REMOTE OXIDATION OF CYCLIC AND ACYCLIC ESTERS

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ABSTRACT

The oxidation of octadecyl acetate (97; n=16), dodecyl acetate (97; n=10), tetradecyl acetate (97; n=12), hexadecyl acetate (97; n=14) and docosyl acetate (97; n=20) by chromium trioxide in glacial acetic acid/acetic anhydride to a mixture of mono-oxo-acetates and the method used to determine the relative amounts of isomeric oxo-acetates present in the product mixture, is described. Evidence is given for the validity of the analytical method to estimate the relative amounts of isomeric oxo-acetates. Subsequent conversion of the mixture of mono-oxo-hexadecyl acetates (98; x+y=13), mono-oxo-dodecyl acetates (98; x+y=19), and mono-oxo-tetradecyl acetates (98; x+y=11) to the corresponding mixture of mono-unsaturated acetates is described. These compounds are considered to be sex pheromones for the bertha armyworm, oak leaf roller moth and some fruit moths respectively.

The oxidation of 16-hexadecanolide (117; n=15), 15-pentadecanolide (117; n=14) and 12-dodecanolide (117; n=11) by chromium trioxide in glacial acetic acid/acetic anhydride to a mixture of mono-oxo-lactones and the method employed to determine the relative amounts of isomeric mono-oxo-lactones present in the product mixture, is reported. Subsequent conversion of the mixture of mono-oxo-16-hexadecanolides (118; x+y=14) to the

mixture of mono-unsaturated hexadecanolides (123; a+b=13) has been achieved. The latter mixture is believed to be part of the sex pheromone of the oak leaf roller moth.

The oxidation of cyclopentadecyl acetate (135) and cyclotridecyl acetate (145) by chromium trioxide in glacial acetic acid/acetic anhydride to a mixture of mono-oxo-cyclic acetates and the method used to identify and determine the relative amounts of isomeric cyclic oxo-acetates, is described.

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ABBREVIATION

broad s	broad singlet
broad m	broad multiplet
mixed t	mixed triplet
s	singlet
t	triplet
m	multiplet

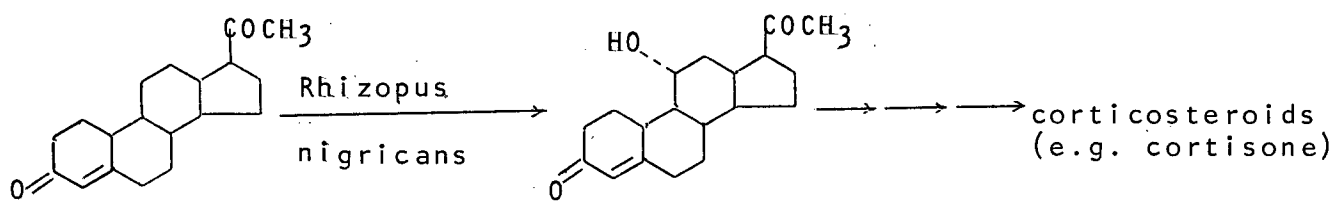
INTRODUCTION

The ability of enzymic systems to functionalise substrates at positions remote from activating groups is well documented. Reactions of this type include the biological oxidation of stearic acid to oleic acid and the microbiological hydroxylation of

$$CH_3(CH_2)_{16}CO_2H \longrightarrow CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$$

stearic acid — oleic acid

steroids (e.g. pregn-18,19nor-Δ^4-3,20-dione) in the commercial production of corticosteroids such as cortisone. The term "remote



pregn-18,19nor-Δ^4-3,20-dione

oxidation" has been given to describe oxidative transformations of this type and recent research in several laboratories (principally those of Professor R. Breslow in Columbia University, N.Y.) has been concerned with the development of laboratory methods to achieve similar remote functionalisation of natural products.[1]

For the purpose of discussion, remote oxidation will be divided into two categories; laboratory and biological remote oxidation.

(A) Laboratory remote oxidation of acyclic and alicyclic substrates

In the past several laboratories have developed techniques to achieve selective functionalisation of unactivated and otherwise unreactive chemical positions. Process like the Barton reaction,[2] the Loeffler-Freytag reaction,[3] the Yang photolysis,[4] and the Heusler reaction[5] all involve the production of a reactive heteroatom radical in a molecule which then, by intramolecular attack on a hydrogen atom located six atoms away, initiates functionalisation of a chemically unactivated position.

More recently, a process defined as " remote oxidation" was developed by Breslow and his co-workers.[6] A series of unbranched aliphatic esters of benzophenone carboxylic acid was used as starting material. On irradiation, the benzophenone group is excited to a triplet state which is capable of abstracting a hydrogen atom from a methylene group remote from the ester functionality. A summary of the regiospecificity of this process is shown in figures 1 and 2. The results indicated that some positions in the aliphatic chain were preferentially functionalised and it was suggested that this could be associated with the preferred conformation of the substrate in the reaction medium.

Substrates with known preferred conformations were later examined. For example, photolysis of the ester (1) derived from benzophenone-4-propionic acid and 3α-cholestanol produced Δ^{14}-cholest-3α-enol (2) and a mixture of lactones (3).[7] The

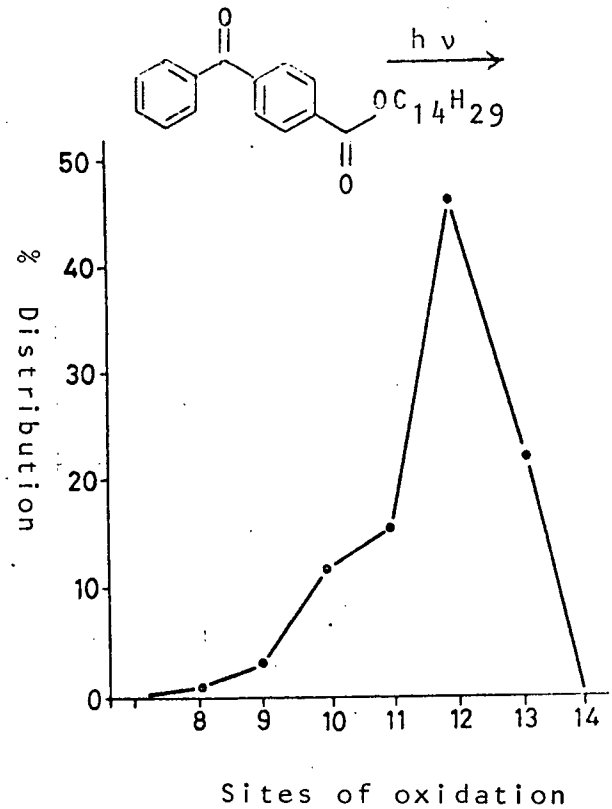


Figure 1. Photo-oxidation of the C_{14} ester.

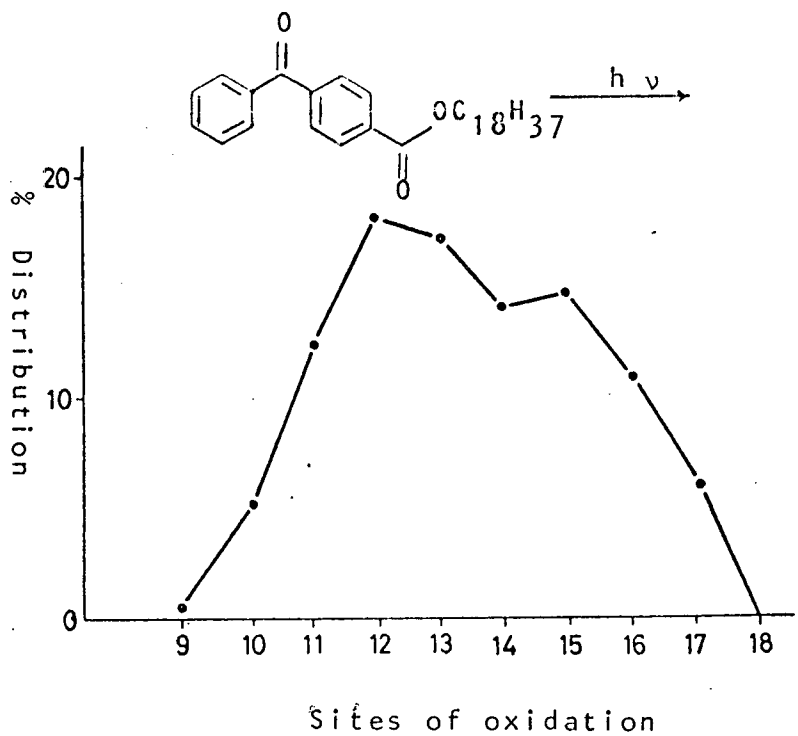
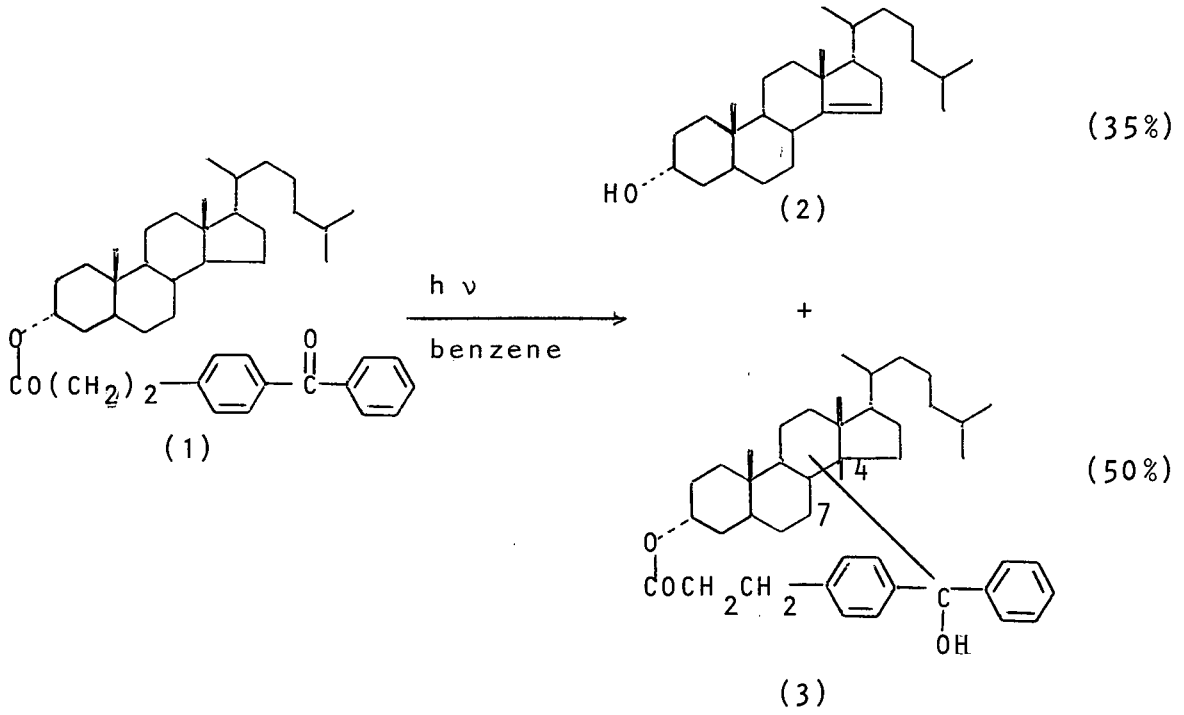
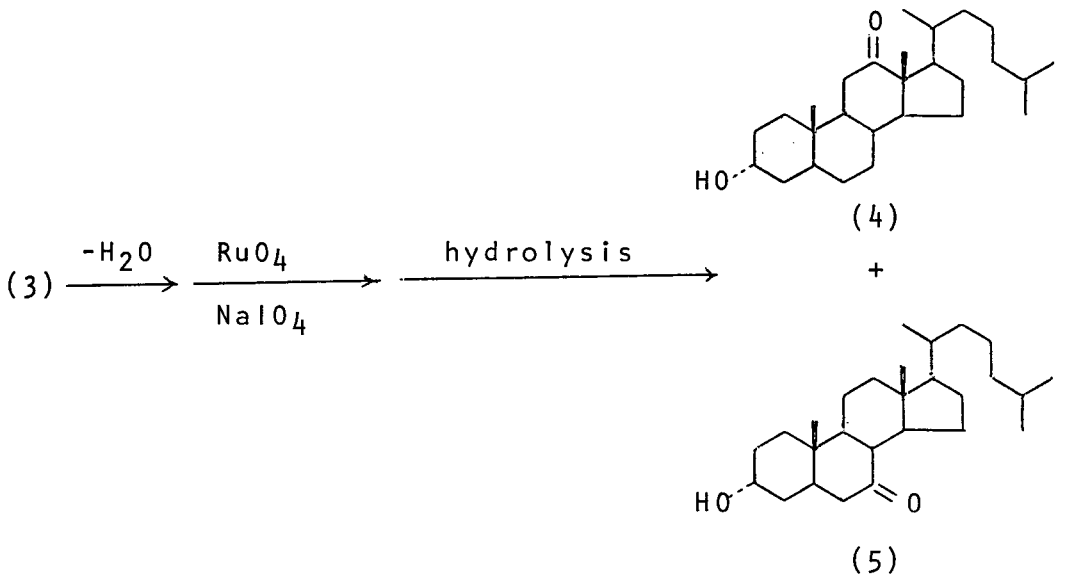


Figure 2. Photo-oxidation of the C_{18} ester.

lactones (3) were dehydrated, hydrolysed and oxidatively cleaved

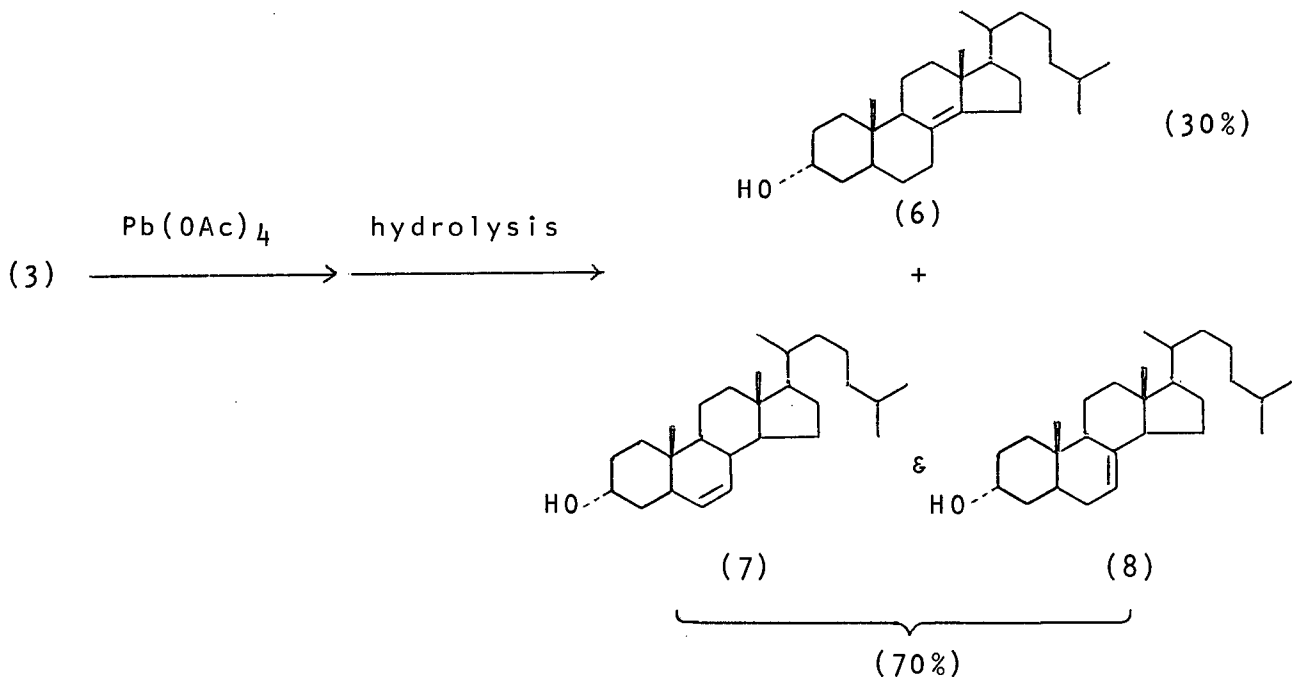


to produce 12-ketocholestan-3α-ol (4) and 7-ketocholestan-3α-ol (5). Alternatively, the lactone mixture (3) can be degraded by

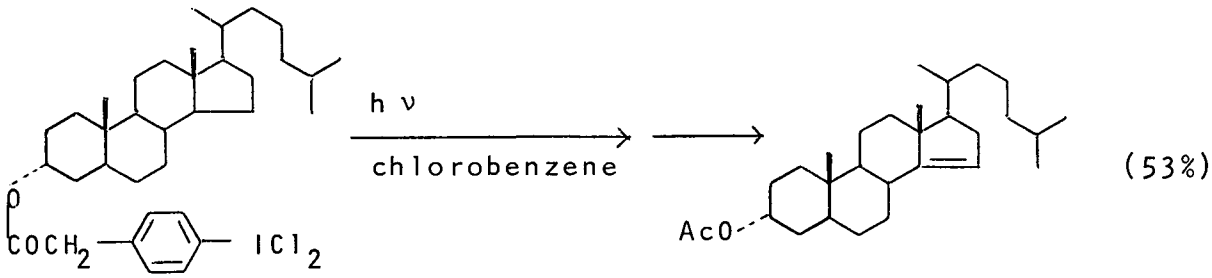


lead tetraacetate oxidation to produce $\Delta^{8(14)}$-cholesten-3α-ol (6)

[derived from a lactone attached at C(14)] and a mixture of Δ^{6}- and Δ^{7}-cholesten-3α-ols (7) and (8) [derived from a lactone attached at C(7)].

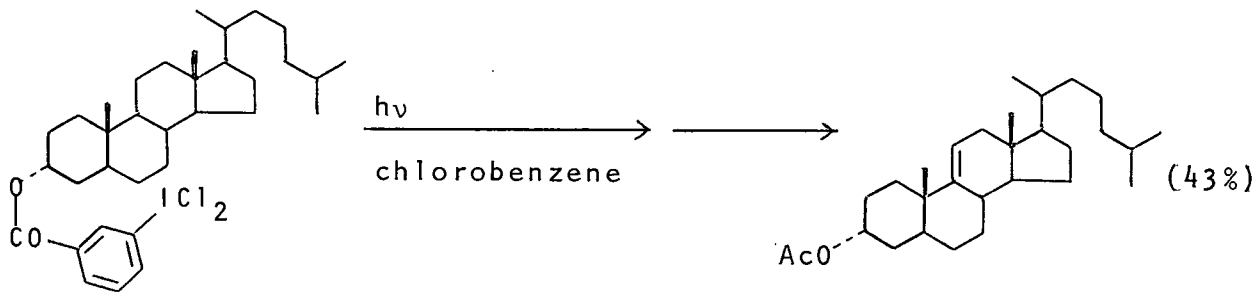


Selective functionalisation at C-14 and C-9 was later obtained by an intramolecular halogenation process. Irradiation of ester (9) in chlorobenzene at -25°C ultimately provided Δ^{14}-cholestenyl-3α-acetate (10) (53% yield) while ester (11)



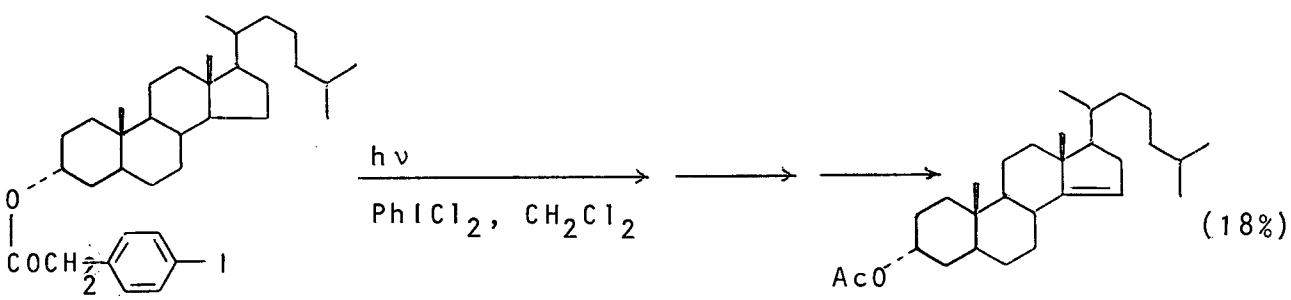
after photolysis gave $\Delta^{9(11)}$-cholestenyl-3α-acetate in 43% yield.[8]

The selective attack at C-14 in (9) and C-9 in (11) is consistent with predictions from molecular models assuming hydrogen abstraction by the chlorine atom in the [Ar-I-Cl]· intermediate.

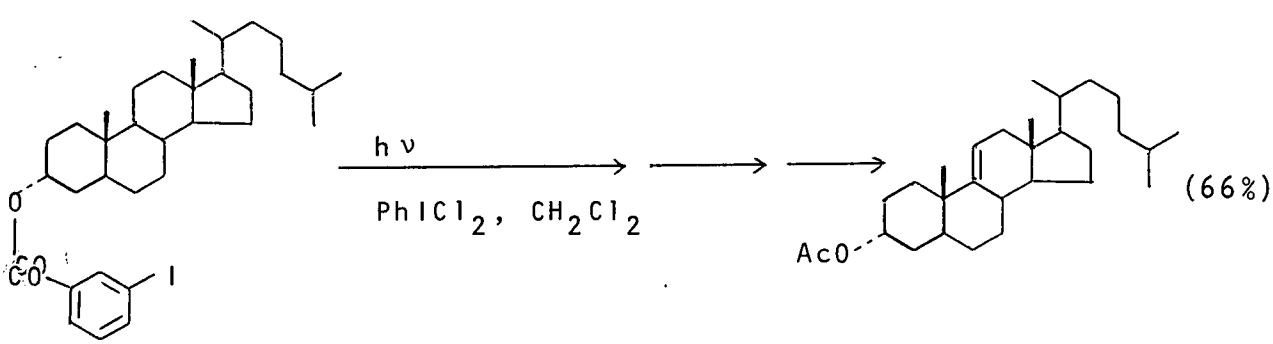


(11) (12)

Compound (13) undergoes chlorination preferentially at C-14 while (14) is chlorinated at C-9.[9] The most reasonable

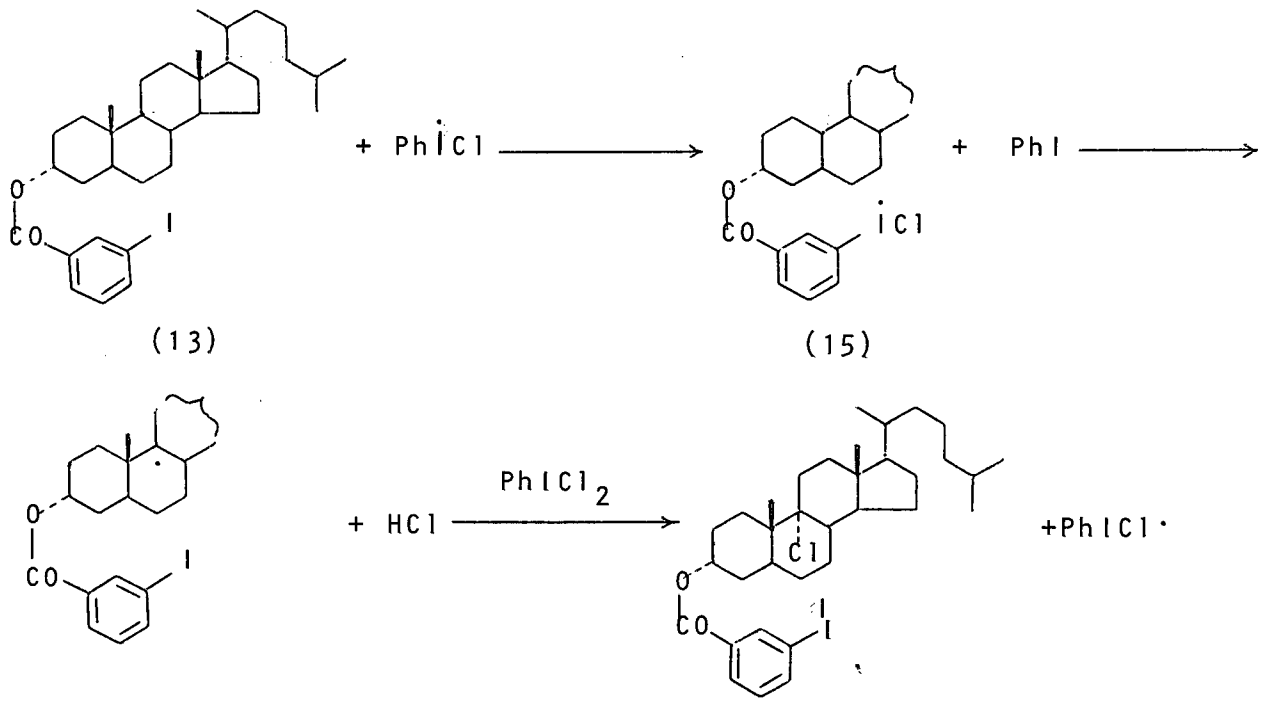


(13)



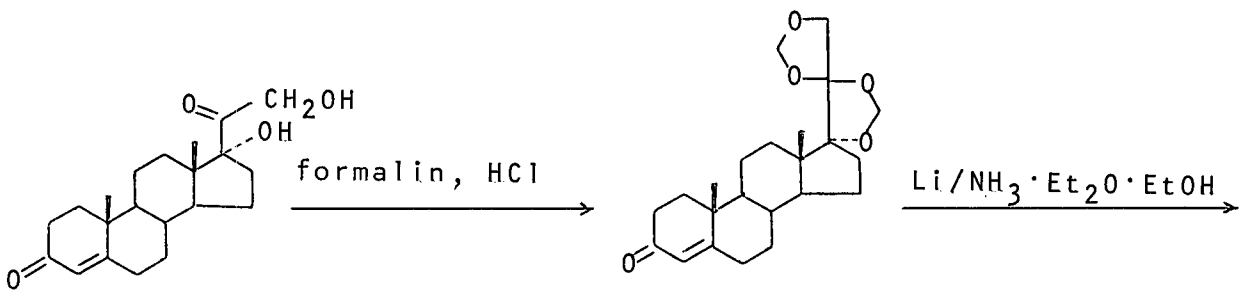
(14)

explanation of these selective halogenations is the radical relay mechanism (scheme 1) in which (15) can be generated by transfer of a chlorine atom to (13) from an external radical reagent.

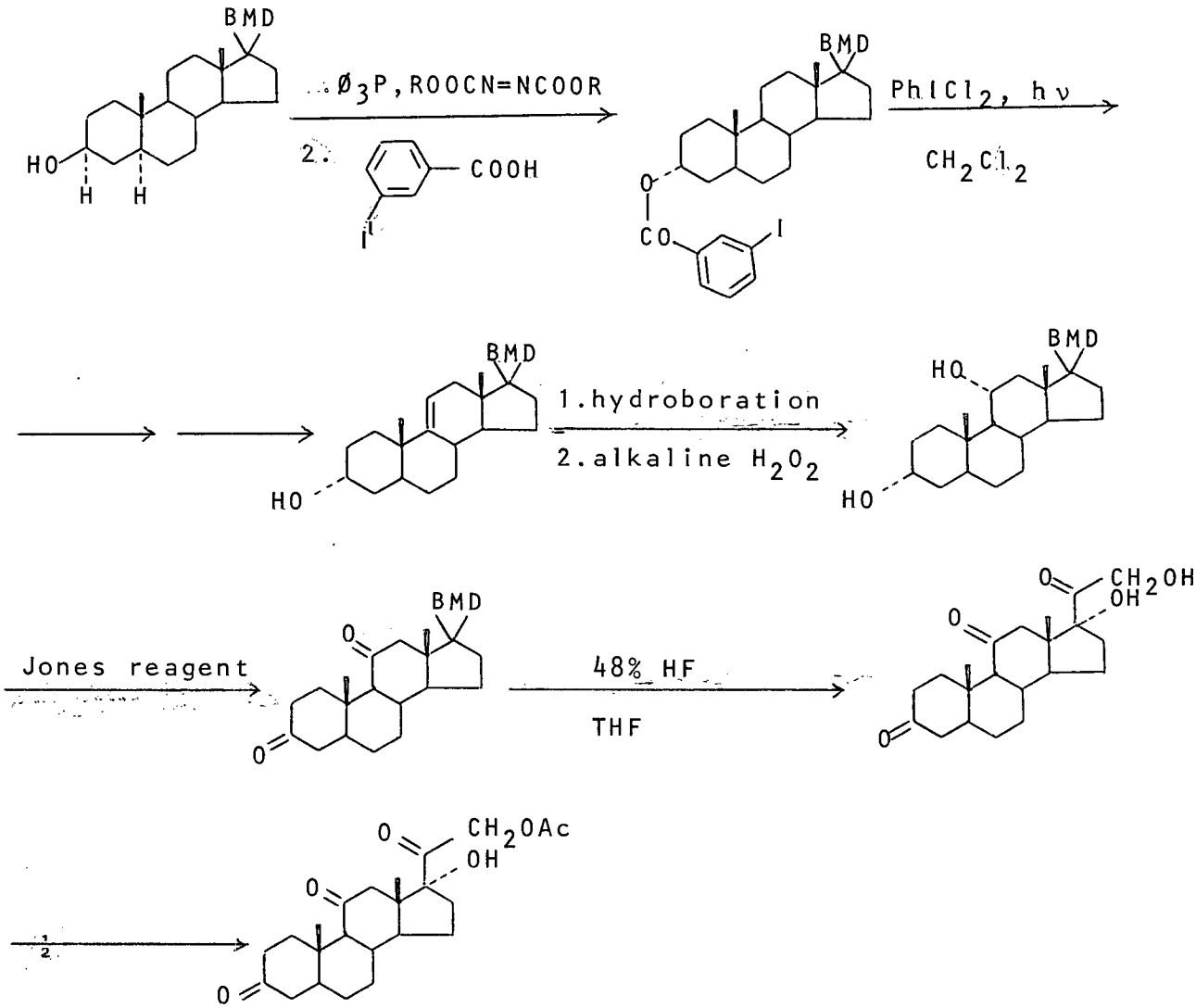


Scheme 1

Application of this remote halogenation by utilising an external ArICl· radical was found useful in synthesis of cortisone[10] (scheme 2).



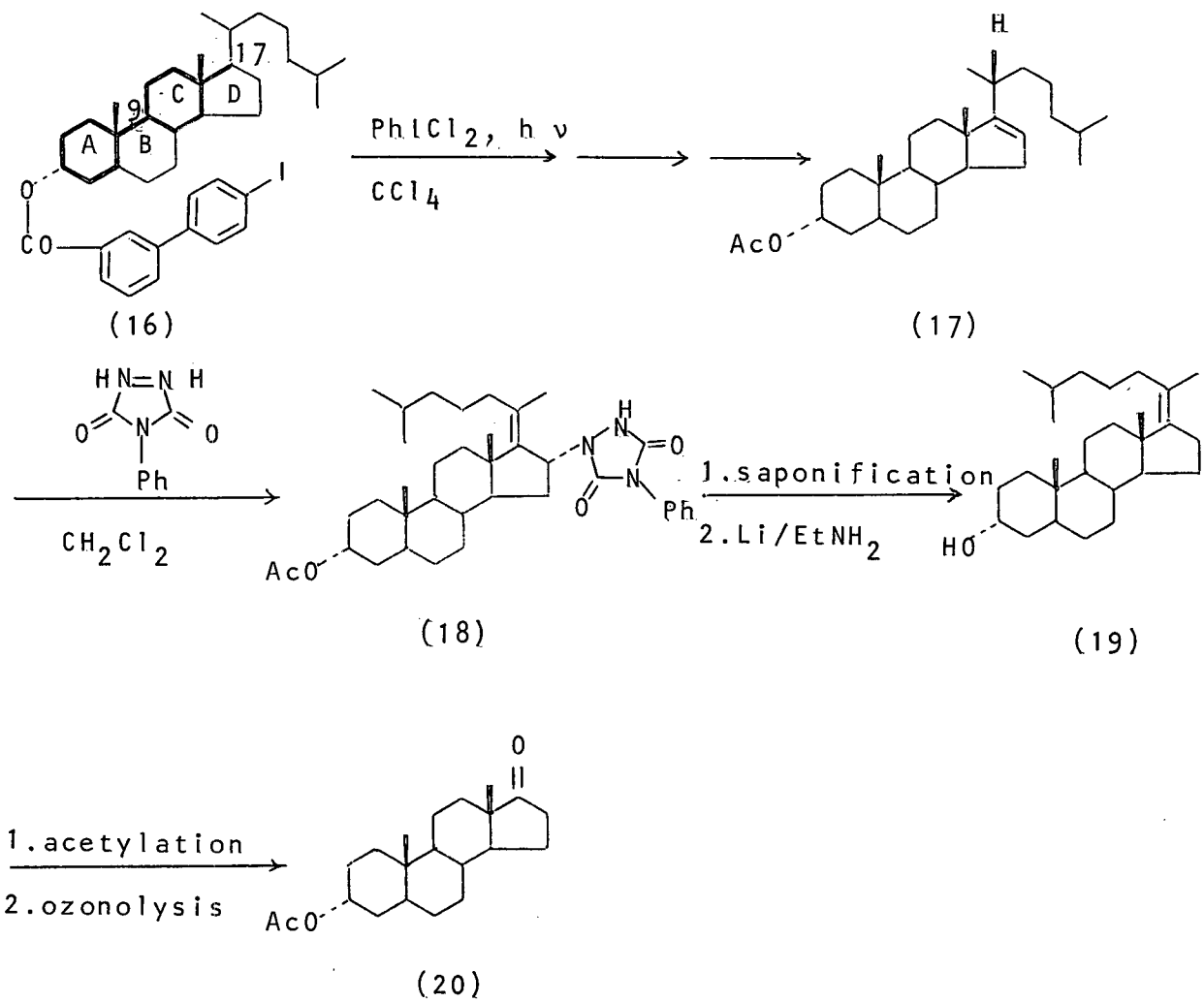
Cortexolone



Scheme 2

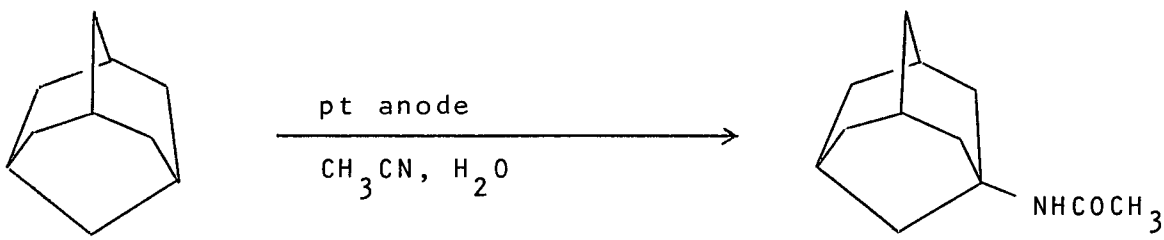
Further application of this remote functionalisation to halogenate selectively at C-17 is the key step in an efficient conversion of 3β-cholestanol to androsterone acetate. The steroid structure (16) shows that C-9 is directly attached to ring A while C-17 is attached to ring A with the six-membered ring C. Inserting a phenylene into m-iodobenzoic acid to give (16) should

provide a reagent capable of attacking C-17 from C-3. Thus photolysis of (16) with $PhICl_2$ in carbon tetrachloride gave, after processing, 41% of Δ^{16}-3α-cholestenyl acetate(17) which by reaction with N-phenyltriazolinedione in methylene chloride provided the ene adduct (18). The stereochemistry of the double bond would result from α attack on the steroid and intramolecular hydrogen transfer. (18) was then saponified and reduced with lithium in ethylamine to give Z-$\Delta^{17(20)}$-3α-cholestenol (19). Acetylation of (19) followed by ozonolysis provided androsterone acetate (20).



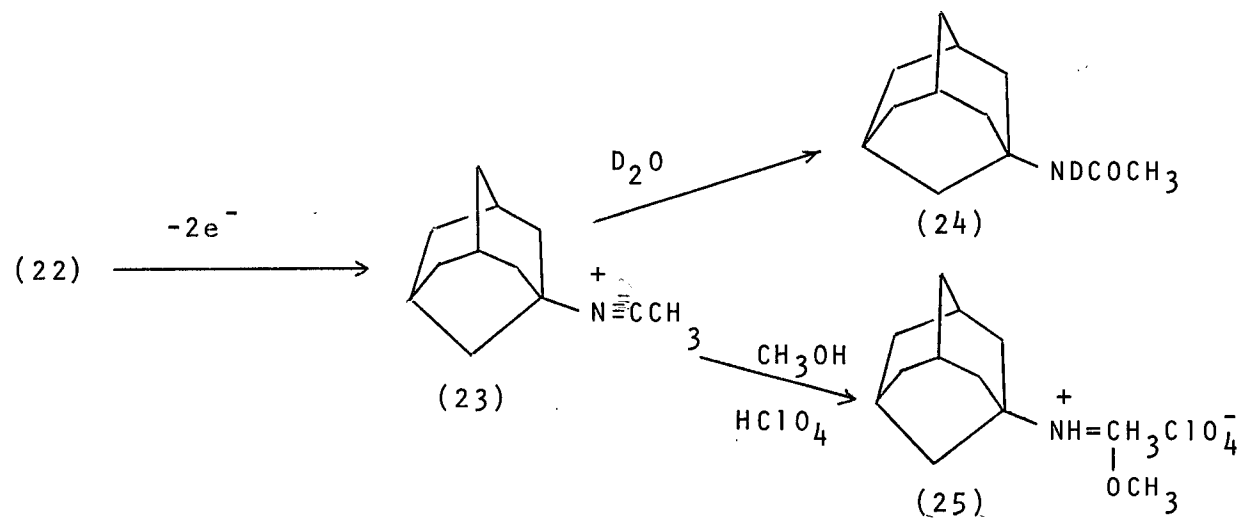
Miller and his co-workers reported that alkanes (21) and adamantanes (22) were oxidized to produce acetamide at a platinum anode in acetonitrile.[12] The oxidation involves

$$\underset{(21)}{(CH_3)_2CH\text{-}CH(CH_3)_2} \xrightarrow[CH_3CN,\ H_2O]{\text{pt anode}} (CH_3)_2CH\text{-}NHCOCH_3$$



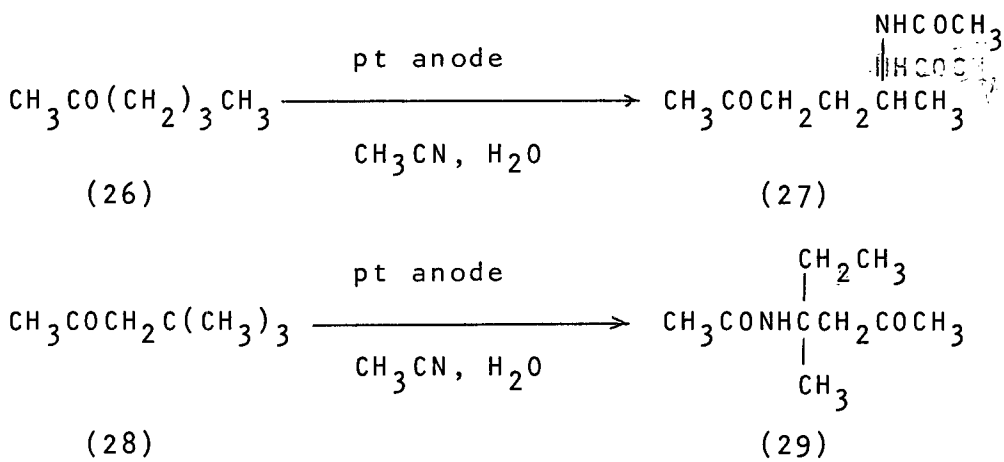
(22)

direct electron transfer from hydrocarbon to the electrode. After initial electron transfer and subsequent fragmentation, (21) provided the isopropyl cations which are the precursors of acetamides in acetonitrile. The presence of intermediate carbonium ions was also demonstrated in the oxidation of adamantanes. The presence of adamantyl cation was implied by the existence of acetonitrilium ion (23) which was verified by quenching the

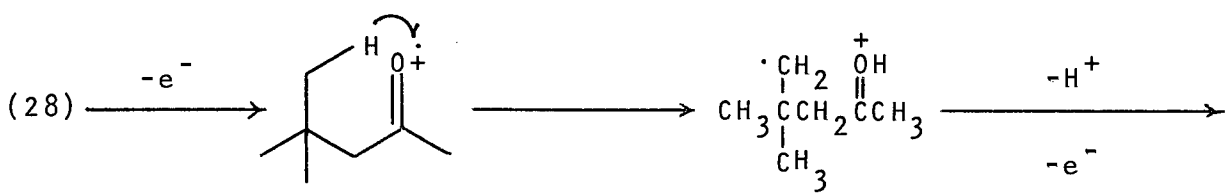


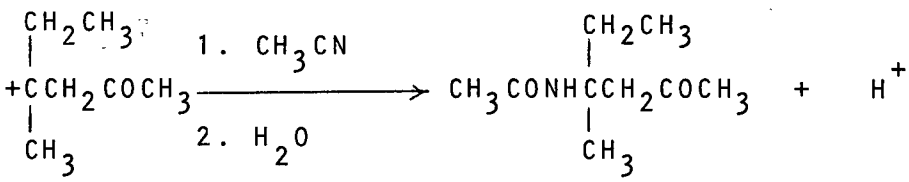
reaction after electrolysis with deuterium oxide and with methanol.

These anodic oxidations were very useful in acetamidation of ketones[13] and esters[14] at remote positions. Oxidation of 2-hexanone (26) produced 5-acetamido-2-hexanone (27) and 4,4-dimethyl-2-pentanone (28) oxidation produced 4-acetamido-4-methyl-2-hexanone (29). The proposed mechanism for these



oxidations involves (i) direct oxidation of the ketone, (ii) an intramolecular attack on the remote hydrogen-carbon bond by oxygen and a second electron transfer, and (iii) trapping, or rearrangement and trapping reactions of the resulting carbonium ions. This can be envisaged for (28) as shown in scheme 3. A direct oxidation of substrate at the electrode is indicated since background current at 2.3V is only ∿2% of that



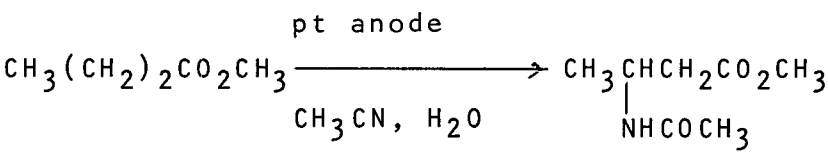


(29)

Scheme 3

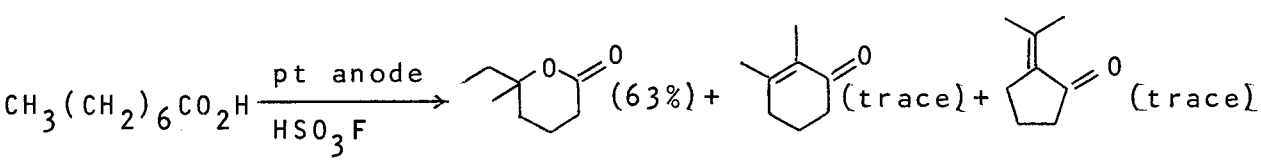
due to added ketone.

Simple esters can be cleanly mono-acetamidated and straight-chain esters undergo preferential ω-1 (carbon next to the end of the chain) substitution, e.g.



As in remote anodic acetamidation of ketones, the reaction occurs via carbonium ion intermediates. For straight chain esters the carbonium ion is formed at the secondary position most remote from the electron-withdrawing ester function, and as the chain becomes longer, more ω-2 product is observed.

Anodic oxidation of carboxylic acids in fluorosulphuric acid provides lactones and unsaturated cyclic ketones.[15] For example, oxidation of octanoic acid (30) produces (31), (32) and (33). In strongly acidic medium, the

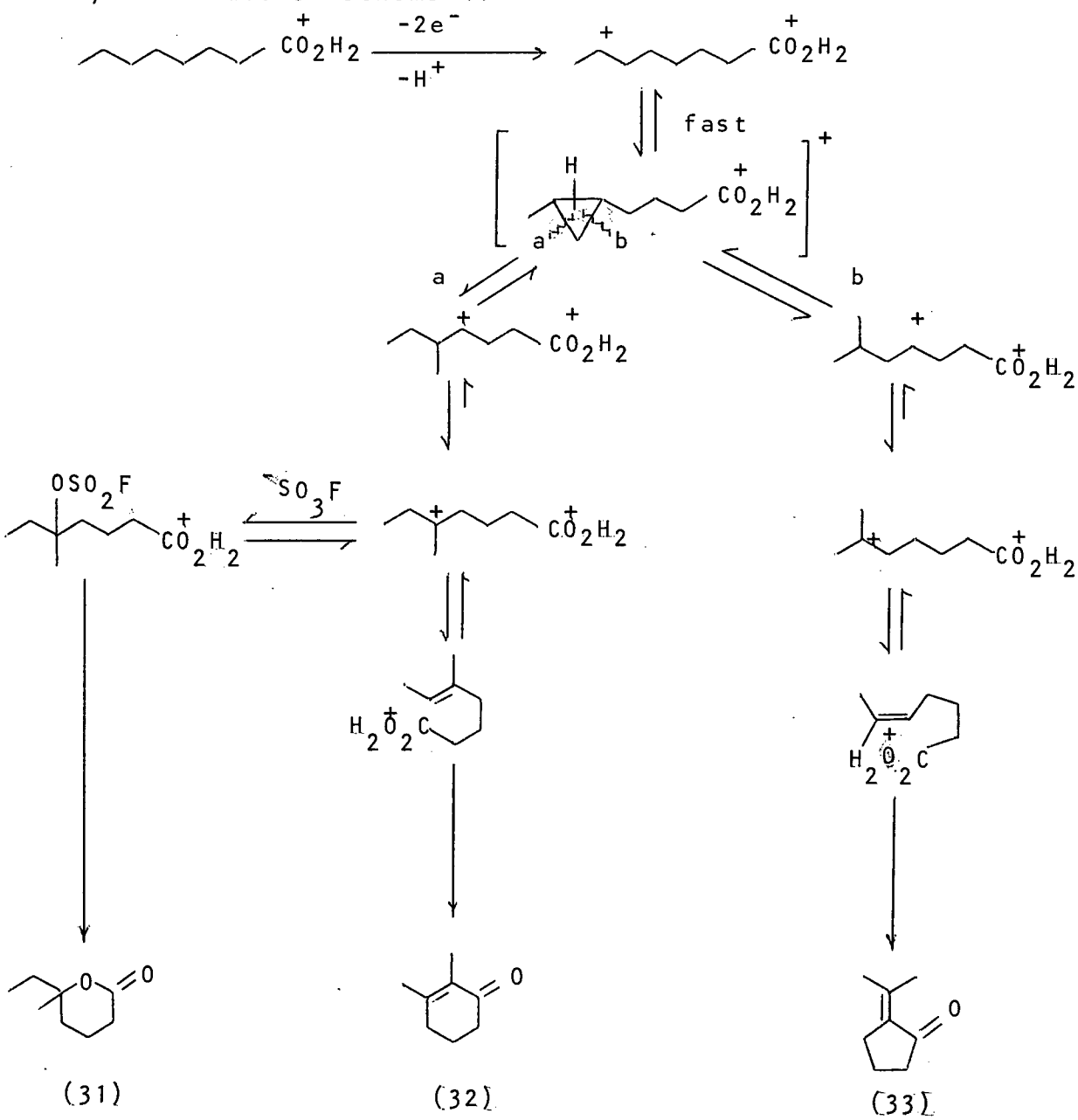


(30) (31) (32) (33)

electroactive species is the protonated carboxylic acid $RCO_2H_2^+$ because of the equilibrium

$$RCO_2H \quad + \quad HSO_3F \rightleftharpoons RCO_2H_2^+ \quad + \quad FSO_3^-$$

The products from this anodic oxidation could be rationalised by the reaction scheme 4.



Scheme 4

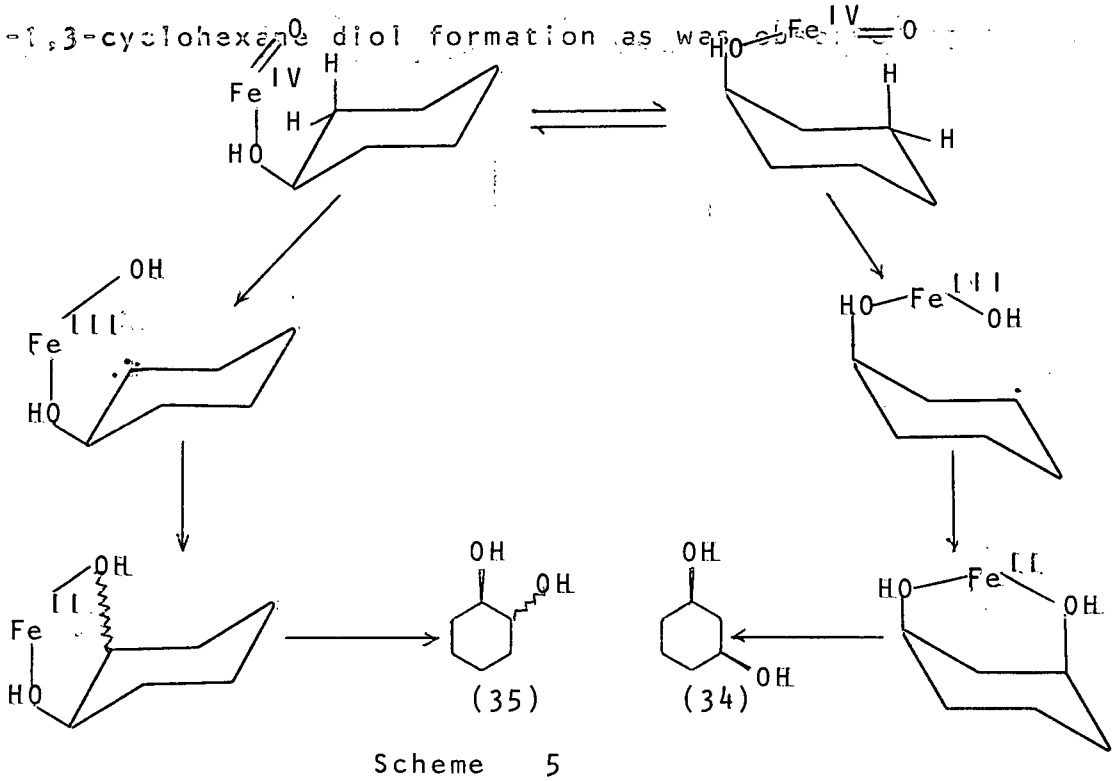
Stereospecific remote hydroxylation of cyclohexanol was achieved with ferrous ion-hydrogen peroxide reagent. The major product is cis-1,3-cyclohexane diol (34) together with small amounts of 1,2-diols (35).[16] This process proceeds by direct oxidation through a cyclic transition state by a bound iron species, formally equivalent to a ferryl iron (36), and leading to discrete radical and carbonium ion intermediates (scheme 5). Ferryl ion (36) can also be obtained by photoreduction of ferric

$$Fe^{2+} + H_2O_2 \xrightarrow{H^+} Fe^{3+} + OH^- + \cdot OH$$

$$Fe^{3+} + \cdot OH \rightleftharpoons FeO^{2+} + H^+$$

(36)

perchlorate hexahydrate, and it shows the same preference for cis-1,3-cyclohexane diol formation as was observed



Scheme 5

cis-1,3-cyclohexane diol formation as was observed in the ferrous ion-hydrogen peroxide reaction.[17] This stereospecific hydroxylation upon photoreduction of iron (III) proffers evidence that regiospecificity observed is due to alcohol-oxidant complexation.

Cyclohexane, 1-octyl trifluoroacetate, heptane and decane are oxidized by Fe(II)-Et_3NO in CF_3CO_2H and the reactions stop at the alcohol stage.[18] In the oxidation of 1-octyl trifluoroacetate, 72% selectivity in the 7 position is shown. This is due to polar selectivity which favour oxidation at the penultimate carbon. Although the mechanism is not yet completely established, it is believed that hydrogen abstraction by $R_3N^{+\cdot}$, producing an alkyl radical, is involved. The alkyl radical is then converted into the ester product via an encumbered carbonium ion, produced by Fe(III) oxidation (scheme 6).

$$R'_3NOH^{+\cdot} + Fe(II) \longrightarrow Fe(III) + R'_3N^{+\cdot}$$

$$R'_3N^{+\cdot} + RH \longrightarrow R'_3NH^{+} + R\cdot$$

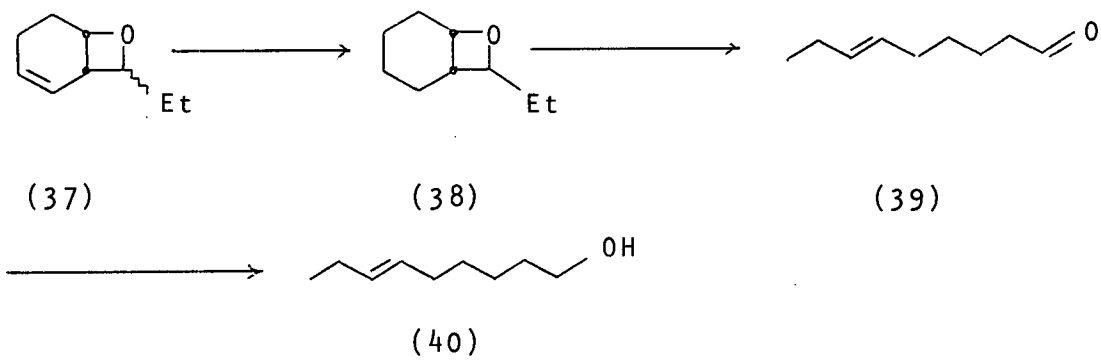
$$R\cdot + Fe(III) \longrightarrow Fe(II) + R^{+}$$

$$R^{+} + CF_3CO_2H \longrightarrow CF_3CO_2R + H^{+}$$

Scheme 6

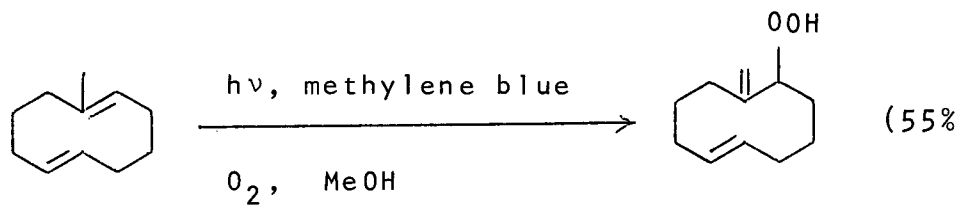
Carbonyl-carbonyl-olefin metathesis is applied to synthesis of trans-non-6-en-1-ol (40), a sex attractant of the Mediterranean

fruit fly, by Jones and his co-workers.[19] Photolysis of propionaldehyde and cyclohexa-1,3-diene in acetonitrile gave (37) (80% exo-) in 77% yield. Hydrogenation of (37) to (38) was quantitative. Pyrolysis of (38) at 270-340°C gave (39) which was then reduced by $LiAlH_4$ to give (40). The thermal decomposition of bicyclic oxetans is highly regioselective. It favours the formation of metathesis products over regenerated carbonyl-olefin pairs.



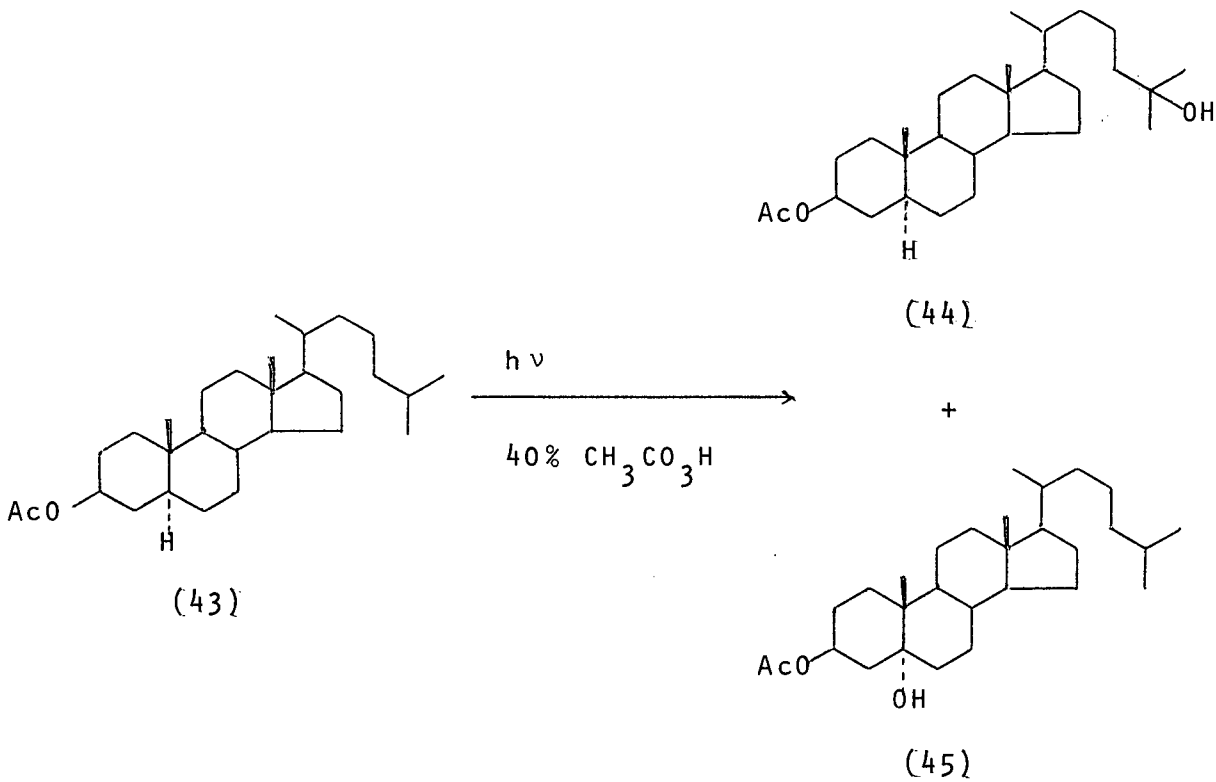
(37) (38) (39) (40)

Regiospecific hydroperoxidation of a double bond was observed in the photosensitized oxygenation of trans,trans-1-methylcyclodeca-1,6-diene (41) with singlet oxygen.[20] A methanol solution of (41) was irradiated in the presence of methylene blue at 10°C for 4.5 hr. while pure oxygen was bubbled through the solution. A single product (42) was isolated in 55% yield.

