SOME APPLICATIONS OF MASS SPECTROMETRY IN ORGANIC CHEMISTRY

A Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

by

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ABSTRACT

The evidence for the constitution and stereochemistry of a number of sesquiterpene lactones and related compounds is reviewed. Their fragmentations under electron impact in the Associated Electrical Industries' M.S.9 mass spectrometer are discussed from the evidence provided by high resolution mass spectrometry and deuterium labelling studies. Structural and stereochemical features are related where possible to the observed fragmentations. The preparation of several deuterated sesquiterpenes is reported. The mass spectrum of the diterpene lactone, rosenonolactone, is reappraised.

The anomalous loss of a methyl radical occurring in the electron impact induced fragmentation of 1-tetralone and benzsuberone enol acetates is reported and the mechanism discussed from the evidence of deuterium labelling experiments. A new method for labelling benzylic positions with deuterium is described. This method is shown to be capable of extension to the introduction of deuterium next to the benzylic position. The preparation of a comprehensive series of deuterated 1-tetralones and benzsuberones is reported. A few aspects of mass spectra of some 1-indanones and 1-tetralones are discussed.

To Daphne

"Beware that you do not lose the substance by grasping at the shadow"

Aesop, c. 550 B.C.
Fables. The Dog and the Shadow

ACKNOWLEDGEMENTS

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CONTENTS

INTRODUCTION

Mass spectrometry is a relatively new tool available to the organic chemist. The advent of high-resolution mass spectrometry enables molecular formulae to be determined. However, the greatest potential of mass spectrometry is in the field of structure determination. As with other physical techniques, compounds of known structure must first be investigated before the method can be applied to compounds of unknown structure. In this way generalisations can be made regarding the fragmentations caused by certain functional groups and structural features. Much work has been done already in this field and several* excellent compilations of fragmentation modes have been made. These investigations have stimulated the preparation of deuterium labelled compounds to provide evidence for proposed fragmentations.

In the mass spectrometer, the sample is introduced, under high vacuum, into a beam of high energy electrons, which has the effect of removing one electron from the molecules to give positively charged ions. Multiply charged ions are also formed but these are usually of low abundance. Little is known about the electronic state of these ions and how the positive charge is distributed over the molecule. However, many fragmentations of ions can be rationalised by assuming the positive charge is localised at specific sites, These are usually atoms bearing the most loosely bound electrons. For example, the fragmentations of cyclohexanone can be rationalised if the positive charge is localised on the carbonyl oxygen.

Fragmentation pathways are effected by the stabilities of neutral moieties which are eliminated, as well as the stabilities of the ions themselves. However, only the latter are detected in the mass spectrometer.

Fragmentations often occur in the field free regions away from the magnetic and electrostatic analysers. These give rise to low abundance metastable ions which occur in the spectra as broad peaks at non integral mass numbers. In the double focusing instruments these ions occur at a mass to charge ratio $\left(\frac{M_2}{M_1}\right)^2$ when an ion of mass to charge ratio M_1 fragments to give an ion of mass to charge ratio M_2. This allows fragmentation pathways to be established.

* see for example

H. Budzikiewicz, C. Djerassi and D. H. Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day, San Francisco, 1964.

(by same authors), Structure Elucidation of Natural Products by Mass Spectrometry, Vol 1 and 2. Holden-Day, San Francisco 1964.

REVIEW OF THE

STRUCTURE AND STEREOCHEMISTRY

OF SOME SESQUITERPENE

LACTONES

α-Santonin

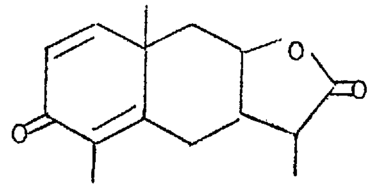
Various species of Artemisia found widely in nature and particularly in the Volga districts of Russia, in Turkestan, in Persia and in the North West Frontier area of India, contain several closely related lactones. Santonin, $C_{15}H_{18}O_3$ is by far the most abundant, occurring to the extent of several percent in the leaves and immature flower buds. It was first isolated[1] by Kahler in 1830.

Early work on the carbon skeleton of santonin[2] showed it to be a ketonic lactone since it dissolved in alkali to give salts of santoninic acid, which gave an oxime, and could be regenerated by acid. Distillation of santonin with zinc dust gave 1,4-dimethylnaphthalene and all the identifiable products of other reactions contained two methyl groups attached to an aromatic ring.

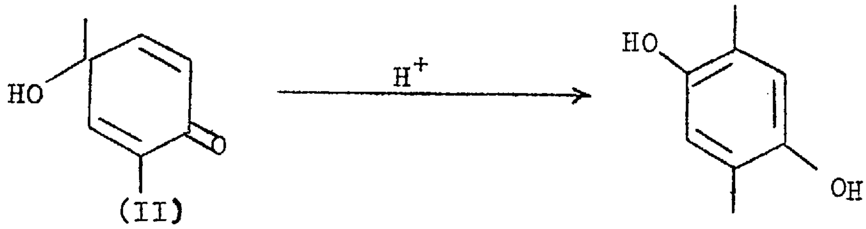
Gucci[3] showed that when santonin β-oxime was reduced by zinc dust and alcoholic sulphuric acid it gave santoninamine, which by boiling in water was converted to hyposantonin. Hyposantonin, together with its stereoisomer, isohyposantonin, was also obtained by reduction of santonin β-oxime, its acetate, or santonin phenyl hydrazone with sodium amalgam. Hyposantonin was converted to isohyposantonin simply by dissolution in alkali and reprecipitation with acid. The two compounds were both lactones and on oxidation with permanganate gave 3,6-dimethylphthalic acid. Since the lactone grouping was assumed to be the same as in santonin, it was concluded that it could not be in the same ring as the methyl groups and the ketonic oxygen. At this time it was not realised that a methyl group migrated during these reactions and several formulae were proposed[4] for santonin, all of which contained a 1, 4-dimethylated six membered ring.

Santonin was known to contain two double bonds (by hydrogenation) and the ready conversion of santoninamine into compounds containing an aromatic nucleus suggested that the two double bonds were in the same ring as the ketone group. Extra evidence for this was the conversion[5] of santonin, in ice cold fuming hydrochloric acid, to an isomeric phenolic lactone, (-)-α-desmotroposantonin.

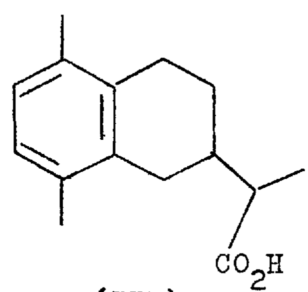
The first criticism of the proposed formulae was made by Clemo, Haworth and Walton[6] who pointed out that none of them could be regarded as built up from isoprene units. They suggested the formula (I) for santonin, and that the formation of (-)-α-desmotroposantonin must involve the migration of a tertiary methyl group as was known[7] for 2,4-dimethyl-4-hydroxycyclohexa-2,5-dien-1-one (II). They also synthesised (-)-α-santonous acid (III), one of the products from the reduction of santonin with red phosphorous and hydriodic acid, thus establishing the position of the lactone side chain. In a later publication[8] the same authors synthesised racemic desmotroposantonin (IV) and thus revised the constitution of santonin to (V), which is the correct one (the numbering system is as shown).



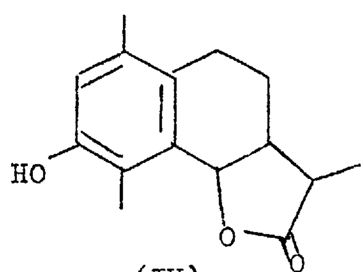
(I)



(II)



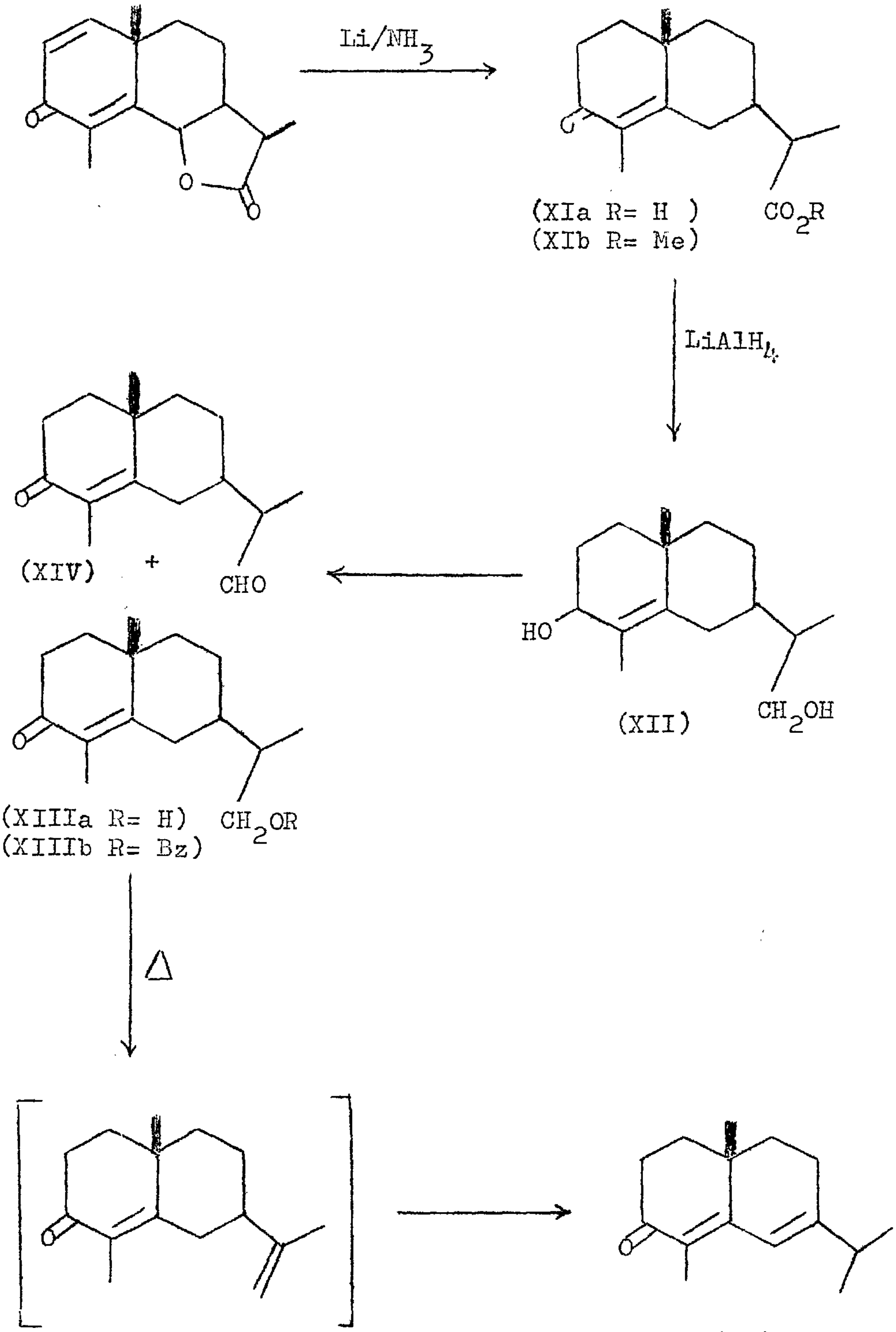
(III)



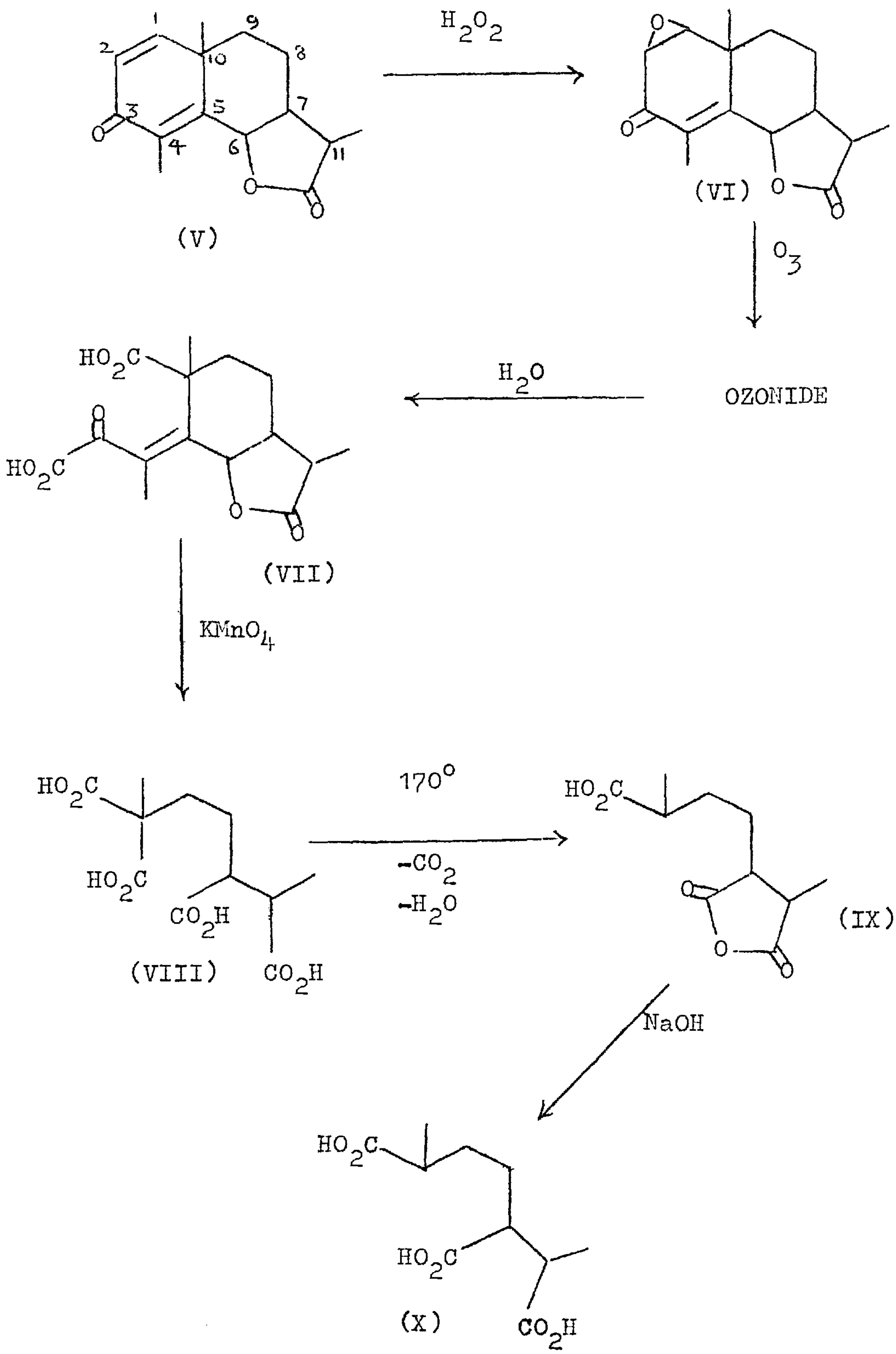
(IV)

The oxidative degradation[9] of santonin has provided proof of the angular methyl group. Santonin, when treated with hydrogen peroxide or perbenzoic acid in acetic acid, gave two stereoisomeric mono-oxides (VI). One of these when ozonised and treated with water gave a dicarboxylic acid (VII), which on oxidation with potassium permanganate afforded a tetracarboxylic acid (VIII). The latter, on heating at 170° gave an anhydride (IX) which on hydrolysis yielded heptane-2,3,6-tricarboxylic acid (X), the structure of which was confirmed by synthesis.[10]

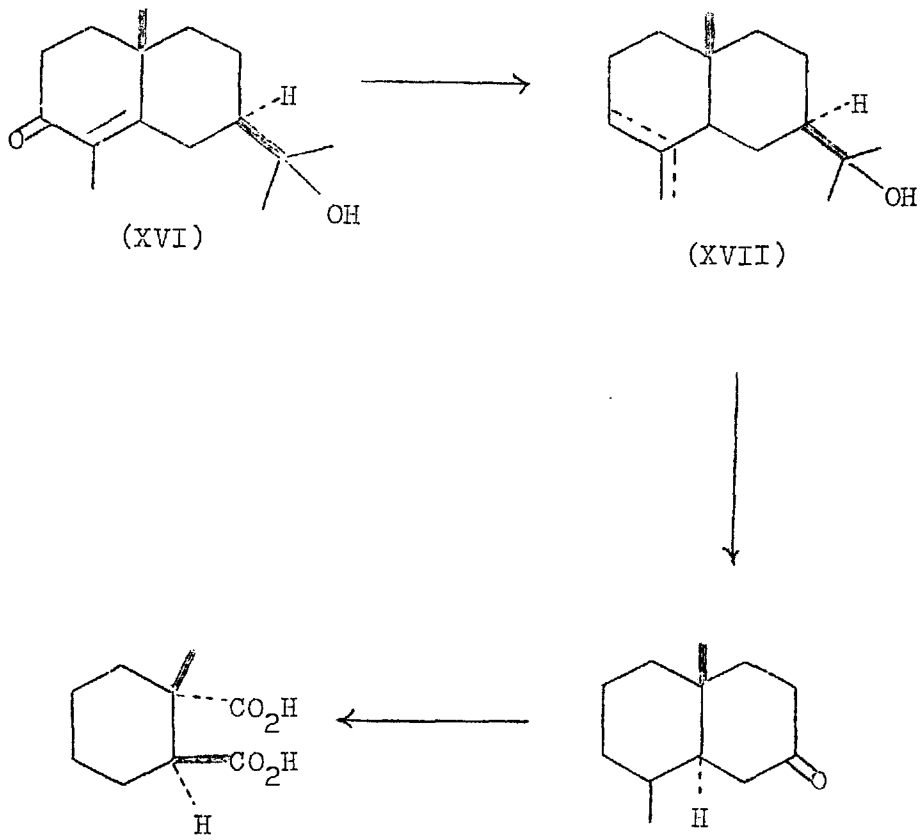
It remained for the stereochemistry of santonin to be elucidated. Several reviews[11,12] have appeared concerning the stereochemistry of santonin and related compounds. The establishment of the configuration at C(10) in santonin as β-methyl was based on its conversion[13] to β-cyperone. Reduction of santonin with lithium in liquid ammonia afforded the acid (XIa). The corresponding ester (XIb), when reduced with lithium aluminium hydride, gave the diol (XII), which on allylic oxidation with manganese dioxide gave the ketol (XIIIa) and the aldehyde (XIV). Pyrolysis of the ketol benzoate (XIIIb) gave β-cyperone (XV), although α-cyperone (XIV) was probably formed first. The cyperones have been related[14] to carrisone (XVI) which in turn has been related to eudesmol (XVII). Eudesmol in turn has been related[15,16] to the known decalone (XVIII) and the dicarboxylic acid (XIX).


Li/NH3
(XIa R= H)
(XIb R= Me)
CO2R
LiAlH4
(XIV)
+
CHO
HO
(XII)
CH2OH
(XIIIa R= H)
(XIIIb R= Bz)
CH2OR
Δ

(XIV) (XV)



(V)
H_2O_2
(VI)
O_3
OZONIDE
H_2O
(VII)
$KMnO_4$
(VIII)
170°
$-CO_2$
$-H_2O$
(IX)
NaOH
(X)



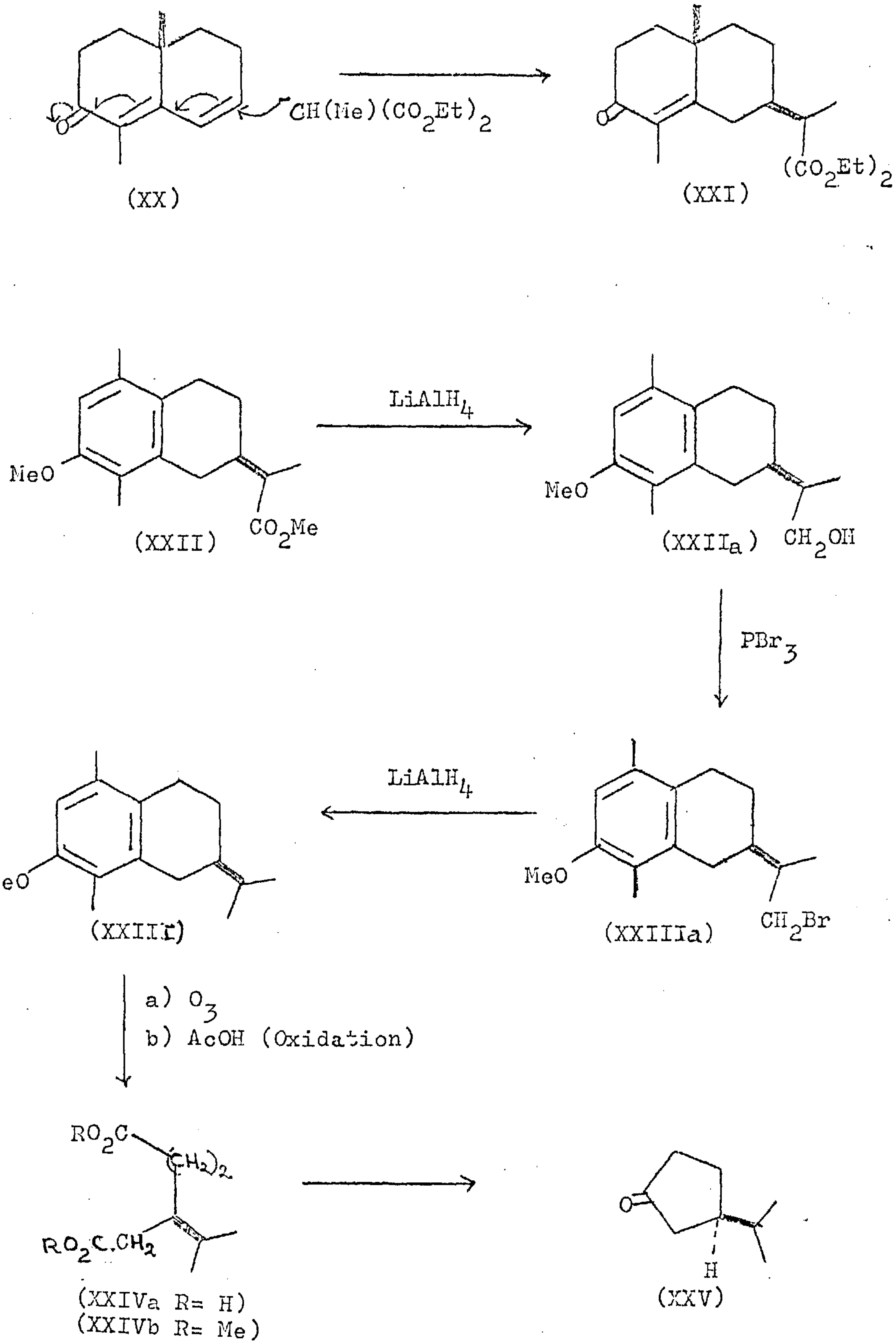
(XVI) (XVII)

(XIX) (XVIII)

In all eudesmanes where the configuration at C(7) was known, the isopropyl side chain was β. That this was so for santonin, followed from a stereospecific synthesis[16] of the santonins. This involved the attack [17] on the dienone (XX) by the 2-methyl-diethylmalonate anion which takes up the more stable equatorial configuration[18,19] giving (XXI).

The absolute configuration[20] of (-)-α-desmotroposantonin has been determined. It was realised[12] that the configuration at C(7) in santonin was not inverted in the transformation to (-)-α-desmotroposantonin. The compound (XXII) prepared from (-)-α-desmotroposantonin, on reduction with lithium aluminium hydride, gave the alcohol (XXIIa) which on treatment with phosphorous tribromide afforded the bromide (XXIII). This on reduction with lithium aluminium hydride gave the isopropyl compound (XXIIIa). Exhaustive ozonolysis of this, followed by acetic acid oxidation, gave the dicarboxylic acid (XXIVa), the methyl ester (XXIVb) of which, on heating with barium hydroxide, yielded R-(+)-3-isopropylcyclopent-1-one (XXV). This confirmed the 7αH configuration in (-)-α-desmotroposantonin and hence in santonin itself.

The configuration at C(11) was the last to be determined and necessitated X-ray studies. On the basis of the interconversions of the desmotroposantonins (see section on the dienone-phenol rearrangement) and conformational considerations, many workers[11,21,22] came to the conclusion that the

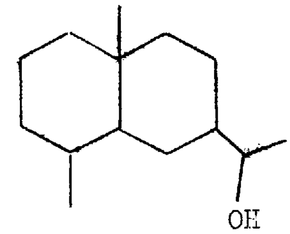

CH(Me)(CO2Et)2
(XX)
(XXI)
(CO2Et)2
LiAlH4
MeO
(XXII)
CO2Me
(XXIIa)
CH2OH
PBr3
LiAlH4
(XXIII)
(XXIIIa)
CH2Br
a) O3
b) AcOH (Oxidation)
RO2C
(CH2)2
RO2C.CH2
(XXIVa R= H)
(XXIVb R= Me)
H
(XXV)

configuration at C(11) was β-methyl. Abe[23] and his coworkers applied Prelog's[24] method to the alcohol (XXVI) derived from santonin. This involves the conversion of the alcohol (XXVI) to the phenylglyoxalate ester (XXVII). The attack of methyl magnesium bromide is then stereospecific on the ketone group, depending on the size and configuration of the alcohol substituents. The acid (XXVIII) is thus optically active. On this basis the methyl group was considered to be α.

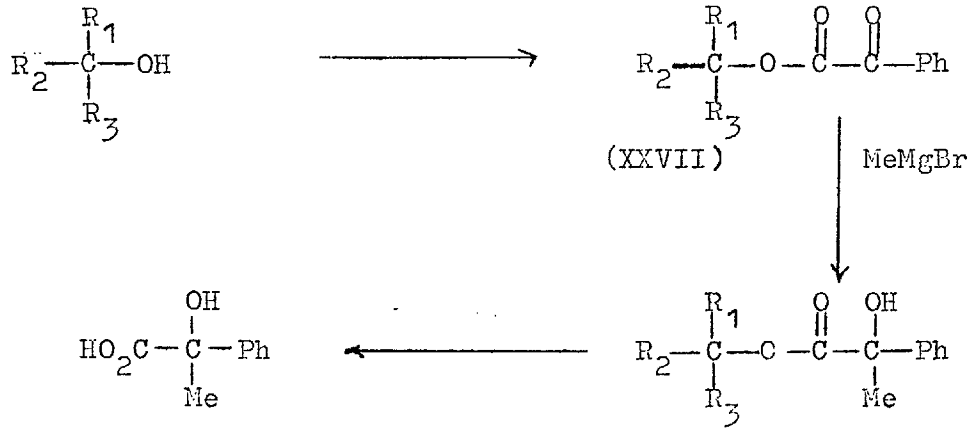
X-ray analysis[25] of 2-bromodihydroisophotosantonic lactone acetate[26] (XXIX) proved it to have the absolute configuration shown and therefore that isophotosantonic lactone (XXX), a photoirradiation product of santonin, had the configuration indicated (XXX). That santonin had inverted at position 11 on conversion to the bromolactone was unlikely, since conversion of isophoto-β-santonic lactone (the 11-epimer of (XXX)) through the same reaction sequence gave different compounds at each stage. The α-methyl configuration was confirmed by X-ray analysis[27] of 2-bromosantonin and also by the degradation[28] of the santonin side chain to (+)-benzoyl alanine. Santonin thus has the absolute configuration shown (XXXI).

Artemisin

Artemisin was first isolated by Merck from the last mother liquors of the technical treatment of Artemisia maritima L.

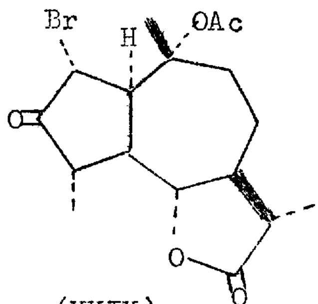


(XXVI)

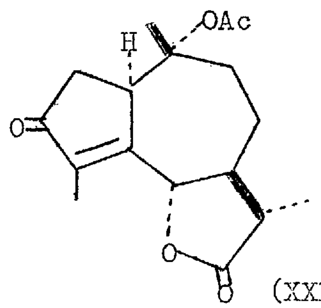


(XXVII)

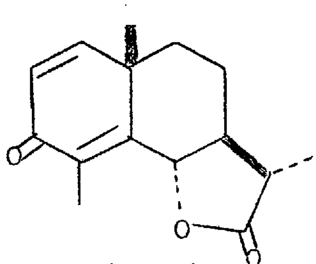
(XXVIII)



(XXIX)



(XXX)



(XXXI)

It was initially assigned the structure of 7-hydroxysantonin on the basis of the work by Bertolo[29] and Tettweiler.[30]

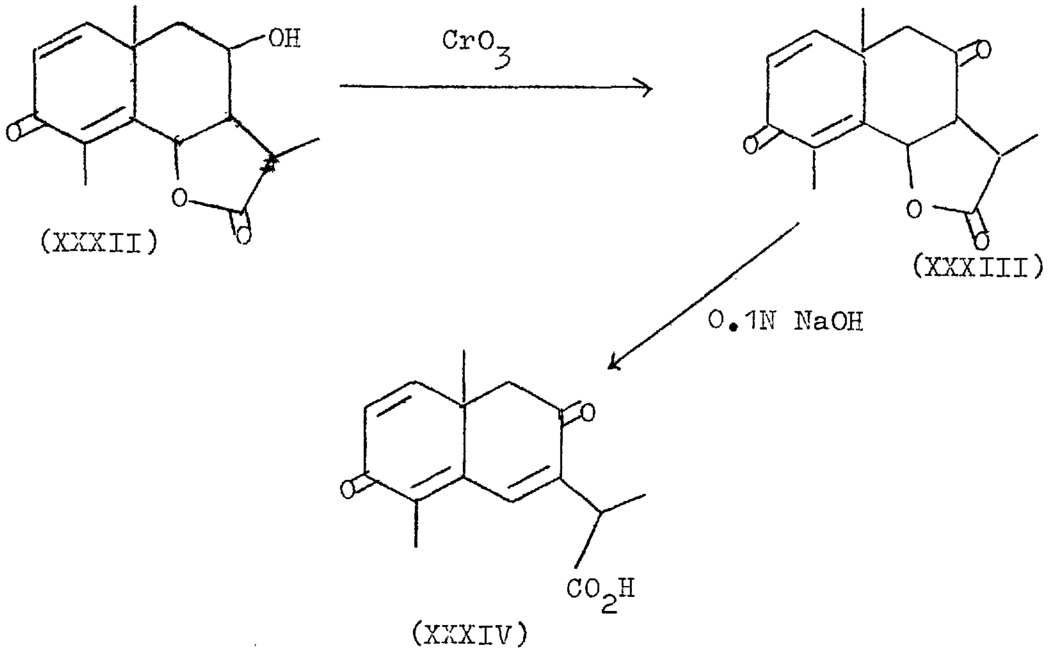
Dehydrogenation of a hexahydroartemisin with selenium gave 1-methyl-7-ethylnaphthalene, indicating that artemisin belonged to the eudalene group of sesquiterpenes.[30] Artemisin also underwent the dienone-phenol rearrangement[31,32] to produce a desmotropo compound. Therefore artemisin possessed the cross conjugated dienone structure with an angular methyl group, confirmed by the infra red spectrum. On warming with dilute alkali, artemisin afforded the sodium salt of an hydroxy acid[33] which was reconverted to artemisin on acidification. Artemisin was thus a lactone and from the degradation experiments it was concluded that the lactone was joined to C(7). Sumi[34] demonstrated the positions of the lactonic and free hydroxyl group in the following way. Oxidation of artemisin with chromium trioxide in pyridine gave a diketone, which on treatment with base eliminated the lactone hydroxyl group and introduced another double bond in conjugation with the new carbonyl group. On this basis the lactonic hydroxyl group was formulated as β[35,36] to the carbonyl group, and artemisin therefore had the constitution of an 8-hydroxysantonin (XXXII). The diketone thus was (XXXIII) and the dehydration product (XXXIV). The behaviour[34] of artemisin in giving two different desmotropoartemisin diacetates, simply by a change in reaction temperature, suggested that, like santonin, artemisin had a <u>trans</u>-fused lactone ring.

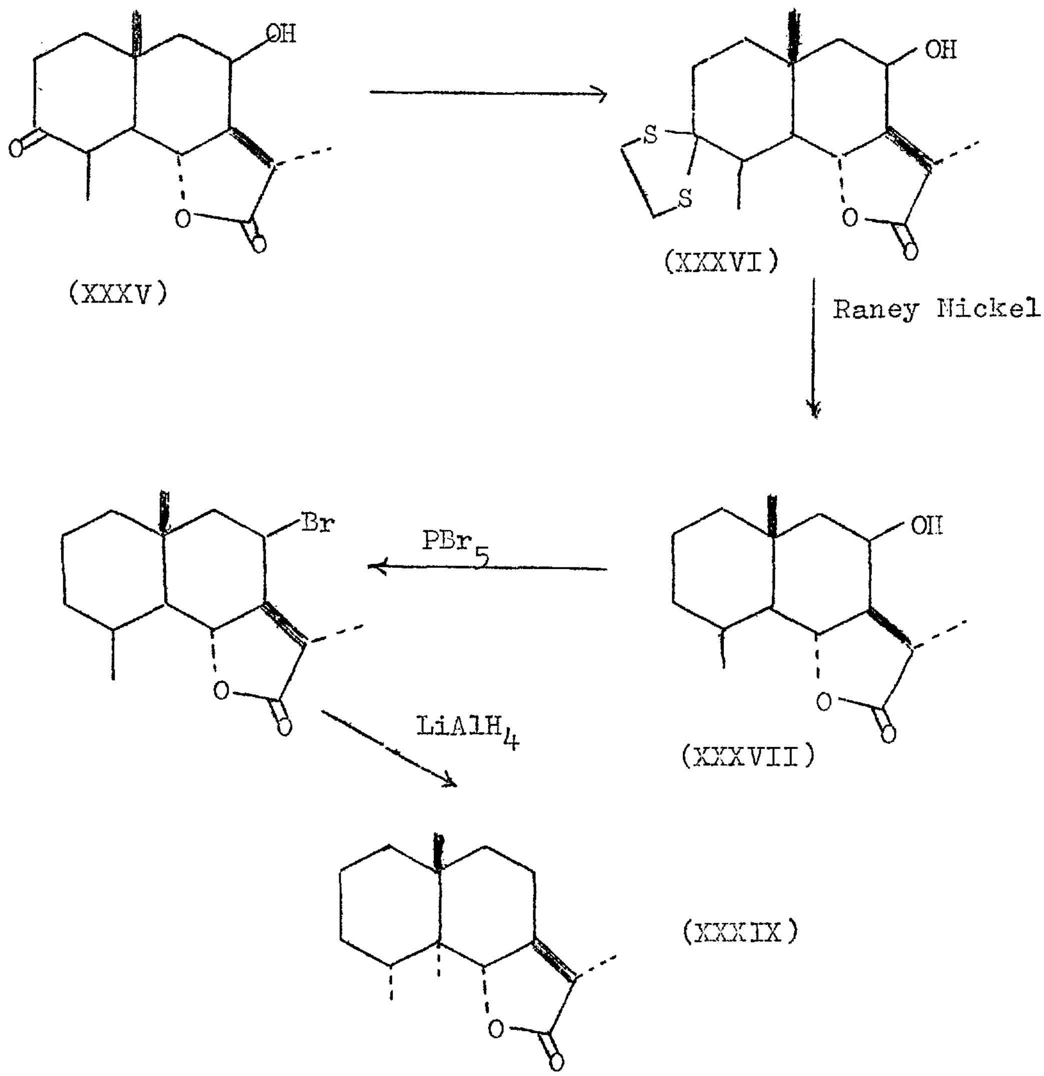
Two routes have been used to correlate[34] the stereochemistry of artemisin to santonin. A tetrahydroartemisin (XXXV) was converted to its thioketal (XXXVI) and desulphurised with Raney nickel to a deoxytetrahydroartemisin (XXXVII). This when treated with phosphorous pentabromide, gave a bromide (XXXVIII) which on reduction with zinc in acetic acid afforded a known deoxytetrahydrosantonin (XXXIX). The other route involved the treatment of artemisin with triphenylphosphite methiodide to give 8-iodosantonin (XXXX) which gave santonin on reduction with poisoned Raney nickel. The author has been unable to repeat this last route either with artemisin or its 8-epimer.

The configuration at C(8) was initially based on physical evidence. For example, the large positive molecular rotational difference on going from santonin to artemisin indicated by Klyne's generalisation that the hydroxyl group is α and equatorial in artemisin.

<u>ψ-Santonin</u>

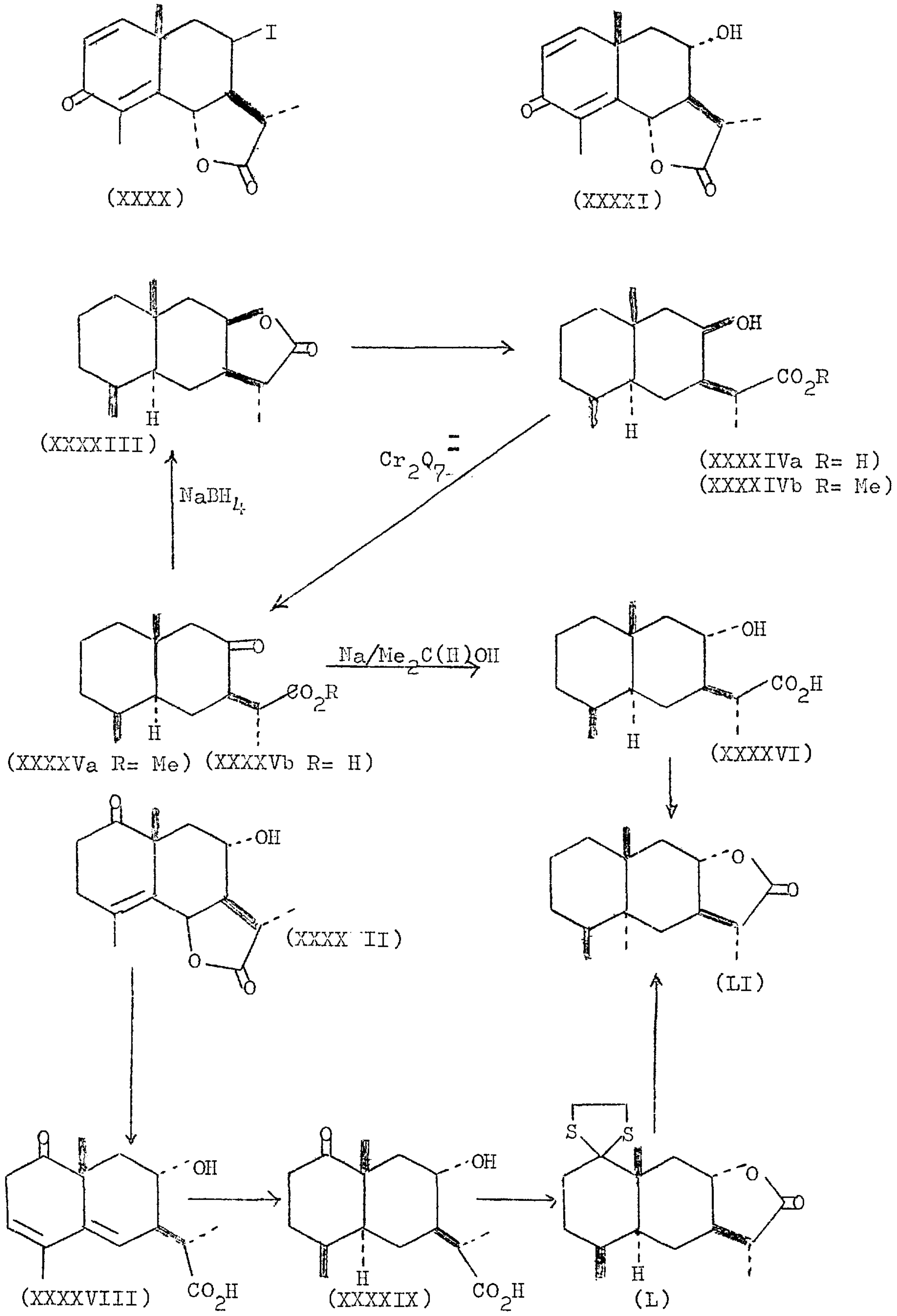
ψ-Santonin was also isolated[39] from various species of the Artemisia family. Degradation studies[40,41] established a normal skeleton of the eudalene type as for santonin. The


OH
CrO_3
(XXXII)
(XXXIII)
0.1N NaOH
CO_2H
(XXXIV)


OH
S
S
OH
(XXXV)
(XXXVI)
Raney Nickel
Br
PBr_5
OH
$LiAlH_4$
(XXXVII)
(XXXIX)

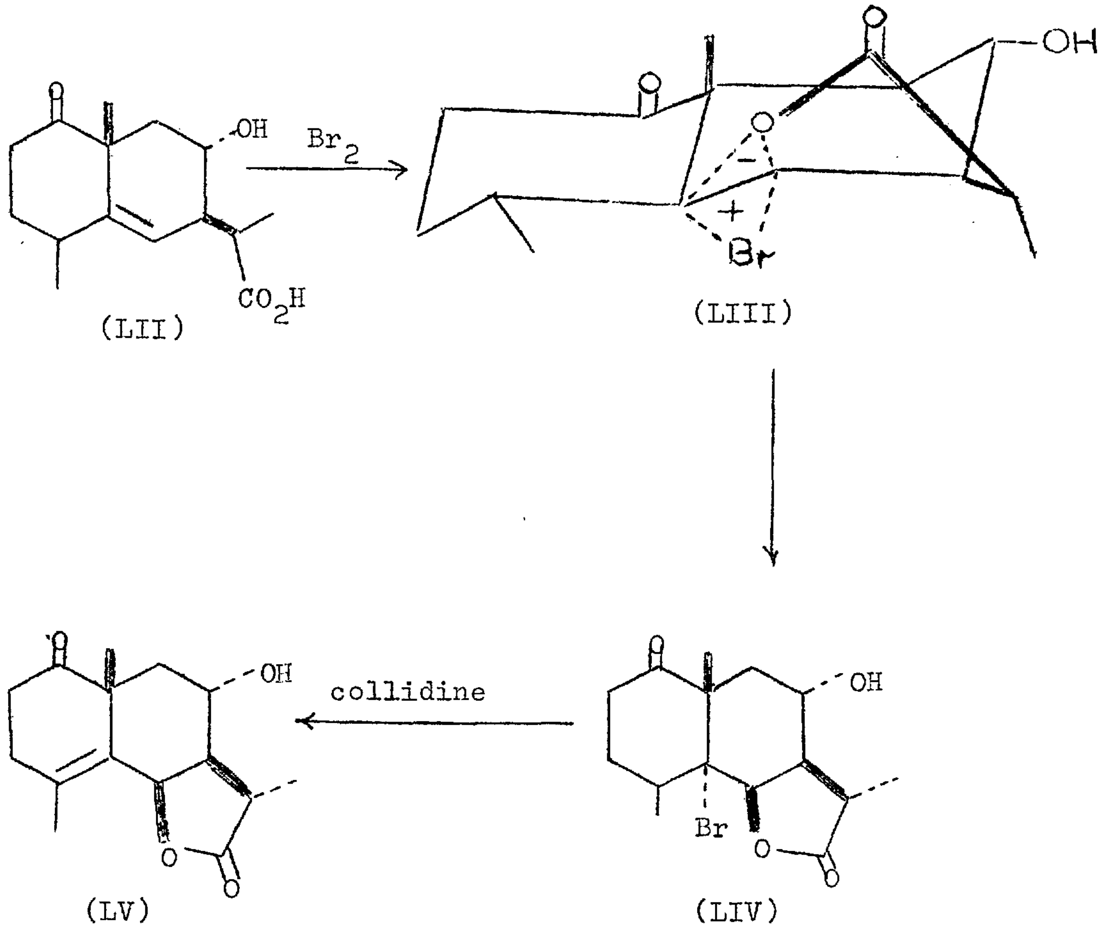
presence of a lactone, a carbonyl group, a carbon-carbon double bond and a free hydroxyl group were demonstrated. The action of 55% sulphuric acid gave a desmotropo-Ψ-santonin, which on careful dehydrogenation,[42] gave 2,4-dimethyl-6-ethylnaphth-1-ol, thus fixing the position of the carbonyl group at C_1. Ψ-Santonin was also hydrogenolised[41,43] with the uptake of one mole of hydrogen to give an acid in which the lactone hydroxyl had been removed. The same acid was formed by hydrogenolysis of Ψ-santonin acetate and subsequent hydrolysis. When this acid was heated with acetic anhydride, a lactone was obtained, formed by cyclisation to the free hydroxyl group. The infra red spectrum of this new compound indicated a γ-lactone as did the spectrum of Ψ-santonin. Thus, the two hydroxyl groups were both γ to the carboxyl group. The double bond in Ψ-santonin was also tetrasubstituted as indicated by characteristic bands in the infra red which disappeared in the spectrum of the epoxide. The only possible structure[43] for Ψ-santonin was thus (XXXXII).

The stereochemistry of Ψ-santonin has been correlated to both artemisin[46] and tetrahydroantolactone[45] (XXXXIII). When tetrahydroantolactone was hydrolysed with alkali and carefully neutralised it gave the acid (XXXXIVa) which with diazomethane afforded the methyl ester (XXXXIVb).[47] Oxidation of this ester with dichromate in acetic acid gave the keto ester (XXXXVa) which on hydrolysis gave the keto acid (XXXXVb). Reduction of this acid with sodium in isopropanol afforded the hydroxy acid (XXXXVI), which was lactonised to (LI). Sodium borohydride reduction of


(XXXX)
(XXXXI)
(XXXXIII)
NaBH4
Cr2O7=
(XXXXIVa R= H)
(XXXXIVb R= Me)
Na/Me2C(H)OH
(XXXXVa R= Me) (XXXXVb R= H)
(XXXXVI)
(XXXXII)
(LI)
(XXXXVIII)
(XXXXIX)
(L)

(XXXXVb) gave tetrahydroantolactone.[47] Therefore (XXXXIII) and (LI) have the opposite configuration at C(8). Ψ-Santonin undergoes an acid catalysed rearrangement to give Ψ-santonic acid[41,48](XXXXVIII) which afforded a tetrahydro derivative.[41,48,49] The keto group was removed from this via the ethylene thioketal (L) and the deoxy compound was converted to the corresponding acid which was identical to (XXXXVI). Ψ-Santonin thus had the same configuration at C(9) and C(7) as tetrahydroantolactone and the opposite configuration at C(8). The correlation[46] with artemisin showed Ψ-santonin to have the same configuration at C(11).

The configuration at C(6) was suspected[50] to be αH on the basis that the hydrogenolysis product[51] of Ψ-santonin (LII), on treatment with bromine gave a bromo lactone (LIV), which on dehydrobromination regenerated Ψ-santonin (LV). The formation of such a bromolactone was viewed as a <u>trans</u> addition of the carboxylate anion to the bromonium ion[52,53,54](LIII) and this was expected to be a <u>trans</u> diaxial electrophilic addition.[55] The initial approach of bromine from the less hindered α face of the molecule demanded that Ψ-santonin have the <u>cis</u>-fused lactone (LV). Nuclear magnetic resonance studies[56] have since confirmed this.


OH
Br2
CO_2H
(LII)
OH
Br
(LIII)
OH
collidine
O
(LV)
OH
Br
O
(LIV)

Isophoto-α-santonic lactone

Isophotosantonic lactone[57,58,59,60] is one of the photochemical transformation products of santonin and the main product[61] of ultra violet irradiation of santonin in acetic acid.

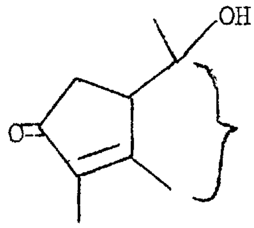
Early work showed it to contain a lactone, an hydroxyl group and one carbonyl group. Oxidation experiments[61] showed the hydroxyl group to be tertiary and the carbonyl group to be ketonic. The infra red and the ultra violet spectra showed the presence of a cyclopentenone ring. Dehydration with thionyl chloride in pyridine gave an anhydro compound containing a methylene group. The original lactone therefore contained the grouping $>C<^{OH}_{CH_3}$. Furthermore, the methylene group was not conjugated with the cyclopentenone system. However, under acidic conditions, dehydration of isophotosantonic lactone gave a conjugated dienone. One of the ozonolysis products of the isophoto compound was acetic acid which in an αβ-unsaturated ketone implied the presence of the system $-\overset{O}{\overset{\|}{C}}-\underset{Me}{\underset{|}{C}}=C<$. A part structure for isophotosantonic lactone could therefore be written (LVI), and knowing the structure of santonin the full constitution was (LVII) (numbering as shown).

The stereo-chemistry (LVII) of the compound followed from the x-ray analysis[27] of 2-bromo-4,5-dihydroisophotosantonic lactone[26,62] (see p. 19). β-Santonin (the 11 epimer of santonin), 6-episantonin and 6-epi-β-santonin also undergo the photochemical rearrangement, the configurations at C(6), C(7) and C(11) being unaltered.

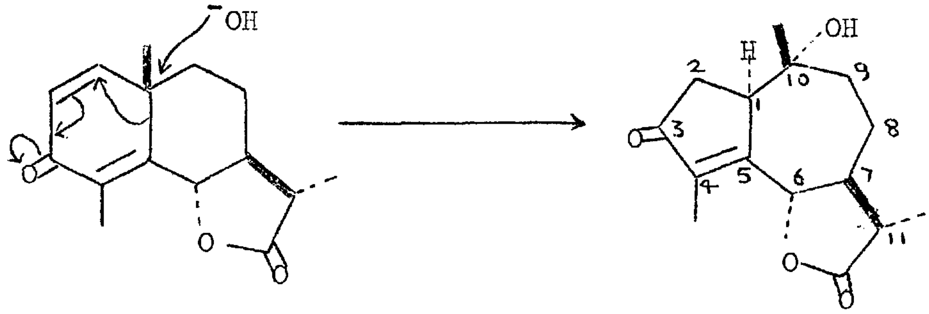
Geigerin

The sesquiterpenoid lactone geigerin was first isolated by Rimington and Roets[63] from Geigeria aspera Harv. Perold showed that it could be dehydrogenated to guaiazulene (LVIII) and that it was therefore a guaianolide. The constitution and partial stereochemistry were elucidated by Barton and Levisalles.[66] It was known that geigerin was an αβ-unsaturated derivative of cyclopentanone and ozonolysis gave acetic acid thus confirming the position of the αβ-unsaturated ketone grouping (see LIX). Geigerin gave a monoacetate and thus contained one hydroxyl group. Reduction of geigerin with zinc and acetic acid gave a deoxygeigerin. This required the presence of an α-ketol or vinylogous α-ketol in geigerin. The presence of the latter was indicated by oxidation of geigerin to an ene-1,4-dione. The constitution of geigerin was thus formulated as (LIX, R=OH) and the deoxygeigerin as (LIX, R=H) (numbering as shown).

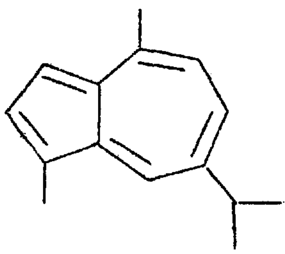
A partial determination of the stereochemistry of geigerin followed from its conversion with mild alkali to allogeigeric acid (LX). This compound did not lactonise even on sublimation at 200° and therefore the hydroxyl group and carboxyl bearing side chain were assumed to be trans to each other. It was also assumed that the lactone ring in geigerin was <u>cis</u> fused, because allogeigeric acid on treatment with acetic acid always reverted to geigerin rather than the isomeric <u>trans</u> lactone involving the free hydroxyl group. The configuration of the lactone ring at C(7)



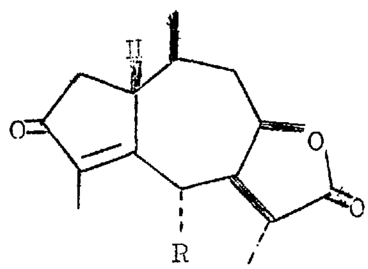
(LVI)



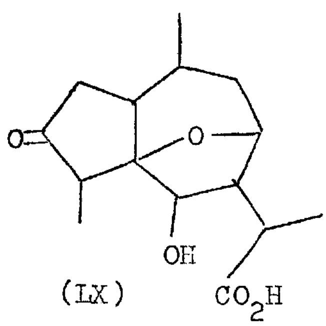
(LVII)



(LVIII)



(LIX)



(LX)

was assumed to be β because all naturally occurring sesquiterpenes had this configuration. From this it followed that the configurations at C(6) and C(8) were also fixed. This was confirmed by the x-ray analysis[25] of 1-bromogeigerin. This did not assign the configuration at C(1) but it was considered to be βH on the basis of optical rotatory dispersion studies.[67] This was confirmed by a synthesis[68] from artemisin of deoxygeigerin and, in radiochemical yield, of geigerin itself.

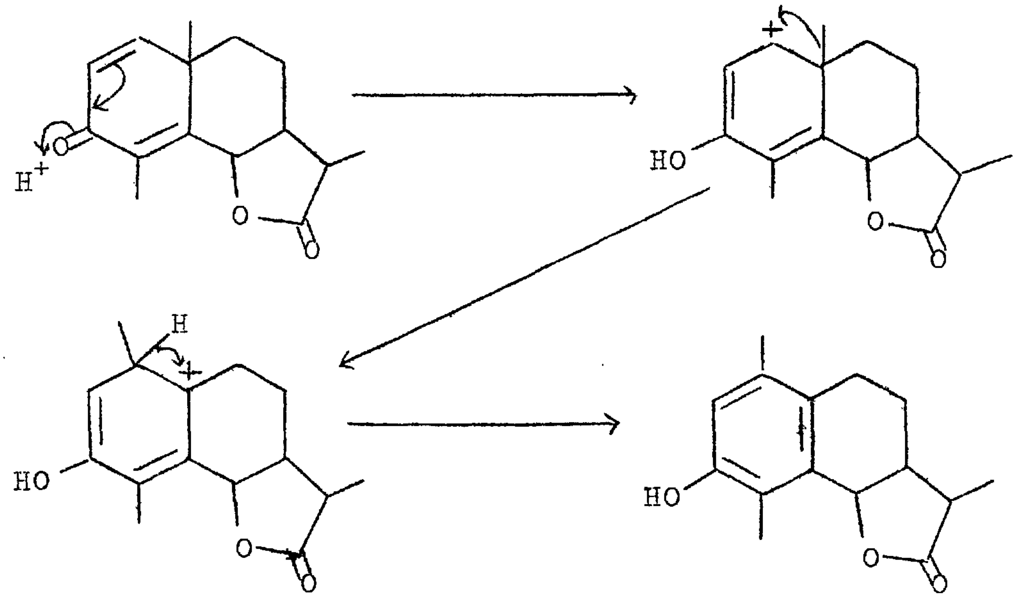
REVIEW OF

THE DIENONE-PHENOL REARRANGEMENT OF SANTONIN

AND RELATED COMPOUNDS

It had been known for a long time that when santonin was treated with mineral acid a molecular rearrangement took place to give a compound known as desmotroposantonin containing 1,4 dimethylated benzene ring.[5,69,70] The nature of this rearrangement was obscure because the structure of santonin was unknown. The correct dienone structure for santonin was suggested[6,8] by Clemo, Haworth and Walton who pointed out that the rearrangement under acidic conditions paralleled the conversion[7] of 2,4-dimethyl-4-hydroxyclyclohexa-2,5-dien-1-one to 2,5-dimethylquinol.

Much later, it was found that some transformation products of cholesterol containing the dienone structure could easily be converted[71,72] to the phenolic compound by treatment with acetic anhydride containing a drop of concentrated sulphuric acid. Application of this technique to santonin gave an acetate, hydrolysis of which afforded the known (-)-α-desmotroposantonin. The mechanism was postulated[74] as follows:



(-)-α-Desmotroposantonin was known to be converted[71] by dilute sulphuric acid into another isomer,(+)-β-desmotroposantonin which on fusion with base gave a third isomer, (+)-α-desmotroposantonin, the enantiomer of the (-)-α compound (see reaction scheme). Huang-Minlon showed[74] that the

$$\begin{tikzcd}
\text{(-)-}\alpha\text{-DESMOTROPOSANTONIN} \arrow[d, "H^+"] & & \text{(-)-}\beta\text{-DESMOTROPOSANTONIN} \arrow[ll, "OH^-"'] \\
\text{(+)-}\beta\text{-DESMOTROPOSANTONIN} \arrow[rr, "OH^-"] & & \text{(+)-}\alpha\text{-DESMOTROPOSANTONIN} \arrow[u, "H^+"']
\end{tikzcd}$$

(+)-α isomer, when treated with dilute sulphuric acid, gave yet a fourth isomer, (-)-β-desmotroposantonin, enantiomeric with the (+)-β isomer. This fourth isomer was converted to the (-)-α isomer on fusion with base thus setting up the cyclic reaction scheme shown.

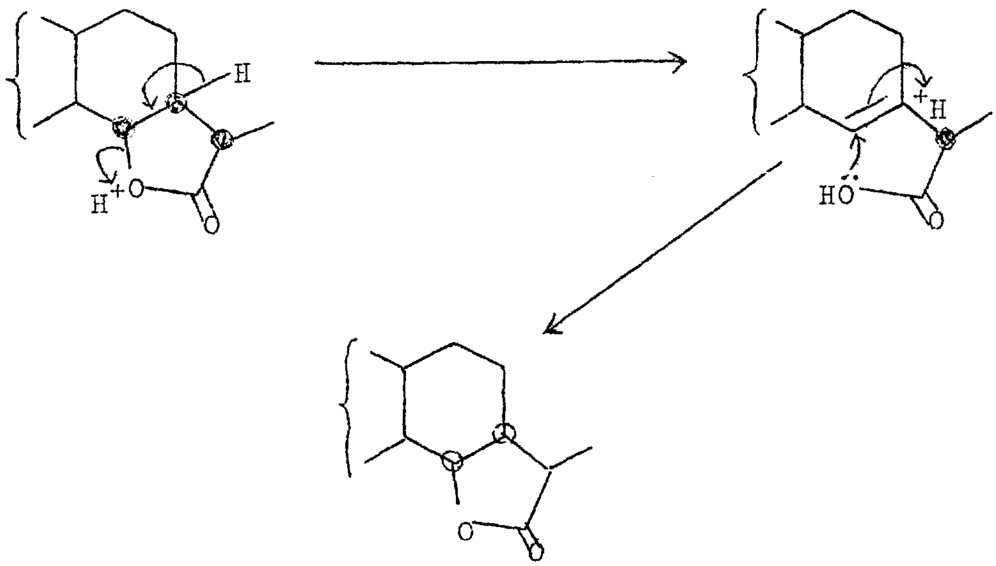
The stereochemical changes involved in these transformations were discussed by Huang-Minlon[74] and later by Barton.[12] The observed cycle suggested that position 11 was inverted by base and that the acidic conditions inverted positions 6 and 7 simultaneously. Consequently, the desmotroposantonins had either all <u>cis</u> or all <u>trans</u>-fused lactone rings. The proposed[74] mechanism A for the acid catalysed inversions was supported by the known[75] conversion of isohyposantonin (LXIa) to the ethyl ester of dihydrosantinic acid (LXII) by ethanolic hydrochloric acid.

From a consideration of molecular models, Clemo[78] suggested that the desmotroposantonins were cis fused lactones. The immediate closure of the lactone ring when basic solutions of the desmotroposantonins were acidified, supported this proposal. Hyposantonin[3] (LXIb), the product from the mild reduction of santonin oxime, was considered to have a trans fused lactone. It could be converted to a stereo-isomer isohyposantonin, simply by dissolution in alkali and reprecipitation with acid. Isohyposantonin could be converted to the cis fused (-)-α-desmotroposantonin by nitration, reduction to the amine and subsequent conversion to the phenol. Santonin and hyposantonin were thus considered to be trans fused lactones and Barton[12] pointed out that this required a third mechanism B for the inversion of position 6 when santonin rearranged to (-)-α-desmotroposantonin. The configuration of the desmotroposantonins then became:

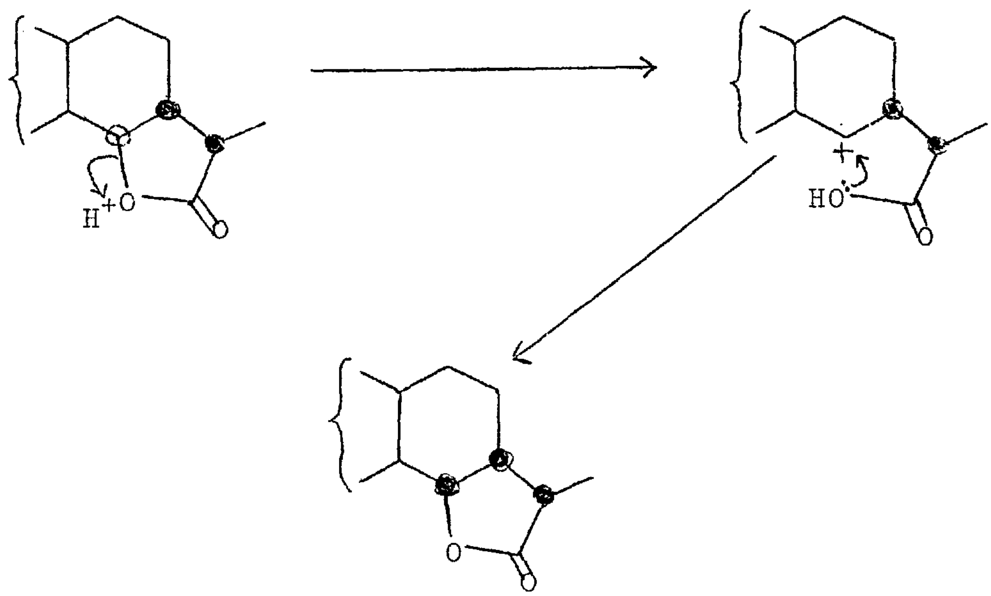
	6H	7H	11H
(-)-α-DESMOTROPOSANTONIN	α	α	β
(+)-β- "	β	β	β
(+)-α- "	β	β	α
(-)-α- "	α	α	α

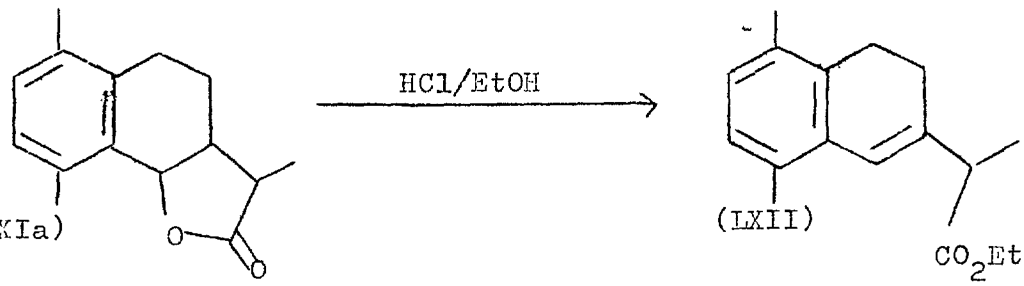
More recently[80] it has been shown that santonin, when treated with acetyl chloride/acetic anhydride mixtures, can undergo the dienone phenol rearrangement with retention of the trans fused lactone. Artemisin also retains[34] the trans fused lactone, even when treated with the acetic anhydride/sulphuric acid reagent at room temperature, and is only converted with difficulty to the cis fused lactone with the same reagent at 90°. The two diacetates formed in these reactions both, on hydrolysis, give the desmotropoartemisin with the cis fused lactone.

