CHARACTERIZATION OF A $C_{30}H_{48}O_3$ CONSTITUENT OF *ARBUTUS MENZIESII*

by

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Supervisor: Professor Frank P. Robinson

ABSTRACT

Characterization of a $C_{30}H_{48}O_3$ Constituent of Arbutus menziesii

A crystalline compound, $C_{30}H_{48}O_3$, m.p. 275.0-278.0°C (dec.), was isolated from the bark of Arbutus menziesii (1.5%). Spectroscopic evidence suggests the presence of a hydroxyl group and an isopropenyl group in the molecule. Because of the absence of double bonds other than that of the isopropenyl group, the molecule is thought to be pentacyclic. The nature of the remaining two oxygen functions and the exact nature of the skeleton of the molecule remain to be investigated. Spectral studies on the acetylation and the lithium aluminum hydride products are also reported.

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I. INTRODUCTION

The popular belief that some birds behave erratically after ingestion of the berries of the madrone tree (Arbutus menziesii) vaguely suggested that a narcotic property could be attributed to the plant. Furthermore, the fact that a few Indian tribes of the American Northwest used the species in their folk medicine brought the question an enticing dimension.

Gunther (1) reported that a Skokomish informant called the madrone tree "tsī´ xwēxē" and described how the leaves were boiled and the infusion drunk for colds, sore throat and ulcerated stomach. Sometimes, Oregon grape roots or licorice were added. Reagan (2) mentioned that the Quileute smoked the leaves. Stuhr (3) stated that an astringent infusion made from the bark, roots and leaves was used by "the Indians" for a cold. However, Teit (4) made no mention of any use of the tree by the Thompson Indians of British Columbia.

The almost complete lack of previous investigation of the chemical constituents of the madrone tree and the ready availability of its bark suggested a study of extracts from this portion of the tree.

(a) Description of the plant.

The generic name of Pacific madrone (Arbutus menziesii) is the ancient name of Arbutus unedo (strawberry tree, a very similar plant) cultivated for centuries and native of south western Ireland and southern Europe (5). It was named after Alexander Menzies, a Scottish botanist and early visitor to the Northwest Coast (6).

The madrone (or madrona) tree is one of the most widely occurring tree species to the Pacific Coast. This member of the Ericaceae (heath family) grows as a narrowly oblong to broadly round topped, broadleaf evergreen with a mature height of about 100 feet on good growing sites.

Northern limits of the tree's range are at about latitude 50°N. (see Figure 1, page 3), in the vicinity of Seymour Narrows on the eastern coast of Vancouver Island, British Columbia. From this point south, the madrone tree is of fairly common occurrence west of the Cascade Range in Washington and Oregon. It extends south into coastal mountain ranges of southern California (7).

The madrone tree is easily identified by its shiny dark green leaves which remain green all winter, and by the bright red bark on its trunk and branches (8). The bark exfoliates in July-September. The Pacific madrone grows in rocky soil without too much rain (9). The wood is too rare to be of any commercial importance. However, it possesses a close grain and is hard, heavy and strong. It is suitable for fuel, flooring, small cabinet-work and small wood turnery. The bark is sometimes used for tanning leather.

(b) Literature survey.

In 1950, Sosa (10) presented a general chemical investigation of the strawberry tree (Arbutus unedo). The plant (roots, leaves, branches, fruits, etc...) yielded the following list of products.

Hentriacontane	$C_{31}H_{64}$	m. p. 69°C
Nonacosanol	$C_{29}H_{59}OH$	m. p. 84°C
Triacontanol	$C_{30}H_{61}OH$	m. p. 86°C
Dotriacontanol	$C_{32}H_{65}OH$	m. p. 89°C
Unedosterol	$C_{29}H_{48}O$	m. p. 218°C
Arbutolic acid	$C_{37}H_{60}O_4$	m. p. 256°C

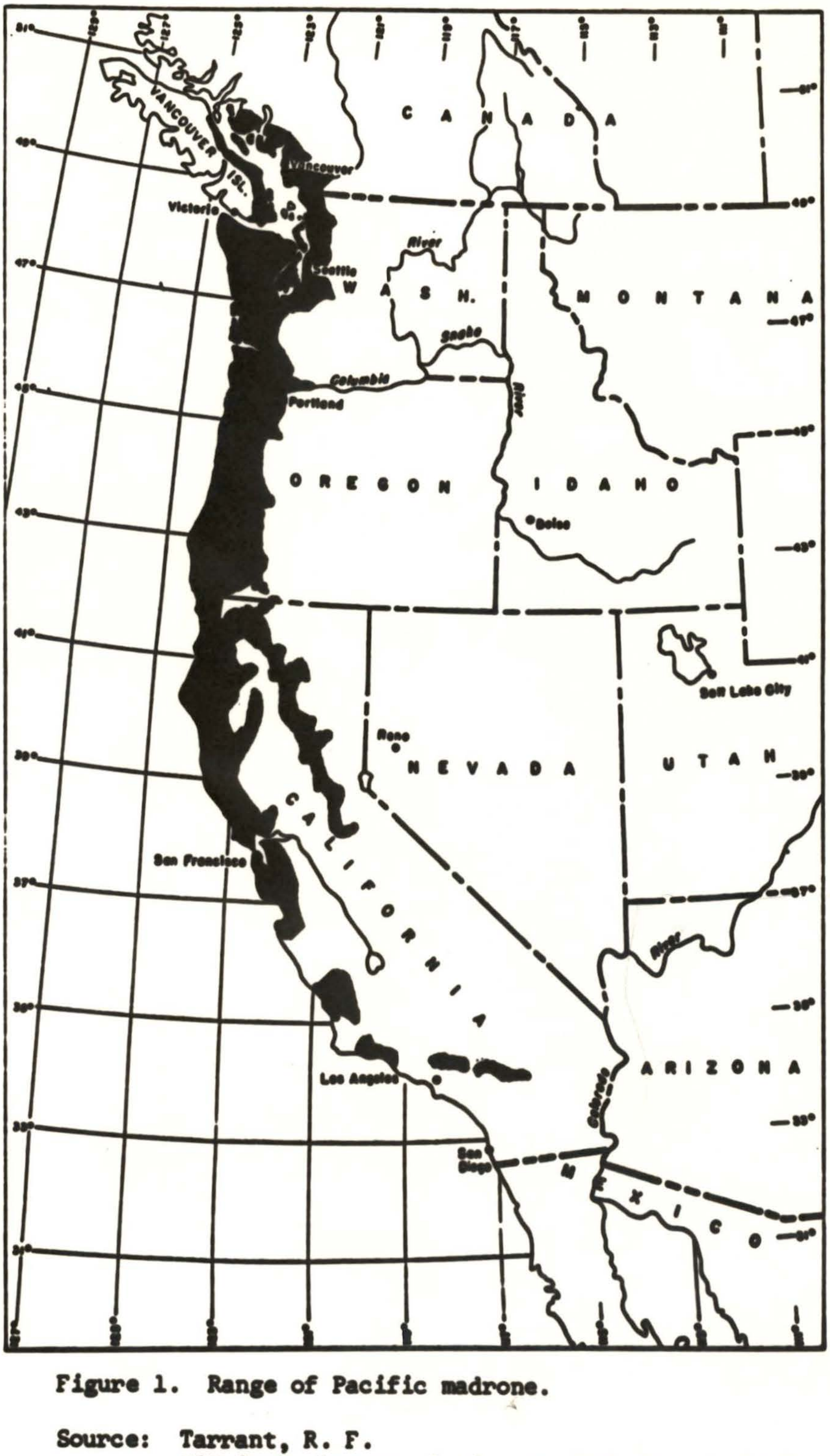


Figure 1. Range of Pacific madrone.

Source: Tarrant, R. F.
Silvical characteristics of Pacific madrone.
United States Department of Agriculture
Forest Service
July 1958

Carotenoid pigment		
Saccharose	$C_{12}H_{22}O_{11}$	m. p. 190°C
Arbutoside	$C_{12}H_{16}O_{7}$	m. p. 190°C
Phenolic combination	$C_{9}H_{10}O_{5}$	m. p. 142°C, 158°C
Unedoside	$C_{18}H_{26}O_{2}$	m. p. 232°C
Ursolic acid	$C_{30}H_{48}O_{3}$	m. p. 290°C
Arbutoflavonol A	$C_{22}H_{10}O_{16}$	m. p. 320°C
Arbutoflavonol B	$C_{23}H_{18}O_{11}$	m. p. 348°C
Pigment C	$C_{21}H_{10}O_{11}$	m. p. 495°C

According to Thies and Sulc (11), the leaves have been found to contain 2.7% arbutin and 16.1% tannins. Brozetti (12) reported the dried fruits to contain 5.7% crude protein and 39.9% soluble non-nitrogenous matter. Also from the leaves, Schön (13) extracted cryptoxanthin, α-carotene, β-carotene, lycopene, violaxanthin (to the extent of 80% of the total pigment), zeaxanthin and lutein.

Some unpublished work concerning a chemical study on the bark of the madrone tree, done by Lind (14) in 1957, was brought to our attention after our investigation was under way. Two main components (designated Am-70: m. p. 66-73°C, and Am-270: m. p. 265-271°C) were studied through microanalyses, molecular weight determinations, chemical tests, polarography and spectrophotometry (infrared and ultraviolet). Approximate molecular formulas of $C_{50}H_{96}O_{2}$ for Am-70 and $C_{50}H_{80}O_{5}$ for Am-270 were assigned. A few cyclic structures were proposed for both components. Among other conclusions, Am-70 was reported to contain one C-methyl group, two oxygen atoms in ether groups or possibly a lactone while C-methyl, carbonyl, ester, ether and hydroxyl groups were found in Am-270.

Finally, in 1963, a preliminary identification of the antibacterial principle "madronin" from the leaves of Arbutus menziesii was completed by Kabadi and Hammarlund (15). "Madronin" has been tentatively identified as a mixture of gallotannin and catechol tannin in addition to varying amounts of their degradation products, gallic acid, m-digallic acid, possibly trigallic acid, catechol, phloroglucinol and glucose. The previous observations on "madronin" (16, 17) were explained according to its newly determined composition.

II. ISOLATION OF THE $C_{30}H_{48}O_3$ CONSTITUENT

Bark was gathered in July 1965 (exfoliating time) from madrone trees in areas adjacent to the campus of the University of Victoria. Since the narcotic properties of many plants are attributable to alkaloids, the bark was extracted with alcohol and the alkaloidal extractive procedure used by Djerassi and his collaborators (18) was adopted (see Figure 2, page 6). However, when it was noticed that component IX was present in such abundance (7%), it was decided to undertake an investigation of component IX instead of searching for alkaloids.

A large scale chromatography of component IX over silica gel yielded a series of about ten different substances. A preliminary infrared study of the fractions collected revealed that these compounds could possibly have the same basic skeleton and differed by the presence or absence of unsaturation centers, hydroxyl groups, carbonyl groups, ester groups and carboxyl groups. The last component eluted from the column (with chloroform) was the $C_{30}H_{48}O_3$ constituent.

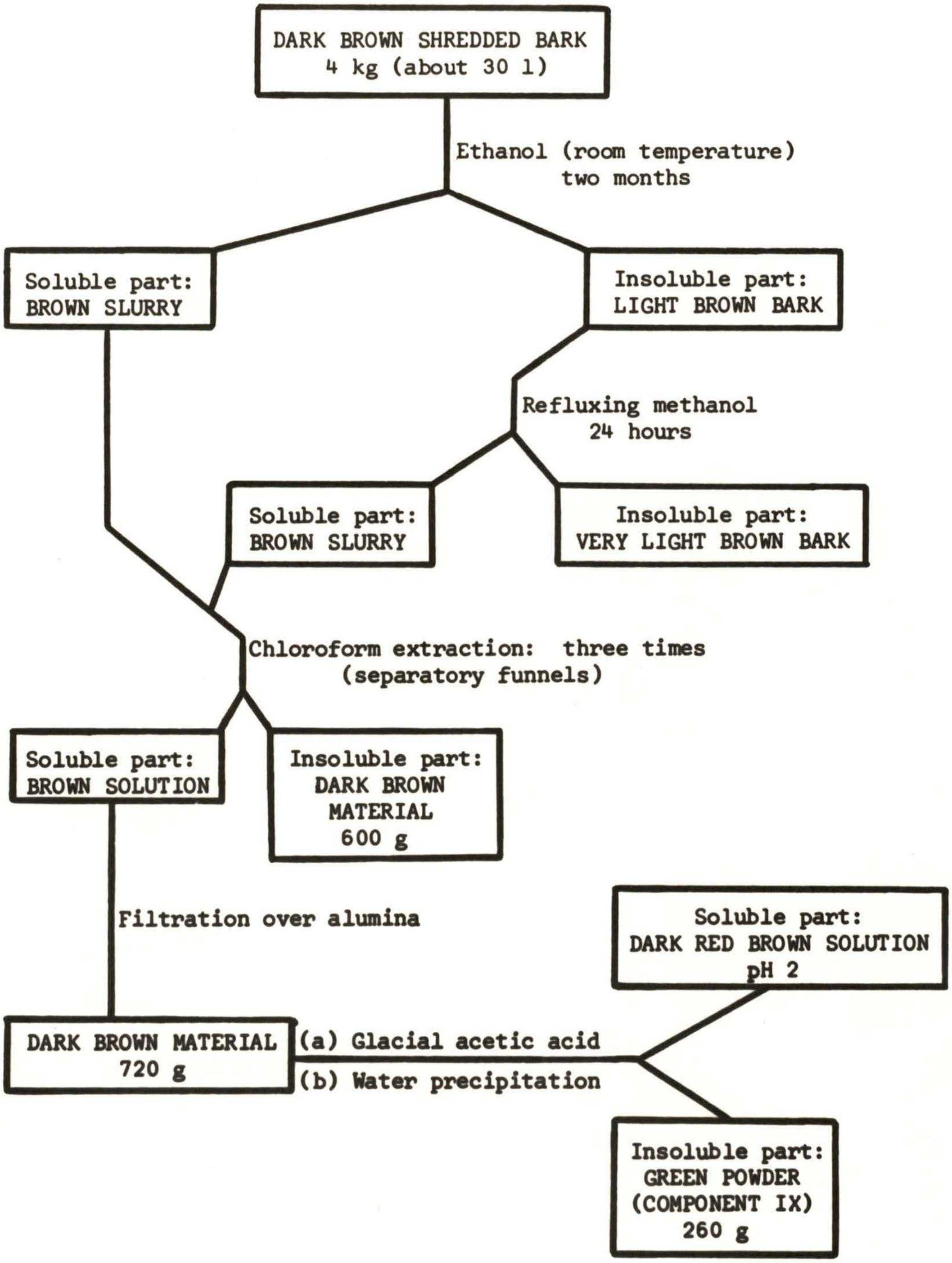


Figure 2. Extraction of component IX.

III. CHARACTERIZATION OF THE $C_{30}H_{48}O_3$ CONSTITUENT

(a) Physical constants.

