SYNTHETIC STUDIES ON

SOME FATTY ACIDS

being a Thesis

presented by

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to the

UNIVERSITY OF ST ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY.

December 1961.

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DECLARATION.

I hereby declare that this thesis is a record of the results of my own experiments, that it is my own composition, and that it has not previously been presented in application for a higher degree.

CERTIFICATE.

I hereby certify that Mr. Charles Derek Baker has spent eleven terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying Thesis in application for the Degree of Doctor of Philosophy.

Research Supervisor.

UNIVERSITY CAREER.

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SUMMARY

Part I. Synthesis of some Monoethenoid Acids with Potential Essential Fatty Acid Activity.

The cis-isomers of the four acids, tetradec-8-enoic, hexadec-10-enoic, octadec-12-enoic, and eicos-14-enoic have been synthesised via the corresponding acetylenic acids.

Part II. Configuration of Natural 9-Hydroxyoctadecanoic Acid.

9D-Hydroxyoctadecanoic acid has been synthesised and found to possess no measurable optical activity. It is suggested, on the evidence of a mixed melting point, that the natural acid has the D-configuration.

Part III. Synthetic Studies on 6,8-Dihydroxyoctanoic Acid.

Two new synthetic routes to 6,8-dihydroxyoctanoic acid have been examined. Both were eventually abandoned.

PART 1

SYNTHESIS OF SOME MONOETHENOID ACIDS

WITH POTENTIAL ESSENTIAL FATTY ACID ACTIVITY.

INTRODUCTION.

(1) ESSENTIAL FATTY ACIDS.

(a) Atherosclerosis.

One of the problems facing the medical profession today concerns the dietary factors leading to atherosclerosis and coronary heart disease[1]. Epidemiological surveys have shown some correlation between dietary fats and the coronary death rate, though this is still a controversial subject and many other factors are involved.

In countries where the ratio of saturated to unsaturated acids in dietary fats is low the coronary death rate is low, but in countries where this ratio is high the coronary death rate is high

Autopsies performed on cases of fatal coronary heart disease have shown extensive deposits of lipids in the walls of blood vessels. This condition, atherosclerosis, always preceeds coronary heart disease, and the predominant lipid in these deposits is free cholesterol.

Fatty deposits occur to some extent, depending upon age, in the blood-vessel walls of most people, but fewer deposits are found where diets are predominantly low in total fats or in saturated fats, than where this is not the case.

Although no definite correlation has been established between the composition of atheromatous lipids and blood lipids, it has been

observed that supranormal concentrations of cholesterol in the blood are associated with coronary heart disease. It has also been found that fats containing polyunsaturated acids (specifically linoleic acid) lower the blood cholesterol level, whilst fats rich in saturated acids raise the cholesterol level.

(b) Essential Fatty Acids.

Essential fatty acids are those acids which cannot be synthesised by the body and which, since they are essential to bodily growth, must be present in the diet.

Most of the work on essential fatty acid deficiency has been done on animals, especially rats, but there is some clinical evidence that they are equally essential to the growth of children, and that their absence causes similar symptoms to those in animals[2].

Both linoleic and arachidonic acids are found in organ fats of the normal rat. As this animal cannot synthesise linoleic acid[3], and as arachidonic acid is not found in plant lipids[4], it seems likely that the arachidonic acid is synthesised by the rat from dietary linoleic acid. This theory was given experimental backing when it was found that arachidonic acid, absent in the liver of fat-deficient rats, reappeared on feeding them with linoleic acid[5]. The conversion by rats of labelled $^{14}C_1$ linoleic acid to $^{14}C_3$ arachidonic acid finally proved this theory[6].

It has also been shown that of the polyenoic acids only those of

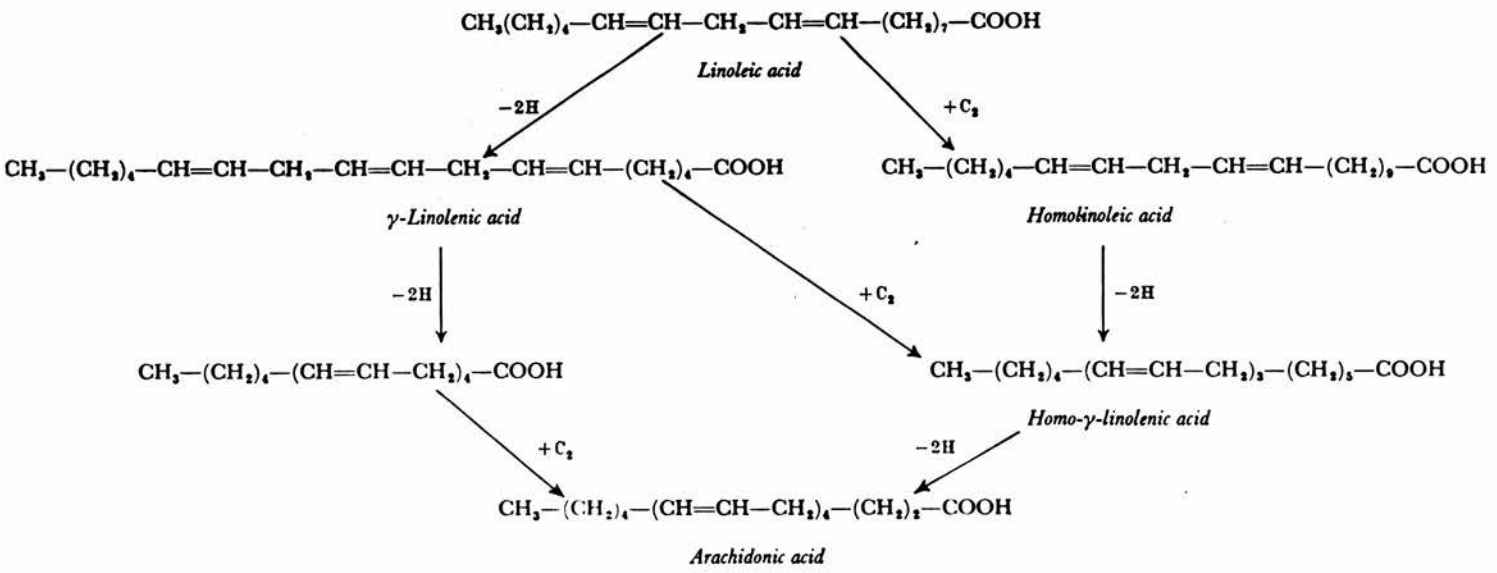

CH3(CH2)4—CH=CH—CH2—CH=CH—(CH2)7—COOH
Linoleic acid
−2H
+C2
CH3—(CH2)4—CH=CH—CH2—CH=CH—CH2—CH=CH—(CH2)4—COOH
γ-Linolenic acid
CH3—(CH2)4—CH=CH—CH2—CH=CH—(CH2)9—COOH
Homolinoleic acid
−2H
+C2
−2H
CH3—(CH2)4—(CH=CH—CH2)4—COOH
CH3—(CH2)4—(CH=CH—CH2)3—(CH2)5—COOH
Homo-γ-linolenic acid
+C2
−2H
CH3—(CH2)4—(CH=CH—CH2)4—(CH2)2—COOH
Arachidonic acid

Figure 1

the linoleic type, where the first double bond counting from the methyl group is located at the same position as in linoleic acid (see fig. 1), show much activity as essential fatty acids[7,8].

(c) Conversion of Unsaturated Fatty Acids in Animals.

In the animal body arachidonic acid is formed from linoleic acid by the addition of two carbon atoms from acetate[9], and the introduction of two olefinic groups (double bonds). Figure 1 shows a summary of the possible pathways of this transformation[10]. γ-Linolenic acid possesses the same essential fatty activity as linoleic acid, whereas homolinoleic acid possesses only about 40% of this activity[7] indicating that γ-linolenic acid is the first intermediate in this transformation.

Using esters labelled with ^{14}C, Mead and Howton demonstrated that γ-linolenic[11] and homo-γ-linolenic[12] acids respectively are converted to arachidonic acid in the rat. This has confirmed that the sequence in the conversion of linoleic acid to arachidonic acid in the animal body is:- linoleic $\longrightarrow$ γ-linolenic $\longrightarrow$ homo-γ-linolenic $\longrightarrow$ arachidonic, (fig. 2).

Mead and Klenk have suggested that there are families of polyunsaturated acids, two of which are based upon linoleic and linolenic acids respectively. These families are presumed to be formed by the introduction of double bonds in the 1,4-pentadiene relationship between the existing double bonds and the carboxyl group. When a double bond added in this way would appear either adjacent to, or

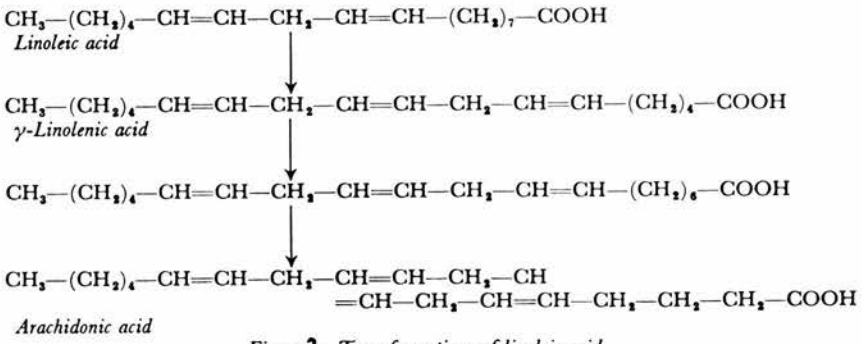


Figure **2** *Transformations of linoleic acid*

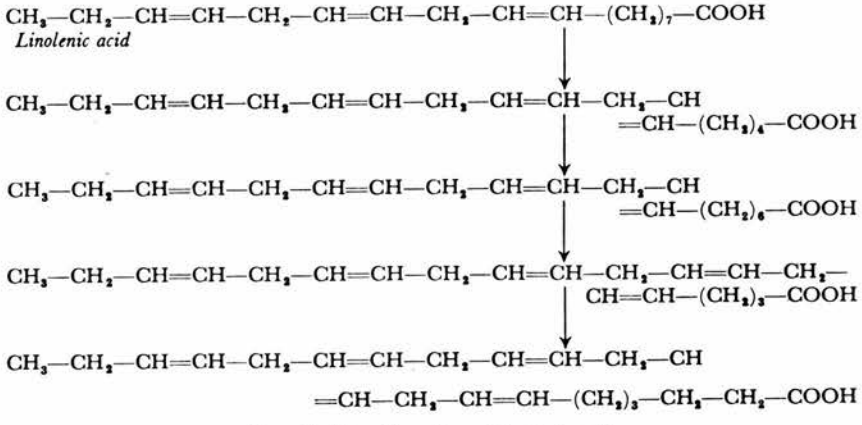


Figure **3** *Transformations of linolenic acid*

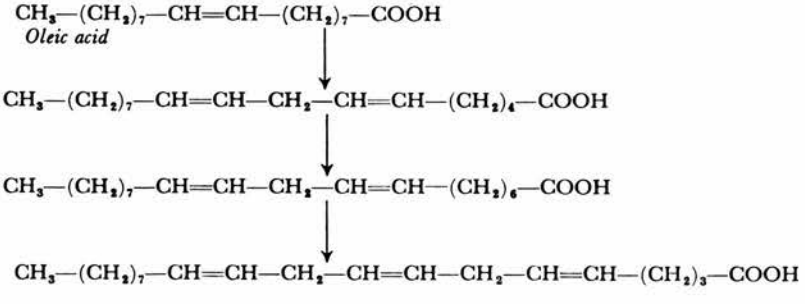


Figure **4** *Transformations of oleic acid*

separated by only one methylene group from, the carboxyl group, two carbon atoms must first be added before dehydrogenation can occur. Fig. 3 shows the transformation of linolenic acid to docos-7,10,13,16, 19-pentaenoic acid.[13]

Fulco and Mead[14] have shown that oleic acid is the precursor of eicos-5,8,11-trienoic acid found in fat-deficient rats.[15] The isolation of a small amount of eicos-8,11-dienoic acid indicates that the proposed pathway (fig. 4) via octadec-6,9-dienoic acid and eicos-8,11-dienoic acid may be correct.

Klenk and Debuch[16] suggest that the occurrence of eicos-5,8,11, 14-tetraenoic, docos-7,10,13,16-tetraenoic, and tetracos-9,12,15,18-tetraenoic acids in the phospholipids of brain[17,18] may be an example of simple chain extension, and eicos-5,8,11,14-tetraenoic and docos-4,7,10,13,16-pentaenoic acids an example of chain extension with simultaneous dehydrogenation to give the 1,4-pentadiene relationship described above.

The co-occurrence of eicos-11,14-dienoic, eicos-8,11,14-trienoic, and eicos-5,8,11,14-tetraenoic acids[17] may also be an example of successive dehydrogenation.

There remains the possibility that other acids may act as precursors in the biosynthesis of arachidonic acid. The simplest essential fatty acid so far known is linoleic acid, which has its first double bond between the sixth and seventh carbon atoms counting from the methyl group. Thus the structural basis of an essential fatty acid

is considered to be:

$$CH_3.(CH_2)_4.CH{:}CH.CH_2.CH{:}CH-$$

Mead[19] has suggested, and attempted to show, that the rat may be able to convert octadec-12-enoic acid into linoleic acid, but when the labelled acid was fed no linoleic acid from this source was found. There was, however, some evidence for the presence of γ-linolenic acid, the first intermediate in the transformation of linoleic to arachidonic acid, and this was perhaps enzyme bound. Further work is to be done on this problem.

As eicos - 5,8,11 - trienoic acid is only found in fat-deficient rats, and as normal animals were used by Mead for the experiment described above, if no transformation of octadec-12-enoic acid did in fact occur, then one possible reason is that it can only take place in fat-deficient animals.

Turpeinen[20] and Thomassen[7] have both reported that octadec-cis-12-enoic acid has no essential fatty acid activity, but there is some doubt that their acids, obtained from dehydrated castor oil, actually consisted of the pure cis-isomer.

It is possible that hexadec-10-enoic acid may possess EFA activity, if the rat can convert it to linoleic acid by dehydrogenation and chain extension ($-2H, +C_2$). Similarly in the case of tetradec-8-enoic acid ($-2H, +C_2, +C_2$) or ($+C_2, -2H, +C_2$).

The four even numbered monoethenoid acids from C_{14} to C_{20}, all with the double bond Δ^6 from the methyl group have therefore been

prepared for use in further studies on this subject elsewhere. The aim is to determine whether they possess EFA activity, and possibly to identify their metabolic products.

It is obvious from the work done so far that we need to distinguish between the metabolism of dietary fats in normal animals and in fat-deficient animals. They may be quite different. Also, experiments in this field need to determine both the EFA activity, by measurement of weight gain and absence of dermal symptoms, as well as the resultant metabolic products.

(2) THE SYNTHESIS OF MONOENEOID FATTY ACIDS.

(a) Synthesis of Fatty Acids.

Although the common fatty acids such as palmitic, stearic, oleic, and linoleic have been known for some time, it was not until 1934 that oleic acid was first synthesised[21], and linoleic[22] in 1950.

A contributory factor in the recent increase in our knowledge of the chemistry of fats and fatty acids has been the development of improved or new techniques of separation, analysis and synthesis. With the advent of gas-liquid chromatography requiring not grams but micrograms of material, future progress should be even more rapid.

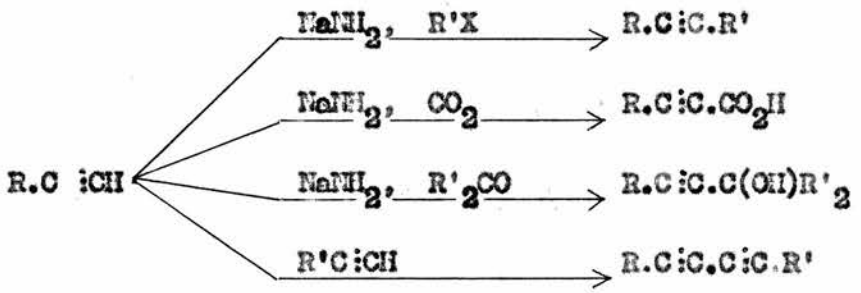
Stimulated, no doubt, by the increasing number and complexity of the natural fatty acids, it is not surprising that within the last twenty years the synthesis of numerous fatty acids, some of complicated

structure, should have been accomplished. Recent reviews have been written on this subject by Gensler[23] and Gunstone[24].

Of the many synthetic methods now available, two have made a greater contribution to recent progress than perhaps any other, namely, synthesis involving acetylenic intermediates and anodic synthesis. Gensler comments that about one out of every three papers consulted for his review in some way involved the triple bond.

(b) Reactions of Ethynyl Compounds.

Acetylene and ethynyl compounds readily form sodium and magnesium derivatives, which react with alkyl halides, carbon dioxide, and ketones. Ethynyl compounds can also be coupled to give diacetylenes[25] These reactions are summarised below.



Acetylenic compounds are widely used in synthetic chemistry[26], in particular for the preparation of long chain compounds which can then be stereospecifically reduced to the corresponding cis or trans olefins. A general method[27] for the preparation of monoethenoid acids is illustrated by the synthesis of vaccenic acid (octadec-trans-

11-enoic acid)[28].

$CH_3.(CH_2)_5.C{:}CH + I.(CH_2)_9.Cl \xrightarrow{NaNH_2}$

$CH_3.(CH_2)_5.C{:}C.(CH_2)_9.Cl \xrightarrow{(i)\ NaCN\quad (ii)\ KOH}$

$CH_3.(CH_2)_5.C{:}C.(CH_2)_9.CO_2H \xrightarrow{(i)\ H_2\text{-}Ni\quad (ii)\ Se}$

$CH_3.(CH_2)_5.CH{:}CH.(CH_2)_9.CO_2H$ (trans)

Other more complex acids have also been synthesised from acetylenes, including elaeostearic(octadec-cis,trans,trans-9,11,13-trienoic acid),[29] erythrogenic(octadec-17-en:9,11-diynoic acid),[30] linoleic(octadeo-cis,cis,-9,12-dienoic acid),[32] linolenic(octadec-cis,cis,cis-9,12,15-trienoic acid),[31] ricinoleic(12-hydroxyoctadec-cis-9-enoic acid),[33] and arachidonic(eicos-cis,cis,cis,cis--5,8,11,14-tetraenoic acid)[35]

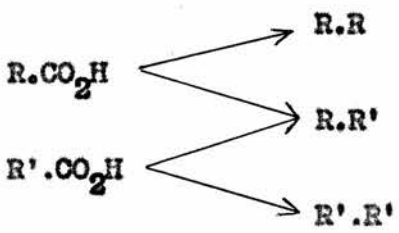
(c) Anodic Synthesis.

Anodic synthesis is an example of the recent wide use of a reaction discovered some time ago and is the subject of two reviews by Weedon.[38]

Faraday[35] in 1834 reported the formation of hydrocarbons in the electrolysis of solutions of acetates. Kolbe[36] in 1849 studied the electrolysis of the salts of carboxylic acids, which results in the production of symmetrical hydrocarbons and carbon dioxide.

$$2\ R.CO_2^- \xrightarrow{-2e} R.R + 2\ CO_2$$

Wurtz[37] in 1855 used mixed acids and obtained three products, one of them from crossed coupling.



A significant advance was the discovery in 1891 by Brown and Walker[38] that half-esters could be used in this reaction, since the products are now not hydrocarbons but esters, which can be hydrolysed to give the free acids.

Although in the electrolysis of mixed acids three products are obtained, these are often easily separated, particularly if the two acids are very dissimilar. The yield of product from crossed coupling, though not very high (ca. 30%), can be increased by using an excess of one of the reactants, and often compares favourably with the overall yield of other multi-stage syntheses. The product is also obtained in a fairly pure state.

Methanol is normally used for the solvent, as the conditions for optimum yield are then less critical than for those in aqueous solution[39].

The mechanism of the reaction[34] is believed to involve free radicals. The carboxylate ion is neutralised at the anode to form a carboxylate radical, which decarboxylates to give an alkyl radical and carbon dioxide. Two alkyl radicals then combine.

$$R.CO_2^- \xrightarrow{-e} R.CO_2. \longrightarrow R. + CO_2$$

$$2\,R. \longrightarrow R.R$$

For the synthesis of fatty acids, the half-ester of a dibasic acid is coupled to a monobasic acid. Either or both can contain unsaturated centres, provided they are not α/β or $\beta\gamma$ to the carboxyl group. Substituents must not be in the α-position. Coupling can be repeated several times to give the desired final product. Optical activity due to an asymmetric centre is preserved[40] (see Part II, p. 57), as is the configuration of an ethylenic bond[41].

