identified as 8-prenylnodakenetin (XII) (Found: C, 72.50; H, 6.90. $C_{19}H_{22}O_4$ requires C, 72.60; H, 7.0%).

Fractions 43-45 (1.2 g) were a mixture of 8-prenylnodakenetin and suietenone.

Fractions 46-48 (0.2 g) crystallised as colourless prisms, m.p.160°, and the compound was characterised as suietenone.

Fractions 49-54 (0.35 g) contained suietenocoumarin H (XXIX) as the major compound.

Fractions 55-60 (0.1 g) on purification over a column of silica gel yielded suietenocoumarin G (0.03 g).

The column was further eluted with acetone, which gave 5.2 g. of residue which showed no separation on TLC (silica gel, with various solvent systems).

The chloroform extract (10 g) was chromatographed on a column of silica gel (200 g) using benzene and

benzene-acetone mixtures with increasing polarity as eluent.

Chalepin (0.73 g), swietenone (1.2 g), three new coumarins: swietenocoumarin D (0.5 g), swietenocoumarin E (0.43 g) and swietenocoumarin F (0.85 g) were isolated in addition to an alkaloid swietenidin B (0.35 g).

Swietenocoumarin D (0.5 g) was obtained as colourless needles from benzene, m.p. 150° (M^+ 300) (Found: C, 68.40; H, 5.19. $C_{17}H_{16}O_5$ requires C, 68.60; H, 5.30%).

Swietenidin B (0.35 g) crystallised as colourless light needles from the benzene-acetone mixture, m.p. 182° (M^+ 205). It gave an orange colour with Dragendorff's reagent indicating a positive test for alkaloids (lit.[26] m.p. 182°) (Found: C, 64.40; H, 5.30; N, 6.69. $C_{11}H_{11}NO_3$ requires C, 64.40; H, 5.36; N, 6.80%).

Swietenocoumarin E (0.43 g) crystallised as colourless prisms from acetone-benzene mixture, m.p. 164-66° (M^+ 288) (Found: C, 66.43; H, 5.19. $C_{16}H_{16}O_5$ requires C, 66.70; H, 5.50%).

Swietenocoumarin F (0.85 g) obtained as pale brown prisms from benzene-acetone mixture, m.p. 178-79° (M^+ 318) (Found: C, 64.38; H, 5.70. $C_{17}H_{18}O_6$ requires C, 64.20; H, 5.70%).

Swietenocoumarin E diacetate

A mixture of swietenocoumarin E (0.07 g), acetic anhydride (1.5 ml) and pyridine (2 drops) was heated on a water bath for 6 hr. The usual work up gave colourless needles from methanol in quantitative yield, m.p. 106°.

Swietenocoumarin F diacetate

A mixture of swietenocoumarin F (0.05 g), acetic anhydride (1 ml), pyridine (2 drops) was heated on a water bath for 5 hr. The product crystallised as needles from benzene in quantitative yields, m.p.145°.

Conversion of swietenocoumarin B (XXIII) to swietenocoumarin D (XXV)

A solution of (XXIII, 0.02 g) in chloroform (3 ml) was added to an ice-cold solution of perbenzoic acid) (0.015 g) in $CHCl_3$ (3 ml). The reaction mixture was kept at 0° for 2 days. The excess of perbenzoic acid was removed by washing with 10% aqueous Na_2CO_3 (2 x 5 ml) and finally with water (2 x 5 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to dryness. The product crystallised from benzene (0.015 g), m.p. 150°, m.m.p. undepressed with the natural sample swietenocoumarin D (XXV).

Similar epoxidation of swietenocoumarin A (XXII) gave a product identical with swietenocoumarin C (XXIV).

Conversion of swietenocoumarin D (XXV) to swietenocoumarin F (XXVII)

Swietenocoumarin D (0.01 g) and 1% oxalic acid(5 ml) were refluxed for 1 hr , the clear solution cooled and neutralised with aqueous $NaHCO_3$. The white precipitate was filtered and crystallised from methanol, m.p. 178°, mixed m.p., undepressed with the natural sample of swietenocoumarin F.

Hydrolysis of swietenocoumarin D (XXV)

Swietenocoumarin D (0.1 g) and 10% aqueous NaOH (25 ml) were refluxed for 4 hr. and cooled. On acidification with HCl a white solid obtained which was crystallised from ethyl acetate in colourless prisms (m.p. 160°) (0.07 g). It was characterised as the acid (XXXV) (m.p. 160°) from its NMR spectrum.

Extraction of the heartwood obtained from Madhya Pradesh

The powdered heartwood (6 kg) was extracted with cold acetone. Removal of solvent gave a reddish syrupy extract (112 g). The extract was adsorbed on extracted wood powder (200 g) and successively extracted with hexane, benzene, chloroform and acetone. It gave 36, 60, 8 and 6 g. of extracts respectively.

Isolation of xanthoxyletin (IV) and 7-demethylsuberosin (IX) from hexane extract

Hexane extract (10 g) was dissolved in ether and extracted with sodium hydroxide solution (10%). The alkaline extract was neutralised with hydrochloric acid (2N) and extracted with ether. The ether layer was dried over anhydrous sodium sulphate and the solvent removed. The gummy product (5.6 g) was dissolved in a minimum amount of hexane and kept at room temperature, when 7-demethyl-suberosin crystallised in colourless needles (3.9 g), m.p.133° (lit.[7] m.p. 133°) (Found: C, 72.50; H, 6.20. $C_{14}H_{14}O_3$ requires C, 73.00; H, 6.10%).

The alkali insoluble portion was dissolved in hexane and kept at room temperature, when a colourless crystalline compound (3 g), m.p.130°, was obtained. It was characterised as xanthoxyletin (lit.[7] m.p.132°) (Found: C, 69.70; H, 5.33. $C_{15}H_{14}O_4$ requires C, 69.77; H, 5.43%).

Isolation of xanthoxyletin (IV), alloxanthoxyletin (VII), skimmianine (XIII) and 7-demethylsuberosin (IX) and nodakenetin (XI) from the benzene extract

The benzene extract (10 g) was dissolved in ether and successively extracted with sodium hydroxide (10%) and hydrochloric acid (2%).

The alkali soluble fraction was neutralized with dilute hydrochloric acid and extracted with ether. Solvent removal gave a gummy product (4 g), which was dissolved in benzene, when 7-demethylsuberosin crystallised as colourless needles (1.4 g). The mother liquor showed a complex mixture of phenolics on TLC silica gel (2:8 acetone-benzene) and was not examined further.

The hydrochloric acid soluble fraction was neutralized with dilute sodium hydroxide and extracted with ether. Removal of ether gave a solid (1.8 g), which crystallised from methanol as colourless crystals, m.p.172° (1.2 g) and was characterised as skimmianine on the basis of spectral properties (Found: C, 65.0; H, 5.2; N, 5.1. $C_{14}H_{13}O_4N$ requires C, 65.5; H, 5.0; N, 5.4%). The neutral product (3.5 g) was chromatographed on a column of silica gel using benzene and benzene containing increasing percentage of acetone. Xanthoxyletin (0.8 g) (IV), alloxanthoxyletin (1 g) (VII) and nodakenetin (0.3 g) (XI) were thus isolated. Alloxanthoxyletin crystallised from benzene in colourless needles, m.p.116° (Found: C, 69.91 H, 8.5. $C_{14}H_{12}O_3$ requires C, 69.8; H, 8.6%). Nodakenetin was obtained as colourless needles from benzene, m.p.191° (lit.[7] m.p.191-92°) (Found: C, 74.30; H, 6.12. $C_{14}H_{14}O_4$ requires C, 74.33; H, 6.19%).

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P A R T - II

ALKALOIDS OF THE STEMWOOD OF MURRAYA KOENIGII SPRENG

INTRODUCTION

The genus Murraya (F. Rutaceae)[1] has seventeen species and consists of shrubs or small trees distributed from South and East Asia to Australia. Two species, M. koenigii and M. paniculata occur in India.

M. koenigii is a small, strong smelling pubescent tree with a short trunk. It is leafless for a short time during hot season. Its bark is thin grey or dark grey with shallow netted fissures. Wood is greyish white or pale brownish yellow, hard, close-grained and durable. It occurs in Western Ghats of Bombay to Kerala, Deccan, Karnatak and Madras States, also in Assam, Burma, along the foots of Himalayas from Garwhal to Sikkim upto 5000ft. and Bengal.[1]

The entire plant has medicinal value.[2,3] Its bark and roots are used as a stimulant and they are externally used to cure eruptions and bites of poisionous animals. The root is slightly purgative. Raw leaves are eaten as a cure for dysentery; they are also bruised and applied externally to cure eruptions and decoction with bitters as a febrifuge. The plant is mentioned in Indian Pharmacopoeia as having tonic and stomachic properties. The leaves are extensively used as flavouring material in curries and chutneys throughout India.

A number of Indian workers have extensively examined the leaves and stembark of M. koenigii because of its richness in the carbazole alkaloids. Two excellent reviews on carbazole alkaloids have appeared in recent years.[4,5]

The leaves have been found to yield essential oil, the chief constituents of which are carophyllene, cadinene, cadinol and d-sabinene.[6] Girinimbine was the first carbazole alkaloid isolated by Chakraberty et al. from the stem bark of M. koenigii.[7] but the structure was arrived at a later date. The same group have first arrived at the structure of murrayanine,[8] a C_{13} alkaloid, presumably due to its simplicity compared to girinimbine. Besides the Calcutta group, three more groups, Naresimhan et al. of Poona University, Joshi et al. from Ciba-Geigy Research Centre, Bombay, and Popli and co-workers from Central Drug Research Institute, Lucknow, have contributed mainly to the chemistry of carbazole alkaloids either from fruits, leaves or stem bark of M. koenigii. The structures of these alkaloids have been determined by physical methods by using especially PMR spectral analysis. A good number of these compounds have been synthesised to confirm the suggested structures.

The carbazole alkaloids isolated from this plant can be conveniently classified into three groups: (1) simple products having C_{13} skeleton, (2) compounds derived with an

additional isoprenoid group on the main skeleton (C_{18} skeleton) and (3) compounds having a C_{23} skeleton and have derived by the modification of an extra C_{10} unit on the carbazole unit. Very recently Chakraberty[5] has reviewed the chemistry of carbazoles including the synthesis of these alkaloids, and hence no attempt has been made to deal with these compounds in detail. Table I gives a list of carbazole alkaloids from the stem bark or leaves of M. koenigii. Four of them have simple carbazole skeleton, six have C_{18} skeleton, and the rest ten have C_{23} skeleton. All the C_{23} alkaloids can be considered to have been originated from various modifications resulted by the cyclization of a C_{10} unit adjacent to a phenolic hydroxyl group. In fact mahanimbinol (VI), which has not been reported so far, can be regarded as a biogenetic precursor for all the C_{23} carbazole alkaloids.

A few more carbazole alkaloids having C_{13} and C_{18} skeletons have also been reported from two other genera of Rutaceae, viz. Clausena and Glycosmis as given in Table II. In addition to these alkaloids, coumarins[9-17] and flavones[13,18,19] have been isolated from other Murraya species.

TABLE I

CARBAZOLE ALKALOIDS FROM MURRAYA KOENIGII

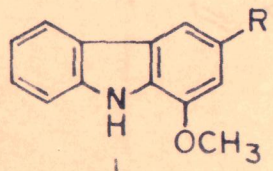
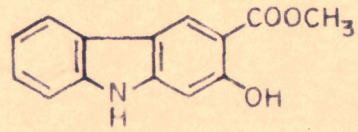
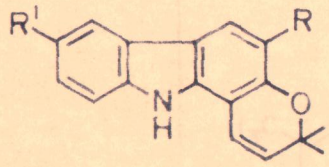
Sr. No.	COMPOUND		PART OF THE PLANT	REFERENCE	
	NAME	STRUCTURE		ISOLATION	SYNTHESIS
	C_{13} ALKALOIDS				
1	MURRAYANINE	R = CHO	STEM BARK	8	28, 29
2	MUKOEIC ACID	R = COOH	STEM BARK	30	–
3	MUKONINE	$R = COOCH_3$	STEM BARK	31	–
4	MUKONIDINE		STEM BARK	31	–
	C_{18} ALKALOIDS				
5	GIRINIMBINE	$R = CH_3, R' = H$	STEM BARK	7, 32	33, 34, 35
6	KOENIMBINE	$R = CH_3, R' = OCH_3$	FRUITS, LEAVES	36	34
7	MURRAYACINE	R = CHO, R' = H	STEM BARK	37	38, 39
8	KOENINE	$R = CH_3, R = OH$	LEAVES	40	34

TABLE I (contd)

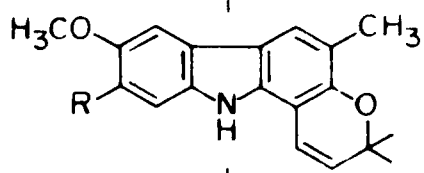
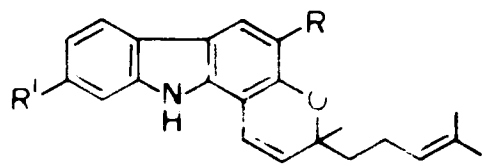
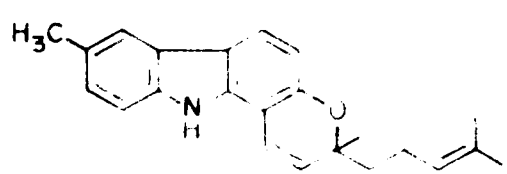
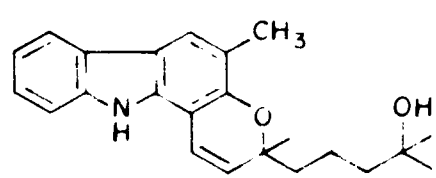
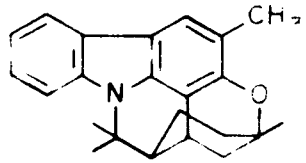
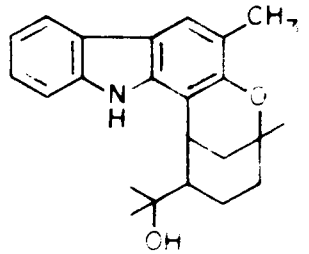
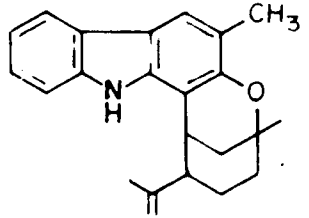
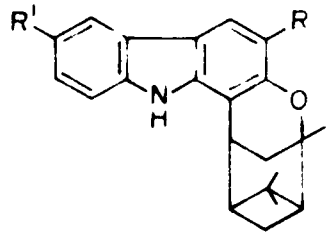
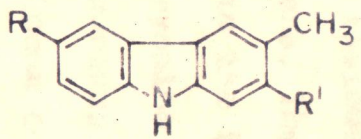
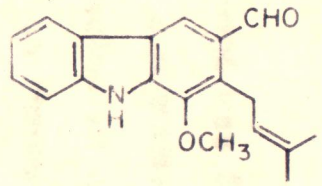
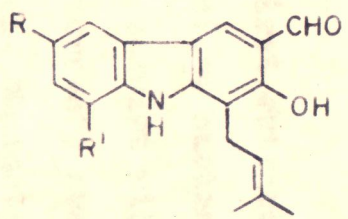
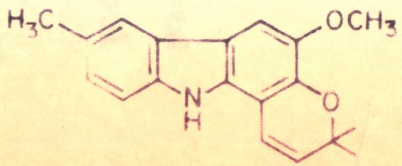
Sr. No.	COMPOUND NAME	COMPOUND STRUCTURE	PART OF THE PLANT	REFERENCE ISOLATION	REFERENCE SYNTHESIS
					
9	KOENIGINE	R = OH	LEAVES	40	–
10	KOENIDIN (KOENIGICINE)	R = OCH_3	LEAVES	20, 40, 41	–
	C_{23} ALKALOIDS				
					
11	MAHANIMBINE	R = CH_3, R' = H	STEM BARK	25	24, 35, 42, 43
12	MAHANINE	R = CH_3, R' = OH	LEAVES	40, 44	45
13	MURRAYACININE	R = CHO, R' = H	STEM BARK	46	47
					
14	MAHANIMBICINE (ISOMAHANIMBICINE)		LEAVES	48, 41, 44	48
					
15	MAHANIMBININE		LEAVES	49	49

TABLE I (contd)

Sr. No.	COMPOUND		PART OF THE PLANT	REFERENCE	
	NAME	STRUCTURE		ISOLATION	SYNTHESIS
16	MAHANIMBIDINE [MURRAYAZOLINE CURRYANGIN]		LEAVES STEM BARK STEM BARK	23, 22, 50 51 22	22, 43 – –
17	MURRAYAZOLININE			51	–
18	CYCLOMAHANIMBINE [MURRAYAZOLIDINE CURRAYANINE]		STEM BARK LEAVES	23, 43, 52	 –
19	BICYCLOMAHANIMBINE	 $R = CH_3$, $R' = H$	LEAVES	23	24
20	BICYCLOMAHANIMBICINE	$R = H$, $R' = CH_3$	–	48	–

Sr. No.	SOURCE	COMPOUND		PART OF THE PLANT	REFERANCE
		NAME	STRUCTURE		
		C_{13} ALKALOIDS			
1	GLYCOSMIS PENTAPHYLLA	GLYCOZOLINE	$R=OCH_3$, $R'=H$	ROOT BARK	53, 54, 55
2	GLYCOSMIS PENTAPHYLLA	GLYCOZOLIDINE	$R=OCH_3$, $R'=OCH_3$	ROOT BARK	56, 57
3	CLAUSENA HEPTAPHYLLA & CLAUSENA INDICA	3-METHYL CARBAZOLE	$R=H$, $R'=H$	ROOTS	27
		C_{18} ALKALOIDS			
4	CLAUSENA INDICA	INDIZOLINE	 	ROOTS	58
5	C. HEPTAPHYLLA	HEPTAPHYLLINE	$R=H$, $R'=H$	ROOTS	59
6	C. INDICA	6-METHOXYHEPTAPHYLLINE	$R=OCH_3$, $R'=H$	ROOTS	60
7	C. HEPTAPHYLLA	HEPTAZOLINE	$R=H$, $R'=OH$	STEM BARK	61
8	C. HEPTAPHYLLA	HEPTAZOLIDINE		ROOT BARK	

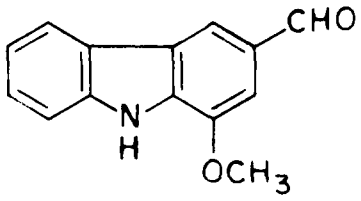
PRESENT WORK

The work described earlier by the various workers have led to the isolation of twenty carbazole alkaloids either from the stem bark or leaves/or fruits of M. koenigii. Surprisingly no one had investigated either the stem wood or the root constituents of this plant. The present investigation deals with the stem wood of M. koenigii obtained from Bijapur (Karnatak State).

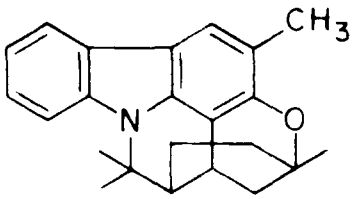
The powdered stem wood was first extracted with cold acetone. Concentration and removal of acetone gave a dark residue which was extracted in a soxhlet with hexane and benzene. The hexane extract on chromatography over silica gel led to the isolation of three compounds, characterized as murrayanine (I), mahanimbidin (II) and bicyclomahanimbine(III). The benzene extract on chromatography over silica gel yielded two known compounds, mahanimbine (IV) and girinimbine(V) and a new C_{23} carbazole alkaloid isomeric with mahanimbine which is named as mahanimbinol (VI).

Hexane extract

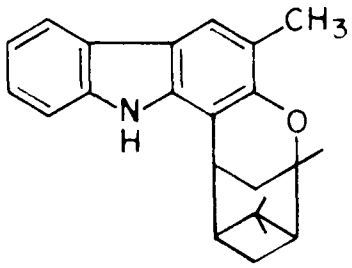
Murrayanine (I). It crystallizes from benzene in colourless needles, m.p. 168°, $C_{14}H_{11}NO_2$ (M^+ 225). Its NMR spectrum shows the presence of a methoxyl group at 3.98 and six aromatic protons [broad signals at 7.39(4H), 8.10(2H)], NH proton at 8.80. A downfield signal at 9.96 shows the presence of aldehydic proton. The data are in agreement with murrayanine (I), first isolated by Chakraborty et al. from the stem bark.[8]



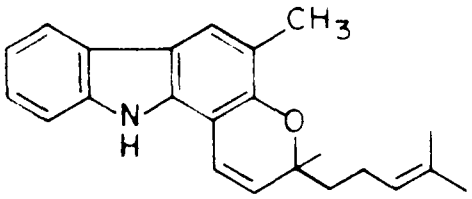
MURRAYANINE (I)



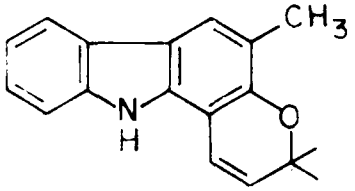
MAHANIMBIDINE (II)



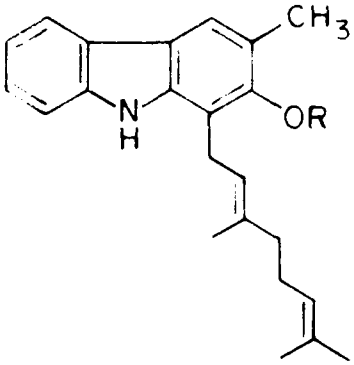
BICYCLOMAHANIMBINE (III)



MAHANIMBINE (IV)

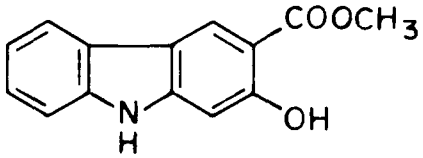


GIRINIMBINE (V)



MAHANIMBINOL, R=H, (VI)

MAHANIMBINOL ACETATE, R=$COCH_3$ (VII)



MUKONIDINE (VIII)

Mahanimbidine (II), $C_{23}H_{25}NO$ (M^+ 331), m.p. 265°. Its NMR spectrum shows the presence of three methyl signals at 1.28, 144 and 1.93 indicating that three methyl groups are on the carbons attached to either oxygen or nitrogen function and a fourth methyl singlet at 2.33, accounting for an aromatic methyl group. One benzylic methine appears as multiplet at 3.30. Five aromatic protons are seen as a multiplet between 7.10-7.90. This data are in conformity with the known compound mahanimbidine (II), first isolated by Kureel et al.[23] from the pet.ether extract of the leaves of M.koenigii. Subsequently, it has been isolated by others from the stem bark and named as murrayazoline[21] and curryangin.[22]

Bicyclomahanimbine (III), colourless needles from benzene, m.p. 145°, $C_{23}H_{25}NO$ (M^+ 331). The NMR spectrum shows the presence of four methyl groups: one of these is at a very high field and appears at 0.70, the other three are at 1.45, 1.51 and 2.37. In addition, a benzylic methine (3.30, d, J=10 Hz), five aromatic protons and a NH proton are seen in the region 7.05-8.10. This data are consistent with the data reported for bicyclomahanimbine (III), first isolated from the leaves.[23] Bicyclomahanimbine was also obtained during the synthesis of mahanimbine by the same authors.[24]

Benzene extract

Benzene extract on chromatography over silica gel yielded two known alkaloids, mahanimbine (IV) and girinimbine(V) and a new carbazole alkaloid mahanimbinol(VI) in small quantity.