The $C_{30}H_{48}O_3$ constituent was found to be readily soluble in concentrated sulfuric acid, pyridine, tetrahydrofuran and dioxane. The compound was sparingly soluble (hardly enough to permit spectroscopic measurements in solution) in methanol, ethanol, chloroform, ether and ethyl acetate. However, the product becomes soluble when gently heated in a large volume of methanol, ethanol, chloroform, ether and ethyl acetate. Finally, the component appeared to be insoluble in a concentrated and boiling aqueous solution of sodium hydroxide, in hot concentrated hydrochloric acid, in acetone, benzene, carbon tetrachloride, dichloromethane, carbon disulfide and petroleum ether. According to the solubility tables published by Cheronis and Entrikin (19), the $C_{30}H_{48}O_3$ constituent could possibly belong to one of the following classes of compounds: alcohol, aldehyde, ketone, ester, ether, acetal, anhydride, lactone or polysaccharide.

A sodium fusion showed the lack of nitrogen, sulfur, chlorine, bromine and iodine.

Figure 3 (see page 8) presents the physical constants of the $C_{30}H_{48}O_3$ constituent.

(b) Infrared spectrophotometry.

The study of the infrared data (see Figure 4, page 9) led to the following possible conclusions.

(i) The ν and δ olefinic vibrations.

The presence of a terminal methylene group in the molecule was quickly established with a high degree of confidence. The medium

m. p. 275.0-278.0°C (dec.)

Sublimes at 150°C (0.5 mm Hg)

R_f: 0.61 (silica gel, $CHCl_3$:EtOAc - 9:1)

ANALYSIS

$C_{30}H_{48}O_3$

	Calc. %	Found %
C:	78.90	78.46
H:	10.59	10.49

$C-CH_3$ DETERMINATION

5 (4.9) methyl groups

ROTATION IN PYRIDINE

Conc: 5.7 mg/1 ml

Observed rotation: 0.045°

$[\alpha]_D^{23°}$ + 7.9°

$[\alpha M]_D^{23°}$ +36.1°

Figure 3. Physical constants of the $C_{30}H_{48}O_3$ constituent.

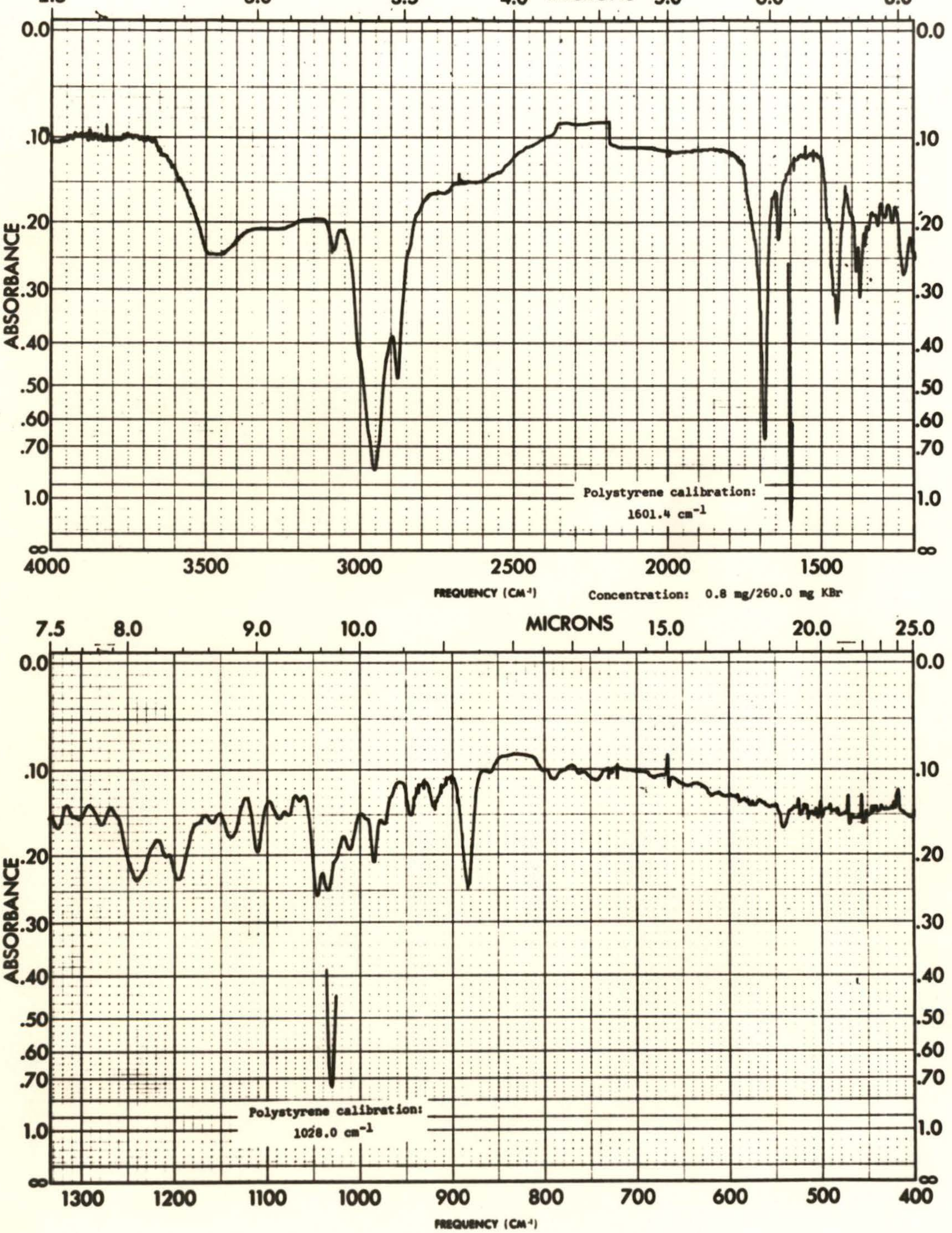


Figure 4. Infrared spectrum of the $C_{30}H_{48}O_3$ constituent.

absorption at 1640 cm^{-1} was attributed to the νC=C in $CH_2=CR_2$ (20) and the medium signal at 880 cm^{-1} to the δC-H (out of plane) of the methylene group (20). A close study of the spectrum revealed a shoulder at 1401 cm^{-1}, possibly given by the δC-H (in plane) of the $CH_2=CR_2$ group (20); another shoulder, at 1746 cm^{-1}, could be an overtone of the δC-H (out of plane) produced by the terminal methylene group (20).

(ii) The νC-H vibrations.

The strong band recorded at 2956 cm^{-1} (shoulders included) was attributed to the different νC-H vibrations given by $-CH_3$ (asymmetric vibrations) (21), $-CH_2-$ (asymmetric vibrations) (21), $CH_2=CR_2$ (symmetric vibrations) (20) and $\geq$C-H (21). The symmetric νC-H vibrations produced by $-CH_3$ and $-CH_2-$ were detected with the strong signal at 2879 cm^{-1} (including shoulder) (21) while the weak singlet at 3085 cm^{-1} was attributed to the asymmetric νC-H vibrations generated by the terminal methylene group (20).

(iii) The δC-H vibrations.

The use of a grating instrument made easier the detection of the gem-dimethyl function (22). The medium doublet centered at 1382 cm^{-1} was attributed to the δC-H vibrations of $-CH-(CH_3)_2$ (21). Furthermore, the skeletal vibrations of the gem-dimethyl group (shoulder at 1207 cm^{-1} on the 1193 cm^{-1} medium band) indicated that $>C-(CH_3)_2$ (a quaternary central carbon) and not $-CH-(CH_3)_2$ was more likely the case (21).

A strong band (shoulders included) at 1451 cm^{-1} was due to the different δC-H vibrations caused by $-CH_3$ (asymmetric vibrations) and $-CH_2-$ [scissors (usually 1445 cm^{-1} in cyclopentanes and 1450 cm^{-1} in cyclohexanes) (21) and active methylene as in $-CH_2-CO-$ (23)].

(iv) The ν and δ vibrations of carbon-oxygen and O-H bonds.

The strong absorption at 1685 cm^{-1} strongly suggested the presence of νC=O vibrations (24). The broad medium band centered at 3480 cm^{-1} was attributed to the νO-H vibrations in the molecule (25). The νC-O vibrations were located at 1043 cm^{-1} while the δO-H (in plane) vibrations were detected at 1238 cm^{-1} (26).

(v) Spectrum in nujol.

The comparison of major peaks in the spectrum in potassium bromide with values obtained from a run in nujol gave the following data:

KBr (cm^{-1})	Nujol (cm^{-1})
3480	3462
3085	3070
2956	Nujol region (27)
2879	" "
1685	1681
1640	1637
1451	Nujol region (27)
1382	" "
1238	1240
1193	1190
1043	1037
880	878

(vi) Discussion.

The infrared results solidly established the presence of one or more gem-dimethyl (with a quaternary central carbon) groups and one or more terminal methylene groups.

However, the interpretation of the oxygenated functions was somewhat ambiguous. The 1685 cm^{-1} absorption could fit the case of an unsaturated ketone (24) or a γ-pyrone (28). The possibility of an aliphatic ester was rejected on the basis of the lack of important asymmetric νC-O-C (29). The absence of the aldehyde overtone at 2720 cm^{-1} ruled out the -CHO function (30). Then, it was speculated that the νC=C vibrations band at 1640 cm^{-1} was too weak to be part of a $>$C=COH-CO- group (30). In addition to the possibilities of the unsaturated ketone and the γ-pyrone, the carboxylic acid and the lactone have to be considered. Nakanishi (30) lists the νC=O vibrations of α,β-unsaturated acids (monomers) at 1720 cm^{-1} and the saturated dimers at 1710 cm^{-1}. The constituent under investigation absorbs at 1685 cm^{-1}. Also, according to the solubility tests (see page 7), the compound in question was insoluble in a boiling concentrated solution of sodium hydroxide.

(c) Ultraviolet spectrophotometry.

The ultraviolet measurements (see Figure 5, page 13) revealed only one absorption:

$$\lambda_{max}^{dioxane} \quad 220 \text{ m}\mu \ (\varepsilon = 136)$$

The scanning was operated between 210 and 360 mμ.

Dioxane is transparent only down to about 220 mμ (31). Thus, the assignment of the observed band is difficult.

The possibility of an unsaturated ketone was quickly rejected because it is well known that the conjugation of a double bond with a carbonyl group usually leads to intense absorption corresponding to a

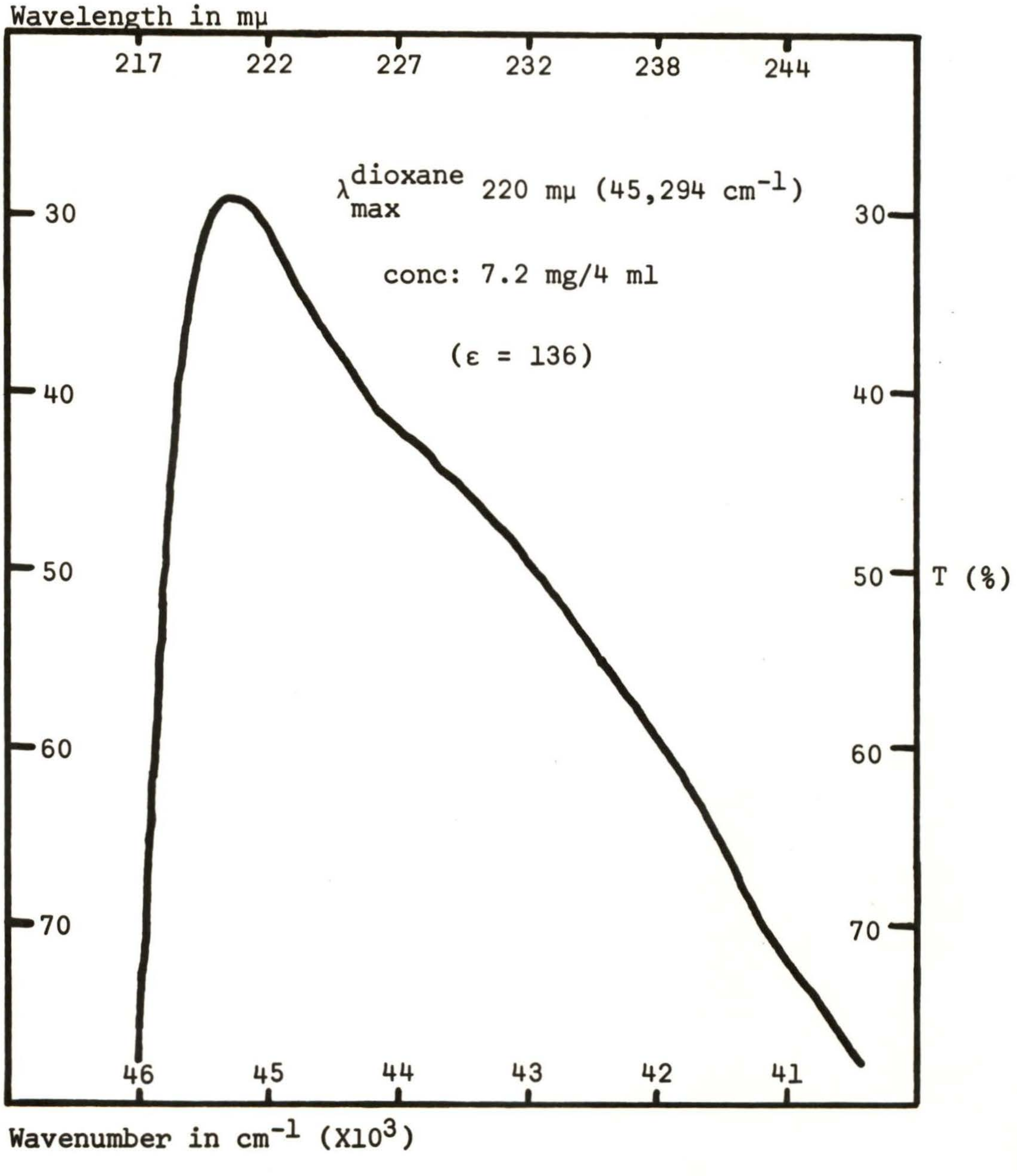


Figure 5. Ultraviolet spectrum of the $C_{30}H_{48}O_3$ constituent.

transfer of a π electron from the ethylene orbital to the $>C=O$ orbital (32). The electron transfer band ($\pi \rightarrow \pi^*$) is found in simple enones between 230 and 250 mμ (ε = 10,000-20,000). Furthermore, a second characteristic absorption band (ε = 50-100) usually appears at 310-330 mμ and corresponds to the displaced $n \rightarrow \pi^*$ band of the $>C=O$ group. In the present case, no 310 mμ band was observed.

The γ-pyrone case was found to be very improbable. Scott (33) mentions many γ-pyrone examples and the range was from 240 to 320 mμ. However, the possibility of a lactone or an acid could not be ruled out on the basis of the ultraviolet results (34).

The combined conclusions from infrared and ultraviolet spectrophotometry suggested that the possibilities of the compound being an acid or a lactone required serious consideration. In the case of a lactone, the low νC=O absorption might possibly be explained by the totalized effects of three factors: a possible β,γ-unsaturation, some steric hindrance effects and a large size (seven or more) (29) of the lactone ring.

