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I. ISOLATION, IDENTIFICATION, AND STRUCTURE DETERMINATION OF COMPOUNDS ISOLATED FROM THE GORGONIANS, PTEROGORGIA ANCEPS AND PTEROGORGIA GUADALUPENSIS. II. INVESTIGATION OF A NOVEL METHOD FOR THE SYNTHESIS OF BUTYROLACTONES. III. INVESTIGATION OF THE THERMAL DECOMPOSITION OF 1, 1, 3, 3-TETRAOXO-2, 2-DIPHENYL-1, 3-DITHIANE.

The University of Oklahoma, Ph.D., 1977

THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

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A DISSERTATION

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Dedication

To Phyllis, Teddy, and Andy

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INTRODUCTION

The occurrence of sesquiterpene and diterpene hydrocarbons, diterpene lactones, and prostaglandins in a group of sessile tropical reef invertebrates known as gorgonians (Class Anthozoa, Subclass Alcyonaria, Order Gorgonacea)[1] has been reported by many investigators[2-13]. The gorgonians, Pterogorgia anceps Pallas[1] and Pterogorgia guadalupensis Duchassaing and Michelin[1], appear to have an insignificant hydrocarbon content but are rich in a group of crystalline, nonterpenoid lactones. The most abundant of these lactones, ancepsenolide (1) Scheme 2, has been found to crystallize from the hot hexane extracts of Pt. anceps[15] and Pt. guadalupensis. The structure of lactone 1 has been been established by degradation and total synthesis. The work reported here involves a re-examination of the hexane extracts of Pt. anceps and examination of the hexane extracts of Pt. guadalupensis and Pt. citrina Esper[1].

A series of three hot hexane extractions were done using a continuous percolator-extractor[16]. Ancepsenolide (1) was found in the first extract (18 hours) of both Pt. anceps and Pt. guadalupensis. A second lactone (2) was found in the second extract (96 hours) of Pt. anceps. Nothing significant was found in the second extract (48 hours) of Pt guadalupensis or the third extract (96 hours) of Pt. anceps. The third extract (96 hours) of Pt. guadalupensis, however, contained a third lactone (10). All three lactones above precipitated from the cooled hexane extracts. No similar precipitates were found in the extracts of Pt. citrina (kindly provided by Dr. A. J. Weinheimer). Thin-layer chromatography of these extracts compared to pure samples of lactones 1,2, and 10 indicated the absence of these lactones in Pt. citrina. The relative distribution of these lactones in the genus Pterogorgia as indicated by the results of the work reported here is summarized in Table 1. The elucidation of structures for lactones 2 and 10 is reported in this work.

Sterols of the gorgonians, Pt. anceps and Pt. citrina, have been previously examined[18,19]. This work includes an examination of the sterols of Pt. anceps and Pt. guadalupensis in an attempt to affirm the identity of the sterols present.

In each of the first hexane extracts of Pt. anceps and Pt. guadalupensis a quantity of lipids other than sterols was noted. However, an anomalous behavior was noted in a single colony of Pt. guadalupensis where a very large quantity

of fatty esters was obtained. This mixture of fatty esters was examined to determine its composition.

The total extracts of certain gorgonians have been shown to possess antimicrobial activity[4,14]. The crude hexane extract of Pt. anceps exhibited mild antibiotic activity against the test organism Staphylococcus aureus, and the crude extracts of Pt. guadalupensis exhibited mild antibiotic activity against the test organism Candida albicans. Screening of lactones 1 and 2 from the hexane extracts of Pt. anceps indicated that neither lactone exhibited antibiotic activity against four common test organisms (Eschericia coli, Candida albicans, Staphylococcus aureus, and Mycobacterium smegmatis). Lactones 1 and 10 from Pt. guadalupensis were subjected to similar screening with 1 showing no activity and 10 showing mild antibiotic activity against the test organisms Staphylococcus aureus and Mycobacterium smegmatis.

Variation in the optical rotation of samples of ancepsenolide (1) isolated from different batches of dried animal has been noted[2,15]. It has been observed that a sample of lactone 1 isolated from a single colony of Pt. anceps exhibited a rotation of $+13.2^{\circ}$ [2] while 1 from other extractions gave small negative and positive rotations[15]. In the work reported here an examination of the optical totations of lactone 1 isolated from single colonies of both Pt. anceps and Pt. guadalupensis has been made in an attempt

to determine the correct value for the rotation of 1. All the samples examined appeared to be homogeneous as judged by thin layer chromatography. Mixture melting points and infrared, ultraviolet, and proton magnetic resonance (pmr) spectral comparisons indicated the identity of the samples.

According to Bayer[1] the distributions of the gorgonians studied here are quite similar. Pt. citrina has been found in Bermuda, southern Florida, and the Keys to Curacao. Pt. Anceps and Pt. guadalupensis inhabit a slightly lower zone with Pt. anceps being found from southern Florida to Curacao and Pt. guadalupensis being found from the Florida Keys to Curacao. Specimens used in this report were collected in Bimini, Bahamas (Pt. anceps); along the outside of Boca Chita Key, Miami, Florida (Pt. anceps); off Soldier's Key, Miami, Florida (Pt. citrina, provided by Dr. R. E. Middlebrook); and near Port Royal, Jamaica (Pt. guadalupensis).

RESULTS AND DISCUSSION

Lactones from the Genus Pterogorgia

The gorgonians Pt. anceps Pallas and Pt. guadalupensis Duchassaing and Michelin were subject to sequences of extractions with solvents of increasing polarity which effectively removed the organic material from the coarsely ground gorgonians. The procedure included successive extractions with hexane, benzene, and methanol. Ancepsenolide (1) Scheme 2 was obtained in the first of three hexane extractions. Purification was accomplished by chromatography over silicic acid and recrystallization from a chloroform-hexane mixture. The yield of 1 was approximately 0.80% of the dry weight of Pt. anceps and 3.1% of the dry weight of Pt. guadalupensis (Table 1).

Because of the reported variations in the optical rotation of lactone 1[2,15] a single colony of Pt. anceps was extracted, and the ancepsenolide (1) was purified as above. The lactone 1 obtained exhibited a rotation of $+12.03^{0}$ (mp 91.2-92.0° C, Lit.[15] 91.5-92.0° C). When a single colony of Pt. guadalupensis was extracted as above and the lactone 1 isolated and purified, a rotation of -47.9^{0} was observed (mp 90.5-92.0° C). Since there are two chiral

Table 1

Lactones from the Genus Pterogorgia

	Pt. anceps (Bimini, Bahamas)	Pt. guadalupensis (Port Royal, Jamaica)	Pt. citrina (Soldier's Key, Miami, Florida)
Compound 1	0.80%*	3.1%	None
Compound 2	0.09%	None	None
Compound 10	None	1.0%	None

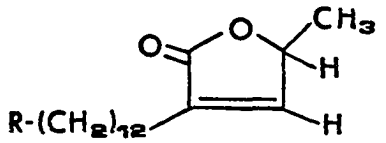
*Approximate percent yield based on the dry weight of the animal.

centers in 1 it seems probable that the samples isolated from both Pt. anceps and Pt. guadalupensis were mixtures of diasteromers of different compositions rather than pure enantiomers. Various extractions of Pt. anceps have been reported to give 1 with small rotations both positive and negative[15] and +13.2°[2]. From the limited data available it seems likely that the composition of the mixtures of diastereomers varies from one colony to another. The value for the rotation of pure enantiomers of 1 remains to be determined.

The second hexane extraction of Pt. anceps (several colonies combined) yielded hydroxyancepsenolide (2) in nearly pure form. This compound composed approximately 0.09% of the dry weight of the animals (Table 1). Chromatography over neutral silicic acid and recrystallization from isopropyl alcohol gave a white solid with a melting point of 122.5-123.7° C, $[\alpha]_D^{24}$+3.4°. Combustion data and mass spectral analysis (m/e 380) established the molecular formula as $C_{22}H_{36}O_5$.

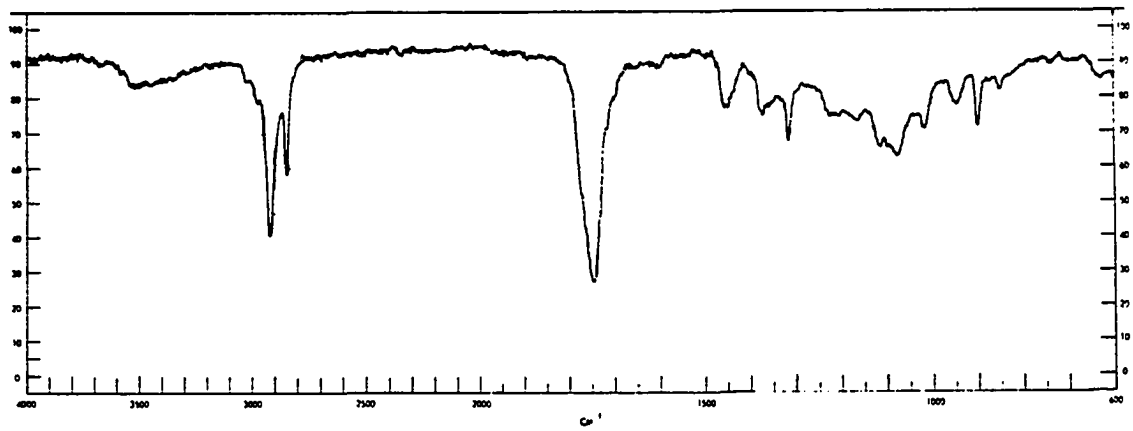
Initial examination of the spectral data (Figure 1) indicated several similarities to those of ancepsenolide (1). The ultraviolet spectrum (95% ethanol) od 2 exhibited an absorption at 209 nm with an extinction coefficient (15,800), approximately one-half that reported for lactone 1 (28,000)[15].

The infrared spectrum (KBr) exhibited a band at 1720 cm^{-1} consistent with an α, β-unsaturated γ-lactone. Bands were also observed at 3600 and 1760 cm^{-1}. When the infrared spectrum of 2 was obtained using chloroform as solvent, the carbonyl absorptions appeared as one broad intense band at 1750 cm^{-1} (1730-1780 cm^{-1} at one-half peak intensity). The proton magnetic resonance (pmr) spectrum (chloroform-d_1) of 2 exhibited one proton multiplets at δ 7.0 (J = 1.3 and 1.5 Hz) and 5.0 (J = 1.5 and 7 Hz) and a three proton doublet at 1.4 ppm (J = 7 Hz) identical with those occurring in the spectrum of ancepsenolide (1)[15]. A strong, sharp absorption at δ 1.28 ppm in the pmr spectrum and a long series of peaks in the mass spectrum of 2 differing by 14 mass units indicated the presence of a long methylene chain in hydroxyancepsenolide (2). The multiplet observed at δ 2.28 ppm corresponding to two protons was also consistent with the absorption reported for the allylic methylene groups of lactone 1[15]. These data with their similarities to data from lactone 1 allowed the partial structure 2a to be proposed for hydroxyancepsenolide. The number of carbons in the methylene chain is suggested by analogy to lactone 1,

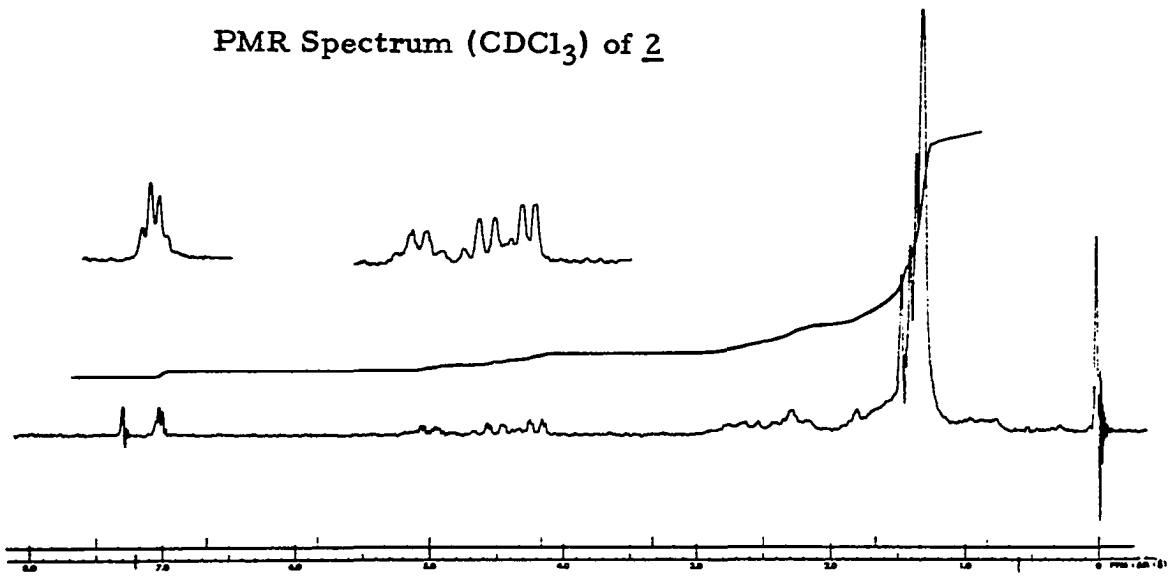


2a

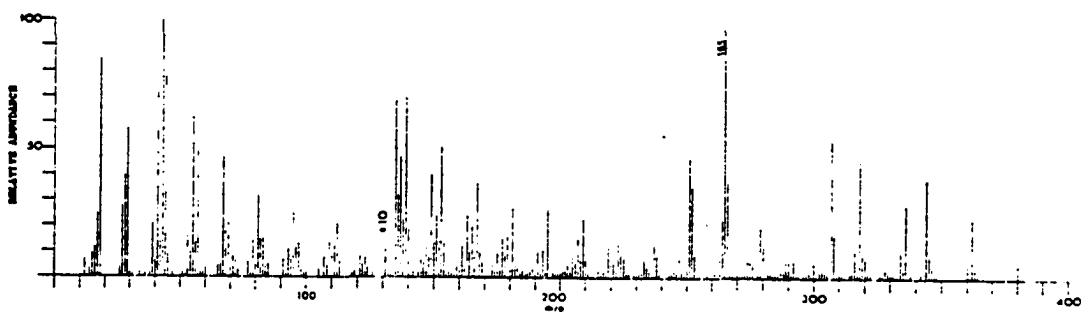
Figure 1
Spectra of Hydroxyancepsenolide (2)
IR Spectrum ($CHCl_3$) of 2



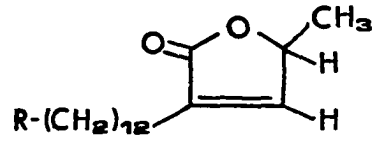
PMR Spectrum ($CDCl_3$) of 2



Mass Spectrum of 2



integration of the pmr spectral band a δ 1.28 ppm, and mass spectral data.



2a

The presence of an alcohol hydroxyl group was suggested by the weak absorption at 3600 cm^{-1} in the infrared spectrum of 2. Further evidence was found in the difficulty experienced in detecting the parent peak at m/e 380 in the mass spectrum. Special care in scanning the m/e 380 region was necessary to observe a very small peak. A large peak was observed at m/e 362 corresponding to the facile loss of water from the parent ion. The pmr spectrum of 2 also gave evidence for the possibility of a hydroxyl group. No absorption was readily observed for the hydroxyl proton. However, when the lactone 2 was treated with deuterium oxide, the broad absorption at δ 2.45-3.0 ppm was decreased in area by an amount corresponding to one proton.

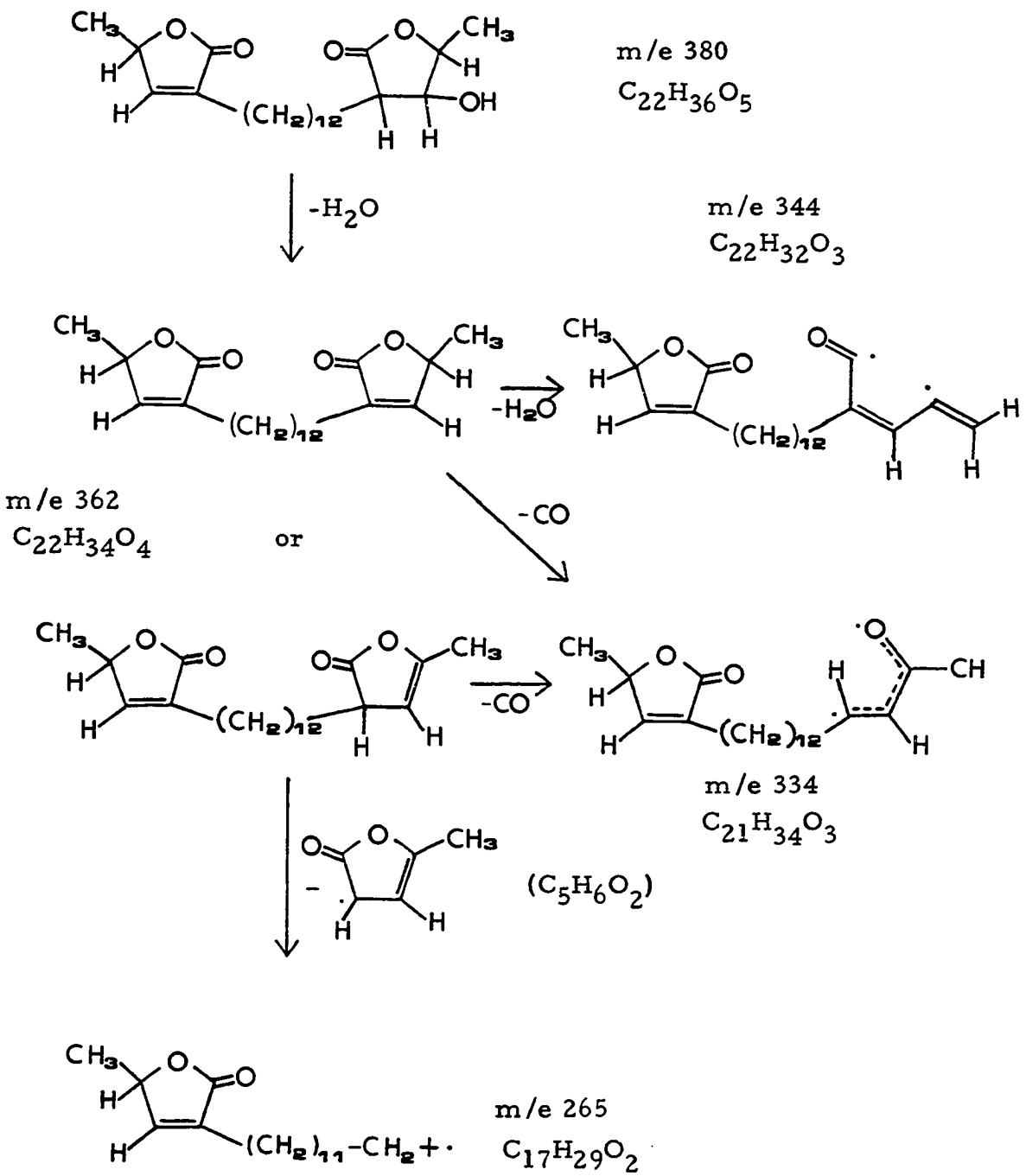
The carbonyl abosorption at 1760 cm^{-1} in the infrared spectrum (KBr) of 2 suggested the possibility of a saturated γ-lactone. Details of this lactone were inferred by the remainder of the pmr spectrum of 2. A doubled quartet was

observed at δ4.5 ppm (J = 1 and 6 Hz) corresponding to one proton, and a doubled doublet was observed at δ 4.2 ppm (J = 6 and 1 Hz) corresponding to one proton. The chemical shifts of these bands were consistent with protons on carbons attached to oxygen. The two proton multiplet at δ 2.45-3.0 ppm had one unassigned proton. The chemical shift was consistent with a proton alpha to a carbonyl group. The last band observed in the pmr spectrum was a three proton doublet at δ1.35 ppm (J = 6 Hz) consistent with a methyl group attached to a carbon bearing one proton. These data suggested that the partial structure 2a might be expanded to structure 2b, Scheme 2.

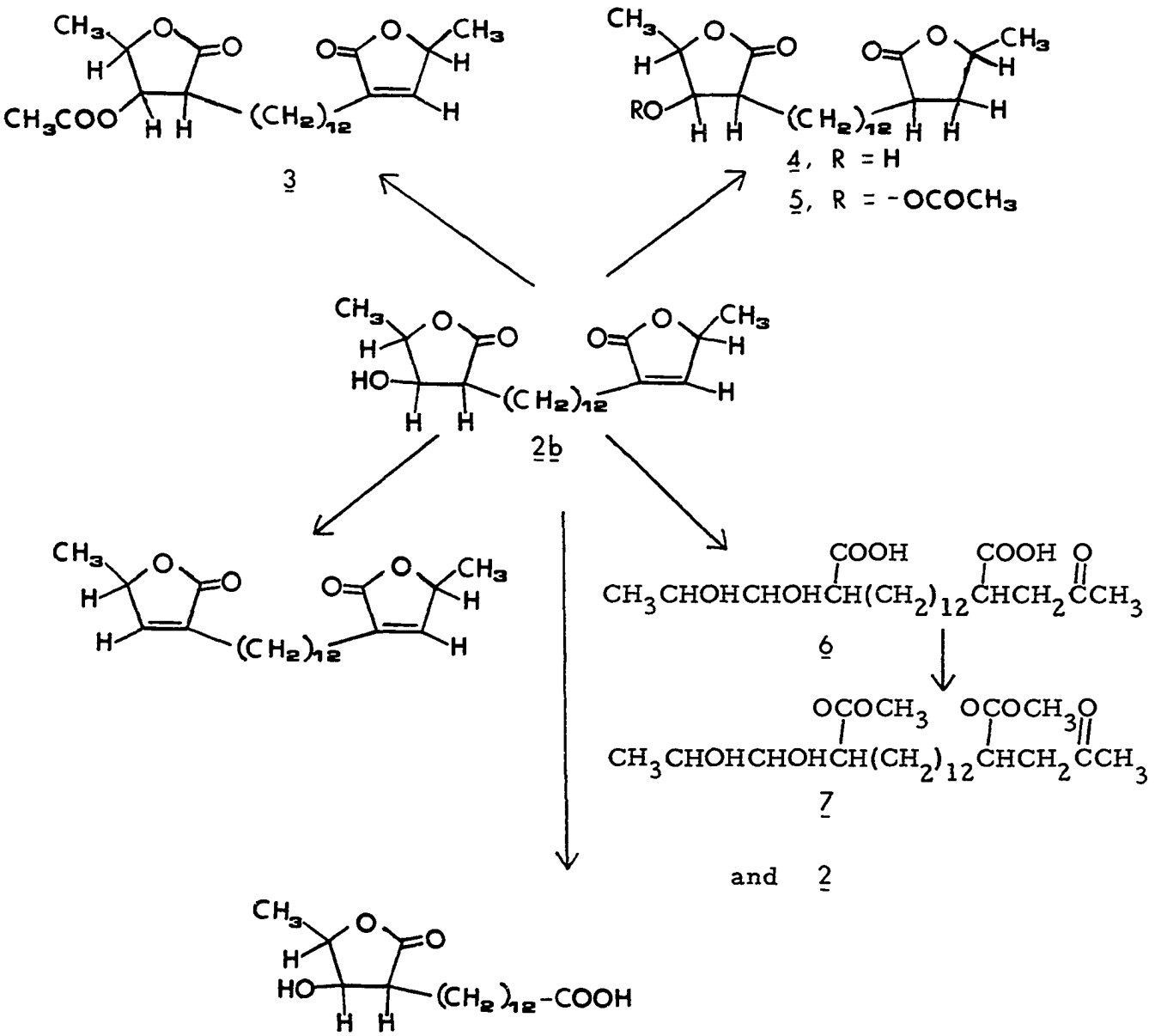
The one proton doubled quartet observed at δ4.5 ppm was consistent with the gamma proton of the saturated lactone. It was shown to be coupled with the methyl group (δ1.35 ppm, J = 6 Hz) and with the beta proton of the lactone (δ4.2 ppm, J = 1Hz). The one proton doubled doublet observed at 4.2 ppm was consistent with the beta proton of lactone which was coupled with the gamma proton (J = 1 Hz) and the alpha proton (δ 2.45-3.0 ppm, J = 6 Hz). Analogy to the structure of lactone 1 again supported the expanded structure 2b.