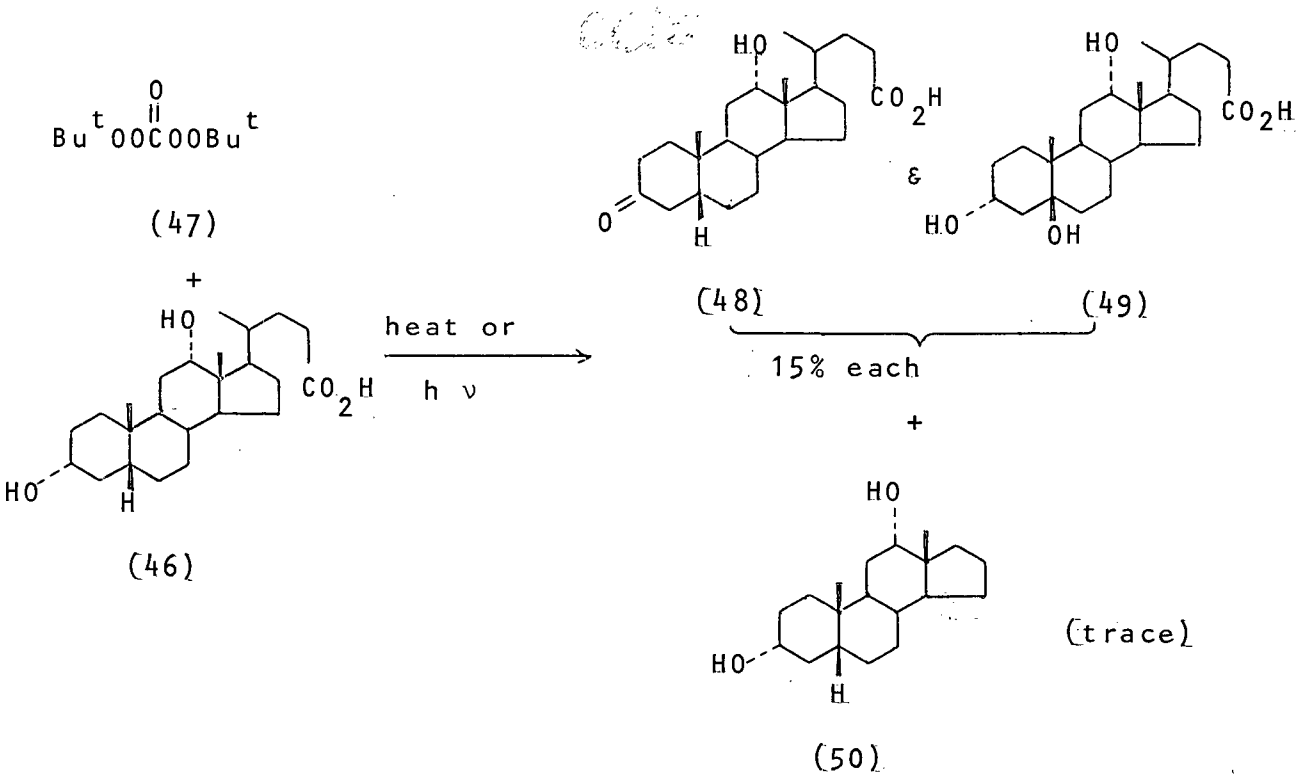


(41) (42)

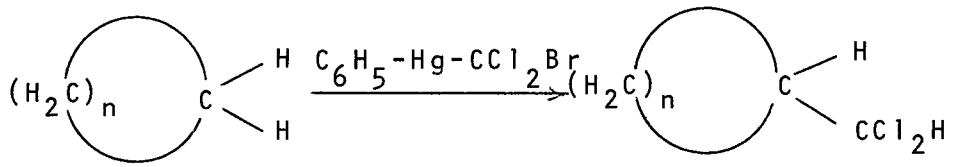
Irradiation of 3β-acetoxycholestane (43) containing 10 mol equiv. of peracetic acid resulted in hydroxylation at the 25- and 5α-positions [i.e. product (44) and (45)]. This method is used to introduce a hydroxyl group at 25 position in cholesterol.[21]



Another one-step regiospecific and stereospecific hydroxylation at position 5 of deoxycholic acid has been reported.[22] A 4:1 molecular complex is formed by mixing (46) with stoichiometric amounts of di-t-butyldiperoxycarbonate (47). Heating of the complex at 90°C or photolysis at 25°C leads to formation of two major products (48) (15%) and (49) (15%) and traces of (50).



Cycloalkane (51) with completely unactivated C-H bonds was found to react with phenyl(bromodichloromethyl)mercury to give dichloromethyl cycloalkane (52) in reasonable yield (48-83%).[23] The introduction of the dihalomethyl substituent provides a reactive site for further transformation.

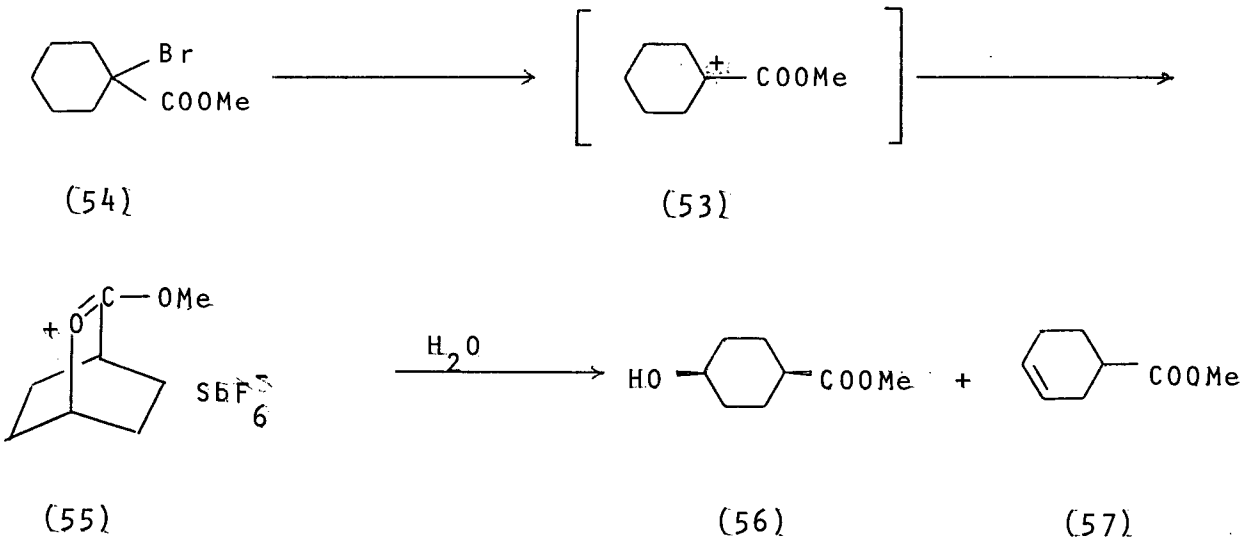


n=6, 7, 11 n=6,48%;n=7,83%;n=11,64%

(51) (52)

α-keto carbonium ion (53) formation is believed to be involved in the dehalogenation of α-bromo carbonyl compounds (54) with $AgSbF_6$.[24] The ion (53) is stabilized by hydride shift to give (55) which is then hydrolysed with water to provide (56) and (57). Thus the hydroxyl group is regiospecifically

introduced to the cis-4 position.



(B) Biological remote oxidation of acyclic and alicyclic substrates

Many reactions involving regiospecific oxidation at unactivated C-H bonds are inaccessible to organic chemists but can occur readily in microorganisms. Although microbial oxidation is widely applied in both industry and research, little is known about the actual mechanism of the enzymatic process responsible for oxidation of unactivated C-H bonds. The following discussion will be grouped in two areas (1) steroids, and (2) isoprenoids.

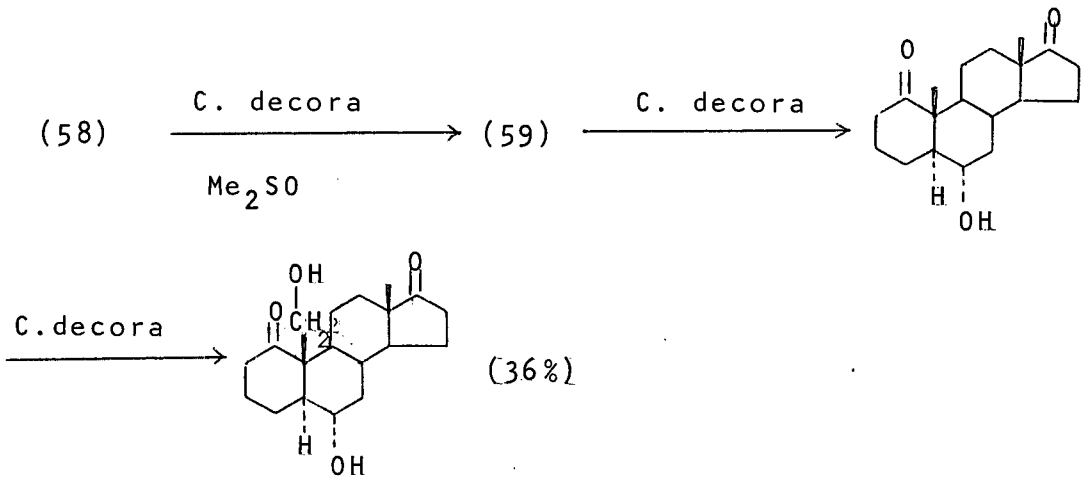
(1) Steroids

When a solution of 5α-androstan-17-one (58) in ethanol is incubated with *Calonectria decora* for 2 days, the 1β,6α-dihydroxy-17-ketone (59) is formed cleanly.[25] In a similar experiment, using dimethyl sulphoxide as the medium, (58) is

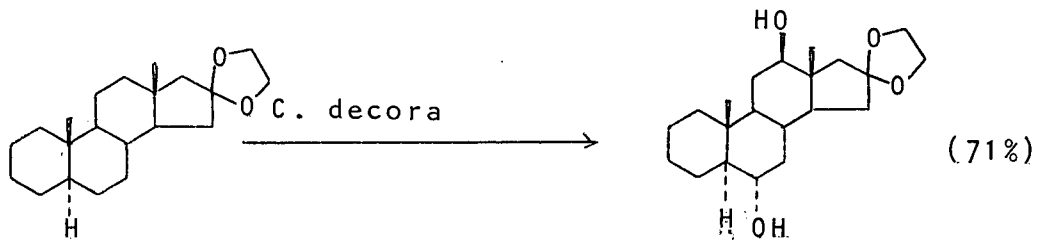
(58) (59)

oxidized with *Calonectria decora*. The initial product (59) is further oxidized at the 1β-hydroxy-group and then hydroxylated [illegible]

at C-19 to give 6α,19-dihydroxy-5α-androstane-1,17-dione (60) in 36% yield.[26] The acetals (61) derived from 5α-androstan-16-



one is hydroxylated more efficiently than its parent ketone (62).[27]

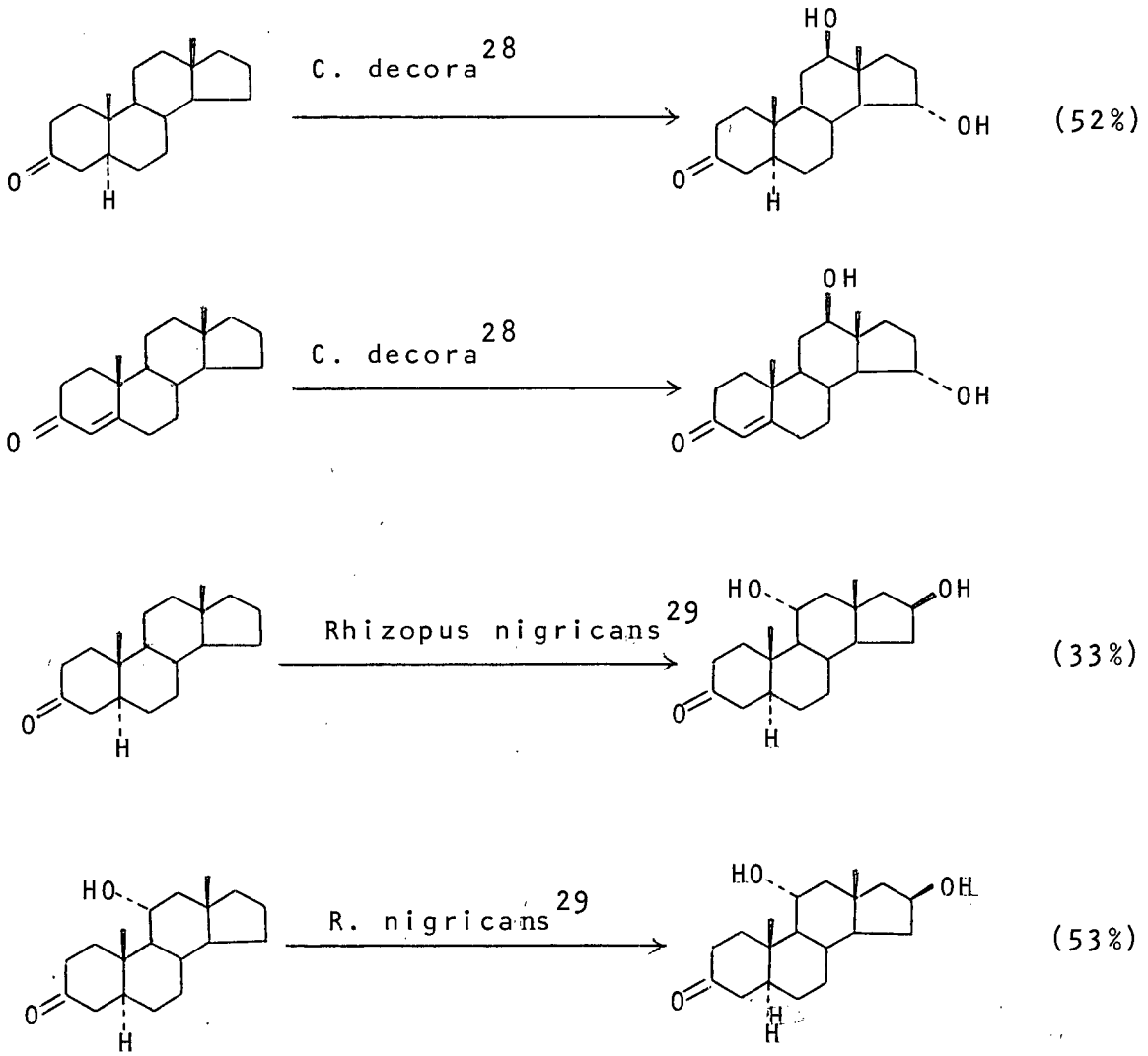


(61)

(62)

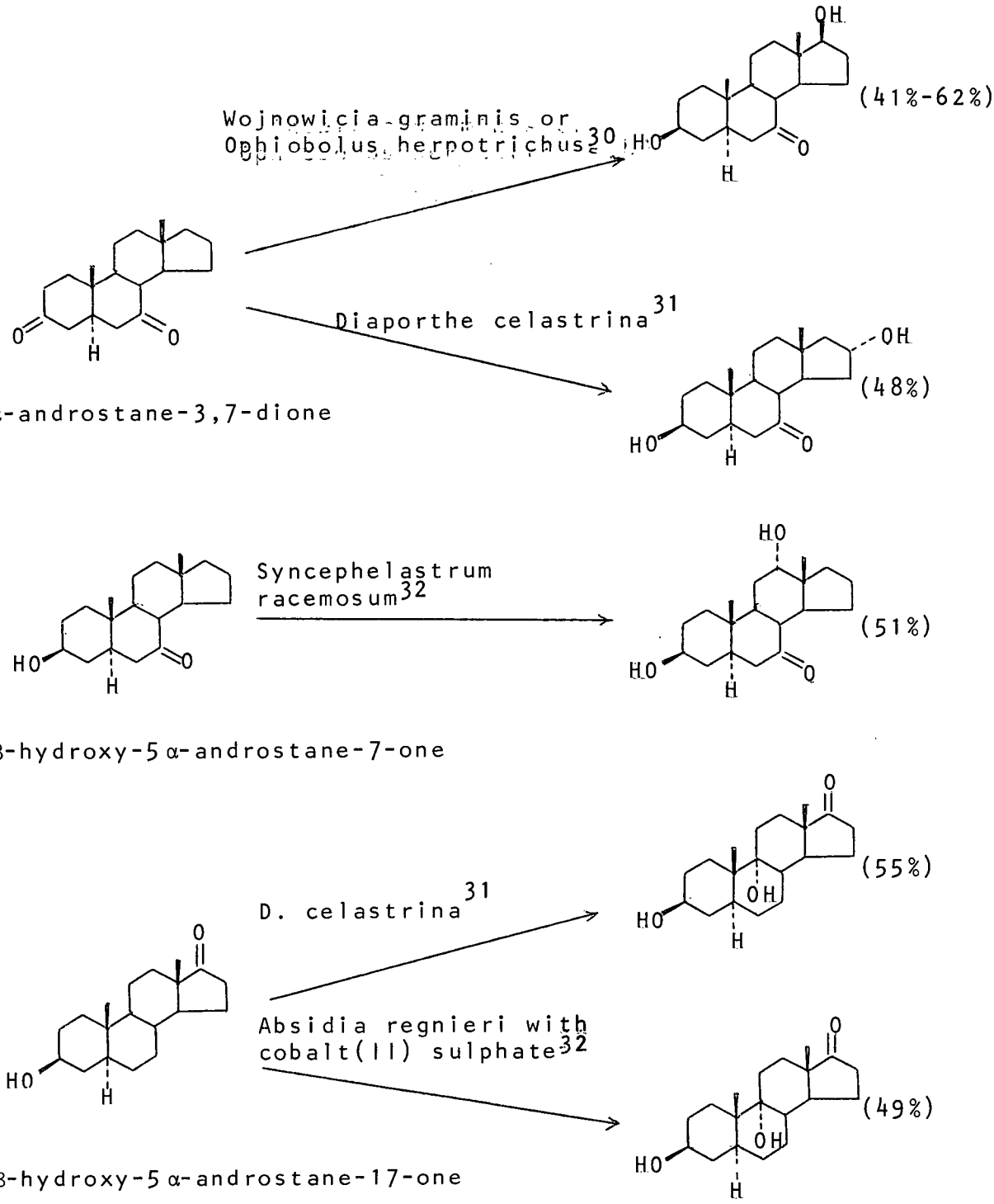
Microbiological hydroxylation of a large number of mono- and di-oxygenated C_{19} steroids has been investigated

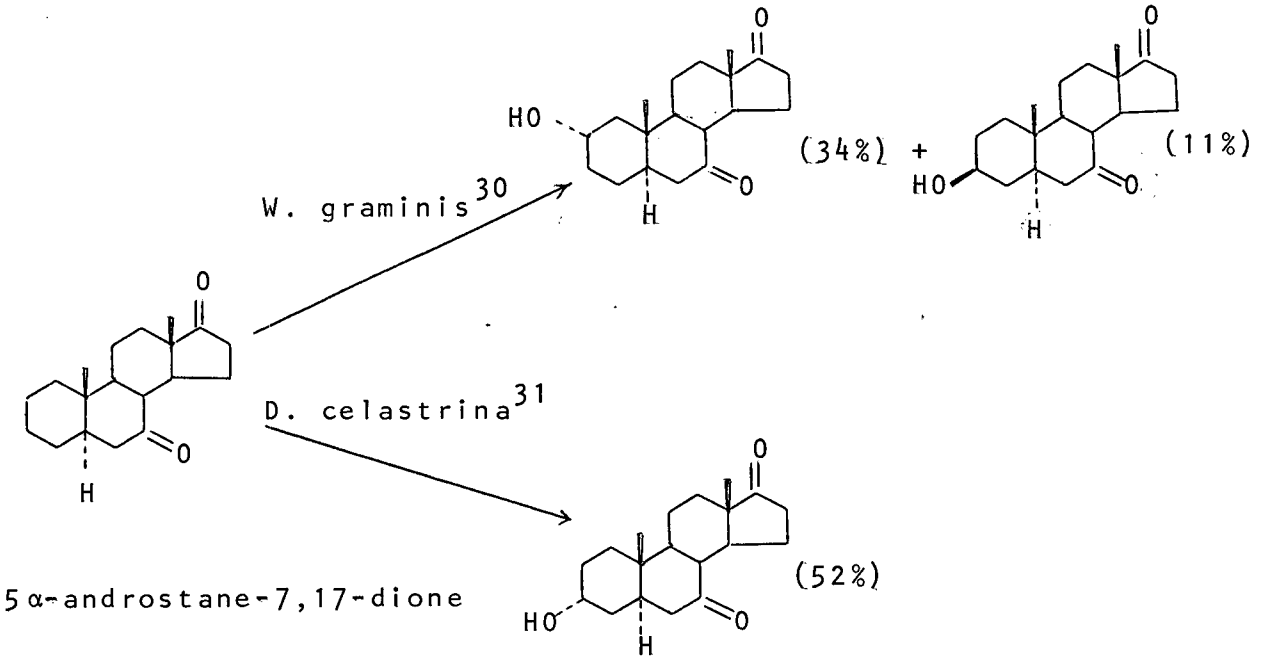
in order to ascertain the effect of varying the positions of the oxygen functions on the hydroxylation pattern. A few examples are illustrated. This study should eventually lead to predictions

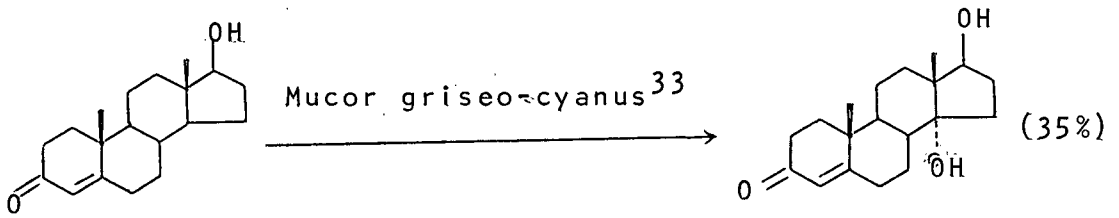


regarding the position of microbiological hydroxylation of steroids with certain microorganisms. The steroid substrates for this study carry oxygen substituents at two of the 3,7,17

positions and are oxygenated at the positions that carrying no oxygen atom.

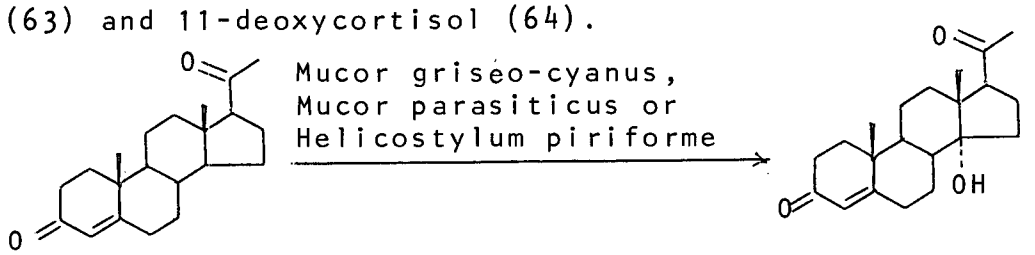




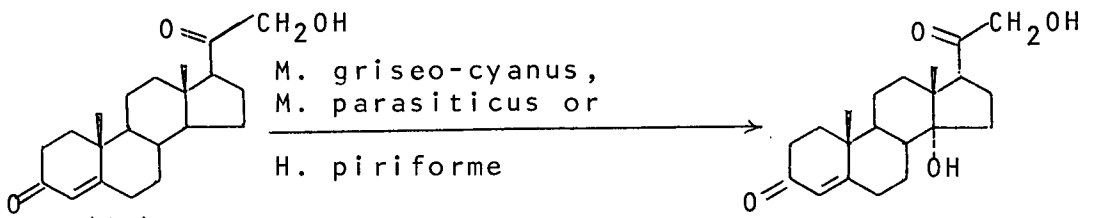


testosterone

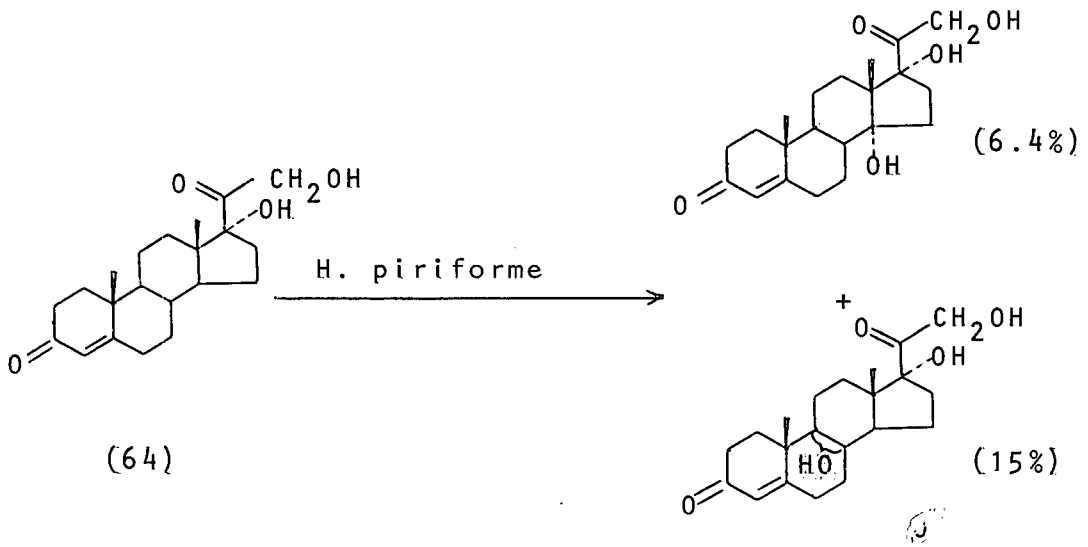
Mucor parasiticus, Mucor griseo-cyanus and Helicostylum piriforme are found to oxygenate progesterone, deoxycorticosterone (63) and 11-deoxycortisol (64).[33]



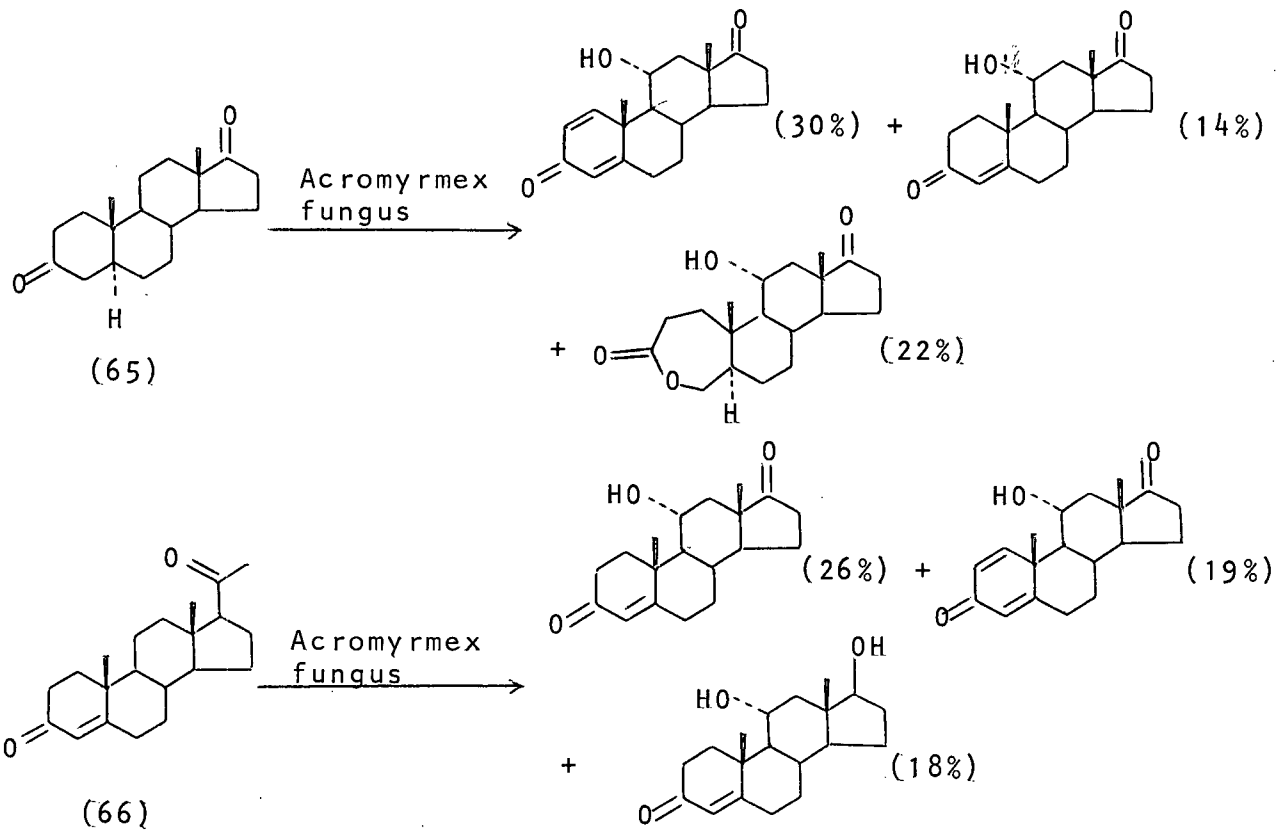
progesterone



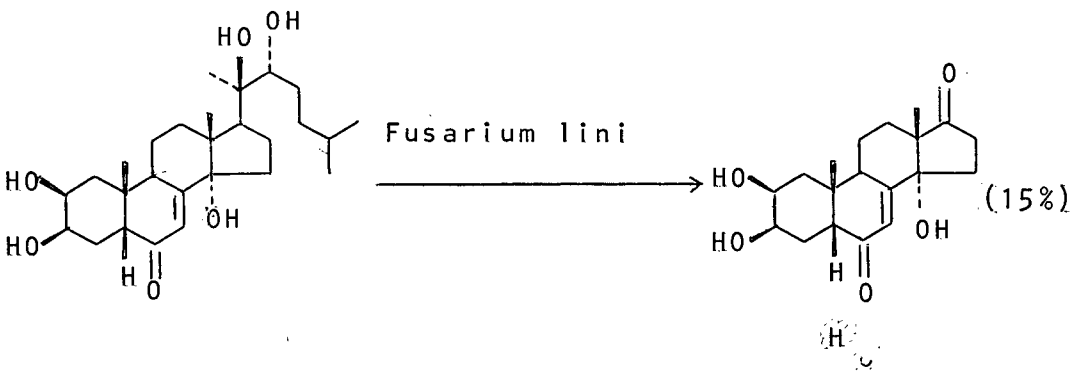
(63)



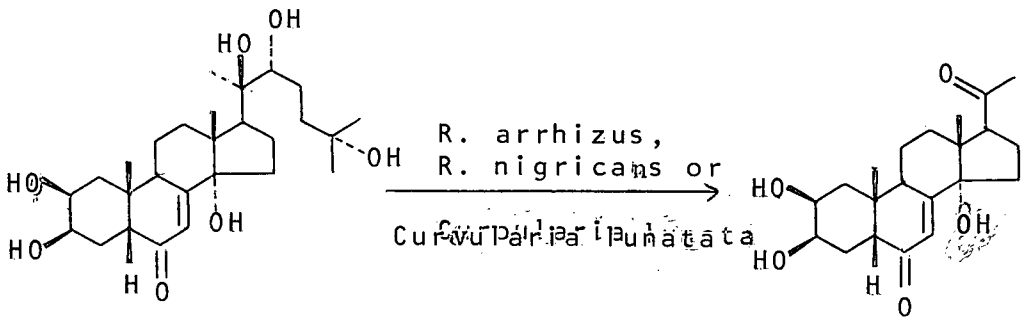
The acromyrmex fungus obtained from the nest of the ant species Acromyrmex octospinosus is an efficient 11α-hydroxylating organism in spite of the complexity of the mixture as exemplified by the incubation of androstane-3,17-dione (65) and pregnane-Δ^4-3,20-dione (66).



Degradation of the side chain of steroids can be carried out by using microbial oxidation. Examples are given for ponasterone A (67)[35] and crustecdysone (68).[36]

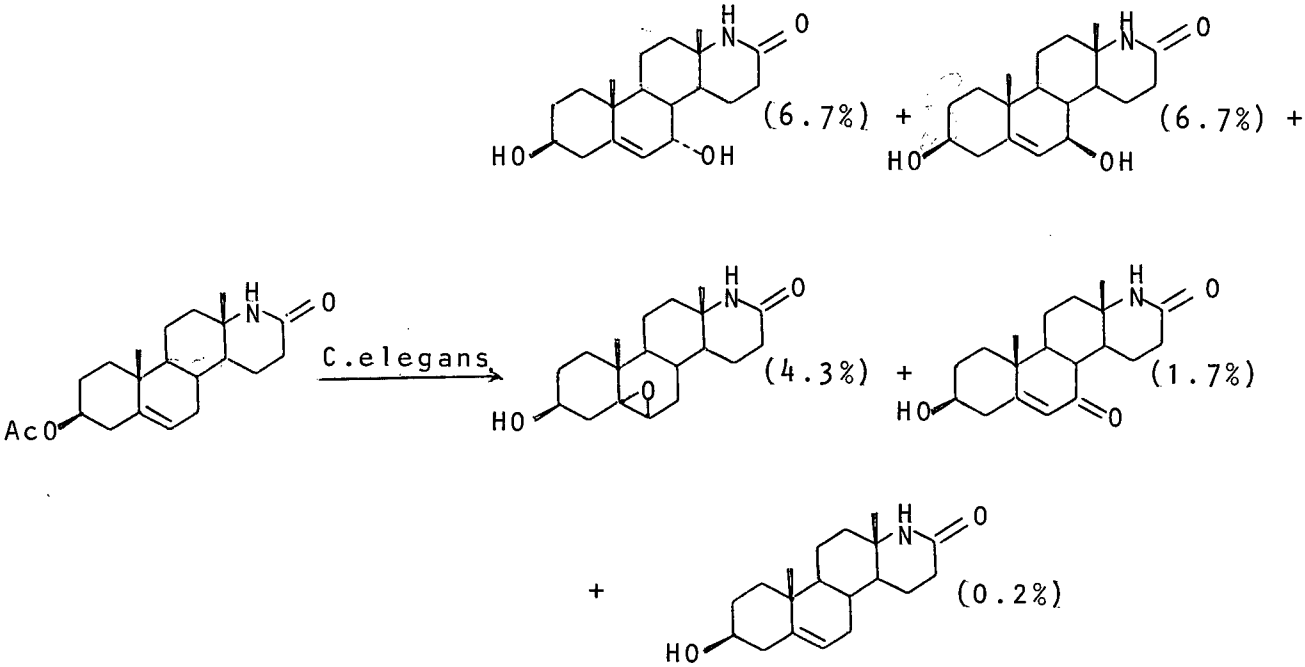


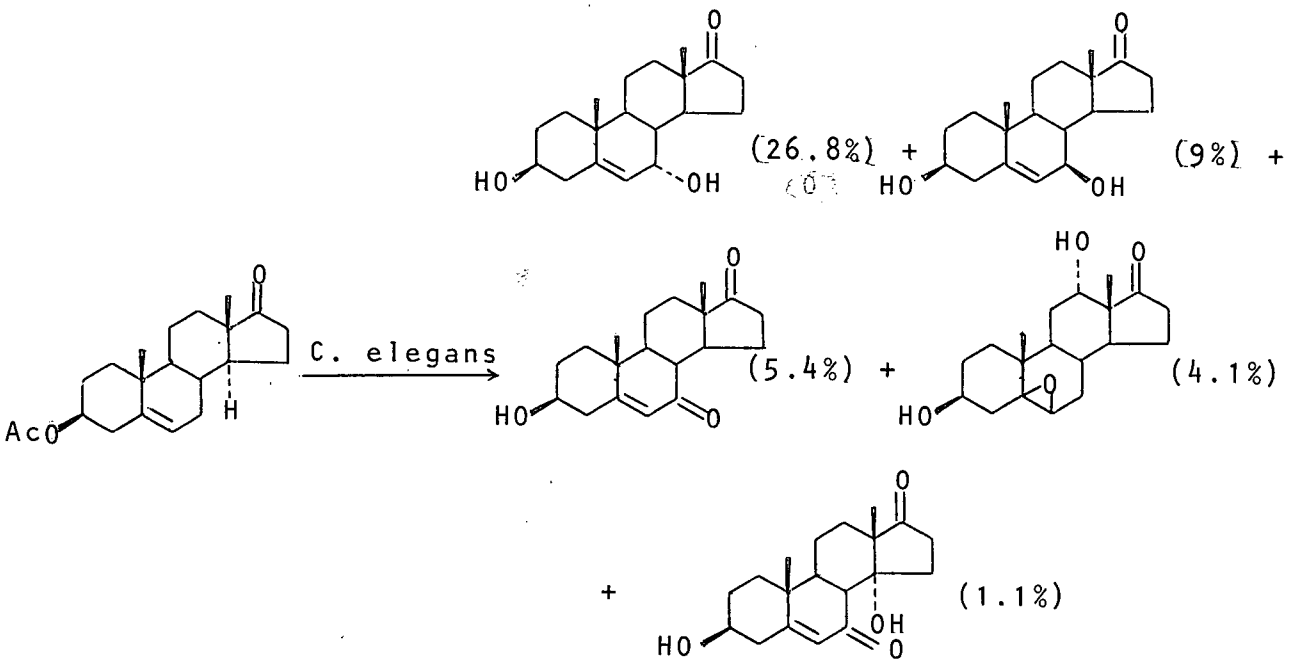
(67) Rubrosterone



(68) Poststerone

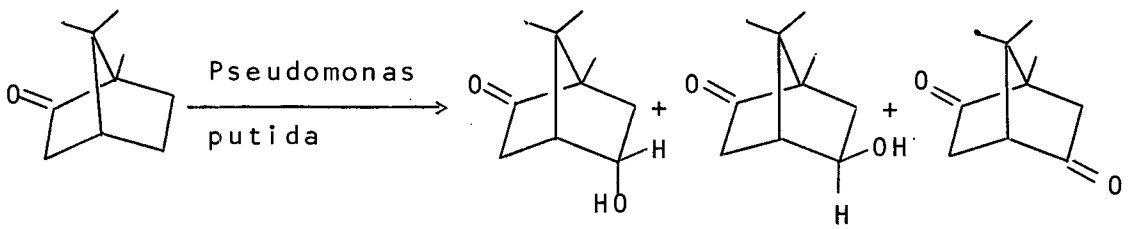
A heterocyclic steroid like 3β-acetoxy-17a-aza-D-homo-androst-5-en-17-one (69) is oxidized by <u>Cunninghamella elegans</u> to give a complex mixture, while its steroidal ketone (70) gives a mixture with more dioxygenated products.[37]


C.elegans
(6.7%)
(6.7%)
(4.3%)
(1.7%)
(0.2%)


C. elegans
(26.8%)
(9%)
(5.4%)
(4.1%)
(1.1%)

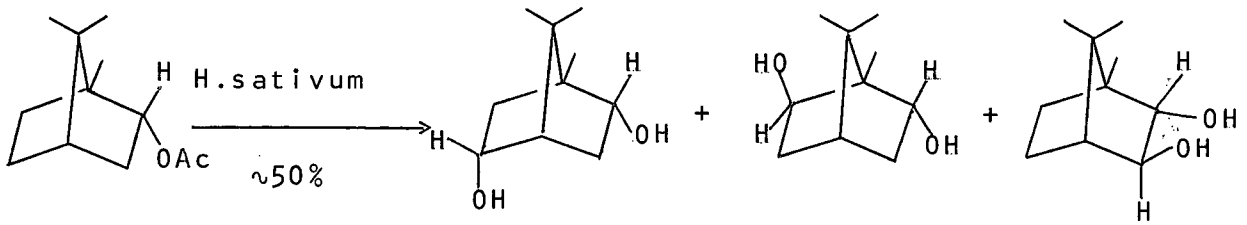
(2) Isoprenoids

The classical example of microbiological oxidation is the hydroxylation of (+) camphor by Pseudomonas putida. (+) camphor (71) is oxidized to give a mixture containing 5-endo- and 5-exohydroxycamphor (72 and 73) and 2,5-diketocamphane (74).[38]



(71) (72) (73) (74)

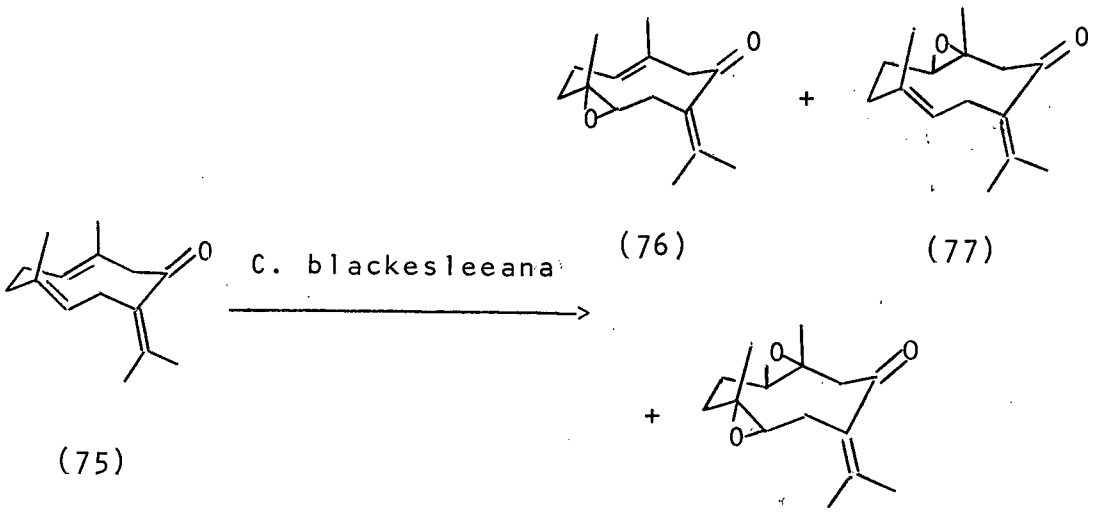
In our laboratory, we are investigating the oxidation of bornyl acetate by Helminthosporium sativum to give a mixture of three products.[39]



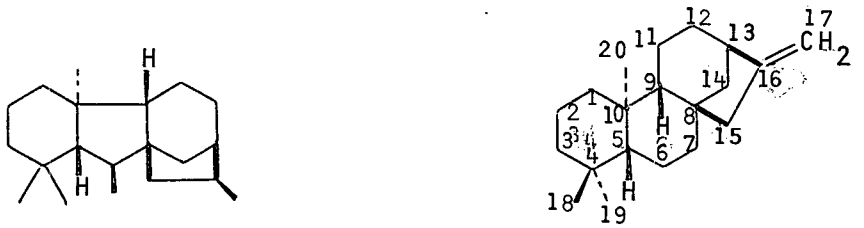
bornyl acetate 4 : 1 : 1.5

On incubation with Cunninghamella blackesleeana, germacrone (75) gives epoxides (76), (77) and diepoxides(78). A stereochemistrical study shows that all the epoxides have the same conformation as that of (75) and thus the microorganism

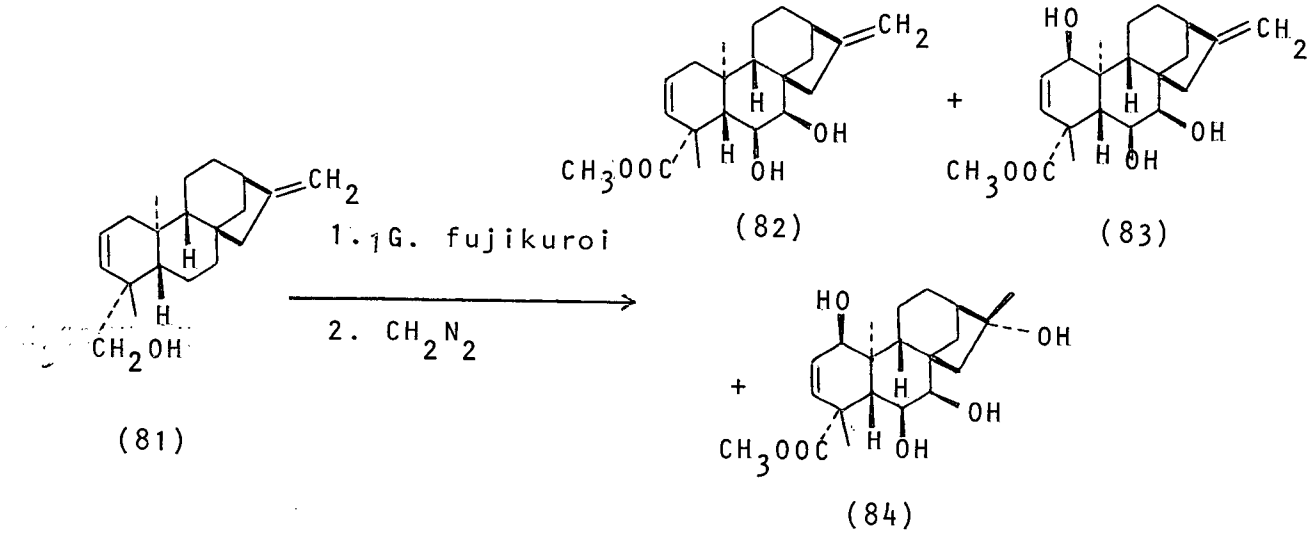
attacks preferentially one of the enantiomeric conformations.[40]



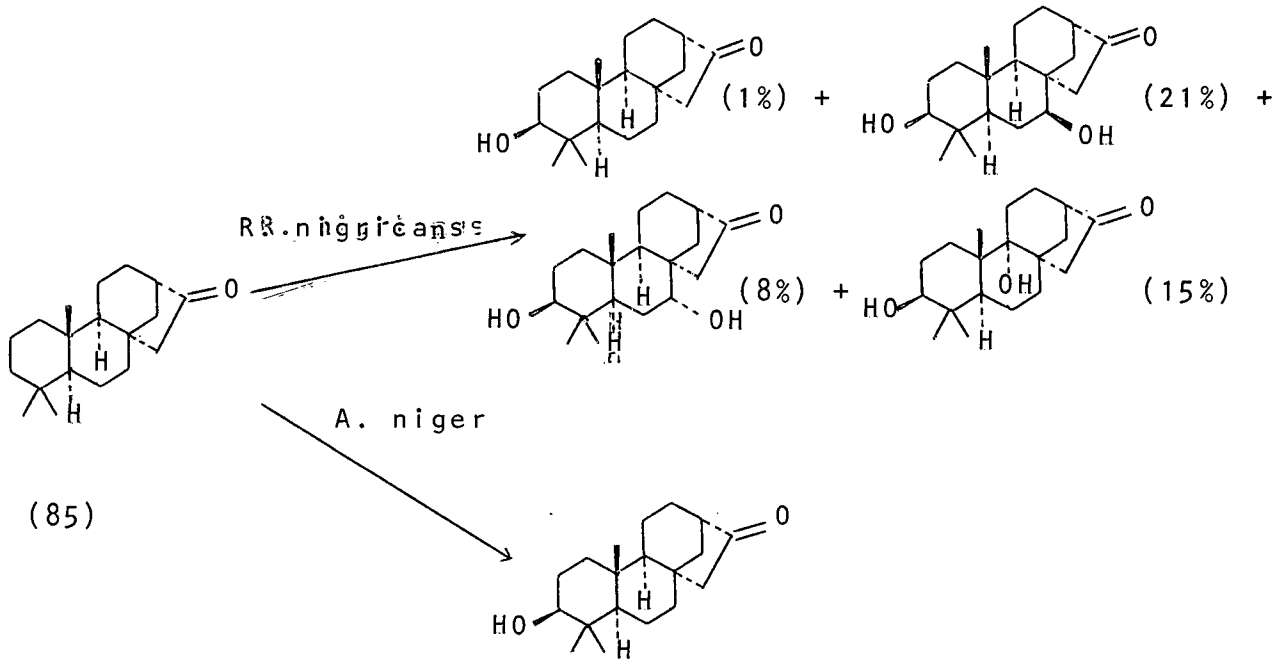
Gibberellins, a class of non-diterpenes which have the gibbane skeleton (79), have an unusual influence on the growth and development of plants. It is believed that gibberellins are biosynthesized in plants via ent-16-kaurene (80) or corresponding derivatives. Because of its importance, extensive research has been carried out. Incubation of dienol (81) with <u>Gibberella fujikuroi</u> gives three acids which are isolated as the methyl esters (82, 83, 84).[41]

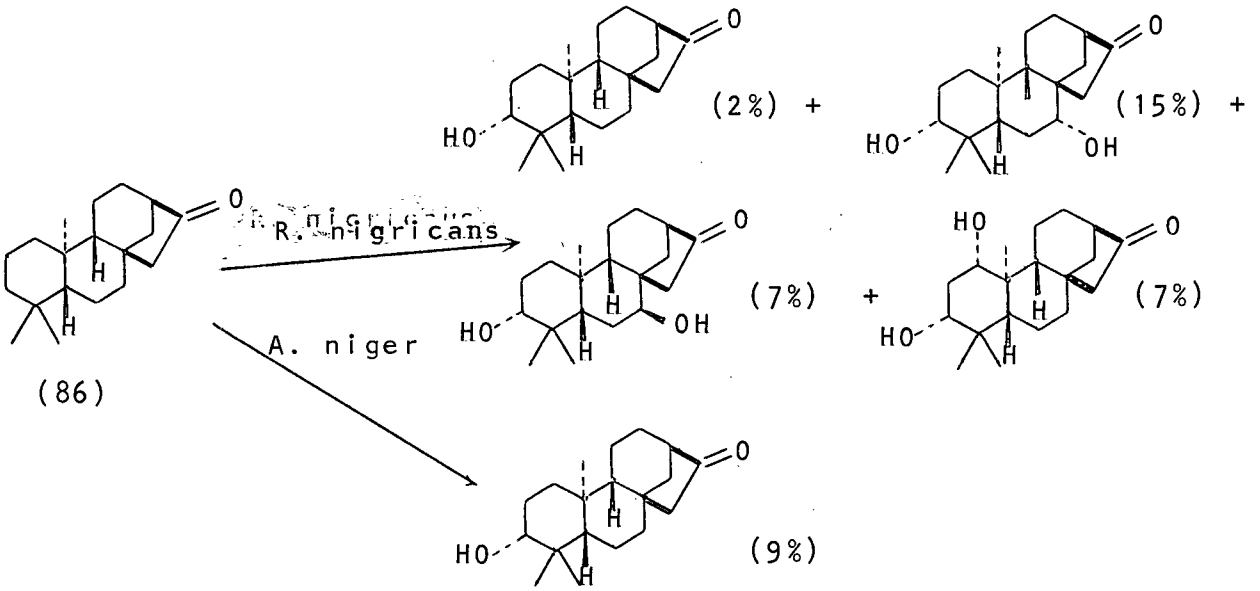


(79) (80)

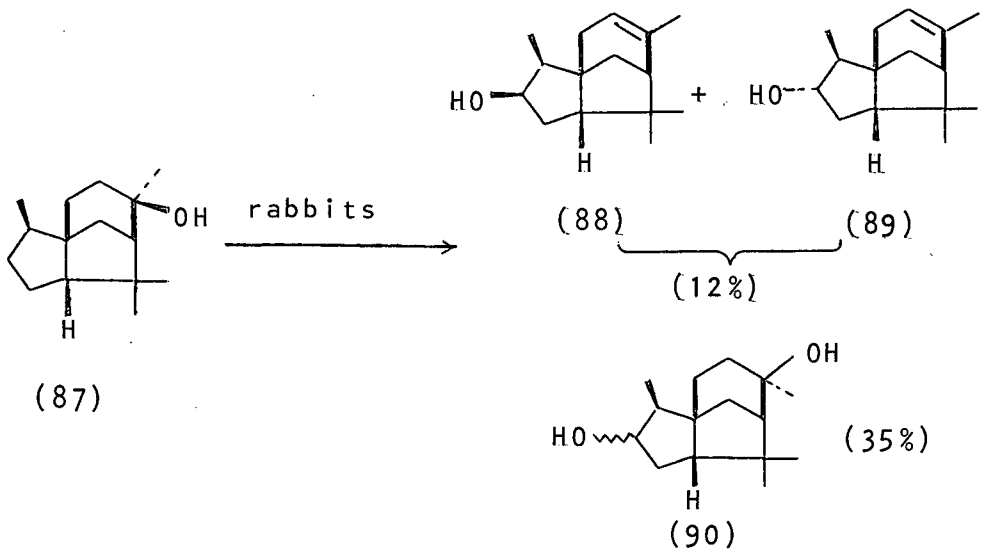


17-norkauran-16-one (85) and ent-17-norkauran-16-one (86) are hydroxylated at C-1, C-3, C-7, or C-9 positions by the fungus <u>Aspergillus niger</u> and <u>R. nigricans</u>. A mechanism is proposed for these remote hydroxylations. The hydroxylase first binds to the oxygen function at C-16 in such a way that the site of oxygenation of the substrate bears a fixed geometrical relationship to the carbonyl. The enzyme then seemingly singles out the most favorable proton.[42]



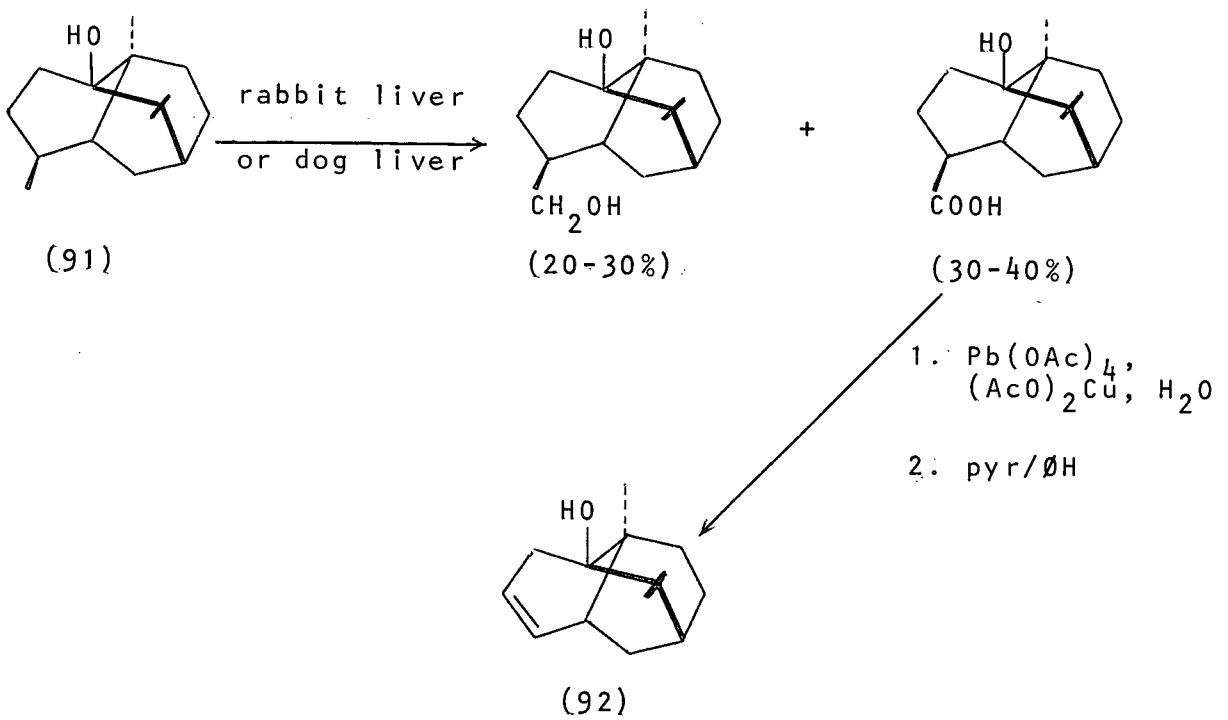


Biotransformation can also be carried out by mammals. Cedrols(87) is functionalised by rabbits at an unactivated site. The products so formed are (88), (89) and (90).[43] The most useful transformation of this type is the oxidation of



patchoulol (91) to give products which can be used to obtain nor-patchoulenol (92), the odour carrier of patchouli oil.[44]

The occurrence of nor-patchoulenol in patchouli leaves may be due to the bio-oxidation of patchoulol in the plant, followed by an elimination reaction.