(d) Optical rotatory dispersion data.

The results from the optical rotatory dispersion curve (see Figure 6, page 15) were in general agreement with the infrared and ultraviolet results. The $C_{30}H_{48}O_3$ constituent could possibly be a lactone or an acid. The most notable observation with respect to the O. R. D. results was the total absence of a Cotton effect. Crabbé (35) and Djerassi (36) show many curves of acids and lactones which are similar

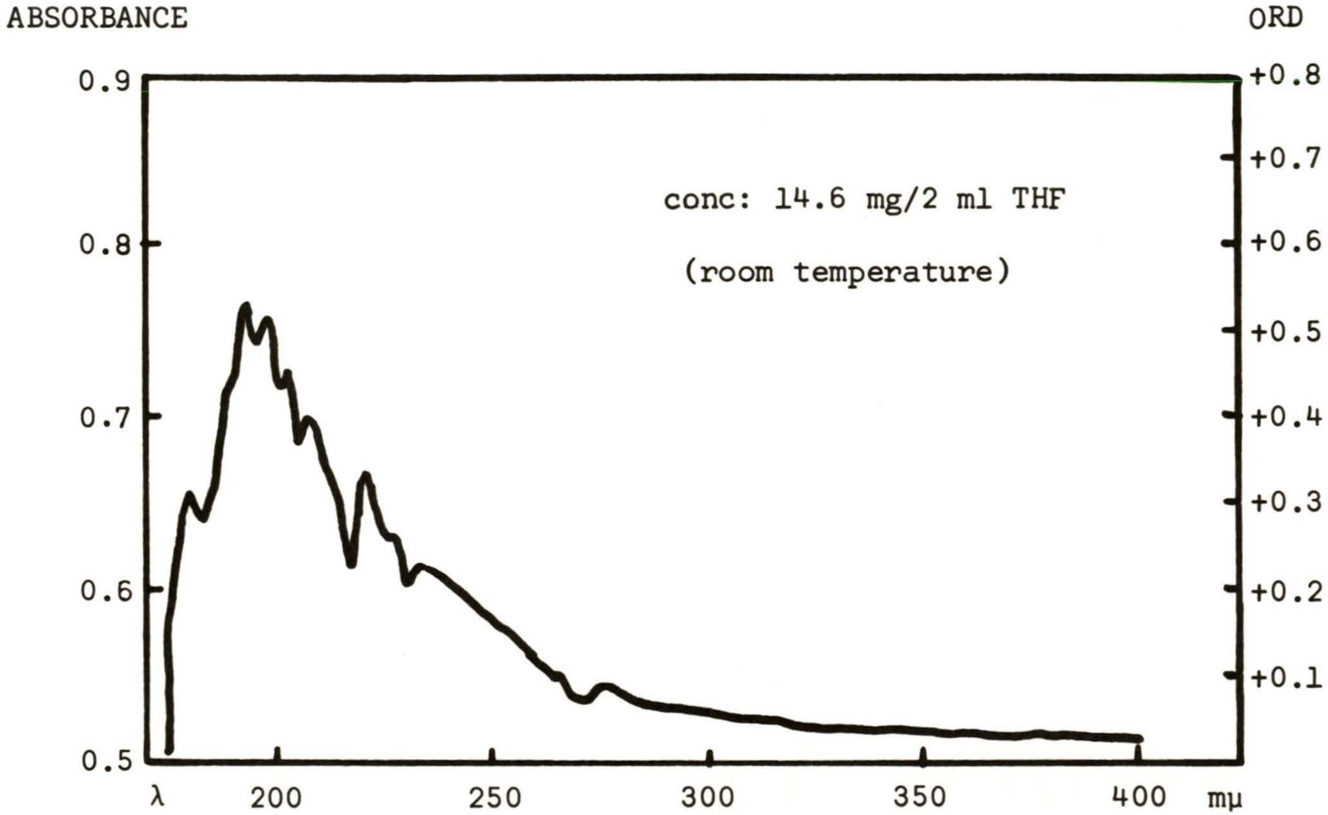


Figure 6. Optical rotatory dispersion curve of the $C_{30}H_{48}O_3$ constituent.

to the curve obtained in the case of the $C_{30}H_{48}O_3$ constituent under investigation.

(e) Nuclear magnetic resonance spectroscopy.

The nuclear magnetic resonance spectrum of the $C_{30}H_{48}O_3$ constituent is shown in Figure 7 on page 17. The peaks between 2.00 and 3.00 τ were assigned to residual protons in pyridine-d_5.

The doublet centered at 5.10 τ (individual peaks measured at 5.03 τ and 5.20 τ) was attributed to the two protons of a terminal methylene group (37). Assuming that only one terminal methylene group was present, the integration curve conveniently fitted one frame per proton. The rest of the spectrum, upon this basis of one frame per proton, integrated for 46 protons. Since the molecule has 48 protons, and since an offset sweep of 500 cps (in tetrahydrofuran) revealed no other proton, it was established, with a fair confidence, that the molecule has only one double bond (the terminal methylene group) and is likely not an acid (37).

At this point, a study of the "unsaturated sites" (38) was done. For $C_{30}H_{48}O_3$, the C_nH_{2n+2} gave $C_{30}H_{62}$. The "unsaturated sites" were then fixed at seven. Since the possibility of an acid was rejected because of the absence of an acidic proton, a lactone structure at least needed to be considered. The terminal methylene group accounted for one "unsaturated site" while the lactone group accounted for one other. Five "unsaturated sites" remained and this strongly suggested that the compound was pentacyclic. Furthermore, recalling that the infrared data showed the δC-H vibrations (scissoring) of $-CH_2-$ at 1451 cm^{-1} (see page 10), the probabilities of six-membered rings seemed to be far more likely than the possibilities of five, four or three-membered rings. This last assumption was also partly supported by Bible (39), who lists

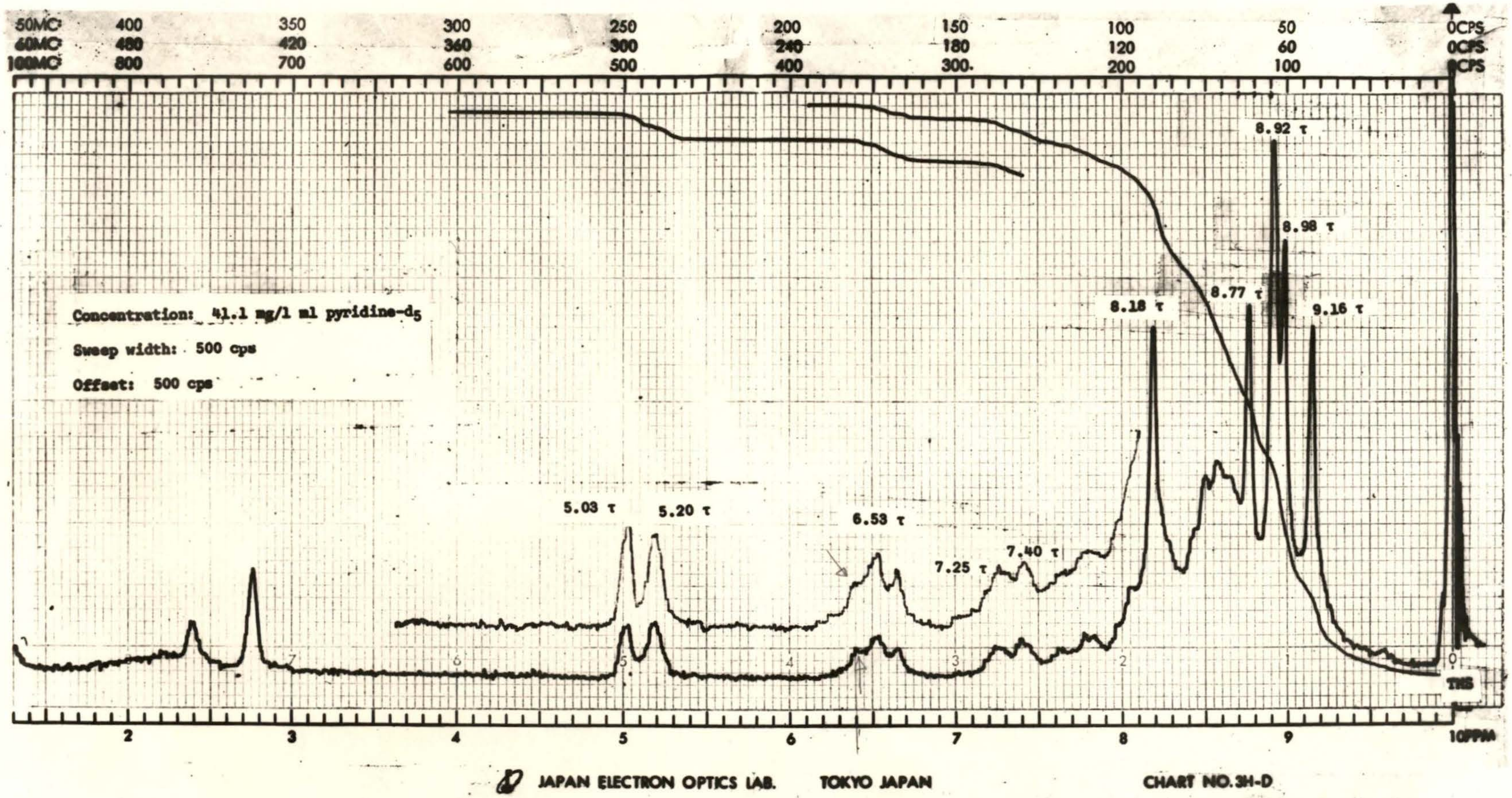
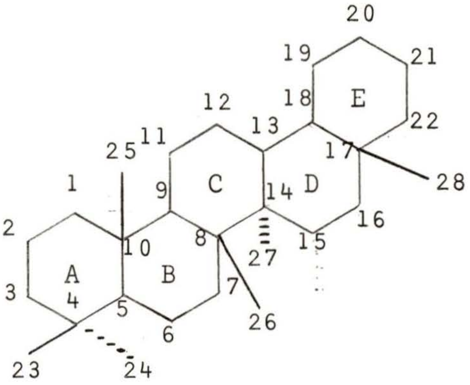


Figure 7. Nuclear magnetic resonance spectrum of the $C_{30}H_{48}O_3$ constituent.

protons in a three-membered ring at 9.7 to 9.8 τ; no absorption was shown in this region by the component under investigation. The fact that the molecule is pentacyclic and has the formula of $C_{30}H_{48}O_3$ suggested that a pentacyclic triterpenoid structure was worthy of serious consideration.

Since two of the oxygen functions are involved in the proposed lactone ring, only one remained to be assigned. The νO-H band in the infrared spectrum (see page 9) suggested that this remaining oxygen was present as an alcoholic group. A study of the nuclear magnetic resonance spectrum of the compound bore this out, at least in part. The protons attached to the same carbon as a hydroxyl function are deshielded and usually appear in the 5.5 to 6.5 τ region (40). The position and shape of the proton resonance depends not only on its axial or equatorial nature, but also on the number and orientation of neighbouring vicinal protons (41). The triplet centered at 6.53 τ (individual peaks measured at 6.40 τ, 6.53 τ and 6.65 τ) and integrating for one proton strongly suggested an α-H configuration (thus a β-OH) (42). The alcoholic proton of a β-OH is generally found around 8.2 τ (42, 43). The spectrum showed a singlet at 8.18 τ. A deuterium oxide exchange run on the component gave only a solvent effect on the peaks in the 9.00 τ region. The analysis of the integration of the 8.18 τ absorption was difficult but indicated three to four protons. Because of this difficulty, the -OH absorption is possibly masked by other protons in this region and the disappearance of the alcoholic absorption cannot be claimed with any certainty. In addition to the alcoholic absorption at 8.18 τ, it is evident that the peak could be attributed to a methyl group linked to the terminal methylene group (44).

In order to check the possibility of a pentacyclic triterpenoid structure, an extensive literature survey of the nuclear magnetic resonance methyl absorptions of known pentacyclic triterpenes was undertaken (44, 45, 46). The methyl region of the $C_{30}H_{48}O_3$ constituent integrated for approximately 15 protons or five methyl groups. These five methyl groups, added to the one linked to the terminal methylene group (8.18 τ), fitted the $C\text{-}CH_3$ determination of five. The difference of one was obviously caused by the presence of a gem-dimethyl group (47). Three of the methyl groups [C_{23} (4β), C_{24} (4α) and C_{26} (8β)] agree very well with the literature values. The absorptions of the other two methyl groups deviate from the literature values but a solvent effect due to pyridine-d_5 is possibly the cause of this deviation.



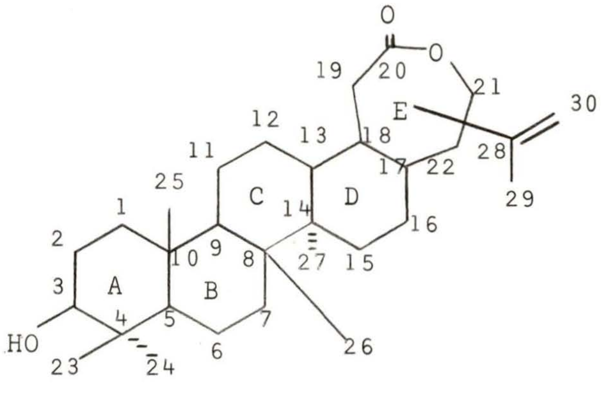
	Literature (44, 45, 46) (τ)	Found (pyridine-d_5) (τ)
C_{23} (4 β)	9.02	8.98
C_{24} (4 α)	9.14	9.16
C_{25} (10 β)	9.20-9.23	8.92 or 8.77
C_{26} (8 β)	8.94	8.92
C_{27} (14 α)	9.06	8.92 or 8.77
C_{28} (17 β)	9.20-9.23	--

The remaining protons were attributed to the different methylene and methine protons in the molecule. The absorption centered at 7.35 τ (two protons; individual peaks measured at 7.25 τ and 7.40 τ) was attributed (39) to a probable active methylene group detected in infrared (see page 10). It is reasonable to assume that this methylene group is adjacent to the carbonyl group of the proposed lactone function. Because of the absence of peaks in the 5.3 to 6.3 τ region, it was assumed that the carbon atom adjacent to the "ether" oxygen of the proposed lactone had no protons.

At this juncture, it seemed reasonable to propose a pentacyclic lactone structure with an isopropenyl group, a cyclic β-OH function, a gem-dimethyl function (with a central quaternary carbon) and three other methyl groups. A detailed analysis of the mass spectral data was undertaken to test this proposal.

(f) Mass spectrometry.

To facilitate the handling of the fragmentation pattern, the following tentative structure was proposed.



