SYNTHETIC APPROACHES TO CLOVENE

ROBERT D.H. MURRAY

THESIS

presented to the University of Glasgow

for the degree of Ph.D.

1960.

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I wish to express my thanks to Professor R.A. Raphael and Dr. W. Parker for their help and advice during the past three years. Their interest and guidance have been a constant source of encouragement to me.

I also wish to thank the Department of Scientific and Industrial Research for a maintenance award. My thanks are also due to Mr. J.M.L. Cameron and Dr. R.I. Reed of Glasgow University for microanalyses and mass spectrometric determinations.

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SUMMARY OF THESIS

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The total synthesis of clovene, a tricyclic rearrangement product of caryophyllene has been undertaken.

PART ONE.

Methyl 3-methylcyclohexanone-3-acetate was prepared from 3-methylcyclohex-2-enone by treatment with diethyl malonate and sodium ethoxide, followed by hydrolysis, decarboxylation and re-esterification. Treatment of the keto-ester with malononitrile afforded 3-carbomethoxymethyl-3-methylcyclohexylidenemalononitrile, which was converted to 3-carbomethoxymethyl-3-methyl-1-cyano-1-dicyanomethylcyclohexane as a mixture of stereoisomers. Hydrolysis, decarboxylation, re-esterification and high-dilution, intra-molecular Dieckmann cyclisation furnished a separable mixture of 5-methylbicyclo[3:3:1] nonan-3-one-1-carboxylic acid and 5-methylbicyclo[3:2:1] octan-7-one-1-acetic acid.

5-methyl-1-(isopropenylaceto)-bicyclo[3:3:1] nonan-3-one was then prepared from the 5-methylbicyclo[3:3:1] nonan-3-one-1-carboxylic acid chloride, but it was found to be impossible to cyclise the enedione to clovan-2:6-dione. Further modifications of 5-methylbicyclo[3:3:1] nonan-3-one-1-carboxylic acid and several alternative unsuccessful cyclisations to the clovene skeleton are described.

PART TWO.

2-Carbethoxy-6-methylcyclohexanone, on treatment with acrolein, gave 3-(1-carbethoxy-2-keto-3-methylcyclohexyl)-propionaldehyde which cyclised in concentrated sulphuric acid to ethyl 5-methylbicyclo[3:3:1]non-3-ene-9-one-1-carboxylate. Clemmensen reduction of the corresponding keto-acid furnished 5-methylbicyclo[3:3:1]-non-3-ene-1-carboxylic acid, which by direct allylic oxidation followed by catalytic reduction afforded 5-methylbicyclo[3:3:1]nonan-2-one-1-carboxylic acid. A stepwise allylic oxidation of the olefinic-ester has been devised. Treatment with t-butyl perbenzoate, followed by trans-esterification with sodium methoxide and oxidation with manganese dioxide afforded methyl 5-methylbicyclo[3:3:1]-non-3-ene-2-one-1-carboxylate in good overall yield in a high state of purity. Hydrogenation and saponification furnished 5-methylbicyclo[3:3:1]nonan-2-one-1-carboxylic acid. Various synthetic pathways from this system to the clovene skeleton have been pursued.

5-Methylbicyclo[3:3:1]nonane-1-carboxylic acid has been synthesised by Wolff-Kishner reduction of 5-methylbicyclo-[3:3:1]nonan-3-one-1-carboxylic acid and by catalytic hydrogenation of 5-methylbicyclo[3:3:1]non-3-ene-1-carboxylic acid. The structure of the parent bicyclo[3:3:1]nonane system is thus authenticated by its synthesis from two totally independent synthetic pathways.

CONTENTS

HISTORICAL

(Formulae flowsheets for this section on p. 12).

The liquid sesquiterpene fraction obtained as a by-product in the processing of clove oil (from Eugenia caryophyllata) provides a ready source of a mixture of hydrocarbons whose major constituent is the substance caryophyllene (I). The early literature (1) distinguished three caryophyllenes designated as α, β and γ. The α compound has since been shown (2) to be identical with humulene while γ-caryophyllene, now referred to as isocaryophyllene (II), is an isomeric artifact of the naturally occuring isomer, β-caryophyllene (I), now simply referred to as caryophyllene (3). African copaiba oil (from Oxystigma mannii HARMS) and French Lavender oil have also been reported to contain caryophyllene.

One of the outstanding characteristics of caryophyllenic compounds is the readiness with which they undergo acid catalysed rearrangements with the formation of tricyclic products. The severe skeletal changes resulting from these rearrangements together with the lack of crystalline derivatives to characterise the oily products, served to complicate much of the

early investigations on caryophyllene (1). Under a variety of acid hydrating conditions caryophyllene gives rise to two isomeric $C_{15}H_{26}O$ alcohols designated α and β-caryophyllene alcohols and a mono-unsaturated hydrocarbon, clovene $C_{15}H_{24}$ (1). β-Caryophyllene alcohol, or as it is now called, caryolan-1-ol (4) has been assigned structure (IV; R=OH) (5) while structures (V) and (VI) respectively have been ascribed to α-caryophyllene alcohol and clovene (5, 14).

Caryophyllene was formulated as 4:11:11-trimethyl-8-methylenebicyclo[7:2:0]undec-4-ene (I) by Barton and his co-workers (5) in 1951 and subsequently (6) this was shown to be correct. On the basis of substantial degradative evidence Barton, Bruun and Lindsey (5) have formulated caryolan-1-ol (IV; R=OH) as 1-hydroxy-4:4:8-trimethyltricyclo[6:3:1:$0^{2:5}$]dodecane. Phosphorus pentachloride treatment of caryolanol (7) yields a highly crystalline chloro compound (IV; R=Cl). That no rearrangement of the caryolane skeleton had occurred during this conversion was shown by Barton and his co-workers (5b) in an elegant stepwise degradation, which paralleled that for caryolanol (IV; R=OH), to the same keto-acid (III). This showed that the hydroxyl group in (IV; R=OH) and the halogen substituent in (IV; R=Cl) were

attached to the ring residues in identical fashion and that no readjustment of the carbon atoms was involved in their interconversion.

The brilliant X-ray crystallographic determination of the structure of caryolanol chloride (IV; R=Cl) by Robertson and Todd (8) not only confirmed the bridge-head nature of the alcohol but established also the structure (IV) and the stereochemistry of the molecule. Thus the cyclobutane moiety was shown to be fused in a trans manner to the larger ring. Further the hydrogen at C_5 in caryolanol chloride was seen to lie on the same side of the molecule as the C_{12} methylene bridge.

The tricyclic mono-unsaturated sesquiterpene, clovene, $C_{15}H_{24}$, is reported to be formed from caryophyllene by a variety of acid hydrating agents (1). Thus Wallach and Walker (7) employing the Bertram-Walbaum reagent (glacial acetic and dilute sulphuric acids) obtained clovene as an oily hydrocarbon mixture together with the crystalline caryolanol. A liquid mono-hydrochloride of caryophyllene gave, on treatment with silver acetate in acetic acid, an oil, considered by Bell and Henderson (9) to be clovene, together with the acetate of α-caryophyllene alcohol which when hydrolysed and dehydrated furnished an olefin,

likewise considered to be clovene. The work of Asahina and Tsukamoto (10, 11) showed that hydration of caryophyllene with Aschan's reagent (sulphuric acid monohydrate in ether) furnished not only a mixture of clovene and caryolanol but also α-caryophyllene alcohol, dehydration of which with phosphorus pentoxide (9) afforded clovene.

Owing to the lack of crystalline derivatives no satisfactory criteria were available for either the purity or the identity of the terpene and this led to clovene being wrongly identified as the dehydration product of caryolanol (19). The only crystalline product known was the oxidative degradation product clovenic acid (VII) (12) which, while useful for identification could not be used for regeneration of pure clovene.

Clovene has been rigorously purified by Lutz and Reid (13). Crude distilled clovene, obtained from caryophyllene by treatment with Aschan's reagent (10), was treated with bromine. The mixture of isomeric dibromides obtained in relatively poor yield were separated by fractional crystallisation and extremely pure clovene b.p. 115·0°/12·5mm., $n_D^{25.0}$ 1·4913, $[\alpha]_D^{25.0}$ - 23·37° regenerated from each dibromide by extended treatment with zinc dust.

Both clovene and α-caryophyllene alcohol are tricyclic and possess an identical carbon skeleton as is shown by the ready oxidation of each to the dibasic bicyclic acid, clovenic acid $C_{15}H_{24}O_2$ (9,12) and the dehydration of α-caryophyllene alcohol to clovene (9,10,11). The formulae for these compounds were advanced independently by Eschenmoser and Günthard (14), (mainly on infra-red spectral data) and by Barton, Bruun and Lindsey (5) as a result of exhaustive degradation studies. The formulae proposed were consistent with older observations (1) that clovene contains the unit $-\overset{\diagup}{C}-CH=CH-\overset{\diagdown}{C}-$, and that clovenic acid readily forms an anhydride but resists bromination and enolisation (12).

The rigorous structural proof for the clovene skeleton (5) may be summarised as follows:-

In 1947, Treibs (15) reported that treatment of caryophyllene with hydrogen peroxide afforded a crystalline mono-epoxide which was later formulated as (VIII) (5). This epoxide afforded, on treatment with aqueous acid, a tricyclic glycol (IX) which could be oxidised successively to a keto-alcohol (X) and thence to a diketone (XI). That (X) had the carbonyl function within a five-membered ring was shown by the infra-red spectrum of the substance ($\lambda_{max.}$ 1732 $cm.^{-1}$).

The diketone (XI) exhibited a further band (λmax.1702cm.$^{-1}$) indicative of a carbonyl group in a six-membered ring. Acetylation of the keto-alcohol (X) followed by selenium dioxide oxidation afforded the α-diketone (XIII) which on alkaline hydrogen peroxide cleavage furnished the hydroxy-dicarboxylic acid (XIV). Removal of the hydroxyl group by oxidation and Wolff-Kishner reduction of the resulting ketone, afforded clovenic acid (VII), the authenticity of which was demonstrated by direct comparison.

An independent preparation of the glycol (IX) has been effected by Reid and his co-workers (13) by the action of performic acid on caryophyllene followed by alkaline hydrolysis. Wolff-Kishner reduction of the corresponding diketone (XI) (13) and catalytic reduction of clovene (VI) (13) afforded the same saturated hydrocarbon, termed clovane (XII).

These results thus established unequivocally that clovene and the glycol (IX) possessed identical carbon skeletons.

The proof of the structure of clovenic acid was completed (4) by the step-wise degradation of clovan-2:9-dione (XI) to p-cymene (XXI).

Further oxidation of the dione (XI) with chromium trioxide in acetic acid afforded the keto-dicarboxylic acid (XV) which exhibited infra-red absorption at 1688 $cm.^{-1}$ (carboxyl) and 1728 $cm.^{-1}$ (cyclopentanone). Selenium dioxide oxidation afforded the diketo-dicarboxylic acid (XVI) which on fission with alkaline hydrogen peroxide furnished the tetra-carboxylic acid (XVII). By pyrolysis at 260° this acid was smoothly converted into the keto-dicarboxylic acid (XVIII; R=H).

The constitution (XVIII) was assigned rather than the alternative (XXII) on the following basis:-

All compounds with two carboxyl groups derived from the original five-membered ring of the glycol (IX) decomposed on melting to afford the corresponding anhydrides. No decomposition or anhydride formation was observed at the melting point of the keto-dicarboxylic acid. This could be explained by the structure (XVIII; R=H) where the two carboxyls are necessarily trans in a six-membered ring and thus could not afford a monomeric anhydride. It would not be explained by the alternative formula (XXII).

Oxidation of the keto-diester (XVIII; R=Me) with selenium dioxide afforded a diketo-diester (XIX) which on fission with alkaline hydrogen peroxide followed by dehydrogenation over palladised charcoal furnished p-cymene. (XXI).

Perphthalic oxidation of isocaryophyllene (II) gave a new mono-epoxide (XXIII) (3,18) which with aqueous acid rearranged to a tricyclic glycol (XXIV) epimeric with (IX). Oxidation however afforded the same dione (XI); thus the diols differed only in the configuration of the hydroxyl group at C_9. This variation in stereochemistry was to be expected if the oxide ring of each respective precursor possessed the same stereochemistry at the tertiary centre (C_4) and differed configurationally at the secondary carbon (C_5). Thus the configuration of the double bond is the only difference between caryophyllene (I) and isocaryophyllene (II) and it is likely that isocaryophyllene, having the more stable cis-cyclononene system, is formed from caryophyllene during extraction from natural sources.

From the proposed formulae for clovene (VI) and caryolanol (IV; R=OH) it seemed likely that a direct relationship should exist between them since dehydration with Wagner-Meerwein rearrangement of the latter would be expected to furnish the hydrocarbon. Indeed, the early literature contains statements in support of this dehydration (7, 19). Careful repetition of this dehydration (14) of caryolanol (IV; R=OH) with phosphorus pentoxide by Lutz and Reid (13) has shown that the

product closely resembles clovene in so far as boiling point and refractive index are concerned, but that the optical rotation is of the opposite sign and its infra-red spectrum shows distinct differences from that of clovene (14).

Lutz and Reid (13) have termed this new dehydration product pseudoclovene, which showed distinct chemical differences from clovene. Thus, in comparison with clovene, pseudoclovene formed an unstable compound with bromine and on oxidation formed an oily dibasic acid, isomeric with clovenic acid. That this acid possesses hydrogen atoms α to the carboxyl groups was shown by the ready substitution in the Hell-Vollhard-Zelinski reaction affording a dibromo-acid. Further, pseudoclovene must contain hydrogen atoms alpha to the double bond for, unlike clovene, it reacted smoothly with N-bromosuccinimide to give an unstable bromo-derivative. On the basis of these observations, Lutz and Reid have tentatively proposed formula (XXV) for pseudoclovene and (XXVI) for pseudoclovenic acid.

Lutz and Reid (13) have not only shown that caryolanol (IV; R=OH) on dehydration does not afford clovene but also that caryolanol is completely inert to the mild acid dehydrating conditions employed in the conversion of caryophyllene to clovene.

From the mixture of hydrocarbons obtained by the dehydration of caryolanol, Henderson, McCrone and Robertson (19) isolated a higher boiling mono-unsaturated tricyclic sesquiterpene which they termed isoclovene. Isoclovene may be characterised by a crystalline hydrochloride from which the pure hydrocarbon may be regenerated.

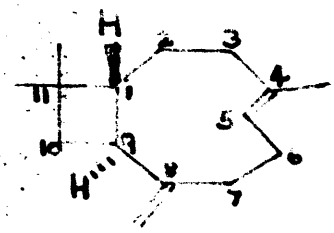
On the basis of X-ray crystallographic determinations on the isomorphous hydrochloride and hydrobromide, Clunie and Robertson (20) have recently shown isoclovene to be (XXVII). Barton has commented (20) that this rearrangement of caryolanol represents an unusual problem in carbonium-ion mechanistics.

The reaction may occur according to the scheme (IV) ⟶ (XXVIII) ⟶ (XXIX) ⟶ (XXVII) involving a 1, 3 hydride shift, or else via (XXVIII) ⟶ (XXX) ⟶ (XXXI) ⟶ (XXVII). Both routes involve intermediates which would be excluded on a strict application of Bredt's rule. It is known however that this rule breaks down in the reactions of caryolanol (cf. the facile conversion of caryolanol to the chloride with phosphorus pentachloride (5,7)).

Barton and Nickon (21) have recently prepared both epimers of clovan-2-ol (V), each of which on oxidation gave clovan-2-one. It is of interest that neither

epimer is identical with α-caryophyllene alcohol as would be expected on the basis of the known properties of this compound (9). No alternative formula for α-caryophyllene alcohol has been proposed.

A conformational study (4) of the caryophyllene molecule has shown that, because it is trans within a nine-membered ring, the endocyclic ethylenic linkage must lie with its plane perpendicular to that of the cyclobutane ring. If the C_4 methyl group projects downwards (relative to the upward β-hydrogen at position C_1), then only β-attack is possible which will lead (equation 1) to clovane-type cyclisation, whilst if it projects upwards only α-attack is possible leading to caryolane-type cyclisation (equation 2).



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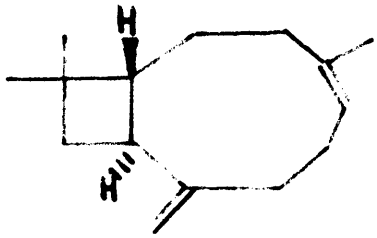

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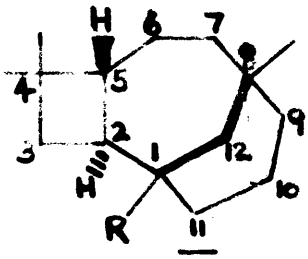

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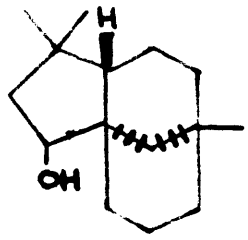

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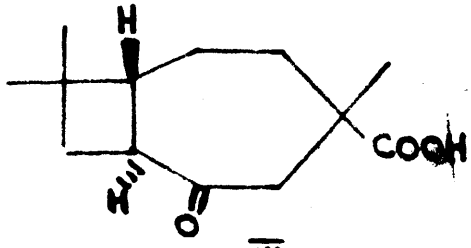

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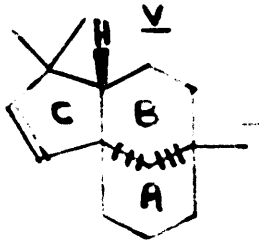

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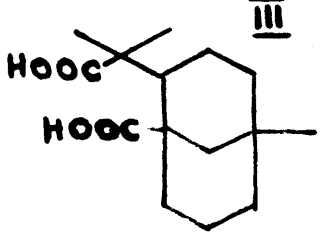

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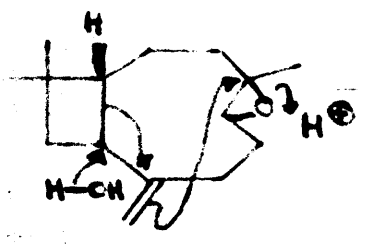

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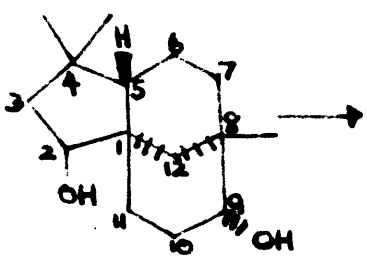

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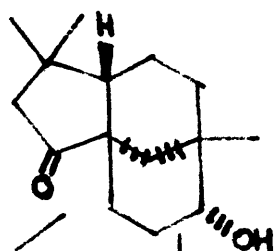

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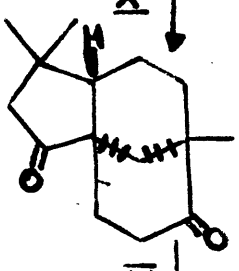

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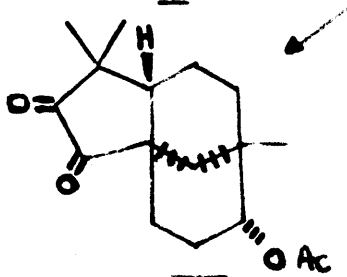

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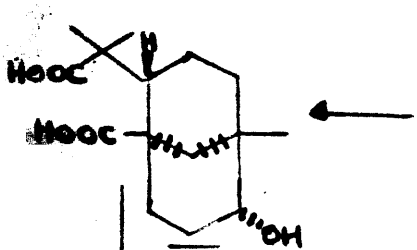

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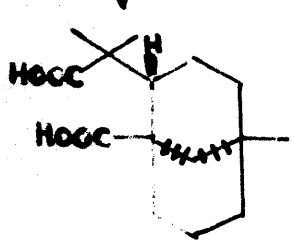

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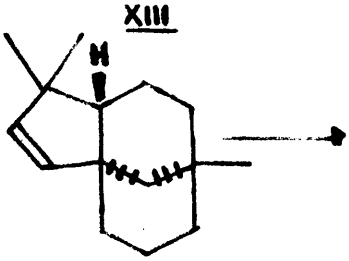

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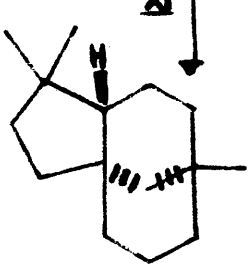

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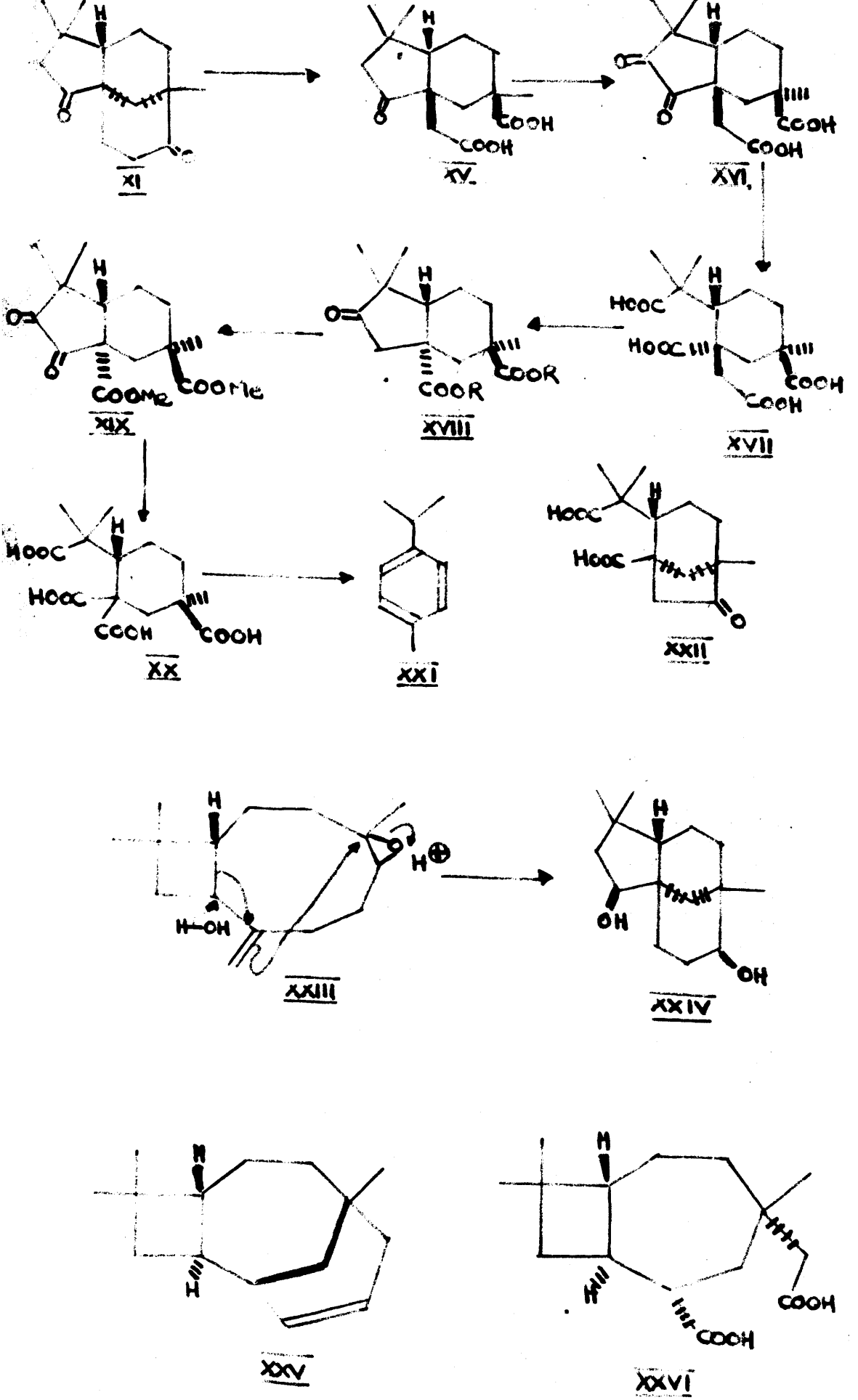
XI
XV
XVI
XVII
XVIII
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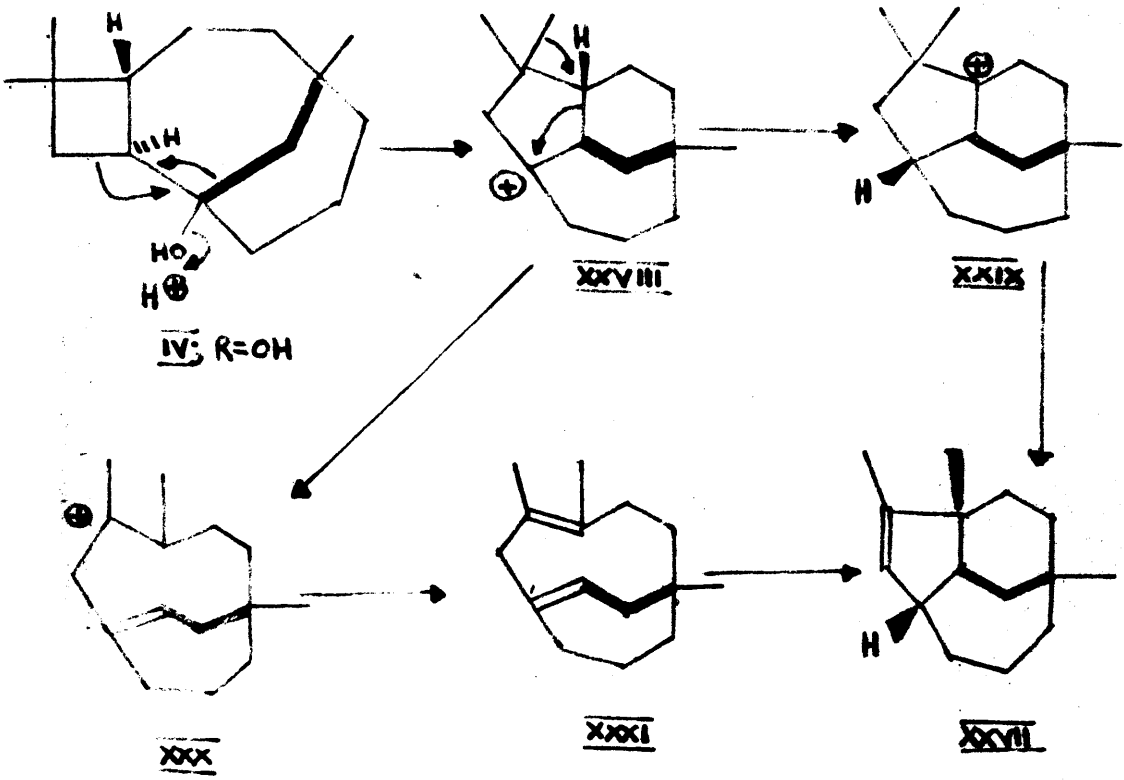
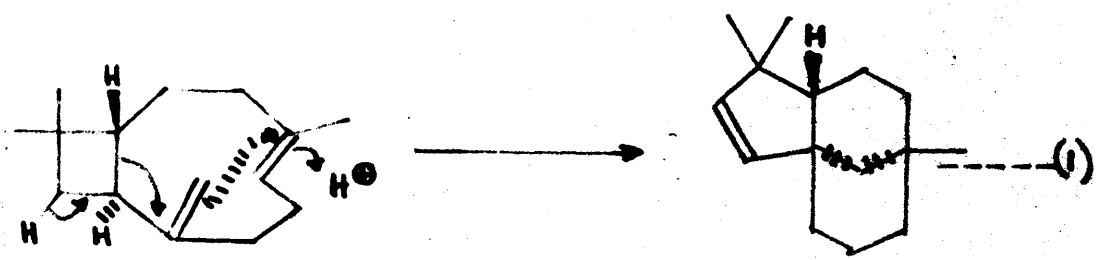
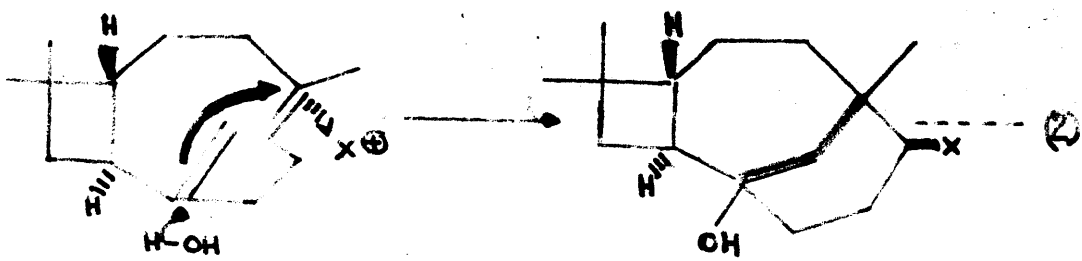
XXIII
XXIV
XXV
XXVI


H
HO
H⊕
XXVIII
XXIX
IV; R=OH
XXX
XXXI
XXVII


H
H⊕
(1)


H
X⊕
H-OH
OH
X
(2)

PART ONE

The Synthesis of 5-Methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid and Attempts at Conversion to Clovene

THE SYNTHESIS OF 5-METHYLBICYCLO[3:3:1]NONAN-3-ONE-1-CARBOXYLIC ACID AND ATTEMPTS AT CONVERSION TO CLOVENE.

Theoretical

(Formulae flowsheets for this section on p. 53).

At the outset of this synthetic approach to clovene (VI) it was decided to construct a suitably substituted bicyclo[3:3:1]nonane system as this entity is present in the arbitrarily designated rings A and B of clovene. It was felt that the most useful intermediate fitting our requirements would be 5-methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid (XXXII; R=H). This key intermediate would provide rings A and B in the correct stereochemical form with the bridge-head methyl group correctly placed. It was hoped that the carboxyl group at the other bridge-head position could be extended to give a suitably activated side-chain which by cyclisation on to the activated methylene group, adjacent to the carbonyl group, would afford ring C of clovene.

As very few compounds in the bicyclo[3:3:1]nonane systems had been synthesised with different functional groups at the two bridge-head positions (see literature survey p.59-75), and as those which had been so prepared were unsuited to our purpose, it was decided to devise a

new and flexible synthetic route to the bicyclo[3:3:1]-nonane system.

FORMATION OF RING A

It was essential therefore to construct a cyclohexane compound suitably substituted so as to afford (XXXII) on cyclisation, and the most favourable compound from which to start seemed to be 3-methylcyclohexanone-3-acetic acid (XXXIII; R=H), which had been prepared by Farmer and Ross (22) in 1925.

Thus ethyl acrylate underwent a Michael reaction with ethyl acetoacetate in the presence of sodium ethoxide (23,24) affording ethyl 3-carbethoxy-3-acetobutyrate (XXXIV) which on hydrolysis with dilute sulphuric acid gave, in 65% yield, 3-acetobutyric acid (XXXV; R=H) also obtainable from the barium hydroxide cleavage of dihydroresorcinol (XXXVI) (25,26). The corresponding ethyl ester (XXXV; R=Et) underwent the Guareschi reaction (22) with ethyl cyanoacetate in saturated ammoniacal ethanol solution affording the dicyanoimide (XXXVII) in poor yield. Hydrolysis with concentrated sulphuric acid afforded 2-methylpimelic-2-acetic acid (XXXVIII; R=H). Dieckmann cyclisation of the triethyl ester (XXXVIII; R=Et) with sodium hydride in ether (27) afforded in high yield a β-keto-ester which on mild acid hydrolysis (27) furnished

the desired keto-acid (XXXIII; R=H). A yield of 20% in the first stage of the Guareschi reaction could not be improved upon even after considerable modifications (28) in the reaction conditions. This approach was therefore abandoned as a practical route. Farmer and Ross (22) described the synthesis of 3-methylcyclohexanone-3-acetic acid (XXXIII; R=H) by the Michael addition of diethyl malonate to 3-methylcyclohex-2-enone (XXXIX) in the presence of sodium ethoxide at room temperature, followed by prolonged hydrolysis of the intermediate (XLI) with ethanolic hydrochloric acid.*

*Footnote: Farmer and Ross suggested that the first step was a normal Michael addition affording the keto-diester (XLII) which then cyclised to a bridged β-keto-ester (XLIII) and then underwent a reverse Dieckmann reaction to furnish (XLI) as the only isolatable product. Johnson and his co-workers (29) have rationalised the reaction mechanism in a different manner following their studies on the Michael addition of ethyl cyanoacetate to 3-methylcyclohex-2-enone (XXXIX). They proposed that the first step was an abnormal Michael reaction affording the keto-diester (XL) which then underwent ethanolysis affording the open-chain triester (XXXVIII; R=Et). This then cyclised in a known manner (22) to (XLI). If the reaction was carried out in boiling ethanol the triester (XXXVIII; R=Et) was the only isolatable product.

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Ethyl acetoacetate and formaldehyde were condensed in the presence of piperidine to the keto-diester (XLIV) which on acid hydrolysis afforded 3-methylcyclohex-2-enone (XXXIX) (30,31). A modification of the method of Farmer and Ross (22) was employed for the condensation of diethyl malonate with (XXXIX) and the keto-acid (XXXIII; R=H) obtained on hydrolysis of the intermediate (XLI) readily crystallised as colourless prisms m.p.51-53° (lit. (22) m.p. 37°).

When the keto-acid (XXXIII; R=H) was esterified under Fischer-Speier conditions the corresponding ethyl ester (XXXIII; R=Et) was obtained in only 40% yield together with an equivalent amount of a high-boiling by-product. Esterification with diazomethane (32), however, afforded the desired keto-ester (XXXIII; R=Me) in high yield as a colourless oil. The product exhibited infra-red absorption (33) at 1730 $cm.^{-1}$ (carbomethoxyl) and 1710 $cm.^{-1}$ (cyclohexanone).

FORMATION OF RING B

It was hoped to construct, from either the keto-ester (XXXIII; R=Me) or 3-methylcyclohex-2-enone (XXXIX), a compound of the general structure (XLV), symmetrically substituted at C_1 such that on Dieckmann cyclisation the bicyclo[3:3:1] nonane system (XLVI) would be the only bicyclic material formed. If, however, C_1 is

unsymmetrically substituted then the possibility of stereoisomers exists with the C_3 position, such that on cyclisation two bicyclic systems will be afforded (see later).

3-Methylcyclohex-2-enone (XXXIX) underwent a facile Knoevenagel reaction (34) with malononitrile affording the highly crystalline conjugated dienedinitrile (XLVII). It was hoped that diethyl malonate could be induced to add 1:6 across this system to furnish the mono-unsaturated dinitrile-diester (XLVIII), which should still be capable of undergoing a further Michael reaction with diethyl malonate affording a compound readily capable of conversion to the general structure (XLV). That (XLVIII) was formed was shown by the ultra-violet maximum of the product at 246mμ, but no satisfactory method of purification for the crude reaction product could be developed.

A Guareschi reaction (28) of ethyl cyanoacetate on the keto-ester (XXXIII; R=Me) in saturated ammoniacal ethanol solution was attempted. The reaction, if it had gone, would have furnished the general structure (XLV) directly, but cyanoacetamide proved to be the only isolatable crystalline material, the residue being an unworkable oil.

Ethyl cyanoacetate reaction with the keto-ester (XXXIII; R=Me) under Knoevenagel conditions (34) in

low yield, the product being assigned structure (XLIX) on the basis of the ultra-violet maximum at 236 mμ.

The elaboration of the carbonyl group in the keto-ester (XXXIII; R=Me) was successfully achieved in high yield by reaction with pure malononitrile under Knoevenagel conditions (35). Structure (L), containing a highly polarised olefinic double bond, was ascribed to the molecule on the basis of the ultra-violet maximum at 239 mμ (ε 13,500) and the infra-red absorption bands at 2200 $cm.^{-1}$ (conjugated nitrile) and 1597 $cm.^{-1}$ (conjugated double bond).

We now desired to effect a Michael addition (36) to this compound, such that the general structure (XLV) would be readily obtainable from the intermediate. It was found that diethyl malonate probably did add 1:4 across the activated double bond of (L) in low yield, but the product readily decomposed on fractionation. Using cyclohexylidenemalononitrile (LI; R=CN) as a reference compound, it was found that the Reformatsky complex of ethyl bromoacetate could be induced to add in low yield across the activated double bond. As there was also great difficulty in separating the product from the reagents, this reaction was not applied to the dinitrile-ester (L).

It was then decided to attempt addition of hydrogen

cyanide across the double bond, which unfortunately might lead to the possibility of formation of stereoisomers. As, however, it was still probable that a bicyclo [3:3:1] nonane system might be furnished on subsequent cyclisation, it was decided to pursue this approach.

McRae and Lapworth (37,38) in 1922 reported that hydrogen cyanide could be added across the olefinic double bond of the cyano-ester (LI; R=CO_2Et) affording, after acid hydrolysis of the crude dinitrile-ester, 1-carboxycyclohexane-1-acetic acid (LII) in good overall yield. Applying their conditions of potassium cyanide in aqueous ethanol (37) to (L) we found that the desired trinitrile (LIII) could be isolated in, at best, 23% yield and that the reaction was not reproducible. Employing a solution of sodium cyanide in dimethylformamide, however, and with careful isolation techniques, we were able to isolate the trinitrile (LIII) as a mixture of crystalline stereoisomers in 66% yield, with good recovery of starting material which could be re-cycled. It was found that the two trinitrile stereoisomers so formed could not be separated by fractional crystallisation. Careful chromatography on silica or on activated charcoal, combined with crystallisation, also effected no separation; whilst

the alkaline nature of alumina effected β-elimination of hydrogen cyanide furnishing substantial amounts of (L). Satisfactory separation of one of the stereoisomers, later shown to be (LIV) by conversion to 5-methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid (XXXII; R=H), was achieved by repeated crystallisation from aqueous methanol. As the separation of the stereoisomers was so tedious, it was decided to proceed with the mixture and effect separation at a later stage.

An attempt was made to cyclise the trinitrile (LIII) in a Dieckmann reaction as it was expected that under mild conditions the anion $^{\ominus}C(CN)_2$ would be formed exclusively and might react with the ester grouping to afford the keto-trinitrile (LV). This compound would then possess reactive groupings suitably placed in the bicyclo[3:3:1]nonane system for the construction of the remaining cyclopentene ring C of clovene. Not unexpectedly, however, the intermediate anion readily lost cyanide ion from the β-position with formation of substantial amounts of (L) in preference to cyclisation.

Similarly an attempt was made to effect a Michael addition of the trinitrile (LIII) under mild basic conditions with methyl β:β-dimethylacrylate. If condensation had resulted, the product (LVI) would have

readily been capable of conversion by acid hydrolysis, esterification and Dieckmann cyclisation to a bicyclo[3:3:1]nonane diacid (LVII) suitably substituted for cyclisation to ring C of cloyene. As in the above experiment however, mild base effected preferential removal of cyanide ion from the β-position and no Michael addition ensued.

The trinitrile (LIII) when vigorously refluxed with fuming hydrochloric acid (37) was smoothly converted to the crystalline tricarboxylic acid (LVIII; R=H)* which with diazomethane (32) afforded the trimethyl ester (LVIII; R=Me)

*Footnote: Sublimation of the triacid (LVIII; R=H) afforded a highly crystalline anhydride-monoacid as a mixture of inseparable stereoisomers assigned structure (LX) on the basis of infra-red absorption (33), at 1850 and 1770 cm^{-1} (substituted succinic anhydride). The fore-run of the distillation of the triester (LVIII; R=Me) contained considerable amounts of complex amido-esters which could not be separated by repeated fractionation. These amido-esters probably arise through incomplete hydrolysis of the trinitrile (LIII) and account for the low conversion (56%) of the trinitrile (LIII) to the triester (LVIII; R=Me).