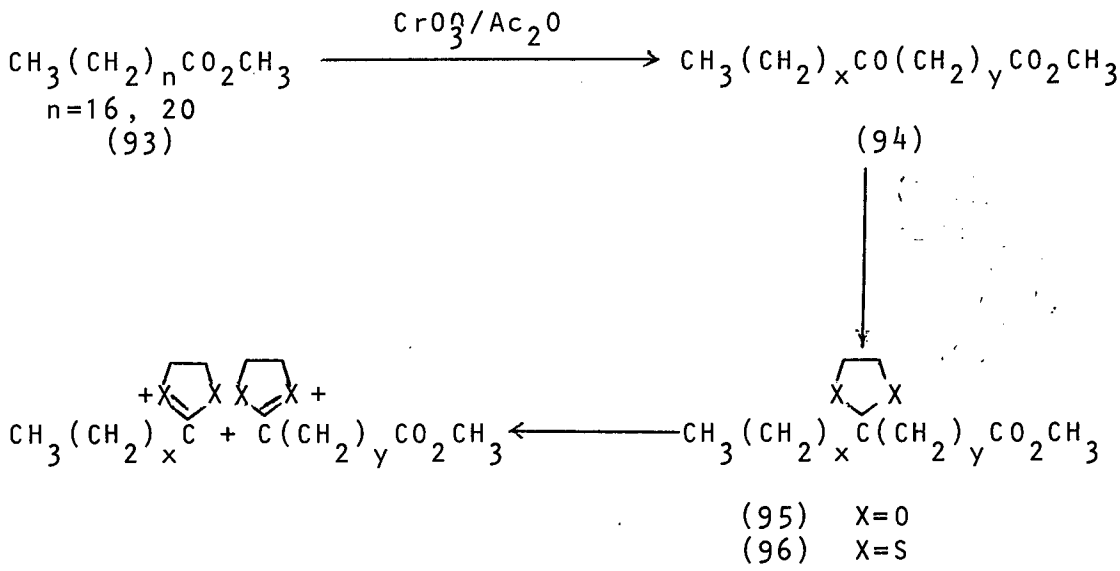


DISCUSSION

(A) Remote oxidation of acyclic acetates

Sometime ago, Breslow and his co-workers elaborated a synthetic procedure (remote oxidation), to functionalise some straight-chain substrates. The resulting products could then be converted to products with a new carbonyl group selectively introduced into the chain.[45] This in vitro reaction imitates the selective functionalisation by an enzyme of unactivated methylene groups.

Later, from this laboratory, a novel oxidation of unactivated methylenes in fatty acid methyl esters by chromium trioxide in acetic anhydride was reported.[46] The fatty acid esters (93) were oxidized by CrO_3-Ac_2O to give a mixture of keto-esters (94) which were then identified by examining the mass spectra of the corresponding ethylene acetals (95) and ethylene thioacetals (96). The results (cf. figures 3 and 4) indicated that there was



modest selectivity for attack at biologically interesting

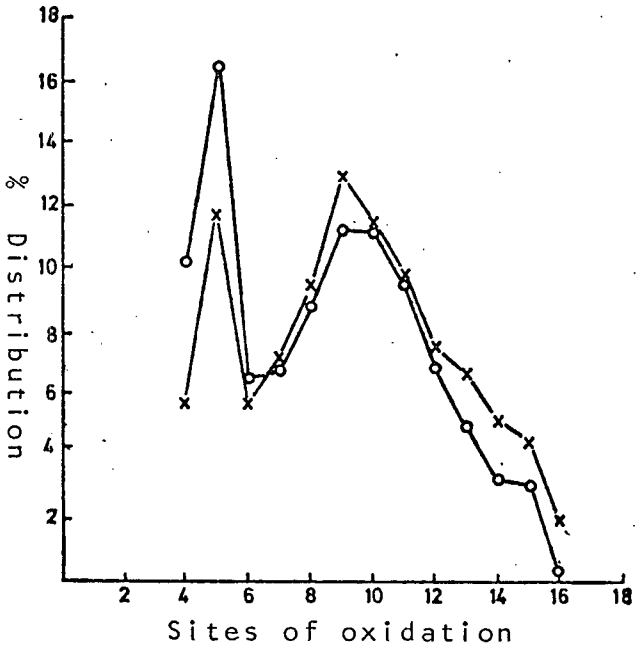
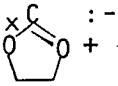
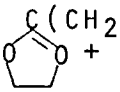


Figure 3. Oxidation of methyl stearate [data from the low resolution (15eV) spectrum of acetals (95; x+y=15) -x——x- based on fragment $CH_3(CH_2)_x$  :-o——o- based on fragment  $(CH_2)_yCO_2CH_3$].

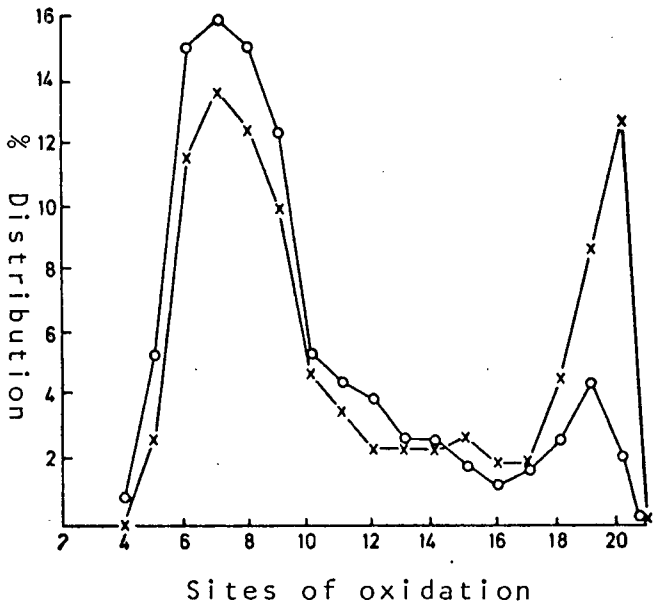
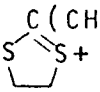
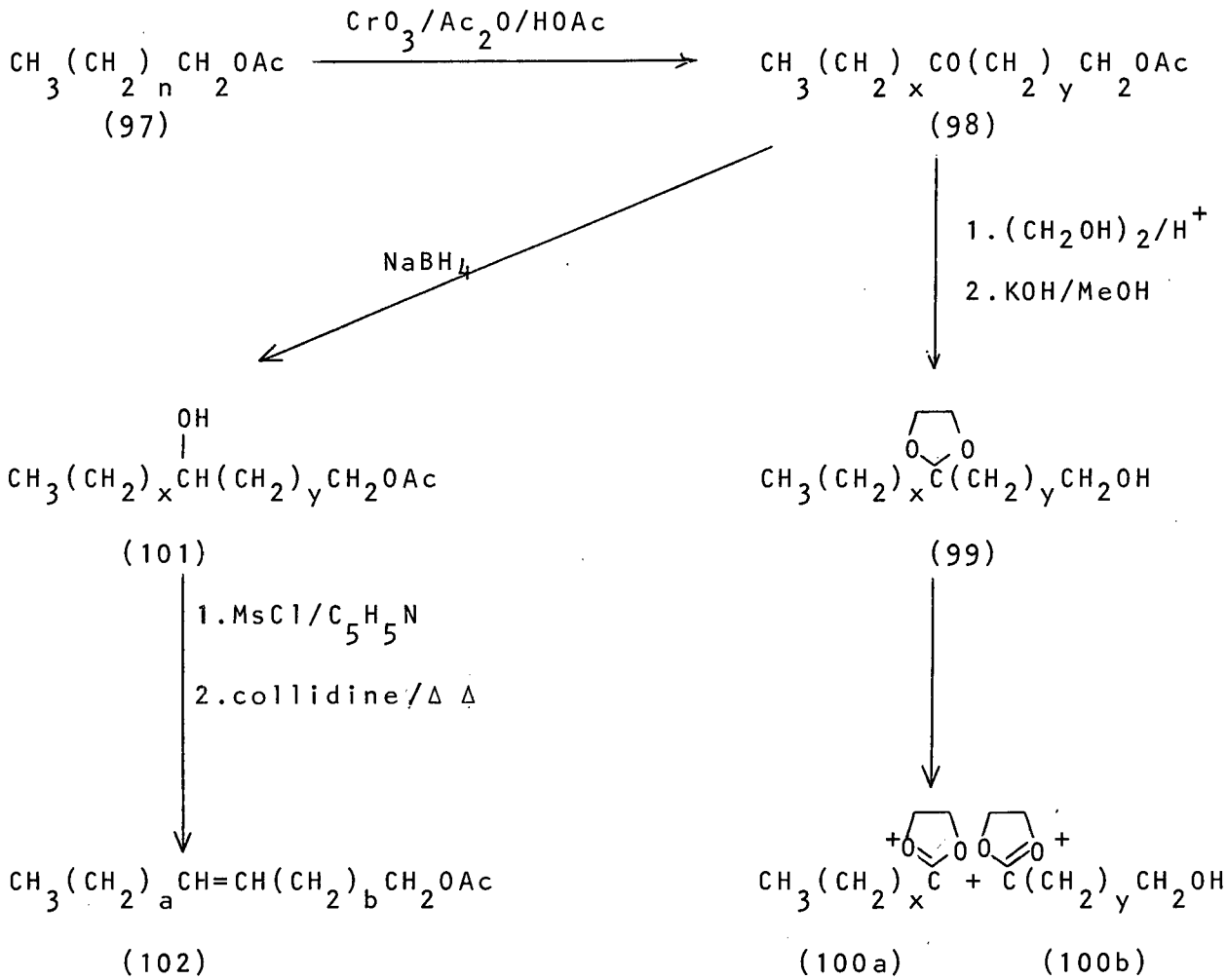


Figure 4. Oxidation of methyl docosanoate [data from the low resolution (15eV) mass spectrum of thioacetals (96; x+y=19):-x——x- based on fragment $CH_3(CH_2)_x$  :-o——o- based on fragment  $(CH_2)_yCO_2CH_3$].

positions. This provided evidence that certain molecules are susceptible to oxidation at centres which are generally considered to be unreactive.

To extend these investigations, we have examined the oxidative vulnerability of acyclic acetates.[47] Treatment of pure 1-octadecyl acetate (97; n=16) in glacial acetic acid/ acetic anhydride with chromium trioxide/acetic anhydride (i.e. chromyl acetate) at room temperature for 48 hours provided a mixture of mono-oxo-acetates (98; x+y=15) and starting material. Careful column chromatography [Woelm silica gel grade III (1: 50); pet. ether/ether] separated the oxo-acetates from starting material. The yield of product based on consumed starting material was ∿30%. The mass spectrum, elemental analysis, infrared and NMR data were satisfactory for mono-oxo-acetates. The infrared spectrum (CCl_4) showed absorption bands at 1737 and 1715 cm^{-1} and the NMR spectrum exhibited resonances at τ 6.00 (t, 2H, $-C\underline{H}_2OAc$), 7.70 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.02 (s, 3H, $-O_2CC\underline{H}_3$), 8.70 (broad s, 26H, $CH_3(C\underline{H}_2)_{13}$) and 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$). In addition, the mass spectrum showed the correct molecular ion peak at 326.

It was a simple matter to determine the position of oxidation since the resulting acetates could be converted into the corresponding ethylene acetal alcohols (99), which could be examined by mass spectroscopy, to determine where functionalisation had occurred. At low ionizing voltages, (99) fragmented mainly at the carbon carrying the acetal to give



fragments (100a,b). However, discrepancies between the two sets of results (from ions 100a and 100b) at the terminal sites (figures 5-6) indicated that the fragmentation process was non-random when the acetal group was located towards the end of the chain. This discrepancy could be avoided if the per cent distribution was calculated on basis of the combined relative intensity of fragments (100a) and (100b), as shown in figures (7-8). The results clearly indicate that octadecyl acetate

can be directly oxidized to a mixture of mono-oxo derivatives, and that the process is partially regiospecific.

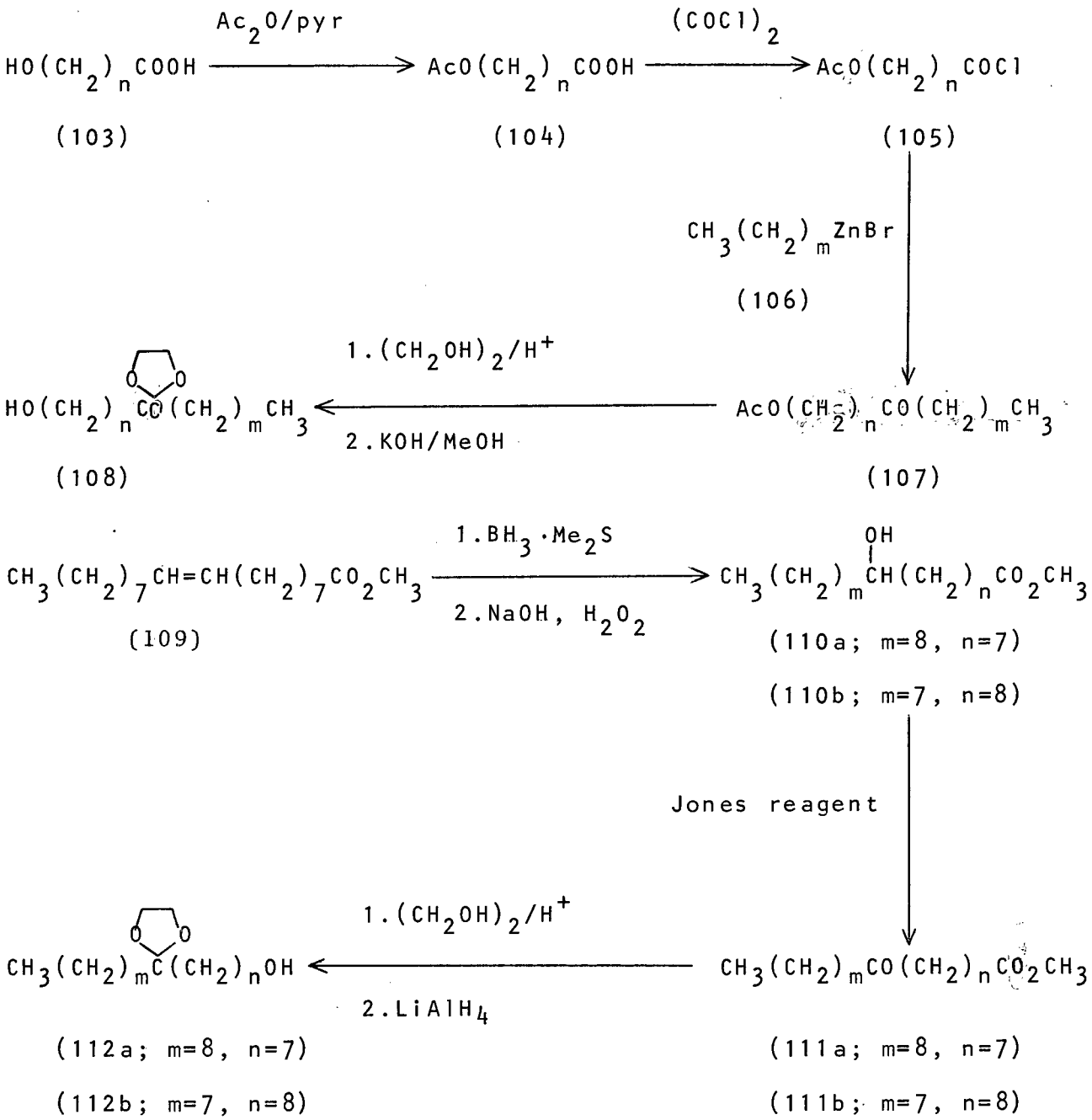
The analytical technique used here to determine the position of functionalisation in a straight-chain substrate is valid on the assumption that the relative intensities of the peaks in the mass spectra of the ethylene acetals (99) are a true representation of the relative amounts of isomeric oxo-acetates present in the product mixture. A condition for this assumption is that the intensity of the parent peak is small compared to that of the α-cleavage peaks in the mass spectra.

Later studies showed that dodecyl acetate (97; n=10), tetradecyl acetate (97; n=12) and docosyl acetate (97; n=20) were oxidized to a mixture of mono-oxo-acetates by the chromyl acetate reagent. By the analysis described above, the distribution of isomeric oxo-acetates are as summarized in figures 9-20. These results indicate that the oxidation of shorter chain analogues (figures 9-16) is more regiospecific than the longer chain analogues (figures 5-8, 17-20). This is reasonable because in a strongly polar medium, the longer the non-polar chain the more it prefers to fold around itself and more methylene hydrogens achieve close proximity to the chromate oxygens. This explanation is hypothetical because the conformations of non-polar chain in polar solvent are not well studied.

The validity of the mass spectroscopic method used to estimate the relative amounts of positional isomers was tested

by using mixtures of ethylene acetals of known composition derived from synthetic 9-, 10-, 11- and 15-oxo-1-octadecanol. The long-chain hydroxy acid (103; n=10) was converted to acetoxy acid (104; n=10) by reaction with acetic anhydride/ pyridine. Oxalyl chloride then gave the corresponding acid chloride (105; n=10), which was treated with heptylzinc bromide (106; m=6) to give the keto-acetate (107; n=10, m=6); this was in turn converted to the ethylene acetal alcohol (108; n=10, m=6) through the intermediate ethylene acetal acetate. The same reaction sequence was used to synthesize 15-oxo-1-octadecyl acetate (107; n=14, m=2) which was then converted to the ethylene acetal alcohol (108; n=14, m=2). In order to get the ethylene acetals of 9- and 10-oxo-1-octadecanol (112a and b), borane-dimethyl sulfide in tetrahydrofuran was added to a solution of methyl oleate (109) in tetrahydrofuran; after 3 hours at room temperature, sodium hydroxide and hydrogen peroxide were added to give, after a further 1 hour reflux, a mixture of methyl 9- and 10-hydroxystearate (110a,b). Jones oxidationnof (110a,b) gave a mixture of methyl 9- and 10-keto-stearate (111a,b) which was then converted to the ethylene acetal esters. Reduction of ethylene acetal esters with $LiAlH_4$ provided a mixture of ethylene acetals of 9- and 10-oxo-1-octadecanol (112a,b). The mass spectra of the known mixture of ethylene acetals derived from synthetic 9-, 10-, 11- and 15-oxo-1-octadecanol showed clean fragmentation and provided a

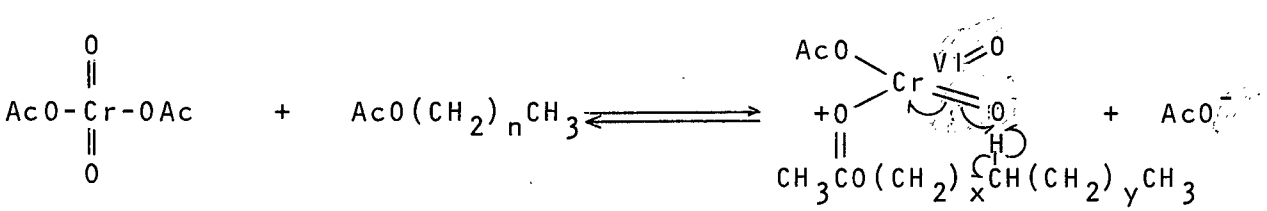
quantitative distribution in good agreement with the known compositions of the mixtures (figures 21-35).



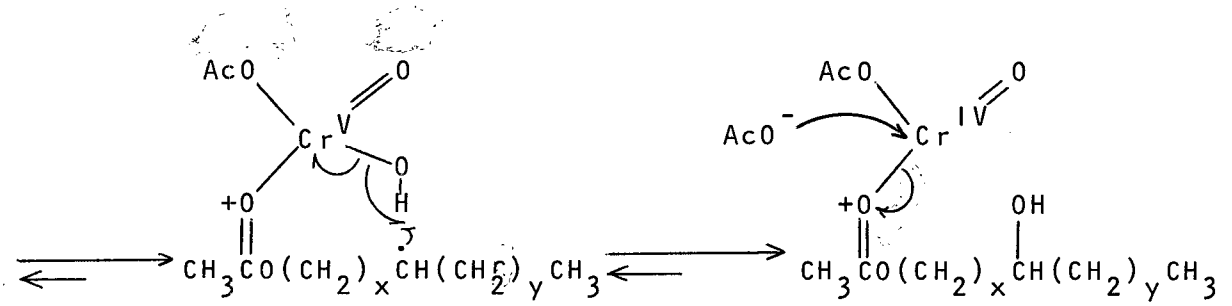
We attempted to increase the selectivity of the reaction

by carrying out the oxidation of (97; n=16) in ten times the amount of solvent and the same amount of CrO_3-Ac_2O. The results shown in figures 36 and 37 indicate that this attempt was unsuccessful: a broader distribution of products covering carbons 3 to 17 was obtained. Further attempts to increase the selectivity by using other oxidizing agents also failed. For example, no reaction occurred between the substrate (97; n=16) and $Na_2Cr_2O_7/H_2SO_4/H_2O$.

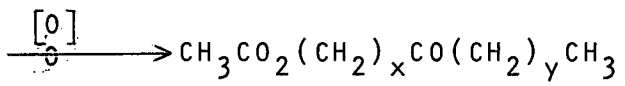
The mechanism of these oxidation reactions remains uncertain. It might be proposed, as a first step, that the polar functional groups (esters) can interact with chromyl acetate to form a reactive complex (113) in such a way that the site of oxygenation of the substrate bears a geometrical relationship to the metal.[48] The second step involves an intramolecular hydrogen abstraction. This chelation of chromyl acetate by substrate and hydrogen abstraction leads to discrete radical intermediates (114) which accordingly are expected to be oxidized by chromium (V) to give hydroxyacetate complex (115). Further oxidation of (115) provides keto-acetates (116).



(113)



(114) (115)



(116)

An interesting application of this work is that it provides a simple synthetic route to a mixture of mono-unsaturated C_{16} acetates (102; a+b=12). Recent research has shown that the potent sex pheromone produced by the female bertha armyworm is cis-11-hexadecen-1-yl acetate.[49] The bertha armyworm is an insect that inflicts major damage to rapeseed crops of the Canadian prairie provinces. The discovery of this pheromone, cis-11-hexadecen-1-yl acetate, provides a possible way to control this insect biologically. With the usual oxidation reagent, hexadecyl acetates (97; n=14) wase converted to a mixture of mono-oxo-acetates (98; x+y=13) which were then reduced with sodium borohydride in methanol. The hydroxyhexadecyl acetates (101; x+y=13) were then reacted with mesyl chloride. Elimination of the mesylates(hot collidine) provided a mixture of mono-unsaturated C_{16} acetates (102; a+b=12) whose sex pheromonal activity was tested by Dr. M.D. Chisholm (Prairie Regional

Laboratory, Saskatoon). The results showed that the synthetic mixture is positively active to the male bertha armyworm.[50] The occurrence of unsaturated acetates in bertha armyworm may be due to the oxidation of hexadecyl acetates in the insect, followed by an elimination reaction, which is the biological equivalent of the step (101) ⟶ (102) described earlier.

Recent reports have revealed that the sex pheromone of the oak leaf roller moths contains a series of tetradecenyl acetates having double bonds in positions 2 to 12[51] and the sex pheromone of some fruit moths (cabbage looper moth, oriental fruit moth and grape berry moth) is a mixture of mono-unsaturated C_{12} acetates.[52] Following the same reaction scheme (see P.36), the corresponding mixture of mono-oxo-tetradecyl acetates (98; x+y=11) and mono-oxo-dodecyl acetates (98; x+y=9) were converted to mixtures of mono-unsaturated C_{14} acetates (102; a+b=10) and mono-unsaturated C_{12} acetates (102; a+b=8) whose sex pheromonal activity is currently being evaluated respectively by Professor L.B. Hendry (Pennsylvania State University) and Professor W.L. Roelofs (Cornell University).

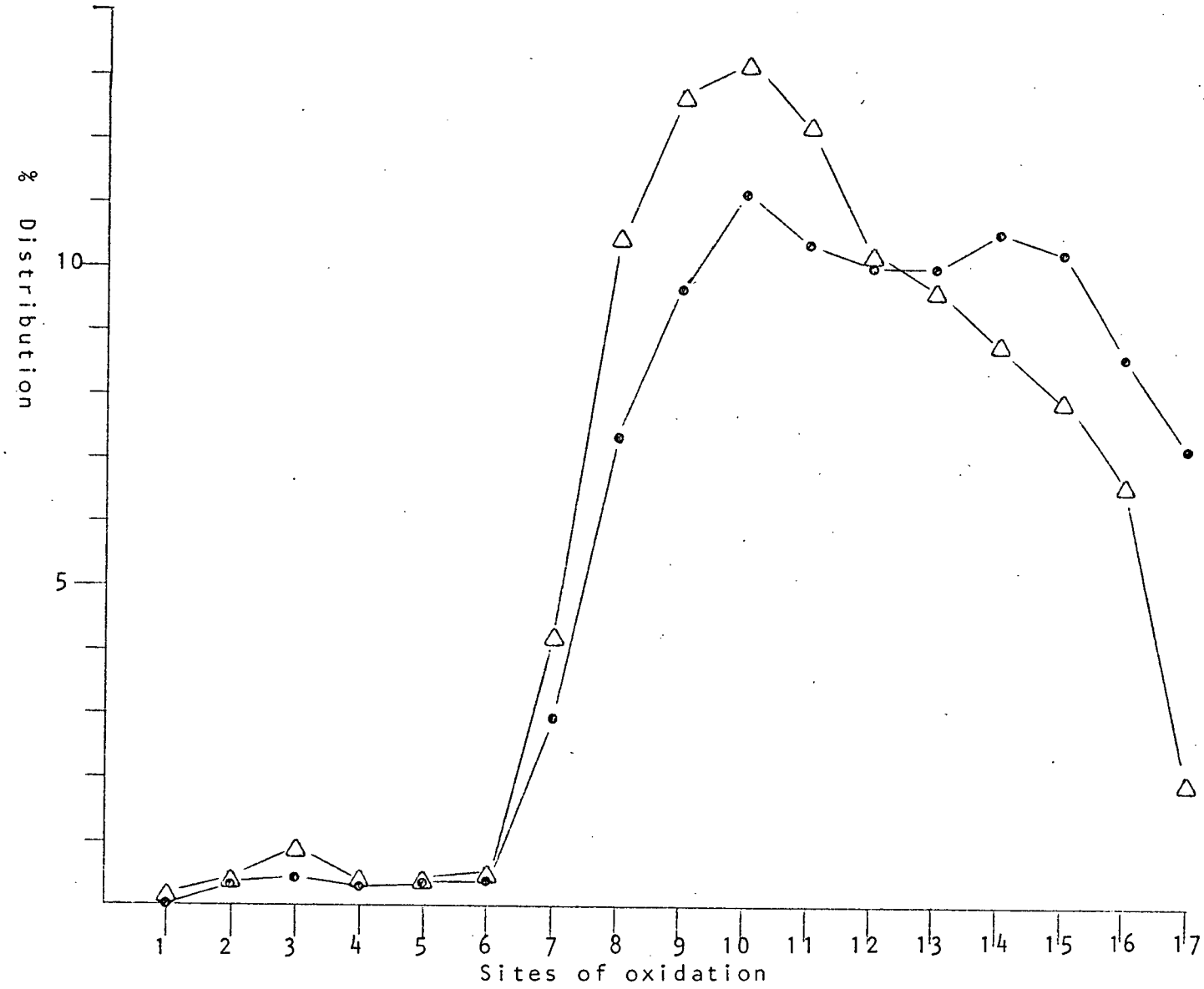


Figure 5. Oxidation of octadecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=15):-o——o- based on fragment (100a):-Δ——Δ- based on fragment (100b)].

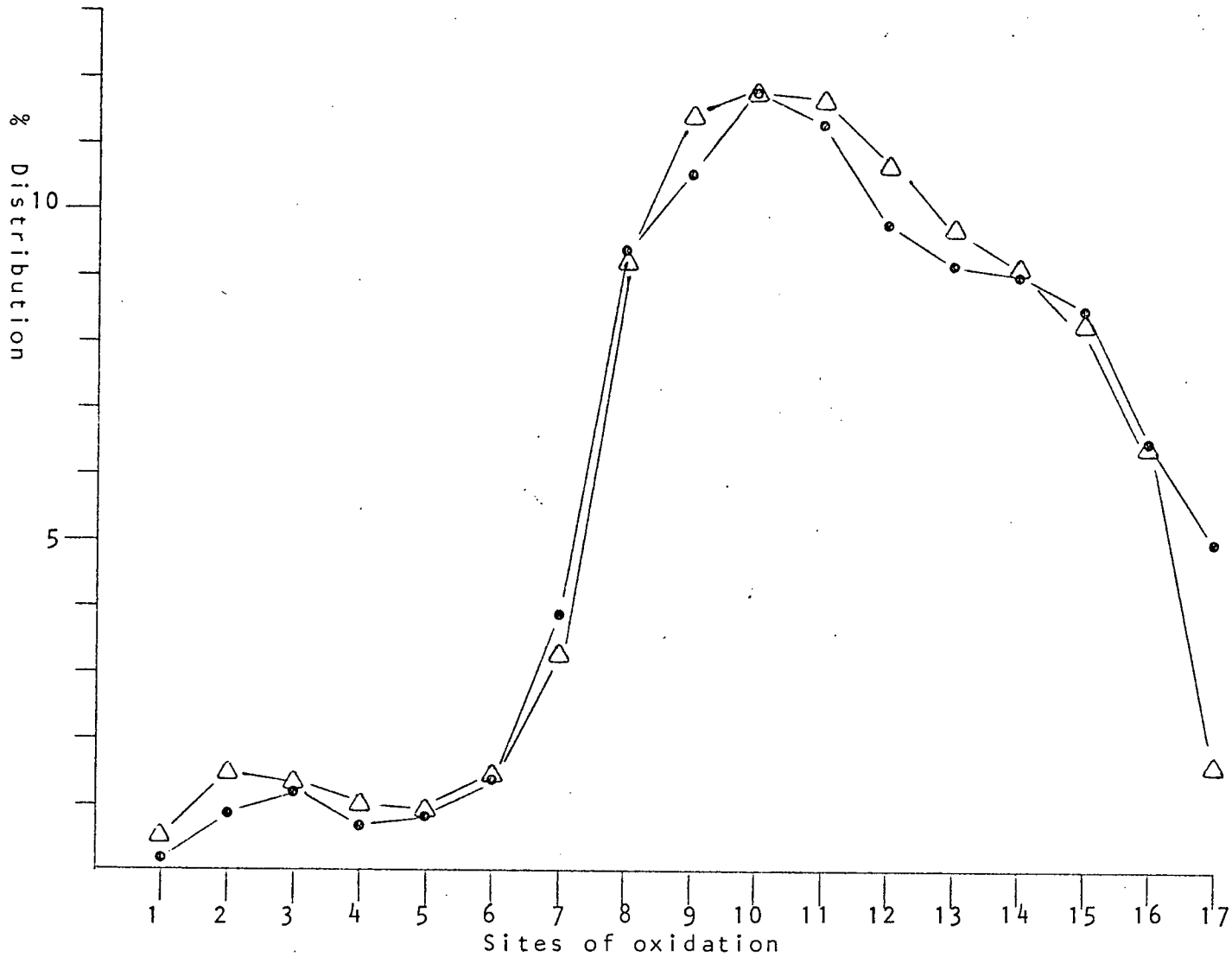


Figure 6. Oxidation of octadecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=15) :-o——0- based on fragment (100a) :-Δ—Δ- based on fragment (100b)].

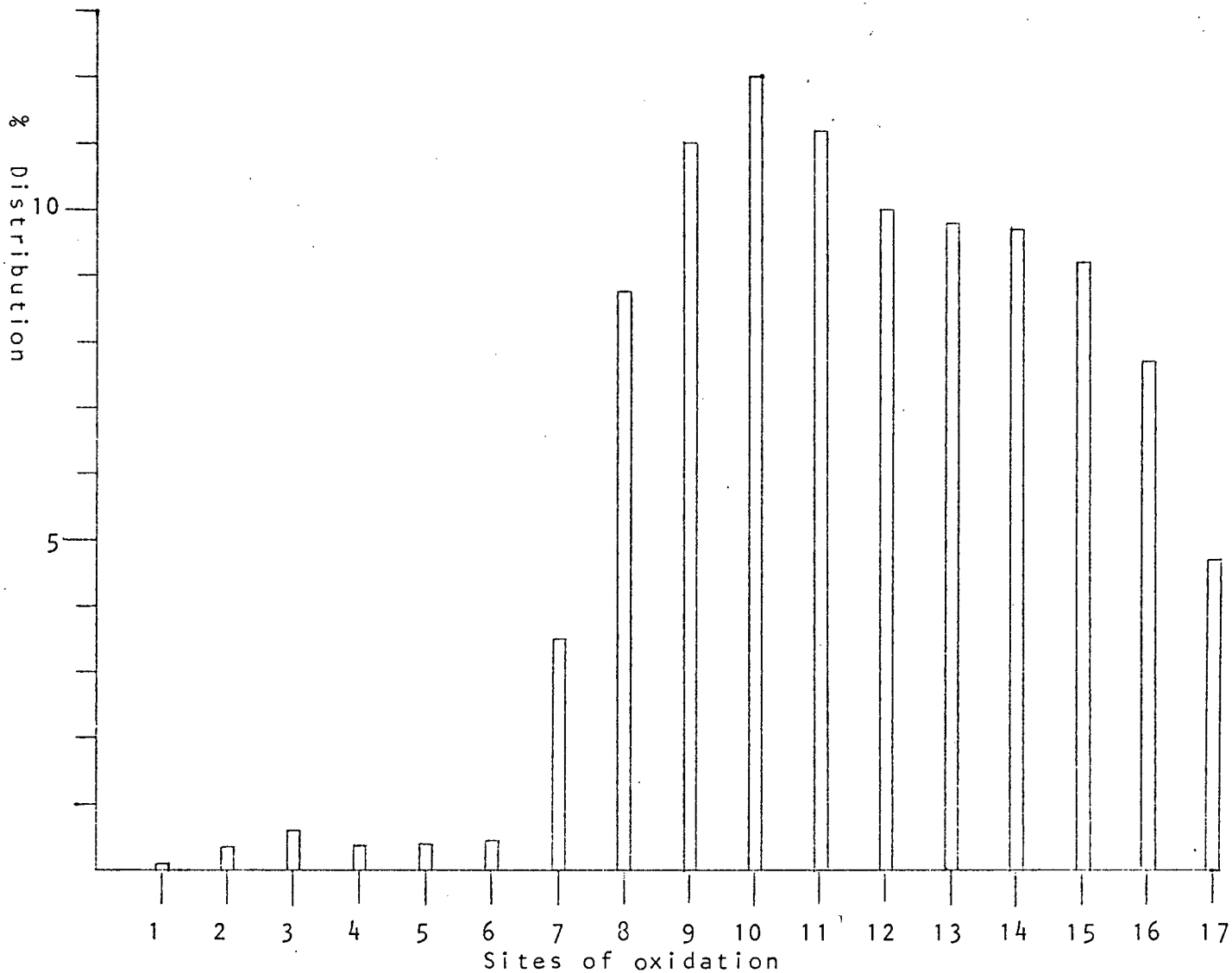


Figure 7. Oxidation of octadecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=15) based on the combined relative intensity of fragments (100a and b)].

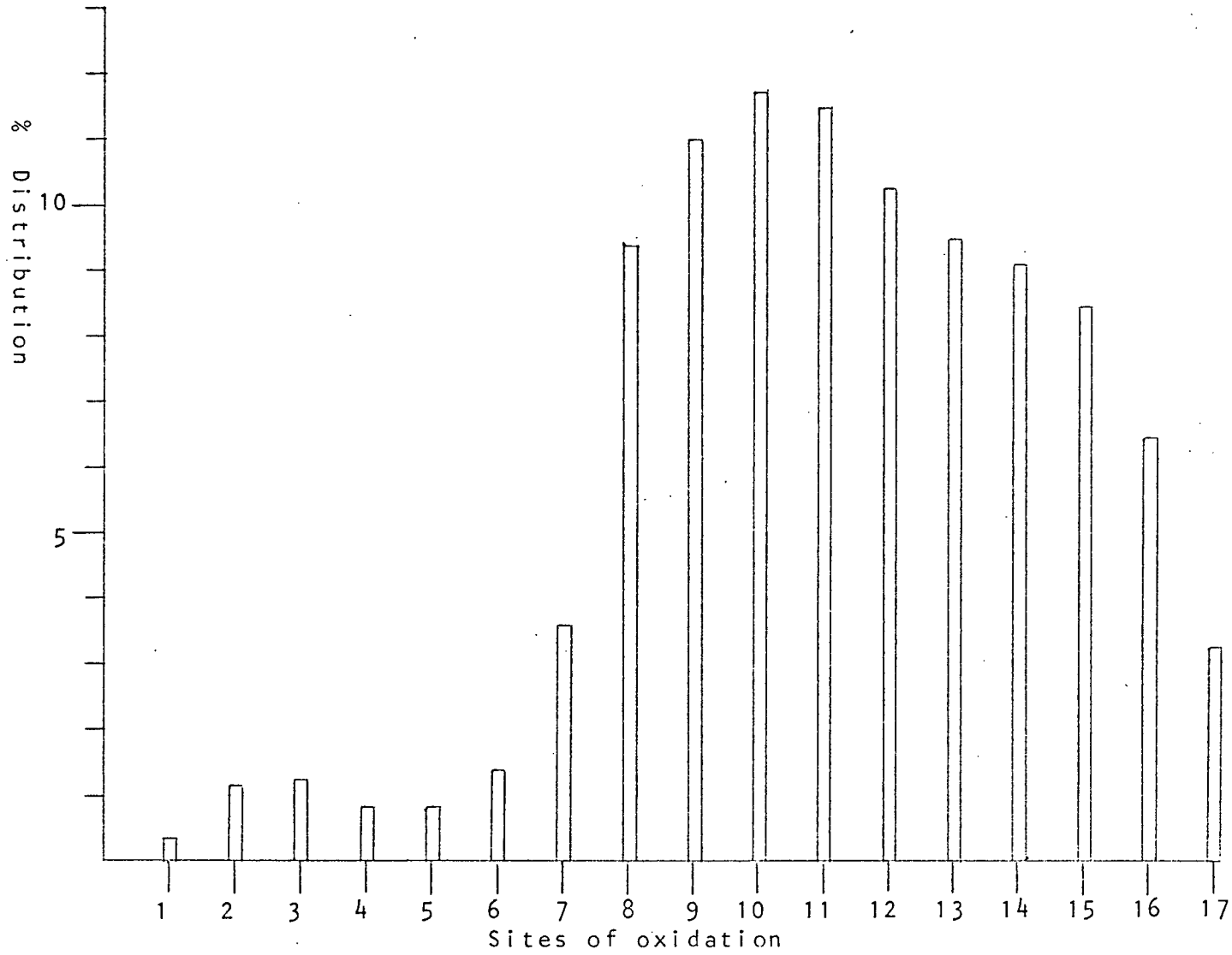


Figure 8. Oxidation of octadecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=15) based on the combined relative intensity of fragments (100a and b)].

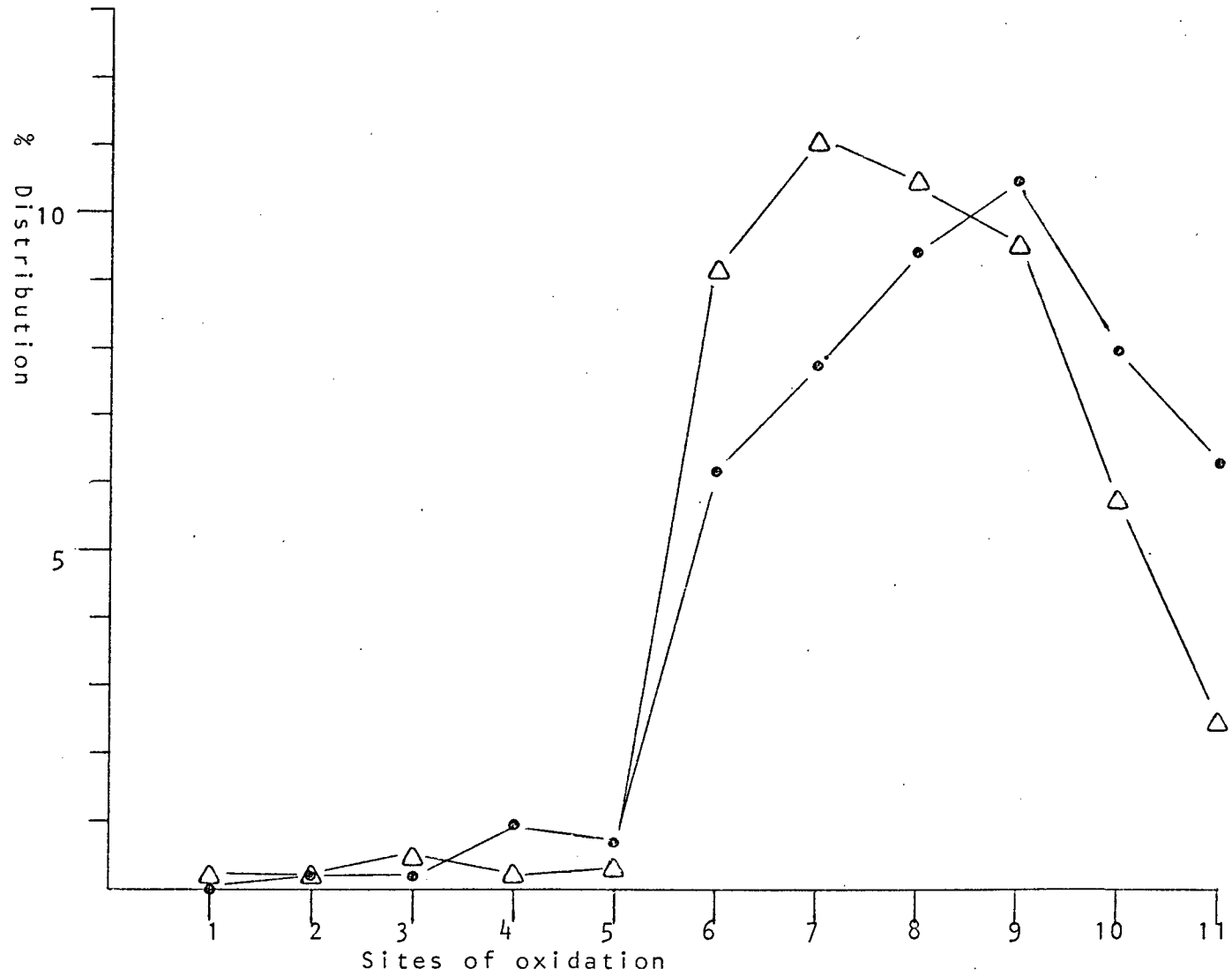


Figure 9. Oxidation of dodecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=9):-o——o- based on fragment (100a):-Δ——Δ- based on fragment (100b)].

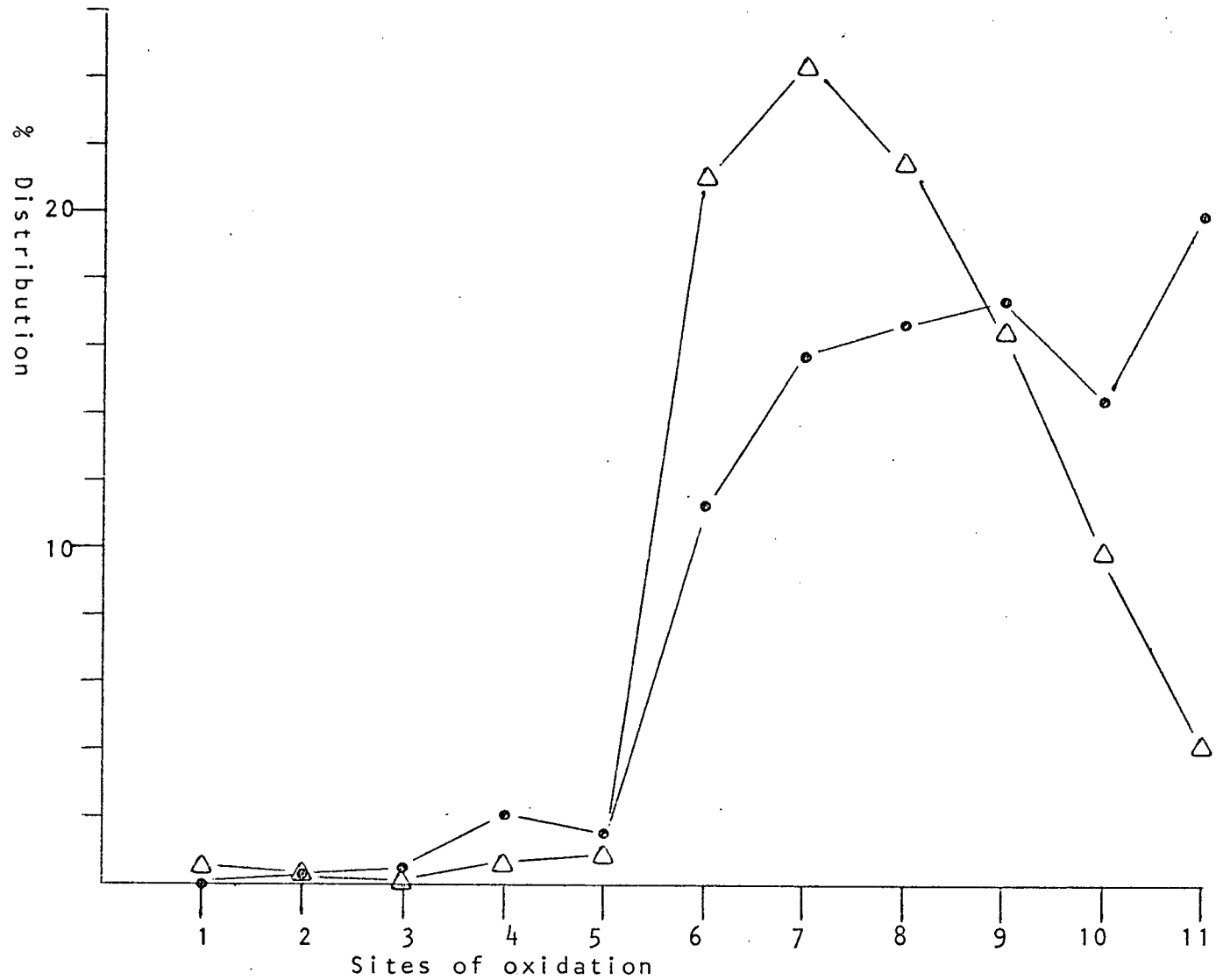


Figure 10. Oxidation of dodecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=9):-o——o- based on fragment (100a):-Δ——Δ- based on fragment (100b)].

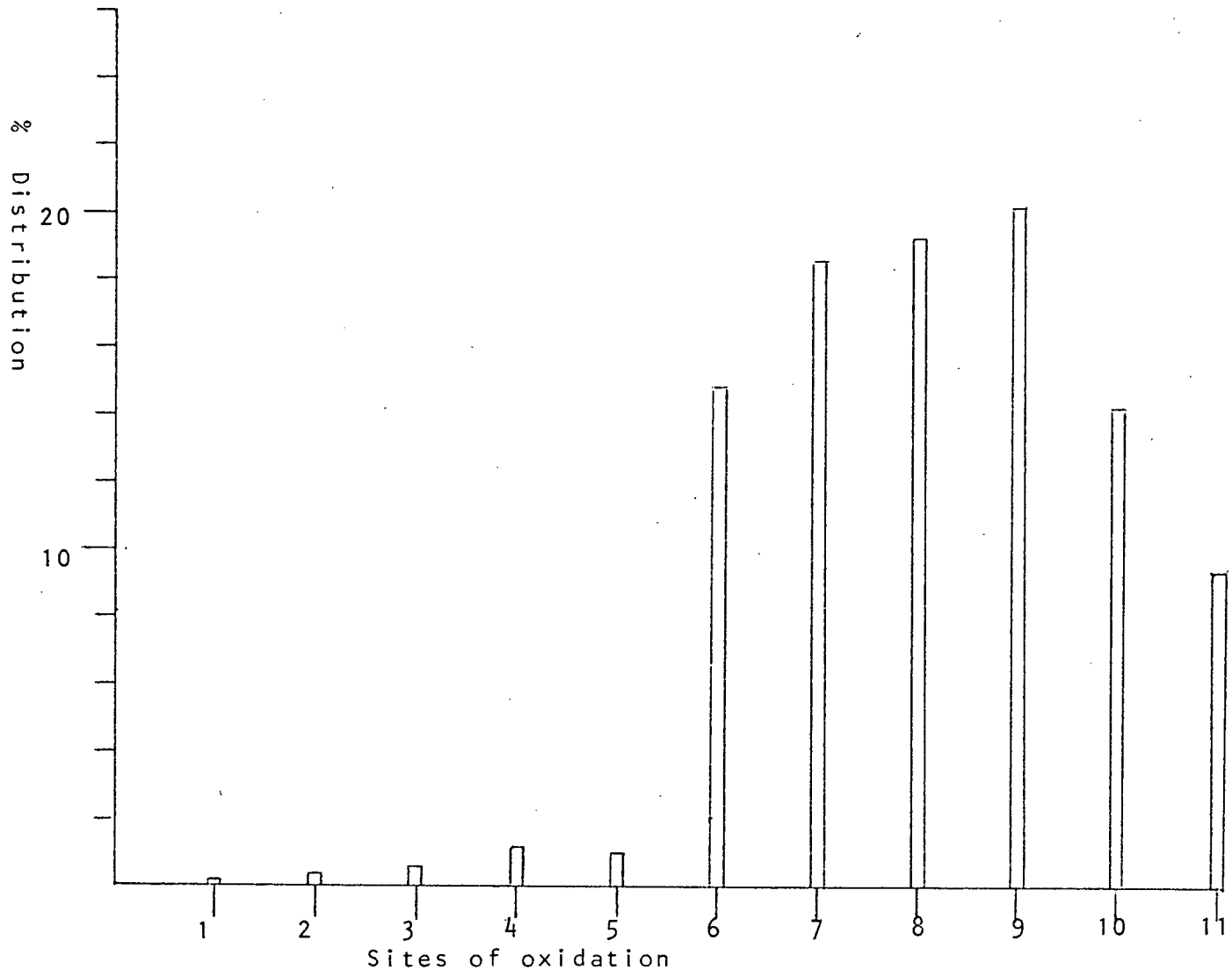


Figure 11. Oxidation of dodecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=9) based on the combined relative intensity of fragments (100a and b)].

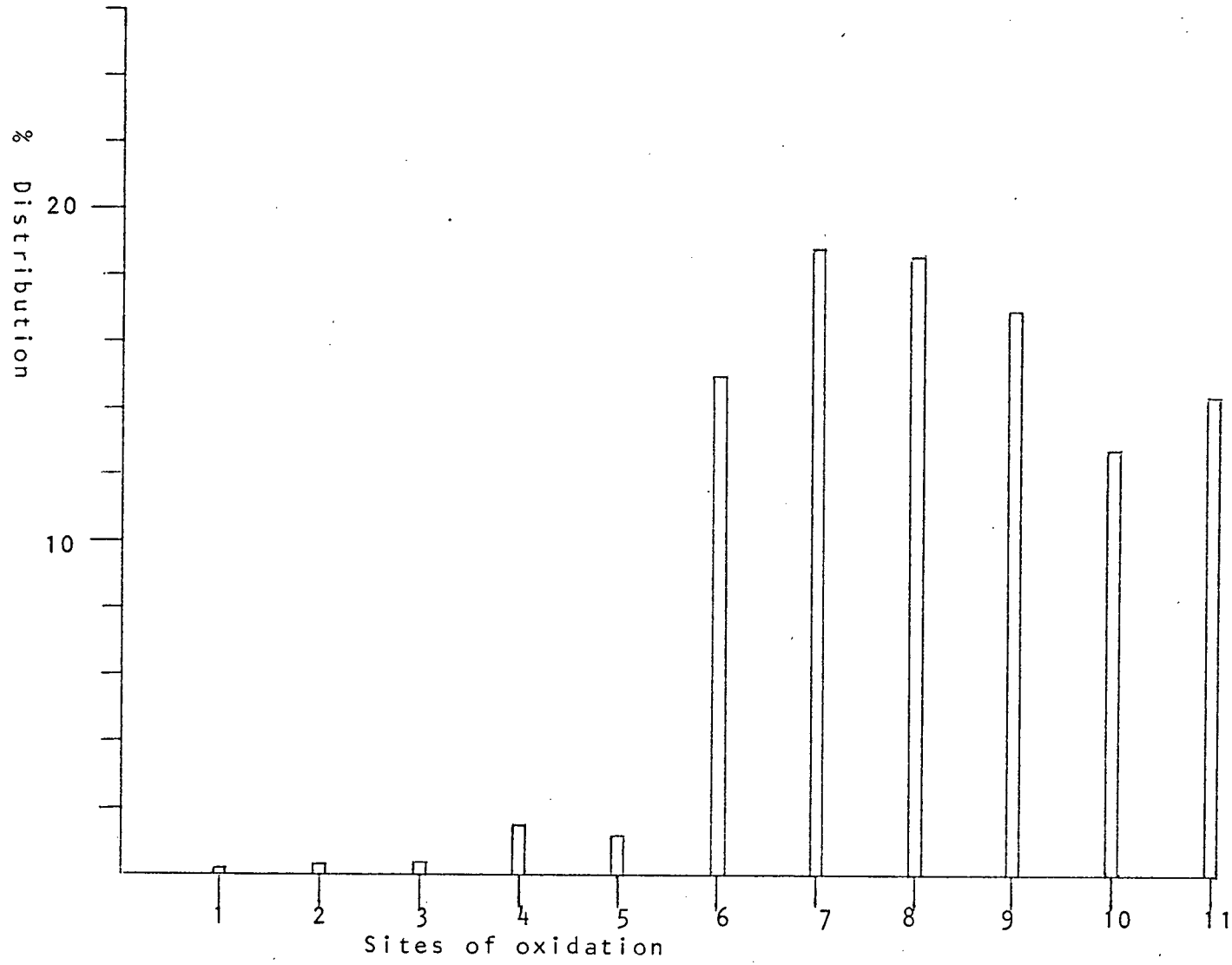


Figure 12. Oxidation of dodecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=9) based on the combined relative intensity of fragments (100a and b)].

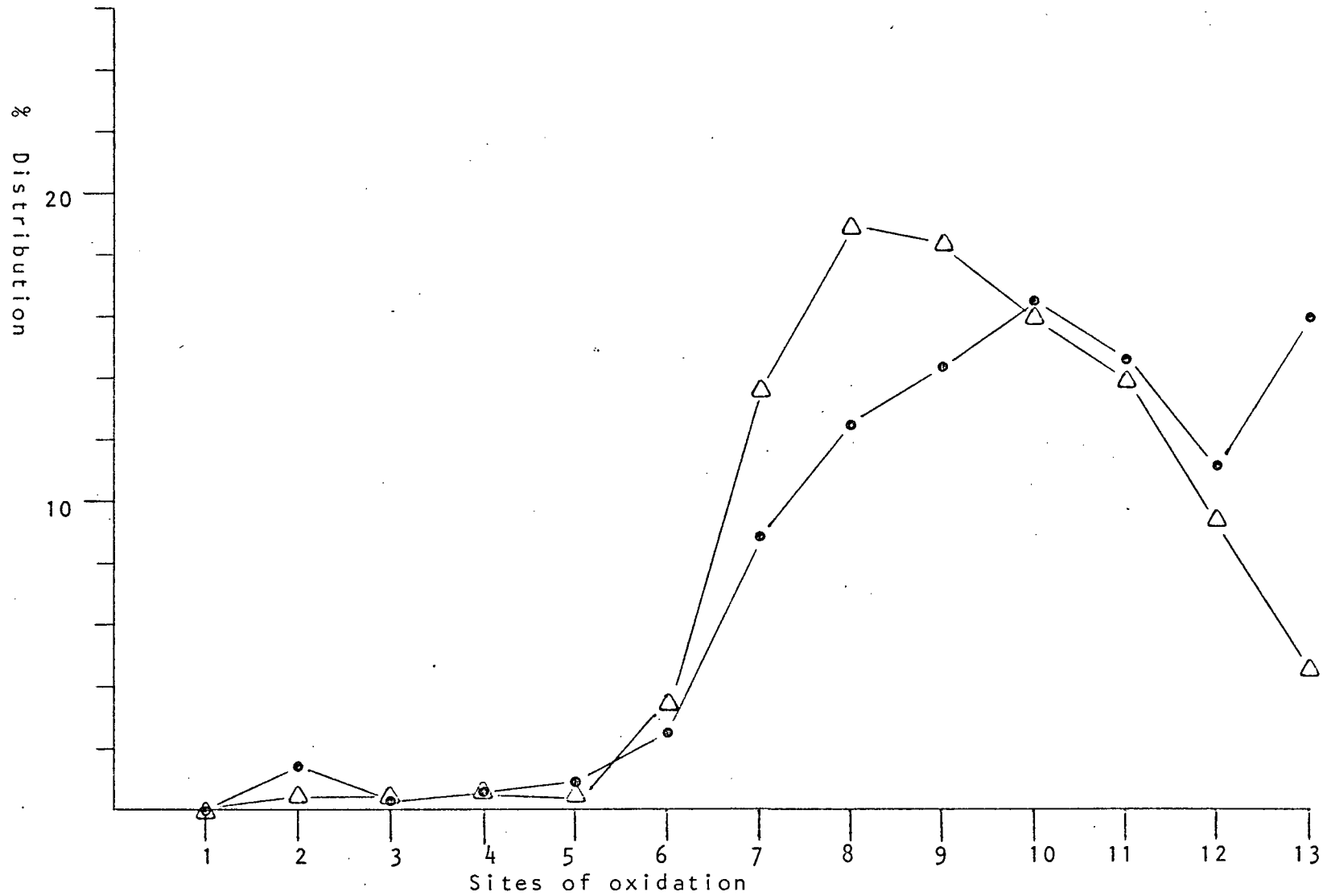


Figure 13. Oxidation of tetradecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=11) :-o——o- based on fragment (100a) :- Δ—Δ - based on fragment (100b)] .

