SYNTHESES OF MACROCYCLIC MUSK COMPOUNDS

A N D

ALLIED PRODUCTS

A

THESIS

SUBMITTED TO

THE UNIVERSITY OF POONA

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THE DEGREE OF

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by

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J. M. P. K. Nair
21. 4. 1964

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C O N T E N T S

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I N T R O D U C T I O N

Naturally occurring 'musk' and 'civet' possess a characteristic pleasant aroma termed as the musk odour. Its value had been fully recognised as early as the nineth century, when the Arab writer Masudi rated musk odour among the best perfume-notes. These animal perfumes owe their aroma to the presence of macrocyclic ketones in them.

Due to the limited occurrence of these compounds in nature and due to their high cost, many synthetic substitutes having similar odour have been prepared, though none of them is similar in chemical nature to the macrocyclic musks. Later it was found that some steroidal compounds especially those belonging to the androstan group also possess the same odour; but these compounds are commercially of little value.

In spite of the tremendous developments achieved in the field of 'synthetic musks', these could not effectively substitute the 'natural musks'.

Natural macrocyclic compounds having this particular note are either ketones or lactones. Ketones, which are isolated invariably from animal sources possess an 'animal-like' note which renders them invaluable in synthetic perfumery blends. Lactones are obtained solely from vegetable sources and they have a 'floral musk odour' and are therefore valuable in the blending of floral perfumes.

Occurrence:

Musk, a secretion obtained from the ruminant musk-deer, Moschus moschiferus, and civet, a glandular excretion of civet cat Viverra civetta, are the chief sources of these compounds in nature. Recently[1] the American musk rat Ondatra zibethicus rivalicius also has proved to be a potential source of 'musk'; the macrocyclic compounds present in this being in the form of odourless alcohols which on oxidation yield the corresponding odorous ketones, dihydrocivetone and exaltone.

Many other sources of this odour in animal[2-4] and vegetable[4] kingdom have been detected in recent years; but none of them can be exploited economically.

Chemistry of Macrocyclic Musks:

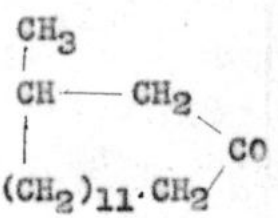
Although these compounds have been known for years, systematic studies to unravel their constitution started only by the beginning of this century. The first major success was the isolation of the odorous component of musk by Walbaum[5] in the form of a ketone, $C_{16}H_{30}O$. This was called muscone. Studies on civet also started at about the same time,[6,7] but only in 1915 its odoriferous component was isolated by Sack.[8] This was called civetone and was found to be a ketone $C_{17}H_{30}O$ different from Walbaum's muscone.

In 1918 Mohr[9] as a result of important deliberations stated that 'Baeyer's strain theory'[10] was not applicable to

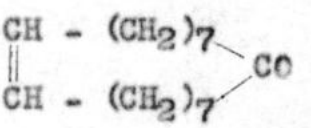
large ring compounds and thus conceived for the first time the possibility of strainless rings.

The presence of large rings in nature was first shown by Ruzicka in 1926 when he established the constitution of civetone[11a] and muscone[11b] as large ring ketones.

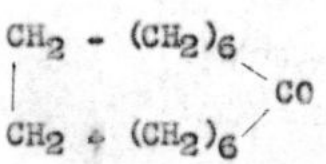
Macrocyclic Musks found in nature



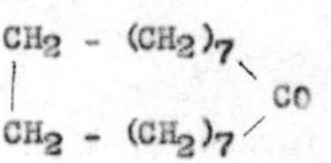
(-) Muscone



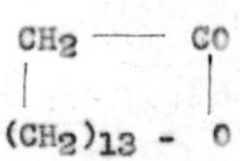
Civetone



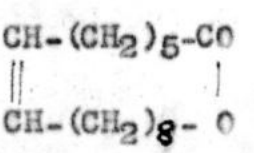
Exaltone



Dihydrocivetone



Exaltolide



Ambrettolide

The oil from the roots of Angelica archangelica officinalis was found to possess a faint musk odour by Ciamician and Silber[12] in 1889, and they isolated a hydroxy pentadecanoic acid from the hydrolysis products of this oil.* Later in 1927 Kerschbaum[13] proved this acid to be identical with 15-hydroxy pentadecanoic acid and synthesised the lactone from 15-bromopentadecanoic acid. In the same year another macrocyclic lactone, ambrettolide was isolated from the oil of musk seed (Hibiscus abelmoschus, Linn.), and its constitution was established by degradation and synthesis.

Chuit's syntheses of dicarboxylic acids[15a] and ω-hydroxy acids[15b] facilitated the research in this field and soon many more members of this group were prepared.

Later developments showed that the musk odour was not confined to ketones and lactones only, eventhough they are far superior to the other groups of this family. The characteristic features of the macrocyclic musk odorants were proved to be a polymethylene ring in which methyl/ene groups can to some extent be substituted by atoms like oxygen, sulphur, nitrogen and groups like imino, and one or more polar groups, preferably the carbonyl groups. The odour was found to be very much dependent on the ring size and was limited to rings having 14 to 18- members.

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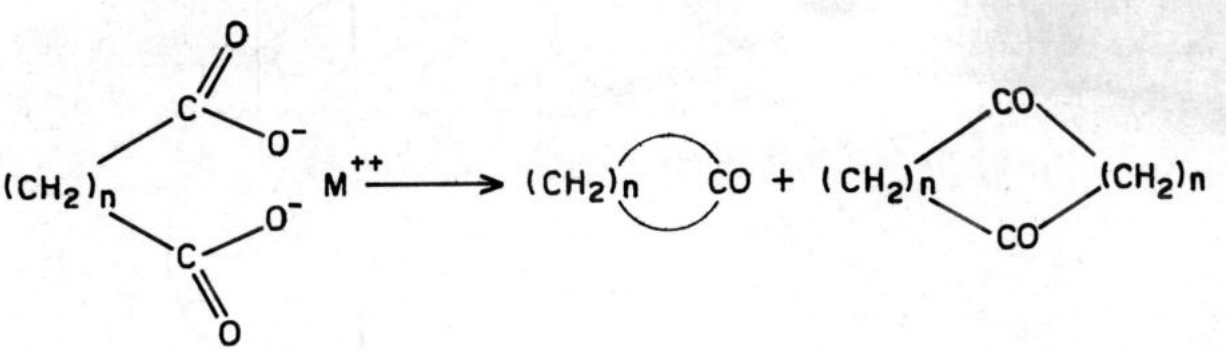
* Recently Carnduff and Eglinton[14] have proved the presence of this lactone in the angelica root oil by gas liquid chromatography.

Development in the synthesis of macrocyclic compounds:

A. Ketones.

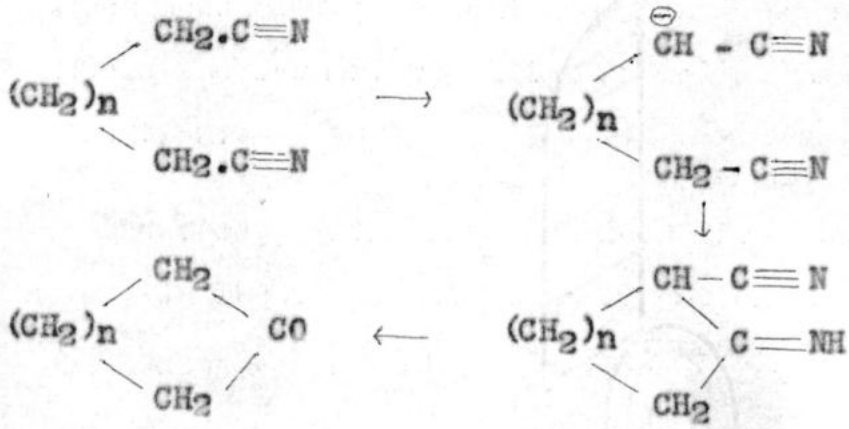
Once the constitution of the macrocyclic musk compounds were established, attempts were made to synthesise them using the known methods of cyclisation. But experience soon showed that methods applicable in the case of small and common rings are of little or no value in the synthesis of medium and large rings. The main difficulty was the tendency of the starting materials to polymerise rather than cyclise. The probability of the two ends of a randomly coiled chain meeting each other decreases with the increasing chain length, and the chances of two molecules meeting each other increases and exceeds the former, resulting in polymerisation in preference to cyclisation.

The first synthesis of macrocyclic ketones[16] was achieved by Ruzicka in 1926. He used a modification of the procedure developed by Zelinsky[17] and Willstätter[18] in which the salt of a dicarboxylic acid with a bivalent metal was pyrolysed to yield the ketone.



The cyclisation resulted by the proximity of the two ends of the chain in certain salt structures. This method however, gave very poor yields with medium and large rings, the maximum yield obtained being 5%.

Ruggli[19] in 1912 found that the polymerisation can be checked and internal cyclisation can be promoted by using high dilution. But this method was not applied to the synthesise of macrocyclic compounds until Ziegler[20] twenty years later used Thorpe's reaction under high dilution conditions to prepare macrocyclic ketones.



Success of this method is due to the choice of the reaction that can be carried out in homogenous medium under high dilution conditions. The rate of the intramolecular cyclisation is dependent only on the carbanion concentration, whereas the bimolecular polymerisation reaction is dependent on the concentration of the dinitrile as well.

The rate of cyclisation $= Kc \times (R.\overset{\ominus}{C}H\text{-}CN)$

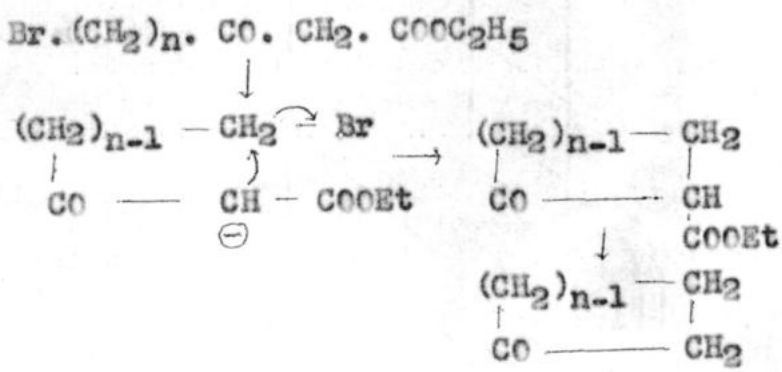
The rate of polymerisation: $= Kp \times (R\overset{\ominus}{C}HCN)\ (RCH_2CN)$

$$\frac{\text{Rate of cyclisation}}{\text{Rate of polymerisation}} = \frac{Kc}{Kp\ (RCH_2CN)} \times \frac{1}{} = \frac{Kr}{(RCH_2CN)}$$

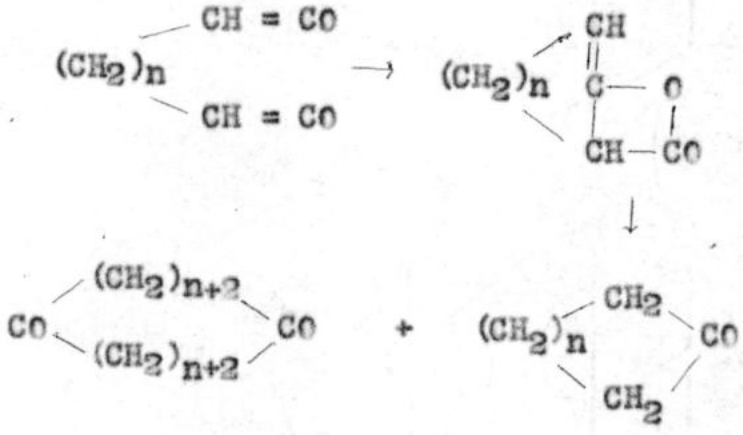
Where Kc is the reaction constant of cyclisation and Kp that of polymerisation.

Lower the concentration of the dinitrile higher will be the yield of the monomeric product. This method gave excellent yields for cyclo-octanone and cyclononanone; fairly good yields for large rings and poor yields with rings containing ten to thirteen carbon atoms.

In 1942, Hunsdiecker[21] employed the 'high dilution principle' successfully to the cyclisation of the esters of ω-bromo-3-oxo-acids to get macrocyclic β-keto esters which could be converted to the corresponding ketones[22]. This method also gave good yields when applied for the synthesis of the larger ring ketones.



Blomquist[23] employed ∝,ω-diketenes for the synthesis of macrocyclic ketones.

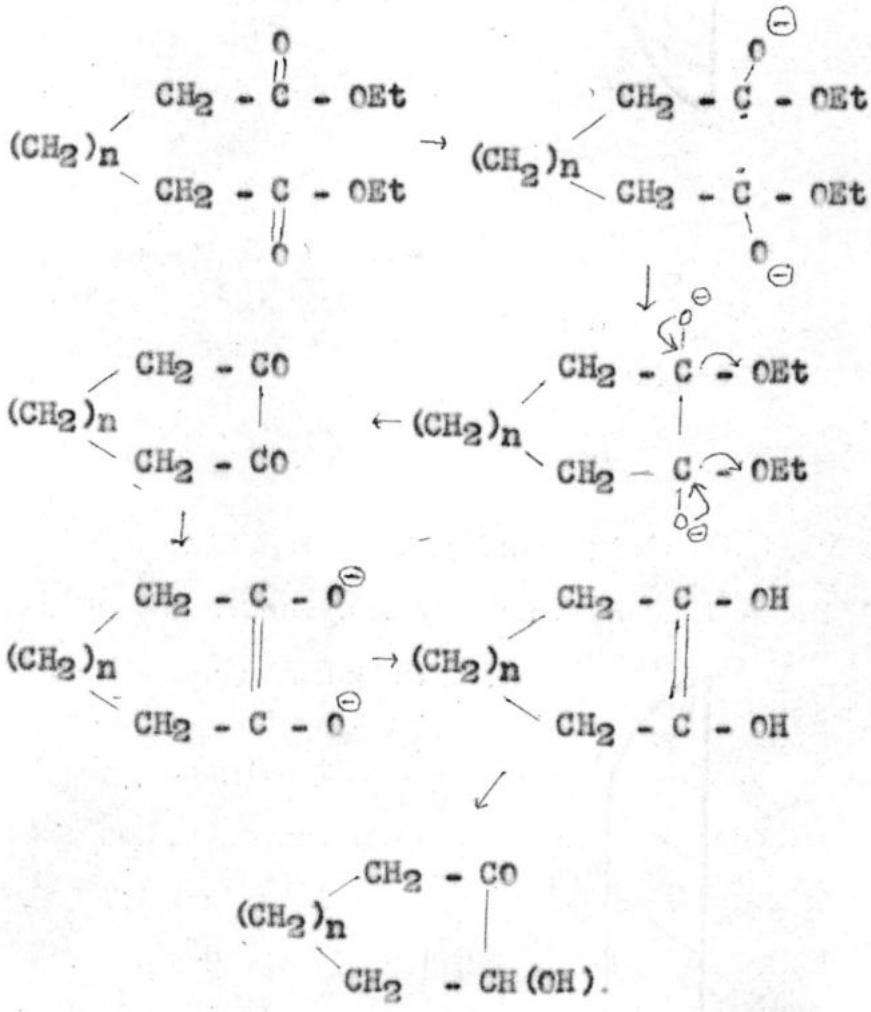


This method furnished yields better than that of Ruzicka's method but inferior to that of Ziegler's and Hunsdiecker's methods.

Despite the success of the high dilution technique, a dramatic improvement was achieved by the macrocyclic acyloin condensation developed independently by Prelog[24] and Stoll[25], in which they applied Hansley's[26] cyclic acyloin reaction with surprisingly good results.

The two electrophilic carbon atoms at the ends of the chain of the diester are first absorbed at the electron-covered surface of molten sodium. So far as chain-flexibility allows, the electrophilic residues can slide over the metal surface to approach each other. The energy required for this process is less than that required for splitting the molecule off the surface; the collis ions of absorbed molecules with

other molecules lead to the close proximity of the two terminal carbon atoms, and finally to the ring closure.



This method proved to be extremely useful in the synthesis of medium and large ring compounds. Yields were excellent, the minimum being 50% for cyclodecanone. Larger ring acyloins were obtained in a yield of about 80%. This reaction did not require high dilution conditions and afforded the cyclic ketone containing the same number of carbon atoms

as the starting dicarboxylic acid, which no other hitherto known method was able to furnish. Further, by this method even 2-substituted dicarboxylic esters could be cyclised, which was not possible by Ruzicka's method.

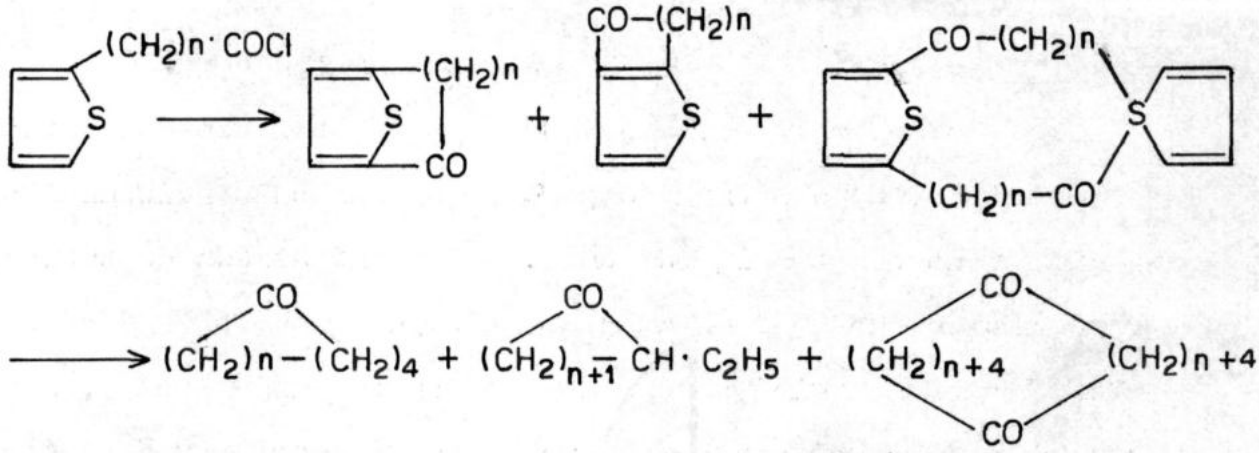
Many procedures have been described for the conversion of these ketols to ketones. Reduction of the acyloin with zinc and acid[27] has been used by several workers to obtain the ketone, but the yields are only fair due to the accompanying Clemmenson reduction of the carbonyl group. Metalamine reductions of the acyloin[28] and acyloin acetate[29] have also been used for the conversion of the former to the corresponding ketone. Acyloins or their acetates on treatment with 1,3-propane dithiol, hydrogen chloride and zinc chloride in benzene[30] yield mercaptals which can be hydrolysed to the ketones.

Several other approaches have been reported, since this procedure has been developed, but acyloin condensation still retains its place of eminence in the cyclisation reactions.

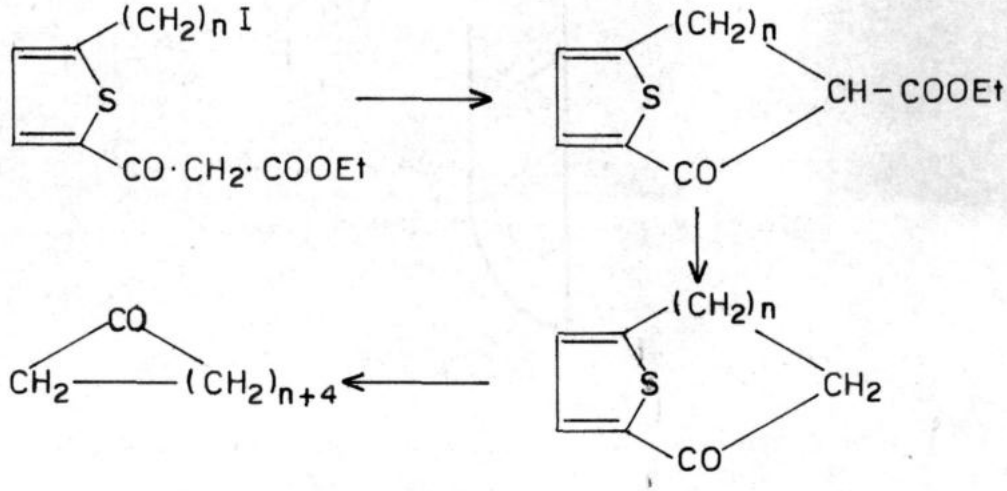
Dieckmann's cyclisation[31] of diesters had been known for years, but only recently in 1958 it was employed for the synthesis of macrocyclic ketones by Leonard and Schimelpfenig.[32]

This method gave fairly good yields for large ring ketones but was not of much significance in the synthesis of medium rings.

In 1956, Gol'dfarb[33] prepared macrocyclic thienyl ketones by the cyclisation of ω-thienyl long chain acid chlorides. These compounds on reductive desulphurisation[34] afforded macrocyclic ketones.



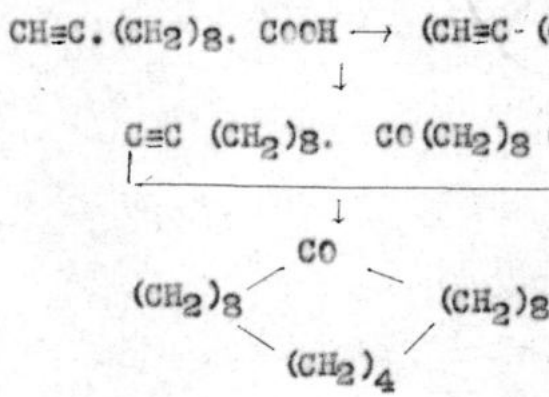
Later another method was developed by Gol'dfarb[35] to prepare the thienyl macrocyclic ketone. In this method 2-(ω-iodoalkyl)5-(carbethoxy acetyl) thiophenes were cyclised in presence of solid potassium. By this method pure 2,2'-thienyl macrocyclic ketones could be obtained which was not possible in the earlier method.



Eglinton and Galbraith[36] found that the intramolecular coupling of large chain α,ω-diynes lead to the formation of large rings.

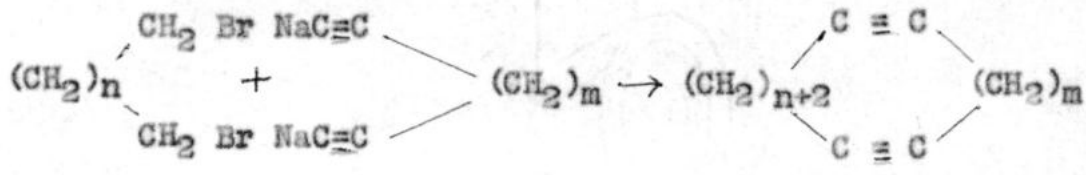
Bergel'son[37] and Carnduff[14] employed this method to prepare macrocyclic lactones.

Bergel'son[38] prepared macrocyclic ketones from ω-acetylenic acids by ketene dimerisation followed by intramolecular oxidative coupling at high dilution.

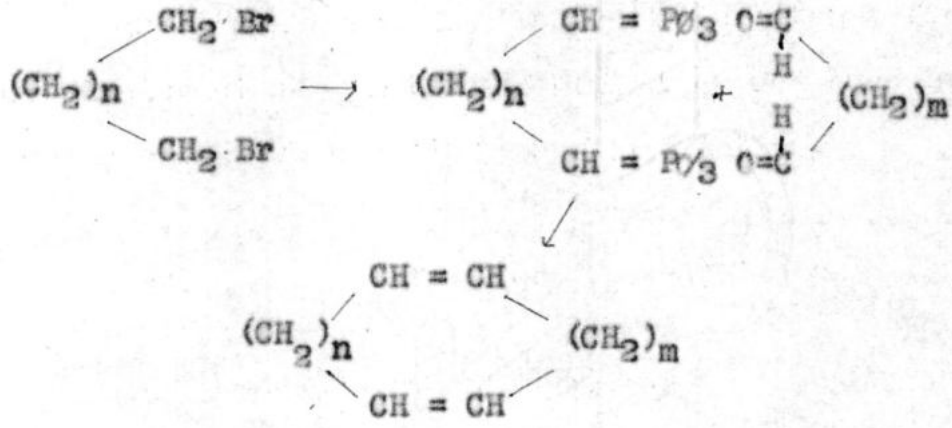


Sondheimer[39] showed that cyclic dimers, trimers, and polymers could be obtained by the oxidative coupling of α,ω-diynes.

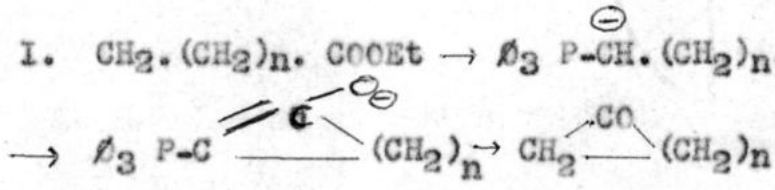
Dale[40] employed Gillman's method[41] successfully in the synthesis of macrocyclic compounds by condensing sodio derivatives of terminal diynes with α,ω-dibromides.



Wittig's reaction[42] has served as a useful tool in the synthesis of many organic molecules. Wittig[43] in 1958 condensed bifunctional phosphorylenes with dialdehydes to get large ring compounds.