An example of anodic synthesis is the chain extension of oleic acid to give erucic acid[42].

$$CH_3.(CH_2)_7.\underset{\underline{cis}}{CH{:}CH}.(CH_2)_7.CO_2H$$

$$\Big\downarrow \quad \begin{array}{l}(i)\ HO_2C.(CH_2)_4.CO_2Me \\ (ii)\ \text{hydrolysis}\end{array}$$

$$CH_3.(CH_2)_7.\underset{\underline{cis}}{CH{:}CH}.(CH_2)_{11}.CO_2H$$

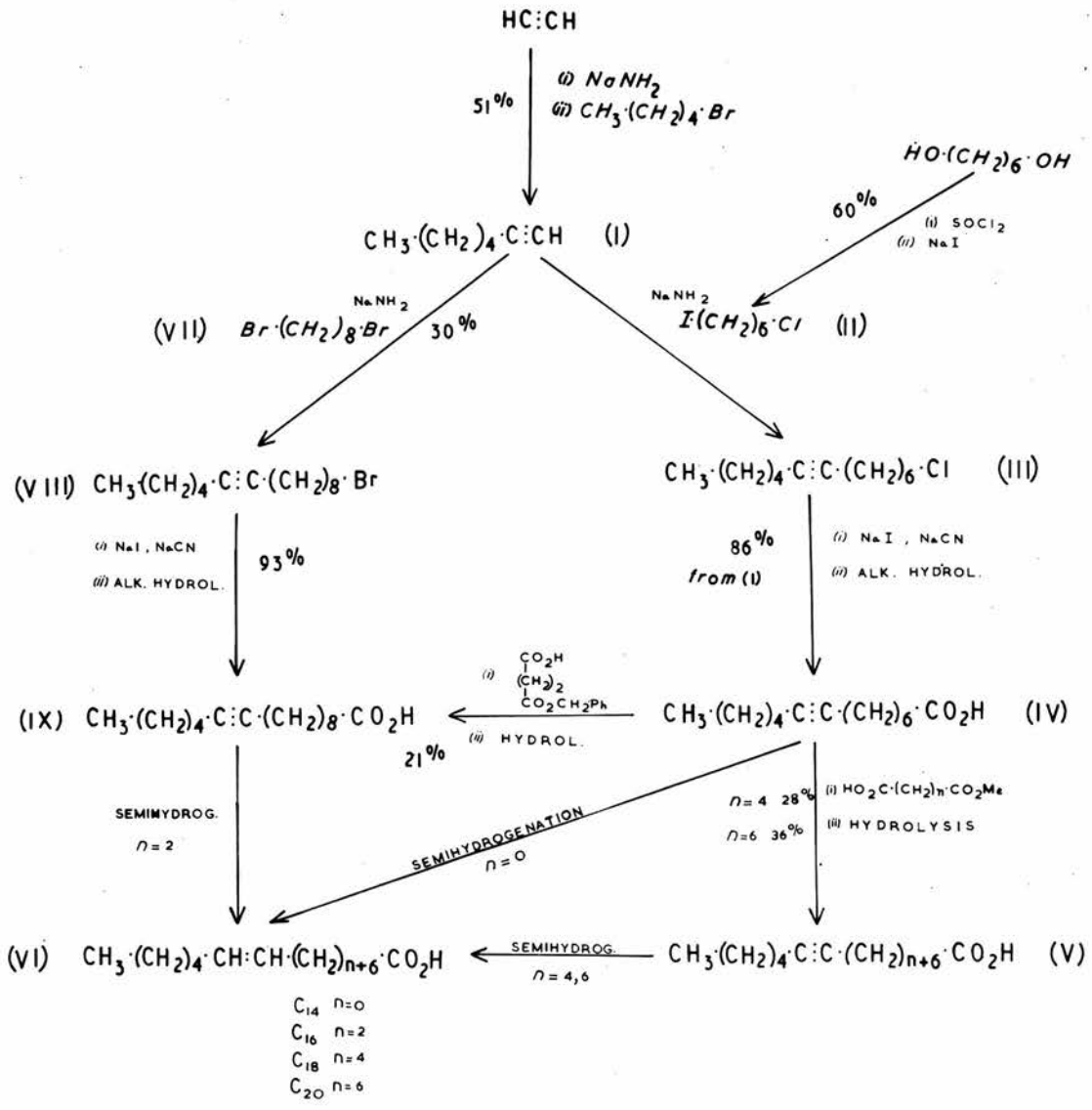

HC:CH
51%
(i) NaNH2
(ii) CH3·(CH2)4·Br
CH3·(CH2)4·C:CH (I)
HO·(CH2)6·OH
60%
(i) SOCl2
(ii) NaI
NaNH2
I·(CH2)6·Cl (II)
(VII) Br·(CH2)8·Br
NaNH2
30%
(VIII) CH3·(CH2)4·C:C·(CH2)8·Br
CH3·(CH2)4·C:C·(CH2)6·Cl (III)
(i) NaI, NaCN
(ii) ALK. HYDROL.
93%
86% from (I)
(i) NaI, NaCN
(ii) ALK. HYDROL.
(IX) CH3·(CH2)4·C:C·(CH2)8·CO2H
21%
(i) CO2H (CH2)2 CO2CH2Ph
(ii) HYDROL.
CH3·(CH2)4·C:C·(CH2)6·CO2H (IV)
SEMIHYDROG.
n = 2
SEMIHYDROGENATION
n = 0
n = 4 28%
n = 6 36%
(i) HO2C·(CH2)n·CO2Me
(ii) HYDROLYSIS
(VI) CH3·(CH2)4·CH:CH·(CH2)n+6·CO2H
SEMIHYDROG.
n = 4,6
CH3·(CH2)4·C:C·(CH2)n+6·CO2H (V)
C14 n=0
C16 n=2
C18 n=4
C20 n=6

FIG. 5

DISCUSSION

The cis-isomers of the four acids, tetradec-8-enoic, hexadec-10-enoic, octadec-12-enoic, and eicos-14-enoic (VI, n= 0,2,4,6) mentioned on p. 6 are required elsewhere for biological examination as potential essential fatty acids.

It was originally proposed to prepare these acids according to the Scheme in fig. 5, synthesising tetradec-8-ynoic acid (IV) first by coupling 1-heptyne (I) with 1-chloro-6-iodohexane (II) to give 1-chlorotridec-7-yne (III), followed by hydrolysis of the cyanide, and converting the acid by anodic synthesis into the three homologues (V, n= 2,4,6) required. However, owing to difficulty experienced with the preparation of hexadec-10-ynoic acid by anodic synthesis, this acid was finally prepared in the same way as tetradec-8-ynoic acid substituting 1,8-dibromo-octane (VII) for 1-chloro-6-iodohexane (II). Semihydrogenation of the acetylenic acids with Lindlar catalyst gave the corresponding cis-olefinic acids.

Of the eight acids synthesised, see table 1, five have not so far been reported in the literature. These are: tetradec-8-ynoic, tetradec-cis-8-enoic, hexadec-10-ynoic, eicos-14-ynoic, and eicos-cis-14-enoic acids

Summary of Acids Synthesised.

		C_{14}, Δ^{8}	C_{16}, Δ^{10}	C_{18}, Δ^{12}	C_{20}, Δ^{14}
acetylenic acids	m.p.	22-22.5°	35-36°	46-47°	54.5-55.5°
	n_D^{23}	1.4304			
cis-ethylenic acids	m.p.		15-16°	26.5-27.5°	40-40.75°
	n_D^{17}	1.4503	1.4503		
	% trans	1.5%	0.5	1.7	nil
methyl esters (undistilled)	n_D^{t}	1.4460^{20}	$1.4469^{20.5}$	$1.4516^{21.5}$	1.4536^{20}

(1) LITERATURE SURVEY.

(a) Hexadec-10-enoic acid. has been reported, though not isolated, by Hilditch and Vidyarthi,[43] who obtained it by the partial hydrogenation (30%) of methyl palmitoleate (hexadec-9-enoate) with a nickel/ kieselkuhr catalyst. This gave the cis and trans forms of hexadec-8, 9, and 10-enoic acids, which were characterised by oxidation with potassium permanganate in acetone and isolation of the mono and dibasic acids produced.

(b) Octadec-12-ynoic acid is reported twice in the literature, first by Grun and Czerny,[44] who dehydrobrominated the ethyl ester of 12 (or 13) -bromo-octadec-12-enoic acid (obtained from ricinoleic acid) with potassium hydroxide, and obtained a product m.p. 54.2°, which gave the correct cleavage products for octadec-12-ynoic acid. However, the m.p. of the acid is 12° too low and so must have contained some positional isomers.

More recently Huber[45] has synthesised the acid from 1-heptyne and 1-chloro-10-iododecane. His product had m.p. 46.2-47.2° and agrees with that of this work.

(c) Octadec-12-enoic Acid reported by Bhatak and Patwardhan[46] to occur in cow and buffalo milk fat, may occur in trace amounts in the fats of the ruminants, as a result of secondary changes of dietary fats.

In this case both the cis-and trans-forms will be present. (See Hilditch.[47])

This acid was produced in early synthetic work by the dehydration of 12-hydroxystearic acid (obtained from ricinoleic acid) either catalytically[44] or by heating with oxalic acid,[48] and also by the dehydrobromination of the bromide.[49] The methods used, and the melting points found, indicate that the products were mixtures of the cis-and trans-forms of 11- and 12-octadecenoic acids.

Partial hydrogenation of linoleic and linolenic acids,[50] to which there are many references, also gives rise to the cis-and trans-forms of the acid.

The only complete synthesis of both the cis-and trans-acids reported to date is by Huber[45] who reduced the acetylenic acid stereospecifically to give the cis-acid, m.p. 26.8-27.6°, which was elaidinised to give the trans-acid, m.p. 52-53°.

The trans-acid, m.p. 52-53°, has also been partially synthesised by Barucha and Gunstone[51] by debromination with zinc of erythro-12,13-dibromo-octadecanoic acid obtained from natural epoxyoleic acid.

(2) PREPARATION OF TETRADEC- and HEXADECYNOIC ACIDS.

In 1948 Strong and his colleagues[27] published a general method for synthesising monoethenoid acids via acetylenic intermediates (see p. 8). In this, a 1-alkyne is coupled to an α,ω-iodochloride and converted to the cyanide, which on hydrolysis gives the required acid. Since then their method has been used by them to prepare monoethenoid acids of varying chain length,[52] by Huber[45] to prepare 7 to 12-octadecenoic acids, and by many others.[23,24].

Tetradec-8-ynoic acid (IV) was prepared from 1-heptyne (I) and 1-chloro-6-iodohexane (II) via 1-chlorotridec-7-yne (III) in 86% yield, and hexadec-10-ynoic acid (IX) from 1-heptyne and 1,8-dibromo-octane (VII), via 1-bromopentadec-9-yne (VIII) in 28% yield. (See fig. 5).

1-Chloro-6-iodohexane was prepared from hexamethylene glycol, via 1,6-dichlorohexane as described by Raphael and Sondheimer.[22] The yield of iodochloride from dichloride was increased to 62% by recycling the recovered dichloride.

The synthesis of 1-chlorotridec-7-yne (not previously reported in the literature) was first attempted by the method used successfully by Raphael and Sondheimer[53] to prepare 1-chlorononn-5-yne, by reacting 1-chloro-6-iodohexane with 1-heptyne prepared in situ, avoiding an excess of acetylene. The crude product was distilled to give five fractions, each of which were analysed by Gas Liquid Chromatography. These interpreted with the help of later evidence showed that the

desired product was in the last two fractions in about 36% yield. However, this method had to be abandoned due to lack of information at the time, and chlorotridecyne was prepared by coupling iodochloride with heptyne from a separate preparation.

Sodamide, sodium acetylide, and 1-heptyne were prepared by standard proceedures.[54] Although Raphael[55] recommends that alkyl halides for reaction with sodium acetylide are not added in ether if the volatility of the product indicates otherwise, presumably owing to the difficulty of separating ether and product, greater losses would be expected to occur on a small scale if the organic layer had to be separated, washed, and dried, in the absence of solvent. It was found that removal of ether (b.p. 34°) by simple distillation resulted in loss of heptyne (b.p.100°), but that little loss occurred if the ether was removed through a ½ metre column packed with Fenske helices.

As G.L.C. showed the crude chlorotridecyne to be contaminated only with chloroiodohexane (15%), the product was converted to the cyanide and hence by hydrolysis to tetradecynoic acid without purification. Under these conditions the iodochloride gives suberic acid which is not extracted by petroleum ether. Crude tetradecynoic acid obtained in a trial run was shown by G.L.C. to be practically pure, apart from ca 3% of the iso-acid.

The source of the iso-tetradecynoic acid was traced to the 1-bromopentane used in the preparation of 1-heptyne. Since sodium acetylide only reacts with primary halogen compounds containing the

group $-CH_2.CH_2.X$ to produce mono-substituted acetylenes,[56] whereas secondary and tertiary halogen compounds, and primary derivatives branched at the second carbon atom are dehydrohalogenated to ethylenes by the reagent, the impurity is probably 1-bromo-3-methylbutane. This was not separated from 1-bromopentane by a previous distillation and was only detected in the bromopentane, at a later stage, by G.L.C.

1-Bromopentadec-8-yne not previously reported in the literature, was prepared by coupling 1,8-dibromo-octane with the sodium derivative of 1-heptyne in liquid ammonia This gave, after fractionation, the required bromoalkyne (30%). Although this was a much lower yield than would have been expected with an α,ω-bromochloride or iodochloride (ca 90%), it was offset by the commercial availability of the α,ω-dibromide thus saving a tedious and time consuming preliminary preparation.

(3) ANODIC SYNTHESIS.

The recent use of anodic synthesis (see p. 9) in preparative organic chemistry has been pioneered by Linstead and Weedon, who with their colleagues have published since 1950 a long series of papers on the subject. The fourteenth, and last, paper[57] in this series, dealing with acetylenic acids, confirms the view that the triple bond is unaffected during anodic synthesis provided that it is not $\alpha\beta$ or $\beta\gamma$ to the carboxyl group, though the limiting case of a $\gamma\delta$ triple bond was not examined because of inaccessibility of the starting materials required. The triple bond can be in either the monobasic or the dibasic acid, but it is particularly useful if it is in the dibasic acid, which can then be coupled at both ends to give any required monoacetylenic acid.

In the intended synthesis of hexadec-, octadec-, and eicosenoic acids from tetradec-8-ynoic acid two possible routes were considered:-

(i) C_{14}-ynoic $\longrightarrow$ C_{14+n}-ynoic $\longrightarrow$ C_{14+n}-enoic.

(ii) C_{14}-ynoic $\longrightarrow$ C_{14}-enoic $\longrightarrow$ C_{14+n}-enoic.

As yields in anodic synthesis are comparatively low, the first of these, involving the hydrogenation of less material, was chosen.

The apparatus used was similar to that described by Weedon in his latest review on the subject,[58] and is described on p. 35. Several trial experiments were conducted with a mixture of myristic acid and

methyl hydrogen succinate before satisfactory electrolyses were obtained. To avoid overheating the distance between the electrodes had to be reduced to the barest minimum of 1-2 mm. Cooling by any other means than ice and water, such as ice-salt, or acetone-solid carbon dioxide, caused the solution of acids to solidify, owing to their lowered solubilities, with the consequent cessation of mixing.

In a preliminary experiment tetradec-8-ynoic acid was electrolysed alone (cf.[59]) to give hexacos-6,20-diyne in 47% yield. Compared with later electrolyses this one took place with great difficulty, there was much over heating, and a large amount of insoluble material was formed.

Linstead and Weedon[42,60,61] report that during the electrolysis of a fatty acid, some esterification with the methanol used as solvent may accompany the coupling process. This is a particular disadvantage when an acid is being chain extended by only two carbon atoms as the product will then be contaminated with the ester of the starting material which is difficult to remove. One method of overcoming this is to use the benzyl half-ester in place of the methyl half-ester.[60] In this case the desired benzyl ester is contaminated with the methyl ester of the starting material and can be easily separated by distillation, or in the case of saturated acids, the benzyl ester can be converted directly into the acid by hydrogenolysis.

The anodic chain extension of tetradec-8-ynoic acid to hexadec-10-ynoic acid in methanol was tried using both methyl hydrogen

succinate and benzoyl hydrogen succinate. In both cases the neutral product contained a small amount of methyl tetradecynoate (as did the neutral product of all the syntheses involving tetradecynoic acid), but only in the case of the benzyl ester, were the two separated by distillation. However, as the synthesis involving the benzyl half-ester was very tedious, even on a small scale, because the electrodes had to be cleaned frequently to allow the electrolysis to proceed, this acid was prepared on a larger scale by direct acetylenic synthesis as described above (p.16).

The electrolysis of tetradec-9-ynoic acid with methyl hydrogen adipate, and with methyl hydrogen suberate to give octadec-13-ynoic and eicos-14-ynoic acids, followed by their isolation, was carried out successfully.

(4) SEMIHYDROGENATION

The publication in 1952 of a paper by Lindlar[62] describing a palladium/calcium carbonate catalyst, partially inactivated by treatment with lead acetate, and with enhanced specificity by the addition of quinoline, has rendered other catalysts obsolete for the semihydrogenation of acetylenic acids to the corresponding cis-ethylenic acids. Raney nickel, the most recently used catalyst for this reduction[63] prior to the advent of Lindlar's, gave at best a mixture of all the possible products. In the reduction of stearolic acid, Khan[64] found that fractional crystallisation of the crude product after the absorption of 1 mol. of hydrogen gave 72% of oleic, 16% of stearolic, and 12% of stearic acids. Infra-red examination of the crude product showed ca. 6% of trans-olefin.

These biproducts can be removed by crystallisation but the result is often a comparatively low yield for what should be a quantitative reaction. Lindlar's catalyst, however, when used correctly gives a product containing no saturated or acetylenic acids, and only ca. 1% or less of the trans-olefin.

For the solvent, petroleum ether (b.p. 80-100°), purified by treatment with Raney nickel, is reported as giving the best selectivity[65] though ethyl acetate[57] and ethyl propionate[66] are also used. Methanol has been used with mixed success.[67]

When the reduction of tetradec-8-ynoic acid, with an equal weight

of catalyst and 0.4 times the weight of quinoline, was attempted in purified petroleum ether (b.p. 80-100°) no absorption of hydrogen took place. In the absence of quinoline the required hydrogen absorption was observed, but analysis of the crude product by infra-red spectroscopy showed 2% of the trans-olefin, and by G.L.C. 5% of the saturated or acetylenic acid.

With ethyl acetate as solvent and no quinoline present, 5% of the trans-olefin, was produced, with 3% acetylenic or saturated acid; but with quinoline added only 1% of the trans-olefin, and no acetylenic or saturated acid. In each case the reaction became extremely slow after the absorption of 1 mol. of hydrogen. A higher proportion of quinoline caused the reduction to become too slow. The standard proceedure adopted was therefore reduction in ethyl acetate with an equal weight of catalyst and one quarter of the weight of quinoline.

On a 5-10 g. scale the semihydrogenation of the C_{14}, C_{16}, and C_{18} acids prepared gave acceptable amounts of trans-olefin (1.5, 0.5, and 1.7% resp.), but the C_{20} acid gave 7.6% trans-olefin which had to be removed by fractional crystallisation from ethanol. Lindlar catalyst is a partially poisoned palladium catalyst, which has quinoline added to give a greater stereospecificity. Quinoline itself acts to some extent as a poison, as is shown by the results of the trial reductions of tetradecynoic acid described above. Baker, Linstead, and Weedon[71] found that in the semi-hydrogenation of stearolic acid, by doubling the amount of quinoline from 0.4 times the

weight of catalyst, to 0.8 times, the percentage of trans-olefin was decreased from 5% to 1-2%, though they do not mention whether the rate of reduction was affected. As the C_{20} acid was both distilled (as the methyl ester obtained from an anodic synthesis) and recrystallised, it was probably in a purer state than the other three acetylenic acids, therefore requiring a higher proportion of quinoline.

The acids were finally purified by treatment with animal charcoal, followed by distillation under high vacuum.

(5) PROOF OF STRUCTURE.

In synthetic chemistry the route by which a product has been obtained can often be regarded as circumstantial evidence of all or part of its structure. In the case of the eight acetylenic and olefinic acids being considered this is certainly so regarding chain length, and the position and type of unsaturation, but each of these has been checked by other means.

Gas liquid chromatography shows first of all the purity of the acids, though run as the methyl esters. This assumes the absence of a non-volatile residue, but since each acid was distilled in its final purification this is a reasonable assumption.

Secondly, the retention volume, relative to methyl myristate, or some other standard, can be compared with the values for known acids. This gives not only the chain length but also an indication of the amount of unsaturation in the molecule. On the Apiezon L Column used, semihydrogenation caused the required shift in the position of the emergent peak, but no resolution of cis- and trans- forms could be achieved. As the saturated and acetylenic acids ran together, the total shift of the peak was an indication of the selectivity of the semihydrogenations.

Infra-red spectroscopy was used to determine the amount of trans- acid present, by the method recommended by the Spectroscopy Committee of the American Oil Chemists' Society (1959).[68] This consists in

comparing the absorption at 10.36 μ of a solution of the sample in carbon disulphide with that of pure methyl eloidate under the same instrument conditions. The result is obtained in terms of % trans as methyl eloidate, but can be converted to the absolute % trans by multiplying by the ratio of the molecular weight of the sample to that of methyl eloidate.

Oxidative cleavage of the unsaturated acids by von Rudloff oxidation,[69] and identification of the mono and dibasic acid fragments by G.L.C. at 150 and 200°, confirmed the position of the triple bond in tetradec-8-ynoic acid, and of the double bond in the four ethylenic acids.

EXPERIMENTAL.

Unless otherwise stated the petroleum ether used in this work was b.p. 40-60°. Solutions were dried with anhydrous sodium sulphate. Melting points were determined in a capillary-tube and oil-bath, and are uncorrected.

Gas Liquid Chromatography.

All the chromatograms were run on a Pye Argon Chromatograph with a radium D β-ray ionising detector. The columns used were either 5, 10, or 20% Apiezon L on alkali-washed Celite prepared according to Farquhar et al.[70] and were run at 200° with a gas flow of ca. 55 ml./min. Samples, either as liquids or as ether solutions, were injected by stopping the gas flow, removing the gas lead, discharging the sample on to the top of the column from a 0.025, 0.05, or 0.1 microlitre pipette, and replacing the gas lead and restoring the Argon flow. Retention times were measured from the negative air-peak. Retention volumes are quoted relative to myristic acid (V_r), although in the case of the longer chain acids these values were determined using palmitic or stearic acids as standards. See appendix (p. 77) for a list of data obtained.

Neutral products were run as such, but acidic products were run as methyl esters prepared by methylation with a 5% solution of anhydrous hydrogen chloride in methanol either for 2 hrs. under reflux or at room temperature overnight.

1,6-Dichlorohexane.[22] Hexamethylene glycol (20.5 g.) and dry pyridine (3.5 ml.) were melted together and thionyl chloride (10 g.) was then added to lower the melting point. To the cooled, stirred mixture, thionyl chloride (109 g.) was added at such a rate that the temperature remained at about 25°. After the addition, the flask and contents

were heated under reflux for 2 hrs., ice and water were then carefully added to the cooled mixture and the precipitated oil was extracted with petroleum ether. The extract was washed with c. sulphuric acid, aqueous sodium bicarbonate, and water, dried and evaporated.

The crude product (38.6 g.) was distilled to give dichlorohexane (36.6 g., 95%), b.p. 83°/13 mm., n_D^{20} 1.4570. On a two molar scale the yield was 93.5%.

1-Chloro-6-iodohexane. (II)[22] 1,6-Dichlorohexane (36.6 g.) was added to a solution of sodium iodide (36.6 g.) in dry acetone (225 ml.), and the solution was heated under reflux for 2 hrs. (much bumping occurred). Water (540 ml.) was then added, the product extracted with petroleum ether, and the extract washed with water, dried and evaporated. The crude product (54.9 g.) on fractionation through a ½ metre Fenske column gave:

Fr.	Weight	b.p.	pressure	$n_D^{21.5}$
1	9.34 g	42-48°	0.5-0.75 mm.	1.4566
2	2.67 g.	52-67°	0.6 mm.	1.4752
3	16.97 g.	68-73°	0.5-0.65	1.5196
4	8.52 g.	68-73°	0.5-0.65	1.5224
5	1.19 g.	68-75°	0.5-0.65	1.5234
6	15.56 g.	residue		1.5762

Fractions 1 and 6 were mainly dichloride and di-iodide resp. Yield of iodochloride (fract. 3-5) 46%, but when the preparation was repeated twice on a 1.7 molar scale using recovered dichloride from the first

in the second, the net yield was 62%.