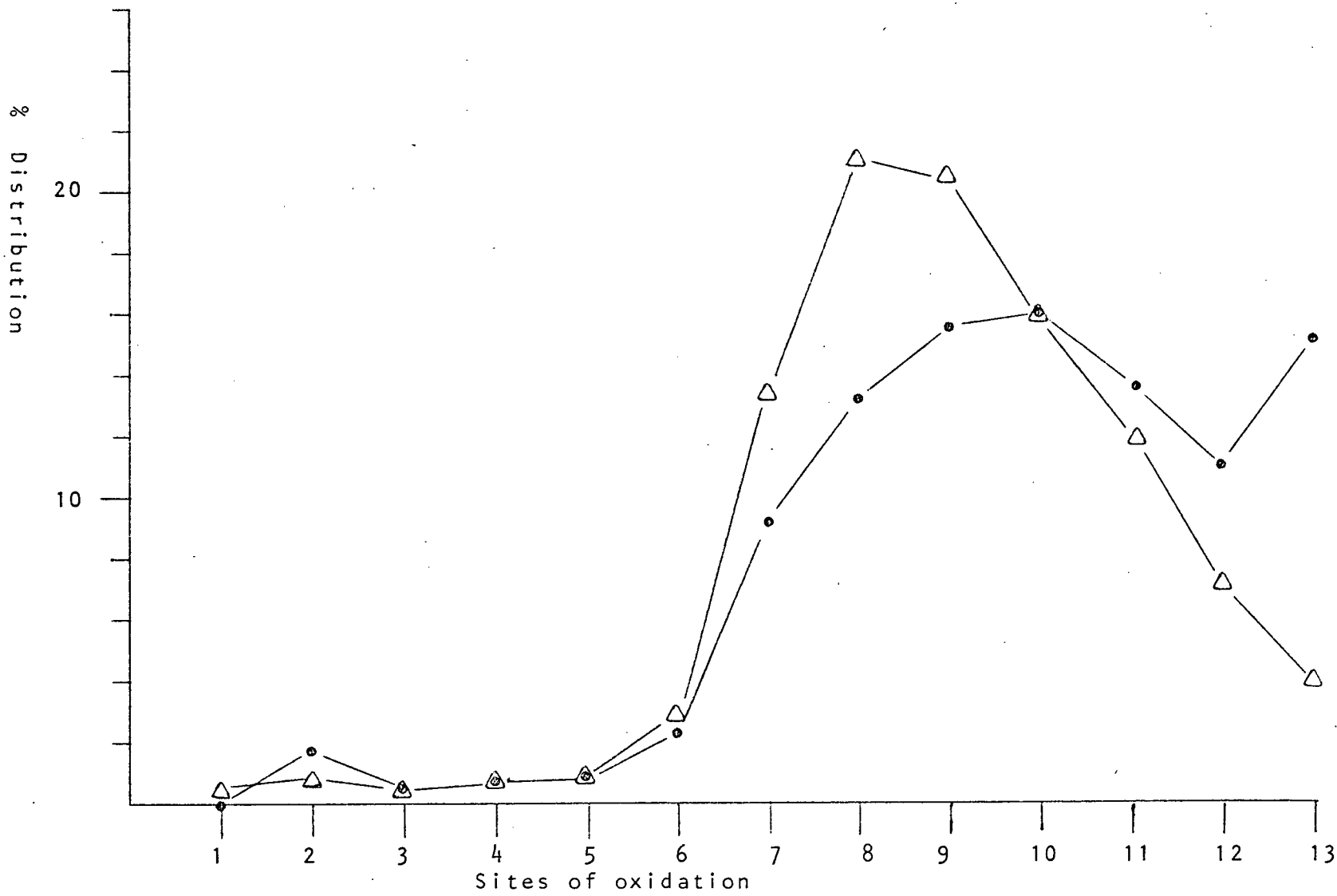


Figure 14. Oxidation of tetradecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=11):-o——o- based on fragment (100a):-Δ——Δ- based on fragment (100b)].

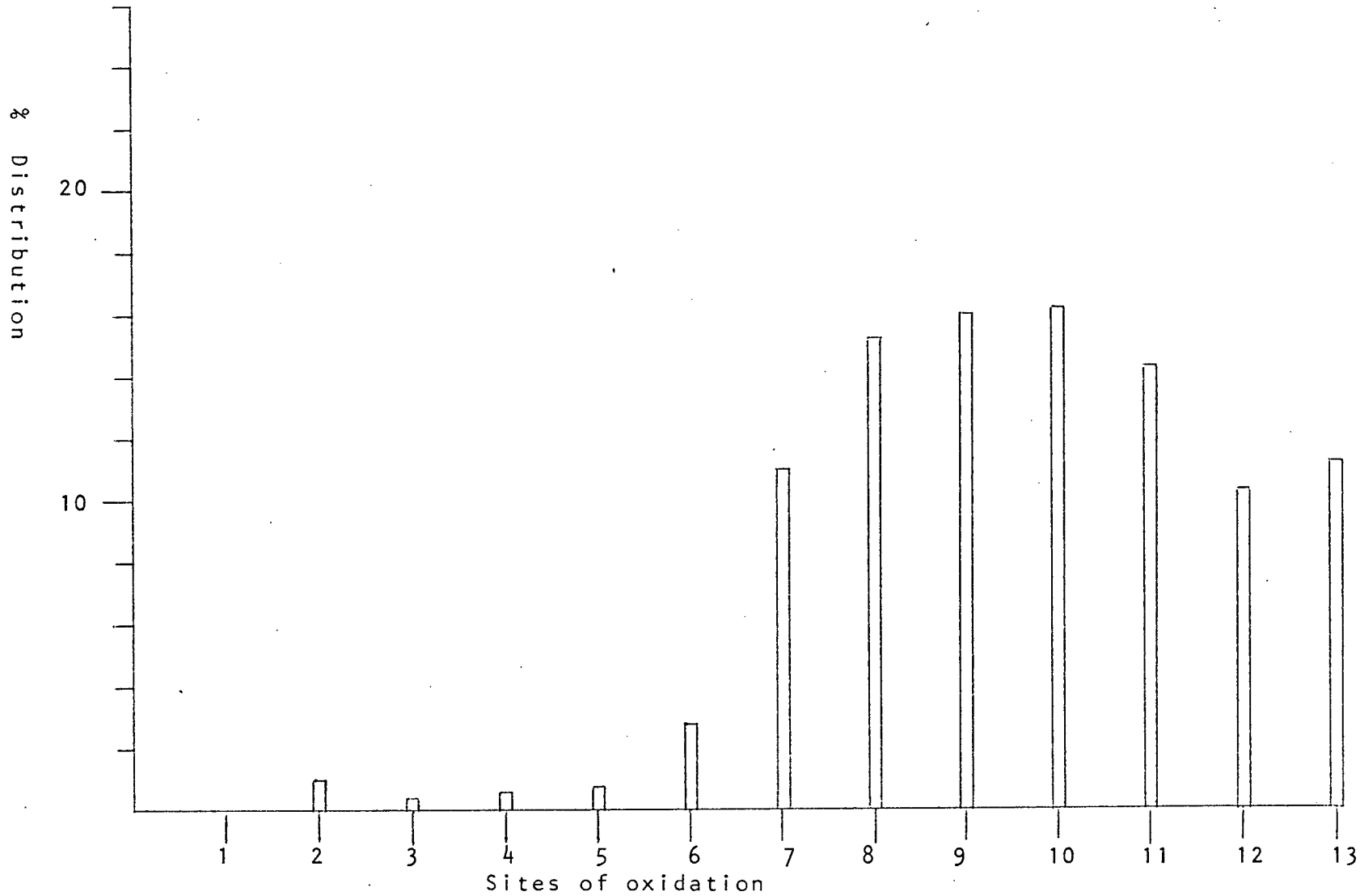


Figure 15. Oxidation of tetradecyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=11) based on the combined relative intensity of fragments (100a and b)].

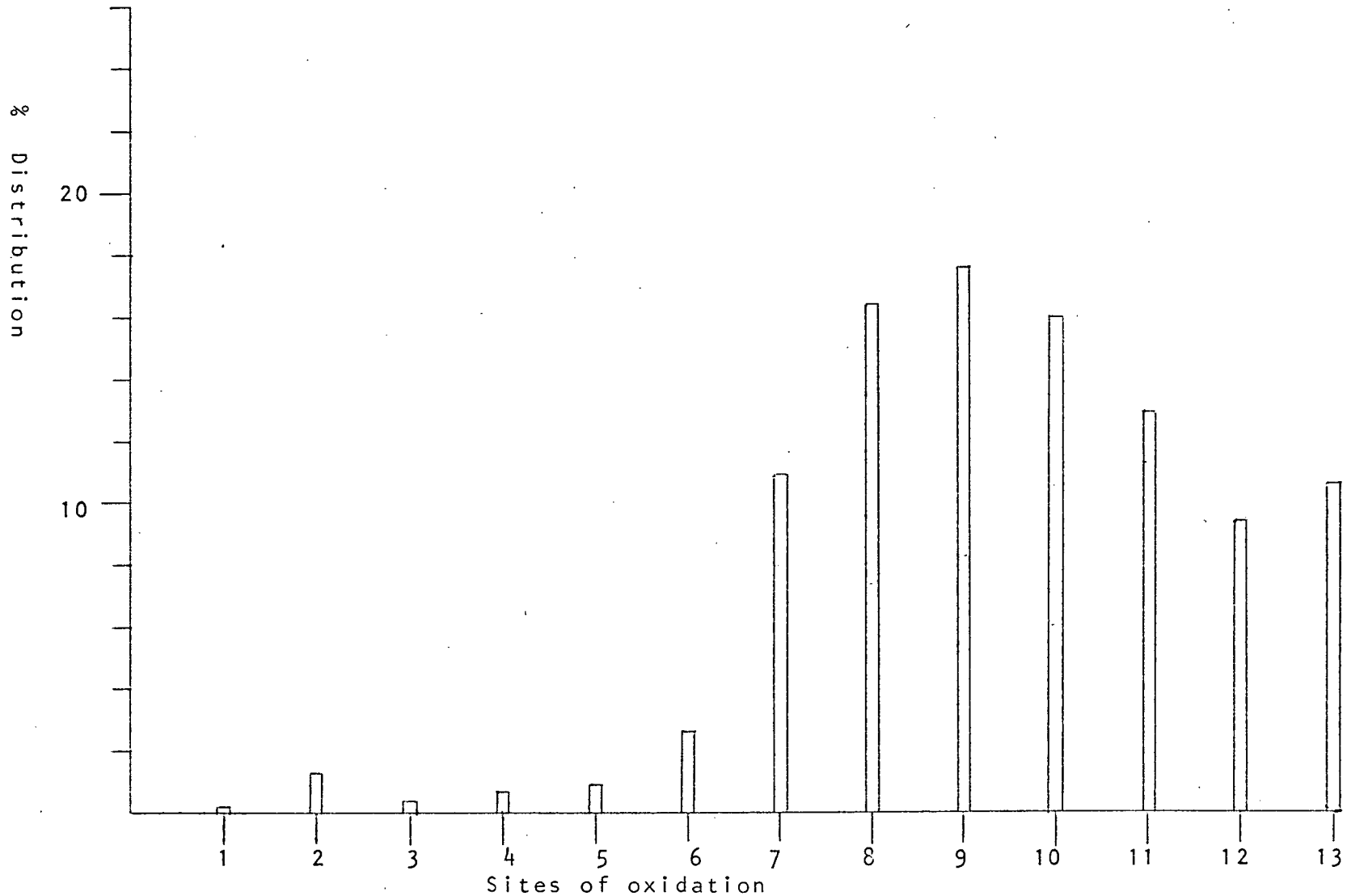


Figure 16. Oxidation of tetradecyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=11) based on the combined relative intensity of fragments (100a and b)].

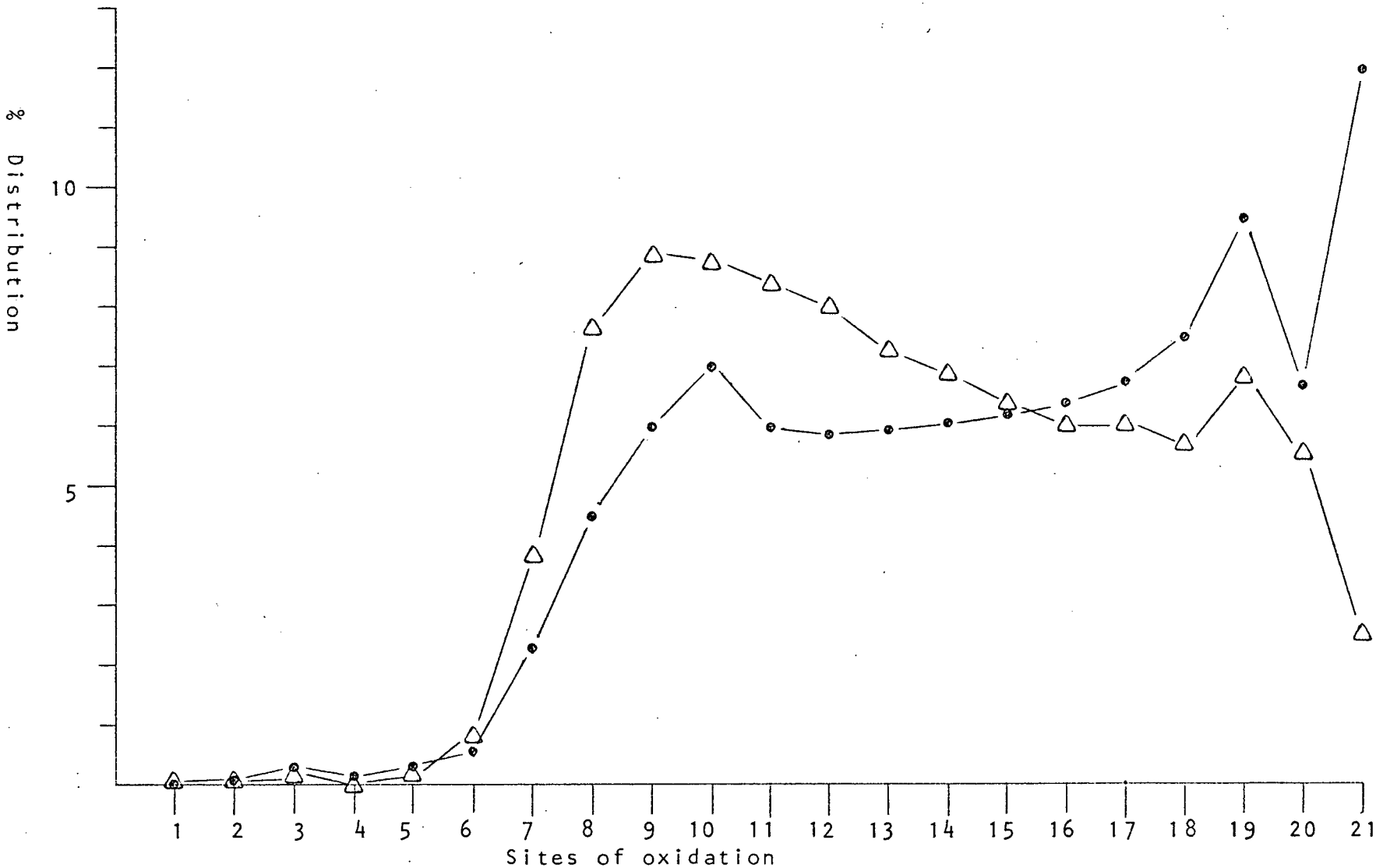


Figure 17. Oxidation of docosyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=19):-o——o- based on fragment (100a):-Δ—Δ- based on fragment (100b)].

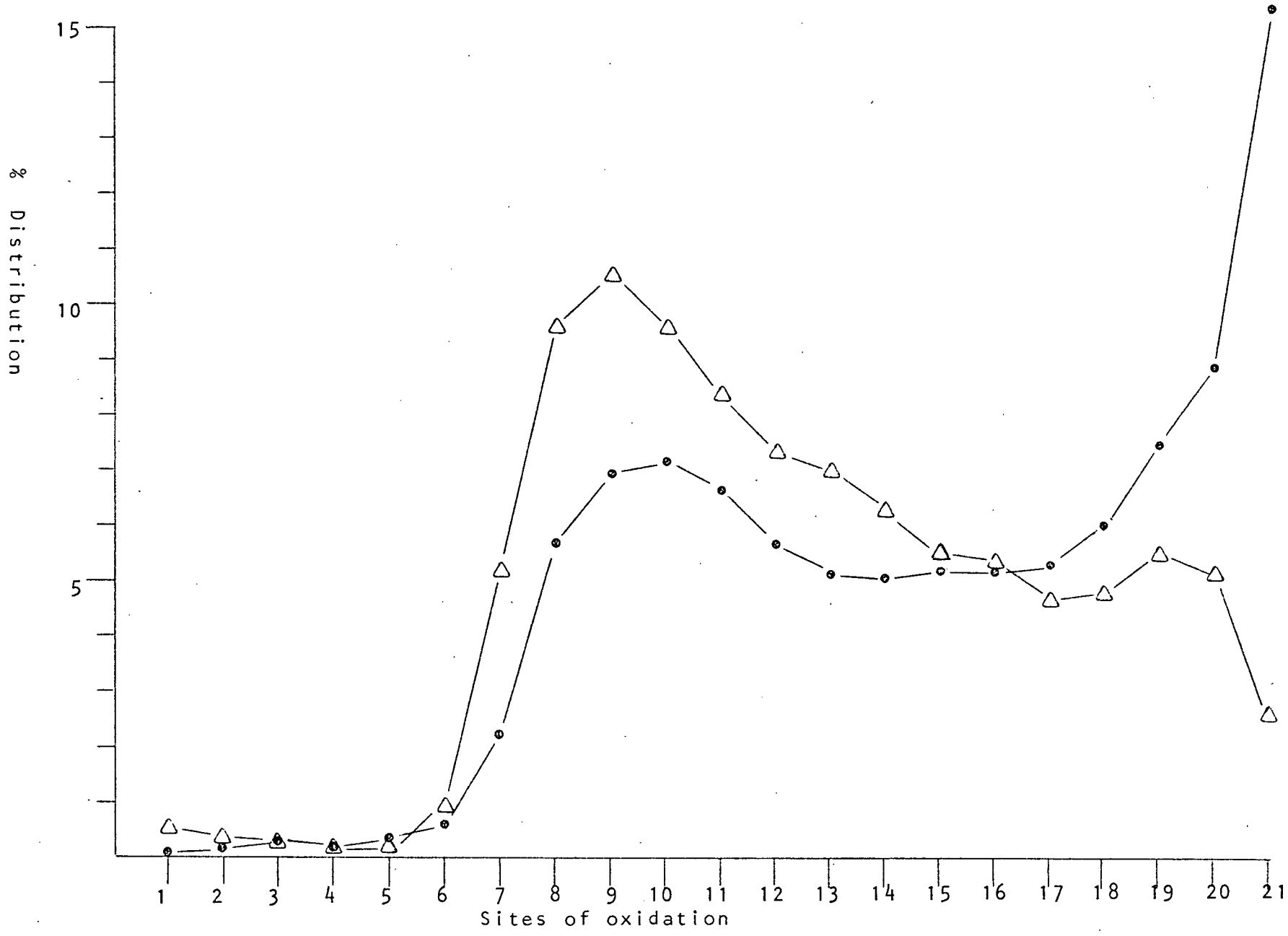


Figure 18. Oxidation of docosyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=19):-o—o- based on fragment (100a):-Δ—Δ- based on fragment (100b)].

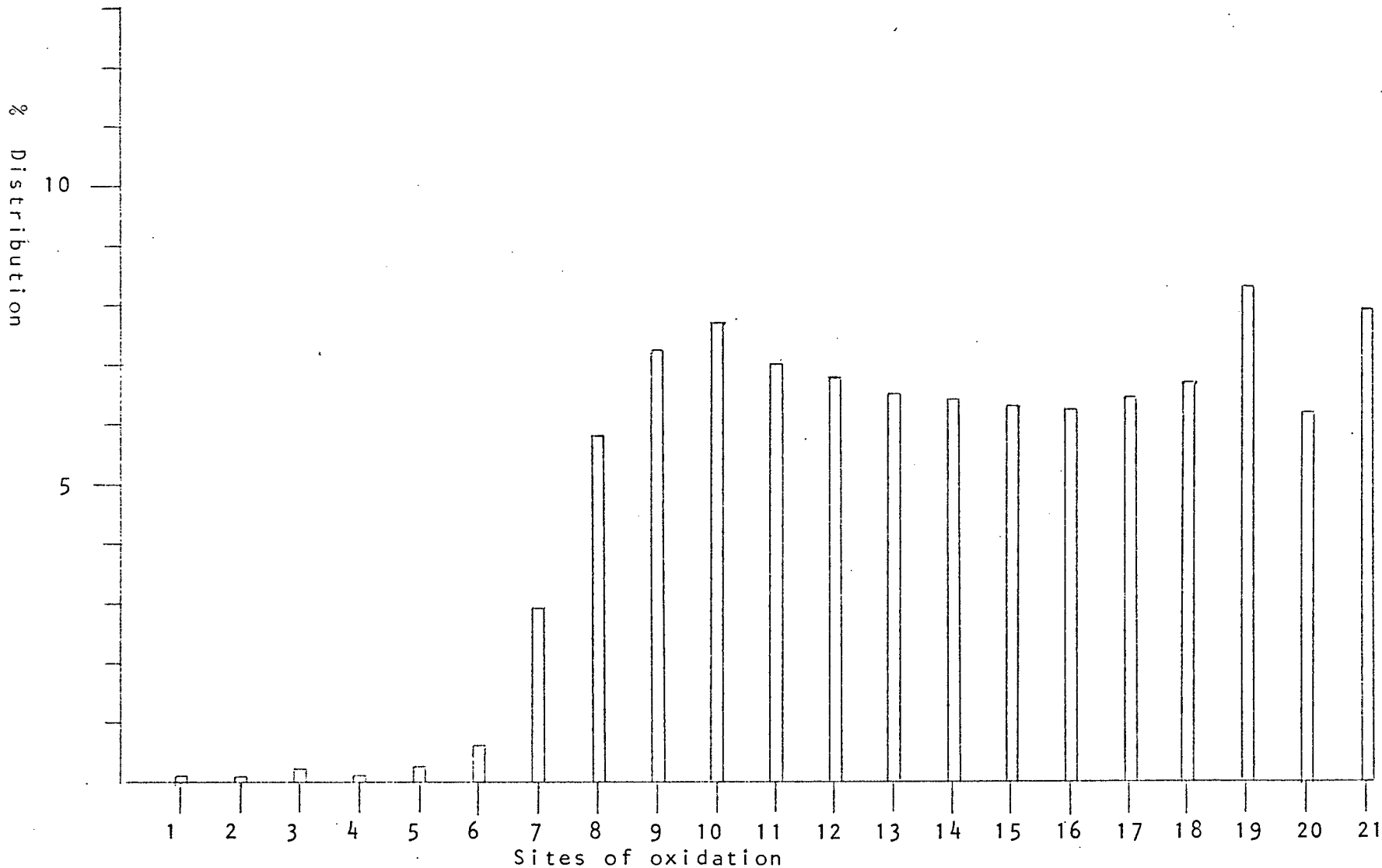


Figure 19. Oxidation of docosyl acetate [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=19) based on the combined relative intensity of fragments (100a and b)].

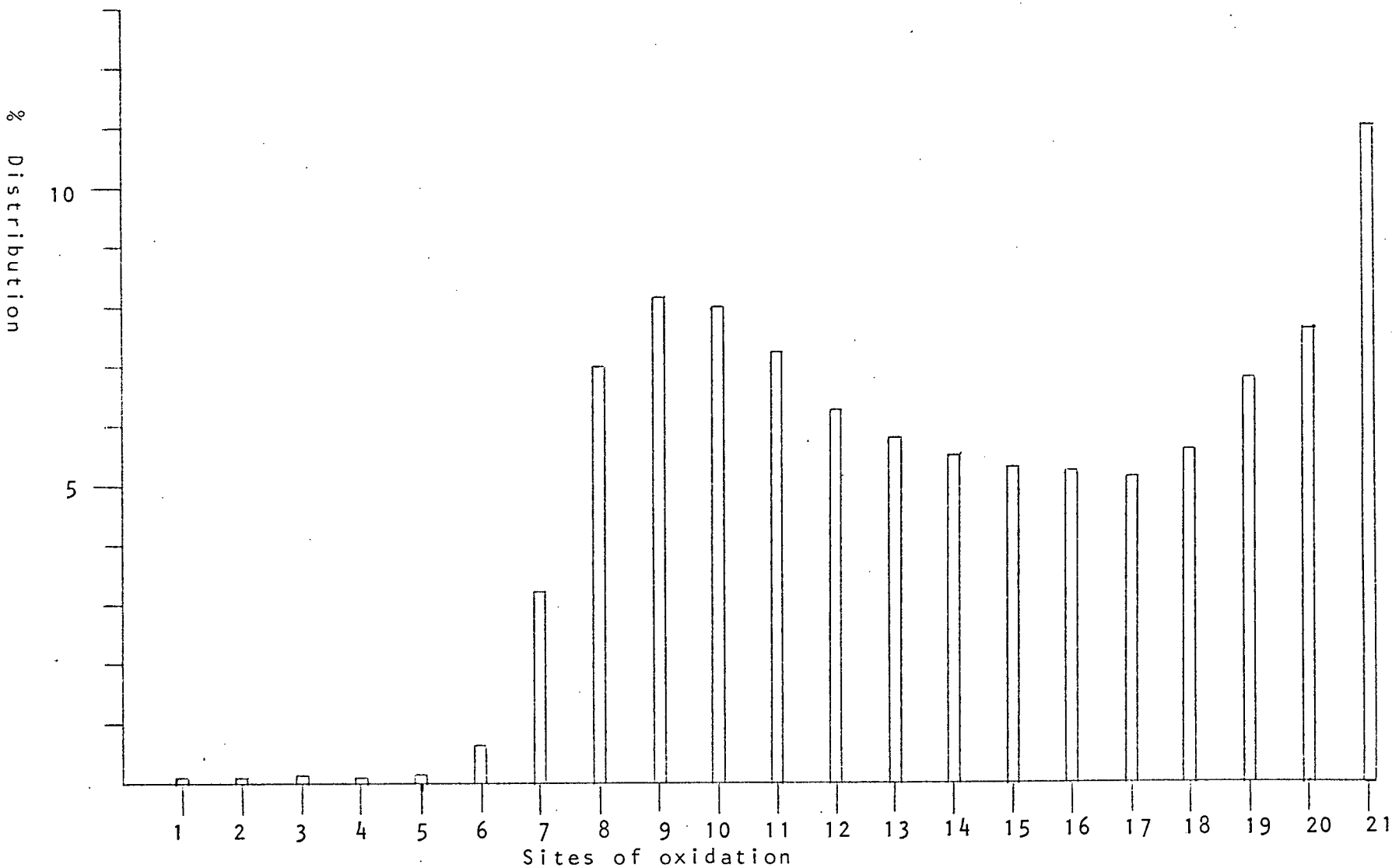


Figure 20. Oxidation of docosyl acetate [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=19) based on the combined relative intensity of fragments (100a and b)].

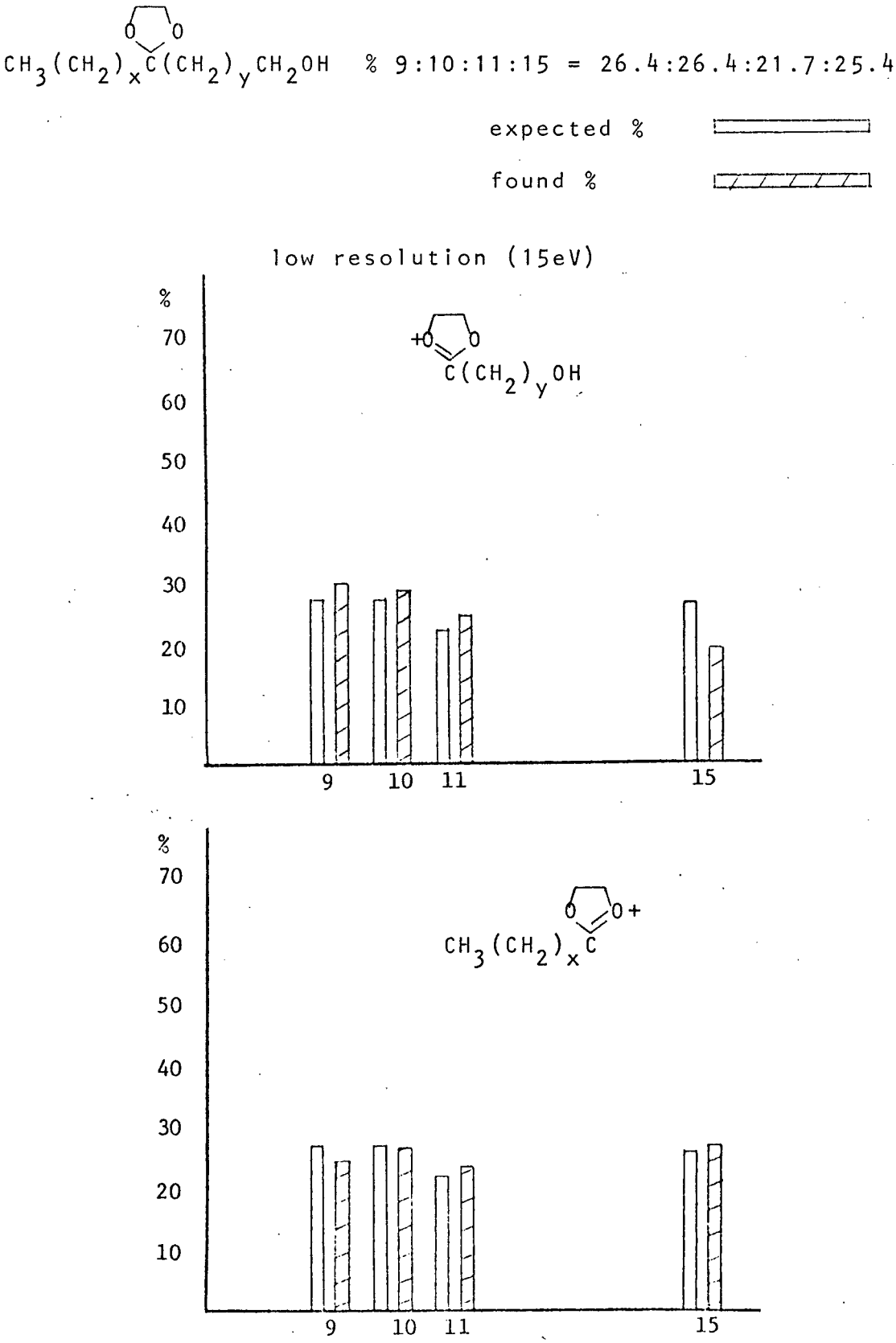


Figure 21. Quantitative study of mixture of known composition [data from the low resolution (15eV) mass spectrum].

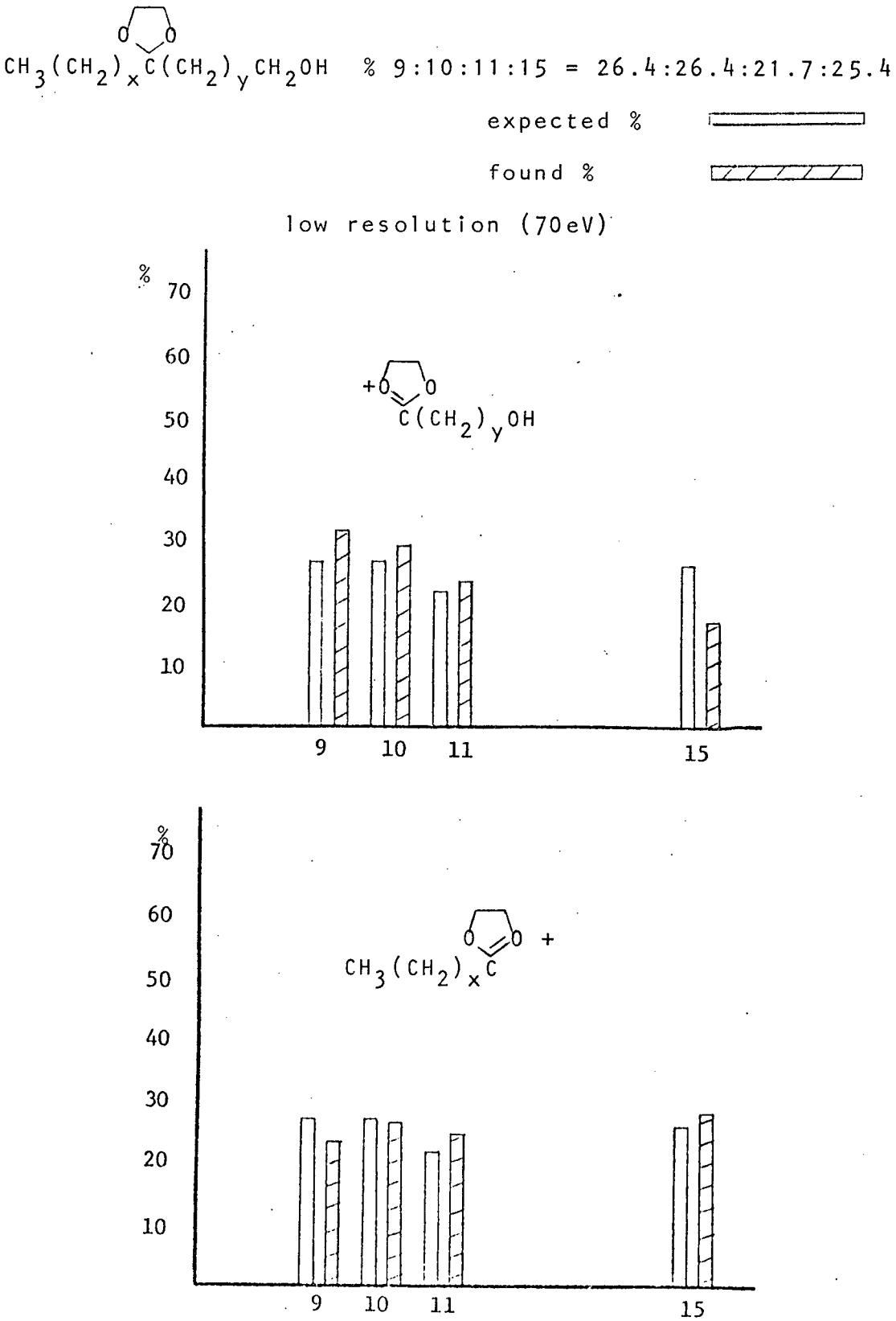


Figure 22. Quantitative study of mixture of known composition [data from the low resolution (70eV) mass spectrum]

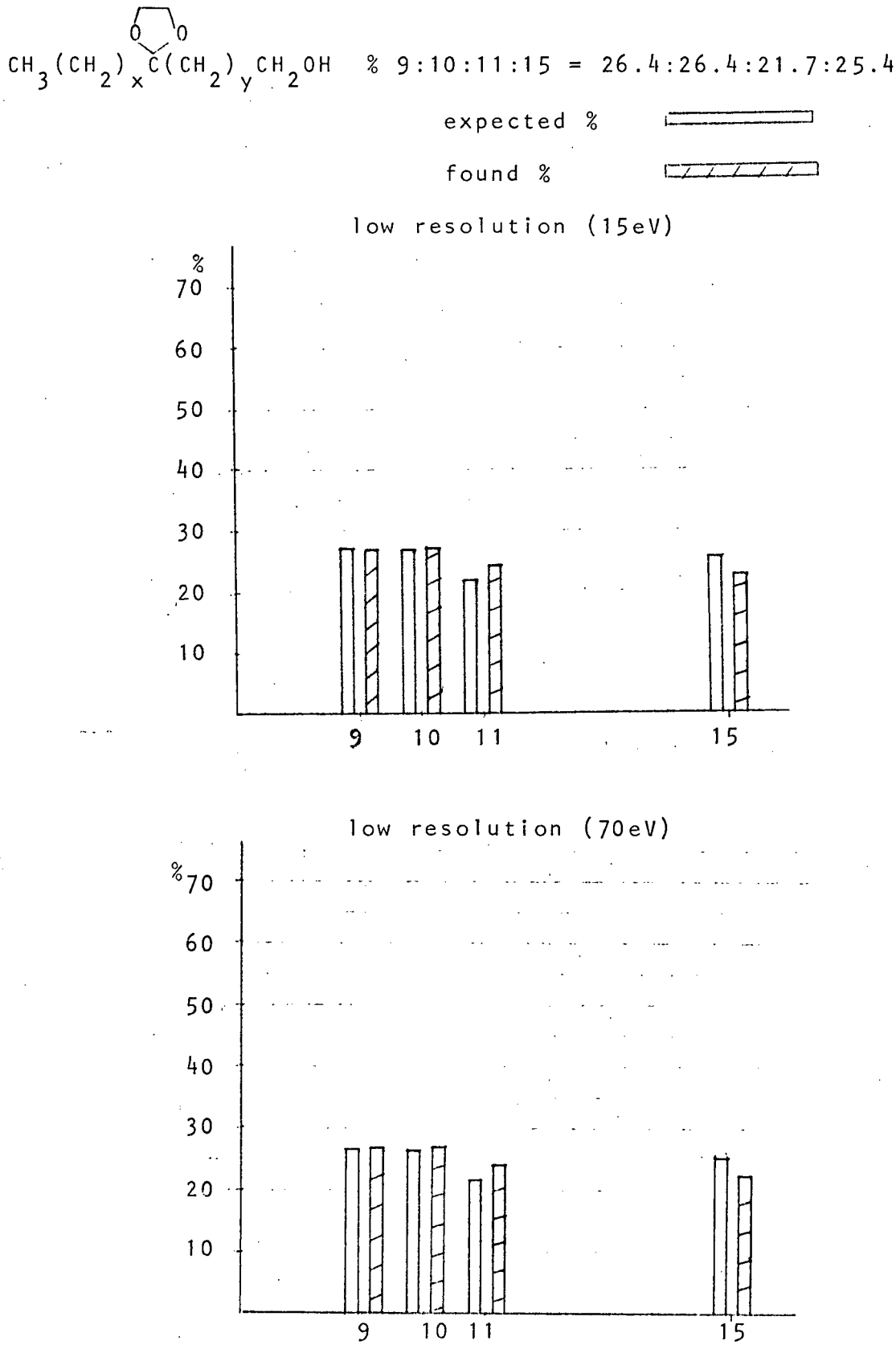


Figure 23. Quantitative study of mixture of known composition [data from the low resolution mass spectra based on the combined relative intensity of fragments (100a and b)].

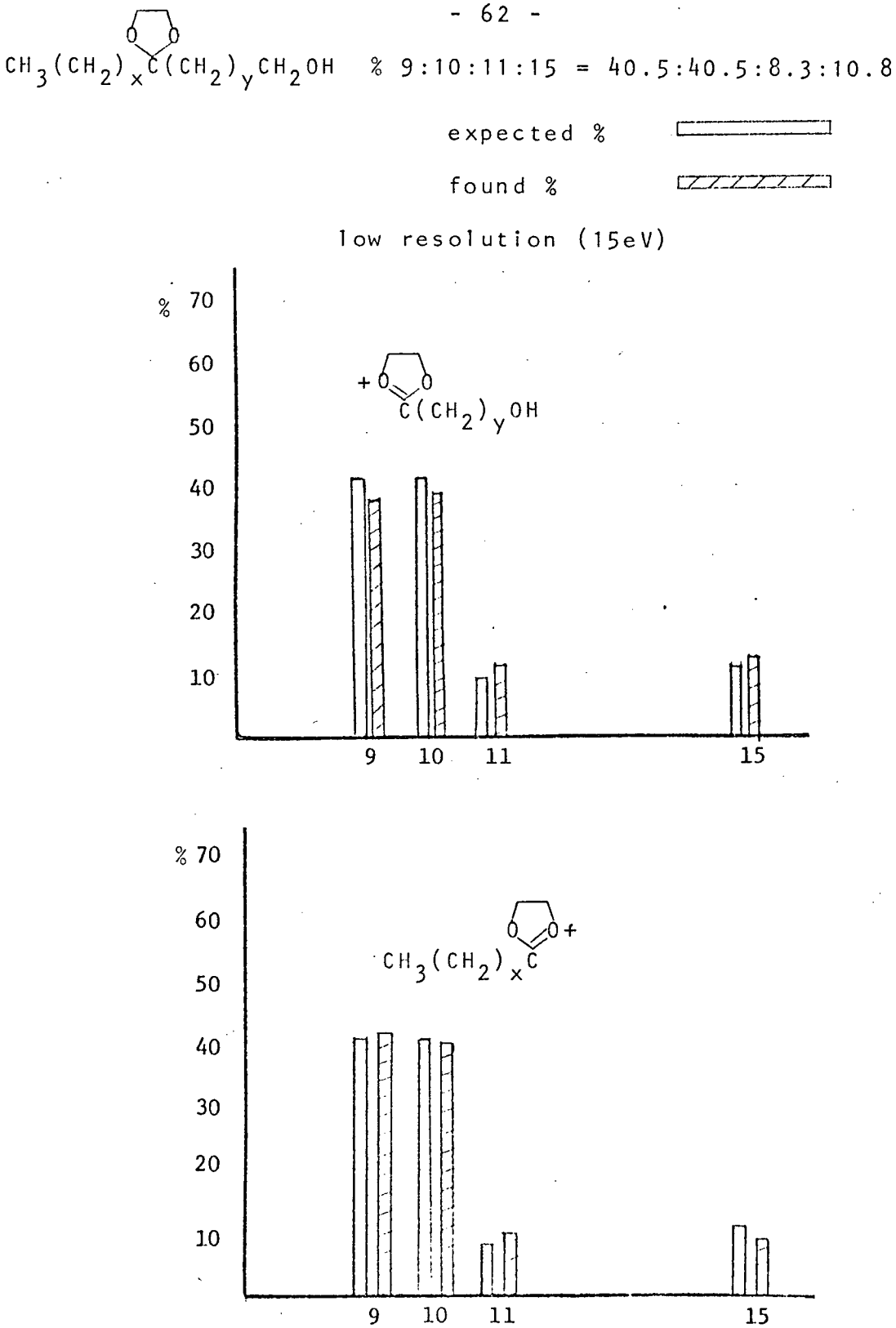


Figure 24. Quantitative study of mixture of known composition [data from the low resolution (15eV) mass spectrum].

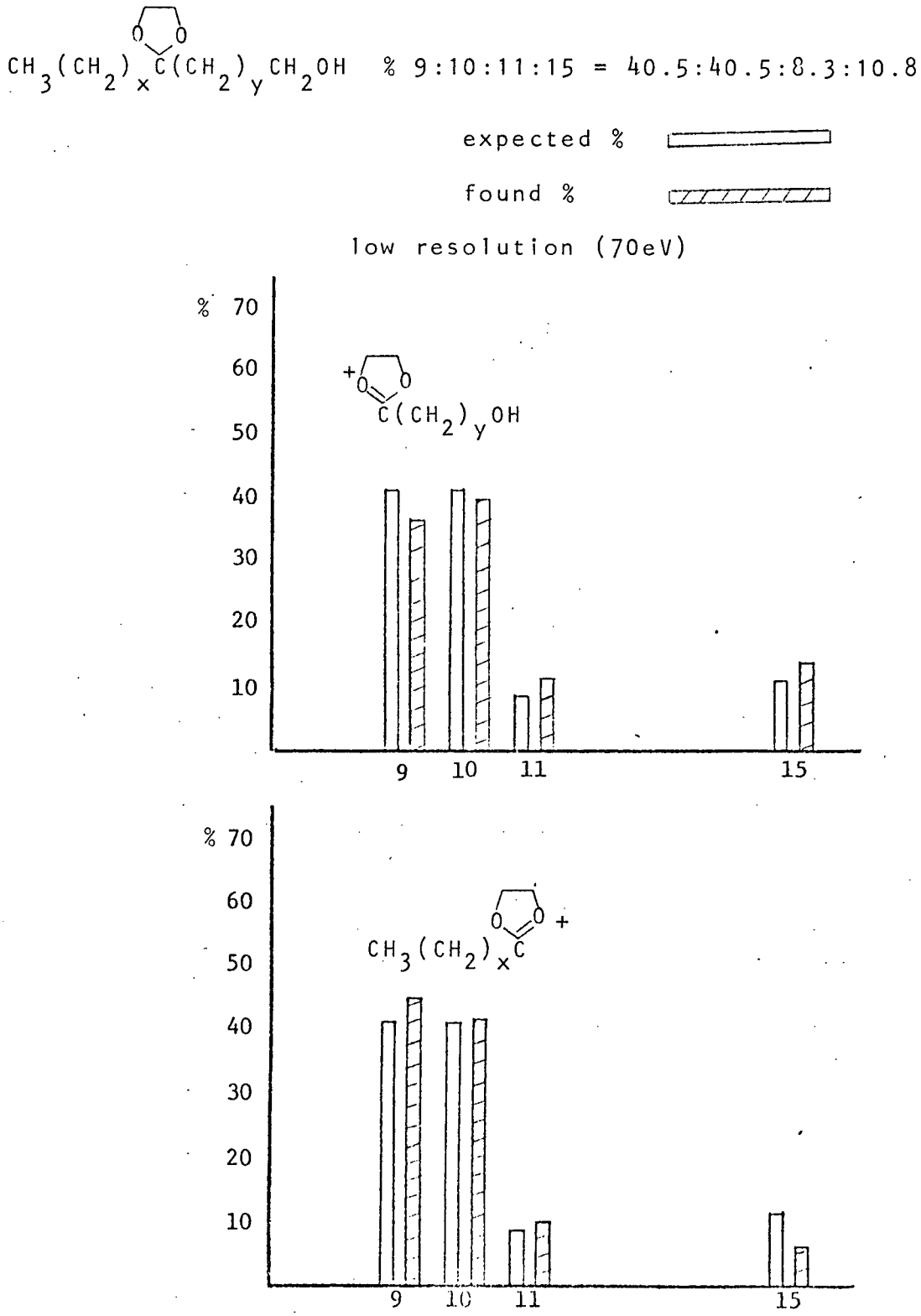
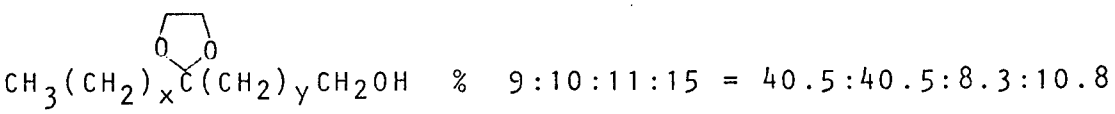
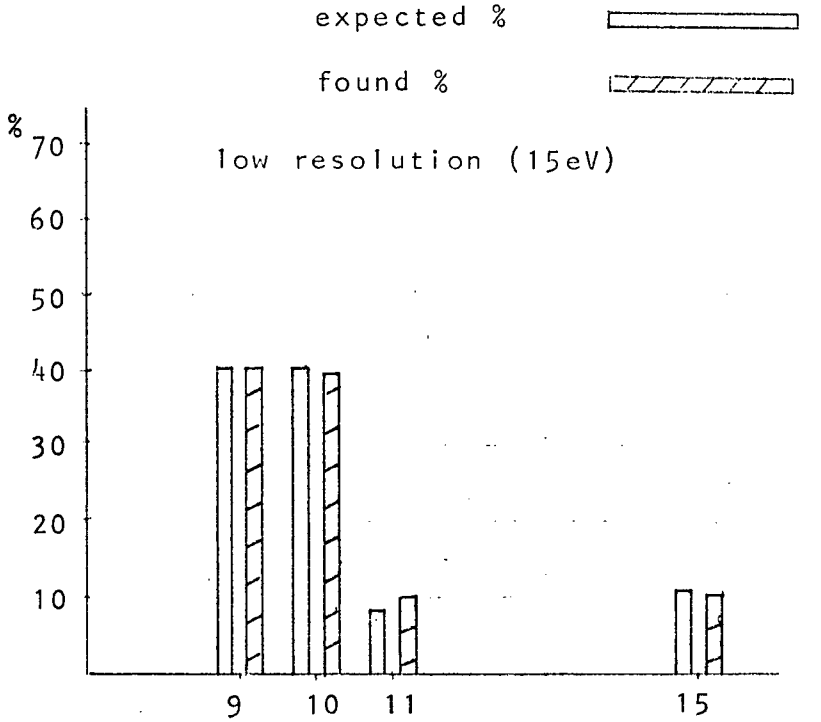


Figure 25. Quantitative study of mixture of known composition [data from the low resolution (70eV) mass spectrum].





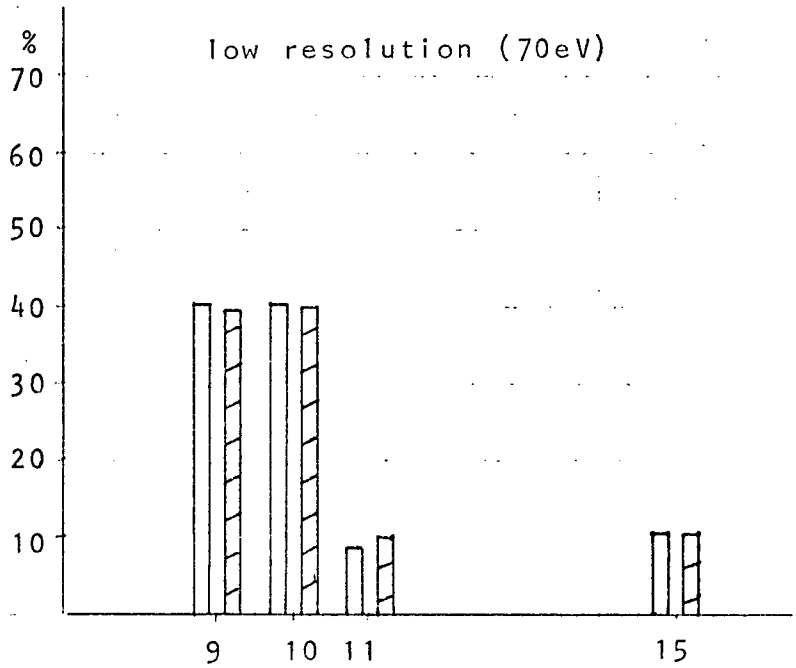


Figure 26. Quantitative study of mixture of known composition [data from the low resolution mass spectra based on the combined relative intensity of fragments (100a and b)].

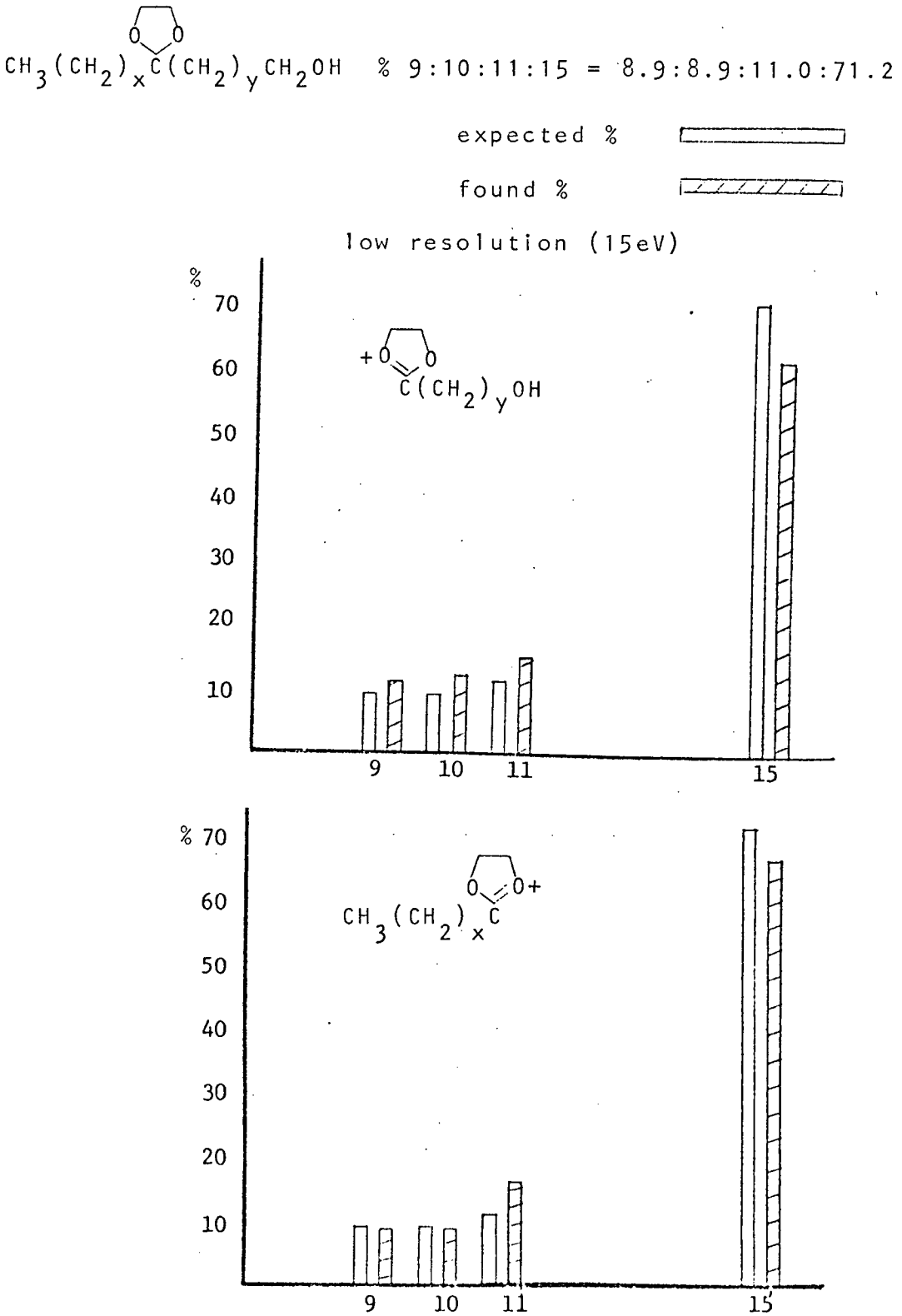


Figure 27. Quantitative study of mixture of known composition [data from the low resolution (15eV) mass spectrum].