The mass spectral data (Figure 1) also supported the assignment of structure 2b to hydroxyancepsenolide. The small parent ion peak (m/e 380) with a comparatively large peak

Scheme 1


m/e 380
$C_{22}H_{36}O_5$
$-H_2O$
m/e 344
$C_{22}H_{32}O_3$
$-H_2O$
m/e 362
$C_{22}H_{34}O_4$
or
$-CO$
$-CO$
m/e 334
$C_{21}H_{34}O_3$
$(C_5H_6O_2)$
m/e 265
$C_{17}H_{29}O_2$

Scheme 2

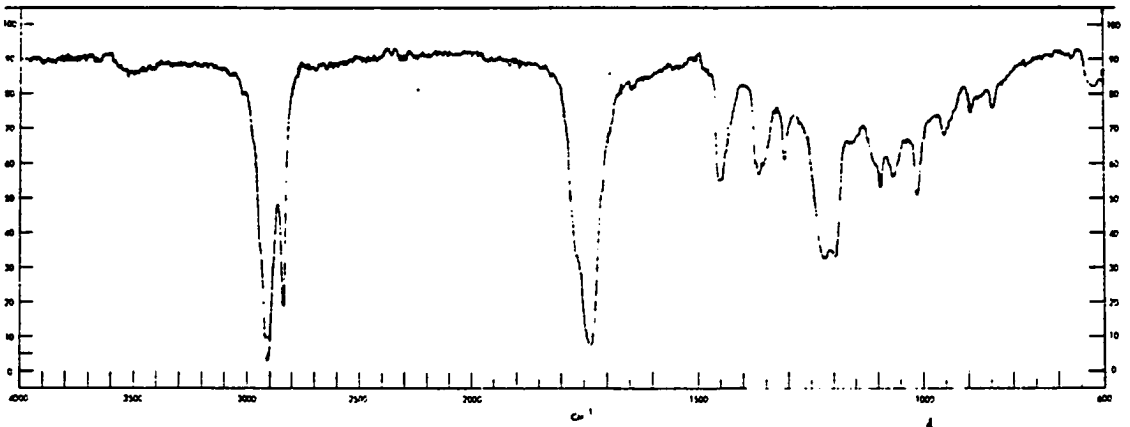


corresponding to the loss of water (m/e 362) was mentioned earlier in support of the presence of an alcohol function. Also the series of peaks differing by 14 mass units has been mentioned in support of the long methylene chain. In addition peaks corresponding to those indicated in Scheme 1 have been observed and appear to be quite consistent with the proposed structure 2b.

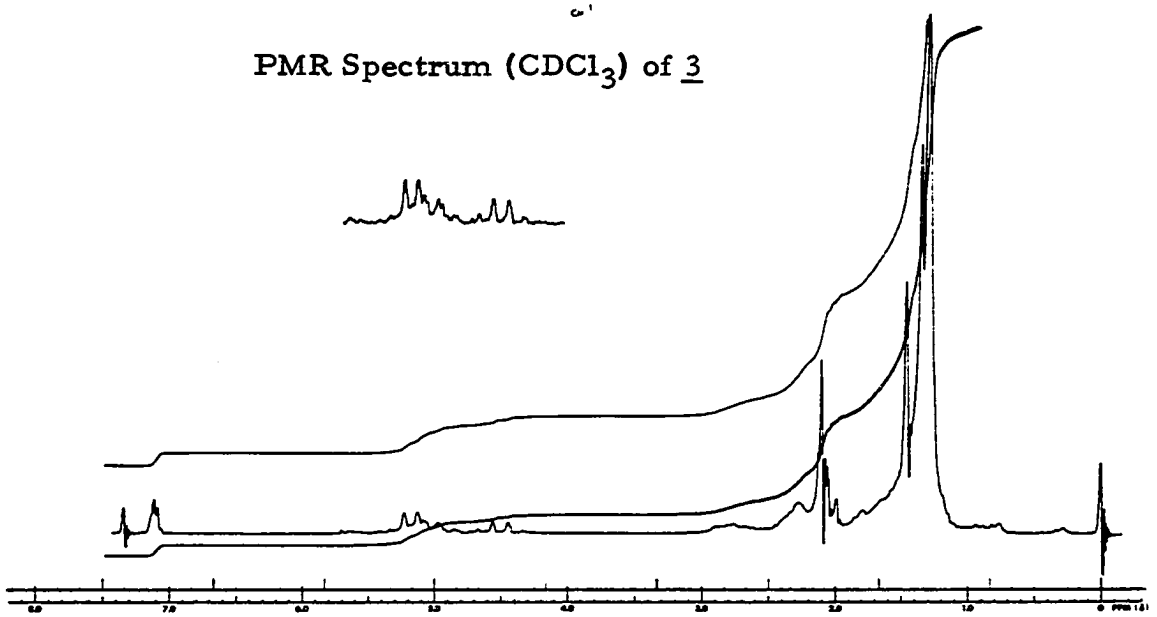
Examination of 2b suggested the possibility of several chemical reactions and derivatives which could support the structural assignments. These reactions with their proposed products are outlined in Scheme 2.

Treatment of lactone 2 with acetic anhydride in pyridine gave the monoacetate 3, mp 68.3-70.3°. Combustion data indicated the molecular formula $C_{24}H_{38}O_6$. Formation of this monoacetate confirmed the presence of the hydroxyl group. It was found that the acetate 3 had a much greater solubility in the common spectral solvents (chloroform-d_1, carbon tetrachloride, and benzene) than the parent compound 2. Examination of the spectral data (Figure 2) derived from the monoacetate 3 afforded further insight into the matter of structural assignments. The infrared spectrum of 3 exhibited a broad, intense absorption centered between 1740 and 1765 cm^{-1} consistent with the lactone carbonyls and a band at 1735 cm^{-1} for the acetate carbonyl. The weak absorption at 3600 cm^{-1} observed in the infrared spectrum of 2 was absent in the

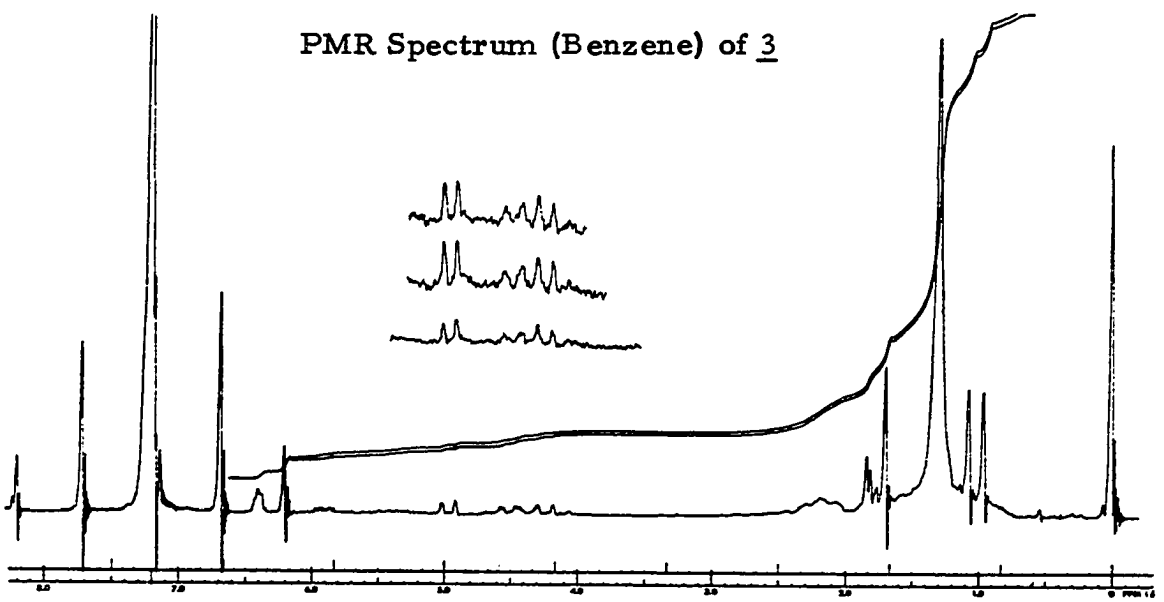
Figure 2
Spectra of Hydroxyancepsenolide Acetate (3)
IR Spectrum ($CHCl_3$) of 3



PMR Spectrum ($CDCl_3$) of 3



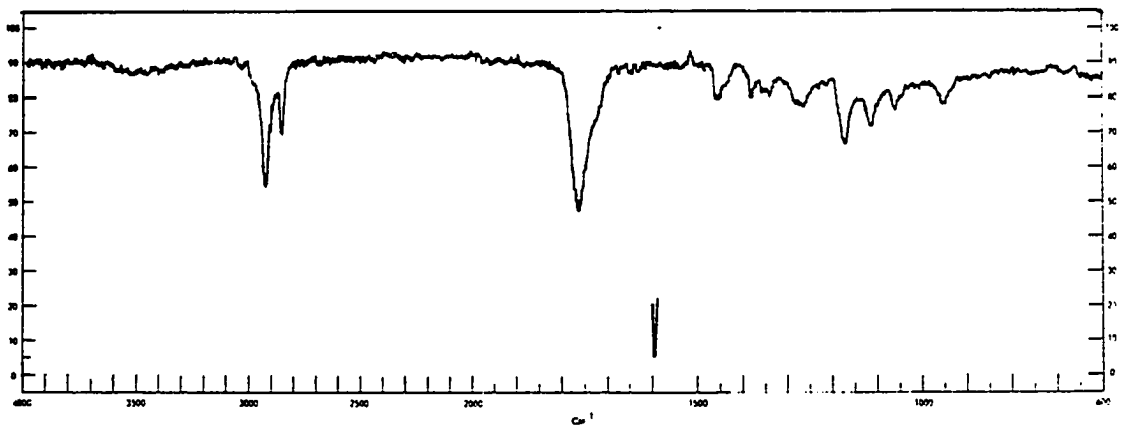
PMR Spectrum (Benzene) of 3



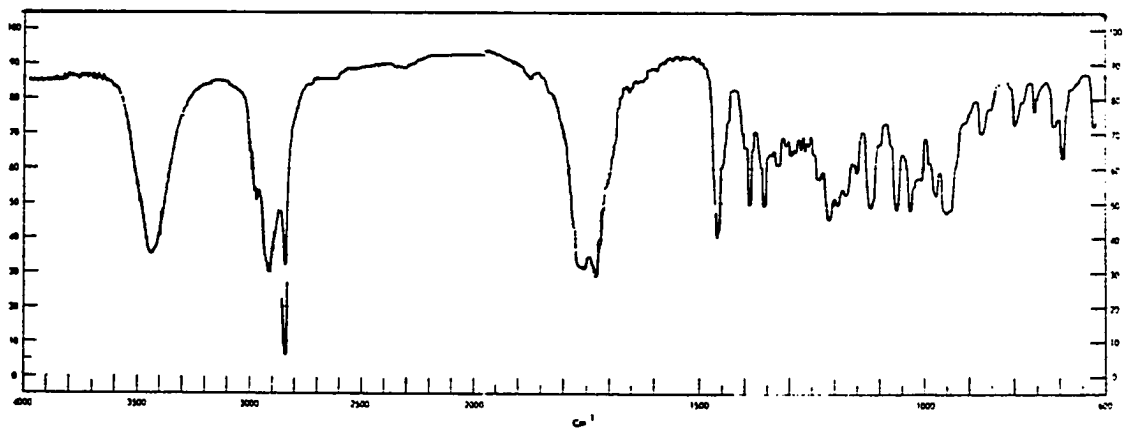
corresponding spectrum of 3. The pmr spectrum (chloroform-d_1) of 3 exhibited a three proton singlet at δ 2.1 ppm corresponding to an acetate methyl group. The region at δ 2.45-3.0 ppm integrated for one less proton than did the same region in the spectrum of 2. The secondary nature of the alcohol in 2b was inferred by a shift in the pmr spectrum of the one proton band (doubled doublet) centered at δ 4.2 in hydroxyancepsenolide (2) to δ 5.15 ppm in the corresponding monoacetate 3. The two methyl doublets found in the pmr spectrum (chloroform-d_1) of 3 at δ 1.4 and 1.32 ppm partially overlapping the large methylene absorption (δ 1.28 ppm) were shifted away from the methylene signal (δ 1.29 ppm) when benzene was used as the solvent. In benzene these signals exactly overlapped giving a six proton doublet at δ 1.02 ppm.

Hydrogenation of 2 in ethyl acetate using platinum (IV) oxide as a catalyst resulted in the uptake of slightly more than one mole equivalent of hydrogen and gave as a product a mixture of diastereomers (4) which melted over a range 119.3-133.0°. No separation of this mixture of diastereomers could be detected by thin layer chromatography, nor could the mixture be separated by fractional crystallization. Combustion data indicated the molecular formula $C_{22}H_{38}O_5$. The infrared spectrum of 4 (Figure 3) exhibited an intense absorption at 1765 cm^{-1} for the carbonyl groups of the satured lactones and a weaker absorption at 3500 cm^{-1} for

Figure 3
Spectra of Dihydrohydroxyancepsenolide (4)
IR Spectrum ($CHCl_3$) of 4



IR Spectrum (KBr) of 4



PMR Spectrum ($CDCl_3$) of 4

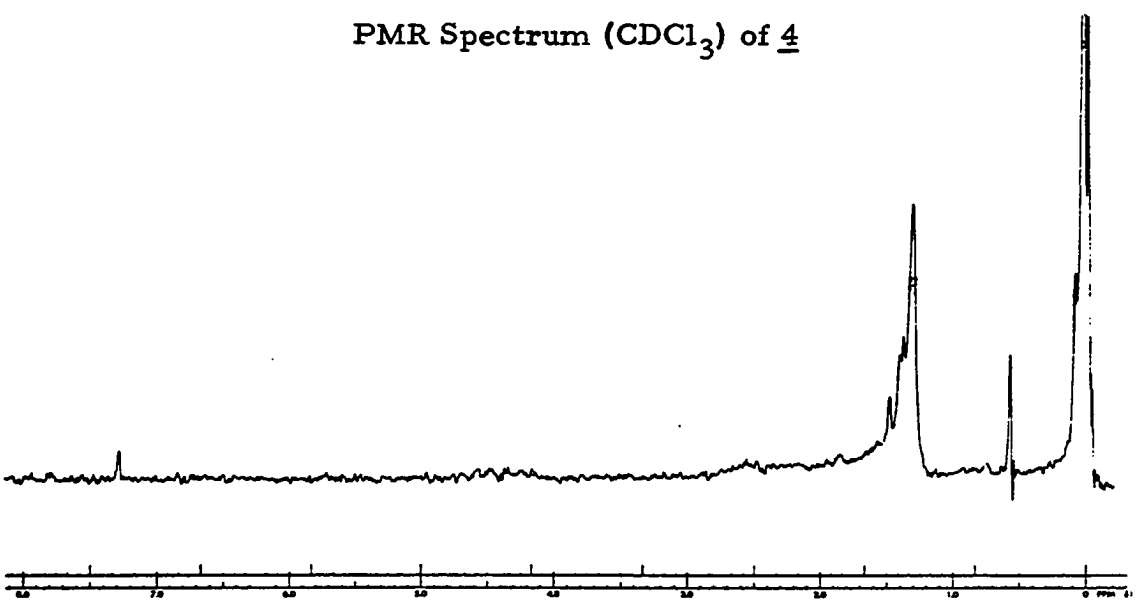
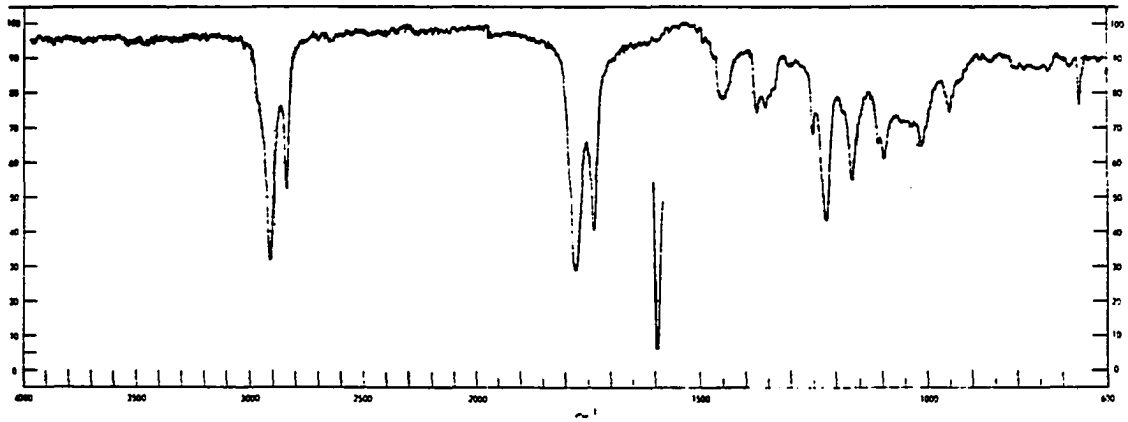
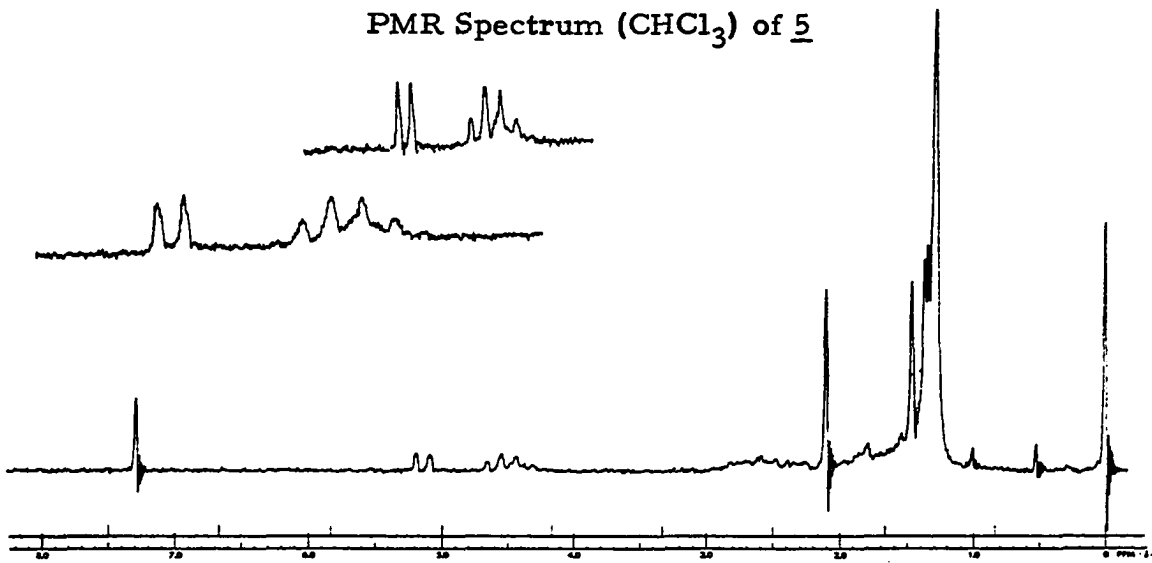


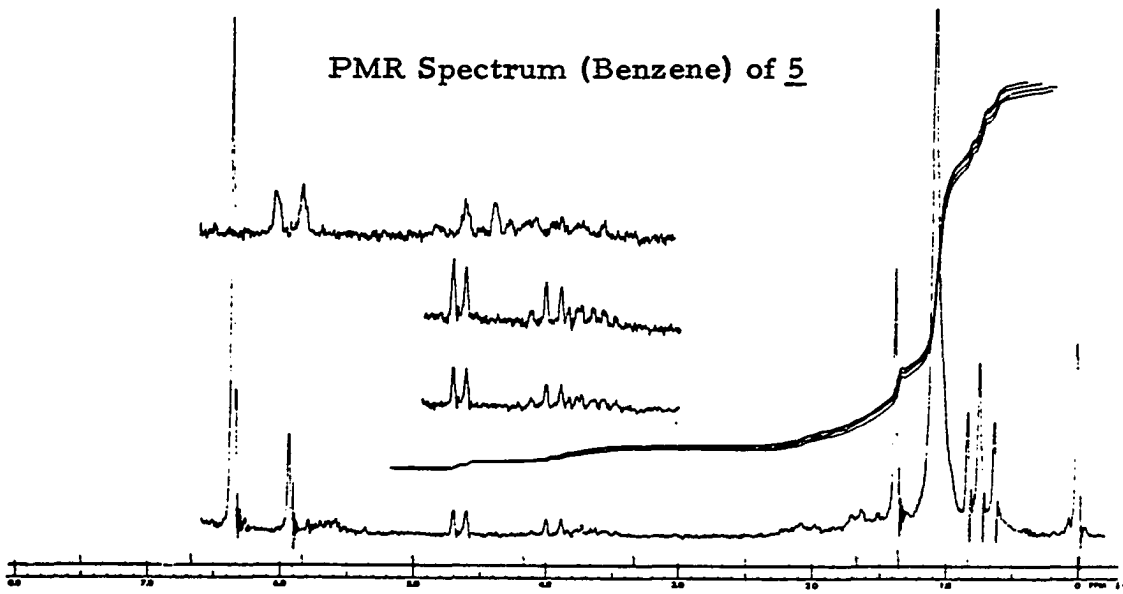
Figure 4
Spectra of Dihydrohydroxyanceps enolide Acetate (5)
IR Spectrum ($CHCl_3$) of 5



PMR Spectrum ($CHCl_3$) of 5



PMR Spectrum (Benzene) of 5



the hydroxyl group. In the pmr spectrum (chloroform-d_1) (Figure 3) of 4 the signals for the protons of the lactone already saturated in 2 were essentially unchanged compared to the spectrum of 2. The one proton signal at δ 7.0 ppm in the spectrum of 2 assigned to the vinyl hydrogen of the unsaturated lactone was absent in the spectrum of 4 while a complex absorption envelope extending from δ 4.1 to 4.9 ppm was observed which was attributed to a combination of the absorptions due to the three protons attached to carbons bearing oxygen atoms.

The relative insolubility of 4 in chloroform and benzene as well as other common solvents caused some difficulty in obtaining good pmr spectral data. Since the monoacetate 3 was more soluble than the parent lactone 2, it was decided to attempt to convert 4 to its corresponding monoacetate 5. This conversion was accomplished by treatment of 4 with acetic anhydride in pyridine giving 5, mp 71.2-72.5° C. Combustion data indicated the molecular formula $C_{24}H_{40}O_6$. The infrared spectrum of 5 (Figure 4) exhibited absorptions at 1765 for the saturated lactone carbonyls and 1740 cm^{-1} for the acetate group. The pmr spectrum (chloroform-d_1) of 5 (Figure 4) gave a one proton signal at δ 5.15 (doubled doublet) for the beta hydrogen of the acetylated lactone, a two proton multiplet between 4.15 and 4.55 for the gamma hydrogens on each lactone, and a three proton singlet at 2.1 ppm for the acetate methyl group. In deuteriochloroform the

two methyl doublets overlapped the large methylene peak (δ1.28 ppm). However, when the spectrum was obtained in benzene, these signals were shifted upfield giving partially overlapping doublets at δ1.02(J = 7) for the methyl group of the unsubstituted lactone and 0.9 ppm (J = 6) for the methyl group of the acetylated lactone ring.

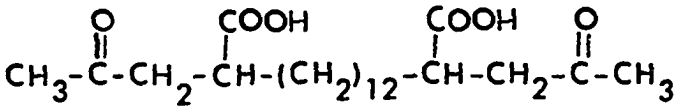
Among the degradation procedures used to elucidate the structure of ancepsenolide (1)[15] were saponification and ozonolysis of 1. In an attempt to further confirm the similarity of 1 and 2 and gain more insight into the structure of 2, these reactions were attempted on hydroxyancepsenolide (2).

Saponification of 2 by treatment with potassium hydroxide in methanol followed by acidification gave an acidic material which melted over a range 63-77° C. Thin layer chromatography showed no traces of remaining starting material. The infrared spectrum of the acidic material exhibited a broad and weak bank at 3350-3600 for acid and alcohol hydroxyl, a band at 1722 for a ketone, and 1695 cm^{-1} for an acid. The pmr spectrum of the acidic material gave a four proton signal at δ7.05 ppm for two carboxylic acid protons and two alcohol hydroxyl protons. This signal was lost when the acid was treated with deuterium oxide. The pmr spectrum also exhibited a complex absorption envelope extending from δ4.1 to 4.8 ppm which was attributed to a combination of absorptions due to the two protons attached to carbons

bearing oxygen atoms. In addition a four proton multiplet was observed at δ 2.45-3.1 for two methylene hydrogens alpha to the ketone and two hydrogens alpha to the two carboxyl groups, a three proton singlet band at 2.18 for the methyl hydrogens alpha to the ketone, and a large band at 1.1-1.85 ppm which integrates for 27 protons consistent with 24 methylene protons and the remaining methyl group. The infrared and pmr spectra of the acidic material were consistent with the proposed structure 6. No further characterization of the acid was attempted.