1-Heptyne. (I) Liquid ammonia (500 ml), in a 1 litre three-necked flask surrounded by a cooling-bath at -40 to -55°, was stirred while acetylene (via a mercury safety-valve, and purified by passage through a solid carbon dioxide-acetone trap, two conc. sulphuric acid wash-bottles, and a reversed wash-bottle) was rapidly passed in for 5 min. to saturate the ammonia. Sodium (11.8 g.) was added in small pieces, the stirring and acetylene being continued, the next piece of sodium not being added until the blue colour due to the previous piece had been discharged. 1-Bromopentane (77.6 g.) was then added over 2 hr. and the mixture stirred for a further 2 hr. The flask was removed from the cooling-bath, ammonium hydroxide (65 ml., .880 g./ml.), followed by water (150 ml.) was added, and the organic layer was taken up in ether, washed with water, dil. sulphuric acid, sodium bicarbonate, water, and dried.

The ethereal solution was fractionated through a ½ metre Fenske column to give 1-heptyne (25.2 g., 51%), b.p. 99-101°, n_D^{24} 1.4066 (lit.[71] b.p. 99.8°, n_D^{20} 1.4048).

1-Chlorotrideo-7-yne. (III) To a stirred suspension of sodamide in liquid ammonia (250 ml.) prepared from sodium (2.53 g.) by the usual ferric nitrate process[72] was added 1-heptyne (9.6 g.) over ½ hour., and stirring was continued for a further 3 hr. 1-Chloro-6-iodohexane (25.9 g.) was then added with cooling over ½ hr., and the stirring continued overnight. The ammonia was allowed to evaporate off at

room temperature after the addition of ammonium chloride (10 g.), water and ether were then added, and the separated ether layer was washed successively with water, dil. sulphuric acid, aqueous sodium bicarbonate, and water before being dried and the solvent removed, finally under vacuum. This gave a crude product (21.7 g.) which G.L.C. showed to consist of two components, one of them being recovered iodochloride (ca. 15%). It was used for the next stage without further purification. Repeated on a 0.6 molar scale an exactly proportional yield was obtained.

1-Chlorotrideo-7-yne (III) [without isolation of heptyne]. To a stirred liquid ammonia (120 ml.), through which acetylene was being bubbled, were added small pieces of sodium at such a rate that the blue colour due to dissolved sodium just disappeared before the next piece was introduced. The acetylene flow was stopped at the exact moment when the blue colour due to the last piece of sodium was discharged, 1-bromopentane (15.1 g.) was then slowly added, and the reaction mixture was stirred for a further 4 hr.

A suspension of sodamide in liquid ammonia (75 ml.), prepared from sodium (2.48 g.) by the ferric nitrate process of Vaughn et al.,[72] was then added in portions with strong cooling, the mixture was stirred for 1 hr., 1-chloro-6-iodohexane (24.6 g.) was added dropwise, and the reaction was completed by stirring for a further 12 hr. The ammonia was evaporated off on a steam-bath, water and ether were added to the residue, and the ethereal layer was washed successively with

dil. sulphuric acid, aqueous sodium bicarbonate, and water, then dried and evaporated.

The crude product (24.7 g.) fractionated through a 10 cm. Vigreux column gave the following fractions, (analysed by G.L.C. on a 20% Apiezon L column at 150°):

Fr.	w.t.(g.)	b.p.(°C)	press.(mm)	$n_D(t°)$	main components.
1	0.45	27-28	20	1.4365(21)	heptyne & bromopentane
2	6.25	56-55.5	0.2-0.3	1.4644(21)	dodecyne (?)
3	6.79	72-76	0.5	1.5169(20)	iodochloride
4	2.6	85-103	0.5-0.6	1.4689(20)	iodochloride & chlorotridecyne (1:9)
5	5.4	78-87	0.2	1.4656(19.5)	chlorotridecyne

1-Bromopentadec-9-yne (VIII) 1-Heptyne (21.0 g.) in an equal volume of ether was added over ¼ hr. to a stirred suspension of sodamide from sodium (5.05 g.) in liquid ammonia (500 ml.), and stirring was continued for a further 5½ hr. 1,8-Dibromo-octane (60.0 g.) was then rapidly added with strong cooling, and stirring was continued overnight.

After addition of ammonium chloride (20 g.) the ammonia was allowed to evaporate at room temperature, the product was extracted with ether and the ethereal layer was washed successively with water, dilute sulphuric acid, sodium bicarbonate, water and dried. Ether and heptyne were distilled off at atmospheric pressure through a ½ metre column packed with Fenske helices, and the residue was distilled under reduced pressure.

Fr.	b.p.	Press.	n_D^{22}	Wt.
1	87-95°	0.25 mm	1.4929	10.44 g.
2	95-101°	0.4-0.6	1.4949	7.51 g.
3	100-110°	0.4	1.4959	7.31 g.
4	118-134°	0.8	1.4809	3.21 g.
5	140°	0.8-0.2	1.4759	18.96 g.
6	140-160°	0.2	1.4714	7.08 g.

Fractions 1,2 and 3 were mainly dibromo-octane (shown by G.L.C. of 3 and refractive indices). Fraction 5 contained ca. 95% bromopentadecyne with dibromooctane and/an uncharacterised compound present as impurities (30% yield), and was used for the next stage without further purification. Fraction 6 consisted of bromopentadecyne (V_r 2.35) and a less volatile component (V_r 3.61).

Fraction 5 (100 mg.) rapidly absorbed 2.02 mols. hydrogen when it was hydrogenated with Palladium charcoal catalyst in ethanol.

Tetradec-8-ynoic acid (IV). A mixture of crude 1-chlorotridec-7-yne (21.65 g.), sodium iodide (17.25 g.), sodium cyanide (17.25 g.) and ethanol (80%, 170 ml.) was refluxed for 48 hr., potassium hydroxide (57.5 g.) in water (144 ml.) was then added and refluxing was continued for a further 48 hr. The reaction mixture was cooled, diluted with water, extracted with petroleum ether to remove any non-acidic material, acidified with dil. sulphuric acid and extracted with petroleum ether to remove the monobasic acid, and finally extracted with ether to remove

the dibasic acid. The dried extracts yielded tetradec-3-ynoic acid (17.6 g., 79% from heptyne), n_D^{25} 1.4504 and suberic acid (5.9 g.), m.p. 135-137° (lit.[73] 140°). G. .C. showed the monobasic acid to be chromatographically pure (V_r 1.00), except for ca 3% of the dec-acid (V_r 0.833). On a 0.6 molar scale the yield from heptyne was 88%.

When a solution of the acid (235 mg.) in ethanol was hydrogenated with 30% palladium-charcoal catalyst, the absorption of hydrogen (47 ml. at N.T.P., equivalent to 2.0 double bonds) was complete in 15 min. The catalyst and solvent were removed to give a residue m.p. 53-55°, which G.L.C. showed to be myristic acid (lit[74] m.p.54°).

Attempts to purify the acid by recrystallisation from ethanol, and from aqueous ethanol, at room temperature and at 0°, were unsuccessful. The product of the second batch was distilled four times under high vacuum to give a product pure enough for semi-hydrogenation with Lindlar catalyst. In the first two distillations, iodine, probably formed by decomposition of an impurity, was condensed in the traps. The equivalent weight of the 3rd. distillate determined by simple titration was found to be 224.5 and 223.5, mean value 224 (theoretical 224).

Hexadec-10-ynoic Acid (IX). (By acetylenic synthesis.) A mixture of 1-bromopentadec-8-yne (13.72 g.), sodium iodide (10.0 g.) sodium cyanide (10.0 g.) and 80% ethanol (100 ml.) were refluxed for 48 hr, potassium hydroxide (33.0 g.) in water (82 ml.) was then added and

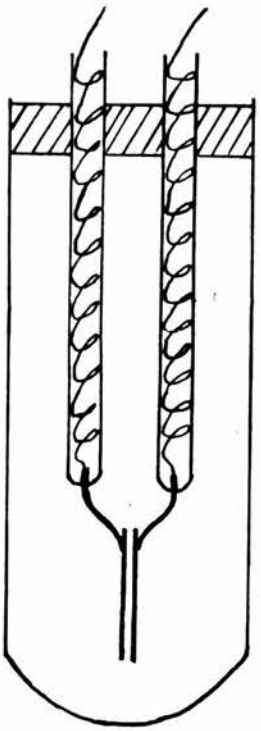


FIG. 6 ELECTROLYSIS CELL

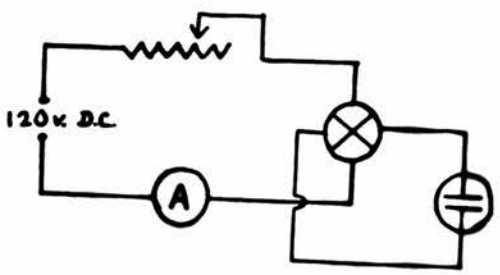


FIG. 7 CIRCUIT DIAGRAM

refluxing was continued for a further 48 hr. After cooling, dilution with water, and extraction with petroleum ether to remove nonacidic material, the reaction mixture was acidified with 5 N sulphuric acid and the monobasic acid extracted with petroleum ether. The extracts were washed with water, dried and evaporated to give hexadec-10-ynoic acid (15.22 g., 93%), which was shown by G.L.C. to contain ca. 1% decanedioic acid.

The acid was distilled twice under high vacuum (10^{-4} mm.) and then recrystallised from methanol at 4° (later with addition of increasing amounts of water) to give the following fractions:

Fr.	Wt.	m.p.
1	4.91 g.	55-56°
2	6.94 g.	54.5-56°
3	1.12 g.	26°

Flooding the mother-liquor with water and extraction with ether gave a residue (0.71 g.)

Anodic Synthesis.

The apparatus (fig. 6) consisted of a cylindrical glass cell (two sizes were used: 5 x 24 cm., and 3.5 x 15 cm.), containing two parallel platinum-foil electrodes (2.5 x 3 cm) kept ca. 2 mm. apart by glass spacers. The cell was cooled in an ice-water bath, and a thermometer suspended with the bulb near to the plates measured the internal temperature, which was kept below 50°. Stirring of the electrolyte was unnecessary owing to the vigorous evolution of carbon

dioxide.

Each electrode was attached, by spot-welding, to a short piece of platinum wire sealed into the end of a length of glass tubing. Electrical contact was obtained by attaching the other end of the platinum wire to a copper lead. The power was supplied from a 120 volt D.C. source, with a commutator, rheostat, and ammeter in series with the cell, (fig. 7).

The solvent used was commercial methanol, to which enough sodium was added to neutralise about 2% of the acids. Electrolysis was continued until the electrolyte became slightly alkaline (pH 7-8, B.D.H. wide range indicator paper).

During the electrolysis the direction of the current was reversed periodically, and especially when the current began to fall towards the end of the electrolysis. An insoluble product usually formed on the electrodes, in varying amounts depending on the acids used. This was not always completely removed by reversing the current, and cleaning of the electrodes failed to make any appreciable difference, so that for the last 20% of an electrolysis the current had to be reduced to keep the cell temperature down to below 50°.

After electrolysis, the insoluble product was filtered off, the filtrate neutralised with a few drops of 2N hydrochloric acid, most of the methanol removed under reduced pressure, and the residue poured into water and extracted with ether. In the later electrolyses the methanol was not removed first, but the whole filtrate was poured into

an excess of water and extracted with ether. The ether extract was washed with 2N sodium hydroxide, then with water, dried and evaporated. The recovered acids were isolated by acidification of the alkaline washings and extraction with ether.

Hydrolysis of the neutral products was carried out, where stated, by refluxing with 10% potassium hydroxide in 80% methanol for 2-3 hr.

Methyl Hydrogen Succinate. This was prepared according to the method of Bone, Sudborough, and Spranklin.[75] Succinic anhydride (100 g.) and methanol (80 ml) were refluxed together for 45 mins., the excess methanol was then removed under reduced pressure, and the residue recrystallised from ether/petroleum ether (b.p. 60-80°), to give methyl hydrogen succinate (77.6 g., 59%), m.p. 52-55° (lit.[75] 58°).

Benzyl hydrogen succinate. This was prepared by the method of Linstead, Weedon and Wladislaw.[60] A mixture of succinic anhydride (200 g.) and benzyl alcohol (220 g.) was heated under reflux for 4 hr. and then cooled. The product was extracted thoroughly with ether, and the ethereal solution was separated from the insoluble residue of succinic acid and washed repeatedly with saturated sodium carbonate solution. The alkaline extracts were acidified with 2N hydrochloric acid and the product (216 g., 52%), m.p. 53-55°, thus precipitated, was isolated in the usual way with ether. Crystallisation from benzene-petroleum ether (b.p. 80-100°) gave the half-ester, m.p. 58.75 - 59.75° (lit.[60] 55-56°).[76]

Methyl hydrogen adipate. (See Swann et al.)[77] A mixture of adipic acid (244 g.), di-n-butyl ether (200 ml.), conc. hydrochloric acid (42 ml.) and methanol (63 ml.) was heated under reflux for 2 hr., more methanol (23 ml.) was then added and refluxing was continued for a further 2 hr. Excess methanol, water, and butyl ether were removed by distillation under reduced pressure (water-pump) until the bath temperature reached 125°, and the residue was fractionated on a ½ metre Fenske column with an oil pump.

Fr.	b.p.	Press.	wt.	n_D^{17}	Eq. wt.
1	80°	1.25 mm.	45.9 g.	1.4283	
2	92°	1.5	7.5	1.4304	
3	140-142°	1.5	106.0	1.4406	162.5
4	131-133°	0.8	16.4	1.4413	158
5	133-134°	0.8	2.7	1.4414	

Fraction 1 was dimethyl adipate, and fractions 3-5 were methyl hydrogen adipate (123 g., 47%).

Methyl hydrogen suberate. This was prepared as described for methyl hydrogen adipate using suberic acid (150 g.), butyl ether (100 ml.), c. hydrochloric acid (22 ml.), and methanol (35 ml., and 12 ml.) The following fractions were obtained:

Fr.	b.p.	press.	wt.	n_D (t°)
1	77-92°	0.25 mm.	5.5 g.	1.4529 (19)
2	94-96°	0.4-0.5	25.1	1.4539 (19)
3	96-110°	0.5-0.4	2.1	1.4534 (22)
4	110-106°	0.4-0.25	4.2	1.4546 (22)
5	122-128°	0.2-0.3	7.2	1.4404 (21.5)
6	128-134°	0.3	51.3	1.4426 (22)
7	134°	0.3	6.4	1.4426 (24)
8	135-160°	0.3	2.5	1.4429 (22)

Fractions 1 and 2 were dimethyl suberate, and 6 and 7, equivalent weights 192, 191 (theoretical 188), methyl hydrogen suberate, (58.5 g., 36%).

Hexacos-6,20-diyne. Tetradec-8-ynoic acid (5.0 g.) was electrolysed (current 0.25-0.5 amps., faradays passed ca. 1.3 times theoretical) in methanol (25 ml.) to which enough sodium was eventually added to neutralise 8% of the acid. Even at low currents it was difficult to prevent overheating, the polarity had to be reversed frequently, and a large amount of insoluble product was obtained.

Isolation of organic material (petroleum ether) yielded neutral product (2.16 g.) and recovered acid (1.91 g., n_D^{22} 1.4609). Hydrolysis of the neutral product (2.08 g.) yielded an acid (0.11 g.) and hexacos-6,20-diyne (1.82 g., 47%), n_D^{20} 1.4625, which was shown by G.L.C. to contain minor impurities. 4.0 Mols. of hydrogen were rapidly absorbed when the diacetylene was hydrogenated in ethanol over 20% palladium-charcoal catalyst. On removal of catalyst and solvent a white solid, m.p. 35-49° (lit.[59] 57-58° for hexacosane) was obtained.

Hexadec-10-ynoic Acid (V, n=2) by Anodic Synthesis.

(a) Using methyl hydrogen succinate. A solution of tetradec-8-ynoic acid (4.5 g., 1 mol.) and methyl hydrogen succinate (7.96 g. 3 mol.) in methanol (46 ml.) was electrolysed (current 1 amp., faradays passed ca. 1.05 times theoretical). When the current began to drop, and the cell to overheat, the electrodes were cleaned but to no effect, so more half ester (2.65 g.,1 mol.) was added and the electrolysis continued until the same trouble was again experienced, (pH 6). The products were isolated in the usual way, to give a neutral product (7.02 g.) and recovered acids (1.65 g.).

The neutral product was fractionated through a 9 cm. Vigruex column and the fractions analysed by G.L.C.

Fr.	b.p.	press.	wt.	% C_{16}
1	60-100°	0.7-0.6 mm.	3 g.	nil
2	114-122°	0.6	1 g.	40
3	125-130°	0.6	1 g.	70
4	130-131°	0.6	1 g.	85
5	135-138°	0.6	½ g.	85

The weights and percentages of hexadecynoic acid are both approximate. In each fraction there was a greater or lesser amount of tetradecynoic acid showing the inadequecy of the separation.

(b) Using benzyl hydrogen succinate. A solution of tetradec-8-ynoic acid (3.0 g., 1 mol.) and benzyl hydrogen succinate (8.3 g., 3 mols.) in methanol (38 ml.) was electrolysed (current 0.5 amp., faradays passed ca. 2.5 times theoretical). The electrodes were cleaned frequently to allow the electrolysis to proceed. The products were isolated in the usual way to give recovered acids (0.77 g.), and a neutral product (6.94 g.) which was fractionated through a 9 cm. vacuum jacketed Vigreux column, the fractions being examined by G.L.C.

Fr.	b.p.	press.	wt.
1	44-50°	0.3 mm.	0.69 g.
2	70-104°	0.3	0.08
3	104-124°	0.3	0.62
4	124-148°	0.3	0.28
5	140-175°	0.1	2.18
6	175-180°	0.075	1.41
residue	bath at 230-240°		1.12

Hydrolysis of fractions 5 and 6 and the residue, followed by extraction of the monobasic acid with petroleum ether yielded crude hexadec-10-ynoic acid (0.71 g., 21%). G.L.C. showed it to be a C_{16} acid containing ca. 2.5% C_{14}.

Octadec-12-ynoic acid. (V, n=4) A solution of tetradec-8-ynoic acid (3.1 g., 1 mol.) and methyl hydrogen adipate (6.6 g., 3 mol., Eq. wt. 162.5) in methanol (32 ml.) was electrolysed (current 1.0 - 0.5 amp., faradays passed ca. 1.25 times theoretical), and the products were isolated in the usual way to give neutral material (6.03 g.) and recovered acids (0.28 g.). The neutral product was fractionated through a 9 cm. Vigreux column.

Fr.	b.p.	press.	wt.
1	60-110° 87-98°	0.5 m.m. 0.25	3.04 g.
2	98-132°	0.25	0.50
3	132-139°	0.25	0.97
4	134-152°	0.07	0.56
5	152-166°	0.05 - 0.03	0.47
res.			0.14

Fractions 3,4, and 5 were found (by G.L.C.) to contain only C_{16} (except that F3 contained a very small amount of C_{14}) with small amounts of hydrocarbon (hexacosdiyne) and dibasic acid (C_{10}), both removable by hydrolysis and petroleum ether extraction.

This preparation was repeated twice on a three times larger scale giving (from 20 g. tetradecynoic acid) neutral product (37.28 g.) and recovered acids (3.24 g.). The neutral product was distilled, and the fraction (11.0 g.) b.p. 135°/0.25 mm to 168°/0.05 mm. was combined with fractions 3,4, and 5 from the trial synthesis, hydrolysed and the octadec-12-ynoic acid (8.01 g., 28%), m.p. 43-44°, extracted with petroleum ether. The m.p. was raised to 46-47° (lit.[45] 46.2 - 47.2°) by recrystallisation from ethanol at 4°.

Eicos-14-ynoic Acid. (V, n=6). A solution of tetradec-8-ynoic acid (3.1 g., 1 mol) and methyl hydrogen suberate (7.8 g., 3 mols) in methanol (32 ml.) was electrolysed (current 0.9 - 1.0 amps., faradays passed ca. 1.32 times theoretical), and the products were isolated in the usual way to give neutral material (7.95 g.) and recovered acids (0.22 g.). The neutral material was through a 9 cm. Vigreux column.

Fr.	b.p.	press.	wt.
1	55-60° 72-132°	0.25 mm. 0.1	0.87 g
2	132-157°	0.1	0.43
3	157-166°	0.1	2.98
4	166-168° 143-155°	0.1 6×10^{-3}	2.39

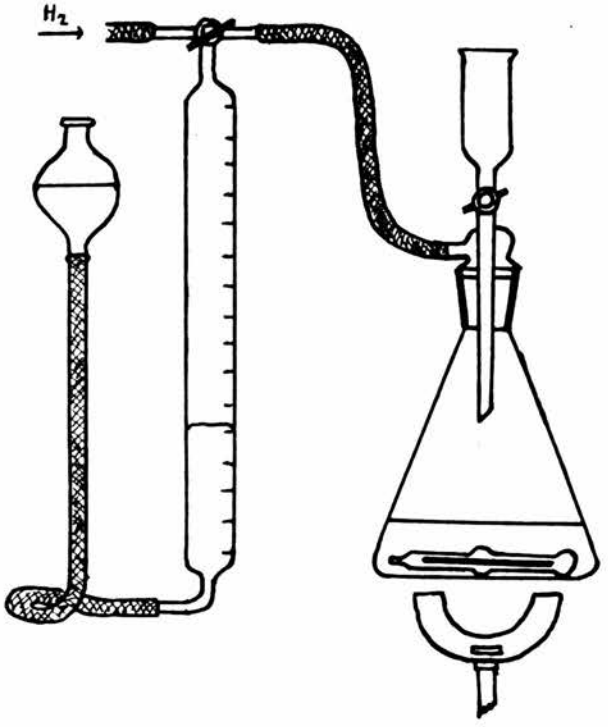
Fractions 3 and 4 were shown by G.L.C. to contain only C_{20} monobasic and C_{14} dibasic acids.

The synthesis was repeated twice (with 19.0 g. of tetradecynoic acid) to give neutral product (49.3 g.) and recovered acids (1.59 g.). The neutral product was distilled and the fractions b.p. 126-164°/ 0.06 mm. (33.24 g.) and b.p. 156-182°/ 2 X 10^{-3} mm. (2.12 g.) were combined with fractions 3 and 4 from above and hydrolysed with aqueous-alcoholic potassium hydroxide. The reaction mixture was poured into water, washed with petroleum ether to remove non-acidic material, and the mixed acids were precipitated by the addition of excess 2N hydrochloric acid. The precipitate was filtered off, washed and dried to give a mixture (33.44 g.) of eicosynoic and tetradecanedioic acids. Extraction in a Soxhlet with petroleum ether gave crude eicos-14-ynoic acid (10.98 g., 36%), leaving a residue of tetradecanedioic acid which was shown by G.L.C. to contain ca. 23% eicosynoic acid.

