



<https://theses.gla.ac.uk/>

Theses Digitisation:

<https://www.gla.ac.uk/myglasgow/research/enlighten/theses/digitisation/>

This is a digitised version of the original print thesis.

Copyright and moral rights for this work are retained by the author

A copy can be downloaded for personal non-commercial research or study,  
without prior permission or charge

This work cannot be reproduced or quoted extensively from without first  
obtaining permission in writing from the author

The content must not be changed in any way or sold commercially in any  
format or medium without the formal permission of the author

When referring to this work, full bibliographic details including the author,  
title, awarding institution and date of the thesis must be given

Enlighten: Theses

<https://theses.gla.ac.uk/>  
[research-enlighten@glasgow.ac.uk](mailto:research-enlighten@glasgow.ac.uk)

SYNTHETIC APPROACHES TO NATURALLY  
OCCURRING CYCLOPENTANES

THESIS

presented to

The University of Glasgow

by

John Peter Clayton, B.Sc.,

for the Degree of Doctor of Philosophy

1966

ProQuest Number: 10984266

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 10984266

Published by ProQuest LLC (2018). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code  
Microform Edition © ProQuest LLC.

ProQuest LLC.  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106 – 1346

### ACKNOWLEDGEMENTS

I would like to thank Professor R.A. Raphael for his patience and understanding in the early stages of this work and for his guidance and encouragement throughout.

I am indebted to the Scientific Research Council for a grant which enabled me to carry out this research.

## SUMMARY

PART I. Five synthetic routes to the prostaglandins, a group of highly substituted cyclopentanes, have been explored. The first four routes were unsuccessful but have provided interesting and useful information on a variety of substituted cyclopentanes. The fifth route has resulted in the isolation of 2-(6-cyanoethyl)-3-(oct-1-yn-3-ol)cyclopent-2-enone. The transformation of this important intermediate into the prostaglandin structure requires three further structural changes - the hydrolysis of the nitrile group, the selective reduction of the enyne system to a trans double bond and the introduction of a second oxygen function into the cyclopentane ring.

PART II. Synthetic pathways to the cyclopentanoid monoterpenes, the iridoids, have been explored. These attempts which have been based on the use of simple phenols as precursors, have so far proved unsuccessful. The isolation of methyl nepetinate as its 2,4-dinitrophenylhydrazone represents the nearest approach to the natural products.

## CONTENTS

### PART I

#### SYNTHETIC APPROACHES TO THE PROSTAGLANDINS

	<u>Page</u>
Review .....	
Discussion - Route 1 .....	16
Route 2 .....	24
Route 3 .....	30
Structures of Cyclopentanepolyones, .....	40
Route 4 .....	46
Route 5 .....	53
Tables .....	76
Experimental .....	79
Formula Flow Sheets .....	A - F inc.

### PART II

#### SYNTHETIC APPROACHES TO THE IRIDOID MONOTERPENES

Review .....	152
Discussion .....	162
Experimental .....	178
Formula Flow Sheets .....	G, H
REFERENCES .....	195

PART I

Synthetic Approaches to the Prostaglandins

## REVIEW

### Introduction.

The presence of a lipid soluble acidic fraction stimulating smooth muscle and depressing blood pressure in human seminal plasma and in sheep vesicular glands was first reported by Goldblatt<sup>1</sup> and von Euler<sup>2</sup>. The active principle was called prostaglandin because of its supposed origin from the prostate gland which encircles the base of the male bladder and secretes an important proportion of semen.

In 1957 Bergström and Sjövall isolated two crystalline compounds from sheep vesicular glands<sup>3, 4, 5</sup>. One of these compounds, prostaglandin  $E_1$  ( $PGE_1$ ) showed both a strong vasopressor and smooth muscle stimulating activity, whereas the other,  $PGF_{1\alpha}$ , mainly showed the latter activity. Later two related compounds,  $PGE_2$  and  $PGE_3$ , were isolated by Bergstrom from the same source<sup>6</sup> and were found to have similar physiological activities. Two additional prostaglandins,  $PGF_{2\alpha}$  and  $PGF_{3\alpha}$  were first isolated from animal lung tissue<sup>7, 8</sup> and have since been shown to occur widely in various other animal tissues.



The structures of these compounds are presented on flow sheets A1 and A2. The C<sub>20</sub> parent acid has been given the trivial name prostanoic acid from which the names of the prostaglandins are derived. The subscript one in PGE<sub>1</sub> refers to the number of double bonds in the molecule. The subscript a in PGE<sub>1a</sub> refers to the configuration of the C<sub>9</sub> - hydroxyl group.

Chemistry (40)

The structure of PGE<sub>1</sub> was reported in 1962<sup>9</sup>. The molecular formula, C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>, was deduced from microanalytical, mass spectral and X-ray data<sup>5</sup>. PGE<sub>1</sub> was shown to contain one carboxyl, one carbonyl (cyclopentanone), two hydroxyls and one trans double bond<sup>10</sup>.

Treatment of PGE<sub>1</sub> (1), (see flow sheet A3) with sodium hydroxide (0.5 N) at room temperature gave a compound (2) with  $\lambda_{\max}$ , 278 m $\mu$ . On oxidative ozonolysis, the acetylated methyl ester of (2) gave monomethyl suberate (3) succinic acid (4) and  $\alpha$ -acetoxyheptanoic acid (5). That is, nineteen of the twenty carbon atoms of (2), were accounted for. The degradation products were separated by gas-liquid chromatography and identified by mass spectrometry. The isolation of succinic acid, which must originate

in the ring, showed that two vicinal methylene groups were present in the five-membered ring and that, accordingly, the three carbon atoms carrying the side chains and the keto group must be adjacent. Furthermore, the isolation of monomethyl suberate, produced by oxidation of the vicinal diketone initially formed, indicated that the carboxyl side chain must be attached to the carbon atom that is in the  $\alpha$ -position relative to the keto group. The proposed structure of (2) was further supported by the infra red data.

Hydrogenation of  $\text{PGE}_1$  (1) gave a dihydrocompound (6) which on base treatment lost water to form (7), with  $\lambda_{\text{max}}$ , 237  $\text{m}\mu$ . Oxidative ozonolysis of the methyl ester acetate of (7) gave two products, monomethyl suberate (3) and 7-acetoxy-4-oxo-dodecanoic acid (8). Thus all twenty of the carbon atoms were accounted for.

Treatment of  $\text{PGE}_1$  (1) with acetic anhydride gave a derivative (9),  $\lambda_{\text{max}}$ , 218  $\text{m}\mu$ . Oxidative ozonolysis of the methyl ester acetate of (9) gave 1, 2, 8-octanetricarboxylic acid (10),  $\alpha$ -acetoxyheptanoic acid (5) and carbon dioxide. The formation of these degradation products provided firm support for the proposed structure of (9).

The physical data of the derivatives of PGE<sub>1</sub>, namely (2),  $\lambda_{\text{max}}$ , 278 m $\mu$ , (7),  $\lambda_{\text{max}}$ , 237 m $\mu$  and (9),  $\lambda_{\text{max}}$ , 218 m $\mu$  and the identification of their degradation products rigorously established their structures. From this work followed the structures of the side chains of PGE<sub>1</sub> (1) as well as their positions on the ring and the position of the keto group. The position of the hydroxyl group was derived from indirect evidence. The facile dehydration of PGE<sub>1</sub> with alkali suggested a  $\beta$ -hydroxyl ketone. A tertiary  $\beta$ -hydroxyl was ruled out by the ease of acetylation of the two hydroxyls in dihydro - PGE<sub>1</sub> (6) and also by N.M.R. data. An hydroxyl at the secondary carbon atom  $\alpha$  to the keto group was excluded by the finding that neither PGE<sub>1</sub> (1) nor PGF<sub>1 $\alpha$</sub>  or PGF<sub>1 $\beta$</sub>  were oxidised by periodate or lead tetra acetate.

Finally, catalytic reduction of PGE<sub>1</sub> with platinum in acetic acid gave among other products compound (11) which was isolated by partition chromatography and identified by gas liquid chromatography and mass spectral comparison with a synthetic specimen, thus establishing the carbon skeleton of PGE<sub>1</sub><sup>40</sup>.

Reduction of PGE<sub>1</sub> with borohydride resulted in two epimeric alcohols, PGF<sub>1α</sub> (12) and PGF<sub>1β</sub> (13). An X-ray analysis<sup>11</sup> of the tri-p-benzoate of the methyl ester of PGE<sub>1β</sub> confirmed the structural assignment and provided the stereochemical features. Ozonolysis of PGF<sub>1β</sub> gave 2-hydroxyheptanoic acid which was assigned the (R) - configuration on the basis of its rotational value and sign. This established the absolute configuration.

The structures of PGE<sub>2</sub> (14) and PGE<sub>3</sub> (15) were partly elucidated by mass spectrometry, which showed that the molecular weight of PGE<sub>3</sub> was two units less than that of PGE<sub>2</sub> and four units less than that of PGE<sub>1</sub><sup>16</sup>. That the parent structure was the same for all three compounds followed from their conversion by catalytic reduction into the same derivative (6) as judged by mass spectrometry. Since all three compounds were transformed into derivatives with the same chromophore at  $\lambda_{\max}$  278 mμ, on treatment with alkali, it was evident that they all had the  $\Delta^{13}$  double bond demonstrated for PGE<sub>1</sub> (1). The location of the additional double bond of PGE<sub>2</sub> (14) in the carboxyl side chain was indicated by mass spectrometry and its position established by the identification of glutaric acid as a product of chromic acid oxidation. Using the same methods it was

also established that PGE<sub>3</sub> (15) only differed from PGE<sub>2</sub> (14) by having an additional double bond. This double bond was determined as  $\Delta^{17}$  by N.M.R. spectroscopy.<sup>12</sup>

That the stereochemical features of PGE<sub>1</sub> (1), PGE<sub>2</sub> (14) and PGE<sub>3</sub> (15) are the same was recently demonstrated by conversions of PGE<sub>2</sub> into PGE<sub>1</sub>, and of PGE<sub>3</sub> into PGE<sub>2</sub> by selective catalytic hydrogenation of the  $\Delta^{17}$  and  $\Delta^5$  double bonds respectively.<sup>38</sup>

With regard to the stereochemistry of the double bonds, it was observed that PGE<sub>1</sub> (1) exhibits infrared absorption at  $970\text{ cm}^{-1}$ , demonstrating that the  $\Delta^{13}$  double bond has the trans configuration. PGE<sub>2</sub> (14) and PGE<sub>3</sub> (15) also show absorptions at this wave length but it could not be decided whether the absorption was due to the  $\Delta^5$  and  $\Delta^{17}$  double bonds in addition to the  $\Delta^{13}$  double bond. This question has recently been solved by the selective reduction of the  $\Delta^{13}$  double bond in PGE<sub>2</sub> and PGE<sub>3</sub> by enzymes from lung tissue.<sup>39</sup> The reduction products (16) and (17) did not show any absorption at  $970\text{ cm}^{-1}$  demonstrating that the  $\Delta^5$  and  $\Delta^{17}$  double bonds of PGE<sub>2</sub> and PGE<sub>3</sub> have the cis configuration.

Occurrence.

Compounds of the prostaglandin structural type have not previously been reported as occurring in nature. A cyclopentenolone nucleus is present in pyrethrolone (18), which results from the hydrolysis of the pyrethrin extract from *Pyrethrum* flowers.

The wide distribution of the prostaglandins in various tissues is apparent from Table 1. The highest concentrations, however, have been found in sheep vesicular glands and in male semen. In the latter instance Bygdeman and Samuelsson<sup>13</sup> have developed a method for the quantitative determination of the prostaglandins in human seminal plasma of normal men. Their first average data were in  $\mu\text{g}$  per ml:  $\text{PGE}_1$ : 20;  $\text{E}_2$ : 20;  $\text{E}_3$ : 4;  $\text{F}_{1a}$ : 3;  $\text{F}_{2a}$ : 3. The concentration in lung tissue was determined by isotope dilution and found to be about 0.5  $\mu\text{g}$  of  $\text{PGF}_{2a}$  per gram of tissue.<sup>14</sup>

The isolation of  $\text{PGE}_2$  and  $\text{PGF}_{2a}$  from menstrual fluid was carried out in this department<sup>18</sup>. The concentrations of these two prostaglandins were reported as being much less than those in male semen. It has been suggested<sup>25</sup> that the prostaglandins in seminal fluid may be absorbed from the vagina into the circulation after coitus, subsequently to act upon the female reproductive tract smooth muscle. This suggestion is the basis of current clinical trials, discussed below.

TABLE 1 - Distribution of Prostaglandins 15, 20

Source	E <sub>1</sub>	E <sub>2</sub>	E <sub>3</sub>	F <sub>1a</sub>	F <sub>2a</sub>	F <sub>3a</sub>	Reference
Semen (human)	+	+	+	+	+		13, 16
Semen (sheep)	+						17
Vesicular gland (sheep)	+	+	+	+			3, 4
Menstrual fluid (human)		+			+		18
Lung (human)					+		19
Lung (monkey)					+		19
Lung (ox)					+	+	19
Lung (pig)					+		7
Lung (sheep)		+			+		7, 14
Lung (guinea pig)					+		19
Iris (sheep)					+		21
Brain (ox)					+		22
Thymus (calf)	+						23
Pancreas (cattle)		+			+		24

Biosynthesis.

Early work on the relationship of fatty acid structure to biological activity suggested that either the 6 - term (that is a double bond between 6th and 7th carbon atoms counted from the terminal methyl group) or the 9 - term double bonds or both were fundamental for essential fatty acid activity. Later however it was shown that the 6, 9 - term structure was not an exclusive condition and fatty acids with additional double bonds and of varying chain lengths could also be biologically active<sup>26</sup>. Of the acids examined arachidonic acid (20) appeared to have the highest activity.

Following the structural elucidation of the prostaglandins PGE<sub>1</sub>, PGE<sub>2</sub> and PGE<sub>3</sub> it appeared possible that their biosynthesis might be a result of a direct cyclisation of respectively, homo- $\gamma$ -linolenic acid (19), arachidonic acid (20) and 5, 8, 11, 14, 17-eicosa-pentaenoic acid (21). This was shown to be the case<sup>27, 28</sup>.

Tritium labelled arachidonic acid was converted into labelled PGE<sub>2</sub> in high yield by homogenates of the vesicular gland of sheep.

Similarly <sup>14</sup>C-labelled homo- $\gamma$ -linolenic acid (19) was converted into labelled PGE<sub>1</sub><sup>29</sup> and the formation of PGE<sub>3</sub> from all-cis-eicosa-5, 8, 11, 14, 17-pentaenoic acid (21) has been demonstrated with unlabelled precursor by the net increase of PGE<sub>3</sub> in the homogenate<sup>29</sup>.



The C<sub>22</sub>-homologue of homo- $\gamma$ -linolenic acid has been found to yield products with the expected physical properties<sup>29</sup> and the C<sub>19</sub>-homologues of both homo- $\gamma$ -linolenic and arachidonic acid have been found to yield nor - PGE<sub>1</sub> and nor - PGE<sub>2</sub> respectively<sup>30</sup>. The corresponding C<sub>18</sub>-acids, however, did not appear to be substrates for the enzyme system present in sheep vesicular glands.

Other enzymatic cyclisations of fatty acids into prostaglandins have been reported as follows. From homo- $\gamma$ -linolenic acid was obtained<sup>31</sup> in addition to PGE<sub>1</sub> a less polar compound which was shown to be the dehydrated form of PGE<sub>1</sub>- (22). This compound was similar to PGE<sub>1</sub> in its blood pressure reducing ability but had much less smooth muscle stimulating properties. The incorporation of labelled homo- $\gamma$ -linolenic acid by ovine and bovine enzymatic systems resulted in the isolation of labelled PGF<sub>1 $\alpha$</sub>  in addition to PGE<sub>1</sub><sup>32</sup>. Tritium labelled arachidonic acid was found<sup>33</sup> to be converted by guinea pig lung homogenate into PGF<sub>2 $\alpha$</sub> , PGE<sub>2</sub> and two new prostaglandins (23) and (24). These two new less polar prostaglandins are presumably metabolised from PGE<sub>2</sub>. PGE<sub>1</sub> has been shown to be metabolised in the same way by homogenates of guinea-pig lung by the isolation of the analogous 11 $\alpha$ , 15-dihydroxy-9-oxoprostanoic acid (25) and 11 $\alpha$ -hydroxy-9, 15-dioxoprostanoic acid (26)<sup>41</sup>.

The metabolism of  $\text{PGF}_{1\alpha}$  (12) has been studied in vivo in the rat<sup>42</sup>. Administration of labelled  $\text{PGF}_{1\alpha}$  resulted in the isolation of the metabolite (27) in which the carboxyl side chain had been degraded by two carbon units.

A further new prostaglandin has recently<sup>34</sup> been isolated from male seminal fluid and assigned the structure (28) - 15, 19-dihydroxy-9-oxo-prosta-5, 10, 13-trienoic acid.

Finally the biosynthetic picture has been completed by demonstrating that the three oxygen function in the prostaglandin molecule at  $\text{C}_9$ ,  $\text{C}_{11}$  and  $\text{C}_{15}$  are derived from the incorporation of molecular oxygen<sup>34, 35</sup>.

A suspension of a particulate fraction of sheep vesicular gland homogenate was incubated with homo- $\gamma$ -linolenic acid in the presence of labelled [<sup>18</sup>O<sub>2</sub>] oxygen. The mass spectrum of the labelled  $\text{PGE}_1$  obtained indicated that the  $\text{C}_9$  - keto group and  $\text{C}_{11}$ ,  $\text{C}_{15}$  hydroxyls were derived from oxygen incorporation.

The biosynthesis of the prostaglandins from essential fatty acid precursors by the incorporation of molecular oxygen suggests a Diels-Alder photosensitised oxygen addition to the  $\Delta^8$ ,  $\Delta^{11}$ , 1, 4-diene grouping present in the fatty acids. Diels-Alder reactions in which molecular oxygen acts as the dienophile have been recently reviewed<sup>43</sup>. The typical reaction is one in which 1, 3-dienes undergo photosensitised oxidation to give 1, 4-epidioxides.

Cyclopentadiene for example gives the epidioxide (29).

In the present instance the photosensitised oxidation of homo- $\gamma$ -linolenic acid (19) could result in the epidioxide (30) as a result of an internal cyclisation and Diels-Alder type of addition across the C<sub>9</sub> and C<sub>11</sub> positions. Models suggest that a cyclisation of this nature would force the side chains into a trans relationship. A further mole of oxygen could then attack the remaining position of unsaturation at C<sub>15</sub>, with the introduction of a hydroperoxide group at this position and concomitant displacement of the cis double bond into the  $\Delta^{13}$  trans position. Cleavage of the peroxide links would result in PGF<sub>1 $\alpha$</sub>  (12).

### Biological Effects.

The suggestion that prostaglandins can influence muscular activity in the female reproductive tract has already been referred to and is the basis of current clinical trials at University College Hospital, London<sup>36</sup>. The fertility of a man can be assessed by the concentration of spermatozoa in his semen. When the sperm count is low so is the chance of the wife conceiving. A survey of fifty men with low sperm counts showed that the conception rate in

their wives was directly related to the prostaglandin content of the husband's seminal fluid. The present trials are designed to test the idea that prostaglandins in semen promote conception by influencing the muscular activity of the woman's birth canal in such a way as to help spermatozoa reach the oviduct.

Other experiments have shown that when injected into the brain of a cat, PGE types of prostaglandins cause the animal to become inert and withdrawn in a manner resembling certain types of schizophrenia in man. Prostaglandins can also relax the walls of the small air tubes of the lung which are in spasm during asthmatic attack. The same prostaglandins can release body fat from storage depots (such as fatty layers under the skin) and so increase blood fat levels, and a high blood fat level appears to be associated with arterial disease and coronary thrombosis<sup>36</sup>.

A review of these and similar experiments is contained in references 15 and 37. It will be apparent from these brief comments that the physiological properties of the prostaglandins have aroused considerable interest.

### Synthesis

The only reported synthesis of a derivative of prostanoic acid is that very recently published by Wiesner and co-workers<sup>44</sup>, who synthesised 9 $\beta$ ,15-dihydroxyprost-13-enoic acid (31) as a mixture of two alcohols epimeric at carbon-15.

The potassium salt of ethyl 2-cyclopentanone carboxylate was condensed with ethyl 7-bromoheptanoate to give the diester (32). Bromination of this diester (32) with one mole of bromine resulted in a monobromo derivative which when refluxed for 18 hours in 20% sulphuric acid in ethanol, followed by chromatography of the crude product, resulted in the cyclopentenone (33), ( $\lambda_{\text{max}}$  228,  $\epsilon$  10,000). This was then transformed into the nitrile (34) by the action of acetone cyanohydrin in the presence of sodium carbonate in aqueous methanol. The keto-nitrile (34) was hydrolysed in base to give the diacid (35). The diacid (35) on treatment with methanol in the presence of p-toluenesulphonic acid resulted in the monoester (36). This was converted to the acid chloride (37) which on treatment with acetylene in the presence of aluminium chloride, followed by chromatography, gave the chlorovinyl ketone (38). The chlorovinyl ketone (38) was converted to the acetal (39) by treatment with methanolic caustic soda.

Reduction of the diketone (39) with borohydride gave a mixture of stereoisomers of alcohols (40). This crude mixture when treated with 2N sulphuric acid was transformed into a mixture of two epimeric aldehydes from which the predominant isomer was isolated and assumed to have the stereochemistry shown (41).

Treatment of (41) with pentyl magnesium bromide gave the methyl ester (42) from which (31) was obtained by alkaline hydrolysis.

Note added in proof.

1. A total synthesis of the racemic ethyl ester of (15 R)-9-oxo-11 $\alpha$ , 15-dihydroxyprostanic acid (Dihydro-PGE<sub>1</sub>), a naturally occurring metabolite of PGE<sub>1</sub>, has just been reported<sup>149</sup>.
2. It is further reported<sup>149</sup> that re-examination of the original data indicates that the absolute configuration of the prostaglandins should now be represented by the mirror image of that used throughout this thesis.

## DISCUSSION

Five distinct attempts have been made to synthesise the prostaglandin structure. These are designated Routes 1 to 5, and are discussed below under these headings. Route 5, which has proved the most successful of these attempts, is currently under investigation.

### Route 1

The first synthetic approach to the prostaglandins visualised the preparation of two key compounds, diethyl 2-acetylnonanedioate (44) and 1,1-dimethoxy-2-bromodec-3-yn-5-ol (47), neither of which was reported in the literature. The condensation of the known ethyl 7-bromoheptanoate (43),<sup>45</sup> with ethyl acetoacetate appeared to be a practical route to (44). The preparation of (47) was envisaged as a two-step process, an initial Grignard addition of 1-methoxybut-1-en-3-yne (45) to n-hexanal, which should result in 1-methoxydec-1-en-3-yn-5-ol (46), followed by the 1,2 addition to (46) of one mole of methyl hypobromite. These reactions are outlined on flow sheet (B1).

The crucial step in this synthesis was the condensation of the anion of the  $\beta$ -ketoester (44) with the bromoacetylene (47). It was

anticipated that this would proceed by a normal Sn2 mechanism with bromide elimination and the formation of (48). Compound (48) on hydrolysis would be expected to lose the ester group  $\beta$  to the carbonyl function. Subsequent hydrolysis of the acetal group and ring closure by means of an aldol condensation would lead to (49), from which it was considered the prostaglandin structure could be readily obtained by trans reduction of the triple bond and hydrolysis of the ester group.

Ethyl 7-bromoheptanoate (43) was prepared as described in the literature<sup>45</sup>. Tetrahydropyran on treatment with acetyl chloride in the presence of zinc chloride was readily converted into 5-chloroamylacetate (50). The latter was condensed with sodio-malonic ester and the product cyclised to the lactone (51), which was hydrolysed and decarboxylated in refluxing sulphuric acid. The lactone ring was opened by hydrobromic acid and the product, 7-bromoheptanoic acid, esterified to give (43) in 60% overall yield.

Condensation of (43) with the sodium salt of ethyl acetoacetate gave the first key compound, diethyl 2-acetylnonanedioate (44), in excellent yield. It was found that too prolonged a reaction time in this condensation caused cleavage of the acetyl group with the formation of diethyl nonanedioate.



The Grignard complex of the acetylene (45), was condensed with n-hexanal in a solvent medium of tetrahydrofuran and methylene chloride.<sup>46</sup> The product was the expected, 1-methoxydec-1-en-3-yn-5-ol (46), isolated in 48% yield. The addition of one mole of methyl hypobromite to the enyne (46) proceeded smoothly with N-bromosuccinimide in ice-cold methanol to give a compound of the expected molecular formula.

There are two ways in which methyl hypobromite may add to an enyne system. In the present instance, 1, 2 addition would result in the hoped for acetylene (47), whereas the product from 1, 4 addition would be the allene (52). The absence of acetylenic absorption at  $2200\text{ cm}^{-1}$  in the infra red spectrum of the product together with a weak band at  $1980\text{ cm}^{-1}$ , suggested that addition had indeed predominantly proceeded by the 1, 4 route, and that the product was the bromoallene (52).

The formation of the allene (52) rather than the acetylene (47) did not necessarily invalidate the remaining synthetic sequence. It was considered that nucleophilic substitution of the allene (52) by the  $\beta$ -ketoester (44) could occur in an  $\text{Sn}2^{\text{I}}$  manner with bromide displacement and allene-acetylene rearrangement as illustrated and with the formation of the desired compound (48).

This hypothesis was supported by a recent investigation<sup>47</sup> which described the condensation of 1-bromo-3-methylpenta-1, 2-diene (53) and 3-chloro-3-methylpent-1-yne (54) with diethyl ethylmalonate. It was found that both (53) and (54) gave the same proportion of allenic (55) and acetylenic (56) malonic ester. The formation of the latter (56) from the bromoallene (53) was evidence of an  $\text{Sn2}^1$  mechanism exactly analogous to that desired in the present case.

In the event condensation of the  $\beta$ -ketoester (44) with the bromoallene (52) did not produce a product with physical and spectroscopic properties compatible with (48), and it proved impossible to define the nature of the complex reaction mixture actually obtained.

It was considered that methyl hypochlorite might add 1, 2 to the enyne system in (46) rather than 1, 4 as observed for methyl hypobromite. The result of 1, 2 addition would be the chloroacetylene (57) with which the  $\beta$ -ketoester (44) might react by direct chlorine displacement to give (48).

The addition of methyl hypochlorite to (48) was effected by N-chlorosuccinimide in refluxing methanol. The product showed weak absorption in the infra red at  $2200 \text{ cm}^{-1}$  (acetylene) and at  $1980 \text{ cm}^{-1}$  (allene) suggesting that both 1, 2 and 1, 4 addition had occurred.

Condensation of the product with (44) again proved complex and no evidence of the desired (48) was obtained.

In view of the complexity of the above condensations it was decided to investigate this reaction using simpler model compounds.

The addition of methyl hypobromite to 1-methoxybut-1-en-3-yne (45) resulted in exclusive 1, 4 addition with the formation in 80% yield of the bromoallene (58). The proof of the structure of (58) was based on the infra red spectrum which showed a weak band at  $1980\text{ cm}^{-1}$  (allene) and no absorption at  $2200\text{ cm}^{-1}$  (acetylene) or  $3300\text{ cm}^{-1}$  (terminal acetylene). Rigorous confirmation of the assigned structure was elegantly provided by n.m.r. The six methoxyl protons appeared as a singlet at  $\tau = 6.71$ . The terminal allenic proton was split into a doublet,  $\tau = 3.90$ ,  $J = 6\text{ c.p.s.}$ , by the other allenic proton and each peak of the doublet was again split by the remaining methine proton into two further doublets,  $J = 2\text{ c.p.s.}$  The non-allenic methine proton at  $\tau = 5.09$ , showed primary splitting,  $J = 6\text{ c.p.s.}$ , by the adjacent allenic proton into a doublet and further secondary splitting,  $J = 2\text{ c.p.s.}$  into a quartet by the terminal allenic proton. The non-terminal allenic proton appeared at  $\tau = 4.72$  as a quartet and was split equally by the other two protons into two doublets with  $J = 6\text{ c.p.s.}$

Condensation of the sodium salt of ethyl n-propylacetoacetate with (58) proceeded smoothly and an acetylenic ester was isolated in good yield. Detailed examination showed this product to have the unexpected structure (59) which was unambiguously assigned by the following evidence. The infra red spectrum showed absorption at  $2280\text{ cm}^{-1}$  (acetylene) and  $1740\text{ cm}^{-1}$  (ester). The molecular weight was determined by mass spectrometry as 242 as required by the molecular formula. The compound did not give a tractable 2, 4-dinitrophenylhydrazone as previously observed for acetals of  $\alpha, \beta$ -unsaturated acetylenic aldehydes<sup>48</sup>, but like other acetylenic acetals of this type readily formed a crystalline bis-urethane. This derivative was formulated as (60) on the basis of microanalytical and n.m.r. data.

Final confirmation of the structure of (59) came from its n.m.r. comparison with the model acetylene (61), prepared by the Grignard addition of pentyne-1 to ethyl orthoformate. The methine proton, adjacent to the triple bond, appeared as a triplet in (59),  $\tau = 5.01$  and  $J = 1\text{ c.p.s.}$ , and in (61),  $\tau = 4.88$ ,  $J = 1\text{ c.p.s.}$ , coupling occurring through the triple bond with the methylene group.

The formation of 1,1-dimethoxy-5-carboethoxy-oct-2-yne (59) in this condensation may be rationalised in terms of nucleophilic attack of the carbanion of the  $\beta$ -ketoester at the terminal carbon of the bromoallene (58), followed by base catalysed allene-acetylene prototropic rearrangement and the normal  $\beta$ -ketoester fission of the acetyl group. While interesting in itself this mode of attack was not fruitful as far as prostaglandin synthesis was concerned.

Attention was next directed to the preparation of the morpholine enamine (62) corresponding to the vinyl ether (46). Condensation of the bromoester (63) derived from the  $\beta$ -ketoester (44), with such an enamine (62), followed by hydrolysis of the enamine function should result in the aldehyde (64). Hydrolysis and decarboxylation of the ester group,  $\beta$  to the keto function, followed by ring closure should lead to (49), from which the prostaglandin structure could be derived as described above.

The preparation of enamines from secondary amines and both ketals and acetals, simply by heating the two together and distilling off the alcohol formed, is well established.<sup>49</sup> Recently the preparation of dienamines has been described by heating morpholine with the ketals of a series of methyl n-alkyl ketones.<sup>50</sup>

However, all attempts to form the enamine (62), under a variety of conditions failed. Unchanged vinyl ether (46) was identified in the reaction products in each case.

The double bond in an enyne system is known to react preferentially with electrophilic epoxidising reagents. An attempt to obtain the epoxide (65) was therefore made, from the vinyl ether (46). It was considered that nucleophilic substitution of (65) by the anion of the  $\beta$ -ketoester (44) would result in the aldehyde (64), which has already been discussed as an intermediate in the prostaglandin synthesis.

However, attempts to form the epoxide (65) with a variety of peracids were unsuccessful. At 0° the vinyl ether (46) was recovered unchanged. At higher temperatures, the reaction proceeded violently and a complex mixture resulted.

A method of epoxidation<sup>51</sup> successfully applied to vinyl ethers in which equimolar concentrations of vinyl ether, acetonitrile and hydrogen peroxide were reacted together at a pH of 10 in methanol, was applied to (46); complete recovery of the starting material was obtained however.

Finally a further attempt at the preparation of the bromoacetylene (47) from the vinyl ether (46) was made by the addition to (46) of methanolic mercuric acetate, followed by treatment of the product with potassium

bromide and then bromine. A number of successful additions of methyl hypobromite to double bonds have been reported using this technique.<sup>52</sup>

In the present instance, successful 1, 2 addition of mercuric acetate to (46) would result in the mercuric salt (66), which with potassium bromide would be expected to form the mercuric bromide (67). Reaction of (67) with bromine should lead to the desired bromoacetylene (47).

In the event treatment of (46) in the described manner resulted in an intractable mixture.

### Route 2

The second approach to the prostaglandins was similar in some respects to the first and involved the preparation of two key compounds (44) and (71) which incorporated the two side chains of the prostaglandin molecule. Condensation of these two key compounds by an Sn2 type reaction, followed by the formation of the cyclopentane ring as a result of an internal cyclisation, would result in the gross prostaglandin structure.

The two key compounds were the previously described diethyl 2-acetylnonane dioate (44) and 1,1-dichloro-2-mesyloxy-5-(tetrahydro-2H-pyranyloxy) dec-3-yne (71). The proposed route to the latter is outlined on the flow sheet (C1). Thus the condensation of the mono-Grignard complex of acetylene with n-hexanal would give the acetylenic alcohol (68), the hydroxyl of which could be blocked with dihydropyran giving (69). The Grignard derivative of (69) would be expected to react with dichloroacetaldehyde to give (70). The preparation of the mesylate of (70) would lead to the second key compound (71).

Condensation of the anion of the  $\beta$ -ketoester (44) with (71) should result in the displacement of the mesylate group and formation of (72). Hydrolysis and decarboxylation of the ester group  $\beta$  to the carbonyl function, followed by removal of the tetrahydropyranyl protection group and hydrolysis of the dichloro group, should lead to the aldehyde (64). This aldehyde and its transformation into the prostaglandin structure has already been discussed.

The acetylenic alcohol, oct-1-yn-3-ol (68) was reported in the literature<sup>53</sup>, but few details given of its preparation. It was prepared initially by the condensation of sodium acetylide with n-hexanal



but the yield was poor - 12%. A 12% yield of (68) was also obtained when sodium acetylide in dimethylformamide was condensed with n-hexanal.<sup>54</sup> Satisfactory results were obtained however when the mono-Grignard of acetylene, prepared in tetrahydrofuran,<sup>55</sup> was condensed with n-hexanal; by this technique the yield was raised to 50%.

Treatment of (68) with dihydropyran in the presence of a catalytic amount of acid resulted in an excellent yield of 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69).

To establish optimum conditions for the condensation with dichloroacetaldehyde, preliminary reactions were investigated between the Grignard derivative of (69) and the much more readily available chloral. The latter was prepared by the distillation of chloral hydrate from concentrated sulphuric acid followed by a second distillation of the distillate. The product from the Grignard reaction between (69) and chloral was a high boiling viscous liquid which slowly crystallised on standing. The presence of a strong absorption band at  $3450\text{ cm}^{-1}$  in the infra red spectrum together with acetylenic absorption at  $2300\text{ cm}^{-1}$  suggested that the product was the expected (73). However when this product was

treated with an excess of methanesulphonyl (mesyl) chloride, in an attempt to form the mesylate (74), two new compounds were formed and isolated by chromatography. The less polar of these two compounds showed sulphonyl ( $1180\text{ cm}^{-1}$ ) and acetylenic ( $2200\text{ cm}^{-1}$ ) absorption in the infra red spectrum but no hydroxyl absorption at  $3500\text{ cm}^{-1}$ . The more polar compound showed sulphonyl, acetylenic and hydroxyl absorption.

These observations suggested that the product from the Grignard reaction with chloral was not (75) but the diol (75). This was confirmed by microanalysis. The less polar material from the reaction of (75) with mesyl chloride was presumably the bis-mesylate (76) and the more polar material the mono-mesylate (77) rather than the isomeric (78) which would be less favoured for steric reasons.

The loss of the tetrahydropyranyl protecting group in this Grignard reaction was surprising, particularly so since some 30% of the starting acetylene (69) was recovered unchanged with the protecting group still intact. However the instability of the tetrahydropyranyl group in the acetylene (69) towards the conditions of the Grignard reaction was observed on a number of subsequent occasions.

When the Grignard of (69) was condensed with dichloroacetaldehyde, loss of the protecting group again occurred and the product was 1,1-dichlorodec-3-yne-2,5-diol (79). In refluxing sodium methoxide chlorine displacement occurred readily and (79) was converted to the liquid acetal, 1,1-dimethoxydec-3-yne-2,5-diol (80). The structure of (80) was confirmed by its hydrolysis in boiling methanolic 2% sulphuric acid to the aldehyde which readily formed a 2,4-dinitrophenylhydrazone.

Attempts to react the less hindered of the two hydroxyl groups in (80) with dihydropyran and hence obtain (81) were unsuccessful. Likewise efforts to obtain (73) by selective reaction of (75) with dihydropyran were also unsuccessful.

A further attempt at the preparation of (70) by making the lithium salt of (69), rather than the Grignard derivative and condensing this with dichloroacetaldehyde in dimethylformamide failed; the acetylene was recovered unchanged.

In view of the instability of the tetrahydropyranyl group to the conditions of the Grignard reaction in the above examples, it was decided to investigate the use of chloromethyl methyl ether as a means of protecting the alcohol function in the acetylenic alcohol (68).

This reagent has been used frequently to protect phenolic groups but has found little application in the protection of alcohols.<sup>56</sup>

The addition of chloromethyl methyl ether to the alcohol (68) at 0°, in the presence of an equimolar concentration of triethylamine, caused the precipitation of a white, water soluble, crystalline solid, presumed at this stage to be the base hydrochloride. However when the reaction mixture was worked up, the starting material (68) was recovered quantitatively. It appeared likely therefore that chloromethyl methyl ether itself had attacked the base to form the quaternary salt. Apparent confirmation of this came from the observation that addition of chloromethyl methyl ether to both pyridine and triethylamine caused an immediate white precipitate.

Surprisingly the desired 3-(methoxymethoxy)oct-1-yne (82), was obtained in 22% yield with 66% recovery of unchanged alcohol (68), simply by mixing the reagents together and allowing them to stand for two days at room temperature.

The addition of the Grignard complex of the acetylene (82) to dichloroacetaldehyde in an attempt to form the alcohol (83) resulted in a black intractable product, which contained some starting material as shown by its infra red spectrum and T.L.C. comparison.

Route 3

The first two unsuccessful attempts at prostaglandin synthesis visualised the construction of the two side chains of the prostaglandin molecule in the initial stages of the synthesis and the introduction of the cyclopentane ring at an advanced stage and as a result of an internal condensation. The third synthetic attempt differed in that the formation of the carbocyclic ring was conceived as a first step. The scheme is outlined on flow sheet D1.

Thus condensation of diethyl 2-acetylnonanedioate (44) with diethyl oxalate should, on the basis of many precedents, lead to the cyclopentane - 1, 2, 4-trione (84). In view of the facility which cyclopentanetriones, of the type represented by (84), form mono-semicarbazones, reaction occurring at the 1-keto position, it was considered that such triones might form the analogous mono-ethylene ketal. In the case of (84) this would be represented by the structure (85). Reaction of (85) with diazomethane should result in the formation of the two possible isomeric enol-ethers, in which the isomer (86) should predominate for steric reasons.

The addition of the Grignard derivative of the acetylene (68) to (86) should result in the tertiary alcohol (87) which on treatment with acid would be expected to rearrange to the cyclopentenone (88). The conversion of (88) to the prostaglandin structure should be readily achieved by reduction of the double bond, trans reduction of the triple bond, removal of the ketal protecting group and hydrolysis of the ester group.

This approach was studied using readily available model compounds.

3-Methyl-cyclopentane-1, 2, 4-trione (89) was prepared as described in the literature<sup>57</sup> by the condensation of diethyl oxalate with methyl ethyl ketone and hydrolysis of the intermediate glyoxalate (90). At a later stage the trione (89) was more readily prepared by hydrolysis of the semicarbazone (91), a quantity of which became available.

When the trione (89) was treated over 23 hours with a ten-fold excess of ethylene glycol in an attempt to make the mono-ketal (92) an excellent yield of a new compound was obtained which had no absorption in the ultra violet and was shown to be the unexpected tri-ketal (93). When one mole equivalent of glycol was used in

this reaction, the only identifiable product in the reaction mixture was starting material (89). Attempts to make the mono-ketal (92) by the ethyl orthoformate technique and the exchange ketalisation method, employing 2-ethyl-2-methyl-1,3-dioxolane, had similar results; the starting material (89) was the only component identified in the reaction products.

In view of the lack of success in obtaining the mono-ketal, by the usual ketalisation procedures, it was decided to repeat the experiment with excess ethylene glycol which had resulted in the tri-ketal (93), and to examine the products at selected time intervals. This resulted, after a reaction time of one hour and 45 minutes in the isolation of a new ketal which was identified as a cyclopentane-1,3-dione on the basis of its infra red and ultra violet absorption properties. The latter were particularly diagnostic, the shifts in wavelength caused by the addition of acid and base corresponded closely to those observed for 2-methyl-cyclopentane-1,3-dione (94) - see Table 2. This new ketal was consequently thought to be the desired mono-ketal (92). However the molecular weight was determined by mass spectrometry to be 214 which necessitated two moles of ethylene glycol in the structure.

Since N.M.R. showed the presence of one methyl group and one ring methylene group the structure of this ketal was considered to be (95). Although (95) would have been a suitable alternative to the mono-ketal (92) in the synthetic scheme, all attempts to repeat its formation failed.

One final attempt at the preparation of the mono-ketal (92) was made starting with the mono-semicarbazone (91). This highly insoluble compound was treated in the usual manner with an excess of ethylene glycol in the hope of replacing the semicarbazide group by ethylene ketal. However after a reaction period of 20 hours, the starting material (91) was recovered unchanged.

In view of the ready preparation of the tri-ketal (93), it was decided to examine the selective hydrolysis of this compound, since if the bis-ketal (96) could be obtained this would allow the introduction of the second side chain by means of a Grignard reaction with the acetylene (68). The resulting tertiary alcohol (97) would obviously be a very useful intermediate, and could be transformed to the prostaglandin structure.



When an ethereal solution of the tri-ketal (93) was shaken with dilute sulphuric acid for a period of two days, complete hydrolysis occurred to the trione (89). However when the reaction was stopped after one hour, a 60% yield of a new compound was obtained by chromatographic separation from the trione (89). This new compound, which absorbed at  $1740 \text{ cm.}^{-1}$  in the infra red, was shown by its molecular weight, determined by mass spectrometry, to be a bis-ketal. In addition to the hoped for bis-ketal (96) two other bis-ketals, (98) and (99) were possible. To resolve this uncertainty the preparation of a benzylidene derivative was attempted and the formation of this derivative,  $\lambda_{\text{max}} 304 (\epsilon 30,700)$ , was disappointingly observed. This immediately ruled out the desired (96) as the structure for the bis-ketal. A distinction between the remaining two structures was possible on the basis of N.M.R. The N.M.R. data of this whole series of extremely interesting oxygenated cyclopentanes is discussed in detail in a later section. Briefly the distinction was made on the basis of the secondary methyl group appearing as a simple doublet,  $J = 11 \text{ c.p.s.}$ , in the N.M.R. of the bis-ketal in question which can only be reconciled with the

structure (99). The alternative structure (98) would be expected to show further splitting of the methyl group by the ring methylene protons through the ring ketone function.

It was reported<sup>58</sup> that treatment of the trione (89) with sodium borohydride resulted in selective reduction of the C - 1, keto group and formation in high yield of the alcohol (100). The isomeric enol ethers (101) and (102) were then formed by the action of diazomethane on this alcohol, and separated by fractional crystallisation<sup>57</sup>. It was not possible to distinguish between the alternative structures for the two isomers. The hydroxy-cyclopentenone (102) is analogous to the ketal (86), an hydroxyl group replacing the ketal function, and should therefore be similarly transformed into the prostaglandin structure by an identical series of reactions to that described for the ketal (86).

This work was therefore repeated and the two isomeric enol-ethers (101) and (102) obtained. By means of N.M.R. it was possible to assign structure (102) to the predominant isomer, m.p. 164 - 166<sup>o</sup>, and the lower melting, m.p. 84 - 86<sup>o</sup>, isomer was represented by (101).

Before proceeding to the addition of the Grignard derivative of the acetylene (68) to the hydroxy-cyclopentenone (102) the addition of phenylacetylene to 2-methyl-3-methoxy-cyclopent-2-enone (103) was examined as a pilot experiment. The latter compound (103) was readily obtained by the action of diazomethane on 2-methylcyclopentane-1, 3-dione (94).

When the Grignard derivative of phenylacetylene was condensed with (103) and the resulting complex decomposed with dilute sulphuric acid, 2-methyl-3(2-phenylethynyl)-cyclopent-2-enone (104), was obtained in 20% yield. The formation of (104) in this reaction showed that the initially formed tertiary alcohol had rearranged in the hoped for manner on acid treatment.

Attempts were then made to repeat this Grignard reaction using the acetylene, oct-1-yn-3-ol (68) and (103). In this case however no detectable reaction occurred and in a variety of solvents, the starting acetylene (68) was recovered unchanged. However when the Grignard derivative of 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69), the preparation of which from (68) has already been described, was condensed with (103), the reaction proceeded as

anticipated and a mixture of (105) and (106) was obtained in about 25% yield together with recovery of starting material. The predominant product, 2-methyl-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne]-cyclopent-2-enone (105), was separated by chromatography. Treatment of the reaction mixture with 2,4-dinitrophenylhydrazine in acid gave rise to only one derivative, that corresponding to (106), the tetrahydropyranyl protecting group in (105) having cleaved under the strong acid conditions. It will be observed that in this Grignard reaction involving the acetylene (69) partial loss of the protecting group has again occurred as on a previous occasion.

Having established that acetylenic Grignards add to the 3-methoxycyclopent-2-enone system in the desired manner, attention was directed at analogous addition to the hydroxy-cyclopentenone (102). However when the Grignard derivatives of 3-(tetrahydro-2-pyranyloxy)oct-1-yne (69) and of phenylacetylene were reacted with (102) the predominant components, and the only ones identified, of the reaction products were the starting acetylenes.

It was considered that if the secondary hydroxyl group of (102) was blocked, Grignard acetylenic addition might be more successful.

Accordingly (102) was treated with dihydropyran in the presence of a catalytic amount of acid, when hydrolysis occurred and 1-hydroxy-3-methylcyclopentane-2,4-dione (100) was recovered quantitatively. This extreme lability of the 3-methoxycyclopent-2-enone system towards hydrolysis to give the parent 1,3-dione was observed in all compounds containing this system. Indeed 3-methoxy-2-methylcyclopent-2-enone (103) hydrolysed even when exposed to the laboratory atmosphere for a period of four days.

An attempt to block the hydroxyl group of (102) with chloromethyl ether also caused hydrolysis and again (100) was obtained in high yield. A number of attempts were then made to prepare the benzyl derivative of (102) but the usual procedure, refluxing the reagents in pyridine, resulted in recovery of the starting material (102).

An alternative to protecting the hydroxyl in the hydroxy-cyclopentenone (102) was the attractive possibility of a similar reaction with the precursor to (102), 1-hydroxy-3-methylcyclopentane-2,4-dione (100). This could lead to the cyclopentenone (107) directly thus eliminating the need for intermediate enol ether formation. Accordingly (100) was treated with two moles equivalent of dihydropyran but no appreciable reaction occurred and a 70% recovery of

starting material was obtained. When benzyl chloride was used in place of dihydropyran a black intractable oil resulted.

The cyclopentanetrione (89), the precursor of all the above compounds, crystallises from water as the monohydrate, the form in which it is generally used. It is probable that the molecule of water of crystallisation is attached to the non-enolic ketone function at C - 1. If this is so, treatment of (89) with diazomethane might lead directly to the acetal, 1,1-dimethoxy-3-methyl-4-methoxycyclopent-3-en-2-one (108). In the event treatment of (89) with diazomethane lead to the isolation of a new compound in 55% yield, which was shown by its spectroscopic properties to be, 3-methyl-4-methoxycyclopent-3-ene-1,2-dione (109). This 1,2-dione existed entirely in the diketone form as was shown by the fact that it did not give a colour with ferric chloride solution and by its N.M.R. spectrum (discussed in a later section). No evidence for the formation of the isomeric enol-ether (110) was obtained in this reaction.

The preparation of (109) seemed to provide a means of obtaining the ethylene ketal (111), the object of the early part of this work. However when (109) was reacted with an excess of ethylene

glycol in the usual manner, there was obtained in addition to recovery of starting material, a small amount of a crystalline compound which was identified as the tri-ketal (93).