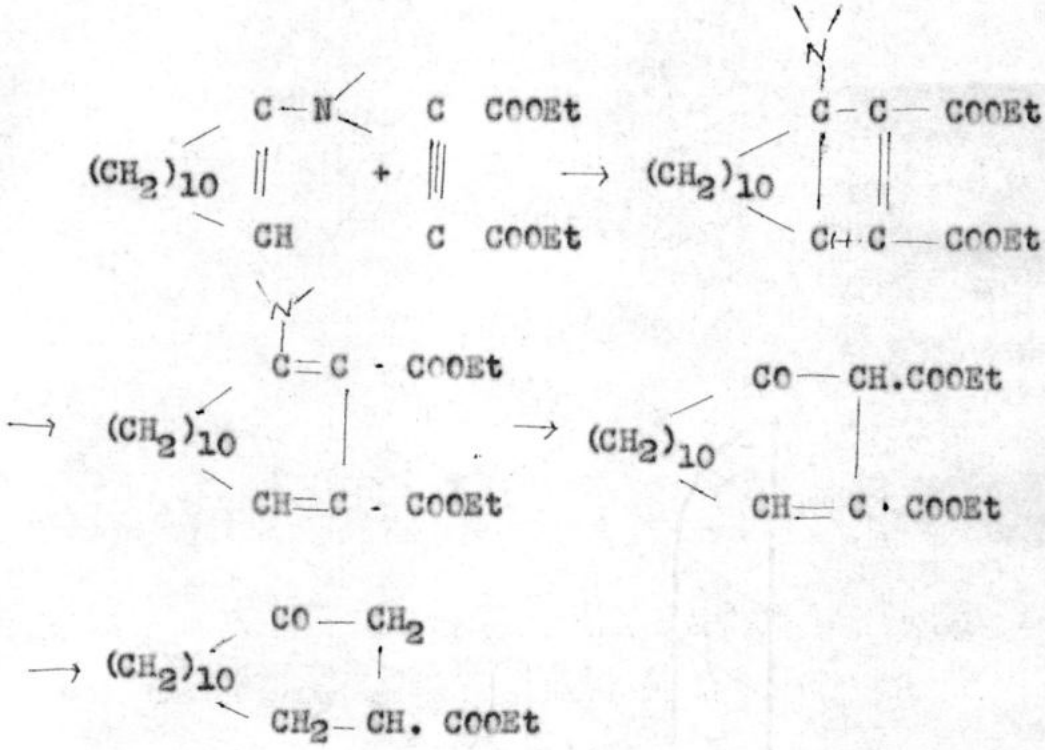


Babad and House[44] have recently employed Wittig's reaction for the preparation of cyclic ketones.



Apart from these cyclisation reactions ring expansion[45,46] also has been employed in the synthesis of macrocyclic ketones, though with little success. But the method developed recently by Berchtold[47] and Brannock[48] is of great value since it affords an increment of two carbon atoms in the ring and is not accompanied by any side

reaction giving rise to undesirable products. The method consists in the condensation of a cyclic ketone, as its enamine with cyclic secondary amines, with acetylene dicarboxylic ester.



B. Lactones

Ruzicka[49] employed Baeyer-Villiger oxidation[50] of ketones with peracids to get macrocyclic lactones. Since the ketones, themselves are very difficultly obtained this method is not of much practical value.

Kerschbaum[51] employed the internal esterification of ω-hydroxy acids for the synthesis of large ring lactones.

Stoll and Rouve[53] conducted the cyclisation at high dilution in benzene in presence of p-toluene sulphonic acid.

Kerschbaum used ω-bromo acids as their silver salts for lactone synthesis. Stoll found that better results were obtained by using potassium salts rather than silver salts.[54] This reaction was further improved by Hunsdiecker[55] by heating ω-bromo acids in presence of an excess of potassium carbonate.

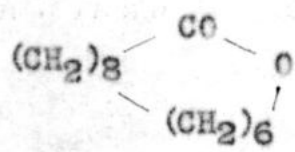
But the most fruitful method developed is the one reported by Carothers[56] in 1935. He polymerised the hydroxy acids by heating and then depolymerised them to the monomeric lactones by heating in vacuum in the presence of a catalyst. The simplicity of the technique along with high yield makes this reaction the best suitable one for the synthesis of macrocyclic lactones. Another advantage of this technique is that it does not require high dilution.

Collaud[57] in 1942 esterified ω-hydroxy acids with glycerine and then trans-esterified to get the lactones.

Beets and Van Essen[58] used thermally polymerised molecules as the basis of depolymerisation in presence of a catalyst, with glycerine as the carrier for the cyclic monomer.

Macrocyclic lactones have also been prepared by the intramolecular oxidative coupling of esters of terminal acetylenic acids and alcohols.[14,31]

$CH{\equiv}C.\ (CH_2)_8.\ COO.(CH_2)_2.\ C \equiv CH.$



Raw materials suitable for cyclisation:

With the advent of the acyloin condensation and Carother's method, for the preparation of macrocyclic ketones and lactones respectively, the problem in the synthesis of these compounds has narrowed down to the development of practical methods for the preparation of suitable α,ω-dicarboxylic acids and ω-hydroxy acids.

These compounds can be prepared either by degradation and simple modifications of naturally occurring acids or by chain lengthening. Thus, methods have been developed for the synthesis of α,ω-dicarboxylic acids and ω-hydroxy acids from ustilagic acid[59] and in our laboratory[60] from erucic acid, kamlolenic acid, nervonic acid and aleuritic acid. Juniperic acid is another compound which has been used in the synthesis of many macrocyclic compounds. A number of chain extension processes have been employed for the syntheses of these bifunctional acids. These methods are enumerated in some excellent reviews published recently.[61]

In the present investigation, undecylenic acid, oleic acid and aleuritic acid have been employed for the

synthesis of macrocyclic musks and chain extension has been achieved by Grignard reactions,[62a] enamine condensations[62b] and aldol condensation. ±-3-Methyl cyclopentadecanone (muscone), cyclopentadecanone (exaltone), cyclohexadecanone, cyclopentadecanolide (exaltolide), cyclohexadecanolide (dihydroambrettolide) and the intermediates, 4-methyl-6-oxo-pentadecanedioic acid, pentadecanedioic acid, hexadecanedioic acid (thapsic acid), 15-hydroxy pentadecanoic acid and 16-hydroxy hexadecanoic acid (Juniperic acid) have been prepared by these procedures.

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C H A P T E R I

A NOVEL SYNTHESIS OF (±) MUSCONE

ABSTRACT

A novel synthesis of optically inactive muscone (3-methyl cyclopentadecanone) is described.

4-Methyl cyclohexanone on condensation with 9-aldehydo-nonoic ester followed by the dehydration of the resultant aldol condensation product furnished 9-(2-methyl-5-oxo-cyclohexylidenyl) nonoic ester. This compound was hydrogenated and was converted to 4-methyl-6-oxo-pentadeca-nedioic acid by the oxidative or nitrosative cleavage of the ring. The keto-acid so obtained was esterified and its ethylene ketal derivative was cyclised to the acyloin which was converted to (±) muscone, through the intermediates of the corresponding diol, bromo-acetoxy derivative and the unsaturated ketone, namely, 3-methyl cyclopentadec-6-enone (muscenone).

Synthesis of (±) Muscone

Occurrence:

Musk is a secretion of the male musk-deer, Moschus moschiferus, which forms in a gland under the abdomen and serves to attract the female during the mating season. This deer-like ruminant lives alone, never in pairs or herds, in the Tibetan Himalayas and the high mountains of Mangolia, India and Indo-China. The strong odour with which the male deer is provided is essential for the preservation of the species.

To obtain musk, the deer is killed and pods are cut off and dried. Musk-content of the gland is appreciable only during the rutting period and is very much dependent on the age of the animal.[1] Since the male musk-deer is not recognizably different from the female at a distance, many females are also killed during the hunting. This killing of the animals especially during the mating season, may lead in the near future, to the extermination of the species, as is already indicated by the decreasing amount of musk-pods marketed from year to year inspite of the ever-increasing demand.[2] It is therefore imperative that some commercially feasible methods should be developed for the synthesis of the essential constituent of this costly perfume, namely muscone.

Natural musk contains[3] ammonia, olein, cholestine, fat, wax, gelatinous and albuminous materials, leaves and

inorganic salts along with muscone, which constitutes only 0.5 to 2.0% of the musk pod. Muscone is the only macrocyclic compound present in 'musk' and it does not contain any muscol, its reduction product. In this respect it differs from the other naturally occurring macrocyclic ketones which are generally associated with the corresponding alcohols. The biogenesis of muscone from stearic acid[4] suggested by Stevens explains this behaviour.

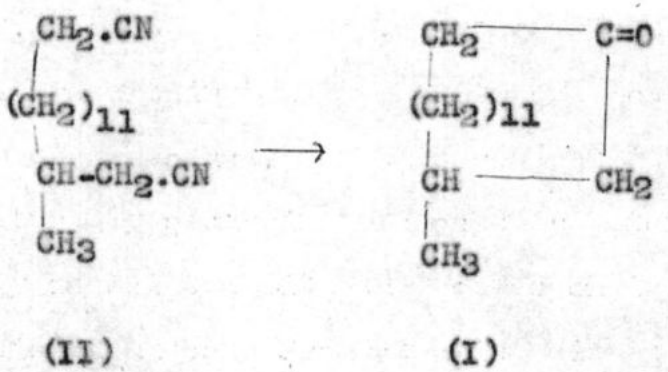
Isolation:

Muscone, $C_{16}H_{30}O$, was first isolated[5] in the form of a liquid from the volatile fraction of musk by Walbaum in 1906. He oxidised it with chromic acid to an acid $C_{16}H_{30}O_4$. Ruzicka[6,7] established the identity of this acid and proved muscone to be 3-methyl cyclopentadecanone. He found this compound to be laevo-rotatory.

Earlier syntheses

Ruzicka's[8] attempts to synthesise muscone from 3-methyl hexadecanedioic acid by the pyrolysis of its salts failed, because α- and β- alkyl dicarboxylic acids could not be cyclised to ketones by this method due to steric hindrance. The first synthesis of (±) muscone was achieved by Ziegler[9] in 1934. In this procedure 2-methyl-1,14-dicyano tetradecane (II) was cyclised[10] using Thorpe's reaction[11] at high dilution to obtain muscone (I).

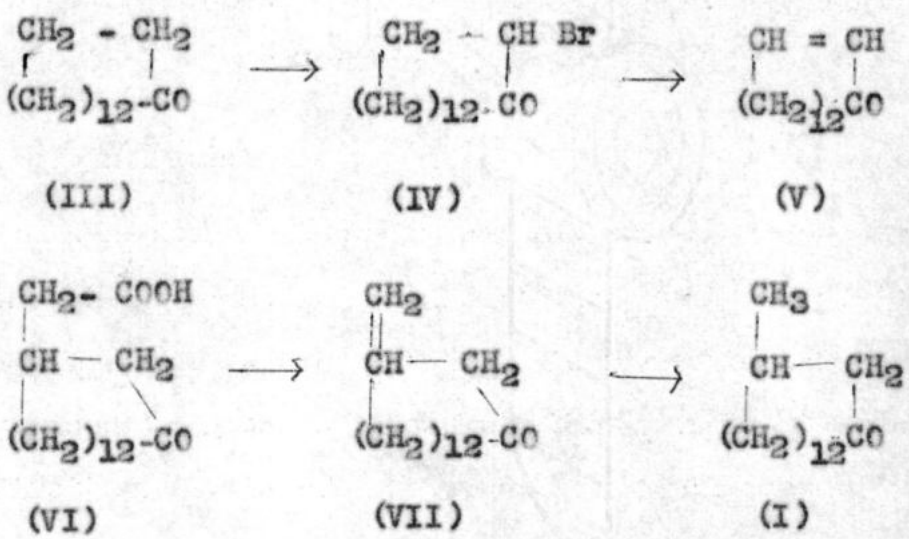
Scheme I



(II) (I)

Later in the same year, Ruzicka[12] converted exaltone (III) to muscone by a series of reactions.

Scheme II



(III) (IV) (V)

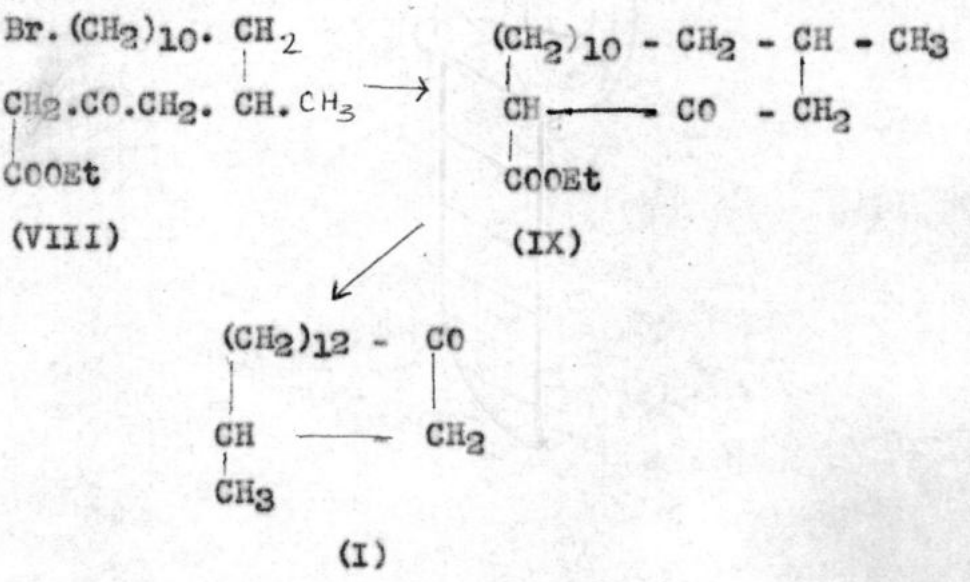
(VI) (VII) (I)

Exaltone (III) was α-brominated and dehydrobrominated to get cyclopentadec-2-enone (V) which on Michael condensation with malonic ester followed by

hydrolysis and decarboxylation yielded 3-oxo-cyclopentadecyl acetic acid (VI). This acid was converted by electrolysis and hydrogenation to muscone.

Hunsdiecker[13] used the ethyl ester of 3-oxo-5-methyl, 16-bromo-hexadecanoic acid (VIII) for the synthesis of muscone. Base-catalysed internal alkylation[14] of this ester gave the β-keto ester (IX) which was decarboxylated to obtain muscone.

Scheme III



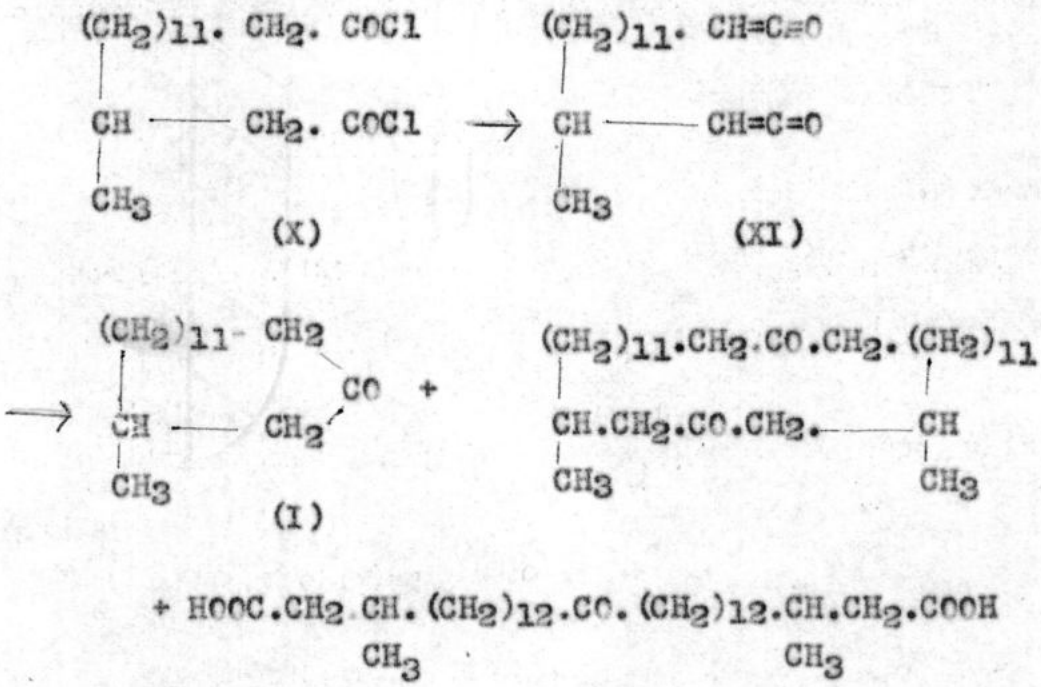
Stoll and Commarmont[15] converted cyclopentadec-1-one-2-ol by dehydration to cyclopentadec-2-enone (V); 1:4-addition of methyl magnesium bromide with this unsaturated ketone in presence of cupric salts afforded muscone in poor yields.

Stoll[16] prepared a mixture of methyl cyclopentadecanones by the acyloin condensation of 3-methyl pentadecanedioic

ester and subsequent reduction of the cyclic acyloins thus obtained.

Blomquist[17] prepared muscone from the diketene (XI) obtained from 3-methyl hexadecanedioyl chloride (X).

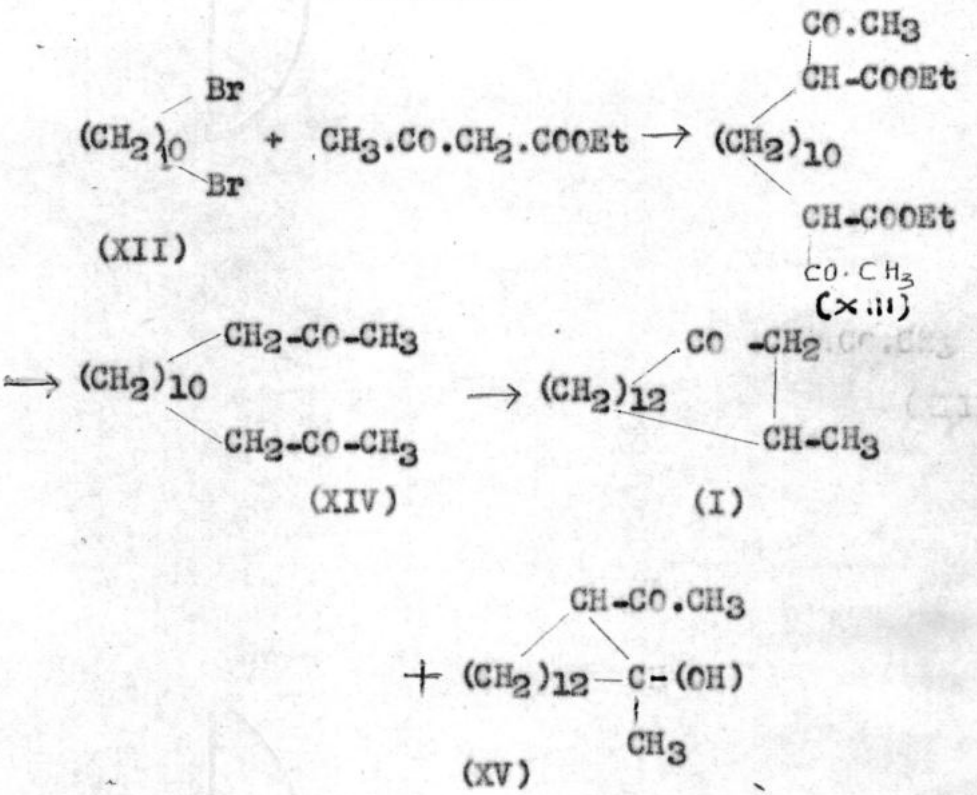
Scheme IV



+ $HOOC.CH_2.CH.(CH_2)_{12}.CO.(CH_2)_{12}.CH.CH_2.COOH$
CH_3 CH_3

But the most elegant method yet, was developed by Stoll and Rouve'[18] in which 2,15-dioxo-hexadecane (XV) was converted by intramolecular aldol condensation to muscone.

Scheme V



Merits and demerits of earlier methods

Methods reported by Ruzicka and Stoll starting from cyclic compounds, apart from their academic interest, are of limited practical significance, due to the difficulty of getting the starting compounds. The processes developed by Hunsdiecker, Ziegler and Blomquist suffer from low yields which make them unsuitable for commercial exploitation. Although it is considered to be the best among the available procedures, the intramolecular aldol condensation of the β-β'-dioxo hexadecane gives only 7% overall yield on the starting compound, namely ∝,ω-dibromodecane. Further an undesirable side product (XV) is formed during the reaction, the removal of which is possible only at the cost of the muscone formed.

Present Synthesis of Muscone

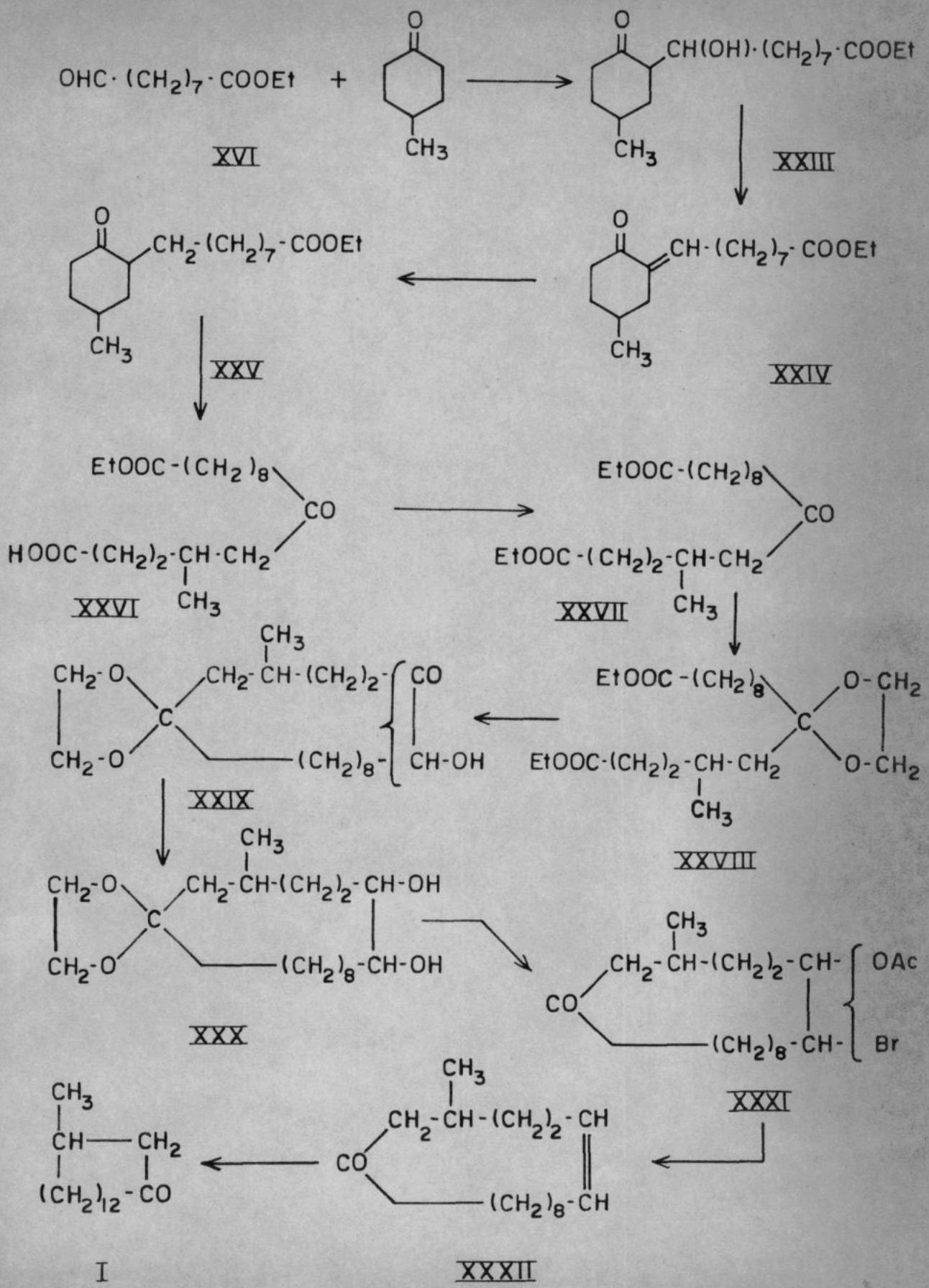
The main handicap in muscone synthesis had been the apparent uselessness of cyclic acyloin reaction. In the present investigation this hurdle has been conveniently overcome by introducing the keto group in β-position to the methyl group in the dicarboxylic acid chain before cyclisation. This diethyl 4-methyl-6-oxo-pentadecanedioate was cyclised as its ketal. The resultant acyloin could easily be converted to muscone[19] (I).

Many methods[20] have been reported for the synthesis of long chain aliphatic compounds by chain extension, but one of the most practicable procedures consists in attaching an alicyclic fragment to an aliphatic chain followed by the opening of the ring to form a part of the chain. This process was adopted in the present synthesis using 4-methyl cyclohexanone and methyl or ethyl esters of 9-aldehydononoic acid as the starting materials.

p-Cresol by hydrogenation in presence of Raney nickel catalyst in alkaline medium[21] could be conveniently converted to 4-methyl cyclohexanone.

Ethyl 9-aldehyde nonoate (XVI) was prepared from ethyl oleate (XVII). Ethyl oleate on hydroxylation with peracetic acid[22] followed by hydrolysis and esterification afforded ethyl 9,10-dihydroxy stearic acid (XVIII), which was oxidised[23] with a neutral solution of sodium metaperiodate

SCHEME VI


OHC·(CH2)7·COOEt
XVI
CH(OH)·(CH2)7·COOEt
XXIII
CH2·(CH2)7·COOEt
XXV
CH·(CH2)7·COOEt
XXIV
EtOOC·(CH2)8
HOOC·(CH2)2·CH·CH2
XXVI
EtOOC·(CH2)2·CH·CH2
XXVII
CH2·O
CH2·CH·(CH2)2
(CH2)8
CO
CH·OH
XXIX
EtOOC·(CH2)8
O·CH2
EtOOC·(CH2)2·CH·CH2
XXVIII
CH2·CH·(CH2)2·CH·OH
(CH2)8·CH·OH
XXX
CH2·CH·(CH2)2·CH·
OAc
Br
XXXI
CH2·CH·(CH2)2·CH
XXXII
CH·CH2
(CH2)12·CO
I

in ethanol medium to obtain ethyl-9-aldehydononoate in high yields; pelargonic aldehyde (XIX), valuable as a perfumery material was a byproduct in this reaction.