Mahanimbinol (VI): $C_{23}H_{27}NO$ (M^+ 333) is obtained as a gummy product (0.007%) and resisted crystallisation. Its UV spectrum [λ_{max}^{EtOH} (log ε): 244(4.26), 260(4.14), 296(3.98), 325(3.40), 339(3.38)] is in close resemblance with girinimbine. Its IR spectrum shows a broad absorption at 3400 cm^{-1}, which may account for -NH, -OH or both.

The compound forms a monoacetate, m.p. 69° (M^+ 375) on treatment with acetic anhydride in presence of ~~palladium~~ ~~carbon~~ pyridine. The monoacetate on hydrogenation in presence of 10% palladium carbon absorbs two molecules of hydrogen giving a crystalline tetrahydro derivative (m.p.115°, M^+ 379).

The NMR spectrum of mahanimbinol (Fig.I) clearly demonstrates the presence of a C-geranyl group attached to the aromatic nucleus. Three methyl singlets at 1.58, 1.73 and 1.83, a four proton signal at 2.05 (two allylic methylene groups), a two proton doublet at 3.43 (J=7 Hz) accounting for the methylene which is both allylic and benzylic and two olefinic protons (broad triplets) at 5.00 and 5.39. The spectrum indicates the presence of a three proton singlet at 2.30 for aromatic methyl group. Two of the five aromatic protons present appear at low field and can be assigned to the mutually deshielded C-4 (δ, 7.80) and C-5 (δ 7.83) protons of the carbazole ring. The other three aromatic protons are seen in the region at

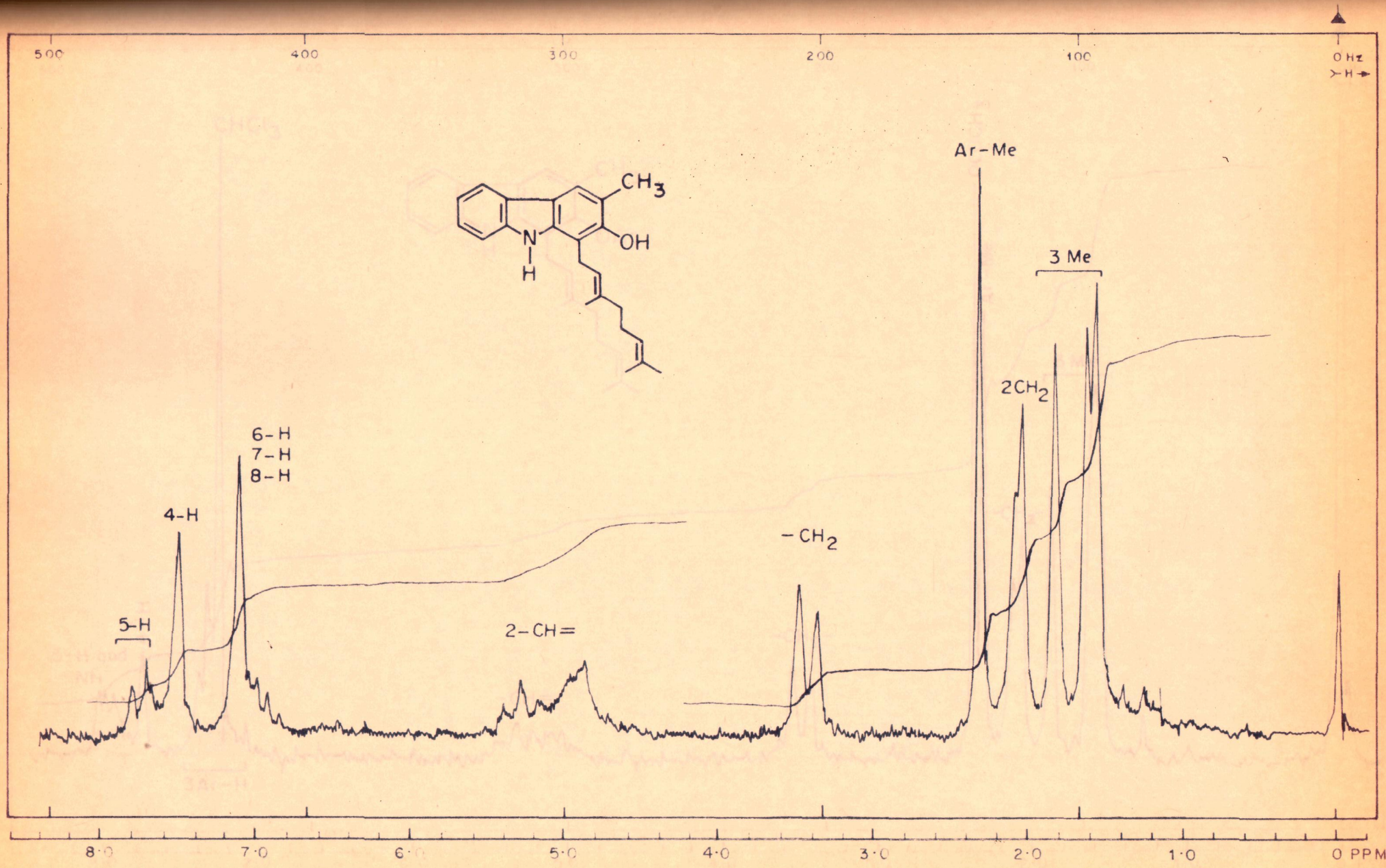


FIG. 1. NMR SPECTRUM OF MAHANIMBINOL IN CCl_4

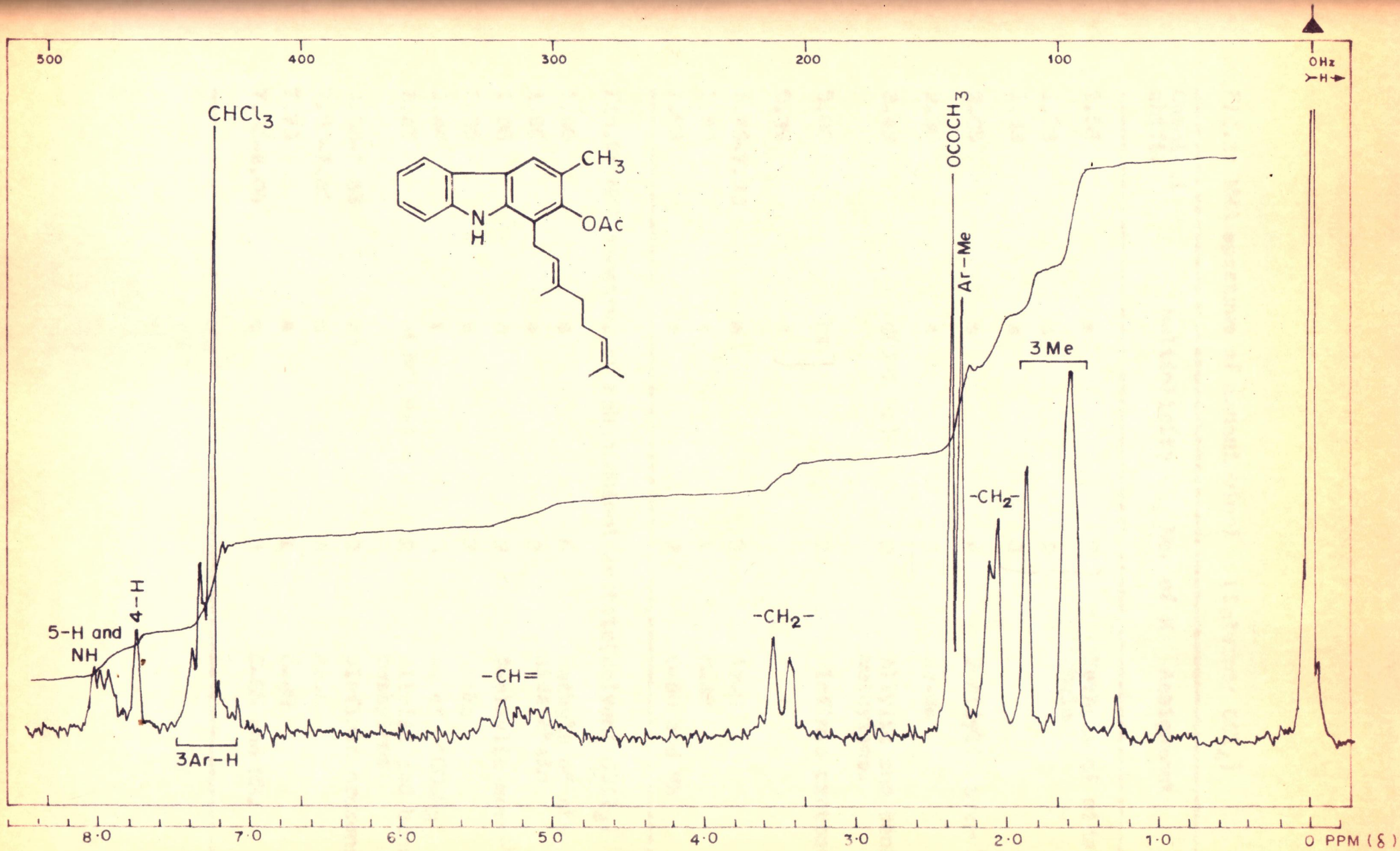


FIG. 2. NMR SPECTRUM OF MAHANIMBINOL ACETATE IN $CDCl_3$

Fig.1: NMR spectrum of mahanimbinol (Solvent: CCl_4)

Chemical shift.	Multiplicity	No. of H	Assignment
1.58	s	3	Methyls of side chain.
1.73	s	3	
1.83	s	3	
2.05	s	4	2-Allylic methylenes
2.30	s	3	Ar-Me
3.43	d(J=7 Hz)	2	Allylic and benzylic methylene.
5.00	bt	2	olefinic protons
5.39	t		
6.76-7.23	m	3	Ar-H
7.50	s	1	C-4H
7.83	m	2	C-5H and NH

Fig.2: NMR spectrum of mahanimbinol acetate(solvent $CDCl_3$)

1.56	s	6	Methyls of the side chain
1.86	s	3	
2.08	d	2	2-allylic methylenes
2.36	s	3	Ar-Me
2.44	s	3	Me of $-OCOCH_3$
3.45	d(J=7 Hz)	2	Allylic and benzylic methylene
4.08-5.58	bm	2	olefinic protons
7.03-7.40	m	3	Ar-H
7.73	s	1	C-4H
7.86-8.06	m	2	C-5H and NH.

6.76 to 7.23 and the NH proton is merged with the multiplet for C-5 proton. Its mass spectrum shows a molecular ion at m/e 333 and other intense peaks at m/e 332 (M-1), 264 (M-69), 248 (M-85), 210 (M-123). The base peak at m/e 210 is due to the loss of C_9H_{15} which provides evidence for a C_{10} side chain in the molecule. (Fig.3, Chart 1).

The above evidence together with the NMR spectral data of its acetate (Fig.2) suggests structure (VI) for mahanimbinol.

Mahanimbine (IV): Colourless prisms, m.p.94-95°, $C_{23}H_{25}NO$ (M^+ 331). The NMR spectrum exhibits four singlets, integrating for three protons each, at 1.44, 1.60 and 1.70 due to the side chain methyls, and the fourth is seen at 2.37 due to aromatic methyl. The methylene protons appear as unresolved signals in the region 1.55-2.17. A pair of doublets (d, J=10 Hz) at 5.17, 5.67 and a triplet at 6.68 are assigned to the olefinic and vinylic proton respectively. In the aromatic region three protons appear as multiplet at 7.13-7.40 which are assigned to C-6, C-7 and C-8 protons. The proton singlet at 7.70 for C-4H and a one-proton multiplet centrered at 7.90 accounts for C-5H. The NH proton appears at 8.64 as a broad signal.

Its mass spectrum shows m/e 331 as a molecular ion and other intense peaks at m/e 249, 248, 247, 204. The data are in conformity with mahanimbine (IV) isolated from the stem bark by Chakraborty *et al.*[25]

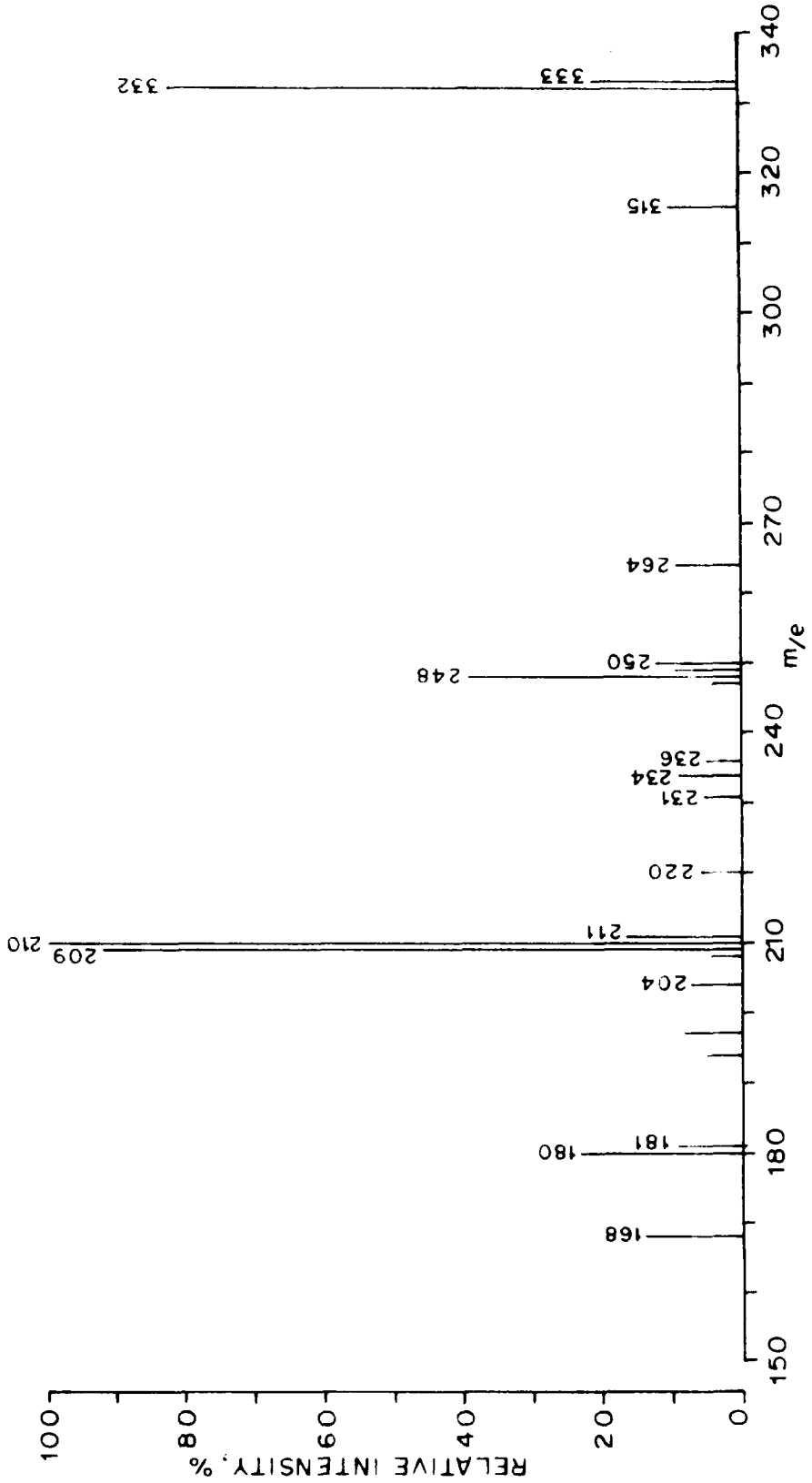
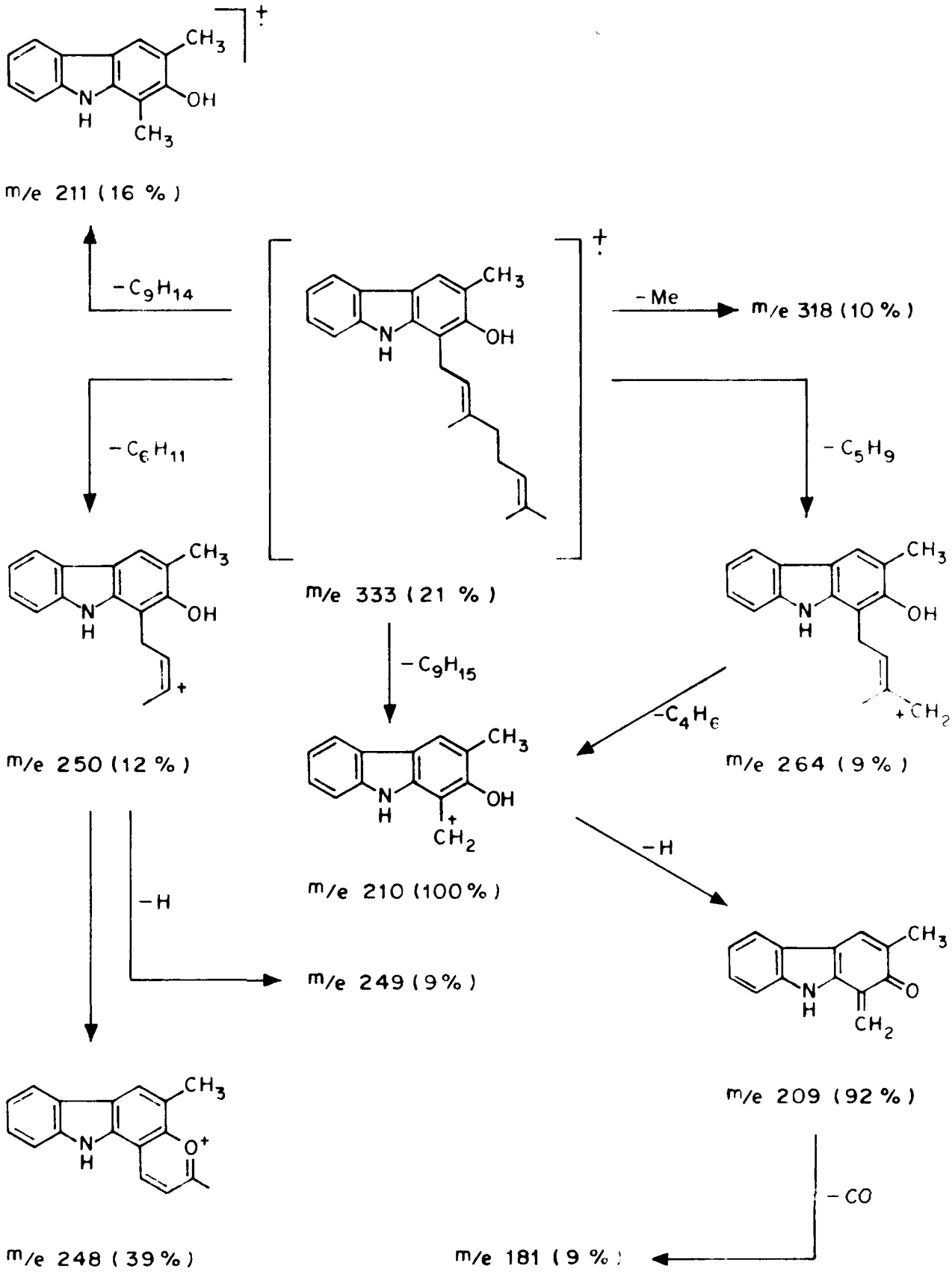

RELATIVE INTENSITY, %
100
80
60
40
20
0
150
180
210
240
270
300
320
340
m/e
168
180
181
204
209
210
211
220
231
234
236
248
250
264
315
332
333

FIG. 3

CHART 1 MASS SPECTRAL FRAGMENTATION OF MAHANIMBINOL



Girinimbine (V) crystallized from benzene, m.p.174°, $C_{18}H_{17}NO$ (M^+ 263). Its NMR spectrum shows a six proton singlet at 1.41 for two methyls, and a singlet at 2.30 for the aromatic methyl group. The doublets at 5.45 and 6.24 (d, J=10 Hz) account for the olefinic protons. In the low field region of the spectrum two aromatic protons appear at 7.50, and three at 7.08 as a multiplet. The NH proton is seen at 7.75.