The crude eicos-14-ynoic acid was recrystallised from ethanol at room temperature (1st fraction), then at 4°.

Fr.	Weight.	M.P.
1	2.20 g.	54.5 - 55.5°
2	4.28	53.5 - 55°
3	0.91	49 - 52°
4	0.46	48 - 52°

The residue (2.61 g.) was recovered by removal of the solvent from the last mother-liquor. Each fraction gave a single peak when analysed by G.L.C.



HYDROGENATION APPARATUS

Fig. 8

Catalytic Hydrogenations. These were performed at room temperature and at just above atmospheric pressure in a conical flask fitted with a magnetic stirrer, (fig. 8). The hydrogen was produced chemically by the action of 5N-hydrochloric acid on arsenic free zinc in the apparatus designed by Tucker.[78] The catalyst and solvent were first saturated with hydrogen before the sample was introduced in more solvent. Addition of further solvent after the saturation of the catalyst with no subsequent absorption of hydrogen showed that the solvent introduced with the sample did not of itself absorb any of the measured hydrogen.

Tetradec-cis-8-enoic acid. (VI, n=0) A mixture of Lindlar catalyst (6.0 g.), quinoline (1.5 g.) and ethyl acetate (90 ml.) was vigorously stirred in hydrogen until absorption was complete. A solution of tetradec-8-ynoic acid (6.01 g.) in ethyl acetate (30 ml.) was then added and stirring was continued until the absorption of hydrogen became very slow, (627 ml. hydrogen absorbed, equivalent to 1.04 mols.). The catalyst was filtered off, and the filtrate washed with 2N-hydrochloric acid, then with water, dried and evaporated. The pale yellow acid was distilled twice under high vacuum (2.5×10^{-4} mm.), treated with animal charcoal in petroleum ether, and finally distilled for a third time to give a colourless product, n_D^{17} 1.4569. An infra-red spectrum showed it to contain 1.5% trans-olefin, and G.L.C. to be chromatographically pure, containing no acetylenic or saturated acid. Von Rudloff oxidation gave only hexanoic and suberic acids.

Hexadec-cis-10-enoic acid. (VI, n=2) Hexadec-10-ynoic acid (8.55 g.) in ethyl acetate (180 ml.) was reduced over Lindlar catalyst (9.0 g.) containing quinoline (2.25 g.) as described for tetradecenoic acid, (827 ml. hydrogen absorbed, equivalent to 1.055 mols). The product, isolated in the usual way, was distilled twice under high vacuum (2.5×10^{-4}mm.) and then treated with animal charcoal in petroleum ether to remove final traces of colour, to give hexadec-cis-10-enoic acid, n_D 1.4593, m.p. 15-16°, containing 0.5% trans isomer. G.L.C. showed the absence of the acetylenic and saturated acids, and von Rudloff oxidation gave hexanoic and 1,10-decandioic acids.

Octadec-cis-12-enoic acid. (VI, n=4) Octadec-12-ynoic acid (6.95 g.) in ethyl acetate (140 ml.) was reduced over Lindlar catalyst (7.0 g.) containing quinoline (1.75 g.) as described for tetradecenoic acid, (581 ml. hydrogen absorbed, equivalent to 1.045 mols.). The product was isolated in the usual way, decolourised with animal charcoal in petroleum ether and finally distilled under high vacuum (2.5×10^{-4}mm.) to give octadec-cis-12-enoic acid, m.p. 26.5 - 27.5°, containing 1.7% of the trans-isomer. G.L.C. showed the absence of the acetylenic and saturated acids, and von Rudloff Oxidation gave hexanoic and 1,12-dodecandioic acids.

Eicos-cis-14-enoic acid (VI, n=6) Eicos-14-ynoic acid (5.90 g.) in ethyl acetate (140 ml.) was reduced over Lindlar catalyst (6.0 g.) containing quinoline (1.5 g.) as described for tetradecenoic acid, (458 ml. hydrogen absorbed, equivalent to 1.07 mols.). The product was isolated in the usual way, decolourised with animal charcoal in petroleum ether and distilled under high vacuum (2.5×10^{-4} mm.) to give eicos-14-enoic acid, m.p. 40 - 40.75°, containing 7.0% of the trans-isomer. G.L.C. showed the absence of both the saturated and the acetylenic acid, and von Rudloff oxidation gave hexanoic and 1,14-tetradecdioic acids. The acid was recrystallised from ethanol at 4° to give the following fractions:

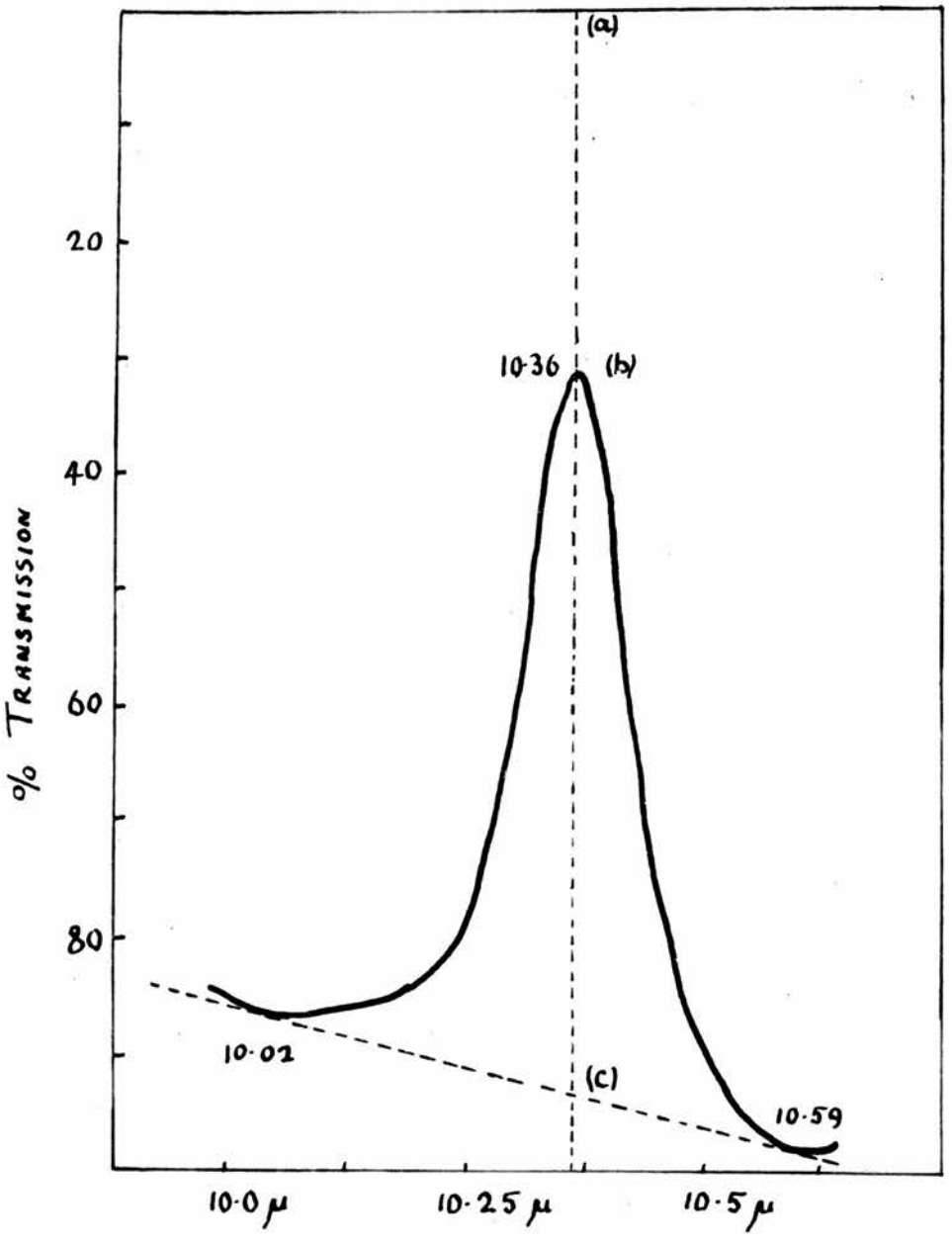
Fraction	weight	m.p.	% trans.
1	1.57 g.	41.5°	nil
2	0.81	41 - 41.5°	nil
3	0.99	41 - 41.5°	nil
4	0.65	41 - 41.5°	nil
5	0.46	40 - 40.5°	3.9%
residue	0.99	36.5 - 38°	19%

Cleavage of Unsaturated Acids by von Rudloff Oxidation.[69]

The unsaturated acid (0.25 mM.), potassium carbonate (0.75 mM), potassium periodate (2 mM.), potassium permanganate (0.0555 mM.), and water (100 ml.) were shaken together for 2½ hr., then left overnight at room temperature. The resulting solution was acidified, saturated with salt, and thoroughly extracted with ether. The acids obtained were methylated and analysed by G.L.C. at 150 and 200°, to give the following cleavage products:

	monobasic	dibasic
tetradecynoic	C_6	C_8
tetradecenoic	C_6	C_8
hexadecenoic	C_6	C_{10}
octadecenoic	C_6	C_{12}
eicosenoic	C_6	C_{14}

The chromatograms showed the absence of other degradation products with the exception of the C_{12} and C_{14} dibasic acid fragments which showed evidence of minor secondary degradation. In both cases there was no evidence of the corresponding monobasic acids which would have been present had these fragments been produced by cleavage of isomeric acids.



SPECTRUM OF METHYL ELAIDATE

FIG. 9

Infra-red Determination of Trans-Acid.[68]

The transmittance of a solution of known concentration (ca. 20 mg/ml.) of the methyl ester of the sample in carbon disulphide (cell width 0.8 mm.) was measured over the range 9-11μ at a scanning speed of 4 min./μ . This was compared with that obtained for a solution of methyl elaidate with the instrument programming controls set at identical positions.

On the charts (fig. 9) a line was drawn through the absorption peak from 10.02μ to 10.59 μ and the fractional transmission was calculated as the distance to the absorption peak at 10.36μ (ab), divided by the distance to the base line (ac). From this the background corrected absorptivity was calculated.

$$\text{Transmittance, } T = \frac{\text{transmitted light}}{\text{incident light}} = \frac{(ab)}{(ac)}$$

$$\text{Absorbance, } A = \log 1/T$$

$$\text{absorptivity (background corrected), } a = A/bc$$

where b = internal cell length (cm.)

c = concentration (g./l.).

$$\% \text{ trans as methyl elaidate} = \frac{a\ (\text{sample})}{a\ (\text{methyl elaidate})}$$

$$\text{Absolute \% trans} = \% \text{ trans as methyl elaidate} \times \frac{\text{molecular weight of sample}}{\text{mol.wt. of methyl elaidate.}}$$

* * * *

BIBLIOGRAPHY TO PART I

1. Hilditch and Jasperson, "Lipids in Relation to Arterial Disease," Bibby, Liverpool, 1959.
   Rathmann, J. Amer. Oil Chemists' Soc., 1960, 37, 601.
   Hilditch, Reports Progr. Appl. Chem., 1959, 44, 173.
2. Hansen, Adam, Weise, Boelsche, and Haggard, "Essential Fatty Acids" ed. Sinclair, Butterworths, London, 1958, p.216.
3. Bernhard and Schoenheimer, J. Biol. Chem., 1940, 133, 707.
   Bernhard, Steinhauser, and Bullet, Helv. Chim. Acta, 1942, 25, 1315.
4. Klenk and Debuch, Z. physiol. Chem., 1950, 286, 55.
5. Munn and Smedley - Maclean, Biochem. J., 1938, 32, 2178.
6. Steinberg, Slayton, Howton and Mead, J. Biol. Chem., 1956, 220, 257.
7. Thomassen, Internat. Z. Vitaminforsch., 1953, 25, 62.
8. Klenk, "Essential Fatty Acids" ed. Sinclair, Butterworths, London, 1958, p.57.
9. Mead, Steinberg and Howton, J. Biol.Chem., 1955, 205, 665. *
10. Mead and Howton, "Essential Fatty Acid" ed. Sinclair, Butterworths, London, 1958, p.66.
11. Mead and Howton, J. Biol. Chem., 1957, 229, 575.
12. Howton and Mead, J. Biol. Chem., 1960, 235, 3385.
13. Mead, J. Biol. Chem., 1957, 227, 1025.
    Klenk, Experientia, 1961, 17, 199.
14. Fulco and Mead, J. Biol. Chem., 1959, 234, 1411.
15. Mead and Slayton, J. Biol. Chem., 1956, 219, 705.
16. Klenk and Debuch, "Modern Scientific Aspects of Neurology", ed. Cumings, Arnold, London, 1960, chap. 7, "The Glycerophosphatides and Sphingolipids of Brain", p. 277.
17. Klenk and Lindlar, Z. physiol. Chem., 1955, 301, 156.
18. Klenk and Lindlar, Z. physiol. Chem., 1955, 299, 74.
    Klenk and Bongard, Z. physiol. Chem., 1952, 291, 104.
    Klenk and Montag, J. Neurochem., 1958, 2, 235, 266.

* Klenk, Z. physiol Chem., 1955, 302, 268.

19. Fulco and Mead, J. Biol. Chem., 1960, 235, 3379.
20. Turpeinen, J. Nutrit., 1938, 15, 531.
21. Moller and Bannerot, J. Amer. Chem. Soc., 1954, 56, 1563.
22. Raphael and Sandheimer, J. Chem. Soc., 1950, 2100.
23. Gensler, Chem. Rev., 1957, 57, 191.
24. Gunstone, Quart. Rev., 1953, 7, 175; Progr. Chem. Fats and Other Lipids, 1957, 4, 1.
25. Glaser, Ber., 1869, 2, 422; Annalen, 1870, 154, 159.
26. Weedon, Progr. Org. Chem., 1952, 1, 154.
Raphael, "Acetylenic Compounds in Organic Synthesis" Butterworths, London, 1955.
27. Ahmad and Strong, J. Amer. Chem. Soc., 1948, 70, 1609.
28. Ahmad, Bumpus, and Strong, J. Amer. Chem. Soc., 1948, 70, 3391.
29. Crombie and Jacklin, Chem. and Ind., 1955, 1186; J. Chem. Soc., 1957, 1632.
30. Black and Weedon, J. Chem. Soc., 1953, 1785.
31. Nigran and Weedon, J. Chem. Soc., 1956, 4049.
32. Crombie and Jacklin, Chem. and Ind., 1954, 1197; J. Chem. Soc., 1955, 1740.
33. Osbond and Wickens, Chem. and Ind., 1959, 1288.
Osbond, Philpott and Wickens, J. Chem. Soc., 1961, 2779.
34. Weedon, Quart. Rev., 1952, 6, 380; Adv. Org. Chem.,1960, 1, 1.
35. Faraday, Pogg. Ann., 1834, 33, 458.
36. Kolbe, Annalen, 1849, 69, 257.
37. Wurtz, Ann. Chim. Phys., 1855, 44, 291; Jahresbericht., 1855, 575.
38. Brown and Walker, Annalen, 1891, 261, 107; Trans. Roy. Soc. Edinburgh, 1891, 36, 291.
39. Hickling, Quart. Rev., 1949, 3, 121.
Salauze, Bull. Soc., chim., 1925, 37, 522.
40. Linstead, Lunt, and Weedon, J. Chem. Soc., 1950, 3333.
Stallberg-Stenhagen, Arkiv Kemi, 1950, 2, 95.
41. Bounds, Linstead, and Weedon, J. Chem. Soc., 1954, 448.

42. Bounds, Linstead and Weedon, J. Chem. Soc., 1955, 2393.
43. Hilditch and Vidyarthi, Proc. Roy. Soc., 1929, 122, 552.
44. Grün and Czerny, Ber., 1926, 59, 61.
45. Huber, J. Amer. Chem. Soc., 1951, 73, 2730.
46. Phatak and Patwardhan, Nature, 1953, 172, 456.
47. Gupta, Hilditch, Paul, and Shrivastava, J. Chem. Soc., 1950, 3484.
48. Fokin, J. Russ. Phys. Chem. Soc., 1914, 46, 224.
49. Fokin, J. Russ. Phys. Chem. Soc., 1912, 44, 653.
50. Gunstone, "An Introduction to the Chemistry of Fats and Fatty Acids" Chapman and Hall, London, 1958, p.93.
51. Barucha and Gunstone, J.Chem. Soc., 1956, 1611.
52. Taylor and Strong, J. Amer. Chem. Soc., 1950, 72, 4263.
53. Raphael and Sandheimer, J.Chem. Soc., 1950, 115.
54. Raphael, "Acetylenic Compounds in Organic Synthesis", Butterworths, London, 1955, p. 193.
Jacobs, Org. Reactions, 1949, 5, 48.
Campbell and Campbell, Org. Synth., 1950, 30, 15.
55. Raphael, "Acetylenic Compounds in Organic Synthesis", Butterworths, London, 1955, p.194.
56. Jacobs, Org. Reactions, 1949, 5, 28.
57. Baker, Linstead and Weedon, J. Chem. Soc., 1955, 2218.
58. Weedon, Adv. Org. Chem., 1960, 1, 24.
59. Linstead, Elvidge, and Whalley, "A Course in Modern Techniques of Organic Chemistry" Butterworths, London, 1955, p.113
60. Linstead, Weedon, and Wladislaw, J. Chem. Soc., 1955, 1097.
61. Bounds, Linstead, and Weedon, 1954, 4219.
62. Lindlar, Helv. Chim. Acta, 1952, 35, 446.
63. Fusari, Greenlee, and Brown, J. Amer. Oil Chemists' Soc., 1951, 28, 416.
Ahmed et al., ref. 27,28; Huber, ref. 45; Taylor and Strong, ref. 52.
64. Khan, J. Amer. Oil Chemists' Soc., 1953, 30, 40.

65. Raphael, "Acetylenic Compounds in Organic Synthesis" Butterworths, London, 1955, p.26.
Crombie, J. Chem. Soc., 1955, 3510.
66. Crombie and Jacklin, J. Chem. Soc., 1957, 1632.
67. Crombie and Jacklin, J. Chem. Soc., 1955, 1740.
68. O'Connor et al., J. Amer. Chem. Oil Chemists' Soc., 1959, 36, 627.
69. Lemieux and von Rudloff, Canad. J. Chem., 1955, 33, 1701.
70. Farquhar, Insull, Rosen, Stoffel and Ahrens, 1959, 17, no.8, pt. 2, (Supplement), p.1.
71. Kemme and Greenlee, J. Amer. Chem. Soc., 1945, 67, 484.
72. Vaughn, Vogt and Nieuwland, J. Amer. Chem. Soc., 1934, 56, 2120.
73. Markley, "Fatty Acids", Interscience, New York, 1960, vol. 1,p.96.
74. Markley, "Fatty Acids", Interscience, New York, 1960, vol. 1,p.34.
75. Bone, Sudborough, Spranklin, J. Chem. Soc., 1904, 559.
76. Howard, J. Amer. Chem. Soc., 1922, 44, 1763.
77. Swann, Oehler, and Buswell, Org. Synth., Coll. vol. 2, p. 276.
78. Tucker, J. Chem. Educ., 1950, 27, 489.

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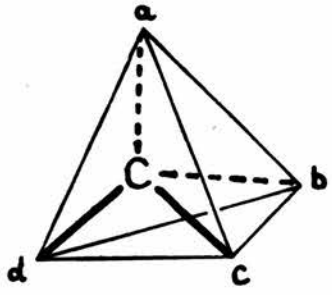
PART II

CONFIGURATION OF

NATURAL 9-HYDROXYOCTADECANOIC ACID



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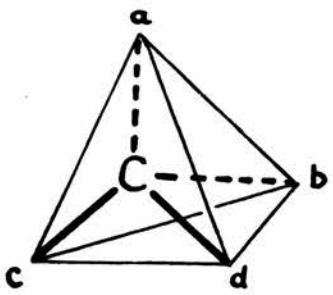

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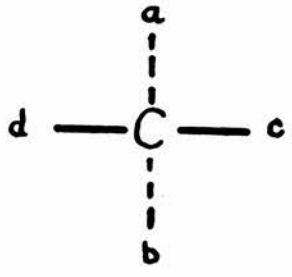

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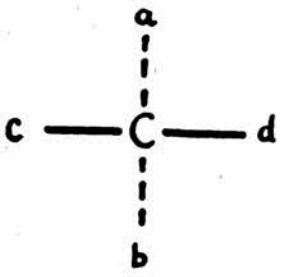


(IV)

INTRODUCTION.

(1) Asymmetry in Carbon Compounds.

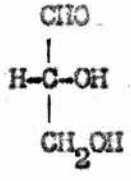
Carbon is a tetravalent atom, and as such it can form compounds of the general formula Cabcd. According to the theory of van't Hoff and Le Bel the four valencies are directed towards the corners of a tetrahedron, with the carbon atom at the centre.

If a,b,c, and d are all different atoms or groups then the C atom is said to be asymmetric, and the compound Cabcd can exist in two enantiomorphous forms (I) and (II), each possessing a different configuration. These can be represented more simply by means of the unambiguous Fischer[1] projections (III) and (IV) respectively. In these the bonds Ca and Cb are considered to lie below the plane of the page, the other two, Cc and Cd, above it. These two configurations are mirror images which cannot be superimposed, and are optically active, rotating a beam of polarised light equally in opposite directions.

In order to fully describe a compound containing one or more asymmetric centres it is necessary to establish which of the two possible configurations it possesses, as this cannot generally be deduced from the sign of the rotation. The standard substance to which all other optically active compounds are related, if possible, is optically active glyceraldehyde, $CH_2OH.CHOH.CHO$.

(2) Nomenclature.

The nomenclature suggested by Klyne[2] will be followed. Acyclic compounds are drawn as a Fischer projection with the principal numbered chain vertical and numbered from the top. A substituent at an asymmetric carbon atom is given the designation L if it lies on the left-hand side of the vertical chain, and the designation D if it lies on the right-hand side. Thus the glyceraldehyde (V) would be 2D,3-dihydroxypropanal or more simply, as it is often called, D-glyceraldehyde.



(V)

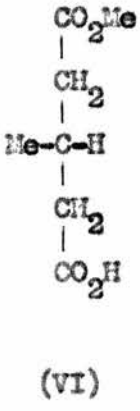
Fischer assigned (+)-glyceraldehyde the D-configuration so that compounds which can be related to (+)-glyceraldehyde also possess the D-configuration. This correlation is independent of the correctness of the configuration of the standard, and also of the system of nomenclature used.