Mechanism A



Mechanism B





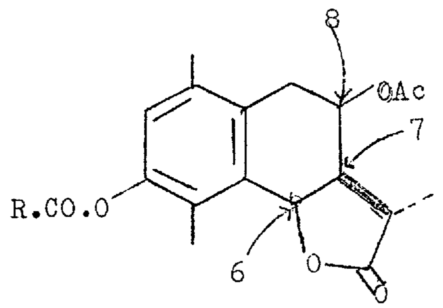
(LXIa) (LXII)

DISCUSSION OF PRACTICAL WORK

(PART I)

The Preparation of Desmotropoartemisin Diesters

The mass spectra of three of the four stereoisomeric artemisin acetates showed the loss of ketene from the molecular ion as well as acetic acid. In order to investigate the effect of the angular methyl group on this fragmentation it was necessary to obtain the four stereoisomeric desmotropoartemisin-8-acetate-3-butyrates differing in configuration at positions 6 and 8. The two desmotropoartemisin diacetates (LXIII, R = CH_3, 6α and 6βH, 7βH, 8βH) were already known.[34]



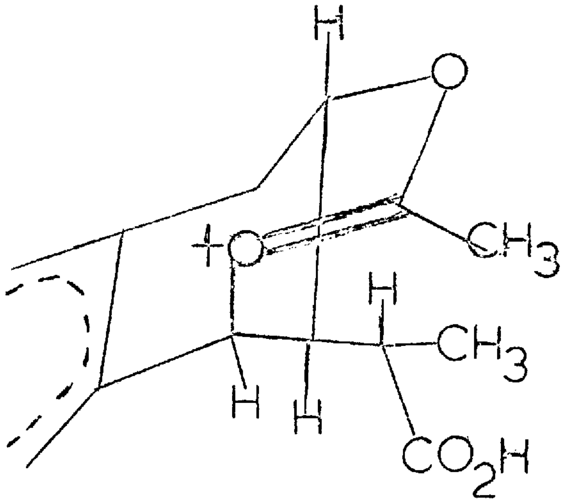
(LXIII)

The *trans*-lactone was made by the treatment of artemisin with the acetic anhydride/sulphuric acid reagent at room temperature, whereas the *cis*-lactone was formed at steam bath temperatures from either artemisin or the *trans*-lactone. The author was unable to repeat the preparation of the *cis*-lactone by either of these methods but hydrolysis of the *trans*-lactone followed by reacetylation, as described in the same paper,[34] was successful. The same difficulty was encountered on treatment of artemisin acetate with butyric anhydride and concentrated sulphuric acid.

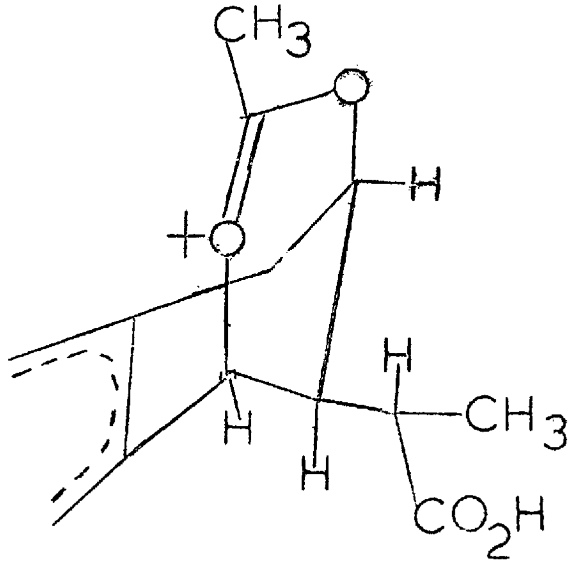
At room temperature the new 6βH, 7αH, 8βH-desmotropoartemisin-8-acetate-3-butyrate (LXIII, R=nC_3H_7) was isolated but no 6αH compound could be isolated on raising the temperature.

In contrast however, 8-epiartemisin, on treatment with the same reagent at room temperature, yielded 6βH, 7αH, 8αH-desmotropoartemisin-8-acetate-3-butyrate and at steam bath temperature smoothly yielded the _cis_-lactone, 6αH, 7αH, 8αH-desmotropoartemisin-8-acetate-3-butyrate. The formation of the corresponding _cis_-lactone diacetate was equally facile.

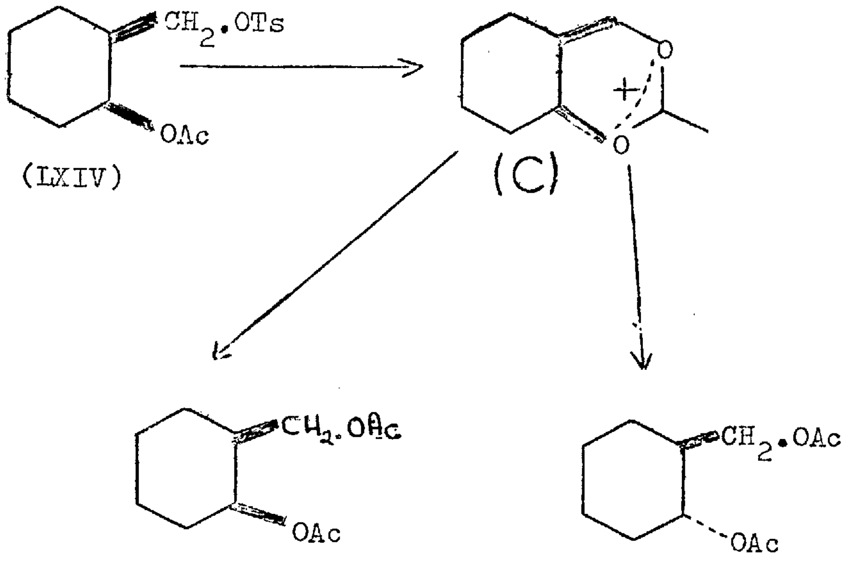
The apparent difficulty of inversion of the 6 position is probably caused by neighbouring group participation from the 8-acetoxy group. The carbonium ion at position 6, necessary[12] for inversion of that position, is probably stabilised by formation of the acetoxonium ion (A). Reclosure of the lactone ring will then occur with retention of configuration. The acetoxonium ion (B) is probably not formed as easily in the 8-epiacetates as it involves the interaction of two large 1,3 diaxial groups. A precedent for a six ring acetoxonium ion occurs[81] in the acetolysis of _cis_-2-toluene-_para_-sulphonyloxymethylcyclohexyl acetate (LXIV). A mixture of _cis_ and _trans_ 2-acetoxymethylcyclohexyl acetates is formed which necessitates the formation of the acetoxonium ion (C).


H
+
CH3
H
CH3
H
H
CO2H

(A)


CH3
H
+
H
CH3
H
H
CO2H

(B)


CH2.OTs
OAc
(LXIV)
+
(C)
CH2.OAc
OAc
CH2.OAc
OAc

DISCUSSION OF PRACTICAL WORK

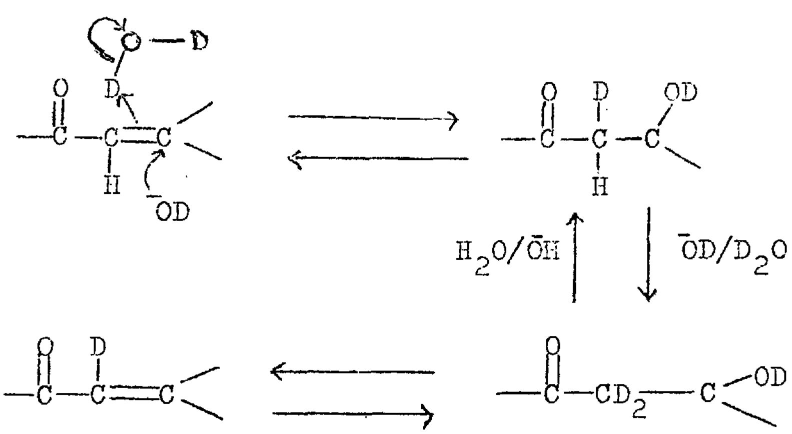
(PART II)

The Preparation of Deuterated Sesquiterpenes

Several deuterated sesquiterpenes have been prepared to help elucidate the mechanisms occurring under electron impact.

[11-$^{2}H_{1}$]-α-Santonin was made by refluxing α-santonin with 0.1 N [$^{2}H_{1}$]-sodium hydroxide in deuterium oxide. Although excess base is used the exchange must occur on the lactone itself and not the sodium salt. An isotope effect has been noted[82] in the tritiation of the 11-position, when only 60% of the theoretical tritium incorporation was obtained. When 0.25 N base was used, [2,11-$^{2}H_{2}$]-α-santonin was isolated, although the recovery of santonin was only 40%. Approximately 60% deuterium was incorporated into position 2. The ready exchange of an α proton in a non-enolisable position of α,β-unsaturated ketones is well known as in the case of Δ^{1}-5α-androsten-3-one.[83] The reversible addition of a solvent molecule to the enone system is postulated (see Equation 1).

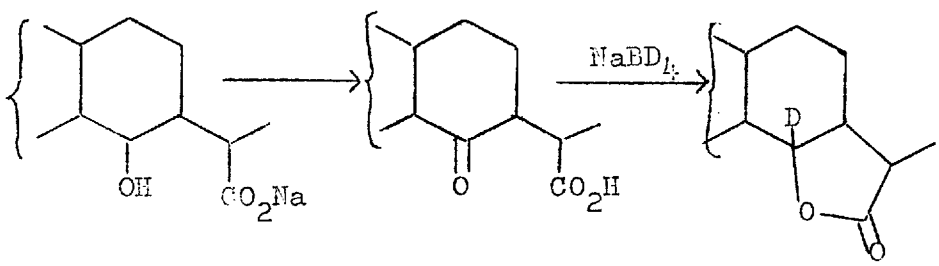
Equation 1



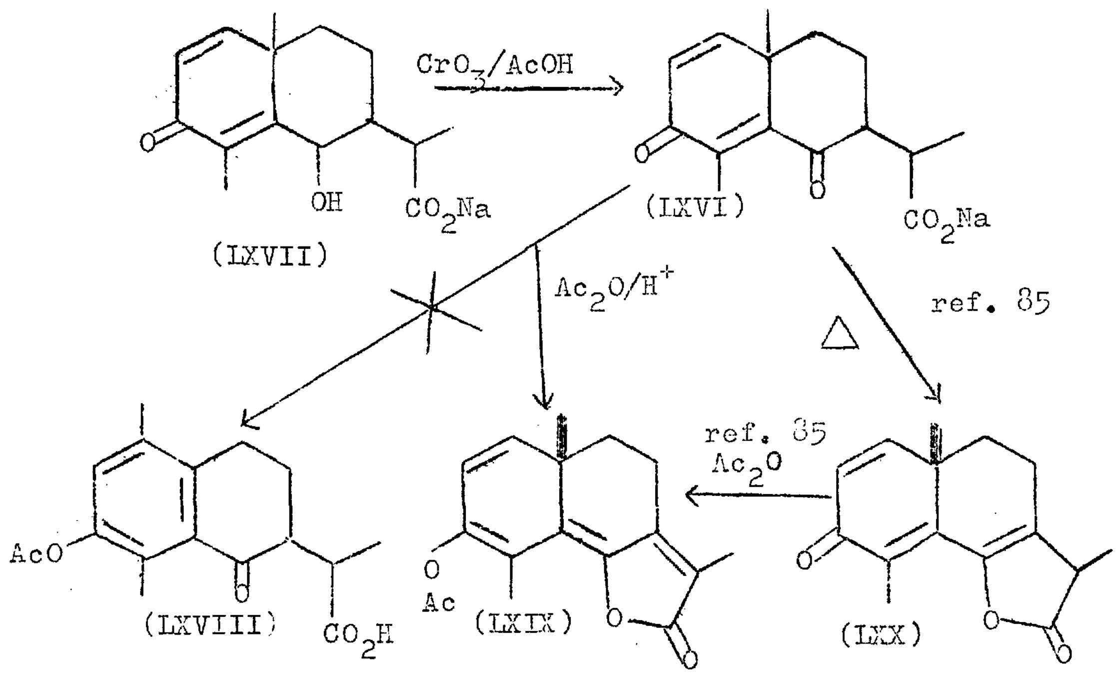
Several compounds deuterated at the 11-position were made directly from [11-$^{2}H_1$]-α-santonin (LXV). Hydrogenation of (LXV) over Raney nickel gave [11-$^{2}H_1$]-1,2-dihydro-α-santonin.[84] Photolysis[62] of (LXV) in aqueous acetic acid gave [11-$^{2}H_1$]-isophoto-α-santonic lactone. [11-$^{2}H_1$]-6αH, 7αH-desmotroposantonin acetate, (the (-)-α-isomer), was made by the dienone-phenol rearrangement of (LXV) and subsequent hydrolysis gave the deuterated free phenol.

[11-$^{2}H_1$]-Artemisin was made in the same way as [11-$^{2}H_1$]-α-santonin. The dienone-phenol rearrangement[34] gave [11-$^{2}H_1$]-6βH, 6αH-desmotropoartemisin diacetate.

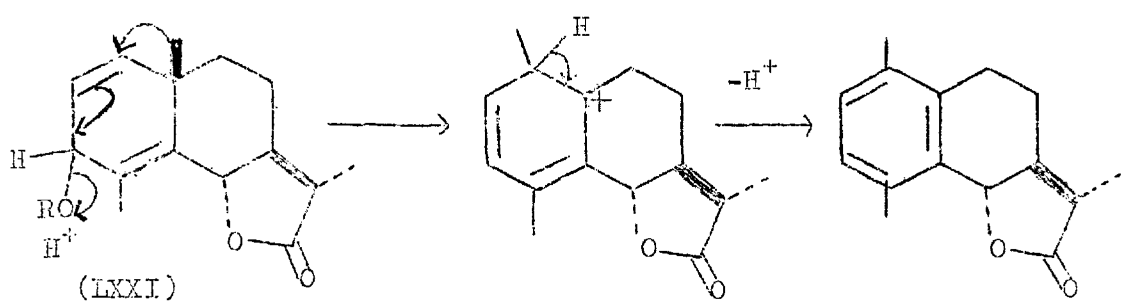
It was necessary to make suitable compounds deuterated at positions 6, 7 and 8, to elucidate the mechanism for the 'lactone' fragmentation by tracing the sites from which the additional proton was abstracted. The most obvious way to label position 6 was to open the lactone ring and oxidise the 6-hydroxyl group to the ketone. This could then be reduced with sodium borodeuteride with subsequent relactonisation.



α-Santonin had already been converted[85] to santenoic acid (LXVI) by oxidising the sodium salt of santonic acid (LXVII). At this stage it was expected that reduction with sodium borodeuteride would lead to reduction of the 3-keto group and thus yield unwanted products. Consequently, the dienone-phenol rearrangement was attempted on santenoic acid in the hope that 7-acetoxy-5,8-dimethyl-2(1'-carboxyethyl)-1-tetralone (LXVIII) would be obtained. However, this resulted in the formation of a yellow compound. The same compound could be obtained almost instantaneously and quantitatively by treating santenoic acid with an acetic acid/anhydride mixture containing a trace of sulphuric acid. The compound was identical with the conjugated enol acetate (LXIX) obtained by Nishikawa[85] on refluxing santonene (LXX) with acetic anhydride.



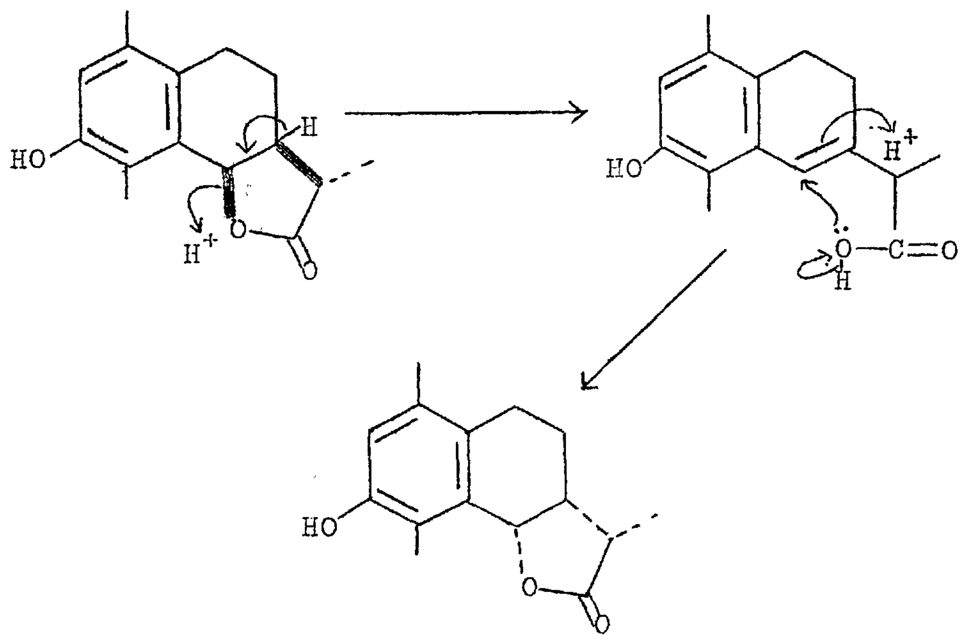
It was thought that if the dienone ring were aromatised prior to the oxidation at position 6, then this would ultimately lead to the required compound. Hyposantonin was therefore oxidised under the same conditions as for α-santonin. However, isohyposantonin was isolated. It is known that the dissolution of hyposantonin in base followed by reprecipitation with acid yields isohyposantonin. Isohyposantonin is a cis-fused lactone, the sodium salts of which, closes very rapidly on acidification. Obviously, the lactone ring was being reformed before oxidation could take place. The sodium salt of santonin closes more slowly as it gives a trans-fused lactone. While these studies were proceeding, it had been found[82] that one of the sodium borohydride reduction products of α-santonin was the dienol (LXXI, R=H). On acetylation with acetyl chloride in pyridine and subsequent addition of excess acid, a 20% yield of hyposantonin was obtained. Obviously, the acetate (LXXI, R=CH_3.CO) can undergo a similar elimination as santoninamine.



(LXXI)

Because of these results, the sodium salt of santenoic acid was reduced with sodium borohydride and then refluxed under acidic conditions to eliminate the hydroxyl group from the dienol itself. The main neutral product, isolated in 12% yield, was isohyposantonin. The same reduction with sodium borodeuteride gave [3,6-$^{2}H_{2}$]-isohyposantonin, the nuclear magnetic resonance spectrum of which showed the disappearance of the signals from the 6-proton and one aromatic proton.

To obtain a suitable compound containing deuterium at position 7, the known[71] isomerisation of (–)-α-desmotroposantonin (6βH, 7αH) to (+)-β-desmotroposantonin (6αH, 7αH), was utilised. This occurs[12,73] by alkyl oxygen fission with the reversible conversion to the βγ -unsaturated acid.

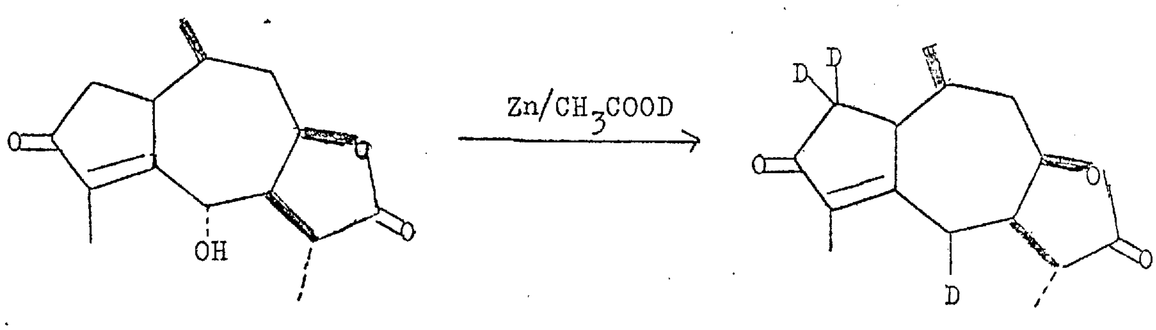


Santonin, on treatment with 50% sulphuric acid, undergoes this conversion _via_ (-)-α-desmotroposantonin. When 50% [$^2H_2$]-sulphuric acid was used, [2,7,-$^2H_2$]-(+)-β-desmotroposantonin was isolated, the aromatic proton having exchanged also. The aromatic deuterium atom was replaced by a proton using the method developed by Kirby and Ogunkoya,[86] to yield [7-$^2H_1$]-(+)-β-desmotroposantonin.

It seemed obvious to use artemisin as the starting point for a suitable compound deuterated at the 8-position. One direct conversion of artemisin to santonin has been reported.[34] This involved the conversion of artemisin to 8-iodosantonin using triphenylphosphite methiodide, followed by reduction with poisoned Raney nickel to give α-santonin. The author was unable to prepare the iodo compound from artemisin or its 8-epimer. The 8 position of artemisin is hindered by the angular methyl group and is resistant[87] to S_N2 type displacements. It was thus decided to aromatise the dienone ring before introducing an iodide atom at position 8. Consequently, artemisin was converted to its mesylate.[26] This, on treatment with acetic anhydride containing a drop of sulphuric acid, gave 6βH, 7αH-desmotropoartemisin-3-acetate-8-mesylate in which the lactone ring was still _trans_-fused. This compound on treatment with sodium iodide in refluxing acetone gave a mixture of two iodides which were separated by fractional recrystallisation to give iodide A, m.p. 109°, $[\alpha]_D^{22}$ + 32 and iodide B, m.p. 120°, $[\alpha]_D^{22}$ +162. Iodide A was assigned as the 8β-iodide because it had the less positive optical rotation. The iodides were shown to be epimeric because on mild reduction with zinc in acetic acid, they both gave 6βH, 7αH-desmotroposantonin acetate.[80] This is the first conversion of a desmotropoartemisin to a desmotroposantonin and is particularly interesting as the trans-lactone was retained. Treatment of 6βH, 7αH-desmotroposantonin acetate with the acetic anhydride/sulphuric acid reagent gave (-)-desmotroposantonin acetate.

Both iodides were reduced with zinc in $[O^2H_1]$-acetic acid and in $[O^2H_1]$-$[^2H_3]$-acetic acid and in all cases no more than 70% of monodeuterated species was present in the desmotroposantonin acetate isolated. The explanation for this is not apparent, as there were no external sources for proton donation, especially in the case of the fully deuterated acetic acid.

$[2,2,6-^2H_3]$-deoxygeigerin was made by reduction[66] of geigerin with zinc in $[O^2H_1]$-acetic acid.



The nuclear magnetic resonance spectrum showed the disappearance of the signals attributed to the protons at C_2.

$H_{2a}\,\tau(7.87,\ 7.85,\ 7.69,\ 7.67)$	$J_{2a.2b}$	18 c/s
	$J_{2a.1}$	2 c/s
$H_{2b}\,\tau(7.48,\ 7.41,\ 7.30,\ 7.23)$	$J_{2b.1}$	7 c/s

Geigerin, when refluxed with weakly basic deuterium oxide gave, on isolation of the neutral fraction, $[^2H_3]$-geigerin (presumably the $[2,2,11-{}^2H_3]$ compound). This was mutually consistent with the most obvious fragmentation of this compound.

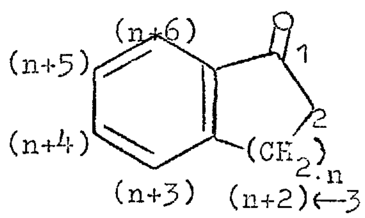
8-epialloartemisin-$[^2H_3]$-acetate was made by acetylation of 8-epialloartemisin[62] with $[^2H_3]$-acetyl chloride and pyridine.

DISCUSSION OF PRACTICAL WORK

(PART III)

Nomenclature of the Aromatic Bicyclic Ketones and their Enol Acetates

The nomenclature of the benzenoid bicyclic ketones presents difficulties. The common names are not recommended by either the I.U.P.A.C. or the Chemical Society and are in themselves inconsistent. However, in the interests of clarity, the common names have been retained. In addition, the ketone group is given the position 1 and the molecule numbered through the alkane ring.



n = 1, 1-INDANONE

n = 2, 1-TETRALONE

n = 3, BENZSUBERONE

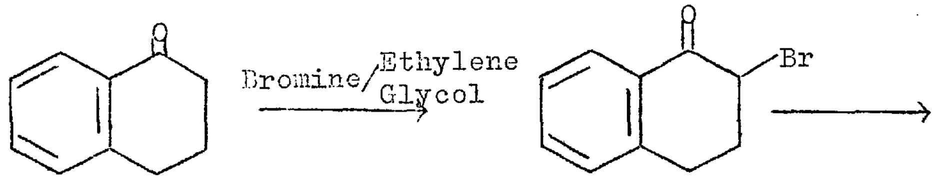
n = 4, BENZCYCLO-OCTANONE

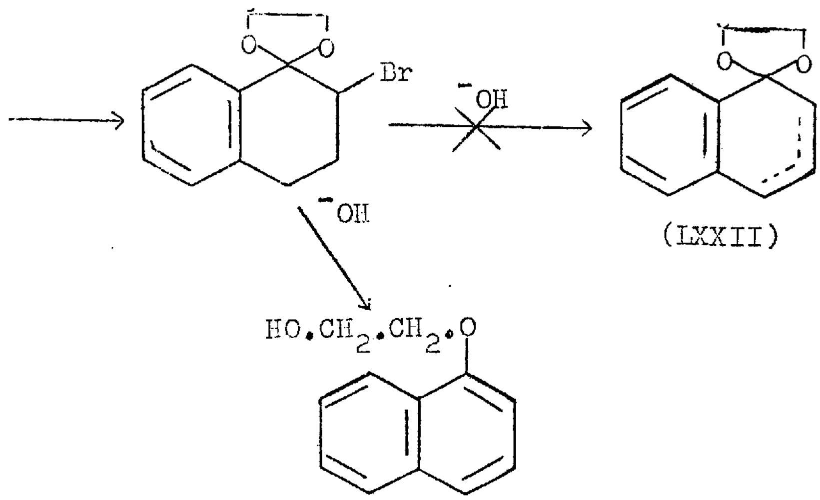
The Preparation of Some Deuterium Labelled Aromatic Ketones and Related Compounds

The anomalous loss of a methyl radical from the (M-42) ion formed in the fragmentation of the enol acetates of 1-tetralone and benzsuberone obviously required the preparation of deuterated compounds.

One of the earlier attempts, which is worthy of mention, is shown in Scheme 1.

Scheme 1

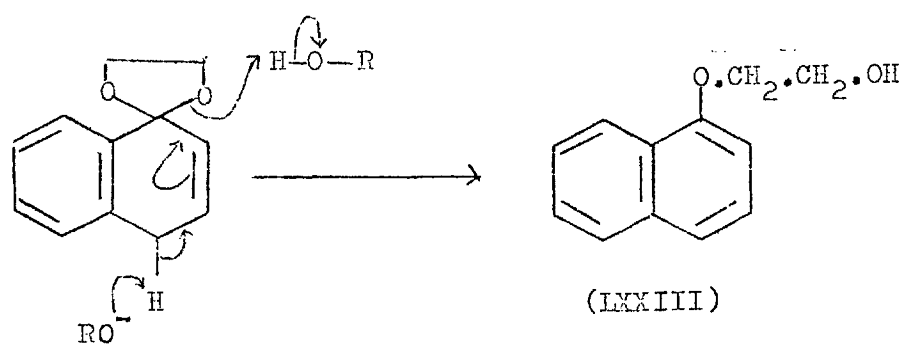




(LXXII)

(LXXIII)

The idea was to obtain the ethylene ketal of 2-bromo-1-tetralone. It was hoped that dehydrobromination would give one of the unsaturated compounds (LXXII) which could be deuterogenated and the ketone regenerated. 2-Bromo-1-tetralone[88] was a known compound, but the corresponding ethylene ketal was not. 2-Bromo-1-tetralone was refluxed with ethylene glycol in benzene, in the presence of p-toluene sulphonic acid, continuously removing the water formed. The product, on work up, was a mixture of the ketal and the ketone which co-distilled. The same difficulty has been observed[89,90] with 2-bromo-1-indanone. However, it was known that when cyclohexanone was brominated[91] in ethylene glycol, the 2-bromo ethylene ketal was isolated directly. Application of the same method to 1-tetralone gave only the 2-bromo-ketone. However, addition of benzene to the bromination mixture, followed by reflux for three days, gave 2-bromo-1-tetralone ethylene ketal in 65% yield. Treatment of the bromoketal with potassium t-butoxide in t-butyl alcohol, reaction conditions[89] which convert 2-bromo-1-indanone ethylene ketal to indenone ethylene ketal, gave unchanged starting material. The butoxide ion must abstract a proton from the benzylic position. 2-Bromo-1-indanone ethylene ketal can then lose a bromide ion, whereas this is not possible in the case of 2-bromo-1-tetralone ethylene ketal. The latter compound was therefore refluxed with sodium hydroxide in methanol and gave 2-(1'-naphthoxy)-ethanol[92] (LXXIII).



(LXXIV)

(LXXIII)

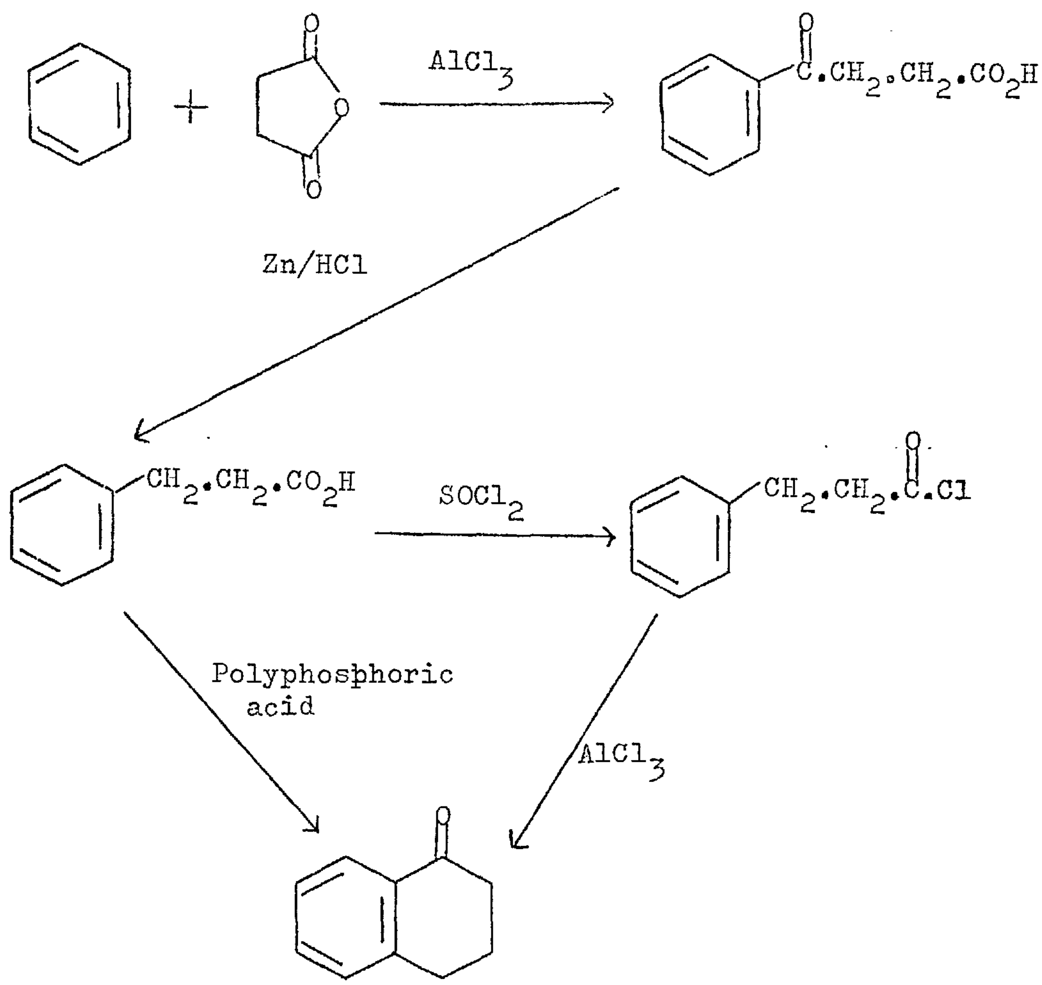
The dehydrobrominated compound (LXXIV) must be formed which immediately rearranges to the naphthyl compound (LXXIII).

At this point, another ultimately successful approach was made to the problem. The normal synthesis of[93a] 1-tetralone involves the Friedel-Crafts reaction between benzene and succinnic anhydride (see Scheme 2) to give 3-benzoylpropionic acid. Clemmensen reduction of this gives 4-phenylbutyric acid. This can either be converted to the acid chloride followed by a Friedel-Crafts cyclisation to 1-tetralone, or the acid can be cyclised directly using polyphosphoric acid.[93b] Hartung[94] has shown that aryl ketones may be catalytically reduced over palladium on charcoal catalyst to the corresponding benzyl compound. It was hoped that if deuterium gas were used [4,4-$^{2}H_2$]-4-phenylbutyric acid could be isolated from the reduction of 3-benzoylpropionic acid.

$$\mathrm{Ar.\,CO.R} \xrightarrow[\mathrm{Pd/C}]{\mathrm{H_2}} \mathrm{Ar.CH_2.R}$$

When 3-benzoylpropionic acid was reduced in ethanol in an atmosphere of deuterium gas, considerable exchange occurred between gas and solvent. Obviously a different solvent system had to be used. The best one was a 4:1 (by volume) mixture of either dioxan or tetrahydrofuran with deuterium oxide.

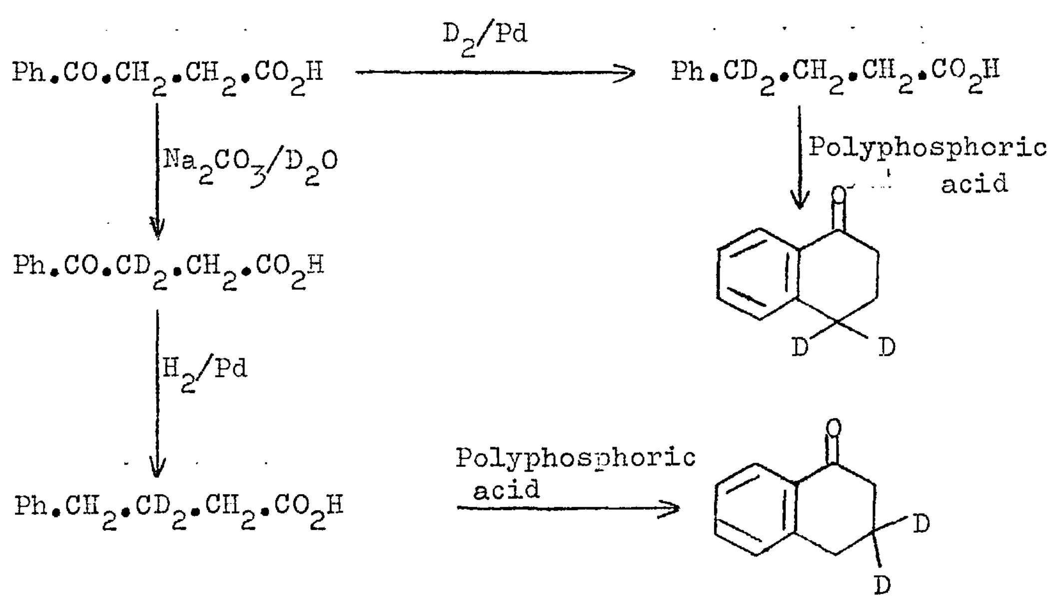
Scheme 2


AlCl$_3$
C.CH$_2$.CH$_2$.CO$_2$H
Zn/HCl
CH$_2$.CH$_2$.CO$_2$H
SOCl$_2$
CH$_2$.CH$_2$.C.Cl
Polyphosphoric acid
AlCl$_3$

Contrary to Hartung's[94] observation, the reduction was found to proceed faster if a drop of concentrated deuterosulphuric acid was added to the solution. Acid-catalysed exchange of the α-protons before reduction, occurred to the extent of 5% i.e. 5% of the trideuterated acid was formed. Likewise, if the α-protons were previously exchanged with deuterium and the reduction carried out in ethanol with an atmosphere of hydrogen, about 5% of undeuterated acid was obtained. This degree of exchange was tolerable, but in aryl ketones, where the α-protons are more acidic, greater exchange can occur. Thus, when benzyl phenyl ketone was reduced with deuterium using the conditions described, dibenzyl containing 22% trideuterated species was obtained. However, simple aryl ketones carrying the group $Ar - \overset{O}{\overset{\|}{C}} - CH_2 - CH_2 -$, should show no more than about 5% exchange. Reduction of 3-benzoylpropionic acid with deuterium gas in 4:1 dioxan/deuterium oxide gave [4,4-$^{2}H_2$]-4-phenylbutyric acid (see Scheme 3). This was cyclised in polyphosphoric acid to [4,4-$^{2}H_2$]-1-tetralone.

Exchange of the 3 position of 3-benzoylpropionic acid with sodium carbonate in deuterium oxide gave [3,3-$^{2}H_2$]-3-benzoylpropionic acid. Reduction of this compound with hydrogen gave [3,3-$^{2}H_2$]-4-phenylbutyric acid. This was cyclised to [3,3-$^{2}H_2$]-1-tetralone in polyphosphoric acid.

Scheme 3

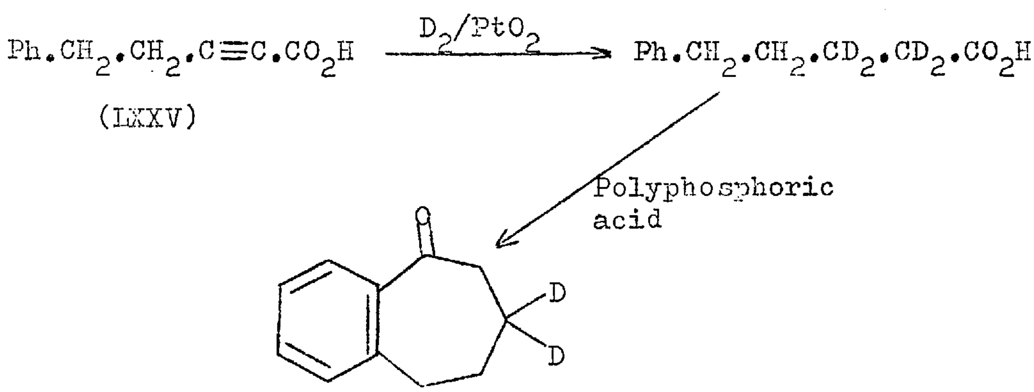


[5,6,7,8-$^2H_4$]-1-tetralone was made by employing [$^2H_6$]-benzene in the first stage. (see Scheme 2).

Deuteropolyphosphoric acid (from deuterium oxide and phosphorous pentoxide) was used in the final cyclisation step. The enol acetate made from this deuterated tetralone contained 79.8% d_4 species, thus indicating that each aromatic position contained 94.5% deuterium.

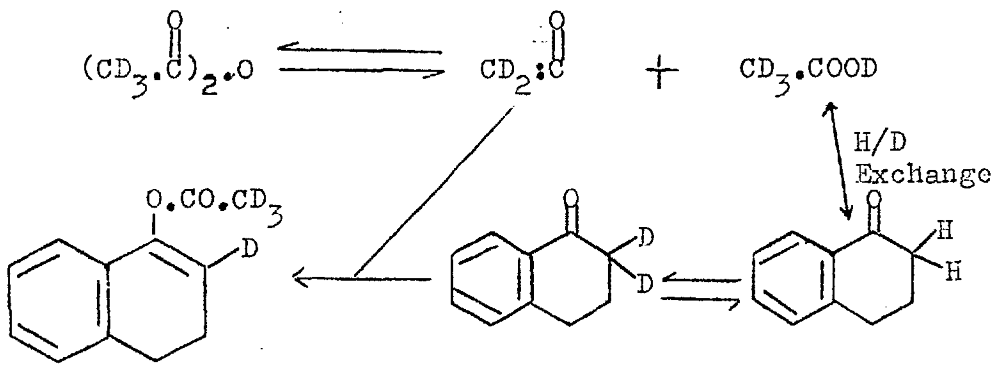
4-Benzoylbutyric acid was made by the Friedel-Crafts reaction between benzene and glutaric anhydride. Reduction with deuterium gas and subsequent cyclisation gave [4,4-$^2H_2$]-benzsuberone. Prior exchange of the α -proton with deuterium, reduction with hydrogen, and subsequent cyclisation gave [5,5-$^{2}H_2$]-benzsuberone.

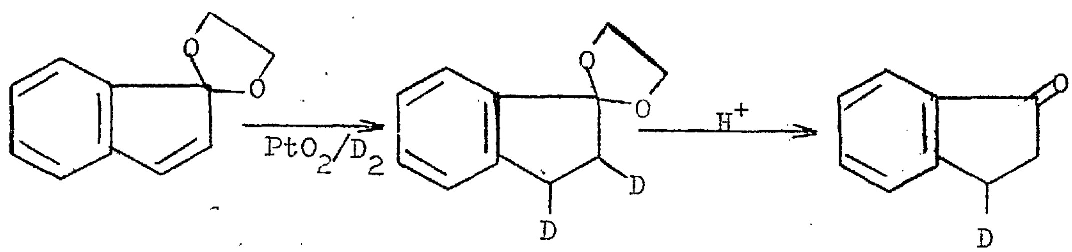
[3,3-$^{2}H_2$]-Benzsuberone was obtained from 5-phenylpent-2-ynoic acid[95,96,97](LXXV). The latter compound was deuterogenated to [2,2,3,3-$^{2}H_4$]-5-phenylpentanonic acid. Cyclisation with polyphosphoric acid also exchanged out the deuterium atoms α to the ketone group to give [3,3-$^{2}H_2$]-benzsuberone.



The deuterated ketones were then converted[98] to their enol acetates using acetic anhydride and p-toluene sulphonic acid.

The enol acetates, deuterated on the double bond and in the acetate group were also required. The enol acetate made from [2,2-$^{2}H_2$]-1-tetralone and acetic anhydride was undeuterated whereas 1-tetralone and [$^{2}H_6$]-acetic anhydride gave [2-$^{2}H_1$]-1-tetralone-enol-[$^{2}H_3$]-acetate. Obviously, the acetic anhydride in the presence of p-toluene-sulphonic acid, dissociates to ketene and acetic acid. The acetic acid exchanges with the α-protons of the ketone and the ketene acts as the acetylating agent (see below)

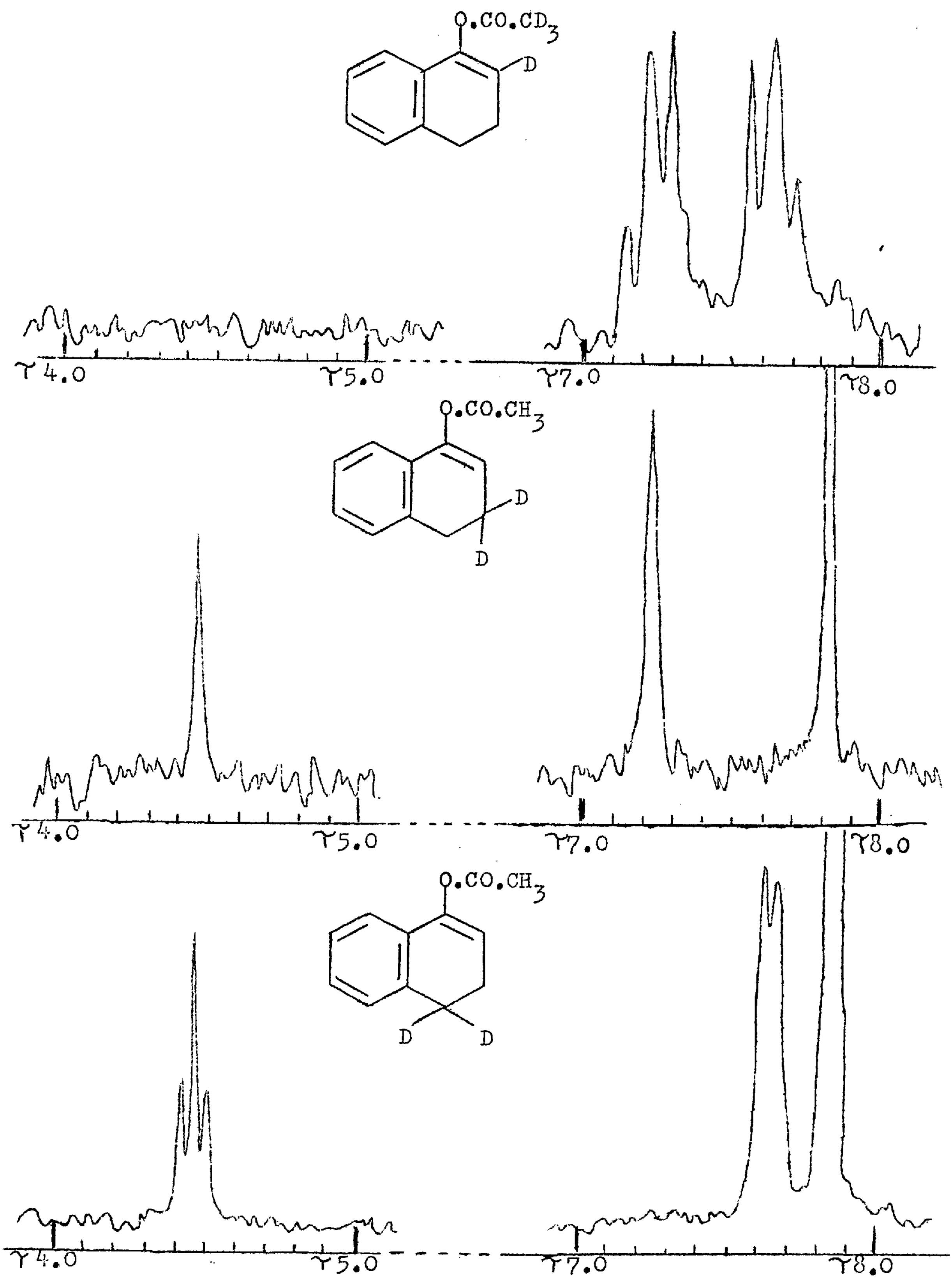




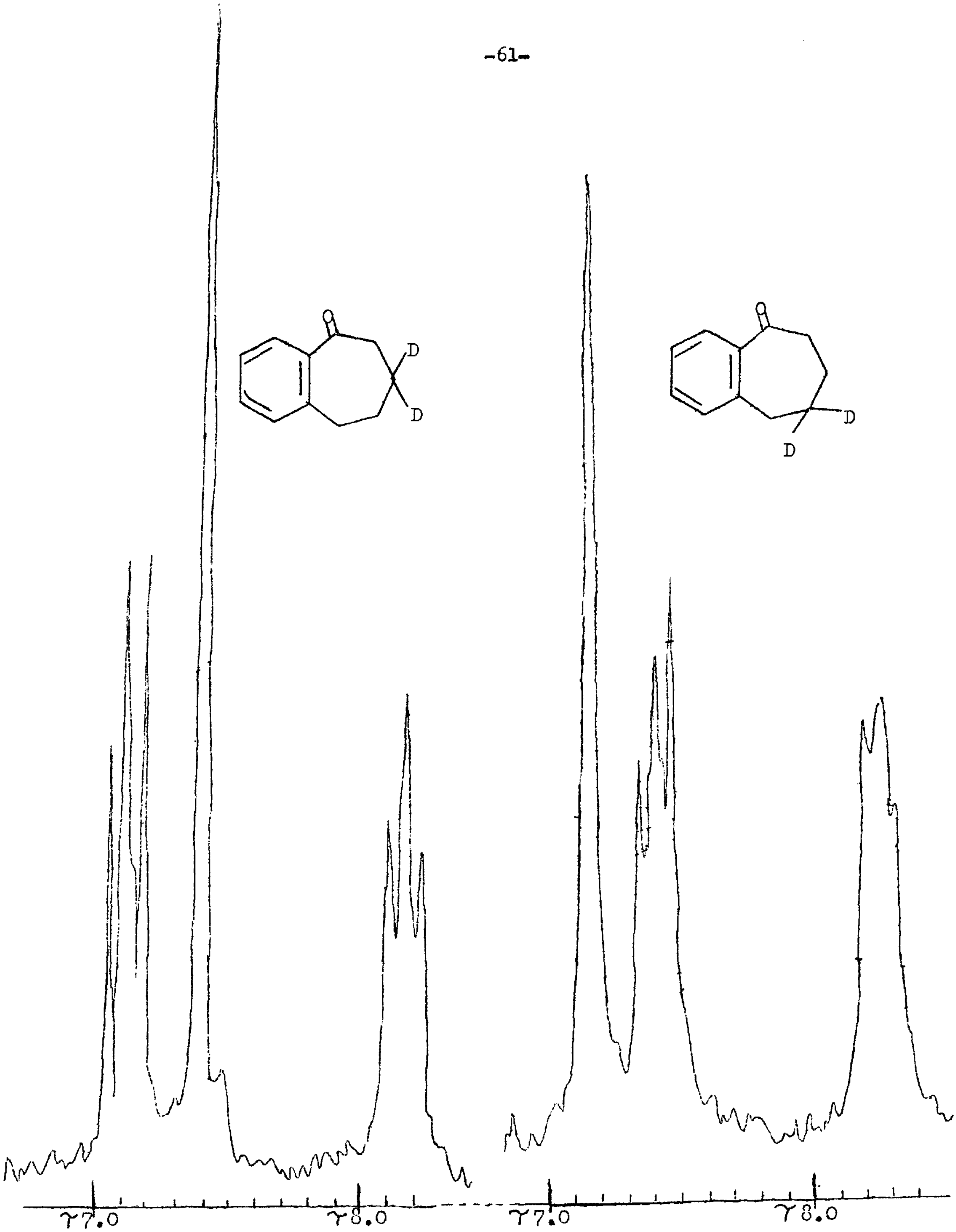
The positions occupied by the deuterium atoms were confirmed from the nuclear magnetic resonance spectra (see pp. 60-62)

2-[2',2',2'-$^{2}H_{3}$]-ethyl-1-tetralone was made from [2,2,2-$^{2}H_{3}$]-ethyl iodide[99] and 2-carbethoxy-1-tetralone.[100]

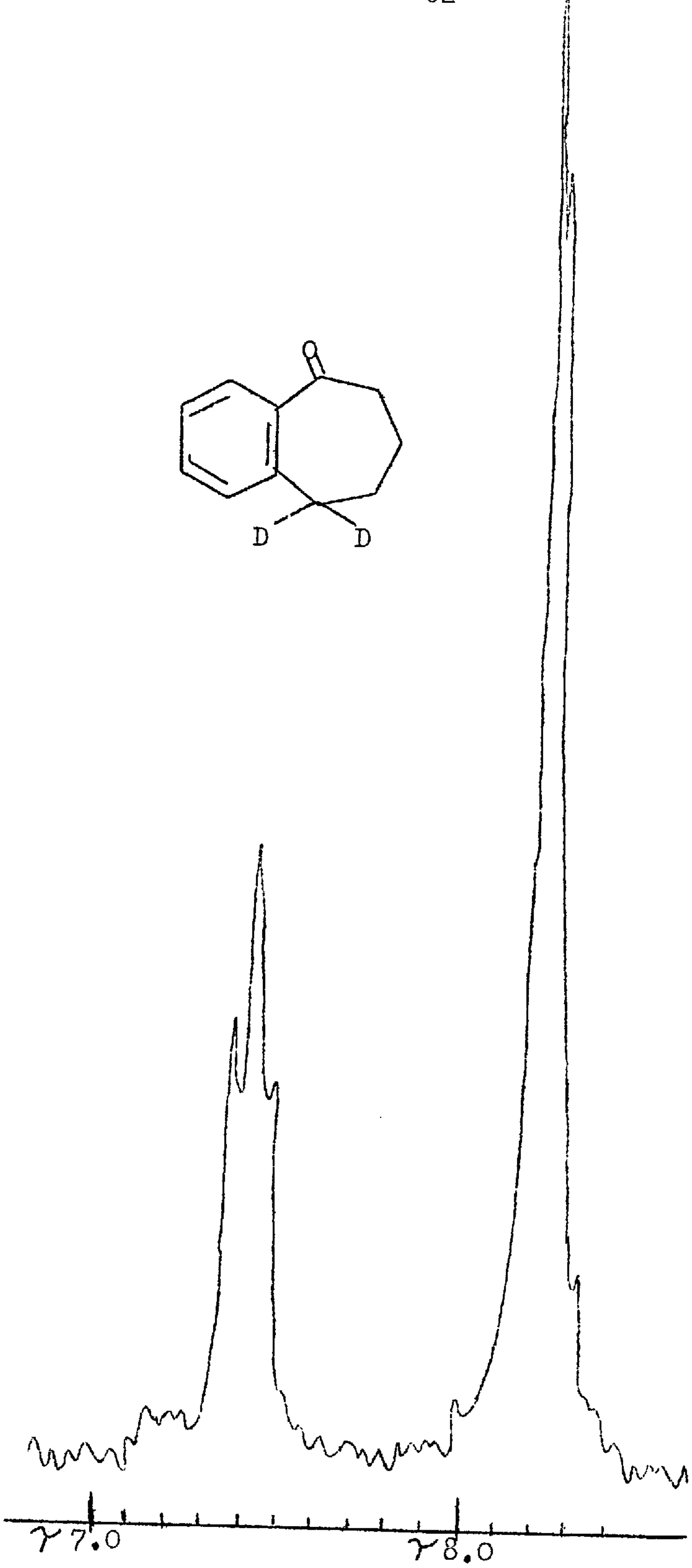
[3-$^{2}H_{1}$]-1-Indanone was also made by deuterogenation of indenone ketal, followed by hydrolysis (see above)



The vinylic and aliphatic proton regions in the 60 Mc. n.m.r. spectra of the deuterated 1-tetralone enol acetates.



Aliphatic proton regions in the 100 Mc n.m.r. spectra of deuterated benzsuberones. (see p. 62 also)


D
D
τ7.0
τ8.0

DISCUSSION OF MASS SPECTRA

(PART I)

Spectra were determined with an A.E.I. MS9 double-focusing mass spectrometer at ionising voltage 70ev and trap current 100μa. High-resolution measurements were made at resolving power of approximately 10,000 (10 % valley) using heptacosafluorotri-n-butylamine as the mass standard. Sesquiterpenes were introduced directly into the source using the probe technique. Benzcycloalkanes and enol acetates were introduced <u>via</u> the hot inlet system. The ion block temperature was normally about 200°.

Many of the sesquiterpenes and derivatives were generously provided by Professor D.H.R. Barton. I am indebted to Professor J.A. Elvidge for the samples of methyl-1-indanones and to Dr. J.P. de Villiers for a sample of geigerin. Other compounds were prepared as described in the practical section.

Spectra have been reproduced as line diagrams in the conventional manner. The mass to charge ratio (<u>m</u>/<u>e</u>) is on the abcissa and the relative abundance (in percent) is shown on the ordinate. The relative abundance of an ion is defined as the intensity of that ion divided by the intensity of the most intense ion (base peak).

If no relative abundance is indicated for a particular <u>m</u>/<u>e</u> value, it may be assumed that the relative abundance is less than 5%.

In the proposed mechanistic schemes a fishook arrow thus, indicates a one electron shift. Metastable ions are referred to in the text. The presence of the appropriate metastable ion is also indicated by an asterisk * in the mechanistic schemes.

α-Santonin

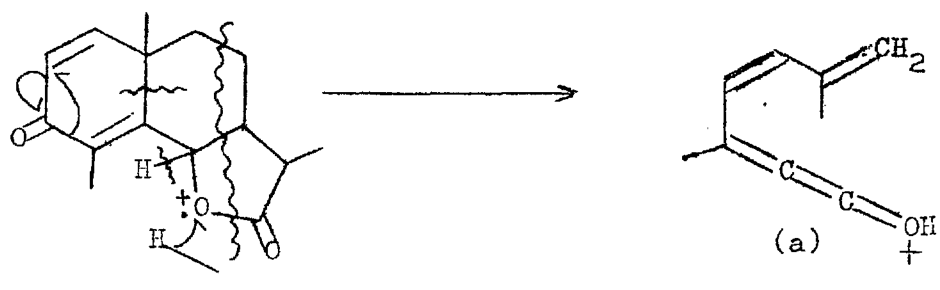
The mass spectrum (1) of α-santonin (XXXI) shows the molecular ion, m/e 246 as the base peak.

The most abundant fragment ion, m/e 173, ($C_{12}H_{13}O$), is unshifted in the spectrum (2) of [11-$^2H_1$]-α-santonin, but is shifted up one mass unit in the spectrum (3) of [2,11-$^2H_2$]-α-santonin. There is a metastable ion, indicating the direct formation of the ion from the molecular ion. The ion therefore, arises by loss of the lactone ring together with an additional proton. The mechanism for this fragmentation is discussed in the section on desmotroposantonin. The ion, m/e 172 ($C_{12}H_{12}O$), is also only shifted one mass unit in the spectrum of [2,11-$^2H_2$]-α-santonin. It is considered to arise by loss of the lactonic function together with two additional protons. The ion, m/e 174, ($C_{12}H_{14}O$), is only half shifted in the spectrum of [11-$^2H_1$]-α-santonin. This is considered to be the loss of the lactone ring with donation of a proton back to the main ring system. This proton must come equally from the 11-methyl group and the 11-proton. However, this fragmentation must require a relatively high energy as decreasing the energy of the ionising electron beam to 15 electron volts causes the ion to virtually disappear.

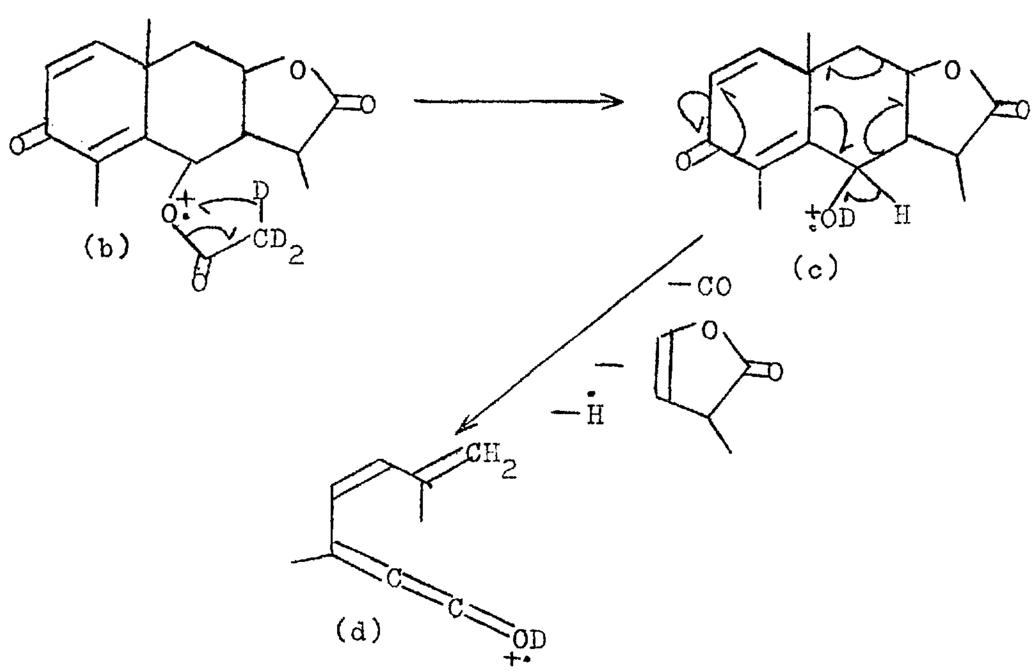
There is an ion, m/e 231 corresponding to the loss of a methyl radical from the molecular ion. It is not clear whether this is the 10-angular methyl group or that at the 11-position. The lack of an ion corresponding to the lactone fragmentation and the loss of a methyl radical independently, suggests that the 11-methyl group may be that which is lost.

The ion, m/e 203, ($C_{13}H_{15}O_2$), is formed by the loss of a methyl radical and carbon monoxide. The appropriate metastable ions confirm that these two processes occur in either order.

The ion, m/e 91, (C_7H_7), is considered to be the tropylium ion. It is shifted up one mass unit in the spectrum of [2,11-$^2H_2$]-α-santonin. The mechanism for its formation must be quite complicated as is the mechanism which gives the ion, m/e 135, ($C_9H_{11}O$). The latter ion, is also unshifted in the spectrum of [11-$^2H_1$]-α-santonin, but is shifted up one mass unit in the spectrum of [2,11-$^2H_2$]-α-santonin. Structure (a) is a possibility for this ion.



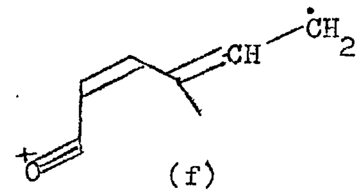
All four artemisin stereoisomers (spectra 5-8) show the $C_9H_{11}O$ ion in their spectra. The 8-hydroxyl proton is partially incorporated in the ion, the degree of incorporation decreasing in the order 6-epi-8-epiartemisin $>$ $\begin{matrix}\text{6-epiartemisin}\\ \text{8-epiartemisin}\end{matrix}$ $>$ artemisin. This would be consistent with migration of the hydroxylic proton to the C(6)-oxygen atom. Extra evidence is provided from the spectrum of 8-epialloartemisin and its acetate (spectrum 40). Both show the ion m/e 135. Also, the [$^2H_3$]-acetate loses [$^2H_2$]-ketene (presumably via a four-membered transition state to give the parent hydroxy ion). The deuterium atom left behind is incorporated into the m/e 135 ion. A suitable mechanism is shown below, (b $\longrightarrow$ d).



The mass spectra of three other stereoisomers have been obtained. These are β-santonin (11-epi-α-santonin), 6-epi-α-santonin and 6-epi-β-santonin. The mass spectrum of β-santonin is virtually identical to that of α-santonin (spectrum 1). The spectra of the two 6-epi-santonins (spectrum 4) are virtually identical with each other but differ from α- and β-santonin in the following ways.

In the spectra of the 6-epi-santonins, the ion, <u>m/e</u> 228 ($C_{14}H_{18}O_2$), which corresponds to the loss of carbon monoxide, is as abundant as the (M-15) ion. There is also a prominent ion <u>m/e</u> 145 ($C_{11}H_{13}$, M-73-28) which presumably is formed <u>via</u> the independent losses of carbon monoxide and the lactone ring, although there are no metastable ions to indicate the order. The 3-oxo group is almost certainly the source of the carbon monoxide. This fragmentation is analagous to that occurring in anthraquinones.[103] A sample of 4-(dichloromethyl)-4-methylcyclohexa-2,5-dien-1-one also showed this fragmentation. This apparent increase in the loss of carbon monoxide is attributed to the increased strain in the 6-epi-compounds which is evident from molecular models.