The acid 6 was treated with methanol and hydrochloric acid under reflux for 24 hours. Thin layer chromatography of the product showed no traces of acid 6, and two spots were observed one of which corresponded to hydroxyancepsenolide (2). On the basis of the following spectral data, structure 7 is proposed for the material giving the second spot in the thin layer chromatograph. The infrared spectrum of the mixture from the esterification attempt exhibited absorptions at 3475 cm^{-1} consistent with hydroxyl groups and overlapping bands at 1780, 1735, and 1720 cm^{-1} consistent with a saturated γ-lactone, an unsaturated γ-lactone, esters, and a ketone. The pmr spectrum showed signals corresponding to those reported earlier for 2 and singlets at δ 3.7 and 2.18 ppm consistent with methoxyl protons and a methyl ketone. No further characterization of this mixture was attempted. The observation of hydroxyancepsenolide (2) as a product of the

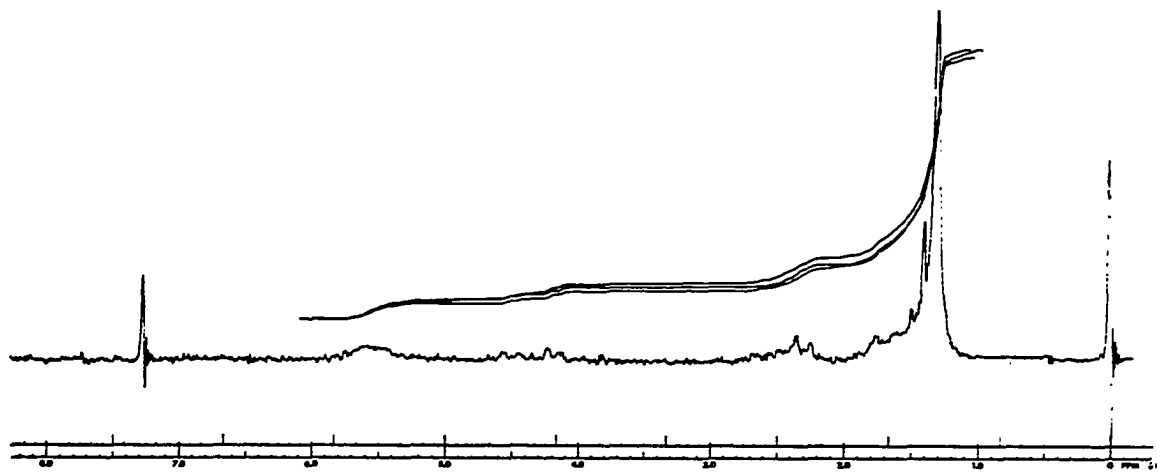
esterification attempt is consistent with the fact that the diketo diacid 8 obtained from saponification of 1 may be reconverted to 1 by heating with an acid catalyst[15].



8

Ozonolysis of 2 in chloroform at room temperature followed by treatment with hydrogen peroxide yielded the acid 9, which after recrystallization from ethyl acetate melted at 94.5-96.0° C. The assignment of structure 9 for the acid was made on the basis of the infrared and pmr spectra and analogy to the ozonolysis product from 1[15]. No further characterization was attempted. The infrared spectrum of 9 exhibited absorptions at 3300-3500, 1770, and 1710 cm^{-1} expected for acid and alcohol hydroxyl groups, a saturated γ-lactone and a carboxylic acid respectively. The pmr spectrum (Figure 5) gave a two proton signal at δ 5.35.9 for the carboxylic and hydroxyl protons, a one proton signal at 4.34.75 for the gamma proton of the lactone, a one proton signal at 4.18 for the beta proton of the lactone, and a three proton multiplet at 2.1-2.8 ppm consistent with two protons alpha to the carboxyl group and one proton alpha to the lactone carbonyl. A large signal also occurred at

Figure 5
PMR Spectrum ($CDCl_3$) of the Ozonolysis Product 9

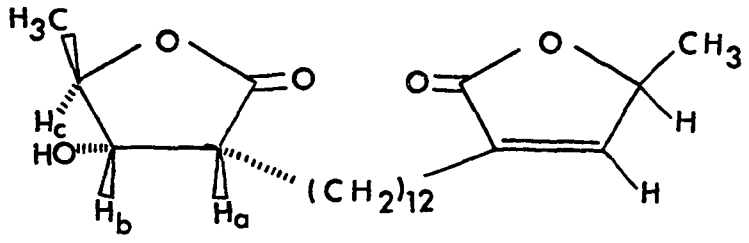


δ1.15-2.0 ppm which integrated for 25 protons and was consistent with 22 methylene protons and the lactone methyl group.

The final evidence for structure 2b for hydroxyancepsenolide was obtained by conversion of lactone 2 to ancepsenolide (1) via treatment with phosphorus oxychloride in pyridine at room temperature. The crude product was chromatographed over silicic acid and recrystallized from chloroform giving 1, mp 92.8-94.3° C. No melting point depression was observed on admixture with authentic ancepsenolide (1). The infrared and pmr spectra of the dehydration product were identical with those of authentic ancepsenolide (1)[15].

The relative stereochemical assignments for the saturated γ-lactone ring of hydroxyancepsenolide (2) are given in structure 2. These assignments were based on pmr coupling constant data. Proton c of the saturated γ-lactone in 2 appeared as broadened quartet (δ 4.5 ppm) in which the coupling to the methyl group was large (J = 6 Hz) and the second splitting attributed to coupling with proton b was small (J = 0.5-1 Hz). The signal assigned to proton b appeared as a doubled doublet (δ 4.2 ppm) in which the small coupling constant (J = 0.5-1 Hz) was consistent with a J_{bc} assignment and the larger coupling constant (J = 6 Hz) must be due to coupling with proton a of the lactone. A trans orientation of protons b and c should impose a dihedral angle of 105-115° between these protons, and this was

consistent with the observation of a very small coupling constant for J_{bc} [17]. A dihedral angle of close to 0° would be expected between protons a and b if they were cis to one another, and this is consistent with the larger coupling constant assigned to J_{ab} [17].



2

As has been mentioned, Pt. guadalupensis was subjected to a sequence of extractions with various solvents. The first hexane extraction afforded lactone 1, a second hexane extraction gave nothing of significance, and a third hexane extraction gave a third lactone, 10, which will be referred to as ancepsenolidic acid. The procedure for determining the structure of 10 (Scheme 3) will now be discussed.

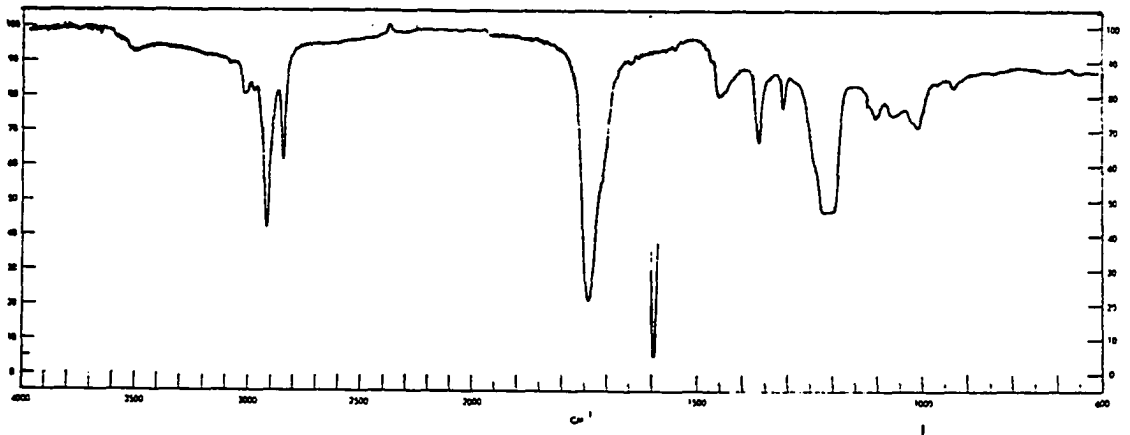
Crude lactone 10 precipitated from the cooled hexane extract in a yield of 0.99% of the dry weight of the animal (Table 1). Chromatography of 10 over silicic acid and recrystallization from aqueous isopropyl alcohol gave a white solid which melted at 81.1-82.9° C, $[\alpha]_D^{24} = -8.3°$.

Table 2

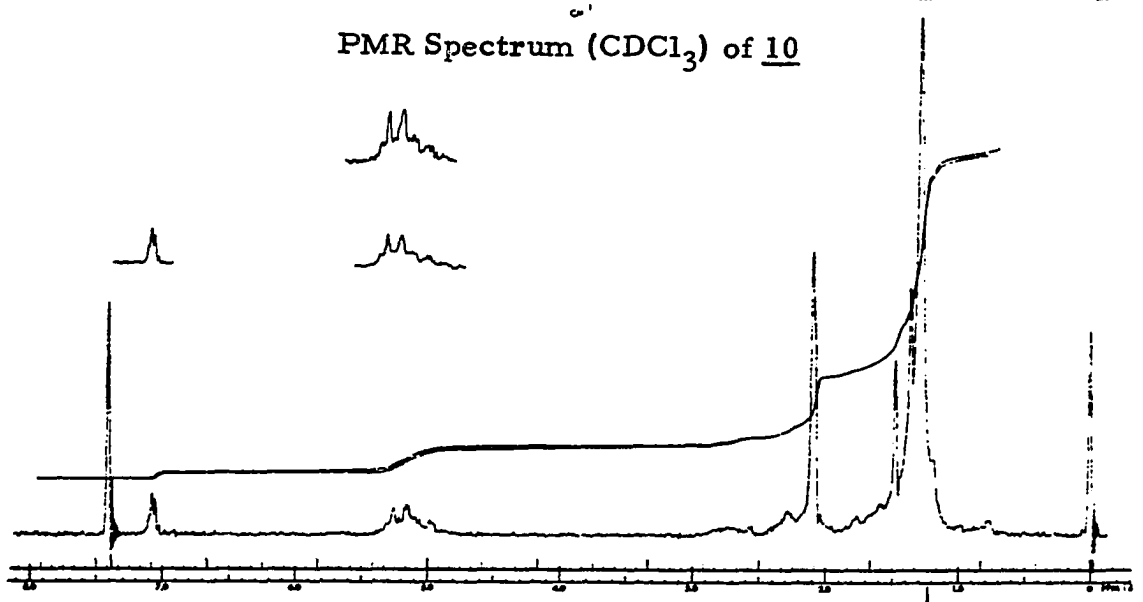
Optical rotations and melting ranges for various samples of ancepsenolidic acid, 10 (Scheme3)

	Melting Range	Optical Rotation
Sample from a single colony		
a) precipitate from first recrystallization after four further recrystallizations	61-65°C	-0.3°
b) material from supernatant of first recrystallization after five further recrystallizations	152-153.5°C	-13.0°
Sample from a single colony		
a) precipitate from first recrystallization after four further recrystallizations	81.1-82.9°C	-8.3°
b) material from supernatant of first recrystallization after no further purification	———	-7.0°
Sample from several colonies mixed		
solid recovered after five recrystallizations	105.2-106.9°C	-2.4°

Figure 6
Spectra of Ancepsenolidic Acid (10)
IR Spectrum ($CHCl_3$) of 10



PMR Spectrum ($CDCl_3$) of 10



PMR Spectrum (DMSO-d_6) of 10

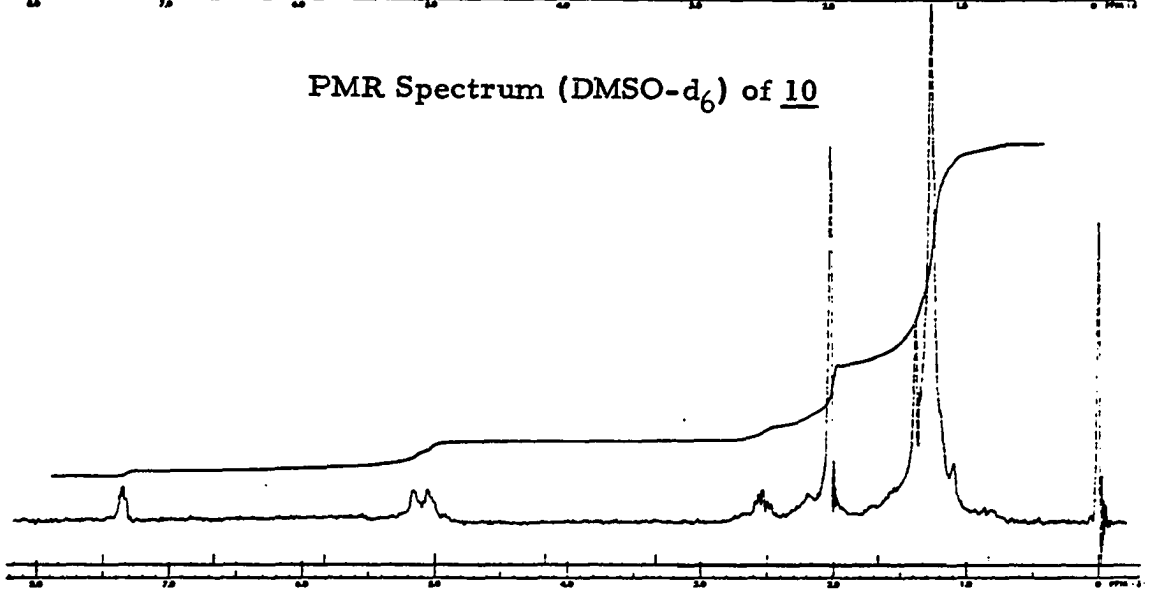
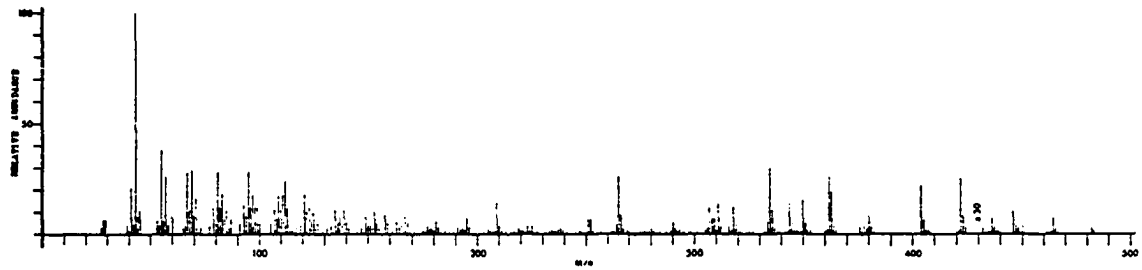
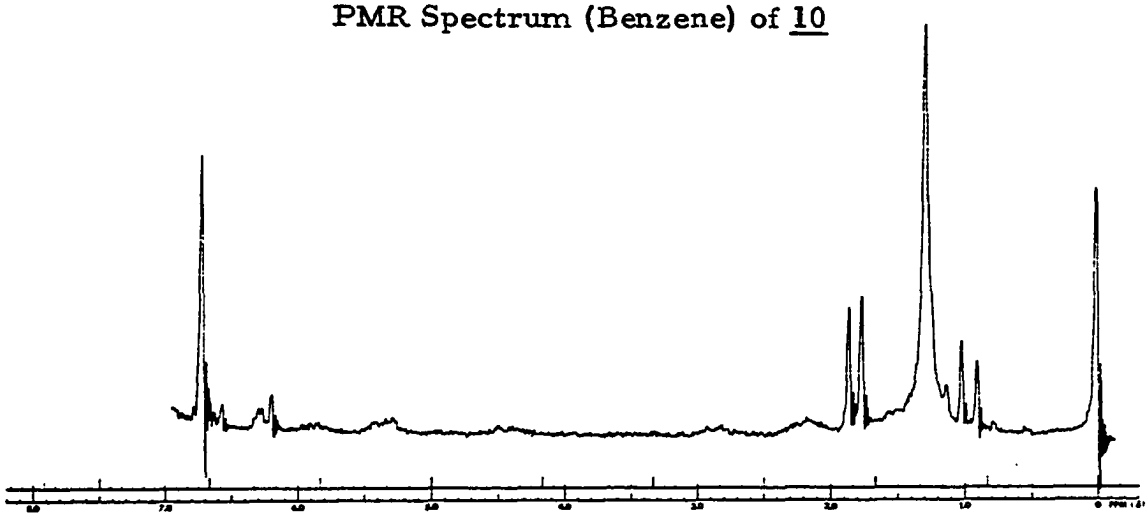


Figure 7
Spectra of Ancepsenolidic Acid (10)
Mass Spectrum of 10



PMR Spectrum (Benzene) of 10



PMR Spectrum (Acetone-d_6) of 10

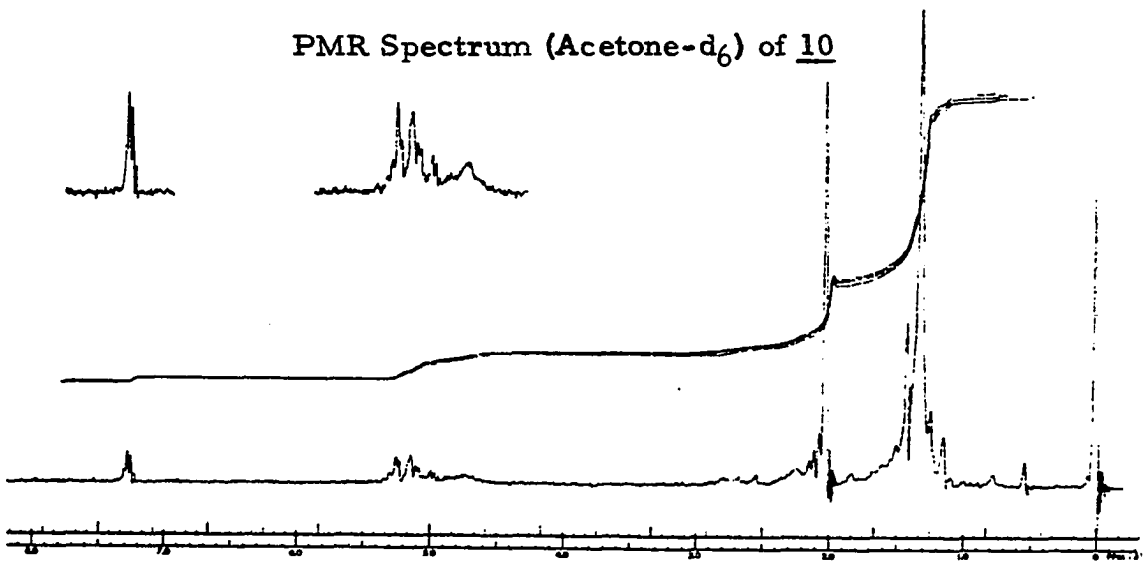
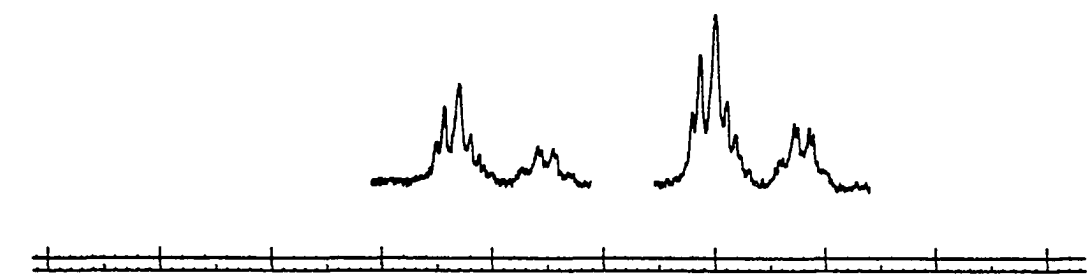
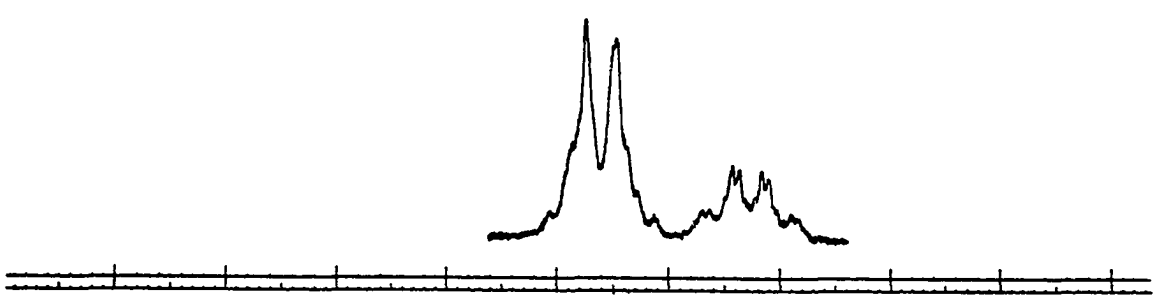


Figure 8
220 MHz PMR Spectrum ($CDCl_3$-acetone-d_6) of 10

Region Between δ 4.0 and 6.0 ppm (Two successive magnification and a third magnification with an expanded sweep)

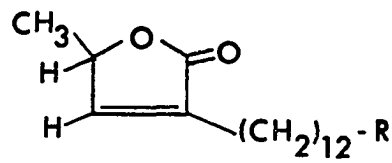




Samples of lactone 10 from different extractions gave a variety of optical rotations and melting point ranges. Table 2 summarizes these data. With four chiral centers being present in the structure proposed for 10, the possibility of a mixture of diastereomers seems probable for 10 as it was in the case of ancepsenolide (1). Some separation of these diastereomers was observed by fractional crystallization as was evidenced by changes in the melting ranges. Data from thin layer chromatography, infrared and pmr spectra, and combustion analysis indicated that all the samples were indeed lactone 10.

Details of the structure of ancepsenolidic acid (10) became evident from examination of spectral data (Figures 6, 7, and 8). Combustion data and mass spectral analysis established the molecular formula as $C_{26}H_{42}O_8$. The ultraviolet spectrum (95% ethanol) indicated similarity between lactones 1, 2, and 10. Ancepsenolidic acid gave a maximum at 204 nm with an extinction coefficient (ϵ= 17,436) which was roughly half that reported for ancepsenolide (1) and similar to that reported earlier for hydroxyancepsenolide (2). The infrared spectrum (chloroform) (Figure6) exhibited a very intense absorption at 1740 (width at half intensity was 1700-1770 cm^{-1}) and a weak absorption at 3500 cm^{-1}. The pmr spectrum (chloroform-d_1)(Figure 6) of 10 exhibted a one proton signal at δ7.0 ppm (J = 1.3 and 5 cps) identical with the vinyl proton absorption occurring in the spectrum of 1.

The region between δ 4.8 and 5.4 ppm, however, contained a complex absorption envelope which integrated for four protons. When the spectrum was run at 220 mHz (chloroform-d_1-acetone-d_6) a one proton double quartet (J = 1.5 and 7 Hz) was well resolved (Figure 8) at δ 5.0 ppm. A three proton doublet signal was also observed at δ 1.4 ppm consistent with a methyl group of a butenolide ring as in 1 and 2. A strong sharp absorption at δ 1.28 ppm in the pmr spectrum and a long series of peaks in the mass spectrum differing by 14 mass units, similar to features found in the spectra of 1 and 2, indicated a long methylene chain of probably 12 carbons. These data led to the proposal of partial structure 10a for ancepsenolidic acid.



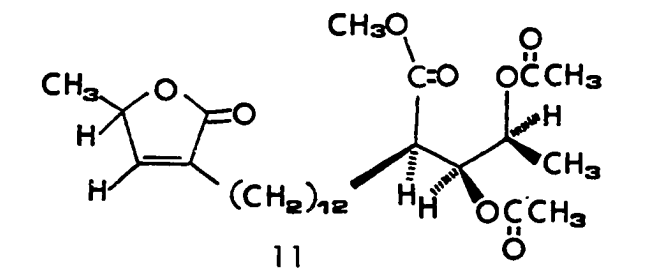
10a

The infrared spectrum of 10 exhibited a weak absorption at 3500 cm^{-1} which could represent an alcohol or a carboxylic acid. No signals were observed in the pmr spectrum in the region normally expected for carboxylic acid protons.

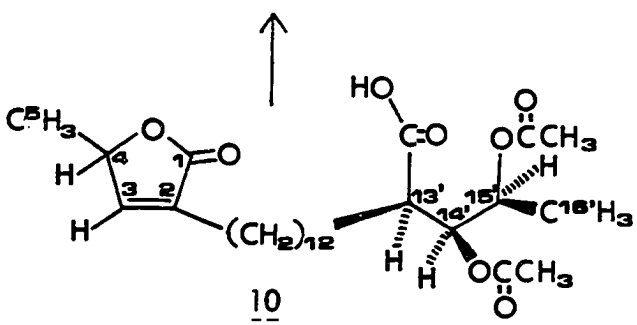
However, when 10 was treated with deuterium oxide the area of the multiplet at δ4.8-5.4 ppm was decreased by an amount corresponding to one proton. A neutralization equivalent verified that 10 contained a free carboxyl group. The rather high field position for the carboxyl proton absorption was assumed to be due, at least in part, to the dilute solutions used for determining the pmr spectrum because of the limited solubility of 10 in deuteriochloroform [20, 21]. Ancepsenolidic acid (10) was also converted to its methyl ester 11 by treatment with diazomethane. Combustion analysis of methyl ancepsenolidate (11) established its molecular formula as $C_{27}H_{44}O_8$. These data established the presence of a free carboxyl group in 10.