Since the work of Bijvoet, Peerdeman and van Bommel[3] on X-ray crystallography applied to sodium rubidium tartrate, it has become accepted that Fischer's arbitrary assignment was correct. Thus, the absolute configuration of an optically active substance is known if it can be correlated with glyceraldehyde.

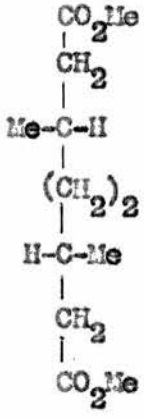
(3) Anodic Synthesis Using Optically Active Compounds.

Linstead and Weedon[4], and Stallberg-Stenhagen[5] have shown that in an electrolysis involving an asymmetric centre β to the carboxyl group the configuration is retained.

(-)-Methyl 3L-methyl-4-carboxybutanoate (VI) electrolysed alone gave (-)-methyl 3L,6D-dimethyl suberate (VII), and the (+)-D form gave the (+)-3D,6L isomer.



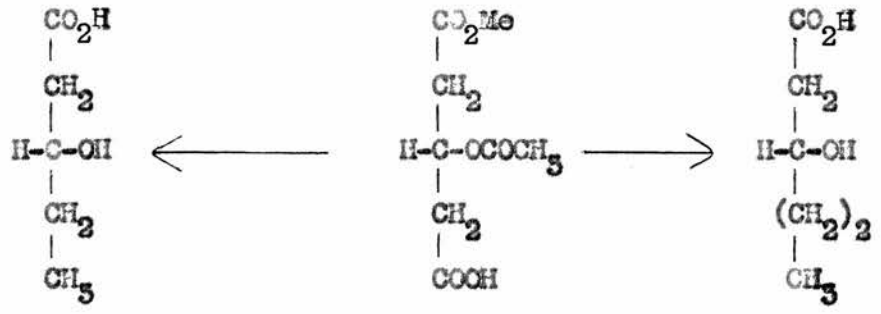
(VI)



(VII)

(4) Optically Active Monohydroxy-Acids.

A general method for the synthesis of optically active monohydroxy-acids has been described by Serck-Hanssen.[6,7] Racemic methyl hydrogen β-acetoxyglutarate was synthesised and resolved into its optically active forms. By anodic coupling of the dextro-rotatory half-ester (X) to acetic and propionic acids (-)-3-hydroxypentanoic (VIII) and (-)-3-hydroxyhexanoic (IX) acids were obtained. These acids are known to have the D-configuration,[7,8] and so the half-ester used can be fully described as (+)-methyl 3D-acetoxy-4-carboxybutanoate.



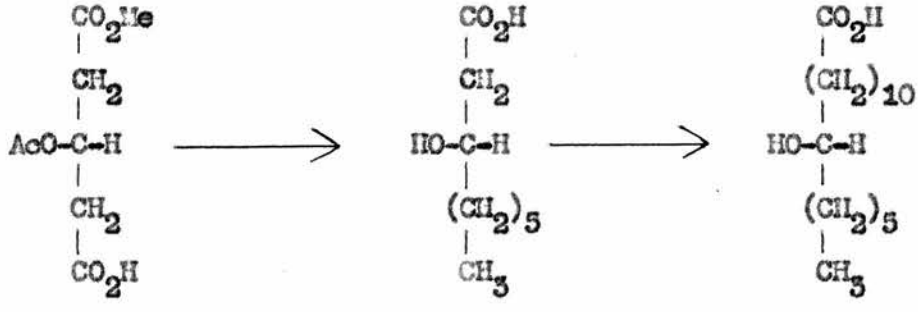
(VIII) (X) (IX)

By coupling either enantiomorph of this half-ester, first with a monobasic acid, and then with the half-ester of a dibasic acid, optically active acids of the general formula

$R.CH_2.CHOH.(CH_2)_n.CO_2H$ can be obtained.

(5) 12-Hydroxyoctadecanoic Acid.

By the method indicated above Serck-Hanssen[9] has synthesised 12L-hydroxyoctadecanoic acid (XII) via 9L-hydroxynonanoic acid (XI) and found them to be the enantiomorphs of the corresponding acids obtained from ricinoleic acid [(+)-12-hydroxyoctadec-9-enoic acid]. He therefore assigned the D-configuration to ricinoleic acid.

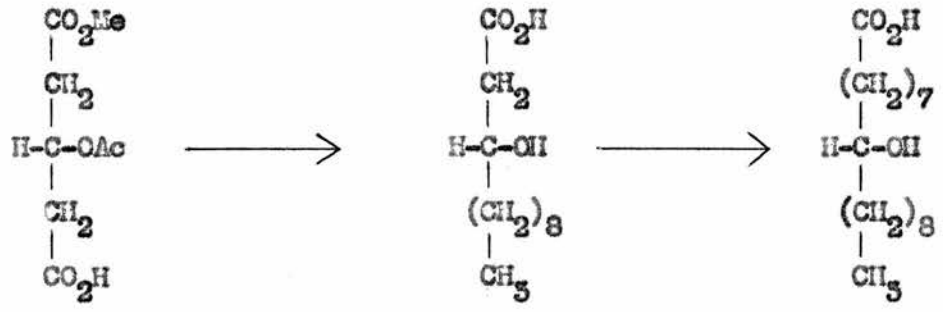


(XI) (XII)

The purpose of the present investigation was to synthesise 9D-hydroxyoctadecanoic acid and hence to determine the configuration of the acid obtained from natural 9-hydroxyoctadec-12-enoic acid.

DISCUSSION

In this work 9D-hydroxyoctadecanoic acid (XIV) has been synthesised from (+)-methyl 5D-acetoxy-4-carboxybutanoate (X) via (-)-5D-hydroxydodecanoic acid (XIII).



(X) (XIII) (XIV)

Synthetic 9D-hydroxyoctadecanoic acid was found to possess no optical rotation, but the configuration of the natural acid is suggested on the basis of melting points.

The synthesis of 5D-hydroxydodecanoic acid adds another member to the list of laevo-rotatory β-hydroxyacids known to have the D-configuration.

(1) Literature Survey.

(a) 5-Hydroxydodecanoic Acid. Three syntheses of the dl-acid are reported, by Adickes and Andresen[10] (m.p. 70-70.5°), by Skogh[11] (m.p. 68.8 - 69.1°), and by Breusch[12] (m.p. 69°). 5D-Hydroxydodecanoic acid, m.p. 60 - 60.5°, $[\alpha]_D^{17}$ -16.1° ± .4 (Chloroform, C5, 11) has now been prepared.

(b) 9-Hydroxyoctadecanoic Acid.

(i) Synthetic. The dl-acid has been synthesised by Tomecko and Adams[15] (m.p. 74-75°), by Ames and Bowman[14] (m.p. 74°), by Bergström[15] (m.p. 75.4 - 75.9°), and by Cochrane and Harwood[16] (m.p. 76-77°).

(ii) From Natural Sources. dl-9-Hydroxyoctadecanoic acid has been isolated by Bergström[17] from, and identified by Sephton and Sutton[18] in, reduced linoleate hydroperoxides produced by catalytic autoxidation or lipoxidase oxidation of sodium or methyl linoleate.

(+)-9-Hydroxyoctadec-12-enoic acid, described by Gunstone[19,20] and isolated from Strophanthus sarmentosus seed oil, gives on reduction 9-hydroxyoctadecanoic acid, m.p. 81 - 82°, $[\alpha]_D$ + 0.4° in acetic acid.[20]

(+)-Methyl 9-Hydroxyoctadec-trans, trans-10,12-dienoate isolated from Dimorphotheca aurantiaca seed oil by Smith et al.,[21] has been reduced to give methyl 9-hydroxyoctadecanoate which they claim is optically active from its melting point (49 - 51°) and infra-red spectrum, though no rotation was measured.

The presence of a 9-hydroxyoctadec-10,12-dienoic acid with cis-trans conjugation is reported to occur in several seed oils by other workers,[22] but no mention is made of any associated optical activity.

9D-Hydroxyoctadecanoic acid, m.p. 83.5 - 84.5°, but with no measurable optical rotation has now been prepared.

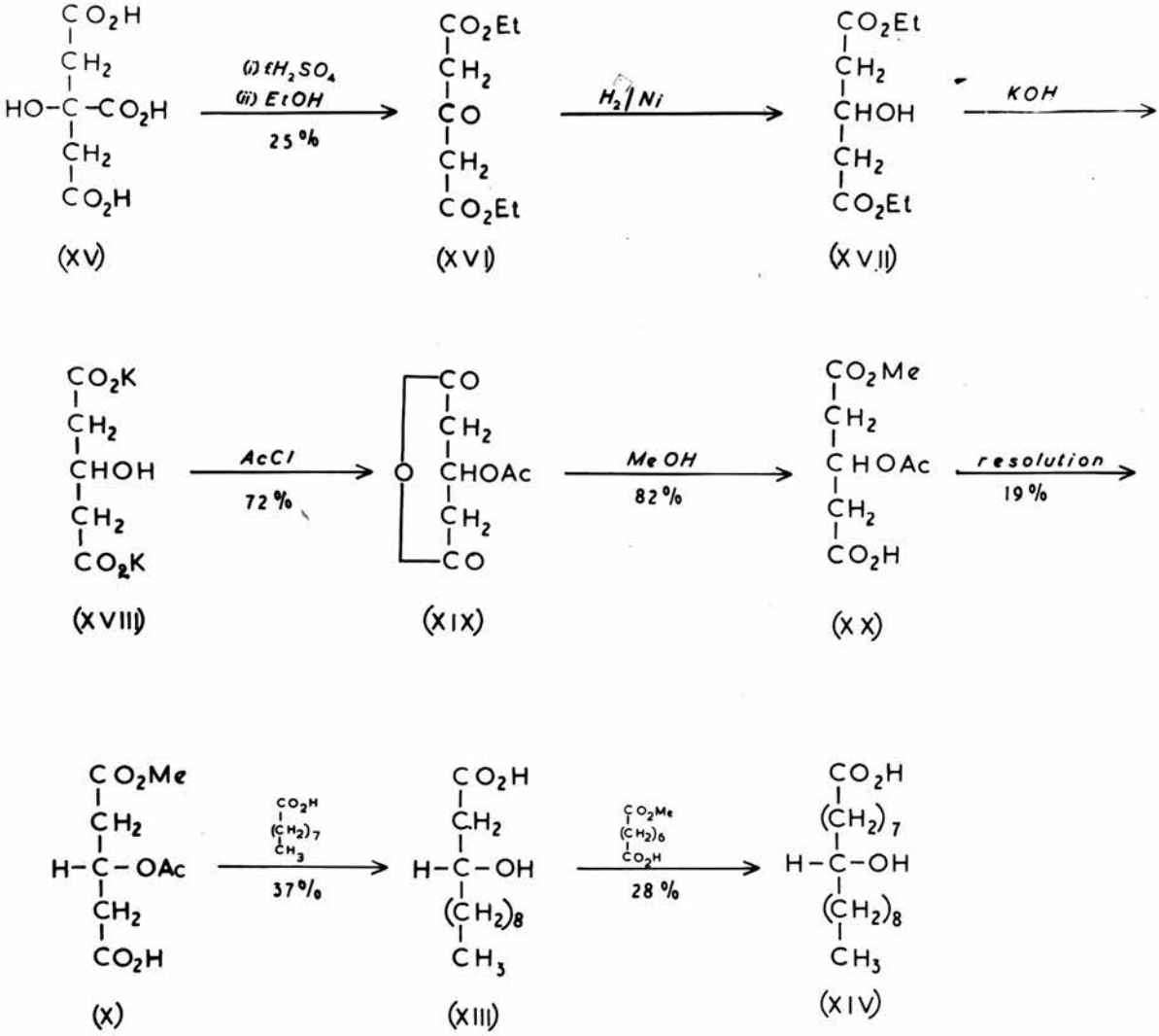

(i) EtH_2SO_4
(ii) EtOH
25 %
H_2/Ni
KOH
AcCl
72 %
MeOH
82 %
resolution
19 %
37 %
28 %
(XV)
(XVI)
(XVII)
(XVIII)
(XIX)
(XX)
(X)
(XIII)
(XIV)

Fig. I

(2) Synthesis of 9D-Hydroxyoctadecanoic Acid.

(a) Methyl Hydrogen β-Acetoxyglutarate. (XX).

Methyl hydrogen β-acetoxyglutarate (XX) was prepared from citric acid by the method of Serck-Hanssen.[7] Citric acid (XV) was dehydrated with oleum and esterified with ethanol to give diethyl β-oxoglutarate (XVI) as described by Baker.[23] This was reduced to diethyl β-hydroxyglutarate (XVII) with Raney nickel in ethanol, and the dipotassium salt (XVIII) was treated with acetyl chloride to give the acetoxy-anhydride (XIX) which with methanol gave racemic methyl hydrogen β-acetoxyglutarate (XX).

Serck-Hanssen reduced the keto-ester (XVI) with Raney nickel at 100° and 140 atm., but in this work the reaction was effected at room temperature and atmospheric pressure. The yields of crude β-acetoxyglutaric anhydride (XIX) were variable. Attempts at recrystallisation from various solvents on a larger scale proved uneconomic owing to loss of material.

The half-ester (XX) was prepared by esterification of the anhydride with a large excess of methanol at 35 - 40° overnight. Diester is only formed by this method if the anhydride has previously been recrystallised from acetyl chloride, when traces of hydrogen chloride are liable to be present.[24]

(b) Resolution of the Half-Ester.

The resolution of methyl hydrogen β-acetoxyglutarate to give the dextro-rotatory antipode ($[\alpha]_D^{17}$ + 6.14°, chloroform, C20, l 1) in

19% yield was achieved only with great perseverance. Equimolecular quantities of half-ester and cinchonidine were dissolved together in ethyl acetate, an equal amount of ether was added, and the salt was left to crystallise at 0° in a stoppered flask. Even after two weeks, however, no crystallisation took place.

Unsuccessful attempts were made to induce crystallisation by concentrating the solution, by increasing the proportion of ether, by seeding with crystals supplied by Serck-Hanssen, and by cooling in stages down to -70°.

Eventually, successful crystallisation was achieved using open beakers in place of the stoppered flasks used previously. It was then discovered that the salt is dimorphous, one form, m.p. 89°, being obtained at 0° as large needles, the other at room temperature, m.p. 138-9°, as small soft needles.

Although Serck-Hanssen reported the salt to have m.p. 89° the sample supplied by him had in fact m.p. 138-9°. This sample had been stored at room temperature for 2 years before use, during which time the change to the stable form may have taken place.

During one recrystallisation of the salt, the hot solution was disturbed whilst cooling to 0°, resulting in the simultaneous crystallisation of both forms, with the higher-melting predominating. On redissolving and cooling more carefully both forms again crystallised out, this time with the lower-melting predominating. This shows that the two forms are physically interconvertable and therefore are truly

dimorphous.

Melting points were taken on a Kofler block as they were diffuse in a capillary-tube. When heating of the lower melting form, m.p. 86-89°, was continued above its melting point, the higher melting form crystallised from the melt and subsequently melted at 137.5-139°.

The progress of the resolution was followed by measuring the rotation of the half-ester recovered from the mother-liquors. The rotation of the cinchonidine salt proved unreliable as a guide to this.

The resolved half-ester was not distilled before use in case of decomposition. The value of $[\alpha]_D^{17}$ + 6.14° compares favourably with those of Serck-Hanssen for the undistilled product $[\alpha]_D^{25}$ + 5.8°, and the distilled product $[\alpha]_D^{25}$ + 6.1° (all chloroform, C20, 11).

Serck-Hanssen indicates that because of evidence of decomposition in a second distillation, the rotation of the product after one distillation may not be a maximum. If these values are low because of the presence of impurities of a different species, then the rotations of products obtained from syntheses starting with them will not be affected, but if they are low because of the presence of a small amount of the antipode then the rotations of any products will be lowered by the same percentage.

(c) 5D-Hydroxydodecanoic Acid (XIII).

This was prepared by anodic coupling of (+)-methyl hydrogen β-acetoxyglutarate with nonanoic acid, followed by acid-catalysed de-acetylation and hydrolysis. The product, $[\alpha]_D^{17}$ - 16.1°

(chloroform, C5, 11) was obtained in 37% yield. A trial experiment using partly resolved laevo-rotatory half-ester recovered from the mother-liquors of the resolution gave partially active 3-hydroxy-dodecanoic acid $[\alpha]_D^{17}$ + 5.3°.

In both of these electrolyses, the electrolyte became black when the reaction was about three-quarters complete. The black particles were later identified as colloidal platinum. This had not previously been observed in these laboratories, nor has it been reported by any other worker.

The neutral biproduct of this electrolysis was shown by infra-red spectroscopy to be a hydrocarbon, but the retention volume relative to myristic acid by G.L.C. was found to be 0.69, whereas that expected for $C_{16}H_{34}$ is 0.107. The molecular weight of this hydrocarbon has not been determined.

(d) 9D-Hydroxyoctadecanoic Acid. (XIV).

This was synthesised by the anodic coupling of 5D-acetoxydodecanoic acid and methyl hydrogen suberate in 28% yield. The infra-red spectrum of the synthetic acid was identical to that of the natural acid.

The melting point of 83.5 - 84.5° could not be improved by repeated recrystallisation, though on one occasion a m.p. of 88.25 - 88.75° was observed. The acid may therefore possess dimorphous crystalline forms.

(5) Configuration of Natural 9-Hydroxyoctadecanoic Acid.

As Gunstone and Morris[20] give the rotation of natural 9-hydroxyoctadecanoic acid to be $[\alpha]_D$ + 0.4° (acetic acid, C 5.75, 12) it was hoped to determine the absolute configuration of the natural acid by comparison with the synthetic D-acid. However, under the same conditions (acetic acid, C4, 12) no measurable rotation was observed (i.e. $\alpha < 0.01°$) with the synthetic acid. With more concentrated solutions the acid crystallised whilst the polarimeter tube was equilibrating to room temperature.

Even a rotation of 0.01° would have made $[\alpha]_D$ 0.012°, considerably less than that reported. Since there is no reason to doubt the authenticity of the synthetic acid which was checked by G.L.C. and infra-red spectroscopy, as well as the circumstantial evidence of its synthesis, it seems reasonable to question the accuracy of the value reported for the natural acid.

A possible correlation of the natural and synthetic acids can be made from their melting points. The synthetic D-acid melts at 83.5 - 84.5°, the natural acid at 81 - 82°, and a mixture of these at 82.5 - 83.5°, whereas the dl-acid is reported to melt in the range 74 - 77°.[13-16] These values indicate that the synthetic acid has not racemised despite its zero rotation, and probably show the natural and synthetic acids to be identical. Had the L-acid been synthesised a mixed melting point with the natural acid might have been more informative.

It is of interest that optically active 12-hydroxyoctadecanoic acid from ricinoleic acid has the D-configuration,[9] whilst the 17-hydroxy acid from yeast fermentation products[25] has the L-configuration. There is no evidence about the configuration of 8-hydroxyoctadecanoic acid also available from natural sources.[26]

EXPERIMENTAL

Solutions were dried with anhydrous sodium sulphate. Melting points were determined on a Kofler block and are corrected.

Diethyl β-Oxoglutarate. (XVI)[23]

Oleum (200 ml., 25% SO_3) was added to citric acid (200 g.) in a 2 litre beaker with manual stirring. After 45 min. the solution was covered with benzene (400 ml.), cooled in an ice-bath and treated with ethanol (200 ml.) at such a rate that the temperature remained at 35-40° (ca 5 min.). The mixture was transferred to a round-bottom flask using a little ethanol as a rinse, stirred for 4 hr. protected from moisture, and poured on to ice and water (400 ml.). The organic layer was thoroughly washed with aqueous sodium bicarbonate, then with water, dried and evaporated. The residue was distilled on a ½ metre fractionating column to give diethyl β-oxoglutarate (48 g. 25%), b.p. 102 - 106°/ ca 1 mm. (lit.[23] b.p. 104°/1mm), $n_D^{18.5}$ 1.4442. The copper enolate, recrystallised from ethanol, had m.p. 142° (lit.[27] 142 - 5°).

Diethyl β-Hydroxyglutarate (XVII).

Diethyl β-oxoglutarate (10.0 g.) was reduced over Raney nickel (3 g.) in ethanol in the apparatus described on p. 45 part I. Absorption of hydrogen (1085 ml., equivalent to 0.99 mols.) ceased

after 1 hr. Removal of catalyst by centrifuge, and evaporation of solvent, gave an undistilled product $n_D^{12.5}$ 1.4412 (lit. n_D^{20} 1.4392,[7] 1.4381[28]).

Dipotassium β-Hydroxyglutarate (XVIII)[7]

A mixture of diethyl β-hydroxyglutarate (9.89 g.), potassium hydroxide (6.6 g.) and methanol (19.5 ml.) was distilled to dryness on a water-bath. Still on the water-bath, the crude yellow salt was dried under vacuum using first a water-pump and then an oil-pump, and the product was kept protected from moisture for use in the next stage without purification.

β-Acetoxyglutaric Anhydride (XIX)[7]

Acetyl chloride (92 ml., 1.29 moles) was added to dry crude dipotassium β-hydroxyglutarate (from diethyl β-hydroxyglutarate 46.4 g., 0.227 mole), both at 0°, the temperature was allowed to rise to 55° and was kept there for 1 hr. Excess acetyl chloride was distilled from a water-bath at 70°, the residue was extracted with hot chloroform and concentrated under vacuum. The crystalline anhydride (28.1 g., 72%) m.p. 76 - 80° (lit.[7] 86°) was obtained by diluting the chloroform concentrate with ether and cooling to 0°. Recrystallisation of a portion from ethyl acetate by addition of ether raised the m.p. to 82 - 84°, but the yield was poor and the crude product was generally used for the next stage.

Methyl Hydrogen β-Acetoxyglutarate. (XX)[7]

A solution of β-acetoxyglutaric anhydride (37.4 g.) in methanol (37 ml.) was kept at 35 - 40° overnight, excess methanol was then removed under vacuum, and the residue (n_D^{21} 1.4476) distilled twice to give methyl hydrogen β-acetoxyglutarate (44.7 g., 80%), b.p. 142 - 150° / 0.2 mm, n_D^{16} 1.4496 (lit.[7] b.p. 145 - 155°/0.5 mm, n_D^{22} 1.4470), equivalent weight 200 (theoretical 204). An infra-red spectrum as a liquid film gave peaks at the following wave-lengths: 5.75μ (s) ester c = o, 5.85μ (s) acid c = o, 6.96μ (m) and 7.30μ (m) C-CH_3, 8.1μ (s) acetate C-O, 9.66μ (s) 2° alcohol C-O (?), 10.7μ (w) acid O-H. In carbon tetrachloride the absorbance of the ester carbonyl peak was approximately twice that of the acid carbonyl.

