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MACROCYCLIC PERFUMERY CHEMICALS

A

THESIS

SUBMITTED TO

THE UNIVERSITY OF BOMBAY

FOR

THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

ORGANIC CHEMISTRY

BY

PRASAD GOPALRAO DEVANE, M.Sc.

ESSENTIAL OILS DIVISION

NATIONAL CHEMICAL LABORATORY

POONA 8

INDIA

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By

VASANT VINAYAK DHEKNE, M.Sc.

ESSENTIAL OILS DIVISION,
NATIONAL CHEMICAL LABORATORY,
POONA-8
(INDIA)

(1964)

To

The Registrar,
University of Bombay,
BOMBAY.

Sub: Statement under O.413 by the University teacher and the candidate.

Sir,

The candidate is submitting original work dealing with the synthesis of macrocyclic musk compounds such as exaltolide, exaltone, civetone etc. These products are widely used in the perfumery industry and are also themselves very important and interesting from the chemistry point of view because of their unusual ring size. During the course of this investigation, apart from the use of new raw material, entirely new approaches have been made for the reduction of acyloins to the desired ketones.

The candidate's work on exaltolide forms part of the paper which has already appeared in the Journal of the Chemical Society (J.Chem.Soc., 2348,1962). This paper deals with the result of two independent projects. Those dealing with exaltolide from erucyl alcohol and which are being presented in the thesis were carried out by the candidate.

Some of the results on exaltone have been preliminarily reported from this laboratory in the form of a note (Chem. & Ind., 1334,1960). The candidate has thoroughly standardised this method with addition of newer knowledge

and has worked out all the details as a result of which the method can now be used for preparative purposes.

The newer methods developed for the reduction of acyloin to the corresponding ketones form the unpublished work of the candidate which will be communicated for publication in due course. These results are of considerable importance and in some respects, are advancement over the existing knowledge specially for unsaturated ketones. Synthesis of civetone and iso-civetone carried out by the candidate following the new procedures for reduction may be mentioned as examples.

Yours faithfully,

V. V. Dhekne.

(V. V. Dhekne)
Candidate.

(S. C. Bhattacharyya)
Research-Guide.

P O O N A
December 1964.

A C K N O W L E D G M E N T S

The author is deeply indebted to Dr. S. C. Bhattacharyya, Assistant Director, National Chemical Laboratory, Poona, for his valuable guidance throughout the course of this investigation, and to Drs. B.B. Ghatge and H.H. Mathur for their keen interest and constant encouragement.

The author is especially thankful to Professor K. Venkataraman, Director, National Chemical Laboratory for permission to submit this work in the form of a thesis.

He gratefully acknowledges the help rendered by the microanalysis and spectrophotometric departments. He is grateful to all his colleagues in the laboratory especially Mr. K.C. Abraham and Mr. S.K. Rangachar, for their cheerful cooperation.

(V. V. DHEKNE)

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December 1964.

C O N T E N T S

INTRODUCTION

Macrocyclic perfumery chemicals provide a very fascinating field of research both from the practical as well as from the theoretical point of view. The term 'macrocyclics' is generally used to denote carbocyclic compounds containing nine or more carbon atoms in the ring, though compounds containing nine to thirteen carbon atoms are sometimes classified as medium ring compounds. According to a proposal due to Prelog,[1] and Brown *etal*.[2] the three and four membered cycles are denoted as small rings, the five to seven membered as common rings, the eight to twelve membered rings as medium rings and cycles greater than the twelve membered as large rings. Large ring compounds, particularly those containing fifteen to seventeen carbon atoms are of interest to perfumers due to their musk-like odour, which creates an exalting effect in perfumery compositions.

The macrocyclic musks are amongst the most valued perfumery fixatives and blending substances, of which the ketones are of animal origin, whereas the lactones occur in plant materials. The lactones have a 'floral musk odour' and are, therefore, valuable in the blending of floral perfumes, while the ketones possess 'animal-like' note, which render them invaluable in perfumery blends. The natural sources for these compounds are very limited, and therefore, the musks, at present, are very expensive.

The object of the present investigation was to evolve practical syntheses for the macrocyclic musks starting from easily available indigenous raw materials.

Exaltolide (cyclopentadecanolide) and exaltone (cyclopentadecanone) have been synthesised starting from erucic acid obtainable from mustard oil. Several inter-related routes leading to these two perfumery chemicals have also been developed and are described in Part I and II. The acyloin condensation has been employed for the cyclisation leading to the ketones and in case of the lactones Carother's method of depolymerisation has been used.

With a view to develop an improved process for the reduction of macrocyclic acyloins to ketones, the following methods have been tried and are described in Part III.

(i) Wolff-Kishner reduction of 2-hydroxycyclopentadecanone and 2-hydroxycycloheptadecanone (acyloins) followed by chromic acid oxidation of the resultant monoalcohols.

(ii) Lithium aluminium hydride reduction of tosyl derivatives of 2-hydroxy cyclopentadecanone and 2-hydroxy cycloheptadecanone followed by chromic acid oxidation of the mono alcohols thus obtained.

The methods available for the reduction of unsaturated acyloins are rather limited. The method (ii) has been successfully employed for this purpose, in the synthesis of civetone and iso-civetone.

Heptadec-8-ene dioic acid prepared from aleuritic acid on acyloin condensation yielded a mixture of acyloins, the tosyl derivatives of which have been reduced with lithium-aluminium hydride. The mono alcohols thus obtained were oxidised with chromic acid to obtain civetone and iso-civetone which could be resolved by column chromatography. This is described in Part IV.

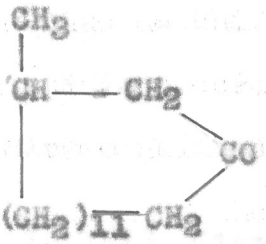
Analytical tools like spectrophotometry, and chromatography have been extensively employed for identification and characterisation of the various intermediates.

Occurrance of the Macrocyclic Musks

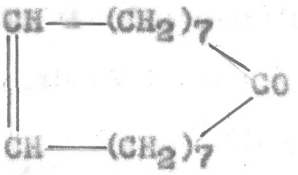
Musk is obtained from a gland of the male musk deer, Moschus moschiferus, a native of the mountains of Central Asia, especially the Himalayas. From approximately 60,000 animals killed yearly, an average of 2,000 kilogram of the valuable musk pod is obtained.[3] Similarly civet[4] is the glandular excretion of civet cat, the Abyssinian Viverra civetta and the Asiatic Viverra zibetha, and is noted for its strong animal odour. These are the sources of musk compounds in nature and have been employed in perfumery from the time immemorial. Recently[5] the American musk rat Ondatra zibethicus rivalicius has proved to be a potential source of musk. The macrocyclic compounds present in the excretion is partly in the form of odourless alcohols which on oxidation yield the corresponding odorous ketones, viz. dihydrocivetone and exaltone. Cyclopentadecanolide known in the trade as exaltolide and ambrettolide occur in angelica root oil (Archangelica officinalis Hoffm) and ambrette seed oil (Hibiscus abelmoschus) respectively.

Many other sources of this odour in the animal[6-8] and the vegetable[8] kingdom have been detected in recent years but none of them can be exploited economically.

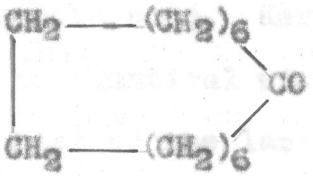
The macrocyclic musks found in nature are listed below:



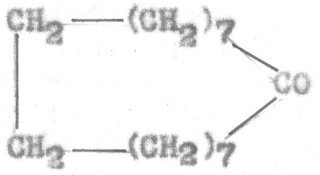
(-) Muscone



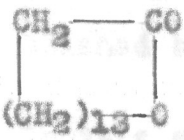
Civetone



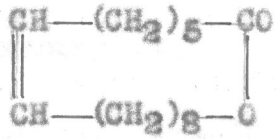
Exaltone



Dihydrocivetone



Exaltolide



Ambrettolide

In 1906, Walbaum,[9] for the first time, isolated the odorous principle of the natural musk in the form of a ketone, $C_{16}H_{30}O$. This was called muscone. Similarly in 1915 Sack[10] isolated civetone from 'civet paste'. In

the year 1926, Ruzicka and co-workers succeeded in establishing the constitution of civetone[11] and muscone[12] as large ring ketones with sixteen and seventeen carbon atoms. This was the first instance of the presence of large rings in nature. Prior to this the largest known carbon ring contained only eight memberes.

In 1889, Ciamician and Silber[13] found that the oil from the roots of Archangelica officinalis Hoffm. possesses a faint musk odour. They isolated a hydroxy pentadecanoic acid. Kerschbaum[14] in 1927 proved this acid to be identical with 15-hydroxy pentadecanoic acid and synthesised the lactone, exaltolide from 15-bromo-pentadecanoic 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[15] and ω-hydroxy acids[16] facilitated the research in this field and soon many more members of this group were prepared.

Later developments[17] 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

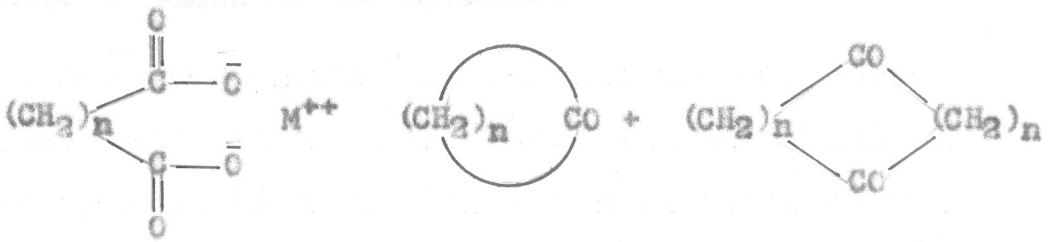
methylene groups can to some extent be substituted by atoms like oxygen, sulphur, nitrogen and groups like imino and one or more polar groups, preferably the carbonyl group. The odour was found to be very much dependent on the ring size and was limited to rings having fourteen to eighteen members. It is worthwhile to mention here that in recent years odours similar to musk have been ~~isolated~~ observed in a new class of compounds namely sterols such as ∝- and β- Δ^{16}-androsten-3-ol.[18]

Development in the Synthesis of Macrocyclic Compounds

(A) Ketones

The first synthesis of macrocyclic ketone was achieved by Ruzicka[19] in 1926. He used a modification of the procedure developed by Zelinsky[20] and Willstatter[21] in which the salt of a dicarboxylic acid with a bivalent metal was pyrolysed to yield the ketone.

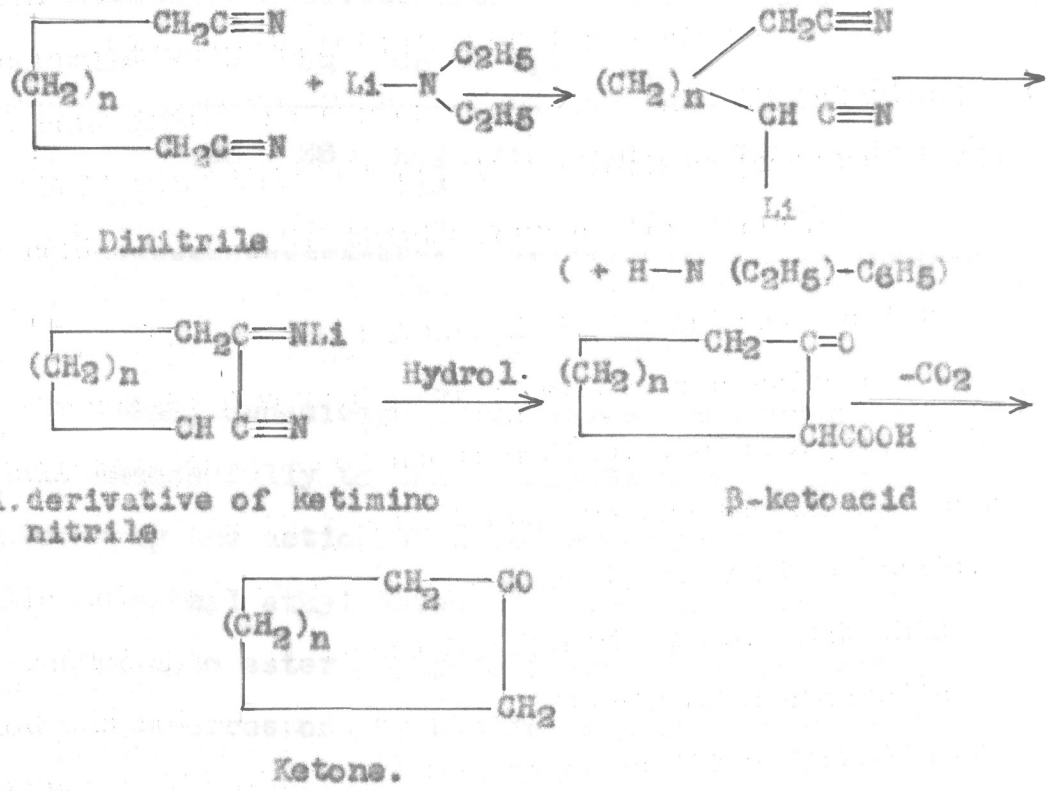
Scheme 1



Ruzicka and his co-workers[22] found that the thorium, cerium or yttrium salt mixed with copper powder gave comparatively good yields of large ring ketones (2-5%) containing one carbon atom less than the starting acid. Following this method, these workers prepared large rings containing up to thirty four carbon atoms.

Ruggli[23] in 1912 found that the intramolecular ring closure is favoured when reaction is carried out at high-dilution in a homogeneous medium. The main principle of this method is that conditions are created where dicarboxylic acid molecule is surrounded by solvent molecules, thus reducing the chances of polymerisation. But this method was not applied to the synthesis of macrocyclic compounds until Ziegler[24] twenty years later (1933) used Thorpe's reaction under high dilution conditions to prepare macrocyclic ketones. He applied this reaction to dinitriles using the ether-soluble lithium salt of ethyl aniline, $C_6H_5 - N - C_2H_5Li$ as the reagent. The dinitrile was converted into a lithium derivative, which was cyclised to ketone as shown in the scheme.2.

Scheme 2



Dinitrile

Li. derivative of ketimino nitrile

β-ketoacid

Ketone.

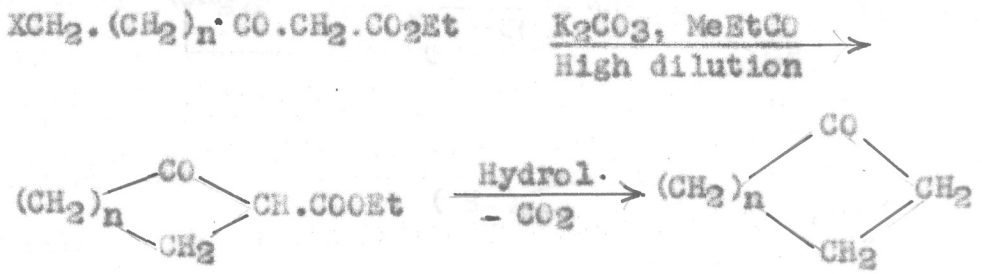
The reaction product was separated out as the lithium compound insoluble in ether rendering the reaction irreversible. High dilution at the critical stage of cyclisation was accomplished without use of a large volume of solvent by adding a solution of the dinitrile in ether at a very slow rate to a vigorously stirred refluxing solution of the condensing agent in ether or benzene. By this method remarkably high yields were obtained which are summarised in Table I.

T A B L E I

Cycloalkanone	C_7	C_8	C_9 to C_{11}	C_{12}	C_{13}	$C_{14}C_{15}$
Yield %	95	88	negligible	8	15	60

In 1942, Hunsdiecker[25] employed the high-dilution principle successfully to the cyclisation of an ω-halo-β-ketoester by the action of potassium carbonate in dilute solution in methyl ethyl ketone to yield a cyclic β-keto ester. This keto ester on hydrolysis and decarboxylation furnished the corresponding cyclic ketone[26] as shown in Scheme 3.

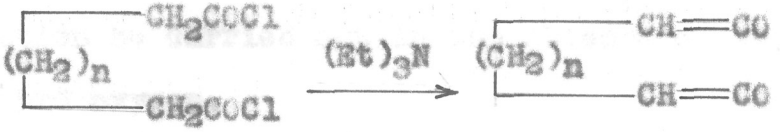
Scheme 3

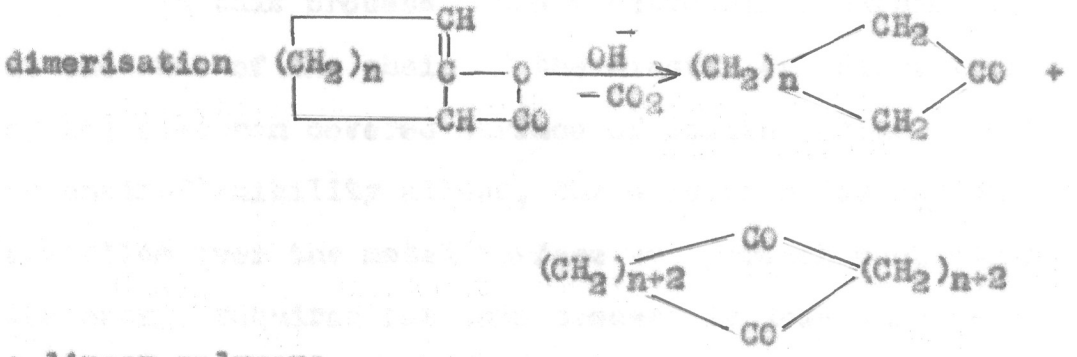


Macrocyclic ketones with fourteen to seventeen carbon atoms were synthesised by this method in good yields.

Blomquist and his co-workers[37] synthesised large ring ketones by an internal 'dimerisation' of bifunctional ketenes. The acid chloride of an ∝,ω-dicarboxylic acid on treatment with triethylamine in ether solution employing the high dilution conditions furnished the bifunctional ∝,ω-diketenes which readily underwent intramolecular condensation to a product analogous to a ketene dimer, and this on alkaline hydrolysis and decarboxylation yielded cyclic ketones and the diketone, together with polymeric products as shown in the scheme 4.

Scheme 4



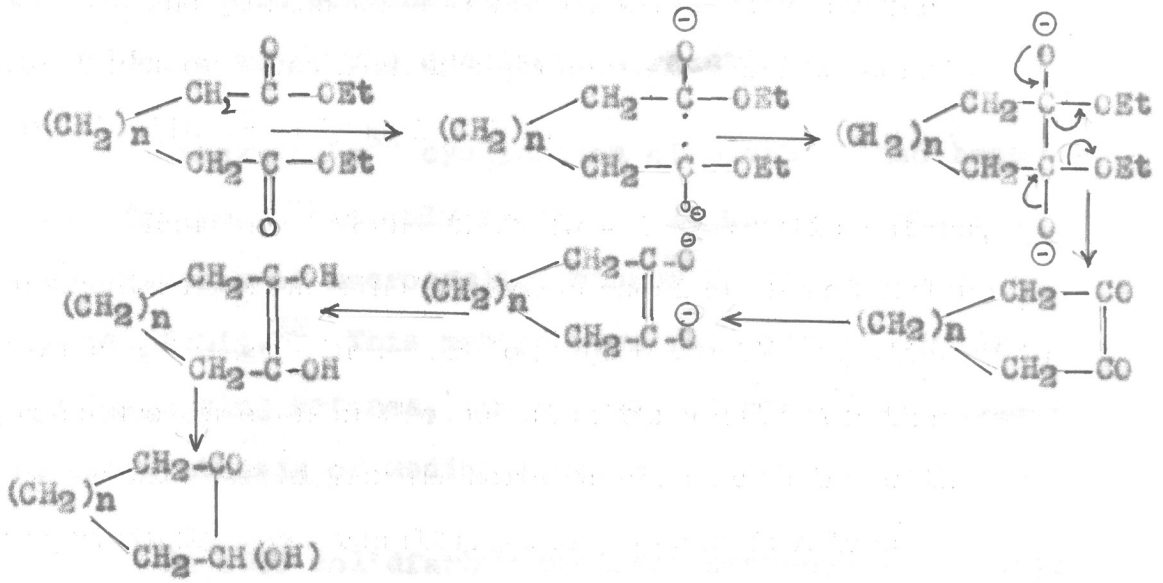


The yields were lower than obtained by the Ziegler's or Hunsdiecker's processes owing to considerable linear polymerisation.

Hansley[28] found that α,ω-dicarboxylic esters, on treatment with finely divided sodium in hot xylene gave cyclic acyloins. Prelog[29] and Stoll[30] applied this procedure independently and simultaneously for the preparation of higher membered cyclic acyloins with surprisingly good results. The process involves vigorous stirring of a solution of the ester of a α,ω-dicarboxylic acid in hot xylene with molten sodium. An intramolecular acyloin condensation takes place to give cyclic α- hydroxy ketone. It is important that the reaction be carried out in the absence of any free alcohol and oxygen.

In this process[31] two electrophilic carbon atoms at the ends of the chain of the diester are first absorbed by 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 molecules off the surface; the collisions of absorbed molecule with other molecules lead to the close proximity of the two terminal carbon atoms and finally to the ring closure.

Scheme 5



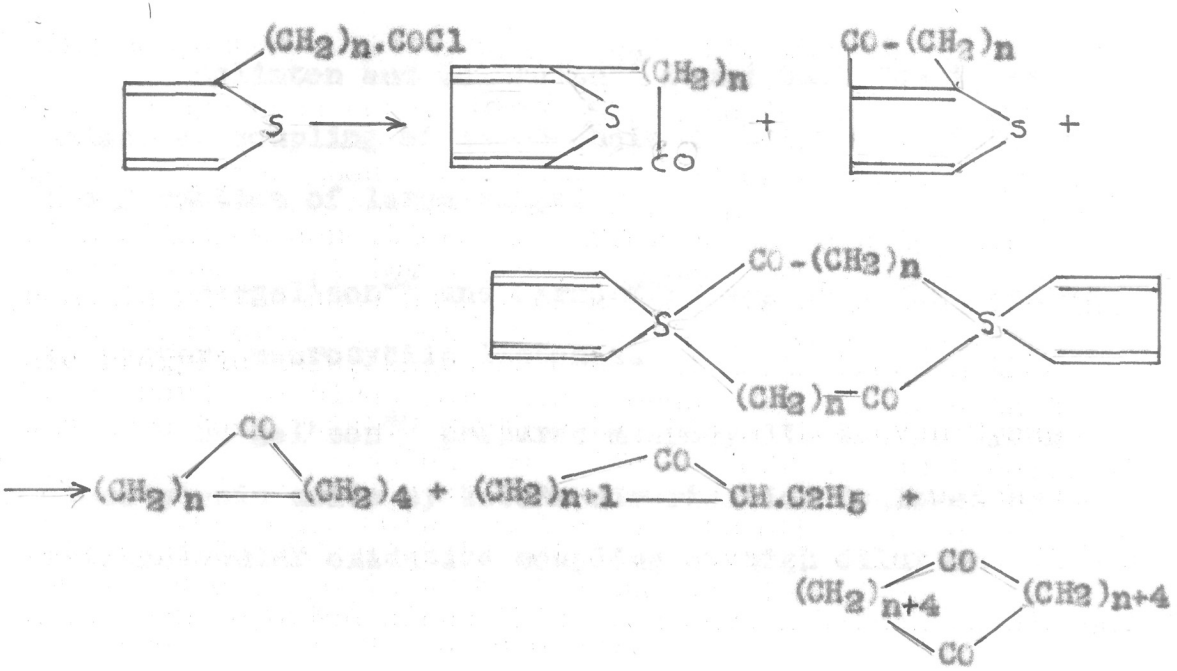
After the ring closure the molecule no longer possesses electrophilic centres and is therefore no longer bound to the surface. This method proved to be extremely useful in the synthesis of medium and large ring compounds. Yields were excellent, the minimum being 40% for cyclodecanone. Larger ring acyloins were obtained in an 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. Several other approaches have been reported since this procedure has been developed,

but the acyloin condensation still retains its place of eminence among the cyclisation reactions.

Dieckmann's[32] cyclisation of diesters had been known for years but only recently, it was employed for the synthesis of macrocyclic ketones by Leonard and Schimelpfenig.[33] This method gave fairly good yields for large ring ketones, but was not of much significance in the synthesis of medium rings.

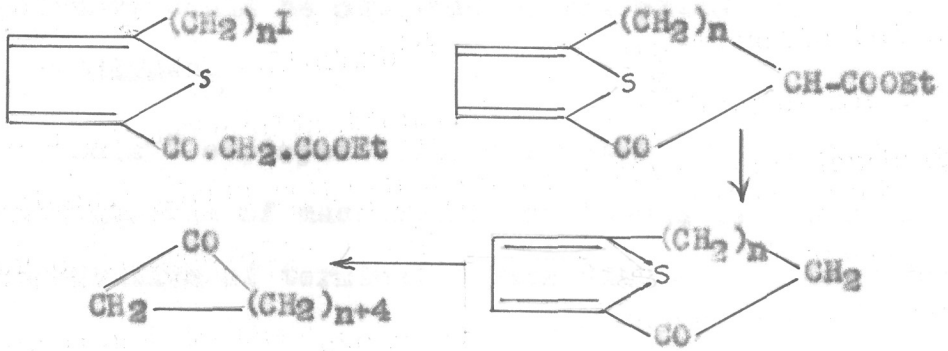
In 1956 Gol'dfarb[34] prepared macrocyclic thienyl ketones by the cyclisation of ω-thienyl long chain acid chlorides. These compounds on reductive desulphurisation[35] afforded macrocyclic ketones.

Scheme 6



Later another method was developed by Gol'dfarb[36] to prepare the thienyl macrocyclic ketone. In this method 2-(ω-idoalkyl)-5-(carbethoxy acetyl) thiophenes were cyclised in the presence of solid potassium. By this method pure 2,2'-thienyl macrocyclic ketones could be obtained which was not possible by the earlier methods.

Scheme 7

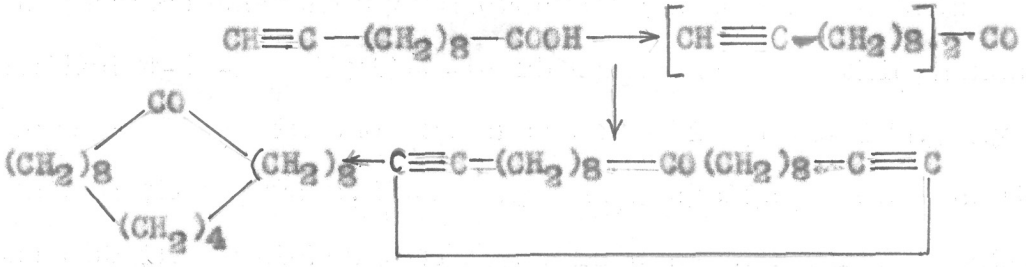


Eglinton and Galbraith[37] found that the intramolecular coupling of ~~large~~ long chain α,ω-diynes lead to the formation of large rings.