Further examination of the pmr spectrum of 10 showed two partially resolved singlets at δ2.08 and 2.06 ppm which integrated for a total of six protons. When benzene was used as the solvent these singlets appeared well resolved at δ1.85 and 1.75 ppm. The presence of two acetate groups was suggested by these singlets and was confirmed by acetyl analysis. The position of the acetate moieties and the carboxylic acid group in 10 was suggested by analogy to the structures of ancepsenolide (1) and hydroxyancepsenolide (2). This allowed structure 10 (without stereochemical details) to be postulated for ancepsenolidic acid. This tentative assignment was supported by the presence of two distinct

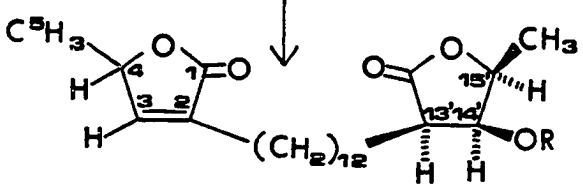
Scheme 3



11

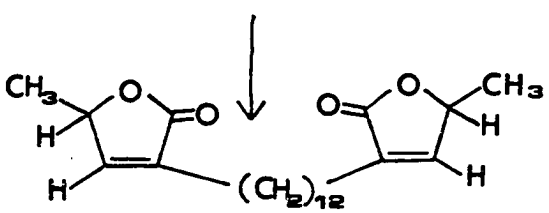


10



12, R=H

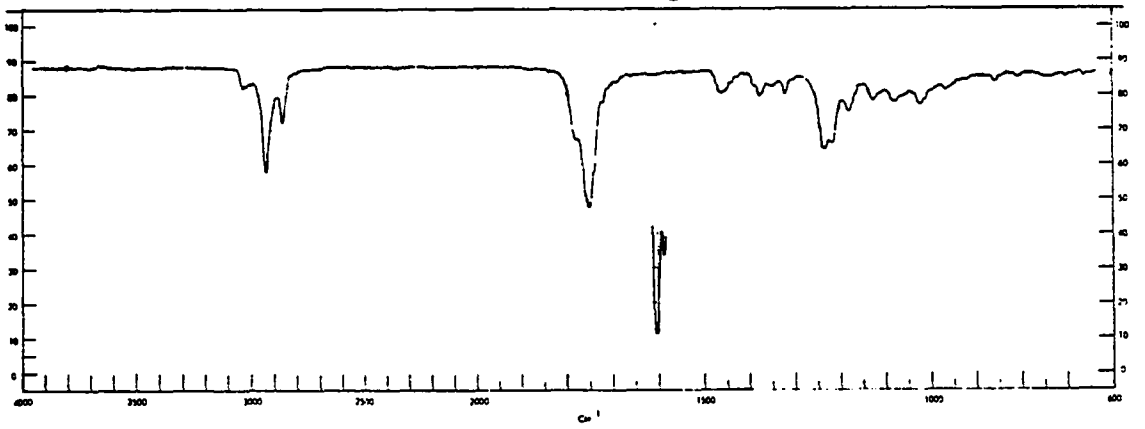
13, R=OOCCH$_3$



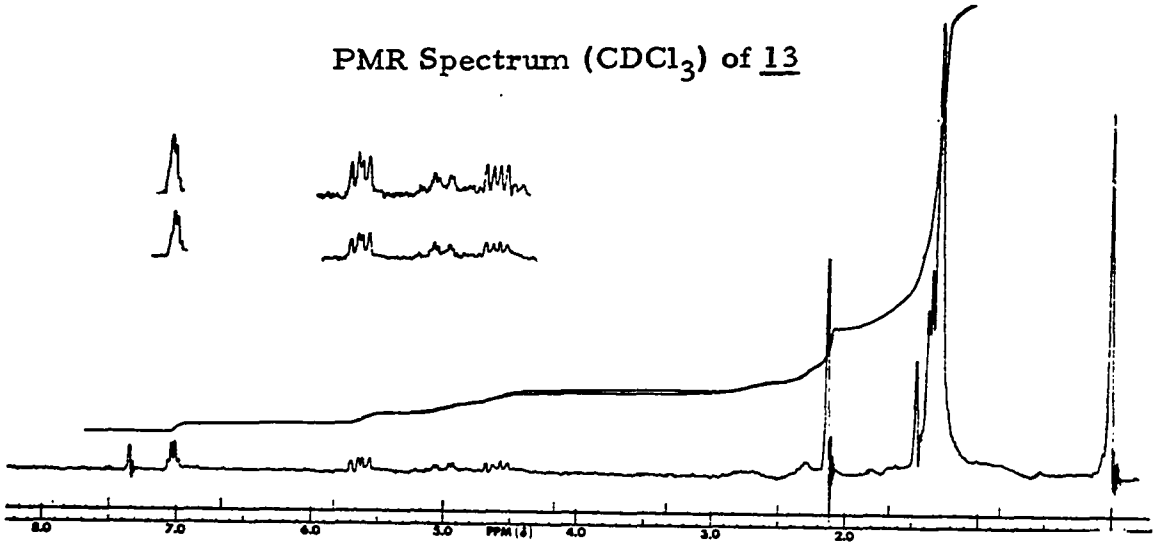
1

Figure 9
Spectra of Acetate 13

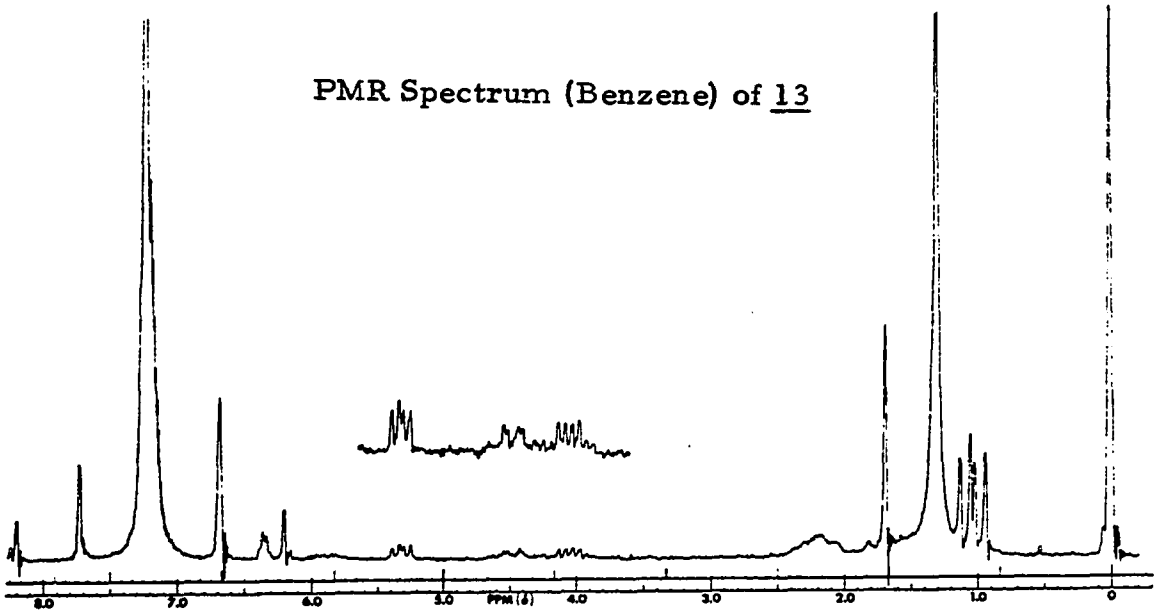
IR Spectrum ($CHCl_3$) of 13



PMR Spectrum ($CDCl_3$) of 13



PMR Spectrum (Benzene) of 13



doublets at δ1.35 (J = 7 Hz) and 1.17 ppm (J = 6 Hz) in the 220 MHz pmr spectrum (chloroform-d_1-acetone-d_6) of 10. These doublets are consistent with the pentenolide methyl group and another methyl group in a very similar environment, i.e., CH_3-CH(OAc)-. Compound 10 was found to give a positive periodate test which indicated the vicinal character of the acetates. The secondary nature of the two acetate moieties was indicated by the pmr spectrum of 10 (chloroform-d_1) which showed a two proton absorption in the δ4.8-5.4 ppm region in addition to the signals due to the gamma proton of the unsaturated lactone and the acid proton.

Confirmation of the structure 10 (without stereochemical details) for ancepsenolidic acid was achieved by conversion of 10 via acidcatalyzed methanolysis to lactone 12 whose spectral properties were quite similar to those of 2, and by dehydration of 12 upon treatment with phosphorus oxychloride in pyridine to give ancepsenolide (1) in good yield (Scheme 3). These conversions established the overall carbon skeleton of 10 and confirmed the assignment of one of the acetate groups to carbon-15' in the hexadecanyl residue of 10 (lactone formation).

The pmr signals of the protons attached to carbons bearing oxygen atoms in both 10 and 12 overlap to give complex multiplets which are not easily interpreted. When 12 was routinely acetylated, the corresponding acetate 13 was obtained. Examination of the pmr spectrum 13 (Figure 9)

Table 3

Lactone Pmr Absorptions and Coupling Constants[a]

	Compound 13			Compound 3		
Proton	δ	J H-14', H-15'	J	δ	J H-14', H-15'	J
H-14'	5.6	3	5(H-14', H-13')	5.15	0.5-1	6(H-14', H-13')
H-15'	4.6	3	6(H-15', -Me)	4.5	0.5-1	6(H-15', -Me
H-4	5.0			5.0		

[a]Measured in chloroform-d_1 at 60 MHz

showed that the absorptions due to protons attached to carbons bearing oxygen were now well resolved and provided confirmation of the presence of three single protons on carbons bearing oxygen in 13 and also in 10 and 12. Both of the acetate groups in 10 must, therefore, be secondary. Since only an endocyclic double bond was formed upon dehydration of 12, the hydroxyl group in 12 and its acetate progenitor in 10 must be located at carbon-14' in the hexadecanyl moiety.

The transesterification of 10 leading to 12 should not affect the carbon-oxygen bonds at carbon-14' or carbon-15'. Therefore, the relative stereochemistry for 10 and 12 could be proposed by comparing the coupling constant data from the acetate 13 with that observed for the hydroxyancepsenolide acetate (3) (Table 3). The resonance signals for protons at carbon-4, carbon-14', and carbon-15' were sufficiently separated in the acetates 13 and 3 to permit a first-order analysis of the coupling constants. Since $J_{H\text{-}15',\ Me}$ in 13 could be determined from the spacing of the methyl doublet (J = 6 Hz), the second coupling of H-15' (J = 3 Hz) must be due to $J_{H\text{-}15',\ H\text{-}14'}$. It followed, therefore, that the 5 Hz splitting in H-14' must be due to $J_{H\text{-}14',\ H\text{-}13'}$. The large value of $J_{H\text{-}14',\ H\text{-}13'}$ is consistent with a small dihedral angle [17] and, therefore, the cis stereochemistry for H-14' and H-13' in 13 just as in 3. The much larger value of $J_{H\text{-}15',\ H\text{-}14'}$ in 13 compared to 3 provided argument for a cis

Table 4

Sterol Distribution in Pt. anceps and Pt. guadalupensis

Sterol	GC Elution Order[a]	m/e[d]	Content in Pt. anceps[b]	Content in Pt. guadalupensis[b]	m. p.[23] observed	m. p. literature
Unidentified Sterol	1	384	7[c]	11[c]	none	
Cholesterol	2	386	55	38	150°C	149°C[30]
24-α-Methyl-7-dehydrocholesterol or Brassicasterol	3	398	12	16	151°C	153°C[30] or 148°C[30]
22,23-dihydrobrassicasterol or Campesterol	4	400	10	21	151-153°C	158°C[30] or 157-158°C[30]
Poriferasterol	5	412	6	4	152°C	156°C[30]
Clionosterol	6	414	6	4	125-130°C	138°C[30]
Gorgosterol	7	426	5	6	184-186°C	183°C[32]

a) on 3% JXR or 1% OV-1 columns

b) free sterol content

c) approximate percent yield based on GC peak areas

d) the m/e for Pt. anceps, sterols were found in reference 19 and the m/e for Pt. guadalupensis sterols were provided by Dr. T. Pattabhiraman[23]

H-15', H-14' arrangement in 13 as opposed to the trans H-15', H-14' assignment in 3.

Sterols from the Species Pterogorgia

Bergmann[18], in his survey of sterols of marine organisms, reported that the sterol mixture from Pt. anceps contained cholesterol and probably clionosterol. This sterol mixture was analyzed further by mass spectrometric techniques by Ciereszko [19] who reported the presence of six sterols. These sterols were assumed[22] to be cholesterol (m/e 386), brassicasterol (m/e 398, neospongesterol (m/w 400), poriferasterol (m/e 412), clionosterol (m/e 414), and gorgosterol (m/e 426). The work reported here revealed the presence of a seventh sterol in Pt. anceps (m/e 384). The same seven sterols in similar quantities were also found in Pt. guadalupensis (Table 4). Identification of these sterols was accomplished using gas chromatographic analysis on two different partitioning agents (3% JXR and 1% OV-1) using peak enhancement technique[27], mass spectral analysis[23], and melting point data[23,30]. The composition of the sterol mixtures isolated from Pt. anceps and Pt. guadalupensis is outlined in Table 4. The m/e 384 sterol was not identified. The presence of cholesterol (m/e 386) was confirmed by melting point data (Lit.[30] m. p. 149° C). Melting point data[22] indicated that the m/e 398 sterol reported earlier to be brassicasterol[22] could also be 24-α-methyl-7-dehydrocholesterol. The m/e 400 sterol reported earlier to be

Table 5

GC and Mass Spectral Data for Fatty Esters and Alcohols

GC Elution Order	Formula	m/e	Retention time (sec)	Log retention time	Carbon Number	Name
1	$C_{14}H_{29}OH$	214	288	2.46	14	Tetradecyl alcohol (Myristyl alcohol)
2	$C_{13}H_{27}COOCH_3$	242	354	2.55	15	Methyl myristate
3	$C_{16}H_{33}OH$	242	738	2.87	16	Cetyl alcohol
4	$C_{15}H_{31}COOCH_3$	270	900	2.95	17	Methyl palmitate
5	$C_{18}H_{35}OH$	268	1584	3.20	18	Octadecenyl alcohol (Oleyl alcohol)
6	$C_{17}H_{33}COOCH_3$	296	1884	3.28	19	Methyl oleate
7	$C_{17}H_{35}COOCH_3$	298	2196	3.34	19	Methyl stearate

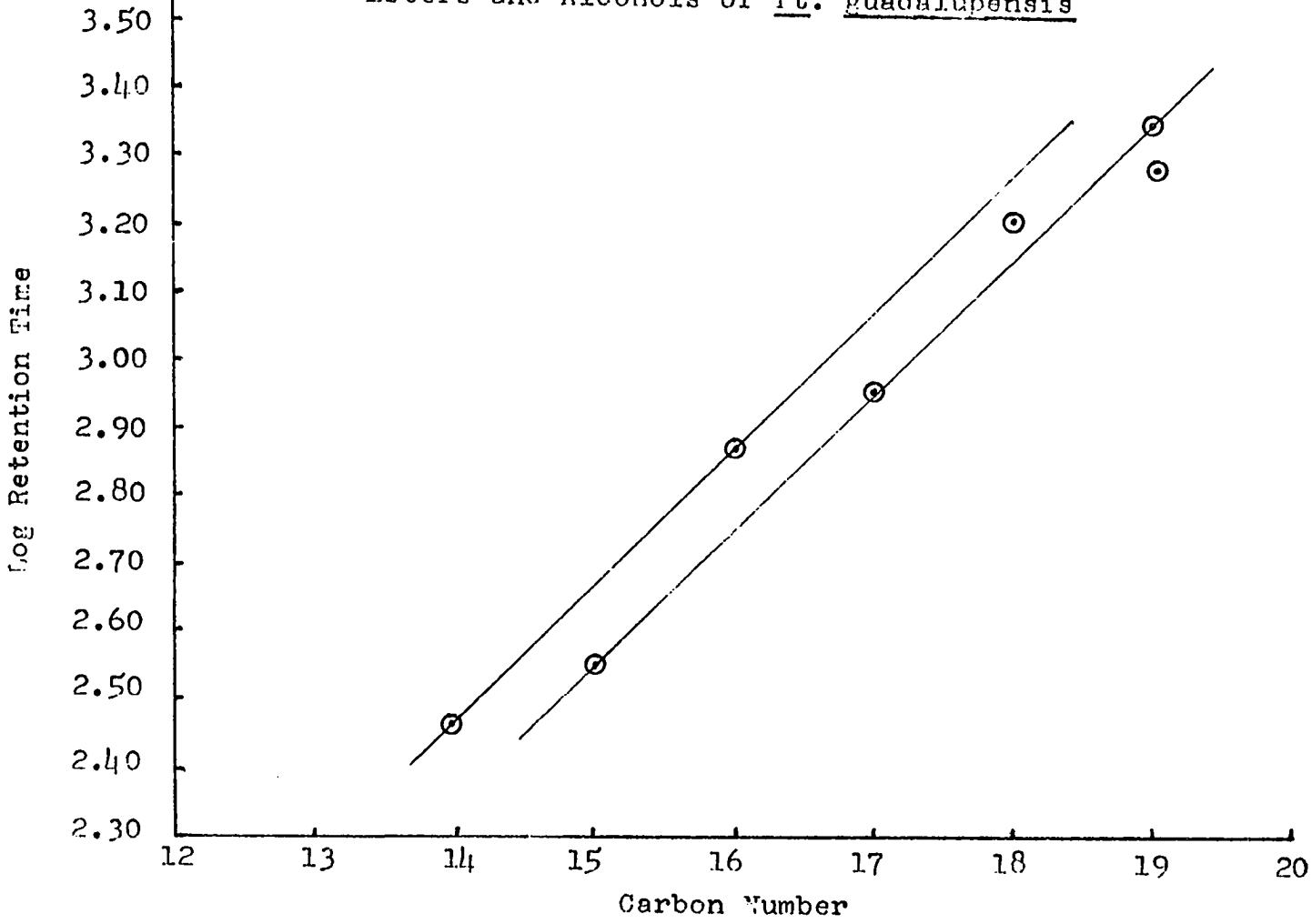
neospongesterol[22] was found to be either 22,23-dihydrobrassicasterol or campesterol on the basis of mass spectral and melting point data[23,30,31]. The mass spectrum for the m/e 412 sterol was consistent with the published spectrum for stigmasterol[23,31]. The presence of a very small peak at m/e 314, characteristic of demethylgorgosterol, indicated that if demethylgorgosterol was present it was only a very minor component. Melting point data[22] confirmed that the m/e 412 sterol was poriferasterol (Lit.[30] m. p. 156°C) rather than stigmasterol (Lit.[30] m.p. 170° C). The m/e 414 sterol was assumed to be clionosterol as reported earlier[22] although the observed melting point (m. p. 125-130° C)[22] did not distinguish between β-sitosterol (Lit.[30] m. p. 136-137° C) The m/e 426 sterol was confirmed by melting point data[22] to be gorgosterol (Lit. [32] m. p. 186.5-188° C).

Fatty Esters from Pt. guadalupensis

Quantities of fatty esters were found in the hexane extracts of both Pt. anceps and Pt. guadalupensis. However, one colony of Pt. guadalupensis (from Ragged Keys, Florida) yielded fatty esters in a quantity not observed in other colonies extracted. The third hexane extraction, which in other extractions of Pt. guadalupensis yielded ancepsenolidic acid (10) as the only significant product, afforded a very large quantity of a mixture of fatty esters (19% of the dry weight of the colony). No conclusions were drawn regarding the reasons for this apparent anomaly. The colony was

Figure 10

Plot of Log Retention Time versus Carbon Number for Fatty Esters and Alcohols of Pt. guadalupensis



collected in the same area and at the same time as other colonies which did not exhibit this behavior.

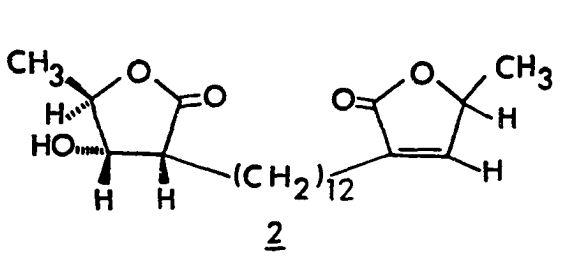
Identification of the mixture of fatty esters was accomplished by saponification and methylation of the resulting acids followed by gas chromatographic and mass spectral analysis. Table 5 shows the results of gas chromatographic analysis using the peak enhancement technique[27]. Fatty acids identified in this way were myristic acid, palmitic acid, oleic acid, and stearic acid. Three peaks in the gas ghromatogram remained unidentified at this point. Combined use of gas chromatography and mass spectroscopy afforded mass spectra for each of the seven peaks observed in the chromatogram. Data from the mass spectra were analyzed using a computer program designed for analysis of fatty methyl esters (kindly provided by Dr. W. J. Youngblood). This technique confirmed the identity of the aforementioned fatty acids.

Examination of the mass spectral data for the remaining three components of the mixture indicated that these compounds were not fatty acids but probably were high molecular weight alcohols[24,25]. The molecular weights indicated the possibility of two saturated alcohols (GC peak 1, m/e 214, $C_{14}H_{29}OH$ and GC peak 3, m/e 242, $C_{16}H_{33}OH$) and one monounsaturated alcohol (GC peak 5, m/e 268, $C_{18}H_{35}OH$). These compounds showed insignificant parent peaks but relatively strong peaks for the M-H_2O fragments. The long

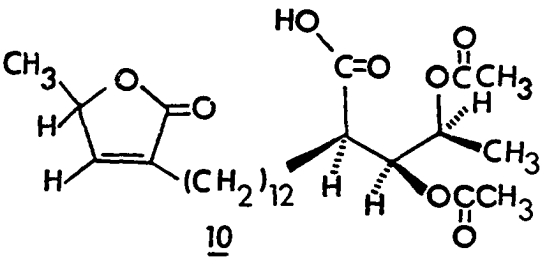
hydrocarbon chain in each was indicated by a series of peaks 14 mass units apart with gradually increasing intensities for smaller fragments. The position of the double bond could not be determined from the mass spectrum for the unsaturated alcohol[26]. The alcoholic nature of the compounds was confirmed by converting them to silyl ethers and observing the characteristic shifts in retention time for the three compounds in a gas chromatogram[27,28]. Further information was provided by a plot of log retention time versus carbon number (Table 5 and Figure 10). The saturated fatty esters gave a straight line which roughly paralleled the line connecting the points for the two saturated alcohols. This indicated the possibility of two sets of homologs, the saturated fatty esters and saturated alcohols[29]. The compounds observed as peaks 1 and 3 in the gas chromatogram were, therefore, assumed to be tetradecyl alcohol (myristyl alcohol) and hexadecyl alcohol (cetyl alcohol). The unsaturated alcohol (GC peak 5) was assumed to be an octadecenyl alcohol, possibly oleyl alcohol. The exact combinations of the alcohols and fatty acids in their original ester forms were not determined.

SUMMARY

Chemical and spectral evidence is presented which forms the basis for proposing structure 2 for hydroxyancepsenolide and 10 for ancepsenolidic acid (only relative stereochemistries are implied). These compounds were novel, nonisoprenoid lactones found in two members of the genus, Pterogorgia. Hydroxyancepsenolide (2)and the previously



2



10

reported lactone, ancepsenolide (1), were found in Pt. anceps, while ancepsenolide (1) and ancepsenolidic acid (10)were found in Pt. guadalupensis. None of these lactones was found in a third species of this genus, Pt. citrina.

The conversion of 2 to its monoacetate 3, to its dihydro and dihydro acetate derivatives (4 and 5), and to lactone 1 is outlined in Scheme 2. Also saponification and ozonolysis experiments are described. The conversion of 10 to its methyl ester 11, to an isomer of lactone 2, and subsequently to lactone 1 is outlined in Scheme 3. Extensive spectral data on compounds 2 and 10 and their derivatives are discussed. Pmr spectral data were used to propose the relative stereochemical assignments in structures 2 and 10.

The sterols cholesterol, 24-α-methyl-7-dehydrocholesterol or brassicasterol, 22, 23-dihydrobrassicasterol or campesterol, poriferasterol, clionosterol, and gorgosterol were tentatively identified in the extracts of both Pt. anceps and Pt. guadalupensis, and their relative quantities in the sterol mixtures from the two species are reported.

The fatty acids, myristic acid, palmitic acid, oleic acid, and stearic acid, and the fatty alcohols, myristyl alcohol, cetyl alcohol, and an octadecenyl alcohol are reported to be present in undetermined ester combinations in a sample of fatty esters found in unusual quantity in a single colony of Pt. guadalupensis.

EXPERIMENTAL

All melting points are corrected and were determined in capillary tubes with a Thomas-Hoover melting point instrument. All solvents were redistilled before use. Supports used in column chromatography were alumina (Activity III)(Merck AG, Darmstadt), Florisil (Floridin, 100-200 mesh), and silicic acid (Mallinckrodt, SilicAR CC-7, 100-200 mesh). Glass plates (5 x 20 cm) coated with silica gel H (Merck AG, Darmstadt) were used for thin layer chromatography. Visualization of thin layer chromatograms was accomplished in chambers containing iodine vapor.

Ultraviolet spectra were measured in 95% ethanol on either a Beckman DK-1 spectrophotometer or a Hitachi Perkin-Elmer Model 124 spectrophotometer. Infrared spectra were recorded using a Beckman IR-8 spectrophotometer. The infrared spectra were obtained using chloroform or carbon tetrachloride solutions in 0.1 mm cells or using potassium bromide pellets. Gas chromatographic analyses were performed on Varian Aerograph Models 1400 or 1700.