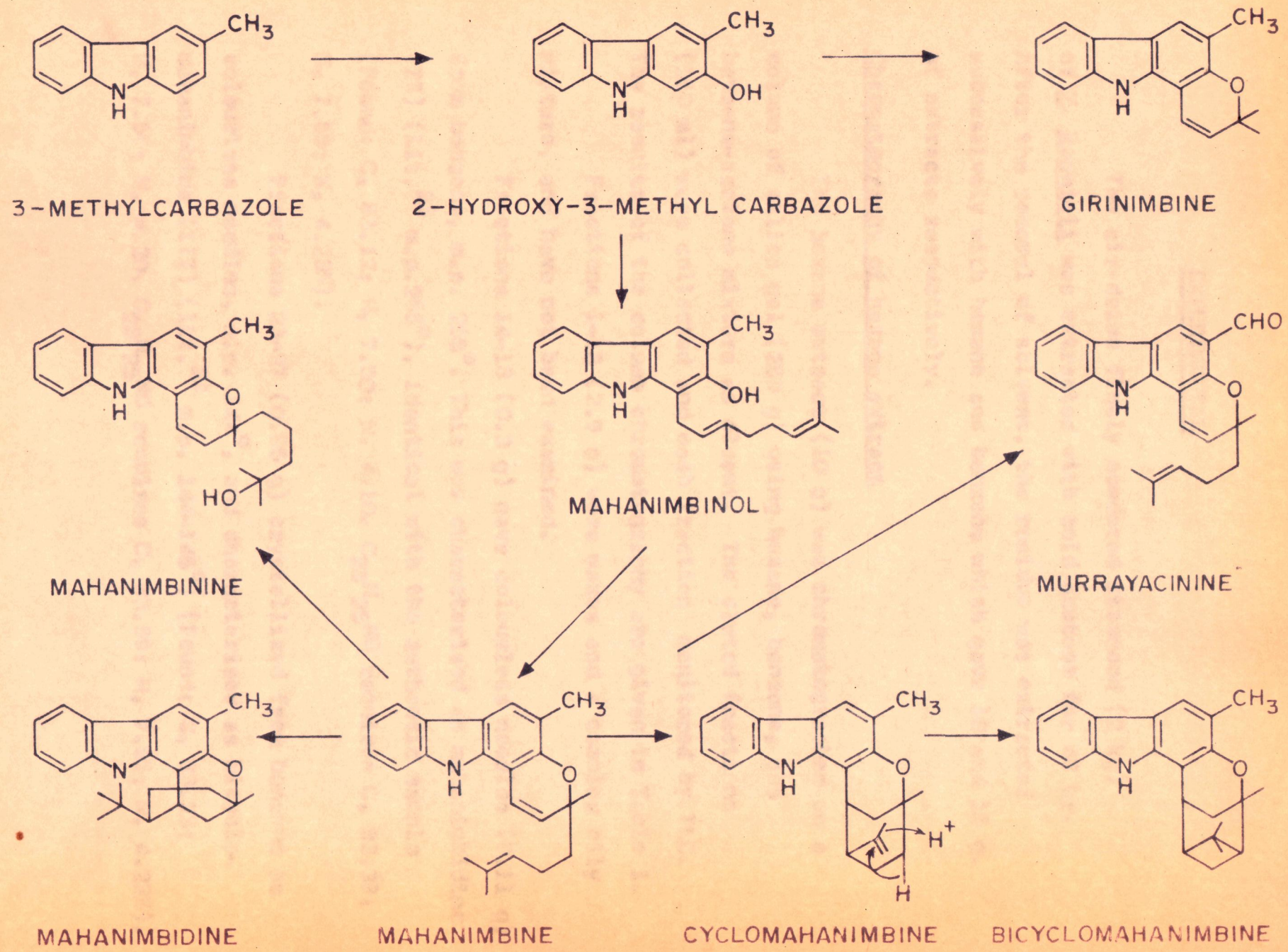
The mass spectrum shows m/e 263 as a molecular ion and other peaks at m/e 248, 204, 191, 167. The above data corresponds to the girinimbine (V) isolated from the bark.[7]

Biogenesis

Several routes have been suggested by different workers on the biogenesis of carbazole alkaloids.[5] Apparently, the C ring might have originated from the mevalonate unit as was advocated by Kureel et al.[4] and by Erdtman.[26] Further confirmation by feeding experiments shows that the ring carrying the extra methyl group is of mevalonate origin. If this is so, one can assume that 3-methylcarbazole is the key compound which can give rise to the various structural patterns in carbazole alkaloids. This view had been substantiated by the isolation of 3-methylcarbazole from the genus Clausena.[27] Further hydroxylation of this compound may lead to the formation of 2-hydroxy-3-methyl carbazole. The isolation of mukonidine (VIII) also strengthens this view.

Mahanimbinol (VI) can be considered as the first member of the carbazole alkaloids with a C_{23} skeleton. The incorporation of a C_{10} unit (monoterpene) at 1-position of 2-hydroxy-3-methyl carbazole resulting in the formation of mahanimbinol has ample precedence in a number of natural phenolic compounds. The C_{10} unit in mahanimbinol can undergo various transformations giving rise to isomeric compounds such as mahanimbine, bicyclomahanimbine, mahanimbidine, and murrayazolidine (Chart II). In fact the isolation of mahanimbinol together with mahanimbine and bicyclomahanimbine provides circumstantial evidence for the above hypothesis.

CHART II BIOGENETIC PATHWAY OF FORMATION OF CARBAZOLE ALKALOIDS



EXPERIMENTAL

The air-dried finely powdered stemwood (2 kg) of *M. koeniii* was extracted with cold acetone for 48 hr. After the removal of solvent, the residue was extracted successively with hexane and benzene which gave 10 and 15 g. of extracts respectively.

Chromatography of hexane extract

The hexane extract (10 g) was chromatographed on a column of silica gel (250 g) using hexane, benzene, and benzene-acetone mixture as eluent. The eluted fractions (150 ml) were collected and each fraction monitored by TLC. The results of the column chromatography are given in Table 1.

Fractions 1-13 (2.9 g) were waxes and a complex oily mixture, and have not been examined.

Fractions 14-18 (0.3 g) gave colourless needles (0.11 g) from benzene, m.p. 265°. This was characterised as mahanimbidine (II) (Lit.[23] m.p.266°), identical with the authentic sample (Found: C, 83.12; H, 7.50; N, 4.10. $C_{23}H_{25}NO$ requires C, 83.39; H, 7.55; N, 4.23%).

Fractions 23-27 (0.85 g) crystallized from benzene as colourless needles, m.p. 144°, and characterised as bicyclomahanimbine (III) (lit.[23] m.p. 144-145°) (Found: C, 83.23; H, 7.50; N, 4.20. $C_{23}H_{25}NO$ requires C, 83.39; H, 7.55; N, 4.23%).

Fractions 31-38 (3.5 g) gave a residue which on crystallisation from benzene gave colourless needles, m.p. 165°. This compound gave an orange colour with 2:4 DNP and was characterised as murrayanine (I) (Lit.[8] m.p. 165°). (Found: C, 74.6; H, 4.81; N, 6.15. $C_{14}H_{11}NO_2$ requires C, 74.66; H, 4.89; N, 6.22%).

Chromatography of benzene extract

Benzene extract (15 g) was chromatographed on a column of silica gel (300 g). The column was initially eluted with benzene and then with benzene-acetone mixture with increasing polarity. The eluted fractions (100 ml) were collected and similar fractions were pooled together by TLC. Table 2 shows the results of the column chromatography.

Fractions 1-3 (3.2 g) were oily mixtures and not examined. Fractions 10-12 (0-13 g) contained a mixture of two compounds and further purification on silica gel gave murrayanine (0.08 g), and dark red needles (0.02 g), m.p. 230-232°(decomp) unidentified.

Fractions 13-21 (0.5 g) gave colourless crystalline compound from hexane-benzene, m.p. 194°, characterised as mahanimbine (IV) (lit.[25] m.p. 94-95°) (Found: C, 83.30; H, 7.23; N, 4.10. $C_{23}H_{25}NO$ requires C, 83.39; H, 7.55; N, 4.23%).

Fractions 26-31 (2.4 g) crystallised as colourless prism from benzene, m.p. 175°, and identified as girinimbine(V).

(lit.[7] m.p.175°) (Found: C, 82.00; H, 6.45; N, 5.30. $C_{18}H_{17}NO$ requires C, 82.13; H, 6.46; N, 5.32%).

Fractions 32-37 (0.15 g) gave a gummy residue which was purified by repeated chromatography over silica gel using benzene and benzene-acetone mixture as eluent. The compound was gummy and resisted crystallisation. It was characterised as mahanimbinol (VI) (Found: C, 82.70; H, 8.10; N, 4.15. $C_{23}H_{27}NO$ requires C, 82.80; H, 8.10; N, 4.20%).

Acetylation of mahanimbinol (VI)

A mixture of mahanimbinol (0.05 g), acetic anhydride (2 ml) and pyrifine (2 drops) were heated on a water bath for 4 hr. The mixture was then poured on crushed ice, extracted with ether, and the ether layer washed with water and dried (Na_2SO_4). Removal of the solvent gave solid which crystallised into colourless needles from benzene, m.p. 69°, and characterised as mahanimbinol mono-acetate (VII).

Hydrogenation of mahanimbinol mono-acetate (VII)

A solution of acetate (0.03 g) in dry methanol was stirred with Pd/C (10%; 20 mg) for 4 hr. The solution was filtered and concentrated, which gave a tetrahydro derivative as colourless needles, m.p. 115°.

TABLE 1

Fractions	Approximate weight (g)	Remarks
1-13	2.9	waxes and oily mixture
14-18	0.3	mahanimbidine
19-22	0.7	mixture of mahanimbidine and bicyclomahanimbine.
23-27	0.85	bicyclomahanimbine
28-30	0.75	bicyclomahanimbine and complex mixture
31-38	3.5	murrayanine

TABLE 2

1-3	3.2	oily compound
4-9	2.7	murrayanine
10-12	0.13	mixture of murrayanine and dark red needles (unidentified)
13-21	0.5	mahanimbine
22-25	1.6	mixture of mahanimbine and girinimbine
26-31	2.4	girinimbine
32-37	0.15	mahanimbinol
eluted with acetone	1.3	complex mixture and not examined further.

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PART - XII

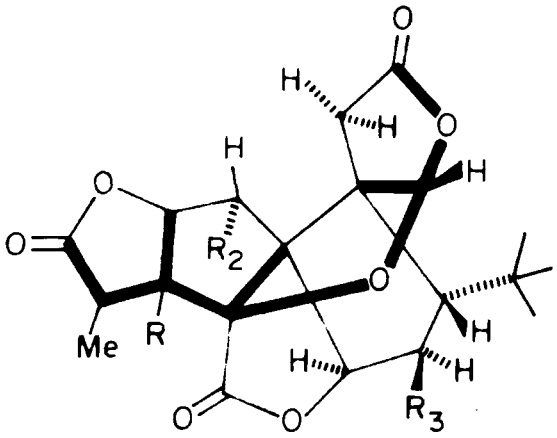
Chapter X

ABNORMAL REACTIONS OF ANHYDROUS ALUMINIUM CHLORIDE

INTRODUCTION

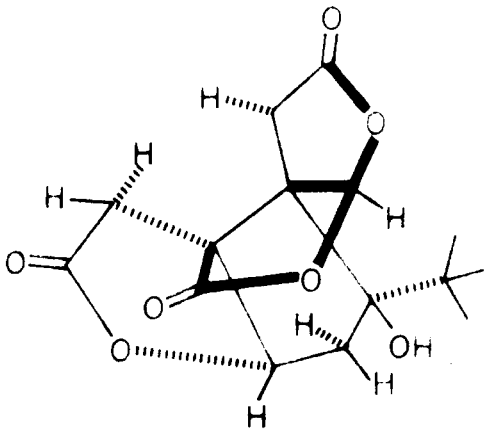
Natural products with tert-butyl group have not been known till recently. Nakanishi et al.[1] have reported for the first time four diterpenoids, ginkgolides A, B, C and M (I) and a sesquiterpene, bilobalide (II), with a tert-butyl group, all of which occur in Ginkgo biloba. The origin of the tert-butyl group in ginkgolides and bilobalide is not from the terpenoid precursor as reported by Nakanishi et al.[2]

Mujumdar[3] from this group had earlier isolated the first natural phenolic compound with a tert-butyl ketone, swietenone (III) from the bark of Chloroxylon swietenia DC (F. Rutaceae). Apparently, the tert-butyl group may be arising from angeloyl or isoprenyl group which are common in naturally occurring coumarins (Charts I and II). The tert-butyl ketone in swietenone might have originated from a prenyl group rather than an angeloyl substituent, based on the fact that coumarins with latter substituents are confined to plants belonging to Umbelliferae. The biogenesis of swietenone was postulated as shown in Chart I. Although 8-prenylpsoralen was regarded as the precursor, it has now been isolated from the bark of Chloroxylon swietenia DC obtained from Achalpur and Channapatnam.[4] Recently Joshi et al.[5] have isolated a new furocoumarin, clausinidine (IV) from Clausena indica



I

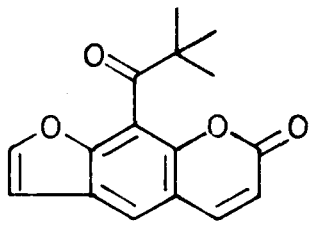
GINKGOLIDE



II

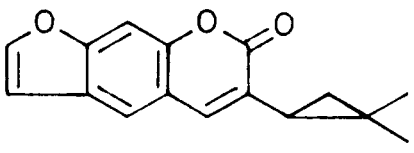
BILOBALIDE

	R_1	R_2	R_3
A	OH	H	H
B	OH	OH	H
C	OH	OH	OH
M	H	OH	OH



III

SWIETENONE



IV

CLAUSINDINE

CHART I

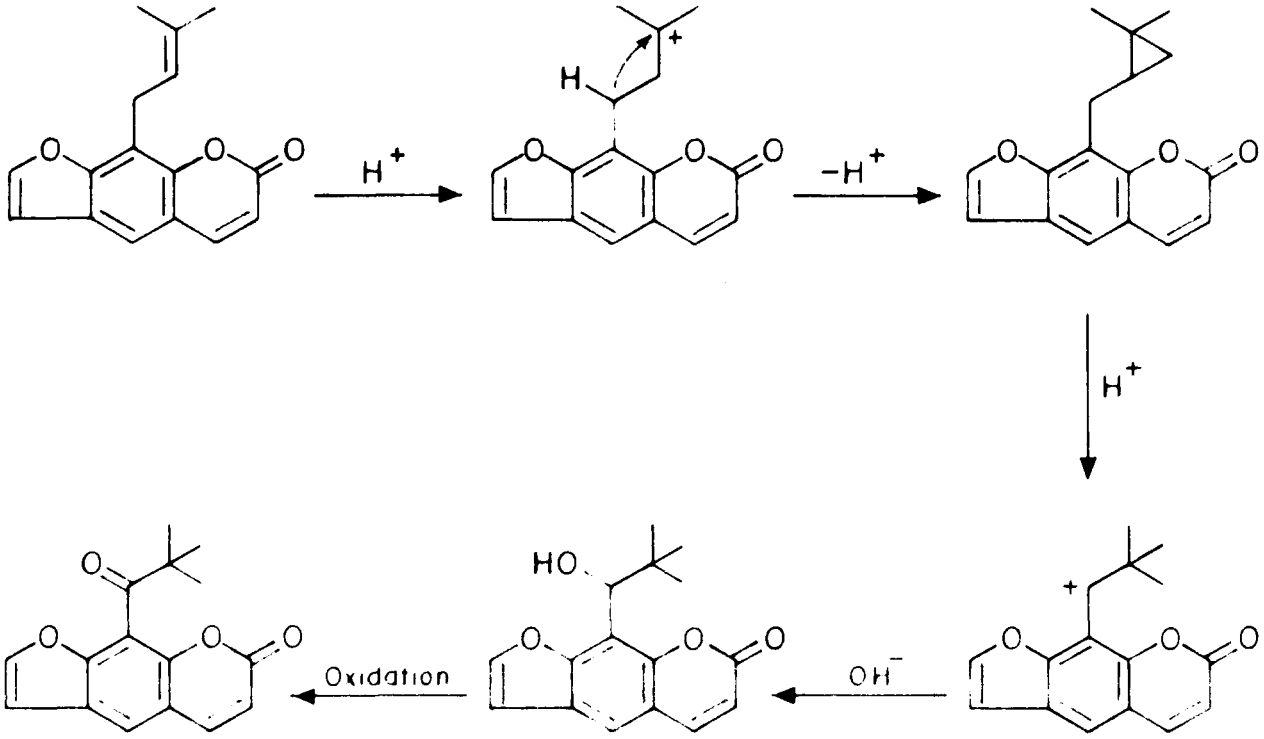
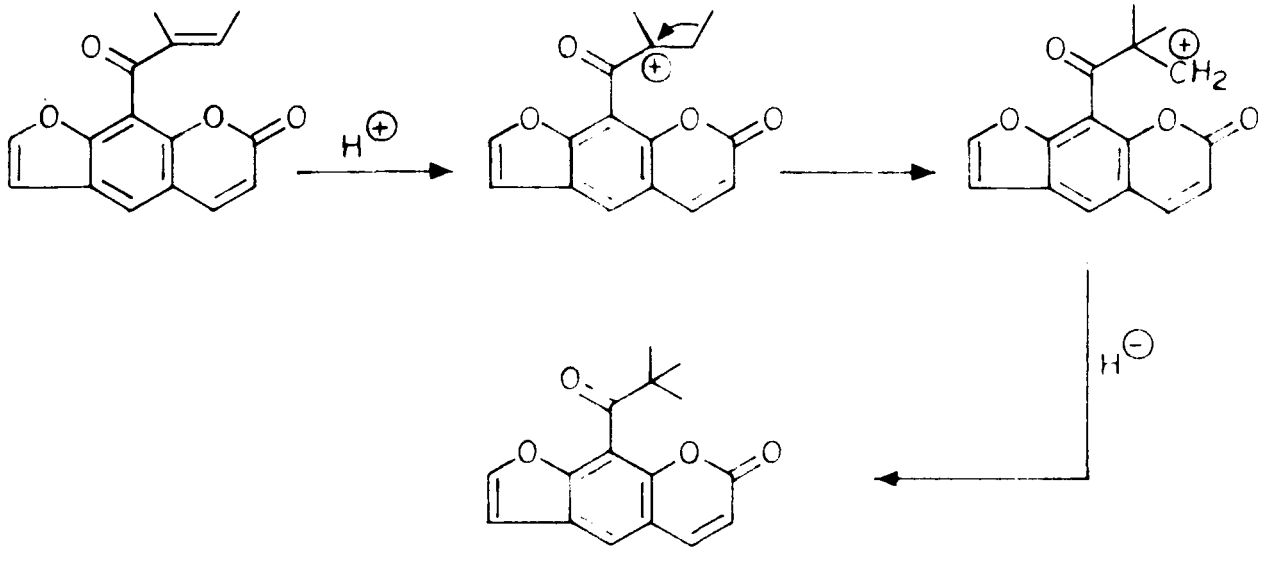


CHART II



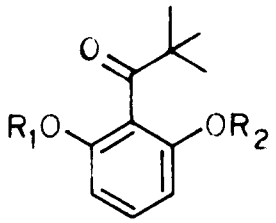
SWIETENONE

(F. Rutaceae) in which "the ubiquitous isoprenoid unit is attached to the aromatic nucleus as a gem-dimethylcyclopropane grouping" and will support the biogenetic postulates. Because of its structural interest, attempts have been made to synthesise evietenone.

PRESENT WORK

2-Pivalylresorcinol (V) is the right choice as a starting material for the synthesis of eudesmone (III). Although various ways can be considered for its synthesis, the shortest one being the metalation of dimethyl ether of resorcinol and treating the metalated product with pivalyl chloride. It is a well established fact that resorcinol dimethyl ether on lithiation and subsequent alkylation or acylation gives exclusively 2-alkyl or 2-acyl resorcinol dimethyl ether.[6] Similarly 2-pivalyl resorcinol dimethyl ether is also prepared. Various attempts have been made to convert the dimethyl ether (VI) to the corresponding dihydroxy compound. Using anhydrous aluminium chloride in benzene (a common dealkylating agent) the major product formed is not the expected 2-pivalyl resorcinol, but the 4-hydroxy-2,2-dimethyl-3-methylene coumaran (VIII). This interesting observation led to investigate the various aspects of this reaction.

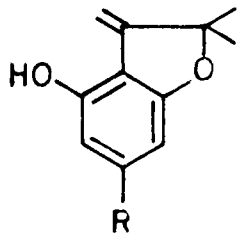
Metalation of resorcinol dimethyl ether and subsequent treatment with pivalyl chloride yielded the 2-pivalyl resorcinol dimethyl ether (VI). Attempted partial demethylation of (VI) to the monomethyl ether(VII) by means of BF_3-etherate, hydroiodic or hydrobromic acid in acetic acid and aluminium tribromide-pyridine complex



V $R_1 = R_2 = H$

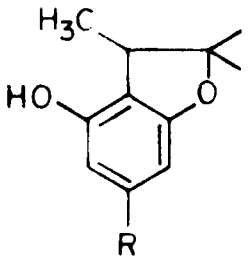
VI $R_1 = R_2 = Me$

VII $R_1 = H$, $R_2 = Me$

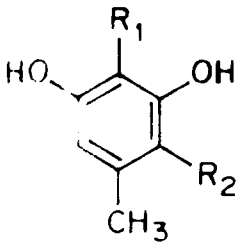


VIII R = H

IX R = Me

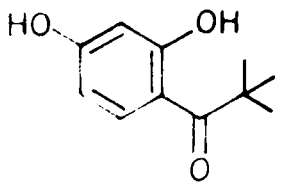


X R = H

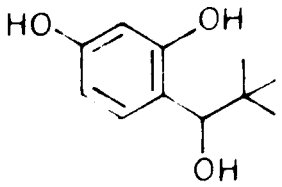


XII $R_1 = CO{\cdot}C(CH_3)_3$, $R_2 = H$

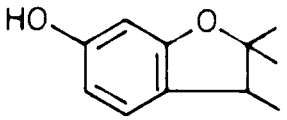
XIII $R_1 = H$, $R_2 = CO{\cdot}C(CH_3)_3$



XI

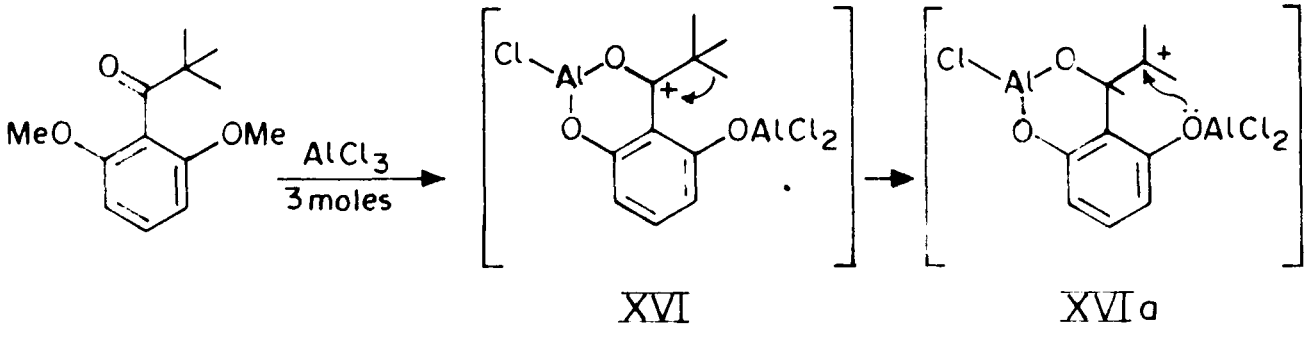


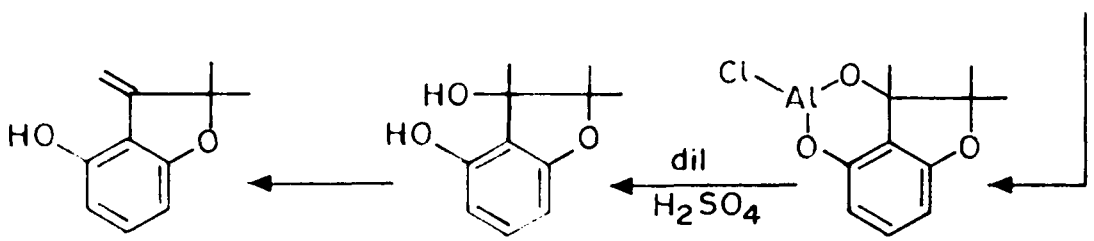
XIV



XV

CHART III





has been unsuccessful. But when the 2-pivalyl resorcinol dimethyl ether is treated with anhydrous aluminium chloride in dry refluxing benzene for 5 hr., a colourless crystalline product is obtained which has been purified by chromatography. This product, $C_{11}H_{12}O_2$ (M^+ 176), m.p.186°, shows in its IR spectrum an absorption band at 3400 cm^{-1} (-OH group) and no carbonyl absorption. The absence of the methoxyl signal in the NMR spectrum (Fig.1) indicates that the product has completely dealkylated, but undergone some unexpected changes. The negative ferric chloride test and the absence of carbonyl absorption in its IR spectrum shows the absence of a pivalyl group.