According to the nuclear magnetic resonance data (44, 45, 46), the gem-dimethyl group was placed at C_4 (C_{23} and C_{24}). For the same reason, another methyl group was placed at C_8 (C_{26}). Since many pentacyclic triterpenes have a functional group, other than methyl, at C_{17} (48, 49) (acid, alcohol, lactone, etc.), it was speculated that maybe the C_{17} methyl group was not present in the molecule under investigation. The two remaining methyl groups were placed at C_{10} (C_{25}) and C_{14} (C_{27}). It should be noted that the methyl group configurations given here are those found in common pentacyclic triterpenes (48, 49). Since a very large number of pentacyclic triterpenes containing an alcoholic group have this group at the 3β position, it seemed reasonable to place the hydroxyl group of the present molecule in this position. The isopropenyl and the lactone groups were assumed to be located in the E ring since they could not be conveniently placed elsewhere in the molecule.

Fortunately, the proposal of a pentacyclic triterpenoid structure was borne out by the mass spectral data. The available literature concerning the mass spectral fragmentation of pentacyclic triterpenes made it possible to formulate a fragmentation pattern for the proposed structure (50, 51, 52, 53, 54). A mass spectrum line diagram is presented in Figure 8 on page 22. Figures 9 and 10 (see pages 23 and 24) show the proposed fragmentation scheme. Finally, Table I and Table II (see pages 25 and 26) give a comparison table between the results obtained and the proposed fragmentation.

It was found that the most common fragmentation was between rings B and C to give the 208 and the 248 fragments. The subsequent fragmentation of the 208 fragment clearly indicated an identical fragmentation to known 3β-ol, C_4 gem-dimethyl and 10β-CH_3 components (50, 54). The fragmentation of the 248 fragment suggested that no groups, other than methyl groups, were on the C and D rings of the molecule (54). Finally, the fragmentation of the E ring suggested that the ether part of the

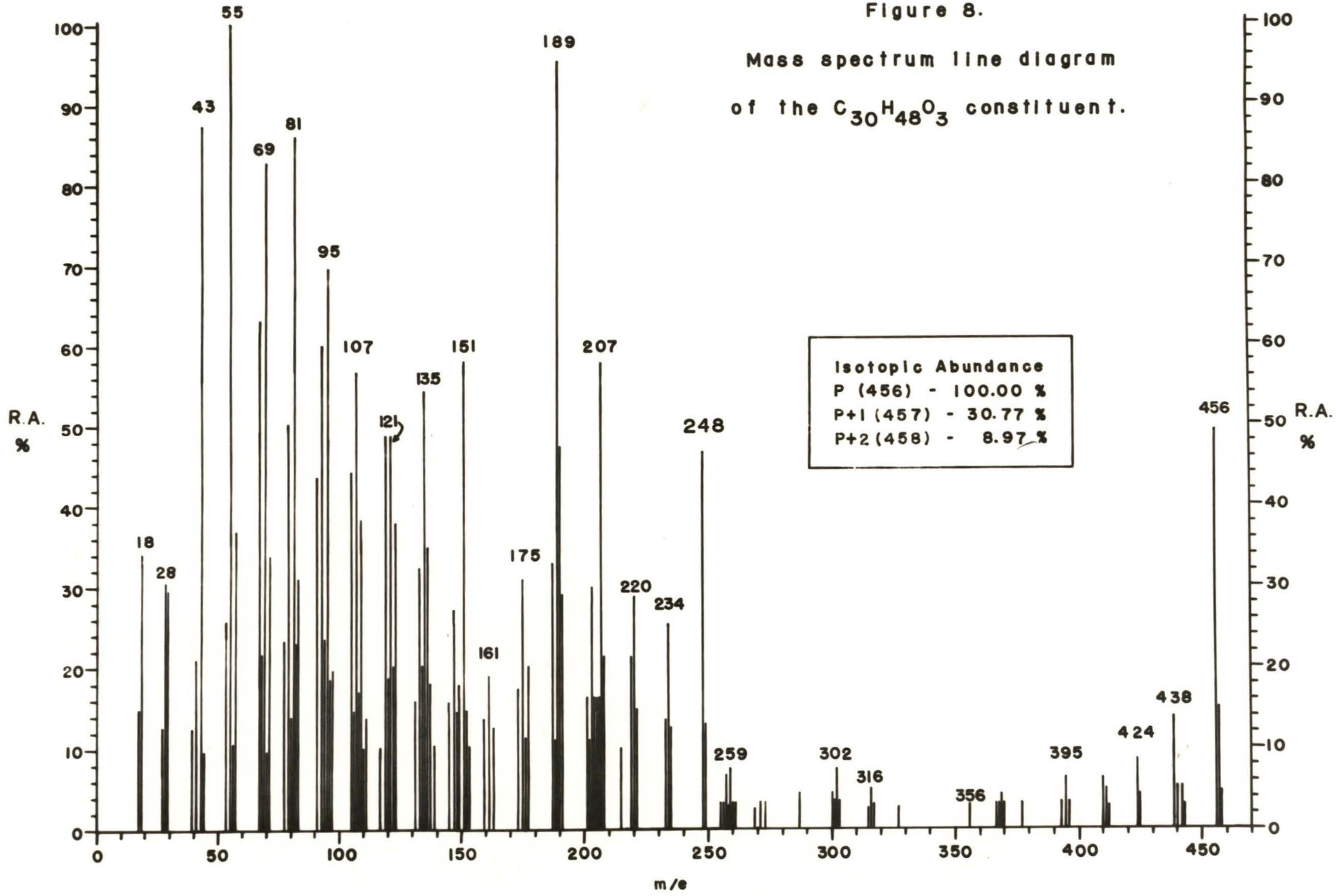


Figure 8.

Mass spectrum line diagram of the $C_{30}H_{48}O_3$ constituent.

Isotopic Abundance

P (456) - 100.00 %

P+1 (457) - 30.77 %

P+2 (458) - 8.97 %

Figure 9. Proposed fragmentation for the $C_{30}H_{48}O_3$ constituent (Part A).

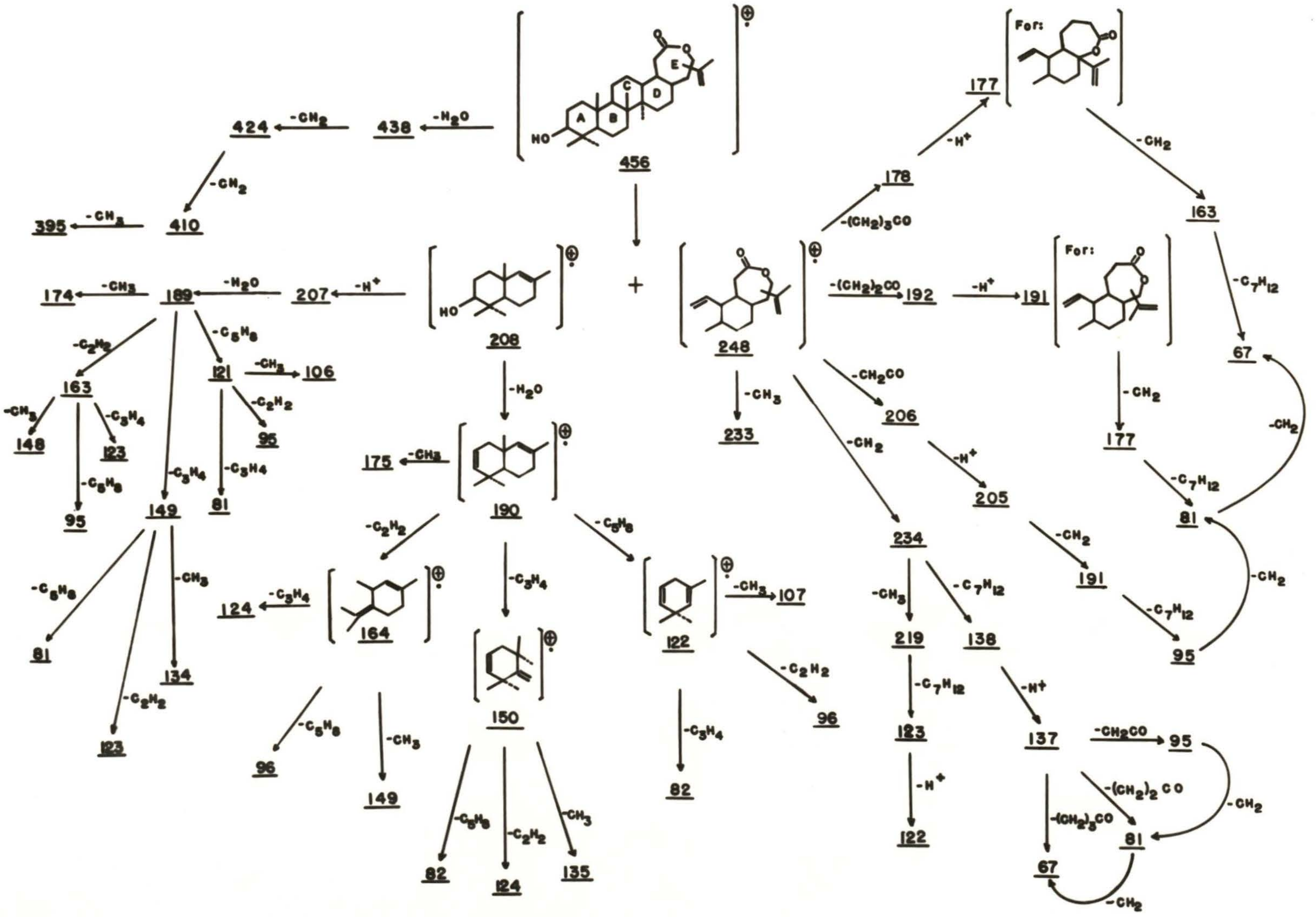


Figure 10. Proposed fragmentation for the $C_{30}H_{48}O_3$ constituent (Part B).

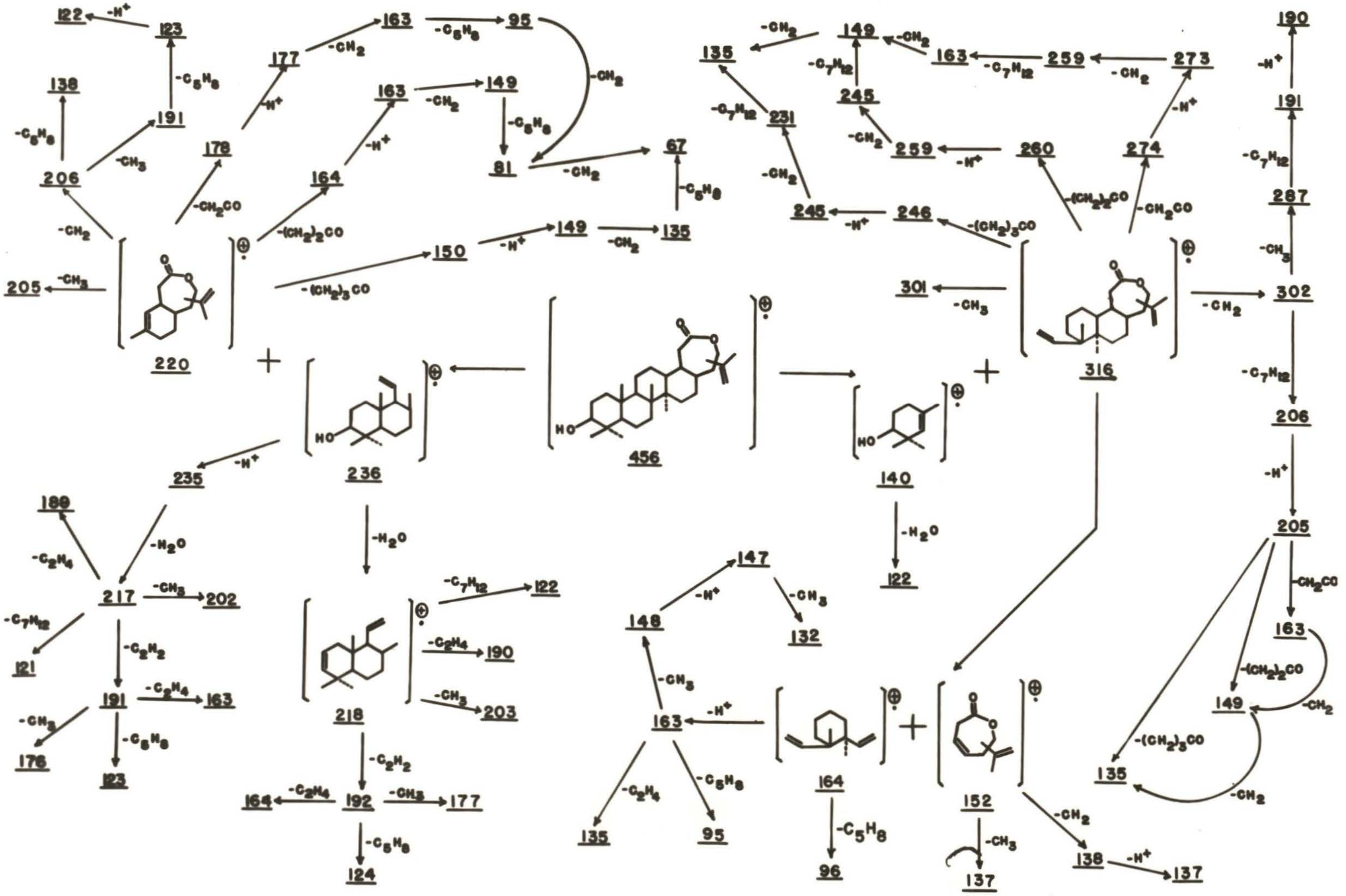


TABLE I

Comparison Table for the $C_{30}H_{48}O_3$ Constituent Mass Spectral Data

(Part A)

GENERAL

Fragment	R. A. %
438	13.75
424	8.13
410	6.25
395	6.25

THE 248 FRAGMENT

Fragment	R. A. %
248	46.25
234	25.00
233	13.75
219	21.25
206	16.25
205	16.25
192	8.75
191	28.75
178	7.50
177	20.00
163	13.75
138	6.25
137	18.75
123	36.25
122	21.25
95	70.00
81	85.00
67	62.50

THE 208 FRAGMENT

Fragment	R. A. %
208	21.25
207	57.50
190	37.50
189	96.25
175	32.50
174	6.25
164	5.00
163	13.75
150	6.88
149	18.75
148	13.75
135	53.75
134	21.25
124	7.50
123	36.25
122	21.25
121	48.75
107	56.25
106	13.75
96	18.75
95	70.00
82	22.50
81	85.00

TABLE II

Comparison Table for the $C_{30}H_{48}O_3$ Constituent Mass Spectral Data

(Part B)

THE 236 FRAGMENT

Fragment	R. A. %
236	9.38
235	12.50
218	4.38
217	7.50
203	30.00
202	11.25
192	8.75
191	28.75
190	37.50
189	96.25
177	20.00
176	10.63
164	5.00
163	13.75
124	7.50
123	36.25
122	21.25
121	48.75

THE 220 FRAGMENT

Fragment	R. A. %
220	28.75
206	16.25
205	16.25
191	28.75
178	7.50
177	20.00
164	5.00
163	13.75
150	6.88
149	18.75
138	6.25
135	53.75
123	36.25
122	21.25
95	70.00
81	85.00
67	62.50

THE 140 FRAGMENT

Fragment	R. A. %
140	3.75
122	21.25

THE 316 FRAGMENT

Fragment	R. A. %
316	5.00
302	7.50
301	3.75
287	4.38
274	--
273	3.75
260	3.75
259	7.50
246	5.00
245	3.75
231	4.38
206	16.25
205	16.25
191	28.75
190	37.50
164	5.00
163	13.75
152	15.00
149	18.75
148	13.75
147	27.50
138	6.25
137	18.75
135	53.75
132	6.25
96	18.75
95	70.00

lactone is adjacent to a quaternary carbon (55) as it was previously established by the nuclear magnetic resonance data (see page 20).