Scheme VII

$$\underset{\text{(XVII)}}{CH - (CH_2)_7.COOEt \;\|\; CH - (CH_2)_7.CH_3} \longrightarrow \underset{\text{(XVIII)}}{CH(OH).(CH_2)_7.COOEt \;|\; CH(OH).(CH_2)_7.CH_3}$$

$$\longrightarrow \underset{\text{(XIX)}}{CH_3(CH_2)_7.CHO} + \underset{\text{(XVI)}}{EtOOC.(CH_2)_7.CHO}$$

Methyl 9-aldehydononoate (XXII) was prepared by the rupturing of the methyl ester of aleuritic acid (XX) with neutral sodium metaperiodate. Aleuritic acid is an easily available raw material and constitutes about 30% of Indian shellac.

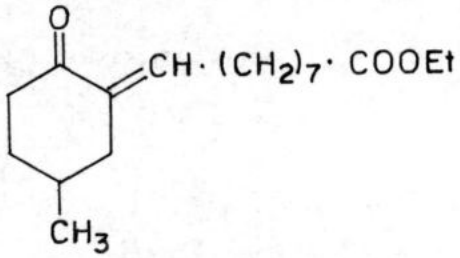
$$HO.CH_2.(CH_2)_5.CH(OH).CH.(OH).(CH_2)_7.COOMe$$

$$\text{(XX)} \downarrow$$

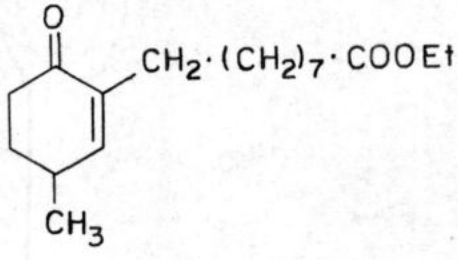
$$\underset{\text{(XXI)}}{HO.CH_2.(CH_2)_5.CHO} + \underset{\text{(XXII)}}{OHC.(CH_2)_7.COOMe}$$

This oxidation was carried out in methanol to avoid any possibility of trans-esterification. However, due to the closer boiling points of the two aldehydes, as compared to the aldehydes obtained from dihydroxy stearic ester, the yield of the desired aldehyde was somewhat poorer.

4-Methyl cyclohexanone was subsequently condensed with ethyl 9-aldehydo nonoate (XVI) in the presence of sodium hydroxide[24] in alcoholic medium at -10°. The catalytic amounts of the alkali employed did not hydrolyse the ester group as was ascertained by testing the solution after the reaction. The aldehyde showed a tendency to attack both the α-carbon atoms of the ketone. By using a large molar ratio of the cyclic ketone, this could be minimised; this excess also served to check the self condensation of the aldehydo ester. On the removal of the unreacted aldehyde and ketone by distillation, a residue was obtained consisting mainly of 9-hydroxy-9-(2-oxo-5-methyl-cyclohexyl) nonoate (XXIII). This could not be purified by distillation due to its tendency towards dehydration. This hydroxy ester (XXIII) was dehydrated at elevated temperature and reduced pressure by potassium bisulphate and the product of dehydration distilled out. This was found to be ethyl 9-(2-oxo-5-methyl cyclohexylidenyl) nonoate (XXIV) and not the cyclohexenyl compound (XXXIII) from an examination of its spectrum, though there was every possibility of the isomerisation of (XXIV) to the stabler ketone (XXXIII), under the acidic conditions employed for dehydration.

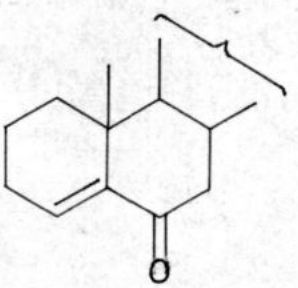


XXIV



XXXIII

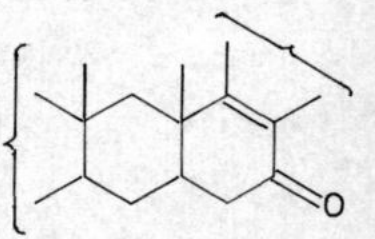
This distillate gave a UV absorption maximum at λ_{244} mμ (ε 5860). Absorption due to the compound (XXIV) containing the exocyclic double bond would conform more to this wavelength than that of the cyclohexenyl isomer (XXXIII), containing the endocyclic unsaturation. The low extinction coefficient 5860 is also indicative of the 'cisoid' enone system (XXIV); the 'transoid' compound (XXXIII) is expected to give $\varepsilon_{max.} > 10^4$ For example the steroidal ketone (XXXIV) having the 'cisoid enone' system shows $\varepsilon_{max.} = 6300$, whereas the transoid enone (XXXV) gives absorption at λ_{max} 253 mμ, ($\varepsilon_{max.}$ 11200^{25}).



XXXIV

$\lambda_{max.}$ 244 mμ

$\epsilon_{max.}$ 6300



XXXV

$\lambda_{max.}$ 253 mμ

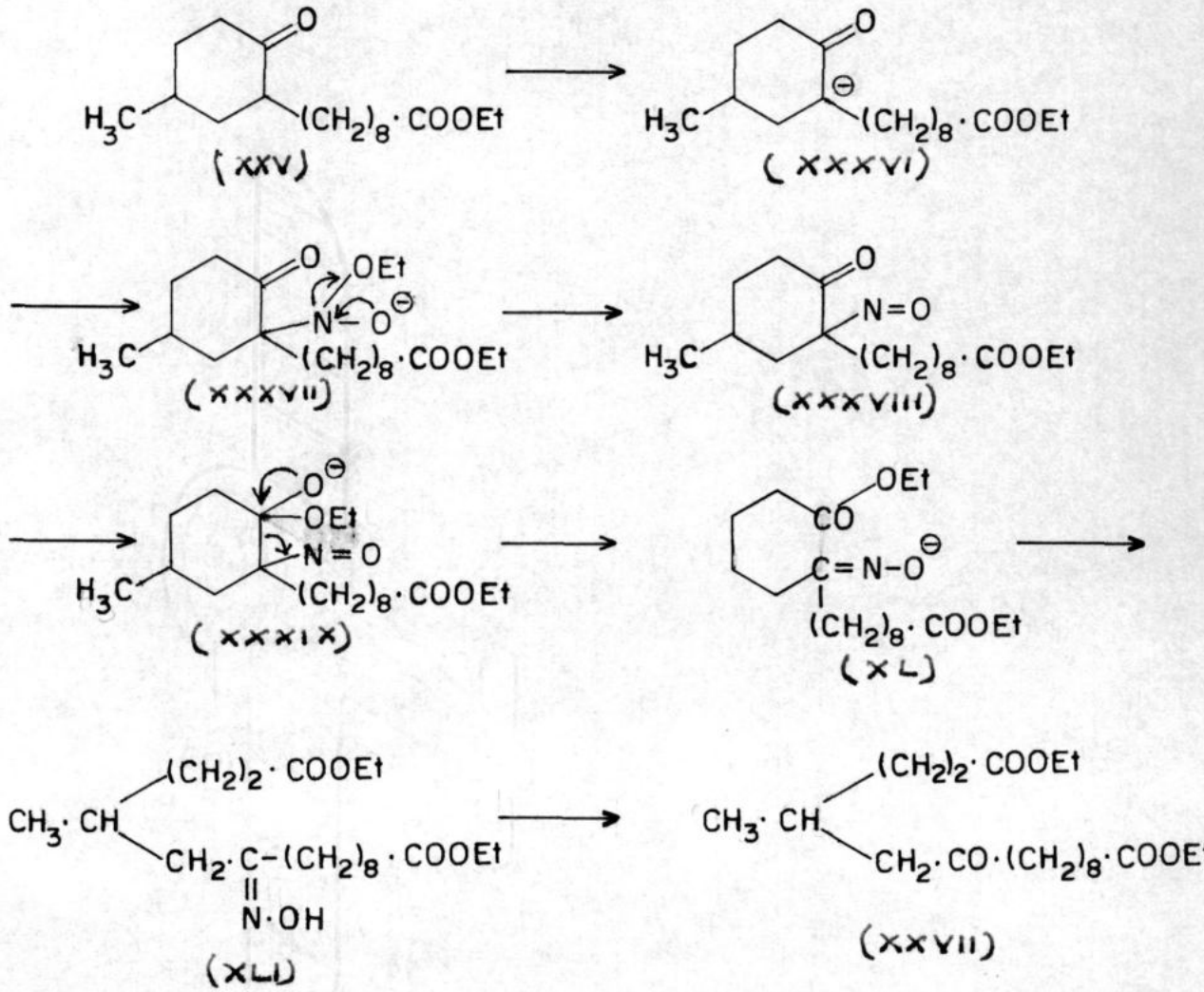
$\epsilon_{max.}$ 11200

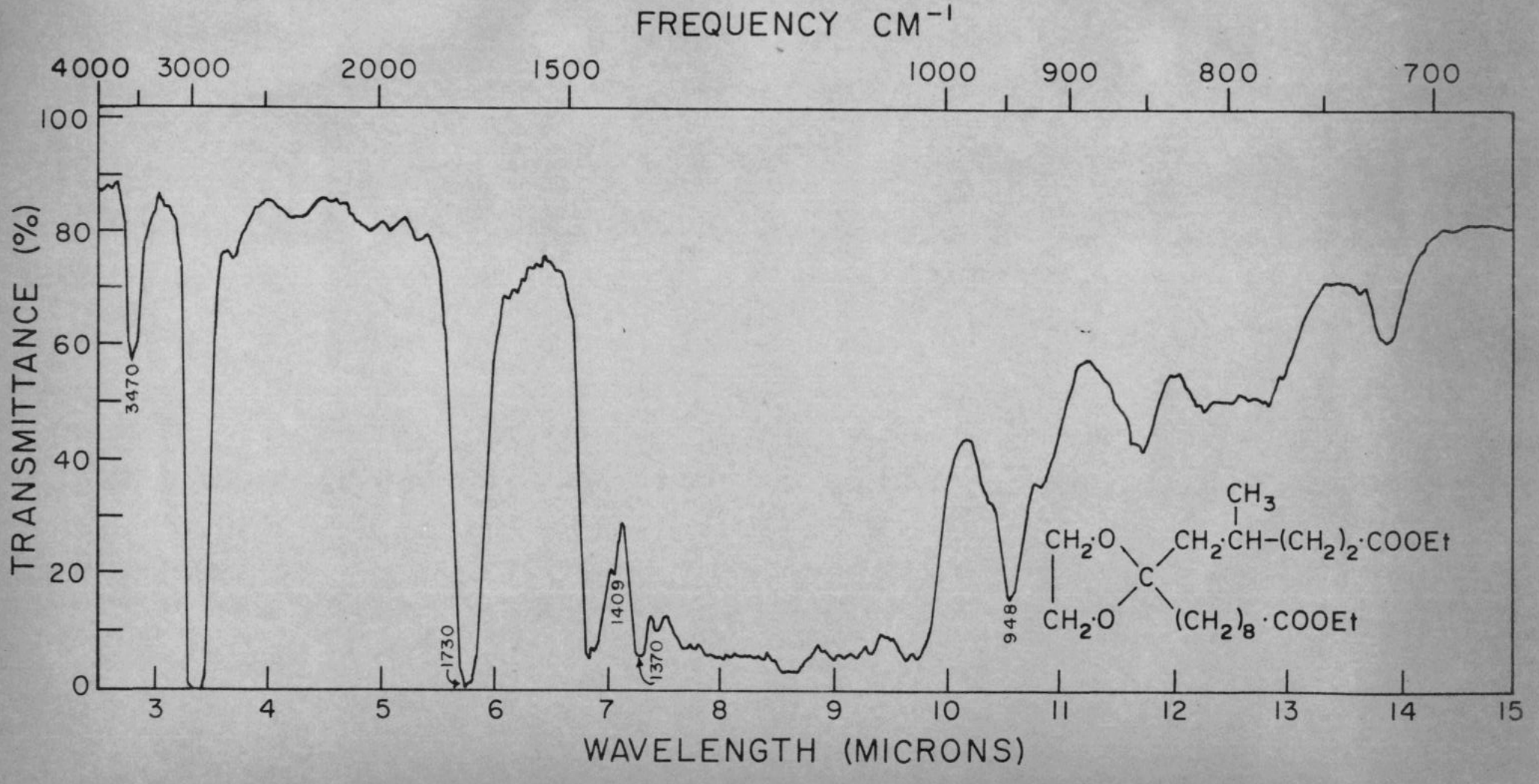
This unsaturated keto-ester (XXIV) was hydrogenated in presence of palladised charcoal to yield ethyl-9-(2-methyl-5-oxo-cyclohexyl) nonoate (XXV).

The ring cleavage of (XXV) was achieved by two methods. In the first, this keto-ester dissolved in acetic acid was oxidised with an 8N solution of chromium trioxide in 8N sulphuric acid (Jones reagent).[26] This method gave a

yield of 80% of the mono-ester of 4-methyl 6-oxo-pentadecane-dioic acid (XXVI), contaminated by traces of azelaic monoester. This was detected by thin layer chromatography, and was removed by esterification followed by fractionation.

In the second method, the ring opening was carried out by nitrosation using ethyl nitrite and sodium ethoxide.[27] The oximino diester (XLI) formed through the intermediate compound (XXXVIII) gave on acid hydrolysis the keto-diester (XXVII). This method gave pure ketodiester, since no side-product could be formed due to the exclusive cleavage at the more substituted α carbon atom.[28] Further the diethyl ester





DIETHYL-4-METHYL-6-ETHYLENE KETAL-PENTADECANE-DIOATE (XXVIII)

was obtained directly, saving the esterification step. However, the yield of the diester was lower than that obtained by the oxidation method.

This ketodiester was converted to the ethylene ketal (XXVIII); ketal formation was accompanied by the expected increase in weight and disappearance of the corresponding carbonyl absorption bands in the infrared and ultraviolet region.

The ketal (XXVIII) gave the acyloin (XXIX) on treating with well-dispersed sodium in boiling xylene.[29] The acyloin on reduction with lithium aluminium hydride yielded the diol (XXX).

This diol was converted to the bromo acetoxy derivative by heating with hydrogen bromide in glacial acetic acid. The latter on debromoacetoxylation furnished muscenone (3-methyl cyclopentadec-6-enone) (XXXII)

The intermediates from (XXVIII) to (XXXI) could not be distilled without decomposition. But the spectral characteristics were in accordance with the expected structures. The unsaturated ketone (XXXII) was found to contain a trans-double bond (νmax. 971 cm^{-1}). This was hydrogenated over palladised charcoal to yield (±) muscone. It gave a single peak in gas liquid chromatography over 3% polyester column. Its NMR spectrum showed the presence of a secondary methyl group and $-CH_2-CO-CH_2-$ group in the system.

EXPERIMENTAL

The melting points and boiling points are uncorrected.

The infrared spectra were recorded as thin films or in the case of solids as nujol mulls unless otherwise mentioned on a Perkin-Elmer Infracord Spectrophotometer, Model 137B, with sodium chloride optics. Ultraviolet spectra were recorded in ethanol solution on a Beckman DK-II Ratio Recording Spectrophotometer and N.M.R. Spectra on a 60 m.c. Varian instrument in carbon tetrachloride solution with T.M.S. as the internal standard.

Acid washed activated alumina, standardised as per Brockmann's procedure was employed for column chromatography. Gas liquid chromatographic analyses were carried out on a Griffin V.P.C. Apparatus MK IIA, with polyester column employing hydrogen as carrier gas.

Unless otherwise stated petroleum ether refers to the fraction boiling at 60-80°.

All temperatures are recorded on the centigrade scale.

EXPERIMENTAL

Ethyl 9-aldehydo nonoate (XVI).

Ethyl oleate (XVII) purified by fractionation (b.p. 195°/0.05 mm., 150 g) was dissolved in glacial acetic acid (500 ml) containing concentrated sulphuric acid (Sp. gr. 1.84, 70 ml) and was kept in a thermostat maintained at 40°. Hydrogen peroxide (70 g., 30%) was added to this mixture with stirring during 1 hr. and the reaction was allowed to continue for 20 hr. Sulphuric acid was destroyed by using sodium acetate (30 g) and excess of hydrogen peroxide with sodium bisulphite (ca. 30 g). Acetic acid was distilled off from the mixture at reduced pressure, and the residue saponified with sodium hydroxide (60 g) in aqueous alcohol (1:1, 500 ml) by refluxing for 4 hr. Acidification after removing most of the alcohol gave 9,10-dihydroxystearic acid (105 g), m.p. (ethanol) 132°.

Dihydroxy stearic acid, m.p. 132°, (100 g) was taken in benzene (0.6 l) containing absolute ethanol (100 ml) and sulphuric acid (98%, 2 ml) and was refluxed for 16 hr, removing the water formed employing an azeotropic head. When water formation ceased, the benzene solution was cooled, washed with water, saturated sodium bicarbonate solution and finally with water until neutral. Benzene was recovered and the residue crystallised from petroleum ether to obtain ethyl 9,10-dihydroxy-stearate (85 g, m.p. 59-60°).

This dihydroxy ester (XVIII) (85 g) was dissolved in absolute alcohol (600 ml) and to this with stirring at 30° was added a neutral solution of sodium metaperiodate (500 ml, 12%) in 1 hr. The stirring was continued for 30 minutes and the precipitated sodium iodate was filtered, washed thoroughly with alcohol and petroleum ether. The filtrate, after diluting with water was extracted with petroleum ether, washed free of periodate (starch iodide paper), solvent removed and the residue fractionated through a 12" column to obtain (i) pelargonic aldehyde (XIX) (34 g), b.p. upto 80° at 4 mm., and (ii) ethyl 9-aldehydononoate (43 g), b.p. 96-100°/1 mm., n_D^{28} 1.4635 (Found: C, 66.3; H, 10.4. Calc. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.0%).

Ethyl-9-aldehydo-nonoate thus obtained was found to be pure by vapour phase chromatography.

Methyl 9-aldehydononoate (XXII)

Aleuritic acid was decolorised by charcoal treatment and crystallised from methanol (m.p. 99-100°). This was esterified with methanol, saturated with hydrogen chloride and the methyl ester obtained crystallised from ethyl acetate, m.p. 62-63°.

Methyl aleuritate (XX) (100 g) in methanol (600 ml) was oxidised with a solution of sodium metaperiodate (600 ml, 12%) at 30° as described previously. Due to the increased solubility in this case, the alcoholic solution after completion of the reaction was diluted with water (five volumes)

and saturated with ammonium sulphate extracted four times with ether. After drying (sod.sulphate) the solvent was removed to give the aldehyde mixture (85 g) which was fractionated to yield (i) hydroxyheptanal (34 g), b.p. upto 90°/1 mm., and (ii) 9-aldehydomethylnonoate (42 g), b.p. 95-100°/1 mm. (Found: C, 64.8; H, 9.3. Calc. for $C_{10}H_{18}O_3$: C, 64.5; H, 19.7%).

Ethyl 9-hydroxy 9-(2-oxo-5-methyl cyclohexyl) nonoate (XXIII)

4-Methyl cyclohexanone (II) (b.p. 164-165°, 80 g) was dissolved in absolute alcohol (80 ml) and mixed with a 30% solution of sodium hydroxide (1.5 ml). The solution was cooled at -10° and the 9-aldehydo ester (50 g) was added dropwise with stirring during 30 min. The temperature was maintained at 10° and the stirring continued for 90 minutes.

The solution which was alkaline to phenolphthalein was neutralised using 30% aqueous acetic acid (2.5 ml), diluted, extracted with pet.ether, washed, dried (Na_2SO_4) and petroleum ether was recovered. From the residue the unreacted aldehyde and ketone were removed by vacuum distillation to afford (i) 4-methyl cyclohexanone (50 g), b.p. 100-160°/30 mm (bath), and (ii) 9-aldehydononoate (23 g), b.p. 95-170°/0.3 mm. (bath).

The crude ethyl 9-hydroxy-9-(2-oxo-5-methyl cyclohexyl) nonoate was obtained as the residue (40 g). This showed a tendency to thermal dehydration and therefore was not distilled; $\nu_{max.}$ 3448, 1729, 1709, and 1656 cm^{-1} (due to partial dehydration).

Ethyl 9-(2-oxo-5-methyl cyclohexylidenyl) nonoate (XXIV)

The hydroxy ester (XXIII) obtained as residue was mixed with potassium bisulphate (5 g) and was heated at 150°/3 mm. for 30 min. to effect dehydration. The product was dissolved in benzene, washed with water, benzene removed and the residue distilled to yield ethyl 9-(2-oxo-5-methyl cyclohexylidenyl) nonoate (XXIV) (20 g), b.p.165°/0.4 mm., n_D^{28} 1.4720; λ_{max}. 244 mμ (ε max. 5860); ν max.1730, 1684, 1613, 1468, and 856 cm^{-1} (Found: C, 73.28; H, 10.9. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.3%).

By employing methyl 9-aldehydononoate for condensation the corresponding methyl ester was obtained, b.p. 154°(bath)/0.1 mm., n_D^{28} 1.4680; ν max. 1736, 1689, 1613, 1453, 1429, 1418, 1370, 1355, 1255, 1031 and 862 cm^{-1}, λ_{max} 243 mμ, (εmax. 6320). The higher εmax. as compared to the ethyl ester is due to partial isomerisation of the 'transoid' enone form, since the dehydration in this case was carried out at atmospheric pressure. (Found: C, 73.26; H, 10.46. $C_{17}H_{28}O_3$ requires: C, 72.82; H, 10.06%).

Ethyl 9-(2-oxo-5-methyl cyclohexyl) nonoate (XXV)

The unsaturated ester (XXIV) (20 g) was hydrogenated in ethanol (100 ml) over 5% palladised charcoal (2 g) to obtain ethyl 9-(2-oxo-5-methyl cyclohexyl) nonoate (20 g), b.p. 145°/0.2 mm., n_D^{28} 1.4565; ν max. 1733 and 1710 cm^{-1}.

(Found: C, 73.28; H, 11.03. $C_{18}H_{32}O_3$ requires C, 72.92; H, 10.88%). Methyl ester, b.p. 139°/0.2 mm., n_D^{28} 1.4540. ν max. 3450, 1727, 1706, 1449, 1430, 1408, 1355, 1308, 1170, 1120, 1020 and 720 cm^{-1} (Found: C, 72.36; H, 10.77. $C_{17}H_{30}O_3$ requires C, 72.3; H, 10.7%).

14-Carbethoxy-4-methyl-6-oxo-tetradecanoic acid (XXVI)

The saturated ester (XXV) (20 g) dissolved in glacial acetic acid (200 ml) was heated to 40° and the oxidising solution (45 ml) prepared by dissolving chromium trioxide (26.7 g) in concentrated sulphuric acid (23 ml) containing water (40 ml) and diluting it with water to 100 ml was added gradually during 20 minutes with stirring. The reaction after an induction period of about 3 min. was rapid and exothermic, and the temperature was maintained at 40-45° by controlling the rate of addition of the reagent. The reaction was continued for another 10 min. and then the excess of reagent was destroyed with aqueous methanol. The reaction product was diluted with water and extracted with ether. The residue after removal of ether was dissolved in 5% sodium carbonate solution and extracted with ether to remove the unreacted ester. The alkaline solution on acidification yielded 14-carbethoxy-4-methyl-6-oxo-tetradecanoic acid (XXVI) (18 g), b.p.193°/0.05 mm. (Equiv. wt. 312. $C_{17}H_{31}O_3$ COOH requires 328.4) ν max. 3125, 2899, 2703, 1695, 1450, 1420, 1370, 1299, 1250, 1220, 1190, 1160, 1026, 952 and 719 cm^{-1}. This semiester was found to contain a small impurity of azelaic acid semiester on thin layer

chromatography on silica gel using pet.ether-ethyl acetate solvent system.

The neutral portion in ether gave on solvent removal the unreacted keto-ester (XXV) (0.5 g).

The crude monoester (XXVI) (18 g) was esterified by refluxing with absolute ethanol (30 ml), benzene (120 ml) and concd. sulphuric acid (0.1 ml), using an azeotropic water removal system. After the water separation ceased, the benzene solution was washed with water, saturated sodium bicarbonate solution and finally with water until neutral. The residue obtained after removing benzene on fractionation gave diethyl 4-methyl-6-oxo-pentadecanedioate (XXVII) (16.8 g), b.p.181-183°/ 0.1 mm., n_D^{28} 1.4480; $\lambda_{max.}$ 280 mμ, ε 130; $\nu_{max.}$ 3460, 1730, 1704, 1453, 1408, 1368, 1250, 1176, 1093, and 1031 cm^{-1}. (Found: C, 67.7; H, 10.5. $C_{20}H_{36}O_5$ requires: C, 67.4; H, 10.19%).

The same ester could also be prepared by opening the cyclic ester (XXV) with sodium ethoxide and ethyl nitrite.