The NMR spectrum (Fig.1) of this compound shows a six proton singlet at 1.30 accounting for two methyl groups on a saturated carbon attached to an oxygen function. In addition, the spectrum shows two singlets at 4.90 and 5.60, integrating for one proton each, and the aromatic protons (a single proton triplet centrered at 7.10 and two proton doublets (J=9 Hz) centered at 6.40). A one-proton singlet at 5.20, exchangeable with D_2O accounts for a phenolic hydroxyl group. All this data are in support of the structure (VIII) for this compound.

The interesting feature of the NMR spectrum is that the terminal methylene protons appear as singlets separated by 42 ppm. Normally the Sp^2 hybridized protons are expected to show geminal coupling of the order of 2 to 3 Hz. The chemical shifts of the hydrogens in formaldehyde[7]

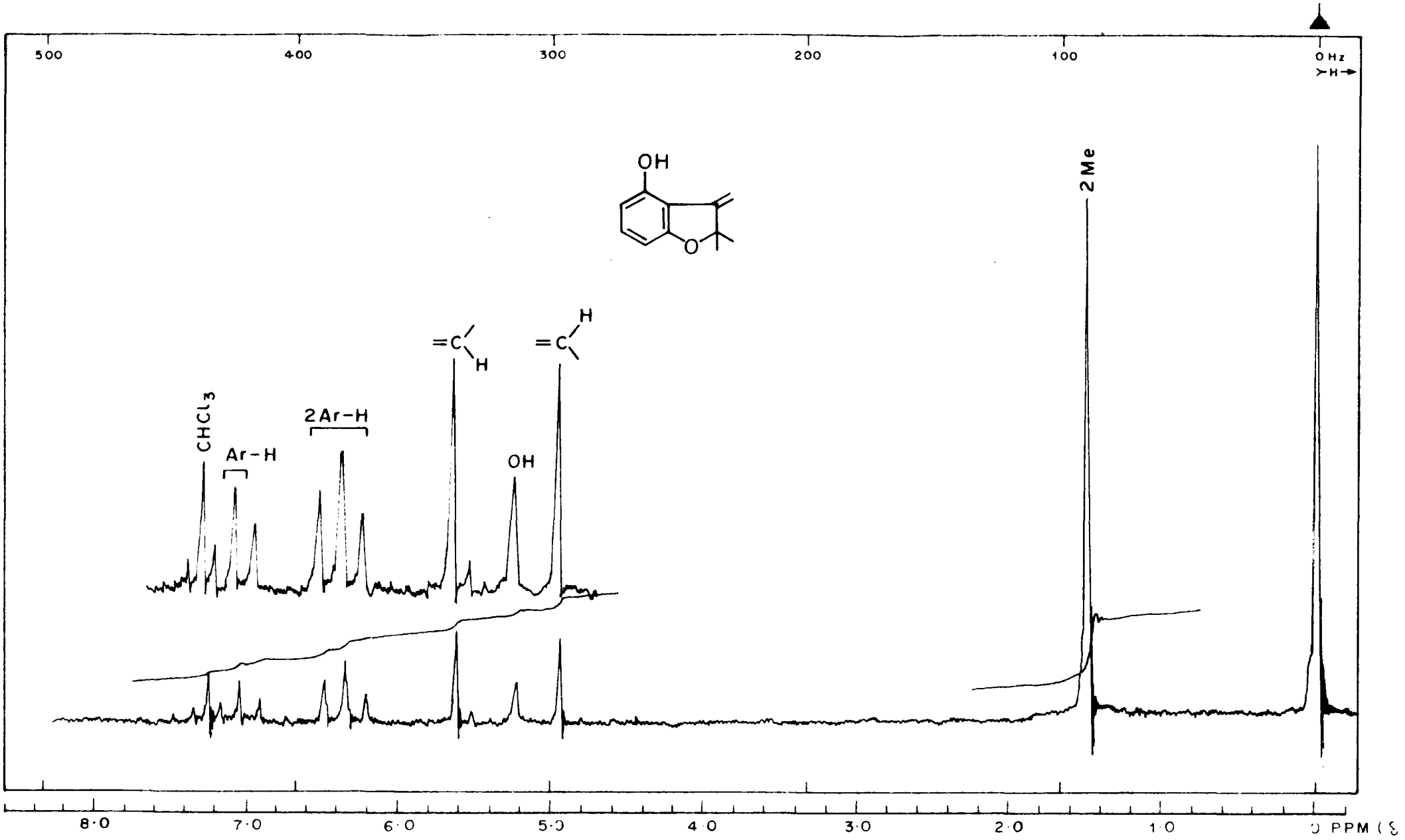


FIG. 1. NMR SPECTRUM OF 4-HYDROXY-2,2-DIMETHYL-3-METHYLENE COUMARAN (VII) IN $CDCl_3$

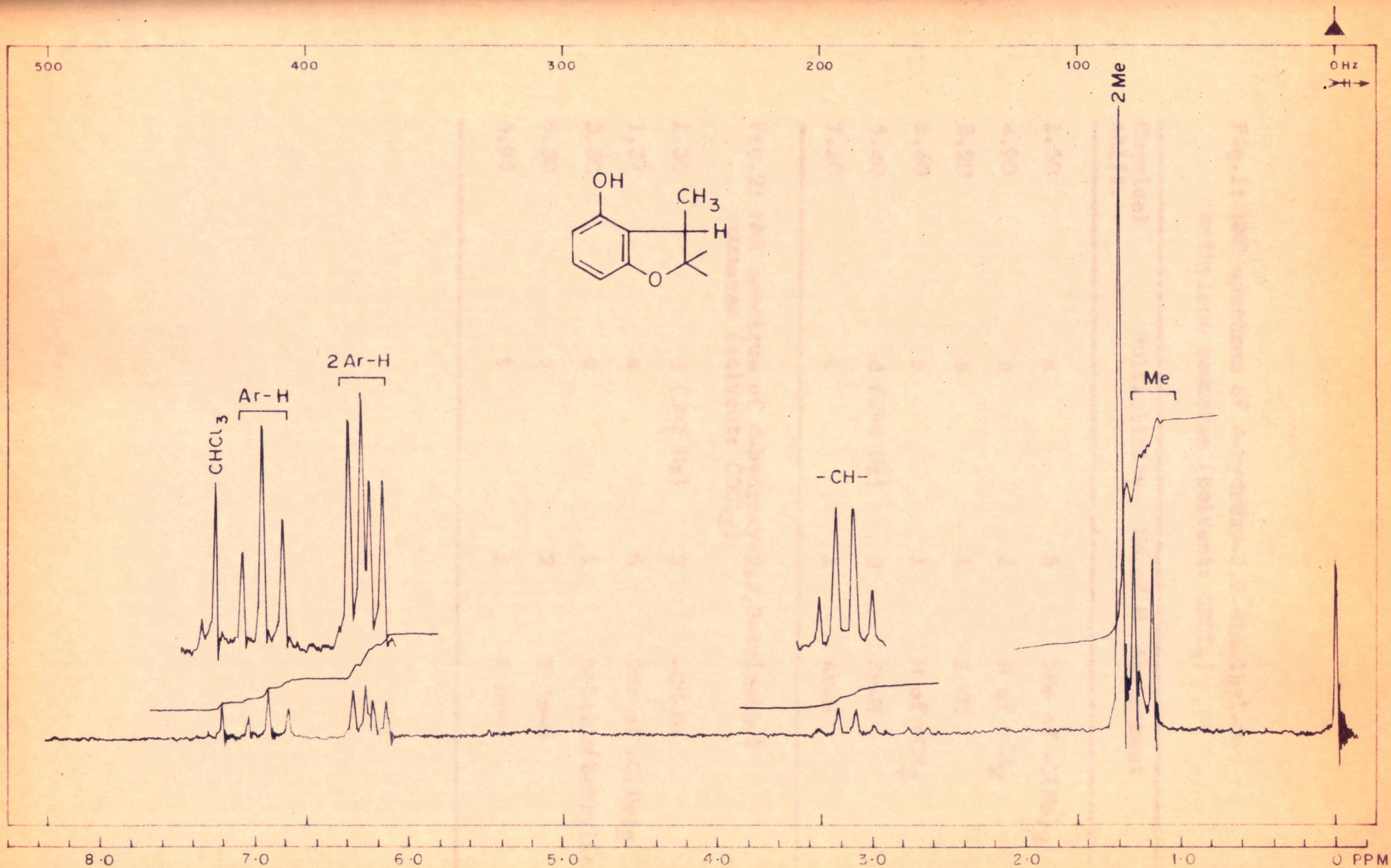


FIG. 2. NMR SPECTRUM OF 4-HYDROXY-2,2,3-TRIMETHYL COUMARAN (X) IN $CDCl_3$

Fig.1: NMR spectrum of 4-hydroxy-2,2-dimethyl-3-methylene coumaran (solvent: $CDCl_3$)

Chemical shift.	Multiplicity	No.of H	Assignment
1.50	s	6	2Me of $-C(Me)_2$
4.90	s	1	H of $=CH_2$
5.20	s	1	1 OH
5.60	s	1	H of $=CH_2$
6.40	d (J=9 Hz)	2	Ar-H
7.10	t	1	Ar-H

Fig.2: NMR spectrum of 4-hydroxy-2,2,3-trimethyl coumaran (solvent: $CDCl_3$)

1.30	d (J=7 Hz)	3	-CH-Me
1.37	s	6	2Me of $-C(Me)_2$
3.30	q	1	methine(benzylic)
6.30	q	2	2 Ar-H
6.96	t	1	1 Ar-H

also fall wide apart (42 Hz) as in the above case. The probable reason in this case may be that one of the hydrogens of the $=CH_2$ is in close proximity of the hydroxyl group. The appearance of the terminal methylene protons as a singlet has analogy in other exocyclic $=CH_2$ groups.[8] Its mass spectrum shows M^+ 176 as a molecular ion and other intense peaks at m/e 175, 162, 161 and 147.

The structure (VIII) is confirmed by its catalytic hydrogenation over palladium-carbon (10%) which gave (X). The NMR spectrum (Fig.2) indicates the expected signals: a doublet (J=7 Hz) at 1.30 (methyl group of CH_3-CH); a six proton singlet at 1.37 (gem-dimethyl group) and a quartet at 3.30 (benzylic methine). Two out of the three aromatic protons appear as a quartet at 6.30 and one as a triplet at 6.96.

In its mass spectrum it shows m/e 178 as a molecular ion and the base peak at m/e 163.

4-Pivalylresorcinol (XI) is obtained by condensation of resorcinol with pivalic acid using BF_3-etherate as a condensing agent. Its dimethyl ether undergoes normal demethylation with anhydrous aluminium chloride to give the phenolic ketone under similar condition.

In another set of experiments, orcinol has been condensed with pivalic acid in presence of BF_3-etherate

to give the two isomers, 4-pivalyl orcinol (XII) and 2-pivalyl orcinol (XIII). 4-Pivalyl orcinol (XII) on treatment with anhydrous aluminium chloride in dry refluxing benzene gave a cyclized compound (IX), whose NMR spectrum in CCl_4 (Fig.3) indicates the presence of a six proton singlet 1.40 (gem-dimethyls); a singlet at 2.17 (aromatic methyl); two singlets at 4.70 and 5.37 integrating for one proton each, accounting for the hydrogens of terminal methylene group. The two signals in the low field region of the spectrum appearing at 5.90 and 6.07 account for the two aromatic protons. However, 2-pivalyl orcinol (XIII) under similar reaction conditions remained unreacted.

The above reactions suggest that both ortho positions in the aryl pivalyl ketone should have either hydroxyl or methoxyl substituents to yield a cyclised product. After a normal demethylation, the intermediate R-O-$AlCl_2$ probably exists in the form of a complex (XVI) promoting the formation of the product (XVII) via methyl migration as shown in chart III. The complex (XVII) on treatment with dilute acid gives the alcohol (XVIII) which readily dehydrates to (VIII). If the benzylic carbonium ion intermediate (XVI) is valid, then the carbonium ion tert-but.-$\overset{+}{C}$-C_6H_4(ortho-OR) should lead to a 2,2-dimethyl-3-methylene coumaran system.

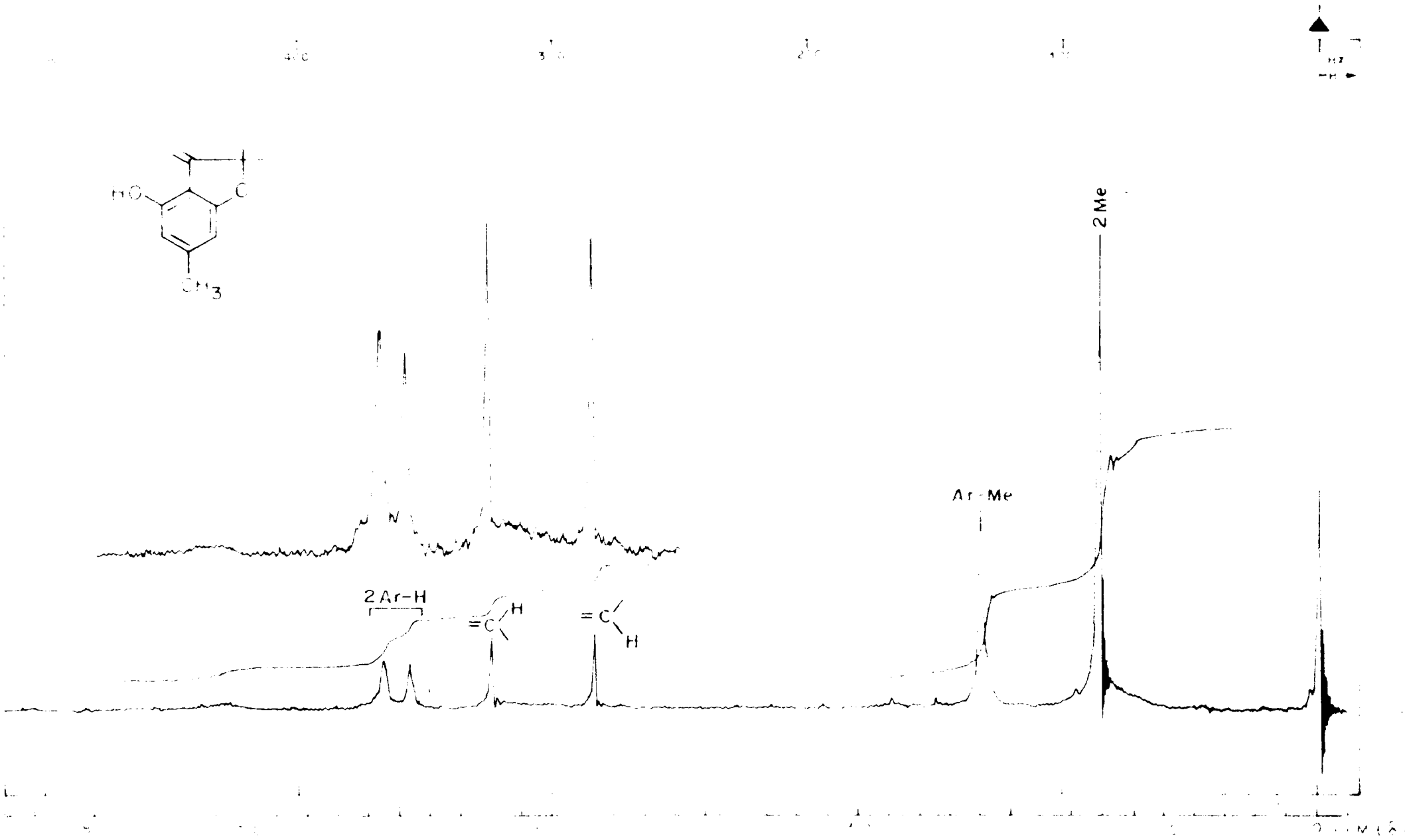


FIG 3. NMR SPECTRUM OF 4-HYDROXY-6-METHYL-2,2-DIMETHYL-3-METHYLENE COUMARAN (IX) IN [illegible]

Fig.3: NMR spectrum of 4-hydroxy-6-methyl-2,2-dimethyl-3-methylene coumaran (solvent: CCl_4)

Chemical shift.	Multiplicity	No. of H	Assignment
1.40	s	6	2 Me of $-C(Me)_2$
2.17	s	3	Ar-Me
4.70	s	1	H of $=CH_2$
5.37	s	1	H of $=CH_2$
5.90	s	1	Ar-H
6.07	s	1	Ar-H

To substantiate the above facts, 4-pivalylresorcinol (XI) has been reduced to the alcohol (XIV) which on treatment with acid gave a cyclised product (XV).

Apparently the steric factor will also play its role in the formation of the coumaran system. Because of the steric hindrance, the carbonium ion in (XVI) cannot stabilize by delocalization via the π -orbitals of the benzene nucleus, and the rearrangement to the carbonium ion (XVIa) is energetically advantageous. It is necessary to note that if halide $Me_2CCH_2Cl.Ph$ is hydrolysed under S_N1 conditions, no rearrangement from neo-pentyl to tert-amyl group could take place as the carbonium ion can stabilise itself by delocalization.[9]

However, when the partial demethylation is carried out under basic conditions, such as C_2H_5SH/NaH in dimethyl-formamide under nitrogen atmosphere, the monomethyl ether (VII) is obtained in 90% yield.

Lauer and Moe[10] have also obtained 2,2,3-trimethyl-5-carbethoxy coumaran as a abnormal rearrangement product during the pyrolysis reaction of γ,γ -dimethyl allyl phenyl ethers. Other methods of synthesis of 2,2,3-trimethyl coumaran in literature include: (1) addition of 3-bromo-2,2-dimethyl-coumaran to the excess of methyl magnesium iodide, yielded

53% of 2,2,3-trimethylcoumaran;[11] (2) a Grignard's reaction of isopropylmagnesium bromide on ortho-hydroxyacetophenone;[10] (3) reaction of substituted or unsubstituted phenols having at least one free ortho position to the hydroxyl group, with a conjugated diene at elevated temperature in presence of metallic phenolates (e.g. Zn, Al, Mg, Ca, Na, Li).[12]

Anisoxide, isolated from star aniseed oil (from Illicium verum) by Jackson and Short,[13] is the only natural product so far known with a 2,2,3-trimethylcoumaran system.

EXPERIMENTAL

Lithiation of resorcinol dimethyl ether and preparation of (VI)

A solution of butyl lithium in dry ether (150 ml) (prepared from 4 g. of lithium and 28 g. of n-butylbromide) was added to resorcinol dimethyl ether (17 g) in dry ether (100 ml). The solution was refluxed for 24 hr. under nitrogen atmosphere. To this was then added a solution of pivalyl-chloride (30 g) in dry ether (50 ml) and the mixture refluxed for 12 hr. The reaction mixture was filtered, the filtrate washed with water and dridd (Na_2SO_4). Evaporation of solvent gave a solid residue which on crystallisation from benzene gave colourless plates (5 g), m.p. 86° (Found: C, 70.28; H, 8.26. $C_{13}H_{18}O_3$ requires C, 70.26; H, 8.10%).

NMR (CCl_4): 1.20 (s, 9H, $-CMe_3$); 3.80 (s, 6H, -OMe), 6.60 (d, J=9 Hz, 2H, 4-H and 6-H); 7.29 (t, 1H, 5-H).

MS: M^+ 222 and m/e 165, 150.

Demethylation of 2-pivalyl resorcinol dimethyl ether (VI)

Method 1: A solution of (VI) (0.5 g) in dry benzene (20 ml) was heated under reflux with anhydrous aluminium chloride (0.9 g; 3 moles) for 5 hr. The mixture was poured into dilute sulphuric acid and extracted with more of benzene. The organic layer was washed with water and dried (Na_2SO_4). The removal of solvent gave an oil (0.4 g). Purification of the oil over a column of silica gel (20 g), using benzene-

acetone mixture as eluent, gave (VIII) (0.16 g; 40%), m.p. 186° (M^+ 186) (Found: C, 75.20; H, 6.90. $C_{11}H_{12}O_2$ requires: C, 75.00; H, 6.90%); and monomethyl ether (VII) (0.12 g), m.p. 82° (Found: C, 69.00; H, 7.40. $C_{12}H_{16}O_3$ requires: C, 69.20; H, 7.70%).

Method 2: A solution of (VI; 0.5 g) in dry benzene (20 ml) was heated under reflux with anhydrous aluminium chloride (0.3 g; 1 mole) for 5 hr. Work up as above gave an unreacted compound (VI) (0.35 g) and monomethyl ether (VII) (0.07 g).

NMR of monomethyl ether (CCl_4): 1.15 (s, 9H, $-CMe_3$), 3.67 (s, 3H, -OMe); 6.27 (q, 2H, Ar-H); 6.94 (s, 1H, Ar-H); 7.67 (bs, 1H, exchangeable with D_2O).

MS: M^+ 208, m/e 165, 151, 136, 108.

Hydrogenation of compound (VIII): The compound (VIII) (0.02 g) in ethanol (15 ml) was hydrogenated in presence of 10% palladium carbon for 4 hr. to yield an oil (X). (Found: C, 74.31; H, 7.81. $C_{11}H_{14}O_2$ requires C, 74.33; H, 7.86%).

4-Pivalylresorcinol (XI)

A mixture of resorcinol (2 g), pivalic acid (2 g) and BF_3 etherate (20 ml) was kept at room temperature for 30 hr. The reaction mixture was poured on crushed ice,

extracted with ether and washed with sodium bisulphite and sodium bicarbonate solutions respectively. Evaporation of the solvent gave thick oil (1.8 g). This was washed with hot water (4 x 25 ml) to remove the unreacted resorcinol. Crystallisation from benzene gave pink needles (1 g), m.p. 129° (Found: C, 68.30; H, 7.00. $C_{11}H_{14}O_3$ requires C, 68.10; H, 7.20%)

4-Pivalylresorcinol dimethyl ether

A mixture of 4-pivalylresorcinol (0.5 g), dimethyl sulphate (1 ml) and anhydrous potassium carbonate (3 g) in dry acetone (15 ml) was refluxed for 4 hr. and worked up in the usual way. It gave a crystalline dimethyl ether (0.4 g), m.p. 150°.(Found: C, 70.28; H, 8.26. $C_{13}H_{18}O_3$ requires C, 70.26; H, 8.1%).

Demethylation of 4-pivalylresorcinol dimethyl ether with aluminium chloride (3 moles)

A mixture of 4-pivalyl resorcinol dimethyl ether (0.3 g), benzene (20 ml) and aluminium chloride (0.54 g; 0.3 moles) was refluxed for 5 hr. and worked up in the usual way. It gave 4-pivalylresorcinol (XI) (0.21 g).

Preparation of 4-pivalyl orcinol (XII) and 2-pivalylorcinol (XIII).