#### Structures of Cyclopentanepolyones

The spectroscopic properties of the oxygenated cyclopentanes discussed in the previous section (Route 3) are of considerable interest and have been very useful in structural assignments. This spectroscopic data is tabulated in Table 2 (ultra violet), Table 3 (infra red) and Table 4 (nuclear magnetic resonance).

It is known that cyclopentane-1, 2-dione exists almost entirely in the enol-ketone form (112)<sup>62</sup>, and a similar observation has recently been made<sup>63</sup> for 2-acetylcyclopentane-1, 3-dione (113). The structure of 2-methylcyclopentane-1, 3-dione (94) has been discussed by Hiraga<sup>64</sup>, and he concluded that in the solid state a polymeric enol-ketone form predominated (114). This conclusion was based on the presence in the infra red spectrum (nujol mull) of

two bands, one in the 1550 - 1580  $\text{cm.}^{-1}$  region and the other in the 2300 - 2700  $\text{cm.}^{-1}$  region, which were found to be characteristic of a series of 2-substituted cyclopentane-1,3-diones. The strong and broad band at 1550 - 1580  $\text{cm.}^{-1}$  was attributed to a conjugated and a chelated carbonyl group. The band at 2300 - 2700  $\text{cm.}^{-1}$  was attributed to a strongly hydrogen bonded group. The weak, sharp band at 1680 - 1700  $\text{cm.}^{-1}$  was considered to be a function of the non-chelated carbonyl group either at the terminal positions of the polymer or on the monomeric molecule.

The N.M.R. of (94) strongly suggested that it was present in solution entirely as the enol-ketone and that a rapid equilibrium occurred between the tautomeric forms (115). Thus the four methyl protons, which occur as a singlet, have identical environments and there was no indication of a signal for the active hydrogen between the two keto groups.

The infra red spectrum (nujol mull) of the 1,3-dione, 1-hydroxy-3-methylcyclopentane-2,3-dione (100) was similar to that of (94) with the characteristic bands in the 1550 - 1580  $\text{cm.}^{-1}$ , 1680 - 1700  $\text{cm.}^{-1}$ , and 2300 - 2700  $\text{cm.}^{-1}$  regions. In addition a



hydroxyl band occurred at  $3350 \text{ cm.}^{-1}$ . This would suggest that in the crystalline state a similar polymeric structure to that described for 2-methylcyclopentane-1, 3-dione exists. In solution the N.M.R. showed the methyl group as a singlet which suggested that the keto-enolic structure is again the preferred form.

The N.M.R. of 3-methylcyclopentane-1, 2, 4-trione (89) has been described both by Elvidge<sup>65</sup> and Hiraga<sup>64</sup>. Hiraga stated that both the methyl and methylene groups appeared as singlets and concluded that of the two likely enolic forms (116) and (117), the former may be preferable. On the other hand Elvidge described the signals from the methyl and methylene groups as a triplet ( $J = 1 \text{ c.p.s.}$ ) and quartet ( $J = 1 \text{ c.p.s.}$ ) respectively. The addition of trifluoroacetic acid, expected to catalyse prototropy and of triethylamine, expected to yield a mesomeric anion, did not, it was stated, increase the coupling constant of  $1 \text{ c.p.s.}$  On this basis Elvidge suggested a rapid equilibrium existed between the tautomeric forms (118).

The N.M.R. of both the hydrated and anhydrous forms of 3-methylcyclopentane-1, 2, 4-trione was measured on a 100 m/c.

instrument, but no splitting of the methyl and methylene signals was observed. It is necessary therefore to question the basis on which Elvidge has postulated a rapid tautomeric equilibrium. Such an equilibrium may exist but intramolecular hydrogen bonding could result in one form (116) being preferred. It is unlikely that the enolic form (117) is a possible structure for this trione, as suggested by Hiraga, since no olefinic proton was observed in the N.M.R.

The N.M.R. of 2-methyl-3-methoxycyclopent-2-enone (103) showed the methyl group split as a triplet,  $J = 1.5$  c.p.s., the ring methylene protons appearing as asymmetric multiplets. This suggested long-range coupling through four carbon atoms. It was possible to show that splitting of the methyl group in this compound is a result of coupling with the methylene protons alpha to the carbonyl group and not with the alternative allylic methylene protons. This was clearly demonstrated by the isolation of 3-methyl-4-methoxycyclopent-3-ene-1,2-dione (109). The infra red spectrum (chloroform solution) of this compound showed bands at  $1745 \text{ cm.}^{-1}$ , attributed to the non-conjugated carbonyl,  $1695 \text{ cm.}^{-1}$  (conjugated carbonyl) and

1626  $\text{cm.}^{-1}$ , (Carbon double bond). The presence of the carbonyl band at 1745  $\text{cm.}^{-1}$ , ruled out the possibility of the isomeric compound (110) being the correct structure, for the latter would be expected to have only one carbonyl band at around 1700  $\text{cm.}^{-1}$  (compare cyclopentene-1,3-dione (120) which has one carbonyl absorption at 1700  $\text{cm.}^{-1}$ ).

The N.M.R. of this 1,2-dione (109) showed both the methylene and methyl groups as singlets so that no coupling occurs through the olefinic bond. Consequently the long range coupling observed in (103) must occur through the ring ketone function.

This observation was useful in assigning structure to the isomeric enol-ethers (101) and (102). One of these enol ethers showed a singlet for the methyl hydrogens and the other a triplet ( $J = 1.5 \text{ c.p.s.}$ ). The isomer with the singlet methyl was therefore assigned the structure (102) with the methylene group allylic to the double bond and the isomer with the methyl as a triplet assigned the structure (101), which would permit long range coupling through the carbonyl function. This assignment agreed with the infra red absorption measurements for the hydroxyl group.

The isomeric enol ether assigned structure (102) had an hydroxyl absorption band at  $3568 \text{ cm.}^{-1}$  (chloroform high dilution), whereas the value in the isomer (101) was  $3608 \text{ cm.}^{-1}$ . One would expect intramolecular hydrogen bonding to occur in (102) but not in (101) and this would account for the lower value in the former.

In the previous section it was stated that the bis-ethylene-ketal resulting from the hydrolysis of the tri-ketal (93) had the structure (99) rather than (98), on the basis of its N.M.R. The N.M.R. showed the methyl protons as a simple doublet,  $J = 11 \text{ c.p.s.}$ , and this can only be reconciled with structure (99). For if the isomeric (98) was the correct structure, further splitting of the methyl group would be expected to occur by long range coupling with the ring methylene group through the carbonyl function.

It is of interest to note that in the compounds, (104), (105) and (106) the methyl group appears as a triplet,  $J = 1.5 \text{ c.p.s.}$ , as to be expected in the light of the above discussion.

Route 4.

The fourth attempt at prostaglandin synthesis, outlined on flow sheet E.2, involved the preparation of the substituted cyclohexenol, 2-(6-carboxyhexyl)-4-methylcyclohex-4-enol (121a), by the synthetic sequence discussed below. Cleavage of the double bond in (121a) should result in the keto-aldehyde (122a) which on base treatment should undergo an internal aldol condensation and form the cyclopentane-diol (123a). It will be observed that (123a) contains both the requisite ring oxygen functions present in the prostaglandin molecule together with one of the side chains. Extension of the acetyl group into an eight carbon side chain containing a trans double bond and an hydroxyl group would result in the prostaglandin structure. A somewhat similar extension was used by Wiesner<sup>44</sup> in his partial synthesis of the prostaglandin structure described in the Review. In this case an acid chloride group rather than an acetyl function was extended into the requisite eight carbon side chain.

The preparation of the substituted cyclohexenol (121b) was carried out as follows. Esterification of pimelic acid gave

the diethyl ester (124), from which the acid ester (125) was prepared by partial hydrolysis<sup>66</sup>. Treatment of (125) with thionyl chloride resulted in 6-carboethoxycaproyl chloride (126). The Friedel-Crafts<sup>67</sup> condensation of the acid chloride (126) with p-methylanisole (127) in tetrachloroethane as solvent proceeded in virtually quantitative yield to give ethyl 7-(2-methoxy-5-methylphenyl)-7-oxo-n-heptoate (128). The use of nitrobenzene as solvent in this condensation reaction resulted in a somewhat lower yield.

The ester (128) was readily hydrolysed with alcoholic potassium hydroxide to the acid, 7-(2-methoxy-5-methylphenyl)-7-oxo-n-heptoic acid (129). Reduction of this keto-acid by the Clemmensen procedure,<sup>68</sup> gave an excellent yield of 7-(2-methoxy-5-methylphenyl)-n-heptoic acid (130).

Birch reduction of the substituted anisole (130) resulted in the diene (131), which was not isolated but treated directly with 2 M. oxalic acid at room temperature. Under these mild acid conditions, the diene (131) was hydrolysed to the non-conjugated acid, 2-(6-carboxyhexyl)-4-methylcyclohex-4-enone (132), a colourless liquid. This acid was identified by its formation of a

yellow crystalline 2, 4-dinitrophenylhydrazone on treatment with the reagent in phosphoric acid<sup>73</sup>. The ultra violet spectrum of this derivative, ( $\lambda_{\text{max}}$  365 m $\mu$ ;  $\epsilon$  19, 500) was typical of non-conjugated cyclohexanones. The N.M.R. spectrum provided convincing evidence for the structure of (132) and demonstrated the presence of one olefinic proton ( $\tau = 4.59$ , multiplet) as required by a trisubstituted double bond.

The acid (132) proved difficult to isolate by distillation or by chromatography of its methyl ester. In an attempt to obtain a crystalline solid at this stage, the aromatic acid (130) was converted into its amide (133) and the latter subjected to the Birch reaction. However the product from the Birch reaction could not be induced to crystallise neither would it form a tractable 2, 4-dinitrophenylhydrazone and consequently this aspect was not pursued.

The crude acid (132) as obtained from the Birch reaction, was treated with excess of diazomethane and the methyl ester (134) reduced directly with sodium borohydride. The product, the desired (121b), was obtained as a pale yellow liquid and was readily isolated by chromatography in 60% overall yield from the aromatic acid (130).

Evidence for the structure (121b) assigned to the borohydride reduction product was based on a positive colour reaction with tetranitromethane which indicated an isolated double bond. The molecular weight as determined by mass spectrometry was in agreement with the calculated value for the assigned structure and N.M.R. demonstrated the presence of one olefinic proton ( $\tau = 4.80$ , multiplet). Thin layer chromatography suggested that the product was homogeneous but gas liquid chromatography clearly demonstrated an approximately 1:1 epimeric mixture.

The next stage in the synthesis, the opening of the six membered ring in (121b), followed by cyclisation of the product (122b) to the cyclopentane-diol (123b), is well illustrated by reference to limonene (135).<sup>69</sup> In a successful synthesis of the naturally occurring 1-acetyl-4-isoprenyl-1-cyclopentene (136), limonene was converted to the monoepoxide (137), which in acid solution formed the diol (138). Sodium periodate cleaved the diol (138) to the ketoaldehyde (139), which cyclised in base to give the required (136) together with the hydroxy-ketone (140). This conversion of limonene into the hydroxy-ketone (140) duplicates exactly the hoped-for transformation of the cyclohexenol (121b) to the cyclopentane-diol (123b).



Initially a direct conversion of (121b) to the keto-aldehyde (122b) was attempted, but found unsuccessful. Thus treatment of (121b) with an excess of ozone at  $-70^{\circ}$  in ethyl acetate or at  $0^{\circ}$  in aqueous methanol<sup>70</sup>, afforded an intractable mixture of compounds which did not give a crystalline derivative when treated with 2, 4-dinitrophenylhydrazine. Rudloff's<sup>71</sup> method for cleaving double bonds, using an oxidising mixture of sodium periodate and potassium permanganate, was also unsuccessful in producing a tractable product and again the reaction mixture did not form a crystalline 2, 4-dinitrophenylhydrazone.

Treatment of (121b) with osmium tetroxide in an attempt to form the triol (141), resulted on work up in a black viscous liquid which streaked on a T.L.C. plate. This black liquid was treated directly with sodium periodate and over three days at room temperature, a white precipitate, presumably sodium iodate, was observed. This suggested some reaction was occurring but subsequent work up gave an intractable black liquid mixture which decomposed on distillation. The small amount of distillate did not give a crystalline precipitate with 2, 4-dinitrophenylhydrazine.

Finally the sequence of reactions used to convert limonene (135) to the keto-aldehyde (139) was repeated with the cyclohexenol (121b). Epoxidation of (121b) with *m*-chloroperbenzoic acid appeared to give a mixture of isomeric epoxides (142). Acid treatment of this epoxide mixture in an attempt to form the triol (141) followed by cleavage with sodium periodate to the keto-aldehyde (122b), did not appear hopeful on brief examination. A thorough investigation was not carried out however in view of the more promising developments in the next synthetic approach (Route 5).

Before completing the account of this section of the work the possibility was examined of extracting the cyclopentenediol, in which the hydroxyls are *cis*-orientated, from a mixture of *cis* and *trans* diols by acetal formation. This would obviously be useful in simplifying the stereochemical aspects of prostaglandin synthesis.

This possibility was examined using 'technical cyclopentenediol' as a model compound. This material was in fact a 70:30 mixture of the 1,4-(143) and 1,2-(144) cyclopentenediols. When this mixture was refluxed with an equimolar concentration

of paraformaldehyde in benzene containing a catalytic amount of p-toluenesulphonic acid, the product was more viscous and more polar than the starting diol. The infra red spectrum showed a reduced hydroxyl absorption (compared with the starting diol), and a broad band at  $1140 \text{ cm.}^{-1}$  (ether bonds). This suggested that intermolecular bonding had occurred to give (145) rather than the hoped for (146).

It was reported <sup>72</sup> that the reaction between cis-cyclopentane-1, 3-diol and p-nitrobenzaldehyde gave the acetal (147) in excellent yield. In deed this reaction was given as proof of the cis orientation of the hydroxyls in the starting compound. When 'technical cyclopentenediol' was reacted with p-nitrobenzaldehyde a crystalline compound was isolated which analysed correctly for a p-nitrobenzylideneacetal.

A distinction between the two possible acetals, (148) and (149), was possible on the basis of N.M.R. Thus in view of the symmetrical nature of (148), the two olefinic protons would be equally deshielded; similarly the two allylic protons. In fact the N.M.R. showed four multiplets ( $\tau = 3.85, 4.24, 4.67, 5.19$ ), each which integrated for one proton, showing clearly that (149) is the correct structure.

Route 5

The fifth route to the prostaglandins and the one currently being pursued envisaged a synthetic scheme which is outlined on flow sheet F.1. The starting point was the known compound, 2-(6-bromohexyl) cyclopentanone (150) which on bromination and elimination of hydrogen bromide should readily form the  $\alpha, \beta$ -unsaturated ketone (151). The crucial step in the synthesis was the Grignard addition of the acetylene (69) to this cyclopentenone (151). It was considered that the initially formed tertiary alcohol (152) would on acid treatment undergo an anionotropic rearrangement to give the allylic alcohol (153). A similar type of rearrangement has been observed with analogous cyclohexenones.

Replacement of bromine by nitrile and hydrolysis of the nitrile group would convert the allylic alcohol (153) to the acid (154). Allylic oxidation of (154) and removal of the tetrahydropyranyl protecting group would lead to (155). The remaining problems would be to introduce a further oxygen function into the cyclopentenone ring at the allylic position and to achieve selective reduction of the enyne system to a trans-double bond, so resulting

in the prostaglandin structure. One way of accomplishing the former, introduction of a ring oxygen function, would be a Wohl-Ziegler reaction between the cyclopentenone (155) and N-bromosuccinimide to give (156) followed by displacement of the bromine atom with hydroxyl. The double bond in the ring could be saturated by formation of the epoxide (157), replacement of the oxide bridge by sulphur and removal of sulphur by reaction with Raney nickel to give (158). Trans reduction of the triple bond would afford PGE<sub>1</sub>.

A possible route to 2-(6-bromohexyl) cyclopent-2-enone (151) appeared to be a direct alkylation of cyclopent-2-enone with 1,6-dibromohexane. Thus Conia<sup>74</sup> prepared 2-(prop-2-enyl)-cyclohex-2-enone (159) by condensation of allyl bromide with cyclohex-2-enone using sodium t-amylate as base. The yield in this case however was only 4%. When n-propyl bromide was condensed with cyclopentenone in the presence of sodium t-amylate, as a trial experiment, a considerable amount of resinous material was obtained and there was no evidence for the formation of 2-n-propylcyclopent-2-enone (160).

2-(6-Bromohexyl) cyclopentanone (150) was prepared as described in the literature <sup>75</sup> as follows. The Dieckmann condensation of diethyladipate resulted in 2-carboethoxycyclopentanone (161). <sup>76</sup> 1,6-Dibromohexane was prepared initially by lithium aluminium hydride reduction of diethyl adipate, and treatment of the resulting 1,6-hexanediol with hydrobromic acid <sup>77</sup>. The condensation of 1,6-dibromohexane with 2-carboethoxycyclopentanone (161) resulted in 2-carboethoxy-2-(6-bromohexyl) cyclopentanone (162) from which (150) was obtained by hydrolysis and decarboxylation in refluxing hydrobromic and acetic acid.

The formation of the cyclopentenone (151) by bromination of the ketone (150) and hydrogen bromide elimination appeared a plausible proposition in view of the tendency of ketones to react preferentially with bromine at the more substituted  $\alpha$ -position in acidic solution. The known ability of silica to selectively eliminate tertiary bromine as hydrogen bromide <sup>78</sup> would then lead to the desired cyclopentenone (151).

In practice this procedure caused considerable difficulty. Bromination resulted in mixtures of various bromoketones which

being unstable rapidly darkened on standing with hydrogen bromide evolution.

Thus when the ketone (150) was treated in tetrahydrofuran with one mole equivalent of phenyltrimethylammonium bromide perbromide<sup>79</sup> and the product directly chromatographed on silica, a complex mixture of compounds was obtained including the starting material and a small amount of the desired cyclopentenone (151).

With one mole equivalent of N-bromosuccinimide in refluxing carbon tetrachloride, mono-bromination appeared to occur primarily at the less substituted  $\alpha$ -position. Similarly with one mole equivalent of bromine in ether, the ketone (150) appeared to afford 2-bromo-5-(6-bromohexyl) cyclopentanone (163) exclusively.

With one mole equivalent of bromine in acetic acid followed by immediate silica chromatography of the product, the ketone (150) gave a mixture of compounds which included a small amount, identified by T.L.C., of the desired enone (151). The use of the bromine-dioxan complex<sup>80</sup> as brominating agent, followed by silica chromatography afforded an approximate 20% yield of the desired enone (151).

The best results were obtained when pyridinium bromide perbromide<sup>81</sup> in acetic acid was used as the brominating agent. With one mole equivalent of this reagent followed by silica chromatography, the ketone (150) gave an approximate 1:1 mixture of starting material and cyclopentenone (151). With 70% excess reagent, the same procedure resulted in 14% of unchanged starting material, established by G.L.C., and the main product, the desired enone (151) was present to the extent of about 60% by G.L.C. Other bromo-ketones appeared to make up the rest of the product mixture and chromatographic separation was difficult. The best results were obtained with a 20% excess of pyridinium bromide perbromide followed by a combination of silica gel chromatography and distillation. By this technique yields of reasonably pure 2-(6-bromohexyl) cyclopentenone (151) varied between 20 - 35%

It might be added that methods other than silica chromatography for hydrogen bromide elimination were tried, namely lithium chloride in dimethylformamide and propylene oxide, but neither were as efficient as silica.



In view of the difficulty in preparing the cyclopentenone (151) by the above procedures, other methods of preparation were investigated. The preparation of the enol acetate (164) from the ketone (150) followed by treatment of (164) with one mole equivalent of bromine would result in the exclusive formation of the tertiary bromide (165) from which the desired cyclopentenone (151) might be prepared by silica dehydrobromination. Unfortunately when the ketone (150) was refluxed with isopropenyl acetate in the presence of *p*-toluenesulphonic acid, the product was shown by G. L. C. to be a 1:1 mixture of the two possible enol acetates (164) and (166). Treatment of this mixture with one mole equivalent of pyridinium bromide perbromide followed by silica chromatography resulted in a complex mixture of products which included only a small amount of the desired (151).

Ansell has summarised the methods of preparing cyclopentenones<sup>82</sup> and developed a new route to these compounds which involved the Grignard reaction of alkyl halides with 2-isobutoxy-cyclopent-2-enone (167). The initially formed tertiary alcohol (168) on acid treatment lost water with concomitant hydrolysis to

give the 2-substituted cyclopentenone (169). A series of cyclopentenones were prepared in good yield by this reaction. This approach, the Grignard addition of a suitable alkyl halide to 2-isobutoxycyclopent-2-enone (167), appeared useful in the present instance.

Cyclopentane-1, 2-dione (170) was therefore prepared in excellent yield by a method described in the literature<sup>83</sup>. Glutaric acid was esterified and condensed with diethyl oxalate to give 3, 5-dicarboethoxycyclopentane-1, 2-dione (171). Hydrolysis of this diester (171) in 20% sulphuric acid afforded cyclopentane-1, 2-dione (170) as a white, low melting, crystalline solid, which was converted immediately into 2-isobutoxycyclopent-2-enone (167)<sup>82</sup>.

A suitable alkyl halide for Grignard addition to (167) appeared to be the previously undescribed 7-(tetrahydro-2-pyranyloxy) heptyl bromide (172). This was readily prepared by lithium aluminium hydride reduction of ethyl 7-bromoheptanoate (173)<sup>45</sup> to 7-bromoheptyl alcohol (174) as described in the literature<sup>84</sup> and treatment of this alcohol with dihydropyran in the presence of a catalytic amount of acid.

It was considered that Grignard addition of the alkyl halide (172) to 2-isobutoxycyclopent-2-enone (167) would result in the formation of the cyclopentenone (175). Grignard reaction of the acetylene (69) with (175) would, it was hoped, result in (176) by an anionotropic rearrangement as described earlier. The compound (176) would be suitable for elaboration into the prostaglandin structure by reactions similar to those described above for elaboration of (154).

Unfortunately the alkyl halide (172) would not react with magnesium in the usual Grignard solvents. Similarly attempts to make the lithium salt of (172) and react this with 2-isobutoxycyclopent-2-enone (167) were also unsuccessful. The use of a different protection group to dihydropyran, namely trityl chloride, resulted in the formation of 7-triphenylmethoxyheptyl bromide (177), from the alcohol (174), but this likewise would not react with magnesium or lithium.

Attempts to prepare the mono-Grignard derivative of 1,6-dibromohexane and react this with 2-isobutoxycyclopent-2-enone (167) not surprisingly failed, a complex mixture resulting.

Thus the use of 2-isobutoxycyclopent-2-enone (167) as a means of preparing a suitably 2-substituted cyclopent-2-enone was unsuccessful.

In the synthetic work of Weisner<sup>44</sup>, described earlier in the review section, the 2-substituted cyclopentenone (178) was prepared surprisingly from the  $\beta$ -ketoester (179) which was first treated with one mole of bromine, to form a monobromo derivative. The latter when refluxed for sixteen hours in ethanolic 20% sulphuric acid was converted to the cyclopentenone (178), separated by chromatography. Presumably the monobromo derivative was (180) which dehydrobrominated to give (181). Ester hydrolysis, decarboxylation and double bond isomerisation would lead to (178). On this basis it seemed reasonable to assume that treatment of 2-(6-bromohexyl) cyclopentanone (150) with one mole of bromine, which had been shown to give the mixture of bromo-ketones, followed by refluxing of the crude product with ethanolic 20% sulphuric acid for sixteen hours might lead to the desired cyclopentenone (151).

Accordingly the ketone (150) was treated with one mole equivalent of the bromine-dioxan reagent<sup>80</sup> and the crude product refluxed for eleven hours in ethanolic 20% sulphuric acid.

Separation of the products by chromatography gave a 12% yield of the cyclopentenone (151).

When the ketone (150) was treated with one mole equivalent of bromine in acetic acid and the product refluxed for seventeen hours in ethanolic 20% sulphuric acid, there was isolated in addition to the cyclopentenone (151) formed in 22% yield, a new compound which was shown to be the diosphenol, 3-(6-bromohexyl) cyclopentane-1, 2-dione (182), formed in about 25% yield. The formation of this compound (182) was presumably a result of the hydrolysis and dehydrobromination of an intermediate 2, 2-dibromo-derivative (183).

In view of the unpromising results obtained by the application of Wiesner's bromination - refluxing ethanolic sulphuric acid treatment to the 2-substituted cyclopentanone (150), it was decided to repeat this procedure with the  $\beta$ -ketoester (162), which is exactly analogous to the  $\beta$ -ketoester (179) used by Wiesner to prepare the cyclopentenone (178), and which is the initial product from the condensation of 1, 6-dibromohexane with 2-carboethoxy cyclopentanone (161).

When the  $\beta$ -ketoester (162) was treated with one mole equivalent of bromine in acetic acid and the product immediately refluxed with ethanolic 20% sulphuric acid, there remained after a period of eighteen hours, a brown oily layer at the bottom of the reaction flask. Work up of the product at this stage showed only a small amount of cyclopentenone to be present. It was considered that the brown heavy layer in the reaction flask was probably unreacted bromoketone and T.L.C. appeared to support this. The reflux time was therefore extended until the heavy brown layer disappeared and the reaction solution became homogeneous - about thirty six hours. From the reaction product at the end of this period there was isolated by silica chromatography a cyclopentenone in 23% yield which was considered initially to be the desired cyclopentenone (151). It soon became apparent however that the product was not (151) but 2-(6-ethoxyhexyl) cyclopent-2-enone (184), resulting from the replacement of bromide by ethoxide.

Similarly when the  $\beta$ -ketoester (185) was subjected to the same treatment the product was 2-(5-ethoxypentyl) cyclopent-2-enone (186).

It will be recognised that a considerable amount of effort was expended to prepare the cyclopentenone (151) by a number of methods but recourse had to be made to the bromination, dehydrobromination procedure, described earlier. This method was not entirely satisfactory and presented practical difficulties of separation. After a period of trial and error the best yields of cyclopentenone (151) were obtained by treatment of the ketone (150) in acetic acid with 20% excess pyridinium bromide perbromide, immediately followed by silica chromatography of the bromo-product. The very crude cyclopentenone (151) obtained at this stage was distilled, chromatographed again and then distilled for a second time to give a 25-35% yield of acceptably pure material.

Attention was then turned to the addition of the Grignard derivative of 3-(tetrahydro-2-pyranyloxy)oct-1-yne (69) to the cyclopentenone (151). It will be recollected that the initially formed tertiary alcohol (152) from this reaction would, it was hoped, on acid treatment undergo an anionotropic rearrangement to give the allylic alcohol (153). Before proceeding with this reaction a preliminary investigation was made of the addition of the Grignard

derivative of phenylacetylene to cyclopent-2-enone. When the Grignard complex from this preliminary reaction was decomposed with saturated ammonium chloride, there was identified in the reaction mixture in addition to unchanged starting materials and a certain amount of resinous material, a new product which was separated by chromatography. This new product, formed in about 25% yield, was identified as the unexpected 3-(2-phenylethynyl) cyclopent-2-enone (187). Spectroscopic comparison with the previously prepared 2-methyl-3-(2-phenylethynyl) cyclopent-2-enone (104) provided complete proof of structure. In order to explain the formation of (187) in this reaction it was assumed that the initially formed tertiary alcohol (188) underwent the desired anionotropic rearrangement on treatment with ammonium chloride to give the allylic alcohol (189). The mode of oxidation of this alcohol (~~188~~<sup>189</sup>) to the unsaturated ketone (187) is not readily explicable although aerial oxidation is an obvious candidate.

A second trial experiment was then run between the Grignard derivative of 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69) and cyclopent-2-enone. Distillation of the crude product gave a



15% recovery of starting acetylene (69) and a higher boiling fraction which was chromatographed on silica. From the eluted fractions there was isolated by further chromatography a liquid acetylene with absorption in the ultra violet at 232  $\mu$ , ( $\epsilon$  10,000) which supported the presence of an enyne system in the molecule. On the basis of this and N.M.R. evidence this acetylene was considered to be 3-(3-hydroxyoct-1-yne) cyclopent-2-enol (190). In this experiment therefore it appeared that the expected anionotropic rearrangement did indeed occur resulting in the allylic alcohol (190). The yield however was very poor and furthermore loss of the tetrahydropyranyl protecting group occurred. Repetition of this experiment in other Grignard solvents and also the preparation of the lithium salt of 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69) and the attempted addition of this to cyclopent-2-enone in liquid ammonia did not improve the yield. It did appear however that in addition to the allylic alcohol (190) being formed in ~~these~~ reactions some of the allylic alcohol (191) in which the protecting group was intact was also present.

When the Grignard derivative of 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69) was condensed in ether with 2-(6-bromohexyl) cyclopent-2-enone (151) and the resulting complex decomposed with ice-cold 5% sulphuric acid, the major product, formed in 40-50% yield, was identified as the allylic alcohol 2-(6-bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy) oct-1-yne] cyclopent-2-enol (192). The assigned structure was firmly based on spectroscopic evidence. The ultra violet spectrum showed one maximum at 234 m $\mu$  ( $\epsilon$  10, 400). In the infra red bands were observed at 3500 (hydroxy), 2250 (very weak, acetylenic), 1700 (weak, tetra-substituted double bond), 1130 (pyranyl ether), 1050 (secondary alcohol) cm.<sup>-1</sup>. The N.M.R. was particularly diagnostic and demonstrated the presence of an  $\alpha$ -bromomethylene group ( $\tau$  = 6.63, triplet) and a primary methyl group ( $\tau$  = 9.09 singlet). Distillation of this alcohol (192) and its transformation products resulted in extensive decomposition.

The separation of the allylic alcohol (192) by chromatography of the reaction mixture was complicated by three factors. Firstly some 40-50% of the starting cyclopentenone (151) remained unchanged and the R<sub>f</sub> value of this material was only slightly greater than that of the alcohol (192).

Secondly the alcohol (192), which contains three asymmetric centres, was present as an isomeric mixture and did not elute cleanly from silica chromatographic columns. Thirdly the Grignard reaction resulted in some loss of the tetrahydropyranyl protecting group and a small amount of the allylic alcohol (193) was present.

Repetition of the Grignard reaction between the acetylene (69) and the cyclopentenone (151) in tetrahydro-furan as solvent in an effort to improve the yield, resulted in little if any of the desired allylic alcohol (192) being formed.

Oxidation of (192) by means of Brown's two phase, ether-chromic acid procedure<sup>85</sup> resulted in the smooth conversion of (192) to 2-(6-bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne] cyclopent-2-enone (194). This reaction was conveniently followed by observing the change in the ultra violet maximum from 234 m $\mu$  to 269 m $\mu$ . The absorption maximum of 269 m $\mu$  for (194) was in complete agreement with the previously recorded value for this chromophore observed in the intermediate (105).

It was of interest that T.L.C. evidence suggested the

unprotected alcohol (193) present in the starting material was converted in the above oxidation reaction to the cyclopentenone (195); the propargylic hydroxyl did not appear affected by the oxidation conditions.

When (194) was boiled for fifteen minutes in aqueous-methanolic 5% sulphuric acid, the tetrahydropyranyl protection group was cleaved to give 2-(6-bromohexyl)-3-(oct-1-yn-3-ol) cyclopent-2-enone (195). The structure of (195) was unambiguously established as follows. The observation of only one peak when the compound was run on G.L.C. demonstrated the likelihood of its being a single substance. The infra red spectrum showed bands at 3500 (hydroxyl), 2260 (acetylene), 1700 (ketone) and 1615 (double bond)  $\text{cm.}^{-1}$ . The position of the carbonyl was measured exactly at 1703  $\text{cm.}^{-1}$  by means of a high dilution spectrum. The ultra violet maximum,  $\lambda_{269}$  ( $\epsilon$  18,000), was in agreement with previously recorded values for this chromophore. The N.M.R. provided strong evidence for the assigned structure and showed one primary methyl as a singlet ( $\tau$ , 9.08), an  $\alpha$ -bromomethylene ( $\tau$ , 6.61, triplet) and a propargylic methine proton attached to a carbon carrying a

hydroxyl ( $\tau$ , 5.4, multiplet). The molecular weight determined by mass spectrometry agreed with the calculated value of 368 and confirmed the presence of one bromine atom.

The ketone (195) formed a red 2,4-dinitrophenylhydrazone the microanalysis of which was in agreement with the calculated value. When the ultra violet spectrum of this derivative was compared with that for the 2,4-dinitrophenylhydrazone of the intermediate (105), the two were found to be superimposable.

The next stage in the synthesis was the replacement of the terminal bromine in the cyclopentenol (192) by nitrile to give (196) and hydrolysis of the nitrile (196) to the acid (154). Allylic oxidation of this acid and removal of the protecting group by the above procedures would lead to the intermediate (155).

Treatment of the cyclopentenol (192) with sodium cyanide in aqueous methanol resulted in recovery of starting material. However, when the reaction was carried out in dimethylformamide the bromine atom was smoothly displaced by cyanide to give (196),  $\lambda_{\text{max}}$  238 ( $\epsilon$  7600). The infra red spectrum of this nitrile showed a peak at 2245  $\text{cm.}^{-1}$  (nitrile) and a weaker peak at 2215  $\text{cm.}^{-1}$  (acetylene).

The resolution and intensity of these two bands were increased in the keto-nitrile (197) resulting from the oxidation of (196) and removal of the tetrahydropyranyl protecting group by the above procedure.

Attempts to hydrolyse the nitrile to the acid have so far proved unsuccessful. The keto-nitrile (197) was largely unaffected by refluxing 50% sulphuric acid. When refluxed with dilute sodium hydroxide, the hydroxy nitrile (196) was recovered unchanged and similarly with ethylene glycol as co-solvent. In ethanolic 50% sulphuric acid (196) gave no evidence for the formation of the desired acid (154). In an attempt to make the amide (198) the nitrile (196) was treated with 30% hydrogen peroxide in base but was unaffected by these conditions.

In view of the difficulties of nitrile hydrolysis, the allylic alcohol (199) was prepared by the addition of the Grignard derivative of the acetylene (69) to 2-(5-bromopentyl) cyclopent-2-enone (200) in a manner analogous to the preparation of (192). Condensation of the sodium salt of malonic ester with (199) should result in (201), which on hydrolysis and decarboxylation should afford the desired acid (154). This malonic ester condensation with (199) is

currently under investigation. Preliminary results have so far been disappointing.

One final aspect of this work has received attention and that has been the problem of introducing a second oxygen function into the cyclopentane ring. This has been attempted in two ways. There are a number of examples in the steroid field where ketalisation of the 3-keto group in  $\Delta^4$ -3-keto-steroids results in the double bond moving out of conjugation into the  $\Delta^{5,6}$  position. It seemed possible therefore that ketalisation of the cyclopentenone (155) would result in the ethylene ketal (202) in which the double bond has undergone an allylic shift. Selective hydroboration of the double bond in (202), followed by removal of the ketal group and trans reduction of the triple bond would result in the prostaglandin structure. This method was evaluated on two suitable model compounds namely (195) and (203). The latter was prepared by the addition of the Grignard derivative of the acetylene (69) to 2-(6-ethoxyhexyl) cyclopent-2-enone (184) followed by the usual oxidation and protecting group removal procedures.

Treatment of either of these compounds with an excess of ethyleneglycol in the presence of p-toluene sulphuric acid caused darkening of the reaction mixture and the reaction product tended to smear on T.L.C. plates. Two discernible compounds appeared to be present however, one with the same  $R_f$  value as the starting material and one with a higher  $R_f$  value. The ultra violet spectrum of the product mixture showed a major maximum at 269  $m\mu$  (starting material) and a less intense maximum at 228  $m\mu$  (possibly an enyne system). It was considered that the latter maximum was due either to the desired ethylene ketal (204) or to the non-conjugated ketone (205) isomeric with the starting material.

When the less polar material was separated from unchanged starting material (> 50%) by silica chromatography, a small amount of liquid was obtained which by its infra red and ultra violet spectroscopic properties was now shown to be identical to the starting material (195). The  $R_f$  value of this material which before chromatography had been higher than the starting material was now, after chromatography, equal to the starting material. In other words, assuming that this initially less polar material was (204)



or (205), silica chromatography appeared to have caused deketalisation or isomeration respectively to give in both cases starting material. In view of the major recovery of starting material, this method did not appear suitable for the purpose of introducing a second oxygen function into the cyclopentane ring.

The second method of achieving this objective, and the one mentioned in the early part of this discussion, was by means of a Wolf-Ziegler<sup>86</sup> reaction between the cyclopentenone (155) and N-bromosuccinimide. There are pertinent precedents for this type of reaction. Thus an intermediate in a successful synthesis<sup>87</sup> of dihydrocinerolone (206) was the bromocompound (207) which was formed by the reaction of N-bromosuccinimide with 2-n-butyl-3-methylcyclopent-2-enone (208). Tetrahydropyretrolone (209) was synthesised in an analogous manner<sup>88</sup> from 2-n-amyl-3-methylcyclopent-2-enone (210). More recently the reaction of cyclopent-2-enone with N-bromosuccinimide has been stated to give the 4-bromocompound (211) rather than the 5-bromocompound (212) on the basis of N.M.R. evidence,<sup>89</sup> although there must remain some doubt about this assignment.

In order to obtain comparative N.M.R. data 2-methylcyclopent-2-enone (213) was prepared by the Grignard reaction between methyl iodide and 2-isobutoxycyclopent-2-enone (167)<sup>82</sup>. When this compound (213) was treated with N-bromosuccinimide for twenty-two hours, an excellent yield of a bromo-cyclopentenone was obtained which was shown by N.M.R. to be either (214) or (215). A distinction between these two possibilities could not be made on the basis of the evidence. Treatment of the product of this reaction with 2,4-dinitrophenylhydrazine in acid caused loss of bromine and a red derivative to form. The nature of this derivative is not at the moment clear but is presumed to correspond to (216) or possibly to a dimer of this<sup>89</sup>. When the reaction between (213) and N-bromosuccinimide was repeated, it proceeded much more quickly than on the first occasion and two products were identified by T.L.C., as against one product on the first occasion. Further the products from the second reaction turned black on standing at room temperature whereas the product from the first reaction was quite stable. Clearly this reaction requires further investigation.

The reaction of the model cyclopentenone (203) with N-bromosuccinimide to form (217) is currently being evaluated.

TABLE 2

Ultraviolet Spectra of Oxygenated Cyclopentanones ( $m\mu$ )

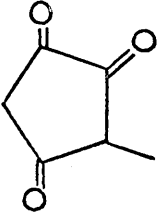
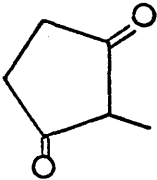
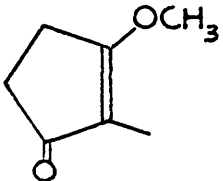
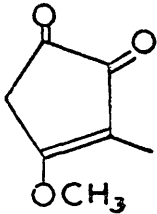
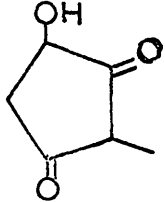
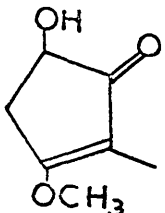
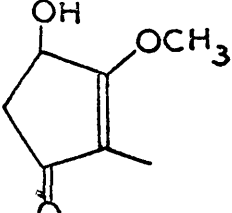
COMPOUND	Methanol		0.1 N. HCl		0.1 N. NaOH	
	$\lambda_{\max}$	$\epsilon$	$\lambda_{\max}$	$\epsilon$	$\lambda_{\max}$	$\epsilon$
	274,	8350	267, 10850 (literature value)		310, 13450 (lit. value)	
	256,	14000	252, 15750		269, 20800	
	252,	18650				
	273,	12100				
	249,	14800				
	257,	18400				
	251,	18400				

TABLE 3

Infrared Spectra ( $\text{cm}^{-1}$ ) of Oxygenated Cyclopentanones

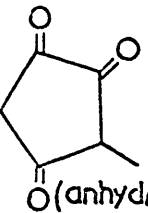
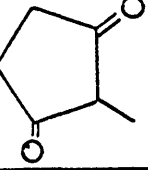
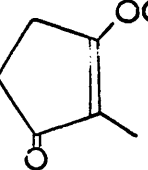
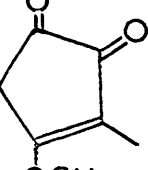
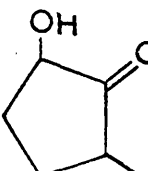
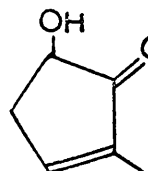
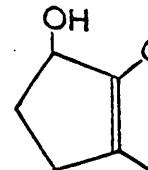
COMPOUND	NUJOL	$\text{CHCl}_3$ solution			$\text{CCl}_4$ solution		
		$\nu$	$\Delta\nu_{\frac{1}{2}}$	$\epsilon$	$\nu$	$\Delta\nu_{\frac{1}{2}}$	$\epsilon$
 (anhydrous)	3540 3420 2620 1735 1675 1650	3476	56		3476	36	
	2620 1690 1575	1742	23		1742	31	
	1680 1635	1686	21	270	1700	15	450
	1740 1700 1630	1745	13	190	1746	9	200
	3300 2620 1670 1540						
	3350 1675 1605	3568	55	40	3570	21	
		3608	45	60			
		1697	26	250			
		1637	24	680			

TABLE 4

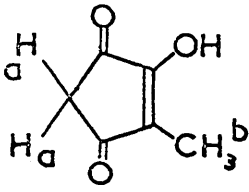
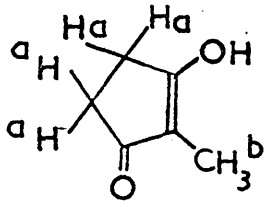
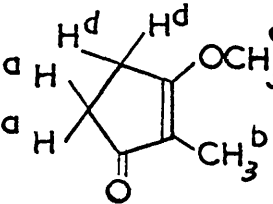
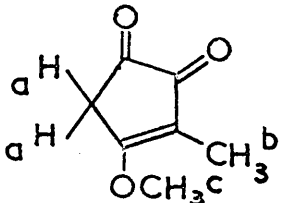
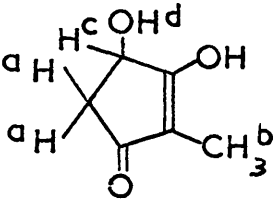
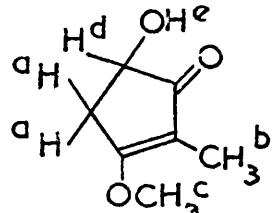
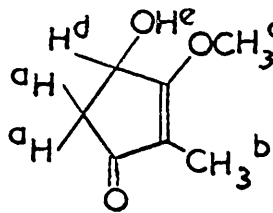
78

N.M.R Spectra of Oxygenated Cyclopentanones ( $\tau$  values)

s=singlet

t=triplet

m= multiplet

COMPOUND	H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>	H <sub>d</sub>	H <sub>e</sub>	SOLVENT
	6.94(s) 7.00(s)	7.98(s) 8.00(s)				PYRIDINE CDCl <sub>3</sub>
	7.53(s)	8.14(s)				PYRIDINE
	7.40(m)	8.44(t) J=1.5 cps.	6.05(s)	7.70(m)		CCl <sub>4</sub>
	7.21(s)	8.15(s)	5.71(s)			CCl <sub>4</sub>
	7.15(m)	8.08(s)	5.04(m)	7.00(s)		PYRIDINE
	7.50(m)	8.28(s)	5.81(s)	5.05(m)	6.79(s)	CDCl <sub>3</sub>
	7.20(m)	8.35(t) J=1.5 cps.	6.01(s)	5.70(m)	6.76(s)	CDCl <sub>3</sub>

EXPERIMENTAL

All melting points were determined on a Kofler block and are uncorrected. All boiling points are uncorrected.

Infrared solution spectra were recorded by Mrs. F. Lawrie on a Unicam S.P.100 double-beam spectrophotometer equipped with an S.P.130 sodium chloride prism-grating double monochromator. Some infrared solution spectra were recorded on a Perkin-Elmer 237 spectrophotometer. The infrared spectra of nujol mulls and of liquid films were recorded on a Unicam S.P.200 spectrophotometer,

Ultra-violet spectra were recorded on a Unicam S.P.800 spectrometer.

Nuclear magnetic resonance spectra were recorded by Mr. J. Galt and Mr. J. Lennon on a 60 megacycle spectrometer unless otherwise stated. Tetramethylsilane was used as the internal reference.

Thin layer chromatoplates (T.L.C.) and thick layer preparative chromatoplates were prepared from Merck's 'Kieselgel G.'

Gas-liquid chromatograms (G.L.C.) were run on a Pye-Argon Chromatograph with a Strontium-90 ionisation detector.

Mass spectral data was recorded on an A.E.I. M.S.9 mass spectrometer.

Microanalyses were by Mr. J.M.L. Cameron, B.Sc., and his staff.

Diethyl 2-acetylnonanedioate (44)

Sodium (7.22 g., 0.314 m.) was dissolved in dry methanol (100 cc.). To this solution was added sodium iodide (1.8g.) and ethyl acetoacetate (40.8 g., 0.314 m.). To the stirred and heated solution was dripped in ethyl 7-bromoheptanoate (47.26 g., 0.20 m.) and refluxing continued for 2 hours 45 minutes.

The solution was cooled and poured into an excess of ice cold dilute sulphuric acid. The acid solution was ether extracted, the ether extract washed with sodium bicarbonate, brine and dried. The solvent was removed and the liquid residue distilled. After an initial recovery of ethyl acetoacetate, diethyl 2-acetylnonanedioate distilled as a colourless liquid, b.p. 132-135<sup>o</sup>/0.02 mm., 42.18 g. (74% yield).  $n_D^{20} = 1.4455$ .  $\nu_{\max.}$  (neat) 1740, 1720, 1650 ( $\beta$ -ketoester)  $\text{cm}^{-1}$ ,  $\lambda_{\max.}$  245  $\text{m}\mu$ , ( $\epsilon = 600$  in methanol) N.M.R. ( $\text{CCl}_4$ ),  $\tau = 5.85$  (4 H; two overlapping quartets, ester methylene groups),  $\tau = 6.71$  (1 H; triplet; enolic proton),  $\tau = 7.86$  (3 H; singlet; acetyl methyl). (Found: C, 62.66; H, 8.62.  $\text{C}_{15}\text{H}_{26}\text{O}_5$  requires C, 62.92; H, 9.15).

1-Methoxydec-1-en-3-yn-5-ol (46)

Magnesium (24 g., 1.0M.) was placed in a two litre 3-necked flask fitted with reflux condenser, stirrer and dropping funnel. The magnesium was covered with 200 cc. of dry tetrahydrofuran and nitrogen passed through the system. Ethyl bromide (109 g., 1 mole) was added dropwise and the reaction initiated by grinding. On completion of the formation of ethyl magnesium bromide, the solution was cooled in ice and freshly distilled 1-methoxybut-1-en-3-yne (45), (90 g., 1.1 m.), in 600 cc. of dried methylene chloride added dropwise over 20 minutes. A vigorous reaction occurred which was completed by refluxing for 10 minutes.

To the ice cold solution of the acetylenic Grignard, n-hexanal (100 g., 1.0 m) was added dropwise. A mild reaction occurred. After the addition, the solution was refluxed for 45 minutes.

The Grignard complex was decomposed by the addition of 250 cc. of saturated ammonium chloride. The organic layer was separated, brine washed and dried. After solvent removal, the liquid residue was distilled to give 1-methoxydec-1-en-3-yne-5-ol as a pale yellow oil, b.p. 109-112°/0.02 mm., 47.12 g., (48% yield).  $n_D^{20} = 1.4927$ .  $\nu_{\max.}$  (neat), 3500, 2220, 1635  $\text{cm}^{-1}$   $\lambda_{\max.}$  241 m $\mu$  (c13600) in  $\text{CH}_3\text{OH}$ ). (Found: C, 72.36; H, 9.97.  $\text{C}_{11}\text{H}_{18}\text{O}_2$  requires C, 72.49; H, 9.96).