Sodium (0.36 g) was dissolved in absolute ethanol(9 ml) in a moisture free system and the ethoxide formed was cooled to -12°-15°. The saturated keto-ester (XXV) (3.4 g) was added dropwise to this solution with stirring during 30 min. The mixture was stirred for 1 hr. and ethyl nitrite was passed into it (ca. 2.5 g) which condensed inside the cold reaction vessel. The stirring was continued for another hour and the mixture was left overnight at -20°. The cold solution with stirring was treated with conc. hydrochloric acid (2.1 ml) and stirred for

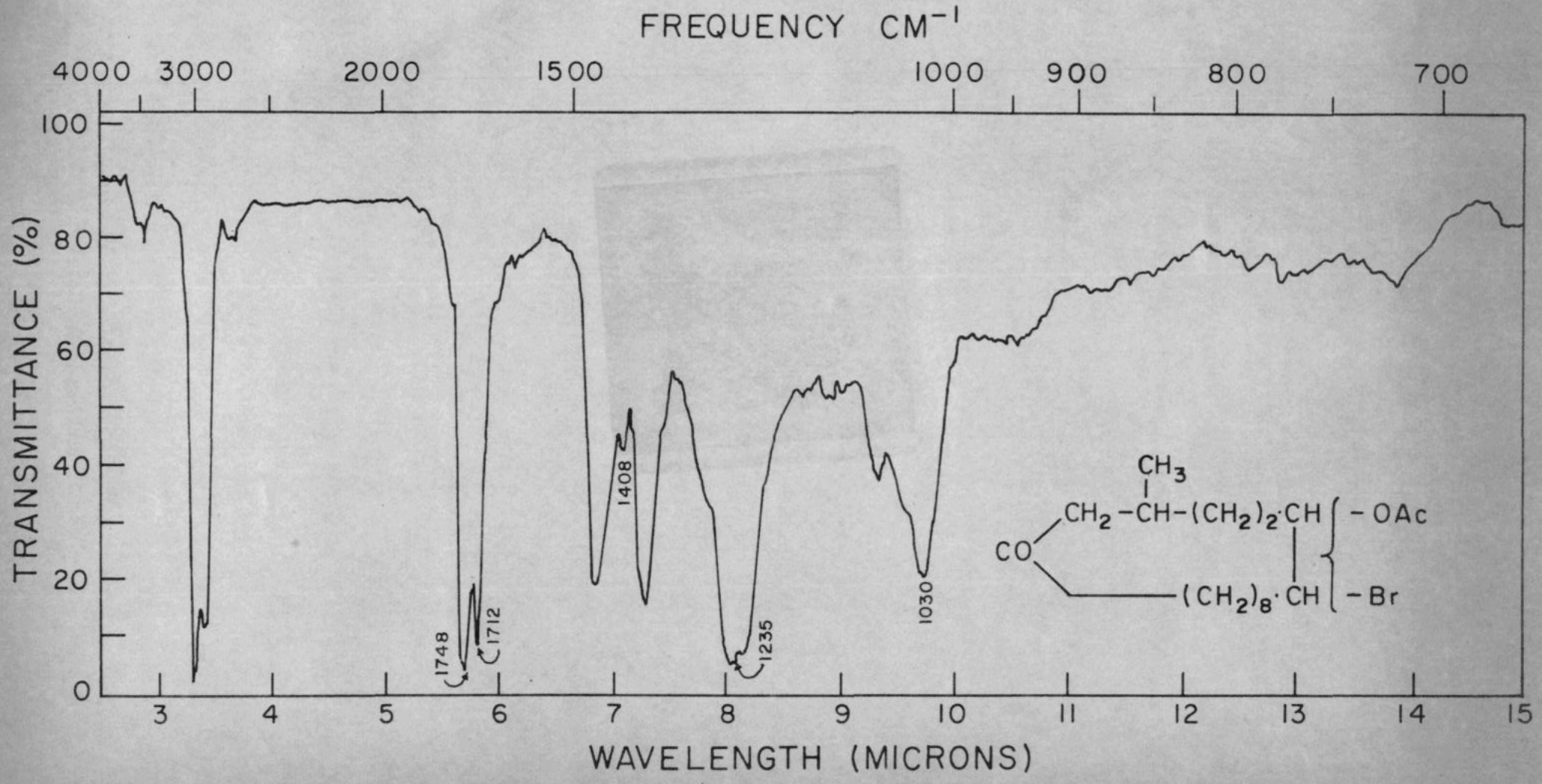
30 min. The mixture was taken in benzene and washed with water, followed by an ice cold solution of sodium hydroxide. Benzene was removed and the residue distilled to yield the diester (XXVII) (1.6 g), b.p. 181-183°/0.1 mm.

Saponification gave the corresponding acid, which on crystallisation from ethanol melted at 66-67° (Found: C, 64.3; H, 9.3. $C_{16}H_{28}O_5$ requires C, 64.0; H, 9.4%).

Ethyl nitrite used in the experiment was generated by adding a solution of alcohol (29 ml) in water (160 ml) containing conc. sulphuric acid (26 ml) to a solution containing sodium nitrite (62 g), alcohol (29 ml) in water (200 ml), and the gaseous reagent was passed through a U-tube containing silica gel and sodium hydroxide pellets.

Diethyl 4-ethyl-6-ethylene ketal pentadecanedioate (XXVIII)

The diester (16 g) (XXVII) in benzene (400 ml) was mixed with ethylene glycol (16 ml) containing p-toluene sulphonic acid (0.1 g) and refluxed for 16 hr. using an azeotropic head for water removal. The benzene solution was transferred to a dry separating funnel and the lower layer of the glycol was drained off. The benzene layer was washed twice with 20 ml. portions of ethylene glycol, followed by water, saturated sodium bicarbonate and finally with water until neutral. Benzene was distilled off to obtain the ethylene ketal (XXVIII) (17.4 g), n_D^{29} 1.4510, $\nu_{max.}$ 3480 (overtone) 2857, 1730, 1453, 1370, 1030, 948, 854 and 721 cm-1; no UV absorption (Found: C, 66.1; H, 10.2. $C_{22}H_{40}O_6$ requires C, 66.0; H, 10.0%).

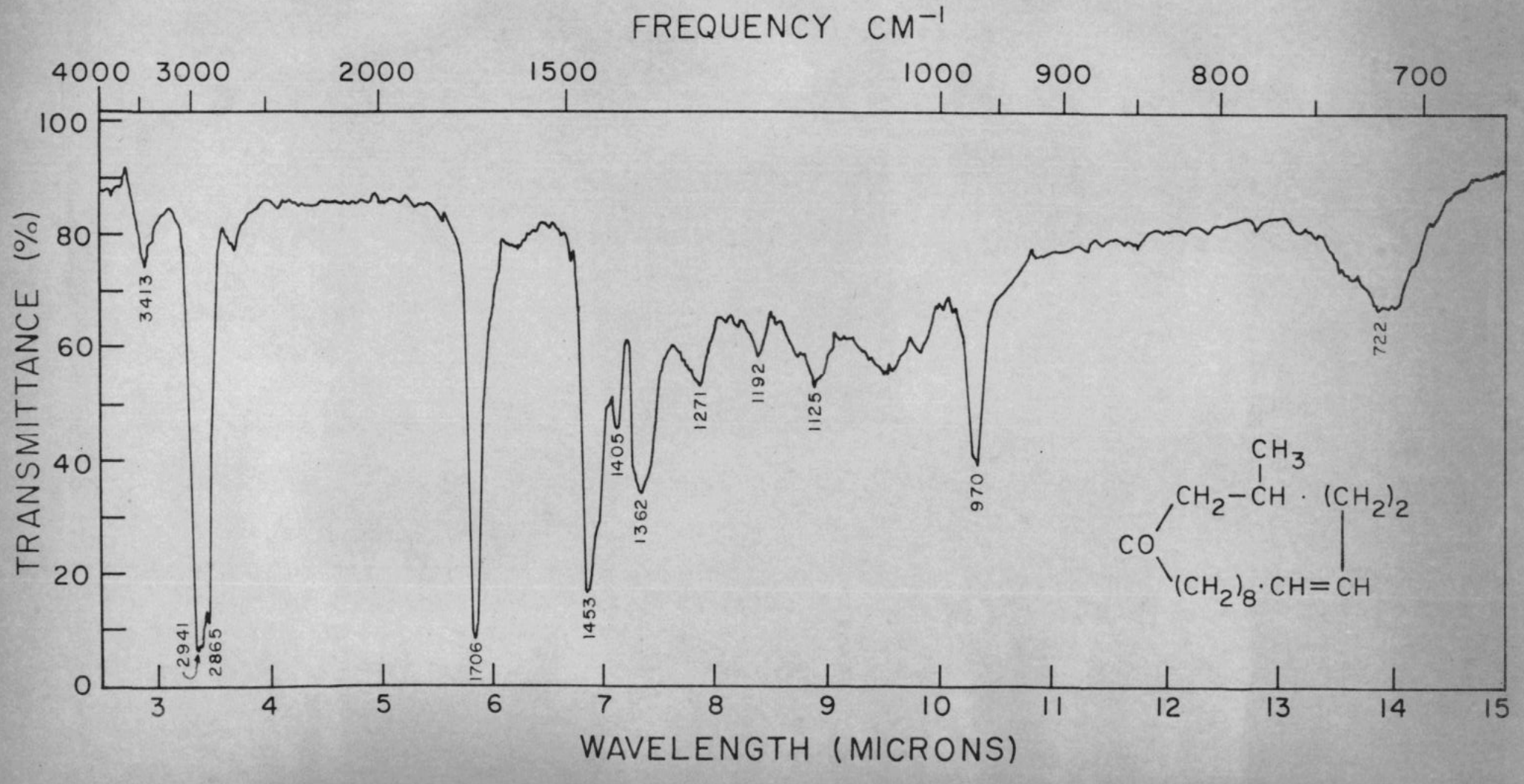


3-METHYL-6,7-BROMO-ACETOXY-CYCLO PENTADECANONE (XXXI)

Acyloin (XXIX). Sodium (7 g) was pulverised in xylene (1 l) under nitrogen atmosphere and the ketal (15.8 g) (XXVIII) in xylene (20 ml) was added dropwise during 1 hr. with vigorous stirring and maintaining the heating so as to reflux xylene during the reaction which was continued for 2 hr. Sodium was then destroyed by gradually adding ethanol (50 ml). Xylene was washed free of alkali and distilled under reduced pressure to obtain the cyclic acyloin (XXIX) (8.3 g) as the residue, $\nu_{max.}$ 3546, 2921, 1706, 1460, 1404, 1370, and 740 cm^{-1}. The acyloin was not analytically pure (Found: C, 67.4; H, 9.4. $C_{18}H_{32}O_4$ requires: C, 69.1; H, 10.3%).

5-Methyl-7-ethylene ketal cyclopentadecane 1,2-diol (XXX)

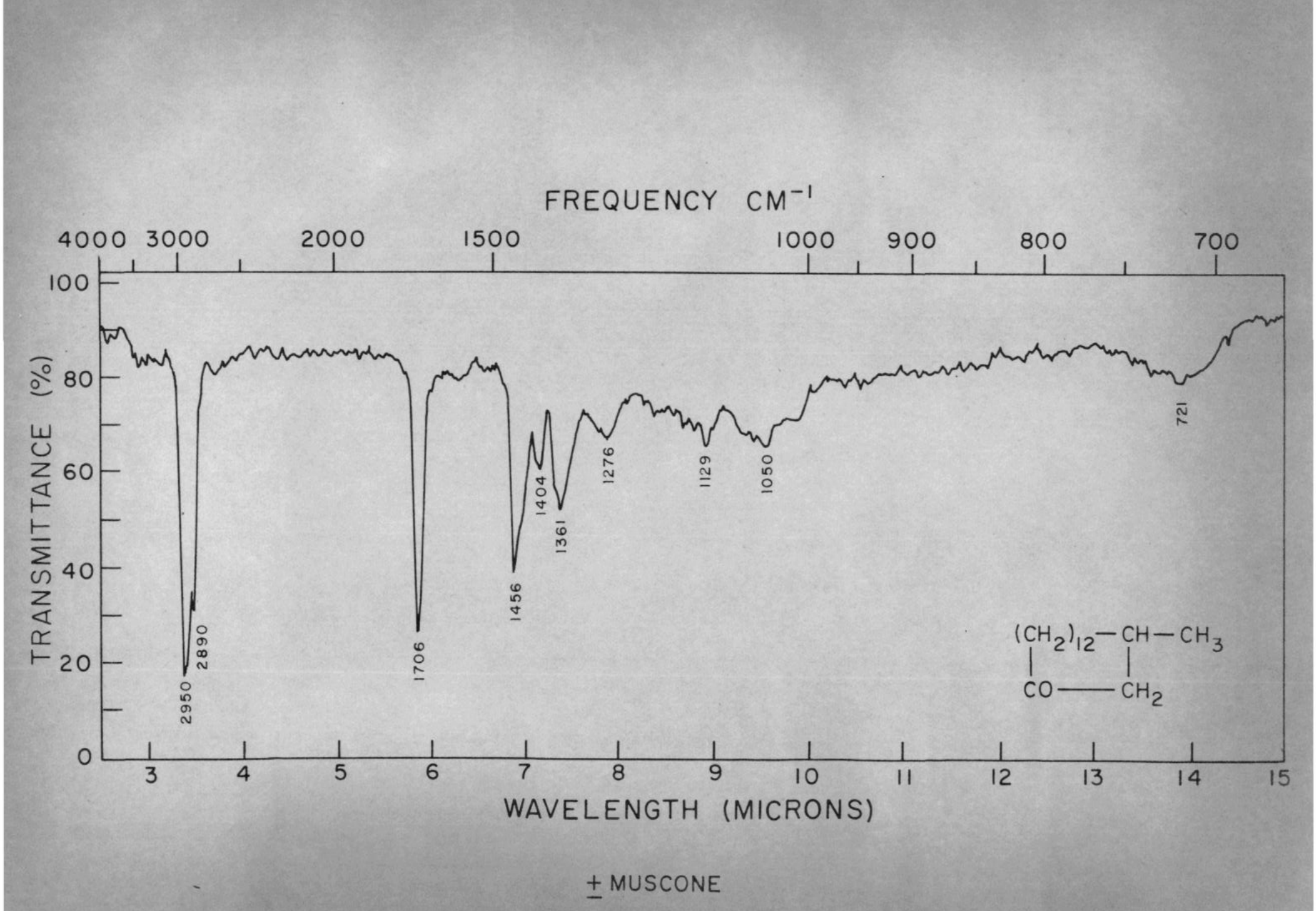
The acyloin (XXIX) (7.8 g) in ether (20 ml) was added to a well stirred suspension of lithium aluminium hydride (2 g) in ether (100 ml) during 30 min. The mixture was refluxed for 10 hr, excess of the reagent was then decomposed with alcohol (10 ml) and the ether solution filtered, residue washed and the filtrate was washed free of alkali. On removing the ether slightly impure 5-methyl 7-ethylene ketal cyclopentadecane 1,2-diol was obtained as a viscous oil (5.8 g) which could not be distilled even under high vacuum without decomposition, n_D^{29} 1.5990, $\nu_{max.}$ 3509, 2860, 1456, 1368, 1075, and 948 cm^{-1} (Found: C, 68.3; H, 10.6. $C_{18}H_{34}O_4$ requires: C, 68.75; H, 10.9%).



MUSCENONE (TRANS-3-METHYL CYCLOPENTADEC-6-ENONE)

3-Methyl pentadec-6-enone (XXXII)

The diol (XXX) (5.8 g) was mixed with a 30% solution of hydrogen bromide in glacial acetic acid (40 ml), kept at room temperature for 24 hr, and then heated at 60° for 2 hr. Acetic anhydride (6 g) was added to the mixture which was heated for another 3 hr. The cooled reaction mixture was treated with a solution of sodium acetate (15 g) in water (100 ml) to destroy excess of hydrogen bromide and then was extracted with pet.ether (some tarry matter remained undissolved) which was removed to afford the bromo-acetoxy derivative (XXXI) as yellowish red oil, $\nu_{max.}$ 2985, 2924, 1748, 1712, 1458, 1408, 1370, 1235, 1075, 1030 and 722 cm^{-1}. It was dissolved in absolute methanol (50 ml) and refluxed for 12 hr. with zinc dust (4 g) under stirring (zinc dust used was freshly prepared by washing the commercial variety with dilute acid, water and absolute methanol and drying at 120° for 3 hr. It was activated in the methanolic solution by adding a drop of 30% hydrogen bromide in acetic acid). Methanol was removed and the residue was taken in pet.ether, filtered and the filtrate washed with dilute acetic acid and water until neutral. The solvent was removed and the residue was saponified to convert the impurity of an acetate detected in the IR spectrum to the alcohol. The saponified product was passed over 20 times of Grade III alumina to obtain trans-3-methyl cyclopentadec-6-enone (XXXII), b.p. 135°/0.1 mm.,


FREQUENCY CM⁻¹
4000 3000 2000 1500 1000 900 800 700
TRANSMITTANCE (%)
100 80 60 40 20 0
2950
2890
1706
1456
1404
1361
1276
1129
1050
721
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
(CH2)12—CH—CH3
CO——CH2

± MUSCONE

n_D^{29} 1.4282; $\nu_{max.}$ 3425, 1712, 1460, 1433, 1408, 1368, 1277, 1190, 1124, 1049, 1020, 971, and 719 cm^{-1} (Found: C, 81.4; H, 12.3. $C_{16}H_{28}O$ requires C, 81.3; H, 11.9%). 2,4-Dinitrophenyl hydrazone crystallised from benzene melted at 107° (Found: N, 14.0. $C_{22}H_{32}O_4N_4$ requires N, 13.45%).

(±) Muscone (I)

Muscenone (XXXII) (0.8 g) in alcohol (50 ml) was hydrogenated in presence of 5% palladised charcoal (0.18 g) to yield (±) muscone (I) (0.7 g), b.p. 148°/1 mm., n_D^{29} 1.4225; $\nu_{max.}$ 3413, 1704, 1450, 1407, 1354, 1260, 1122, 1011, and 718 cm^{-1}.

GLC over a 3% polyester column at 200° at aflow rate (4 lit/hr) gave a single peak at 17.5 min. retention time. (Found: C, 80.8; H, 12.5. Calc. for $C_{16}H_{30}O$: C, 80.6; H, 12.6%).

NMR spectrum of muscone gave a signal at τ 9.09 (J = 6.5 c.p.s.) indicating the presence of a secondary methyl group, intensity corresponding to three protons; a signal at τ 8.72 due to methylene protons other than those flanked by CO and a multiplet below τ 8 intensity corresponding to 4 protons attributable to $-CH_2-CO-CH_2-$ group.

Muscone gave a semicarbazone, m.p. 131-132° (Found: C, 69.2; H, 11.35; N, 14.7. Calc. for $C_{17}H_{33}N_3O$: C, 69.1; H, 11.3; N, 14.2%).

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CHAPTER II

SYNTHESIS OF EXALTONE AND CYCLOHEXADECANONE FROM UNDEC-10-ENOIC ACID USING GRIGNARD REACTION FOR CHAIN EXTENSION

ABSTRACT

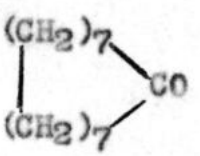
Grignard reaction has been utilised for the chain extension of undec-10-enoic acid to synthesise pentadecanedioic and hexadecanedioic acids.

Undec-10-enyl bromide was converted to the Grignard reagent and was condensed with cyclopentanone and cyclohexanone and the resultant tertiary alcohols were oxidised directly with chromium trioxide or after dehydration with potassium permanganate to obtain the corresponding keto-dicarboxylic acids. These keto-acids could also be obtained by conducting the oxidation stepwise by hydroxylating and rupturing the double bond followed by the dehydration and oxidative cleavage of the ring. Huang-Minlon reduction of these keto-dicarboxylic acids furnished pentadecanedioic and hexadecanedioic acids which were converted through the acyloins to cyclopentadecanone (exaltone) and cyclohexadecanone respectively.

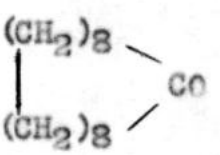
Syntheses of Exaltone and Cyclohexadecanone from Undec-10-enoic acid using Grignard reaction for chain extension

Occurrence:

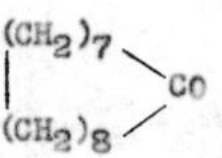
Exaltone (cyclopentadecanone) (I) is present in traces, alongwith cycloheptadecanone (dihydrocivetone) (II) and the alcohols derived from these two ketones in a glandular secretion of the American musk-rat Ondatra zibethicus rivalicius. Presence of cyclohexadecanone (III) has not yet been reported in any of the natural musk sources.



(I)



(II)



(III)

Exaltone is an excellent fixative and is extensively employed in the blending of perfumes. This ketone closely resembles muscone in its odour qualities and is more easily accessible than the latter; therefore, in the recent years it has become an indispensible ingredient of all high grade perfumes. Cyclohexadecanone, probably due to its non-occurrence in nature, has not yet received much attention from the chemists and the perfumers, although this compound also possesses the sweet 'musk odour' and fixing properties. Cyclopentadecanone has a low melting point (65°) and a high

cryoscopic constant,[2] (21.3°); this along with its easy miscibility with a variety of organic compounds render it an ideal solvent for the microdetermination of the molecular weights, especially of organic compounds which decompose at the temperatures used when camphor is employed as the solvent.

Earlier Syntheses

These ketones can be prepared by any of the general cyclisation procedures described by Ruzicka,[3] Ziegler,[4] Hunsdiecker[5] and Blomquist.[6] Recently Leonard and Schimelpfenig[7] prepared these compounds by the Dieckmann condensation[8] of ∝,ω-dicarboxylic esters. Desulphurisation[9] of thienyl macrocyclic ketones[10,11] enabled Gol'dfarb to prepare exaltone. But no method developed till now, equals the elegant macrocyclic acyloin procedure reported simultaneously and independently by Prelog and Stoll,[12] in convenience, yield and economy. The reduction[13] of these acyloins furnishes the required ketones in high overall yield. Therefore, in the recent years, stress has mainly been on new synthetic approaches for obtaining ∝,ω-dicarboxylic acids from cheap raw materials employing economic processes.

Raw Materials

Pentadecanedioic acid was first synthesised by Chuit[14] in 1926 from azelaic and sebacic acids; chain extension was effected by nitrile formation and malonic acid condensation. Klenk[15] oxidised nervonic acid (IV), present

in the brain lipids, to get pentadecanedioic acid. Nervonic acid has since been isolated from the seed fats of the

$$CH_3.(CH_2)_7.CH{=}CH.(CH_2)_{13}.COOH \quad (IV)$$

Ximenia species[16] and has been synthesised from erucic acid in this Laboratory[17] and by electrolytic process from oleic acid.[18] Buu-Hoi[19] prepared pentadecanedioic acid from undecenyl bromide (V) by malonic acid condensation, hydrobromination, nitrile formation and hydrolysis. By the

$$CH_2{=}CH.(CH_2)_8.CH_2.Br \quad (V)$$

ozonisation of 1-(undec-10-enyl) cyclopentene, Diaper[20] could obtain pentadecanedioic acid; Plesek[21] and Nikishin[22] also prepared this acid by the cleavage of alicyclic compounds. Enamine acylation,[23,24] of cyclic ketones and the acid cleavage[25] of the resultant β-diketones has been conveniently employed in the synthesis of this dibasic acid. Electrolytic cross coupling has been tried with poor results for the preparation of this dicarboxylic acid. Pentadecanedioic acid has been synthesised in this Laboratory[26] from erucic acid, kamlolenic acid, nervonic acid and aleuritic acid.

$$CH_2(OH).CH(OH).(CH_2)_{13}.COOH \quad (VI)$$

$$COOH.(CH_2)_{14}.COOH \quad (VII)$$

$$CH_2OH.(CH_2)_{14}.COOH \quad (VIII)$$

$$HOCH_2.(CH_2)_5.CH(OH).CH(OH).(CH_2)_7.COOH \quad (IX).$$

Hexadecanedioic acid (thapsic acid) (VII) is present in the dried roots of Thapsia garganica.[27]

Bougault[28] obtained this acid from the 'etholides' of conifer. By the electrolytic coupling of azelaic-monoester sodium salt, Stocius and Wiesler[29] prepared thapsic acid; after that many improvements and modifications regarding this process have been reported.[30-32] Chuit[14] synthesised hexadecanedioic acid in 1926 from dodecane-1,12-dibromide by malonic ester condensation. Lukes[33] prepared this acid by the Grignard additions with N-methyl cyclic imides. Juniperic acid (VIII), ustillagic acid (VI)[34] and aleuritic acid[26] (IX) also would yield thapsic acid on suitable treatments. Cadmium alkyls[35] has also been employed in the synthesis of hexadecanedioic acid.

Procedures for chain extension

As can be seen, the methods described above consist mainly in the extension of chainlength of more easily available shorter α,ω-bifunctional compounds or in the suitable treatments of a double bond producing a hydroxyl, carboxylic or carbonyl group or in the addition of halogens and hydrohalides to the double bonds followed by displacement and condensation reactions.