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An attempt to cyclise the triester (LVIII; R=Me) by a Dieckmann reaction failed when the mild condition of sodium hydride in methanolic ether was employed (27,39) However a conversion to the bicyclic system in high yield was possible when potassium t-butoxide (40,41) was used and reaction carried out under high dilution conditions. The resulting complex mixture of β-ketoesters on hydrolysis with dilute hydrochloric acid afforded a mixture of bicycloketo-acids (XXXII; R=H) and (LIX; R=H) of which only the former with the desired bicyclo[3:3:1] nonane system could be obtained crystalline.*

*Footnote: That no triester (LVIII; R=Me) remained after the Dieckmann reaction was shown by the lack of absorption at 1380, 1362 and 1345 cm⁻¹, characteristic of the infra-red spectrum of the triester (LVIII; R=Me), in the product. Again, analysis of the vapour phase chromatogram of the ester mixture resulting from the diazomethane treatment of the crude keto-acids showed only two compounds to be present viz. (XXXII; R=Me) and (LIX; R=Me). It was noted that during the distillation of the complex β-ketoester mixture afforded by the Dieckmann reaction the later fractions contained progressively greater amounts of material with infra-red absorption (33) at 1831 and 1782 cm⁻¹ (substituted succinic anhydride). Initially this was thought to be

due to the presence of the methyl ester of (LX) but from the above evidence the impurity has been assigned structure (LXI), which is probably formed by the action of traces of hydrochloric acid on the β-keto-ester (LXII) at high temperatures. The anhydride could never be obt obtained pure nor could it be formed in greater yield by distillation of the β-keto-ester mixture from p-toluenesulphonic acid.

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When the unsaturated dinitrile (L) is written as (LXIII) it is seen that addition of cyanide ion may take place in two ways thus affording two stereoisomers. The less hindered, equatorial approach of cyanide ion affords the ion (LXIV) in which there must be a large 1:3 diaxial non-bonded interaction between the methyl and the bulky $-\overset{\ominus}{C}(CN)_2$ group. If however the cyanide ion approaches in the more hindered axial fashion the resulting ion (LXV) (having the bulky $-CH_2.CO_2Me$ and $-\overset{\ominus}{C}(CN)_2$ groupings orientated equatorially) will have the smaller methyl and cyanide groups diaxial and should thus be more stable than the ion (LXIV). This latter statement could also be interpreted by assuming the less hindered equatorial attack of cyanide ion to the conjugated dinitrile (L) in the less stable conformation (LXVI) (with the bulky $-CH_2.CO_2Me$ group axial). This

would afford the less favourable conformation (LXVII) of the ion which would be readily transposed to (LXV). Therefore, if the reaction is thermodynamically controlled, on protonation there should be a greater preponderance of (LIV) over (LXVIII). Though this could not be proved with the trinitriles as separation of the stereoisomers could not be effected, it was later shown to be correct because of the greater proportion of the keto-acid (XXXII; R=H) with the bicyclo[3:3:1]-nonane system to the keto-acid (LIX; R=H). The only pure trinitrile isomer (m.p. 120·5-122°) isolated was shown to be (LIV) by direct conversion to the semicarbazone of the keto-ester (XXXII; R=Me) in good yield.

The triester (LXIX), furnished by the isomer (LXVIII), must afford on Dieckmann reaction the keto-diester (LXX) which on acid hydrolysis afforded 5-methylbicyclo[3:2:1]octan-7-one-1-acetic acid (LIX; R=H), shown to be one of the components of the keto-acid mixture. The trinitrile (LIV) afforded the triester (LXXI) which for cyclisation must adopt conformation (LXXII) in which both bulky substituents are in energetically unfavourable axial positions, which may account for the strongly activating conditions required for the Dieckmann reaction. A mixture of β-keto-esters (LXII) and (LXXIII) was probably formed, each of which

on acid hydrolysis furnished 5-methylbicyclo [3:3:1] - nonan-3-one-1-carboxylic acid (XXXII; R=H), which on the basis of infra-red data was shown to be the crystalline keto-acid isolated.

Trituration of the keto-acid mixtures gave (XXXII; R=H) as the only crystalline form in 36·5% yield, the residue being an approximately 1:1 mixture of keto-acids (XXXII; R=H) and (LIX; R=H), as shown by close examination of the infra-red spectrum and vapour phase chromatogram of the corresponding keto-ester mixture (XXXII; R=Me) and (LIX; R=Me).* It was not possible to separate the keto-acids by chromatography on silica as the mixture was eluted with 5% n-butanol in benzene. The corresponding esters (XXXII; R=Me) and (LIX; R=Me), though not separable by distillation were partially separated by chromatography on silica, the bicyclo [3:2:1] octanone-acetic ester (LIX; R=Me) being eluted first. From the proportion of keto-acids formed it is seen that the ratio of the ions (LXV):(LXIV) is roughly 2:1 at equilibrium.

Wolff-Kishner reduction (42) of the keto-acid (XXXII; R=H) smoothly afforded the parent acid, 5-methylbicyclo [3:3:1] nonane-1-carboxylic acid (LXXIV).

*Footnote: Reaction of the pure keto-acid (XXXII; R=H)

with oxalyl chloride in benzene (43) afforded the corresponding liquid acid chloride (LXXV) in high yield. When a sample of acid chloride, [obtained from slightly impure keto-acid (m.p. 193-112°) contaminated with some of the bicyclo-octanone acid (LIX; R=H)], was treated with ethyl t-butyl malonate, condensation ensued (see later). The fore-run from the distillation of the condensation product on standing overnight afforded crystalline material which was assigned the pseudo acid chloride structure (LXXVI) on the basis of the infra-red absorption at 1811 $cm.^{-1}$ (44). This was further confirmed by the discovery that sodium methoxide effected quantitative conversion to the keto-ester (LIX; R=Me).

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FORMATION OF RING C

In the elaboration of the third ring C of clovene we attempted first to extend the carboxyl function, but to avoid ambiguity we decided to protect the carbonyl function of the keto-ester (XXXII; R=Me) as a ketal. Unexpectedly no reaction occurred with ethylene glycol (45,46) or with ethyl orthoformate (47) and even under the forcing conditions of exchange dioxolanation (48) with the ketal of methyl ethyl ketone and an acid catalyst no ketal formation resulted. The lack of

reactivity of the carbonyl function was also noted when a 2:4-dinitrophenylhydrazone could not be prepared, although a semicarbazone was formed with the less bulky semicarbazide acetate reagent. Again the keto-ester (XXXII; R=Me) was unaffected by sodium borohydride in dry methanol at 0°, though an oily hydroxy-ester resulted from reduction with sodium borohydride in aqueous methanol at room temperature.*

* Footnote: The unreactive nature of the carbonyl function can probably be explained on steric grounds. Attack of a nucleophile ($X^{\ominus}$) on the carbonyl group must change the trigonal C_3 atom in (XXXII; R=Me) to the tetrahedral disposition in which the axial C_3-$O^{\ominus}$ function would experience large steric repulsion from the two axially substituted methylene groups C_6 and C_8 of ring A (see LXXVII).

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As the carbonyl function was so reluctant to ketalise, it was decided to attempt to elaborate the carboxyl function without prior protection of the carbonyl group.

Many attempts were made to convert the keto-acid (XXXII; R=H) to the enedione (LXXVIII) as it was thought that this latter compound should undergo a facile Michael

reaction to furnish a dione (LXXIX) which should readily afford clovene (VI). The obvious conversion of the keto-acid to the enedione (LXXVIII) appeared to be by way of Friedel-Crafts reaction (49) between the acid chloride (LXXV) and isobutene(50). This would afford a β-chloroketone (LXXX) which would readily dehydrochlorinate to the enedione. When the reaction was carried out in cold methylene chloride or ethanol-free chloroform solution with powdered aluminium chloride as catalyst no condensation took place. Condensation of the keto-acid (XXXII; R=H) with isobutene in methylene chloride solution under the catalytic effect of trifluoracetic anhydride (51) also failed to afford more than a trace of neutral material.

As the yields of enedione (LXXVIII) in these experiments were negligible, the acid chloride (LXXV) was condensed with diazoisobutane (52,53) affording the diazoketone (LXXXI). This should be readily converted to the α-chloroketone (LXXXII) (54) which on dehydrochlorination would furnish the enedione (LXXVIII). The diazoketone, which formed in low yield, was stable in ethereal solution but appeared to decompose when the solvent was removed and thus was never obtained pure. The crude product was treated with dry hydrochloric acid

gas (54) to give the α-chloroketone (LXXXII) which was separated from the keto-acid (XXXII; R=H) by washing the product with sodium bicarbonate solution. The α-chloroketone was dehydrohalogenated by treatment with collidine (55) but the infra-red spectrum of the product exhibited only weak conjugated carbonyl absorption, resembling the spectrum of the keto-ester (XXXII; R=Me). The product however exhibited ultra-violet maximum at 240 mμ(ε2,400) equivalent to 20% enedione (LXXVIII) character in the final product or approximately 6% from the acid chloride (LXXV).

Condensation of the acid chloride (LXXV) with diazomethane (32,53) afforded the crystalline diazo-ketone (LXXXIII) albeit in low yield. Even after treatment with a large excess of diazomethane over a long period of time, the recovery of unchanged acid chloride was high. The diazoketone, on treatment with 55% hydroiodic acid (55), was quantitatively converted to the dione (LXXXIV) which gave a positive iodoform test (56) and afforded a bis-2:4-dinitrophenylhydrazone (57).

The next approach to the direct synthesis of the enedione (LXXVIII) was to be a condensation between lithium isobutenyl and the lithium salt of the keto-acid (XXXII; R=H) following a method developed by Braude and

Coles (58,59). Isobutenyl chloride (60) could only be prepared in very low yield by the dehydrochlorination of isobutylidene dichloride afforded by the action of phosphurus pentachloride on isobutyraldehyde (60). Contrary to Braude and Coles (60) there was no evidence for formation of lithium isobutenyl when isobutenyl chloride was reacted with freshly cut lithium metal under strictly anhydrous conditions; thus no attempt was made at a condensation with the lithium salt of the keto-acid (XXXII; R=H).

Following a method devised by Percival, Wagner and Cook (61) for selective action of a Grignard reagent (62) with a carboxylic acid chloride at -65° in the presence of catalytic amounts of ferric chloride, we desired to effect condensation between the acid chloride (LXXV) and methallyl magnesium chloride (63). The initial product would be the unconjugated enedione (LXXXV) which would be equilibrated in basic solution to the conjugated enedione (LXXVIII).

There appeared to be little reaction, the product consisting mainly of a mixture of unreacted acid chloride and keto-acid (XXXII; R=H). The neutral fraction on hydrolysis with dilute sulphuric acid afforded mainly the keto-acid (XXXII; R=H) together with small amounts of

neutral material, the nature of which was determined from the infra-red spectrum of the product. It was found to be a mixture of dimethallyl (63), formed by interaction of two molecules of the Grignard reagent, and the dione (LXXXIV) produced by acid-catalysed equilibration of the enedione (LXXXV) to the enedione (LXXVIII) which then underwent retro-aldol fission.

The enedione (LXXVIII) was eventually synthesised directly from the acid chloride (LXXV) in acceptable yields but in a slightly impure state. The synthetic pathway followed closely the route we had attempted initially, namely the direct condensation of the acid chloride with isobutene in a Friedel-Crafts reaction catalysed by a Lewis acid. Previously it had been shown that with aluminium chloride the yield of enedione had been so poor as to be unacceptable as a synthetic route. With stannic chloride (64,65) however the reaction was effected in far better yield, at least as far as disappearance of acid chloride from reaction mixture was concerned.

Thecondensation was effected in a methylene chloride solution at -5° of a large excess of liquid isobutene with catalytic amounts of stannic chloride. When the reaction was worked up, generally after two days, about

30% of unreacted acid chloride remained. If the crude product however was dissolved in methylene chloride and treated with isobutene and stannic chloride for a further two days, then, on work up, only traces of acid chloride were manifest. It would appear that the isobutene may be removed from the reaction mixture in two ways; one, in a Friedel-Crafts reaction with the acid chloride (LXXV) affording the β-chloroketone (LXXX), the other in a Lewis-acid catalysed polymerisation to a complex mixture of poly-isobutenes. The polymeric mixture could be separated from non-paraffinic material by partition between petroleum and aqueous methanol, but a more efficient method was by filtering a light petroleum solution of the crude product through a short column of alumina (Grade I). This also served to dehydrochlorinate the intermediate β-chloroketone (LXXX) to the enedione (LXXVIII) which was eluted with ether. Extended elution with ether never accounted for more than 80% of acid chloride, yet if the same column was eluted with chloroform three days later, small but significant amounts of the dione (LXXXIV) were furnished. It would appear that the enedione (LXXVIII) adheres strongly to the alumina which is sufficiently basic to

effect a retro-aldol reaction. It is noteworthy that the intermediate β-chloroketone (LXXX) does not dehydrochlorinate when shaken with a cold saturated sodium carbonate solution or when filtered through alumina (Grade III), and only to a small extent when distilled.

The crude enedione, obtained in 70% yield exhibited infra-red absorption at 1710 $cm.^{-1}$ (Cyclohexanone), 1685 $cm.^{-1}$ (conjugated ketone), 1620 $cm.^{-1}$ (olefin) with only a weak band at 1790 $cm.^{-1}$ (acid chloride) and a strong band at 1740 $cm.^{-1}$. The presence of a β:β-disubstituted α:β-unsaturated carbonyl system was characterised by the ultra-violet maximum at 241 mμ though the ε value was only 4000-5000. It was thus apparent that the impurity in the enedione, characterised by the band at 1740 $cm.^{-1}$, was transparent in the ultra-violet, and from the relative intensities of the bands at 1740 $cm.^{-1}$ and at 1685 $cm.^{-1}$ (conjugated ketone) with respect to the cyclohexanone band at 1710 $cm.^{-1}$ it was apparent that the 1740 $cm.^{-1}$ band was associated with some function of the carboxyl group.

An immediate explanation of the nature of the impurity was not obvious but two possibilities were proposed. The first ascribed the 1740 $cm.^{-1}$ band to a

cyclopentanone moiety in the tricyclic dione (LXXIX) which molecule could conceivably arise through a Lewis-acid catalysed cyclisation of the β-chloroketone (LXXX). The second attributed the 1740 $cm.^{-1}$ band to an ester grouping in the keto-ester (XXXII; R=Bu^t) which should readily be afforded by a Lewis-acid catalysed esterification of the keto-acid (XXXII; R=H) with isobutene. Though initially the reaction mixture was strictly anhydrous it was thought that sufficient moisture for hydrolysis of a portion of the acid chloride (LXXV) to the keto-acid (XXXII; R=H) could be incorporated on addition of the extremely hygroscopic stannic chloride.

From analytical data on slightly impure enedione, it was always found that the carbon analysis was low, which would not be consistent with the presence of the isomeric tricyclic dione (LXXIX). However assuming the keto-ester (XXXII; R=Bu^t) to be the impurity, the analytical figures are satisfactorily explained.

The purification of the enedione was an extremely tedious task necessitating careful chromatography on silica; chromatography on alumina or distillation effecting no separation of the impurity from the enedione. Elution with benzene of the crude enedione on silica afforded small amounts of a simple ester, probably arising

from traces of oxalyl chloride in the acid chloride (LXXV) or from impurities in the methylene chloride. Elution with 1% ether in benzene afforded traces of acid chloride (LXXV) together with a complex mixture with infra-red absorption at 1740 $cm.^{-1}$, 1710 $cm.^{-1}$ (cyclohexanone) and 1650 $cm.^{-1}$, the intensity of the 1650 $cm.^{-1}$ band decreasing and the intensity of 1740 $cm.^{-1}$ band increasing with respect to 1710 $cm.^{-1}$ band on continued elution. Further elution with 1% ether in benzene furnished the enedione (LXXVIII) contaminated with the keto-ester (XXXII; R=Bu^t). Elution with 2% ether in benzene immediately afforded the enedione containing progressively less of the keto-ester impurity. Careful rechromatography on silica furnished the enedione still containing the keto-ester impurity, but in lower proportion than in the crude product. Careful fractionation now afforded the enedione (LXXVIII), in pure form, as the lower boiling component of the mixture, with ultra-violet maximum at 241 $m\mu(\varepsilon 12,800)$. The higher boiling fraction contained a mixture of the enedione and the keto-ester (XXXII; R=Bu^t). The latter was never isolated in a pure state either by repeated chromatography and/or fractionation.

As it required a long time to develop successful purification techniques for the enedione, most of the attempts to cyclise the enedione were performed on partially purified material containing significant amounts of the keto-ester impurity.

When the crude β-chloroketone was gently refluxed with 7·5% hydrochloric acid (a), quantitative conversion to the crude enedione resulted. If the resulting enedione was gently refluxed with 6N sulphuric acid (b) however, retro-aldol cleavage ensued affording the dione (LXXXIV), together with the keto-acid (XXXII; R=H) from hydrolysis of the keto-ester impurity (XXXII; R=Bu^t). It was thought that acidic reagents should catalyse the internal Michael reaction of the enedione (LXXVIII) to the tricyclic dione (LXXIX) but as shown above, aqueous acid led to preferential retro-aldol fission. When anhydrous acidic conditions were employed, namely napthalene-2-sulphonic acid (c) (66) in refluxing benzene solution, the enedione was recovered unchanged though the intensity of the 1740$cm.^{-1}$ band in the infra-red spectrum of the product had decreased with concomitant product of the keto-acid (XXXII; R=H). This may be ascribed to a slow thermal decomposition of the t-butyl group in the keto-ester (XXXII; R=Bu^t) catalysed by the sulphonic acid (67).

As the Michael reaction (36) is supposedly an exothermic reaction it was thought that a Lewis-acid might catalyse the cyclisation if the reaction were carried out at room temperature over a period of days. However the crude enedione was recovered completely unchanged when so treated with either anhydrous stannic chloride (d) or with boron trifluoride (e) in glacial acetic acid.

Following a method employed by Woodward and his co-workers (68) for the internal Michael cyclisation of β-santonin to meta-santonic acid (69), the crude enedione was gently refluxed with aqueous methanolic potassium hydroxide (f). The acidic fraction of the product was shown to be the keto-acid (XXXII; R=H) formed by saponification of the keto-ester impurity (XXXII; R=But). The neutral fraction was composed of traces of unreacted enedione and keto-ester (XXXII; R=But) with the dione (LXXXIV), furnished by retro-aldol fission, as the main component. Prolonged treatment of the crude enedione with sodium methoxide (g) (70) in refluxing methanol slowly afforded the keto-acid (XXXII; R=H) and the dione (LXXXIV), and the same mixture was furnished by refluxing a methanolic solution of the crude enedione with N-benzyl trimethyl ammonium methoxide (h) (71). When the crude enedione

was refluxed with potassium acetate (i) in glacial acetic acid no reaction occurred, the material being recovered unchanged.

It was thought that one reason for non-cyclisation of the enedione might be that an anion was not being formed adjacent to the cyclohexanone group, thus necessitating a stronger base. When sodamide (j) (72) in refluxing benzene solution was employed, ammonia was evolved as would be expected if the anion were formed, but the product appeared to be a complex mixture comprising the keto-acid (XXXII; R=H), unchanged enedione and possibly the corresponding β-aminoketone of the enedione (LXXVIII).

Again as the Michael reaction is reputed to be exothermic (36) it was thought that the catalytic effect of a strong base in non-aqueous solution over a long period of time at low temperature might effect the desired cyclisation of the enedione. However the crude enedione was recovered completely unchanged when so treated with a large excess of potassium t-butoxide (k) (73) in cold xylene, similar results being obtained with sodium t-amylate (l) (74) in cold benzene. With sodium t-amylate (m) in refluxing t- amyl alcohol, however,

the infra-red spectrum of the product showed decreased intensity of the bands at 1685 $cm.^{-1}$ and 1620 $cm.^{-1}$ attributed to the conjugated ketone. Careful chromatography of the product on alumina did not afford any homogeneous fractions, the infra-red spectra of the fractions showing complex decomposition to have taken place. As a last resort a "push-pull" reaction (75) was attempted, pyridine (n) (76) being used to remove a proton from the methylene group adjacent to the cyclohexanone in the enedione (LXXVII) and p-toluene-sulphonyl chloride (n) (76) to "pull" or polarise the conjugated carbonyl group towards the oxygen with production of a partial positive charge at the β-position. Not unexpectedly the enedione was recovered unchanged from this treatment.

In the above series of experiments no evidence was ever obtained for the production of the tricyclic dione (LXXIX) from the bicyclic enedione (LXXVIII). It is readily seen that the conjugated ketone function is necessarily planar with free rotation about the single bond of the O=C-C-moiety only. In the closest approach of the β-position of the enone, necessary for bonding, to the C_2 methylene group α to the cyclohexanone carbonyl, the bulky methyl group attached to the β-position of the

enone is extremely close to the methylene group. From studies of molecular models it can be seen that this non-bonded steric repulsion is sufficient to retain the β-position of the enone outwith bonding distance. In the intermediate β-chloroketone (LXXX) however, the bonds attached to the β-carbon atom are tetrahedrally disposed which means that, in the closest approach of the β-position to the methylene group, the bulky β-methyl groups can take up sterically more favourable positions staggered with respect to the C_1-C_2-C_3 plane. Thus in the β-chloroketone there appears to be a greater chance of cyclisation taking place, which was our reason for suggesting that the by-product in the preparation of the enedione with the infra-red band at 1740 $cm.^{-1}$ could conceivably be the tricyclic dione (LXXIX). Again, if the tricyclic dione were attacked by hydroxide ion (or equivalent) at the cyclopentanone carbonyl with concomitant retro-aldol fission (LXXXVI) a mechanism exists whereby the production of the keto-acid (XXXII; R=H) from the crude enedione can be explained without recourse to assuming the presence of an ester. From the accumulated evidence however it seems most unlikely that this is the correct explanation.

One further explanation of the impracticability of converting the enedione to the tricyclic dione lies in the reversible nature of the Michael reaction, the equilibrium lying mainly towards the bicyclic enedione form rather than the closed tricyclic form. From the wide range of reagents, temperature and length of reaction time however used in the attempted cyclisation of the enedione it seems unlikely that this last explanation is valid.

It was thought that the possibility of effecting an internal cyclisation of the enedione (LXXVIII) might be greatly increased if the $\alpha:\beta$-unsaturated ketone moiety could be polarised in an irreversible manner towards the carbonyl group, so creating a large electron deficiency at the β-carbon atom. With this in view, we desired to selectively reduce the enedione (LXXVIII) to the ketol (LV; R=H) the p-toluenesulphonate of which should be highly polarised in the desired fashion. Treatment of this keto-tosylate (LXXXVII; R=p-Me.C_6H_4.SO_2-) under basic conditions should then afford a tricyclic ketone (LXXXVIII) readily convertible to clovene (VI). (cf. the facile conversion of the tosylate of 4-hydroxycyclo-hexanone to bicyclo[3:1:0]hexan-2-one with potassium

t-butoxide in t-butanol (77)).

When the crude enedione (LXXVIII) was treated with an excess of sodium borohydride in aqueous methanol at room temperature the desired selective reduction of the enone did occur as indicated by the infra-red spectrum of the product which showed a large decrease in intensity of the bands at 1685 and 1620 cm^{-1} (enone) with retention of the strong band at 1710 cm^{-1} (cyclohexanone). The infra-red spectrum of the product was also most informative in that it indicated that the intensity of the band at 1740 cm^{-1} was not reduced during the course of reduction. This can be explained only by it representing the ester frequency in the keto-ester (XXXII; R=Bu^t) and not the cyclopentanone carbonyl in the tricyclic dione (LXXIX). If it were the latter, the cyclopentanone carbonyl function, being subject to the same steric factors as the carbonyl group in the enone of the enedione (LXXVIII), should be reduced with consequent reduction in intensity of the band at 1740 cm^{-1}.

When the crude ketol was subjected to careful chromatography on silica it was found that, after removal of traces of enedione and acid chloride (LXXV)

with 1% ether in benzene, the ketol (LXXVII) in admixture with the keto-ester (XXXII; R=Bu^t) was eluted with 5% ether in benzene. Further elution with ether afforded a syrup, presumably resulting from reduction of both carbonyl groups in the enedione (LXXVIII) as the infra-red spectrum exhibited a broad band at 3500 cm.$^{-1}$ (hydroxyl) with only weak bands in the carbonyl region. Careful reduction of purer enedione was thus required. Almost quantitative production of the ketol (LXXXVII; R=H) was afforded if the pure enedione was treated with only a slight excess of sodium borohydride in dry methanol at 0°. During purification of the ketol it was noted that, for effective fractionation, pressures of not higher than 0·01 mm. must be employed. At higher pressures, with consequently higher distillation temperatures, it was found that the ketol was partially dehydrated to the dieneone (LXXXIX) as evidenced by the appearance of weak bands at 1645 cm.$^{-1}$ and 1605 cm.$^{-1}$ (conjugated diene) in the infra-red spectrum (33). It is interesting that under the acidic conditions of work-up, the ketol showed no tendency to undergo an allyl alcohol rearrangement, the gradient of the end-absorption in the ultra-violet spectrum indicating a tri-substituted double bond (78,79)

also evidenced by the fact that the ketol was quantitatively converted to the corresponding acetate (LXXXVII; R=CH_3.CO) in the cold.

After a pyridine solution of the crude ketol (LXXVII; R=H) had been warmed with a slight excess of p-toluenesulphonyl chloride for 2 hours, the infra-red spectrum of the product indicated slow disappearance of the hydroxyl band (3500 cm^{-1}) with concomitant appearance of bands at 1600, 1290 and 1275 cm^{-1} attributed to the keto-tosylate (LXXXVII; R=p-$CH_3.C_6H_4.SO_2$). Further treatment with p-toluenesulphonyl chloride at room temperature for 18 hours resulted in complete reaction of the hydroxyl function. It was later shown that, during the initial warmed reaction, the keto-tosylate first formed, slowly thermally decomposed to the dieneone (LXXXIX), because the proportion of dienone did not increase with further conversion of ketol to keto-tosylate in the cold. When the product was chromatographed on alumina, benzene eluted the bulk of the material as mainly the keto-tosylate (LXXXVII; R=p-$CH_3.C_6H_4.SO_2$) containing 36% dieneone (LXXXIX) character from the ultra-violet maximum at 230 mμ (ε 8,500). Further elution with ether afforded a mixture of the keto-tosylate, keto-ester (XXXII; R=Bu^t) (through incomplete purification

of the ketol (LXXXVII; R=H)) and 19% dienone (LXXXIX), from the ultra-violet maximum at 230 mμ(ε4,500). As, at the time of preparation of the keto-tosylate, the presence of the dienone (LXXXIX) was not fully recognised; the crude keto-tosylate was treated with sodium t-amylate in refluxing t-amyl alcohol in the hope of effecting cyclisation to the tricyclic ketone (LI). Chromatography of the product on alumina afforded the dienone (LXXXIX) as a sweet-smelling volatile oil, as the principal component of the benzene eluate. Further elution with ether afforded a thick oil which was shown to be a complex mixture of at least keto-ester (XXXII; R=Bu^t), dienone (LXXXIX) and hydroxylic material, from the infra-red spectrum.

A pyridine solution of the ketol (LXXXVII; R=H) was treated with p-bromobenzenesulphonyl chloride (80) as it was thought that the resulting p-bromobenzenesulphonate would be more crystalline and more reactive (81) than the corresponding p-toluenesulphonate. When the reaction was carried out in the cold, the ketol was recovered unchanged together with a small amount of crystalline material (m.p. 168-172°). As the infra-red spectrum of the product exhibited only aromatic absorption, it was assigned the p-bromobenzenesulphonic anhydride structure

when the reaction mixture was warmed on a steam bath for 2 hours, however, reaction did occur. The product was chromatographed on alumina and elution with benzene afforded the dienone (LXXXIX) as a volatile sweet-smelling oil in 73% yield. The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohenanone), 3050, 1645, 1610, 973 and888 $cm.^{-1}$ (disubstituted conjugated trans diene) with ultra-violet maximum at 230 mμ(ε23,900) characteristic of a disubstituted conjugated trans diene. Further elution with ether afforded the keto-brosylate (LXXXVII; R=p-Br.C_6H_4.SO_2) as small amounts of a non-crystallisable glass which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 3100, 1620 and 1580 $cm.^{-1}$ (aromatic bands of p-bromo-bensenesulphonate).

The ketol (LXXXVII; R=H) was readily acetylated in the cold with acetic anhydride in pyridine, without concomitant formation of dienone (LXXXIX). The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 1740 and 1240 $cm.^{-1}$ (acetate) with end-absorption in the ultra-violet characteristic of a trisubstituted olefinic double bond (78,79).

As the original intention of synthesising clovene (VI) directly from the keto-acid (XXXII; R=H) and a four-carbon unit had met with very limited success it was thought that a two-stage process might be more practicable.

Thus we constructed the dione-ester (XC) containing a reactive methylene group which we hoped would condense in a Knoevenagel reaction with acetone affording an intermediate dione-ester (XCI), which would be readily converted to the desired dione (LXXIX) containing the fifteen carbon atoms of the clovene skeleton correctly placed.

The acid chloride (LXXV) condensed with ethyl sodio-acetoacetate (82) affording in moderate yield the dione-diester (XCII; R=Me), which was unstable to heat and could not be selectively hydrolysed and decarboxylated to the dione-ester (XC) (83), nor converted to the trione (XCIII).

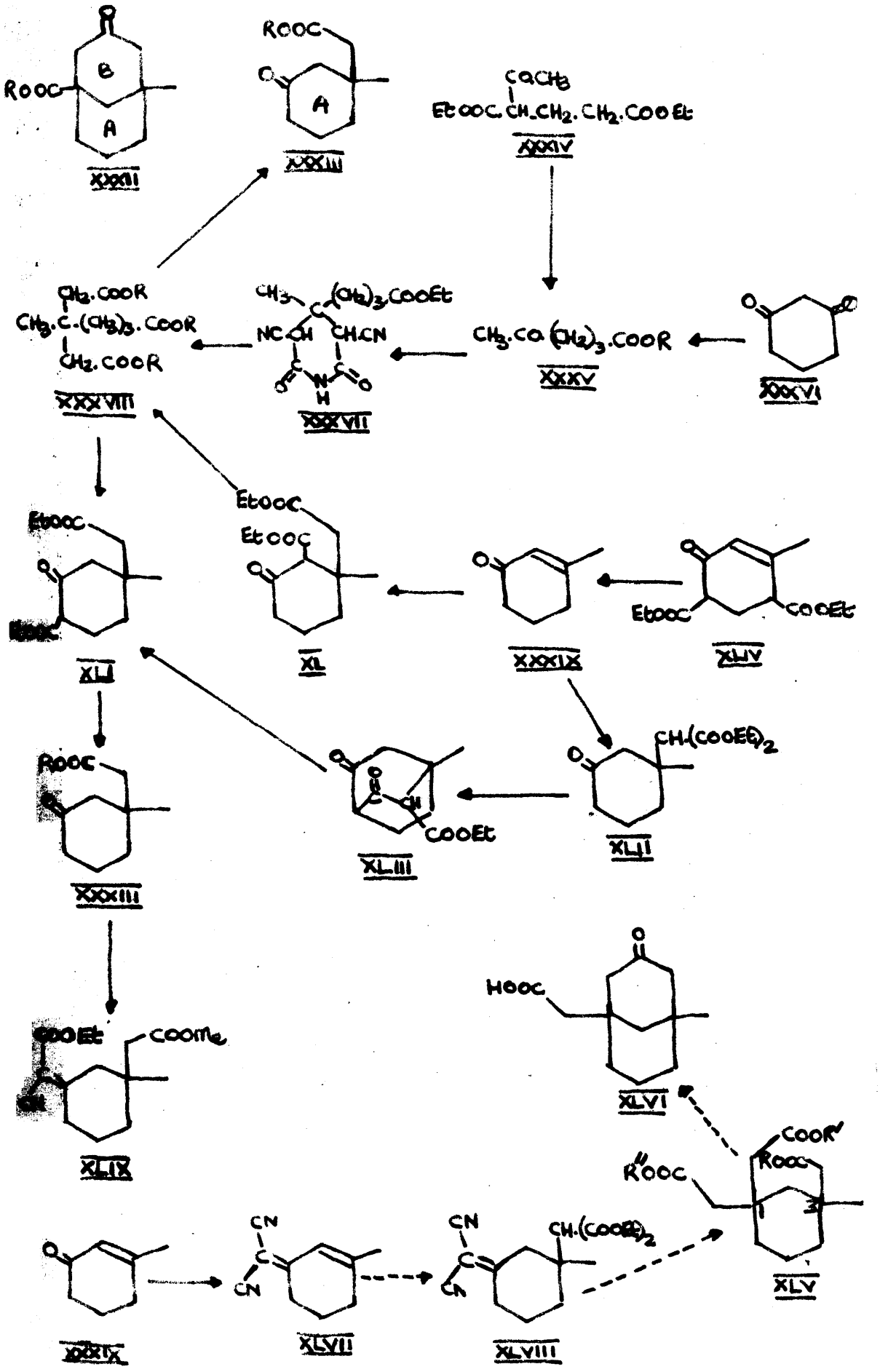
The dione-ester (XC) was successfully prepared in good yield by condensing the acid chloride (LXXV) with the ethoxymagnesium derivative of ethyl t-butyl malonate (67). The t-butoxycarbonyl group was selectively removed from the intermediate dione-diester (XCII; R=t-BuO) by warming in benzene solution with p-toluensulphonic acid (67).

Attempts were made to condense the dione-ester (XC) with acetone in a Knoevenagel reaction under varied conditions employing a variety of catalysts. No condensation ensued when piperidine or ω-aminocaproic acid (84) were employed in conjunction with glacial acetic acid. A further attempt at the Knoevenagel reaction was made by saturating an acetone solution of the dione-ester (XC) with dry hydrogen chloride at 0° (85,86) and dehydrochlorinating the crude product by extended treatment with piperidine. Mesityl oxide, a by-product of the reaction, was removed by evaporation under reduced pressure, but the resulting oil decomposed with loss of hydrogen chloride despite repeated treatment with piperidine and chromatography on silica. The infra-red and ultra-violet absorption spectra of the product were slightly different from the starting material and were compatible with the formation of the dione-ester (XCI). That no cyclisation to a tricyclic system had occurred was shown when acidic hydrolysis of the product afforded no acidic material and the dione (LXXXIV) as the only neutral fragment. The nature of this product, furnished by hydrolysis and an acid-catalysed retro-aldol reaction, was shown by its characteristic infra-red absorption spectrum and by conversion to a bis 2:4-dinitrophenyl-hydrazone identical to a sample prepared from authentic dione.

One final attempt to construct a suitable intermediate from the keto-acid (XXXII; R=H) was made. The potassium salt of the acid, prepared in situ, readily condensed with chloroacetone (87) affording the acetol ester (XCIV) in high yield. It was expected that this compound would readily undergo a base-catalysed internal aldol reaction with dehydration furnishing the keto-lactone (XCV). This compound, which would contain the reactive conjugated ketone and δ-lactone groupings, should have interesting properties and should also serve as a precursor of clovenic acid (VII).

The acetol ester was recovered unchanged when refluxed for 2 hours with pyridine and diethylamine in benzene, and when refluxed for 2 hours with excess potassium t-butoxide in xylene. When treated with one equivalent of sodium hydroxide, the acetol ester, in cold methanolic solution, was almost quantitatively saponified to the keto-acid (XXXII; R=H). There was only slight reaction when a benzene solution of the acetol ester was treated with a benzene solution of methylanilinomagnesium bromide (88). The infra-red spectrum of the product was almost identical with that of starting material but exhibited weak absorption at 3500 $cm.^{-1}$ (hydroxyl).

As all attempts to furnish a tricyclic system by extension of the carboxyl function in the keto-acid (XXXII; R=H) had failed we attempted to effect a condensation at the C_2 position of the keto-ester (XXXII; R=Me) (89) and so build on the third ring. Extended treatment of the keto-ester with sodamide afforded ammonia and doubtless an equilibrium mixture of the anion of the keto-ester with the negative charge being manifest at either C_2 or C_4 positions. Attempts at a nucleophilic displacement of bromine from ethyl α-bromoisobutyrate failed completely, probably due to the large steric hindrance to approach of the bulky bromo-ester to within bonding distance.