1, 1-Dimethoxy-4-bromodeca-2, 3-dien-5-ol (52)

1-Methoxydec-1-en-3-yn-5-ol (46), (16.47 g., 0.09 m.), was placed in a 250 cc., 3-necked flask and dry methanol (100 cc.) added. The stirred solution was cooled to  $-3^{\circ}\text{C}$ . in an ice salt cooling bath. To this solution was added over 20 minutes N-bromosuccinimide (17.01 g., 0.095 m.), previously recrystallised and dried. Stirring was continued at  $-3^{\circ}\text{C}$ . for a further 45 minutes and then for 2 hours at room temperature. The reaction mixture was filtered, poured into excess sodium bicarbonate and ether extracted. The ether layer was brine washed and dried. After removal of solvent there remained 23.92 g., (91% crude yield), of a pale yellow oil, 1, 1-dimethoxy-4-bromodeca-2, 3-dien-5-ol.  $n_{\text{D}}^{20} = 1.4938$ .  $\nu_{\text{max}}$  (neat), 3500, 1980 (weak), 1120, 1060  $\text{cm}^{-1}$ . The product distilled with decomposition at  $114^{\circ}/0.01\text{mm}$ . A pure sample was isolated by silica thick plate chromatography with benzene as the solvent system. The pure sample had  $n_{\text{D}}^{20} = 1.4980$ . (Found: C, 49.16; H, 6.97;  $\text{C}_{12}\text{H}_{21}\text{O}_3\text{Br}$  requires C, 49.15; H, 7.17).

Condensation of Diethyl 2-acetylnonanedioate (44) with  
1,1-Dimethoxy-4-bromodeca-2,3-dien-5-ol (52)

(a) Sodium ethoxide as base. Sodium (0.254 g., 0.011 m.) was dissolved in dry ethanol(30 cc.) and to the cooled solution was added the ketoester (44), (3.17 g., 0.011 m.). To the stirred and refluxing solution was added dropwise the bromoallene (52), (2.535g., 0.009 m.). Stirring and refluxing was continued for 2 hours, 15 minutes. The solution was cooled, filtered from sodium bromide, and the filtrate ether extracted. The ether extract was brine washed, dried and the solvent removed. The liquid residue distilled as a pale yellow liquid, b.p. 110 - 115<sup>o</sup>/0.03 mm.,  $n_D^{20} = 1.4452$ .  $\nu_{\max.}$  (neat), 2280, 1730, 1060  $\text{cm}^{-1}$ . The N.M.R. ( $\text{CCl}_4$ ) showed the absence of an acetyl methyl group. The product did not form a 2,4-dinitrophenylhydrazone. (Found C, 63.25; H, 9.03.  $\text{C}_{27}\text{H}_{46}\text{O}_8$  requires C, 65.03; H, 9.30).

(b) Potassium butoxide in tertiary butanol as base. Potassium (0.403 g., 0.010 m.) was dissolved in tertiary butanol (40 cc.) under a nitrogen atmosphere. To the cooled solution was added the keto-ester (2.986 g., 0.010 m.). To the stirred and heated solution was added dropwise the bromoallene (5B), (3.842 g., 0.0131 m.) and refluxing continued for 45 minutes. The solution was cooled and filtered from potassium bromide (1.2 g) the weight of which corresponded to a reaction approximately 50% completed. The filtrate was worked up as in (a) and the liquid residue distilled over a wide range, 88 - 124<sup>o</sup>/0.04 mm., and was shown by T.L.C. to be a mixture of compounds including both starting materials.

(c) Potassium butoxide in benzene as base. A solution of potassium butoxide was made from potassium (0.540 g., 0.0138 m.) and tertiary butanol under nitrogen. The excess tertiary butanol was distilled off, and replaced by dry benzene in which the potassium salt formed a suspension. To this was added bromodecallene (52) & (44), (3.94g., 0.0138m.) and the mixture stirred and refluxed for 15 hours under nitrogen. At the end of this period the solution was cooled, ether extracted, brine washed and dried. After solvent removal the liquid residue distilled over a range 96 - 132<sup>o</sup>/0.02 mm., and was shown by T.L.C. to be largely a mixture of unchanged starting materials.

Methyl hypochlorite addition to 1-methoxydec-1-en-3-yn-5-ol (46)

To 1-methoxydec-1-en-3-yn-5-ol (46), (5.551 g., 0.031 m.) in dry methanol (50 cc.) was added N-chlorosuccinimide (4.204 g., 0.0315 m.). The solution was stirred and refluxed for 30 minutes, cooled, filtered, and excess sodium bicarbonate added to the filtrate. The filtrate was ether extracted, the ether extract washed with brine and dried. Removal of solvent left 6.00 g., (88% crude yield), of a colourless oil.  $n_D^{20} = 1.4775$ .  $\nu_{\max.}$  (neat), 3500, 2250 (weak), 1980 (weak), 1120, 1080  $\text{cm}^{-1}$ . The product distilled with decomposition at  $100^\circ/0.01$  mm.

Condensation of Diethyl 2-acetylnonanedioate (44) with the product from the previous reaction.

Sodium (0.263 g., 0.0114 m.) was dissolved in dry ethanol (40 cc.) and the ketoester (44), (3.243 g., 0.0113 m.) added. To the stirred and heated solution was added the chloro-compound (2.787 g., 0.0112 m.) dropwise and stirring and refluxing continued for 2 hours 45 minutes. The solution was cooled and filtered from sodium chloride (0.65 g.), equivalent to a reaction approximately 50% completed. The filtrate was ether extracted, brine washed,

dried and the solvent removed. A pale yellow liquid (4.336 g.) remained.  $n_D^{20} = 1.4575$ . This was distilled at  $90 - 114^\circ / 0.01$  mm. The distillate was shown by T.L.C. to consist of a number of compounds, the spectroscopic properties of which were incompatible with those of the desired product (48).

1, 1-Dimethoxy-4-bromobuta-2, 3-diene (58)

Freshly distilled 1-methoxybut-1-en-3-yne (45), (7.02 g., 0.0856 m.) was dissolved in dry methanol (50 cc.) and placed in a 100 cc., 3-necked flask. The solution was cooled to  $-3^\circ$ , in an ice-salt freezing mixture. To this stirred solution was added over 25 minutes N-bromosuccinimide (16.14 g., 0.091 m.) previously recrystallised and dried. Stirring was continued at  $-3^\circ$  for a further 30 minutes and then for 2 hours at room temperature. The solution was filtered, excess sodium bicarbonate added and ether extracted. The ether extract was brine washed, dried and the solvent removed. The liquid residue distilled to give 1, 1-dimethoxy-4-bromobuta-2, 3-diene as a pale yellow liquid, b.p.  $78^\circ / 15$  mm., 12.88 g. (78% yield).

$n_D^{20} = 1.5050$ .  $\nu_{\max}$ . (neat), 1980 (weak), 1120, 1080  $\text{cm}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 6.71$  (6H; singlet; 2,  $\text{OCH}_3$ ),  $\tau = 3.90$  (1H; doublet,

$J = 6$  c.p.s. showing further splitting into a quartet,  $J = 2$  c.p.s.; terminal allenic H),  $\tau = 5.09$  (1 H; doublet,  $J = 6$  c.p.s. showing further splitting into a quartet,  $J = 2$  c.p.s.; methine H),  $\tau = 4.72$  (1 H; doublet,  $J = 6$  c.p.s. further split into a quartet,  $J = 6$  c.p.s.). The molecular weight was determined by mass spectrometry as 193, in agreement with the calculated value. (Found: C, 37.32; H, 5.03; 2, OMe, 31.5.  $C_{10}H_9O_2Br$  requires C, 37.32; H, 4.70; 2, OMe, 32.2). It was of interest to note that the analysis for the methoxyl content of (58) indicated initially only one OMe group. Suitable pretreatment of the sample however gave the correct result. A similar observation has been recorded for other methoxylated compounds <sup>61</sup>

1,1-Dimethoxy-5-carboethoxy-oct-2-yne (59)

Sodium (0.63 g. 0.027 m.) was dissolved in dry ethanol (50 cc.). Ethyl n-propylacetoacetate (4.72 g. 0.027 m.) was added. To the stirred and refluxing solution was added dropwise the bromoallene (58), (6.595 g., 0.034 m.) and refluxing continued for 1 hour 45 minutes. The solution was cooled, filtered from sodium bromide and the filtrate ether extracted. The ether extract was brine washed and dried and the solvent removed. The liquid residue was distilled to give 1,1-dimethoxy-5-carboethoxy-oct-2-yne as a pale yellow liquid,

b.p. 88 - 90°/0.03 mm., 3.996 g. (60% yield).  $n_D^{20} = 1.4483$ .

$\nu_{\max}$ . (neat), 2290, 1740, 1060  $\text{cm}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 5.01$

(1 H; triplet,  $J = 1$  c.p.s.; propargylic methine proton),  $\tau = 6.10$

(6 H; singlet; 2, OMe),  $\tau = 7.52$  (3 H; multiplet; propargylic

methylene and adjacent methine protons). The molecular weight

was determined by mass spectrometry as 242, in agreement with

the calculated value. (Found: C, 63.98; H, 8.87.  $\text{C}_{13}\text{H}_{22}\text{O}_4$

requires C, 64.44; H, 9.15).

Urethane (0.245 g.) was shaken with (59), (0.075 g.) in (3 cc.) of normal hydrochloric acid at room temperature for 2 hours.

A white precipitate formed and was filtered off. Recrystallisation

from 60/80 petrol gave white microcrystals of the bis-urethane (60),

m.p. 110 - 111°. N.M.R. ( $\text{CCl}_4$ ),  $\tau = 5.82$  (6 H; quartet; 3,  $\text{OCH}_2$ ),

$\tau = 7.52$  (3 H; multiplet; propargylic methylene and adjacent methine

protons),  $\tau = 3.80$  (2 H; diffuse doublet; secondary amine),  $\tau = 4.25$

(1 H; multiplet; propargylic methine). (Found: C, 57.16; H, 7.72;

N, 7.75.  $\text{C}_7\text{H}_{28}\text{N}_2\text{O}_6$  requires C, 57.29; H, 7.92; N, 7.86).

1,1-Dimethoxyhex-2-yne (61)

Magnesium (1.758 g., 0.073 m.) was placed in a 100 cc., 3-necked flask with dry ether (25 cc.). Ethyl bromide (10.17 g., 0.093 m.) was added and ethyl magnesium bromide prepared under nitrogen in the usual way. To the ice cold solution pent-1-yne (5.046 g., 0.081 m.) was added in ether (20 cc.). The solution was stirred for 30 minutes at room temperature and then refluxed for an additional 90 minutes. At the end of this period, ethyl orthoformate (10.88 g., 0.073 m.) was added to the solution of the acetylenic Grignard at room temperature. The mixture was stirred and refluxed for 5 hours and 30 minutes. The complex was decomposed by the addition of saturated ammonium chloride (100 cc.), ether extracted, brine washed and dried. After solvent removal, 1,1-dimethoxyhex-2-yne distilled as a colourless liquid, b.p. 110-112°/0.2 mm., 7.03 g. (57% yield).  $n_D^{22} = 1.4306$   $\nu_{\max.}$  (neat), 2280, 1150, 1070  $\text{cm}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 4.88$  (1H; triplet,  $J = 1$  c.p.s.; propargylic methine),  $\tau = 7.79$  (2H; hextet; propargylic methylene). (Found C, 68.42. H, 10.13.  $\text{C}_{10}\text{H}_{18}\text{O}_2$  requires C, 70.54; H, 10.66)



Attempted preparation of the enamine (62) from

1-methoxydec-1-en-3-yn-5-ol (46)

(a) The vinyl ether (46), (2.056 g., 0.0113 m.), morpholine (1.419 g., 0.0163 m.) and p-toluene sulphonic acid (26 mg.) were refluxed for 1 hour 45 minutes. Distillation of the reaction mixture gave solely starting materials identified by, boiling point, refractive index, infrared spectrum and T.L.C.

(b) The vinyl ether (2.025 g., 0.0111 m.), morpholine (1.346 g., 0.0155 m.) were refluxed with p-toluene sulphonic acid (0.173 g.) for 13 hours. The reaction mixture was distilled to give a fraction (1.53 g.), b.p.  $80 - 100^{\circ}/0.09$  mm. This was shown to be substantially vinyl ether (46).

(c) Vinyl ether (1.843 g., 0.010 m.), morpholine (1.216 g., 0.0139 m.), and a crystal of p-toluene sulphonic acid were placed in a conical flask fitted with a distillation head and thermometer. The mixture was magnetically stirred and heated so as to maintain a head temperature of  $70 - 80^{\circ}$  at which temperature any methanol produced by the reaction would distill off. After 28 hours the solution had turned black. It was distilled to give a fraction (0.79 g.), b.p.  $100 - 110^{\circ}/0.3$  mm., which was shown to be substantially vinyl ether (46).

Attempted preparation of the epoxide (65) from 1-methoxydec-1-en-3-yne-5-ol (46).

(a) To the vinyl ether (1.232 g., 0.0067 m.) in dry ether (15 cc.) at 0°, was added an equimolar weight of perbenzoic acid in ether (3 ccs.) at 0°. The solution was left 89 hours at 0°, by which time the concentration of peracid, as estimated by sodium thiosulphate, had fallen to 10% of its initial value. The acid in the reaction mixture was neutralised by shaking for 24 hours with calcium hydroxide. The solution was filtered, and the filtrate was evaporated to leave a yellow liquid (0.54 g.), b.p. 85 - 90°/0.09 mm. This was shown to be substantially vinyl ether (46).

(b) Vinyl ether (1.700 g.), was treated at room temperature with an equimolar concentration of perbenzoic acid in ether. After 66 hours, the product was worked up as in (a) to give a liquid (1.46 g.), which decomposed on distillation. The distillate (0.30 g.) was shown by T.L.C. to be a complex mixture.

(c) The vinyl ether (2.95 g., 0.016 m.) was treated at 0° in ether with an equimolar amount of m-chlorperbenzoic acid. After 7 days at 0°, the product was worked up as in (a) and shown to be essentially starting material.

(d) The vinyl ether (1.218 g., 0.0066 m.) was treated with formic acid (0.5 cc.) and 30% hydrogen peroxide (0.833 g.) in methanol at room temperature. After 5 days, the solution was ether extracted and the ether extract washed with sodium bicarbonate, brine and dried. Removal of solvent left 1.035 g. of a liquid which was shown to be a mixture of compounds, including vinyl ether ( 46 ).

Attempted preparation of 1,1-dimethoxy-2-bromodec-3-yn-5-ol (47) by mercuric salt addition.

Mercuric acetate (7.86 g., 0.0247 m.) was dissolved in methanol (200 cc.) and added to the vinyl ether (46), (4.479 g., 0.0247 m.) in methanol (5 cc.) at room temperature. After a few minutes a flocculent white precipitate appeared and this was filtered off. After 3 days, potassium bromide (4 g.) dissolved in water (25 cc.) was added, the solution concentrated, extracted with chloroform and the chloroform extract washed with brine and dried.

To the amber coloured chloroform solution at 0° was added dropwise a solution of bromine in chloroform. The bromine addition was stopped after 0.013 m. of bromine had been added when the solution had turned black. The solution was brine washed, dried and the solvent removed at room temperature under vacuum to leave 6.3 gm. of a black liquid residue. This was shown by T.L.C. to be a mixture of at least eight compounds. Distillation resulted in severe decomposition.

68

Oct-1-yn-3-ol (26)

A 500 cc., 3-necked flask was fitted with a mechanical stirrer, reflux condenser and a pressure equalising dropping funnel. Magnesium (12g., 0.5 m.) was placed in the flask and tetrahydrofuran (300 cc.), dried by refluxing with lithium aluminium hydride and then distilling, added. Under an atmosphere of nitrogen, ethyl bromide (60 g., 0.55 m.) in tetrahydrofuran (100 cc.) was run in and the reaction initiated by grinding.

A 1-litre, 3-necked flask was fitted with a mechanical stirrer, tube for acetylene passage, and a 500 cc. pressure equalising dropping funnel. The warm solution of ethyl magnesium bromide in tetrahydrofuran was transferred under nitrogen pressure, via a glass wool filter, to the 500 cc. dropping funnel.

Dry tetrahydrofuran (200 cc.) was placed in the 1-litre flask, the stirrer started and acetylene (via a cardice-acetone cooling trap, concentrated sulphuric acid and soda lime wash bottles and a mercury escape valve) bubbled through the tetrahydrofuran at a fast rate. After five minutes, 5 cc. of the ethylmagnesium bromide was run in and portionwise addition continued over three hours. During this time the ethylmagnesium bromide separated as a solid in the 500 cc. dropping funnel and was broken up with a piece of wire.

After the addition of the ethylmagnesium bromide, n-hexanal (55 g., 0.55 m.) in tetrahydrofuran (55 cc.) was added dropwise over thirty minutes to the ice-cooled solution of the acetylene Grignard. Acetylene passage was maintained during the addition. At the end of this period, the acetylene flow was stopped and the solution stirred overnight at room temperature.

The reaction mixture was poured into saturated ammonium chloride (1500 cc.), the organic layer separated, the aqueous layer extracted twice with ether and the organic layers combined, washed with brine and dried. After removal of solvent, the liquid residue was distilled to give oct-1-yn-3-ol (32 g., 50%), as a colourless liquid, b.p. 80 - 90°/19 mm. (literature value 85 - 90°/20 mm.).  
 $n_D^{23} = 1.4399$   $\nu_{\max}$  (neat), 3400 (sh), 3300, 2150, 1030  $\text{cm}^{-1}$ .

3-(Tetrahydro-2-pyranyloxy)oct-1-yne (<sup>69</sup>~~28~~)

To oct-1-yn-3-ol (<sup>68</sup>~~28~~), (9.43 g., 0.075 m.) in a 50 cc. flask was added dihydropyran (6.51g., 0.078 m.) and two drops of concentrated hydrochloric acid. The mixture was gently swirled and the temperature maintained below 40° by cooling under the water tap. When the reaction temperature started to fall, the flask was left overnight at room temperature.

The solution in the flask, was taken up in ether, washed with sodium bicarbonate, brine and dried. After removal of solvent the liquid residue distilled to give 3-(tetrahydro-2-pyranyloxy)oct-1-yne (12.8 g., 82%) as a colourless liquid, b.p. 60 - 65°/0.25 mm.,  
 $n_D^{20} = 1.4521$ .  $\nu_{\max}$  (neat), 3300, 1110, 1020  $\text{cm}^{-1}$ . (Found: C, 74.44; H, 9.83.  $\text{C}_{13}\text{H}_{22}\text{O}_2$  requires C, 74.24; H, 10.54).

1, 1, 1-Trichlorodec-3-yne-2, 5-diol <sup>75</sup> (~~38~~)

Chloral was obtained as a colourless liquid,  $n_D^{20} = 1.4567$ , by distilling chloral hydrate from concentrated sulphuric acid and then redistilling the distillate. Chloral is extremely hygroscopic and turns blue litmus paper red.

To a stirred solution of ethyl magnesium bromide, from magnesium (0.57 g.) and ethyl bromide (3.07 g.), in ether (20 cc.) was added under nitrogen, the acetylene <sup>69</sup> (~~27~~), (5.01 g., 0.024 m.) in ether (5 cc.). A vigorous evolution of ethane occurred and stirring was continued for 15 minutes at room temperature and then 45 minutes under gentle reflux. Chloral (3.54 g., 0.024 m.) in ether (10 cc.) was then added to the reaction solution and refluxing continued for 6 hours. After standing overnight, the reaction mixture was poured into saturated ammonium chloride (100 cc.), the organic layer separated, washed with brine and dried. After solvent removal, the liquid residue was distilled to give unchanged starting material <sup>69</sup> (~~27~~), (1.49 g., 32%) and crude 1, 1, 1-trichlorodec-3-yne-2, 5-diol (2.58 g., 48%) as a brown viscous oil, b.p. 142 - 144°/10<sup>-4</sup> mm.  $n_D^{20} = 1.5017$ . On standing the oil crystallised. Recrystallisation from petrol afforded transparent plates, m.p. 93 - 101°, presumably a mixture of the erythro and

three forms.  $\nu_{\max}$  ( $\text{CCl}_4$  solution), 3450, 2300, 1070  $\text{cm}^{-1}$ .

(Found: C, 43.95; H, 5.44  $\text{C}_{10}\text{H}_{15}\text{C}_{13}\text{O}_2$  requires C, 43.89; H, 5.53).

Reaction of 1,1,1-trichlorodec-3-yne-2,5-diol (<sup>75</sup>~~33~~) with mesyl chloride

The diol (<sup>75</sup>~~33~~), (0.78 g., 0.0029 m.) was dissolved in pyridine (2 cc.) and mesyl chloride (0.46 g., 0.004 m.) added. The solution was left at 0° for 24 hours, filtered from pyridine hydrochloride and water (10 cc.) added to the filtrate. The solution was ether extracted, the ether extract washed with dilute hydrochloric acid, sodium bicarbonate solution, brine and dried. Removal of solvent left a yellow oily residue which was chromatographed on silica and eluted with benzene/ether. Two new compounds were obtained. The less polar material gave a positive sulphur fusion test and had  $\nu_{\max}$  (neat), <sup>76</sup> 2200, 1180  $\text{cm}^{-1}$  and was assumed to be the bis-mesylate (~~33~~). The more polar compound, positive to sulphur fusion test, had  $\nu_{\max}$  (neat), <sup>77</sup> 3500, 2200, 1180  $\text{cm}^{-1}$  and was assumed to be the mono-mesylate (~~33~~).



1, 1-Dichlorodec-3-yne-2, 5-diol (<sup>79</sup>~~34~~)

An ethereal solution of ethyl magnesium bromide was prepared under nitrogen from magnesium (0.427 g.) and ethyl bromide (2.28 g.). To this was added the acetylene (<sup>69</sup>~~27~~), (3.56 g., 0.017 m.) in ether and the solution stirred for 15 minutes at room temperature and 45 minutes under reflux.

Freshly distilled dichloroacetaldehyde (1.83 g., 0.0162 m.) in benzene (10 cc.) was added to the reaction mixture and the solution refluxed for 2 hours and 15 minutes during which time the colour changed from yellow to black. After standing overnight the Grignard complex was decomposed with saturated ammonium chloride, the organic layer separated, brine washed and dried. After removal of solvent the residual dark brown liquid was distilled to give unchanged starting material (<sup>69</sup>~~27~~), (1.57 g., 44%) and crude 1, 1-dichlorodec-3-yne-2, 5-diol (1.99 g., 51%) as a dark brown viscous liquid, b.p. 140 - 150°/0.07 mm.,  $n_D^{20} = 1.4926$ . This liquid slowly crystallised on standing. The structure was assumed on the basis of the infra red spectrum,  $\nu_{\max}$  (neat), 3500, 2300, 1070  $\text{cm}^{-1}$ , and by subsequent conversion into the acetal (<sup>80</sup>~~28~~).

1, 1-Dimethoxydec-3-yne-2, 5-diol (<sup>80</sup>~~38~~)

Sodium (0.165 g., 0.0072 m.) was dissolved in methanol (20 cc.) and the diol (<sup>79</sup>~~37~~), (0.818 g., 0.0034 m.) in methanol (5 cc.) added at room temperature. The solution was refluxed for 1 hour, cooled and filtered from sodium chloride. The filtrate was ether extracted, washed with brine and dried. After removal of solvent, the liquid residue was distilled to give 1, 1-dimethoxydec-3-yne-2, 5-diol (0.396 g., 50%) as a clear yellow liquid, b.p. 105 - 125°/0.1 mm.,  $n_D^{20} = 1.4658$ ,  $\nu_{\max}$  (neat) 3500, 2150, 1120, 1080  $\text{cm}^{-1}$ .

The acetal (<sup>80</sup>~~38~~) was hydrolysed to the aldehyde by boiling a methanolic solution with an equal volume of 2% sulphuric acid. The solution was ether extracted, and after removal of solvent, the liquid residue readily formed an orange 2, 4-dinitrophenylhydrazone, m.p. 145 - 146° (Found: C, 53.48; H, 6.19; N, 15.11.  $\text{C}_{16}\text{H}_{20}\text{O}_6\text{N}_4$  requires C, 52.74; H, 5.53; N, 15.38).

Reaction of 1, 1-dimethoxydec-3-yne-2, 5-diol (<sup>80</sup>~~38~~) with dihydropyran.

To the acetal (<sup>80</sup>~~38~~), (0.407 g., 0.0018 m.) in ether was added dihydropyran (0.174 g., 0.0020 m.) and two drops of concentrated hydrochloric acid. An immediate colour change occurred. The solution was cooled under the tap and left overnight at room temperature. The solution was washed with sodium bicarbonate, brine and dried. Removal of solvent left a brown liquid (0.50 g.). This liquid was distilled to give a yellow distillate (0.27 g.),  $n_D^{22} = 1.4668$ ,  $v_{\max}$  (neat), 3500, 1720, 1680 (weak), 1620 (weak), 1100  $\text{cm}^{-1}$ . T.L.C. showed smearing. Attempts to form a tractable 2, 4-dinitrophenylhydrazone in sulphuric acid and in pyridine failed.

Reaction of 1, 1, 1-trichlorodec-3-yne-2, 5-diol (<sup>75</sup>~~38~~) with dihydropyran.

To the diol (<sup>75</sup>~~38~~), (1.50 g., 0.0055 m.) in ether was added dihydropyran (1.70 g., 0.020 m.) and two drops of concentrated hydrochloric acid. An exothermic reaction occurred and the solution was cooled in ice. After standing over the weekend, the solution was ether extracted, washed with sodium bicarbonate, brine and dried. After solvent removal the liquid residue was distilled to give a fraction (0.27 g.), b.p. 50-70°/0.02 mm.,  $n_D^{21} = 1.4667$ , and unchanged

starting material (0.939 g.), b.p. 130-140°/0.02 mm. The fraction (0.27 g.) had  $\nu_{\max} = 1710 \text{ cm}^{-1}$ , and T.L.C. showed one spot, less polar than the starting material. It was not further investigated.

Attempted condensation of the lithium salt of 3-(tetrahydro-2-pyranyloxy)oct-1-yne (<sup>69</sup>~~27~~) with dichloroacetaldehyde in dimethylformamide

A suspension of lithamide in liquid ammonia was prepared from lithium (0.104 g., 0.015 m.), a crystal of ferric nitrate being used to catalyse the reaction. The ammonia was evaporated off and replaced by dimethyl formamide. To this suspension was added the acetylene (<sup>69</sup>~~27~~), (2.92 g., 0.014 m.) in dimethylformamide (5 cc.). After stirring 3 hours at room temperature, dichloroacetaldehyde (1.47g., 0.013 m.) in dimethylformamide (5 cc.) was added and the solution stirred for a further 3 hours at room temperature. It was then left overnight. Dilute sulphuric acid was added to the ice cold reaction mixture, which was then ether extracted, the ether extract washed with saturated sodium bicarbonate, brine and dried. Removal of solvent left the starting material (<sup>69</sup>~~27~~), (3.01 g.) which was identified by its infra red spectrum, refractive index and T.L.C. comparison.

3-(Methoxymethoxy) oct-1-yne (<sup>82</sup>~~40~~)

(a) All reagents were dried and distilled prior to use. To an ice-cold solution of oct-1-yn-3-ol (<sup>68</sup>~~26~~), (0.75 g., 0.006 m.) and triethylamine (0.70 g., 0.007 m.) in benzene was added chloromethyl methyl ether (0.619 g., 0.008 m.). After standing overnight at 0°, the solution was filtered and the filtrate extracted with ether. The ether extract was washed with sodium bicarbonate, brine and dried. Removal of solvent left a liquid (0.83 g.) which was shown to be substantially starting material (<sup>68</sup>~~26~~) by its infra red spectrum, refractive index, boiling point and T.L.C. comparison.

(b) The acetylene (<sup>68</sup>~~26~~), (3.73 g., 0.03 m.) in ether was added to chloromethyl methyl ether (2.94 g., 0.036 m.) at room temperature and the solution left for 2 days. It was then ether extracted, the ether extract washed with sodium bicarbonate, brine and dried. After removal of solvent the liquid residue was distilled to give unchanged starting material (2.43 g., 66%) and a higher boiling fraction (1.08 g., 22%), b.p. 92 - 94°/0.07 mm.,  $n_D^{24} = 1.4430$ . The structure of the higher boiling fraction was assigned as 3-(methoxymethoxy) oct-1-yne (<sup>82</sup>~~40~~) on the basis of the infra red spectrum,  $\nu_{\max}$  (neat) 3300 (terminal acetylene), 2150, 1080, 1020 cm.<sup>-1</sup>.

Grignard addition of 3-(methoxymethoxy) oct-1-yne (<sup>80</sup>~~40~~) to  
dichloroacetaldehyde

An ethereal solution of ethyl magnesium bromide was made under nitrogen from magnesium (0.175 g., 0.0073 m.) and ethyl bromide (0.928 g., 0.0085 m.). To this solution the acetylene (<sup>80</sup>~~40~~), (1.065 g., 0.0063 m.) in benzene (15 cc.) was added at room temperature. The solution was stirred under reflux for 1 hour and 30 minutes. Dichloroacetaldehyde (0.813 g., 0.0072 m.) in benzene (10 cc.) was run into the warm solution, which was then refluxed for 3 hours. During this time the colour darkened. The solution was left overnight, decomposed with saturated ammonium chloride, ether extracted, and the ether extract washed with brine and dried. The solvent was removed to leave a black oil (1.76 g.),  $\nu_{\max.}$  (neat) 3500, 3300  $\text{cm.}^{-1}$ . T.L.C. showed smearing. Distillation gave a black distillate (0.54 g.), b.p. 90-100°/0.06 mm. which consisted partly of unchanged starting material (<sup>80</sup>~~40~~) as shown by infra red, boiling point, and T.L.C. comparison.

3-Methyl-cyclopentane-1, 2, 4-trione (89)

This compound was prepared in two ways:-

- (a) by the literature method<sup>57</sup> from diethyl oxalate and methyl ethyl ketone.
- (b) from the C-1 semicarbazone (91). The semicarbazone (approximately 2 gms.) was boiled for one hour with dilute sulphuric acid. The solution was allowed to cool and filtered. The filtrate was extracted repeatedly with ether and the ether solution on evaporation gave very pure crystals of the trione (89), (approximately 0.3 gm.).

For spectroscopic data see tables.

1, 2, 4-Triethylenedioxy-3-methylcyclopentane (93)

In a conical flask equipped with a magnetic stirrer, reflux condenser and Dean and Stark side arm were placed 3-methyl-cyclopentane-1, 2, 4-trione (89), (2.95 g., 0.012 m.), ethylene glycol (12.27 g., 0.20 m.), p-toluenesulphonic acid (70 mgs.) and dry benzene (50 cc.). The solution was refluxed for 23 hours, the solution cooled, the benzene layer separated and the glycol layer extracted with ether. The organic layers were washed

with sodium bicarbonate, brine and dried. After removal of solvent and one crystallisation from petrol, 1, 2, 4-triethylenedioxy-3-methylcyclopentane was obtained as colourless plates (3.18 g., 72%) m.p. 108 - 110°  $\nu_{\max}$  (CCl<sub>4</sub> solution) 1105 cm<sup>-1</sup>. No absorption in the ultra violet. N.M.R. (CCl<sub>4</sub>): 12 protons between  $\tau = 5.7$  and 7.0, complex splitting. 3 protons between  $\tau = 7.0$  and 8.3, again complex splitting.  $\tau = 9.15$  (3 H; doublet,  $J = 12$  c.p.s.; secondary methyl). Molecular weight determined by mass spectrometry as 258 in agreement with the calculated value. (Found C, 56.18; H 6.89. C<sub>12</sub>H<sub>18</sub>O<sub>6</sub> requires C, 55.80; H, 7.03).

10-Methyl-1, 4, 7-trioxaspiro [7, 4]deca-9, 11-dione (95)

In a conical flask equipped with a magnetic stirrer was placed the trione hydrate (89), (0.65 g, 0.0045 m.), ethylene glycol (3.12 g., 0.05 m.), p-toluenesulphonic acid ( 8 mg.) and dry benzene (50 cc.). The solution was refluxed with a Dean and Stark side arm. After one hour and 45 minutes, the reaction was stopped, the solution cooled and solid potassium carbonate added to the reaction mixture. The solution was shaken and the



benzene layer decanted off. The residue of glycol and solid material was washed twice with fresh benzene and the benzene extracts decanted off. The combined benzene layers were dried. After removal of solvent and trituration with petrol the pasty residue (0.62 g.) crystallised. Recrystallisation from benzene gave white needles, m.p. 119 - 121<sup>o</sup>, of 10-methyl-1,4,7-trioxaspiro[7,4]deca-9,11-dione.  $\nu_{\max}$  (nujol) 3400, 1690, 1610, 1050  $\text{cm}^{-1}$ .  $\lambda_{\max}$  263, 274, 249  $\text{m}\mu$  ( $\epsilon$  16400, 18100, 9700 in methanol, 0.1N sodium hydroxide, 0.1N hydrochloric acid respectively). N.M.R. (pyridine):  $\tau = 8.32$  (3 H; triplet,  $J = 1.5$  c.p.s.; methyl),  $\tau = 6.75$  (2 H; quartet,  $J = 1.5$  c.p.s.; ring methylene),  $\tau = 5.4$  to  $6.0$  (8 H; multiplet;  $-\text{OCH}_2-$ ). Molecular weight determined by mass spectrometry as 214 in agreement with the assigned structure. (Found C, 56.26; H 5.63.  $\text{C}_{10}\text{H}_{14}\text{O}_5$  requires C, 56.07; H, 6.59). This reaction could not be repeated despite a number of attempts.

2, 4-Bis(ethylenedioxy)-3-methylcyclopentanone (99)

The tri-ketal (93), (228 mgs.) in ether (10 cc.) was shaken with dilute sulphuric acid (10 cc.) for 1 hour. The ether layer was separated, washed with brine, dried and the solvent removed to leave a solid residue (126 mgs.). This residue was chromatographed on a silica thick plate and eluted with benzene-ether to give the bis-ketal (109 mgs. 60%). Recrystallisation from petrol afforded white rhombs, m.p.  $132 - 134^{\circ}$ , which underwent polymorphic change between  $80^{\circ}$  and  $120^{\circ}$  from rhombs to hexagons. A sublimed sample exhibited the same behaviour on heating. G.L.C. (20% polyethylene glycol at  $175^{\circ}$  flow rate 50cc/minute) gave one peak, at  $12\frac{1}{2}$  minutes.  $\nu_{\max}$  ( $\text{CHCl}_3$  solution) 1753, 1110  $\text{cm}^{-1}$ . N.M.R. ( $\text{CDCl}_3$ ),  $\tau = 8.95$  (3H; doublet,  $J = 11$  c.p.s.; secondary methyl). Remaining protons show complex splitting. 8H between  $\tau = 5.6$  and 7.0, 3H between  $\mu = 7.0$  and 8.4. Mass spectrometry showed molecular weight to be 214 in agreement with calculated value. (Found C, 56.26; H, 6.47.  $\text{C}_{10}\text{H}_{14}\text{O}_5$  requires C, 56.07; H, 6.59).

The bis-ketal (99) formed a benzylidene derivative when treated with benzaldehyde in base. Recrystallisation of this derivative from absolute ethanol afforded almost colourless straw-like

crystals, m.p. 115 - 145<sup>o</sup>,  $\lambda_{\text{max}}$  304 m $\mu$  ( $\epsilon$  30,700 in methanol).

(Found C, 67.19; H, 6.35.  $\text{C}_{17}\text{H}_{18}\text{O}_5$  requires C, 67.54; H, 6.00).

1-Hydroxy-3-methylcyclopentane-2,4-dione (100)

This was prepared as described in the literature<sup>58</sup> by sodium borohydride reduction of the trione hydrate (89).

Spectroscopic properties are given in the tables.

1-Hydroxy-2-methoxy-3-methylcyclopent-2-en-4-one (101) and

1-Hydroxy-3-methyl-4-methoxycyclopent-3-en-2-one (102).

These isomeric enol-ethers were prepared as described<sup>57</sup> by the action of diazomethane on (100). The isomer crystallising from benzene, m.p. 167 - 168<sup>o</sup>, was assigned the structure (102). The isomer crystallising from petrol, m.p. 84 - 86<sup>o</sup>, the less polar of the two isomers, was assigned the structure (101). Structural assignments were based on the spectroscopic properties which are reported in the tables.

3-Methoxy-2-methylcyclopent-2-enone (103)

2-Methoxycyclopentane-1,3-dione (94), (2.00 gm.) was suspended in dry ether (20 cc) and to the stirred suspension diazomethane was added until nitrogen evolution ceased, and all the starting material was in solution. The ethereal solution was dried, solvent removed and after one crystallisation from petrol, 2-methyl-3-methoxycyclopent-2-enone (1.98 g. 88%) was obtained as white needles, m.p. 63 - 65°. Spectroscopic properties are reported in the tables. (Found: C, 66.45; H, 8.14.  $C_7H_{10}O_2$  requires C, 66.64; H, 7.99).

2-Methyl-3(2-phenylethynyl)-cyclopent-2-enone. (104).

A solution of ethyl magnesium bromide was made in ether in the usual manner under nitrogen from magnesium (0.21 g., 0.009 m.) and ethyl bromide (1.5 g., 0.014 m.). To this solution was added phenylacetylene (0.873 g., 0.009 m.) in dry benzene (10 cc.). The solution was refluxed for 1 hour. The solution was then cooled and to the cooled solution was added 2-methyl-3-methoxycyclopent-2-enone (103), (1.05 g., 0.008 m.) in benzene (10 cc.). The solution was

stirred and refluxed for 2 hours and then cooled in ice. The Grignard complex was decomposed with ice-cold 5% sulphuric acid, the ether layer separated, the aqueous layer extracted with ether and the ether layers combined. After washing with sodium bicarbonate, brine and drying the solvent was removed to leave a dark red liquid (1.10 g.). Extraction of this liquid with petrol and cooling of the petrol extract gave pale yellow crystals (0.4g., 25%) of 2-methyl-3(2-phenylethynyl)-cyclopent-2-enone, m.p. 63 - 66°  $\nu_{\max}$  (CCl<sub>4</sub> solution), 2210, 1700, 1620 cm.<sup>-1</sup>  $\lambda_{\max}$  ~~222~~<sup>305</sup>, 228, ~~305~~<sup>222</sup> m $\mu$  ( $\epsilon$  26,900; 9,100; 9,600 in methanol). N.M.R. (CCl<sub>4</sub>)  $\tau$  = 2.52 (5H; multiplet; aromatic),  $\tau$  = 7.30 (2H; multiplet, ring methylene),  $\tau$  = 7.60 (2H; multiplet; allylic ring methylene),  $\tau$  = 8.08 (3H; triplet, J = 1.5 c.p.s.; allylic methyl). A sample was sublimed to give a white solid for analysis, m.p. 68 - 70°. (Found C, 84.65; H, 6.14. C<sub>14</sub>H<sub>12</sub>O requires C, 85.68; H, 6.16)

The 2,4-dinitrophenylhydrazone was recrystallised from acetic acid as deep-red crystals, m.p. 242 - 244°. (Found: C, 63.71; H, 4.31; N, 15.17. C<sub>20</sub>H<sub>16</sub>O<sub>4</sub>N<sub>4</sub> requires C, 63.82; H, 4.29; N, 14.89).

2-Methyl-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne]-cyclopent-2-enone (105)

The Grignard derivative of 3-(tetrahydro-2-pyranyloxy)-oct-1-yne (69) was condensed with 2-methyl-3-methoxycyclopent-2-enone (103) in ether, tetrahydrofuran and in benzene. The lithium salt of (69) was also prepared and condensed with the ketone in liquid ammonia and in dimethylformamide. In all these reactions the starting acetylene was recovered in amounts varying from 25% in the case of the Grignard reaction in benzene to over 90% in the case of the lithium salt reaction. The optimum conditions were found to be as follows.

An ethereal solution of ethyl magnesium bromide was prepared under nitrogen from magnesium (0.43 g., 0.018 m.) and ethyl bromide (2.3 g., 0.02 m.). To this solution was added at room temperature the acetylene (69), (3.21 g., 0.015 m.) in dry benzene (15 cc.). The solution was refluxed for 90 minutes. To the cooled solution was added the ketone (103), (1.95 g., 0.016 m.) in dry benzene (15 cc.). The solution was refluxed for 2 hours, cooled and the Grignard complex decomposed with ice-cold dilute

sulphuric acid. The organic layer was separated, washed with sodium bicarbonate, brine and dried. After removal of solvent the residual dark red liquid (4.3 g.) was distilled. After an initial recovery of starting acetylene (25%), a fraction (0.1 g., 25%) b.p. 120 - 140°/0.01 mm., was collected. This was identified as crude 2-methyl-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne]-cyclopent-2-enone. A pure sample was isolated by silica chromatography, with benzene-ether as the eluant.  $n_D^{23} = 1.509$   $\nu_{\max}$  (neat) 2260, 1705, 1620, 1130 (pyranyl ether), 1040  $\text{cm.}^{-1}$   $\lambda_{\max}$  267  $\text{m}\mu$  ( $\epsilon$  7420 in methanol). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 7.40$  (2 H; multiplet; ring methylene),  $\tau = 7.65$  (2 H; multiplet; allylic ring methylene),  $\tau = 8.15$  (3 H; triplet,  $J = 1.5$  c.p.s.; allylic methyl),  $\tau = 9.04$  (3 H; singlet; primary methyl). (Found: C, 74.03; H, 8.45.  $\text{C}_{19}\text{H}_{28}\text{O}_3$  requires C, 74.96; H, 9.27).

A small amount of a second compound was identified in the chromatographic fractions as 2-methyl-3(3-hydroxyoct-1-yne)-cyclopent-2-enone.  $\nu_{\max}$  (neat), 3450, 2240, 1700, 1620, 1060  $\text{cm.}^{-1}$   $\lambda_{\max}$  268  $\text{m}\mu$  ( $\epsilon$  18,650 in methanol). N.M.R. ( $\text{CDCl}_3$ ),  $\tau = 7.65$  (4 H; multiplet; ring protons),  $\tau = 8.15$  (3 H; triplet,  $J = 1.5$  c.p.s.; allylic methyl),  $\tau = 9.04$  (3 H; singlet; primary methyl). (Found: C, 75.19; H, 9.19.  $\text{C}_{14}\text{H}_{20}\text{O}_2$  requires C, 76.32; H, 9.15).

Treatment of the crude product with 2, 4-dinitro-phenylhydrazine in concentrated sulphuric acid caused cleavage of the pyranyl ether group and gave a deep-red derivative which was recrystallised from methanol, m.p. 146 - 147°.  $\lambda_{\text{max}}$  393, 300, 266, 239 m $\mu$  ( $\epsilon$  36, 900; 11, 700, 16, 250; 14, 700 in methanol). (Found C, 60.02; H, 6.02; N, 14.04.  $\text{C}_{20}\text{H}_{24}\text{O}_5\text{N}_4$  requires C, 59.99; H, 6.04; N, 13.99).

Attempted addition of the acetylene (69) to 1-hydroxy-3-methyl-4-methoxycyclopent-3-en-2-one (102)

An ethereal solution of ethyl magnesium bromide was made under nitrogen from magnesium (62 mgs.) and ethyl bromide (415 mgs.). To this solution was added the acetylene (69), (480 mgs.) in dry benzene (5 cc). The solution was refluxed for 1 hour 45 minutes, cooled, and the cyclopentenone (102), (150 mg.) added in dry benzene (10 cc.). After further refluxing for 3 hours, the solution was cooled, the Grignard complex decomposed with ice-cold dilute sulphuric acid and the organic layer separated.



The usual work up gave a brown liquid (0.523 g.) which had no carbonyl absorption in the infra-red spectrum. This liquid was distilled to give the starting acetylene (0.26 g., 55% recovery), identified in the usual way.

A further addition to the cyclopentenone (102) was attempted using the Grignard derivative of phenylacetylene and a methylene-chloride-tetrahydrofuran solvent system.<sup>46</sup> Phenyl acetylene was the only component identified in the reaction product.

Attempted O-alkylation of 1-hydroxy-3-methyl-4-methoxy  
cyclopent-3-en-2-one (102)

(a) The secondary alcohol (102), (13 mgs.) in chloroform (3 cc.) was treated at  $-10^{\circ}$  with dihydropyran (8 mgs.) and a micro-drop of concentrated hydrochloric acid added. After standing overnight at room temperature crystals of the highly insoluble 1-hydroxy-3-methylcyclopentane-2, 4-dione (100), (9 mg.) were filtered off and identified by melting point and mixed melting point.

(b) The secondary alcohol (102), (13 mgs.) in chloroform (3 cc.) was treated at room temperature with chloromethyl methyl ether (8 mg.) and the solution sealed. After standing overnight crystals (8 mg.) of the dione (100) were filtered off and identified as in (a).

(c) The secondary alcohol (102), (50 mg.) in pyridine (0.5 cc.) was stirred for 8 hours on the water bath with benzyl chloride (54 mgs.). The solution was cooled, pyridine removed under vacuum and the liquid residue extracted with hot benzene. The benzene extract on cooling deposited crystals of the starting material (46 mgs.), identified by melting point and mixed melting point.

(d) Sodium (24 mgs.) was dispersed by heating in xylene and shaking. The xylene was decanted off, the sodium washed with ether by decantation, and dioxan (3 cc.) added<sup>59</sup>. The secondary alcohol (102), (122 mgs.) in dioxan (5 cc.) was added to the solution which was then refluxed for 6 hours. To the cooled solution was then added benzyl chloride (114 mgs.) in dioxan (3 cc.) and the solution refluxed for a further 14 hours. The solution was cooled,

filtered through celite, solvent removed and the residue extracted with hot benzene. The benzene extract on cooling deposited crystals of the starting material, identified as in (c).

(e) The secondary alcohol (102), (63 mgs.) in dioxan (5 cc.) was stirred magnetically at 50° together with benzyl chloride (105 mgs.) and solid potassium hydroxide (109 mg.)<sup>60</sup>. After 1 hour, water was added and the solution chloroform extracted. The chloroform extract was washed with brine, dried and solvent removed. The residual liquid showed no carbonyl or double bond absorption in the infra red spectrum.

Treatment of 1-hydroxy-3-methylcyclopentane -2, 4 - dione (100)  
with dihydropyran

1-Hydroxy-3-methylcyclopentane-2, 4-dione (104 mg.) in dry ether (10 cc) was treated with dihydropyran (181 mg., 2.6 moles equivalent) and two drops of concentrated hydrochloric acid. After stirring for 18 hours at room temperature the ether insoluble material was filtered off and identified as unchanged starting

compound (100), (70 mgs.). The ether layer was evaporated to leave a brownish liquid residue which was not further examined.

3-Methyl-4-methoxycyclopent-3-ene-1, 2-dione (109)

The trione hydrate (89), (4.69 g.) was treated in ether with an excess of diazomethane. After no further nitrogen evolution, the ether was evaporated and the semi-liquid residue distilled at 0.1 mm. The distillate crystallised in the receiver and was identified as 3-methyl-4-methoxycyclopent-3-ene-1, 2-dione (2.6 g. 57%). Recrystallisation from petrol afforded colourless needles, m.p. 48 - 49°. The spectroscopic properties are recorded in the tables. The compound did not colour ferric chloride solution. (Found: C, 59.77; H, 5.30.  $C_7H_8O_3$  requires C, 59.99; H, 5.75).

Attempted preparation of the ethylene ketal of 3-methyl-4-methoxycyclopent-3-ene-1, 2-dione (109).

(a) The 1, 2-dione (109), (300 mg.), ethylene glycol (1.31 g. 10 moles equivalent) and p-toluenesulphonic acid (20 mg.) were

refluxed in toluene (20 cc.) with stirring and a Dean and Stark side arm receiver. After 6 hours, the solution was cooled, the toluene layer separated, washed with sodium bicarbonate, brine and dried. Removal of solvent left a liquid residue (377 mgs.). This was extracted with petrol and the petrol extract chromatographed on a silica thick plate. This resulted in the isolation of a crystalline compound (16 mgs.), m.p. 109 - 111<sup>o</sup>, which was identified as 1, 2, 4-triethylenedioxy-3-methylcyclopentane (93) by its melting point, mixed melting point, infra red, N.M.R., and T.L.C.