Bergel'son[38] and Carnduff[39] employed this method to prepare macrocyclic lactones.

Bergel'son[40] prepared macrocyclic ketones from ω-acetylenic acids by ketene dimerisation followed by intramolecular oxidative coupling at high dilution.

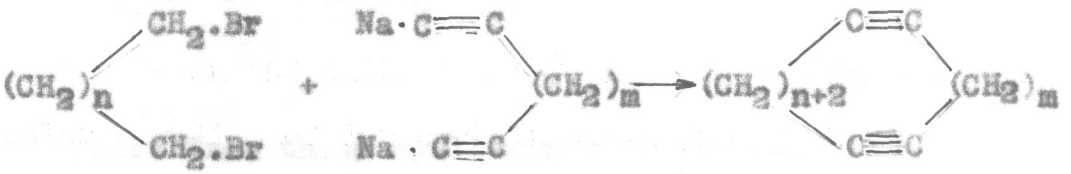
Scheme 8



Sondheimer[41] showed that cyclic dimers, trimers, and polymers could be obtained by the oxidative coupling of ∝, ω- diynes.

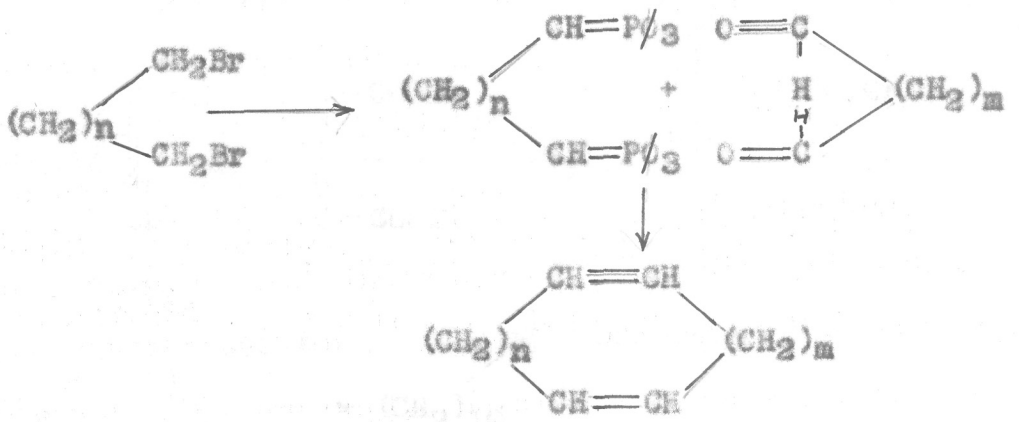
Dale[42] employed Gillman's method[43] successfully in the synthesis of macrocyclic compounds by condensing sodioderivative of terminal diynes with ∝,ω- dibromides.

Scheme 9



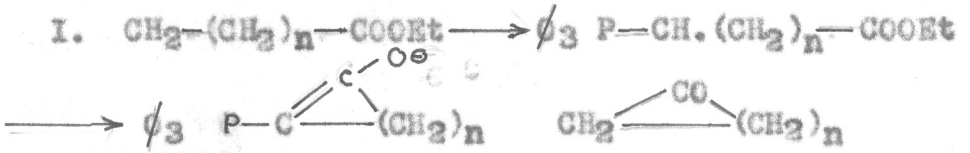
Wittig's reaction[44] has served as a useful tool in the synthesis of many organic molecules. Wittig[45] in 1958 condensed bifunctional phosphorylenes with dialdehydes to get large ring compounds.

Scheme 10



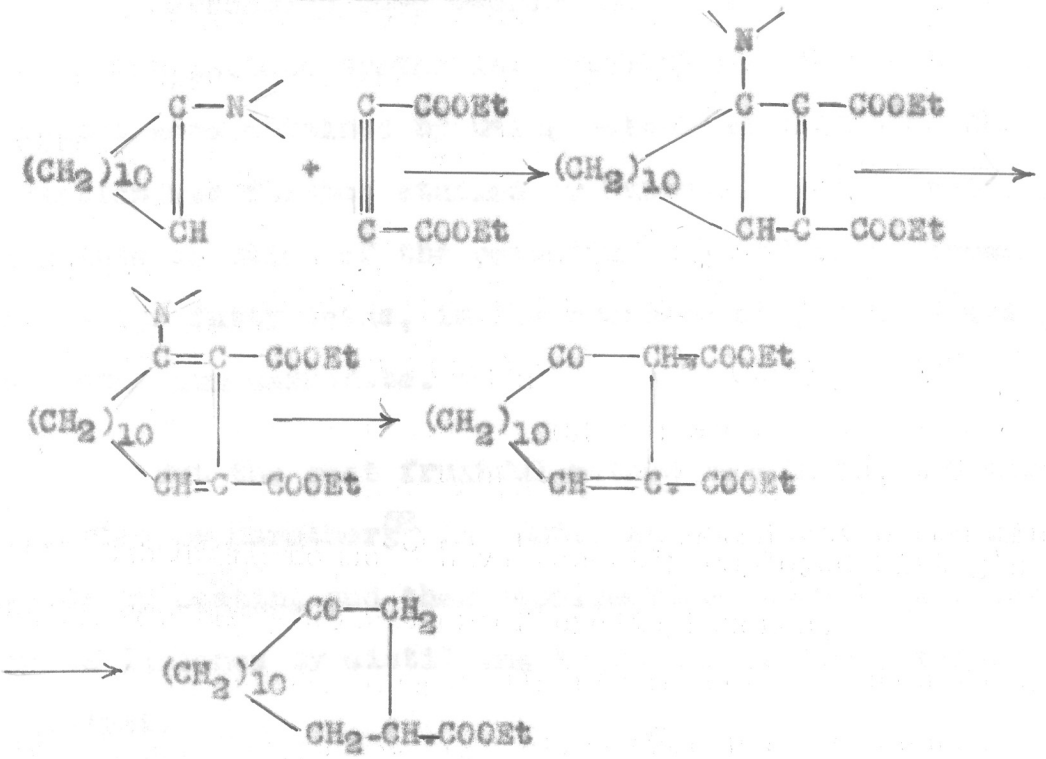
Babad and House[46] have recently employed Wittig's reaction for the preparation of cyclic ketones.

Scheme 11



Apart from these cyclisation reactions, ring expansion[47,48] also has been employed in the synthesis of macrocyclic ketones, though with less success. But the method developed recently by Berchtold,[49] and Brannock[50] 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.

Scheme 12



(B) Lactones

Ruzicka[51] employed Baeyer-Villiger oxidation[52] of ketones with peracids to get macrocyclic lactones. Since the ketones, themselves are obtained with difficulty, this method is not of much practical value.

Kerschbaum[53] employed the internal esterification of ω-hydroxy acids for the synthesis of large ring lactones.

Stoll and Rouvé[54] 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[55] found that better results were obtained by using potassium salts.[56] This reaction was further studied by Hunsdiecker[57] by refluxing a dilute solution of the potassium salt of an ω- bromo or ω- iodo fatty acids, in the presence of large excess of potassium carbonate.

But the most fruitful method developed is the one reported by Carothers[58] in 1935. He polymerised the hydroxy acids by heating and then depolymerised them to the monomeric lactones by distilling in vacuum in the presence of a catalyst.

Collaud[59] in 1942 esterified ω-hydroxy acids with glycerine and then transesterified to get the lactones.

Beets and van Essen[60] used thermally polymerised molecules as the basis of depolymerisation in presence of a catalyst, with glycerine as the carrier for cyclic monomer.

These methods will be discussed in detail in Part I of this thesis.

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P A R T I

SYNTHESIS OF EXALTOLIDE

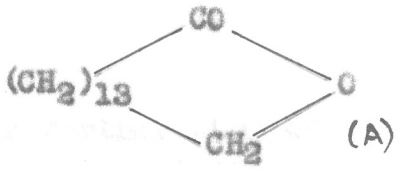
****

A B S T R A C T

Several interrelated new routes for the syntheses of exaltolide are reported. Erucic acid, obtained from mustard oil and 15, 16-dihydroxy lignoceric acid, obtained by the hydroxylation of nervonic acid have been used as the starting materials. Nervonic acid was synthesised from erucyl alcohol, obtained by reduction of ethyl erucate.

15-Hydroxy pentadecanoic acid obtained by the various routes was converted to polyester by the thermal treatment and depolymerised by Carother's method to yield exaltolide.

The methods developed are likely to be of considerable value for the commercial production of this widely used macrocyclic musk lactone.



(A)

Exaltolide

Exaltolide (A) is the musk odorous principle of angelica root oil. Its presence in the oil has been recently confirmed by gas liquid chromatography.[1]

Several syntheses of this lactone have been reported and it is available in the market under different trade names such as Exaltolide (Firmenich & Co.), Thibettolide (Givaudin) and Musk lactone (Polak & Schwarz).

The earlier syntheses of macrocyclic lactones were achieved by the oxidation of the corresponding cyclic ketones with persulphuric acid.[2] Later Ruggli[3] and Ziegler[4] introduced their theoretically interesting high dilution principle which was supported and developed by Stoll and co-workers[5] by their admirable kinetic studies. It was based on the simple consideration that in all cases where an intramolecular reaction competed with an inter-molecular one, the latter could be checked and former enhanced, by carrying out the reaction in high-dilution. This technique enabled Stoll and Rouve'[6] to reduce the lactonisation to simple azeotropic esterification. These workers effected the ring closer by intramolecular esterification of the ω-hydroxy acids in 0.002 -0.008 molar solutions of benzene in the presence of benzene sulphonic acid. Exaltolide was obtained in an yield of 87% from 15-hydroxy pentadecanoic acid.

Stoll[7] has further studied the cyclisation of the salts of higher ω-bromo fatty acids. The best results were obtained when potassium-15-bromo-pentadecanoate was lactonised in a specially designed apparatus in methyl ethyl ketone giving 85% yield of exaltolide. Hunsdiecker[8] and Erlbach prepared exaltolide by refluxing a dilute solution of the potassium salts of ~~ω~~ ω-bromo- or ω-iodo fatty acids in methyl ethyl ketone, in the presence of large excess of potassium carbonate. The potassium salts were formed which got cyclised to the lactones. Stoll[9] later on proved that this reaction was essentially homogeneous.

Stoll and Bolle[10] ~~further~~ developed another method which consisted in passing the vapours of the formates of ω-hydroxy aliphatic acids or the corresponding esters over titanium dioxide at about 300°. Exaltolide was prepared in this way in an yield of 50%.

Carothers[11] developed the interchange method for the preparation of ~~macrolides~~ lactones. The method consisted in depolymerising the corresponding linear polyester by vacuum distillation around 270° using magnesium chloride as catalyst to obtain the monomeric lactone in a 70% yield. This process has advantage in speed and simplicity over the high dilution method and is therefore better suited for large scale preparation. The high temperature

employed may however contribute a somewhat charred odour which can be eliminated by aging.

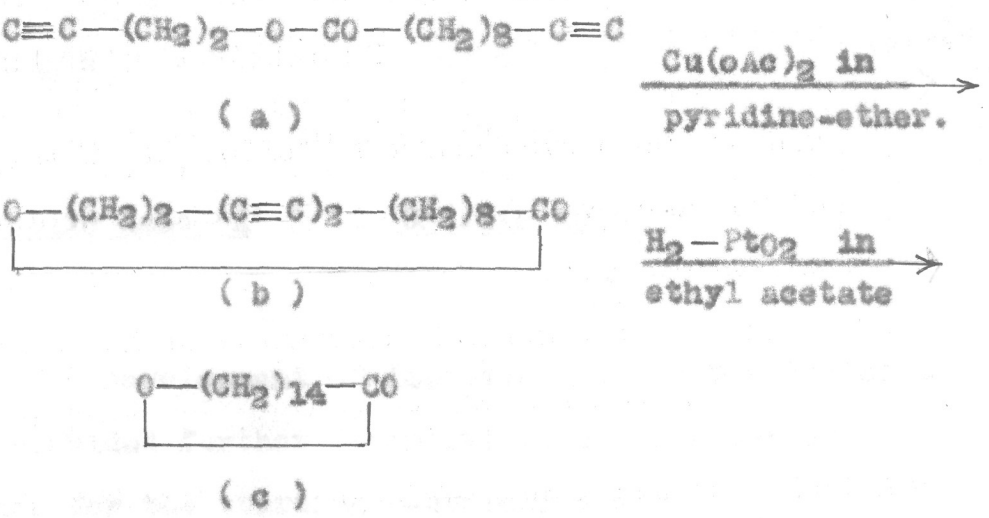
With a view to effect the interchange reaction at temperature lower than those employed by Carothers, a number of ester interchange catalysts have been tried.

A British patent[12] reveals the preparation of monocyclic lactones having at least twelve ring carbon atoms in good yield by heating under reduced pressure esters of the general formula $ROOC(CH_2)_n-CH_2OX$, where R is a lower alkyl, X is acetyl or boric acid group and n is atleast ten, in the presence of ester interchange catalyst, such as sulphuric acid, phosphoric acid, organic carboxylic acid, arylsulphonic acid, sodium derivatives of uni- or multivalent alcohol or phenols etc. Thus, methyl-16-acetoxy-hexadecanoate on heating for 1.5 hr at 220-235°/3 mm. in the presence of sodium methoxide yielded cyclo-hexadecane-1,16-olide, yield 71.3%.

Beets and Essen[13] have reported an improved method which consisted in heating polymers of hydroxy acids or their copolymers with polyhydric alcohols, preferably in vacuum, in the presence of a trans-esterification catalyst such as sodium methoxide and an entraining agent (glycerol) which should be immiscible with the lactone formed. Exaltolide, m.p. 35-38° was prepared in this manner.

Recently Eglinton[14] and his co-workers have reported a new synthesis of exaltolide in which the sixteen membered ring was closed by a high dilution intramolecular oxidative coupling involving the terminal ethynyl groups of but-4-ynyl-undec-10-ynoate (a) to produce an 88% yield of crystalline 1,15-pentadec-10,12-diynolide (b) catalytic hydrogenation of which gave pure exaltolide (c) according to the scheme.

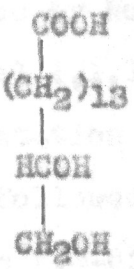
Scheme 1



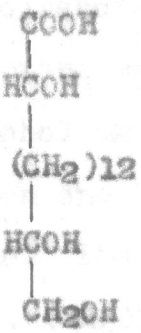
With the object of studying ways for the synthesis of macrolide and polyenic antibiotics, Bergelson[15] and co-workers have developed a method similar to that of Eglinton described above, for the preparation of diacetylenic macrocyclic lactones, by the cyclisation of terminal diacetylenic esters in high dilution conditions.

Macrocyclic lactones from Ustilagic acid:

Ustilagic acid[16] is a metabolic product of corn smut in artificial culture. On degradation, it liberates the hydroxy hexadecanoic acids, termed ustilic acids, which serve as starting materials for the preparation of variety of macrocyclic musks, of which exaltolide is the most desirable.



Ustilic Acid 'A'



Ustilic Acid 'B'

The development of improved methods for lactonisation provided further incentive to explore better syntheses for the starting ω-hydroxy acids.

The Russian workers[17] have developed the Kolbe's electrolytic reaction for the synthesis of ω-hydroxy acids. By the electrolysis of a mixture of ω-acetoxy undecanoic acid and mono-ethyl adipate, they obtained a range of products from which ethyl-ω-acetoxy pentadecanoate was separated by fractionation in an yield of about 16%.

Belov *et al.*[18] have further improved the electrolytic method and obtained 15-hydroxy pentadecanoic acid in an yield of 22-23%. The hydroxy acid lactonised in the usual manner gave exaltolide in 70% yield.

Another approach towards the synthesis of ω-hydroxy acids with fifteen and sixteen carbon atoms has been reported by Nesmeyanov[19] and collaborators. The starting material 1,1,1,7-tetrachloroheptane was dimerised through hydrogenation in ammonical alcohol under specified conditions followed by dehalogenation and hydrogenation to furnish α,ω-dichlorotetradecane. The latter was converted to the monocarboxylic acid (Cl. $(CH_2)_{14}$.COOH) by controlled treatment with sodium cyanide followed by hydrolysis with hydrochloric-acetic acid mixture. The chloro acid on heating with alkali gave 15-hydroxy pentadecanoic acid.

Recently, 15-hydroxy pentadecanoic acid has been synthesised in our laboratory by Bhattacharyya[20] and co-workers, from aleuritic acid.

PRESENT INVESTIGATION

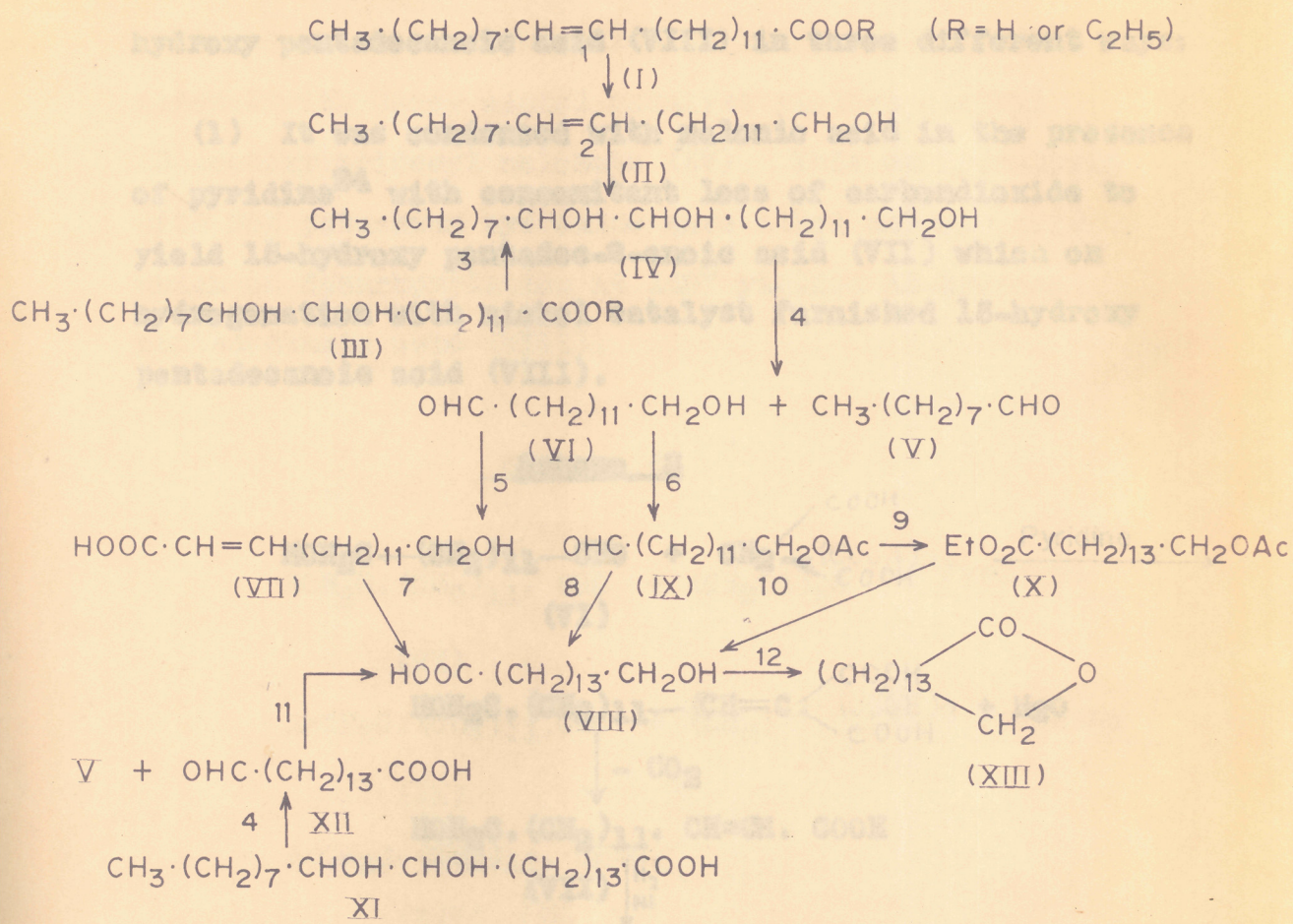
In India mustard oil and rape seed oil are produced in large quantities, and to some extent are even exported. Erucic acid is the major constituent of these oils. It constitutes about 50% of mustard seed fatty acids and about 60-65% of rape seed fatty acids.[21]

Erucyl alcohol, which has been employed as the starting material for the preparation of exaltolide was obtained by the reduction of erucic acid[22] (I) or its ester with lithium aluminium hydride or sodium and alcohol.

The steps employed for the synthesis of 15-hydroxy pentadecanoic acid and exaltolide are summarised in scheme 2.

Erucyl alcohol (II) was converted in high yields to 13,14-dihydroxy behenyl alcohol (IV) by using hydrogen peroxide and acetic acid[23] in the presence of acid catalyst followed by alkaline hydrolysis. Alternatively this triol was also obtained from 13,14-dihydroxybehenic acid or its ester (III, R=H or C_2H_5) by reduction with lithium aluminium hydride in ether, by sodium and alcohol or hydrogenation in presence of copper chromite catalyst. This triol (IV) on oxidation in alcoholic solution with aqueous neutral sodium metaperiodate furnished nonanal (V) and 13-hydroxy-tridecanal (VI) in almost quantitative yields.

SCHEME 2.

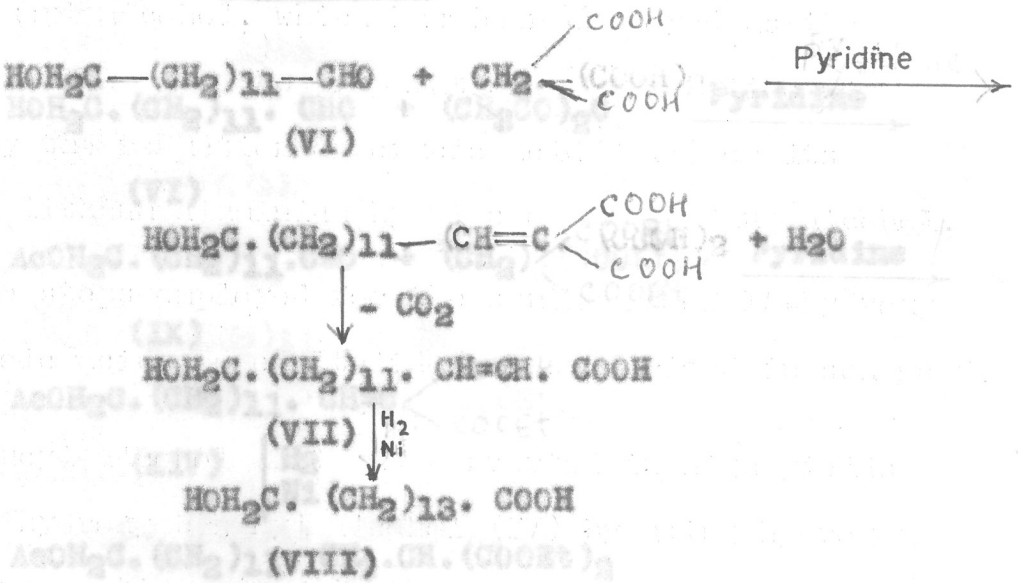


1, $LiAlH_4-(Et_2)_2O$; 2, H_2O_2-AcOH; 3, H_2–Cu chromite; 4, $NaIO_4$ 5, $CH_2(CO_2H)_2$ Pyridine; 6, Ac_2O; 7, H_2–Ni or PtO_2; 8, $CH_2(CO_2Et)_2$ – piperidine, H_2–Ni or PtO_2, $NaOH, -CO_2$; 9, $CH_2Br\ CO_2Et$-zn, H_2-Ni or PtO_2; 10, NaOH; 11, H_2-PtO_2-$FeSO_4$; 12, Lactonisation.

13-Hydroxy tridecanal (VI) was converted to 15-hydroxy pentadecanoic acid (VIII) in three different ways:

(1) It was condensed with malonic acid in the presence of pyridine[24] with concomitant loss of carbondioxide to yield 15-hydroxy pentadec-2-enoic acid (VII) which on hydrogenation with nickel catalyst furnished 15-hydroxy pentadecanoic acid (VIII).

Scheme 3



(2) Condensation with malonic ester. Direct condensation of 13-hydroxytridecanal with malonic ester in the presence of pyridine, piperidine and in solvents like dry benzene, dioxane etc. gave only polymeric material. Hence it was converted into its acetate, 13-acetoxy tridecanal (IX). The latter then condensed with diethyl malonate in the presence of piperidine to the

alkylidene malonic ester, diethyl 13-acetoxy tridecylidene malonate (XIV) which on hydrogenation in alcohol with Raney nickel catalyst yielded diethyl 13-acetoxy tridecyl malonate (XV). This on hydrolysis with 20% potassium hydroxide gave alkyl malonic acid which on decarboxylation at 140° yielded 15-hydroxy pentadecanoic acid (VIII).

Scheme 4

$HOH_2C.(CH_2)_{11}.CHO + (CH_3CO)_2O \xrightarrow{\text{Pyridine}}$

(VI)

$AcOH_2C.(CH_2)_{11}.CHO + (CH_2)(COOEt)_2 \xrightarrow{\text{Pyridine}}$

(IX)

$AcOH_2C.(CH_2)_{11}.CH=C(COOEt)_2$

(XIV) $\downarrow H_2, Ni$

$AcOH_2C.(CH_2)_{11}.CH_2.CH.(COOEt)_2$

(XV) $\downarrow$ i) KOH, ii) $-CO_2$

$HOH_2C.(CH_2)_{13}.COOH$

(VIII)

(3) By Reformatsky reaction. All attempts to condense 13-hydroxy tridecanal directly with ethyl bromoacetate via Reformatsky reaction failed. It gave only polymeric product which could not be crystallised

nor distilled. Hence 13-hydroxytridecanal was converted to its acetate as before and then condensed with ethyl bromoacetate in the presence of zinc in the usual way. The resulting hydroxy ester (XVI) on dehydration with phosphorous pentoxide furnished 15-acetoxy-pentadec-2-enoate (XVII). This on hydrogenation with nickel catalyst yielded 15-acetoxy pentadecanoate (X) which was converted by saponification to 15-hydroxy pentadecanoic acid (VIII).