A mixture of orcinol (2 g), pivalic acid (10 ml) and BF_3 etherate (25 ml) was kept at room temperature

for 5 days, and it gave an oil (1.4g.). The product showed a mixture of two compounds on TLC (silica gel, 2:8 acetone-benzene). Purification on a column of silica gel gave (1) 4-pivalylorcinol (0.5 g), m.p.148°, M^+ 208 (Found: C, 68.00; H, 7.60. $C_{12}H_{16}O_3$ requires C, 69.30; H, 7.7%).

NMR ($CDCl_3$): 1.35 (s, 9H, CMe_3), 2.30 (s, 3H, Ar-Me), 6.2 (s, 2H, Ar protons). (2) 2-Pivalylorcinol (0.8 g), pale yellow oil, b.p. 220°/1 mm. at air bath temp. 220°.

NMR (CCl_4): 1.35 (s, 9H, CMe_3), 2.20 (s, 3H, Ar-Me), 5.94 (bs, exchangeable with D_2O), 6.27 and 6.37 (d, J=2 Hz, 4-H and 6-H).

Reaction of 4-pivalylorcinol (XII) with aluminium chloride (3 moles):

A mixture of (XII, 0.125 g), dry benzene (15 ml) and aluminium chloride (0.24 g) (3 moles) was refluxed for 5 hr. Working up in the usual way the product gave a colourless crystalline compound (IX) (0.05 g; 42%), m.p.143°, M^+ 190 (Found: C, 75.60; H, 7.30; $C_{12}H_{14}O_2$ requires C, 75.80; H, 7.40%).

2-Pivalylorcinol under similar experimental conditions remained unreacted.

Reduction of 4-pivalylresorcinol with sodium borohydride

To a solution of (XI; 0.2 g) in methanol (15 ml) was added sodium borohydride (0.033 g) in 5 ml. of NaOH solution (2 ml of 2N NaOH solution, diluted to 20 ml) and

stirred for 2 hr. at 15-20°. Methanol was removed and the residue diluted with water (25 ml) and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and solvent removed. The product was purified by passing it through a column of silica gel, and crystallised from benzene to get the carbinol (XV), m.p. 153°; M^+ 196. (Found: C, 67.30; H, 8.16. $C_{11}H_{16}O_3$ requires C, 67.35; H, 8.16%).

Conversion of (XIV) to (XV)

To 0.075 g of carbinol (XIV) was added cold 98% H_2SO_4 (3 ml) and kept at room temperature for 30 min. This was poured on ice and extracted with ether. The ether extract was washed with bicarbonate solution, water and then dried (Na_2SO_4). Evaporation of the solvent gave an oil (XV) (Found: C, 74.21; H, 7.83. $C_{11}H_{14}O_2$ requires C, 74.33; H, 7.86%).

IR: 3400 cm^{-1} (-OH group).

NMR (CCl_4): 1.15 (d, J= 7 Hz; 3H, -CH-Me); (s, 6H, $-CMe_2$): 3.00 (q, 1H, -CH-Me); 5.54(bs, exchangeable with D_2O; -OH proton); 6.10-6.30 (m, 2H, 5-H and 7-H); 6.80 (d, J=9 Hz, 1H, 4-H).

MS: M^+ 178.

Partial demethylation of (VI) using sodium thioethoxide

Sodium thioethoxide (5 equivalents) was prepared by the addition of ethanethiol (5 ml; 1.1 mole) to sodium hydride (2 g; 1.5 mole) in DMF (250 ml) for 30 min. During addition, the flask was cooled in an ice bath. A solution of 2-pivalylresorcinol dimethyl ether (12.6 g) in DMF (100 ml) was then added at room temperature. The mixture was refluxed in an oil bath for 4 hr. under nitrogen atmosphere. DMF was distilled out under reduced pressure. The residue was then taken in ether and extracted with 1.2 N NaOH (2 x 50 ml). The alkaline extract was neutralised with dilute HCl and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4). Removal of solvent gave an oil, which was purified by passing through a column of silica gel to get 2-pivalyl resorcinol monomethyl ether (VII; 10.7 g; 90%).

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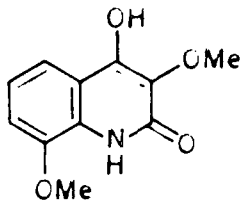
PART - III

Section II

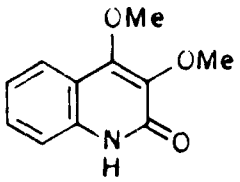
SYNTHESIS OF SAIETENIDIN-A METHYL ETHER

INTRODUCTION

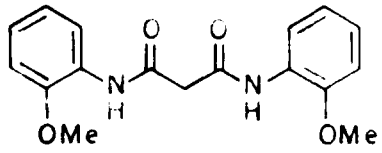
Intensive investigation of the plants belonging to Rutaceae has brought to light a number of new alkaloids derived from quinoline, such as quinolones, furoquinolines and pyranoquinolines. Alkenyl substituents at 3-position and oxygenation at 4-position is a common feature of quinolone alkaloids. However, Mujumdar,[1] from the same group earlier isolated a new 2-quinolone alkaloid, swietenidin A (I) from the bark of Chloroxylon swietenia having a methoxyl substituent at 3-position. Later on another alkaloid, swietenidin B (II) with similar oxygenation pattern has been isolated from the same plant. Swietenidin A (I) and B (II) are the first alkaloids with a methoxyl substituent at 3-position. However, swietenidin B is synthetically known. The structure (I) was provisionally assigned to swietenidin A mainly on the basis of spectral data and in the present work its synthesis from p-anisidine has been described.(Scheme I).



SWIETENIDIN-A (I)

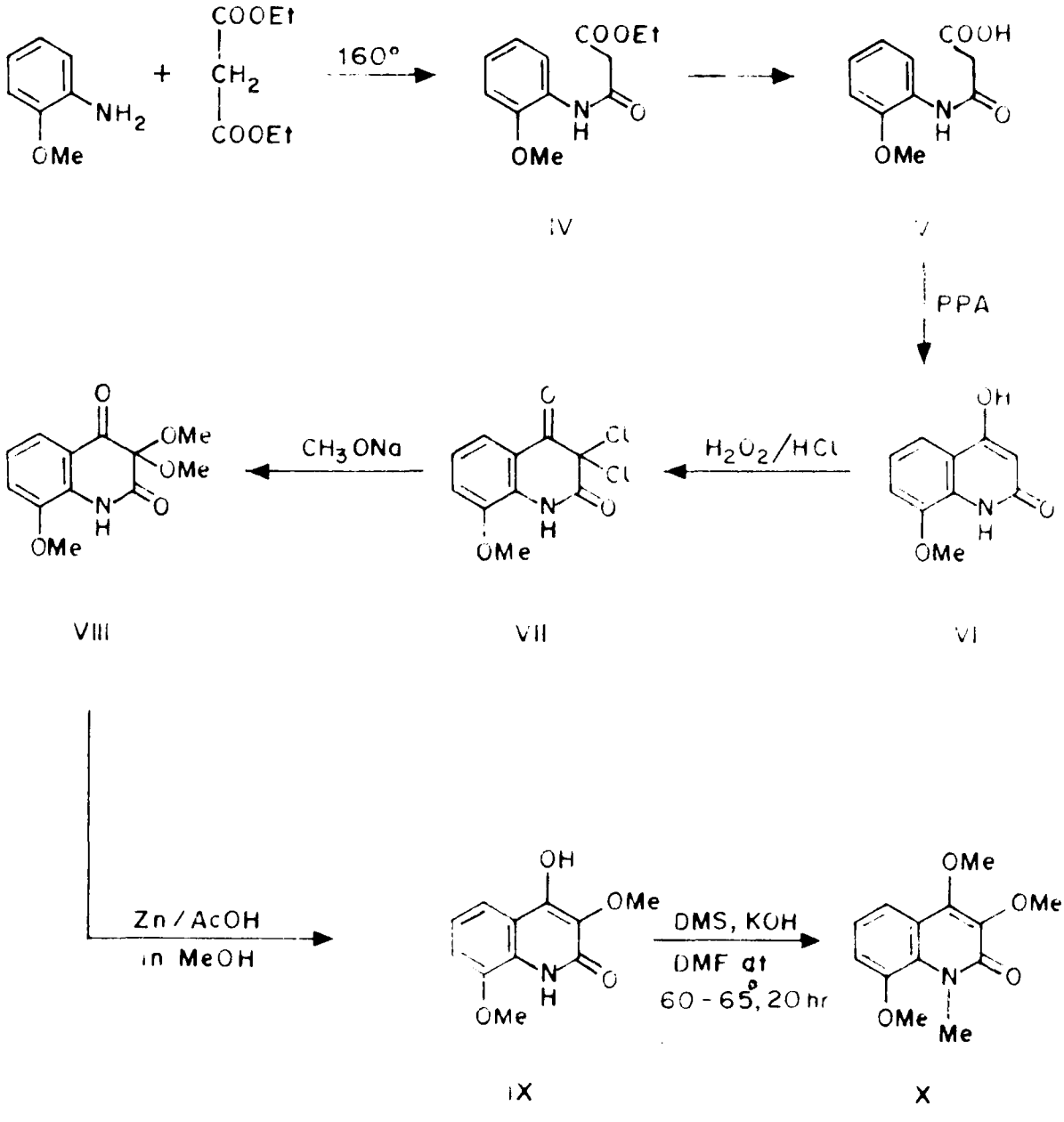


SWIETENIDIN-B (II)



III

SCHEME - I



IV

V

VI

VII

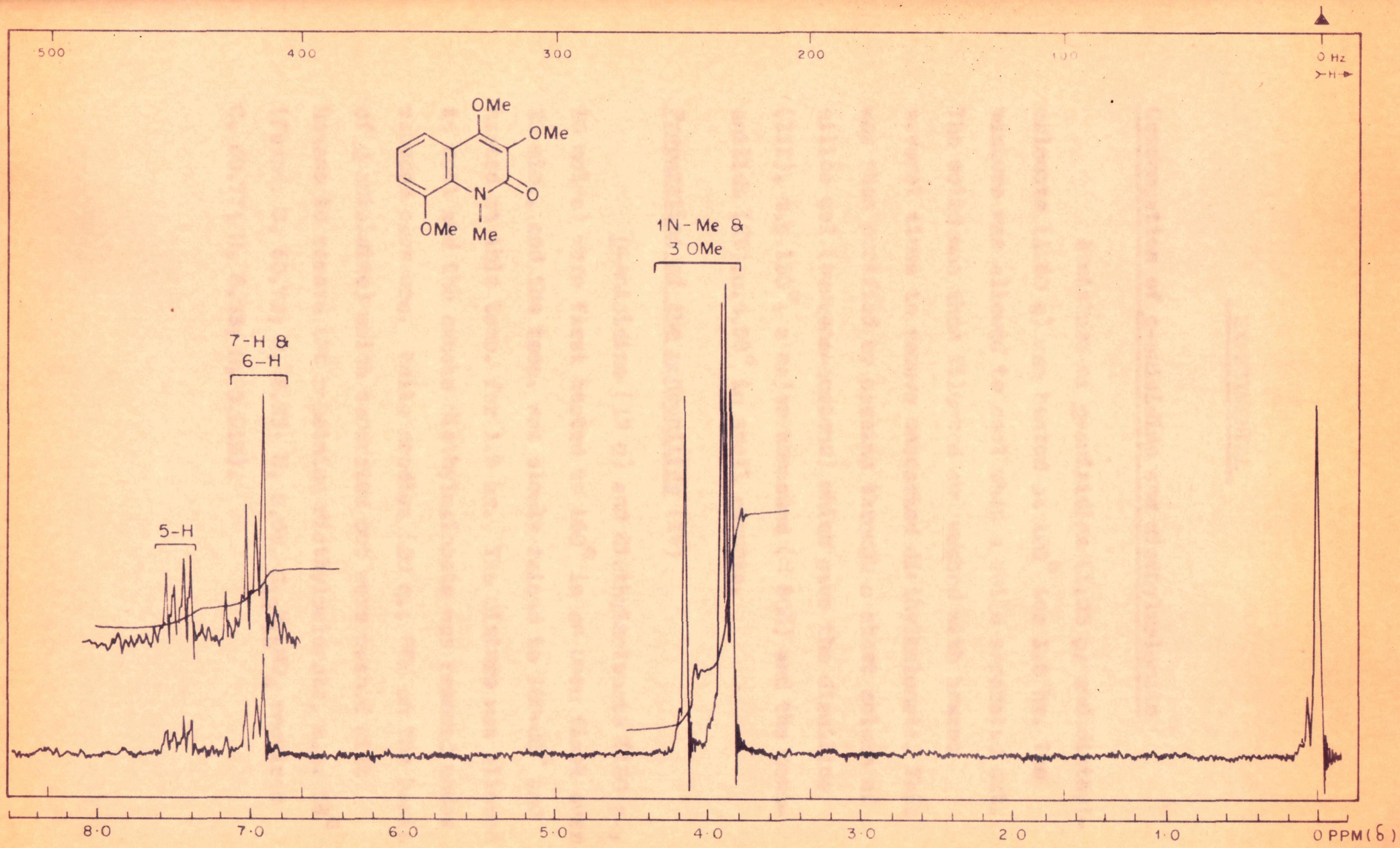
VIII

IX

X

PRESENT WORK

Heating together equimolar quantities of p-anisidine and diethylmalonate resulted in a mixture of dianilide (III) $C_{17}H_{18}N_2O_4$, m.p. 150°, and the monoanilide (IV), $C_{12}H_{15}NO_4$, m.p. 58°. The latter could be obtained as a sole product in quantitative yields (80%) when large excess (10 moles) of diethylmalonate is used.[2] Hydrolysis of the monoanilide(IV) with dilute alkali gave the corresponding acid (V), $C_{10}H_{11}NO_4$, m.p. 145-46°, which on subsequent cyclization with polyphosphoric acid (sp.gravity 2.2) gave 4-hydroxy-8-methoxycarbostyril (VI), $C_{10}H_9NO_3$, m.p. 246°. This on treatment with hydrogen peroxide, conc. HCl and acetic acid gave 8-methoxy-3,3-dichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline(VII) as dark yellow needles. The transformation of (VII) to the ketal (VIII) has been carried out by its treatment with sodium methoxide. Further the ketal (VIII) on reduction with zinc and acetic acid in methanol yielded 4-hydroxy-3,8-dimethoxycarbostyril (IX). Methylation of the carbostyril(IX) with dimethyl sulphate using potassium hydroxide in dimethylformamide gave N-methyl-3,4,8-trimethoxy-2-quinolone (X), which is identical in all respects with the swietenidin A methyl ether (TLC and mixed m.p.).



NMR SPECTRUM OF SWIETENIDIN-A METHYL ETHER IN CCl_4

EXPERIMENTAL

Condensation of p-anisidine and diethylmalonate

A mixture of p-anisidine (1.23 g) and diethylmalonate (1.60 g) was heated at 180° for 1.5 hr. The mixture was allowed to cool when a solid separated out. The solid was then filtered and washed with hexane several times to remove unreacted diethylmalonate. This was then purified by passing through a short column of silica gel (benzene-acetone) which gave the dianilide (III), m.p.180°, a major compound (≃ 80%) and the monoanilide (IV), m.p.58° in small amounts.

Preparation of the monoanilide (IV)

o-Anisidine (13 g) and diethylmalonate (180 g., 10 moles) were first heated to 160° in an open flask over 30 min., and the temp. was slowly raised to 180-85° and heated at this temp. for 1.5 hr. The mixture was allowed to cool and the excess diethylmalonate was removed under reduced pressure. White needles (20 g., 80% on the basis of p-anisidine) which separated out were washed with hexane to remove the remaining diethylmalonate, m.p. 58° (Found: C, 60.73; H, 6.33; N, 5.63. $C_{12}H_{15}NO_4$ requires C, 60.77; H, 6.33; N, 5.91%).

N-(2-Methoxyphenyl) malonamic acid (V)

The compound (IV) was shaken with 1N NaOH (180 ml) for 1 hr., filtered and the filtrate neutralised with 2N HCl which gave the acid (V), as pale yellow needles (12 g), m.p. 145-46° (Found: C, 57.30; H, 5.15; N, 6.70. $C_{10}H_{11}NO_4$ requires C, 57.42; H, 5.26; N, 6.70%).

4-Hydroxy-8-methoxycarbostyril (VI)

The acid (V; 5 g) was suspended in polyphosphoric acid (sp.gravitity 2.2, 25 g) and heated at 140-50° for 40 min. The dark red viscous solution was allowed to cool, and water (200 ml) added to it and the precipitated quinolone was filtered. It was then purified by passing it through a column of silica gel (100 g) (eluent: 0.5:9.5 methanol-chloroform) to get colourless needles (4.10 g., 87%), m.p. 246° (lit.[3] 245-248°) (Found: C, 62.80; H, 4.70 : N, 7.33. $C_{10}H_9NO_3$ requires C, 62.84; H, 4.71 : N, 7.33%).

8-Methoxy-
3,3-Dichlore-2,4-dioxo-1,2,3,4-tetrahydroquinoline(VII)

A mixture of (VI) (1.5 g), hydrogen peroxide (16.5 ml) and acetic acid (0.6 ml) was heated to 80° and then 2.1 ml. of conc.hydrochloric acid added to it. After a short time more of hydrogen peroxide (3.6 ml) and acetic acid (0.6 ml) were added and kept at 85° for 30 min.

Finally water (4 ml) was added for dilution. The precipitated solid was filtered, and the residue crystallised from benzene to get dark yellow needles (1.8 g; 87.7%), m.p.204-8 205°. (Found: C, 46.05; H, 2.45; N, 5.30; Cl, 27.20. $C_{10}H_7NO_3Cl_2$ requires C, 46.14; H, 2.69; N, 5.38; Cl, 27.31%).

Conversion of (VII) to the ketal (VIII)

To a cold solution of sodium methoxide (prepared from 0.55 g. of sodium in 6 ml. of absolute methanol), a cold solution of (VII) (1.8 g) in 15 ml. of methanol was added and heated to boiling for 10 min. The mixture was cooled and transferred with good stirring into hydrochloric acid solution (1.8 ml. conc.HCl in 27 ml. of water) and filtered after keeping it for 1.5 hr. to get 1.8 g.(80.5%) of the ketal (VIII), m.p.87-88° (Found C, 57.45; H, 5.01; N, 5.38. $C_{12}H_{13}NO_5$ requires C, 57.61; H, 5.20; N, 5.38%).

Reduction of ketal (VIII) to (IX)

The ketal (VIII) (1.0 g) was dissolved in dry methanol (15 ml) and acetic acid (2.5 ml) and zinc dust (1.2 g) and gradually added to the refluxing solution. After 10 min. conc. hydrochloric acid (0.5 ml) was added, and the heating continued for another 5 minutes and then allowed to cool, and filtered. The filtrate was concentrated, diluted with water (25 ml) and extracted with chloroform. The organic

layer was washed with water and dried (Na_2SO_4). Removal of solvent gave a solid, which on recrystallisation from benzene yielded brown coloured prisms (0.5 g., 56.8%), m.p. 197-98° (Found: C, 59.8; H, 4.89; N, 6.30. $C_{11}H_{11}NO_4$ requires C, 60.01; H, 5.00; N, 6.33%).

Methylation of 4-hydroxy-3,8-dimethoxy-2-quinolone (IX)

A mixture of (IX; 0.130 g) in dimethylformamide (8.5 ml), powdered potassium hydroxide (0.45 g) and dimethylsulphate (0.7 ml) was heated at 60-65° for 20 hr. The solution was poured into water (20 ml) and extracted with chloroform, washed with water, and dried (Na_2SO_4). The removal of solvent gave a solid residue which was purified by passing it through a short column of silica gel to get pale brown needles, m.p.55°.

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PART - IV

EXPLORATORY WORK ON THE SYNTHESIS OF MAYTANSINOIDS

...

INTRODUCTION

It is known that about twenty per cent of the population in Western countries die of neoplastic diseases, commonly known as 'cancer'. This has engaged the attention of research workers throughout the world in recent years. The few drugs now available for the treatment of certain types of cancer are however highly toxic. These can be broadly classified as (1) alkylating agents, (2) anti-metabolites, (3) antibiotics, and (4) miscellaneous compounds.

Although a large number of synthetic compounds have been made and they are subjected to extensive biological screening, the results so far obtained have not been encouraging. The reason seems to be that due to high reactivity of these compounds and with many cell constituents, they reduce therapeutic indexes. Increasing stress is therefore being laid on natural products which might act as prototypes for synthetic chemist in building more effective and less toxic compounds.

The anti-tumor activity of some plant materials has been known for many centuries. Plant preparations were prescribed for what is thought to have been 'cancer' as early as 1500 B.C. Even now in almost all the countries plant extracts are in use as remedies for cancer.[1]

For the last twenty years several groups are engaged in the isolation and structure elucidation of plant-derived tumor inhibitors. The results are promising and have yielded many novel types of growth inhibitory compounds. Many of the compounds possess structures and chemical properties, which suggest that they may act by selective alkylation of growth regulatory macromolecules. This approach may finally result in synthesising safe and clinically useful chemotherapeutic agents.

The pioneering work of Prof. Kupchan and his associates on plant extract and their success in locating the active constituents as anti-tumor agents has resulted in the isolation of some very active anti-cancer agents.

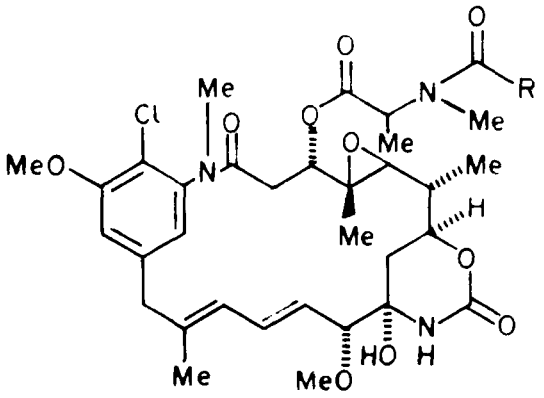
For many years African witch doctors have been using a plant extract for treating cancer. An alcoholic extract of this plant, Maytenus serrata (formerly known as M. oratus, F.Celastraceae) showed potent inhibitory activity against five standard animal tumor systems. Kupchan and his group have isolated the active principle, maytansine, and its structure was determined by X-ray crystallography.[2] It is present in very minute quantity and the plant is grown in Kenya.

Maytansine is an exceptionally interesting macrolide producing anti-tumor activity at the level of micrograms per

kg. of animal body weight. Further, it shows significant inhibitory activity against the L-120 mouse leukemia, Lewis lung carcinoma and B-16 melanocarcinoma solid murine tumor systems. Now the National Cancer Institute is conducting tests on humans. It is estimated to be 10 times more effective in animal tests than any anticancer drug that is now available.

Further investigations by Kupchan and his colleagues led to the isolation and characterisation of three more maytansinoid esters, maytanprine, maytanbutine and maytanvaline. All of them show antileukemic activity. Three other macrolides, maysenine, maysine and normaysine, also isolated from the same plant and not having the ester group at the 3-position, lack antileukemic activity and show about 1/10,000 of the cytotoxicity of maytaniside esters.