(b) The 1, 2-dione (109), (282 mgs.) was dissolved in 2-ethyl-2-methyl-1, 3-dioxalane (3 cc.) and p-toluenesulphonic acid (10 mg.) added. The solution was refluxed for 16 hours, cooled, ether added and the solution washed with sodium bicarbonate, brine and dried. Removal of the solvent and dioxalane under vacuum left a dark brown liquid (100 mg.) which gave six spots on T.L.C. The major spot was equivalent to starting material and the infra red spectrum confirmed that this was the predominant component.

Experimental (4)

Ethyl 7-(2-methoxy-5-methylphenyl)-7-oxo-n-heptoate (128)

p-Methyl anisole (23.0g., 0.188 m.) was placed in a 250 cc, 3-necked flask and tetrachloroethane (100 cc., dried over potassium carbonate) added. To the stirred solution at 0°, anhydrous aluminium chloride (45.2 g., 0.336 m.) was added in portions and the reaction temperature maintained below 5° during the addition. The acid chloride (126), (34.1 g., 0.165 m.) was then added over 20 minutes. Stirring was continued for 3 hours at 0°, and then overnight at room temperature. The complex in the reaction flask was decomposed by cautious addition of crushed ice to the stirred and cooled solution. The solvent was removed by steam distillation and on cooling, the aqueous oily residue crystallised. The crystals of ethyl 7-(2-methoxy-5-methylphenyl)-7-oxo-n-heptoate (47.2 gm., 98%), were filtered off and a sample recrystallised from methanol as white spars, m.p. 50-51°.

$\nu_{\max}$  (CCl<sub>4</sub> solution), 1737, 1679 cm.<sup>-1</sup>     $\lambda_{\max}$  216, 248, 313 m $\mu$   
( $\epsilon$  16900, 5700, 2850 in methanol). (Found: C, 70.13; H, 8.38

C<sub>17</sub>H<sub>24</sub>O<sub>4</sub> requires C, 69.83; H, 8.27).

7-(2-Methoxy-5-methylphenyl)-7-oxo-n-heptoic acid (129)

The ester (128), (47.2g., 0.161 m.) was hydrolysed by refluxing for 3 hours with alcoholic 10% potassium hydroxide (115 cc) and water (5 ccs). The solution was cooled, acidified and ether extracted. The ether extract was washed with sodium bicarbonate, and the bicarbonate layer reacidified and ether extracted. The ether extract was brine washed, dried, and the solvent removed to give after one recrystallisation from petrol/benzene, 7-(2-methoxy-5-methylphenyl)-7-oxo-n-heptoic acid (33.5 g., 78%). m.p. 59-60°.  $\nu_{\max}$  (CCl<sub>4</sub> solution) 3530, 1758, 1711, 1680 cm.<sup>-1</sup>.  $\lambda_{\max}$  216, 249, 312 m $\mu$  ( $\epsilon$  17,000, 5700, 2550 in methanol). (Found: C, 68.41; H, 7.47. C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> requires C, 68.16; H, 7.63).

7-(2-Methoxy-5-methylphenyl)-n-heptoic acid (130)

Zinc (32 g.) was amalgamated by shaking with mercuric chloride (3 g.), water 45 cc) and concentrated hydrochloric acid (1.9 cc.). After 5 minutes shaking, the aqueous solution was decanted and to the zinc amalgam was added water (22 cc.), concentrated hydrochloric acid (56 cc.), toluene (32cc.) and acetic

acid (1 cc.). To this solution was added the keto-acid (129), (14.8 g., 0.056 m.) and the whole refluxed for 24 hours. During this period three additions of concentrated hydrochloric acid, each of 15 ccs. were made to the refluxing solution. The solution was cooled, filtered from the zinc, and the organic layer separated. The aqueous phase was re-extracted with ether, the organic phases combined, washed with brine and dried. After removal of solvent the liquid residue distilled to give 7-(2-methoxy-5-methylphenyl)-n-heptanoic acid as a colourless viscous oil (10.6 g., 76%), b.p. 158-168° at 0.2 mm.  $n_D^{22}$  1.513.  $\nu_{\max}$  (neat), 3200 (broad), 1710, 1610 (weak)  $\text{cm.}^{-1}$ .  $\lambda_{\max}$  220, 279, 285  $\text{m}\mu$  ( $\epsilon$  7750, 1950, 1840 in methanol). The anilide was recrystallised from 60/80 petrol, m.p. 84-86° (Found C, 77.82; H, 8.39; N, 4.29.  $\text{C}_{27}\text{H}_{27}\text{O}_2\text{N}$  requires C, 77.50; H, 8.36; N, 4.30). The amide was recrystallised from petrol/benzene, m.p. 88-89°. (Found: C, 72.21; H, 8.98; N, 5.84  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{N}$  requires C, 72.25; H, 9.30; N, 5.62).



2-(6-Carboxyhexyl)-4-methylcyclohex-4-enone (132)

The acid (129), (2.804g., 0.0112 m.) dissolved in dry tetrahydrofuran (45 cc) was placed in a 500 cc., 3-necked flask and to the stirred solution approximately 200 cc. of liquid ammonia added. To this solution lithium (2.40 g., 0.34 m.) was added in small pieces, and stirring continued for 1 hour 30 minutes. At the end of this period isopropanol (23.5 g., 0.39 m.) was added cautiously over 20 minutes. The solution was stirred for a further hour when it had turned white. The ammonia was evaporated on a water bath, and the liquid residue acidified with ice cold 2 M oxalic acid. The organic layer was separated and the aqueous layer extracted with ether. The organic layers were combined and brine washed. The organic phase was stirred overnight at room temperature with an equal volume of 2M oxalic acid. The organic layer was then separated, brine washed, dried and the solvent removed to leave a pale yellow liquid (2.68g.)  $n_D^{20} = 1.4874$ , b.p.  $153^{\circ}/0.07$  mm. The crude acid product had  $\nu_{\max}$  (neat) 3200 (broad), 1700 (broad),  $\text{cm.}^{-1}$ .  $\lambda_{\max}^{222}$  (shoulder), 281  $\text{m}\mu$  ( $\epsilon$  1430, 238 in methanol). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 0.01$  (1 H, multiplet, acidic H),  $\tau = 4.45$  (1H, multiplet, olefinic H).

The 2, 4-dinitrophenylhydrazone, made in phosphoric acid<sup>73</sup>,  
recrystallised from aqueous methanol as yellow plates, m.p. 114-117<sup>o</sup>.  
 $\lambda_{\max}$  365 m $\mu$  ( $\epsilon$  19,500 in methanol). (Found C, 57.35; H, 5.91;  
N, 13.35.  $C_{20}H_{26}O_6N_4$  requires C, 57.40; H, 6.26; N, 13.39).  
Attempts to make a crystalline S-benzylisothiuronium derivative  
were unsuccessful.

The methyl ester (134) of the above acid (132) prepared  
by treating the acid with diazomethane had b.p. 130-134<sup>o</sup>/0.2 m.,  
 $n_D^{22} = 1.474$ .  $\nu_{\max}$  ( $CCl_4$  solution) 1745, 1725, 1680 (weak shoulder)  
cm.<sup>-1</sup>.  $\lambda_{\max}$  220 (shoulder), 281 m $\mu$  ( $\epsilon$  1445, 315 in methanol).  
N.M.R. ( $CCl_4$ ).  $\tau = 4.59$  (1 H; multiplet; olefinic H),  $\tau = 6.37$   
(3 H, singlet, methoxyl). (Found: C, 70.37; H, 9.16.  $C_{15}H_{24}O_3$   
requires C, 71.39; H, 9.59).

7-(2-Methoxy-5-methylphenyl)-n-heptamide (133)

To the acid (130), (0.844 g., 0.00337 m.) in a 50 cc.  
long-necked flask was added redistilled thionyl chloride (2.5 cc.)  
and the solution gently refluxed for 30 minutes on a hot water bath.

At the end of this period, excess thionyl chloride was removed under vacuum and to the ice cold residue, ammonia (5 cc.) was added cautiously. The solid in the flask was extracted with ether, the ether extract washed with brine and dried. After removal of solvent and one crystallisation from petrol/benzene, 7-(2-methoxy-5-methylphenyl)-n-heptamide (0.644 g., 76%) was obtained as white crystals, m.p. 88-89°  $\nu_{\max}$  (nujol) 3500, 3300, 1660  $\text{cm.}^{-1}$ .  $\lambda_{\max}$  220, 279, 285  $\text{m}\mu$  ( $\epsilon$  6800, 1850, 1700 in methanol). (Found: C, 72.21; H, 8.98, N, 5.84,  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{N}$  requires C, 72.25; H, 9.30; N, 5.62).

Attempted Birch reaction with the amide (133)

To a stirred solution of liquid ammonia (400 cc.) in a 1-litre, 3-necked flask, was added the amide (133), (2.030g., 0.00814 m.) dissolved in dry ether (145 cc.). After 15 minutes, lithium (0.873 g., 0.125 m.) was added in small pieces and stirring continued for 45 minutes. At the end of this period dry ethanol (6.8 g., 0.148 m.) was added slowly. After 1 hour's further stirring the solution had turned white, the ammonia was evaporated off, and the

liquid residue ether extracted. The ether extract was washed once with brine and then stirred overnight at room temperature with an equal volume of 2M oxalic acid. The organic layer was separated, washed with sodium bicarbonate, brine and dried. Removal of solvent left a pale yellow liquid (1.650g.)  $\nu_{\max}$  (neat), 3500, 1710, 1610 (weak)  $\text{cm.}^{-1}$ . Attempts to form a crystalline 2, 4-dinitrophenylhydrazone and a xanthylamide derivative were unsuccessful.

2-(6-Carboethoxyhexyl)-4-methylcyclohex-4-enol (121b).

The crude acid product (132) from the Birch reaction was esterified with diazomethane and the resulting methyl ester (134), (6.74g., 0.0267 m.) dissolved in methanol (50 cc.) and a few drops of water added. To the methanolic solution was added sodium borohydride (0.65 g.) and the solution left at room temperature for 45 minutes. The solution was acidified with dilute hydrochloric acid, ether extracted, the ether extract washed with sodium bicarbonate, brine and then dried. Removal of solvent left a pale yellow liquid (5.94 g.) which was chromatographed on silica. Elution with benzene/ether gave 2-(6-carboethoxyhexyl)-4-methylcyclohex-4-enol (4.10g., 60%) as a liquid, b.p. 95-97°/0.09 mm.,  $n_D^{25} = 1.4780$ ,

$\nu_{\max}$  ( $\text{CCl}_4$ ), 3620, 3597 (shoulder), 1742  $\text{cm.}^{-1}$ . U.V.-end absorption only. N.M.R. ( $\text{CCl}_4$ ),  $\tau = 4.71$  (1H; multiplet; olefinic H),  $\tau = 6.29$  (3H; singlet; methoxyl),  $\tau = 8.36$  (3H; multiplet, allylic methyl). The molecular weight determined by mass spectrometry was 254 in agreement with the calculated value. The mass spectrum showed peaks at P-2 and P-4 of approximately equal intensity to the parent ion and suggested the loss of first two and then four protons from the cyclohexene ring. A strong peak at P-18 was due to loss of water from the parent ion. (Found: C, 70.42; H, 10.40,  $\text{C}_{15}\text{H}_{26}\text{O}_5$  requires C, 70.83; H, 10.30).

The product decolourised 1% potassium permanganate and gave a brown-yellow colouration with tetranitromethane. G.L.C., (2% polyethylene glycol at 150 $^{\circ}$ , flow rate 60 cc/min.) indicated a 1:1 mixture of epimeric alcohols with retention times of 113 and 132 minutes.

Attempts to form a crystalline amide, phenyl- and  $\alpha$ -naphthylurethane and 3, 5-dinitrobenzoate from the hydroxy-ester (121b) were unsuccessful. Hydrolysis of (121b) by refluxing for 3 hours with 4 N sodium hydroxide gave a liquid acid (121a) from which a crystalline amide, S-benzylisothiuronium salt,  $\alpha$ -naphthylurethane or 3, 5-dinitrobenzoate could not be derived.

Ozonolysis of the hydroxy-ester (121b)

(a) The hydroxy-ester (121b), (203 mgs.) was ozonised in ethyl acetate (50 cc.) at  $-70^{\circ}$  until the solution acquired a pale blue colour (excess ozone). The solvent was removed under vacuum and to the liquid residue glacial acetic acid (15 cc.), water (3 cc.) and zinc dust (72 mgs.) added and the solution stirred for 30 minutes at room temperature. The solution was filtered through celite, and evaporated to dryness under vacuum. The white residue was taken up in brine, ether extracted, and the ether extract washed with sodium bicarbonate, brine and dried. Removal of solvent left a pale yellow liquid (131 mg.). The product showed absorption in the infra red spectrum at 3500, 1720 (broad), 1240 (broad)  $\text{cm.}^{-1}$ . T.L.C. showed considerable streaking. The product was chromatographed on silica and eluted with benzene/ether. Individual fractions were shown by T.L.C. to be complex mixtures and treatment with 2, 4-dinitrophenylhydrazine failed to give a crystalline derivative.

(b) The hydroxy-ester (121b), (285 mgs.) was dissolved in 50 ccs. of a 70:30 mixture of methanol to water, and the solution treated with excess ozone at  $0^{\circ}$ . The volume was reduced under vacuum on a water bath to about 20 ccs. and the aqueous solution

ether extracted, the extract washed with brine, dried and solvent removed to leave a clear liquid (311 mg.).  $\nu_{\max}$  (neat) 3500, 1700 (broad). T.L.C. indicated a mixture of compounds and treatment with 2,4-dinitrophenylhydrazine again failed to give a tractable derivative.

Rudloff oxidation of the hydroxy-ester (121b)

The hydroxy-ester (121b), (198 mgs. 0.00078 m.) was dissolved in dioxan (75 ml.) and placed in a 500 cc flask. Water (100 ml.), potassium carbonate (91 mgs. 0.00066 m.) and sodium periodate (1.350 g. 0.0063 m.) were added. Potassium permanganate (0.441 g.) was dissolved in water (500 ccs.) and 25 cc. of this solution (containing 0.000139 m. of potassium permanganate) added to the 500 cc. flask. The flask was shaken overnight at room temperature, the solution filtered through celite, and the volume reduced. The reduced volume was extracted with ether, the ether extract washed with brine, dried and solvent removed to leave a pale yellow liquid (193 mg.).  $\nu_{\max}$  (neat), 3500, 1720 (broad)  $\text{cm.}^{-1}$ . T.L.C. showed considerable streaking. G.L.C. (2% polyethylene glycol at 175°, flow rate 50 cc/min.) gave six major peaks with retention times

between 4 and 28 minutes. The crude product did not give a tractable 2,4-dinitrophenylhydrazone. Micro-distillation of the product gave a clear liquid distillate which was by T.L.C. substantially the same as before distillation.

Osmylation of the hydroxy-ester (121b) and sodium periodate treatment of the product.

The hydroxy-ester (121b), (0.939 g., 0.0037 m.) was dissolved in pyridine (10 cc.) and treated with osmium tetroxide (1.00 g., 0.00393 m.). The solution was left in the dark for 38 hours during which time a black deposit formed. The reaction product was worked up by adding water (10 cc.), pyridine (15 cc.) and sodium bisulphite (1.8 g.) and the mixture stirred for 1 hour at room temperature. The solution was then evaporated to dryness under vacuum, three successive quantities of benzene added and the solution again evaporated, to remove water and pyridine by azeotrope formation, after which the black residue was extracted three times with boiling ethyl acetate. The ethyl acetate extract was boiled with charcoal and filtered through celite. Removal of solvent from the filtrate left a dark black viscous liquid (1.05 g.).  $\nu_{\max}$  (neat),



3500 (strong), 1720 (broad). T.L.C. showed smearing and indicated some of the starting material present together with highly polar compounds (base line spots). On distillation, the product gave two fractions, b.p. 130-150<sup>o</sup>/0.1 mm. and b.p. 200<sup>o</sup>/0.1 mm., together with extensive decomposition. T.L.C. showed both fractions to be mixtures. They were therefore combined (0.720 g.) and dissolved in dioxan (20 ml.). To this solution was added sodium periodate (0.637 g., 0.003 m.) in water (25 cc.). The solution was left in the dark for 36 hours, at the end of which a crystalline water soluble solid, (349 mgs.) presumably sodium iodate was filtered off. Water was added to the filtrate which was ether extracted, the ether extract washed with brine, dried and solvent removed to leave a black liquid (0.72 g.)  $\nu_{\max}(\text{neat})$ , 3500, 1740, 1720 (sh), 1700 (sh)  $\text{cm.}^{-1}$ . Distillation gave a mobile, dark coloured liquid (0.25 g.), b.p. 135-140<sup>o</sup>/0.1 mm. This liquid did not give a tractable 2,4-dinitrophenylhydrazone.

Epoxidation of the hydroxy-ester (121b).

The hydroxy-ester (121b), (198 mgs., 0.00078 m.) was treated at 0<sup>o</sup> in chloroform with m-chloroperbenzoic acid (183 mgs,

15% excess). After 80 hours at 0°, the excess peracid was destroyed by the addition of 10% sodium bisulphate, the solution extracted with chloroform, the chloroform extract washed with brine, dried and solvent removed to leave a clear colourless liquid (204 mgs.). The crude epoxide mixture was chromatographed on silica and eluted with benzene/ether. Two main fractions were obtained. The more polar fraction (89 mgs.), gave one major peak on G.L.C. (2% polyethylene glycol, 175°, flow rate 50 cc/min.), retention time 73 mins. The N.M.R. (CDCl<sub>3</sub>) agreed with the epoxide structure,  $\tau = 6.35$  (3 H; singlet, methoxyl),  $\tau = 8.71$  (3 H; singlet; ring methyl). The less polar fraction (84 mgs.) gave four peaks on G.L.C. (2% polyethylene glycol, 175°, flow rate 50 cc/min) with retention times of 18, 20, 34, 38 mins. The N.M.R. (CDCl<sub>3</sub>) of this fraction suggested an epoxide mixture,  $\tau = 6.35$  (3 H; singlet, methoxyl),  $\tau = 8.68$  (3 H; singlet; ring methyl).

Both fractions were treated separately with 1% sulphuric acid (5 cc) in methanol at 0°. After 9 days, the more polar fraction gave a clear liquid (50 mgs.) and the less polar fraction also a liquid (71 mgs.). Both liquids were treated separately

with a slight excess of sodium per<sup>o</sup>iodate. No precipitate of sodium iodate was observed during the reaction and neither product on work up gave crystalline derivatives on treatment with 2,4-dinitrophenylhydrazine.

Acetal formation from "technical cyclopentenediol"

(a) With formaldehyde. A mixture (1.35 g., 0.014 m.) of 1,4-(70%) and 1,2-(30%) cyclopentenediols was refluxed with paraformaldehyde (0.418 g., 0.014 m.) in dry benzene (50 ml.) containing a catalytic amount of p-toluenesulphonic acid. Water was removed from the reaction mixture by a Dean and Stark collector. After 3 hours the reaction was stopped, the reaction mixture washed with sodium bicarbonate, brine and dried. The benzene was removed to leave a viscous, clear coloured liquid (1.71 g.),  $n_D^{21} = 1.5145$ . T.L.C. showed the product to be more polar than the starting diol. The infra red spectrum,  $\nu_{\max}(\text{neat})$ , 3500, 3100, 1710 (medium), 1695 (medium), 1100 (broad and strong)  $\text{cm.}^{-1}$  suggested intermolecular bonding. Distillation caused decomposition, b.p.  $> 120^\circ/0.05 \text{ mm.}$ , and only a small amount of distillate (0.03g.) was obtained.

(b) With p-nitrobenzaldehyde. "Technical cyclopentenediol", (1.09 g., 0.011 m.) and p-nitrobenzaldehyde (1.64 g., 0.011 m.) were dissolved in dry xylene (50 cc) and a catalytic amount of p-toluenesulphonic acid added. The volume was reduced to about 25 cc. by distillation and the remaining solvent removed under vacuum. The black liquid residue was extracted with ether and the ether extract filtered through celite. Removal of solvent left a red oily solid (1.66 g.), consisting mainly of p-nitrobenzaldehyde. Fractional crystallisation from methanol gave the p-nitrobenzylideneacetal (100 mgs.) which was recrystallised further from 60/80 petrol as colourless plates, m.p. 123-125°.  $\nu_{\max}$  (CCl<sub>4</sub> solution), 3060 (weak), 1615, 1080 cm.<sup>-1</sup>  $\lambda_{\max}$ , 205, 213 (sh), 262 m $\mu$  ( $\epsilon$  8200, 6600, 11,000 in methanol) N.M.R. (CCl<sub>4</sub>),  $\tau = 2.15$  (4H; quartet; aromatic H),  $\tau = 3.85$  (1H; multiplet; olefinic H),  $\tau = 4.24$  (1H; multiplet, olefinic H),  $\tau = 4.38$  (1H, singlet, benzylic H),  $\tau = 4.67$  (1H; multiplet; allylic H),  $\tau = 5.19$  (1H; multiplet; allylic H),  $\tau = 7.35$  (2H; multiplet, ring methylene). (Found: C, 61.63; H, 4.29; N, 6.5, C<sub>12</sub>H<sub>11</sub>O<sub>4</sub>N requires C, 61.80; H, 4.75; N, 6.0).

Experimental 5

Cyclopent-2-enone. This was prepared as described in Organic Syntheses<sup>90</sup> from dihydroxycyclopentene.

2-(6-Bromohexyl) cyclopent-2-enone (151)

2-(6-Bromohexyl) cyclopentanone (150), (11.2 g., 0.0454 m.) was placed in a 100 cc. conical flask and glacial acetic acid (20 cc.) added. To this solution at room temperature was added pyridinium bromide perbromide (17.5 g. 0.0545 m) and the solution warmed for about one minute until the reagent dissolved. After standing 4 hours at room temperature, the solution was poured into excess brine and ether extracted. The ether extract was washed repeatedly with brine and then with saturated sodium bicarbonate, again brine, dried and the solvent removed undervacuum (water pump) at warm water temperature. The residual brown liquid was chromatographed immediately on silica and eluted with chloroform-ether. The crude product was distilled, chromatographed again and finally distilled for a second time to give 2-(6-bromohexyl) cyclopent-2-enone as a yellow liquid (3.9 g., 35%), b.p. 100°/0.05 mm.,  $n_D^{21} = 1.509$ .  $\nu_{\max}$  (neat), 1700 (doublet), 1630, 800  $\text{cm.}^{-1}$   $\lambda_{\max}$  228  $\text{m}\mu$

( $\epsilon$  9100 in methanol). N.M.R. ( $\text{CCl}_4$ )  $\tau = 2.80$  (1 H; multiplet; vinylic proton),  $\tau = 6.63$  (2 H; triplet,  $J = 6$  c.p.s;  $\text{CH}_2\text{Br}$ ).

A sample was prepared for analysis by a silica preparative thick plate and benzene/ether used as the solvent system. (Found: C, 53.48; H, 6.95.  $\text{C}_{11}\text{H}_{17}\text{BrO}$  requires C, 53.87; H, 6.99).

A sample of crude bromoketone prior to silica chromatography was treated with 2,4-dinitrophenylhydrazine in acid. Hydrogen bromide was eliminated to give an orange red crystalline derivative,  $\lambda_{\text{max}} 375$  ( $\epsilon$  21,500 in methanol), corresponding to the  $\alpha, \beta$ -unsaturated cyclopentenone (151). The tendency of  $\alpha$ -bromo alicyclic ketones to lose hydrogen bromide in this manner is well known.

A sample of this 2,4-dinitrophenylhydrazone was recrystallised from methanol, m.p. 114-115°. (Found: C, 47.73; H, 5.26; N, 12.96.  $\text{C}_{17}\text{H}_{21}\text{N}_4\text{O}_4\text{Br}$  requires C, 48.00; H, 4.98; N, 13.17).

1-Acetoxy-2-(6-bromohexyl)cyclopentene (164, 166)

2-(6-Bromohexyl)cyclopentanone (150), (1.10 g., 0.0044 m.) was refluxed for 6 hours in isoprenyl acetate (30 cc.) and p-toluenesulphonic acid (0.110 g.). The volume was then reduced undervacuum, the organic phase washed with sodium bicarbonate, brine and dried. After removal of solvent the residual liquid was distilled to give a colourless distillate, (0.957 g., 76%), b.p. 100-105°/0.04m.,  $n_D^{20} = 1.4906$ .  $\nu_{\max}$  (neat), 1750, 1695, 1660, 1650 (shoulder)  $\text{cm.}^{-1}$ . The N.M.R. ( $\text{CCl}_4$ ) showed a mixture of the two possible end acetates (164) and (166);  $\tau = 4.60$  (0.5 H; multiplet; vinylic proton);  $\tau = 6.65$  (2 H; triplet,  $J = 7$  c.p.s.;  $\text{CH}_2\text{Br}$ ),  $\tau = 7.95$  (3 H; singlet;  $\text{COCH}_3$ ). G.L.C. confirmed that the product was a 1:1 mixture of enol acetates with retention times of 16.5 and 19.5 minutes (5% Q.F.1, 150°, 35 ccs/min).

(Found: C, 53.94; H, 7.61.  $\text{C}_{13}\text{H}_{21}\text{O}_2\text{Br}$  requires C, 53.98; H, 7.32).

7-(Tetrahydro-2-pyranyloxy) heptyl bromide (172)

To 7-bromoheptyl alcohol (3.28 g., 0.0160 m.) in ether (5 cc.) was added dihydropyran (1.476 g., 0.0175 m.) and two drops of concentrated hydrochloric acid. The solution was left

standing at room temperature overnight, and then washed with sodium bicarbonate, brine and dried. After removal of solvent the liquid residue was distilled to give 7-(tetrahydro-2-pyranyloxy) heptyl bromide (3.43 g., 77%), as a colourless liquid, b.p.  $111^{\circ}/0.07\text{mm}$ ,  $\nu_{\text{max}}$  1130, 1040  $\text{cm.}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 5.49$  (1 H; multiplet; methine),  $\tau = 6.63$  (2H; triplet,  $J = 6$  c.p.s.;  $\text{CH}_2\text{Br}$ )  $\tau = 6.4$  (4H, broad multiplet;  $\text{O}-\underline{\text{CH}_2}$ ). (Found: C, 52.05; H, 8.13.  $\text{C}_{12}\text{H}_{23}\text{O}_2\text{Br}$  requires C, 51.62; H, 8.30).

#### 7-Triphenylmethoxyheptyl bromide (177)

7-Bromoheptyl alcohol (2.63 g., 0.0135 m.), together with trityl chloride (4.37 g., 0.0156 m) recrystallised from benzene-acetyl chloride, was stirred magnetically at  $50^{\circ}$  in dry pyridine (15 cc.) for one hour and then for 10 hours at room temperature. The solution was filtered, ether added and the solution washed with dilute hydrochloric acid, sodium bicarbonate, brine and dried. After solvent removal the liquid residue was distilled to give 7-triphenylmethoxyheptyl bromide (3.75 g. 63%) as a highly viscous oil, b.p.  $180-190^{\circ}/0.01$  mm.,  $n_D^{23} = 1.5766$ .  $\nu_{\text{max}}$  (neat), 3100 (aromatic), 1600, 1080  $\text{cm.}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 2.65$  (15 H; multiplet; aromatic),  $\tau = 6.60$  (2H; triplet;  $\underline{\text{CH}_2}\text{Br}$ ),  $\tau = 6.91$  (2H; triplet;  $\underline{\text{CH}_2}-\text{O}$ ).



3-(6-Bromohexyl) cyclopentane-1, 2-dione (182)

2-(6-Bromohexyl) cyclopentanone (4.92 g., 0.020 m.) was treated at room temperature in glacial acetic acid (20 cc.) with bromine (3.26 g., 0.020 m.). The solution was poured into brine, ether added and the ether layer washed with brine, sodium bicarbonate, and brine again. To the crude bromo-product was added ethanol (20 cc.), 20% sulphuric acid (40 cc.) and the solution refluxed for 17 hours. The volume was reduced, cooled, ether extracted and the ether extract washed with sodium bicarbonate, brine and dried. A small portion (205 mgs.) of the reaction product (4.6 g.) was chromatographed on a silica thick plate using benzene-ether as the solvent system. This afforded 2-(6-bromohexyl)cyclopent-2-enone (48 mgs., 22%) and a more polar material 3-(6-bromohexyl) cyclopentane-1, 2-dione (69 mg., 30%), white spars from petrol, m.p. 48-50°  $\nu_{\max}$  ( $\text{CCl}_4$  solution) 3487, 3290 (bonded hydroxyl), 1712, 1665,  $\text{cm.}^{-1}$ .  $\lambda_{\max}$  260, 295, 260  $\text{m}\mu$  ( $\epsilon$  15, 050; 11, 500; 15, 050 in methanol; 0.1 N NaOH; 0.1 N HCl). (Found: C, 50.58; H, 6.06.  $\text{C}_{11}\text{H}_{17}\text{O}_2\text{Br}$  requires C, 50.58; H, 6.56).

2-(5-Ethoxy-pentyl) cyclopent-2-enone (186)

2-Carboethoxy-2-(5-bromopentyl) cyclopentanone (185), (39.6 g., 0.130 m.) in acetic acid (50 cc.) was treated at room temperature with bromine (21.5 g., 0.134 m.). The solution was poured into brine, ether added, and the ether extract washed with brine, sodium bicarbonate and then brine. The crude product at this stage was refluxed with 20% sulphuric acid (300 cc.) and ethanol (200 cc.) for a period of 42 hours until the solution was practically homogeneous. The volume was reduced, cooled, and ether extracted. The ether extract was washed with sodium bicarbonate, brine, dried and the solvent removed. The residual liquid (15.3 g.) was chromatographed twice on silica and then distilled to give 2-(5-ethoxy-pentyl) cyclopent-2-enone (3.29 g., 13%) as a yellow liquid, b.p. 90-93°/0.04 mm;  $n_D^{23} = 1.4737$   $\nu_{\max}$  (neat) 1700 (doublet), 1635, 1120 (ether), 800  $\text{cm.}^{-1}$ .  $\lambda_{\max}$  228  $\text{m}\mu$  ( $\epsilon$  9800 in ethanol) N.M.R. ( $\text{CCl}_4$ )  $\tau = 2.71$  (1H; multiplet; vinylic ring proton),  $\tau = 6.55$  (4H; quartet;  $\text{OCH}_2$ ),  $\tau = 8.84$  (3H; triplet; methyl). Molecular weight 196 determined by mass spectrometry in agreement with the calculated value. (Found C, 72.56; H, 9.79.  $\text{C}_{12}\text{H}_{20}\text{O}_2$  requires C, 73.43; H, 10.27).

2-(6-Ethoxyhexyl) cyclopent-2-enone (184)

2-Carboethoxy-2-(6-bromohexyl) cyclopentanone (162), (36.2g., 0.114 m.) was treated with bromine (18.8 g., 0.118 m.) as described above and the product refluxed for 34 hours with ethanol (200 cc.) and dilute 20% sulphuric acid (300 cc.). The product was chromatographed three times and then distilled to give 2-(6-ethoxyhexyl) cyclopent-2-enone (5.61 g., 23%). b.p. 100-110°/0.04 mm.

3-(2-Phenylethynyl) cyclopent-2-enone (187)

A solution of ethyl magnesium bromide was made in ether under nitrogen in the usual way from magnesium (0.675 g.) and ethyl bromide (3.4 g.). To this solution was added phenyl acetylene (2.77 g., 0.0269m.) in dry benzene and the solution stirred and heated for one hour. Cyclopent-2-enone (2.22 g., 0.0272 m.) was then run in as a solution in benzene. No reaction was observed and the solution was refluxed with stirring for 3 hours. At the end of this period, the complex was decomposed with saturated ammonium chloride, extracted with ether and the ether extract washed with brine and dried. The

liquid residue after solvent removal was distilled and after recovery of starting material (1.59 g.), a higher boiling distillate, 180-200°/0.05 mm., was collected (0.472 g.). A portion of this (108 mg.) was chromatographed on a silica thick plate using benzene-ether as the solvent system. This afforded 3-(2-phenylethynyl) cyclopent-2-enone (29 mg., 25%), m.p. 86-88°, needles from petrol.  $\nu_{\max}$  (nujol) 2240, 1695, 1670, 1605  $\text{cm.}^{-1}$   $\lambda_{\max}$  306, 227, 221  $\text{m}\mu$  ( $\epsilon$  23,500; 9850, 9650 in methanol). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 2.62$  (5 H; diffuse singlet; aromatic),  $\tau = 3.72$  (1 H; triplet,  $J = 2$  c.p.s.; vinylic ring proton),  $\tau = 7.21$  (2 H; multiplet;  $\text{CH}_2\text{CO}$ ),  $\tau = 7.75$  (2 H; multiplet; allylic methylene). (Found C, 85.65; H, 5.49.  $\text{C}_{13}\text{H}_{16}\text{O}$  requires C, 85.69; H, 5.53).

3-(3-Hydroxyoct-1-yne) cyclopent-2-enol (190)

A solution of ethyl magnesium bromide was made in ether under nitrogen from magnesium (0.343 g., 0.0143 m.) and ethyl bromide (1.80 g., 0.0165 m.). To this solution in dry benzene (15 cc.) was added 3-(tetrahydro-2-pyranyloxy) oct-1-yne (69), (2.54 g., 0.0121 m.) and the solution stirred and refluxed for 1 hour. Cyclopent-2-enone (1.124 g., 0.0137 m.) was then added in benzene (20 cc.), the solution stirred for 2 hours with reflux and then left

overnight. The Grignard complex was decomposed with saturated ammonium chloride, the solution ether extracted, the ether extract washed with brine and dried. The liquid residue after solvent removal was distilled and after a recovery of starting material (0.39 g.), a high boiling fraction (0.64 g.), b.p. 178-195°/0.02 mm. was collected. From the latter a small amount of material was isolated by chromatography on silica, benzene-ether as the solvent system, which was considered to be 3-(3-hydroxyoct-1-yne) cyclopent-2-enol.  $\nu_{\max}$  3450 (strong), 2250, 1670 (weak), 1040  $\text{cm.}^{-1}$   $\lambda_{\max}$  232  $\text{m}\mu$  ( $\epsilon$  7650). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 4.10$  (1H; multiplet; vinylic ring proton),  $\tau = 5.65$  (1H; multiplet; propargylic methine)  $\tau = 9.09$  (3 H; diffuse singlet; methyl).

2-(6-Bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne] cyclopent-2-enol (192).

A solution of ethyl magnesium bromide was prepared under nitrogen in the usual way from magnesium (0.070 g., 0.0029 m.) and ethyl bromide (0.362 g., 0.0033 m.) in a small (5 cc.) volume of dry ether. To this solution was added

3-(tetrahydro-2-pyranyloxy)oct-1-yne (69), (0.585 g., 0.00278 m.) in ether (3 cc.) and the solution stirred on a warm water bath for one hour. 2-(6-Bromohexyl)cyclopent-2-enone (0.633 g., 0.00258 m.) was then added in ether (5 cc.) and the solution stirred for 3 hours on a warm water bath and then left overnight. It was observed in this reaction that if the ether volume was increased the originally green transparent reaction solution changed to a milky suspension.

The Grignard complex was decomposed with ice-cold 5% sulphuric acid and ether extracted. The extract was washed with sodium bicarbonate, brine and dried. After solvent removal the residual yellow liquid (1.2 g.),  $n_D^{23} = 1.4913$ , was chromatographed on silica and eluted with benzene-ether. This resulted in an approximate 40-50% recovery of starting 2-(6-bromohexyl)cyclopent-2-enone, followed by the desired 2-(6-bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne]cyclopent-2-enol in a yield of 40-45% and in the final chromatographic fractions a small amount of 2-(6-bromohexyl)-3-(oct-1-yn-3-ol)cyclopent-2-enol was obtained.

The title compound on short path distillation distilled at approximately  $170^{\circ}/0.01$  mm. with extensive decomposition to give a yellow-brown distillate. A molecular weight could not

be obtained by mass spectrometry. When the compound was run on G.L.C. (1% F.60, 30 mls/min., 200°) it decomposed.

A crystalline  $\alpha$ -naphthyl-urethane could not be obtained.

$\nu_{\max}$  (neat), 3500 (medium), 2250 (very weak), 1700 (weak), 1130, 1040  $\text{cm.}^{-1}$        $\lambda_{\max}$  234  $\text{m}\mu$  ( $\epsilon$  10,400 in methanol).

N.M.R. ( $\text{CCl}_4$ ).  $\tau = 6.63$  (2 H; triplet,  $J = 6$  c.p.s.;  $\text{CH}_2\text{Br}$ ),

5 other protons between  $\tau = 5.0$  and 7.0.  $\tau = 9.09$  (3 H; diffuse

singlet, methyl). (Found: C, 62.10; H, 7.83.  $\text{C}_{24}\text{H}_{39}\text{O}_3\text{Br}$

requires C, 63.27; H, 8.63).

2-(6-Bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy) oct-1-yne]

cyclopent-2-enone (194)

The allylic alcohol (192), (1.52 g., 0.00333 m.) in ether (20 cc.) was stirred at room temperature for two hours with a three-fold excess of sodium dichromate oxidising solution prepared as described in the literature<sup>85</sup>. The ether layer was separated, washed with sodium bicarbonate and brine, dried and solvent removed to leave a yellow-brown liquid (1.28 gm.), consisting mainly of 2-(6-bromohexyl)-3-[3-(tetrahydro-2-pyranyloxy) oct-1-yne]cyclopent-2-enone.  $\nu_{\max}$  (neat), 3500 (weak)

2250, 1700, 1620, 1110, 1040  $\text{cm.}^{-1}$ .  $\lambda_{\text{max}}$  269  $\text{m}\mu$ . When treated with 2,4-dinitrophenylhydrazine in acid, the pyranyl ether group cleaved and a red derivative, m.p. 116-118 $^{\circ}$ , was obtained. When this derivative was subjected to a mixed melting point with 2,4-dinitrophenylhydrazone of 2-(6-bromohexyl)-3-(oct-1-yn-3-ol)cyclopent-2-enone (195), see below, no depression of the melting point occurred.

2-(6-Bromohexyl)-3-(oct-1-yn-3-ol)cyclopent-2-enone (195)

The product from the previous reaction (194), (1.28 g.) was boiled on a water bath with 5% sulphuric acid (20 cc.) and methanol (60 cc.) for 15 minutes, The solution was cooled, poured into brine, and ether extracted. The ether extract was washed with sodium bicarbonate, brine and dried. Removal of solvent left a yellow liquid (1.24 g.) which was chromatographed on silica and eluted with chloroform-ether to give 2-(6-bromohexyl)-3-(oct-1-yn-3-ol)cyclopent-2-enone (0.52 g., 42% from the allylic alcohol (192)).  $\nu_{\text{max}}$  (neat), 3500, 2250, 1700, 1615, 1070 (broad)  $\text{cm.}^{-1}$   $\nu_{\text{max}}$  ( $\text{CCl}_4$  solution), 1703, 1612  $\text{cm.}^{-1}$ .  $\lambda_{\text{max}}$  269  $\text{m}\mu$  ( $\epsilon$  16,450 in methanol). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 5.38$



(1 H, diffuse triplet; propargylic methine),  $\tau = 6.60$  (2 H; triplet,  $J = 7$  c.p.s.;  $\underline{\text{CH}}_2\text{Br}$ ); 7 H between  $\tau = 7.0$  and  $7.9$ ,  $\tau = 9.07$  (3 H; singlet; methyl). The mass spectrum showed a parent ion at 368 (in agreement with the calculated value) and an equally intense peak at  $m/e$ , 370 ( $P + 2$ ) showing the presence of one bromine atom. Peaks at mass numbers 367 and 369 of the same intensity and twice that of the parent ion were also noted. When run on G.L.C. the compound gave one peak (1% F.60, 30 cc/min.,  $200^\circ$ ) of retention time  $17\frac{1}{2}$  minutes. On distillation decomposition occurred at  $> 170^\circ/0.01$  mm. (Found: C, 62.98; H, 7.53.  $\text{C}_{19}\text{H}_{29}\text{O}_2\text{Br}$  requires C, 61.79; H, 7.91).

When treated with 2,4-dinitrophenylhydrazine a red derivative was obtained, m.p.  $116-118^\circ$ , after recrystallisation from methanol. The ultra violet spectrum was identical to that of the 2,4-dinitrophenylhydrazone of (105).  $\lambda_{\text{max}}$  393; 300; 266; 239 m $\mu$  ( $\epsilon$  36,100; 11,500; 16,100; 14,500 in methanol). (Found: C, 54.63; H, 5.81; N, 10.15.  $\text{C}_{25}\text{H}_{33}\text{O}_5\text{BrN}_4$  requires C, 54.64; H, 6.05; N, 10.20).

2-(6-Cyanohexyl)-3-[3-(tetrahydro-2-pyranyloxy) oct-1-yne]  
cyclopent-2-enol (196)

The allylic alcohol (192), (0.473 g., 0.00104 m.) was placed in dry dimethylformamide (10 cc.) together with potassium cyanide (0.200 g., 0.0031 m.). The solution darkened, and was stirred magnetically at 60° for 2 hours. At the end of this period, the solution was filtered, ether extracted and the ether extract washed with brine and dried. After solvent removal 2-(6-cyano-hexyl)-3-[3-tetrahydro-2-pyranyloxy) oct-1-yne]cyclopent-2-enol (0.113 g., 27%) was obtained by preparative silica thick plate chromatography using benzene-ether as the solvent system. The product gave a positive nitrogen fusion test result and a negative halogen.  $\nu_{\max.}$  (neat) 3440, 2240, 2220 (very weak), 1740 (weak and broad), 1040 (broad)  $\text{cm.}^{-1}$   $\lambda_{\max.}$  238  $\text{m}\mu$  ( $\epsilon$  7600 in methanol).

A sample was oxidised with sodium dichromate as described above and the pyranyl group removed by treatment with boiling 5% sulphuric acid. The product, 2-(6-cyano-hexyl)-3-(oct-1-yn-3-ol) cyclopent-2-enone (197), had  $\nu_{\max.}$  (neat), 3440, 2240 (nitrile), 2215 (acetylene), 1700, 1615, 1060 (broad)  $\text{cm.}^{-1}$   $\lambda_{\max.}$  269  $\text{m}\mu$ .

2-(5-Bromopentyl)cyclopent-2-enone (200)

2-(5-Bromopentyl)cyclopentanone (10.6 g., 0.0454m.) described in the literature<sup>91</sup>, was treated in acetic acid (20ccs.) with 20% excess of pyridinium bromide perbromide (17.5 g., 0.0545m.), in a manner exactly analogous to the preparation of 2-(6-bromohexyl)cyclopent-2-enone (151) above.

The product, 2-(5-bromopentyl)cyclopent-2-enone, was obtained as a pale yellow liquid, b.p. 95°/0.05 mm.,  $n_D^{20} = 1.5071$ ,  $\nu_{\max.}$  (neat), 1700 (doublet), 1630, 800  $\text{cm.}^{-1}$   $\lambda_{\max.}$  228  $\text{m}\mu$  ( $\epsilon$  12,600 in methanol). Molecular weight determined as 230 by mass spectrometry in agreement with the calculated value. (Found: C, 50.58, H, 6.38.  $\text{C}_{10}\text{H}_{15}\text{OBr}$  requires C, 51.96; H, 6.54).

Attempted hydrolysis of the nitrile (196)

1. The nitrile (196), (113 mgs.) was refluxed for 6 hours with dilute sodium hydroxide. From the neutral layer was recovered starting material (66 mgs.). From the basic layer was obtained a liquid (14 mgs.), which was esterified and shown by T.L.C. to be a mixture of components.

2. The nitrile (196), (66mgs.) was refluxed with dilute sodium hydroxide and ethylene glycol as co-solvent, for 24 hours. The neutral layer afforded the starting material (53 mgs.) on recovery.

3. To the nitrile (196), (50 mgs.), in acetone (2 cc.) was added 30% hydrogen peroxide (0.4 cc.) and dilute sodium hydroxide (0.4 cc.). After 5 minutes, when oxygen evolution had ceased, the solution was stirred at 50° for 1 hour. From the neutral layer was recovered the nitrile (50 mgs.).

4. The nitrile (196), (59 mgs.), was refluxed with ethanol (3 cc.) and 50% sulphuric acid (1 cc.), for 5 hours. From the black solution at the end of this period was recovered, after washing with base, a brown liquid (52 mgs.) which was mainly starting nitrile as shown by T.L.C. and infrared.

2-(5-Bromopentyl)-3-[3-(tetrahydro-2-pyranyloxy)oct-1-yne]  
cyclopent-2-enol (199)

This compound was prepared by the addition of the Grignard derivative of 3-(tetrahydro-2-pyranyloxy)oct-1-yne (69) to 2-(5-bromopentyl)cyclopent-2-enone (200) in a manner analogous to the preparation of the allylic alcohol (192). The product was

chromatographed and an approximate 55% recovery of the starting cyclopentenone (200) obtained. 2-(5-bromopentyl)-3-[tetrahydro-2-pyranyloxy]oct-1-yne]cyclopent-2-enol, had  $\nu_{\max.}$  3500, 1700 (weak), 1125, 1030  $\text{cm.}^{-1}$   $\lambda_{\max.}$  235  $\text{m}\mu$  ( $\epsilon$  8700 in methanol).

Attempted Ketalisation of 2-(6-bromohexyl)-3-(oct-1-yn-3-ol) cyclopent-2-enone (195)

The cyclopentenone (195), (58 mgs.), ethylene glycol (97 mgs.) and p-toluenesulphonic acid (1 crystal) were refluxed in benzene with a Dean and Stark collector for 48 hours. The solution darkened. The product (82 mgs.) showed two peaks in the ultra violet at 228  $\text{m}\mu$  and 269  $\text{m}\mu$ . T.L.C. showed two major spots. The more polar spot was separated by silica thick plate chromatography and identified as the starting ketone (195). The less polar was similarly separated and a liquid (23 mgs.) obtained. This was also identified as starting material suggesting that silica chromatography caused isomerisation or deketalisation.

In other ketalisation experiments, the main component of the reaction mixture was always the starting material (195).

Reaction of N-bromosuccinimide with 2-methylcyclopent-2-enone (213)

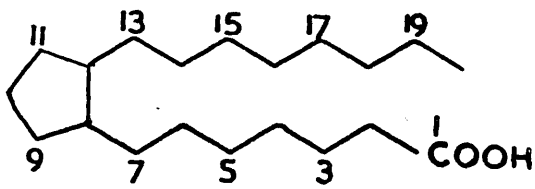
1. The cyclopentenone (213), (0.369g., 0.0038 m.) was refluxed in carbon tetrachloride with N-bromosuccinimide (0.663 g., 0.0038 m.). After 22 hours, the solution was filtered and solvent removed to leave a pale yellow liquid (0.640 g.). T.L.C. showed a single major spot of higher  $R_f$  value than the starting material.

A pure sample was isolated by silica chromatography, benzene-ether as the solvent system, and had  $\lambda_{\text{max}}^*$  224 m $\mu$  ( $\epsilon$  10,700). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 2.75$  (1 H; diffuse quartet; vinylic),  $\tau = 4.91$  (1 H; multiplet;  $-\underline{\text{CH}}-\text{Br}$ ),  $\tau = 7.15$  (2 H; multiplet; methylene),  $\tau = 8.14$  (3 H; triplet,  $J = 2$  c.p.s., methyl).

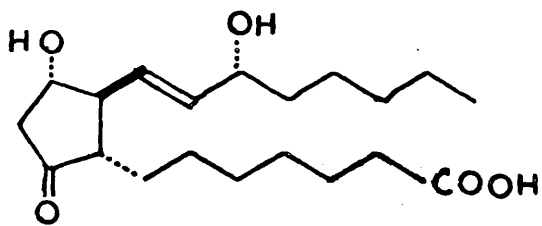
2. The ketone (213), (0.682 g.) was refluxed in carbon tetrachloride with N-bromosuccinimide (1.24 g.) for 3 hours. The solution was filtered, the volume reduced, taken up in ether, washed with sodium bicarbonate, brine and dried. After removal of solvent, the brown liquid residue (1.028 g.) was distilled to give a brown distillate (0.564 g.), b.p. 55-60 $^{\circ}$ /0.04 mm. T.L.C. showed two spots both of higher  $R_f$  value than the starting material.