Proton magnetic resonance (pmr) spectra were obtained using a Varian Model A-60 spectrometer with tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in δ-units (parts per million from TMS) and are followed by the multiplicity of the signal, the number of protons, the corresponding coupling constant (s) measured in Hz, and the assignment. The multiplicities are reported using the following symbols: s, singlet; d, doublet; dd, doubled doublet; t, triplet; dt, doubled triplet; q, quartet; dq, doubled quartet; and m, multiplet. The 220 mHz proton magnetic resonance spectrum was provided by Dr. N. Bhacca, Louisiana State University.

Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7E spectrometer using perfluorokerosene-H as an reference or were provided by (a) Mr. Paul Fenessey, Massachusetts Institute of Technology, (b) Dr. Ronald Grigsby, Continental Oil Company, Ponca City, Oklahoma, (c) the National Institute of Health Laboratory, Purdue University (Hitachi Perkin-Elmer RMU-6A spectrometer), or (d) the University of Arkansas (Hitachi Perkin-Elmer RMU-6E spectrometer) at 75 or 80 ev. Major peaks and molecular ions are reported followed by percentage of the base peak. Combined gas chromatographic and mass spectral analyses were done using instrumentation at Oklahoma State University.

Combustion analyses were carried out by the Alfred Bernhardt Laboratories, Mulheim, West Germany.

Isolation of Ancepsenolide (1). Air-dried, coarsely ground gorgonian (several colonies mixed; 1,919 g), collected along the outside of Boca Chita Key, Miami, Florida, and in Bimini, Bahamas, was extracted with a series of organic solvents. Consecutive extractions were made in a continuous percolator-extractor[12] with the following solvents and periods of extraction: (1) hexane, 18 hours; (2) hexane, 96 hours; (3) hexane, 48 hours; (4) benzene, 47 hours; (5) benzene, 72 hours; (6) methanol, 28 hours; and (7) methanol, 48 hours.

The first hexane extract contained a complex mixture of lipid material. Some of the ancepsenolide (1) contained in this mixture precipitated from solution (6.38 g). Purification by chromatography over silicic acid and recrystallization from a chloroform-hexane mixture gave ancepsenolide (1) as a white crystalline solid, mp 91.2-92.0°C (lit.[15] mp 91.5-92.0° C).

Isolation of Hydroxyancepsenolide (2). Hydroxyancepsenolide (2) precipitated from the second hexane extract which contained a total of 1.87 g of this material. A 1.54 g sample of crude lactone 2 was chromatographed on neutral silicic acid (200-300 mesh). The eluent was 25% ethyl acetate in benzene (30-50 ml fractions). Fractions 5-28 contained 0.946 g of white crystalline hydroxyancepsenolide (2). Recrystallization several times from isopropanol gave white platelets: mp 122.5-123.7° C; $[\alpha]_D^{24}$ 3.4°; λ_{max} (95% ethanol) 209 nm (ϵ=15,800);

ir ($CHCl_3$) 3600 cm^{-1} (very weak, hydroxyl) and 1750 cm^{-1} (broad, lactone); ir (KBr) 3600 cm^{-1} (very weak, hydroxyl) and 1760 and 1720 cm^{-1} (saturated and unsaturated lactones respectively); pmr ($CDCl_3$) δ 7.0 (dt, 1, J = 1.3 and 1.5 Hz, vinyl hydrogen of unsaturated lactone), 5.0 (m, 1, J = 1.5 and 7 Hz, γ-hydrogen on the unsaturated lactone), 4.5 (dq, 1, J = 1 and 6 Hz, γ-hydrogen on the saturated lactone), 4.2 (dd, 1, J = 6 and 1 Hz, β-hydrogen on the saturated lactone), 2.45-3.0 (m,2, hydroxyl hydrogen and α-hydrogen on the saturated lactone; decreased by an area corresponding to one hydrogen on addition of deuterium oxide), 2.28 (m, 2, hydrogens allylic to the double bond of the unsaturated lactone), 1.4 (d, 3, J = 7 Hz, hydrogens on the methyl group attached to the unsaturated lactone), 1.35 (d, 3, J = 6 Hz, hydrogens on the methyl group attached to the saturated lactone), and 1.28 ppm (s, 22, methylene hydrogens).

The mass spectrum of 2 (Figure 1) showed significant peaks at 380 (0.6), 362 (2.4), 345 (1.0), 344 (4.0), 336 (3.0), 334 (2.0), 319 (1.2), 318 (4.6), 316 (1.1), 308 (1.7), 307 (5.3), 280 (1.3), 279 (2.0), 266 (3.8), 265 (18.5), 264 (2.3), 252 (3.6), 251 (4.8), 237 (1.4), 224 (1.0), 223 (1.6), 219 (1.2), 209 (2.3), 207 (1.5), 205 (1.0), 195 (2.7), 193 (1.1), 191 (1.0), 181 (2.9), 179 (1.6), 177 (1.6), 175 (1.0), 168 (1.0), 167 (3.7), 165 (2.0), 163 (2.4), 161 (1.3), 154 (1.5), 153 (5.1), 152 (1.5), 151 (2.4), 150 (1.4), 149 (4.1), 147 (1.9), 145 (1.1), 140 (1.9), 139 (7.0), 138 (2.3),

137 (4.8), 136 (3.2), 135 (6.9), 134 (1.1), 133 (2.2), 121 (10), 112 (21), 111 (13), 110 (9), 109 (14), 97 (15), 96 (12), 95 (26), 93 (12), 83 (16), 82 (15), 81 (34), 79 (17), 69 (30), 68 (18), 67 (47), 57 (49), 56 (14), 55 (70), 54 (10), 53 (16), 45 (9), 44 (78), 43 (100), 42 (14), 41 (79), 39 (21), 29 (58), 28 (40), 27 (28), 18 (85), 17 (25), and 16 (12).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.47; H, 9.47. Found: C, 69.60; H, 9.74.

Hydroxyancepsenolide acetate (3). Hydroxyancepsenolide (2)(0.266 g, 0.70 mmol) was dissolved in a mixture of 10 ml of pyridine and one ml of acetic enhydride. The solution was stirred overnight at room temperature and then poured into ice water whereupon a curdy white precipitate formed. The precipitate was recovered by extraction with ethyl ether. The ether solution was washed sequentially with dilute aqueous hydrochloric acid solution, aqueous sodium bicarbonate solution, and water, and then dried over anhydrous magnesium sulfate. The ether was evaporated leaving 0.288 g (97% yield) of white solid. Recrystallization of 0.180 g of this solid four times from isopropyl alcohol gave 0.053 g of pure hydroxyancepsenolide acetate (3), mp 68.3-70.3° C.

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.24; H, 9.01. Found: C, 68.23; H, 9.03.

Ir ($CHCl_3$) 1740-1765 cm^{-1} (very broad and intense, two five-membered lactones) and 1735 cm^{-1} (acetate, shoulder on

the preceding intense carbonyl absorption); pmr ($CDCl_3$) δ7.07 (dt, 1, J = 1.3 and 1.5 Hz, vinyl hydrogen of the unsaturated lactone), 5.0 (dq, 1, J = 1.5 and 7 Hz, γ-hydrogen on the unsaturated lactone), 5.15 (dd, 1, J = 6 and 1 Hz, β-hydrogen on the saturated lactone), 4.5 (dq, 1, J = 1 and 6 Hz, γ-hydrogen on the saturated lactone), 2.2- 3.0 (m, 3, two allylic hydrogens and one hydrogen alpha to the lactone carbonyl), 2.1 (s, 3, acetate methyl hydrogens), 1.4 (d, 3, J = 7 Hz, methyl hydrogens on the unsaturated lactone), 1.32 (d, 3, J = 6 Hz, methyl hydrogens on the saturated lactone), and 1.28 ppm (s, 22, methylene hydrogens); pmr (benzene) δ6.4 (dt, 1, J = 1.3 and 1.5 Hz, vinyl hydrogen), 4.97 (dd, 1, J = 6 and 1 Hz, β-hydrogen on the saturated lactone), 4.5 (dq, 1, J = 1.5 and 7 Hz, γ-hydrogen on the unsaturated lactone), 4.24 (dq, 1, J = 1 and 6 Hz, γ-hydrogen on the saturated lactone), 1.9-2.6 (m, 3, two allylic hydrogens and one alpha hydrogen to the lactone carbonyl), 1.7 (s, 3, acetate methyl hydrogens), 1.29 (s, 22, methylene hydrogens), and 1.02 ppm (d, 6, overlapping absorption for the methyl hydrogens on both the saturated and unsaturated lactones).

Saponification of Hydroxyancepsenolide (2). Hydroxyancepsenolide (2) (0.123 g, 0.323 mmol) was dissolved in a mixture of 8.8 ml of methanol and 1.7 ml of water, and the solution was treated with 0.669 g of 85% potassium hydroxide pellets (0.569 g, 10.2 mmol). The mixture was heated under reflux

for 1.25 hours. About 10 ml of methanol and water was removed from the reaction mixture by distillation. Then 10 ml of methanol and water was removed from the reaction mixture by distillation. Then 10 ml of water was added, and the resulting mixture was extracted three times with ether to remove any unreacted starting material. The remaining aqueous solution was cooled and treated with one ml of concentrated hydrochloric acid solution. The resulting white precipitate was washed and dried giving 0.091 g of an acidic material which melted over the range 63-77° C. Ir ($CHCl_3$) 3350-3600 (broad and weak, carboxylic acid and alcohol), 1722 (ketone), and 1695 cm^{-1} (carboxylic acid); pmr ($CDCl_3$) δ 7.05 (brd s, 4, two carboxylic acid hydrogens and two alcohol hydroxyl hydrogens; this band was lost after treatment with deuterium oxide), 4.3-4.75 (m, 1, -CHOH-C<u>H</u>OH-CH_3), 4.2 (dd, 1, J = 6 and 1 Hz, -C<u>H</u>OH-CHOH-CH_3), 2.45-3.1 (m, 4, two methylene hydrogens <u>alpha</u> to the ketone and to hydrogens <u>alpha</u> to carboxyl groups), 2.18 (s, 3, methyl hydrogens <u>alpha</u> to the ketone), and 1.1-1.85 ppm (m, 27, 24 methylene hydrogens and $C\underline{H}_3$-CHOH-CHOH-).

<u>Preparation of Methyl Ester 7</u>. The acidic material from the preceding reaction was dissolved in 20 ml of methanol, and two ml of concentrated aqueous hydrochloric acid was added. The mixture was heated under reflux for 24 hours, cooled, and then neutralized with aqueous sodium bicarbonate to about pH 8. After dilution with water, the mixture was

extracted four times with ethyl ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave 0.073 g of an oily mixture which showed two spots on a thin layer chromatogram. Comparison of RF values indicated that one of the spots was hydroxyancepsenolide (2), and the other spot was assumed to be the methyl ester 7: ir (CCl_4)(mixture) 3475 (Hydroxyl), 1780 (saturated lactone), 1735 (unsaturated lactone and ester), and 1720 cm^{-1} (ketone); the pmr spectrum ($CDCl_3$) gave weak absorptions corresponding to hydroxyancepsenolide (2) and strong signals at δ 3.7 (s, methoxyl hydrogens) and 2.18 ppm (s, methyl ketone).

Hydrogenation of Hydroxyancepsenolide (2). Platinum (IV) oxide (0.178 g, 0.78 mmol) was suspended in 20 ml of ethyl acetate and hydrogenated. Hydroxyancepsenolide (2) (0.370 g, 0.97 mmol) was dissolved in 150 ml of ethyl acetate (this large volume of solvent was necessary due to the limited solubility of 2) and added to the reduced platinum suspension. The mixture was stirred under hydrogen at atmospheric pressure and room temperature. Slightly more than one mole equivalent of hydrogen was taken up, and as the hydrogen uptake ceased, a fine white precipitate was apparent in the reaction mixture. The reaction mixture was warmed, and the warm solution was filtered through filter aid. The solvent was evaporated to yield 0.351 g (94.6%) of hydrogenated product. Dihydrohydroxyancepsenolide (4) was expected as a

mixture of diastereomers in this reaction. No separation of this mixture of diastereomers could be detected by thin layer chromatography, nor could the mixture be separated by fractional crystallization. A 0.148 g sample of the mixture was recrystallized five times from ethyl acetate giving 0.029 g of material having a melting point range of 119.3-133.0° C. The material in the mother liquor of the first recrystallization was recrystallized three times from ethyl acetate, and the resulting material had a similar melting range, 118.8-125.5° C.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.11;H, 9.95. Found: C, 68.90; H, 9.98.

Ir ($CHCl_3$) 3500 (hydroxyl) and 1765 cm^{-1} (saturated lactone); ir (KBr) 3450 (hydroxyl), 1760, and 1730 cm^{-1} (lactones); pmr ($CDCl_3$) δ 4.1-4.8 (m, 3, β- and γ-hydrogens on the substituted lactone and γ-hydrogen of the other lactone), 2.55 (m, 2, one α-hydrogen on each lactone), 1.4 (d, 3, J = 7 Hz, methyl hydrogens on the unsubstituted lactone), and 1.2-2.0 ppm (m, 30, 26 methylene hydrogens, one hydroxyl hydrogen and methyl hydrogens on the substituted lactone).

Acetylation of Dihydrohydroxyancepsenolide (4). A sample of lactone 4 (0.104 g, 0.27 mmol), recrystallized once from ethyl acetate (mp 117-133° C), was dissolved in a mixture of 10 ml of pyridine and one ml of acetic anhydride. The reaction mixture was stirred overnight at room temperature.

It was then poured into ice water whereupon a curdy white precipitate formed which was recovered from the aqueous mixture by extraction with ether. The ether solution was washed with aqueous hydrochloric acid (5%) until the washes remained acidic, then with aqueous sodium bicarbonate solution (10%) until the washes remained basic, and finally twice with water. The ether solution was dried over anhydrous magnesium sulfate and then evaporated giving the monoacetate 5 in quantitative yield. Recrystallization of the product once from isopropyl alcohol and then twice from a carbon tetrachloride-hexane mixture gave 0.057 g of white crystals of dihydrohydroxyancepsenolide acetate (5): mp 71.2-72.5° C;ir ($CHCl_3$) 1765 (saturated lactones) and 1740 cm^{-1} (acetate); pmr ($CDCl_3$) δ 5.15 (dd, 1, J = 6 and 1 Hz, β-hydrogen of the acetylated lactone), 4.15-4.55 (m, 2, one γ-hydrogen on each lactone), 2.2-2.95 (m, 2, one α-hydrogen on each lactone), 2.1 (s,3, acetate methyl hydrogens), 1.42 (d, 3, J = 7, methyl hydrogens on the unsaturated lactone), 1.3 (d,3, J = 6 Hz, methyl hydrogens on the substituted lactone), and 1.28 ppm (s, 26, methylene hydrogens); pmr (benzene) δ4.88 (dd, 1, J= 6 and 1 Hz, β-hydrogen on the acetylated lactone), 3.65-4.4 (m, 2, one γ-hydrogen on each lactone), 1.6 (s, 3, acetate methyl hydrogens), 1.31 (s, 26, methylene hydrogens), 0.80 (d, 3, J = 7 Hz, methyl hydrogens on the unsubstituted lactone), and 0.70 ppm (d, 3, J = 6 Hz, methyl hydrogens on

the substituted lactone); the protons alpha to the carbonyls and the β-hydrogens on the unsubstituted lactone appear as multiplets overlapping the acetate methyl band and the large methylene singlet.

Anal. Calcd for $C_{24}H_{40}O_6$: C, 67.92; H, 9.43. Found: C, 67.70; H, 9.16.

Ozonolysis of Hydroxyancepsenolide (2). Lactone 2 (0.287 g, 0.755 mmol) was dissolved in about 50 ml of chloroform. Ozone was bubbled through the solution for ten minutes. Two ml of 30% hydrogen peroxide solution and two ml of distilled water were added, and the reaction mixture was stirred for 16 hours at room temperature. More distilled water was added, and the mixture was stirred vigorously for a short period. The aqueous layer was extracted three times with ether. The organic layers were combined and washed with ferrous sulfate solution (3 g of ferrous sulfate and 1 ml of concentrated sulfuric acid in 34 ml of water) and with two portions of water. The organic solution was extracted with three 25 ml portions of sodium bicarbonate solution and three 25 ml portions of sodium carbonate solution and then dried over anhydrous magnesium sulfate. Evaporation of the organic solution afforded 0.200 g of lactone 2.

Upon acidification of the carbonate and bicarbonate washes with aqueous hydrochloric acid a small amount of precipitate formed. Extraction of the acidified basic extracts with ether afforded 0.067 g of acidic material 9.

The recovered lactone 2 was again subjected to the preceding ozonolysis and workup procedures, and an additional 0.045 g of acid 9 was obtained. Recrystallization of the acid from ethyl acetate gave a white crystalline solid: mp 94.5-96.0° C; ir ($CHCl_3$) 3300-3500 (very weak and broad absorption, alcohol and carboxylic acid), 1770 (saturated lactone), and 1710 cm^{-1} (carboxylic acid); pmr ($CDCl_3$) δ5.3-5.9 (m, 2, carboxyl and hydroxyl hydrogens), 4.3-4.75 (m, 1, γ-hydrogen on the lactone), 4.18 (dd, 1, J = 6 and 1 Hz, β-hydrogen on the lactone), 2.1-2.8 (m, 3, two hydrogens alpha to the carboxylic acid and one α-hydrogen on the lactone), and 1.15-2.0 ppm (m, 25, 22 methylene hydrogens and three methyl hydrogens).

Dehydration of Hydroxyancepsenolide (2). Lactone 2 (0.253 g, 0.665 mmol) was stirred overnight at room temperature with a mixture of 0.2 ml of phosphorus oxychloride and 11 ml of pyridine. Dilution of the reaction mixture with 50 ml of water caused precipitation of a white solid. This precipitate was recovered by extraction with ethyl ether. The ether solution was washed with aqueous hydrochloric acid and water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave a material which appeared to be ancepsenolide (1) from thin layer chromatography, ir analysis, and pmr analysis. The yield was 0.143 g (60%). Chromatography on silicic acid (eluent: 10% ethyl acetate in benzene) and recrystallization from chloroform gave 0.103 g

of ancepsenolide (1): mp 92.8-94.3° C, $[\alpha]_D^{24}$ 7.7°. A mixed melting point with an authentic sample of lactone 1 (mp 91.3-92.2° C) showed no depression. The ir and pmr spectra were identical with those reported for authentic ancepsenolide[15].

Isolation and Analysis of Sterols from Pterogorgia anceps. Sterols in Pt. anceps were found in the first extract (hexane, 24 hr). A part of this extract (20 g) was absorbed on Florosil (600 g, 6.5 x 150 cm) and eluted with hexane followed by 50% hexane in benzene, benzene, 10% ethyl ether in benzene, 50% ethyl ether in benzene, ethyl ether, and finally ethyl acetate. Some sterols were obtained near the end of the benzene elution (fractions 26-41), but the majority were eluted by 10% ethyl ether in benzene (fractions 42-86). The sterol mixture was purified by recrystallization from a mixture of ethyl ether and methanol. Thin layer chromatography showed only one spot whose R_f value was the same as that of a cholesterol reference sample.

Saponification of the total steroid mixture (fractions 27-86, 6.5 g) was accomplished by adding a solution of 3.5 g of 85% potassium hydroxide pellets in 20 ml of methanol to a solution of the sterols in about 25 ml of methanol and heating the resulting mixture under reflux for four hours. During the heating process the reaction mixture became quite dark. It was poured onto ice and water, and the resulting mixture was extracted several times with ethyl ether. The ether layer was washed with water until the water washes

were no longer basic to litmus. The ether was dried over anhydrous magnesium sulfate and removed by evaporation under vacuum. The product (4.3 g) was recrystallized from a mixture of ethyl ether and methanol. Gas chromatographic analyses were performed on 3% JXR, 3% OV-1, and 1% OV-17 absorbents packed in glass columns. Peak enhancement was accomplished using known reference samples of sterols (cholesterol, stigmasterol, β-sitosterol, and gorgosterol) for comparison of retention times and relative peak areas. See Table 4 for sterols with their retention times.

Isolation of Ancepsenolide (1) from Pterogorgia guadalupensis. A single colony of dried, coarsely ground Pt. guadalupensis, 115 g, collected near Port Royal, Jamaica, June, 1967, was extracted using a continuous percolator extractor[16] using the following solvent sequence and duration of extractions: (1) hexane, 18 hours; (2) hexane, 48 hours; (3) hexane, 96 hours; (4) benzene, 28 hours; (5) benzene, 72 hours; (6) methanol, 48 hours; and (7) methanol, 72 hours. The total material extracted was 15 percent of the original dry weight of the colony.

Ancepsenolide (1) precipitated from the first hexane extract in nearly pure form (3.2 g, 3.5% crude). Chromatography over alumina (activity 3) and recrystallization from a mixture of chloroform and hexane gave lactone 1 as a white crystalline solid: mp 90.5-92.0° C, $[\alpha]_D^{24}$ -47.8°. The

pmr, uv, and ir spectra and the melting point of this material were consistent with those of authentic ancepsenolide[15].

Isolation of 2-(13'-Carboxy-14', 15'-diacetoxyhexadecanyl) -2-penten-4-olide (Ancepsenolidic acid) (10). Only a very small quantity of an oily material was found in the second hexane extract (48 hours) from above. However, from the third extract crude ancepsenolidic acid (10) precipitated (1.14 g, 0.99%). Chromatography of 10 over 58 g of silicic acid (eluent: benzene followed by benzene-ethyl acetate mixtures in which the percentage of ethyl acetate was gradually increased to 30%) and recrystallization from aqueous isopropyl alcohol gave white crystals of the acid: mp 81.1-82.9° C; $[\alpha]_D^{24}$ = -8.3° (0.47 g/100 ml, chloroform); uv λ_{max} 204 nm (ϵ = 17,436)(95% ethanol); ir ($CHCl_3$) 3500 (broad and weak, carboxylic acid) and 1740 cm^{-1} (intense and broad; width at one-half intensity, 1700-1770 cm^{-1}; a lactone, a carboxylic acid, and two acetates); pmr ($CDCl_3$) δ 7.02 (dt, 1, J = 1.3 and 1.5, vinyl hydrogen of the unsaturated lactone), 4.78-5.42 (m, 4, acid hydrogen, γ-hydrogen of the lactone, and single hydrogens on carbons 14' and 15'), 2.5-2.95 (m, 1, hydrogen on carbon 13'), 2.08 and 2.06 (two singlets, 6, methyl hydrogens of two acetate groups), 1.4 (d, 3,J = 7 Hz, methyl hydrogens of carbon 5), and 1.28 ppm (m, 25, 22 methylene protons on carbons 2' to

12' and 3 methyl hydrogens on carbon 16').

Addition of deuterium oxide to the sample in chloroform-d_1 resulted in the loss of absorption corresponding to one hydrogen in the region δ 4.78-5.42 ppm. The spectra obtained in dimethyl sulfoxide-d_6 or acetone-d_6 were essentially the same as when chloroform-d_1 was the solvent with the exception of minor chemical shift changes. In acetone-d_6 the δ 7.02 ppm peak was shifted downfield slightly, and the multiplet at δ4.78-5.42 ppm was spread apart somewhat relative to the spectrum in chloroform-d_1. The most significant difference was found in the methyl doublet signals at δ1.40 ppm and approximately δ1.28 ppm (obscured by the methylene envelope). When acetone-d_6 was used the downfield doublet was shifted upfield slightly and overlapped part of the large methylene absorption, whereas the upfield doublet, partially obscured by the methylene peak in chloroform-d_1, was now fully visible at δ1.17 ppm.

Pmr (220 MHz, chloroform-acetone-d_6) δ 7.02 (dt, 1, J = 1.5 and 1.3 Hz, vinyl hydrogen of the lactone), 5.15 (m, 2, hydrogens on carbons 14' and 15'), 5.0 (dq, 1, J = 1.5 and 7 Hz, γ-hydrogen of the lactone), 2.21 (m, 2, hydrogens on carbon 1'), 2.0 and 2.02 (two singlets, 6, methyl hydrogens of two acetate groups), 1.35 (d, 3, J = 7 Hz, methyl hydrogens of carbon 5), 1.28 (s, 22, methylene hydrogens on carbons 2' to 12'), and 1.17 ppm (d, 3, J = 6 Hz,

methyl hydrogens on carbon 16'); mass spectrum 423 (8), 422 (25), 405 (6), 404 (22), 380 (8), 364 (5), 363 (19), 362 (26), 351 (5), 350 (15), 345 (5), 344 (14), 336 (11), 335 (30), 318 (12), 311 (14), 309 (7), 308 (8), 307 (12), 290 (5), 266 (8), 265 (26), 252 (7), 251 (7), 209 (14), 195 (7), 181 (6), 168 (5), 167 (8), 163 (6), 159 (5), 158 (9), 154 (5), 153 (10), 149 (8), 140 (6), 139 (11), 138 (5), 137 (8), 135 (11), 127 (5), 126 (5), 125 (10), 124 (6), 123 (12), 122 (10), 121 (18), 113 (12), 112 (24), 111 (18), 110 (11), 109 (17), 108 (7), 107 (11), 99 (12), 98 (12), 97 (18), 96 (12), 95 (28), 94 (8), 93 (13), 87 (7), 85 (11), 84 (7), 83 (18), 82 (12), 81 (28), 79 (12), 71 (16), 70 (8), 69 (29), 68 (11), 67 (28), 60 (8), 57 (26), 55 (38), 53 (6), 45 (11), 44 (8), 43 (100), 41 (21), 29 (6), and 28 (6). To observe the peaks for masses greater than m/e 422, it was necessary to increase the amplitude (30 x). The spectrum then showed peaks at 482 (0.1), 464 (0.3), 446 (0.4), and 436 (0.3).