The prominent ion, <u>m/e</u> 108 (C_7H_8O) which occurs in the spectra of the 6-episantonins is of unknown structure but a possibility is ion (f).



(f)

An ion, m/e 187 ($C_{13}H_{15}O$), occurs in the spectra of the 6-epi compounds. This should correspond to the loss of a methyl radical and carbon dioxide, although there is a metastable ion, indicating a one step process from the molecular ion. There is also a prominent ion, m/e 159 ($C_{12}H_{15}$), accounted for by the further loss of carbon monoxide.

The ion m/e 134 may be similar to the ion m/e 135 without the proton migration to the C(6)-oxygen. The *cis*-fused lactone may make this process more difficult in the 6-epi compounds.

The Artemisins

The mass spectra (5-8) of the four stereoisomeric artemisins (8-hydroxysantonins) have been obtained. Generally, the four compounds show more fragmentation than the santonins. In all but one spectrum, the tropylium ion, m/e 91 gives the base peak. The ion, m/e 135 is also very prominent in all four spectra. The ions analogous to the M-73 and M-71 ions in the santonin spectra, are present at m/e 171 ($C_{12}H_{11}O$, M-73-18) and m/e 173 (M-71-18). The spectra are complicated by the loss of water from the molecular ions. This latter process is not a 1,2 elimination and so mechanisms cannot be written for the fragmentations which follow. However, it is pertinent to discuss the four spectra from the viewpoint of stereochemistry. Table 1 lists the relative abundance of ions in the upper mass region corresponding to the loss of water, carbon monoxide, and a methyl radical both singularly and in all possible combinations.

Table 1

Compound m/e	247	244	234	229	219	216	201
	(M-15)	(M-18)	(M-28)	(M^{-15}_{-18})	(M^{-15}_{-28})	(M^{-18}_{-28})	$\begin{matrix}-15\\(M-18)\\-28\end{matrix}$
Artemisin	6	28	0	11	0	17	20
8-Epiartemisin	7	8	0	13	0	12	22
6-Epiartemisin	7	32	18	0	0	0	0
6-Epi-8-epiartemisin	9	6	26	0	12	6	10

The results can be best explained if the following assumptions are made.

(a) The elimination of water from the 8α-OH compounds (i.e. artemisin and 6-epiartemisin) is FAST whereas the elimination of water from 8β-OH compounds (i.e. 8-epi and 6-epi-8-epiartemisin) is a MEDIUM rate process.

(b) The elimination of carbon monoxide is FAST from the 6αH compounds (i.e. 6-epi and 6-epi-8-epiartemisins) and SLOW from the 6βH compounds (i.e. Artemisin and 8-epiartemisin).

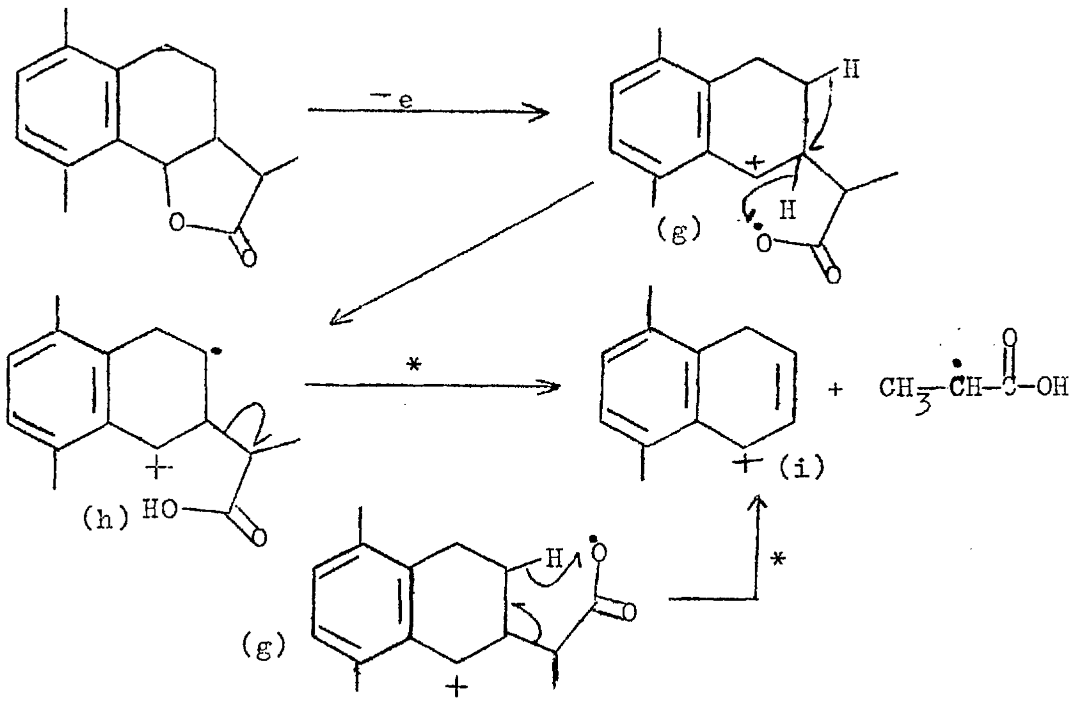
(c) The loss of a methyl radical is a MEDIUM rate process in all compounds.

These assumptions would explain the lack of (M-28) and (M-15-28) ions in the spectrum of artemisin whereas there is an (M-15-18-28) ion. The lack of ions corresponding to loss of combinations of the groups in the spectrum of 6-epiartemisin is difficult to explain. The assumption that the 8α-OH compounds lose water faster than the 8β-OH compounds is the reverse of what might be expected from Biemann and Seibl's[102] results. They found that the isomer with the axial hydroxyl group usually showed the more abundant(M-18) ion, but these results were not obtained using a direct inlet system and therefore thermal dehydration could not be ruled out.

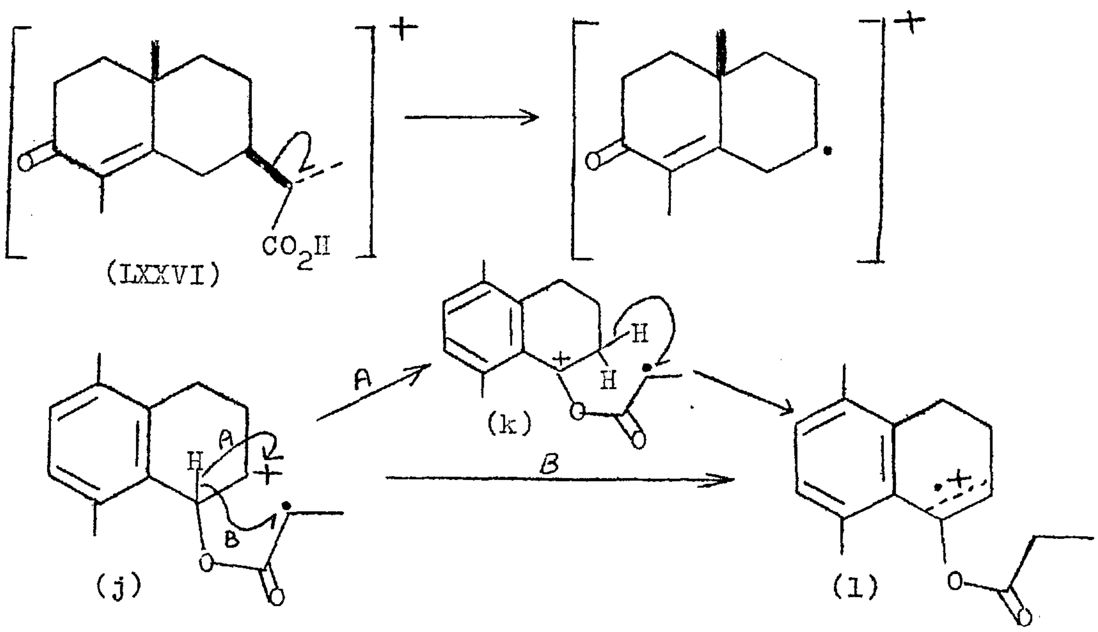
Desmotroposantonins

The mass spectra (9) of (-)-α-desmotroposantonin and (+)-β-desmotroposantonin are identical. The loss of a methyl radical is a negligible process and the ions m/e 202 and m/e 187 formed by loss of carbon dioxide and carbon dioxide, together with a methyl radical, amount to only 5% and 10% of the base peak respectively. The only major fragment ion, m/e 173 is that corresponding to loss of the lactone ring and one additional proton as noted in the spectrum of santonin.

(-)-α-Desmotroposantonin acetate (Spectrum 10) also shows the same fragmentation after the loss of ketene from the phenolic acetate. The single major fragment ion, m/e 157, in the spectrum (11) of isohyposantonin arises by the same cleavage. The spectrum (12) of [11-$^2H_1$]-(-)-α-desmotroposantonin acetate shows the deuterium to be lost in this fragmentation. The spectrum (13) of [7-$^2H_1$]-(+)-β-desmotroposantonin shows that 33% of the additional proton comes from the 7-position. The spectrum (14) of [8-$^2H_1$]-(-)-α-desmotroposantonin shows that 14% comes from the 8-position. This assumes no isotope discrimination against deuterium. If there is discrimination the true figure will be in excess of 14%. The fragmentation of [3,6-$^2H_2$]-isohyposantonin (spectrum 15) indicates that not more than 10% of the proton source is at position 6. Thus, the mechanism is by no means specific. The abstractions from positions 7 and 8 probably occur by preliminary alkyl-oxygen fission at C(6) to give (g). Migration of the proton from C(7) to the oxygen radical can then occur, accompanied by a 1,2 migration of a proton from C(8) to C(7) to give (h). Cleavage between the positive charge and the radical gives the ion (i). Alternatively, a proton can migrate directly from C(8) to the oxygen radical to again give ion (i).

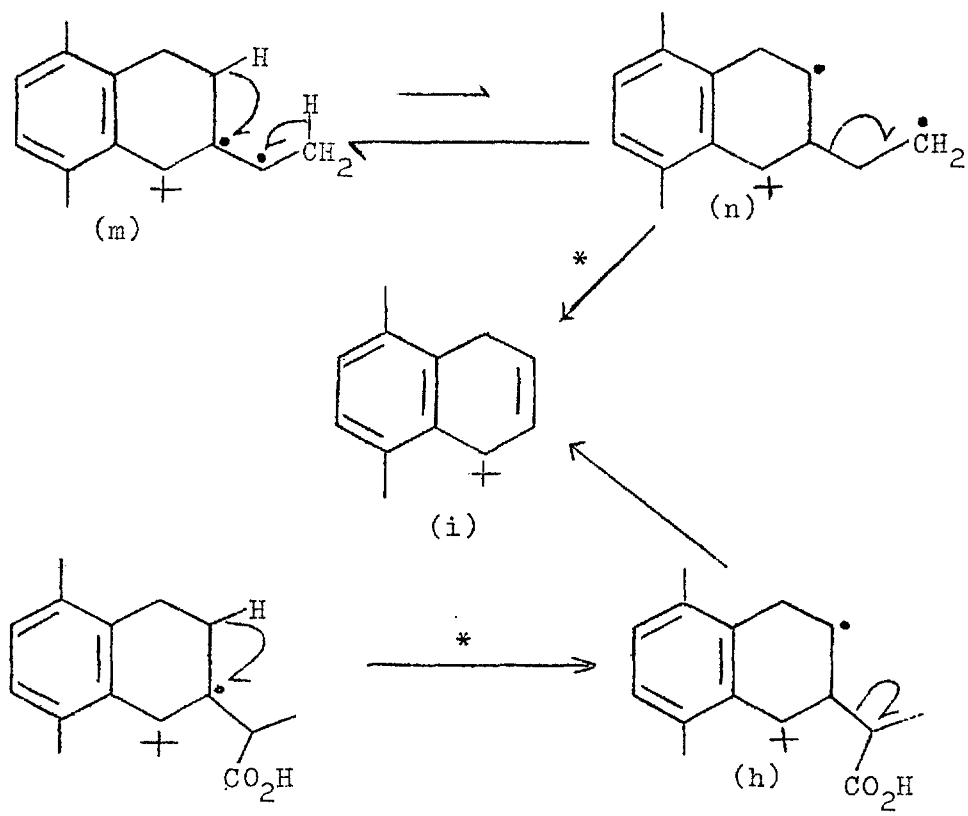


The small proton loss from C(6) is not accountable for. The possibility was considered that fission took place initially between C(7) and C(11) as we have noted in 1,2-dihydro-6-deoxy santonic acid (LXXVI) (spectrum 16) to give ion (j). Migration

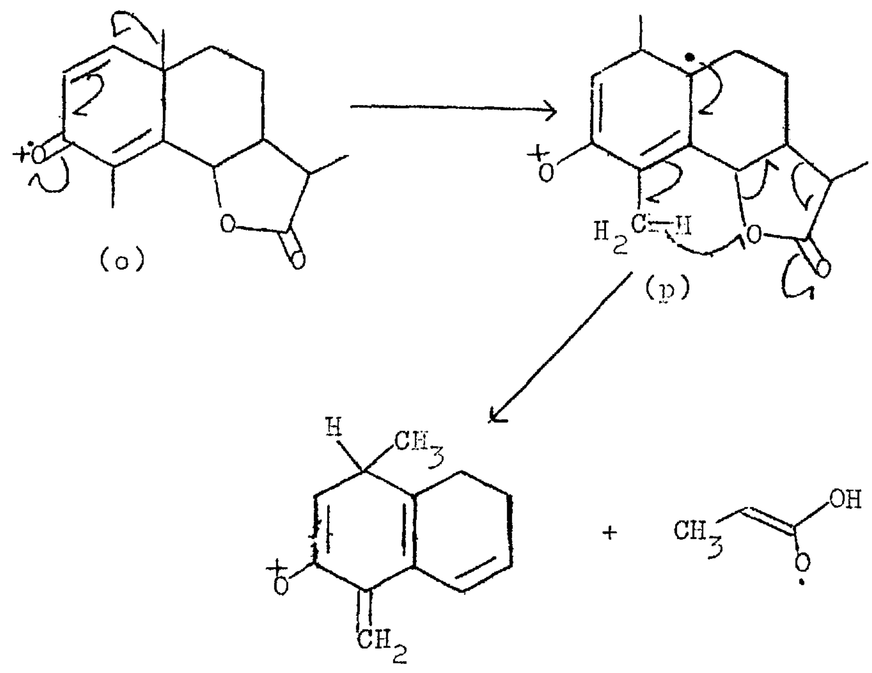


of the C(6)-proton either directly or via C(7) was considered. However, this produces an ionised enol propionate (1). 1-Tetralone enol acetate loses ketene and does not undergo alkyl oxygen fission, so such a mechanism is considered unlikely.

If in ion (g), the C(7)-proton migrates before the 1,2-shift from C(8) then an ionised form of a dihydrosantinic acid would be an intermediate. Dihydrosantinic acid showed a rather surprising fragmentation. The spectrum (17) contains two major fragment ions. The first, m/e 185, corresponds to the loss of a carboxyl radical. There is also an ion, m/e 157, with the appropriate metastable indicating the loss of ethylene from ion m/e 185. A third metastable shows that part of the ion m/e 185 is formed directly from the parent ion. The loss of a carboxyl radical gives ion (m). The further loss of ethylene must involve two apparently energetically unfavourable 1,2-proton migrations to give ion (n). These are energetically unfavourable because the π-electrons of a double bond are being separated. Even if the π-electrons are looked upon as constituting a diradical, the shifts convert tertiary and secondary radicals to secondary and primary radicals. However, the driving force may come from the production of a stable ion and the ethylene molecule. Also, if the C(6)-C(7) bond is breaking as the two protons migrate, then the energy barrier is probably not high. The direct loss of the side chain must involve a 1,2-proton migration from C(8) to C(7) to again give ion (i) <u>via</u> ion (h). This provides extra evidence for the proposed mechanism (g) $\rightarrow$ (i). However, as the losses of a carboxyl radical and ethylene are not noted in the lactone spectra, the 1,2-proton shift from C(8) to C(9) and the proton shift from C(7) to the oxygen radical must be concerted.

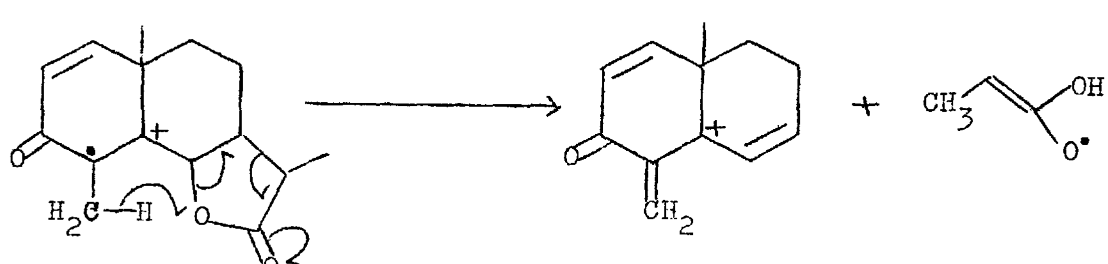


Only 50-60% of the 'extra' proton has been accounted for. At one time it was considered[103] that the 4-methyl group was a proton source. A proposed mechanism paralleling the dienone-phenol rearrangement was published, (o) $\longrightarrow$ (p) $\longrightarrow$ (q), for santonin.



(o) (p) (q)

It has been pointed out by Brown[104] and Djerassi that there was no need to propose a methyl migration and that the mechanism could simply be written as (r) ⟶ (s). This



(r) (s)

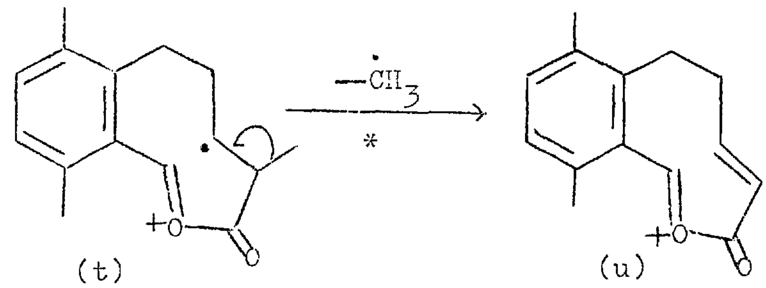
mechanism was considered by the author but rejected because 1,2-dihydrosantonin (spectrum 28) shows only an ion of small abundance at M-73 amounting to only 10% of the base peak. The mechanism proposed by Brown and Djerassi should not be greatly affected by removing the 1,2-double bond. However, the mechanism (o) ⟶ (q) can be criticised on the basis that the further loss of a methyl radical would be expected from ion (q) and this is not observed.

All the compounds cited so far in which the lactone fragmentation occur, contain a high degree of unsaturation in ring A. However, this is not a criterion for the fragmentation, which occurs, although to a lesser extent, in compounds in which ring A is not highly unsaturated and also where the C(6)-O bond does not occupy an allylic or benzylic position. For example, the ion m/e 81 (C_6H_9) in the spectrum (43) of trans-2-hydroxycyclohexyl acetic acid γ-lactone must arise by a similar fragmentation. However, in such compounds the loss of carbon dioxide becomes a major competing process.

Desmotropoartemisin (spectrum 18) also shows the lactone fragmentation with an ion, m/e 189 (M-73). The ion, m/e 171 is formed by the same fragmentation accompanied by the loss of water. Surprisingly, there is a metastable ion, m/e 111.6, indicating a one step process from the molecular ion.

All the aromatic lactones discussed so far have had the cis-fused lactone ring. However, two compounds containing the less chemically stable trans-fused lactone rings have been studied. These are hyposantonin (spectrum 19) and 6βH, 7αH-desmotroposantonin acetate (spectrum 20). The spectra of both differ markedly from those of their 6-epimers. The loss of a methyl radical is much more pronounced at the expense of the lactone fragmentation. This may be visualised as an initial cleavage between C(6) and C(7) to give the ion (t). Removal of the methyl group next to the radical site then gives the stabilised ion (u). The initial cleavage may be caused by increased strain in the C(6)-C(7) bond as a consequence of the trans-fused lactone ring.

The mechanism also requires delocalisation of the positive charge on the oxygen atom. The trans-fused lactone has only one possible conformation in which the C(6)-O bond lies almost in the plane of the benzene ring. This is evident from the nuclear magnetic resonance spectra of the cis and trans-fused lactones. The C(6) proton in the cis-fused lactones, which in one of the two possible conformations occupies the same position as the C(6)-O bond in the trans-compound, gives a signal τ 0.5 to lower field than the same proton in the trans-fused lactone. Therefore, in the trans-lactone the oxygen atom should be able to carry the positive charge, which can be stabilised by overlap with the π-electrons of the benzene ring.



The ion, m/e 159, observed in the spectrum of hyposantonin must correspond to the high energy loss of 71 mass units observed in the spectrum of santonin. This process is a very minor one in the spectrum of the 6βH, 7αH-desmotroposantonin acetate, probably because the prior elimination of ketene from the phenolic acetate removes some of the energy in the molecular ion. The lack of this fragmentation in isohyposantonin probably parallels the difference in the santonins, where the *cis*-fused lactones show less of this fragmentation.

Artemisin acetates and Desmotropoartemisin-8-acetates

The acetates of four stereoisomeric artemisins have been studied (spectra 21-24). The percentage of the total ion current carried by the molecular ion has been calculated. (see Table 2)

Table 2

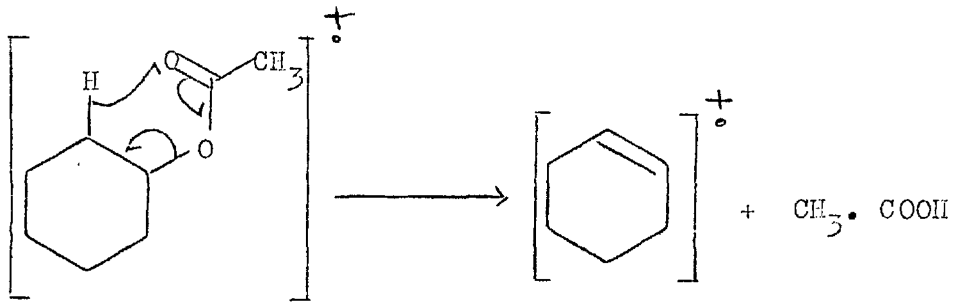
Compound	$\frac{M^+}{\sum_{29}^{306}}$ (percent)
Artemisin acetate	3.0
8-Epiartemisin acetate	5.75
6-Epiartemisin acetate	0.36
6-Epi-8-epiartemisin acetate	0.53

The molecular ions of the 6-epi-compounds are obviously less stable than the 6βH compounds. In all spectra the acetoxy ion, m/e 43, is the base peak.

All the compounds, except artemisin acetate, show loss of ketene from the molecular ion as well as the expected loss of acetic acid. This loss of ketene, to give the ion m/e 262, most probably occurs by a four-membered transition state to give the parent hydroxy ion. It is assumed that this then fragments to give most of the ions in the lower mass region. Artemisin, which only loses acetic acid, shows only medium intensity ions in the lower mass region. The ion, m/e 135, is again prominent in the spectra of the 6-epi-compounds. The ion, m/e 171, is formed by the lactone fragmentation and the loss of acetic acid. The loss of acetic acid should 'quench' the lactone fragmentation (see later, desmotropoartemisin diacetates) but it is possible that the ion m/e 171 arises from ion, m/e 242 in a similar way as for the artemisins.

The competing losses of acetic acid and ketene make the interpretation of spectra difficult but are in themselves interesting.

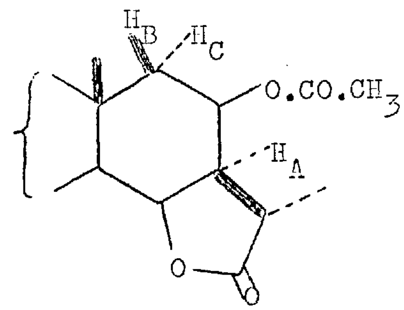
Loss of acetic acid is known[105] to occur by a 1,2 elimination.



The loss of ketene is therefore surprising as the acetates contain three protons α to the carbon atom bearing the acetoxy acetoxy group. Table 3 lists the internuclear distances (in Å), calculated from Dreiding models, between these protons and the acetate carbonyl group, the cyclohexane ring being in the chair form.

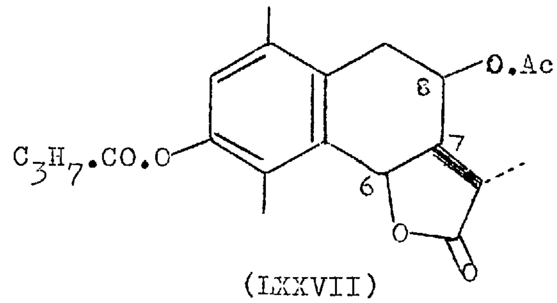
Table 3 (see p. 82 for diagram)

	H_A	H_B	H_C
Artemisin	1.6	1.2	1.2
6-Epiartemisin	1.1	1.25	1.5
8-Epiartemisin	Large	1.2	Large
6-Epi-8-epiartemisin	Large	1.6	Large



The approach of the acetate carbonyl group to proton H_A is probably hindered by the lactone ring. The angular methyl group is known[87] to sterically prevent S_N2 reactions at the 8-position of artemisin and thus it is expected that the mobility of the axial acetoxy group in the 8-epi-compounds is restricted and cannot abstract proton H_B easily. The reason why 6-epiartemisin acetate loses ketene is not clear. However, this compound contains two bulky axial groups (angular methyl group and the C(6) oxygen atom) and the introduction of a double bond in the 7-8 position may not be a favourable process. Artemisin acetate is the only isomer which contains only one large axial group.

The effect of the angular methyl group on the fragmentation of the acetate was further investigated by studying the mass spectra of the stereoisomeric desmotropoartemisin-8-acetates-3-butyrates (LXXVII) (see spectra 25 and 26) differing in configuration at positions 6 and 8. Only three of the possible four isomers could be isolated (see experimental section). These were 6βH, 7αH, 8α-OAC; 6βH, 7αH, 8β-OAC; 6αH, 7αH, 8β-OAC; (see p. 83 for diagram).



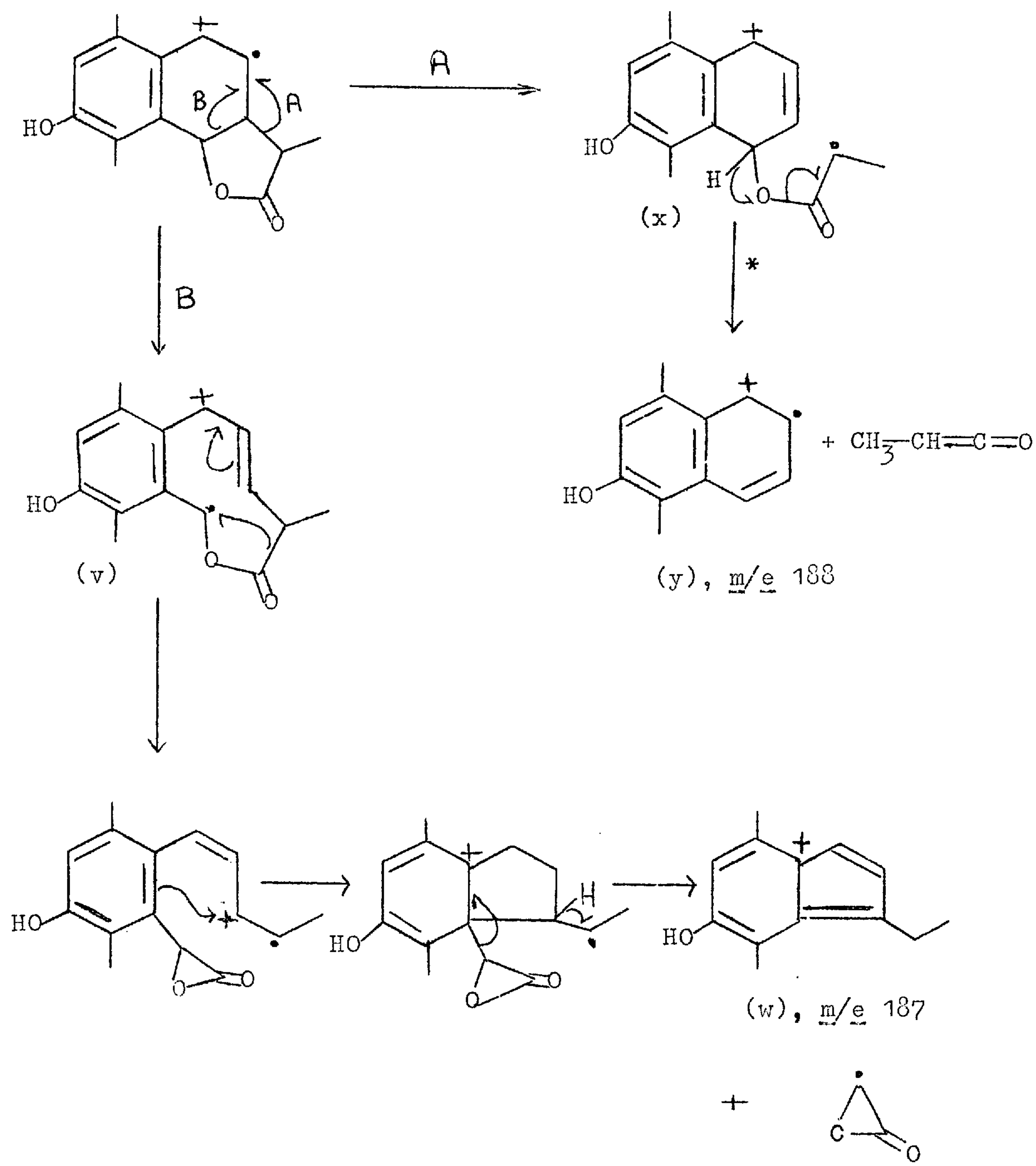
(LXXVII)

All of these compounds show the loss of 93 mass units (ethyl ketene) from the 3-position followed by acetic acid from the 8-position. Loss of ketene is not detectable, indicating that the methyl group is responsible for the ketene losses.

However, these compounds and the diacetates show a minor fragmentation which allows the fusion type of the lactone ring to be determined. After the loss of the two ester functions from positions 3 and 8 to give the ion, m/e 244, a further fragmentation occurs to give two ions, m/e 187 ($C_{13}H_{15}O$) and m/e 188 ($C_{12}H_{12}O_2$). These ions are of approximately equal intensity in the compounds with the trans-fused lactone but ion m/e 188, predominates in the cis-fused lactones (see Table 4).

In the spectrum of 6βH, 7αH-[11-$^2H_1$]-desmotropoartemisin -3, 8-diacetate, the ion, m/e 187, is shifted up one mass unit and under high resolution there is an equal intensity doublet at m/e 188. It is assumed that the elimination of the 8 -ester group gives mainly the ion with the 8-9 double bond (x).

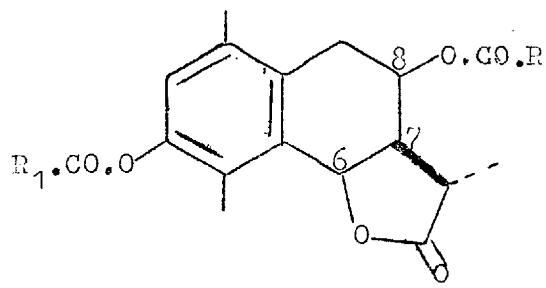
There are two favourable carbon-carbon bond cleavages which can occur. Cleavage between C(6) and C(7)(fragmentation B) gives the ion (v). Elimination of CHO_2, possibly as a 3 membered



ring lactone radical gives the ion m/e 187. The probable driving force for the mechanism is the stability of the ion (w) which is formed.

The C(6)-C(7) bond cleavage parallels that postulated for hyposantonin. However, the C(8) double bond is not present in hyposantonin and thus the ion analogous to (w) cannot be formed.

The alternative cleavage is between C(7) and C(11) (fragmentation A) to give ion (x). A proton shift from C(6) to the oxygen atom with concomitant elimination of methyl ketene gives the ion, m/e 188 (y). Obviously the *cis*-lactones prefer to cleave between C(7) and C(11) whereas the C(6)-C(7) bond cleavage becomes important in the *trans*-lactones.

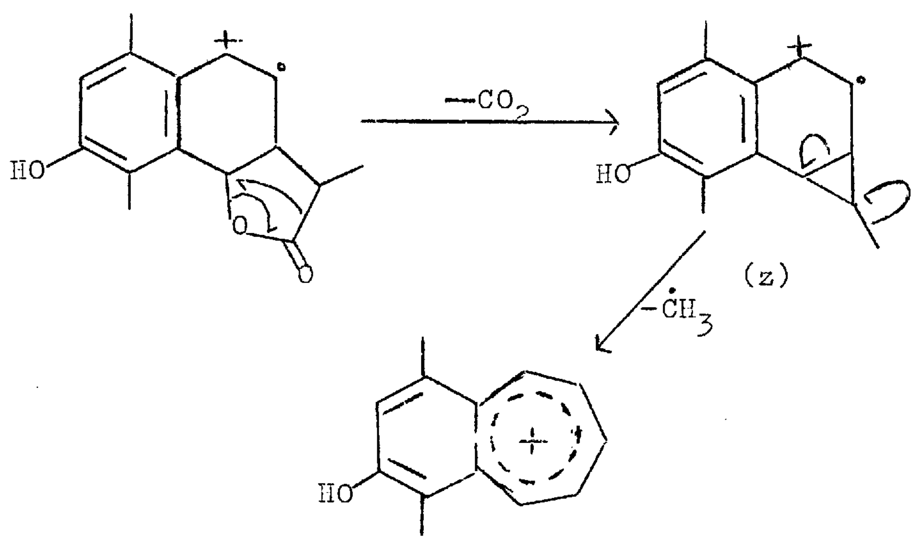


(LXXVIIa)

Table 4 (see p. 97 for diagram)

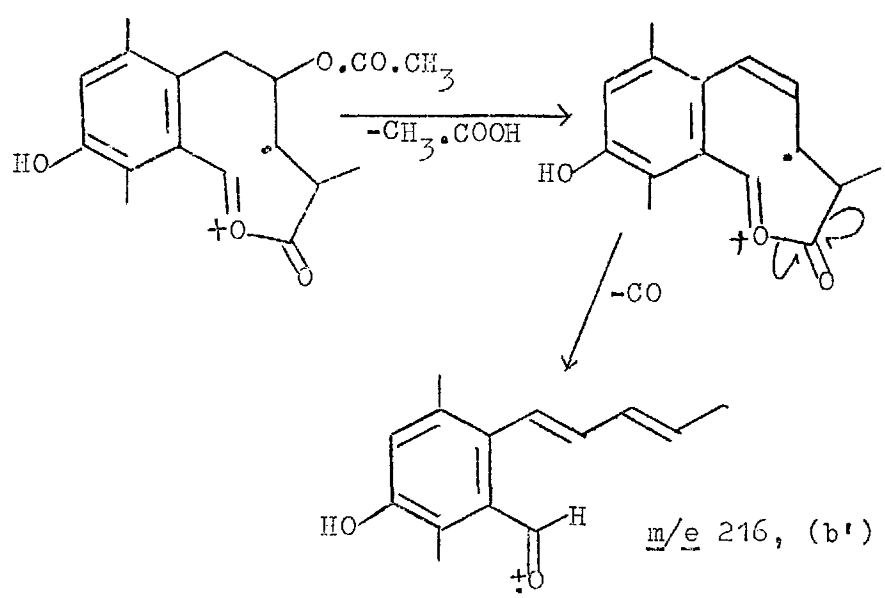
Compound (LXXVIIa)			Relative Abundance m/e 188 / Relative Abundance m/e 187
6βH,	8βH,	$R = R_1 = CH_3$	1.0
6αH,	8βH,	$R = R_1 = CH_3$	5.5
6βH,	8βH,	$R = CH_3$, $R = C_3H_7$	0.9
6βH,	8αH,	$R = R_1 = CH_3$	1.0
6αH,	8αH,	$R = R_1 = CH_3$	4.6
6βH,	8αH,	$R = CH_3$, $R_1 = C_3H_7$	1.1
6αH,	8αH,	$R = CH_3$, $R_1 = C_3H_7$	3.4

The ion, m/e 200 (2) corresponds to the loss of carbon dioxide from the ion, 244. The ion, m/e 185 corresponds to the further loss of a methyl radical to give what is probably a benztropylium ion (a').



(a')

There is an ion, m/e 216 prominent in the spectra of the two compounds having the 8-axial-acetoxy group and trans-lactone ring (see spectrum 25). This must be the loss of carbon monoxide from the ion, m/e 244. The reason for this is not obvious. The 8-axial-acetate should only be able to lose acetic acid to give the 9-10 double bond, the proton at C(7) being too far away. Therefore it is assumed that the loss of carbon monoxide is a consequence of a cleavage taking place before the acetic acid is lost. It is suggested that the presence of the 8-axial-acetate, together with the restriction in conformation caused by the trans-lactone ring, produces homolytic cleavage in the lactone ring. The acetic acid is then lost to give the 9-10 double bond followed by the loss of carbon monoxide to give ion (b').

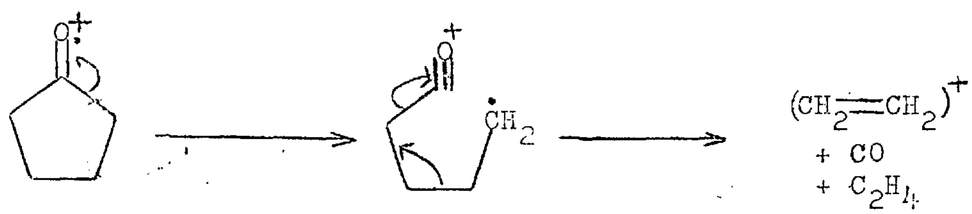


1,2-Dihydrosantonin and 1,2-Dihydrolumisantonin

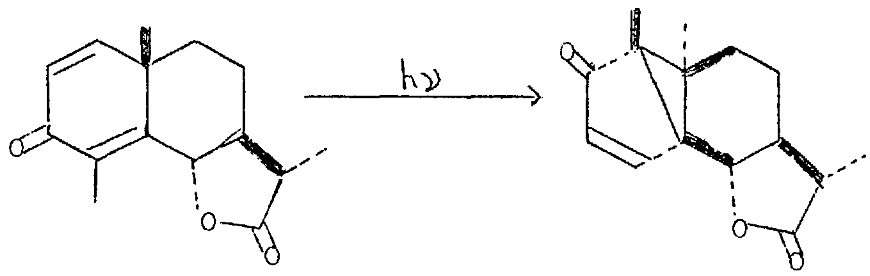
The spectrum (28) of 1,2-dihydro-α-santonin shows little of the lactone fragmentation, the ion, m/e 175, being of low intensity.

The major fragment ion, m/e 192 ($C_{12}H_{16}O_2$) formed by loss of C_3H_4O is shifted up one mass unit in the spectrum of [11-$^2H_1$]-1,2-dihydrosantonin but is unshifted in the [1,2-$^2H_2$]-compound. It thus corresponds to loss of C(1), C(2) and C(3). This is surprising in view of the studies on 3-ketosteroids[106] in which C(2) and C(3) are lost to give an M-42 ion.

The loss of C_2H_4CO is a characteristic fragmentation of compounds containing a cyclopentanone ring and occurs in estrone methyl ether[107] for example. It also occurs in the fragmentation of cyclopentanone[108] itself where the ion, m/e 28 is ethylene and not carbon monoxide.[109]



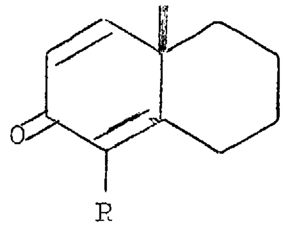
It is also known that one of the ultra-violet irradiation products of santonin is a compound known as lumisantonin (LXXVIII).[110,111,112,113]



(LXXVIII)

If under election impact 1,2-dihydrosantonin can undergo a similar rearrangement, then 1,2-dihydrolumisantonin would be formed, which contains a cyclopentanone ring. The spectrum (27) of dihydrolumisantonin showed the same cracking pattern as dihydrosantonin. The spectrum only differed in that the lower mass ions were more intense. This would be consistent with the prior rearrangement of 1,2-dihydrosantonin to the lumi-compound before fragmentation. The spectrum (29) of lumisantonin itself resembles that of santonin fairly closely except for a prominent M-29 ion. However, there is no evidence, apart from this, to indicate the conversion of one into the other prior to fragmentation.

An analogy for the apparent failure of Δ^4-3-ketosteroids to undergo rearrangement to the lumi-compound on electron impact, occurs in the field of photochemistry. The 1,4-dien-3-one (LXXIX, R=Me), on photolysis in dioxan[114] gives the lumi-compound

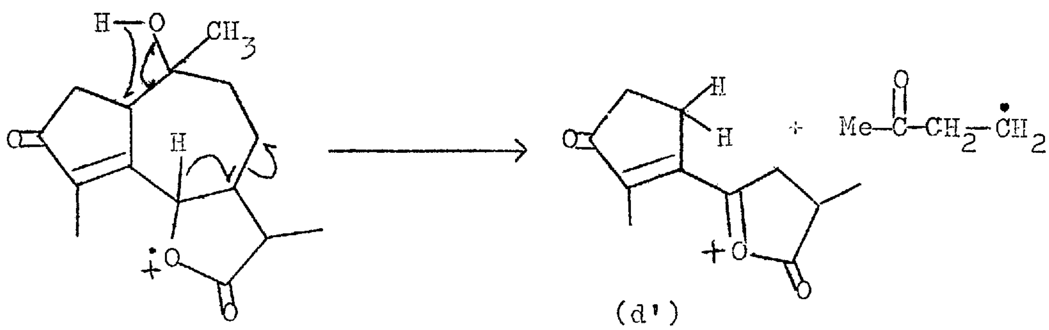


(LXXIX)

in 70% yield, whereas the compound (LXXIX, R=H)[115] under the same conditions yields a complex mixture, with no single product present in greater than 18% yield.

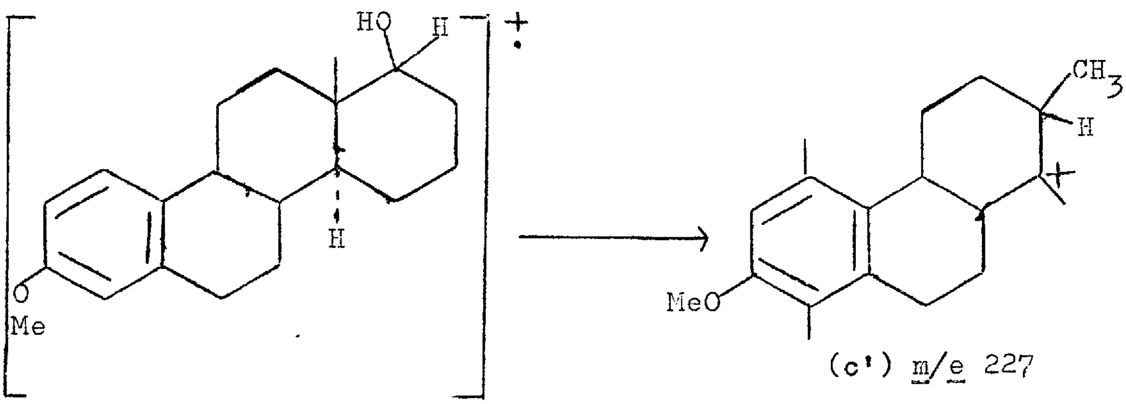
Isophotosantonic lactones

The mass spectra (30) of isophoto-α-santonic lactone and its 11-epimer are virtually identical. They show two major fragment ions, *m/e* 193 ($C_{11}H_{13}O_3$) and *m/e* 169 ($C_9H_{13}O_3$). There is a metastable ion for the formation of the ion, *m/e* 193 directly from the molecular ion. Both ions are shifted up one mass unit in the spectrum (31) of [11-$^2H_1$]-isophoto-α-santonic lactone but only the ion, *m/e* 193 is shifted in the spectrum (32) of [OD]-isophoto-α-santonic lactone. These observations require the migration of the hydroxylic proton in the formation of both ions.



(d')
m/e 193

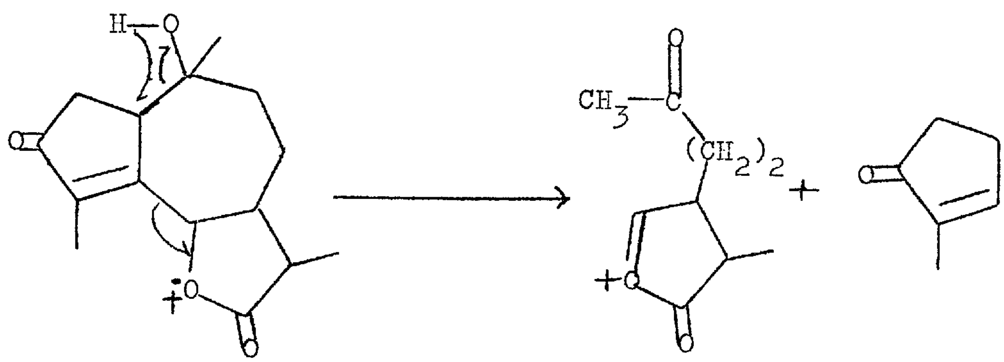
A similar migration has been observed[116] in 3-methoxy-17a-alkyl- $\Delta^{1,3,5(10),8}$-D-homoestratetraene-17α-ols(LXXX) in the formation of ion (c') m/e 227. This is shifted to m/e 228 in the OD compound. The formation of the ion (d') m/e 193 is probably an analogous process, (see above).



(LXXX)

(c') m/e 227

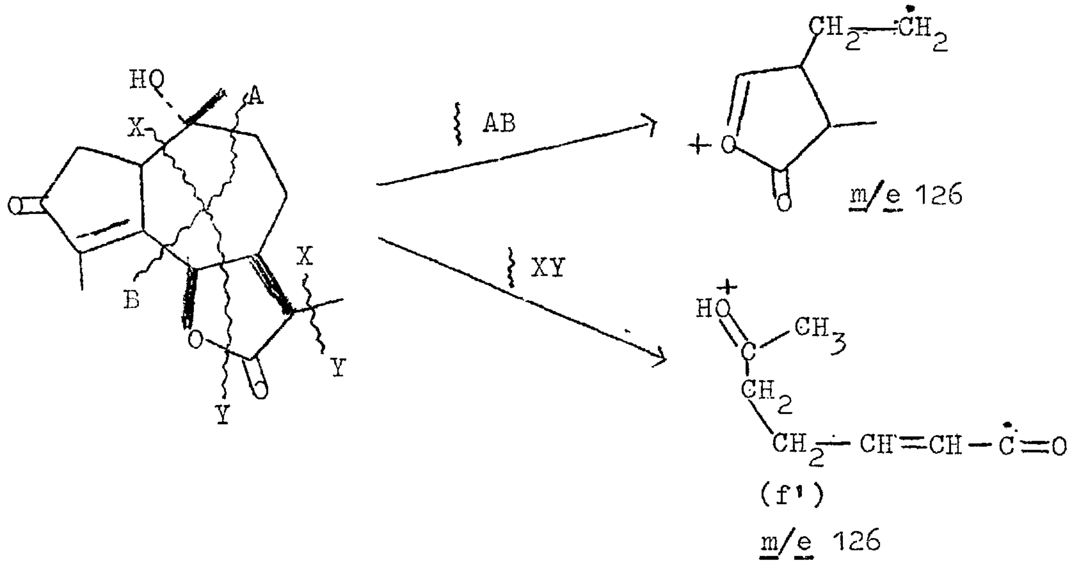
The formation of ion, m/e 169 necessitates a similar rearrangement involving a seemingly unfavourable cleavage on a double bond to give (e').



(e'), m/e 169

The fragmentation of 6-epi-isophoto-α-santonic lactone and its 11-epimer have been investigated. The two spectra (33) are virtually identical but are quite different from those of the trans-fused lactones. There is only one major fragment ion, m/e 126 ($C_7H_{10}O_2$), which is also the base peak.

There are two possible cleavages for the formation of the ion. Cleavage across AB (see diagram) or cleavage across XY with loss of the 11-methyl group. The cleavage XY would also account for the ion, m/e 123 which would correspond to the other fragment. The spectrum of $[O^2H_1]$-6-epi-isophoto



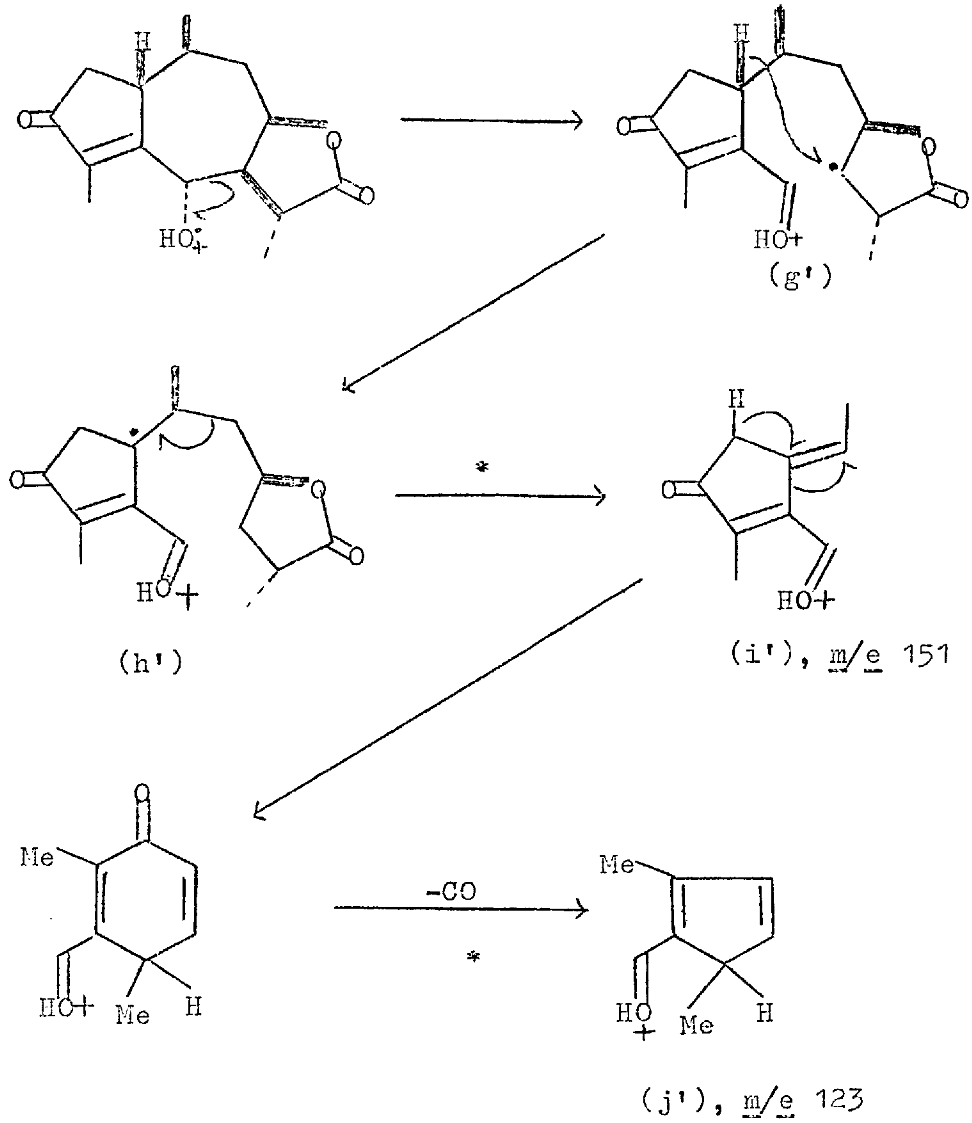
santonic lactone shows that the deuterium is retained in the ion, m/e 126 and thus it is cleavage XY which appears to be operating to give ion (f').

Geigerin and 6-Epigeigerin

The spectrum (34) of geigerin shows one major fragment ion, m/e 151 ($C_9H_{11}O_2$) which is formed directly from the molecular ion. The fragment ion is shifted up two mass units in the spectrum of $[2,2,11-{}^2H_3]$-geigerin. The formation of the ion can be rationalised by assuming that the positive charge is localised on the hydroxyl group. Subsequent cleavage of the C(6)-C(7) bond gives the ion (g'). Migration of the proton from C(1) to C(7) in a six-membered transition state gives the ion (h'), which by cleavage next to the radical site gives the highly stable ion (i') *m/e* 151. The ion, *m/e* 173 ($C_{12}H_{13}O$) is shifted to *m/e* 175 in the trideuterated compound and corresponds to the lactone fragmentation after the loss of water from the molecular ion. The appropriate metastable ions are present.

The ion, *m/e* 123 is formed by further loss of carbon dioxide from the ion (i') as evidenced by the appropriate metastable ion. This suggests that ion (i') may ring expand to give the ketone form of a phenol which then loses carbon dioxide to give ion (j').

The spectrum of 6-epigeigerin (35) differs from the geigerin spectrum in that the main fragmentation is the loss of water from the molecular ion to give the ion, *m/e* 246. This must be a consequence of the *pseudo*-axial configuration of the hydroxy group, assuming the seven-membered ring exists in the *pseudo*-chair form. This loss of water 'quenches' the main fragmentation which occurs in geigerin and the ion, *m/e* 151, is of low abundance. The difference in the spectra of geigerin and 6-epigeigerin seems to parallel the preferred cleavage in the *cis* and *trans*-lactones (e.g. hyposantonin and isohyposantonin). A *trans*-relationship of the C(6) and C(7) substituents favours cleavage of the C(6)-C(7) bond, whereas a *cis*-relationship favours elimination of the 6-oxygen function.

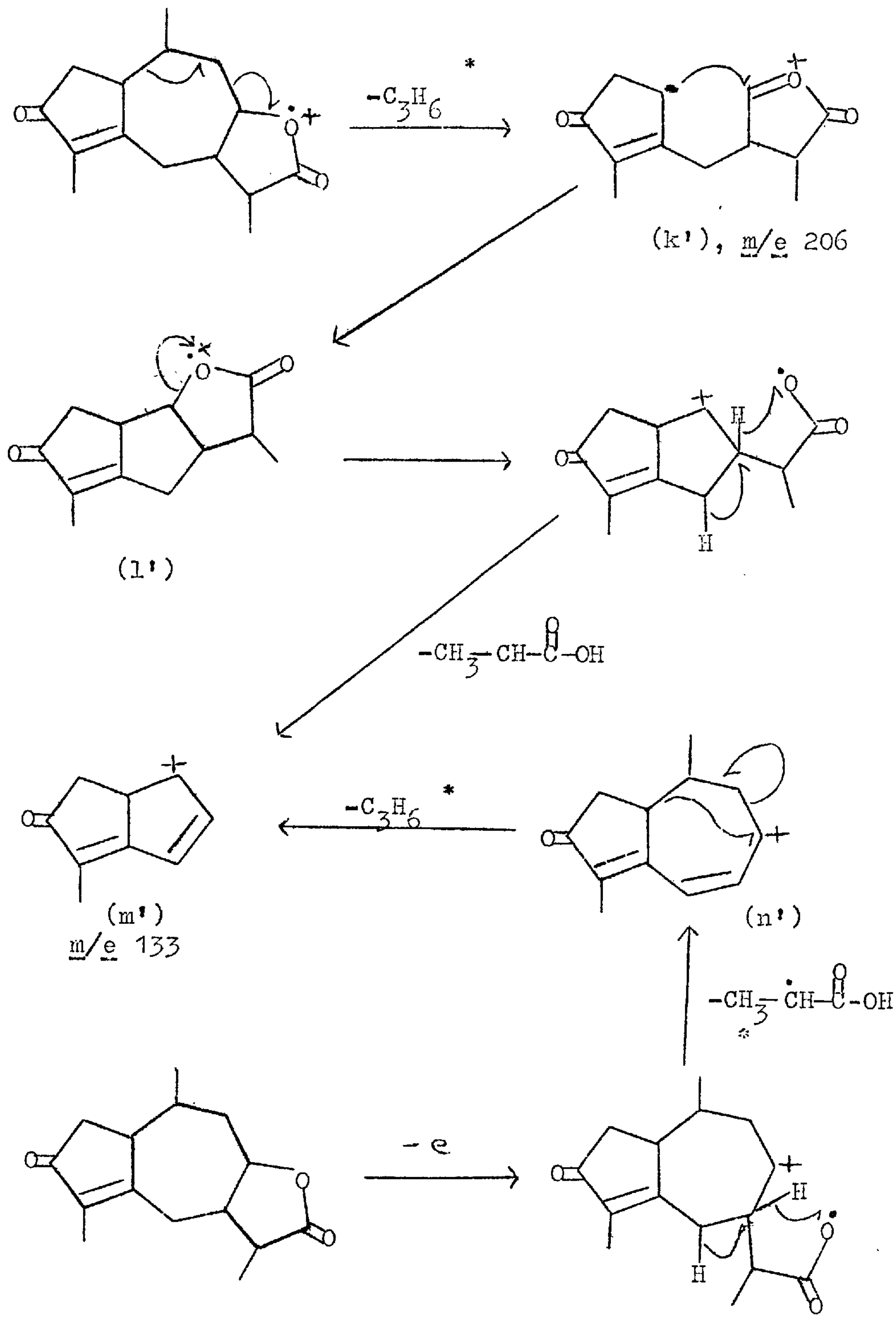


6-Deoxygeigerin

The effect of removing the 6-hydroxyl group from geigerin can be seen in the spectrum (36) of 6-deoxygeigerin. Three major fragment ions are present, m/e 206 ($C_{12}H_{14}O_3$, $M-C_3H_6$), m/e 175 ($C_{12}H_{15}O$, $M-C_3H_5O_2$), m/e 133 (C_9H_9O, $M-C_3H_6-C_3H_5O_2$). The two former ions come directly from the molecular ion, as evidenced from the appropriate metastable ions. Metastable ions also indicate that the ion, m/e 133 is formed from either of the other two. All the ions are unshifted in the spectrum of $[2,2\text{-}^2H_2]$ and $[2,2,6\text{-}^2H_3]$-deoxygeigerin. (spectrum 37) The ion, m/e 175 corresponds to the lactone fragmentation, whilst the loss of C_3H_6 must be from the seven-membered ring. The appropriate shifts in the deuterated compounds and the observation of two independent fragmentations, confines the source of the additional proton for the 'lactone' fragmentation in the formation of ion, m/e 133 to C(1), C(4)-methyl, C(6) and C(7).

Two routes must be considered for the formation of this ion. The initial elimination of propene to give the ion (k') is probably assisted by localisation of the positive charge on the lactone oxygen. It is suggested that ring closure occurs to give (l') which then loses the lactone ring in a similar way as has been suggested for santonin to give (m') as the ion, m/e 133.

If the lactone fragmentation takes place first with specific transfer of the C(7)-proton, ion (n') is formed. In those cases where the C(7) proton is not abstracted the resulting ion probably does not fragment further. Cleavage of the C(1)-C(10) bond in ion (n') followed by elimination of propene probably gives ion (m') again. It is noteworthy that

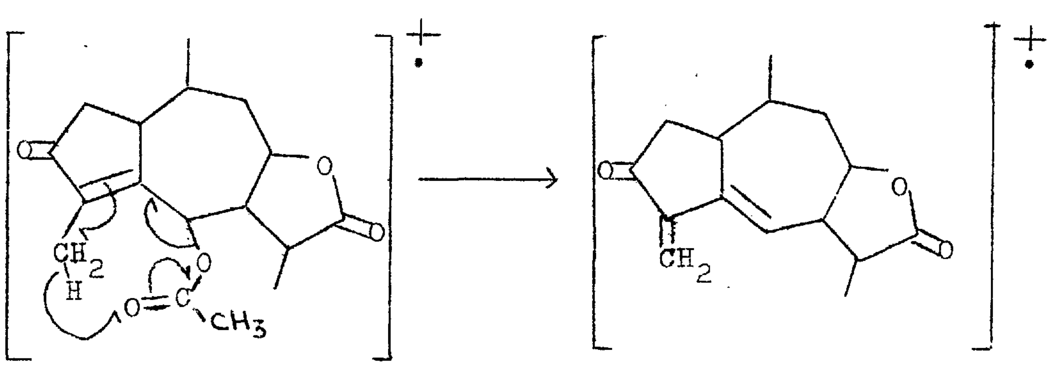


$-C_3H_6$ *
(k'), m/e 206
(l')
$-CH_3-CH-\overset{O}{\overset{\|}{C}}-OH$
$-C_3H_6$ *
(m')
m/e 133
(n')
$-CH_3-\dot{C}H-\overset{O}{\overset{\|}{C}}-OH$
- e

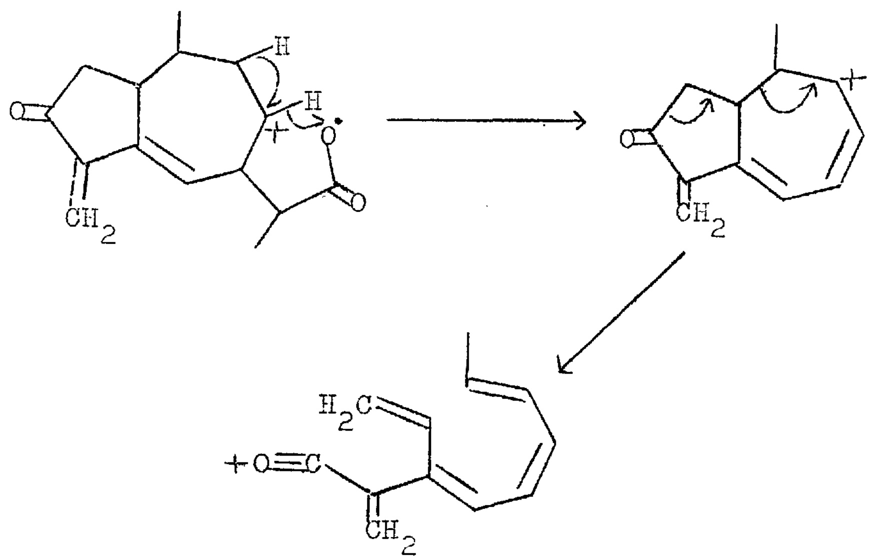
the lactone fragmentation with abstraction of two extra protons (m/e 174) and the loss of propene do not occur consecutively.

Geigerin acetate

Geigerin acetate shows several major ions in its mass spectrum (38). The acetoxy ion, m/e 43 is the base peak. The ions, m/e 246 ($C_{15}H_{18}O_3$) and m/e 264 ($C_{15}H_{20}O_4$) correspond to the loss of acetic acid and ketene respectively. The loss of acetic acid is surprising in view of the virtual absence of this process in 8-epialloartemisin acetate (spectrum 40) where the loss of ketene predominates. Obviously, the increased conformational mobility of the seven-membered ring is responsible for this. The two ions, m/e 173 ($C_{12}H_{13}O$) and m/e 191 ($C_{12}H_{15}O_2$) correspond to the lactone fragmentation operating on ions, m/e 246 and m/e 264 respectively. The 1,2-elimination of acetic acid should 'quench' the lactone fragmentation by introduction of a C(6)-C(7) double bond. However, there is a possibility that the loss of acetic acid may occur by an eight-membered transition state with abstraction of a proton from the C_4-methyl group.