ROOC
B
A
XXXII
ROOC
A
XXXIII
CO.CH3
Et OOC. CH. CH2. CH2. COOEt
XXXIV
CH2. COOR
CH3. C. (CH2)3. COOR
CH2. COOR
XXXVIII
CH3
C
(CH2)3 COOEt
NC. CH
CH. CN
XXXVII
CH3. CO. (CH2)3. COOR
XXXV
XXXVI
Et OOC
Et OOC
XL
XXXIX
Et OOC
COOEt
XLIV
XLI
ROOC
XXXIII
CH. (COOEt)2
XLII
XLIII
COOEt
COOEt
COOMe
XLIX
HOOC
XLVI
COOR'
ROOC
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XLV
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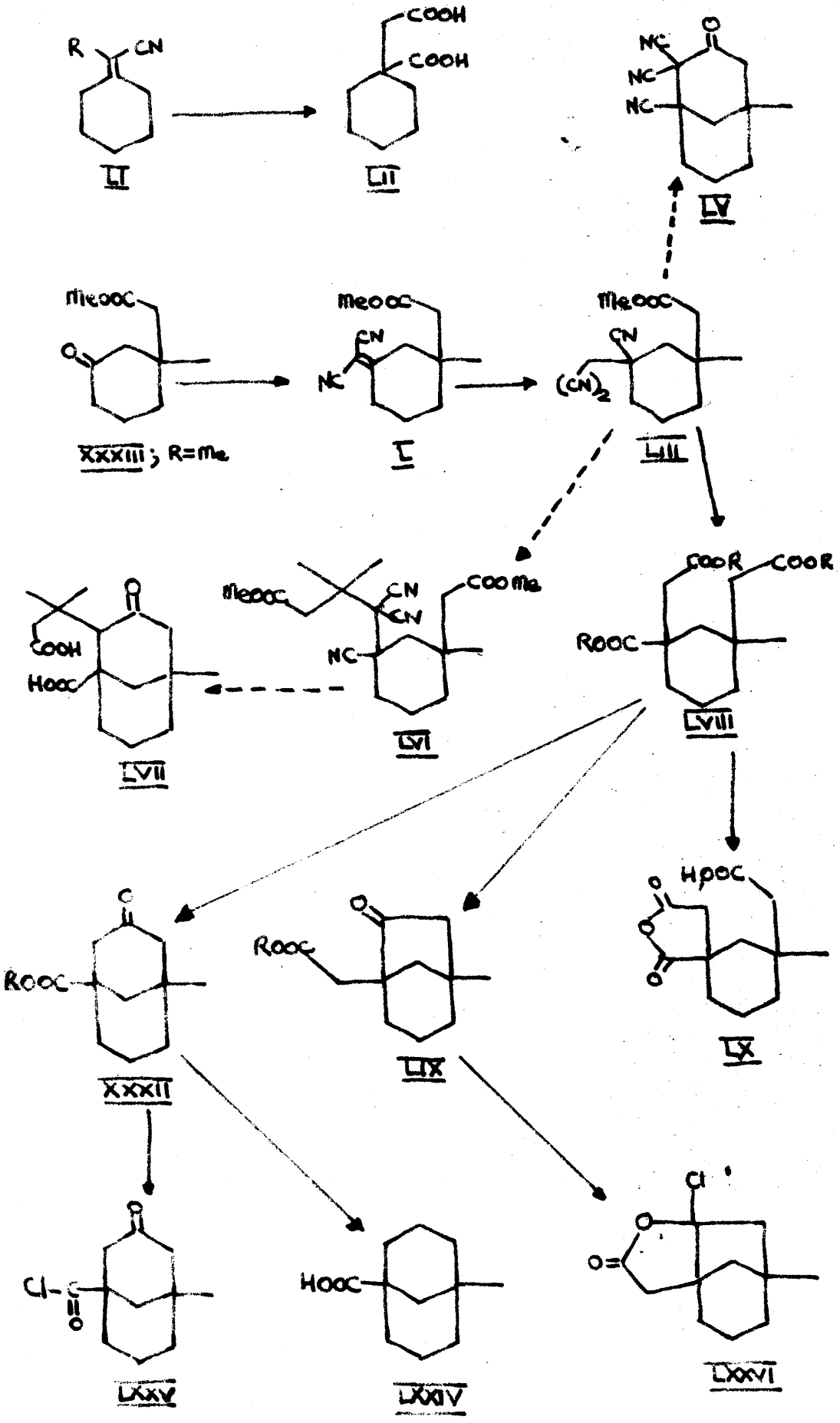
CN
C
CN
XLVII
CN
C
CH
CH. (COOEt)2
XLVIII



II

III

IV

XXXIII; R=Me

I

LIII

LVII

LVI

LVIII

XXXII

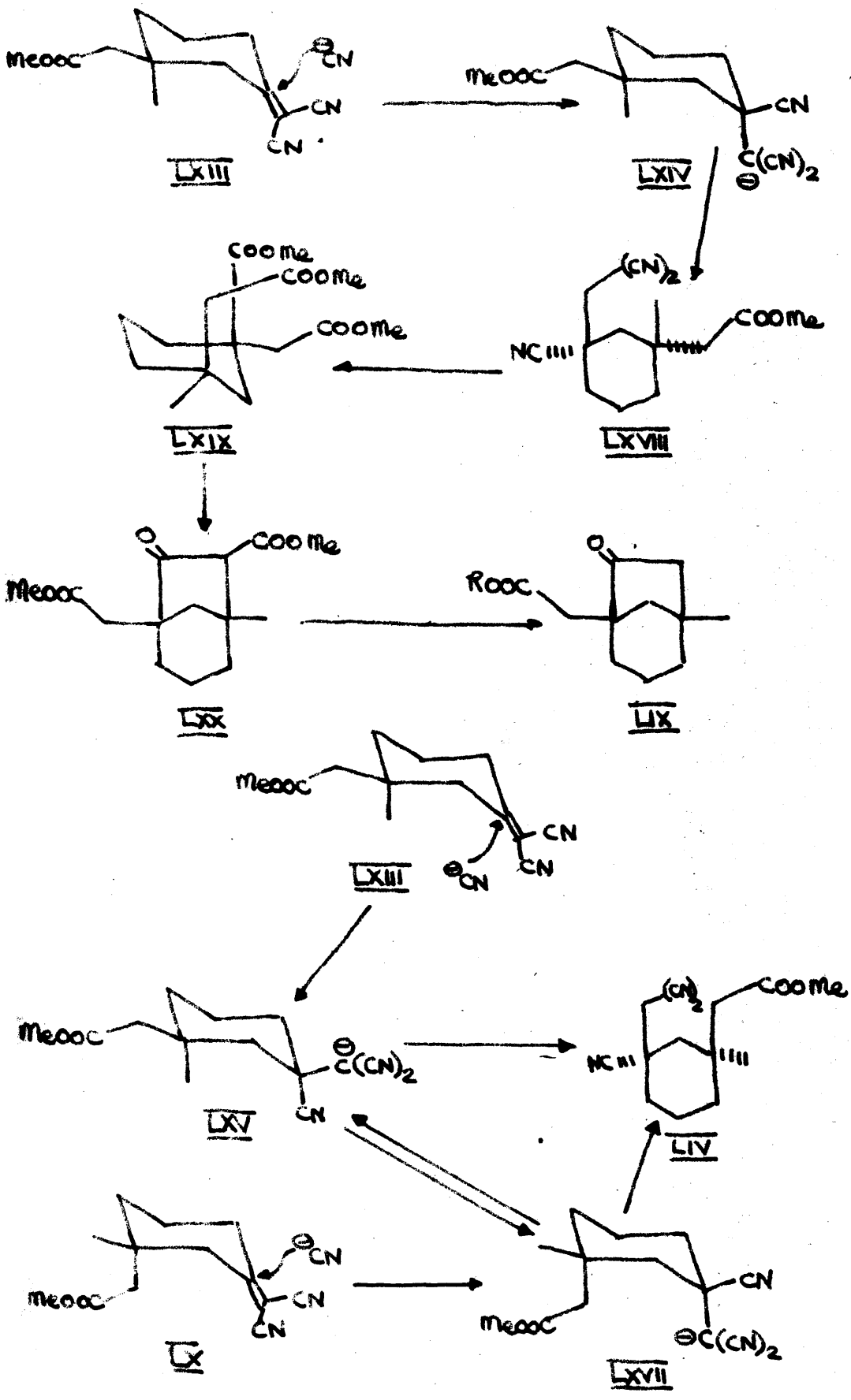
LIX

LX

LXXV

LXXIV

LXXVI


MeOOC
CN
CN
CN
LXIII
MeOOC
CN
C(CN)2
LXIV
COOMe
COOMe
COOMe
LXIX
(CN)2
NC
COOMe
LXVIII
O
COOMe
MeOOC
LXX
O
ROOC
LIX
MeOOC
CN
CN
LXIII
MeOOC
C(CN)2
CN
LXV
(CN)2
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NC
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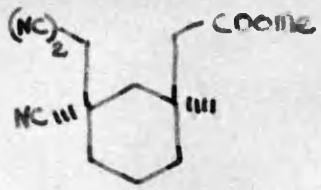
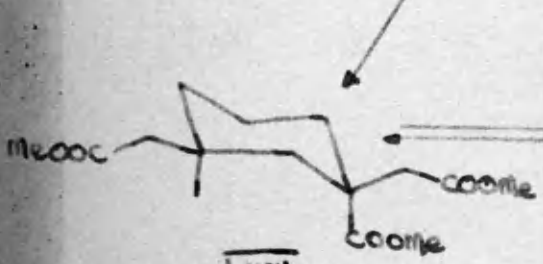
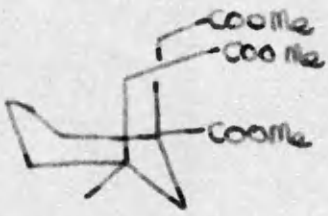
CN
CN
CN
LX
MeOOC
CN
C(CN)2
LXVII



LIV



LXXI



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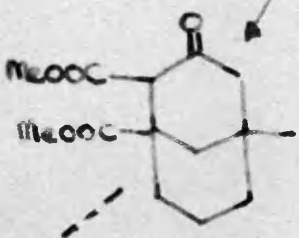
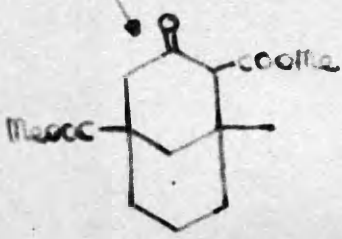


LXII



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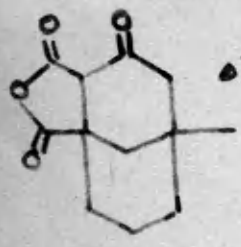
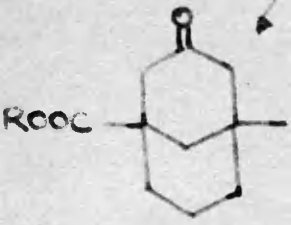
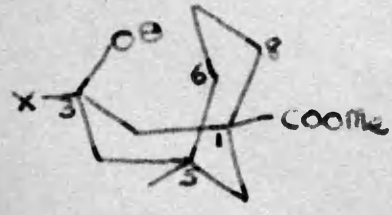


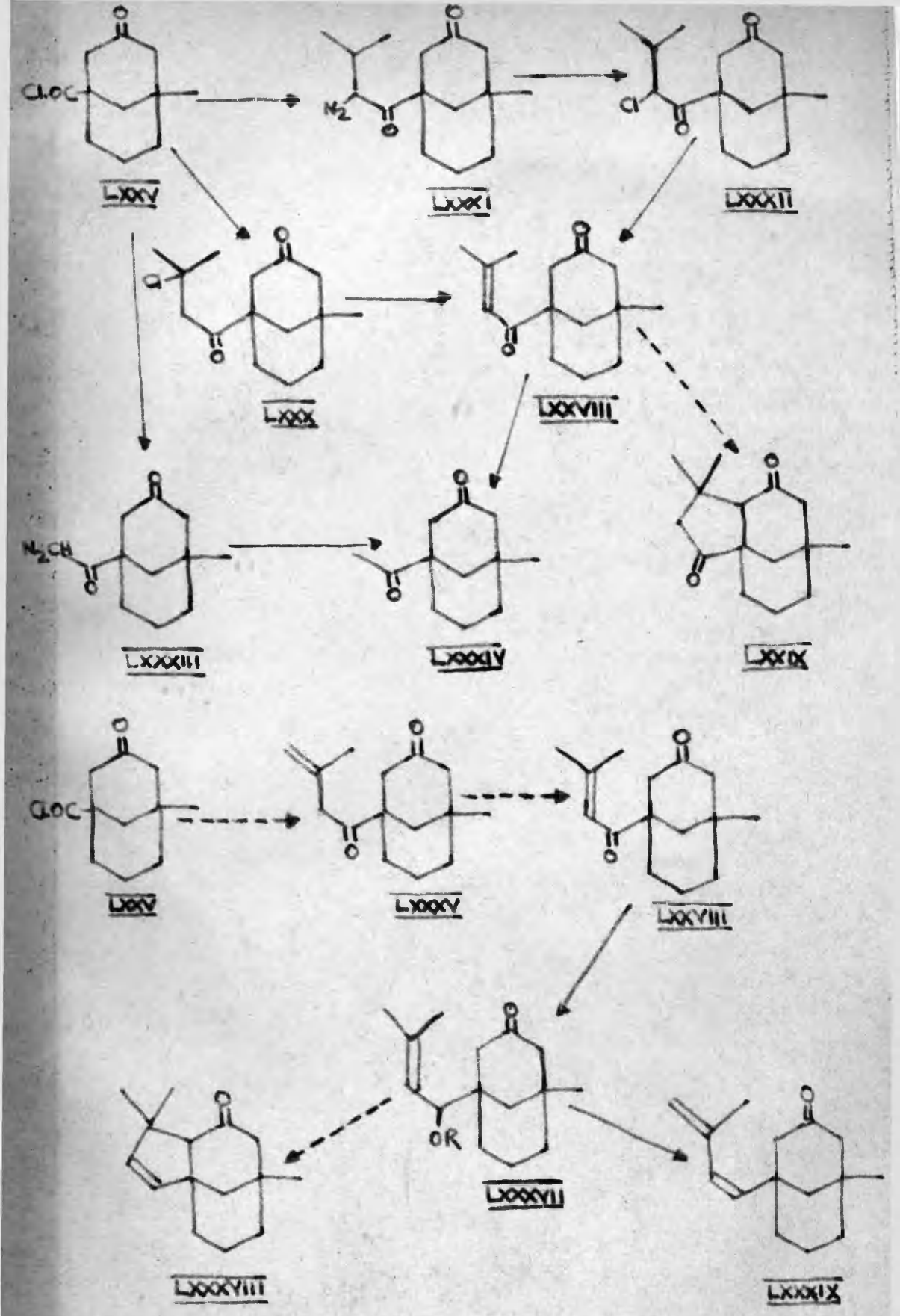
LXI

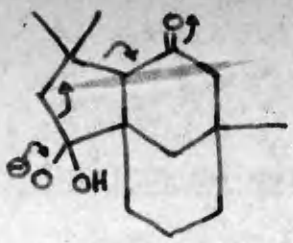


XXXII

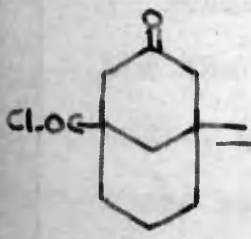


LXXVII

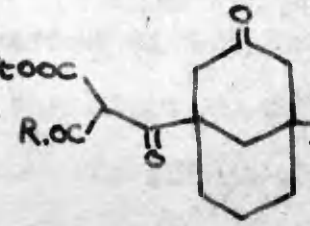

ClOC
LXXV
N2
LXXI
Cl
LXXII
Cl
LXXX
LXXVIII
N2CH
LXXXIII
LXXIV
LXXIX
ClOC
LXXV
LXXXV
LXXVIII
OR
LXXXVII
LXXXVIII
LXXXIX



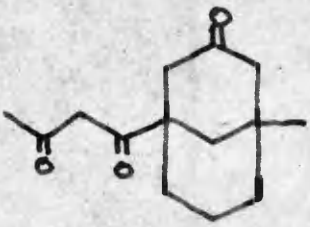
LXXXVI



LXXV



XCII



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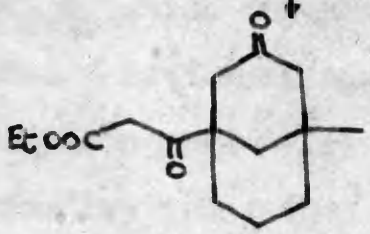
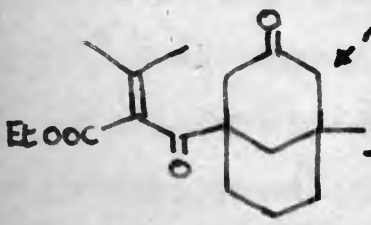
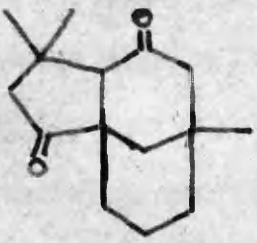


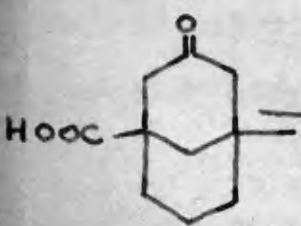
XC



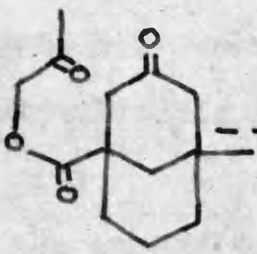
XCI



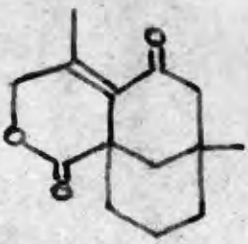
LXXIX



XXXII; R=H



XCIV



XCV

LITERATURE SURVEY of Bicyclo[3:3:1]nonane system

Rabe and his school, who were primarily concerned with the nature of the isomerism of 1:5 diketones to cyclic keto-alcohols, were the first to synthesise the bicyclo[3:3:1]nonane system. In 1898, Rabe (90) studied the addition of ethyl sodio-acetoacetate to d-carvone in hot ethanol and isolated, after basic hydrolysis, a compound $C_{13}H_{20}O_2$ which did not show the properties of a 1:5-diketone. With Weilinger, Rabe (91, 92) in 1903 studied this reaction more fully and proposed structure (XCVI) for the product. In 1904 (93,94) they suggested that the first step was a Michael addition affording the intermediate 1:5-diketone (XCVII) which was further cyclised by base to give, after hydrolysis, the keto-alcohol (XCVI). The reaction of hydrogen iodide and phosphorus on the corresponding diol afforded an optically inactive hydrocarbon (XCVIII). This work was extended to 3-methylcyclohex-2-enone (XXXIX) (94) and to 3:5-dimethylcyclohex-2-enone (95,96) and the corresponding bicyclic keto-alcohols (XCIX) and (C) produced.

Soon after the inception of the study (90) of the isomerism 1:5-diketones—cyclic keto-alcohols, the

phenomenon of tautomerism was realised. The above rearrangement is not tautomerism under Huckel's definition (97,98) but an irreversible rearrangement under basic conditions (99). The main difficulty in proving this is that basic reagents are generally required for the initial formation of the 1:5-diketones. However diethyl $\alpha:\alpha'$-methylene bisacetoacetate (CI), prepared from formaldehyde and ethyl acetoacetate without a basic condensation agent (90), was easily converted into the isomeric keto-alcohol (CII) with sodium ethoxide. (CI) could be distilled unchanged whereas (CII) decomposed with loss of water and (CII) could not be reconverted to (CI) by chemical means. A sample of (CI) was placed in a sealed tube by Rabe and Elze (100) in 1902 and re-examined forty years later when Rabe (99) showed that there had been absolutely no rearrangement to (CII), thus showing that base is required for the rearrangement.

Theoretically the 1:5-diketone intermediate (CIII) from the condensation of ethyl acetoacetate with 3:5-dimethylcyclohex-2-enone (96) may cyclise to give the bicyclo [3:3:1] nonane system (CIV) or the bicyclo [2:2:2] octane system (CV), depending on which carbonyl group takes part in ring closure. That the

former is formed exclusively was elucidated by Rabe and Appuhn (101) in 1943. The smooth decarboxylation of the intermediate bicyclic keto-ester showed that the ester was β as in (CIV) rather than γ as in (CX) to the ketone. The hydrazone of the resulting keto-alcohol when heated to 180° under nitrogen afforded the alcohol (CVI). That this compound contained a tertiary hydroxyl group was readily shown, as dehydration could not be effected under the most vigorous conditions. This was expected from a consideration of Bredt's rule (102)

Schuler (103) in an interesting addendum suggests that the methyl group (a) in (CII) should be more acidic than the methylene group (b). Also the cyclohexanone grouping should retain its ketonic character, whereas the ketone in the acetoacetate residue should be largely enolic in the basic reaction conditions, thus accounting for the non-formation of the bicyclo[2:2:2]octane system.

A most simple synthesis of the bicyclo[3:3:1]nonane system was developed by Meerwein and Schürmann (104) in 1913. The symetrical dione-tetra-ester (CVII) was prepared, either by treating dimethyl malonate with formaldehyde and refluxing the subsequent mixture of methylenemalonic ester, methylenebismalonic ester and pentanehexacarboxylic ester with sodium methoxide in

dry methanol or more simply by warming dimethyl malonate with methylene iodide and sodium methoxide in dry methanol.

(CVII) shows very interesting properties in that it may be selectively hydrolysed and decarboxylated to either (CVIII), by heating with water in a sealed tube, or to (CIX) by hydrolysis with barium hydroxide and subsequent pyrolysis. Meerwein and his co-workers (105) prepared the diketone (CX) and converted this to the parent hydrocarbon, bicyclo[3:3:1]nonane (CXI), (b.p. 170°; m.p. 145-146°). Reduction of the diketone (CX) with sodium amalgam gave the corresponding 2:6-diol from which one hydroxyl group could be preferentially removed. In the above reduction an interesting by-product (CXII) containing the tricyclo[1,3^2,3^6o]nonane system was obtained and the similar tricyclo[1,3^3,3^7o]-nonane system in (CXIII) was obtained by treating the sodium salt of the dione-tetraester (CVII) with bromine followed by sodium methoxide.

Meerwein (105) made the interesting remark that the geometrical arrangement of carbon atoms in the bicyclo[3:3:1]nonane system (CXI) is identical with the crystal structure assigned to diamond by Bragg (106) and thus these compounds should occur in nature.

The possibility of rearrangements with 1:5-diketones was noted also by Stobbe (107) in 1912. He treated the condensation product of benzalacetophenone and menthone with sodium ethoxide and suggested that the product, either (CXIV) or (CXV) contained the bicyclo[3:3:1]nonane system. This work was repeated by Allan and Ballans (108) in 1933, who carried out the cyclisation with concentrated sulphuric acid in ethanol. Cyclohexanone was treated with benzalacetophenone and further cyclised to give a mixture of stereoisomers of (CXVI).

A facile route to the bicyclo[3:3:1]nonane system has been devised by Bărbulescu (109) in which ethylidenebiscyclohexanone, prepared in 40% yield from cyclohexanone and acetaldehyde, was quantitatively converted to 2-methyl-3,4-tetramethylenebicyclo[3:3:1]-nonan-4-ol-9-one (CXVII) in the presence of hydroxide ion.

Adamantane (CXVIII) is the simplest representative of "diamondoid" compounds, i.e. organic compounds in which the skeletal carbon atoms are arranged in the same order as the carbon atoms in the diamond lattice. As forecast by Meerwein (105), adamantane was isolated by Landa and Machăček (110) from a Hodonin naphtha in 1933, and more recently thioadamantane, in which the sulphur

bridge is probably between the C_3 and the C_7 carbon atoms of bicyclo[3:3:1]nonane, has been isolated from the kerosene fraction of crude Middle East oil distillate (111).

Bottger (112) attempted to synthesise adamantane from Meerwein's dione-tetraester (CVII). Only one further carbon atom need be introduced between the C_3 and C_7 positions and this was achieved by treating the disodium salt of (CVII) with methylene dibromide in a sealed tube. Unfortunately the resulting adamantane dione-tetraester (CXIX) could not be decarboxylated nor could the ketonic functions be converted to methylene groups.

Adamantane was successfully synthesised by Prelog and Seiwerth (113) in 1941 from Meerwein's (104) dione-diester (CIX). A similar condensation with sodium methoxide and methylene bromide afforded dimethyl adamantane-2,6-dione-1,5-dicarboxylate (CXX), which was hydrolysed to the corresponding dione-diacid. Wolff-Kishner reduction afforded a diacid which was decarboxylated over bronze at 400°, in small yield, furnishing adamantane (CXVIII) identical with that of Landa and Machăček (110).

Better yields of diethyl bicyclo[3:3:1]nonane-

2,6-dione-3,7-dicarboxylate (CIX) were obtained (114) by treating diethyl glutaconate with formaldehyde in ethanol, followed by reduction of the tetraethyl 1,6-heptadiene-1,3,5,7-tetracarboxylate over platinum oxide. Dieckmann cyclisation of the latter ester with potassium ethoxide furnished (CIX) in good yield.

In the course of his studies on the validity of Bredt's rule, Prelog (115) had recourse to synthesise some bicyclo[3:3:1] nonane compounds. Wichterle (116) had shown that β-keto-esters could be condensed with 1,3-dichloro-2-butene affording the 3-chlorocrotyl derivative, which on treatment with concentrated sulphuric acid introduced the 3-ketobutyl group. Prelog showed that 1-(3-ketobutyl)-2-cyclanone-1-carboxylic esters (CXXI) when saponified and decarboxylated gave bicyclic α:β unsaturated ketones of structure (CXXII) when n is 6 or 7 and of structure (CXXIII) when n is 9 or more. With n=8 a mixture of (CXXII) and (CXXIII) was formed.

To study the validity of Bredt's rule further Prelog studied the behaviour of 1-(3-chlorocrotyl) derivatives towards concentrated sulphuric acid. In this connection ethyl cyclohexanone-2-carboxylate was treated with 1,3-dichloro-2-butene and sodium ethoxide and the product allowed to react with concentrated sulphuric acid at

room temperature for 5 days, affording ethyl 4-methyl-bicyclo[3:3:1]non-3-ene-9-one-1-carboxylate (CXXIV; R=Et) from which the acid (CXXIV; R=H) was obtained on alkaline hydrolysis. This acid was stable to quinoline at 250°. Recently Julia (117) has shown that cyclohexanone may be condensed with 1,3-dichloro-2-butene under similar conditions and the product cyclised to 4-methylbicyclo[3:3:1]non-3-ene-9-one (CXXV); likewise 2-methylcyclohexanone afforded 1:4-dimethyl bicyclo[3:3:1]non-3-ene-9-one (CXXVI).

A novel synthesis of the bicyclo[3:3:1]nonane system from the readily available dihydroα-ionone (CXXVII) has been developed industrially (118). Thus (CXXVII) with hydrochloric acid in ethanol gives the ethyl ether (CXXVIII; R=Et). Dehydration of the corresponding alcohol (CXXVIII; R=H) afforded a mixture of isomers (CXXIX) and (CXXX). 2,2,6-Trimethyl-9-methylenebicyclo-[3:3:1]non-6-ene (CXXX) has been prepared directly by treatment of dihydroα-ionone (CXXVII) with phosphoric acid (119). Büchi (118) has also shown that treatment of dihydroα-ionone with boron trifluoride in benzine gives the epoxide (CXXXI).

In 1950 Cope (120) suggested that the removal of the carbonyl bridge in compounds containing the

bicyclo[3:3:1] nonan-9-one ring system appeared to offer a promising method for the synthesis of substituted cyclo-öctapolyenes. The most readily prepared compound of this type was (CXVI) already prepared by Allan and Sallans (108). Cope and his co-workers (120) were able to increase the yield in the cyclisation of the intermediate (CXXXII), prepared in 80% yield by the Michael addition of cyclohexanone to benzalacetophenone, to 88% employing hydrochloric acid in acetic acid as condensing agent. When the oxime of (CXVI) was subjected to the Beckmann rearrangement using p-toluenesulphonyl chloride in pyridine, the amide (CXXXIII) was formed in 69% yield. Prolonged acid hydrolysis, followed by Hofmann exhaustive methylation led to 2:4-diphenylcyclo-öcta-1,4-diene (CXXXIV). When (CXVI) and the amide (CXXXIII) were heated with a mixture of sodium hydroxide and potassium hydroxide at 250° quite surprising rearrangements occured. Thus (CXVI) gave (CXXXV) and the amide (CXXXIII) afforded 2,4-diphenylbicyclo[3:3:0]octa-1,4-diene (CXXXVI). Cope and his co-workers (121) have proved the structure of these rearrangement products but as yet have offered no mechanism for their formation.

By condensing cyclohexanone with β-dimethylamino-propiophenone in the presence of sodium hydroxide, followed

by acid cyclisation of the intermediate 1:5-diketone (CXXXVII), Cope and Hermann (122) synthesised 2-phenylbicyclo[3:3:1]non-2-ene-9-one (CXXXVIII), the oxime of which also underwent the Beckmann rearrangement giving the cyclo-öctane ring system.

One of the simplest syntheses of the bicyclo[3:3:1]-nonane system was developed by Cope and Synerholm (123) in 1950. This involved Michael addition of α-carbethoxycyclohexanone to acrolein at -70° followed by cyclisation of the resulting aldehyde with concentrated sulphuric acid giving (CXXXIX; R=Et) in good yields. The first stage of the synthesis may also be accomplished by alkylation of the potassium enolate of α-carbethoxy-cyclohexanone with β-chloropropionaldehyde diethylacetal though the yields are much lower. It is noteworthy that the corresponding acid, (CXXXIX; R=H) obtained by basic hydrolysis of the ester, was resistant to decarboxylation on heating. In the presence of sodium ethoxide the ester (CXXXIX; R=Et) readily underwent a reverse acetoacetic ester condensation giving diethyl cyclo-öct-1-ene-1,5-dicarboxylate (CXL) in good yield (124).

Papadakis (125) has recently extended Cope and Synerholms' method (123) by condensing the potassium salt of 5-(p-methoxyphenyl)-cyclohexan-1,3-dione in a

hydrocarbon solvent with β-chloropropionaldehyde diethylacetal and subsequent ring closure to the dione (CXLI).

A new ring enlargement sequence has been developed by Stork and Landesman (126), who have shown that treatment of the pyrrolidine enamine of cyclohexanone with one equivalent of acrolein in dioxan at 0° affords (CXLII) in 75% yield. As expected (120) when the methiodide of (CXLII) was heated with aqueous base 4-cyclo-öctenecarboxylic acid was formed.

The acid (CXXXIX; R=H) was hydrogenated over palladised barium sulphate to the corresponding dihydro compound, the silver salt of which, with bromine, underwent the Hunsdiecker reaction affording 1-bromobicyclo[3:3:1]nonan-9-one (CXLIII) (123). The structure was proved by conversion to bicyclo[3:3:1]-nonane (CXI), identical with that prepared by Meerwein (105).

It was shown (127) that the α-bromoketone (CXLIII) gave an immediate precipitate of silver bromide with ethanolic silver nitrate with concomitant formation of bicyclo[3:3:0]octane-1-carboxylic acid (CXLIV; R=OH) and the corresponding ethyl ester (CXLIV; R=OEt). The same result was obtained using mercuric acetate in ethanol and with potassium hydroxide in ether, the more usual

reagent for the Favorskii rearrangement. Treatment of the α-bromoketone (CXLIII) with sodamide or sodium in liquid ammonia afforded the corresponding amide (CXLIV; R=NH_2), while reduction of (CXLIII) with lithium aluminium hydride also affected rearrangement to the volatile solid alcohol (CXLV) (124).

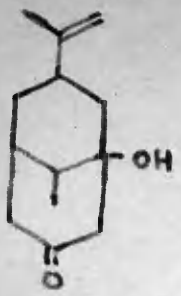
The ability of silver nitrate and mercuric acetate to catalyse the rearrangement can be interpreted in terms of the 'push-pull' mechanism suggested by the work of Swain (75), concerning the termolecular kinetics of S_{N1} and S_{N2} displacements. According to this interpretation, ethanol or water first adds to the carbonyl group, and, establishing the C_5-C_1 bond, supplies the 'push'. The electron pair of the C_5-C_9 bond is in a sterically favourable position to attack the C_1 carbon atom from the backside as the bromine is displaced, aided by the 'pull' by the silver or mercuric ion. Such a process is similar to the commonly accepted mechanism of pinacol rearrangement. Formation of an intermediate cyclopropanone in the rearrangement of (CXLIII) by establishment of a bond between C_5 and C_1 with elimination of hydrogen bromide, postulated for certain Favorskii rearrangements (128) is unlikely. Formation of such an intermediate would require loss of a proton from C_5 to produce an anion, that would not be

stabilised by resonance, for the C_5-C_9 bond could not have partial double bond character without violating Bredt's rule (see ref. 127).

During a recent study of the intermediary ketols in the Robinson annellation reaction, Johnson and his co-workers (129) have shown the presence of the bicyclo[3:3:1] nonane ring system. The C_6 epimeric ketols, produced from the condensation of the tricyclic ketone (CXLVI) with methyl vinyl ketone have been shown to have the bicyclo[3:3:1] nonane ring structure (CXLVII) rather than the formerly proposed constitutions (CXLVIII) and CXLIX) respectively.

It was shown however that the ketol from cyclohexanone and methyl vinyl ketone has the normal structure (CL), but the pair of ketols derived from the octalindione (CLI) have the bridged ring constitution (CLII).

As a result of this work some doubt must be cast on the structural assignments which have been made in other similar cases (see ref. 129 and ref. 7 therein).



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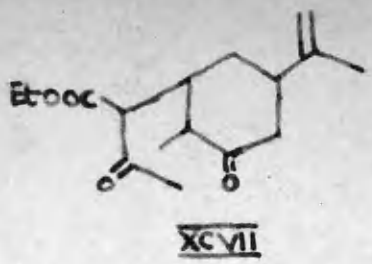
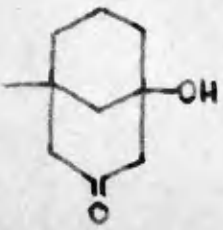


XCVII

XCVIII



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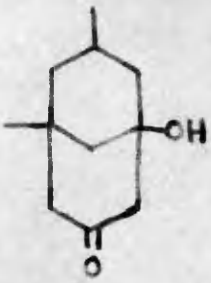

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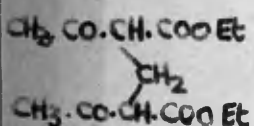

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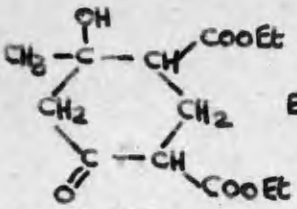

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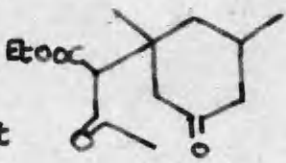

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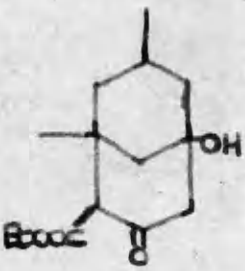

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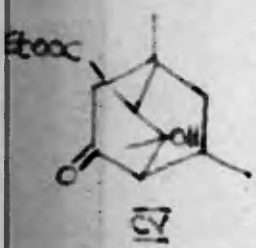

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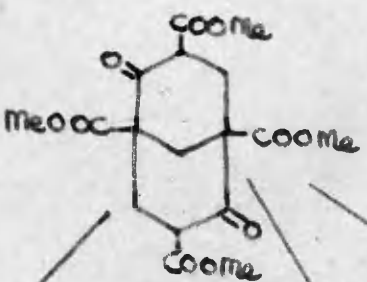

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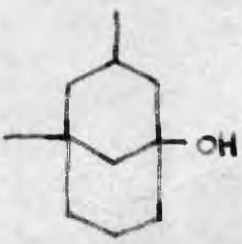

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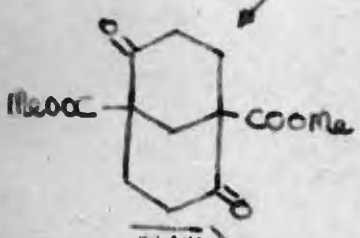

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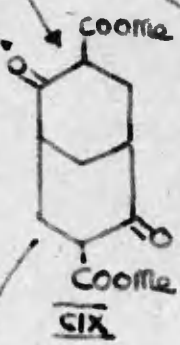

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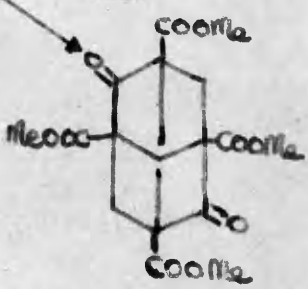

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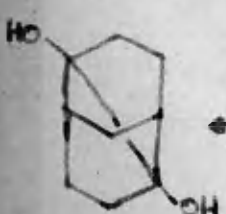

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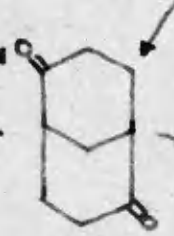
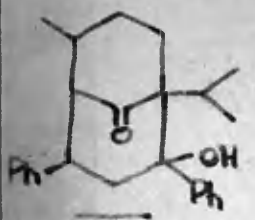


CX

CXI



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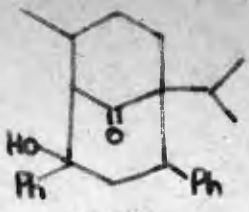

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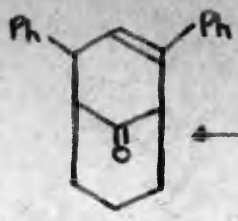

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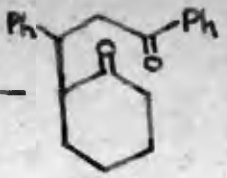

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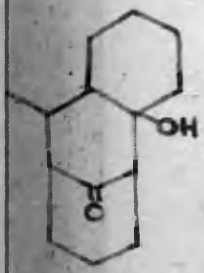

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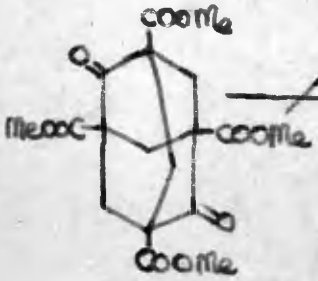

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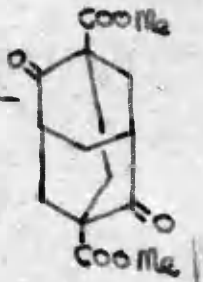

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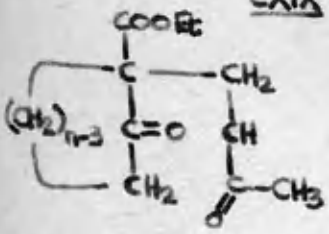

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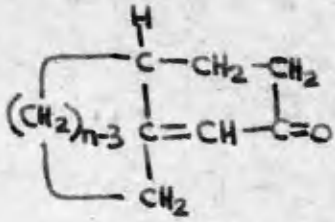

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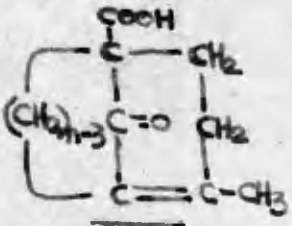

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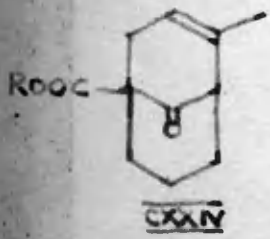

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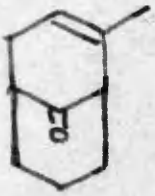

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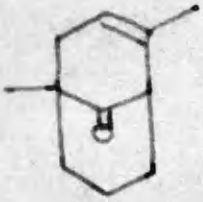

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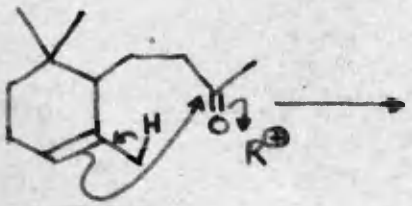

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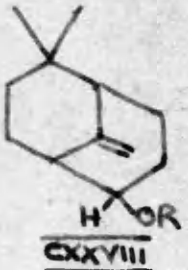

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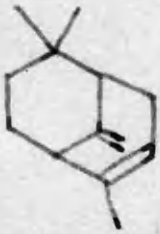

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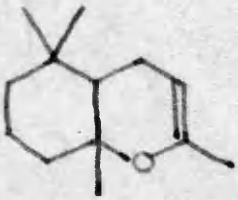

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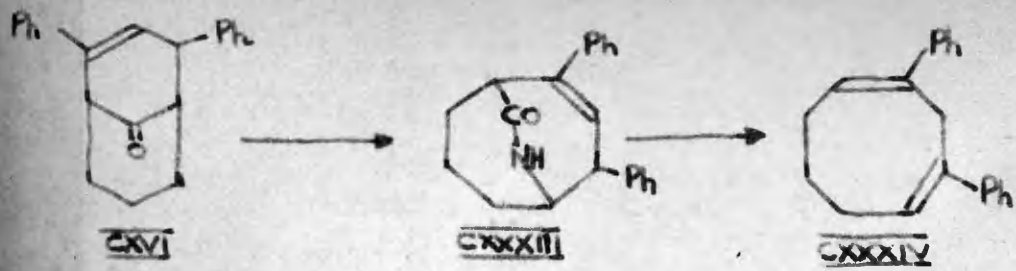

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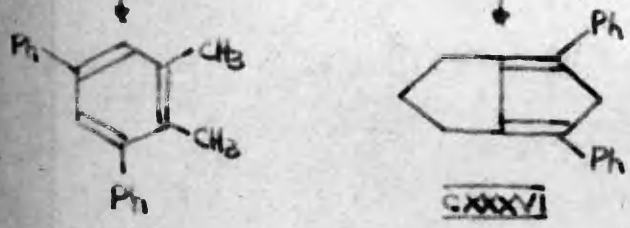

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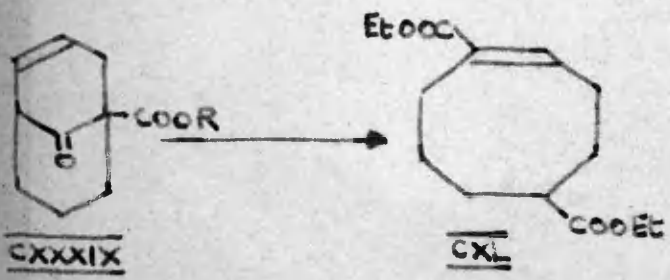

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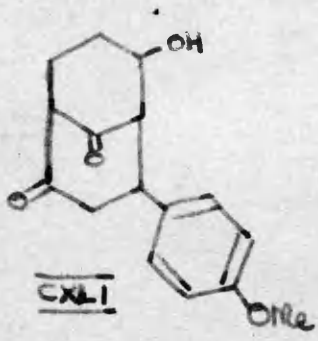

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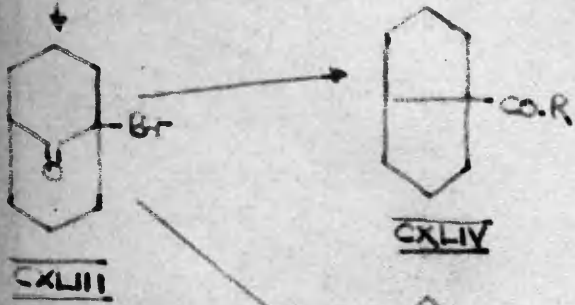

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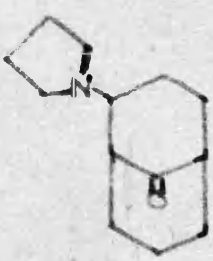

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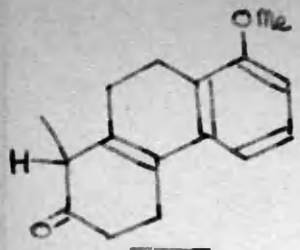

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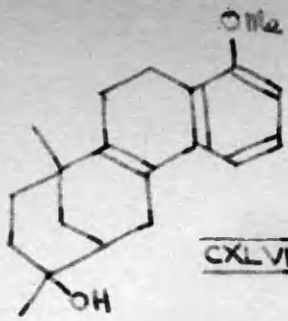

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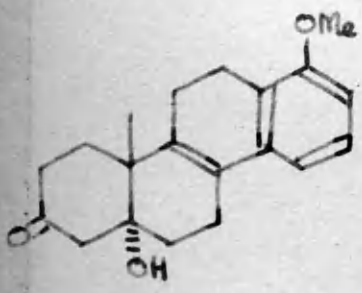

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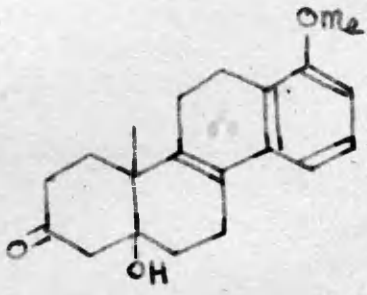

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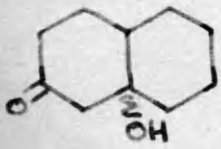

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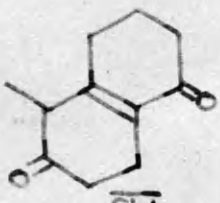

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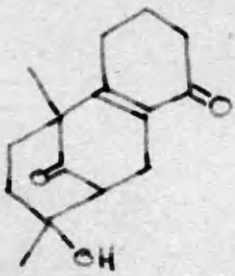

CLII

EXPERIMENTAL

Ultra-violet absorption spectra refer to ethanol solutions, unless stated otherwise, and were measured with a Unicam S.P. 500 spectrophotometer. Infra-red spectra were determined for natural films and nujol mulls on the Perkin-Elmer Infracord spectrophotometer and Perkin-Elmer 13 spectrophotometer.