Some structural requirements for the antileukemic activity has also been noticed in all these compounds. The C-3 ester function is essential for the biological activity. Any variations in the nature of the ester group are not accompanied by marked changes in antileukemic activity. The carbinolamide and the epoxide functions are essential for

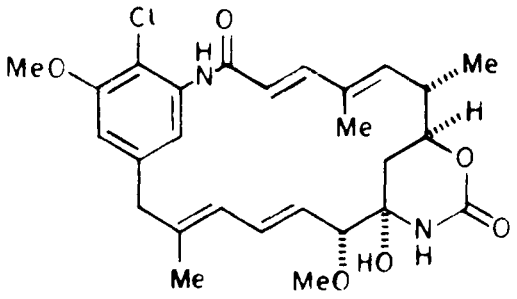


MAYTANSINE, R = Me

MAYTANPRINE, R = CH_2Me

MAYTANBUTINE, R = $CHMe_2$

MAYTANVALINE, R = CH_2CHMe_2



MAYSENINE

MAYSINE (N-Me; 4,5-EPOSIDE)

NORMAYSINE (4,5-EPOSIDE)

the selective alkylation with growth regulatory biological macromolecules. Thus maytansine ethyl ether, in which the reactive carbinolamide is no longer available as a potential alkylating function, shows no antileukemic activity.

The very low concentration of maytansine in Maytenus species and the high cost of isolation has made many groups to undertake its total synthesis.

PRESENT WORK

Maytansine is the first ansa macrolide known to contain carbinolamine, epoxide and aryl halide function, and it appears to be the first member of the series reported to produce antileukemic activity.

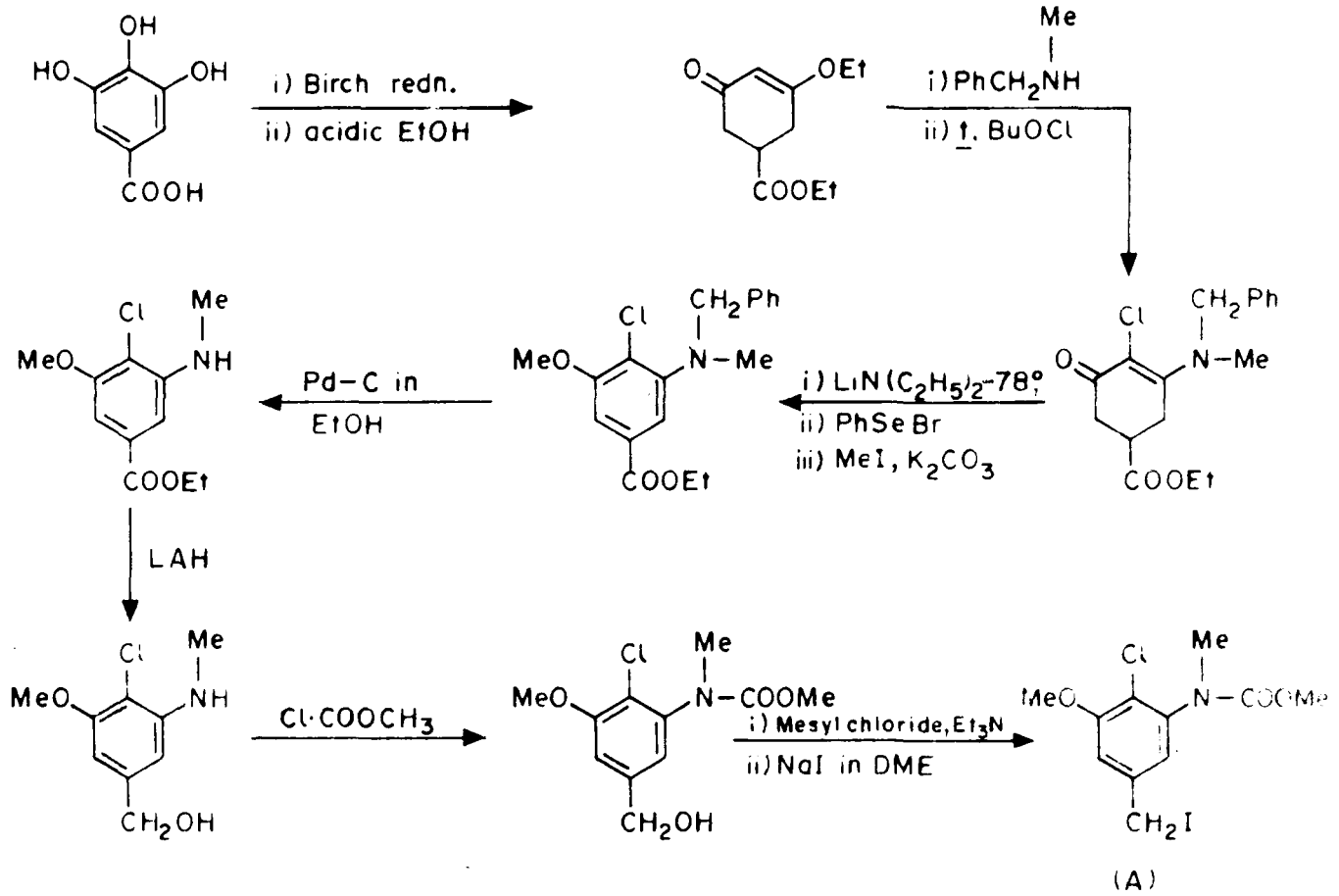
A number of approaches made so far on the synthesis of various parts of Maytansine (I) have been published.[3] Very recently Prof. Corey's group at Harvard have succeeded in reporting the first synthesis of N-methyl maysenine.[4]

For convenient reasons, the molecule can be divided into four zones: The western zone (the aromatic part) contains an unusual substitution. The synthesis of the aromatic part had been reported almost simultaneously by four different groups.[3a-e] The method adopted by Kane and Mayers[3b] seems to be simpler. The different schemes have been indicated in charts 1-4.

During the present investigation, it was felt that the western zone together with the southern zone constitute the a key synthesis, the dienal (II), and if developed by a simpler procedure, may constitute an important intermediate for allowing the synthesis of other maytansinoid analogues, possessing useful anticancer properties. To achieve such a goal, it seems to be more logical to first

CHART-1

COREY et al.



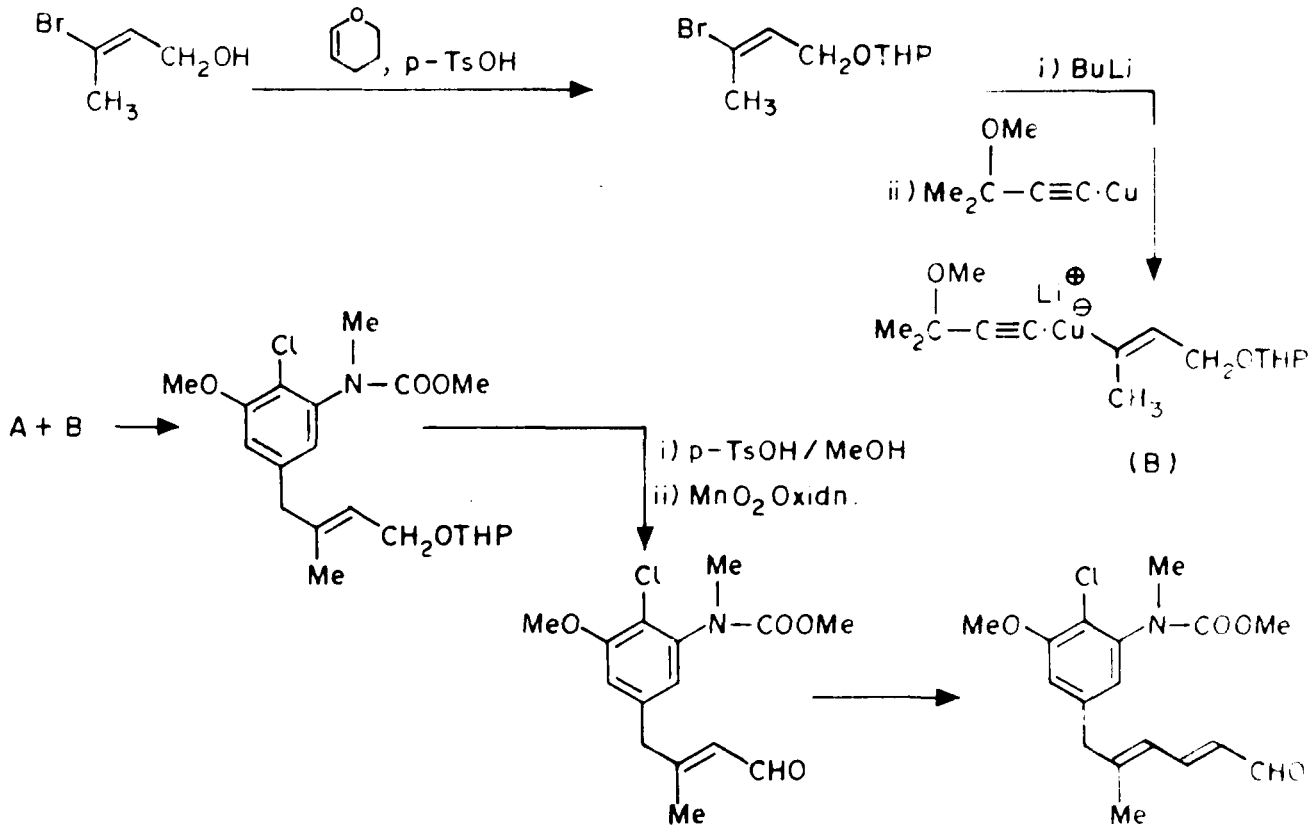


CHART-2

MEYERS et al.

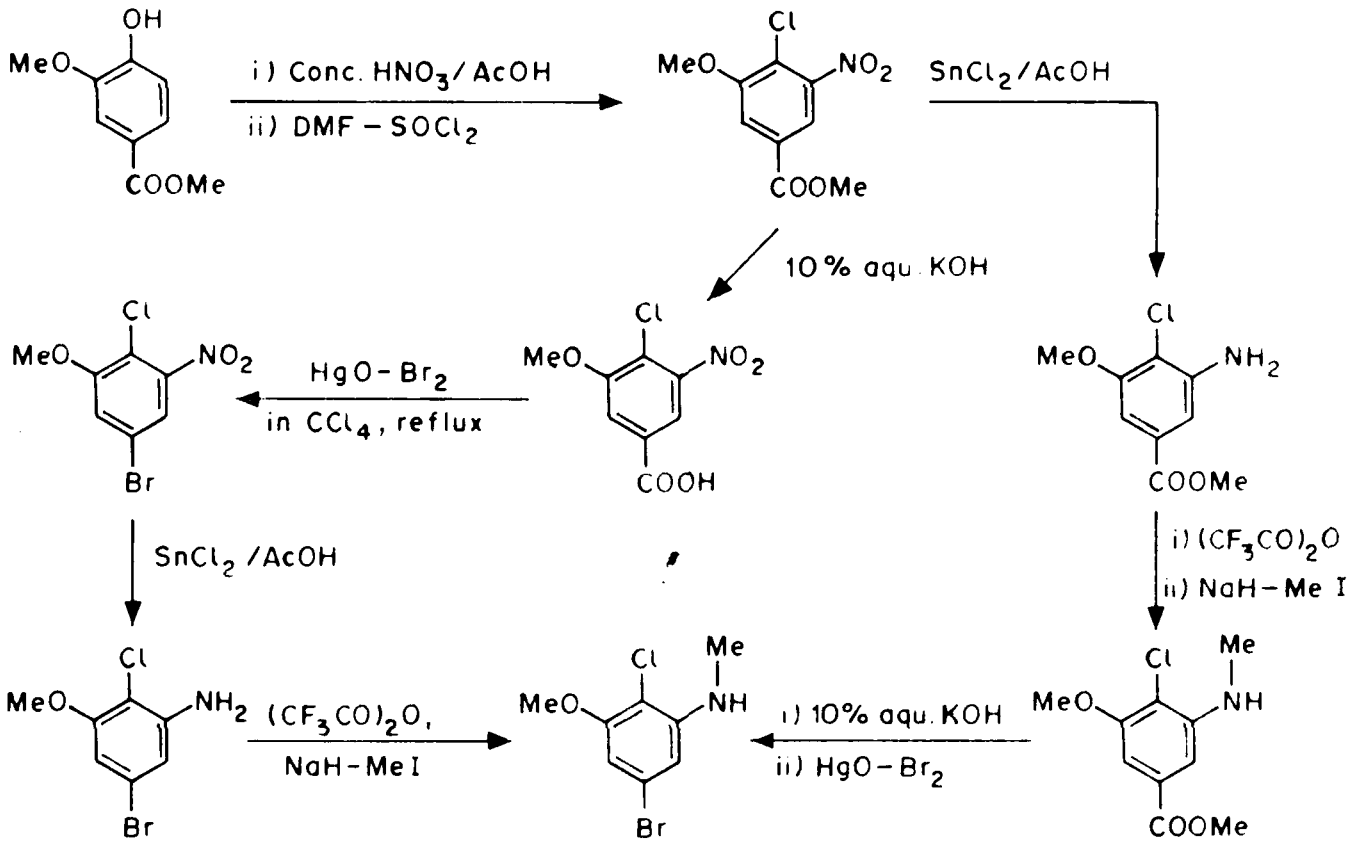


CHART-3

BRUCE et al.

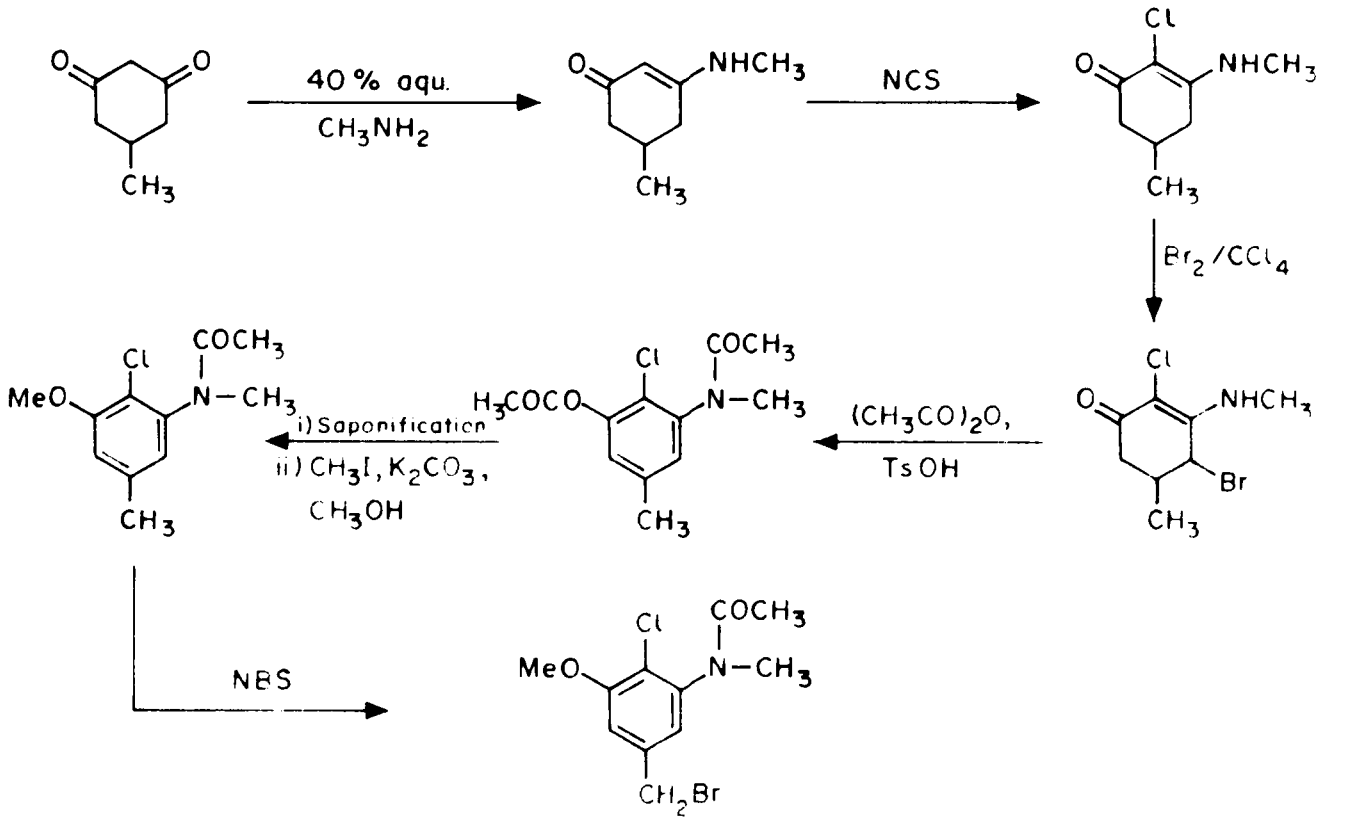
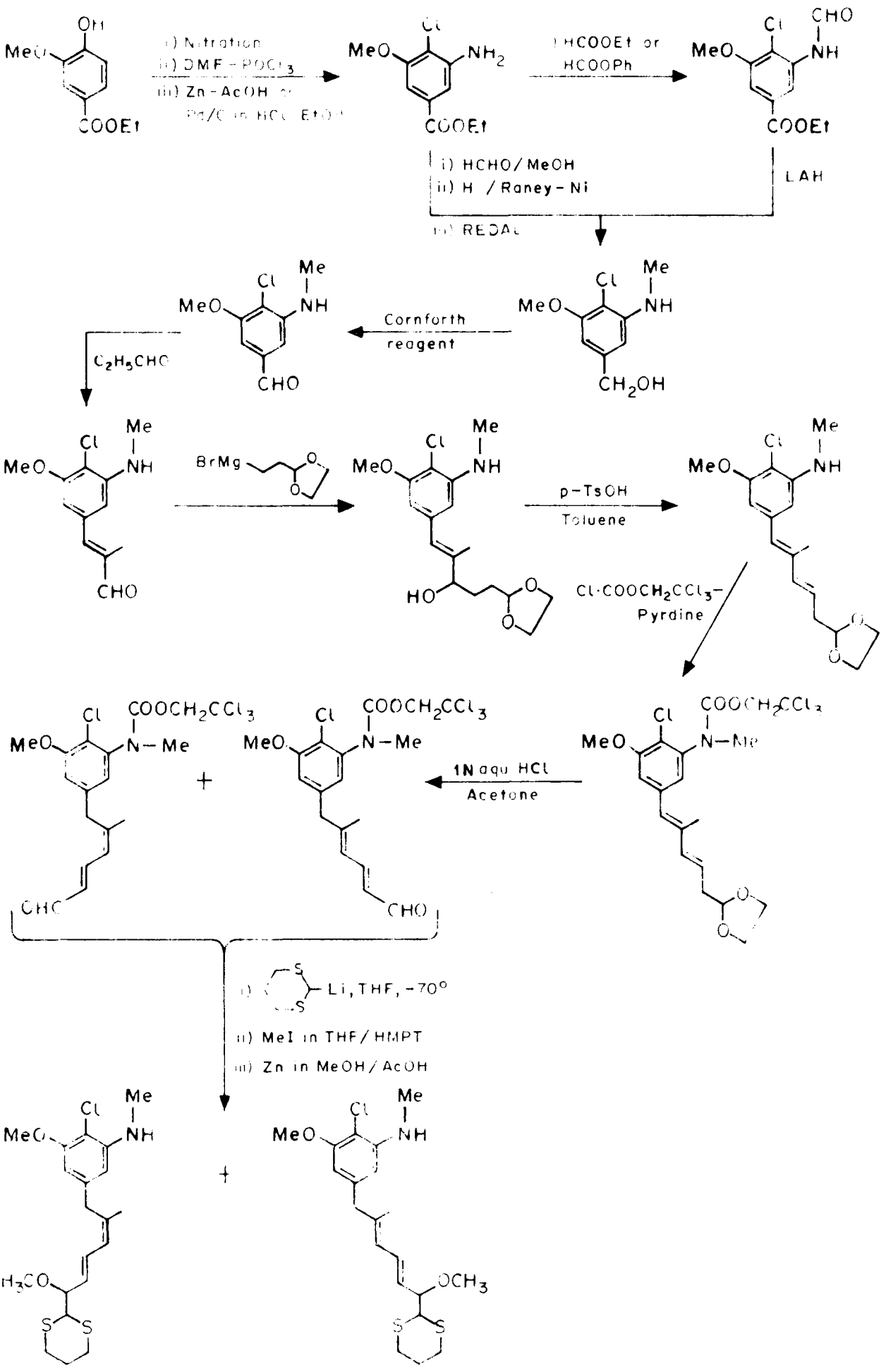


CHART-1

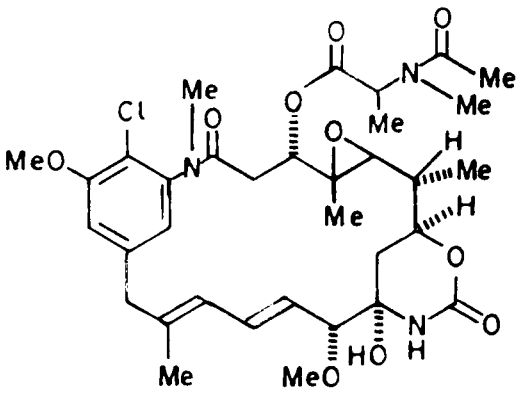
G. TSCH et al



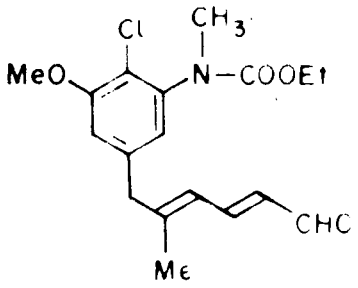
synthesise the key ketone (III), which on Wittig or other suitable reaction, should give the dienal (II).

The synthesis of ketone (III), has now been achieved in the present synthesis starting from vanillic acid. Methyl vanillate, obtained by esterification of vanillic acid, was nitrated in glacial acetic acid with conc. nitric acid (d=1.42) to give the nitro derivative (IV) in more than 80% yield. The nitro compounds on heating to 100° in a mixture of dimethylformamide-thionyl chloride for overnight gave a mixture, containing essentially the desired chloro compound (V) together with the starting nitrocompound (IV). Pure chloro compound (V) was obtained by passing a chloroform extract of the crude mixture over a dry column of alumina and its subsequent crystallisation from methanol. Alternatively, the chloro-compound (V) is also made from (IV) by heating a DMF solution of the latter with triphenylphosphine-carbon tetrachloride complex.