On standing the product turned black.

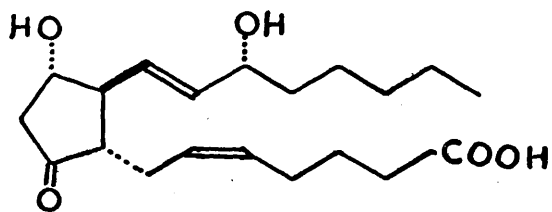
\*  
 $\nu_{\text{max}}$  1710, 1635  $\text{cm}^{-1}$   $\rightarrow$ I



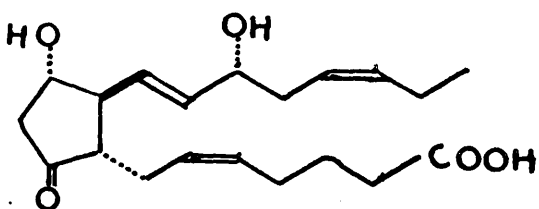
Prostanic Acid



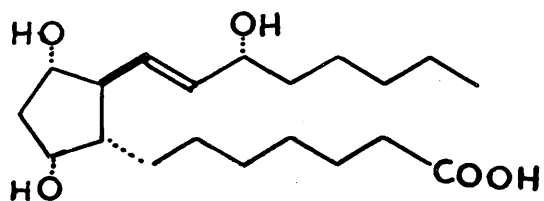
PGE<sub>1</sub> 15a, 15-Dihydroxy-9-Keto-Prosta-13,7-Enoic Acid



PGE<sub>2</sub> 15a, 15-Dihydroxy-9-Keto-Prosta-5,13-Dienoic Acid

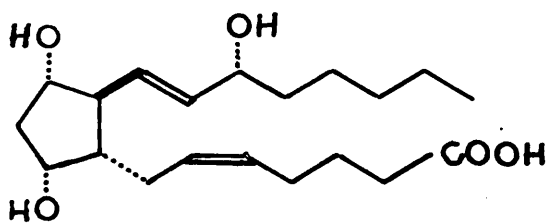


PGE<sub>3</sub> 15a, 15-Dihydroxy-9-Keto-Prosta-5,13,17-Trienoic Acid



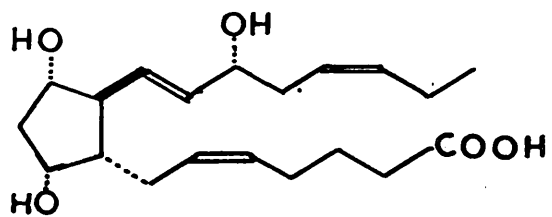
PGF<sub>1a</sub>

9a, 11a, 15-Trihydroxy-  
Prost-13-Enoic Acid



PGF<sub>2a</sub>

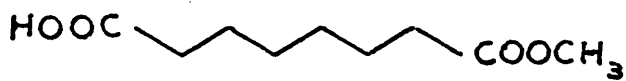
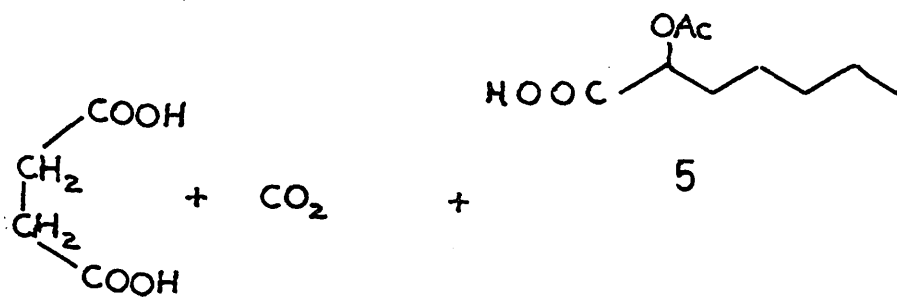
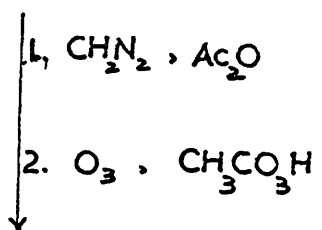
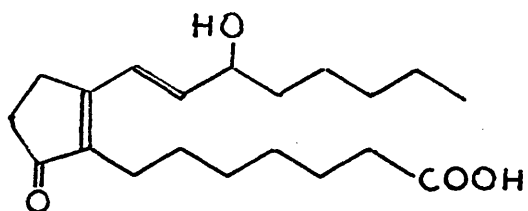
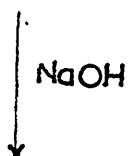
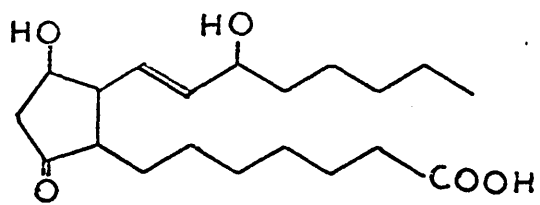
9a, 11a, 15-Trihydroxy-  
Prost-5, 13-Dienoic  
Acid

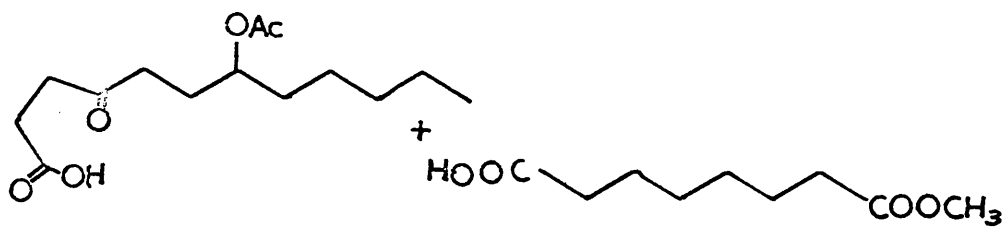
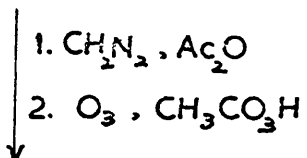
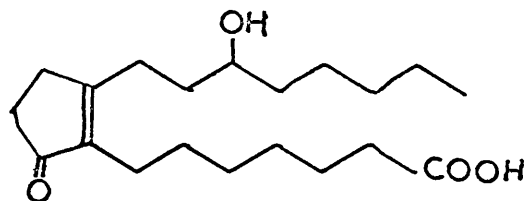
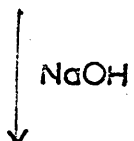
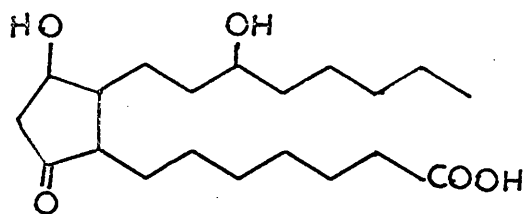
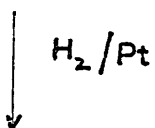
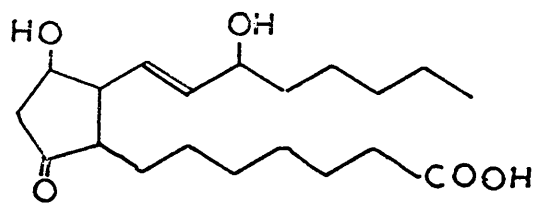


PGF<sub>3a</sub>

9a, 11a, 15-Trihydroxy-  
Prost-5, 13, 17-Tri-  
enoic Acid

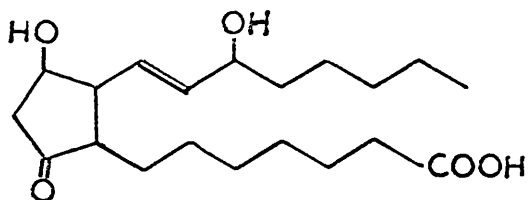






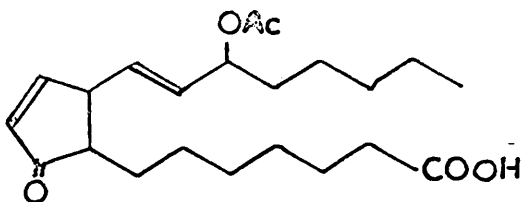
8

3



1

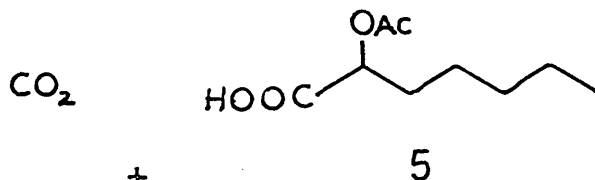
$\text{Ac}_2\text{O}$



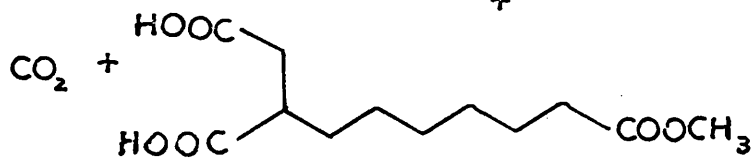
1.  $\text{CH}_2\text{N}_2$

9

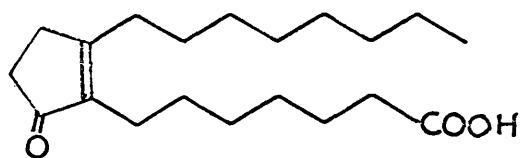
2.  $\text{O}_3, \text{CH}_3\text{CO}_3\text{H}$



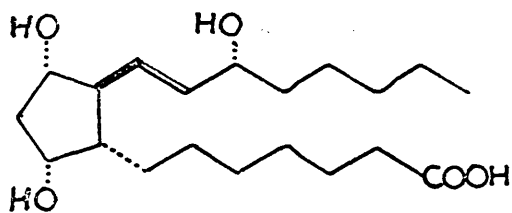
5



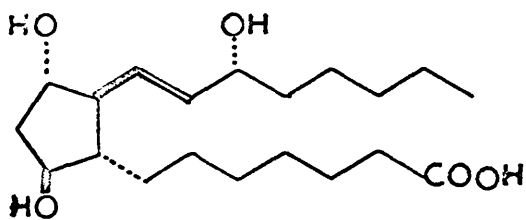
10



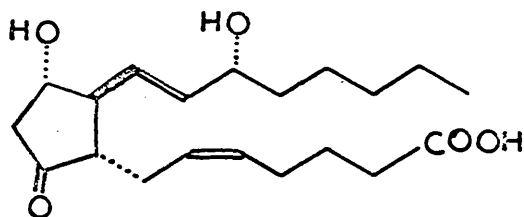
11



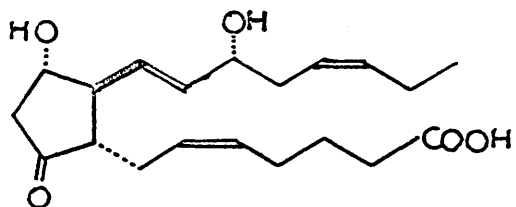
12



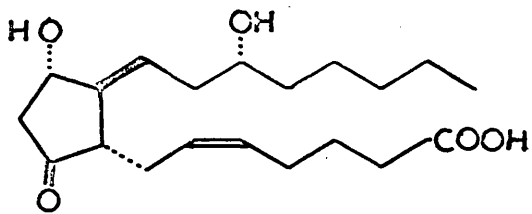
13



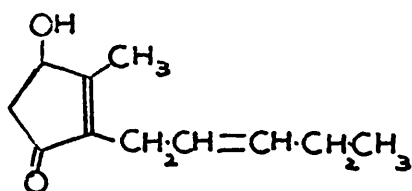
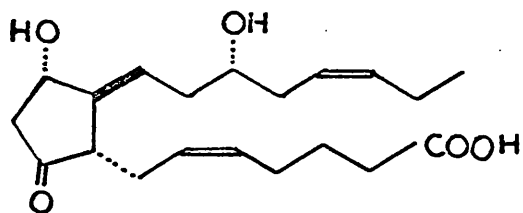
14

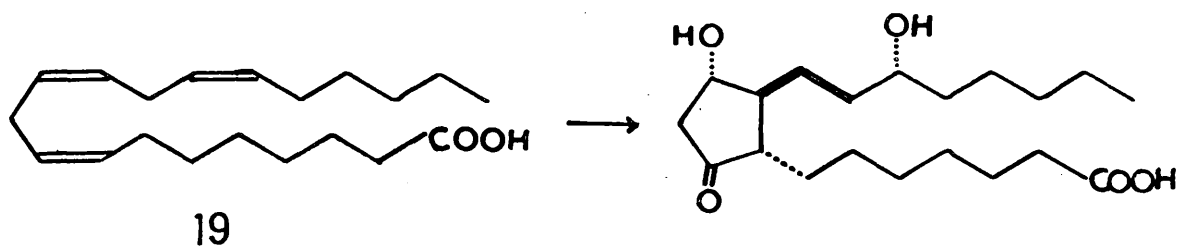


15



16

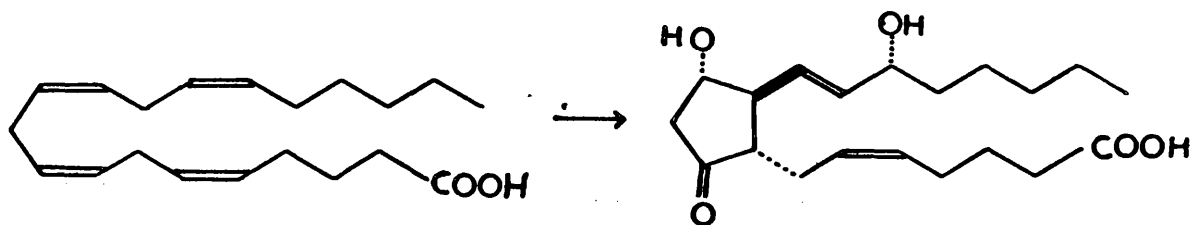




HOMO- $\gamma$ -LINOLENIC ACID

PGE<sub>1</sub>

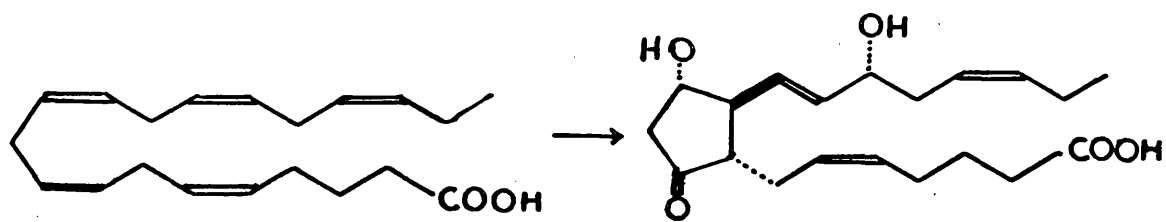
(All cis, 8, 11, 14-eicosa-trienoic acid)



ARACHIDONIC ACID

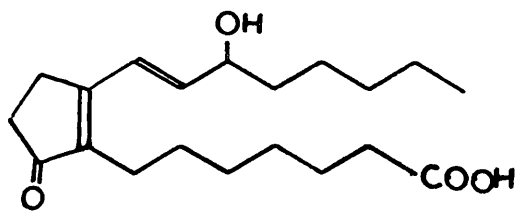
PGE<sub>2</sub>

(All cis, 5, 8, 11, 14-eicosa-tetraenoic acid)

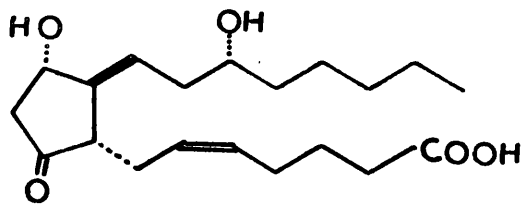


(All cis, 5, 8, 11, 14, 17-eicosa-pentaenoic acid)

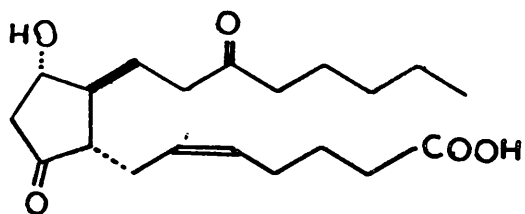
PGE<sub>3</sub>



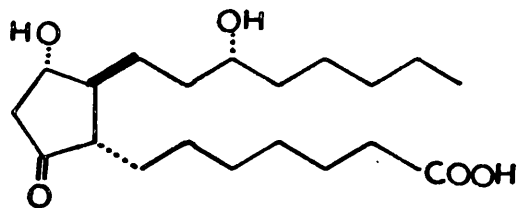
22



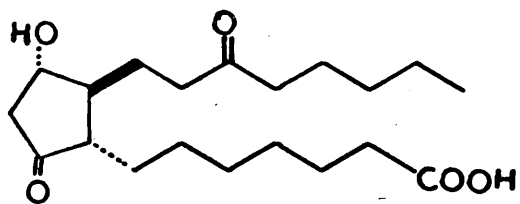
23



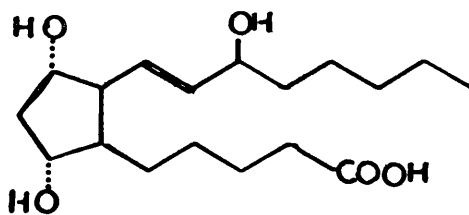
24



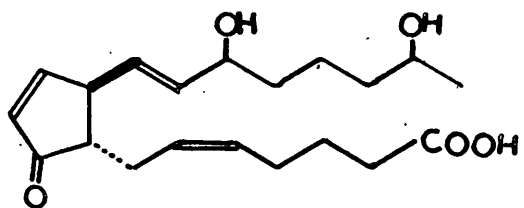
25



26



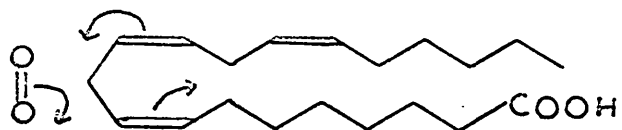
27



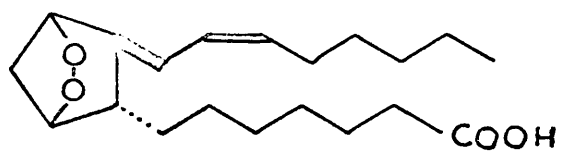
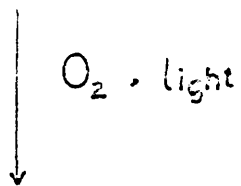
28



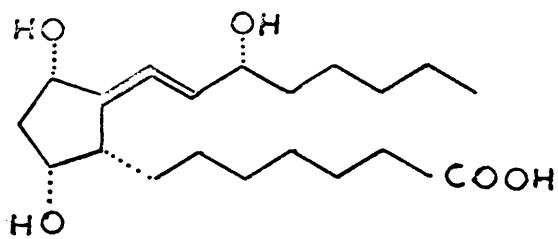
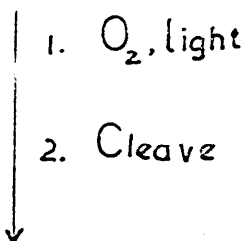
29



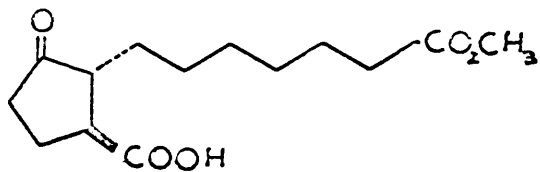
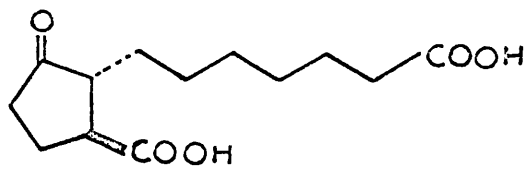
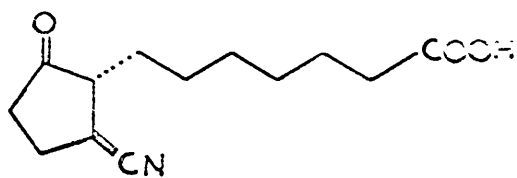
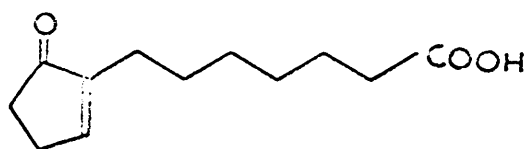
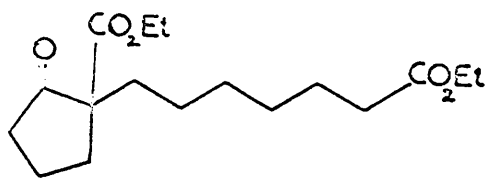
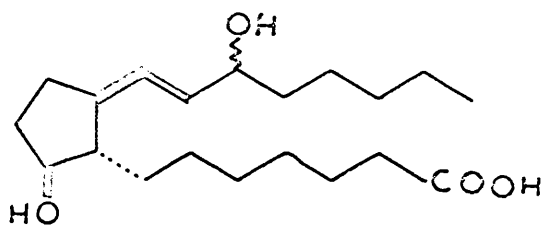
19



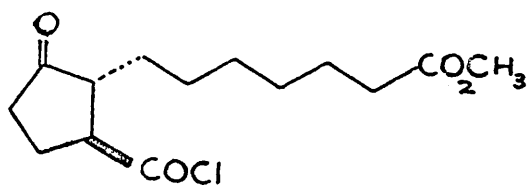
30



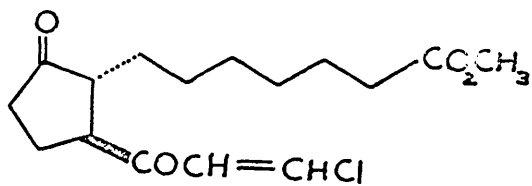
12



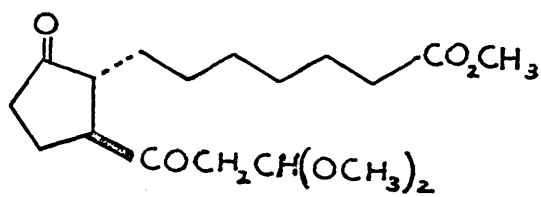




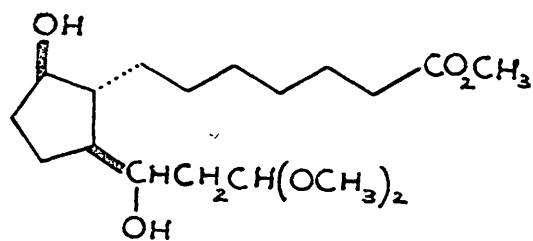
37



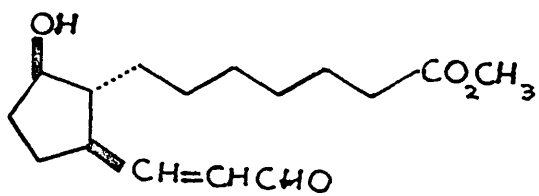
38



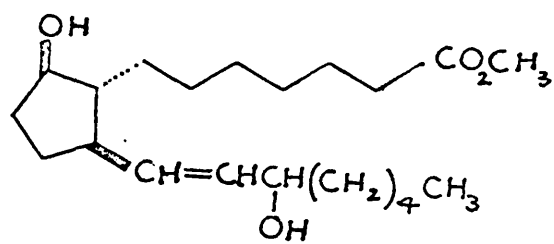
39



40

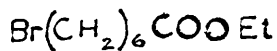


41

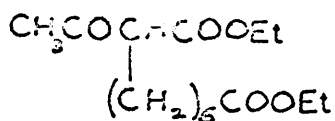


42

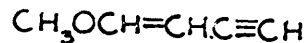
ROUTE 1 — SCHEME



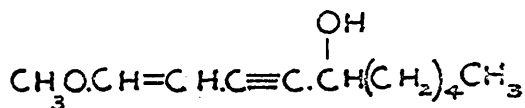
43



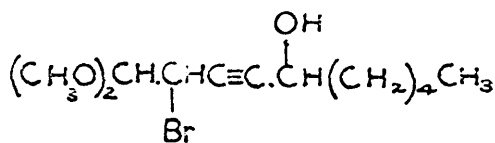
44



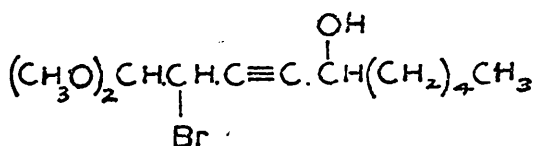
45



46

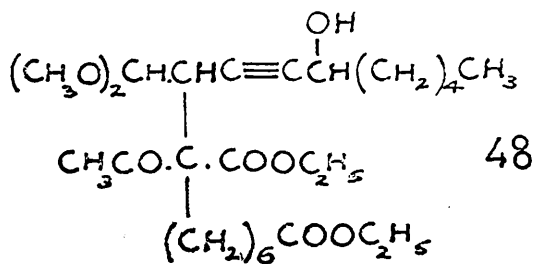
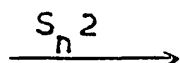


47

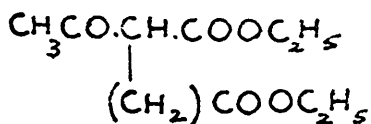


47

+

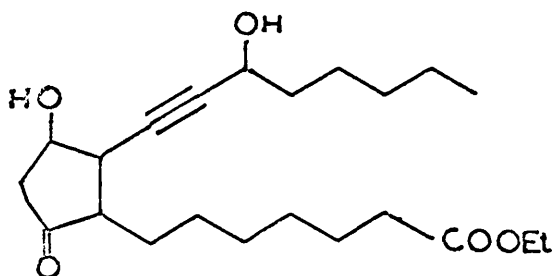


48

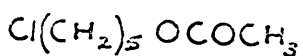


44

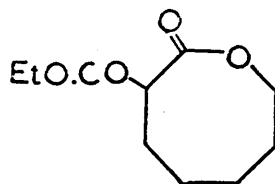
1. Hydrolysis  
2. Ring Close



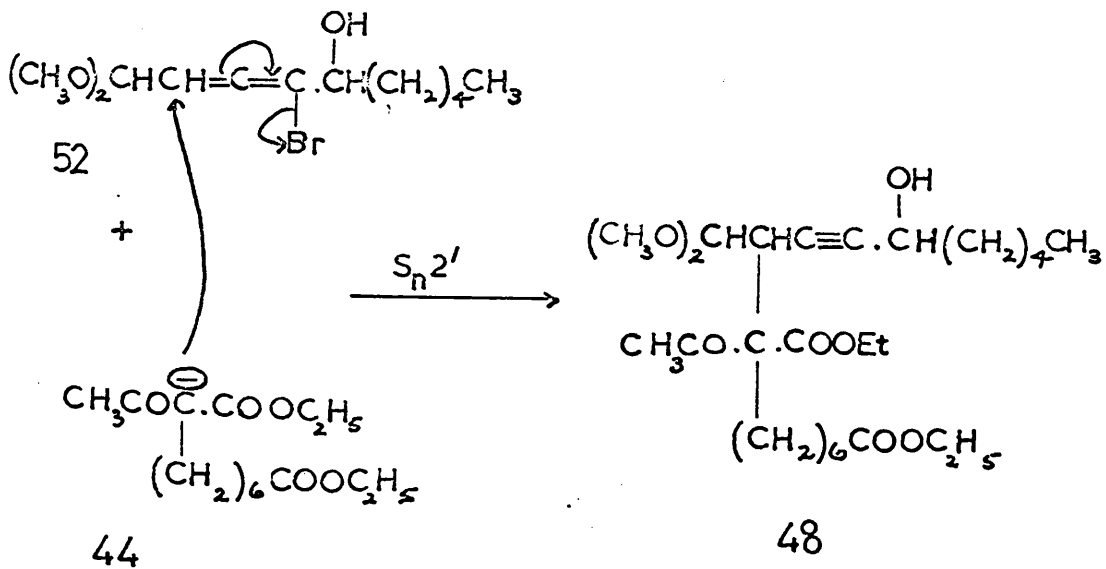
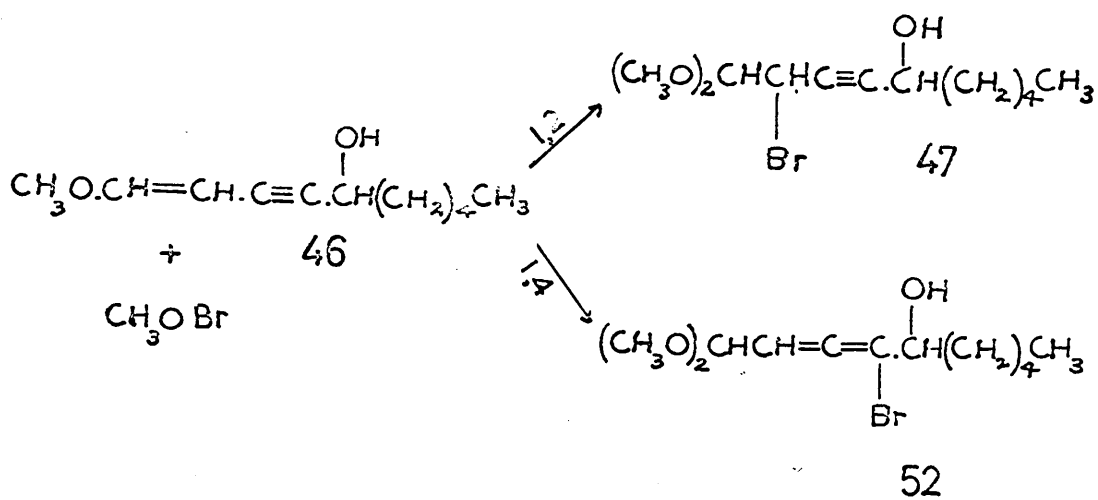
49

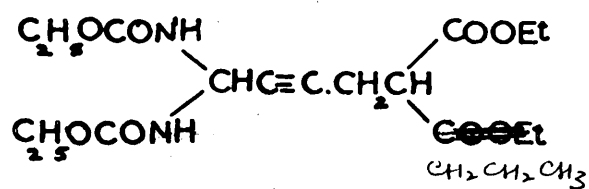
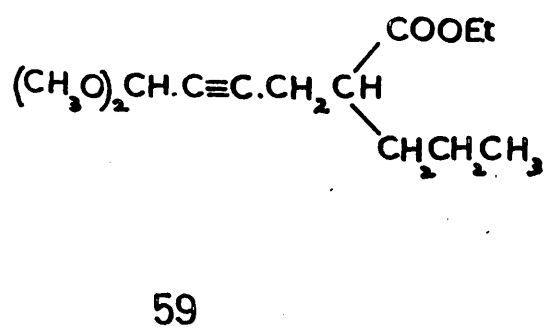
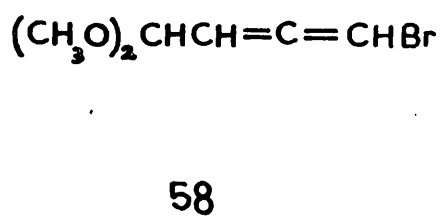
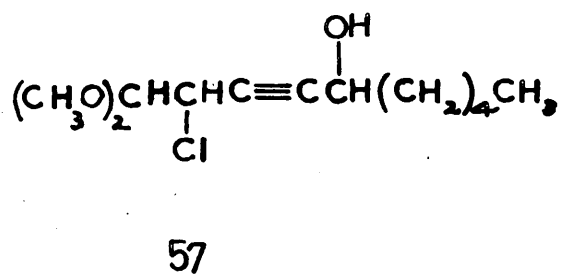
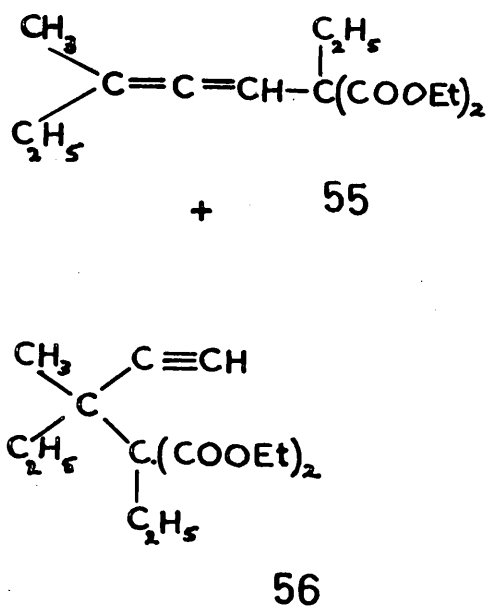
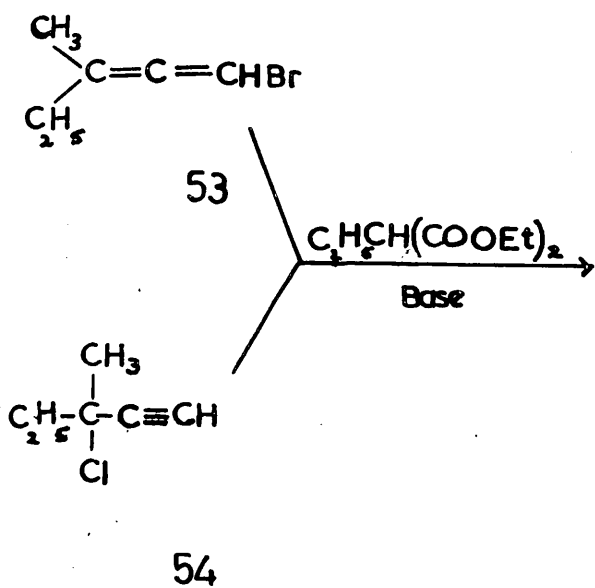


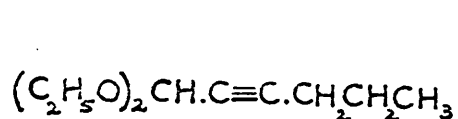
50



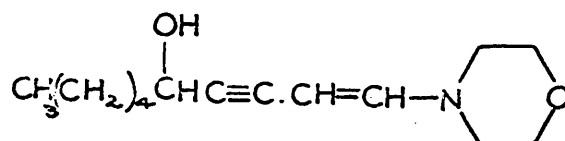
51



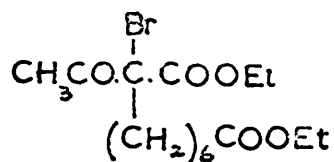




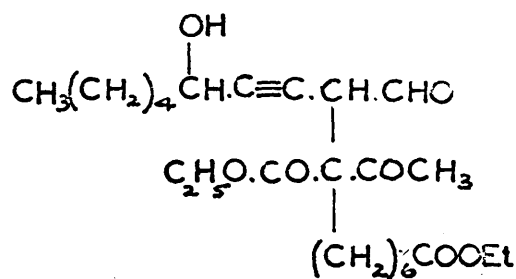
61



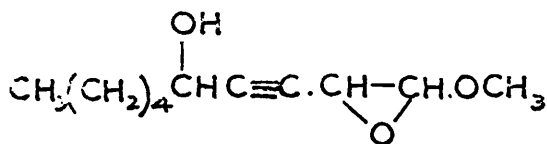
62



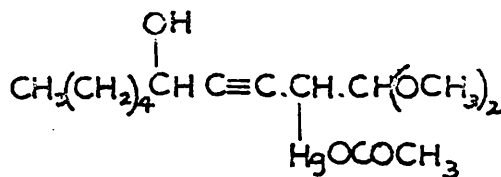
63



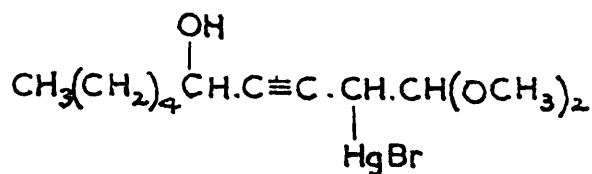
64



65

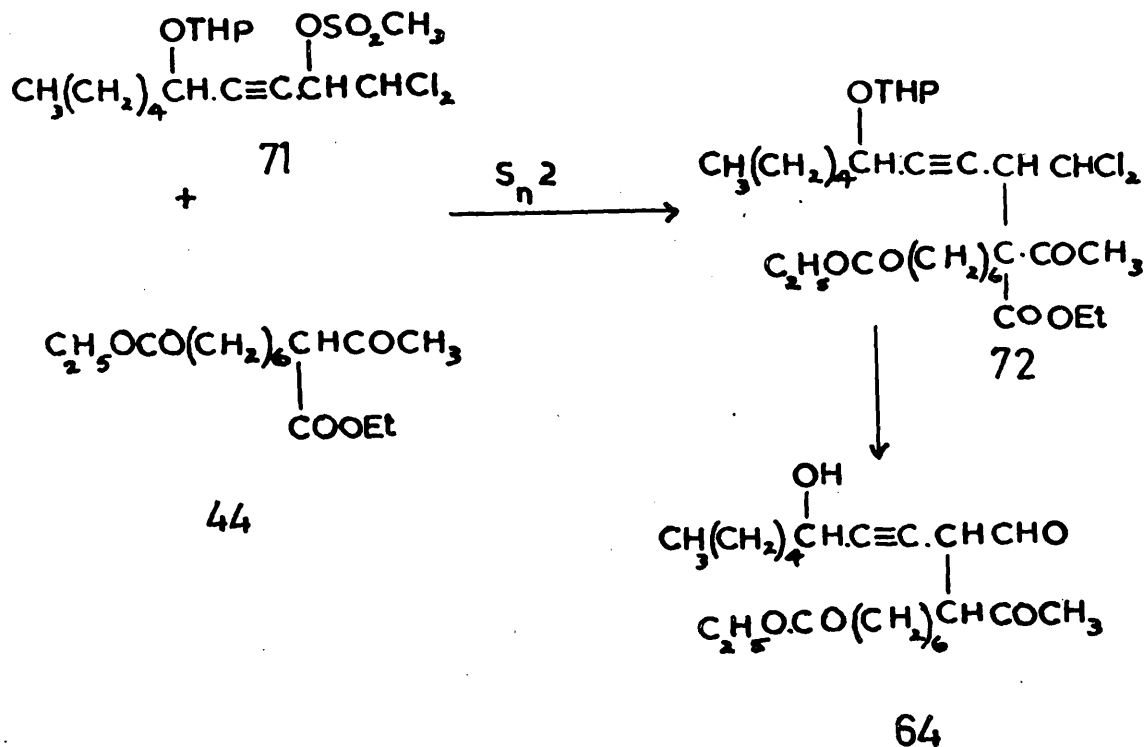
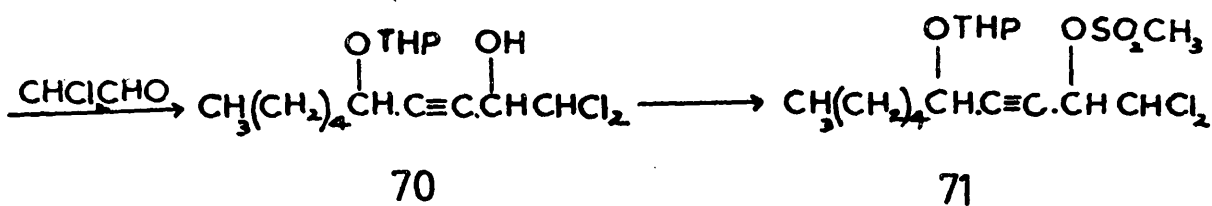
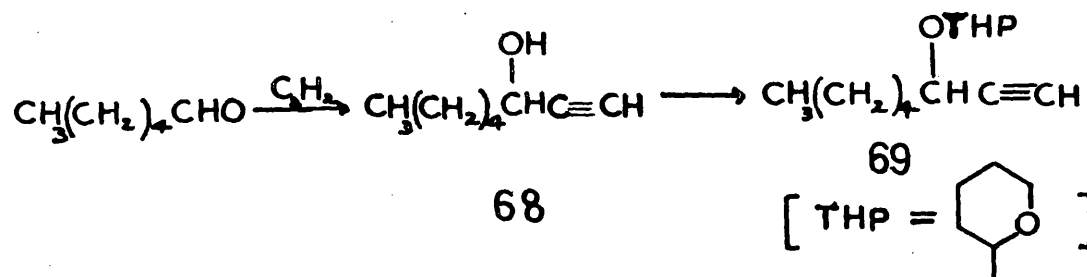


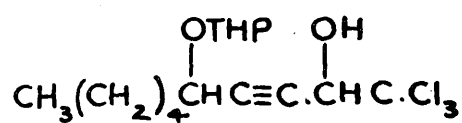
66



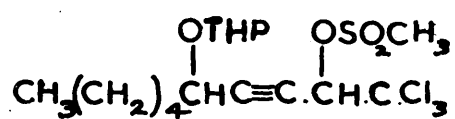
67

ROUTE 2 SCHEME

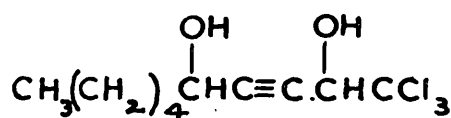




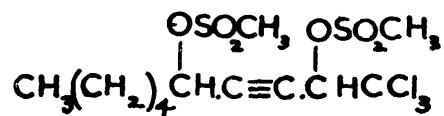
73



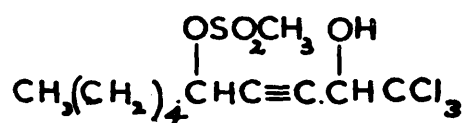
74



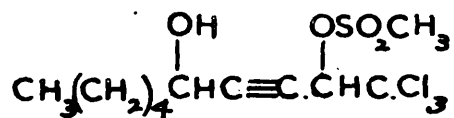
75



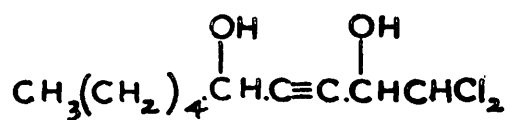
76



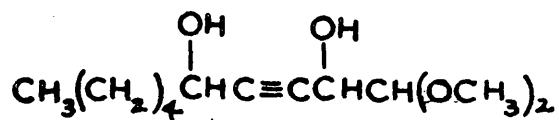
77



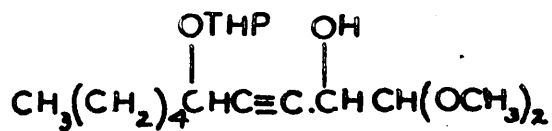
78



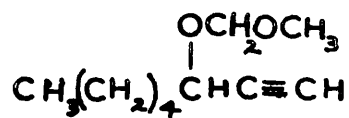
79



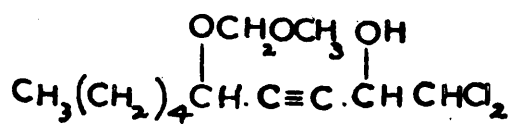
80



81



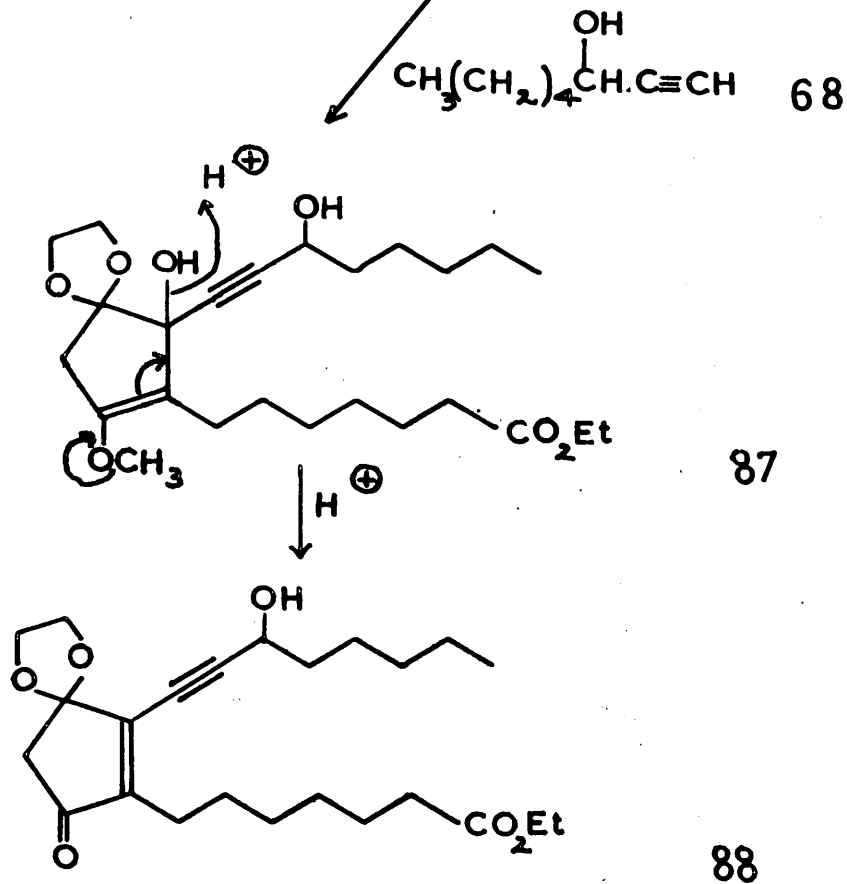
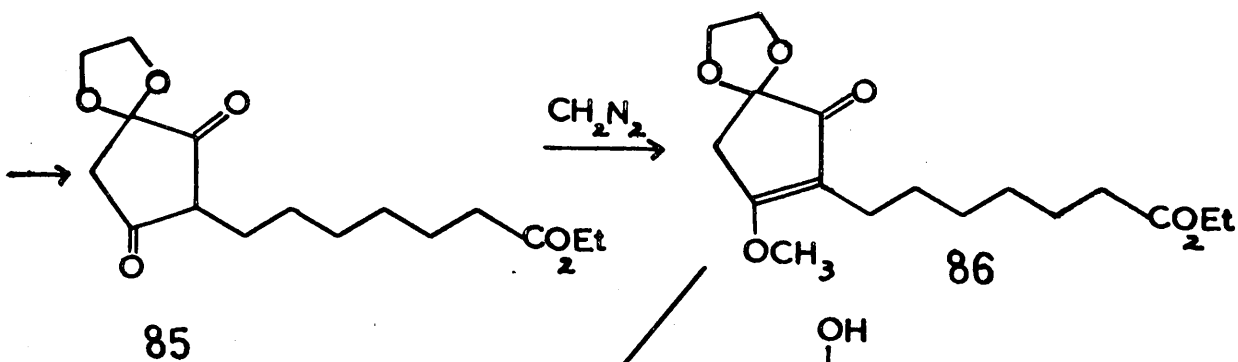
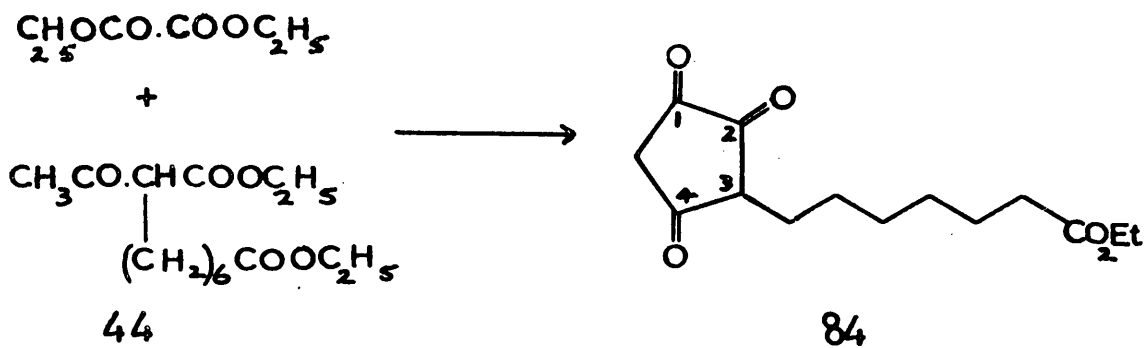
82