Alkyl magnesium bromides react with cyclic ketones to form α-alkyl cyclanols which on oxidative cleavage afford keto-acids with increased chain-length. But due to the poor selectivity of the reagents employed for the cleavage, this method had failed in many of the earlier instances. Kelkar, Phalnikar

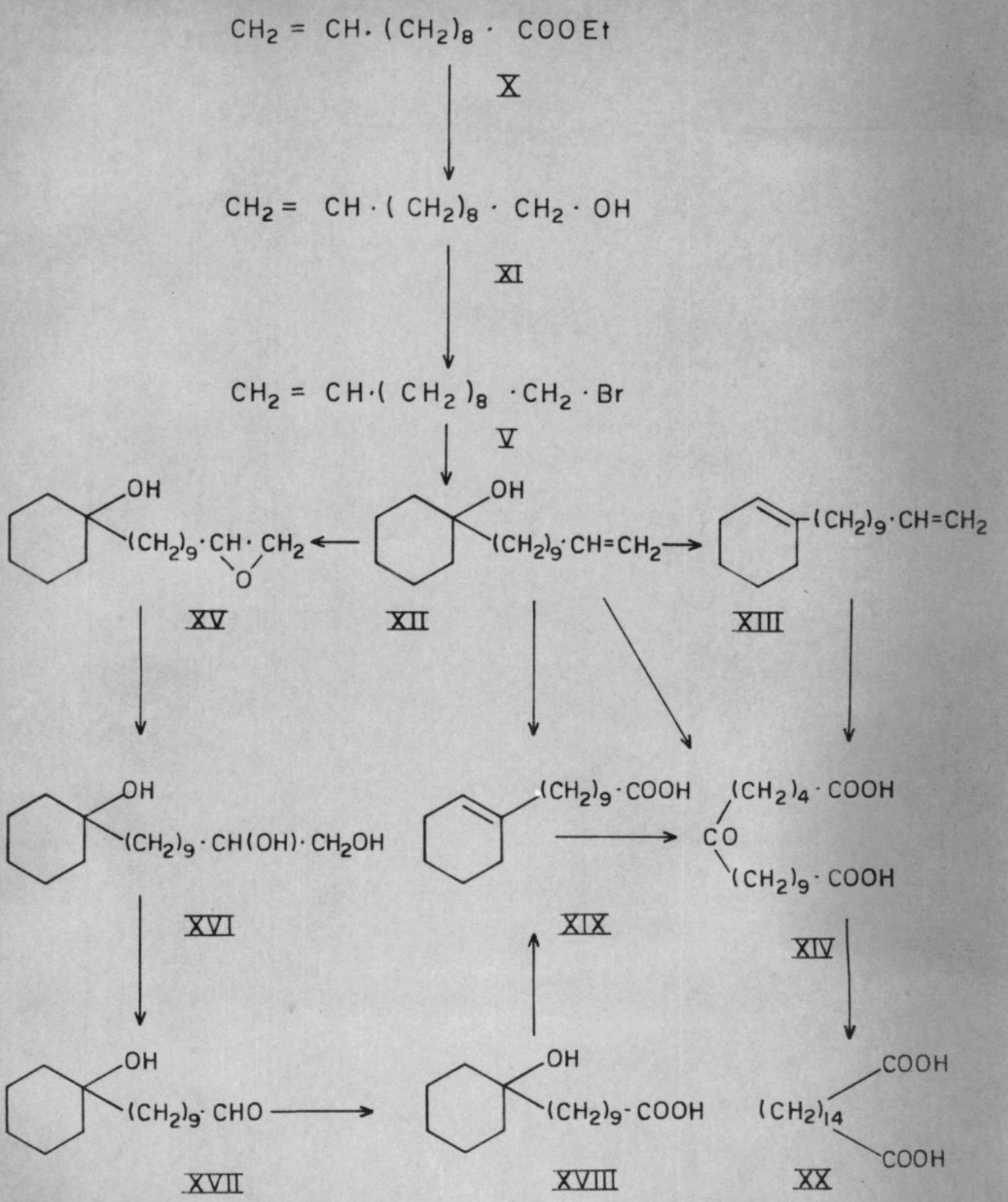
and Bhide[36] encountered difficulties in oxidising 1-alkyl cyclohexanols. Schnieder and Spielman[37] also could obtain the expected 6-keto acids from 1-alkyl cyclohexanols only in very low yields. Collaud[38] in 1942 employed ozonisation of the dehydration products of these tertiary alcohols for the ring opening in the synthesis of ambrettolic and iso-ambrettolic acids. Diaper[20] employed this procedure in the preparation of a series of 5,6- and 7-keto acids. Fieser and Szmuszkovicz[39] oxidised 1-alkyl cycloalkanols with chromium trioxide in glacial acetic acid to obtain 6-keto acids. This procedure has since been applied for the preparation of a variety of keto acids.[40-42]

Present Synthesis of Macrocyclic Ketones

In the present investigation undec-10-enyl bromide(V) was condensed with cyclic ketones and the products were oxidised to get ketodicarboxylic acids. These acids on Huang-Minlon reduction afforded dicarboxylic acids, which could easily be converted to macrocyclic ketones by the acyloin cyclisation procedure (Chart I).

Undec-10-enoic acid (X) obtained from castor oil[43] by pyrolysis was converted to the alcohol (XI) via its ester by reduction with lithium aluminium hydride. Undec-10-enol(XI) was then converted to undec-10-enyl bromide (V) by treatment with phosphorous tribromide. In an attempt to standardise the

SCHEME 1


CH2 = CH·(CH2)8·COOEt
X
CH2 = CH·(CH2)8·CH2·OH
XI
CH2 = CH·(CH2)8·CH2·Br
V
OH
(CH2)9·CH·CH2
O
XV
OH
(CH2)9·CH=CH2
XII
(CH2)9·CH=CH2
XIII
OH
(CH2)9·CH(OH)·CH2OH
XVI
(CH2)9·COOH
(CH2)4·COOH
CO
(CH2)9·COOH
XIX
XIV
OH
(CH2)9·CHO
XVII
OH
(CH2)9·COOH
XVIII
COOH
(CH2)14
COOH
XX

conditions for optimum yield, this reaction was carried out under different conditions. When the bromination was conducted in aromatic hydrocarbon solvents at -5° by adding the alcohol to the tribromide in the solvent[44] the yield of the bromide (V) was ca. 40%. This could slightly be improved by increasing the temperature[45] after adding the alcohol. But definite improvement in yield was observed when phosphorous tribromide was added to the alcohol in light petroleum ether[46] at temperatures below -15°. In all these cases pyridine was added to the mixture to minimise the possible hydrobromination of the double bond. Since the reaction was invariably incomplete and the alcohol boils at about the same temperature as the bromide, the unreacted undecenol had to be removed before distillation. Diaper's phosphorous pentoxide treatment[20] was effective in this; but due to the cumbersome nature of this procedure other methods were tried to achieve this. Treatment of the crude bromide with powdered calcium chloride, and filtration through a short column of grade III alumina (20 fold) were equally effective.

Subsequently, Grignard reagent prepared from this bromide was condensed with cyclohexanone, to obtain 1-(undec-10-enyl) cyclohexanol (XII) as the principal product. Fractionation of the crude product by distillation followed by chromatography yielded two hydrocarbons (XXXIII) and (XXXIV), presumably formed as by-products.

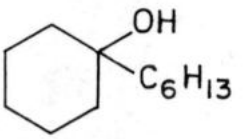
$CH_2=CH.(CH_2)_8.CH_3$ (XXXIII)

$CH_2=CH.(CH_2)_{18}.CH=CH_2$ (XXXIV)

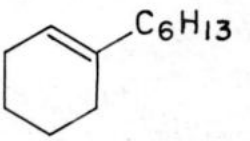
The hydrocarbon (XXXIII) showed peaks at 3080, 1818, 1640, 1360, 995, 909 and 721 cm^{-1} indicating the presence of $-CH=CH_2$ and $-CH_3$ groups and a polymethylene chain. Its boiling point ($60^{o}/6$ mm.) and elemental analysis showed it to be undec-10-ene. The second hydrocarbon showed strong bonds at 3080, 1818, 1640, 995, 909 and 720 cm^{-1}. It was found to be not identical with 1-(undec-10-enyl) cyclohexene. In conformity with this, its IR spectrum did not show any bands at 854 and 839 cm^{-1}, characteristic of all the other compounds prepared from the cyclohexanone-addition product (XII). Its identity with docosa-1,21-diene was confirmed by oxidation to eicosadioic acid. Apart from these, undec-10-enol and its acetate also were isolated from the reaction product.

Chromic acid oxidation of the alcohol (XII) gave poor yields of the expected keto-dicarboxylic acid (XIV), due to the nonspecificity of the reagent employed. Mild conditions of the reaction resulted in the incomplete oxidation of the double bond and the alcoholic group, whereas, on employing drastic conditions, the carbonyl group created by the ring cleavage was further oxidised to short-chain products. Therefore, with a view to standardise the conditions for ring opening α-n-hexyl cyclohexanol (XXII) was prepared as a model compound and was converted to 6-oxo-lauric acid (XXIII). Oxidation by Fieser's procedure[45] yielded 6-keto-dodecanoic acid in 40% yield, 20% of the material was over

oxidised to hexanoic and adipic acids and 40% of the alcohol was recovered unreacted. When dilute acetic acid was used



XXII



XXIV

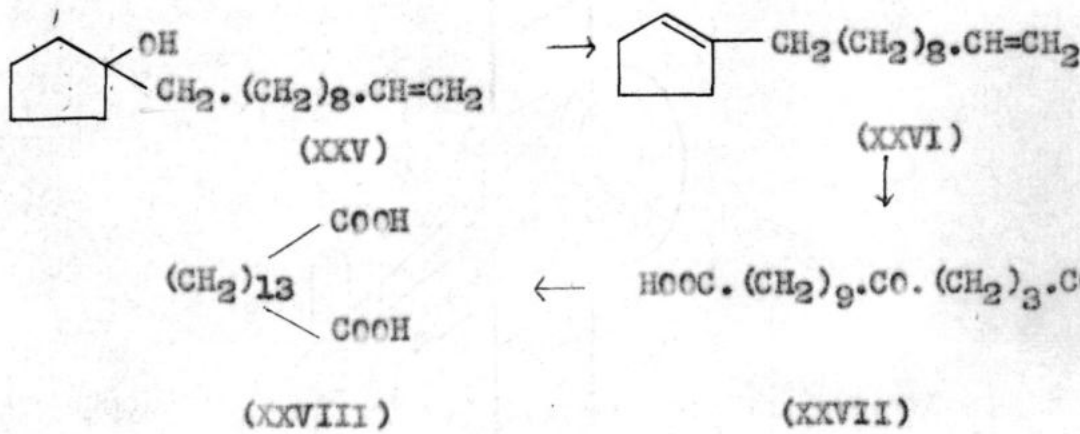
$C_6H_{13} \cdot CO \cdot (CH_2)_4 \cdot COOH$

XXIII

as the reaction medium, the amount of the oxo-dodecanoic (XXIII) acid did not increase; however, the unreacted alcohol recovered was more. Heating of the reaction mixture resulted in increased amounts of the degradation products and poorer yields of the desired keto-acid. Hexyl-cyclohexanol(XXII) was then dehydrated using iodine,[47] thionyl chloride,[48] potassium bisulphate[49] and formic acid[50] at elevated temperatures, the yield was found to be the best when potassium bisulphate was employed as the dehydrating agent. n-Hexyl cyclohexene-1 (XXIV) thus obtained could be oxidised with neutral permanganate[51] in acetone to afford 6-oxo-dodecanoic acid in fair yields. The neutral reagent was found to be superior to the acidic and alkaline ones. After the examination of the model compound described above, 1-(undec-10-enyl) cyclohexanol (XII) was dehydrated to the hydrocarbon (XIII) employing potassium-bisulphate. This compound was oxidised with neutral potassium permanganate to 6-keto-thapsic acid (XIV).

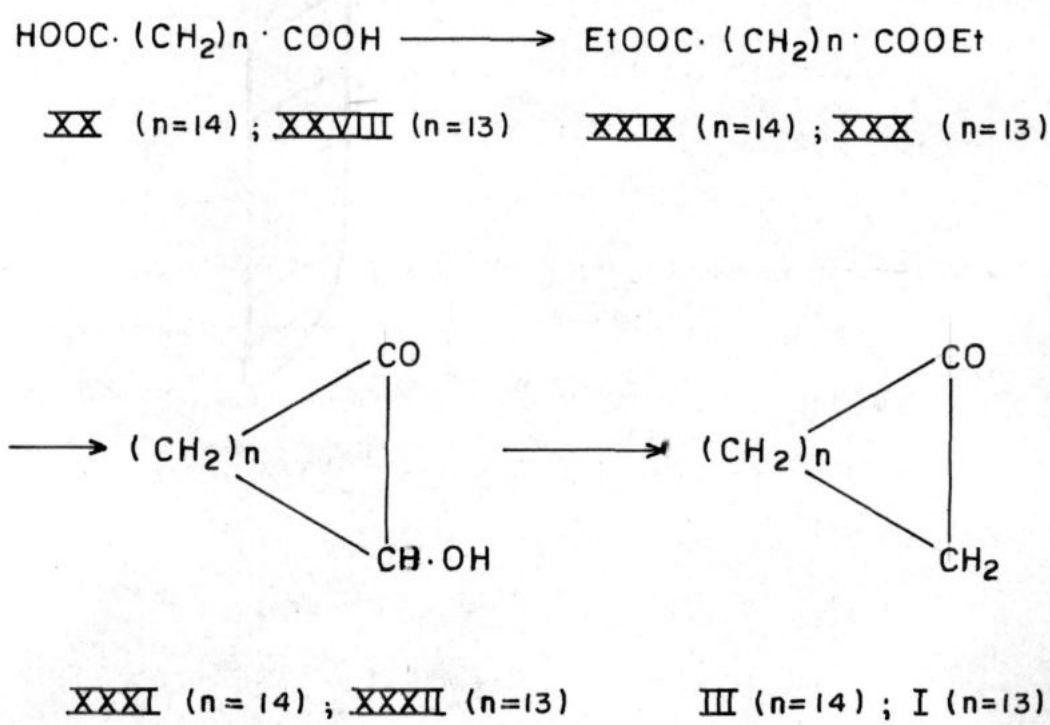
The alcohol (XII) on oxidation with perbenzoic acid[52] yielded an epoxide (XV) which was opened to the triol (XVI) by treatment with acetic acid followed by saponification. On oxidation with neutral sodium metaperiodate[53] this triol yielded the hydroxy-aldehyde (XVII), which gave the corresponding acid (XVIII) on oxidation with hydrogen peroxide. Dehydration of the hydroxy acid with potassium bisulphate furnished the unsaturated acid (XIX).

Oxidation of the alcohol (XII) with potassium permanganate followed by working up the product by passing sulphur dioxide to remove manganese dioxide resulted in the formation of the unsaturated acid (XIX). The hydroxy acid (XVIII) which was initially formed was presumably dehydrated during the passage of sulphur dioxide. Oxidation of the acid (XIX) also afforded the keto-thapsic acid (XIV).



In a similar manner the Grignard reagent from undec-10-enyl bromide (V) and cyclopentanone were condensed to give (undec-10-enyl) cyclopentanol (XXV). This alcohol on oxidation

with chromic acid gave keto-pentadecanedioic acid (XXVII). Dehydration of (XXV) to 1-(undec-10-enyl) cyclopentene (XXVI) and the oxidation of this hydrocarbon with permanganate also yielded this keto-dicarboxylic acid.



These keto-dicarboxylic acids furnished the corresponding saturated acids (XX) and (XXVIII) on Huang-Minlon reduction.[54] The diesters of these on cyclisation in presence of well-dispersed sodium in boiling xylene[12] gave the acyloins (XXXI) and (XXXII) respectively. Reduction[13] of the hydroxy group in the corresponding acyloins afforded cyclohexadecanone (III) and cyclopentadecanone (exaltone) (I) respectively.

EXPERIMENTAL

Ethyl undec-10-enoate (X):

Undec-10-enoic acid (900 g) taken in benzene (2.5 l.) was mixed with absolute alcohol (450 ml) and conc. sulphuric acid (4 ml) and was refluxed using an azeotropic distillation head until the water separation ceased (ca. 16 hr.). The benzene solution was washed with water, saturated sodium bicarbonate solution and finally with water till neutral. On recovering benzene the crude ester (920 g) was obtained which was purified by fractional distillation, b.p.100-101°/1.5 mm., $n_D^{27.5}$ 1.4330; ν max. 3080, 1818, 1735, 1641, 990, 909 and 721 cm^{-1}.

Undec-10-enol (XI):

A solution of ethyl undecenoate (212 g) in anhydrous ether (200 ml) was added under cooling and mechanical stirring to a suspension of lithium aluminium hydride (25 g) in anhydrous ether (200 ml) during 2 hr., care being taken to avoid any vigorous reaction. Anhydrous ether (1.2 l.) was added to the mixture from time to time to maintain a smooth stirring. After the addition was over, the ice-bath was replaced by a hot water bath and the mixture was refluxed for 2 hrs. Excess of lithium aluminium hydride was decomposed using aqueous alcohol(100 ml) and the ethereal layer was decanted off. The residual hydroxides were washed several times with ether by shaking and decantation.

All the ether washings were mixed, washed, dried and solvent was removed to obtain the crude alcohol (160 g). The residue of hydroxides was dissolved in dilute hydrochloric acid and extracted to yield another 10 g. of the alcohol. The crude product on distillation furnished pure undec-10-enol, b.p. 118-119°/3 mm., n_D^{23} 1.4460; ester content 0.6%; unsaturation value 0.993 double bonds; $\nu_{max.}$ 3408, 3080, 1820, 1640, 1420, 1062, 990, 910 and 721 cm^{-1}, (Found: C, 77.2; H, 13.0. Calc. for $C_{11}H_{22}O$: C, 77.6; H, 13.0%).

Undec-10-enyl bromide (V)

(i) Bromination in benzene:

To a mixture of phosphorous tribromide (15 g), dry benzene (50 ml) and pyridine (1.5 ml), a solution of the alcohol (XI) (75 g) in benzene (30 ml) containing pyridine (0.75 ml) was gradually added in 2 hr. with stirring at 0-5°. Stirring was stopped and the homogeneous mixture was left at room temperature for 48 hr. The bromide solution in benzene was washed with dilute acid, saturated sodium bicarbonate solution and finally with water. Benzene was recovered and the residue of crude bromide (32 g) which contained some unreacted alcohol as shown by its infrared spectrum was treated with phosphorous pentoxide (12 g) in dry ether (130 ml) and was left overnight. After adding another lot of phosphorous pentoxide (12 g), the ether solution was kept for 4 hr. with occasional shaking. The mixture was then poured into aqueous

methanol (1:1, 250 ml) and was rendered alkaline to phenolphthalein with liquor ammonia. Ether layer was separated, washed with aqueous ammoniacal methanol and water. The solvent was removed and the residue fractionated to yield undec-10-enyl bromide (13 g), b.p.92-94°/0.2 mm., n_D^{24} 1.4720; $\nu_{max.}$ 3080, 1820, 1639, 1449, 1429, 990, 961, 905 and 720 cm^{-1}, (Found: C, 56.6; H, 9.0; Br, 34.3. Calc. for $C_{11}H_{21}Br$: C, 56.65; H, 9.01; Br, 34.35%).

In another experiment, undec-10-enol (50 g) was converted to the bromide in benzene (160 ml) with phosphorous tribromide (30 g) in presence of pyridine (4.5 ml) in a similar manner. The reaction mixture was set aside at room temperature for 48 hr. and then refluxed for another 2 hr. By this method after the removal of the unreacted alcohol a slightly increased yield (32 g) of the bromide (V), b.p.94°/0.3 mm., $n_D^{22.5}$ 1.4685 was obtained.

(ii) Bromination in petroleum ether:

Undec-10-enyl alcohol (175 g) in dry petroleum ether (b.p.40-60°, 200 ml) was cooled below -15° (solid carbon-dioxide-carbon tetrachloride bath) and was mixed with anhydrous pyridine (10 g). Phosphorous tribromide (100 g) was added to this mixture with stirring during 2 hr. The reaction mixture was then kept at 15° for 18 hr. The petroleum ether solution was washed with sodium carbonate, followed by dilute hydrochloric acid and water until neutral. The dried ($CaCl_2$) extract on removal of solvent yielded the crude bromide (210 g).

Purification of undec-10-enyl bromide

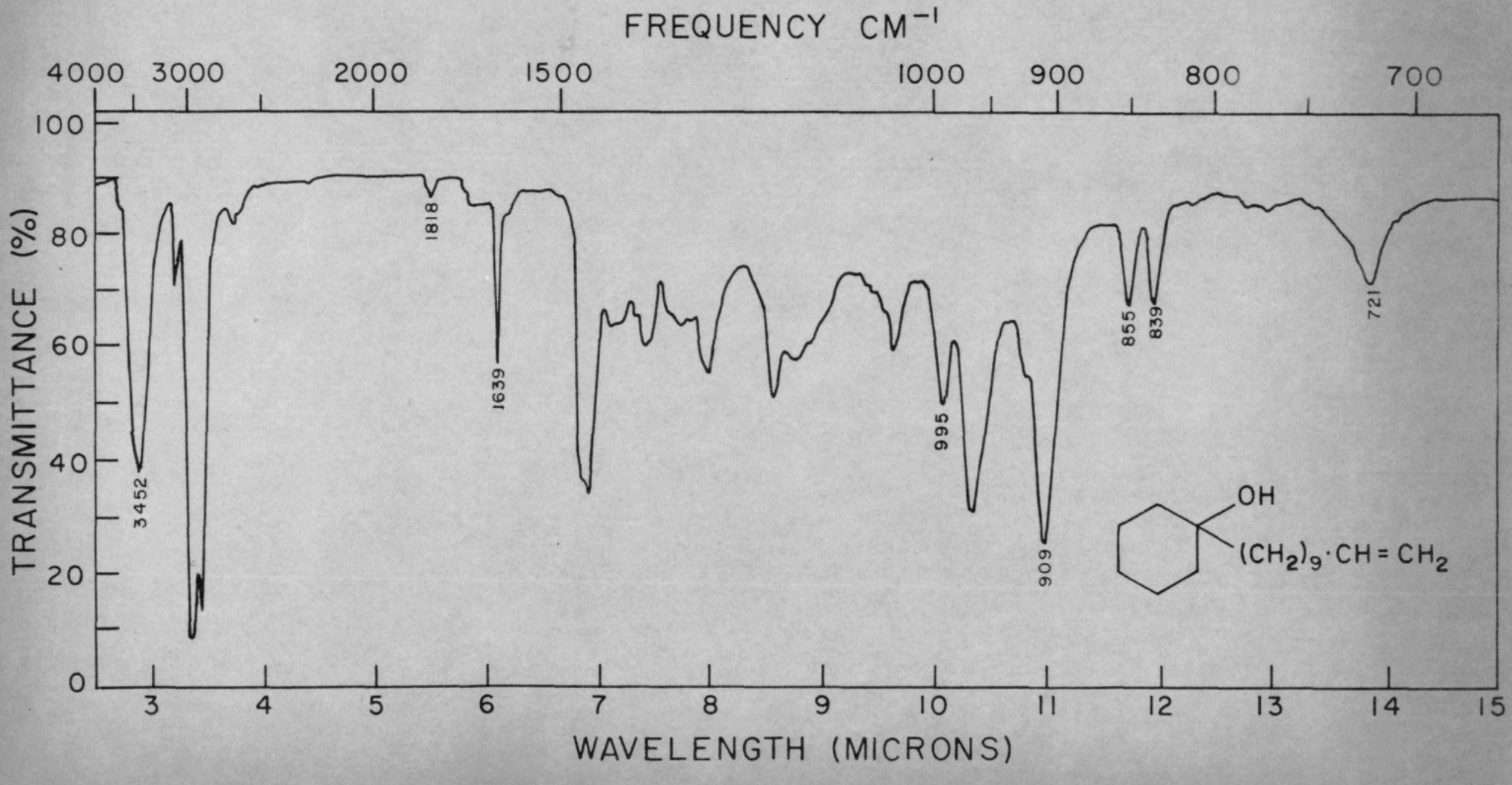
(i) The crude bromide (150 g) on removal of the unreacted alcohol with phosphorous pentoxide and fractionation yielded the pure bromide (80 g).

(ii) The crude bromide (42 g) in ether (200 ml) was kept over freshly fused and well powdered calcium chloride with shaking for 24 hr. Fractionation of the residue obtained on filtration and removal of solvent gave the bromide (24 g) free from alcohol (IR spectrum).

(iii) Crude bromide (5 g) in petroleum ether (300 ml) was filtered through a short column (10") of alumina (grade III, 100 g). Solvent was removed from the filtrate and the residue was fractionated to yield the pure bromide (V) (2.9 g).

1-Hexyl-cyclohexanol (XXII)

Magnesium turnings (8 g) were taken in ether (50 ml) and a crystal of iodine was added to it in a moisture free system provided with a dropping funnel, condenser and mechanical stirrer. With stirring n-hexyl bromide (48 g) in dry ether (50 ml) was added dropwise to the mixture during 1 hr. The rate of addition was adjusted to keep the mixture refluxing. The mixture was then refluxed for another 3 hr. by external heating and then was cooled (ca. 5°) and cyclohexanone (b.p. 153-154°, 30 g) was added dropwise during 1 hr, and the mixture refluxed for 4 hr. The complex was then decomposed



1-(UNDEC-10-ENYL) CYCLOHEXANOL (XII)

with dilute acetic acid at about 0°. The ether layer was washed, dried, solvent removed and the residue fractionated to yield 1-hexyl-cyclohexanol. This product was purified by chromatography and redistillation to yield the pure alcohol (30 g), b.p.90°/1 mm., n_D^{28} 1.4440; ν max. 3580, 1370 and 1057 cm^{-1}. (Found: C, 78.5; H, 13.3. Calc. for $C_{12}H_{24}O$: C, 78.2; H, 13.1%).

1-(Undec-10-enyl) cyclohexanol (XII)

Undec-10-enyl bromide (V) (23 g) in anhydrous ether (20 ml) was added to a stirred suspension of magnesium (2.4 g) in ether (10 ml) pre-activated with a crystal of iodine. Reaction was carried out as described previously, by adding cyclohexanone (9.8 g) in ether (10 ml) to yield the crude tertiary alcohol (27 g) which was distilled to give fractions (i) b.p.<120°/0.6 mm. (8 g) and (ii) b.p.120-165°/0.6 mm. (17 g).

Fraction (i) (5 g) on chromatography over alumina (grade II, 100 g) gave in petroleum ether eluate a hydrocarbon proved to be undec-10-ene (1.5 g), b.p.60°/6 mm., n_D^{26} 1.4685, ν max. 3080, 1818, 1640, 1420, 995, 909 (-CH=CH_2), 1360 (-CH_3) and 721 cm^{-1} (Found: C, 85.8; H, 13.6. Calc. for $C_{11}H_{22}$: C, 85.6; H, 14.4%).

From the benzene eluate undecenyl acetate (0.5 g) was obtained, b.p.102°/1.5 mm., ν max. 1745, 1365, 1248 (-O.CO.CH_3), 3080, 1816, 1420, 1640, 995, 909 (-CH=CH_2) and 721 cm^{-1}. (Found: C, 73.33; H, 9.92. Calc. for $C_{13}H_{24}O_2$: C, 72.5; H, 11.4%). This was not further purified.

Undecenyl alcohol (2 g) b.p.91°/0.6 mm. was obtained from the ether-eluate.

Fraction (ii) (17 g) on chromatography over alumina (grade II, 350 g) gave in petroleum ether eluate docosa-1, 21-diene (2 g), b.p.168°/1 mm., $\nu_{max.}$ 3080, 1818, 1640, 1450, 1420, 995, 909 and 721 cm^{-1}. (Found: C, 86.4; H, 13.7. Calc. for $C_{22}H_{42}$: C, 86.2; H, 13.8%).

On oxidation with permanganate, this hydrocarbon yielded eicosadioic acid, m.p.125° (Found: C, 70.4; H, 11.6. Calc. for $C_{20}H_{38}O_4$: C, 70.1; H, 11.2%).