Figure 10 (see page 24) shows two other schemes of the less important fragmentations. However, these minor fragmentation schemes corroborate preceding conclusions.

IV. DERIVATIVES

(a) Acetylation product.

(i) Physical constants.

The acetylation of the $C_{30}H_{48}O_3$ constituent in pyridine and acetic anhydride (at room temperature) yielded a product whose physical constants are presented in Figure 11 on page 28.

(ii) Infrared spectrophotometry.

The infrared spectrum of the acetylation product (see Figure 12, page 29) clearly indicated the presence of an acetate group.

The strong absorption caused by the νC-O vibrations of the proposed lactone remained unchanged (1888 cm^{-1}). The small broad band centered at 3472 cm^{-1} was attributed to moisture of the KBr pellet. The presence of an acetate group was clearly indicated by the presence of a strong band at 1733 cm^{-1} [νC=O vibrations (29)]. The rest of the spectrum was found to be similar to the spectrum of the $C_{30}H_{48}O_3$ constituent.

In order to insure that the small broad band at 3472 cm^{-1} was indeed due to moisture in the KBr pellet, a comparison was made between the original $C_{30}H_{48}O_3$ constituent in nujol and the acetate derivative in chloroform (see Figure 13, page 30). The comparison of the two spectra suggested that no νO-H vibrations remained after acetylation.

m. p. 269.0-271.0°C (dec.)

Sublimes at ~150°C (0.5 mm Hg)

ANALYSIS

$C_{32}H_{50}O_4$

	Calc. %	Found %
C:	77.06	76.23
H:	10.10	10.30

ROTATION IN CHLOROFORM

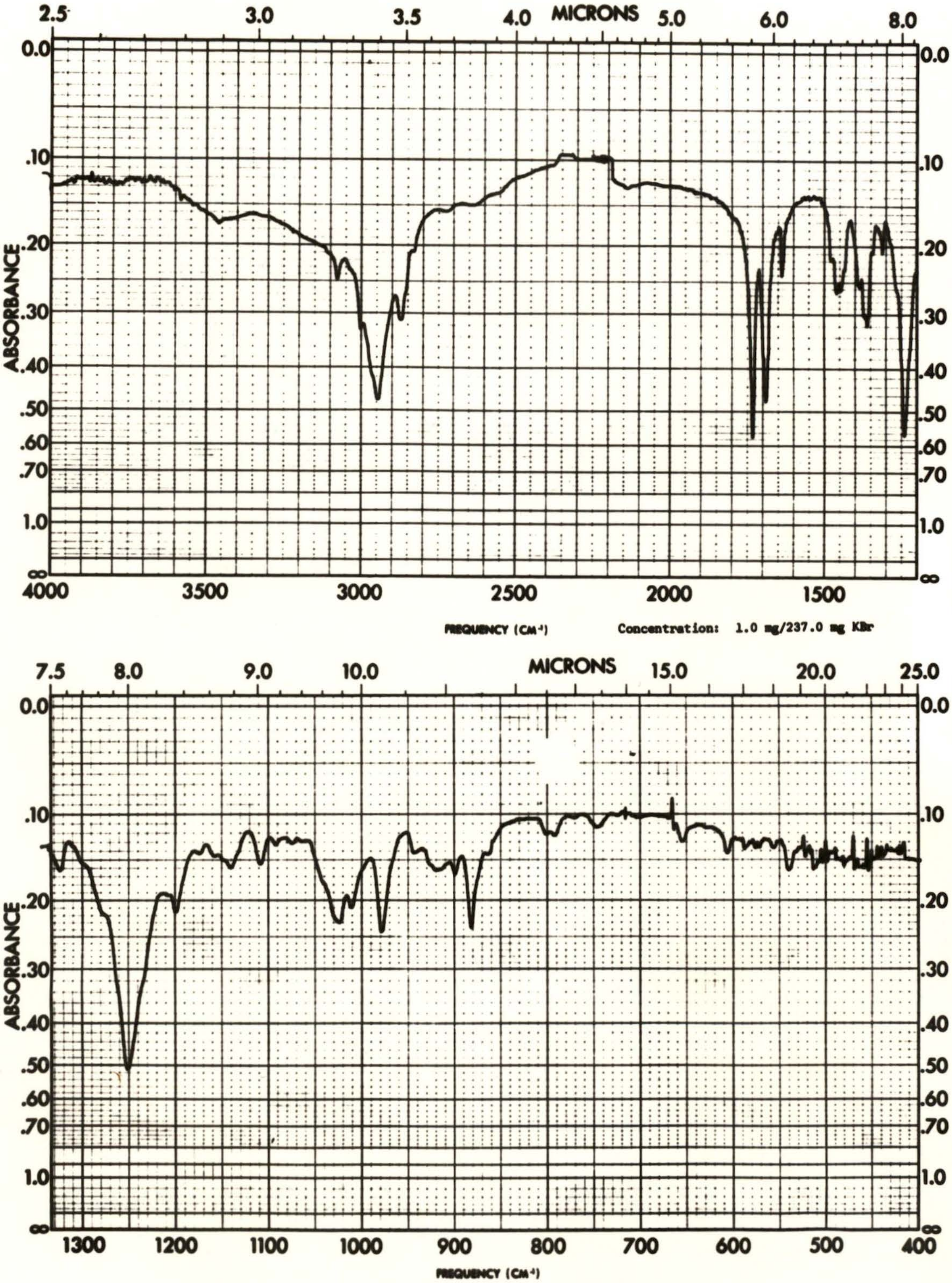
Conc.: 12.0 mg/1 ml

Observed rotation: 0.208°

$[\alpha]_D^{23°}$ +17.3°

$[\alpha M]_D^{23°}$ +79.0°

Figure 11. Physical constants of the acetylation product.



Concentration: 1.0 mg/237.0 mg KBr

Figure 12. Infrared spectrum of the acetylation product.

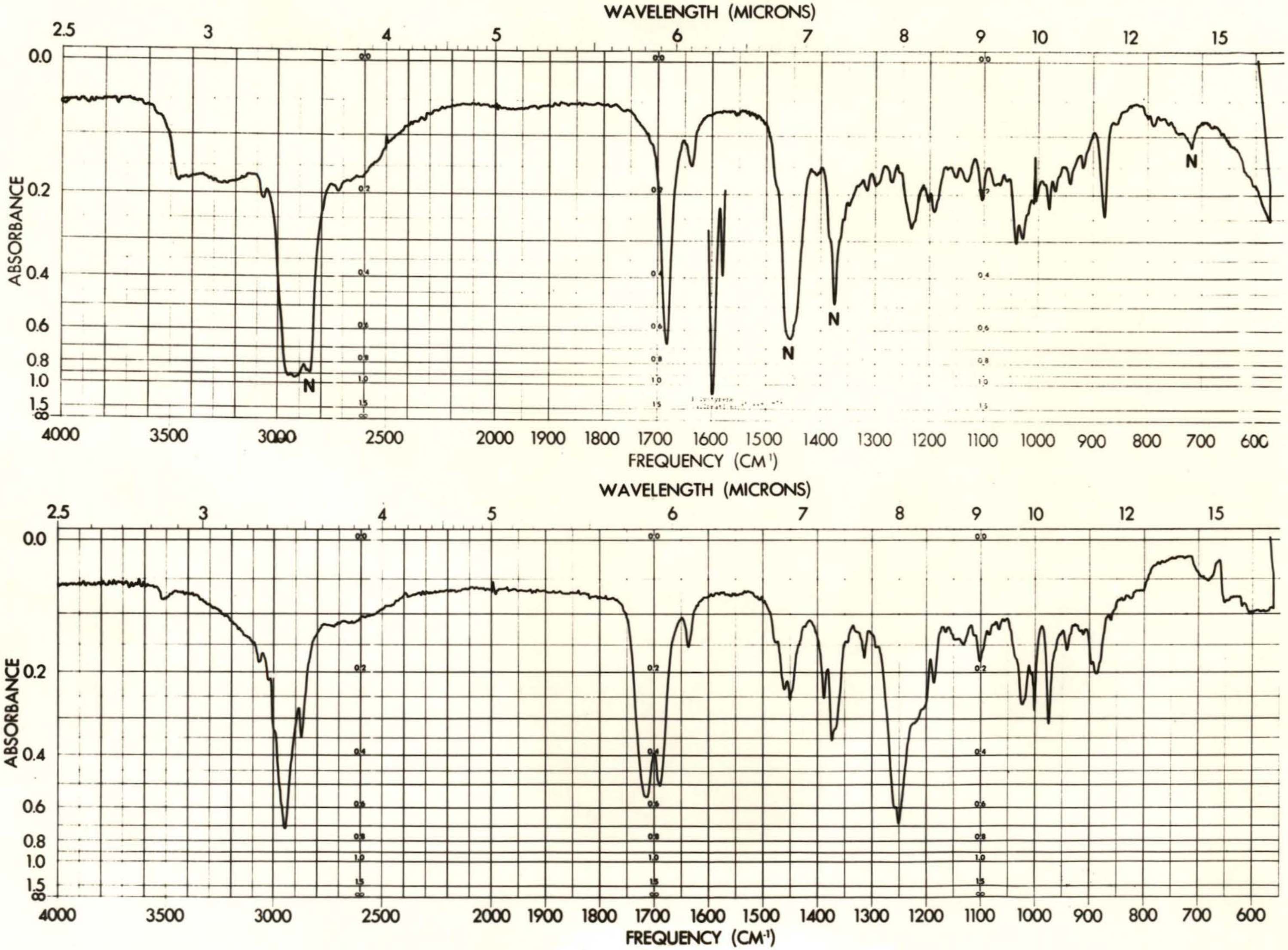


Figure 13. Infrared spectra of the $C_{30}H_{48}O_3$ constituent (in nujol) and of the acetylation product (in chloroform).

(iii) Ultraviolet spectrophotometry.

The ultraviolet spectrum of the acetylation product (see Figure 14, page 32) revealed the following band:

$$\lambda_{\max}^{\text{THF}} \quad 216\ \text{m}\mu \quad (\varepsilon = 606)$$

The region of the spectrum scanned was 210 to 360 mμ.

As expected (32), the ultraviolet spectrum was similar to that of the $C_{30}H_{48}O_3$ constituent.

(iv) Optical rotatory dispersion data.

A similar curve to that of the parent compound was obtained. This curve is reproduced in Figure 15 on page 33.

(v) Nuclear magnetic resonance spectroscopy.

The nuclear magnetic resonance spectra (pyridine-d_5 and $CDCl_3$) of the acetylation product are shown in Figure 16 on page 34. A striking solvent effect was observed.

The spectra showed that the absorption bands due to the isopropenyl group and the methyl groups were unchanged. The signal at 7.97 τ was attributed to the methyl part of the acetate group (56). As expected (41), the α-proton of the carbon bearing the β-acetate group was found in the 5.20 τ region, accompanying the signal of the protons of the methylene group.

However, the shift observed with different solvents underline the relative weakness of the conclusions made about the two protons adjacent to the carbonyl part of the proposed lactone (see page 20). It is assumed that the signal of the protons in question is moved into the 8.00 τ region when the spectrum is run in $CDCl_3$. This clearly indicated

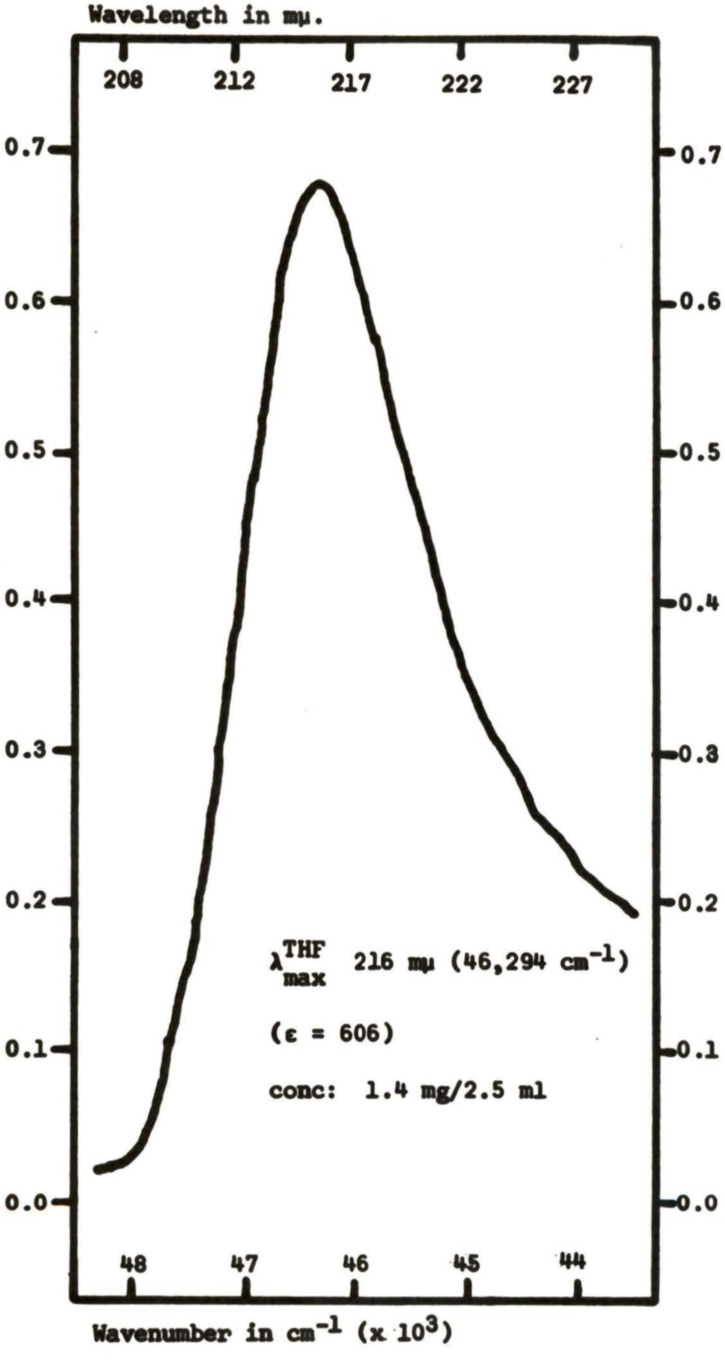


Figure 14. Ultraviolet spectra of the acetylation product.