If this is so then the lactone fragmentation can be rationalised with the formation of the highly stabilised ion (o').



(o')

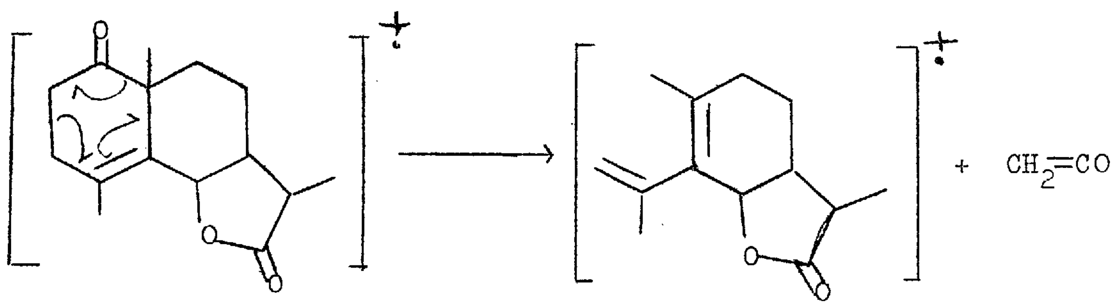
The loss of C_3H_6 also occurs from the ion, m/e 246 to give m/e 204. This is analogous to the loss occurring in deoxygeigerin. However, there is no ion corresponding to the loss of C_3H_6 and the lactone fragmentation consecutively. The ion, m/e 151 must be formed from the ion, m/e 264 via the same mechanism as for geigerin. It is interesting to compare the mass spectra of geigerin acetate and its isomer, dihydroanhydro-8-epi-isophotoartemisin acetate (spectrum 39). The configuration in both compounds is identical except for C(1). The latter compound shows very little fragmentation compared with geigerin acetate. The loss of ketene to give the ion, m/e 262 is a little surprising but the 10-methyl group may cause some steric hindrance.

The ion, m/e 218 ($C_{14}H_{18}O_2$) must be formed from the ion, m/e 246 but the source of this carbon monoxide is unknown.

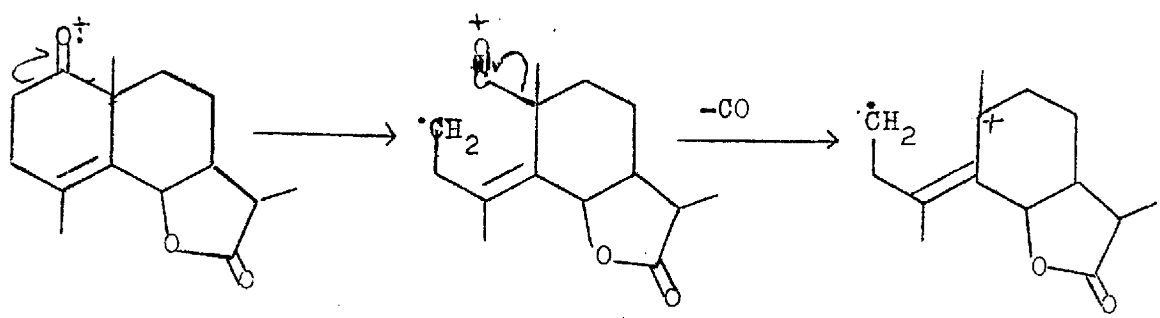
The ion, m/e 190 was thought to correspond to the loss of methyl ketene from the lactone ring after the loss of acetic acid. This would be analogous to the fragmentation operating in the desmotropoartemisin diesters after the loss of the 8-ester group (see p 84). High resolution shows the ion, m/e 190 to be a doublet. Accurate mass measurement shows it to consist of 60% $C_{12}H_{14}O_2$, the expected formula for the above fragmentation, and 40% $C_{13}H_{18}O$. The alternative cleavage involving the loss of the C_2HO_2 moiety as observed in the spectra of the desmotropoartemisin diesters, is not expected to occur, as the same highly stabilised ion cannot be formed.

ψ-Santonin and 8-Deoxy-ψ-Santonin (Spectra 41 and 42)

ψ-Santonin and the 8-deoxy compound undergo the retro-Diels-Alder fragmentation to give the ions, m/e 222 and 206 respectively.



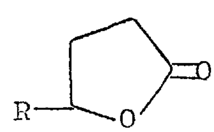
In deoxy-ψ-santonin a methyl group is then lost to give the ion, m/e 191. The 'lactone' fragmentation also occurs to form the ion, m/e 133. The ion, m/e 220 corresponds to the loss of carbon monoxide from the molecular ion. Carbon monoxide is almost certainly lost, together with a methyl group in the formation of the ion, m/e 205 although no mass measurement has been made. This fragmentation bears resemblance to the loss of carbon monoxide occurring in the 6-episantonins. However, in ψ-santonin the fragmentation probably occurs by cleavage on the least favourable side of the carbonyl group followed by expulsion of carbon monoxide.



ψ-Santonin itself shows a modification of the lactone fragmentation. The appropriate metastable ion shows the loss of 73 mass units from the ion, m/e 222 to give the ion, m/e 149 ($C_{10}H_{13}O$). A second metastable ion indicates the further loss of a proton to give the ion, m/e 148 ($C_{10}H_{12}O$). This process is not observed in the artemisins where water is lost more easily and an (M-18-73) ion is seen. It is suggested that the hydroxylic proton is lost. Deuterium labelling is still necessary in this instance.

Trans-2-hydroxycyclohexylacetic acid- γ-lactone and a tetrahydrodeoxysantonin

The observation of the 'lactone' fragmentation in the sesquiterpene lactones made it necessary to investigate a simple γ-lactone. Some monocyclic-lactones have been studied by McFadden and Day[133] (see structure LXXXI). They found that when R was H, Me or Et the loss of carbon dioxide predominated. When R was larger than Et the loss of the group R was the main fragmentation.



(LXXXI)

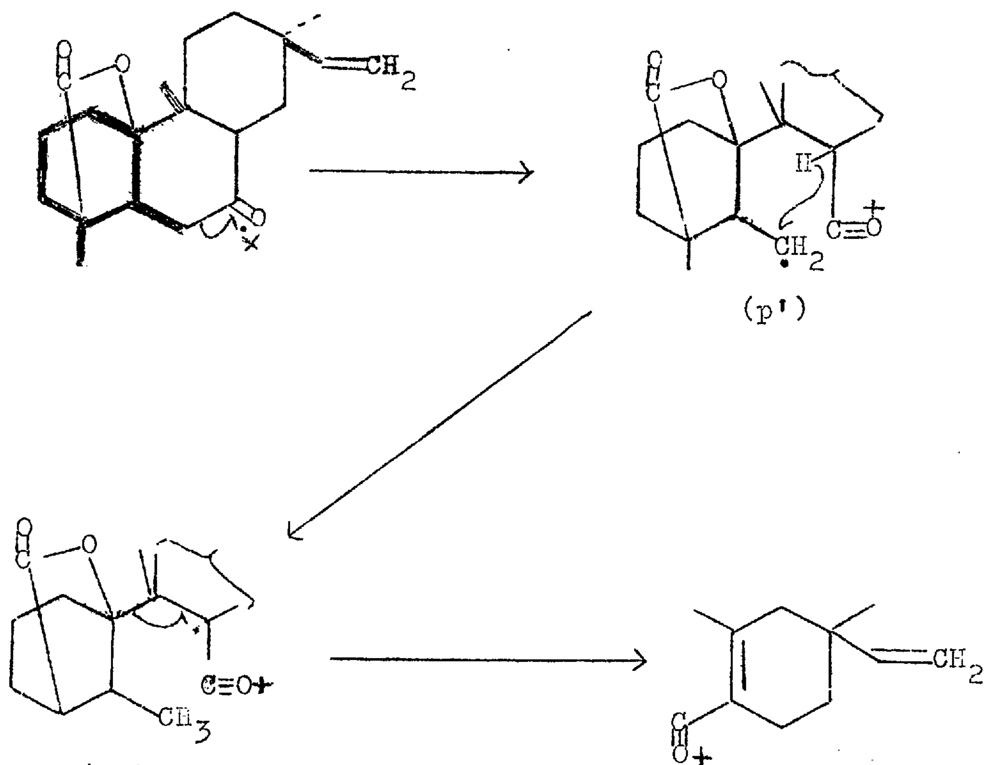
Trans-2-hydroxycyclohexylacetic acid- γ-lactone was made in which the γ-lactone was fused to a cyclohexane ring. The base peak in the spectrum (43) is the hydrocarbon ion, *m/e* 67 (C_5H_7) but how this arises is unknown. The molecular ion is of low abundance and the M-1 ion is slightly larger.

The 'lactone' fragmentation does occur to some extent to give the ion, m/e 81 (C_6H_9) but the loss of carbon dioxide to give the ion, m/e 96 (C_7H_{12}) is a competing process. The ion, m/e 79 has the formula C_6H_7. The competing loss of carbon dioxide in the absence of unsaturation can be seen in the spectrum (44) of a deoxytetrahydrosantonin of unknown stereochemistry obtained from pyrethrosin. The occurrence of the 'lactone' fragmentation gives the ion, m/e 163. However, the major fragmentation is the loss of carbon dioxide and a methyl group and the formation of ion, m/e 177.

Rosenonolactone

The mass spectrum (45) of the diterpene lactone rosenonolactone has been investigated. The results are at variance with those obtained by Reid[117] in that the two major fragment ions, m/e 108 and m/e 163 both occur two mass units lower than quoted in the reference. This requires a different interpretation of the spectrum to that given by Reid. High resolution work shows the ion, m/e 163 to have the formula, $C_{11}H_{15}O$. There is an ion, m/e 165 in the spectrum (46) of dihydrorosenonolactone and the fragmentation is thus thought to be analogous to that occurring in cyclohexanone. Localisation of the positive charge on the carbonyl oxygen followed by α cleavage gives the ion (p'). Migration of a proton in a six-membered transition state gives the ion (q') which cleaves next to the radical site to produce the ion, m/e 163 (r').

The ion, m/e 108 (C_8H_{12}), occurring in the spectra of both rosenonolactone and dihydrorosenonolactone is thought to come from that part of the molecule shown by heavy lines, but no suitable structure can be suggested for it.



(p')

(q')

(r'), m/e 163

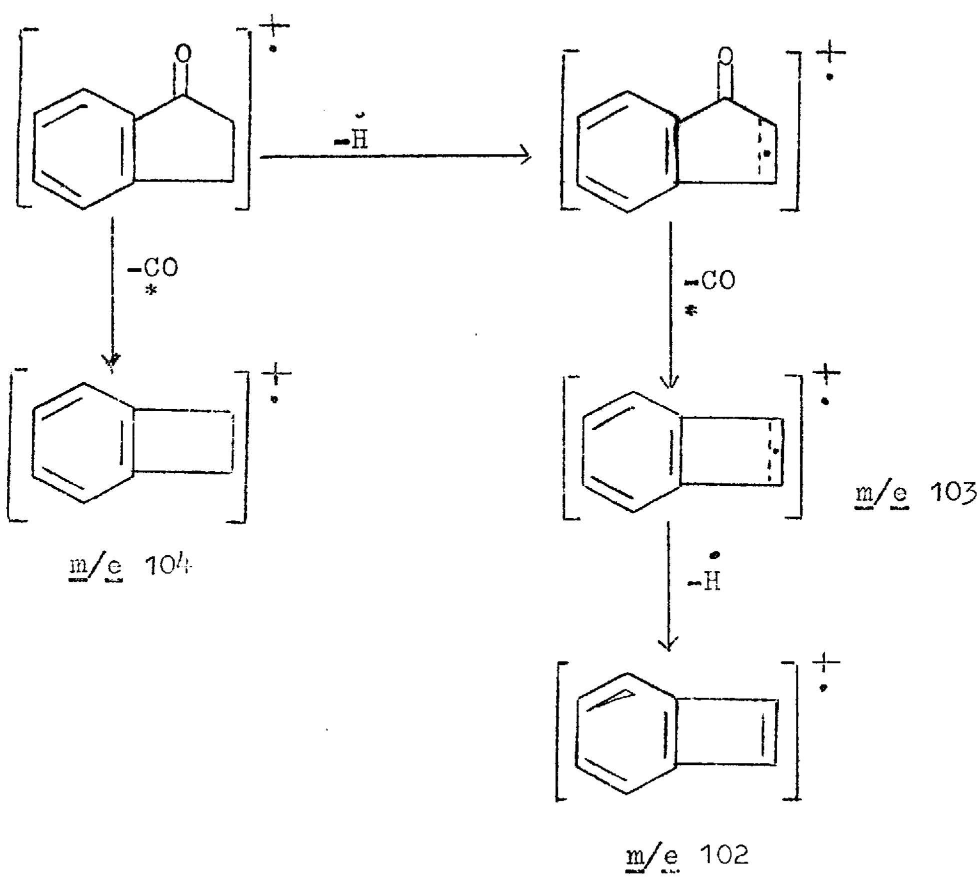
It can be seen from the spectrum of dihydrorosenonolactone that the ethyl group is lost in preference to methyl to give the ion, m/e 289.

DISCUSSION OF MASS SPECTRA

(PART II)

1-Indanone

1-Indanone (spectrum 47) has been studied by Bowie[118] who reported that the indenone ion is formed by loss of two protons from the molecular ion. The author has found no evidence for an M-2 ion. There is an M-1 ion, and carbon monoxide is lost from this and the molecular ion (as evidenced from metastable ions) to give ions, m/e 104 and m/e 103. A further proton is lost from the ion, m/e 103 to give what may be the ion (a) proposed by Bowie. Acetylene is also lost from ions, m/e 104 and 103 to give ions, m/e 78 and 77.



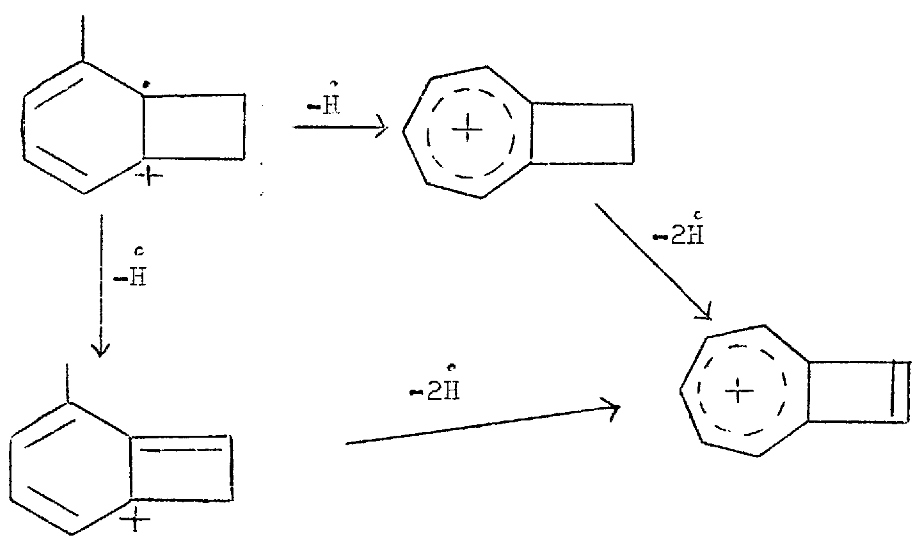
An attempt was made to determine the position from which the first proton was lost. The spectrum of [2,2-$^{2}H_{2}$]-1-indanone was of no use as undeuterated and monodeuterated molecular ions confused the spectrum. However, [3-$^{2}H_{1}$]-1-indanone, containing only about 4% dideuterated species was made. From the spectrum (48) of this compound it was calculated that 26% of the proton in question comes from the 3-position, assuming that no isotope effect occurs. Although this figure is not accurate it indicates that the proton does not come from a specific site. Even in the monodeuterated compound, the M-2 ion was not as abundant as in Bowie's spectrum of 1-indanone.

2-Ethyl-1-indanone

2-Ethyl-1-indanone (spectrum 49) is able to undergo the McLafferty[119] rearrangement to give the ion, m/e 132. The ion, m/e 131 is presumably formed by the direct loss of an ethyl group rather than the further loss of a proton. The lower mass ions are of small abundance but there is a metastable ion for the formation of ion, m/e 103 from m/e 131. This is analogous to the loss of carbon monoxide occurring from the M-1 ion in 1-indanone.

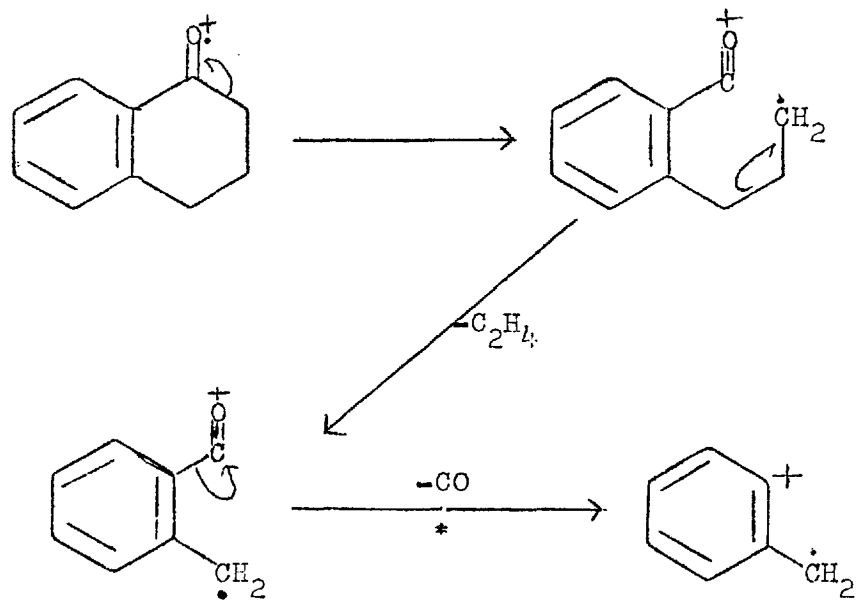
4,5,6 and 7-Monomethyl-1-indanones

The mass spectra (50) of these four compounds are virtually identical. They show the initial loss of a proton to give an M-1 ion as for 1-indanone. This ion and the molecular ion both lose carbon monoxide to give the ions, m/e 118 and m/e 117. There is then a metastable ion at m/e 113 for the formation of the ion, m/e 115 by the simultaneous loss of two protons from the ion, m/e 117. Although it is obvious which three protons are lost overall, it is not apparent which two are involved in the simultaneous loss. The two possibilities are shown:

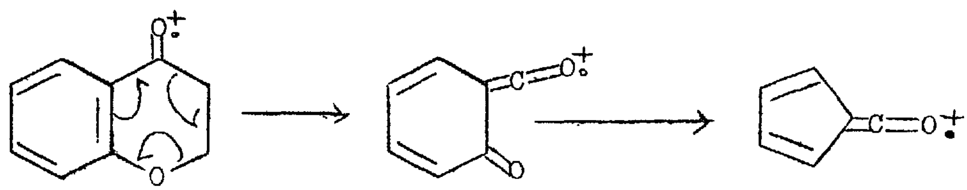


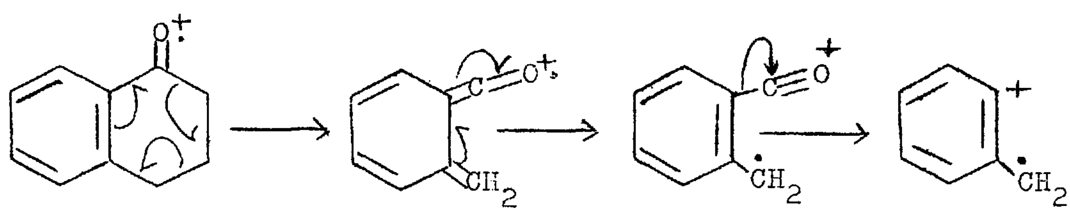
1-Tetralone

Deuterium labelling of all the aliphatic positions of 1-tetralone (spectra 51-54) conclusively proves the main fragmentation proposed by Bowie[118] which involves positive charge localisation on the carbonyl oxygen followed by α-cleavage.



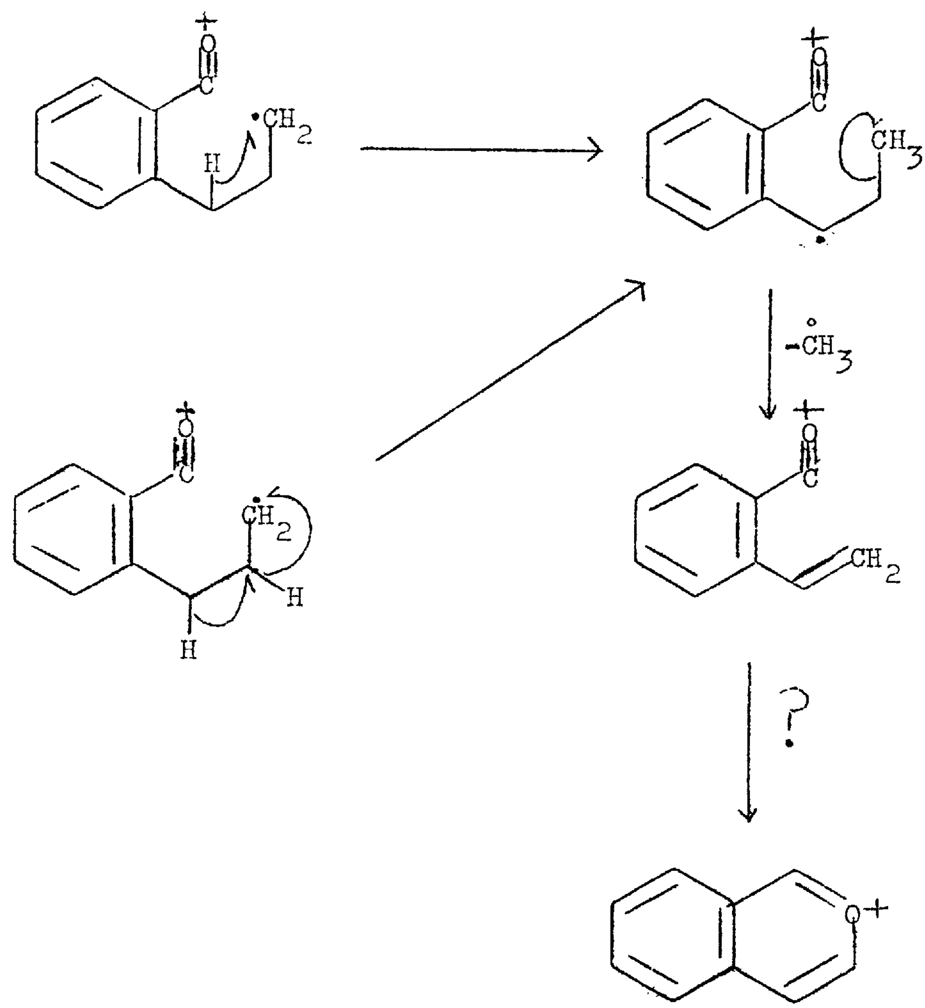
There is no proton at the angular 9-position which can migrate as is noted in 1-decalone,[120] and so cleavage occurs next to the benzylic position with loss of ethylene to give the ion, m/e 118. This is followed by loss of carbon monoxide to give the ion, m/e 90 (metastable ion). This is analogous to the loss of carbon monoxide from acetophenones[121] after the loss of a methyl radical. Alternatively, the fragmentation may be considered to occur by a *retro*-Diels-Alder mechanism as is proposed for chroman-4-one.[122] The latter compound also loses ethylene followed by carbon monoxide which is proposed does not come from the original carbonyl group. ^{18}O labelling would certainly be useful in determining the source of the carbon monoxide in this case.





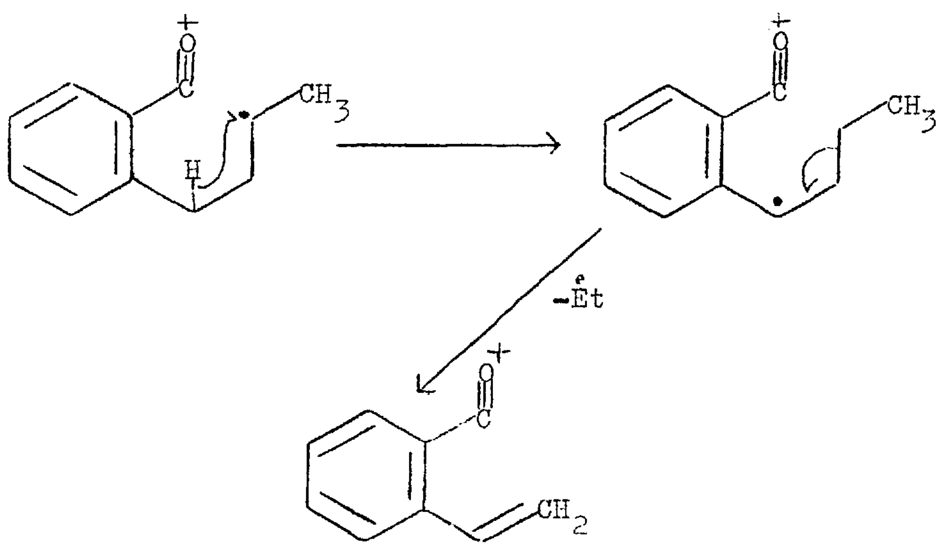
Bowie's spectrum (run on an M.S.9 instrument) showed the molecular ion was the most abundant whereas in the author's spectrum the ion, *m/e* 118 was the most abundant ion. This was so for the deuterated compounds also, which were all run on different days. The difference must be an instrumental one, since the inlet temperatures were the same in both cases.

1-Tetralone also shows the loss of a methyl radical to give an ion, m/e 131. Bowie concluded from the spectrum of $[2,2\text{-}^{2}H_{2}]$-1-tetralone that this loss was random. The results now obtained from the three deuterated tetralones indicate that the process is specific in that the two protons at C(2) are lost in the process and that the third proton comes 59% from the C(4) and 41% from C(3). Therefore two mechanisms are operating in this process. The first of these must involve transfer of a proton from C(4) to C(2) in a four-membered transition state.



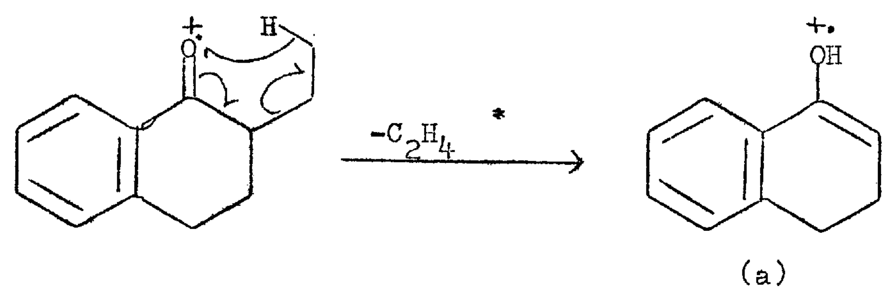
The second mechanism probably involves two successive 1,2-shifts. Both of these are energetically favourable because the two shifts convert a primary to a secondary and then to a benzylic radical. The ion formed probably rearranges to the benzpyrilium ion, which would account for lack of further loss of carbon monoxide.

The spectrum (55) of 2-methyl-1-tetralone closely parallels that of 1-tetralone. The two main fragment ions are again m/e 118 and m/e 90, the fragmentation being the same as for 1-tetralone. Besides the expected loss of a methyl radical there is an ion corresponding to the loss of an ethyl radical. This fragmentation is probably similar to the loss of the methyl radical from 1-tetralone.



2-Ethyl-1-tetralone

2-Ethyl-1-tetralone (spectrum 56*) differs from the 2-methyl compound in that it can undergo the McLafferty rearrangement.

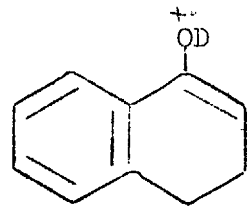


The base peak ion, m/e 146 corresponds to this fragmentation (metastable ion, 122.5). A peak at m/e 145 indicates the loss of the ethyl group also. The spectrum of 2-(2′-$^{2}H_3$-ethyl)-**1-tetralone.** indicates the loss of two deuterium atoms in the former process and three in the latter. The 'tetralone' fragmentation also occurs to give ions, m/e 118 and m/e 90.

All three deuterium atoms are lost in the formation of m/e 118.

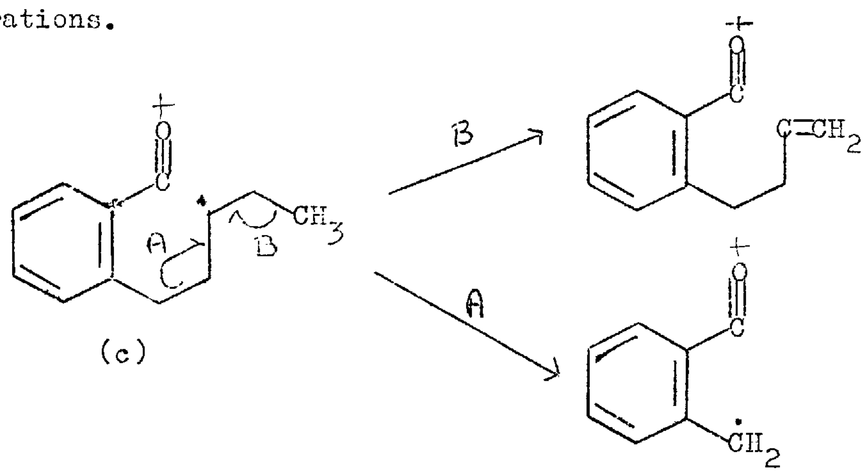
The proposed mechanism for the McLafferty rearrangement gives the ion (a) which is the same as is postulated to arise from 1-tetralone enol acetate (see later). If this is so, the CD_3 compound should give ion (b).

* The spectrum shown is that of the deuterated compound.



(b)

There is an ion, m/e 131 in the spectrum of 2-ethyl-1-tetralone and metastable ion, m/e 117.6 for the loss of a methyl radical from ion, m/e 146. High resolution measurements shows the ion, m/e 131 to consist of 80% C_9H_7O and 20% $C_{10}H_{11}$. The former thus corresponds to $(M-C_2H_4-CH_3)$ and the latter to $(M-CO-CH_3)$. In the spectrum of the CD_3 compound, this ion becomes 50% m/e 131 and 50% m/e 132. It is expected that 20% of the ion, m/e 131 is $(M- CO-CD_3)$. Thus 30% will be $(M-C_2D_2-CH_2D)$. The ion, m/e 132 should be $(M-C_2D_2-CH_3)$ and there is the appropriate metastable ion shift for this latter process. There is the possibility that ion, m/e 131 is partly formed by loss of a propyl group in the same way as the ethyl group is lost from 2-methyl-1-tetralone. However, the intermediate ion (c) would be expected to lose a methyl group or propene rather than undergo proton migrations.



(c)

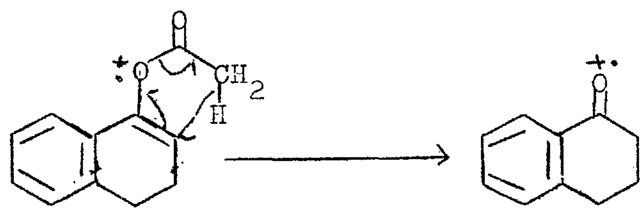
Enol acetates of some benzcycloalkanones

The mass spectrum (57) of 1-tetralone enol acetate was studied because it was thought that an enol ester ion might be an intermediate in the lactone fragmentation occurring in certain sesquiterpene lactones (see p. 74). The spectrum shows the expected loss of ketene from the molecular ion, to give the ion, m/e 146. However, there is a prominent ion, m/e 131 corresponding to the further loss of a methyl radical as evidenced by the appropriate metastable ion. The loss of a methyl group from an ion which does not apparently contain a methyl substituent is obviously of interest. Such fragmentations occurring in unknown compounds could obviously lead to incorrect assignments of structure.

The effect of the alkane ring on this fragmentation has been investigated. The fragmentation does not occur in 1-indanone enol acetate (spectrum 58) but occurs in benzsuberone enol acetate (spectrum 59) to give the ion, m/e 145. Benzcyclo-octanone enol acetate (spectrum 61) loses an ethyl group (determined by mass measurement) after the loss of ketene to give an ion, m/e 145. The mass spectrum (60) of 2-tetralone enol acetate shows no loss of the methyl group indicating that the position of the acetoxy group is also important.

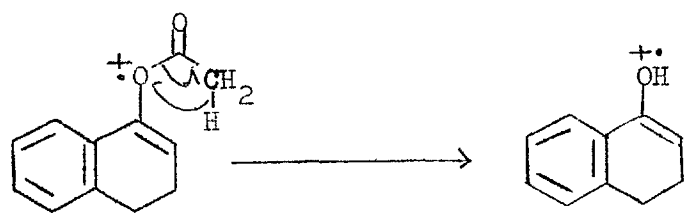
Before the mechanism for the loss of the methyl group can be discussed, it is necessary to comment on the structure of the ion formed by loss of ketene from the molecular ion. Two possible mechanisms for the loss of ketene can be considered. These are the mechanism A, involving a six-membered transition state to give the ketone ion (d) and the mechanism B, whereby a four-membered transition state gives the enol ion (e). The same two mechanisms can be considered for the loss of ketene from phenolic acetates where there is the choice of proton migration to either the aromatic ring or the ester oxygen.

A



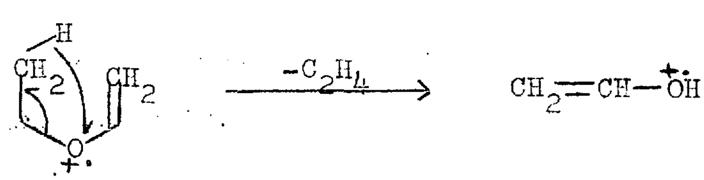
(d)

B



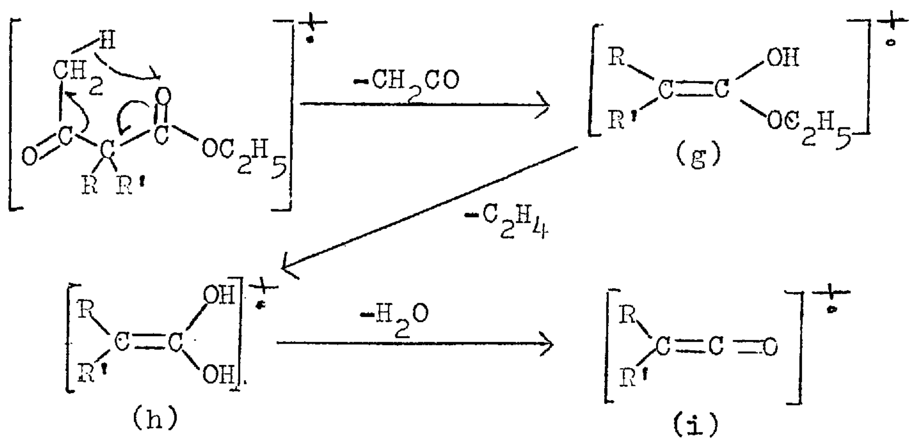
(e)

McLafferty[123] in his discussion of the mass spectra of vinyl ethers proposed a six- rather than the four-membered transition state for the loss of the olefine moiety. However, appearance potential data[124] suggest that a hydrogen atom is transfered to the oxygen atom to yield the vinyl alcohol. This is supported[124] by the observation that dipropenyl ether (f) which should not undergo McLafferty rearrangement, shows an abundant ion of m/e 58.



$$\underset{(f)}{(CH_3CH{=}CH)_2O} \xrightarrow{-e} \underset{m/e\ 58}{CH_3CH{=}CH\overset{\bullet+}{O}H}$$

The fragmentation of β-keto esters provides evidence for a four- membered transition state. It is proposed[125] that β-keto esters lose ketene via a McLafferty rearrangement to give the ion (g). This ion then loses ethylene to give the ion assigned the structure (h), because it loses a molecule of water to give ion (i). This demands that the loss of ethylene from ion (g) occurs by a four-membered transition state. A six-membered transition state would produce an acid which would not be expected to lose water.



If mechanism A occurs in 1-tetralone enol acetate, then the 1-tetralone ion should be formed. The mass spectrum of the enol acetate shows none of the major fragment ions occurring in the spectrum of 1-tetralone and thus it is assumed that the enol ion is formed via mechanism B. Deuterium labelling of 1-tetralone and its enol acetate show that the mechanism for the loss of a methyl group is different in the two compounds.

The spectra of the deuterated enol acetates of 1-tetralone and benzsuberone (see discussion of practical section) were obtained to elucidate the mechanism for the methyl loss. The following procedure was adopted to calculate the percentages of deuterated species in the $M-CO.CH_2-CH_3$ ion (hereafter called ion A).

1. The regions of the spectra containing the molecular ion and the ion A were scanned ten times and the peak heights thus averaged.

2. The undeuterated peak of ion A was scanned several times under high resolution. The contribution from a deuterated hydrocarbon ion could thus be subtracted to give a corrected height for the peak.

3. The peak heights were then corrected for ^{13}C isotope contributions[126] and the percentages (d_0, d_1, d_2 etc.) for the various deuterated species calculated.

However the molecular ions do not contain 100% dideuterated or tetradeuterated species. A correction therefore had to be made to find the percentages of deuterated species which would be observed for ion A if the molecular ion did contain 100% dideuterated or tetradeuterated species. The assumption was made that the trideuterated species in [2-$^{2}H_1$]-1-tetralone enol-[$^{2}H_3$]-acetate and [2-$^{2}H_1$]-benzsuberone enol-[$^{2}H_3$]-acetate is caused by incomplete deuteration at the 2-position(vinylic proton). The percentages of trideuterated and tetradeuterated species in the molecular ion are then the same as the monodeuterated and dideuterated species in the M-CO.CH_2 ion. The theory for the correction is then as follows:

a_o, a_1 and a_2 are the percentages of undeuterated, monodeuterated and dideuterated species in the molecular ion (or more correctly, in the M-CO.CH_2 ion) and b_o, b_1 and b_2 are the corresponding values for the ion A. The values for b_o, b_1 and b_2 when the M-CO.CH_2 ion is completely dideuterated are represented by B_o, B_1 and B_2 and these are the values which are required. Therefore B_o represents the percentage of the fragmentation in which two deuterium atoms are lost from the M-CO.CH_2 ion. The value of B_2 is given directly by the expression:

$$B_2 = b_2.\frac{100}{a_2}$$

The values of B_o and B_1 can be obtained from two simultaneous equations. The increase in the value of the undeuterated species in going from the molecular ion to ion A is given by the expression:

$$b_o - a_o = a_2.\frac{B_o}{100} + a_1.\frac{B_o}{100} + a_1.\frac{B_1}{200}$$

The first term, $a_2.\frac{B_o}{100}$ is the increase in the undeuterated species by the loss of two deuterium atoms from the dideuterated molecular ion.

The second term, $a_1.\frac{B_o}{100}$ is the increase in the undeuterated species by the loss of one proton and one deuterium atom from the monodeuterated molecular ion.

The third term, $a_1.\frac{B_1}{200}$ is the increase in the undeuterated species by the loss of one deuterium atom from the monodeuterated molecular ion. (No isotope effect allowed for).

Similarly, the increase in the monodeuterated species on going from the molecular ion to the ion A is given by:

$$b_1 - a_1 = a_2.\frac{B_1}{100} - a_1.\frac{B_o}{100} - a_1.\frac{B_1}{200}$$

The first term, $a_2.\frac{B_1}{100}$ is the increase in the monodeuterated species by loss of one deuterium atom from the dideuterated molecular ion.

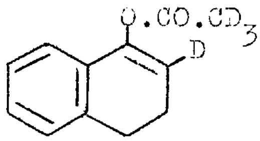
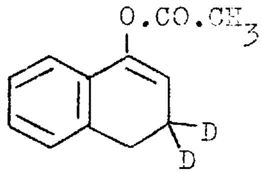
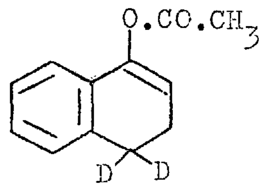
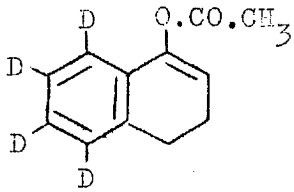
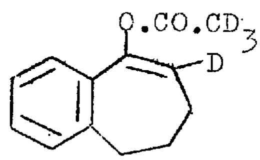
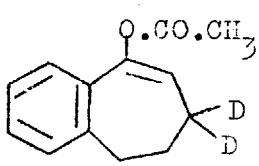
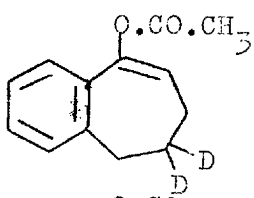
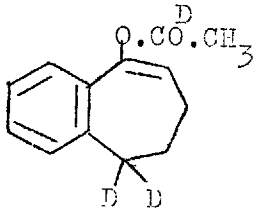
The second term, $a_1.\frac{B_o}{100}$ is the decrease in monodeuterated species by loss of one deuterium atom and one proton from the monodeuterated molecular ion.

The third term, $a_1.\frac{B_1}{200}$ is the decrease in monodeuterated species by loss of one deuterium atom from the monodeuterated molecular ion (No isotope effect allowed for)

Using these two equations, B_o and B_1 were calculated. In those cases where the molecular ion contained a small percentage of trideuterated, and in one case tetradeuterated species, a small initial correction was made by inspection. For example, in the case of $[5,5-{}^{2}H_{2}]$-benzsuberone enol acetate the 7.7% trideuterated species in the molecular ion is only reduced to 5.4% in ion A. Thus, the 7.7% was added to a_2 and the 5.4 was added to b_2. The 2.3% lost was added to b_1, (the loss of two deuterium atoms being negligible).

The observed percentages, d_0, d_1, d_2 etc. for the molecular ion, M and the ion A (A) are given in the table (see p.122), together with the corrected percentages for ion A (A corr.). The relationship between the various symbols (a, b and B) and the deuterated species is clarified below the same table. It can be seen that although B_2 was corrected separately from B_0 and B_1 the value of $(B_0 + B_1 + B_2)$ is 100 ∓ 1% in all cases.

The results show that the main source of two protons for the methyl fragmentation is the allylic position in both 1-tetralone enol acetate and benzsuberone enol acetate. The main source of a third proton is either the proton which is donated back from the acetate group in the ketene fragmentation, or the vinyl proton. At least 47% of the methyl fragmentation in both compounds involves both the two allylic protons and this third proton. A possible mechanism for this may involve ring contraction to give ion (j) which can then lose a methyl radical as shown:-

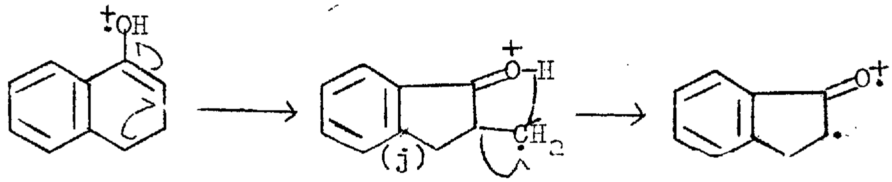
Compound	Ion	d_0	d_1	d_2	d_3	d_4 %
	M^+	0	0	0	11.0	89.0
	A^+	6.2	74.2	19.8	0	0
	A^+corr.	2.0	75.5	22.0	0	0
	M^+	0	9.0	91.0	0	0
	A^+	50.3	38.2	11.1	0	0
	A^+corr.	52.0	36.0	12.0	0	0
	M^+	0	5.2	91.1	3.7	0
	A^+	10.6	29.0	60.4	0	0
	A^+corr.	10.0	26.5	63.5	0	0
	M^+	0	0	2.7	17.5	79.8
	A^+	0	0	5.5	24.3	70.2
	A^+corr.	0	0	1.0	9.5	88.0
	M^+	0	0	0.2	11.3	88.3
	A^+	6.7	69.0	24.0	0	0
	A^+corr.	2.5	70.5	28.0	0	0
	M^+	0	5.5	84.0	7.5	3.0
	A^+	60.5	17.3	20.9	1.3	0
	A^+corr.	67.0	12.0	20.5	0	0
	M^+	5.4	10.1	84.5	0	0
	A^+	10.9	16.1	72.6	0	0
	A^+corr.	8.0	5.5	86.0	0	0
	M^+	0	8.8	83.5	7.7	0
	A^+	9.8	31.7	54.2	5.4	0
	A^+corr.	9.0	30.0	62.0	0	0

The values of A^+corr. have been altered to the nearest 0.5%

NB. $M^+(d_0)=a_0$ $A^+(d_0)=b_0$ $A^+\text{corr.}(d_0) = B_0$

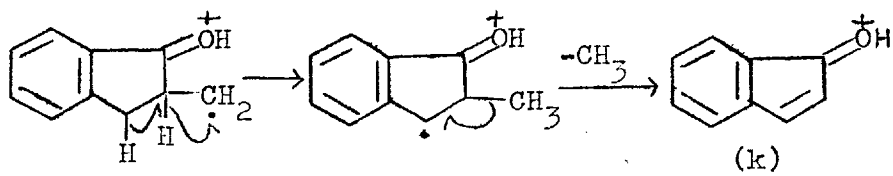
$M^+(d_1)=a_1$ $A^+(d_1)=b_1$ $A^+\text{corr.}(d_1) = B_1$

$M^+(d_2)=a_2$ $A^+(d_2)=b_2$ $A^+\text{corr.}(d_2) = B_2$



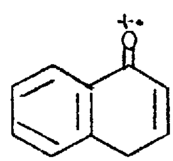
It is doubtful whether the 2-methyl-1-indanone ion is formed from 1-tetralone enol acetate or if the 2-methyl-1-tetralone ion is formed from benzsuberone enol acetate. This is because 2-methyl-1-tetralone (spectrum 55) does not lose the methyl group as readily as the enol acetates.

An alternative mechanism involves two successive 1,2, proton shifts.



(k)

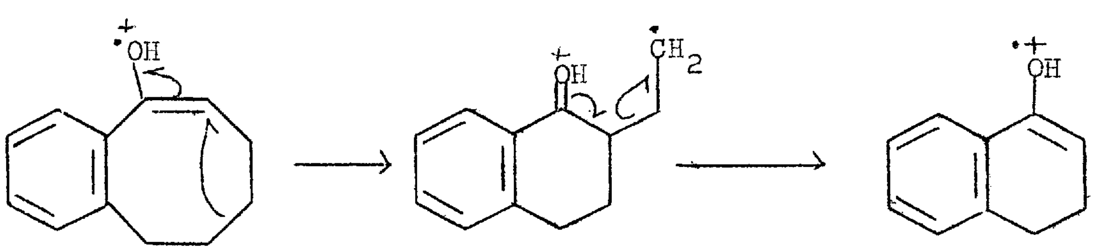
In the case of 1-tetralone enol acetate this produces the indenone ion (k). In the case of benzsuberone enol acetate the analogous ion (1) is not so stable and thus seems inconsistent with the slight enhancement of the fragmentation.



(1)

An attempt was made to determine exactly which was the 'third' proton in the methyl fragmentation. The deuterium labelling had shown it to be either the hydroxylic or vinylic proton in the enol ion (a). The spectrum of $[2'-{}^{2}H_{3}]$-2-ethyl-1-tetralone was investigated. This compound undergoes the McLafferty rearrangement to give the enol ion (b) with the hydroxyl proton specifically labelled with deuterium. High resolution studies show that only 30% of the ion current carried by the ions, m/e 131 and m/e 132 is formed by loss of $C_2H_2D_2$ followed by CH_2D from the molecular ion. This assumes that a propyl group is not lost directly. The alternative loss of $C_2H_2D_2$ and CH_3 accounts for all of the ion m/e 132 which carries 50% of the total ion current for the two ions. The remaining 20% of the ion current is formed by loss of CO and CD_3. Thus, the results are inconclusive. It is noteworthy that the loss of a methyl group from the enol ion is more facile in the enol acetate than in 2-ethyl-1-tetralone.

The possibility exists that the loss of an ethyl group noted in benzcyclo-octanone enol acetate also occurs by a ring contraction mechanism. However, ion (m) should be an intermediate in this mechanism and should lose ethylene rather than an ethyl group. Deuterium labelling shows that 55% of either the hydroxylic or vinylic proton in the enol ion is lost in the fragmentation.



(m)

There is a discrepancy in the percentages of undeuterated and monodeuterated species calculated for ion A in the 1-tetralone enol acetates. The results indicate that only positions 3 and 4 act as 2-proton sources, Therefore, only two types of mechanism are operating. These are:

a) Loss of two protons from either position 3 or position 4 together with one other proton.

b) Loss of one proton from each of positions 3, and 4 together with one other proton.

The result of this is that the undeuterated species of ion A in one compound should be balanced by an equal percentage of dideuterated species in another compound. The sum of the monodeuterated species of ion A for the first three compounds listed on p. 122 should then equal the sum of the dideuterated species for the same ion. The two values are 64% and 97%. Even the observation that an aromatic proton is lost in 10% of the fragmentations cannot account for the discrepancy. It is therefore assumed that some kind of isotope effect is operating.

Finally it can be seen from the results that the alkane positions (other than the allylic position) contribute about 10% each to the total fragmentation. This suggests that there is partial scrambling of these positions. Assuming that the the allylic position takes part equally in this scrambling, it follows that this occurs to the extent of 20% in 1-tetralone enol acetate and 30% in benzsuberone enol acetate.

P R A C T I C A L

(PART I)

The infra-red spectra were recorded on a Unicam S.P.200 spectrometer Ultra violet spectra were recorded on a Unicam S.P.800 spectrometer. Nuclear magnetic resonance spectra were obtained on the Varian Associates H.A 60 and H.A.100 spectrometers using tetramethylsilane as internal standard. The Perkin-Elmer F.11 gas chromatograph was used for examining the homogeneity of certain samples. Optical rotations were determined on an Hilger-Watts microptic photoelectric polarimeter.

Unless otherwise stated, solutions were dried over anhydrous sodium sulphate. The silica gel used in all cases for column chromatography was Hopkin and Williams' M.F.C. grade. The palladium catalyst used was 'Engelhard' (Baker platinum division) 10% palladium on charcoal.

Dry tetrahydrofuran was prepared by distillation from calcium hydride and lithium aluminium hydride. Dry dioxan was prepared by distillation from calcium hydride. The distillate was refluxed over lithium aluminium hydride and distilled from the mixture after addition of calcium chloride. The dried tetrahydrofuran and dioxan were stored over molecular sieves.

Deuterium labelled compounds were obtained from the following sources:

Deuterium oxide	Norsk Hydro-Elektrisk Kvaelstofaktieselskab
Deuterosulphuric acid	CIBA(A.R.L.) Ltd.
Deuteroacetic anhydride	Merck, Sharp and Dohme.

Sodium borodeuteride	Merck Sharp and Dohme.
$[2\text{-}^{2}H_{3}]$-Ethyl iodide	prepared[99] from deuteroacetic acid
Deuteroacetic acid	CIBA(A,R.L.) Ltd.
Deuteroacetyl chloride	provided by Mr. T. C. Smale.

[11-$^2H_1$]-α-Santonin

Sodium metal (25 mg.) was added carefully to a mixture of dioxan (2 ml.) and deuterium oxide (1 ml.). α-Santonin (254 mg.) was added and the resulting solution refluxed for 21 hours. Precautions were taken to exclude atmospheric moisture throughout. The solution was cooled and acidified with concentrated hydrochloric acid. The santonin was extracted with chloroform (2 x 5 ml.). The combined extracts were washed with water, dried and filtered. Removal of the solvent left an oil which recrystallised from ethanol to give 11-[$^2H_2$]-α-santonin, identified by m.p., ultra violet spectrum and optical rotation. The mass spectrum showed the presence of the following deuterated species: d_0 9.9%, d_1 90.1%.

[2,11-$^2H_2$]-α-Santonin

Potassium-t-butoxide (20 mg.) and α-santonin (312 mg.) were added to deuterium oxide (3 ml.). The resulting mixture was refluxed for 24 hours. During this time the santonin was not all dissolved. Sodium metal (80 mg.) was added carefully and the mixture refluxed for a further two hours. The reaction mixture was left at room temperature for 65 hours and then acidified with concentrated hydrochloric acid. The products were extracted with chloroform (2 x 5 ml.) and the combined extracts washed several times with saturated sodium bicarbonate solution and finally with water. The chloroform solution was dried and the chloroform removed. The residual oil was recrystallised from ethanol to give [2,11-$^{2}H_{2}$]-α-santonin (40 mg.) identified by m.p. and ultra violet spectrum. The mass spectrum showed the following deuterated species: d_0 4.5%, d_1 33.5%, d_2 62%. The n.m.r. spectrum showed the disappearance of one vinylic proton (doublet, τ3.78, J 9.5c/s.)

[11-$^{2}H_{1}$]-Artemisin

Sodium metal (15 mg.) was added carefully to deuterium oxide (3 ml.). Artemisin (300 mg.) was added and the mixture refluxed for 20 hours. The mixture was cooled and acidified with concentrated hydrochloric acid. The precipitate was filtered off and washed twice with warm saturated sodium bicarbonate solution and then water. The residue was recrystallised from chloroform to give [11-$^{2}H_{1}$]-artemisin as its chloroformate. This was dried at 140^{o} for 1 hour under reduced pressure to give [11-$^{2}H_{1}$]-artemisin identified by m.p. (from ethanol) and optical rotation. The n.m.r. spectrum showed the disappearance of the one proton multiplet, τ7.1 assigned[56] to the signal from the 11 proton. The mass spectrum showed the following deuterated species: d_0 3%, d_1 97%.

$[11-{}^{2}H_{1}]$-Isophoto-α-santonic lactone[61]

$[11-{}^{2}H_{1}]$-α-Santonin (39 mg.) in 4:5 (by volume) acetic acid-water (7 ml.) was irradiated in a quartz flask under reflux with a bare arc mercury lamp for 23 hours. The solvent was then removed at the pump. The residue was washed with aqueous sodium bicarbonate and the remaining solid separated on a large silica gel thin layer plate using 2:3 benzene-ethyl acetate as eluent. The band containing the lactone was removed and extracted with ethanol. The solvent was removed and the residue shown by mass spectrometry to be isophotosantonic lactone containing one deuterium atom. The following deuterated species were present: d_0 5%, d_1 95%.

$[11-{}^{2}H_{1}]$-1,2-Dihydro-α-santonin

$[11-{}^{2}H_{1}]$-α-Santonin (19 mg.) in sodium dried benzene (2 ml.) was hydrogenated over Raney nickel (40 mg.) for one hour. The catalyst was filtered off and the dihydrosantonin separated from unchanged α-santonin on a silica gel thin layer plate using 2:1 benzene-ethyl acetate as eluent. The band containing the dihydrosantonin was extracted into chloroform which was evaporated and the residue used directly in the mass spectrometer. The mass spectrum showed the following deuterated species: d_0 6%, d_1 94%.

$[1,2\text{-}^{2}H_{2}]$-1,2-Dihydro-α-santonin

Raney nickel (200 mg.) in sodium dried benzene (10 ml.) was shaken for 10 minutes in an atmosphere of deuterium gas. The gas was pumped away and santonin (250 mg.) was added. Deuterium gas was reintroduced and shaking continued until 23.7 ml. of gas had been taken up. The reduction was stopped and the catalyst filtered off. The benzene was removed at the pump and the residue recrystallised from di-isopropyl ether to give a mixture of santonin and 1,2-dihydrosantonin. 20 mg. were separated on a thin layer plate as described previously. Mass spectrometry showed the following deuterated species: d_1 27.3%, d_2 64.7%, d_3 7.9%.

$[11\text{-}^{2}H_{1}]$-(−)-α-Desmotroposantonin acetate[73]

$[11\text{-}^{2}H_{1}]$-α-Santonin (20 mg.) was added to acetic anhydride (0.2 ml.) containing a drop of concentrated sulphuric acid. After 4 hours the mixture was poured into water (1 ml.) and the precipitate recrystallised from ethanol to give (−)-α-desmotroposantonin m.p. and mixed m.p. 156-157°. Mass spectrometry showed the following deuterated species: d_0 9.5%, d_1 90.5%.

$[2,7\text{-}^{2}H_{2}]$-(+)-β-Desmotroposantonin

α-Santonin (250 mg.) was heated for 48 hours on a steam bath with a mixture of [$^{2}H_{2}$]-sulphuric acid (d_{20} = 1.86, >99% $^{2}H_{1}$) (1 ml.) and deuterium oxide (2 ml.). The solution was cooled and the brown amorphous solid filtered off. It was then heated on a steam bath with saturated sodium bicarbonate for 3 minutes and filtered. The procedure was repeated with the residue, which was then washed with water. Recrystallisation of a small sample gave [2,7-$^{2}H_{2}$]-(+)-β-desmotroposantonin (51 mg., 20%), m.p. and mixed m.p. 260°. The n.m.r. spectrum (in dimethyl sulphoxide) showed that the signal from the 6 proton, which in the undeuterated compound was a doublet (τ 4.63, J_{67} 4.5 c/s), collapsed into a singlet. The aromatic proton signal also disappeared.

[7,-$^{2}H_{1}$]-(+)-β-Desmotroposantonin

[2,7-$^{2}H_{2}$]-(+)-β-Desmotroposantonin (10 mg.) in a mixture of 0.05 N sodium hydroxide (0.8 ml.) and water (0.2 ml.) was heated in a sealed tube for 5 days over refluxing acetic acid. Periodically the tube was removed and shaken. The mixture was then acidified with concentrated hydrochloric acid and filtered. The residue was recrystallised from ethanol-water to give [7-$^{2}H_{1}$]-(+)-β-desmotroposantonin (2 mg.), m.p. and mixed m.p. 260°. The following deuterated species were present: d_0 8.8%, d_1 83.0%, d_2 5.6%, d_3 2.6%.

Santenoic Acid[85]

To α-santonin (5.0 g.) in 75% aqueous ethanol (200 ml.) was added sodium hydroxide (1.5 g.) over a period of 15 minutes.

The reaction mixture was heated until the pink colour disappeared. The ethanol and water were then removed at the pump. A little water was then added to the residual sodium salt and the resulting solution was added dropwise to chromium trioxide (7.5 g.) in 80% acetic acid with stirring, keeping the temperature between 10 and 20°. Excess sodium metabisulphite was added to decompose the chromium trioxide and the reaction mixture was then concentrated to one third of the original volume. An equal volume of water was added and the mixture allowed to stand overnight. The product was separated and washed with water by centrifugation to yield after drying 2.1 g. (37%) of santenoic acid, m.p. 100-105° [<u>Lit</u>[85] 102-105°] (Found: C, 64.6; H, 7.0. $C_{15}H_{18}O_4.H_2O$ requires C, 64.3; H, 7.2%)

Treatment of hyposantonin by the above method gave isohyposantonin.

<u>α-Acetyl santonene (LXIX). Method A</u>

Santenoic acid (100 mg.) was added to acetic anhydride containing one drop of concentrated sulphuric acid. The solution turned orange. It was left to stand for 2 hours and then poured into water with stirring. A yellow oil formed which finally solidified. This was filtered off and dried: Recrystallisation from acetic acid-water gave α-acetyl santonene m.p. 118-120°, [<u>Lit</u>[85] 112-114°], $\lambda_{max,}^{EtOH}$ 389 mμ (ϵ 14,600), 265 mμ (ϵ 8,800). ν_{max} (Nujol) 1720 (shoulder), 1735 $cm.^{-1}$.

(Found: C, 71.4; H, 6.4. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%)
The n.m.r. spectrum (in $CDCl_3$) showed four singlet methyl signals, τ 7.82, 7.97, 8.15, 8.59. The two vinylic protons showed as a broadened singlet at τ4.34 in the 60 Mc. spectrum, but were separated in the 100 Mc. spectrum.

Method B

Santenoic acid (200 mg.) was dissolved in glacial acetic acid (2 ml.) containing a drop of concentrated sulphuric acid. Acetic anhydride (0.5 ml.) was added and after 5 minutes the whole solution was poured into water. A bright yellow precipitate formed which on recrystallisation from acetic acid-water gave α-acetylsantonene.

Sodium salt of Santenoic Acid

Santenoic acid (500 mg.) was suspended in water (50 ml.) and one drop of phenolphthalein indicator solution added. 0.5 N sodium hydroxide was added dropwise with stirring until the pink colour just persisted. The solution was filtered and the water removed at the pump. The sodium salt was dried under vacuum.

[3,6-$^2H_2$]-Isohyposantonin

The sodium salt of santenoic acid (100 mg.) was dissolved in deuterium oxide (2 ml.). Sodium borodeuteride was added with stirring which was continued for 15 hours. The solution was just made acid by addition of hydrochloric acid and then refluxed with vigorous stirring for 20 minutes. Water was then added and the mixture extracted with ethyl acetate (2 x 5 ml.). The combined extracts were washed several times with sodium bicarbonate solution and then water. After drying, the ethyl acetate was removed to leave a yellowish oil. This was chromatographed on silica gel using 4:1 benzene-ethyl acetate as eluent. 3.5 ml. fractions were collected and the required product was in fractions 2 and 3. Removal of solvent and recrystallisation from ethanol gave [3,6-$^{2}H_{2}$]-isohyposantonin (4 mg.), m.p. and mixed m.p. 168-169^{o}. The n.m.r. spectrum (in $CDCl_3$) showed the disappearance of the signals from the 6 proton (doublet, τ 4.47, J_{67} 6 c/s) and one aromatic proton. The mass spectrum showed the following deuterated species: d_0 2.9%, d_2 79.6%, d_3 17.5%.

In one experiment using sodium borohydride, 12 mg. of isohyposantonin were isolated.

6βH, 7αH-Desmotropoartemisin-3-acetate-8-mesylate

Artemisin mesylate (200 mg.) was added to acetic anhydride (2 ml.) containing a drop of sulphuric acid at room temperature and left for two hours. It was then poured into water with stirring. The precipitate was filtered off and

and recrystallised from ethanol to yield the <u>title compound</u> (180 mg.) m.p. 141-143°, $[\alpha]_D^{23}$ + 62°, ν_{max} 1755, 1775 cm.$^{-1}$ λ_{max}^{EtOH} 271.5, 279.5 mμ (ϵ 1040, 1070). (Found: C, 56.5; H, 5.65; S, 8.3. $C_{18}H_{22}SO_7$ requires C, 56.5; H, 5.8; S, 8.4%). The n.m.r. spectrum (in $CDCl_3$) showed the lactone to be still <u>trans</u>-fused, the doublet signal from the 6 proton at τ 4.86 having J_{67} 10 c/s. The low field methyl signal from the mesylate group was at τ 6.9.

<u>8α- and 8β-Iodo-6βH, 7αH-Desmotroposantonin acetate</u>

Desmotropoartemisin-3-acetate-8-mesylate (200 mg.) in acetone (18 ml.) containing sodium iodide (2 g.) was refluxed for 16 hours. The acetone was removed at the pump. Water was added to the residue and the mixture extracted with ethyl acetate (2 x 20 ml.). The combined extracts were washed with sodium thiosulphate solution, water and then dried. The ethyl acetate was removed and the residue recrystallised five times from ethanol to yield a compound A, (20 mg.) m.p. 120° (dec.), $[\alpha]_D^{22}$ + 162°, λ_{max}^{EtOH} 271, 280 mμ (ϵ 1900, 2100) (Found: C, 49.1; H, 4.3. $C_{17}H_{19}O_4I$ requires C. 49.3; H, 4.6). M.W. (by mass spectrometry) 414. $C_{17}H_{19}O_4I$ requires 414.