Ether eluate gave the alcohol (XII, 12 g), b.p.135°/0.7 mm., n_D^{23} 1.4750, $\nu_{max.}$ 3452, 1818, 1415, 1170, 1036, 994, 967, 909, 855, 839 and 721 cm^{-1} (Found: C, 80.8; H, 12.9. $C_{17}H_{32}O_2$ requires: C, 80.9; H, 12.8%).

1-(Undec-10-enyl) cyclopentanol (XXV)

By condensing Grignard reagent prepared from undecenyl bromide (23 g) and magnesium turnings (2.4 g) with cyclopentanone (11 g), 1-(undec-10-enyl) cyclopentanol was prepared. The crude product was fractionated and chromatographed to yield, along with the by-products obtained in the previous experiment, the tertiary alcohol (XXV, 13 g), b.p.117°/0.3 mm., n_D^{23} 1.4730; $\nu_{max.}$ 3448, 3080, 1640, 1208, 1188, 995, 909 and 721 cm^{-1}. (Found: C, 80.1; H, 12.4. Calc. for $C_{16}H_{30}O$: C, 80.6; H, 12.7%).

On treatment with 3,5-dinitrobenzoyl chloride in pyridine it gave a crystalline derivative, m.p.68° (Found: N, 6.3; Calc. for $C_{23}H_{32}O_5N_2$: N, 6.7%).

Dehydration of the 1-alkyl cycloalkanols

(a) 1-Hexyl cyclohexene (XXIV)

(i) With formic acid: The alcohol (XXII) (5 g) in formic acid (98%, 100 ml) was refluxed for 2 hr. to obtain hexyl cyclohexene (XXIV) (3 g), b.p.62-63°/0.3 mm., $\nu_{max.}$ 1667, 1370, 1130, 912, 800 and 721 cm^{-1}. (Found: C, 85.1; H, 13.8. Calc. for $C_{12}H_{24}$: C, 85.7; H, 14.3%).

(ii) With thionyl chloride: Hexyl-cyclohexanol (5 g) in pyridine (120 ml) was mixed with thionyl chloride (15 ml) and was left at room temperature for 2 hr. The mixture was poured into cold water and was extracted with ether. The extract was successively treated with dilute hydrochloric acid, sodium carbonate solution (5%) and water. The residual hydrocarbon obtained on removal of solvent was distilled to afford hexyl cyclohexene (XXIV), (1.5 g), b.p.62-63°/0.3 mm.

(iii) With iodine: The tertiary alcohol (5 g) was taken in xylene (200 ml) and iodine (0.1 g) was added. The mixture was refluxed for 8 hrs. and the water formed was removed with an azeotropic head. The product was washed with sodium thiosulphate solution and water. Removal of xylene gave the hexyl cyclohexene (1.5 g), b.p.67-68°/1 mm.

(iv) With potassium bisulphate: The alcohol (XXII) (5 g) was heated with freshly fused potassium bisulphate (2 g) at 160° under reflux to obtain 1-hexyl cyclohexene (3.5 g), b.p.67-68°/1 mm.

(b) 1-(Undec-10-enyl) cyclohexene (XIII).

The alcohol (XII, 10 g) was mixed with potassium bisulphate (4 g) and was heated at 160° for 2 hr. to obtain the hydrocarbon (XIII), b.p.142°/2.5 mm., n_D^{20} 1.4730. $\nu_{max.}$ 1665, 1640, 1420, 995, 909, 854 and 721 cm^{-1} (Found: C, 86.8; H, 13.3. $C_{17}H_{30}$ requires: C, 87.1; H, 12.9%).

(c) 1-(Undec-10-enyl) cyclopentene (XXVI). 1-(Undec-10-enyl) cyclopentanol (5 g) was heated with potassium bisulphate (2 g) to yield the corresponding hydrocarbon (XXVI) (3.5 g), b.p.135-136°/2 mm., n_D^{24} 1.4680. $\nu_{max.}$ 1818, 1662, 1640, 1420, 995, 970, 909, 800 and 721 cm^{-1} (Found: C, 86.9; H,13.3. Calc. for $C_{16}H_{28}$: C, 87.2; H, 12.8%).

Oxidation of 1-alkyl cycloalkanols

(a) 6-Oxo-dodecanoic acid (XXIII).

(i) The alcohol (XXII) (5 g) was dissolved in glacial acetic acid (120 ml) and with stirring at 30°, it was treated with powdered chromium trioxide (8 g) added in small lots. After a short induction period the exothermic reaction started, the temperature being controlled by cooling externally. The addition was completed in 1 hr. and the reaction continued for another 2 hr. The reaction mixture was diluted with water, extracted with ether, the extract washed. The solvent removed and the residue dissolved on 5% sodium carbonate solution and was extracted with ether to recover the unreacted alcohol(1.0 g). Acidification of the alkaline portion gave an acid mixture

which was fractionated to obtain (i) hexanoic acid (1 g) b.p.76-80°/1 mm., acid equivalent 117.3. Calc. for $C_5H_{11}COOH$: 116.2 and (ii) 6-oxo-dodecanoic acid (1.75 g), b.p. 165-167°(bath)/1 mm., m.p.61-62°, acid equivalent 212.5. Calc. for $C_{11}H_{21}O\,COOH$, 214.3. (Found: C, 67.2; H, 10.4%. Calc. for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3%). Semicarbazone, m.p. 131° (Found: N, 15.2; Calc. for $C_{13}H_{25}O_3N_3$: N, 15.5%).

(ii) The alcohol (XXII) (5 g) was taken in glacial acetic acid (50 ml) and a solution of chromium trioxide (8 g) in a mixture of acetic acid (75 ml) and water (40 ml) was added to it in 1 hr. at 80° with stirring.[55] The reaction was continued for 2 hr., and mixture was diluted with water and extracted with ether. Ether was removed and the neutral portion comprising of the unreacted alcohol (1.5 g) was separated from the residue to obtain the acidic portion(2.9g). Fractionation of the acid mixture afforded hexanoic acid (0.6 g) and 6-oxo-lauric acid (1.9 g).

(b) 6-Oxo-hexadecanedioic acid (XIV)

1-(Undec-10-enyl) cyclohexanol (XII) (5 g) in glacial acetic acid (120 ml) was oxidised at 30° with chromium trioxide powder (16 g) added in small lots during 1 hr. The reaction was carried out as in (a-i) to obtain a neutral portion of the unreacted alcohol (1 g) and an acid mixture (3.8 g). This acid mixture on repeated crystallisations gave 6-oxo-thapsic acid (0.1 g), m.p. 112°, undepressed on mixing with an authentic sample.

Oxidation of 1-alkyl cycloalkenes.

(a) 6-Oxo-dodecanoic acid (XXIII)

(i) The hydrocarbon (XXIV) was hydroxylated[56] to 1-hexyl-1,2-dihydroxy cyclohexanol and this was oxidised with potassium permanganate to obtain the acid (XXIII).

Hexyl cyclohexene (5 g) was hydroxylated with hydrogen peroxide (30%, 7 ml) in formic acid (70 ml) containing conc. sulphuric acid (0.2 ml). The reaction was carried out during 2 hr. Sulphuric acid was destroyed with sodium acetate and excess of the peroxide with sodium bisulphite. Formic acid was then distilled off and the residue was saponified with alcoholic potash (0.5 N, 60 ml) to obtain the diol (XXXV, 1.5 g), b.p.160-164°/2.5 mm.

This diol was also prepared by the hydroxylation of the hydrocarbon (5 g) in acetic acid (75 ml) containing sulphuric acid (0.5 ml) with hydrogen peroxide (30%, 7 ml) at 40°. The mixture was kept at that temperature for 16 hr. and the product was worked up as in the case of performic acid hydroxylation to obtain the diol (2.5 g), b.p.150°/2 mm. (Found: C, 72.3; H, 11.8. $C_{12}H_{24}O_2$ requires C, 72.0; H, 12.1%).

This diol (4 g) taken in acetone (100 ml) was oxidised with potassium permanganate powder (6 g) added in small lots during 30 min. at room temperature. The reaction was continued for 2 hr. at the boiling point of acetone; manganese dioxide

was removed with sulphur dioxide and the resulting acid was purified by dissolving in alkali and extracting with ether to remove the unreacted diol to obtain 6-oxo-lauric acid (3 g), m.p.62-63°.

(ii) 1-Hexyl cyclohexene (XXII) (3 g) in acetone (60 ml) was oxidised with a saturated solution of potassium permanganate (8 g) in water. The mixture was stirred at 60° for 6 hrs. to yield after usual processing the acid (2.2 g), m.p.62-63° and neutral portion (0.7 g).

(iii) The hydrocarbon (XXIV) (3 g) in acetone (60 ml) containing acetic acid (1 ml) was oxidised with potassium permanganate (8 g), added during 1 hr. to obtain the ketolauric acid (XXIII) (2.4 g). Unreacted hydrocarbon (0.5 g) was recovered.

(iv) The hydrocarbon (XXIV, 3 g) was also oxidised in acetone (60 ml) with potassium permanganate (8 g) without adding acetic acid; yield of acid (2.3 g).

(v) In another experiment, 1-hexyl cyclohexene (3 g) was oxidised in aqueous acetone (1:1; 60 ml) containing potassium hydroxide (3 g) with potassium permanganate (8 g). No appreciable oxidation took place and the hydrocarbon (2.8 g) was recovered unchanged.

(vi) Ozonisation of the hydrocarbon (3 g) in carbon tetrachloride (50 ml) gave the keto-dodecanoic acid (0.8 g).

(b) 6-Oxo-hexadecanedioic acid (XIV).

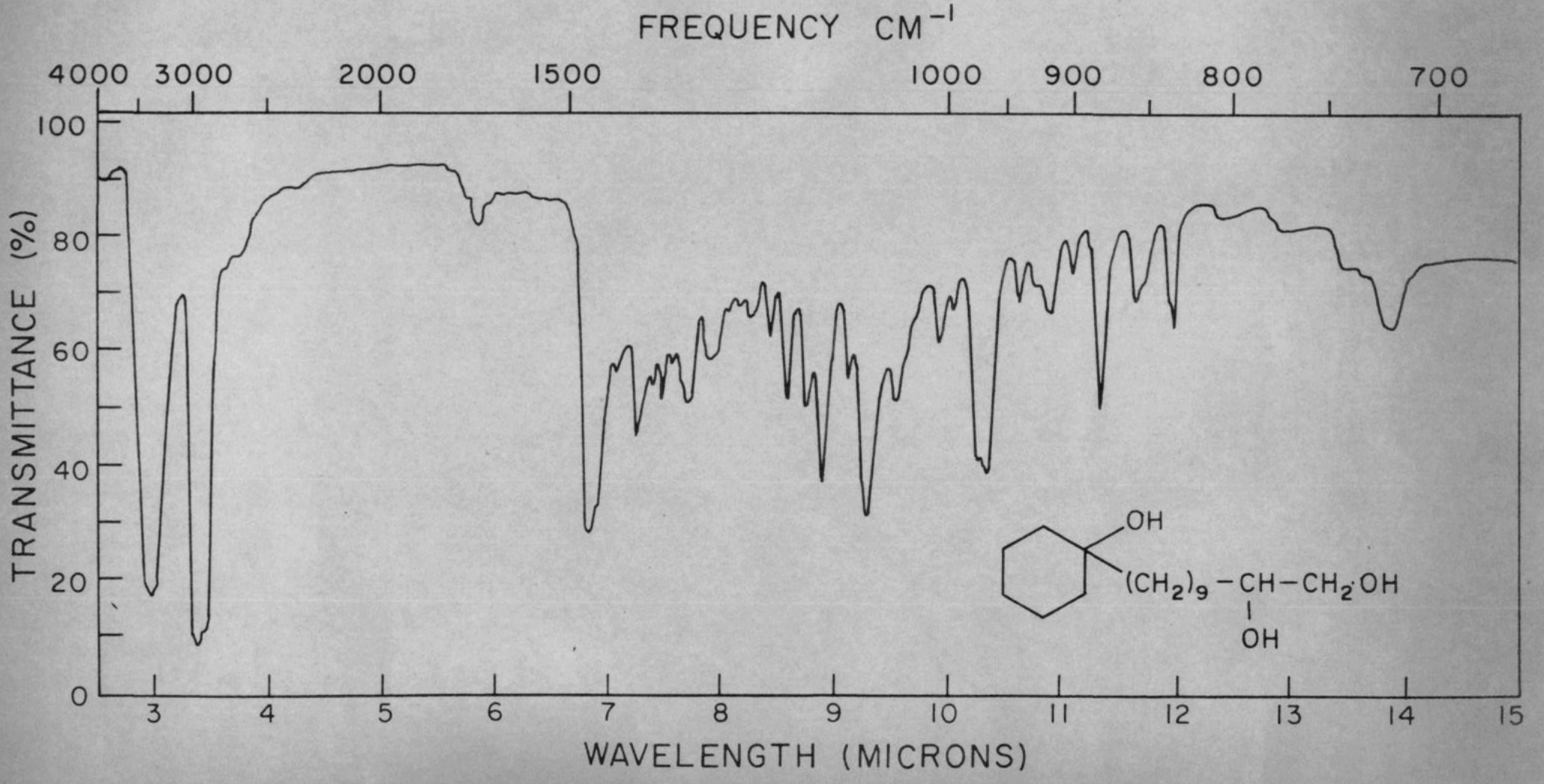
1-Undec-10-enyl cyclohexene (2 g) in acetone (60 ml) containing acetic acid (0.3 ml) was cooled to 0° and potassium permanganate (8 g) was added gradually in 1 hr. with stirring. The mixture was left overnight at room temperature and refluxed for 2 hr. and acetone was removed. The residue was taken in cold water and sulphur dioxide was bubbled through to remove the manganese dioxide. The acid thus obtained was extracted with ether, ether removed, the residue was dissolved in 5% sodium hydroxide solution and extracted with ether. The alkaline solution on acidification and filtration yielded 6-oxo-hexadecanedioic acid (1.2 g). Further purification was effected by regeneration from the semicarbazone, m.p.147°, (Found: N, 11.6. Calc. for $C_{17}H_{31}O_5N_3$: N, 11.81%) and recrystallisation from acetic acid to obtain the pure keto acid, m.p.115-116° (Found: C, 64.2; H, 9.6. Calc. for $C_{16}H_{28}O_5$: C, 64.0; H, 9.4%).

(c) 5-Oxo-pentadecanedioic acid (XXVII)

1-(Undec-10-enyl) cyclopentene (2 g) was similarly oxidised to crude oxo-pentadecanedioic acid. This acid was found to contain a small amount of sebacic acid by paper chromatography. Purification was effected by repeated crystallisations from acetic acid, m.p.107°. (Found: C, 62.6; H, 9.7. Calc. for $C_{15}H_{26}O_5$: C, 62.9; H, 9.2%).

1-(10,11-Dihydroxy undecyl) cyclohexanol (XVI)

1-(Undec-10-enyl) cyclohexanol (1 g) in chloroform (20 ml) was mixed with perbenzoic acid (0.97 N, 25 ml) in



1-(10,11-DIHYDROXY UNDECYL) CYCLOHEXANOL (XVI)

chloroform and was kept at 10° for 72 hr. The reaction mixture was washed with water, dilute sodium carbonate solution and finally with water till neutral. Removal of the solvent and distillation of the residue, furnished the epoxide (XV, 1 g), b.p.158°/0.4 mm., n_D^{20} 1.4775. From IR spectrum it was found to be contaminated with small amounts of the isomeric ketone and traces of the starting olefinic compound. The crude epoxide (0.9 g) was treated with glacial acetic acid (10 ml) on a water bath for 6 hrs. The hydroxy acetate was saponified to afford the triol (.9 g), m.p.93-94°, $\nu_{max.}$ 3420, 1460, 1408, 1124, 1075, 1047, 854, 837 and 721 cm^{-1}. (Found: C, 71.7; H, 12.2. $C_{17}H_{34}O_3$ requires: C, 71.31; H,12.0%).

Semicarbazone of 10-(1-hydroxy cyclohexyl) decanal (XVII)

The triol (0.184 g) was treated with an aqueous solution of sodium metaperiodate (1.8%, 2 ml) in absolute alcohol (20 ml) at room temperature for 30 min. The precipitated sodium iodate was filtered off and the diluted solution was extracted with ether. Removal of ether and treatment of the residue with semicarbazene hydrochloride (0.2 g) and sodium acetate (0.3 g) in 70% ethanol gave the semicarbazone of 10-(1-hydroxy cyclohexyl) decanal, m.p. 94-95°. (Found: N, 13.5. Calc. for $C_{17}H_{31}O_2N_3$: N, 13.2%).

10-(1-Hydroxy-cyclohexyl) decanoic acid (XVIII)

The triol (1 g) was oxidised as described above. The aldehyde obtained as residue was taken in alcoholic potash (0.5 N, 25 ml) and hydrogen peroxide (10%, 10 ml) was added

to it. The mixture after heating for 15 minutes at 60° was diluted, acidified and extracted with ether to obtain the acid, b.p.180°/0.7 mm., n_D^{27} 1.4790; ν max. 3448, 2631, 1709; 1260, 1167, 1099, 965, 855, 839 and 721 cm^{-1} (Found: C, 70.7; H, 11.3. $C_{16}H_{30}O_3$ requires C, 71.1; H, 11.2%).

10-(Cyclohex-1-enyl) decanoic acid (XIX)

(i) The acid (XVIII) (5 g) was dehydrated at 160° with potassium bisulphate (0.2 g). The product thus obtained was esterified with diazomethane and was chromatographed over alumina (grade III, 20 g) to yield the methyl ester of (XIX), b.p.134°/0.6 mm., n_D^{22} 1.4720; ν max. 1733, 1655, 1429, 1361, 1190, 1163, 1096, 918, 800 and 721 cm^{-1}. (Found: C, 77.2; H, 11.1. $C_{17}H_{30}O_2$ requires: C, 76.6; H, 11.4%).

(ii) Undec-10-enyl cyclohexanol (XII) (2 g) in acetone (40 ml) was oxidised with powdered potassium permanganate (5 g) at 20°. After refluxing for 2 hr. and removing acetone the residue was taken in water, sulphur dioxide was passed to remove manganese dioxide and the resultant acid was extracted with ether. Esterification with diazomethane and distillation gave the methyl ester of (XIX), b.p.140°/0.8 mm. Oxidation of this ester with potassium permanganate as described in earlier experiments followed by hydrolysis furnished the keto-thapsic acid (XIV), m.p.113°.

Hexadecanedioic acid (XX)

Keto-thapsic acid (0.6 g), potassium hydroxide (0.5 g) and hydrazene hydrate (0.3 ml) were taken in diethylene glycol (4 ml) and was heated at 140° for 1 hr. and at 220° for 6 hr. The mixture was then poured into cold dilute hydrochloric acid, the precipitated hexadecanedioic acid (0.5 g) was filtered and crystallised from acetic acid, m.p. 125°, undepressed on mixing with an authentic sample (Found: C, 67.3; H, 10.7. Calc. for $C_{16}H_{30}O_4$: C, 67.1; H, 10.6%).

Pentadecanedioic acid (XXVIII)

The keto-pentadecanedioic acid (2 g) was reduced in a similar manner, with potassium hydroxide (2 g) and hydrazine hydrate (1 ml) in diethylene glycol (10 ml) to obtain pentadecanedioic acid, m.p. and mixed m.p. with an authentic sample 114° (Found: C, 66.1; H, 10.9. $C_{15}H_{29}O_4$ requires: C, 66.1; H, 10.4%).

Diethyl hexadecanedioate (XXIX)

The dicarboxylic acid (XX) (55 g) was esterified with absolute alcohol (20 ml) in benzene (120 ml) containing conc. sulphuric acid (0.5 ml) using an azeotropic head for the removal of water to obtain the diester (56 g), b.p.160°/ 0.1 mm., $\gamma_{max.}$ 1725, 1241 and 721 cm^{-1} (Found: C, 70.25; H, 11.3. Calc. for $C_{20}H_{30}O_4$: C, 70.1; H, 11.2%).

Diethyl pentadecanedioate (XXX)

Pentadecanedioic acid (54 g) was esterified by refluxing with a mixture of ethanol (20 ml), benzene (120 ml)

and conc. sulphuric acid (0.3 ml) until water separation ceased to obtain the diethyl ester (55 g), b.p. 150-152°/ 0.1 mm., ν max. 1727, 1241 and 721 cm^{-1} (Found: C, 69.9; H, 10.9. Calc. for $C_{19}H_{36}O_4$: C, 69.5; H, 11.05%).

Cyclohexadecane-2-ol-1-one (XXXI)

The diester (XXIX) (37 g) was treated with pulverised sodium (20 g) in refluxing xylene (2 l.) (following the procedure described in Chapter I). The crude acyloin (21 g) was distilled, b.p.139-141°/0.05 mm., ν max. 3400, 1716, 1453, 1410, 1353, 1297 and 1060 cm^{-1} (Found: C, 75.8; H, 11.95. Calc. for $C_{16}H_{32}O_2$: C, 75.5; H, 11.9%).

Cyclopentadecan-2-ol-1-one (XXXII)

Diethyl pentadecanedioate (XXX) (27.6 g) was similarly cyclised by treating with well dispersed sodium (10 g) in boiling xylene (1 l.) under an atmosphere of nitrogen to obtain the acyloin (13 g), b.p.141°/0.05 mm., ν max. 3455, 2350, 1817, 1703, 1445, 1410, 1372, 1060 and 724 cm^{-1} (Found: C, 75.1; H, 11.8. Calc. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.7%).

Cyclohexadecanone (III)

The acyloin (XXXI) (21 g) was taken in acetic acid (35 ml) and zinc wool (25 g) was introduced into the mixture. At about 98° conc. hydrochloric acid (50 ml) was added to the mixture during 85 minutes with stirring. Heating and stirring were continued for another 30 minutes. The solution was

diluted with water, extracted with ether and ether was removed. The residue was distilled to obtain the crude ketone. This on treatment with semicarbazene hydrochloride (15 g) and sodium acetate (20 g) in alcohol (200 ml) furnished the semicarbazone of cyclohexadecanone which was recrystallised from alcohol, m.p. 184-185°. (Found: C, 68.8; H, 11.2; N, 14.0. Calc. for $C_{17}H_{33}N_3O$: C, 69.1; H, 11.3; N, 14.2%). Regeneration by treatment with oxalic acid furnished cyclohexadecanone, m.p. 63°, ν max. 1711, 1412, 1284, 1206, 1177, 1046, 730 cm^{-1} (Found: C, 80.6; H, 12.6. Calc. for $C_{16}H_{30}O$: C, 80.6; H, 12.7%).

Cyclopentadecanone (I)

Cyclopentadecanone was similarly prepared from cyclopentadec-2-ol-1-one (XXXII), m.p. 63°, $\nu_{max.}$ 1711, 1404, 1281, 1208, 1154, 1125, 1073, 1052, and 835 cm^{-1}. (Found: C, 80.4; H, 12.6. Calc. for $C_{15}H_{28}O$: C, 80.3; H, 12.6%).

Semicarbazone, m.p. 188-189° (Found: C, 68.7; H, 11.4; N, 14.9. Calc. for $C_{16}H_{31}N_3O$: C, 68.5; H, 11.1; N, 14.9%).

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CHAPTER III

SYNTHESIS OF C_{15} AND C_{16} α,ω- DICARBOXYLIC ACIDS AND ω-HYDROXY ACIDS USING ENAMINE CONDENSATIONS FOR CHAIN EXTENSION AND THEIR SUBSEQUENT CYCLISATION TO MACROCYCLIC KETONES AND LACTONES.

ABSTRACT

Employing enamine acylation for chain extension ∝,ω-dicarboxylic acids and ω-hydroxy acids containing 15- and 16- carbon atoms in the chain have been prepared, from undec-10-enoic acid.

Undec-10-enoyl chloride on condensation with morpholine enamines derived from cyclopentanone and cyclohexanone afforded 2-undec-10-enoyl cycloalkananones which were converted to the corresponding keto acids by their acid cleavage. The keto acids so obtained furnished hexadec-15-enoic acid and heptadec-16-enoic acid on Huang-Minlon reduction. These acids were converted to the ∝,ω-dicarboxylic acids by oxidation with potassium permanganate or potassium permanganate-sodium metaperiodate mixture. ω-Hydroxy acids were obtained by the reduction of the ozonides of these terminally unsaturated acids. Reduction of these acids to alcohols followed by the oxidation of the end-double bond after protecting the hydroxyl function as its acetate also effected this conversion.

The ∝,ω-dicarboxylic acids and ω-hydroxy acids prepared thus were cyclised to cyclopentadecanone (exaltone), cyclohexadecanone, cyclopentadecanolide (exaltolide), and cyclohexadecanolide (dihydroambrettolide) respectively.

Exaltone was also prepared from oleic acid employing a similar procedure.

Occurrence of Macrocyclic Lactones

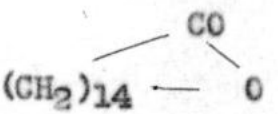
Exaltolide (I) is present in the oil of Angelica archangelica Officinalis, though it has not been actually isolated from this source. Müller[1] was the first to undertake the chemical investigation of this oil and reported the presence of an unknown terpene, a pentanoic acid and a hydroxy myristic acid. Later Beilstein and Wiegland[2] suggested that this oil contained only terpenoids. In 1896, Ciamician and Silber[3] studied the higher boiling fraction of this oil and found that it had a "not very agreeable odour remotely of musk". This was the first indication of a musk odorant in this oil. Due to the complexity of the mixture, it however could not be isolated in a pure form. But these workers could isolate a hydroxy pentadecanoic acid, $C_{15}H_{30}O_3$, m.p. 83°, from the hydrolysis product of this fraction. Kerschbaum[4] in 1927 proved this acid to be identical with 15-hydroxy pentadecanoic acid (IV) and prepared the lactone itself from the silver salt of 15-bromo pentadecanoic acids. Later several syntheses of this lactone have been reported and now it is available in the market in different trade names like exaltolide (Firmenich and Co.), Thibettolide (Givaudin) and Musk lactone (Polak and Schwarz).