Anal. Calcd for $C_{26}H_{42}O_8$: C, 64.73; H, 8.71. Found: C, 64.85; H, 8.82.

Neutralization equivalent, Calcd for $C_{26}H_{42}O_8$: 482. Found: 478. Acetyl group analysis, Calcd for two acetates: 17.84. Found: 16.91.

2-(13'-Carbomethoxy-14', 15'-diacetoxyhexadecanyl)-2-penten-4-olide (Methyl Ancepsenolidate) (11). To a solution of ancepsenolidic acid (10) (mp 105.2-106.9° C, 0.110 g, 0.23 mmol) in about 25 ml of ethyl ether was added

diazomethane in ethyl ether until a light yellow color persisted. The mixture was placed in a refrigerator for about one hour and then kept at room temperature for about three hours. The excess diazomethane was destroyed with acetic acid. The mixture was then washed with 10% aqueous sodium carbonate solution and water and dried over anhydrous sodium sulfate. The reaction gave the oily ester 11 in 97% yield (0.110 g). The ester was purified by chromatography over silicic acid (57 g, 2.1 x 40 cm, eluent: benzene).

Anal. Calcd for $C_{27}H_{44}O_8$: C, 65.35; H, 8.87. Found: C, 65.60; H, 9.12.

Ir ($CHCl_3$) 1750 (broad and intense, lactone) and 1730 cm^{-1} (broad and intense, acetate and methyl ester); pmr ($CDCl_3$) δ7.02 (dt, 1, J = 1.5 and 1.3 Hz, vinyl hydrogen of the lactone), 4.80-5.45 (complex multiplet, 3, hydrogens on carbons 15' and 15' and the γ-hydrogen of the lactone), 3.69 (s, 3, hydrogens on the ester methyl group), 2.50-2.95 (m, 1, hydrogen on carbon 13'), 2.10-2.45 (m, 2, allylic hydrogens on carbon 1' partially overlapping the acetate absorption), 2.07 (s, 6, single band for identical hydrogens on two acetate methyl groups), 1.40 (d, 3, J = 6.5 Hz, hydrogens of the lactone methyl group), and 1.28 ppm (m, 25, methylene hydrogens on carbons 2' to 12' with a doublet for the methyl hydrogens on carbon 16' partially visible as a shoulder at about δ1.20 ppm).

Periodate Test on Ancepsenolidic Acid (10). A solution of the pentenolide 10 (0.107 g, 0.22 mmol) and five ml of 10% aqueous sodium carbonate in methanol was stirred at room temperature for four days after which most of the methanol was removed by distillation. Five percent aqueous hydrochloric acid was added until the mixture was acidic and precipitation of product was complete. This precipitate was recovered by extraction with ethyl ether. The ether solution was dried over anhydrous sodium sulfate and evaporated giving deacetylated ancepsenolidic acid.

The preceding acid was dissolved in tetrahydrofuran, and a slight excess of sodium metaperiodate was added with enough water to affect dissolution. Dry nitrogen was bubbled through the reaction mixture with stirring at room temperature overnight. The nitrogen from the reaction vessel was bubbled into a solution of 2,4-dinitrophenylhydrazine to react with any acetaldehyde formed in the reaction. However, after 24 hours no 2, 4-dinitrophenylhydrazone was observed. It seemed probable that the minute quantity of acetaldehyde theoretically formed (0.0097 g) might not be enough to cause an observable precipitate with 2,4-dinitrophenylhydrazine.

A two ml aliquot of reaction mixture was removed, and one drop of silver nitrate solution was added whereupon a dark brown precipitate formed. Nitric acid was added until the brown precipitate just dissolved. There was left a

granular white precipitate assumed to be silver iodate. This is the standard indication of a positive periodate test.

Methanolysis of Ancepsenolidic Acid (10). A solution of the pentenolide 10 (0.148 g, 0.31 mmol) in 30 ml of methanol was prepared in a round-bottomed flask fitted with a dry ice/acetone cooled cold-finger condenser. A few drops of concentrated hydrochloric acid solution were added, and the mixture was heated under reflux for eight hours and then was stirred at room temperature for five days. The progress of the reaction was monitored by thin layer chromatography. The presence of methyl acetate in the reaction mixture at the end of the reaction period was confirmed by vapor phase chromatography on a 3% JXR column (comparison of retention time to that of authentic methyl acetate). When the reaction was concluded, the methanol was evaporated under reduced pressure, and the residue was dissolved in ethyl ether. The ether solution was washed with aqueous sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. Upon evaporation of the solvent there was obtained in quantitative yield isohydroxyancepsenolide (12), an epimer of hydroxyancepsenolide (2). Recrystallization from aqueous isopropyl alcohol gave pure lactone 12: mp 115.4-115.9° C; mass spectrum 380 (3), 362 (10), 344 (3), 265 (10), 252 (4), 209 (6), 167 (3), 153 (3), 139 (4), 135 (3), 125 (22), 121 (6), 112 (8), 111 (6), 110 (4), 109 (4), 99 (4), 97 (3), 95

(7), 93 (4), 83 (4), 81 (8), 79 (5), 69 (8), 68 (3), 67 (11), 57 (38), 55 (28), 53 (3), 43 (100), 41 (24), 39 (3), 32 (13), 29 (27), 28 (47), 27 (3), 18 (14), and 17 (4); ir ($CHCl_3$) 3320-3540 (broad and weak, hydroxyl) and 1752 cm^{-1} (broad and intense, lactones); uv λ_{max} 209 nm (ϵ =16,700) (95% ethanol), pmr ($CDCl_3$) δ7.03 (dt, 1, J = 1.5 and 1.3 Hz, vinyl hydrogen on the unsaturated lactone), 5.0 (dq, 1, J = 1.5 and 7 Hz, γ-hydrogen of the unsaturated lactone), 4.25-4.80 (complex multiplet, 2, hydrogens on carbons 14' and 15'), 2.1-2.8 (m, 3, hydrogens on carbons 1' and 13'), 1.44 (d, 3, J = 6.5 Hz, methyl group on the saturated lactone), 1.40 (d, 3, J = 7 Hz, methyl group on the unsaturated lactone), and 1.27 ppm (s, 22, methylene hydrogens on carbons 2' to 12').

Acetylation of Isohydroxyancepsenolide (12). Lactone 12 (0.078 g, 0.21 mmol) was treated with pyridine (10 ml) and acetic anhydride (one ml) at room temperature for 24 hours. The reaction mixture was poured into ice water and the curdy white precipitate which formed was recovered by extraction with ethyl ether. The ether solution was washed with aqueous hydrochloric acid solution, aqueous sodium bicarbonate solution, and water and dried over anhydrous sodium sulfate. The ether was evaporated to give the monoacetate 13 in quantitative yield. Recrystallization from aqueous isopropyl alcohol gave pure 13: mp 55.4-56-5° C; ir ($CHCl_3$) 1772 (saturated lactone) and 1745 cm^{-1}

(unsaturated lactone and acetate); uv λ_{max} 209 nm (ϵ = 18,840) (95% ethanol); pmr ($CDCl_3$) δ 7.02 (dt, 1, J = 1.5 and 1.3 Hz, β-hydrogen on the unsaturated lactone), 5.62 (dd, 1, J = 3 and 5 Hz, hydrogen on carbon 14'), 5.0 (dq, 1, poorly resolved, γ-hydrogen on the unsaturated lactone), 4.59 (dq, 1, J = 3 and 6.5 Hz, γ-hydrogen on the saturated lactone), 2.10-2.80 (m, 3, two allylic hydrogens on carbon 1' and the α-hydrogen on the saturated lactone), 2.13 (s, 3, methyl hydrogens of the acetate group), 1.42 (d, 3, J = 6.5 Hz, methyl group on the saturated lactone), 1.38 (d, 3, J = 7 Hz, methyl group on the unsaturated lactone), and 1.28 ppm (s, 22, methylene hydrogens); pmr (benzene) δ 6.35 (dt, 1, J = 1.3 and 1.5 Hz, vinyl hydrogen on the unsaturated lactone), 5.33 (dd, 1, J = 6.5 and 1 Hz, β-hydrogen on the saturated lactone), 4.48 (dq, 1, J = 1.5 and 7 Hz, γ-hydrogen on the unsaturated lactone), 4.05 (dq, 1, J = 1 and 6.5 Hz, γ-hydrogen on the saturated lactone), 1.95-2.50 (m, 3, two allylic hydrogens and one hydrogen alpha to the lactone carbonyl), 1.68 (s, 3, acetate methyl hydrogens), 1.28 (s, 22, methylene hydrogens), 1.08 (d, 3, J = 6.5 Hz, methyl group on the saturated lactone), and 1.00 ppm (d, 3, J = 7 Hz, methyl group on the unsaturated lactone).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.25; H, 9.24. Found: C, 68.39; H, 9.16.

Dehydration of Isohydroxyancepsenolide (12). Isohydroxyancepsenolide (12) (0.129 g, 0.34 mmol) was placed in a reaction flask with 0.2 ml of phosphorus oxychloride and 10 ml of pyridine and stirred overnight at room temperature. The reaction mixture was then diluted with 50 ml of water and immediately a white precipitate formed. This precipitate was removed by extraction with ethyl ether. The ether solution was washed with aqueous hydrochloric acid solution and then water to remove the pyridine, and thereafter the ether solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 0.096 g (78% yield) of 1. Recrystallization from a mixture of chloroform and hexane gave pure ancepsenolide (1): mp 91.5-94.0° C (lit. [15] mp 91.5-92.0° C). The melting point of a mixture of authentic ancepsenolide (1) (mp 89.5-91.5° C) and the product above was 89.5-92.0° C. The ir and pmr spectra of the dehydration product were identical with those reported for ancepsenolide[15].

Isolation of Sterols from Pt. guadalupensis. The sterols in Pt. guadalupensis were found in the first extract (Hexane, 24 hours). This extract (13.6 g) was adsorbed on Florosil (575 g, 65 x 150 cm column) and wluted first by benzene followed by 5%, 10%, 20%, 30%, 40%, and 50% ethyl acetate in benzene solutions and finally pure ethyl acetate. Sterols were found near the end of the elution with 10% ethyl acetate in benzene and the beginning of the elution with 20%

ethyl acetate in benzene. Thin layer chromatography showed only one spot whose R_f value was the same as that of a cholesterol reference sample. Fractions 36-43 were used for further analysis.

Gas chromatographic analyses were done with glass columns packed with 3% JXR or 3% OV-1 adsorbents. Peak enhancement was accomplished using reference samples of authentic sterols (cholesterol, stigmasterol, β-sitosterol, and gorgosterol). See Table 4 for sterols with their retention times.

Mass spectrum for campesterol[22]: 402 (9), 401 (34), 400 (100), 398 (4), 386 (9) 385 (24), 384 (9), 383 (19), 382 (50), 368 (9), 367 (19), 340 (5), 316 (9), 315 (31), 314 (31), 301 (6), 300 (9), 299 (11), 290 (8), 289 (32), 288 (9), 283 (6), 281 (12), 274 (7), 273 (20), 272 (10), 271 (20), 270 (5), 261 (9), 257 (6), 256 (10), 255 (24), 253 (5), 246 (5), 241 (5), 231 (18), 229 (16), 228 (9), 227 (7), 217 (6), 215 (10), 214 (9), 213 (27), 205 (5), 201 (7), 199 (11), 191 (6), 189 (6), 187 (10), 185 (10), 178 (11), 177 (8), 176 (6), 175 (10), 174 (8), 173 (15), 171 (10), 163 (17), 162 (7), 161 (25), 160 (15), 159 (30), 158 (13), 151 (6), 149 (15), 148 (7), 147 (26), 146 (11), 145 (40), 144 (7), 143 (17), 137 (8), 136 (7), 135 (22), 134 (10), 133 (30), 132 (7), 131 (21), 130 (6), 129 (12), 125 (10), 124 (13), 123 (16), 122 (8), 121 (30), 120 (25), 119 (35), 118 (9), 117 (15), 111 (9), 109 (28), 108 (13), 107 (53), 106 (13), 105 (43), 97 (22),

96 (8), 95 (48), 94 (19), 93 (42), 92 (9), 91 (40), 85 (11), 83 (32), 82 (10), 81 (58), 80 (7), 79 (40), 77 (15), 73 (8), 71 (26), 70 (7), 69 (55), 68 (7), 67 (38), 60 (5), 57 (40), 56 (10), 55 (77), 53 (11), 43 (90), and 41 (63).

Mass spectrum for poriferasterol[22]: 414 (7), 413 (23), 412 (68), 400 (4), 398 (3), 397 (5), 393 (6), 379 (3), 370 (4), 369 (13), 352 (5), 351 (12), 314 (7), 302 (5), 301 (10), 300 (28), 299 (6), 285 (6), 283 (4), 282 (3), 281 (2) 273 (15), 272 (18), 271 (32), 270 (6), 267 (4), 258 (7), 257 (5), 256 (7), 255 (31), 231 (5), 229 (5), 215 (6), 213 (9), 199 (5), 175 (6), 173 (6), 166 (5), 163 (7), 161 (10), 159 (18), 157 (6), 151 (8), 149 (6), 147 (16), 146 (5), 145 (19), 143 (8), 139 (11), 137 (6), 135 (10), 133 (21), 131 (11), 129 (5), 123 (19), 122 (5), 121 (15), 120 (8), 119 (17), 117 (8), 109 (13), 107 (21), 105 (22), 97 (24), 95 (27), 93 (27), 91 (23), 83 (55), 81 (50), 79 (23), 77 (10) 71 (7), 69 (100), 67 (25), 57 (14), 55 (65), 53 (8), 43 (25), and 41 (33).

Isolation and Saponification of Fatty Esters from a Single Colony of Pt. guadalupensis. A large quantity of fatty esters was found in the third extract (hexane, 71 hours) of a single colony of Pt. guadalupensis from Ragged Keys, Florida. This extract (27 g, 19% of the dry weight of the colony) was adsorbed on Florisil (700 g, 6.5 x 150 cm column). Most of the mixture of fatty esters was eluted with 10% ethyl acetate in benzene.

A portion of the fatty ester mixture (0.372 g) was added to a solution of 85% potassium hydroxide pellets (1.53 g) in 25 ml of methanol and 4.5 ml of water. Just enough chloroform was added to effect solution. The mixture was heated under reflux for three hours. Twenty ml of solvent was removed by distillation, and the remaining material was poured into a mixture of ice and dilute hydrochloric acid. A white precipitate formed which was removed by extraction with chloroform. The chloroform solution was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure to give 0.365 g of a mixture of fatty acids and alcohols.

Methylation of the Fatty Acids and Analysis of the Resulting Fatty Ester-Alcohol Mixture. The product of the preceding saponification was dissolved in 50 ml of ethyl ether at room temperature. A cold solution of diazomethane in ethyl ether was added until the yellow color of diazomethane persisted. The mixture was placed in the refrigerator for one hour and then was allowed to stand at room temperature overnight. The excess diazomethane was destroyed with acetic acid, and the mixture was washed with aqueous sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. The ether was removed by evaporation under reduced pressure giving 0.370 g of product.

The preceding mixture of methyl fatty esters and alcohols was analyzed by gas chromatography using a glass column packed with 3% JXR adsorbent. Peak enhancement was accomplished using reference samples of authentic methyl esters of fatty acids. Combined use of gas chromatography and mass spectrometry provided mass spectra for each component of the mixture. See Table 5 for results of these analyses.

Mass spectrum for GC peak 1 (myristyl alcohol): 214 (1), 196 (2), 182 (1), 168 (6), 154 (2), 140 (6), 139 (4), 126 (7), 125 (11), 113 (3), 112 (12), 111 (20), 110 (5), 98 (20), 97 (49), 96 (12), 96 (6), 85 (17), 84 (33), 83 (66), 82 (27), 81 (8), 74 (6), 73 (4), 71 (31), 70 (53), 69 (77), 68 (31), 67 (18), 58 (5), 57 (77), 56 (62), 55 (97), 54 (11), 53 (6), 44 (6), 43 (100), 42 (23), 41 (77), 39 (11), 32 (14), 31 (16), 29 (37), 28 (53), 27 (17), and 18 (14).

Mass spectrum of GC peak 2 (methyl myristate): 242 (9), 213 (3), 210 (8), 199 (12), 185 (3), 157 (3), 143 (20), 129 (8), 125 (4), 115 (3), 112 (3), 111 (6), 109 (3), 101 (9), 99 (4), 98 (4), 98 (7), 97 (21), 96 (3), 95 (5), 88 (12), 87 (100), 85 (11), 84 (10), 83 (20), 82 (8), 81 (7), 75 (25), 74 (94), 73 (4), 71 (22), 70 (12), 69 (30), 68 (7), 67 (9), 59 (14), 58 (3), 57 (43), 56 (17), 55 (45), 54 (6), 53 (4), 45 (3), 44 (4), 43 (7), 42 (13), 41 (52), 39 (8), 32 (11), 31 (3), 29 (29), 28 (34), 27 (10), 18 (9), and 15 (6).

Mass spectrum of GC peak 3 (cetyl alcohol): 242 (1), 224 (1), 196 (5), 182 (1), 168 (3), 154 (3), 140 (5), 139 (5), 126 (8), 125 (12), 112 (12), 111 (27), 110 (5), 99 (4), 98 (21), 97 (57), 96 (12), 95 (4), 85 (19), 84 (36), 83 (84), 82 (34), 81 (8), 71 (35), 70 (52), 69 (82), 68 (34), 67 (15), 58 (4), 57 (83), 56 (56), 55 (97), 54 (11), 53 (4), 44 (5), 43 (100), 42 (22), 41 (75), 39 (8), 31 (15), 29 (36), 28 (5), and 27 (13).

Mass spectrum of GC peak 4 (methyl palmitate): 270 (8), 239 (4), 227 (7), 185 (3), 171 (3), 143 (12), 129 (6), 101 (5), 97 (6), 88 (6), 87 (60), 85 (3), 84 (4), 83 (9), 75 (19), 74 (100), 71 (6), 70 (3), 69 (14), 67 (3), 59 (15), 57 (17), 56 (6), 55 (24), 43 (30), 42 (5), 41 (24), 29 (12), and 27 (5).

Mass spectrum of GC peak 5 (octadecenyl alcohol): 268 (1), 250 (5), 222 (2), 208 (1), 194 (2), 180 (1), 166 (2), 152 (4), 151 (3), 138 (7), 137 (6), 125 (5), 124 (12), 123 (11) 112 (4), 111 (11), 110 (22), 109 (25), 98 (8), 97 (29), 96 (54), 95 (45), 94 (3), 87 (4), 85 (8), 84 (11), 83 (46), 82 (75), 81 (56), 80 (6), 79 (7), 74 (5), 71 (14), 70 (18), 69 (62), 68 (48), 67 (61), 66 (6), 57 (41), 56 (26), 55 (100), 54 (40), 53 (7), 44 (3), 43 (61), 42 (13), 41 (67), 39 (9), 32 (14), 31 (13), 29 (22), 28 (39), 27 (10), 18 (8), and 17 (3).

Mass spectrum of GC peak 6 (methyl oleate): 296 (2), 265 (9), 264 (14), 222 (7), 180 (5), 166 (3), 165 (3), 153 (3), 152 (4), 151 (3), 141 (3), 139 (5), 138 (5), 137 (5), 129 (3), 128 (3), 125 (7), 124 (6), 123 (8), 115 (5), 114 (3), 112 (6), 111 (15), 110 (12), 109 (7), 101 (5), 99 (4), 98 (18), 97 (26), 96 (19), 95 (14), 94 (3), 88 (3), 87 (21), 85 (8), 84 (28), 83 (43), 82 (18), 81 (20), 79 (5), 75 (5), 74 (39), 73 (4), 71 (13), 70 (17), 69 (89), 68 (20), 67 (24), 59 (10), 57 (31), 56 (22), 55 (100), 54 (16), 53 (5), 43 (45), 42 (10), 41 (52), 39 (7), 29 (19), 28 (9), and 27 (8).

Mass spectrum of GC peak 7 (methyl stearate): 298 (13), 267 (5), 254 (10), 213 (3), 199 (5), 143 (16), 129 (9), 125 (3), 111 (5), 101 (5), 98 (5), 97 (11), 96 (3), 95 (4), 88 (7), 87 (56), 85 (5), 84 (6), 83 (14), 82 (4), 81 (4), 75 (22), 74 (100), 71 (8), 70 (5), 69 (20), 68 (4), 67 (6), 59 (6), 57 (22), 56 (6), 55 (30), 54 (3), 43 (39), 42 (6), 41 (29), 39 (4), 32 (7), 29 (11), 28 (18), 27 (7), and 18 (5).

Trimethylsilyl ethers of the fatty alcohols were prepared by adding trimethychlorosilane to the alcohol-ester mixture in a few ml of ethyl ether. The mixture was stirred for 30 minutes and was then used for gas chromatographic analysis using the peak-shift technique[27,28] (glass column, 3% JXR adsorbent). Only peaks 1, 3, and 5 (Table 5) were shifted after silylation.

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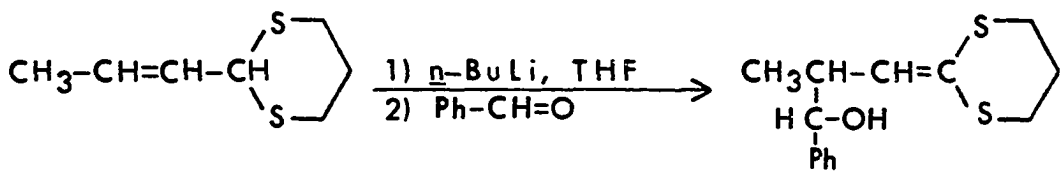
II. Investigation of a Novel Method for the Synthesis of Butyrolactones

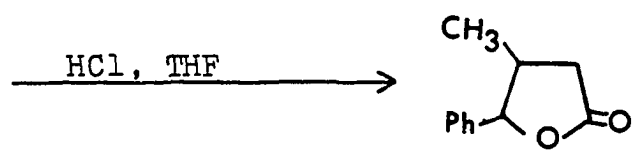
INTRODUCTION

In an investigation of the reactivity of the anion derived from 2-(1-propenyl)-1, 3-dithiane (1), Tuggle[1] reported the synthesis of 1-(1-3-propylenedithio)-3-methyl-4-phenyl-1-butene (2) in 79% yield. Establishment of the structure of 2 was accomplished by analysis of spectral data



1 2

and by the conversion of 2 to β-methyl-γ-phenyl-γ-butyrolactone (3). This conversion seemed to provide a novel approach to the synthesis of butyrolactones. It appeared reasonable that this approach could be readily extended to



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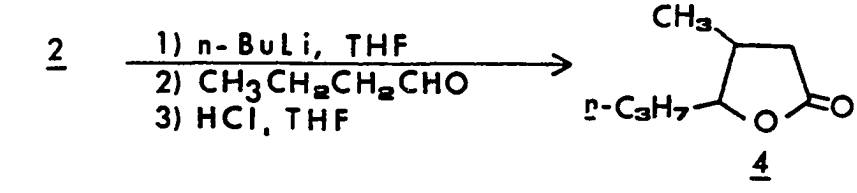
other butyrolactones. For example, the anion from 1 could possibly be added to other aldehydes such as butyraldehyde or propionaldehyde to give compounds 4 and 5. Furthermore, altering the substitution at the beta position should be



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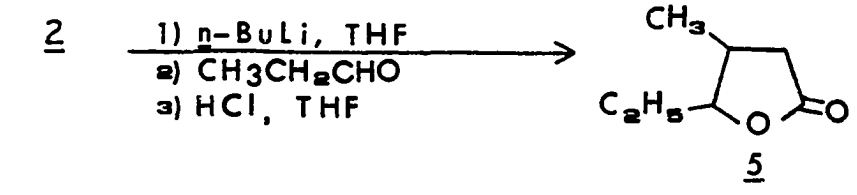

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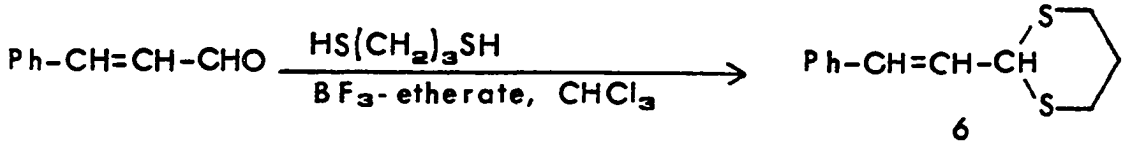
accomplished by preparing the 1, 3-dithiane from different α, β-unsaturated aldehydes, e. g., synthesis of 7 and 8.