Melting points (corrected) were determined on a Kofler block. Boiling points are uncorrected.

The alumina used for chromatography (Spence, type H) was acid-washed and activated and graded according to the method of Brockmann and Schodder (130). Light petroleum refers to the fraction of b.p. 40-60° unless stated otherwise.

Gas-liquid chromatography was carried out on a Pye 'Argon Chromatograph' with 46" x 1/5" columns of 5% Apiezon L on Celite 545 (120-150 mesh).

Molecular weights were determined on the Metropolitan Vickers M.S.2 mass spectrometer.

3-Methylcyclohex-2-enone (XXXIX).

Ethyl acetoacetate and paraformaldehyde were condensed in the presence of piperidine according to the method of Cronyn and Riesser (30,31). Hydrolysis of the keto-

diester (XLIV) with 20% sulphuric acid afforded 3-methylcyclohex-2-enone which was fractionated before use.

Ethyl 6-carbethoxy-3-methylcyclohexanone-3-acetate (XLI)

Freshly distilled diethyl malonate (480g. 3 moles) was added dropwise with stirring over 1 hr. to a solution of sodium (70g., 3g. atom) in absolute ethanol (3 l.) at room temperature and stirring continued for 1 hr. after the addition was complete. To the cold solution, 3-methylcyclohex-2-enone (330g., 3 moles) was added dropwise with stirring over 1 hr. and stirring continued at room temperature for five days. The dark red solution was poured on to crushed ice (5 kg.) and carefully acidified with 10% hydrochloric acid. The mixture was thoroughly extracted with ether (3 x 1.5 l.); the combined ethereal extracts washed successively with saturated sodium bicarbonate solution and water, then dried over magnesium sulphate. Evaporation of solvent and starting materials by distillation under 15mm. pressure in an oil bath at 180° afforded a thick red oil (550g.), which on repeated fractionation afforded a colourless oil b.p. 121°/0.13mm., n_D^{20} 1.4696. (Found: C, 62.4; H, 8.1. Calc. for $C_{14}H_{22}O_5$: C, 62.2; H, 8.15%).

3-Methylcyclohexanone-3-acetic acid (XXXIII; R=H)

The crude keto-diester (550g.) was refluxed with 10% hydrochloric acid (3 l.) with vigorous stirring for 2 days until the evolution of carbon dioxide ceased. The cooled mixture was saturated with salt and extracted with ether (4 x 1 l.). The combined ethereal extracts were extracted with saturated sodium carbonate solution and the combined aqueous extracts, after careful acidification with 10% hydrochloric acid, saturated with salt and extracted with ether (3 x 1 l.). The combined ethereal extracts were washed with saturated salt solution and dried over magnesium sulphate. Evaporation of solvent afforded a non-crystallisable thick red oil (220g.) which gave the desired keto-acid on distillation as a colourless oil b.p. 131°-140°/0.25mm.; yield 100g. (20%). Repeated fractionation afforded the pure keto-acid as a colourless oil b.p. 145°/0.52mm., n_D^{20} 1.4840. (Found: C, 63.25; H, 8.2. Calc. for $C_9H_{14}O_3$: C, 63.55; H, 8.25%). Trituration with ligroin afforded a solid which crystallised from ether-light petroleum as colourless prisms m.p. 51-53°. (Lit. (22) m.p. 37°). (Found: C, 63.45; H, 8.2%).

Ethyl 3-methylcyclohexanone-3-acetate (XXXIII; R=Et)

A solution of 3-methylcyclohexanone-3-acetic acid (XXXIII; R=H) (3.4g.) in absolute ethanol (60 ml.) was saturated at 0° with dry hydrogen chloride gas and the solution kept at room temperature overnight. After pouring into ice-cold water (300 ml.), the solution was extracted with carbon tetrachloride (4 x 50 ml.). The combined carbon tetrachloride extracts were washed with dilute sodium carbonate solution and water and dried over magnesium sulphate. After evaporation of solvent the pale yellow oil (3.6g.) was fractionated:-

(1) b.p. 90°/0.7mm., n_D^{21} 1.4616 (1.5g.)

(2) b.p. 200-202°/0.7mm., n_D^{22} 1.4820 (1.5g.).

Refractionation of fraction (1) furnished the ethyl ester (XXXIII; R=Et) as a colourless oil b.p. 82°/0.3mm., n_D^{20} 1.4621. (Found: C, 66.6; H, 9.05. Calc. for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15%).

Refraction of fraction (2) afforded a colourless oil b.p. 162-164°/0.001mm., n_D^{21} 1.4918.

Methyl 3-methylcyclohexanone-3-acetate (XXXIII; R=Me)

A slight excess of a dry ethereal solution of diazomethane (32) was added to a cold solution of 3-methylcyclohexanone-3-acetic acid (XXXIII; R=H) (50g.) in ether (250 ml.). After standing at room temperature

for 2 hrs. the excess diazomethane was decomposed with a little acetic acid and the ethereal solution washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded the methyl ester as a colourless oil b.p. 90-91°/0.5mm., n_D^{20} 1.4666, yield 50gs. (93%). (Found: C, 64.95; H, 8.85. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%). The semicarbazone crystallised from methanol as colourless needles m.p. 150-151.5°. (Found: C, 55.0; H, 8.15. $C_{11}H_{19}O_3N_3$ requires C, 54.75; H, 7.95%).

3-Methylcyclohex-2-enylidenemalononitrile (XLVII)

A solution of malononitrile (6.7g., 0.1 mole) and 3-methylcyclohex-2-enone (XXXIX) (11.3g., 0.11 mole) in dry benzene (25ml.) containing dry ammonium acetate (0.8g.) and glacial acetic acid (1.3g.) was refluxed for 2.5 hrs. under a Dean and Stark apparatus, until 1.7 ml. water was collected. The cooled red solution was washed with dilute sodium carbonate solution, water, then dried over magnesium sulphate. Evaporation of solvent afforded a solid mass which crystallised from methanol as colourless places m.p. 87-88°; yield 8g. (52%) The product exhibited an ultra-violet maximum at 300mμ

(ε23,300). (Found:C,75.9; H, 6.45; N, 17.7. $C_{10}H_{10}N_2$ requires C,75.9; H, 6.35; N, 17.7%).

3-Methyl-3-(dicarbethoxymethyl)-cyclohexylidene-malononitrile (XLVIII)

A solution of freshly distilled diethyl malonate (3.2g., 0.02 mole) in dry ether (40 ml.) was added dropwise with stirring to a solution of sodium (0.46g., 0.02g. atom) in absolute ethanol (12.5 ml.) and dry ether (50 ml.), at room temperature under an atmosphere of nitrogen. Stirring was continued for 0.5 hr. before a solution of 3-methylcyclohex-2-enylidenemalononitrile (XLVII) (3.25g., 0.02 mole) in dry ether (50 ml.) was added dropwise over 0.5 hr, then stirred at room temperature for 14 hrs. The deep red solution was poured into ice-cold water (300 ml.) containing 6N hydrochloric acid (20 ml.), and extracted with ether (2 x 250 ml.). The combined ether extracts were washed with saturated sodium carbonate solution and water, then dried over magnesium sulphate. Evaporation of solvent afforded a non-crystallisable red oil which on distillation furnished diethyl malonate (1.7g) and a thick red oil, which would not distil (b.p. 200°/0.03mm.) nor could it be crystallised. This product exhibited an ultra-violet maximum at 246mμ (ε12,000). Chromatography

on alumina (Grade I) was of no avail as the product was only recoverable in low yield with no improvement of its physical state.

Ethyl 3-methyl-3-carbomethoxymethylcyclohexylidene-cyanoacetate (XLIX)

A solution of methyl 3-methylcyclohexanone-3-acetate (XXXIII; R=Me) (0.96g., 5m. mole) and ethyl cyanoacetate (0.6g., 5m. mole) in dry benzene (20 ml.) containing dry ammonium acetate (0.04g.) and glacial acetic acid (0.08g.) was refluxed for 3.5 hrs. under a Dean and Stark apparatus. The cooled solution was washed with dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a mobile oil (1.4g.) from which the starting materials were removed by distillation b.p. 75-90°/0.5mm. Further distillation afforded a colourless oil (0.2g.) b.p. 140-143°/0.5mm., n_D^{20} 1.4659 which exhibited an ultra-violet maximum at 239mμ (ε4,000).

3-Carbomethoxymethyl-3-methylcyclohexylidenemalononitrile (L)

A solution of methyl 3-methylcyclohexanone-3-acetate (XXXIII; R=Me) (50g., 0.27 mole) and pure malononitrile (25g., 0.38 mole) in dry benzene (1 l.) containing dry ammonium acetate (7.5g.) and glacial acetic acid (10 ml.) was refluxed for 12 hrs. under a Dean and Stark apparatus

until water (4.8 ml., 0.27 mole) was collected. Ammonium acetate (1.5g.) and acetic acid (2 ml.) were then added and the solution refluxed for 24 hrs. Blue silica gel was placed in the water separator to ensure complete removal of water from the reaction mixture. The cooled solution was washed with sodium carbonate solution, water and dried over magnesium sulphate. After evaporation of solvent the residual oil was fractionated. The fore-run, b.p. 58-111°/0.1mm., contained malononitrile and traces of the keto-ester (XXXIII; R=Me), and the product distilled as a colourless oil b.p. 122-123°/0.1mm.; yield 57.2g. (91.5%). Refractionation afforded a sample b.p. 144°/0.3mm., n_D^{19} 1.5068. (Found: C, 67.35; H, 7.0; N, 12.15. $C_{13}H_{16}O_2N_2$ requires C, 67.2; H, 6.95; N, 12.05%). The product exhibited infra-red absorption at 2200cm.$^{-1}$ (conjugated nitrile), 1728cm.$^{-1}$ (carbomethoxyl) and 1597 cm.$^{-1}$ (conjugated olefinic double bond) with an ultra-violet maximum at 239mμ (ε13,500).

Attempted Michael addition of diethylmmalonate to (L)

A solution of redistilled diethyl malonate (810mg., 4,5m. mole) in dry ethanol (20 ml.) was added to a solution of sodium (120mg., 5 mg. atom) in dry ethanol (10 ml.) at room temperature. To the stirred solution was added almost immediately a solution of the dinitrile-

ester (L) (865mg., 3.7 m.mole) in dry ether (10 ml.), followed by dry ether (100 ml.). The solution, which rapidly became golden-yellow in colour, was stirred at room temperature for 24 hrs., then poured into ice-water (1 l.), acidified with dilute hydrochloric acid, saturated with ammonium sulphate, and extracted with ether (2 x 200 ml.). The combined ether extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a pale red mobile oil (1.12g.), which exhibited infra-red absorption at 1730 $cm.^{-1}$ (carboethoxyl) with a weak band at 1644 $cm.^{-1}$ and only extremely weak absorption at 2200 and 1597 $cm.^{-1}$ (conjugated dimitrile), with an ultra-violet maximum at 223mμ (ε4,700). The product was fractionated at 0.1 mm., affording a colourless distillate (0.6g.) with concomitant decomposition of the residue during the distillation.

(1) b.p. 80°, n_D^{23} 1.4230. The product exhibited infra-red absorption at 1735 $cm.^{-1}$ (carboethoxyl), with a weak band at 2285 $cm.^{-1}$ (saturated nitrile) and a weak band at 1644 $cm.^{-1}$, and appeared to be mainly diethylmalonate, (which has b.p. 90°/14mm., n_D^{24} 1.4130).

(2) b.p. 117-125°, n_D^{23} 1.4579. The product exhibited

infra-red absorption at 1727 $cm.^{-1}$ (carboethoxyl), 1708 $cm.^{-1}$ and a medium band at 1644 $cm.^{-1}$, with a weak band at 2285 $cm.^{-1}$ (saturated nitrile). The product gave no test with ferric chloride or with Brady's reagent. (3) b.p. 153-168°, n_D^{23} 1.4840. The product exhibited infra-red absorption at 1730 $cm.^{-1}$ (carboethoxyl), 2200 and 1597 $cm.^{-1}$ (conjugated dinitrile) with a weak band at 2285 $cm.^{-1}$ (saturated nitrile).

Attempted addition of Reformatsky complex to cyclohexylidenemalononitrile (LI; R=CN)

Zinc wool was cut into small pieces and activated by washing with 2% hydrochloric acid, distilled water, alcohol, acetone and dry ether, then dried in a vacuum dessicator. A solution of cyclohexylidenemalononitrile (LI; R=CN) (1.46g., 0.01 mole) and ethyl bromoacetate (2.0g., 0.012 mole) in dry benzene (150 ml.) was added over 1 hr. to purified zinc wool (1.3g., 0.02 g.atom) and the mixture refluxed with stirring. After 2.5 hrs. reflux, the solution was pale green and the zinc wool coated with a green oil. The solution was decanted and refluxed for 2 hrs. with activated zinc wool (2g.) then the process repeated with zinc (2g.) for a further 3 hrs.

The separate cooled complexes were decomposed with glacial acetic acid, poured into a large volume of water

and extracted with ether. The ether extracts were combined with the cooled benzene solution and the combined extracts washed with dilute sulphuric acid, dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a red mobile lachrymatory oil (1.78g.) which exhibited an ultra-violet maximum at 236mμ (ε8800) (conjugated dinitrile). Excess ethyl bromoacetate was removed from the product by prolonged evaporation at 100°/11mm., and the residue fractionated at 0.2mm.

(1) b.p. 50-129°, n_D^{20} 1.5043. The product exhibited infra-red absorption at 2200 and 1595 $cm.^{-1}$ (conjugated dinitrile). (Cyclohexylidenemalononitrile has b.p. 73°/0.1mm., n_D^{17} 1.5132).

(2) b.p. 129-133°, n_D^{20} 1.4872.

(3) b.p. 133-144°, n_D^{21} 1.4791. The product exhibited infra-red absorption at 1723 $cm.^{-1}$ (carboethoxyl) with medium bands at 2200 and 1593 $cm.^{-1}$ (conjugated dinitrile).

(4) b.p. 144-190°, n_D^{21} 1.4820. The product exhibited infra-red absorption at 1723 $cm.^{-1}$ (carboethoxyl), with a weak band at 2153 $cm.^{-1}$ (saturated nitrile) with medium bands at 1670 and 1618 $cm.^{-1}$ (conjugated carbonyl), and with weak bands at 2200 and 1593 $cm.^{-1}$ (conjugated dinitrile).

3-Carbomethoxymethyl-3-methyl-1-cyano-1-dicyanomethylcyclohexane (LIII)

(a) A solution of potassium cyanide (1.6g. 0.025 mole) in water (25 ml.) was added to a solution of 3-methyl-3-carbomethoxymethylcyclohexylidenemalononitrile (L) (2.3g., 0.01 mole) in ethanol (100 ml.) and the resulting solution allowed to stand at room temperature for 2 days then shaken vigorously for 24 hrs. After removal of ethanol under reduced pressure without heating, the solution was carefully acidified with 6N sulphuric acid and the hydrogen cyanide removed under reduced pressure before extracting with ether (3 x 50 ml.). The combined ether extracts were washed with saturated sodium bicarbonate solution, saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a thick red oil (2.66g.) which on trituration with methanol afforded the trinitrile as a white powder m.p. 90-115°; yield 0.59g. (23%).

(b) 3-Carbomethoxymethyl-3-methylcyclohexylidene-malononitrile (L) (35g., 0.15 mole) were added to a solution of sodium cyanide (12g., 0.25 mole) in dimethylformamide (1.75 l.) contained in a 2 l. conical flask, and the solution, which gradually became yellow, was allowed to stand at room temperature for 4 days with

occasional shaking. The excess sodium cyanide was decomposed by adding glacial acetic acid (100 ml.), the hydrogen cyanide evolved being left to evaporate overnight in a fume-cupboard. The solution was diluted to 5 l. with water and extracted with ether (2 x 500 ml.). The aqueous liquors were further diluted to 7 l. with water and again extracted with ether (500 ml.). The combined ether extracts were washed once with water (500ml.) and dried over magnesium sulphate. After evaporation of solvent, the excess acetic acid was removed under reduced pressure on a steam bath, affording a thick yellow oil (35g.) which was dissolved in benzene (50 ml.) and chromatographed on silica (200g.). Elution with benzene (2 x 500 ml.) afforded unreacted starting material 10g. (29%) identified by its infra-red absorption spectrum. Further elution with benzene (6 x 500 ml.) afforded a crystalline solid m.p. 102-115° which was crystallised once from benzene-light petroleum as colourless needles m.p. 106-120°; yield 26g. (66%). Repeated crystallisation of the mixture of stereoisomers from aqueous-methanol afforded one isomer, later shown to be (LIV), as colourless hexagonal plates m.p. 120.5-122° (Found: C, 64.65; H, 6.6; N, 15.95. $C_{14}H_{17}O_2N_3$ requires C, 64.85; H, 6.6; N, 16.2%). Evaporation of the benzene-light petroleum liquors afforded small

amounts of starting material.

Attempted Dieckmann cyclisation of the trinitrile-ester (LIII)

A solution of the trinitrile-ester (LIII) (0.26g., 1 m.mole) in ether (25 ml.) was added dropwise with stirring over 0.5 hrs. to a solution of sodium hydride (0.05g., 2 m.mole) in dry ether (100 ml.) containing dry methanol (5 ml.) and stirring continued at room temperature for 4 hrs. The yellow solution was poured into ice-water (100 ml.), carefully acidified with 6N hydrochloric acid, and the aqueous layer extracted with ether (2 x 50 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a gummy solid (0.24g.), which exhibited infra-red absorption bands at 2200 $cm.^{-1}$ and 1597 $cm.^{-1}$, attributed to (L), whilst the ultra-violet maximum at 239mμ (ε3,900) showed that the conjugated dinitrile (L) was present to the extent of 25%. Trituration of the oil with ether afforded the crystalline trinitrile (LIII) m.p. 112-119°, identical (m.p.; mixed m.p. and infra-red spectrum) with starting material.

Attempted Michael reaction between the trinitrile (LIII) and methyl β:β-dimethylacrylate.

A stirred mixture of sodium hydride (100mg., 4 m.mole) in dry ether (100 ml.) was treated with sufficient dry

methanol to ensure complete solution. A solution of the trinitrile ester (LIII) (520mg., 2 m.mole) in dry ether (20 ml.) and dry methanol (5 ml.) was added and the resultion solution, which became yellow in colour and afforded a colourless precipitate, stirred at room temperature for 1 hr. A solution of redistilled methyl β:β-dimethylacrylate (240mg., 2 m.mole) in dry ether (10 ml.) then added dropwise over 0.25 hr., and the resulting mixture stirred at room temperature for 3 hrs.

The mixture was poured into water, acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed to neutrality with water and dried over magnesium sulphate. Evaporation of solvent afforded a mixture of the trinitrile ester (LIII) and methyl β:β-dimethylacrylate as a thick yellow oil, the latter material being removed by prolonged evacuation at 100°/11mm. Trituration of the residual oil with ether gave starting material which crystallised from methanol as colourless hexagonal plates m.p. 100-112°. Evaporation of the mother liquors afforded a yellow oil, which exhibited infra-red absorption at 1730 $cm.^{-1}$ (carbomethoxyl) and 2200 and 1597 $cm.^{-1}$ (conjugated dinitrile).

1-Carboxy-3-methylcyclohexane-1:3-diacetic acid (LVIII; R=H)

A solution of the trinitrile-ester (LIII) (26g., 0.1 mole) (m.p. 106-120°) in fuming hydrochloric acid (1 l.) was refluxed vigorously for 72 hrs., then evaporated to 500 ml. The cooled solution was saturated with ammonium sulphate and extracted with ether (3 x 250 ml.) The combined ether extracts were washed with saturated ammonium sulphate solution (6 x 100 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil which on trituration with ether furnished the crystalline triacid as a mixture of stereoisomers m.p. 157-164°; yield 23.5g. (90%). Fractional crystallisation from water afforded colourless needles m.p. 173-175°. (Found: C, 55.7; H, 7.05. $C_{12}H_{18}O_6$ requires C, 55.8; H, 7.05%).

On sublimation the triacid (LVIII; R=H) (m.p.157-164°) furnished an anhydride (LX) as a mixture of stereoisomers, which crystallised from ether-n-hexane as colourless prisms m.p. 118-136° (Found: C, 60.25; H, 6.55. Calc. for $C_{12}H_{16}O_5$: C, 60.0; H,6.7%). The product exhibited infra-red absorption at 1850 and 1770 $cm.^{-1}$ (succinic anhydride).

Dimethyl 1-carbomethoxy-3-methylcyclohexane-1:3-diacetate (LVIII; R=Me)

A solution of the triacid (LVIII; R=H) (35g.) in ether (250 ml.) was treated with a slight excess of a dry ethereal solution of diazomethane and allowed to stand at room temperature overnight. After decomposing the excess diazomethane with a little acetic acid, the solution was taken to 250 ml. by evaporation of ether on a steam bath. The cooled solution was washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a pale yellow oil (33g.) which on fractionation furnished the trimethyl ester as a colourless oil b.p. 130-155°/0.2mm; yield 27.2g. (67%). Refractionation afforded a sample b.p. 135°/0.1mm., n_D^{20} 1.4708 (Found: C, 60.15; H, 8.15. $C_{15}H_{24}O_6$ requires C, 60.0; H, 8.05%).

Dieckmann cyclisation of the triester (LVIII; R=Me)

Finely divided potassium (8g., 0.2 g.atom) was added carefully to redistilled xylene (2 l.) containing dry t-butanol (32g., 0.4 mole) under an atmosphere of nitrogen. The mixture was gently refluxed and agitated with a Hershberg stirrer until solution complete, when the excess t-butanol was removed as an azeotrope with xylene using a partial-take-off condenser. A solution of the trimethyl ester (LVIII; R=Me) (30g., 0.1 mole) in

redistilled xylene (500 ml.) was added dropwise from a Herschberg dropping funnel over 24 hrs. to the vigorously stirred refluxing reagent; the t-butanol, liberated during the reaction, being periodically removed as an azeotrope with xylene. Refluxing with vigorous stirring was continued for 8 hrs., after the addition was complete, until t-butanol could no longer be detected in the xylene distillate. The cooled solution was poured on crushed ice (1 kg.) and water (1 l.) and carefully acidified with 6N hydrochloric acid, and the xylene layer separated. The aqueous layer was extracted with ether (2 x 500 ml.) and the combined extracts washed thoroughly with water (6 x 600 ml.) and dried over magnesium sulphate. Evaporation of solvent under reduced pressure gave a thick red oil (27.4g.), which gave a deep purple colour with ferric chloride. Distillation afforded a thick colourless oil b.p. 122-150°/0.01mm.; yield 19.2g. (72%). The product exhibited infra-red absorption typical of an enolisable β-keto-ester, at 1733 $cm.^{-1}$ (carbomethoxyl), 1710 $cm.^{-1}$ (cyclohexanone), 1655 $cm.^{-1}$ (conjugated ester of enol form) and 1614 $cm.^{-1}$ (olefinic double bond of enol form), and also showed an ultra-violet maximum at 250mμ (ε2,300) and at 284mμ (ε5,650) in ethanol containing 1% 1N sodium hydroxide, also typical of an enolisable β-keto-ester.

5-Methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid (XXXII; R=H)

The distilled Dieckmann product (19.2g.) was refluxxed with 6N hydrochloric acid (100 ml.) for 6 hrs. The cooled solution was saturated with ammonium sulphate and extracted with ether (3 x 100 ml.). The combined ether extracts were washed with saturated sodium carbonate solution and the combined alkaline extracts, after careful acidification with 6N sulphuric acid, were saturated with ammonium sulphate and extracted with ether (3 x 150 ml.). The combined ether extracts were washed thoroughly with saturated ammonium sulphate solution and dried over magnesium sulphate. The solvent was removed by evaporation from a large Petri dish, affording a thick pale yellow oil (16.5g.) which on trituration with ether and light petroleum (b.p. 60-80°) afforded a crystalline acid m.p. 103-112° (6g.) and ether-light petroleum soluble material (10.5g.). Crystallisation from ethyl acetate afforded the keto-acid (XXXII; R=H) as colourless prisms m.p. 127-129°. (Found: C, 67.4; H, 8.1. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%). The product exhibited infra-red absorption at 1728 $cm.^{-1}$ (carboxylic acid dimer) and 1690 $cm.^{-1}$ (cyclohexanone hydrogen bonded by carboxylic acid), and in carbon tetrachloride (5.0 mm. cells) at 1748 $cm.^{-1}$ (carboxylic acid monomer) and at 1705 $cm.^{-1}$ (cyclohexanone and carboxylic acid dimer).

Methyl 5-methylbicyclo[3:3:1] nonan-3-one-1-carboxylate (XXXII; R=Me)

A solution of 5-methylbicyclo[3:3:1] nonan-3-one-1-carboxylic acid (0.38g.) in ether (10 ml.) was treated with a slight excess of a dry ethereal solution of diazomethane and allowed to stand at room temperature for 2 hrs. After decomposition of excess diazomethane with acetic acid, the ethereal solution was washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a pale yellow oil, which on distillation afforded the keto-ester as a colourless oil b.p. 90°/0.05mm. n_D^{25} 1.4835; yield 0.32g. (81%). (Found: C, 68.2; H, 8.6. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%). The product exhibited infra-red absorption at 1733 $cm.^{-1}$ (carbomethoxyl) and 1710 $cm.^{-1}$ (cyclohexanone) with a distinctive band at 1121 $cm.^{-1}$.

The semicarbazone crystallised from aqueous methanol as rosettes of fine needles m.p. 193-194° (Found: C, 58.4; H, 7.75; N, 15.65. $C_{13}H_{21}O_3N_3$ requires C, 58.4; H, 7.9; N, 15.7%).

Attempted ketal formation of the keto-ester (XXXII; R=Me).

(a) A solution of the keto-ester (XXXII; R=Me) (140mg.) in dry benzene (50 ml.) was refluxed with ethylene glycol (50 mg.) and p-toluenesulphonic acid (10 mg.) under a Dean and Stark apparatus for 2 hrs. The cooled solution

was neutralised with sodium carbonate solution, washed with water and dried over magnesium sulphate. Evaporation of solvent under reduced pressure afforded an oil ((140 mg.) with an infra-red absorption spectrum identical with that of starting material. Repetition of the reaction on the keto-ester (140 mg.) with ethylene glycol (100 mg.) and naphthalene-2-sulphonic acid (50 mg.) in benzene (50 ml.) for 12 hours afforded no ketal.

(b) A mixture of the keto-ester (110 mg.) and ethyl orthoformate (133 mg.) was refluxed for 3 hrs. with absolute ethanol (25 ml.) containing concentrated sulphuric acid (55 mg.). The cooled solution was neutralised with solid sodium carbonate and poured into water (150 ml.), and extracted with ether (2 x 25 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (100 mg.) with an infra-red absorption spectrum identical with that of starting material.

(c) Methyl ethyl ketone 1:3-dioxolane, prepared by Dauben's method (48), had b.p. 118°.

A solution of keto-ester (65 mg.) and naphthalene-2-sulphonic acid (20 mg.) in methyl ethyl ketone 1:3-dioxolane (20 ml.) was refluxed for 120 hrs. At twelve-hourly intervals 0.5 ml. portions of the distillate

were removed. It was hoped to facilitate reaction by preferential removal of butan-2-one (b.p. 80°), formed during the reaction. The cooled solution was diluted with benzene (50 ml.) and neutralised with solid sodium carbonate. The benzene extract was washed with water and dried over magnesium sulphate. Evaporation of solvent by warming under reduced pressure afforded an oil (50 mg.) with an infra-red spectrum almost identical with that of starting material.

Attempted reduction of the carbonyl group in the keto-ester (XXXII; R=Me)

(a) A solution of the keto-ester (110 mg.) in dry methanol (25 ml.) was treated with sodium borohydride (28 mg.) at 0° for 1 hr. After removal of solvent under reduced pressure, water (25 ml.) was added and the solution, after acidification with dilute sulphuric acid, extracted with ether (2 x 25 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (90 mg.) with an infra-red absorption spectrum identical to that of starting material.

(b) A solution of the keto-ester (300 mg.) in methanol (20 ml.) was treated with a solution of sodium borohydride (300 mg.) in water (10 ml.) and the mixture allowed to stand at room temperature for 10 hrs. The mixture, after

acidification with dilute sulphuric acid was diluted with water (100 ml.), saturated with ammonium sulphate and extracted with ether (3 x 25 ml.). The combined ether extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded the hydroxy-ester as a thick oil (225 mg.) with an infra-red absorption band at 1735 $cm.^{-1}$ (carbomethoxyl) and bands at 3500 and 1045 $cm.^{-1}$ (secondary hydroxyl) with disappearance of the absorption at 1710 $cm.^{-1}$ (cyclohexanone).

A solution of the crude hydroxy-ester (225 mg.) in acetic anhydride (15 ml.) was warmed on a steam bath for 2 hrs. with dry pyridine (5 ml.) then allowed to stand at room temperature overnight. Evaporation of reagents under reduced pressure afforded the ester-acetate as a non-crystallisable oil (230 mg.) with infra-red absorption at 1730 $cm.^{-1}$ (acetate and carbomethoxyl) and at 1220 $cm.^{-1}$ (acetate) with disappearance of the absorption at 3500 $cm.^{-1}$ (hydroxyl).

5-Methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid chloride (LXXV)

A solution of the keto-acid (XXXII; R=H) (2.95g.) in dry benzene (25 ml.) was treated with oxalyl chloride (5 ml.) andthe solution allowed to stand overnight at room temperature. Evaporation of solvent and reagent

under reduced pressure afforded the acid chloride as a pale yellow oil which distilled as a colourless oil b.p. 88°/0.04 mm., n_D^{22} 1.5082; yield 2.70 g. (84%). (Found: C, 61.85; H, 7.15; Cl, 16.25. $C_{11}H_{15}O_2Cl$ requires C, 61.55; H, 7.0; Cl, 16.5%). The product exhibited infra-red absorption at 1790 $cm.^{-1}$ (Carboxylic acid chloride) and at 1710 $cm.^{-1}$ (cyclohexanone).

NOTE:- Distillation of acid chloride must be effected at pressures of 0.2mm. otherwise pyrolytic decomposition occurs. Again thionyl chloride should not be used in place of oxalyl chloride as the yield of acid chloride is 60% and product is not so pure.

5-Methylbicyclo[3:3:1] nonane-1-carboxylic acid (LXXIV)

A mixture of the keto-acid (XXXII; R=H) (m.p.112-118°) (50 mg.), sodium (100 mg.), ethanol (2 ml.), and hydrazine hydrate (0.5 ml.) was placed in a sealed tube and heated at 185° for 18 hours. The cooled mixture was poured into water, acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a crystalline acid (40 mg.), purified by sublimation as colourless needles m.p. 141-143°. (Found: C, 72.9; H, 9.7. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.9%).

Attempts to prepare the enedione (LXXVIII)

Isobutene was prepared according to Kistiakowsky (50) from t-butanol and concentrated sulphuric acid and purified by passing the gas through (a) water and (b) a tower of potassium hydroxide pellets before liquification by cooling. The liquid olefin was allowed to evaporate and passed into the reaction vessel in gaseous form.

(i) Isobutene was passed for 0.25 hr. through a solution of the acid chloride (LXXV) (180 mg.) in pure, ethanol-free, methylene chloride (40 ml.). Powdered aluminium chloride (180 mg.) was added and the mixture stirred at 0° for 2 hrs. with a constant flow of isobutene bubbling under the liquid surface. The mixture, containing a black oily aluminium chloride complex, was decomposed by pouring into dilute hydrochloric acid and the solution extracted with methylene chloride (2 x 25 ml.). The combined methylene-chloride extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (650 mg.) which was mostly polymerised isobutene. The relative intensities of the bands at 1790 $cm.^{-1}$ (acid chloride) and 1710 $cm.^{-1}$ (cyclohexanone) in the infra-red spectrum of the product were identical to those in the starting material.

It was found that a solution of the acid chloride (LXXV) was unaffected when shaken with saturated sodium

carbonate solution, and that hydrolysis of the acid chloride with warm dilute sodium hydroxide was required for conversion to the keto-acid (XXXLL; R=H).

(ii) Chloroform (45 ml.) was saturated with isobutene at 0° during 0.5 hr.. Powdered aluminium chloride (150mg) added, followed by a solution of the acid chloride (LXXV) (215 mg.) in chloroform (25 ml.) and the solution stirred at 0° for 2 hrs. with isobutene passing in, then stirred for a further 12 hrs. at room temperature. The clear solution was poured on to crushed ice (50 g.), acidified with dilute hydrochloric acid and extracted with chloroform (2 x 25 ml.). The combined chloroform extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a colourless oil (690 mg.) which contained large amounts of polymerised isobutene. The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone) and 1790 $cm.^{-1}$ (acid chloride), the relative intensities being almost identical to those in the starting material.

The crude product (690 mg.) was refluxed for 1 hr. with collidine (40 ml.). The cooled solution was poured into water (150 ml.), acidified with dilute hydrochloric acid and extracted with ether (2 x 40 ml.). The combined ether extracts were washed with water and dried

over magnesium sulphate. Evaporation of solvent afforded an oil from which the isobutene polymer was removed by partition between light petroleum and methanol containing 1% water. The methanol extract afforded an oil (80 mg.), which gave a positive 2:4-dinitrophenylhydrazone test and had an ultra-violet maximum at 243mμ (ε1,100), equivalent to 9% enedione (LXXVIII) character. (see later).

The crude product (30 mg.) was refluxed for 1 hr. with 6N hydrochloric acid (15 ml.). The cooled solution was saturated with ammonium sulphate and extracted with ether (2 x 25 ml.). The product was separed into acidic and neutral fractions by extraction of the combined ether extracts with saturated sodium carbonate solution. The acidic fraction (20 mg.) was shown to be the keto-acid (XXXII; R=H) from the infra-red spectrum and conversion to the corresponding ester (XXXII; R=Me) with diazomethane. The neutral fraction (2 mg.) was shown to be the dione (LXXXIV) from the infra-red absorption spectrum.

(iii) A solution of the keto-acid (XXXII; R=H) (207 mg.) in methylene chloride (50 ml.) was saturated with isobutene at 0° over 0.5 hr. and a solution of trifluoracetic anhydride (390 mg.) in methylene chloride

(5 ml.) added. Isobutene was passed into the reaction vessel for 2 hrs. at 0°, then the solution allowed to stand overnight at room temperature. The colourless solution was poured on to ice (2 0 g.) and water (50 ml.). The methylene chloride layer was extracted thoroughly with saturated sodium bicarbonate solution, washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (75 mg.), containing mostly isobutene polymer; the infra-red absorption spectrum indicating onlysmall amounts of carbonyl compounds, which showed no absorption in the ultra-violet.

N-nitroso isobutylurethane was prepared according to the method of Cook, Raphael and Scott (52). Isobutylamine was condensed with ethyl chloroformate in the presence of sodium hydroxide affording isobutylurethane as a colourless oil b.p. 52°/0.3mm., n_D^{25} 1.4260 in 95% yield; and the urethane nitrosated at 10° with sodiumnitrite and dilute nitric acid.

Diazoisobutane. A solution of N-nitroso isobutylurethane (17.5 g.) in ether (50 ml.) was added over 5 mins. to a mixture of potassium hydroxide (13 g.), n-propanol (50 ml.) and ether (50 ml.) in a water bath at 50°. The orange diazoisobutane was co-distilled with ether and collected below the surface of ice-cooled ether until the distillate

was colourless, (500 ml. distillate) (53). Standardisation (53) against benzoic acid showed 100 ml. ether solution to contain 2.75×10^{-3} equivalents of diazoisobutane. That diazoisobutane had indeed been formed was demonstrated by the smooth conversion of 3:5-dinitrobenzoic acid, on neutralisation with the ethereal solution, to isobutyl alcohol 3:5-dinitrobenzoate isolated from light petroleum as colourless needles m.p. 86-87° (Lit. m.p. 87°).

Attempted condensation of acid chloride (LXXV) with diazoisobutane

A solution of the acid chloride (250 mg.) in dry ether (25 ml.) was added slowly with swirling to five equivalents of a sodium-dried ethereal solution of diazoisobutane and the solution allowed to stand at 0° for 14 hrs. Evaporation of solvent at room temperature under reduced pressure (20 mm.) afforded a yellow oil which appeared to decompose on continued evacuation. The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone) with medium bands at 1790 $cm.^{-1}$ (acid chloride), 2070, 1650 and 1625 $cm.^{-1}$ (diazoketone).

Dry hydrogen chloride was passed through a solution of the oil in dry ether (25 ml.) for 0.5 hr. at 0°. The decolorised ethereal solution was washed thoroughly with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded the

α-chloroketone (LXXXII) (120 mg.) as a thick yellow oil. A solution of the oil (120 mg.) inxylene (50 ml.) was refluxed for 4 hrs. with collidine (5 ml.), then allowed to stand at room temperature for 12 hrs. during which time collidine-hydrochloride was precipitated as colourless needles. The solution was washed with dilute sulphuric acid, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick yellow oil (80 mg.). The infra-red spectrum of the product was very similar to that of the keto-ester (XXXII; R=Me) and showed weak absorption in the conjugated carbonyl region. The ultra-violet maximum at 240 mμ (ε2,400) was equivalent to 20% enedione (LXXVIII) character in the final product.

Condensation of the acid chloride (LXXV) with diazomethane

An ethereal solution of diazomethane (32) was thoroughly dried over potassium hydroxide pellets and standardised (53) (1 ml. ethereal solution contained 10^{-4} mole diazomethane).