Dihydroambrettolide (III) does not occur in nature although its hydrolysis product, juniperic acid (V), is present in many plant and animal waxes.

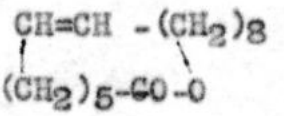
$HO.\ CH_2.\ (CH_2)_{13}.\ COOH$ (IV)
$HO.\ CH_2\ (CH_2)_{14}.\ COOH$ (V)

This compound has also got the characteristic musk odour, and blending properties comparable to those of exaltolide.

To some extent, these compounds especially exaltolide (I) and ambrettolide (II) are employed in the flavour industry as well. These lactones are also valuable as fixing agents for perfumery spirit, their action being more marked than that of the usual fixatives.



(I)



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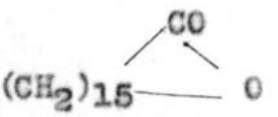


(III)

Recently Guillot[5] and Le Magnan[6] studied the reaction of normal men and women to the odour of exaltolide and found that the effect differed considerably with the sex. Their experiments showed that this phenomenon can conveniently be employed as a criterion to detect the deficiency in the female sex-hormones.

Earlier Syntheses

The earlier syntheses of macrocyclic lactones had been through the oxidation of macrocyclic ketones,[7] by the Baeyer-Villiger procedure.[8] The next step was the application in this field of the theoretically highly interesting high dilution principle which had previously been introduced by Ruggli[9] and Ziegler,[10] and supported and worked out by Stoll and co-workers[11] by their admirable kinetic studies. It is based on the simple consideration that in all cases where an intramolecular reaction competes with an intermolecular one, the latter can be checked and the former enhanced by carrying out the reaction at high dilution. This technique enabled Stoll[12] to reduce the lactonisation to simple azeotropic esterification. Stoll and collaborators by employing the same principle prepared lactones from the lithium[13] and potassium[14] salts of ω-halo acids. A new application of the same process, though incorrectly interpreted, was reported by Hunsdiecker,[15] where the ω-bromo acids were refluxed in a large volume of methyl ethyl ketone over an excess of potassium carbonate. The potassium salts were formed which got cyclised to lactones. This reaction is essentially homogeneous as was proved later by Stoll.[16]

Although yields are high, the high dilution technique is not convenient from the preparative point of view, as the output per unit time per unit volume of the apparatus is very low. In 1935, the brilliant investigations of Carothers[17]

led to a new lactonisation method which overcame this difficulty. He prepared linear polyesters of the ω-hydroxy acids by thermal polymerisation. These polymers were then depolymerised in presence of catalysts in vacuo to obtain the monomeric lactones in 70% yield. Another useful method employing the trans-esterification for the synthesis of lactones was reported by Collaud[18] in 1942. In this method, glycerol esters of the hydroxy acids were heated under vacuum in presence of glycerine and trans-esterification catalysts to get monomeric lactones, which distilled out alongwith glycerol. Beets and Essen[19] improved and extended this reaction by heating polymers of hydroxy acids or their copolymers with polyhydric alcohols in presence of alkaline catalysts and an entraining agent like glycerol to obtain the monomeric lactones. Several other ester-interchange catalysts have been tried to effect the depolymerisation.[20]

Stoll and Bolle[21] effected lactonisation in the gaseous phase by employing the formates of hydroxy acids which were passed over heated titanium oxide catalyst.

Recently Carnduff[22] and co-workers, and Bergelson and collaborators[23] prepared exaltolide through the intra-molecular oxidative coupling of the appropriate terminal diacetylenic compounds.

Raw Materials

Due to the incentive provided by the development of newer and improved methods of cyclisations, the attention in recent years has mainly been centered on the synthesis of ∝,ω-bifunctional compounds. 15-Hydroxy pentadecanoic acid (IV) was first isolated by Ciamician and Silber,[3] and Kerschbaum[4] established its constitution. 16-Hydroxy hexadecanoic acid (V) (juniperic acid), is present in wool wax, and waxes of many plants.[24] These acids have been prepared by the electrolytic process by the Russian school.[24,25] Another synthesis of these acids consist in the reduction[26] of the monoesters of corresponding dicarboxylic acids. Recently Nesmeyanov[27] prepared a series of ω-hydroxy acids from ω-trichloro alkyl chlorides obtained from the telomerisation reactions.[28] In this Laboratory, methods have been developed for the synthesis of these acids from erucic[29] and aleuritic acids.[30]

Chain Extension Procedures

Most of the earlier methods of chain extension excepting the electrolytic coupling[31] and acyloin reaction[32] effected an increment of three or less carbon atoms[33-35] in the chain. Later, better methods which could effect chain lengthening by 5 or more carbon atoms were evolved, the added advantage being the easier separation of the starting and resultant compounds. Of these methods, the more practicable

ones consist in the opening of substituted homo- or hetero-cyclic compounds. Fieser[36] oxidised tertiary alcohols obtained from the condensation of cyclohexanone with alkyl magnesium bromides, with chromium trioxide in glacial acetic acid, to obtain 6-keto acids. This method has since been employed for the synthesis of a series of 5-, 6-, 7-, 8-, and 15-keto acids;[37-40] but the yields were seldom better than 15%. Collaud,[18] Smith and later Diapers[41] dehydrated these tertiary alcohols and ozonized the resultant unsaturated compounds to obtain the keto acids. These unsaturated compounds could also be oxidised by potassium permanganate (vide Part II). Kharasch[42] showed that in presence of peroxides or ultraviolet radiation, end-olefines reacted with cyclic ketones to afford 2-substituted products. Nikishin, Somov and Petrov,[43] oxidised these 2-alkyl cycloalkanones with potassium dichromate and sulphuric acid to obtain keto acids. Crombie and Gold[44] used tetrahydropyran derivatives, whereas Eglinton, Jones and Whiting[45] employed tetrahydrofuran derivatives for the synthesis of acids, by the cleavage of the hetero-ring. Rodd[46] et al. prepared long chain acids by the reductive desulphurisation of thiophene derivatives. Lukes[47] prepared a series of long chain acids employing N-methyl succimide and glutarimide.

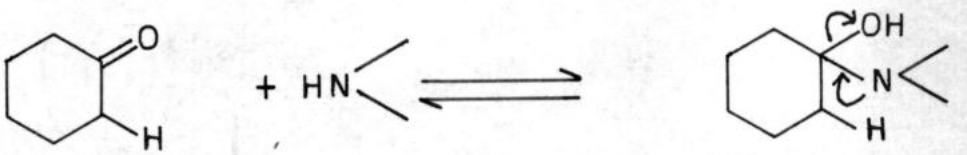
A convenient method for ring-cleavage was developed by Hauser and Swamer.[48] They treated cyclic β-diketones with alkali to obtain keto acids. Many methods are available

for the synthesis of β-dicarbonyl compounds. Adam and Hauser,[49] prepared these by the action of acid anhydrides on cyclic ketones in presence of borontrifluoride. Dimedone[50] and ethyl cyclopentanone-2-carboxylate[51] have also been employed for their syntheses. But the method reported by Stork and co-workers[52] surpasses all the rest in convenience and yield. In this procedure enamines derived from cyclic ketones and cyclic secondary amines were treated with acyl halides when the acylation in 2-position took place.

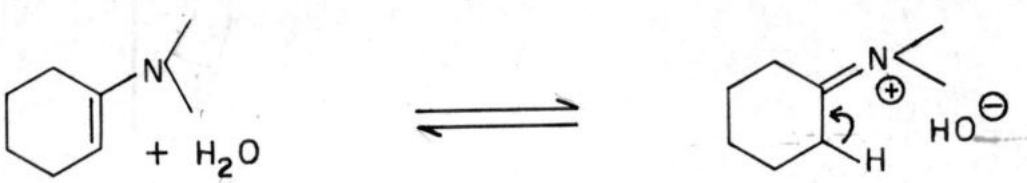
Present Synthesis

In the present investigation the enamine condensation has been employed for chain extension.

Cyclic ketones react with secondary amines to yield enamines in presence of catalysts like p-toluene sulphonic acid and Dowex-50.

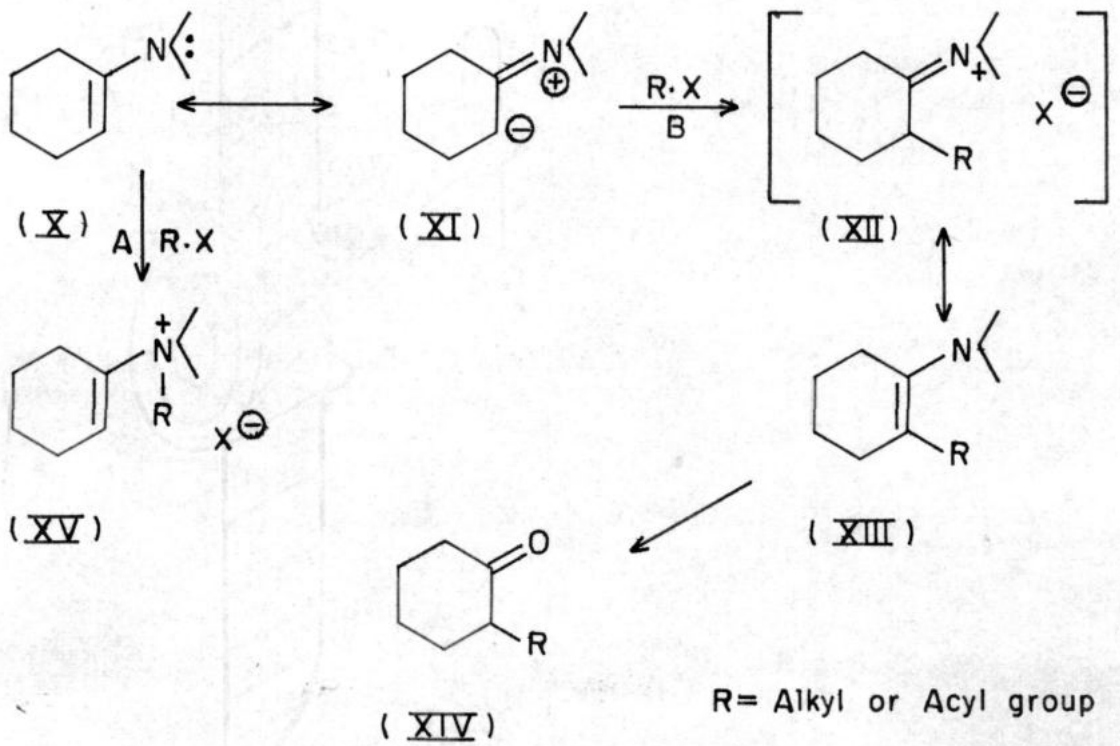


(VI) (VII) (VIII)



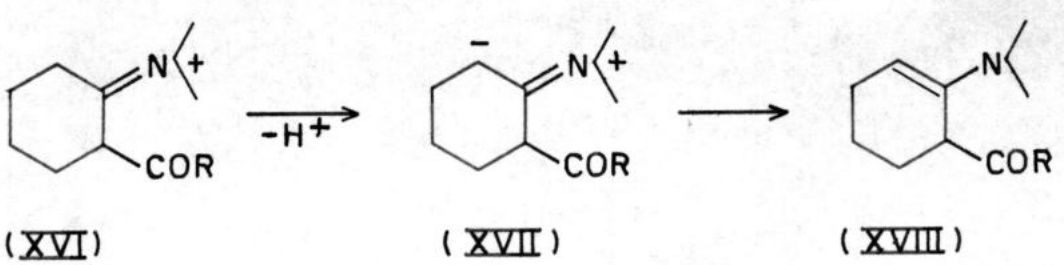
(X) (IX)

These enamines can undergo alkylation and acylation in an irreversible manner by path (A) to form quarternary salts by N-substitution or by path (B) to form C-adducts which would yield substituted ketones on hydrolysis.

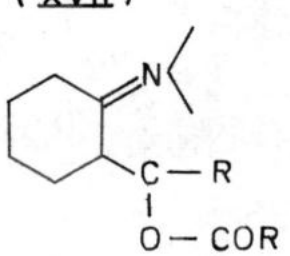


(X) (XI) (XII) (XV) (XIII) (XIV)

Due to the much lower reactivity of the mono-acylated enamine (XVIII) formed from the salt of the type (XVI) by the loss of a proton, the reaction does not proceed further to form 2,2' diacylated product.



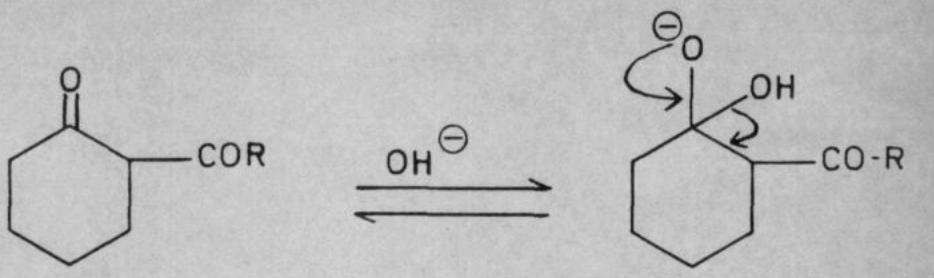
(XVI) (XVII) (XVIII)



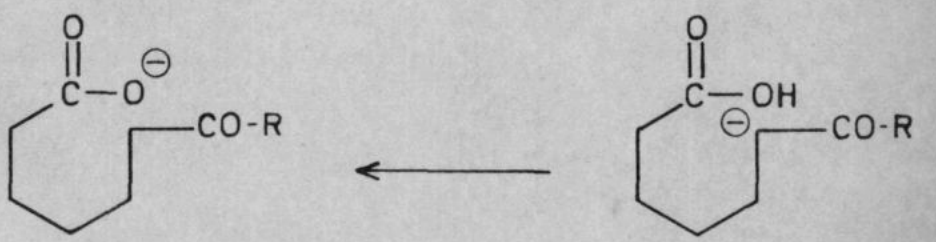
(XIX)

Acid cleavage of 1,3-diketones

Path-C

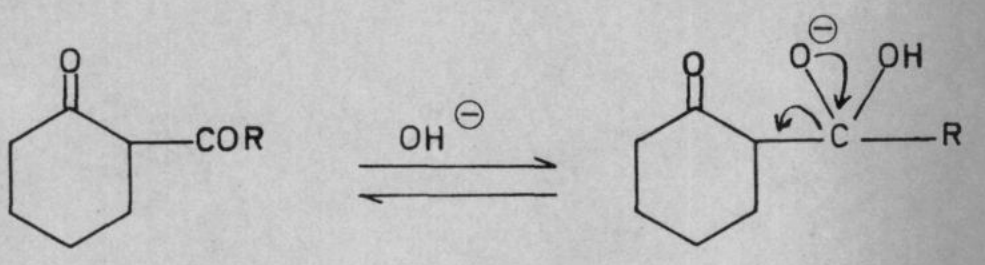


XX XXI

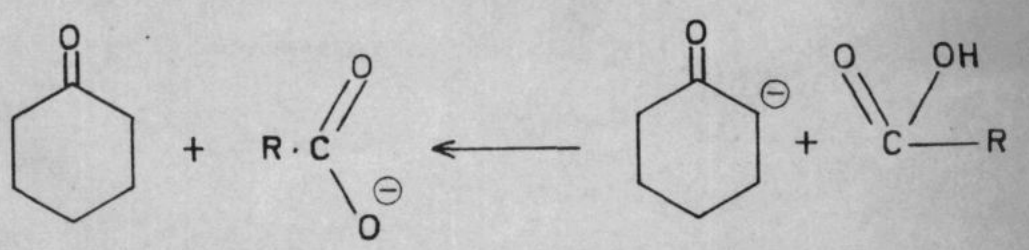


XXIII XXII

Path-D



XX XXIV



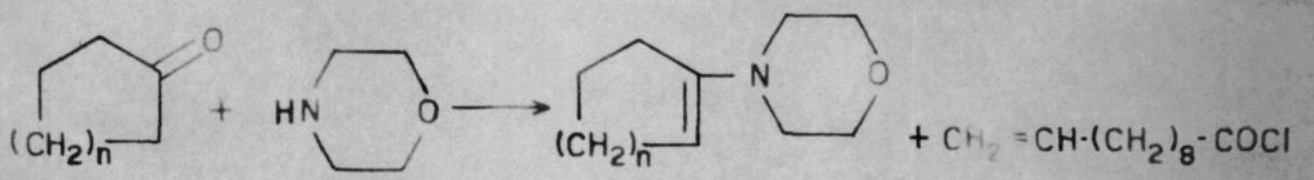
XXVII XXVIII XXXV XXXVI

The intermediate vinylogous amide, being much less basic than the parent enamine, does not form salt and therefore Stork employed two moles of the enamine for the reaction. Hünig et al.[54] employed triethyl amine to remove the hydrogen chloride formed, thus saving the consumption of the more costly enamine. They also demonstrated that for acylation, the less reactive morpholine enamines were better than the more reactive ones derived from piperidine and pyrolidine. Excess of acid chloride resulted in the formation of the vinylogous anhydride (XIX).

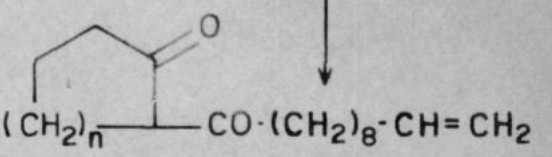
The 2-acyl cycloalkanones can undergo cleavage on alkali treatment either by path (C) or by path (D), but it has been shown that the reaction proceeds mainly by path (C)[55] to yield about 60-70% of the acid (XXIII).

In the syntheses reported in this chapter morpholine enamines of cyclopentanone and cyclohexanone were employed. Morpholino cyclopentene (XXIX) on condensation with undec-10-enoyl chloride gave 2-(undec-10-enoyl) cyclopentanone (XXX). This on acid cleavage afforded 6-oxo-hexadec-15-enoic acid (XXXI) which could be oxidised with potassium permanganate - sodium metaperiodate in alkaline medium[56] to 6-oxo-pentadecanedioic acid (XXXIII). The unsaturated keto acid (XXXI) on Huang-Minlon reduction[57] gave hexadec-15-enoic acid (XXXII) which on oxidation afforded pentadecanedioic acid (XXXIV). Pentadecanedioic acid was also obtained by the reduction of

Dicarboxylic acids from Undec-10-enoyl chloride



XXIX (n=1), XXXV (n=2)



XXX (n=1); XXXVI (n=2)

$CH_2=CH-(CH_2)_{12+n}-COOH$ ← $CH_2=CH-(CH_2)_8-CO-(CH_2)_{n+3}-COOH$

XXXII (n=1); XXXVIII (n=2) XXXI (n=1); XXXVII (n=2)

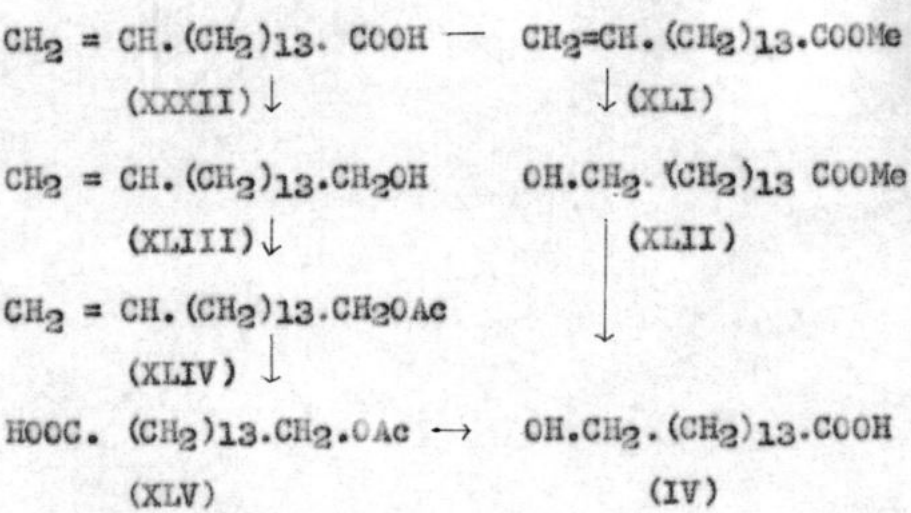
$HOOC-(CH_2)_{n+12}-COOH$ ← $HOOC-(CH_2)_8-CO-(CH_2)_{n+3}-COOH$

XXXIV (n=1); XL (n=2) XXXIII (n=1); XXXIX (n=2)

the keto-dicarboxylic acid (XXXIII) with hydrazine hydrate and alkali. By a similar series of reactions hexadecanedioic acid (XL) was prepared from 2-(undec-10-enoyl) cyclohexanone (XXXVI) through the intermediates of 7-oxo-heptadec-16-enoic acid (XXXVII), heptadec-16-enoic acid (XXXVIII) and 7-oxo-hexadecanedioic acid (XXXIX).

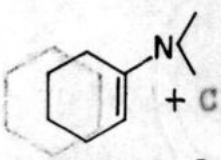
These dicarboxylic acids were cyclised to exaltone and cyclohexadecanone respectively, as described in Chapter II.

Heptadec-16-enoic acid (XXXVIII) was ozonised and the ozonide in the cold was reduced with sodium borohydride to obtain 16-hydroxy hexadecanoic acid (V). Thin layer chromatography revealed a slight impurity of thapsic acid which was removed by chromatography of the ester. In the case of hexadec-15-enoic acid (XXXII), the acid was first esterified with diazomethane to the methyl ester (XLI). The hydroxy ester (XLII) obtained by the reduction of the ozonide of (XLI) was purified by chromatography and was hydrolysed to 15-hydroxy pentadecanoic acid (IV).



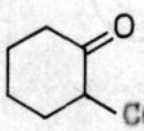
Hexadec-15-enoic acid (XXXII) gave hexadec-15-enol (XLIII) on lithium aluminium hydride reduction.[59] The alcohol as its acetate (XLIV) on oxidation with potassium permanganate in presence of acetic acid, sufficient to neutralise the alkali liberated which would otherwise hydrolyse the protecting acetate group leading to the formation of the dicarboxylic acid, furnished 15-acetoxy-pentadecanoic acid (XLV) which was hydrolysed to the hydroxy acid (IV).

These hydroxy acids were heated to yield a polyester which was depolymerised by distilling under vacuum in presence of magnesium oxide as a catalyst to obtain exaltolide (I) and dihydroambrettolide (III).



+ ClOC.$(CH_2)_7$ CH=CH.$(CH_2)_7$.CH_3

(XLVI)



CO.$(CH_2)_7$. CH=CH.$(CH_2)_7$.CH_3

(XLVII)

HOOC.$(CH_2)_5$. CO.$(CH_2)_7$. CH=CH.$(CH_2)_7$.CH_3

(XLVIII)

CH_3.$(CH_2)_7$.CH=CH.$(CH_2)_{13}$.COOH → HOOC.$(CH_2)_5$.CO.$(CH_2)_7$.COOH

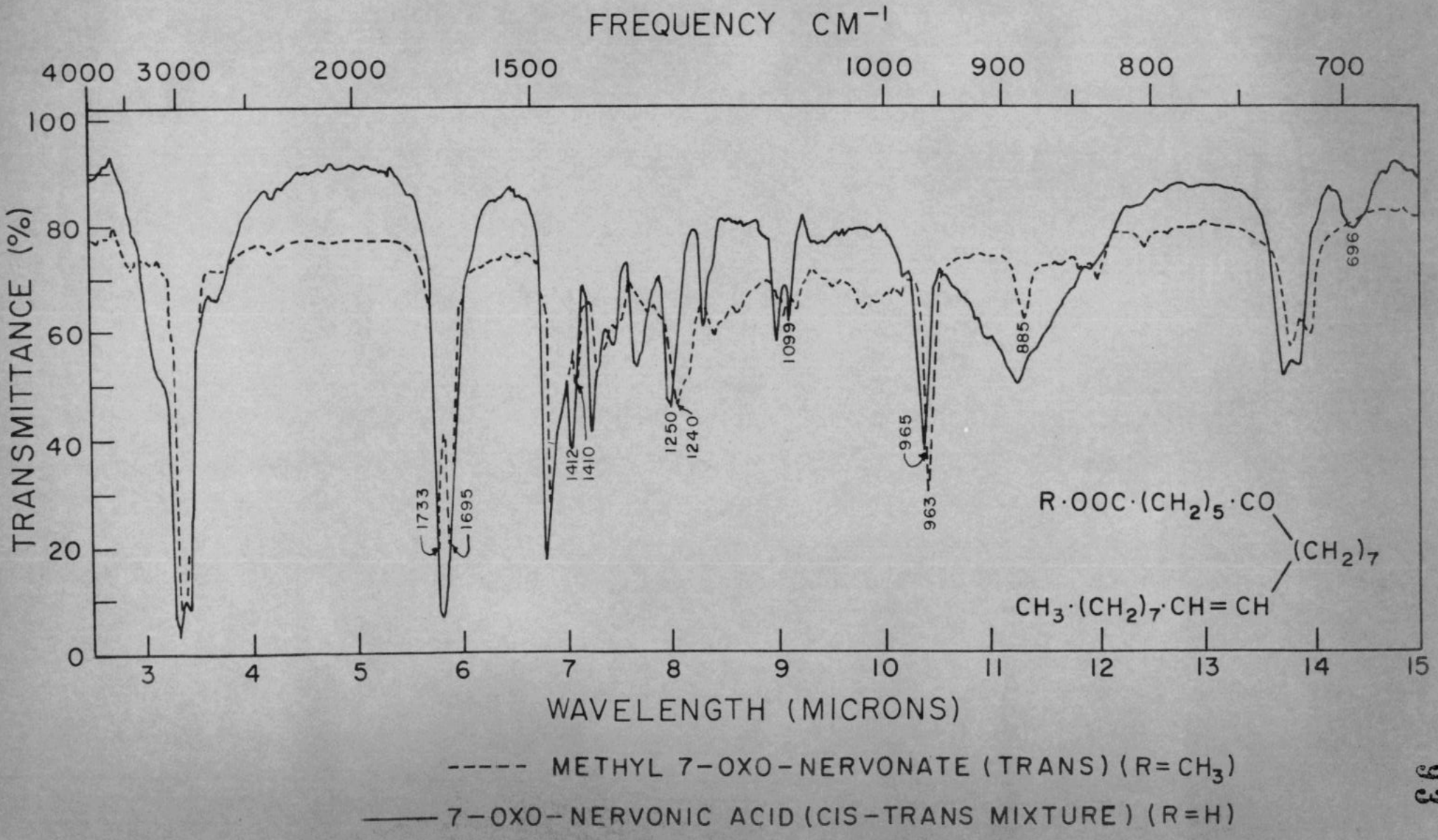
(XLIX) (L)

CH_3.$(CH_2)_7$.CH(OH).CH(OH).$(CH_2)_{13}$.COOH. HOOC.$(CH_2)_{13}$.COOH

(LI) (XXXIV)

OHC.$(CH_2)_{13}$.COOH

(LII)


FREQUENCY CM⁻¹
4000 3000 2000 1500 1000 900 800 700
TRANSMITTANCE (%)
100 80 60 40 20 0
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
1733
1695
1412
1410
1250
1240
1099
965
963
885
696
R·OOC·(CH2)5·CO
(CH2)7
CH3·(CH2)7·CH=CH
----- METHYL 7-OXO-NERVONATE (TRANS) (R=CH3)
—— 7-OXO-NERVONIC ACID (CIS-TRANS MIXTURE) (R=H)

Oleoyl chloride (XLVI) was prepared by the action of thionyl chloride on oleic acid. This was condensed with morpholino cyclohexene to obtain 2-oleoyl cyclohexanone (XLVII). This compound, in its infrared spectrum revealed a peak at 971 cm^{-1}, attributable to a trans-disubstituted double bond.[62] It was proved by the examination of the spectra of the acid chloride that this 'elaidinization' did not occur during treatment with thionyl chloride. Heating oleoyl chloride with triethyl amine, and hydrochloric acid also did not result in any isomerisation to the trans-form. But the adduct before treatment with hydrochloric acid for hydrolysis also showed this band in the spectrum. Therefore, the partial "elaidia-nation" presumably took place during the addition reaction.