Scheme 5

From 15,16-dihydroxylignoceric acid:

15,16-Dihydroxylignoceric acid[25] was obtained by the hydroxylation of nervonic acid. Nervonic acid was synthesised starting from erucyl alcohol by the method described by Hale *et al*.[26]

Erucyl alcohol was converted to erucyl bromide (XVIII) which was condensed with malonic ester. The condensation product after usual processing yielded nervonic acid (XX).

Scheme 6

$CH_3.(CH_2)_7.CH=CH.(CH_2)_{11}.CH_2Br + CH_2(COOEt)_2$

(XVIII)

$CH_3.(CH_2)_7.CH=CH.(CH_2)_{11}.CH_2.CH(COOEt)_2$

(XIX)

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

(Nervonic acid) (XX)

H_2O_2

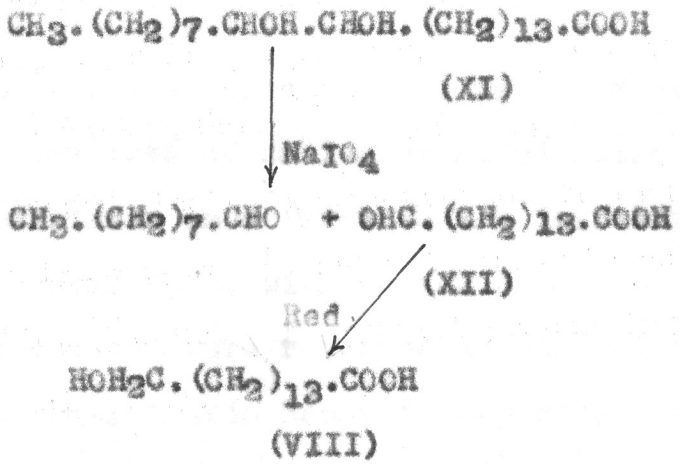
$CH_3.(CH_2)_7.CHOH.CHOH.(CH_2)_{13}.COOH$

(XI)

15,16-Dihydroxylignoceric acid (XI) was oxidised in alcohol with 10% aqueous sodium metaperiodate solution at 35-36° to nonanal (V) and 14-formyl tetradecanoic acid (XII). 14-Formyl tetradecanoic acid on reduction with

sodium amalgum in acetic acid yielded 15-hydroxy pentadecanoic acid (VIII).

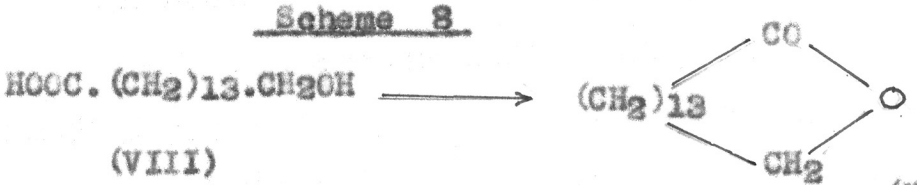
Scheme 7



Synthesis of Exaltolide

15-Hydroxy pentadecanoic acid was converted into its polyester by the azeotropic method in xylene containing toluene-p-sulphonic acid. The polyester was depolymerised employing magnesium oxide as catalyst, at a bath temperature of 270° under vacuum.[27] The crude product was dissolved in light petroleum, washed with 5% sodium bicarbonate solution and finally with water (free from alkali). The residue after removing the solvent on distillation under vacuum furnished exaltolide, b.p. 110°/0.25 mm. It was sublimed in vacuum, m.p. 32°, $\nu_{max.}$ 1726 cm^{-1} (lactone).

Scheme 8



Exaltolide(cyclopentadecanolide).

GENERAL REMARKS

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 Spectrometer and NMR 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 VPC apparatus MK IIA and va-pour fractometer 154 D 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.

***

E X P E R I M E N T A L

Isolation of fatty acids

Mustard seed oil (460 g) was refluxed with a 10% solution of alcoholic sodium hydroxide (800 ml) for four hours. After partial removal of alcohol, the contents were poured into large amount of water and acidified with hydrochloric acid. Fatty acids were extracted with pet. ether (40-60°); the extract was washed free of mineral acid, dried over anhydrous sodium sulphate and the pet. ether was distilled (yield 415 g).

Esterification of fatty acids

Esterification was carried out by azeotropic distillation of water from the reaction mixture. Fatty acids (680 g) were dissolved in thiophene free benzene (2160 ml). Absolute alcohol (360 ml; 99.5%) and sulphuric acid (2 ml; d. 1.84) were added to the above solution. It was refluxed on a water bath and the water formed during esterification was azeotropically removed. After the reaction was complete (no more water separation; 24 hrs), the benzene solution was first washed with water to remove mineral acids, then with 5% sodium carbonate solution in order to make it free from unreacted fatty acids and again with water. The benzene solution was then dried over anhydrous sodium sulphate and the benzene distilled. Fatty acid esters were weighed as residue (yield 708 g).

Fractional distillation of fatty acid esters:

Isolation of ethyl erucate.

Fatty acid esters (100 g) were fractionally distilled using Towers fractionating column (30 plates) fitted with a batch-strip head[28] and the following fractions (stripping time 20 minutes) were collected:

TABLE 1

No.	b. p.	n_D^{26}	Wt. (g)
I	146°/0.4-0.5 mm.	1.4506	10
II	146°/0.5 mm.	1.4530	8
III	146-155°/0.5 mm.	1.4535	10
IV	154-168°/0.4 mm.	1.4530	8
V	168-180°/0.4 mm.	1.4528	10
VI	180-182°/0.45-0.5 mm.	1.4528	10
VII	182°/0.5 mm.	1.4528	9
VIII	182°/0.5 mm.	1.4530	26

The last three fractions which were composed of ethyl erucate were combined together and redistilled rejecting some forerun (5 ml), b.p.182°/0.5 mm., n_D^{26} 1.4530 (yield 39 g).

Isolation of erucic acid

The above fraction containing ethyl erucate (30 g) was saponified with 10% alcoholic potash (200 ml) by refluxing for four hours. The alcohol was removed and the residue dissolved in water. On acidification with hydrochloric acid erucic acid (20 g) was separated. It was filtered, washed with water and crystallised from alcohol, m.p. 33°; lit. 33°.

13,14-Dihydroxybehenic acid (III)

Erucic acid (I) (m.p. 33°; 33.8 g) was treated with 30% hydrogen peroxide (15 g) and glacial acetic acid (150 ml) containing sulphuric acid (2.2 g; d 1.84). The reaction temperature was maintained at 40° for 24 hours. Excess per acetic acid was decomposed with sodium bisulphite and acetic acid was distilled under vacuum (water pump) at 100°. The residue which was hydroxy monoacetoxy derivative, was washed with water and refluxed with 10% alcoholic sodium hydroxide solution on a water bath for four hours. The alcohol was removed and the residue was acidified with dilute hydrochloric acid. 13,14-Dihydroxy behenic acid thus separated was filtered, washed with water, dried and crystallised from alcohol, m.p. 101° (yield 25 g), (Found: C, 70.8; H, 12.1. Calc. for $C_{22}H_{44}O_4$: C, 70.9; H, 11.9%).

Alternatively ethyl erucate (366 g) isolated from fatty acid esters of mustard oil was directly hydroxylated

with 30% hydrogen peroxide (135 g) and glacial acetic acid (1500 ml) containing sulphuric acid (22 g) as catalyst following the same procedure.

Preparation of erucyl alcohol (II)

In a three-necked 5 L flask fitted with stirrer, condenser and a dropping funnel, lithium aluminium hydride (27 g) was taken. To this sodium dried ether (3 l) was added. The addition of erucyl ester (400 g) was made dropwise through the dropping funnel over a period of about one and half hour under ice cooling. The reaction mixture was then refluxed for four hours at 35-40°. The excess of $LiAlH_4$ and the complex was decomposed by judicious addition of absolute alcohol, rectified spirit and then with water in turn. The ether portion was decanted out. The sludge was repeatedly extracted with ether (300X3 ml). The combined ether extract was washed with water, dried over anhydrous sodium sulphate and ether removed to afford erucyl alcohol (yield 350 g), m.p. 34° (Found: C, 81.10; H, 13.5. Calc. for $C_{22}H_{44}O$: C, 81.41; H, 13.66%).

Preparation of 13:14-dihydroxybehenyl alcohol (IV)

In a 10 l. three necked R.B. flask fitted with a stirrer, a dropping funnel and a thermometer, erucyl alcohol (500 g), glacial acetic acid (2.2 l), sulphuric acid (21 ml, d 1.84) were added. Hydrogen peroxide (30%)

(275 g) was added to it through the dropping funnel over a period of 3 to 4 hours. The temperature of the reaction was maintained at 40°. After the addition was over the stirring was continued for another 20 hours. Excess of per acetic acid was decomposed with sodium bisulphite and acetic acid distilled off under ~~vacuum~~ reduced pressure at 100°. The residue which was hydroxy monoacetoxy derivative was extracted with ether, washed with water and ether removed. The residue (480 g) was saponified with 10% alcoholic potassium hydroxide solution on a water bath for four hours. The alcohol was removed and the content was acidified with dilute hydrochloric acid. 13,14-Dihydroxy-benyl alcohol so obtained was filtered, washed with water, dried and crystallised from alcohol (yield 430 g), m.p.91° (Found: C, 74.0; H, 12.85. $C_{22}H_{46}O_3$ requires: C, 73.68; H, 12.93%).

Reduction of ethyl ester of 13,14-dihydroxybehenic acid with lithium aluminium hydride[29]

Ethyl ester of 13,14-dihydroxybehenic acid (185 g) was reduced with $LiAlH_4$ (30 g) in dry ether following the procedure described earlier. The excess of $LiAlH_4$ was decomposed with absolute alcohol, rectified spirit and water in turn. The ether portion was decanted off. The residual sludge was repeatedly extracted with ether, but

it was observed that ether dissolved very little of the material. Hence the whole sludge was extracted with hot alcohol (reflux) which dissolved all organic material. The alcohol was removed and the contents in the flask poured in ice water. The solid dihydroxy behenyl alcohol which separated, was filtered, washed with water and dried. It was crystallised from alcohol, m.p. 91-92° (yield 160 g).

Methyl ester of dihydroxybehenic acid (57 g) was reduced with $LiAlH_4$ (9 g) in dry ether (2 L) following the same procedure to yield 50 g. of the same triol.
(The preparation of esters are given on page 70 part-II)

Reduction of ethyl ester of dihydroxy behenic acid by using copper chromite catalyst.[30]

Ethyl ester of dihydroxybehenic acid (25 g) was dissolved in alcohol (250 g). Copper chromite catalyst (2. 5 g) was added to it. The reduction was carried out with hydrogen under pressure (2000-3000 lbs/sq.in.) at a temperature of 200-250° for 3 to 4 hours. It was filtered and the alcohol was removed. The material was crystallised from alcohol, m.p. 91°, mixed m.p. with authentic sample of dihydroxy behenyl alcohol was undepressed.

Oxidation of 13,14-dihydroxybehenyl alcohol (IV)

13,14-Dihydroxybehenyl alcohol (45 g) was dissolved in alcohol (600 ml) and oxidised by the addition of aqueous solution of neutral sodium metaperiodate (300 ml of 10%) during thirty minutes under vigorous stirring at 35°

(internal temp). Stirring was continued for another hour, after which the reaction mixture was filtered to remove precipitated sodium iodate. The filtrate which contained the organic material was diluted with water and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and the ether removed. The residue was fractionated under a vacuum to give (a) nonanal (17 g), b.p. 70°/10 mm., n_D^{27} 1.4207 (V) and (b) 13-hydroxy-tridecanal (25 g), b.p. 153-155°/0.9 mm., m.p. 74° (VI) (Found: C, 72.9; H, 12.1. $C_{13}H_{26}O_2$ requires: C, 72.8; H, 12.2%).

Semicarbazone was prepared by the pyridine method and crystallised from methyl alcohol, m.p. 116° (Found: C, 61.54; H, 10.71; N, 15.7. $C_{14}H_{29}N_3O_2$ requires: C, 61.95; H, 10.77; N, 15.45%).

Preparation of 15-hydroxy pentadec-2-enoic acid (VII)

To a cooled solution of malonic acid (18 g) in pyridine (55 g), 13-hydroxytridecanal (VI) (24 g) dissolved in pyridine (20 g) was added slowly under shaking in about ten minutes. The mixture was kept at room temperature for 36 hours to complete the reaction and then heated on a water bath for 3 hr. (Alternatively, after mixing and without further keeping at room temperature, the reaction mixture was heated on a boiling water bath for 8 hours to complete the reaction). After removing pyridine from the

reaction mixture under suction, the residue was extracted with ether, washed with dilute hydrochloric acid, again with water and finally extracted with aqueous sodium carbonate solution (10%). The carbonate extract on acidification gave 15-hydroxy pentadec-2-enoic acid(25 g) which was crystallised from alcohol, m.p. 80° (yield 22 g) (Found: C, 69.95; H, 11.1. $C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.0%).

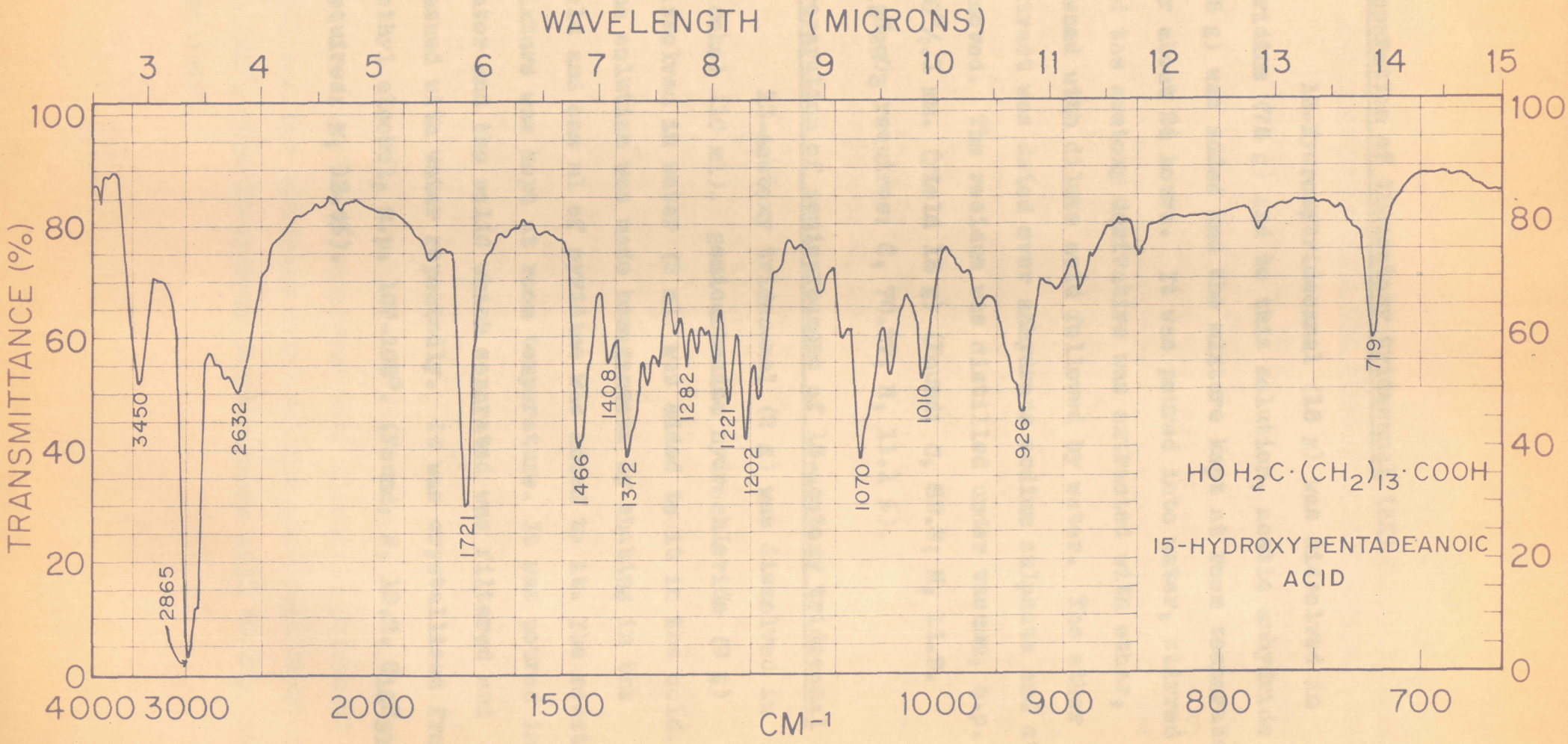
15-Hydroxypentadecanoic acid (VIII)

15-Hydroxypentadec-2-enoic acid (VII) (8 g) was hydrogenated in alcohol (200 ml) with Raney nickel[31](0.1 g) for four hours, at 100-110°/ 500-750 lb./sq.in. The reaction mixture was filtered and after the removal of alcohol the residue 15-hydroxy pentadecanoic acid was crystallised from ethyl acetate (7 g) had m.p. 85.5° (Found: C, 70.1; H,11.8; eq. wt. 254.6. $C_{15}H_{30}O_3$ requires: C, 69.7; H, 11.7%, and eq. wt. 256).

Condensation of 13-hydroxytridecanal with malonic ester

It was carried out in the presence of pyridine and piperidine as catalysts in solvents like dry benzene, dioxane etc.

In all experiments only polymeric compound was obtained which could not be crystallised nor distilled. Hence it was converted to the acetyl derivative.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15-HYDROXY PENTADEANOIC ACID
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Preparation of 13-acetoxy tridecanal (IX)

13-Hydroxytridecanal (15 g) was dissolved in pyridine (75 g) and to this solution, acetic anhydride (75 g) was added and the mixture kept at room temperature for about 24 hours. It was poured into water, stirred and the acetoxy derivative was extracted with ether, washed with dilute acid followed by water. The ether extract was dried over anhydrous sodium sulphate and ether removed. The residue was distilled under vacuum, b.p. 130°/.1 mm. (yield 15 g) (Found: C, 69.8; H, 11.3. $C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.1 %).

Preparation of semicarbazone of 13-acetoxy tridecanal

13-Acetoxy tridecanal (2 g) was dissolved in alcohol (10 ml). Semicarbazide hydrochloride (2 g) dissolved in water (3 ml) was added to it in the cold. The solution was made homogeneous by shaking in the cold and one ml of pyridine was added to it. The reaction mixture was kept at room temperature. It was poured into water and the solid which separated was filtered and washed with water repeatedly. It was crystallised from methyl alcohol, m.p. 107-108°. (Found: N, 13.2. $C_{16}H_{31}N_3O_3$ requires: N, 13.4%).

Preparation of diethyl 13-acetoxy tridecylidine malonate(XIV) and its conversion into the 15-hydroxypentadecanoic acid

Diethyl malonate (4 g) and 13-acetoxytridecanal(5 g) were mixed together and cooled. Piperidine (3 ml) was added to it. The mixture was left at about 15° for 12 hours and then at room temperature for another 24 hr. It was then added to cold water and extracted with ether. The ether extract was washed with dilute acid, and then with water. It was dried over anhydrous sodium sulphate and fractionally distilled. The alkylidene malonic ester (4.5 g) had b.p. 150°/0.005 mm., m.p. 38.5-39.5° (Found: C, 65.9; H, 10.0. $C_{22}H_{38}O_6$ requires: C, 66.3; H, 9.6%).

The above alkylidine malonic ester derivative(3 g) was hydrogenated in alcoholic solution using Raney nickel (0.3 g) as catalyst at a pressure of 700-1000 lbs/sq.in. and temperature 100-120°. The product worked up as usual and the diethyl 13-acetoxytridecylmalonate (XV) (2.5 g) was crystallised from light petroleum ether (b.p. 40-60°), had m.p. 44-45°; b.p. 145-146°/9.86 X 10^{-3} mm. (Found: C, 65.50; H, 10.02. $C_{22}H_{40}O_6$ requires: C, 65.97; H,10.07%).

Diethyl 13-acetoxytridecyl malonate (1 g) thus obtained was then hydrolysed with alcoholic potash(20 ml; 20%) and the resultant alkyl malonic acid decarboxylated at 140°, when 15-hydroxy pentadecanoic acid (0.5 g) was obtained.

15-Hydroxy pentadecanoic acid via Reformatsky reaction[32]

Attempts to condence 13-hydroxytridecanal directly with ethyl bromoacetate via Reformatsky reaction failed. It gave polymeric product which could not be crystallised nor distilled. Hence 13-hydroxy tridecanal was acetylated as described earlier and condensed with ethyl bromoacetate as follows:

In a three necked 500 ml flask, fitted with mercury sealed mechanical stirrer, condenser and a dropping funnel, freshly cleaned and dry zinc (3.6 g) was taken. A small amount of hydrobromic acid was added to it for activation followed by benzene (100 ml). A mixture of 13-acetoxy tridecanal (10 g) and ethyl bromoacetate (6 g) dissolved in 150 ml of dry benzene, was added slowly through the dropping funnel during one hour. Initially the addition was done by cooling the flask in ice cold water and afterwards the reaction mixture was gently heated on a water bath for three hours. After the reaction was complete, it was decomposed with dilute sulphuric acid and the residue extracted thoroughly with benzene. The benzene extract was washed with water, dried over anhydrous sodium sulphate and benzene removed. The residue (hydroxy ester)(6g) (XVI) was distilled under vacuum, b.p.162°/0.015 mm (yield 5 g) (Found: C, 66.6; H, 10.7. $C_{19}H_{36}O_5$ requires: C, 66.2; H, 10.5%).

It was a low melting solid and was dehydrated by refluxing it (4 g) with phosphorous pentoxide (6 g) in dry benzene (30 ml) for three hours. The benzene solution was decanted, washed with cold water and dried over anhydrous sodium sulphate. Benzene was removed and residue distilled giving ethyl 15-acetoxypentadec-2-enoate (XVII), b.p.140°/ 9.8 X 10^{-3} mm. (yield 3 g) (Found: C, 70.3; H, 10.8. $C_{19}H_{34}O_4$ requires: C, 69.9; H, 10.5%). This (3 g) on hydrogenation with nickel catalyst (0.1 g) in alcoholic solution (50 ml) at 110° under pressure of 500 lb/sq.in. gave 15-acetoxy-pentadecanoate (X) (2.8 g), b.p.154-55°/ 0.015 mm. (Found: C, 69.5; H, 10.95. $C_{19}H_{36}O_4$ requires: C, 69.5; H, 11.0%) which after saponification was converted to 15-hydroxypentadecanoic acid (yield 2 g).

Synthesis of nervonic acid (XX) from erucyl alcohol

A solution of erucyl alcohol (26 g) in toluene (150 ml) was cooled to -10° in a 500 ml flask equipped with a mechanical stirrer and a dropping funnel. To this solution phosphorous tribromide (8 g) in anhydrous toluene (50 ml) was added with stirring at such a rate that the temperature did not rise above -5°. The mixture was then heated on a water bath for four hours and the toluene removed by distillation. The product was dissolved in 100 ml of ether, washed with two 100 ml portions of a solution containing 10% potassium hydroxide and 10% common salt and finally with water.

The ether solution was dried over anhydrous magnesium sulphate, the ether removed and the product purified by distillation, b.p. $162^{\circ}/2.3 \times 10^{-3}$ (yield 10 g).

Preparation of erucyl malonic ester

To a solution containing sodium (5 g) dissolved in absolute alcohol (12 ml), diethyl malonate (4 g) was added. Erucyl bromide (6 g) was then added slowly and the mixture refluxed with stirring for thirty six hours. After this period the reaction product was only faintly alkaline to moist litmus paper. The alcohol was distilled off and water (50 ml) containing hydrochloric acid (5 ml) was added. The product which appeared on the surface as a brown oil was separated from the rest.

The crude erucyl malonic ester obtained above (8 g) was saponified without further purification by refluxing with alcoholic potash (6 g in 50 ml of 60% alcohol) for several hours. After most of the alcohol was removed, water (50 ml) containing sulphuric acid (6 g) was added. The resulting precipitate was extracted several times with ether. The ether extract was dried over anhydrous sodium sulphate and filtered. After removal of ether the product was heated at 175° for one hour to facilitate decarboxylation. The mixture of cis and trans (m.p.38-40°) nervonic acid thus obtained was crystallised to yield trans nervonic acid, m.p. 60-61°. (m.p. of cis nervonic acid 40-41°)

Preparation of 15,16-dihydroxylignoceric acid(XI)

Nervonic acid (4 g) in acetic acid (60 ml) containing conc. sulphuric acid (2 ml) was hydroxylated with hydrogen peroxide (10 ml) to obtain the hydroxy acetoxy derivative. This on usual saponification and acidification yielded 15,16-dihydroxylignoceric acid. It was crystallised from alcohol, m.p. 128° (Found: C, 71.75; H, 12.0. Calc. for $C_{24}H_{48}O_4$: C, 71.9; H, 12.1%).