A solution of the acid chloride (511 mg., 2.5 m.mole) in dry ether (50 ml.) was added dropwise with swirling to six equivalents (150 ml.) of the ethereal diazomethane solution at 0° and allowed to stand at 0° for 6 hrs. The infra-red spectrum of an aliquot evacuated to dryness indicated that large amounts of unreacted acid chloride remained. The solution was allowed to warm to room

temperature, triethylamine (5 ml.) and a further six equivalents (150 ml.) of the ethereal diazomethane solution were added and the solution allowed to stand at room temperature for 10 hrs. Evaporation of solvent at room temperature under reduced pressure afforded a yellow oil which on trituration with light petroleum furnished the diazoketone (LXXXIII) as a pale yellow solid m.p. 60-85° (dec.); yield 162 mg. (29.5%). The product exhibited infra-red absorption at 2100 $cm.^{-1}$ (N≡N), 1708 $cm.^{-1}$ (cyclohexanone), 1625 $cm.^{-1}$ (diazoketone), 3070 and 1375 $cm.^{-1}$ (C-H vibrations in diazoketone).

1-Acetyl-5-methylbicyclo[3:3:1]nonan-3-one (LXXXIV)

A solution of the diazoketone (LXXXIII) (160 mg.) in chloroform (20 ml.) was shaken for 5 mins. with 55% hydroiodic acid solution (55). After evolution of nitrogen had ceased the chloroform solution was washed with water (2 x 10 ml.), dilute sodium thiosulphate solution (2 x 15 ml.), water (2 x 10 ml.), and dried over magnesium sulphate. Evaporation of solvent afforded the dione (LXXXIV) as a colourless oil; yield 140 mg.(99%). A sample had b.p. 50°/0.01 mm., n_D^{23} 1.4951 (Found: C, 74.65; H, 9.35. $C_{12}H_{18}O_2$ requires C, 74.2; H,9.35%). The product gave a positive iodoform test (56). Brady's reagent (57) afforded the bis-2:4-dinitrophenylhydrazone as a yellow powder which on repeated crystallisation from

chloroform-methanol crystalised as yellow needles m.p. 248-250°. (Found: N, 19.7. $C_{24}H_{26}O_8N_8$ requires N, 20.20%). The product exhibited an ultra-violet maximum (in chloroform) at 366mμ (ε43,100). Isobut-1-enyl chloride was prepared by a modification of the method of Braude and Coles (60).

Redistilled isobutyraldehyde (160 g.) was added dropwise over 1 hr. at 0° to powdered phosphorus pentachloride (475g.) and the mixture stirred at 0° for 6 hrs., and for a further 12 hrs. at room temperature. The mixture was decomposed by pouring on to crushed ice (1 kg.) and extracted with ether (4 x 250 ml.). The combined ether extracts were washed with water (6x100ml) and dried over magnesium sulphate. Evaporation fo solvent afforded a mobile red oil (156 g.) which furnished isobutylidene dichloride as a pale yellow oil (79 g.), b.p. 78-126°. The crude dichloride (79 g.) was added dropwise over 1 hr. to a solution of potassium hydroxide (38 g.) in ethylene glycol (200 ml.) at 120° and the mixture stirred for 6 hrs. at 120°. The product, obtained by slow distillation from the reaction vessel, was fractionated from a little sodium as a colourless oil b.p. 66-74°. The product exhibited infra-red absorption at 2795 and 1730 $cm.^{-1}$ attributed to isobutyraldehyde, which was removed by shaking for 1 hr.

with saturated sodium bisulphite solution. After filtration the oily layer was separated and dried over magnesium sulphate. Fractionation afforded isobut-1-enylchloride as a colourless oil n_D^{25} 1.4170 (Lit. (60) n_D^{20} 1.4224); yield 9 g. (4.5%).

Attempted preparation of lithium isobutenyl (58)

A solution of isobutenyl chloride (1.35 g.) in dry ether (100 ml.) was placed in a dry 250 ml. three-necked flask equipped with a mercury sealed stirrer and a double-surface coil condenser under an atmosphere of nitrogen. Lithium (250 mg.) was carefully scraped free of oxide film under dry ether then cut into small pieces in a stream of nitrogen and dropped immediately into the reaction flask such that the shiny metal surface was still exposed. The mixture was then gently refluxed with stirring for 20 hrs. The cooled ethereal solution was filtered through a filter-stick from the residual black powder and stored at 0° under nitrogen. Shaking an aliquot with water gave no alkaline reaction, hence, contrary to Braude and Coles (58) lithium isobutenyl was not formed.

Attempted elaborations of the acid chloride (LXXV)

(a) With methallyl magnesium chloride. A solution of redistilled methallyl chloride (9.05 g., 0.1 mole) in dry ether (35 ml.) was added dropwise over 6 hrs. to a

vigorously stirred mixture of magnesium turnings (7.3 g., 0.3 g.atom) and dry ether (100 ml.) under an atmosphere of nitrogen. One crystal of iodine sufficed to initiate the reaction, and after the reagent had been added, the grey complex in ether was stirred at room temperature for 8 hrs. The ethereal solution was removed from the grey complex by filtration through a filter-stick under nitrogen pressure and stored at room temperature under nitrogen. Standardisation against 0.1N hydrochloric acid (62) showed that 1 ml. ether contained 3.35×10^{-4} mole of methallyl magnesium chloride.

One equivalent of the Grignard solution (17.1 ml.) was added over 1 min. to a solution of the acid chloride (LXXV) (1.23 g., 5.7 m.mole) in dry ether (50 ml.) under a nitrogen atmosphere at -70°, followed by anhydrous ferric chloride (10 mg.) (61) and the mixture stirred at -70° for 3 hrs. The mixture was poured on to crushed ice and acidified with dilute sulphuric acid. The ether layer was separated, washed with dilute ammonium sulphate solution (2 x 50 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil (1.2 g.) which appeared to be mainly a mixture of the keto-acid (XXXII; R=H), unreacted acid chloride (LXXV) and dimethallyl (63) from the infra-red spectrum. Acidic

material was removed by washing with saturated sodium carbonate solution, which gave 600 mg. neutral material which appeared to be mainly acid chloride from the infra-red spectrum. The oil (600 mg.) was refluxed for 60 hrs. with dilute sulphuric acid (10 ml.) and the cooled solution separated by saturated sodium carbonate solution into neutral and acidic fractions. The acidic fraction proved to be the keto-acid (XXXII;R=H) (290 mg.), whilst the neutral fraction (290 mg.) appeared to be a mixture of dimethyallyl (63) and the dione (LXXXIV), from the infra-red spectrum.

5-Methyl-1-(isopropenylaceto)-bicyclo[3:3:1]nonan-3-one (LXXVIII)

A solution of the acid chloride (LXXV) (6.0 g.) in pure dry methylene chloride (120 ml.) was cooled to -10°. Pure isobutene was passed through a tower of potassium hydroxide pellets, condensed by cooling to -10°, and a large excess (ca. 25 ml.) dissolved in the reaction mixture. Freshly distilled stannic chloride (ca. 1g.) was added through a capillary dropper and the flask immediately stoppered and allowed to stand at -5° for 42 hrs. with occasional shaking. The solution was poured into water (100 ml.) and acidified with 10% hydrochloric acid. The methylene chloride layer was separated, washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate.

Evaporation of solvent afforded an oil, the infra-red spectrum of which exhibited a band at 1790 $cm.^{-1}$ corresponding to unreacted acid chloride (LXXV) (ca. 30%) A solution of the oil in methylene chloride (150 ml.) was again treated with isobutene (ca. 25 ml.) and stannic chloride (ca. 1 g.) and allowed to stand at +5° for 72 hrs., then worked up as before. The product (33g.) exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone and β-chloroketone), with a weak band at 1790 $cm.^{-1}$ (acid chloride) and bands at 1740 $cm.^{-1}$ (carbo t-butoxy) and 1650 $cm.^{-1}$. A solution of the oil in light petroleum was chromatographed on a short column of alumina (Grade I)(90 gr). Elution with light petroleum (300 ml.) afforded mainly polymeric isobutene together with small amounts of the β-chloroketone (LXXX). Elution with ether (300 ml.) furnished the impure enedione as a pale yellow oil (3.48 g.). Further elution with ether afforded no useful material. The light petroleum eluate (above) was filtered through alumina (Grade I) (100 g) Elution with light petroleum (300 ml.) afforded a complex mixture of polymeric isobutenes, whilst further elution with ether (300 ml.) afforded more crude enedione as a pale yellow oil (1.04 g.). Elution of the first alumina column with chloroform (300 ml.) after 72 hrs. furnished a pale yellow oil (0.45 g.) which was shown to be identical

with the dione (LXXXIV), prepared by hydrogen iodide treatment of the diazoketone (LXXXIII), from the characteristic infra-red spectrum and the bis-2:4-dinitrophenylhydrazone (m.p.; mixed m.p. and ultra-violet spectrum). The crude enedione (4.52 g.; (69%)) exhibited infra-red absorption at 1740 $cm.^{-1}$ (carbot-butoxyl or cyclopentanone), 1710 $cm.^{-1}$ (cyclohexanone), 1685 $cm.^{-1}$ (conjugated ketone) and 1620 $cm.^{-1}$ (olefinic double bond) and a band at 1650 $cm.^{-1}$ A solution of the enedione (4.52 g.) in benzene (20 ml.) was chromatographed on silica (225 g.), and each fraction analysed from the infra-red absorption spectrum. Elution with:-

Benzene (5 x 150 ml):- (116 mg.). Traces of acid chloride (LXXV) and simple ester impurity (band at 1735 $cm.^{-1}$)

1% ether-benzene (11 x 150 ml.):- (462 mg.). Complex mixture with traces of acid chloride (1790 $cm.^{-1}$). As fractions increased the intensity of the band at 1650 $cm.^{-1}$ decreased, the 1740 $cm.^{-1}$ (carbot-butoxyl) band increasing with respect to the 1710 $cm.^{-1}$ (cyclohexanone) intensity.

1% ether-benzene (7 x 150 ml.):- (643 mg.). Last traces of acid chloride and material with band at 1650 $cm.^{-1}$ were removed. The enedione began to be eluted associated with large amounts of the keto-ester (XXXII; R=Bu^t)(1740 $cm.^{-1}$ band).

2% ether-benzene (22 x 150 ml.):- (2,690 mg.). The enedione was completely eluted in association with the

keto-ester (XXXII; R=Bu^t) i.e. 1740 cm.$^{-1}$ band which decreased with increasing fractions until negligible at fraction 40.

10% ether-benzene (9 x 150 ml.):- (343 mg.). Traces of enedione and small amounts of the dione (LXXXIV).

The combined 2% ether-benzene eluates were slowly fractionated at 0.01 mm.

(1) b.p. 110-116°, n_D^{23} 1.5149.

(2) b.p. 117-120°, n_D^{23} 1.5146.

(3) b.p. 120-122°, n_D^{23} 1.5140.

(4) b.p. 122-130°, n_D^{23} 1.5070.

The infra-red spectra of the fractions indicated that the enedione distilled first, the higher boiling keto-ester (XXXII; R=Bu^t) contaminating the later fractions.

Refractionation of fraction (1) afforded the enedione (LXXVIII) as a colourless oil b.p. 108°/0.007 mm., n_D^{20} 1.5165; yield 2.13 gr. (32.5%). (Found: C, 76.65; H, 9.7. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.45%). The product exhibited infra-red absorption at 1710 cm.$^{-1}$ (cyclo-hexanone), 1685 cm.$^{-1}$ (conjugated ketone) and 1620 cm.$^{-1}$ (olefinic double bond) with an ultra-violet maximum at 241mμ (ε12,800). The bis semicarbazone crystallised from methanol as colourless needles m.p. 253-254°. (Found: N, 24.15. $C_{17}H_{28}O_2N_6$ requires N, 24.15%).

Attempted cyclisations of the enedione (LXXVIII)

(a) A solution of the crude β-chloroketone (LXXX) (350 mg.) containing ca. 10% dissolved polyisobutene in methanol (2 ml.) was warmed on a steam bath for 2 hrs. with 7.5% hydrochloric acid (15 ml.). The cooled solution was extracted with ether (2 x 20 ml.). The combined ether extracts were washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a pale yellow oil (250 mg.), the infra-red spectrum of which indicated a mixture of the enedione (1710, 1685 and 1620 cm^{-1}) and the keto-ester (XXXII; R=But) (1740 and 1710 cm^{-1}) with only traces of the acid chloride (LXXV) and the dione (LXXXIV) by comparison of the spectrum with that of an authentic sample.

(b) The crude enedione (250 mg., from expt. (a)) was warmed on a steam bath for 8 hrs. with 6N sulphuric acid (25 ml.) and the mixture allowed to stand at room temperature for 100 hrs., before extraction with ether (2 x 25 ml.). The combined ether extracts were washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a colourless oil (150 mg.) which was shown to consist mainly of the dione (LXXXIV) from the infra-red spectrum, which also indicated the presence of small

amounts of the enedione and keto-ester (XXXII; R=Bu^t). The sodium carbonate extract on acidification furnished small amounts of the keto-acid (XXXII; R=H).

(c) A solution of the crude enedione (105 mg.) in dry benzene (5 ml.) was refluxed for 5 hrs. with a solution of naphthalene-2-sulphonic acid (40 mg.) in dry benzene (30 ml.). The cooled solution was filtered through a short column of alumina (Grade V), which was then eluted with ether (250 ml.) affording a yellow oil (68 mg.). The infra-red spectrum of the product was identical to that of the starting material save that the band at 1740 cm.$^{-1}$ (carbo*t*-butoxyl) had decreased in intensity by 25%. The product was refluxed with naphthalene-2-sulphonic acid (40 mg.) in benzene (35 ml.) for 11 hrs. The reagent was filtered from the cooled solution which was then evaporated to dryness. The infra-red spectrum of theproduct indicated that the relative intensities of the bands at 1710, 1685 and 1620 cm.$^{-1}$ were unchanged, but that the intensity of the 1740 cm.$^{-1}$ band had again decreased with concomitant formation of carboxylic material, assumed to be the keto-acid (XXXII; R=H).

(d) Pure stannic chloride (215 mg.) was added quickly to a solution of the crude enedione (125 mg.) in pure methylene chloride (20 ml.) and the tightly-stoppered reaction vessel allowed to stand at -5° for 24 hrs.

The solution was diluted with ether (30 ml.) and washed successively with dilute hydrochloric acid (3 x 20 ml.), saturated sodium carbonate solution (2 x 30 ml.), water (2 x 30 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (86 mg.), the infra-red spectrum of which was identical in all respects with that of the starting material.

(e) A solution of the crude enedione (104 mg.) in glacial acetic acid (5 ml.) was treated with 7g. of a 40% w:w solution of boron trifluoride in acetic acid and the solution allowed to stand at room temperature for 3 days The solution was poured into water (40 ml.) and extracted with ether (50 ml.). The ether layer was thoroughly washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (78mg.) the infra-red spectrum of which was identical with that of the starting material.

(f) A solution of the crude enedione (113 mg.) in methanol (10 ml.) was gently refluxed on a steam bath for 4 hrs. with a solution of potassium hydroxide (43 mg.) in distilled water (20 ml.). After evaporation of some methanol under reduced pressure, the cooled solution was poured into water (20 ml.) and extracted with ether (30 ml.). The ether extract was washed thoroughly with saturated

sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (70 mg.) the infra-red spectrum of which showed it to be a mixture of the dione (LXXXIV), unchanged enedione and small amounts of the keto-ester (XXXII; R=Bu^t). The alkaline extracts were carefully acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 30 ml.) The combined ether extracts were washed with saturated salt solution (2 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded the keto-acid (XXXII; R=H) initially as a pale yellow oil (22 mg.) which solidified on trituration with ether.

(g) A solution of the crude enedione (100 mg.) in methanol (10 ml.) was refluxed for 48 hrs. with one equivalent of a standard solution of sodium methoxide in methanol (20 ml.). After evaporation to dryness under reduced pressure, the cooled material was acidified with dilute sulphuric acid and extracted with ether (2 x 20 ml.) The combined ether extracts were washed with water (2 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil (100 mg.), the infra-red spectrum of which showed decreased intensities in the bands at 1740 cm.$^{-1}$ (carbo*t*-butoxyl), 1685, and 1620 cm.$^{-1}$ (conjugated ketone) with concomitant appearance

of bands attributed to the keto-acid (XXXII; R=H) and the dione (LXXXIV).

(h) 10 drops of a 40% w:w solution of N-benzyl trimethyl ammonium methoxide (Triton B methoxide) in methanol were added to a solution of the crude enedione (108 mg.) in methanol (15 ml.), and the resulting solution gently refluxed for 24 hrs. Methanol was evaporated under reduced pressure and the cooled material acidified with dilute sulphuric acid and extracted with ether (2 x 20 ml.). The combined ether extracts were washed with water (2 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil (100 mg.) with an infra-red spectrum identical to that above (expt. (g)) save that slightly more of the enedione had been converted to the dione (LXXXIV) as indicated by the relative intensities of the bands at 1685 and 1620 $cm.^{-1}$ (enone) and 1710 $cm.^{-1}$ (cyclohexanone and methyl ketone).

(i) A solution of the crude enedione (100 mg.) in glacial acetic acid (15 ml.) containing potassium acetate (49 mg.) was refluxed for 3 hrs. The cooled solution was poured into water (100 ml.) and extracted with ether (2 x 25 ml.). The combined ether extracts were washed thoroughly with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent

afforded an oil (85 mg.), the infra-red spectrum of which was indentical in all respect with that of the starting material.

(j) A solution of the crude enedione (90 mg.) in dry benzene (20 ml.) containing crystalline sodamide (30 mg.) was refluxed for 18 hrs. with vigorous stirring. After 1 hr. ammonia was evolved and continued to be evolved (litmus) for at least 8 hrs. The cooled solution was acidified with dilute sulphuric acid and the separated benzene layer washed with water (3 x 10 ml.) and dried over magnesium sulphate. Evaporation of solvent gave a thick yellow oil (86 mg.), the infra-red spectrum of which indicated the presence of carboxylic material. The oil was dissolved in ether (2 0 ml.) and separated into neutral and acidic fractions by washing with saturated sodium carbonate solution. The neutral fraction was isolated as a thick oil (58 mg.) which exhibited a complex infra-red spectrum. The intensities of the bands at 1740 $cm.^{-1}$ (carbo<u>t</u>-butoxyl) and 1685 and 1620 $cm.^{-1}$ (enone) had decreased but there was no evidence for formation of the dione (LXXXIV) - by critical comparison with the spectrum of an authentic sample. The product exhibited a broad band at 3400 $cm.^{-1}$ (hydrogen bonded N-H). The acidic fraction furnished a

very thick oil (24 mg.), the infra-red spectrum of which closely resembled that of the keto-acid (XXXII; R=H).

(k) Potassium (100 mg.) was dissolved in dry t-butanol (10 ml.) and dry xylene (50 ml.). The excess t-butanol was removed by twice azeotroping to small bulk with xylene (50 ml.) and the resulting potassium t-butoxide dissolved in dry xylene (100 ml.) The cooled solution was added to a solution of the crude enedione (100 mg.) in dry xylene (25 ml.) and the resulting solution allowed to stand at room temperature for 12 hrs. with occasional swirling. The solution was poured into cold water (100 ml.) and acidified with dilute sulphuric acid. The separated xylene layer was washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent under reduced pressure afforded a yellow oil (86 mg.) the infra-red spectrum of which was identical with that of the starting material.

(l) A solution of the crude enedione (100 mg.) in dry benzene (20 ml.) was treated with ten equivalents of a standard solution of sodium t-amylate in benzene and the resulting solution stirred vigorously at room

temperature for 10 hrs. The solution was poured into ice-water (50 ml.) and acidified with dilute sulphuric acid. The benzene layer was washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (93 mg.), the infra-red spectrum of which ressembled those found in experiments (g) and (h), the intensities of the bands at 1685 and 1620 cm^{-1} (enone) having decreased with subsequent enhancement of the 1710 cm^{-1} band. The band at 1740 cm^{-1} showed decreased intensity with production of carboxylic material in small amounts. A similar complex mixture was afforded when the crude enedione was refluxed with excess sodium t-amylate in benzene for 18 hrs.

(m) The crude enedione (1.60 g.) was added to a solution of sodium t-amylate (sodium 300 mg.) in t-amyl alcohol (50 ml.) and the resulting solution refluxed for 8 hrs. under an atmosphere of nitrogen. Benzene (50 ml.) was added and the solvents evaporated under reduced pressure. The cooled mixture was carefully acidified with dilute sulphuric acid and extracted with ether (2 x 50 ml.). The combined ether extracts were washed with water (3 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (1.24 g.), the infra-red spectrum of which showed decrease

in intensity of the bands at 1685 and 1620 $cm.^{-1}$ (enone) in a complex carbonyl range, and a new band at 3400 $cm.^{-1}$ (hydroxyl). A solution of the oil in light petroleum (b.p. 60-80°) was chromatographed on alumina (Grade I). Elution with 1% benzene-light petroleum afforded small amounts of a simple ester. Elution with 5% benzene-light petroleum afforded an oil which exhibited medium bands at 1740 and 1660 $cm.^{-1}$ with respect to the strong band at 1710 $cm.^{-1}$ (cyclohexanone) in the infra-red spectrum. Continued elution afforded the same mixture with increasing proportion of the material which exhibited the band at 1660 $cm.^{-1}$. Elution with benzene afforded a complex mixture comprising the acid chloride (LXXV), the enedione (LXXVIII), with small amounts of the keto-ester (XXXII; R=Bu^t) and probably the dione (LXXXIV). Elution with 5% ether-benzene afforded a complex mixture which exhibited bands at 1740, 1710, 1660, 1620 and 1550 $cm.^{-1}$. The column was eluted with ether after being allowed to stand for one week. The thick oil exhibited weak bands at 1685 and 1620 $cm.^{-1}$(enone) with a broad band at 1710 $cm.^{-1}$ and a new strong band at 3500 $cm.^{-1}$ (hydroxyl). By comparison with the infra-red spectrum of authentic dione (LXXXIV) the product was shown to contain only small

amounts of the dione, being principally the β-hydroxyketone of the enedione (LXXVIII).

(n) Recrystallised p-toluenesulphonyl chloride (104 mg.) was added to a solution of the crude enedione (87 mg.) in dry pyridine (1 ml.) and the mixture allowed to stand at room temperature for 65 hrs. After dilution with ether (15 ml.), the mixture was acidified with 7.5% hydrochloric acid and the separated ether layers washed thoroughly with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a brown oil (150 mg.), the infra-red spectrum of which exhibited bands at 1600, 1190, 1175 and 840 $cm.^{-1}$ attributed to p-toluenesulphonyl chloride, the intensities of the bands at 1740, 1710, 1685 and 1620 $cm.^{-1}$ being relatively unchanged.

1-(3-Methylbut-1-ol-2-enyl)-5-methylbicyclo[3:3:1]nonan-3-one (LXXXVII; R=H)

Sodium borohydride (71 mg., 1.75 m.mole) was added to a solution of the pure enedione (LXXVIII) (1.64 g., 7.0 m.mole) in dry methanol (10 ml.), cooled to 0° in an ice-salt bath. After the initial effervescence, the mixture was allowed to stand at 0° for 1.5 hr. with occasional shaking. The solvent was removed under reduced pressure without heating and the residue acidified with

dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (3 x 25 ml.). The combined ether extracts were washed thoroughly with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil, the infra-red spectrum of which exhibited a strong band at 1710 $cm.^{-1}$ (cyclohexanone) with medium bands at 3500 $cm.^{-1}$ (hydroxyl) and 1685 and 1620 $cm.^{-1}$ (enone). A solution of the oil in dry methanol (10 ml.) was cooled to 0° and allowed to stand at 0° for 4 hrs. with sodium borohydride (55 mg.) before being worked up as before. The ketol was furnished as a thick oil (1.66 g.) the infra-red spectrum of which exhibited a strong band at 1710 $cm.^{-1}$ with only weak bands at 1685 and 1620 $cm.^{-1}$. A solution of the crude ketol (1.66 g.) in benzene was chromatographed on a short column of silica (50 g.). Elution with 2% ether-benzene (8 x 150 ml.) afforded small quantities of the enedione (LXXVIII), the latter fractions showing increasing amounts of the ketol. Elution with 5% ether-benzene afforded the ketol as a thick colourless oil (1.45 g.), which was too thick to be satisfactorily fractionated. A portion of the ketol was fractionated by short path distillation on to a cold finger as a colourless non-crystallisable oil b.p. 130°/0.01 mm. (Found: C, 76.9; H, 10.25. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.25%).

The product exhibited infra-red absorption at 3500 $cm.^{-1}$ (Hydroxyl), 1710 $cm.^{-1}$ (cyclohexanone, broadened by hydrogen bonding) and a weak band at 1635 $cm.^{-1}$ (olefin) with ultra-violet absorption ε^{210} =1890; ε^{220}=284; $\varepsilon^{210}/\varepsilon^{220}$=6.65 characteristic of a molecule possessing a trisubstituted double bond (78,79). It was found that element analyses were high in carbon if the sample of ketol had been distilled at 0.1 mm. Careful analysis of the infra-red spectra indicated the appearance of weak bands at 1645 and 1605 $cm.^{-1}$, later attributedto the dieneone (LXXXIX) furnished by pyrolytic dehydration of the ketol (LXXXVII; R=H).

Reduction of both carbonyl groups in the enedione (LXXVIII)

A solution of sodium borohydride (100 mg.) in distilled water (10 ml.) was added quickly to a solution of the crude enedione (103 mg.) in methanol (10 ml.) and the resulting solution allowed to stand at room temperature for 2 hrs. The solution was acidified with dilute sulphuric acid and extracted with ether (3 x 20 ml.) The combined ether extracts were washed with water (2 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (93 mg.) which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone) and 3500 $cm.^{-1}$ (hydroxyl) with weak bands at 1685 $cm.^{-1}$ and

1620 $cm.^{-1}$ (enone), though the intensity of the 1740 $cm.^{-1}$ band (carbo-t-butoxy) was the same as in the crude dienone. A solution of the oil (93 mg.) in light petroleum (b.p. 60-80°) was chromatographed on silica (5 g.). Elution with light petroleum (b.p. 60-80°) and with benzene (4 x 50 ml.) afforded a complex mixture of the acid chloride (LXXV), keto-ester (XXXII; R=Bu^t), enedione (LXXVIII) and the ketol (LXXXVII; R=H). Elution with 10% ether-benzene (4 x 50 ml.) furnished a mixture (49 mg.) of the keto-ester (XXXII; R=Bu^t) and the ketol (LXXXVII; R=H). Further elution with ether afforded small quantities of a syrup, the infra-red spectrum of which exhibited a strong broad band at 3500 $cm.^{-1}$ (hydroxyl) with only a weak carbonyl band. The syrup, which could not be purified was assigned a structure in which both carbonyl groups in the enedione (LXXVIII) had been reduced to hydroxyl.

Attempted formation of the p-toluenesulphonate of the ketol (LXXXVII; R=H)

A solution of the crude ketol (340 mg.) containing some keto-ester (XXXII; R=Bu^t) in dry pyridine (5 ml.) was warmed on a steam bath for 2 hrs. with p-toluene-sulphonyl chloride (305 mg.). After evaporation to small bulk under reduced pressure, the mixture was acidified

with dilute hydrochloric acid and extracted with chloroform (2 x 15 ml.). The combined chloroform extracts were washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (365 mg.) which exhibited infra-red absorption at 3500 $cm.^{-1}$ (hydroxyl), 1600 $cm.^{-1}$ (aromatic) with a doublet at 1290 and 1275 $cm.^{-1}$ (p-toluenesulphonate). p-Toluenesulphonyl chloride (500 mg.) was added to a solution of the oil (365 mg.) in dry pyridine (5 ml.) and the solution allowed to stand at room temperature for 18 hrs. in a stoppered flask. Work-up as above afforded a thick oil (525 mg.), containing unchanged reagent. The product, which exhibited only weak absorption at 3500 $cm.^{-1}$ (hydroxyl), was dissolved in benzene and chromatographed on alumina (Grade III) (15 g.). Elution with benzene (5 x 50 ml.) afforded an oil (190 mg.) which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 1600 $cm.^{-1}$ (aromatic), 1290 and 888 $cm.^{-1}$ (later shown to be conjugated diene). Fraction (1) exhibited an ultra-violet maximum at 230mμ (ε8,500) corresponding to 36% dienone (LXXXIX) character. Further elution with 10% ether-benzene (6 x 50 ml.) afforded an oil (90 mg.) which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 1740 $cm.^{-1}$ (carbo-t-butoxyl) and

with dilute hydrochloric acid and extracted with chloroform (2 x 15 ml.). The combined chloroform extracts were washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (365 mg.) which exhibited infra-red absorption at 3500 $cm.^{-1}$ (hydroxyl), 1600 $cm.^{-1}$ (aromatic) with a doublet at 1290 and 1275 $cm.^{-1}$ (p-toluenesulphonate). p-Toluenesulphonyl chloride (500 mg.) was added to a solution of the oil (365 mg.) in dry pyridine (5 ml.) and the solution allowed to stand at room temperature for 18 hrs. in a stoppered flask. Work-up as above afforded a thick oil (525 mg.), containing unchanged reagent. The product, which exhibited only weak absorption at 3500 $cm.^{-1}$ (hydroxyl), was dissolved in benzene and chromatographed on alumina (Grade III) (15 g.). Elution with benzene (5 x 50 ml.) afforded an oil (190 mg.) which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 1600 $cm.^{-1}$ (aromatic), 1290 and 888 $cm.^{-1}$ (later shown to be conjugated diene). Fraction (1) exhibited an ultra-violet maximum at 230mμ (ε8,500) corresponding to 36% dienone (LXXXIX) character. Further elution with 10% ether-benzene (6 x 50 ml.) afforded an oil (90 mg.) which exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 1740 $cm.^{-1}$ (carbo-t-butoxyl) and

1600 $cm.^{-1}$ (aromatic), 1290 and 1275 $cm.^{-1}$ (p-toluenesulphonyl) with only weak bands at 973 and 888 $cm.^{-1}$ (conjugated diene). Fraction (7) exhibited an ultraviolet maximum at 230mμ (ε4,500) corresponding to 19% dieneone (LXXXIX) character. Further elution with ether afforded small amounts of a complex mixture containing unreacted ketol.

Attempted cyclisation of the p-toluenesulphonate of the ketol (LXXXVII; R=H)

A solution of the crude keto-tosylate (190 mg.) in dry t-amyl alcohol (15 ml.) was treated with one equivalent of sodium t-amylate (11.5 mg. sodium) in t-amyl alcohol (15 ml.) and the resulting solution refluxed with stirring for 16 hrs. under an atmosphere of nitrogen. The solution, which became cloudy, was evaporated to small bulk and the cooled material acidified with dilute sulphuric acid, diluted with water and extracted with ether (2 x 20 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a sweet-smelling oil (170 mg.) which exhibited a weak band at 3500 $cm.^{-1}$ (hydroxyl) in the infra-red spectrum, with virtual disappearance of the bands at 1600, 1290 and 1275 $cm.^{-1}$ (p-toluenesulphonate). A solution of the oil (170 mg.) in benzene was chromatographed on alumina (Grade I) (10g.).

Elution with 5% ether-benzene (6 x 50 ml.) afforded a thick sweet-smelling oil (45 mg.), the infra-red spectrum of which indicated a complex mixture of at least keto-ester (XXXII; R=But), dienone (LXXXIX) and keto-tosylate (LXXXVII; R=p-$CH_3.C_6H_4.SO_2$). Further elution with ether afforded small amounts of a thick oil which exhibited hydroxylic bands in the infra-red spectrum.

1-(3-Methylbutadienyl)-5-methylbicyclo[3:3:1]nonan-3-one (LXXXIX)

(a) A solution of ketol (LXXXVII; R=H) (330 mg.) in dry pyridine (5 ml.) was treated with a solution of p-bromobenzenesulphonate (535 mg., 1.5 equivalents) in dry pyridine (5 ml.) and the solution allowed to stand at room temperature for 18 hrs. The solution was poured into ice-water (100 ml.) and extracted with ether (2 x 25 ml.). The combined ether extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (195 mg.) which on trituration with light petroleum (b.p. 60-80°), afforded a solid (15 mg.) which crystallised from ether-light petroleum (b.p. 60-80°) as colourless needles m.p. 168-172°. The product exhibited only aromatic bands in the infra-red spectrum. Evaporation of the light petroleum soluble fraction afforded relatively unchanged

ketol as a thick oil (180 mg.).

(b) A solution of the ketol (LXXXVII; R=H) (305 mg.) in dry pyridine (2 ml.) was treated with a solution of p-bromobenzenesulphonyl chloride (665 mg., 2 equivalents) in dry pyridine (2 ml.) and the solution warmed on a steam bath for 2 hrs. After removing the pyridine under reduced pressure, the cooled mixture was poured into water (50 ml.), acidified with dilute hydrochloric acid, saturated with ammonium sulphate and extracted with ether (2 x 25 ml.). The combined ether extracts were washed with saturated sodium bicarbonate solution, saturated ammonium sulphate solution and dried over magnesium sulphate. Solvent was removed under reduced pressure without warming, affording a mobile yellow oil (295 mg.), which exhibited a complex infra-red spectrum with bands at 1710 $cm.^{-1}$ (cyclohexanone), 3100 and 1580 $cm.^{-1}$ (aromatic bands of p-bromobenzenesulphonate), 3050, 1645 and 1610 $cm.^{-1}$ (conjugated diene) and a weak band at 3500 $cm.^{-1}$ (hydroxyl). A solution of the oil (295 mg.) in 25% benzene-light petroleum (b.p. 60-80°) was chromatographed on alumina (Grade I) (13 g.). Elution with 25% benzene-light petroleum (b.p. 60-80°) (6 x 50 ml.) afforded the dieneone (LXXXIX) as a volatile sweet-smelling mobile oil; yield 210 mg. (73%). Elution with benzene afforded no useful material but further elution with ether (200 ml.) afforded a non-crystallisable glass (50mg.).

The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone) with weak bands at 3100, 1620 and 1580 $cm.^{-1}$ (aromatic of p-bromobenzenesulphonate). Fractionation of the 25% benzene-light petroleum (b.p. 60-80°) eluate furnished the enedione (LXXXIX) as a colourless oil b.p. 70°/0.01 mm., n_D^{23} 1.5197. (Found: C, 82.2; H, 9.95. $C_{15}H_{22}O$ requires C, 82.5; H, 10.15%). The product exhibited infra-red absorption at 1710 $cm.^{-1}$ (cyclohexanone), 3050, 1645, 1610, 973 and 888 $cm.^{-1}$ (disubstituted conjugated diene) (33) with an ultra-violet maximum at 230mμ (ε 23,900).

1-(3-Methylbut-1-acetate-2-enyl)-5-methylbicyclo[3:3:1]-nonan-3-one (LXXXVII; R=$CH_3.CO$)

Acetic anhydride (1 ml.) was added to a solution of the ketol (LXXXVII; R=H) (200 mg.) in dry pyridine (1 ml.) and the solution allowed to stand at room temperature for 75 hrs. in a stoppered flask. Evaporation under reduced pressure afforded the keto-acetate as a colourless oil (220 mg.) b.p. 124°/0.05 mm., n_D^{24} 1.4964. The product exhibited infra-red absorption at 1740 and 1240 $cm.^{-1}$ (acetate) and 1710 $cm.^{-1}$ (cyclohexanone) with a weak band at 1620 $cm.^{-1}$ (olefin). The ultra-violet spectrum exhibited end-absorption ε^{210}=605 ; ε^{220}=310 ; $\varepsilon^{210}/\varepsilon^{220}$=1.95 characteristic of a trisubstituted double bond (78,79). During acetylation there was no evidence in the infra-red and ultra-violet spectra for formation of the dieneone (LXXXIX).

Attempted elaboration of the acid chloride(LXXV) (See p.108)

(b) With ethyl sodio-acetoacetate. A solution of ethyl-acetoacetate (10 g.) in anhydrous ethanol (50 mg.) was added to a solution of sodium (1.6 g.) in anhydrous ethanol (100 ml.) and the resulting solution warmed to 50° with stirring for 1 hr. Evaporation of volatile materials at 100° under reduced pressure afforded ethyl sodio-acetoacetate as a pale yellow solid. A solution of the acid chloride (450 mg., 2.5 m.moles) in dry benzene (50 ml.) was added over 0.5 hr. at 40° with stirring to a solution of ethyl sodio-acetoacetate (878 mg., 6 m.mole) in dry benzene (100 ml.) and dimethylformamide (2 ml.). The solution was refluxed for 2 hrs., during which time sodium chloride separated from the solution. The ice-cooled mixture was carefully acidified with dilute sulphuric acid, the benzene layer separated, washed with water and dried over magnesium sulphate. Evaporation of solvent and reagent under reduced pressure at 100° afforded a thick oil (227 mg.) which gave an orange colour with ferric chloride. The product, which was unstable to distillation, exhibited infra-red absorption bands at 1735, 1710 and 1640 $cm.^{-1}$ attributed to an enolisable β-keto-ester. There was no ultra-violet maximum in ethanol, but in ethanol containing 1% 1N sodium hydroxide the product exhibited

an ultra-violet maximum at 273mμ (ε10,700) which was to be expected from formation of structure (XCII; R=Me). The product could not be selectively hydrolysed to the dione-ester (XC), or the trione (XCIII).

(c) With ethyl t-butyl ethoxymagnesiummalonate (83)

Magnesium ethoxide was prepared by adding anhydrous ethanol (10 ml.) to magnesium turnings (217 mg., 8.9mg.atom) activated with 5 drops carbon tetrachloride, and the mixture refluxed for 2 hrs. until all the magnesium had dissolved. The excess ethanol was removed at 100° under reduced pressure, the last traces being removed by azeotroping with xylene (100 ml.).

A solution of ethyl t-butyl malonate (1.68 g., 8.9 m.mole) in dry ether (25 ml.) was added to a suspension of magnesium ethoxide (8.9 m.mole) in dry ether (150 ml.) and the mixture refluxed gently for 3 hrs. The solvent and ethanol were removed as above.

A solution of the acid chloride (1.91 g., 8.9 m.mole) in dry ether (25 ml.) was added over 0.5 hr. to a stirred suspension of the reagent (8.9 m.mole) in refluxing ether (250 ml.). Immediately on addition of the acid chloride the complex partially dissolved only to be replaced at once with a suspension of ethoxymagnesium chloride. The mixture was gently refluxed with stirring for 18 hrs. The ice-cooled mixture was acidified with

dilute sulphuric acid, the ether layer separated and the aqueous layer extracted with ether (2 x 50 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil from which the starting materials were removed at 0.1 mm. in an oil bath at 150°. The dione-diester (XCII; R=Bu^{t}O), which would not distil at 180°/0.1 mm. and decomposed rapidly at 190° was isolated as a thick oil; yield 2.30 g. (71%). The product, which gave a red ferric chloride test, could be furnished in almost quantitative yield if a 10% excess of reagent were used.

It was found that the distillate above solidified overnight affording a product which crystallised from n-pentane as colourless prisms m.p. 49-51° (Found: C, 61.85; H, 7.2; Cl, 16.3. $C_{11}H_{15}O_2Cl$ requires C, 61.55; H, 7.0; Cl, 16.5%). The product which exhibited infra-red absorption (carbon tetrachloride, 5.0 mm. cells) at 1811 cm.$^{-1}$ (pseudo acid chloride) was assigned structure (LXXVI).