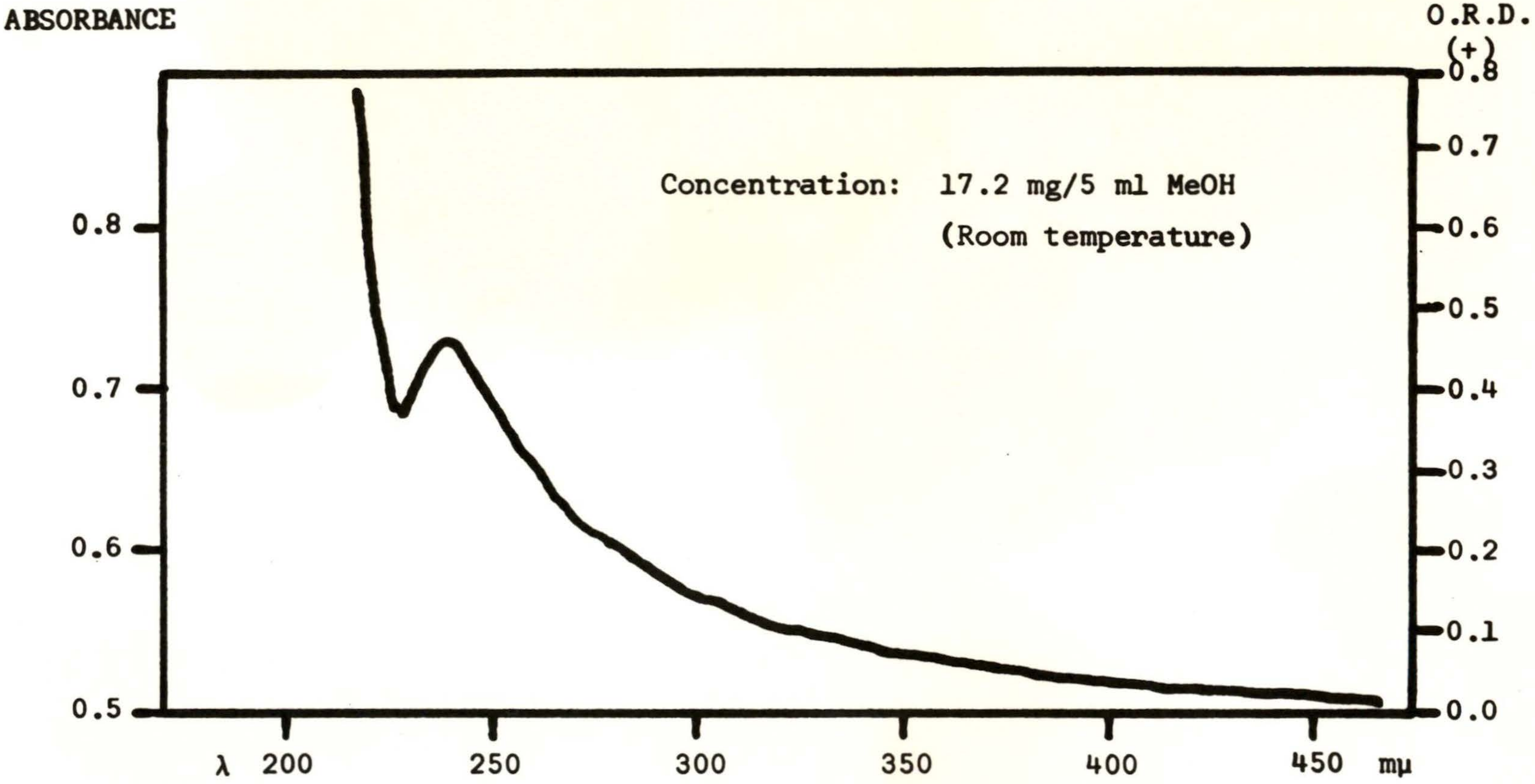
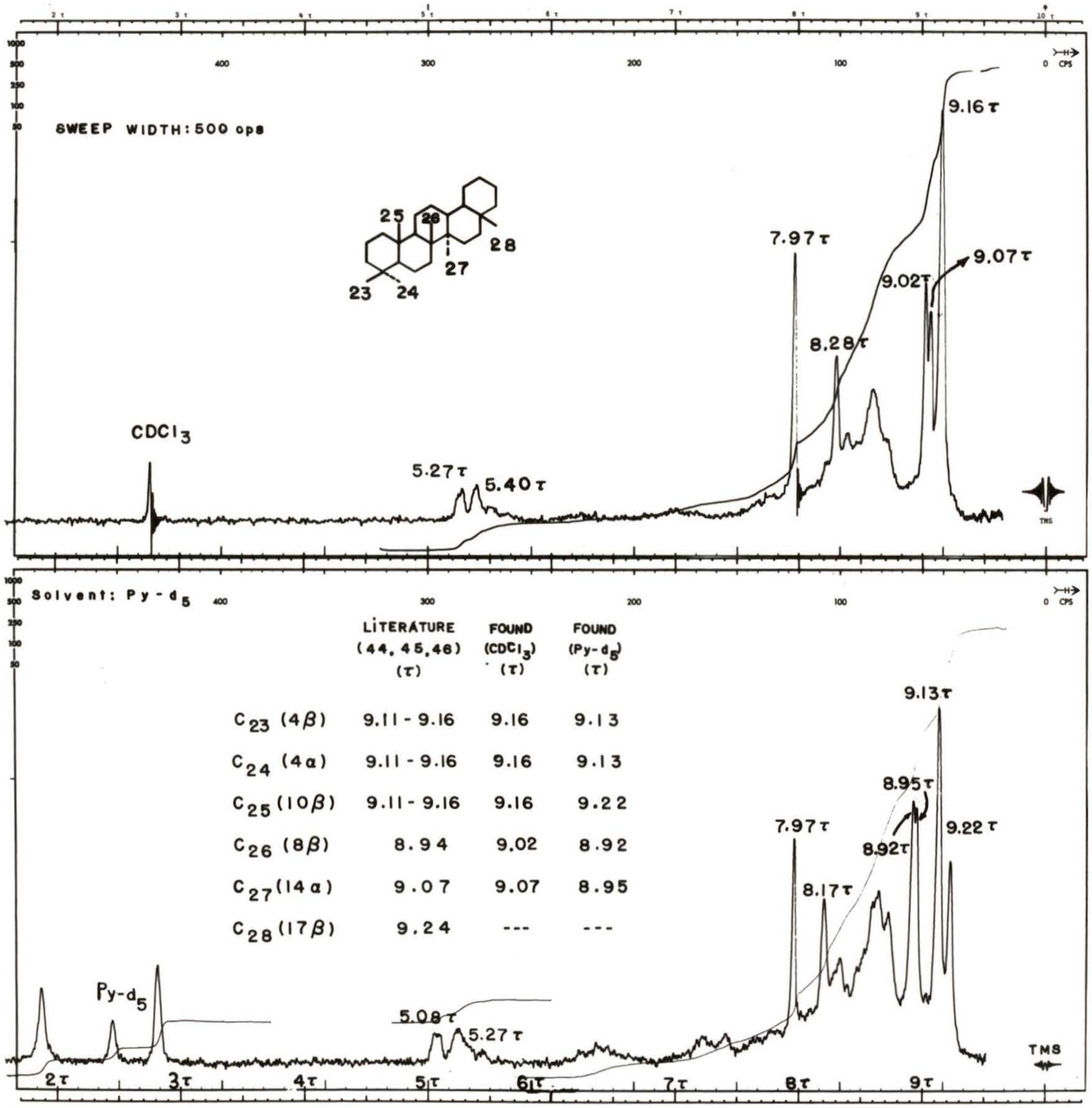


Figure 15. Optical rotatory dispersion curve of the acetylation product.



	LITERATURE (44, 45, 46) (τ)	FOUND ($CDCl_3$) (τ)	FOUND (Py-d_5) (τ)
C_{23} (4β)	9.11 - 9.16	9.16	9.13
C_{24} (4α)	9.11 - 9.16	9.16	9.13
C_{25} (10β)	9.11 - 9.16	9.16	9.22
C_{26} (8β)	8.94	9.02	8.92
C_{27} (14α)	9.07	9.07	8.95
C_{28} (17β)	9.24	---	---

Figure 16. Nuclear magnetic resonance spectra of the acetylation product.

the need for the preparation and study of other derivatives of the original compound.

(vi) Mass spectrometry.

The proposed fragmentation for the acetylation product is presented in Figure 17 on page 36. The predicted fragments are in very good agreement with those found in the actual mass spectrum results (see Figure 18, page 37).

The most predominant fragmentation is obviously the one generating the 248 and 250 fragments (see Table III and Table IV on pages 38 and 39).

(b) LAH reduction product.

Because only a small amount of pure lithium aluminum hydride reduction product was available, it was only possible to perform some preliminary investigations on this material.

The product was found to melt at 237.0-240.0°C and a determination of its molecular weight through double focus mass spectrometry gave m/e = 442.3812 [calculated for $C_{30}H_{48}O_3$ (57): 442.3811].

Theoretically, the proposed lactone should, upon lithium aluminum hydride reduction, yield a compound having a parent peak at m/e 460. The parent peak found is at m/e 442. This immediately suggests that the functional group being reduced is a carboxylic acid group:

$$-CO_2H \xrightarrow{\text{LAH}} -CH_2OH$$

$$45 \xrightarrow{(-14)} 31$$

However, the insolubility of the parent compound in base and the failure to find an acidic proton in its nuclear magnetic resonance spectrum make this

Figure 17. Proposed fragmentation for the acetylation product.

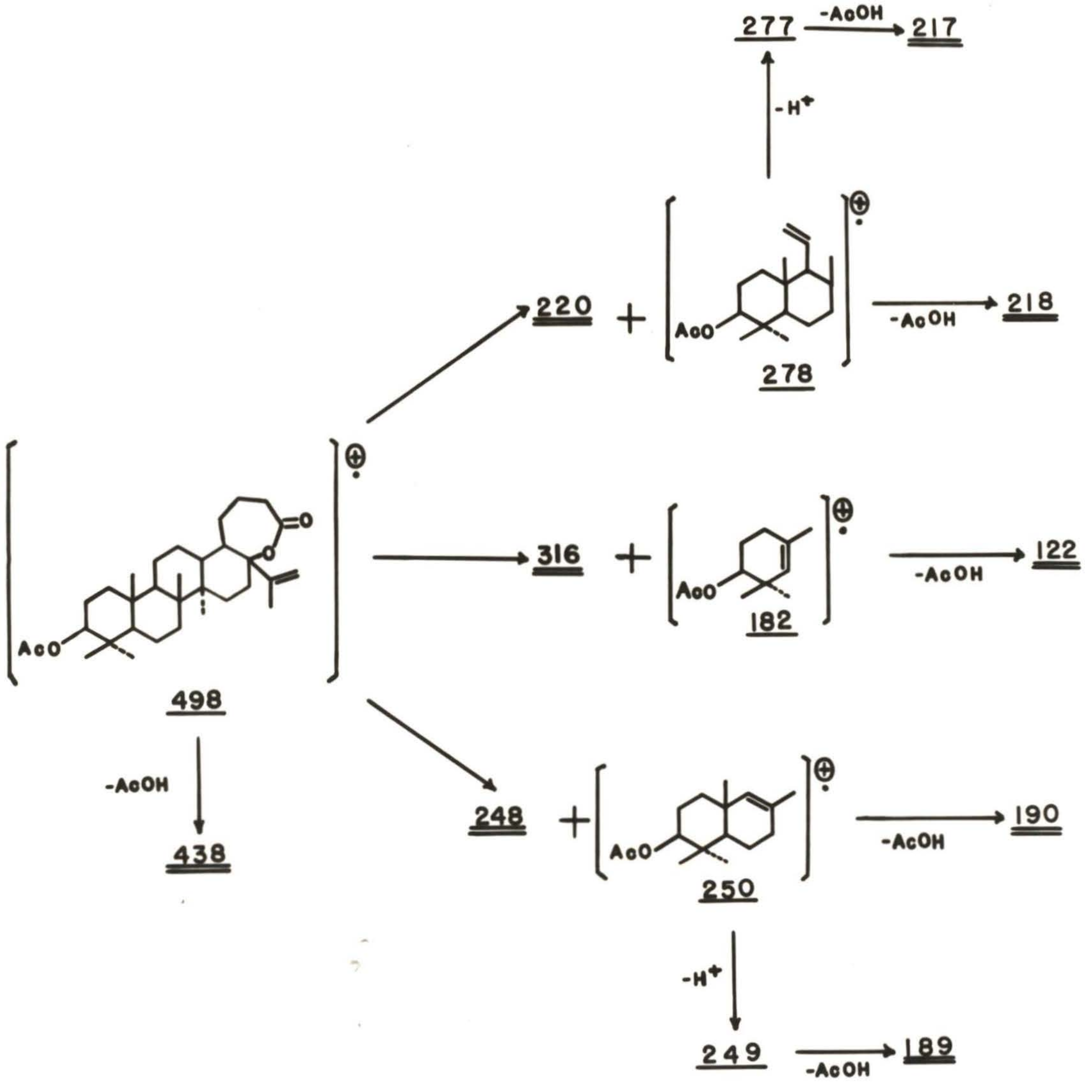


Figure 18. Mass spectrum line diagram of the acetylation product.