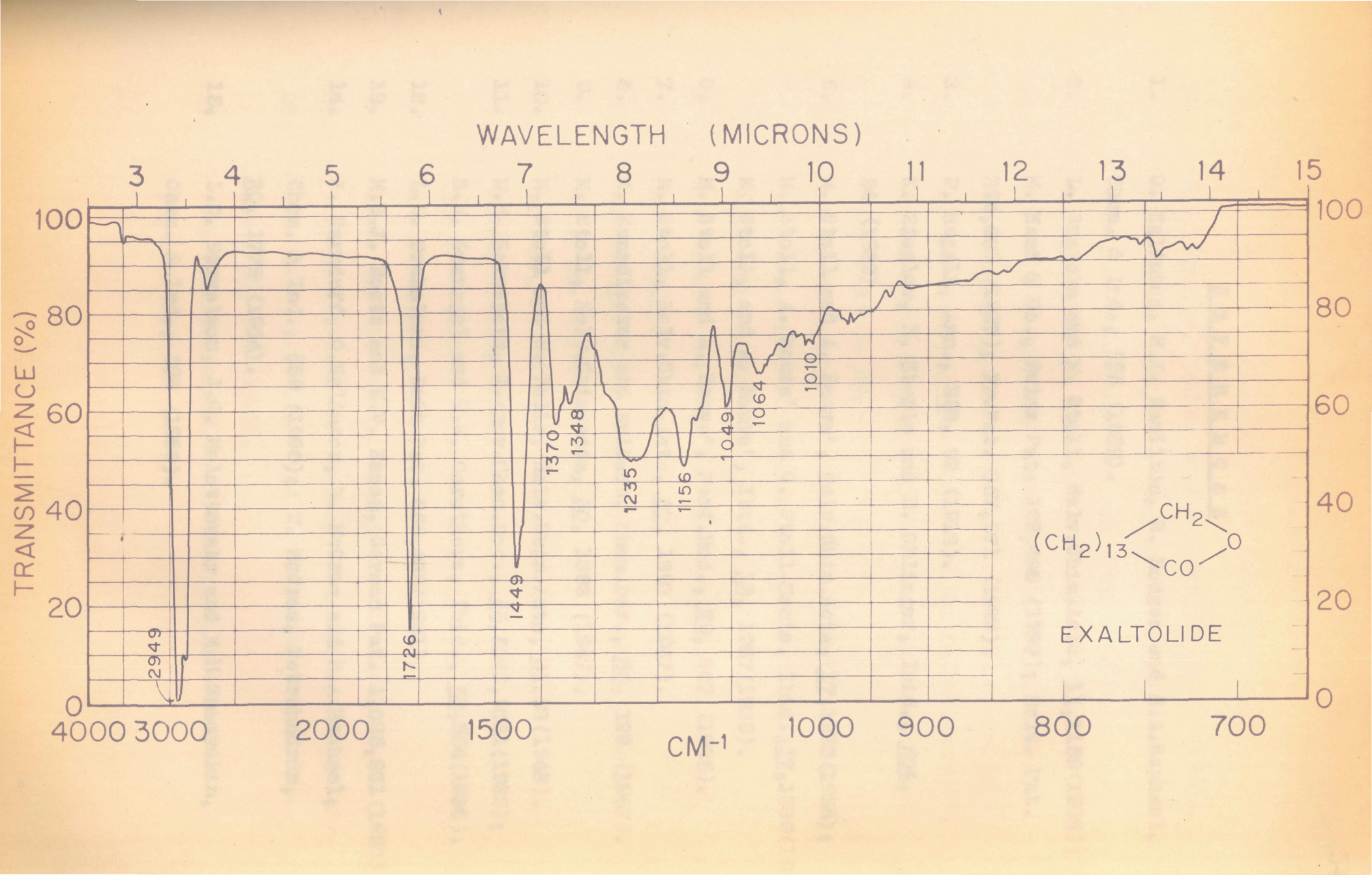
15-Hydroxypentadecanoic acid from 15,16-dihydroxy lignoceric acid

15,16-Dihydroxylignoceric acid (1 g; m.p.128°)(XI) (Found: C, 71.75; H, 12.0. Calc. for $C_{24}H_{48}O_4$: C, 71.95; H, 12.1%) was dissolved in alcohol (15 ml) and oxidised by addition of an aqueous solution of sodium metaperiodate (8 ml of 10%) during 20 minutes under stirring at 35-36°. After further stirring for 20 minutes the reaction mixture was filtered to remove precipitated sodium iodate and worked up in the usual way. Nonanal was distilled off upto 100°/1 mm. 14-Formyltetradecanoic acid left as residue (XII), was extracted with light petroleum from which it crystallised, m.p. 91° (Found: C, 70.5; H, 10.8. $C_{15}H_{28}O_3$ requires: C, 70.3; H, 11.0). Its semicarbazone was prepared by the pyridine method as usual. It was crystallised from methyl alcohol, m.p. 159° (Found: N, 13.75. $C_{16}H_{31}N_3O_3$ requires: N, 13.41%). This aldehydo acid (0.2 g) was reduced with

sodium amalgum (1 g) in acetic acid (10 ml) or catalytically (platinum oxide) to 15-hydroxypentadecanoic acid.

Synthesis of Exaltolide

15-Hydroxypentadecanoic acid (50 g) was converted into its intermolecular polyester by the azeotropic method in xylene (2 l) containing toluene-p-sulphonic acid (5 g). After the separation of water stopped (24 hr), the product was worked up in the usual way. The polyester thus formed was depolymerised in the presence of magnesium oxide (10 g, C.P. grade) at a bath temperature of 270° under vacuum (0.015 mm.). The crude product obtained (40 g) was taken up in pet.ether, washed with bicarbonate and finally with water. Pet.ether was removed and the exaltolide distilled under vacuum, b.p.110°/0.25. It was sublimed in vacuum, had m.p.32°; $\nu_{max.}$ 1726 cm^{-1} (lactone group) (Found: C, 74.7; H, 11.6. Calc. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.7%).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EXALTOLIDE

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P A R T II

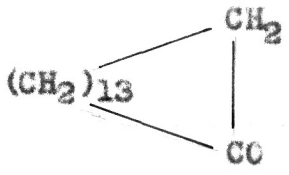
SYNTHESIS OF EXALTONE

***

A B S T R A C T

Several convenient new routes have been developed for the synthesis of exaltone using erucic acid and 15,16-dihydroxy lignoceric acid, as the starting materials. Since the raw materials are easily available, these methods are likely to be of considerable value for the commercial production of this macrocyclic perfumery chemical which is widely used in the industry.

For the preparation of exaltone, pentadecanedioic acid was cyclised to the corresponding acyloin which was subsequently reduced with zinc and hydrogen chloride to yield exaltone. Presence of a 'liquid exaltone' possibly containing an 'O inside conformation' has also been indicated. Cyclopentadecane and another liquid hydrocarbon containing methyl group (CH_3-CH) formed during the reduction of the acyloin group are obtained as by-products. The latter presumably was obtained via rearrangement and ring contraction.



EXALTONE

Exaltone (cyclopentadecanone), is one of the most outstanding perfumery chemical of the 'macrocyclic group'. It has similar blending and fixing properties as muscone. As it is comparatively easily accessible than muscone, it is preferably employed in the perfumery industry. Besides its main use in perfume compositions, it has been used for analytical purposes as solvent[1] for the micro determination of molecular weight by Rast method. Giral[2] has reported cryoscopic constant 21.3 and a favourable m.p. 65.6° for exaltone; this alongwith its easy miscibility with a variety of organic compounds make it more suitable as a solvent in place of camphor, particularly for substances that decompose at high temperature.

Earlier Syntheses

During the early years[3] of commercial production, exaltone was prepared by vacuum distillation of the cerium or thorium salt of hexadecanedioic acid (thapsic acid) in an yield of about 5%. Later Ziegler[4] synthesised exaltone by high dilution cyclisation of 1,14-dicyanotetradecane. Recently Leonard and Schimelpfenig[5] have carried out

Dieckmann[6] cyclisation of ∝,ω- dicarboxylic esters with potassium tert.butoxide in xylene under high dilution condition with high speed stirring in nitrogen atmosphere to obtain medium and large ring monoketones and large ring diketones with di-meric products. Starting from diethyl thapsate, they obtained 45% yield of exaltone.

Gol'dfarb[7] prepared macrocyclic thienyl ketone which on reductive desulphurisation[8] afforded exaltone.

However, no method developed so far, equals the elegant macrocyclic acyloin procedure reported simultaneously and independently by Prelog[9] and Stoll[10] in convenience, yield and economy. The reduction[11] of these acyloins furnishes the required ketones.

Known syntheses of pentadecanedioic acid

Pentadecanedioic acid was first synthesised by Chuit[12] in 1926 from azelaic and sebacic acids; chain extension was effected by nitrile formation and malonic acid condensation.

Buu-Hoi[13] prepared pentadecanedioic acid from undecenyl bromide by malonic acid condensation hydro-bromination, nitrile formation and hydrolysis.

By the ozonisation of 1-(undec-10-enyl) cyclo-pentene, Diaper[14] could obtain pentadecanedioic acid. Plesek[15] and Nikishin[16] also prepared this acid by cleavage

of alicyclic compounds. Enamine acylation[17] of cyclic ketones and the acid cleavage[18] of resultant β-diketones has been conveniently employed for the synthesis of this diabasic acid.

Yonetani and Kubo[19] employed undecylenic acid as the starting material and converted it to undecyl chloride which was then condensed with malonic ester. The product $CH_2=CH-(CH_2)_9-CH-(COOC_2H_5)_2$ was treated with hydrobromic acid followed by malonic ester condensation, saponification acidification and decarboxylation to yield pentadecanedioic acid.

Klenk[20] oxidised nervonic acid present in brain lipids to get pentadecanedioic acid. Nervonic acid has since been isolated from the seed fats of the Ximenia species[21] and also obtained by electrolytic process from oleic acid. In the present investigation nervonic acid has been synthesised starting from erucic acid.

Recently pentadecanedioic acid has been synthesised in our laboratory by Bhattacharyya and co-workers from aleuritic acid[22] and kamlolenic acid.[23]

PRESENT INVESTIGATION

In this part several interrelated convenient new routes have been developed for the synthesis of pentadecanedioic acid and its subsequent cyclisation to exaltone. The dicarboxylic acid was cyclised to the acyloin which on reduction with zinc and hydrogen chloride furnished exaltone.

Erucic acid, obtained from mustard oil and 15,16-dihydroxylignoceric acid obtained by the hydroxylation of nervonic acid have been used as the starting materials. Nervonic acid itself has been synthesised from erucyl alcohol. The reactions are summarised in Scheme 1

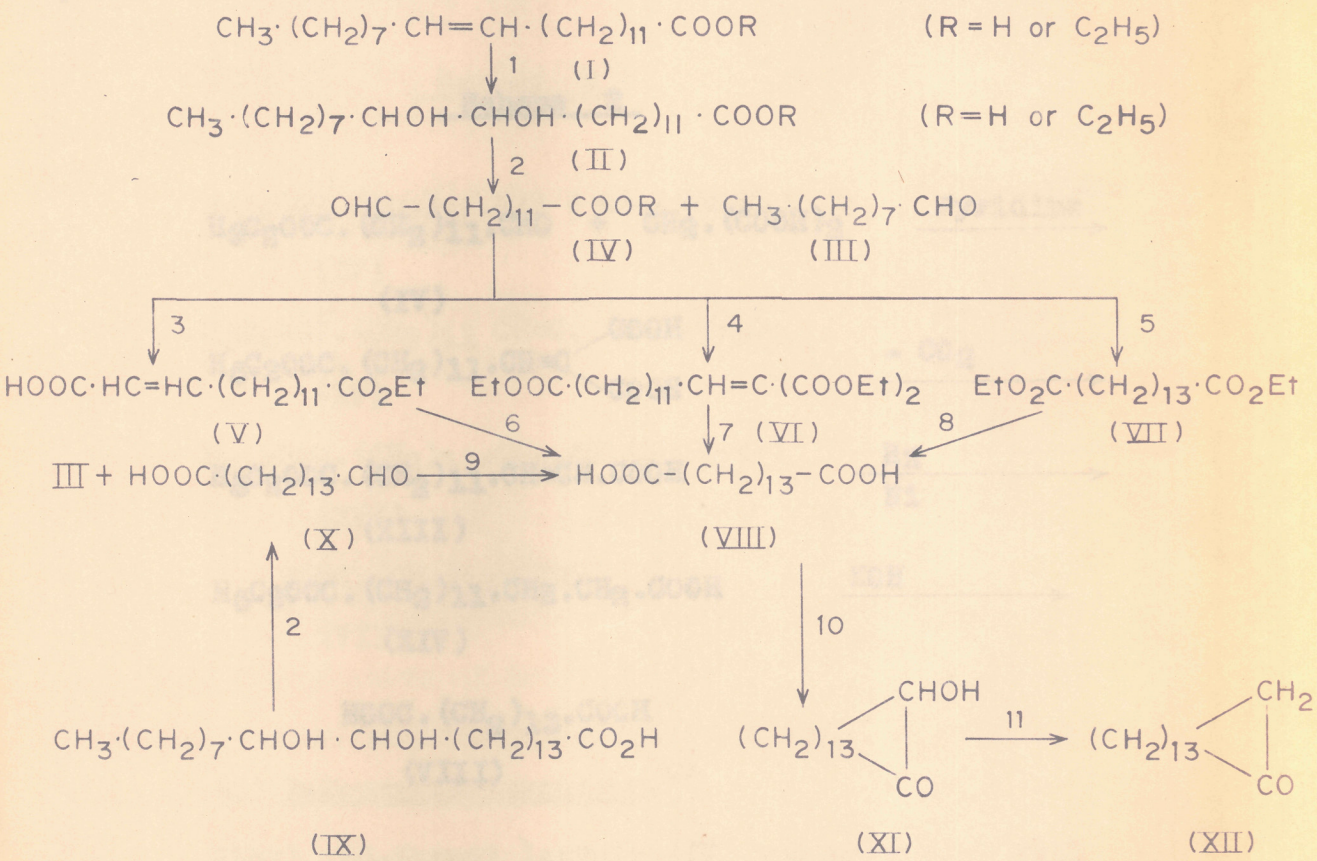
Ethyl erucate (I) was converted in high yield to 13,14-dihydroxybehenic acid (II) by treating with 30% hydrogen peroxide and acetic acid in the presence of acid catalyst followed by alkaline hydrolysis (method of Swern etal).[24]

Ethyl ester of 13,14-dihydroxybehenic acid, prepared by the usual azeotropic method on oxidation in alcoholic solution with aqueous solution of neutral sodium metaperiodate furnished ethyl-12-formyl laurate (IV) and nonanal (III) in quantitative yields.

Ethyl 12-formyl laurate (IV) was converted to pentadecanedioic acid (VIII) in three different ways.

SYNTHESES OF PENTADECANEDIOIC ACID AND EXALTONE

SCHEME I.



Reagents: 1, H_2O_2 AcOH; NaOH. 2, $NaIO_4$. 3, $CH_2(COOH)_2$-Pyridine. 4, $CH_2(COOC_2H_5)_2$· piperidine. 5, CH_2Br-COOEt, zn; P_2O_5, H_2-Ni or PtO_2. 6, H_2-Ni or PtO_2; NaOH. 7, H_2-Ni or PtO_2; NaOH; $-CO_2$. 8, NaOH. 9, $KMnO_4$-AcOH. 10, Na-Xylene. 11, zn-HCl.

(A) It was condensed with malonic acid in the presence of pyridine[25] with concomitant loss of carbon-di-oxide to yield the 14-ethoxy-carbonyl tetradec-2-enoic acid(XIII), which on hydrogenation followed by saponification yielded pentadecane dioic acid (VIII).

Scheme 2

$H_5C_2OOC.(CH_2)_{11}.CHO + CH_2.(COOH)_2 \xrightarrow{\text{Pyridine}}$

(IV)

$H_5C_2OOC.(CH_2)_{11}.CH=C(COOH)(COOH) \xrightarrow{-CO_2}$

$H_5C_2OOC.(CH_2)_{11}.CH=CH.COOH \xrightarrow[Ni]{H_2}$

(XIII)

$H_5C_2OOC.(CH_2)_{11}.CH_2.CH_2.COOH \xrightarrow{KOH}$

(XIV)

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

(VIII)

(B). Condensation with malonic ester.

Ethyl, 12 formyl laurate (IV) was condensed with malonic ester in the presence of (i) piperidine,[26] (ii) pyridine, (iii) quinoline, (iv) acetic anhydride and (v) potassium tertiary butoxide to yield the corresponding unsaturated triester, diethyl-2 ethoxy carbonyl pentadec-2- ene dioate (XV). This triester on hydrogenation with

nickel catalyst furnished diethyl 2-ethoxy carbonyl pentadecane dioate (XVI), which on hydrolysis with alcoholic potassium hydroxide gave alkyl malonic acid. This acid, without isolation, was decarboxylated at 140° to yield pentadecanedioic acid (VIII).

Scheme 3

$H_5C_2OOC.(CH_2)_{11}.CHO + CH_2.(COOC_2H_5)_2 \xrightarrow{\text{Piperidine}}$

(IV)

$H_5C_2OOC.(CH_2)_{11}\,CH{=}C.\,(COOC_2H_5)_2 \xrightarrow[Ni]{H_2}$

(XV)

$H_5C_2OOC.(CH_2)_{11}.CH_2.CH.(COOC_2H_5)_2 \xrightarrow[(ii)\ -CO_2]{(i)\ KOH}$

(XVI)

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

(VIII)

(C) Reformatsky reaction.[27]

Ethyl 12-formyl laurate (IV) was condensed with ethyl bromo acetate in the presence of zinc and dry benzene to yield the hydroxy ester, diethyl 3-hydroxypentadecane-dioate (XVII) which on dehydration with phosphorus pentoxide yielded the corresponding unsaturated ester, diethyl pentadec-2-ene-dioate (XVIII). This unsaturated ester on hydrogenation with nickel catalyst gave the saturated diester, diethyl, pentadecane-dioate (XIX). On hydrolysis with alcoholic potassium it gave pentadecanedioic acid (VIII).

Scheme 4

$H_5C_2OOC.(CH_2)_{11}.CHO + BrCH_2.COOC_2H_5$ —Zn→

(IV)

$H_5C_2OOC.(CH_2)_{11}.CH(OH).CH_2.COOC_2H_5$ —P_2O_5→

(XVII)

$H_5C_2OOC.(CH_2)_{11}.CH=CH.COOC_2H_5$ —H_2, Ni→

(XVIII)

$H_5C_2OOC.(CH_2)_{13}.COOC_2H_5$ —alc. KOH→

(XIX)

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

(VIII)

(D) Pentadecanedioic acid from 15,16-dihydroxy lignoceric acid

15,16-Dihydroxylignoceric acid (XXI) was prepared by the hydroxylation of nervonic acid (XX). Nervonic acid was synthesised starting from erucyl alcohol and following the method described by Hale (see Part I, page 50).

15,16-Dihydroxylignoceric acid (XXI) was oxidised in alcoholic solution with 12% aqueous neutral solution of sodium metaperiodate at 35-36° to yield nonanal and 14-formyl-tetradecanoic acid (XXII). This acid on dissolving in acetone and oxidising with potassium permanganate gave pentadecanedioic acid (VIII).

Scheme 5

$CH_3.(CH_2)_7.CH=CH.(CH_2)_{13}.COOH$ —H_2O_2→

(XX)

$CH_3.(CH_2)_7.CHOH.CHOH.(CH_2)_{13}.COOH$ —$NaIO_4$→

(XXI)

$CH_3.(CH_2)_7.CHO$ + $OHC.(CH_2)_{13}.COOH$

(XXII) $KMnO_4$ ↓

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

(VIII)

cyclisation to

Synthesis of Exaltone

Pentadecanedioic acid (VIII) obtained by the various routes described above, was converted into its diester by employing the usual azeotropic method. The diester (XXIII) thus obtained was then converted to 2-hydroxycyclopentadecanone (acyloin) (XI) in the presence of sodium and boiling xylene.[28,29] This acyloin was then reduced with zinc and hydrogen chloride using dioxane as solvent at 90° to yield exaltone (XII).

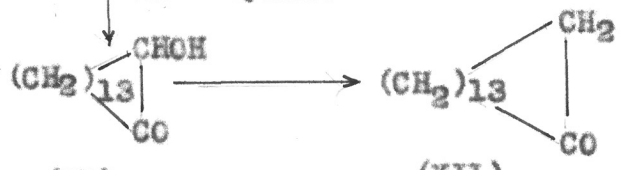
Scheme 6

$HOOC.(CH_2)_{13}.COOH$ (VIII)

↓

$H_5C_2OOC.(CH_2)_{13}.COOC_2H_5$ (XXIII)

Na + Xylene ↓



(XI) (XII)

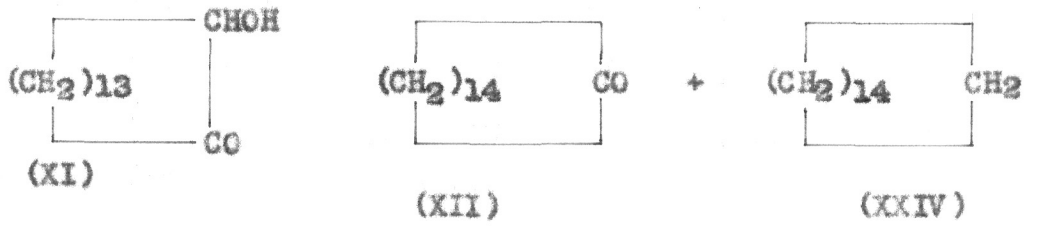
Exaltone.

Non-semicarbazone forming fraction

After reduction of the acyloin by treatment with zinc and hydrogen chloride, the exaltone formed was easily separated as its crystalline semicarbazone. A portion of the reaction product, however, failed to form semicarbazone under the condition mentioned vide infra. This portion was separated and after preliminary examination, including examination of its infrared spectrum was found to consist mainly of hydrocarbon alongwith small amount of ketone and only traces of alcohol. These components were separated by column chromatography.

Hydrocarbon

This fraction contained traces of unsaturated impurities which were removed by treatment with oleum. The saturated portion on chromatography using a large ratio of alumina followed by rechromatography and subsequent cooling was separated into solid and liquid fractions. The solid portion was identified as cyclopentadecane (XXIV), an authentic sample of which was obtained by the Wolff-Kishner reduction of pure exaltone (XII).



(XI) (XII) (XXIV)

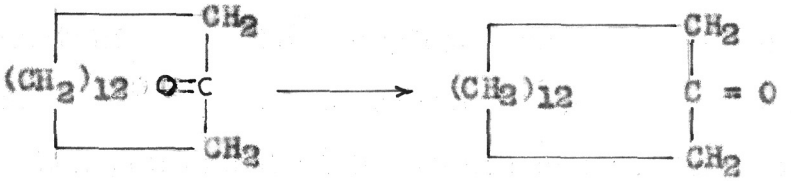
The liquid portion remained liquid after repeated chromatography and protracted cooling. On VPC analysis it showed the presence of two components. Its infrared spectrum and specially the NMR spectrum showed the presence of methyl group (CH_3-CH). It is assumed that formation of such group took place as a result of rearrangement and ring contraction during the reduction of acyloin under acidic condition. This has not been further examined.

Examination of the liquid ketonic portion

This portion remained a liquid after rechromatography and also after protracted cooling. It, however, showed identical analytical values with that of exaltone, had the same infrared spectrum and gave the same semicarbazone. Identity of the semicarbazone was established in the usual way, including examination of mixed m.p. Decomposition of the semicarbazone gave pure solid exaltone.

A comparative study of the rate of formation of semicarbazone under identical conditions showed that the liquid ketone was somewhat slower in reacting with semicarbazide hydrochloride, though it also eventually gave exaltone semicarbazone. From this, one is led to the conclusion that this liquid ketone is presumably cyclopentadecanone (exaltone) with '0 inside' conformation (XXV) which however changes to the usual '0 outside'

conformation (normal exaltone) during the formation of semicarbazone.



(XXV) (XII)

Normal exaltone.

Existence of products with '0 inside' conformation for medium ring[30] compounds is now generally accepted. But from the results described above it would appear that such conformational pecularities are also possible for macrocyclic exaltone. In the latter case, however, stability difference is comparatively less and the '0 inside' changes into '0 outside' conformation easily during semicarbazone formation.

EXPERIMENTAL

Preparation of ethyl 13,14-dihydroxybehenate (II)

13,14-Dihydroxybehenic acid (367 g) was taken in a 3 L. flask. Benzene (750 ml), absolute alcohol (150 ml) and sulphuric acid (2 ml) were added to it. Esterification was carried out by using azeotropic method. After 24 hours esterification was complete (no separation of water). The mixture of alcohol and benzene was taken up in a 5 L. separating funnel. It was first washed with water and then with sodium carbonate (10%) in order to remove the unreacted acid and then with water till free from alkali. Benzene was distilled off and the residue crystallised from pet. ether (60-80°) or ethyl alcohol (yield of the ester 325 g), m.p. 70° (Found: C, 71.60; H, 12.20. $C_{24}H_{48}O_4$ requires: C, 71.90; H, 12.10%).

Isolation of methyl 13,14-dihydroxybehenate

13,14-Dihydroxybehenic acid (50 g) was taken in a 1 L flask and dissolved it in methyl alcohol (700 ml). Dry hydrogen chloride gas was passed into this solution at room temperature for 5 hours. Methyl alcohol was removed and the residue taken up in the pet.ether (60-80°). It was first washed with 5% solution of sodium carbonate and then with water till free from alkali. Pet.ether was removed and the ester crystallised from pet.ether (60-80°), m.p. 71-72° (yield 40 g).

Oxidation of ethyl 13,14-dihydroxybehenate

Ethyl 13,14-dihydroxybehenate (II) (200 g) in alcohol (1500 ml) was taken in a three necked round bottomed flask fitted with a stirrer, a dropping funnel and a thermometer. Aqueous neutral sodium metaperiodate solution(950 ml; 12%) was slowly added to it through the dropping funnel during half an hour with stirring at 35-37°. It was stirred for another half an hour. The sodium iodate precipitated was separated by filtration. The filtrate was diluted with water and extracted with pet.ether (60-80°) three times (3 X 1000 ml). The combined extract was washed with water, dried over anhydrous sodium sulphate. The pet.ether was distilled and the residue fractionated under vacuum.

The first fraction collected consisted of nonanal (III) (71 g), b.p.70°/10 mm., n_D^{27} 1.4207 and the remaining fraction which distilled at 132°/0.3 mm consisted of ethyl 12-formyl laurate (IV) (110 g) (Found: C, 70.50; H, 11.40. $C_{15}H_{28}O_3$ requires: C, 70.30; H, 11.01%).

The semicarbazone prepared by the pyridine method was crystallised from methyl alcohol and melted at 88° (Found: N, 13.50. $C_{16}H_{31}O_3N_3$ requires: N, 13.40%).