Methyl 5-methylbicyclo[3:2:1]octan-7-one-1-acetate (LIX; R=Me)

A solution of the pseudo acid chloride (114 mg.) in dry methanol (20 ml.) was refluxed on a steam bath for 3 hrs. with one equivalent of sodium methoxide (sodium(12.2 mg.)). Evaporation of solvent afforded

an oily mixture which was thoroughly washed with ether. Evaporation of ether afforded the keto-ester (LIX; R=Me) as a colourless oil; yield 108 mg. (98%). A sample had B.P. 60°/0.02 mm., n_D^{25} 1.4719. (Found: C, 68.85; H, 8.85. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%). The product exhibited a characteristic infra-red absorption spectrum, markedly different from that of the keto-ester (XXXII; R=Me) with one band at 1743 $cm.^{-1}$ (carbon tetrachloride, 5.0 mm. cells) (cyclopentanone and carbomethoxyl) and a distinctive band at 1108 $cm.^{-1}$ (film)

1-(2-Carbethoxyacetyl)-5-methylbicyclo[3:3:1]nonan-3-one (XC)

A solution of the dione-diester (XCII; R=But) (2.30 g.) in dry benzene (30 ml.) was added to a solution of p-toluenesulphonic acid (150 mg.) in dry benzene (40 ml.) and the solution refluxed gently for 18 hrs. The cooled solution was washed with dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick red oil which on fractionation afforded the dione-ester (XC) as a pale yellow oil b.p. 138-150°/0.2 mm.; yield 1.25 g. (75%). A sample had b.p. 140°/0.03 mm., n_D^{25} 1.4925. (Found: C, 68.1; H, 8.4. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%). The product exhibited infra-red absorption bands at 1706 $cm.^{-1}$ (cyclohexanone), 1740 $cm.^{-1}$ (carbomethoxyl) and at 1643 and 1618 $cm.^{-1}$ (enolisable β-keto-ester). The product

exhibited an ultra-violet maximum at 249mμ (ε3,500) in ethanol and at 276mμ (ε13,500) in ethanol containing 1% 1N sodium hydroxide which taken with the violet colour with ferric chloride was also typical of an enolisable β-keto-ester.

1-Acetyl-5-methylbicyclo[3:3:1]nonan-3-one (LXXXIV)

A solution of the dione-ester (XC) (210 mg.) in methanol (50 ml.) was gently refluxed with dilute sulphuric acid (10 ml.) for 1.5 hr. The cooled solution was poured into ice-water (250 ml.) and extracted with ether (2 x 100 ml.). The combined ether extracts were washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded the dione (LXXXIV) as a paleyellow oil; yield 138 mg. (90%). The product had an identical infra-red spectrum with that of the dione prepared by hydrogen iodide decomposition of the diazoketone (LXXXIII). The corresponding bis-2:4-dinitrophenylhydrazones were identical (m.p.; mixed m.p. and ultra-violet spectrum).

Attempted condensations of dione-ester (XC) with acetone.

(a) A solution of the dione-ester (224 mg.) in dry benzene (50 ml.) containing acetone (82 mg.) was stirred at room temperature for 2 hrs. with anhydrous ethanol (10 drops) and piperidine (5 drops). Glacial acetic acid (5 drops) was added and the solution stirred for 1 hr.

at room temperature, then washed with water (2 x 15 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil (224 mg.) identical with starting material (infra-red and ultra-vilet spectra).

(b) A solution of the dione-ester (218 mg.) in dry benzene (50 ml.) containing acetone (185 mg.), glacial acetic acid (40 mg.) and ω-aminocaproic acid (4 mg.) was refluxed vigorously for 12 hrs., under a Soxhlet extraction (60 ml. capacity) containing dry acetone (5 ml.), dry benzene (15 ml.) and blue silica gel to trap any water formed during the reaction. The cooled solution was washed with dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (215 mg.) identical with starting material (infra-red and ultra-violet spectrum).

(c) A solution of the dione-ester (214 mg.) in benzene (120 ml.) containing acetone (20 ml.), ω-aminocaproic acid (500 mg.) and glacial acetic acid (1 ml.) was refluxed for 6 hrs. under a Dean and Stark apparatus containing blue silica gel. The cooled solution was washed with water (4 x 25 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil (214 mg.) identical with starting material (infra-red and ultra-violet spectra).

(d) Dry hydrogen chloride was passed into a solution

of the dione-ester (525 mg.) in dry acetone (40 ml.) at 0° for 2 hrs. and the saturated solution allowed to stand in a stoppered flask at 0° for 36 hrs. The solution was poured on to crushed ice (200 g.), neutralised with saturated sodium bicarbonate solution and extracted with ether (3 x 100 ml.). The combined ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil which rapidly turned violet with loss of hydrogen chloride. When piperidine (10 ml.) was added to a solution of the oil the ether (100 ml.), a vigorous exothermic reaction ensued. A solution of piperidine (40 ml.) in ether (100 ml.) was added to the cooled solution, and the mixture shaken vigorously in a stoppered flask at room temperature for 65 hrs. Piperidine hydrochloride was separated by filtration and the filtrate washed with dilute sulphuric acid, dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent and mesityl oxide, by warming under reduced pressure, afforded a thick red-black oil (400 mg.) which was partially purified by chromatography on silica, the oily product (360 mg.) being eluted with 50% chloroform-benzene. The infra-red spectrum of the product was similar, but not identical, to that of the starting material. The

ultra-violet spectrum of the product was also similar, but not identical, with starting material having a maximum at 242mμ (ε6,270) in ethanol and at 266mμ (ε11,700) in ethanol containing 1% 1N sodium hydroxide.

A solution of the product in methanol (20 ml.) was refluxed with dilute sulphuric acid (30 ml.) for 1.5 hrs. The cooled solution was diluted with water (100 ml.) and extracted with ether (3 x 50 ml.). The combined ether extracts were washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. The sodium bicarbonate extract afforded no acidic material. Evaporation of solvent afforded an oil which was purified by filtration through a short column of silica, the product (200 mg.) being eluted with 10% chloroform-benzene. The infra-red spectrum of the product was identical with that of the dione (LXXXIV) prepared by hydrogen iodide decomposition of the diazoketone (LXXXIII). The product which showed no ultra-violet absorption afforded a bis-2:4-dinitrophenylhydrazone identical (m.p.; mixed m.p. and ultra-violet spectrum) with that of the dione (LXXXIV).

Acetomethyl 5-methylbicyclo[3:3:1]nonan-3-one-1-carboxylate (XCIV)

A solution of the keto-acid (XXXII; R=H) (4.63 g.) in dry ethanol (50 ml.) was neutralised to phenolphthalein with an ethanolic potassium hydroxide solution. Redistilled chloroacetone (7.0 g., 3 equivalents) was added and the

solution refluxed with stirring for 3 hrs., potassium chloride being almost completely precipitated within 15 min. After evaporation of solvent under reduced pressure, the product was poured into water (150 ml.) and extracted with ether (2 x 50 ml.). The combined ether extracts were washed with saturated sodium carbonate solution, saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded the acetol ester as a mobile oil b.p. 148°/0.05mm., n_D^{22} 1.4910; yield 5.32 g. (89%). (Found: C, 66.0; H, 7.7. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.0%). The product exhibited infra-red absorption at 1735 $cm.^{-1}$ (acetocarbomethoxyl) and 1705 $cm.^{-1}$ (cyclohexanone).

Attempted cyclisation of the acetol-ester (XCIV)

(a) A solution of the acetol ester (250 mg.) in dry benzene (15 ml.) was refluxed for 2 hrs. with diethylamine (1 ml.) and pyridine (1 ml.). The cooled solution was washed with dilute hydrochloric acid, dilute sodium bicarbonate, water and dried over magnesium sulphate. Evaporation of solvent afforded a colourless oil (225 mg.), the infra-red spectrum of which was identical with that of starting material.

(b) A solution of the acetol ester (200 mg., 0.8 m.mole) in methanol (5 ml.) was treated with 0.1N sodium hydroxide (8 ml.). The solution, which became exothermic,

was allowed to stand at room temperature for12 hrs. The solution was poured into water (50 ml.) and extracted with ether (2 x 20 ml.). The combined ether extracts were washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (6 mg.), the infra-red spectrum of which was identical with that of starting material. The alkaline extract was carefully acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 50 ml.). The combined ether extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (125 mg.), the infra-red spectrum of which was very similar to that of the keto-acid (XXXII; R=H).

(c). A solution of the acetol ester (500 mg., 2 m.mole) in dry xylene (20 ml.) was refluxed for 2 hrs. with a solution of potassium t-butoxide (potassium (120 mg., 3 g. atom)) in xylene (5 ml.) under a nitrogen atmosphere. The cooled red mixture was acidified with dilute hydrochloric acid and the separated xylene layer washed with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent under reduced pressure afforded an oil (435 mg.), the infra-red spectrum of which was identical with that of the starting material.

(d) A solution of the acetol ester (112 mg.) in benzene (20 ml.) was refluxed for 3 hrs. with a dry solution of excess naphthalene-2-sulphonic acid in benzene (5 ml.). The cooled solution was washed with sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (103 mg.), identical with starting material.

(e) A solution of methylanilinomagnesium bromide in benzene under nitrogen was prepared according to method of Nielsen, Gibbons and Zimmermann (88) and standardised. A solution of the acetol ester (250 mg., 1 m.mole) in benzene (15 ml.) was added to one equivalent of a freshly prepared solution of the reagent in benzene (5 ml.) and the solution allowed to stand at room temperature for 2 hrs. under nitrogen. The solution was washed with dilute hydrochloric acid (4 x 10 ml.), water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (230 mg.), the infra-red spectrum of which was very similar to that of starting material but exhibited a weak band at 3500 cm^{-1} (hydroxyl).

Attempted alkylation of the keto-ester (XXXII; R=Me) with ethyl ~~α~~-bromoisobutyrate

A solution of the keto-ester (490 mg., 2.3 m.mole) in dry benzene (50 ml.) was refluxed with crystalline sodamide (180 mg., 4.6 m.mole) for 20 hrs. with vigorous

stirring under a nitrogen atmosphere until evolution of ammonia ceased. To the cooled solution was added a solution of ethyl α-bromoisobutyrate (455 mg., 2.3 m.mole) in dry benzene (15 ml.) over 0.25 hr., and the solution stirred at room temperature for 0.5 hr. As no sodium bromide precipitated from the solution, the solution was gently refluxed for 5 hrs. The cooled solution was acidified with dilute sulphuric acid, the benzene layer separated, washed with water (6 x 20 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded an oil from which unchanged ethyl α-bromoisobutyrate was removed by prolonged warming under reduced pressure. The infra-red spectrum of the product (340 mg.) was identical with that of the starting material.

PART TWO

The Synthesis of 5-Methylbicyclo[3:3:1]nonan-2-one-1-carboxylic Acid and Attempts at Conversion to Clovene

THE SYNTHESIS OF 5-METHYLBICYCLO[3:3:1]NONAN-2-ONE-1-CARBOXYLIC ACID AND ATTEMPTS AT CONVERSION TO CLOVENE

Theoretical

(Formulae flowsheets for this section on p. 170).

The main conclusion drawn from the investigations described in Part One was that a precursor with a carbonyl group at C_3 of the bicyclo[3:3:1]nonane system, e.g. (XXXII; R=H), was not the most favourable for the elaboration of ring C of clovene. It was readily seen that a more useful intermediate would be 5-methylbicyclo-[3:3:1] non-2-one-1-carboxylic acid (CLIII; R=H), possessing the carbonyl group in the C_2 position adjacent to the carboxyl function. In this compound the reactive carbonyl and carboxyl functions are situated at the correct "junction" points for elaboration to the five-membered ring of clovene. This would circumvent the difficulty experienced in the earlier work where the carbonyl group in the keto-acid (XXXII; R=H) had only a weak activating influence on the adjacent C_2 position, i.e. the position where condensation must necessarily occur if cyclisation to the clovene skeleton were to succeed. The placing of the carbonyl group in the C_2 position of the keto-acid (CLIII; R=H) should both off-set the difficulties encountered previously in the elaboration of the bridge-head carboxyl group and help to diminish the steric problems previously experienced.

It was noted (see lit. review p.p. 59 - 75) that Cope and Synerholm (123) had synthesised bicyclo[3:3:1]-non-3-ene-9-one-1-carboxylic acid (CXXXIX; R=H) containing the carboxyl function in the desired C_1 position. This route appeared to be suitable for modification to furnish the desired keto-acid (CLIII; R=H). Initially the C_5 hydrogen atom had to be replaced by a methyl group; this could be brought about by using methyl-substituted starting materials in the synthesis of the bicyclo[3:3:1]nonane system. Next, the C_9 carbonyl group had to be converted to methylene, and the resulting olefinic-acid (CLV; R=H) then oxidised in the allylic position to the conjugated ketone (CLVI; R=H) which on hydrogenation would afford the desired keto-acid (CLIII; R=H). It should be noted that the C_9 carbonyl group had to be removed completely before introduction of the C_2 carbonyl otherwise ambiguity would arise in the position of attack of reagents on these carbonyl groups.

Formation of the Bicyclic System (CLX)

Cope and Synerholm (123) started from 2-carbethoxy-cyclohexanone, but our starting material was 2-carbethoxy-6-methylcyclohexanone (CLVII), prepared by condensing 2-methylcyclohexanone with diethyl oxalate and pyrolytically decarbonylating the intermediate dione-ester (CLVIII) (131). The keto-ester (CLVI) was condensed with redistilled

acrolein at -70°, in the presence of catalytic amounts of sodium ethoxide (123), to furnish the aldehydo-ester (CLIX). An internal aldol reaction with simultaneous dehydration was then effected by adding the freshly distilled aldehydo-ester to vigorously stirred, ice-cold concentrated sulphuric acid (123). The crude keto-ester (CLX; R=Et) was obtained as a colourless oil of wide boiling range.* Saponification with warm aqueous methanolic sodium hydroxide furnished the desired crystalline keto-acid (CLX; R=H). This structure (CLX; R=H) was assigned to the compound on the following basis:-

The infra-red spectrum of the keto-acid exhibited a broad band from 3300 to 2300 cm^{-1} (carboxyl), strong

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*FOOTNOTE:- Two by-products have been isolated in 15% yield from the acid treatment of the aldehydo-ester(CLIX). One has been characterised (132) as 4-methylhydrindene-7-carboxylic acid (CLXI) (133), while the other, $C_{13}H_{18}O_3$, containing a readily decarboxylated carbethoxy group, together with a cyclohexenone function, has been tentatively assigned structure (CLXII) or (CLXIII). As the structures of these by-products and the mechanisms for their formation by some complex rearrangement of the intermediate ketol-ester (CLXIX), have proved to be worthy of fuller study, they are being pursued by Miss Jhaveri in this department.

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bands at 1705 $cm.^{-1}$ (cyclohexanone) and 1685 $cm.^{-1}$ (carboxyl), and a weak band at 1630 $cm.^{-1}$ (olefinic double bond) (33). The infra-red spectrum of the corresponding keto-ester (CLX; R=Me) had bands at 1728 $cm.^{-1}$ (carbomethoxyl), 1705 $cm.^{-1}$ (cyclohexanone) and weak bands at 3000 and 1637 $cm.^{-1}$ (olefinic double bond), and also showed ultra-violet end-absorption characteristic of a disubstituted double bond (78,79). The keto-ester (CLX; R=Me) did not react in the cold with 2:4-dinitrophenylhydrazine (57) or with semi-carbazide acetate, but readily reacted with hydrazine hydrate in warm methanol affording a crystalline pyrazolone (CLXIV). As neither of the keto-esters (CLX; R=Me) and (CLX; R=Et) nor the parent keto-acid (CLX; R=H) gave any colour with ferric chloride solution, the facile formation of a pyrazolone indicated the presence of a non-enolisable β-keto-ester.

The presence of the carbonyl group in the keto-acid (CLX; R=H) and the keto-ester (CLX; R=Me) was indicated by the ease in which sodium borohydride treatment afforded a crystalline hydroxy-acid (CLXV; R=R′=H) and a liquid hydroxy-ester (CLXV; R=Me, R′=H) respectively. The latter compound, which exhibited infra-red absorption at 3470 $cm.^{-1}$ (hydroxyl), 1720 $cm.^{-1}$ (carbomethoxyl), 3005 and 1643 $cm.^{-1}$ (olefinic double bond), was readily reduced to a crystalline diol (CLXVI) with

lithium aluminium hydride thus confirming the presence of the carbomethoxyl group. The infra-red spectra of all the above compounds exhibited bands at 3005, 1640, 1300 and 700 $cm.^{-1}$, characteristic of the presence of a cis-disubstituted unconjugated olefinic double bond, in a carbocyclic ring system (33,134), the presence of which was further confirmed by the distinctive ultra-violet end absorption (78,79).

The presence of a double bond in the keto-acid (CLX; R=H) was proved by the slow uptake of one mole equivalent of hydrogen over 10% palladium-charcoal affording a dihydro keto-acid (CLXVII) which was transparent in the ultra-violet. Hydrogenation of the keto-acid (CLX; R=H) over Adam's catalyst, however, resulted in the ready uptake of two mole equivalents of hydrogen and production of a hydroxy acid (CLXVIII). The presence of the double bond in the keto-acid (CLX; R=H) seemed proven and it was placed as shown from consideration of the mechanism of its introduction. The aldehydo-ester (CLIX) must undergo a sulphuric acid catalysed internal aldol reaction affording a hydroxy-keto-ester (CLXIX) which on dehydration must furnish the keto-ester (CLX; R=Et). If the double bond were capable of migration to the Δ^2 position, one would expect an equimolar mixture of two double bond isomers (CLXX; R=Et) and (CLX; R=Et). However, we have shown

that the keto-acid (CLX; R=H) is recovered completely unchanged after refluxing with concentrated hydrochloric acid, (conditions which should have brought about isomerisation if the double bond were labile). Thus there was no evidence at this stage to suggest that the double bond was not in the Δ^3 position.

It should be noted that with the introduction of a C_9 hydroxyl group, the possibility of epimeric hydroxy compounds arises. It would appear from the melting points of the crude hydroxy compounds in this series that a mixture of epimers was produced. In general, crystallisation did not improve the melting points of these compounds, although repeated sublimation generally resulted in the isolation of one sharply melting epimer. As the environment of the carbonyl group in the keto-acid (CLX; R=H) or in the keto-ac ester (CLX; R=Me) is almost uniform it is impossible to hazard a guess as to which epimeric hydroxy compound should be more readily formed or the more ready to sublime; but from later work it seemed that, under the vigorous reducing conditions employed, almost equimolar mixtures of the epimers were formed.

When modifications of the carbonyl group of the keto-ester (CLX; R=Me) and reactions of the corresponding hydroxy-esters (CLXV; R=Me, R′=H) were undertaken, a lack of reactivity was encountered which can best be

explained in terms of the steric hindrance associated with a tetrahedral disposition at this position, e.g., it was impossible to form the dioxolane (45,46) of the carbonyl group at C_9 in the keto-ester (CLX; R=Me). In addition the hydroxy-ester (CLXV; R=Me, R′=H) reacted very slowly with acetic anhydride in pyridine at room temperature. Complete acetylation of the hydroxyl group was only satisfactorily achieved by refluxing the hydroxy-ester with sodium acetate in acetic anhydride. The infra-red spectrum of the crude product exhibited a broad band at 1735 $cm.^{-1}$ (carbomethoxyl and acetate), but no absorption at 3470 $cm.^{-1}$ (hydroxyl). A strong band at 1650 $cm.^{-1}$ in conjunction with an ultra-violet maximum at 241mμ (ε2000-3000) indicated concomitant rearrangement of the hydroxy-ester to an α:β- or β:β-disubstituted, α:β-unsaturated carbonyl system (135). Chromatography of the crude acetate-ester on alumina afforded the desired liquid acetate-ester (CLXV; R=Me, R′=$CO.CH_3$) on elution with 50% benzene-light petroleum (b.p. 60-80°). Further elution with 50% ether-benzene afforded small amounts of the oily by-product, but as the isolation of pure rearranged material proved difficulty the nature of this rearrangement has not yet been elucidated. It should be noted that, when the hydroxy-ester was treated with acetic anhydride in pyridine, the infra-red spectrum again

showed the anomalous maximum at 1650 $cm.^{-1}$, although the hydroxy-ester was recovered unchanged when refluxed with pyridine alone. There was only very slow reaction when the hydroxy-ester was treated with p-toluenesulphonyl chloride in pyridine at room temperature, but in this case no band at 1650 $cm.^{-1}$ was evident in the product.

Conversion of C_9 carbonyl to methylene

At first we decided that a Clemmensen reduction (136,137) of the keto-acid (CLX; R=H) would probably not be feasible since the carbonyl group appeared to be sterically hindered. It was obvious that a Wolff-Kishner reaction would lead initially to the pyrazolone (CLXIV), but it was thought that it might be possible to eliminate nitrogen from this molecule with formation of the desired acid (CLV; R=H). The pyrazolone, however, was recovered unchanged when heated to 170° with potassium hydroxide in ethylene glycol (138) or to 210° with sodium in diethylene glycol (139). Presumably the reason for the non-decomposition of the pyrazolone is to be found in the formation of a very stable resonating anionic system (CLXXI) ↔ (CLXXII) ↔ (CLXXIII) on treatment with base. We noted the facile removal of the hydroxyl group from the ketol (CLXXIV;R=H) affording the ketone (CLXXV) by treatment of the d-camphorsulphonate (CLXXIV; R=d-camphorsulphonyl) with

zinc and acetic acid (140) and thought that such a reaction might be applied to a sulphonate of the hydroxy-ester (CLXV; R=Me, R′=H). Although the hydroxy-ester reacted only slowly with p-toluenesulphonyl chloride, probably because of the bulky nature of the reagent and the relatively hindered hydroxyl function, a facile reaction with the less bulky methanesulphonyl chloride (141) afforded an almost equimolar mixture of liquid and solid epimeric methanesulphonates (CLXV; R=Me, R′=$SO_2.CH_3$). The solid epimer could be recrystallised without decomposition, but prolonged drying in a vacuum oven at 50° served to decolorise the crystals with concomitant production of a band at 254mμ in the ultra-violet spectrum of the slightly decomposed product. The liquid epimer, the infra-red spectrum of which was very similar to that of the crystalline epimer, was unstable to heat and slowly decomposed at room temperature. Treatment of a mixture of liquid and solid methanesulphonates with zinc in refluxing acetic acid (140) furnished in poor yield a volatile oil, initially thought to be the olefinic- ester (CLV; R=Me). The infra-red spectrum of the product was quite dissimilar to that of authentic olefinic ester (see later), but was very similar to that of the product from distillation of the crude methanesulphonate mixture. This material which exhibited a band at 243mμ in the

ultra-violet spectrum, appears to be the result of a complex pyrolytic rearrangement.

Clemmensen reduction (137) of the keto-acid (CLX; R=H), under forcing conditions, furnished the desired olefinic-acid (CLV; R=H) as the light petroleum soluble extract of the acidic fraction of the reaction mixture.*

*FOOTNOTE:- It was noted during the work-up of the Clemmensen reduction of the keto-acid (CLX; R=H) that 12% of the product was present as a thick sweet-smelling neutral oil, the infra-red spectrum of which indicated it to be a mixture of a paraffin and a γ-lactone. Fractional distillation of the mixture furnished the lactonic material as the more volatile fragment. The product, $C_{12}H_{16}O_2$, exhibited an infra-red maximum band at 1779 $cm.^{-1}$ (γ-lactone) with ultra-violet end-absorption characteristic of a di-substituted double bond. A molecular weight determination using the mass spectrum (142) gave a value of 190 (calculated 192). Reduction of the lactone with lithium aluminium hydride afforded a viscous diol which exhibited infra-red absorption at 3250 $cm.^{-1}$ (hydroxyl), 1048 $cm.^{-1}$ (secondary hydroxyl) and 1015 $cm.^{-1}$ (primary hydroxyl).

Asthe keto-acid (CLX; R=H), on which the Clemmensen reduction is performed, contains only eleven carbon atoms, it is difficult to understand how a $C_{12}H_{16}O_2$

compound can arise. Though no structural determinations have been made, the lactone has been tentatively assigned structure (CLXXVI). It is conceivable that some of the dione-ester (CLVIII) might not be completely decarbonylated and therefore be taken through the same synthetic steps, with the keto-ester (CLVII), thus affording the dione-acid (CLXXVII). As α-keto-acids are known to undergo Clemmensen reduction (136,137), it is possible that small amounts of the hydroxy-acid (CLXXVIII), which would immediately lactonise to the product (CLXXVI), might be formed.

The paraffinic fraction was separated in 30% yield from the crude mixture as the light petroleum eluate from chromatography on alumina. Fractionation afforded a thick colourless odourless oil $C_{10}H_{16}$, which exhibited infra-red absorption bands at 2890, 2830, 1460, 1450 and 1360 $cm.^{-1}$ (C-H) with weak bands at 1660 $cm.^{-1}$ (olefinic double bond) and 1235 $cm.^{-1}$. A molecular weight of 136 (calculated 136) was suggested from mass spectrometric measurements. It would seem likely that the product is 1-methybicyclo[3:3:1]non-2-ene (CLXXIX) arising from pyrolytic decarboxylation of the olefinic acid (CLV; R=H) during the vigorous reducing conditions of Clemmensen reaction.

The non-petroleum soluble acidic residue was a mixture of the epimeric hydroxy-acids (CLXV; R=R′=H) as the infra-red spectrum of the product was identical with that of the mixture of hydroxy-acids afforded by sodium borohydride reduction of the keto-acid (CLX; R=H). It proved difficult to purify the olefinic-acid as it was very soluble in petrol and sublimation on a large scale did not afford sharply melting material. The olefinic-acid was readily esterified with diazomethane affording a sweet-smelling volatile ester (CLV; R=Me). Although this ester appeared homogeneous from the infra-red and ultra-violet absorption spectra, it was later found that the vapour phase chromatogram exhibited two main bands corresponding to 10% of an impurity in the olefinic-ester. We suspected that the impurity might be the keto-ester (CLX; R=Me) carried through as some un-reduced keto-acid (CLX; R=H) with the olefinic-acid (CLV; R=H) in the light petroleum-soluble acidic fraction from the Clemmensen reduction. Although the keto-acid (CLX; R=H) is not petrol soluble it is conceivable that a small amount may be soluble when intimately mixed with the olefinic-acid. The impure olefinic-ester was therefore treated with sodium borohydride in methanol and the crude product, which exhibited infra-red absorption at 3470 $cm.^{-1}$ (hydroxyl), chromatographed on alumina. Elution with 20% benzene-

light petroleum afforded pure olefinic-ester (CLV; R=Me) in 38% yield from the keto-acid (CLX; R=H). The product exhibited infra-red absorption at 1735 $cm.^{-1}$ (carbomethoxyl), 3000 $cm.^{-1}$ and 1650 $cm.^{-1}$ (olefinic double bond) with ultra-violet absorption characteristic of a di-substituted double bond (33,134). The vapour phase chromatogram of the product exhibited only one band. Further elution with ether afforded a complex mixture which exhibited six bands in the vapour phase chromatogram. The infra-red spectrum of the mixture suggested that the main component was the hydroxy-ester (CLXV; R=Me, R′=H).

As the epimeric hydroxy-acids (CLXV; R=R′=H) were insoluble in light petroleum, it was thought that it would be possible to remove the small amounts of the keto-acid (CLX; R=H) contaminating the crude olefinic acid (CLV; R=H) by treating the light petroleum-soluble acidic material from the Clemmensen reduction with sodium borohydride, followed by trituration with light petroleum. Unfortunately this method of purification was not completely successful on a large scale, the method outlined above being more efficient.

Hydrogenation of the olefinic-acid (CLV; R=H) in ethyl acetate over platinum oxide resulted in the rapid uptake of one mole equivalent of hydrogen, furnishing 5-methylbicyclo[3:3:1]nonane-1-carboxylic acid (LXXIV),

transparent in the ultra-violet. The product was identical (m.p., mixed m.p., and infra-red spectrum) with the acid afforded by Wolff-Kishner reduction of 5-methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid (XXXII; R=H). The structure of the parent bicyclo-[3:3:1]nonane system is thus authenticated by its synthesis from two totally independent synthetic pathways.

Homologation of the keto-acid (CLX; R=H)

It was fore-seen that, in the later stages of the clovene synthesis, it would be preferable to have an acetic acid residue in the C_1 position of the bicyclo-[3:3:1]nonane system rather than the carboxyl group, as the acetic acid residue would possess an activated methylene group adjacent to the carboxyl function, suitable for a Dieckmann cyclisation to give ring C of clovene. Thus it was advantageous to discover whether the keto-acid (CLX; R=H) could be readily homologated to the keto-acid (CLXXX; R=H) in an Arndt-Eistert reaction.

The keto-acid (CLX; R=H) was quantitatively converted by treatment with oxalyl chloride (43) to the acid chloride (CLXXXI) which readily reacted with ethereal diazomethane (32,53) affording the oily diazoketone (CLXXXII). The diazoketone readily rearranged when refluxed in dry t-butanol with catalytic amounts of a solution of silver benzoate in triethylamine (143) to give the keto-ester (CLXXX; R=Bu^t) in good yield.

Both the t-butyl ester and the corresponding methyl ester, furnished by saponification to the keto-acid (CLXXX; R=H) and esterification with diazomethane, proved to be thick oils, while the keto-acid was a non-crystallisable glass. It was evident that homologation could be effected easily and in good yield, but the oily nature of the products deemed it undesirable to carry out this step at this stage of the synthetic route. The infra-red spectra of the t-butyl and methyl esters, (CLXXX; R=Bu^t) and (CLXXX; R=Me) respectively, each exhibited bands at 3400 cm^{-1} (hydroxyl) and 1760 cm^{-1} (γ-lactone) which may be accounted for by the presence of small amounts of the cyclised γ-lactol form (CLXXXIII) of the keto-acid (CLXXX; R=H).

Conversion of the olefinic-ester (CLV; R=Me) to 1-carbomethoxy-5-methylbicyclo[3:3:1]nonan-2-one(CLIII;R=Me)

The next step in this approach was the preparation of the keto-ester (CLIII; R=Me) from the olefinic-ester (CLV; R=Me). The carbonyl group of this molecule (CLIII; R=Me) should be capable of undergoing a Reformatsky reaction with ethyl α-bromoisobutyrate to furnish (CLIV) as a precursor of clovenic acid (VII). Although this would not lead directly to conversion to clovene (VI) (13), homologation of the keto-acid (CLIII; R=H) to (CLXXXIV; R=Me) prior to the Reformatsky

reaction should afford a product (CLXXXV), readily capable of Dieckmann cyclisation to the clovene skeleton.

The most straight-forward method for introducing a carbonyl group at the C_2 position of the olefinic-ester (CLV; R=Me) appeared to be direct allylic oxidation. Initially, the olefinic-ester was treated with excess t-butyl chromate (144) at 48° for 135 hrs., when the product exhibited an ultra-violet maximum at 231mμ (ε2,200) which indicated that the desired allylic oxidation had occurred, albeit in low yield. When the reaction was carried out at 52°, the percentage conversion was greater as witnessed by the ultra-violet maximum intensity of 4,600. This method, however, proved wasteful of material and extraction of the product from chromium residues proved troublesome. The difficulty of holding the reaction temperature steady over the long reaction time proved dangerous (t-butyl chromate is reputed to explode when heated to 60° (145)). Oxidation with chromium trioxide in acetic acid was then pursued, optimum yields of the enone-ester (CLVI; R=Me), as evidenced by the intensity of the ultra-violet maximum at 230mμ, being obtained with 1.1 equivalents of chromium trioxide at 100° for 10 mins. Excess oxidant degraded the product while lower temperatures or shorter reaction times decreased the percentage conversion. The most satisfactory method, for direct

allylic oxidation, employed 1.6 equivalents sodium dichromate in acetic acid at 90° for 10.5 hrs., (146) with recovery of 39% starting material which could be re-cycled.

Purification of the enone-ester (CLVI; R=Me)

A series of pilot experiments were now undertaken to determine the method of isolating the enone-ester (CLVI; R=Me) in a pure state.

(a) Chromatography on alumina effected a separation of still impure enone-ester from starting material, but the recovery from the column was not sufficiently high for large-scale work.

(b) Chromatography on silica sufficed to separate the olefinic-ester (CLV; R=Me), which could be re-cycled, from the enone-ester which, however, contained lactonic and other oxidative by-products.

(c) Fractional distillation was not applicable on a large-scale, co-distillation occuring, even although the boiling points of the two esters differed by 40° at 0.1 mm.

(d) Saponification with methanolic sodium hydroxide afforded the olefinic-acid (CLV; R=H) as the crystalline, light petroleum-soluble fraction, and the crude enone-acid (CLVI; R=H) as the oily light petroleum-insoluble fraction. The latter on esterification had an intensity of only 3,000 at the ultra-violet maximum of 230mμ which

suggested cleavage of the β-keto-ester system under the vigorous alkaline conditions.

(e) Attempts to prepare crystalline derivatives of the carbonyl function of the enone-ester, capable of regeneration were pursued. (i) The enone-ester did not react quantitatively with the Girard T reagent (147), nor could the derivative be regenerated, probably because of formation of a water-soluble pyrazolone. (ii) The enone-ester reacted quantitatively with semicarbazide acetate, but the semicarbazone was too soluble in methanol to be of practical value.

(f) It was thought that the saturated keto-ester (CLIII; R=Me) might be more suitable for purification than the enone-ester. (i) Reduction with lithium in liquid ammonia (148) successfully reduced the conjugated carbonyl grouping of the enone-ester (CLVI; R=Me) but also converted the carbomethoxyl group to a primary alcohol (149). Oxidation with chromium trioxide in acetic acid (149) followed by esterification afforded a mixture of the olefinic-ester (CLV; R=Me) and the keto-ester (CLIII; R=Me), separable by chromatography on alumina. This method was not practicable on a large scale. (ii) Hydrogenation over palladium charcoal resulted in a slow uptake of hydrogen affording a mixture of, at least, the keto-ester (CLIII; R=Me) and the saturated ester (CLXXXVI). Repeated acidic hydrolysis,

to safe-guard against possible β-keto-ester cleavage, afforded a mixture of the light petroleum-soluble crystalline acid (LXXIV), and the oily keto-acid (CLIII; R=H), which could not be induced to crystallise.

Of the above purification methods, chromatography on silica appeared to be the most valuable. From a large-scale oxidation of the olefinic-ester (CLV; R=Me) with sodium dichromate, the starting material could be recovered in 39% yield in the 50% benzene-light petroleum eluate. Further elution with 50% ether-benzene furnished the enone-ester (CLVI; R=Me) in 28% yield. We expected this enone-ester to have an extinction coefficient of 7000-8000 when pure, (c.f. the enone (CLXXXVII), prepared during the structural studies on gibberellic acid, which has an ultra-violet maximum at 229mμ (ε7,500) (150)). This sample of the enone-ester which had an ultra-violet maximum intensity of 5,500 was therefore still impure. Repeated chromatography on silica eventually afforded a sample with an ultra-violet maximum at 230mμ (ε6,900). This product exhibited bands of almost equal intensity at 1735 $cm.^{-1}$ (carbomethoxyl) and 1678 $cm.^{-1}$ (conjugated ketone), but the vapour phase chromatogram exhibited two bands, one approximately half as intense as the other. This sample of the enone-ester (CLVI; R=Me) gave one semicarbazone and two isomeric 2:4-dinitrophenyl-

hydrazones, one orange and the other orange-yellow, as yet not interconvertable by crystallisation techniques.*

* FOOTNOTE:- Initially it was thought that the formation of two 2:4-dinitrophenylhydrazones, coupled with the two bands in the vapour phase chromatogram, indicated the presence of the enone-ester (CLXXXVIII), possibly formed by an allylic rearrangement during the vigorous oxidation step. This however would not explain the relatively low intensity of the ultra-violet maximum, which requires any impurity to be transparent in the ultra-violet. To meet these requirements, it was thought that, during the vigorous oxidation step, the intermediate chromate-ester (CLXXXIX; R=CrO_3H) could be exchanged by an acetate residue furnishing an allylic acetate (CLXXXIX; R=$CO.CH_3$). No evidence for the presence of such a compound has been found in the mother liquors from the semicarbazone of the enone-ester (CLVI; R=Me).

It is now thought that the two 2:4-dinitrophenylhydrazones are simply *syn* and *anti* forms about the C=N bond.

Because of the purification difficulties encountered in the above experiments it was now considered preferable to effect allylic oxidation of the olefinic-ester (CLV; R=Me) in a more controlled fashion. Thus the olefinic-

ester was treated with t-butyl perbenzoate and cuprous bromide affording the allylic benzoate (CLXXXIX; R=CO.Ph) in a reaction which is known to proceed without rearrangement (151). The best yields were obtained when the olefinic-ester, which could be recovered and re-cycled, was present in excess of the oxidant. The viscous benzoate was successfully converted, by methanolysis, to the corresponding allyl alcohol ester (CLXXXIX; R=H), under conditions which are reputed not to bring about allylic rearrangement (152). Oxidation of the liquid hydroxy-ester with manganese dioxide effected quantitative conversion to the enone-ester (CLVI; R=Me), the infra-red spectrum of which was almost identical with that prepared by the direct oxidation method, except for a more intense band at 1678 cm^{-1} (enone). The ultra-violet maximum at 230mμ also had a slightly greater intensity (ε7,375) than that found previously.

Hydrogenation of the enone-ester (CLVI; R=Me), obtained by sodium dichromate oxidation, resulted in the uptake of 83% of the theoretical volume of hydrogen, whereas the enone-ester, prepared by the indirect oxidation technique, required the theoretical volume of hydrogen, affording the keto-ester (CLIII; R=Me). The product, which exhibited infra-red absorption at 1735 cm^{-1} (carbomethoxyl) and 1712 cm^{-1} (cyclohexanone),

was eluted as one band on the vapour phase chromatogram. The keto-ester, when treated with Brady's reagent in the cold, afforded one yellow 2:4-dinitrophenylhydrazone, while warming with Brady's reagent or hydrazine hydrate furnished the corresponding 2:4-dinitrophenylpyrazolone and pyrazolone respectively. The formation of these cyclic derivatives proved the formation of the desired keto-ester (CLIII; R=Me), possessing a non-enolisable β-keto-ester system.

Attempted conversion of the keto-ester (CLIII; R=Me) to clovenic acid (VII)

Having thus synthesised the desired keto-ester (CLIII; R=Me), we now desired to make use of the reactive carbonyl group at the C_2 position, with a view to preparing clovenic acid (VII), preparatory to further modification of the keto-ester (CLIII; R=Me) so as to obtain clovene(VI).

We hoped to react the keto-ester with cyanoacetic acid such that the initially formed cyano-acid (CXC) would be pyrolytically decomposed to the cyano-ester (CXCI; R=H) (153). This compound would be readily alkylated (154) affording an olefinic-cyano-ester (CXCI; R=Me) which on reduction would furnish clovenic acid (VII). However, the keto-ester did not react with cyanoacetic acid, though condensation was effected with malononitrile affording an unstable dinitrile-ester (CXCII). This reaction indicated that the C_2 position of the keto-ester (CLIII; R=Me) was not unreactive.

As stated previously (p. 158), a Reformatsky reaction between the keto-ester (CLIII; R=Me) and ethyl α-bromoisobutyrate might give a hydroxy-diester (CLIV) which should be capable of modification to clovenic acid (VII). There was a vigorous exothermic reaction between a mixture of the keto-ester, ethyl α-bromoisobutyrate and zinc. The product was separated into three fractions by distillation. The low-boiling fraction was probably a mixture of ethyl isobutyrate and the keto-ester (CXCIII), formed through condensation of two molecules of the reagent (155). The next fraction contained appreciable amounts of crystalline material which co-distilled with the low-boiling fraction. This material $(C_4H_6O)_x$, to which no structural assignments have yet been made, exhibited a strong band at 1700 $cm.^{-1}$ and a weak band at 1749 $cm.^{-1}$ in the infra-red. It was difficult to determine whether the high-boiling fraction was the desired condensation product because the infra-red spectrum, which exhibited only weak hydroxylic absorption, was similar to that of the starting material. It was thought that the product might be the olefinic-diester (CXCIV), but as the product could not be obtained pure nor converted to a crystalline diacid on hydrolysis, the validity of the condensation is not yet proved. It might be preferable to perform the Reformatsky reaction with magnesium in place of

zinc and with isobutyl α-bromoisobutyrate as the reaction is reputed to proceed in better yield (156).