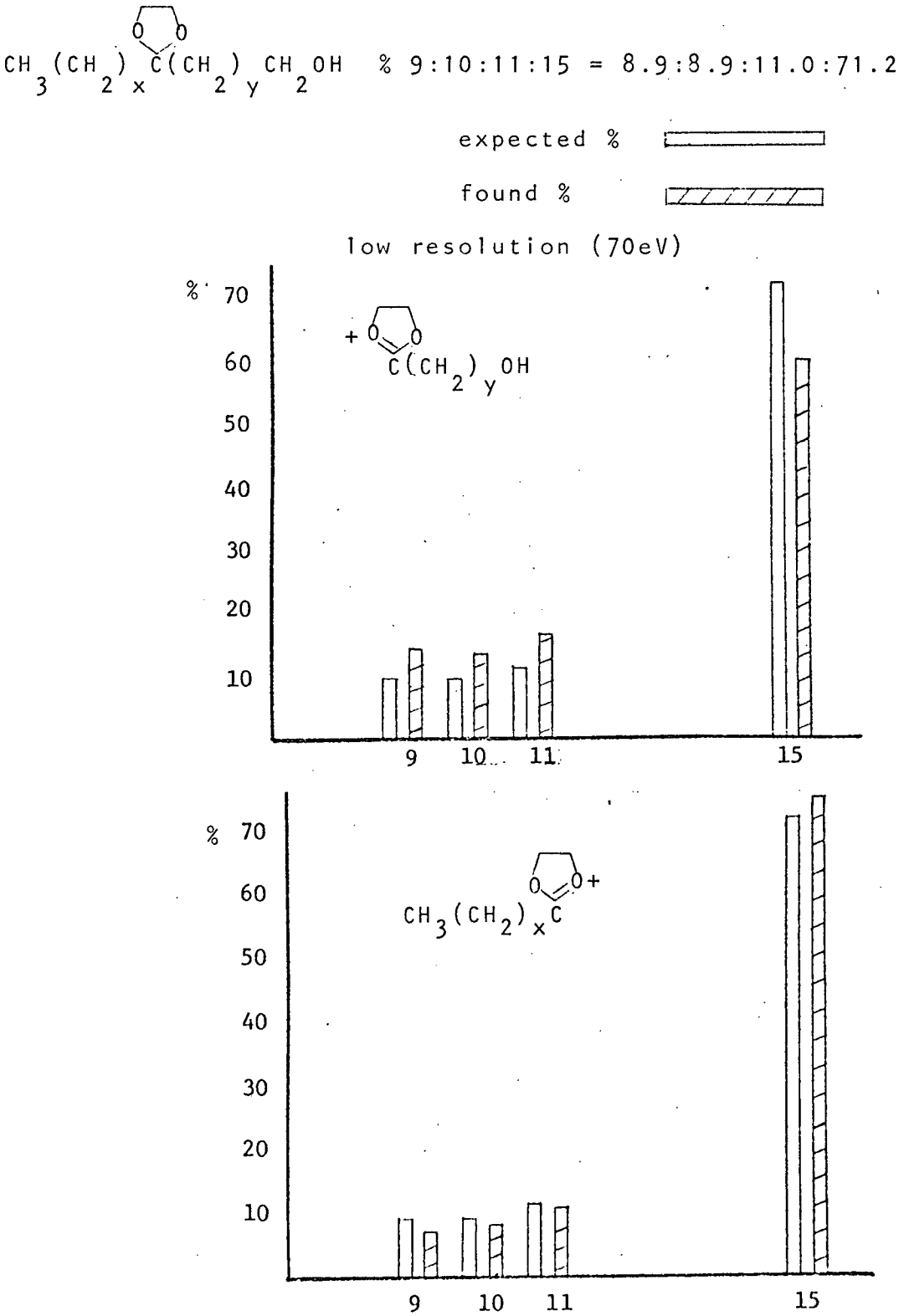
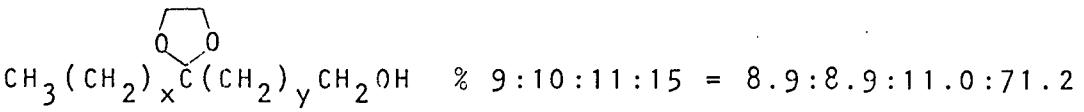


Figure 28. Quantitative study of mixture of known composition [data from the low resolution (70eV) mass spectrum].



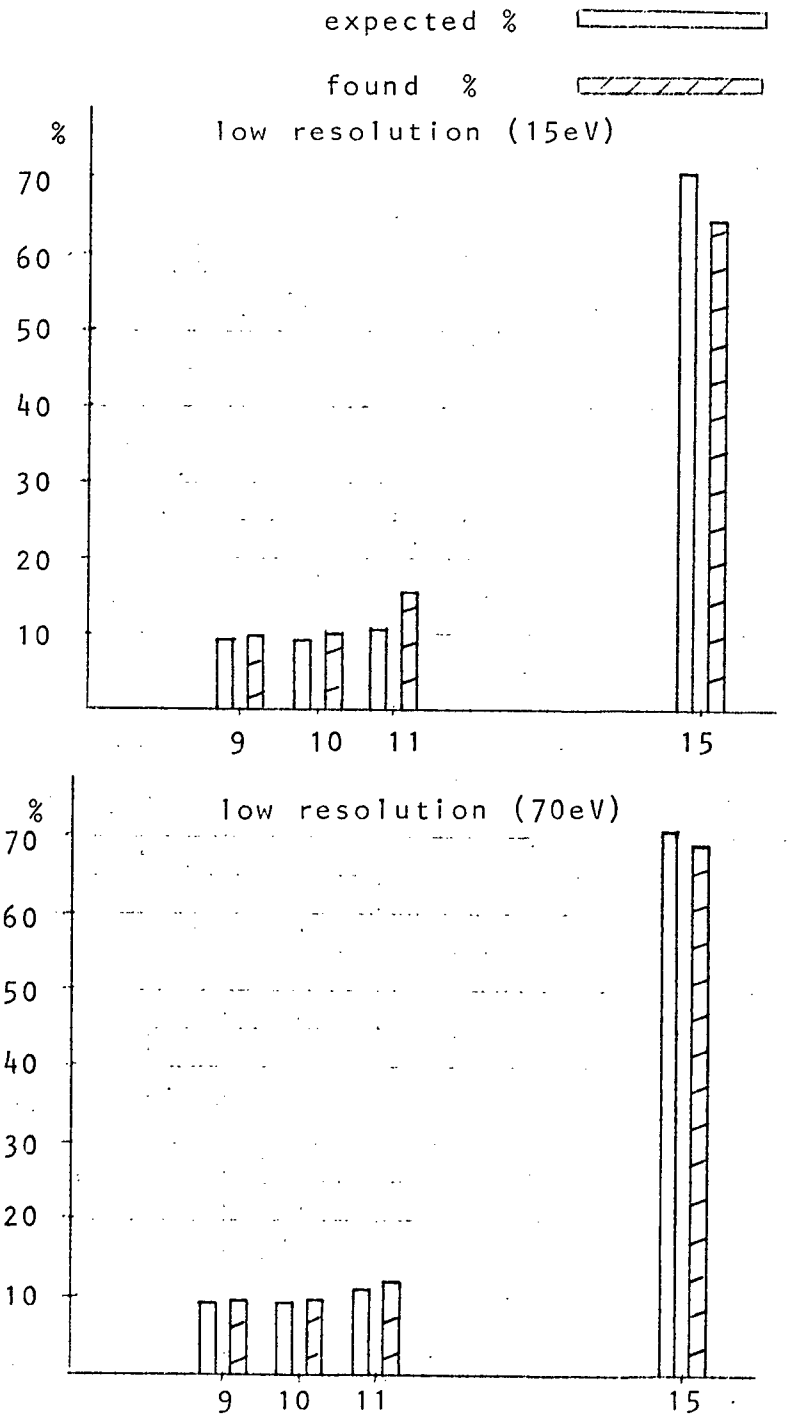


Figure 29. Quantitative study of mixture of known composition [data from the low resolution mass spectra based on the combined relative intensity of fragments (100a and b)].

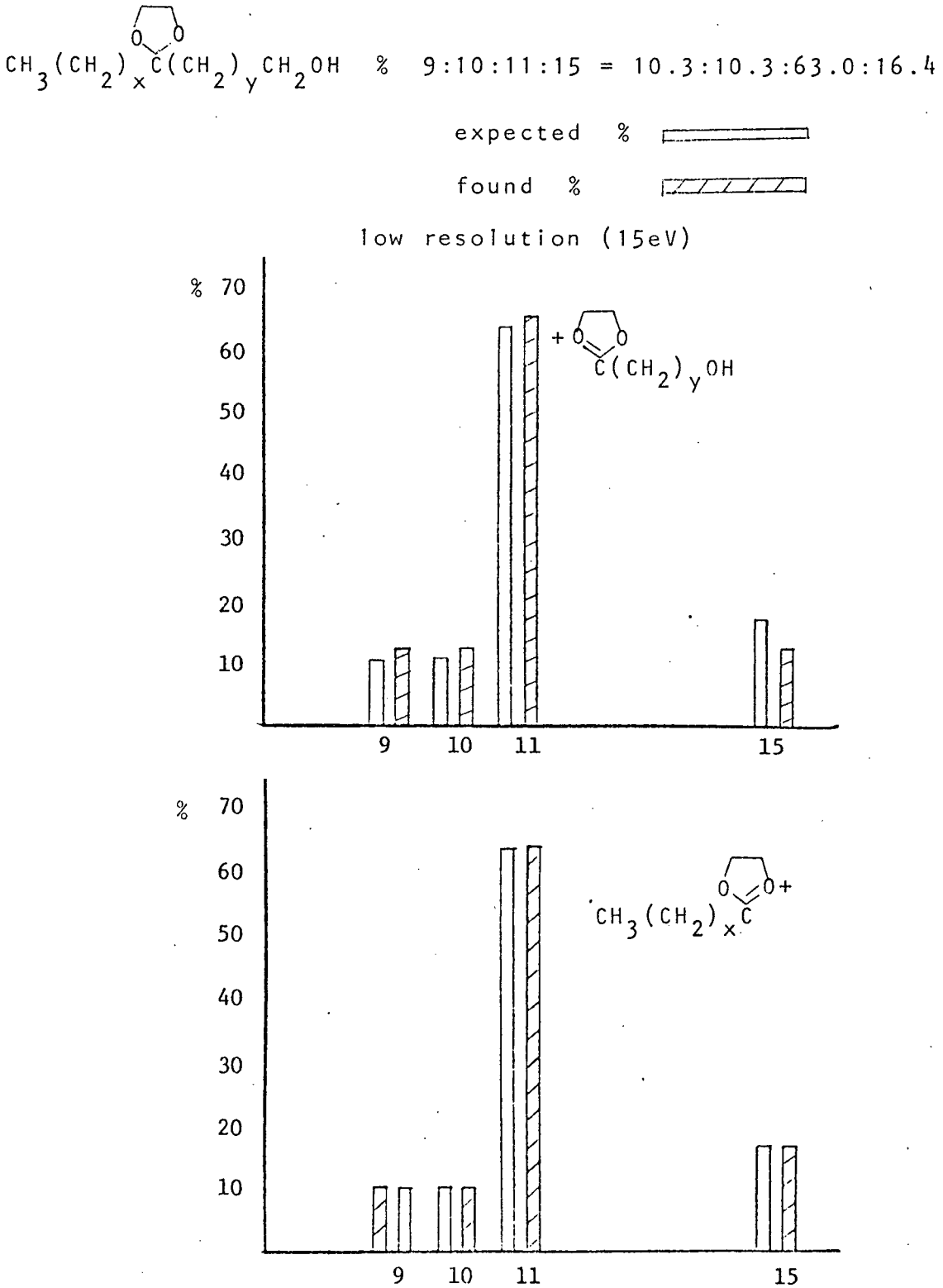


Figure 30. Quantitative study of mixture of known composition [data from the low resolution (15eV) mass spectrum].

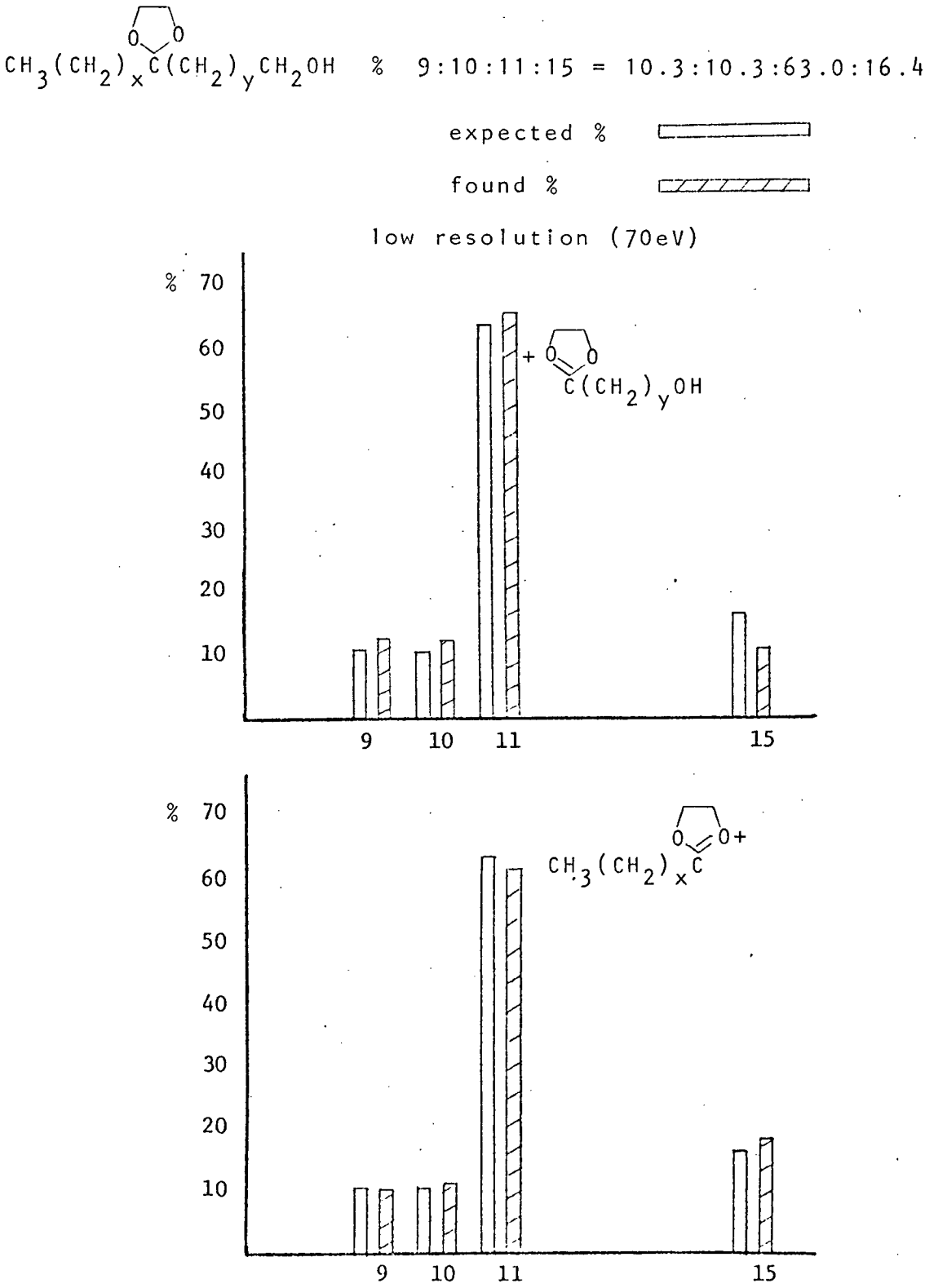
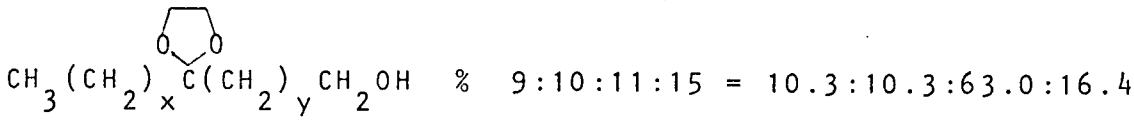
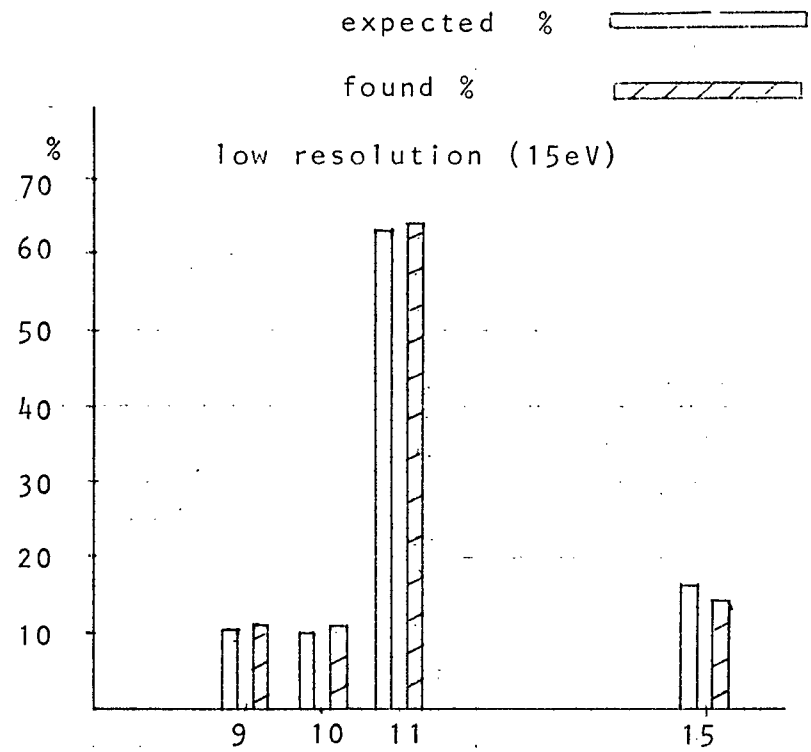


Figure 31. Quantitative study of mixture of known composition [data from the low resolution (70eV) mass spectrum].





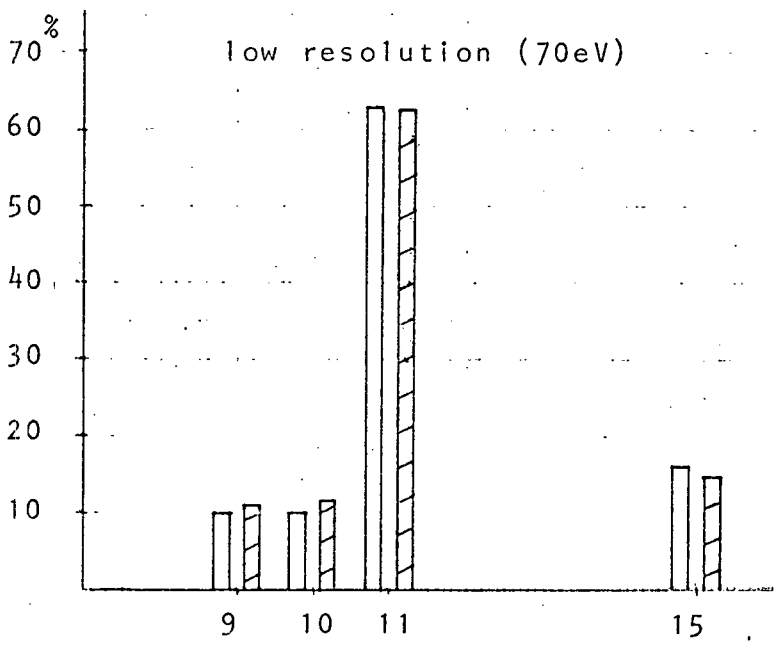


Figure 32. Quantitative study of mixture of known composition [data from the low resolution mass spectra based on the combined relative intensity of fragments (100a and b)].

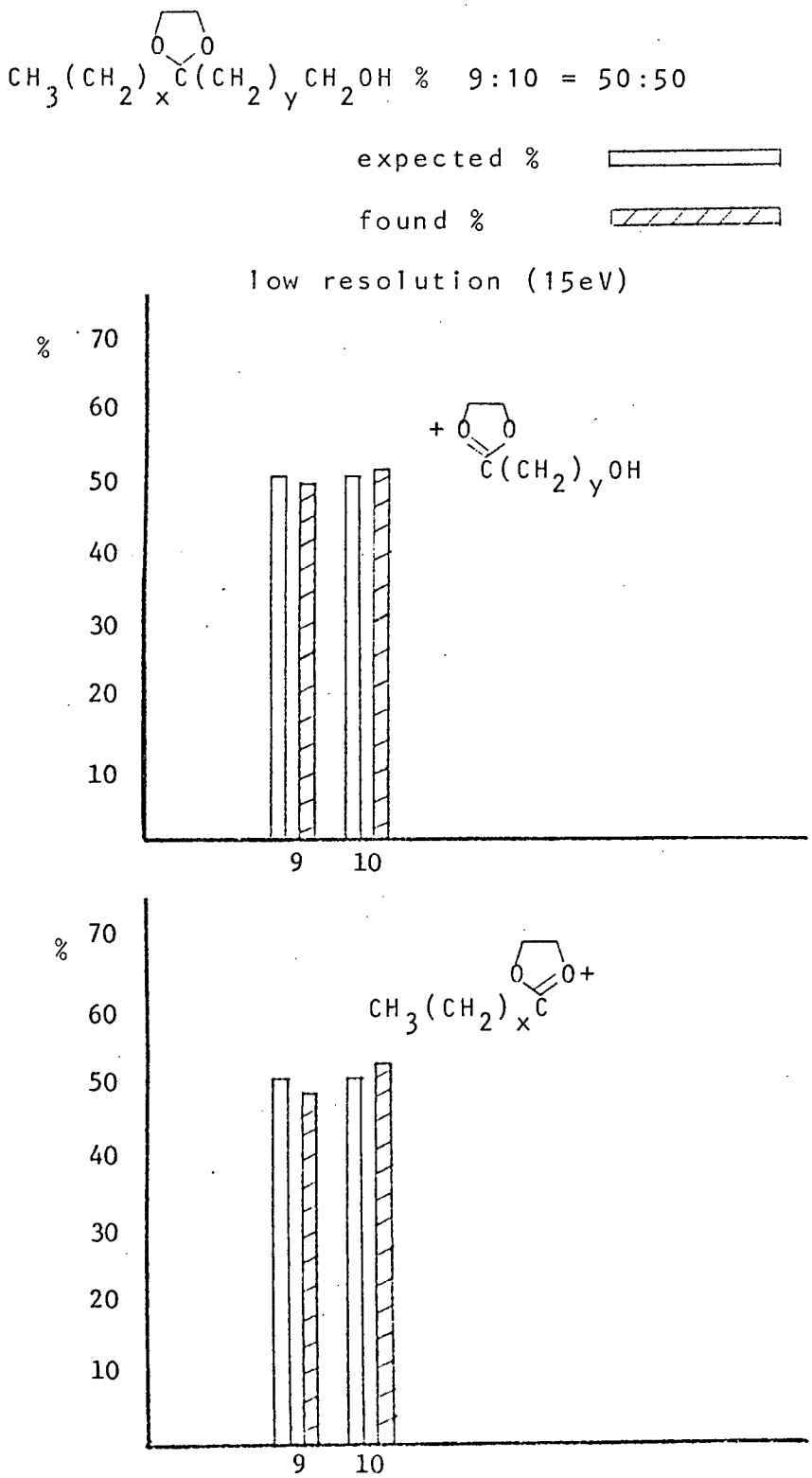


Figure 33. Quantitative study of mixture of known composition [data from the low resolution (15eV) mass spectrum].

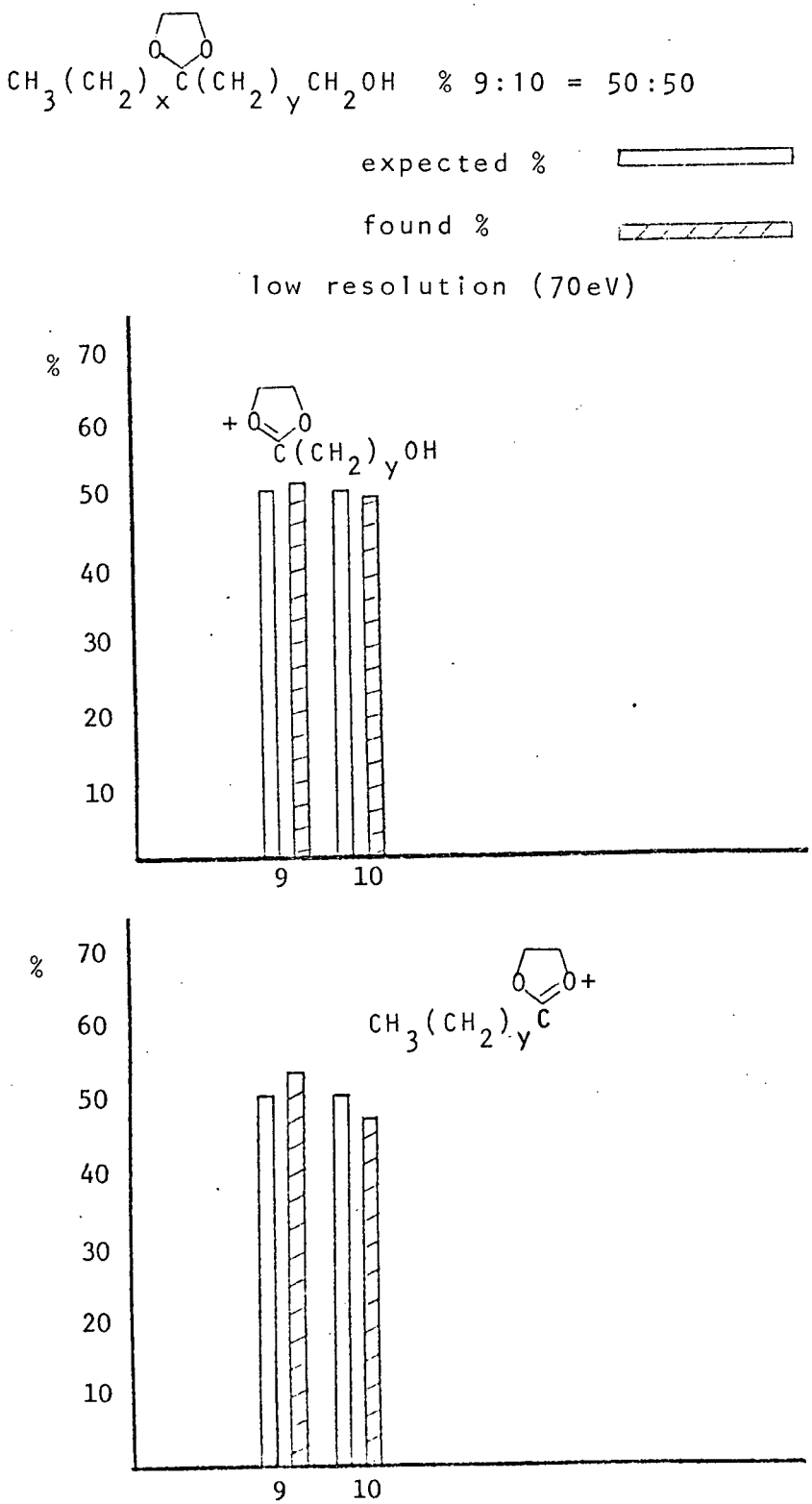


Figure 34. Quantitative study of mixture of known composition [data from the low resolution (70eV) mass spectrum].

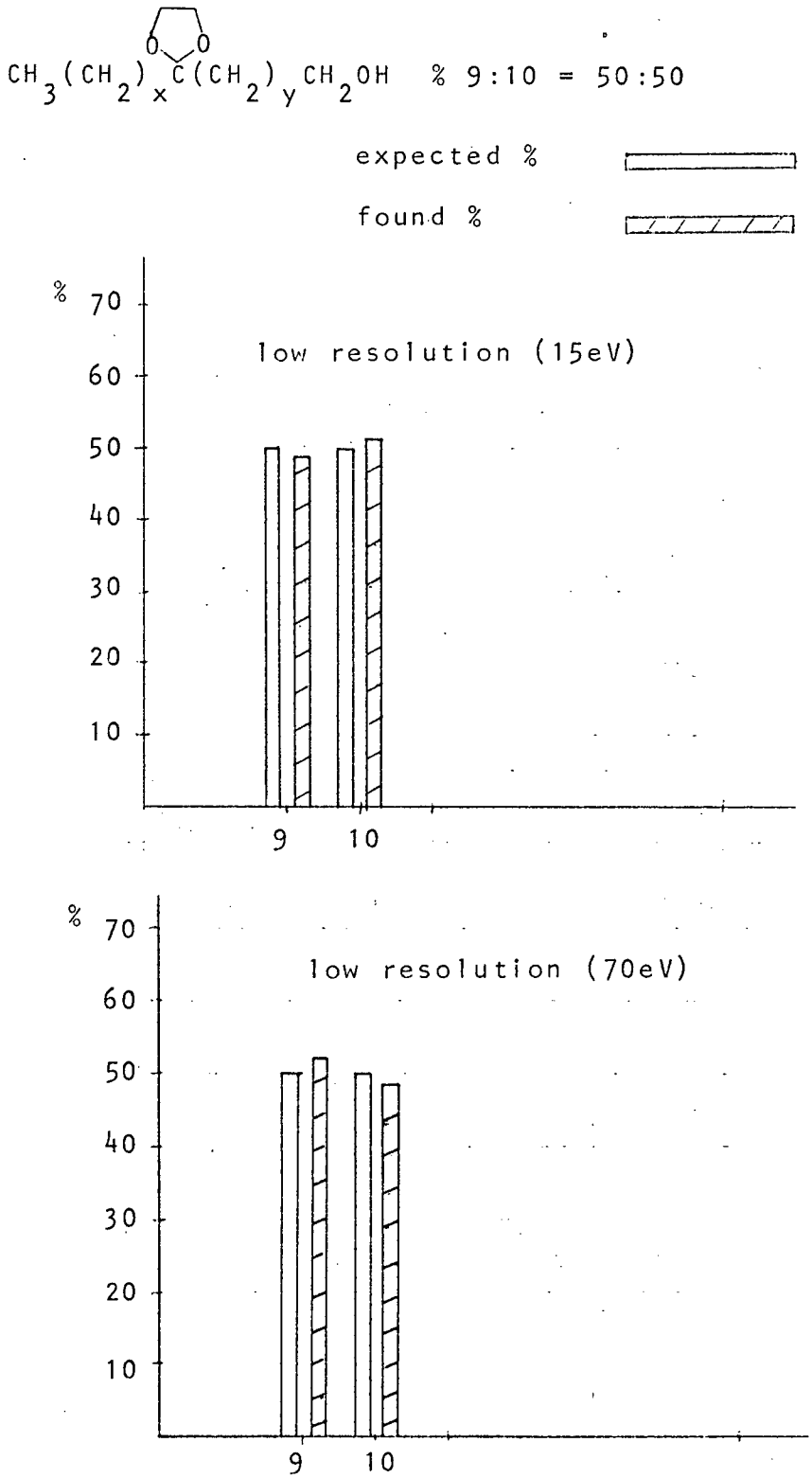


Figure 35. Quantitative study of mixture of known composition [data from the low resolution mass spectra based on the combined relative intensity of fragments (100a and b)].

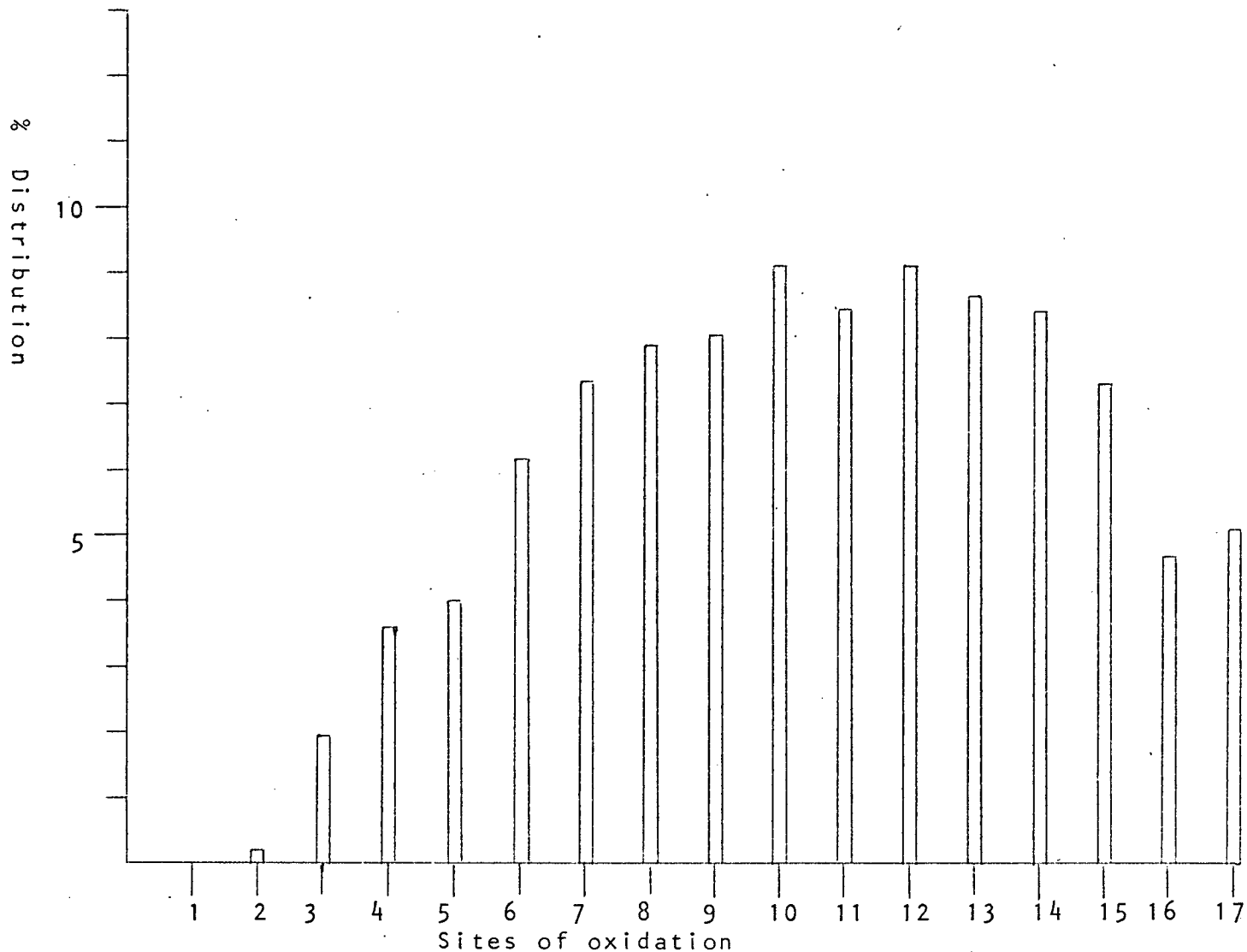


Figure 36. Oxidation of octadecyl acetate in ten times amount of solvent and the same amount of CrO_3-Ac_2O [data from the low resolution (15eV) mass spectrum of acetals (99; x+y=15) based on the combined relative intensity of fragments (100a and b)].

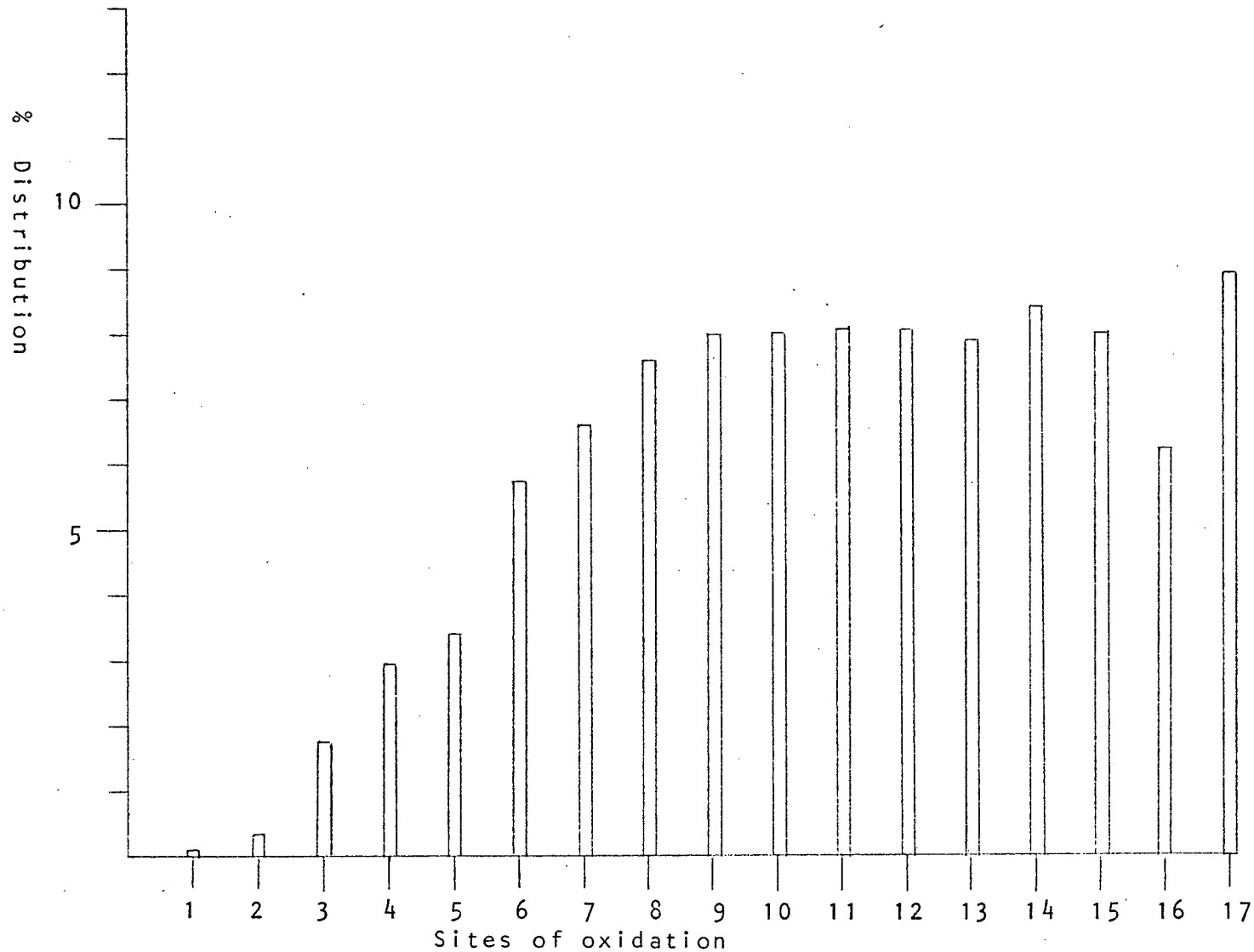


Figure 37. Oxidation of octadecyl acetate in ten times amount of solvent and the same amount of CrO_3-Ac_2O [data from the low resolution (70eV) mass spectrum of acetals (99; x+y=15) based on the combined relative intensity of fragments (100a and b)] .

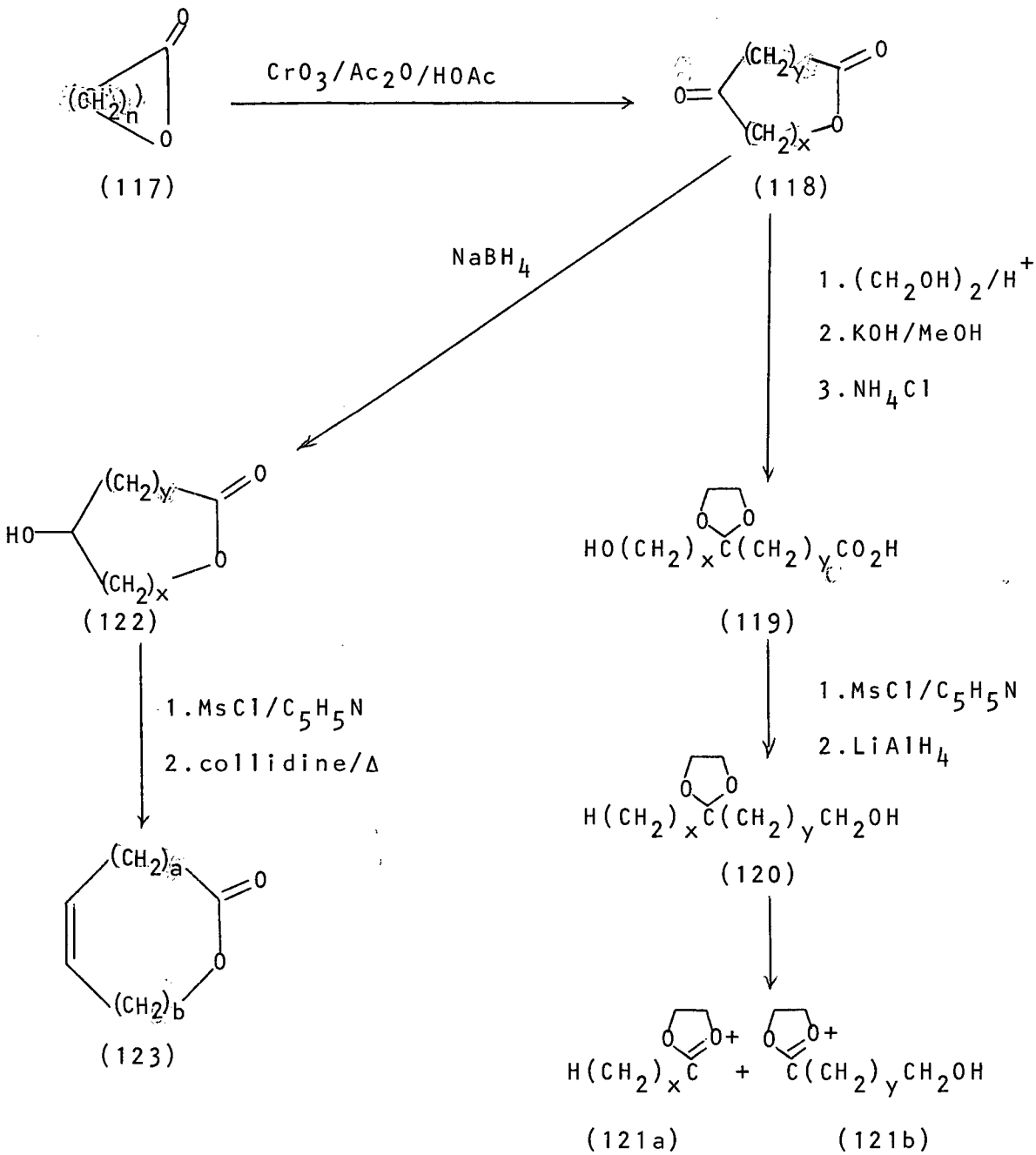
(B) Remote oxidation of macrocyclic lactones

After some preliminary examination of flexible long chain acetates, we decided to explore the oxidative vulnerability of macrocyclic lactones, a class of compounds which have less flexibility. The oxidation of macrocyclic lactones leads to a variety of well-known and clinically important macrolide antibiotics.[53]

Treatment of pure 16-hexadecanolide (117; n=15) in glacial acetic acid/acetic anhydride with chromium trioxide/acetic anhydride (i.e. chromyl acetate) at room temperature for 5 days provided a mixture of mono-oxo-16-hexadecanolides (118; x+y=14) and starting material.[54] Careful column chromatography [Woelm silica gel grade III (1:50); pet. ether/ether] separated the mono-oxo-16-hexadecanolides from starting material. The yield of these products based on consumed starting material was ∿33%. The elemental analysis, infrared and NMR data identified the products as mono-oxo-16-hexadecanolides. The infrared spectrum (CCl_4) showed absorption bands at 1738 and 1720 cm^{-1} and the NMR spectrum exhibited resonances at τ5.97 (t, 2H, $-CO_2\underline{CH_2}-$), 7.72 (mixed t, 6H, $-\underline{CH_2}CO\underline{CH_2}-$, $-\underline{CH_2}CO_2-$), 8.42,8.70 (m, broad s, 20H, $-(\underline{CH_2})_{10}-$).

The position of the keto-group and relative amounts of the isomeric mono-oxo-16-hexadecanolides could be deduced by examining the mass spectra of the ethylene acetals of the corresponding hydroxyacids (120; x+y=14). In the mass spectra measured at 15eV and 70eV, the only significant peaks arise from

fragments (121a,b). Therefore the method described earlier (see P.36) could be applied here. The mixture of oxo-16-hexadecanolides (118; x+y=14), on reaction with ethylene glycol/



p-toluenesulfonic acid followed by hydrolysis, yielded the acetals of the oxo-16-hydroxyhexadecanoic acids (119; x+y=14). Their structures were established by reduction to a mixture of acetals of mono-oxo-hexadecanols (120; x+y=14) whose mass spectra showed both the relative amounts of the oxo-16-hexadecanolides and the position of the keto group (figures 38-41).

Similar oxidations were carried out on 15-pentadecanolide (117; n=14) and 12-dodecanolide* (117; n=11) and the procedures described above were used to determine the relative amounts of isomeric oxo-macrolides. The results (summarized in figures 42-49) indicate that the oxidation of dodecanolide (figures 46-49) is more regiospecific than that of the higher homologues (figures 38-45). A very interesting fact is that we did not observe any

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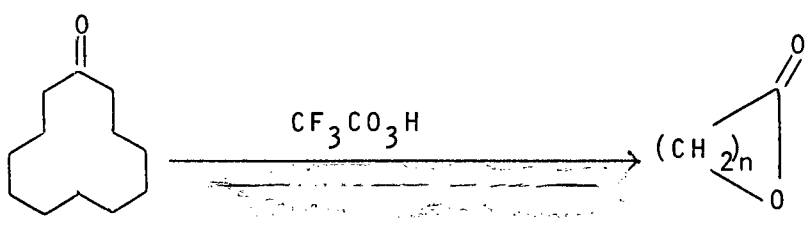
* 12-dodecanolide is not commercially available. It was made from cyclododecanone (124) by the action of trifluoroperacetic acid.[55]



(124) (117; n=11)

significant oxygenation at the four carbons closest to the functional group. If the mechanism proposed earlier (see P.40) applied here, those hydrogens that are attached to the four nearest carbons cannot reach the reactive oxygen on chromium. Another interesting aspect is that the highest yield of mono-oxo-macrolide resulted from attack at the carbon atom most remote from the lactone functionality, i.e. C-9 of 16-hexadecanolide (6.5%), C-8 (6.1%) of 15-pentadecanolide and C-7 (12.3%) of 12-dodecanolide.

Attempts to oxidize 8-octanolide to mono-oxo-8-octanolide were not very successful. After oxidation at room temperature for 3 days, usual work-up provided a trace of deep brown oil. Gas chromatography showed only one peak with a shoulder and no starting material. The infrared and NMR data showed this brown oil to be composed of mono-oxo-macrolides. The very low yield may arise from the degradation of 8-octanolide to tar instead of mono-oxygenation by the chromyl acetate.

Efforts to increase the selectivity of the oxidation by using another oxidation reagent ($Na_2Cr_2O_7/H_2SO_4/HOAc$) failed. No mono-oxo products were formed.

Recent investigation have shown that ambrettolide (123; a=5, b=8) and its isomers are part of the pheromone complex of the oak leaf roller moth. This insect destroys millions of dollars worth of forest in the northeastern United States.[56] Ambrettolide and similar macrocycles have been

associated with sexual activity in musk oxen, civet cats, musk rats and black-tailed deer. Ambrettolide is also the principle odorous constituent of ambrette seed and is an important base for the perfume industry. A very interesting aspect of our research is that we can now convert 16-hexadecanolide to a mixture of mono-unsaturated hexadecanolides (123; a+b=13). Reduction of mono-oxo-16-hexadecanolides (118; x+y=14) with sodium borohydride in methanol provided the hydroxy lactones (122; x+y=14) which were then reacted with mesyl chloride. Demesylation, by heating the mesylates in collidine, gave a pleasant smelling mixture of mono-unsaturated hexadecanolides (123; a+b=13) whose sex pheromonal activity is being evaluated by Professor L.B. Hendry (Pennsylvania State University).

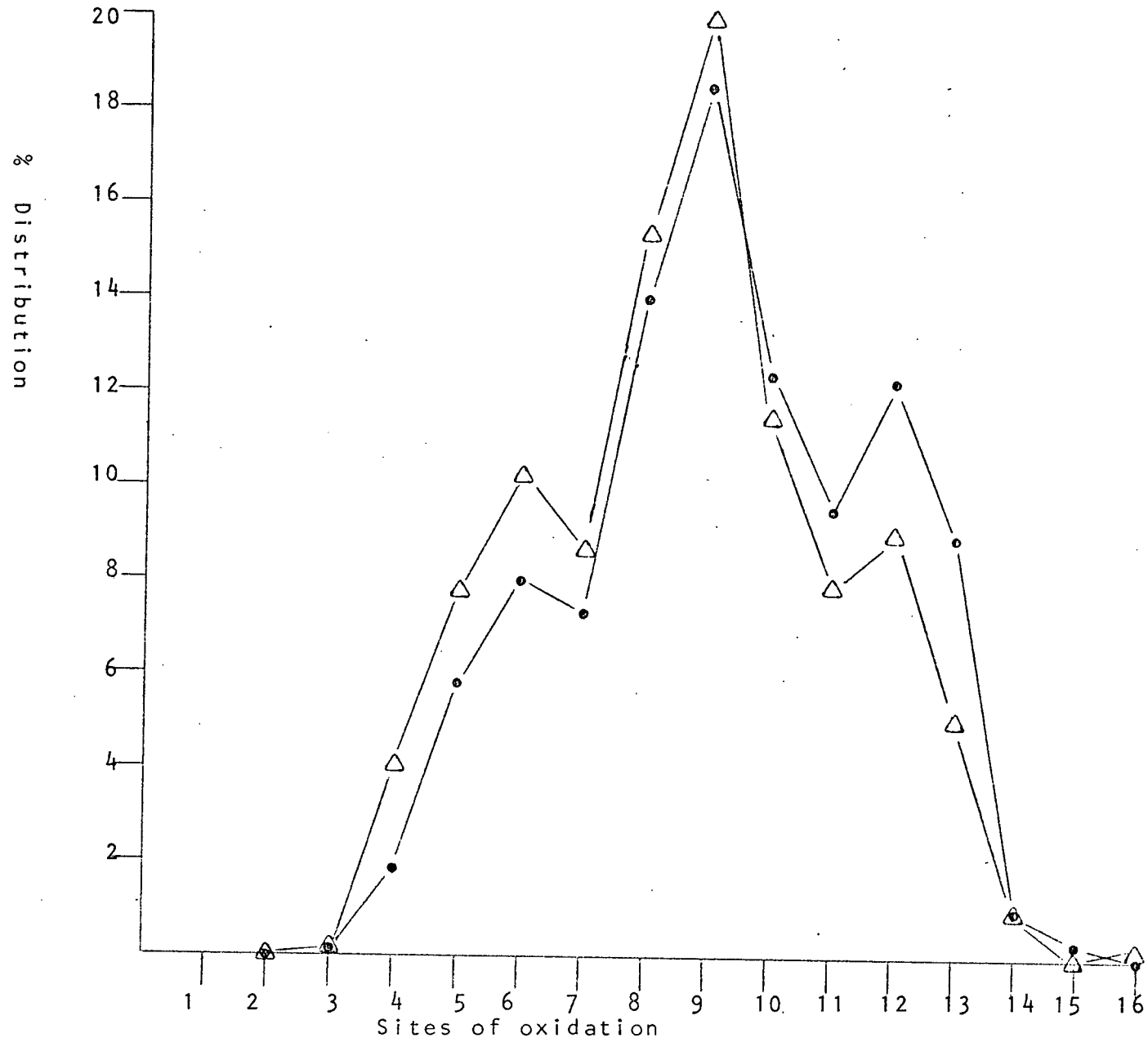


Figure 38. Oxidation of 16-hexadecanolide [data from the low resolution (15eV) mass spectrum of acetals (120; x+y=14) :-o—o- based on fragment (121a) :-Δ—Δ- based on fragment (121b)].

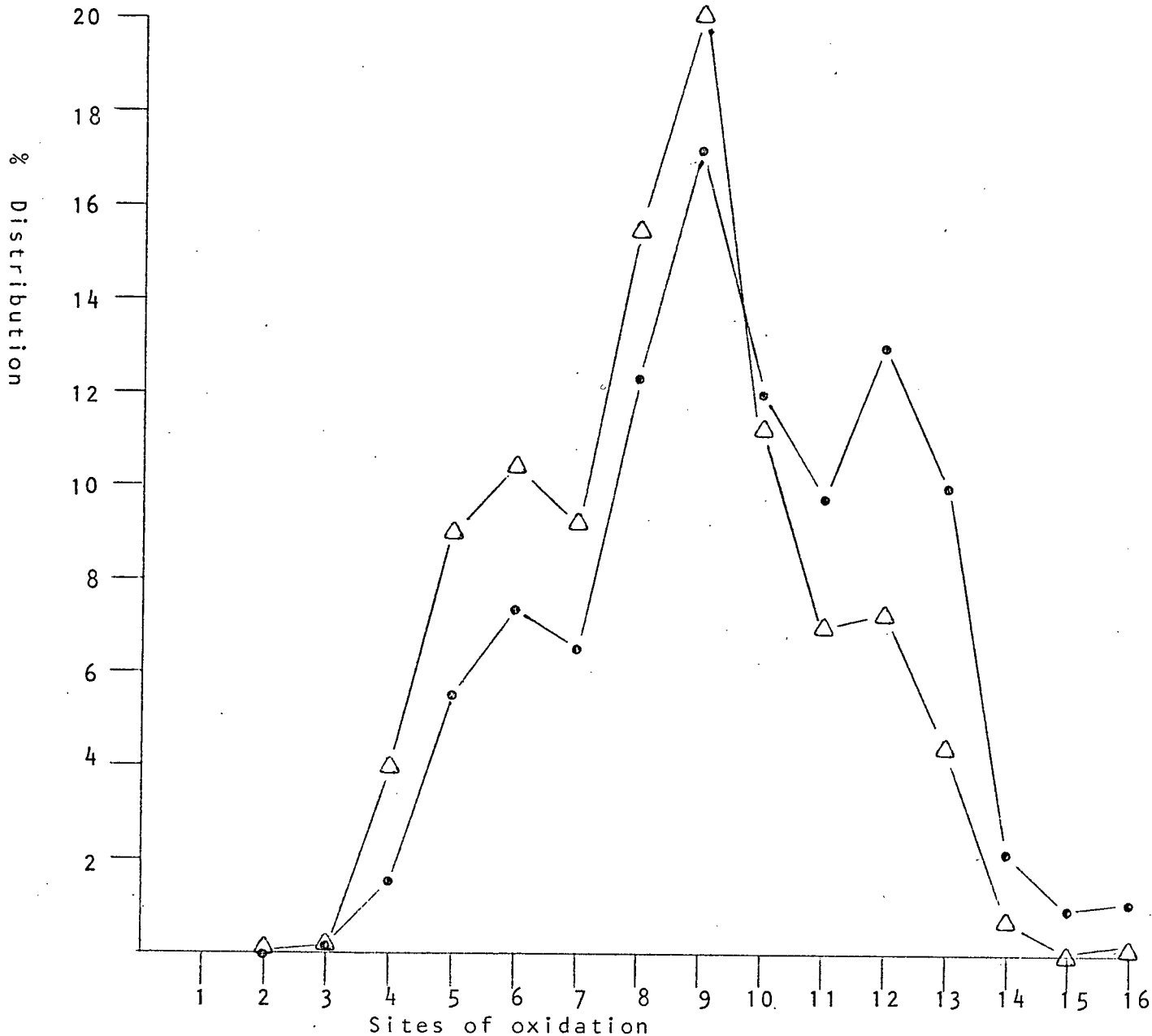


Figure 39. Oxidation of 16-hexadecanolide [data from the low resolution (70eV) mass spectrum of acetals (120; x+y=14):-o—o- based on fragment (121a):-Δ—Δ- based on fragment (121b)].

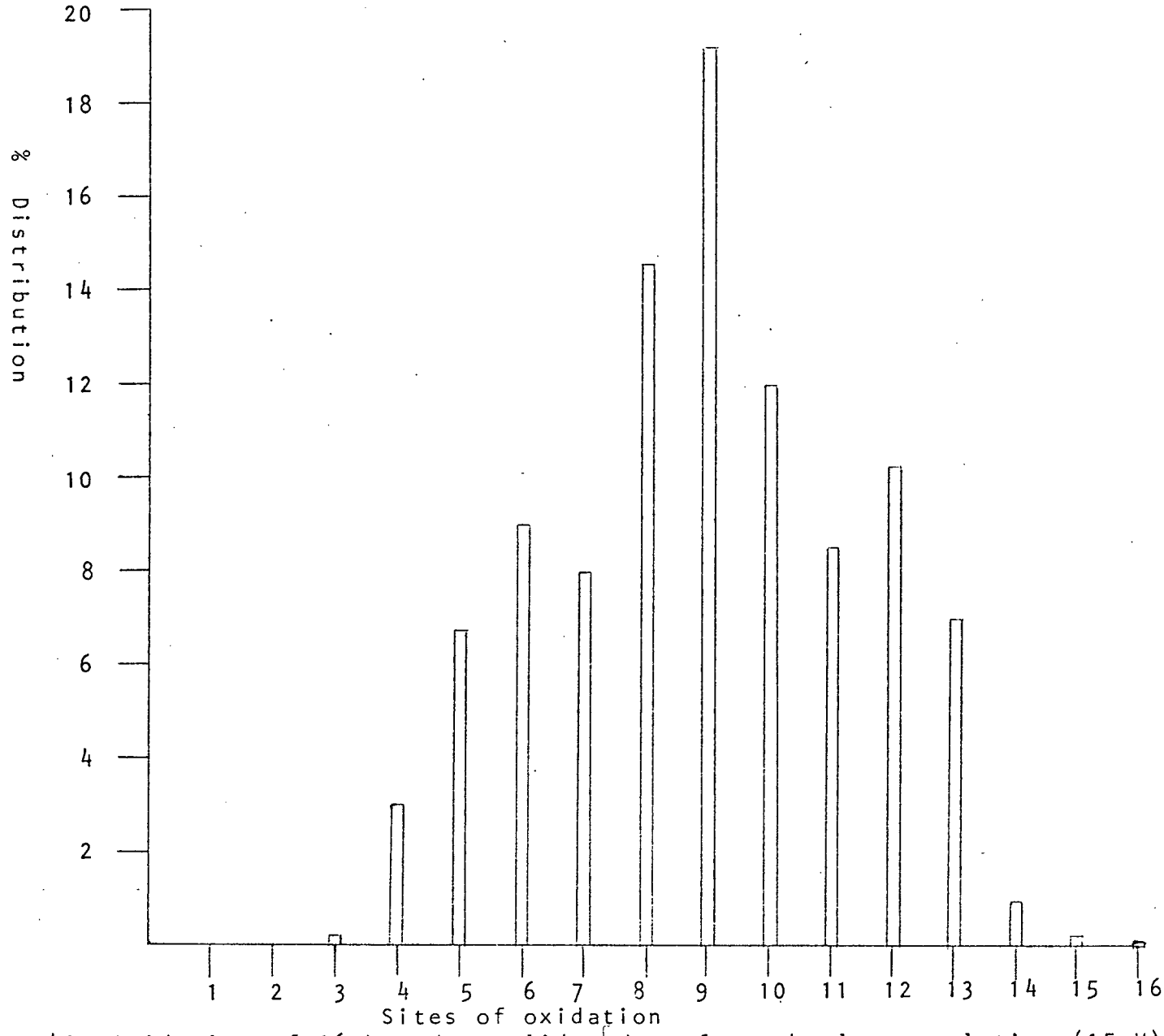


Figure 40. Oxidation of 16-hexadecanolide [data from the low resolution (15eV) mass spectrum of acetals (120; x+y=14) based on the combined relative intensity of fragments (121a and b)].