The combined mother liquors and filtrates from the recrystallisations, on standing, deposited more crystals. These were filtered off and the filtrate concentrated. More crystals were deposited which were filtered off and recrystallised from ethanol several times to yield a compound B, m.p. 109° (dec.), $[\alpha]_D^{22}$ + 32, λ_{max} 271, 280 mμ (ϵ 1900,2120), (Found: C, 49.1; H, 4.4. $C_{17}H_{19}O_4I$ requires C, 49.3; H, 4.6%). M.W. by mass spectrometry 414, $C_{17}H_{19}O_4I$ requires 414.

6βH, 6αH-Desmotroposantonin acetate

To either the iodide A or B (10 mg.) in glacial acetic acid (1.0 ml.), was added zinc powder (100 mg.) with stirring at room temperature. Stirring was continued for 5 hours. Ethyl acetate (5 ml.) was added and the mixture filtered through 'Celite'. The ethyl acetate was washed several times with sodium bicarbonate solution and water. After drying, the solvent was removed. The residue was separated on a thin layer silica gel plate using 2:1 benzene-ethyl acetate as eluent. The major u.v. sensitive band was removed, and extracted into ethanol. This was filtered and evaporated to deposit 6βH, 7αH-desmotroposantonin acetate m.p. 178-179° [Lit[80] 180°]. M.W. (by mass spectrometry) 288. $C_{17}H_{20}O_4$ requires 288. The fragmentation is basically the same as for (−)-α-desmotroposantonin acetate.

[8-$^2H_1$]-6βH, 7αH-Desmotroposantonin acetate

Reduction of either iodide A or iodide B in [O $^2H_1$]-acetic acid or [$^2H_3$, O$^2H_1$]-acetic acid by the same method gave

[8-$^{2}H_1$]-6βH-7αH-desmotroposantonin. The following deuterated species were present: d_0 30%, d_1 70%.

[8-$^{2}H_1$]-(-)-α-Desmotroposantonin

[8-$^{2}H_1$]-6βH, 7αH-Desmotroposantonin (5 mg.) was added to acetic anhydride (0.1 ml.) containing a trace of concentrated sulphuric acid. The reaction mixture was allowed to stand for 1 hour and water (2.5 ml.) added. It was extracted with ethyl acetate (2 x 2.5 ml.). The combined extracts were washed with sodium bicarbonate solution, water and then dried. Removal of solvent gave an oil. Addition of ethanol and slow removal of solvent gave crystals m.p. and mixed m.p. 157-158°. The following deuterated species were present: d_0 30%, d_1 70%.

Desmotropoartemisin-3-butyrate-8-acetate

Artemisin (300 mg.) was added to butyric anhydride (2.5 ml.) containing two drops of concentrated sulphuric acid. After 5 hours the reaction mixture was poured into water which was then heated on a steam bath for 1 hour. On cooling, a white solid formed, which was filtered off and recrystallised from ethanol to give 295 mg. of title compound m.p. 122.5-123° $[\alpha]^{22}_{D}$ + 62.5 (Found: C, 67.4; H, 6.8. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%). The n.m.r. spectrum (in $CDCl_3$) shows the C(6)proton as a doublet, τ4.83, J_{67} 9.5 c/s.

6βH, 7αH-8-Epidesmotropoartemisin-8-acetate-3-butyrate

8-Epiartemisin acetate (50 mg.) was dissolved in butyric anhydride (1 ml.) containing one drop of concentrated sulphuric acid at -5^{o} and left overnight. The reaction mixture was poured into excess water at room temperature and stirred for 24 hours. A white solid formed which was filtered off and recrystallised from ethanol to give the title compound 37.6 mg. m.p. 105-107°, $[\alpha]_D$ -18° (Found: C, 67.5; H, 6.9. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%). The n.m.r. spectrum showed the C(6)proton as a doublet, τ 4.65, J_{67} 10.5 c/s.

6βH, 7αH-8-Epidesmotropoartemisin-3,8-diacetate prepared by the same method had m.p. 202°, $[\alpha]_D$ -33° (Found: C, 65.7; H, 6.2. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%). The n.m.r. spectrum showed the C(6) proton as a doublet τ 4.6, J_{67} 10 c/s.

6αH, 7αH-Desmotropoartemisin-8-acetate-3-butyrate

8-Epiartemisin acetate (100 mg.) was added to butyric anhydride (1 ml.) containing one drop of concentrated sulphuric acid. The mixture was heated on a steam bath for 15 minutes and then left to stand overnight. It was then poured into water which was heated on a steam bath until a solid formed. It was filtered hot and washed several times with hot water. Recrystallisation from ethanol gave the title compound (57.6 mg.) m.p. 150-151°, $[\alpha]^{22}_D$ - 131.5° (Found: C, 67.25; H, 6.8.

$C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%). The n.m.r. spectrum showed the C(6) proton as a doublet τ 4.29, J_{67} 6.5 c/s.

<u>6αH, 7αH-desmotropo-8-epiartemisin-3,8-diacetate</u> prepared by the same method had m.p. 205-211°, $[\alpha]_D^{23}$ - 150° (Found: C, 65.75; H, 6.4. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%). The n.m.r. spectrum showed the C(6) proton as a doublet, τ 4.27, J_{67} 6.5 c/s.

6βH, 7αH and 6αH, 7αH-desmotropartemisin diacetate were made by the method of Sumi.[34]

(-)-α-Desmotroposantonin and its acetate were made by the method of Huang Minlan.[74] The propionate made in the same way had m.p. 117-118°, $[\alpha]_D^{21}$ - 143°, (Found: C, 71.7; H, 7.3. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%). The n.m.r. spectrum showed the C(6) proton as a doublet, τ 4.42, J_{67} 5.5 c/s.

<u>α-Santonin oxime</u>

α-Santonin (1 g.), hydroxylamine hydrochloride (2 g.) and sodium acetate (3 g.) were refluxed in a mixture of water (4 ml.) and ethanol (10 ml.) for 16 hours. The solution was cooled, diluted with water and filtered. The solid was recrystallised from ethanol to give santonin-β-oxime (583 mg.) m.p. 223°.

Hyposantonin (see ref. 46)

Santonin-β-oxime (750 mg.) was added to ethyl alcohol (32 ml.) containing concentrated sulphuric acid (1.5 ml.) and several drops of saturated copper sulphate solution. Zinc powder (5 g.) was added with stirring, which was continued for 20 hours. The solution was then filtered through 'Celite'. The ethanol was removed under vacuum. Water (20 ml.) was added and a small amount of white solid filtered off. The filtrate was refluxed for 45 minutes. It became turbid and produced a heavy precipitate. This was filtered off and recrystallised from ethanol to give hyposantonin (270 mg.), m.p. 150-152° (Lit 152°), M.W. (by mass spectrometry) 230. $C_{15}H_{18}O_2$ requires 230. The n.m.r. spectrum showed the C(6)-proton as a doublet, τ 5.02, J_{67} 9.5 c/s.

Isohyposantonin

Hyposantonin (50 mg.) was dissolved in dilute potassium hydroxide with slight warming and stirring. Stirring was continued for a further 15 minutes and the solution acidified with concentrated hydrochloric acid. The precipitate was filtered off and recrystallised from ethanol to yield isohyposantonin (40 mg.), m.p. 168-169 [Lit 168.5°]. The n.m.r. spectrum showed the C(6)-proton as a doublet, τ 4.47, J_{67} 6 c/s.

[2,2,6-$^{2}H_3$]-Deoxygeigerin (see ref. 66)

Redistilled acetic anhydride (0.33 ml.) and deuterium oxide (0.66 ml.) were refluxed together for 15 minutes. Zinc dust (125 mg.) and geigerin (19 mg.) were added and the solution refluxed for 18 hours. The solution was cooled. diluted with water and neutralised with sodium bicarbonate. It was then extracted with chloroform (3 x 10 ml.). The chloroform extracts were washed, dried and the solvent removed. The residue was separated on a thin layer silica gel plate. The band containing the deoxygeigerin was extracted with chloroform and used directly in the mass spectrometer. The following deuterated species were present: d_0 2.5%, d_1 15.6%, d_2 78.7%, d_3 3.2%.

2,2-[$^{2}H_2$]-Deoxygeigerin

Acetic anhydride (1.2 ml.) and deuterium oxide (2.4 ml.) were refluxed together for 15 minutes. Zinc powder (514 mg.) and deoxygeigerin were added and the mixture refluxed for 18 hours. It was then cooled and water added. Excess acetic acid was neutralised with sodium bicarbonate. The aqueous solution was extracted with chloroform (3 x 20 ml.). The combined chloroform extracts were washed with water, dried and the ethyl acetate removed under reduced pressure. The residue was recrystallised from ethyl acetate-hexane to give [2,2-$^{2}H_2$]-deoxygeigerin, m.p. 130-131° [Lit 131-135°].

The following deuterated species were present: d_1 5.2%, d_2 74.5%, d_3 17.5%, d_4 2.7%.

[2,2,11-$^2H_3$]-Geigerin

Geigerin (10 mg.) was refluxed for 18 hours in deuterium oxide (1 ml.) containing sodium metal (2.5 mg.) and then left to stand for 24 hours. The water was extracted with ethyl acetate (2 x 2.5 ml.) and the combined extracts washed with sodium bicarbonate solution and water. They were then dried and the solvent removed. The residue was chromatographed on silica gel (6 g.) using ethyl acetate as eluent and collecting 3.5 ml. fractions. Fractions 2-5 contained geigerin and those were evaporated to leave [2,2,11-$^2H_3$]-geigerin.

Dihydrosantinic acid and Isodihydrosantinic acid[75]

Hyposantonin (500 mg.) in 90% ethanol (12.5 ml.) was saturated with hydrochloric acid gas for 15 minutes. The reaction mixture was then poured into water and extracted with ether (2 x 20 ml.). The combined extracts were washed with sodium bicarbonate solution and water. They were then dried and the solvent removed to leave a pale yellow oil. This was chromatographed on silica gel (40 g.) collecting 20 ml. fractions. Fractions 1-6 were eluted with benzene and thereafter the fractions were eluted with 1:4 ethyl acetate-benzene. The ethyl ester of the two acids was in fractions 12-14. The combined fractions were evaporated down and the residue hydrolysed by refluxing in 0.5 N sodium hydroxide (10 ml.) containing ethanol (2 ml.) for 6 hours. The hydrolysis mixture was then acidified and the precipitate filtered off and redissolved in sodium bicarbonate solution. It was reprecipitated with acid and recrystallised from petroleum ether 40/60 containing a trace of ethanol to give a mixture of dihydro- and isodihydro-santinic acids (50.5 mg.), m.p. 95-110°. The infra red spectrum (Nujol) showed the band at 1700 cm.$^{-1}$ and no trace of lactone carbonyl stretches.

<u>The attempted dehydration of Desmotropoartemisin 8α- or 8βH-Desmotropoartemisin-8-acetate</u>

Desmotropoartemisin (100 mg.) in 60% perchloric acid-acetic acid (1:9, 10 ml.) was kept at 70-80° on a steam bath for 2 hours. The reaction mixture was poured into water and the acetic acid neutralised with sodium bicarbonate. The solution was then extracted with ethyl acetate (2 x 20 ml.). The combined extracts were washed with water and dried. The solvent was removed and the residue chromatographed on silica gel (7 g.) using 1:4 ethyl acetate-benzene as eluent. Fractions 2-4 contained a single product. Removal of solvent gave 18 mg. of product which were recrystallised from benzene-80/100 petroleum ether to give 6 mg. of crystalline solid m.p. 188-191^{o} λ_{max} 289.5 mμ (ϵ3690), ν_{max} 1735 (acelate), 1760 cm.$^{-1}$ (γ-lactone).

(Found: C, 67.5; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%) M.W. (by mass spectrometry) 304, $C_{17}H_{20}O_5$ requires 304. The predominance of the ion m/e 188 over m/e 187 indicates a cis fused lactone as does the n.m.r. spectrum, C(6) proton, doublet 4.34, J_{67} 6.5c/s.

P R A C T I C A L

(PART II)

Cinnamylidene malonic acid [126]

Cinnamaldehyde (50 g.), malonic acid (40 g.) and quinoline (50 g.) were warmed on a steam bath until a clear red solution formed. Piperidine (2 ml.) was added and the solution cooled and allowed to stand in the dark for 24 hours. The solid formed, was dissolved up in excess sodium hydroxide solution and extracted with ether (3 x 100 ml.) to remove the quinoline. The solution was acidified with concentrated hydrochloric acid and the precipitate filtered off, washed with water and dried under vacuum to give cinnamylidene malonic acid (75 g. 91%).

5-Phenylvaleric acid [126]

Raney nickel alloy (67.5 g.) was added during two hours to a stirred, almost boiling solution of cinnamylidene malonic acid (68.5 g.) in 4 N sodium hydroxide (750 ml.). The solution was stirred for a further hour at 90° C. and then filtered. The filtrate was slowly run into a hot solution of sulphuric acid (225 ml. of sulphuric acid in 500 ml. water). The precipitated brown oil was separated off and heated slowly to 180°. After the evolution of carbon dioxide had ceased, water was added. The solid material was filtered off and recrystallised from 60/80 petroleum ether to give 5-phenylvaleric acid (30 g. 54.5%) m.p. 57° [Lit. 56-58°].

Benzsuberone [132]

Phosphorous pentoxide (180 g.) and 90% orthphosphoric acid were heated together on a steam bath for 4 hours. 5-Phenylvaleric acid (29 g.) was added in portions and the mixture heated for a further two hours. The mixture was then poured into iced water, left to stand for one hour, and then extracted with benzene (3 x 250 ml.). The combined extracts were washed with 5% sodium hydroxide (2 x 100 ml.) and water. They were then dried, filtered and the benzene removed under reduced pressure. The residue was distilled to give benzsuberone (11 g. 42%) b.p. 74^{o}/0.1 mm. [Lit[132] $90\text{-}93^{o}$/1 mm.].

Benzsuberone enol acetate [98]

Benzsuberone (3 g.), acetic anhydride (13 ml.) and p-toluene sulphonic acid (0.2 g.) were slowly distilled through a 'Vigreux' column so that 10 ml. of distillate were collected over a period of four hours. The reaction mixture was then stirred with water at room temperature for one hour and then extracted with ether (2 x 50 ml.). The combined extracts were washed with 10% sodium bicarbonate solution, until no more carbon dioxide was evolved, and then with water. The ether solution was then dried, filtered and the ether removed to yield crude benzsuberone enol acetate (3.4 g. 90%). It was recrystallised from 40/60 petroleum ether, with the addition of a

little charcoal, to give the pure enol acetate m.p. 57-58°
Lit[98] m.p. 57-60°.

Indene bromohydrin[127]

Bromine water was added dropwise to indene (53 g.) stirred continuously and kept emulsified with 'Dreft'. Solutions of bromine containing sodium bromide were used to enable the use of smaller volumes of water. When the bromine colouration persisted, the water was poured off and the remaining paste extracted with 40/60 petroleum ether. The residue was recrystallised from ethanol to give indene bromohydrin (52 g. 49%) m.p. 127-129° Lit[127] m.p. 128-129°.

1-Indanone[128]

Indene bromohydrin (25 g.) was refluxed in 7% sulphuric acid for 8 hours. The reaction mixture was steam distilled and 400 ml. of distillate collected. The distillate was cooled in ice and the crude indanone which solidified was filtered off. Recrystallisation from 40/60 petroleum ether gave 1-indanone (16 g. 52%).

1-Indanone enol acetate (see ref. 98)

1-Indanone (2.5 g.), acetic anhydride (10 ml.) and p-toluene sulphuric acid were heated together under nitrogen with slow distillation. 6.5 ml. of distillate were collected in two hours. The reaction mixture was cooled, poured into water (25 ml.) and stirred for 30 minutes. It was then extracted with ether (2 x 25 ml.) and the combined extracts washed with saturated sodium bicarbonate solution until carbon dioxide ceased to be evolved, and then with water. The ether solution was dried, filtered and the ether removed to leave a brown oil, the infra red spectrum of which showed a 1:1 mixture of the enol acetate and the ketone. Chromatography of 60 mg. of the mixture on silica gel (6 g.) gave, after elution with 16 ml. of benzene, the enol acetate in the next 15 ml. of eluent. Removal of the solvent and recrystallisation from 40/60 petroleum ether gave the enol acetate (24 mg.) m.p. 44.5-46.5° [Lit[89] 48.5-49.5°].

Diethyl-α-ethyl-α-benzylmalonate [129]

Potassium metal (5.2 g.) was heated in xylene (150 ml.) with vigorous stirring. The mixture was then cooled stirring continuously so that small droplets of solid potassium metal were formed. Diethyl-α-ethylmalonate (25 g.) was added with stirring and the mixture refluxed for 17 hours. The xylene solution was washed with water and the xylene distilled off. The residue was distilled to give diethyl-α-ethyl-α-benzylmalonate (17.25 g. 47%) b.p. 146°/1.5 mm. Lit b.p. 173°/12.5 mm.

2-Ethyl-3-phenylpropionic acid

Diethyl-α-ethyl-α-benzylmalonate (17 g.) was refluxed for 90 minutes with 50% aqueous ethanol (40 ml.) containing potassium hydroxide (10 g.). The alcohol was distilled off and the remaining solution acidified to congo red with concentrated hydrochloric acid. An oil separated out which was decarboxylated by heating to 180°. It was then distilled to give 2-ethyl-3-phenylpropionic acid (7 g. 63%) b.p. 120°/1.5 mm.

2-Ethyl-1-indanone [130]

2-Ethyl-3-phenylpropionic acid was treated with excess hydrofluoric acid in a polythene bottle with one outlet. The mixture was stirred for 92 hours and the excess hydrofluoric acid allowed to evaporate. The residue was treated with sodium bicarbonate until neutral. The mixture was extracted with ether (3 x 25 ml.). The combined extracts were dried and the ether removed. The residue was distilled under reduced pressure to give 2-ethyl-1-indanone (1.6 g. 35%) b.p. 80°/0.15 mm., n_D^{18} 1.5490 [Lit[89] b.p. 144°/18 mm. n_D^{31} 1.5420]. The product was homogeneous by gas-liquid chromatography.

1-Tetralone-2-ethylglyoxalate [100]

1-Tetralone (5 g.), diethyloxalate (10 g.) and dry benzene (12 ml.) were mixed together and added to sodium ethoxide (from 1.6 g. of sodium) in dry benzene, cooled in ice. The mixture was shaken and left at room temperature for 17 hours. It was then poured into iced water and extracted several times with ether. The mixture was acidified and again extracted with ether, which was then dried and evaporated. The residue was a brown oil which formed yellow crystals on adding ethanol. These were filtered off and recrystallised from ethanol to yield 1-tetralone-2-ethylglyoxalate (2.7 g. 32%) m.p. 47-48° [Lit[100] 47.5-48°].

2-Carbethoxy-1-tetralone[100]

1-Tetralone-2-ethylglyoxalate (2.3 g.) together with powdered glass was heated with stirring at 180° for 1 hour. It was then distilled to give 2-carbethoxy-1-tetralone (1.45 g. 71%) b.p. 116-120°/0.3 mm.

2-Ethyl-1-tetralone (see ref. 100)

2-Carbethoxy-1-tetralone (0.5 g.), ethyl iodide (0.625 g.) and sodium (58 mg.) were refluxed in absolute ethanol (3.5 ml.) for 2 hours. Potassium hydroxide (0.5 g.) in water (1.3 ml.) was added and the mixture refluxed for a further 5 hours. Ethanol (3 ml.) was then distilled off and the remaining solution acidified with concentrated hydrochloric acid and diluted with water. The solution was extracted with ether (2 x 5 ml.) and the combined extracts dried and filtered. The ether was removed and the residue distilled b.p. 70-72^{o}/0.2 mm. to give a mixture of the required ketone and 1-tetralone. Chromatography on silica gel (30 g.) gave on elution with benzene, 2-ethyl-1-tetralone as the first product. It was redistilled to yield 120 mg. 30% of product, homogeneous by gas-liquid chromatography.

2-Methyl-1-tetralone (see ref. 100)

2-Carbethoxy-1-tetralone (250 mg.) and methyl iodide (500 mg.) were added to methanol (1 ml.) containing sodium (30 mg.). The mixture was refluxed for 2 hours. Potassium hydroxide (0.25 g.) in water (0.5 ml.) was added and the mixture refluxed a further 2 hours. Methanol (1.5 ml.) was distilled off and the residual solution acidified with concentrated hydrochloric acid and water added. The solution was extracted with ether (2 x 5 ml.) and the combined extracts were dried, filtered and concentrated. The residual oil was chromatographed on silica gel (30 g.). After elution with benzene (160 ml.), the 2-methyl-1-tetralone was collected in the next 80 ml. of eluent. The benzene was removed and the residue microdistilled under reduced pressure to yield 2-methyl-1-tetralone (65 mg. 34%) shown to be homogeneous by gas-liquid chromatography, ν_{max} 740 (1,2-disubstituted benzene ring), 1605 (aromatic), 1680 cm.$^{-1}$ (carbonyl). The n.m.r. spectrum shows the methyl signal as a doublet, τ 8.78, J 7.2 c/s.

2-Bromo-1-indanone[131]

Indene bromohydrin (35 g.) was added to a solution of sodium dichromate (47.5 g.) in water (230 ml.) containing concentrated sulphuric acid (32 ml.). The mixture was stirred at 50° for 3 hours. The solution was cooled and the product solidified. The aqueous layer was poured off and the product washed with water by decantation. The residue was extracted several times with 60/80 petroleum ether from which it was recrystallised to give 2-bromo-1-indanone (25 g. 72%) m.p.35-36°.

2-Bromo-1-indanone ethylene ketal and Indenone ketal[89]

Benzene (200 ml.), 2-bromo-1-indanone (23.5 g.) ethylene glycol (30 g.) and *p*-toluene sulphuric acid (0.05 g.) were refluxed for 92 hours. A Dean-Stark head was used to separate off the water formed. Benzene (120 ml.) was distilled off and the residue washed with sodium bicarbonate and dried. Removal of the benzene and distillation under reduced pressure gave the crude bromoketal which was not purified further.

To the crude bromoketal (12 g.) in *t*-butylalcohol (14 ml.) was added, with stirring, a solution of potassium-*t*-butoxide (0.07 ml.) in *t*-butylalcohol. The solution became dark purple. The reaction mixture was stirred for 3 hours and then poured into iced water. The organic layer was extracted twice with ether and the ether removed at the pump. The residue was distilled under reduced pressure and the indenone ketal collected b.p. 110/0.35 mm; n_D^{18} 1.5750, λ_{max} 276 mμ (ϵ, 2885) [Lit[89] n_D^{28} 1.5699, λ_{max} 276 mμ (ϵ, 2800)].

The n.m.r. spectrum shows:

2 vinylic protons,	double doublet	τ 3.53, 4.02, J 6 c/s
4 ketal protons	multiplet	τ 6.07
4 aromatic protons	c.a.	τ 2.9

<u>[2,3-$^2H_2$]-1-Indanone-ethylene ketal and [3-$^2H_1$]-1-indanone</u>

Indenone ketal (185 mg.) in sodium dried benzene (5 ml.) was deuterogenated over platinum oxide catalyst (12 mg.). The catalyst was filtered off and the benzene removed. The indanone ketal solidified on cooling. It was refluxed with 2 N hydrochloric acid (10 ml.) for 10 minutes and then steam distilled. The distillate was cooled in ice and the solid filtered off to yield [3-$^2H_1$]-1-indanone (69 mg.). The n.m.r. spectrum showed:

1 benzylic proton, broadened triplet	τ 6.95, J 6 c/s.
2 protons, α to carbonyl group, doublet,	τ 7.5, J 6 c/s.

Mass spectrometry indicates only 4% d_3 species.

2-Bromo-1-tetralone ethylene ketal

Bromine was added dropwise with stirring to 1-tetralone (5.0 g.) in ethylene glycol (50 ml.) until the yellow colour just persisted. Benzene (250 ml.) was added and the mixture refluxed for 3 days using a Dean-Stark separating head to remove water. Solid sodium carbonate was then added to neutralise the hydrobromic acid. Water was added and the benzene layer was separated off. It was washed with water, dried, and the benzene removed to leave an orange oil. An ultra violet measurement indicated that it contained 15% by weight of the bromoketone. Addition of methanol and cooling induced crystallisation. The crystals were filtered off and recrystallised from methanol to give 2-bromo-1-tetralone ethylene ketal (6 g. 65%), m.p.53-54°, (Found: C, 53.7; H, 4.7; Br, 29.8. $C_{12}H_{11}BrO_2$ requires C, 53.5; H, 4.9; Br, 29.7%).

The n.m.r. spectrum shows:

4 aromatic protons,	τ 2.5-3.0
1 proton, multiplet,	τ 5.54
4 ketal protons broadened singlet,	τ 5.79
2 benzylic protons, distorted triplet,	τ 7.09
2 aliphatic protons, multiplet,	τ 7.51

2-(1^1-Naphthoxy)-ethanol

2-Bromo-1-tetralone ethylene ketal (1.0 g.) was refluxed in methanol (4.0 ml.) containing sodium hydroxide (1.0 g.).

A white precipitate formed during the reaction. The reaction mixture was poured into water saturated with sodium chloride and extracted twice with benzene. The combined extracts were washed with water and dried. The benzene was removed to give a pale yellow oil which could be distilled b.p. $140^{\circ}/0.5$ mm. The oil was left at -5° overnight when partial recrystallisation occurred. Scratching produced total crystallisation. Recrystallisation gave $2(1^{1}$-naphthoxy)ethanol m.p. 41.5-42.5 [Lit[92] 42°] (Found: C, 76.6; H, 6.5. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%).

$[4,4-{}^{2}H_2]$-4-Phenylbutyric acid

3-Benzoylpropionic acid (0.5 g.) was dissolved in dry redistilled dioxan (4 ml.) and deuterium oxide (1 ml.). One drop of concentrated deuterosulphuric acid was added, followed by 10% palladium on charcoal catalyst (20 mg.). The mixture was shaken in an atmosphere of deuterium until 140 ml. of deuterium had been taken up. Water (5 ml.) was added followed by a little animal charcoal. The mixture was heated on a steam bath for 1 minute and filtered through 'Celite' supported on a sintered glass funnel. The solvents were removed from the filtrate under reduced pressure to yield quantitatively $[4,4-{}^{2}H_2]$-4-phenylbutyric acid. The n.m.r. spectrum showed two triplets τ 8.05, τ 7.64, J 6 c/s.

[4,4-$^{2}H_{2}$]-1-Tetralone

Phosphorous pentoxide (15.3 g.) was added to 90% orthophosphoric acid (10 ml.) and the mixture heated on a steam bath for 2 hours. The polyphosphoric acid produced was then mixed with melted [4,4-$^{2}H_{2}$]-4-phenylbutyric acid (474 mg.) and heating continued for 3 hours on the steam bath. The mixture was then poured into iced water and left to stand for two hours. It was then extracted with benzene (2 x 20 ml.) and the combined extracts washed twice with 5% sodium hydroxide and then water. The extracts were dried and the benzene removed to yield crude 1-tetralone which was microdistilled under reduced pressure to give [4,4-$^{2}H_{2}$]-1-tetralone (182 mg.) which was homogeneous by gas-liquid chromatography.

[3,3-$^{2}H_{2}$]-3-Benzoylpropionic acid

3-Benzoylpropionic acid (1.0 g.) was added to deuterium oxide (5.0 ml.) containing anhydrous potassium carbonate (250 mg.) and the mixture refluxed for 22 hours. The mixture was then acidified with concentrated hydrochloric acid and the precipitate filtered off, washed with water and dried at 50° under vacuum. The n.m.r. spectrum shows a two proton singlet τ 7.19 indicating exchange of the protons α to the ketone group.

[3,3-$^{2}H_2$]-4-Phenylbutyric acid

This was made from [3,3-$^{2}H_2$]-3-benzoylpropionic acid as for 4-phenylbutyric acid, but employing non deuterated chemicals for the reduction. In this way, a quantitative yield of [3,3-$^{2}H_2$]-4-phenylbutyric was obtained.

[3,3-$^{2}H_2$]-1-tetralone

Cyclisation of [3,3-$^{2}H_2$]-4-phenylbutyric acid with polyphosphoric acid as described gave [3,3-$^{2}H_2$]-1-tetralone (130 mg.)

[3,3-$^{2}H_2$]- and [4,4-$^{2}H_2$]-1-tetralone enol acetate

The deuterated tetralone (100 mg.), acetic anhydride (300 mg.) and a small crystal of p-toluene sulphonic acid were heated together at 160° so that slow distillation occurred. 50 mg. of acetic anhydride were added after half an hour, 1 hour, 2 hours and 3 hours. After 4 hours the residue was cooled and stirred with water for half an hour. It was then extracted with ether (2 x 10 ml.). The combined ether extracts were washed with sodium bicarbonate until effervescence ceased, and then with water. The extracts were dried and the solvent removed to leave a residue which partially solidified. Chromatography on silica gel (7.0 g.) using benzene as eluent and collecting 3 ml. fractions gave the enol acetate in fractions 8-14. Removal of the benzene and recrystallisation from 40/60 petroleum ether gave the enol acetate identified by m.p. and mixed m.p. The yield of [3,3-$^{2}H_{2}$]-1-tetralone enol acetate was 46 mg. and of [4,4-$^{2}H_{2}$]-1-tetralone enol acetate, 30 mg.

[2-$^{2}H_{1}$]-1-tetralone-enol-[$^{2}H_{3}$]-acetate

This compound was made as for the other deuterated enol acetates but employing undeuterated tetralone and deuterated acetic anhydride. The yield from 100 mg. of ketone was 25 mg.

The n.m.r. spectra of the three deuterated enol acetates are shown on p. 60.

[4,4-$^{2}H_{2}$]- and [5,5-$^{2}H_{2}$]-5-Phenylvaleric acid

Application of the same methods, as for the production of [3,3-$^{2}H_{2}$]- and [4,4-$^{2}H_{2}$]-4-phenylbutyric acid, to 4-benzoylbutyric acid (500 mg.) gave the two title compounds in yields of 113 mg. and 130 mg. respectively.

[4,4-$^{2}H_{2}$]- and [5,5-$^{2}H_{2}$]-Benzsuberone enol acetate

These were made by the same method as for the deuterated tetralone enol acetates. The yields from 50 mg. of ketone were 27 and 28 mg. respectively.

[$^2H_1$]-Benzsuberone-enol-[$^2H_3$]-acetate

This was made in the same way as [$^2H_1$]-1-tetralone-enol-acetate. The yield from 100 mg. of ketone was 21 mg.

[2,23,3-$^2H_4$]-5-Phenylvaleric acid

5-Phenylpent-2-ynoic acid in a mixture of dry tetrahydrofuran (4 ml.) and deuterium oxide (1 ml.) was deuterogenated over 10% palladium on charcoal catalyst (20 mg.). The total uptake of deuterium gas was 135 ml. The solution was filtered and the solvents removed from the filtrate under reduced pressure. The residual oil crystallised on cooling to give [2,2,3,3-$^2H_4$]-5-phenylvaleric acid.

[3,3-$^2H_2$]-Benzsuberone

Cyclisation of [2,2,3,3-$^2H_2$]-5-phenylvaleric acid (500 mg.) cyclised in polyphosphoric acid as described gave 223 mg. of the title compound.

[3,3-$^2H_2$]-Benzsuberone enol acetate

Application of the procedure previously described gave 18 mg. of enol acetate from 50 mg. of ketone.

Benzcyclo-octanone enol acetate

Benzcyclo-octanone (250 mg.), acetic anhydride (750 mg.) and a crystal of p-toluene sulphonic acid were slowly distilled. Acetic anhydride (100 mg.) was added every half hour. After four hours the mixture was poured into water and worked up as described for the other enol acetates. Chromatography of the residue on silica gel (40 g.) using benzene as eluent gave benzcyclo-octanone enol acetate (193 mg.), m.p. 62-62.5^{o} (Found: C, 77.5; H, 7.3. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.5%). The n.m.r. spectrum shows 4 aromatic protons (τ 2.84), 1 vinylic proton (triplet, τ 4.46 J 7 c/s.) and the acetyl protons (singlet τ 7.98).

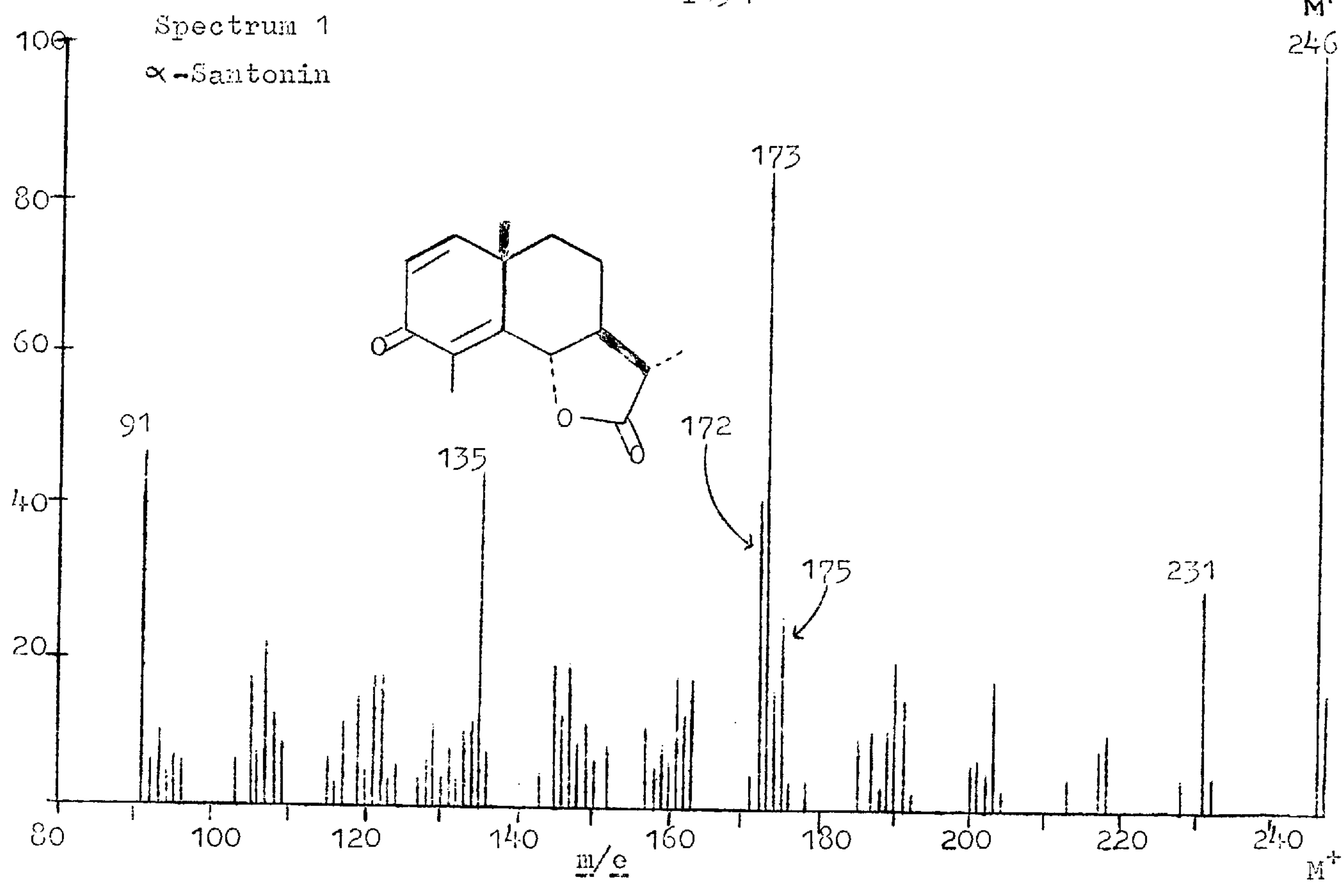
2-Tetralone-enol-acetate

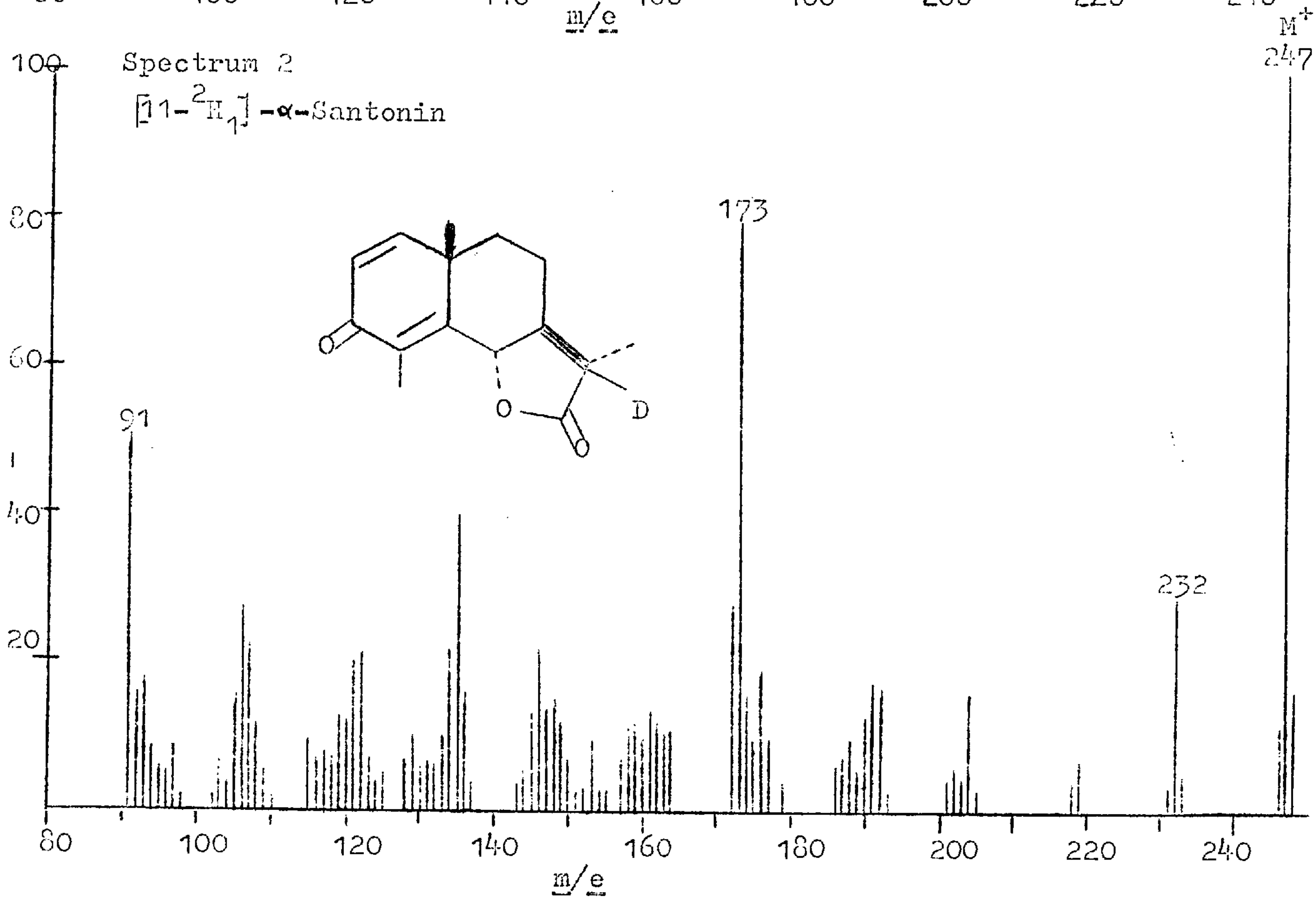
This was made in a similar way to the other enol acetates. Distillation gave 60% of the title compound b.p. 82-84/0.1 mm. homogeneous by gas-liquid chromatography. ν_{max} 1660 (c=c), 1750 cm.$^{-1}$ (acetate).

The n.m.r. spectrum showed:

4 aromatic protons	(τ 3.02)
1 vinylic proton	(broadened singlet, τ 3.89)
2 protons	(triplet, τ 7.20, J 7 c/s.)
2 protons	(triplet, τ 7.57, J 7 c/s.)
3 acetyl protons	(singlet, τ 7.90)

MASS SPECTRA


Spectrum 1
α-Santonin
M+
246
173
172
175
135
91
231
m/e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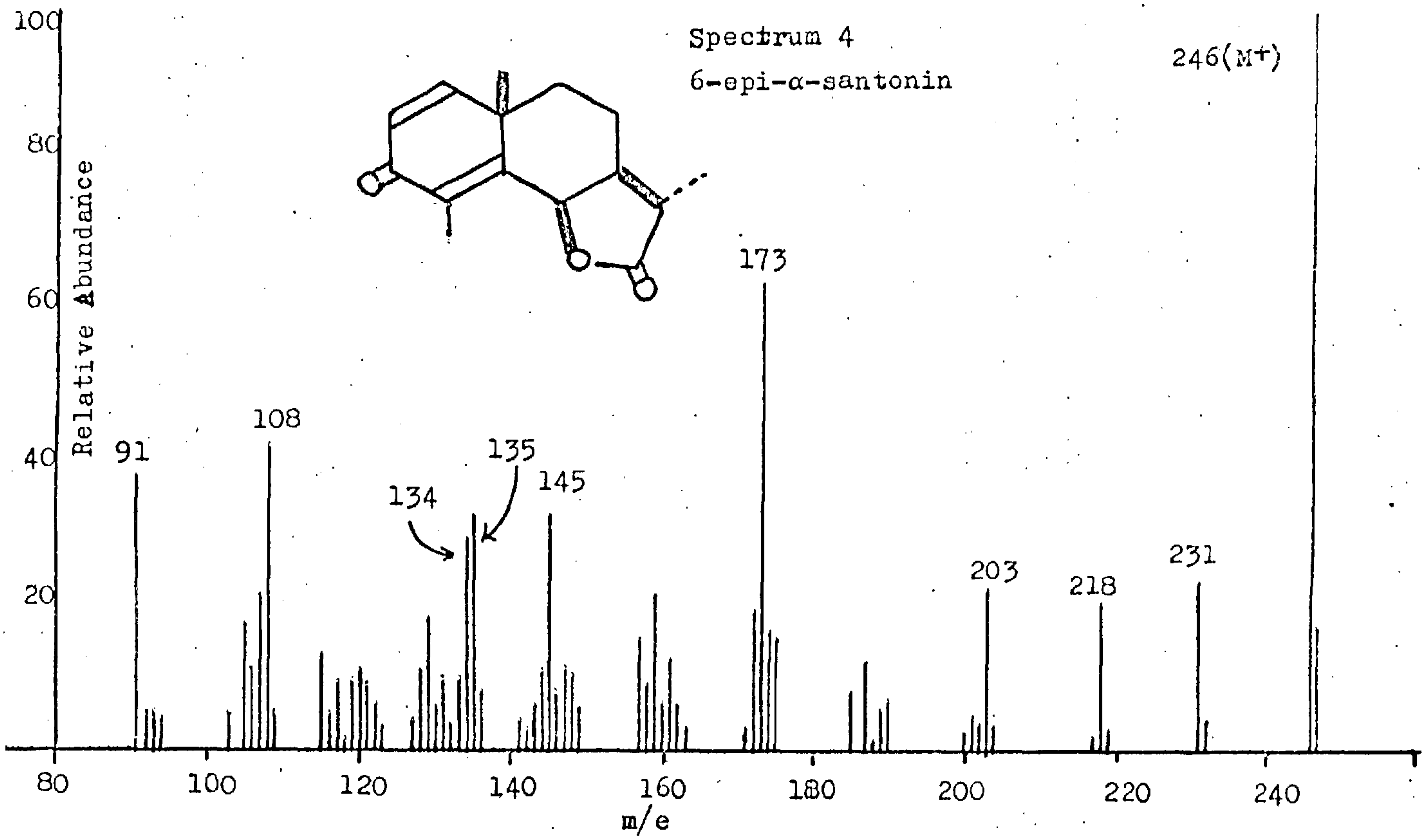
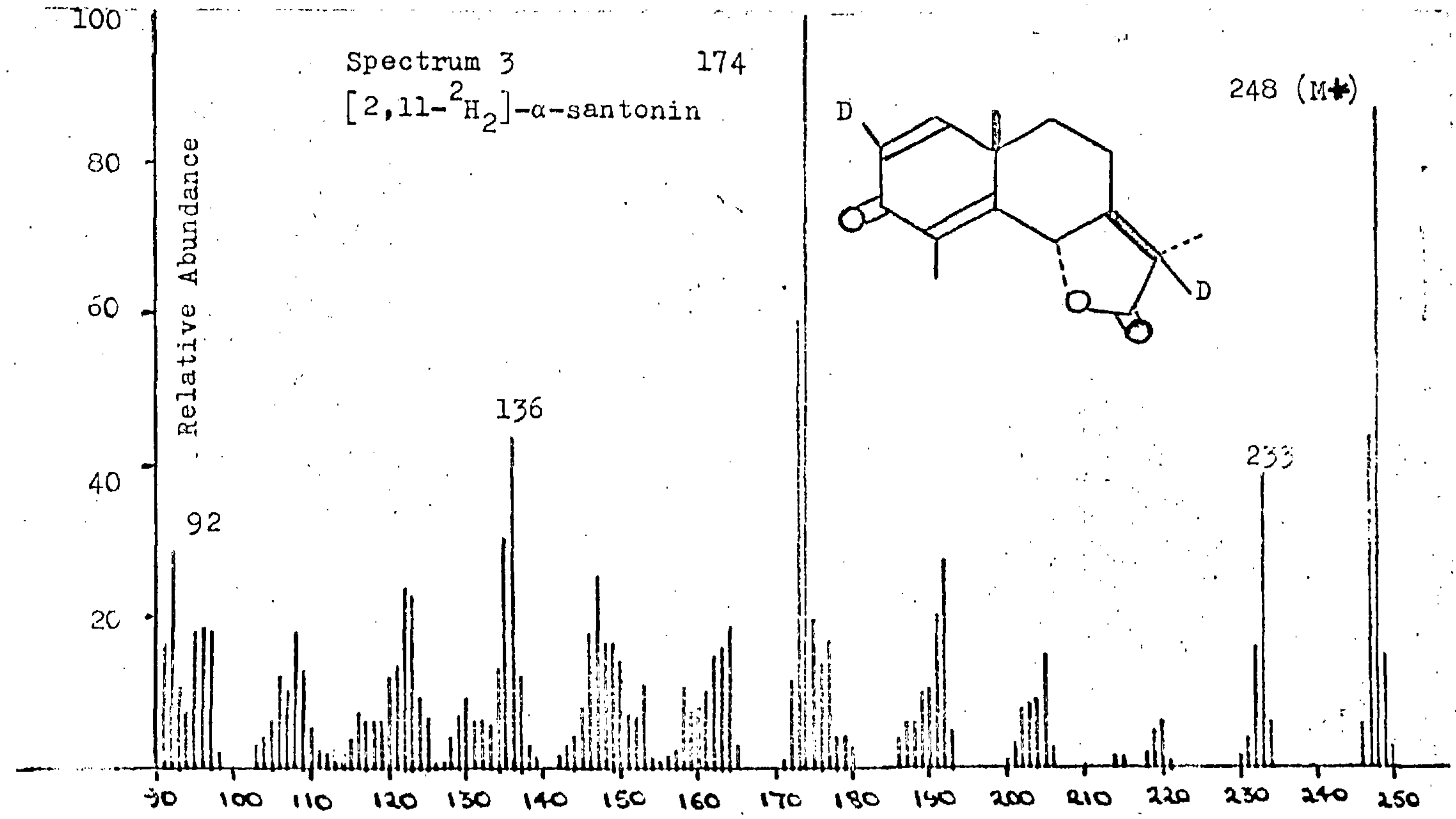
[11-^{2}H$_{1}$]-α-Santonin
M+
247
173
91
232
D
m/e


Spectrum 4
6-epi-α-santonin
246(M+)
Relative Abundance
100
80
60
40
20
91
108
134
135
145
173
203
218
231
80
100
120
140
160
180
200
220
240
m/e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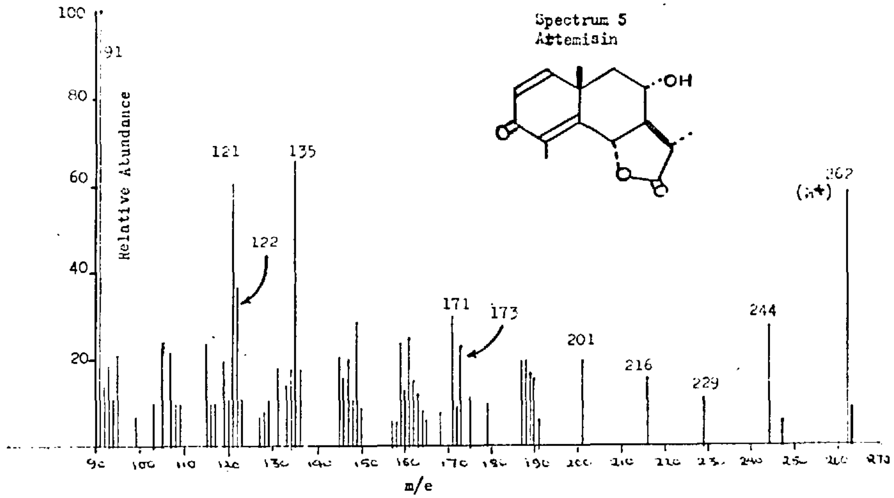
[2,11-²H₂]-α-santonin
174
248 (M+)
D
D
Relative Abundance
100
80
60
40
20
92
136
233
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250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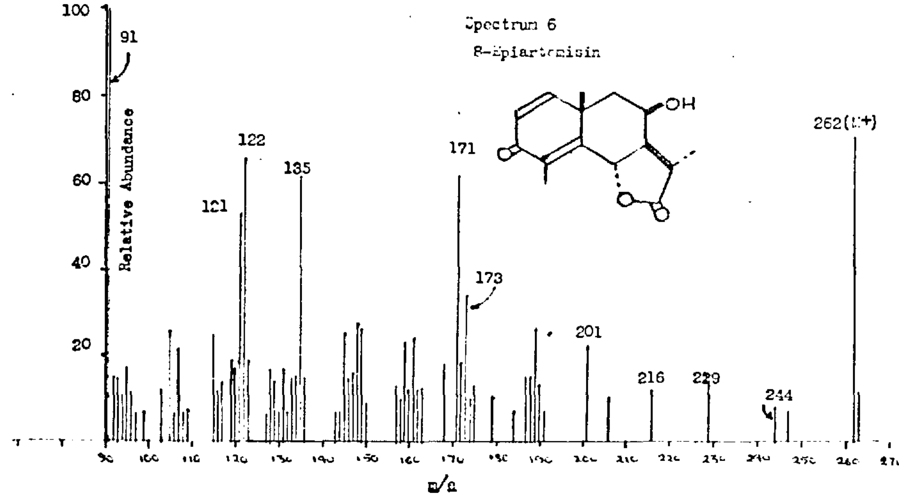
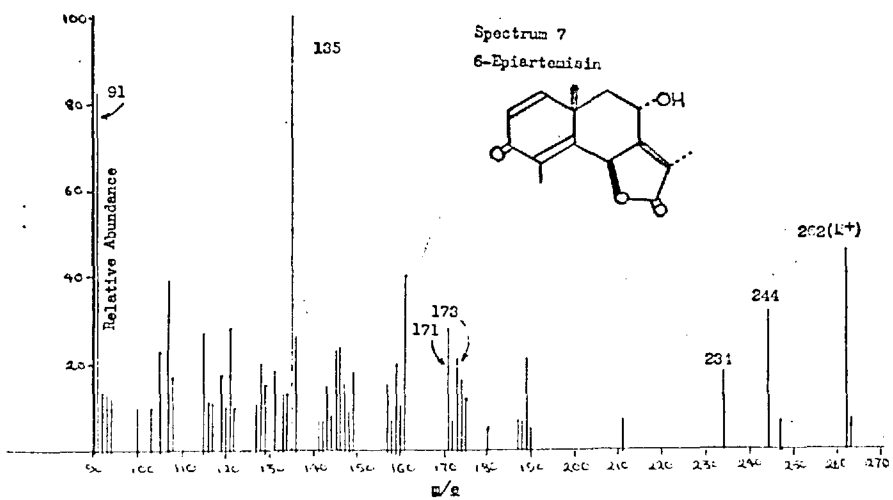
Artemisin
OH
Relative Abundance
m/e
91
121
122
135
171
173
201
216
229
244
262
(M+)


Spectrum 6
8-Epiartemisin
OH
Relative Abundance
m/e
91
121
122
135
171
173
201
216
229
244
262(M+)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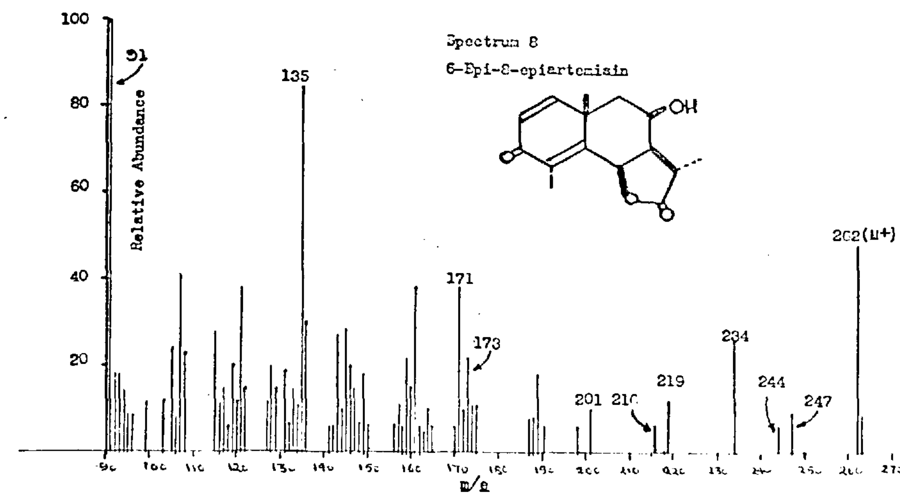
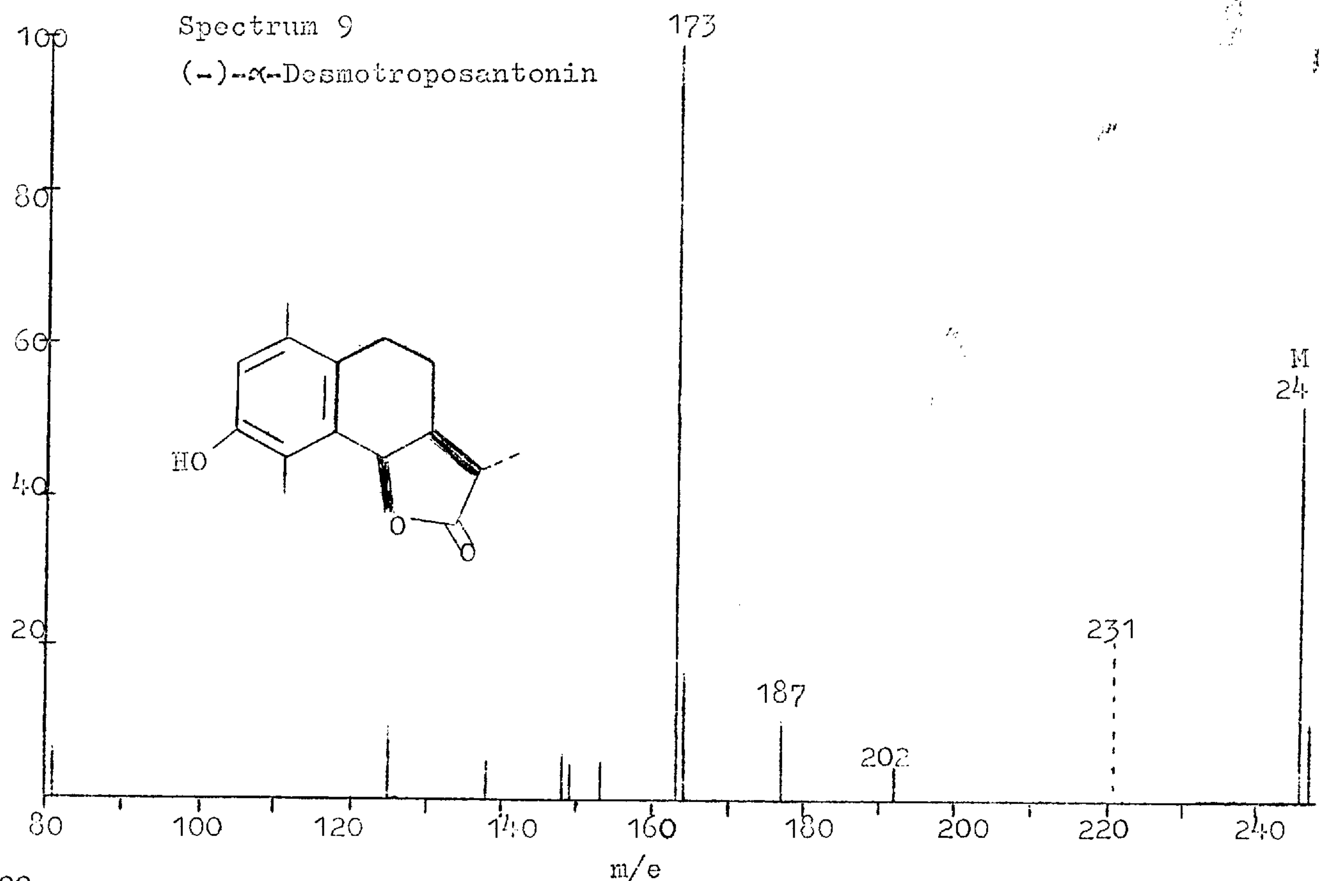
6-Epiartemisin
OH
Relative Abundance
m/e
91
135
171
173
231
244
262(M+)


Spectrum 8
6-Epi-8-epiartemisin
OH
Relative Abundance
m/e
91
135
171
173
201
216
219
234
244
247
262(M+)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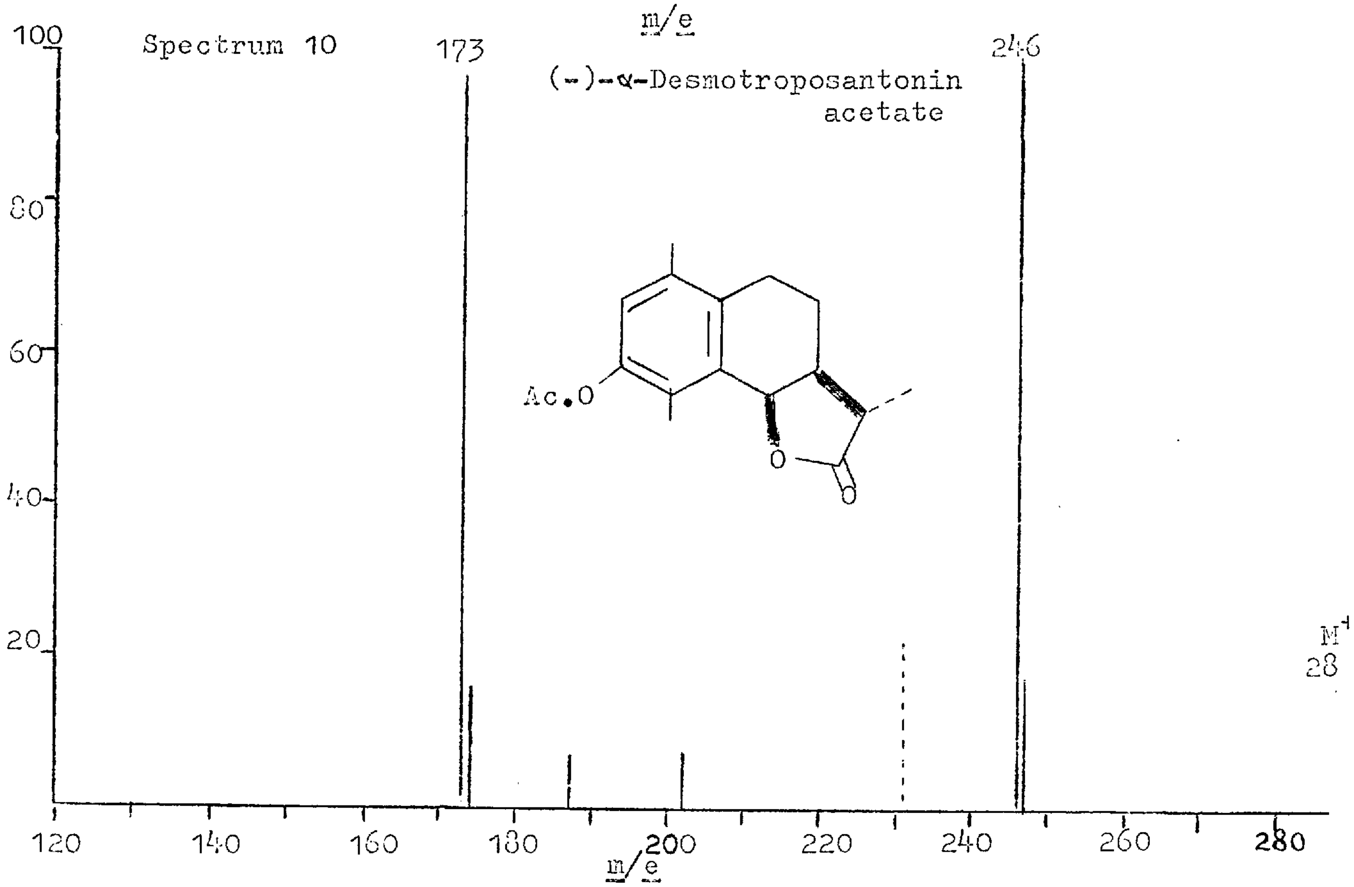
(-)-α-Desmotroposantonin
173
M
24
231
187
202
HO
O
O
100
80
60
40
20
80
100
120
140
160
180
200
220
240
m/e