Since the Reformatsky reaction did not appear to offer a direct route to clovenic acid (VII), we decided to perform an Arndt-Eistert reaction (143) on the keto-acid (CLIII; R=H) to furnish the keto-acid (CLXXXIV; R=H). The carboxyl group of this latter keto-acid should react with lithium methyl (157) to give a dione (CXCV) which should readily undergo an internal aldol reaction to furnish (CXCVI). Once such a tricyclic system has been formed, it should be comparatively simple to modify it to the clovene skeleton.

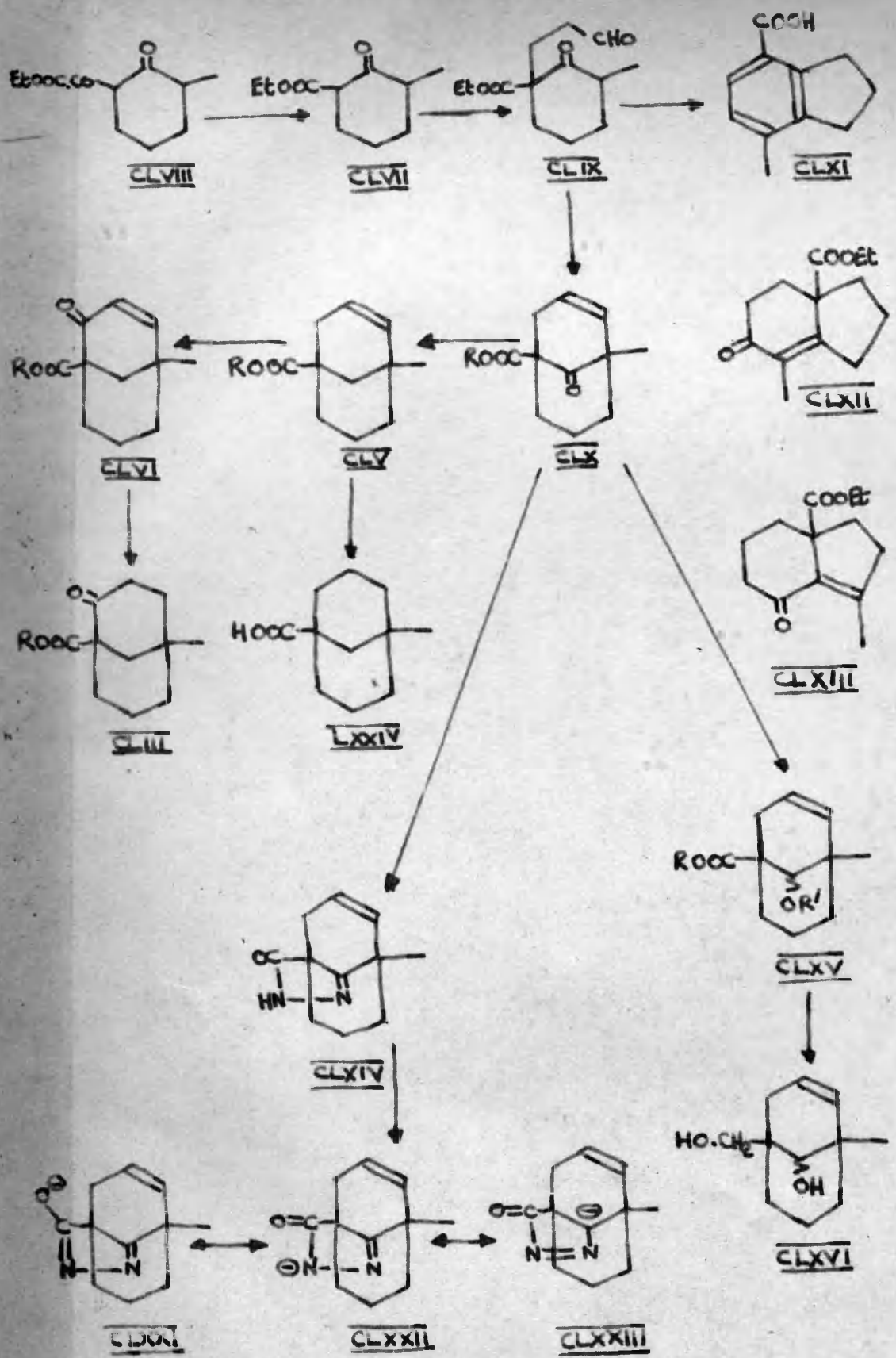
Saponification of the keto-ester (CLIII; R=Me), from either oxidative pathway, with methanolic potassium hydroxide, afforded the keto-acid (CLIII; R=H) as a thick oil, of which only a small portion could be induced to crystallise. This material melted over a wide range and could not be satisfactorily re-crystallised. The oily keto-acid formed crystalline cyclohexylamine and S-benzylisothiouronium salts, but the yield of the former was too low to be of any practical value for regeneration of the keto-acid. Chromatography of the keto-acid on silica sufficed to remove the keto-acid, together with the impurity, in the 5% ether-benzene eluate. The latter fractions of the eluate became progressively more crystalline but the bulk of the

product remained oily.

The impurity, which prevented the keto-acid from crystallising, could conceivably have been the diacid (CXCVII) furnished by cleavage of the β-keto-ester, but as yet, we have obtained no evidence that this is indeed the case. Previous work (p. 163) indicated that any impurity present was non-ketonic. Therefore, it was decided to purify the keto-acid (CLIII; R=H) through the hydroxy-esters (CXCVIII; R=Me), followed by hydrolysis (which should not result in any skeletal cleavage) and oxidation. The keto-ester (CLIII; R=Me) required extended treatment with sodium borohydride to convert the carbonyl function to hydroxyl, as evidenced by the slow disappearance of the infra-red band at 1712 $cm.^{-1}$ (cyclohexanone). Chromatography on silica afforded the hydroxy-ester (CXCVIII; R=Me) in the 5% ether-benzene eluate, but further elution with ether furnished significant amounts of a crystalline diol (CXCIX), presumably formed by concomitant reduction of the carbomethoxyl function. Saponification of the hydroxy-ester (CXCVIII; R=Me) and repeated crystallisation, afforded one of the epimers of the hydroxy-acid (CXCVIII; R=H). For the purification of the keto-acid (CLIII;R=H) through the hydroxy-acid (CXCVIII; R=H) to be of any practical value, it was imperative that the carboxyl function should not be reduced at the same time.

Hydrogenation of the keto-ester (CLIII; R=Me) over Adam's catalyst resulted in the theoretical uptake of hydrogen, and the resulting hydroxy-ester (CXCVIII; R=Me) was chromatographed on silica. Preliminary elution with 2% ether-benzene removed small amounts of lactonic and non-hydroxylic ketonic compounds. Further elution with 20% ether-benzene then furnished the pure hydroxy-ester (CXCVIII; R=Me). Saponification of the hydroxy-ester with methanolic potassium hydroxide afforded a mixture of crystalline hydroxy-acid epimers (CXCVIII; R=H), which could not be separated by repeated crystallisation. Oxidation of the mixture of epimeric hydroxy-acids with chromium trioxide in sulphuric acid (158) afforded the crystalline keto-acid (CLIII; R=H) which was further purified by repeated crystallisation from benzene.

The final steps necessary for the total synthesis of clovene by the synthetic route outlined on p. 158 are still under investigation in this department.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CHo
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CLXI
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ROOC
ROOC
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CLVI
CLV
CLX
COOEt
ROOC
HOOC
CLXIII
CLIII
LXXIV
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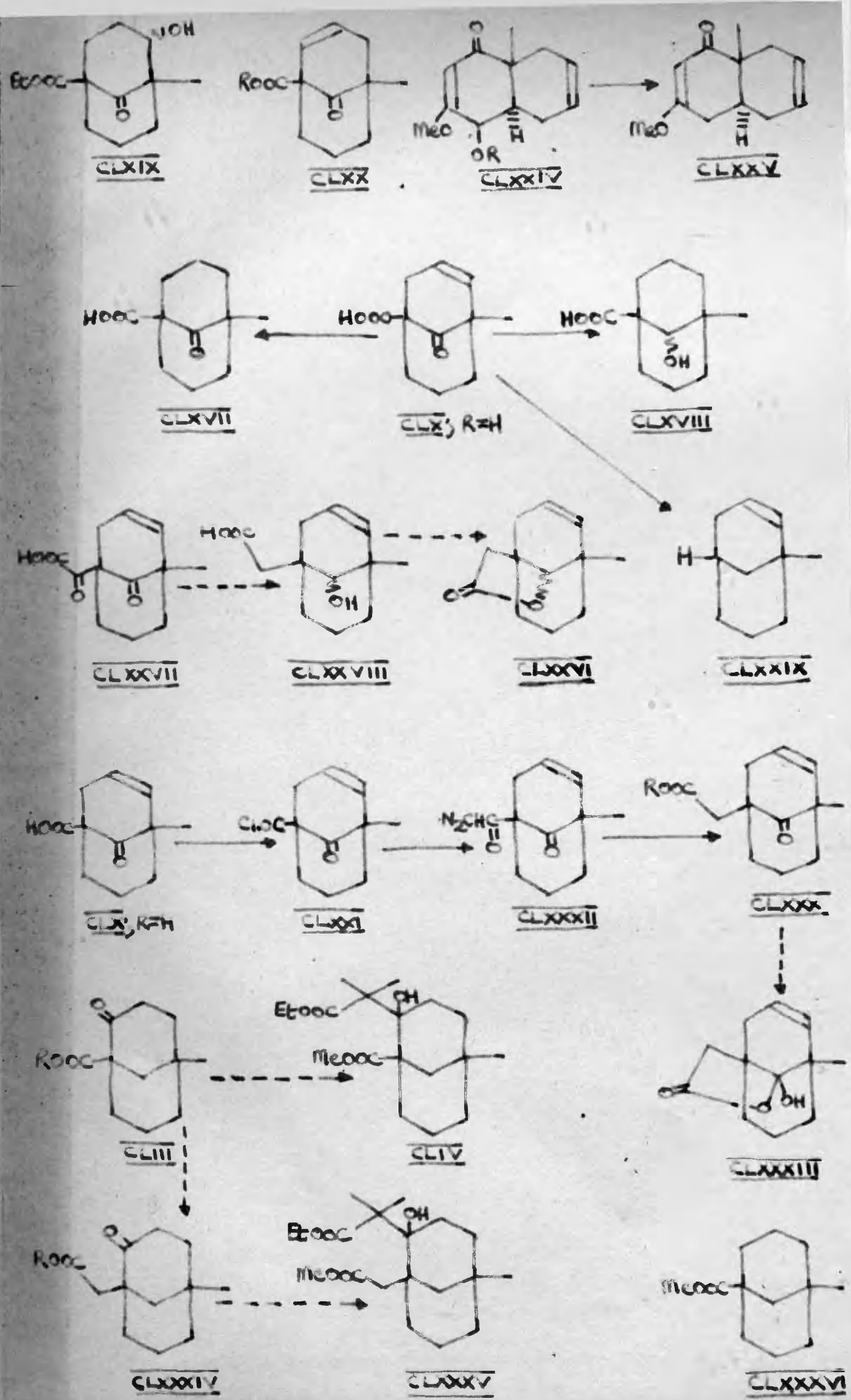
OR'
CLXV
CLXIV
HO.CH2
OH
CLXVI
CLXXI
CLXXII
CLXXIII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OH
CLXIX
ROOC
CLXX
MeO
OR
CLXXIV
MeO
CLXXV
HOOC
CLXVII
HOOC
CLX; R=H
HOOC
OH
CLXVIII
HOOC
CLXXVII
HOOC
OH
CLXXVIII
CLXXVI
H
CLXXIX
HOOC
CLX; R=H
ClOC
CLXXI
N2CHC
O
CLXXXII
ROOC
CLXXX
ROOC
CLIII
EtOOC
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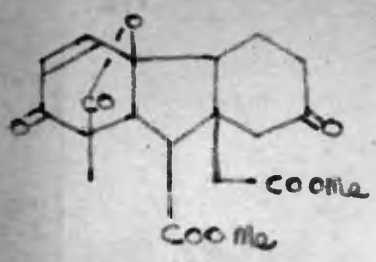
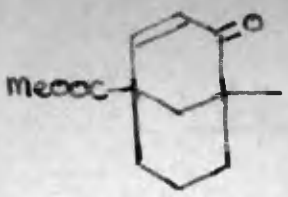
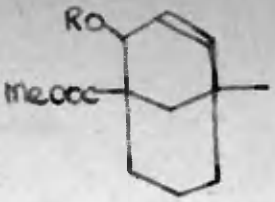
MeOOC
CLXXXVI



CLXXXVII



CLXXXVIII



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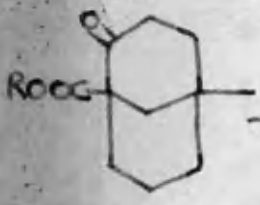
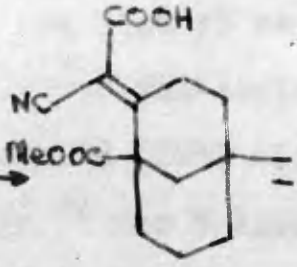
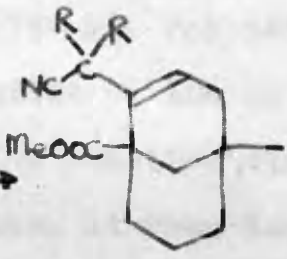


CLIII



CXC



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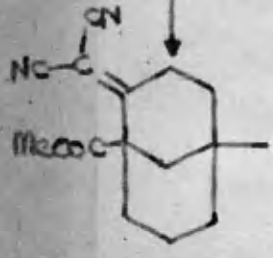

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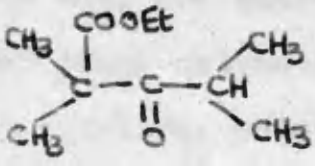

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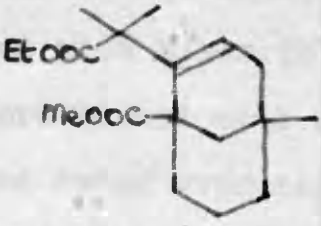
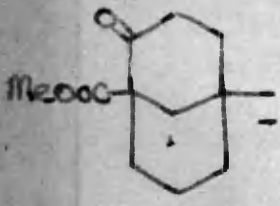
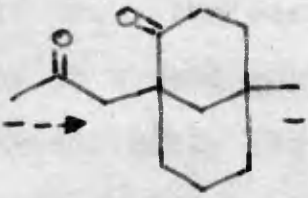


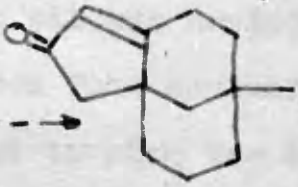
CXCIV



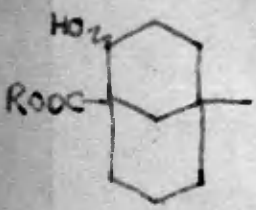
CLIII



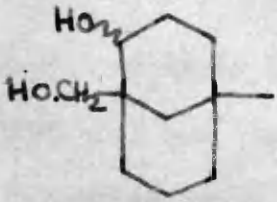
CXCV



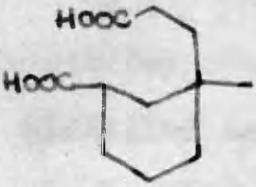
CXCVI



CXCVIII



CXCIX



CXCVII

EXPERIMENTAL

2-Carbethoxy-6-methylcyclohexanone (CLVII)

An ice-cold mixture of 2-methylcyclohexanone (500 g.) and diethyl oxalate (750 g.) was added with stirring to an ice-cooled solution of sodium (100 g.) in dry ethanol (1650 ml.). The reaction mixture was stirred at 0° for 5 hrs. and then at room temperature for 12 hrs. The orange solution was poured on to crushed ice and water, acidified with concentrated hydrochloric acid and extracted with ether (2 x 1 l.). The combined ether extracts were washed with sodium bicarbonate solution, water and dried over magnesium sulphate. After evaporation of the solvent, any unreacted starting materials were removed by evaporation at 140°/15 mm. The residual oil was heated at 190° for 5 hrs. in a well ventilated fume cupboard, and the product fractionally distilled to give the keto-ester as a colourless oil b.p. 135-140°/30 mm.; yield 600 g. (73%).

3-(1-Carbethoxy-2-keto-3-methylcyclohexyl)propionaldehyde (CLIX)

An ice-cold mixture of 2-carbethoxy-6-methylcyclohexanone (275 g.) and freshly distilled acrolein (100 g.) was added dropwise over 2 hrs. to a stirred solution of

sodium (1.7 g.) and hydroquinone (2.0 g.) in anhydrous ethanol (500 ml.) at -70°. After removing the cooling bath, the solution was stirred for a further 0.5 hr. at room temperature then brought to approximately pH 7 by adding glacial acetic acid. After evaporation of solvent under reduced pressure, the viscous residue was dissolved in ether (2 l.), washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent under reduced pressure followed by fractionation of the product afforded the aldehydo-keto-ester as a viscous colourless oil, b.p. 164°/2 mm.; yield 205 g. (57%). (Found: C, 64.85; H, 8.15. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%). The product exhibited infra-red absorption at 2700 $cm.^{-1}$ (aldehyde), and 1720 $cm.^{-1}$ (carbethoxyl and cyclohexanone and aldehyde). The corresponding bis 2:4-dinitrophenylhydrazone crystallised from methanol as orange needles (Found: C, 49.95; H, 4.45; N, 13.45. $C_{25}H_{28}O_{10}N_8$ requires C, 50.0; H, 4.7; N, 18.65%).

1-Carbethoxy-5-methylbicyclo[3:3:1]non-3-ene-9-one (CLX; R=Et)

The freshly distilled aldehydo-ester (CLIX) (200 g.) was added in very fine drops to vigorously stirred concentrated sulphuric acid, cooled in an ice-bath. After the addition was complete, the ice-bath was removed and the

solution allowed to stand at room temperature overnight. The dark red solution was poured carefully with stirring on to crushed ice and water and the mixture extracted with ether (2 x 1 l.) The combined ether extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick red oil which distilled as a colourless oil b.p. 114-144°/0.2 mm.; yield 135 g.).

A solution of the keto-ester (2 g.) in light petroleum was chromatographed on alumina (Grade I) (50 g.). Elution with light petroleum (10 x 50 ml.) afforded the keto-ester (CLX; R=Et) as a colourless oil (1.17 g.). The product, which gave no reaction with 2:4-dinitrophenylhydrazine or semicarbazide acetate, exhibited infra-red absorption at 1730 $cm.^{-1}$ (carbethoxyl), 1715 $cm.^{-1}$ (cyclohexanone) and 1650 $cm.^{-1}$ (olefinic double bond) with ultra-violet end-absorption $\varepsilon^{210}=1280$; $\varepsilon^{220}=425$; $\varepsilon^{210}/\varepsilon^{220}=3.0$. The keto-ester distilled as a colourless oil b.p. 106°/0.1 mm., n_D^{18} 1.4898 (Found: C, 70.25 ; H, 7.95 . $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%).

Further elution with benzene (4 x 50 ml.) afforded a colourless oil (0.80 g.), b.p. 92-94°/0.25 mm. The product, $C_{13}H_{18}O_3$, exhibited infra-red absorption at

1720 cm^{-1} (carbethoxyl) and 1652 cm^{-1} (conjugated ketone), with an ultra-violet maximum at 252mμ (ε10,450).

5-Methylbicyclo[3:3:1]non-3-ene-9-one-1-carboxylic acid (CLX; R=H)

A solution of the crude keto-ester (CLX; R=Et) (5.0 g.) in methanol (25 ml.) was gently refluxed for 2 hrs. with a solution of sodium hydroxide (1.0 g.) in water (5 ml.). After evaporation of methanol under reduced pressure the cooled mixture was diluted with water and extracted with ether (2 x 15 ml.). The aqueous extracts were acidified with concentrated hydrochloric acid, saturated with ammonium sulphate and extracted with ether (2 x 30 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Removal of solvent gave a crystalline solid (4.1 g.) m.p. 98-136°, which was recrystallised twice from benzene-light petroleum (b.p. 60-80°) as colourless needles of (CLX; R=H) m.p. 140-142°; yield 2.57 g. (59%). (Found: C, 68.1; H, 7.35. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%). Evaporation of the mother liquors afforded a thick oil, the infra-red spectrum of which exhibited broad absorption bands at 1650 cm^{-1} (conjugated carbonyl) and from 3300 to 2300 cm^{-1} (carboxyl).

1-Carbomethoxy-5-methylbicyclo[3:3:1]non-3-ene-9-one (CLX; R=Me)

A solution of the keto-acid (CLX; R=H) (1.75 g.) in dry ether (20 ml.) was treated with a slight excess of a dry ethereal solution of diazomethane, and the solution allowed to stand at room temperature for 2 hrs. After addition of a little acetic acid, the ethereal solution was washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (1.85 g.) which rapidly solidified. Crystallisation from light petroleum furnished the keto-ester (CLX; R=Me) as colourless needles m.p. 79-82°. (Found: C, 69.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%). The product exhibited infra-red absorption at 1728 cm^{-1} (carbomethoxyl), 1705 cm^{-1} (cyclohexanone) and weak bands at 3000 and 1637 cm^{-1} (olefinic double bond) with ultra-violet absorption $\varepsilon^{210}=920$; $\varepsilon^{220}=390$; $\varepsilon^{210}/\varepsilon^{220}=2.35$.

9-Hydroxy-5-methylbicyclo[3:3:1]nonane-1-carboxylic acid (CLXVIII)

A solution of the keto-acid (CLX; R=H) (19 mg.) in ethyl acetate was hydrogenated using platinum oxide (35 mg.) at room temperature and atmospheric pressure; hydrogen (2 mole equivalents) was absorbed within 0.25 hr. Evaporation of the filtered solution afforded a stereoisomeric mixture of crystalline hydroxy-acids (CLXVIII) as colourless leaves m.p. 144-165° from

benzene-light petroleum (b.p. 60-80°). Repeated sublimation afforded one epimer as rectangular plates m.p. 178.5-180.5°. (Found: C, 66.5; H, 9.3. $C_{11}H_{18}O_3$ requires C, 66.65; H, 9.15%).

5-Methylbicyclo[3:3:1]nonan-9-one-1-carboxylic acid (CLXVII)

A solution of the keto-acid (CLX; R=H) (30 mg.) in ethyl acetate was hydrogenated using 10% palladium-charcoal at room temperature and atmospheric pressure; hydrogen (0.9 mole equivalent) was absorbed over 6 hrs. Evaporation of the filtered solution afforded the keto-acid (CLXVII) as colourless leaves, m.p. 125-140° from benzene-light petroleum (b.p. 60-80°), which sublimed as rectangular plates m.p. 140.5-142° (Found: C, 67.35 ; H, 7.85 $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.15%).

9-Hydroxy-5-methylbicyclo[3:3:1]non-3-ene-1-carboxylic acid (CLXV; R=R'=H)

A solution of the keto-acid (CLX; R=H) (5.0 g.) in aqueous methanol was treated with excess sodium borohydride at room temperature, and, after the initial effervescence, the mixture was allowed to stand at room temperature for 2 hrs. After acidification with dilute sulphuric acid and saturation with ammonium sulphate, the mixture was extracted with ether. The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate.

Evaporation of solvent afforded the hydroxy-acid as a colourless solid (5.1 g.) which crystallised as leaves from benzene m.p. 171-173° with moisture from 130° and sublimation from 150°. The hydroxy-acid sublimed as rectangular plates m.p. 173-174°. (Found: C, 67.5; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.15%). The product exhibited infra-red absorption at 3340 $cm.^{-1}$ (hydroxyl) with a broad band from 3500 to 2300 $cm.^{-1}$ and a band at 1695 $cm.^{-1}$ (carboxyl). The ultra-violet spectrum exhibited $\varepsilon^{210}=230$; $\varepsilon^{220}=105$; $\varepsilon^{210}/\varepsilon^{220}=2.2$.

1-Hydroxymethyl-9-hydroxy-5-methylbicyclo[3:3:1]non-3-ene (CLXVI)

A stirred solution of the hydroxy-ester (CLXV; R=Me, R′=H) (1.05 g.) in dry ether (25 ml.) was refluxed for 12 hrs. with lithium aluminium hydride (0.24 g.). The cooled mixture was treated carefully with dry ethyl acetate (5 ml.), acidified with dilute sulphuric acid and the ethereal layer washed with dilute sodium bicarbonate solution, saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (0.95 g.) which rapidly solidified. The diol, which on repeated crystallisation from benzene-light petroleum as colourless needle clusters had m.p. 127-133° (moisture from 114°), sublimed as plates m.p. 134-136°. (Found: C, 72.7; H, 9.65. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%). The product exhibited infra-red absorption

at 3250 $cm.^{-1}$ (hydroxyl) and a weak band at 1630 $cm.^{-1}$ (olefinic double bond) with ultra-violet absorption ε^{210}=130; ε^{220}=51; $\varepsilon^{210}/\varepsilon^{220}$ = 2.6.

1-Carbomethoxy-9-hydroxy-5-methylbicyclo[3:3:1]non-3-ene (CLXV; R=Me, R'=H)

A solution of the keto-ester (CLX; R=Me) (8.0 g.) in methanol (50 ml.) and water (5 ml.) was treated at room temperature with sodium borohydride (1.2 g.), added in 0.2 g. portions over 0.5 hr. After the initial vigorous effervescence had subsided, the solution was allowed to stand at room temperature overnight. After methanol had been removed under reduced pressure without warming, the mixture was poured into water (100 ml.), acidified with dilute sulphuric acid and extracted with ether (2 x 40 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded the hydroxy-ester as a non-crystallisable colourless oil; yield 7.85 g. (97%). Fractionation afforded a colourless oil b.p. 82°/0.02 mm., n_D^{26} 1.4961. (Found: C, 68.35; H, 8.4. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%). The product exhibited infra-red absorption at 3470 $cm.^{-1}$ (hydroxyl), 1720 $cm.^{-1}$ (carbomethoxyl) with weak bands at 3005 and 1643 $cm.^{-1}$ (olefinic double bond), with ultra-violet absorption ε^{210} = 236; ε^{220} = 93; $\varepsilon^{210}/\varepsilon^{220}$ = 2.53.

1-Carbomethoxy-2-acetoxy-5-methylbicyclo[3:3:1]non-3-ene (CLXV; R=Me, R'=$CO.CH_3$)

A solution of the hydroxy-ester (CLXV; R=Me, R'=H) (500 mg.) in pyridine (5 ml.) and acetic anhydride (5 ml.) was allowed to stand at room temperature for 11 hrs. Evaporation to dryness under reduced pressure afforded a pale yellow oil, the infra-red spectrum of which exhibited a band at 3470 $cm.^{-1}$ (hydroxyl) (intensity of band corresponded to presence of at least 70% starting material in the product) and a weak band at 1650 $cm.^{-1}$.

A solution of the hydroxy-ester (500 mg.) in dry acetic anhydride (10 ml.) was refluxed for 3 hrs. with anhydrous sodium acetate (1 g.). After evaporation of the solvent under reduced pressure, the residue was poured into water and extracted with ether (2 x 25 ml.). The combined ethereal extracts were washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick yellow oil (600 mg.), the infra-red spectrum of which exhibited no band at 3470 $cm.^{-1}$ (hydroxyl), a strong band at 1735 $cm.^{-1}$ (acetate and carbomethoxyl) and medium bands at 1650 and 1620 $cm.^{-1}$ (conjugated carbonyl) with an ultra-violet maximum at 241mμ (ε2000-3000). A solution of the crude acetate (600 mg.) in light petroleum (b.p. 60-80°) was chromatographed on alumina (Grade III) (19 g.). Elution with light petroleum (b.p. 60-80°) (6 x 50 ml.); 50% benzene-light petroleum

(5 x 50 ml.); and benzene (3 x 50 ml.) afforded the acetoxy-ester as a colourless oil (300 mg.) b.p. 80°/0.02 mm., n_D^{23} 1.4810. (Found: C, 67.05; H, 8.05. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.0%). The product exhibited infra-red absorption at 1735 $cm.^{-1}$ (acetate and carbomethoxy), 1230 $cm.^{-1}$ (acetate) with a medium band at 3000 $cm.^{-1}$ and a weak band at 1650 $cm.^{-1}$ (olefinic double bond). The ultra-violet end-absorption exhibited $\varepsilon^{210} = 814$; $\varepsilon^{220} = 480$; $\varepsilon^{210}/\varepsilon^{220} = 1.7$.

Further elution with 50% ether-benzene (4 x 50 ml.) afforded a yellow oil (48 mg.), the infra-red spectrum of which exhibited bands at 1735 $cm.^{-1}$ (carbomethoxyl), 1650 and 1620 $cm.^{-1}$ (conjugated carbonyl) with a medium band at 3470 $cm.^{-1}$ (hydroxyl).

NOTE:- The phenomenon that the acetate-ester (above) was not eluted completely with one eluent but required three solvent mixtures for complete elution, is characteristic of chromatograms of compounds of the bicyclo 3:3:1 nonane system.

A solution of the hydroxy-ester (CLXV; R=Me, R =H) (1.0 g.) in dry pyridine (10 ml.) was refluxed for 12 hrs. Evaporation to dryness under reduced pressure afforded a pale yellow oil (1.0 g.), the infra-red spectrum of which was identical with that of starting material.

Attempted formation of p-toluenesulphonate of the hydroxy-ester (CLXV; R=Me, R′=H)

A solution of the hydroxy-ester (500 mg.) in dry pyridine (5 ml.) containing p-toluenesulphonyl chloride (1 g.) was allowed to stand at room temperature for 11 hrs. The mixture was poured into water (5 0 ml.), acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 25 ml.). The combined ethereal extracts were washed with sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a mobile oil (650 mg.), the infra-red spectrum of which indicated it to be mainly starting material. The only crystalline material obtained by trituration proved to be p-toluenesulphonyl chloride m.p. 67-68°.

1-Carbomethoxy-9-methanesulphoxy-5-methyl-bicyclo[3:3:1]-non-3-ene (CLXV; R=Me, R′=$SO_2.CH_3$)

Redistilled methanesulphonyl chloride (16.0 g., 0.14 mole) was added to a solution of the hydroxy-ester (CLXV; R=Me, R′=H) (14.5 g., 0.07 mole) in dry pyridine (16.6 g., 0.21 mole). After the initial exothermic reaction had subsided the solution was allowed to stand in the dark at room temperature for 12 hrs. The reaction mixture, containing large amounts of pyridine hydrochloride, was poured into a large excess

of saturated sodium carbonate solution and allowed to stand, with occasional shaking, for 2 hrs., and then extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with dilute sulphuric acid, water and dried over magnesium sulphate. Evaporation of solvent under reduced pressure without heating afforded a pale yellow oily solid. Trituration with ether-light petroleum afforded the crystalline epimeric methanesulphonate (6.6 g.), m.p. 86-103°. The oily mother liquors (9.3 g.) which contained some starting material (infra-red band at 3470 $cm.^{-1}$ (hydroxyl)), were retreated with methanesulphonyl chloride in pyridine and worked up as above affording the thick liquid epimeric methanesulphonate (8.9 g.). The crystalline methanesulphonate crystallised from benzene-light petroleum as colourless hexagonal prisms m.p. 115-117°, which melted without decomposition and resolidified on cooling. (Found: C, 54.6; H, 6.55. $C_{13}H_{20}O_5S$ requires C, 54.15; H, 6.95%). The product exhibited infra-red absorption at 1728 $cm.^{-1}$ (carbomethoxyl), 1267 and 1170 $cm.^{-1}$ (methanesulphonate) with a medium band at 3000 $cm.^{-1}$ and a weak band at 1650 $cm.^{-1}$ (olefinic double bond). The ultra-violet end-absorption exhibited $\varepsilon^{210} = 190$; $\varepsilon^{220} = 115$; $\varepsilon^{210}/\varepsilon^{220} = 1.67$. Discoloration resulted when the

crystals were dried in a vacuum oven at 50°/0.1 mm. overnight. The infra-red spectrum of the product was almost identical with that of starting material except for an increase in intensity of the band at 1650 $cm.^{-1}$ with concomitant appearance of a maximum in the ultra-violet at 254mμ (ε ca. 500).

The infra-red spectrum of the liquid epimeric methanesulphonate was very similar to that of the crystalline epimer, with bands at 1728 $cm.^{-1}$ (carbomethoxyl), 1257 $cm.^{-1}$ and 1170 $cm.^{-1}$ (methanesulphonate) with a medium band at 3000 $cm.^{-1}$ and a weak band at 1650 $cm.^{-1}$ (olefinic double bond). A portion of the liquid could be distilled as a mobile colourless oil b.p. 60°/0.02 mm.; n_D^{21} 1.4950, but rapid decomposition occurred at 80°. The infra-red spectrum of the distillate was markedly different from that of starting material exhibiting weak bands at 1770 $cm.^{-1}$ (γ-lactone), 1665 $cm.^{-1}$ (conjugated carbonyl) and 1600 $cm.^{-1}$ (aromatic) in conjunction with the strong band at 1730 $cm.^{-1}$ (Carbomethoxyl).

Attempted elimination of the methanesulphonate residue

A stirred solution of a mixture of epimeric methanesulphonates (CLXV; R=Me, $R'=SO_2CH_3$) (700 mg.) in glacial acetic acid (100 ml.) was refluxed for 14 hrs. with zinc powder (50 g.). Zinc was removed from the

cooled mixture by filtration and washed thoroughly with ether. The filtrate was neutralized with dilute sodium hydroxide; the ether layer separated, washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a pale yellow mobile oil (400 mg.) b.p. 82°/0.6 mm., n_D^{23} 1.5000. The infra-red spectrum of the product was almost identical with that of the distillate from the liquid methane-sulphonate and was markedly different to that of authentic olefinic-ester (CLV; R=Me) (see later). The product exhibited an ultra-violet maximum at 243mμ (ε2000-2500).

Attempted dioxolanation of the keto-ester (CLX; R=Me).

A solution of the keto-ester (570 mg.) in dry benzene (50 ml.) was refluxed with ethylene glycol and catalytic amounts of naphthalene-2-sulphonic acid for 15 hrs. under a Dean and Stark apparatus. The cooled solution was washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a colourless oil (725 mg.) which, unlike starting material, would not crystallise spontaneously. The product exhibited infra-red absorption at 1735 $cm.^{-1}$ (carbomethoxyl) and 1712 $cm.^{-1}$ cyclohexanone) with a medium band at 3450 $cm.^{-1}$ (hydroxyl). As the intensity of the 1735 $cm.^{-1}$ (carbomethoxyl) band had decreased with respect to the 1712 $cm.^{-1}$ (cyclohexanone) band, in the product, it appeared that trans-esterification had occurred affording a mixture of keto-ester (CLX; R=Me) and (CLX; R= $CH_2 \cdot CH_2$ OH).

Pyrazolone of 1-carbomethoxy-5-methylbicyclo[3:3:1]non-3-ene-9-one (CLXIV)

A solution of the keto-ester (CLX; R=Me) (2.0 g.) in methanol (10 ml.) was refluxed on steam bath for 1.5 hrs. with 100% hydrazine hydrate (1 g.). After evaporation of the methanol, the cooled mixture was diluted with benzene, washed with water and dried over magnesium sulphate. Evaporation of solvent afforded the pyrazolone (1.6 g.) m.p. 144-148°, which crystallised from methanol as colourless prisms, m.p. 147-149°. (Found: C, 69.35; H, 7.35. $C_{11}H_{14}O_2N$ requires C, 69.45; H, 7.4%). The product exhibited infra-red absorption at 3130, 1680 and 1610 $cm.^{-1}$.

Attempted Wolff-Kishner reduction of the pyrazolone (CLXIV)

(a) The pyrazolone (700 mg.) was added to a cooled solution of sodium (0.5 g.) in diethylene glycol (25 ml.) and the mixture heated to 210° for 1.5 hrs. The pyrazolone dissolved at 60° and there was a vigorous evolution of gas, probably hydrogen, between 150-200°. The cooled mixture was poured into saturated ammonium sulphate solution, acidified with dilute sulphuric acid and extracted with ether (2 x 25 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a brown solid (610 mg.) m.p. 140-143.5°, the infra-red spectrum of which was almost identical with that of starting material.

(b) A mixture of the pyrazolone (610 mg.) and potassium hydroxide (5 g.) in ethylene glycol (25 ml.) was heated at 170° overnight and worked up as before. The infra-red spectrum of the brown solid was identical with that of the starting material.

Attempted isomerisation of the keto-acid (CLX; R=H)

A solution of the keto-acid (1.0 g., m.p. 140-142°) in xylene (25 ml.) was refluxed with concentrated hydrochloric acid (15 ml.) for 9 hrs. The cooled mixture was saturated with ammonium sulphate and the separated xylene extract washed thoroughly with sodium carbonate solution. The alkaline extracts were carefully acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a crystalline solid (700 mg.)(m.p. 137-140°), the infra-red spectrum of which was identical with that of the starting material.

5-Methylbicyclo[3:3:1]non-3-ene-1-carboxylic acid(CLV;R=H)

Zinc amalgam was prepared by shaking a mixture of zinc powder (200 g.), mercuric chloride (20 g.), concentrated hydrochloric acid (10 ml.) and water (100 ml.) for 5 mins. The aqueous layer was decanted and the zinc amalgam covered with water (100 ml.) and concentrated hydrochloric acid (200 ml.). The keto-acid (CLX; R=H) (20.8 g.) and xylene (100 ml.) were then added and the

mixture refluxed vigorously for 12 hrs. Further portions of concentrated hydrochloric acid (2 x 50 ml.) were added at intervals of 4 hrs. The cooled mixture was filtered, and the filtrate saturated with ammonium sulphate and extracted with ethyl acetate (2 x 250 ml.). The combined ethyl acetate extracts were washed thoroughly with saturated sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick sweet-smelling oil (2.98 g.)

The alkaline extracts were carefully acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ethyl acetate (2 x 150 ml.). The combined ethyl acetate extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a colourless solid (13.96 g.) which was warmed with light petroleum. The light petroleum insoluble material was removed by filtration and the light petroleum extracts taken to dryness and the process repeated. The light petroleum insoluble material (2.50 g.) m.p. 130-157°, exhibited an infra-red spectrum almost identical with that of the mixture of epimeric hydroxy acids (CLXV; R=R′=H) afforded by sodium borohydride reduction of the keto-acid (CLX; R=H).

The light petroleum soluble material (11 g., 57%) m.p. 75-105° could be purified by crystallisation from

light petroleum as colourless needles or by sublimation as rods to give the required pure olefinic-acid (CLV; R=H) m.p. 104-106° (Found: C, 73.55; H, 9.1. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%). The product exhibited infra-red absorption at 1700 cm.$^{-1}$ (carboxyl), 1650, 1207, 724 and 712 cm.$^{-1}$ (*cis* disubstituted olefinic double bond), with ultra-violet end-absorption $\varepsilon^{210} = 433$; $\varepsilon^{220} = 201$; $\varepsilon^{210}/\varepsilon^{220} = 2.15$.

NOTE:- The yield of olefinic-acid (CLV; R=H) decreased, and the yield of neutral by-products increased, with increasing reaction time.