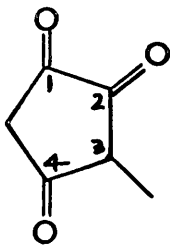


83

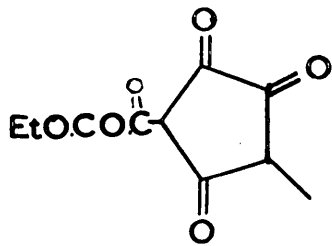


ROUTE 3 - SCHEME

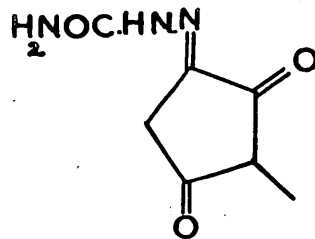




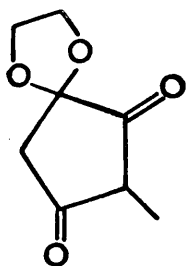
89



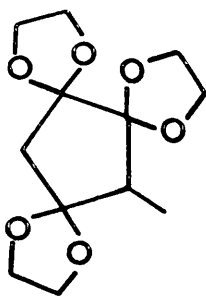
90



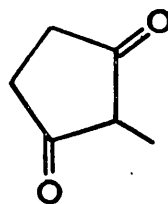
91



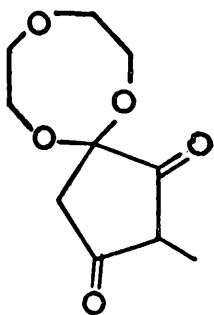
92



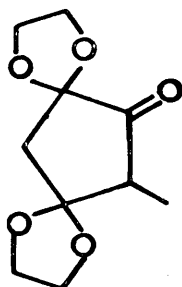
93



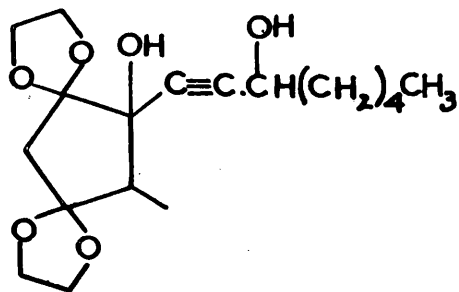
94



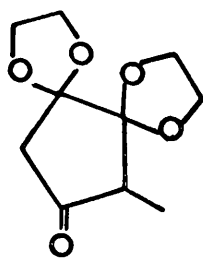
95



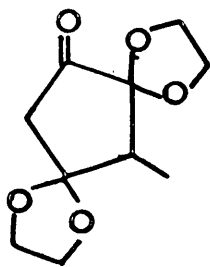
96



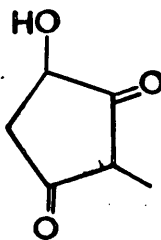
97



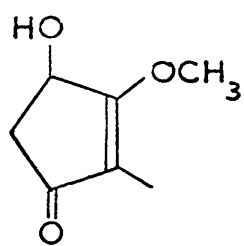
98



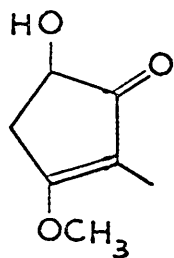
99



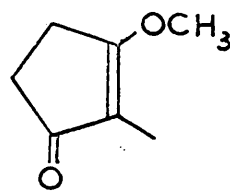
100



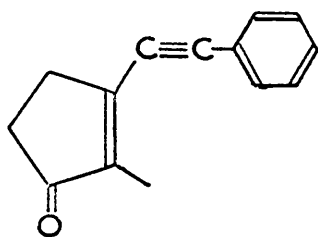
101



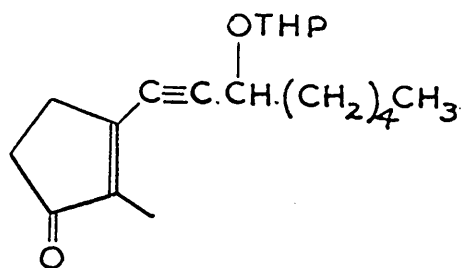
102



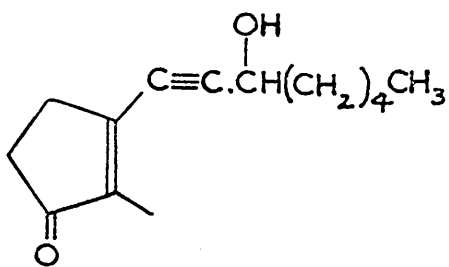
103



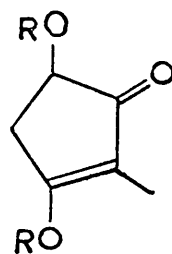
104



105

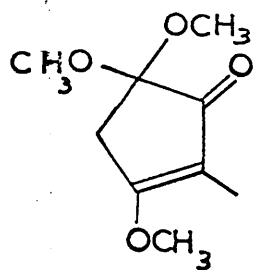


106

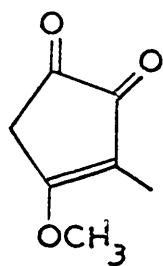


107

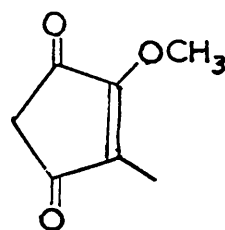
(R=THP, Benzyl)



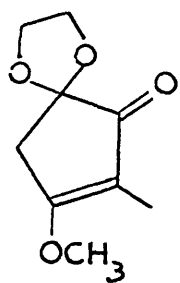
108



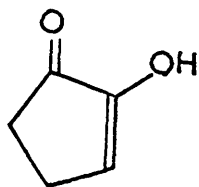
109



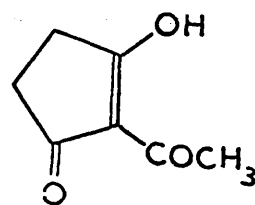
110



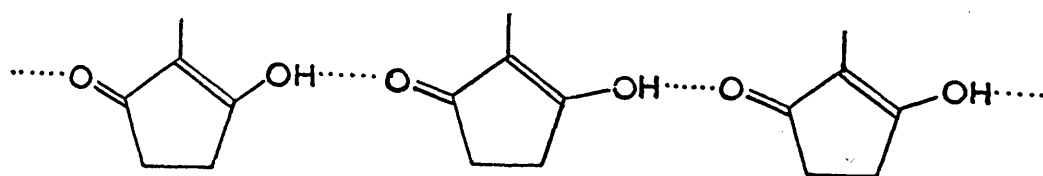
111



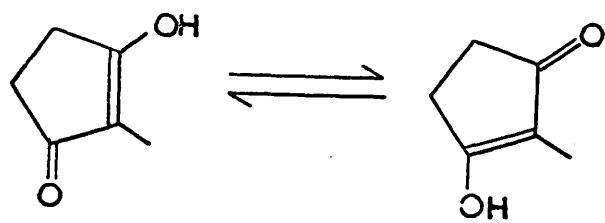
112



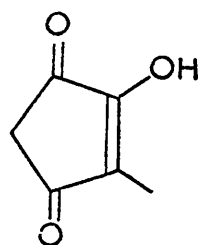
113



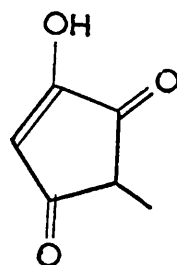
114



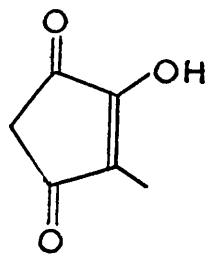
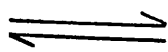
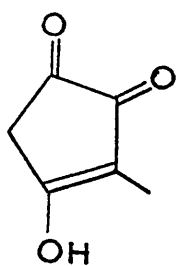
115



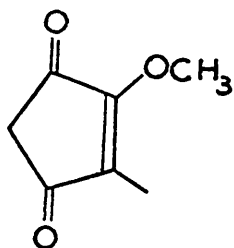
116



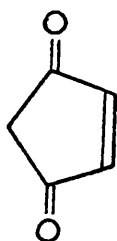
117



118

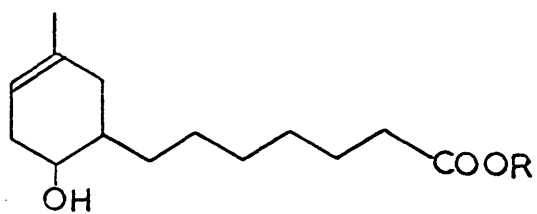


119

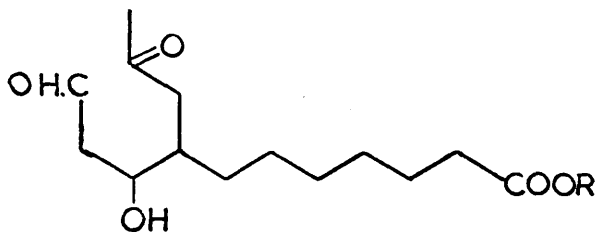


120

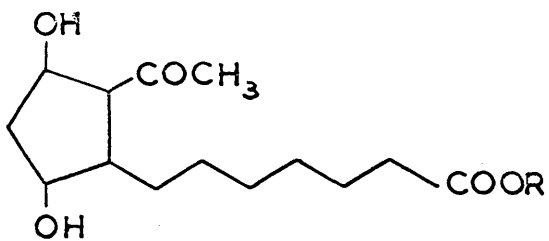
ROUTE 4



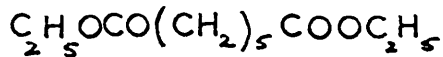
121 (a, R=H. b, R=CH<sub>3</sub>)



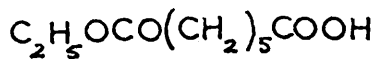
122 (a, R=H. b, R=CH<sub>3</sub>)



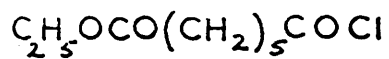
123 (a, R=H. b, R=CH<sub>3</sub>)



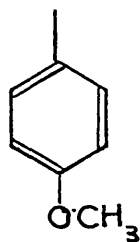
124



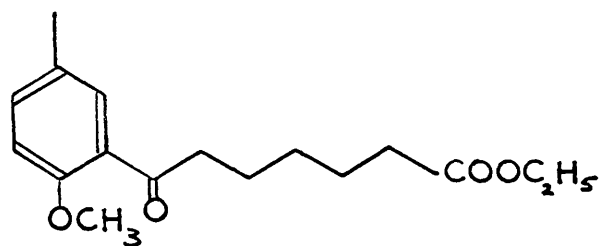
125



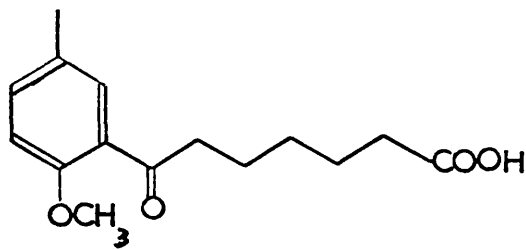
126



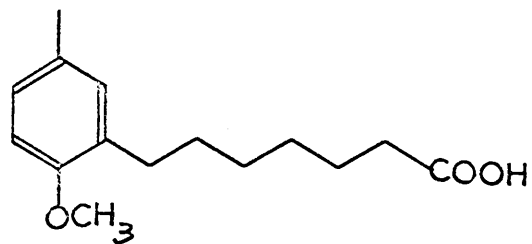
127



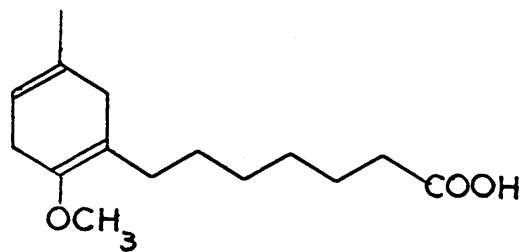
128



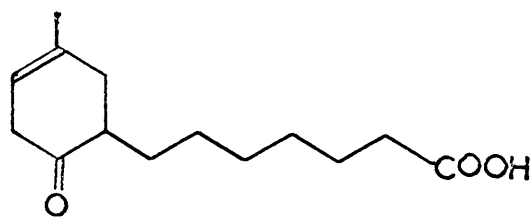
129



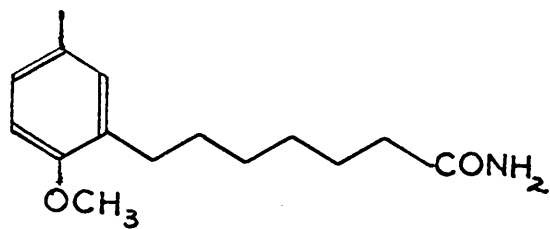
130



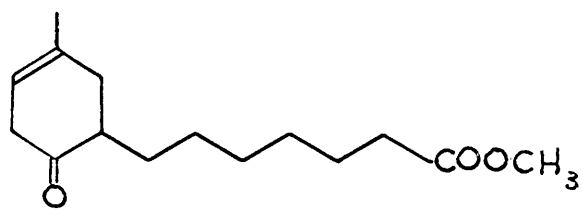
131



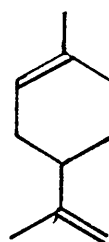
132



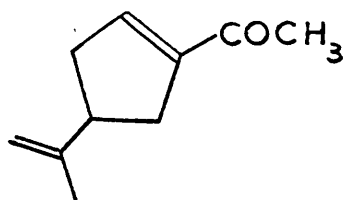
133



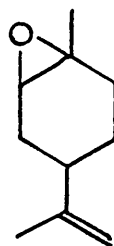
134



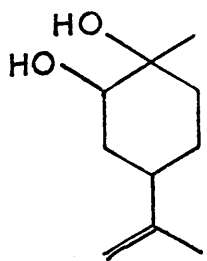
135



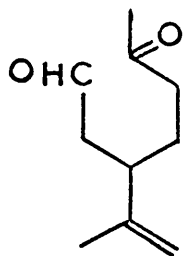
136



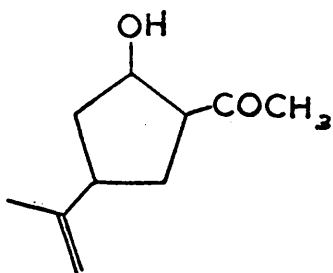
137



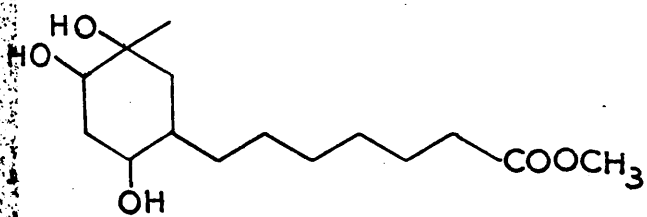
138



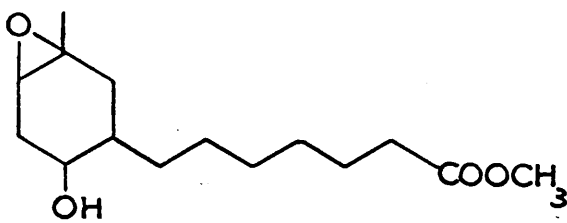
139



140



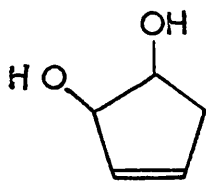
141



142

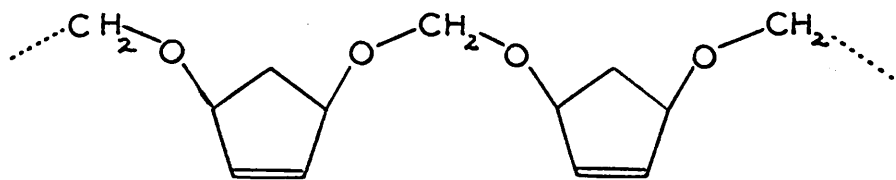


143

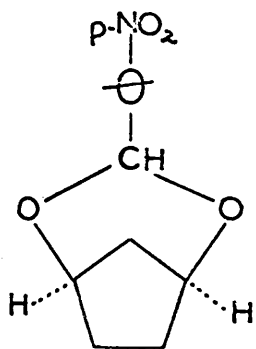


144

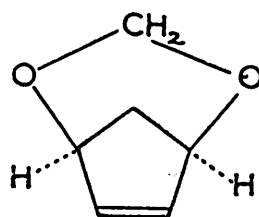




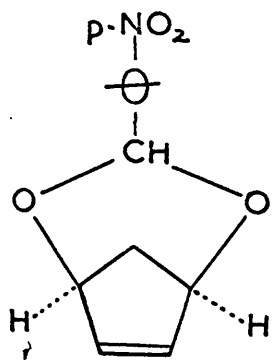
145



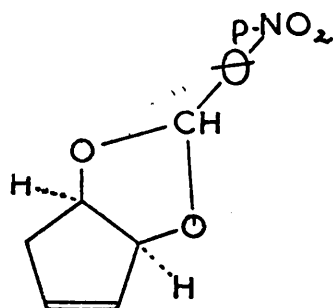
147



146

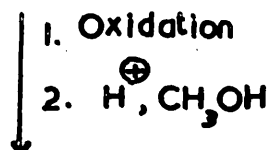
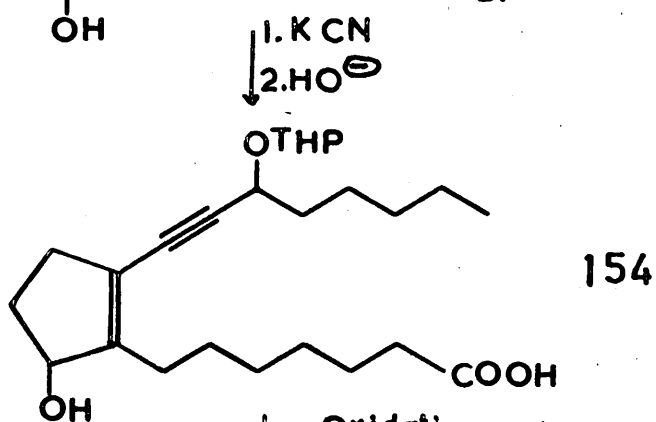
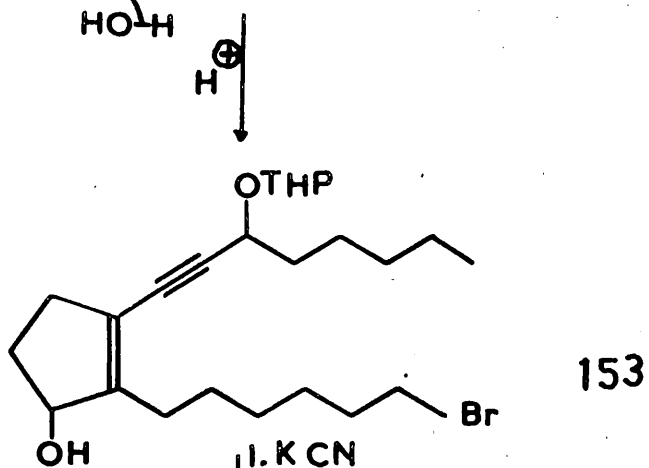
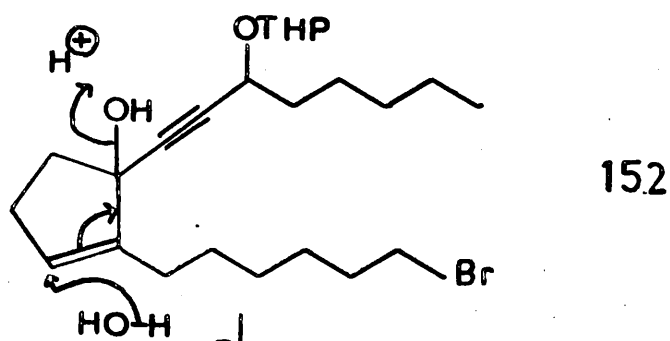
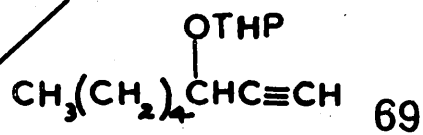
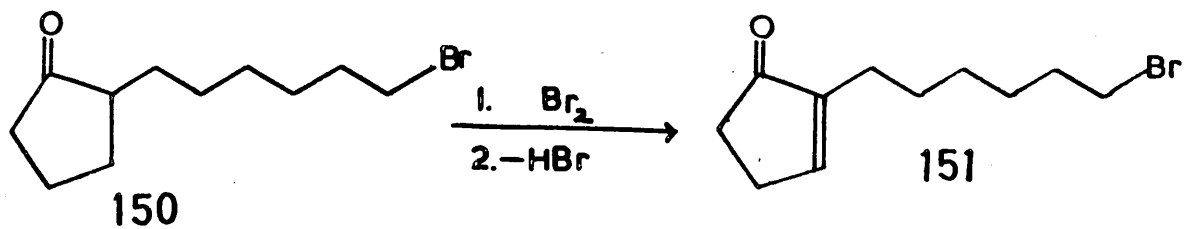


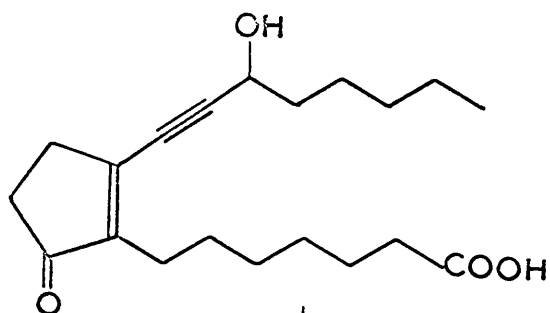
148



149

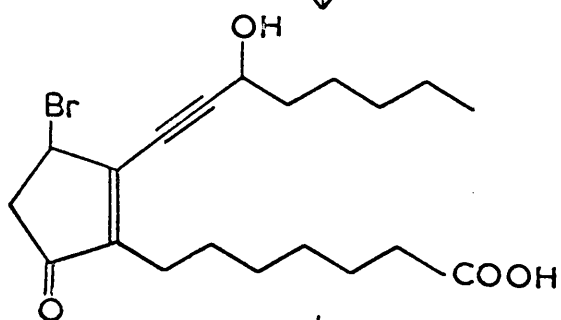
ROUTE 5





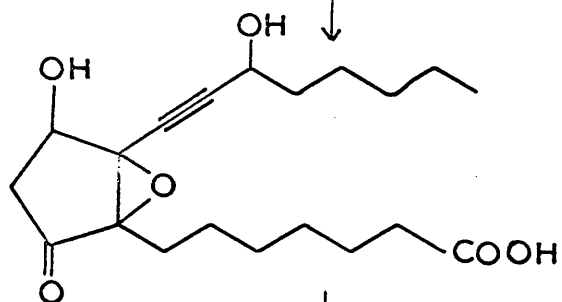
155

N-Bromosuccinimide

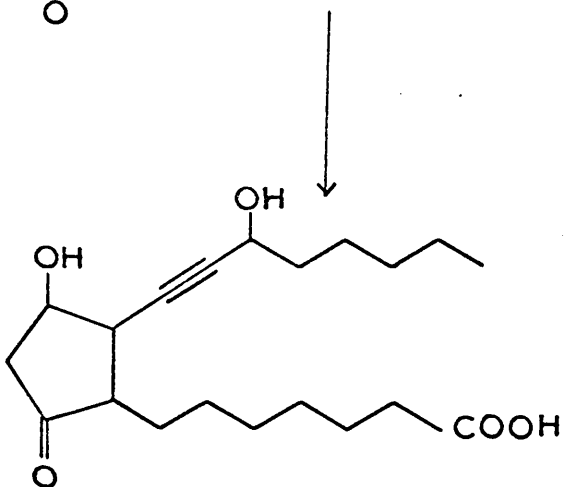


156

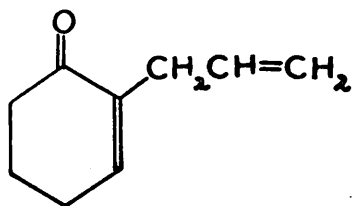
1.  $\text{Ac}_2\text{O}$ ;  $\text{OH}^\ominus$   
2.  $\text{H}_2\text{O}_2$ ,  $\text{OH}^\ominus$



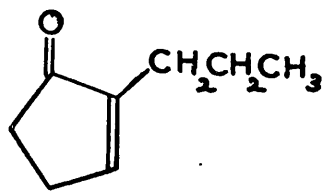
157



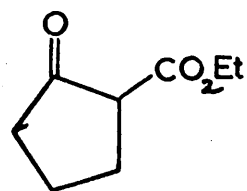
158



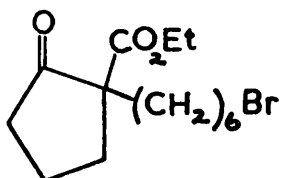
159



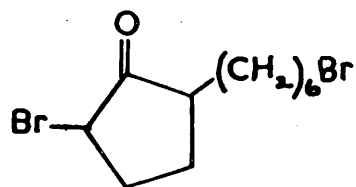
160



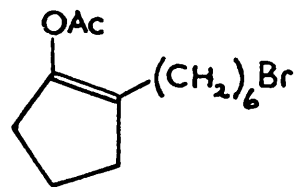
161



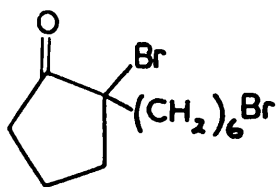
162



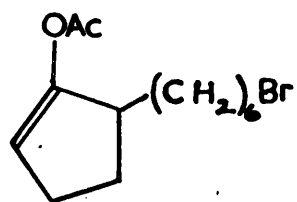
163



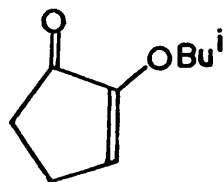
164



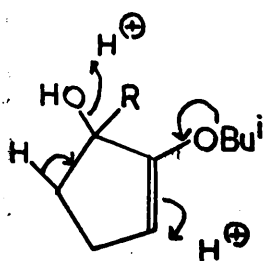
165



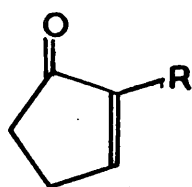
166



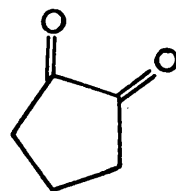
167



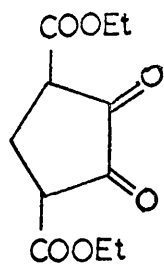
168



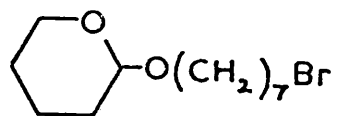
169



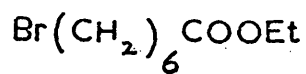
170



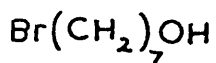
171



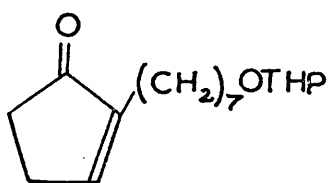
172



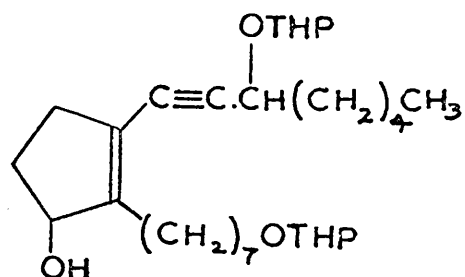
173



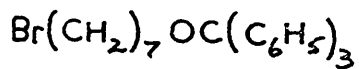
174



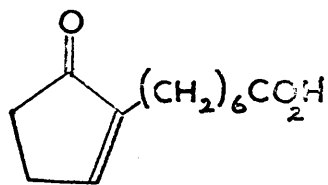
175



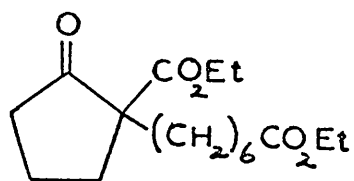
176



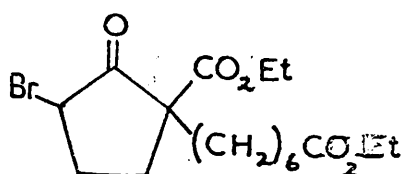
177



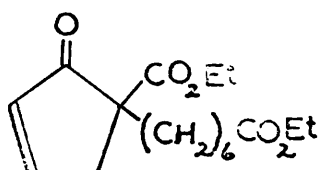
178



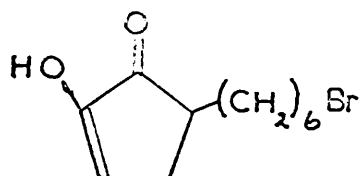
179



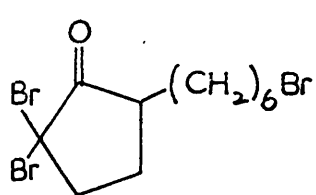
180



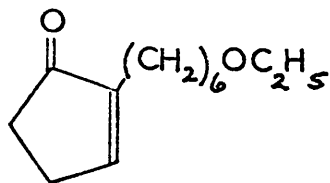
181



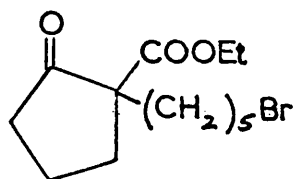
182



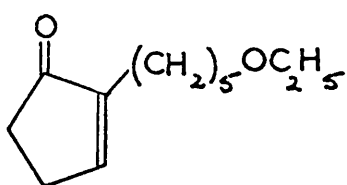
183



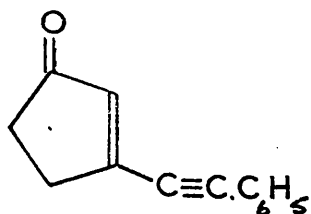
184



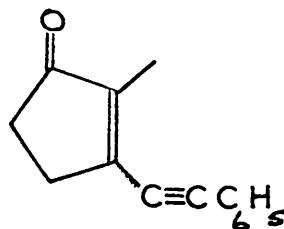
185



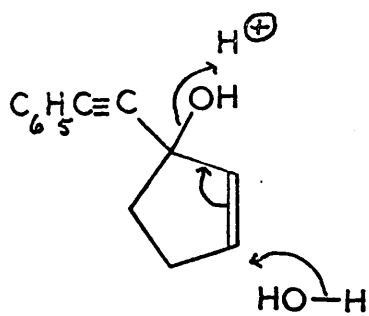
186



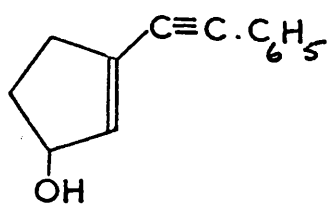
187



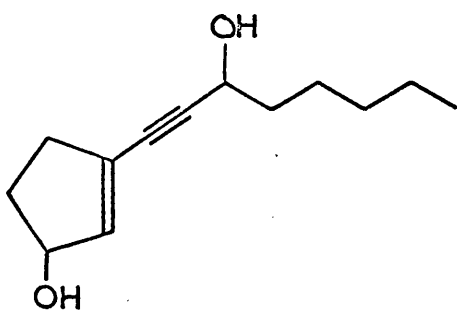
104



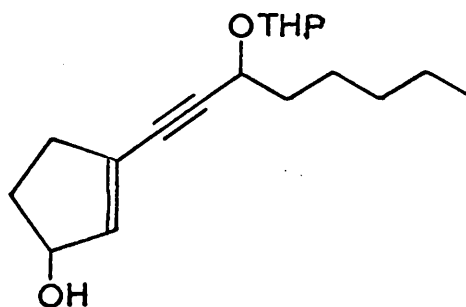
188



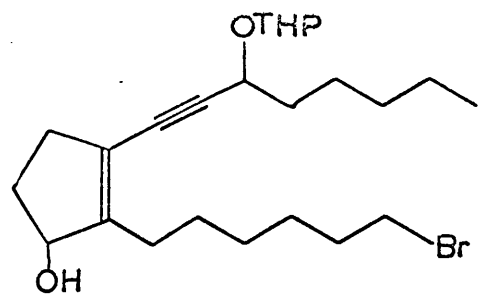
189



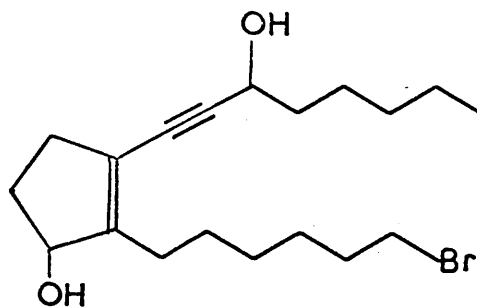
190



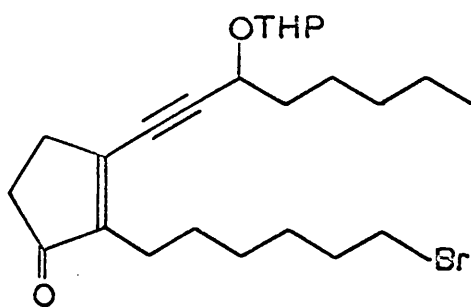
191



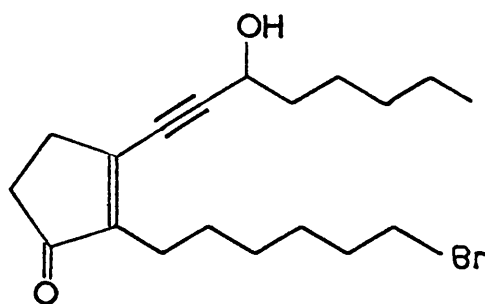
192



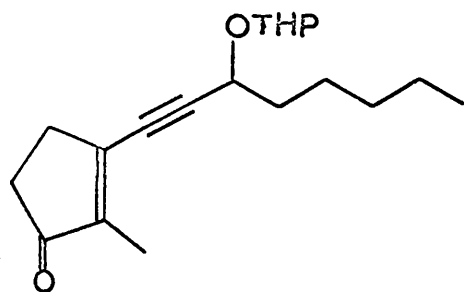
193



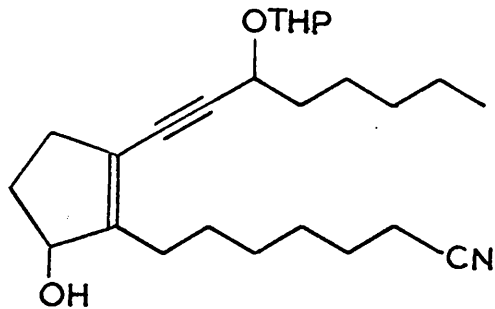
194



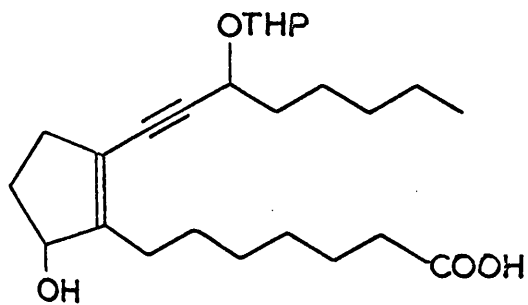
195



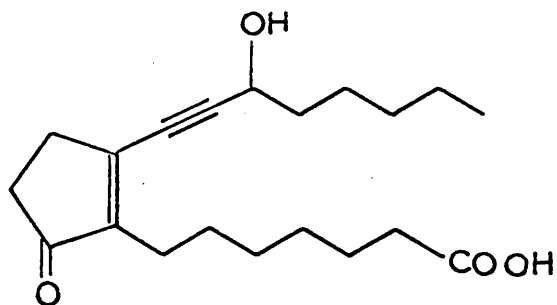
105



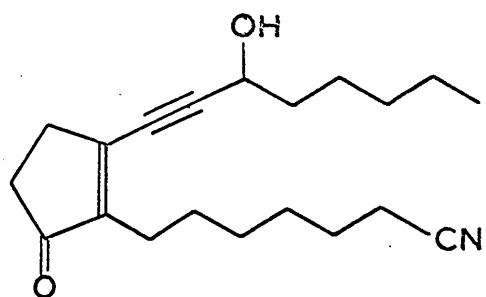
196



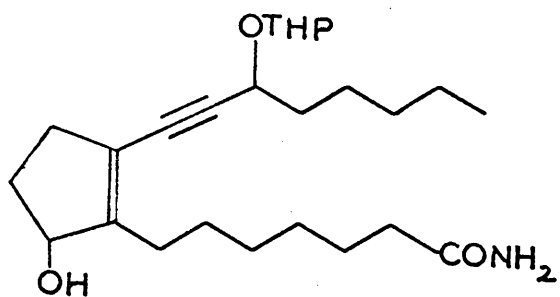
154



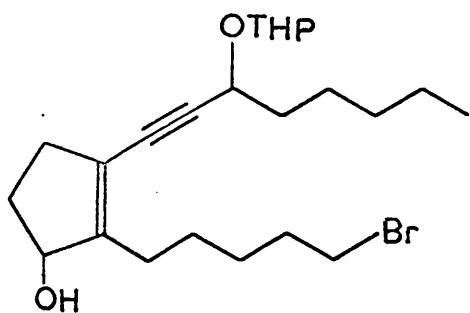
155



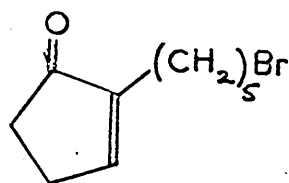
197



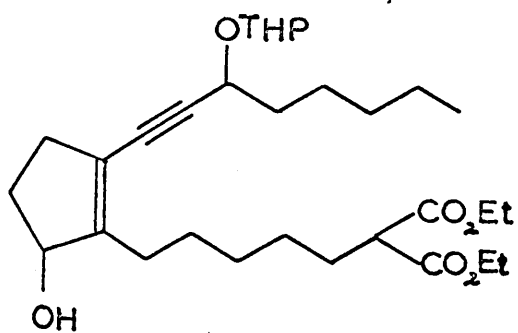
198



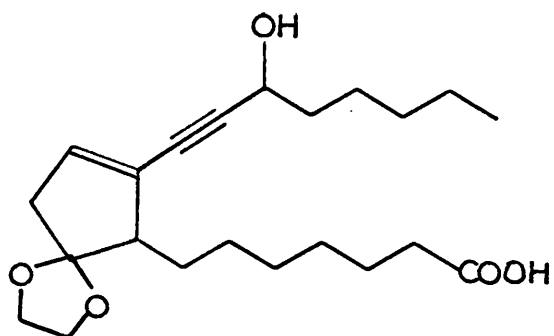
199



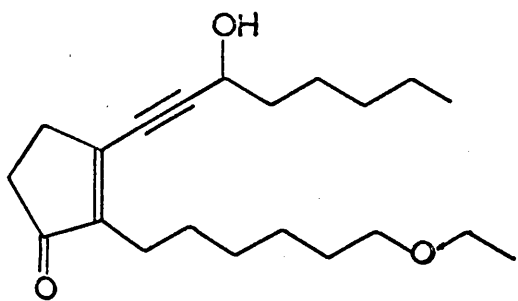
200



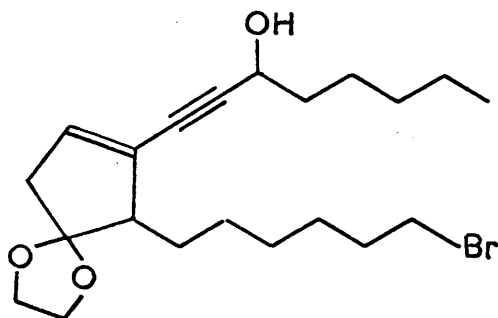
201



202

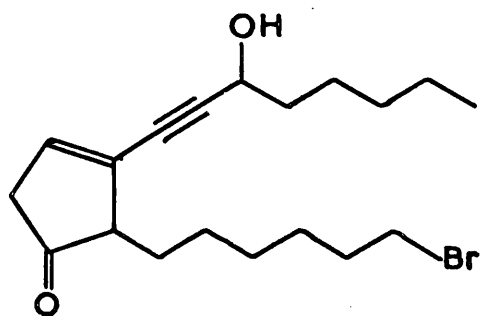


203

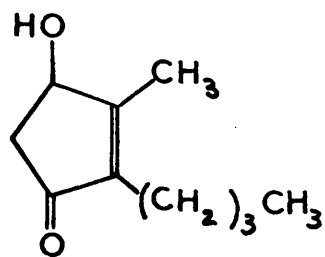


204

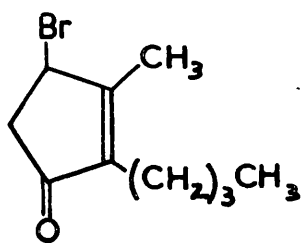




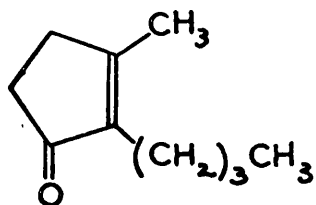
205



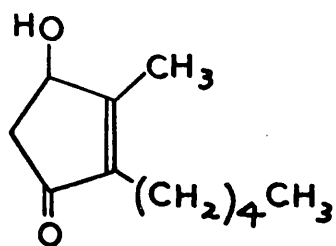
206



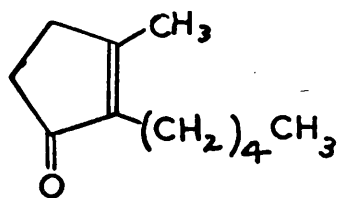
207



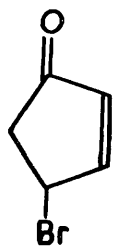
208



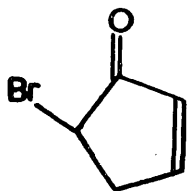
209



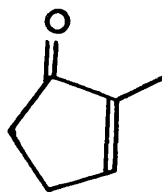
210



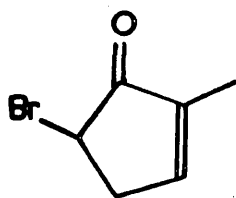
211



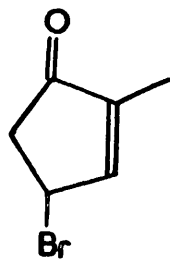
212



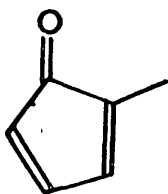
213



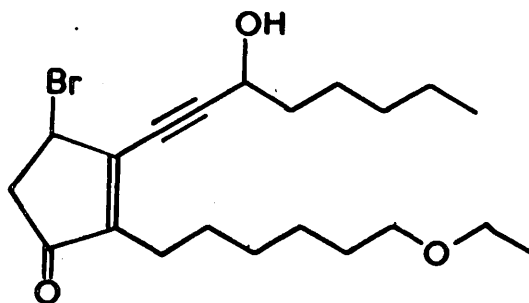
214



215



216



217

PART II

Synthetic Approaches to the Iridoid

Monoterpenes

REVIEW

The term 'iridoid' has been used to describe that group of monoterpenes which possess the carbon skeleton (218). Naturally occurring compounds of this type were not known until fairly recently, but in the last five or six years a fairly large group of monoterpenes has been identified which are characterised by possession of the iridoid skeleton.

The varied biological properties of the iridoid monoterpenes has aroused considerable interest in their structure and synthesis. Thus nepetalactone from catnip is an attractant to cats. The ant extractives iridomyrmecin, isoiridomyrmecin, iridodial and dolichodial have lacrymatory, repellent, insecticidal and antibiotic properties. The more complex iridoid glucosides are often responsible for the blackening on standing of the leaves of certain plants and have therefore been collectively named pseudo-indicans. Aucubin is known to increase the rate of excretion of uric acid.<sup>92</sup>

Interconversions of the different substances are many and have been of considerable value in structure determination. In particular, the allocation of structure and stereochemistry to

the more complex compounds has often depended on a relationship with nepetalactone or its degradation products.

Nepetalactone (219) was isolated from catnip, Nepeta cataria, in 1936.<sup>93</sup> On alkaline hydrolysis it yields the two epimeric nepetalic acids (220) which can be reconverted to the lactone on pyrolysis. Oxidation of the aldehyde function gives a nepetalinic acid (221) or a nepetonc acid (222) which can be further degraded with sodium hypiodite to nepetic acid (223). The evidence leading to the structure and stereochemistry of these compounds has been summarised by Cavill<sup>94</sup>. All the possible nepetic acids have been synthesised and identified<sup>95</sup>. Comparison with samples made from the natural sources and cyclisations and epimerisations observed with the natural materials enabled McElvain<sup>96</sup> to allocate to nepetalactone the stereochemistry shown in (219). Its absolute configuration as (219) follows from degradation of the cyclopentane ring to L-(+)- $\alpha$ -methylsuccinic acid<sup>97</sup>.

In 1949, Pawan<sup>98</sup> isolated from the Argentine ant, Iridomyrmex humilis, a monoterpene lactone named iridomyrmecin, which accounted for approximately one per cent of the body weight of the ant. Subsequently Cavill has discovered the closely related

substances isoiridomyrmecin, iridodial and dolichodial in species of Australian ants. Iridomyrmecin and isoiridomyrmecin also occur in the Japanese plant Actinidia polygama;<sup>101, 94</sup> these two compounds are known collectively as the iridolactones.

Iridomyrmecin is epimerised by base to isoiridomyrmecin<sup>102</sup>. Iridomyrmecin on oxidation gives one of the nepetalinic acids derivable without epimerisation from nepetalactone while isoiridomyrmecin gives the C<sub>8</sub> - epimer<sup>102</sup>. The iridolactones are therefore epimeric about C<sub>8</sub> and X-ray studies have confirmed that iridomyrmecin is (224) and isoiridomyrmecin is (225).

Iridodial undergoes disproportionation with base giving isoiridomyrmecin. On oxidation it gives a mixture of nepetalinic acids. Its infra red spectrum suggests that it exists largely as the enol-hemiacetal. It is therefore best represented as an equilibrium mixture (226)<sup>104</sup>.

Dolichodial has been assigned the structure (227)<sup>105</sup>. It gives iridodial (226) on hydrogenation and formaldehyde on ozonolysis. Its ultra violet spectrum is typical of an  $\alpha$ -monosubstituted acrolein.

Treatment of iridodial bis-dinitrophenylhydrazone with acid gives actinidine (228)<sup>104</sup>, which occurs naturally in Actinidia polygama<sup>101</sup>.

In addition to the naturally occurring iridoid monoterpenes already mentioned, further examples of the group have recently been identified. A reinvestigation<sup>106</sup> of the terpenes from Actinidia polygama resulted in the isolation of three new lactones, dihydronepetalactone (229), isodihydronepetalactone (230) and neonepetalactone (231), together with the cyclic ether, matatabiether (232). The same workers also reinvestigated the extracts of Nepeta cataria and were able to isolate two dihydronepetalactones, which were identified as (229) and (230), and in addition obtained methyl nepetionate (233), an aldehyde ester (234) and a hydroxy lactone (235). Isonepetalactone (236) was also identified in oil of catnip and was converted to nepetalactone (219) by heating with potassium carbonate in xylene<sup>106</sup>.

Another variation on the skeletal structure, anisomorpha, has been isolated from the southern walking-stick, Anisomorpha cuprestoides and characterised as<sup>107</sup> the dialdehyde (237), an isomer of dolichodial.

Several highly oxygenated forms of the iridoid mono-terpenes occur naturally such as loganin (238)<sup>108</sup>, verbanalin (239)<sup>109</sup>, genipin (240)<sup>110</sup>, asperuloside (241)<sup>111</sup>, aucubin (242)<sup>112</sup>, catalposide (243)<sup>113</sup>, and its p-hydroxybenzoate, agnuside<sup>114</sup>, plumieride (244)<sup>115</sup>,

plumericin (245)<sup>116</sup> and harpagide (246)<sup>117</sup>. A reduced form of the iridoid skeleton exists in the alkaloid skytanthin (247)<sup>118</sup>.

The essential structural features of these compounds, the cyclopentane ring, can be derived biogenetically by an internal Michael condensation on an intermediate such as (249), which can itself be derived from citronellal (248) by oxidation of one of the two methyl groups activated by the double bond. Indeed both the oxidation and cyclisation have been realised in Robinson's in vitro synthesis of the dialdehyde (250) from which isoiridomyrmecin and related compounds were then prepared<sup>119</sup>.