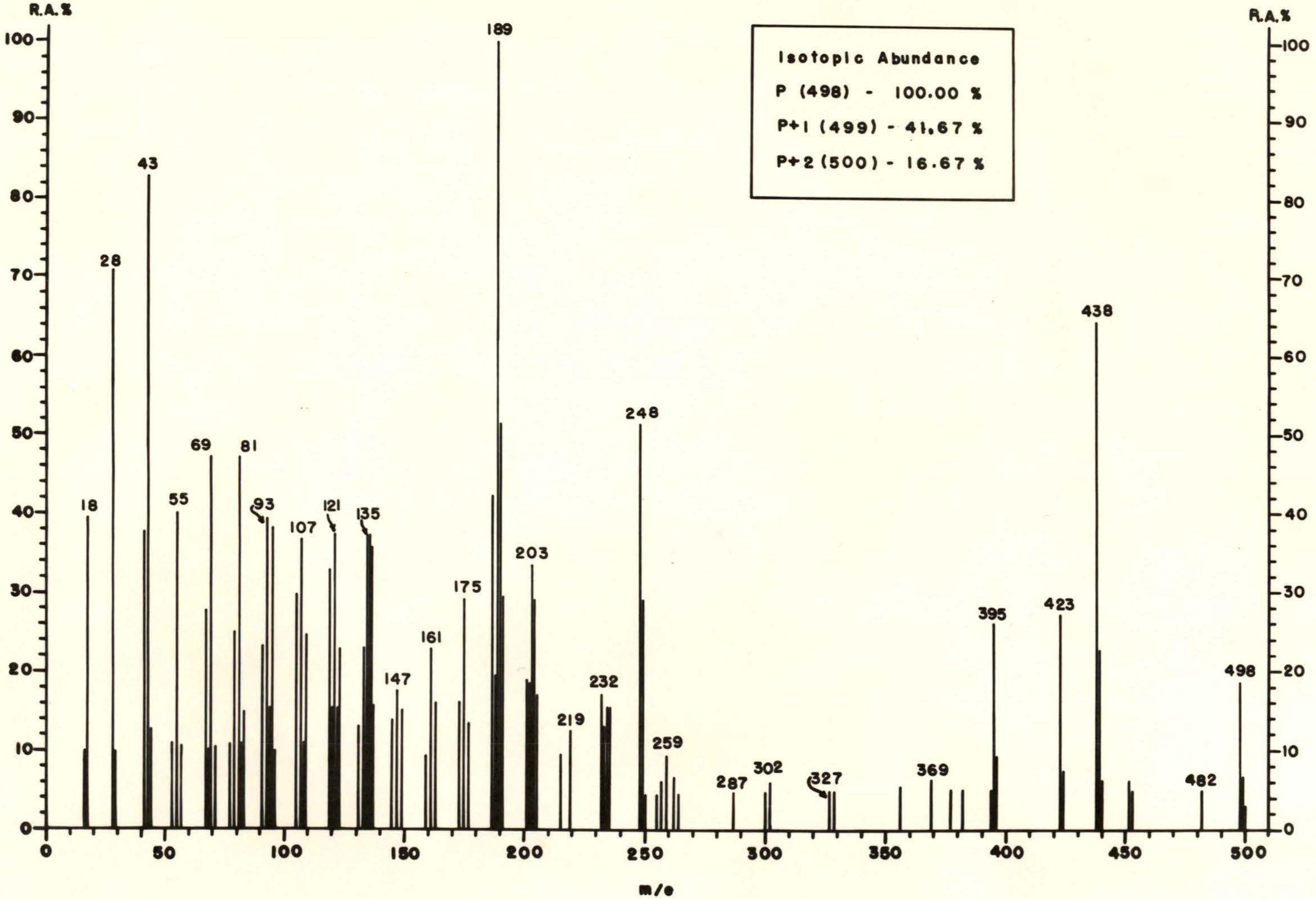


TABLE III

Comparison Table for the Acetylation Mass Spectral Data

(Part A)

GENERAL

Fragment	R. A. %
438	64.12
424	7.63
410	--
395	25.95

THE 248 FRAGMENT

Fragment	R. A. %
248	50.38
234	15.27
233	12.98
219	12.21
206	7.63
205	16.79
192	7.63
191	29.77
178	5.34
177	13.74
163	19.08
138	--
137	15.27
123	22.90
122	15.27
95	38.17
81	46.56
67	27.48

THE 250 FRAGMENT

Fragment	R. A. %
250	4.58
249	29.01
190	51.91
189	100.00
175	29.00
174	6.87
164	5.34
163	19.08
150	6.11
149	15.27
148	9.16
135	37.40
134	37.40
124	5.34
123	22.90
122	15.27
121	36.64
107	36.64
106	8.40
96	9.92
95	38.17
82	11.45
81	46.56

TABLE IV

Comparison Table for the Acetylation Mass Spectral Data

(Part B)

THE 182 FRAGMENT

Fragment	R. A. %
182	--
122	15.27

THE 316 FRAGMENT

Fragment	R. A. %
316	--
302	6.11
301	--
287	4.58
274	--
273	--
260	--
259	9.16
246	7.63
245	--
231	--
206	7.63
205	16.79
191	29.77
190	51.91
164	5.34
163	19.08
152	6.87
149	15.72
148	9.16
147	22.90
138	--
137	15.27
135	37.40
132	6.10
96	9.92
95	38.17

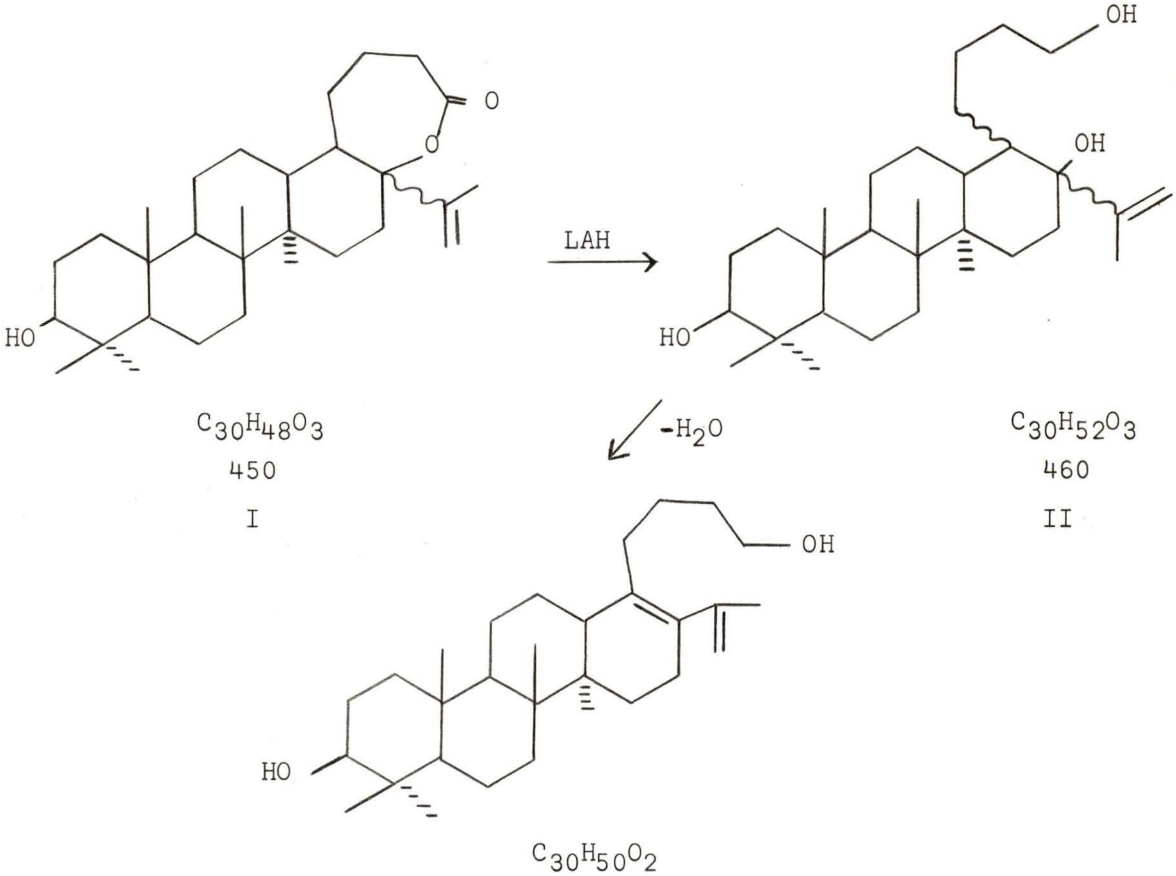
THE 278 FRAGMENT

Fragment	R. A. %
278	--
277	--
218	4.58
217	8.40
203	33.59
202	18.32
192	7.63
191	29.77
190	51.91
189	100.00
177	13.74
176	9.16
164	5.34
163	19.08
124	4.58
123	22.90
122	15.27
121	36.64

THE 220 FRAGMENT

Fragment	R. A. %
220	7.63
206	7.63
205	16.79
191	29.77
178	5.34
177	13.74
164	5.34
163	19.08
150	6.11
149	15.27
138	--
135	37.40
123	22.90
122	15.27
95	38.17
81	46.56
67	27.48

possibility very unlikely. A more attractive explanation seems to be rapid dehydration favouring the formation of a diene.



$C_{30}H_{48}O_3$
450
I

$C_{30}H_{52}O_3$
460
II

$C_{30}H_{50}O_2$
442 III

The mass spectrum line diagram of the lithium aluminum hydride reduction product is shown in Figure 19 on page 41.

Figure 20, on page 42, presents a proposed fragmentation for the reduction product. The fragmentation reconfirms the structure of the rings A and B and is in reasonable agreement with the tentative formula III (see above). A comparison of the proposed fragmentation with the actual fragments obtained is shown in Tables V and VI (see pages 43 and 44.)

Figure 19.

Mass spectrum line diagram of the LAH reduction product.

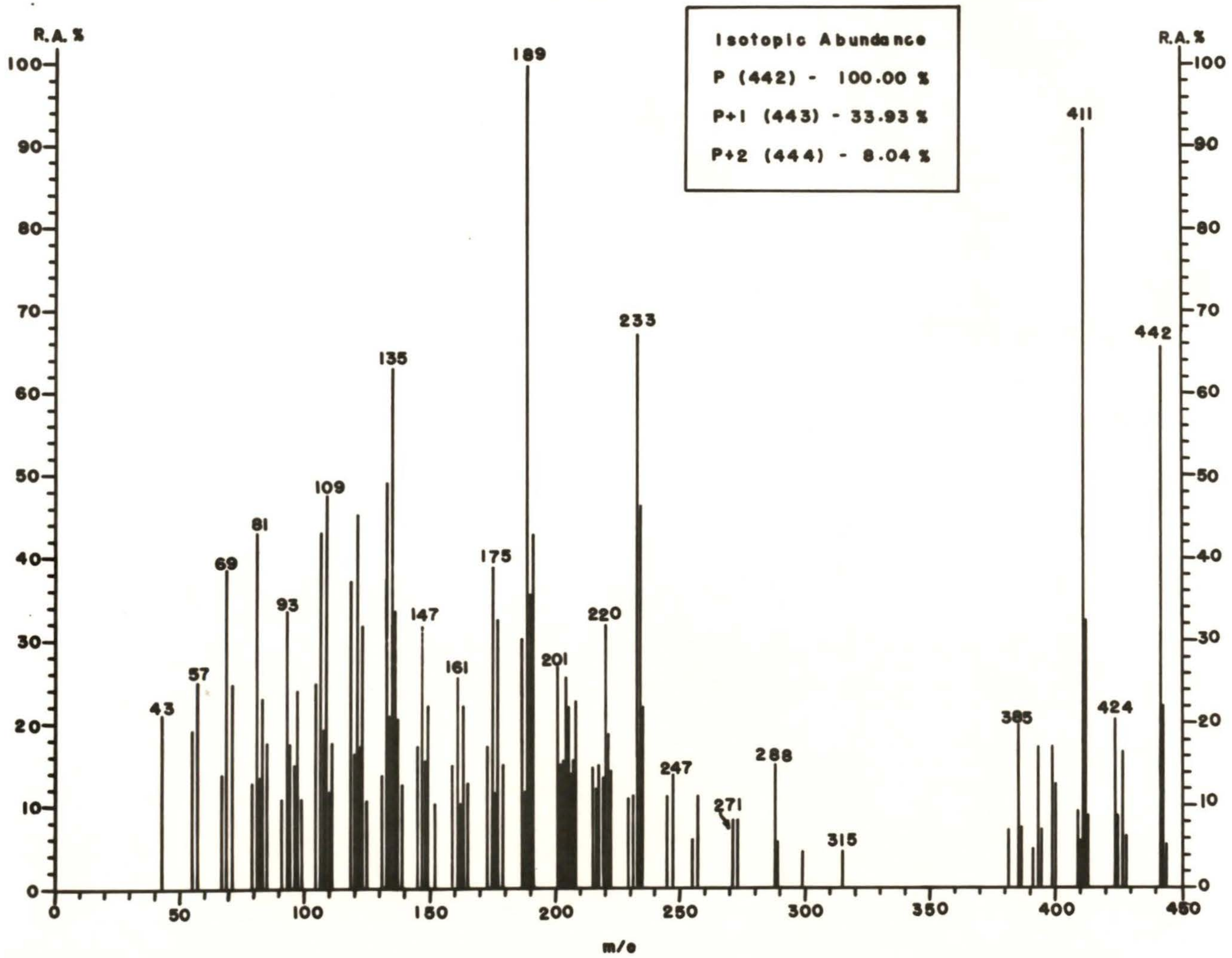


Figure 20. Proposed fragmentation for the LAH reduction product.

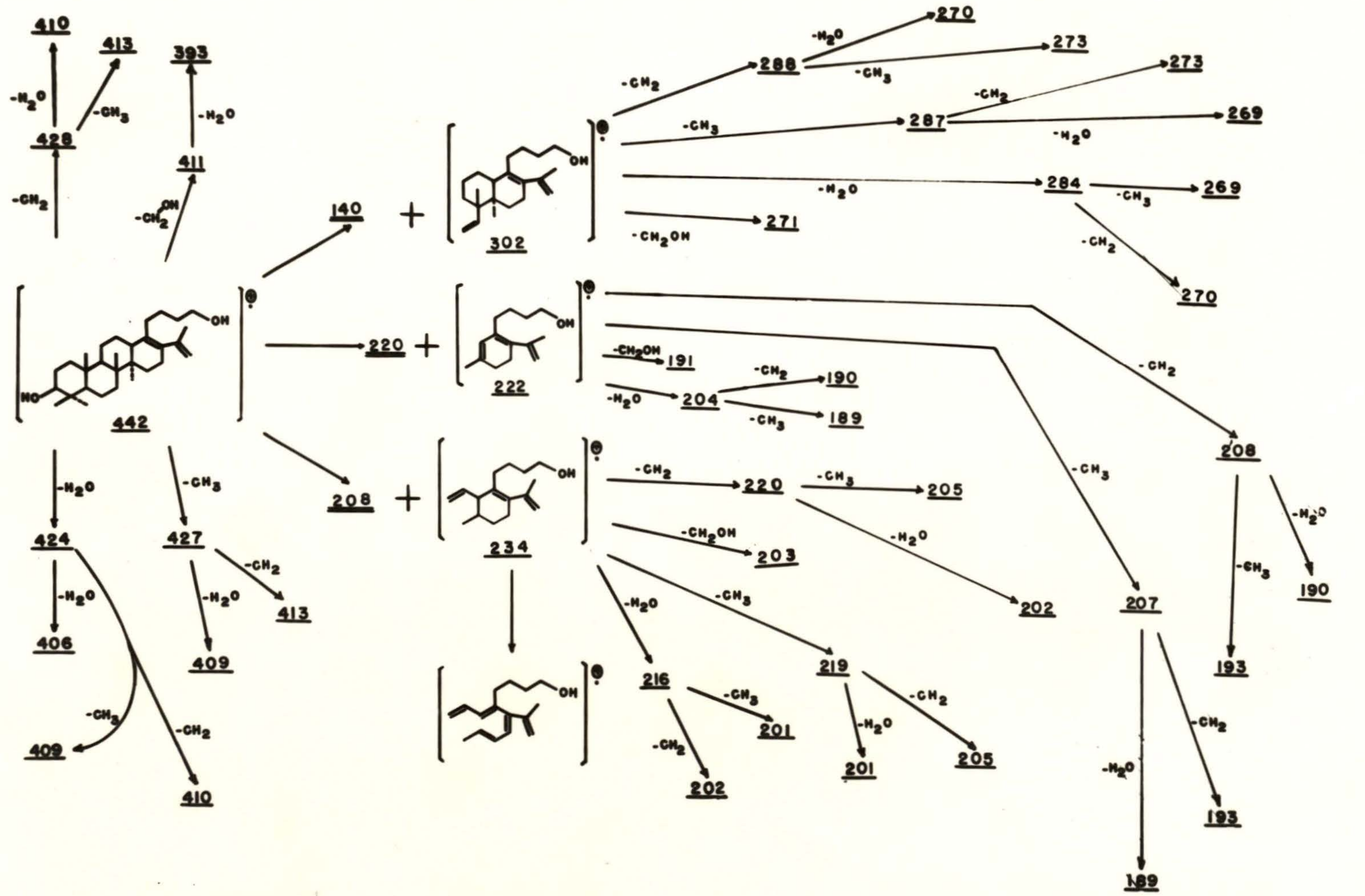


TABLE V

Comparison Table for the LAH Reduction Product Mass Spectral Data

(Part A)