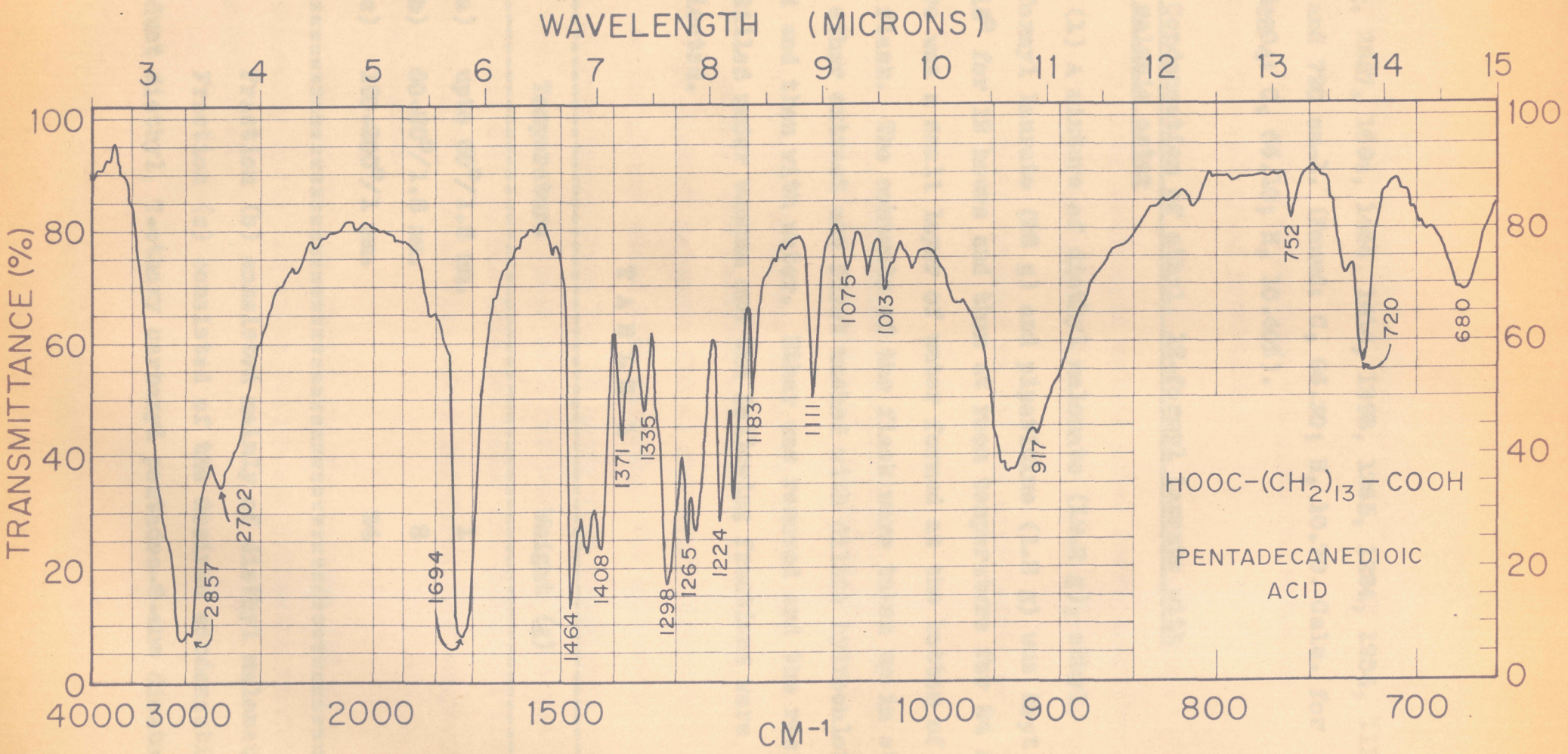
(A) Pentadecane-dioic acid via malonic acid condensation

To a cooled solution of malonic acid (60 g) in pyridine (110 g), ethyl 12-formyl laurate (IV) (100 g) was added slowly with shaking in about 10 minutes. The

reaction mixture was kept at the room temperature for 36 hours, and then heated on a water bath for 3 hours. Pyridine was removed under reduced pressure and the residue extracted with ether, The ether extract was washed with dilute hydrochloric acid, water and finally with 10% sodium carbonate. The carbonate extract on acidification with hydrochloric acid gave 14-ethoxy carbonyl tetradec-2-enoic acid (XIII) (yield 120 g), which was crystallised from pet.ether (60-80°), m.p.61°-62° (Found: C, 68.40; H, 10.30. $C_{17}H_{30}O_4$ requires: C, 68.45; H, 10.10%).

14-Ethoxy carbonyl tetradec-2-enoic acid (XIII) (70 g) was dissolved in alcohol (300 ml) and hydrogenated at 100-110° temperature and 500-750 lb/sq. pressure with Raney nickel (1 g) as a catalyst for four hours. The product was filtered and after partial removal of alcohol, the residue was crystallised from alcohol to give 14-ethoxy carbonyl tetradecanoic acid (XIV), m.p.66° (yield 45 g). (Found: C, 68.10; H, 11.10. $C_{17}H_{32}O_4$ requires: C, 68.00; H,10.70%).

The above ester (45 g) on hydrolysis by refluxing with 10% alcoholic potassium hydroxide (200 ml) gave after usual processing the free acid (VIII) which was crystallised from alcohol and recrystallised from glacial acetic acid to give pure pentadecane dioic acid, m.p.114°.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TRANSMITTANCE (%)
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20
0
4000
3000
2000
1500
1000
900
800
700
CM-1
2857
2702
1694
1464
1408
1371
1335
1298
1265
1224
1183
1111
1075
1013
917
752
720
680
HOOC-(CH2)13-COOH
PENTADECANEDIOIC
ACID

max. 2857, 1694, 1464, 1414, 1298, 1265, 1224, 1204, 1111, 917 and 720 cm-1. (Found: C, 66.30; H, 10.70. Calc. for $C_{15}H_{28}O_4$: C, 66.10; H, 10.40%).

(B) Condensation of ethyl 12-formyl laurate with malonic ester

(1) A mixture of diethyl malonate (19.2 g), ethyl 12-formyl laurate (28 g) and piperidine (1.2 g) was kept at 15° for 12 hours and then at room temperature for 24 hrs. There was a small layer of water formed at the bottom of the flask. The contents of the flask were taken up in ether. The ether extract was first washed with dilute hydrochloric acid and then with water. Ether was removed and the residue distilled under vacuum and the following fractions were collected.

T A B L E 1

	Temperature	Weight (g)
(a)	upto 60°/1.5 mm.	1
(b)	60-80°/1.5 mm.	8
((c)	190-200°/1 mm.	24

Fraction (b) consisted mainly of diethyl malonate.

Fraction (c) consisted of the desired condensation product diethyl 2-ethoxy carbonyl pentadec-2-ene dioate (XV)

(Found: C, 66.10; H, 9.50. $C_{22}H_{38}O_6$ requires: C, 66.30; H, 9.80%).

The above condensation was again repeated by changing the following conditions:

i) Addition of the reactants at room temperature

ii) By using azeotropic method under inert atmosphere, and

iii) Addition of anhydrous sodium sulphate for removing water.

The yields obtained in all the experiments were almost the same.

(2) Malonic ester condensation with ethyl 12-formyl laurate in the presence of potassium tertiary botoxide

Potassium (6 g) was dissolved in dry tertiary butyl alcohol (36 g). The solution was cooled in ice and to it a mixture of diethyl malonate (30 g) and ethyl 12-formyl laurate (30 g) was added with stirring. The mixture was kept at room temperature for 36 hours with occasional shaking and then heated on a water bath for two hours. The reaction mixture was then poured into ice water and extracted with pet. ether (40-60°), washed with water and dried over anhydrous sodium sulphate.

Pet. ether was removed and the residue (32 g) was fractionally distilled under vacuum and following fractions were collected.

T A B L E 2

	Temperature	Weight (g)
(d)	upto 130°/0.5 mm.	4
(e)	130-150°/0.5 mm.	5
(f)	140-150°/0.03 mm.	20

Fractions (d) and (e) consisted mainly of unreacted ethyl, 12-formyl laurate and malonic ester.

Fraction (f) consisted of the desired triester (XV).

The above condensation was repeated by changing the following conditions:

iv) Addition of more dry tertiary butyl alcohol

v) Using other dry solvents (e.g. benzene).

The results did not show any significant change in the yield.

(3) Malonic ester condensation with ethyl 12-formyl laurate in the presence of pyridine and quinoline as catalyst

It was carried out following exactly the same procedure as in the case of piperidine but there was no condensation product formed.

(4) Malonic ester condensation with ethyl, 12-formyl laurate in the presence of piperidine and acetic anhydride

Ethyl, 12-formyl laurate (70 g), malonic ester (40 g), piperidine (5 ml) and acetic anhydride (27 g) were condensed

together following the same procedure as described in the experiment (1). Acetic anhydride was used, to remove the water formed in the reaction. Piperidine was added in five instalments (1 ml at a time).

After working up the product in the usual way, the residue was fractionally distilled and only 20 g. of the desired condensation product was obtained. The rest of the product was recovered as unreacted ethyl 12-formyl laurate.

Hydrogenation of diethyl 2-ethoxy carbonyl pentadec-2-ene dioate (XV)

The unsaturated triester (XV) (10 g) obtained in the preceeding experiment was dissolved in alcohol(50 ml) and hydrogenated at 100°/500/700 lb.sq. pressure using Raney nickel as catalyst (0.25 g), for four hours. The mixture was filtered, and after removal of alcohol, the residue was fractionally distilled. The saturated triester, diethyl, 2-ethoxy carbonyl pentadecane dioate (XVI) distilled at 200°/1 mm. (Found: C, 65.91; H, 10.21. $C_{22}H_{40}O_6$ requires: C, 65.97; H, 10.07%).

The saturated triester (XVI) obtained above was hydrolysed with 20% alcoholic potassium hydroxide (20 ml) and the resultant alkyl malonic acid without isolation, decarboxylated at 140° when pentadecane dioic acid was obtained, m.p. 114°.

(C) Condensation of ethyl, 12-formyl laurate with ethyl bromoacetate in the presence of zinc (Reformatsky reaction)

In a 500 ml three necked flask, fitted with stirrer and condenser, zinc (5 g) and dry benzene (150 ml) were added. Ethyl bromo acetate (10 g) and ethyl, 12-formyl laurate (10 g) were dissolved in dry benzene (50 ml) and added slowly to it through the dropping funnel. After the addition was complete the reaction mixture was refluxed on a water bath for three hours. Benzene was then removed and the residue decomposed with 10% sulphuric acid. It was then extracted with ether, washed with water, dried over anhydrous sodium sulphate. Ether was removed and the residue, diethyl 3-hydroxypentadecane-dioate (XVII) was distilled at 150°/0.08 mm (4 g) (Found: C, 66.60; H, 10.10. $C_{19}H_{36}O_5$ requires: C, 66.28; H, 10.46%).

The above hydroxy ester (4 g) was dehydrated by refluxing it with phosphorous pentoxide (6 g) in dry benzene (50 ml) for four hours. The unsaturated ester, diethyl pentadec, 2-ene dioate (XVIII) obtained after usual processing, was distilled, b.p.167°/0.4 mm. (2 g). (Found: C, 70.04; H, 10.90. $C_{19}H_{34}O_4$ requires: C, 69.9; H, 10.5%). This unsaturated ester was hydrogenated to give diethyl, pentadecane dioate (XIX), b.p.165°/0.35 mm., m.p. 30° (Found: C, 69.60; H, 11.37. $C_{19}H_{36}O_4$ requires: C, 69.47; H, 11.05%). It was saponified with 20% alcoholic potassium hydroxide to yield pentadecanedioic acid (1 g), m.p. 114°.

Synthesis of pentadecanedioic acid from 15,16-dihydroxy lignoceric acid

Dihydroxy lignoceric acid was prepared by the method described in Part I of this thesis.

Dihydroxy lignoceric acid (2 g) in absolute alcohol (80 ml) was oxidised with 12% solution of neutral sodium metaperiodate (20 ml) during 30 minutes at 35°. The mixture was diluted and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and ether removed. The residue left was freed from nonanal by distillation, b.p. upto 100°/.5 mm. The residue on crystallisation from pet.ether gave 14-Formyl tetradecanoic acid, m.p. 90°.

14-Formyl tetradecanoic acid (1 g) was dissolved in acetone (10 ml) and oxidised with potassium permanganate (2 g) to yield pentadecanedioic acid, m.p. 114°.

Preparation of diethyl ester of pentadecanedioic acid (XXIII)

Esterification was carried out by azeotropic distillation of water from the reaction mixture. Pentadecanedioic acid (300 g) was dissolved in thiophene free dry and benzene (900 ml). Absolute alcohol (180 ml) and sulphuric acid (3 ml; d, 1.84) were added to the above solution. It was refluxed on a water bath and the water formed during esterification was occasionally tapped. After the reaction was complete (24 hrs), benzene solution was first washed

with water to remove the mineral acid, then with 5% sodium carbonate solution in order to make it free from unreacted acid, followed by water. The benzene solution was dried over anhydrous sodium sulphate and the benzene removed by distillation. The diester obtained was fractionally distilled, b.p. 165°/0.05 mm., m.p.30° (200 g)/ ν max. 1727 cm^{-1} (ester carbonyl) and 1247 cm^{-1} (C-O vibration of ester group)/ (Found: C, 69.60; H, 11.37. Calc. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05%).

Preparation of 2-hydroxy cyclopentadecanone (acyloin)

A mixture of sodium (50 g) in purified dry xylene (6.5 l) was initially heated to boiling under a current of dry/oxygen free nitrogen without stirring in a 10 l. flask fitted with a three necked adaptor and a mechanical stirrer. About 300 ml of xylene were distilled off and then the xylene was allowed to cool down to about 100°. The molten sodium was then stirred vigorously until the sodium was in the finely pulverised state. While stirring was continued the temperature of the xylene was raised to its boiling point. The diester (164 g) dissolved in xylene (200 ml) was added through the dropping funnel during one hour. After the addition was complete, stirring was continued for 1/2 hour, the reaction mixture was cooled and then decomposed by gradual addition of 600 ml of absolute alcohol.

The alkaline xylene solution was taken in a separatory funnel, washed carefully with water, and then with dilute hydrochloric acid, and finally with water. Xylene solution was kept over anhydrous sodium sulphate over night and then xylene was removed by distillation using a fractionating column under nitrogen atmosphere. The acyloin (70 g) was obtained by distillation, b.p. 138°/0.1 mm. ν max. 3448 (OH), 1710 (>C=O), 1451, 1370, 1265, 1063 and 725 cm^{-1}. (Found: C, 75.30; H, 11.79. Calc. for $C_{18}H_{28}O_2$: C, 74.95; H, 11.74%). The acyloin could be crystallised from pet.ether, m.p. 60-61°.

Cyclisation to exaltone (cyclopentadecanone)

In a 3 l. three necked flask fixed inside an oil bath and fitted with a stirrer, condenser and an inlet for passing hydrogen chloride gas, acyloin (70 g), zinc wool (140 g) and dioxan (1400 ml) were added. Hydrogen-chloride gas was passed at the rate of 20-22 g. per hour for 13 hours, during which the temperature of the oil bath was maintained at 90-95°. A fresh quantity (70 g) of zinc wool was added after 9 1/2 hours. Dioxan was then removed under reduced pressure and the residue extracted with pet. ether. After removing the pet.ether the residue (60 g) was directly put for the preparation of semicarbazone.

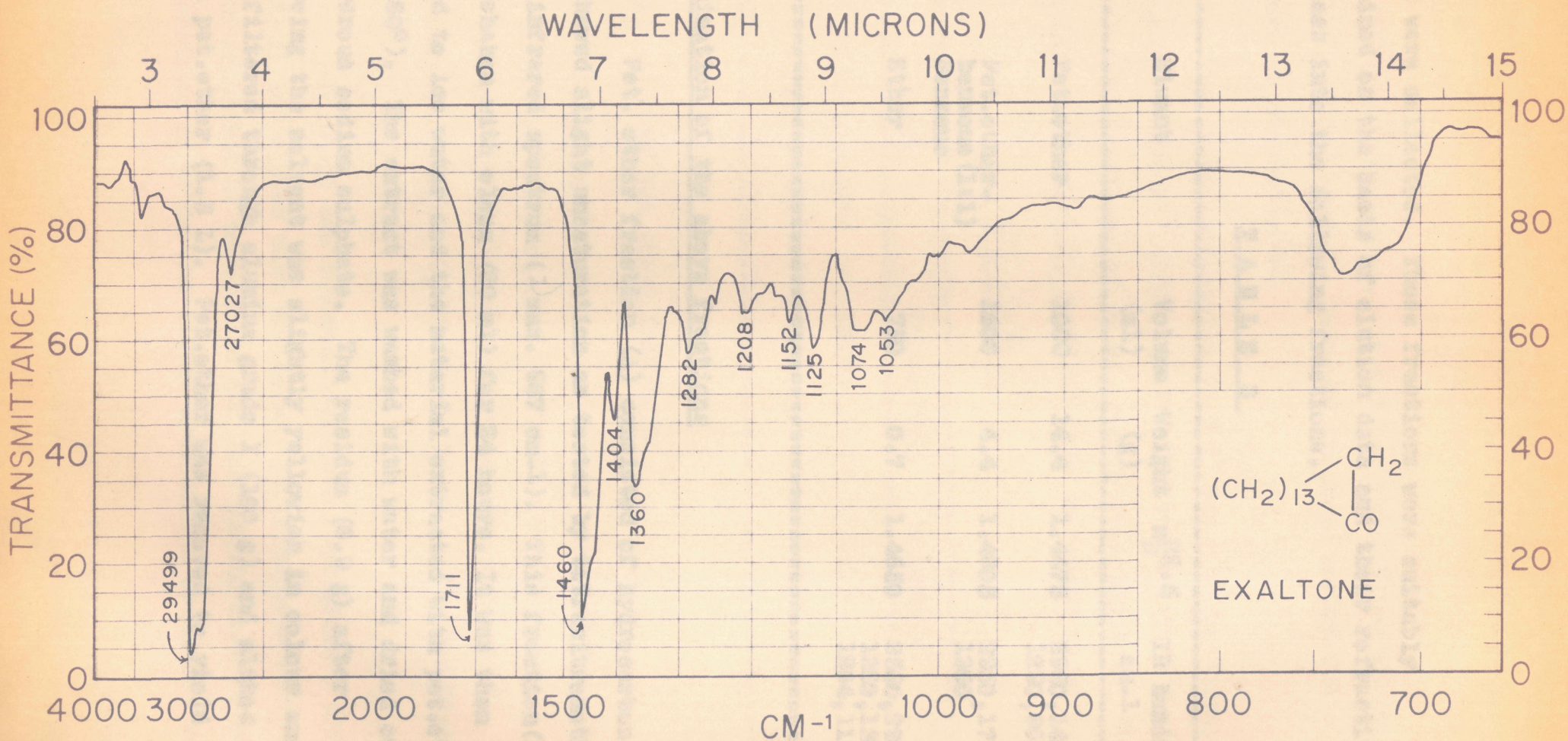
Preparation of the semicarbazone of exaltone

A mixture of semicarbazide hydrochloride (60 g) and sodium acetate (90 g) dissolved in minimum quantity of water

was added to the exaltone residue (60 g), dissolved in alcohol (250 ml). The reaction mixture was made homogeneous by the addition of requisite amount of alcohol and refluxed on a water bath for one hour. It was then diluted with water and the semicarbazone separated was filtered and washed with pet.ether. The filtrate was extracted with pet.ether. The pet.ether extract and the pet.ether washings of the semicarbazone were combined together, washed with water and the pet.ether removed to yield an oily residue. This was investigated separately. The semicarbazone obtained was crystallised from ethyl alcohol, m.p.187-188° (Found: N, 14.80. Calc. for $C_{16}H_{31}ON_3$: N, 14.90%). On decomposition with oxalic acid, it gave exaltone (cyclopentadecanone) which was crystallised from methanol to yield pure exaltone (30 g), m.p. 63°, $\nu_{max.}$ 1711 cm^{-1} (>C=O) (Found: C, 80.50; H,12.70. Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.60%).

Non-semicarbazone forming portion

An amount of non-semicarbazone forming residue (19.5 g) was collected from several experiments described above. Examination of infrared spectrum and other preliminary properties showed it to be consisting of hydrocarbon, ketone and also alcohol. It was chromatographed initially over twenty fold amount of alumina grade II (200 g) and eluted successively with pet.ether, pet.ether-benzene(1:1), benzene, ether and alcohol. Sixty seven fractions of 50 ml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TRANSMITTANCE (%)
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1404
1360
1282
1208
1152
1125
1074
1053
4000
3000
2000
1500
1000
900
800
700
CM-1
(CH2)13
CH2
CO
EXALTONE

each were collected. These fractions were suitably combined on the basis of elution data and their refractive indices into the following fractions.

TABLE 3

Fr.	Eluent	Volume (ml)	Weight (g)	$n_D^{28.5}$	IR bands cm-1
A	Pet.ether	1000	14.4	1.4475	2950,1460,1348, 1290,967
B	Pet.ether-benzene (1:1) Benzene	1600	4.4	1.4805	2950,1711,1456, 1360
C	Ether	750	0.7	1.4650	3650,2950,1460, 1360,1307,1283, 1204,1130,1050

Examination of the above fractions

Pet. ether fraction (A) consisted of hydrocarbon. It showed slight unsaturation as tested by tetranitromethane and infrared spectrum (ν_{max}. 967 cm-1). This fraction(10 g) was shaken with oleum (20 ml) for 24 hours. It was then added to ice water and the material extracted with pet.ether (60-80°). The extract was washed with water and dried over anhydrous sodium sulphate. The residue (6.9 g) after removing the solvent was slightly yellowish in colour and was filtered through alumina grade I (100 g) and eluted with pet.ether (1.5 L). Pet.ether was removed to yield

6.5 g of the hydrocarbon. It did not show colour reaction with tetranitromethane. Infrared spectrum showed the absence of unsaturation.

The above hydrocarbon (6.5 g) was rechromatographed over alumina grade I (650 g). It was eluted with pet.ether. Thirty nine fractions of 50 ml. each were collected. These fractions were suitably combined into two major fractions.

TABLE 4

Fr.	Eluent	Volume (ml)	Weight (g)
(D)	Pet. ether	1150	5.1
(E)	Pet. ether	800	1.2

Examination of the above fractions

Fraction (D) was refluxed over sodium for two hours and distilled under vacuum, b.p.170° (bath)/1.5 mm., n_D^{28} 1.4720. Infrared spectrum showed the absence of unsaturation (Found: C, 85.96; H, 14.41. Calc. for $C_{15}H_{30}$: C, 85.60; H, 14.40%).

It (4 g) was rechromatographed over grade I alumina (400 g) and eluted with pet.ether. Two fractions were collected. Both consisted of some solid and some liquid matter. However, separation of solid and liquid hydrocarbon could not be

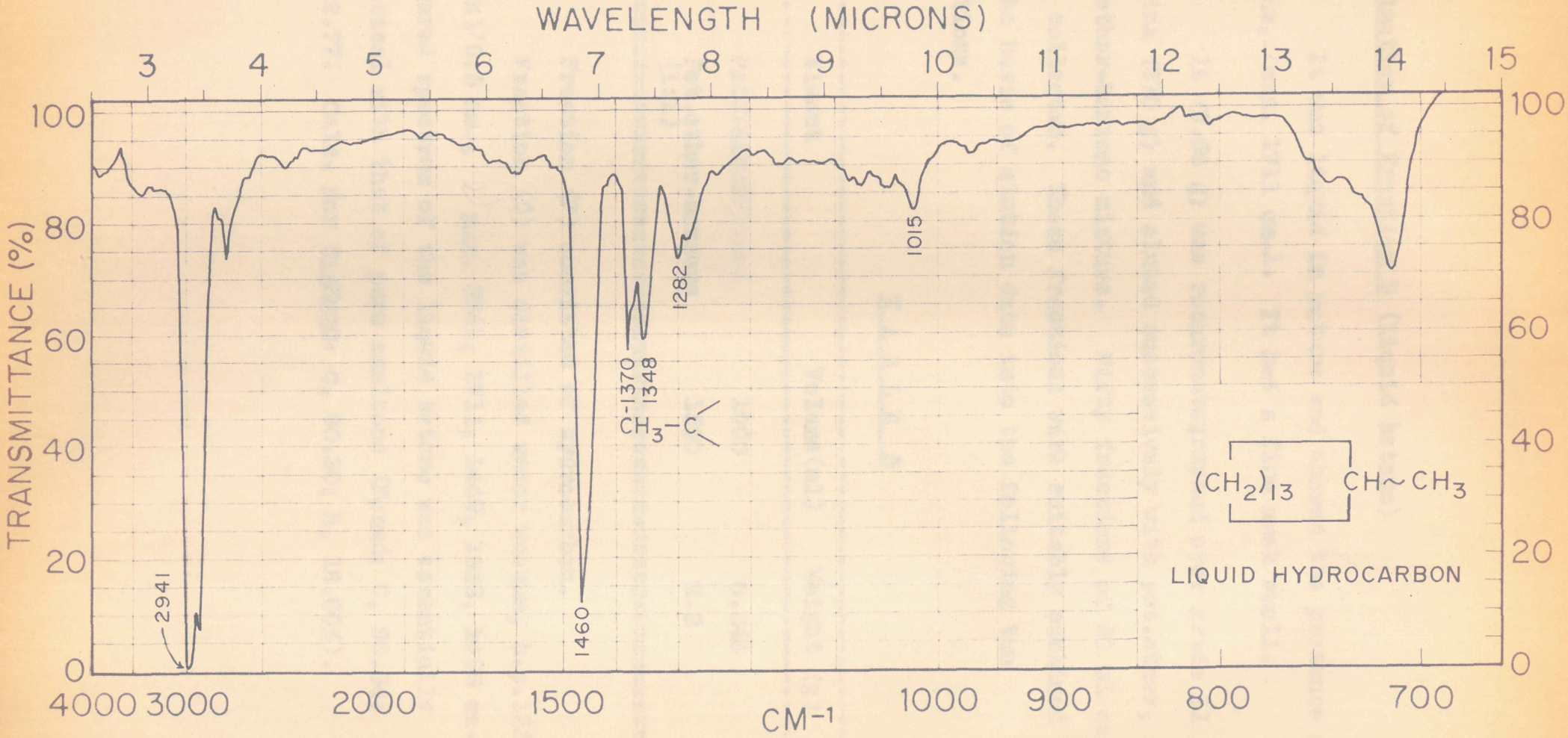
effected after repeated chromatography. Hence these fractions were combined together and small quantity of alcohol (2 ml) was added to it. It was then cooled in ice salt mixture and the solid separated was filtered in the cold condition. It was washed with cold alcohol. The solid hydrocarbon thus obtained was twice crystallised from methyl alcohol (needles), m.p. 61° (Found: C,86.00; H, 14.43. Calc. for $C_{15}H_{30}$: C, 85.60; H, 14.40%). $\nu_{max.}$ 2941, 1449, 1335, 1282 cm-1.

It was identified as cyclopentadecane (for comparison purposes an authentic sample was prepared by Wolff-Kishner reduction of pure exaltone) by taking m.p. and mixed m.p. with authentic sample, comparison of infrared spectra, VPC and TLC analyses.

The hydrocarbon left in the filtrate was liquid in nature. It was repeatedly given the same ice salt cooling treatment till no more solid hydrocarbon separated. The liquid hydrocarbon finally obtained was distilled under vacuum, b.p.155° (bath)/0.3 mm.

This fraction remained liquid after repeated column chromatography and even after storage in the cold for two years.

Attempts to separate this liquid hydrocarbon by VPC were not very successful. $\nu_{max.}$ 2941, 1460,1370 (CH_3-CH), 1348, 1282, 1015 cm-1. NMR spectrum showed the presence of CH_3 group. VPC showed two peaks.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TRANSMITTANCE (%)
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40
20
0
2941
1460
1370
1348
1282
1015
CH3-C
(CH2)13
CH~CH3
LIQUID HYDROCARBON
4000
3000
2000
1500
1000
900
800
700
CM-1

Examination of Fraction B (liquid ketone)

It was liquid in nature and showed the presence of ketone, $\nu_{max.}$ 1711 cm-1. It has a fine musk smell.