Spectrum 10
(-)-α-Desmotroposantonin
acetate
173
246
Ac.O
O
O
M+
28
100
80
60
40
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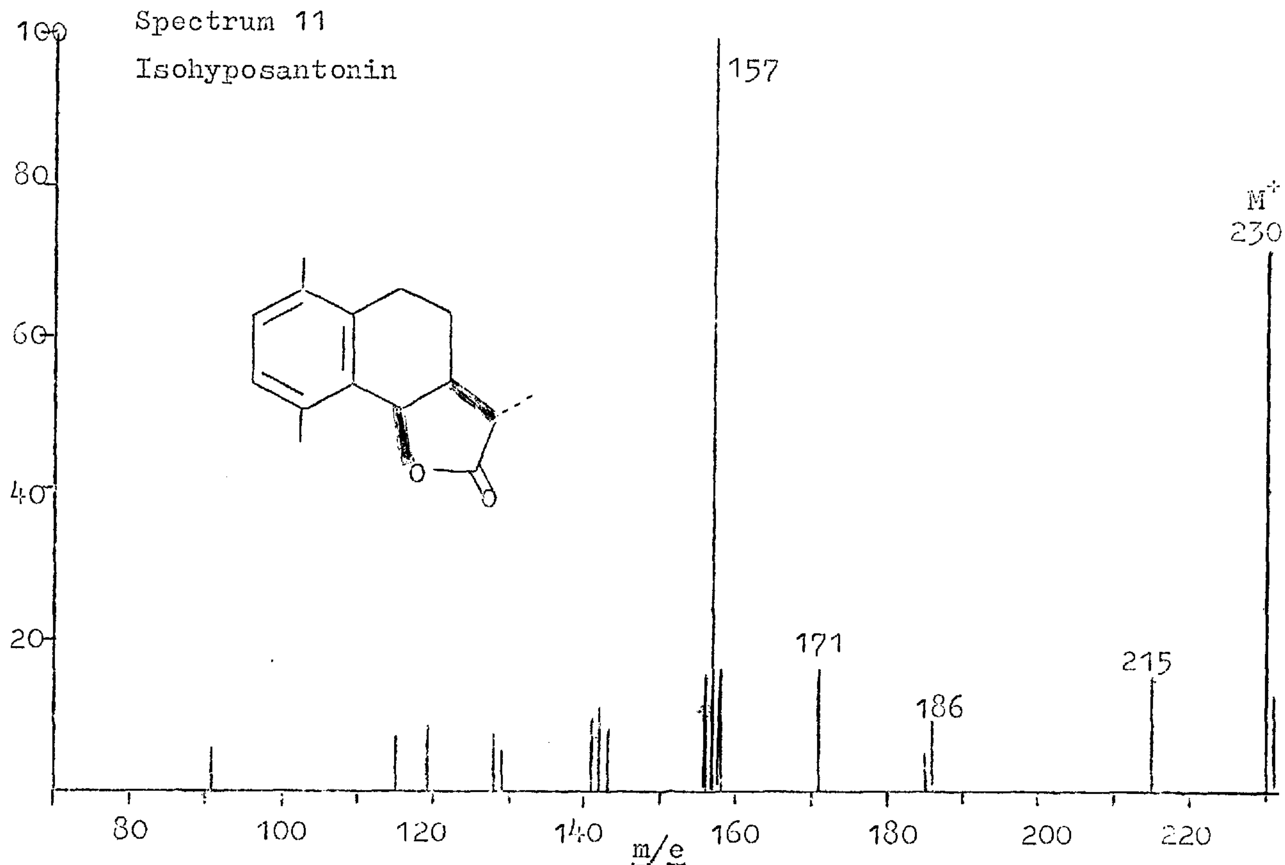
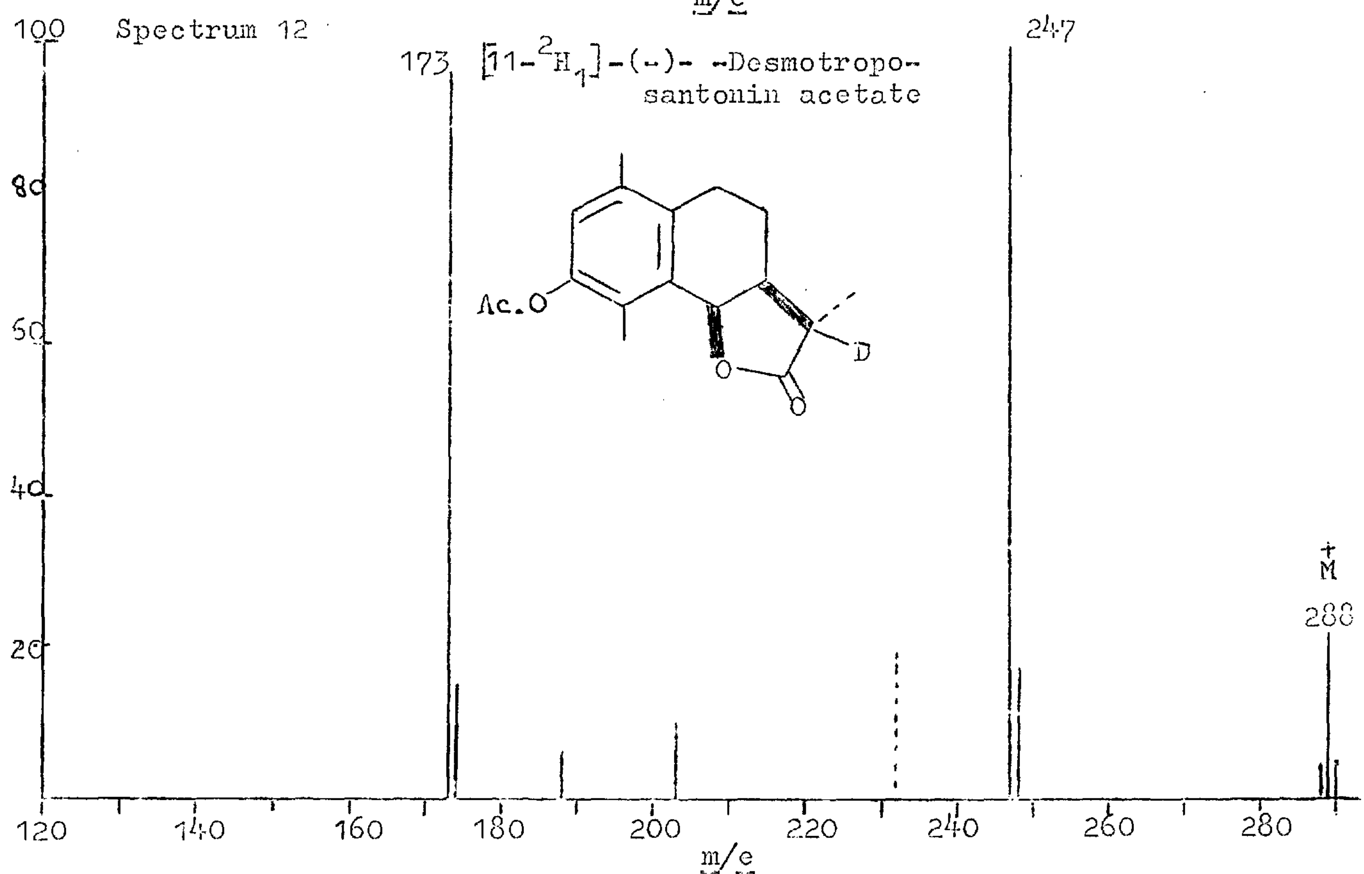
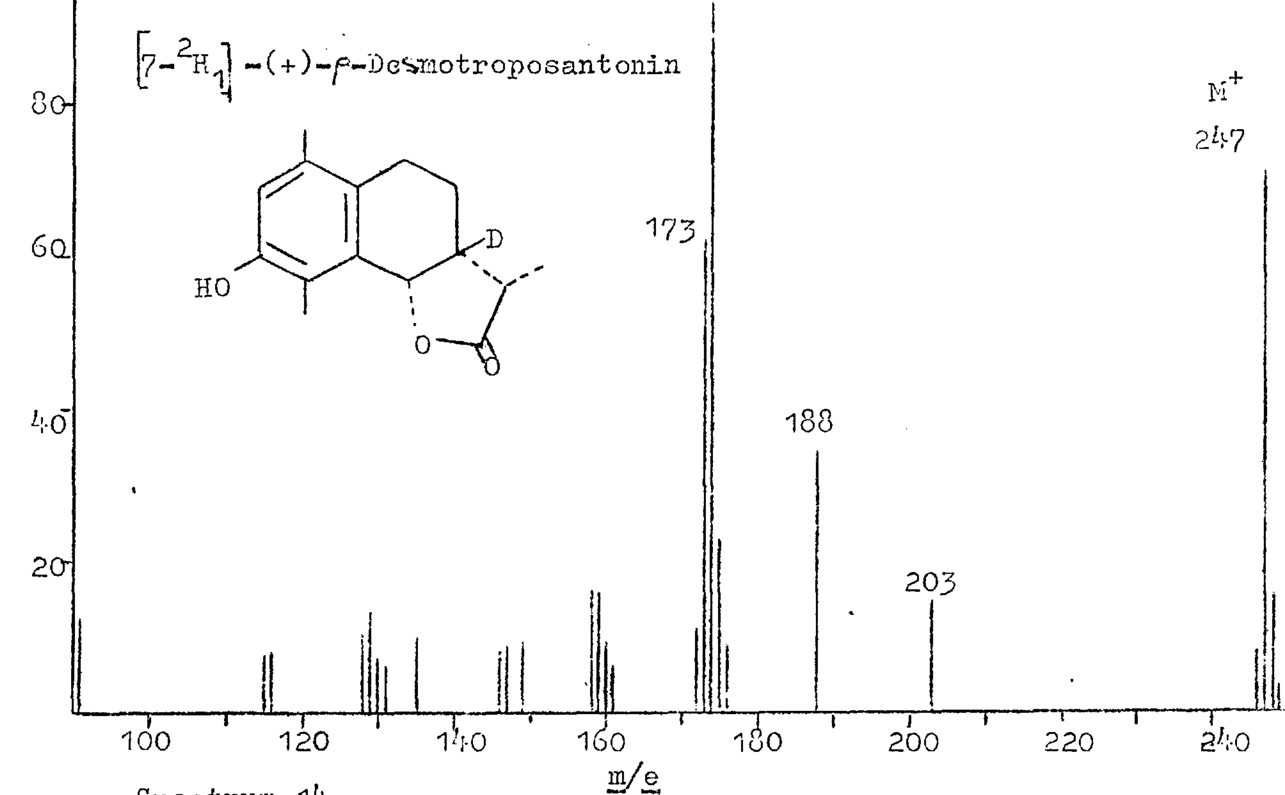
220
240
260
280
m/e

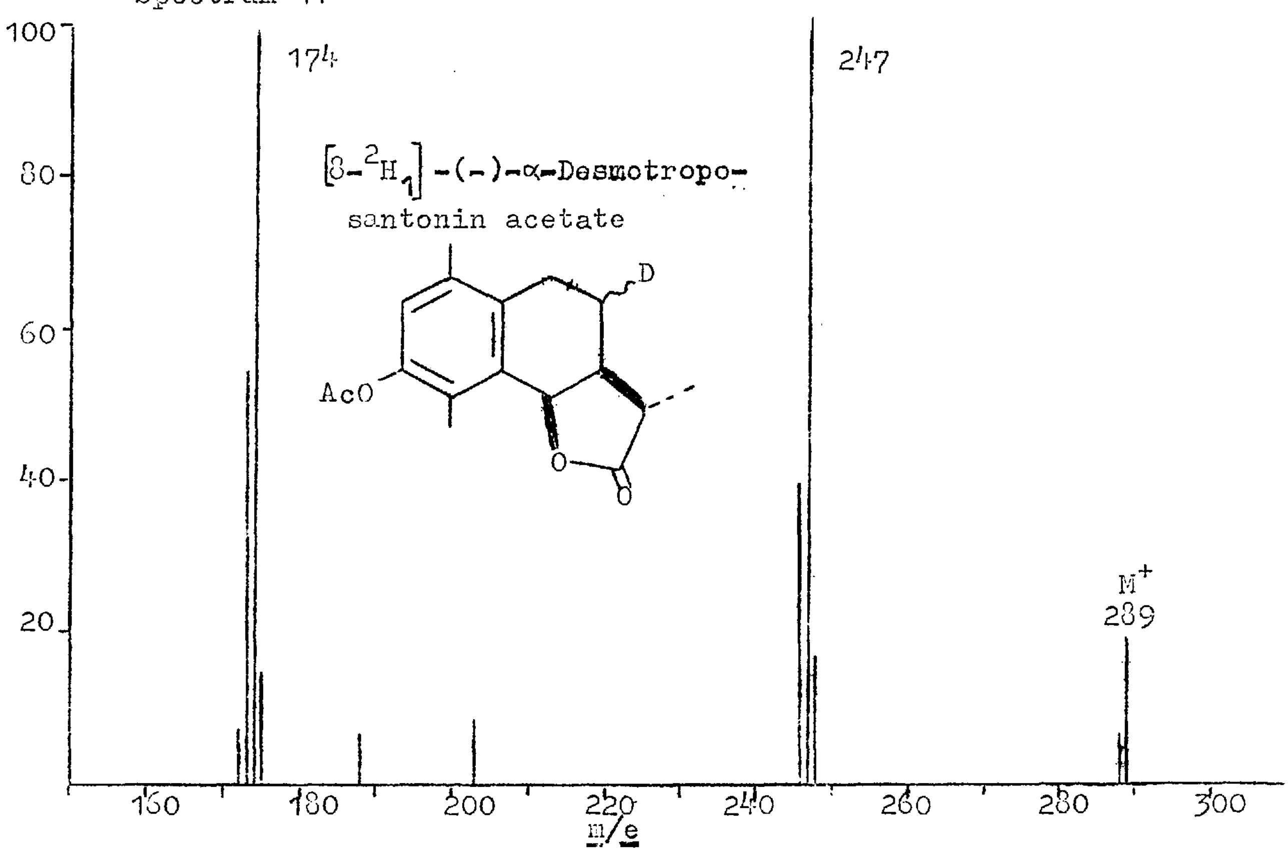

Spectrum 11
Isohyposantonin
100
80
60
40
20
157
M+
230
171
215
186
O
O
80
100
120
140
160
180
200
220
m/e

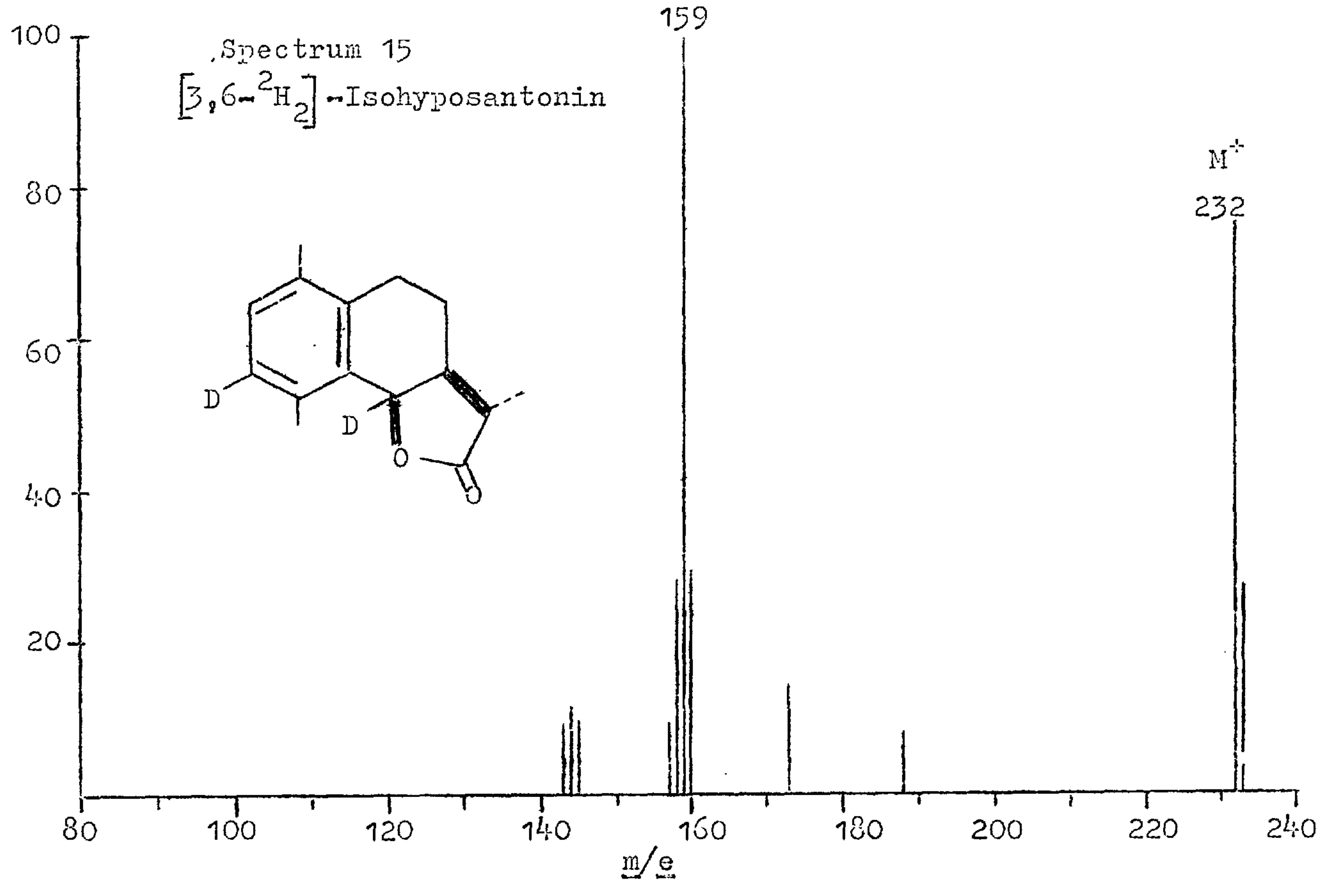

100
Spectrum 12
173
[11-²H₁]-(-)- -Desmotroposantonin acetate
247
80
60
40
20
Ac.O
D
O
O
M+
288
120
140
160
180
200
220
240
260
280
m/e

Spectrum 13



Spectrum 14




Spectrum 15
[3,6-$^2H_2$]-Isohyposantonin
159
M⁺
232
D
D
O
O
100
80
60
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80
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140
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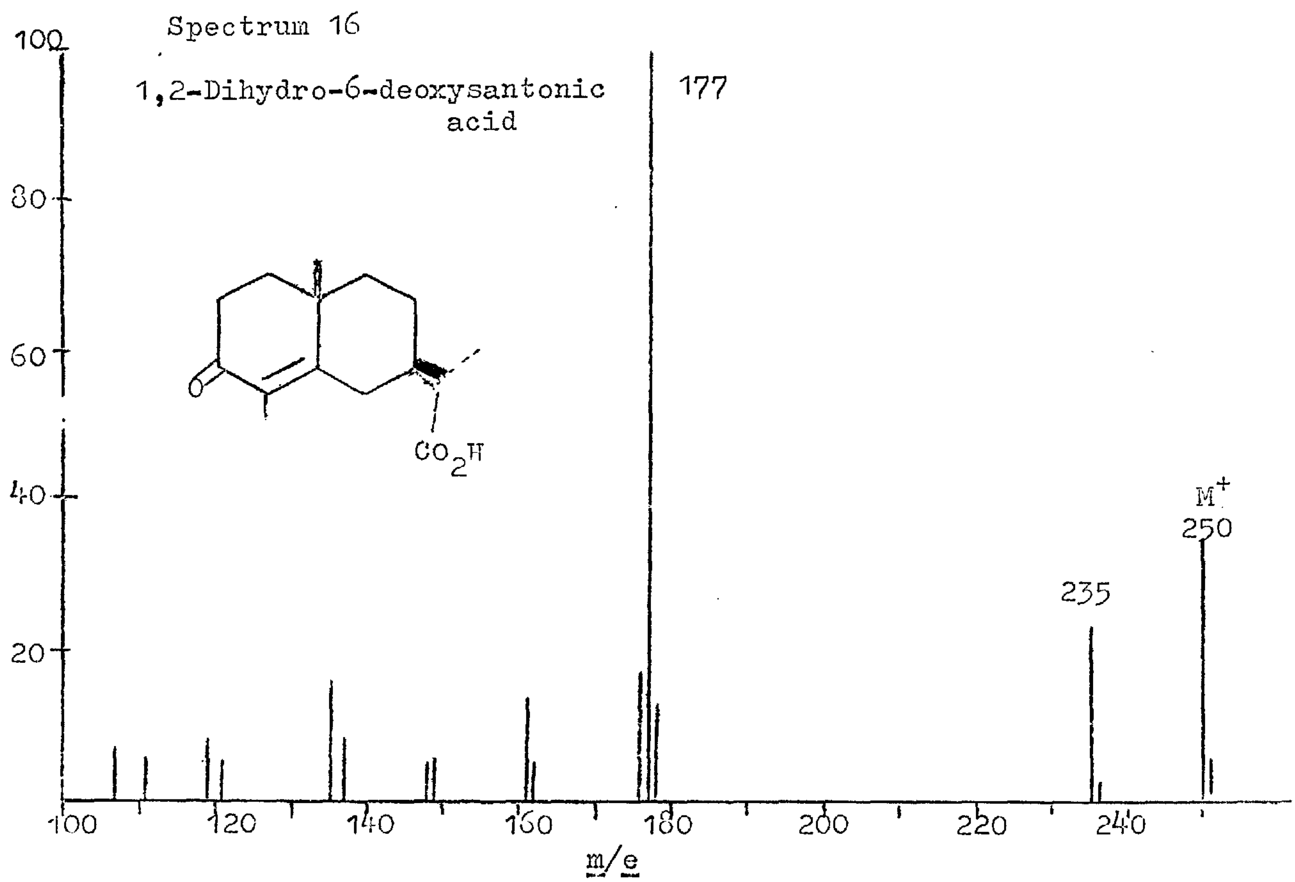
180
200
220
240
m/e


Spectrum 16
1,2-Dihydro-6-deoxysantonic acid
177
O
CO_2H
M⁺
250
235
100
80
60
40
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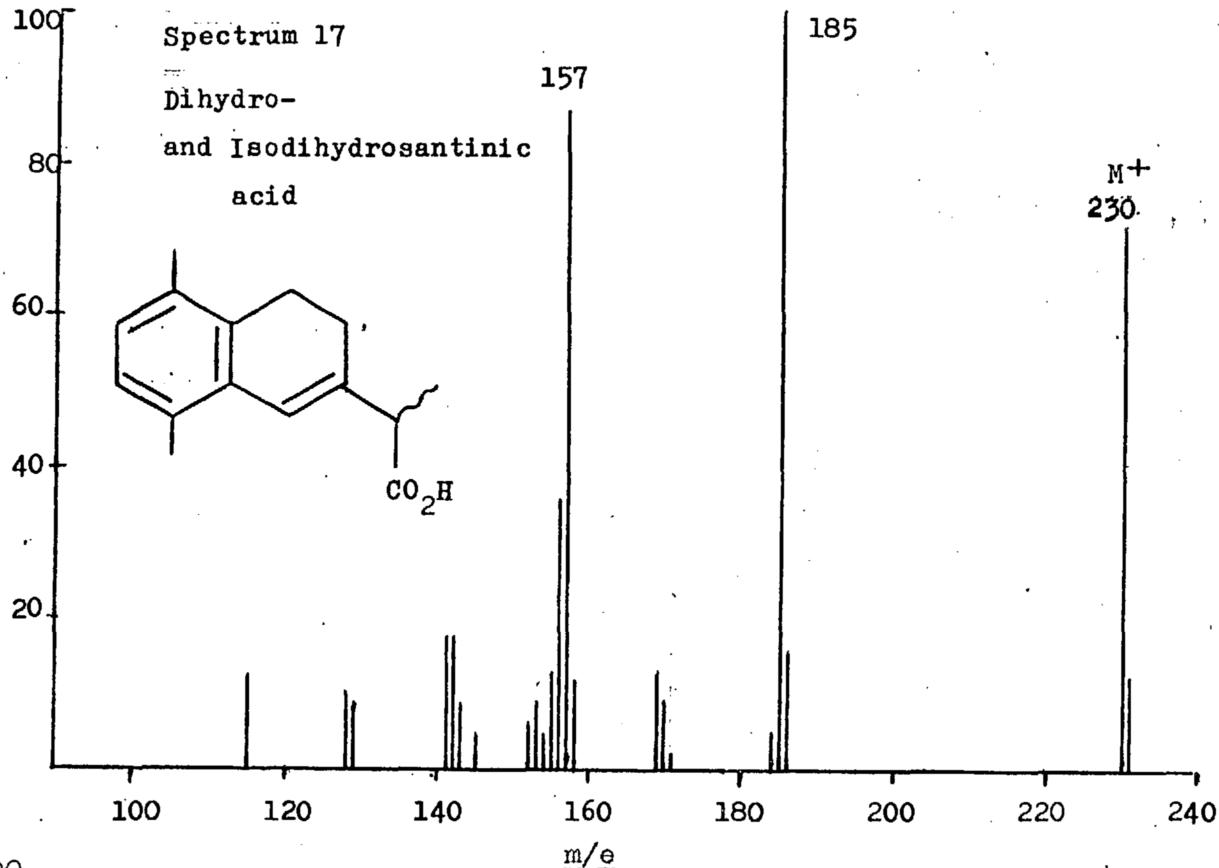
180
200
220
240
m/e


Spectrum 17
Dihydro-
and Isodihydrosantinic
acid
CO_2H
185
157
M+
230
100
80
60
40
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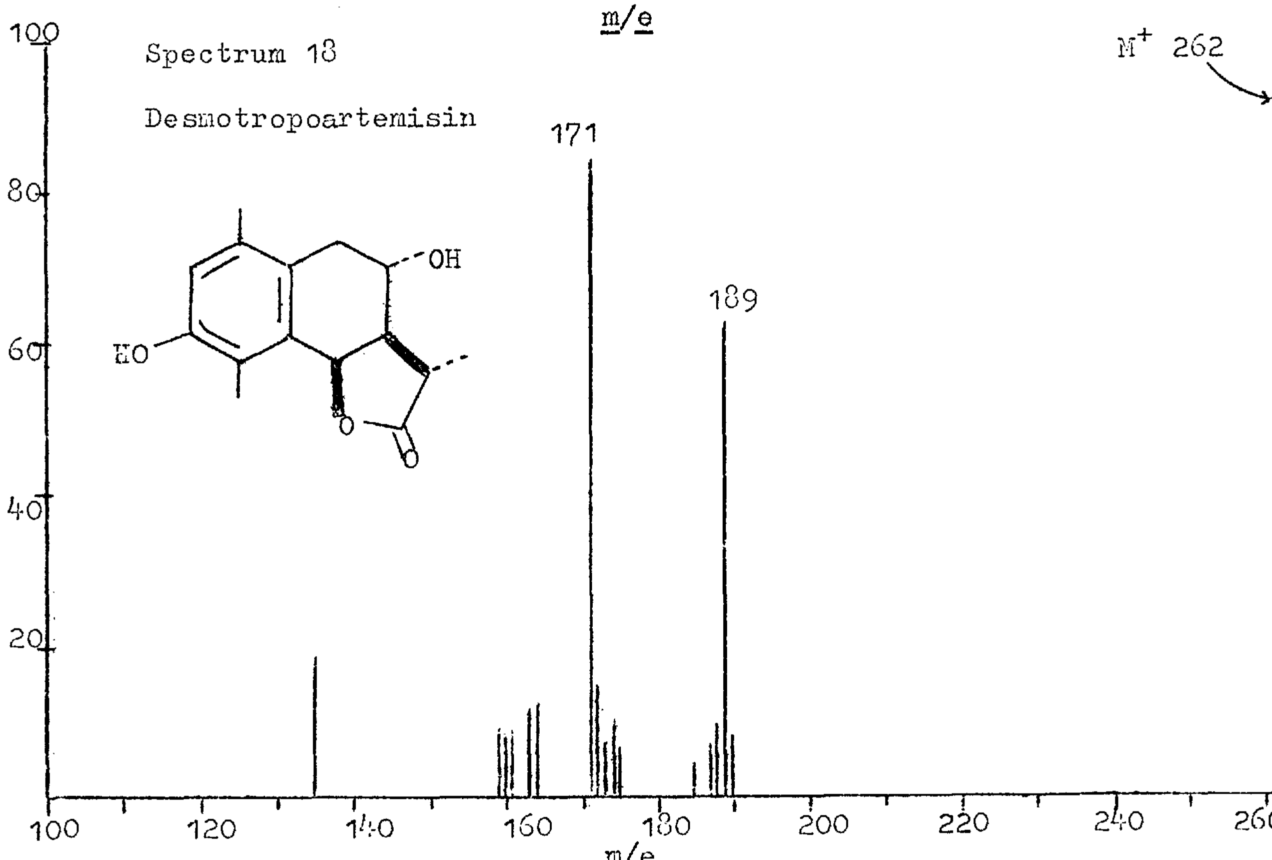
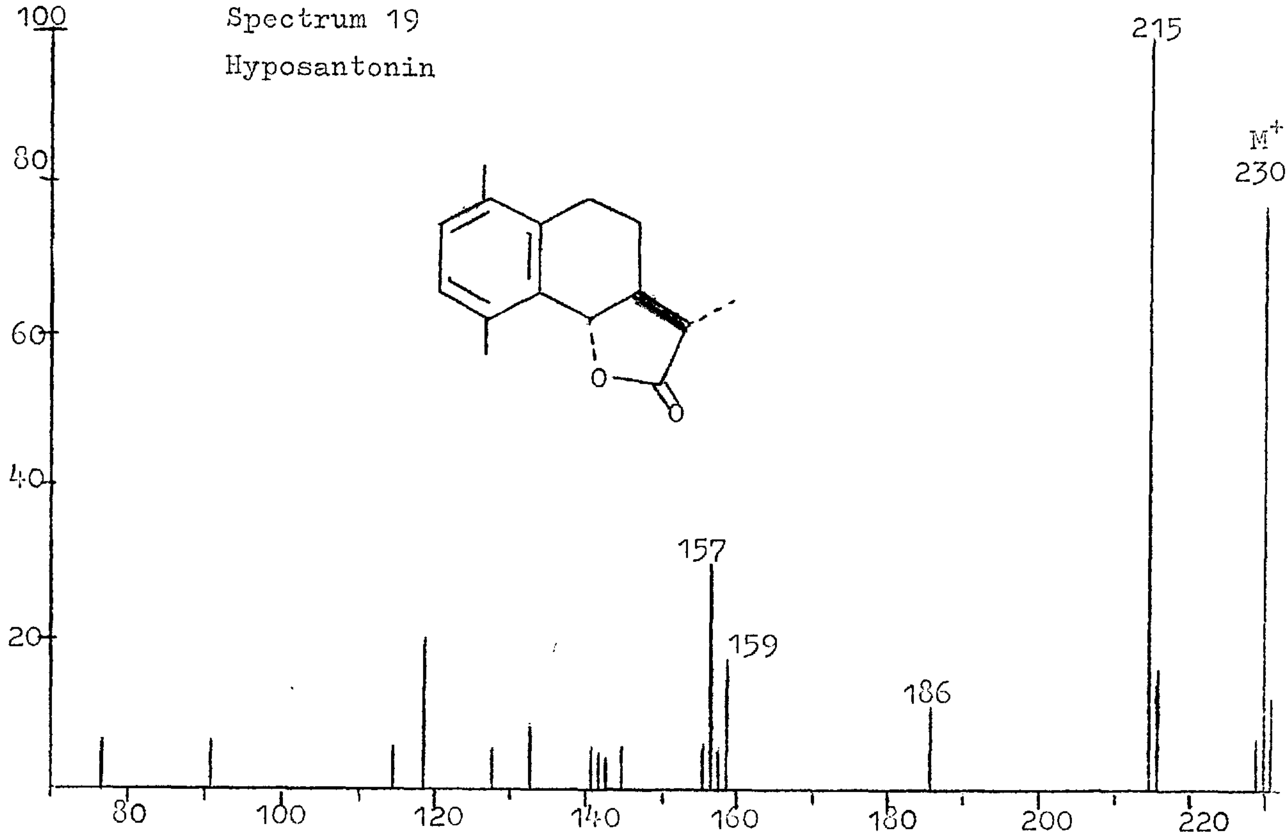
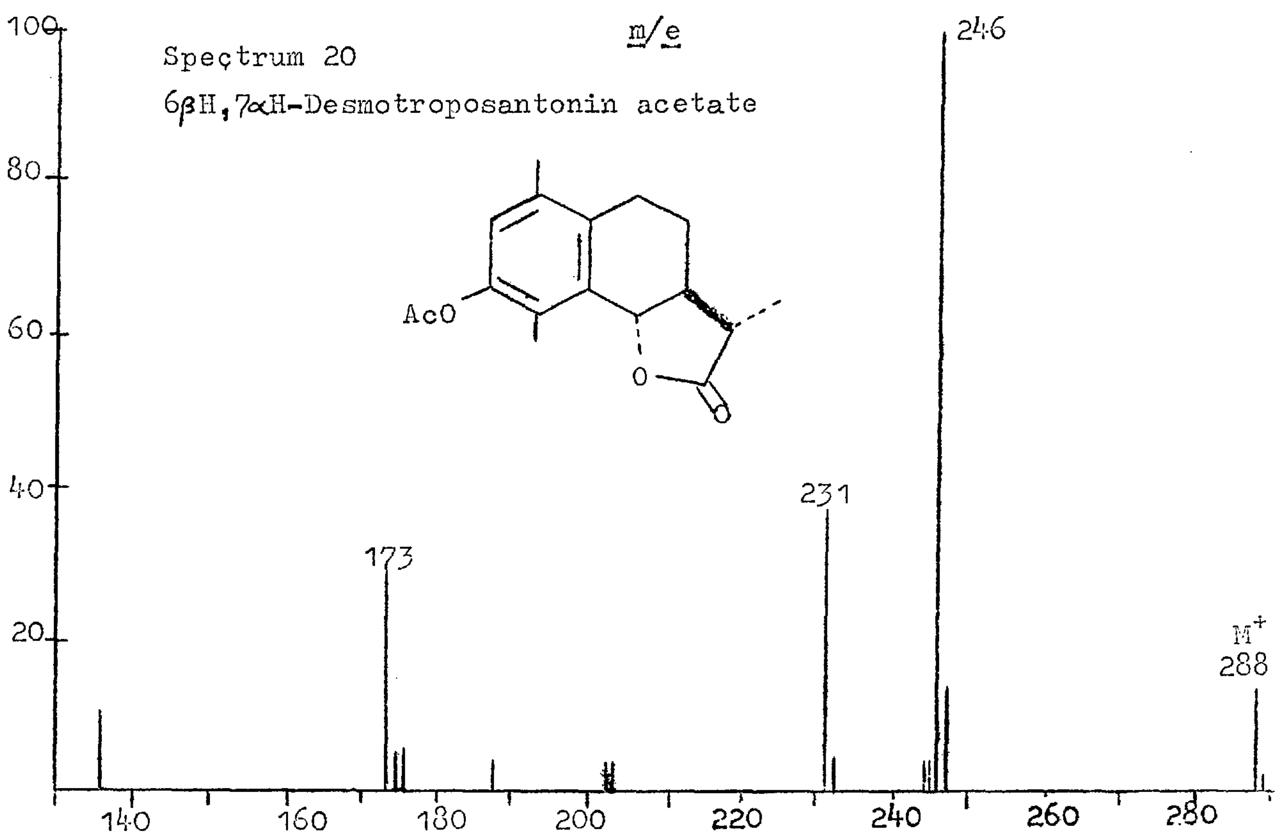
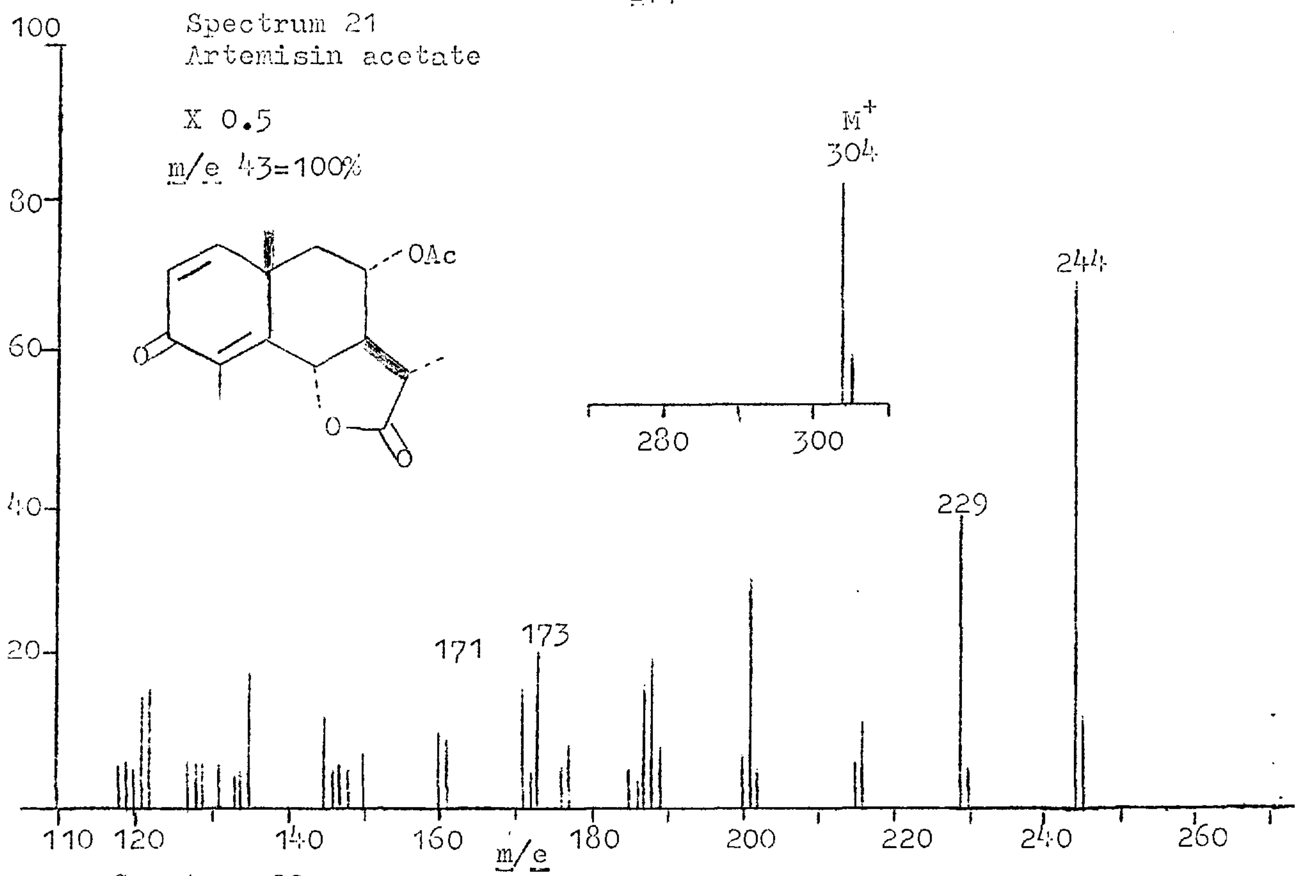
180
200
220
240
m/e

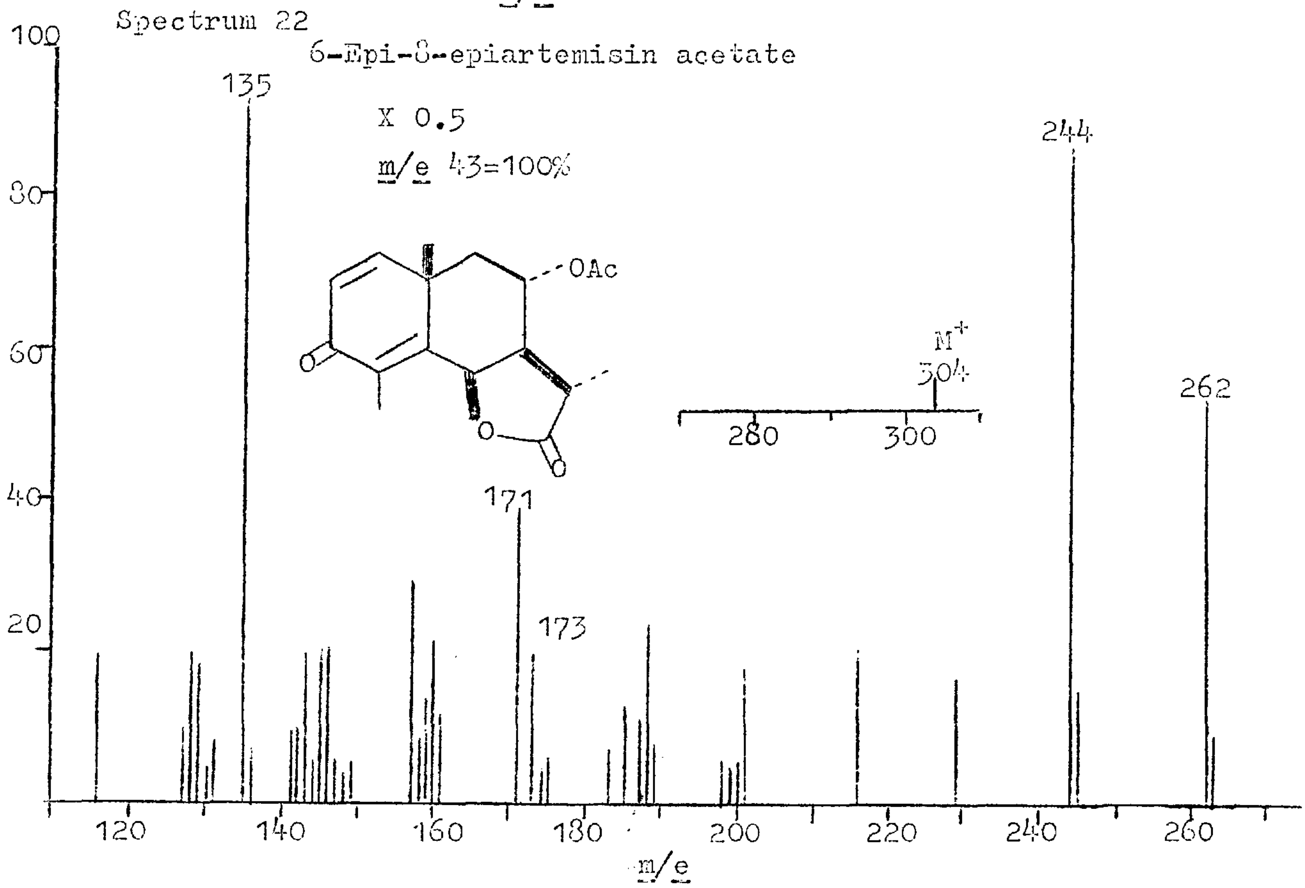

Spectrum 18
Desmotropoartemisin
OH
HO
O
O
M+ 262
171
189
100
80
60
40
20
100
120
140
160
180
200
220
240
260
m/e

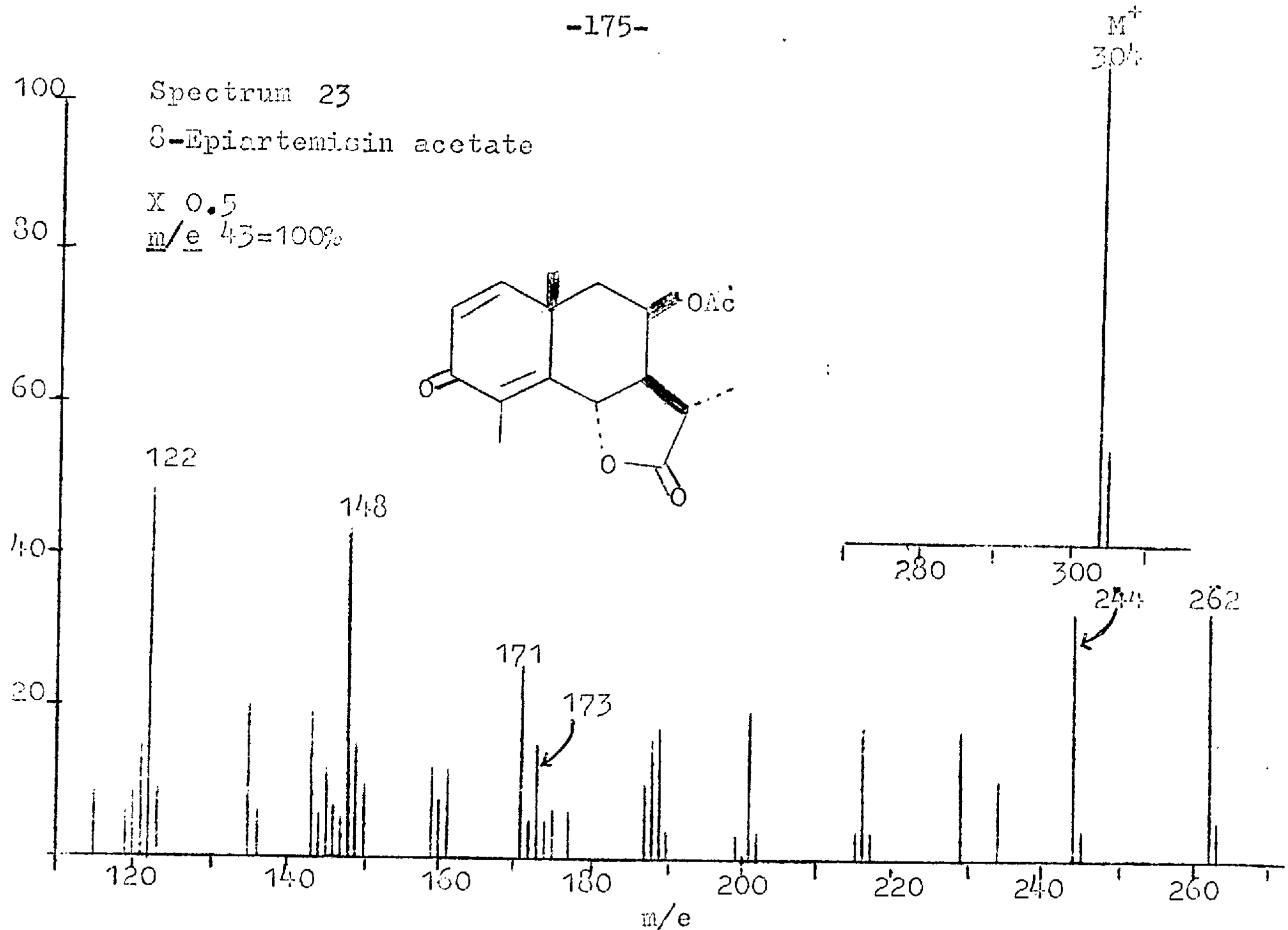

Spectrum 19
Hyposantonin
100
80
60
40
20
O
O
157
159
186
215
M+
230
80
100
120
140
160
180
200
220

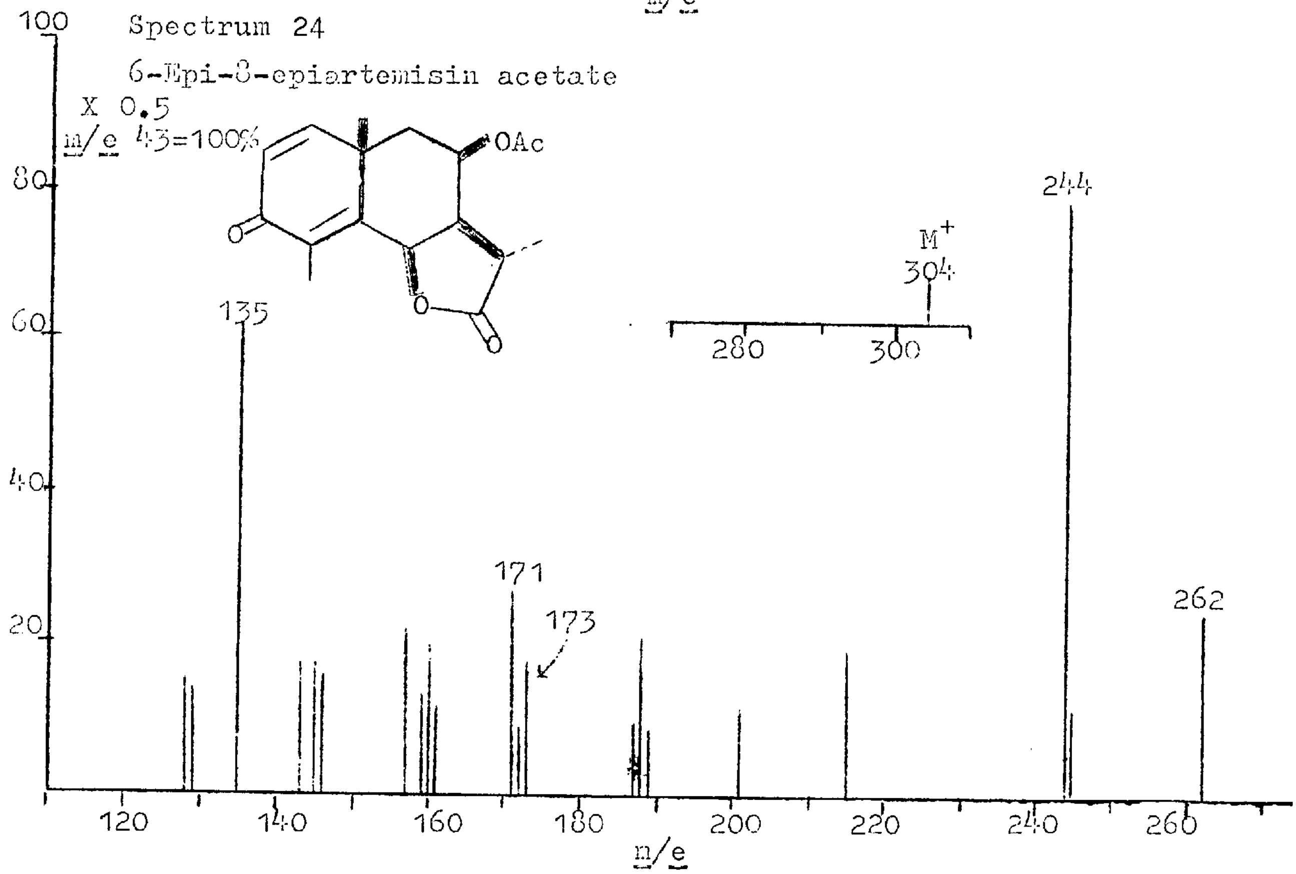
m/e

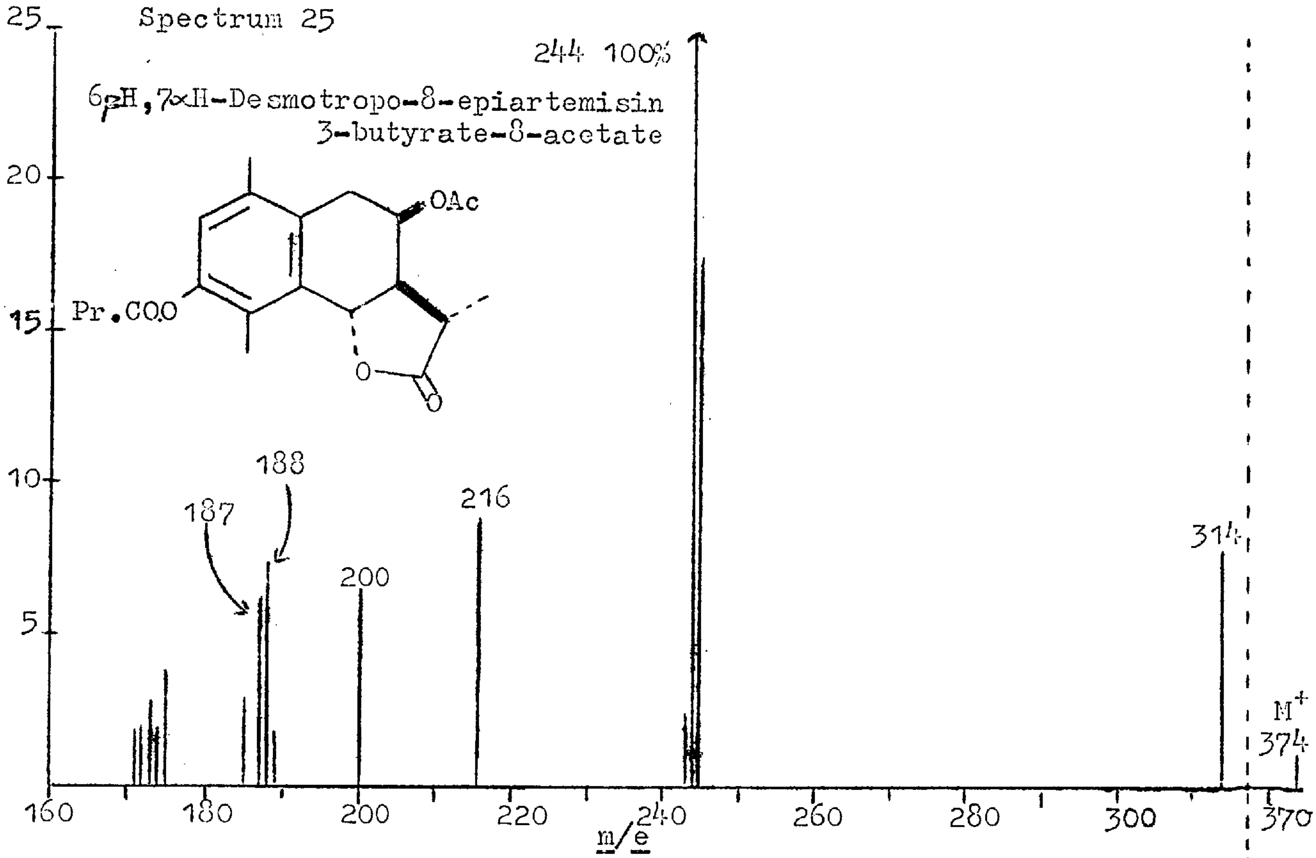

Speçtrum 20
6βH,7αH-Desmotroposantonin acetate
100
80
60
40
20
AcO
O
O
173
231
246
M+
288
140
160
180
200
220
240
260
280

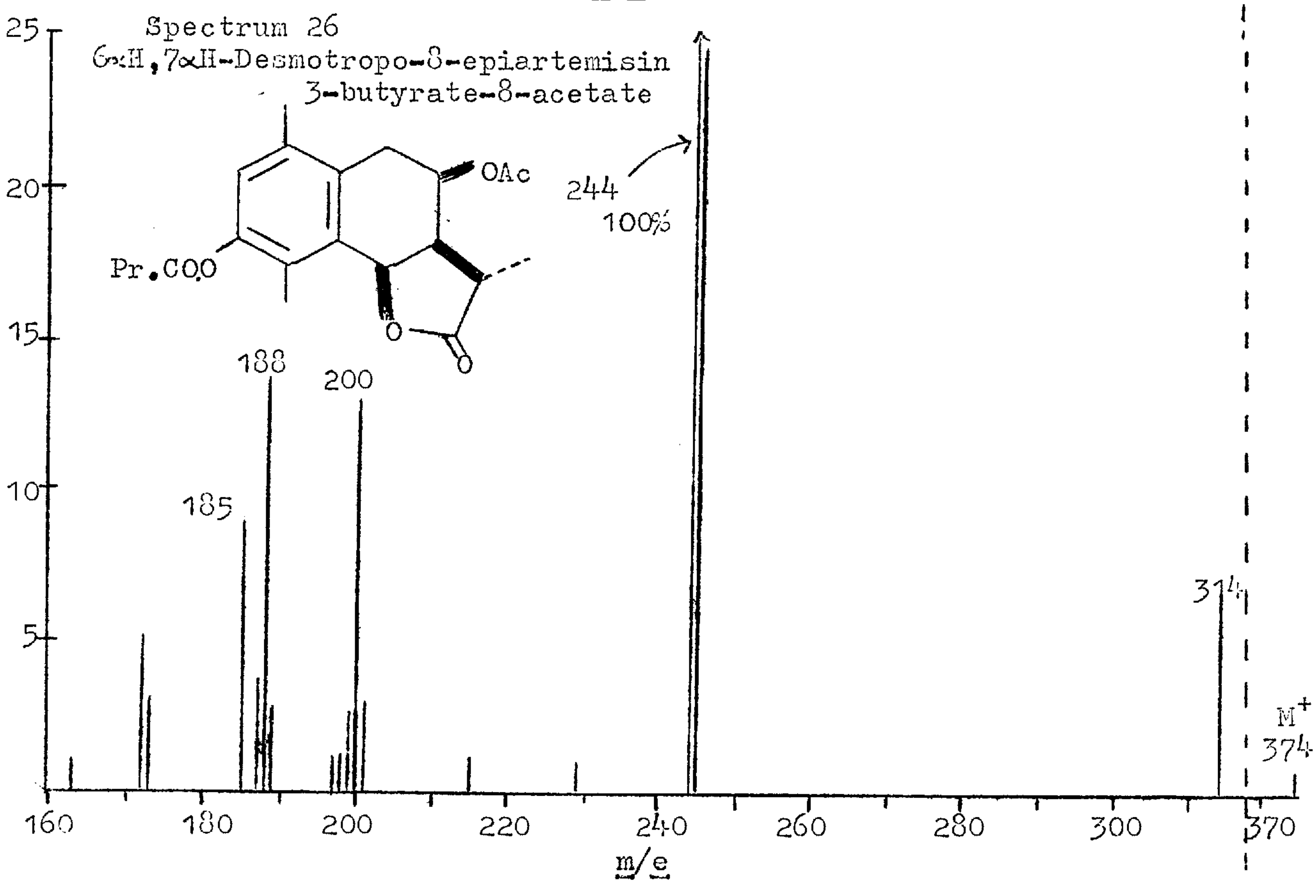

Spectrum 21
Artemisin acetate
X 0.5
m/e 43=100%
OAc
O
M+
304
280
300
244
229
171
173
100
80
60
40
20
110
120
140
160
180
200
220
240
260
m/e

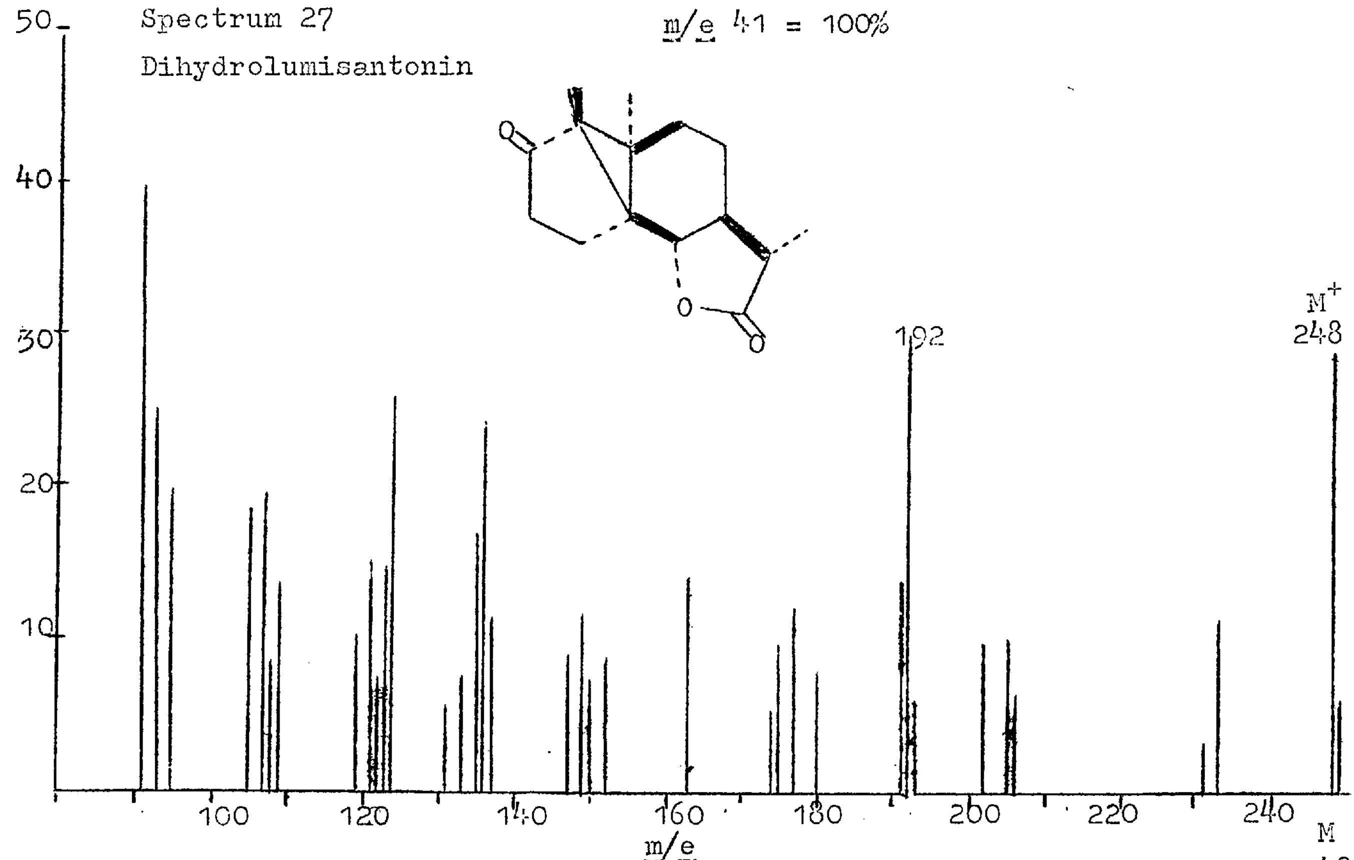

Spectrum 22
6-Epi-8-epiartemisin acetate
135
X 0.5
m/e 43=100%
244
OAc
O
M+
304
280
300
262
171
173
100
80
60
40
20
120
140
160
180
200
220
240
260
m/e

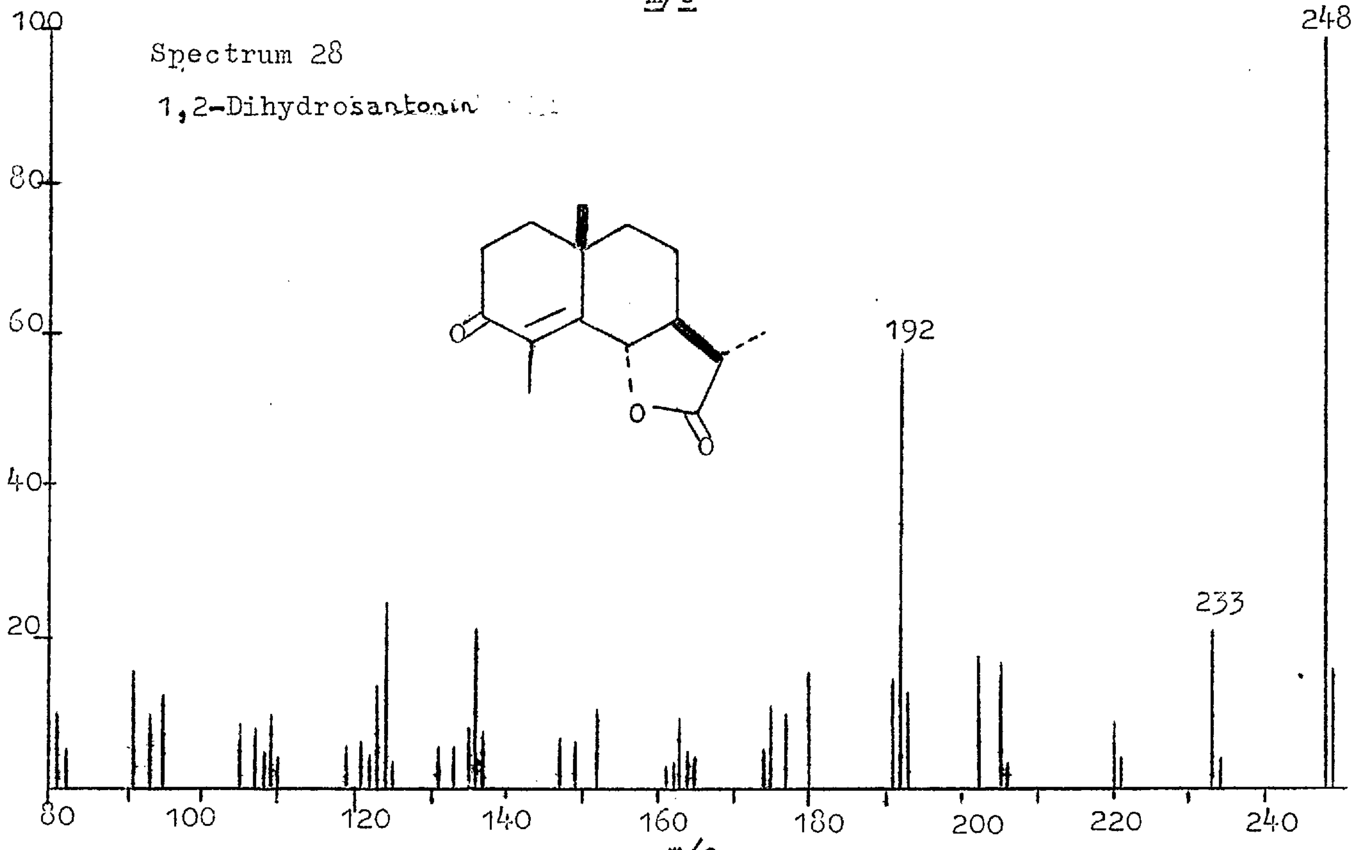

Spectrum 23
8-Epiartemisin acetate
X 0.5
m/e 43=100%
OAc
O
O
O
M+
304
280
300
122
148
171
173
244
262
100
80
60
40
20
120
140
160
180
200
220
240
260
m/e