GENERAL

Fragment	R. A. %
428	6.36
427	16.19
424	20.23
413	8.09
411	91.91
410	5.78
409	9.83
406	--
393	17.34

THE 234 FRAGMENT

Fragment	R. A. %
234	46.24
220	31.79
219	12.72
216	12.14
205	21.97
203	15.61
202	15.03
201	26.59

THE 208 FRAGMENT

Fragment	R. A. %
208	22.54
207	15.61
190	35.83
189	100.00
175	38.73
174	--
164	--
163	21.97
150	--
149	21.97
148	15.03
135	62.43
134	20.81
124	9.25
123	31.79
122	17.34
121	45.09
107	42.77
106	9.25
96	15.03
95	9.25
82	13.29
81	42.77

TABLE VI

Comparison Table for the LAH Reduction Product Mass Spectral Data

(Part B)

THE 222 FRAGMENT

Fragment	R. A. %
222	13.87
208	22.54
207	15.61
204	25.43
203	15.61
193	--
191	42.77
190	35.83
189	100.00

THE 220 FRAGMENT

Fragment	R. A. %
220	31.79
206	13.87
205	21.97
191	42.77
178	--
177	32.37
164	--
163	21.97
150	--
149	21.97
138	--
135	62.43
123	31.79
122	17.34
95	9.75
81	47.77
67	13.82

THE 302 FRAGMENT

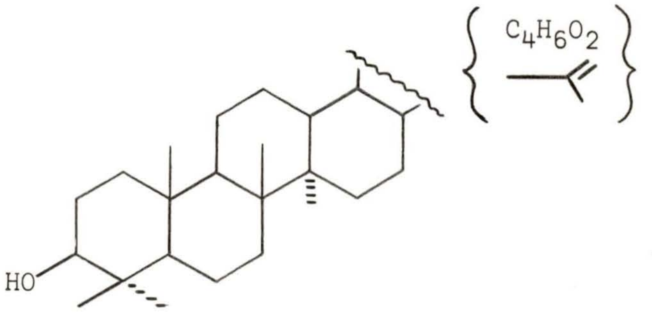
Fragment	R. A. %
302	--
288	15.03
287	--
284	--
273	8.09
271	8.09
270	--
269	--

THE 140 FRAGMENT

Fragment	R. A. %
140	--
122	17.34

V. DISCUSSION

On the basis of the results obtained, the following structure was tentatively proposed for the $C_{30}H_{48}O_3$ constituent.

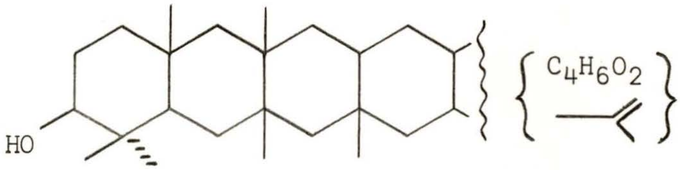


The existence of the isopropenyl group was firmly established through infrared and nuclear magnetic resonance measurements. Since the mass spectral data suggested that the B, C and D rings were free from substituents (except for methyl groups) and since the A ring contains only the alcoholic group (plus the methyl groups), the isopropenyl group was placed on the E ring. Because of the absence of protons neighbouring the ether part of the proposed lactone in the nuclear magnetic resonance spectrum, it was thought that the isopropenyl group was located on a quaternary carbon atom. The only way this could be conveniently placed was at the D-E ring junction, as shown in the structure above. More evidence is obviously needed to ascertain the position of the isopropenyl group in the molecule. Study of derivatives involving reduction and oxidation of the isopropenyl group and reactions leading to alterations of the proposed lactone function will certainly establish clearly the position and configuration of the isopropenyl group in the molecule.

The presence of the alcoholic function is strongly supported by the infrared results and the fact that a monoacetylation product was easily obtained. The nuclear magnetic resonance spectra of the parent compound and of the acetate derivative clearly indicate that the alcoholic function in ring A has the β configuration. Nakanishi (58) and Allsop (59) indicate that the fact that axial bonds appear at higher frequencies in infrared spectra of triterpenes (a behaviour which is contrary to steroids) has been attributed to the presence of a gem-dimethyl group at C_4. The infrared data collected for the present compound under investigation indicate that this is precisely the situation in this case. Furthermore, all the mass spectra are in complete agreement with the proposed A-B rings. It should be noted that the mass spectral data do not fit very well cases where the -OH and the gem-dimethyl are located in other positions in the A ring. However, an oxidation of the hydroxyl group would give further support to this assignment. But, the fact that no deuterium exchange of the alcohol is observed in the nuclear magnetic resonance spectrum remains a tantalizing question. It was proposed, but not proved, that the alcoholic proton is masked by the 8.18 τ peak (given by the methyl group in the isopropenyl function) and therefore observation of the deuterium oxide exchange is rendered difficult. The question could be settled by a reduction of the isopropenyl group. The new isopropyl function formed would likely shift towards the other methyl groups (in the nuclear magnetic resonance spectrum) and therefore render it possible to determine if the 8.18 τ peak is really masking the alcoholic proton.

The optical rotatory dispersion curve and the ultraviolet measurements helped to eliminate certain possibilities. The mass fragmentation situates it in the E ring while the nuclear magnetic resonance clearly shows no proton neighbouring the ether part of the lactone and suggests (with reservations due to shift in different solvents) two protons on the other side of the function. The infrared νC=0 absorption recorded for the $C_{30}H_{48}O_3$ constituent is somewhat low for a lactone (29) and the case was tentatively explained, but not proved, by the concerted effects generated by steric hindrance, possible β, γ-unsaturation and the size of the lactone ring. Once again, the preceding proposed reactions (reduction and oxidation of the double bond and alteration of the proposed lactone group) will be very useful to gather more confirmations about the problem.

The nuclear magnetic resonance spectra and the mass data were greatly helpful in assigning positions and configurations to the different methyl groups in the molecule. The rule of "unsaturated sites" suggested that the molecule is pentacyclic. However, the assertion that the molecule has a triterpenoid skeleton still remains a logical assumption only. The rings could very well be disposed as follows:



This, of course, represents only one of the remaining possibilities. It should be noted that this type of structure is quite uncommon in natural product chemistry but is possible. A dehydrogenation of the molecule would help to firmly establish its skeletal structure.

A thorough literature survey revealed that a very large percentage of the known $C_{30}H_{48}O_3$ compounds were acids. Since the evidence is against the possibility of the present compound being an acid, and since the physical constants of this component were different from those of the remaining known $C_{30}H_{48}O_3$ compounds, the present component was thought to be a new compound.

Much work remains to be done in order to firmly establish a complete structure of this constituent. A series of key chemical reactions should be performed and, of course, the ultimate proof of structure would be the total synthesis of the $C_{30}H_{48}O_3$ constituent isolated from the bark of the madrone tree.

VI. EXPERIMENTAL

All melting points are corrected and were determined on a Monoscop VS (Hans Bock). Microanalyses and C-methyl determinations were carried out by Dr. A. Bernhardt in Mülheim, West Germany. Rotations were measured on a Perkin-Elmer, 141, polarimeter. Some of the infrared spectra were done by Mr. R. N. Swindlehurst on a Perkin-Elmer, 521, spectrophotometer at the University of Alberta, but all other infrared spectra were determined on a Perkin-Elmer, 337, grating infrared spectrophotometer. The ultraviolet curves were recorded on a Unicam, SP 700, spectrophotometer. The optical rotatory dispersion curves were measured by Mr. W. Flyer on a ORD/UV-5 (Japan Spectroscopic Co.) spectrophotometer at the University of Alberta. A few nuclear magnetic resonance spectra were done by Dr. E. Piers on a JEOLCO, C-60-H, and a Varian, A-60, NMR spectrometer at the University of British Columbia, and all the other spectra were determined on a Varian, HA-60-IL, NMR spectrometer. Finally, most of the mass spectra were measured on a Hitachi Perkin-Elmer, RMU-6E, mass spectrometer; a few mass spectra were done by Dr. E. Piers on an AEI-MS9 spectrometer at the University of British Columbia, and by Dr. A. Hogg on an AEI-MS12 spectrometer at the University of Alberta.

(a) Isolation of the $C_{30}H_{48}O_3$ constituent.

Four kilograms of dried dark brown shredded bark were extracted by immersion in 95% ethanol (at room temperature) for two months. A filtration followed by evaporation of the solvent on a rotary evaporator, heating to a maximum of 35°C, yielded a brown slurry and a residual light brown bark. The bark was reextracted in refluxing methanol for 24 hours. The filtration of the methanol extract yielded more brown slurry and the residual bark, which was of a very light brown colour, was stored. The slurries obtained were combined and extracted three times (in separatory funnels) with chloroform using ten times the volume of chloroform for each extraction. The material insoluble in chloroform was evaporated to dryness and yielded 600 g of dark brown powder which was stored. After drying over anhydrous Na_2SO_4, the dark brown chloroform solution was filtered through a column of alumina (Fisher). Some dark material was left on the alumina column and the evaporation of the eluate yielded 720 g of dark brown solid material.

A small volume of methanol was added to the 720 g of dark brown material obtained from the eluate. Then, glacial acetic acid (500 ml) was added to the solution, while stirring, followed by five portions (500 ml) of distilled water. The solution was stirred for six hours and no sign of exothermic reaction was detected at any stage. A green solid suspended in a red orange solution was obtained. Filtration yielded a red brown liquid (pH 2) and a green powder (component IX). The red brown liquid was stored and the green powder was air dried. Component IX (260 g) was found to melt at 170.0-195.0°C. Qualitative thin layer chromatography on Eastman chromagram sheets (silica gel, #6061; solvent: chloroform : ethyl acetate - 9:1; detector: crystals of iodine) showed that component IX contained at least five different products.

Chromatography of 18.0 g of component IX over 1361 g of silica gel (Baker) was carried out. The length of the adsorbent column was 17 times the diameter of the column. Infrared spectrophotometry was used to follow the chromatogram. Elution yielded the following results:

(i) Petroleum ether fraction:

An oily solid (362 mg) was isolated ($\nu_{max}^{CHCl_3}$ 2900, 1450, 1350 cm^{-1}).

(ii) Petroleum ether-benzene (4:1) fraction:

A yellow oily solid (190 mg) was isolated ($\nu_{max}^{CHCl_3}$ 2900, 1480, 1420, 1270, 870, 825 cm^{-1}).

(iii) Petroleum ether-benzene (1:1) fraction:

A yellow oil (848 mg) was isolated ($\nu_{max}^{CHCl_3}$ 2900, 1740, 1470, 1375, 1268, 1185, 1105, 980, 892 cm^{-1}).

(iv) Petroleum ether-benzene (1:4) fraction:

A yellow oily solid (660 mg) was isolated ($\nu_{max}^{CHCl_3}$ 3400, 2950, 1735, 1480, 1390, 1290, 1070, 910 cm^{-1}).

(v) Benzene fraction:

A yellow, slightly oily solid (2.805 g) was isolated ($\nu_{max}^{CHCl_3}$ 3500, 2950, 1740, 1640, 1470, 1390, 1030, 980, 890 cm^{-1}).

(vi) Benzene-chloroform (9:1) fraction:

A green oil (1.105 g) was isolated ($\nu_{max}^{CHCl_3}$ 3450, 2950, 1735, 1470, 1380, 1265, 1040, 980, 890 cm^{-1}).

(vii) Chloroform fraction:

A greenish solid (slightly oily) (6.230 g) was isolated. Recrystallizations in methanol and three successive sublimations yielded the $C_{30}H_{48}O_3$ constituent [m.p.: 275.0-278.0°C (dec.). Anal. Calcd. for $C_{30}H_{48}O_3$ (456) : C, 78.90; H, 10.59. Found (mol. wt., 456, mass spectrometry): C, 78.46; H, 10.49].

(vii) Methanol fraction:

About 5 g of brown solid was isolated.

(b) Acetylation of the $C_{30}H_{48}O_3$ constituent.

The $C_{30}H_{48}O_3$ constituent (25 mg) was dissolved in 4 ml of pyridine while stirring. Acetic anhydride (2 ml) was added to the solution. No

heat evolution or colour change was detected. The solution was stirred at room temperature for 13 hours. Ice was added to the slightly yellow solution, followed by about 5 ml of methanol. The product was precipitated by addition of cold water. The precipitate was extracted three times with chloroform (volume: 300 ml for each extraction). The chloroform layer (from each extraction) was washed successively with water (3X), 2N cold hydrochloric acid (3X), water (1X), cold saturated Na_2CO_3 solution in water (3X) and water (1X). The combined chloroform extract was dried over anhydrous $MgSO_4$.

Evaporation of the chloroform yielded a slightly yellow crystalline solid (24.5 mg). Two recrystallizations in CH_2Cl_2/Et_2O followed by two successive sublimations yielded white crystals (15 mg) which melted at 269.0-271.0°C (dec.) [Anal. Calcd. for $C_{32}H_{50}O_4$ (498): C, 77.06; H, 10.10. Found (mol. wt., 498, mass spectrometry): C, 76.23; H, 10.30].

(c) Lithium aluminum hydride reduction of the $C_{30}H_{48}O_3$ constituent.

To a stirred mixture of lithium aluminum hydride (0.5 g) in 50 ml of anhydrous tetrahydrofuran was added slowly a solution of the $C_{30}H_{48}O_3$ constituent (15.6 mg) in 20 ml of anhydrous tetrahydrofuran. The resulting mixture was refluxed for 4 hours, and then cooled to 0°C. After the excess lithium aluminum hydride had been destroyed by dropwise addition of 10 ml of ethyl acetate, ice-cold water (150 ml) was added.

The reaction mixture was extracted three times with chloroform (volume: 300 ml for each extraction). The chloroform layer (from each extraction) was washed with water (3X) and dried over anhydrous $MgSO_4$.

Evaporation of the chloroform yielded 20 mg of slightly yellow crystals. Two successive sublimations yielded few white crystals [m.p., 237.0-240.0°C. Infrared data of the crude material: ν_{max}^{KBr} 3380, 3085, 2950, 2865, 1685 (very small), 1640, 1450, 1370, 1305, 1190, 1108, 1030, 982, 880 cm^{-1}. M.W.: (double focus mass spectrometry) m/e = 442.3812 (calcd. $C_{30}H_{50}O_2$: 442.3811)].

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