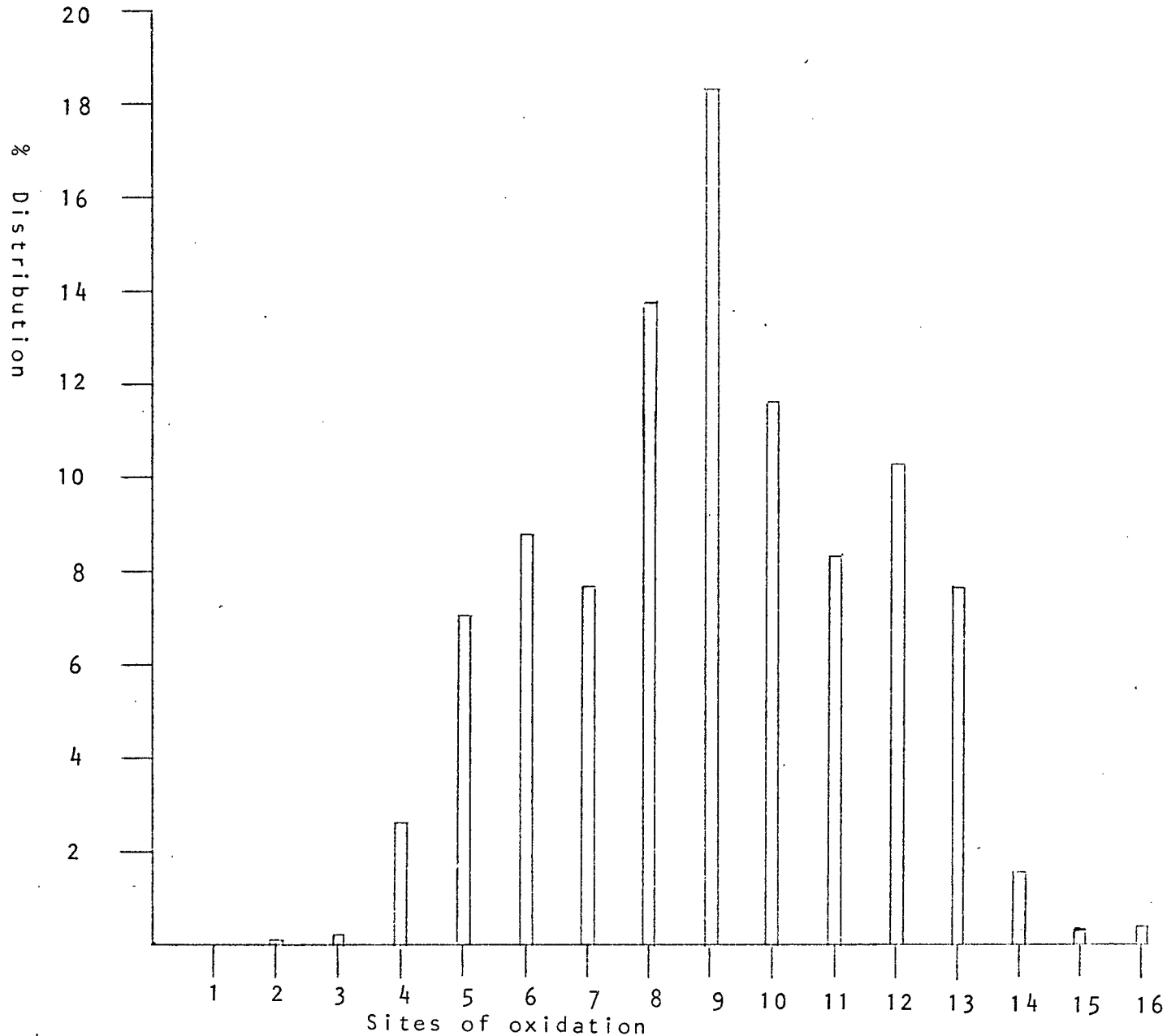


Figure 41. Oxidation of 16-hexadecanolide [data from the low resolution (70eV) mass spectrum of acetals (120; x+y=14) based on the combined relative intensity of fragments (121a and b)].

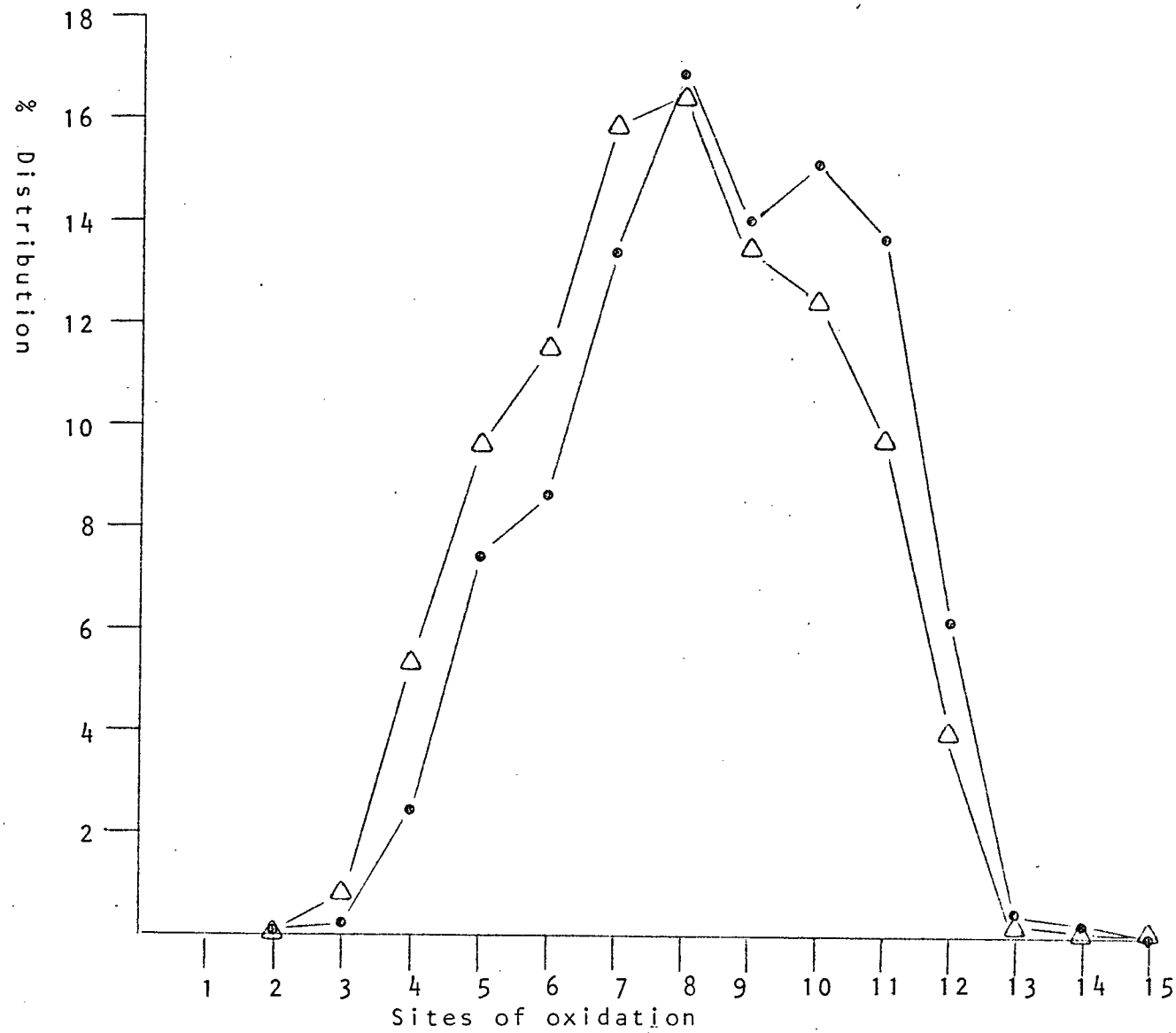


Figure 42. Oxidation of 15-pentadecanolide [data from the low resolution (15eV) mass spectrum of acetals (120; x+y=13) :-o—o- based on fragment (121a) :-Δ—Δ- based on fragment (121b)] .

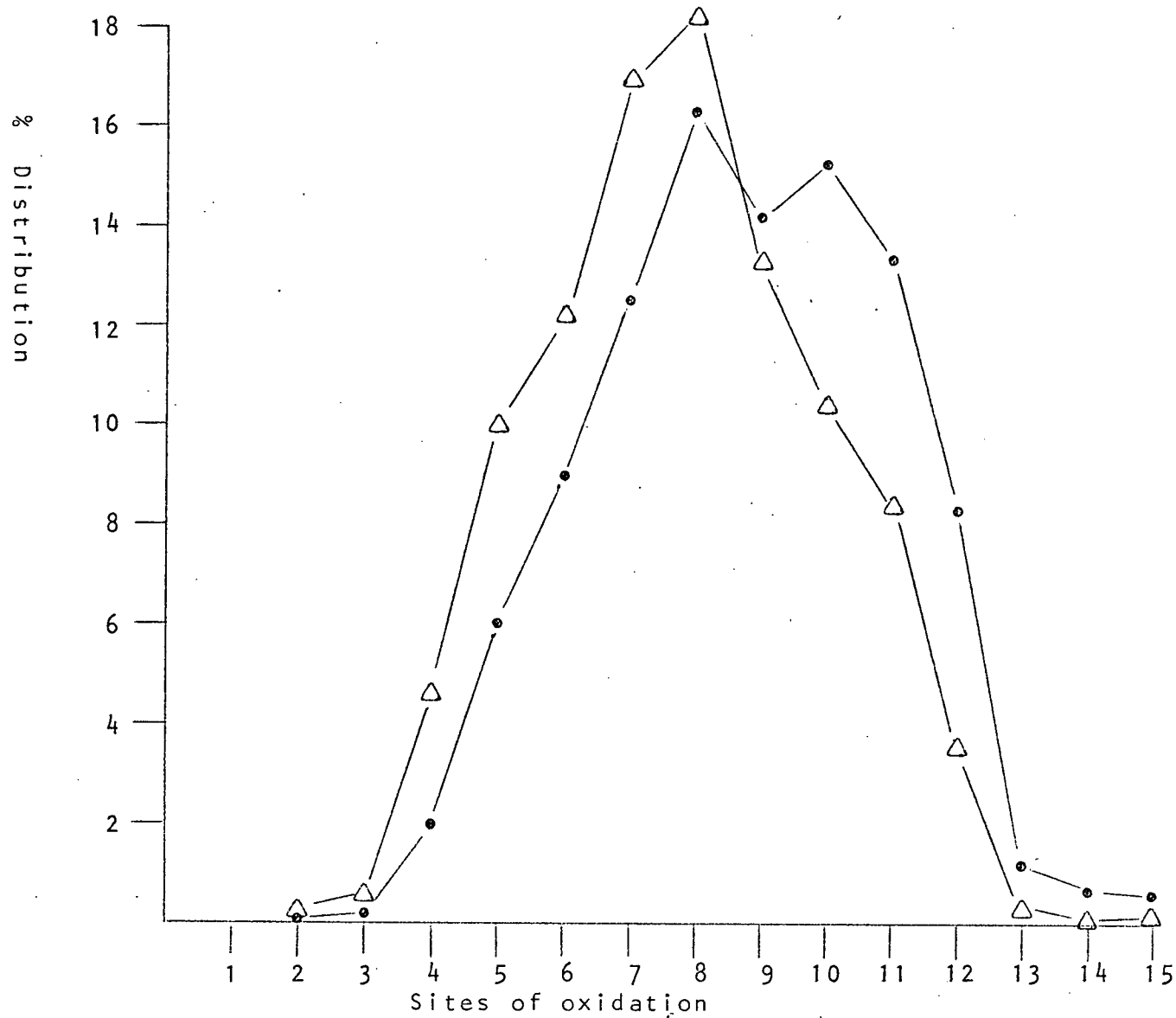


Figure 43. Oxidation of 15-pentadecanolide [data from the low resolution (70eV) mass spectrum of acetals (120; x+y=13):-o—o- based on fragment (121a):-Δ—Δ- based on fragment (121b)].

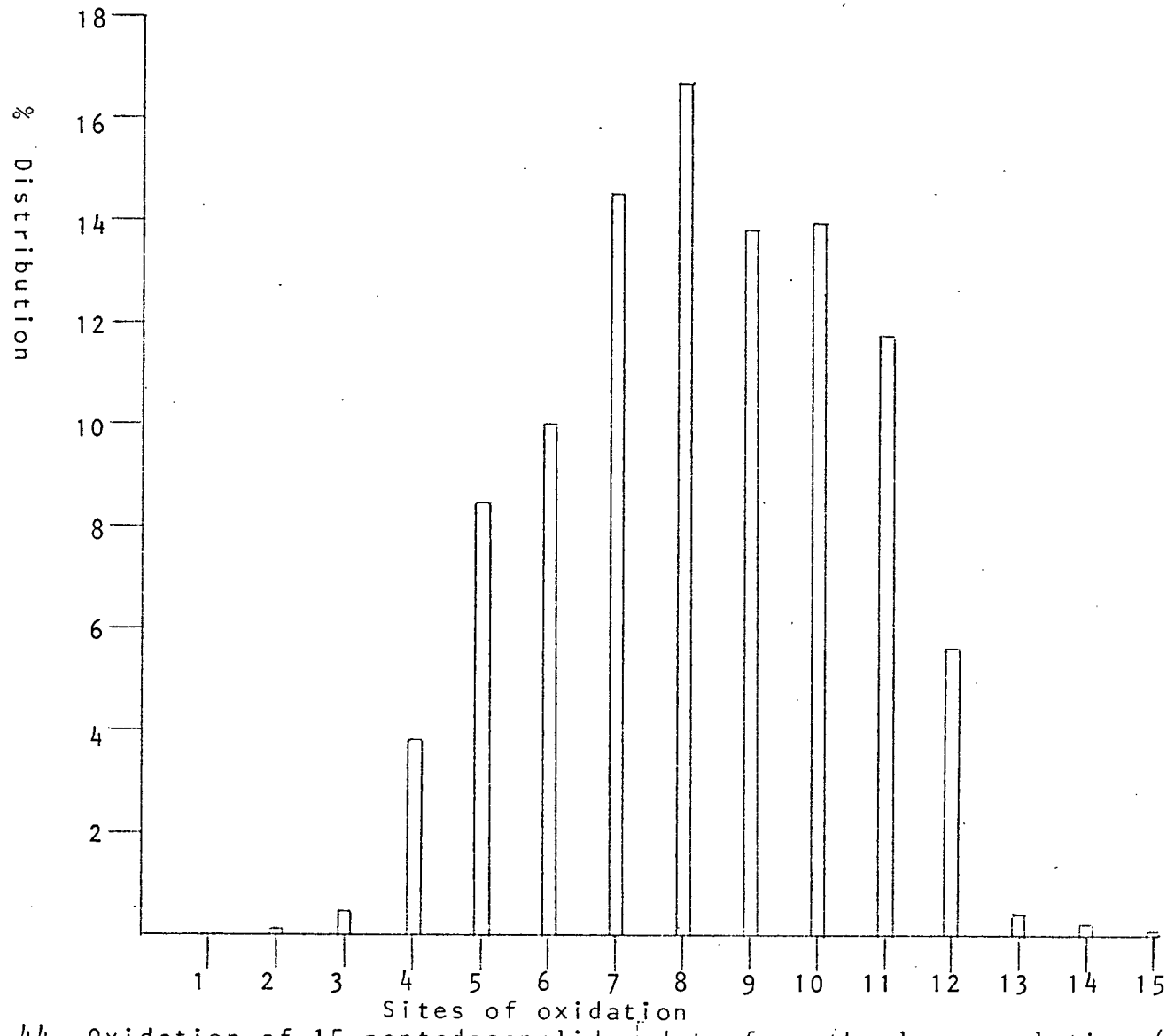


Figure 44. Oxidation of 15-pentadecanolide [data from the low resolution (15eV) mass spectrum of acetals (120; x+y=13) based on the combined relative intensity of fragments (121a and b)].

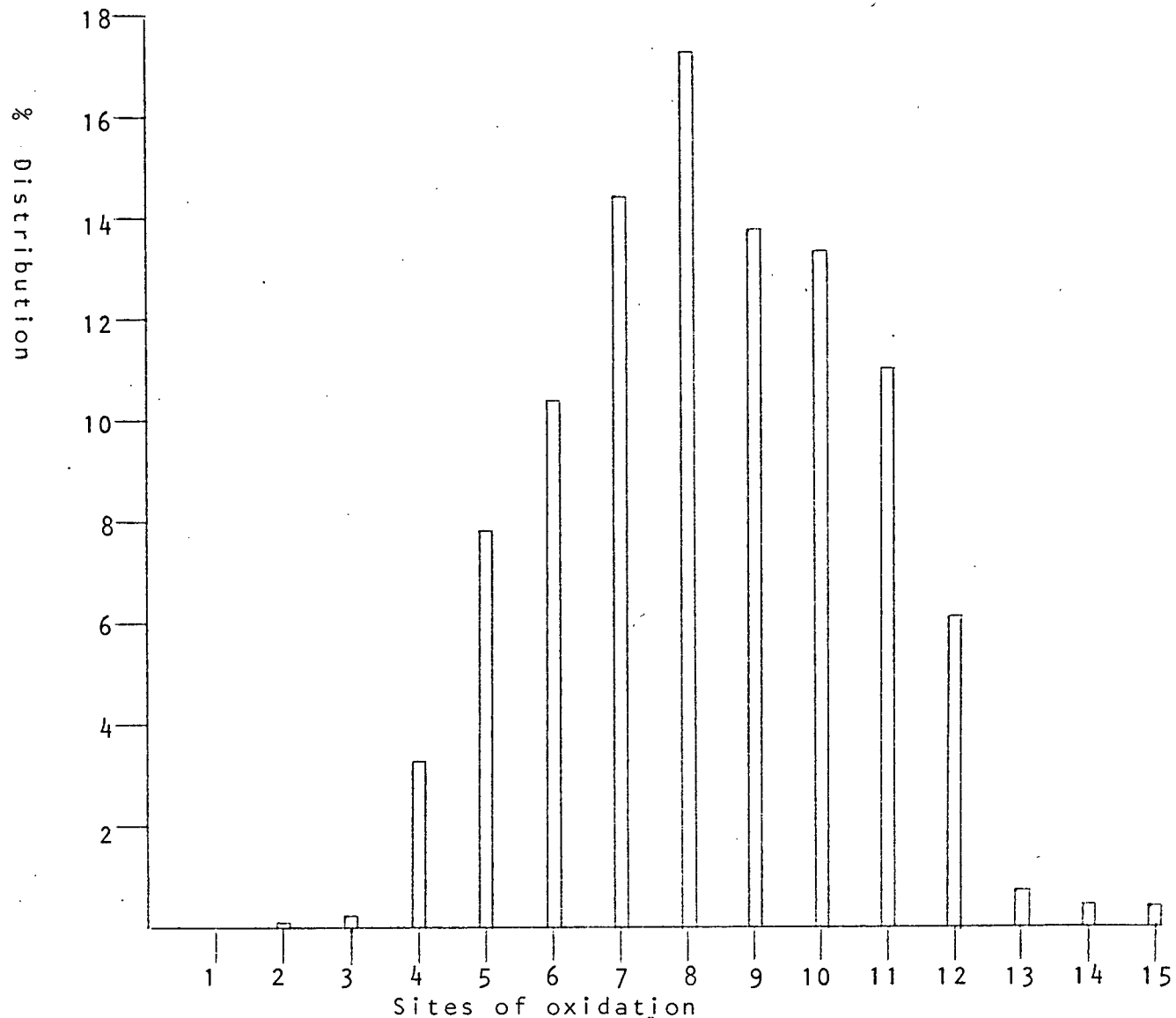


Figure 45. Oxidation of 15-pentadecanolide [data from the low resolution (70eV) mass spectrum of acetals (120; x+y=13) based on the combined relative intensity of fragments (121a and b)].

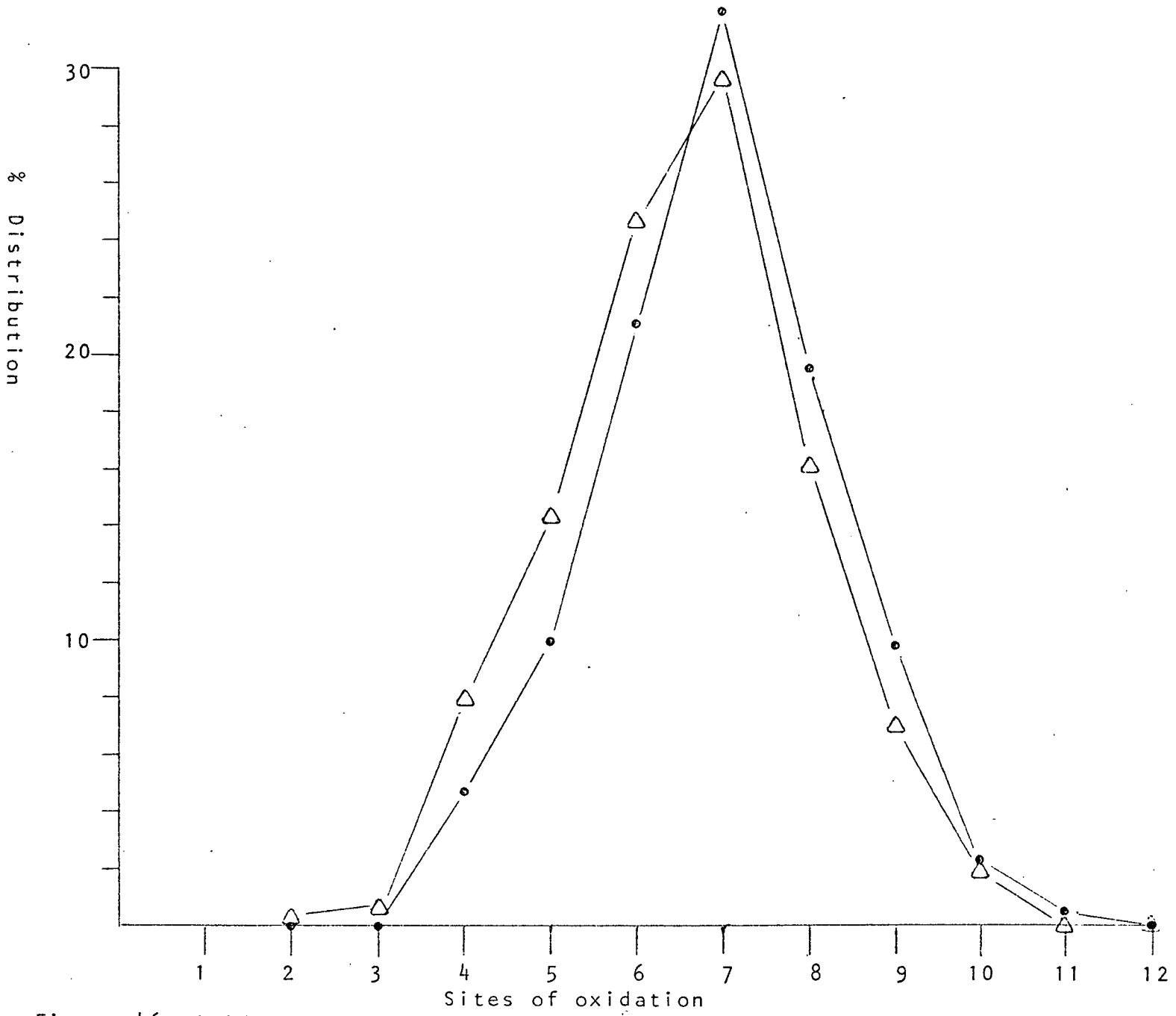


Figure 46. Oxidation of 12-dodecanolide data from the low resolution (15eV) mass spectrum of acetals (120; x+y=10):-o-- o- based on fragment (121a):-Δ---Δ based on fragment (121b)

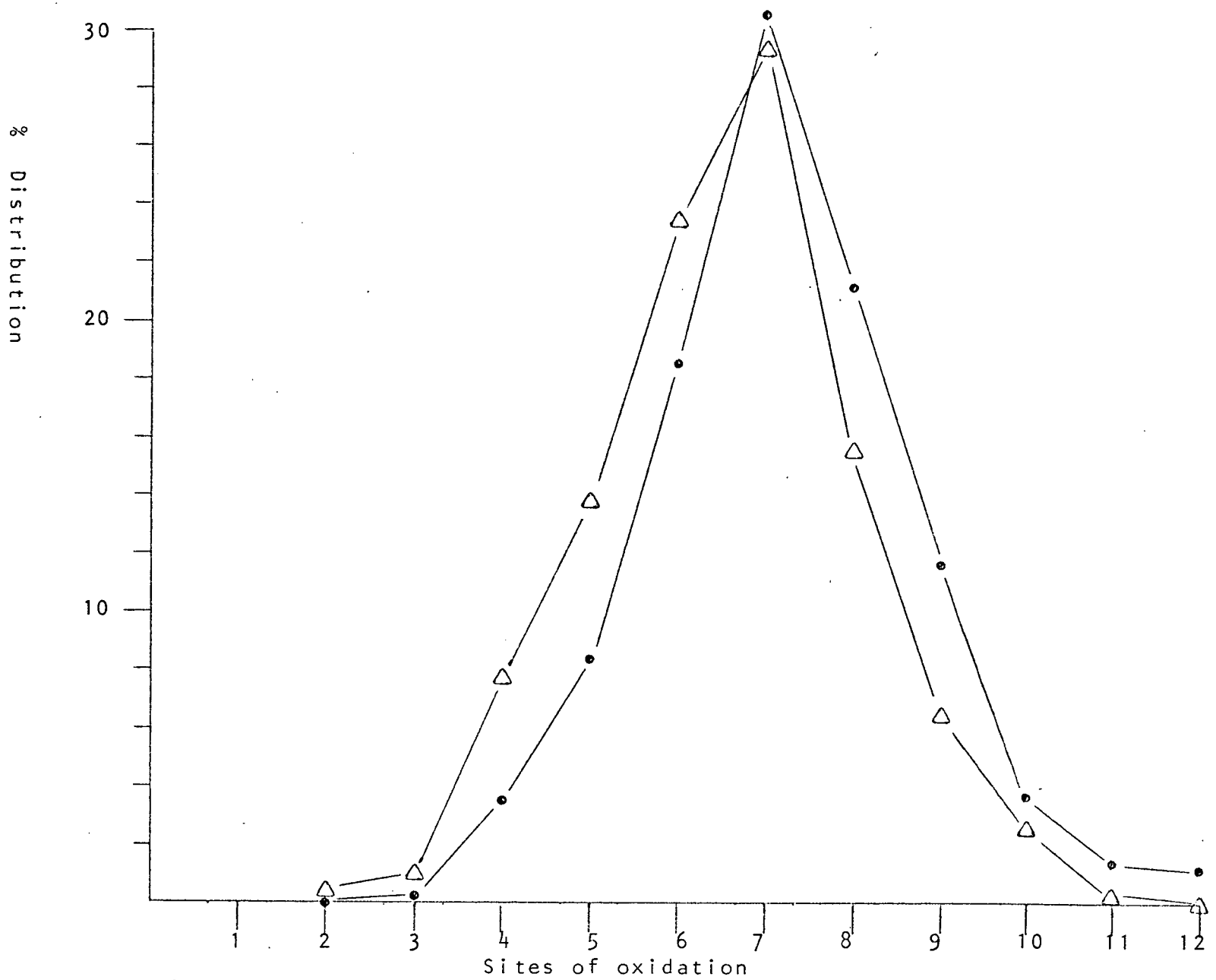


Figure 47. Oxidation of 12-dodecanolide [data from the low resolution (70eV) mass spectrum of acetals (120; x+y=10):-o—o- based on fragment (121a):-Δ—Δ- based on fragment (121b)]

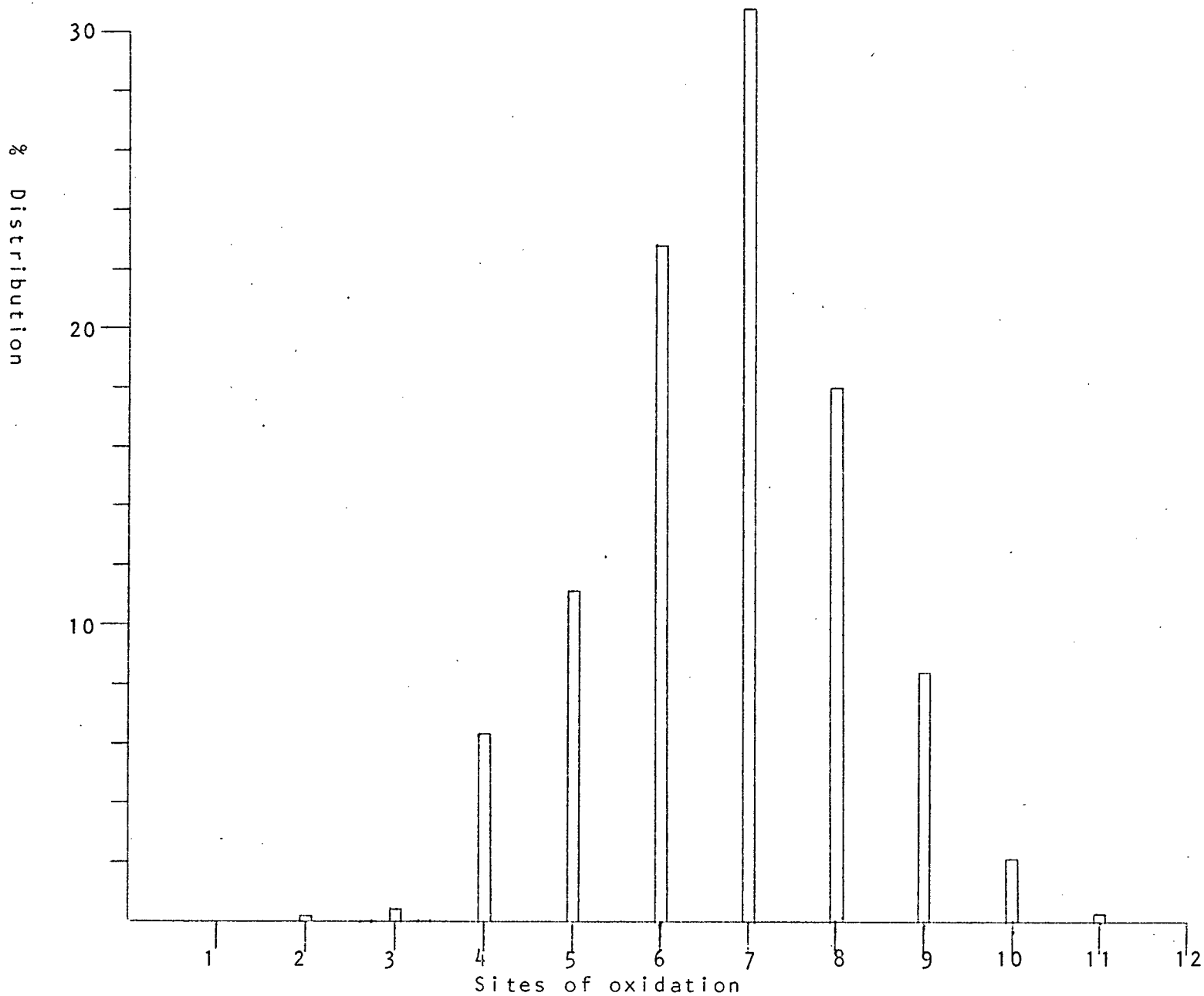


Figure 48. Oxidation of 12-dodecanolide [data from the low resolution (15eV) mass spectrum of acetals (120; x+y=10) based on the combined relative intensity

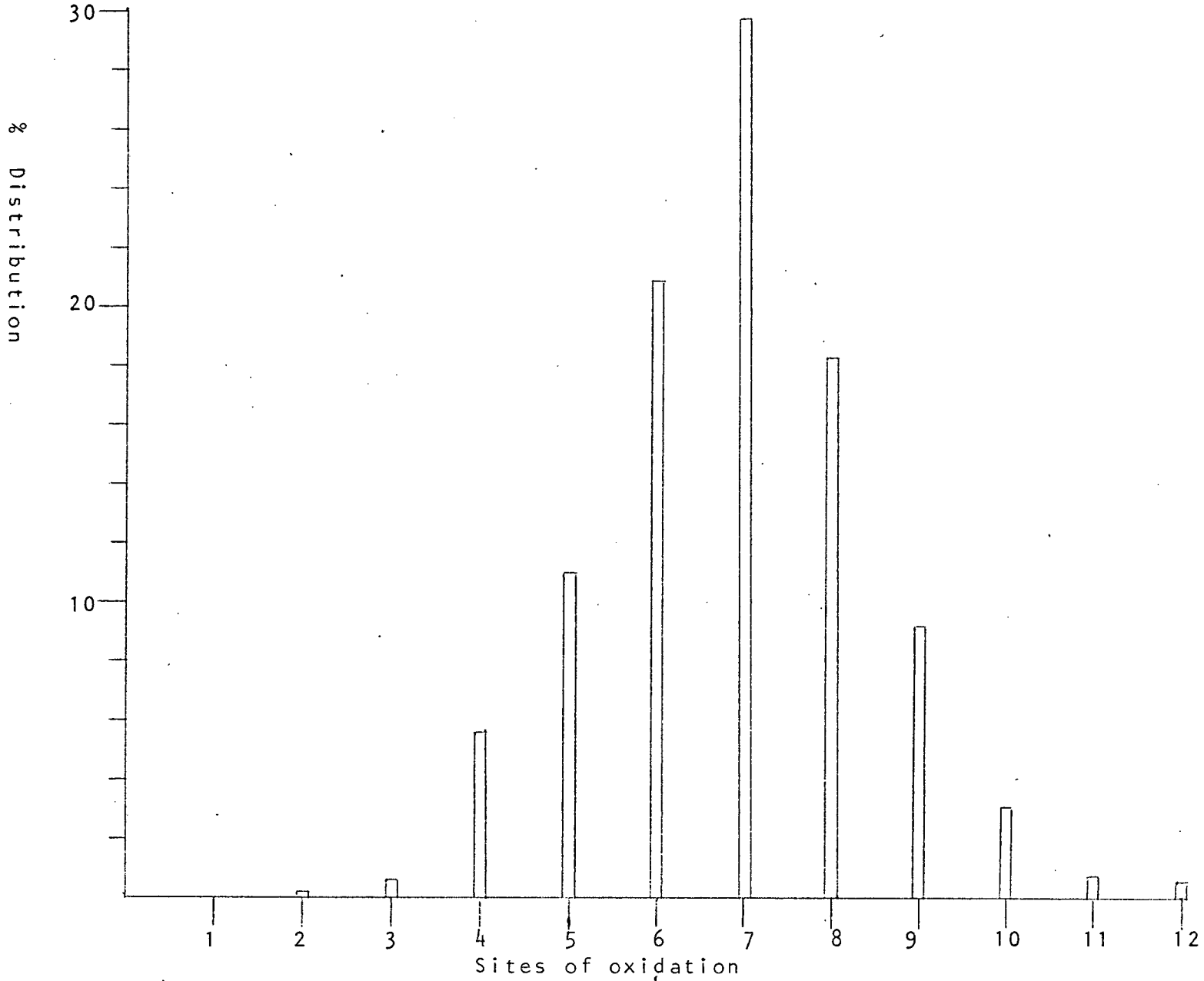
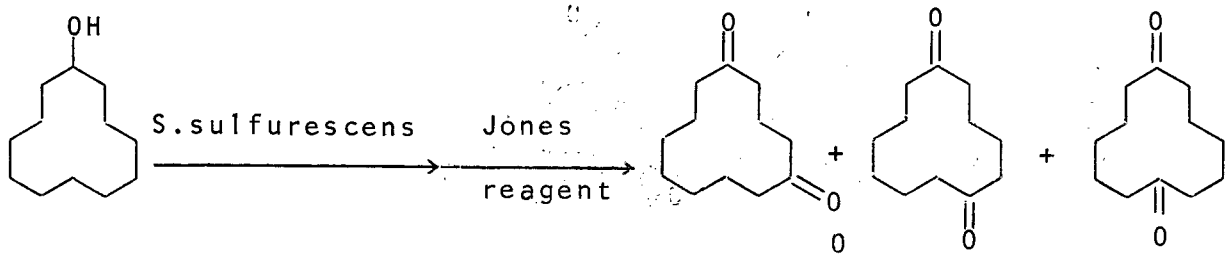


Figure 49. Oxidation of 12-dodecanolide data from the low resolution (70eV) mass spectrum of acetals (120; x+y=10) based on the combined relative intensity of fragments (121a and b)

(C) Remote oxidation of macrocyclic acetates

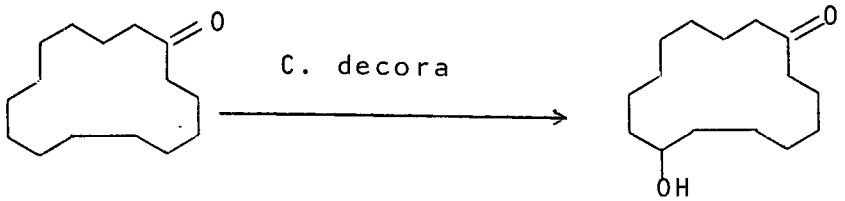
Few examples are known of the microbiological oxygenation of simple monocyclic systems. Incubation of cyclododecanol (125) with Sporotrichum sulfurescens provided dioxygenated products that were oxidized to 1,5-cyclododecyl-dione (126), 1,6-cyclododecyl-dione (127) and 1,7-cyclododecyl-dione (128).[57]



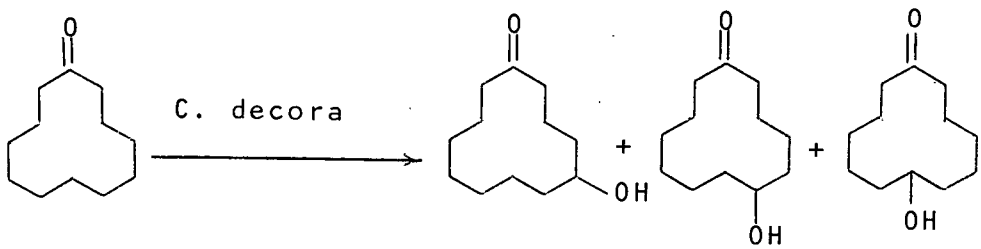
(125) (126) (127) (128)

Oxygenations of cyclotridecanol to 1,7-cyclotridecyl-dione and of cyclotetradecanol to 1,6-cyclotetradecyl-dione were also observed with the same organism.

Later Jones and his co-workers carried out a study of the incubation of two ketones, cyclopentadecanone and cyclododecanone, with five fungi.[58] Incubation of cyclopentadecanone (129) with Calonectria decora for 3 days provided the highest yield (26% based on consumed starting material) of 8-hydroxy-cyclopentadecanone (130), while cyclododecanone (131) gave 5-hydroxy-cyclododecanone (132), 6-hydroxy-cyclododecanone (133) and 7-hydroxy-cyclododecanone (134).

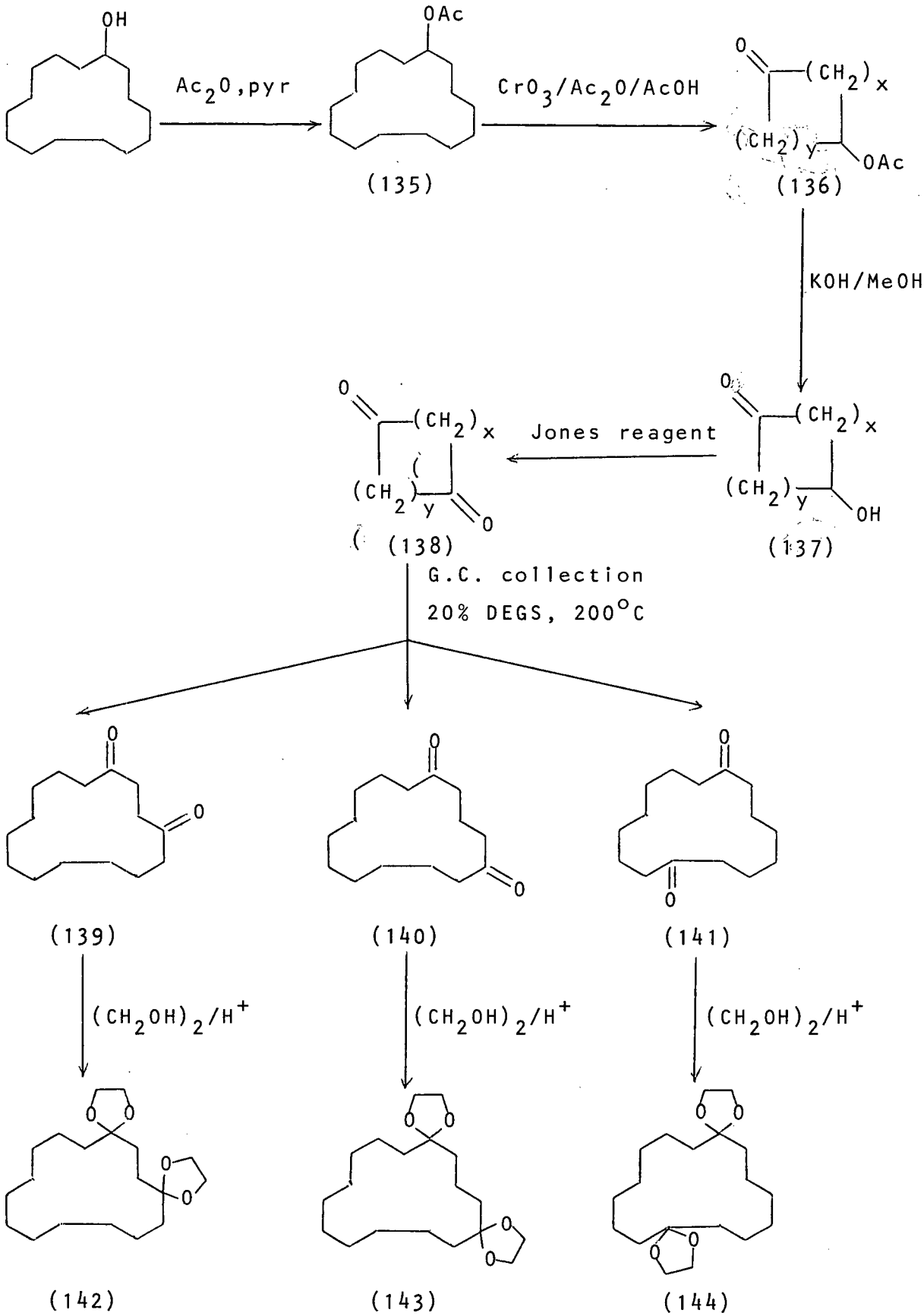


(129) (130)



(131) (132) (133) (134)

With these examples in mind, we decided to oxidize appropriate macrocyclic acetates with chromyl acetate (CrO_3-Ac_2O). Treatment of pure cyclopentadecyl acetate (135) in glacial acetic acid/acetic anhydride with chromium trioxide/acetic anhydride (i.e. chromyl acetates) at room temperature for 5 days provided a mixture of mono-oxo-cyclopentadecyl acetates (136) and starting material. Careful column chromatography [Woelm silica gel grade III (1:50); pet. ether/ether] separated the acetoxy-cyclopentadecanones from starting material. The yield of product based on consumed starting material was 39.2%. Elemental analysis, infrared and NMR data showed the product to be composed of acetoxy-cyclopentadecanones. The infrared spectrum (CCl_4) showed absorption bands at 1745 and 1720 cm^{-1} and its NMR spectrum exhibited resonances at τ 5.27 (m, 1H, -C<u>H</u>OAc), 7.66 (mixed t, 4H, -C<u>H</u>$_2$COC<u>H</u>$_2$-),

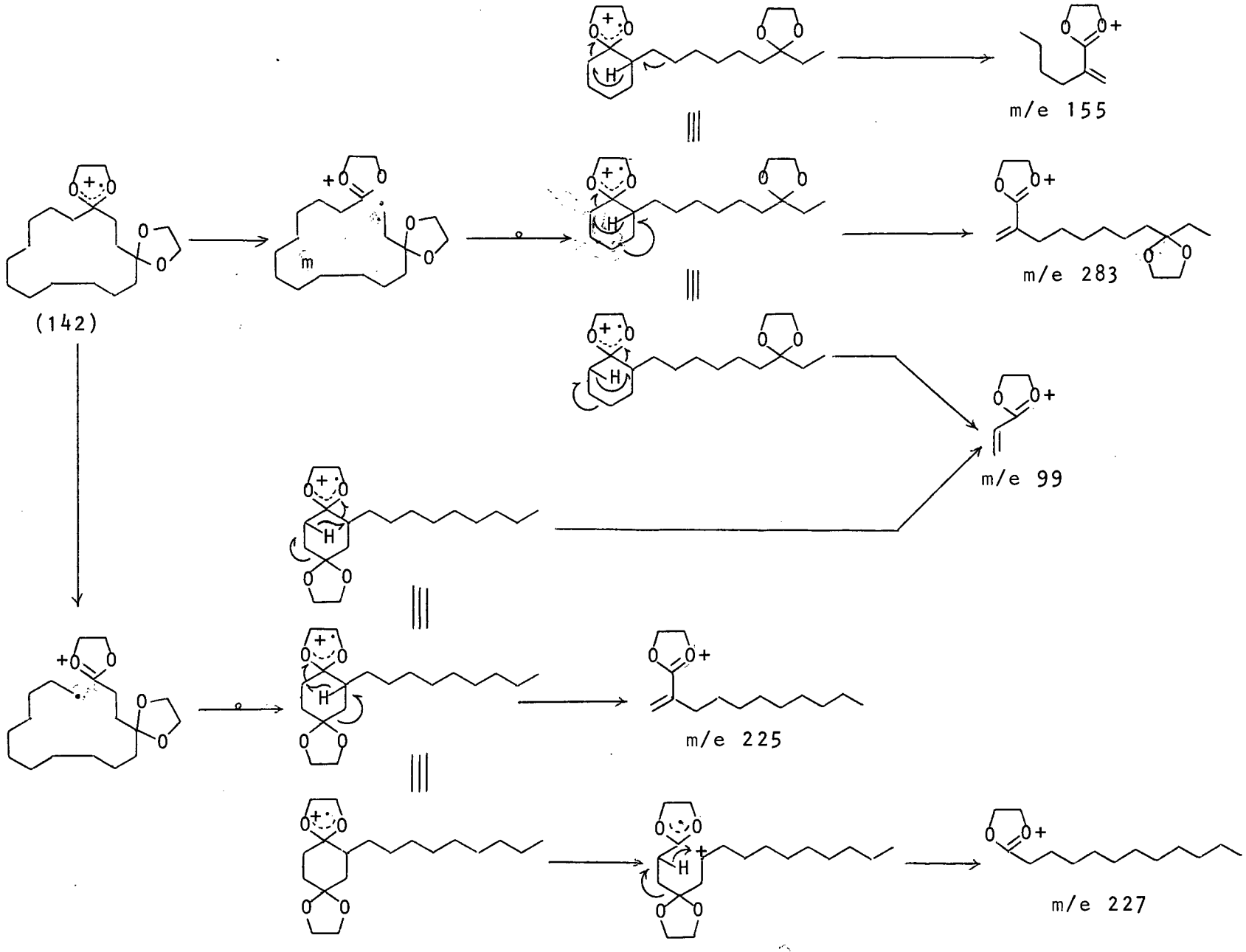

OH
Ac_2O,pyr
OAc
(135)
$CrO_3/Ac_2O/AcOH$
O
$(CH_2)_x$
$(CH_2)_y$
OAc
(136)
KOH/MeOH
O
$(CH_2)_x$
$(CH_2)_y$
OH
(137)
Jones reagent
O
$(CH_2)_x$
$(CH_2)_y$
O
(138)
G.C. collection
20% DEGS, 200°C
O
O
(139)
O
O
(140)
O
O
(141)
$(CH_2OH)_2/H^+$
$(CH_2OH)_2/H^+$
$(CH_2OH)_2/H^+$
O
O
O
O
(142)
O
O
O
O
(143)
O
O
O
O
(144)

8.06, 8.08 (s, 3H, $-O_2CC\underline{H}_3$), 8.42, 8.70 (m, broad s, 22H, $-(C\underline{H}_2)_{11}-$).

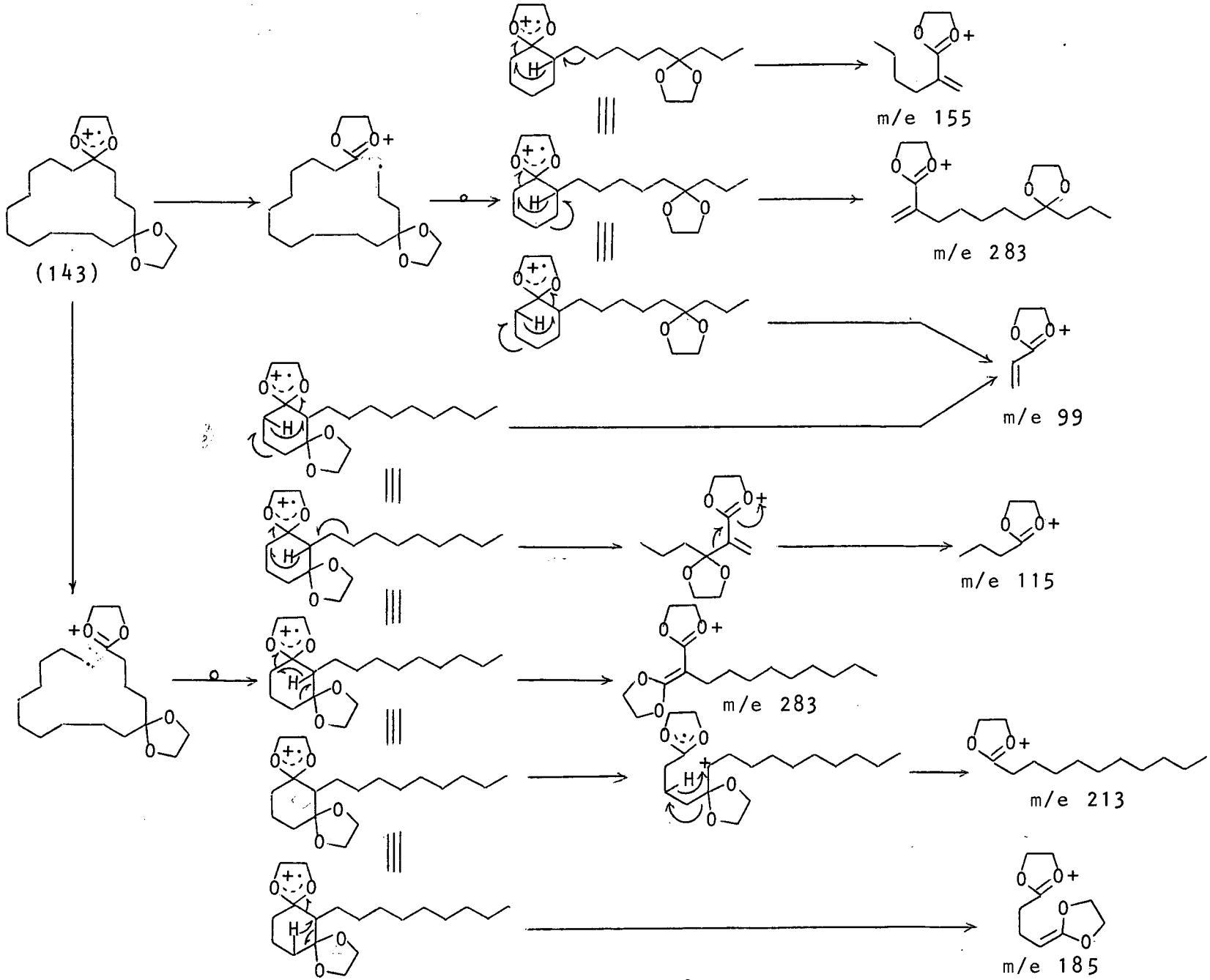
The relative amounts of the acetoxy-cyclopentadecanones (136) can be deduced by chromatographic analysis of the mixture of cyclopentadecyl-diones (138), while the position of the keto group can be determined by examining the mass spectra of the corresponding diacetals (142, 143, 144). The acetoxy-cyclopentadecanones (136), on reaction with potassium hydroxide in methanol followed by Jones reagent, yield a mixture of cyclopentadecyl-diones (138) which could be separated by preparative G.C. using a 20% DEGS column at 200°C. This provided 1,4-cyclopentadecyl-dione (139, 10.3%), 1,5-cyclopentadecyl-dione (140, 17.5%) and 1,8-cyclopentadecyl-dione (141, 72.2%). The individual diketones were then converted to their diketals.

Recently, Fetizon investigated the fragmentation pattern of cyclanone ethylene acetals in the macrocyclic ring. It can be explained entirely on the basis of a ring contraction and associated hydrogen migrations.[59] Using this rationalization, the 1,4-diketal (142) would fragment as shown in scheme 7, and this fragmentation is consistent with the peaks found in the mass spectrum (figures 50-51). The 1,5-diketal (143) and 1,8-diketal (144) were identified in the same way (schemes 8 and 9; figures 52-55).