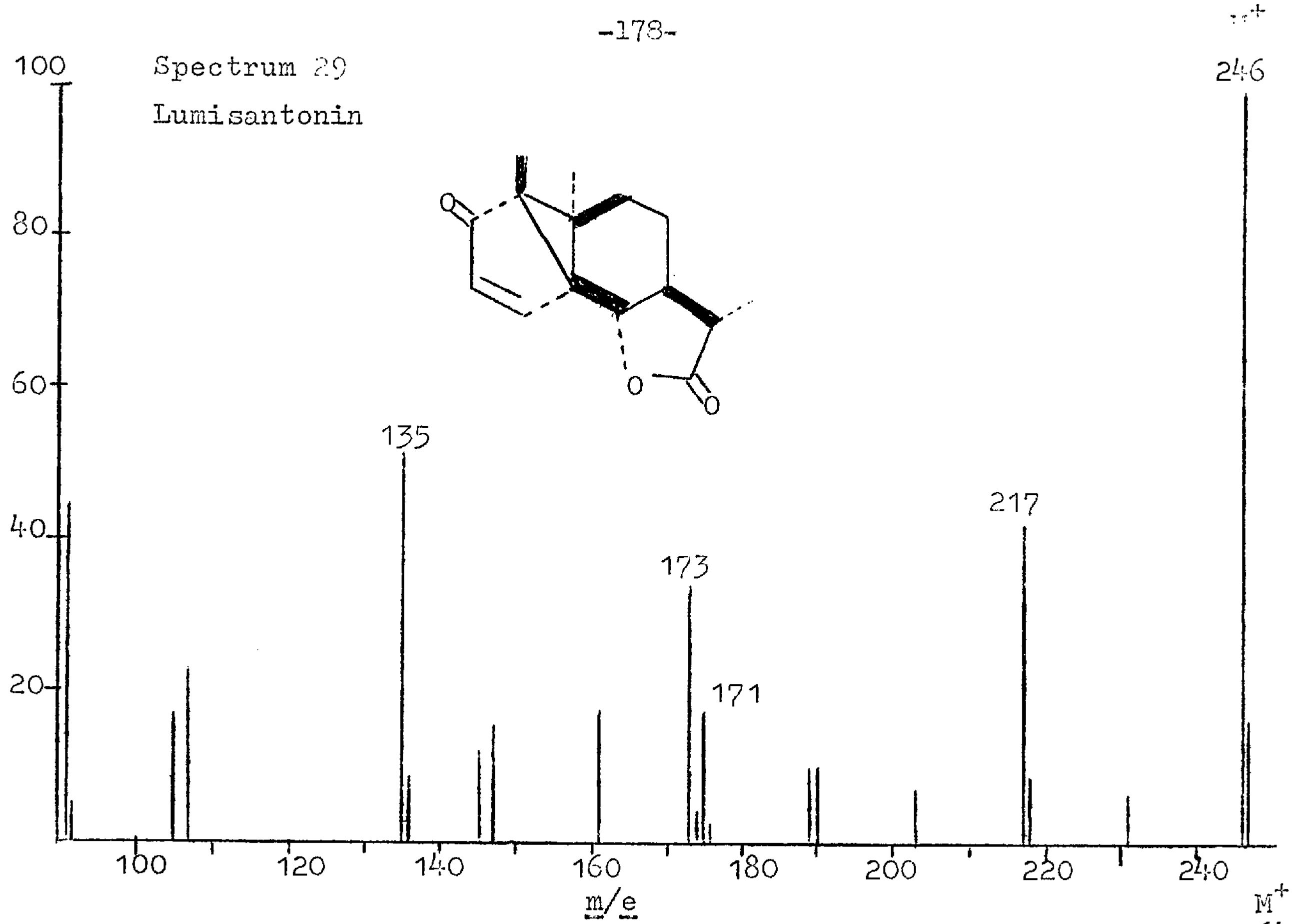

Spectrum 24
6-Epi-8-epiartemisin acetate
X 0.5
m/e 43=100%
OAc
O
O
O
M+
304
280
300
244
135
171
173
262
100
80
60
40
20
120
140
160
180
200
220
240
260
m/e


Spectrum 25
6βH,7αH-Desmotropo-8-epiartemisin
3-butyrate-8-acetate
OAc
Pr.COO
O
O
244 100%
188
187
216
200
314
M+
374
25
20
15
10
5
160
180
200
220
240
260
280
300
370
m/e

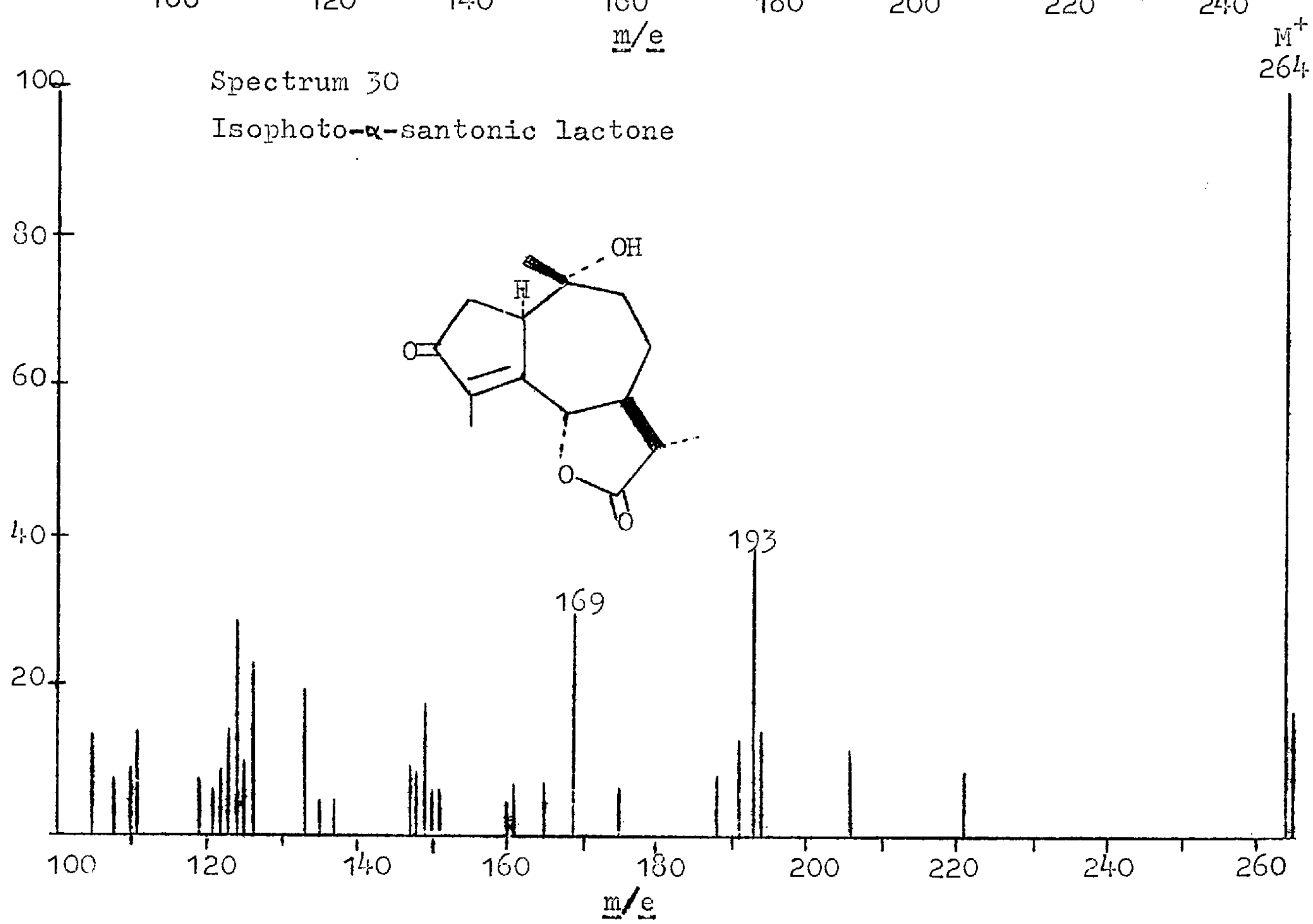

Spectrum 26
6αH,7αH-Desmotropo-8-epiartemisin
3-butyrate-8-acetate
OAc
Pr.COO
O
O
244
100%
188
200
185
314
M+
374
25
20
15
10
5
160
180
200
220
240
260
280
300
370
m/e


Spectrum 27
Dihydrolumisantonin
m/e 41 = 100%
50
40
30
20
10
O
O
O
192
M+
248
100
120
140
160
180
200
220
240
m/e

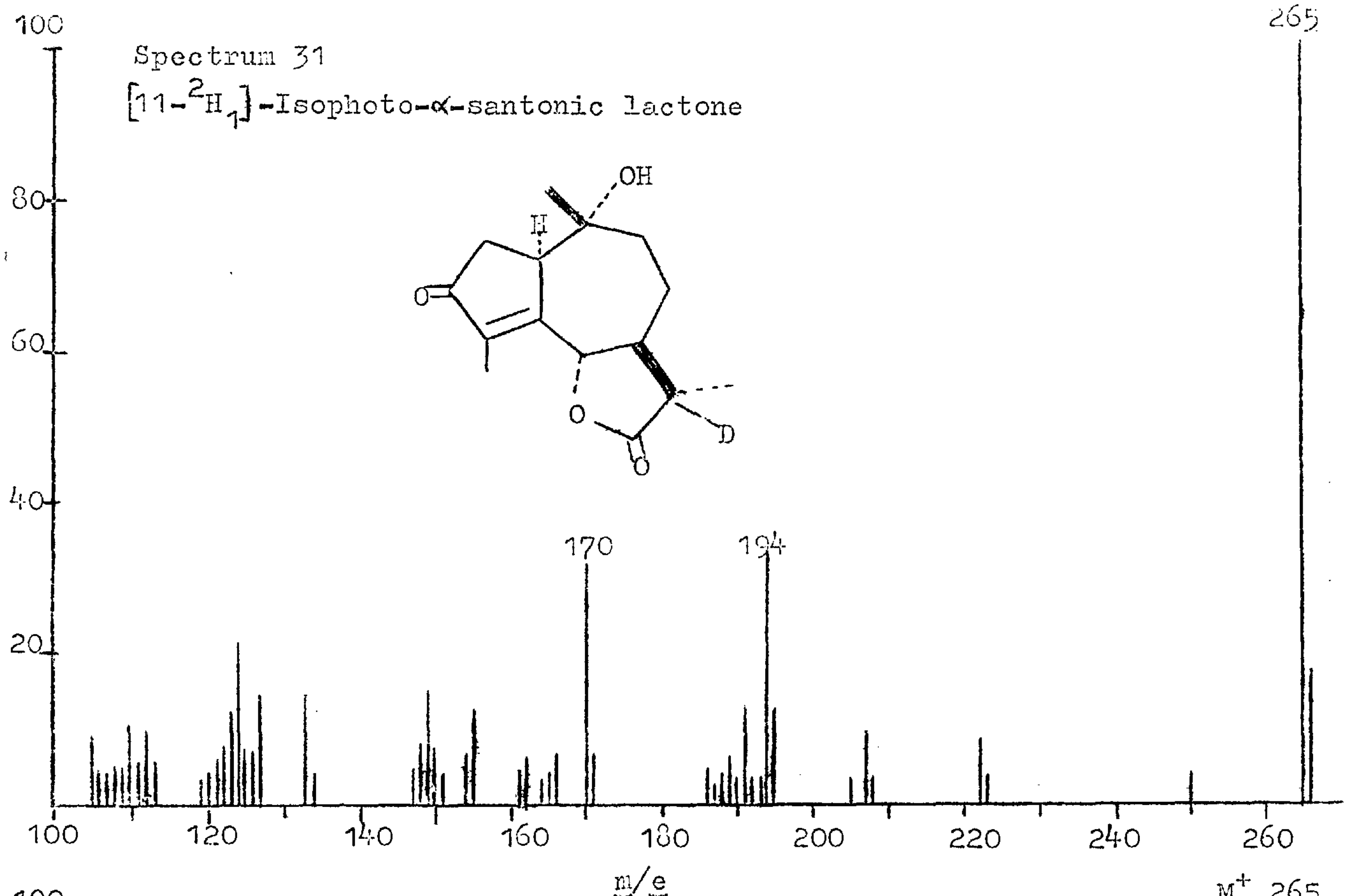

Spectrum 28
1,2-Dihydrosantonin
100
80
60
40
20
O
O
O
192
233
M
248
80
100
120
140
160
180
200
220
240
m/e

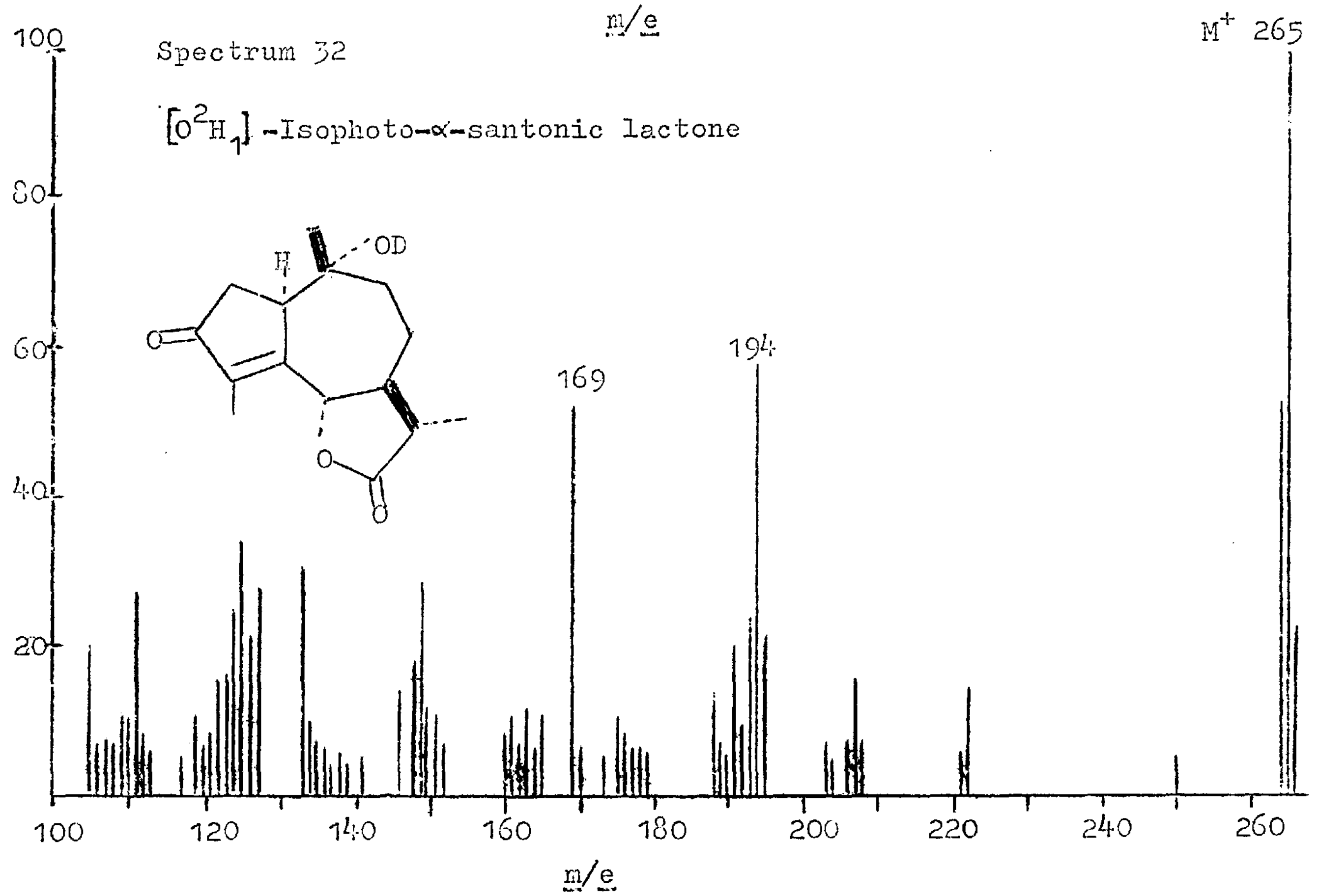


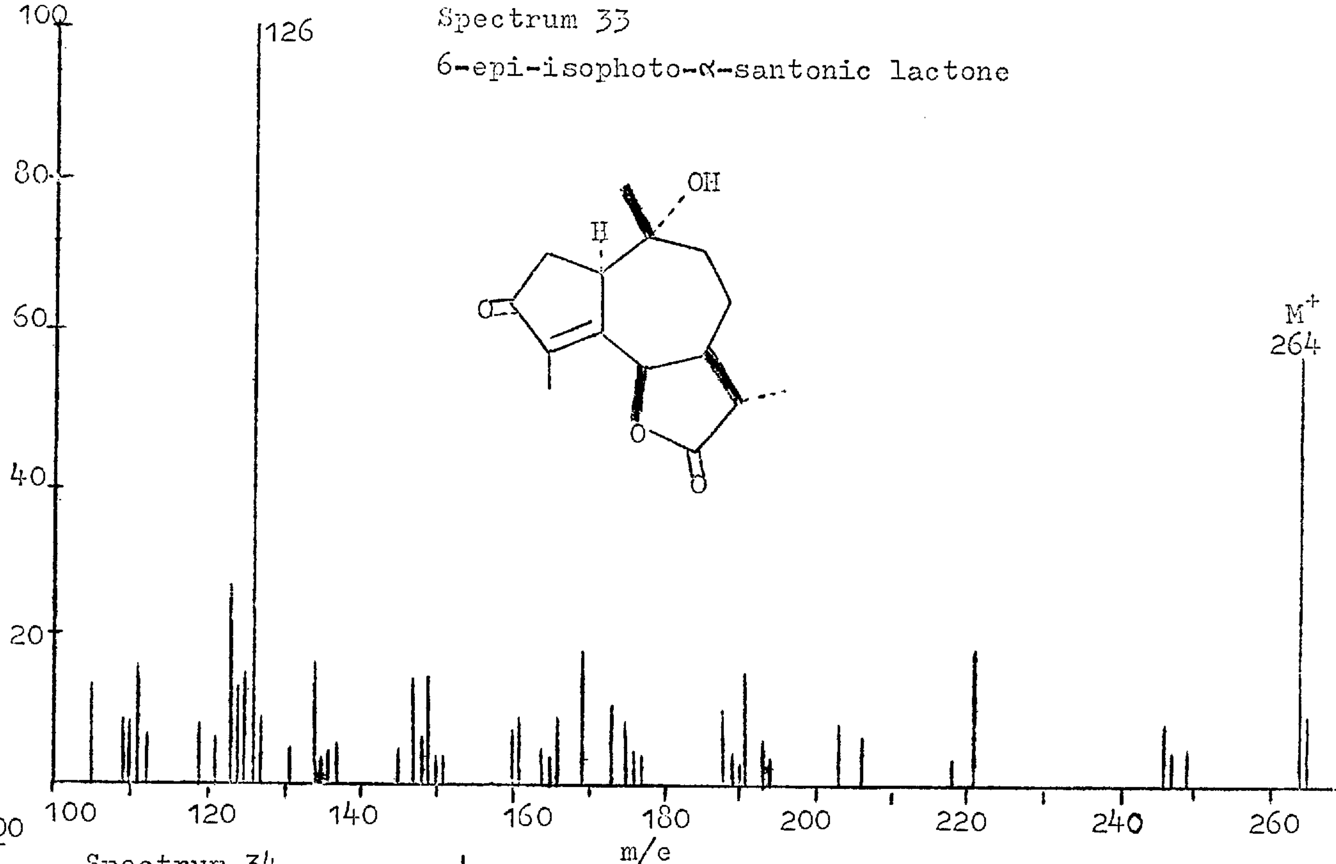
M+
246
100
Spectrum 29
Lumisantonin
80
60
135
217
40
173
20
171
100
120
140
160
180
200
220
240
m/e

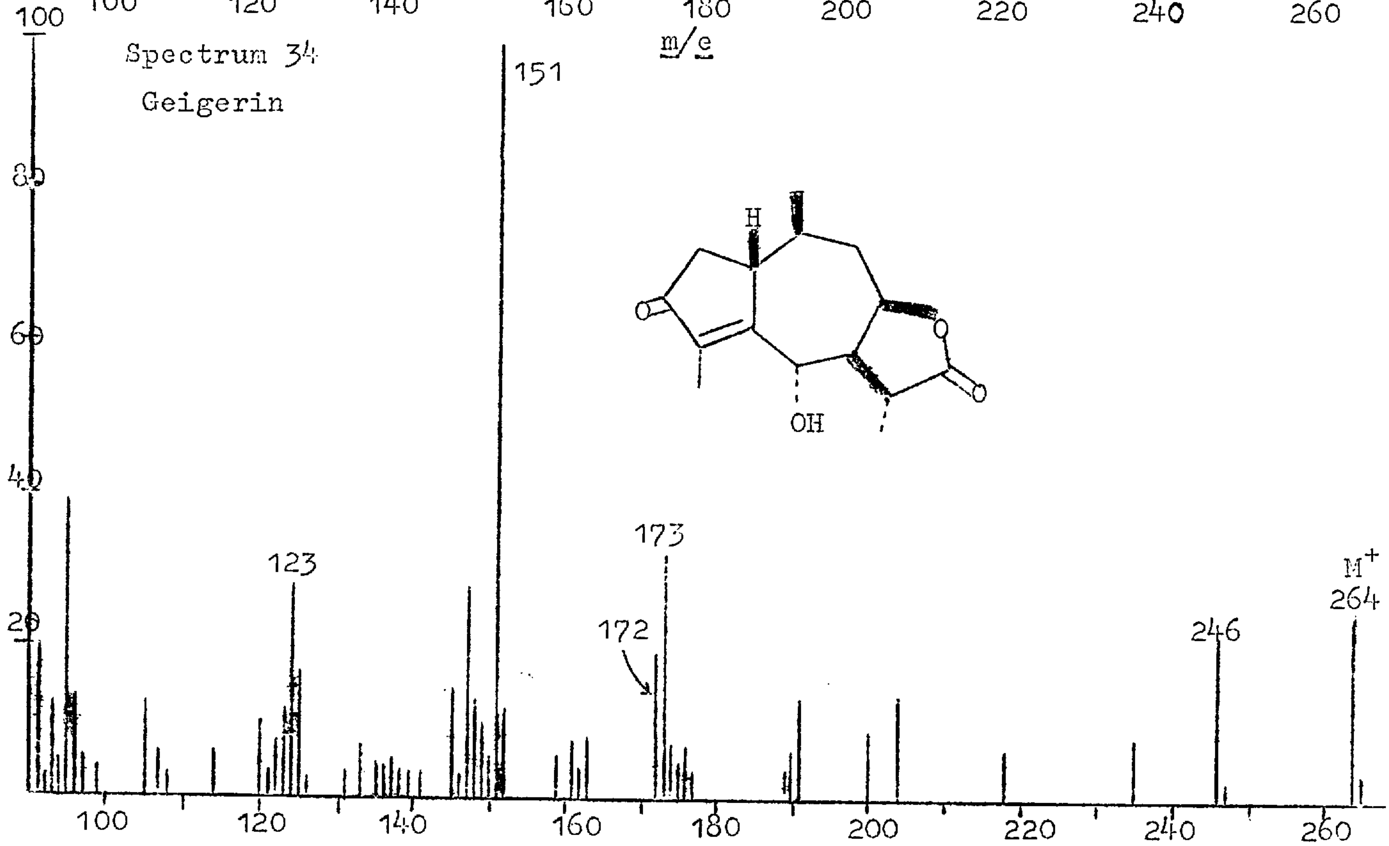


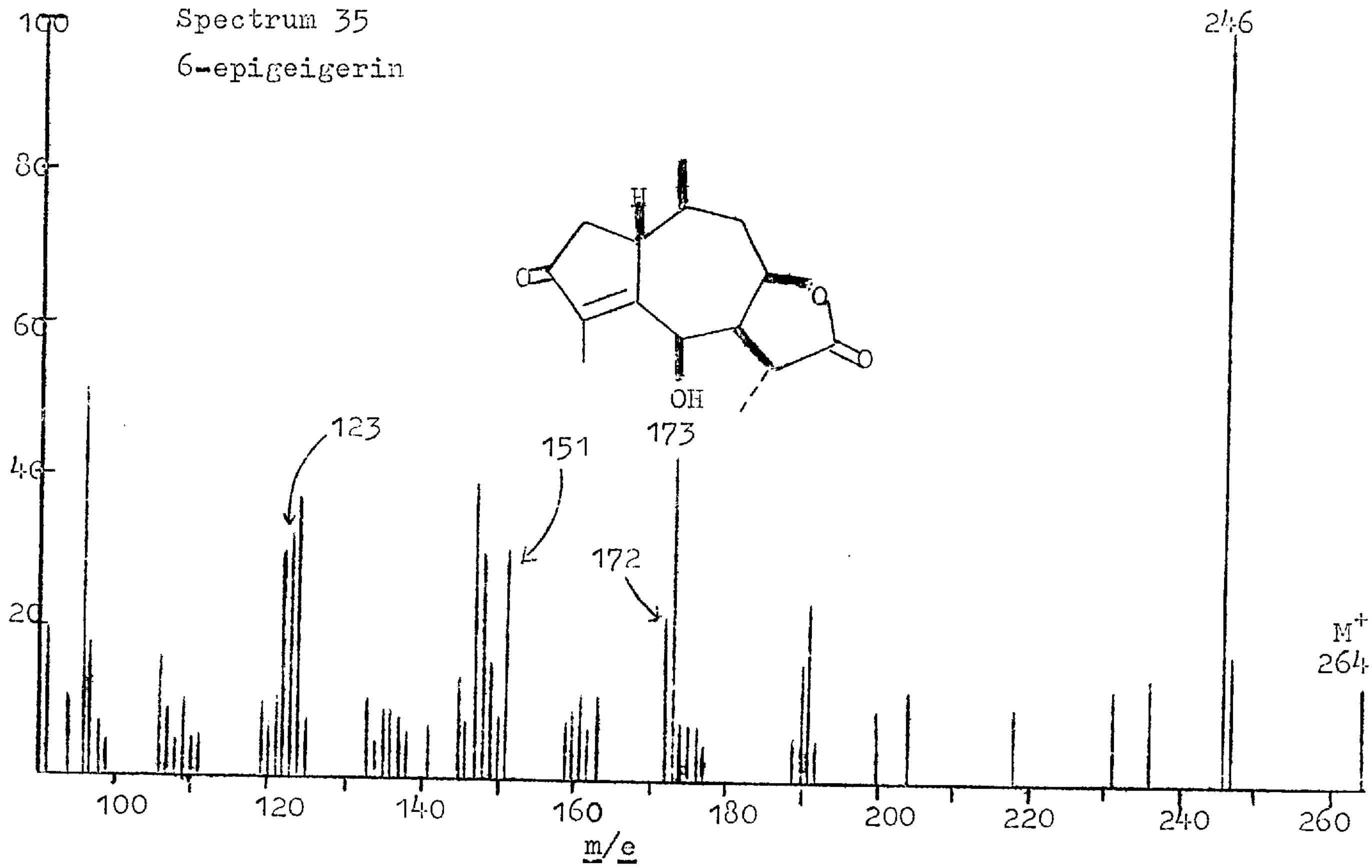
M+
264
100
Spectrum 30
Isophoto-α-santonic lactone
80
OH
H
60
40
193
169
20
100
120
140
160
180
200
220
240
260
m/e

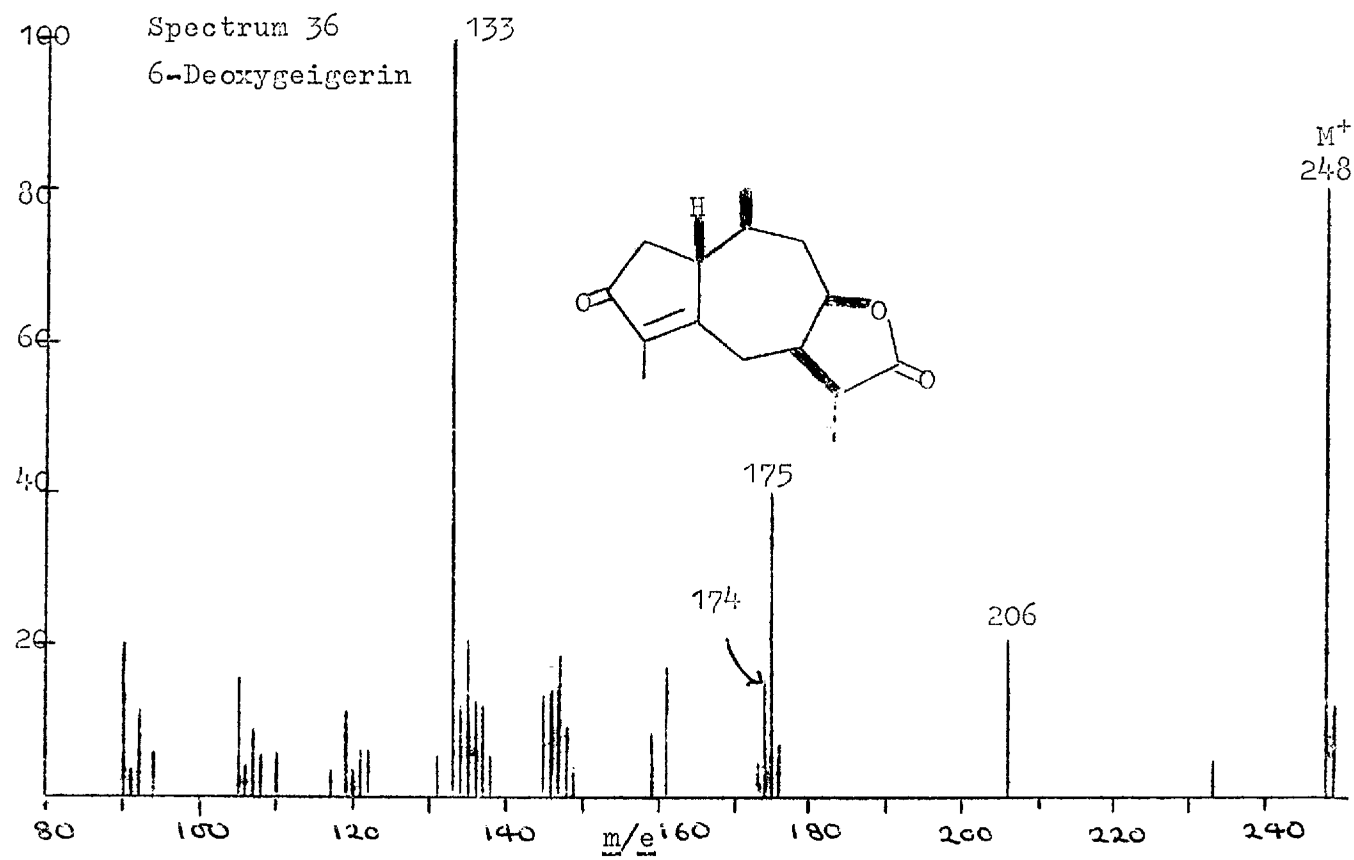

Spectrum 31
[11-$^{2}H_{1}$]-Isophoto-α-santonic lactone
OH
H
O
O
O
D
M+
265
170
194
100
80
60
40
20
100
120
140
160
180
200
220
240
260
m/e

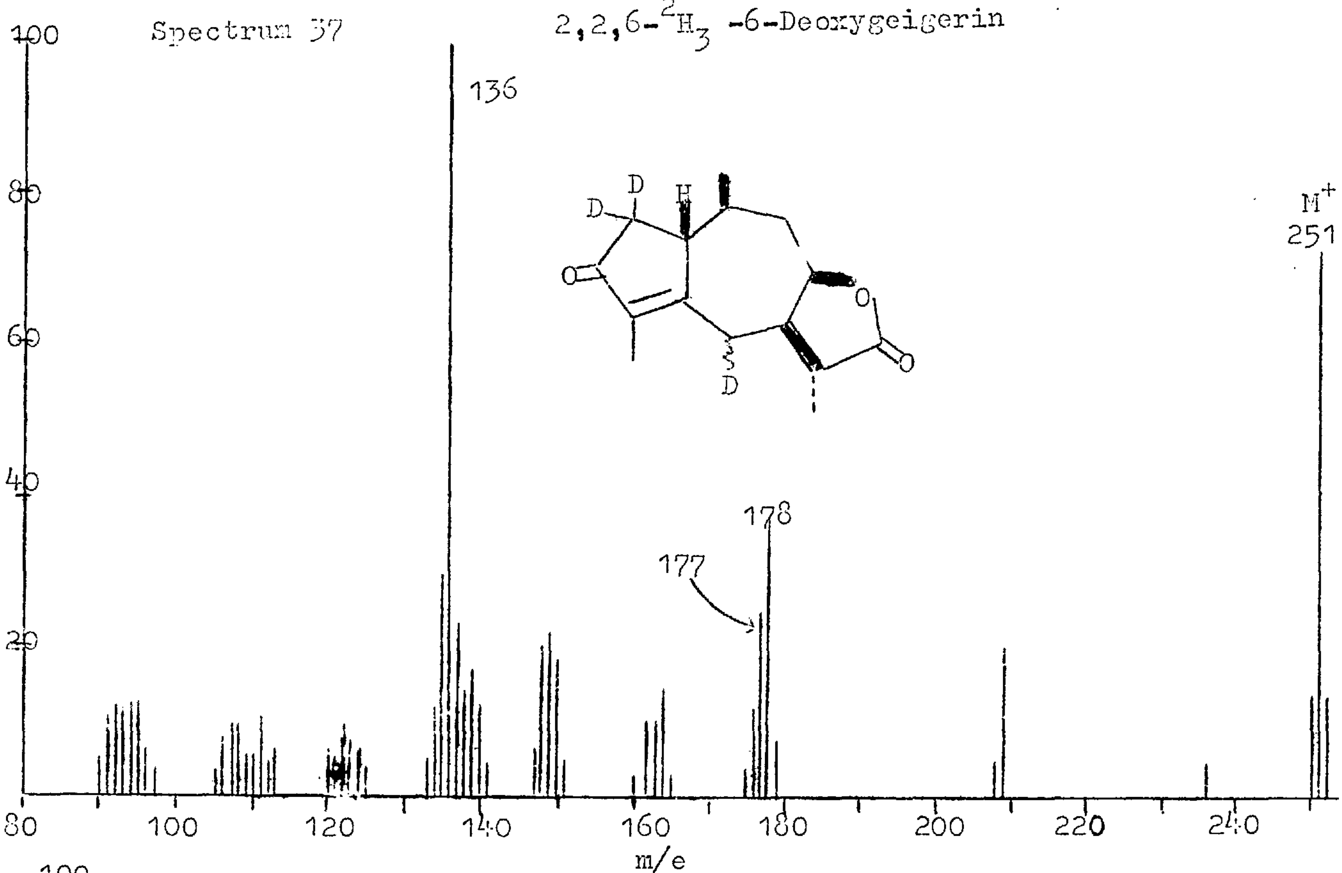

Spectrum 32
[$O^{2}H_{1}$]-Isophoto-α-santonic lactone
OD
H
O
O
O
M+ 265
169
194
100
80
60
40
20
100
120
140
160
180
200
220
240
260
m/e

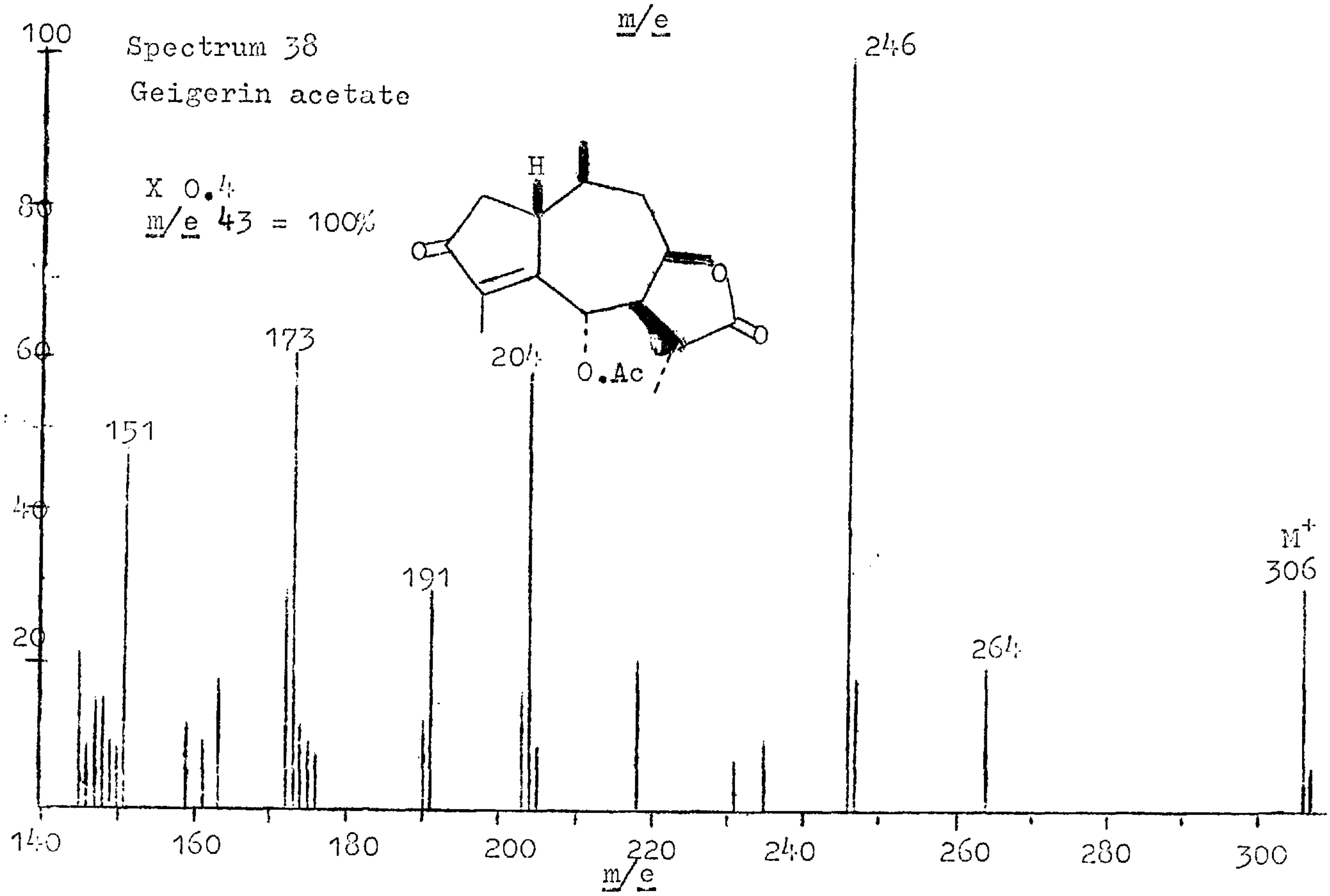

Spectrum 33
6-epi-isophoto-α-santonic lactone
100
80
60
40
20
126
OH
H
O
O
O
M+
264
100
120
140
160
180
200
220
240
260
m/e

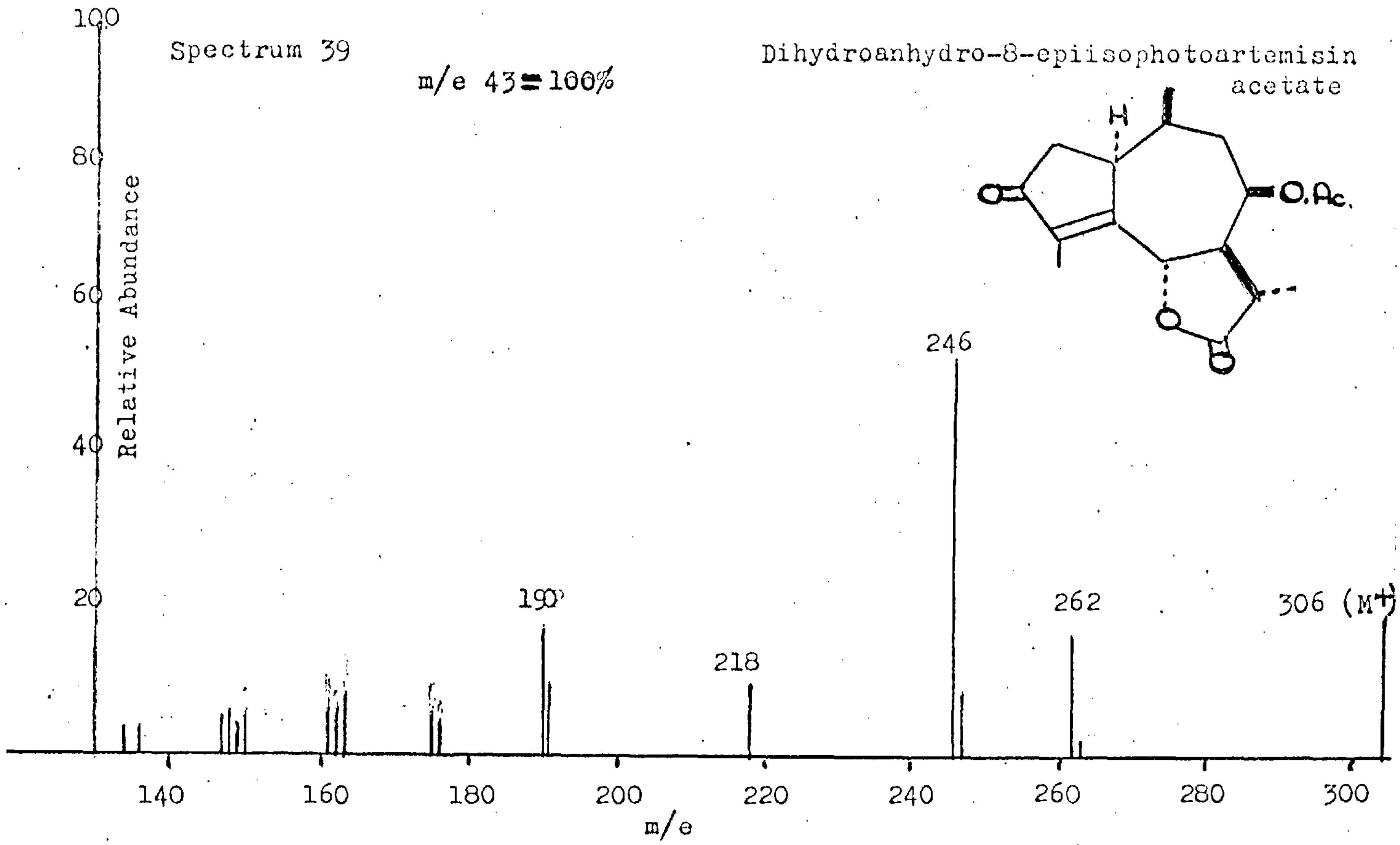

Spectrum 34
Geigerin
100
80
60
40
20
151
H
O
O
O
OH
123
173
172
246
M+
264
100
120
140
160
180
200
220
240
260

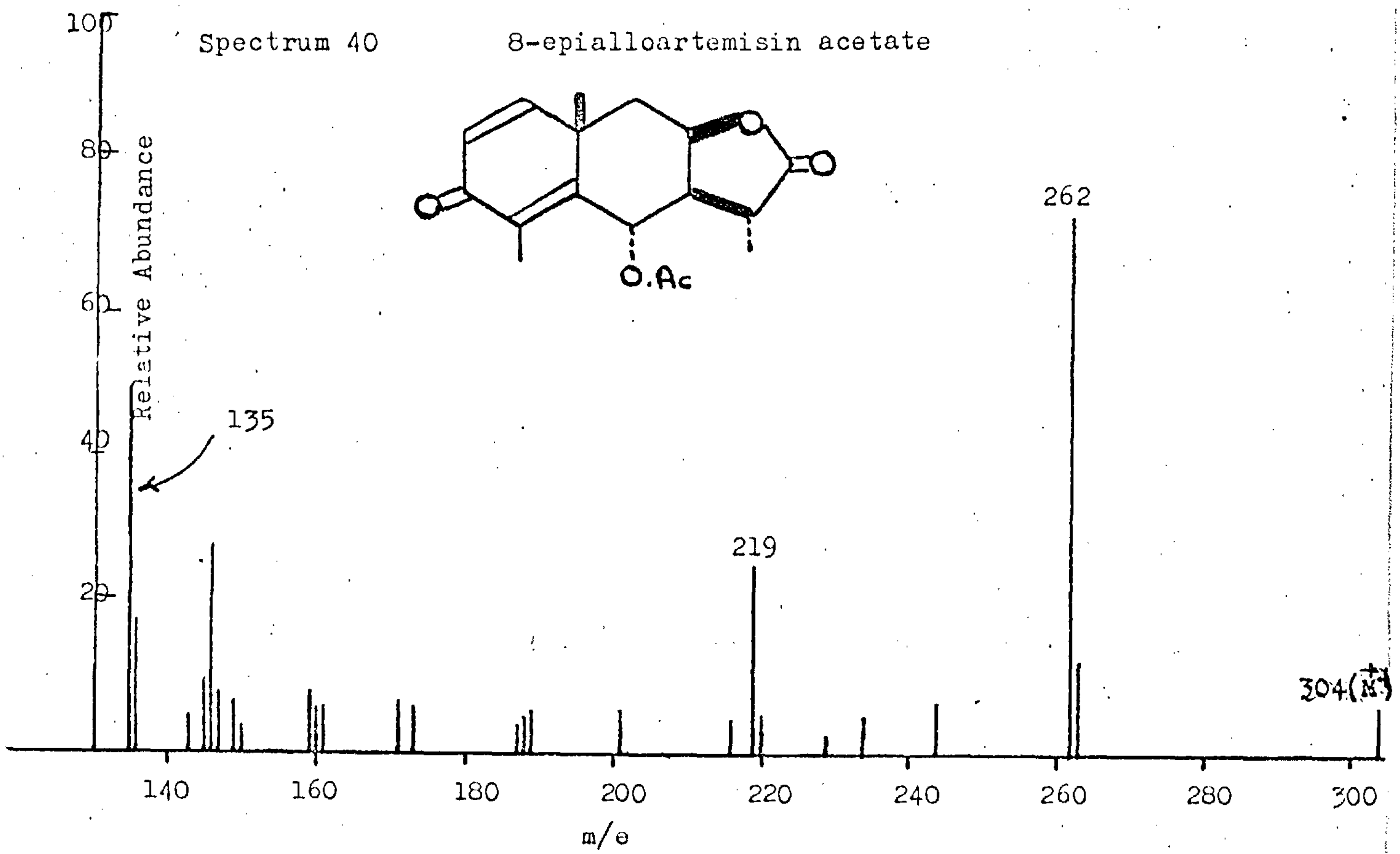

100
80
60
40
20
Spectrum 35
6-epigeigerin
H
O
O
O
OH
123
151
173
172
246
M+
264
100
120
140
160
180
200
220
240
260
m/e

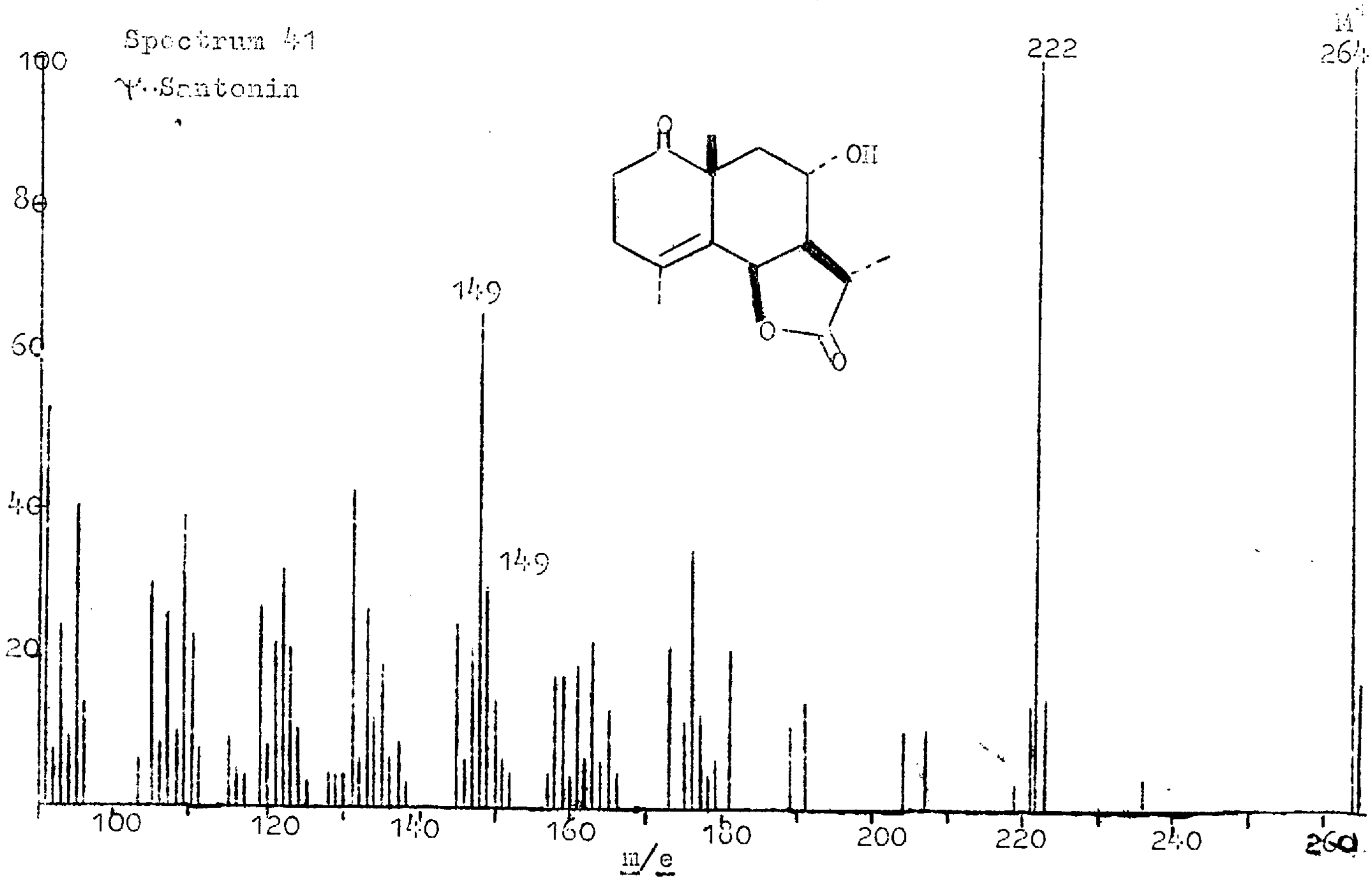

100
80
60
40
20
Spectrum 36
6-Deoxygeigerin
133
H
O
O
O
M+
248
175
174
206
80
100
120
140
160
180
200
220
240
m/e

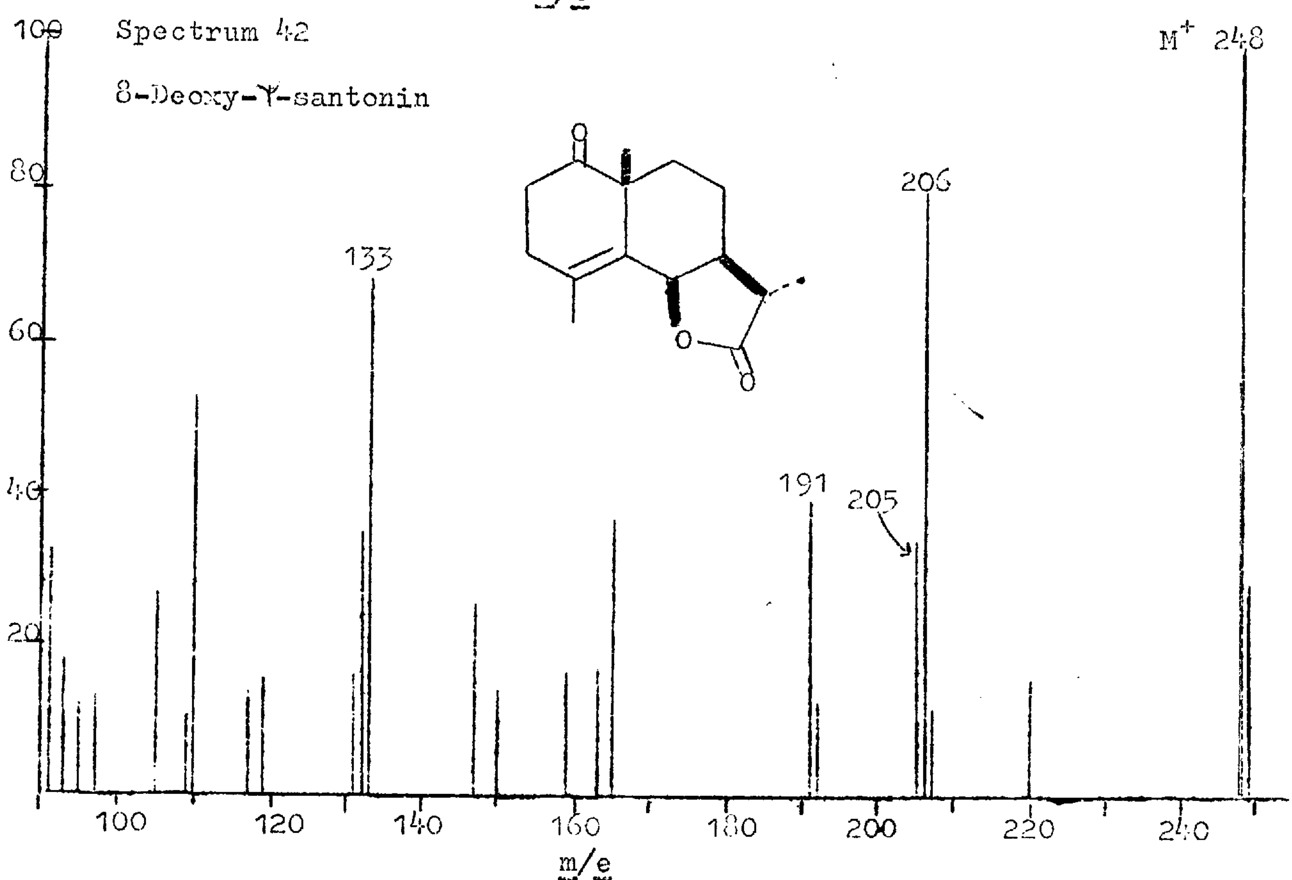

Spectrum 37
$2,2,6\text{-}{}^{2}H_{3}$ -6-Deoxygeigerin
136
178
177
M+
251
D
D
H
O
O
O
D
100
80
60
40
20
80
100
120
140
160
180
200
220
240
m/e

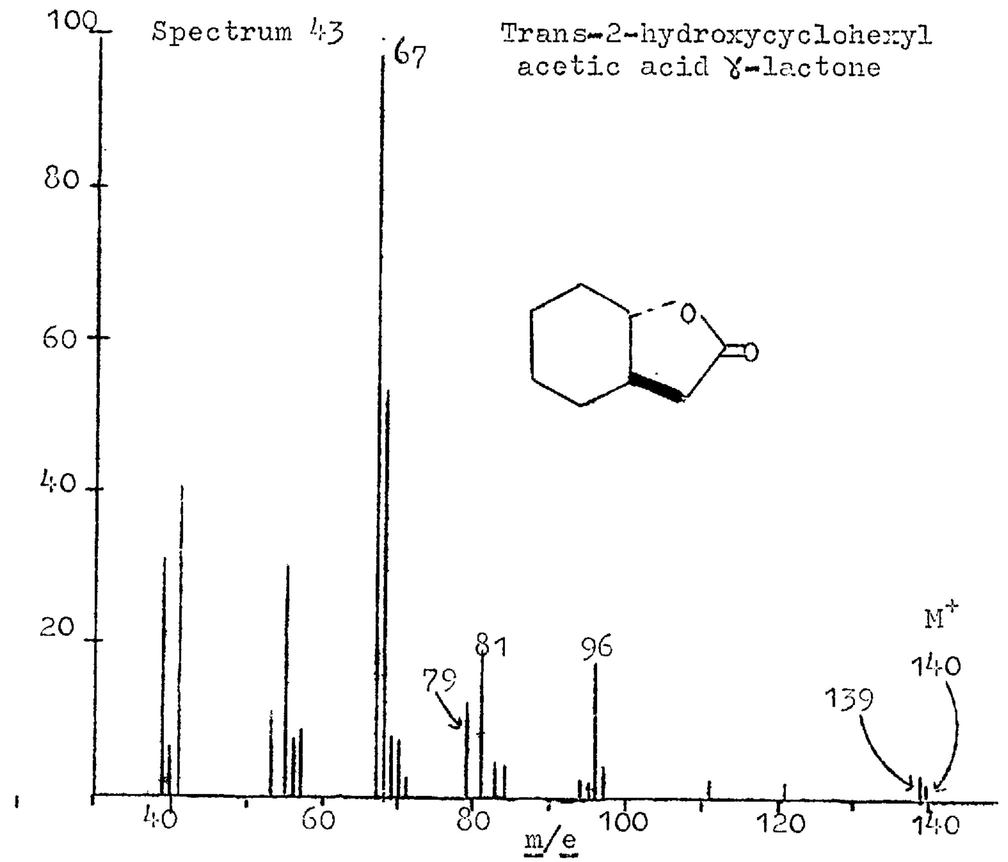

Spectrum 38
Geigerin acetate
X 0.4
m/e 43 = 100%
246
173
204
151
191
264
M+
306
H
O
O
O
O.Ac
100
80
60
40
20
140
160
180
200
220
240
260
280
300
m/e

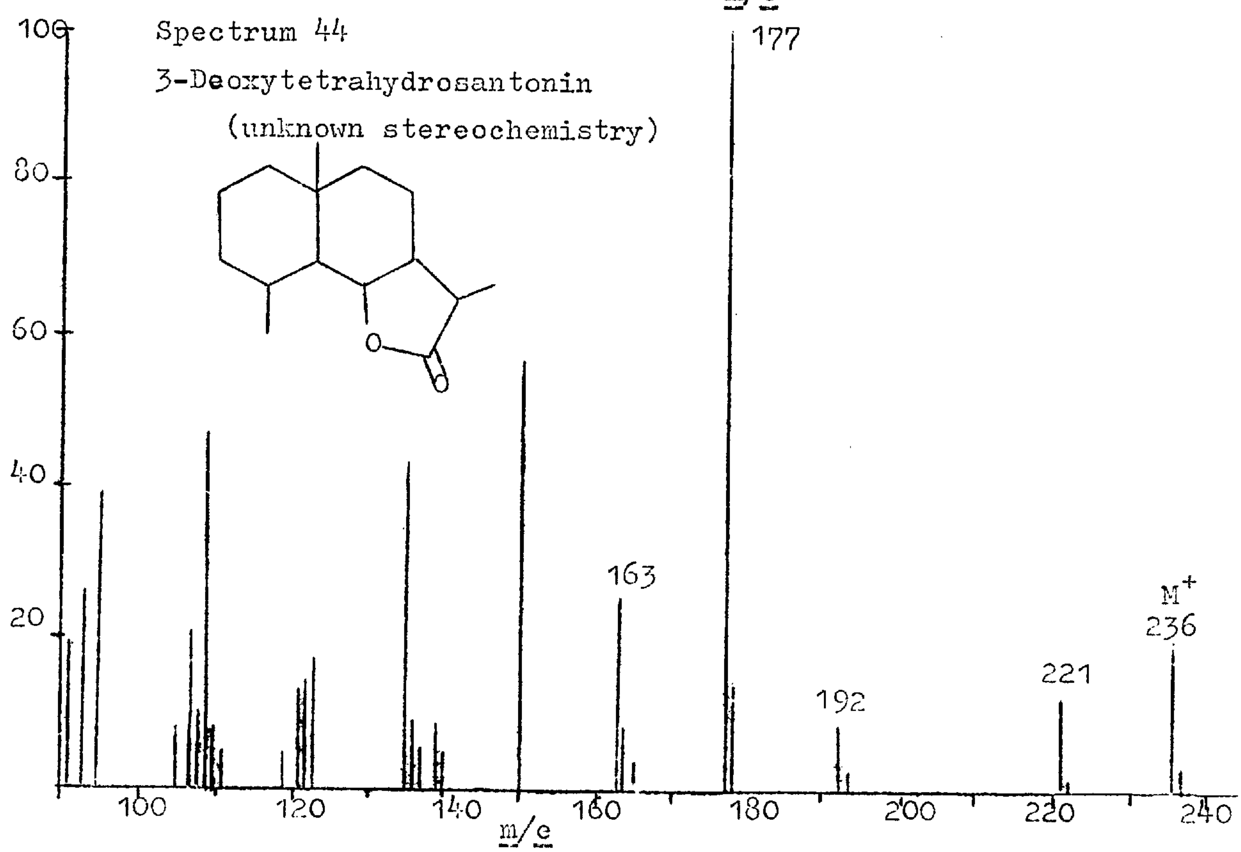

Spectrum 39
m/e 43 = 100%
Dihydroanhydro-8-epiisophotoartemisin acetate
H
O.Ac.
Relative Abundance
100
80
60
40
20
190
218
246
262
306 (M+)
140
160
180
200
220
240
260
280
300
m/e


Spectrum 40
8-epialloartemisin acetate
O.Ac
Relative Abundance
100
80
60
40
20
135
219
262
304(M+)
140
160
180
200
220
240
260
280
300
m/e