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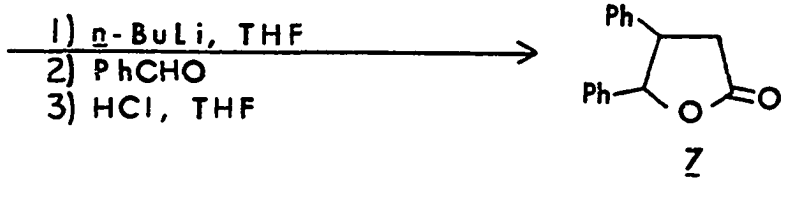

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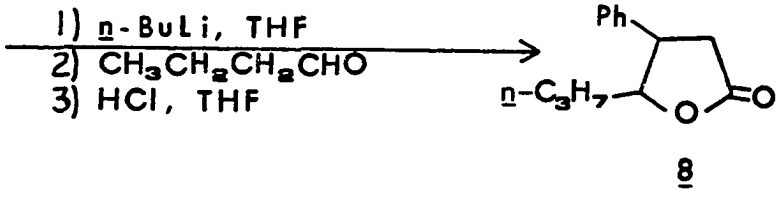

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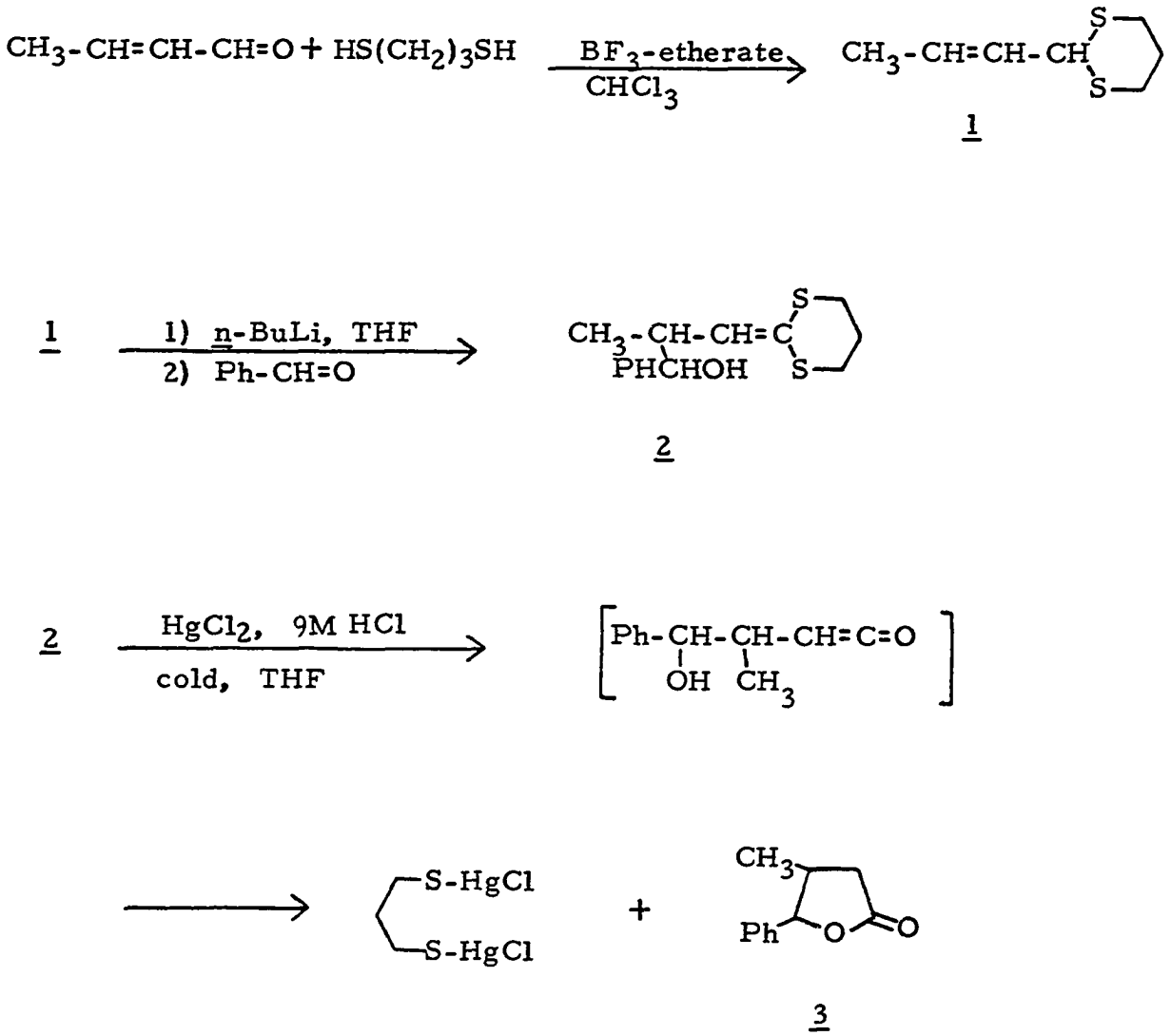
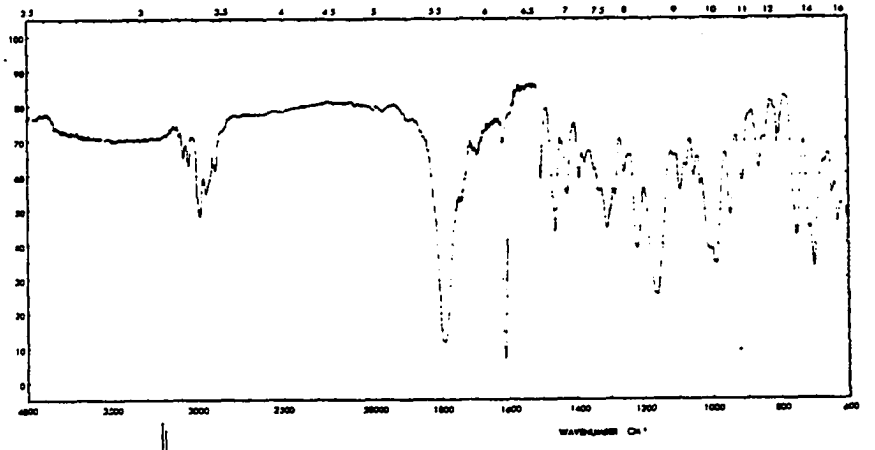
Scheme 1

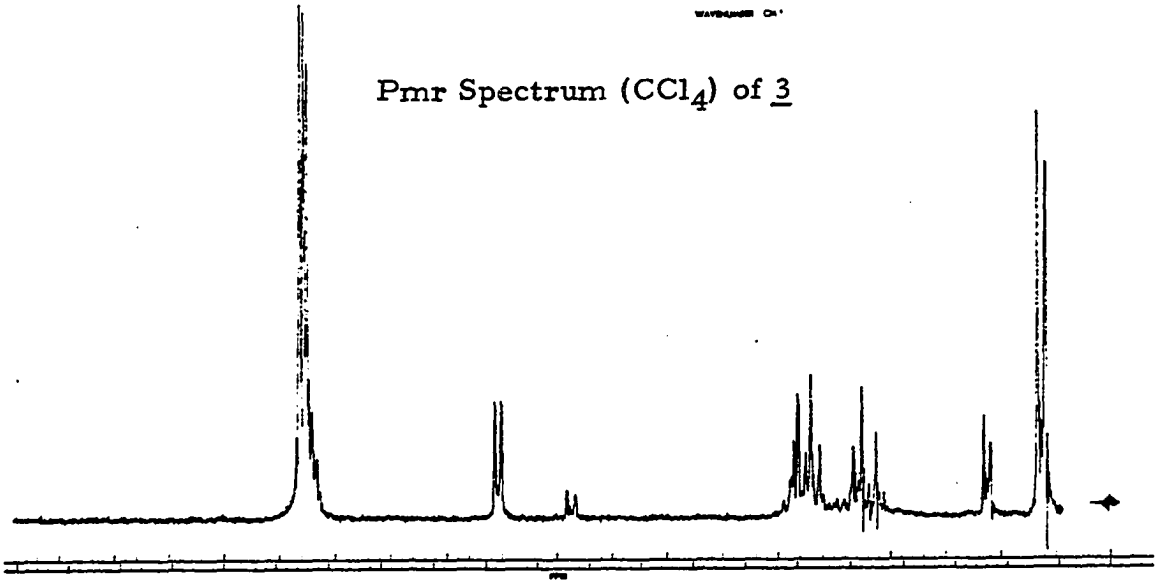

CH3-CH=CH-CH=O + HS(CH2)3SH
BF3-etherate
CHCl3
CH3-CH=CH-CH
S
S
1
1) n-BuLi, THF
2) Ph-CH=O
CH3-CH-CH=C
PHCHOH
S
S
2
HgCl2, 9M HCl
cold, THF
Ph-CH-CH-CH=C=O
OH
CH3
S-HgCl
S-HgCl
+
CH3
Ph
O
O
3

Spectra of β-Methyl-γ-phenyl-γ-butyrolactone (3)

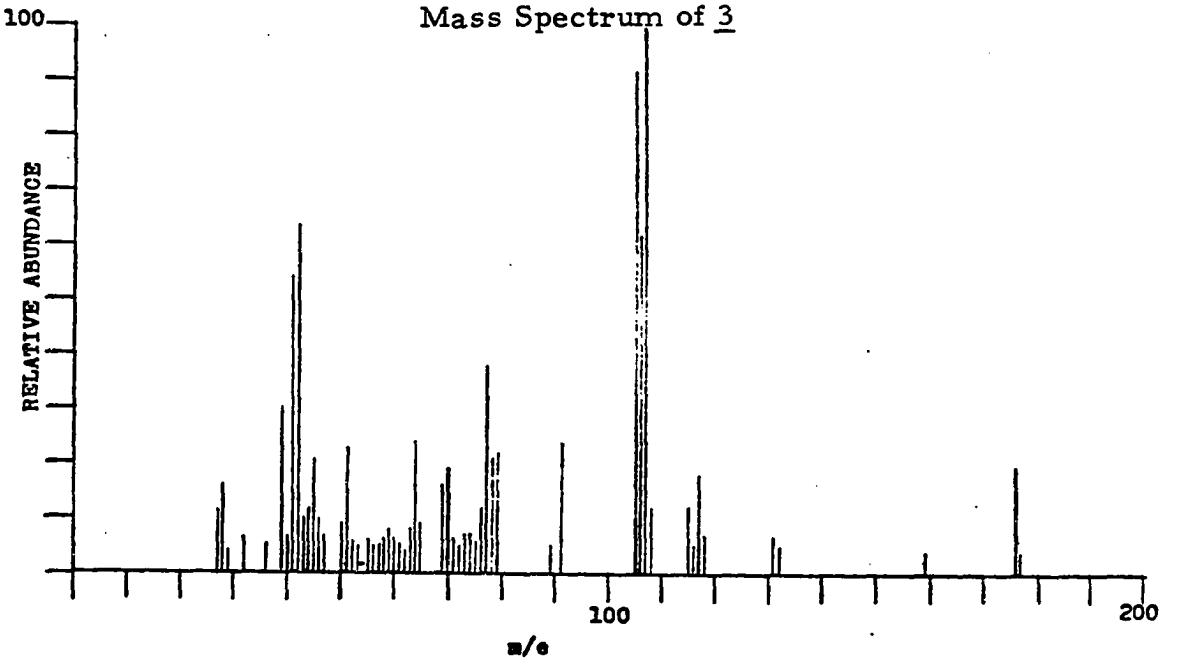
Ir Spectrum (film) of 3



Pmr Spectrum (CCl_4) of 3



Mass Spectrum of 3

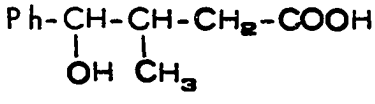


The method used by Tuggle to prepare the lactone 3, however, gave only a 60% yield. It is the purpose of this investigation to develop a procedure which would optimize the yield for the conversion of 2 to 3.

RESULTS AND DISCUSSION

The procedure used by Tuggle[1] for synthesis of lactone 3 involved hydrolysis of 2 with 10% aqueous hydrochloric acid in tetrahydrofuran. A mixture of lactone 3 and 1,3-propanedithiol was produced in 77% yield. To remove the 1,3-propanedithiol, the mixture was refluxed with potassium hydroxide in 95% ethanol and evaporated to dryness. The residue was washed several times with ethyl ether and air dried. The remaining potassium salt was treated with concentrated hydrochloric acid to reform the lactone 3 (60% yield from 2).

The primary cause of the low yield seemed to be the method used for removing the dithiol. According to Corey[2] separation of the products of hydrolysis of dithianes could be effectively accomplished by column chromatography. Therefore, as a first approach, the hydrolysis step was repeated using 5% aqueous hydrochloric acid in tetrahydrofuran.



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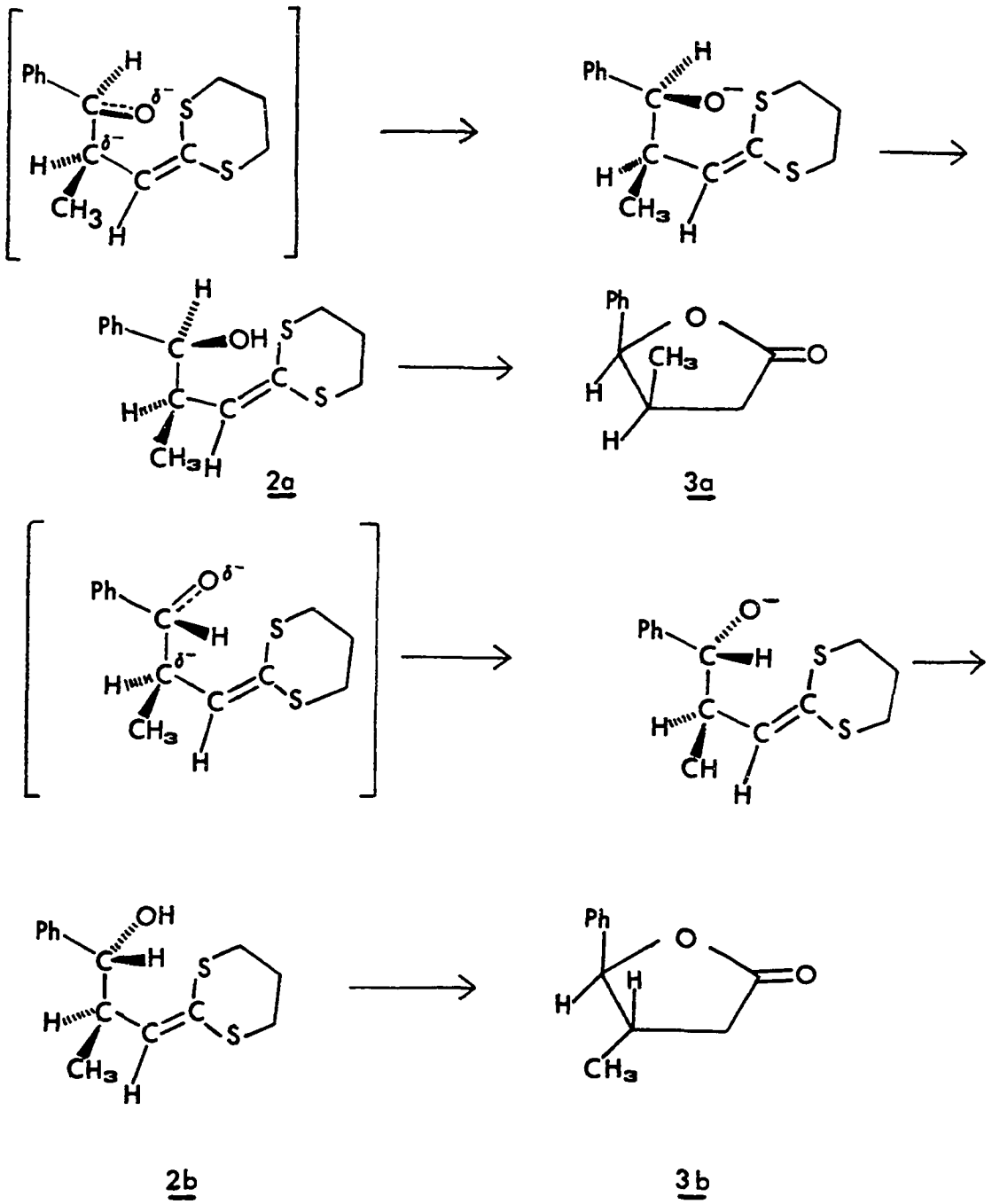
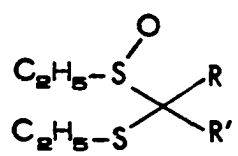
Scheme 2



The product appeared to be a mixture of lactone 3, hydroxyacid 9, and 1,3-propanedithiol. Chromatography over silicic acid provided a mixture of lactone 3 and hydroxyacid 9 which was still contaminated with dithiol. This mixture was treated with 6% aqueous hydrochloric acid in tetrahydrofuran to convert the remaining acid to lactone 3. The yield was good (83%), but this method did not effect complete removal of the dithiol. The failure of the initial hydrolysis step to effect complete lactonization could possibly be avoided by use of a more concentrated acid solution.

Richman, Herrmann, and Schlessinger[3] reported the hydrolysis of the sulfoxide 10 with concentrated hydrochloric acid in tetrahydrofuran in the presence of excess mercuric chloride. This procedure gave the corresponding aldehyde or ketone uncontaminated by the disulfide by-product. The use of mercuric



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salts to remove the organosulfur by-products of thioketal and thioacetal hydrolysis has been reported by many authors[4-11]. However, Tuggle[1] and Corey[6] reported difficulties when unsaturated dithianes were hydrolyzed in this manner because of the concomitant reaction of the double bond. While 2 is unsaturated, its initial hydrolysis product should be a

ketene which would immediately react further in the presence of aqueous acid to give hydroxyacid 9. Therefore, precipitation of 1,3-propanedithiol as its mercury salt should provide a feasible means for its separation from the reaction product.

Following the Richman procedure[3], 2 was added to a suspension of mercuric chloride (4 equivalents) in a mixture of concentrated hydrochloric acid and tetrahydrofuran (1:5 ratio by volume). A white precipitate of mercury salt immediately began to form. On completion of the reaction this salt was removed by filtration through Celite, and the lactone was obtained without contamination by 1,3-propanedithiol (see Scheme 1). The yields of 3 for two attempts using this procedure were 81% and 84%. Spectral data for 3 (Figure 1) agreed with those reported for -methyl- -phenyl- -butyrolactone by Tuggle[1].

The presence of two disatereomeric forms of 3 was evident from the pmr spectrum and from gas chromatographic analysis. When 3 was analyzed using a 10% FFAP gas chromatographic column, two closely spaced peaks were observed with approximately a 3:1 ratio of peak areas. In the pmr spectrum (Figure 1) the gamma-proton of the lactone appeared as two distinct doublets (5.53 ppm, J = 5 Hz; 4,87 ppm, J = 8 Hz) which integrated for one proton. Also, the beta-methyl group appeared as two doublets (1.11 ppm, J = 5 Hz; 0.61 ppm, J = 6 Hz) which integrated for three protons.

The unusually high field absorption for the methyl doublet corresponding to the major component of the mixture provided evidence for relative stereochemical assignments. When the beta-methyl and the gamma-phenyl group are cis, the methyl group should be in the proper position to experience a marked shielding effect from the benzene ring. Due to steric crowding the benzene ring should be limited in its ability to rotate about the single bond connecting it to the lactone carbon. The favored conformation should place the methyl group in a shielded position above the benzene ring. When the methyl and phenyl groups are trans, the methyl group cannot experience such shielding by the benzene ring and, therefore, should exhibit a normal chemical shift (e. g. δ 1.11 ppm).

Further evidence was provided by the pmr spectrum in benzene-d_6. The use of benzene-d_6 as solvent caused a general upfield shift of the spectrum. A shift of 0.57 ppm was observed for the methyl doublet of the minor component of the mixture (δ1.11 ppm to δ0.53 ppm) while a shift of only 0.37 ppm was observed for the larger methyl doublet (δ0.61 ppm to δ0.24 ppm). In the trans isomer the methyl group should be more susceptible to solvent effects than in the cis isomer where the large phenyl group hinders approach of the solvent molecule. Therefore, the methyl doublet of the cis isomer should exhibit a smaller upfield shift than the trans isomer. It was concluded then that the

cis isomer was the major component of the mixture. No nuclear Overhauser effect was observed for either component of the mixture.

Compound 2 also occurred as two diastereomeric forms in the same ratio as the isomers of 3. The synthesis of 2 should then have been the point of generation of the mixture of isomers. Examination of models suggested that the transition state leading to isomer 2a (Scheme 2), which is the precursor of the cis-lactone, 3a, involved fewer steric interactions than the transition state leading to 2b, the precursor of the trans-lactone, 3b. The transition state leading to 2a could assume an orientation with the phenyl group of benzaldehyde staggered between the methyl and hydrogen of the anion, while the carbonyl group was staggered between the methyl and vinyl groups of the anion. In the transition state leading to 2b, when the phenyl group was in a favorable position staggered between the methyl and hydrogen, the carbonyl with its developing negative charge was then in a position where interactions could occur with the vinyl group of the anion and with a sulfur atom in the dithiane ring. Therefore, the observation that the major component of the mixture of lactones, 3, was the cis-isomer, 3a, could be explained by steric interactions in the transition state leading to 2.

SUMMARY

The conversion of 1-(1,3-propylenedithio)-3-methyl-4-hydroxy-4-phenyl-1-butene (2) to β-methyl-γ-phenyl-γ-butyrolactone (3) in yields of 81-84% illustrated a novel method for the synthesis of butyrolactones. The synthetic route beginning with crotonaldehyde and 1,3-propanedithiol is outlined in Scheme 1.

EXPERIMENTAL

All melting points and boiling points are uncorrected. All solvents were redistilled prior to use. Column chromatography support was silicic acid (SilicAR CC-7, Mallinckrodt, 100-200 mesh). Thin layer chromatography was performed using 5 x 20 cm glass plates coated with silicic acid (SilicAR TLC-7, Mallinckrodt) or plastic sheets pre-coated with silica gel (Polygram Sil G/UV, Machery-Nagel, Duren). The developed plates were exposed to iodine vapor for visualization of the chromatogram.

Gas chromatographic analyses were performed on a Varian Aerograph Model 1220-1 gas chromatograph. The infrared spectra were taken on a Beckman IR-8, Beckman Microspec, or Beckman IR-10 spectrophotometer in solutions of chloroform or as thin films of pure compound. Proton magnetic resonance (pmr) spectra were taken on Varian T-60 or XL-100 spectrometers using tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in δ-units (parts per million from TMS). Multiplicities are reported using the following symbols: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; dq, double quartet; and m, multiplet. Mass spectra were taken on a Hitachi

Perkin-Elmer RMU-7 spectrometer using perfluorokerosene as an internal reference. Major peaks and molecular ions are reported followed by their percentage of the base peak.

Combustion analyses were carried out by Mr. Erick Meier, Department of Chemistry, Stanford University.

Synthesis of 2-(1-Propenyl)-1,3-dithiane (1)[1]. A solution of 30.0 g (0.43 mol) of crotonaldehyde and 40.5 g (0.38 mol) of 1,3-propanedithiol in 190 ml of chloroform was placed in a one liter threenecked flask containing a magnetic stirring bar and equipped with an addition funnel. The flask was immersed in an ice-water bath and six ml of boron trifluoride etherate was added slowly with stirring to the flask contents. The reaction mixture was stirred for 12 hrs as the temperature of the bath was allowed to rise to room temperature. The chloroform solution was washed with a 10% sodium bicarbonate solution and a saturated solution of sodium bisulfite. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to give 59.1 g (86%) of crude dithiane 1. Distillation of the entire crude product yielded 34.8 g (51%) of 2-(1-propenyl)-1,3-dithiane (1) as a colorless liquid: bp98.0-99.5° C (3 mm) (lit.[1] bp 77-78° C (1 mm)). A sample for spectral analysis was obtained from the middle fraction from the distillation, bp 99.0-99.5° C (3 mm). Ir (thin film) 1658 (carbon-carbon double bond) and 1419 cm^{-1} (carbon-sulfur stretch). The ir spectrum is in accord with reported data[1].