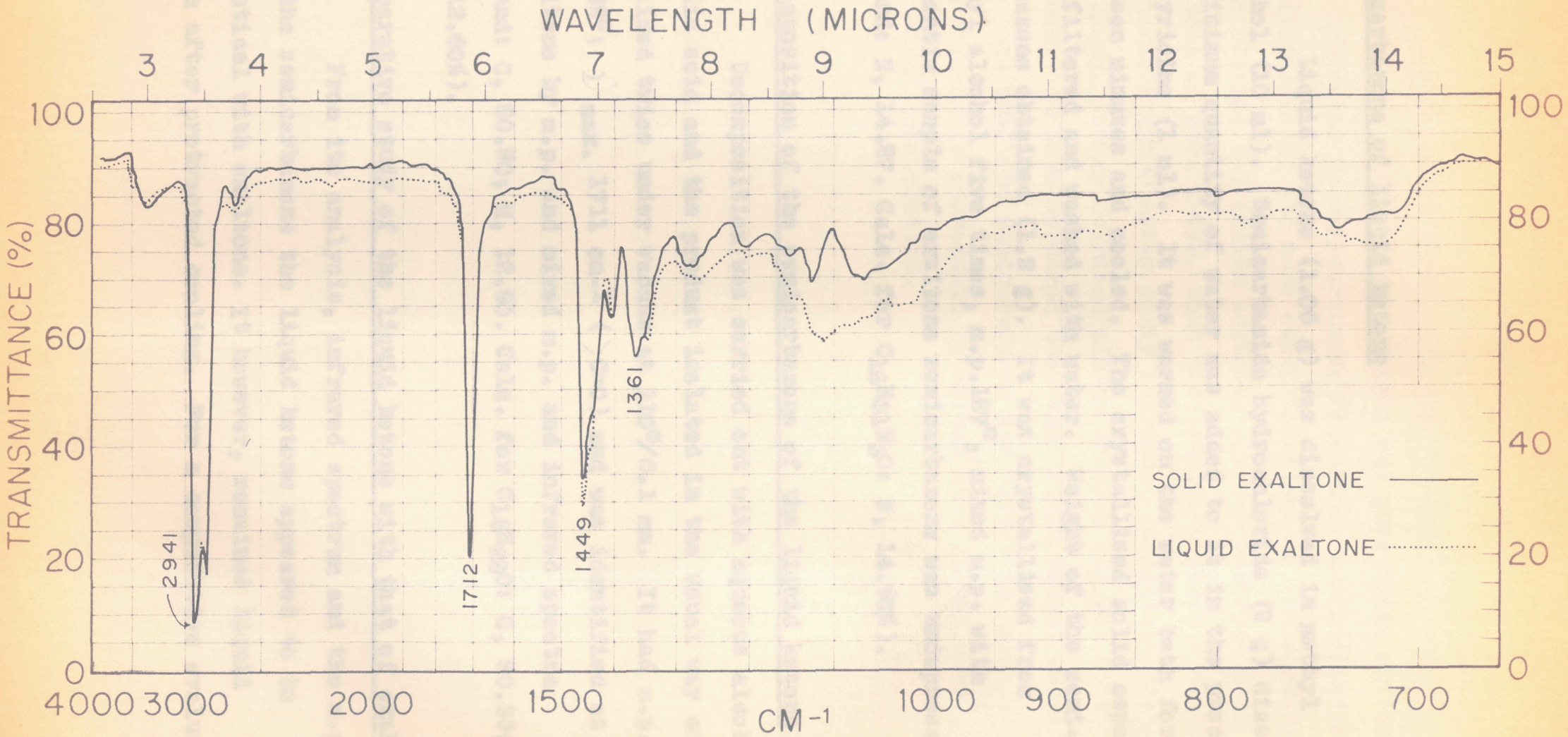
It (2.66 g) was rechromatographed over grade II alumina (270 g) and eluted successively with pet.ether, and pet.ether-benzene mixture. Fifty fractions of 50 ml each were collected. These fractions were suitably combined on the basis of elution data into the following two fractions.

TABLE 5

Fr.	Eluent	Volume(ml)	Weight (g)
(F)	Pet.ether	1000	0.340
(G)	Pet.ether-benzene (1:1)	1500	2.3

Fraction (F) consisted of hydrocarbon.

Fraction (G) was distilled under vacuum, b.p.155-58° (bath)/0.5 mm., $\nu_{max.}$ 2941, 1711, 1449, 1358, 1099 cm-1. Infrared spectrum of the liquid ketone was essentially identical with that of pure exaltone (Found: C, 80.54; H, 12.77. Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.60%).


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
TRANSMITTANCE (%)
100
80
60
40
20
0
2941
1712
1449
1361
SOLID EXALTONE
LIQUID EXALTONE
4000
3000
2000
1500
1000
900
800
700
CM-1

Semicarbazone of liquid ketone

Liquid ketone (1.06 g) was dissolved in methyl alcohol (10 ml). Semicarbazide hydrochloride (2 g) dissolved in minimum quantity of water was added to it in the presence of pyridine (1 ml). It was warmed on the water bath for fifteen minutes and cooled. The crystallised solid separated was filtered and washed with water. Weight of the semicarbazone obtained (1.2 g). It was crystallised from methyl alcohol five times, m.p.187°, mixed m.p. with authentic sample of exaltone semicarbazone was undepressed (Found: N, 14.87. Calc. for $C_{16}H_{31}N_3O$: N, 14.90%).

Decomposition of the semicarbazone of the liquid ketone

Decomposition was carried out with aqueous alcoholic oxalic acid and the product isolated in the usual way and sublimed twice under vacuum at 110°/0.1 mm. It had m.p. 61-62°; $\nu_{max.}$ 1711 cm^{-1} (>C=O) and was identified as exaltone by m.p. and mixed m.p. and infrared spectra (Found: C, 80.80; H, 12.90. Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.60%).

Comparative study of the liquid ketone with that of exaltone

From its analysis, infrared spectrum and the m.p. of the semicarbazone the liquid ketone appeared to be identical with exaltone. It however, remained liquid even after protracted cooling. For a comparative evaluation,

equal amounts of the liquid ketone and pure solid exaltone were subjected to semicarbazone formation, under identical conditions using the same stock solutions of semicarbazide hydrochloride and sodium acetate. It was observed with the help of stop watch, that pure exaltone started depositing the semicarbazone after sixty seconds. As against that, the liquid ketone required ninety seconds for the same purpose. It thus appeared that the liquid ketone which also gave exaltone semicarbazone was slower in action. From this it is reasonable to assume that it may have '0 inside' conformation.

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P A R T III

ALTERNATIVE ROUTES FOR THE REDUCTION OF ACYLOINS

***

A B S T R A C T

Two new alternative routes for the reduction of acyloins to yield the corresponding ketones have been developed.

(i) Wolff-Kishner reduction of 2-hydroxy cyclopentadecanone and 2-hydroxy cycloheptadecanone yielded the corresponding mono alcohols which on oxidation with chromic acid furnished exaltone and dihydrocivetone respectively.

(ii) Lithium aluminium hydride reduction of the tosyl derivative of the 2-hydroxy cyclopentadecanone and 2-hydroxy cycloheptadecanone gave corresponding mono alcohols in quantitative yields. The mono alcohols, thus obtained were oxidised with chromic acid to yield the corresponding ketones viz. exaltone and dihydrocivetone.

The method No.(ii) was also found to be very useful for the reduction of the unsaturated acyloins.

Alternative routes for the reduction of acyloins

Development of the acyloin cyclisation is of great importance for the commercial preparation of macrocyclic musks ketones. With proper stirring facilities, it is possible to obtain the acyloin in an yield of about 80%. The reduction[1] of acyloin to the corresponding ketone by using zinc and hydrogen chloride, however, is not so satisfactory. Considerable amount of by-products, containing mainly hydrocarbons, arising out of over reduction and rearrangement are obtained. The method is also quite unsuitable for the reduction of unsaturated acyloins, as the double bond contained therein is attacked by hydrogen chloride.

It was, therefore, felt desirable to explore alternative possibilities for the reduction of the acyloin to the corresponding ketones. With this objective two alternative routes have been investigated.

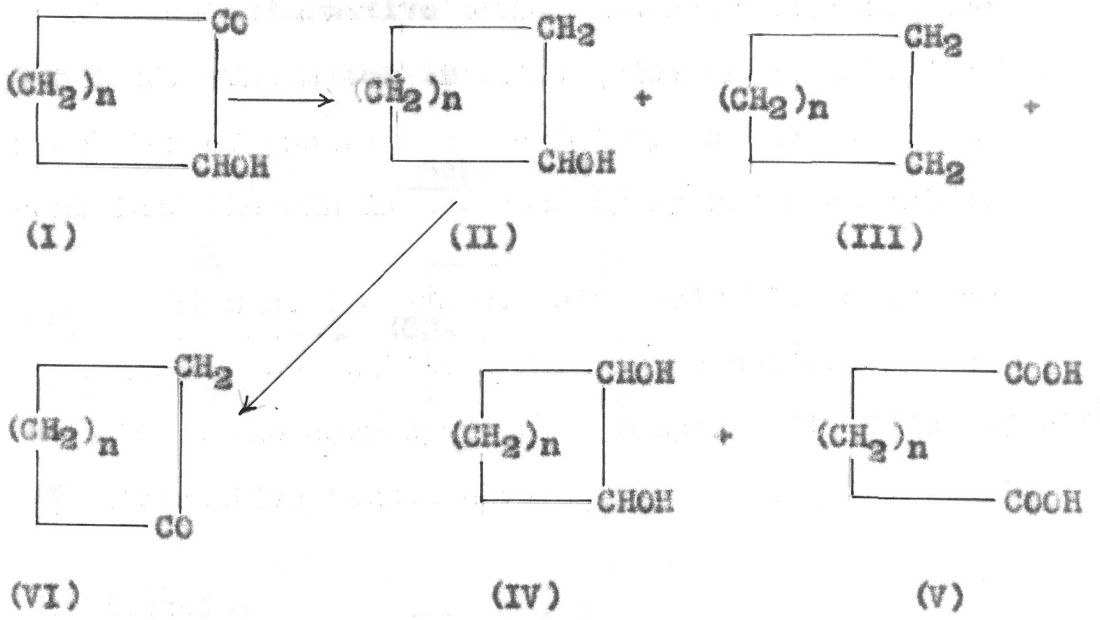
Route (1)

According to this route the acyloin (I) was reduced by Wolff-Kishner reduction to the corresponding mono alcohol (II) which was then oxidised with chromic acid and acetic acid,[2] pyridine-chromic acid complex[3] or more preferably with Jones' chromic acid reagent[4]

to the corresponding ketone (VI) as shown in Scheme 1.

By adopting this procedure, exaltone (cyclopentadecanone) and dihydrocivetone (cycloheptadecanone) could be prepared from the corresponding acyloins. In this reaction also small amounts of the saturated hydrocarbon (III), diol (IV) and the parent dicarboxylic acid (V) were formed due to over reduction and oxidative cleavage.

Scheme 1

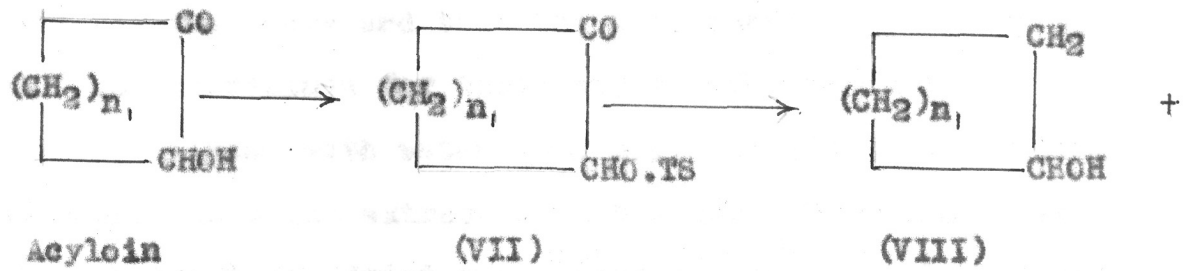


Route (2)

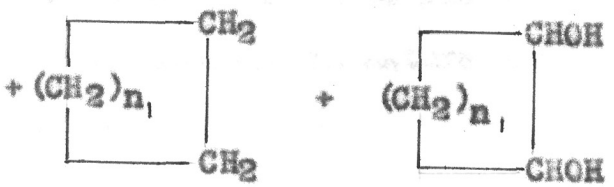
In this route the acyloin, via its tosyl derivative (VII) was reduced with lithium aluminium hydride to the corresponding mono alcohol (VIII) which was

subsequently oxidised with Jones' chromic acid reagent to the corresponding ketone (XI). This method has been successfully employed for the preparation of exaltone and dihydrocivetone. It was specially suited for the reduction of unsaturated acyloin and has been used for the preparation of civetone and iso-civetone, details of which have been described in Part IV. In this case also during the reduction of the tosyl derivative, small amounts of the hydrocarbon (IX) and the diol (X) were obtained as minor by-products. There is reason to feel that these alternative routes described in this part may find application in wider areas.

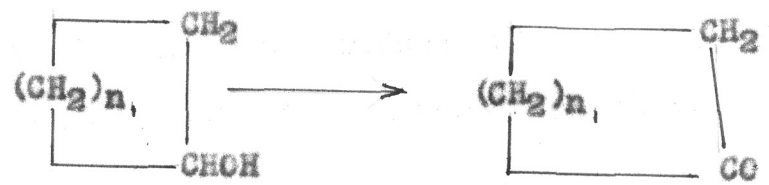
Scheme 2



Acyloin (VII) (VIII)



(IX) (X)



(VIII) (XI)

EXPERIMENTAL

Wolff-Kishner reduction[5] of 2-hydroxy cyclopentadecanone (C_{15} - Acyloin)

The preparation of the acyloin has been described earlier. The acyloin was crystallised from pet.ether (40-60°), m.p. 60-61° (Found: C, 75.54; H, 12.24. Calc. for $C_{15}H_{28}O_2$: C, 75.00; H, 11.74%).

In a three necked 500 ml flask fitted with a long condenser and an inlet for passing nitrogen, diethylene glycol (120 ml), acyloin (10 g), sodium hydroxide (8 g) and hydrazine hydrate (80 ml, 98%) were added. The reaction mixture was heated under nitrogen atmosphere at 190° for two hours and then the temperature was raised to 210° and maintained for three hours. The product was cooled, diluted with water (500 ml), acidified with dilute sulphuric acid and extracted with ether (3 x100 ml). The ether extract was dried over anhydrous sodium sulphate and the ether removed to yield (6 g) of the material, which was semi-solid in nature and could not be crystallised from any solvent.

The above residue was, therefore, distilled under reduced pressure and the following fractions were collected:

T A B L E I

Fr.	b. p.	Weight (g)	
FI	95-100°/0.2 mm.	1.2	semi-solid
FII	100-130°/0.2 mm.	2.0	solid
FIII	Residue	1.8	solid

Examination of the fractions

Fraction F.I. ν_{max} 2949, 1459, 1350, 1294, 1010, 967 cm-1, shown CH=CH. It analysed for the molecular formula $C_{15}H_{30}$. (Found: C, 85.35; H, 13.80. Calc. for $C_{15}H_{30}$: C, 85.60; H, 14.40%).

Analytical data and infrared spectrum indicated that this fraction consisted mainly of hydrocarbon. It (1 g) was chromatographed over twenty five fold of alumina, grade I (25 g) and eluted with pet.ether. Twelve fractions of 25 ml each were collected.

T A B L E 2

Fr.	Eluent	Volume (ml)	Weight (g)	
(a)	Pet.ether	50	0.5086	solid
(b)	"	25	0.1236	solid
(c)	"	25	0.1054	solid
(d)	"	200	-	

Infrared spectra of all the fractions were essentially identical. ν max. 2949, 1468, 1350, 1294, 1010 and 967 cm^{-1}.

Fractions (a) to (c) were solid in nature. Infrared spectra indicated unsaturation. These fractions were combined together and treated with oleum to remove the unsaturation in the usual way. The solid thus obtained was sublimed under vacuum at 110°/0.1 mm. had m.p.60° and was identified as cyclopentadecane by comparison of infrared spectra and mixed m.p. with authentic sample, ν max. 2941, 1468, 1350, 1294 cm^{-1}. (Found: C, 85.40; H, 14.50. Calc. for $C_{15}H_{30}$: C, 85.60; H, ~~13.49~~ 14.40%).

Fraction F II. Analytical data and infrared spectra indicated that this fraction consisted mainly of the mono alcohol. ν max. 3344, 2941, 1499, 1370, 1014 cm^{-1}. (Found: C, 79.02; H, 13.27. Calc. for $C_{15}H_{30}O$: C, 79.50; H, 13.36%).

It (2 g) was chromatographed over fifty fold amount of alumina grade II (100 g) and eluted with pet. ether, pet.ether-benzene mixture and alcohol. ~~Sixteen~~ Thirty seven fractions of 50 ml. each were collected. These were suitably combined on the basis of elution data into the following three fractions.

TABLE 3

Fr.	Eluent	Volume	Weight (g)
(e)	Pet. ether	100 ml	0.380
(f)	Pet.ether-benzene (1:1)	250 ml	1.4
(g)	Alcohol	1.5 L.	0.150

Examination of the fractions

Fraction (e), m.p. 60-61°, consisted of cyclopentadecane which was identified by the infrared spectrum, mixed m.p. and analysis.

Fraction (f), consisted of the mono alcohol, m.p. 78-79°. It was sublimed under vacuum at 110°/0.1 mm, m.p. 80-81°, ν_{max}. 3333, 2941, 1449, 1366, 1342, 1015 cm-1. (Found: C, 79.46; H, 13.10. Calc. for $C_{15}H_{30}O$: C, 79.50; H, 13.36%).

It was further characterised by taking mixed m.p. with authentic sample of mono alcohol which remained undepressed.

Authentic sample of the mono alcohol was prepared by the reduction of pure exaltone with lithium aluminium hydride, m.p. 80-81°.

Oxidation of the mono alcohol with chromic acid in acetic acid to yield exaltone.

The mono alcohol (400 mg) was dissolved in acetic acid (10 ml), and chromic acid (300 mg) dissolved in acetic acid (10 ml) was added to it slowly. The reaction mixture was heated on the water bath with stirring for three hours. It was poured in water and extracted with ether(~~50X4~~ 4x50 ml). Ether was removed to yield a residue (300 mg). This was divided into pet.ether soluble (100 mg) and pet.ether insoluble (200 mg) portion. The former was exaltone and was purified by chromatography and vacuum sublimation, m.p. 60-61°. Infrared spectra, ν_{max} 2941, 1712, 1449, 1361, 1274, 1124, 1020 cm^{-1} (Found: C, 80.39; H, 12.4. Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.60%). Semicarbazone was prepared by the usual method, m.p. 187-188°, mixed m.p. with authentic sample was undepressed.

The pet.ether insoluble portion showing a m.p. of 105-106° was actually pentadecane dioic acid and was further purified by washing with hot pet.ether, followed by crystallisation from acetic acid, m.p. 113-114°, mixed m.p. with authentic sample of pentadecanedioic acid was undepressed.

Fraction (g), consisted of cyclopentadecane diol, m.p. 84-85°. It was sublimed under vacuum at 110°/0.1 mm, m.p. 86-87° ~~(lit. 87°)~~ (Found: C, 74.60; H, 12.40. Calc. for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48%).

Fraction FIII (Residue) (page 97) obtained during Wolff-Kishner reduction of the acyloin also consisted of pentadecanedioic acid which was obtained in the pure state by crystallisation from alcohol and acetic acid, m.p. 113-114° (Found: C, 66.60; H, 10.50. Calc. for $C_{15}H_{28}O_4$: C, 66.10; H, 10.40%). Mixed m.p. with authentic sample of pentadecanedioic acid was undepressed.

Wolff-Kishner reduction of 2-hydroxy cycloheptadecanone (C_{17} Acyloin)

The acyloin (10 g) was reduced by following the procedure previously described using diethylene glycol (120 ml), sodium hydroxide (8 g) and hydrazine hydrate (80 ml). The crude reaction product (5 g) was separated into neutral (4.5 g) and acidic (0.5 g) components. The acidic portion consisted of heptadecanedioic acid; crystallised from acetic acid, m.p. 116-117°, mixed m.p. with authentic sample 116-117° (Found: C, 67.60; H, 10.50. Calc. for $C_{17}H_{32}O_4$: C, 67.90; H, 10.72%).

The neutral portion (4.5 g) was chromatographed on alumina grade II (200 g) and divided into the following fractions.

T A B L E 4

Fr.	Eluent	Volume	Weight(g)	
(h)	Pet. ether	500 ml	1.9	semi-solid
(i)	Benzene) Ether)	500 ml	1.2	solid
(j)	Alcohol	3 L	1.2	solid

Fraction (h), consisted of hydrocarbon. It showed slight unsaturation when tested with tetranitromethane, and infrared spectrum $\nu_{max.}$ 2941, 1449, 1335, 1282, 1010 and 968 cm-1. The unsaturation was removed by treatment with oleum as usual and the residue was rechromatographed over alumina grade I (100 g) and eluted with pet.ether (500 ml) to yield solid cycloheptadecane which was purified by sublimation in vacuum at 110°/0.1 mm, m.p. and mixed m.p. with an authentic sample, 60-61°, $\nu_{max.}$2941, 1449, 1380, 1282, 1010 cm-1. (Found: C, 86.10; H, 14.20. Calc. for $C_{17}H_{34}$; C, 85.60; H, 14.40%). The authentic sample was prepared from pure cycloheptadecanone via Wolff-Kishner reduction.

(Fraction (i) consisted of the mono alcohol, cycloheptadecanol (dihydrocivetol), m.p. 78-79°. It was sublimed under vacuum at 115°/0.1 mm., m.p.80-81°. $\nu_{max.}$ 3333, 2941, 1449, 1342, 1290, 1075, 1010 cm-1. (Found: C, 80.54; H,13.06. Calc. for $C_{17}H_{34}O$: C, 80.24; H, 13.47%).

Oxidation of the mono alcohol (dihydrocivetol) to dihydrocivetone

The mono alcohol (400 mg) was oxidised with chromic acid (800 mg) in acetic acid (10 ml) as described earlier. In this case instead of heating the reaction mixture, it was kept shaking for 24 hours at room temperature. It was worked up as usual to yield 350 mg of the material. This was separated into neutral (210 mg) and acidic (140 mg) components by usual treatment with alkali. The neutral portion contained cycloheptadecanone (dihydrocivetone) and was further purified by chromatography followed by sublimation under vacuum at 115°/.01 mm., m.p. 61-62°, ν_{max} 2941, 1711, 1449, 1408, 1361, 1280, 1124, 1015 cm^{-1}. (Found: C, 80.98; H, 12.50. Calc. for $C_{17}H_{32}O$: C, 80.90; H, 12.80%). Semicarbazone was prepared as usual, m.p. 192°, mixed m.p. with dihydrocivetone semicarbazone 192°.

The acidic material was crystallised from alcohol and then from acetic acid to yield pure heptadecanedioic acid, m.p. 116-117°; mixed m.p. with the authentic sample was undepressed. (Found: C, 67.84; H, 10.32. Calc. for $C_{17}H_{32}O_4$: C, 67.90; H, 10.72%).

Fraction (i) containing the diol initially had m.p. 90-91°. It was sublimed under vacuum at 125°/0.1 mm., m.p. 96-97° (~~lit. 98°~~). ν_{max} 3390, 2941, 1449, 1342, 1290, 1010 cm^{-1}. (Found: C, 75.58; H, 12.59. Calc. for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67%).

Preparation of the tosyl derivative of 2-hydroxy-cyclopentadecanone (C_{15}- acyloin)

Acyloin (10 g) was dissolved in pyridine (40 ml). p-Toluene sulphonyl chloride (25 g) dissolved in pyridine (15 ml) was added to it slowly under shaking in ice cold condition. The reaction mixture was shaken several times and kept at room temperature for forty eight hours. It was then poured into ice cold water and extracted with ether. The ether extract was washed with dilute hydrochloric acid and then with water. It was again washed with 10% sodium carbonate solution and finally with water. The ether extract was dried over anhydrous sodium sulphate, filtered and the ether removed. The tosyl derivative thus obtained was dried under vacuum, (yield 12 g). It was viscous, semi-solid in nature and could not be crystallised; ν_{max}. 2941, 1709, 1587, 1481, 1449, 1364, 1183, 1170, 1115, 1042, 1076, 1036, 1015 cm-1. (Found: C, 66.94; H, 8.60; S, 8.09. $C_{22}H_{34}O_4S$ requires: C, 66.98; H, 8.69; S, 8.11%).

Lithium aluminium reduction of the tosyl derivative

In a 250 ml three necked flask, fitted with a condenser, a guard tube and a dropping funnel, lithium aluminium hydride (1.5 g) and dry ether (100 ml) were added. Tosyl derivative (10 g), dissolved in dry ether (50 ml) was added slowly to it through the dropping funnel

during forty five minutes. The addition was done under stirring and in cold condition. The reaction mixture was refluxed for three hours and then decomposed with alcohol, alcohol-water mixture and finally with dilute hydrochloric acid in the usual way. It was extracted with ether. The ether extract was washed with water, 5% sodium carbonate solution and finally again with water. It was dried over anhydrous sodium sulphate. Ether was removed and the residue (4.5 g) was chromatographed over fifty fold amount of alumina grade II (225 g) and eluted successively with pet.ether, pet.ether-benzene, benzene, ether and alcohol. ~~Forty~~ Sixty fractions of 50 ml each were collected. These were suitably combined on the basis of elution data into the following three fractions described in the table.

T A B L E 5

Fr.	Eluent	Volume (ml)	Weight (g)
(k)	Pet.ether	500	0.390
(l)	Pet.ether-benzene (1:1)	1500	3.835
(m)	Alcohol	1000	0.215

Fraction (k) was semi-solid in nature and consisted of hydrocarbon. It became solid after keeping and contained

cyclopentadecane. It was sublimed under vacuum at 110°/0.1 mm m.p. 60°, $\nu_{max.}$ 2941, 1449, 1370, 1018 cm-1. (Found: C85.40; H, 14.10 Calc. for $C_{15}H_{30}$: C, 85.63; H, 14.37%)

Fraction (1) was solid in nature and consisted of the mono alcohol, cyclopentadecanol, m.p. 78-79°. It was sublimed under vacuum at 115°/0.1 mm., m.p. 80-81°; $\nu_{max.}$ 3390, 2941, 1449, 1342, 1282, 1170, 1015 cm-1. (Found: C, 79.35; H, 13.10. Calc. for $C_{15}H_{30}O$: C, 79.57; H, 13.36%).