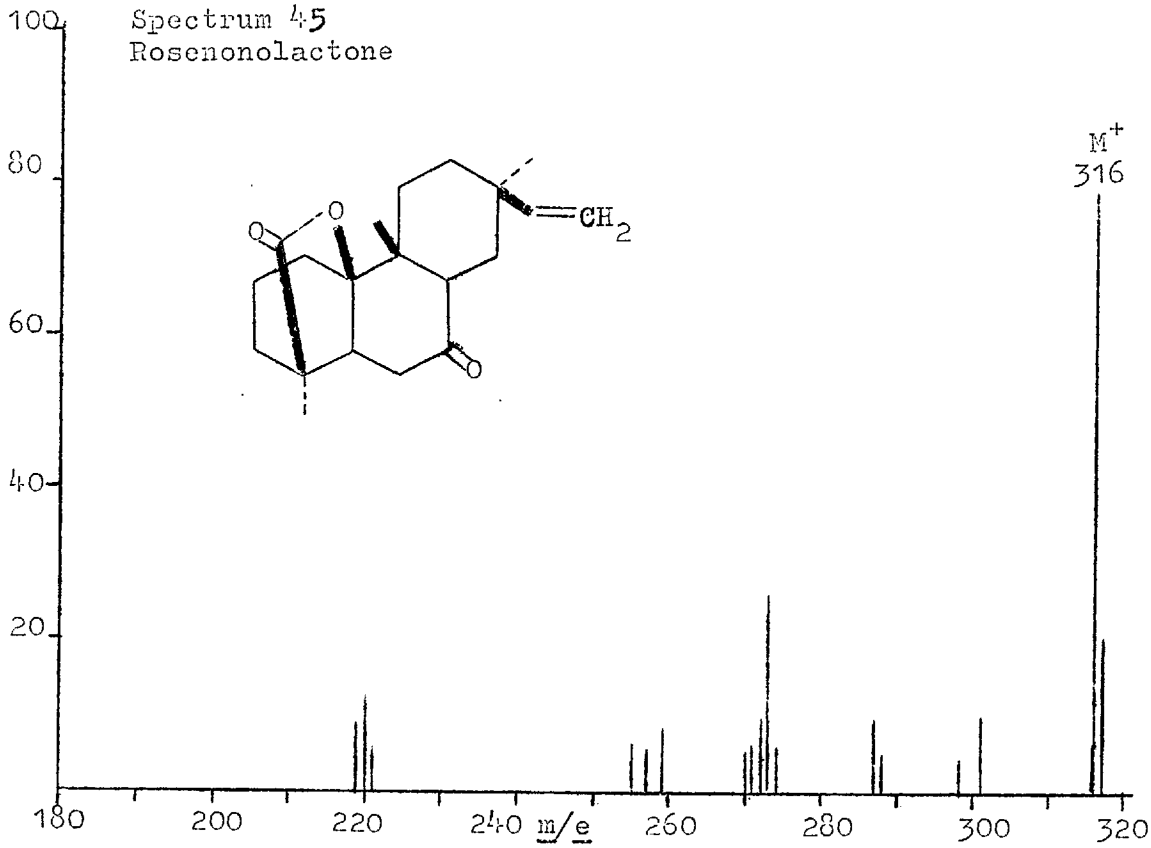

Spectrum 41
Y-Santonin
OH
O
222
M+
264
149
149
100
80
60
40
20
100
120
140
160
180
200
220
240
260
m/e

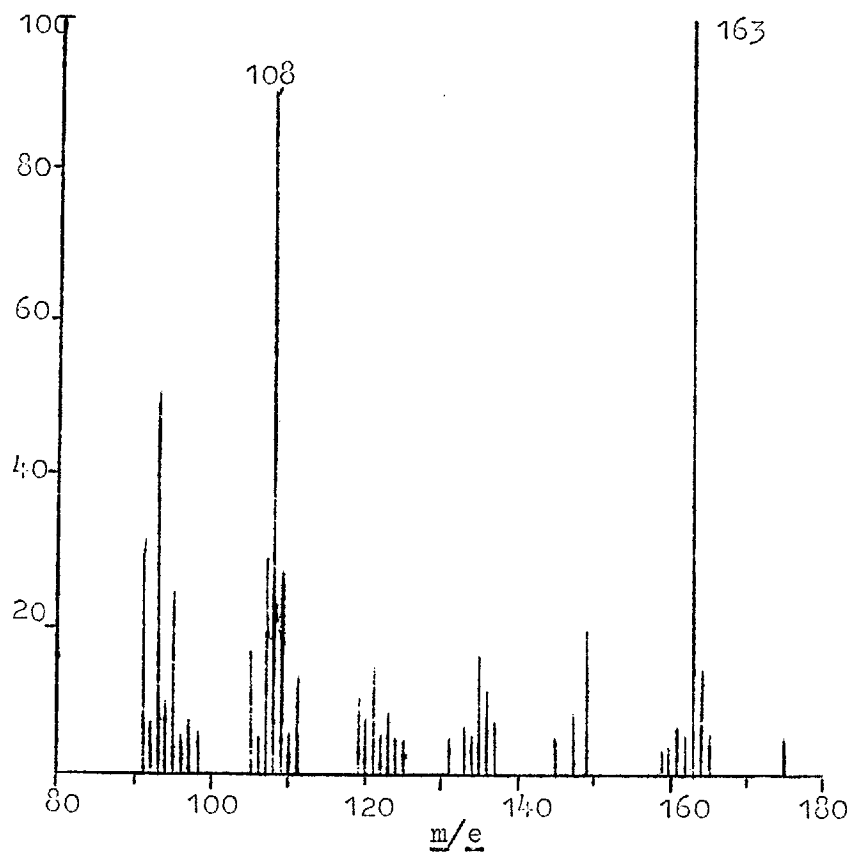

Spectrum 42
8-Deoxy-Y-santonin
O
M+ 248
206
133
191
205
100
80
60
40
20
100
120
140
160
180
200
220
240
m/e


100
80
60
40
20
Spectrum 43
Trans-2-hydroxycyclohexyl acetic acid γ-lactone
67
81
96
79
139
M+
140
40
60
80
100
120
140
m/e


100
80
60
40
20
Spectrum 44
3-Deoxytetrahydrosantonin
(unknown stereochemistry)
177
163
192
221
M+
236
100
120
140
160
180
200
220
240
m/e

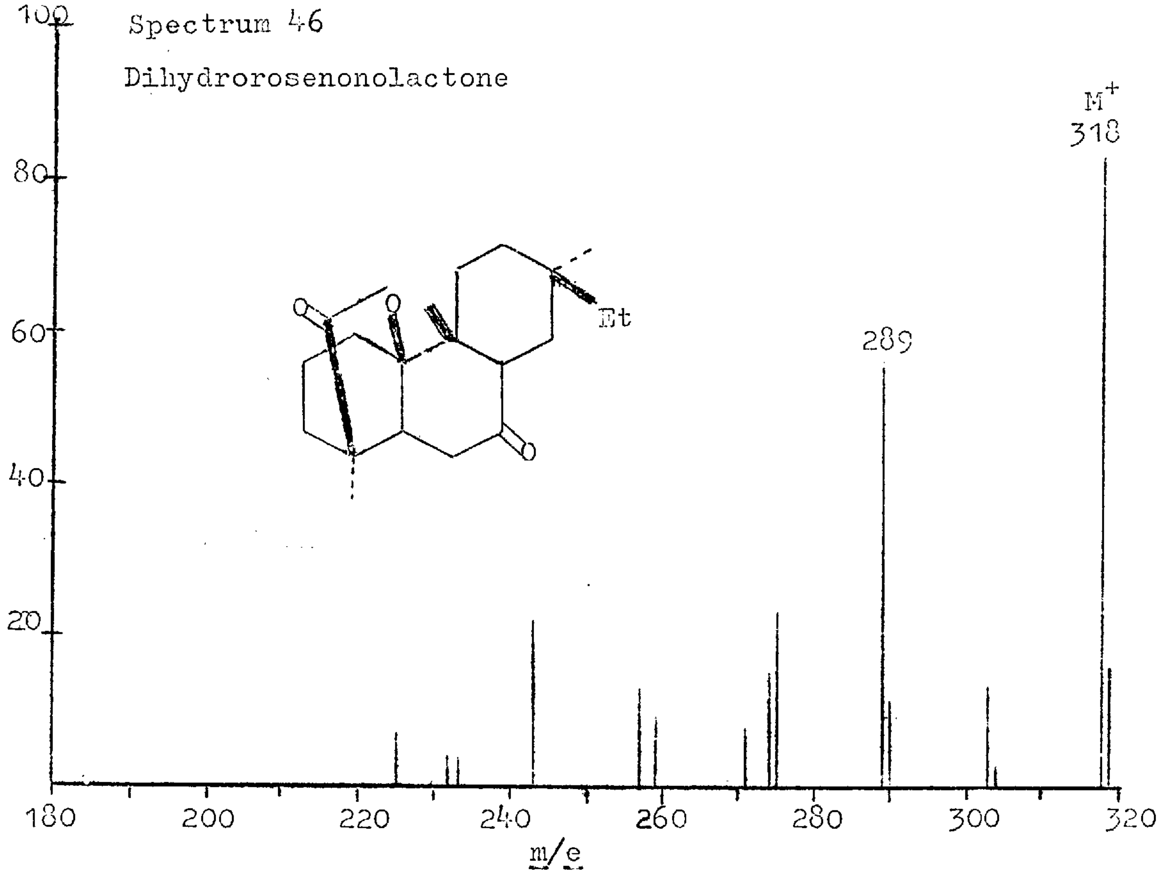
Spectrum 45
Rosenonolactone

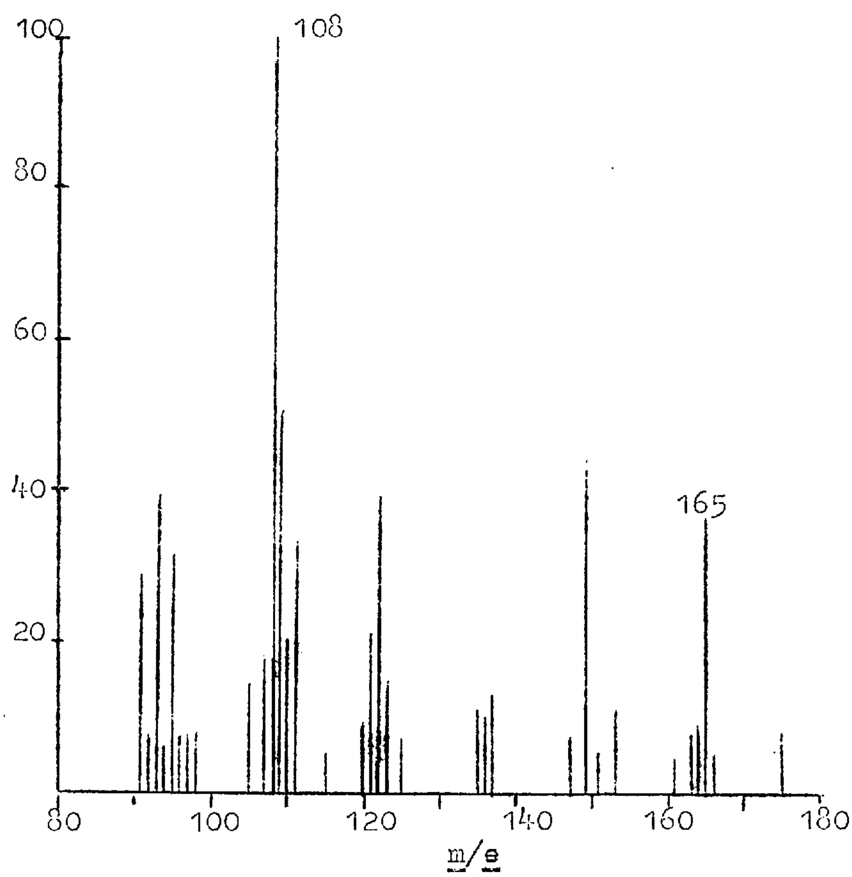


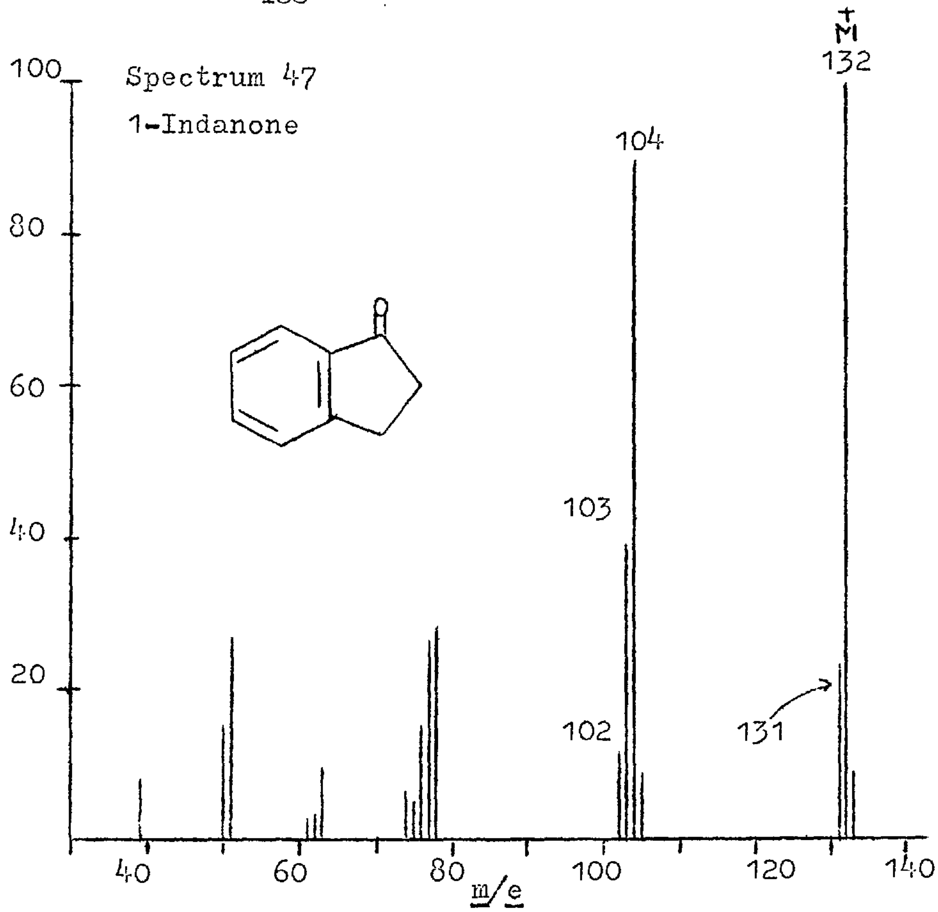


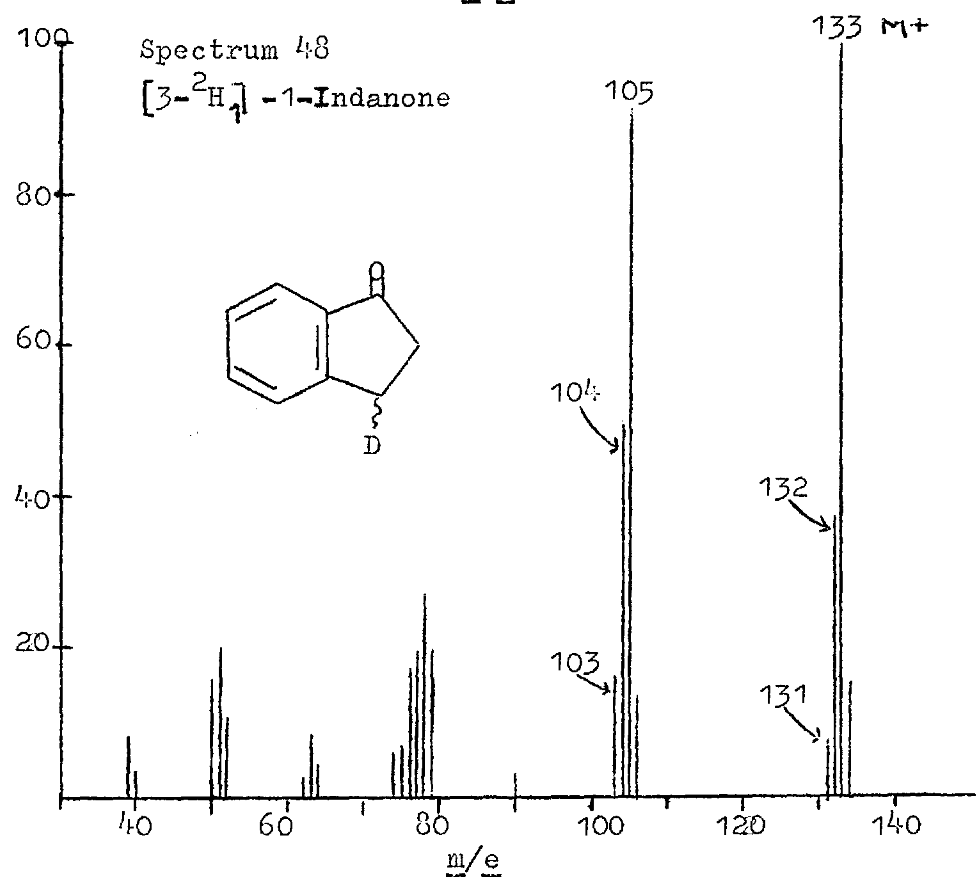
Spectrum 46

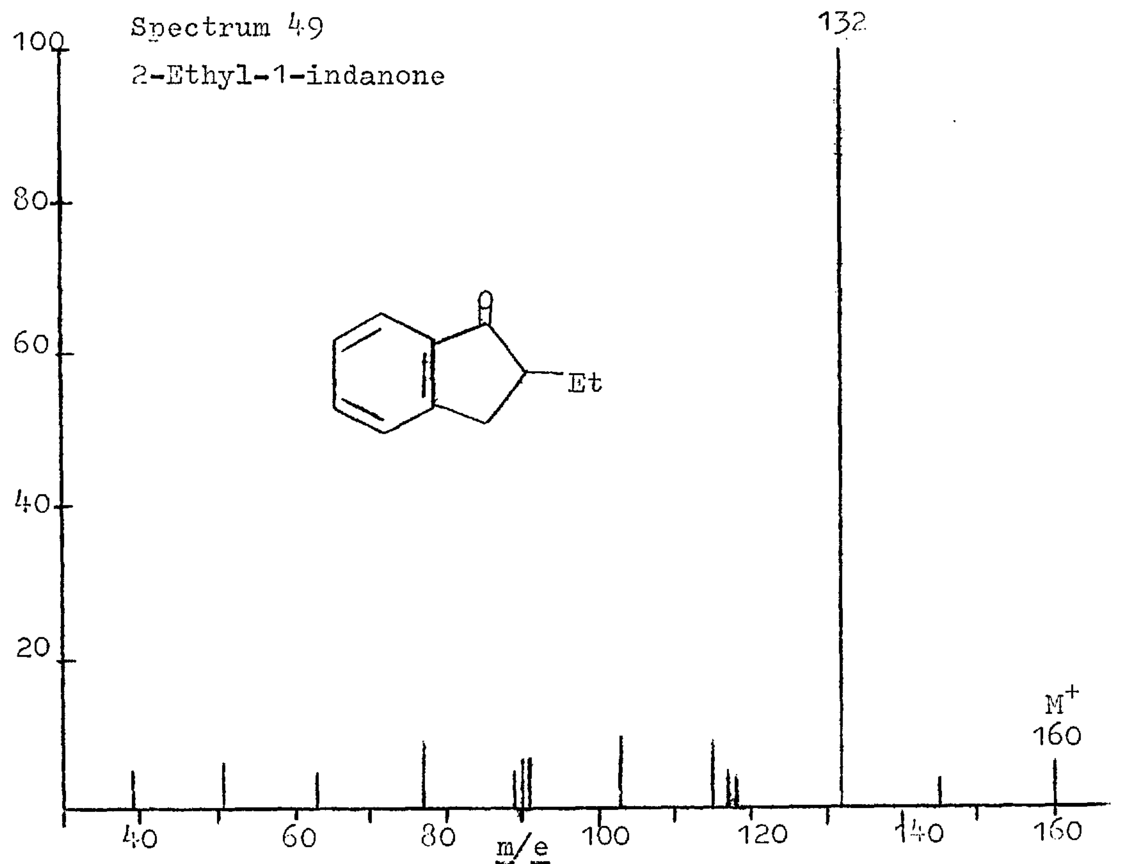
Dihydrorosenonolactone

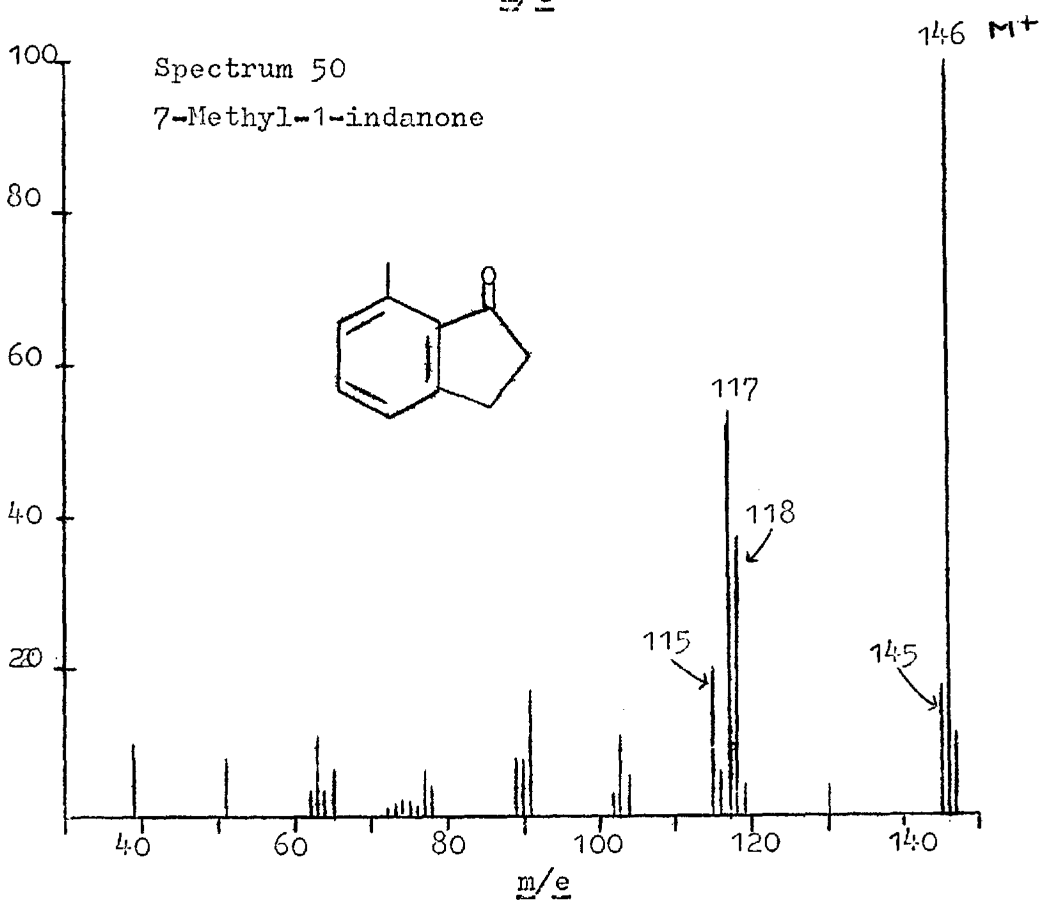


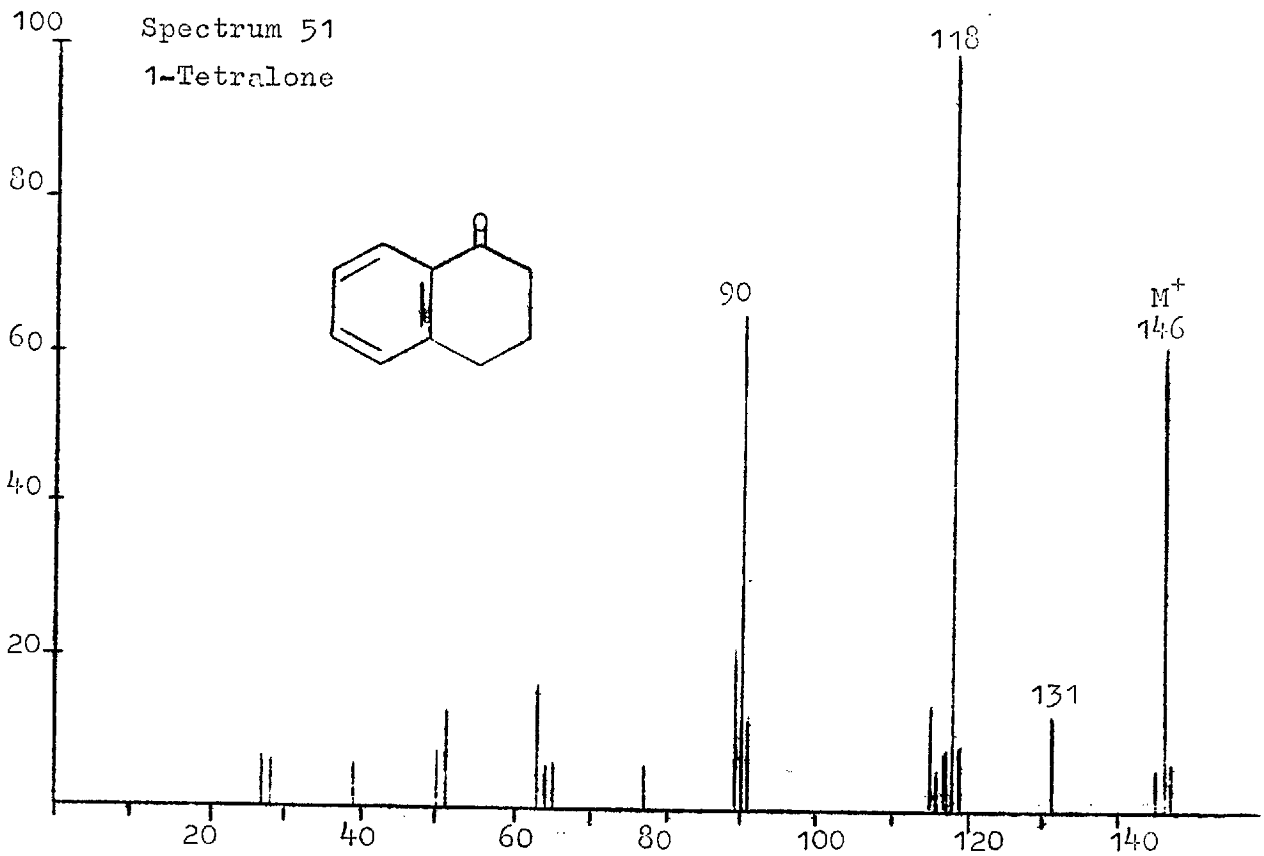


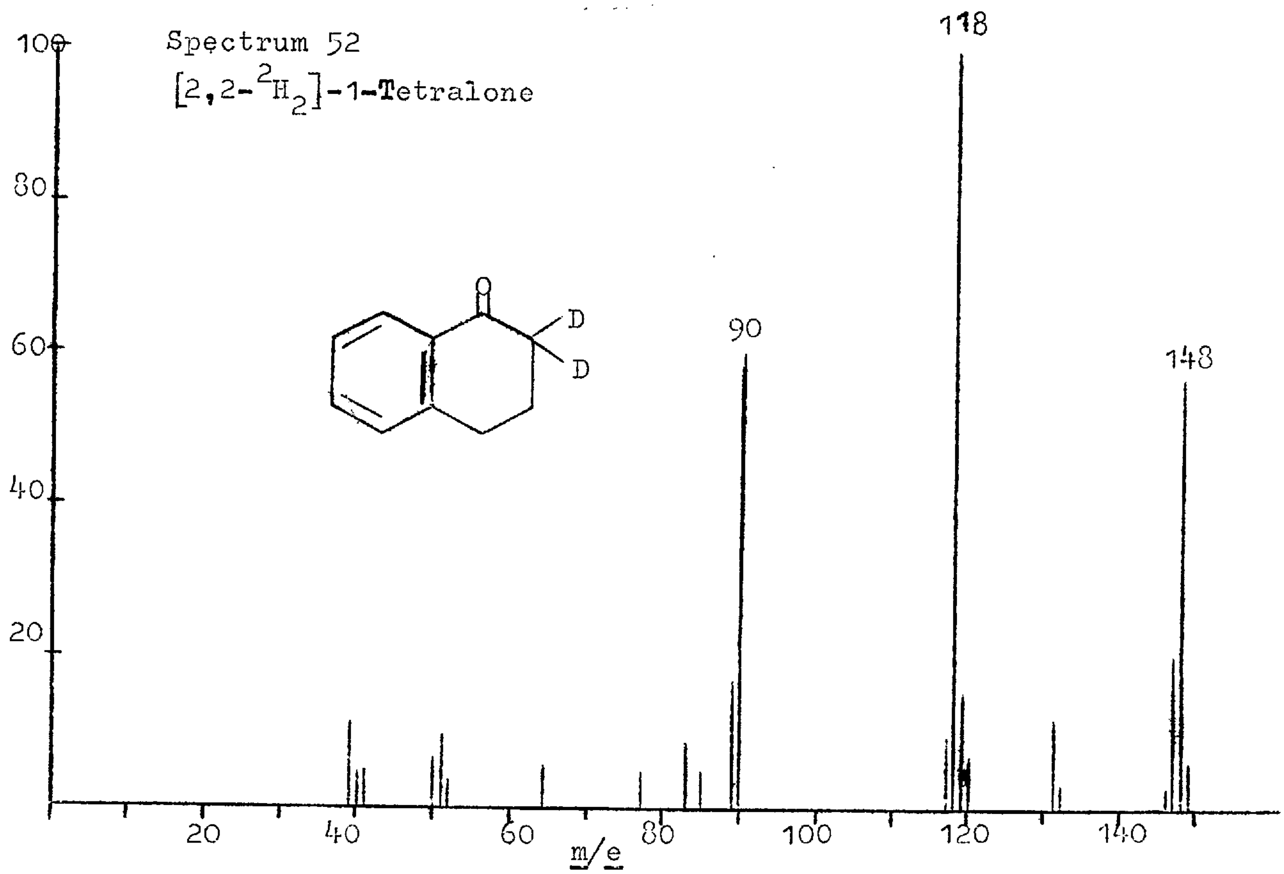

Spectrum 47
1-Indanone
M+
132
104
103
102
131
100
80
60
40
20
40
60
80
100
120
140
m/e

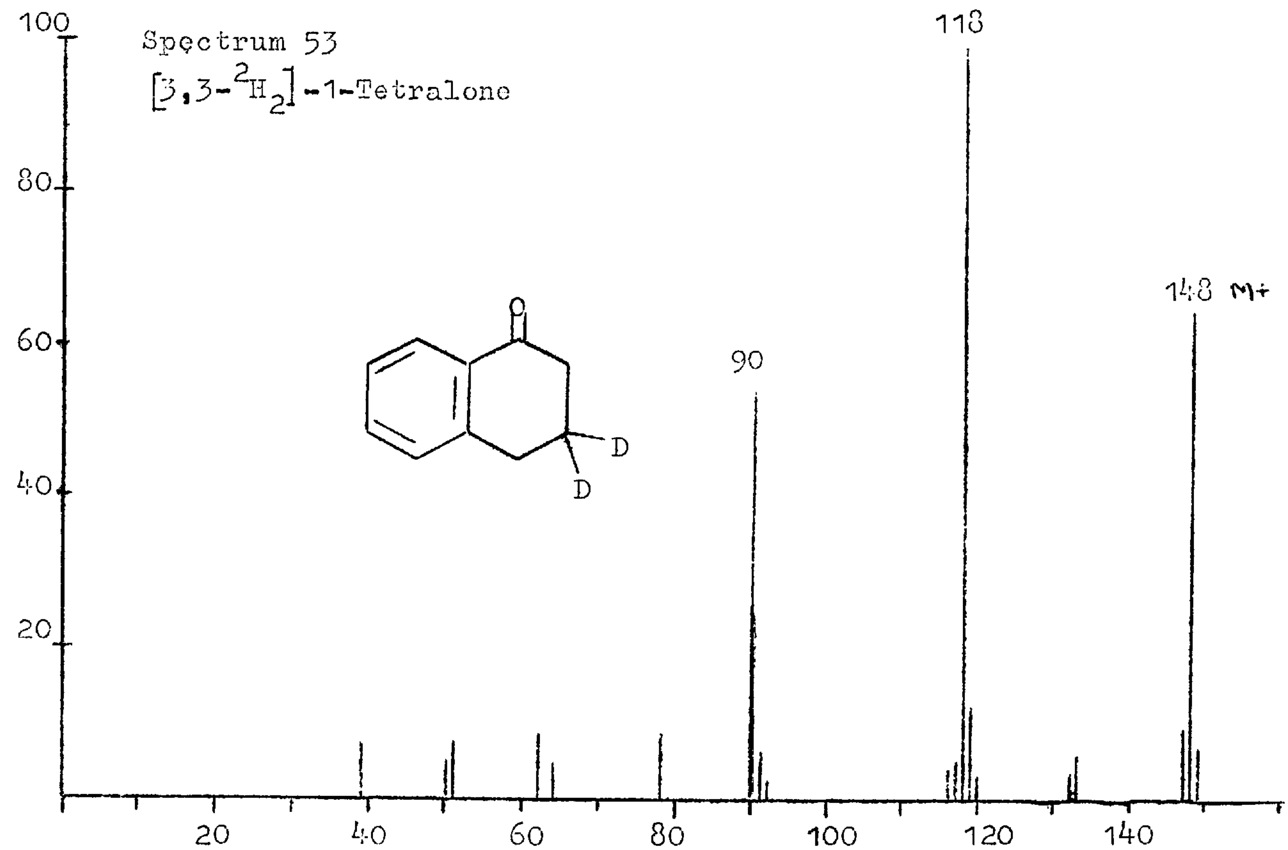

Spectrum 48
[3-^{2}H$_{1}$]-1-Indanone
133 M+
105
104
132
103
131
D
100
80
60
40
20
40
60
80
100
120
140
m/e

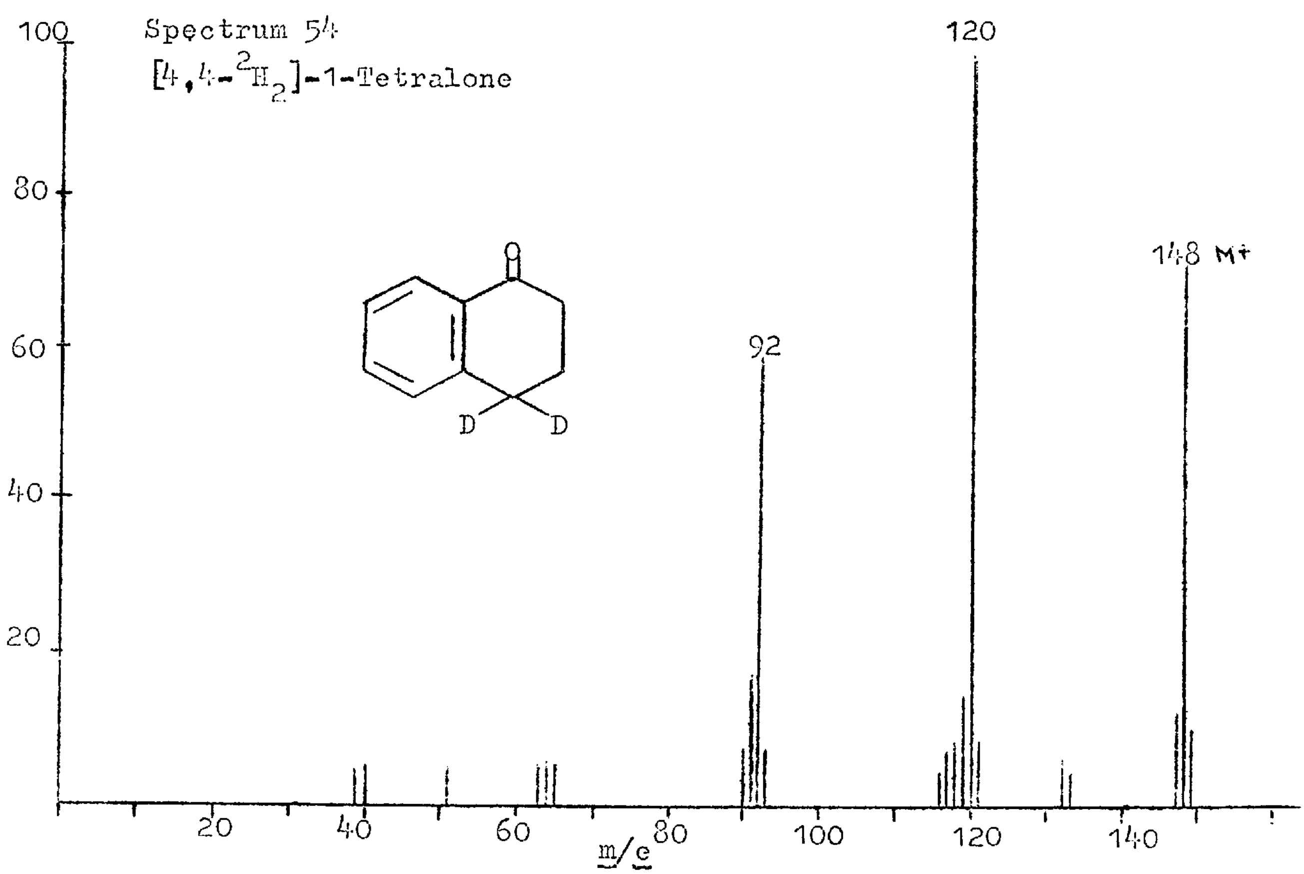

Spectrum 49
2-Ethyl-1-indanone
132
M+
160
Et
O
100
80
60
40
20
40
60
80
100
120
140
160
m/e

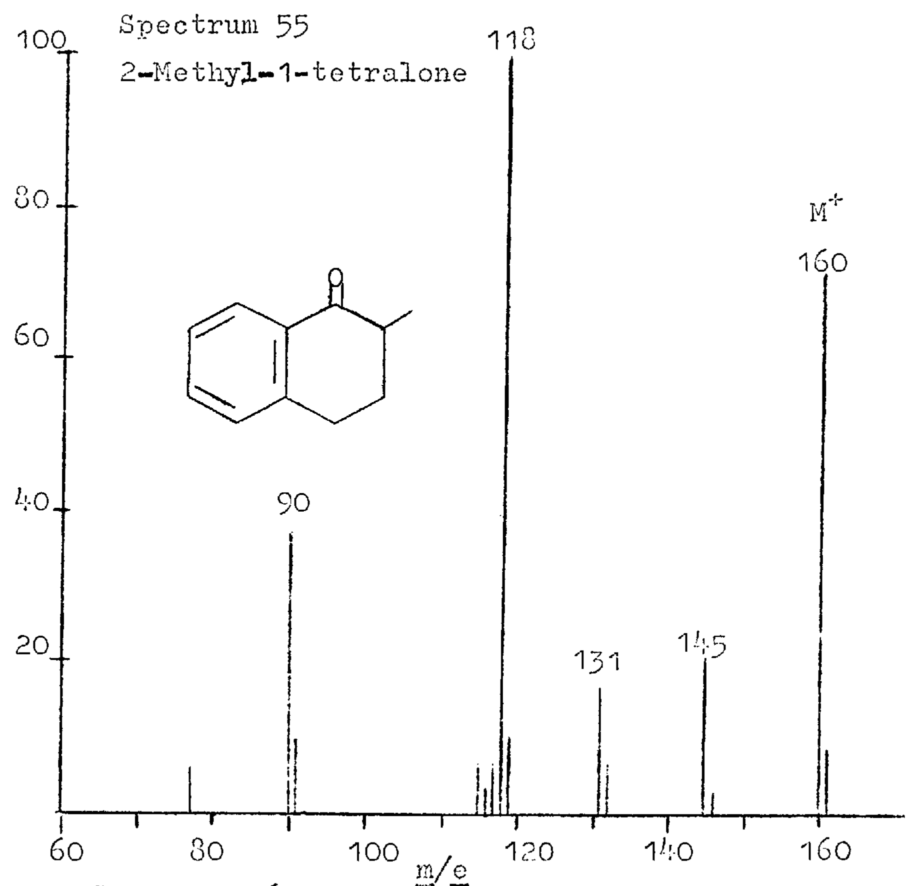

Spectrum 50
7-Methyl-1-indanone
146 M+
117
118
115
145
O
100
80
60
40
20
40
60
80
100
120
140
m/e

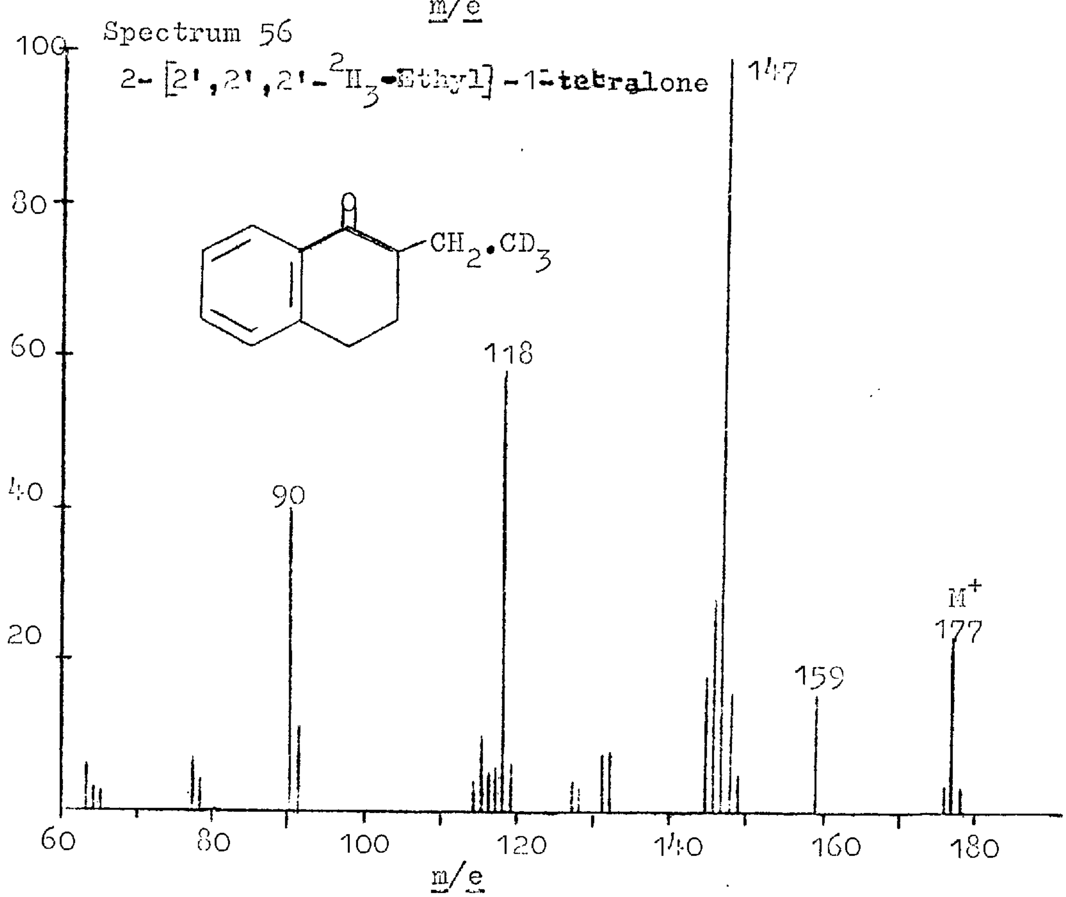

Spectrum 51
1-Tetralone
100
80
60
40
20
118
90
M+
146
131
20
40
60
80
100
120
140

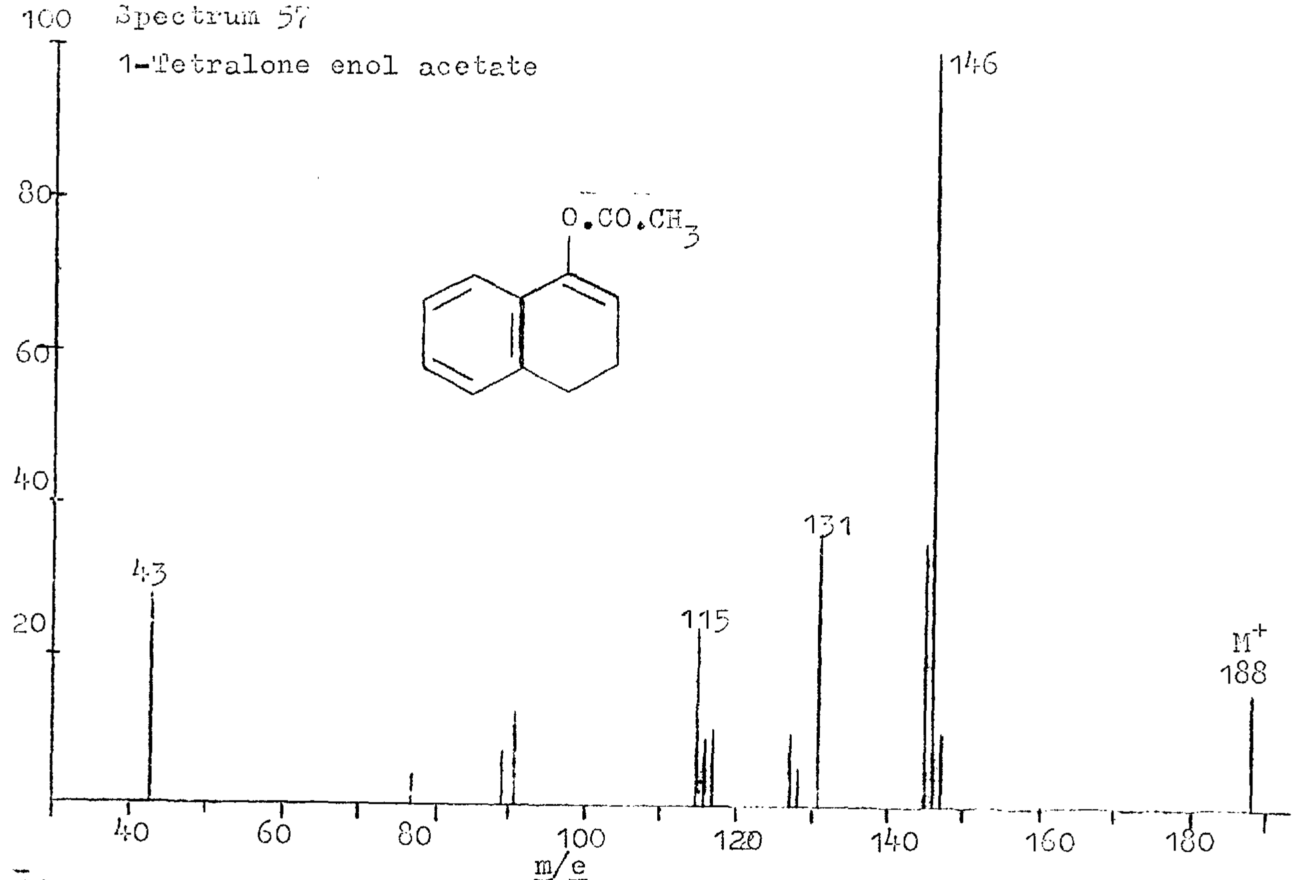

Spectrum 52
[2,2-2H2]-1-Tetralone
100
80
60
40
20
118
90
148
D
D
20
40
60
80
100
120
140
m/e


Spectrum 53
[3,3-$^{2}H_{2}$]-1-Tetralone
100
80
60
40
20
118
148 M+
90
D
D
20
40
60
80
100
120
140

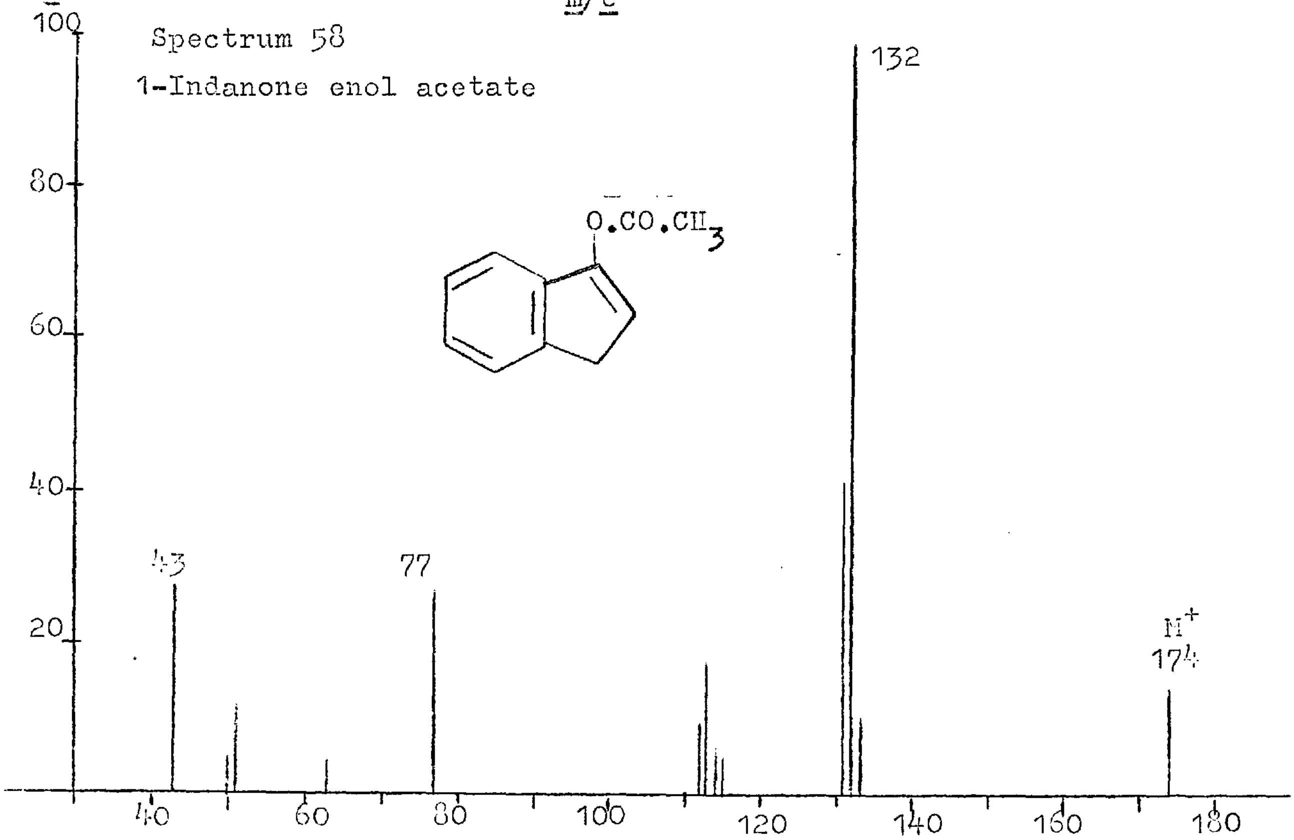

Spectrum 54
[4,4-$^{2}H_{2}$]-1-Tetralone
100
80
60
40
20
120
148 M+
92
D
D
20
40
60
80
100
120
140
m/e


Spectrum 55
2-Methyl-1-tetralone
100
80
60
40
20
118
M+
160
90
131
145
60
80
100
120
140
160
m/e

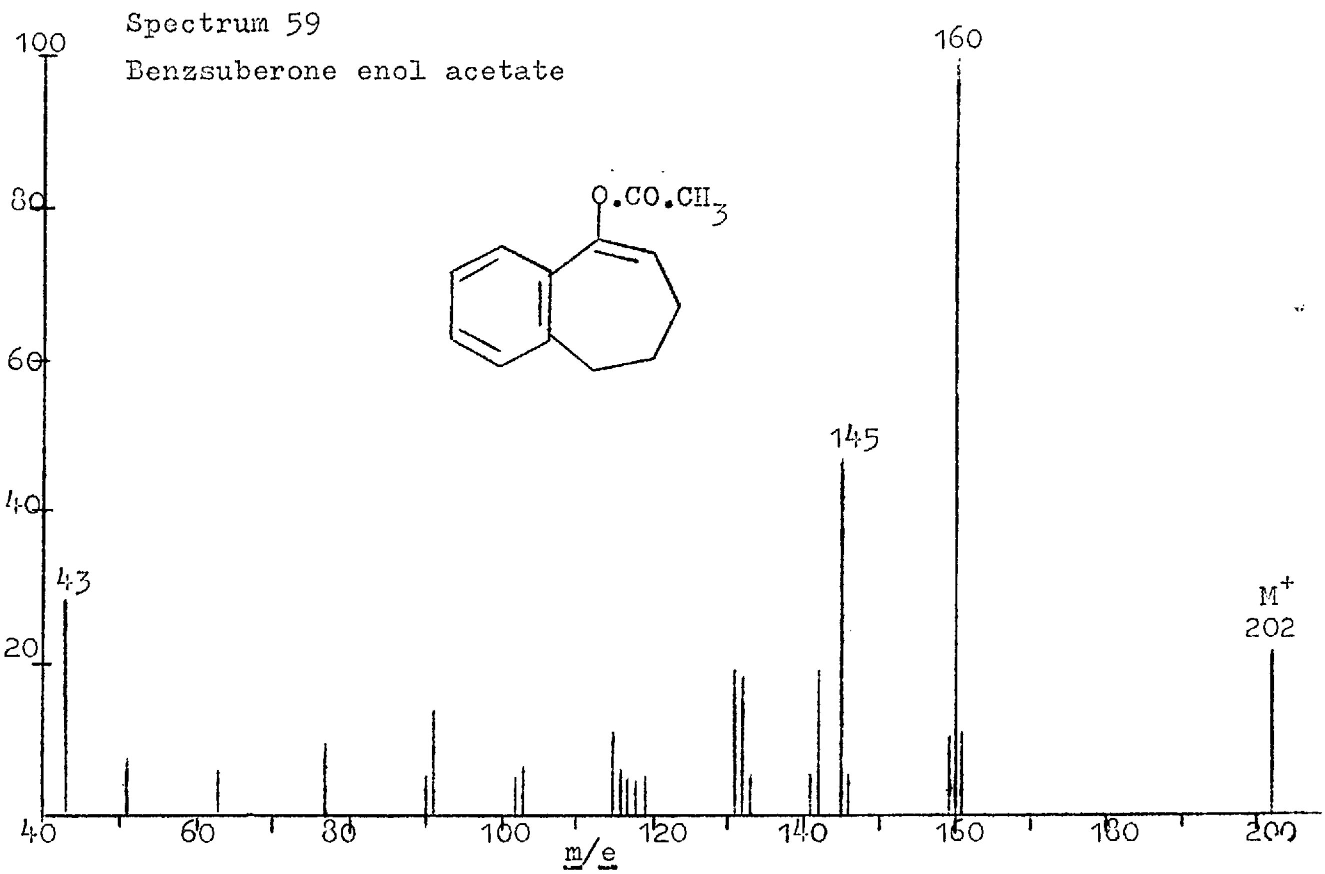

Spectrum 56
2-[2',2',2'-$^{2}H_{3}$-Ethyl]-1-tetralone
$CH_2.CD_3$
100
80
60
40
20
147
118
90
159
M+
177
60
80
100
120
140
160
180
m/e

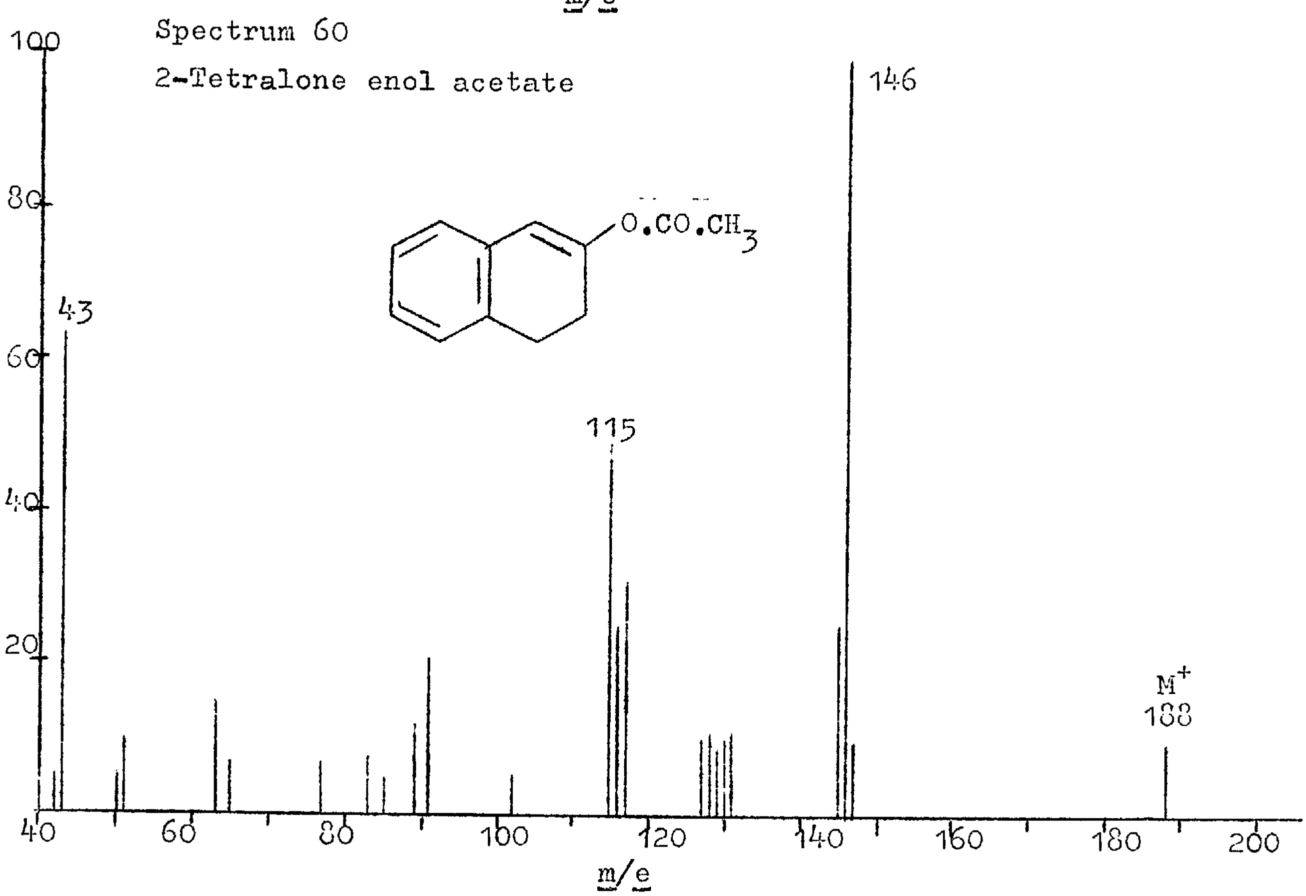


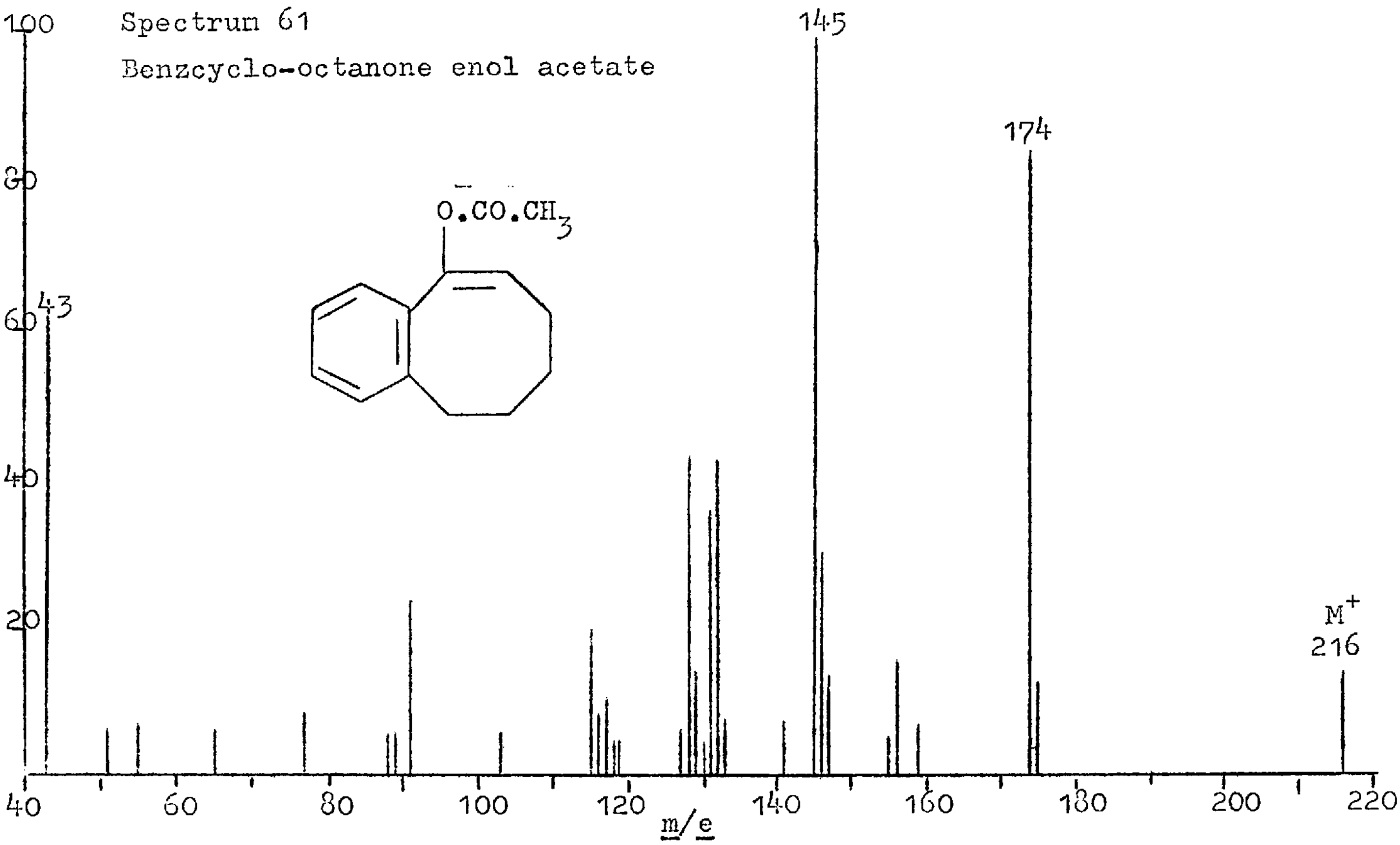
Spectrum 57
1-Tetralone enol acetate
O.CO.CH3
146
131
115
43
M+
188
100
80
60
40
20
40
60
80
100
120
140
160
180
m/e



Spectrum 58
1-Indanone enol acetate
O.CO.CH3
132
43
77
M+
174
100
80
60
40
20
40
60
80
100
120
140
160
180


Spectrum 59
Benzsuberone enol acetate
O.CO.CH$_3$
100
80
60
40
20
43
145
160
M$^+$
202
40
60
80
100
120
140
160
180
200
m/e


Spectrum 60
2-Tetralone enol acetate
O.CO.CH$_3$
100
80
60
40
20
43
115
146
M$^+$
188
40
60
80
100
120
140
160
180
200
m/e


Spectrum 61
Benzcyclo-octanone enol acetate
O.CO.CH3
100
80
60
40
20
43
145
174
M+
216
40
60
80
100
120
140
160
180
200
220
m/e

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