(+)-Methyl Hydrogen β-Acetoxyglutarate [(+)-Methyl 5D-Acetoxy-4-carboxybutanoate]. (X).

A mixture of optically inactive methyl hydrogen β-acetoxyglutarate (30 g.) and cinchonidine (45 g.) in ethyl acetate (200 ml.) was refluxed until a clear solution was obtained. The solution was transferred to an open beaker and the salt crystallising at 0° was recrystallised five times from 3 parts of ethyl acetate to give the cinchonidine salt of the dextro-rotatory half-ester (15.75 g., 21%), m.p. 86 - 88° and 137.5 - 139° (lit.[7] 89°).

The resolution was followed by extracting the salt from the

mother-liquors with water (3x), acidifying with excess dil. hydrochloric acid, saturating with salt, and extracting the half-ester with ether (6x). The rotation of the recovered half-ester progressed from a -ve value, through zero to a maximum +ve value.

The resolved salt (15.75 g.) was dissolved in dil. hydrochloric acid, saturated with salt, and the half-ester extracted with ether (6x). The extracts were washed once with saturated brine, dried and evaporated to give undistilled (+)- methyl hydrogen β-acetoxy-glutarate (5.81 g., 90% from the salt, 10% from unresolved half-ester), n_D^{23} 1.4456, $[\alpha]_D^{17}$ + 6.14° ± .15 (chloroform, C20, 11; see p.64).

(-)-3D-Hydroxydodecanoic Acid. (XIII)

A solution of (+)-methyl hydrogen β-acetoxyglutarate (5.74 g., 1 mol.) and nonanoic acid (15.5 g., 5 mol.) in methanol (25 ml.) containing sodium (0.06 g.) was electrolysed (current 0.5 amp., faradays passed ca. 1.12 times theoretical) to pH 6-7. During the latter part of the electrolysis colloidal platinum was formed from the electrodes. The insoluble product was filtered off, the filtrate neutralised with a few drops of dil. hydrochloric acid, poured into water and extracted with ether. The extract, after washing with aqueous sodium carbonate, and with water, was dried and evaporated. The recovered acids (1.59 g.) were isolated by acidification of the alkaline washings and extractions with ether.

The neutral product, dissolved in methanol (250 ml.) containing

conc. hydrochloric acid (5 ml.), was concentrated to about 60 ml. by distillation at atmospheric pressure over ½ hr. This was repeated with two further portions of methanol (250 ml.) with 2.5 ml. and 0 ml. acid. The resulting solution was diluted with ether, washed with aqueous sodium bicarbonate, then with water and evaporated under vacuum to give a product (9.15 g.) containing methyl 3D-hydroxydodecanoate.

This product was hydrolysed by shaking with potassium hydroxide (2.5 g.) in aqueous methanol (100 ml., 1:1) overnight. The resulting solution was diluted with water, extracted with ether to remove neutral material (5.69 g.), acidified with dil. hydrochloric acid, and the acidic product (3.06 g.) extracted with ether. Two recrystallisations from petroleum ether (b.p. 40 - 60°) gave 3D-hydroxydodecanoic acid (2.25 g., 37%), m.p. 60 - 60.5°, $[\alpha]_D^{17}$ - 16.1° ± 0.4° (chloroform, C5, 11). G.L.C. showed it to be practically pure, and an infra-red spectrum contained peaks at 2.82μ (O-H) and 5.96μ (acid C=O).

9 12D-Hydroxyoctadecanoic Acid (XIV)

3D-Hydroxydodecanoic acid (2.10 g.) was refluxed with acetyl chloride (2 ml.) for 15 min., excess acetyl chloride was removed under vacuum, the residue shaken with a large excess of water at 100° for 5 min., and the 3D-acetoxydodecanoic acid was extracted with ether, dried and evaporated. An infra-red spectrum showed the presence of

ester and acid groups, and the absence of hydroxyl, acid halide, and anhydride groups.

A solution of the 5D-acetoxydodecanoic acid (ex. 2.10 g., 1 mol., hydroxy-acid) and methyl hydrogen suberate (5.5 g., 3 mol.) in methanol (20 ml.) containing sodium (0.02 g.) was electrolysed (0.75 amp., faradays passed ca. 1.28 times theoretical) to pH 6-7. The products were isolated as before (except that the ether extract was washed with sodium hydroxide instead of sodium carbonate) to give a neutral product (6.02 g.) and recovered acids (0.18 g.)

G.L.C. showed the neutral product to have two main components, the desired acetoxyoctadecanoic ester and tetradecanedioic ester. The latter was removed by the formation of its urea inclusion compound.[29] The mixed esters (6 g.) and urea (25 g.) were dissolved in hot methanol (150 ml.) and the solution was cooled to room temperature. The urea inclusion compound (white needles) was filtered off after 1 hr., decomposed by addition of water, and the esters were extracted with ether to give a product (2.07 g.) consisting (G.L.C.) mainly of tetradecanedioic ester. The filtrate was diluted with water and extracted with ether go give esters (3.70 g.) still containing some tetradecanedioic ester.

The procedure was repeated on the esters (3.70 g.) from the filtrate with urea (5 g.) and methanol (30 ml.) allowing crystallisation of the complex to proceed overnight. The filtrate yielded a product (2.91 g.) containing no tetradecanedioic acid, and the inclusion compound a mixture of both esters (0.67 g.)

A mixture of crude methyl 9D-acetoxyoctadecanoic acid (2.91 g.) and potassium hydroxide (2.0 g.) in aqueous methanol (64 ml., 1:1) was refluxed for ½ hr., cooled, and the neutral material (0.28 g.) extracted with chloroform. The acidic product (2.14 g.) was extracted with chloroform from the acidified alkaline solution, and recrystallised from petroleum ether (b.p. 80 - 100°) to give a solid (0.98 g.), m.p. 70 - 83°, and by evaporation of the mother-liquor a residue (1.11 g.), m.p. ca. 20°. The solid was recrystallised twice from petroleum ether (b.p. 80 - 100°), and then twice from aqueous methanol to give 9D-hydroxyoctadecanoic acid (0.82 g., 28%), m.p. 83.5 - 84.5° and mixed m.p. 82.5 - 83.5° with the natural acid (lit.[20] m.p. 81 - 82°). An infra-red spectrum in Nujol was identical with that of the natural acid. No measurable optical rotation was observed ($\alpha < 0.01°$; acetic acid, C4, 12; see p. 66).

BIBLIOGRAPHY TO PART II.

1. Fischer, Ber., 1891, 24, 2683.
   Hudson, Adv. Carbohydrate Chem., 1948, 3, 1.
2. Klyne, Chem. and Ind., 1951, 1022.
3. Bijvoet, Peerdeman, and van Bommel, Nature, 1951, 168, 271.
4. Linstead, Lunt, and Weedon, J. Chem. Soc., 1950, 3333.
5. Ställberg-Stenhagen, Arkiv Kemi, 1950, 2, 95.
6. Serck-Hanssen and Stenhagen, Acta Chem. Scand., 1955, 9, 866.
7. Serck-Hanssen, Arkiv Kemi, 1956, 10, 135.
8. Lemieux and Giguere, Canad. J. Chem., 1951, 29, 678.
9. Serck-Hanssen, Chem. and Ind., 1958, 1354.
10. Adickes and Andresen, Annalen, 1944, 555, 41.
11. Skogh, Acta Chem. Scand., 1952, 6, 809.
12. Breusch, Ber., 1954, 87, 1051.
13. Tomecko and Adams, J. Amer. Chem. Soc., 1927, 49, 522.
14. Ames and Bowman, J. Chem. Soc., 1951, 2752.
15. Bergström, Aulin-Erdtman, Rolander, Stenhagen, and Östling, Acta Chem. Scand., 1952, 6, 1157.
16. Cochrane and Harwood, J. Org. Chem., 1961, 26, 1278.
17. Bergström, Nature, 1945, 156, 717; Arkiv Kemi, Min.,Geol., 1945, 21A (14), 1; (15), 1.
18. Sephton and Sutton, J. Amer. Oil Chemists' Soc., 1956, 33, 263.
19. Gunstone, J. Chem. Soc., 1952, 1274; J. Sci. Food Agric., 1952, 3, 185; 1953, 4, 129.
20. Gunstone and Morris, J. Sci. Food Agric., 1959, 10, 522.
21. Smith, Wilson, Melvin, and Wolff, J. Amer. Chem. Soc., 1960, 82, 1417.
22. Chisholm and Hopkins, Canad. J. Chem., 1960, 38, 2500.
    Morris, Holman, and Fontell, J. Amer. Oil Chemists' Soc., 1960, 37, 323.
23. Baker, Schanb, Querry and Williams, J. Org. Chem., 1952, 17, 97.
24. Serck-Hanssen, private communication.

25. Goren, Spencer, and Tulloch, Canad. J. Chem.,1961, 39, 846.
26. Ligthelm, Chem. and Ind., 1954, 249.
27. Dünschmann and Pechmann, Annalen, 1891, 261, 176.
28. Lochte and Pickard, J. Amer. Chem. Soc., 1946, 68, 721.
29. Schlenk, Progr. Chem. Fats and Other Lipids, 1954, 2, 251.

* * *

APPENDIX TO PARTS I AND II.

DATA FROM GAS LIQUID CHROMATOGRAMS.

Values of retention volumes relative to myristic acid, $V_r(C_{14})$, were determined on Apiezon L columns at 200°. Those marked * were actually determined relative to the appropriate higher homologue, and the value relative to myristic acid found by calculation. Carbon numbers were found from a straight line plot of log $V_r(C_{14})$ against carbon number for the saturated acids.

Compound	$V_r(C_{14})$	C.no.
Hydrocarbons:		
hexacosane	0.190	10.1
hexacos-6,20-diyne	0.198	10.25
Halogen compounds:		
1-chloro-6-iodohexane	0.307	11.25
1,8-dibromo-octane	0.634	12.95
1-chlorotridec-7-yne	0.657	13.05
1-bromopentadec-9-yne	2.35	16.0
1-bromopentadecane	2.42	16.05
Unsaturated acids:		
tetradec-8-enoic acid	0.914	13.8
tetradec-8-ynoic acid	1.00	14.0
hexadec-10-enoic acid	2.15 *	15.8

Compound.	$V_r(C_{14})$	C.no.
hexadec-10-ynoic acid	2.34 *	16.0
octadec-12-enoic acid	4.95 *	17.75
octadec-12-ynoic acid	5.50 *	18.0
eicos-14-enoic acid	11.65 *	19.75
eicos-14-ynoic acid	12.90 *	20.0
Hydroxy-acids:		
3-hydroxydodecanoic acid	0.84	15.6
9-hydroxyoctadecanoic acid	11.6 *	19.8
9-acetoxyoctadecanoic acid	12.1 *	19.85

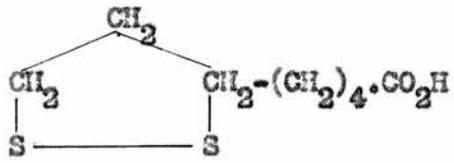
PART III

SYNTHETIC STUDIES ON

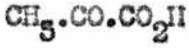
6,8-DIHYDROXYOCTANOIC ACID.

INTRODUCTION.

(1) 6,8-Thioctic Acid.

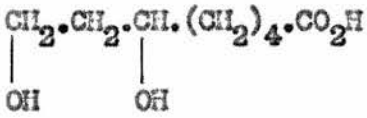


I

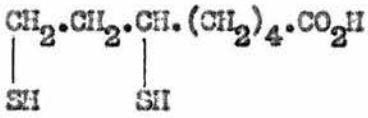


II

6,8-Thioctic acid or α-lipoic acid (I), first isolated from liver in 1951, has been shown to fulfil a number of important biological functions, including those of growth factor for certain bacteria, and of co-enzyme for the oxidative decarboxylation of pyruvic acid (II).[1]



III



IV

6,8-Dihydroxyoctanoic acid (III), the oxygen analogue of 6,8-dihydrothioctic acid (IV) was originally required for biological research elsewhere.

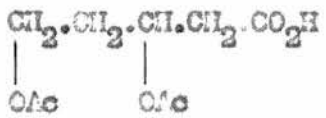
(2) 6,8-Dihydroxyoctanoic Acid.

6,8-Dihydroxyoctanoic acid[2] and its immediate derivatives such as the dihydroxy-ester,[3,4] the diacetoxy-ester,[5] the hydroxy-ϵ-lactone,[5] the acetoxy-ϵ-lactone,[6] the diphenoxy-acid,[7] and the methylenedioxy-

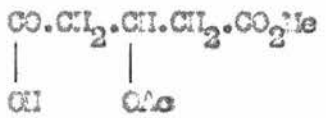
ester[8] have been prepared recently, often as intermediates in the synthesis of 6,8-thioctic acid which has been required for biological work.

In the present work two new routes to 6,8-dihydroxyoctanoic acid have been examined.

(a) Anodic Synthesis.



V

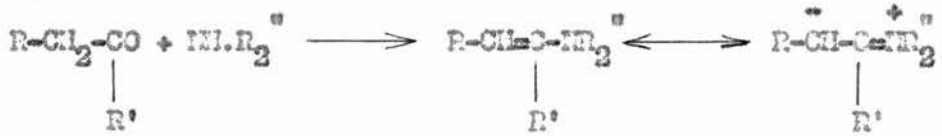


VI

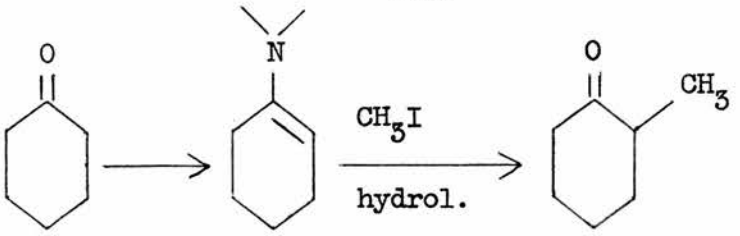
5,5-Diacetoxypentanoic acid (V) could be prepared from methyl hydrogen β-acetoxyglutarate (VI, see Part II) by reduction to the alcohol followed by acetylation, and this when submitted to anodic synthesis with methyl hydrogen glutarate should give methyl 6,8-diacetoxyoctanoate, easily convertible to the required acid.

(b) Enamine Synthesis.

(i) The General Method. The condensation of ketones and amines to give enamines has been known for some time.[9]



Stork and his colleagues[10] have developed a new method for the acylation and alkylation of ketones via the enamine. For example, the alkylation of cyclohexanone (VII) to give 2-methylcyclohexanone (VIII), previously a tedious preparation, can now be done in two stages.

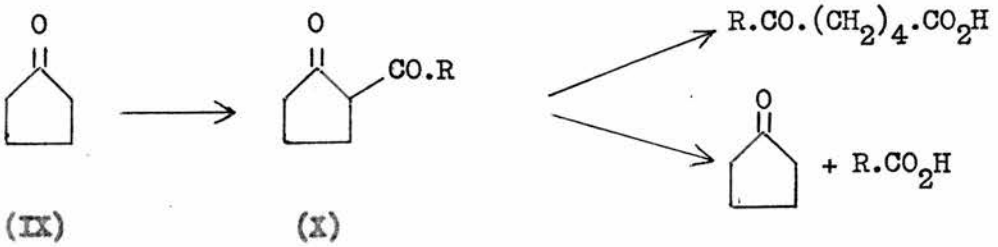


(VII) (VIII)

This general method has since been used by many workers with a variety of compounds, and is reviewed by Kuehne,[11] and by Dulon, Elkik and Veillard.[12]

(ii) Oxo-alkanoic Acids. This method has been applied by Hünig[13] to the synthesis of 7-keto-acids. Cyclohexanone-enamines treated with acid chlorides give 2-acylcyclohexanones, which are cleaved by alkali to give the corresponding 7-keto-acids.

Alkaline cleavage of acyl-cycloalkanones can take place in two different ways:



(IX) (X)

It has been shown[14] for 2-acetylcyclopentanone (X, R=CH_3) that the yield of keto-acid (85 - 90%) is even higher than that for 2-acetylcyclohexanone (60 - 64%). Acylation of the enamine of cyclopentanone (IX), followed by alkaline cleavage will therefore result in a 6-keto-acid.

Further, acylation with acetoxypropionylchlorides ($AcO.CH_2.CH_2.COCl$)

should give 8-acetoxy-6-oxo-octanoic acid, which could easily be converted to the required 6,8-dihydroxy acid. Experiments on this subject will be described.

When this work was nearing completion Hünig published a further paper in his series, describing the acylation of cyclopentanone-enamines with the acid chlorides of mono- and dibasic acids.[15] His findings were substantially the same as some of those described here.

On the publication by Yurugi, Fushimi, and Numata of a series of excellent papers on the synthesis of α-lipoic acid, the first four[16] of which describe the preparation of 6,8-dihydroxyoctanoic acid and some oxygen derivatives, by the acylation of cyclopentanone-enamines with alkoxy-propionyl chlorides, the work described here was discontinued.

DISCUSSION.

Two attempts to synthesise 6,8-dihydroxyoctanoic acid from methyl hydrogen β-acetoxyglutarate and from cyclopentanone are now described.

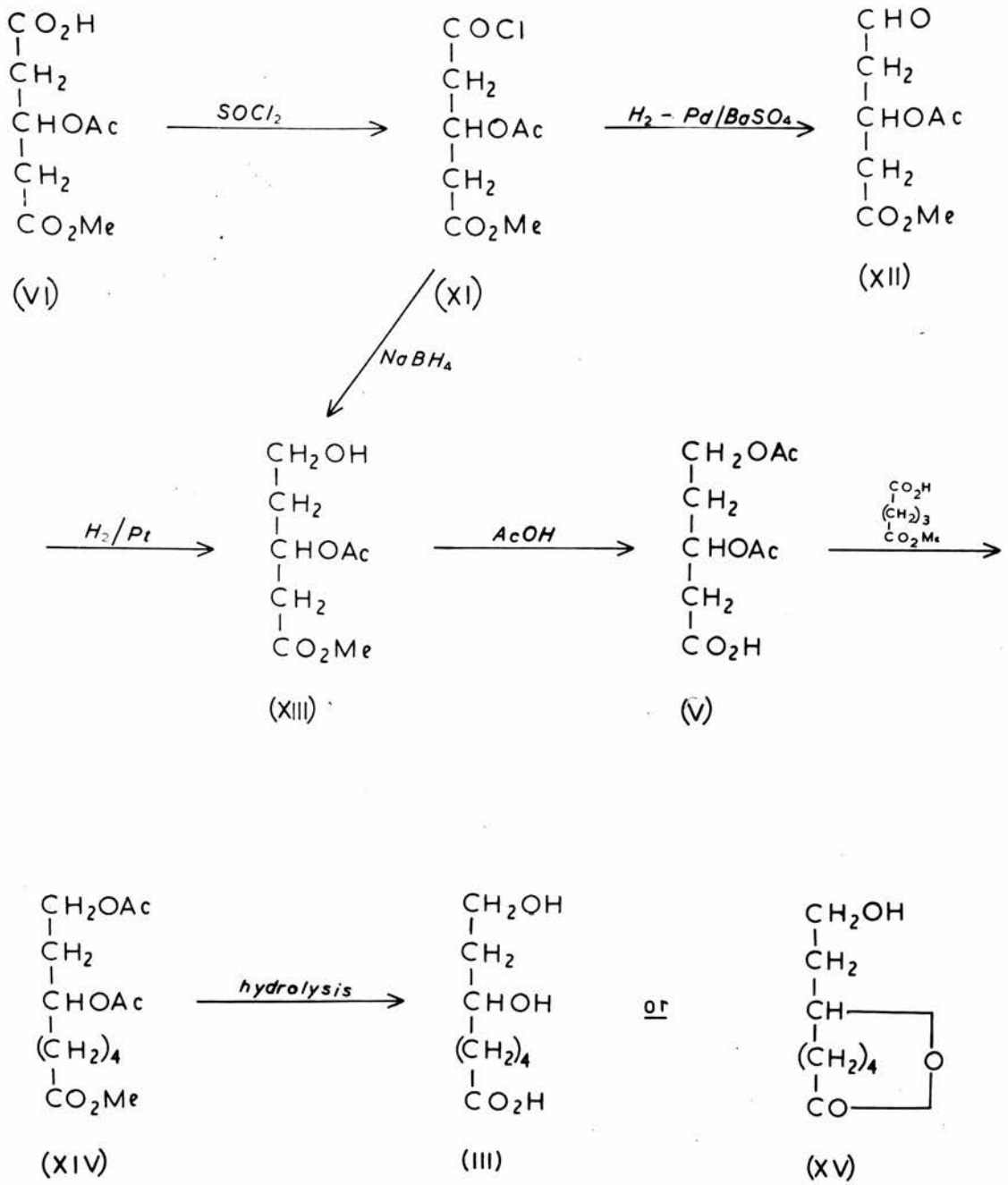

CO2H
CH2
CHOAc
CH2
CO2Me
(VI)
SOCl2
COCl
CH2
CHOAc
CH2
CO2Me
(XI)
H2 - Pd/BaSO4
CHO
CH2
CHOAc
CH2
CO2Me
(XII)
NaBH4
H2/Pt
CH2OH
CH2
CHOAc
CH2
CO2Me
(XIII)
AcOH
CH2OAc
CH2
CHOAc
CH2
CO2H
(V)
CO2H
(CH2)3
CO2Me
CH2OAc
CH2
CHOAc
(CH2)4
CO2Me
(XIV)
hydrolysis
CH2OH
CH2
CHOH
(CH2)4
CO2H
(III)
or
CH2OH
CH2
CH
(CH2)4
O
CO
(XV)

Fig. 1

(1) Synthesis from Methyl Hydrogen β-Acetoxyglutarate.

It was first proposed to prepare 6,8-dihydroxyoctanoic acid (III) by the scheme shown in fig. 1. Treatment of methyl hydrogen β-acetoxyglutarate (VI) with thionyl chloride should yield the acid chloride (XI), which could then be reduced to the alcohol, methyl 5-acetoxy-5-hydroxypentanoate (XIII) either directly with sodium borohydride[17] or by Rosenmund reduction[18] to the aldehyde (XII) followed by reduction with Adam's catalyst.[19] Catalysed acidolysis of the alcohol with acetic acid should give 5,5-diacetoxypentanoic acid(V) which could then be coupled with methyl hydrogen glutarate by anodic synthesis to give methyl 6,8-diacetoxyoctanoate (XIV), hydrolysable to 6,8-dihydroxyoctanoic acid (III), or the ε-lactone (XV).