Synthesis of 1-(1,3-Propylenedithio)-3-methyl-4-hydroxy-4-phenyl-1-butene (2)[1]. A solution of 13.3 g (0.083 mol) of 2-(1-propenyl)-1,3-dithiane (1) in 100 ml of dry tetrahydrofuran was placed in a 500 ml three-necked flask containing a magnetic stirring bar and equipped with a nitrogen inlet and a septum cap. The flask was immersed in a dry ice-acetone bath, and the solution was stirred under a nitrogen atmosphere which was maintained throughout the experiment. A solution of 0.083 mol of n-butyl lithium in hexane (46.2 ml of a 1.8 M solution) was added to the contents of the flask using a syringe. The reaction mixture was stirred for four hr at -70° C, and benzaldehyde (8.9 g, 0.083 mol) was added to the mixture using a syringe. Stirring was continued for five min at the same temperature. The reaction mixture was then acidified with 10% hydrochloric acid solution and extracted twice with 100 ml portions of chloroform. The chloroform solution was washed five times with a saturated solution of sodium bisulfite and dried over anhydrous magnesium sulfate. Evaporation of the chloroform yielded 21.5 g (97.3%) of a diastereomeric mixture of 2 as an oily white solid. Six recrystallizations from 95% ethanol gave a sample which melted at 88-101° C. Ir ($CHCl_3$) 3400 (hydroxyl), 1650 (carbon-carbon double bond), and 1420 cm^{-1} (carbon-sulfur bond); pmr ($CDCl_3$) δ 7.1-7.5 (m, 5, aromatic protons), 5.3 and 4.6 (Two doublets, total one proton, J = 6 Hz and J = 8 Hz, olefinic proton), 3.1-3.9 (m, 2, allylic proton and

benzylic proton), 1.7-3.0 (m, 7, protons of the dithiane ring and hydroxyl proton), and 1.05 and 0.70 ppm (two doublets, total three protons, J = 6 Hz and J = 7 Hz, methyl protons). This data is in accord with that reported in the literature[1].

Synthesis of β-Methyl-γ-phenyl-γ-butyrolactone (3). A solution of 2 (0.50 g, 1.88 mmol) in a mixture of 5% hydrochloric acid solution (10 ml) and tetrahydrofuran (30 ml) was stirred at 50-60° C for two hr. The reaction mixture was cooled and extracted with three 50 ml portions of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate yielding 0.57 g of a mixture of 3, hydroxyacid 9, and 1,3-propanedithiol (100% yield). Chromatography over silicic acid provided a mixture of 3 and 9 in quantitative yield (0.35 g). A strong odor of 1,3-propanedithiol was evident although its presence was no longer evident from thin layer chromatography. The mixture of 3 and 9 from the chromatographic separation (0.35 g) was dissolved in tetrahydrofuran (30 ml), and 6% hydrochloric acid solution (10 ml) was added. The mixture was heated at 50-55° for two hr, cooled, and extracted with three 50 ml portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, and evaporated giving 0.29 g (83%) of 3 contaminated with 1,3-propanedithiol.

A solution of 2 (1.00 g, 376 mmol) in tetrahydrofuran (15 ml) was added to an ice-bath cooled suspension of

mercuric chloride (4.1 g, 15.1 mmol) in a solution of 20 ml of tetrahydrofuran and four ml of 36.5% hydrochloric acid. A white precipitate formed on addition of 2. The reaction mixture was stirred at ice-bath temperature for two hr and then diluted with water. The resulting mixture was extracted three times and 50 ml portions of chloroform. The combined chloroform solutions were washed several times with 10% aqueous sodium carbonate, filtered through Celite to remove the mercury salts, and dried over anhydrous magnesium sulfate. A second filtration through Celite and evaporation gave 0.588 g (84.3%) of 3 as a clear oil.

This procedure was repeated using 0.48 g (1.80 mmol) of 2 in 15 ml of tetrahydrofuran, 2.05 g (7.55 mmol) of mercuric chloride in 10 ml of tetrahydrofuran, and 2 ml of 36.5% hydrochloric acid. The yield of lactone 3 was 0.26 g (81.2%).

Column chromatography of the product 3 (from the first hydrolysis attempt using mercuric chloride) over silicic acid (21 g, bed: 1.8 x 26 cm, eluent: benzene) provided samples for spectral analyses. Gas chromatographic analysis (3% OV-17 and 10% FFAP adsorbents) of fraction four from this chromatography indicated that no impurities were present (the 10% FFAP column showed separation of the two diastereomeric forms of 3 into two closely spaced peaks with a ratio of peak areas approximately 3:1). Bulb to bulb distillation (bp 70.5-72.5^{o} C, 0.6 mm) of fraction four

provided a sample for elemental analysis. Ir (thin film) 1785 cm^{-1} (lactone); pmr (100mHz) (CCl_4) δ 7.15-7.45 (m, 5, aromatic protons), 5.53 and 4.87 (two doublets, total one proton, J = 5 Hz and 8 Hz, benzylic proton on a carbon bearing oxygen), 2.0-3.0 (m, 3, remaining lactone ring protons), and 1.11 and 0.61 ppm (two doublets, total three protons, J = 5 Hz and 6 Hz, methyl protons); pmr (60mHz) (benzene-d_6) δ 6.80-7.20 (m, 5, aromatic protons), 5.50 and 4.36 (two doublets, total one proton, J = 5Hz and 8Hz, benzylic proton on a carbon bearing oxygen), 1.50-2.40 (m, 3, remaining lactone ring protons), and 0.53 and 0.24 ppm (two doublets, total three protons, J = 5Hz and 6 Hz, methyl protons); mass spectrum 177 (4), 176 (20), 117 (18), 116 (5), 115 (12), 108 (12), 107 (100), 106 (62), 105 (92), 91 (24), 79 (22), 78 (21), 77 (38), 76 (12), 70 (19), 69 (16), 65 (9), 64 (24), 51 (23), 50 (9), 46 (10), 45 (21), 44 (12), 43 (10), 42 (64), 41 (54), 39 (30), 28 (16), and 27 (11).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.00;H, 6.82. Found: C, 74.69; H, 6.99.

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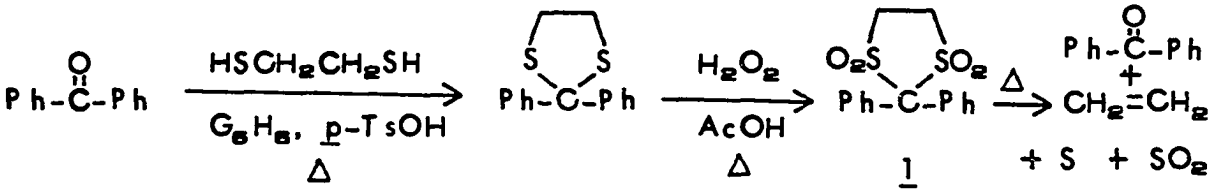
III. Investigation of the Thermal Decomposition of 1,1,3,3-Tetraoxo-2,2-diphenyl-1,3-dithiane

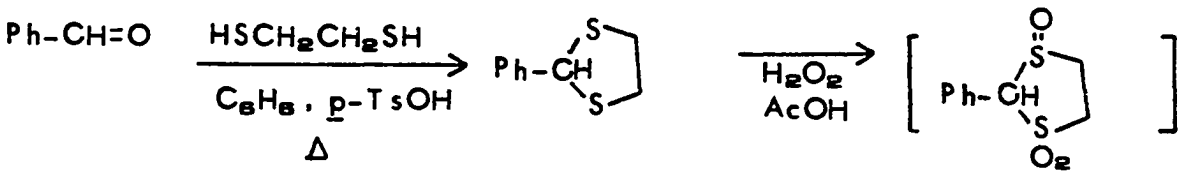
INTRODUCTION

In an investigation of the thermal decomposition of sulfones and sulfoxides, Tuggle[1] reported the synthesis and pyrolysis of several sulfones and sulfoxides. A typical example was 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiolane (1) which was pyrolyzed giving benzophenone, ethylene, sulfur, and sulfur dioxide. The sequence was successful only



when the starting carbonyl compound was benzophenone or acetophenone. Unsuccessful attempts were made using benzaldehyde, 2-octanone, and 4-tert-butylcyclohexanone. The oxidation of the dithiolane 2 prepared from benzaldehyde

and 1,2-ethane-dithiol did not yield the desired disulfone but probably the trioxide 3. 2-Octanone and 4-tert-butylcyclohexanone both yielded the desired disulfones



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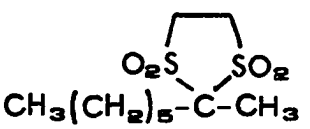
(4 and 5) which were found to be thermally stable at temperatures 100-200° above their melting points. Sulfone 6 and sulfoxide 7 decomposed smoothly on heating to give



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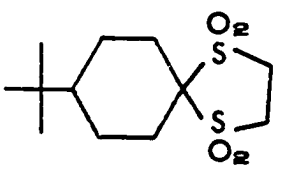

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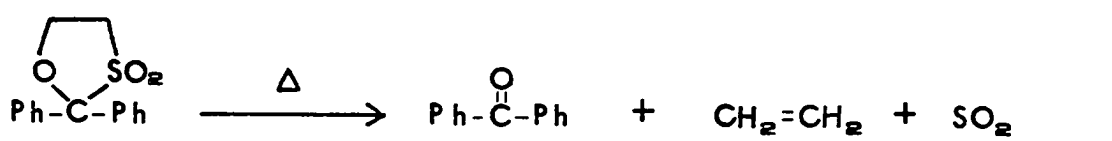
benzophenone and ethylene. Mechanistic pathways were proposed for these thermal transformation. When 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiane (8) was pyrolyzed,



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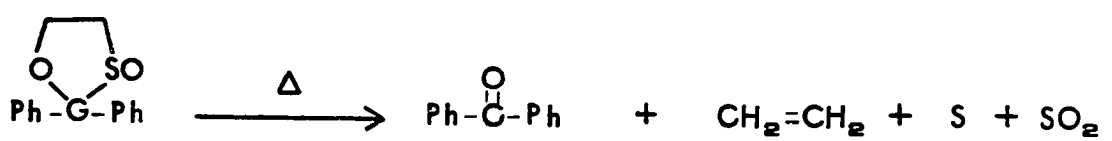

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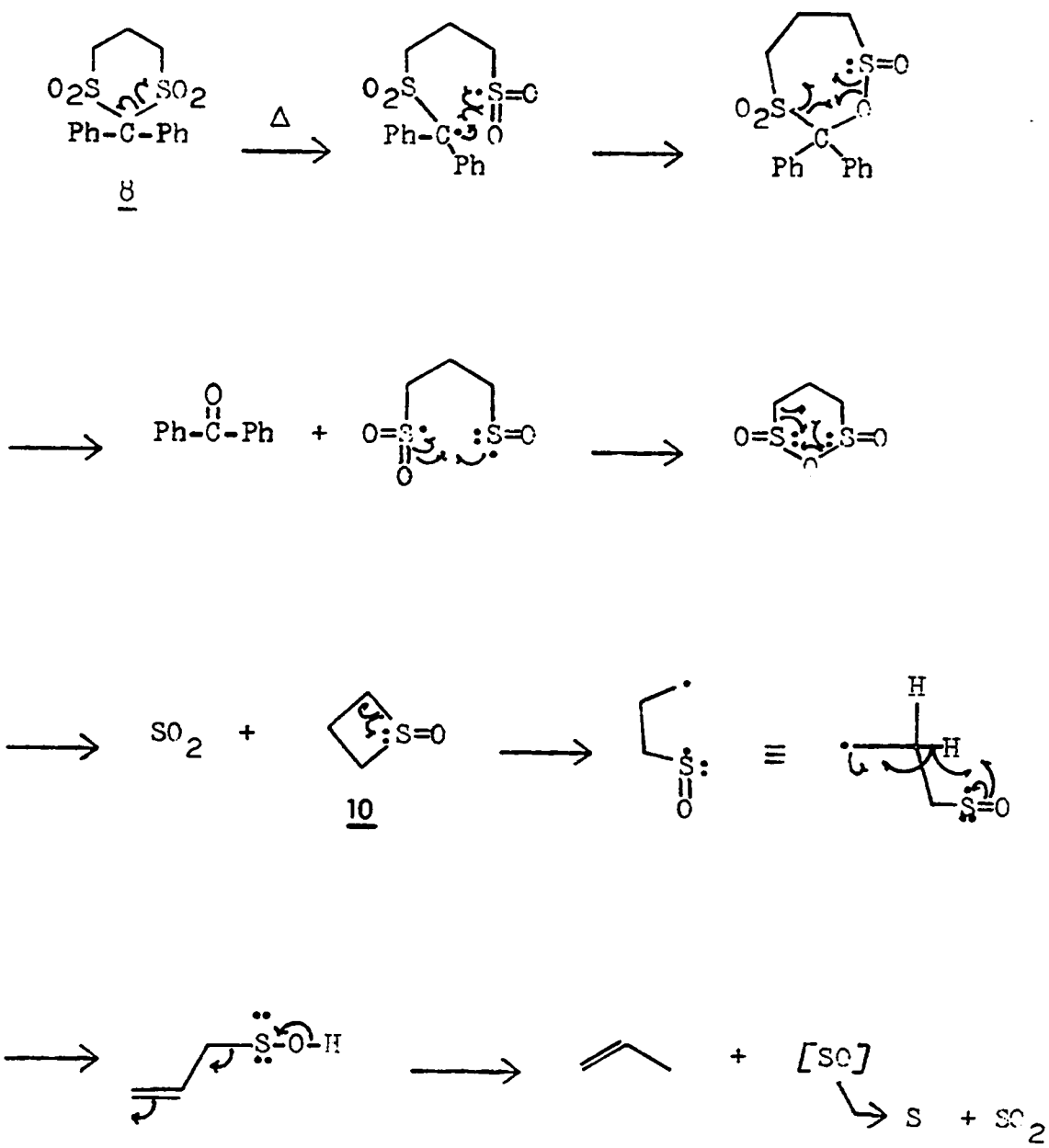
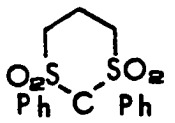
Scheme 1





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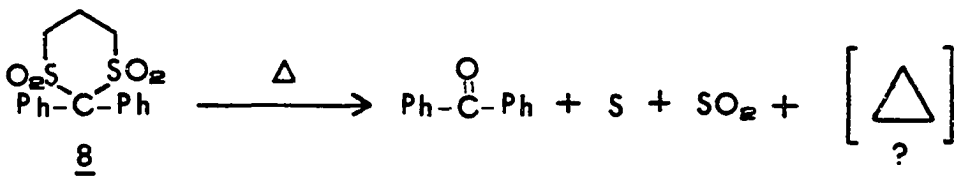
benzophenone was obtained as expected, and what appeared to be cyclopropane was observed among the volatile products. A mechanism was proposed to account for the formation of these products.



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The purpose of this investigation was to reexamine the products of the thermal decomposition of 8 in an attempt to confirm their identity.

RESULTS AND DISCUSSION

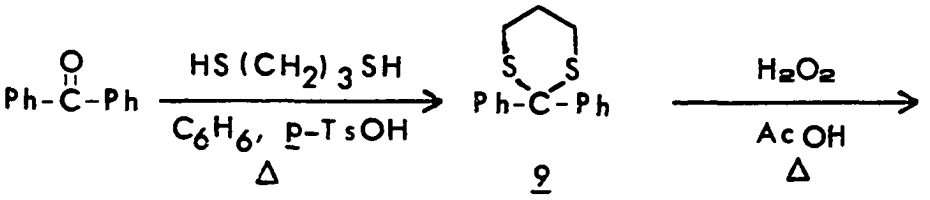
The synthetic sequence reported by Tuggle was used for the preparation of 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiane (8), see below. Pyrolyses were attempted either at 300° C and atmospheric pressure in a nitrogen atmosphere or at 290° C and 1 mm pressure.

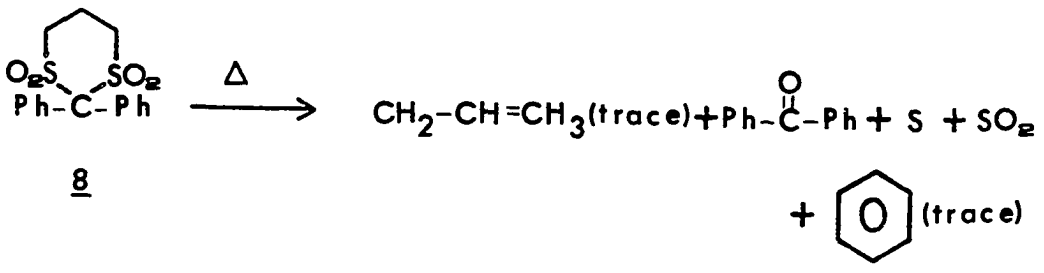
For the pyrolyses at atmospheric pressure, two methods were considered for trapping the volatile hydrocarbon product: condensation in a cold trap or by reaction with an electrophilic reagent. Olefins react readily with bromine in carbon tetrachloride, and according to many organic chemistry textbooks[2,3,4] cyclopropane, while not as reactive as propane, does react readily with aqueous mineral acids and with halogens in the presence of a Lewis acid. Accordingly, cyclopropane from pyrolysis of 8 should be trapped by passage through a solution of bromine in carbon tetrachloride in the presence of ferric bromide giving 1, 3-dibromopropane. However, a closer check of the literature indicated that while cyclopropane does react under these conditions it does so slowly and in poor yield[5,6].

The efficacy of the second method considered was tested

by injection of a small amount of cyclopropane into the nitrogen flow in the pyrolysis apparatus. Condensation of cyclopropane (b. p. 33° C) was observed in the trap cooled by dry ice-acetone.

Using the cold trapping method and the pyrolysis apparatus described by Tuggle, 8 was pyrolyzed at 300°C and atmospheric pressure in a nitrogen atmosphere. A small amount of a material which was liquid at room temperature condensed in the cold trap. Spectral analysis indicated that this material was benzene. No other volatile hydrocarbon was observed. Benzophenone and sulfur were produced in yields similar to those reported by Tuggle. The pyrolysis reaction was repeated using the same appartus and conditions four times with benzene being the only volatile hydrocarbon observed.





In order to confirm the absence of cyclopropane from the reaction products, the pyrolysis was attempted in a closed system at 1 mm pressure and 290° C. Benzophenone and sulfur were produced in yields lower than those reported by Tuggle. Sulfur dioxide and a small amount of benzene were also observed along with a mixture of other volatile products. The infrared spectrum of this volatile mixture was compared with spectra of cyclopropane and propene published by Pierson, Fletcher, and Gantz[7]. No absorption corresponding to cyclopropane were observed. However, propene did appear to be present along with a small quantity of unidentified gases.

The mechanism proposed by Tuggle for the thermal decomposition of 8 was modified (Scheme 1) to account for the production of propylene rather than cyclopropane. Sulfoxides such as 10 (Scheme 1) usually undergo concerted thermal eliminations involving a shift of six electrons[8]. The five-centered transition state required for such an elimination[8,9] was unlikely in the case of 10. Therefore, a stepwise process involving homolytic cleavage[11] (Scheme 1) or even one involving heterolytic cleavage[10] could produce an intermediate unsaturated sulfenic acid[8,12,13,14]. This extremely unstable intermediate could then lose sulfur monoxide to give propene. The thermodynamically unstable sulfur monoxide would then undergo disproportionation to sulfur and sulfur dioxide[15].

The small quantities of benzene could result from generation of a phenyl radical from 8 which could pick up a hydrogen atom from the methylene groups of the dithiane ring.

SUMMARY

The thermal decomposition of 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiane (8) was shown to produce benzophenone, sulfur, sulfur dioxide, and small quantities of benzene and probably propene. Cyclopropane, which had previously been hypothesized as a product of this reaction, was not observed. A mechanism was proposed to account for the production of propene.

EXPERIMENTAL

All melting points and boiling points are uncorrected. All solvents were redistilled prior to use. Thin layer chromatography was performed using 5 x 20 cm glass plates coated with silicic acid (Silicar TLC-7, Mallinckrodt) or plastic sheets precoated with silica gel (Polygram Sil G/UV, Machery-Nagel, Duren). The developed plates were exposed to iodine vapor for visualization of the chromatogram.

The infrared spectra were taken on a Beckman IR-8, Beckman Microspec, or Beckman IR-10 spectrophotometer in potassium bromide pellets, in solutions of carbon tetrachloride, or in the gas phase. Proton magnetic resonance (pmr) spectra were taken on Varian T-60 or XL-100 spectrometers using tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in δ-units (parts per million from TMS). Multiplicities are reported using the following symbols: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; dq, double quartet; and m, multiplet.

Synthesis of 2,2-Diphenyl-1,3-dithiane (9). A mixture of 9.1 g (0.050 mol) of benzophenone, 5.4 g (0.050 mol) of

1,3-propanedithiol, 0.5 g of p-toluenesulfonic acid, and 300 ml of benzene was prepared in a 500 ml round-bottomed flask fitted with a reflux condenser and a Dean-Stark trap for separation of water from the reaction mixture. The reaction mixture was refluxed for 24 hr. The resulting benzene solution was washed with 10% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of the benzene gave 12.7 g (93%) of the dithiane 9 as a white crystalline solid, mp 100-106° C. Two recrystallizations from 95% ethanol gave 9.59 g (70%) of 2,2-diphenyl-1,3-dithiane, mp 110-112° C (Lit.[1] mp 110° C). Ir (CCl_4) 1440 cm^{-1} (carbon-sulfur stretch); pmr ($CDCl_3$) δ 7.0-7.8 (m, 10, aromatic protons), 2.7 (t, 4, J = 5 Hz, methylene protons on carbon atoms bearing sulfur), and 1.72.1 ppm (m, 2, remaining methylene protons).

Synthesis of 1,1,3,3-Tetraoxo-2,2-diphenyl-1,3-dithiane (8). A mixture of 5.44 g (0.020 mol) of 9, 20 ml of 30% hydrogen peroxide, and 150 ml of glacial acetic acid was prepared in a 500 ml round-bottomed flask. The mixture was heated on a steam bath for two hr and cooled in a refrigerator overnight. The crystals formed were collected by suction filtration and air dried to give 5.82 g (87%) of 8, mp 251-253° C. After two recrystallizations from benzene, the melting range was 252-253° C (Lit.[1] mp 254-254.5° C). Ir (KBr) 1335 and 1130 cm^{-1} (sulfone stretches): pmr (CF_3COOH) δ 7.35-7.90 (m, 10, aromatic pro-

tons), 3.70 (t, 4, J = 6 Hz, methylene protons on carbon atoms bearing sulfone groups), and 2.50-3.00 ppm (m, 2, remaining methylene protons).

Pyrolysis of 1,1,3,3-Tetraoxo-2-diphenyl-1,3-dithiane (8) at Atmospheric Pressure under Nitrogen. The pyrolysis apparatus consisted of a pyrex tube 1.4 x 23 cm which was packed with glass beads and glass wool (length of packing 15 cm). The tube was attached to a series of three traps at one end and a flask for adding solids at the other. The first trap was empty and immersed in an ice-water bath, the second trap was loosely packed with 85% potassium hydroxide pellets, and the third trap was immersed in a dry ice-acetone bath.

The system was swept continuously with nitrogen, and the pyrolysis tube was heated to 300° C. To the tube was slowly added 2.03 g (6.0 mmol) of 8 over a 30 min period, and the temperature was maintained for another 10 min. The first trap was rinsed with chloroform. Evaporation of the chloroform gave 0.83 g (75.4%) of benzophenone, mp 48-49° C. The benzophenone was also characterized by comparison of its ir and pmr spectra to those published for an authentic sample. A yellow residue remained in the first trap. This material was dissolved in carbon disulfide. Evaporation of the carbon disulfide gave 0.22 g (58%) of sulfur, mp 118-121° C. The third trap contained a small quantity of benzene (0.033 g, 1.6%) and no other observable

material. The benzene was characterized by comparing its ir spectrum (gas phase) with that of an authentic sample.

Pyrolysis of 1,1,3,3-Tetraoxo-2,2-diphenyl-1,3-dithiane (8) under Reduced Pressure. The pyrolysis apparatus consisted of a pyrex reaction vessel connected to a series of three traps. The first trap consisted of a Dewar cold-finger condenser filled with dry ice and acetone. The second and third traps were U-tubes placed in liquid nitrogen baths.

To the reaction vessel was added 0.679 g (2.0 mmol) of 8 which was pyrolyzed under 1 mm pressure. The temperature was raised to 265° C where pyrolysis began. The temperature was increased to 290° and then allowed to drop to room temperature. The temperature remained between 265 and 290° C for about 40 min to insure complete pyrolysis. Pyrolysis occurred smoothly leaving a black oily solid residue in the reaction vessel. From the first trap a small amount of volatile material was distilled into a gas ir cell and examined. The spectrum indicated the presence of benzene and sulfur dioxide by comparison with published spectra. Trap one also contained a solid material part of which was soluble in chloroform and the remainder in carbon disulfide. The chloroform was evaporated to give 0.035 g of benzophenone (identified by comparing the pmr spectrum with that from an authentic sample). The carbon disulfide was evaporated giving 0.021 g of sulfur, mp 118-120° C.

The reaction vessel was washed with chloroform, and the chloroform was evaporated giving 0.124 g of benzophenone (identified by comparing the ir and pmr spectra to those from an authentic sample). The total yield of benzophenone was 0.159 g (43.2%). The residue in the reaction vessel consisted of a black solid mass (0.370 g) which was insoluble in chloroform.

Trap two contained a small amount of volatile materials, and trap three was empty. The material from trap two was distilled into a gas or cell (10 mm pressure) and examined. The ir spectrum suggested the presence of propylene and sulfur dioxide by comparison of the spectrum with published spectra for these compounds. Other unidentified materials also appeared to be present. The quantity of sample was so small that a pmr spectrum was unobtainable.

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