Oxidation of the mono alcohol with pyridine-chromic acid complex

Mono alcohol (3.2 g) was dissolved in dry pyridine (30 ml). Powdered chromic acid (3 g) was added slowly to pyridine (10 ml)(yellow slurry formed). To this, the solution of the mono alcohol in pyridine was added slowly in ice cold condition. The reaction mixture was shaken thoroughly and kept at room temperature for 24 hours. It was poured into water and extracted with ether. The ether extract was washed with dilute hydrochloric acid and again with water. It was dried over anhydrous sodium sulphate. The ether was removed, and the residual exaltone purified by chromatography on alumina grade II (500 g) and elution with pet.ether (500 ml) to yield pure exaltone (2.3 g), which was sublimed at 110°/0.1 mm., m.p. 60-61°; $\nu_{max.}$ 1711 cm-1 (>C=O) (Found: C, 79.90; H, 12.80. Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.60%).

Semicarbazone was prepared in the usual way and crystallised twice from ethyl alcohol, m.p. 186-187°; mixed m.p. with authentic sample 186-187°.

Fraction (m) consisted of cyclopentadecane diol, m.p. 85°. It was sublimed under vacuum at 120°/0.1 mm., m.p. 86-87°. (Found: C, 74.50; H, 12.10. Calc. for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48%).

Preparation of the tosyl derivative of 2-hydroxy-cycloheptadecanone (C17-acyloin)

Acyloin (20 g) was dissolved in pyridine (40 ml). p-Toluene sulphonyl chloride (35 g) dissolved in pyridine (50 ml) was added to it in cold condition under shaking. The reaction mixture was kept at room temperature for 48 hours. The reaction product was worked up as usual to yield crude tosylate (28 g), $\nu_{max.}$ 2941, 1712, 1590, 1484, 1449, 1364, 1299, 1282, 1185, 1170, 1115, 1093, 1075, 1036, 1015 cm-1.

Lithium aluminium hydride reduction of the tosyl derivative

Tosyl derivative (20 g) was reduced with lithium aluminium hydride (5 g) in dry ether as described earlier. It was worked up as usual and the crude product (12 g) was distilled under vacuum at 180°(bath)/3.8 X 10-2 mm (yield 10.1 g), $\nu_{max.}$ 3448, 2941, 1626, 1592, 1449, 1348, 1294, 1099, 1055 cm-1.

The distillate (10 g) was chromatographed over alumina grade II (500 g) and eluted successively with pet. ether, pet.ether-benzene, benzene, ether and alcohol. ~~Thirty~~ Eighty five fractions of 100 ml each were collected. These were suitably combined on the basis of elution data into the following three fractions.

T A B L E 6

Fr.	Eluent	Volume(L)	Weight(g)
(n)	Pet. ether	1.0	0.9
(o)	Pet.ether-benzene(1:1)	2.0	7.6
(p)	Alcohol	5.2	1.5

Examination of the fractions

Fraction (n) was semi-solid in nature and consisted of hydrocarbon. It became solid after keeping. It was sublimed under vacuum at 110°/0.1 mm., m.p. 60° and was identified as cycloheptadecane in the usual way.

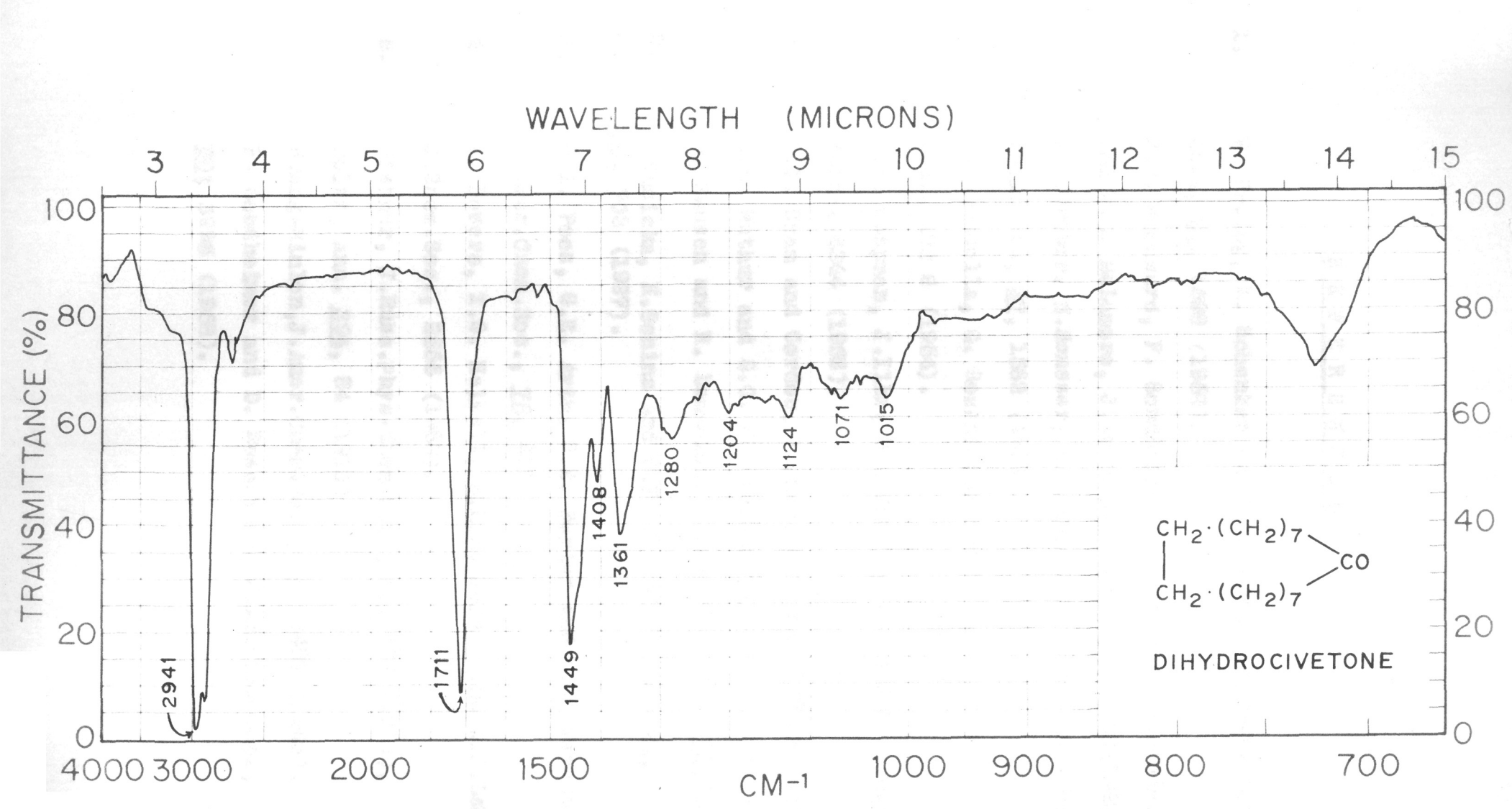
Fraction (o) was solid and consisted of the mono alcohol, cycloheptadecanol, m.p. 78-79°. It was sublimed under vacuum at 115°/0.1 mm., m.p.80-85°. ν_{max}. 3448, 2941, 1449, 1370, 1342, 1015 cm^{-1}. (Found: C, 80.30; H, 13.10. Calc. for $C_{17}H_{34}O$: C, 80.24; H, 13.40%). Mixed m.p. with an authentic sample prepared by the lithium aluminium hydride reduction of dihydrocivetone was undepressed.

Oxidation of the mono alcohol to dihydro-civetone with Jones' chromic acid reagent

Mono alcohol (1.9 g) was dissolved in dry and distilled acetone (50 ml). Jones' chromic acid reagent (8 N solution of chromic acid in 8N H_2SO_4) was added to it dropwise till the yellow colour persisted. The reaction mixture was shaken for half an hour. Excess of the reagent was destroyed by aqueous methanol. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulphate. The ether was removed to yield crude dihydrocivetone (1.8 g) which was chromatographed over twenty fold alumina grade II and eluted with pet.ether (600 ml) and then sublimed to yield (1.6 g) of the pure material, m.p. 61-62°, νmax. 1712 cm-1 (>C=O) (Found: C, 80.60; H, 12.70. Calc. for $C_{17}H_{32}O$: C, 80.90; H, 12.80%).

Semicarbazone was prepared as usual and crystallised from ethyl alcohol, m.p. ~~189-190°~~ 191-192°; mixed m.p. with an authentic sample of the semicarbazone of dihydrocivetone 192° (undepressed).

Fraction (p) contained the diol. It was solid in nature, m.p. 84-85°. It was crystallised from benzene, m.p. 86-87°. It was again crystallised from pet.ether and benzene to melt at 96-97° (Found: C, 75.25; H, 12.72. Calc. for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67%).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1204
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900
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700
CM-1

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P A R T IV

SYNTHESIS OF CIVETONE & ISO-CIVETONE

***

ABSTRACT

A new approach has been developed for the synthesis of olefinic macrocyclic ketones by the reduction of unsaturated cyclic acyloins to the corresponding ketones.

Heptadec-8-ene dioic acid prepared from aleuritic acid was converted to 2-hydroxy cycloheptadecen-1-one (acyloin), the tosyl derivative of which on reduction with lithium aluminium hydride yielded the mixture of two isomeric monoalcohols with small amount of unsaturated hydrocarbon. The mixture of mono alcohols was separated from the hydrocarbon by chromatography and oxidised with Jones' chromic acid reagent to yield a mixture of civetone and iso-civetone. Civetone and iso-civetone were separated by column chromatography and further characterised through their semicarbazones.

This method of reduction of unsaturated acyloins is expected to find wider use.

PRESENT INVESTIGATION

In this part, the new method developed in Part III of this thesis for the reduction of macrocyclic acyloins to the corresponding ketones has been successfully employed for the preferential reduction of unsaturated acyloins, to the corresponding ketones. This represents a new approach for the synthesis of unsaturated macrocyclic ketones and has led to the successful synthesis of civetone and iso-civetone.

Recently Mathur and Bhattacharyya[1] have reported the synthesis of civetone, iso-civetone and dihydrocivetone from aleuritic acid employing the acyloin condensation technique. For the reduction of the unsaturated acyloins to civetone, these workers have developed the use calcium in liquid ammonia as a preferential reducing agent. In the present work 2-hydroxy cycloheptadecen-1-one prepared according to the method of Mathur and Bhattacharyya has been reduced via its tosyl derivative with lithium aluminium hydride to the corresponding mixture of mono alcohols, along with a small amount of hydrocarbon. The former on oxidation with Jones chromic acid reagent[2] furnished a mixture of civetone and iso-civetone. The mixture of the ketones was separated into the constituents by elaborate chromatography.

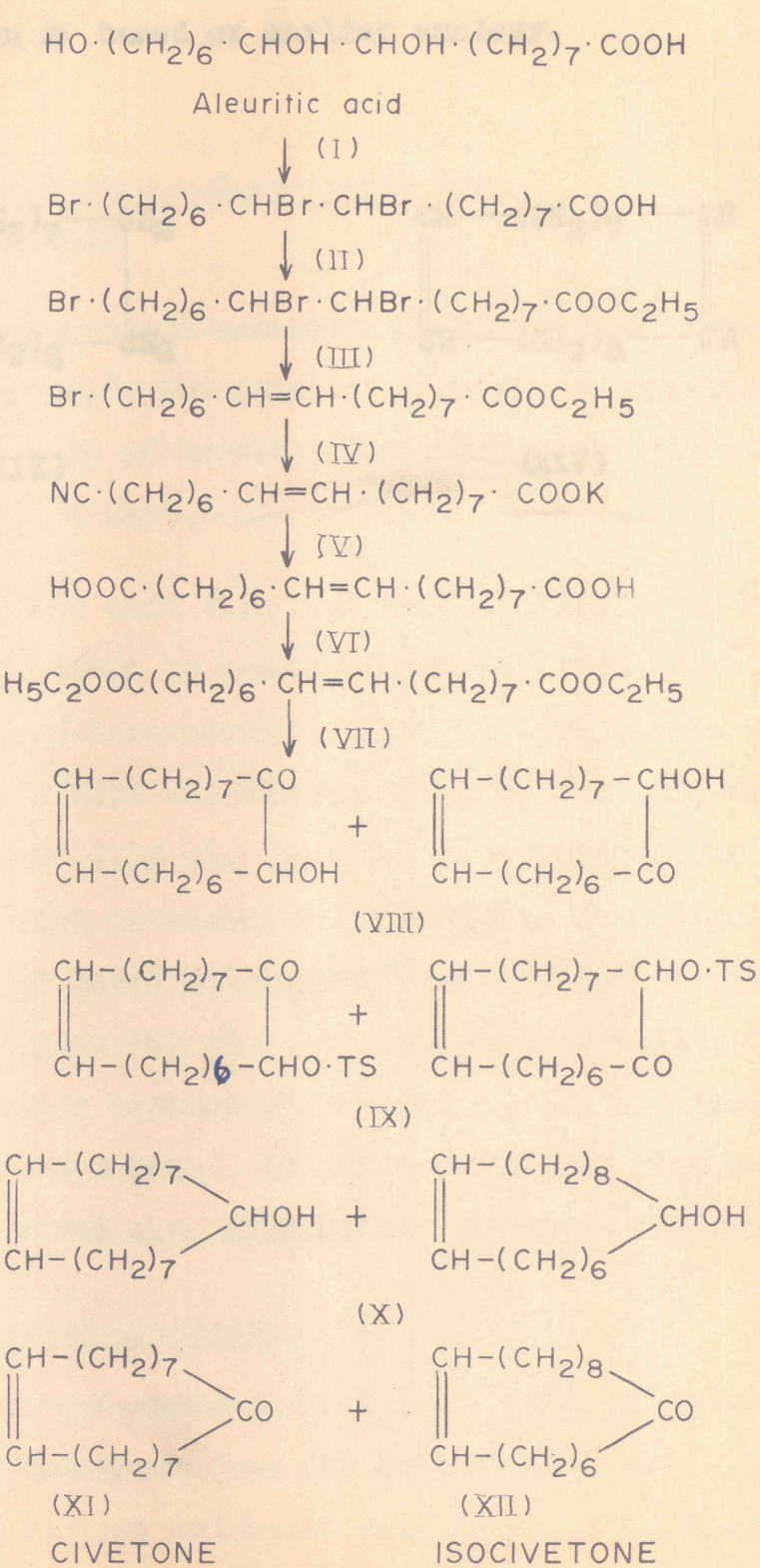
The sequence of reactions leading to the synthesis of civetone and iso-civetone are (given in scheme I) 9,10,16-tribromohexadecanoic acid (II) obtained from aleuritic acid (I) prepared according to the method of Mathur and Bhattacharyya was debrominated in the form of its ester (III) by treatment with zinc dust and alcohol to yield ethyl-16-bromo hexadec-9-enoate (IV) in quantitative yield. The ω-bromo ester (IV) was converted to the nitrile (V), which without isolation was directly hydrolysed by alkali and the solution on acidification yielded heptadec-8-ene dioic acid (VI). This unsaturated dicarboxylic acid in the form of its diester (VII) was converted to a mixture of acyloins (VIII). The (mixture of) tosyl derivatives (IX) was then reduced with lithium aluminium hydride to the corresponding mixture of mono alcohols (X) which on oxidation with Jones' chromic acid reagent furnished a mixture of civetone and iso-civetone which was separated by elaborate chromatography to yield pure civetone (XI) and iso-civetone (XII). These isomeric ketones were further characterised by their semicarbazones.

This newly developed method is thus particularly suitable for the reduction of unsaturated acyloins for which adequate methods were so far not available.

During the reduction of the tosylate (IX) with lithium aluminium hydride a small amount of hydrocarbon was also obtained. It is possibly a mixture of (XIII & XIV).

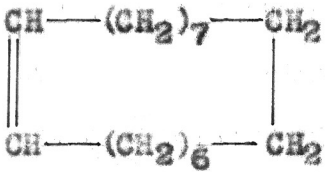
SYNTHESIS OF CIVETONE AND ISOCIVETONE

SCHEME 1.

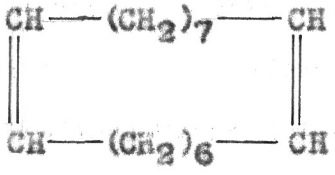


115

This assumption is based on earlier analogy.



(XIII)



(XIV)

EXPERIMENTAL

Preparation of heptadec-8-ene dioic acid from aleuritic acid

It was prepared according to the method of Mathur and Bhattacharyya,[1] the details of which are not being given for the sake of brevity. Only brief description is being recorded here.

Aleuritic acid (I), m.p. 99-100° (150 g) on hydrobromination followed by azeotropic esterification gave ethyl-9,10,16-tribromo-hexadecanoate (230 g), debromination of which with zinc dust and ethanol afforded ethyl-16-bromo-hexadec-9-enoate (125 g). This was converted to the nitrile by refluxing with potassium cyanide (70 g) in alcoholic solution for 10 hours followed by the addition of potassium hydroxide (60 g in 100 ml water) and further refluxing for 36 hours to yield heptadec-8-ene dioic acid (VI) (105 g), after usual processing. It was crystallised from benzene, m.p. 94-95°, mixed m.p. with authentic sample was undepressed.

Diethylheptadec-8-enedioate (VII)

Heptadec-8-enedioic acid (m.p. 95°) (VI; 65 g) was dissolved in thiophene free dry benzene (600 ml). Absolute alcohol (100 ml) and sulphuric acid (2 ml, d 1.84) were added to the above solution. The esterification was carried out by

azeotropic distillation of water from the reaction mixture as usual. After the completion of the reaction (24 hr), the benzene solution was first washed with water to remove mineral acid, then with 5% sodium carbonate solution in order to make it free from unreacted fatty acid and again with water. The benzene solution was then dried over anhydrous sodium sulphate and the benzene distilled. Yield of crude ester (75 g). It was distilled under vacuum, b.p. 160°/0.3 mm. ν_{max}. 2949, 1727, 1453, 1365, 1312, 1294, 1246, 1176, 1093, 1036, 968 cm-1. (Found: C, 70.70; H, 10.85. Calc. for $C_{21}H_{38}O_4$: C, 71.10; H, 10.80%).

2-Hydroxy cycloheptadecen-1-one (mixture) (VIII)

In a three-necked 5 l. flask fitted with a mechanical stirrer, a dropping funnel and a condenser, sodium (20 g) and purified, dry, distilled xylene (3 l.) were added. It was first heated to boiling under a current of nitrogen without stirring. About 180 ml of xylene was distilled off and then the xylene was allowed to cool down to about 90-100°. The sodium was then pulverised as usual and the temperature of the xylene raised to 140°. The diester (65 g) dissolved in xylene (100 ml) was added slowly through the separating funnel under vigorous stirring during one hour. After the addition was over, the stirring was continued for half hour, the reaction mixture was cooled and then decomposed with 300 ml of absolute alcohol. The reaction product was worked

up as usual. The residue (acyloin) after removing the xylene was distilled under vacuum, b.p.148°/0.1 mm. (yield 31 g). $\nu_{max.}$ 3500, 2950, 1711, 1450, 1398, 1357, 1052, 1015, 967 cm-1.(Found: C,77.00; H,11.57. Calc. for $C_{17}H_{30}O_2$: C, 76.70; H, 11.35%).

Tosyl derivative (IX) of the 2-hydroxycycloheptadecen-1-one (Acyloin)

Acyloin (30 g) was dissolved in dry pyridine(40 ml). p-Toluene sulphonyl chloride (35 g) dissolved in pyridine (40 ml), was added to it in ice cold condition. The reaction mixture was shaken several times and kept at room temperature for 48 hours. It was then poured into ice cold water, stirred for some time and then extracted with ether. The ether extract was washed with dilute hydrochloric acid and then with water. It was again washed with 10% sodium-carbonate solution and finally with water. The ether extract was dried over anhydrous sodium sulphate, filtered and the ether removed to yield the tosylate (26 g). $\nu_{max.}$ 2950, 1721, 1592, 1488, 1452, 1438, 1398, 1370, 1302, 1285, 1208, 1190, 1176, 1121, 1096, 1018, 967, 870, 813, 813, 724 cm-1. (Found: C, 68.76; H, 9.14. $C_{24}H_{36}O_4S$ requires: C, 68.54; H, 8.63; S, 7.61%).

Reduction of the tosyl derivative (IX) with lithium aluminium hydride

The tosyl derivative (30 g) was reduced with lithium aluminium hydride (5 g) in anhydrous ether (100 ml) following the usual procedure described earlier. The crude mixture of

mono alcohols obtained after usual processing was 12 g. On total distillation (b.p. 160°/0.1 mm) 11 g. of colourless semi-solid was obtained.

Chromatographic resolution

The above reaction product (10.5 g) was chromatographed over fifty fold amount of alumina, grade II (550 g). It was eluted successively with pet.ether, pet.ether-benzene, benzene ether and alcohol. ~~Fifty~~ 120 fractions of 100 ml each were collected. These were suitably combined on the basis of elution data into the following five fractions.

TABLE 1

Fraction	Eluent	Volume (ml)	Weight (g)
(A)	Pet. ether	600	1.81
(B)	Pet.ether-benzene	400	1.19
(C)	Benzene	2000	6.8
(D)	Ether	1000	-
(E)	Alcohol	8000	-

Examination of fractions

Fraction (A). This fraction consisted of hydrocarbon (liquid) only. It was distilled under vacuum, b.p.155° (bath)/ 1 mm. IR spectrum ν_{max} 2949, 1458, 1348, 1292, 1020, 968 cm-1. (Found: C, 86.73; H, 13.20. Calc.for $C_{17}H_{30}$: C, 87.10; H, 12.90%).

Fraction (B). It was semi-solid and became a solid after keeping, m.p. 43-44°. It showed the presence of >C=O group, $\nu_{max.}$ 1711 cm-1. It was distilled under vacuum at 190° (bath)/1 mm. and was crystallised from alcohol, m.p.44-45°, $\nu_{max.}$ 2949, 1711, 1365, 1293, 1149, 1020 and 967 cm-1. (Found: C, 81.41; H, 12.23. Calc. for $C_{17}H_{30}O$: C, 81.50; H, 12.10%). It formed a semicarbazone somewhat slowly, had m.p. 186-187°, which remained undepressed on mixing with a sample of iso-civetone semicarbazone. Evidently, this portion of the ketone ~~escaped unreacted~~ formed & escaped further reduction to the mono during the reduction of the tosyl derivative.

Fraction (C). This fraction consisted of solid mono-alcohol, m.p. 65-66°. It was sublimed under vacuum at 110°/0.1 mm, and m.p. 66-67°, $\nu_{max.}$ 3400, 2950, 1460, 1368, 1020 and 967 cm-1. (Found: C, 80.58; H, 12.72. Calc. for $C_{17}H_{32}O$: C, 80.88; H, 12.78%).

Oxidation of the above mono alcohol with Jones' chromic acid reagent to civetone-iso-civetone mixture

Mono alcohol (3.3 g) was dissolved in dry acetone (50 ml), Jones' chromic acid reagent (50 ml) was added to it drop by drop till the yellow colour persisted (4 ml). The reaction mixture was shaken for one hour. Excess of reagent was destroyed by aqueous methyl alcohol. The reaction mixture was then poured into cold water and extracted with ether. The ether extract was washed with water, dried over anhydrous-sodium sulphate and ether removed. Yield of crude ketone

(3.2 g). It was a viscous liquid having civetone like odour; ν_{max}. 2941, 1710, 1456, 1433, 1404, 1361, 1274, 1190, 1330, 1053, 1016 and 967 cm-1.

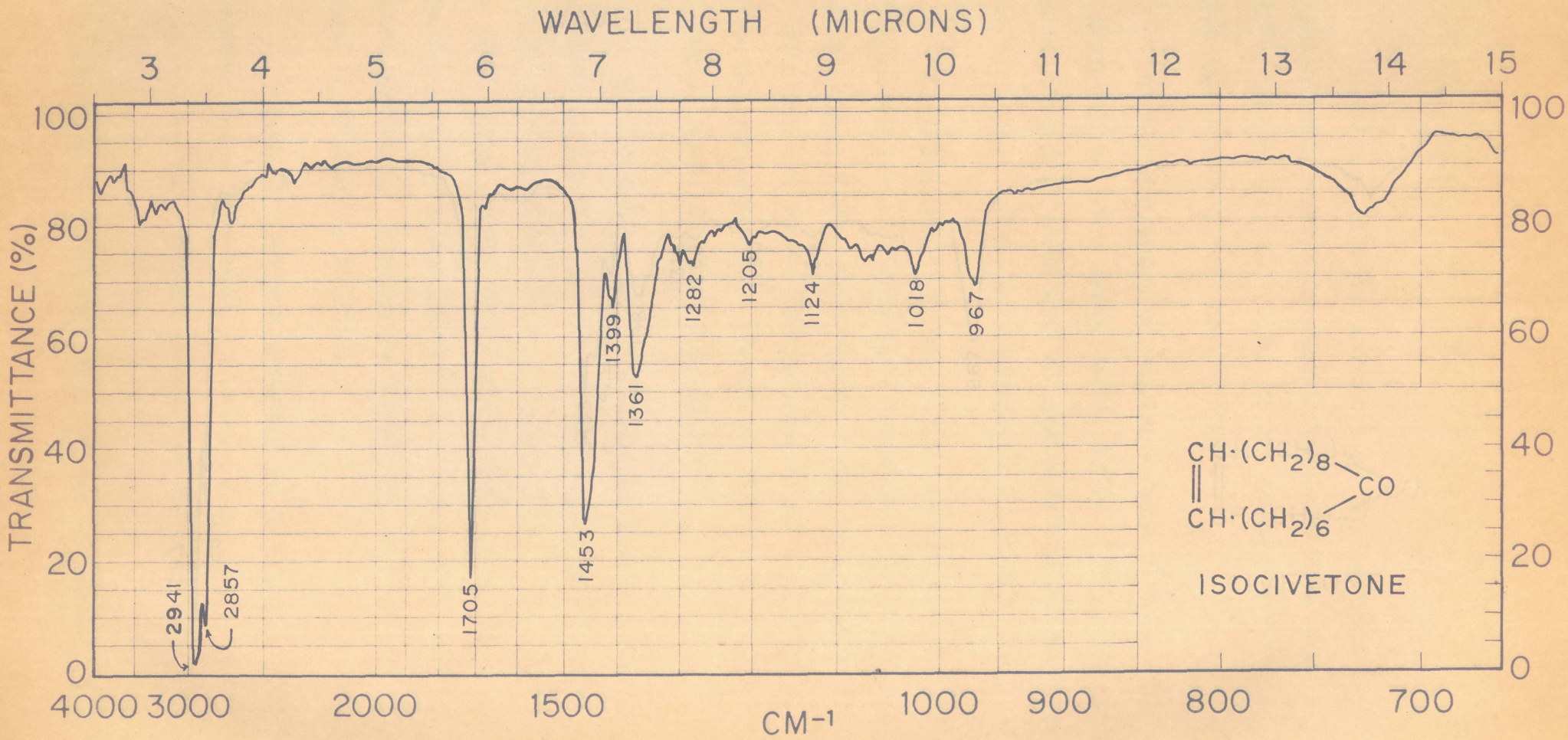
The above mixture of civetone and iso-civetone (3 g) was chromatographed over hundred fold amount of alumina (grade II; 300 g). It was eluted successively with pet.ether. ~~Thirty~~ 25 fractions of 100 ml each were collected. These were suitably combined on the basis of elution data into the following fractions.