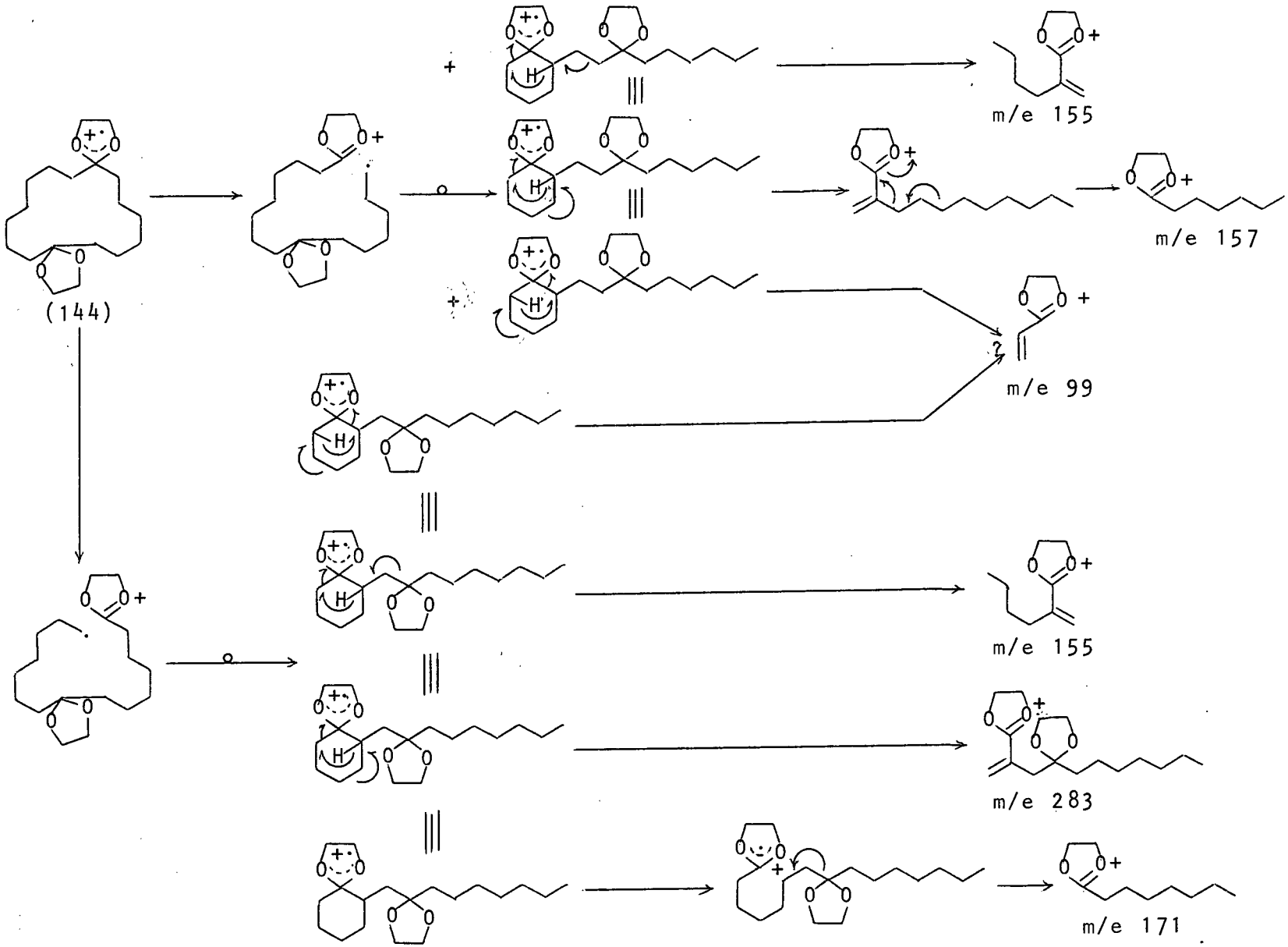
The same reaction sequence was applied to cyclotridecyl acetate (145). It was oxidized to a mixture of mono-oxo-cyclo-



Scheme 7

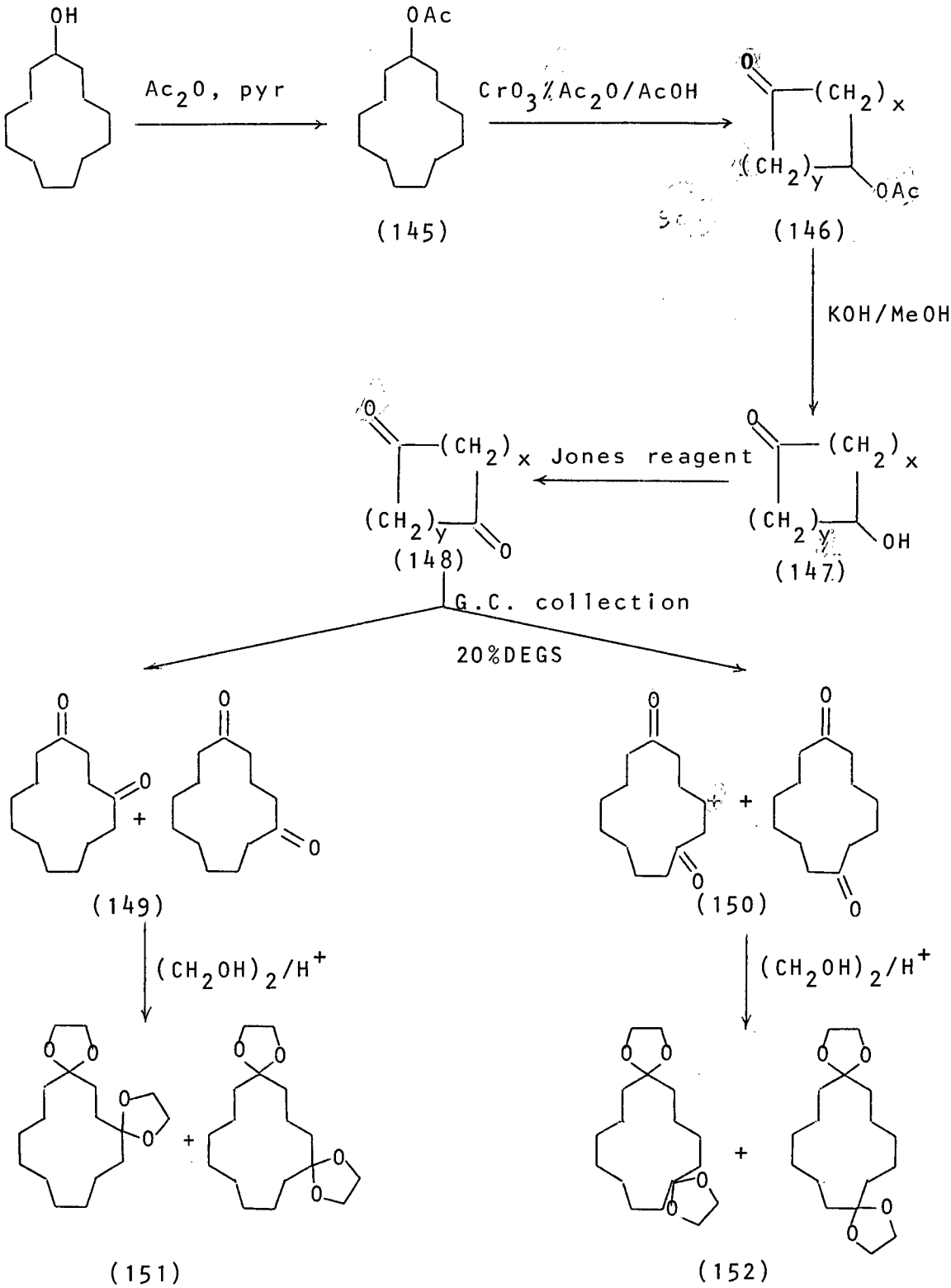


Scheme 8



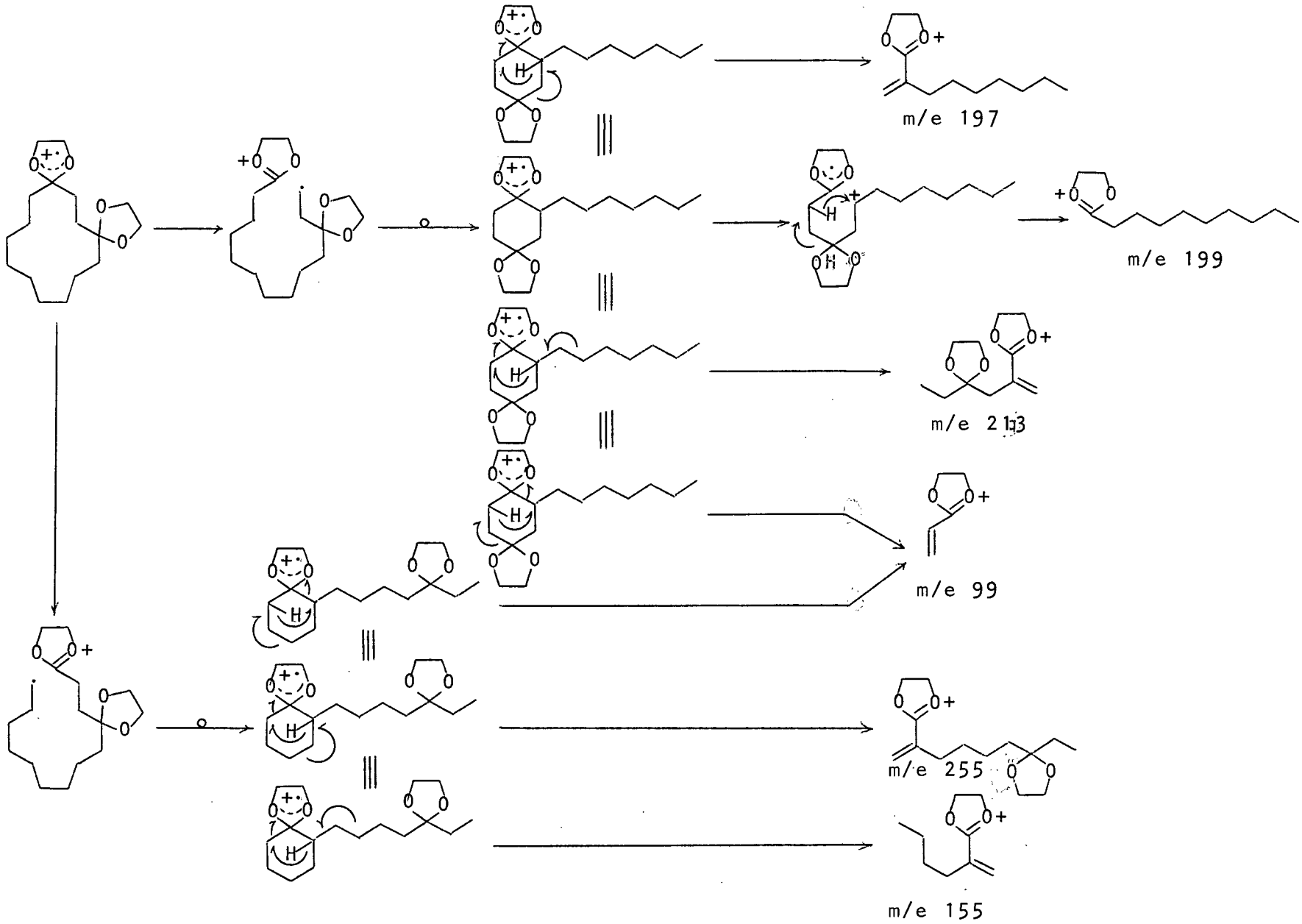
Scheme 9

tridecyl acetates (146). Employing the procedure described earlier, a mixture of diketones (148) was obtained. They were

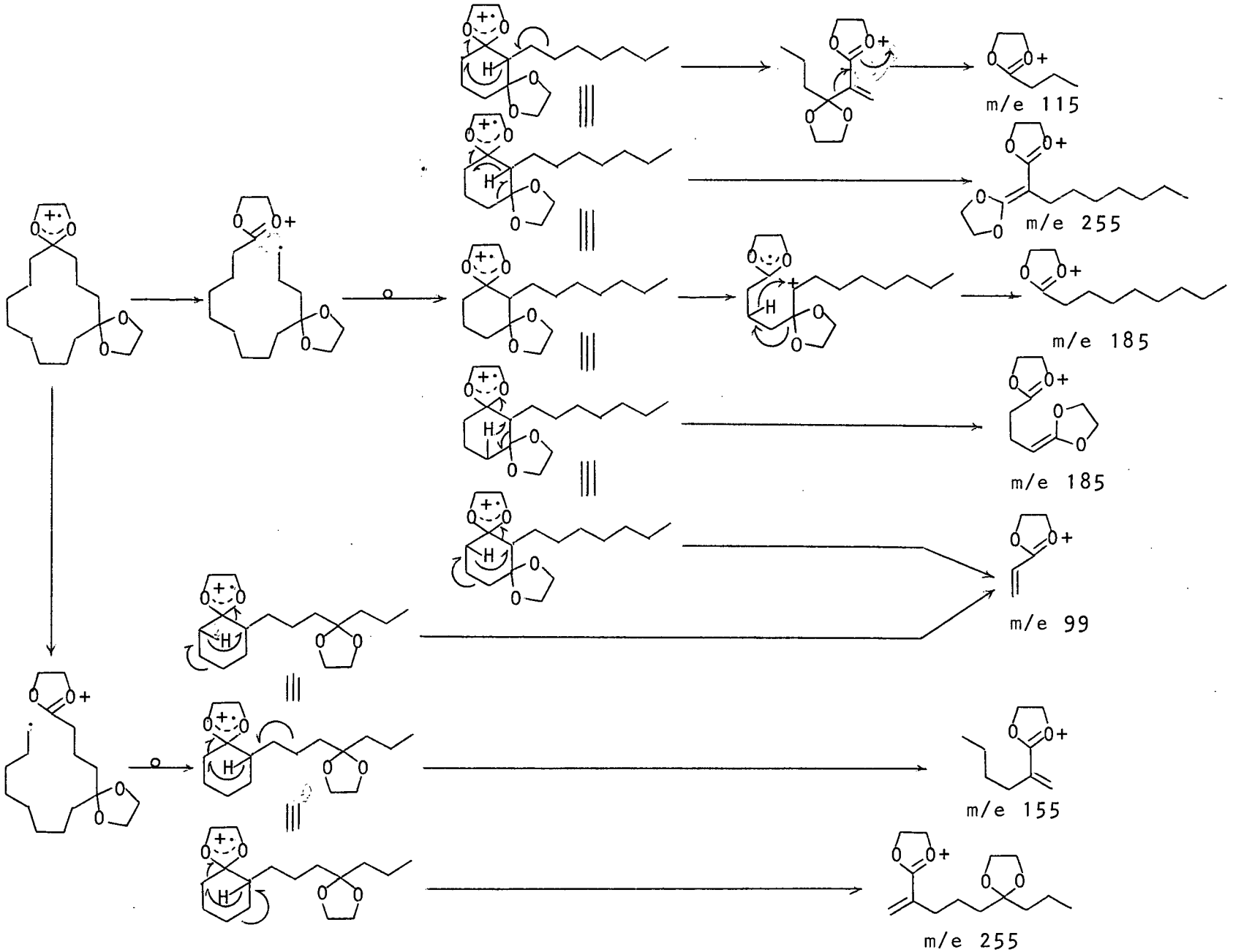


separated by preparative G.C. using a 20% DEGS column at 200°C into two fractions. The first fraction (149) was a mixture of two isomers (11.9% and 20.5% of the total mixture by g.c.). The mass spectrum of the diacetals of this mixture indicated the isomers to be 1,4-cyclotridecyl-dione and 1,5-cyclotridecyl-dione (figures 56 and 57; schemes 10 and 11). The second fraction (150) was also a mixture of two isomers (31.4% and 36.2% of the total by g.c.) and the mass spectrum of the diacetals showed the isomers to be 1,6-cyclotridecyl-dione and 1,7-cyclotridecyl-dione (figures 58 and 59; schemes 12 and 13).

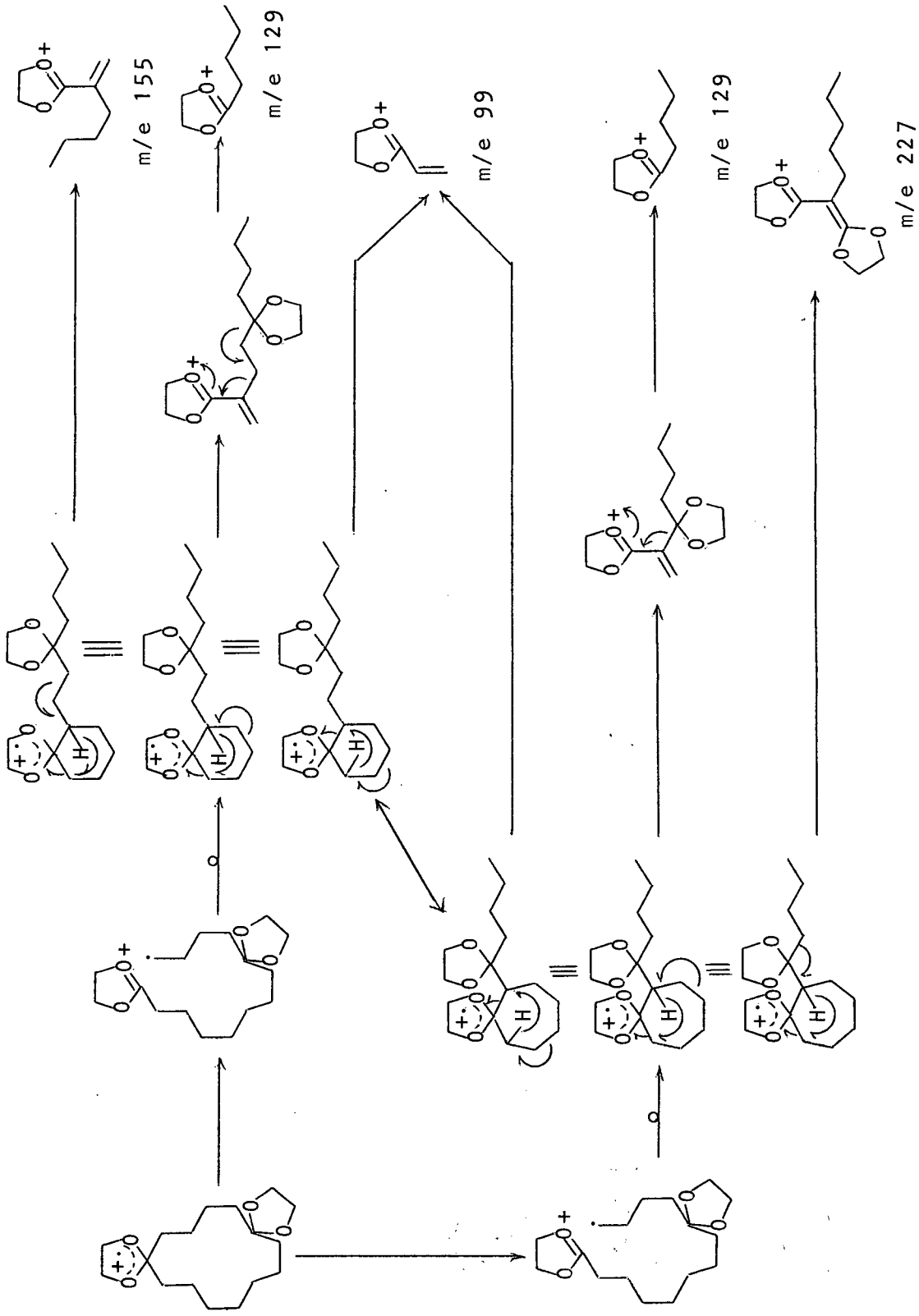
Studies are continuing on the oxidative vulnerability of cyclododecyl acetates.



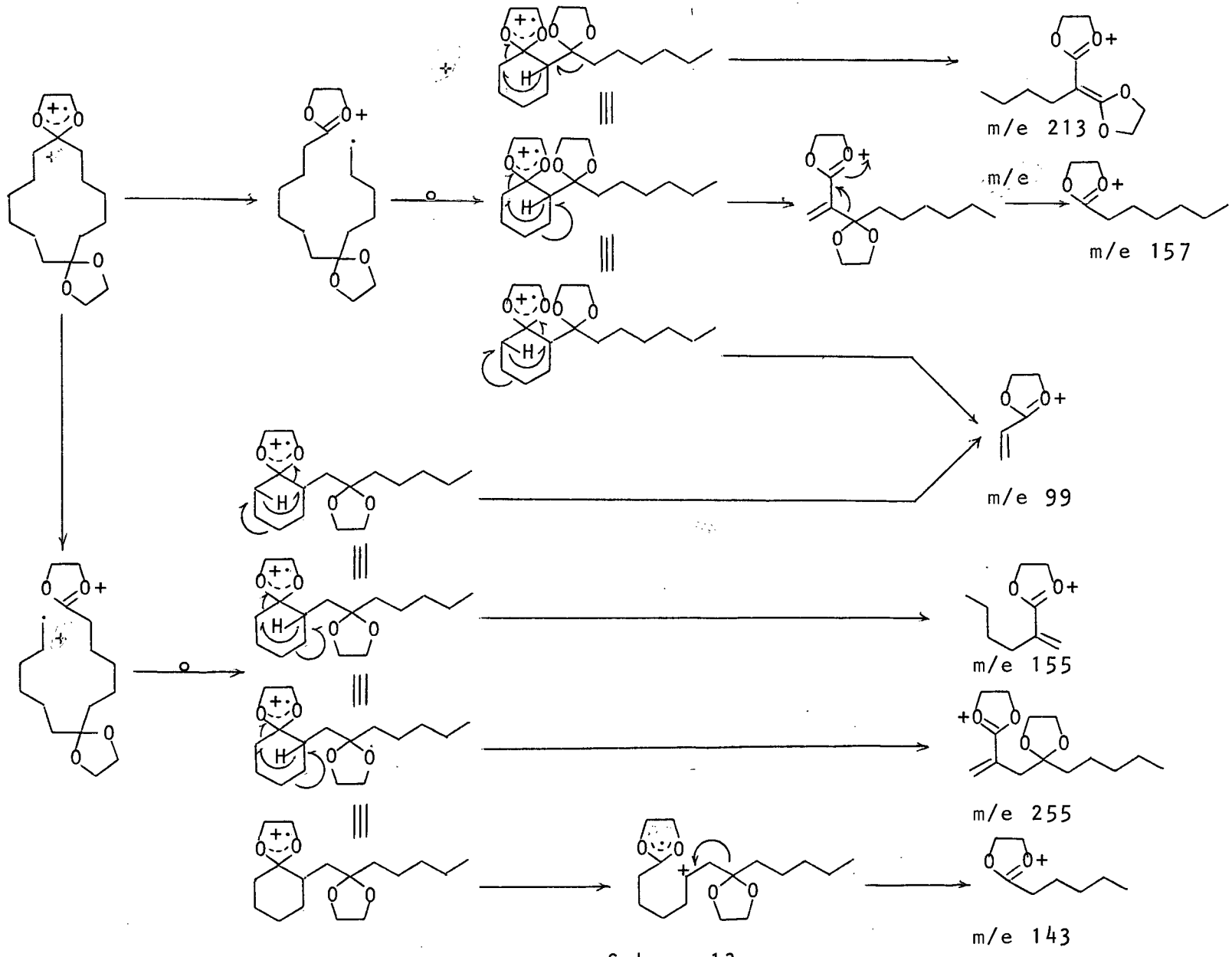
Scheme 10



Scheme 11



Scheme 12



Scheme 13

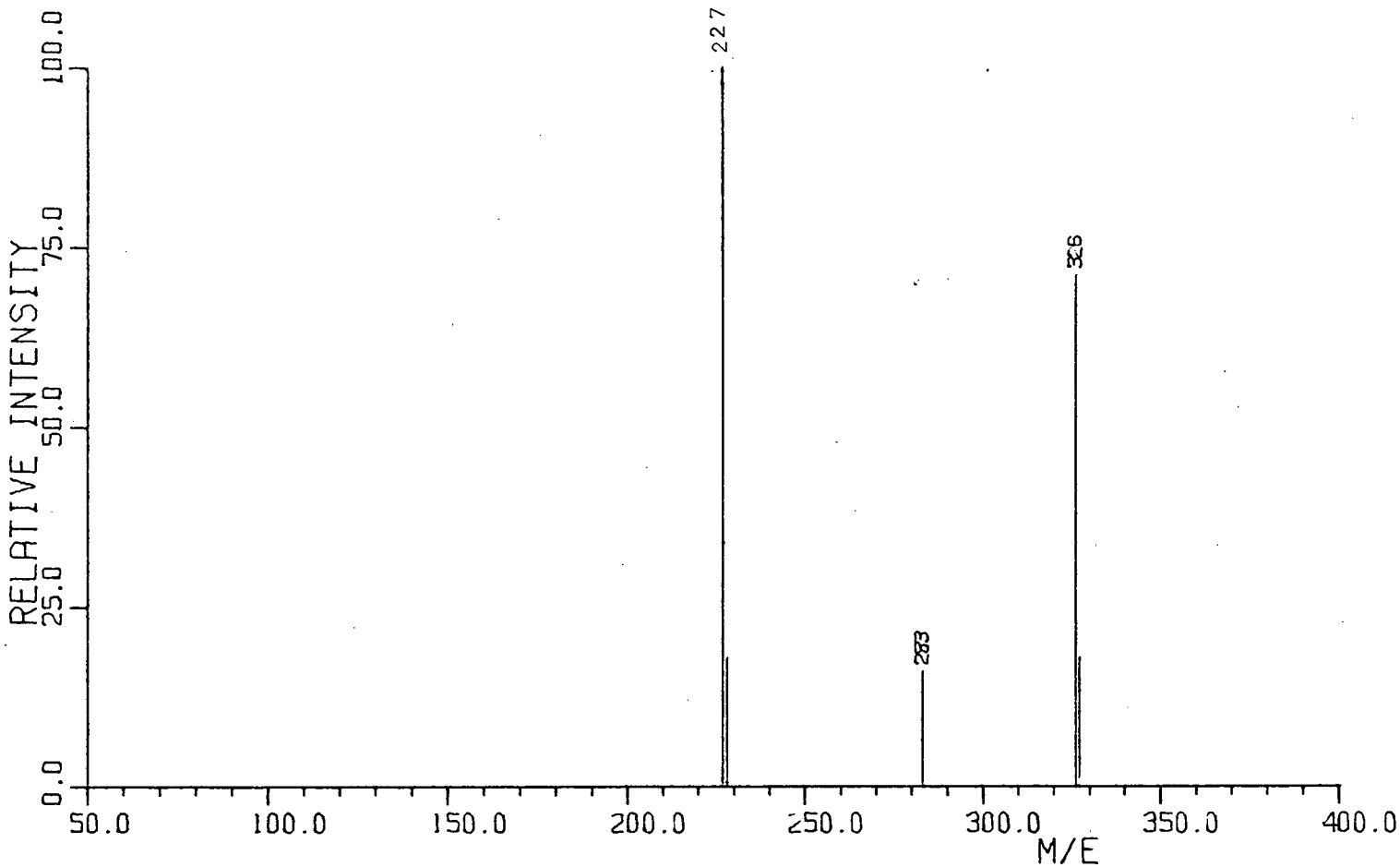


Figure 50. Mass spectrum of diacetal of 1,4-cyclopentadecyl-dione [low resolution (15eV)].

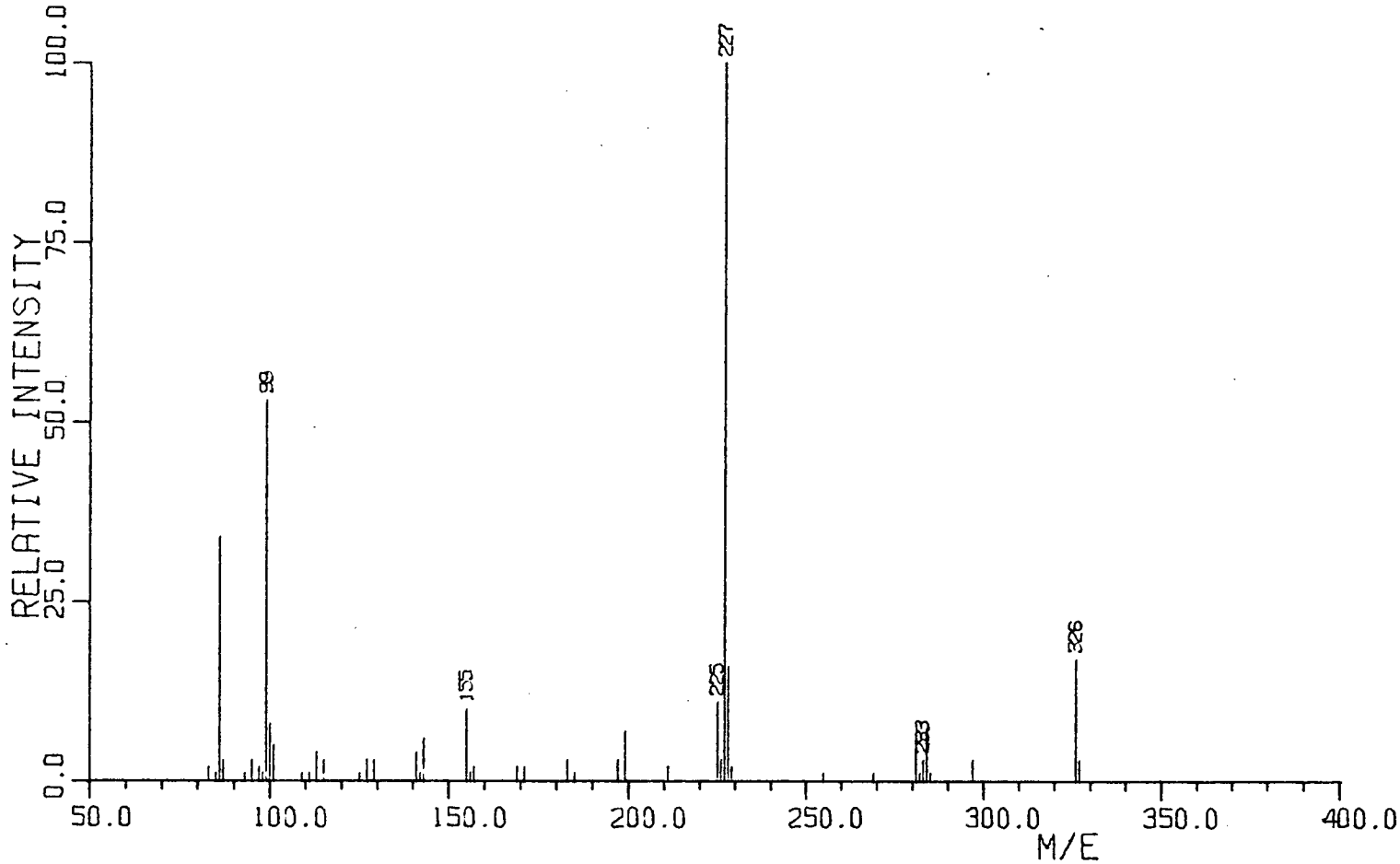


Figure 51. Mass spectrum of diacetal of 1,4-cyclopentadecyl-dione [low resolution (70eV)].

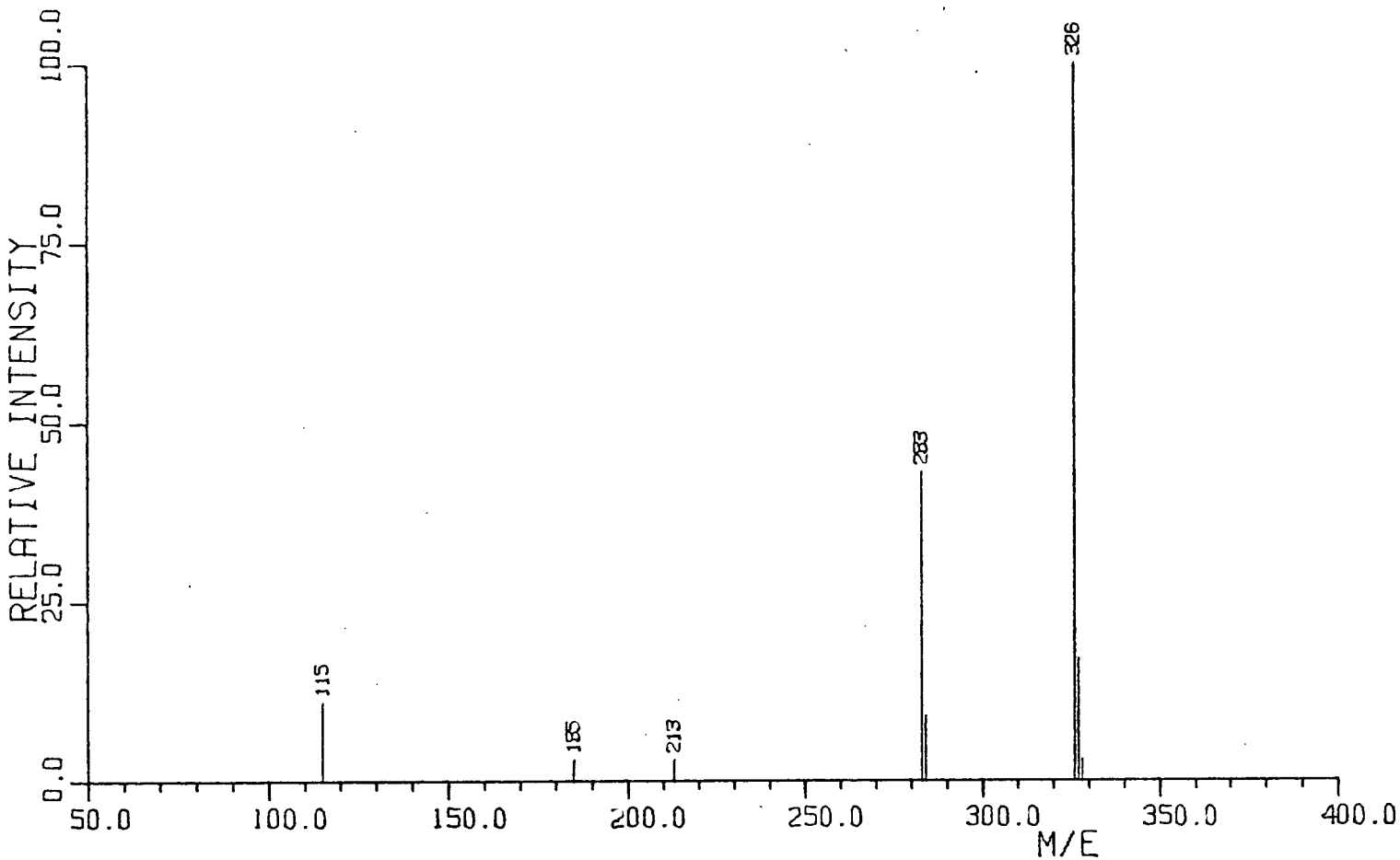


Figure 52. Mass spectrum of diacetal of 1,5-cyclopentadecyl-dione [low resolution (15 eV)].

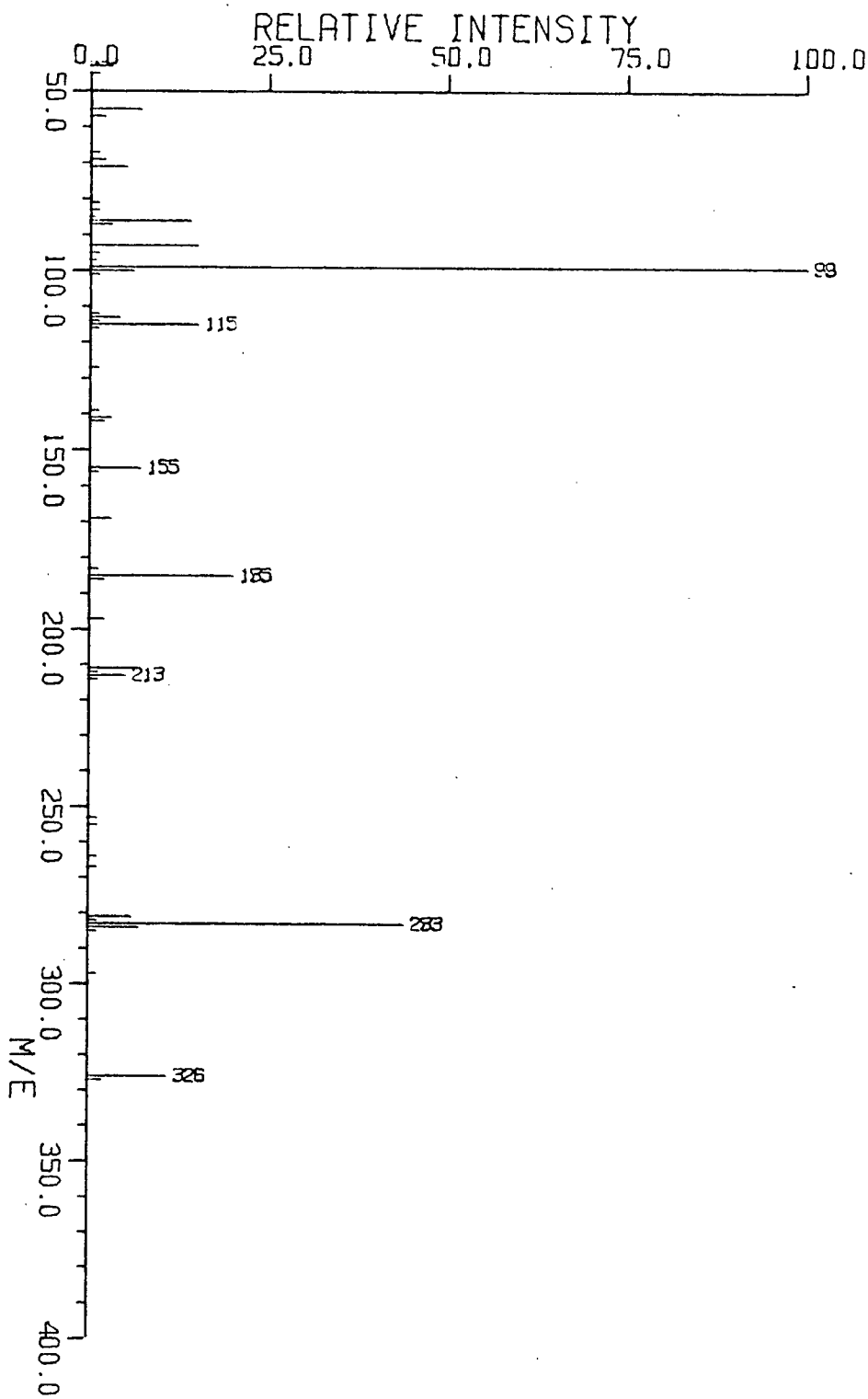


Figure 53. Mass spectrum of diacetal of 1,5-cyclopentadecyl-dione [low resolution (70eV)].

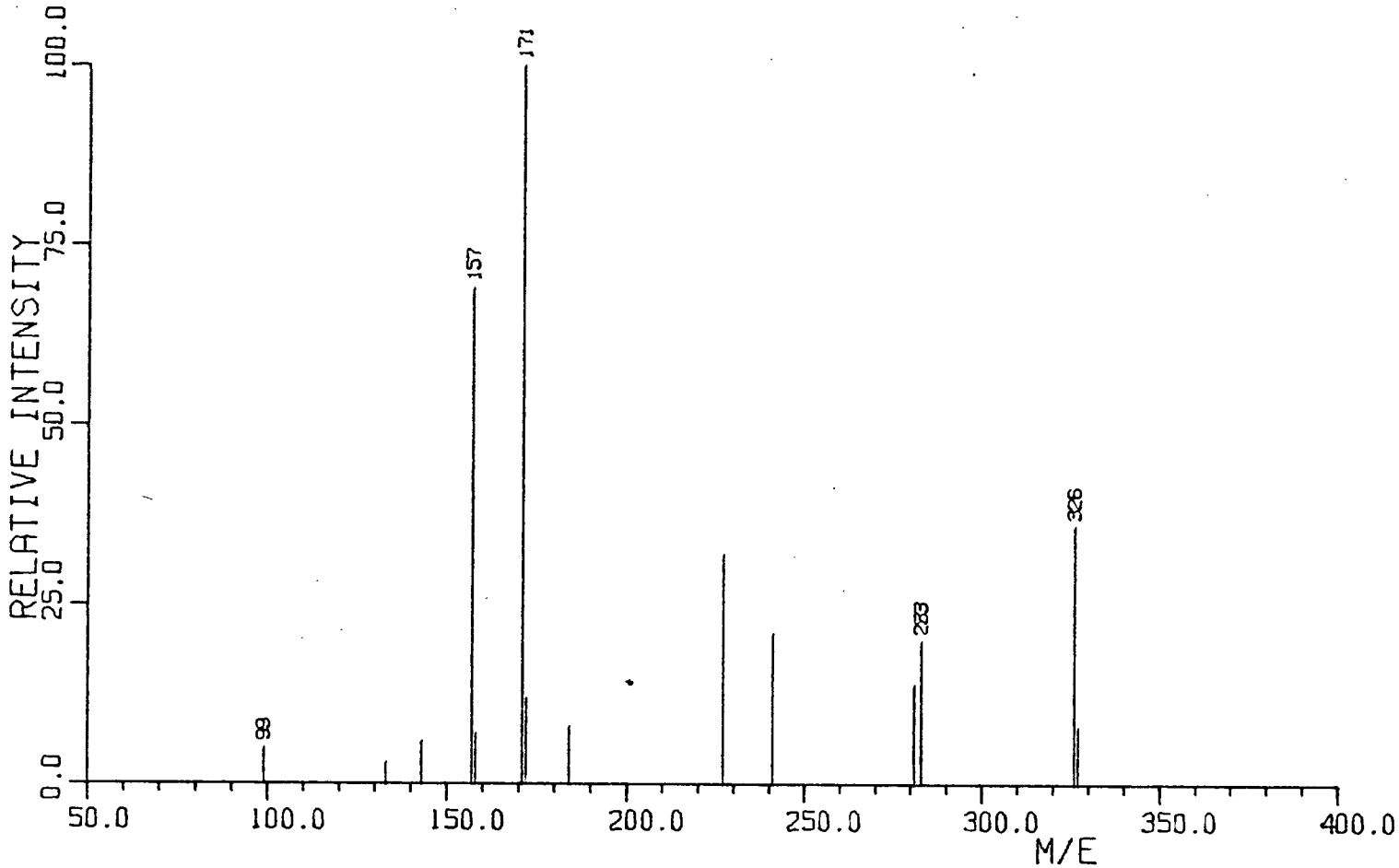


Figure 54. Mass spectrum of diacetal of 1,8-cyclopentadecyl-dione [low resolution (15eV)].

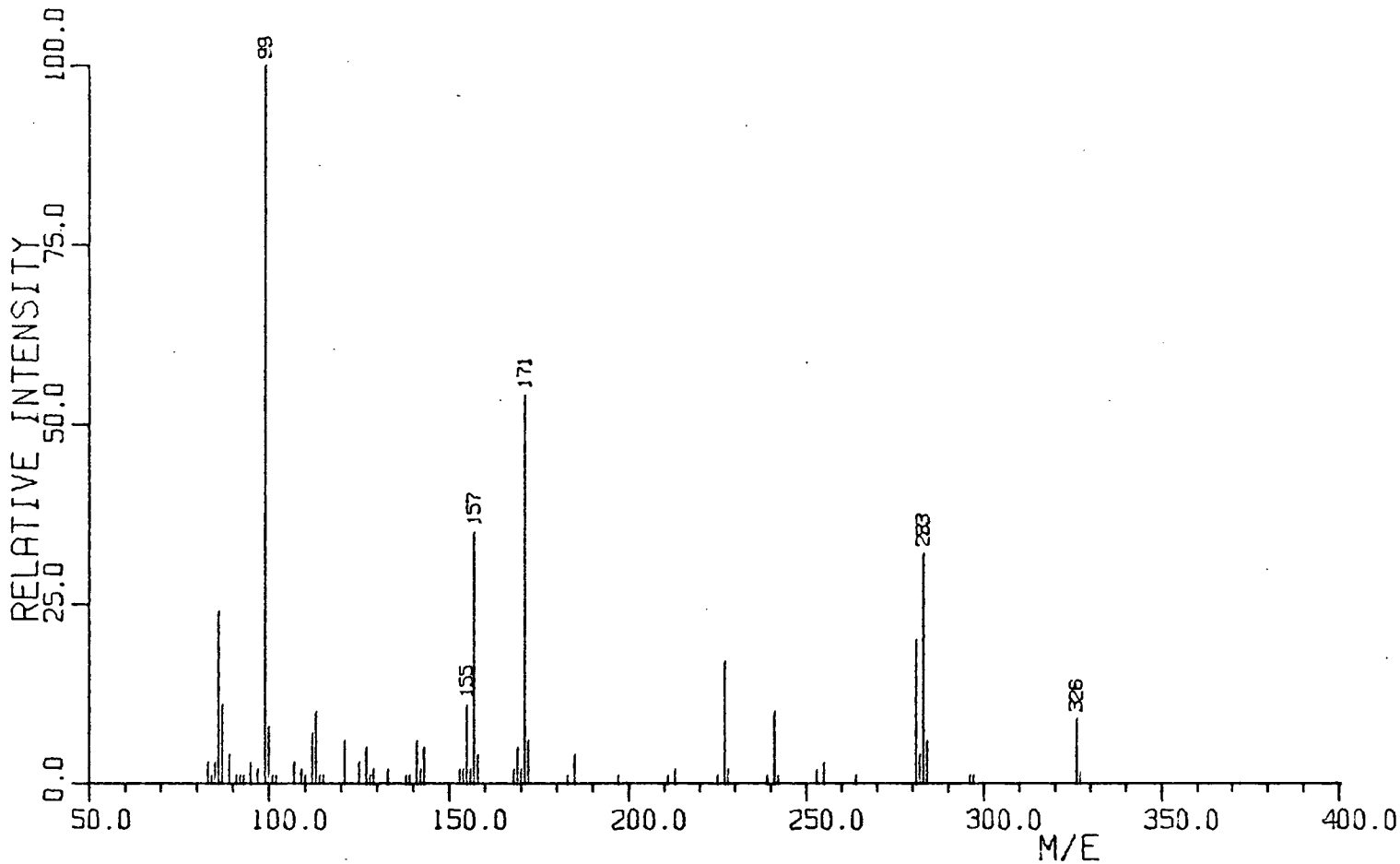


Figure 55. Mass spectrum of diacetal of 1,8-cyclopentadecyl-dione [low resolution (70eV)].

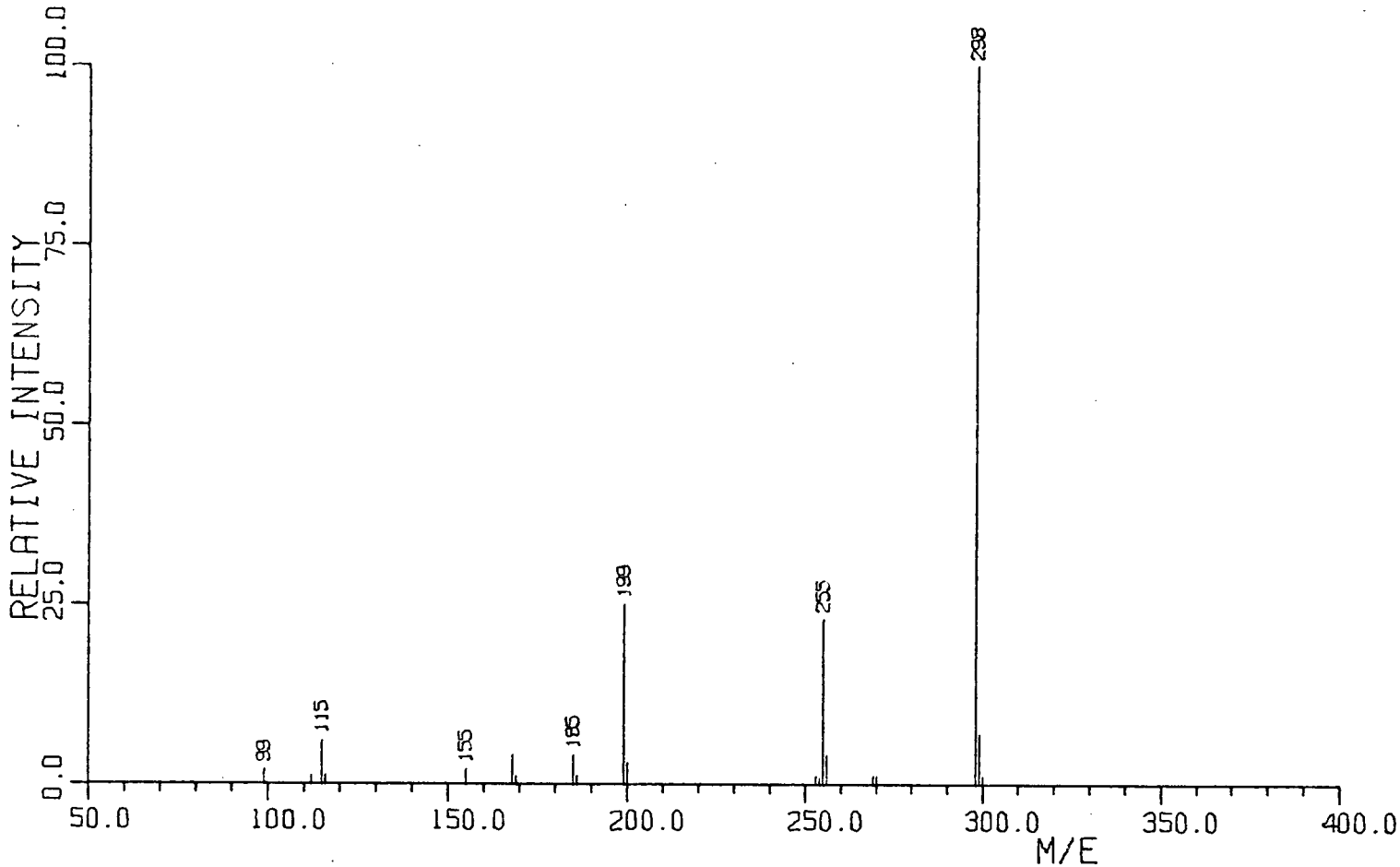


Figure 56. Mass spectrum of mixture of diacetals of 1,4-cyclotridecyl-dione and 1,5-cyclotridecyl-dione [low resolution (15eV)].

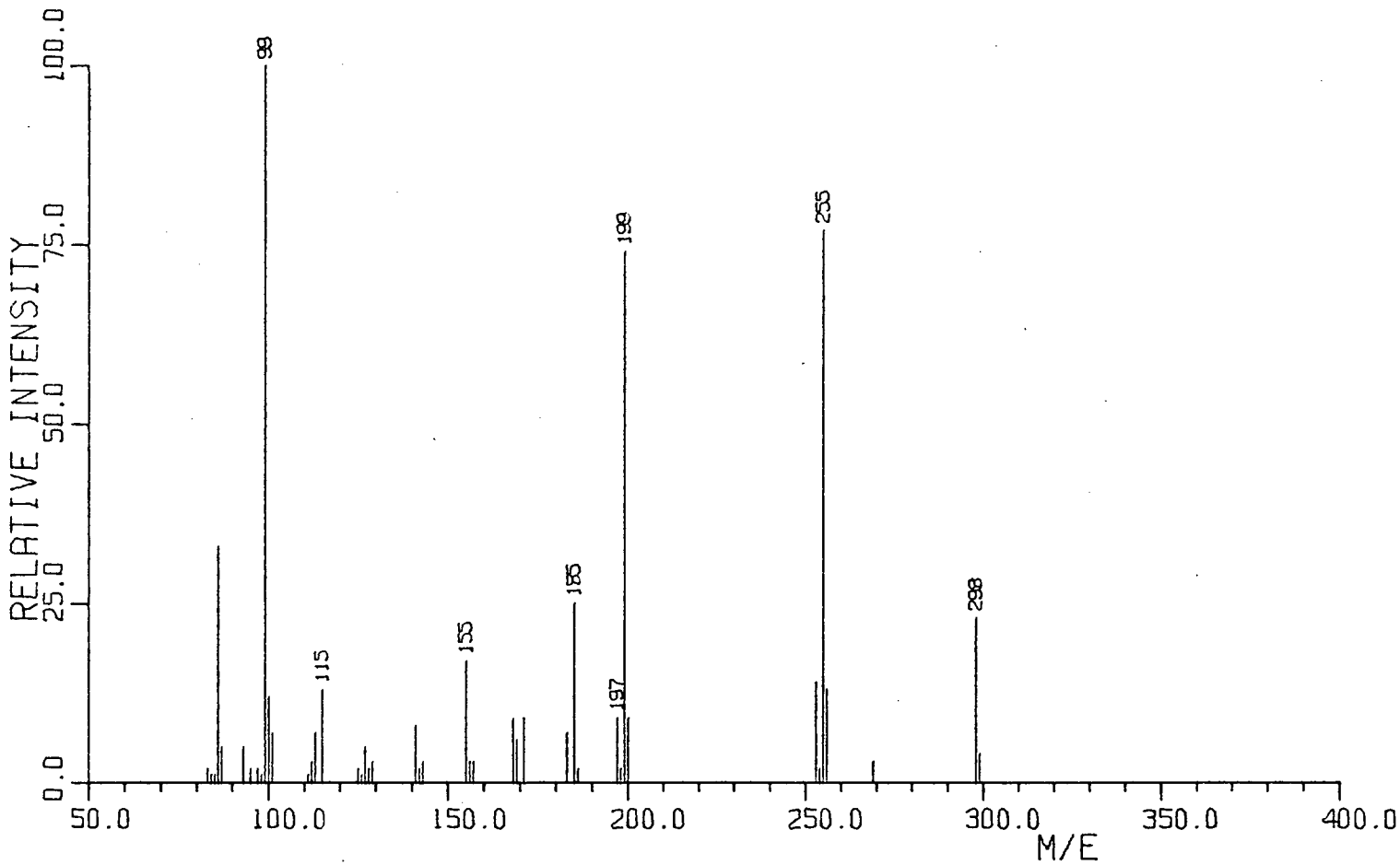


Figure 57. Mass spectrum of mixture of diacetals of 1,4-cyclotridecyl-dione and 1,5-cyclotridecyl-dione [low resolution (70eV)].

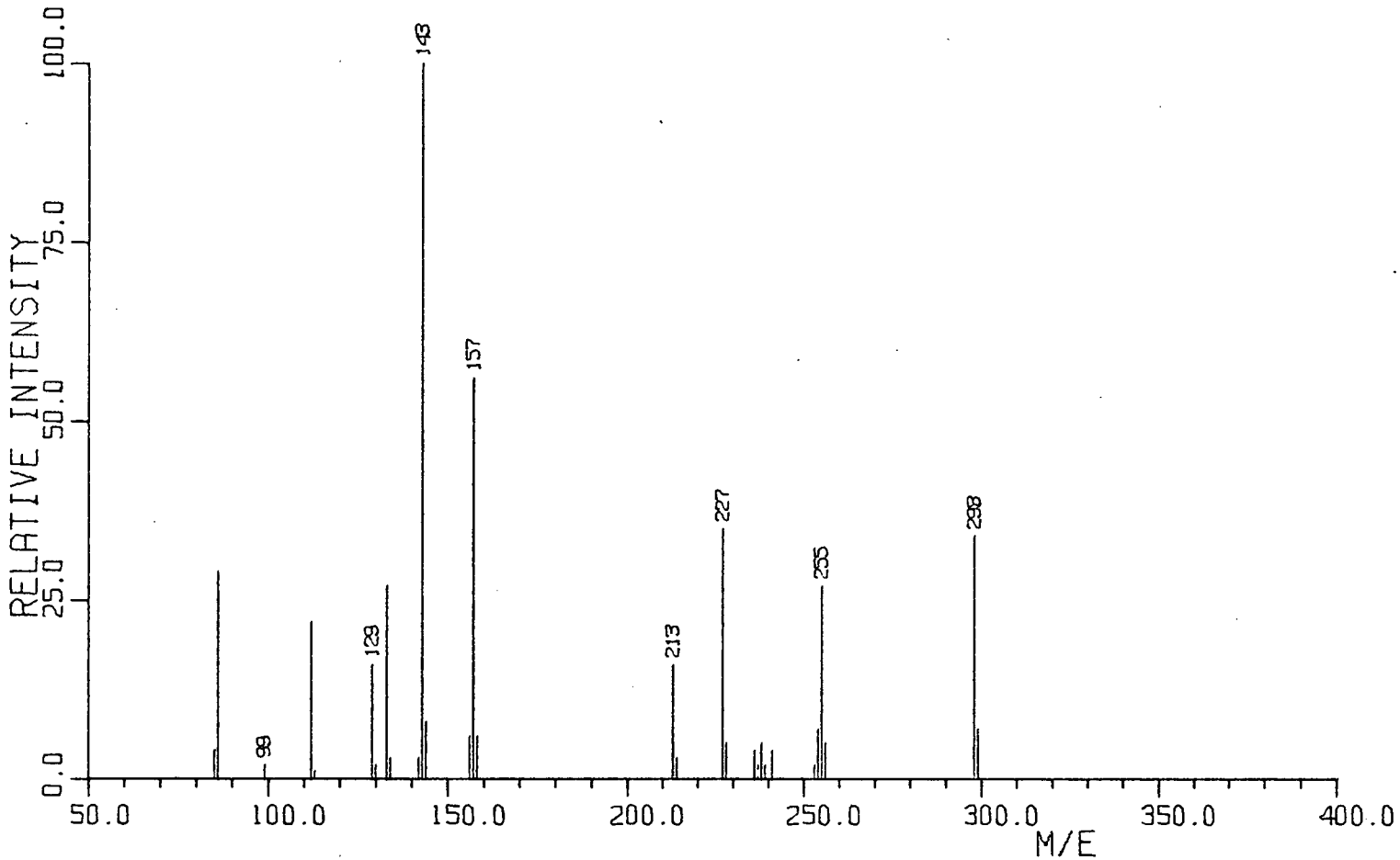


Figure 58. Mass spectrum of mixture of diacetals of 1,6-cyclotridecyl-dione and 1,7-cyclotridecyl-dione [low resolution (15eV)].

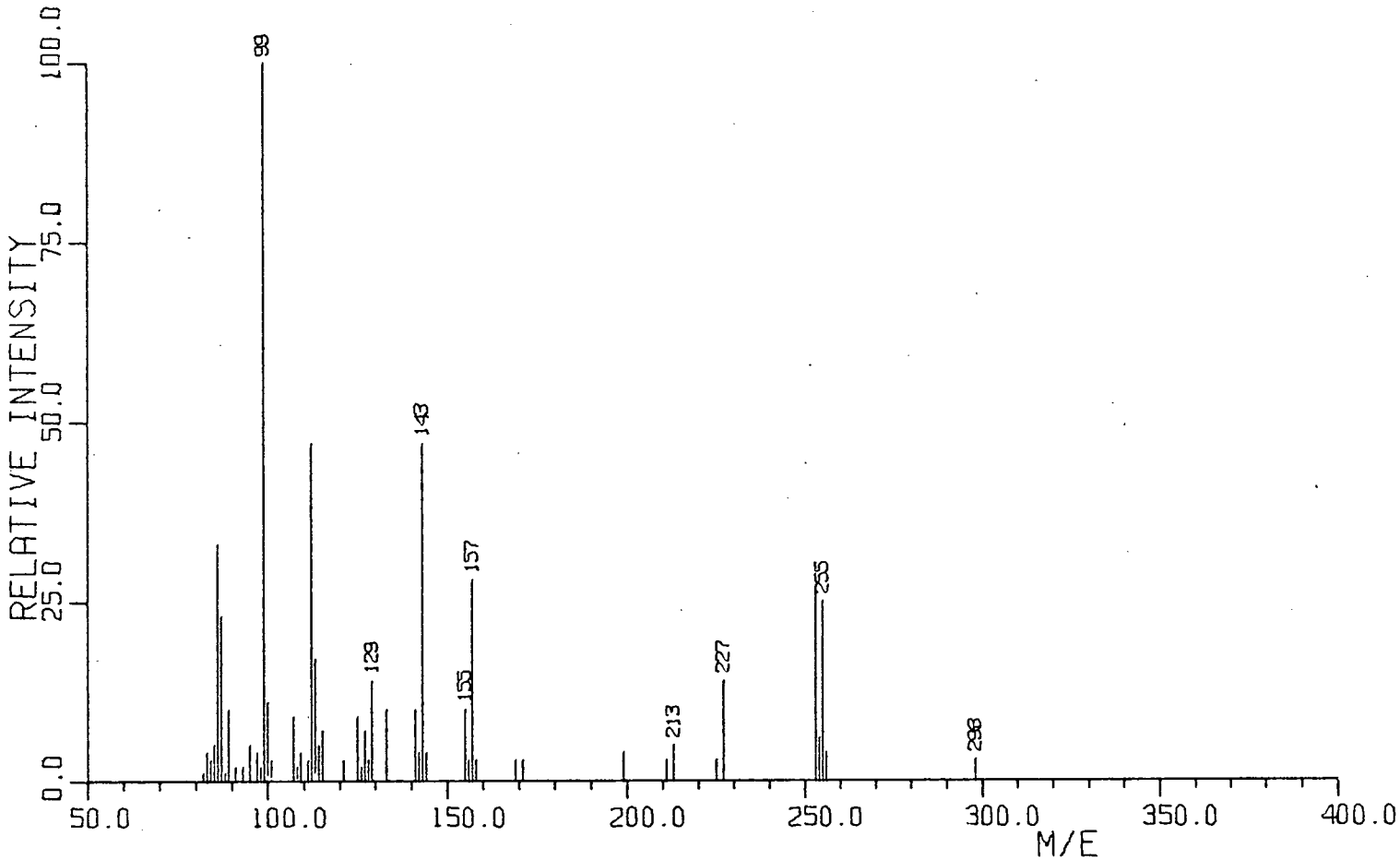


Figure 59. Mass spectrum of mixture of diacetals of 1,6-cyclotridecyl-dione and 1,7-cyclotridecyl-dione [low resolution (70eV)].