The likely precursor to citronellal (248) is citral (251) which has been isolated from at least one species of ant and on retroaldol cleavage would give 6-methylhept-5-en-2-one which occurs together with iridodial in many Iridomyrmex and Dolichoderus species.

An oxidation and cyclisation of citral itself, without reduction to citronellal, would give the dialdehyde structure (252). This would appear to be a possible precursor of all the more oxygenated iridoids since the extra oxygen functions, as in asperuloside (241), occur at the allylic positions, while loganin (238) and catalposide (243) would require hydration or epoxidation of the double bond.



Cyclisation to produce the heterocyclic ~~six~~-membered rings presents no special problem. In the case of aucubin (242) for example, cyclisation could be accompanied by decarboxylation of the  $\beta$ -formyl carboxylic acid system as shown in (253). In the case of the alkaloids actinidine (228) and skytanthin (247), ammonia or a biological equivalent could be incorporated at an appropriate stage.

An opening of the cyclopentane ring as in (254) could lead, via an open chain intermediate (255) to such structures as swertiamarin (257) and gentiopicrin (258) in which the original isoprenoid nature of the precursor has been lost<sup>120</sup>.

Two other biogenetic routes to the iridoids have been considered<sup>121</sup>. Thus citral (251) has been cyclised by irradiation to give the aldehyde (259)<sup>122</sup>. Enzymatic allylic oxidation of (259) would give dolichodial (227) which after reduction and disproportionation would afford iridodial and the iridolactones respectively.

The third biogenetic scheme visualises limonene (260) as precursor. Oxidation of limonene to (261), **aldol cyclisation** to the unsaturated aldehyde (262) and enzymatic reduction would

afford (259). The latter could then be converted to the iridolactones in the manner described above. The plausibility of this scheme is suggested by the preparation of (262) from the keto-aldehyde (261)<sup>123</sup>.

A biosynthetic theory for the main classes of indole alkaloids involve the intermediacy of the iridoid monoterpenes to account for the derivation of the non-tryptophan-derived segment of these types of alkaloid. The type of open chain intermediate (255) envisioned above in the formation of swertiamarin (257) and gentiopicrin (258) can be successfully used to derive the structures of many of the indole alkaloids. Very recent tracer work supports this theory, by demonstrating not only mevalonate incorporation but also geraniol (263) incorporation into a number of indole alkaloids<sup>124, 125, 126</sup>. Geraniol may be regarded as the immediate precursor in the plant of the iridoid monoterpenes.

### Synthesis

The most noteworthy synthesis in the iridoid field still remains that by Robinson<sup>119</sup>, which simulates a proposed biogenetic route. Reference was made to this work in the section

on biosynthesis. The starting point was citronellal (248) which was suitably protected, subjected to allylic oxidation and then ring closed as in (249) to give iridodial (250).

Cavill<sup>127</sup> also used citronellal to prepare the unsaturated cyano-ester (264). This intermediate was cyclised to the irido-lactones and dolichodial. Korte developed two routes from non natural sources. In the first of these<sup>128</sup> 3-methylcyclopentanone was converted by Reformatski reaction with ethyl  $\alpha$ -bromopropionate, dehydration and hydrolysis to a mixture of unsaturated acids (265). A Prins reaction with formaldehyde was used to insert the final carbon atom and so lead to iridomyrmecin. The method was complicated however by the stereochemical ambiguities.

In Korte's second method<sup>129</sup>, homocatechol (266) was hydrogenated, cleaved and cyclised to (267). This aldehyde when heated with cis-1-(n-propoxy)-propene gave the enol acetate (268). The latter was hydrogenated, hydrolysed, oxidised and lactonised to give isoiridomyrmecin.

Sakan has synthesised nepetalactone from 2-carboethoxy-5-methylcyclopentanone (~~269~~<sup>269</sup>)<sup>130</sup>. Alkylation with 3-bromobut-1-yne gave (270) which was then converted to (271). This diketone was cyclised to (272) which was converted to nepetalactone (219) in seven steps.

Cavill<sup>131</sup> has described a neat synthetic route to these monoterpenes. Pulegone (273) was converted via trans-pulegenic acid (274) to the bicyclo-octenone (275). The direct Baeyer-Villiger oxidation of this to nepetalactone could not be effected but epoxidation of the enone (275), rearrangement and reduction could be made to yield a hydroxyketone (276) or a diol (277) which could be converted on oxidation or periodate cleavage to nepetalactone or iridodial respectively.

Pulegenic acid (274) was also used by Wolinsky<sup>121</sup> in a synthesis of iridomyrmecin and related iridolactones.

2-Carboethoxy-5-methylcyclopentanone (269), used by Sakan above as a starting point for his synthesis of nepetalactone was converted by Sisido<sup>132</sup> to the keto-ester (278) by alkylation with ethyl  $\alpha$ -bromopropionate. The keto group in (278) was converted to an *exo*-methylene by a Wittig reaction and hydroborated to give (279). Cyclisation of (279) gave a mixture of iridolactones.

The final reported total synthesis of an iridoid monoterpene is that of neonepetalactone (231)<sup>106</sup>. The keto-aldehyde (262)<sup>123</sup> prepared from limonene as mentioned above, was oxidised and esterified to give (280). Selective hydroboration gave (281) which was ring closed to give neonepetalactone (231).

It is of interest to note that a synthesis of skytanthin (247) has been reported<sup>133</sup> from iridomyrmecin. With lithium aluminium hydride, iridomyrmecin gives the diol (282), the ditosylate or dibromide of which was condensed with methylamine to yield skytanthin (247).

## DISCUSSION

For some time work in this department had been directed at developing a synthetic route to the iridoid monoterpenes from simple aromatic precursors<sup>134, 135</sup>. A short review of this work follows.

Pechmann condensation of ethyl acetoacetate (see flow sheet H1) with pyrogallol gave the coumarin (283) which was converted via the trimethoxycinnamic acid (284) by hydrogenation and cyclisation with polyphosphoric acid to the indanone (285). This on Clemmensen reduction, chloromethylation and hydrolysis gave the indane (286). All attempts to degrade this or its derivatives to a substance with the skeleton of iridodial failed, apparently owing to the tendency of the trialkyl-trioxygenated system to resinify. An attempt to make the simpler analogue (287) failed when the intermediate (288) could not be induced to cyclise.

The coumarin (289) resulted from the Pechmann condensation of p-cresol with ethyl acetoacetate. Reduction of (289) with Raney nickel-aluminium alloy in hot alkali, followed

by treatment of the alkaline solution of the product with dimethyl sulphate gave the acid (290). This acid was readily cyclised in polyphosphoric acid to the indanone (291). Clemmensen reduction of (291) gave the indane (292) in excellent overall yield.

The indane (292) was subjected to the Birch reduction reaction in an attempt to obtain the  $\alpha, \beta$ -unsaturated ketone (293) which by cleavage of the double bond would result in the desired iridoid skeleton. Unfortunately the Birch reaction resulted in an intractable mixture.

The indane (292) was nitrated to give (299) but this could not be demethylated at all and on reduction it gave an amine whose mono- or di- acetate could not be degraded satisfactorily by ozonolysis.

Demethylation of the indane (292) was accomplished with methyl magnesium iodide to give 7-hydroxy-1,4-dimethylindane (294). Attempts to oxidise this phenol to the ortho-quinone (295) with Fremy's salt or with ferric chloride were unsuccessful. In an attempt to introduce a further oxygen function at the 5-position of the benzene ring, and so facilitate ring cleavage, the phenol (294) was treated with lead tetracetate.

However the product was not the hoped-for acetoxycyclohexa-dienone (296) which should rearrange to the 5-substituted phenol (297), but the isomeric fully conjugated dienone (298).

Such was the situation when the present work was initiated; a suitable means of degrading the aromatic ring of the phenol (294) was required.

A quantity of the phenol (294) was prepared by the reaction sequence outlined above. When this phenol (294) was subjected to the conditions of the Reimer-Tiemann reaction<sup>136</sup>, the cross conjugated dienone (300), 1,4-dimethyl-4-dichloromethyl-7-keto-dihydroindane was isolated in 22% yield by chromatography. The N.M.R. showed the two olefinic protons as a typical AB quartet,  $J_{AB} = 10$  c.p.s. The dichloromethine proton appeared as a singlet at  $\tau = 4.18$ , and the 4-methyl as a singlet at 8.57. N.M.R. comparison with the model dienone (304) prepared from p-cresol<sup>137</sup>, provided additional proof of structure.

An attempt was then made to selectively cleave the disubstituted double bond of the dienone (300) which would lead to the dicarboxylic acid (301). This diacid should be readily transformed into the iridoid skeleton.



Accordingly the formation of the epoxide (302) was attempted from the bicyclo-dienone (300). Acid opening of the epoxide ring followed by cleavage of the 1, 2-diol (303) with sodium periodate would result in the dibasic acid (301). In view of the small amount of bicyclic dienone (300) available screening experiments were carried out on the model system (304)

Surprisingly the dienone system proved highly stable to hydrogen peroxide in caustic soda, sodium hypochlorite in pyridine<sup>138</sup>, t-butylhydroperoxide<sup>139</sup> and to hydrogen peroxide in the presence of sodium tungstate<sup>140</sup>. Treatment of the dienone (300) with one mole equivalent of osmium tetroxide in an attempt to form the diol (303) directly resulted in an intractable mixture of products which included starting material.

It is of interest to consider similar reactions with 1, 4-diene-3-ketosteroids in which the same cross-conjugated dienone system is present. Thus cholest-1, 4-diene-3-one<sup>141</sup> on prolonged treatment with perbenzoic acid in refluxing benzene gave a small yield of the 4, 5-epoxide. Treatment of 1, 4-androstadiene-3, 17-dione with osmium tetroxide<sup>142</sup> gave as the predominant product the 4, 5-dihydroxy compound. It will

be observed that in both these examples oxidation occurred at the more electrophilic of the two double bonds.

The rather more stringent conditions of the Rudolff reaction<sup>71</sup> for cleaving double bonds, if successful in the present instance could lead directly to the diacid (301). The dienone (300) however was recovered unchanged when treated with an oxidising mixture of sodium periodate and potassium permanganate.

In view of the stability of (300) to the above oxidative procedures, ozonolysis was attempted. A preliminary reaction in which (300) had been treated with an excess of ozone had established the complete breakdown of the molecule to produce an intractable mixture. It was therefore necessary to establish conditions for selective ozonisation of the dienone system in an attempt to achieve preferential cleavage of the less-hindered double bond and formation of the diacid (301).

Preliminary studies were carried out with the model compound (304). Treatment of this with three moles equivalent of ozone in ethyl ~~acetate~~-acetic at  $-10^{\circ}$ , followed by an oxidative work-up procedure, resulted in the isolation of a crystalline acid, m.p.  $134-136^{\circ}$ , which was identified as 2-methyl-3-chloroacrylic

acid (305). N.M.R. showed that the methyl and hydrogen were cis; the methyl appeared as a doublet,  $J = 8.57$ , coupling constant with hydrogen 4 c.p.s. and the hydrogen as a multiplet at  $\tau = 3.98$ . This acid had no C=C stretching vibration in the infra red spectrum and this may be attributed to the symmetrical position of the double bond<sup>143</sup>. A possible mechanism for the formation of the acid (305) is depicted on the flow sheet (H 3). The initially formed dibasic acid, resulting from oxidative cleavage of the two double bonds in the molecule, loses one chlorine atom with concomitant decarboxylation.

In his definitive work on the cyclohexadienones, Von Auwers<sup>144</sup> reported that treatment of the dienone (304) with potassium dichromate in sulphuric acid resulted in 2-methyl-3-chloroacrylic acid, m.p.  $138^{\circ}$ , which on the basis of the present work may be assumed to be the same acid as (305). It was also reported in the same paper that 2-methyl-3-chloroacrylic acid, m.p.  $59-60^{\circ}$ , was obtained when the same dienone (304) was oxidised with potassium permanganate in sulphuric acid. It appeared likely that this lower melting acid was the geometrical isomer (306) and repetition of this work proved that this was the case. The N.M.R. of this acid, m.p.  $59-60^{\circ}$ , showed the methyl at  $\tau = 8.00$  split by the hydrogen into a doublet,  $J = 1.5$  c.p.s. The vinylic hydrogen

appeared as a diffuse quartet at  $\tau = 1.21$ . The infra red spectrum of this lower melting acid showed strong carbon double bond absorption at  $1615 \text{ cm.}^{-1}$ .

The isolation of ~~this~~ isomeric 2-methyl-3-chloroacrylic acids invalidates previous work on these compounds<sup>145</sup>. It was reported that pyrolysis of chloroacetone cyanohydrin at  $500^{\circ}$  gave a mixture of the isomeric 2-methyl-3-chloro-acrylonitriles. The trans-isomer (chlorine and nitrile trans) was stated to have b.p.  $47-48^{\circ}/40 \text{ mm.}$ , and the cis-isomer (chlorine and nitrile cis) to have b.p.  $57.5-58^{\circ}/20 \text{ mm.}$

Configuration was assigned to the nitriles on the basis of their hydrolysis to the isomeric 2-methyl-3-chloroacrylic acids. The trans-nitrile was hydrolysed by base to an acid, m.p.  $57-58.5^{\circ}$ , which showed infra red absorption attributed to the carbon carbon double bond at  $1607 \text{ cm.}^{-1}$ .

The cis-nitrile gave an acid, m.p.  $65.5-67^{\circ}$ , with absorption in the infra red at  $1601 \text{ cm.}^{-1}$ . This latter acid was assigned the cis-configuration on

the basis of its greater solubility, the fact that it was more easily isomerised and it being a stronger acid than the isomer, m.p.  $57-58.5^{\circ}$ .

It is evident from the present work that both these acids have in fact the trans-configuration (306).

When the bicyclic dienone (300) was ozonised with three moles equivalent of ozone, a viscous liquid acid was isolated in good yield. The dimethyl ester of this acid showed broad infra red absorption at  $1740\text{ cm.}^{-1}$  and olefin absorption at  $1640\text{ cm.}^{-1}$ . This suggested that the acid had the desired structure (301), and microanalytical data for the dimethyl ester appeared to confirm this. However the N.M.R. of the dimethyl ester showed in addition to the dichloromethine singlet at  $\tau = 4.07$  and the adjacent tertiary methyl singlet at  $\tau = 8.39$ , two olefinic protons at  $\tau = 3.52$  and  $\tau = 4.02$  as an AB quartet with  $J_{AB} = 12\text{ c.p.s.}$  Further, the two methoxyl groups appeared as separate singlets at  $\tau = 6.29$  and  $\tau = 6.39$ . This suggested that the ozonolysis product was not (301) but the dibasic acid (307) resulting from the cleavage of the tetra-substituted double bond of the dienone. The microanalytical data was equally in agreement with this alternative structure. A high dilution infra red spectrum of the dimethyl ester produced convincing evidence for (307) being the correct structure. Absorption maxima occurred at  $1737$  (ester),  $1727$  (conjugated ester),  $1714$  shoulder (ketone) and  $1643$  (olefin)  $\text{cm.}^{-1}$ .

The mass spectrum of the dimethyl ester did not give a parent ion unfortunately. The first major peaks occurred at  $m/e = 274, 276, 278$  in the ratio 9, 6, 1 demonstrating the presence of two chlorine atoms and in agreement with the loss of two molecules of methanol ( $2 \times 32$ ) from

the molecular ion ( $m/e$ , 338). The loss of one chlorine atom from the fragment  $m/e$  274 gave rise to the base peak at  $m/e$  239. An abundant fragment at  $m/e$  143 (90% of base peak) corresponded to the ion (300) arising from cleavage alpha to the carbonyl group.

An attempt to form the anhydride of the ozonolysis product was unsuccessful providing additional evidence against the substituted glutaric acid structure (301), which should readily form an anhydride.

Ozone has therefore reacted preferentially with the more electrophilic of the two double bonds in the dienone (300), despite this being the more sterically hindered. This is in keeping with the oxidation of 1,4-diene-3-ketosteroids previously discussed.

The ready availability of the model dienone (304) suggested a direct route to the iridoid structure by means of a condensation between (304) and diacetyl. It was considered that an initial Michael addition to the  $\alpha, \beta$ -unsaturated double bond might be followed by an aldol condensation and result in the bicyclic (309) or the dehydrated product (310). These compounds would be obviously useful intermediates in iridoid synthesis. However under basic reaction conditions the diacetyl self-condensed, and the dienone was recovered unchanged.

Hydrogenation of the indane (294) would lead to the bicyclo-[4, 3, 0]-nonanol (311). Oxidation of this, followed by preferential monobromination of the ketone at the  $\alpha$ -methylene group would give (312), which on dehydro-bromination would give the  $\alpha, \beta$ -unsaturated ketone (293). Cleavage of the double bond in (293) would result in the iridoid skeleton.

When the indane (294) was hydrogenated in dilute sodium hydroxide<sup>146</sup> or in ethanol at room temperature with a rhodium-alumina catalyst, the starting material was recovered almost quantitatively. Under more stringent conditions - forty eight hours at 100° and 1640 p.s.i. -using the same catalyst, the major component of the reaction product was again the starting indane (294). Similar observations were recorded when ruthenium-charcoal and platinum oxide-charcoal were used as catalysts.

It was reported in the literature<sup>147</sup> that the model dienone (304) could be readily hydrogenated with a palladium-charcoal catalyst to the cyclohexanone (313). When hydrogenation of the bicyclic dienone (300) was attempted under similar conditions, the uptake of hydrogen was complete in fifteen minutes and a 60% yield of 1, 4-dimethyl-4-dichloromethyl-7-keto-hexahydroindane (314) was

obtained. Bromination of (314) at the less-substituted  $\alpha$ -position to the keto group, followed by elimination of hydrogen bromide and cleavage of the double bond, would result in the dibasic acid (315) from which the iridoid skeleton could be derived.

Preliminary brominations were carried out using 4-methyl-4-dichloromethylcyclohexanone (313), prepared by hydrogenation of the dienone (304),<sup>147</sup> as a model. The brominating agent used was the convenient phenyltrimethylammonium bromide perbromide,<sup>79</sup> which has found wide use for the bromination of ketals. When (313) was treated with one mole equivalent of the reagent in tetrahydrofuran the monobromide (316) was formed in good yield.

The bicyclic ketone (314) was then treated with the brominating agent in a similar fashion and the product run on a T.L.C. silica plate when one major spot appeared with a lower  $R_f$  value than the starting ketone (bromo-ketones have generally higher  $R_f$  values than the corresponding ketone). This major spot gave a red colouration when sprayed with 2,4-dinitrophenylhydrazine in sulphuric acid. In view of the known tendency of tertiary bromides to lose hydrogen bromide when chromatographed on silica,<sup>78</sup> this suggested that bromination of (314) had occurred



in the more substituted position alpha to the carbonyl group to give (317) which had then lost hydrogen bromide on silica to give either (318) or (319).

The structure of the dehydrobrominated product formed in 47% yield from the ketone (314) was shown by N.M.R. to be (318). The methyl group attached to the cyclopentane ring appeared as two overlapping doublets (isomeric mixture) at  $\tau = 8.91$ ,  $J = 11$  c.p.s. The compound exhibited a maximum in the ultra violet spectrum at  $249 \text{ m}\mu$  in agreement with Woodward's rules which predict a value of  $254 \text{ m}\mu$  for (319) and  $249 \text{ m}\mu$  for (318).

An alternative route to the iridoid skeleton visualised preparation of the benzylidene derivative (320) of the ketone (314). It was considered that acid treatment of (320) would result in an allylic shift and lead to the formation of the more stable isomer (321) in which the formerly exo-double bond has entered the ring. Oxidative cleavage of the double bond of (321) would result in the dibasic acid (315).

As on previous occasions preliminary investigations were carried out with the model compound (313). Treatment of this with one mole equivalent of benzaldehyde resulted in the

formation in the ethanolic reaction solution of yellow crystalline needles which were filtered off and identified as the bis-benzylidene (322), ( $\lambda_{\text{max.}}$  327 m $\mu$ ,  $\epsilon$  29,500). The yield was 19%. The mother liquors contained a mixture of compounds, in which, judging by the ultra violet maximum at 292 m $\mu$ , the mono-benzylidene (323) was prominent.

When the bicyclic ketone (314) was treated with a slight excess of benzaldehyde, the benzylidene derivative did not crystallise from the reaction solution. However the solution did exhibit a maximum in the ultra violet at 292 m $\mu$  suggesting the benzylidene (320) had formed, but attempts to isolate (320) by chromatography were unsuccessful. When the crude reaction product was refluxed with concentrated hydrochloric acid a shift occurred in the ultra violet maximum to 251 m $\mu$  ( $\epsilon$  6000), [Woodward's rules predict  $\lambda_{\text{max.}}$  237 m $\mu$  for the desired (321)], but again the product proved to be an intractable mixture.

It was reported in the literature<sup>148</sup> that oxidation of 1,17 $\beta$ -dihydroxy-4-methyloestra-1,3,5(10)-triene (324) with alkaline hydrogen peroxide gave rise to an acidic mixture from which, after differential partition between sodium bicarbonate and

sodium hydroxide and esterification with diazomethane the methyl esters (325) and (326) were isolated. The oxidation of the indane (292) under similar conditions might therefore be expected to lead to the methyl nepetonates (327) and (328) from which the iridoid skeleton could be derived by the addition of a one carbon unit to the carbonyl centre by means of a Wittig reaction.

When the indane (292) was oxidised in the described manner the sodium bicarbonate extract gave an acidic fraction which was esterified with diazomethane to a mixture of liquid methyl esters with a mint-like odour. This crude ester mixture gave a positive iodoform test and formed a yellow 2, 4-dinitrophenylhydrazone the analysis and the molecular weight of which agreed with that for the 2, 4-dinitrophenylhydrazone of methyl nepetonate (327). Further evidence for the formation of (327) was obtained from the high dilution spectrum of the crude methyl esters which showed absorption at 1713 (ketone) and 1740 (ester)  $\text{cm.}^{-1}$  in addition to a shoulder at 1754  $\text{cm.}^{-1}$ . The ultra violet spectrum of the crude ester product depicted a flat maximum at 233  $\text{m}\mu$  ( $\epsilon$  698) which suggested that little of the unsaturated ester (328) was present since this type of

chromophore was shown in the case of (326) to have  $\lambda_{\text{max.}}$  240 (  $\epsilon$  5550 ).

G. L. C. (10% polyethylene glycol at 100°) of the crude ester product produced six major peaks at retention times and concentrations of 11 (5%), 17 (9%), 30 (10%), 34 (4%) 44 (35%). 51 (37%) minutes. It seemed reasonable to assume that the two major peaks at 44 and 51 minutes, which accounted for about 70% of the mixture were the diastereo isomers, the cis-trans (329) and trans-trans (330) forms of methyl nepetonate, since the oxidation reaction was carried out in base which would ensure the two functional groups in the product having the stable trans-relationship.

Chromatography of the crude product gave a fraction which G. L. C. showed to be almost (> 90%) exclusively a mixture of the two major components with retention times of 44 and 51 minutes. The infra red of this fraction showed absorption at 1710  $\text{cm.}^{-1}$  and 1742  $\text{cm.}^{-1}$ . The N. M. R. showed all the structural features required by methyl nepetonate, that is, one methoxyl group, an acetyl methyl, and a cyclopentane methyl split as a doublet, but the integration was sufficiently incompatible to cause concern. This concern was subsequently justified

when it was found that the microanalysis of the fraction was over 3% low in carbon for the value required by methyl nepetionate and further, the molecular weight, as determined by mass spectrometry, was 198 as against a value of 184 for methyl nepetionate.

At this stage it was decided to discontinue this approach to the synthesis of the iridoid monoterpenes.

EXPERIMENTAL

1, 4-Dimethyl-4-dichloromethyl-7-keto-dihydroindane (300)

7-Hydroxy-1, 4-dimethylindane (294), (2.25 g., 0.014 m.) was placed in a 100 cc. 3-necked flask equipped with stirrer, reflux condenser and dropping funnel. Sodium hydroxide (60 cc. of 20% solution) was added and the solution stirred and heated to an oil bath temperature of 80-90°. Chloroform (7.5 cc.) was added to the reaction solution over 30 minutes and stirring and refluxing continued for an additional 3 hours. The cooled solution was extracted with chloroform, the chloroform extract washed repeatedly with 5% sodium hydroxide and then brine. After drying and removal of solvent, a black viscous oil (2.4 g.) remained. This oil was chromatographed on silica and eluted with benzene, when 1, 4-dimethyl-4-dichloromethyl-7-keto-dihydroindane was obtained as crude yellow crystals. After treatment with charcoal and recrystallisation from petrol, the product (0.753 g., 22%) had m.p. 93-95°  $\nu_{\max.}$  (CCl<sub>4</sub> solution) 1670, 1645, 1615, 850 cm.<sup>-1</sup>  $\lambda_{\max.}$  235, 273 m $\mu$  ( $\epsilon$  9960, 4850 in methanol). N.M.R. (CCl<sub>4</sub>),  $\tau$  = 3.04 (1 H; doublet, J = 10 c.p.s.; olefinic),  $\tau$  = 3.68 (1H; doublet, J = 10 c.p.s.; olefinic),  $\tau$  = 4.18 (1H; singlet; dichloromethine),  $\tau$  = 8.57

(3 H; singlet; 4-methyl),  $\tau = 8.7$  (3 H; doublet,  $J = 10$  c.p.s.; secondary methyl). (Found C, 58.88; H, 6.08.  $C_{12}H_{14}OCl_2$  requires C, 58.79; H, 5.76).

Attempted epoxidation of 1,4-dimethyl-4-dichloromethyl-7-keto-dihydroindane (300)

(a) Alkaline hydrogen peroxide. The dienone (300), (0.016 g., 0.00043 m.) in methanol (10 cc.) to which 4 N sodium hydroxide (0.1 ml.) had been added was stirred at room temperature with 30% hydrogen peroxide (0.0019 m.) for 7 hours. The solution was extracted with ether, washed, dried and the dienone (300), (0.078 g., 74%) recovered. It was identified by its melting point, mixed melting point, infra red spectrum and T.L.C. comparison.

When the experiment was repeated using 60 moles equivalent of hydrogen peroxide over a period of 20 hours, a 30% recovery of (18) was obtained.

(b) Sodium hypochlorite. The sodium hypochlorite (bleach) solution was standardised against sodium thiosulphate. The reaction was carried out with the model dienone, 4-methyl-4-dichloromethylcyclohexa-2,5-dienone (304). The dienone (304),

(0.328 g., 0.0017 m.) in pyridine (5 cc.) was stirred with sodium hydrochlorite (8 ccs., 0.0017 m.) for 30 minutes. After extraction with ether, the ether layer was washed with dilute hydrochloric acid and brine, dried and solvent removed. The residue was crystallised from petrol to give a 66% recovery of starting material (304) identified as in (a).

(c) t-Butylhydroperoxide. The model dienone (304), (0.189 g., 0.001 m.) was dissolved in benzene (5 cc.) and t-butylhydroperoxide (0.1 cc., 0.001 m.) added. From a fine pipette two drops of Triton B (approximately one fortieth the concentration of the peroxide) were also added. The solution was stirred for 12 hours at room temperature, extracted with ether and the ether extract washed with dilute acid, brine and dried. The liquid residue proved difficult to crystallise owing to the presence of t-butylhydroperoxide but T.L.C. and infra red confirmed the major component to be starting material (304).

A repeat experiment using a large excess of peroxide and Triton B also resulted in the starting material remaining unchanged.



(d) Sodium tungstate and hydrogen peroxide. The model dienone (304), (0.210 g., 0.0011 m.) was dissolved in ethanol (3 cc.) and 30% hydrogen peroxide (1.65 cc., 0.0145 m.) together with sodium tungstate (0.080 g.) added. The solution was refluxed for 2 hours, cooled, ether extracted, the ether extract washed with brine and then dried. A 75% recovery of the starting material was obtained and identified as in (a).

Attempted osmylation of 1, 4-dimethyl-4-dichloromethyl-7-keto-dihydroindane (300).

To (300), (0.283 g., 0.0012 m.) in pyridine (2 cc) was added osmium tetroxide (0.34 g., 0.0013 m.) in ether (35 cc.). After standing 43 hours in the dark, during which time a black precipitate formed, pyridine (20 cc.), water (18 cc.) and sodium bisulphite (0.61 g.) were added. The solution was stirred for 30 minutes and then extracted with ether. The ether layer was washed with dilute hydrochloric acid, sodium bicarbonate, brine and dried. After removal of solvent a dark green liquid (0.392 g.) remained, which gave five spots on T.L.C., one of which was equivalent to the starting material.

The infra red spectrum confirmed the presence of starting material (bands at 1670, 1645 and 1615  $\text{cm.}^{-1}$ ). Chromatography of the product on silica followed by elution with benzene-ether failed to isolate a tractable product.

Attempted Rudloff oxidation of 1,4-dimethyl-4-dichloromethyl-7-keto-dihydroindane (300)

The dienone (300), (0.134 g., 0.00054 m.) was dissolved in dioxan (75 cc.) and water (100 cc.) added. To this solution was added sodium periodate (0.95 g., 0.0044 m.), potassium carbonate (0.070 g., 0.0005 m.) and potassium permanganate (20 cc., 0.00011 m.). The solution was shaken for 15 hours, filtered from a brown deposit (38 mgs.) presumably manganese dioxide, and the filtrate acidified with dilute hydrochloric acid. Extraction with ether, washing with brine and drying left after removal of solvent a liquid (120 mgs.), from which the starting dienone (40 mgs.) was recovered. This was identified in the usual manner.

Cis-2-methyl-3-chloroacrylic acid (305)

The ozoniser was calibrated by passing the ozone into

2% potassium iodide and titrating the liberated iodine with standard thiosulphate. The dienone (304), (2.03 g., 0.011 m.) was dissolved in ethyl acetate (25 cc.) and acetic acid (25 cc.) and cooled to  $-10^{\circ}$ . Ozone (3 moles equivalent) was passed through the solution. To this solution was then added 30% hydrogen peroxide (2.5 ccs., 2 moles equivalent) and water (2 cc.). The solution was then refluxed for 45 minutes, the volume concentrated and extracted with ether. The ether extract was washed with brine and then with saturated sodium bicarbonate. The sodium bicarbonate layer was acidified; ether extracted and the ether extract washed with brine and dried. After removal of solvent the liquid residue (0.89 g.) slowly crystallised. Recrystallisation from hot water, followed by sublimation gave a pure sample of cis-2-methyl-3-chloroacrylic acid (305), m.p.  $134-136^{\circ}$ .  $\nu_{\max.}$  ( $\text{CHCl}_3$  solution)  $1740 \text{ cm.}^{-1}$   $\lambda_{\max.}$  209  $\text{m}\mu$  ( $\epsilon$  4750 in methanol). N.M.R. ( $\text{CDCl}_3$ ),  $\tau = 8.57$  (3 H; doublet,  $J = 4 \text{ c.p.s.}$ ; methyl),  $\tau = 3.98$  (1 H; multiplet; vinylic hydrogen). (Found: C, 40.03; H, 3.84.  $\text{C}_4\text{H}_5\text{O}_2\text{Cl}$  requires C, 39.87; H, 4.18).

The neutral layer from this reaction gave unchanged starting material.

Trans-2-methyl-3-chloroacrylic acid (306)

This was prepared by the oxidation of 4-methyl-4-dichloromethylcyclohexa-2,5-dienone (304) with potassium permanganate as described by Von. Auwers.<sup>144</sup>  $\nu_{\max.}$  (CHCl<sub>3</sub> solution) 1700, 1615 cm.<sup>-1</sup> N.M.R. (CCl<sub>4</sub>),  $\tau = 8.00$  (3 H; doublet, J = 1.5 c.p.s.; methyl),  $\tau = 1.21$  (1H; diffuse quartet; vinylic hydrogen).

2,6-Dimethyl-5-keto-6-dichloromethyl- $\Delta^7$ -azelaic acid (307)

The ozoniser was calibrated as described above. The dienone (~~300~~<sup>300</sup>), (0.670 g., 0.0027 m.) in ethylacetate (25 cc.) and acetic acid (25 cc.) was ozonised at -10<sup>o</sup> with three moles equivalent of ozone. 30% Hydrogen peroxide (1 cc.) was added to the solution which was then refluxed for 1 hour. The volume was reduced and extracted with ether. The ether extract was washed first with brine and then with sodium bicarbonate. The sodium bicarbonate was acidified, ether extracted and the ether extract washed with brine, dried and the solvent removed to leave a viscous yellow liquid (0.614 g.). After treatment with charcoal, a colourless viscous glass (0.464 g.) remained. Chromatography on silica and elution with benzene-ether did not yield a crystalline fraction.

The acidic product was esterified with diazomethane and distilled to give 2, 6-dimethyl-5-keto-6-dichloromethyl- $\Delta^7$ -azelate, b.p.  $120^\circ/0.1$  mm.  $n_D^{23.5} = 1.4880$ ,  $v_{\max.}$  ( $\text{CCl}_4$  solution) 1737, 1727, 1714 (sh.), 1643  $\text{cm.}^{-1}$   $\lambda_{\max.}$  207  $\text{m}\mu$  ( $\epsilon$  6500 in methanol). N.M.R. ( $\text{CCl}_4$ ),  $\tau = 3.52$  (1H; doublet,  $J = 12$  c.p.s.; olefinic),  $\tau = 4.02$  (1H; doublet,  $J = 12$  c.p.s.; olefinic),  $\tau = 4.07$  (1H; singlet; dichloromethine),  $\tau = 6.29$  (3H; singlet; methoxyl),  $\tau = 6.39$  (3H; singlet; methoxyl),  $\tau = 8.39$  (3H; singlet; tertiary methyl),  $\tau = 8.86$  (3H; doublet,  $J = 12$  c.p.s.; secondary methyl). The mass spectra did not give a parent ion. Major fragments observed at  $m/e$ , 278, 276, 274, 239 (base peak), 143 (cleavage alpha to the ketone group). (Found: C, 50.09; H, 5.87.  $\text{C}_{14}\text{H}_{20}\text{O}_5\text{Cl}_2$  requires C, 49.56; H, 5.94).

Attempts to make the  $\delta$ -benzylisothiuronium salt and the 2,4-dinitrophenylhydrazone of the dibasic acid were unsuccessful.

Reaction between diacetyl and 4-methyl-4-dichloromethyl-cyclohexa-2, 5-dienone (304)

A solution of sodium methoxide was prepared from sodium (0.052 g., 0.0023 m.) and methanol (25 cc.) To this

solution at room temperature was added the dienone (1.05 g., 0.006 m.) followed by diacetyl (0.372 g., 0.0043 m.). The solution colour turned black as soon as the diacetyl was added. After standing 5 days at room temperature, the solution was poured into ice-cold dilute sulphuric acid, ether extracted, the ether extract brine washed and dried. After removal of solvent and petrol extraction of the liquid residue, a 66% recovery of starting dienone was obtained. It was identified in the usual manner.

Attempted hydrogenation of 7-hydroxy-1, 4-dimethylindane (294)

(a) The indane (294), (0.241 g.) in dilute caustic soda and 5% rhodium/alumina catalyst (64 mg.) was hydrogenated at room temperature and atmospheric pressure for 66 hours. The indane (294), (0.200 g.) was recovered from the reaction solution and identified in the usual manner.

(b) The indane (294), (0.191 g.) in ethanol and 5% rhodium/alumina catalyst (63 mg.) was hydrogenated at room temperature and atmospheric pressure for 5 days. The starting material (180 mg.) was recovered unchanged from the reaction solution.

(c) The indane (294), (169 mg.) in ethanol (500 cc.) and 5% rhodium/alumina catalyst (120 mg.) was hydrogenated for 48 hours at 1640 psi and 100°. The solution was filtered through celite and ethanol removed to leave a greenish liquid (0.49 g.), which could not be induced to crystallise. This liquid was extracted with petrol, the petrol extract treated with charcoal and the residual colourless liquid shown to consist substantially of starting material by its infra red spectrum and T.L.C. comparison. The absence of the desired cyclohexanol in the product was confirmed by oxidation of the product with Jones' reagent and the failure of the oxidised product to form a tractable 2,4-dinitrophenylhydrazone.

(d) Reductions of the indane (294) using ruthenium in ethanol and platinum in acetic acid catalysts were carried out in a similar manner to that described in (c). Starting material was the only component identified in the products.

1,4-Dimethyl-4-dichloromethyl-7-keto-hexahydroindane (314)

The dienone (300), (121 mgs.) in rectified spirit (50 cc.) was hydrogenated for one hour over a 5% paladium/charcoal (33mgs.) catalyst. The solution was filtered through celite,

solvent removed, and the liquid residue chromatographed on silica and eluted with benzene to give 1,4-dimethyl-4-dichloromethyl-7-ketohexahydroindane (74 mgs., 60% yield), b.p.  $90^{\circ}/0.05$  mm.,  $\nu_{\max}$  (neat)  $1710$   $\text{cm.}^{-1}$ . The N.M.R. ( $\text{CCl}_4$ ) indicated a mixture of four isomers as shown by the dichloromethine peak at  $\tau$  values of 3.90 (9%), 4.0 (19%), 4.38 (29%), 4.42 (43%). (Found: C, 57.57; H, 7.14.  $\text{C}_{12}\text{H}_{18}\text{OCl}_2$  requires C, 57.82; H, 7.28). The 2,4-dinitrophenylhydrazone was recrystallised from methanol as orange spars, m.p.  $170-190^{\circ}$ .

$\lambda_{\max}$   $365$  ( $\epsilon$  22,400 in methanol). (Found: C, 50.67; H, 4.98; N, 13.41.  $\text{C}_{18}\text{H}_{22}\text{N}_4\text{Cl}_2$  requires C, 50.36; H, 5.16; N, 13.05).

#### 1-Bromo-4-methyl-4-dichloromethylcyclohexanone (316)

4-Methyl-4-dichloromethylcyclohexanone (0.81 g., 0.0042 m.) was dissolved in tetrahydrofuran (5 cc.) and phenyltrimethyl ammonium bromide perbromide (1.63 g., 0.0043 m.) added. After one hour the inorganic precipitate was filtered off, the filtrate ether extracted and the ether extract washed with sodium bicarbonate, brine and dried. The residual yellow oil remaining after removal of solvent was extracted with 40/60 petrol and the petrol extract crystallised on standing to give 1-bromo-4-methyl-4-dichloromethyl



cyclohexanone (0.56 g., 50%), white crystals, m.p. 68-95°

$\nu_{\max}$  (nujol) 1715  $\text{cm.}^{-1}$ . N.M.R. ( $\text{CCl}_4$ ),  $\tau = 4.28$  (1 H; singlet; dichloromethine),  $\tau = 5.38$  (1 H; quartet; bromohydrogen),  $\tau = 8.56$  (3 H; singlet; tertiary methyl). (Found: C, 34.61; H, 4.23.

$\text{C}_8\text{H}_{11}\text{OCl}_2\text{Br}$  requires C, 35.06; H, 4.05).

1,4-Dimethyl-4-dichloromethyl-7-keto- $\Delta^{8,9}$ -tetrahydroindane (318)

The bicyclic ketone (314), (78 mgs.) in tetrahydrofuran (3 cc.) was treated with the above brominating agent (120 mgs.). After 5 hours, excess 5% sodium bicarbonate was added, the solution ether extracted, the ether extract brine washed and dried. Removal of solvent left a dark purple liquid (105 mgs.), consisting mainly of the tertiary bromide (317). This residual liquid was extracted with petrol and the petrol extract chromatographed on silica and eluted with benzene to give 1,4-dimethyl-4-dichloromethyl-7-keto- $\Delta^{8,9}$ -tetrahydroindane (36 mgs. 47%) as a liquid.  $\nu_{\max}$  (neat) 1680, 1620, 780  $\text{cm.}^{-1}$ .  $\lambda_{\max}$  249 ( $\epsilon$  10,400 in methanol). N.M.R. ( $\text{CDCl}_3$ )  $\tau = 4.10$  (1 H; singlet, dichloromethine),  $\tau = 8.62$  (3 H; singlet; tertiary methyl),  $\tau = 8.89$  (3 H; doublet,  $J = 11$  c.p.s.; secondary methyl). The 2,4-dinitrophenylhydrazone formed red

crystals, m.p. 198-210°,  $\lambda_{\max.}$  386 ( $\epsilon$  28,300 in methanol).

(Found: C, 50.31; H, 4.57; N, 12.89  $C_{18}H_{20}O_4N_4Cl_2$  requires C, 50.60; H, 4.72; N, 13.11).

1,5-Dibenzylidene-4-methyl-4-dichloromethylcyclohexanone (322)

4-Methyl-4-dichloromethylcyclohexanone (313), (122 mgs.)

in rectified spirit (5 cc.) was treated with freshly distilled benzaldehyde (66 mgs.) and one drop of dilute sodium hydroxide added.

After standing overnight the bis-benzylidene (44 mgs., 19%) was filtered off and recrystallised from ethanol as yellow needles,

m.p. 159-165°.  $\nu_{\max.}$  ( $CCl_4$  solution), 1675, 1615  $cm.^{-1}$ .  $\lambda_{\max.}$  327, 233, 205  $m\mu$  ( $\epsilon$  29,500; 14,100; 23,700 in methanol). N.M.R. ( $CCl_4$ ),

$\tau = 2.16$  (2 H; diffuse singlet; vinyl protons),  $\tau = 2.62$  (10 H; singlet; aromatic),  $\tau = 4.29$  (1 H; singlet; dichloromethine),  $\tau = 7.00$

(4 H; singlet; ring protons),  $\tau = 8.83$  (3 H; singlet; tertiary methyl).

(Found: C, 71.25; H, 5.77.  $C_{22}H_{20}CCl_2$  requires C, 71.15; H, 5.43).

The filtrate, after removal of the bis-benzylidene, was diluted with water and the precipitate which formed filtered (82 mgs.).

$\nu_{\max.}$  (nujol), 1705, 1610  $cm.^{-1}$ .  $\lambda_{\max.}$  292  $m\mu$  in methanol.

Chromatography on silica and elution with benzene-petrol did not produce a tractable product.

Attempted benzylidene formation from 1,4-dimethyl-4-dichloromethyl-7-keto-hexahydroindane (314)

To (314), (115 mgs.) in rectified spirit (3 cc.) was added freshly distilled benzylaldehyde (56 mgs. 15% excess) and one drop of dilute sodium hydroxide. The initial colourless solution immediately turned brown. After standing overnight the solution was diluted with water, ether extracted and the ether extract washed with brine and dried. Removal of solvent left a yellow liquid (100 mgs.) smelling of benzaldehyde.  $\nu_{\max}$  (neat), 1710, 1680, 1610  $\text{cm.}^{-1}$ .  $\lambda_{\max}$ , 292  $\text{m}\mu$  in methanol. T.L.C. showed closely associated spots. Chromatography of the crude product on silica followed by elution with benzene-ether did not produce an identifiable product.

The crude reaction product (64 mgs.) was dissolved in glacial acetic acid and concentrated hydrochloric acid (5 cc.) added. The solution was refluxed for 30 minutes. At the end of this period the reaction solution was worked-up in the usual manner to give a

brownish liquid (30 mgs.),  $\nu_{\text{max}}$  (neat), 1710, 1680, 780  $\text{cm.}^{-1}$ .

$\lambda_{\text{max}}$  251 ( $\epsilon$  5950 in methanol), T.L.C. showed a complex mixture.

Oxidation of 7-hydroxy-1,4-dimethylindane (294)

The indane (294), (3.20 g.) was dissolved in methanol (300 cc.) and 2N sodium hydroxide (200 cc.). To this refluxing solution on the water bath was added over 20 minutes, 30% hydrogen peroxide (80 cc.). Refluxing was continued for 1 hour. At the end of this period, the volume was reduced and the cooled reduced volume was extracted with ether three times. The ether extract gave a 14% recovery of starting material. The basic layer was acidified with concentrated hydrochloric acid, ether extracted and the ether extract washed first with saturated sodium bicarbonate and then with N sodium hydroxide. These basic layers were acidified with hydrochloric acid, extracted with ether, the ether extracts brine washed and dried. The N sodium hydroxide layer gave a yellowish liquid (100 mg.) the infra red of which appeared similar to the starting phenol. This fraction was not further pursued.

The sodium bicarbonate fraction gave a brown liquid (1.57 g.), which did not form a tractable derivative with 2,4-dinitrophenylhydrazine. Treatment of this crude acid with diazomethane gave an

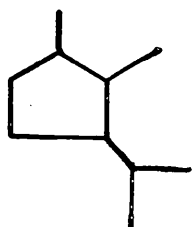
ester product with a mint-like odour,  $\nu_{\max.}$  ( $\text{CCl}_4$  solution) 1754 (shoulder), 1740, 1713  $\text{cm.}^{-1}$ . The ester mixture distilled over a range, 70-100°/0.1 mm. to give a clear, colourless distillate. Four fractions were collected with  $n_D^{22}$  between 1.451 and 1.459.  $\lambda_{\max.}$  (middle fraction) 232, 207  $\text{m}\mu$  ( $\epsilon$  698, 1000 in methanol). The distillate gave a positive iodoform test and formed a 2,4-dinitrophenylhydrazone which was recrystallised from methanol as yellow crystals, m.p. 111-113°.  $\lambda_{\max.}$  363  $\text{m}\mu$  ( $\epsilon$  21,500 in methanol). The molecular weight of this derivative was 364, determined by mass spectrometry, in agreement with the calculated value for the 2,4-dinitrophenylhydrazone of dimethyl nepetionate. (Found: C, 53.03; H, 5.48; N, 15.14.  $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_6$  requires C, 52.74; H, 5.53; N, 15.38).

G.L.C. of the crude ester mixture prior to distillation gave (10% polyethylene glycol at 100°, flow rate 70 cc/min.) major peaks at retention times and concentrations of 11 (5%), 17 (9%), 30 (10%), 34 (4%), 44 (35%), 51 (37%) minutes. The ester mixture was chromatographed on silica, eluted with benzene-ether and finally distilled to give a fraction consisting (> 90%) of the two

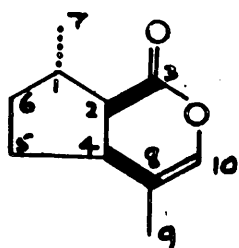
\*  
components with retention times 44 and 51 minutes. ~~N.M.R.~~ <sup>N.M.R.</sup> ( $\text{CCl}_4$ ),  
 $\tau = 6.22$  ( 3 H; singlet; methoxyl),  $\tau = 7.80, 7.85$  ( 3 H; two singlets;  
acetyl),  $\tau = 8.90$  ( 3 H; overlapping doublets, secondary methyl).  
The molecular weight was determined by mass spectrometry as 198;  
dimethyl nepetonate has value 184. (Found: C, 62.03; H, 7.35.  
Dimethyl nepetonate requires C, 65.19; H, 8.75).

An attempt to extract the ketonic material from the  
crude ester product via semi-carbazone fraction was unsuccessful.  
This derivative could not be obtained crystalline. A similar  
attempt with Girard's T reagent resulted in the extraction of  
50 mgs. of liquid, from 457 mgs. of crude ester. G.L.C.  
showed the small amount of extracted material (50 mgs.) to  
consist of four components with a major peak at 17 minutes and  
no peak at 44 minutes.

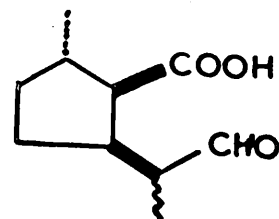
\*  
 $\nu_{\text{max}}$  (neat) 1745, 1710, 1270  $\text{cm}^{-1}$ .  $\lambda_{\text{max}}$  207  $\mu$  ( $\epsilon$  1260).