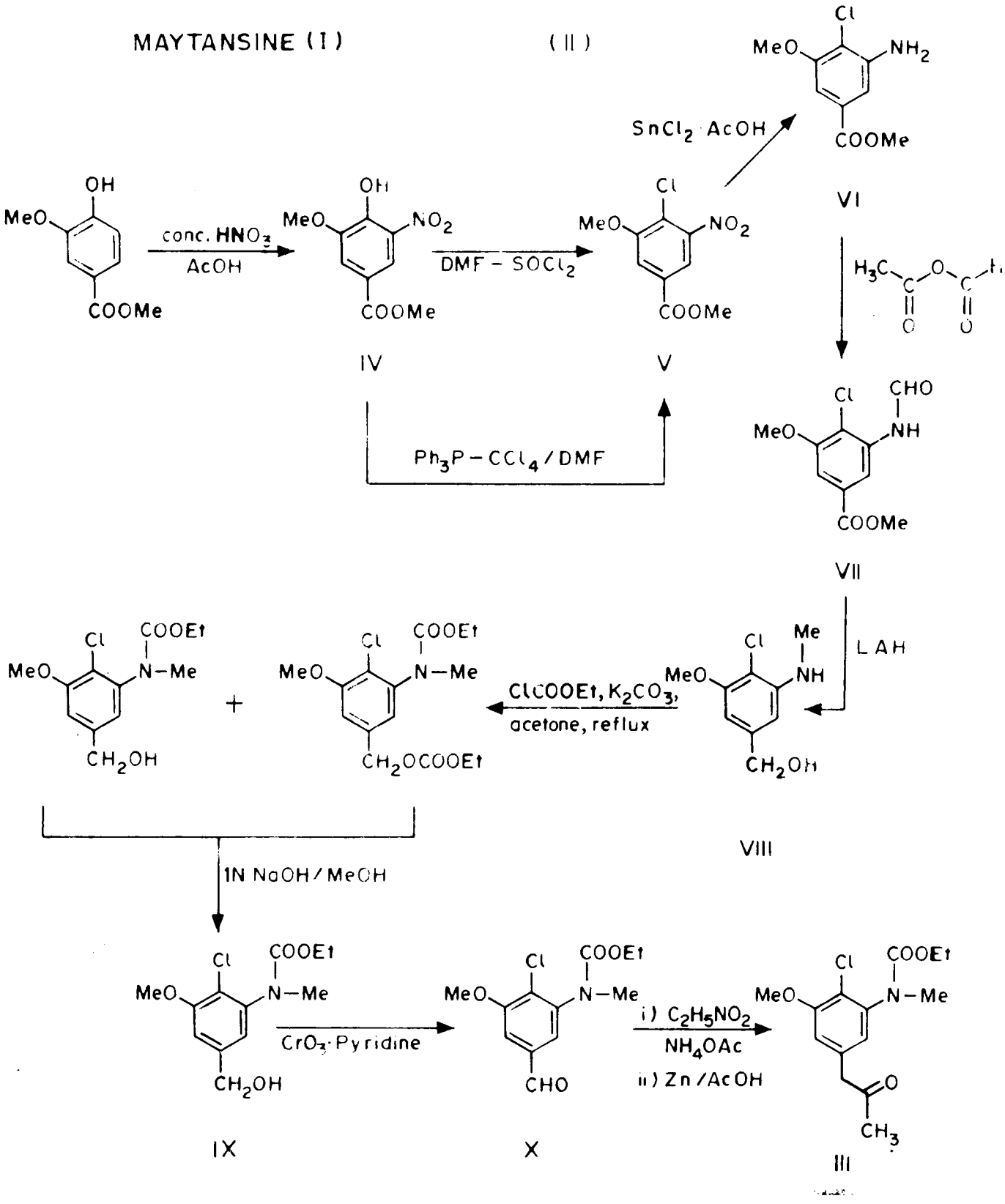
The chloro compound (V) was then subjected to reduction in methanol using stannous chloride and acetic acid at room temperature to obtain methyl 3-amino-4-chloro-5-methoxyvanillate (VI). Compound (VI) can also be conveniently made from (V) by hydrogenation using 10% palladium carbon as a catalyst. However, hydrogenation



MAYTANSINE (I)



(II)

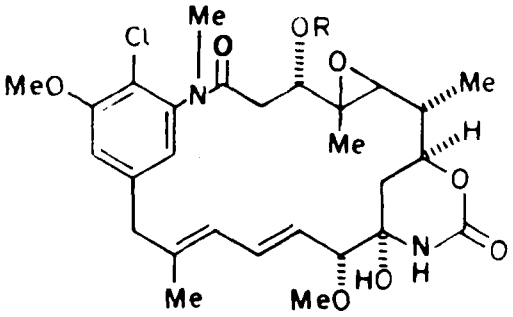


often gives trouble due to the poisoning of the catalyst by traces of sulfur compounds left in the previous thionyl chloride reaction. The amine compound (VI) is obtained in pale yellow needles, m.p. 88-89° (Kane and Mayers have reported this compound as a low melting solid). Formylation of (VI) with acetic formic anhydride in methylene chloride gave the N-formyl derivative (VII) in almost quantitative yield. Both the formyl group and the ester function in (VII) were reduced with lithium aluminium hydride in tetrahydrofuran at 0° to give 3-methylamino-4-chloro-5-methoxy-benzyl alcohol (VIII).

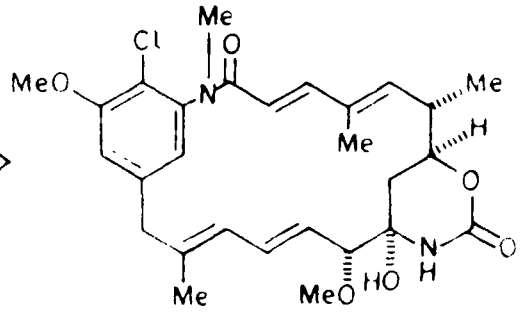
The benzyl alcohol (VIII) was then converted to the corresponding N-carbethoxy derivative (IX) by refluxing with ethyl chloroformate and anhydrous potassium carbonate in acetone and hydrolysing the carbonate function with mild alkaline hydrolysis. The benzyl alcohol was then converted to the benzaldehyde (X) by oxidation with chromium trioxide in pyridine in 87% yield.

Condensation of the aldehyde (X) with nitro ethane in the presence of ammonium acetate gave (XI) which on reductive hydrolysis with iron powder in acetic acid yielded the desired ketone, 3(N-carbethoxy)-methylamino-4-chloro-5-methoxybenzyl methyl ketone (III).

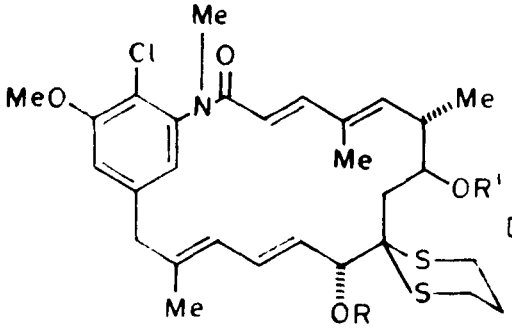
RETRO SYNTHESIS OF MAYTANSINE AND N-METHYL MAYSINININE

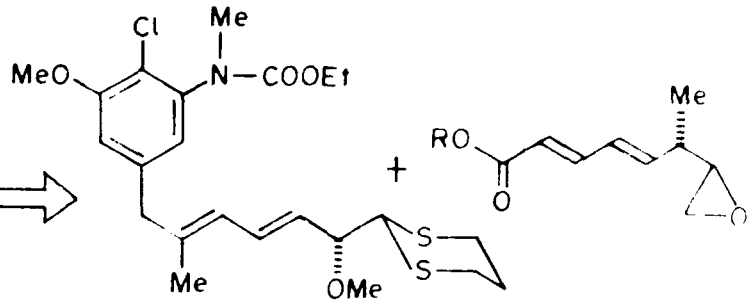


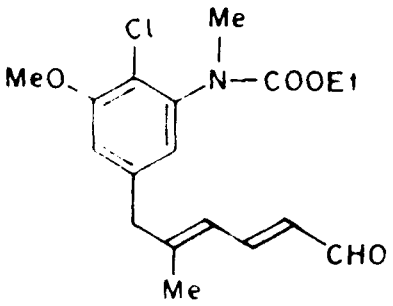
MAYTANSINE

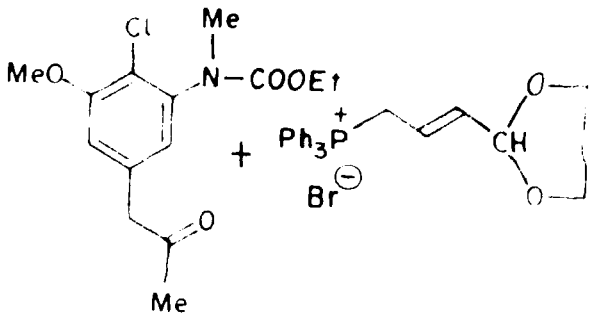


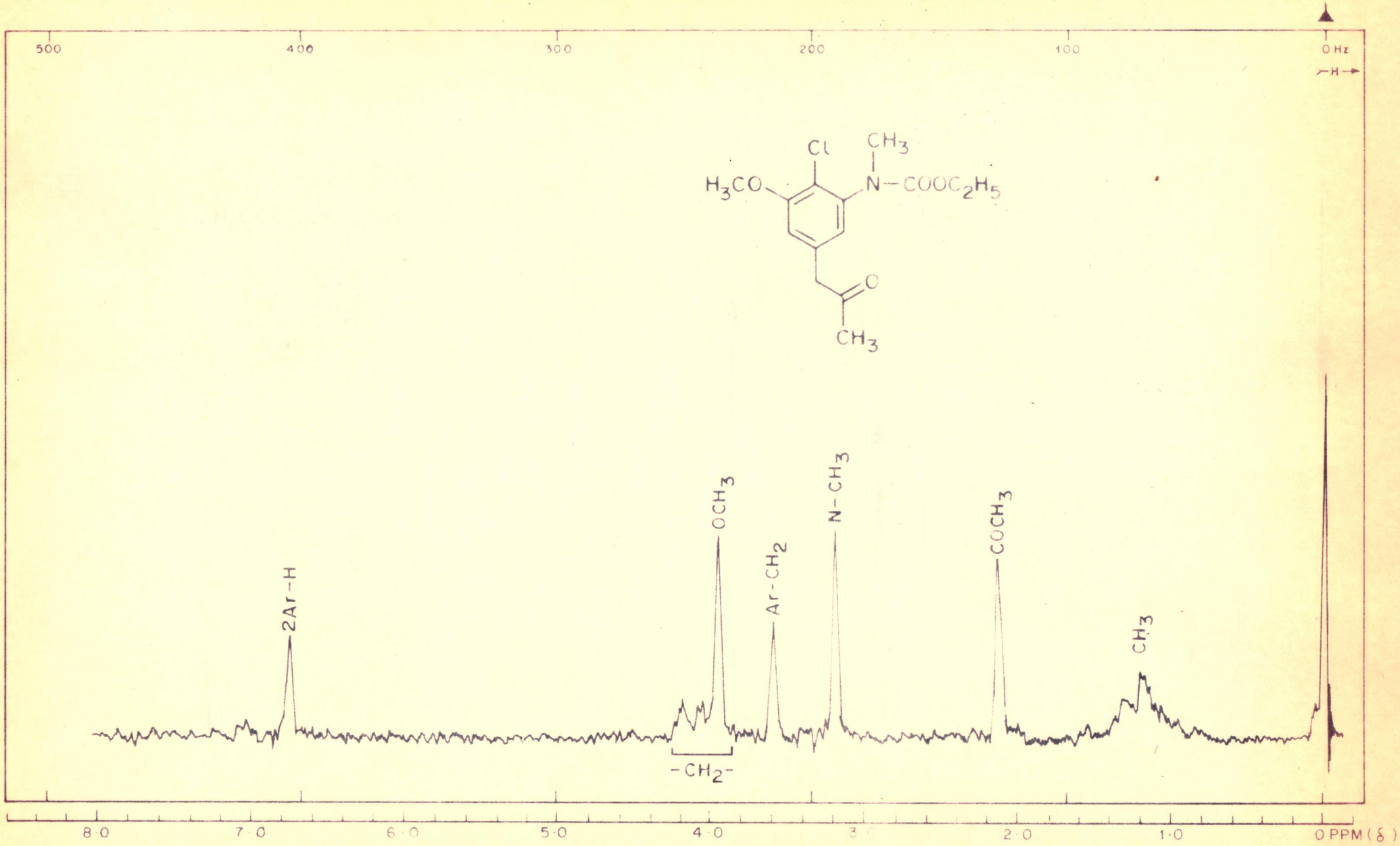
N-METHYLMAYSENINE



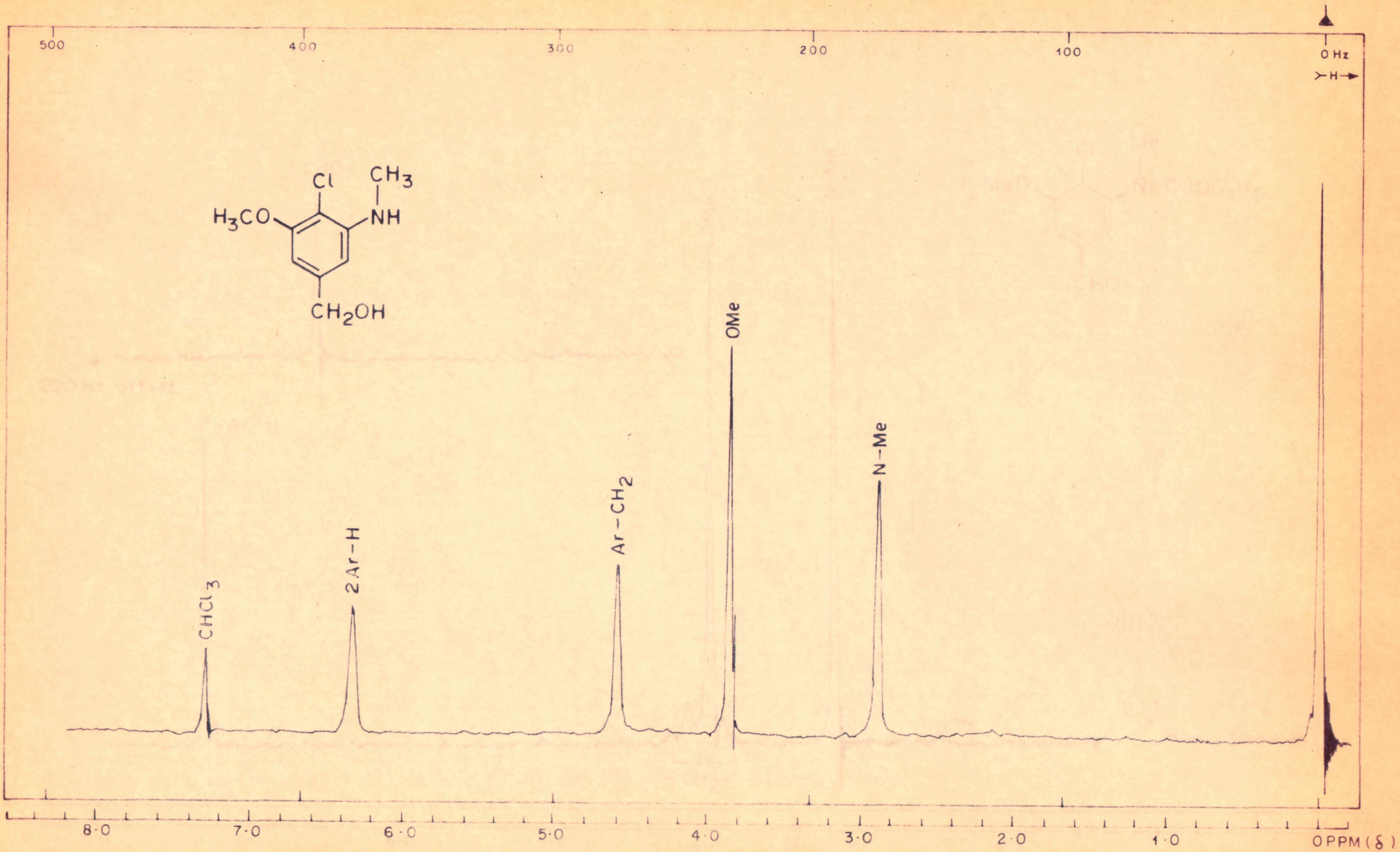




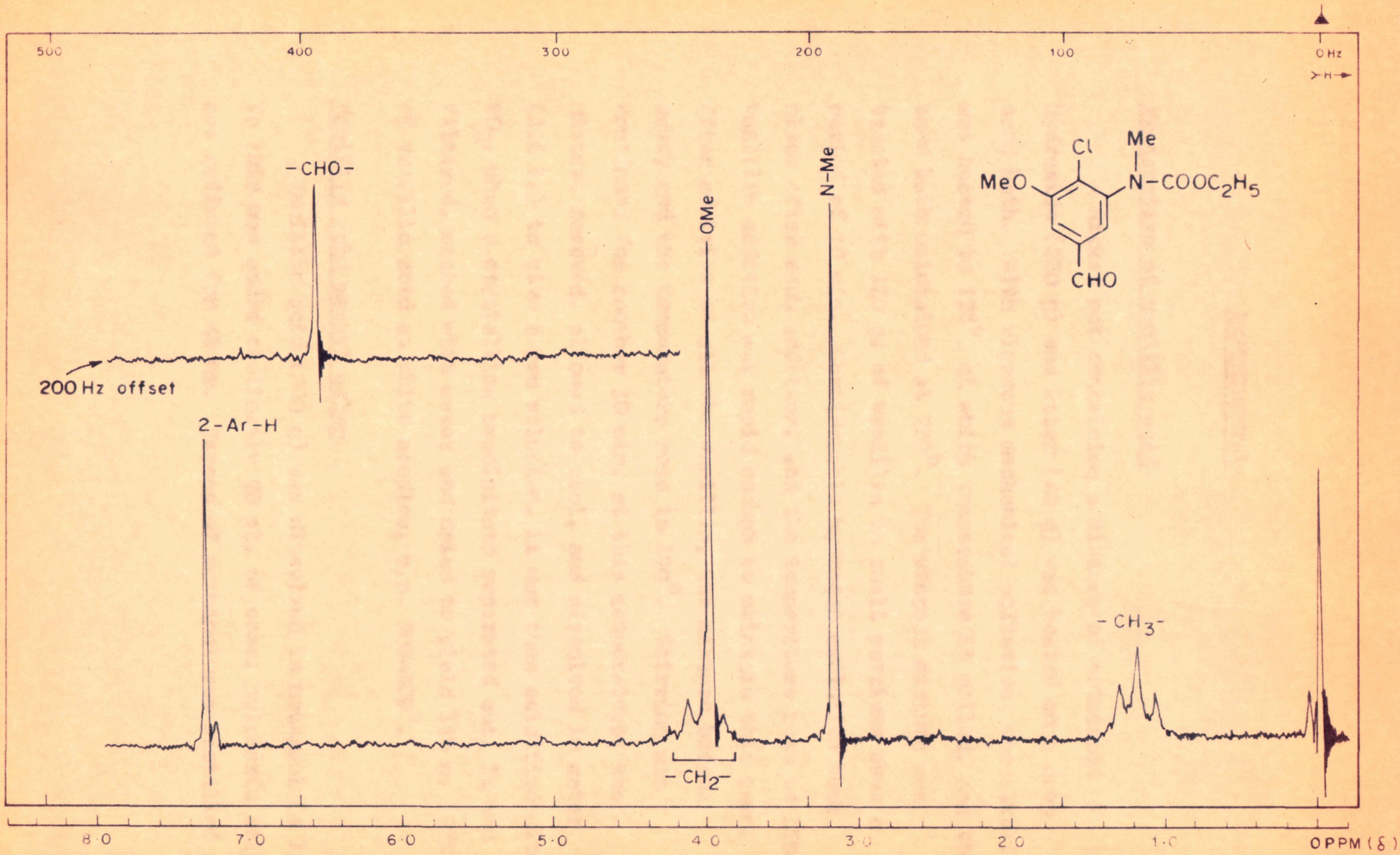




NMR SPECTRUM OF 3-(N-CARBOETHOXY)-METHYLAMINO -4-CHLORO-5-METHOXY BENZYLMETHYLKETONE (III) IN CCl_4



NMR SPECTRUM OF 3-METHYLAMINO-4-CHLORO-5-METHOXY BENZYL ALCOHOL (VIII) IN $CDCl_3$



NMR SPECTRUM OF 3-(N-CARBOETHOXY)-METHYLAMINO-4-CHLORO -5-METHOXY BENZALDHYDE (X) IN CCl_4

EXPERIMENTAL

Preparation of vanillic acid

A nickel pot containing a mixture of potassium hydroxide (330 g) and water (40 g) was heated on a deep sand bath. With vigorous mechanical agitation, the alkali was heated to 125°, at which temperature it gelled, and the sand bath maintained at 250°. The viscous mixture was treated with 120 g. of vanillin in small portions over a period of 10 min. Considerable hydrogen evolution took place after each addition, and the temperature rose to 150°. Vanillin addition was rapid enough to maintain this temp. After addition of all the vanillin, the mixture became pasty and the temperature rose to 190°. Stirring was continued for another 10 min. at this temperature; the mixture removed, allowed to cool, and dissolved in water (1.6 l.) to give a red solution. It was then acidified with SO_2, when a crystalline precipitate separated out. It was filtered, washed with water and dried to yield 115 g. (87%) of vanillic acid as white needles, m.p. 208-209°.

Vanillic acid methyl ester

Vanillic acid (200 g) was dissolved in methanol (4 lit.). To this was added cautiously 20 ml. of conc. sulphuric acid and refluxed for 48 hr. Excess of methanol was distilled off

and the solution concentrated to a volume of 500 ml., and water (1 l.) was added to it when an oily layer separated out. This was extracted with chloroform, washed with sodium bicarbonate solution (10%), water and dried (Na_2SO_4). Removal of chloroform gave an oily compound which crystallised in colourless needles on addition of hexane, m.p. 62°(180 g.,83%).

Preparation of methyl-3-nitro-4-hydroxy-5-methoxybenzoate

In a 2 lit. three-necked RB flask fitted with a dropping funnel and a mechanical stirrer, methyl vanillate (182 g., 1 mole) and acetic acid (1 l.) were added. The contents were stirred at room temperature for 30 min. It was cooled externally by ice-water mixture. When the temp. of the reaction mixture reached to 0-5°, a solution of 100 g. of conc. HNO_3 (sp.gravity 1.42) in 100 ml. of acetic acid was added slowly through the dropping funnel. The time of addition was 2 hr. during which period the temperature was kept around 5°. After the addition was complete, the mixture was allowed to warm slowly to room temperature and the mixture stirred for another 4 hr. Most of the nitro compound separated out as yellow needles. The mixture was then poured into ice water (1.5 l.). The light yellow solid was filtered through a Büchner funnel, washed with water and dried in vacuum at room temperature. The dried product weighed 190 g. (83.7%), m.p. 153° (lit. m.p.154-55°).

NMR($CDCl_3$): 3.95 and 4.02 (s, two OMe); 7.73 and 8.40 (d, J=2 Hz, two Ar-H).