T A B L E 2

Fr.	Eluent	Volume	Weight (g)	Nature	Remarks
(F)	Pet.ether	1.5 L.	1.27	Solid	Iso-civetone
(G)	Pet.ether	600 ml.	0.30	Semi-solid	Mixture
(H)	Pet.ether	400 ml	1.3	Liquid	Civetone

Examination of the fractions

Fraction (F). It was solid in nature, m.p.43-44°, ν_{max}. 1705 cm-1 (>C=O group). It was sublimed under vacuum at 120° (bath)/0.1 mm., m.p. 44-45°. ν_{max}. 2941, 1705, 1453, 1399, 1361, 1282, 1205, 1124, 1018 and 967 cm-1. Infrared spectrum was identical with that of iso-civetone.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1282
1205
1124
1018
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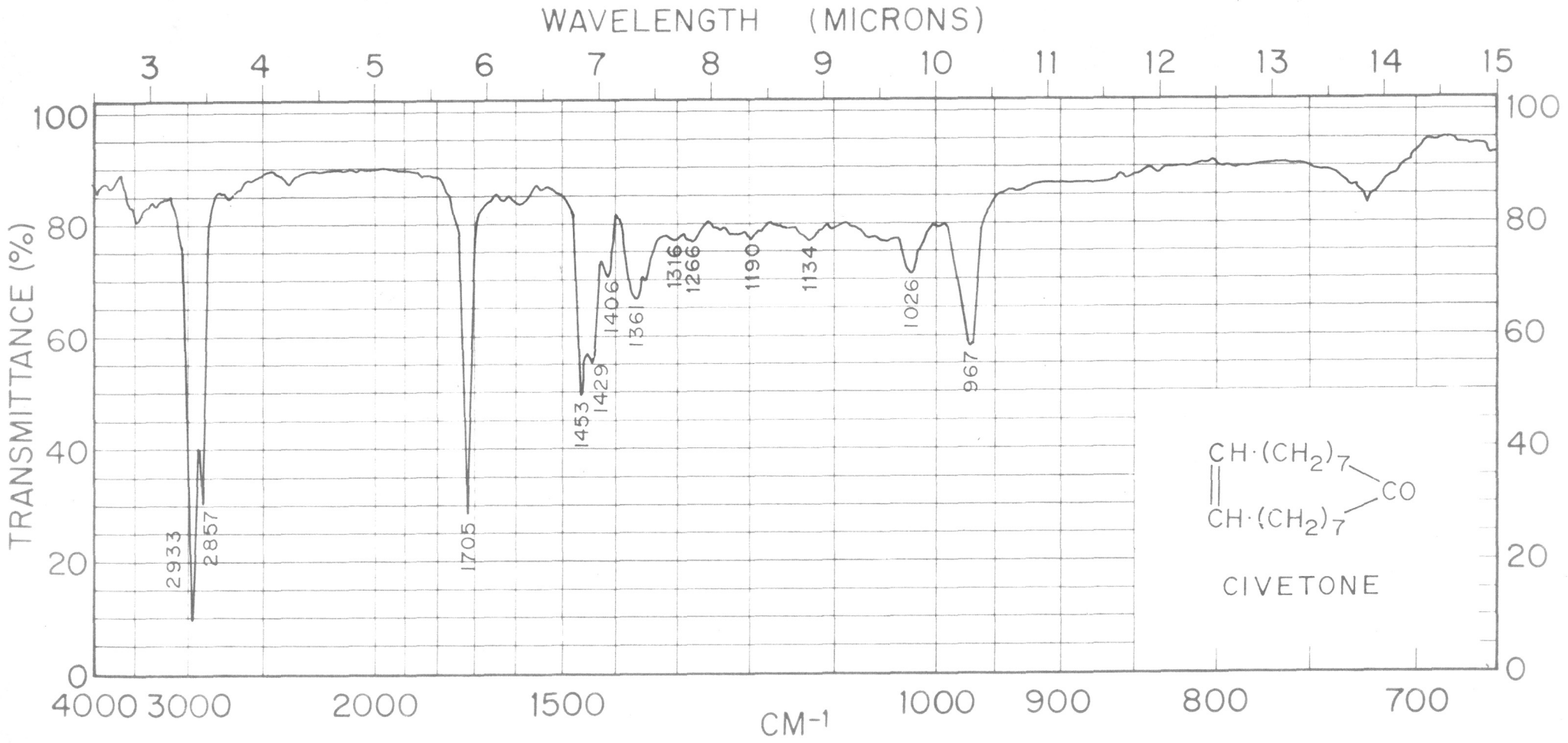
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1026
967
CH·(CH2)7
CO
CH·(CH2)7
CIVETONE
4000
3000
2000
1500
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900
800
700
CM-1

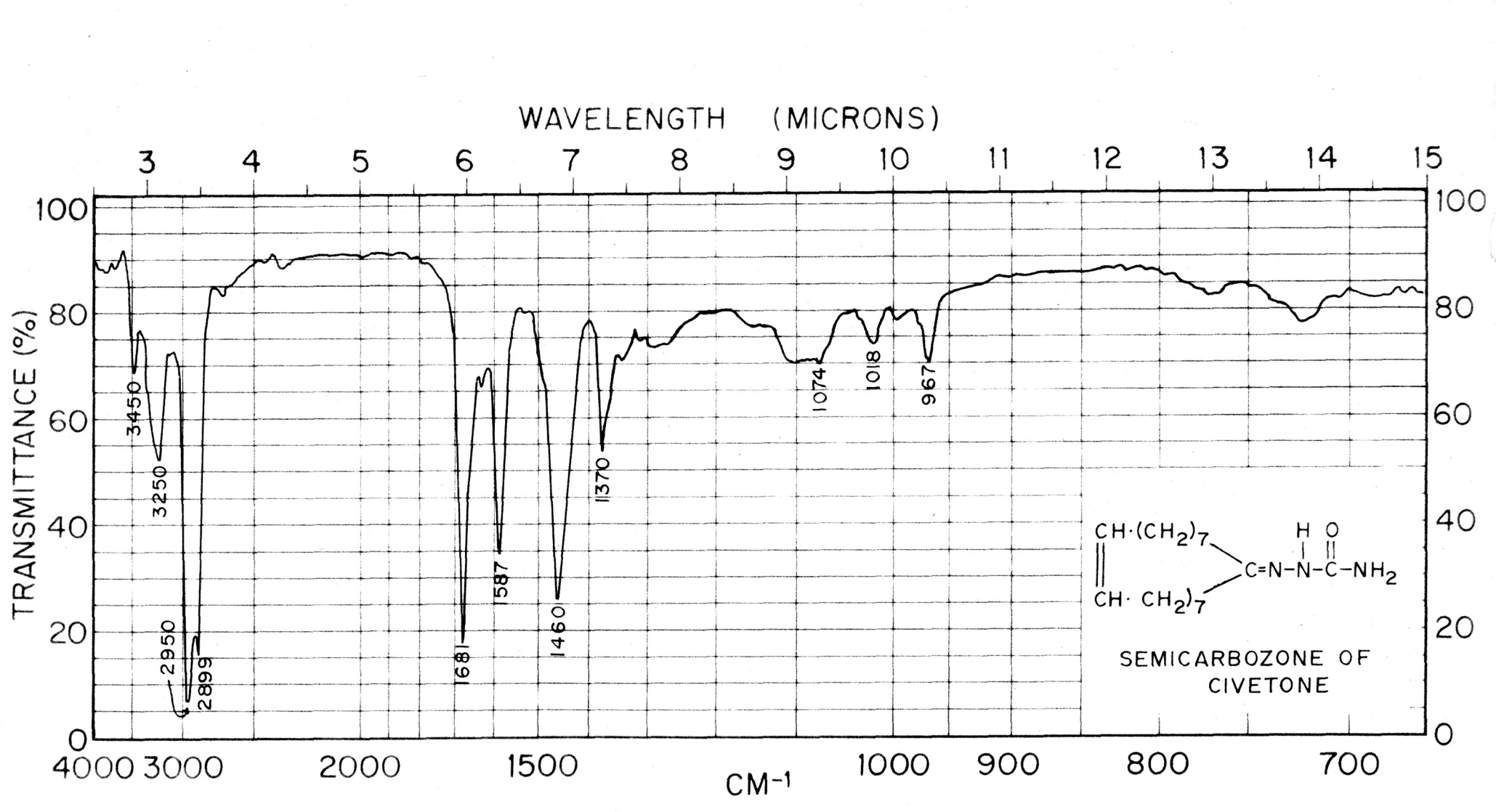
Semicarbazone was prepared by the usual method and crystallised repeatedly from methyl-alcohol, m.p. 186-187°. Mixed m.p. with that of the semicarbazone of standard iso-civetone was undepressed.

Infrared spectrum of semicarbazone, νmax. 3500, 3250, 2985, 1684, 1590, 1462, 1374, 1299, 1093, 1021 and 968 cm-1; identical with that of iso-civetone semicarbazone. (Found: N, 13.40. Calc. for $C_{18}H_{33}N_3O$: N, 13.70%).

Fraction (G). It was a low melting solid. It had the characteristic civetone like fragrance. Infrared spectrum in nujol: νmax. 2950, 1724, 1471, 1449, 1410, 1370, 1296, 1335, 1024 and 970 cm-1. It appeared to be a mixture of civetone and iso-civetone. (Found: C, 81.80; H, 11.92. Calc. for $C_{17}H_{30}O$: C, 81.50; H, 12.10%).

Fraction(H). It was liquid in nature and had characteristic fragrance. It was distilled under high vacuum at 150° (bath)/0.005 mm. νmax. 2933, 1705, 1453, 1429, 1406, 1361, 1316, 1276, 1266, 1190, 1134, 1026 and 967 cm-1. Infrared spectrum was identical with that of standard civetone. (Found: C, 81.60; H, 11.80. Calc. for $C_{17}H_{30}O$: C, 81.50; H, 12.10%).

Semicarbazone was prepared by the usual method and crystallised from methyl alcohol, m.p. 191°; mixed m.p. with authentic semicarbazone was undepressed.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2950
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1460
1370
1074
1018
967
CH·(CH2)7
H O
C=N-N-C-NH2
CH· CH2)7
SEMICARBOZONE OF
CIVETONE
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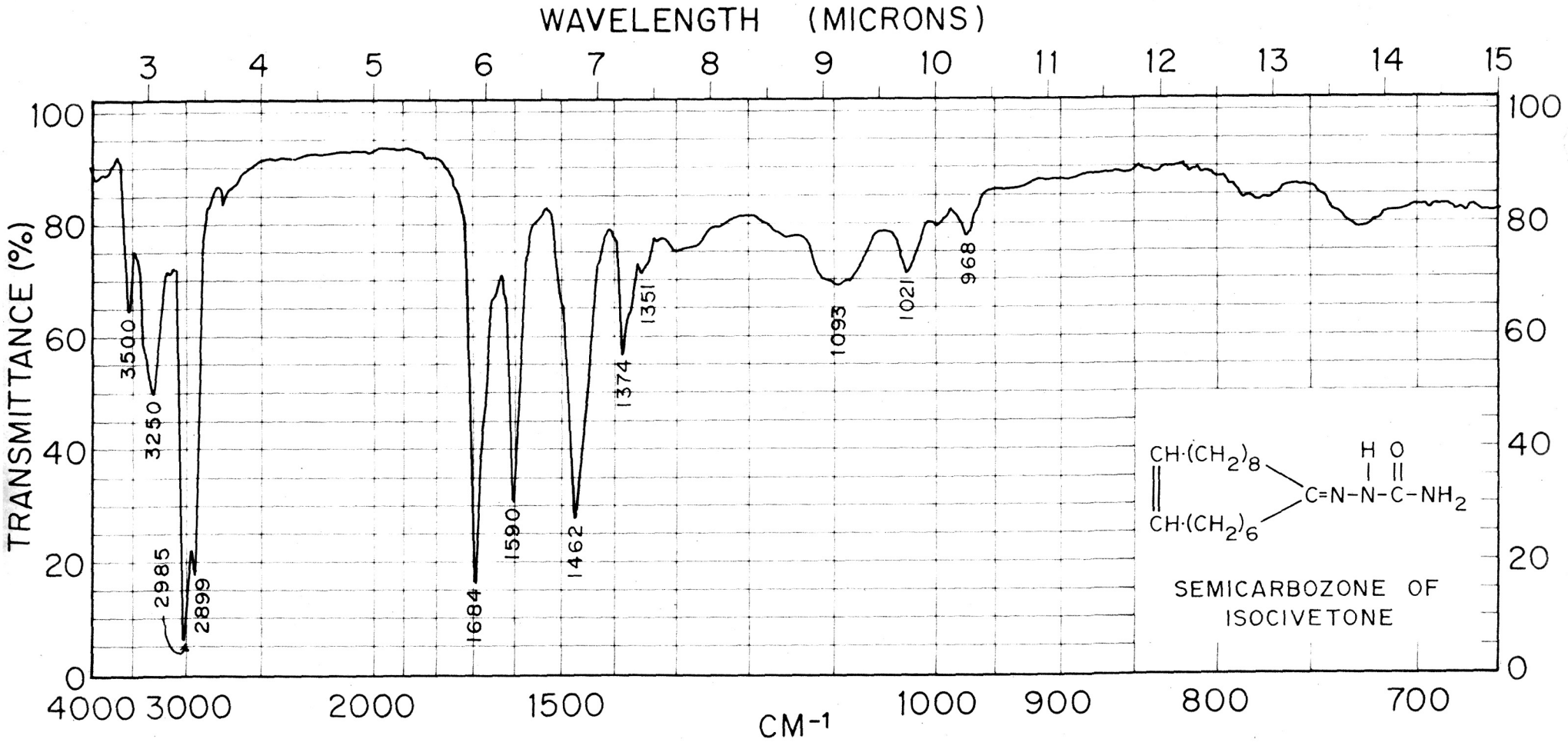
1500
CM-1
1000
900
800
700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10
11
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13
14
15
TRANSMITTANCE (%)
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80
60
40
20
0
3500
3250
2985
2899
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1462
1374
1351
1093
1021
968
4000
3000
2000
1500
1000
900
800
700
CM-1
CH·(CH2)8
CH·(CH2)6
H O
C=N-N-C-NH2
SEMICARBOZONE OF
ISOCIVETONE

Infrared spectrum of semicarbazone, ν max. 2950, 1681, 1587, 1460, 1370, 1335, 1282, 1094, 1074, 1018, and 967 cm-1. (Found: N, 13.55. Calc. for $C_{18}H_{33}N_3O$: N, 13.70%).

REFERENCES

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2. A. Bowers , T,G. Halsal, E**.R.H.** Jonas **and A**.J. **Lemin, J .** Chem.Soc ., 2555 (1953)

S Y N O P S I S

Muscone, civetone, exaltone and exaltolide are the most outstanding and valuable perfumery materials for the 'Macrocyclic Musk group'. These compounds have a delicate musk odour and stimulating effect and hence are employed in high grade perfumes as fixatives and blending substances. Their occurrance in nature is very limited, hence the necessity to develop practical methods for their syntheses from easily available raw materials. Several synthetic methods have been established by pioneer workers like Ruzicka, Stoll, Prelog and Hunsdiecker.

In the present investigation we have developed new practical syntheses of exaltone and exaltolide starting from erucic acid, obtained from mustard oil. 15,16-Dihydroxy lignoceric acid has also been used for the preparation of both exaltone and exaltolide. Several inter-related routes have been developed leading to the preparation of these two perfumery chemicals.

The acyloin condensation has been employed for the cyclisation reaction leading to exaltone and in the case of exaltolide Carother's method of depolymerisation of the poly-esters of ω-hydroxy acids has been used. The syntheses developed are simple and straightforward and do not require application of complicated reactions.

The work can be divided into the following parts:

(1) Synthesis of exaltolide from erucic acid.

(2) Synthesis of exaltone from erucic acid.

(3) Newer methods for the reduction of macrocyclic acyloins to the corresponding ketones.

(4) Synthesis of civetone and iso-civetone.

Part I - New Syntheses of exaltolide from erucic acid.

Erucic acid and 15,16-dihydroxylignoceric acid were used for the syntheses of exaltolide.

Scheme 1

$CH_3.(CH_2)_7.CH{=}CH.(CH_2)_{11}.COOR$ (R=H or C_2H_5)

(I)

$CH_3.(CH_2)_7.CH{=}CH.(CH_2)_{11}.CH_2OH$

(II)

$CH_3.(CH_2)_7.CHOH.CHOH.(CH_2)_{11}.CH_2OH$

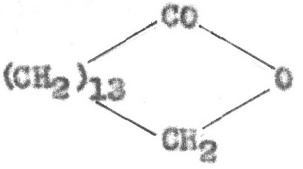
(III)

$OHC.(CH_2)_{11}.CH_2OH + CH_3.(CH_2)_7.CHO$

(IV) (V)

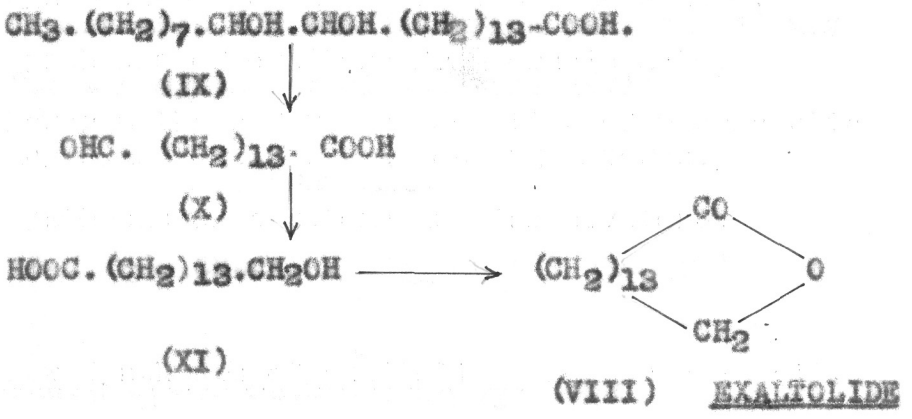
$HOOC.HC{=}HC.(CH_2)_{11}.CH_2OH$

(VI)

$HOOC.(CH_2)_{13}.CH_2OH$ → 

(VII) (VIII) EXALTOLIDE

Scheme 2



Erucyl alcohol (II) obtained by the reduction of ethyl erucate (I), was converted to 13,14-dihydroxybehenyl alcohol (III), which on treatment with sodium metaperiodate furnished 13-hydroxytridecanal (IV) in almost quantitative yield. This 13-hydroxy tridecanal on reaction with malonic acid, ethyl malonate or bromoacetic ester and subsequent reactions was converted to 15-hydroxy pentadecanoic acid(VII) which on lactonisation furnished exaltolide (VIII).

In another route 15,16-dihydroxylignoceric acid(IX) obtained by the hydroxylation of nervonic acid was oxidised with sodium metaperiodate to yield 14-formyl tetradecanoic acid (X). This on reduction with sodium amalgam furnished 15-hydroxy pentadecanoic acid (XI) which on lactonisation yielded exaltolide.

Part II - New Syntheses of exaltone from erucic acid

Erucic acid (I) obtained from mustard oil was employed for the syntheses of exaltone (VII).

Scheme 3

$CH_3(CH_2)_7.CH=CH.(CH_2)_{11}.COOR$ ($R=C_2H_5$)

(I)

$CH_3.(CH_2)_7.CHOH.CHOH.(CH_2)_{11}.COOR$ ($R=C_2H_5$)

(II)

$OHC.(CH_2)_{11}.COOR$ + $CH_3.(CH_2)_7.CHO$

(III) (IV)

$HOOC.HC=HC.(CH_2)_{11}.COOR$

(V)

$HOOC.(CH_2)_{13}.COOH \longrightarrow (CH_2)_{13}$ (with CH_2 and CO)

(VI) (VII)

EXALTONE

Scheme 4

$CH_3.(CH_2)_7.CHOH.CHOH.(CH_2)_{13}.COOR$ ($R=H$ or C_2H_5)

(IX)

$CH_3.(CH_2)_7.CHO$ + $OHC.(CH_2)_{13}.COOR$

(X)

$HOOC.(CH_2)_{13}.COOH \longrightarrow (CH_2)_{13}$ (with CH_2 and CO)

(XI)

EXALTONE

Ethyl 13,14-dihydroxybehenate (II), obtained by the hydroxylation of ethyl erucate was converted to ethyl-ω-aldehydoundecane-1-carboxylate (III) by treatment with sodium metaperiodate. This aldehydo ester on reaction with malonic acid, ethyl malonate or ethyl bromoacetate and subsequent reactions was converted to pentadecanedioic acid (VI). Its diethyl ester furnished exaltone (VII) on cyclisation and reduction.

In an alternative route (Scheme 4) 15,16-dihydroxy-lignoceric acid (IX), obtained by the hydroxylation of nervonic acid, was oxidised with aqueous sodium metaperiodate solution to yield 14 formyl, tetradecanoic acid (X) which on oxidation with potassium permanganate yielded pentadeca-nedioic acid (XI).

2-Hydroxy cyclopentadecanone (acyloin) was reduced with zinc and hydrogen chloride to obtain exaltone (35%) which was isolated through the semicarbazone. The residue which did not form the semicarbazone has been resolved by elaborate chromatography. Solid and liquid saturated macrocyclic hydrocarbons, and liquid ketone have been isolated. An attempt has been made to isolate these products in pure form.

Part III - Newer methods for the reduction of macrocyclic acyloins to the corresponding ketones

With a view to develop an improved process for the reduction of macrocyclic acyloins to ketones the following alternative methods have been tried:

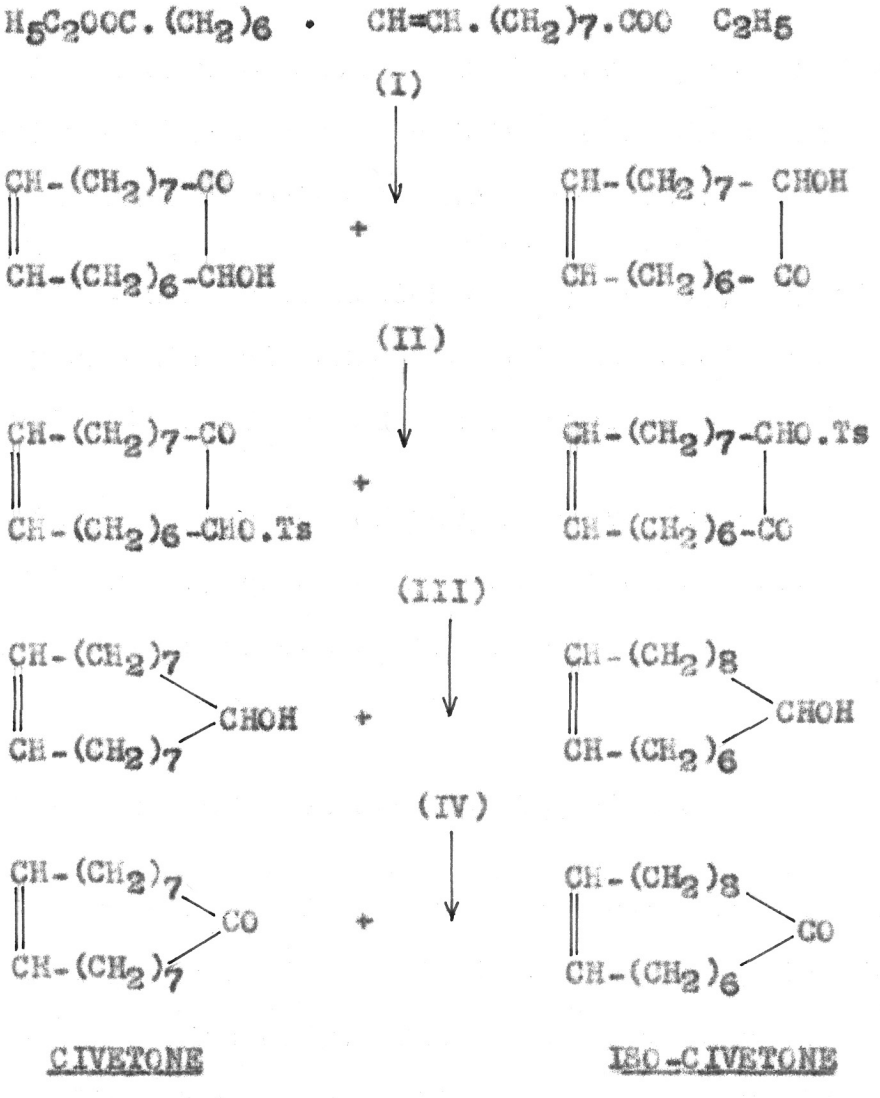
(i) Wolff-Kishner reduction of C_{15} and C_{17} acyloins followed by chromic acid oxidation of the monols resulted in an overall yield of 12% of the ketone.

(ii) $LiAlH_4$ reduction of tosyl derivative of C_{15} and C_{17} acyloins followed by chromic acid oxidation of monols resulted in an overall yield of 46% of the ketone.

Part IV- Synthesis of civetone and iso-civetone

The conventional method of reducing acyloins with zinc and hydrogen chloride is limited in its application to saturated acyloins only. The method developed in Part III has been applied for the reduction of the unsaturated acyloin, namely 2-hydroxy cycloheptadecenone (II). Its tosyl derivative (III) (mixture) was reduced with $LiAlH_4$ to the corresponding monols (IV) which on oxidation furnished civetone and iso-civetone.

Scheme 5


H5C2OOC.(CH2)6 · CH=CH.(CH2)7.COO C2H5
(I)
CH-(CH2)7-CO
CH-(CH2)6-CHOH
+
CH-(CH2)7-CHOH
CH-(CH2)6-CO
(II)
CH-(CH2)7-CO
CH-(CH2)6-CHO.Ts
+
CH-(CH2)7-CHO.Ts
CH-(CH2)6-CO
(III)
CH-(CH2)7
CHOH
CH-(CH2)7
+
CH-(CH2)8
CHOH
CH-(CH2)6
(IV)
CH-(CH2)7
CO
CH-(CH2)7
+
CH-(CH2)8
CO
CH-(CH2)6
CIVETONE
ISO-CIVETONE

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