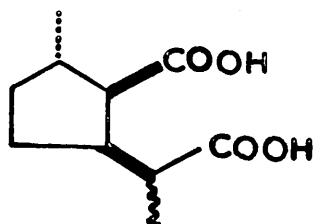
218



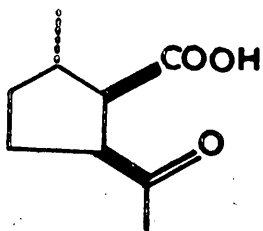
219



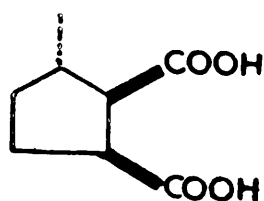
220



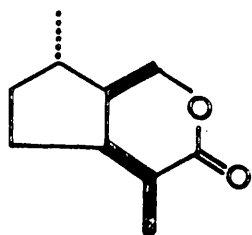
221



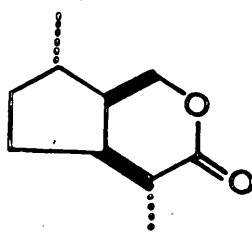
222



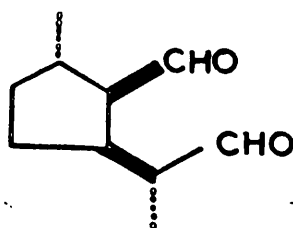
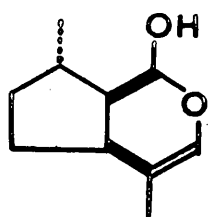
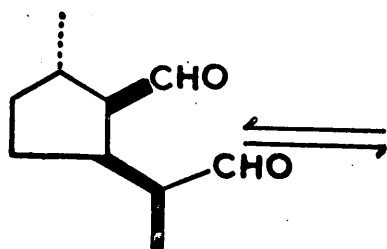
223



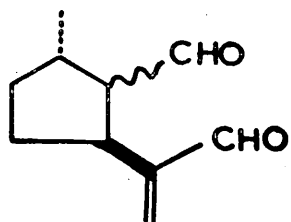
Iridomyrmecin  
224



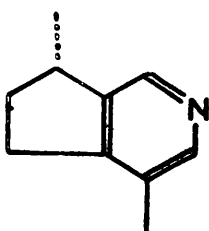
Iso-Iridomyrmecin  
225



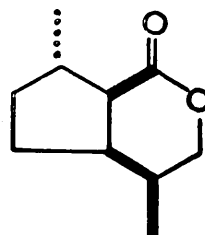
226



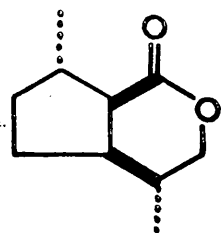
227



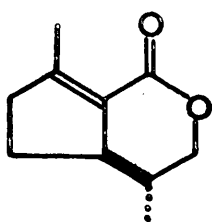
228



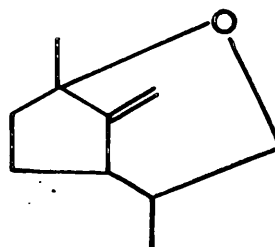
229



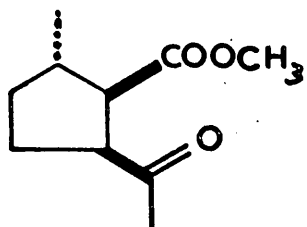
230



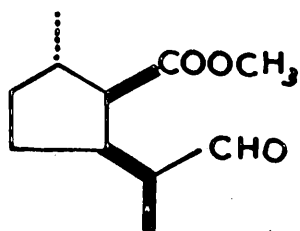
231



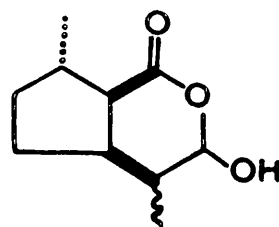
232



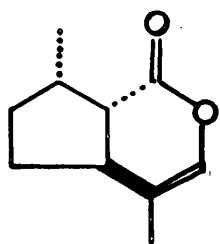
233



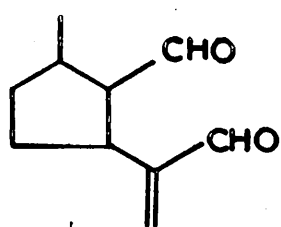
234



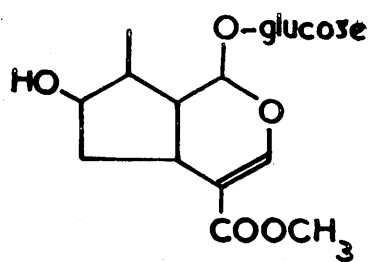
235



236

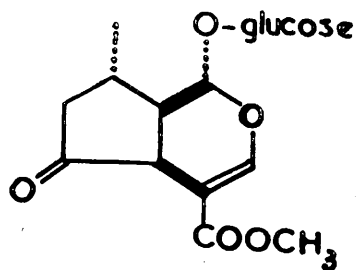


237

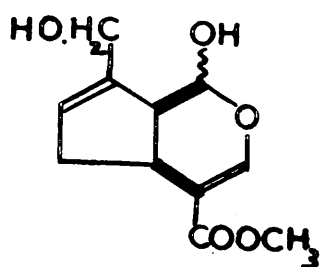


238

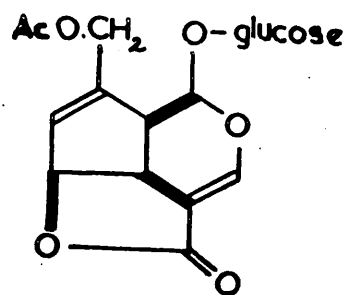




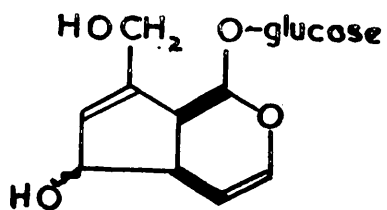
239



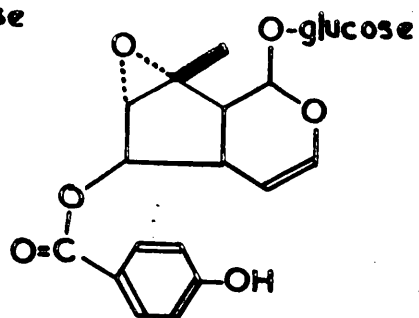
240



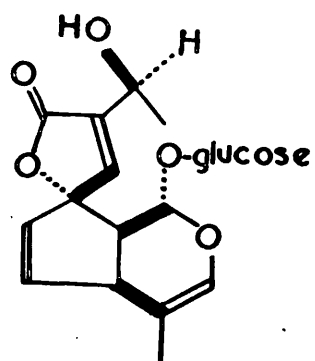
241



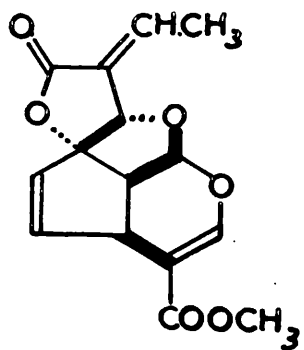
242



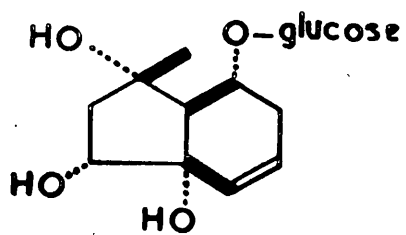
243



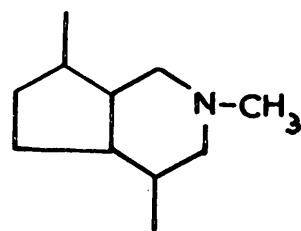
244



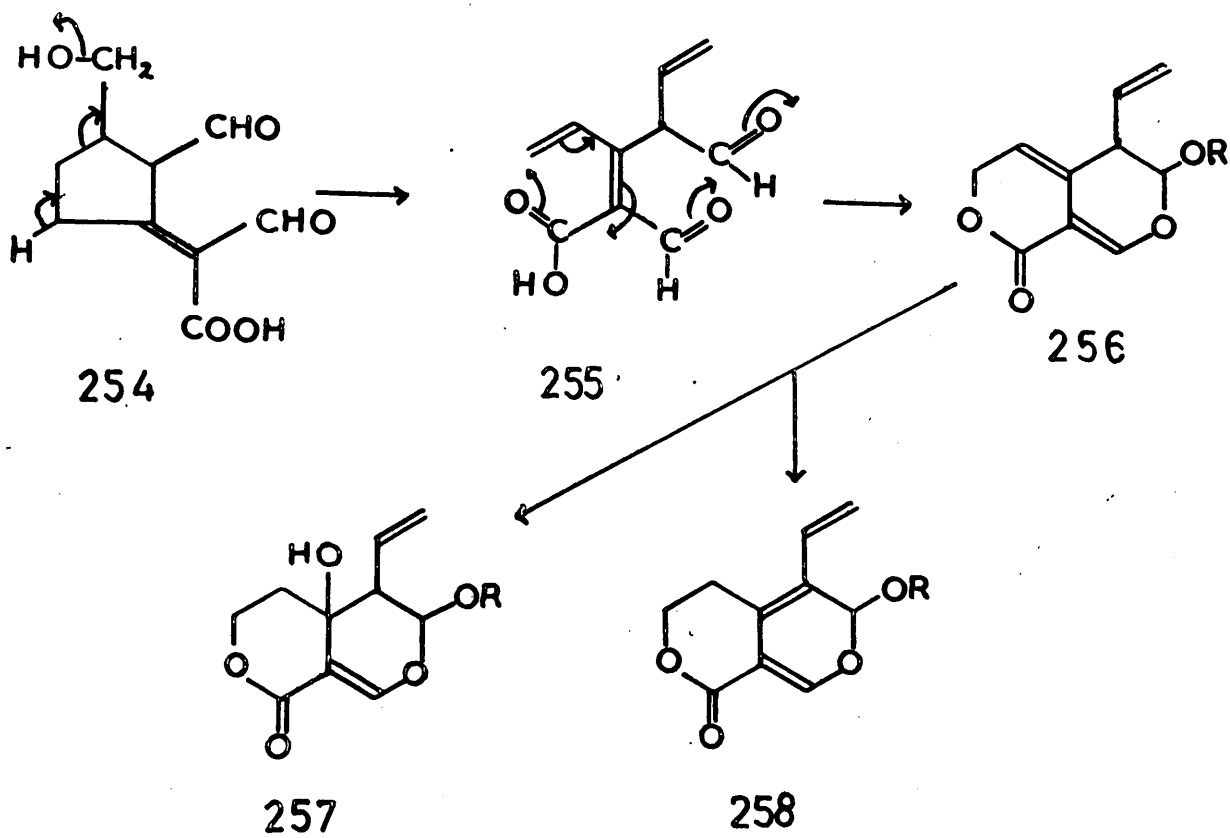
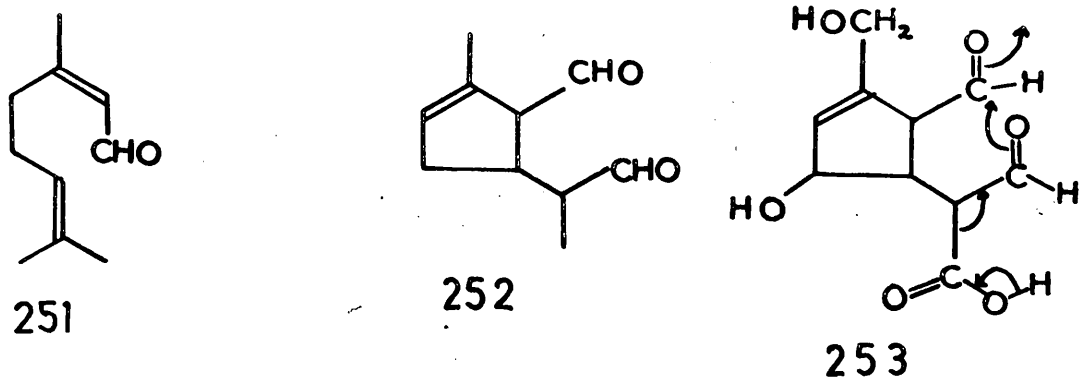
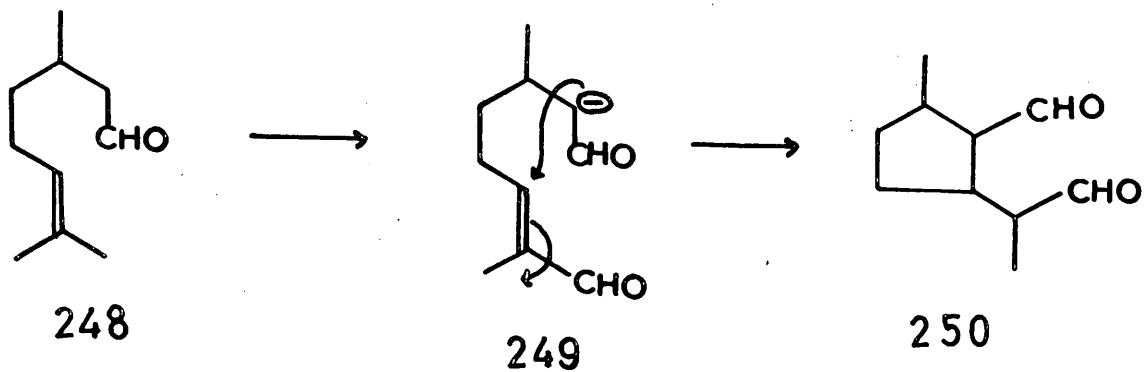
245

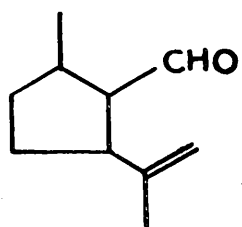


246

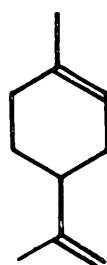


247

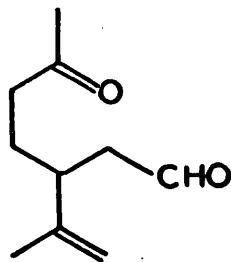




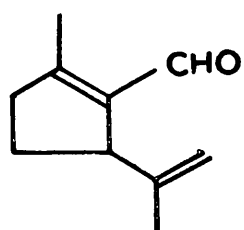
259



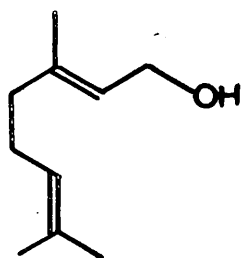
260



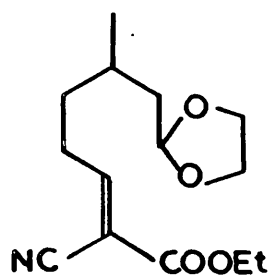
261



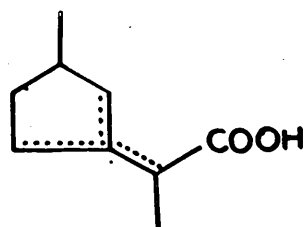
262



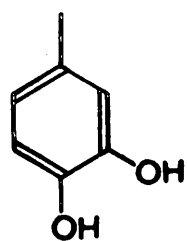
263



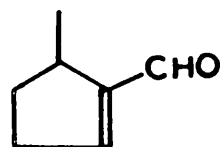
264



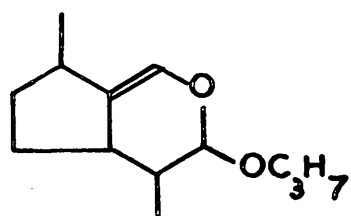
265



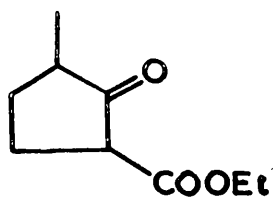
266



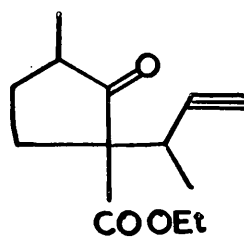
267



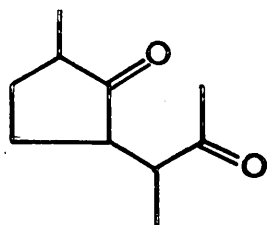
268



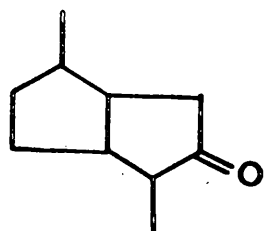
269



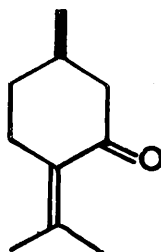
270



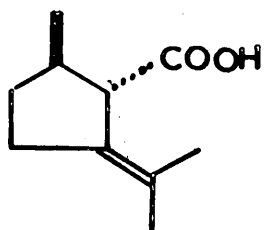
271



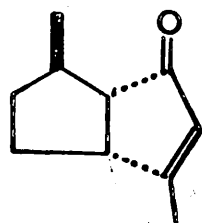
272



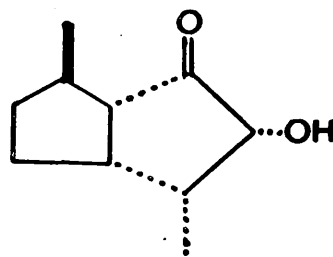
273



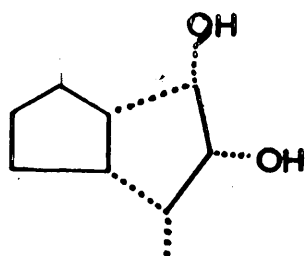
274



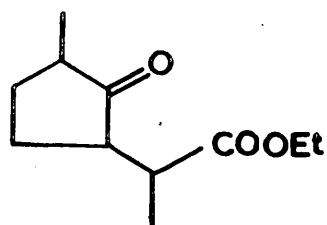
275



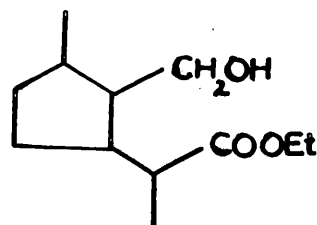
276



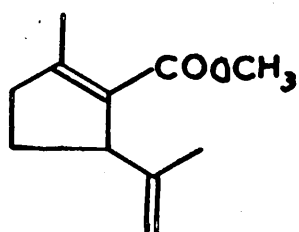
277



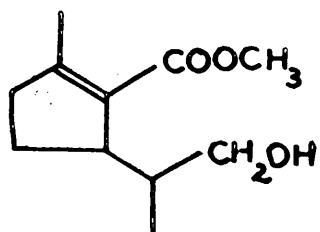
278



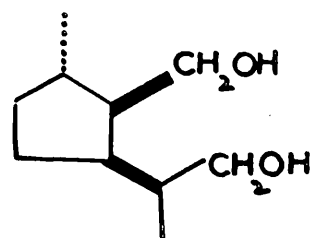
279



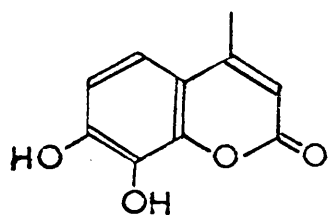
280



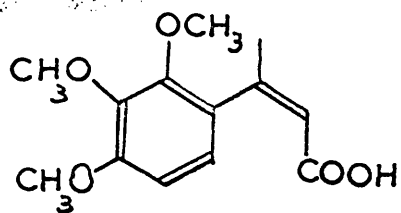
281



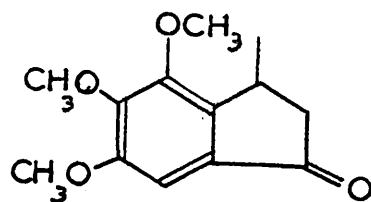
282



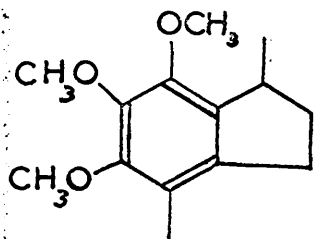
283



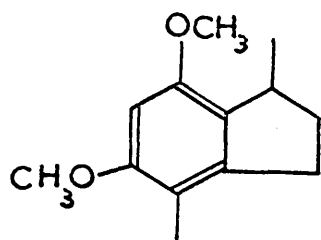
284



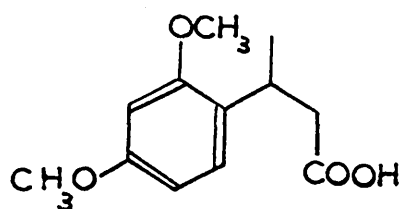
285



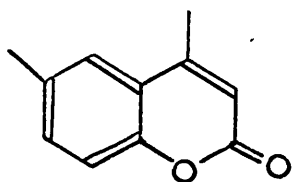
286



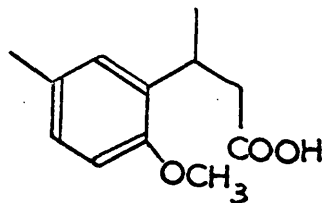
287



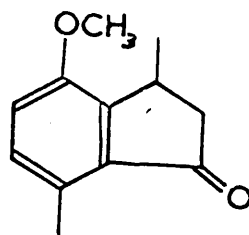
288



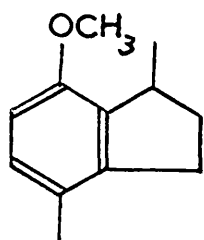
289



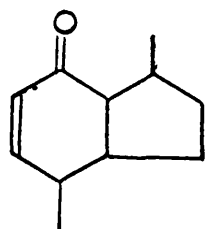
290



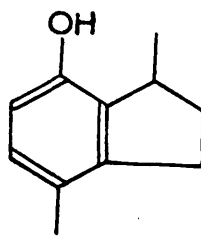
291



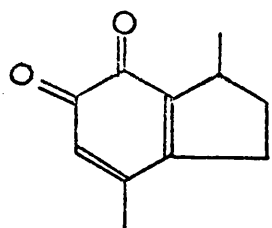
292



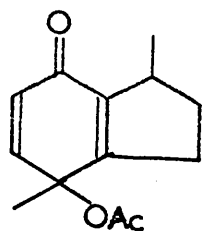
293



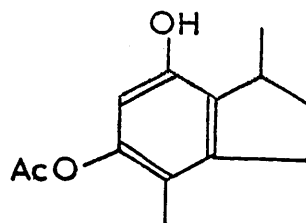
294



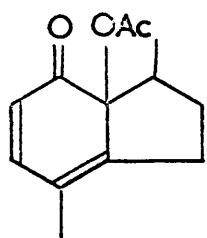
295



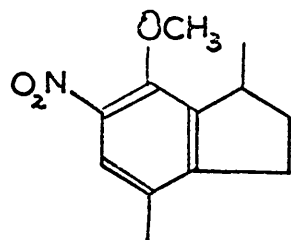
296



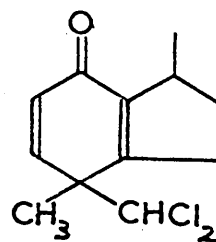
297



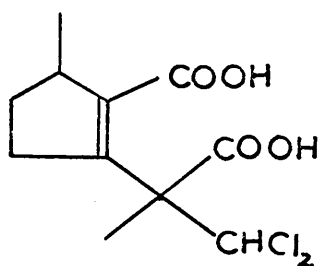
298



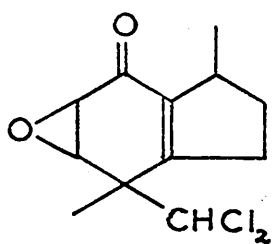
299



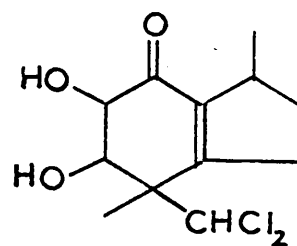
300



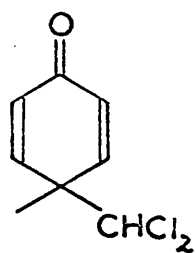
301



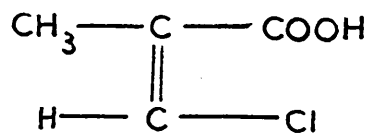
302



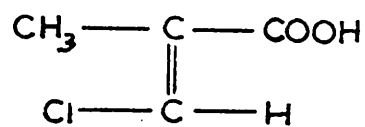
303



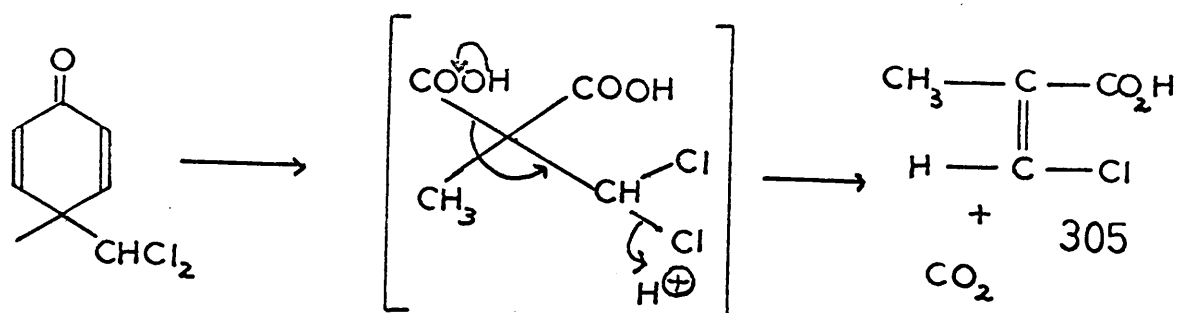
304



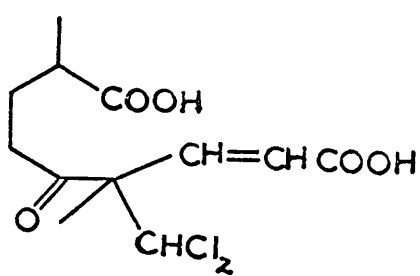
305



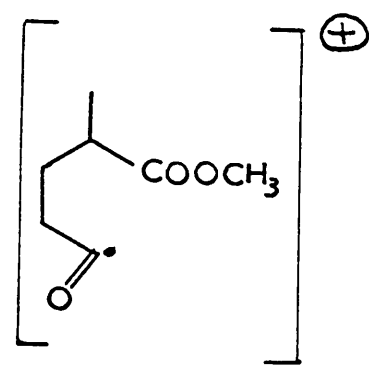
306



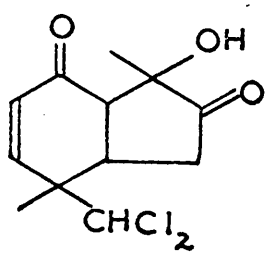
304



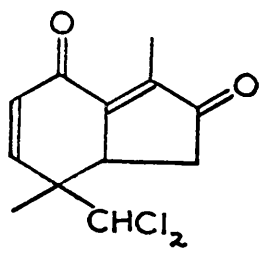
307



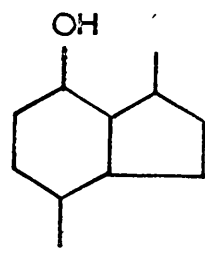
308



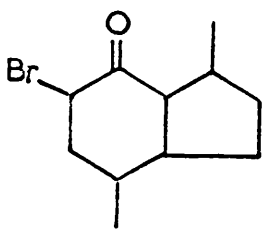
309



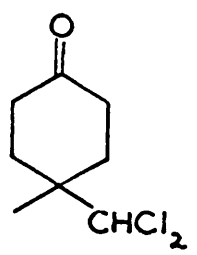
310



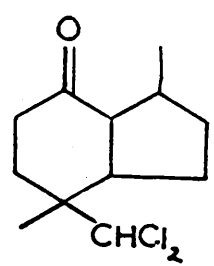
311



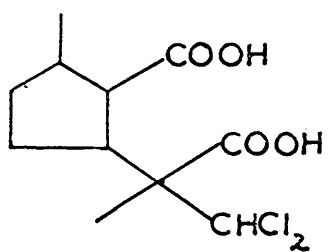
312



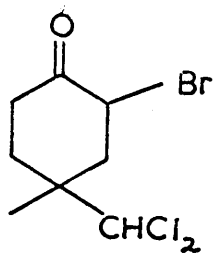
313



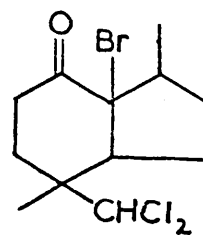
314



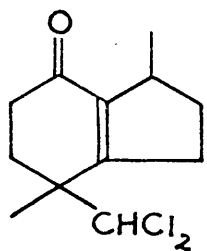
315



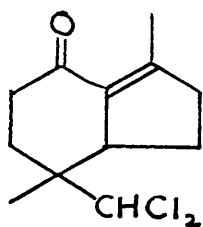
316



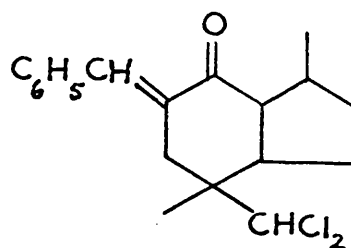
317



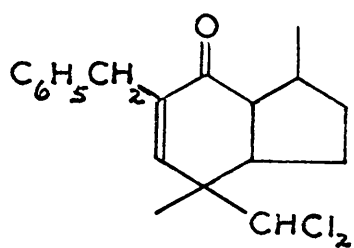
318



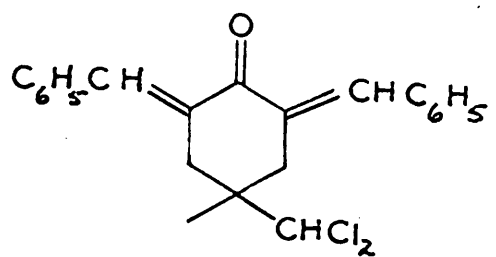
319



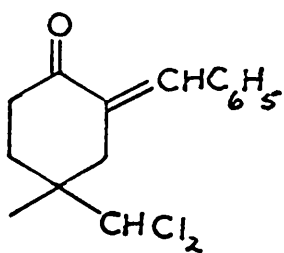
320



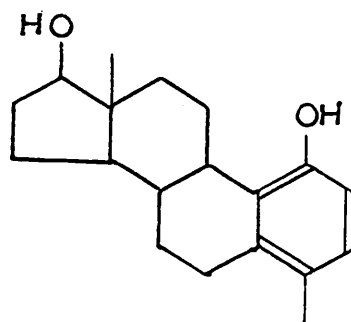
321



322

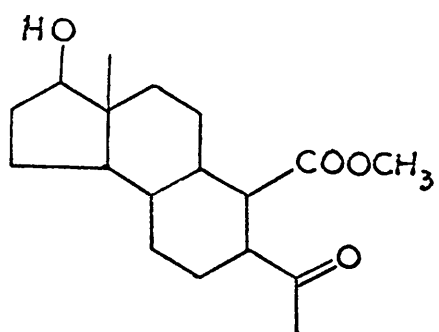


323

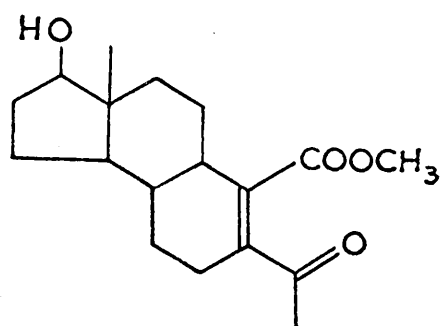


324

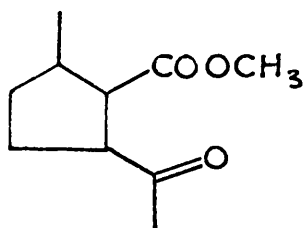




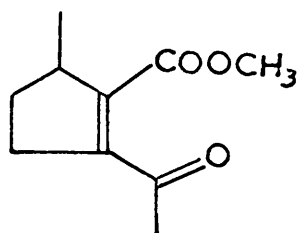
325



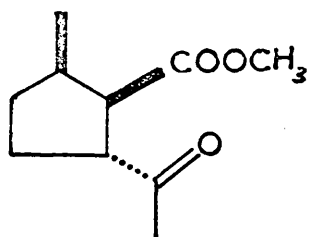
326



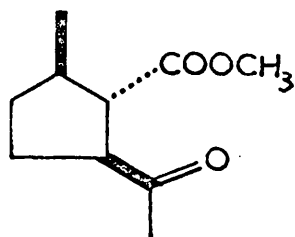
327



328



329



330

REFERENCES

1. Goldblatt, M.W., Chem. Ind., 52, 1056, (1933).
2. V. Euler, U.S., Arch. Exp. Path. Pharmac, 175, 78, (1934).
3. Bergström, S., and Sjövall, J., Acta Chem. Scand.,  
11, 1086, (1957).
4. Bergström, S., and Sjövall, J., Acta Chem. Scand.,  
14, 1693,(1960).
5. Bergström, S., and Sjövall, J., Acta Chem. Scand.,  
14, 1701, (1960).
6. Bergström, S., and Dressler, F., Ryhage, R., Samuelson, B.,  
and Sjövall, J., Arkiv Kemi, 19, 563, (1962).
7. Bergström, S., Dressler, F., Krabisch, L., Ryhage, R.,  
and Sjövall, J., Arkiv Kemi, 20, 63, (1962).
8. Samuelsson, B., Biochim. Biophys., Acta, 84, 707, (1964).
9. Bergström, S., Ryhage, R., Samuelsson, B., and Sjövall, J.,  
Acta Chem. Scand., 16, 501, (1962).
10. Bergström, S., Krabisch, L., Samuelsson, B., and Sjövall, J.,  
Acta Chem. Scand., 16, 969, (1962).

11. Abrahamsson, S., Bergström, S., and Samuelsson, B.,  
Proc. Chem. Soc., 332, (1962).
12. Samuelsson, B., J. Amer. Chem. Soc., 85, 1878, (1963).
13. Bygdeman, M., and Samuelsson, B., Clin. Chim. Acta,  
10, 566, (1964).
14. Änggard, E., and Samuelsson, B., Acta Physiol. Scand.,  
(S.213) 59, 170, (1963).
15. Horton, E.W., Experientia, 21, 113, (1965).
16. Samuelsson, B., J. Biol. Chem., 238, 3229-3234, (1963).
17. Bergström, S., Krabisch, L., Sjövall, J., Acta Chem. Scand.,  
14, 1706, (1960).
18. Eglinton, G., Raphael, R.A., Smith, N., Hall, W.J.,  
Pickles, V.R., Nature, 200, 993, (1963).
19. Änggard, E., Abstracts, Sixth International Congress of  
Biochemistry, New York, (1964).
20. Bergström, S., J. Amer. Oil Chemists Socy., 42, 608, (1965).
21. Änggard, E., Samuelsson, B., Biochem. Pharmacol.,  
13, 281, (1964).
22. Samuelsson, B., Biochim. Biophys. Acta, 84, 218, (1964).

23. Bergström, S., Samuelsson, B., *Acta Chem. Scand.*,  
17, 282, (1963).
24. Samuelsson, B., unpublished data, (1964), see reference 20.
25. Sandberg, F., Ingelman-Lundberg, A., Ryden, G.,  
*Acta. obstet. gynec. Scand.*, 42, 269, (1963).
26. Thomasson, H.J., *Nature*, 194, 973, (1962).
27. van Dorp, D.A., Beerthuis, R.K., Nugteren, D.H., and  
Vonkeman, H., *Biochim. Biophys. Acta*, 90, 204, (1964).
28. Bergström, S., Danielsson, H., Samuelsson, B.,  
*Biochim. Biophys. Acta*, 90, 207, (1964).
29. Bergström, S., Danielsson, H., Klenberg, D., Samuelsson, B.,  
*J. Biol. Chem.*, 239, FC 4006, (1964).
30. van Dorp, D.A., Beerthuis, R.K., Nugteren, D.H., and  
Vonkeman, H., *Nature*, 203, 839, (1964).
31. Daniels, et al., *Biochem. Biophys. Res. Commun.*,  
21, 413, (1965).
32. Kupiecki, *Life Science*, 4, 1811, (1965).
33. Anggard, E., Samuelsson, B., *J. Biol. Chem.*, 240, 3518, (1965).
34. van Dorp, D.A., Nugteren, D.H., *Biochim. Biophys. Acta*,  
98, 654, (1965).

35. Samuelsson, B., J. Amer. Chem. Soc., 87, 3011, (1965).
36. New Scientist, November 4th., (1965).
37. World Medicine, 1, 28, (1965).
38. Samuelsson, B., J. Biol. Chem., 239, 4091, (1964).
39. Anggard, E., Samuelsson, B., unpublished work, see  
reference, 40.
40. Samuelsson, B., Angew. Chem. Internat. Edit., 4, 412, (1965).
41. Anggard, E., Samuelsson, B., J. Biol. Chem., 239, 4097, (1964).
42. Granström, E., Inger, U., Samuelsson, B., J. Biol. Chem.,  
240, 457, (1965).
43. Arbuzov, Yu, A., Russian Chemical Reviews, 34, 558, (1965).
44. Bagli, J.F., Bogri, T., Deghenghi, R., Wiesner, K.,  
Tetrahedron Letters, 5, 465, (1966).
45. Ames, D.E., Bowman, R.E., Mason, R.G., J. Chem. Soc.,  
174, (1950).
46. Winter, M., Helv. Chim. Acta, 46, 1796, (1963).
47. Landor, S.R., Whiter, P.F., J. Chem. Soc., 5625, (1965).
48. Heilbron, I.M., Jones, E.R.H., Koch, H.P., J. Chem. Soc.,  
736, (1942).
49. Hoch, J., Compt. Rend., 200, 938, (1935).

50. Bianchetti, G., Croce, P.D., Pocar, D.,  
Tetrahedron Letters, 25, 2039, (1965).
51. Payne, G.B., Deming, P.H., Williams, P.H.,  
J. Org., Chem., 26, 659, (1961).
52. Chatt, J., Chemical Reviews, 48, 7, (1951).
53. Boissier, J.R., Dumont, C., Mauge, R., Thérapie, II,  
4, 692, (1956).
54. Görlich, B., Hildebrandt, G., Ber., 91, 2388, (1958).
55. Organic Syntheses, p. 56, vol. 39.
56. McOmie, J.F.W., in Advances in Organic Chemistry, vol. 3.
57. Orchin, M., Butz, L.W., J. Amer. Chem. Soc., 2296, (1943).
58. Panouse, J.J., Sannié, C., Bull. Soc. Chim., 1036, (1955).
59. Haskins, W.T., Hann, R.M., Hudson, C.S., J. Amer. Chem. Soc.,  
132, (1942).
60. Nicholls, B., Henbest, H.B., J. Chem. Soc., 4608, (1957).
61. McMaster, W.J., Scott, A.I., Trippett, S., J. Chem. Soc.,  
4628, (1960).
62. Schwarzenback, G., Wittwer, C., Helv. Chim. Acta.,  
30, 663, (1947).

63. Vandwalle, M., Bull. Soc. Chim. Belg., 73, 628, (1964).
64. Hiraga, K., Chem. Pharm. Bull., 13, 1300, (1965).
65. Elvidge, J.A., Stevens, R., J. Chem. Soc., 2252, (1965).
66. Blaise, E.E., Koehler, A., Bull. Soc. Chim., 7, 215, (1910).
67. Papa, D., Schwenk, E., Hankin, H., J. Amer. Chem. Soc.,  
3018, (1947).
68. Martin, E.L., J. Amer. Chem. Soc., 1438, (1936).
69. Wolinsky, J., Barker, W., J. Amer. Chem. Soc., 636, (1960).
70. Sturrock, M.G., Cline, E.L., Robinson, K.R.,  
J. Org. Chem., 28, 2340, (1963).
71. Edward, J.T., Holder, D., Lunn, W.H., Puskas, I.,  
Canad. J. Chem., 39, 599, (1961).
72. Saegbarth, K.A., J. Org. Chem., 25, 2212, (1960).
73. Braude, E.A., Webb, A.A., Sultanbawa, M.U.S.,  
J. Chem. Soc., 3329, (1958).
74. Conia, J.M., Le Craz, A., Bull. Soc. Chim., 1934, (1960).
75. Mayer, R., Alder, E., Ber., 1866, (1955).
76. Organic Syntheses, Coll. vol. II., p. 116.
77. Vogel, "A Textbook of Practical Organic Chemistry".
78. Fisch, M., Ourisson, G., Chem. Comm., 407, (1965).

79. Marquet, A., Jacques, J., et al., Bull. Soc. Chim.,  
1822, (1961) and 90, (1962).
80. Suvorov, N.N., et al., J. Gen. Chem., U.S.S.R.,  
31, 3469, (1961).
81. Djerassi, C., Schotz, C.R., J. Amer. Chem. Soc.,  
70, 417, (1948).
82. Ansell, M.F., Ducker, J.W., J. Chem. Soc., 329, (1959).
83. Tkachuk, R., Lee, C.C., Canad. J. Chem., 37, 1644, (1959).
84. Salmon-Legagneur, F., Neveu, Cecile, Compt. Rend.,  
248, 2217, (1959).
85. Brown, H.C., Garg, C.P., J. Amer. Chem. Soc., 83, 2952, (1961).
86. Review of Wohl-Ziegler reaction, Chem. Revs., 43, 271, (1948).
87. Soloway, S.B., Laforge, F.B., J. Amer. Chem. Soc., 69, 979, (1947).
88. Dauben, H.J., Wenkert, E., J. Amer. Chem. Soc., 69, 2074, (1947).
89. Depuy, C.H., Isaks, M., Eilers, K.L., Morris, G.F.,  
J. Org. Chem., 3503, (1964).
90. Organic Syntheses, vol. 42, p.38.
91. Mayer, R., Wenschuh, G., Topelmann, W., Ber., 1616, (1958).
92. Birch, A.J., Grimshaw J. and Juneja, H.R., J. Chem. Soc.,  
5194, (1961), and Haegele, W., Kaplan, F., Schmid, H.,  
Tetrahedron Letters, 110, (1961).



93. Kremers and Meyer, Arch. Pharm., 7, 17, (1936).
94. Cavill, G.W.K., Rev. Pure and Appl. Chem., 10, 169, (1960).
95. Bates, R.B., Eisenbraun, E.J., McElvain, S.M.,  
J. Amer. Chem. Soc., 80, 3413, (1958).
96. Bates, R.B., Eisenbraun, E.J., McElvain, S.M.,  
J. Amer. Chem. Soc., 80, 3420, (1958).
97. Eisenbraun, E.J., and McElvain, S.M., J. Amer. Chem. Soc.,  
77, 3383, (1955).
98. Pavan, M., Ricerca Sci., 19, 1011, (1949), (C.A. 45, 7309, 1951).
99. Cavill, G.W.K., Ford, J.D., Locksley, H.D., Austral.J.Chem.,  
9, 288, (1956).
100. Cavill, G.W.K., Hinterberger, H., Austral.J.Chem., 13, 514, (1960).
101. Sakan, T., Fujino, A., Murai, F., Butsugan, Y., Suzui, A.  
Bull. Chem. Soc., Japan, 32, 315, (1959).
102. Cavill, G.W.K., and Locksley, H., Austral.J.Chem., 10, 352, (1957).
103. McConnell, J.F., Mathieson, A.M., Schoenborn, B.P.  
Tetrahedron Letters, 445, (1962).
104. Cavill, G.W.K., and Ford, D.L., Austral.J.Chem., 13, 296, (1960).
105. Cavill, G.W.K. and Hinterberger, H., Austral. J. Chem.,  
14, 143, (1961).

106. Sakan, T., Wolinsky, J., et al., Tetrahedron Letters,  
46, 4097, (1965).
107. Meinwald, J., Chadha, M.S., Hurst, J.J., Eisner, T.,  
Tetrahedron Letters, 29, (1962).
108. Sheth, K., Ramstad, E., Wolinsky, J., Tetrahedron Letters,  
394, (1961).
109. Büchi, G., Manning, R.E., Tetrahedron, 18, 1049, (1962).
110. Djerassi, C., Nakano, T., James, A.N., Zalkor, L.H.,  
Eisenbraun, E.J., Shoolery, J.N., J. Org. Chem.,  
26, 1192, (1961).
111. Grimshaw, J., Chem. and Ind., 403, (1961) and Briggs, L.H.,  
Cain, B.F., Le Quesne, P.W., Shoolery, J.N.,  
Tetrahedron Letters, 69, (1963).
112. Birch, A.J., Grimshaw, J., Juneja, H.R., J. Chem. Soc.,  
5194, (1961).
113. Bobbitt, J.M., Spiggle, D.W., Mahoob, S., von Philipsborn, W.,  
Schmid, H., Tetrahedron Letters, 321, (1962).
114. Winde, E., Hänsel, R., Arch. Pharm., 293, 556, (1960).
115. Halpern, O., Schmid, H., Helv., 41, 1109, (1958).

116. Albers-Schonberg, G., Schmid, H., Helv., 44, 1447, (1961).
117. Scarpati, M.L., Guiso, M., Panizzi, L., Tetrahedron Letters, 39, 3439, (1965).
118. Djerassi, et al., Chem. and Ind., 210, (1961).
119. Clark, K.J., Fray, G.I., Jaeger, R.H., Robinson, R., Tetrahedron, 6, 217, (1959).
120. See, " The Biosynthesis of Steroids, Terpenes and Acetogenins ", by Richards, J.H., and Hendrickson, J.B., p.223.
121. Wolinsky, J., Gibson, T., Chan, D., Wolff, H., Tetrahedron, 21, 1247, (1965).
122. Cookson, R.C., Hudec, J., Knight, S.A., Whitear, B.R.D., Tetrahedron, 19, 1995, (1963).
123. Wolinsky, J., Slabaugh, M., Gibson, T., J. Org. Chem. 29, 3740, (1964).
124. Battersby, A.R., et al., Chem. Comm., 346, (1966).
125. Arigoni, D., et al., Chem. Comm., 347, (1966).
126. Scott, A.I. et al., Chem. Comm., 348, (1966).
127. Cavill, G.W.K., Whitfield, F.B., Austral. J. Chem., 1245, (1964) and 1260, (1960).

128. Korte, F., Falbe, J., Zschocke, A., *Angew. Chem.*,  
70, 704, (1958), and *Tetrahedron*, 6, 201, (1959).
129. Korte, F., Buchel, K.H., Zschocke, A., *Ber.*, 94, 1952, (1961).
130. Sakan, et al., *Bull. Chem. Soc., Japan*, 33, 1737, (1960).
131. Cavill, G.W.K., Achmad, S.A., *Austral. J. Chem.*, 1989, (1965).
132. Sisido, K., Utimoto, K., Isida, T., *J. Org. Chem.*, 29, 3361, (1964).
133. Casinovi, C.G. et al., (*C.A.* vol. 63, 4 349, 1965).
134. Nabney, J., Ph.D. Thesis, Queen's University, Belfast, (1959).
135. Carnduff, J., Ph.D. Thesis, University of Glasgow, (1963).
136. For a review of the Reimer-Tiemann reaction, see Wynberg, H.,  
*Chem. Revs.*, 60, 169, (1960).
137. Auwers, K., Keil, G., *Ber.*, 35, 4207, (1902).
138. Marmor, S., *J. Org. Chem.*, 28, 250, (1963).
139. Yang, N.C., Finnegan, R.A., *J. Amer. Chem. Soc.*,  
80, 5845, (1958).
140. Igarashi, M., Midorikawa, H., *J. Org. Chem.*, 29, 2080, (1964).
141. Burgess, E.M., *J. Org. Chem.*, 27, 1433, (1962).
142. Pappo, R., Jung, C.J., *Tetrahedron Letters*, 365, (1962).
143. "The Infra red Spectra of Complex Molecules", Bellamy, L.J.,

144. Auwers, K., Ann. de Chemie, 352, 279, (1907).
145. Ferris, A.F., Marks, I.G., J. Org. Chem., 19, 1971, (1954).
146. Zymalkowski, F., Angew Chemie, 4, 369, (1965).
147. Reinecke, M.G., J. Org. Chem., 29, 299, (1964).
148. Caspi, E., Grover, P.K., Piatak, D.M., Shimizu, Y.,  
J. Chem. Soc., 3052, (1965).
149. Beal, P.F., Babcock, J.C., Lincoln, F.H., J. Amer. Chem. Soc.,  
88, 3131, (1966).