EXPERIMENTAL

General

Infrared spectra (IR) were obtained on Perkin-Elmer 137 and 710A spectrophotometer and calibrated by means of the 1601 cm^{-1} band of polystyrene. Nuclear magnetic resonance (NMR) were recorded on the following spectrometers: Varian Model T-60 and XL-100. Signal positions were reported on the τ- scale, with CCl_4 as solvent and tetramethylsilane as an internal standard. Mass spectra were recorded on Atlas CH-4 and A.E.I. MS902 instruments. Microanalyses were performed by Mr. P. Borda of this department. Melting points were determined on a Kofler apparatus and are uncorrected. Gas - liquid chromatography (g.l.c.) was carried out on Varian Aerograph Model 90-P, Perkin- Elmer Model 900 and Hewlett - Packard Model 5830A, using the following columns: 5'x¼", 3% SE30 on 100/120 Varoport 30; 5'x¼", 20% DEGS on 60/80 chromosorb W; 6'x1/8", 20% DEGS on 80/100 chromosorb W AW-DMCS; 10'x3/8", 20% DEGS on 60/80 chromosorb W; 5'x¼", 10% FFAP on 60/80 chromosorb W; 6'x1/8", 5% OV 210 on 80/100 chromosorb W, with helium as the carrier gas. Solvents employed were either Reagent grade or Certified grade. The term " petroleum ether" refers to the low boiling fraction of Certified petroleum distillate (b.p. 30-60°C).

Octadecyl acetate (97; n=16)

Acetic anhydride (16 ml.) was added to octadecanol (30 g.) in pyridine (60 ml.) and the mixture was refluxed overnight. After cooling, the solution was diluted with water and extracted with ether (3X). The combined extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and dried with anhydrous magnesium sulfate. Removal of solvent provided a white solid (28.5 g., 83%).

$\nu_{max}(CCl_4)$ 1745, 1240 cm^{-1}; $\tau(CCl_4$, 60 MHz) 5.96 (t, 2H, $-C\underline{H}_2-OAc$), 8.00 (s, 3H, $-O_2CC\underline{H}_3$), 8.43, 8.75 (broad s, 32H, $CH_3-(C\underline{H}_2)_{16}$), 9.10 (t, 3H, $C\underline{H}_3-(CH_2)_n$).

Oxidation of octadecyl acetate (97; n=16)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of octadecyl acetate (97; n=16) (5 g., 0.016 moles) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.) over a period of one and half hours. After stirring at room temperature for 5 days, water was cautiously added to the reaction mixture. Excess acetic anhydride was removed under reduced pressure and the resulting green solution was shaken with enough ether until organic layer present. The whole mixture was then filtered through a thin layer of celite and extracted with ether (5x). The combined extracts were washed successively with 2N sodium hydroxide (2x), saturated sodium bicarbonate

solution (4x) and water (2x). After drying with anhydrous magnesium sulfate, removal of solvent provided a yellow solid (3.2 g.) which was shown by g.l.c. (3% SE30) to consist of octadecyl acetate (28%), a mixture of keto-octadecyl acetates (59%)(unresolved on g.l.c.) and a mixture of poly-keto-octadecyl acetates (13%). Careful column chromatography of the mixture over Woelm silica gel grade III gave, by elution with pet.ether/ether (98:2), a mixture of keto-octadecyl acetates (98; x+y=15) (1.33 g., 31% based on consumed starting material).

ν_{max}(CCl_4), 1737, 1715, 1232 cm^{-1}; τ (CCl_4, 60 MHz) 6.00 (t, 2H, $-C\underline{H}_2OAc$), 7.70 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.02(s, 3H, $-O_2CC\underline{H}_3$), 8.70 (broad s, 26H, $CH_3(C\underline{H}_2)_{13}$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$); m/e 326 (M^+).

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.61; H, 11.65. Found: C, 73.67; H, 11.53.

Keto-octadecyl acetate acetals

Ethyl orthoformate (0.8 ml.), ethylene glycol (0.2 ml.) and p-toluenesulfonic acid (19 mg.) were added to keto-octadecyl acetates (400 mg.). After 6 hours at 90°C, the solution was heated at 150°C for 2 hours while excess ethyl orthoformate distilled off. After cooling, saturated sodium bicarbonate solution was added and the solution extracted with ether (3x). The combined extracts were washed with saturated sodium chloride solution. After drying with anhydrous magnesium sulfate, removal of solvent provided a yellow oil (378 mg.) which was shown by g.l.c. (3% SE30) to consist of small amount of keto-octadecyl acetates and a mixture of keto-

octadecyl acetate acetals. Double column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet.ether/ether, a mixture of keto-octadecyl acetate acetals (300 mg.).

$\nu_{max}(CCl_4)$ 1748, 1232, 1070 cm^{-1}; τ (CCl_4, 60 MHz) 6.04 (t, 2H, $-C\underline{H}_2OAc$), 6.20 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 8.06 (s, 3H, $-OCOC\underline{H}_3$), 8.72 (broad s, 30H, $CH_3(C\underline{H}_2)_{15}$), 9.13 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Keto-octadecanol acetals (99; x+y=15)

Sodium hydroxide (30 mg.), methanol (5 ml.) and keto-octadecyl acetate acetals (126 mg.) were heated at 100°C for 5 hours. Methanol was then removed by distillation. After cooling, the residue was diluted with water and extracted with ether (4x). The combined extracts were washed with saturated sodium chloride solution (3x), water (2x), and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (118 mg.).

$\nu_{max}(CCl_4)$ 3400, 1070 cm^{-1}; τ (CCl_4, 60 MHz) 6.20 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 6.50 (t, 2H, $-C\underline{H}_2OH$), 8.72 (broad s, 30H, $CH_3(C\underline{H}_2)_{15}$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Anal. Calcd. for $C_{20}H_{40}O_3$: C, 73.17; H, 12.20. Found: C, 72.61; H, 12.08.

Oxidation of octadecyl acetate (97; n=16) in ten times amount of solvent and the same amount of CrO_3-Ac_2O

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of octadecyl acetate (97;

n=16) (5 g., 0.016 mole) in glacial acetic acid (200 ml.) and acetic anhydride (90 ml.). After stirring at room temperature for 2 days, usual work-up as described earlier provided a yellow oil (4.48 g.) which was shown by g.l.c. (3% SE30) to consist of octadecyl acetate (26.9%), a mixture of keto-octadecyl acetates (44.3%) and a mixture of polyketo-octadecyl acetates (28.8%). Chromatography, as described earlier, provided a mixture of keto-octadecyl acetates (98; x+y=15) (1.19 g., 25% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1750, 1720, 1235 cm^{-1}; τ (CCl_4, 100 MHz) 6.30 (t, 2H, $-C\underline{H}_2OAc$), 7.72 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.05 (s, 3H, $-OCOC\underline{H}_3$), 8.50, 8.75 (broadmm, s, 26H, $CH_3(C\underline{H}_2)_{13}-$), 9.11 (t, 3H, $C\underline{H}_3(CH_2)_n-$).

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.62; H, 11.66. Found: C, 73.58; H, 11.49.

Acetates of dodecanol (97; n=10), tetradecanol (97; n=12), docosanol (97; n=20), hexadecanol (97; n=14)

Dodecanol, tetradecanol, docosanol and hexadecanol were converted to the acetates as described for octadecyl acetate.

The I.R. and N.M.R. characteristics of these acetates were similar to those of octadecyl acetate (97; n=16).

Oxidation of dodecyl acetate (97; n=10)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of dodecyl acetate (97; n=10) (4.82 g., 0.023 mole) in glacial acetic acid (20 ml.) and

acetic anhydride (9 ml.) over a period of one and half hours. After stirring at room temperature for 2 days, water was cautiously added to the reaction mixture. Usual work-up, as described earlier provided a yellow oil (2.81 g.) which was shown by g.l.c. (3% SE30) to consist of dodecyl acetate (55%) and a mixture of keto-dodecyl acetates (45%) (unresolved on g.l.c.). Chromatography, as described earlier, provided a mixture of keto-dodecyl acetates (98; x+y=9) (1.2 g., 29% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1745, 1720, 1235 cm^{-1}; τ (CCl_4, 60 MHz) 6.02 (t, 2H, $-C\underline{H}_2OAc$), 7.70 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.03 (s, 3H, $-OCOC\underline{H}_3$), 8.70 (broad s, 14H, $CH_3(C\underline{H}_2)_7$), 9.11 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Anal. Calcd. for $C_{14}H_{26}O_3$: C, 69.42; H, 10.74. Found: C, 69.22; H, 10.64.

Oxidation of tetradecyl acetate (97; n=12)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of tetradecyl acetate (97; n=12) (5.05 g., 0.02 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.) over a period of one and half hours. After stirring at room temperature for 4 days, water was cautiously added to the reaction mixture. Usual work-up as described for octadecyl acetate (cf. P.117) provided a pale yellow oil (3.19 g.) which was shown by g.l.c. (3% SE30) to consist of tetradecyl acetate (49%), a mixture of keto-tetradecyl acetates (48%) (unresolved on g.l.c.) and a mixture of polyketo-tetradecyl acetates (3%). Chromatography, as described for octadecyl acetate, provided a mixture of keto-tetradecyl acetates (98; x+y=11)

(1.04 g., 24% based on consumed starting material).

ν_{max} (CCl_4) 1737, 1720, 1230 cm^{-1}; τ(CCl_4, 60 MHz) 6.00 (t, 2H, $-C\underline{H}_2OAc$), 7.72 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.07 (s, 3H, $-OCOC\underline{H}_3$), 8.43, 8.72 (broad m, s, 18H, $CH_3(C\underline{H}_2)_9$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.11; H, 11.11.
Found: C, 71.06; H, 11.22.

Oxidation of docosyl acetate (97; n=20)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of docosyl acetate (97; n=20) (5.03 g., 0.014 moles) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.) over a period of one and half hours. After stirring at room temperature for 2 days, water was cautiously added to the reaction mixture. Usual work-up, as described earlier provided a pale yellow solid (3.55 g.) which was shown by g.l.c. (3% SE30) to consist of docosyl acetate (35%), a mixture of keto-docosyl acetates (44%) (unresolved on g.l.c.) and a mixture of polyketo-docosyl acetates (21%). Chromatography, as described earlier, provided a mixture of keto-docosyl acetates 98; x+y=19) (1.10 g., 24% based on consumed starting material).

ν_{max} (CCl_4) 1750, 1720, 1235 cm^{-1}; τ (CCl_4, 60 MHz) 6.02 (t, 2H, $-C\underline{H}_2OAc$), 7.72 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.02 (s, 3H, $-OCOC\underline{H}_3$), 8.74 (broad s, 34H, $CH_3(C\underline{H}_2)_{17}$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Anal. Calcd. for $C_{24}H_{46}O_3$: C, 75.39; H, 12.04.
Found: C, 75.28; H, 11.93.

Oxidation of hexadecyl acetate (97; n=14)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of hexadecyl acetate (97; n=14) (5 g., 0.018 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). After stirring at room temperature for 3 days, water was cautiously added to the reaction mixture. Usual work-up as described earlier, provided a yellow oil (3.32 g.) which was shown by g.l.c. (3% SE30) to consist of hexadecyl acetate (36%), a mixture of keto-hexadecyl acetates (49.7%) (unresolved on g.l.c.) and a mixture of polyketo-hexadecyl acetates (14.3%). Chromatography as described earlier, provided a mixture of keto-hexadecyl acetates (98; x+y=13) (1.18 g., 26% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1745, 1720, 1235 cm^{-1}; τ (CCl_4, 60 MHz) 6.02 (t, 2H, $-C\underline{H}_2OAc$), 7.70 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.03 (s, 3H, $-OCOC\underline{H}_3$), 8.70 (broad s, 22H, $CH_3(C\underline{H}_2)_{11}$), 9.11 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.48; H, 11.41. Found: C, 72.20; H, 11.29.

Acetals of keto-dodecyl acetates, keto-tetradecyl acetates, keto-docosyl acetates

The oxidation products from dodecyl acetate (98; x+y=9), tetradecyl acetate (98; x+y=11), docosyl acetate (98; x+y=19) were converted to the acetals as described for keto-octadecyl acetates.

The I.R. and N.M.R. characteristic of these acetals were similar to those of keto-octadecyl acetate acetals.

Acetals of keto-dodecanols (99; x+y=9), keto-tetradecanols (99; x+y=11), keto-docosanols (99; x+y=19)

Acetals of keto-dodecyl acetates, keto-tetradecyl acetates, keto-docosyl acetates were converted to the alcohol as described for keto-octadecyl acetate acetals.

The I.R. and N.M.R. characteristics of these acetal alcohols were similar to those of keto-octadecanol acetals.

Anal. Calcd. for $C_{24}H_{48}O_3$: C, 75.00; H, 12.50. Found: C, 75.64; H, 12.83.

Hydroxytetradecyl acetates (101; x+y=11)

Sodium borohydride (30 mg.) in methanol (1 ml.) was added dropwise to a solution of keto-tetradecyl acetates (98; x+y=11) (300 mg.) in methanol (2 ml.). After stirring at room temperature for half hour, excess sodium borohydride was destroyed by the addition of dilute hydrochloric acid and the solution was extracted with ether (3x). The combined extracts were washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying with anhydrous magnesium sulfate, removal of solvent provided a clear oil (281 mg.).

ν_{max}(CCl_4) 3450, 1737, 1235 cm^{-1}; τ (CCl_4, 60 MHz) 5.95 (t, 2H, $-C\underline{H}_2OAc$), 6.40 (broad s, 1H, $-C\underline{H}OH$), 8.07 (s, 3H, $-OCOC\underline{H}_3$), 8.25, 8.63 (s, broad s, 23H, $CH_3(C\underline{H}_2)_{11}$, $-CHO\underline{H}$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Mesyloxytetradecyl acetates

Mesyl chloride (0.1 ml.) was added dropwise to a solution of hydroxytetradecyl acetates (256 mg.) in dry pyridine

(0.5 ml.) at 0-5°C under nitrogen. After stirring at 0-5°C for two hours, the mixture was diluted with 3N hydrochloric acid (2 ml.) and extracted with ether (3x). The combined extracts were washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying with anhydrous magnesium sulfate, removal of solvent gave a clear oil (318 mg.);

ν_{max} (CCl_4) 1737, 1365, 1345, 1235, 1180, 910 cm^{-1};
τ (CCl_4, 60 MHz) 5.37 (broad s, 1H, -C<u>H</u>OMs), 5.95 (t, 2H, -C<u>H</u>$_2$OAc), 7.12 (s, 3H, -OSO$_2$C<u>H</u>$_3$), 8.07 (s, 3H, -OCOC<u>H</u>$_3$), 8.63 (broad s, 22H, CH_3(C<u>H</u>$_2$)$_{11}$), 9.10 (t, 3H, C<u>H</u>$_3$(CH_2)$_n$).

<u>Tetradecenyl acetates (102; a+b=10)</u>

A solution of mesyloxytetradecyl acetates (321 mg., vacuum dried for two hours) in dry collidine (5 ml.) was heated at 140°C overnight. After cooling to room temperature, the mixture was diluted with water and extracted with ether (3x). The combined extracts were washed with 5% hydrochloric acid, saturated sodium bicarbonate solution and water. After drying with anhydrous magnesium sulfate, removal of solvent gave a pale yellow oil (193 mg.).

ν_{max}(CCl_4) 1737, 1650, 1235 cm^{-1}; τ(CCl_4, 100 MHz) 4.68 (m, 2H, -C<u>H</u>=C<u>H</u>-), 6.02 (t, 2H, -C<u>H</u>$_2$OAc), 8.07 (m, 7H, -C<u>H</u>$_2$C=CC<u>H</u>$_2$-, -OCOC<u>H</u>$_3$), 8.40, 8.74 (m, broad s, 16H, CH_3(C<u>H</u>$_2$)$_8$), 9.12 (t, 3H, C<u>H</u>$_3$(CH_2)$_n$).

Hydroxydodecyl acetates (101; x+y=9)

Sodium borohydride (48 mg.) in methanol (1 ml.) was added dropwise to a solution of keto-dodecyl acetates (98; x+y=9) (313 mg.) in methanol (2 ml.). After stirring at room temperature for half hour, usual work-up as described for keto-tetradecyl acetates (cf. P.124) provided a pale yellow oil (254 mg.).

The I.R. and N.M.R. characteristic of these hydroxydodecyl acetates were similar to those of hydroxytetradecyl acetates.

Mesyloxydodecyl acetates

Mesyl chloride (0.1 ml.) was added dropwise to a solution of hydroxydodecyl acetates (220 mg.) in dry pyridine (0.5 ml.) at 0-5°C under nitrogen. After stirring at 0-5°C for two hours, usual work up as described for hydroxytetradecyl acetates (cf. P.124) provided a pale yellow oil (235 mg.).

The I.R. and N.M.R. characteristic of these mesyloxydodecyl acetates were similar to those of mesyloxytetradecyl acetates.

Dodecenyl acetates (102; 2+b=8)

A solution of mesyloxydodecyl acetates (230 mg.) in dry collidine (5 ml.) was heated at 110 °C overnight. Usual work-up as described for mesyloxytetradecyl acetates provided a golden yellow oil (138 mg.) which was chromatographed on aluminum oxide (grade IV); petroleum ether (30-60 °C) eluted the mixture of dodecenyl acetates (pale-yellow oil, 116 mg.).

The I.R. and N.M.R. characteristic of these dodecenyl acetates were similar to those of tetradecenyl acetates.

Hydroxyhexadecyl acetates (101; x+y=13)

Sodium borohydride (60 mg.) in methanol (3 ml.) was added dropwise to a solution of keto-hexadecyl acetates (98; x+y=13) (400 mg.) in methanol (7 ml.). After stirring at room temperature for 50 minutes, usual work-up as described for keto-tetradecyl acetates (cf. P.124) provided a pale yellow oil (358 mg.).

The I.R. and N.M.R. characteristic of these hydroxyhexadecyl acetates were similar to those of hydroxytetradecyl acetates.

Mesyloxyhexadecyl acetates

Mesyl chloride (0.3 ml.) was added dropwise to a solution of hydroxyhexadecyl acetates (358 mg.) in dry pyridine (0.7 ml.) at 0-5 °C under nitrogen. After stirring at 0-5 °C for 2 hours, usual work-up as described for hydroxytetradecyl acetates (cf. P.124) provided a yellow oil (423 mg.).

The I.R. and N.M.R. characteristic of these mesyloxyhexadecyl acetates were similar to those of mesyloxytetradecyl acetates.

Hexadecenyl acetates (102; a+b=12)

A solution of mesyloxyhexadecyl acetates (401 mg.) in dry collidine (5 ml.) was heated at 140°C overnight. Usual work-up as described for mesyloxytetradecyl acetates provided a golden yellow oil (271 mg.) which was chromatographed on aluminum oxide (grad IV); petroleum ether (30- 60°C) eluted the mixture of hexadecenyl acetates (pale- yellow oil, 201 mg.).

The I.R. and N.M.R. characteristic of these hexadecenyl acetates were similar to those of tetradecenyl acetates.

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 76.60; H, 12.07. Found: C, 76.55; H, 12.20.

11-acetoxyundecanoic acid (14; n=10)

11-hydroxyundecanoic acid (3gg.) in pyridine (15 ml.) and acetic anhydride (5mml.) was refluxed overnight and then diluted with water (50mml.). The aqueous mixture was extracted with ether (3x) and the combined ether extracts were washed with 5% hydrochloric acid, saturated sodium bicarbonate solution. After drying with anhydrous magnesium sulfate, removal of solvent provided a white solid (3.26gg., m.p. 31-32°C).

ν_{max} (CCl_4) 3300-2500, 1735, 1700, 1240cm^{-1}; τ (CCl_4, 60MHz) 6.00 (t, 2H, -C$\underline{H}_2$OAc), 7.70 (t, 2H, -C$\underline{H}_2$COOH), 8.00(s, 3H, -O_2CC$\underline{H}_3$), 8.75(broad s, 16H, -(C$\underline{H}_2$)$_8$-).

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.93; H, 9.84. Found: C, 64.30; H, 10.00.

11-acetoxyundecyl chloride (105; n=10)

Freshly distilled oxalyl chloride (2 ml.) was added to 11-acetoxyundecanoic acid (1.59 g.) at room temperature. The mixture was then refluxed for about 2 hours and the excess oxalyl chloride was removed under atmospheric pressure. Distillation at diminished pressure provided a clear oil (0.77 g., b.p. 126-127 ^{o}C at 0.04 m.m. Hg).

ν_{max} (CCl_4) 1790, 1725, 1240 cm^{-1}; τ (CCl_4, 60 MHz) 6.00 (t, 2H, -$C\underline{H}_2$OAc), 7.13 (t, 2H, -$C\underline{H}_2$COCl), 8.00 (s, 3H, -OCO$C\underline{H}_3$), 8.67 (broad s, 16H, -$(C\underline{H}_2)_8$-).

11-oxo-octadecyl acetate (107; n=10, m=6)

AAmixture of magnesium turnings (0.7 g.) and a small crystal of iodine in dry ether (50 ml.) was stirred until the brown color disappeared. 1-bromoheptane (1.6 ml.) in dry ether (50 ml.) was added dropwise. After addition, the stirred reaction mixture was refluxed for 2 hours. A portion of this Grignard reagent (10 ml.) was diluted with water (25 ml.) and 0.05 N hydrochloric acid (50 ml.). The excess acid was titrated with standard 1 N sodium hydroxide solution. The molarity of Grignard reagent was 0.15.

Heptyl magnesium bromide solution (15 ml.) was added to dry zinc chloride (304 mg.) in dry ether (10 ml.). After the initial addition, the mixture was stirred and refluxed for 4 hours. With continued stirring,a solution of 11-acetoxyundecyl chloride (0.17 g.) in dry benzene (5 ml.) was added during twenty minutes. The mixture was stirred and refluxed for another

3 hours and then hydrolyzed with 5% hydrochloric acid (50 ml.). The aqueous layer was separated and extracted with benzene (3x). The combined benzene solution was washed with 5% hydrochloric acid (2x), saturated sodium bicarbonate (2x) and water (1x). After drying with anhydrous sodium sulfate, removal of solvent provided a yellow solid (242 mg.) which was chromatographed on Woelm silica gel (grade III); 5% ether in petroleum ether (30-60°C) eluted the pure 11-oxo-octadecyl acetate (143 mg., white solid).

ν_{max} (CCl_4) 1750, 1725, 1235 cm^{-1}; τ (CCl_4, 60 MHz) 6.00 (t, 2H, $-C\underline{H}_2OAc$), 7.68 (t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.00 (s, 3H, $-O_2CC\underline{H}_3$), 8.67 (broad s, 26H, $-(C\underline{H}_2)_{13}-$), 9.10 (t, 3H, $-C\underline{H}_3(CH_2)_n$) $\frac{m}{e}$ 326 (M^+).

Acetal of 11-oxo-octadecyl acetate

A mixture of 11-oxo-octadecyl acetate (96.7 mg.), ethylene glycol (0.1 ml.) and p-toluenesulfonic acid monohydrate (5 mg.) in benzene (10 ml.) was refluxed for 43 hours. Water was removed by Dean-Stark water separator. The resulted mixture was cooled and washed with saturated sodium bicarbonate solution (1x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (87 mg.) which was chromatographed on alumina (grade IV); petroleum ether (30-60°C) eluted the pure acetal of 11-oxo-oxtadecyl acetate (34.1 mg., pale yellow oil).

ν_{max} (CCl_4), 1725, 1235, 1070 cm^{-1}; τ (CCl_4, 60 MHz) 6.00 (t, 2H, $-C\underline{H}_2OAc$), 6.20 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 8.06 (s, 3H, $-OCOC\underline{H}_3$), 8.72 (broad s, 30H, $CH_3(C\underline{H}_2)_{15}$), 9.13 (t, 3H, $C\underline{H}_3(CH_2)_n$).

Acetal of 11-oxo-octadecanol (108; n=10, m=6)

A mixture of acetal of 11-oxo-octadecyl acetate (30 mg.) and potassium hydroxide (9 mg.) in methanol/water (1 ml.: 0.5 ml.) was refluxed for 15 hours. Then the methanol was removed by distillation. The residue was diluted with water and extracted with ether (3x). The combined ether extracts were washed with saturated sodium chloride solution (2x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a pale-yellow oil (22.1 mg.).

ν_{max} (CCl_4), 3400, 1070 cm^{-1}; τ (CCl_4, 60 MHz) 6.20 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 6.50 (t, 2H, $-C\underline{H}_2OH$), 8.72 (broad s, 30H, $CH_3(C\underline{H}_2)_{15}-$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$).

15-acetoxypentadecanoic acid (104; n=14)

15-hydroxypentadecanoic acid was converted to the acetates as described for 11-acetoxyundecanoic acid.

The I.R. and N.M.R.R. characteristic of this 15-acetoxypentadecanoic acid were similar to those of 11-acetoxyundecanoic acid.

15-acetoxypentadecyl chloride (105; n=14)

15-acetoxypentadecanoic acid was converted to the acyl chloride as described for 11-acetoxyundecyl chloride.

The I.R. and N.M.R. characteristic of this 15-acetoxypentadecyl chloride were similar to those of 11-acetoxyundecyl chloride.

15-oxo-oxtadecyl acetate (107; n=14, m=2)

15-acetoxypentadecyl chloride was converted to 15-oxo-oxtadecyl acetate with n-propyl magnesium bromide as described for 11-oxo-octadecyl acetate.

The I.R. and N.M.R. characteristic of this 15-oxo-octadecyl acetate were similar to those of 11-oxo-oxtadecyl acetate.

Acetal of 15-oxo-octadecyl acetate

The acetal of 15-oxo-octadecyl acetate was prepared in the same way as that for acetal of 11-oxo-octadecyl acetate.

The I.R. and N.M.R. characteristic of this acetal of 15-oxo-octadecyl acetates were similar to those of acetal of 11-oxo-oxtadecyl acetate.

Acetal of 15-oxo-octadecanol (108; n=14, m=2)

Acetal of 15-oxo-octadecyl acetate was converted to acetal of 15-oxo-oxtadecanol as described for acetal of 11-oxo-octadecanol.

The I.R. and N.M.R. characteristic of this acetal of 15-oxo-octadecanol were similar to those of acetal of 11-oxo-octadecanol.

Methyl 9- and 10-hydroxystearates (110 a & b)

Borane-methyl sulfide (0.5 ml.) was added dropwise to a solution of methyl oleate (1.71 g.) in dry tetrahydrofuran (100 ml.) at 0-5°C. Following the addition of the hydride, the cooling bath was removed and the solution was stirred at room temperature for 3 hours. 3N aqueous sodium hydroxide (25 ml.) was then added. After cooling to 0-5°C in an ice water bath, 30% hydrogen peroxide solution (35 ml.) was added. Then the cooling bath was removed and the reaction mixture was heated at reflux for 1 hour. The reaction mixture was then poured into water (200 ml.) and extracted with ether (3x). The combined ether extracts were washed with saturated sodium chloride solution (2x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a white solid (1.56 g.).

ν_{max} (CCl_4) 3450, 1750 cm^{-1}; τ (CCl_4, 60 MHz) 6.40 (s, 3H, $C\underline{H}_3OCO$-), 6.53 (s, 1H, -$C\underline{H}OH$), 7.18 (broad s, 1H, -$O\underline{H}$), 7.80 (t, 2H, -$C\underline{H}_2CO_2Me$), 8.70 (broad s, 28H, $CH_3(C\underline{H}_2)_{14}$-), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n$-).

Methyl 9- and 10- keto-sterate (111 a and b)

Methyl 9- and 10-hydroxysterate (0.8 g.) were dissolved in acetone (5 ml.). Jones reagent (CrO_3-H_2SO_4-H_2O) (3 ml.) was added dropwise until oxidation was complete. The mixture was diluted with water (25 ml.) and extracted with ether (3x). The combined ether extracts were washed with saturated sodium bicarbonate (2x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow solid which was crystallized from pentane to give a white solid (0.65 g.).

ν_{max} (CCl_4) 1750, 1735 cm^{-1}; τ (CCl_4, 60 MHz) 6.41 (s, 3H, $-CO_2C\underline{H}_3$), 7.74 (3 overlapping triplets, 6H, $-C\underline{H}_2CO_2CH_3$, $-C\underline{H}_2COC\underline{H}_2-$), 8.48, 8.74 (broad s, m, 24H, $CH_3(C\underline{H}_2)_{12}-$), 9.12 (t, 3H, $C\underline{H}_3(CH_2)_n-$).

Methyl 9- and 10-keto-stearate acetals

A mixture of methyl 9- and 10-keto-stearates (300 mg.) ethylene glycol (0.3 ml.) and p-toluenesulfonic acid monohydrate in benzene (25 ml.) was refluxed for 43 hours while water was removed by Dean-Stark water separator. Usual work-up provided a pale-yellow oil (242.7 mg.) which was chromatographed on alumina (grade III); and eluted with pentane to provide pure methyl 9- and 10- ketostearate acetals (120 mg.) .

ν_{max} (CCl_4) 1750, 1150 cm^{-1}; τ (CCl_4, 60 MHz) 6.18 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 6.40 (s, 3H, $-CO_2C\underline{H}_3$), 7.77 (t, 2H, $-C\underline{H}_2CO_2CH_3$), 8.48, 8.76 (broad s, m, 28H, $CH_3(C\underline{H}_2)_{14}-$), 9.12 (t, 3H, $C\underline{H}_3(CH_2)_n-$) .

Acetals of 9- and 10-oxo-octadecanol (112 a and b)

Lithium aluminium hydride (54 mg.) in dry ether (15 ml.) was refluxed for ∿½ hours. Methyl 9- and 10-oxo-stearate acetal (120 mg.) in dry ether (10 ml.) was added dropwise. After stirring and refluxing for 2½ hours, excess lithium aluminium hydride was destroyed by adding water (2 ml.). 2N sodium hydroxide solution (6 ml.) was then added and the mixture was extracted with ether (2x). The combined ether extracts were washed with water (1x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a pale-yellow oil (89 mg.).

ν_{max} (CCl_4) 3400, 1070 cm^{-1}; τ (CCl_4, 60 MHz) 6.20 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 6.50 (t, 2H, $-C\underline{H}_2OH$), 8.72 (broad s, 30H, $CH_3(C\underline{H}_2)_{15}-$), 9.10 (t, 3H, $C\underline{H}_3(CH_2)_n-$).

Oxidation of 16-hexadecanolide (117; n=15)

Chromium trioxide (7.6 g.) in acetic anhydride (16 ml.) was added dropwise to a cold mixture of 16-hexadecanolide (5.8 g., 0.023 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). The mixture was stirred at 0-5 °C for 3 hours and then at room temperature for 5 days. Water (200 ml.) was added in and the excess acetic anhydride was removed. The mixture was extracted with ether (6x). The combined extracts were washed successively with saturated sodium bicarbonate solution (4x), water (2x) and

dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (3.6 g.) which was shown by g.l.c. (3% SE30) to consist of 16-hexadecanolide (34%), a mixture of oxo-16-hexadecanolides (62%) (unresolved on g.l.c.) and a mixture of polyketo-16-hexadecanolides (4%). Column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet. ether (30-60 °C)/ether, a mixture of mono-oxo-16-hexadecanolides (118; x+y=14) (1.72 g., 33% based on consumed starting material).

ν_{max} (CCl_4) 1738, 1720, 1250, 1175 cm^{-1}; τ (CCl_4, 100 MHz) 5.97 (t, 2H, -COOC$\underline{H}_2$), 7.72 (mixed t, 6H, -C$\underline{H}_2$COC$\underline{H}_2$-, -C$\underline{H}_2$COO-), 8.42, 8.70 (m, broad s, 20H, -$(CH_2)_{10}$-).

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.64; H, 10.45. Found: C, 71.43; H, 10.23.

Acetals of oxo-16-hexadecanolides

A mixture of oxo-16-hexadecanolides (361 mg., 1.35 millimole), ethylene glycol (0.4 ml.) and p-toluenesulfonic acid monohydrate (15 mg.) in benzene (30 ml.) was refluxed for 4 days and water was removed by Dean- Stark water separator. The resulted mixture was cooled and washed with saturated sodium bicarbonate solution (2x), water (1x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (371 mg.) which was chromatographed on alumina (grade IV); pentane eluted the pure acetals of oxo-16-

hexadecanolides (275 mg.).

ν_{max} (CCl_4) 1738, 1240, 1150, 1075 cm^{-1}; τ (CCl_4, 60 MHz) 5.97 (t, 2H, -COOC$\underline{H}_2$-), 6.23 (s, 4H, -OC$\underline{H}_2$C$\underline{H}_2$O-), 7.80 (t, 2H, -C$\underline{H}_2$COO-), 8.40, 8.67 (m, broad s, 24H, -(C$\underline{H}_2$)$_{12}$-).

Acetals of oxo-16-hydroxyhexadecanoic acids (119; x+y=14)

A mixture of oxo-16-hexadecanolide acetals (160 mg.) and potassium hydroxide (41 mg.) in methanol (4 ml.) was refluxed overnight and then acidified to ph 6. The mixture was extracted with ether (5x). The combined ether extracts were washed with water (1x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (130 mg.).

ν_{max} (CCl_4), 3400, 3000-2500, 1715, 1075 cm^{-1}; τ (CCl_4, 60 MHz), 3.65 (s, 2H, -COO$\underline{H}$, -O$\underline{H}$), 6.07 (s, 4H, -OC$\underline{H}_2$C$\underline{H}_2$O-), 6.37 (t, 2H, -C$\underline{H}_2$OH), 7.65 (t, 2H, -C$\underline{H}_2$COOH), 8.57 (broad s, 24H, -(C$\underline{H}_2$)$_{12}$-).

Acetals of oxo-hexadecanols (120; x+y=14)

Mesyl chloride (0.05 ml.) was added to a solution of acetals of oxo-16-hydroxyhexadecanoic acids in dry pyridine (0.21 ml.) at 0-5°C. After stirring at room temperature for 2 hours, the solution was diluted with water (5 ml.) and extracted with methylene chloride (3x). The combined methylene chloride extracts were washed with saturated ammonium chloride solution, water and dried with anhydrous magnesium sulfate. Removal of solvent provided a golden yellow oil (119 mg.) which was dissolved in dry tetrahydrofuran (10 ml.) and added

to a mixture of lithium aluminium hydride (127 mg.) in dry ether (25 ml.) which was refluxed for half hour before addition. After stirring and refluxing for 2½ hours, excess lithium aluminium hydride was destroyed by addition of water. The reaction mixture was then treated with 2N sodium hydroxide solution, water and filtered. The filtrate was extracted with ether (3x). The combined ether extracts were washed with saturated ammonium chloride solution, water and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow brown oil (72 mg.) which was passed down a column (alumina grade IV) and gave, by elution with 10% ether in pet. ether (30-60°C), a yellow oil (55 mg.).

νm_{max} (CCl_4) 3400, 1075, 1050 cm^{-1}; τ (CCl_4, 100 MHz), 6.22 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 6.52 (t, 2H, $-C\underline{H}_2OH$), 8.58, 8.76 (m, broad s, 26H, $CH_3(C\underline{H}_2)_{13}-$), 8.14 (t, 3H, $C\underline{H}_3(CH_2)_n-$).

Oxidation of 15-pentadecanolide (117; n=14)

Chromium trioxide (7.6 g.) in acetic anhydride (16 ml.) was added dropwise to a cold mixture of 15-hexadecanolide (6 g., 0.025 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). The mixture was stirred at 0-5°C for 3 hours and then at room temperature for 5 days. Usual work-up, as described for 16-hexadecanolide (cf. P.135) provided a yellow oil (3.84 g.) which was shown by g.l.c. (3% SE30) to consist of 15-pentadecanolide (49%), a mixture of oxo-15-pentadecanolides (48%) (unresolved

on g.l.c.) and a mixture of poly-keto-15-pentadecanolides (3%). Column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet. ether (30- 60°C)/ ether,,a mixture of mono-oxo-15-pentadecanolides (118; x+y=13) (1.802gg., 36% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1736, 1716, 1250, 1175 cm^{-1}; τ (CCl_4, 100 MHz), 5.96 (t, 2H, $-COOC\underline{H}_2-$), 7.72 (mixed t, 6H, $-C\underline{H}_2COC\underline{H}_2-$, $-C\underline{H}_2COO-$), 8.40, 8.72 (m, broad s, 18H, $-(C\underline{H}_2)_9-$).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.87; H, 10.24. Found: C, 70.84; H, 10.40.

Cyclododecanone (124)

Jones Reagent (125 ml.) was added dropwise to a solution of cyclododecanol (25 g., 0.14 mole) in acetone (400 ml.). The reaction mixture was stirred for 15 minutes. Excess Jones Reagent was destroyed by adding isopropyl alcohol. The mixture was diluted with water (200 ml.) and extracted with ether (4x). The combined ether extracts were washed with saturated sodium bicarbonate solution (3x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow solid which was crystallized from petroleum ether (30-60°C) to give a white solid (24 g.).

$\nu_{max}(CCl_4)$ 1715 cm^{-1}; τ (CCl_4, 60 MHz), 7.67 (mixed t, 4H, $-C\underline{H}_2COC\underline{H}_2-$), 8.33 (m, 4H, $-C\underline{H}_2CH_2COCH_2C\underline{H}_2-$), 8.73 (s, 14H, $-(C\underline{H}_2)_7-$).

12-dodecanolide (117; n=11)

A solution of cyclododecanone (11.8 g., 0.065 mole) in methylene chloride (80 ml.) was added dropwise to peroxytrifluroacetic acid (78 ml.) at 0°C over a period of 1 hour. The reaction mixture was stirred for 3 hours. Saturated Potassium iodide solution (80 ml.) was added and the mixture was stirred while adding saturated sodium bisulfite solution (75 ml.) until the colour of liberated iodine was discharged. The pale yellow mixture was extracted with methylene chloride (4x). The combined extracts were washed with saturated sodium bicarbonate solution (3x), water (1x) and dried with anhydrous sodium sulfate. Removal of solvent provided a pale yellow oil (14 g.). Vacuum distillation of the pale yellow oil provided a colourless oil (6.8 g., b.p. 61-70°C/0.01-0.03 mm.) which was then chromatographed on alumina (grade IV); 5% ether in pet. ether (30-60°C) eluted the pure 12-dodecanolide (4.9 g.).

ν_{max} (CCl_4) 1725, 1248, 1137 cm^{-1}; τ (CCl_4, 100MHz) 5.92 (t, 2H, -COOC$\underline{H}_2$-), 7.74 (t, 2H, -OOCC$\underline{H}_2$-), 8.36, 8.67 (m, broad s, 18H, -$(CH_2)_9$-).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.72; H, 11.11. Found: C, 72.76; H, 11.00.

Oxidation of 12-dodecanolide (117; n=11)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of 12-dodecanolide (4.8 g., 0.024 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). The mixture was stirred at 0-5°C for 3 hours

and then at room temperature for 5 days. Usual work-up, as described for 16-hexadecanolide (cf. P.135) provided a brown oil (2.57 g.) which was shown by g.l.c. (3% SE30) to consist of 12-dodecanolide (22%), a mixture of oxo-12-dodecanolides (73.8%) (unresolved on g.l.c.) and a mixture of polyketo-12-dodecanolides (4.2%). Column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet. ether (30-60°C)/ether, a mixture of mono-oxo-12-dodecanolides(118; x+y=10) (1.868 g.,40% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1736, 1716, 1238, 1150 cm^{-1}; τ (CCl_4, 100 MHz) 5.93 (t, 2H, $-COOC\underline{H}_2-$), 7.69 (mixed t, 6H, $-C\underline{H}_2COC\underline{H}_2-$, $-C\underline{H}_2COO-$), 8.36, 8.69 (m, m, 12H, $-(C\underline{H}_2)_6-$).

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.60; H, 9.41.

Acetals of oxo-15-pentadecanolides, oxo-12-dodecanolides

The mono-oxidation products from 15-pentadecanolide (118; x+y=13) and 12-dodecanolide (118; x+y=10) were converted to the acetals as described for oxo-16-hexadecanolides.

The I.R. and N.M.R. characteristics of these acetals were similar to those of oxo-16-hexadecanolides acetals.

Acetals of oxo-15-hydroxypentadecanoic acids (119; x+y=13), oxo-12-hydroxydodecanoic acids (119; x+y=10)

The acetals of oxo-15-pentadecanolides and oxo-12-dodecanolides were converted to the acetals of oxo-15-hydroxy-

pentadecanoic acids (119; x+y=13) and oxo-12-hydroxydodecanoic acids (119; x+y=10) as described for acetals of oxo-16-hexadecanolides.

The I.R. and N.M.R. characteristics of these acetals were similar to those of oxo-16-hydroxyhexadecanoic acid acetals (119; x+y=14).

Acetals of keto-pentadecanols (120; x+y=13), keto-dodecanols (120; x+y=10)

The acetals of oxo-15-hydroxypentadecanoic acids (119; x+y=13) and oxo-12-hydroxydodecanoic acids (119; x+y=10) were converted to the acetals of keto-pentadecanols (120; x+y=13) and keto-dodecanols (120; x+y=10) as described for acetals of oxo-16-hydroxyhexadecanoic acids.

The I.R. and N.M.R. characteristics of these acetals were similar to those of keto-hexadecanol acetals (120; x+y=14).

Hydroxy-16-hexadecanolides (122; x+y=14)

Sodium borohydride (16 mg.) in methanol (3 ml.) was added dropwise to a solution of oxo-16-hexadecanolides (118; x+y=14) (394 mg.) in methanol (7 ml.). After stirring at room temperature for 50 minutes, excess sodium borohydride was destroyed by the addition of dilute hydrochloric acid. Usual work-up provided a pale-yellow oil (330 mg.).

$\nu_{max}(CCl_4)$ 3600, 1740 cm^{-1}; $\tau(CCl_4$, 60 MHz) 5.95 (t, 2H, $-COOC\underline{H}_2-$), 6.45 (m, 1H, $-C\underline{H}OH$), 7.75 (t, 2H, $-C\underline{H}_2COO-$), 8.38, 8.65 (m, broad s, 24H, $-(CH_2)_{12}-$).

Mesyloxy-16-hexadecanolides

Mesyl chloride (0.2 ml.) was added dropwise to a solution of hydroxy-16-hexadecanolides (302 mg.) in dry pyridine (0.7 ml.) at 0-5°C under nitrogen. After stirring at room temperature for 2 hours, usual work-up provided a pale yellow oil (326 mg.).

$\nu_{max}(CCl_4)$ 1735, 1350, 1333, 1236, 1175, 910 cm^{-1}; τ (CCl_4, 60 MHz) 5.37 (m, 1H, $-C\underline{H}OMs$), 5.93 (t, 2H, $-COOC\underline{H}_2-$), 7.13 (s, 3H, $-OSO_2C\underline{H}_3$), 7.76 (t, 2H, $-C\underline{H}_2COO-$), 8.36, 8.63 (m, broad s, 24H, $-(C\underline{H}_2)_{12}-$).

16-hexadecenolides (123; a+b=13)

A solution of mesyloxy-16-hexadecanolides (315 mg.) in dry collidine (6 ml.) was heated at 140°C overnight. Usual work-up (cf. P.125) provided a pale yellow oil (191 mg.) which was chromatographed on alumina (grade IV); petroleum ether (30-60°C) eluted the pure 16-hexadecenolides (a colourless oil, 135 mg.).

$\nu_{max}(CCl_4)$ 1735, 1236 cm^{-1}; τ (CCl_4, 60 MHz) 4.67 (m, 2H, $-C\underline{H}=C\underline{H}-$), 5.93 (t, 2H, $-COOC\underline{H}_2-$), 7.83 (m, 6H, $-C\underline{H}_2C=CC\underline{H}_2-$, $-OOCC\underline{H}_2-$), 8.36, 8.63 (m, broad s, 18H, $-(C\underline{H}_2)_9-$); m/e 252 (M^+).

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.19; H, 11.11. Found: C, 76.199; H, 11.20.

Cyclopentadecyl acetate (135)

Acetic anhydride (13 ml.) was added to cyclopentadecanol (10 g.) in pyridine (30 ml.) and the mixture was refluxed overnight. After cooling, the solution was diluted with water and extracted with ether (3x). The combined extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and dried with anhydrous magnesium sulfate. Removal of solvent provided a golden yellow oil which was then vacuum distilled and gave a clear oil (10.9 g., b.p. 109-116°C at 0.01-0.02 mm. Hg).

ν_{max} (CCl_4) 1730, 1240 cm^{-1}; τ (CCl_4, 60 MHz) 5.24 (m, 1H, -C<u>H</u>OAc), 8.10 (s, 3H, -OCOC<u>H</u>$_3$), 8.70 (broad s, 26H, -(C<u>H</u>$_2$)$_{13}$-).

Oxidation of cyclopentadecyl acetate (135)

Chromium trioxide (7 g.) in acetic acid (14 ml.) was added dropwise to a cold mixture of cyclopentadecyl acetate (5 g., 0.019 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). The mixture was stirred at room temperature for 5 days. Water (200 ml.) was then added in and the excess acetic anhydride was removed. The mixture was extracted with ether (6x). The combined extracts were washed successively with saturated sodium bicarbonate solution (4x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow oil (3.2 g.) which was shown by g.l.c.

(3% SE30) to consist of cyclopentadecyl acetate (35%), a mixture of oxo-cyclopentadecyl acetates (54.5%) (unresolved on g.l.c.) and a mixture of poly-oxo-cyclopentadecyl acetates (10.5%). Column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet. ether/ether, a mixture of mono-oxo-cyclopentadecyl acetates (136; x+y=13) (1.73 g., 39.2% based on consumed starting material).

$\nu_{max}(CCl_4)$ 1745, 1720, 1245 cm^{-1}; τ (CCl_4, 100 MHz) 5.27 (m, 1H, -C<u>H</u>OAc), 7.66 (mixed t, 4H, -C<u>H</u>$_2$COC<u>H</u>$_2$-), 8.06, 8.08 (s, 3H, -OCOC<u>H</u>$_3$), 8.42, 8.70 (m, broad s, 22H, -(C<u>H</u>$_2$)$_{11}$-).

Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.34; H, 10.64. Found: C, 72.60; H, 10.63.

<u>Hydroxy-cyclopentadecanones (137; x+y=13)</u>

A mixture of acetoxycyclopentadecanones (690 mg.) and potassium hydroxide (246 mg.) in methanol (20 ml.) was refluxed overnight. Methanol was then removed by distillation. After cooling, the residue was diluted with water and extracted with ether (4x). The combined extracts were washed with 5% hydrochloric acid (3x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a yellow solid (559 mg.).

$\nu_{max}(CCl_4)$ 3600, 1725 cm^{-1}; τ (CCl_4, 100 MHz, D_2O added) 6.44 (m, 1H, -C<u>H</u>OH), 7.65 (mixed t, 4H, -C<u>H</u>$_2$COC<u>H</u>$_2$-), 8.39, 8.70 (m, broad s, 22H, -(C<u>H</u>$_2$)$_{11}$-).

Oxo-cyclopentadecanones (138; x+y=13)

Hydroxy-cyclopentadecanones (300 mg.) were dissolved in acetone (5 ml.). Jones reagent (CrO_3-H_2SO_4-H_2O) (3 ml.) was added dropwise until oxidation was complete. The mixture was diluted with water (25 ml.) and extracted with ether (3x). The combined ether extracts were washed with saturated sodium bicarbonate (2x), water (2x) and dried with anhydrous magnesium sulfate. Removal of solvent provided a pale-yellow solid (254 mg.) which was shown by g.l.c. (20% DEGS, 10% FFAP, 5% OV210) to consist of 4-oxo-cyclopentadecanone (10.28%), 5-oxo-cyclopentadecanone (17.47%) and 8-oxo-cyclopentadecanone (72.25%). Gas chromatography of the mixture over the preparative 20% DEGS column at 200°C gave pure 4-oxo-cyclopentadecanone (white solid) (139), 5-oxo-cyclopentadecanone (white solid) (140) and 8-oxo-cyclopentadecanone (white solid) (141) consecutively.

ν_{max} (CCl_4) 1720 cm^{-1}; τ (CCl_4, 100 MHz) 7.69 (m, 8H, ($-C\underline{H}_2COC\underline{H}_2-)_2$), 8.41 (m, 8H, ($-C\underline{H}_2CH_2COCH_2C\underline{H}_2-)_2$), 8.77 (broad s, 10H, $-(C\underline{H}_2)_5-$); m/e 238 (M^+).

Bis-ethylene acetals of 1,4-cyclopentadecyl-dione (142)

A mixture of 1,4-cyclopentadecyl-dione (19 mg.), dry ethylene glycol (0.1 ml.) and p-toluenesulfonic acid monohydrate (5 mg.) in dry benzene (20 ml.) was refluxed for 10 days and water was removed by Dean-Stark water separator. The resulted mixture was washed with saturated sodium bicarbonate solution (2x), water (1x) and dried with anhydrous magnesium

sulfate. Removal of solvent provided a white solid (26 mg.) which was chromatographed on Woelm silica gel (grade III), 5% ether/pet. ether eluted the pure bis-ethylene acetals of 1,4-cyclopentadecyl-dione (17.6 mg.).

ν_{max} (CCl_4) 1080, 1100 cm^{-1}; τ (CCl_4, 60 MHz) 6.23 (s, 8H, $(-OC\underline{H}_2C\underline{H}_2O-)_2$), 8.47 (s, 8H, $-(C\underline{H}_2)_4-$), 8.63 (broad s, 18H, $-(C\underline{H}_2)_9-$); m/e 326 (M^+).

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.94; H, 10.43. Found: C, 69.48; H, 10.73.

Bis-ethylene acetals of 1,5-cyclopentadecyl-dione (143)

1,5-cyclopentadecyl-dione was converted to the diacetal as described for 1,4-cyclopentadecyl-dione.

ν_{max} (CCl_4) 1080, 1100 cm^{-1}; τ (CCl_4, 60 MHz) 6.20 (s, 8H, $(-OC\underline{H}_2C\underline{H}_2O-)_2$), 8.63 (broad s, 26H, $-(C\underline{H}_2)_{13}-$); m/e 326 ($M^+$).

Bis-ethylene-acetals-of-1,8-cyclopentadecyl-dione (144)

1,8-cyclopentadecyl-dione was converted to the diacetal as described for 1,4-cyclopentadecyl-dione.

ν_{max} (CCl_4) 1090 cm^{-1}; τ (CCl_4, 60 MHz) 6.23 (s, 8H, $(-C\underline{H}_2C\underline{H}_2O-)_2$), 8.60 (broad s, 26H, $-(C\underline{H}_2)_{13}-$); m/e 326 ($M^+$).

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.94; H, 10.43. Found: C, 69.76; H, 10.20.

Cyclotridecanol

Sodium borohydride (3.1 g.) in methanol (25 ml.) was added dropwise to a solution of cyclotridecanone (14.8 g.) in methanol (25 ml.). After stirring at room temperature for 2 hours, excess sodium borohydride was destroyed by the addition of dilute hydrochloric acid and the solution extracted with ether (3x). The combined extracts were washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying with anhydrous magnesium sulfate, removal of solvent provided a white solid (14.85 g.).

ν_{max} (CCl_4) 3400 cm^{-1}; τ (CCl_4, 60 MHz) 6.33 (m, 1H, -C<u>H</u>OH), 8.23 (s, 1H, -CHO<u>H</u>), 8.63 (broad s, 24H, -($C\underline{H}_2)_{12}$-).

Cyclotridecyl acetate (145)

Cyclotridecanol was converted to the acetate as described for cyclopentadecyl acetate.

The I.R. and N.M.R. characteristic of this acetate were similar to those of cyclopentadecyl acetate.

Oxidation of cyclotridecyl acetate (145)

Chromium trioxide (7 g.) in acetic anhydride (14 ml.) was added dropwise to a cold mixture of cyclotridecyl acetate (5 g., 0.021 mole) in glacial acetic acid (20 ml.) and acetic anhydride (9 ml.). After stirring at room temperature for 5 days, usual work-up as described for cyclopentadecyl acetate (cf. P.144) provided a yellow oil (3.27 g.) which was shown by g.l.c. (3% SE30, 20% DEGS) to consist of cyclotridecyl acetate (34%), a

mixture of oxo-cyclotridecyl acetates (66%) (unresolved on g. l.c.) and a very polar mixture. Column chromatography of the mixture over Woelm silica gel (grade III) gave, by elution with pet. ether/ether, a mixture of mono-oxo-cyclotridecyl acetates (146; x+y=11) (1.79 g., 39.7% based on consumed starting material).

ν_{max} (CCl_4) 1745,1720, 1245 cm^{-1}; τ (CCl_4, 100 MHz) 5.28 (m, 1H, -C<u>H</u>OAc), 7.64 (mixed t, 4H, -C<u>H</u>$_2$COC<u>H</u>$_2$-), 8.06, 8.08, 8.12 (s, 3H, -OCOC<u>H</u>$_3$), 8.42, 8.72 (m, broad s, 18H, -(C<u>H</u>$_2$)$_9$-).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.86; H, 10.24. Found: C, 70.72; H, 10.59.

<u>Hydroxy-cyclotridecanones (147; x+y=11)</u>

A mixture of acetoxycyclotridecanones (926 mg.) and potassium hydroxide (375 mg.) in methanol (20 ml.) was refluxed overnight. Usual work-up as described for acetoxy-cyclopentadecanones (cf. P.145) provided a yellow oil (700 mg.) which solidified upon standing.

The I.R. and N.M.R. characteristic of these hydroxy-cyclotridecanones were similar to those of hydroxy-cyclopenta-decanones.

<u>Oxo-cyclotridecanones (148; x+y=11)</u>

Hydroxy-cyclotridecanones (630 mg.) was dissolved in acetone (20 ml.). Jones reagent (CrO_3-H_2SO_4-H_2O) (6 ml.) was added dropwise until oxidation was complete. Usual work-up as

described for hydroxy-cyclopentadecanones (cf. P.146) provided a oily yellow solid (530 mg.) which was shown by g.l.c. (20% DEGS, OV17, 5% OV210) to consist of four isomers. Gas chromatography of the mixture over the preparative 20% DEGS column at 200°C gave the first fraction (white solid) (149) which was a mixture of two isomers (11.9% and 20.5% of the total mixture) and the second fraction (pale-yellow oily solid) (150) which was also a mixture of two isomers (31.37% and 36.17% of the total mixture).

The I.R. and N.M.R. characteristic of these oxo-cyclotridecanones were similar to those of oxo-cyclopentadecanones.

Ethylene acetals of 1,4- and 1,5-cyclotridecyl-dione (151)

The mixture of 1,4- and 1,5-cyclotridecyl-dione was converted to the diacetals as described for 1,4-cyclopentadecyl-dione.

ν_{max} (CCl$_4$) 1090 cm^{-1}; τ (CCl$_4$, 60 MHz) 6.20 (s, 8H, (-OC$\underline{H}_2$C$\underline{H}_2$O-)$_2$), 8.43, 8.50, 8.63 (broad s, 22H, -(C$\underline{H}_2$)$_{11}$-); m/e 298 (M$^+$).

Ethylene acetals of 1,6- and 1,7-cyclotridecyl-dione (152)

The mixture of 1,6- and 1,7-cyclotridecyl-dione was converted to the diacetals as described for 1,4-cyclopentadecyl-dione.

ν_{max} (CCl$_4$) 1100 cm^{-1}; τ (CCl$_4$, 60 MHz) 6.20 (s, 8H (-OC$\underline{H}_2$C$\underline{H}_2$O-)$_2$), 8.53 (broad s, 22H, -(C$\underline{H}_2$)$_{11}$-); m/e 298 (M$^+$).

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