This diketone (XLVII) on treatment with strong alkali at 100 and 125° for 30 and 60 min. respectively, followed by acidification afforded a mixture of cis- and trans- isomers of 7-oxo-tetracos-15-enoic acid, m.p. 71-73° (XLVIII). Stork et al.[52] obtained 7-oxo-tetracos-15-enoic acid, m.p. 54-64°, by effecting the cleavage by heating with aqueous potassium hydroxide in methanol-dioxan mixture. More drastic nature of the conditions employed in the present investigation may be responsible for the higher percentage of the trans-form present. This cis-trans- mixture could be converted to the pure trans-isomer by treatment with nitrous acid.[63] The trans-acid melted at 82°. The acids, m.p.71-73° and m.p. 82° gave

the same trans-nervonic acid (XLIX), m.p. 66.5-68° (from pet. ether), 68-69° (from acetic acid) on Huang-Minlon reduction. This confirms the earlier assumption that the isomerisation is due to the presence of concentrated alkali at high temperatures.

Nervonic acid on oxidation gave pentadecanedioic acid (XXXIV). This dibasic acid was also obtained by the reduction of the 7-keto-pentadecanedioic acid (L) obtained by the oxidation of the keto acid (XLVIII).

Nervonic acid was also oxidised to pentadecanedioic acid, through dihydroxy lignoceric acid (LI) and the aldehyde (LII). This dicarboxylic acid was converted to exaltone.

EXPERIMENTAL

Morpholinocyclohexene (XXXV)

Cyclohexanone (92 g) in benzene (800 ml) was mixed with morpholine (93 g) and p-toluene sulphonic acid (8 g) in benzene and the mixture was refluxed for 8 hr. removing the water formed azeotropically. Solvent was removed and the residue distilled through a fractionating column. The earlier fractions comprising the ketone and amine were discarded and morpholino cyclohexene was collected, b.p. 93-95°/4 mm., n_D^{23} 1.5085, $\nu_{max.}$ 1668, 1639, 1447, 1379, 1339, 1304, 1124, 1092, 1066, 1035, 1024, 941, 934, 898, 870, 833, 787, 755 and 650 cm^{-1} (Found: C, 72.0; H, 9.75. Calc. for $C_{10}H_{17}NO$: C, 71.80; H, 10.2%).

Morpholinocyclopentene (XXIX)

By condensing cyclopentanone (84 g) with morpholine (93 g) in benzene (800 ml) containing p-toluene sulphonic acid as described above, morpholinocyclopentene was prepared, b.p. 120-123°/30 mm., n_D^{26} 1.5050.

Undec-10-enoyl chloride

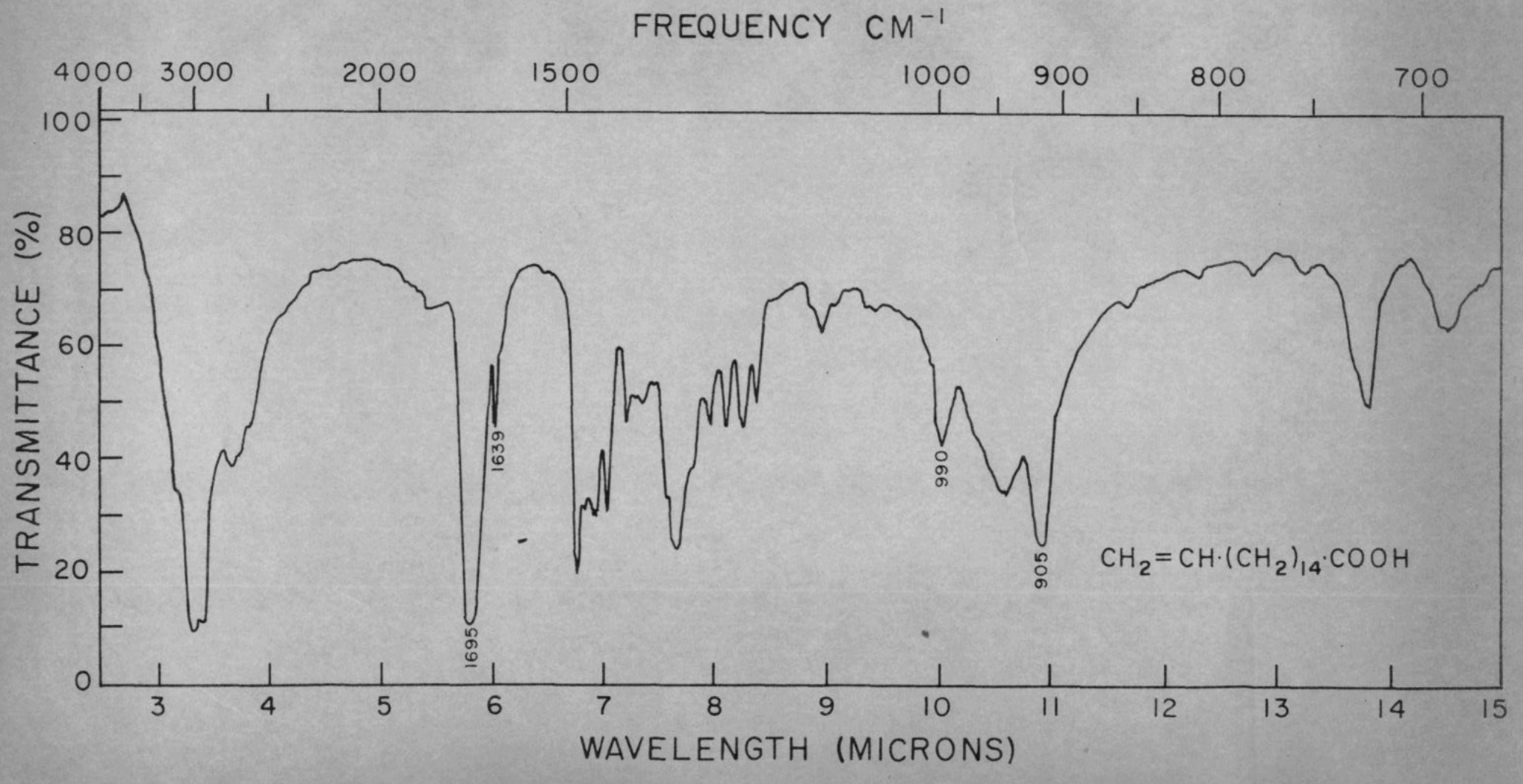
Undec-10-enoic acid (40 g) was refluxed with thionyl chloride (40 g) for 30 min. Excess of thionyl chloride was removed under reduced pressure. The last traces of thionyl chloride were removed by adding dry benzene and distilling it off under reduced pressure. The crude product was purified by distillation (45 g), b.p. 120° (bath)/0.8 mm.

2-(Undec-10-enoyl) cyclohexanone (XXXVI)

To a mixture of morpholinocyclohexene (25 g) and triethylamine (18 g) in dry chloroform (300 ml), undec-10-enoyl chloride (40 g) in chloroform (100 ml) was added with stirring during 1 hr. The temperature was maintained at ca. 35°, stirring continued for another 3 hr. and the mixture was allowed to stand overnight at room temperature. Solvent was removed under reduced pressure and the residue in ether was washed with water to remove mineral acid followed by 5% sodium carbonate solution to remove the organic acid impurities and finally with water until neutral. The ethereal solution was dried (Na_2SO_4), solvent was recovered and the residue distilled to obtain the 2-(undec-10-enoyl) cyclohexanone (30 g), b.p. 168°/0.5 mm. (Found: C, 77.1; H, 11.2. $C_{17}H_{28}O_2$ requires: C, 77.2; H, 10.7%).

7-Oxo-heptadec-16-enoic acid (XXXVII)

The diketone (XXXVI, 10 g) was mixed with potassium hydroxide (10 g) in water (7 ml) with vigorous stirring. The temperature was raised to 100° and maintained for 10 min. and then at 125° for 30 min. The reaction product was cooled and the solid mass dissolved in water and poured with stirring into an excess of cold dilute hydrochloric acid. The acid was filtered off (6 g) and crystallised from glacial acetic acid to obtain pure 7-oxo-heptadec-16-enoic acid, m.p. 68°, ν max. 1702, 1638, 995, 909 cm^{-1} (Found: C, 72.8; H, 10.7. $C_{17}H_{30}O_3$ requires: C, 72.3; H, 10.7%).



HEPTADEC-16-ENOIC ACID

7-Oxo-hexadecanedioic acid (XXXIX)

To a cooled solution (ca 5°) of 7-oxo-heptadec-16-enoic acid (6.8 g) in acetone (70 ml), finely powdered potassium permanganate (20 g), was added in small lots during 1 hr. with stirring and the mixture stirred for another 2 hr. It was left overnight at 15° finally refluxed for 30 min. Acetone was [illegible] in cold water and sulphur[illegible] bisulphite. The was extracted with eth[illegible] ter concentration of the solution, it was pr[illegible] pet.ether. The crude acid (5 g) [illegible] tallised [illegible] to obtain the pure keto dicarboxylic acid, [illegible] 10° [illegible] 63.8; H, 9.6. Calc. for [illegible]: C, 64.0; H, [illegible]).

Heptadec-16-enoic acid (XXXVIII)

7-Oxo-heptadec-16-enoic acid (XXXVII, 2.5 g), potassium hydroxide [illegible] hydrazine hydrate (1.4 ml) in diethylene glycol (14 [illegible] 95° for 1 hr. under an air condenser. [illegible] and the bath temperature raised [illegible] 210° for 5 hr. The mixture was cooled [illegible] diluted to liberate the unsaturated acid (2.4 g), which crystallised from pet.ether, m.p. 49° $\nu_{max.}$ 1640, [illegible] 909 cm-1. (Found: 75.8; H, 12.1. Calc. for $C_{17}H_{32}O_2$: C, 76.1; H, 12.0%).

Hexadecanedioic acid (XL)

Heptadec-16-enoic acid (1.4 g) was oxidised with potassium permanganate (5 g) in acetone (30 ml) in the cold following the procedure described earlier. The crude dicarboxylic acid was crystallised from acetic acid, m.p. 125°. The same dibasic acid was also prepared by reducing 7-oxohexadecanedioic acid (0.5 g) with hydrazine hydrate (0.28 ml) and potassium hydroxide (0.6 g) in diethylene glycol (10 ml) at 210°. The acid after crystallisation from acetic acid had m.p. 125° (Found: C, 67.0; H, 10.50. Calc. for $C_{16}H_{30}O_4$: C, 67.1; H, 10.6%).

2-Undec-10-enyl cyclopentanone (XXX)

Morpholinocyclopentene (23 g) was condensed with undec-10-enoyl chloride (40 g) in presence of triethyl amine (18 g) in chloroform (400 ml) at 35° and the condensate refluxed with 20% hydrochloric acid (100 ml) under stirring for 8 hr. to obtain the diketone (XXX, 29 g), b.p.170°/2.5 mm. n_D^{26} 1.4615, $\nu_{max.}$ 1710 and 1667 cm^{-1} (Found: C, 75.5; H, 10.6. $C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.5%). This compound was used as such without further purification.

6-Oxo-hexadec-15-enoic acid (XXXI)

The diketone (XXX, 8 g) was treated with potassium hydroxide (9 g) in water (6 ml) with vigorous stirring at 100° for 10 min. and at 125° for 30 min. The mixture was cooled, dissolved in water and acidified with cold dilute hydrochloric acid. The acid so liberated was washed free of mineral acids and crystallised from glacial acetic acid to obtain the pure

keto-enoic acid (XXXI, 5 g), m.p. 65°, $\nu_{max.}$ 1702, 1410, 999 & 905 cm^{-1} (Found: C, 71.55; H, 10.8. Calc. for $C_{16}H_{28}O_3$ C, 71.6; H, 10.5%).

6-Oxo-pentadecanedioic acid (XXXIII)

6-Oxo-hexadec-15-enoic acid (6.7 g) was dissolved in water containing potassium carbonate (10.5 g) and to this was added another solution containing potassium permanganate (0.8 g) and sodium metaperiodate (42 g) in water (1 l). The mixture was kept at room temperature for 24 hr. and was then acidified with 10% sulphuric acid and extracted with 500 ml portions of ether. The combined ethereal extract was washed with water, concentrated and the keto-dicarboxylic acid (6 g) was precipitated by adding petroleum ether. Crystallisation from benzene yielded the pure 6-keto-pentadecanedioic acid, m.p. 108° (Found: C, 62.8; H, 9.3. Calc. for $C_{15}H_{26}O_5$: C, 62.9; H, 9.3%).

Hexadec-15-enoic acid (XXXII)

6-Oxo-hexadec-15-enoic acid (0.5 g) in diethylene glycol (5 ml) was reduced with hydrazene hydrate (0.3 ml) and potassium hydroxide (0.5 g) to obtain hexadec-15-enoic acid (0.8 g), m.p. 47°, $\nu_{max.}$ 1703, 1639, 995 and 909 cm^{-1}. (Found: C, 75.6; H, 11.4. Calc. for $C_{16}H_{30}O_2$: C, 75.5; H, 11.9%).

Pentadecanedioic acid (XXXIV)

The acid (XXXII, 0.13 g) in aqueous potassium carbonate (0.2 g, in 50 ml) was oxidised with sodium metaperiodate (1 g) and potassium permanganate (1 ml of 0.1 M solution) at room

temperature. The crude dicarboxylic acid (XXXIV) (0.12 g) was crystallised from acetic acid, m.p. 113°, undepressed on mixing with an authentic acid (Found: C, 65.7; H, 10.4. Calc. for $C_{16}H_{28}O_4$: C, 66.1; H, 10.4%).

16-Hydroxy hexadecanoic acid (V)

Ozonised oxygen was bubbled through a solution of heptadec-6-enoic acid (0.43 g) in absolute methanol (10 ml) at the rate of 20 mg per hr for 1.5 hr. at 0°. The cold solution of the ozonide was added to a cooled solution (ca 5°) of sodium borohydride (0.37 g) and potassium hydroxide (0.18 g) in water with stirring and cooling. The mixture was left overnight at room temperature. Methanol was removed under pressure and the residue poured into dilute hydrochloric acid. The liberated hydroxy acid (0.4 g) was washed and crystallised thrice from ethyl acetate, m.p. 94° (Found: C, 70.1; H, 11.8. Calc. for $C_{16}H_{32}O_3$: C, 70.5; H, 11.8%).

16-Hydroxy pentadecanoic acid (IV)

Methyl hexadec-15-enoate (XLI, 0.45 g), b.p.165°/0.6 mm., n_D^{26} 1.4500 (Found: C, 75.25; H, 11.0. $C_{17}H_{32}O_2$ requires: C, 75.1; H, 11.8%). In absolute methanol (10 ml) was ozonised (80 mg of ozone per hour) for 1.5 hr. The cold solution of the ozonide was added dropwise to a well stirred solution of sodium borohydride (0.3 g) in absolute methanol (10 ml). After keeping at 15° overnight, methanol was removed.

The ethereal solution of the hydroxy ester (XLII) was washed with 5% sodium carbonate solution. The crude ester was crystallised from pet.ether, m.p. 49° (Found: C, 70.7; H, 12.1. Calc. for $C_{16}H_{32}O_3$: C, 70.5; H, 11.8%). This ester on saponification and acidification yielded 15-hydroxy pentadecanoic acid, m.p. 84° (Found: C, 69.4; H, 11.8. Calc. for $C_{15}H_{30}O_3$: C, 69.7; H, 11.7%).

Hexadec-15-enol (XLIII)

Hexadec-15-enoic acid (XXXII, 2.5 g) in dry ether (10 ml) was added dropwise with stirring to an ice cold suspension of lithium aluminium hydride (0.5 g) in ether(50 ml). The mixture was then refluxed for 5 hr, cooled and decomposed with aqueous alcohol. The ethereal solution was washed with bicarbonate and finally with water. The solution was dried, ether removed and the residue distilled to give hexadec-15-enol (XLIII, 2 g), b.p. 150°/0.5 mm., $\nu_{max.}$ 3380, 1640, 990 and 909 cm^{-1}. (Found: C, 79.8; H, 13.2. $C_{16}H_{32}O$ requires: C, 79.9; H, 13.4%).

15-Acetoxy pentadecanoic acid (XLV)

The alcohol (1 g) was acetylated with acetic anhydride (10 ml) in pyridine (40 ml) at 100° for 3 hr. The acetate (XLIV) was distilled, b.p. 165°/0.9 mm.

The acetate (0.6 g) was oxidised with potassium permanganate (2 g) in acetone (25 ml) containing acetic acid (0.3 ml) at ca 5°. The mixture was kept overnight at 10°.

The acetoxy acid was crystallised from petroleum ether, m.p. 57°, $\nu_{max.}$ 1730, 1700, 1250, and 721 cm^{-1} (Found: C, 68.4; H, 10.9. Calc. for $C_{17}H_{32}O_4$: C, 68.0; H, 10.7%). On alkaline hydrolysis this acid furnished hydroxy pentadecanoic acid, m.p. and mixed m.p. 84°.

Oleoyl chloride (XLVI)

Oleic acid (b.p. 166-167°/0.05 mm., eq. wt. 281.5; Calc. for $C_{17}H_{33}COOH$: 282.45) (Found: C, 76.6; H, 12.2. Calc. for $C_{18}H_{34}O_2$: C, 76.5; H, 12.1%) (80 g) was treated with thionyl chloride (60 g) at the boiling point of the latter for 3 hr. Excess of thionyl chloride was distilled off. The residue was taken in petroleum ether, washed with cold water, the solvent removed and the residue distilled to obtain oleoyl chloride, b.p. 190° (bath)/0.5 mm. (90 g) (Found: C, 71.4; H, 9.7. Calc. for $C_{18}H_{35}OCl$: C, 71.8; H, 10.06%).

2-Oleoyl cyclohexanone (XLVII)

Morpholinocyclohexene (40 g) was condensed with oleoyl chloride (80 g) in chloroform (600 ml) in presence of triethyl amine (30 g) at 35°. The reaction product was hydrolysed with 20% hydrochloric acid (100 ml) by heating for 6 hr. on a water bath to obtain 2-oleoyl cyclohexanone, b.p. 140°/0.002 mm, $\nu_{max.}$ 1736, 1656, 1618, 1600, 1460, 1418, 1250, 965(w) and 721 cm^{-1} (Found: C, 79.2; H, 11.8. $C_{24}H_{42}O_2$ requires: C, 79.5; H, 11.7%).

7-Oxo-tetracos-15-enoic acid (XLVIII)

(a) 2-Oleoyl cyclohexanone (5 g) was opened by heating with 50% potassium hydroxide (25 ml) at 100° for 30 min. and at 150° for 1 hr. to obtain the keto-acid, m.p. 71-73.5°.

(b) 2-Oleoyl cyclohexanone (5 g) was treated with potassium hydroxide (5 g) in water (4.5 ml) at 100° for 3 min. to give the keto-enoic acid (XLVIII), m.p. 74-75.5° νmax. 1695, 1410, 965 (w) and 696 cm^{-1}. (Found: C, 75.5; H, 11.9. $C_{24}H_{44}O_3$ requires: C, 75.7; H, 11.65%).

The keto acid, m.p. 72-73.5° (1 g) was treated with sodium nitrite (0.18 g) and nitric acid (8 ml) diluted to (15 ml) at 75° to get the trans-isomer, m.p. 78.5-80°. Recrystallisation from acetic acid afforded the pure trans-acid, m.p. 82°, ν max. 1698, 1410, 963, 721 cm^{-1} (Found: C, 75.9; H, 12.0. $C_{24}H_{44}O_3$ requires: C, 75.7; H, 11.65%).

Methyl ester was prepared by treatment with diazomethane, m.p. 53°, ν max. 1733, 1700, 1410, and 963 cm^{-1} (Found: C, 76.6; H, 11.9. $C_{25}H_{46}O_3$ requires: C, 76.1; H, 11.75%).

Tetracos-15-enoic acid (XLIX)

Keto nervonic acid (5 g, m.p. 72-73.5°) was reduced with potassium hydroxide (5 g) and hydrazine hydrate (2.5 ml) in diethylene glycol (25 ml) to obtain nervonic acid, m.p. 66.5-68° (from pet. ether), 68-69° (from acetic acid).

Nitrous acid treatment did not raise the melting point, ν max. 1695, 1410 and 965 cm^{-1} (Found: C, 78.3; H, 12.7. Calc. for $C_{24}H_{46}O_2$: C, 78.6; H, 12.6%).

7-Oxo-pentadecanedioic acid (L)

Keto-nervonic acid (0.2 g) was dissolved in water (80 ml) containing potassium carbonate (0.32 g) and a 12% solution of $NaIO_4$ (13 ml) mixed with 0.1 M solution of potassium permanganate (1.5 ml) was added to it. The mixture was kept for 24 hr., acidified, extracted, the extract concentrated and the acid was precipitated with petroleum ether. Recrystallisation from benzene furnished the pure acid, m.p. 114° (Found: C, 62.8; H, 9.3. $C_{15}H_{26}O_5$ requires C, 62.9; H, 9.2%).

Pentadecanedioic acid (XXXIV)

Nervonic acid (0.5 g) in water (35 ml) containing potassium carbonate (1 g) was oxidised with 10% sodium metaperiodate solution (35 ml) and 0.1 M solution of potassium permanganate (5 ml) to obtain pentadecanedioic acid, m.p.114° (Found: C, 65.7; H, 10.4. Calc. for $C_{15}H_{28}O_4$: C, 66.1; H,10.4%).

15,16-Dihydroxy-lignoceric acid (LI)

Nervonic acid (2 g) in acetic acid (50 ml) containing conc. sulphuric acid (1 ml) was oxidised with hydrogen peroxide (3 ml) to obtain the hydroxy acetoxy derivative. This on saponification and acidification yielded 15,16-dihydroxy-lignoceric acid, crystallised from alcohol, m.p. 128°, ν maxi 3240, 1695, 1410, and 1065 cm^{-1} (Found: C, 71.75; H, 12.0. Calc. for $C_{24}H_{48}O_4$: C, 71.9; H, 11.9%).

Dihydroxy lignoceric acid (1 g) in absolute alcohol (100 ml) was oxidised with a 12% solution of sodium meta-periodate (8 ml) during 30 min. at 30°. The mixture was diluted and extracted with ether. Ethereal layer was washed with water, solvent removed, and the residue was freed from pelargonic aldehyde by distillation, b.p. upto 100°/0.5 mm. The residue on crystallisation from pet.ether gave 15-aldehydo-pentadecanoic acid (LII) m.p.80°; $\nu_{max.}$ 2703 and 1730 cm^{-1}.

This acid (0.2 g) in 0.5 N alcoholic potash (10 ml) was oxidised with hydrogen peroxide (10%, 3 ml) to obtain pentadecanedioic acid (XXXIV; m.p. and mixed m.p. 114°).

Cyclisation of the hydroxy acids

(i) Cyclohexadecanolide

ω-Hydroxy hexadecanoic acid (15 g) was heated at 200-230° for 3 hr. and then at 240° for 1.5 hr under reduced pressure (1 mm). To the polyester so obtained, magnesium oxide (2 g) was added and it was depolymerised by distilling under vacuum to yield the crude monomeric lactone, b.p.280-290° (bath)/0.015 mm. The distillate was dissolved in ether, washed with sodium carbonate solution, and then with water until neutral. Removal of solvent followed by the distillation of the residue yielded cyclohexadecanolide (dihydroambrettolide) (9.9 g), b.p.118-120°/0.3 mm., m.p. 33-34°, $\nu_{max.}$ 1729 cm^{-1}. (Found: C, 75.75; H, 11.6. Calc. for $C_{16}H_{32}O_2$: C, 75.5; H, 11.9%).

(ii) Cyclopentadecanolide (Exaltolide)

ω-Hydroxy pentadecanoic acid (1.6 g) was similarly lactonised to cyclopentadecanolide (exaltolide) (0.5 g), b.p.180° (bath)/0.15 mm., $\nu_{max.}$ 1726 cm^{-1}. (Found: C, 74.8; H, 11.5. Calc. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.7%).

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