Methyl-3-nitro-4-chloro-5-methoxybenzoate

Method 1: In a 1 lit. RB flask fitted with a magnetic stirrer, a reflux condenser and a $CaCl_2$ tube was placed 150 ml. of distilled DMF. The flask was immersed in an ice bath and 150 ml. of $SOCl_2$ was added in portions with stirring over a period of 30 min., contents were stirred for another 30 min., and methyl-3-nitro-4-hydroxy-5-methoxybenzoate (25 g) was added while cooling externally. After the addition, the ice bath was replaced by an oil bath and the flask heated gently to 80° and left at that temperature for 2 hr. The temp. of the oil bath was then raised to 100° and maintained the temperature for 8 hr. The contents were cooled to room temp., and poured over ice water (600 ml) in a 2 l. beaker, and stirred for 2 hr. The dark gummy product was extracted with chloroform (600 ml) and washed with water (3 x 300 ml) and dried (Na_2SO_4). The chloroform extract was passed over a dry column of alumina (400 g) and the tarry material with the unreacted nitrophenol were retained on the column. More chloroform was used to elute the desired compound. The solvent was removed to yield the crude product (25-30 g), containing large quantities of sulphur ($\simeq$ 10 g) together with small quantities of coloured impurity.

The crude product was taken in methanol (400 ml), refluxed for 10 min., and the hot solution filtered. The insoluble yellow solid was sulphur. The filtrate was treated with norit ($\simeq$ 12 g), filtered and concentrated to 100 ml., which yielded colourless needles, m.p.103° (16.2 g., 60%).

Method 2: A solution of triphenylphosphine (340 g., 1.3 equiv.) in CCl_4 (3.5 ml) was stirred at reflux temp. for 3 hr. Then the CCl_4 was evaporated under vacuum and the residue was dried. To this was then added a solution of methyl-3-nitro-4-hydroxy-5-methoxyvanillate (0.227 g) 1 mole) in DMF (3 ml) and stirred for 4 hr. at 95-100°. DMF was then removed under reduced pressure and the residue was taken up in $CHCl_3$ (35 ml), washed with water (2 x 10 ml), dried (Na_2SO_4). The residue obtained after removal of solvent was passed through a short dry column of alumina (5 g.)(eluent-benzene), which gave colourless needles, m.p.103° (0.06 g., 25%).

Methyl-3-amino-4-chloro-5-methoxybenzoate

To a well stirred suspension of methyl-3-nitro-4-chloro-5-methoxybenzoate (24.5 g., 0.1 mole) in 400 ml. absolute methanol and 100 ml. glacial acetic acid, was added powdered stannous chloride (100 g). The reaction was

slightly exothermic and in a short time most of the nitro compound went into the solution. After 12 hr., the reaction mixture was tested for completion (TLC 20% Ac:Bz), and an additional quantity of powdered stannous chloride (20 g) was added, and stirred for further 6 hr. The solution was concentrated under reduced pressure and the thick viscous liquid was transferred to a 2 lit. beaker. Chloroform (500 ml) was added and cooled externally with ice. The contents were made alkaline by adding 250 ml. of NH_4OH with stirring. A white precipitate of stannic hydroxide was precipitated from the solution and this was filtered through a celite bed and the filterate transferred to a separatory funnel. Aqueous phase was removed and the organic layer washed with water and dried (Na_2SO_4). Removal of solvent yielded the amine as pale yellow crystalline compound (17 g.; 80%).

The amine can be crystallised from methanol as pale yellow needles, mp. 88-89° (lit. m.p. low melting solid).

Methyl-3-formamido-4-chloro-5-methoxybenzoate

To a well stirred solution of the amine (17.8 g) in 150 ml. of CH_2Cl_2 at room temperature was added 14.6 g (2.0 equivalents) of acetic formic anhydride mixed with 50 ml. of CH_2Cl_2 during a period of 30 min. It was stifred for an additional 3 hr. More CH_2Cl_2 (300 ml) was added and the

mixture transferred to a separating funnel. It was washed with water and sodium bicarbonate solution till the aqueous solution was alkaline, and then it was finally washed with water. The organic phase was dried (Na_2SO_4), and the solvent removed to give almost white crystalline compound. The product was stirred with hexane, filtered and dried to yield 15.2 g. (92.1%) of N-formyl derivative, m.p. 157-58°.

NMR (acetone d_6): 3.88 and 3.96 (s, 3H each, Ar-OMe and Ar-CO_2Me), 7.38 (bs, 2H, ArH), 8.53 and 8.68(NH and -N=C-H). IR ($CHCl_3$): 3400 cm^{-1} (NH), 1710 cm^{-1} (-C=O). MS: M^+ 243.

3-Methylamino-4-chloro-5-methoxybenzyl alcohol

In a dry 500 ml. three necked flask, provided with a stirring bar and a dropping funnel and protected from atmospheric moisture with a positive pressure of dry nitrogen was placed lithium aluminium hydride (8.6 g., 0.22 mole) and 50 ml. of THF. A solution of 24.3 g.(0.2 mole) of N-formyl derivative in 150 ml. of THF was added dropwise with stirring and the flask cooled externally with ice water. After the addition (30 min.) it was stirred at room temp. for 20 hr. The flask was then cooled externally by ice water. The complex was hydrolysed and the excess LAH was destroyed by the cautious addition of aqueous sodium hydroxide

(prepared by mixing 11.0 ml. of water and 8.6 ml. of 15% NaOH). It was stirred for 15 min. and the solution was filtered through a celite bed. The cake was washed with chloroform (3 x 100 ml) and the combined filtrate taken in a 500 ml. separating funnel, washed with water and dried (Na_2SO_4). Removal of the solvent gave a crude yellow thick oil (18.50 g), purification of which over a column of silica gel gave colourless needles, m.p. 83-84° (16 g., 79.3%).

NMR ($CDCl_3$): 2.87 (s, 3H, N-Me); 3.84(s, 3H, OMe); 4.60 (s, 2H, Ar-CH_2O), 6.32 (s, 2H, Ar-H).

3-(N-carboethoxy)-methylamino-4-chloro-5-methoxy benzyl alcohol

A mixture of benzyl alcohol (8.4 g) (from previous experiment), acetone (120 ml), anhydrous potassium carbonate (35 g., 6 equiv.) and ethylchloroformate (18.09 g., 4 equiv.) was refluxed gently for 12 hr. The contents were cooled and the acetone removed at room temperature. To this water was added and stirred for 30 min. and the thick oily compound obtained was taken up in ether (3 x 50 ml). The ether was removed and the thick oil was dissolved in 4% methanolic sodium hydroxide (90 ml) and stirred at room temperature for 2 hr. It was concentrated under reduced pressure, water was added and taken up in ether, washed with

water and dried (Na_2SO_4). Removal of solvent under reduced pressure yielded the desired urethane. The product was dried under vacuum to get an oil 10.10 g.(87.10%).

IR($CHCl_3$): 1720 cm^{-1} (N-$COOC_2H_5$), 3300 cm^{-1} (-OH).

NMR($CDCl_3$): 1.16 (t 3H,-$CO\,CH_2$-CH_3); 3.15(s, 3H, N-Me); 3.60-4.16(broad signal merged with OMe, 2H, -$COOCH_2$-CH_3); 4.35 (s, 2H, Ar-CH_2-O); 6.83 (s, 2H, Ar-H).

MS: $M^{\uparrow}$ 259.

3-(N-carboethoxy)-methylamino-4-chloro-5-methoxybenzaldehyde

Chromium trioxide (1.2 g., 6 equiv.) was added to a magnetically stirred solution of pyridine (1.9 g., 6 equiv.) in 20 ml. of CH_2Cl_2. The deep burgandy solution was stirred for 20 min. at room temperature. At the end of this period a solution of alcohol (0.546 g.) in small volume of CH_2Cl_2 was added in one lot when tarry black material separated out immediately. After stirring for additional 20 min. at room temperature, the solution was decanted from the residue, which was washed with 50 ml. of ether. The combined organic layer was washed with three 50 ml. portions of 5% NaOH, 5% HCl, 5% $NaHCO_3$ each and then with saturated NaCl, and dried (Na_2SO_4). Evaporation of the solvent gave a crude aldehyde (0.470 g., 87%) which was purified by passing through a short column of silica gel to get colourless needles, m.p. 65-66°.

IR($CHCl_3$): 1690 cm^{-1} (-C =O), 1710 cm^{-1} (N-$COOC_2H_5$).
NMR(CCl_4): 1.16 (t, 3H-CO CH_2-CH_3); 3.17 (s, 3H, N-Me); 3.76-4.23 (broad signals merged with OMe, 2H, -COO-CH_2-CH_3); 3.98 (s, 3H, OMe), 7.33(s, 2H, Ar-H); 10.27(s, 1H, -CHO).

3-(N-carboethoxy)-methylamino-4-chloro-5-methoxy benzyl methyl ketone

A mixture of 0.135 g.(0.5 mole) of 3-(N-carbethoxy)-methylamino-4-chloro-5-methoxybenzaldehyde, 0.2 ml. of nitroethane and 0.045 g. of ammonium acetate was prepared in a 10 ml. RB flask. The mixture was heated in an oil bath at 80-90° for 4 hr. during which time all the aldehyde and acetate went into solution, and the mixture became dark red. Excess of nitroethane was removed under reduced pressure and the residual gummy compound was taken in chloroform. The chloroform solution was washed thrice with water (2 x 15 ml) to remove the ammonium acetate and dried (Na_2SO_4). It gave an oil (0.150 g).

It was dissolved in acetic acid (2 ml) and heated at 80-90° with stirring. Iron powder (51 mg) was added in small portions during 40 min. and heating and stirring were continued for further 4 hr. The solution was then allowed to cool at room temperature and poured on water (10 ml) and

then extracted with chloroform, washed with water and dried (Na_2SO_4). The solvent was removed to give an oil (0.130 g) which was purified through a short column of silica gel (0.5: 9.5 acetone-benzene). The pure ketone was obtained as pale yellow oil (0.09 g., 60.4%).

NMR (CCl_4): 1.18(t, 3H, $-COOCH_2-CH_3$); 2.13 (s, 3H, $-COCH_3$); 3.20 (s, 3H, N-Me); 3.60(s, 2H, $Ar-CH_2$); 3.83-4.25(bq merged with one, 2H, $-COOCH_2-CH_3$); 6.73 (s, 2H, Ar-H).

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SUMMARY

SUMMARY

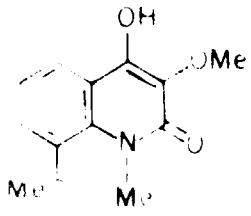
Part I: Phenolic constituents of the bark and heartwood of Chloroxylon swietenia DC

Two samples of Chloroxylon swietenia bark obtained from Achalpur and Chennapatnam have been examined for their chemical constituents.

The powdered bark from Achalpur on extraction with cold acetone yielded a yellowish syrupy extract, which was successively extracted with hexane, benzene, ether and chloroform. The combined hexane-benzene extract gave a bicarbonate soluble alkaloid, swietenidin A (I). From the insoluble bicarbonate part, eight compounds have been isolated: swietenocoumarins A (II) and B (III); two new furanocoumarins and six known coumarins: rutamarin, heliettin, suberosin, xylotenin, aesculetin dimethyl ether and swietenone.

From the combined ether chloroform extract two new coumarins, swietenocoumarin G (IX) and demethyl luvangetin (X) were isolated in addition to the three known compounds, rutamarin, collinusin and syringaresinol.

Extraction of the powdered bark from Chennapatnam produced a gummy material which was successively extracted with hexane, benzene, ether and chloroform. From the



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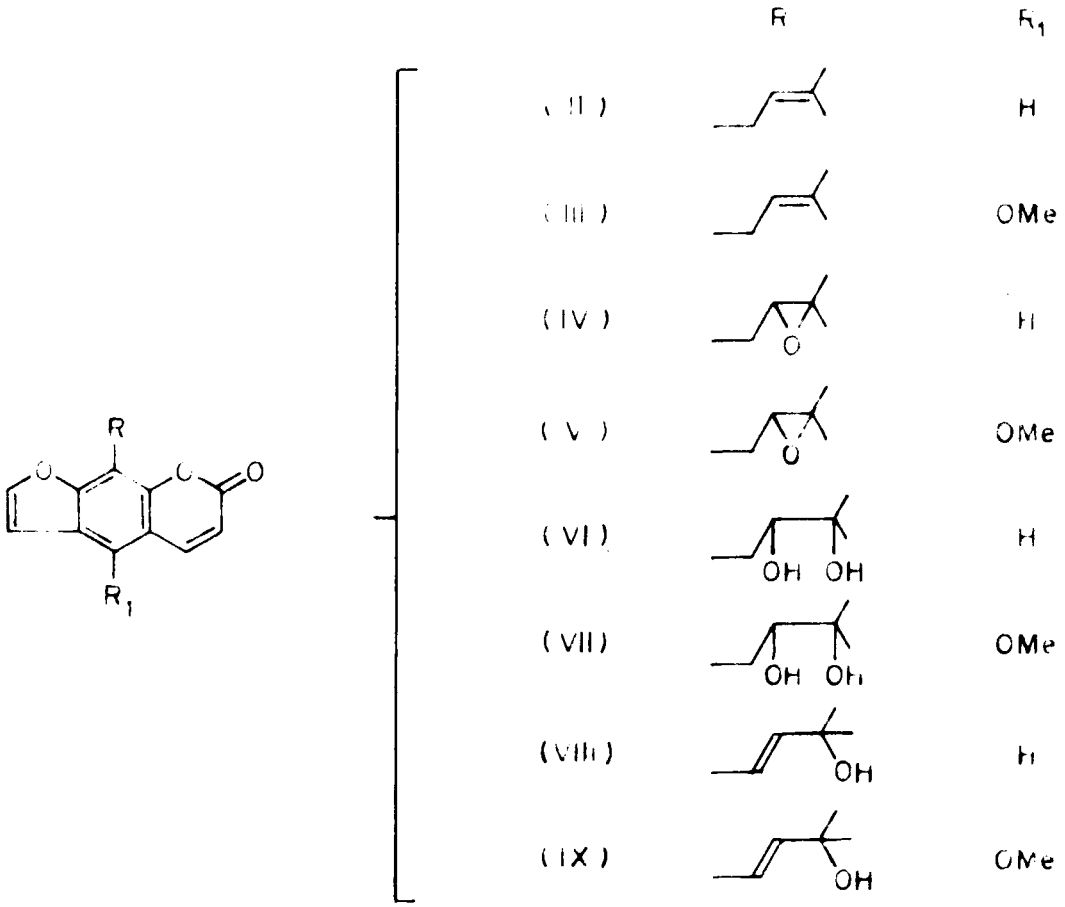
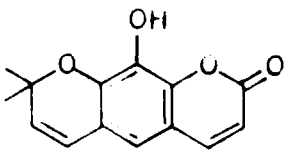
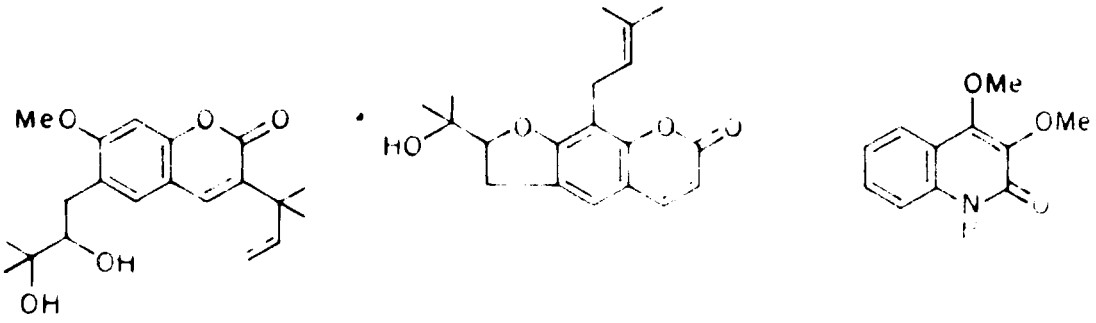




X



XIII

combined hexane-benzene extract, the following seven compounds have been isolated: swietenocoumarins A (II) and B (III), rutamarin, suberosin, isopimpinellin, swietenocoumarins H (VIII) and I (XI).

The alkali-soluble ether extract contained two new compounds: 8-prenylnodakenetin (XII) and swietenocoumarin C (IV) in addition to a known lignan, savinin.

Fractionation of the chloroform extract afforded four new compounds swietenocoumarins D (V), E (VI), F (VII) and an alkaloid swietenidin B (XIII). The presence of chalepin and swietenone was also revealed.

Chalepin, suberosin, the coumarins; savinin, collinusin, syringaresinol and the lignans are reported for the first time from C. swietenia. Although oxygenation in the 4-position is common among the furoquinolines and 3-alkenyl-2-quinolones of the Rutaceae, swietenidin B (XIII) is the only alkaloid other than swietenidin A (I) having a methoxyl substituent at 3-position.

Extraction of the powdered heartwood from Madhya Pradesh with cold acetone yielded a reddish syrupy compound which was successively extracted with hexane, benzene, and chloroform. The hexane extract yielded alkali-soluble 7-demethylsuberosin and the alkali-insoluble part contained xanthoxyletin as a major compound.

The benzene extract gave more of alkali-soluble 7-demethylsuberosin and the hydrochloric acid soluble part led to the isolation of skimmianine. From the neutral benzene extract xanthoxyletin, allexanthoxyletin and nodakenetin have been isolated.

A number of natural products with C-isoprenoid units modified as epoxide and diol have been reported from various plants, but the co-occurrance of all these compounds in the same plant assumes considerable biogenetic significance.

Part II: Alkaloids of the stemwood of Murraya koenigii Sprang

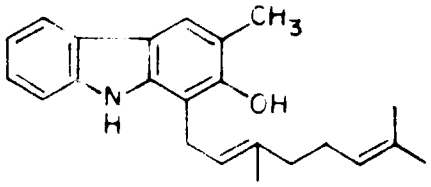
Murraya koenigii is a medicinally important Rutaceous plant and has been extensively examined for its chemical constituents. A number of carbazole alkaloids from the leaves, bark and fruits have been examined by various workers, but there is no literature reference to the stem wood or root constituents of this plant.

Cold acetone extraction of the powdered stemwood gave a dark gummy product which was successively extracted with hexane and benzene in a soxhlet. The hexane extract contained three alkaloids, murrayanine, mahanimbidine,

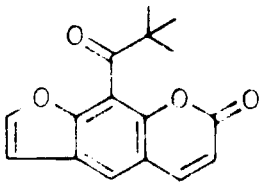
and bicyclomahanimbine. From the benzene extract two known compounds mahanimbine and girinimbine and a new C_{23} alkaloid, mahanimbinol (XIV) have been isolated. Mahanimbinol is a key biogenetic precursor for all the C_{23} carbazole alkaloids reported earlier from various parts of M.koenigii.

Part III: Section I. Abnormal reactions of anhydrous aluminium chloride

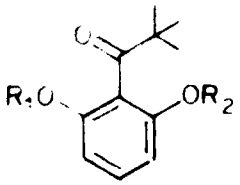
In an attempt to synthesise 2-pivalyl resorcinol (XVI) which is a starting material for the synthesis of swietenone (XV) by the demethylation of 2-pivalyl-resorcinol dimethyl ether (XVII) with anhydrous aluminium chloride in benzene, a considerable quantity of 4-hydroxy-2,2-dimethyl-3-methylene coumaran (XIX) together with the monomethyl ether (XVIII), was obtained. This interesting observation has led to the investigation of various aspects of this reaction and the formation of the hitherto unknown coumaran (XIX). In a further set of experiments, 2-pivalyl and 4-pivalyl orcinol were prepared. 4-Pivalylorcinol (XXI) on treatment with anhydrous aluminium chloride gave a cyclised product (XX), whereas 2-pivalyl orcinol (XXII) under similar reaction conditions remained unreacted. This suggested that both the ortho positions



XIV



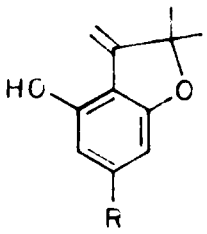
XV



XVI; $R_1=R_2=H$

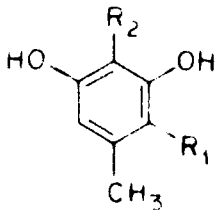
XVII; $R_1=R_2=Me$

XVIII; $R_1=H$, $R_2=Me$



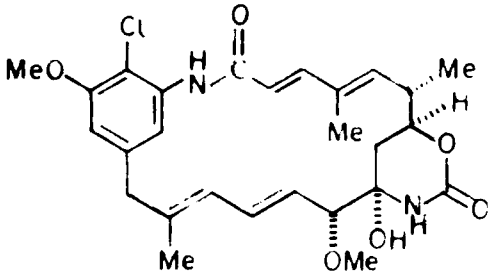
XIX; R = H

XX; R = Me

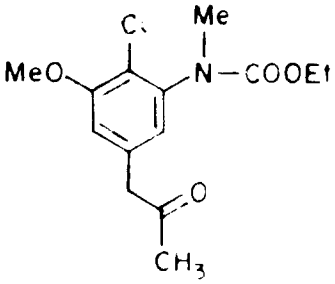


XXI; $R_1=H$,
$R_2=CO\cdot C(CH_3)_3$

XXII; $R_1=CO\cdot C(CH_3)_3$,
$R_2=H$



XXIII



XXIV

in the tert-butyl phenyl ketone should have either hydroxy or methoxy substituents to yield a cyclized product. A probable mechanism of these reactions is discussed.

Section II: Swietenidin A is the first naturally occurring 3-methoxyl-2-quinolone alkaloid and structure (I) was assigned to it provisionally. The structure has been now confirmed by synthesising its methyl ether starting from p-anisidine.

Part IV: Exploratory work on the synthesis of Maytansinoids

Maytansinoids are clinically an interesting class of compounds, first isolated from the species of Maytenus, by Kupchan et al. Many groups are now engaged in the synthesis of these compounds. Maysenine (XXIII) is the simplest compound and is regarded as a biogenetic precursor for other maytensine esters.

In an attempt to synthesise the Western and Southern zones of (N-methyl maysenine, the intermediate ketone(XIV) has been prepared starting from vanillic acid.

ACKNOWLEDGEMENT

I wish to express my deep sense of gratitude to Dr. A. V. Rama Rao, Scientist and Project Leader, National Chemical Laboratory, Poona, for suggesting the problem, inspiring guidance and constant encouragement during the course of the work.

I am also very grateful to Professor K. Venkataraman for his kind help and interest in the work.

I am very much thankful to Drs. R.B.Mujumdar, V.H. Deshpande and S.S. Yemul for their valuable help and fruitful discussions, and to all my friends in the laboratory, especially Mr. M.N. Deshmukh.

Assistance from Spectroscopic and Microanalytical Sections of the laboratory is gratefully acknowledged.

Award of a Fellowship by the U.S. Department of Agriculture under PL-480 and C.S.I.R., New Delhi, is gratefully acknowledged.

I am also thankful to Dr. L.K. Doraiswamy, Director, National Chemical Laboratory, for allowing me to submit this work in the form of a thesis.

K S Bhide

K. S. BHIDE

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January 1979.

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