FOOTNOTE:- The neutral fraction of the product from Clemmensen reduction of the keto-acid (CLX; R=H) (20.8 g.) was isolated as a thick yellow sweet-smelling oil (2.98 g., 12%). The product exhibited infra-red bands at 2900, 2840 and 1440 cm.$^{-1}$ (paraffin), 1779 cm.$^{-1}$ (γ-lactone), with weak bands at 3000 and 1650 cm.$^{-1}$ (olefinic double bond) and 1595 and 1480 cm.$^{-1}$ (aromatic). Fractionation of the mixture afforded the lactonic material as the more volatile fraction b.p. 86-90°/0.05 mm., n_D^{18} 1.5080 and the paraffin as the higher boiling fraction b.p. 128-132°/0.05 mm., n_D^{18} 1.5311. Repeated fractionation of the fore-run afforded the lactonic material (CLXXVI) as a colourless mobile sweet-smelling oil b.p. 80°/0.1 mm., n_D^{20} 1.4968. (Found: C, 74.55; H, 8.45. $C_{12}H_{16}O_2$ requires C, 74.95; H, 8.4%). The product exhibited infra-red absorption at 1779 cm.$^{-1}$ (γ-lactone) with a weak band at 1650 cm.$^{-1}$

(olefinic double bond) and ultra-violet end-absorption $\varepsilon^{210} = 2050$; $\varepsilon^{220} = 1200$; $\varepsilon^{210}/\varepsilon^{220} = 1.71$. A molecular weight of 190 (calculated 192) was determined on the mass spectrometer.

A solution of the lactone (200 mg.) in dry ether (5 ml.) was refluxed with stirring for 2 hrs. with lithium aluminium hydride (200 mg.). The cooled mixture was carefully decomposed with dry ethyl acetate, acidified with dilute sulphuric acid and separated ether layer washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a viscous, colourless, non-crystallisable oily diol (155 mg.), the infra-red spectrum of which exhibited a band at 3250 $cm.^{-1}$ (hydroxyl) with no absorption in the carbonyl region.

A sample of the crude neutral mixture (6.3 g.) was separated into equal fractions by distillation. The latter fraction b.p. 120-132°/0.05 mm.), was chromatographed on alumina (Grade III) (50 g.). Elution with light petroleum (100 ml.) afforded a colourless oil 1.8 g., (30%). The product exhibited infra-red absorption at 2895, 2820, 1440, 1430 and 1360 $cm.^{-1}$ with weak bands at 1660 and 1235 $cm.^{-1}$ Fractionation afforded 1-methylbicyclo [3:3:1] non-2-ene as a colourless, viscous, oil (CLXXIX) b.p. 120°/0.15 mm., n_D^{20} 1.5220. (Found: C, 88.45; H, 11.55. $C_{10}H_{16}$ requires C, 88.15; H,11.85%) A molecular weight of 136 (calculated 136) was determined

on the mass spectrometer. Further elution with light petroleum (100 ml.) afforded a pale yellow oil (0.48 g.), the infra-red spectrum of which was similar to that of the paraffin (above) but contained further bands at 3000, 1595, 1487, 822, 770 and 700 $cm.^{-1}$ (aromatic).

5-Methylbicyclo[3:3:1]nonane-1-carboxylic acid (LXXIV)

A solution of the olefinic acid (CLV; R=H) (31 mg.) in ethyl acetate was hydrogenated over platinum oxide at room temperature; the theoretical uptake of hydrogen (3.6 ml.) being absorbed within 5 mins. Filtration and evaporation of the solvent afforded the parent acid which was purified by sublimation as needles m.p. 141-143°. The product, which was transparent in the ultra-violet, was identical (m.p.; mixed m.p.; infra-red spectrum) with the carboxylic acid afforded by Wolff-Kishner reduction of 5-methylbicyclo[3:3:1]nonan-3-one-1-carboxylic acid (XXXII; R=H).

1-Carbomethoxy-5-methylbicyclo[3:3:1]non-3-ene (CLV; R=Me)

A solution of the olefinic-acid (CLV; R=H) (5.0 g.) in dry ether (25 ml.) was treated with a slight excess of an ethereal diazomethane solution and the solution allowed to stand at room temperature for 2 hrs. After addition of a little acetic acid, the ethereal solution was washed with dilute sodium bicarbonate solution, water

and dried over magnesium sulphate. Evaporation of solvent afforded a pale yellow mobile oil (5.1 g.) with a camphor-like odour. Fractionation afforded the ester as a colourless oil b.p. 55°/0.1 mm., n_D^{21} 1.4825. (Found: C, 74.05; H, 9.4. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%). The product exhibited infra-red absorption at 1728 $cm.^{-1}$ (carbomethoxyl), 3005, 1650, 1202, 713, and 701 $cm.^{-1}$ (cis disubstituted olefinic double bond) with ultra-violet end-absorption, $\varepsilon^{210} = 560$; $\varepsilon^{220} = 260$; $\varepsilon^{210}/\varepsilon^{220} = 2.13$.

In large scale work it was found difficult to purify the olefinic-acid (CLV; R=H), thus the crude light petroleum soluble acidic material from the Clemmensen reduction was esterified directly and the olefinic-ester (CLV; R=Me) purified by distillation. The boiling point, refractive index, infra-red and ultra-violet spectra of the once-distilled ester were identical with the pure ester and it was not until ambiguities arose in later work that doubts as to the purity of the ester, so prepared, were considered. Examination of the vapour phase chromatogram of the ester revealed two bands. The main band, attributed to the olefinic-ester (CLV; R=Me), was eluted after 12 mins at 136°, and a weak band (5-10%), attributed to the keto-ester (CLX; R=Me), eluted after 25 mins.

For large scale purification of the olefinic-ester (CLV; R=Me), a solution of the crude ester in methanol was treated with one equivalent of sodium borohydride in a little water and the mixture allowed to stand at room temperature for 2 hrs. The mixture was poured into a large volume of water, acidified with dilute sulphuric acid and extracted with ether. The ether extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a sweet-smelling mobile oil, the infra-red spectrum of which exhibited a sharp band at 1728 $cm.^{-1}$ (carbomethoxyl) with a weak band at 3470 $cm.^{-1}$ (hydroxyl). A solution of the product in light petroleum was chromatographed on alumina (Grade H) (10 x wt. product). Elution with 20% benzene-light petroleum (4 x 600 ml.) afforded the pure olefinic-ester (CLV; R=Me) which was eluted as one band on the vapour-phase chromatogram after 6 mins. at 150°. The product was then distilled before use.

Further elution with ether (3 x 600 ml.) afforded small amounts of an oil, the infra-red spectrum of which showed it to consist mainly of the olefinic-ester (CLV; R=Me), hydroxy-ester (CLXV; R=Me, R =H) with a band at 1779 $cm.^{-1}$ (γ-lactone). The vapour-phase chromatogram of a sample at 146° identified six bands, eluted after 4½, 5½, 6½, 11, 12 and 14½ mins. respectively. From a number of runs it was found that the keto-acid (CLX; R=H) (174 g.) afforded pure olefinic-ester (CLV; R=Me) (66.8 g.) in 38% overall yield

5-Methylbicyclo[3:3:1]non-3-ene 9-one-1-carboxylic acid chloride (CLXXXI)

Oxalyl chloride (15 ml.) was added to a solution of the keto-acid (CLX; R=H) (15 g.) in dry benzene (50 ml.) and the solution allowed to stand at room temperature overnight. Evaporation of solvent afforded a pale yellow oil (16.4 g.) which rapidly solidified. Crystallisation from light petroleum afforded the acid chloride as colourless prisms m.p. 74-75°. (Found: C, 62.4; H, 6.25; Cl, 16.45. $C_{11}H_{13}O_2Cl$ requires C, 62.15; H, 6.1; Cl, 16.7%). The product exhibited infra-red absorption at 1778 and 740 $cm.^{-1}$ (acid chloride), 1706 $cm.^{-1}$ (cyclohexanone), 3000 and 1650 $cm.^{-1}$ (olefinic double bond).

Arndt-Eistert reaction of the keto-acid (CLX; R=H)

(a) Preparation of the diazoketone (CLXXXII)

A solution of the acid chloride (CLXXXI) (11.3 g.) in dry benzene (25 ml.) was added slowly with stirring to an ice-cold solution of diazomethane (2 equivalents) in ether (1 l.) and the solution stirred gently for 2 hrs. at 0° and for 12 hrs. at room temperature. Evaporation of solvent under reduced pressure without heating afforded the diazoketone as a thick yellow non-crystallisable oil (11.5 g.). The product exhibited infra-red absorption at 3100, 2200 and 1620 $cm.^{-1}$ (diazoketone), 1708 $cm.^{-1}$ (cyclohexanone) and 3000 $cm.^{-1}$ (olefinic double bond).

(b) 1-Carbo-t-butoxymethyl-5-methylbicyclo [3:3:1] non-3-ene-9-one (CLXXX; R=Bu^t)

A gently refluxed, stirred solution of the crude diazoketone (11.5 g.) in dry t-butanol (250 ml.) was treated portionwise over 0.5 hr. with a solution of silver benzoate (1.8 g.) in dry triethylamine (18 ml.) and the reaction mixture refluxed for a further 4 hrs. At the end of this time the infra-red spectrum of an aliquot, removed from the reaction and evaporated to dryness, indicated the presence of 20-30% unreacted diazoketone. A further amount of catalyst solution, silver benzoate (1.5 g.) in dry triethylamine (15 ml.), was then added. When half of this catalyst solution had been added there was no further evolution of nitrogen and the initial precipitate did not readily redissolve as had occurred previously. The remainder of the catalyst solution was then added and the mixture refluxed gently overnight. After evaporation of the solvent under reduced pressure, the crude product was chromatographed on alumina (Grade III) (110 g.). Elution with benzene (4 x 100 ml.) afforded the keto-ester (CLXXX; R=Bu^t) as a thick pale red non-crystallisable oil (8.07 g.). The product exhibited infra-red absorption at 1710 cm.$^{-1}$ (Carbo-t-butoxyl and cyclohexanone), 3000 cm.$^{-1}$ (olefinic double bond), 1760 cm.$^{-1}$ (γ-lactone), 1382 and 1362 cm.$^{-1}$ (gem dimethyl) with weak bands at 3420 cm.$^{-1}$ (hydroxyl), 1640 and 1600 cm.$^{-1}$.

5-Methylbicyclo[3:3:1]non-3-ene-9-one-1-acetic acid (CLXXX; R=H)

A solution of the keto-ester (CLXXX; R=But) (7.17 g.) in methanol (25 ml.) was refluxed for 2 hrs. on a steam bath with a solution of sodium hydroxide (8 g.) in water (5 ml.). After evaporation of the solvent under reduced pressure, the cooled mixture was dissolved in water and extracted with ether. The aqueous extracts were acidified with concentrated hydrochloric acid, saturated with ammonium sulphate and extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent furnished the keto-acid as a non-crystallisable glass (5.66 g.).

1-Carbomethoxymethyl-5-methylbicyclo[3:3:1]non-3-ene-9-one (CLXXX; R=H)

A solution of the keto-acid (5.66 g.) in dry ether(25ml) was treated with a slight excess of an ethereal diazomethane solution and the solution allowed to stand at room temperature for 2 hrs. Evaporation of solvent afforded the keto-ester as a thick red non-crystallisable oil (6.05 g.). The product exhibited infra-red bands at 1720 cm^{-1} (carbomethoxyl and cyclohexanone), 1760 cm^{-1} (γ-lactone), 3400 cm^{-1} (hydroxyl). The product could be decolorised by chromatography on silica, elution with 5% ether-benzene affording the keto-ester, with no improvement in the infra-red spectrum. Fractionation also afforded no chemical purification of the keto-ester b.p. 90-115°/0.02 mm.

Allylic oxidation of the olefinic-ester (CLV; R=Me)

(a) With t-butyl chromate. The reagent was prepared by adding chromium trioxide (24 g.) in small portions to ice-cooled t-butanol (50 g.), followed by dilution with benzene (150 ml.). The benzene solution was dried over magnesium sulphate, filtered and glacial acetic acid (15 ml.) and acetic anhydride (10 ml.) added just prior to the oxidation. The oxidant was added dropwise with stirring over 1 hr. to a solution of the olefinic-ester (11.56 g.) in benzene (50 ml.). Benzoyl peroxide (0.5 g.) was added and the mixture stirred gently and warmed to 48° in an oil bath for 135 hrs. under an atmosphere of nitrogen. Water (100 ml.) and oxalic acid (60 g.) were carefully added to the cooled solution, with vigorous stirring. The benzene layer was then separated and the aqueous layer extracted with benzene. The combined benzene extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a brown oil (9.9 g.), which exhibited an ultra-violet maximum at 231mμ (ε2,200). In a similar experiment in which the reaction temperature was maintained at 52° for 135 hrs., the intensity of the ultra-violet maximum in the product was 4,600. After standing for 24 hrs. the product was dissolved in benzene and filtered from precipitated chromium residues. Evaporation of solvent afforded an oil (9.15 g.).

(b) With chromium-trioxide in acetic acid.

(i) A solution of chromium trioxide (0.3 g.) in aqueous acetic acid (5 ml.) was added to a solution of the olefinic-ester (0.9 g.) in acetic acid (5 ml.) and the solution allowed to stand at room temperature for 8 hrs., then poured into water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a colourless oil (0.6 g.), the infra-red spectrum of which exhibited a weak band at 1677 cm^{-1} (conjugated carbonyl). The alkaline extracts contained no isolable carboxylic material.

(ii) A solution of the olefinic-ester (0.6 g.) in acetic acid (5 ml.) was warmed on a steam bath for 10 mins. with a solution of chromium trioxide in aqueous acetic acid (5 ml.). The cooled green solution was poured into water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (0.53 g.), the infra-red spectrum of which exhibited a medium band at 1677 cm^{-1} (conjugated carbonyl). The product exhibited an ultra-violet maximum at 230mμ (ε1,500).

(iii) A solution of the product (0.53 g.) from

experiment (11), in acetic acid (5 ml.) was warmed on a steam bath for 10 mins. and worked up as above. The neutral fraction (0.15 g.) exhibited medium infra-red bands at 1770 $cm.^{-1}$ (γ-lactone) and 1677 $cm.^{-1}$ (enone) with a strong band at 1735 $cm.^{-1}$ (carbomethoxyl).

(c) With sodium dichromate. A solution of the olefinic-ester (86.7 g., 0.447 mole) and sodium dichromate dihydrate (215.4 g., 0.723 mole) in acetic acid (500 ml.) was heated at 90° for 10.5 hrs. Ethanol (100 ml.) was added to the hot solution to decompose the excess oxidant and the resulting green solution cooled, diluted to 2 l. with water, and extracted with ether (3 x 500 ml.). The combined ethereal extracts were washed to neutrality with dilute sodium hydroxide solution, then with water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow oil (69.5 g.), the infra-red spectrum of which exhibited a medium band at 1677 $cm.^{-1}$ (enone) and a weak band at 1770 $cm.^{-1}$ (γ-lactone), with an ultra-violet maximum at 230mμ (ε2,300).

Purification of the enone-ester (CLVI; R=Me)

(a) A solution of the impure enone-ester (9.15 g.) (from t-butyl chromate oxidation of the olefinic-ester (11.56 g.)), in light petroleum was chromatographed on alumina (Grade III) (170 g.). Elution with light petroleum (20 x 50 ml.) afforded the olefinic-ester (2.2g.),

and further elution with (17 x 50 ml.) of mixtures ranging from 5% benzene-light petroleum to 50% benzene-light petroleum sufficed to elute the olefinic-ester completely (0.9 g.). Elution with benzene (10 x 50 ml.) and ether (5 x 50 ml.) afforded the enone-ester (2.75 g.), which exhibits an ultra-violet maximum at 230 mμ (ε5,000).

(c) Although the olefinic-ester (CLV; R=Me) was quite volatile, (b.p. 55°/0.1 mm.), efficient separation from the enone-ester (CLVI; R=Me) could not be effected by fractional distillation at 0.1 mm.

(d) A solution of the crude enone-ester (5 g.) in methanol (50 ml.) was refluxed on a steam bath for 5 hrs. with a solution of sodium hydroxide (1.5 g.) in water (5 ml.). After evaporation of the solvent under reduced pressure, the cooled mixture was diluted with water (25ml.) and extracted with ether. The aqueous extract was acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 25 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent gave a thick oil (4 g.) which on trituration with light petroleum afforded the olefinic-acid (CLV; R=H), which crystallised as colourless needles (2.5 g.) as the light petroleum soluble fraction. The non-light petroleum soluble fraction was obtained as a thick red

oil (1.1 g.) which was then esterified with diazomethane. The resultant impure ester was triturated with light petroleum affording impure enone-ester (CLVI; R=Me) as the light petroleum soluble fraction (0.8 g.). The product exhibited an ultra-violet maximum at 230mμ (ε3,000). Small amounts of hydroxylic material were found to be insoluble in light petroleum.

(e) (i) A mixture of the crude enone-ester (1.24 g.), the Girard T reagent (2.7 g.) and IR 120 (H) amberlite resin (0.5 g.) (previously activated with 1 N hydrochloric acid) was refluxed for 0.5 hr. with ethanol (40 ml.). The cooled mixture was decanted into water (100 ml.) and extracted with ether (2 x 25 ml.). The combined ethereal extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded an oil (0.77 g.) which exhibited a weak band at 1677 $cm.^{-1}$ (enone) with absorption bands from 1200 to 700 $cm.^{-1}$ similar to those found in the spectrum of the olefinic-ester. 40% formalin solution (25 ml.) was added to the aqueous solution, and the reaction mixture allowed to stand at room temperature overnight before extracting with ether (2 x 50 ml.). The combined ethereal extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a mobile brown oil (0.05 g.) which exhibited a broad band in the infra-red at 1725 $cm.^{-1}$ (carbomethoxyl), with medium bands at 1677 $cm.^{-1}$ (enone) and 1770$cm.^{-1}$ (γ-lactone).

(ii) A solution of the impure enone-ester (232 mg.) in methanol (5 ml.) was allowed to stand overnight at room temperature with excess semicarbazide acetate solution. As no crystalline material separated, the solution was poured into water (25 ml.) and the colourless semicarbazone (24 mg.) filtered off; further dilution with water afforded more semicarbazone (36 mg.), which crystallised from aqueous methanol as colourless needles m.p. 190-192°. (Found: N, 15.3; $C_{13}H_{19}O_3N_3$ requires N, 15.85%).

(f) (i) A solution of the impure enone-ester (2.05g.) in ether(100 ml.) was added slowly to a solution of lithium (1.8 g.) in liquid ammonia (600 ml.) and the reaction mixture stirred for 2 hrs. After neutralising with ammonium chloride, the ammonia was allowed to evaporate and the residue acidified with dilute sulphuric acid and extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (1.45 g.) which exhibited a strong band in the infra-red at 3500 $cm.^{-1}$ (hydroxyl), a medium band at 1695 $cm.^{-1}$ (ketone), a weak band at 1677 $cm.^{-1}$ (enone) with no absorption at 1735 $cm.^{-1}$ (carbomethoxyl). A solution of the product in acetic acid (80 ml.) was treated with chromium trioxide (1.6 g.) at room

temperature overnight, then poured into water (350 ml.) and extracted with ethyl acetate (2 x 100 ml.). The combined ethyl acetate extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a viscous oil (1.19 g.), which was esterified with diazomethane to give a mobile oil (1.14g.). A solution of the ester mixture (1.14 g.) in light petroleum (b.p. 60-80°) was chromatographed on alumina (Grade I) (31 g.). Elution with 50% benzene-light petroleum (b.p. 60-80°) (10 x 50 ml.) afforded pure olefinic-ester (CLV; R=Me) (0.2 g.). Elution with benzene (6 x 50 ml.) gave pure keto-ester (CLIII; R=Me) (0.15 g.), while further elution with ether (4 x 50 ml.) gave a mixture of the keto-ester (CLIII;R=Me) and the enone-ester (CLVI; R=Me) (0.3 g.).

(ii) A solution of the impure enone-ester (38.8 g.) in ethyl acetate was hydrogenated over 10% palladium-charcoal, hydrogen (2,550 ml.) being absorbed over 6 hrs. The filtered solution, on evaporation, afforded a mixture of, at least, the keto-ester (CLIII; R=Me) and the ester (CLXXXVI) as a mobile yellow oil (38.13 g.). The product, which exhibited a weak band in the infra-red at 3500 $cm.^{-1}$ (hydroxyl) and no absorption at 1677 cm^{-1} (enone), showed only low intensity (ε125) at 230mμ in the ultra-violet. The product was stirred with 6N hydrochloric acid (160 ml.) under gentle reflux for 5 hrs.

The cooled solution was saturated with ammonium sulphate and extracted with ether (2 x 300 ml.). The combined ethereal extracts were washed with cold dilute sodium hydroxide solution, water and dried over magnesium sulphate. Evaporation of solvent afforded a yellow mobile oil (12 g.), the infra-red spectrum of which was almost identical with that of the starting material. The alkaline extracts were acidified with 6N hydrochloric acid, saturated with ammonium sulphate and extracted with ether (2 x 300 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent gave a thick oil (23.7 g.), which on trituration with ether-light petroleum gave colourless needles (3.4 g.) m.p. 110-147°, which sublimed as hexagonal plates m.p. 163-173°. The infra-red spectrum exhibited absorption bands at 3500 to 2300 cm^{-1}, 1695 cm^{-1} (carboxyl), and 1710 cm^{-1} (cyclohexanone). The oily keto-acid (CLIII; R=H) (20.3 g.) could not be crystallised but with diazomethane afforded a mobile ester (CLIII; R=Me) which exhibited an infra-red spectrum very similar to that of authentic keto-ester (CLIII; R=Me) but also exhibited a band at 1765 cm^{-1} (γ-lactone). Repeat acidic hydrolysis of the recovered neutral oil (12 g.) afforded acidic material (10.6 g.), which rapidly crystallised from light petroleum as needles m.p. 100-124°.

The infra-red spectrum of the product indicated it to be a mixture of, at least, the acids (CLV; R=H) and (LXXIV).

(b) A solution in 50% benzene-light petroleum of the product (69.5 g.) from the sodium dichromate oxidation of the olefinic-ester (CLV; R=Me) (86.7 g.) (see p.) was chromatographed on silica (1 kg.). Elution with 50% benzene-light petroleum (3 x 500 ml.) and with benzene (4 x 500 ml.) afforded an oil (33.9 g., 39%), the infra-red spectrum of which indicated it to be mainly the olefinic-ester containing only traces of ketonic material. Further elution with 50% ether-benzene (5 x 500 ml.) gave a colourless oil (26.3 g., 28%), the infra-red spectrum of which exhibited strong bands at 1735 cm^{-1} (carbomethoxyl) and 1678 cm^{-1} (conjugated ketone) with a weak band at 1765 cm^{-1} (γ-lactone), and an ultra-violet maximum at 230mμ (ε5,500).

A solution of the impure enone-ester (CLVI; R=Me) (1.15 g.) in benzene was rechromatographed on silica (35g.). Extended elution with 0.5% ether-benzene afforded fairly pure enone-ester (0.68 g.) as evidenced by the ultra-violet maximum intensity of 6,900 at 230.5mμ, and the equally intense bands at 1735 and 1678 cm^{-1} in the infra-red spectrum. The product was eluted as two bands on the vapour-phase chromatogram at 150°, the first band eluted after 17 mins. being about half as intense

as the band eluted after 19 mins. The enone-ester distilled as a colourless oil b.p. 94°/0.1 mm., n_D^{20} 1.4960. (Found: C,68.7; H, 7.6. $C_{12}H_{16}O_3$ requires C, 69.2; H,7.75%). A solution of the enone-ester (0.68 g.) in methanol, on treatment with Brady's reagent at room temperature, readily afforded an orange solid (2.15 g.) m.p. 75-120°, which crystallised from methanol as orange needle clusters (306 mg.) m.p.158-167°. A solution of this product in benzene was filtered through bentonite-kieselguhr, the filtrate evaporated to dryness and the residue recrystallised from methanol affording one 2:4-dinitrophenylhydrazone of the enone-ester (CLVI; R=Me) as orange needle clusters (207 mg.) m.p. 168-170°. (Found: C, 55.5; H, 4.95; N, 14.55. $C_{18}H_{20}O_6N_4$ requires C, 55.65; H, 5.2; N, 14.45%). The product exhibited two maxima, in chloroform, in the ultra-violet, at 380mμ (ε24,400) and at 260mμ (ε9,300). The methanolic mother-liquors were poured into water and extracted with ethylacetate. The ethyl acetate extract was washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a red oil (600 mg.), which was chromatographed on alumina (Grade I) (18 g.). Elution with benzene gave a yellow solid m.p. 110.125°. Repeated crystallisation from methanol afforded an isomeric 2:4-dinitrophenylhydrazone as orange-yellow needle

clusters m.p. 144-146°. (Found: C, 55.7; H, 5.45; N, 14.45%). The product exhibited two maxima, in chloroform, in the ultra-violet, at 375mμ (ε27,000) and at 260mμ (ε9,540). Both 2:4-dinitrophenylhydrazones exhibited strong bands at 1735 cm.$^{-1}$ (carbomethoxyl) in the infra-red. The 2:4-dinitrophenylhydrazones could not be interconverted by seeding a warm methanolic solution of one with the other.

Allylic oxidation of the olefinic-ester (CLV; R=Me) with t-butyl perbenzoate

t-Butyl perbenzoate (0.77 g.) was added dropwise over 1 hr. under nitrogen to a vigorously stirred mixture of the olefinic-ester (1.94 g.) and cuprous bromide (0.1 g.) held at 105°. The reaction mixture was then heated at 110° for a further 1.5 hr. Ether (50 ml.) was added to the cooled mixture and the solution filtered from copper residues. The filtrate was washed with dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded the impure benzoate-ester (CLXXXIX; R=CO.Ph) as a viscous oil which was chromatographed on alumina (Grade III) (50 g.). Elution with 20% benzene-light petroleum (6 x 70 ml.) gave the olefinic-ester (1.48 g., 76%). Further elution with chloroform (4 x 70 ml.) furnished the benzoate-ester as a viscous oil (0.58 g., 15%).

Conversion of the benzoate-ester (CLXXXIX; R=CO.Ph) to the enone-ester (CLVI; R=Me)

A solution of the benzoate-ester (0.58 g.) in dry methanol (8 ml.) was refluxed with sodium (0.015 g.) for 4 hrs. The cooled solution was saturated with carbon dioxide, diluted with ether (50 ml.), washed with dilute brine solution and dried over magnesium sulphate. The infra-red spectrum of the product after removal of the solvent exhibited a strong band at 3400 $cm.^{-1}$ (hydroxyl), 1735 $cm.^{-1}$ (carbomethoxyl) with bands at 3000 and 1600 $cm.^{-1}$ (aromatic). A solution of the product in light petroleum was chromatographed on alumina (Grade III). Elution with 10% benzene-light petroleum (5 x 70 ml.) gave methyl benzoate as a sweet-smelling oil (0.05 g.). Further elution with chloroform (4 x 70 ml.) afforded the hydroxy-ester (CLXXXIX; R=H) as a thick yellow oil (0.2 g.). A solution of the hydroxy-ester (0.2 g.) in light petroleum (20 ml.) was shaken for 6 hrs. at room temperature with activated manganese dioxide (3 g.). Filtration and evaporation of the solvent afforded the enone-ester (CLVI; R=Me), the infra-red spectrum of which was identical with that of the enone-ester prepared by direct allylic oxidation of the olefinic-ester (CLV; R=Me), though the product exhibited a higher ultra-violet maximum intensity of 7,375 than obtained previously.

1-Carbomethoxyl-5-methylbicyclo[3:3:1]nonane-2-one (CLIII; R=Me)

When a solution of the enone-ester (1.164 g.) (prepared by the sodium dichromate method and purified by chromatography on silica) in ethyl acetate was reduced over 10% palladium-charcoal at room temperature, hydrogen (113 ml., 83%) was absorbed. The filtered solution on evaporation afforded the impure keto-ester (CLIII; R=Me) as a mobile oil, which exhibited bands at 1735 $cm.^{-1}$ (carbomethoxyl) and 1712 $cm.^{-1}$ (cyclohexanone) in the infra-red, and which was eluted as one band on the vapour-phase chromatogram. Repeated fractionation afforded the keto-ester as a colourless oil b.p. 84°/0.1mm., n_D^{23} 1.4859. (Found: C, 68.35; H, 8.5. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%). The impure keto-ester (557 mg.) readily reacted with Brady's reagent at room temperature affording a yellow 2:4-dinitrophenylhydrazone m.p. 120-148°, which was further purified by filtration of its solution in benzene through bentonite-kieselguhr. The filtrate was evaporated to dryness and the residue crystallised from methanol as yellow needle clusters m.p. 122-125° (Found: C, 55.65; H, 5.5; N, 14.25. $C_{18}H_{22}O_6N_4$ requires C, 55.4; H, 5.7; N, 14.35%). The product exhibited a maximum in chloroform, in the ultra-violet, at 363mμ (ε21,300) and exhibited a strong band at 1735 $cm.^{-1}$ (carbomethoxyl) in the infra-red.

2:4-Dinitrophenylpyrazolone of the keto-ester (CLIII;R=Me)

A solution of the impure keto-ester (158 mg.) in dry methanol (10 ml.) was refluxed for 1 hr. with excess Brady's reagent. The cooled mixture was dissolved in chloroform, washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil, which was dissolved in benzene and chromatographed on bentonite-kieselguhr. The benzene eluate, on trituration with ether, afforded the 2:4-dinitrophenylpyrazolone as a pale yellow solid (144 mg.) which crystallised from ethanol as pale yellow needles m.p. 179-181° (75 mg.). (Found: C, 57.05; H, 4.75; N, 15.55. $C_{17}H_{18}N_4O_5$ requires C, 57.0; H, 5.05; N, 15.65%).

Pyrazolone of the keto-ester (CLIII; R=Me)

A solution of the impure keto-ester (120 mg.) in dry methanol (10 ml.) was refluxed for 24 hrs. with hydrazine hydrate (0.5 ml.). After evaporation to dryness the residue was dissolved in chloroform and the chloroform solution washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil which was chromatographed on alumina (Grade I) (3 g.). Elution with benzene (3 x 50 ml.) afforded no useful material, but further elution with chloroform (5 x 50 ml.) gave a thick yellow oil (65 mg.) which solidified on trituration with light petroleum (b.p.60-80°).

Recrystallisation from light petroleum (b.p. 60-80°) gave the pyrazolone as pale yellow needles m.p. 112-114° (Found: C, 68.35; H, 8.25; N, 14.35. $C_{11}H_{16}ON_2$ requires C, 68.7; H, 8.4; N, 14.55%).

Attempted condensation of the keto-ester (CLIII; R=Me) with cyanoacetic acid

A solution of the keto-ester (1.18 g.) in benzene (50 ml.) containing cyanoacetic acid (0.93 g.), ammonium acetate (0.1 g.) and glacial acetic acid (0.5 ml.) was refluxed for 8 hrs. under a Dean and Stark apparatus. The cooled solution was washed with water (4 x 25 ml.) and dried over magnesium sulphate. Evaporation of solvent afforded a mobile oil (1.1 g.), the infra-red spectrum of which was identical with that of the starting material.

Condensation of the keto-ester (CLIII; R=Me) with malononitrile

A solution of the keto-ester (1.1 g.) in benzene (25 ml.) containing malononitrile (0.4 g.), ammonium acetate (0.1 g.) and glacial acetic acid (0.5 ml.) was refluxed for 2.5 hrs. under a Dean and Stark apparatus. The cooled solution was washed with water and dried over magnesium sulphate. Evaporation of solvent gave a thick yellow oil (1.2 g.) which on distillation afforded the dinitrile-ester (CXCII) as a colourless oil b.p. 120°/0.02 mm., n_D^{19} 1.5000 which gradually turned yellow with loss of hydrogen cyanide. The product

exhibited infra-red absorption at 2200 $cm.^{-1}$ (conjugated nitrile) and 1735 $cm.^{-1}$ (carbomethoxyl) with only a weak band at 1712 $cm.^{-1}$ (cyclohexanone) with an ultra-violet maximum at 247mμ (ε6,600).

Attempted condensation of the keto-ester (CLIII; R=Me) with ethyl α-bromoisobutyrate

A solution of the keto-ester (1.7 g., 0.008 mole) and ethyl α-bromoisobutyrate (16 g., 0.08 mole) in benzene (50 ml.) was added to freshly activated zinc wool (15 g.) and the mixture refluxed with stirring for 5 mins. until vigorous exothermic reaction commenced with concomitant precipitation of a viscous green oil. The vigorously stirred mixture was gently refluxed for 10 hrs. The cooled mixture was then acidified with acetic acid, poured into water (200 ml.) and extracted with ether (2 x 50 ml.). The combined ethereal extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Prolonged heating under reduced pressure (20 mm.) on the steam bath afforded an oil (12.4 g.), which on distillation gave a mobile oil b.p. 40-80°/0.1 mm. (8.45 g.), from which a crystalline solid (0.9 g.) separated. Crystallisation from light petroleum gave colourless needles m.p. 80-81°. (Found: C, 68.3; H, 8.45. C_4H_6O requires C, 68.55; H, 8.65%). The product exhibited a strong band at 1700 $cm.^{-1}$ and a weak band

at 1749 $cm.^{-1}$ in the infra-red. Further distillation afforded a high-boiling fraction b.p. 80-150°/0.1 mm. (1.92 g.), the infra-red spectrum of which was similar to that of the starting material with apparent increase of the ester band at 1735 $cm.^{-1}$. Saponification of the product (1.92 g.) with 4N sodium hydroxide in methanol furnished a non-crystallisable oily acid (1.29 g.).

Saponification of the Keto-ester (CLIII; R=Me)

A solution of the impure keto-ester (1.5 g.) in methanol (10 ml.) was refluxed for 2 hrs. on a steam bath with a solution of potassium hydroxide (1 g.) in water (3 ml.). After evaporation of solvent, the cooled residue was diluted with water and extracted with ether. The aqueous extracts were acidified with dilute sulphuric acid, saturated with ammonium sulphate and extracted with ether (2 x 30 ml.). The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent gave a thick oil (1.2 g.) which on trituration with ether-light petroleum furnished crystalline material m.p. 85-135° (0.84 g.), which crystallised with difficulty from ethyl acetate-light petroleum as a powder m.p. 70-100°. The infra-red spectrum of the corresponding ester (CLIII; R=Me), prepared by esterification with diazomethane, was similar to that of the starting material, and the

product (0.22 g.) readily afforded the characteristic yellow 2:4-dinitrophenylhydrazone (0.12 g.).

The impure oily keto-acid (120 mg.) readily afforded a cyclohexylamine salt (133 mg.) which crystallised from benzene-light petroleum (b.p.60-80°) as colourless needles m.p. 130-149° with continuous decomposition. (Found: N, 4.95. $C_{17}H_{29}O_3N$ requires N, 4.75%). It also gave a S-benzylisothiouronium salt which crystallised from chloroform-benzene as colourless prisms m.p. 153-155° (decomposition from 142°). (Found: C, 62.5; H, 7.2; N, 7.85. $C_{19}H_{26}O_3N_2S$ requires C, 62.95; H, 7.25; N, 7.75%).

A solution of the oily keto-acid (966 mg.) in benzene was chromatographed on silica (32 g.). Elution with 5% ether-benzene (16 x 50 ml.) afforded the keto-acid as a thick oil (830 mg.), the latter fractions becoming progressively more crystalline, 200 mg. being obtained crystalline, m.p. 146-150° with weeping from 100°. Further elution with ether (5 x 50 ml.) gave a non-crystallisable oil (120 mg.).

Sodium borohydride reduction of the keto-ester (GLIII;R=Me)

Sodium borohydride (5 g.) was added to a solution of the keto-ester (1.51 g.) in methanol (25 ml.) containing water (5 ml.), and the solution allowed to stand at room temperature overnight. After evaporation of solvent under reduced pressure without heating, the

residue was acidified with dilute hydrochloric acid and extracted with ether (2 x 20 ml.). The combined ethereal extracts were washed with water and dried over magnesium sulphate. Evaporation of solvent afforded a thick oil (1.185 g.) which was chromatographed on silica (35 g.). Elution with benzene (5 x 50 ml.) and 5% ether-benzene (2 x 50 ml.) gave an oil (0.175 g.), the infra-red spectrum of which exhibited weak hydroxyl bands, with maxima at 1770 $cm.^{-1}$ (γ-lactone), 1735 $cm.^{-1}$ (carbomethoxyl) and 1712 $cm.^{-1}$ (cyclohexanone). Further elution with 5% ether-benzene (13 x 50 ml.) afforded the hydroxy-ester (CXCVIII; R=Me) as a sweet-smelling oil (0.625 g.), which exhibited bands at 3450 $cm.^{-1}$ (hydroxyl) and at 1735 $cm.^{-1}$ (carbomethoxyl) in the infra-red. Elution with ether afforded the diol (CXCIX) as a crystalline solid (0.46 g.) which crystallised from ethyl acetate-light petroleum as flat rods m.p. 98-99.5° (Found: C, 71.7; H, 10.65. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.95%).

2-Hydroxy-5-methylbicyclo[3:3:1]nonan-1-carboxylic acid (CXCVIII; R=H)

A solution of the hydroxy-ester (CXCVIII; R=Me) (0.45 g.) in methanol (10 ml.) was refluxed on a steam bath for 2 hrs. with a solution of potassium hydroxide (0.3 g.) in water (3 ml.). The cooled solution was diluted with water and extracted with ether. The alkaline solution was acidified with dilute sulphuric acid,

saturated with ammonium sulphate and extracted with ether. The combined ethereal extracts were washed with a brine solution and dried over magnesium sulphate. Evaporation of solvent gave a thick oil (0.40 g.) which on trituration with ether-light petroleum furnished a solid m.p. 127-149°. Repeated crystallisation from ethyl acetate-light petroleum afforded one epimeric hydroxy-acid (CXCVIII; R=H) as colourless prisms m.p. 183.5-184.5°. (Found: C, 66.6; H, 8.95. $C_{11}H_{18}O_3$ requires C, 66.65; H, 9.15%).

Hydrogenation of the keto-ester (CLIII; R=Me)

A solution of the keto-ester (13.43 g.) in ethyl acetate was hydrogenated at 20° over platinum oxide (0.72 g.), hydrogen (1520 ml.) being absorbed over 4 hrs. The filtered solution was evaporated and the residue dissolved in benzene and chromatographed on silica (250 g.). Elution with 2% ether-benzene (4 x 500 ml.) gave an oil (2.32 g.) the infra-red spectrum of which showed weak hydroxyl and strong lactone bands. Further elution with 20% ether-benzene (4 x 500 ml.) furnished the hydroxy-ester (CXCVIII; R=Me) as a colourless oil (11.23g.).

A solution of the hydroxy-ester (11.23 g.) in methanol (50 ml.) was refluxed with a solution of potassium hydroxide (6.1 g.) in water (10 ml.) on a steam bath for 2.5 hrs. After evaporation of solvent, the cooled residue was dissolved in water and extracted with ether.

The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded a mixture of the epimeric hydroxy-acids (CXCVIII; R=H) as a thick oil (10.06 g., 96%) which rapidly solidified to a crystalline mass m.p. 115-145°. Fractional crystallisation from ethyl acetate-light petroleum did not effect separation of the epimers.

5-Methylbicyclo[3:3:1]nonan-2-one-1-carboxylic acid (CLIII; R=H)

A solution of the crystalline epimeric hydroxy-acids (CXCVIII; R=H) (14.1 g.) in acetone (50 ml.), cooled to 0°, was titrated with 9.7N chromium trioxide in sulphuric acid, a 5 ml. excess added and the mixture allowed to stand for 0.5 hr. in an ice-bath. The mixture was poured into a large volume of water, saturated with ammonium sulphate and extracted with ether. The combined ethereal extracts were washed with saturated ammonium sulphate solution and dried over magnesium sulphate. Evaporation of solvent afforded the keto-acid as a viscous oil (13.4 g.) which slowly solidified at 0° (m.p. 93-110°). Repeated crystallisation from benzene or ethyl acetate furnished the keto-acid in 25% yield, as colourless prisms m.p. 151.5-153° with weeping from 139°. (Found: C, 67.1; H, 8.05. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%). The product showed bands at 1706cm. (cyclohexanone), and bands at 3200-2300 and 1663cm. (carboxyl) in the infra-red.

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