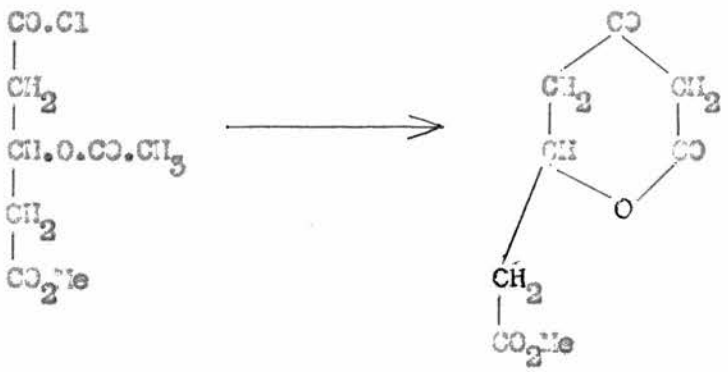
However, this reaction scheme had eventually to be abandoned because unexpected products, which proved difficult to characterise, were obtained in each stage up to the alcohol (XIII). This was perhaps due to the number of reactive methylene groups in the half-ester and its derivatives, making intramolecular condensation and polymerisation liable to occur. Brief descriptions of attempts to reach the diacetoxy-acid (V) are given, but no experimental details of this work are included.

(a) 5-Acetoxy-4-carbomethoxybutyryl chloride (XI).

Several attempts to purify, by distillation, the crude acid chloride obtained by treatment of the half-ester (VI) with thionyl

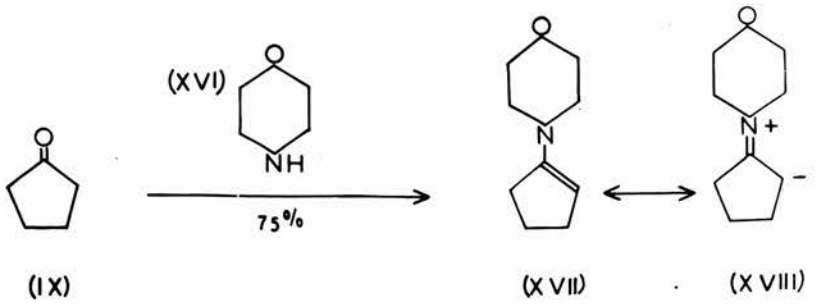
chloride under various conditions, and once with phosphorus pentachloride, were largely unsuccessful

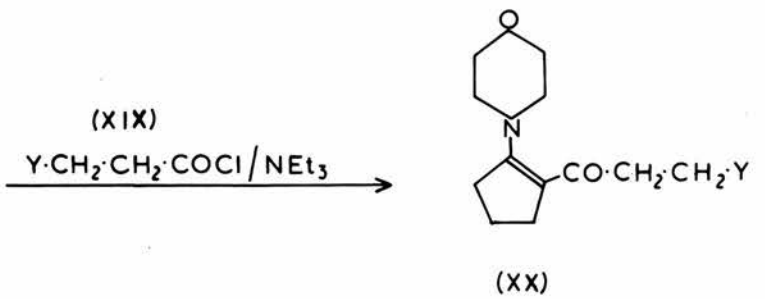
The first distillation gave a product (24%) whose infra-red spectrum contained the desired acid halide absorption peak at 5.55μ with a residue which was probably polymeric. Other distillations resulted in products whose infra-red spectra contained no acid halide peak, and in large polymeric residues. The volatile products from these distillations showed unidentified peaks at 6.05, 6.15, and 6.52μ, perhaps caused by intramolecular condensations such as:

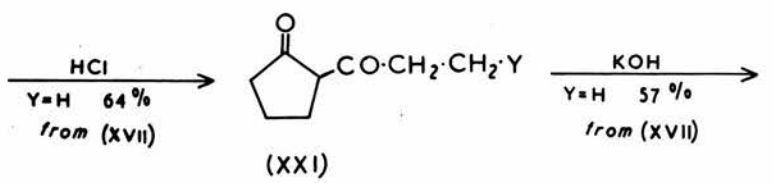


(b) Reduction with Sodium Borohydride.

A trial reduction of the acid chloride of methyl hydrogen succinate gave butyrolactone in 25% yield. Two unsuccessful attempts were made to reduce the crude acid chloride of methyl hydrogen β-acetoxy-glutarate by the same method. The neutral product from the second of these was subjected to acidolysis in acetic acid using p-toluene-sulphonic acid and conc. sulphuric acid as catalysts, but the products could not be characterised.


(XVI)
NH
75%
N
N+
(IX)
(XVII)
(XVIII)


(XIX)
Y·CH2·CH2·COCl / NEt3
N
CO·CH2·CH2·Y
(XX)


HCl
Y=H 64%
from (XVII)
CO·CH2·CH2·Y
(XXI)
KOH
Y=H 57%
from (XVII)

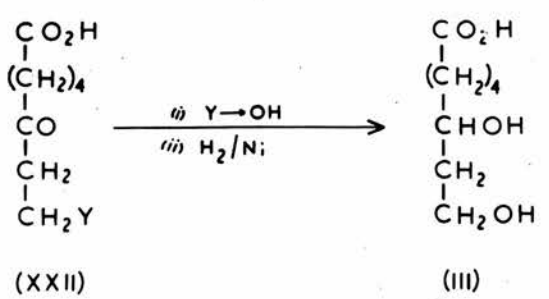

CO2H
(CH2)4
CO
CH2
CH2Y
(ii) Y→OH
(iii) H2/Ni
CO2H
(CH2)4
CHOH
CH2
CH2OH
(XXII)
(III)

Fig. 2

(c) Rosenmund Reduction.

Attempts at reduction of the crude acid chloride of methyl hydrogen glutarate in xylene by this method failed, probably because the acid chloride needs to be pure. When distilled β-naphthoyl chloride was used, β-naphthaldehyde was obtained in 56% yield.

The distilled acid chloride of methyl hydrogen β-acetoxyglutarate produced the required amount of hydrogen chloride in a Rosenmund reduction and gave on distillation a product (22%) whose infra-red spectrum contained an acid/aldehyde absorption peak at 5.38 μ. However, a 2,4-dinitrophenylhydrazone of the product could not be obtained with Brady's reagent, nor could it be reduced with Adam's catalyst under conditions which proved successful for the reduction of n-butyraldehyde.

(2) Synthesis from Cyclopentanone.

This was based upon the method used by Hünig[13] for the preparation of 7-keto-acids from cyclohexanone (see p.82). By using cyclopentanone 6-keto-acids should be produced on cleavage of the corresponding β-diketone.

Condensation of cyclopentanone (IX) with morpholine (XVI) gives the enamine (XVII). This is activated at the 2-position, so that acylation with the acid chloride (XIX) will give the 2-acyl-enamine (XX), which on acid hydrolysis gives the β-diketone (XXI). Alkaline hydrolysis results in ring cleavage to give the 6-keto-acid (XXII).

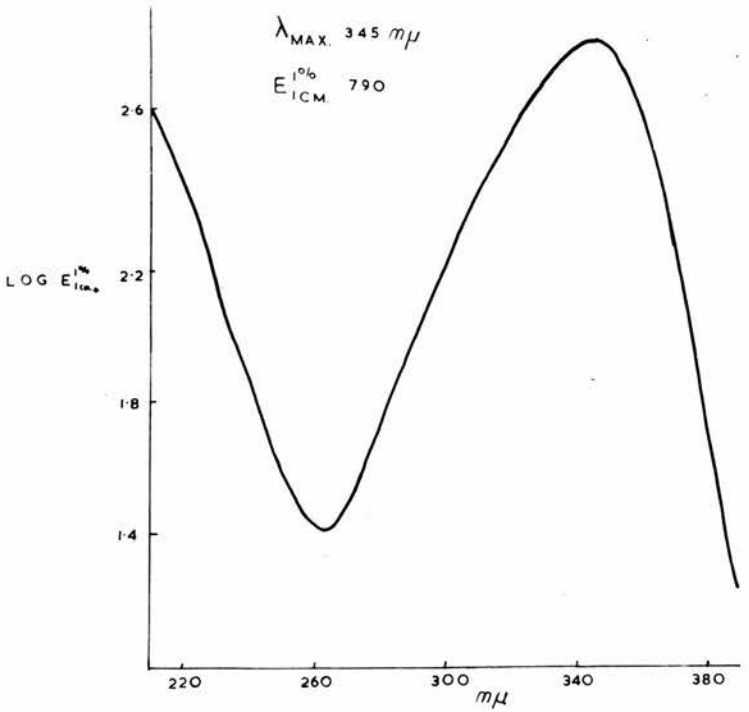
Replacement of the group 'Y' by hydroxyl, and reduction of the keto-group to a secondary alcohol should then give the required 6,8-dihydroxyoctanoic acid (III).

It is well known that there are great differences in the rates of reactions involvingthe cyclopentane and cyclohexane ring systems.[20] For this reason, the optimum conditions of reaction in the scheme above were first determined for the synthesis of 6-oxo-octanoic acid (XXII, Y = H) from the morpholine-enamine of cyclopentanone (XVII) and propinyl chloride (XIX, Y = H).

It was found that much milder conditions were sufficient to carry out this reaction sequence than those used by Hünig for 7-keto-acids from cyclohexanone. A further paper by Hünig describing the preparation of 6-keto-acids from cyclopentanone[15] was published after this work was completed. The conditions described in the later paper were less vigorous than those originally used, but were still not so mild as in this work, though the yields were similar.

(a) Synthesis of 6-oxo-octanoic Acid. (XXII, Y=H).

1-morpholino-1-cyclopentene (XVII) was prepared by refluxing morpholine (XVI) with cyclopentanone (IX) in toluene with p-toluene sulphonic acid as a catalyst in 76% yield. Propanyl chloride was added to a solution of the enamine (XVII) and triethylamine in chloroform at 55° and the ultra-violet absorption curves were plotted for samples removed at intervals. This showed that the reaction is complete as soon as the addition of the acid chloride is over (15 mins). Fig. 5 shows

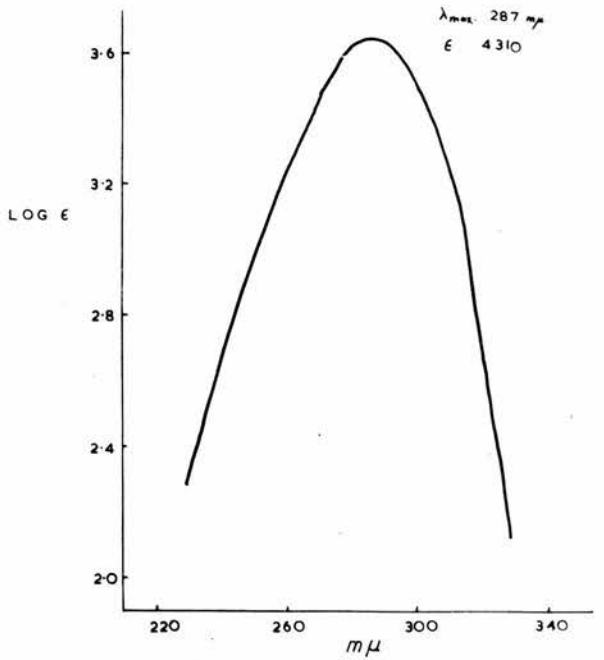


ULTRA-VIOLET SPECTRUM IN METHANOL OF

THE MORPHOLINE ENAMINE OF 2-PROPIONYLCYCLOPENTANONE

(XX, Y=H)

FIG. 3



ULTRA-VIOLET SPECTRUM IN METHANOL OF

2-PROPIONYLCYCLOPENTANONE

(XXI, Y=H)

FIG. 4

the Ultra-violet spectrum for the acyl-enamine (XX, Y=H) in methanol, λ_{max} 345 mμ, $E^{1}_{1\ cm}$ 799 (calculated from concentration of cyclopentanone-enamine).

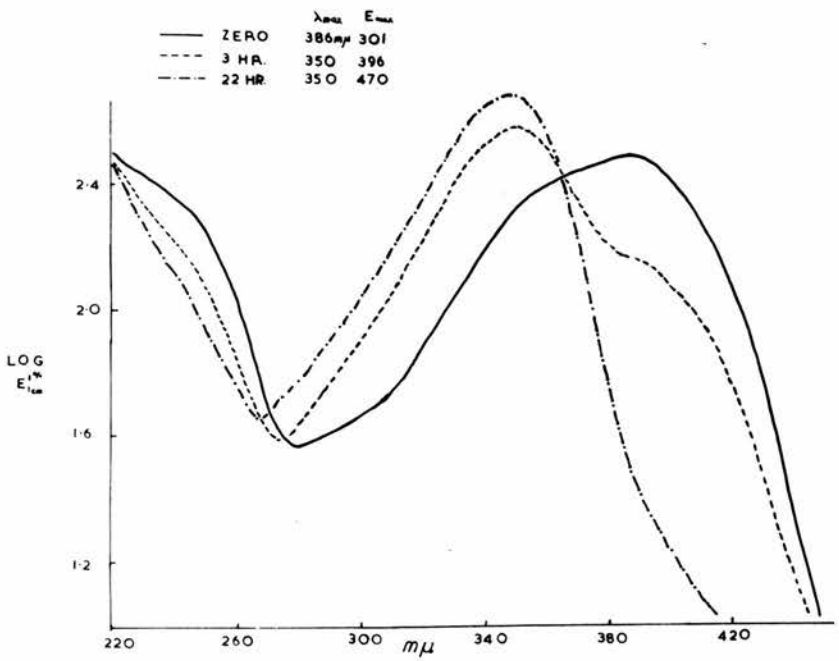
If the acylation of 1-morpholino-1-cyclopentene (XVII) proceeds via the canonical form (XVIII), then the experimental findings are in agreement with the fact that an exocyclic double bond is more stable in cyclopentanone than in cyclohexanone.

Similarly, it was expected that the acyl-enamine (XX, Y=H) could be readily hydrolysed to 2-propionylcyclopentanone (XXI, Y=H). A preliminary experiment showed that 1-morpholino-1-cyclopentene (XVII) gave the 2,4-dinitrophenylhydrazone of cyclopentanone immediately with Brady's reagent[21] in the cold. Vigorous stirring of the chloroform solution of the acyl-enamine (XX, Y=H) with dilute hydrochloric acid for 15 mins. was sufficient to hydrolyse it to the β-diketone (XXI, Y=H). Fig. 4 shows the ultra-violet absorption curve of the distilled diketone, λ_{max} 287 mμ, ε 4310

The β-diketone (XXI, Y=H) was cleaved to give 6-oxo-octanoic acid by refluxing with a 5% aqueous potassium carbonate solution. No increase in the yield of crude product (90%) was obtained by extending the reaction time beyond 1 hr. The overall yield from cyclopentanone was 42.5%.

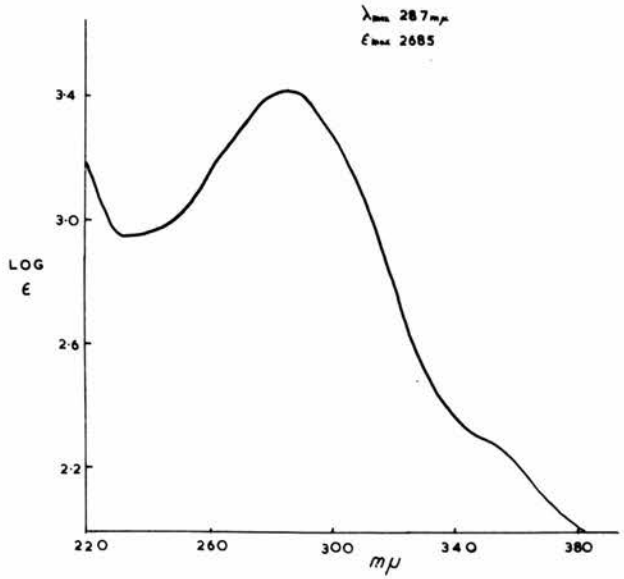
(b) Attempted Synthesis of 8-Hydroxy-6-oxo-octanoic Acid (XXII, Y=OH).

The acylation of 1-morpholino-1-cyclopentene (XVII) with β-acetoxypropionyl chloride (XIX, Y = AcO), prepared from



ULTRA-VIOLET SPECTRUM IN METHANOL OF THE ACYL-ENAMINE (XX, Y=$CH_3CO·O$-)

FIG. 5



ULTRA-VIOLET SPECTRUM IN METHANOL OF THE ACETOXY-β-DIKETONE (XXI, Y=CH_3COO-)

FIG. 6

β-propiolactone and acetyl chloride as described by Cresham, Jansen, and Shaver,[22] was first carried out using the conditions described above. However, distillation of the crude product resulted in a large amount of polymeric residue (40%) and gave distillates with unsatisfactory ultra-violet spectra.

This reaction was therefore also followed by means of the ultra-violet spectra of samples withdrawn at intervals from experiments conducted at different temperatures. Values of $E^{1\%}_{1cm}$ were calculated from the original concentration of cyclopentanone-enamine.

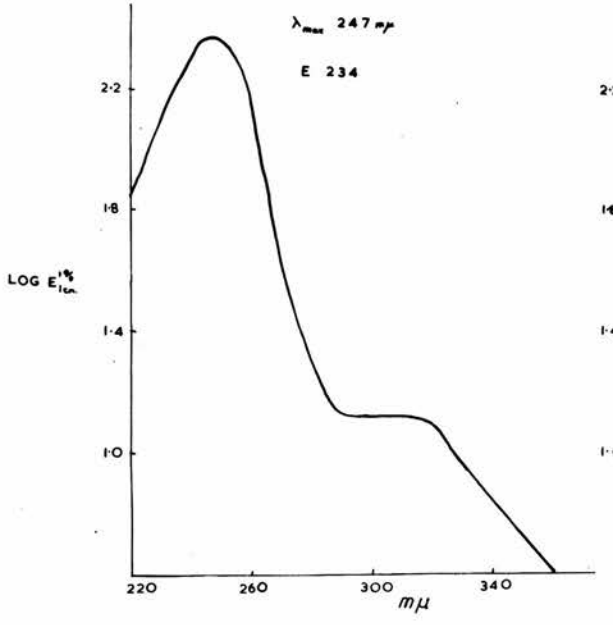
(i) 2-(3-Acetoxypropionyl)-1-morpholino-1-cyclopentene (XX, Y=AcO).

An initial maximum at 306 mμ gradually disappeared and was replaced by the expected absorption peak for the acyl-enamine at 350 mμ. The course of the reaction was followed at room temperature, 35°, and reflux temperature (61°). Fig. 5 shows some of the spectra obtained at 35°. The best reaction time was found to be 24 hr. at 35°.

The effect of varying the proportions of acid chloride and of triethylamine, and of replacing triethylamine with pyridine was also studied. These changes led to no improvement in the reaction.

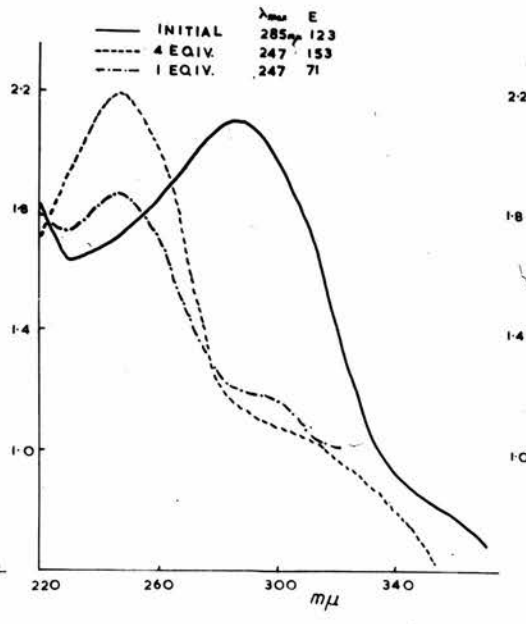
(ii) 2-(3-Acetoxypropionyl)cyclopentanone (XXI, Y = AcO)

In order to have conditions as mild as possible, the acyl-enamine (XX, Y = AcO) was hydrolysed by refluxing its chloroform solution with an equal volume of water, the reaction being followed, as before, by measurement of the ultra-violet spectra of samples withdrawn at intervals. The optimum reaction time was found to be 1-2 hrs. The β-diketone



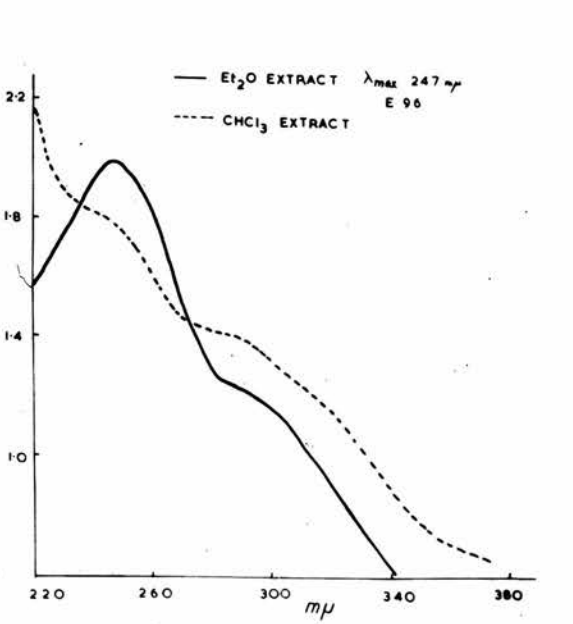
4 EQUIVALENTS KOH CRUDE PRODUCT

FIG. 7



INITIAL & FINAL SPECTRA OF REACTION MIXTURE WITH 1 & 4 EQUIVALENTS KOH

FIG. 8



1 EQUIVALENT KOH CRUDE PRODUCTS

FIG. 9

ULTRA-VIOLET SPECTRA FOR THE ALKALINE CLEAVAGE OF 2-(3-ACETOXYPROPIONYL)-CYCLOPENTANONE (XXI, Y=CH_3COO-)
(ALL IN METHANOL)

(XXI, Y = AcO) was isolated by adding hydrochloric acid to the cold solution and extracting as before. The crude diketone had a satisfactory ultra-violet spectrum, maximum at 287mμ (fig. 6), and an infra-red spectrum contained the expected absorption peaks.

Attempts to purify the product by distillation at 0.05 mm., or by steam-distillation, and to characterise it by formation of the pyrazole were all unsuccessful. Cleavage experiments were therefore performed with the crude product.

(iii) 8-Hydroxy-6-oxo-octanoic Acid. (XXII, Y = OH).

Cleavage of the β-diketone (XXI, Y = AcO) should give the 6-keto-acid

$$RO.CH_2.CH_2.CO.(CH_2)_4.CO_2H$$

where R- will be either H- or $CH_3.CO$- depending upon the conditions used. In either case the system $-CO.CH_2.CH_2.OR$ contains an isolated carbonyl chromophore, and so should possess no strong absorption above 200mμ.

However, experiments on the cleavage of the diketone with 4 equivalents of $\frac{N}{2}$ potassium hydroxide and of $\frac{N}{2}$ potassium carbonate (Eq. wt. 140) showed that although the β-diketone absorption peak at 285mμ decreased with time, a second peak at 247mμ appeared and increased to a maximum value. Fig. 7 shows the ultra-violet spectrum of the crude product.* The preparation of the semicarbazone yielded an unsatisfactory product.

* At this point no further infra-red spectra could be obtained owing to the breakdown of the infra-red spectrophotometer.

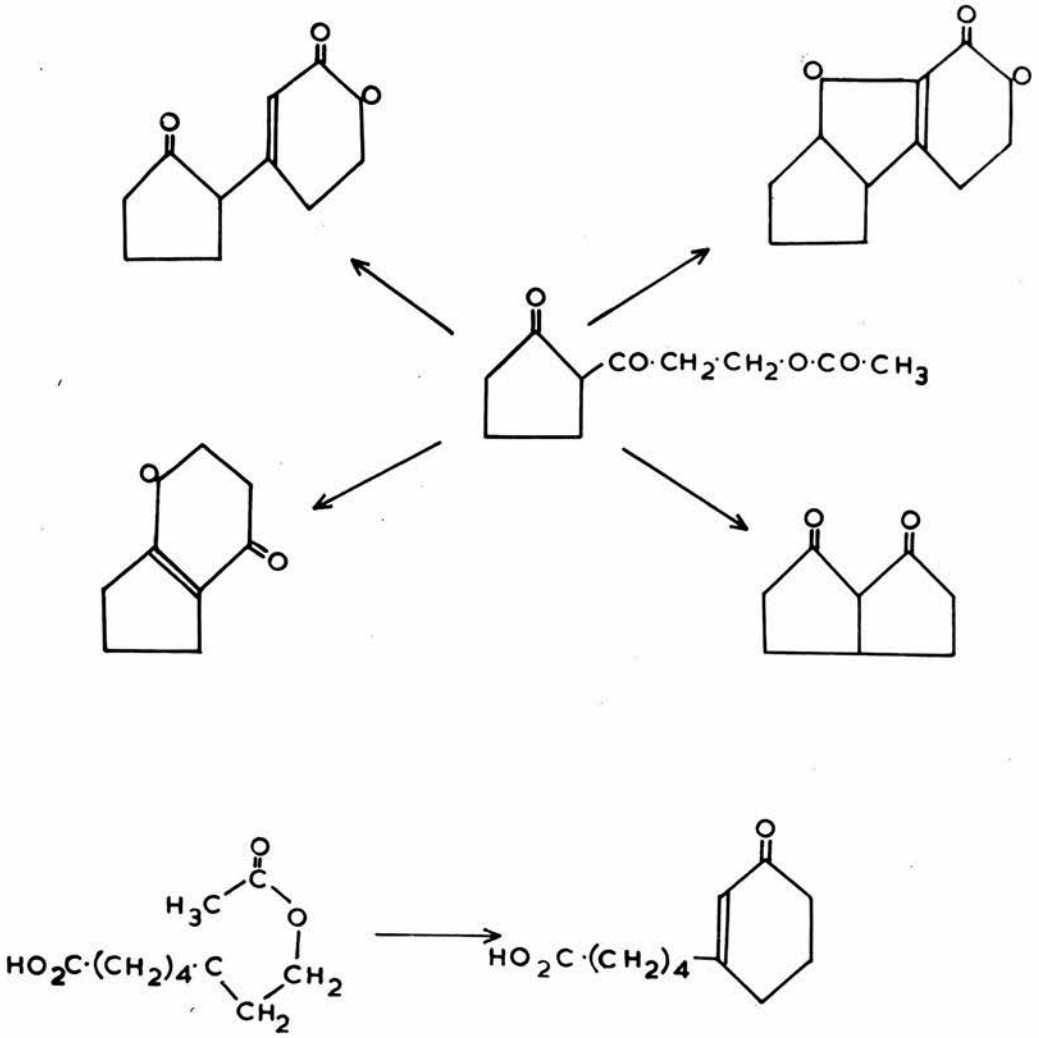
It is possible that the absorption maximum at 247mμ is caused by intra- or intermolecular condensation. Experiments were therefore conducted to determine the optimum conditions for the maximum fall of the β-diketone peak at 285mμ coupled with the minimum rise of the peak at 247mμ. Aqueous solutions of potassium hydroxide, potassium carbonate, potassium bicarbonate, and sodium acetate were tried with various equivalent amounts, concentrations, reactions times and temperatures. Of these one equivalent of $\frac{N}{2}$ potassium hydroxide for ½ hr. at reflux temperature (100°) proved to be the best, closely followed by four equivalents of $\frac{N}{2}$ potassium carbonate for 2 - 5 min. at 100°. Fig. 8 shows the initial and final spectra in the hydrolysis with 1 and with 4 equivalents of $\frac{N}{2}$ potassium hydroxide for ½ hr. at 100°.

Extraction of the acidified hydrolysate, obtained with 1 equivalent of potassium hydroxide, first with ether then with chloroform gave two products (which may not be homogeneous in themselves) with ultra-violet spectra shown in fig. 9.

The crude β-diketone (XXI, Y = AcO) was shown by gas liquid chromatography to contain 5 main components. However, since the chromatogram was run at 150° these may have been produced by thermal reactions on the column. Attempted purification of the crude diketone by absorption chromatography on activated silica gel was unsuccessful.

(iv) Acylation with other Acid Chlorides.

At this point, acylation of the enamine (XVII) with β-acetoxy-



SOME POSSIBLE INTRAMOLECULAR CONDENSATIONS

FIG. 10

propionyl chloride was discontinued. The trouble experienced may have been caused by intramolecular condensation and polymerisation of the acetoxy-derivatives. Possible examples of intramolecular condensation are shown in fig. 10.

Replacement of the acetoxy-group by another containing no active methylene group should perhaps overcome this difficulty. 3-Chloropropionyl chloride was first tried by Fabry.[23] Acylation of the cyclopentanone-enamine (XVII) gave crude 2-(3-chloropropionyl)cyclopentanone (XXI, Y = Cl) with a strong ultra-violet absorption band at 281mμ. However, both distillation and cleavage of the crude product led to polymeric products, probably owing to elimination of hydrogen chloride.

It was next proposed to acylate the enamine with 3-benzoyloxypropionyl chloride ($C_6H_5.CO.O.CH_2.CH_2.CO.Cl$), but attempts to prepare this compound from β- propiolactone and benzoyl chloride by the method used for the preparation of 3-acetoxypropionyl chloride were unsuccessful, possibly owing to the difference between the reactions of β-propiolactone with aliphatic and aromatic compounds, e.g. with alcohols and phenols.[24,25]

3-Methoxypropionic acid ($CH_3O.CH_2.CH_2.CO_2H$) can be prepared by treating β-propiolactone with methanol.[25] This could then be easily converted to the acid chloride with thionyl chloride. Acylation of 1-morpholino-1-cyclopentene (XVII) with 3-methoxypropionyl chloride should give the 3-methoxypropionyl derivatives of the intermediates

(XX), (XXI) and (XXII) where Y = MeO-. However, before this scheme could be put into operation a series of papers by Yuruçi, Fushimi and Kumata[16] were published, describing in great detail the synthesis of 6,8-dihydroxyoctanoic acid by this method. These synthetic studies were therefore discontinued.

EXPERIMENTAL.

Solutions were dried with anhydrous sodium sulphate. Melting points were determined in a capillary-tube and oil-bath, and are uncorrected.

In the experiments followed by ultra-violet spectra tables are given containing the values of $E^{1\%}_{1cm}$. These were determined by withdrawing a sample from the reaction vessel and making up to a known volume in methanol. The values are based upon the original concentration of starting material, either 1-morpholino-1-cyclopentene or 2-(3-acetoxypropionyl) cyclopentanone resp. and have a limited accuracy.

Propionyl Chloride. This was prepared according to the method of Brown.[26] A mixture of propionic acid (74 g.) and benzoyl chloride (210 g.) in a flask with a 25 cm. fractionating column was heated strongly until it began to boil. Propionyl chloride was then distilled out of the reaction mixture at such a rate that the temperature of the top of the column did not exceed the b.p. of the acid chloride. The distillate was redistilled to give propionylchloride (75.5 g., 83%), b.p. 80° , n_D^{18} 1.4054, (lit.[27] b.p. 80°, n_D^{20} 1.4051).

β-Acetoxypropionyl Chloride. (XIX, Y = AcO). This was prepared as described by Gresham, Jansen, and Shaver.[22] β-Propiolactone (72 g.)

was added dropwise to a stirred solution of sulphuric acid (0.1 g.) in acetyl chloride (234 g.) at such a rate (30 min.) as to maintain reflux. After standing for 4 hr. the excess acetyl chloride was distilled at atmospheric pressure, and the residue was fractionated to give β-acetoxypropionyl chloride (62.3 g., 42%), b.p. 85°/16 mm., n_D^{17} 1.4384 (lit.[22] b.p. 79-80°/12 mm, n_D^{20} 1.4365).

1-Morpholino-1-cyclopentene. (XVII). A solution of cyclopentanone (42 g.), morpholine (48 g.), and p-toluene sulphonic acid (80 mg.) in toluene (100 ml.) was refluxed for 4 hr. in a flask fitted with a condenser and water separator. Most of the water had distilled over after 1½ hr. The toluene was removed under reduced pressure and the residue distilled to give 1-morpholino-1-cyclopentanone (57.4 g., 75%), b.p. 105 - 106°/14 mm., n_D^{19} 1.5104 (lit.[28] b.p. 97°/7.5 mm., $n_D^{16.5}$ 1.5098). The enamine rapidly turned yellow in air, and the refractive index dropped.

2-Propionyl-cyclopentanone (XXI, Y = H). Propionyl chloride (10.2 g.) in dry chloroform (50 ml.) was added over ¼ hr. with stirring to a solution of 1-morpholino-1-cyclopentene (15.5 g.) and triethylamine (distilled over sodium, 12.1 g.) in dry chloroform (120 ml.) at 55°. After a further ¼ hr. hydrochloric acid (50 ml., 20%) was added, and the two phase mixture was vigorously stirred for ½ hr., still at 55°.

The separated chloroform layer was washed with water (6 X) until the washings had a pH 5-6. The water layer together with the aqueous

washings were neutralised to pH 5-6 with dilute sodium hydroxide and extracted with chloroform (5 X), the extracts being washed once with water. The combined chloroform solutions were dried, evaporated and the residue was distilled to give 2-propionylcyclopentanone (8.93 g., 64%), b.p. 96-8°/15 mm. n_D^{21} 1.4906, U.V. spectrum (fig. 4), λ_{max} 287mμ, ε 4310 in methanol. (lit. b.p. 90°/15 mm.,[29] n_D^{15} 1.4936 [30] λ_{max} 284mμ, ε 6450 in n-hexane.)[15] The ferric chloride test in methanol gave a wine-red colour. Treatment with hydrazine hydrate gave the pyrazole, m.p. 119.5 - 120.5° (lit.[29] 119°), recrystallised from petroleum ether (b.p. 40 - 60°).

In a preliminary experiment the formation of the acyl-enamine was followed by means of the ultra-violet spectra of samples withdrawn at intervals (see p. 88 , and fig. 5). The values of $E^{1\%}_{1\,cm}$ at the absorption peak were:

Time (hrs.)	$E^{1\%}_{1\,cm}$ (345mμ)
¼	700
1¼	572
7	705
20	660

6-Oxo-octanoic Acid. (XXII, Y = H). A solution of crude 2-propionylcyclopentene (ex. 15.3 g. enamine) in aqueous potassium carbonate (420 ml., 5%) was refluxed for 2½ hr. The cooled solution was extracted with ether to remove neutral material, acidified with hydrochloric acid, and the acid product extracted with ether. The

ethereal solution was dried and evaporated to give crude 6-oxo-octanoic acid (10.67 g., 67.5%), m.p. 51 - 53°, (lit. 52° [51,52] 54° [53]). The crude product recrystallised from petroleum ether (b.p. 40-60°) gave the following fraction (57.5% ex. enamine):

Fr.	wt.	M.P.
1	4.11 g.	52.5 - 53.5°
2	3.50 g.	52 - 53°
3	1.20 g.	51 - 52°
4	0.10 g.	49 - 52°

Micro-analysis, found: C, 60.2; H, 9.0. Calc. for $C_8H_{14}O_3$: C, 60.7; H, 8.0%. Equivalent weight 159.7 (calc. 158.2). Semicarbazone m.p. 134 - 135° (lit. 100 - 7°, [52] 100° [54]) and 2,4-dinitrophenylhydrazone m.p. 134-135° (lit. [53] 96-97°), micro-analysis found: C, 49.4; H, 5.3; N, 13.8. $C_{14}H_{18}N_4O_6$ requires: C, 49.7; H, 5.3; N, 16.6%.

Preliminary experiments on the cleavage of the β-diketone with 5% aqueous potassium carbonate under reflux gave the following yields of keto-acid (See p. 89).

Time (hr.)	% yield.	M.P.
½	76	52 - 54° *
1	88	48 - 50°
2	82	48 - 51°
3	94	51 - 53° *
3½	92	47 - 49°

* Ether solutions of keto-acid dried before evaporation

2-(3-Acetoxypropionyl)Cyclopentanone (XXI, Y = AcO). 3-Acetoxypropionyl chloride (13.2 g.) in dry chloroform (60 ml.) was added dropwise with stirring to a solution of 1-morpholino-1-cyclopentene (11.3 g.) and triethylamine (9.0 g.) in chloroform (90 ml.) over 5 min. at 35°. The solution was kept at 35° for 22 hr., water (100 ml.) was then added and the bi-phase mixture was refluxed with vigorous stirring for 1½ hr. The cooled solution was shaken thoroughly with hydrochloric acid (37 ml. 2N) and the product extracted as described above for 2-propionylcyclopentanone to give crude 2-(3-acetoxypropionyl)cyclopentanone (13.23 g., 84%), n_D^{20} 1.5056, ultra-violet spectrum λ_{max} 287mμ, $E_{1cm}^{1\%}$ 131. The ferric chloride test in methanol gave a wine-red colour. An infra-red spectrum contained peaks at the following wave-lengths: 5.77μ (ester), 5.86μ (ketone), 6.11μ (enol), 6.95 and 7.32μ(C-CH_3), and 8.10μ(acetate).

Ultra-violet spectra obtained in a preliminary series of experiments on the formation of the acyl-enamine showed the following values of $E_{1cm}^{1\%}$ for the absorption peaks at 350mμ and 287mμ(See p. 90, and fig.5):

(a) Room Temperature.

Time	350mμ	287mμ
* ¼ hr	170	205
* 1¼	177	110
20	267	65
72	330	25
120	373	24
168	386	26

* both at 35°.

(b) 72 hrs. room temperature, followed by reflux (61°).

Time	350mμ	307mμ
3 hr	306	33
6	324	28
16	185	21

(c) At 50°

Time	350 mμ	306 mμ
0	210	301
3 hr	306	146
6	425	102
* 10	505	65
22	470	33
30	408	31
46	407	26

* Sample in methanol overnight before spectrum measured.

Similar experiments were carried out with 120% excess of the acid chloride, with 120% excess of both triethylamine and acid chloride, and with triethylamine replaced by pyridine but these changes led to no improvement in the spectra obtained.

Values of $E^{1\%}_{1cm}$ for the water hydrolysis of the acyl-enamine (see p. 90 , and fig. 6) are summarised below:

Time	307mμ	350 mμ
½ hr	211	53
1	226	48
2	220	30
5	223	21

Alkaline Cleavage of 2-(3-Acetylpropionyl)Cyclopentanone.(XXI, Y=AcO).

(i) With 4 Equivalents of Alkali.

Crude 2-(3-acetoxypropionyl)cyclopentanone (0.50 g.) was refluxed with aqueous potassium hydroxide (20 ml., $\frac{N}{2}$) for 4 hr. The cooled solution was extracted with ether to remove neutral material, acidified with hydrochloric acid (10 ml. 2 N), and the acid product extracted with ether. The ethereal solution was washed with water, dried, and evaporated to give a viscous product (0.21 g.), n_D^{20} 1.5130, slightly soluble in water giving a solution acid to litmus and to potassium bicarbonate. Ultra-violet spectrum λ_{max} 247mμ, $E_{1cm}^{1\%}$ 234 (fig. 7).

(ii) With 1 Equivalent of Alkali.

Crude 2-(3-acetoxypropionyl)cyclopentanone (1.0 g.) was refluxed with aqueous potassium hydroxide (10 ml., N/2) for ½ hr. The cooled solution was extracted to remove neutral material (0.07 g., n_D^{19} 1.4924), acidified with hydrochloric acid (5 ml., 2 N), and the acid product extracted with ether. The ethereal solution was washed, dried and evaporated to give a product (0.49 g.), n_D^{21} 1.4954. Further extraction of the aqueous layer with chloroform yielded a second product (0.12 g.), n_D^{21} 1.5084. Both products gave low melting 2,4-dinitrophenylhydrazones. Fig. 9 (facing p.91) shows the ultra-violet spectra of the two products. Evaporation of the aqueous layer and washings gave a third product (0.18 g) n_D^{19} 1.5065.

The preliminary cleavage experiments carried out are summarised below. Values of $E_{1cm}^{1\%}$ at 247mμ and 285 mμ are given where they are

significant. (See p. 91, and fig. 8).

(i) $\frac{N}{2}$ KCl, 4 Equiv., Reflux.

Time (hrs.)	247 mμ	285 mμ
0	51	128
½	153	15
1	156	15
4	160	15

(ii) $\frac{N}{2}$ K_2CO_3, 4 Equiv., Reflux.

Time	247 mμ	285 mμ
"0"	65	78
2 min.	74	23
5	78	17
15	85	14
30	91	14
1 hr.	105	14
2	131	15
4	151	14

(iii) $\frac{N}{2}$ KOH, ½ hr., Reflux.

Equivs.	247 mμ	285 mμ
4	141	15
2	138	15
1	71	16

(iv) $\frac{N}{2}$ KOH, 1 Eq., Reflux.

Time	247 mμ	235 mμ
"0"	59	92
5 min.	72	27
15	73	21
30	76	18

o = zero time in cold.

"0" = zero time at reflux temperature.

Similar experiments were carried out under the following conditions:

Alkali	No. of Equivs.	Temp.
N/2 KOH	4	20°, 40°
N/2 K_2CO_3	4	20°, 40°
N/20 KOH	1/10	100°
N/10 K_2CO_3	4	100°
N/10 $KHCO_3$	4	100°
N/10 NaOAc	4	100°
N/2 K_2CO_3	1	100°
N/2 K_2CO_3	(2 hrs.)	100°

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BIBLIOGRAPHY FOR PART III.

1. Reed, De Busk, Gunsalus, and Hornberger, Science, 1951, 114, 93.
   Reed, Gunsalus, Schnakenberg, Soper, Boaz, Kern, and Parke, J. Amer. Chem. Soc., 1953, 75, 1267.
   Patterson, Pierce, Stokstad, Hoffman, Brockman, Day, Hacchi, and Jukes, J. Amer. Chem. Soc., 1954, 76, 1825.
2. Jones, U.S.P. 2,806,048/1957.
3. Braude, Linstead, and Wooldridge, Chem. and Ind., 1955, 508; J. Chem. Soc., 1956, 3074.
4. Deguchi, J. Pharm. Soc. Japan, 1960, 80, 924.
5. Schmidt and Grafen, Chem. Ber., 1959, 92, 1177.
6. Segre, Viterbo, and Parisi, J. Amer. Chem. Soc., 1957, 79, 5505.
7. Wladislaw, J. Org. Chem., 1961, 26, 711.
8. Acker and Anderson, J. Org. Chem., 1959, 24, 1162.
9. Mannich and Davidson, Ber., 1936, 69, 2106.
10. Stork, Terrell, and Szmuskovicz, J. Amer. Chem. Soc., 1954, 76, 2029.
11. Kuehne, J. Amer. Chem. Soc., 1959, 81, 5400.
12. Dulou, Elkik, and Veillard, Bull. Soc. Chim. France, 1960, 967.
    Elkik, ibid., p. 972.
13. Hünig, Benzing, and Lücke, Chem. Ber., 1957, 90, 2833.
    Hünig, Lücke, and Benzing, ibid., 1958, 91, 129.
    Hünig and Lücke, ibid., 1959, 92, 652.
14. Hauser, Swamer, and Ringler, J. Amer. Chem. Soc., 1948, 70, 4023.
    Hamrick, Hauser, and Hauser, J. Org. Chem., 1959, 24, 583.
15. Hünig and Lendle, Chem. Ber., 1960, 93, 909, 913.
16. Yurugi, Fushimi and Hamata, J. Pharm. Soc. Japan, 1960, 80, 1165, 1170, 1317, 1321.
17. Gaylord, "Reduction with Complex Metal Hydrides", Interscience, New York, 1956, p. 585.
18. Mosettig, Org. Reactions, 1948, 4, 362.
19. Adams, Voorhees, and Shriner, Org. Synth., Coll.vol.I, p. 463.

20. Brown, Brewster, and Shechter, J. Amer. Chem. Soc., 1954, 76, 467.

21. Brady, J. Chem. Soc., 1931, 756.

22. Gresham, Jansen, and Shaver, J. Amer. Chem. Soc., 1950, 72, 72.

23. Fabry, unpublished work.

24. Gresham, Jansen, Shaver, Gregory, and Beears, J. Amer. Chem. Soc., 1948, 70, 1004.

25. Gresham, Jansen, Shaver, Bankert, Beears, and Prendergast, J. Amer. Chem. Soc., 1940, 71, 601.

26. Brown, J. Amer. Chem. Soc., 1938, 60, 1325.

27. Heilbron, Dunburg, and Jones, "Dictionary of Organic Compounds", Eyre and Spottiswoode, London, 1943, vol.3, p.517.

28. Bergmann and Ikan, J. Amer. Chem. Soc., 1956, 78, 1432.

29. Blaise and Koehler, Bull. Soc. chim. France, 1910, (4), 7, 710.

30. Lamant, Compt. rend., 1958, 246, 2390.

31. Blaise and Koehler, Compt. rend., 1909, 148, 489.

32. Keskin, Rev. Fac. Sci. Istanbul, 1952, 17A, 344.
Lamant, ref. 30.

33. Mousseron, Jacquier, and Fontaine, Bull. Soc. chim. France, 1956, 1737.

34. Meŝek, Chem. Listy, 1955, 49, 1840.

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